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A concise and stereospecific synthesis of some cyclitols containing eight-membered rings: cyclooctane-1,2,3,4-tetraoles

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Dedicated to Professor Metin Balci on the occasion of his 62nd birthday

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ABSTRACT

A concise and efficient synthesis of cyclooctane-1,2,3,4-tetraoles, new polyhydroxylated eight-membered carbocycles, is described starting from *cis*,*cis*-1,3-cyclooctadiene. Cyclooctene endoperoxide obtained by photooxygenation of *cis*,*cis*-1,3-cyclooctadiene was the key compound in the synthesis. Reduction of the endoperoxide with zinc or thiourea followed by acetylation of the hydroxyl group and OsO_4/NMO oxidation of the double bond gave (1*R*(*S*),2*S*(*R*),3*R*(*S*),4*S*(*R*))-cyclooctane-1,2,3,4-tetraol. Interestingly, epoxidation of cyclooctene-1,4-diol with *m*-CPBA also afforded *trans*-epoxy-diol **17**. (1*R*(*S*),2*R*(*S*),3*R*(*S*),4*S*(*R*))-cyclooctane-1,2,3,4-tetraol was easily obtained by hydrolysis of epoxy-diol **17**.

1. Introduction

Cyclitol has been used as a generic term to describe polyhydroxycycloalkanes. This class of compounds has received high interest due to the fact that many biologically important molecules and natural products contain a polyhydroxylated carbocycle.[1,2] Several cyclitols have been used as sweeteners, antibiotics, antiviral, antidiabetes, and anticancer agents.[3] Many inositols (**1**) and their derivatives (**2**–**4**) have been synthesized and particularly evaluated for their biological activities, especially glycosidase inhibition.[4,5] More recently, attention has been increasingly accorded to seven- and eight-membered ring systems[5] in order to study the effect of the enhanced flexibility and of the new spatial distribution displayed by these structures on their adaptability in the active site of the enzyme. An advantageous feature of the cycloheptane and cyclooctane polyols is that they offer opportunities for new distributions of hydroxyl functionalities for biological interactions in a conformationally flexible environment compared to the classical conformations present in **2**.[5d,e] For this purpose, nine-membered carbasugar analogs (cyclononitols) **7** have been described in a recent paper[6] for the first time.

Various methods are already available for the construction of functionalized five- and six-membered rings from sugars but only a few approaches have been reported for the synthesis of seven- and eight-membered ring cyclitols.[2] In our previous study,[7] we successively used 1,4-cyclohexadiene for stereospecific synthesis of DL-*proto*-Quercitol, DL-*gala*-Quercitol and *vibo*-Quercitol, which are cyclohexanepentol (**3**) stereoisomers.

Cyclooctanetetraols can exist in six possible diastereoisomeric forms. So far, only two diastereoisomeric forms have been synthesized by different methods. The first synthesis of cyclooctanetetrol was accomplished by Gypser et al.[8] using phenylboronic acid, *N*-methylmorpholine *N*-oxide (NMO), and osmium tetroxide in anhydrous solvent starting from *cis*,*cis*-1,3-cyclooctadiene. The second synthesis was performed by Sinaÿ et al.s[2,9] using the ring-closing metathesis starting from D-arabinose.

In this paper, we describe a concise synthetic route to new cyclooctanoic carbasugar analogs **6**.

2. Results and discussion

Cyclooctene endoperoxide **9** is the key compound for our studies. For the study's purpose, *cis*,*cis*-1,3-cyclooctadiene (**8**) was submitted to photooxygenation in the presence of tetraphenylporphyrine (TPP) as sensitizer to form bicyclic endoperoxide **9**[10] (Scheme 1).

