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Stereoselective syntheses of 3-aminocyclooctanetriols and halocyclooctanetriols

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Abstract

The efficient synthesis of two new stereoisomeric 3-aminocyclooctanetriols and new halocyclitol derivatives of them starting from *cis,cis*-1,3-cyclooctadiene are reported. Reduction of cyclooctene endoperoxide, obtained by photooxygenation of *cis,cis*-1,3-cyclooctadiene, with zinc yielded a cyclooctene diol followed by acetylation of the hydroxyl group, which gave dioldiacetate by OsO_4/NMO oxidation. The cyclooctane dioldiacetate prepared was converted to the corresponding cyclic sulphate *via* the formation of a cyclic sulphite in the presence of catalytic RuO_4. Reaction of this cyclic sulphate with a nucleophilic azide followed by the reduction of the azide group provided the target, 3-aminocyclooctanetriol. The second key compound, bromotriol, was prepared by epoxidation of the cyclooctene diol with *m*-chloroperbenzoic acid followed by hydrolysis with HBr(g) in methanol. Treatment of bromotriol with NaN_3 and the reduction of the azide group yielded the other 3-aminocyclooctanetriol desired. Hydrolysis of the epoxides with HCl(g) in methanol gave stereospecifically new chlorocyclooctanetriols.

Keywords: aminocyclitols; aminocyclooctanetriol; chlorocyclooctanetriol; cyclic sulphate; cyclitols.

Introduction

The synthesis of aminocyclitols has attracted attention because they contain substructures of many biologically active natural products [1-3]. They have become important structural components for drug development with a modifying action as

inhibitors of glycosidases [4-10]. Aminocyclitols are amino polyhydroxy cycloalkanes [2] formally derived from cyclitols [11-15], which are polyhydroxylated cycloalkanes, *via* replace of one of the hydroxyl groups with an amino group. Many aminocyclitols and their derivatives have been found to possess antibiotic properties, such as validamycins (**1**) [16]. Validamycin A (**1**) contains two aminocyclitol units, one valienamine (**2**) and the other validamine (**3**) (Figure 1).

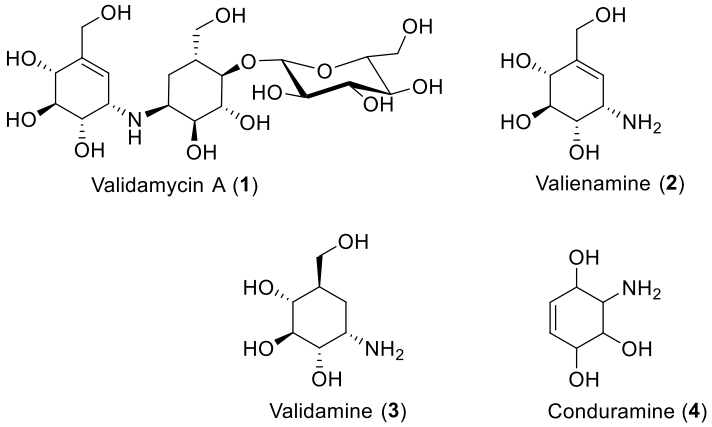


Figure 1: Structures of some important aminocyclitols.

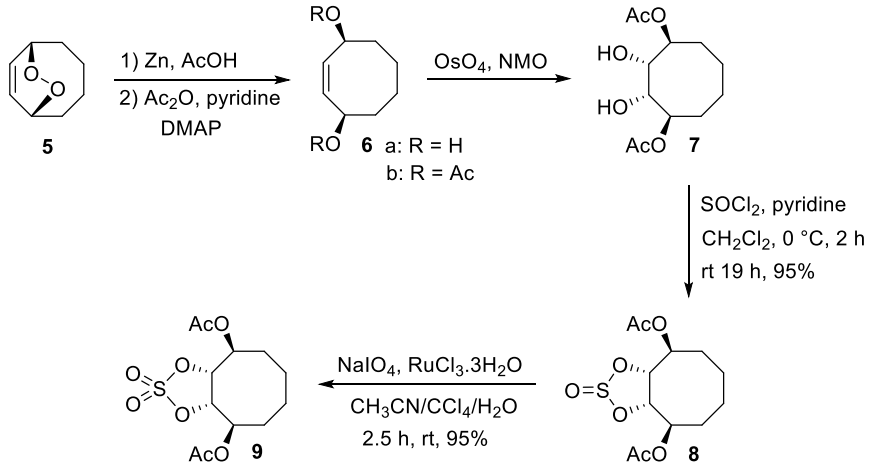
One of the most important conduramines (**4**) is valienamine (**3**) [17], is found as a building block in several aminoglycoside antibiotics [2]. Furthermore, conduramines (**4**) and their derivatives are used as both inhibitors of glycosidases and also useful intermediates in organic synthesis [18]. One of the derivatives of cyclitols is also halocyclitols, in which one of the hydroxyl groups is replaced by a halogen. They have also attracted interest in the last decade because of their biological activities [11, 19]. For instance, some brominated quercitol (cyclohexanepentol) derivatives and bromo-conduritol-B act as strong inhibitors of α-glycosidases [11, 19]. Recent reviews report

on the most recent synthetic methodologies of aminocyclitols and related compounds [1-3, 16].

