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(+)-*proto*-Quercitol, a natural versatile chiral building block for the synthesis of the α-glucosidase inhibitors, 5-amino-1,2,3,4-cyclohexanetetrols

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ABSTRACT

An efficient synthesis of diastereomerically pure 5-amino-1,2,3,4-cyclohexanetetrols (**6** and **11**) and quercitol derivatives from naturally available (+)-*proto*-quercitol (**1**) is described. The stereochemistry of **1** is perfectly set up for regioselective protection of the hydroxy group which was further functionalized into the target aminocyclitol in a straightforward manner. The present approach provides a protocol for preparing aminocyclitols in large quantities. In addition, the absolute stereochemistry of (+)-*proto*-quercitol was addressed using the modified Mosher's method. Of the synthesized aminocyclitols, **11** potentially inhibits α-glucosidase with an IC_{50} value of 12.5 μM, which is 45 times greater than that of the standard antidiabetes drug, Acarbose®.

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Aminocyclitols such as valiolamine, validamine, and valienamine were shown to possess inhibitory activity against various glycosidases (Fig. 1).[1] Subsequent investigations regarding chemical modification, particularly of the amino scaffold, resulted in the discovery of voglibose, a clinically potent remedy to control diabetes mellitus (DM).[2] The inhibitory effect of aminocyclitols has been elaborated on the basis of their structural resemblance to the D-glucopyranosyl cation possibly generated during hydrolysis of their glycosides and strong covalent bonding to the active site of the enzyme.[3] Several syntheses of aminocyclitols have been accomplished using cyclohexanepentols, trivially called quercitols, as starting components.[4] In fact, quercitol has 16 possible stereoisomers, however only (+)-*proto*-, (−)-*proto*-, and (−)-*vibo*-quercitols have been encountered abundantly in Nature.[5]

To date, there have been a few reports on the syntheses of aminocyclitols from natural quercitols. Although Ogawa succeeded in the preparation of 5-amino-1,2,3,4-cyclohexanetetrol analogues from (−)-*vibo*-quercitol, nearly half of the product yield was lost in the early steps.[4b] We considered that protection of a 1,2-diol as an acetonide could not be carried out specifically at C-1/C-2 and C-3/C-4, therefore yielding 3-hydroxy- and 5-hydroxy-bis-acetonide quercitols as an inseparable mixture. In addition, a similar result was also observed by Ogawa in the synthesis of aminocyclitols using unnatural (−)-*epi*-quercitol.[4a]

To circumvent this problem, the use of the correct stereoisomer of quercitol is crucial. Of all the stereoisomers, (+)-*proto*-quercitol

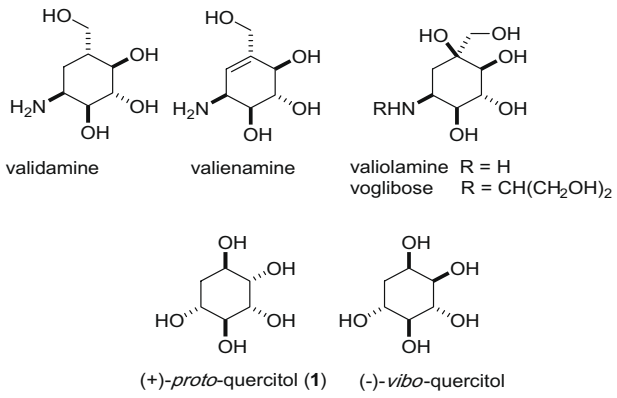

Figure 1.

is likely to be a potential candidate due to the possibility of generating a single bis-acetonide, in addition to its natural availability. In this Letter, we report the first synthesis of diastereomerically pure 5*S*- and 5*R*-amino-1,2,3,4-cyclohexanetetrols (**6** and **11**) using (+)-*proto*-quercitol (**1**). Furthermore, determination of the absolute configuration of **1** using the modified Mosher's method is also described.