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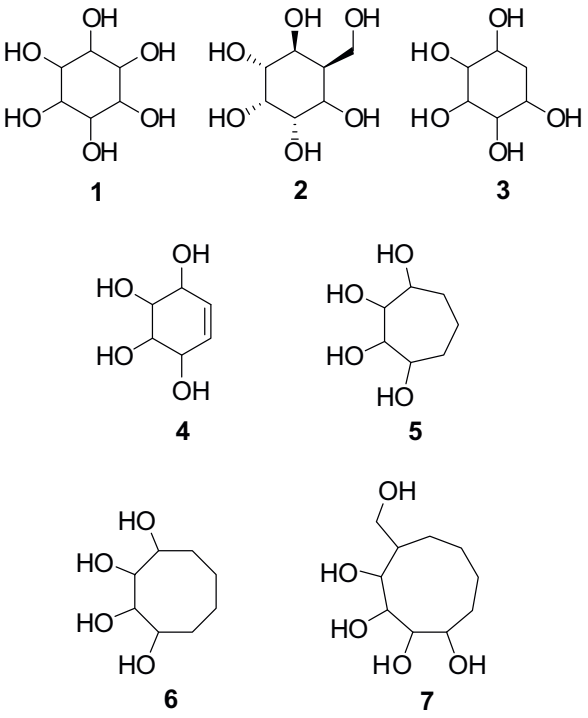
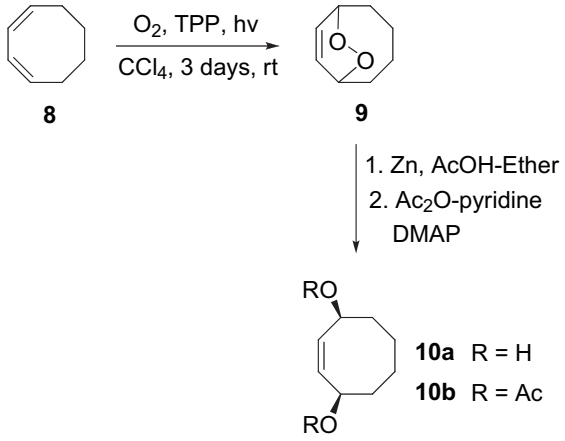
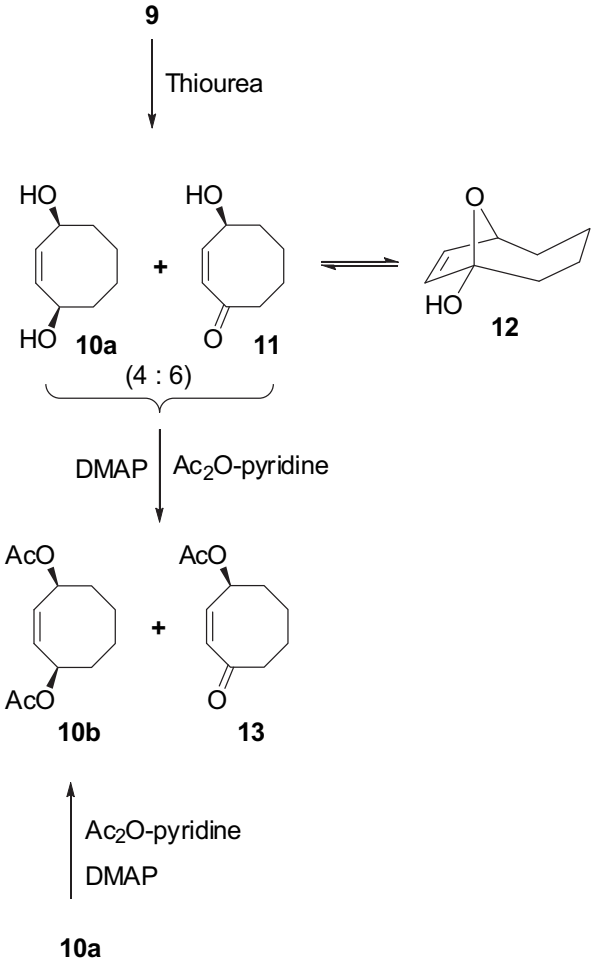


Our initial approach to synthesize the cyclooctanetetraols was based on the reduction of the peroxide linkage in **9**. Peroxide linkage is highly susceptible to reductive cleavage by a variety of reductants,[11] such as Zn/AcOH, thiourea or $LiAlH_4$. Endoperoxide **9** was readily reduced by Zn/AcOH to corresponding *cis*-diol **10a**[10c,12] at room temperature.[11,13] The acetylation of the cyclooctene-1,4-diol (**10a**) with an excess of acetic anhydride in pyridine and 4-(dimethylamino)pyridine (DMAP) resulted in the formation of diacetate[12a] **10b** in 90% yield (Scheme 1). The spectral data of **10a** and **10b** were identical with those reported in the literature[12] by a different synthetic procedure (Scheme 1).



Scheme 1.

The reduction of **9** by thiourea afforded the mixture of unsaturated oxabicycle **12** and the cyclooctene-1,4-diol (**10a**) in a 6:4 ratio (from ^{1}H NMR), respectively (Scheme 2). Similar hydroxyketone/cyclic hemiketale tautomerism[10d,14] has also been observed in the treatment of endoperoxide **9** with triethylamine.[10a] The structure of compound **12** was assigned by ^{1}H and ^{13}C NMR. The spectral data of **12** was identical with those reported in the literature[14a] (Scheme 2). For further structural proof, the mixture of **10a** and **12** was converted to the corresponding acetates, **10b**, and **13**, which were fully characterized from the spectroscopic data.

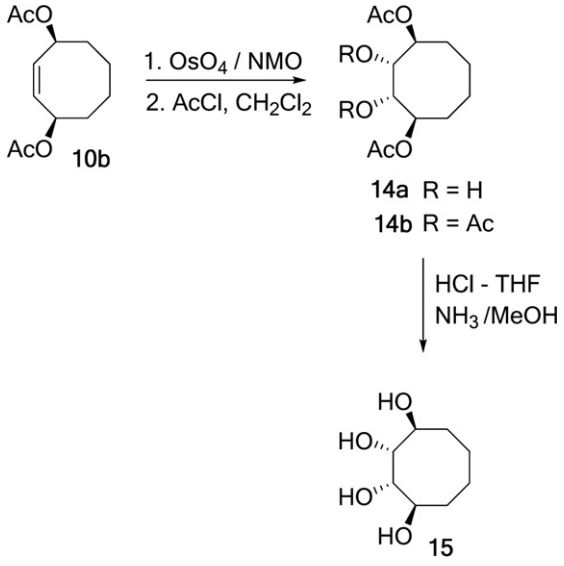


Scheme 2.

