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Synthesis of bromo-conduritol-B and bromo-conduritol-C as glycosidase inhibitors

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ABSTRACT

For the synthesis of bromo-conduritol-B skeleton, bromo-1,4-benzoquinone was subjected to bromination followed by the reduction of the carbonyl groups with $NaBH_4$. Substitution of bromides bonded to sp^3-hybridized carbon atoms with AgOAc gave the bromo-conduritol-B tetraacetate in high yield. For the construction of bromo-conduritol-C skeleton, 2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole was used as the starting material. Photooxygenation of the diene unit gave an unsaturated bicyclic endoperoxide. Bromine was incorporated into the molecule by the addition of bromine to the double bond. Opening of the peroxide linkage followed by HBr elimination and reduction of the carbonyl group provided the conduritol-C structure in good yield. Bromo-conduritol-B exhibited strong enzyme-specific inhibition against α-glycosidase.

1. Introduction

Conduritols (**1–6**) are cyclohexene tetrols. The presence of four stereogenic C-atoms allows them to exist in six different configurations.[1–4] Conduritols and their derivatives have been found to possess antibiotic, antileukemic and tumor-inhibitory properties, and glycosidase inhibitory activity (Chart 1).[1,5]

Conduritols A–F are useful intermediates in organic synthesis, and some derivatives such as epoxides can act as irreversible glycosidase inhibitors.[4] In connection with the conduritols, haloconduritols and double bond-substituted conduritols have also gained importance in the last decade. For instance, bromo-conduritols are interesting molecules in AIDS research because they are active site directed, covalent inhibitors of α-glucosidases. Various groups have reported the synthesis of halo-substituted conduritols starting from *cis*-cyclohexa-3,5-diene-1,2-diols, which are available by microbial oxidation of aromatic compounds.[6–13] We, herein, report two novel, simple, and efficient methodologies for the synthesis of bromo-conduritol-B (**14**) and bromo-conduritol-C (**24**) and their enzyme-specific inhibition against α-glycosidase.

2. Results and discussion

Commercially available hydroquinone (**7**) was used as the starting material for the synthesis of bromo-conduritol-B **14**. Bromination of hydroquinone (**7**) as described in the literature[14,15] followed by oxidation of bromohydroquinone (**8**) with $Ce(NH_4)_2(NO_3)_6$ (CAN) gave the key compound bromo-quinone (**9**)[16] in 85% yield (Scheme 1).

The quinone **9** was brominated at −20 °C to give only the *trans*-dibromide **10** in 94% yield. The NMR spectral studies indicated the regiospecific addition of bromine to the unsubstituted double bond.[17] The regiospecific addition of bromine to the unsubstituted double bond can be attributed to the steric effect caused by the bromine atom as well as by reduced electron density. It is known that bromine decreases the reactivity of the double bond toward electrophiles. Reduction of the carbonyl groups in **10** with $NaBH_4$ in ether at −10 °C followed by acetylation of the hydroxyl groups in **11** with Ac_2O and pyridine gave the diacetate **12**. The NMR spectral studies clearly established the formation of only one isomer of the diacetate **12**.[18] The coupling constant between the protons close to bromine atoms is measured to be $J_{5,6}$ = 10.9 Hz. This value is consistent with a typical axial/axial coupling constant in the cyclohexene ring, indicating the trans-configuration as well as the equatorial/equatorial position of the bromine atoms. Furthermore, the observed coupling constants between the protons H-1

