De novo synthesis and lectin binding studies of unsaturated carba-pyranoses†

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Starting from branched *para*-benzoquinones a practical and highly flexible route is described for the preparation of unsaturated carbapyranoses. The potential of the synthesized galactose analogues to act as competitive inhibitors in lectin-carbohydrate interactions is investigated by means of Surface Plasmon Resonance (SPR) Spectroscopy.

Introduction

A primary event in many biological processes involved in cell–cell recognition/adhesion is the specific attachment of proteins to glycolipids or glycoproteins which are located in cell membranes.[1] Lectins, a class of sugar binding proteins, show specificity to terminal and/or subterminal carbohydrate residues and have at least two sugar combining sites. Highly biological active lectins are for example the lectins of European Mistletoe (ML I, ML II, ML III) recognizing specifically galactosyl/*N*-acetylgalactosamine residues.[2] The mistletoe lectins are the main active principles in preparations like Iscador®, Plenosol® or Iscusin® which are therapeutically widely used in adjuvant cancer therapy.

Up to now the specific recognition of saccharides by lectins has been the subject of many studies[3] and it has been found that even simple monosaccharides are selectively bound. However the possible recognition of carbasugars and other carbohydrate analogues by lectins has not been investigated so far.

Carbasugars[4] in general are characterized by the replacement of the ring oxygen atom of a furanoid or pyranoid sugar by a methylene group.[5] In an interesting manner, these molecules are often recognized by sugar processing enzymes *e.g.* glycosidases and glycotransferases instead of the original monosaccharide and exhibit a large variety of biological activities, for example, antibiotic, antiviral or plant growing inhibiting properties.[6] Not only saturated carbasugars have been isolated from natural sources, but also unsaturated ones bearing a ring double bond. Typical examples of unsaturated naturally occuring carbasugars are streptol,[7] valienamine,[8] validamine,[9] cyclophellitol,[10] (+)-MK7607[11] or the families of gabosines,[12] pericosines[13] and piperinols.[14] (+)-MK7607 shows effective herbicidal activity and is the 4-epimer of streptol, a plant-growth inhibitor. But these are just two of eight possible diastereoisomers within the class of the unsaturated carba-pyranoses with an exocyclic hydroxymethyl moiety (see Fig. 1). In connection with our general interest in carbohydrate mimics we wanted to prepare the whole series of unsaturated carba-pyranoses and also some representative 6-desoxy derivatives, a class of compounds which have not been isolated from natural sources so far.

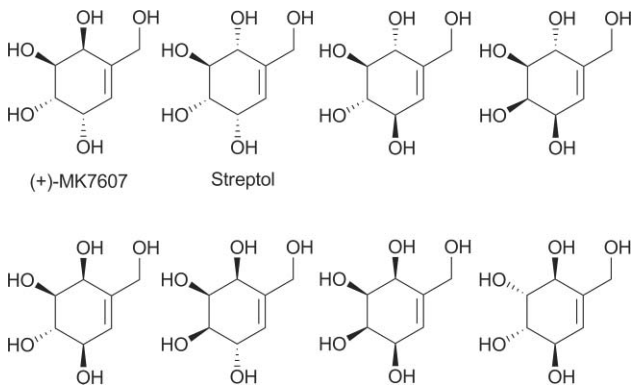

Fig. 1 Possible diastereoisomers of unsaturated carbasugars bearing a hydroxymethyl side chain (only one enantiomer is shown).

Results and discussion

Preparation of unsaturated carbapyranoses

In analogy to the synthetic route towards conduritols, inositols and derivatives thereof which was developed in our laboratory,[15] we considered the possibility of preparing unsaturated carbapyranoses starting from substituted *para*-benzoquinones. After finding that bromination of monosubstituted *para*-benzoquinones takes place regioselectively at the unsubstituted double bond and the reduction with sodium borohydride gives mainly the all-*trans* diastereomer the branched intermediates **3** and **6** can be stereoselectively synthesized in high yields (see Scheme 1). The reaction of **3** and **6** with silver acetate in dry acetic acid (Prévost conditions[16]) provides pentaacetate **7** and tetraacetate **8** which both possess the all-*trans* configuration. Deacetylation is achieved by reacting the acetates with sodium methanolate to deliver the corresponding alcohols **9** and **10** respectively.

Pentaacetate **11** and tetraacetate **12** with the *cis*,*trans*,*cis* configuration can be prepared from the intermediates **3** and **6** by conversion with silver acetate in 90% aqueous acetic acid (Woodward conditions[17]) followed by acetylation of the

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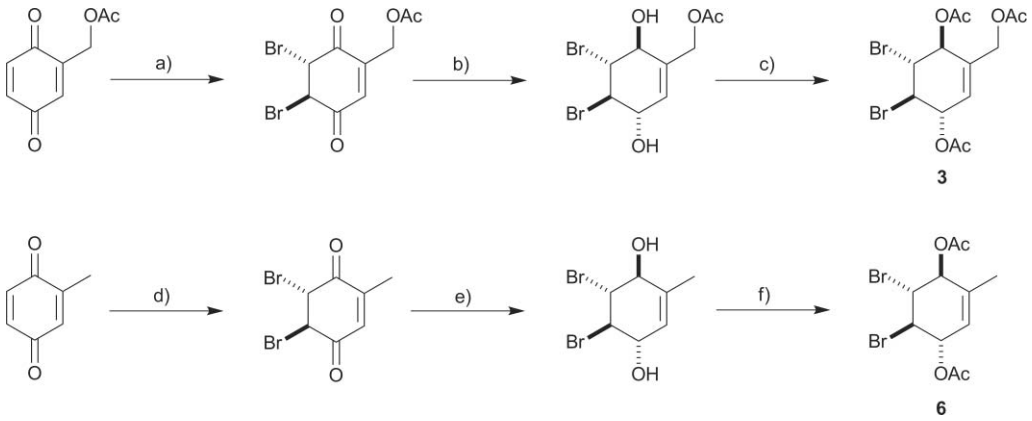
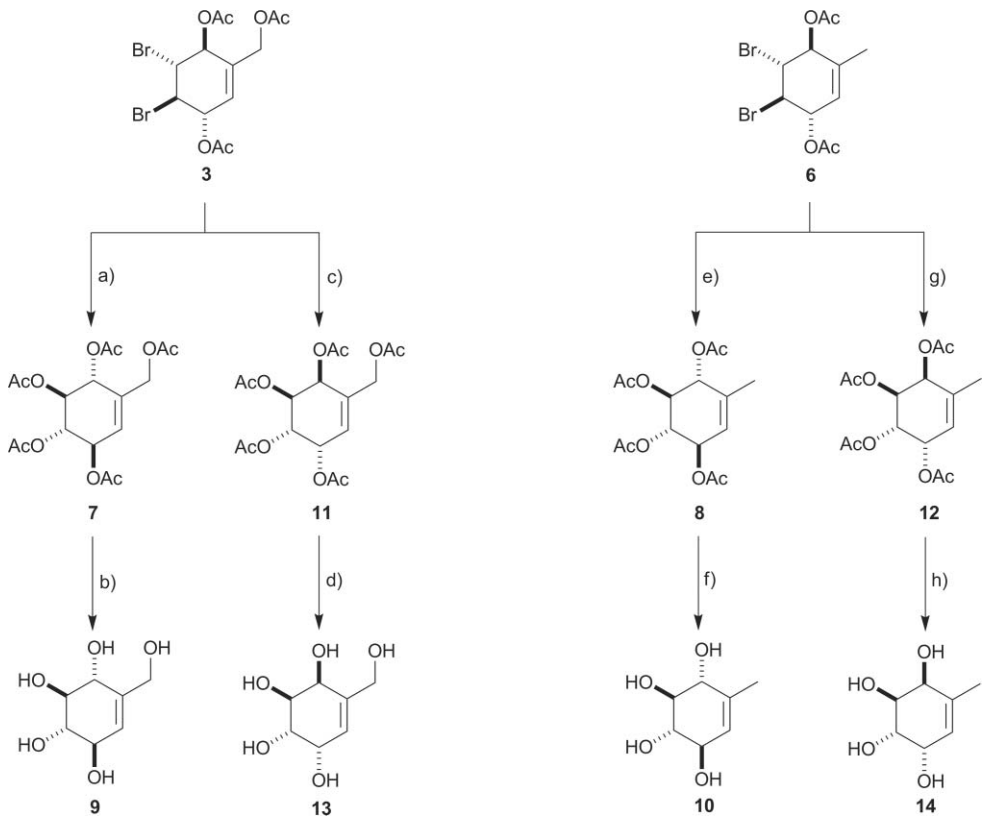


