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Expeditious Synthesis of Tri- and Tetrahydroxyazepanes from D-(−)-Quinic Acid as Potent Glycosidase Inhibitors

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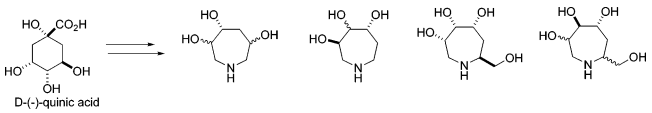

Several new stereoisomers of 3,4,6-trihydroxyazepanes and 7-hydroxymethyl-3,4,5-trihydroxyazepanes as well as known 3,4,5-trihydroxyazepanes were synthesized as potent glycosidase inhibitors from D-(−)-quinic acid in an efficient manner. The key step employs dihydroxylation of protected chiral 1,4,5-cyclohex-2-enetriols under $RuCl_3/NaIO_4$/phosphate buffer (pH 7) condition, followed by reductive amino cyclization. We found the choice of an appropriate protecting group to C1-OH of chiral 1,4,5-cyclohex-2-enetriols would increase the yields of cyclization. The preliminary biological data indicate some of these azepanes possess potent inhibition against α-mannosidase and α-fucosidase.

Azepanes,[1] the seven-membered-ring azasugars or iminocyclitols, along with five- and six-membered rings of azasugars are well-known as glycosidase inhibitors.[2] Their usage in the treatment of diabetics,[2b,3] viral infections,[4] and cancer[2c,5] has attracted a great deal of attention due to good inhibitory potency. A number of tetra-,[1,4c,6,7] tri-,[7d,f,h,o] and dihydroxy[7d,f] azepanes thus have been prepared by different approaches. Among trihydroxyazepanes, only a few methods were reported to prepare 3,4,6-trihydroxyazepanes, such as the Lundt procedure starting from 3-deoxysugars[7d] or the chemoenzymatic approach developed by Wang et al.[7h] Meanwhile, a novel class of azepanes containing an extra hydroxymethyl substituent are considered not only to provide an additional interaction with the active sites of glycosidases,[4c] but also to enhance the conformational flexibility.[7b,8] However, their syntheses were described in a limited number of reports.[4c,7k,n,9] In conjunction with our interest in the syntheses of various glycosidase inhibitors,[10] we report herein an expeditious synthesis of new stereoisomeric 3,4,6-trihydroxyazepanes and 7-hydroxymethyl-3,4,5-trihydroxyazepanes from D-(−)-quinic acid.

The synthesis of 3,4,6-trihydroxyazepanes **1**, **2**, and **3** is depicted in Scheme 1. Protected 1,4,5-cyclohex-2-ene-triols **11**, **12**, and **17**, previously prepared from D-(−)-quinic acid,[11] were subjected to dihydroxylation under $RuCl_3/NaIO_4$/phosphate

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SCHEME 1. Synthesis of 3,4,5- and 3,4,6-Trihydroxyazepanes

