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Synthesis of haloconduritols from an *endo*-cycloadduct of furan and vinylene carbonate

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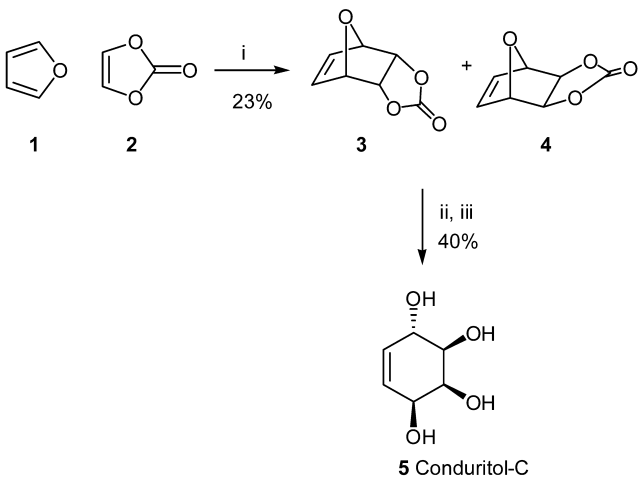
Abstract—A method for preparing haloconduritols having a conduritol-A construction is described. A mixture of *endo*- and *exo*-cycloadduct derivatives prepared from the Diels–Alder reaction of furan and vinylene carbonate was converted into diacetate derivatives by hydrolysis (K_2CO_3/MeOH) followed by acetylation (Ac_2O/pyridine). Boron trihalide (BBr_3 or BCl_3)-assisted ring-opening of the *endo*-diacetate in CH_2Cl_2 at −78°C gave (1α,2α,3β,6β)-6-halogeno-4-cyclohexene-1,2,3-triol 1,2-diacetate from which the corresponding triacetate was prepared by acetylation (AcCl). *trans*-Esterification of the triacetate (MeOH/HCl) afforded (1α,2α,3β,6β)-6-halogeno-4-cyclohexene-1,2,3-triol (X=Br or Cl). BF_3-Assisted ring-opening of the *endo*-diacetate in CH_2Cl_2 gave (1α,2α,3β,6β)-6-chloro-4-cyclohexene-1,2,3-triol 1,2-diacetate by means of halogen exchange.

1. Introduction

Bromoconduritol is a covalent, irreversible, active-site directed glucosidase inhibitor. It inhibits mammalian α-glucosidase II (but not α-glucosidase I), yeast α-glucosidase and some β-glucosidases.[1] Bromoconduritol is a diastereomeric mixture of (1α,2β,3α,6β)-6-bromo-4-cyclohexene-1,2,3-triol (in the construction of conduritol-B) and (1α,2β,3α,6α)-6-bromo-4-cyclohexene-1,2,3-triol (in the construction of conduritol-F) prepared from conduritol-B by treatment with HBr.[1d] Apart from this method, however, only a small number of procedures are reported in the literature for the preparation of the other bromoconduritols. Guo[2] et al. described a method for the preparation of dihalogenoconduritols having a conduritol-A and B construction by the reaction of dilithium tetrachlorocuprate and dilithium tetrabromonickelate with unsaturated epoxides. In addition, they reported an improved procedure for the preparation of conduritol-B, from which they prepared mono and dibromoconduritol and chloroconduritol derivatives having a conduritol-B, E, and F construction.[3] Haines[4] and co-workers have reported the formation of some bromoconduritol derivatives in the synthesis of (1α,2α,4β)-5-cyclohexene-1,2,4-triol. Hudlicky[5] and co-workers showed the preparation of chloro and fluoroconduritol derivatives having conduritol-F and conduritol-E construction by the substitution of an epoxide derived from 3-chloro-cyclohexa-3,5-diene-*cis*-1,2-diol. In this paper, we present a method for the stereoselective preparation of a new bromoconduritol and chloroconduritol having the conduritol-A construction.

2. Results and discussion

Our synthesis was inspired by the conduritol-C synthesis described by Zefirov[6] et al. They prepared conduritol-C by acidic hydrolysis of furan–vinylene carbonate cycloadducts (**3** and **4**) followed by neutralization. In this reaction, the etheric bond is cleaved stereospecifically to give conduritol-C (**5**) (Scheme 1).



Scheme 1. (i) Heating at 123–127°C; (ii) H_2SO_4, H_2O; (iii) $Ba(OH)_2$.

Keywords: haloconduritol; furan; vinylene carbonate; cycloaddition; ring-opening; boron trihalides; neighboring group participation; *trans*-esterification.