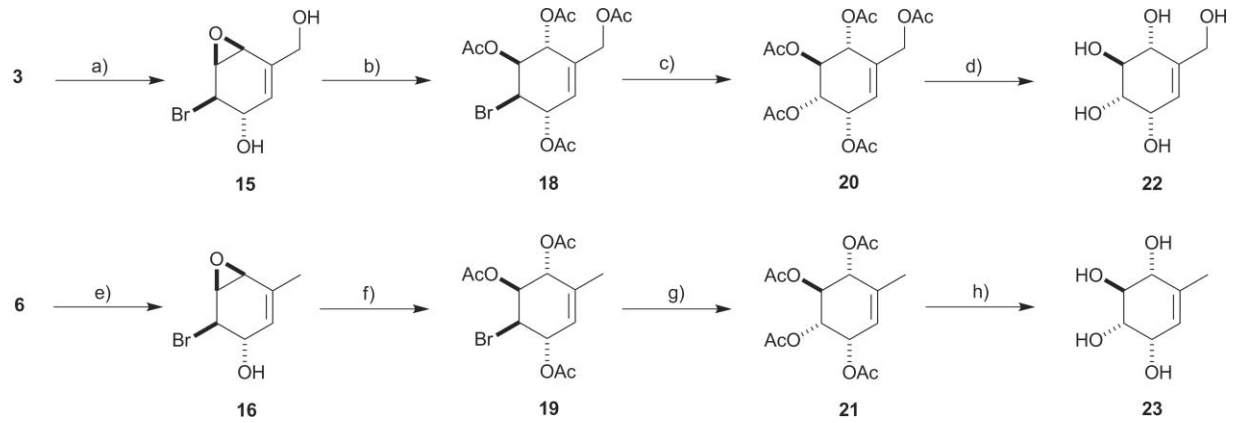
Scheme 1 a) Br_2, CH_2Cl_2, 5–10 °C, 98%; b) $NaBH_4$, Et_2O/H_2O, –15 °C, 82%; c) Ac_2O, pyridine, 0 °C – RT, 51%; d) Br_2, CH_2Cl_2, 5–10 °C, 96%; e) $NaBH_4$, Et_2O/H_2O, –15 °C, 91%; f) Ac_2O, pyridine, 0 °C–RT, 60%.



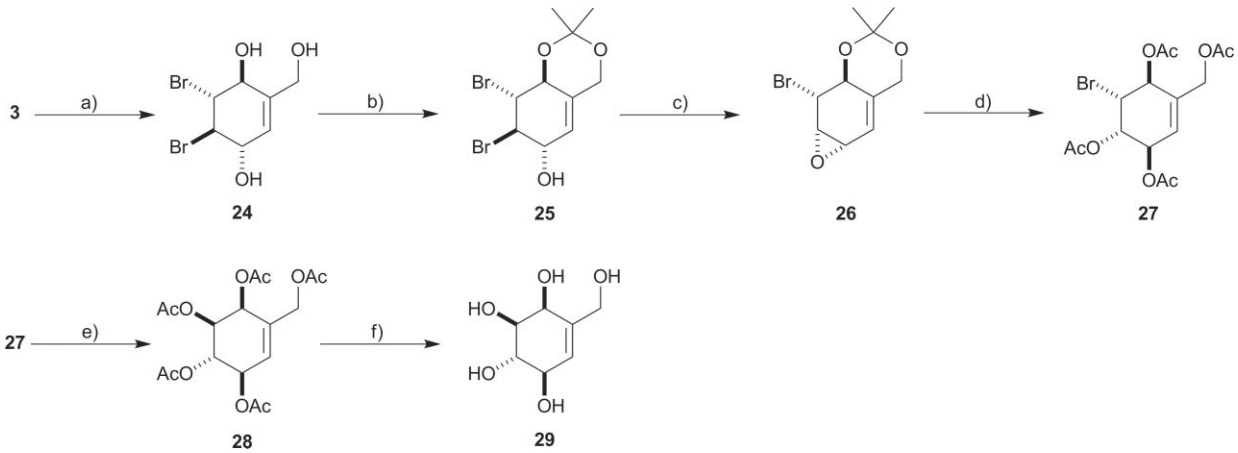
Scheme 2 a) AgOAc, AcOHabs., Ac_2O, RF, 71%; b) NaOMe, MeOH, 0–5 °C, 100%; c) AgOAc, 90% AcOH, reflux, then Ac_2O, pyridine, 35%; d) NaOMe, MeOH, 0–5 °C, 82%; e) AgOAc, AcOHabs., Ac_2O, reflux, 67%; f) NaOMe, MeOH, 0–5 °C, 88%; g) AgOAc, 90% AcOH, reflux, then Ac_2O, pyridine, 32%; h) NaOMe, MeOH, 0–5 °C, 88%.

crude material with acetic anhydride. Cleavage of the protecting groups under the above conditions gives pentol **13** (*rac.* MK7607) and the corresponding desoxy analogue **14** (see Scheme 2).

Epoxides **15** and **16** can be prepared in high yields from **3** and **6** respectively by use of lithium hydroxide as base (see Scheme 3). The regioselectivity of the epoxide formation was quite surprising. However gs-HMBC (Gradient Selected Heteronuclear Multiple Bond Coherence) NMR experiments show a coupling between the methylene group (respectively the methyl group) and the allylic proton H-6 which reveals the neighborship of the side chain and the epoxy functionality. Nucleophilic ring opening with water of epoxides **15** and **16** and subsequent peracetylation with acetic anhydride delivers bromides **18** and **19**. Conversion of the bromides with silver acetate in 90% aqueous acetic acid followed by acetylation of the crude material with acetic anhydride yields compounds **20** and **21** which both possess the *cis*,*trans*,*trans* configuration. Subsequent cleavage of the acetate protecting groups by sodium methanolate gives pentol **22** (*rac.* streptol) and the related desoxy analogue **23**.



Scheme 3 a) LiOH, Et_2O/MeOH, –15–10 °C, 83%; b) *p*-TsOH, H_2O, 0 °C–RT, then Ac_2O, pyridine, 51%; c) AgOAc, 90% AcOH, reflux, then Ac_2O, pyridine, 65%; d) NaOMe, MeOH, 0–5 °C, 81%; e) LiOH, Et_2O/MeOH, 0 °C, 72%; f) CBr_4, H2O, 35 °C, then Ac_2O, pyridine, 37%; g) AgOAc, 90% AcOH, reflux, then Ac_2O, pyridine, 38%; h) NaOMe, MeOH, 0–5 °C, 88%.



Scheme 4 a) K_2CO_3, MeOH, 0 °C, 100%; b) 2,2-dimethoxypropane, *p*-TsOH, acetone (abs.), 100%; c) NaOH, Et_2O/H_2O, room temperature; d) AcOH, H_2O, then Ac_2O, pyridine, 52%; e) AgOAc, 90% AcOH, reflux, then Ac_2O, pyridine, 54%; f) NaOMe, MeOH, 0–5 °C, 79%.

Acetal **25** can be synthesized in two steps from intermediate **3** (see Scheme 4). Cleavage of the acetate protecting groups by potassium carbonate followed by conversion of the resulting triol **24** with 2,2-dimethoxypropane delivers acetal **25**. Epoxide **26** is prepared by reacting **25** with sodium hydroxide. Selective opening of the epoxide in the allylic position and hydrolysis of the acetal moiety is achieved by the addition of acetic acid and the resulting crude material is peracetylated with acetic anhydride to yield tetraacetate **27**. Conversion of **27** with silver acetate in 90% aqueous acetic acid followed by acetylation of the crude material delivers pentaacetate **28**. Subsequent cleavage of the acetate protecting groups with sodium methanolate delivers pentol **29** (*rac.*1-*epi*-MK7607) which possesses the *trans*,*trans*,*cis* configuration.