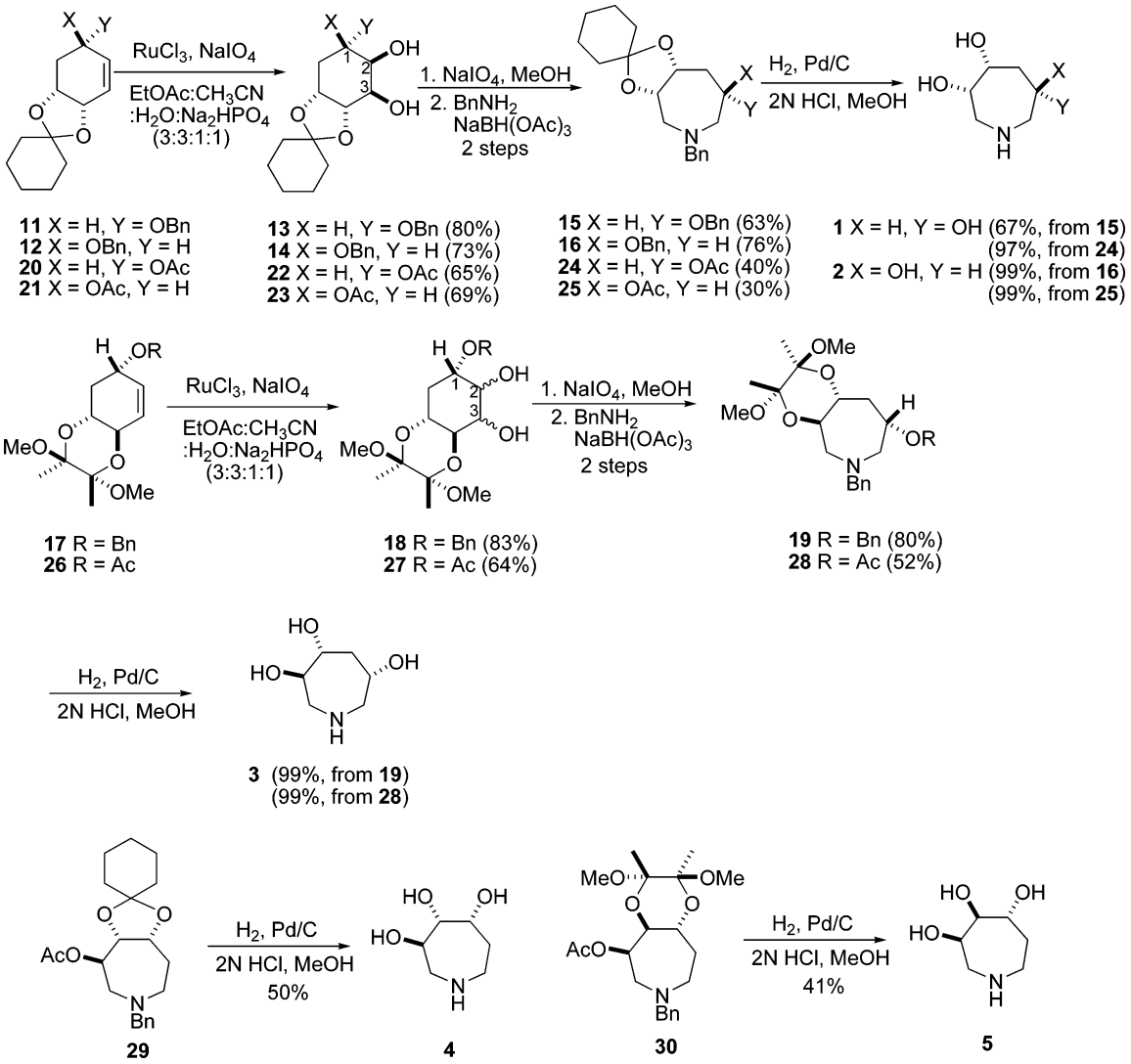

TABLE 1. Yields of Dihydroxylation under Different Conditions

condition	time (min)	**20** → **22** (%)	**21** → **23** (%)	**26** → **27** (%)
a	120	69	69	52
b	30	27	43	64
c	<10	65	69	64

[a] $KMnO_4$, $MgSO_4$, EtOH:H_2O (1:1), rt. [b] $RuCl_3 \cdot 3H_2O$, $NaIO_4$, EtOAc:CH_3CN:H_2O (3:3:1), 0 °C. [c] $RuCl_3 \cdot 3H_2O$, $NaIO_4$, EtOAc:CH_3CN:H_2O:$Na_2HPO_4 \cdot 2H_2O$ (3:3:1:1), 0 °C.

TABLE 2. Yields of Reductive Amino Cyclization with Different Reducing Agents

condition	**22** → **24:29** (%)	**23** → **25:29** (%)	**27** → **28:30** (%)
a	36:9	29:16	33:13
b	40:11	30:12	52:13

[a] $BnNH_2$ (6.1 equiv), $NaBH(OAc)_3$ (3.3 equiv), CH_2Cl_2, rt. [b] $BnNH_2$ (1.0 equiv), $NaBH_3CN$ (1.0 equiv), AcOH (1.0 equiv), MeOH, 0 °C to rt.

buffer (pH 7) condition to afford **13** (80%), **14** (73%), and **18** (83%), respectively. The resulting diols **13**, **14**, and **18** were oxidatively cleaved by $NaIO_4$ to provide the corresponding dialdehydes. Subsequent reductive amino cyclization was optimized by using benzylamine (6.1 equiv) and $NaBH(OAc)_3$ (3.3 equiv) to afford **15** (63%), **16** (76%), and **19** (80%), followed by hydrogenation with 10% Pd/C in MeOH−2 N HCl to afford the target molecules **1** (67%), **2** (99%), and **3** (99%), respectively. The synthesis took four steps from protected cyclohexenetriols **11**, **12**, and **17** with overall yields of 33−66%, or ten steps from D-(−)-quinic acid with 17−34% yields.