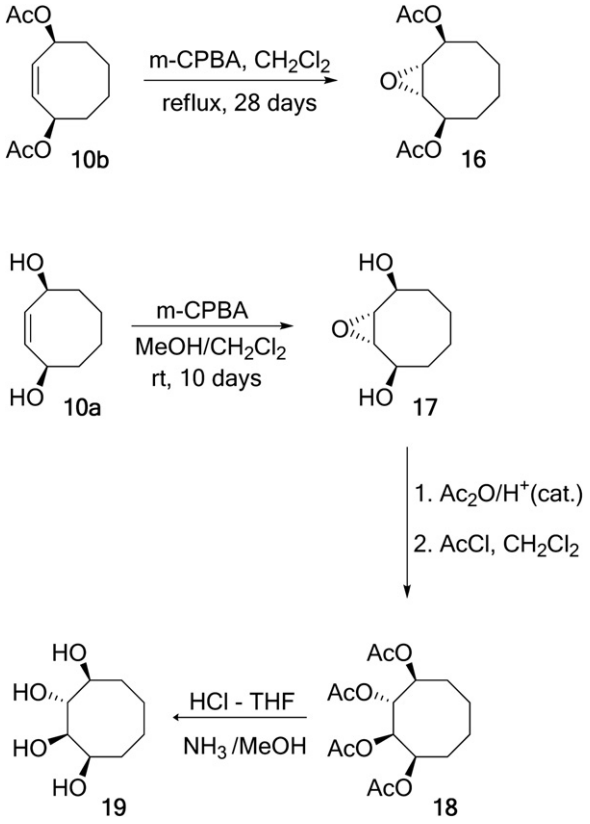
After characterization of **10b**, we turned our attention to the synthesis of symmetrical cyclooctane-1,2,3,4-tetraol. Cyclooctene-diacetate **10b** is an ideal substrate for the synthesis of both cyclooctanetetraols and aminocyclooctanetriols. To introduce two further hydroxyl groups in a cis configuration, we treated diacetate **10b** with catalytic amounts of OsO_4[15] and *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant to give **14a**. Then, the formed diacetoxy diol **14a** (78% yield) was converted to the acetate derivative **14b** as the sole product (95% yield) for further characterization (Scheme 3).

Careful examination of all the reaction mixture did not reveal the formation of any other isomers. The acetyl groups in (1,4/2,3)-cyclooctanetetraacetate (**14b**) were removed using 10% HCl in THF and NH_3/MeOH to give (1,4/2,3)-cyclooctanetetraol (**15**) (98% yield) (Scheme 3). The structures of **14b** and **15** were assigned by double resonance, COSY, NOESY, and ^{13}C NMR data.

The two of acetoxyl protons of **14b** resonate at δ 5.42 and 5.12. On the other hand, acetoxyl carbons resonate at δ 72.9, giving only one broad peak, instead of the expected two peaks. Methylenic carbons also give two distinct broad peaks at δ 29.5 and 23.5. The most noteworthy feature of the peaks is their unusual peak heights and the peak height at δ 29.5 is farther than those at δ 23.5. These values are in agreement with the twist-boat-chair conformation described for eight-membered rings.[16] The broadening of spectral lines were most probably caused by this dynamic process of cyclooctene ring. As known in the literature,[16] the best stable conformation of 1,3-



Scheme 3.



Scheme 4.

cyclooctadiene is the twist-boat-chair. Pseudorotation in conformation of 1,3-cyclooctadiene contributes to the line-shape changes and thus peaks are broadened. On the contrary, the ^{13}C NMR spectrum of tetraol **15** does not show any observable dynamic NMR effect when the bulky acetoxyl groups of **14b** are removed and the spectrum consists of two groups of signals, which are assigned to two alkoxy carbons (δ 76.0, 72.5) and two methylenic carbons (δ 31.7, 23.8). This ^{13}C NMR spectral data are also in agreement with the proposed structure.

The formation of **14a** from **10b** as a sole product can be explained by considering the sterical effects. Since the *cis*-face of the cyclooctene double bond is blocked by cyclooctene ring, OsO_4 approaches to the double bond in **10b** preferentially from the sterically less crowded face of the molecule (Scheme 3).

As it is well known, epoxidation followed by hydrolysis is used for *trans*-hydroxylation of an alkene double bond. Because **10a** and **10b** also include double bonds, they can be subjected to *trans*-hydroxylation by this approach. For this purpose, oxidation of diacetate **10b** with *m*-chloroperbenzoic acid (*m*-CPBA) gave expected *trans*-epoxide isomer **16** (60% yield) as the sole product (Scheme 4). Interestingly, oxidation of diol **10a** with *m*-chloroperbenzoic acid (*m*-CPBA) gave unexpected *trans*-epoxide isomer **17** (79% yield) as the sole product (Scheme 4). The epoxide protons of both **16** and **17** resonate as multiplet. The ^1H NMR spectra of these epoxides (**16** and **17**) are fully in agreement with the proposed structures.

