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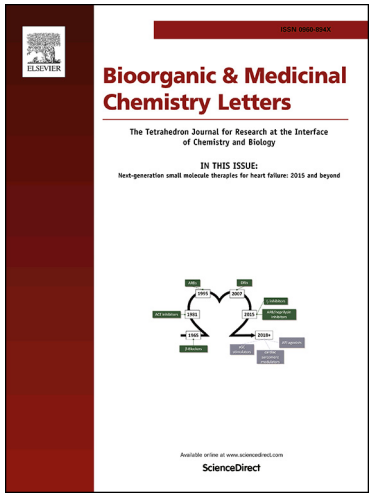

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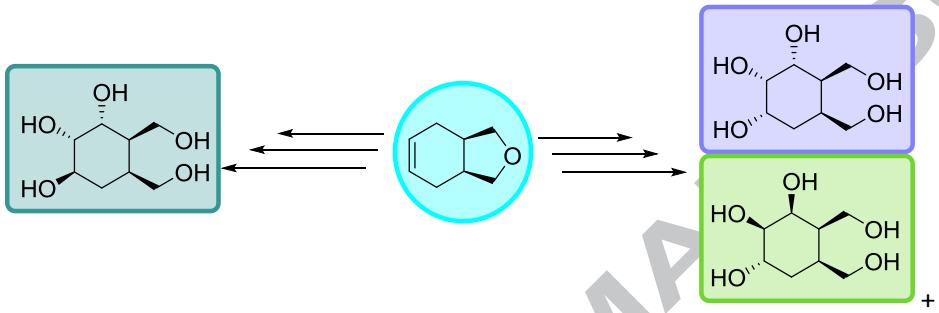
MANUSCRIPT

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

Gokay Aydin, Tahir Savran, Şule Baran, Arif Baran*

Department of Chemistry, Sakarya University, 54187, Sakarya, Turkey.

ABSTRACT



Stereoselective and efficient synthesis of hydroxymethyl-substituted *rac*-quercitols (**13-15**) was achieved, starting from *cis*-furan[3] 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.

Keywords: Quercitol, Carbasugar, Synthetic Method, Biological Activity

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] (Figure 1).

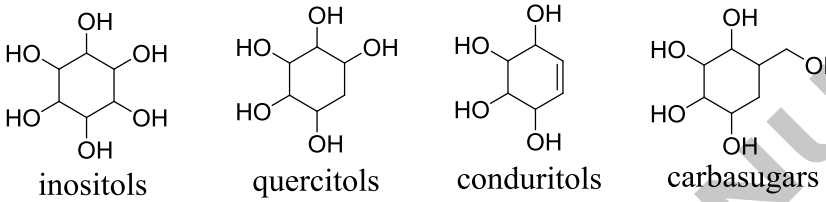


Figure 1. Subclasses of cyclitols.

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 (Figure 2).