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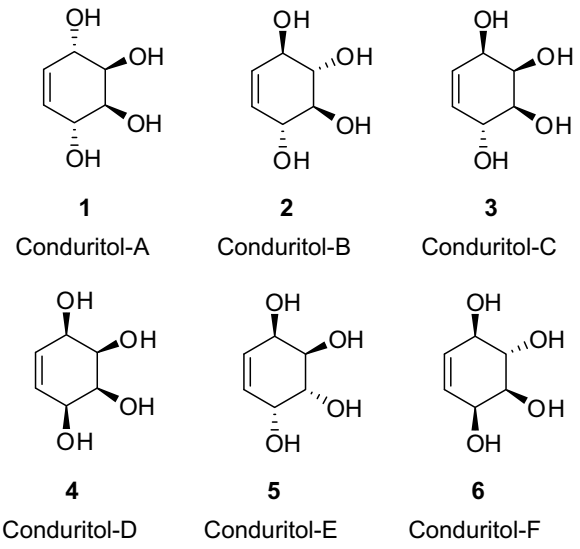
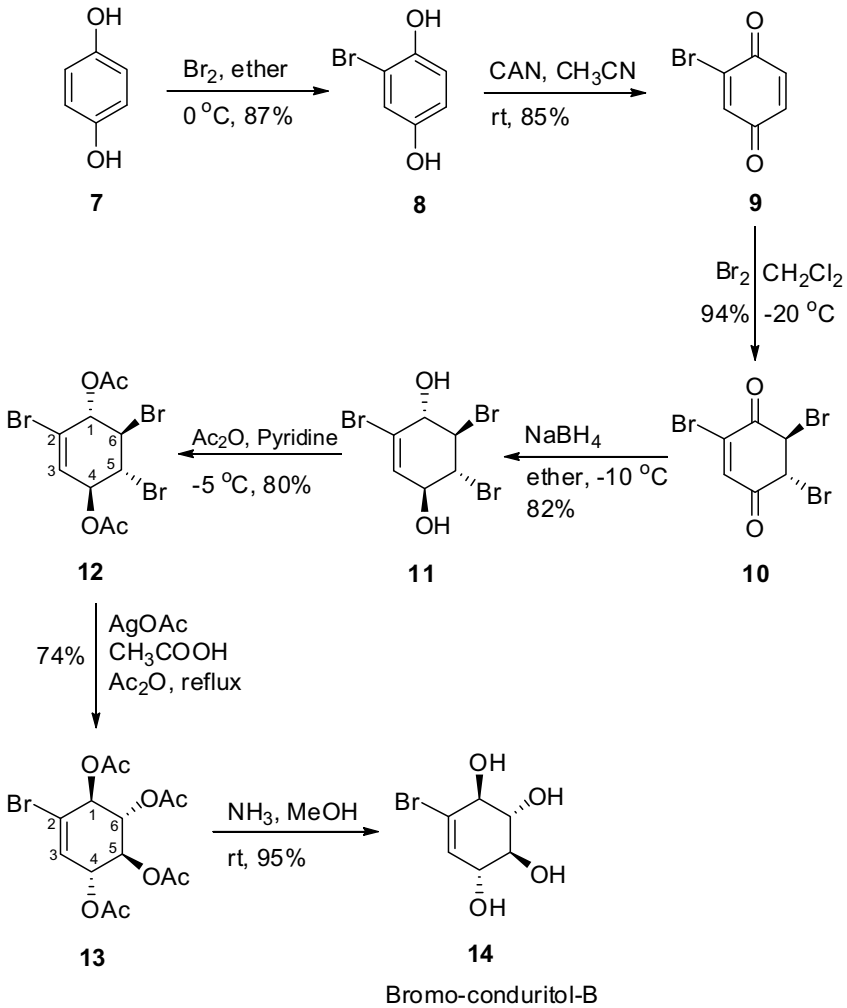


Chart 1.

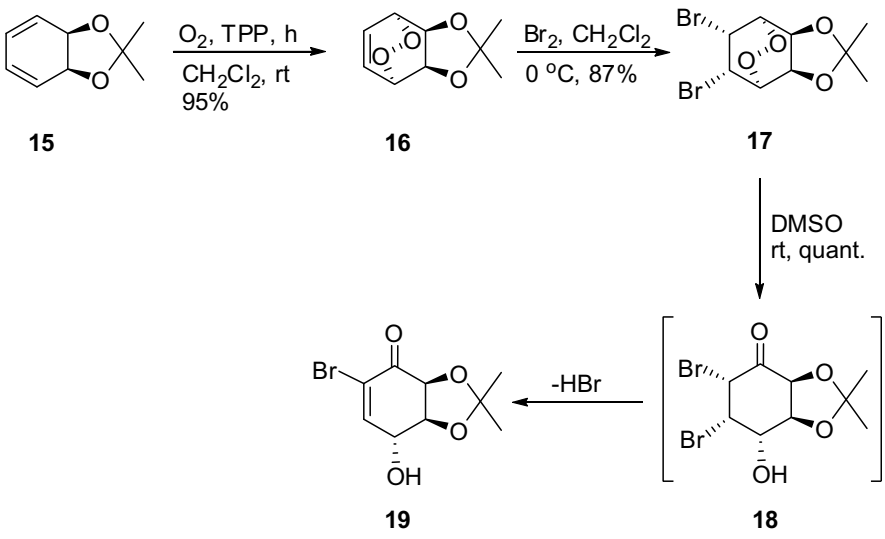
and H-6 ($J_{1,6}$ = 6.6 Hz), and H-4 and H-5 ($J_{4,5}$ = 6.8 Hz) confirm the trans-configuration of the acetate groups and bromine atoms.