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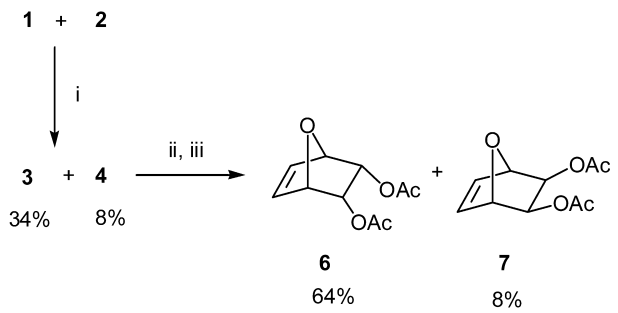
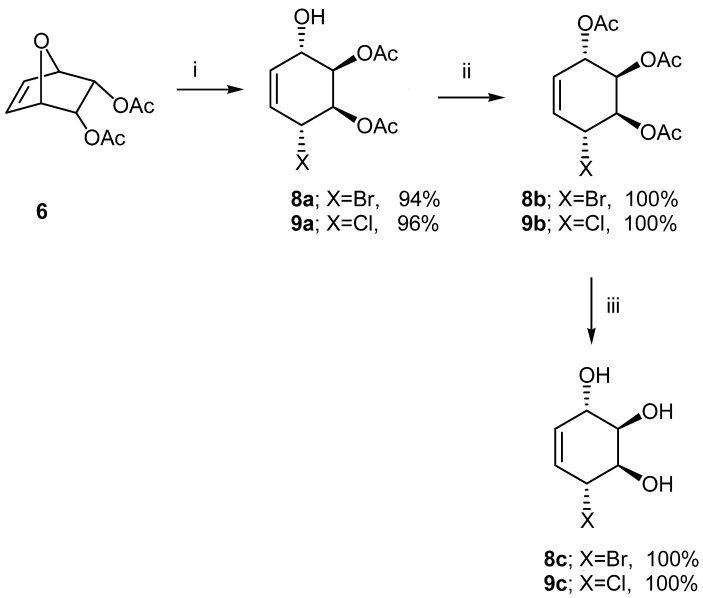


Scheme 2. (i) Heating at 123–127°C in pressure tube, 21 h; (ii) K_2CO_3, MeOH; (iii) Ac_2O, pyridine.

derivative **8b**, reacting with acetyl chloride in quantitative yield for further characterization and safe storage. HCl-catalyzed *trans*-esterification of triacetate **8b** in MeOH gave bromoconduritol **8c** in quantitative yield. In the same manner, the reaction of *endo*-diacetate **6** with BCl_3 gave chloroconduritol diacetate **9a** in a yield of 96%. Acetylation of **9a** with acetyl chloride for further characterization afforded chloroconduritol triacetate **9b**, from which chloroconduritol **9c** was prepared by *trans*-esterification in quantitative yield (Scheme 3). An important point is that if the temperature of the reaction with BBr_3 or BCl_3 rises above −78°C, many reaction products are formed. The *trans*-esterification procedure is also very important for the



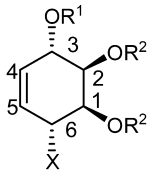
Scheme 3. (i) BX_3, CH_2Cl_2, −78°C, then H_2O (BX_3=BBr_3 or BCl_3); (ii) CH_3COCl, CH_2Cl_2; (iii) MeOH, HCl, 0°C.

Boron tribromide and boron trichloride have been successfully used to cleave ethers for 40 years.[7] Vogel[8] et al. showed stereospecific cleavage of the etheric bond of the Diels–Alder adducts of maleic anhydride to furfuryl esters using BBr_3. We assumed that the cleavage of the etheric bond in furan–vinylenecarbonate cycloadducts (**3** and **4**) with boron trihalides would result in the formation of halogenoconduritols.

In the first step of our synthesis, we prepared cycloadducts **3** and **4** by heating furan (**1**) and vinylene carbonate (**2**) in a sealed tube according to the literature procedure.[9] In this reaction, *endo*-cycloadduct **3** is formed as the main product (ratio of **3/4** is 4:1). Attempts to direct the BBr_3 assisted ring-opening of **3** failed due to insolubility in the solvent (CH_2Cl_2) at the reaction temperature (−78°C). Considering the high polarities and solubility problem in CH_2Cl_2, we directly converted the mixture of cycloadducts **3** and **4** into acetate derivatives **6** and **7** by basic hydrolysis followed by acetylation with acetyl chloride (Scheme 2). Acetate derivatives **6** and **7** were easily separated by column chromatography.