Many methods have been previously reported for the synthesis of aminocyclitols containing five- and six-membered rings, along with their diverse biological activities [1-3, 16-27]. However, only a limited number of synthetic methods are available for the synthesis of seven- [28, 29], eight- [30-39], and nine- [36] membered aminocyclitols. Therefore, we were inspired to work on the development of the first synthesis of some C8-amino- and chloro-substituted cyclitols. Recently, we developed the first synthesis of various C8-amino- [30, 32] and diaminocyclitol derivatives [31]. As part of our work involving the synthesis of C8-cyclitols, we report stereospecific syntheses of two new 3-aminocyclooctanetriols and some chlorinated C8-cyclitols starting from *cis,cis*-1,3-cyclooctadiene.

Results and Discussion

For the synthesis of amino- and chlorocyclitols and their derivatives, we first selected endoperoxide **5** as starting molecule, which was prepared using a procedure described in the literature [34] (Scheme 1). Among the most relevant precursors for the synthesis of aminocyclitols are cyclic sulphates [37, 38, 40, 41] and they have been also used in the synthesis of C8-aminocarbasugars [37, 38] recently. We envisioned that aminotriol (**12**) could be prepared by the reaction with sodium azide of the corresponding cyclic sulphate intermediate (**9**), which contains the only stereocentre. The cyclic sulphate (**9**) could be synthesized from diacetate-diol **7** [34].

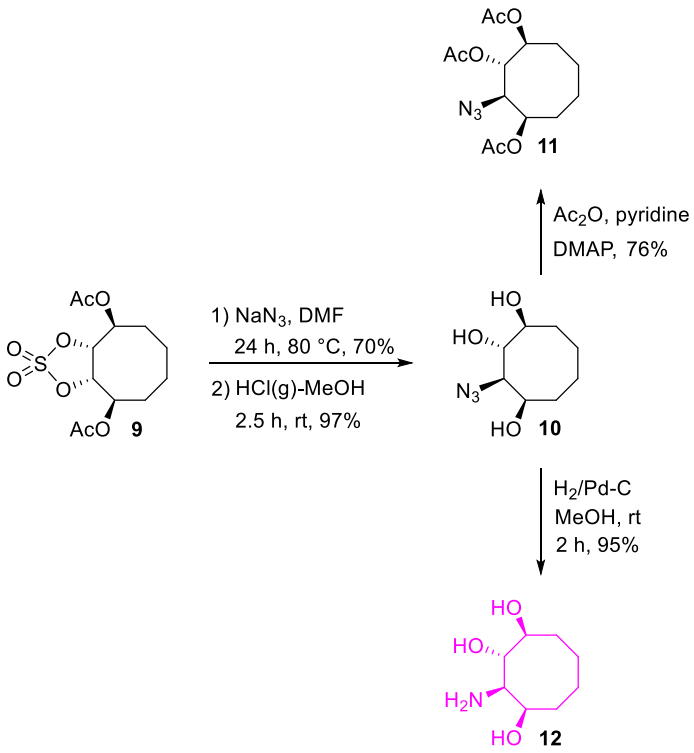


Scheme 1: Synthesis of cyclic sulphate **9**.

For this purpose, reduction of the endoperoxide **5** with zinc followed by acetylation of the hydroxyl group and OsO_4/NMO oxidation of the double bond gave diacetate-diol **7** [34]. Treatment of diacetate-diol **7** with thionyl chloride in pyridine gave the corresponding cyclic sulphite **8** in 95% yield (Scheme 1). Oxidation of the cyclic sulphite **8** with sodium periodate in the presence of ruthenium trichloride provided the corresponding cyclic sulphate **9** in 95% yield.

The cyclic sulphate moiety in **9** was reacted with sodium azide in DMF at 80 °C followed by acidic hydrolysis of the resulting acyclic sulphate ester to give azidotriol **10** as a single stereoisomer in 97% yield (Scheme 2). For further structural proof, the azidotriol **10** was converted into the corresponding triacetate **11** with acetic anhydride in pyridine and 4-(dimethylamino)pyridine (DMAP) (yield 76%). Protons H-3 and H-1 in the triacetate **11** have been irradiated separately at their resonance frequencies and the changes in the spectrum have been observed. Upon irradiation at the resonance frequency of the proton H-3 at 3.87 ppm there is no change in the multiplet at 5.04-4.97

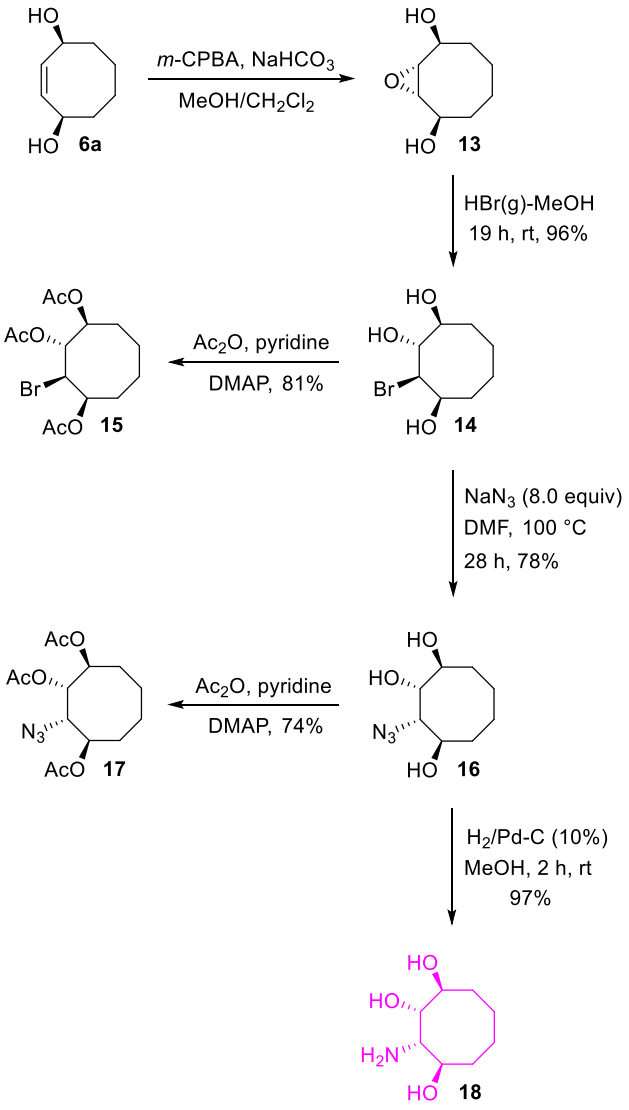
ppm. However, in the multiplet part at 5.24-5.15 ppm, some splittings are removed. This experiment clearly shows that the proton H-3 has couplings to both acetoxy protons H-2 and H-4. Furthermore, the proton H-3 resonates as a doublet of doublets with coupling constants of J = 8.8 and 2.7 Hz, clearly indicating that H-3 and H-2 with a large coupling constant ($J_{2,3}$ = 8.8 Hz) are *trans* to each other. The small coupling constant ($J_{3,4}$ = 2.7 Hz) between H-3 and H-4 shows the *cis* relationship between those protons. Next, reduction of azidotriol **10** by hydrogenation afforded the target aminotriol **12** in 95% yield.



