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Polycyclitols. Novel conduritol and carbasugar hybrids as a new class of potent glycosidase inhibitors

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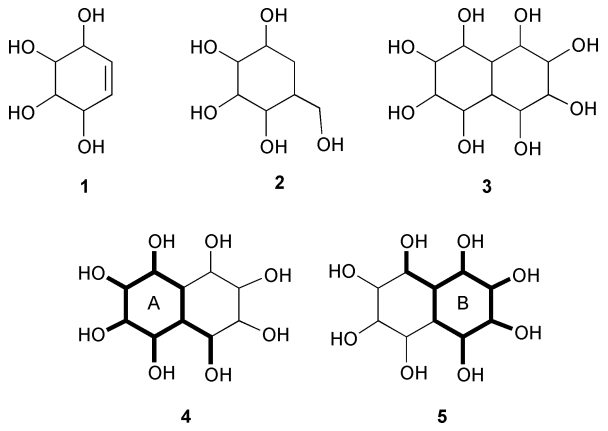
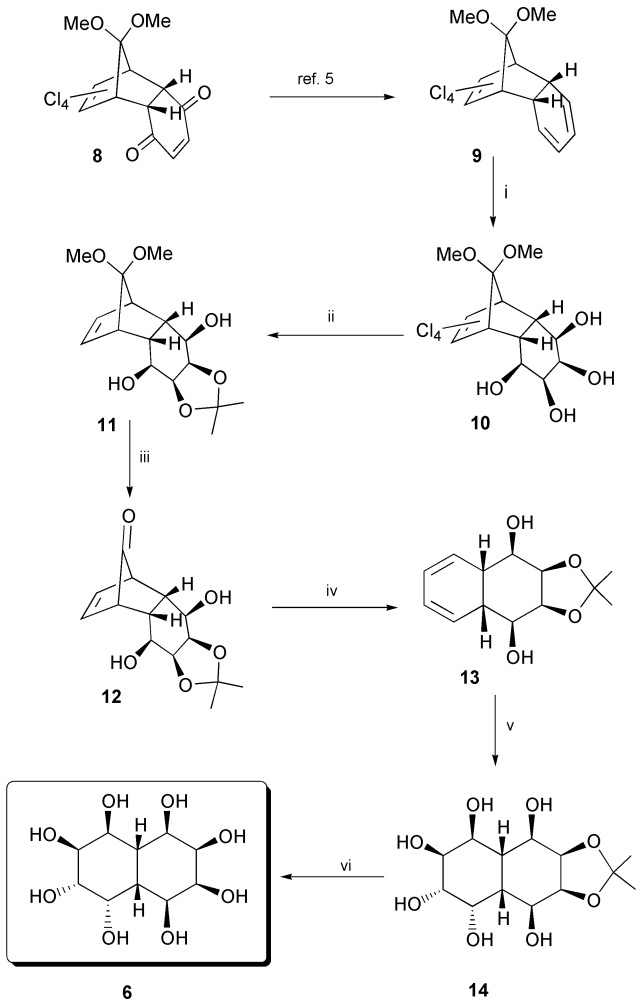
We have conceptualized new molecular entities (bicyclitols) in which two conduritol and two carbasugar moieties are embedded in a polyhydroxylated decahydronaphthalene framework and achieved their syntheses in a stereo- and regioselective manner. One of the bicyclitols was found to be a potent and selective α-glucosidase inhibitor.

Conduritols **1** (six diastereomers designated A–F are known)[1] and carbasugars **2** are a class of polyhydroxylated cyclohexanoids that have evoked a great deal of synthetic interest in recent years.[1,2] In view of their promising therapeutic potential in the management of wide ranging disorders like diabetes, viral infections, HIV and cancer among others, many analogues and structural variants of **1** and **2** have been synthesized and their biological activities, particularly glycosidase inhibition has been evaluated.[3] Considering the fundamental importance of competitive and specific glycosidase inhibition in new drug development, we have conceived of a new family of polyhydroxylated polycyclic systems (polycyclitols) represented by **3** as potential glycomimics.[4] Bicyclitol **3** is an interesting entity which can be considered as a hybrid of two conduritols with shared, common ring junction carbon atoms. Alternately, **3** can be regarded as a hybrid of two carbasugars A and B (see, bold portions in **4** and **5**), both of which are ring annulated. Herein,



we report the stereo- and regioselective syntheses of two polycyclitols **6** and **7** based on the general structure **3**, and show that one of them **6** is a potent and selective inhibitor of α-glucosidase.