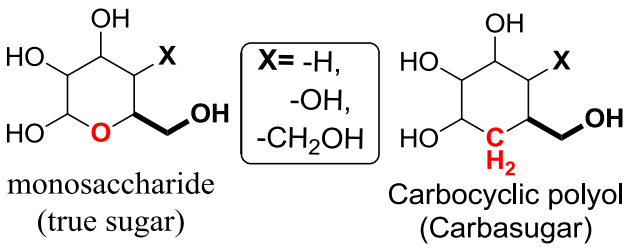


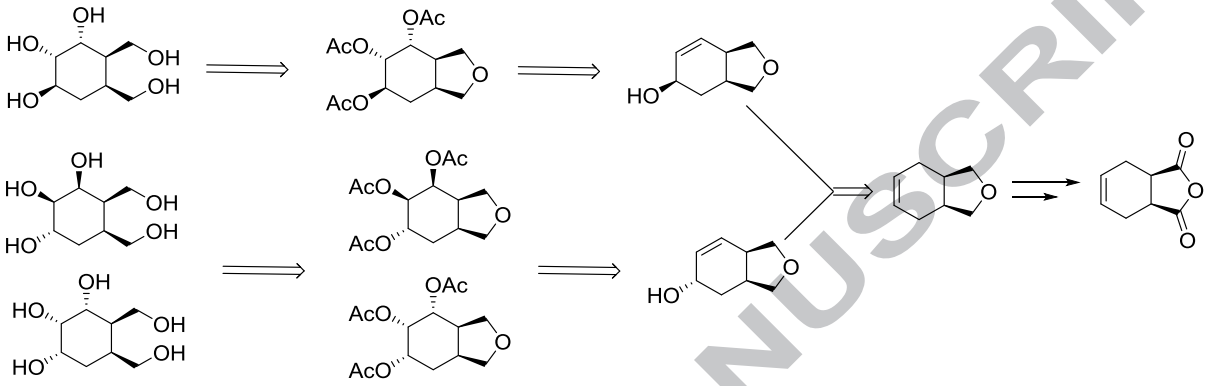
Figure 2. Structures of true sugar and carbasugar.

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,12c,12d,12e] so the development of inhibitors for glucosidases is an important challenge for the treatment of a range of carbohydrate-mediated diseases. [11,13,14,15,16]

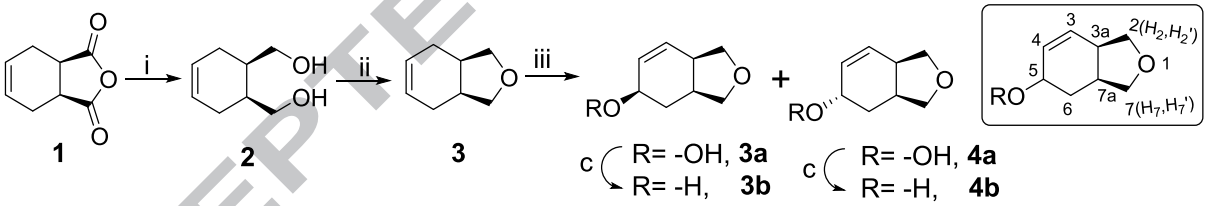
we herein report a stereoselective synthesis of some quercitols from a commercially available and cheap starting material, and their inhibitor activities toward *α*- and *β*-glucosidase enzyme were also investigated.

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.



Scheme 1. Retrosynthetic analysis of the target quercitols.

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.



Reagents and conditions: i. $LiAlH_4$, THF, 95%; ii. TsCl, pyridine, reflux, 85%; iii. (a) TPP, $^1O_2$, hv, DCM, rt, (b) $Ti(OiPr)_4$, $(CH_3)_2S$, DCM, 0 °C, 42% for **3b**, 41% for **4b**.

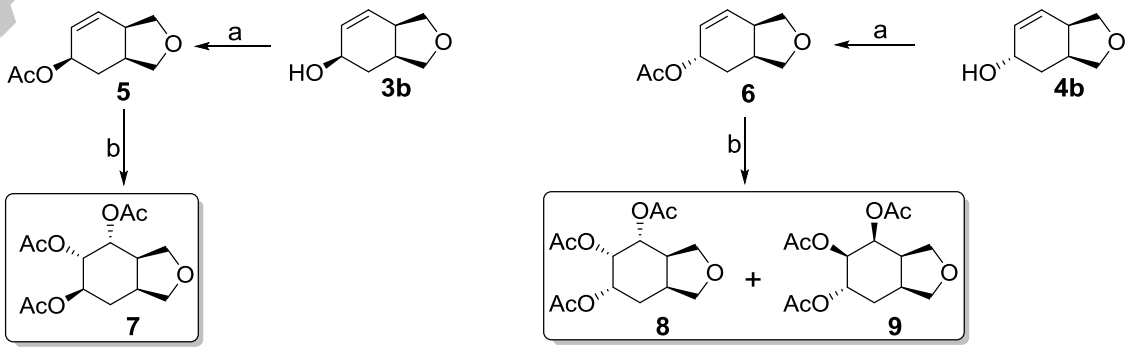
Scheme 2. *"ene"*-Reaction of singlet oxygen of hydrofurane **3**.

