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Synthesis of C_2-symmetric carbohydrate-based macrocycles by introduction of methylene/*p*-xylene linkers

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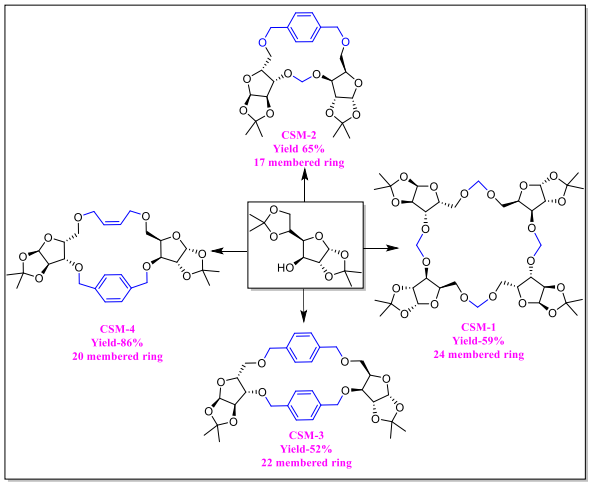
Abstract

Over the last few decades many carbohydrate embedded macrocycles have drawn the attention of synthetic organic chemists because of their interesting chemical and biological properties. Suitably placed chiral 3- and 5- hydroxyl groups of 1,2-*O*-(1-methylethylidene)-α-D-xylofuranose, derived from inexpensive D-glucose, have been judiciously exploited to generate different non-natural C_2-symmetric carbohydrate embedded macrocycles. Different symmetric aromatic and aliphatic hydrophobic spacers have been introduced between highly functionalized cluster of carbohydrate chiral centres through different intra- and intermolecular nucleophilic substitution and ring closing metathesis (RCM) for synthesis of 17 to 24 membered C_2-symmetric macrocycles.



Keywords: D-glucofuranose, macrocyclic compounds, ring closing metathesis, tether-linked 1, 2:5,6-O-isopropylidenefuranosides

Introduction

Macrocycles, a class of compounds containing at least one large ring of more than 12 atoms, have gradually evolved as an important class of compounds due to their high prevalence in natural products,[1,2] medicinally important molecules,[3-5] and their usefulness in the field of catalysis,[6-8] materials science,[9-11] and sensing applications.[12,13] Currently there are more than 100 natural and synthetic chiral macrocyclic drugs in the market and many of these are present in current blockbuster drug list.[3] Macrocycles, with relatively large flexible ring and distributed binding sites, were found to be efficient in interacting with the extended shallow and relatively featureless binding surfaces of complex protein-protein interactions (PPIs)[14-17] and consequently well suited to target conventionally 'undruggable'[18] disease classes.[4,19,20] Furthermore, the flexible cyclic structure of macrocycles was found to favourably impact their membrane permeability,[22] metabolic stability and overall pharmacokinetics.[21,22] In spite of these favourable essential drug like properties, macrocycles are under represented in current drug repertoire.[20] Relatively lesser abundance in natural resources (compared to the traditional small molecules), difficulty and expenses involved in synthesis/purification (natural or synthetic) of these flexible chiral rings in stereoisomerically pure form and spectroscopically determining their final structures with absolute stereochemistry, are among few major reasons behind such under-representation.[20] Judicious exploitation of inexpensive, naturally abundant carbohydrates as starting materials for their synthesis can conveniently overcome most of these challenges. Growing interest in macrocycles in the last few decades have resulted in many new synthetic methods,[22-28] though carbohydrate based synthetic endeavours remain rare. This observation inspired us to synthesize some non-natural macrocyclic structures containing embedded carbohydrates via a simple synthetic methodology. In our work, we have synthesised macrocyclic structures containing two carbohydrate units tethered by some groups so that they can easily conjugate with other important biological[4] molecules leading to biological relevant materials. The said macrocyles can easily be converted to nucleosides[25] by following a known protocol of nucleosidation. The C_2-symmetric molecules thus formed will be very good precursors for synthesising[20] novel chiral ligands in asymmetric catalysis.

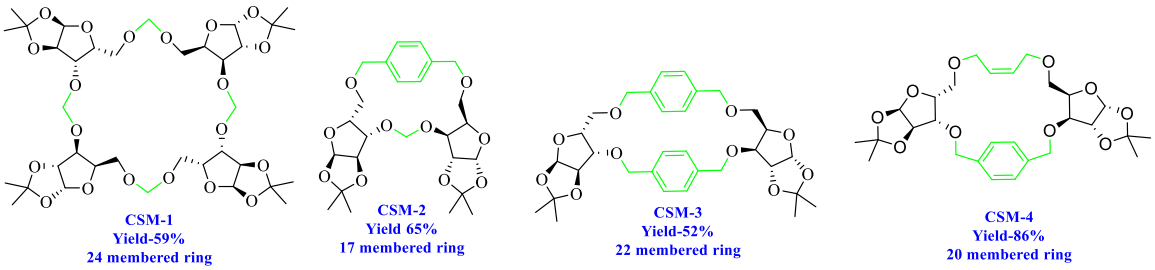


Figure 1. The 24, 17, 22 and 20-membered methylene/*p*-xylene fused 1,2-isopropylidenefuranose rings.

