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Stereoselective synthesis of new *rac*-quercitols containing hydroxymethyl groups as glucosidase inhibitors

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ABSTRACT

Stereoselective and efficient synthesis of hydroxymethyl-substituted *rac*-quercitols (**13–15**) was achieved, starting from *cis*-furan (Kobayashi, 2008) with photooxygenation reaction, which is readily available by the reduction of *cis*-phtalic anhydride. *α*- and *β*-Glucosidase enzyme activity of the target molecules was evaluated and good inhibitor activity was seen. One- and two-dimensional NMR spectroscopy, IR spectroscopy and X-ray crystallography were utilized in the structure characterization of products.

Polyhydroxylated cyclic compounds are numerous in nature. These moieties, also known as cyclitols, have three or more hydroxyl groups on a ring.[1] They are not only isolated from natural sources[2] but also synthesized by several types of synthetic strategies. These compounds have many potential biological activities such as anti-obesity, anti-diabetic, anti-fungal and anti-human immunodeficiency virus (HIV).[3] Quercitols (fundamentally deoxyinositols), used as a generic term for cyclohexanepentols,[4] are a subclass of cyclitols as well as inositols, conduritols and carbasugars along with other varieties[5] (Fig. 1).

The quercitol family contains 16 stereoisomers, all of these stereoisomers can be recognized easily but only three optically active quercitols, the (+)-*proto*-, (−)-*proto*-quercitol and (−)-*vibo*-quercitol, have hitherto been found in nature and only exist in plants[5b,6] Meanwhile, the carbocyclic polyols have been of interest to those concerned with carbohydrates[6] Carbohydrates, the most widespread biomolecules, are represented as free monosaccharides, oligosaccharides, polysaccharides and essential fragments of glycoconjugates, In many biologically active natural products, the sugar units not only increase water solubility, but also decrease toxicity. In addition, some aglycones are also required components for the bioactivity of natural products[7] Highly oxygenated cyclohexanes are often referred to as pseudosugars (or carbasugars) due to the similarity of their structure to that of real sugars[2a] Carbasugars (analogues of monosaccharides)[8] are glycomimics or sugar-mimetics[9] in which the pyranose ring oxygen is replaced with a methylene group like quercitols,[8,10] but carbasugars contain a hydroxymethyl substituent additionally (Fig. 2).

These compounds take part in the regulation and function of biological processes like in cellular recognition, inhibition effects of carbohydrate-based enzymes (amylases, glucosidases) and signal transmitters[5a] The lack of a glucosidic linkage in these entities, which moreover resemble monosaccharides in shape, size and functionalization, makes them hydrolytically stable towards acidic as well as enzymatic hydrolysis[11] These compounds are regarded as potential drug candidates rather than natural sugars and are generally evaluated in glucosidase inhibition applications[2a,12a]

Many enzymes perform function in the synthesis and degradation reactions of carbohydrates and contribute to completing digestion such as glucosidase (*α, β*), maltase and sucrase. *α*- and *β*-Glucosidases break down *α*-, *β*-1 → 4 glucosidic[2g,2h] bond between carbohydrate or sugar molecules in the brush border of intestine and form monosaccharide units such as glucose and fructose. Glucosidase inhibitors (*α, β*) are commonly used as agents to retard carbohydrate digestion and thus decelerate the blood glucose level,[12b–e] so the development of inhibitors for glucosidases is an important challenge for the treatment of a range of carbohydrate-mediated diseases.[11,13–16] We herein report a stereoselective synthesis of some quercitols from a commercially available and cheap starting material, and their inhibitor activities toward *α*- and *β*-glucosidase enzyme were also investigated.

In the present strategy based on retrosynthetic analysis (Scheme 1), we initially synthesized the key molecule *cis*-furan **3** via reduction of readily available *cis*-phthalic anhydride **1**[17] with $LiAlH_4$ in THF to afford *cis*-diol **2** (95%), followed by the ring-closing procedure of **2** utilized with tosyl chloride (TsCl) in pyridine under reflux conditions, which resulted[18] in 85% yield.