Treatment of *endo*-diacetate **6** with BBr_3 at −78°C gave bromoconduritol diacetate **8a** as the sole product in a yield of 94%. Diacetate **8a** was converted into triacetate

Table 1. Proton coupling constants for **8a–c** and **9a–c** (J, Hz)



8a; R^1=H, R^2=Ac, X=Br
8b; R^1=R^2=Ac, X=Br
8c; R^1=R^2=H, X=Br
9a; R^1=H, R^2=Ac, X=Cl
9b; R^1=R^2=Ac, X=Cl
9c; R^1=R^2=H, X=Cl

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{1,6}$	$J_{3,5}$
8a	2.4	7.0	2.2	10.1	3.3	4.3	–
8b	2.1	[a]	2.6	10.0	3.8	4.4	–
8c	2.3	7.0	2.6	9.9	3.6	4.0	1.4
9a	2.1	6.0	2.2	10.3	2.7	5.2	–
9b	2.0	[a]	2.0	10.0	3.1	5.2	–
9c	2.3	6.2	[b]	10.0	[b]	4.8	–

[a] Undetermined from spectrum.
[b] In the ^{1}H NMR spectrum of **9c** H_4 and H_5 resonate as an AB system due to broadening of the peaks. The same broadening is observed with H_3 and H_6.

hydrolysis of triacetates **8b** and **9b**. Due to halides being in an allylic position, they are very reactive to substitution. Thus, experiments performed under basic conditions for the hydrolysis of **8b** and **9b** failed to give halogenoconduritols **8c** and **9c**.

Complete peak assignments of the NMR spectra of **8a–c** and **9a–c** were carried out. Taking into consideration the coupling constants we easily elucidated the relative stereochemistry of H_1, H_2, and H_3 (Table 1).

Looking at $J_{1,2}$ values ranging from 2.0 to 2.4 Hz we easily determined that H_1 and H_2 are *cis*. $J_{2,3}$ values between 6.0 and 7.0 Hz are consistent with a *trans*-construction. The mechanistic considerations also support the idea that H_2 and H_3 are *trans*. Here, the most difficult problem was to determine the relative stereochemistry of H_6. Based on $J_{1,6}$ values ranging from 4.0 to 5.2 Hz indicates that H_1 and H_6 could be *trans* or *cis*. Vogel[10] et al. have reported *cis* coupling constants $J_{1,2}$=2 Hz and $J_{2,3}$=1.5 Hz, and a *trans* coupling constant $J_{3,4}$=8 Hz in conduritol-C (**5**). Comparing the literature value of $J_{1,2}$ (2 Hz, *cis*) in conduritol-C with $J_{1,6}$ (4.0–5.2 Hz) in **8** and **9** suggest differences in these structures. A comparison of our spectral data established that they were different to the reported stereoisomers **10**[4] and **11**[†] having a conduritol-C construction. In halogen-substituted conduritol-A type cyclohexenyl systems[12] *trans* coupling constants ($J_{1,6}$ and $J_{2,3}$ according to our numbering in Table 1) vary from 4.3 to 7.3 Hz while *cis* coupling constants $J_{2,3}$ are 2.1–2.6 Hz. These values are consistent with those in Table 1. In particular, a comparison of coupling constants **8a–c** and **9a–c** with those of A-type dihalogenoconduritols **12**[2] and **13**[2] supplied us with results in good agreement with those of the dihalogenoconduritols (Fig. 1).[13]

The configurations of the halogens at C_6 of **8c** and **9c** were also confirmed by the observation of NOE effects. In **8c**, the irradiation of H–C_6(Br) at δ 4.61 caused signal enhancement of the resonances at the adjacent double bond proton (H_5), and in particular at H_3. In a similar way, in **9c**, irradiation of H–C_6(Cl) at δ 4.49 caused signal enhancement of the resonances at the adjacent double bond proton (H_5), and in particular at H_3.

In the light of structures **8a** and **9a**, we outline the BBr_3 or BCl_3 assisted ring-opening mechanism of **6** in Scheme 4.

Vogel[14] et al. have reported the neighboring group participation of benzoate in BBr_3-assisted ring-opening of furan cycloadducts. Moreover, neighboring group participation of acetates was observed in many conduritol syntheses.[15] Based on these literature reports we propose a similar neighboring group participation. As seen in Scheme 4, first BX_3 is bound to **6** using the etheric oxygen to form intermediate **14**. Then, cleavage by attack of the carbonyl oxygen of the neighboring acetate affords intermediate **15** and a free halide (X^-). An attack of free halide at the allylic carbon by an S_N2 mechanism gives intermediate **16**, which forms **8a** or **9a** by hydrolysis. Alternatively, in the first step