Our synthesis of **6** emanated from the readily available Diels–Alder adduct **8** of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and *p*-benzoquinone, which was elaborated to the tricyclic diene **9** following the tactically modified literature procedure.[5] Exhaustive OsO_4 mediated dihydroxylation of **9** occurred exclusively from the *exo*-face to furnish the all *cis*-tetrol **10**.[6] Selective monoprotection and reductive dechlorination in **10** led to the symmetrical **11**.[6] Careful deketalisation in **11**, while retaining the acetonide protective group led to the desired norbornen-7-one† **12**, Scheme 1. Thermally induced decarbonylation in **12** to the cyclohexadiene derivative **13**[6] was smooth and further catalytic, OsO_4 mediated double dihydroxylation proceeded stereoselectively to furnish **14** as a single diastereomer. Acetonide deprotection in **14** provided the octahydroxydecahydronaphthalene **6**,[6] a hybrid of conduritols D (right ring) and E (left ring), Scheme 1. The absence of symmetry in **6** and **14**, revealed through the presence of 10 and 13 lines, respectively, in the ^{13}C NMR spectra, uniquely settled the stereochemical pattern present in these bicyclitols. Bicyclitol **6** was screened against α- and β-glucosidases (from Bakers' yeast and almonds, respectively) that accept corresponding *p*-nitrophenylglycosides as substrates and it was very satisfying to find impressive inhibition of α-glucosidase with a K_i value[7] of 12 μM (*cf.* K_i = 25.4 μM for deoxynojirimycin, DNJ). Interestingly, **6** exhibited no significant inhibitory activity



Scheme 1 *Reagents and conditions*: i, OsO_4 (cat.), NMMO, Me_2CO:tBuOH (5:2), 2 d, 66%; ii, (*a*) Amberlyst-15, acetone, mol. sieves 4 A, 75%; (*b*) Na, liq. NH_3, THF, EtOH, 49%; iii, Amberlyst-15, acetone, 98%; iv, $C_6H_5NO_2$, 160 °C, 62%; v, OsO_4 (cat.), NMMO, $Me_2CO:H_2O$:tBuOH (5:5:2), 85%; vi, 30% CF_3COOH, 95%.

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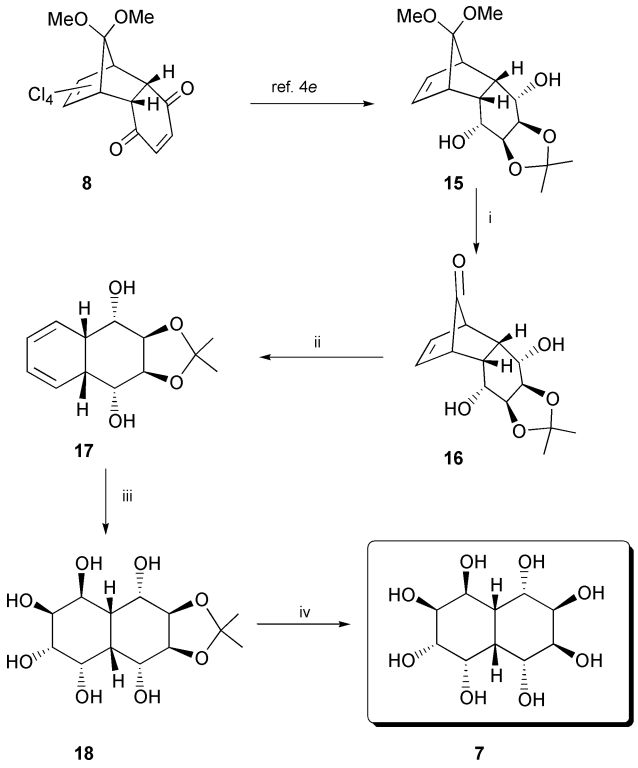

Scheme 2 *Reagents and conditions*: i, Amberlyst-15, acetone, 95%; ii, $C_6H_5NO_2$, 160 °C, 34%; iii, OsO_4 (cat.), NMMO, Me_2CO:H_2O:tBuOH (5:5:2), 73%; iv, 30% CF_3COOH, 90%.

against β-glucosidase at mM concentration, thus highlighting its selectivity towards α-glucosidase.