Diacetate **12** was then treated with AgOAc and Ac_2O in acetic acid in order to substitute the bromine atoms with acetate groups. The NMR spectral studies showed the formation of a single tetraacetate, **13**. The exact configuration of tetraacetate was determined on the basis of the ^1H and ^{13}C NMR spectra in conjunction with 2D-NMR (DEPT, COSY, HMQC, and HMBC) experiments. In particular, the measured coupling constants $J_{1,6}$ = 7.1 Hz, $J_{4,5}$ = 6.6 Hz, and $J_{5,6}$ = 10.4 Hz indicate that the relative configuration of the acetate groups is trans/trans/trans. The stereoselective formation of **13** can be explained by the neighboring group participation.[19] Removal of the acetate groups in **13** with ammonia in methanol resulted in the formation of bromo-conduritol-B **14** in 95% yield.

For the synthesis of the bromo-conduritol-C **24**, we started from 2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole (**15**).[20,21] Photooxygenation of **15** in methylene chloride (500 W, projection lamp) at room temperature using tetraphenylporphyrine as the sensitizer afforded bicyclic endoperoxide **16** in a yield of 95% (Scheme 2).[22] In order to introduce the bromine atom into the molecule, the double bond in **16** was subjected to bromination. Treatment of the endoperoxide **16** with bromine in methylene chloride at 0 °C afforded the dibromo adduct **17** in 87% yield. The structure of the adduct was elucidated on the basis of ^1H and ^{13}C NMR data. The symmetrical NMR spectrum clearly indicates the cis-addition[23] of bromine atoms. The *endo* (relative to the peroxide linkage) stereochemical assignment for the bromine atoms is supported by the absence of a measurable coupling between CHBr protons and



Scheme 1.

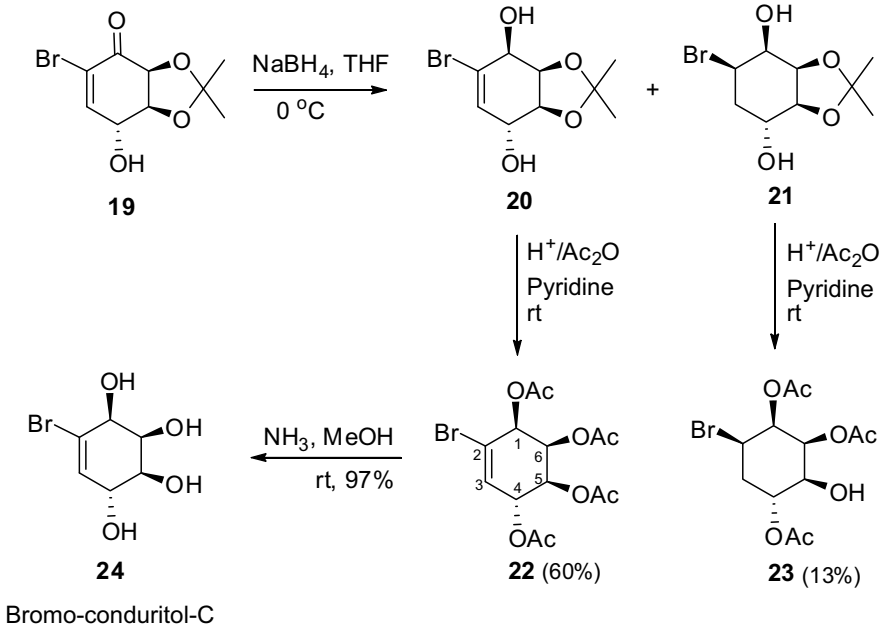


Scheme 2.

bridgehead protons. AM1 calculations also support this finding. In the case of *endo*-configuration, the dihedral angle between the relevant protons is 72°; however, in the *exo*-configuration the corresponding angle is 55°.

After successful isolation and characterization of the endoperoxide **17**, we turned our attention to the opening of the peroxide linkage in **17**. Unsaturated bicyclic endoperoxides can be easily converted into the corresponding hydroxy enones upon treatment with base or acids.[24,25] However, we noted that endoperoxide **17** rearranges quantitatively into the corresponding bromoenone **19** upon dissolving in DMSO. We assume that the endoperoxide first undergoes a rearrangement to form the saturated hydroxyketone **18** followed by HBr elimination to give the bromoketone **19**. Since the bond cleavage takes place at the peroxide linkage, the configuration of the hydroxyl group in **18** as well as in **19** will be preserved.