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).



Reagents and conditions: (a) Ac_2O, pyridine, rt, 84% for **5**, 87% for **6**, (b) i. OsO_4, NMO, $(CH_3)_2CO$:H_2O (1:1) 0 °C, ii. Ac_2O, pyr., rt, 73% for **7**, 54% for **8**, 31% for **9**.

Scheme 3. Synthesis of furane-triacetate **7**, **8** and **9**.

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 (Figure 3).

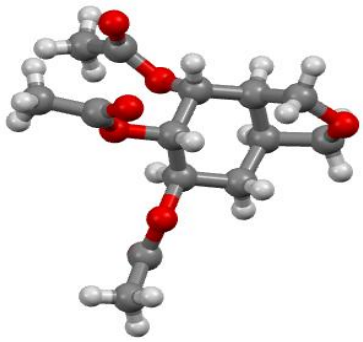
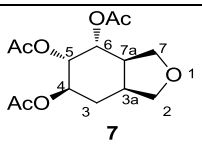
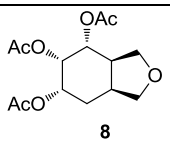
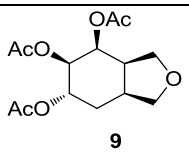


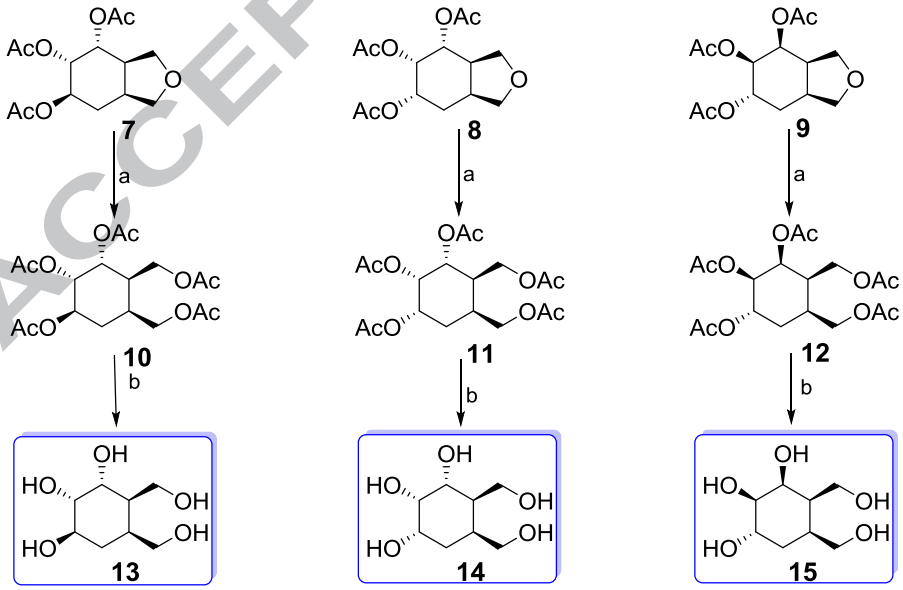
Figure 3. Crystal structure of **7**.

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.

Table 1. $^1H–^1H$ coupling constants in **7**, **8** and **9**.

Compounds	 **7**	 **8**	 **9**
Coupling Constants	J_{45} = 8.5 *Hz dd* J_{56} = 2.8 *Hz dd*	J_{45} = 2.3 *Hz dq* J_{56} = 2.3 *Hz t*	J_{45} = 4.1 *Hz dt* J_{56} = 3.3 *Hz dd*

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 (Figure 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 constant.



