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Stereospecific synthesis of a new class of compounds: bis-homoconduritol-A, -D, and -F

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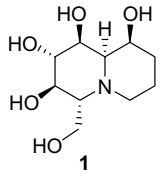
Abstract—Bis-homoconduritol derivatives with conduritol-A, -D, and -F structures have been synthesized starting from cyclooctatetraene. The photooxygenation of *trans*-7,8-dibromo- and *cis*-7,8-dichlorobicyclo[4.2.0]octa-2,4-dienes afforded the bicyclic endoperoxides. Reduction of the endoperoxides with thiourea followed by acetylation gave the corresponding diacetates. The $KMnO_4$ oxidation and epoxidation of the diacetates followed by acetylation gave the tetraacetates. Removal of the halides either with zinc-dust or Na-anthracene followed by the ammonolysis of tetraacetates afforded the bis-homoconduritol derivatives in high yield.

Keywords: Cyclitols; Conduritols; Peroxides; Bicyclic aliphatic compounds; Oxidation; Reduction

1. Introduction

Glycosidases and related enzymes play many fundamental roles in biochemistry and metabolism. For example, they are involved in the biosynthesis of the oligosaccharide chains. Inhibition of these glycosidases can effect many biological processes. Therefore, some glycosidase inhibitors have found application by the treatment of a variety of carbohydrate mediated diseases such as viral infection, cancer, and genetic disorders.[1] Carba-analogues of oligosaccharides (carbasugar) generated by replacing the endocyclic oxygen atom in monosaccharides[2] are thought to be more so as drug candidates than natural sugars, since they are hydrolytically stable. More recently, several polyhydroxylated bicyclic alkaloids such as quinolizidine alkaloid **1**, indolizidine alkaloids castanospermine **2**, and swainsonine **3**, have been identified as naturally occurring glycosidase inhibitors in plants and microorganisms.[3]



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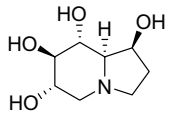

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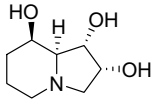

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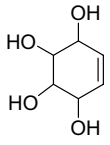
After this discovery, a dramatic increase in the synthesis of cyclitol derivatives[4] and conduritols **4**[5] was observed since the latter also showed glycosidase inhibitory properties.[6] We were interested in designing a new generation of possible glycosidase inhibitors with the bicyclic structures having [4.2.0] skeletons **5**[7] and **6**.[8]



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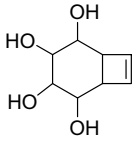

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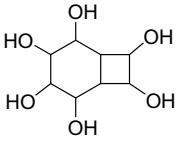

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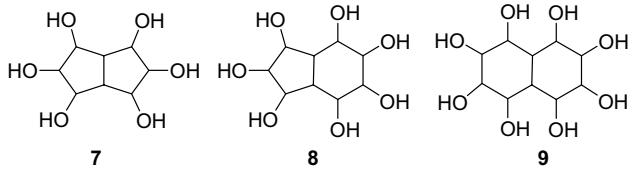
More recently, Mehta and Ramesh[9] have synthesized polyhydroxylated diquinane **7**, hydriindanes **8**, and decalins **9** and termed them *polycyclitols* as potential glycomimics and have shown that some of them exhibit significant and selective inhibition of yeast α-glycosidase.



Herein we report, the synthesis of bis-homoconduritol isomers **5** with [4.2.0] skeleton resembling conduritol-A, -D, and -F structures.

2. Results and discussion

There are many synthetic strategies leading to the various conduritol isomers and their derivatives.[5a] We mainly used the photooxygenation reaction to introduce two oxygen functionalities at C-1 and C-4 of the appropriate dienes followed by the cleavage of the peroxide linkage.[10]

Dibromobicyclooctadiene **11** was synthesized by the bromination of cyclooctatetraene (**10**).[11] Tetraphenylporphyrine (TPP) sensitized photooxygenation of dibromobicyclodiene **11** in carbon tetrachloride at room temperature afforded the bicyclic endoperoxide **12**[7,12] in 80% yield.

The optimized geometry of diene **11** was calculated using the AM1 method. Since the dibromobicyclodiene **11** has no plane of symmetry, singlet oxygen approaches the diene unit exclusively from the less crowded side of the molecule (Fig. 1). The exact configuration of this endoperoxide **12** was later proven by the X-ray analysis of the tetraacetate **15**. Reduction of the peroxide linkage in **12** with thiourea[13] under very mild conditions followed by acetylation in pyridine gave the diacetate **13** in 72% yield. Since only oxygen–oxygen bond is cleaved in this reaction, the configuration of the oxygen atoms in **13** is preserved. cis-Hydroxylation of **13** with $KMnO_4$ at −10 °C gave the diol diacetate **14** as the sole isomer. The stereochemical course of the hydroxylation may be *syn* or *anti* with respect to the cyclobutane ring. NMR spectroscopic studies did not allow the assignment of the exact configuration of the hydroxyl groups, which were introduced by $KMnO_4$ reaction.

The X-ray analysis[7] (Fig. 2) of the dibromotetraacetate **15** revealed the exact configuration of the compound; furthermore, it provided information about the stereochemical course of photooxygenation and hydroxylation reactions. The conduritol-D[14] structure was formed exclusively. In order to rationalize the exclusive formation of **14**, we have carried out some AM1 calculations for the unsubstituted olefines **17** and **18** (Fig. 3).