Lectin binding studies

The Biological Interaction Analysis (BIA) *via* Surface Plasmon Resonance (SPR) Spectroscopy allows the continuous monitoring of interactions between two or more molecules. The SPR technique detects changes expressed in response units (RU) in the interfacial effective refractive index resulting from the binding of an analyte in solution to a ligand immobilized on the sensor chip. We used this technique to investigate the potential of some of the synthesized racemic carbasugars to be recognized by the galactose-specific Misteltoe Lectin I (ML I) and the *N*-acetylgalactosamine-specific Misteltoe Lectin III (ML III). Asialofetuin, with its large number of galactose moieties, is used as the immobilized ligand. As shown by X-ray crystallography of ML I in complex with galactose the 3- and 4-hydroxyl groups of galactose are responsible for the binding to the lectin.[18] Therefore, with the exception of **9**, from the synthesized racemic carba-pyranoses only compounds which exhibit the α- or β-galactose configuration were chosen for testing and compared with the enantiopure unbranched compounds (+)-**30**, (–)-**30**, (+)-**31** and (–)-**31** with such *galacto*-configuration (see Fig. 2).

The measurements with ML I show a remarkable inhibition of the lectin-ASF interaction by compounds **13** and **29** whereas compounds **14** and (+)-**31** exhibit a weaker inhibition (see Fig. 3). Almost no inhibition is obtained with compound **9**, which is the only tested compound not exhibiting a galactose configuration demonstrating the high specificity for this configuration also with carbasugars.

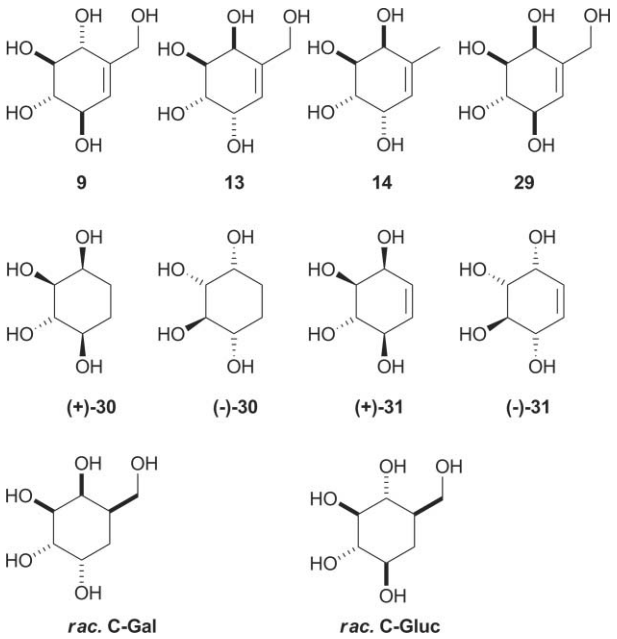


Fig. 2 Carbasugars used for lectin binding studies.

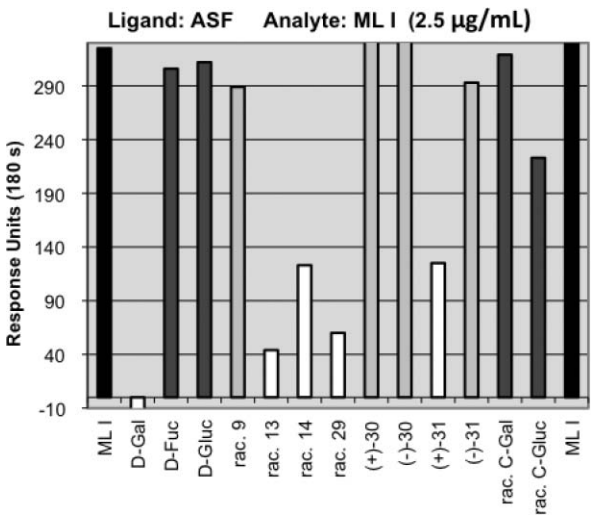


Fig. 3 Inhibition of the ASF-ML I interaction.

The second measurement using ML III instead of ML I shows that an inhibition of the ASF-ML III interaction can not be efficiently achieved by any of the tested compounds with this lectin (see Fig. 4).

The higher inhibition of the ASF-ML I interaction by branched sugar mimetics, such as **13** and **29**, in comparison to **14** or the corresponding unbranched system (+)-**31** indicates that the hydroxymethyl side chain seems to be helpful for the binding to the lectin. The comparison between **13** (α-galactose configuration) and **29** (β-galactose configuration) on the one hand and **9** (α-glucose configuration) on the other shows that the configuration of the hydroxy groups at C-3 and C-4 is also crucial for the recognition by ML I. Remarkably all compounds which exhibit an affinity towards the lectins possess a ring double bond. The racemic carba-α-galactose (*rac.* C-Gal) and carba-α-glucose (*rac.* C-Gluc),

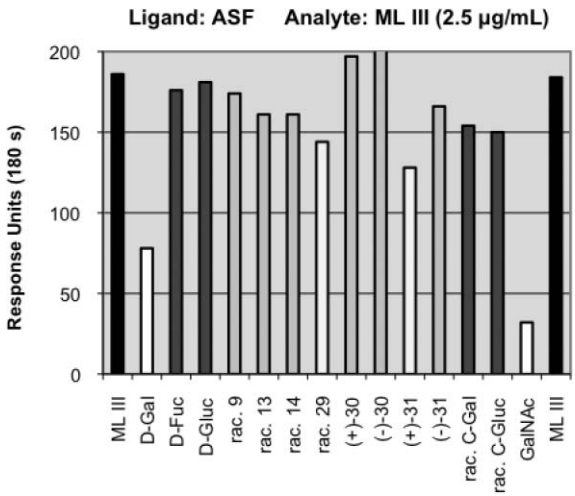


Fig. 4 Inhibition of the ASF-ML III interaction.

wich are lacking the ring double bond, show no affinity towards ML I. This result implies that the steric and electronic environment of the unsaturated carbapyranoses seems to be more similar to that of the natural substrate than that of the corresponding saturated carbasugars. In the case of enantiopure compounds, such as (+)-**31** and (−)-**31**, the lectin selectively binds to the enantiomer which exhibits the D-galactose configuration.

Conclusions

The present work shows the potential of **3** and **6** as versatile building blocks in the construction of unsaturated carbapyranoses bearing an exocyclic hydroxymethyl or methyl moiety. Initial results of the lectin binding studies prove that some of the synthesized carbasugars show interesting inhibitory properties. Future work will focus on the preparation of amino- or halogeno-functionalized derivatives to provide a larger variety of compounds for the further exploration of sugar binding sites in lectins *via* SPR Spectroscopy.

Experimental

General

All NMR spectra were recorded on a Bruker ARX 400 (400 MHz) spectrometer. Beside ^{1}H and ^{13}C experiments, 2D COSY (^{1}H–^{1}H and ^{1}H–^{13}C), gs-HMBC (^{1}H–^{13}C) and DEPT spectra for the unequivocal correlation of the hydrogen and carbon atoms were recorded. The chemical shifts are given in ppm downfield of TMS, although the solvents actually served as internal standard. The multiplicity is given by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and ψt (pseudotriplet for unresolved dd). The coupling constant *J* is given in Hz. Elemental analysis was performed on a Perkin–Elmer elemental analyzer 240B. All organic extracts were dried over Na_2SO_4, filtered and concentrated with a rotary evaporator under reduced pressure. Only distilled solvents were used. The racemic Carba-α-galactose and Carba-α-glucose have been synthesized following a procedure published by Ogawa.[19]

BIAcore measurements

A BIAcore XTM system (Pharmacia Biosensor AB, Sweden) was used to investigate the potential of the synthesized galactose analogues to act as competitive inhibitors in lectin-carbohydrate interactions. The asialofetuin (ASF type II, Sigma–Aldrich) was amine-coupled to a CM5 sensor chip (Pharmacia Biosensor AB, Sweden) according to the manufacturer's instructions. The coupling level was 1100 resonance units (RU) after blocking of the active coupling surface with ethanolamine. The empty activated and blocked channel was used as the background surface. HBS buffer (0.01 M HEPES, pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005% Surfactant P20) was used as running buffer. For the specificity measurements a 1 : 1 (v/v) mixture of an analyte solution (ML I or ML III, 5 μg ml^{-1} in HBS) and a solution of a sugar (D-galactose, D-glucose, D-fucose, 50 mM in HBS) or a carba-sugar (50 mM in HBS for enantiopure compounds and 100 mM in HBS for racemic compounds) was prepared. Prior to use the mixture is filtered through a 0.22 μm filter and degased. The injection volume was 20 μl. All measurements were performed at a flow rate of 20 μl min^{-1} at 25 °C. The response is measured after 180 s using the BIA evaluation software 3.0. For regeneration a solution of D-galactose (50 mM in HBS) was used.

