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A norbornyl route to some novel seven-membered iminocyclitols

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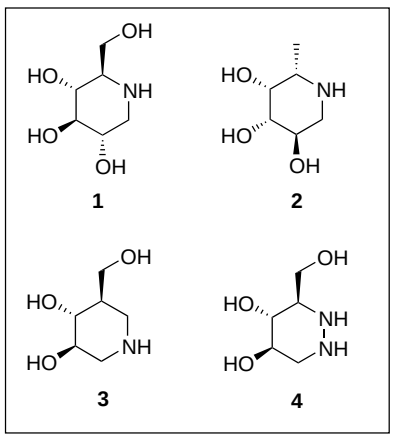
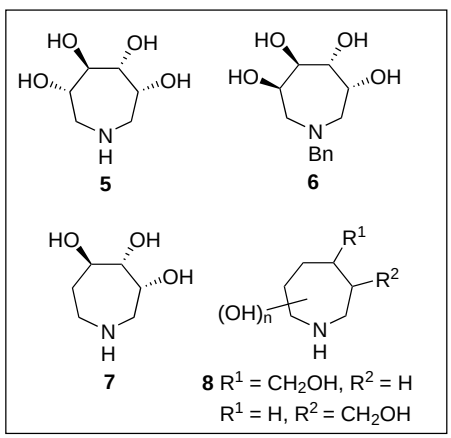
Abstract—New hydroxy azepanes with an additional hydroxymethyl side arm have been conceived and their syntheses achieved from a suitably functionalized cyclohexanoid building-block extracted from the norbornyl framework. The new iminocyclitols (homoisofagomine derivatives) exhibit weak but selective inhibitory activity in enzyme assays.

Replacement of ring oxygen with basic nitrogen in sugars gives rise to azasugars (also referred to as imino sugars) and these entities have not only been found in Nature but also aroused a great deal of synthetic interest in recent years because of their ability to inhibit glycosidases.[1] While deoxynojirimycin **1** constitutes a well known example of a potent naturally occuring glycosidase inhibitor, 1-deoxyfuconojirimycin **2** is a synthetic analogue[2a] and the most powerful inhibitor of α-fucosidases known to date. This impressive biological activity profile of iminosugars and their potential for therapeutic applications has stimulated interest in the synthesis of newer analogues through manipulation of the number and stereochemical disposition of the hydroxyl groups, relocation of the hydroxymethyl arm as in the potent inhibitor isofagomine **3**,[2b,c,e] introduction of additional ring nitrogen atom as in the diazasugar **4**[2d] among others. More recently, iminocyclitols based on seven-membered rings having the same carbon content as the azasugars but endowed with the conformational advantage of a more flexible azepane ring that could lead to favorable binding to the active site of the enzyme have been introduced.[3] Indeed, iminocyclitols **5**–**7** have shown promising glycosidase inhibition profiles. We have visualized another variant of the seven-membered iminocyclitols with an additional binding site in the form of a hydroxymethyl arm, which can be regarded as a hybrid of the polyhydroxyazepanes and isofagomine **3**. Syntheses of several of these new iminocyclitols **8** form the subject matter of this letter.





Recently, we have delineated a convenient access to a functionalized cyclohexenoid **10** from a norbornyl precursor **9** involving a fragmentation protocol.[4a] It has been shown that **10** is a versatile building block, comparable to the cyclohexadiene-diols derived through