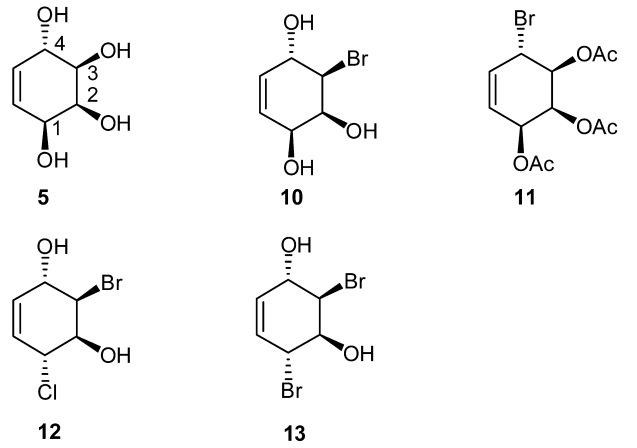
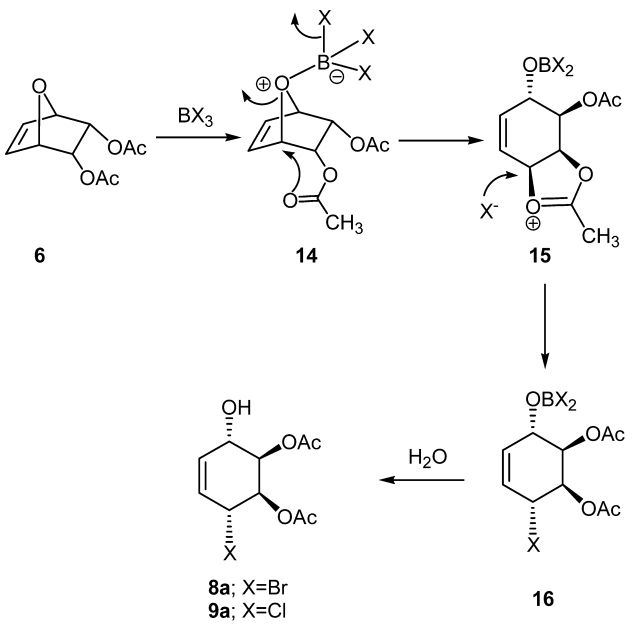


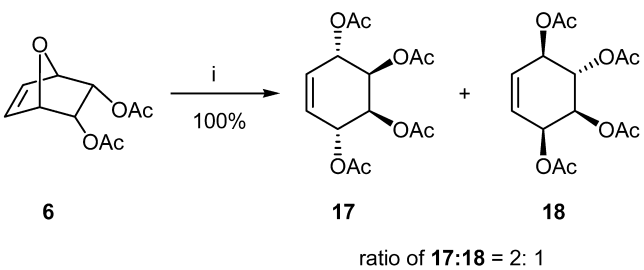
Figure 1.

of the reaction, BX_3 may be bonded to carbonyl oxygen of the acetate, which is presumably more basic. Probably, this is not productive to afford any product.

As outlined in Scheme 1, without any neighboring group participation **3** and **4** would give conduritol-C. As chemical evidence for the mechanism in Scheme 4, we propose that **6** should give conduritol-A tetraacetate (**17**) by acetolysis with acetic anhydride under acidic conditions. Indeed, this reaction afforded conduritol-A tetraacetate (**17**) and



Scheme 4. Suggested mechanism for BX_3 assisted ring opeining of **6**.



Scheme 5. (i) Ac_2O, H_2SO_4, room temperature.

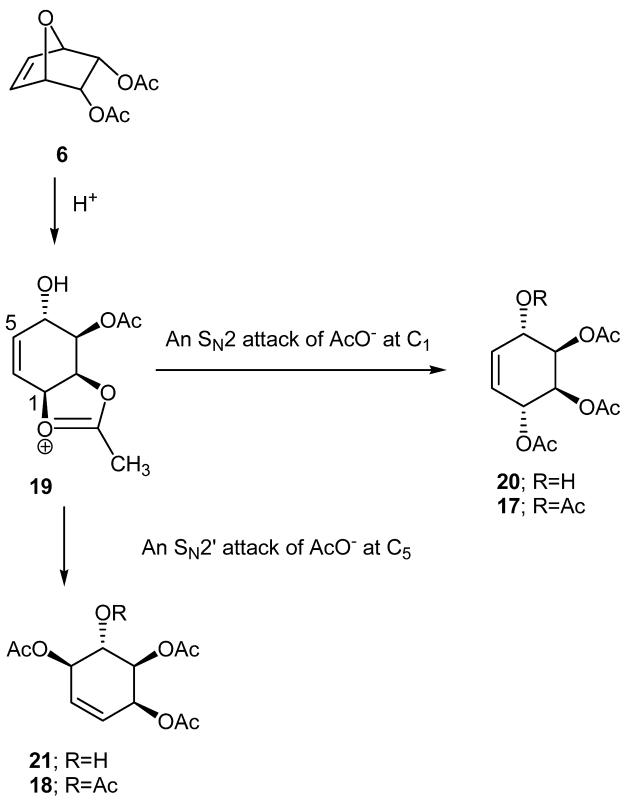
[†] We thank Professor W. B. Motherwell for providing unpublished data on this compound.[11]