[(4*RS*,5*RS*)-4,5-Dibromo-3,6-dioxocyclohex-1-ene-1-yl]methyl acetate (1)

8.1 g (50.4 mmol) bromine in 15 mL dichloromethane are added dropwise over 1 h to a cooled (5–10 °C) solution of 8.9 g (49.4 mmol) 3,6-Dioxocyclohexa-1,4-diene-1-yl)methyl acetate in 90 mL dichloromethane. The reaction mixture is allowed to warm to RT and stirred for another 1.5 h. The dichloromethane is evaporated to give 15.8 g (48.1 mmol, 98%) of the desired product as a brown oil, which is immediately used for reduction without further purification.

[(3*RS*,4*SR*,5*SR*,6*RS*)-4,5-Dibromo-3,6-dihydroxy-cyclohex-1-ene-1yl]methyl acetate (2)

A solution of 15.8 g (48.1 mmol) **1** in 125 mL diethyl ether is cooled to –15 °C. During a period of 1 h a solution of 3.9 g (103.1 mmol) sodium borohydride in 55 mL H_2O is added dropwise to the vigorously stirred solution. The reaction mixture is allowed to warm to room temperature and stirred for additional 2 h. The etheral phase is separated and the aqueous layer is extracted with diethyl ether (5 × 50 ml). The combined organic phases are dried over Na_2SO_4, filtered and the solvent is evaporated to yield 13.0 g (39.5 mmol, 82%) of the desired compound as a brown oil. ^{1}H-NMR (DMSO-d_6): δ 2.02 (s, 3H, CH_3), 4.11–4.31 (m, 4H, H-3, H-4, H-5 and H-6), 4.49 (d, 1H, J = 13.5 Hz, H-7a), 4.57 (d, 1H, J = 13.5 Hz, H-7b), 5.61 (s, 1H, H-2). ^{13}C-NMR (DMSO-d_6): δ 20.6 (CH_3), 61.0, 61.5 (C-4 and C-5), 62.8 (C-7), 71.6, 72.7 (C-3 and C-6), 128.1 (C-2), 135.1 (C-1), 169.9 (C=O). Anal. calcd. for $C_9H_{12}Br_2O_4$: C, 31.42; H, 3.52. Found: C, 31.45; H, 3.47%.

(1*RS*,4*RS*,5*SR*,6*SR*)-2-[(Acetyloxy)methyl]-5,6-dibromo-cyclohex-2-ene-1,4-diyl diacetate (3)

13.0 g (39.4 mmol) **2** are dissolved in a cooled mixture (0 °C) of 16 mL of pyridine and 16 mL of acetic anhydride. The reaction mixture is stirred for 12 h. Ice (100 g) is added and after stirring for 15 min dichloromethane (100 mL) is added. The layers are separated and the aqueous layer is extracted with dichloromethane (2 × 50 mL). The combined organic layer is washed with 0.75 N HCl (3 × 50 mL), saturated aquoeus $NaHCO_3$ (3 × 50 mL) and brine (50 mL), dried over Na_2SO_4 and filtered. After evaporation, the resulting residue is recrystallized from EtOH to yield 8.6 g (20.1 mmol, 51%) of the desired product as colourless crystals. ^{1}H-NMR ($CDCl_3$): δ 2.04 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 4.24–4.32 (AB, 2H, H-5 and H-6), 4.36 (d, 1H, J = 13.5 Hz, H-7a), 4.62 (d, 1H, J = 13.5 Hz, H-7b), 5.68 (m, 1H, H-1 or H-4), 5.80 (s, 1H, H-3), 5.89 (d, 1H, J = 5.9 Hz, H-1 or H-4). ^{13}C-NMR ($CDCl_3$): δ 20.5, 20.6, 20.7 (3 × CH_3), 51.6, 52.7 (C-5 and C-6), 62.5 (C-7), 71.7, 72.8 (C-1 and C-4), 126.4 (C-3), 134.7 (C-2), 169.5, 169.7, 170.1 (3 × C=O). Anal. calcd. for $C1_3H_{16}Br_2O_6$: C, 36.48; H, 3.77. Found: C, 36.49; H, 3.75%.

(1*SR*,2*RS*,3*RS*,4*SR*)-5-[(Acetyloxy)methyl]cyclohex-5-ene-1,2,3,4-tetrayl tetraacetate (7)

To a suspension of 3.30 g (19.8 mmol) silver acetate in 20 mL of dry acetic acid 200 mL of acetic anhydride are added and the mixture is refluxed for 1h. After cooling of the suspension 3.15 g (7.3 mmol) of **3** are added and the mixture is refluxed for 14 h. After cooling in an ice bath 200 mL diethyl ether are added. The reaction mixture is filtered and the residue is washed with 200 mL of diethyl ether. The combined organic phases are washed with saturated $NaHCO_3$-solution (3 × 50 ;mL) and once with brine (50 mL). Removal of the solvent yields a colourless oil which can be recrystallized from EtOH to yield 2.0 g (5.2 mmol, 71%) of a colourless solid. ^{1}H-NMR ($CDCl_3$): δ 1.98 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.01 (s, 3H, CH_3),2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 4.36 (d, 1H, J = 13.4 Hz, H-7a), 4.65 (d, 1H, J = 13.4 Hz, H-7b), 5.31 (AB, 2H, H-2 and H-3), 5.55 (d, 1H, J = 5.8 Hz, H-1), 5.72 (s, 1H, H-6), 5.75 (d, 1H, J = 7.1 Hz, H-4). ^{13}C-NMR ($CDCl_3$): δ 20.5, 20.5, 20.6, 20.8 (5 × CH_3), 62.4 (C-7), 70.2 (C-4), 70.7 (C-1), 70.8 (C-2), 72.0 (C-3), 126.2 (C-5), 133.7 (C-6), 169.7, 169.9, 169.9, 170.1, 170.2 (5 × C=O). Anal. calcd. for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74. Found: C, 52.96; H, 5.78%.

(1*SR*,2*RS*,3*RS*,4*SR*)-5-(Hydroxymethyl)cyclohex-5-ene-1,2,3,4-tetrol (9)

To a solution of 1.02 g (2.6 mmol) **7** in 50 mL MeOH 1.1 mL of a 1 N methanolic NaOMe-solution are added at 0 °C and the reaction mixture is stirred for 14 h at approx. +5 °C. After neutralization of the solution by addition of Dowex 50 × 8 (H^+) and filtration, the solvent is evaporated to yield 470 mg (2.6 mmol, 100%) of the desired pentol as a colourless oil which can be recrystallized from EtOH. ^{1}H-NMR (D_2O): δ 3.43 (ψt, 1H, H-2 or H-3), 3.49 (ψt, 1H, H-2 or H-3), 4.06 (d, 1H, J = 13.9 Hz, H-7a), 4.15–4.19 (m, 3H, H-1, H-4 and H-7b), 5.58 (s, 1H, H-6). ^{13}C-NMR (D_2O): δ 63.3 (C-7), 73.6, 74.2 (C-1 and C-4), 77.4, 77.8 (C-2 and C-3), 127.2 (C-6), 140.6 (C-5). Anal. calcd. for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.75; H, 6.88%.

(1*RS*,2*RS*,3*RS*,4*RS*)-5-[(Acetyloxy)methyl]cyclohex-5-ene-1,2,3,4-tetrayl tetraacetate (11)

To a solution of 1.0 g (2.3 mmol) **3** in 20 mL 90% aqueous acetic acid is added 5.0 g (30.0 mmol) silver acetate and the reaction

mixture is refluxed for 20 h. After cooling 150 mL ethyl acetate are added and the reaction mixture is filtered. The solvent is evaporated and 10 mL acetic anhydride and 10 mL pyridine are added to the residue. After stirring for 45 min all volatiles are removed *in vacuo* and the residue is taken up in 100 mL diethyl ether and 100 mL brine. The organic phase is separated, dried over Na_2SO_4, filtered and the solvent is removed to yield a brown oil which can be recrystallized from EtOH to give 306 mg (0.8 mmol, 35%) of the desired compound as colourless crystals. ^{1}H-NMR ($CDCl_3$): δ 1.96 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 4.44 (d, 1H, J = 13.9 Hz, H-7a), 4.53 (d, 1H, J = 13.9 Hz, H-7b), 5.34–5.42 (AB, 2H, H-2 and H-3), 5.65 (m, 1H, H-1), 5.72 (d, 1H, J = 3.6 Hz, H-4), 5.89 (d, 1H, J = 5.0 Hz, H-6). ^{13}C-NMR ($CDCl_3$): δ 20.5, 20.5, 20.6, 20.6 (5 × CH_3), 63.2 (C-7), 65.5, 65.6 (C-1 and C-4), 66.2, 66.5 (C-2 and C-3), 125.3 (C-6), 135.4 (C-5), 169.7, 169.8, 170.0, 170.1 (5 × C=O). Anal. calcd. for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74. Found: C, 52.74; H, 5.66%.