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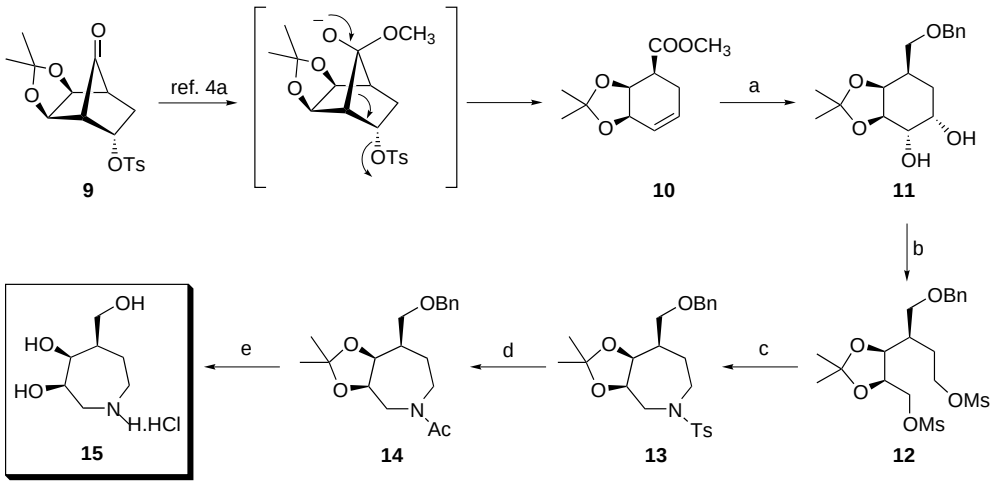
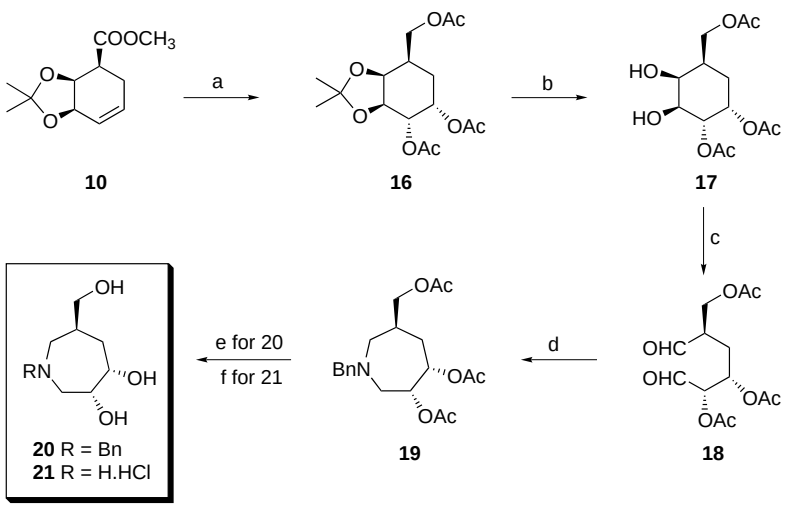
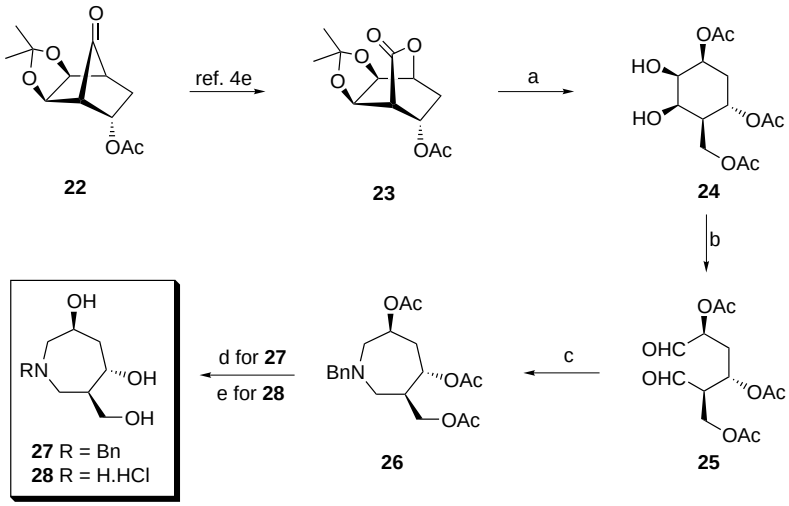
microbial hydroxylation of arenes,[5] for the synthesis of diverse cyclitols and related structures.[4] Herein, we further demonstrate the utility of **10** in the synthesis of novel hydroxyazepanes related to **8** (Scheme 1). Elaboration of **10** to azepanes required oxidative cleavage of the cyclohexanoid ring to set-up either a double reductive amination or inter- and intramolecular *N*-alkylations to deliver system **8**. Towards this end, **10** was transformed to the *cis*-1,2-diol **11**[6] via $LiAlH_4$ reduction, protection of the resulting primary hydroxyl functionality and stereoselective catalytic OsO_4 dihydroxylation. Periodate mediated oxidative cleavage to the dialdehyde, sodium borohydride reduction and mesylation on **11** proceeded uneventfully to furnish the dimesylate **12** (Scheme 1).[6] Exposure of **12** to *p*-toluenesulfonamide under phase transfer conditions resulted in smooth inter- and the intramolecular *N*-alkylations to **13**. The *N*-tosyl group in **13** could be reductively removed with sodium naphthalenide and the resulting free amine was characterized as the acetamide **14**, which existed as a mixture of two rotamers. Deprotection maneuvers in **14** led to a homoisofagomine (carbon inserted between nitrogen and hydroxymethyl group of **3**) derivative **15** (Scheme 1).[6] An isomeric homoisofagomine derivative with a carbon inserted between the hydroxymethyl group and the neighboring hydroxy group was also prepared from **10** through a tactically altered route. Cyclohexenoid **10** was first elaborated to **16** through $LiAlH_4$ reduction, stereoselective catalytic dihydroxylation and acetylation (Scheme 2).[6] Acetonide deprotection in **16** gave **17** and the 1,2-diol functionality was subjected to periodate cleavage to