Cyclohexene units in **17** and **18** can have two interconvertible conformations (chair and boat conformers). AM1 calculations show that the boat conformers **17b** and **18b** have about 0.46 and 0.57 kcal/mol lower heat of formation, respectively. Therefore, we assume that the molecule **13** prefers mainly the boat conformation. Since the *syn*-face of the molecule **13** in boat conformation is blocked by the bulky bromine atom, $KMnO_4$ approaches the double bond exclusively from the *anti*-face to give **14**. Careful examination of the reaction mixture did not reveal the formation of any compound arising from *syn*-attack of $KMnO_4$. To complete the synthesis of the desired tetrol **16a**, the tetraacetate **15** was submitted to a Zn-elimination reaction in DMSO to give the unsaturated tetraacetate **16b**. The exact structure of the formed compound was determined by ^1H and ^{13}C NMR spectral measurements. The presence of an eight-line ^{13}C NMR spectrum is in full agreement with the proposed symmetric structure **16b**. Deacetylation of **16b** with ammonia in methanol yielded the free tetrol **16a** with conduritol-D configuration in a nearly quantitative yield (Scheme 1).

For the synthesis of conduritol-F[15] analogue **22**, the dibromodiacetate **13** was reacted with *m*-CPBA to give **19** as the sole isomer (Scheme 2). The exact configuration of the epoxide **19** was confirmed by differential ^1H NMR–NOE measurements. Irradiation at the resonance signal of the epoxide protons at $\delta = 3.50$ caused signal enhancements at the resonances of the adjacent acetoxy protons at $\delta = 5.51$ and 5.26, respectively. The epoxidation reaction proceeded stereochemically from the less crowded side of the molecule, which is similar to that of the hydroxylation reaction.

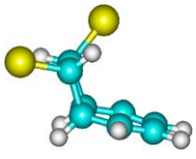
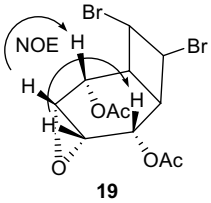


Figure 1. AM1-optimized geometry of dibromide **11**.



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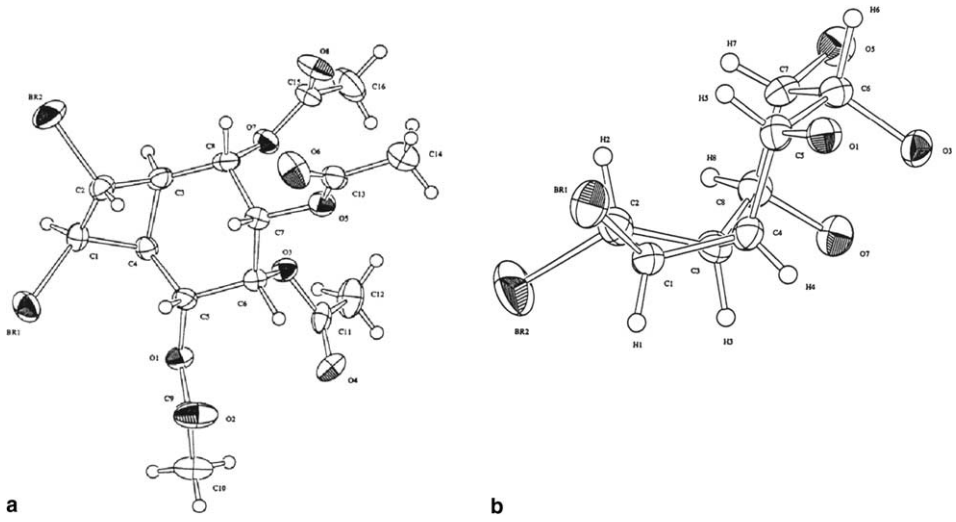


Figure 2. (a) X-ray crystal structure for **15** and (b) rings with attached atoms.

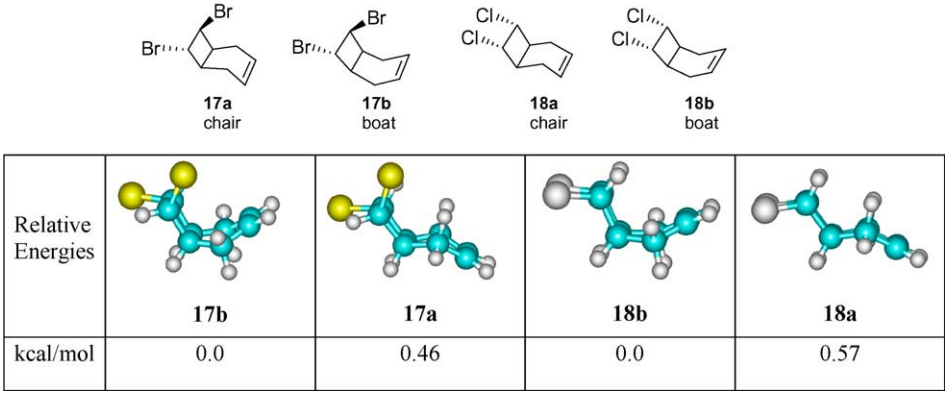
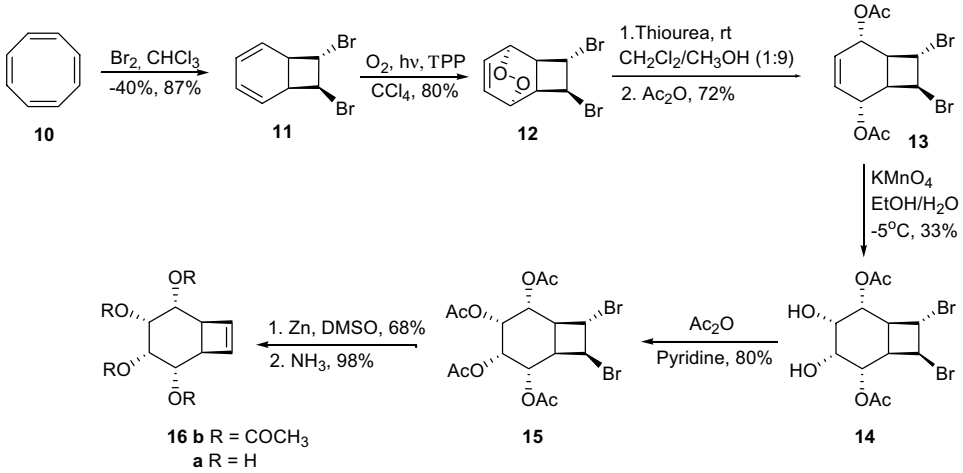
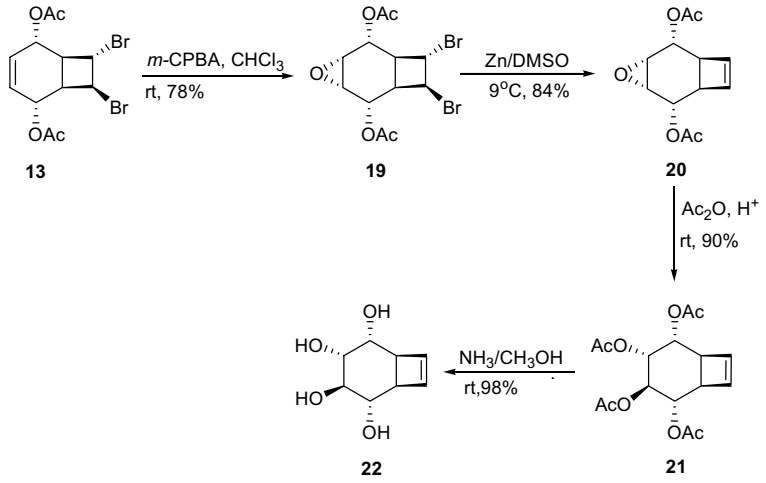