For the synthesis of the target compound **24**, bromoenone **19** was subjected to a $NaBH_4$ reduction in THF at 0 °C followed by acetylation with acetic anhydride in the presence of acid to give two reduced products, **22** and **23** (Scheme 3). Spectral analysis indicated the formation of a conduritol-C derivative. Because of the unsymmetrical environment of the carbonyl group, reduction can proceed in two ways to give a either conduritol-A and/or conduritol-C derivative. To determine the configuration of the formed product, we measured the coupling constant between the protons H-1 and H-6. The coupling constant $J_{1,6}$ = 3.8 Hz of **22**, which is consistent with the typical axial/equatorial coupling constant in a cyclohexene ring, indicates the cis-configuration of the acetate groups. The configuration of the remaining three acetate groups should not be changed during the reduction reaction. Furthermore, the extracted coupling constants were in agreement with the proposed cis/cis/trans configuration of the acetate groups. Having



Scheme 3.

ascertained the configuration of **22**, we suggest the following mechanism. The stereoselective formation of **22** can be attributed to the fact that $NaBH_4$ approaches the carbonyl group from the less-crowded side of the carbonyl group to form **20** exclusively. As a side product, **23** was isolated in 13% yield, arising from the reduction of the double bond followed by reduction of the carbonyl group. The exact constitution and configuration of **23** were elucidated with the help of the ^1H and ^{13}C NMR spectra in conjunction with 2D-NMR (DEPT, HMQC, HMBC, and COSY) experiments. Removal of the acetate groups in **22** by ammonia in methanol resulted in the formation of bromo-conduritol-C[13] **24** in high yield.

2.1. α-Glycosidase inhibition assay

The inhibitory activities of **14** and **24** were screened against α-glycosidase. The results are summarized in Table 1. The isomer **14** showed α-glycosidase inhibition, and the inhibition rate was 84 ± 6.9% for 40 μM concentration. The other isomer **24** also exhibited an 8.75 ± 6.9% inhibition rate for 5 μM concentration. When the concentration of **24** was increased to 200 μM, the inhibition rate did not change.

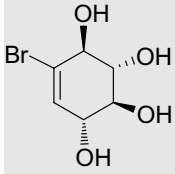
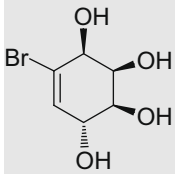
In summary, with relatively little synthetic effort, we achieved the stereoselective synthesis of two isomeric bromo-conduritols **14** and **24** using easily available starting materials. One of the synthesized molecules **14** exhibited enzyme-specific inhibition against α-glycosidase.

3. Experimental

3.1. General

Nuclear magnetic resonance (^1H, ^{13}C, 2D) spectra were recorded on a Bruker Instrument, Avance Series-Spectrospin DPX-400 Bruker, Ultra Shield (400 MHz), High Performance digital FT-NMR spectrometer. Infrared spectra were recorded on a Perkin Elmer 1600 Series FT-IR spectrometer. Column chromatographic separations were performed using Fluka Silica Gel 60 plates with 0.063–0.200 mm particle size. Thin layer chromatography (TLC) was effected using precoated 0.25 mm silica gel plates purchased from Fluka.

Table 1
Inhibition of α-glycosidases **14** and **24**

Compound	Inhibition[a] (%)	IC_{50}[d] (μM)
 **14**	84 ± 6.9[b]	30
 **24**	8.75 ± 0.1[c]	NT[e]

[a] Four experiments are performed for all compounds and in duplicate in each experiment.
[b] Inhibition by 40 μM compound.
[c] Inhibition by 5 μM compound.
[d] Concentration required for 50% inhibition of the enzyme activity under the assay conditions.
[e] NT: Not tested.

3.2. (rel-5*S*,6*S*)-2,5,6-Tribromocyclohex-2-ene-1,4-dione (10)