Scheme 2: Synthesis of aminocyclooctanetriol **12**.

For the synthesis of the other aminocyclooctanetriol (**18**), the diol **6a** [34] was reacted with *m*-CPBA to give *trans*-epoxide isomer **13** [34] (79% yield) as the sole product

(Scheme 3). Ring opening of *trans*-epoxide **13** by HBr(g)-MeOH gave bromotriol **14**, which is an ideal substrate for the synthesis of the aminocyclooctanetriol (**18**). For structural proof, bromotriol **14** was converted into the corresponding acetate **15** using Ac_2O in pyridine and DMAP (81%).

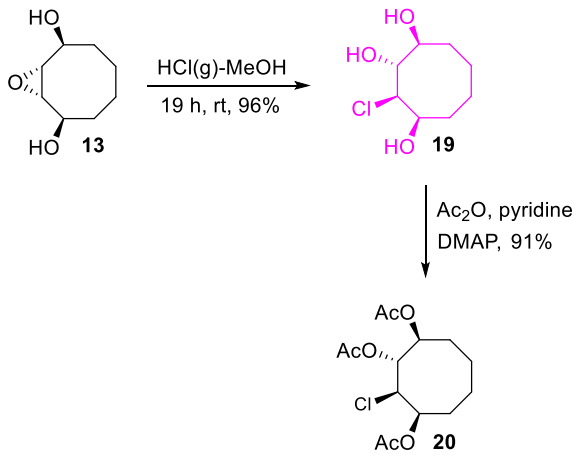


Scheme 3: Synthesis of aminocyclooctanetriol **18**.

Next, to introduce the azido group in a *cis*-configuration, the bromotriol **14** was treated with sodium azide in DMF at 100 °C to afford azidotriol **16** as a single product in 78%

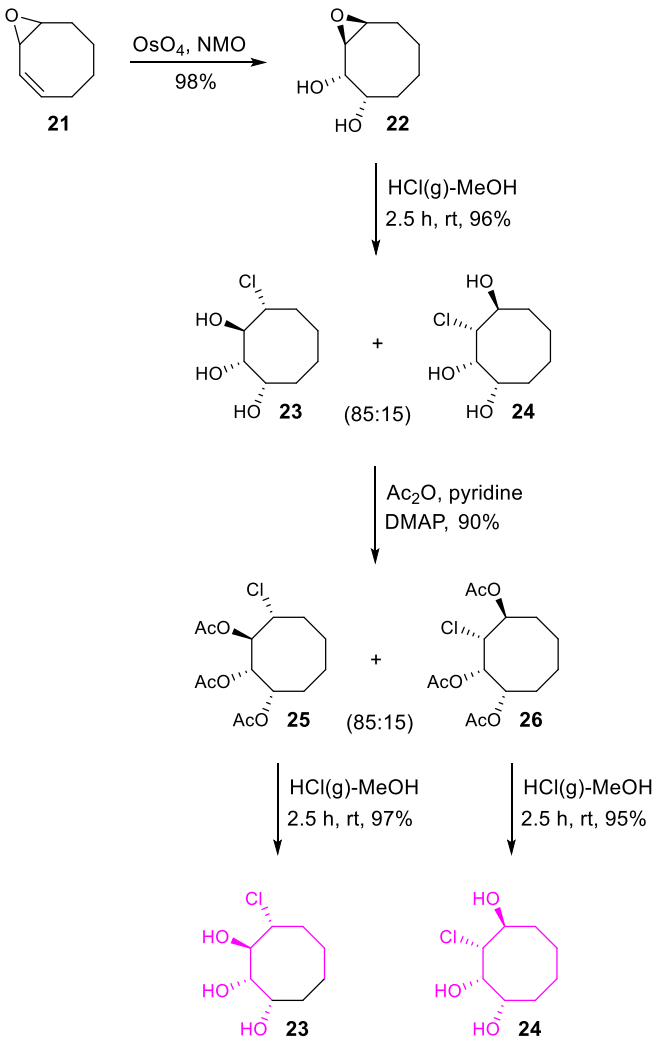
yield. Compound **16** was transformed into the corresponding triacetate **17** for full characterization of the structure (Scheme 3). The position of the azide group in **17** was determined with the help of the COSY spectrum. The diagonal peak at 3.95 ppm has cross peaks with the protons resonating at 4.96 and 5.47 ppm, respectively. Analysis of these cross peaks shows that cross peak at 5.47 ppm is weaker. This weak correlation is due to the small coupling constant (J = 2.2 Hz). On the other hand, the resonance signal of H-3 appears as a doublet of doublet at 3.95 ppm with coupling constants of J = 8.6 and 2.2 Hz. The large coupling constant (J = 8.6 Hz) clearly supports the *trans* relation of the protons H-3 and H-4 and the small coupling constant (J = 2.2 Hz) the *cis* relation of the protons H-3 and H-2. Finally, the desired aminocyclooctanetriol (**18**) was obtained by hydrogenation of the azide functionality in compound **16** in 97% yield.