(+)-*proto*-Quercitol (**1**) utilized in this study was isolated from the stems of *Arfeuillea arborescens* using the previously described method with slight modification.[6] The MeOH extract, after partitioning with hexane and CH_2Cl_2, was concentrated to afford the desired quercitol (ca. 0.6%) as colorless crystals.[7] The structure and relative configuration were determined by spectroscopic tech-

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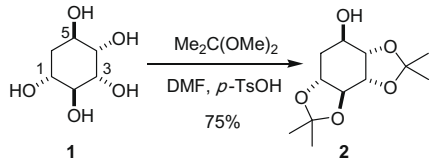
niques, including 2D NMR. Despite the first report of **1** from Nature since 1961,[8] the absolute configurations of all the stereogenic centers have not been addressed.

Prior to applying the modified Mosher's approach, protection of the hydroxy groups was required to avoid combined anisotropy effects caused by multiple MTPA moieties.[9] Treatment of **1** with a large excess of 2,2-dimethoxypropane (10 equiv) in DMF in the presence of *p*-TsOH at ambient temperature yielded 1,2:3,4-di-*O*-isopropylidene derivative **2** as a single product (Scheme 1).[10] The NOESY data indicated that the acetonides that formed between C-1 and C-2 and between C-3 and C-4 were *trans*- and *cis*-oriented, respectively (Fig. 2). The bis-acetonide **2** was then treated with (+)- and (−)-MTPACl, separately, to furnish the desired *R*- and *S*-MTPA esters. The $\Delta\delta_{SR}$ distribution indicated the 5*R* configuration, therefore the absolute configurations of the remaining chiral centers are addressed as shown in Scheme 2.

After the absolute stereochemistry of the carbocyclic framework had been established, we next investigated the synthesis of 5*S*-amino-1,2,3,4-cyclohexanetetrol (**6**) (Scheme 3). In an effort to prepare azide **4**, we first attempted to transform bis-acetonide **2** into the corresponding chloride by reaction with thionyl chloride. Unfortunately, this was unsuccessful, presumably due to steric hindrance from the two adjacent acetonide groups.

Alternatively, the 5-OH group of **2** was activated by converting it to mesylate analogue **3**. Reaction of **3** with an excess of sodium azide in DMF at 100 °C in the presence of 15-crown-5 ether afforded selectively the azide **4** (79%) as the sole product after flash chromatography. The chemical shift at δ_H 3.35 with a large coupling constant ($J_{5,6ax}$ = 11.6 Hz) suggested that the azido group was incorporated with inversion of configuration. Reduction of azide **4** proceeded smoothly upon treatment with $LiAlH_4$, leading to formation of the corresponding amine **5** in good yield. Exposure of the amine **5** to trifluoroacetic acid in THF at room temperature furnished the target molecule, aminocyclitol **6** in 63%.[11]



Scheme 1. Preparation of 1,2:3,4-di-*O*-isopropylidene derivative **2**.

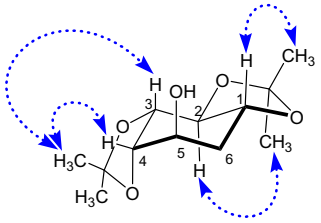
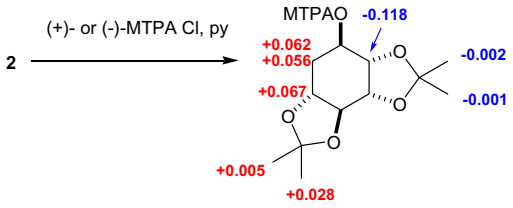
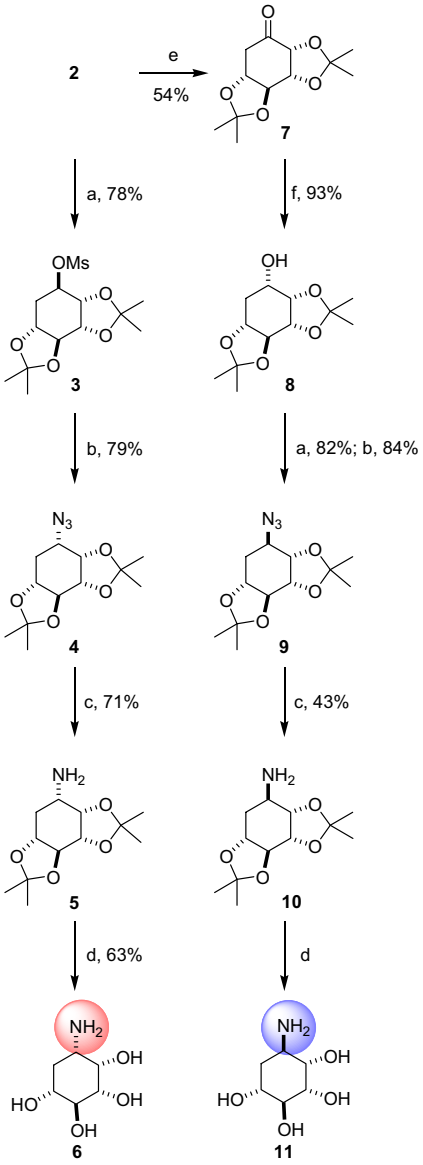