(1*RS*,2*RS*,3*RS*,4*RS*)-5-(Hydroxymethyl)cyclohex-5-ene-1,2,3,4-tetrol (13)

To a solution of 408 mg (1.1 mmol) **11** in 25 mL MeOH 0.5 ml of a 1 N methanolic NaOMe-solution are added at 0 °C and the reaction mixture is stirred for 14 h at approx. +5 °C. After neutralizing of the solution by addition of Dowex 50 × 8 (H^+) and filtration, the solvent is evaporated to yield a brown oil which can be recrystallized from EtOH to give 155 mg (0.9 mmol, 82%) of a beige solid. ^{1}H-NMR (D_2O): δ 3.81–3.89 (AB, 2H, H-2 and H-3), 4.12 (s, 2H, H-7), 4.23 (d, 1H, J = 2.9 Hz, H-4), 4.29 (ψt, 1H, H-1), 5.83 (m, 1H, H-6). ^{13}C-NMR (D_2O): δ 64.3 (C-7), 68.3 (C-1), 68.9 (C-4), 70.6, 70.9 (C-2 and C-3), 126.3 (C-6), 142.5 (C-5). Anal. calcd. for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.59; H, 6.72%.

(1*RS*,2*RS*,3*RS*,6*RS*)-2-Bromo-5-(hydroxymethyl)-7-oxa-bicyclo[4.1.0]hept-4-en-3-ol (15)

A solution of 3.77 g (8.8 mmol) **3** in 70 mL diethyl ether and 30 mL MeOH is cooled to −15 °C, 650 mg (27.1 mmol) lithium hydroxide is added and the reaction mixture is allowed to warm to +10 °C over a period of 3.5 h. After cooling the mixture to 0 °C 250 mL of a buffer solution (pH 7, 50 mmol L^{-1} KH_2PO_4 and 60 mmol L^{-1} Na_2HPO_4) is added and the aqueous phase is made alkaline (pH 7–8) by addition of approx. 800 mg Na_2HPO_4. Extraction with ethyl acetate (3 × 150 mL) and removal of the solvent yields 1.62 g (7.3 mmol, 83%) of a brown oil which is used for the next reaction step without further purification. For analytical purposes the crude product can be purified by column chromatography (cyclohexane: ethyl acetate 2 : 3) and subsequent recrystallization from chloroform/acetone. ^{1}H-NMR (DMSO-d_6): δ 3.44 (dd, 1H, J = 4.0 and 2.3 Hz, H-6), 3.71 (d, 1H, J = 4.0 Hz, H-1), 4.00 (d, 2H, J = 5.6 Hz, CH_2), 4.11 (m, 2H, H-2 and H-3), 5.01 (t, 1H, J = 5.6 Hz, OH), 5.56 (m, 1H, OH), 5.59 (s, 1H, H-4). ^{13}C-NMR (DMSO-d_6): δ 52.6 (C-6), 55.2 (C-1), 56.8 (C-2), 62.1 (C-7), 69.6 (C-3), 128.9 (C-4), 135.7 (C-5). Anal. calcd. for $C_7H_9BrO_3$: C, 38.04; H, 4.11. Found: C, 37.92; H, 4.00%.

(1*SR*,2*RS*,3*SR*,4*RS*)-6-[(Acetyloxy)methyl]-3-bromocyclohex-5-ene-1,2,4-triyl triacetate (18)

A solution of 0.52 g (2.35 mmol) **15** in 30 mL of destilled water is cooled to 0 °C and 30 mg *p*-toluenesulfonic acid are added. After stirring the reaction mixture for 14 h at room temperature 50 mg solid $NaHCO_3$ are added and the water is removed by lyophilization. To the remaining brown oil 10 mL acetic anhydride and 10 mL pyridine are added. After 2 h all volatiles are removed *in vacuo* and the residue is taken up in 20 mL diethyl ether. The organic phase is washed with saturated $NaHCO_3$-solution (2 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered and the solvent is removed. The remaining yellow oil is purified by column chromatography (cyclohexane:ethyl acetate 7 : 3) to yield 0.5 g (1.2 mmol, 51%) of a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 2.04 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 4.34 (dd, 1H, J = 6.4 and 2.7 Hz, H-3), 4.42 (d, 1H, J = 13.8 Hz, H-7a), 4.60 (d, 1H, J = 13.8 Hz, H-7b), 5.30 (dd, 1H, J = 5.2 and 2.7 Hz, H-2), 5.56 (d, 1H, J = 5.2 Hz, H-1), 5.61 (m, 1H, H-4), 5.89 (d, 1H, J = 3.0 Hz, H-5). ^{13}C-NMR ($CDCl_3$): δ 20.6, 20.7, 20.8 (4 × CH_3), 47.0 (C-3), 63.2 (C-7), 67.6 (C-1), 70.8 (C-4), 71.2 (C-2), 125.8 (C-5), 134.3 (C-6), 169.4, 169.6, 169.8, 170.2 (4 × C=O). Anal. calcd. for $C_{15}H_{19}BrO_8$: C, 44.24; H, 4.70. Found: C, 44.73; H, 4.83%.

(1*SR*,2*SR*,3*SR*,4*RS*)-5-[(Acetyloxy)methyl]cyclohex-5-ene-1,2,3,4-tetrayl tetraacetate (20)

To a solution of 0.5 g (1.23 mmol) **18** in 10 mL 90% aqueous acetic acid are added 1.8 g (10.8 mmol) silver acetate and the reaction mixture is refluxed for 20 h. After cooling 50 mL ethyl acetate are added and the reaction mixture is filtered. The solvent is evaporated and 5 mL acetic anhydride and 5 mL pyridine are added to the residue. After stirring for 45 min all volatiles are removed *in vacuo* and the residue is taken up in 50 mL diethyl ether and 50 mL brine. The organic phase is separated, dried over Na_2SO_4, filtered and the solvent is removed to yield a brown oil which is purified by column chromatography (cyclohexane:ethyl acetate 3 : 2) to give 310 mg (0.8 mmol, 65%) of a colourless oil. ^{1}H-NMR (CDCl3): δ 2.00 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 4.40 (d, 1H, J = 13.5 Hz, H-7a), 4.69 (d, 1H, J = 13.5 Hz, H-7b), 5.14 (dd, 1H, J = 10.9 and 3.9 Hz, H-2), 5.51 (dd, 1H, J = 10.9 and 7.3 Hz, H-3), 5.60 (ψt, 1H, H-1), 5.67 (d, 1H, J = 7.3 Hz, H-4), 5.95 (d, 1H, J = 5.6 Hz, H-6). ^{13}C-NMR ($CDCl_3$): δ 20.5, 20.6, 20.6, 20.7, 20.8 (5 × CH_3), 62.6 (C-7), 65.3 (C-1), 68.1 (C-2), 69.9 (C-3), 70.4 (C-4), 123.6 (C-6), 137.7 (C-5), 169.7, 170.0, 170.1, 170.2 (5 × C=O). Anal. calcd. for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74. Found: C, 53.37; H, 5.95%.