In the second part of this work, we turned our attention to the stereospecific synthesis of chlorocyclooctanetriol (**19**) starting from the *trans*-epoxide **13** (Scheme 4). The hydroxyl groups in **19** were acetylated to give **20** for further characterization of the structure. The structure of **20** was assigned on the basis of ^{1}H NMR spectra. The position of the chloro atom was determined with the help of the COSY spectra.



Scheme 4: Synthesis of chlorocyclooctanetriol **20**.

As an alternate method for the synthesis of a novel chlorocyclooctanetriol isomer, epoxy-diol **22**, which was synthesized in our previous work [34], was hydrolysed by HCl(g) in MeOH, resulting in the formation of two chlorocyclooctanetriol isomers (**23** and **24**) in a 85:15 ratio (^{1}H NMR) in 90% combined yield (Scheme 5). Chlorotriols **23** and **24** were transformed into the corresponding triacetates (**25** and **26**) for full characterization of their structures. A mixture of isomeric triacetates (**25** and **26**) was isolated by column chromatography in 74% and 12% yields, respectively. The structures and configurations of these compounds were assigned using ^{1}H NMR and 2D NMR spectroscopic data. Finally, deacetylation of chlorotriacetates (**25** and **26**) was carried out with HCl(g) in MeOH to give the free chlorotriols derivatives **23** and **24**.



Scheme 5: Synthesis of chlorocyclooctanetriols **23** and **24**.

Conclusion

The synthesis of two stereoisomeric 3-aminocyclooctanetriols **12** and **18**, and their halocyclitol derivatives **14**, **19**, **23**, and **24** was achieved for the first time concisely and efficiently from *cis,cis*-1,3-cyclooctadiene. The nitrogen functionalities were introduced by the substitution with NaN_3 of the corresponding cyclic sulphate and

bromo groups while the halogen functionality was introduced to the molecule by opening of the epoxide ring with HBr(g) or HCl(g) in MeOH.

Experimental section

General information

Melting points are uncorrected. Infrared spectra were obtained from solution in 0.1 mm cells or KBr pellets on an FT-IR Mattson 1000 instrument. The ^{1}H and ^{13}C NMR spectra were recorded on 400 (100) MHz Varian or 400 (100) MHz Bruker spectrometer and are reported in d units with $SiMe_4$ as internal standard. Elemental analyses were carried out on a LECO's CHNS-932 instrument. Melting points were determined on a GallenKamp MPD 350. Column chromatography was performed on silica gel (60 mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminium plates.

7,8-Dioxabicyclo[4.2.2]dec-9-ene (5): Compound **5** was prepared as described in the literature [34].

***cis*-2-Cyclooctene-1,4-diol (6a):** Compound **6a** was prepared as described in the literature [34].

***cis*-1,4-Diacetoxy-2-cyclooctene (6b):** Compound **6b** was prepared as described in the literature [34].

(1*R*(*S*),2*R*(*S*),3*S*(*R*),4*S*(*R*))-2,3-Dihydroxycyclooctane-1,4-diyl diacetate (7): Compound **7** was prepared as described in the literature [34].

(2s,3a*R*(*S*),4*S*(*R*),9*R*(*S*),9a*S*(*R*))-2-oxidooctahydrocycloocta[d][1,3,2]dioxathiole-4,9-diyl diacetate (8): To a cooled at 0 °C, magnetically stirred solution of diacetate diol **7** (1.60 g, 6.15 mmol) and pyridine (1.46 g, 18.51 mmol) in CH_2Cl_2 (20 mL) was added a dichloromethane solution (5 mL) of thionyl chloride (2.20 g, 18.51 mmol) dropwise over a period of 10 min. Stirring was continued for 2 h at 0 °C and stirred at room temperature for 19 h (the reaction was followed by TLC). To the reaction mixture was

added water (25 ml) and extracted with ethyl acetate (4x30 mL). The combined organic extracts were washed with 1 N HCl solution (50 mL) and saturated $NaHCO_3$ solution (20 mL) and NaCl solution (20 mL). The organic solution was dried over Na_2SO_4. Evaporation of the solvents gave pure **8** (1.79 g, 95%). Sulphite **8** was recrystallized from CH_2Cl_2/n-hexane (9:1) as a colourless crystal; mp 146-147 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.30-5.20 (m, 2H, CH-OAc), 5.00-4.93 (m, 2H, CH-SO_3), 2.07 (s, 6H, 2xOAc), 2.06-1.48 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.1, 82.2, 69.6, 32.3, 22.6, 21.2; IR (KBr, cm^{-1}): 2951, 2877, 1744, 1465, 1451, 1429, 1374, 1323, 1235, 1205, 1029, 996, 969, 955. Anal. Calcd for $C_{12}H_{18}O_7S$ (306.08): C 47.05; H 5.92; S 10.47; found C 46.89; H 5.81; S 10.47.