conduritol-F tetraacetate (**18**) in a ratio of 2:1 (Scheme 5). We easily characterized conduritol-A tetraacetate **17**[16] and conduritol-F tetraacetate **18**[15b] by comparing their NMR spectroscopic data with those of authentic samples.

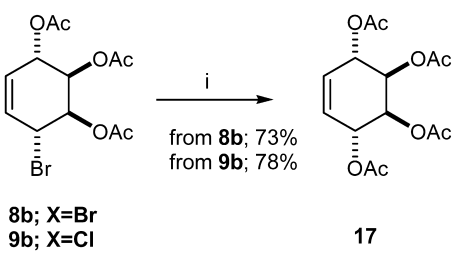
The acetolysis reaction of **6** with neighboring group participation probably proceeds through a **19**-like intermediate. While an S_N2 attack of acetate at C_1 gives conduritol-A tetraacetate **17** through **20**, an S_N2' attack at C_5 gives conduritol-F tetraacetate **18** through **21** (Scheme 6).

We submitted **8b** and **9b** to substitution with KOAc. Both reactions also resulted in the formation of conduritol-A tetraacetate **17** (Scheme 7). The formation of conduritol-A tetraacetate **17** in both reactions shows that they proceed via neighboring group participation, probably through a **19**-like intermediate.

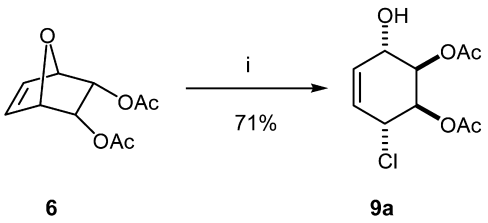
We expected fluoroconduritol formation by the BF_3-assisted ring opening of **6**. The reaction performed in CH_2Cl_2 gave chloroconduritol derivative **9a** instead of a fluoroconduritol



Scheme 6. Suggested mechanism for the formation of **17** and **18** from **6**.



Scheme 7. (i) KOAc, Ac_2O, AcOH, reflux.



Scheme 8. (i) BF_3, CH_2Cl_2, −78°C then H_2O.

derivative, which was a surprising result (Scheme 8). Repeated experiments gave the same result. This reaction probably occurs via in situ halogen exchange[17] between CH_2Cl_2 and BF_3 to form BCl_3 (or $BClF_2$ etc.). There was no reaction when the reaction was performed in Et_2O, THF, benzene or EtOAc.

3. Conclusion

In conclusion, we have described an efficient method for the preparation of bromoconduritol and chloroconduritol having a conduritol-A construction via *endo*-cycloadduct of furan and vinylene carbonate. Our studies on the ring-opening of *exo*-cycloadducts are currently in progress.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures before use. Melting points were determined on a Thomas-Hoover capillary melting apparatus. Infrared spectra were obtained from KBr pellets on a Mattson 1000 FT-IR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a 200 (50) MHz Varian spectrometer. The mass spectra were recorded on VG Zabspec GC–MS instruments. Elemental analyses were carried out on a Carlo Erba 1106 model CHNS-O analyser. Column chromatography was performed on silica gel 60 (70–230 mesh ASTM). Thin layer chromatography was carried out on Merck 0.2 mm silica gel, 60 F_{254} analytical aluminum plates.

4.1.1. Vinylene carbonate (2). The reported procedure[9] was used for the synthesis of vinylene carbonate **2**. Bp 52°C/25 mm Hg (lit.[9] bp 73–74°C/32 mm Hg). ^1H NMR (200 MHz, $CDCl_3$) δ 6.34 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.6, 92.3.

