SYNTHESIS OF TWO NEW GLYCOPHANES COMPRISED OF THIOGLUCOSE MOLECULES LINKED BY HYDROCARBONS

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Abstract. Preparation of two new glycophanes is reported. These compounds are comprised of two glucose molecules linked by hydrocarbon units at the 1, 1' and 3, 3' or 3, 3' and 6, 6' positions. The crystal structure of one of the glycophanes is also described.

Key words. Glycophane, macrocycle, carbohydrate, crystal structure.

1. Introduction

We are preparing new macrocyclic compounds comprised of two monosaccharides linked by hydrocarbon units for use in studying interactions of the monosaccharides with small molecules bound by the macrocycles. Wilcox [1] prepared macrocycles made from hydrocarbon linked carbohydrates and first called the compounds 'glycophanes'. Carbohydrates have also been included in macrocyclic polyethers to give compounds capable of binding of cations [2]. More recently, Penadés and coworkers [3] have reported the preparation of a glycophane comprised of two maltose molecules linked by naphthalene groups. The association behavior of this glycophane with nitrophenyl glycosides was studied in an attempt to observe carbohydrate-carbohydrate interactions in water. The glycophanes we are preparing will be used to gauge the hydrophobic contributions of monosaccharides in the binding of nonpolar molecules in aqueous solutions.

The important roles that carbohydrates play in biological molecular recognition are increasingly recognized [4]. However, the roles that noncovalent forces play in the interactions of sugars with other molecules

are not fully understood [5]. There remains the need to identify and quantify the types of noncovalent interactions in which sugars can participate, especially in aqueous solutions where water can effectively compete for hydrogen bonding interactions. We have prepared two new macrocycles in which two glucose molecules are linked at the 1,1' and 3,3' (1) or the 3,3' and 6,6' (2) positions. By measuring the ability of these new glycophanes to bind small molecules in water, we expect to gain insight into the hydrophobic contributions of the monosaccharides in association with nonpolar or amphiphilic molecules. We now report the preparation of these glycophanes.

2. Results and Discussion

The syntheses of both compounds began with linking of two molecules of diacetone glucose (3) with either a hexyl or a p-xylyl group (Schemes 1 and 2, respectively). Treatment of diacetone glucose with 1,6-dibromohexane, KOH and 18-crown-6 in THF [6] gave linked diacetone glucose 5 (83% yield) as well as elimination product 4 (15%) (Scheme 1). The glucose molecules in 5 were deprotected and isomerized to the pyranose form by refluxing 5 in 80% acetic acid in water for 2-4 hrs. The resulting
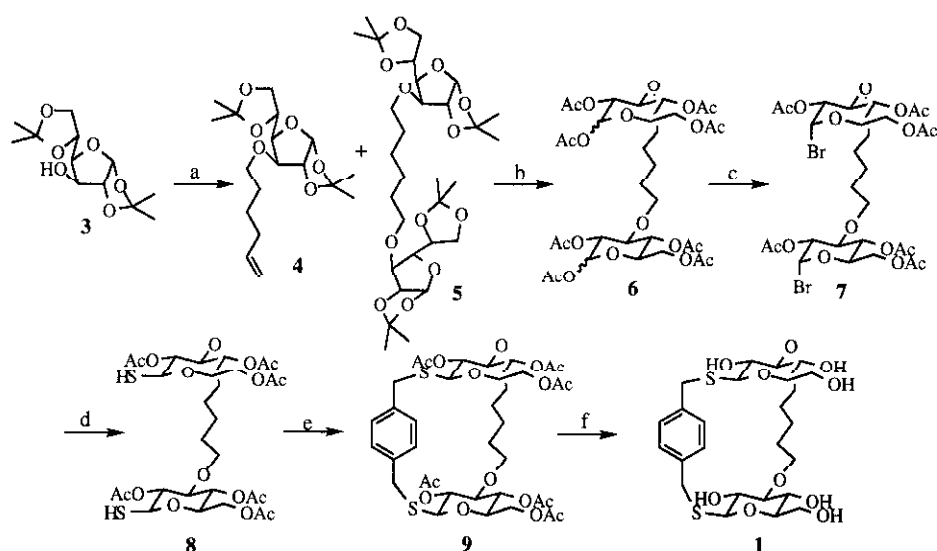
Reagents: a) 1,6-dibromohexane, KOH, 18-crown-6, THF, 15% (4), 83% (5). b) 80% AcOH in H₂O, reflux; Ac₂O, pyridine, 66%. c) HBr, AcOH, 0° C. d) thiourea, acetone, reflux; K₂CO₃, NaHSO₃, H₂O, Et₂O, 68% from 6. e) α,α'-dichloro-p-xylene, Cs₂CO₃, McCN, 28%. f) Abcilite IR-400, MeOH, 96%.