Scheme 1. *Reagents and conditions*: (a) i. LAH, THF, 0–5°C, 1 h, 90%, ii. BnBr, NaH, THF, rt, 6 h, 95%, iii. OsO_4, NMMO, Me_2CO–H_2O (4:1), rt, overnight, 83%; (b) i. $NaIO_4$–silica gel, DCM, 0°C, 2 h, ii. $NaBH_4$, MeOH, 0°C, 1 h, iii. MsCl, Et_3N, DCM, 0°C, 1.5 h, 55% (three steps); (c) *p*$TsNH_2$, KOH, TBAI, C_6H_6–H_2O (9:1), reflux, 24 h, 60%; (d) i. Na-naphthalenide, DME, –60°C, 1 h, ii. Ac_2O, Py, rt, overnight, 67% (two steps); (e) i. H_2, Pd/C, EtOH, 12 h, ii. 1N HCl, 90°C, 85% (two steps).



Scheme 2. *Reagents and conditions*: (a) i. LAH, THF, 0–5°C, 1 h, 90%, ii. OsO_4, NMMO, Me_2CO–H_2O (4:1), rt, overnight, 82%, iii. Ac_2O, DMAP, DCM, rt, 10 h, 78%; (b) Amberlyst-15, THF–H_2O (2:3), rt, 12 h, 85%; (c) $NaIO_4$–silica gel, DCM, 0°C, 2 h; (d) $BnNH_2$, AcOH, $NaCNBH_3$, MeOH, 12 h, 35% (two steps); (e) K_2CO_3, MeOH, rt, 6 h, 95%; (f) i. H_2, Pd/C, EtOH, rt, 5 h, ii. 1N HCl, 90°C, 24 h, 90%.



Scheme 3. *Reagents and conditions*: (a) i. LAH, THF, 0–5°C, 3 h, 70%, ii. Ac_2O, DMAP, DCM, rt, 12 h, 89%, iii. Amberlyst-15, THF–H_2O (2:3), rt, 12 h, 85%; (b) $NaIO_4$–silica gel, DCM, 0°C, 2 h; (c) $BnNH_2$, AcOH, $NaCNBH_3$, MeOH, 15 h, 30% (two steps); (d) K_2CO_3, MeOH, rt, 6 h, quant.; (e) i. H_2, Pd/C, EtOH, rt, 5 h, ii. 1N HCl, 90°C, 20 h, 90%.

deliver the intermediate dialdehyde **18**, which was directly subjected to a double-reductive amination[7] to give the azepane **19** as the major product (Scheme 2).[6] While acetate hydrolysis in **19** gave the *N*-benzyl-protected trihydroxy azepane **20**, reductive removal of the *N*-benzyl group and deprotection gave the trihydroxy azepane **21** (Scheme 2).[6]

Another homoisofagomine related to **21** with a 'skipped hydroxyl' pattern was accessed from the *endo*-norbornyl derivative **22**. Regioselective Baeyer–Villiger oxidation of **22** gave **23** as the major product (87:13 mixture of regioisomers). A sequence consisting of $LiAlH_4$ reduction, per-acetylation and acetonide deprotection in **23** led to cyclohexane-1,2-diol **24** (Scheme 3).[6] Periodate cleavage in **24** led to an intermediate dialdehyde **25**, which was directly subjected to double-reductive amination with benzylamine to give the azepane triacetate **26** as the major product. Acetate hydrolysis in **26** gave the *N*-benzyl trihydroxy derivative **27**. On the other hand, reductive removal of the *N*-benzyl group and acetate deprotection furnished the trihydroxyazepane **28** (Scheme 3).[6]

The new homoisofagomine analogues **15**, **20**, **21**, **27** and **28** were assayed for glycosidase inhibition against a set of six commonly used enzymes (α- and β-glucosidase, α- and β-galactosidase, and α- and β-mannosidase) following standard protocols. All the substrates examined exhibited weak but selective inhibition with **20** and **21** showing relatively better activity against β-glucosidase ($K_i = 470$ μM) and α-galactosidase ($K_i = 600$ μM), respectively. It is quite interesting that while the *N*-benzyl derivative **20** shows inhibition of β-glucosidase, the unprotected **21** inhibits α-galactosidase. This change in enzyme selectivity in the case of **20** and **21** mediated only by the protective group, without any alteration in the disposition or stereochemistry of the hydroxyl groups, is quite unusual and may have useful implications. We have observed similar selectivity in the case of **27** and **28**, as well with the former exhibiting weak inhibition of β-glucosidase and the latter inhibiting α-glucosidase.[8]

In conclusion, we have amplified the synthetic utility of the cyclohexenoid building block **10** by devising stereoselective routes to new hydroxyazepanes with a homoisofagomine framework. While the azepanes reported here have only weak glycosidase inhibitory activity compared to those reported earlier, our results of enzymatic assays reveal the importance of *N*-substitution in modulating selectivity and inhibition efficacy.