As seen in the optimized geometry of diol **10a** (Fig. 1) *syn*[†]-face of the cyclooctene double bond is more blocked by the methylenic protons than the *anti*-face. Therefore, the sterically hindering effect of methylenic protons is observed in the *syn*-face. For this reason, for the formation of this interesting epoxide, we assume that *m*-chloroperbenzoic acid[17] (*m*-CPBA) approaches to the double bond preferentially from the sterically less crowded *anti*-face of the molecule.

An X-ray analysis of the epoxy-diol **17** confirmed the structural assignment for compound **19**, in particular the absolute configuration at C-2 (Fig. 2). The X-ray diffraction analysis of epoxy-diol **17** revealed the exact configuration of the compound and provided further information about the structural assignment for compound **19**. The molecular structure of compound **17** with the atom labeling is shown in Figure 2. Compound **17** crystallizes in the monoclinic space group *P*21/c (no: 14), with four molecules in the unit cell. All the *cis*- and *trans*-stereochemistry of the –OH and epoxy moieties was determined unequivocally as shown in Figure 2a. Cyclooctane has twisted boat-chair (BC) conformation (torsion angles for C5/C4/C2/C1 and C5/C1/C8/C6 planes are 7.5° and 20.9°, respectively). X-ray diffraction measurements on several solid cyclooctane derivatives and related compounds favor the boat-chair conformation in a majority of cases.[18]

Treatment of the epoxy-diol **17** with acetic anhydride and dilute aqueous acid (cat.) gave a regioselective ring opening of the epoxide to afford, after acetylation, **18** as the sole product (91% yield) (Scheme 4). The ^1H NMR spectrum of **18** consists of four singlets δ 2.05–1.99 (OAc protons), multiplets δ 1.90–1.53 (methylenic protons). One of the OC–H protons of **18** resonating at δ 5.47 and the other one resonating at δ 5.25–5.15 gave multiplet. ^{13}C NMR spectral data are also in agreement with the proposed structure.

Finally, the deacetylation of **18** as described above afforded (±)-(1,2,4/3)-cyclooctanetetraol (**19**) (98% yield) (Scheme 4). The

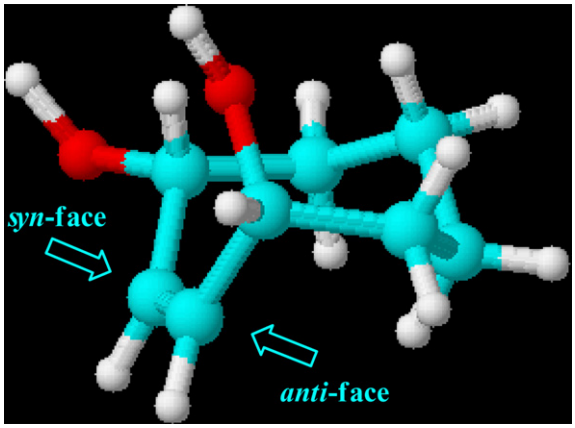


Figure 1. Optimized geometry for diol **10a**.

[†] In relation to the hydroxyl groups

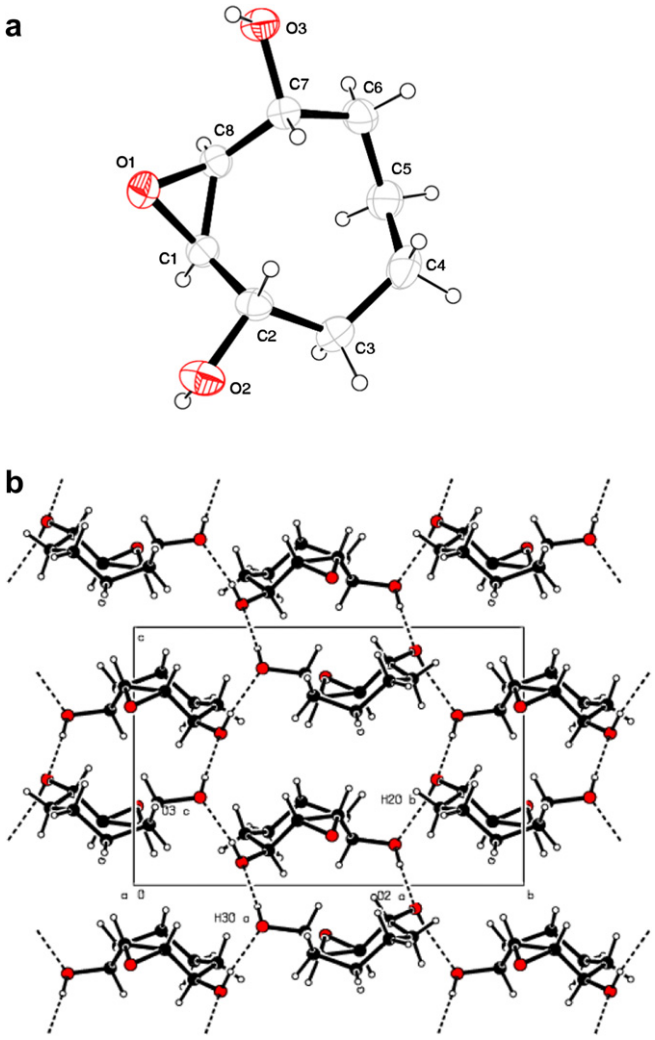


Figure 2. a) The molecular structure of compound epoxy-diol **17** showing the atom numbering scheme. Thermal ellipsoids are drawn at the 40% probability level. (b) The molecular packing of **17**. H-bonding geometry with the unit cell view down the *a*-axis. O(3)–H(3O)···O(2)^{a}=2.717(3) Å, O(3)–H(3O)···O(2)^{a} 176°; O(2)–H(2O) ···O(3)^{c}=2.735(3) Å, O(2)–H(2O) ···O(3)^{c}=167°, Symmetry codes: (a)=1−*x*,1−*y*,−*z*; (c)=1−*x*,−1/2+*y*,1/2−*z*.

structure of **19** was assigned by double resonance, ^{1}H and ^{13}C NMR data.