4.1.2. Diels–Alder reaction of furan (1) and vinylene carbonate (2). The cycloaddition procedure described in the literature[9] was used to afford cycloadducts **3** and **4** in a ratio of 4:1 (Yield: 42% based on furan). Recrystallization of the mixture of **3** and **4** from hexane–ethyl acetate (1:1) gave two types of crystal, which were separated based on appearance.

endo-Cycloadduct **3**. Salt-like colorless crystal, mp 144–146°C, lit.[18] 144–148°C. ^1H NMR (200 MHz, $CDCl_3$) δ 6.51 (br s, 2H) 5.16 (m, AA′ part of AA′BB′ system, 2H), 4.94 (m, BB′ part of AA′BB′ system, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.3, 136.1, 81.2, 76.3.

exo-Cycloadduct **4**. Colorless needless, mp 130–132°C, lit.[18] 137–139°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.38 (s, 2H) 5.05 (s, 2H), 4.65 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.7, 136.7, 82.6, 78.4.

4.1.3. *endo*-Diacetate 6 and *exo*-diacetate 7. A 4:1 isomeric mixture of cycloadducts **3** and **4** (4.62 g, 30 mmol) was dissolved in 100 mL of MeOH–H_2O (20:1) and then K_2CO_3 (1.00 g) was added. The resulting mixture was magnetically stirred at room temperature for 10 h. The mixture was neutralized with AcOH and the solvent was evaporated. To the residue were added Ac_2O (7.35 g, 72 mmol) and 10 mL of pyridine. The mixture was stirred at room temperature for 6 h. The mixture was cooled to 0°C and 70 mL of 10% HCl solution was added, followed by extraction with ethyl acetate (3×50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (3×10 mL) and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a mixture of diacetates **6** and **7** (5.09 g, overall yield of crude acetate mixture: 80%). Chromatography of the diacetates on a silicagel column (40 g) eluting with hexane–ethyl acetate (2:1) gave *endo*-diacetate **6** as the first fraction and *exo*-diacetate **7** as the second.

First fraction endo-cis-7-oxabicyclo[2.2.1]hept-5-ene-2,3-diol diacetate (**6**). R_f=0.35, (4.10 g, 64%). Colorless crystals. Mp 81–83°C (lit.[19] 75–76°C, from Et_2O). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.42 (br s, 2H), 5.07–5.03 (AA′BB′ system, 4H), 1.96 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.6, 136.8, 80.6, 70.7, 22.4. **IR** (KBr) 3185, 2978, 1754, 1439, 1388, 1244, 1105, 1076, 1037, 944 cm^{-1}. Anal. calcd for $C_{10}H_{12}O_5$ (212.20): C, 56.60; H, 5.70; Found: C, 56.56; H, 5.69.

Second fraction exo-cis-7-oxabicyclo[2.2.1]hept-5-ene-2,3-diol diacetate (**7**). R_f=0.19 (0.52 g, 8%). Colorless crystal. Mp 91–92°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.45–6.43 (m, 2H), 4.89–4.87 (m, 2H), 4.81 (br s, 2H), 2.09 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 137.9, 83.5, 72.0, 22.6. IR (KBr) 3104, 3012, 2950, 1758, 1727, 1430, 1380, 1292, 1257, 1052, 944 cm^{-1}. Anal. calcd for $C_{10}H_{12}O_5$ (212.20): C, 56.60; H, 5.70. Found: C, 56.61; H, 5.66

4.1.4. (1α,2α,3β,6,β)-6-Bromo-4-cyclohexene-1,2,3-triol 1,2-diacetate (8a). Under nitrogen atmosphere, to a stirred solution of *endo*-diacetate **6** (1.00 g, 4.7 mmol) in 20 mL of CH_2Cl_2 was added dropwise a solution of BBr_3 (0.5 mL, 1.30 g, 5.2 mmol) in 20 mL of CH_2Cl_2 at −78°C over 10 min. After addition was completed, the mixture was stirred at 0°C for 1 h, and then at room temperature for 4 h under air atmosphere. To the reaction mixture was added 5 mL of saturated $NaHCO_3$ solution. The organic phase was separated. The aqueous phase was additionally extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent gave **8a** (colorless oil, 1.30 g, 94%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.90 (br dd, 1H, H_5, $J_{4,5}$=10.1 Hz, $J_{5,6}$=3.3 Hz), 5.80 (dd, 1H, H_4, $J_{4,5}$=10.1 Hz, $J_{3,4}$=2.2 Hz), 5.42 (dd, 1H, H_1, $J_{1,6}$=4.3 Hz, $J_{1,2}$=2.4 Hz), 5.31 (dd, 1H, H_2, $J_{2,3}$=7.0 Hz, $J_{1,2}$=2.4 Hz), 4.53 (dd, 1H, H_6, $J_{1,6}$=4.3 Hz, $J_{5,6}$=3.3 Hz), 4.46 (br d, 1H, H_3, $J_{2,3}$=7.0 Hz), 3.78 (br s, OH), 2.11 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4, 171.5, 132.6, 129.3, 74.6, 73.7, 68.8, 45.2, 22.9, 22.7. IR (KBr) 3463, 3004, 1769, 1429, 1361, 1240, 1057, 922 cm^{-1}.