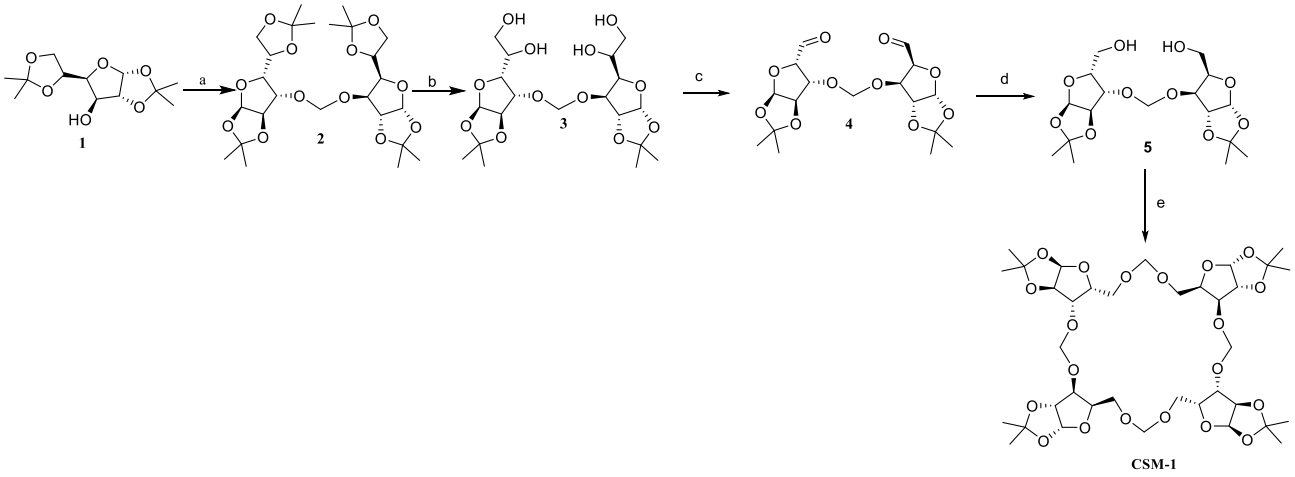
Herein we have presented synthesis of some symmetric macrocycles starting from inexpensive D-glucose. For synthesis of the C_2-symmetric macrocycles, we planned to use 3- and 5-hydroxyl groups of 1,2-*O*-(1-methylethylidene)-α-D-xylofuranose. However, to avoid the problem of competitive reactivity of the hydroxyl groups in such system we wanted to use easily preparable stable D-glucose derivative 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose with single free hydroxyl group as our starting material. We have targeted to exploit this free C-3 hydroxyl group to symmetrically bind to symmetric electrophilic spacer through easy nucleophilic substitution. Once the symmetrically protected dicarbohydrate system is generated, deprotection

of 5, 6-hydroxyl should generate corresponding di-ol in both side of the carbohydrate residue. The diols then can be cleaved and reduced to corresponding hydroxy compound. These hydroxy moiety can now easily be used for synthesis of various C_2-symmetric macrocycles applying various symmetric synthetic operation.

Here a simple synthetic methodology leading to some non-natural C_2-symmetric carbohydrate embedded macrocycles (**CSM-1**, **CSM-2**, **CSM-3** and **CSM-4**) has been reported. Symmetrical bis-3,3'-ether linked (methylene/p-xylene)[29] carbohydrate derivative on further etherification (methylene/*p*-xylene) leads to formation of carbohydrate appended macrocycles **CSM-2**, **CSM-3** and **CSM-4**. Macrocycle containing 20 membered ring (**CSM-4**) is synthesised by ring closing metathesis of corresponding 5-*O*-allylderivative of *p*-xylene tethered bis-symmetrical carbohydrate derivative. As in Thin Layer Chromatography (TLC), we haven't observed any intense spot besides the product, so further investigation regarding the formation of higher macrocycles was not done.

Results and Discussion

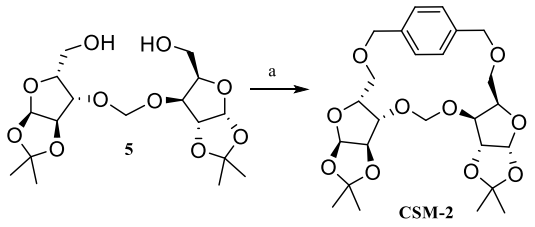
Keeping all these facts in mind we have started our synthesis with 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**1**), which can be easily synthesized in one step from D-glucose and acetone in presence of concentrated sulfuric acid as a catalyst. For the synthesis of our target molecule **CSM-1**, we first reacted 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**1**) with dichloromethane in presence of NaOH to form the compound **2** with an excellent yield of 95%. Successive 5, 6- deprotection, oxidation and finally reduction gave compound **5**.[30] A 24 membered C_2-symmetric macrocycle **CSM-1** (59%) was obtained from **5** following the same etherification technique (Scheme 1). The symmetric character of the product **CSM-1** was indicated by the presence of one set of peaks due to symmetry of the related protons and carbon atoms in the ^{1}H-NMR and ^{13}C-NMR spectra.