(1*SR*,2*SR*,3*SR*,4*RS*)-5-(Hydroxymethyl)cyclohex-5-ene-1,2,3,4-tetrol (22)

To a solution of 227 mg (0.59 mmol) **20** in 15 mL MeOH 0.3 mL of a 1 N methanolic NaOMe-solution are added at 0 °C and the reaction mixture is stirred for 14 h at approx. +5 °C. After neutralization of the solution by addition of Dowex 50 × 8 (H^+) and filtration, the solvent is evaporated to yield a colourless oil which can be recrystallized from EtOH to give 84 mg (0.48 mmol, 81%) of a colourless powder. ^{1}H-NMR (D_2O): δ 3.55 (ddd, 1H,

J = 10.6, 4.0 and 0.8 Hz, H-2), 3.68 (dψt, 1H, H-3), 4.05 (d, 1H, J = 7.7 Hz, H-4), 4.11 (d, 1H, J = 14.2 Hz, H-7a), 4.20 (d, 1H, J = 14.2 Hz, H-7b), 4.25 (ψt, 1H, H-1), 5.82 (m, 1H, H-6). ^{13}C-NMR (D_2O): δ 63.5 (C-7), 68.3 (C-1), 72.9 (C-2), 74.4 (C-4), 74.7 (C-3), 124.4 (C-6), 144.3 (C-5). Anal. calcd. for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.46; H, 6.87%.

(1*SR*,4*SR*,5*RS*,6*RS*)-5,6-Dibromo-1,7-*O*-isopropylidene-2-hydroxymethyl-cyclohex-2-ene-1,4-diol (25)

A solution of 3.0 g (7.0 mmol) **3** in 50 mL MeOH is cooled to 0 °C and 310 mg K_2CO_3 are added. The reaction mixture is stirred for 4 h, acidified by the addition of 7 mL 1 N HCl and the solvent is removed *in vacuo*. The residue is taken up in 50 mL ethyl acetate and 50 mL brine, the phases are separated and the aqueous layer is extracted with ethyl acetate (4 × 50 mL). The organic phase is dried over Na_2SO_4, filtered and the solvent is evaporated to yield 2.1 g (7.0 mmol, 100%) of the corresponding triol **24** as a colourless foam. The foam is dissolved in 20 mL dry acetone and 10 mL 2,2-dimethoxypropane and 20 mg *p*-toluenesulfonic acid are added. The reaction mixture is stirred for 1.5 h at room temperature before 50 mL saturated $NaHCO_3$-solution and 50 mL diethyl ether are added. The layers are separated and the organic phase is washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered and the solvent is evaporated to yield 2.4 g (7.0 mmol, 100%) of a brown oil which can be recrystallized from diethyl ether for analytical purposes. ^{1}H-NMR ($CDCl_3$): δ 1.43 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.75 (d, 1H, J = 4.1 Hz, OH), 4.14–4.18 (m, 3H, H-5, H-6 and H-7a), 4.41 (m, 1H, H-7b), 4.56 (m, 1H, H-4), 4.62 (dd, 1H, J = 5.3 and 1.0 Hz, H-1), 5.55 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$): δ 20.4, 27.4 (2 × CH_3), 54.0, 60.6 (C-5 and C-6), 62.1 (C-7), 73.2 (C-1), 73.5 (C-4), 100.4 (OCO), 121.5 (C-3), 134.8 (C-2). Anal. calcd. for $C_{10}H_{14}Br_2O_3$: C, 35.12; H, 4.13. Found: C, 34.93; H, 4.16%.

(1*RS*,2*SR*,3*RS*,4*SR*)-5-[(Acetyloxy)methyl]-3-bromocyclohex-5-ene-1,2,4-triyl triacetate (27)

To a solution of 1.0 g (2.9 mmol) **25** in 60 mL diethyl ether are added 60 mL of a 1 N aqueous NaOH-solution and the reaction mixture is stirred at ambient temperature for 4 h. The phases are separated and the aqueous layer is extracted with diethyl ether (3 × 50 mL). The diethyl ether is evaporated and 10 mL water and 5 mL acetic acid are added to the resulting residue (epoxide **26**). The reaction mixture is stirred at ambient temperature for 14 h and all volatiles are removed *in vacuo*. 15 mL acetic anhydride and 15 mL pyridine are added to the resulting oil and the mixture is stirred for 1 h. All volatiles are removed *in vacuo* and the residue is taken up in 50 mL diethyl ether and 50 mL brine. The organic layer is dried over Na_2SO_4, filtered and the solvent is evaporated to deliver a brown oil which can be purified by column chromatography (cyclohexane:ethyl acetate 3 : 1) to yield 605 mg (1.5 mmol, 52%) of a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 2.03 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 4.36 (dd, 1H, J = 4.4 and 3.0 Hz, H-3), 4.45 (d, 1H, J = 13.7 Hz, H-7a), 4.56 (d, 1H, J = 13.7 Hz, H-7b), 5.19 (dd, 1H, J = 6.7 and 3.0 Hz, H-2), 5.52 (d, 1H, J = 6.7 Hz, H-1), 5.59 (d, 1H, J = 4.4 Hz, H-4), 5.88 (m, 1H, H-6). ^{13}C-NMR ($CDCl_3$): δ 20.6, 20.7, 20.8 (4 × CH_3), 47.4 (C-3), 63.4 (C-7), 69.1 (C-1), 70.0 (C-2), 70.2 (C-4), 126.7 (C-6), 132.8 (C-5), 169.7, 169.8, 169.9, 170.2 (4 × C=O). Anal. calcd. for $C_{15}H_{19}BrO_8$: C, 44.24; H, 4.70. Found: C, 44.59; H, 4.27%.

(1*RS*,2*SR*,3*SR*,4*SR*)-5-[(Acetyloxy)methyl]cyclohex-5-ene-1,2,3,4-tetrayl tetraacetate (28)

To a solution of 464 mg (1.14 mmol) **27** in 8 mL 90% aqueous acetic acid are added 1.5 g (9.0 mmol) silver acetate and the reaction mixture is refluxed for 20 h. After cooling 50 mL ethyl acetate are added and the reaction mixture is filtered. The solvent is evaporated and 5 mL acetic anhydride and 5 mL pyridine are added to the residue. After stirring for 45 min all volatiles are removed *in vacuo* and the residue is taken up in 50 mL diethyl ether and 50 mL brine. The organic phase is separated, dried over Na_2SO_4, filtered and the solvent is removed to yield a brown oil which is recrystallized from EtOH to give 240 mg (0.62 mmol, 54%) of colourless crystals. ^{1}H-NMR ($CDCl_3$): δ 1.97 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 4.47 (d, 1H, J = 13.7 Hz, H-7a), 4.54 (d, 1H, J = 13.7 Hz, H-7b), 5.11 (m, 1H, H-2), 5.48–5.52 (AB, 2H, H-3 and H-4), 5.69 (d, 1H, J = 3.8 Hz, H-1), 5.81 (s, 1H, H-6). ^{13}C-NMR ($CDCl_3$): δ 20.4, 20.7, 20.7, 20.8 (5 × CH_3), 63.4 (C-7), 65.5 (C-1), 68.5 (C-2), 68.9 (C-3), 71.2 (C-4), 128.0 (C-6), 132.7 (C-5), 169.7, 170.0, 170.2, 170.2 (5 × C=O). Anal. calcd. for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74. Found: C, 52.97; H, 5.78%.

(1*RS*,2*SR*,3*SR*,4*SR*)-5-(Hydroxymethyl)cyclohex-5-ene-1,2,3,4-tetrol (29)

To a solution of 222 mg (0.57 mmol) **28** in 15 mL MeOH 0.3 mL of a 1 N methanolic NaOMe-solution are added at 0 °C and the reaction mixture is stirred for 14 h at approx. +5 °C. After neutralization of the solution by addition of Dowex 50 × 8 (H^+) and filtration, the solvent is evaporated to yield a colourless oil which can be recrystallized from EtOH to yield 80 mg (0.45 mmol, 79%) of a colourless powder. ^{1}H-NMR (D_2O): δ 3.52 (dd, 1H, J = 10.8 and 4.0 Hz, H-3), 3.61 (dd, 1H, J = 10.8 and 7.7 Hz, H-2), 4.05 (d, 1H, J = 7.7 Hz, H-1), 4.11 (s, 2H, H-7), 4.18 (d, 1H, J = 4.0 Hz, H-4), 5.68 (s, 1H, H-6). ^{13}C-NMR (D_2O): δ 64.2 (C-7), 68.9 (C-4), 73.1 (C-3), 74.0 (C-1), 74.7 (C-2), 129.3 (C-6), 139.9 (C-5). Anal. calcd. for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.55; H, 6.74%.