4.1.5. (1α,2α,3β,6β)-6-Chloro-4-cyclohexene-1,2,3-triol 1,2-diacetate (9a). The procedure described above for BBr_3 was applied to **6** using BCl_3 to give **9a** (colorless oil, 96%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.79 (dd, 1H, H_4, $J_{4,5}$=10.3 Hz, $J_{3,4}$=2.2 Hz), 5.73 (dd, 1H, H_5, $J_{4,5}$=10.3 Hz, $J_{5,6}$=2.7 Hz), 5.27 (dd, 1H, H_1, $J_{1,6}$=5.2 Hz, $J_{1,2}$=2.1 Hz), 5.15 (dd, 1H, H_2, $J_{2,3}$=6.0 Hz, $J_{1,2}$=2.1 Hz), 4.42 (dd, 1H, H_6, $J_{1,6}$=5.2 Hz, $J_{5,6}$=2.7 Hz), 4.24 (br d, 1H, H_3, $J_{2,3}$=6.0 Hz), 3.62 (br s, OH), 2.00 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3, 171.7, 132.4, 129.1, 74.2, 73.8, 68.5, 55.5, 22.8, 22.7. IR 3448, 2941, 1749, 1437, 1379, 1240, 1055, 951 cm^{-1}.

4.1.6. (1α,2α,3β,6β)-6-Bromo-4-cyclohexene-1,2,3-triol triacetate (8b). To a solution of **8a** (1.00 g, 3.4 mmol) in 20 mL of CH_2Cl_2 was added acetyl chloride (0.32 g, 4.1 mmol). The resulting mixture was stirred for 12 h. Removal of the solvent, HCl, and excess acetyl chloride under reduced pressure (30°C, 25 mm Hg) gave triacetate **8b** (colorless oil, 1.14 g, quantitative). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.95 (dd, 1H, H_5, $J_{4,5}$=10.0 Hz, $J_{5,6}$=3.8 Hz), 5.68 (dd, 1H, H_4, $J_{4,5}$=10.0 Hz, $J_{3,4}$=2.6 Hz), 5.53–5.42 (m, 2H, H_2 and H_3), 5.38 (dd, 1H, H_1, $J_{1,6}$=4.4 Hz, $J_{1,2}$=2.1 Hz), 4.51 (dd, 1H, H_6, $J_{1,6}$=4.4 Hz, $J_{5,6}$=3.8 Hz), 2.07 (s, 6H), 2.02 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.5, 171.0 (two carbon), 131.2, 128.7, 74.4, 70.4, 70.2, 44.1, 22.7, 22.6 (two carbon). IR (KBr) 3061, 2995, 2961, 1757, 1437, 1379, 1233, 1055, 963.

4.1.7. (1α,2α,3β,6β)-6-Chloro-4-cyclohexene-1,2,3-triol triacetate (9b). The procedure described above for **8a** was applied to **9a** to give triacetate **9b** (colorless oil, 100%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85 (dd, 1H, H_5, $J_{4,5}$=10.0 Hz, $J_{5,6}$=3.1 Hz), 5.68 (dd, 1H, H_4, $J_{4,5}$=10.0 Hz, $J_{3,4}$=2.0 Hz), 5.34–5.25 (m, 2H, H_2 and H_3), 5.22 (dd, 1H, H_1, $J_{1,6}$=5.2 Hz, $J_{1,2}$=2.0 Hz), 4.42 (dd, 1H, H_6, $J_{1,6}$=5.2 Hz, $J_{5,6}$=3.1 Hz), 2.03 (s, 6H), 1.99 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.5, 171.1, 171.0, 131.1, 128.6, 74.1, 70.4, 70.2, 54.7, 22.7, 22.5 (two carbon). IR (KBr) 2978, 2876, 1753, 1446, 1395, 1242, 1063, 961 cm^{-1}.