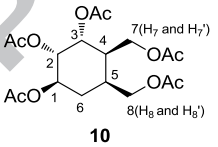
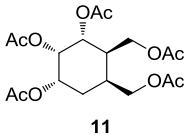
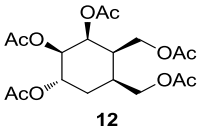
Reagents and conditions: (a) H_2NSO_3H, Ac_2O/AcOH (1:1), reflux, 76% for **10**, 82% for **11**, 78% for **12**; (b) $NH_{3(g)}$, MeOH, rt, 81% for **13**, 85% for **14**, 94% for **15**.

Scheme 4. Synthesis of pentaacetates **10**, **11**, and **12** and the target quercitol analogues **13**, **14**, and **15**.

According to the NMR analysis results given the numbering system in **10** as shown in Table 2, pentaacetate **10** has a *trans-cis-cis-trans* configuration as in **7** in which ring opening resulted in **10** with the same configuration without any neighboring group effect or rearrangement. The resonance signals for H_1, H_2 and H_3 appear at 5.03, 5.48 and 2.50 ppm, respectively, as J_{12} = 10 Hz as a doublet of doublets, J_{23} = 3.1 Hz as a doublet of doublets and J_{34} = 4.1 Hz as a doublet of doublets of doublets of doublets with coupling constant, respectively. In brief, even though the NMR analysis results indicate J_{12} has *trans*, J_{23} has *cis* and J_{34} has *trans* configuration for **10**, X-ray crystallographic analysis was performed to determine the exact configuration.

Using the same numbering system for the other two stereoisomers **11** and **12** according to the relative stereochemistry, the resonance signal for H_1, H_2 and H_3 of **11** indicated that J_{12} = broad singlet at 5.45 ppm, J_{23} = broad singlet at 5.17 ppm and J_{34} = multiplet in the range of 2.56-2.43 ppm, and the resonance signal for H_1, H_2 and H_3 of **12** indicated that J_{12} = 8.6 Hz as a doublet of triplets at 5.14 ppm, J_{23} = 2.9 Hz as a doublet of doublets at 4.95 ppm and J_{34} = multiplet at 5.42 ppm in Table 2, respectively.

Table 2. $^1H-^1H$ Coupling constants in **10**, **11** and **12**.

Compounds	 **10**	 **11**	 **12**
Coupling Constants	J_{12} = 10 *Hz dd*, J_{23} = 3.1 *Hz dd* J_{34} = 4.1 *Hz dddd*	J_{12} = *bs*, J_{23} = *bs*, J_{34} = *m*	J_{12} = 8.6 *Hz dt* J_{23} = 2.9 *Hz dd*, J_{34} = *m*

The results for scaffolds were supported by COSY, HETCOR and DEPT tecnique. The coupling constants of **10**, **11** and **12** were examined and the collected results given in Table 2 showed that the relative stereochemistry of J_{34} for **11** and **12** is very difficult to determine using only NMR techniques. For this reason X-ray crystallographic analysis of **11** and **12** was conducted for elimination of these uncertain configurations and confirmed the expected construction.

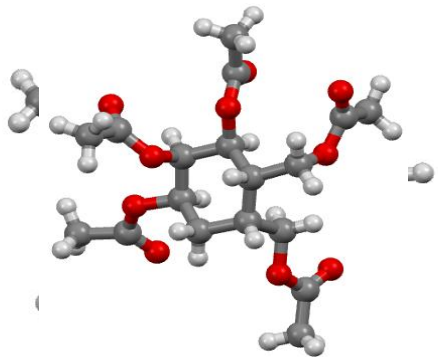


Figure 4. Crystal structure of **11** and **12**.

After determining the structures of **10**, **11** and **12**, the acetyl groups in the structure were hydrolyzed with ammonia[18,22a,22b] in absolute MeOH after evaporation of solution and forming acetamide to give the relevant pentols **13**, **14** and **15** in roughly quantitative yields (Scheme 4). It was deduced that the asymmetry of compounds **13**, **14** and **15** was exactly in agreement with the NMR spectroscopic data and X-ray crystallographic analysis results.