(5*RS*,6*RS*)-5,6-Dibromo-2-methylcyclohex-2-ene-1,4-dione (4)

32.6 g (204.0 mmol) bromine in 50 mL dichloromethane are added dropwise over 1h to a cooled (5–10 °C) solution of 24.4 g (200.0 mmol) 2-methylbenzo-1,4-quinone in 350 mL dichloromethane. The reaction mixture is allowed to warm to RT and stirred for another 1.5 h. The dichloromethane is evaporated to give 54.0 g (191.5 mmol, 96%) of crude (5*RS*,6*RS*)-5,6-dibromo-2-methylcyclohex-2-ene-1,4-dione as a brown solid, which is immediately used for reduction without further purification.

(1*RS*,4*RS*,5*SR*,6*SR*)-5,6-Dibromo-2-methylcyclohex-2-ene-1,4-diol (5)

A solution of 54.0 g (191.5 mmol) **4** in 500 mL diethyl ether is cooled to −15 °C. During a period of 1h a solution of 15.5 g

(409.7 mmol) sodium borohydride in 220 mL H_2O is added dropwise to the vigorously stirred solution. The reaction mixture is allowed to warm to room temperature and stirred for additional 3 h. The ether phase is separated and the aqueous layer is extracted with diethylether (5 × 100 ml). The combined organic phases are dried over Na_2SO_4, filtered and the solvent is evaporated to yield 50.0 g (174.8 mmol, 91%) of the raw diol, which can be recrystallized from toluene for analytical purposes. ^{1}H-NMR (DMSO-d_6): δ 1.66 (s, 3H, CH_3), 4.06–4.25 (m, 4H, H-1, H-4, H-5 and H-6), 5.34 (m, 1H, H-3), 5.56 (d, 1H, $J = 7.1$ Hz, OH), 5.69 (d, 1H, $J = 7.6$ Hz, OH). ^{13}C-NMR (DMSO-d_6): δ 18.8 (CH_3), 61.8, 61.9 (C-5 and C-6), 71.9, 74.6 (C-1 and C-4), 126.5 (C-3), 136.6 (C-2). Anal. calcd. for $C_7H_{10}Br_2O_2$: C, 29.40; H, 3.52. Found: C, 29.39; H, 3.53%.

(1*RS*,4*RS*,5*SR*,6*SR*)-5,6-Dibromo-2-methylcyclohex-2-ene-1,4-diyl diacetate (6)

32.7 g (114.5 mmol) **5** are dissolved in a cooled mixture (0 °C) of 52 mL of pyridine and 52 mL of acetic anhydride. The reaction mixture is stirred for 12 h. Ice (200 g) is added and after stirring for 15 min dichloromethane (200 mL) is added. The layers are separated and the aqueous layer is extracted with dichloromethane (2 × 100 mL). The combined organic layer is washed with 0.75 N HCl (3 × 100 mL), saturated aqueous $NaHCO_3$ (3 × 100 mL) and brine (50 mL), dried over Na_2SO_4 and filtered. After evaporation, the resulting residue is recrystallized from EtOH to yield 25.4 g (68.7 mmol, 60%) of colourless crystals. ^{1}H-NMR (DMSO-d_6): δ 1.57 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 4.66 (AB, 2H, H-5 and H-6), 5.47 (m, 1H, H-3), 5.63 (m, 1H, H-1 or H-4), 5.78 (ψd, 1H, H-1 or H-4). ^{13}C-NMR (DMSO-d_6): δ 18.0, 20.4, 20.6 (3 × CH_3), 53.8, 54.5 (C-5 and C-6), 73.2, 74.7 (C-1 and C-4), 123.9 (C-3), 135.5 (C-2), 169.4, 169.6 (2 × C=O). Anal. calcd. for $C_{11}H_{14}Br_2O_4$: C, 35.70; H, 3.81. Found: C, 35.72; H, 3.80%.

(1*RS*,2*SR*,3*SR*,4*RS*)-5-Methylcyclohex-5-ene-1,2,3,4-tetrayl tetraacetate (8)

To a suspension of 3.3 g (19.8 mmol) silver acetate in 20 mL of dry acetic acid 200 mL of acetic anhydride are added and the mixture is refluxed for 1 h. After cooling of the suspension 2.7 g (7.3 mmol) of **6** are added and the mixture is refluxed for 14 h. After cooling in an ice bath 200 mL diethyl ether are added. The reaction mixture is filtered and the residue is washed with 200 mL of diethyl ether. The combined organic phases are washed with saturated $NaHCO_3$-solution (3 × 50 mL) and once with brine (50 mL). Removal of the solvent yields a colourless oil which can be recrystallized from diisopropyl ether/EtOH to yield 1.6 g (4.9 mmol, 67%) of a colourless solid. ^{1}H-NMR ($CDCl_3$): δ 1.63 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 5.24 (AB, 2H, H-2 and H-3), 5.41 (m, 1H, H-6), 5.50 (m, 1H, H-1 or H-4), 5.62 (ψd, 1H, H-1 or H-4). ^{13}C-NMR ($CDCl_3$): δ 18.2, 20.4, 20.5, 20.5, 20.8 (5 × CH_3), 71.2 (C-1 or C-4), 71.3, 71.7 (C-2 and C-3), 72.9 (C-1 or C-4), 122.9 (C-6), 135.0 (C-5), 169.7, 169.8, 170.1, 170.2 (4 × C=O). Anal. calcd. for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 54.86; H, 6.19%.

(1*SR*,2*RS*,3*RS*,4*SR*)-5-Methylcyclohex-5-ene-1,2,3,4-tetrol (10)

To a solution of 0.5 g (1.5 mmol) **8** in 30 mL MeOH 0.6 mL of a 1 N methanolic NaOMe-solution are added at 0 °C and the reaction mixture is stirred for 14 h at approx. +5 °C. After neutralization of the solution by addition of Dowex 50 × 8 (H^+) and filtration, the solvent is evaporated to yield 210 mg (1.3 mmol, 88%) of a beige solid. ^{1}H-NMR (MeOH-*d4*): δ 1.74 (s, 3H, CH_3), 3.34 (m, 2H, H-2 and H-3), 3.90 (d, 1H, $J = 6.1$ Hz, H-1 or H-4), 4.01 (m, 1H, H-1 or H-4), 4.79 (s, 4H, OH), 5.29 (m, 1H, H-6). ^{13}C-NMR (MeOH-*d4*): δ 18.9 (CH_3), 73.3, 76.0 (C-1 and C-4), 77.3, 77.5 (C-2 and C-3), 126.3 (C-6), 137.6 (C-5). Anal. calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55 Found: C, 52.23; H, 7.38%.

(1*RS*,2*RS*,3*RS*,4*RS*)-5-Methylcyclohex-5-ene-1,2,3,4-tetrayl tetraacetate (12)

To a solution of 1.7 g (4.7 mmol) **6** in 40 mL 90% aqueous acetic acid are added 10 g (60 mmol) silver acetate and the reaction mixture is refluxed for 20 h. After cooling 300 mL ethyl acetate are added and the reaction mixture is filtered. The solvent is evaporated and 20 mL acetic anhydride and 20 mL pyridine are added to the residue. After stirring for 45 min all volatiles are removed *in vacuo* and the residue is taken up in 200 mL diethyl ether and 200 mL brine. The organic phase is separated, dried over Na_2SO_4, filtered and the solvent is removed to yield a yellow oil which can be recrystallized from diisopropyl ether/EtOH to give 500 mg (1.5 mmol, 32%) of a colourless solid. ^{1}H-NMR ($CDCl_3$): δ 1.71 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 5.33 (dd, 1H, $J = 10.7$ and 4.1 Hz, H-2 or H-3), 5.40 (dd, 1H, $J = 10.7$ and 4.1 Hz, H-2 or H-3), 5.57 (ψt, 2H, H-1 and H-4), 5.62 (dd, 1H, $J = 5.1$ and 1.5 Hz, H-6). ^{13}C-NMR ($CDCl_3$): δ 20.1, 20.4, 20.5, 20.6, 20.7 (5 × CH_3), 66.1 (C-1 or C-4), 66.3, 66.6 (C-2 and C-3), 69.1 (C-1 or C-4), 123.1 (C-6), 137.0 (C-5), 169.8, 169.9, 170.2, 170.4 (4 × C=O). Anal. calcd. for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 54.84; H, 6.19%.