Reagent and conditions: a. 50% aq. NaOH, CH_2Cl_2, TBAB, 25 °C, 24 h, 95%. b.70% aq. AcOH, rt, 24 h, 93%. c. $NaIO_4$, MeOH-H_2O, 0-25 °C, 1 h. d. $NaBH_4$, MeOH, 0-25 °C, 6 h, 92%. e.50% aq. NaOH, CH_2Cl_2, TBAB, 25 °C, 72 h, 59%.

Scheme 1. Synthesis of C_2-symmetric 24 membered macrocycle **CSM-1**.

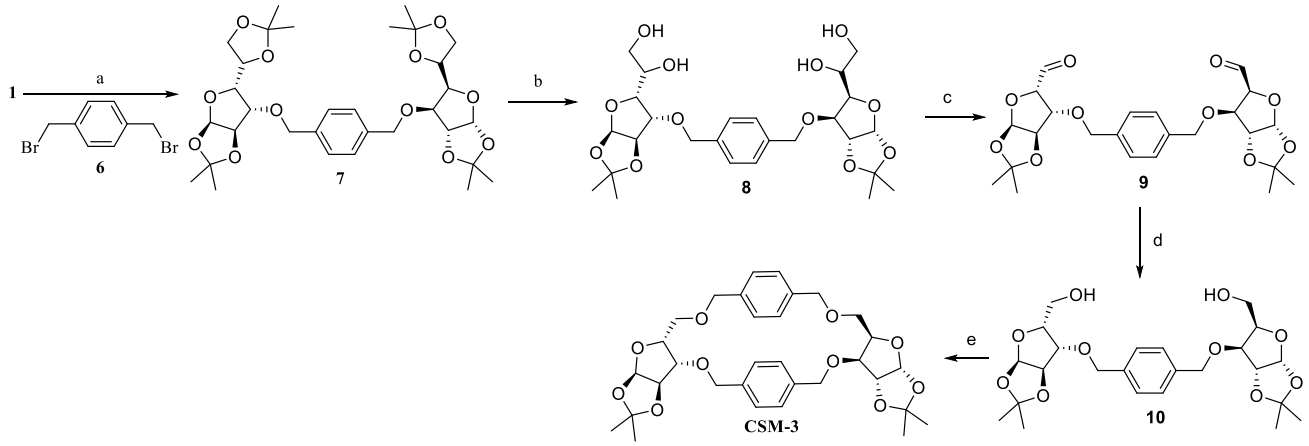
After the successful synthesis of the 24-membered macrocycle **CSM-1**, we have synthesized macrocycle **CSM-2** by simple reaction of 1,4-bis(bromomethyl)benzene (**6**)[31,32] with precursor **5** in presence of 50% aqueous NaOH and tetrabutylammonium bromide (TBAB) in dichloromethane with a yield of 65%. The insertion of the aromatic group in the compound **CSM-2** was confirmed by the appearance of 4H multiplet, δ value 7.45 – 7.35 ppm. Also, appearance of another singlet at 3.14 ppm for the CH_2 attached with the oxygen and the aromatic ring confirms the formation of the compound **CSM-2**. The HRMS (TOF-MS US, positive ion) of **CSM-2** showed a sodiated molecule peak at *m/z* 517.2051 $[M + Na]^+$ confirming its said structure.



Reagent and conditions: a. 50% aq. NaOH, CH_2Cl_2, TBAB, 1,4-bis(bromomethyl)benzene **(6)**, 25 °C, 10 h, 65%.

Scheme 2. Synthesis of C_2-symmetric 17 membered macrocycle **CSM-2**.

One *p*-xylene moiety was introduced between two diacetone-D-glucose moieties by reaction between 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) and 1,4-bis(bromomethyl)benzene (**6**) in basic medium in presence of tetrabutylammonium bromide (TBAB). Compound **8** was then subjected to a series of reaction (deprotection, oxidation, reduction) yielding the corresponding C_2-symmetric hydroxy intermediate (**10**).[33]

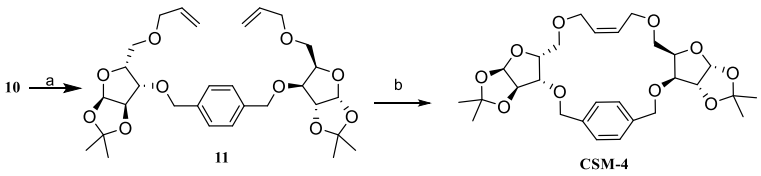


Reagent and conditions: a. 50% aq. NaOH, CH_2Cl_2, TBAB, 1,4-bis(bromomethyl)benzene (**6**), 25 °C, 16 h, 95%. b.70% aq. AcOH, rt, 12 h, 97%. c. $NaIO_4$, MeOH-H_2O, 0-25 °C, 2 h. d. $NaBH_4$, MeOH, 0-25 °C, 6 h, 83%. e. 50% aq. NaOH, CH_2Cl_2, TBAB, 1,4-bis(bromomethyl)benzene (**6**), 25 °C, 16 h, 52%.