To a solution of **9**[16] (6.0 g, 32 mmol) in CH_2Cl_2 was added dropwise a solution of bromine (7.5 g, 47 mmol) in CH_2Cl_2 at −20 °C over 2 h. The mixture was stirred at the same temperature for an additional 2.5 h, and then it was allowed to warm up to room temperature. The solvent was removed under reduced pressure to afford **10** (10.5 g, 94%) from EtOAc–hexane as yellow crystals, mp 63–65 °C. ^1H NMR (400 MHz, $CDCl_3/CCl_4$) δ: 7.24 (d, J = 1.8 Hz, 1H, H-3), 4.97 (d, J = 2.7 Hz, 1H, H-6), 4.81 (dd, J = 2.7 and 1.8 Hz, 1H, H_5); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ: 184.6, 180.6, 137.6, 137.2, 44.7, 43.4; IR (KBr, cm^{-1}) 3048 (w), 3000 (w), 1685 (s), 1577 (m), 1327 (m), 1303 (m), 1269 (s), 1224 (s), 1166 (w), 1126 (w), 1023 (m), 951 (s), 906 (m), 791 (w), 768 (w), 708 (w), 632 (m), 617 (m); MS (*m*/*z*, relative intensity): 350/348/346/344, (M^+, 2, 6, 6, 2), 269/267/265 (M^+−Br, 60, 100, 63), 186/188 (M^+−2Br, 24, 24), 135 (40) 133 (45), 103 (20), 82 (30), 79 (45). Anal. Calcd for $C_6H_3Br_3O_2$: C, 20.78; H, 0.87. Found: C, 20.69; H, 0.98.

3.3. (rel-1*S*,4*S*,5*R*,6*R*)-2,5,6-Tribromocyclohex-2-ene-1,4-diol (11)

Tribromo quinone **10** (8.0 g, 23 mmol) was dissolved in 25 mL of ether and cooled down to −10 °C. To this mixture was added dropwise an aqueous solution of $NaBH_4$ at 0 °C (2.2 g, 58 mmol). The reaction was monitored by TLC. After the completion of the reaction, the organic phase was separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4. Removal of the solvent gave the crude product, which was crystallized from MeOH–hexane (4:1) to give white solid **11** (6.6 g, 82%), mp 160–162 °C. ^1H NMR (400 MHz, MeOH-d_4) δ: 6.17 (br s, 1H, H-3), 4.82 (br s, 2H, –OH), 4.44 (br d, $J_{1,6}$ = 7.4 Hz, 1H, H-1), 4.38 (d, $J_{4,5}$ = 7.8 Hz, 1H, H-4), 4.21 (dd, A part of AB-system $J_{5,6}$ = 10.9 and $J_{1,6}$ = 7.4 Hz, 1H, H-6), 4.16 (dd, B part of AB-system, $J_{5,6}$ = 10.9 and $J_{5,4}$ = 7.8 Hz, 1H, H-5); ^{13}C NMR (100 MHz, MeOH-*d*) δ 134.5, 126.7, 76.8, 74.4, 60.0, 59.2; IR (KBr, cm^{-1}) 3357 (br), 2887 (w), 1648 (w), 1588 (w), 1448 (m), 1299 (m), 1260 (m), 1230 (s), 1194 (m), 1058 (s), 892 (m), 819 (m); MS (*m*/*z*, relative intensity): 353/351/349/347 (M^+, 1), 273/271/269 (M^+−HBr, 15/30/15), 255/253/251 (M^+−HBr, $-H_2O$, 35/60/35), 174/172 (M^+−2HBr, $-H_2O$, 75/80), 110 (M^+−2HBr, 100). Anal. Calcd for $C_6H_7Br_3O_2$: C, 20.54; H, 2.01. Found: C, 20.73; H, 2.05.

3.4. (rel-1*S*,4*S*,5*R*,6*R*)-4-(Acetyloxy)-2,5,6-tribromocyclohex-2-en-1-yl acetate (12)

To a stirred solution of **11** (6.0 g, 17.1 mmol) in 10 mL of pyridine was added acetic anhydride (5.2 g, 51.0 mmol) dropwise at −5 °C. The reaction mixture was stirred at room temperature for 8 h. The mixture was poured into 40 mL of HCl solution in ice and extracted with ether (3 × 50 mL). The combined organic extracts were washed with $NaHCO_3$ and water, and then dried over $MgSO_4$. The removal of the solvent under reduced pressure followed by crystallization from EtOH afforded pure white solid product **12** (6.0 g, 80%), mp 110–112 °C. ^1H NMR (400 MHz, $CDCl_3/CCl_4$) δ: 6.18 (t, $J_{3,4}$ = 2.3 Hz, 1H, H-3), 5.88 (d, $J_{1,6}$ = 6.6 Hz, 1H, H-1), 5.58 (dd, $J_{4,5}$ = 6.8 Hz and $J_{3,4}$ = 2.3 Hz, 1H, H-4), 4.31 (dd, A part of AB-system, $J_{5,6}$ = 10.9 Hz and $J_{1,6}$ = 6.6 Hz, 1H, H-6), 4.29 (dd, B part