β-Glucosidase inhibition for the target molecules **13**, **14** and **15** was evaluated using acarbose as a positive control. All compounds showed *β*-glucosidase inhibitory activity (10-180 µM). The best inhibitory activity was observed for compound **14**. While the inhibition of compound **14** at 51.80 ± 11.36 for 180 µM concentration (IC_{50} = 197.77 µM) was sufficiently strong, the inhibition of acarbose at 66 ± 0.7 for 180 µM concentration (IC_{50} = 57.78. µM) showed good inhibitory activity. However, at low concentration (20 µM), it can be said that *β*-glucosidase inhibitory activity for compound **13** is stronger than that of acarbose. The test assay and the results are summarized in Table 3.

Table 3. Inhibition of *β*-glucosidase by racemic compounds **13**, **14** and **15.**

***β*-Glucosidase inhibition (%)** [a]								
Compo-unds	**10 µM**	**20 µM**	**25 µM**	**45 µM**	**80 µM**	**120 µM**	**180 µM**	**IC_{50} (µM)**[c]
Acarbose[d]	17±0.6	25±2.8	29±1.0	39±1.9	52±0.9	60±0.6	66±0.7	57.78
13	3.4±2.1	27.76±1	28.36±1.1	30.4±0.9	31.78±2.4	32.12±7.1	33.3±0.8	ND [b]
14	18±5.95	20.41±16	28.96±4.4	34.3±4.2	37.5±5.3	42.66±4.1	51.80±11	197.77
15	2.2±1.9	4.98±3.8	12.66±2.7	13.7±2.2	19.1±2.84	20.16±7.85	30.8±7.2	ND [b]

[a] Concentration required for 50% inhibition of the enzyme activity under the assay conditions. [b] Not determined.
[c] Four experiments were performed for all compounds in each experiment triplicated. [d] Positive control.

Consequently, compounds **13**, **14** and **15** appear to have increasing inhibition activity rates compared to acarbose as exhibited by the *β*-glucosidase inhibition (%)-concentration plot in (Figure 5).

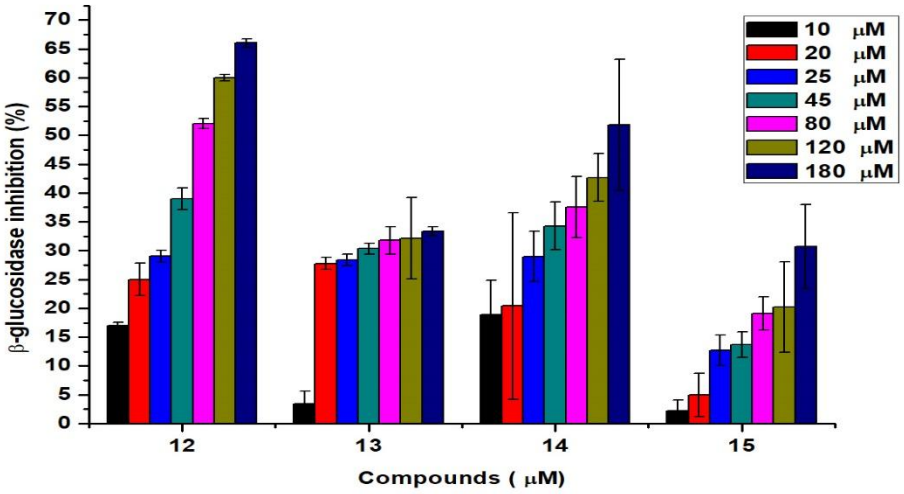


Figure 5. *β*-Glucosidase inhibition % for (10-180 μM) test compounds and acarbose (12) control. Control of *β*-glucosidase inhibition % compared to acarbose (12) concentration of **13**, **14** and **15** compounds. Mean values ± S.D. are shown for triplicate experiments.