A similar route was studied to synthesize the same products **1**, **2**, and **3**, in which the aforementioned benzyl ether was substituted with an acetate as the protecting group. The starting materials **20**, **21**, and **26** were hydroxylated under the condition of $KMnO_4/MgSO_4$ to give moderate yields (52−69%, Table 1, condition *a*).[11,12] Lower yields were obtained under the condition of $RuCl_3/NaIO_4/H_2O$, which was attributed to the undesired deprotection of cyclohexyl ketal at the resulting low pH (condition *b*). The additional presence of phosphate buffer[13] led to improved yields with significant reduction of the reaction time (condition *c*). Phosphate buffer thus helped to maintain the reaction solution at a neutral pH. The stereochemistry of

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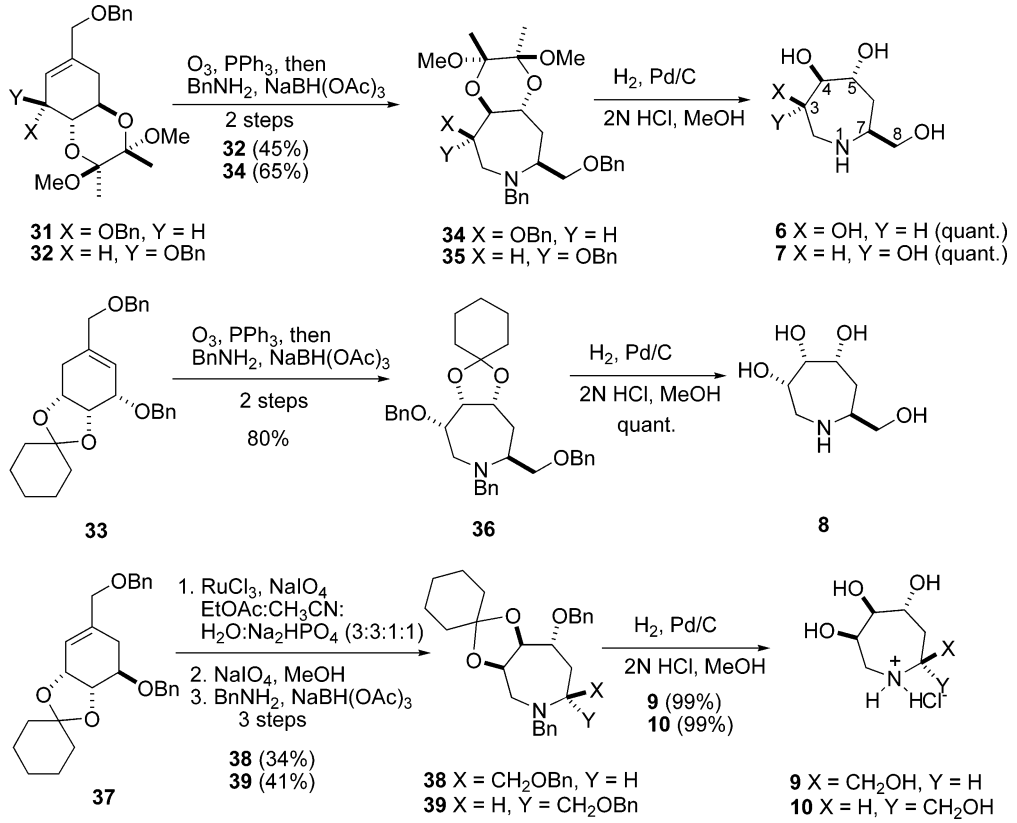
SCHEME 2. Synthesis of 7-Hydroxymethyl-3,4,5-trihydroxyazepanes