3. Conclusion

We have described here the stereospecific synthesis of some cyclitols containing eight-membered rings: (1,4/2,3)-Cyclooctanetetraol (**15**) and (±)-(1,2,4/3)-cyclooctanetetraol (**19**) starting from the easily available *cis*,*cis*-1,3-cyclooctadiene, with a concise, efficiency, and high chemical yields. Interestingly, epoxidation of cyclooctene-1,4-diol (**10a**) with *m*-chloroperbenzoic acid (*m*-CPBA) also gave unexpected *trans*-2,3-epoxy-cyclooctane-1,4-diol (**17**). Further studies of the chemistry of the double bond in **10b** and **8** directed toward the synthesis of other cyclooctanetetraols and aminocyclooctanetriols are currently in progress.

4. Experimental section

4.1. General

Melting points were determined on a Buchi 539 capillary melting apparatus and 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 200 (50) and 400 (100) MHz Varian spectrometer and are reported in d units with $SiMe_4$ as internal standard. HRMS spectra were obtained on a Bruker microTOF-Q instrument. Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyzer. 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 aluminum plates.

*4.1.1. 7,8-Dioxabicyclo[4.2.2]dec-9-ene (**9**).* To a stirred solution of *cis*,*cis*-1,3-cyclooctadiene (**8**) (1.00 g, 9.26 mmol) in 230 mL of CCl_4 was added 20 mg of tetraphenylporphyrin (TPP). The resulting mixture was irradiated with a projection lamp (500 W) while oxygen was being passed through solution and the mixture was stirred for 3 days at room temperature. The solvent was rotoevaporated (at 30 °C, 20 mmHg), giving an oil, which was purified by a silica gel column (35 g) chromatography (ether/hexane 40:60) to yield (**9**) (1.23 g, 95%, lit.[10d] 52%, lit.[10c] 53%, lit.[10b] 26%) as a pale yellow oil. ^{1}H NMR[10d,14a] (400 MHz, $CDCl_3$): δ 6.09–6.06 (m, AA′ part of AA′XX′ system, 2H, CH=CH), 4.70–4.64 (m, XX′ part of AA′XX′ system, 2H, bridgehead H), 2.08–1.45 (series of m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 33.4, 76.7, 128.3.

*4.1.2. cis-2-Cyclooctene-1,4-diol (**10a**).*

*4.1.2.1. By reduction of **9** with activated zinc.* Endoperoxide **9** of 1.00 g (7.14 mmol) was dissolved in 25 mL of ether at 0 °C. To the magnetically stirred mixture was added 2 mL glacial AcOH and 2.0 g (30.77 mmol) zinc. The reaction mixture was stirred at room temperature for 3 days and then the solids were removed by filtration. The solvents were rotoevaporated (40 °C, 20 mmHg), and the residue was purified by column chromatography on silica gel elution with methanol. Evaporation of the solvent gave diol **10a** (0.96 g, 95%): colorless plates; mp 157–160 °C from absolute methanol (lit.[12a] 154–156 °C, lit.[12b] 51%, 159.5–160 °C, lit.[12c] 15%, 154 °C). ^{1}H NMR (400 MHz, D_2O): δ 5.42–5.32 (m, AA′ part of AA′XX′ system, 2H, CH=CH), 4.46–4.39 (m, XX′ part of AA′XX′ system, 2H, OCH), 1.80–1.68 (m, 2H), 1.41–1.26 (m, 6H). ^{13}C NMR (100 MHz, D_2O): δ 23.1, 37.6, 68.9, 132.3.

*4.1.2.2. By reduction of **9** with thiourea.* To a magnetically stirred slurry of 1.09 g (14.27 mmol) of thiourea in 25 mL of methanol was added a solution of 2.00 g (14.27 mmol) of endoperoxide **9** in 100 mL of methanol at 0 °C. After 2 h of stirring at 0 °C, the reaction mixture was stirred at room temperature for 4 days. The solids were removed by filtration, methanol was rotoevaporated (35 °C, 20 mmHg), and chromatography of the residue on a silica gel column (100 g) eluting with methylene chloride/methanol (97:3) gave as the first fraction unsaturated oxabicycle **12** (1.08 g, 54%, mp 92–93 °C colorless solid, recrystallized from methylene chloride/*n*-hexane, lit.[12c] 92–93 °C, lit.[10d] 93–94 °C, lit.[14a] 92–93 °C) and as the second fraction diol **10a** (720 mg, 35%). 9-Oxabicyclo[4.2.1]non-7-en-1-ol (**12**): ^{1}H NMR[14a] (400 MHz, $CDCl_3$): δ 5.96 (dd, *J*=5.8, 1.9 Hz, 1H,=CH), 5.78 (dd, *J*=5.8, 1.3 Hz, 1H,=CH), 5.00–4.90 (m, 1H, H-6), 3.43 (br s, 1H, −OH); 2.00–1.40 (series of m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.4, 132.8, 111.7, 81.7, 39.3, 33.6, 23.9, 23.2.