Scheme 3. Synthesis of C_2-symmetric 22 membered macrocycle **CSM-3**.

Final ring closing was done by introducing the second *p*-xylene moiety by treatment of **10** with **6** under basic medium in presence of tetrabutylammonium bromide (TBAB). So, the attempted synthesis of 22

membered C_2-symmetric macrocycle **CSM-3** became successful. The formation of compound **CSM-3** was confirmed by the appearance of two singlet peaks for eight aromatic hydrogens at δ value 7.32 ppm and 7.05 ppm in the aromatic region of the ^{1}H-NMR spectrum which is further supported by the appearance of corresponding peak of aromatic carbon atoms in the ^{13}C-NMR in the range of 127-137 ppm. The symmetrical nature of the compound **CSM-3** was evident from a single set of protons and carbon atom in the ^{1}H-NMR and ^{13}C-NMR spectra. Further the formation of compound **CSM-3** confirmed by mass spectra analysis for which we got the *m/z* $[M + Na]^+$ value 607.2515 that exactly matches with the calculated molecular mass.



Reagent and conditions: a. 50% aq. NaOH, CH_2Cl_2, TBAB, allyl bromide, 25 °C, 10 h, 88%. b. Grubbs 2nd generation catalyst, dry DCM, 30 °C, 8 h, 86%.

Scheme 4. Synthesis of C_2-symmetric 20 membered macrocycle **CSM-4.**

In a similar manner the free hydroxyl groups of **10** was first allylated using allyl bromide to obtain the corresponding allylated compound **11** which on olefin-metathesis reaction[34-36] using Grubbs 2nd generation[37] catalyst finally affords novel C_2-symmetric 20 membered macrocycle (**CSM-4**). The formation of compound **11** was confirmed by appearance of characteristics allylic proton signals at δ value 5.94 ppm in ^{1}H-NMR. The formation of compound **CSM-4** is confirmed from *m/z* value of 557.2374 in mass spectrum that exactly matches with the calculated molecular mass of the compound.

Conclusions

Four different C_2-symmetric macrocycles with varied ring size (17 to 24 membered) have been synthesized from inexpensive easily available stable carbohydrate derived precusor 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. The symmetric nature of final macrocycles were established by nuclear magnetic spectra that show one set of protons and carbons. Our future goal is to convert these sugar appended C_2-symmetric macrocycles into nucleosides and other biomolecular conjugates which are very important from biological point of view. These macrocycles contain many protected hydroxyl groups which on deprotection will increase their aqueous solubility and in consequence their bioavailability. This simple but potentially useful methodology for synthesis of carbohydrate based C_2-symmetric macrocycles will provide a tool to the synthetic organic chemist for synthesizing many aforesaid important molecules.

Experimental Section

General. Unless otherwise mentioned NMR spectra were recorded on BRUKER AVANCE III 400 (400 MHz for ^{1}H; 100 MHz for ^{13}C) spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) multiplicity

(s=singlet, d=doublet, t=triplet, q=quartet, p=pentet and m=multiplet), coupling constant (*J* values) in Hz relative to $CDCl_3$ (7.28 ppm for ^1H and 77.00 ppm for ^{13}C central peak). The HRMS (HRMS Model Name: Waters - Xevo G2- XS - QToF) spectra were recorded in TOF-MS (US+). Reactions were monitored by thin-layer chromatography using E. Merck Silica Gel 60 F_{254} percolated plates. Organic extracts were dried over anhydrous sodium sulfate. Unless otherwise mentioned, 60-120 mesh silica gel was used for column chromatography. Solvents were distilled and dried prior to use. Petroleum ether refers to a fraction boiling between 60-80 °C.

General procedure for the above compounds is illustrated by the preparation of CSM-1. A mixture of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) (5.0 g, 19.2 mmol), CH_2Cl_2 (20 mL), 50% aq. NaOH (20 mL) and tetrabutylammonium bromide (0.62 g, 1.9 mmol) was stirred vigorously at 25 °C for 24 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried and evaporated to give an oil, which was chromatographed using 1:10 EtOAc–petroleum ether as eluent to give **bis{[(3*aR*,5*R*,6*S*,6*aR*)-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl]oxy}methane (-)-2** (4.86 g, 95%) as a white solid. $[\alpha]_D^{25}$ = -22 (c 0.98, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, J 3.8 Hz, 1H), 4.86 (s, 1H), 4.56 (d, J 3.8 Hz, 1H), 4.38 – 4.28 (m, 2H), 4.16 (dd, J 7.4, 3.1 Hz, 1H), 4.10 (dd, J 8.6, 6.2 Hz, 1H), 4.01 (dd, J 8.6, 5.7 Hz, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.90 (q), 105.23 (CH, anomeric), 92.98 (CH_2), 83.06 (CH), 81.05 (CH), 78.86 (CH), 73.96 (CH), 72.53 (CH), 67.16 (CH_2), 26.80 (CH_3), 26.73 (CH_3), 26.19 (CH_3), 25.34 (CH_3). FABMS: *m/z* 555.24 $[M+Na]^+$; Anal. Calcd for $C_{25}H_{40}O_{12}$: C, 56.38; H, 7.57. Found: C, 56.42; H, 7.29