Figure 3. AM-1 optimized geometries and relative energies of dibromide **17** and dichloride **18**.



Scheme 1.

Dibromoepoxydiacetate **19** smoothly reacted with Zn–DMSO and gave the epoxydiacetate **20**. *trans*-Ring-opening of the epoxide **20** in acidified acetic anhydride resulted in the exclusive formation of the tetraacetate **21**. All analytical methods showed the formation of a single isomer. The asymmetry in the molecule was



Scheme 2.

completely in agreement with the spectroscopic data. Deacetylation of **21**, as described above, gave tetrol **22** in 98% yield (Scheme 2).

To prove the assumption that *endo*-oriented bromine atom in **13** determines the stereoselectivity of hydroxylation and epoxidation reactions, we replaced the bromine atoms in **11** with the cis-configurated chlorine atoms. Furthermore, this opened up the way to the synthesis of other isomeric homoconduritol derivatives. *cis*-Dichlorobicyclooctadiene **23** was synthesized as described in the literature.[16] Photooxidation of *cis*-dichlorobicyclooctadiene **23** with singlet oxygen gave the expected endoperoxide **24** (Scheme 3).[12b] Reduction of the peroxide bond in **24** was performed with thiourea under very mild conditions to give the diol **25a**. For further structural proof, **25a** was converted into the corresponding diacetate **25b**, which was fully characterized by way of spectroscopic methods. cis-Hydroxylation of **25b** with $KMnO_4$ at −10 °C gave a mixture of diols **26a** and **27a** in a ratio of 1:1, which were converted to tetraacetate derivatives **26b** and **27b** with acetyl chloride. The formation of two isomers **26a** and **27a** confirmed our assumption that the bromine atom at *endo*-C-7 in **13** hinders the attack of $KMnO_4$ as well as of *m*-CPBA from the *syn*-face of the diene unit. Furthermore, AM1 calculations on **18** has revealed that the boat-conformer **18b** is 0.57 kcal/mol more stable than the chair-conformer **18a**. Since, the chlorine atoms in **25b** do not block the *syn*-face of the molecule, $KMnO_4$ can approach the double bond in **25b** from the *anti*-face as well as from the *syn*-face. All attempts to separate diastereoisomers **26b** and **27b** by way of chromatographic methods failed. Fortunately, fractional crystallization of the mixture permitted their isolation. However, it was not possible to assign the correct configurations of these isomers. The exact configuration of these isomers was assigned after the removal of the chlorine atoms. For this purpose, **26b** and **27b** were subjected to dehalogenation reaction using Zn/DMSO, NaI/aceton, and electrochemical methods, none of which gave the expected elimination products **28b** and **16b**. Fortunately, the cis-elimination of **27b** and **26b** was achieved by employing an anthracene–sodium system[17] to give the desired elimination products **28b** and **16b**. All spectral data of **16b** was in agreement with the tetraacetate obtained by starting from **13** (see Scheme 1). The olefinic protons of **28b** display a singlet and do not couple with the adjacent protons since the dihedral angle is nearly 90°. Alkoxy protons resonate as two separate multiplets. Especially, an eight-line ^{13}C NMR spectrum of **28b** confirms the proposed structure according to the symmetry in the molecule. Removal of the acetate functionalities with ammonia gave the expected tetrol **28a** with conduritol-A[18] structure in high yield.

