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) 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 OsO4 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 11.7 Careful deketalisation in 11, while retaining the acetone protective group led to the desired norbornen-7-one† 12, Scheme 1. Thermally induced decarbonylation in 12 to the cyclohexadiene derivative 13 was smooth and further catalytic, OsO4 mediated double dihydroxylation proceeded stereoselectively to furnish 14 as a single diastereomer. Acetonide deprotection in 14 provided the octahydroxycyclohexadecanophthalene 6, a hybrid of conduritols C (right ring) and D (left ring), Scheme 1. The absence of symmetry in 6 and 14, revealed through the presence of 10 and 13 lines, respectively, in the 13C 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 of 12 \(\mu\)M (cf. \(K_i = 25.4 \mu\)M for deoxynojirimycin, DNJ).

Interestingly, 6 exhibited no significant inhibitory activity against β-glucosidase.

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against \(\beta\)-glucosidase at mM concentration, thus highlighting its selectivity towards \(\alpha\)-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 of 18 was obtained. Acetonide deprotection in 18 delivered the projected bicyclitol 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 \(\alpha\)- and \(\beta\)-glucosidasises, no significant inhibition was observed for either of the enzymes at mM concentrations, indicating that stereochemical alterations in the hydroxy substituents have 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 octahydroxydeca-

hydrophthalene, which exhibits significant and selective \(\alpha\)-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.

6. All the new compounds reported here were fully characterised on the basis of their spectral IR, \(^1\)H and \(^{13}\)C NMR, MS) and analytical data.

### Scheme 2

Reagents and conditions: i. Amberlyst-15, acetone. 95%; ii. C\(_6\)H\(_5\)NO\(_2\), 160 °C, 34%; iii. OsO\(_4\) (cat.), NMMO, Me\(_2\)CO, 18 °C, 34%; iv. OsO\(_4\) (cat.), NMMO, Me\(_2\)CO, 34%.