(1*RS*,2*RS*,3*RS*,4*RS*)-5-Methylcyclohex-5-ene-1,2,3,4-tetrol (14)

To a solution of 0.5 g (1.5 mmol) **12** in 30 mL MeOH 0.6 mL of a 1 N methanolic NaOMe-solution are added at 0 °C and the reaction mixture is stirred for 14 h at approx. +5 °C. After neutralization of the solution by addition of Dowex 50 × 8 (H^+) and filtration, the solvent is evaporated to yield 208 mg (1.3 mmol, 88%) of an offwhite solid. ^{1}H-NMR (MeOH-*d4*): δ 1.81 (s, 3H, CH_3), 3.81 (m, 2H, H-2 and H-3), 4.01 (d, 1H, $J = 3.6$ Hz, H-1 or H-4), 4.15 (m, 1H, $J = 4.1$ Hz, H-1 or H-4), 4.76 (s, 4H, OH), 5.53 (m, 1H, H-6). ^{13}C-NMR (MeOH-*d4*): δ 20.9 (CH_3), 67.9 (C-1 or C-4), 70.3, 70.6 (C-2 and C-3), 71.7 (C-1 or C-4), 125.7 (C-6), 139.0 (C-5). Anal. calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55 Found: C, 52.28; H, 7.42%.

(1*RS*,2*SR*,3*RS*,6*RS*)-2-Bromo-5-methyl-7-oxabicyclo-[4.1.0]hept-4-en-3-ol (16)

A solution of 13.0 g (35.0 mmol) **6** in 200 mL diethyl ether and 100 mL MeOH is cooled to 0 °C, 1.88 g (78.5 mmol) lithium hydroxide are added and the reaction mixture is stirred for 1.5 h at this temperature. 300 mL H2O are added to the reaction mixture, the phases are separated and the aqueous phase is extracted with diethyl ether (2 × 200 mL). The combined organic phase is dried over Na_2SO_4, filtered and the solvent is evaporated to yield 5.17 g (25.2 mmol, 72%) of a colourless solid. ^{1}H-NMR (DMSO-d_6): δ 1.83 (d, 3H, $J = 1.5$ Hz, CH_3), 3.36 (dd, 1H, $J = 4.1$ and 2.0 Hz,

H-6), 3.67 (ψd, 1H, J = 4.1 Hz, H-1), 4.08 (m, 2H, H-2 and H-3), 5.45 (m, 1H, H-4), 5.50 (d, 1H, J = 5.9 Hz, OH). ^{13}C-NMR (DMSO-d_6): δ 20.5 (CH_3), 55.1 (C-6), 55.4 (C-1), 56.8, 69.6 (C-2 and C-3), 130.0 (C-4), 130.8 (C-5). Anal. calcd. for $C_7H_9BrO_2$: C, 41.00; H, 4.42. Found: C, 41.12; H, 4.31%.

(1*RS*,2*SR*,3*RS*,4*SR*)-3-Bromo-6-methylcyclohex-5-ene-1,2,4-triol (17)

2.3 g (11.2 mmol) **16** are suspended in 20 mL H_2O, 0.4 g (0.6 mmol) tetrabromomethane are added and the suspension is heated to 35 °C for 14 h. The aqueous layer is extracted with *tert*-butyl methyl ether (10 mL) and the water is evaporated to yield 1.4 g (6.3 mmol, 56%) of a colourless oil. ^{1}H-NMR (DMSO-d_6): δ 1.65 (s, 3H, CH_3), 3.67 (d, 1H, J = 4.1 Hz, H-1), 3.76 (ψd, 1H, J = 4.1 Hz, H-2), 4.14 (ψs, 2H, H-3 and H-4), 5.29 (ψs, 1H, H-5). ^{13}C-NMR (DMSO-d_6): δ 19.9 (CH_3), 60.6 (C-3), 69.0 (C-4), 72.5, 73.2 (C-1 and C-2), 125.5 (C-5), 135.5 (C-6). Anal. calcd. for $C_7H_{11}BrO_3$: C, 37.69; H, 4.97. Found: C, 37.71; H, 4.30%.

(1*RS*,2*SR*,3*RS*,4*SR*)-3-Bromo-6-methylcyclohex-5-ene-1,2,4-triyl triacetate (19)

1.4 g (6.3 mmol) **17** are dissolved in a cooled mixture (0 °C) of 27 mL pyridine and 27 mL acetic anhydride and the reaction mixture is stirred for 14 h. Ice (100 g) is added and after stirring for 15 min dichloromethane (100 mL) is added. The layers are separated and the aqueous layer is extracted with dichloromethane (2 × 50 mL). The combined organic layer is washed with 0.75 N HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (3 × 50 mL) and brine (50 mL), dried over Na2SO4 and filtered. After evaporation, the resulting residue is recrystallized from ethanol to yield 1.5 g (4.2 mmol, 66%) of colourless crystals. ^{1}H-NMR (DMSO-d_6): δ 1.65 (s, 3H, CH_3), 2.04 (s, 6H, 2 × CH_3), 2.06 (s, 3H, CH_3), 4.46 (dd, 1H, J = 5.6 Hz and 3.1 Hz, H-3), 5.18 (dd, 1H, J = 5.6 Hz and 3.1 Hz, H-2), 5.30 (d, 1H, J = 5.6 Hz, H-1), 5.41 (m, 1H, H-4), 5.62 (m, 1H, H-5). ^{13}C-NMR (DMSO-d_6): δ 18.7, 20.4, 20.5, 20.6 (4 × CH_3), 48.6 (C-3), 70.1, 70.2 (C-1 and C-2), 70.8 (C-4), 122.6 (C-5), 135.7 (C-6), 169.3, 169.5, 169.8 (3 × C=O). Anal. calcd. for $C_{13}H_{17}BrO_6$: C, 44.72; H, 4.91. Found: C, 44.69; H, 4.95%.

(1*SR*,2*SR*,3*SR*,4*RS*)-5-Methylcyclohex-5ene-1,2,3,4-tetrayl tetraacetate (21)

To a solution of 1.4 g (3.9 mmol) **19** in 30 mL 90% aqueous acetic acid are added 5.7 g (34.2 mmol) silver acetate and the reaction mixture is refluxed for 20 h. After cooling 200 mL ethyl acetate are added and the reaction mixture is filtered. The solvent is evaporated and 15 mL acetic anhydride and 15 mL pyridine are added to the residue. After stirring for 45 min all volatiles are removed *in vacuo* and the residue is taken up in 100 mL diethyl ether and 100 mL brine. The organic phase is separated, dried over Na_2SO_4, filtered and the solvent is removed to yield a yellow oil which can be recrystallized from diisopropyl ether/EtOH to give 503 mg (1.5 mmol, 38%) of a colourless solid. ^{1}H-NMR ($CDCl_3$): δ 1.68 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 5.08 (dd, 1H, J = 10.2 and 3.6 Hz, H-2), 5.47–5.54 (m, 3H, H-1, H-3 and H-4), 5.63 (m, 1H, H-6). ^{13}C-NMR ($CDCl_3$): δ 18.5, 20.4, 20.5, 20.6, 20.8 (5 × CH_3), 66.0 (C-3), 68.6 (C-2), 69.8, 73.4 (C-1 and C-4), 120.9 (C-6), 139.2 (C-5), 169.7, 170.0, 170.1, 170.2 (4 × C=O). Anal. calcd. for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 54.90; H, 6.10%.

(1*SR*,2*SR*,3*SR*,4*RS*)-5-Methylcyclohex-5-ene-1,2,3,4-tetrol (23)

To a solution of 0.5 g (1.5 mmol) **21** in 30 mL MeOH 0.6 mL of a 1 N methanolic NaOMe-solution are added at 0 °C and the reaction mixture is stirred for 14 h at approx. +5 °C. After neutralization of the solution by addition of Dowex 50 × 8 (H^+) and filtration, the solvent is evaporated to yield 210 mg (1.3 mmol, 88%) of a beige solid. ^{1}H-NMR (MeOH-*d4*): δ 1.77 (s, 3H, CH_3), 3.42 (dd, 1H, J = 10.2 and 4.1 Hz, H-2), 3.67 (dd, 1H, J = 10.2 and 7.6 Hz, H-3), 3.77 (d, 1H, J = 6.6 Hz, H-4), 4.10 (t, 1H, J = 4.6 Hz, H-1), 4.85 (s, 4H, OH), 5.53 (m, 1H, H-6). ^{13}C-NMR (MeOH-*d4*): δ 19.2 (CH_3), 68.1 (C-1), 72.8 (C-2), 74.1 (C-3), 76.1 (C-4), 123.7 (C-6), 141.3 (C-5). Anal. calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55 Found: C, 52.27; H, 7.44%.

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