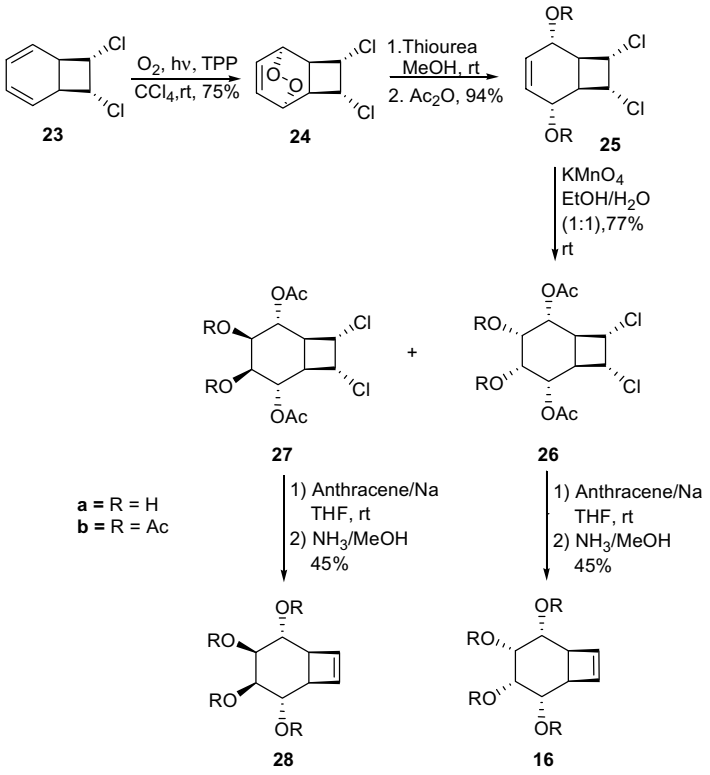
In summary, a short, simple, and stereocontrolled method for the preparation of a new class of compounds, bis-homoconduritols-A, -D, and -F has been accomplished starting from cyclooctatetraene.

3. Experimental

3.1. General

Melting points were determined on a melting apparatus. Infrared spectra were obtained from KBr pellets on an infrared spectrophotometer. ^1H NMR spectra were recorded on 200 MHz spectrometer and reported in δ units with $SiMe_4$ as internal standard. All column chromatography was performed on silica gel (60 mesh, Merck) and basic aluminum oxide (70–230 mesh, ASTM, Merck).

3.1.1. 1*R*(*S*),2*S*(*R*),3*S*(*R*),4*R*(*S*),5*R*(*S*),6*S*(*R*)-3,4-Dibromo-7,8-dioxatricyclo[4.2.2.0^{2,5}]dec-9-ene (12).[12] To a stirred solution of dibromodiene **11**[11] (2.11 g, 8 mmol)



Scheme 3.

in 100 mL of CCl_4 was added 20 mg of tetraphenyl porphyrin (TPP). The resulting mixture was irradiated with a projection lamp (250 W) while oxygen was being passed through the solution and the mixture was stirred at room temperature for 6 h. Evaporation of the solvent (25 °C, 20 mmHg) and chromatography of the residue on a silica gel column (50 g) eluting with hexane/CH_2Cl_2 (1:1) gave pure endoperoxide **12** (1.5 g, 80%). Colorless prisms. Mp 106–107 °C (from hexane/CH_2Cl_2). δ_H (200 MHz, $CDCl_3$) 7.10 (ddd, 1H, $J = 9.9$, 6.4, 1.6 Hz), 6.70 (ddd, 1H, $J = 9.9$, 6.2, 1.5 Hz), 4.90 (m, 1H), 4.75 (m, 2H), 4.26 (m, 1H), 3.60 (m, 2H); δ_C (50 MHz, $CDCl_3$) 134.8, 130.8, 72.7, 71.4, 48.8, 47.4, 45.5, 39.7.

3.1.2. 1*R*(*S*),2*S*(*R*),5*R*(*S*),6*S*(*R*),7*R*(*S*),8*R*(*S*)-5-(Acetyloxy)-7,8-dibromobicyclo[4.2.0]oct-3-en-2-yl acetate (13). To a magnetically stirred slurry of 0.77 g (10.1 mmol) of thiourea in 20 mL of MeOH was added a solution of 3.0 g (10.1 mmol) dibromo-endoperoxide **12** in a 50 mL mixture of CH_2Cl_2/CH_3OH (1:9) at 25 °C. After complete addition (ca. 10 min) the mixture was stirred for 1 h and the solid removed by filtration. Evaporation of the solvent gave diol, which was dissolved in 10 mL of pyridine. To the magnetically stirred solution was added Ac_2O (3.10 g, 30.4 mmol). The reaction mixture was stirred at room temperature for 12 h. The mixture was cooled to 0 °C and was added 80 mL of 4 N HCl solution and extracted with ether (3 × 50 mL). The combined organic extracts were washed with $NaHCO_3$ solution (10 mL) and water (45 mL) and then dried over $NaSO_4$. Removal of the solvent under reduced pressure gave diacetate **13** (2.68 g, 72%). Colorless prisms. Mp 89–90 °C (from hexane/CH_2Cl_2). δ_H (200 MHz, $CDCl_3$) 6.10 (ddd, 1H, $J = 10.3$, 3.1, 1.3 Hz), 5.93 (ddd, 1H, $J = 10.3$, 3.6, 1.6), 5.48 (m, 1H), 5.10 (m, 1H), 4.62 (t, 1H, $J = 8.1$ Hz), 4.18 (t, 1H, $J = 8.2$ Hz), 3.10 (ddd, 1H, $J = 10.4$, 10.0, 5.5 Hz), 2.89 (ddd, 1H, $J = 10.1$, 8.4, 2.5 Hz). δ_C (50 MHz, $CDCl_3$) 170.6, 170.4, 131.7, 128.2, 67.6, 66.5, 50.2, 49.7, 46.6, 40.0, 21.6, 21.5.