Scheme 1. Synthesis of glycophane 1.

polyalcohol was then peracylated with acetic anhydride in pyridine to give compound **6** in 66% overall yield. The anomeric positions in **6** were activated by treatment with HBr in acetic acid at 0° C for 1 hr, providing **7**. Dibromide **7** proved to be unstable at room temperature and was immediately reacted with thiourea in acetone. The resulting bisisothiouronium salt was hydrolyzed with K_2CO_3 and $NaHSO_3$ in water/ether to give **8** in 68% yield from the peracetate. It was expected that dithiol **8** might be easily oxidized to the disulfide, so immediately after preparation the dithiol was cyclized by reaction with α,α'-dichloro-*p*-xylene and Cs_2CO_3 in acetonitrile to form macrocycle **9** in 28% yield.

Macrocycle **9** was crystalline, and its crystal structure was determined (Figure 1). The glycophane forms a rectangular cavity with the glucose portions of the molecule forming two sides of the rectangle. The structure also shows the sterically crowded environment of the acetyl groups at the 2 and 2' positions. Steric crowding at these positions is consistent with observed rates of deacylation of macrocycle **9**; the acetate groups at the 6, 6', 4 and 4' positions were rapidly hydrolyzed by a basic ion-exchange resin (Amberlite®
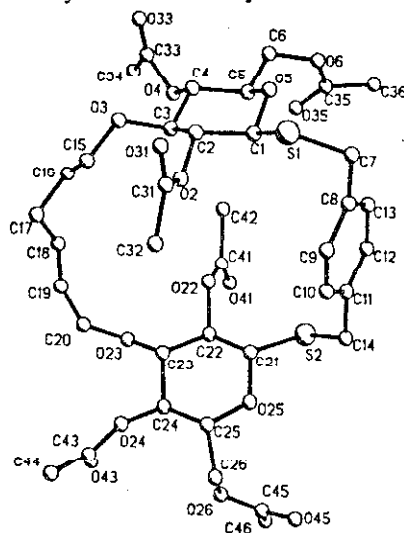

Figure 1. Crystal structure of **9** (hydrogen atoms have been omitted for clarity).

IR-400) in methanol while the acetate groups at the 2 and 2' positions were only slowly cleaved. Nevertheless, full deacylation giving **1** was achieved in methanol with the ion-exchange resin after approximately 48 hrs. Alternatively, reaction of **9** with sodium methoxide in methanol provided **1** in less than 4 hrs.

The synthesis of glycophane **2** (Scheme 2) began with the preparation of *p*-xylyl-linked diacetone glucose (**10**) from diacetone glucose. In contrast to the reaction forming glucose dimer **5**, preparation of **10** proceeded without the complication of elimination; a yield of 99% was obtained. Treatment of **10** with 80% acetic acid in water at reflux for 40 minutes provided tetraalcohol **11** in 58% yield. Tosylation at the 6 and 6' positions was followed by acylation at the 5 and 5' positions giving **12**. The tosylates were displaced with potassium thioacetate in refluxing acetone [7] to give the dithioacetate in 58% yield. The 6,6'-thiols were generated by reducing the acetates with lithium aluminum hydride in THF to give **13**. Dithiol **13** was immediately reacted with α,α'-dichloro-*p*-xylene and Cs_2CO_3 in acetonitrile

