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Polycyclitols: synthesis of novel carbasugar and conduritol analogues as potential glycosidase inhibitors

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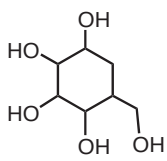
Abstract—Stereoselective syntheses of a new family of hydrindane based bicyclitols with seven hydroxyl groups in a diverse stereochemical array have been accomplished from readily available building-blocks. One of the bicyclitols **12** has been found to exhibit moderate α-glucosidase inhibitory activity in enzymatic assays. © 2001 Elsevier Science Ltd. All rights reserved.

Inhibitors of glycosidases or glycomimics have received considerable attention in the past two decades or so as they are potential therapeutic agents for the treatment of diseases related to metabolic disorders of carbohydrates such as diabetes, cancer, AIDS and viral infections, where glycoprotein processing is crucial.[1,2] A range of carbo- and heterocyclic analogues of carbohydrates that resemble monosaccharides in shape, size and functionalization, and can act as transition state mimics but formally lack a glycosidic linkage, have been devised and their glycosidase inhibitory activities evaluated.[1,2] In this context, carbasugars **1** (with diverse functionalization and stereochemical features)[2] and conduritols **2** (six diastereomers designated A–F are known)[3] have generated a great deal of synthetic interest. We have recently introduced polycyclitols (fused polycarbocyclic systems with dense hydroxyl functionalization) like **3**–**5** as new structural variants embodying the characteristic features present in **1** and **2**.[4,5] Among these, one of the diastereomers of **5** representing a hybrid structure of **1** and **2** has shown potent and selective α-glucosidase inhibition at μM concentration.[4c] This promising lead motivated us to prepare new bicyclitols related to **5**, but having subtle structural and conformational divergence. Herein, we report the stereo- and regioselective synthesis of several bicyclitols based on the hydrindane system **6**, which can be regarded as an annulated conduritol or carbasugar (see bold portion in **6** corresponding to **1**). Our synthetic approaches leading to secured stereochemistry at all the available nine stereogenic centres in the bicyclitols **6** are notable for their brevity and simplicity.



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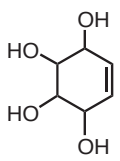

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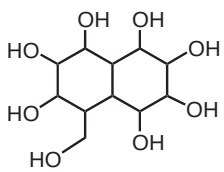

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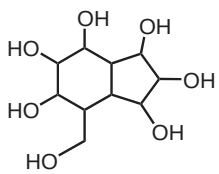

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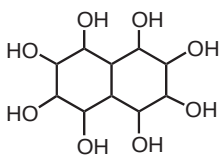

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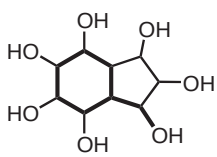

6

Keywords: cyclitols; carbohydrate mimetics; enzyme inhibitors; osmylation.