3.1.3. 1*R*(*S*),2*R*(*S*),3*R*(*S*),4*S*(*R*),5*S*(*R*),6*S*(*R*),7*R* (*S*),8*R*(*S*)-2,4,5-Tris(acetyloxy)-7,8-di-bromobicyclo[4.2.0]oct-3-yl acetate (15). To a stirred solution of 6.2 g (17 mmol) dibromodiacetate **13** in EtOH (105 mL) was added a solution of $KMnO_4$ (3.0 g, 17 mmol) and $MgSO_4$ (2.5 g, 17 mmol) in water (40 mL) at −5 °C over a period of 5 h. After the addition was completed, the reaction mixture was stirred for an additional 15 h at −5 °C and then filtered. The precipitate was washed several times with hot water, and the combined filtrates were concentrated to 20 mL by rotary evaporation (60 °C, 20 mmHg). The aqueous solution was extracted with ethyl acetate (3 × 75 mL) and the extracts were dried over Na_2SO_4. Evaporation of the solvent gave dibromodiacetoxydiol **14** (2.0 g, 33%), which was submitted to acetylation as described above to give dibromotetraacetate **15** (2.27 g, 80%). White crystals, mp 203–204 °C (from hexane/CH_2Cl_2). ν_{max} (KBr)

2930, 1700, 1420, 1220, 1100 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.56 (quasi t, 1H), 5.29 (d, 1H, $J = 4.4$ Hz), 5.28 (dd, 1H, $J = 9.0$, 2.2 Hz), 5.19 (dd, 1H, $J = 4.4$, 2.4 Hz), 4.50 (dd, 1H, $J = 7.8$, 7.7 Hz), 4.27 (dd, 1H, $J = 10.0$, 8.3 Hz), 3.15 (ddd, 1H, $J = 9.3$, 9.2, 1.8 Hz), 2.90 (ddd, 1H, $J = 9.2$, 8.9, 1.2 Hz), 2.11 (s, 3H), 2.08 (s,3H), 2.03 (s, 3H), 2.01 (s, 3H); δ_C (50 MHz, $CDCl_3$) 169.9, 169.8, 169.6, 169.4, 69.7, 68.4, 67.0, 65.0, 47.4, 47.0, 46.8, 39.2, 20.8 (×2), 20.7, 20.5.

3.1.4. 1*R*(*S*),2*R*(*S*),3*R*(*S*),4*S*(*R*),5*S*(*R*),6*S*(*R*)-2,4,5-Tris-(acetyloxy)bicyclo[4.2.0]oct-7-en-3-yl acetate (16b). To a solution of dibromotetraacetate **15** (0.60 g, 1.2 mmol) in 10 mL of DMSO were added 0.12 g (1.2 mmol) of zinc dust and 30 mg of iodine. The mixture was stirred magnetically at 95 °C for 4 h. After cooling to room temperature, 50 mL of water and 50 mL of ethyl acetate was added. The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent (50 °C, 20 mmHg) and chromatography of residue on a silica gel column (15 g) eluting with hexane/ethyl acetate (9:1) gave tetraacetate **16b** (0.27 g, 68%). White crystals, mp 102–103 °C (from hexane/CH_2Cl_2). ν_{max} (KBr) 2930, 1695, 1420, 1200, 1120 cm^{-1}; Found: C, 56.37; H, 5.95; $C_{16}H_{20}Cl_2O_8$ requires C, 56.47; H, 5.92; δ_H (200 MHz, $CDCl_3$) 6.29 (s, 2H), 5.30, 5.20, 3.25 (AA′BB′XX′ systems, 6H), 2.15 (s, 6H), 2.10 (s, 6H); δ_C (50 MHz, $CDCl_3$) 170.2, 169.9, 139.2, 70.3, 68.4 , 45.4 , 20.9, 20.7.

3.1.5. 1*R*(*S*),2*R*(*S*),3*R*(*S*),4*S*(*R*),5*S*(*R*),6*S*(*R*)-2,4,5-Bicyclo[4.2.0]oct-7-ene-2,3,4,5-tetrol:bis-homoconduritol-D (16a). Tetraacetate **16b** (0.10 g, 0.3 mmol) was dissolved in 20 mL of absolute MeOH. While dry NH_3 was being passed through the solution, the mixture was stirred for 2 h at room temperature. Evaporation of MeOH and formed acetamide gave bis-homoconduritol-D **16a** in nearly quantitative yield (50 mg, 98%). Colorless powder, mp 113–114 °C (from $CHCl_3$/hexane). ν_{max} (KBr) 3400, 2920, 1630, 1420, 1200, 1150 cm^{-1}; Found: C, 55.62; H, 7.13; $C_8H_{12}O_4$ requires C, 55.81; H, 7.02; δ_H (200 MHz, $CDCl_3$) 6.13 (s, 2H), 4.10 (br s, 2H), 3.92 (br s, 2H), 3.75 (br s, 4H, –OH), 3.62 (s, 2H); δ_C (50 MHz, $CDCl_3$) 138.6, 72.1, 66.5, 46.3.