On the other hand, the inhibitory effects of the target molecules **13**, **14** and **15** were evaluated for *α*-glucosidase using acarbose as a positive control. All compounds showed *α*-glucosidase inhibitory activity more or less, but did not exhibit IC_{50} values. The results and test assay are summarized in Table 4.

Table 4. Inhibition of *α*-glucosidase by racemic compounds **13**, **14** and **15.**

***α*-Glucosidase inhibition (%)** [a]								
Compo-unds	**10 μM**	**20 μM**	**25 μM**	**45 μM**	**80 μM**	**120 μM**	**180 μM**	**IC_{50} (μM)**[c]
Acarbose[d]	22±0.82	30±3.1	33±1.5	46±3.2	60±0.71	63±0.5	74±1.3	52.47
13	15.8±0.6	18.75±1.1	19.36±1	19.86±1	21.4±0.48	37.6±2.4	42.2±1.1	ND[b]
14	2±1	6±1.9	14±2.3	19±5.1	20±6.1	22±1.8	25±1.3	ND [b]
15	10±2.1	13±1.6	19±1.7	21±2.6	31±3.6	40±2.6	42±2.4	ND [b]

[a] Concentration required for 50% inhibition of the enzyme activity under the assay conditions. [b] Not determined.
[c] Four experiments were performed for all compounds in each experiment triplicated. [d] Positive control.

Acarbose exhibited better α-glucosidase inhibition activity compared to test compounds **13**, **14** and **15**. While in the α-glucosidase inhibition (%)-concentrations (µM) plot an increase was seen for compounds **14** and **15** proportionally with acarbose, compound **13** showed a weak inhibition in the concentration range 10-80 µM, but showed an increase in inhibition after 120 µM concentration (Figure 7).

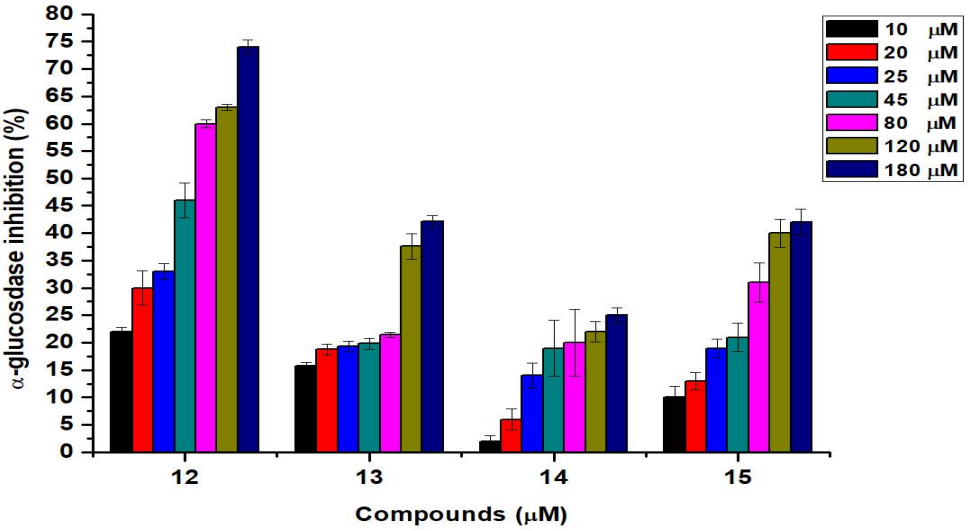


Figure 6. α-Glucosidase inhibition % for (10-180 µM) test compounds and acarbose (12) control. Control of α-glucosidase inhibition % compared to acarbose (12) concentration of **13**, **14** and **15** compounds. Mean values ± SD are shown for triplicate experiments.