3   a →   **10**   b →   **11**   c,d →   **12**

13   e,f →   **14**   g →   h →   **2**
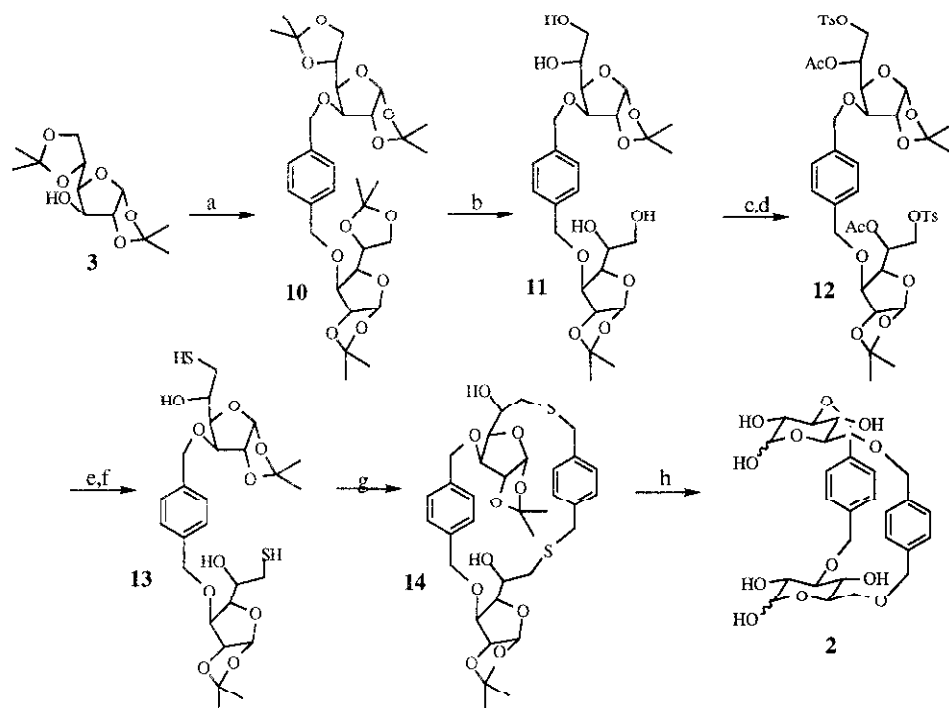
Reagents: a) α,α'-dichloro-p-xylene, KOH, 18-crown-6, THF, 99%. b) 80% AcOH in H₂O, reflux, 40 min. c) TsCl, pyridine, 0° C, 81%. d) Ac₂O, pyridine, 95%. e) AcSK, acetone, reflux, 58%. f) LiAlH₄, THF, 73%. g) α,α'-dichloro-p-xylene, Cs₂CO₃, McCN, 30%. h) 80% AcOH in H₂O, reflux, 92%.
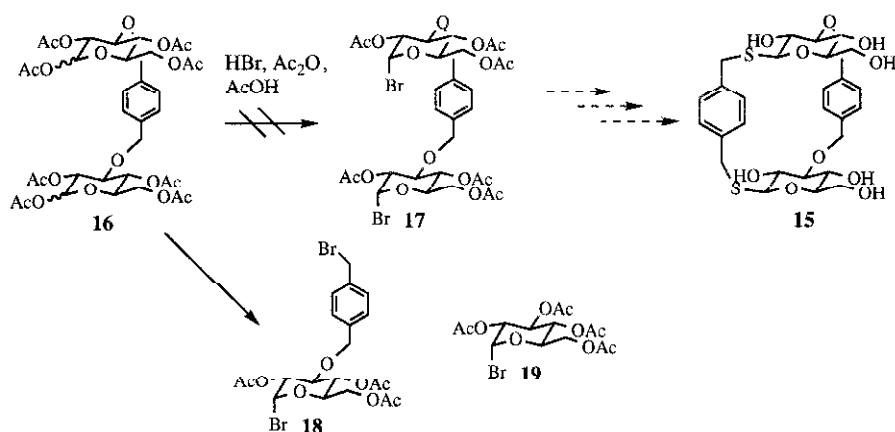
Scheme 2. Synthesis of glycophane **2**.

to give the 3,3'-6,6' linked macrocycle **14** in 30% yield. Macrocycle **14** was deprotected and isomerized to the bispyranose form by treatment with refluxing 80% acetic acid in water to provide macrocycle **2** in 92% yield. NMR spectra (^{1}H and ^{13}C) of **2** suggest an equal number of glucose molecules in the α and β configuration. Therefore, it is expected that **2** exists as a statistical mixture (1 to 2 to 1, respectively) of α,α'-**2**, α,β'-**2** (equivalent to β,α'-**2**) and β,β'-**2**.

Attempts were also made to prepare bis-p-xylyl-1,1',3,3'-linked macrocycle **15** (Scheme 3). During the course of its attempted preparation, it was necessary to treat hexaacetate **16** with HBr in acetic acid (a single equivalent of acetic anhydride was added to remove any water that might enter the reaction) in an attempt to prepare **17**. However, dibromide **17** was isolated in very low yields. Under these conditions the p-xylyl linking group was cleaved giving compounds **18** and **19**.

Work is now underway to characterize the association of macrocycles **1** and **2** with hydrophobic small molecules in water. Of particular interest is

the role(s) that the carbohydrates play in association. We are also working to further rigidify the glycophanes to obtain conformationally stable cavities made of sugar molecules.

Scheme 3. Attempted synthesis of glycophane **15**.

3. Experimental

3.1. SYNTHESIS

3.1.1. *General*

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 spectrometer and are referenced to $CHCl_3(^1H)$ or $CDCl_3(^{13}C)$. IR spectra were recorded on a Perkin Elmer 1600 FTIR instrument. Mass spectrometric data were obtained on a JOEL SX 102A spectrometer. Reagents and solvents were obtained commercially and were used as received.

3.1.2. *Hexyl-linked diacetone glucose dimer 5*

Diacetone glucose (5.00 g, 19.2 mmol) was dissolved in THF (50 ml). To the solution was added 1,6-dibromohexane (2.30 g, 9.6 mmol), 18-crown-6 (0.10 g), and powdered KOH (2.7 g, 48 mmol). The mixture was stirred at room temperature for 12 h and then refluxed for 2 h. Ether (50 ml) was added and the resulting mixture was washed with water (50 ml) and saturated aqueous NaCl (50 ml). The ether solution was dried over MgSO$_4$ and evaporated *in vacuo* to give a yellow oil. Chromatography (silica gel hexanes:ethyl acetate / 1:2) gave 4.80 g (8.0 mmol, 83% yield) of **5** as a

clear glass. ^{1}H NMR (200 MHz, CDCl$_3$) δ 5.86 (d, J = 3.7 Hz, 2 H), 4.52 (d, J = 3.7 Hz, 2 H), 4.32-4.24 (m, 2 H), 4.14-3.97 (m, 6 H), 3.84 (d, J = 2.1 Hz, 2 H), 3.62-3.50 (m, 4 H), 1.59-1.29 (m, 8 H), 1.49 (s, 6 H), 1.42 (s, 6 H), 1.35 (s, 6H), 1.32 (s, 6 H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 111.5, 108.7, 105.1, 82.4, 82.0, 81.1, 72.4, 70.4, 67.1, 29.6, 26.4, 26.67, 26.1, 25.8, 25.3; IR (neat) 2975, 1460, 1125, 1040, 820; HR-FAB-MS m/e obsd: 602.3288 (45%), calcd for C$_{30}$H$_{50}$O$_{12}$: 602.3302.