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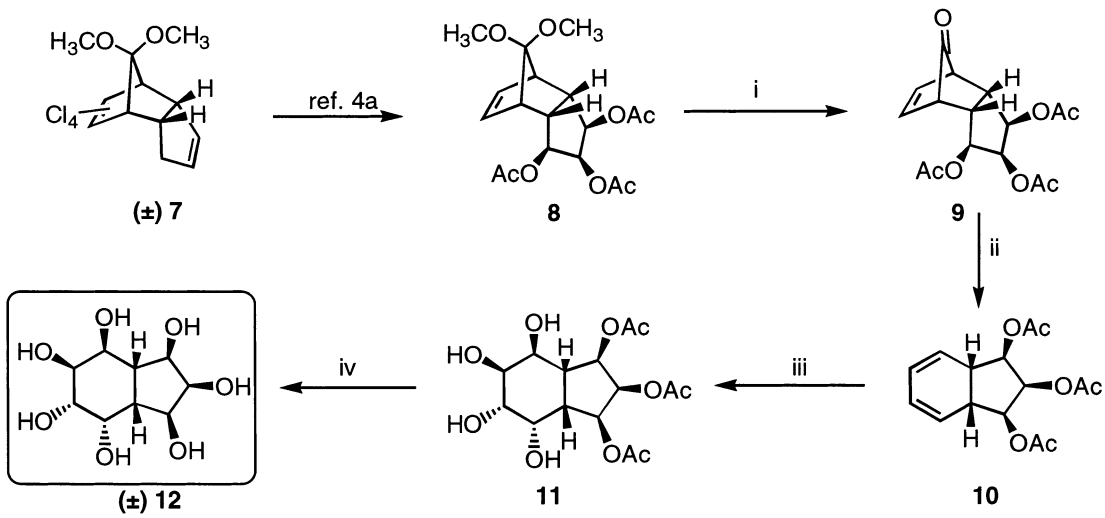
Readily available Diels–Alder *endo*-adduct **(±)-7** between 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and 1,3-cyclopentadiene was stereoselectively elaborated to the triacetate **8**, as reported previously by us. Acetal deprotection in **8** led to the norbornenone derivative **9** which was subjected to thermally induced decarbonylation to deliver the tricyclic diene **10**.[6] The C_s symmetry of **10** was revealed through its spectral characteristics and particularly the nine line ^{13}C NMR spectrum[6] (Scheme 1). Catalytic OsO_4 mediated double dihydroxylation in **10** proceeded quite efficiently to furnish a tetrahydroxy-triacetate **11** which was devoid of any symmetry. Loss of symmetry during the double dihydroxylation reaction on the diene secured the stereochemistry of **11**, which required that the two dihydroxylations on **10** had occurred from the *exo*- and *endo*-face, respectively (Scheme 1). Mild base hydrolysis of triacetate **11** gave the targeted heptahydroxy compound **12**.[6] After full characterization, the bicyclitol **12** was screened against α- and β-glucosidases (from Bakers' yeast and almonds, respectively) that accept corresponding *p*-nitrophenylglycosides as substrates. It was observed that **12** exhibited moderate inhibition of α-glucosidase with a K_i value of 84 μM (cf. $K_i = 25.4$ μM for the well known inhibitor deoxynojirimycin, DNJ).[7] At mM concentrations, **12** exhibited no significant inhibition against β-glucosidase, indicating selectivity in its response towards the two glucosidases.

The activity observed in the case of **12** motivated us to undertake the synthesis of its diastereomeric derivatives, as the stereochemical disposition of the hydroxyl arrays is known to modulate inhibitory activity and selectivity. The starting material for the synthesis of the stereochemical siblings of **12** was the readily available *endo*-tricyclic enone **13** that was elaborated to **14**, as described previously by us.[4a] Careful ketal deprotection in **14** led to the norbornenone derivative **15**. Thermal activation of **15** resulted in the elimination of CO and the bicyclic diene **16** was realized quite smoothly. Singlet oxygen addition to the cyclohexadiene moiety present in **16** resulted in [4+2]-cycloaddition and endoperoxide **17**[6] was the sole product of the reaction, with $^1O_2$ addition occurring from the preferred convex face of the molecule (Scheme 2). Lithium aluminium hydride reduction of the endoperoxide **17** led to the ene-diol **18** along the expected lines. The cyclohexene moiety in **18** on subjecting to catalytic OsO_4 dihydroxylation gave a 3:1 mixture of **19** and **20** with preferred addition from the convex face. The stereochemical outcome is quite interesting in the sense that the preferred dihydroxylation in allylic alcohols from the *anti*-face is overwhelmed by the steric preference for the convex face in **18** and *syn* addition product **19** is obtained as the major product. Separation and stereochemical assignment to **19** and **20** followed from their conversion to the *tris*-acetonide **21** and *bis*-acetonide **22**, respectively (Scheme 2). Hydrolysis of acetonide moieties in **21** and **22** furnished the diastereomeric hepta-hydroxy hydrindanes **23** and **24**, respectively, and these were duly characterized.[6]