(3a*R*(*S*),4*S*(*R*),9*R*(*S*),9a*S*(*R*))-2,2-dioxidooctahydrocycloocta[d][1,3,2]dioxathiole-4,9-diyl diacetate (9): The sulphite **8** (1.81 g, 5.91 mmol) was dissolved in CCl_4 (20 mL). To mixture was added $NaIO_4$ (1.90 g, 8.88 mmol) and acetonitrile (20 mL) and water (20 mL) and $RuCl_3.3H_2O$ (15 mg). The reaction mixture was stirred 2.5 h at room temperature. The mixture was extracted with ethyl acetate (4x30 mL). The organic solution was dried over Na_2SO_4. Evaporation of the solvents gave pure **9** (1.80 g, 95%). Sulphate **9** was recrystallized from CH_2Cl_2/n-hexane (9:1) as a colourless crystal; mp 130-131 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.52-5.41 (m, 2H, CH-OAc), 5.12-5.05 (m, 2H, CH-SO_4), 2.09 (s, 6H, 2xOAc), 2.09-1.46 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.6, 84.5, 69.5, 31.4, 22.6, 21.1; IR (KBr, cm^{-1}): 2950, 2900, 1753, 1477, 1390, 1232, 1106, 1030, 957. Anal. Calcd for $C_{12}H_{18}O_8S$ (322.07): C 44.72; H 5.63; S 9.95; found C 44.91; H 5.48; S 10.04.

(1*S*(*R*),2*S*(*R*),3*R*(*S*),4*R*(S))-3-azidocyclooctane-1,2,4-triol (10): A mixture of the sulphate **9** (1.00 g, 3.10 mmol) and NaN_3 (1.00 g, 15.38 mmol) in absolute DMF (10 mL) was stirred under nitrogen for 24 h at 80 °C. The mixture was cooled to room temperature and added THF (20 mL). Then concentrated H_2SO_4 (4 drop) and water (4 drop) were added to the stirred suspension. After 40 min $NaHCO_3$ (400 mg) was added and the reaction mixture was stirred for 40 min. Filtration through a Celite and silica gel bed and concentration of the filtrate under reduced pressure provided a viscous oil. Column chromatography (silica gel, 100 g) eluting with MeOH/CH_2Cl_2 (3:97) gave azidosulphate diacetate (0.8 g, 70%) as a white solid. Absolute methanol (10 mL)

containing 20% HCl gas was added into the azidosulphate diacetate (220 mg, 0.60 mmol). Mixture was stirred at room temperature for 2.5 h. Evaporation of solvent gave 118 mg (97% yield) of azidotriol **10** as a colourless oil. ^{1}H-NMR (400 MHz, D_2O): δ 4.07 (dt, *J* = 8.7, 2.3 Hz, 1H, H-4), 3.68-3.59 (m, 2H, H-1 and H-2), 3.59-3.52 (m, 1H, H-3), 1.90-1.30 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, D_2O): δ 73.4, 72.1, 70.0, 69.8, 31.8, 30.7, 23.6, 20.5; IR (KBr, cm^{-1}): 3407, 2934, 1420, 1365, 1264, 1230, 1068, 1038, 959.

Anal. Calcd for $C_8H_{15}N_3O_3$ (201.11): C 47.75; H 7.51; N 20.88; found C 47.76; H 7.35; N 20.71.

(1*S*(*R*),2*S*(*R*),3*R*(*S*),4*R*(*S*))-3-azidocyclooctane-1,2,4-triyl triacetate (11). General Procedure for the Acetylation of Hydroxyl Groups: In a similar manner as described in the literature [30], the azidotriol **10** (280 mg, 1.39 mmol) was dissolved in anhydrous pyridine (3 mL) and the solution was cooled 0 °C. Ac_2O (0.7 mL, 8.35 mmol) and 4-(dimethylamino)pyridine (DMAP) (2.8 mg) were added and the solution was stirred for 2.5 day at room temperature. The mixture was cooled to 0 °C and 2 N HCl (70 mL) solution was added. The mixture was extracted with ether (6x30 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (70 mL) and water (3x10 mL) and then dried (Na_2SO_4). After evaporation of solvent, chromatography of the mixture on a silica gel column eluting with EtOAc/n-hexane (3:97) gave 350 mg (76%) of triacetate **11** as a colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.24-5.15 (m, 2H, H-4 and H-2), 5.04-4.97 (m, 1H, H-1), 3.87 (dd, *J* = 8.8, 2.7 Hz, 1H, H-3), 2.06 (s, 3H), 2.05 (s, 3H) 1.98 (s, 3H), 2.10-1.58 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.1, 170.0, 169.8, 72.7, 72.1, 71.3, 65.6, 31.2, 28.6, 23.5, 21.8, 21.1, 21.0, 20.8; IR (KBr, cm^{-1}): 2941, 2870, 2106, 1744, 1433, 1371, 1238, 1028, 974, 906. Anal. Calcd for $C_{14}H_{21}N_3O_6$ (327.14): C 51.37; H 6.47; N 12.84; found C 51.52; H 6.52; N 12.99.