the diols of **22**, **23**, and **27** was rigorously determined in accordance with our previous report.[11] Compounds **22**, **23**, and **27** were further oxidized by $NaIO_4$ and subjected to reductive amino cyclization by treatment with $BnNH_2$ under the reduction condition of either $NaBH(OAc)_3$[14] or $NaBH_3CN$/AcOH.[15] Consistent with the previous report that the reaction yield is often affected by the choice of reducing agents,[15] $NaBH_3CN$/AcOH (Table 2, condition *b*) was found to give slightly better yields than $NaBH(OAc)_3$ (condition *a*). The explanation of the lower yields of **24** (40%), **25** (30%), and **28** (52%) was due to the acyl migration from C1 to C3 in compounds **22**, **23**, and **27** upon the addition of $NaIO_4$ to lead to the diastereomers **29** and **30** as the unexpected products. Compounds **24**, **25**, **28**, **29**, and **30** were finally deprotected by hydrogenolysis in the presence of 10% palladium on charcoal under acidic conditions to give **1**[16] (97%), **2**[17] (99%), **3**[18] (99%), **4** (50%), and **5**[19] (41%), respectively.

The synthesis of 7-hydroxymethyl-3,4,5-trihydroxyazepanes **6**, **7**, and **8** was carried out in an analogous manner (Scheme 2). Protected 1-hydroxylmethyl-3,4,5-cyclohexenetriols **31**, **32**, and **33**, prepared from D-(−)-quinic acid according to the reported procedure,[20,21] were transformed to the desired azepanes **6**, **7**, and **8**, respectively, in three steps, including ozonolysis, reductive amination, and final deprotection. A different route in the synthesis of hydrochloride salt forms of **6** and its C7 epimer furnished **9** and **10**, respectively, derived from **37** which was prepared from D-(−)-quinic acid in six steps.[22] The stereochemistry was lost at C7 while compound **37** was subjected to dihydroxylation, oxidative cleavage, and reductive aminocyclization.[23] Therefore, two separable C7-epimeric prod-

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(16) The synthesis of the enantiomer of compound **1** has been reported. See ref 7d.

(17) The synthesis of compound **2** has been reported. See ref 7h.

(18) The synthesis of the enantiomer of compound **4** has been reported. See ref 7h.

(19) The ^1H NMR of compound **5** was taken in D_2O instead of CD_3OD. See ref 7d.

(20) Alves, C.; Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 8443−8456.

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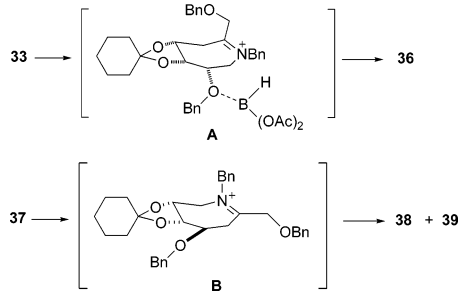
(23) The resulting stereochemistry observed in the oxidation and subsequent reductive amination of **33** and **37** could be explained by following molecular models.



The imine intermediate likely adopts a twist-boat conformation due to the protecting group of cyclohexyl ketal. As for the reduction of the intermediate **A**, the benzyl ether at C6 is situated at the pseudoaxial position (i.e., *endo*-cyclic), making it possible to coordinate the triacetoxyborohydride to have the hydride transfer from the bottom face. On the other hand, the benzyl ether of the intermediate **B** is located at *the* pseudoequatorial position (i.e., *exo*-cyclic), in which the oxygen unlikely interacts with the reducing agent to deliver the hydride. The reducing agent thus attacks from both sides of the imine group to lose stereoselectivity.

ucts, **38** and **39**, were isolated in 34% and 41% total yields. The stereochemistry of **38** and **39** was then distinguished by NOESY and other spectra.

In summary, the new **1** (3*S*,4*R*,6*R*)-, **2** (3*S*,4*R*,6*S*)-, and **3** (3*R*,4*R*,6*S*)-trihydroxyazepanes accompanying with known **4** (3*R*,4*R*,5*R*)- and **5** (3*R*,4*S*,5*R*)-trihydroxyazepanes each have been efficiently synthesized from D-(−)-quinic acid in ten steps. The benzyl group at the C1 position is superior to the acyl group when using protected 1,4,5-cyclohex-2-enetriols as starting materials. The protecting group plays an important role not only in the yields of dihydroxylation reactions, but also in the efficiency of reductive aminocyclization. Obviously, the acyl groups in **22**, **23**, and **27** were sensitive to the acidic condition that made acyl migration possible to cause low reaction yields. Among these synthetic tri- and tetrahydroxyazepanes, the preliminary result indicated that compound **3** is a potent inhibitor against α-mannosidase (from jack bean) and α-fucosidase (from *Thermotoga maritima*) with K_i values of 21.1 and 14.9 μM, respectively.[24] The potency is considered to be equivalent or even better to other reported tri- and tetrahydroxyazepanes.[7d,9b]

