

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

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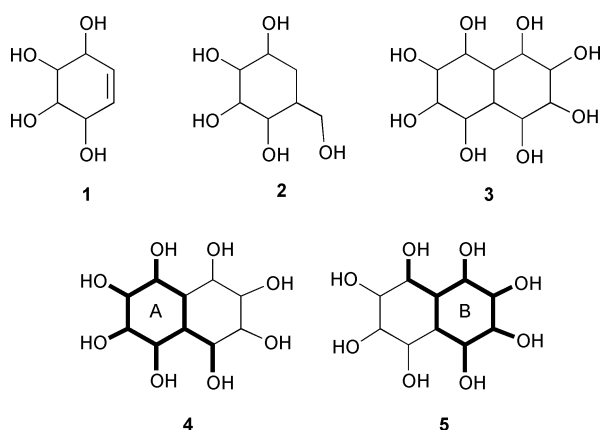
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We have conceptualized new molecular entities (bicyclitols) in which two conduritol and two carbasugar moieties are embedded in a polyhydroxylated decahydronaphthalene framework and achieved their syntheses in a stereo- and regioselective manner. One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

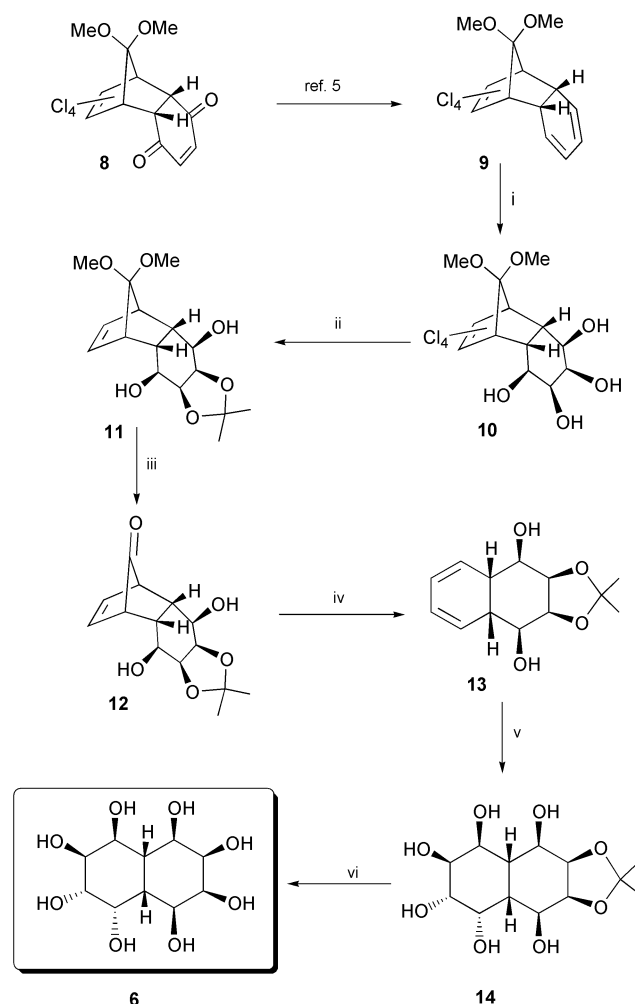
Conduritols **1** (six diastereomers designated A–F are known)¹ and carbasugars **2** are a class of polyhydroxylated cyclohexanoids that have evoked a great deal of synthetic interest in recent years.^{1,2} In view of their promising therapeutic potential in the management of wide ranging disorders 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,



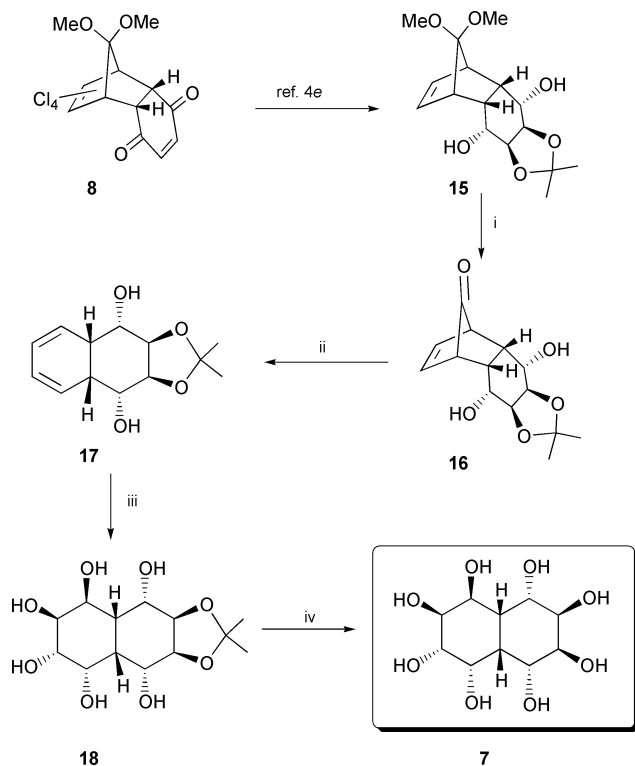
we report the stereo- and regioselective syntheses of two polycyclitols **6** and **7** based on the general structure **3**, and show that one of them **6** is a potent and selective inhibitor of α -glucosidase.