The promising inhibitory profile of **6**, spurred us to prepare a diastereomer **7** of **6**. Diels–Alder adduct **8** was readily transformed to the *endo*,*endo*-diol-**15**.[6] Deketalisation to **16** and decarbonylation led to the cyclohexadiene derivative **17**,[6] Scheme 2. Catalytic OsO_4 mediated double dihydroxylation was once again highly diastereoselective and the hexahydroxyacetal **18** was obtained. Acetonide deprotection in **18** delivered the projected bicyclitol **7**,[6] a hybrid of conduritols A (right ring) and E (left ring). Once again the lack of symmetry (^{13}C NMR) in **7** and **18**, uniquely delineated the stereochemical pattern generated during the double dihydroxylation of **17**. When **7** was evaluated for its inhibitory activity against α- and β-glucosidases, no significant inhibition was observed for either of the enzymes at mM concentrations, indicating that stereochemical alterations in the hydroxy substituents has a major impact on the enzyme inhibitory activity (*cf.* **6**). This result provides further impetus to prepare many more diastereomers of **6** and **7** for further evaluation and efforts towards that end are underway.

In short, we have devised a new family of glycosidase inhibitors, composed of conduritol and carbasugar hybrid structures and describe the synthesis of an octahydroxydecahydronaphthalene, which exhibits significant and selective α-glucosidase activity.

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Notes and references

† The IUPAC name for norbornen-7-one is bicyclo[2.2.1]hept-2-en-7-one.

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6 All the new compounds reported here were fully characterised on the basis of their spectral IR, ^1H and ^{13}C NMR, MS) and analytical data. Selected spectral data: **13**: δ_H(300 MHz; $CDCl_3$) 5.87–5.83 (m, 2H), 5.65–5.61 (m, 2H), 4.42–4.40 (m, 2H), 3.74 (br s, 2H), 3.00–2.98 (m, 2H), 2.70–2.67 (m, 2H), 1.55 (s, 3H), 1.40 (s, 3H); δ_C(75 MHz; $CDCl_3$) 125.8(2C), 122.6(2C), 109.3, 74.8(2C), 69.0(2C), 35.4(2C), 26.0, 24.4. **6**: δ_H(300 MHz; D_2O), 4.00–3.60 (m, 2H), 2.22–2.18 (m, 2H); δ_C(100 MHz; D_2O) 77.0, 76.7, 76.0, 74.2, 73.2, 71.2 (2C), 66.4, 43.1, 40.5; MS (70 eV, EI): *m/z* 264 ($M^+ - 2$). **17**: δ_H(300 MHz; $CDCl_3$) 5.97–5.94 (m, 2H), 5.54–5.50 (m, 2H), 4.50–4.49 (m, 2H), 3.86 (br s, 2H), 3.53 (d, 2H, *J* = 6.9 Hz), 3.20 (br s, 2H), 1.46 (s, 3H), 1.37 (s, 3H); δ_C(75 MHz; $CDCl_3$) 125.8(2C), 123.8(2C), 108.6, 74.9(2C), 69.7(2C), 32.4 (2C), 26.6, 24.0. **7**: δ_H(300 MHz; D_2O,) 4.00–3.67 (m, 8H), 2.36–2.28 (m, 2H); δ_C(75 MHz; D_2O) 73.7, 72.8, 71.3, 70.7, 70.4, 69.3, 69.2, 67.4, 40.2, 38.4.

7 Each enzymatic assay contained α- or β-glucosidase (0.1 to 1.0 U ml^{-1}), compounds **6**/**7** in water and the corresponding *p*-nitrophenylglycosides (2–3 mM) at a pH and temperature optimum for the enzyme. K_i (μM) values were determined using Lineweaver–Burk plots of the inhibition data.