of AB-system, $J_{5,6}$ = 10.9 Hz and $J_{4,5}$ = 6.8 Hz, 1H, H-5), 2.17 (s, 3H, $-CH_3$), 2.13 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ: 168.8, 168.4, 130.2, 122.7, 73.7, 73.3, 51.0, 50.3, 20.6, 20.5; IR (KBr, cm^{-1}) 2934 (w), 1751 (s), 1429 (w), 1371 (m), 1289 (w), 1205 (s), 1031 (s), 913 (m), 873 (m), 729 (w), 682 (m), 634 (m); MS (*m*/*z*, relative intensity): 438/436/434/432, (M^+, 1%), 357/355/353 (M^+, −Br, 5/10/5), 255/253/252 (55/80/56), 233/231 (100), 191/189 (48/47), 172/174 (55/57), 110 (98); Anal. Calcd for $C_{10}H_{11}Br_3O_4$: C, 27.62; H, 2.55. Found: C, 27.80; H, 2.60.

3.5. (rel-1*S*,4*S*,5*R*,6*R*)-4,5,6-Tris(acetyloxy)-2-bromocyclohex-2-en-1-yl acetate (13)

A vigorously stirred mixture of **12** (6.0 g, 13.8 mmol), glacial AcOH (150 mL), Ac_2O (30 mL), and AgOAc (11.5 g, 69 mmol) was heated under reflux for 3 days under nitrogen atmosphere. After filtration of the precipitate, the solvent was removed under reduced pressure. Methanol (20 mL) was added to the residue followed by stirring for 10 min. The solution was concentrated, and the residue was partitioned between ether (50 mL) and water (75 mL). The organic layer was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to yield a solid. The solid was chromatographed on silica gel by elution with EtOAc–hexane (1:9) to afford colorless crystalline product **13** from EtOH (4.1 g, 74%), mp 109–111 °C. ^1H NMR (400 MHz, $CDCl_3/CCl_4$) δ: 6.20 (t, $J_{3,1} = J_{3,4}$ = 2.0 Hz, H-3), 5.73 (dd, $J_{1,6}$ = 7.1 and $J_{1,3}$ = 2.0 Hz, H_1), 5.47 (dt, $J_{4,5}$ = 6.6 Hz and $J_{4,3}$ = 2.0 Hz, H_4), 5.36 (dd, A part of AB-system, $J_{6,5}$ = 10.4 Hz, $J_{6,1}$ = 7.1 Hz, H_6), 5.31 (1H, dd, B part of AB-system, $J_{5,6}$ = 10.4 Hz and $J_{5,4}$ = 6.6 Hz, H_5), 2.10 (3H, s, $-CH_3$), 2.06 (3H, s, $-CH_3$), 2.02 (3H, s, $-CH_3$), 2.01 (3H, s, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ: 169.2, 168.9 (2C), 168.8, 129.9, 122.1, 72.5, 71.1, 70.9, 70.3, 20.5, 20.4, 20.3, 20.2; IR (cm^{-1}) 3474 (w), 2943 (w), 1753 (s), 1650 (w), 1370 (m), 1217 (s), 1050 (w), 1027 (m), 970 (w), 923 (w). Anal. Calcd for $C_{14}H_{17}BrO_8$: C, 42.77; H, 4.36. Found: C, 42.48; H, 4.26.

3.6. 1*S*,4*S*,5*R*,6*R*-2-Bromocyclohex-2-ene-1,4,5,6-tetrol (14)

4.0 g (10.2 mmol) of tetraacetate **13** was dissolved in 40 mL of absolute methanol. While dry NH_3 was being passed through the solution, the mixture was stirred for 2 h at room temperature. Evaporation of methanol and the formed acetamide gave light brown solid **14** (2.17 g, 95%), mp 116–118 °C. ^1H NMR (400 MHz, D_2O) δ: 6.12 (s, 1H, H-3), 4.70 (br s, 4H, –OH), 4.15 (quasi t, J = 7.1 2H, H-1 and H-4), 3.54 (m, 2H, H-5 and H-6); ^{13}C NMR (100 MHz, D_2O) δ: 132.1, 124.7, 74.8, 74.7, 74.5, 71.8; IR (cm^{-1}) 3366 (br), 2912 (m), 1662 (s), 1350 (w), 1314 (m), 1269 (w), 1094 (s), 1041 (s), 853 (m), 617 (m). Anal. Calcd for $C_6H_9BrO_4$: C, 32.02; H, 4.03. Found: C, 32.11; H, 4.15.