(1*S*(*R*),2*S*(*R*),3*R*(*S*),4*R*(*S*))-3-aminocyclooctane-1,2,4-triol (12). General Procedure for Hydrogenation: In a similar manner as described in the literature [30], into a 50 mL flask was placed palladium on charcoal (30 mg, 10%) and azidotriol **10** (250 mg, 1.24 mmol) in absolute methanol (30 mL). The reaction mixture was flushed with hydrogen gas (the air in the solvent was removed under vacuum, and then the flask was filled with

hydrogen gas; this process was repeated three times). The resulting mixture was stirred at room temperature for 2 h under the hydrogen atmosphere. The catalyst was removed by filtration. Evaporation of the solvent gave pure aminotriol **12** (207 mg, 95%) as a colourless viscous oil. ^{1}H-NMR (400 MHz, CD_3OD): δ 3.99-3.91 (m, 1H, H-4), 3.75 (t, *J* = 8.4, 1H, H-2), 3.54-3.47 (m, H-1), 3.08 (dd, *J* = 7.9, 2.8 Hz, H-3), 1.96-1.34 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, CD_3OD): δ 74.8, 69.8, 69.5, 55.1, 30.2, 30.1, 21.7, 20.8; IR (KBr, cm^{-1}): 3390, 2935, 1466, 1386, 1123, 1037. Anal. Calcd for $C_8H_{17}NO_3$ (175.12): C 54.84; H 9.78; N 7.99; found C 54.74; H 9.71; N 7.88.

(1*R*(*S*),2*S*(*R*),7*R*(*S*),8*S*(*R*))-9-oxabicyclo[6.1.0]nonane-2,7-diol (13): Compound **13** was prepared as described in the literature [34].

(1*S*(*R*),2*R*(*S*),3*R*(*S*),4*R*(*S*))-3-bromocyclooctane-1,2,4-triol (14): Absolute methanol (25 mL) containing 35% HBr gas was added into *trans*-epoxide **13** (1.30 g, 8.22 mmol) and stirred at 0 °C for 30 min. Then, the reaction mixture was stirred for 19 h at room temperature. After removal of the solvent, crude product was dissolved in 25 mL of methanol and added into excess $BaCO_3$ (10 g) for neutralization (pH = 8), and stirred magnetically at room temperature for 4 h. The solvent was removed under reduced pressure and the residue was dissolved in acetone and stirred for 5 min. The solid was filtered off. Evaporation of the solvent gave bromotriol **14** (1.89 g, 96%) as a colourless oil. ^{1}H-NMR (400 MHz, CD_3OD): δ 4.25 (dd, *J* = 8.7, 2.2 Hz, 1H, H-3), 4.05-3.97 (m, H-4), 3.93 (t, *J* = 8.6 Hz, 1H, H-2), 3.76-3.64 (m, H-1), 2.00-1.40 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, CD_3OD): δ 76.6, 71.5, 69.1, 68.1, 35.1, 33.2, 23.3, 21.8; IR (KBr, cm^{-1}): 3418, 2986, 2930, 2866, 1456, 1371, 1216, 1171, 1055, 1019, 949. Anal. Calcd for $C_8H_{15}BrO_3$ (238.02): C 40.19; H 6.32; found C 40.09; H 6.40.

(1*S*(*R*),2*R*(*S*),3*R*(*S*),4*R*(*S*))-3-bromocyclooctane-1,2,4-triyl triacetate (15): The bromotriol **14** (3.0 g, 12.55 mmol) was submitted to acetylation with Ac_2O and DMAP in pyridine following the method described above for the acetylation of **10** to give **15**: 3.75 g, 81%. Bromotriacetate **15** was recrystallized from CH_2Cl_2/hexane as colourless crystals; mp 92-94 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.46 (t, *J* = 9.0 Hz, 1H, H-2), 5.21-5.15 (m, 1H, H-4), 5.07 (ddd, *J* = 8.5, 7.3, 3.9 Hz, 1H, H-1), 4.42 (dd, *J* = 9.3, 2.4 Hz, 1H, H-3), 2.08 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.99-1.58 (series of m, 8H, CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.2, 169.8, 169.7, 74.3, 71.8, 71.0, 57.3, 31.8, 30.5, 23.3, 21.9, 21.3, 21.0, 20.8; IR (KBr, cm^{-1}): 2938, 2882, 1743, 1469, 1447, 1380, 1233, 1090, 1033, 975. Anal. Calcd for $C_{14}H_{21}BrO_6$ (364.05): C 46.04; H 5.80; found C 46.06; H 5.66.

(1*S*(*R*),2*S*(*R*),3*S*(*R*),4*R*(*S*))-3-azidocyclooctane-1,2,4-triol (16): To a magnetically stirred solution of **15** (1.26 g, 5.27 mmol) in DMF (15 mL) to the mixture was added NaN_3 (2.74 g, 42.16 mmol) and the mixture heated to 100 °C and was stirred at 100 °C for 28 h. The reaction mixture was filtered with methanol through a pad of silica gel in a sintered glass funnel. After evaporation of the solvents, chromatography of the mixture on a silica gel (100 g) column eluting with MeOH/CH_2Cl_2 (4:96) gave the azidotriol **16** (0.83 g, 78%) as a colourless oil. ^{1}H-NMR (400 MHz, D_2O): δ 3.90 (dd, *J* = 8.7, 2.5 Hz, H-2), 3.88-3.76 (m, 2H, H-1 and H-4), 3.69 (dd, *J* = 9.2, 2.5 Hz, 1H, H-3), 1.96-1.48 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, D_2O): δ 74.9, 72.4, 71.7, 70.0, 32.5, 31.4, 23.8, 23.2; IR (KBr, cm^{-1}): 3399, 2932, 2872, 2114, 1453, 1416, 1359, 1260, 1161, 1092, 1053, 1001, 982. Anal. Calcd for $C_8H_{15}N_3O_3$ (201.11): C 47.75; H 7.51; N 20.88; found C 47.60; H, 7.41; N 20.79.