3.1.6. 1*R*(*S*),2*S*(*R*),3*R*(*S*),5*S*(*R*),6*R*(*S*),7*S*(R*S*),8*R*(*S*),9*R*-(*S*)-6-(Acetyloxy)-8,9-dibromo-4-oxatricyclo[5.2.0.0^{3,5}]non-2-yl acetate (19). To a solution of dibromodiacetate **13** (2.35 g, 6.15 mmol) in 40 mL of chloroform was added 2.13 g (12.3 mmol) of *m*-chloroperbenzoic acid (*m*-CPBA). The mixture was sonicated in an ultrasonic bath (50 kHz) for 24 h. The precipitate was filtered and washed with 50 mL of chloroform. The organic phases were combined and the solvent was removed under reduced pressure. The residue was filtered through a short column (20 g, basic aluminum oxide) with ethyl acetate/hexane (1:1). Evaporation of the solvent gave **19** (1.85 g, 78%). Colorless crystals, mp 185–186 °C (from CH_2Cl_2/hexane). ν_{max} (KBr) 2850, 1695, 1200 cm^{-1} δ_H (200 MHz, $CDCl_3$) 5.51 (d, 1H, $J = 9.8$ Hz), 5.26 (d, 1H, $J = 4.7$ Hz), 4.55 (quasi t, 1H, $J = 7.4$ Hz), 4.26 (quasi t, 1H, $J = 7.7$ Hz), 3.60 (d, A part of AB-system, 1H, $J = 4.8$ Hz), 3.40 (dd, B part of AB-system, 1H, $J = 4.8$, 1.4 Hz), 3.2 (quasi q, 1H, $J = 9.2$ Hz), 2.80 (ddd, 1H, $J = 10.3$, 8.2, 4.7 Hz), 2.10 (s, 6H); δ_C (50 MHz, $CDCl_3$) 171.0, 170.5, 71.4, 69.8, 54.9, 54.4, 51.1, 49.3, 46.2, 40.3, 21.5, 21.4.

3.1.7. 1*R*(*S*),2*S*(*R*),3*R*(*S*),5*S*(*R*),6*R*(*S*),7*S*(*R*)-6-(Acetyloxy)-4-oxatricyclo[5.2.0.0^{3,5}]non-8-en-2-yl acetate (20). To a solution of dibromide **19** (0.52 g, 1.3 mmol) in 10 mL of DMSO were added 0.12 g (1.2 mmol) of zinc dust and 30 mg of iodine. The mixture was stirred magnetically at 95 °C for 4 h. After cooling to room temperature 50 mL of water and 50 mL of ether were added. The aqueous phase was extracted with ether (2 × 50 mL) and the combined organic extracts were dried over Na_2SO_4. Evaporation of the solvent (30 °C, 20 mmHg) and chromatography of residue on a silica gel column (15 g) eluting with hexane/ethyl acetate (9:1) gave epoxydiacetate **20** (0.26 g, 84%). Colorless crystals, mp 122–123 °C (from Et_2O/hexane). ν_{max} (KBr) 2895, 1700, 1560, 1190 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.21 (s, 2H), 5.08 (AA′ part of AA′XX′-system, 2H), 3.08 (XX′ part of AA′XX′-system, 2H), 3.41 (s, 2H), 2.11 (s, 6H); δ_C (50 MHz, $CDCl_3$) 171.3, 127.3, 72.7, 55.7, 44.2, 21.5.

3.1.8. 1*R*(*S*),2*S*(*R*),3*R*(*S*),4*R*(*S*),5*R*(*S*)6*S*(*R*)-2,4,5-Tris-acetyloxy)bicyclo[4.2.0]oct-7-en-3-yl acetate (21). Epoxydiacetate **20** (0.26 g, 1.09 mmol) was dissolved in 5 mL of Ac_2O. To the solution was added 10 mg of concentrated H_2SO_4, and the resulting mixture was stirred magnetically at room temperature for 8 h. To the mixture was added 30 mL water and extracted with ether (3 × 50 mL). The combined organic extracts were washed with $NaHCO_3$ solution (20 mL) and water (20 mL) than dried over Na_2SO_4. The solvent was removed under reduced pressure. Filtering of the residue and removing of the solvent through a short column (15 g, basic aluminum oxide) with ethyl acetate/hexane (1:4) gave tetraacetate **21** (0.35 g, 90%). ν_{max} (KBr) 2930, 1700, 1560, 1350 cm^{-1}; Found: C, 56.87; H, 5.75; $C_{16}H_{20}Cl_2O_8$ requires C, 56.47; H, 5.92; δ_H (200 MHz, $CDCl_3$) 6.24 (d, A part of AB-system, 1H, $J = 2.8$ Hz), 6.11 (d, B part of AB-system, 1H, $J = 2.8$ Hz), 5.30 (m, 3H), 5.05 (quasi t, 1H, $J = 5.8$ Hz), 3.25 (quasi t, 1H, $J = 4.4$ Hz), 2.99 (t, 1H, $J = 4.4$ Hz), 2.07 (s, 3H), 2.04 (s, 3H), 2.01 (s, 6H); δ_C (50 MHz, $CDCl_3$) 170.7, 170.6, 170.3 (2C), 140.7, 138.5, 74.9, 74.5, 71.7, 71.0, 45.2, 44.6, 21.4 (2C), 21.3, 21.2.

3.1.9. 1*R*(*S*),2*S*(*R*),3*R*(*S*),4*R*(*S*),5*R*(*S*)6*S*(*R*)-Bicyclo[4.2.0]-oct-7-ene-2,3,4,5-tetrol:bis-homoconduritol-F (22). 0.10 g (0.3 mmol) of tetraacetate **21** was dissolved in 10 mL of absolute MeOH. While dry NH_3 was being passed through the solution, the mixture was stirred for 2 h at room temperature. Evaporation of MeOH and formed acetamide gave bis-homoconduritol-F **22** in nearly quantitative yield (48 mg, 98%). Mp 119–120 °C (recrystallized from $CHCl_3/CH_3OH$); ν_{max} (KBr) 3400, 2920, 1630, 1420, 1200; Found: C, 55.99; H, 6.91; $C_8H_{12}O_4$ requires C, 55.81; H, 7.02; δ_H (200 MHz, D_2O) 6.3 (d, A part of AB-system, 1H, $J = 2.8$ Hz), 6.2 (d, B part of AB-system, 1H, $J = 2.8$ Hz), 3.82 (m, 2H), 3.62 (m, 2H), 3.45 (m, 1H), 2.83 (m, 1H); δ_C (50 MHz, D_2O) 142.9, 142.8, 81.4, 78.1, 77.2, 73.8, 48.6, 48.1.