4.2. Acetylization of the mixture of 12 and 10a: synthesis of 4-acetoxycyclooct-2-enone (13) and *cis*-1,4-diacetoxy-2-cyclooctene (10b)

Endoperoxide **9** (14.27 mmol, 2.00 g) was reduced with thiourea as described above and the mixture was dissolved in 12 mL of anhydrous pyridine and the solution was cooled to 0 °C. Ac_2O (3.04 g, 28.16 mmol) and 4-(dimethylamino)pyridine (DMAP) (100 mg)

were added and the solution was stirred at room temperature for 24 h. The mixture was cooled to 0 °C and 250 mL of 1 N HCl solution added, and the mixture was extracted with ether (4×70 mL). The combined organic extracts were washed with $NaHCO_3$ solution (35 mL) and water (20 mL) and then dried (Na_2SO_4). Removing of the solvent under reduced pressure gave a mixture of 4-acetoxycyclooct-2-enone (**13**) and *cis*-1,4-diacetoxy-2-cyclooctene (**10b**). Chromatography of the mixture on a silica gel column (100 g) eluting with EtOAc/*n*-hexane (5:95) gave as the first fraction *cis*-1,4-diacetoxy-2-cyclooctene (**10b**) (1.08 g, 33%) and as the second 4-acetoxycyclooct-2-enone (**13**) (0.92 g, 35%). (*Z*)-4-Oxocyclooct-2-enyl acetate (**13**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.22–6.05 (m, 3H, CH=CH ,and OCH), 2.86–2.74 (m, 1H), 2.61–2.52 (m, 1H), 2.09 (s, 3H, OAc), 2.05–1.40 (series of m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 170.4, 142.6, 132.9, 72.1, 42.1, 30.0, 22.9, 21.9, 21.2. IR (KBr, cm^{-1}): 2941, 2864, 1737, 1666, 1458, 1371, 1240, 1170, 1031, 953, 756, 607. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.73; H, 7.49.

*4.2.1. cis-1,4-Diacetoxy-2-cyclooctene (**10b**).* Diol **10a** (1.00 g, 7.04 mmol) was dissolved in 10 mL of anhydrous pyridine and the solution was cooled to 0 °C. Ac_2O (3.04 g, 28.16 mmol) and 4-(dimethylamino)pyridine (DMAP) (100 mg) were added and the solution was stirred at room temperature for 24 h. The mixture was cooled to 0 °C and 200 mL of 1 N HCl solution added, and the mixture was extracted with ether (4×70 mL). The combined organic extracts were washed with $NaHCO_3$ solution (30 mL) and water (15 mL) and then dried (Na_2SO_4). Removing of the solvent under reduced pressure gave pure *cis*-1,4-diacetoxy-2-cyclooctene **10b** (1.44 g, 90%, colorless liquid). ^{1}H NMR[12a] (400 MHz, $CDCl_3$): δ 5.55 (m, 2H, OCH), 5.52 (m, 2H, CH=CH), 2.00 (s, 6H, 2×OAc), 2.01–1.90 (m, 2H), 1.57–1.44 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 23.3, 35.1, 71.9, 129.9, 170.3.

4.3. Epoxidation of diol 10a with *m*-CPBA

m-CPBA (77%, 1.26 g, 5.63 mmol) was added portionwise to a stirred solution of **10a** (0.8 g, 5.63 mmol) and $NaHCO_3$ (0.47 g, 5.63 mmol) in 10 mL of MeOH/CH_2Cl_2 (8:2) at room temperature for 10 days. The solvents were then removed in vacuo and replaced with H_2O (20 mL). The H_2O layer was extracted with EtOAc (4×35 mL); the aqueous layer was then frozen and lyophilized to give a crude solid, which was chromatographed over 50 g silica gel column eluting with EtOAc/MeOH/CH_2Cl_2 (90:5:5) to afford pure *cis*-1,4-dihydroxycyclooctane oxide **17** (0.70 g, 79%) as a colorless solid, recrystallized from absolute methanol, mp 194–195 °C. (1*R*(*S*),2*S*(*R*),7*R*(*S*),8*S*(*R*))-9-Oxabicyclo[6.1.0]nonane-2,7-diol (*meso*-**17**): ^{1}H NMR (400 MHz, D_2O): δ 3.50–3.42 (m, AA′ part of AA′BB′ system, 2H, CHO), 2.97–3.02 (m, BB′ part of AA′BB′ system, 2H, CHO), 1.70–1.60 (m, 2H), 1.50–1.30 (m, 6H). ^{13}C NMR (100 MHz, D_2O): δ 23.1, 34.5, 60.1, 71.1. IR (KBr, cm^{-1}): 3232, 2930, 2396, 1471, 1328, 1261, 1047, 990, 895, 793, 611. HRMS: calcd for $C_{12}H_{19}O_5$ (M^++H): 181.0835, found: 181.0835.