As a result, the inhibitory effect of target molecules **13**, **14** and **15** against both α-glucosidase and β-glucosidase was evaluated as described in the experimental section. Acarbose was used as a positive control for this evaluation. The results are presented in Tables 3 and 4. The concentration range was 10-180 µM. Inhibition behaviors of the compounds to the aforesaid enzymes are presented in Figures 5 and 7. Moreover, the inhibition power of the compounds for both enzymes was compared and the results are shown in Figure 9. Synthesized molecules exhibited both α- and β-glucosidase inhibition but an IC_{50} value could not be obtained for all compounds. The only IC_{50} value calculated was 197.77 µM for compound **14** against β-glucosidase.

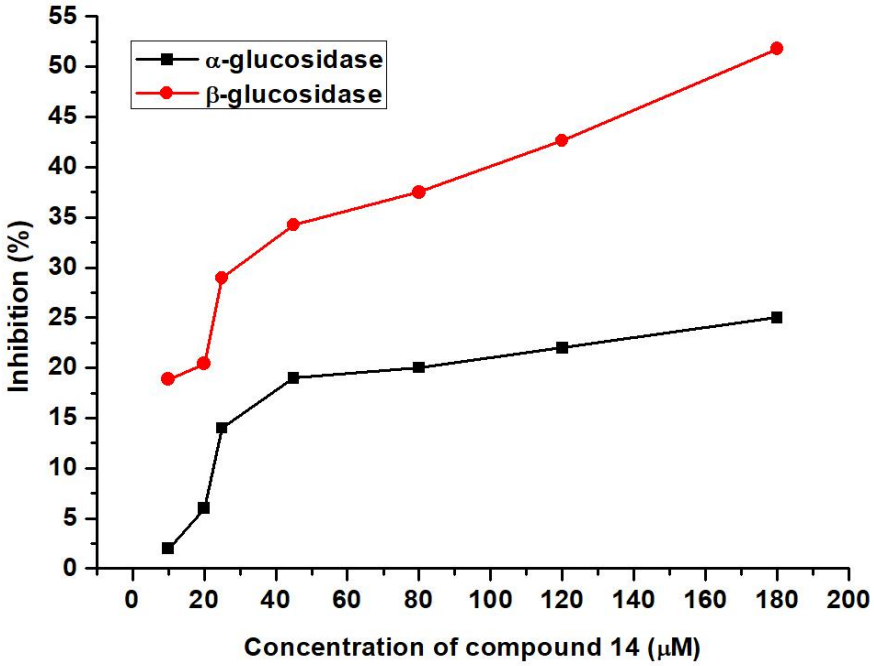


Figure 7. *α*-Glucosidase and *β*-glucosidase % inhibition of compound **14** fractions by different concentrations. The compound was tested with concentrations ranging from 10 μM to 180 μM. Results are the means ± S.D. of three replicates of each group.

We have described the stereoselective synthesis of some *rac*-carbasugar-based quercitols from commercially available anhydride, as result of a series of stereospecific reactions and evaluation of their inhibitory effects toward *α*- and *β*-glucosidases. Initially, *cis*-furan **3**, a key compound obtained from **1**, was subjected to TPP-catalyzed photooxygenation in the presence of oxygen atmosphere and afforded two hydroperoxides. Following the reduction of hydroperoxides, *cis*-dihydroxylation of alkene units, ring-opening of the furan reaction and finally hydrolysis of the pentaacetates afforded the desired pentols **13**, **14** and **15**, respectively. These polyhydroxy compounds were investigated for glucosidase inhibitory activities. All of them exhibited moderate inhibitions against *α*- and *β*-glucosidases in comparison to acarbose. Finally, these quercitol moieties are considered carbasugar-mimetics due to hydroxymethylene substituents and they may serve as novel drug candidates.

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Supplementary Material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1566930 for **7**, 1566924 for **11** and 1566929 for **12**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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Highlights

- Short, selective and efficient synthesis for some carbasugar derivatives was performed.
- It is very important to synthesize these compounds by known methods using cheap starting materials.
- Our knowledge it is the first report where dihydroisobenzofuran system generate “ene reaction”.