3.1.10. 1*R*(*S*),2*S*(*R*),3*S*(*R*),4*R*(*S*),5*R*(*S*),6*S*(*R*)-3,4-Dichloro-7,8-dioxatricyclo[4.2.2.0^{2,5}]-dec-9-ene (24).[12b] To a stirred solution of dichloro-diene **23**[16] (3.0 g, 17 mmol) in 100 mL of CCl_4 was added 30 mg of tetraphenyl porphyrin (TPP). The resulting mixture was irradiated with a projection lamp (500 W) while oxygen was being passed through the solution and the mixture was stirred at room temperature for 8 h. Evaporation of the solvent (30 °C, 20 mmHg) and chromatography of the residue on a silica gel column (50 g) eluting with hexane/CH_2Cl_2 (1:1) gave pure endoperoxide **24** (2.67 g, 75%). Mp 91–92 °C (recrystallized from $CHCl_3$/hexane). Found: C, 46.17; H, 3.95; $C_{16}H_{20}Cl_2O_8$ requires C, 46.41; H, 3.89; ν_{max} (KBr) 3469, 3079, 3016, 2979, 1369, 1331, 1296, 1266, 1250, 1026, 958; δ_H (200 MHz, $CDCl_3$) 6.88 (quasi dd, $J = 4.4$, 1.0 Hz, 2H, C=CH), 4.90 (m, 2H, CH–O), 4.13 (d, 2H, $J = 3.5$ Hz, CH–Cl), 3.37 (m, 2H). δ_C (50 MHz, $CDCl_3$) 134.6, 72.9, 57.3, 45.1.

3.1.11. 1*R*(*S*),2*S*(*R*),5*R*(*S*),6*S*(*R*)-7*S*(*R*),8*R*(*S*)-7,8-Dichlorobicyclo[4.2.0]oct-3-ene-2,5-diol (25a). To a magnetically stirred slurry of 0.44 g (5.79 mmol) of thiourea in 30 mL of MeOH was added a solution of 1.20 g (5.79 mmol) of endoperoxide **24** in 30 mL of $CHCl_3$ at room temperature. After complete addition (ca. 10 min) the mixture was stirred for 1 h and the solid was removed by filtration. Evaporation of the solvent gave diol **25a** as colorless oil (1.15 g, 95%). δ_H (200 MHz, CD_3OD) 5.81 (s, 2H, C=CH), 4.51 (dd, 2H, $J = 3.0$, 1.2 Hz, CH–O), 4.11 (m, 2H, CH–Cl), 2.69 (m, 2H, CH); δ_C (50 MHz, CD_3OD) 134.8, 68.8, 62.0, 50.9.

3.1.12. 1*R*(*S*),2*S*(*R*),5*R*(*S*),6*S*(*R*)-7*S*(*R*),8*R*(*S*)-5-(Acetyloxy)-7,8-dichlorobicyclo[4.2.0]-oct-3-en-2-yl acetate (25b). Diol **25a** (0.81 g, 3.87 mmol) was dissolved in 10 mL of acetyl chloride and the resulting solution was stirred at room temperature overnight. The excess of unreacted acetyl chloride was evaporated (60 °C, 20 mmHg). The residue was dissolved in $CHCl_3$ and filtered over silica gel. Evaporation of the solvent gave **25b** (1.08 g, 94%). Mp 54–55 °C (recrystallized from $CHCl_3$/hexane). Found: C, 49.65; H, 5.08. $C_{12}H_{14}Cl_2O_4$ requires C, 49.17; H, 4.81. ν_{max} (KBr) 3020, 2969, 2935, 1731, 1434, 1373, 1234, 1029, 917, 755; δ_H (200 MHz, $CDCl_3$) 5.92 (s, 2H, C=CH), 5.18 (br s, 2H, CH–O), 4.44 (d, 2H, $J = 4.5$ Hz, CH–Cl), 2.88 (m, 2H, CH), 2.07 (s, 6H, CH_3). δ_C (50 MHz, $CDCl_3$) 172.2, 130.9, 68.9, 60.4, 46.5, 22.9.

3.1.13. 1*S*(*R*),2*S*(*R*),3*S*(*R*),4*R*(*S*),5*R*(*S*),6*R*(*S*),7*S*(*R*),8*R*(*S*)-2,4,5-Tris(acetyloxy)-7,8-dichlorobicyclo[4.2.0]oct-3-yl acetate (26b) and 1*S*(*R*),2*S*(*R*),3*R*(*S*),4*S*(*R*),5*R*(*S*),6*R*(*S*),7*S*(*R*),8*R*(*S*)-2,4,5-tris(acetyloxy)-7,8-dichlorobicyclo-[4.2.0]oct-3-yl acetate (27b). To a stirred solution of (0.55 g, 1.88 mmol) dichlorodiacetate **25b** in EtOH (50 mL) was added a solution of $KMnO_4$ (0.3 g, 1.88 mmol) and $MgSO_4$ (0.23 g, 1.88 mmol) in water (20 mL) at −10 °C over a period of 5 h. After the addition was completed, the reaction mixture was stirred for an additional 15 h at −5 °C and then filtered. The precipitate was washed several times with hot water. The combined filtrates were concentrated to 20 mL by rotary evaporation (60 °C, 20 mmHg). The aqueous solution was extracted with ethyl acetate (3 × 75 mL) and the extracts were dried (Na_2SO_4). After removal of the solvent, the crude mixture was acetylated as described above to give **27b** and **26b** in a ratio of 1: 1 (according to ^1H NMR) (0.59 g, 77%). Compounds **27b** and **26b** were separated by fractional crystallization from hexane/CH_2Cl_2.