4.4. Epoxidation of diacetate 10b with *m*-CPBA

m-CPBA (77%, 4.76 g, 21.20 mmol) was added portionwise to a stirred solution of **10b** (1.20 g, 5.30 mmol) in CH_2C1_2 (10 mL) at room temperature and the mixture was refluxed for 28 days. The mixture was treated with aqueous iodide (10%, 4 mL) followed by aqueous sodium sulfite (10%, 30 mL). CH_2Cl_2 (100 mL) was added and the organic phase separated and then washed with saturated aqueous $NaHCO_3$ (3×60 mL). The organic phase was separated, dried (Na_2SO_4), and evaporated. The residual solid was chromatographed on silica, eluting with ethyl acetate/*n*-hexane (5:95), to give the epoxide **16** (0.77 g, 60%) as sole product. Colorless needle solid, mp 112–113 °C, recrystallized from methylene chloride/*n*-hexane. (1*R*(*S*),2*S*(*R*),7*R*(*S*),8*S*(*R*))-9-Oxabicyclo[6.1.0]nonane-2,7-diyl diacetate (*meso*-**16**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.80–4.68 (m, AA′ part of AA′XX′ system, 2H, CHO), 3.18–3.13 (m, XX′ part of AA′XX′ system, 2H, CHO), 2.06 (s, 6H, 2×OAc); 2.00–1.90 (m, 2H), 1.65–1.45 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 23.6, 32.4, 56.5, 74.4, 170.2. IR (KBr, cm^{-1}): 2935, 1736, 1451, 1370, 1240, 1029, 917, 827, 749, 604. HRMS: calcd for $C_{12}H_{19}O_5$ (M^++0H): 243.1232, found: 243.1236.

*4.4.1. (1R(S),2S(R),3R(S),4S(R))-Cyclooctane-1,2,3,4-tetraacetate (meso-**14b**).* A 50 mL three necked, round-bottomed flask, equipped with a magnetic stirrer and a nitrogen inlet, was charged with 591 mg (4.38 mmol) of NMO, 5 mL of water, and 5.5 mL of acetone. To this solution were added ca. 14.0 mg of OsO_4 (0.008 mmol) and 900 mg (3.98 mmol) of diacetate **10b**. The resulting mixture was stirred vigorously under nitrogen at room temperature. During the overnight stirring, the reaction mixture became homogeneous. After 3 days, the reaction was complete. Sodium hydrosulfite (0.07 g) and 2.25 g of Florisil slurried in 9 mL of water were added, the slurry was stirred for 10 min, and the mixture was filtered through a pad of 2.25 g of Celite in a 50 mL sintered glass funnel. The Celite cake was washed with acetone (3×50 mL). The filtrate was neutralized to pH 7 with H_2SO_4. The organic layer was removed in vacuo. The pH of the resulting aqueous solution was adjusted to pH 5 with sulfuric acid, and diacetoxy diol **14a** was separated from *N*-methylmorpholine hydrosulfate by extraction with ethyl acetate (5×35 mL). The combined ethyl acetate extracts were washed with 9 mL of 25% NaCl solution and two or three times with water and dried (Na_2SO_4). Evaporation of solvent gave 810 mg of diacetoxy diol **14a** (78%). To a magnetically stirred solution of diacetoxy diol **14a** (810 mg, 3.11 mmol) in 5 mL of CH_2Cl_2 was cooled to 0 °C. Acetyl chloride (0.73 g, 9.33 mmol) was added and the solution was stirred at room temperature for 12 h. Evaporation of the solvents gave pure tetraacetate **14b** (1.02 g, 95%); colorless solid, mp 71–72 °C from absolute ethanol. (1*R*(*S*),2*S*(*R*),3*R*(*S*),4*S*(*R*))-Cyclooctane-1,2,3,4-tetraacetate (*meso*-**14b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42 (quasi dd, *J*=9.9, 1.3 Hz, AA′ part of AA′BB′ system, 2H, CHO), 5.16–5.08 (m, BB′ part of AA′BB′ system, 2H, CHO), 2.03 (s, 6H, 2×OAc), 2.00 (s, 6H, 2×OAc), 1.80–1.60 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 21.0, 21.2, 21.3, 23.5, 29.5, 72.9, 170.2, 170.3. IR (KBr, cm^{-1}): 2940, 1740, 1452, 1372, 1234, 1026, 945, 738, 595. HRMS: calcd for $C_{16}H_{25}O_8$ (M^++H): 345.1549, found: 345.1549.