A solution of **2** (4.0 g, 8.84 mmol) in aq. AcOH (75% v/v, 40 mL) was stirred for 24 h at 25 °C. The mixture was then concentrated, and the residue was repeatedly coevaporated with toluene (3×20 mL) yielding **(1*R*,1'*R*)-1,1'-[(3*aR*,3*a'R*,5*R*,5'*R*,6*S*,6*aR*,6'*S*,6*a'R*)-[methylenebis(oxy)]bis(2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]-dioxole-6,5-diyl)]bis(ethane-1,2-diol) (-)-3** (3.16 g, 93%) as a colourless sticky liquid. $[\alpha]_D^{25}$ = -106.1 (c 1.23, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (d, *J* 3.8 Hz, 1H), 4.91 (s, 1H), 4.78 (s, 1H), 4.53 (d, J 3.9 Hz, 1H), 4.36 (d, J 3.2 Hz, 1H), 4.11 (dd, J 9.2, 2.9 Hz, 1H), 4.06 – 3.94 (m, 1H), 3.84 (dd, J 11.7, 2.8 Hz, 1H), 3.68 (dd, J 11.7, 5.7 Hz, 1H), 3.09 (s, 2H), 1.51 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.03 (q), 104.98 (CH, anomeric), 92.02 (CH_2), 82.23 (CH), 79.64 (CH), 78.86 (CH_2), 68.16 (CH), 64.13 (CH_2), 26.55 (CH_3), 26.14 (CH_3). FABMS: *m/z* 475.18 $[M+Na]^+$, 453.26 $[M+H]^+$; Anal. Calcd for $C_{19}H_{32}O_{12}$: C, 50.44; H, 7.13. Found: C, 50.42; H, 7.14

To a solution of this $[\alpha]_D^{25}$ material **3** (3.25 g, 7.17 mmol) in MeOH (30 mL) was added dropwise with stirring a solution of $NaIO_4$ (5.18 g, 24.24 mmol) in water (20 mL) at 0 °C. Stirring was continued at 25 °C for 1 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 and dried and removal of the solvent afforded a syrupy material **4** that was dissolved in methanol (40 mL) and cooled to 0 °C. To this solution $NaBH_4$ (0.66 g, 17.41 mmol) was added in portions with stirring and the mixture was further stirred for 6 h at 25 °C. The mixture was then acidified with AcOH–H_2O (15 mL), removal of methanol and extracted with CH_2Cl_2. Removal of the solvent afforded **5** as a viscous liquid. The residue was chromatographed (EtOAc-petroleum ether, 2:8) to give **[(3*aR*,3*a'R*,5*R*,5'*R*,6*S*,6*aR*,6'*S*,6*a'R*)-[methylenebis(oxy)]bis(2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole-6,5-diyl)]dimethanol (-)-5** (2.89 g, 92%) as sticky colourless liquid. $[\alpha]_D^{25}$ = -110.3 (c 0.60, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (d, J 3.8 Hz, 1H), 5.32 (s, 2H), 4.85 (s, 1H), 4.56 (d, J 3.8 Hz, 1H), 4.32 (dt, J 11.9, 3.1 Hz, 2H), 3.98 – 3.82 (m, 2H), 1.52 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.05 (q), 104.78 (CH, anomeric), 91.50 (CH_2), 82.52 (CH), 80.14 (CH), 78.48 (CH), 59.08 (CH_2), 26.69 (CH_3), 26.24 (CH_3). FTIR (neat, cm^{-1}) 3443, 2941, 2840, 1245. ; FABMS: *m/z* 415.16 $[M+Na]^+$; Anal. Calcd for $C_{17}H_{28}O_{10}$: C, 52.03; H, 7.19. Found: C, 52.09; H, 7.22.