3.7. (rel-1*R*,2*S*,6*R*,7*S*,10*S*,11*R*)-10,11-Dibromo-4,4-dimethyl-3,5,8,9-tetraoxatricyclo-[5.2. $2.0^{2,6}$]undecane (17)

To a stirred solution of cyclohexene-ketal **16** (4.0 g, 21.74 mmol) in $CHCl_3$ (300 mL) was added dropwise a solution of bromine (3.8 g, 2.38 mmol) in hexane (250 mL) at 0 °C over 1.5 h. After bromine addition was completed, the temperature of the reaction mixture was raised to room temperature. Evaporation of the solvent at 40–50 °C and 20 mmHg and purification of the dark residue by chromatography on 45 g of Al_2O_3 using $CHCl_3$ as eluent afforded a dark solid **17**, which was crystallized from CH_2Cl_2/*n*-hexane, (6.5 g, 87%), mp 93–95 °C. ^1H NMR (400 MHz, $CDCl_3$) 4.85 (br s, 2H, H-1 and H-7), 4.56 (br s, 2H, H-2 and H-6), 4.51 (br s, 2H, H-10 and H-11), 1.55 (s, 3H, $-CH_3$), 1.40 (s, 3H, $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) 111.2 (C-4), 78.4 (C-1 and C-7), 71.2 (C-2 and C-6), 43.7 (C-10 and C-11), 25.9 ($-CH_3$) 24.1 (–CH). IR (KBr, cm^{-1}): 2992, 2958, 1460, 1383, 1299, 1269, 1206, 1160, 1076, 1018, 977, 924, 855. Anal. Calcd for $C_9H_{12}Br_2O_4$: C, 31.42; H, 3.52. Found: C, 31.45; H, 3.51.

3.8. 3a*S*,7*R*-7a*S*-5-Bromo-7-hydroxy-2,2-dimethyl-7,7a-dihydro-1,3-benzodioxol-4(3a*H*)-one (19)

Dibromide **17** (3.0 g, 11.41 mmol) was dissolved in DMSO (2 mL) and stirred at room temperature for 20 min. After addition of 150 mL of water, the mixture was extracted with dichloromethane. Organic layers were washed with water and dried ($MgSO_4$). Removal of the solvent gave bromoketone **19** as a colorless liquid almost in quantitative yield. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.85 (br s, 1H, –OH), 7.46 (d, J = 4.2 Hz, 1H, H-6); 4.68 (d, J = 5.2 Hz, 1H, H-3a), 4.44–4.40 (m, 2H, H-7 and H-7a), 1.29 (s, 3H, $-CH_3$), 1.18 (s, 3H, $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) 188.19 (C-4), 149.4 (C-6), 122.4 (C-5), 109.2 (C-2), 78.5 (C-3a or C-7a), 74.6 (C-3a or C-7a), 64.9 (C-7), 27.2, 25.6. IR (KBr, cm^{-1}): 3500, 3000, 1616, 1410, 1351, 1251, 1144, 1031, 981. Anal. Calcd for $C_9H_{11}BrO_4$: C, 41.09; H, 4.21; Br, 30.37. Found: C, 41.31; H, 3.91.

3.9. $NaBH_4$ reduction of bromoenone 19

Bromoenone **19** (2.0 g, 7.6 mmol) was dissolved in 45 mL of THF and cooled to 0 °C. To this mixture was added dropwise an aqueous solution of $NaBH_4$ (0.55 g, 14.5 mmol) at 0 °C over 5 min. The reaction was followed by TLC. After the completion of the reaction (4 h), the organic phase was evaporated at 60 °C/20 mmHg. Without any purification, the crude product consisting of **20** and **21** was dissolved in acetic anhydrate (5 mL), and two drops of H_2SO_4 were added. The mixture was stirred at room temperature for 12 h. Dichloromethane (200 mL) was added. Unreacted acetic anhydrate was hydrolyzed with ice and HCl, and the organic layer was washed with water and saturated $NaHCO_3$. The combined organic extracts were dried over Na_2SO_4. Removal of the solvent gave a mixture of **22** and **23**, which was crystallized from EtOAc–hexane (3:1) to give tetraacetate **22** (1.8 g, 60%) as colorless prisms, mp 114–116 °C.