Figure 2. Selected NOESY correlations of **2**. For clarity, certain H atoms are omitted.



Scheme 2. Preparation of *S*- and *R*-MTPA esters of **2** and the unequal $\Delta\delta SR$ distribution.



Scheme 3. Reagents and conditions: (a) $MeSO_2Cl$, Et_3N, DMAP; (b) NaN_3, DMF, 15-crown-5-ether, 100 °C; (c) $LiAlH_4$; (d) TFA, THF; (e) Ac_2O, DMSO; (f) $LiAlH_4$.

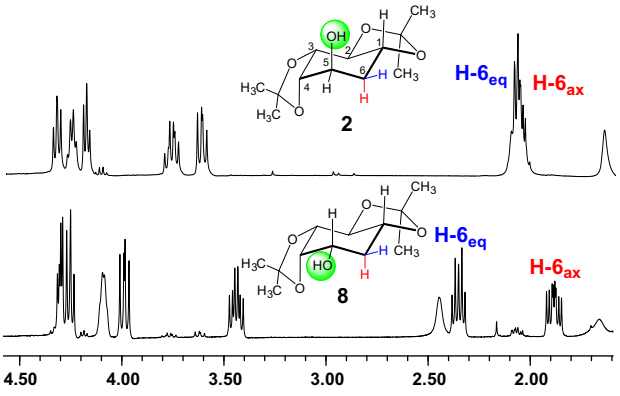
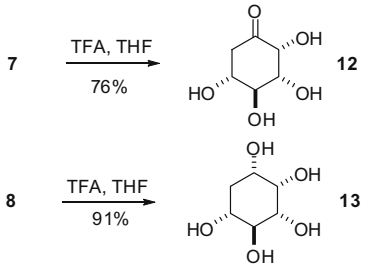


Figure 3. Partial ^1H NMR (400 MHz, $CDCl_3$) spectra of **2** (top) and **8** (bottom).



Scheme 4.

Table 1
α-Glucosidase[a] inhibitory effect of compounds **1**, **6**, **11**, **12**, and **13**

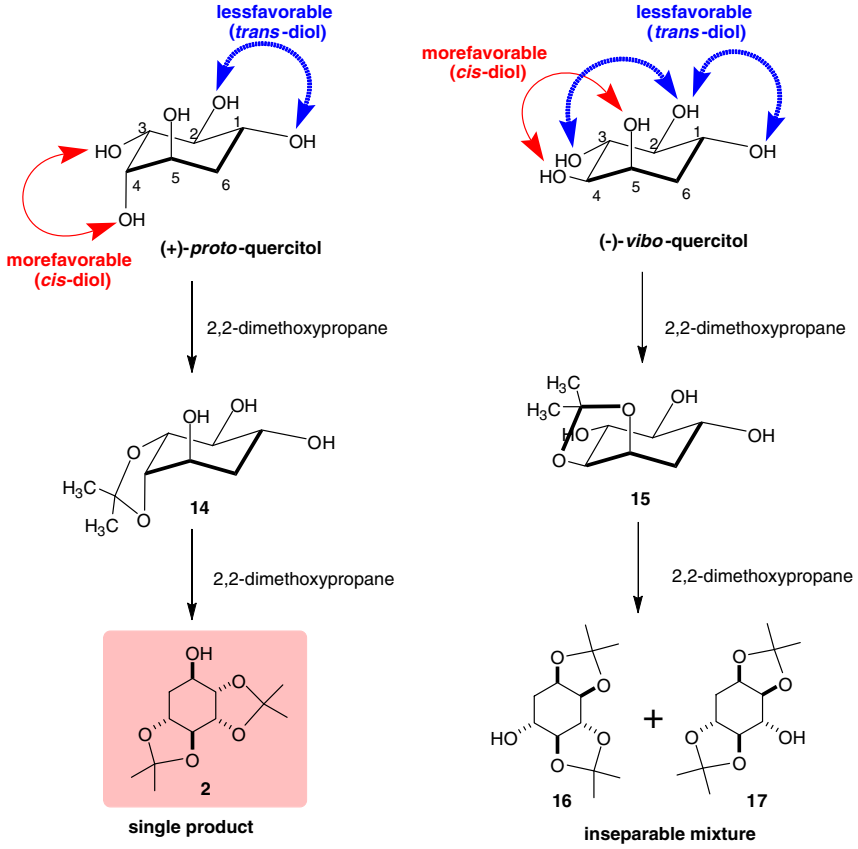
Compound	Inhibitory effect (IC_{50}, μM)
1	NI[b]
6	2890
11	12.5
12	670
13	921
Acarbose®	570
DNJ	173