CSM-1 was synthesised from the alcohol **5** following the procedure described in the conversion of **1** to **2**. **(3*aR*,3*bS*,6*aS*,6*bR*,9*aR*,10*aR*,15*aR*,16*aR*,19*aR*,19*bS*,22*aS*,22*bR*,25*aR*,26*aR*,31*aR*,32*aR*)-2,2,8,8,18,18,24,24-octamethylhexadecahydro-11*H*,15*H*,27*H*,31*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-*d*][1,3]dioxolo[4',5':4,5]furo [2,3-*k*][1,3]dioxolo[4',5':4,5]furo[3,2-*p*][1,3]dioxolo[4',5':4,5]furo[2,3-*w*][1,3,7,9,13,15,19,21] octaoxacyclotetracosine (-)-CSM-1** (3.47 g, 59%) yellow solid. 13.03 (c 0.31, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (dd, J 7.8, 3.7 Hz, 1H, anomeric), 4.81 – 4.71 (m, 2H), 4.52 (dd, J 22.6, 3.8 Hz, 1H), 4.39 (dt, J 7.0, 3.8 Hz, 1H), 4.18 (dd, J 11.6, 3.3 Hz, 1H), 3.87 – 3.67 (m, 2H), 1.50 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.93 (q), 111.89 (q), 105.05 (CH, anomeric), 104.92 (CH, anomeric), 96.18 (CH_2), 90.51 (CH_2), 82.93 (CH), 82.74 (CH), 82.37 (CH), 79.33 (CH), 78.89 (CH), 78.66 (CH), 78.39 (CH), 66.14 (CH), 65.28 (CH_2), 60.43 (CH_2), 26.79 (CH_3), 26.25 (CH_3). FTIR (neat, cm^{-1}) 2939, 1375, 1216, 1165, 1015. Anal. Calcd for $C_{36}H_{56}O_{20}$: C, 53.46; H, 6.98. Found: C, 53.47; H, 6.99.

Procedure for the synthesis of CSM-2

CSM-2 was synthesised from a mixture of **5** (0.160 g, 4.08 mmol) and 1,4-bis(bromomethyl)benzene **6** (0.106 g, 4.09 mmol) following the procedure described in the conversion of **1** to **2**. **($1^{3a}R$,1^5R,1^6S,$1^{6a}R$,$5^{3a}R$,5^5R,5^6S,$5^{6a}R$)-1^2,1^2,5^2,5^2-tetramethyl-1^{3a},1^5,1^6,1^{6a},5^{3a},5^5,5^6,5^{6a}-octahydro-2,4,7,11-tetraoxa-1,5(6,5)-difuro[2,3-*d*][1,3]dioxola-9(1,4)-benzenacyclododecaphane (-)-CSM-2** (0.136 g, 65%) white solid. $[\alpha]_D^{25}$ = -177.28 (c 0.30, $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.35 (m, 2H), 5.79 (d, J 3.4 Hz, 1H, anomeric), 4.78 (d, J 12.1 Hz, 1H), 4.42 (d, J 3.7 Hz, 1H), 4.20 (dt, J 9.8, 3.1 Hz, 1H), 4.14 (d, J 12.0 Hz, 1H), 3.78 (d, J 2.4 Hz, 1H), 3.60 (dd, J 8.0, 3.4 Hz, 1H), 3.53 (dd, J 9.9, 8.1 Hz, 1H), 3.14 (s, 1H), 1.49 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 137.40 (q), 131.20 (CH, aromatic), 130.37 (CH, aromatic), 111.95 (q), 104.35 (CH, anomeric), 96.74 (CH_2), 84.42 (CH), 81.56 (CH), 78.44 (CH), 72.98 (CH_2), 62.85 (CH_2), 26.80 (CH_3), 26.43 (CH_3). FTIR (neat, cm^{-1}) 2958, 2865, 1356, 1270, 1123. TOF-MS (US+) *m/z*: $[M+Na]^+$ Calculated for $C_{25}H_{34}O_{10}Na$-517.2050; Found-517.2051. Anal. Calcd for $C_{25}H_{34}O_{10}$: C, 60.70; H, 6.93. Found: C, 60.70.47; H, 6.91.

Method for the Synthesis of CSM-3. The C_2-symmetric sugar molceule bearing aromatic spacer **7** was synthesised maintaining the same protocol used in conversion of **5** to **CSM-2. 1,4-bis({[(3*aR*,5*R*,6*S*,6*aR*)-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl]oxy}methyl)benzene (-)-7** (4.21 g, 95%) colourless sticky liquid.

$[\alpha]_D^{25}$ = -59.27 (c 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 5.92 (t, J 6.7 Hz, 1H), 4.66 (q, J 11.8 Hz, 2H), 4.60 (d, J 3.8 Hz, 1H), 4.35 (tt, J 18.5, 4.5 Hz, 1H), 4.21 – 4.07 (m, 2H), 4.05 – 3.95 (m, 2H), 1.51 (d, J 5.7 Hz, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.52 (q, aromatic), 127.74 (CH, aromatic), 111.82 (q), 109.00 (q), 105.31 (CH, anomeric), 82.72 (CH), 81.78 (CH), 72.54 (CH), 72.14 (CH_2), 67.44 (CH_2), 26.85 (CH_3), 26.79 (CH_3), 26.26 (CH_3), 25.47 (CH_3). FABMS: *m/z* 645.29 $[M+Na]^+$; Anal. Calcd for $C_{32}H_{46}O_{12}$: C, 61.72; H, 7.45. Found: C, 61.73; H, 7.49