4.1.8. (1α,2α,3β,6β)-6-Bromo-4-cyclohexene-1,2,3-triol (8c). A stirred solution of **8b** (1.00 g, 3.0 mmol) in 20 mL of methanol was cooled to 0°C. At the given temperature, HCl gas was passed through the solution over 20 min. The reaction flask was closed with a stopper and stirred at room temperature for 12 h. Removal of the solvent, methyl acetate and HCl under reduced pressure (30°C, 25 mm Hg) gave bromoconduritol **8c** (0.63 g, quantitative). Colorless crystals, mp 129–130°C (from EtOAc). ^{1}H NMR (200 MHz, CD_3OD) δ 5.84 (ddd, 1H, H_5, $J_{4,5}$=9.9 Hz, $J_{5,6}$=3.6 Hz, $J_{3,5}$=1.4 Hz), 5.71 (dd, 1H, H_4, $J_{4,5}$=9.9 Hz, $J_{3,4}$=2.6 Hz), 4.61 (dd, 1H, H_6, $J_{1,6}$=4.0 Hz, $J_{5,6}$=3.6 Hz), 4.30 (dm, 1H, H_3, $J_{2,3}$=7.0 Hz). 4.16 (dd, 1H, H_1, $J_{1,6}$=4.0 Hz, $J_{1,2}$=2.3 Hz), 3.96 (dd, 1H, H_2, $J_{2,3}$=7.0 Hz, $J_{1,2}$=2.3 Hz). ^{13}C NMR (50 MHz, CD_3OD) δ 134.3, 130.2, 76.9, 74.4, 71.9, 52.1. IR (KBr) 3387, 3182, 2953, 2876, 1472, 1421, 1370, 1319, 1268, 1242, 1217, 1165, 1114,

1063, 1038, 1012, 987. EIMS *m/z* (%): 192.0 [M^+-H_2O] (5),190.0 [M^+-H_2O] (5), 149.9 (98), 147.9 (100), 111.0 (85), 99.0 (80), 83.0 (100) 65.1 (51), 60.1 (37). Anal. calcd for $C_6H_9BrO_3$ (209.04) C, 34.47; H, 4.34. Found: C, 34.81; H, 4.45.

4.1.9. (1α,2α,3β,6β)-6-Chloro-4-cyclohexene-1,2,3-triol (9c). The procedure described above for **8b** was applied to **9b** to give chloroconduritol **9c** in a quantitative yield. Colorless crystals, mp 107–109°C (from EtOAc). ^{1}H NMR (200 MHz, CD_3OD) δ 5.77 (AB system, 2H, H_4 and H_5, $J_{4,5}$=10.0 Hz), 4.49 (br d, 1H, H_6, $J_{1,6}$=4.8 Hz), 4.21 (br d, 1H, H_3, $J_{2,3}$=6.2 Hz), 4.02 (dd, 1H, H_1, $J_{1,6}$=4.8 Hz, $J_{1,2}$=2.3 Hz), 3.80 (dd, 1H, H_2, $J_{2,3}$=6.2 Hz, $J_{1,2}$=2.3 Hz). ^{13}C NMR (50 MHz, CD_3OD) δ 133.9, 130.1, 76.4, 75.0, 72.0, 60.9. IR (KBr) 3387, 3182, 2953, 2876, 1625, 1472, 1421, 1370, 1344, 1268, 1242, 1217, 1191, 1114, 1089, 1038, 1012, 987. EIMS *m/z* (%): 149 [M^+-OH] (9), 147 [M^+-OH] (15), 137 (4), 129 (9), 112 (54), 105 (100), 104 (92), 100 (65), 83 (63). Anal. calcd for $C_6H_9ClO_3$ (164.59): C, 43.78; H, 5.51. Found: C, 44.1, H, 5.3.

4.1.10. Acid-catalyzed acetolysis of *endo*-diacetate 6 with Ac_2O. *endo*-Diacetate **6** (1.00 g, 4.7 mmol) was dissolved in Ac_2O (5 mL). After the addition of one drop of H_2SO_4 the reaction mixture was magnetically stirred at room temperature for 6 h. Ac_2O was removed under reduced pressure. The residue was chromatographed on basic Al_2O_3 (20 g) eluting with $CHCl_3$. Evaporation of the solvent gave the mixture of conduritol-A tetracetate (**17**)[16] and conduritol-F tetraacetate (**18**)[15b] in a ratio of 2:1 (1.47 g, total yield:quantitative).

4.1.11. Substitution of 8b with KOAc. The literature procedure described for 1,4-diacetoxy-2,3-dibromo-5-cyclohexene[3] was applied to **8b** to give conduritol-A tetracetate (**17**)[16] in a yield of 73%.

4.1.12. Substitution of 9b with KOAc. The literature procedure described for 1,4-diacetoxy-2,3-dibromo-5-cyclohexene[3] was applied to **9b** to give conduritol-A tetracetate (**17**)[16] in a yield of 78%.

4.1.13. BF_3-Assisted ring-opening of 6 in CH_2Cl_2. The procedure described for the preparation of **8a** was applied to **6** in CH_2Cl_2 using $BF_3{\cdot}OEt_2$ to give chloroconduritol derivative **9a**, colorless oil, in a yield of 71%.

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