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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.

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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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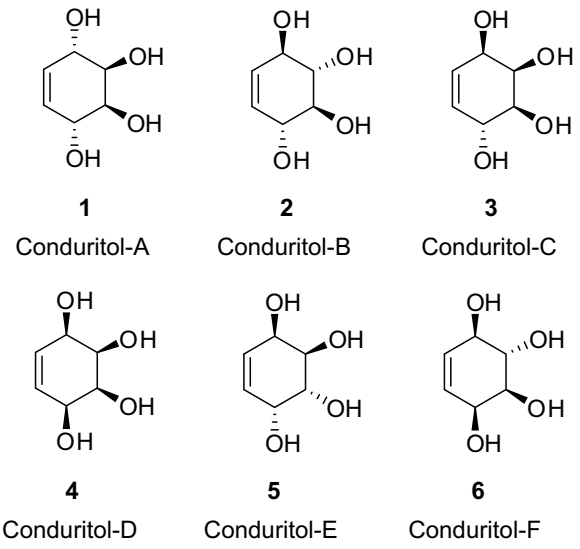
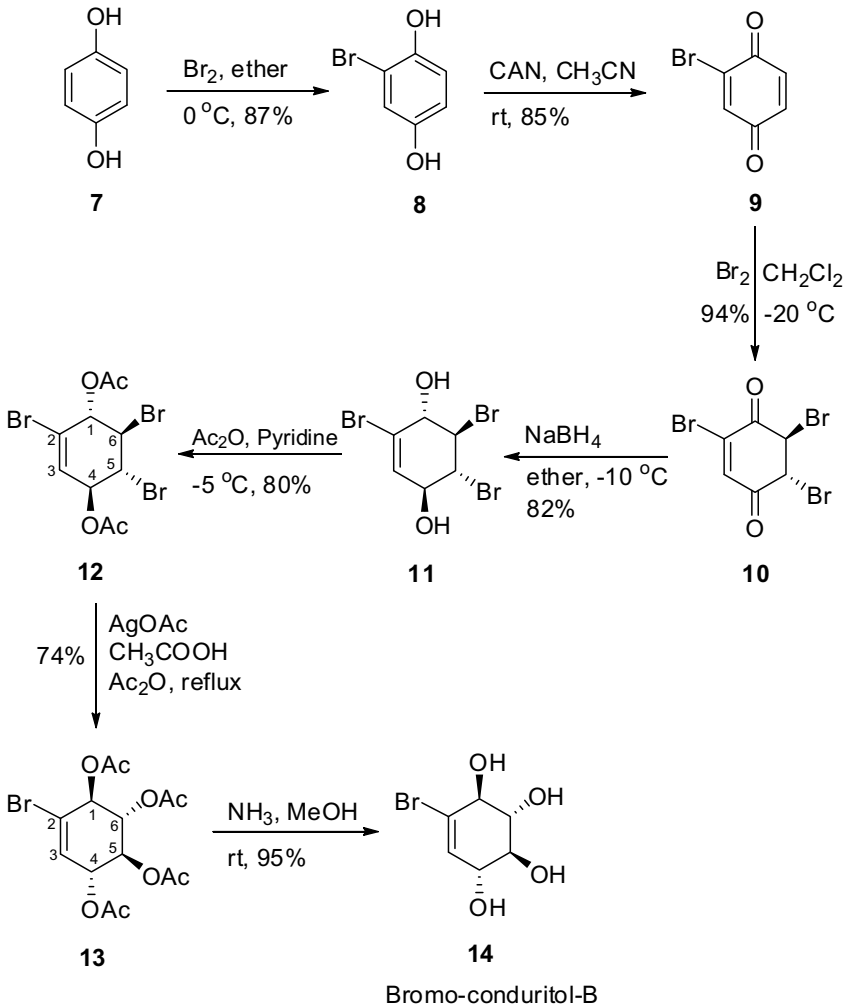


Chart 1.

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.

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