Experimental Section

(3*S*,4*R*,6*S*)-Trihydroxyazepane (1). Flash column chromatography (230−400 mesh SiO_2, MeOH/CH_2Cl_2/10% NH_4OH = 1/15/0.1 then 1/3/0.5) afforded a pale yellow syrup. $[\alpha]^{19}_D$ +18.6 (*c* 0.5, H_2O). ^{1}H NMR (500 MHz, D_2O) δ 3.96−3.85 (m, 2H), 3.78 (ddd, J = 10.1, 3.3, 2.4 Hz, 1H), 3.01 (dd, J = 13.8, 4.2 Hz, 1H), 2.97 (dd, J = 14.4, 5.7 Hz, 1H), 2.91−2.84 (m, 2H), 1.97 (ddd, J = 14.0, 10.1, 8.9 Hz, 1H), 1.85 (dt, J = 14.0, 3.8 Hz, 1H). ^{13}C NMR (125 MHz, D_2O + CD_3OD) δ 71.1, 70.8, 65.9, 53.4, 49.7, 37.7. HRMS (FAB) calcd for $C_6H_{14}NO_3$ ([M + H]$^+$) 148.0974, found 148.0975.

(3*S*,4*R*,6*R*)-Trihydroxyazepane (2). Flash column chromatography (230−400 mesh SiO_2, MeOH/CH_2Cl_2/10% NH_4OH = 1/15/0.1 then 1/3/0.5) afforded a pale yellow syrup. $[\alpha]^{23}_D$ −0.5 (*c* 0.3, H_2O). ^{1}H NMR (300 MHz, D_2O) δ 4.24 (ddd, J = 9.6, 6.3, 3.2 Hz, 1H), 4.20−4.10 (m, 1H), 4.07 (ddd, J = 9.6, 3.9, 2.2 Hz, 1H), 3.34 (dd, J = 13.8, 3.0 Hz, 1H), 3.30−3.20 (m, 2H), 3.16 (dd, J = 13.8, 5.7 Hz, 1H), 2.09 (ddd, J = 14.6, 9.7, 3.3 Hz, 1H), 1.93 (ddd, J = 14.6, 6.5, 3.9 Hz, 1H). ^{13}C NMR (75 MHz, D_2O + CD_3OD) δ 69.8, 69.2, 63.6, 51.4, 47.6, 36.6. HRMS (FAB) calcd for $C_6H_{14}NO_3$ ([M + H]$^+$) 148.0974, found 148.0979.

(3*R*,4*R*,6*S*)-Trihydroxyazepane (3). Flash column chromatography (230−400 mesh SiO_2, MeOH/CH_2Cl_2/10% NH_4OH = 1/15/0.1 then 1/3/0.5) afforded a pale yellow syrup. $[\alpha]^{21}_D$ −6.4 (*c* 0.3, H_2O). ^{1}H NMR (300 MHz, D_2O) δ 4.10−3.90 (m, 1H), 3.78 (td, J = 7.4, 3.4 Hz, 1H), 3.70 (td, J = 7.4, 3.4 Hz, 1H), 3.19 (dd, J = 14.4, 3.2 Hz, 1H), 3.13 (dd, J = 13.8, 4.4 Hz, 1H), 2.90 (dd, J = 14.4, 7.0 Hz, 1H), 2.84 (dd, J = 13.8, 7.6 Hz, 1H), 2.08 (dt, J = 14.3, 3.4 Hz, 1H), 1.82 (dt, J = 14.3, 9.2 Hz, 1H). ^{13}C NMR (75 MHz, D_2O + CD_3OD) δ 75.3, 73.7, 67.5, 55.1, 51.8, 41.2. HRMS (FAB) calcd for $C_6H_{14}NO_3$ ([M + H]$^+$) 148.0974, found 148.0968.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Regarding the conditions of α-mannosidase and α-fucosidase activity assays, please see refs 10a and 10b for the details.