(1*S*(*R*),2*S*(*R*),3*S*(*R*),4*R*(*S*))-3-azidocyclooctane-1,2,4-triyl triacetate (17): The azidotriol **16** (200 mg, 0.99 mmol) was submitted to acetylation with Ac_2O and DMAP in pyridine following the method described above for the acetylation of **10** to give **17**: 243 mg, 74%; as a colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.47 (dd, $J_{2,1}$ = 9.4 Hz, $J_{2,3}$ = 2.2 Hz, 1H, H-2), 5.28-5.21 (m, 1H, H-1), 4.96 (t, *J* = 7.8 Hz, 1H, H-4), 3.95 (dd, *J* = 8.6 Hz, $J_{3,2}$ = 2.2 Hz, H-3), 2.10 (s, 6H, 2xOAc) 2.02 (s, 3H, OAc) 2.10-1.55 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.0, 169.9, 169.7, 75.3, 72.6, 71.9, 65.4, 30.3, 28.4, 24.6, 21.7, 21.1, 21.0, 20.7; IR (KBr, cm^{-1}): 2943, 2887, 2118, 1742, 1472, 1445, 1371, 1253, 1201, 1094, 1033 960. Anal. Calcd for $C_{14}H_{21}N_3O_6$ (327.14): C 51.37; H, 6.47; N, 12.84; found C 51.43; H, 6.33; N, 12.73.

(1*S*(*R*),2*S*(*R*),3*S*(*R*),4*R*(*S*))-3-aminocyclooctane-1,2,4-triol (18): The azidotriol **16** (200 mg, 0.99 mmol) was hydrogenated with Pd (10% on activated carbon; 25 mg) as described above for the synthesis of **12** to give aminotriol **18** (170 mg, 97%); as a colourless oil. ^{1}H-NMR (400 MHz, D_2O): δ 3.74 (ddd, *J* = 8.2, 6.6, 1.4 Hz, 1H, H-1), 3.61 (dd, *J* = 8.8, $J_{2,3}$ = 2.7 Hz, 1H, H-2), 3.60-3.54 (m, 1H, H-4) 2.90 (dd, $J_{3,4}$ = 9.4,

$J_{3,2}$ = 2.7 Hz, 1H, H-3), 1.90-1.32 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, D_2O): δ 76.5, 73.4, 72.8, 56.7, 32.9, 32.2, 24.7, 23.3; IR (KBr, cm^{-1}): 3390, 2935, 1466, 1386, 1123, 1037. Anal. Calcd for $C_8H_{17}NO_3$ (175.12): C 54.84; H 9.78; N 7.99; found C 54.74; H 9.66; N 7.89.

(1*S*(*R*),2*R*(*S*),3*R*(*S*),4*R*(*S*))-3-chlorocyclooctane-1,2,4-triol (19): To a magnetically stirred solution of the *trans*-epoxide **13** (2.0 g, 12.64 mmol) in absolute methanol (5 mL) was cooled to 0 °C. Then, absolute methanol (30 mL) containing 20% HCl gas was added into the reaction mixture and stirred at room temperature for 19 h. Evaporation of the solvent under reduced pressure and crystallization of the residue from MeOH/ether (8:2) gave chlorotriol **19** as colourless crystals (2.37 g, 96%), mp 117-119 °C. ^{1}H-NMR (400 MHz, D_2O): δ 4.14 (dt, J = 9.0, $J_{3,4}$ = 2.8 Hz, H-4), 4.07 (dd, J = 8.6, $J_{3,4}$ = 2.8 Hz, H-3), 3.74 (t, J = 8.8 Hz, H-2), 3.60 (ddd, J = 9.3, 5.7, 4.0 Hz, H-1), 1.90-1.34 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, D_2O): δ 74.8, 71.8, 71.4, 69.4, 33.0, 31.2, 23.6, 20.9; IR (KBr, cm^{-1}): 3292, 2934, 2875, 1459, 1402, 1322, 1295, 1256, 1234, 1215, 1144, 1040, 975. Anal. Calcd for $C_8H_{15}ClO_3$ (194.07): C 49.36; H 7.77; found C 49.42; H 7.75.

(1*S*(*R*),2*R*(*S*),3*R*(*S*),4*R*(*S*))-3-chlorocyclooctane-1,2,4-triyl triacetate (20): The chlorotriol **19** (2.5 g, 12.84 mmol) was submitted to acetylation with Ac_2O and DMAP in pyridine following the method described above for the acetylation of **10** to give **20**: 3.76 g, 91%. Chlorotriacetate **20** was recrystallized from CH_2Cl_2/hexane (9:1) as colourless crystals, mp 75-76 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.39 (t, J = 8.8 Hz, H-2), 5.35 (dt, J = 9.7, $J_{3,4}$ = 2.5 Hz, H-4), 5.12-5.06 (m, H-1), 4.35 (dd, J = 9.0, $J_{3,4}$ = 2.5 Hz, H-3), 2.11 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 2.20-1.57 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.3, 169.8, 169.8, 74.3, 71.4, 71.3, 64.1, 31.7, 29.1, 23.3, 21.9, 21.2, 21.0, 20.8; IR (KBr, cm^{-1}): 3292, 2934, 2875, 1459, 1402, 1322, 1295, 1256, 1215, 1144, 1097, 1040, 975, 948. Anal. Calcd for $C_{14}H_{21}ClO_6$ (320.10): C 52.42; H 6.60; found C 52.47; H 6.49.