3.1.3. Hexyl-linked peracetyl glucose dimer 6

Glucose dimer 5 (4.60 g, 7.6 mmol) was dissolved in 80% aqueous acetic acid (50 ml), and the solution was refluxed for 4 hrs. The acetic acid and water were evaporated *in vacuo*, and the resulting oil was dissolved in pyridine (25 ml) and acetic anhydride (15 ml). The solution was stirred for 8 hrs, then the remaining acetic anhydride was hydrolyzed by addition of ice (~20 g). Ethyl acetate (50 ml) was added, and the mixture was washed with water (50 ml), 2.5 M HCl (2 x 50 ml), and saturated aqueous NaCl (50 ml). The organic solution was dried over MgSO$_4$ and evaporated *in vacuo* to give 3.90 g (5.0 mmol, 66% yield) of a clear oil. The oil consisted a mixture of anomers (α-α, β-β, α-β). The anomers were not separated, but the product was carried on directly to the next step. ^{1}H NMR (200 MHz, CDCl$_3$) δ 6.27 (d, J = 3.7 Hz, 1 H), 5.64 (d, J = 8.1 Hz, 1 H), 5.11-4.95 (m, 4 H), 4.26-3.98 (m, 6 H), 3.81-3.50 (m, 6 H), 2.18 (s, 6 H), 2.08 (s, 6 H), 2.06 (s, 6 H), 2.04 (s, 6 H), 1.52-1.20 (m, 8 H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 170.5, 169.4, 169.0, 168.8, 168.6, 91.7, 89.2, 80.0, 76.7, 72.7, 72.7, 72.2, 71.2, 71.0, 70.0, 68.9, 68.8, 61.6, 60.1, 29.9, 25.6, 25.5, 20.8, 20.5, 20.5, 20.4, 13.9. IR (neat) 2964, 1748, 1223, 1068, 1036 cm^{-1}; HR-FAB-MS m/e obsd: 801.2756 (17%), calcd for C$_{34}$H$_{50}$O$_{20}$Na ([M+Na]$^+$): 801.2793.

3.1.4. Hexyl-linked acetylbromoglucose dimer 7

Glucose dimer 6 (3.90 g, 5.0 mmol) was dissolved in a minimum amount of dichloromethane (~5 ml). The solution was cooled to 0° C, and HBr (30% in acetic acid, 10 ml) was added. The resulting solution was stirred at 0° C for 1 h, then carefully poured into saturated aqueous NaHCO$_3$ (200 ml). Ethyl acetate (100 ml) was added and the layers separated. The organic solution was washed with saturated aqueous NaHCO$_3$ (100 ml) and saturated aqueous NaCl (100 ml), then dried over MgSO$_4$ and evaporated *in vacuo* to give 4.00 g of a light yellow glass (4.9 mmol, 98% yield). ^{1}H NMR shows this to be exclusively the α-α anomer. ^{1}H NMR (200 MHz, CDCl$_3$) δ 6.61 (d, J = 3.9 Hz, 2 H), 5.12 (t, J = 9.6 Hz, 2 H), 4.71 (dd, J = 9.6, 3.9 Hz, 2 H), 4.30-4.06 (m, 6 H), 3.85 (t, J = 9.6 Hz, 2 H), 3.70-3.52 (m, 4 H), 2.14 (s, 6 H), 2.11 (s, 6 H), 2.10 (s, 6 H) 1.48-1.24 (m, 8 H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 170.4, 169.6, 169.0, 88.1, 77.3, 73.2, 72.6, 72.5, 68.2, 61.0, 30.4,

25.7, 20.6, 20.6. Due to the instability of the bisbromide, it was not characterized further, but was carried on directly to dithiol **8**.