A tetraphenylporphyrin-catalyzed photooxygenation reaction[19a] of *cis*-furan **3** in dichloromethane at rt under a 500-W projection lamp gave two hydroperoxides **3a** and **4a** (2:3) according to the NMR spectra over a singlet oxygen ene-reaction[19b–e] as expected.

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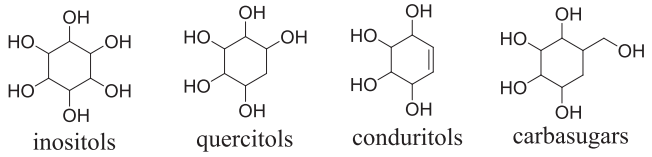


Fig. 1. Subclasses of cyclitols.

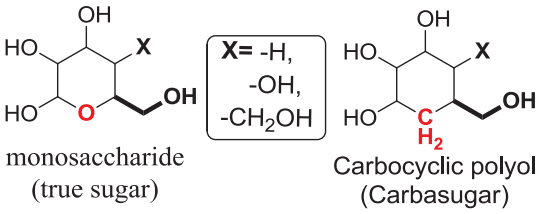


Fig. 2. Structures of true sugar and carbasugar.

The diastereoisomeric **3a** and **4a** were prepared,[19b–e] and without any additional purification were determined in 39% yield for **3a** and 51% yield for **4a** by ^{1}H NMR spectra. Reduction of peroxide **3a** and **4a** with $(CH_3)_2S$ using titanium tetraisopropoxide as a catalyst in methylene chloride[20] as a solvent at 0 °C furnished a mixture of residue. The residue was separated via column chromatography by eluting with CH_2Cl_2, which afforded two isomers, **3b** (42%) and **4b** (41%) (Scheme 2).

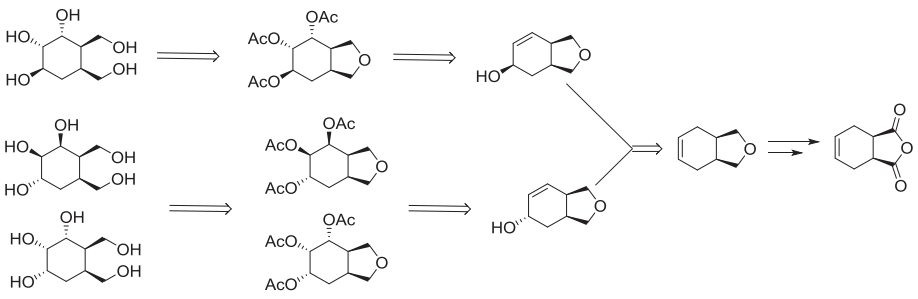
In the ^{1}H- and ^{13}C-NMR analysis, the double bond of **3b** resonates as an AB system that appears at 5.76 ppm and 5.64 ppm with coupling constants J_{34} = 10.0 Hz, J_{33a} = 1.5 Hz, J_{45} = 2.0 Hz for H_3 and H_4, respectively. Likewise the double bond of **4b** resonates as an AB system that appears at 5.83 ppm and at 5.68 ppm with coupling constants J_{43} = 10.0 Hz, J_{45} = 1.5 Hz, J_{33a} = 1.1 Hz for H_4 and H_3. H_5 in both diastereomeric **3b** and **4b** appear as multiplets at 4.21 ppm and 4.13 ppm with H_6. The eight line carbon signal for each construction confirmed the structure but the coupling constants between H_5 and H_6 in both **3b** and **4b** appear as multiplets consequently. The configurations of **3b** and **4b** did not match each other exactly. Therefore, the relative stereochemistry of **3b** and **4b** is not known obviously for the synthesis of the target molecule. In the ongoing stage, for not affording undesired side reactions and for correction of the configuration readily, the hydroxy group in diastereoisomeric **3b** and **4b** was treated with pyridine and Ac_2O at rt (Scheme 3) to afford the corresponding monoacetates **5** and **6** in 84% and 87% yield, respectively[18]