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 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**.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, OsO₄ 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 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 value⁷ of 12 μ M (*cf.* *K*_i = 25.4 μ M for deoxynojirimycin, DNJ). Interestingly, **6** exhibited no significant inhibitory activity



Scheme 1 Reagents and conditions: i, OsO₄ (cat.), NMMO, Me₂CO:tBuOH (5:2), 2 d, 66%; ii, (a) Amberlyst-15, acetone, mol. sieves 4 Å, 75%; (b) Na, liq. NH₃, THF, EtOH, 49%; iii, Amberlyst-15, acetone, 98%; iv, C₆H₅NO₂, 160 °C, 62%; v, OsO₄ (cat.), NMMO, Me₂CO:H₂O:tBuOH (5:5:2), 85%; vi, 30% CF₃COOH, 95%.



Scheme 2 Reagents and conditions: i, Amberlyst-15, acetone, 95%; ii, C₆H₅NO₂, 160 °C, 34%; iii, OsO₄ (cat.), NMMO, Me₂CO:H₂O:tBuOH (5:5:2), 73%; iv, 30% CF₃COOH, 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 OsO₄ 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 (¹³C 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 conduritols 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.

- (a) M. Balci, Y. Sutbeyaz and H. Secen, *Tetrahedron*, 1990, **46**, 3715; (b) H. A. J. Carless, *Tetrahedron: Asymmetry*, 1992, **3**, 795; (c) M. Balci, *Pure Appl. Chem.*, 1997, **69**, 97.
- (a) T. Suami, *Top. Curr. Chem.*, 1990, **154**, 257; (b) R. J. Ferrier and S. Middleton, *Chem. Rev.*, 1993, **95**, 2779; (c) T. Hudlicky, D. A. Entwistle, K. K. Pitzer and A. J. Thorpe, *Chem. Rev.*, 1996, **96**, 1195; (d) C. R. Johnson, *Acc. Chem. Res.*, 1998, **31**, 333; (e) Y. Landais, *Chimia*, 1998, **52**, 104.
- (a) B. Ganem, *Acc. Chem. Res.*, 1996, **29**, 340; (b) M. Bols, *Acc. Chem. Res.*, 1998, **31**, 1.
- For a few related examples of syntheses of annulated conduritols, see: (a) D. C. Billington, F. Perron-Sierra, I. Picard, S. Beaubras, J. Duhault, J. Espinal and S. Challal, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2307; (b) Y. Kara, M. Balci, S. A. Bourne and W. H. Watson, *Tetrahedron Lett.*, 1994, **35**, 3349; (c) M. Desjardins, M. C. Lallemand, T. Hudlicky and K. A. Abboud, *Synlett.*, 1997, 728; (d) G. Mehta and D. S. Reddy, *Tetrahedron Lett.*, 1999, **40**, 9137; (e) G. Mehta, D. S. Reddy, S. S. Ramesh and U. Tatu, *Tetrahedron Lett.*, 1999, **40**, 9141.
- (a) M. A. Forman and W. P. Dailey, *J. Org. Chem.*, 1993, **58**, 1501; (b) T.-C. Chou and J. H. Chiou, *J. Chin. Chem. Soc. (Taipei)*, 1986, **33**, 227.
- All the new compounds reported here were fully characterised on the basis of their spectral IR, ¹H and ¹³C NMR, MS) and analytical data. Selected spectral data: **13**: δ_{H} (300 MHz; CDCl₃) 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; CDCl₃) 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; D₂O), 4.00–3.60 (m, 2H), 2.22–2.18 (m, 2H); δ_{C} (100 MHz; D₂O) 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; CDCl₃) 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; CDCl₃) 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; D₂O) 4.00–3.67 (m, 8H), 2.36–2.28 (m, 2H); δ_{C} (75 MHz; D₂O) 73.7, 72.8, 71.3, 70.7, 70.4, 69.3, 69.2, 67.4, 40.2, 38.4.
- 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 (μ M) values were determined using Lineweaver–Burk plots of the inhibition data.