3.1.5. Hexyl-linked acetylthioglucose dimer **8**

Dibromide **7** (4.00 g, 4.9 mmol) was dissolved in acetonitrile. Thiourea (1.85 g, 24.3 mmol) was added, and the mixture was refluxed for 2 h. The solvent was removed *in vacuo*. The resulting solid was partially dissolved in water (25 ml) and ether (25 ml). To the mixture was added K_2CO_3 (6.4 g, 48 mmol) and $NaHSO_3$ (3.7 g, 36 mmol). The mixture were stirred for 1.5 h and the phases were separated. The ether layer was washed with saturated aqueous NaCl (25 ml), dried over $MgSO_4$ and evaporated *in vacuo*. The aqueous phase was treated with 6 M HCl until a pH of ~ 7 was obtained and extracted with ether (2 x 50 ml). The combined extracts were washed with saturated aqueous NaCl (100 ml), dried over $MgSO_4$ and evaporated *in vacuo*. The concentrates from both extractions were combined and passed through a short silica column (hexanes:ethyl acetate / 1:1 eluent). The solvents were removed *in vacuo* giving 2.50 g of a clear oil (3.4 mmol, 69% yield). ^1H NMR (200 MHz, $CDCl_3$) δ 5.04 (t, J = 9.6 Hz, 2 H), 4.92 (t, J = 9.5 Hz, 2 H), 4.47 (t, J = 9.7 Hz, 2 H), 4.19-4.11 (m, 6 H), 3.65-3.43 (m, 6 H), 2.32 (d, J = 9.9 Hz, 2 H), 2.14 (s, 6 H), 2.10 (s, 6 H), 2.09 (s, 6 H), 1.48-1.24 (m, 8 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 169.5, 169.2, 81.4, 78.9, 76.5, 74.9, 72.4, 69.3, 62.3, 30.1, 25.8, 21.0, 20.8; IR (neat) 2968, 1739, 1219, 1052, 1038 cm^{-1}; HR-FAB-MS *m/e* obsd: 667.2312 (28%), calcd for $C_{30}H_{47}O_{16}S_2$ ([M+H]$^+$): 667.2309.

3.1.6. 1,3-Linked glucose macrocycle **9**

Dithiol **8** (2.40 g, 3.3 mmol) was dissolved in acetonitrile (600 ml). To the solution was added α,α'-dichloro-*p*-xylene (0.57 g, 3.3 mmol) and Cs_2CO_3 (3.3 g, 10 mmol). The solution was stirred for 16 h under N_2, then evaporated *in vacuo*. The resulting oily solid was partially dissolved in ethyl acetate (100 ml) and the mixture was washed with water (100 ml) and saturated aqueous NaCl (100 ml). The organic solution was dried over $MgSO_4$ and evaporated *in vacuo*. Chromatography (silica gel, 2% MeOH in CH_2Cl_2 eluent) provided 0.80 g (0.92 mmol, 28% yield) of a clear glass. ^1H NMR (200 MHz, $CDCl_3$) δ 7.23 (s, 4 H), 4.98 (t, J = 9.5 Hz, 2 H), 4.78 (t, J = 9.6 Hz, 2 H), 4.24-4.18 (m, 6 H), 4.14 (d, J = 9.6 Hz, 2 H), 3.92, 3.83 (ABq, J_{AB} = 13.1 Hz, 4 H), 3.60-3.37 (m, 6 H), 2.18 (s, 6 H), 2.03 (s, 6 H), 1.98 (s, 6 H), 1.48-1.33 (m, 4 H), 1.28-1.16 (m, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6, 169.2, 135.9, 129.3, 82.1, 81.6, 76.1, 72.4, 71.0, 69.7, 62.5, 33.0, 30.1, 25.8, 20.9, 20.8; IR (neat) 3010, 2968, 1739, 1728, 1218, 1052, 1040 cm^{-1}; HR-FAB-MS *m/e* obsd: 829.2768 (58%), calcd for $C_{38}H_{53}O_{16}NaS_2$ ([M+H]$^+$): 829.2776.

3.1.7. *Macrocycle* 1

Hexaacetate **9** (0.50 g, 0.60 mmol) was dissolved in methanol (2 mL). Basic anion-exchange resin (Amberlite® IR-400, ~0.5 g) was added and the mixture was stirred for 48 h. The ion-exchange resin was removed by chromatography on a short silica gel column (20% MeOH in CH_2Cl_2 as eluent). The solvent was removed *in vacuo* to give 0.33 g of a clear glass (96% yield). ^{1}H NMR (200 MHz, CD_3SOCD_3) δ 7.23 (s, 4 H), 4.98 (bs, 6 H), 3.95-3.20 (m, 12 H), 3.14-2.83 (m, 4 H), 2.79-2.71 (m, 6 H), 1.39-1.21 (m, 8 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.5, 129.3, 85.5, 82.0, 81.0, 71.9, 71.0, 70.2, 61.1, 32.0, 27.9, 25.3; IR (neat) 3120, 3009, 2970, 1065, 1030 cm^{-1}; HR-FAB-MS *m/e* obsd: 599.1949 (100%), calcd for $C_{26}H_{40}O_{10}S_2Na$ ([M+Na]$^+$): 599.1961.