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6. All new compounds reported here were racemic and were characterized on the basis of their spectral data (^{1}H and ^{13}C NMR, IR, Mass). Selected spectroscopic data (*J* in Hz). **15**: δ_H (300 MHz, D_2O): 4.02 (1H, br s), 3.95 (1H, ddd, *J* 1.8, 4.5, 9.3), 3.46 (1H, d 1/2 ABq, *J* 6.9, 10.8), 3.37 (1H, d 1/2 ABq, *J* 6, 10.8), 3.29–2.97 (4H, series of m), 1.77–1.62 (3H, m); δ_C (75 MHz, D_2O): 72.4 (CH), 70.0 (CH), 63.8 (CH_2), 46.0 (CH_2), 45.7 (CH_2), 42.2 (CH), 21.9 (CH_2). **20**: δ_H (300 MHz, D_2O): 7.27 (5H, m, br s like), 3.92 (1H, m), 3.8–3.76 (1H, m), 3.7–3.6 (2H, m, ABq like), 3.26 (1H, d 1/2 ABq, *J* 6, 11), 3.2 (1H, d 1/2 ABq, *J* 7, 11), 2.85 (1H, dd, *J* 8.4, 13.2), 2.73 (1H, br dd, *J* 13.5), 2.55 (1H, br dd, *J* 13.5), 2.3 (1H, dd, *J* 9, 13.2), 2.0–1.9 (1H, m), 1.81–1.75 (1H, m), 1.4–1.32 (1H, m); δ_C (75 MHz, D_2O): 137.2 (C), 130.9 (2 CH), 129.4 (2 CH), 128.7 (CH), 71.9 (CH), 71.4 (CH), 65.8 (CH_2), 62.7 (CH_2), 56.8 (CH_2), 55.3 (CH_2), 33.8 (CH), 33.3 (CH_2). **21**: δ_H (300 MHz, D_2O): 4.08–4.02 (2H, m), 3.44 (1H, d 1/2 ABq, *J* 5.4, 11.4), 3.36–3.25 (3H, m), 3.10 (1H, dd, *J* 3, 13.5), 2.81 (1H, dd, *J* 11, 13.5), 2.25–2.17 (1H, m), 1.87 (1H, ddd as dt, *J* 5.1, 15.3), 1.52 (1H, ddd, *J* 3.6, 10.5, 15.3); δ_C (75 MHz, D_2O): 70.8 (CH), 70.1 (CH), 64.7 (CH_2), 48.9 (CH_2), 47.4 (CH_2), 33.5 (CH), 32.9 (CH_2). **27**: δ_H (300 MHz, D_2O): 7.33–7.30 (5H, m), 4.06–4.0 (1H, m), 3.78–3.63 (3H, series of m), 3.53 (1H, d 1/2 ABq, *J* 4.8, 10.8), 3.37 (1H, dd, *J* 6.6, 11.4), 2.93–2.9 (1H, m, dd like), 2.82–2.77 (1H, br d, *J* 13.8), 2.39–2.3 (2H, m), 2.0–1.96 (2H, m), 1.75–1.67 (1H, m); δ_C (75 MHz, D_2O): 138.7 (C), 132.6 (2 CH), 131.1 (2 CH), 130.4 (CH), 69.9 (CH), 67.0 (CH), 65.5 (CH_2), 64.9 (CH_2), 63.9 (CH_2), 55.7 (CH_2), 49.1 (CH), 45.5 (CH_2). **28**: δ_H (300 MHz, D_2O): 4.21–4.18 (1H, m), 3.92–3.83 (1H, m), 3.69–3.62 (1H, m), 3.59–3.51 (1H, m), 3.36–3.25 (2H, m), 3.15–3.01 (2H, m), 2.21–2.11 (1H, m), 1.97–1.86 (2H, m); δ_C (75 MHz, D_2O): 66.5 (CH), 63.3 (CH), 62.3 (CH_2), 52.0 (CH_2), 46.1 (CH_2), 45.3 (CH), 42.2 (CH_2).
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