[a] α-Glucosidase was obtained from Baker's yeast.
[b] Inhibitory effect less than 30% at 10 mg/mL.

To gain insight into the relationship between the stereochemistry of the 5-amino group and the inhibitory effect toward α-glucosidase, the 5*R*-amino congener **11** was also prepared. Initially, bis-acetonide **2** was subjected to oxidation using the Albright-Goldman reagent ($DMSO/Ac_2O$),[12] to afford ketone **7** (54%). Selective reduction of **7** was carried out with $LiAlH_4$ in THF as the solvent, generating exclusively diastereomeric 5-hydroxy-bis-acetonide **8** (93%), with no **2** being detectable. This could be rationalized by preferential hydride attack on the less hindered face of ketone **7**. Obviously, compounds **2** and **8** could be differentiated by ^1H NMR spectra (Fig. 3); H_2-6 of the former resonated at about δ_H 2.04–2.11 while those of the latter were well separated [δ_H 2.36 (H-6 equiv) and 1.88 (H-6_{ax})]. With 5-hydroxy-bis-acetonide **8** in hand, we subsequently accomplished the synthesis of the 5*R*-amino congener **11**[13] in a manner similar to that of aminocyclitol **6**. In order to gain more information on the pharmacophore required for C-5, we synthesized other cyclitol derivatives. Deprotection of **7** and **8** was carried out under the aforementioned conditions, and subsequent purification by recrystallization afforded pure target cyclitols **12**[14] and **13**[15] in moderate yields (Scheme 4).

5-Amino-1,2,3,4-cyclohexanetetrols (**6** and **11**) and deprotected analogues **12** and **13** were evaluated for α-glucosidase inhibition (Table 1) using a method reported previously.[16] The synthesized compounds showed weak inhibition (IC_{50} 670–2890 μM) than the antidiabetes drugs (Acarbose® and DNJ), except for amino cyclitol **11** (IC_{50} 12.5 μM). The very large difference in the inhibitory effect of the two diastereomeric aminocyclitols **6** and **11** (IC_{50} 2890 vs 12.5 μM) suggested that the configuration of the 5-NH_2 was possibly essential for mimicking the conformation and charge of the oxycarbenium ion intermediate.

In summary, we have prepared diastereomerically pure 5*S*- and 5*R*-amino-1,2,3,4-cyclohexanetetrols (**6** and **11**) from natural (+)-*proto*-quercitol (**1**) via two parallel routes. The key to the success involved the exclusive formation of bis-acetonide **2**, which was generated through *cis*-ketal **14** (Scheme 5). In cases where several 1,2-acetonides are possible, formation of a *cis*-cyclic ketal is more favorable than that of the *trans*-derivative. On the other hand, (−)-*vibo*-quercitol afforded an inseparable mixture of bis-aceto-



Scheme 5. Mechanistic formation of bis-acetonides **2**, **16**, and **17** generated from (+)-*proto*-quercitol and (−)-*vibo*-quercitol.

nides **16** and **17**[4b] on treatment with 2,2-dimethoxypropane though *cis*-cyclic ketal **15** was initially generated. This can be rationalized by the possible formation of a second acetonide at C-1/C-2 or C-2/C-3. Interestingly, aminocyclitol **11** displayed more striking inhibition than the diastereomeric congener **6**, indicating that the configuration of the 5-NH_2 is critical for blocking the enzyme. With the excellent biological activity of **11**, (+)-*proto*-quercitol could serve as an alternative chiral pool substrate for the synthesis of diverse aminocyclitols and related analogues.