3.1.8. *p-Xylyl-linked diacetone glucose dimer* **10**

Diacetone glucose (10.00 g, 38.4 mmol) was dissolved in THF (200 mL). KOH (7.8 g, 139 mmol), 18-crown-6 (1.2 g, 1.5 mmol), and α,α'-dichloro-*p*-xylene (3.40 g, 19.4 mmol) were added to the solution. The solution was stirred at room temperature for 48 h. The THF was evaporated *in vacuo* and the resulting yellow oil was dissolved in Et_2O (150 mL). The mixture was washed with saturated aqueous NaCl (2 x 150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a yellow oil. The oil was chromatographed on silica gel with ethyl acetate-hexanes (1:2) as eluent, and 13.40 g (99% yield) of **10** was obtained as a clear oil. ^{1}H NMR ($CDCl_3$, 200 MHz), δ 7.34 (s, 4H), 5.90 (d, $J = 3.5$ Hz, 2 H), 4.61 (m, 6 H), 4.35 (m, 2 H), 4.10 (m, 8 H), 1.49 (s, 6 H), 1.43 (s, 6 H), 1.38 (s, 6 H), 1.31 (s, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.3, 127.7, 111.7, 108.9, 105.3, 82.6, 81.6, 81.2, 72.4, 67.3, 60.2, 26.7, 26.1, 25.4, 14.1; IR (neat) 2985, 1514, 1454, 1372, 1216, 1078, 847, 736 cm^{-1}; HR-FAB-MS m/e obsd: 623.3074 (15.5%), calcd for $C_{32}H_{47}O_{12}$ ([M + H]$^+$): 623.3068.

3.1.9. *p-Xylyl-linked monoacetone glucose dimer* **11**

Disaccharide **10** (8.40 g, 13.5 mmol) was dissolved in 80% $AcOH/H_2O$. The solution was refluxed for 40 min. while progress of the reaction was monitored by TLC (5% $MeOH/CH_2Cl_2$). The solvent was evaporated *in vacuo* and the resulting yellow oil was dissolved in CH_2Cl_2 (150 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2 x 150 mL) and brine (1 x 150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a yellow oil. The oil was chromatographed (silica gel, 5% $MeOH/CH_2Cl_2$), and 4.27 g (58% yield) of the **11** was obtained as a clear oil. ^{1}H NMR ($CDCl_3$, 200 MHz), δ 7.35 (s, 4 H), 5.92 (d, $J = 3.7$ Hz, 2 H), 4.71, 4.52 (ABq, $J = 11.9$ Hz, 4 H), 4.62 (d, $J = 3.8$ Hz, 2 H), 4.08 (m, 4 H), 3.97 (bs, 2 H), 3.71, 3.61(ABq of ABX, $J_{AX} = 0.0$, $J_{BX} = 5.5$, $J_{AB} = 11.2$ Hz, 4 H),

3.11 (bs, 2 H), 3.02 (bs, 2 H), 1.47 (s, 6 H), 1.32 (s, 6 H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 137.5, 128.6, 112.1, 105.3, 82.2, 82.0, 80.1, 71.9, 69.3, 64.5, 26.8, 26.3; IR (neat) 3438, 2936, 1375, 1216, 1165, 1077, 857, 736 cm^{-1}; HR-FAB-MS m/e obsd: 543.2440 (100.0%), calcd for C$_{26}$H$_{39}$O$_{12}$ ([M + H]$^+$): 543.2442.

3.1.10. *p-Xylyl-linked monoacetone glucose dimer-6,6'-ditosylate*

Disaccharide **11** (23.40 g, 43.0 mmol) and pyridine (34.7 mL, 430 mmol) were dissolved in CH$_2$Cl$_2$ (200 mL). The solution was cooled to 0 °C. TsCl (18.9 g, 99.0 mmol) was added to the solution. The solution was kept at 0 °C for 24 h, then washed with 5% HCl (until the water layer was acidic) and with brine (150 mL), dried over MgSO$_4$ and evaporated *in vacuo* to give a yellow oil. The oil was chromatographed (silica gel, 3% MeOH/CH$_2$Cl$_2$) and 29.70 g (80% yield) of the desired disaccharide was obtained as a clear oil. ^{1}H NMR (CDCl$_3$, 200 MHz), δ 7.74 (d, *J* = 8.2 Hz, 4 H), 7.29 (d, *J* = 8.2 Hz, 4 H), 7.27 (s, 4 H), 5.83 (d, *J* = 3.7 Hz, 2 H), 4.62-4.54 (m, 6 H), 4.20-4.01 (m, 10 H), 2.79 (bd, 2 H), 2.39 (s, 6 H), 1.41 (s, 6 H), 1.27 (s, 6 H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 144.7, 136.8, 132.1, 129.6, 127.7, 111.6, 104.8, 81.7, 81.4, 79.0, 72.3, 71.6, 66.6, 26.5, 25.9, 21.3; IR (neat) 3506, 2987, 1598, 1357, 1176, 1077, 816, 668 cm^{-1}; HR-FAB-MS m/e obsd: 873.2430 (99.6%), calcd for C$_{40}$H$_{50}$O$_{16}$S$_2$Na ([M + Na]$^+$): 873.2438.