Usual deprotcetion of **7** by acetic acid yielded **(1*R*,1'*R*)-1,1'-[(3*aR*,3*a'R*,5*R*,5'*R*,6*S*,6*aR*,6'*S*,6*a'R*)-{[1,4-phenylenebis(methylene)]bis(oxy)}bis(2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole-6,5-diyl)]bis(ethane-1,2-diol) (+)-8** (4.1 g, 97%) as a colourless sticky liquid. $[\alpha]_D^{25}$ = +85.96 (c 0.46, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 2H), 5.91 (d, J 3.8 Hz, 1H), 4.71 (d, J 11.7 Hz, 1H), 4.61 (d, J 3.9 Hz, 1H), 4.54 (d, J 12.0 Hz, 1H), 4.09 (d, J 6.6 Hz, 2H), 3.99 (d, J 7.3 Hz, 1H), 3.80 (s, 3H), 3.65 (s, 1H), 2.07 – 1.99 (m, 1H), 1.48 (s, 3H), 1.32 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 137.29 (q, aromatic), 128.25 (CH, aromatic), 111.85 (q), 105.12 (CH, anomeric), 82.11 (CH), 81.88 (CH), 79.95 (CH), 71.83 (CH_2), 69.08 (CH), 64.37 (CH_2), 26.68 (CH_3), 26.20 (CH_3). FABMS: *m/z* 565.22 $[M+Na]^+$; Anal. Calcd for $C_{26}H_{38}O_{12}$: C, 57.56; H, 7.06. Found: C, 57.59; H, 7.11.

Alcohol **10** was synthesised from **8** (4 g, 7.38 mmol) following a series of reaction i.e oxidation and subsequent reduction. **[(3*aR*,3*a'R*,5*R*,5'*R*,6*S*,6*aR*,6'*S*,6*a'R*)-{[1,4-phenylenebis(methylene)] bis(oxy)}bis(2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole-6,5-diyl)]dimethanol (-)-10** (2.45 g, 83%) colourless sticky liquid. $[\alpha]_D^{25}$ = -76.59 (c 0.35, $CHCl_3$). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.32 (s, 2H, aromatic), 5.99 (d, J 3.8 Hz, 1H), 4.71 (d, J 12.0 Hz, 1H), 4.65 (d, J 3.9 Hz, 1H), 4.50 (d, J 11.9 Hz, 1H), 4.29 (q, J 4.9 Hz, 1H), 4.01 (d, J 3.5 Hz, 1H), 3.94 (dd, J 12.0, 5.4 Hz, 1H), 3.85 (dd, J 11.9, 4.9 Hz, 1H), 1.49 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.12 (q, aromatic), 128.00 (CH, aromatic), 111.82 (q), 105.05 (CH, anomeric), 82.74 (CH), 82.42 (CH), 80.17 (CH), 71.55 (CH), 60.85 (CH_2), 60.43 (CH_2), 26.79 (CH_3), 26.32 (CH_3). FTIR (neat, cm^{-1}) 3445, 2945, 2873, 1420, 1220, 1005. FABMS: *m/z* 505.20 $[M+Na]^+$; Anal. Calcd for $C_{24}H_{34}O_{10}$: C, 59.74; H, 7.10. Found: C, 59.71; H, 7.08.

Insertion of second aromatic spacer in alcohol **10** (1.99 g, 4.1 mmol), finally yielded ($1^{3a}R$,1^5R,1^6S,$1^{6a}R$,$7^{3a}R$,7^5R,7^6S,$7^{6a}R$)-1^2,1^2,7^2,7^2-tetramethyl-1^{3a},1^5,1^6,1^{6a},7^{3a},7^5,7^6,7^{6a}-octahydro-2,6,9,13-tetraoxa-1,7(6,5)-difuro[2,3-*d*][1,3]dioxola-4,11(1,4)-dibenzenacyclotetradecaphane (-)-**CSM-3** (1.23 g, 52%) as a colourless sticky liquid. $[\alpha]_D^{25}$ = -56.45 (c 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 2H, aromatic), 7.08 (s, 2H, aromatic), 5.95 (d, J 3.8 Hz, 1H), 5.31 (s, 1H), 4.81 – 4.63 (m, 3H), 4.46 – 4.30 (m, 3H), 3.90 (d, J 3.4 Hz, 1H), 3.70 – 3.56 (m, 2H), 1.51 (s, 3H), 1.35 (s, 3H).^{13}C NMR (100 MHz, Chloroform-*d*) δ 137.19 (q), 136.85 (q), 128.65 (CH, aromatic), 127.76 (CH, aromatic), 111.74 (q), 105.08 (CH, anomeric), 82.02 (CH), 80.57 (CH), 78.77 (CH), 73.49 (CH_2), 70.82 (CH_2), 66.41 (CH_2), 26.81 (CH_3), 26.38 (CH_3). FTIR (neat, cm^{-1}) 2926, 2885, 1717, 1456, 1373, 1214, 1163, 1072. TOF-MS (US+) *m/z*: $[M+Na]^+$ Calculated for $C_{32}H_{40}O_{10}Na$-607.2519; Found-607.2515. Anal. Calcd for $C_{32}H_{40}O_{10}$: C, 65.74; H, 6.90. Found: C, 65.75; H, 6.89.