Acetylation and reaction of epoxy-diol 22 with HCl(g)-MeOH: To a magnetically stirred solution of epoxy-diol **22** (500 mg, 3.16 mmol) in absolute methanol (5 mL) was cooled to 0 °C. Then, Absolute methanol (15 mL) containing 40% HCl gas was added

into the reaction mixture and stirred at room temperature for 2.5 h. Evaporation of the solvent gave a mixture of chlorotriol **23** and chlorotriol **24** (590 mg, total yield 96%). From ^{1}H NMR spectroscopy, it was observed that the mixture of **23** and **24** was in a 85:15 ratio. But these isomers could not be obtained in pure form, although all chromatographic purification methods were employed. Then, 450 mg (2.31 mmol) of the resultant mixture was submitted to acetylation with Ac_2O and DMAP in pyridine following the method described above for the acetylation of **10** to give a mixture of the diacetate isomer (670 mg), total yield 90%. Chromatography of the mixture on a silica gel column (80 g) eluting with EtOAc/hexane (10:90) gave the first fraction of chlorotriacetate **26** (90 mg, 12%, as a colourless oil) and the second chlorotriacetate **25** (0.55 g, 74%, as a colourless oil).

(1*S*(*R*),2*S*(*R*),3*R*(*S*),4*R*(*S*))-4-chlorocyclooctane-1,2,3-triyl triacetate (25): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.62 (dd, *J* = 9.7, 8.1 Hz, H-3), 5.25 (dt, *J* = 7.3, $J_{1,2}$ = 2.3 Hz, H-1), 5.05 (dd, *J* = 8.0, $J_{1,2}$ = 2.3 Hz, H-2) 4.26 (ddd, *J* = 13.1, 8.7, 3.3 Hz, H-4), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.25-1.50 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.2, 169.7, 169.0, 71.9, 71.4, 70.6, 62.3, 30.0, 27.5, 21.5, 20.9, 20.5, 20.5, 19.8; IR (KBr, cm^{-1}): 2942, 2863, 1747, 1434, 1372, 1251, 1053, 966. Anal. Calcd for $C_{14}H_{21}ClO_6$ (320.10): C 52.42; H 6.60; found C 52.53; H 6.70.

(1S(R),2S(R),3R(S),4S(R))-3-chlorocyclooctane-1,2,4-triyl triacetate (26): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.71 (t, *J* = 2.3 Hz, H-2), 5.25-5.18 (m, H-4) 5.15-5.09 (m, H-1) 4.34 (dd, *J* = 9.5, 1.9 Hz, H-3), 2.18 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.00-1.34 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.2, 169.9, 169.7, 75.5, 74.0, 73.6, 62.5, 29.7, 27.1, 22.7, 22.2, 21.0, 21.0, 20.7; IR (KBr, cm^{-1}): 2937, 1740, 1645, 1435, 1370, 1239, 1092, 1035, 963. Anal. Calcd for $C_{14}H_{21}ClO_6$ (320.10): C 52.42; H 6.60; found C 52.30; H 6.64.

(1*R*(*S*),2*R*(*S*),3*S*(*R*),4*S*(*R*))-4-chlorocyclooctane-1,2,3-triol (23): To a magnetically stirred solution of chlorotriacetate **25** (200 mg, 0.62 mmol) in absolute methanol (3 mL) was cooled to 0 °C. Then, Absolute methanol (15 mL) containing 20% HCl gas was added into the reaction mixture and stirred at room temperature for 2.5 h. Evaporation of the solvent gave chlorotriol **23** (118 mg, yield 97%). The chlorotriol **23** was recrystallized from CH_2Cl_2/hexane (9:1) as colourless crystals, mp 107-108 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.03-3.96 (m, H-1), 3.89 (dt, *J* = 7.8, 2.6 Hz, H-4), 3.85

(dd, J = 9.6, $J_{3,2}$ = 7.9 Hz, H-3) 3.54 (dd, $J_{2,3}$ = 7.9, 2.7 Hz, H-2), 2.00-1.20 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 72.5, 72.0, 71.2, 67.9, 30.5, 28.9, 21.5, 20.3; IR (KBr, cm^{-1}): 3400, 2925, 2878, 2863, 2731, 1467, 1458, 1392, 1372, 1284, 1267, 1221, 1067, 980, 959. Anal. Calcd for $C_8H_{15}ClO_3$ (194.07): C 49.36; H 7.77; found C 49.43; H 7.66.

(1*R*(*S*),2*R*(*S*),3*S*(*R*),4*R*(*S*))-3-chlorocyclooctane-1,2,4-triol (24): The chlorotriacetate **26** (300 mg, 0.93 mmol) was submitted to hydrolysis with HCl(g)-MeOH following the method described above for the hydrolysis of **25** to give **24**: 173 mg, 95%, as a colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.17 (dd, J = 3.0, 1.6 Hz, H-2), 4.04 (dd, $J_{3,4}$ = 9.2, J = 1.4 Hz, H-3), 3.92-3.86 (m, H-4), 3.64 (dt, J = 11.9, 3.6 Hz, 1H), 2.00-0.95 (series of m, 8H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 75.7, 74.5, 74.4, 69.7, 30.9, 28.4, 22.8, 21.9; IR (KBr, cm^{-1}): 3410, 2983, 2934, 1466, 1370, 1254, 1218, 1163, 1121, 1051, 961. Anal. Calcd for $C_8H_{15}ClO_3$ (194.07): C 49.36; H 7.77; found C 49.26; H 7.69.

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds, as well as selected 2D NMR spectra are provided. Supplementary data associated with this article can be found in the online version, at http://.....

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