3.1.11. *p-Xylyl-linked monoacetone glucose dimer-5,5'-diacetyl-6,6'-ditosylate* **12**

p-Xylyl-linked monoacetone glucose dimer-6,6'-ditosylate (29.70 g, 34.9 mmol) and pyridine (31.0 mL, 384 mmol) were dissolved in CH$_2$Cl$_2$ (200 mL). Ac$_2$O (20.9 mL, 192 mmol) was added and the solution was stirred at room temperature for 24 h. Ice was added to the solution and stirring continued for another 15 min. The solution was washed with 5% HCl (until the water layer was acidic), then with saturated aqueous NaCl (150 mL) followed by saturated aqueous NaHCO$_3$ (150 mL) and finally with saturated aqueous NaCl again (50 mL). The solution was dried over MgSO$_4$ and evaporated *in vacuo* to give a light yellow oil (30.80 g, 95% yield) of **12** which was of sufficient purity for further use. ^{1}H NMR (CDCl$_3$, 200 MHz), δ 7.76 (d, *J* = 8.2 Hz, 4 H), 7.32 (d, *J* = 8.2 Hz, 4 H), 7.29 (s, 4 H), 5.82 (d, *J* = 3.7, 2 H), 4.75-4.50 (m, 6 H), 4.41-3.98 (m, 10 H), 2.43 (s, 6 H), 2.22 (s, 6 H), 1.48, (s, 6 H), 1.31 (s, 6 H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 169.4, 144.6, 136.6, 132.7, 129.7, 128.0, 112.1, 105.0, 81.5, 80.6, 76.6, 71.6, 68.4, 68.0, 26.7, 26.2, 21.5, 20.8; IR (neat) 2989, 1749, 1598, 1362, 1174, 676 cm^{-1}; HR-FAB-MS m/e obsd: 957.2662 (16.2%), calcd for C$_{44}$H$_{54}$O$_{18}$S$_2$Na ([M + Na]$^+$): 957.2649.

3.1.12. *p-Xylyl-linked monoacetone glucose dimer-5,5'-diacetyl-6,6'-dithioacetate* 13

Ditosylate **12** (41.9 g, 44.8 mmol) and potassium thioacetate (17.9 g, 156.7 mmol) were dissolved in acetone (350 mL). The solution was refluxed for 24 hours. The acetone was evaporated *in vacuo* and the brown-red slurry was partially dissolved in CH_2Cl_2 (200 mL). The mixture was washed with saturated aqueous NaCl (2 x 150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a brown-red oil. The oil was chromatographed (silica gel, EtOAc:hexanes / 1:2) and 19.28 g (58% yield) of the dithioacetate **13** was obtained as a light-yellow oil. ^1H NMR ($CDCl_3$, 200 MHz), δ 7.28 (s, 4 H), 5.89 (d, J = 3.7 Hz, 2 H), 5.35 (m, 2 H), 4.67-4.53 (m, 6 H), 4.42 (d, J = 12.2 Hz, 2 H), 4.27 (dd, J = 8.2, 3.2 Hz, 2 H), 3.83 (dd, J – 11.9, 1.5 Hz, 2 H), 3.04 (dd, J = 12.0, 3.6 Hz, 2 H), 2.33 (s, 6 H), 1.91 (s, 6 H), 1.51 (s, 6 H), 1.33 (s, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.1, 169.8, 137.5, 128.2, 112.4, 105.1, 82.1, 81.0, 79.7, 77.3, 72.2, 68.3, 30.9, 27.2, 26.6, 21.0; IR (neat) 1748, 1700, 1374, 1226, 1374, 1226, 1076 cm^{-1}; HR-FAB-MS m/e obsd: 743.2413 (32.1%), calcd for $C_{34}H_{47}O_{14}S_2$ ([M + H]$^+$): 743.2407.

3.1.13. *Macrocycle* 14

Dithioacetate **13** (9.70 g, 13.1 mmol) was dissolved in THF (50 mL). The solution was added dropwise to a suspension of $LiAlH_4$ (1.20 g, 32.6 mmol) in THF (100 mL). After the addition was completed, the solution was allowed to stir for 1 h. Small aliquots of 5% HCl were added to the cloudy-gray solution until a neutral pH was reached. The solution was extracted with Et_2O (2 x 150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give the dithiol as a clear oil (6.30 g, 73.2% yield) which was carried on without further purification. The dithiol (6.30 g, 9.6 mmol) was dissolved in MeCN (1.9 L), and Cs_2CO_3 (15.6 g, 47.8 mmol) and α,α'-dichloro-*p*-xylene (1.7 g, 9.6 mmol) were added. The solution was stirred at room temperature for 72 h. The MeCN was evaporated *in vacuo*, and CH_2Cl_2 (150 mL) was added to the resulting yellow powder. The mixture was washed with saturated aqueous NaCl (2 x 150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give a yellow powder. The powder was chromatographed (silica gel, EtOAc:CH_2Cl_2 / 1:7), and 2.13 g (30% yield) of **14** was obtained as a white powder, m.p. 125.1-127.0° C; ^1H NMR ($CDCl_3$, 200 MHz), δ 7.29 (s, 4 H), 7.13 (s, 4 H), 5.94 (d, J = 3.7 Hz, 2 H), 4.72, 4.50 (ABq, J = 11.7 Hz, 4 H), 4.65 (d, J = 3.7 Hz, 2 H), 4.14-4.00 (m, 4 H), 3.91-3.86 (m, 2 H), 3.66, 3.49 (ABq, J – 13.6 Hz, 4 H), 2.98 (dd, J = 14.3, 1.0 Hz, 2 H), 2.79 (d, J = 3.3 Hz, 2 H), 2.56 (dd, J = 14.2, 9.9 Hz, 2 H), 1.49 (s, 6 H), 1.34 (s, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.9, 137.2, 128.8, 127.3, 111.7, 105.0, 82.6, 82.1, 82.0, 71.9, 66.7, 38.4, 36.1, 26.7, 26.2, IR (neat) 2990, 1687, 1558, 1261, 1190, 1077, 1051 cm^{-1}; HR-FAB-MS m/e obsd: 699.2281 (100%), calcd for $C_{34}H_{44}O_{10}S_2Na$ ([M + Na]$^+$): 699.2274.