Acknowledgments

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7. (+)-*proto*-*Quercitol* (**1**): colorless crystals; mp 235–236 °C; $[\alpha]_D^{27}$ +27.9 (*c* 0.02, H_2O); ^1H NMR (500 MHz, DMSO-d_6) δ_H 4.66 (1H, d, *J* = 3.4 Hz, OH), 4.49 (1H, d, *J* = 3.7 Hz, OH), 4.42 (1H, d, *J* = 4.3 Hz, OH), 4.37 (1H, d, *J* = 4.9 Hz, OH), 4.26 (1H, d, *J* = 6.1 Hz, OH), 3.67 (1H, ddd, *J* = 7.0, 6.7, 3.7 Hz), 3.59 (1H, dd, *J* = 3.7, 3.3 Hz), 3.40–3.51 (2H, m), 3.28 (1H, dt, *J* = 12.8, 4.0 Hz), 1.56–1.66 (2H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C 75.0, 72.9, 71.4, 68.9, 68.4. 34.9; ^1H NMR (D_2O, 400 MHz) δ_H 3.90 (1H, dd, *J* = 6.4, 3.2 Hz), 3.80 (1H, dd, *J* = 3.2, 2.4 Hz), 3.57–3.66 (2H, m), 3.44 (1H, dd, *J* = 9.6, 9.2 Hz), 1.86 (1H, ddd, *J* = 13.9, 3.2, 3.2 Hz), 1.69 (1H, ddd, *J* = 13.9, 11.6, 2.8 Hz); ^{13}C NMR (100 MHz, D_2O + one drop of acetone-d_6) δ_C 74.2, 71.8, 70.6, 68.5, 68.2, 32.9; ESIMS *m*/*z* $[M+H]^+$ 165.
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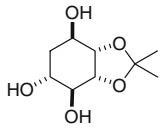
10. We have observed the formation of 3,4-*O*-isopropylidene derivative **14** during purification of the reaction mixture of **2** by silica gel column chromatography using hexane–EtOAc (1:1)



14

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11. 5*S*-Amino-1*R*,2*S*,3*S*,4*S*-cyclohexanetetrol (**6**): ^1H NMR (400 MHz, CD_3OD) δ_H 1.87 (1H, m), 1.94 (1H, m), 3.29–3.25 (2H, m), 3.43 (1H, m), 3.53 (1H, m), 3.98 (1H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C 30.7, 48.3, 69.2, 69.4, 72.6, 74.0; HRESIMS *m*/*z* 164.0921 $[M+H]^+$ (calcd for $C_6H_{13}NO_4$+H, 164.0923).
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13. 5*R*-Amino-1*R*,2*S*,3*S*,4*S*-cyclohexanetetrol (**11**): ^1H NMR (400 MHz, CD_3OD) δ_H 1.95 (1H, m), 2.06 (1H, m), 3.38 (1H, m), 3.53 (1H, m), 3.78 (1H, m), 3.90–3.95 (2H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C 31.1, 49.1, 69.0, 69.8, 70.4, 73.7; HRESIMS *m*/*z* 164.0922 $[M+H]^+$ (calcd for $C_6H_{13}NO_4$+H, 164.0923).
14. Cyclitols **12** ^1H NMR (400 MHz, DMSO-d_6) δ_H 2.32 (1H, dd, *J* = 12.0, 4.0 Hz), 2.71 (1H, dd, *J* = 12.0, 4.0 Hz), 3.81 (1H, br s), 3.92 (1H, br s), 3.93 (1H, br s), 4.27 (1H, br s, 1H), 4.94 (2H, br s), 5.10 (1H, br s), 5.46 (1H, br s).
15. Cyclitol **13**: ^1H NMR (400 MHz, D_2O) δ_H 1.59 (1H, m), 1.79 (1H, m), 3.25 (1H, m), 3.32 (2H, m), 3.60 (1H, br d, *J* = 12.4 Hz), 3.81 (1H, br s).
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