*4.4.2. (1R(S),2S(R),3R(S),4S(R))-Cyclooctane-1,2,3,4-tetraol (meso-**15**).* (1R(*S*),2*S*(*R*),3*R*(*S*),4*S*(*R*))-tetraacetoxycyclooctane (**14b**) (1.16 mmol, 400 mg) was dissolved in THF (6 mL) 10% HCl (10 mL) was added and the mixture was refluxed for 3 h. The solution was cooled to room temperature and the solvents were removed under reduced pressure. 10 mL of MeOH was placed into a two-necked flask, through which dry NH_3 was passed slowly for 30 min. To the solution saturated with NH_3(g) was added the mixture in the other flask solved in 10 mL MeOH. After dry NH_3(g) was passed through it for 4 h, evaporation of solvents gave pure tetraol **15** (200 mg, 98%); mp 120–122 °C, recrystallized from absolute EtOH. ^{1}H NMR (400 MHz, D_2O): δ 3.72–3.63 (m, 4H); 1.77–1.66 (m, 2H), 1.53–1.38 (m, 6H). ^{13}C NMR (100 MHz, D_2O): δ 23.8, 31.7, 72.5, 76.0. IR (KBr, cm^{-1}): 3417, 2927, 2529, 2393, 1441, 1403, 1344, 1277, 1160, 1069, 1042, 901, 715, 626. HRMS: calcd for $C_8H_{16}O_4Na$ (M^++Na): 199.0941, found: 199.0932.

4.5. Acetolysis of epoxide 17

To a stirred solution of **17** (300 mg, 1.90 mmol) in 3 mL of Ac_2O was added a catalytic amount of concentrated H_2SO_4 at 0 °C. The reaction mixture was stirred for 7 h at room temperature. The mixture was cooled to 0 °C and added 10 mL of water, and then stirred for l h. The reaction mixture was extracted with ether (3×50 mL). The combined

organic extracts were washed with $NaHCO_3$ solution (15 mL) and water (5 mL); then dried over Na_2SO_4. After removal of the solvent the residue was submitted to acetylation with AcCl following the method described above for the acetylation of **14a** to give **18**: 468 mg, 91%; colorless solid; mp 92–93 °C, from absolute ethanol. (1*R*(*S*),2*R*(*S*),3*R*(*S*),4*S*(*R*))-Cyclooctane-1,2,3,4-tetrayl tetraacetate (*rac*-**18**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47 (m, 1H), 5.25–5.15 (m, 2H), 5.11 (m, 1H); 2.04 (s, 3H, OAc); 2.02 (s, 3H, OAc); 2.00 (s, 3H, OAc); 2.00 (s, 3H, OAc); 1.90–1.53 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 21.1, 21.2, 21.6, 21.9, 28.1, 28.2, 70.9, 71.2, 71.6, 72.7, 169.7, 169.9, 170.0, 170.4. IR (KBr, cm^{-1}): 2941, 1744, 1434, 1371, 1231, 1025, 903, 760, 602. HRMS: calcd for $C_{16}H_{25}O_8$ (M^++H): 345.1544, found: 345.1532.

4.5.1. (1R(S),2R(S),3R(S),4S(R))-Cyclooctane-1,2,3,4-tetraol (rac-19). The same procedure as described above was applied for hydrolysis of tetraacetate **18** (150 mg, 98%), mp 125–126 °C, recrystallized from absolute EtOH. (1*R*(*S*),2*R*(*S*),3*R*(*S*),4*S*(*R*))-Cyclooctane-1,2,3,4-tetraol (*rac*-**19**): ^{1}H NMR (400 MHz, D_2O): δ 3.87 (m, 1H), 3.64–3.48 (m, 3H), 1.80–1.30 (series of m, 8H). ^{13}C NMR (100 MHz, D_2O): δ 20.7, 22.6, 29.3, 30.8, 70.9, 72.8, 72.9, 73.4. IR (KBr, cm^{-1}): 3398, 2918, 2854, 1639, 1441, 1357, 1217, 1155, 1069, 968, 893, 758, 626. HRMS: calcd for $C_8H_{16}O_4Na$ (M^++Na): 199.0946, found: 199.0952.

4.6. Crystal structure determination

For the crystal structure determination, the single-crystal of the compound **17** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). The graphite-monochromatized Mo K_α radiation (λ=0.71073 Å) and oscillation scans technique with $\Delta\omega$=5° for one image were used for data collection. The lattice parameters were determined by the least-squares method on the basis of all reflections with $F^2>2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement were performed using CrystalClear (Rigaku/MSC Inc., 2005) software.[19] The structures were solved by direct methods using SHELXS-97[20] and refined by a full-matrix least-squares procedure using the program SHELXL-97.[20] H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data for* **17**: $C_8H_{14}O_3$, crystal system, space group: monoclinic, *P*21/c; (no:14); unit cell dimensions: a=7.1410(5), b=13.0430(4), c=8.7750(4) Å, β=98.60(2)°; V=808.1(1) Å^3; Z=4; calculated density: 1.30 mg/m^3; absorption coefficient: 0.098 mm^{-1}; F(000): 344; θ range for data collection 2.8–30.6°; refinement method: full-matrix least-square on F^2; data/parameters: 2482/102; goodness-of-fit on F^2: 1.007; final R indices [$I>2\sigma(I)$]: R_1=0.073, wR_2=0.149; R indices (all data): R_1=0.189, wR_2=0.2190; largest diff. peak and hole: 0.230 and −0.21 e Å^{-3}; CCDC-756059.

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Supplementary data

^{1}H and ^{13}C NMR spectra for all new compounds and crystallographic data for compound **17** are provided. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.052.

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