3.1.14. *Macrocycle* 2

Macrocycle **14** (620 mg, 0.80 mmol) was dissolved in 80% AcOH/H$_2$O (50 mL), and the solution was refluxed for 12 hours. The reaction mixture was evaporated *in vacuo* and the residual oil was immediately chromatographed (silica gel, 10% MeOH in CH$_2$Cl$_2$) to give 0.44 g of a clear glass (92% yield). NMR spectroscopy shows a 1:1 ratio of α and β anomers. ^{1}H NMR (CDCl$_3$, 200 MHz), δ 7.35 (s, 4 H), 7.21 (s, 4 H), 5.11 (d, J = 2.8 Hz, 2 H), 4.95 (d, J = 12.6 Hz, 2 H), 4.65-4.54 (m, 4 H), 4.44-4.34 (m, 6 H), 3.73-3.06 (m, 10 H), 2.74, 2.50 (ABq of ABX, J_{AB} = 12.5, J_{AX} = 0, J_{BX} = 8.6 Hz, 4 H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 138.6, 137.1, 129.1, 129.0, 128.7, 96.6, 92.4, 81.7, 75.0, 74.5, 72.5, 72.2, 69.5, 35.3, 32.5; IR (neat) 3240, 2993, 1187, 1078, 1051 cm^{-1}; HR-FAB MS m/e obsd: 619.1661 (55.7%), calcd for C$_{28}$H$_{36}$O$_{10}$S$_2$Na ([M + Na]$^+$): 619.1648.

3.2. SOLID-STATE STRUCTURE OF COMPOUND 9

3.2.1. *General*

Crystals were grown from vapor diffusion of hexanes into a solution of **9** in diethyl ether. Data were collected with a Siemens R3m/V diffractometer.

3.2.2. *Structure determination summary*

Crystal Data: crystal system: orthorhombic; space group: P2$_1$2$_1$2$_1$; unit cell dimensions: a=10.0820(10) Å, b=19.629(4) Å, c=22.375(4) Å; volume: 4428.1(10) Å^3; Z: 4.

Data Collection: radiation: MoKα; temp.: 295 K; 2Θ range 4.0-50.0°; scan type: 2Θ-Θ; reflections collected: 3594; independent reflections: 3566; observed reflections: 2116.

Solution and Refinement: system used: Siemens SHELXTL plus; solution: direct methods; refinement methods: full-matrix least-squares; number of parameters refined: 495; final R indices (obs. data): R=6.79%; R indices (all data): R=11.71%; goodness of fit: 2.44: data to parameter ratio: 4.3:1.

Atomic coordinates are available upon request from N. K. Dalley.

Acknowledgment

References

1. R. B. Bukownik and C. S. Wilcox: *J. Org. Chem.*, **53** (1988), 463-471.

2. For examples see: (a) P. Bakó, L. Fenichel, L. Tôke: *J. Incl. Phenom. Mol. Rec.* **16**, 17 (1993). (b) P. Bakó, L. Fenichel, L. Tôke: *Liebigs Ann. Chem.* 1161 (1990). (c) B. Walz and G. Schröder: *Liebigs Ann. Chem.* 426 (1985).

3. (a) J. Jiménez-Barbero, E. Junquera, M. Martín-Pastor, S. Sharma, C. Vincent, S. Penadés: *J. Am. Chem. Soc.* **117**, 11198 (1995). (b) J. M. Coterón, C. Vincent, C. Bosso, S. Penadés: *J. Am. Chem. Soc.* **115**, 10066 (1993).

4. For example see: (a) A. Kobata: *Acc. Chem. Res.* **26**, 319 (1993). (b) M. Fukuda (ed.): *Cell Surface Carbohydrates and Cell Development*, CRC Press, Boca Raton, Florida, 1992. (c) J. F. Kennedy and C. A. White: *Bioactive Carbohydrates*; John Wiley & Sons, New York, 1983.

5. For contrasting views on the roles that noncovalent interactions play in carbohydrate binding see. (a) R. U. Lemieux: *Acc. Chem. Res.* **29**, 373 (1996). (b) F. A. Quiocho: *Pure Appl. Chem.* **61**, 1293 (1989). (c) M. D. Percival and S. G. Withers: *Biochemistry* **31**, 498 (1992).

6. M. Bessodes, J. Shamasazar, K. Antonakis: *Synthesis* 560 (1988).

7. J. M. Cox and L. N. Owen: *J. Chem. Soc. (C)* 1121 (1967).