For the synthesis and design of new scaffolds of cyclitol derivatives, our main attempts were to establish their relative stereochemistry. Thus, it was difficult for proving diastereomeric compounds to make a decision about configuration separately and to decide on the configuration of compounds for which H_5 gave a multiplet at 5.20 ppm with H_6 and H_4 or H_3 in compound **5** and H_5 gave a multiplet at 5.34–5.28 ppm with H_6 and H_4 or H_3 in compound **6.** Roughly ten lines of the carbon signals for each construction confirmed monoacetate **5** and **6** as scaffolds. For further characterization we tried to crystalize structures **5** and **6**, but there were no single crystals using different solution ratios in all cases for X-ray crystal analysis. Therefore, the double bond in monoacetates **5** and **6** was exposed to a *cis*-hydroxylation reaction[8,21] separately with a catalytic amount of OsO_4 in the presence of *N*-methyl-morpholine *N*-oxide (NMO) in a solution of acetone:water (1:1) at 0 °C to afford *cis*-diols as racemic mixtures. Without any purification the mixture was followed by acetylation using Ac_2O/pyr. and after separations chromatographically afforded triacetate stereoisomers **7**, **8** and **9**. While compound **7** (in 73% yield) was obtained from **5**, compounds **8** (in 54% yield) and **9** (in 31% yield) were obtained from **6** (Scheme 3).

The configurations of **7**, **8** and **9** were verified by 1D- and 2D-NMR spectrums and also **7** was verified by X-ray crystallographic analysis (Fig. 3).

The analysis of the NMR spectra of **7**, **8** and **9** exhibited different configurations as expected. The result of *cis*-hydroxylation and acetylation reactions gave *trans–cis-cis* configuration of **7** where the coupling constants appear as J_{45} = 8.5 Hz as a doublet of doublets at 5.12 ppm, J_{56} = 2.8 Hz as a doublet of doublets at 5.14 ppm, and J_{65} = 2.8 Hz as a doublet of doublets at 5.35 ppm for H-4, H-5, and H-6. The *cis-cis-cis* configuration for **8** showed coupling constants of J_{45} = 2.3 Hz as a doublet of quartets at 5.05 ppm, J_{56} = 2.3 Hz as a triplet at 5.51 ppm, and J_{65} = 2.3 Hz as a doublet of doublets at 4.86 ppm for H-4, H-5, and H-6. On the other hand, compound **9** showed a *trans–cis-cis* configuration with coupling constants of J_{45} = 4.1 Hz as a doublet of triplets at 5.18 ppm, J_{56} = 3.3 Hz as a doublet of doublets at 5.47 ppm, and J_{65} = 3.3 Hz as a doublet of doublets at 5.08 ppm for H-4, H-5, and H-6. It was easy to confirm the exact position of vicinal protons of H_4 and H_5 for the structures **7**, **8** and **9**. Comparison of the coupling constant between H_4 and H_5 for all compounds indicated the highest values for **7** (J_{45} = 8.5 Hz) and **9** (J_{45} = 4.1 Hz) in *trans* configuration while for compound **8** (J_{45} = 2.3 Hz) indicated a low value in *cis* configuration obviously. After the occurrence of *cis*-hydroxylation reactions and assessment of configurational assignments of **7**, **8** and **9** the results were summarized in Table 1.

Thus the relative stereochemistry of furanes for H_4, H_5, and H_6 was elucidated easily but the most difficult other problem was to measure the coupling constant of H-6 and H-7a or H-3 and H-3a exactly for **7**, **8** and **9**. Single crystal analysis of **7** was performed (Fig. 3) and its structure was determined to be in *trans-cis-cis-trans* configuration. Similarly, we wanted to conduct single crystal analysis of **8** and **9**, but the structures were not formed as expected, and we were not able to attain the final relative chemistry of **8** and **9** constructions. Therefore, triacetates were separately submitted to the acetolysis reaction[18,22a,22b] to open the tetrahydrofuran ring in the structures with sulfamic acid catalyzed in a mixture of acetic acid and acetic anhydride (1:1) at reflux temperature to provide pentaacetates **10**, **11** and **12** as colorless liquids in yields of 76%, 82% and 78%, respectively (Scheme 4). After isolation and purification, the configuration of **10** was not changed as in **7** but pentaacetate isomers **11** and **12** were not determined clearly enough during the tetrahydrofuran ring opening reaction, which was deduced from detailed analysis of the NMR spectrum taking the coupling



Scheme 1. Retrosynthetic analysis of the target quercitols.