Method for the Synthesis of CSM-4

11 was synthesised from alcohol **10** (0.170 g, 0.3 mmol) by simple allylation using allyl bromide (70 µl). **1,4-bis({[(3*aR*,5*R*,6*S*,6*aR*)-5-[(allyloxy)methyl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl]oxy}methyl) benzene (-)-11** (0.150 g, 88%) as a colourless sticky liquid. $[\alpha]_D^{25}$ = -31.72 (c 0.68, $CHCl_3$). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.32 (s, 2H, aromatic), 5.93 (dq, J 22.6, 5.5 Hz, 2H), 5.30 (dd, J 17.0, 1.9 Hz, 1H), 5.21 (d, J 10.2 Hz, 1H), 4.69 (d, J 12.0 Hz, 1H), 4.63 (d, J 3.9 Hz, 1H), 4.54 (d, J 11.9 Hz, 1H), 4.40 (td, J 6.0, 3.1 Hz, 1H), 4.09 (dd, J 13.0, 5.7 Hz, 1H), 4.01 (dd, J 18.1, 4.6 Hz, 2H), 3.73 (dd, J 6.3, 2.2 Hz, 2H), 1.51 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.28 (q, aromatic), 134.54 (CH, allylic), 127.73 (CH, aromatic), 117.29 (CH_2), 111.73 (q), 105.07 (CH, anomeric), 82.33 (CH), 81.75 (CH), 79.15 (CH), 72.46 (CH_2), 71.69 (CH_2), 67.46 (CH_2), 26.80 (CH_3), 26.33 (CH_3). FTIR (neat, cm^{-1}) 2956, 2875, 1456, 1112. FABMS: *m/z* 585.27 $[M+Na]^+$; Anal. Calcd for $C_{30}H_{42}O_{10}$: C, 64.04; H, 7.52. Found: C, 64.09; H, 7.54.

To a solution of **11** (0.1 g, 0.17 mmol) in degassed CH_2Cl_2 (15 ml), Grubbs 2nd generation catalyst (8 mg, 10 mmol %) was added and the mixture was stirred at room temperature for 8 h in an inert atmosphere. After completion of reaction, the solvent was evaporated and the residue was chromatographed using 2:8 EtOAc–petroleum ether as eluent to yield **($1^{3a}R$,1^5R,1^6S,$1^{6a}R$,$7^{3a}R$,7^5R,7^6S,$7^{6a}R$,*Z*)-1^2,1^2,7^2,7^2-tetramethyl-1^{3a},1^5,1^6,1^{6a},7^{3a},7^5,7^6,7^{6a}-octahydro-2,6,9,14-tetraoxa-1,7(6,5)-difuro[2,3-*d*][1,3]dioxola-4(1,4)-benzenacyclopentadecaphan-11-ene (-)-CSM-4** (0.079 g, 86%) as a colourless sticky liquid. $[\alpha]_D^{25}$ = -60.79 (c 0.26, $CHCl_3$). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.36 (s, 2H, aromatic), 5.95 (d, J 3.9 Hz, 1H, anomeric), 5.81–5.76 (m, 1H), 4.87 (d, J 13.1 Hz, 1H), 4.70 (d, J 3.9 Hz, 1H), 4.49 (d, J 13.1 Hz, 1H), 4.34 (dt, J 8.5, 3.9 Hz, 1H), 4.12 (dd, J 11.8, 2.2 Hz, 1H), 4.00 (d, J 3.3 Hz, 1H), 3.94–3.88 (m, 1H), 3.85 (t, J 8.8 Hz, 1H), 3.60 (dd, J 8.7, 4.6 Hz, 1H), 1.49 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.83 (q), 129.42 (CH, double bond), 127.57 (CH, aromatic), 111.71 (q), 104.82 (CH, anomeric), 81.92 (CH), 79.65 (CH), 78.35 (CH), 71.74 (CH_2), 70.20 (CH_2), 66.35 (CH_2), 26.77 (CH_3), 26.33 (CH_3). FTIR (neat, cm^{-1}) 2954, 2846, 1214, 1074. TOF-MS (US+) d_6: $[M+Na]^+$

Calculated for $C_{28}H_{38}O_{10}Na$-557.2363; Found-557.2374. Anal. Calcd for $C_{28}H_{38}O_{10}$: C, 62.91; H, 7.16. Found: C, 62.92; H, 7.16.

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Supplementary Material

All the characterization by ^{1}H NMR, ^{13}C NMR and HRMS spectra of newly synthesized compounds have been shown in supporting information (SI).

Notes

The authors declare no competing financial interest.

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