3.9.1. The data for (rel-1*R*,4*S*,5*S*,6*S*)-4,5,6-tris(acetyloxy)-2-bromocyclohex-2-en-1-yl acetate (22)

^1H NMR ($CDCl_3$, 400 MHz) δ: 6.22 (t, J = 2.1 Hz, 1H, H-3), 5.79 (dt, J = 3.8 and 2.1 Hz, 1H, H-1), 5.58 (dd, J = 3.8 and 2.5 Hz, 1H, H-4), 5.55 (ddd, J = 7.9, 2.5 and 2.1 Hz, 1H, H-5), 5.22 (dd, J = 7.9 and 2.1 Hz, 1H, H-6), 2.11 (s, 3H, $-CH_3$), 2.08 (s, 3H, $-CH_3$), 2.07 (s, 3H, $-CH_3$) 2.03 (s, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.0, 169.9, 169.6, 169.2, 129.6, 122.59, 69.7, 69.3, 69.0, 68.7, 20.8, 20.6 (2C), 20.4. IR (cm^{-1}) 2971, 1755, 1431, 1368, 1233, 1112, 1041, 916, 721. Anal. Calcd for $C_{14}H_{17}BrO_8$: C, 42.77; H, 4.36. Found: C, 42.76; H, 4.36.

3.9.2. The data for (rel-1*S*,2*S*,3*S*,4*S*,6*R*-2,4-bis(acetyloxy)-6-bromo-3-hydroxy-cyclohexyl acetate (23)

As the second fraction **23** was isolated (0.4 g, 1.01 mmol, 13%) mp 142–145 °C as white crystals. ^1H NMR ($CDCl_3$, 400 MHz): δ: 5.58 (br s, 1H, H-1), 5.19 (dt, J = 4.0 and 3.0 Hz, 1H, H-4), 5.13 (t, J = 3.3, 1H, H-2), 4.35 (ddd, J = 12.1, 4.0 and 3.0 Hz, 1H, H-6), 3.93 (br s, 1H, H-3), 2.62 (br d, J = 5.9 Hz, 1H, –OH), 2.56 (ddd, A-part of AB-system, J = 14.8, 12.1 and 3.0 Hz, 1H, $H\text{-}6_{ax}$), 2.24–2.17 (m, 1H, $H\text{-}6_{eq}$), 2.18 (s, 3H), 2.099 (s, 3H), 2.097 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 169.9, 169.8, 169.6, 71.7 (C-4), 71.6 (C-1), 68.8 (C-2), 68.7 (C-3), 42.8 (C-6), 31.1 (C-5), 21.3, 20.99, 20.97. IR (KBr, cm^{-1}) 3489, 3392, 2923, 2851, 1733, 1636, 1370, 1268, 1232, 1043, 931. Anal. Calcd for $C_{12}H_{17}BrO_7$: C, 40.81; H, 4.85. Found: C, 40.20; H, 4.89.

3.10. (rel-1*R*,2*S*,3*S*,4*S*)-5-bromocyclohex-5-ene-1,2,3,4-tetrol (24)

A stirred solution of **22** (1.0 g, 2.54 mmol) in 40 mL of methanol was cooled to 0 °C. At the given temperature, NH_3 gas was passed through the solution over 30 min. The reaction flask was closed with a stopper, and the solution was stirred at room temperature for 2 h. Removal of the solvent and acetamide under reduced pressure (30 °C, 25 mmHg) gave bromo-conduritol-C **24** (0.55 g, 97%) as a colorless viscous liquid. ^{1}H NMR (400 MHz, CD_3OD) δ: 6.10 (br s, 1H), 4.79 (br s, 4H, –OH), 4.27–4.26 (m, 1H), 4.21 (br s, 1H), 4.11–4.09 (m, 1H), 3.64 (dd, J = 6.6 and 1.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 133.1, 127.7, 75.5, 73.2, 72.9, 71.6. IR (KBr, cm^{-1}): 3342, 1661, 1397, 1032, 845, 598. Anal. Calcd for $C_6H_9BrO_4$: C, 32.02; H, 4.03; Br, 35.51; O, 28.44. Found: C, 32.33; H, 4.25.

3.11. α-Glycosidase Inhibition Assay

An enzyme assay was performed for compounds **14** and **24**. The reaction mixtures containing 0.85 mM PNPG (*p*-nitrophenyl α-D-glycopyranoside), phosphate buffer (pH 6.8), and 5–200 μM of the corresponding isomers were incubated at 37 °C for 5 min. Then, 0.075 unit of α-glycosidase (Sigma) was added to the mixtures, which were incubated at 37 °C for 30 min, and the reaction was stopped with 2 mL of 100 mM Na_2CO_3, and the absorbance at 400 nm of the liberated para-nitrophenol was measured.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.12.005.

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