Compound **27b**: Colorless oil; EIMS *m*/*z* (%): 411 (0.5), 375 (5), 315 (17), 273 (18), 215 (15), 213 (44), 177 (28), 175 (52), 171 (100), 152 (81) , 135 (68), 115 (41), 110 (66), 103 (52), 97 (27), 81 (35); ν_{max} (KBr) 3022, 2956, 2835, 1745, 1431, 1370, 1233, 1036, 922, 601; Found: C, 46.79; H, 5.42. $C_{16}H_{20}Cl_2O_8$ requires C, 46.73; H, 4.90; δ_H (200 MHz, $CDCl_3$) 5.24 (br d, A part of AB system, 2H, $J_{AB} = 6.2$ Hz), 5.16 (dm, B part of AB system, 2H, $J_{AB} = 6.2$ Hz), 4.80 (m, 2H, –CHCl), 2.94 (m, 2H, –CH), 2.09 (s, 12H, $-CH_3$); δ_C (50 MHz, $CDCl_3$) 170.6, 170.1, 70.2, 69.0, 58.3, 47.4, 21.7.

Compound **26b**: Colorless crystals from hexane/CH_2Cl_2. Mp 171–173 °C; ν_{max} (KBr) 3025, 2979, 2948, 1751, 1431, 1370, 1235, 1081, 1041, 758; Found: C, 46.68; H, 4.87. $C_{16}H_{20}Cl_2O_8$ requires C, 46.73; H, 4.90; δ_H (200 MHz, $CDCl_3$) 5.30–5.20 (m, 4H, –CHO), 4.55 (m, 2H, –CHCl), 3.05 (m, 2H, –CH), 2.05 (s, 6H, CH_3), 2.03 (s, 6H, $-CH_3$); δ_C (50 MHz, $CDCl_3$) 171.8, 171.6, 70.1, 69.7, 59.0, 47.0, 22.6, 22.5.

3.1.14. 1*R*(*S*),2*S*(*R*),3*R*(*S*),4*S*(*R*),5*R*(*S*),6*S*(*R*)-Tris-(acetyloxy)bicyclo[4.2.0]oct-7-en-3-yl acetate (28b). A mixture of 1.77 g (9.8 mmol) of anthracene in 40 mL of anhydrous tetrahydrofuran was placed in a dry 100-mL flask equipped with a glass covered stirring

bar. Sodium metal (0.23 g, 9.8 g atom) cut into small pieces was added and the mixture was stirred at room temperature for 2 h, after which time no undissolved sodium or anthracene could be detected. The dark blue solution was cooled in an ice bath and 0.45 g (1.09 mmol) of **27b** was added under nitrogen during 10 min. The ice bath was removed and the mixture was stirred for an additional 20 min. MeOH (2 mL) was cautiously added dropwise until an intense color was discharged. The solvent was removed in vacuo and the residue was stirred with acetyl chloride (5 mL) at room temperature for 6 h. Removal of the excess of unreacted acetyl chloride under reduced pressure (50 °C, 20 mmHg) and then chromatography of the residue on a silica gel column (40 g) eluting with hexane subsequently with ethyl acetate gave **28b** (0.17 g, 45%). Colorless oily; ν_{max} (KBr) 3061, 2930, 2861, 1753, 1676, 1600, 1446, 1376, 1238, 1046, 966; δ_H (200 MHz, $CDCl_3$) 6.15 (s, 2H, C=CH), 5.28 (dm, 2H, $J = 6.8$ Hz), 5.14 (dm, 2H, $J = 6.8$ Hz), 3.08 (d, 2H, $J = 1.1$ Hz, –CH), 2.08 (s, 6H, $–CH_3$), 2.04 (s, 6H, $–CH_3$). δ_C (50 MHz, $CDCl_3$) 172.0, 171.8, 140.2, 72.7, 72.3, 48.4, 23.0, 22.8.

3.1.15. 1*R*(*S*),2*S*(*R*),3*R*(*S*),4*S*(*R*),5*R*(*S*),6*S*(*R*)-Bicyclo-[4.2.0]oct-7-ene-2,3,4,5-tetrol:bis-homoconduritol-A (28a). Tetraacetate **28b** (149 mg, 0.43 mmol) was dissolved in 10 mL of absolute MeOH. While dry NH_3 was being passed through the solution, the mixture was stirred for 2 h at room temperature. Evaporation of MeOH and formed acetamide gave bis-homoconduritol-A **28a** (71.0 mg, 94%). Colorless oily. Found: C, 55.58; H, 7.00. $C_8H_{12}O_4$ requires C, 55.81; H, 7.02. ν_{max} (KBr) 3435, 2921, 1650, 1432, 1066, 746; δ_H (400 MHz, CD_3OD) 6.30 (s, 2H), 3.70 (br s, 4H), 2.80 (m, 2H); δ_C (100 MHz, CD_3OD) 140.7, 74.7, 74.4, 48.4.

Compound **16b** from **26b**. The elimination procedure described above for **27b** in Section 3.1.14 was applied to **26b** to give **16b** in a yield of 45%.

Compound **16a** from **16b**. The ammonolysis procedure described above for **28b** in Section 3.1.15 was applied to **16b** to give **16a** in a yield of 94%.

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