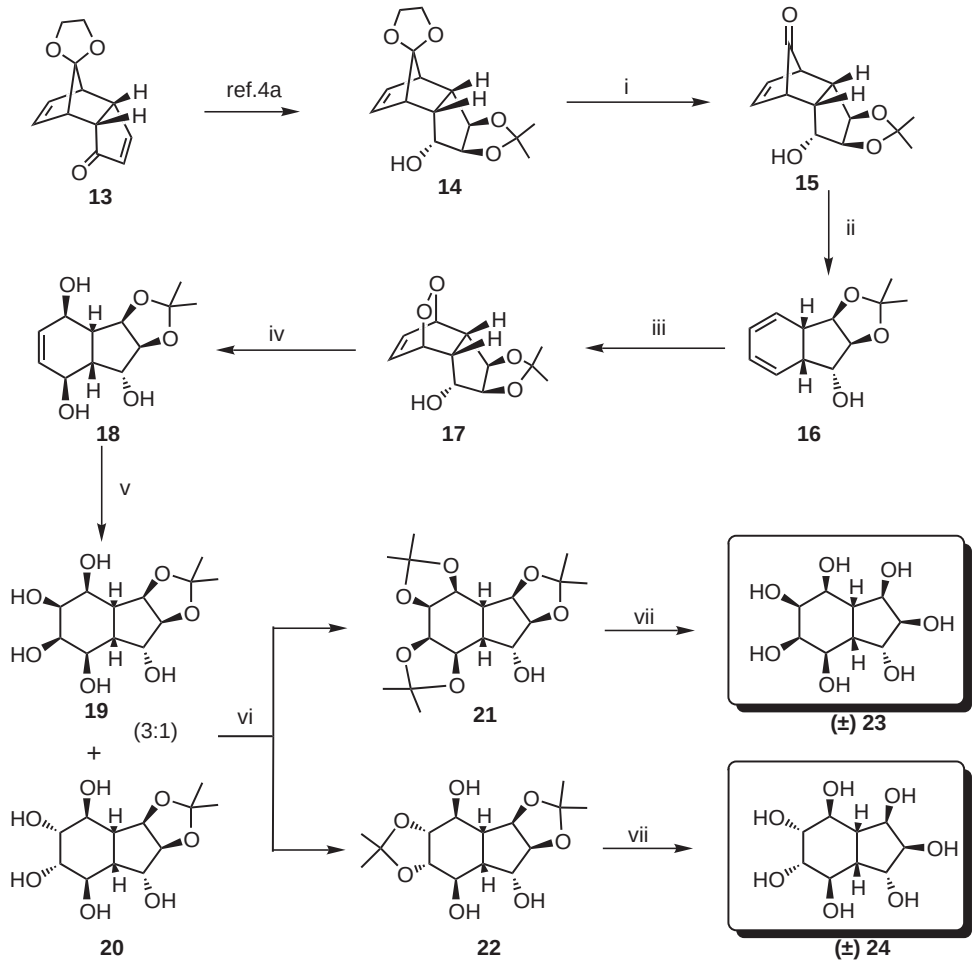
In another stereochemical variation, bicyclohexadiene **16** was directly subjected to OsO_4 mediated double dihydroxylation to furnish pentahydroxy compound **25**, whose stereochemistry follows from the incisive analysis of its spectral data and through analogy with **11** (Scheme 1). Hydrolysis of the acetonide protective group in **25** delivered **26**[6,8] (Scheme 3).

Bicyclitols **23**, **24** and **26** were also subjected to enzymatic assays with α- and β-glucosidases following the protocols similar to that described above for **12**. However, so far we have not encountered any significant inhibitory activity in these compounds. This observation further underscores the importance of the stereochemical disposition of the hydroxyl groups in fine tuning the activity and provides impetus for developing synthetic routes to other diastereomers of these novel bicyclitols.

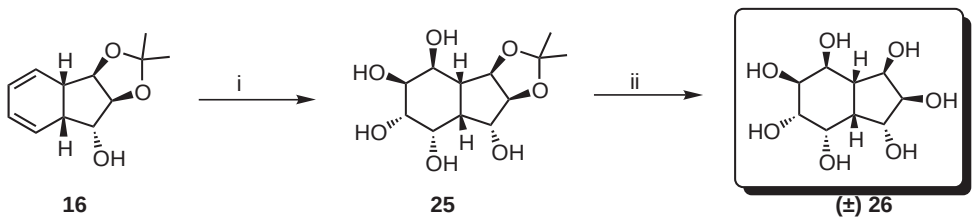
In conclusion, we have outlined the syntheses of a new family of bicyclitols based on the hydrindane framework, with stereocontrol at all the nine stereogenic centres. One of these bicyclitols **12**, a carbasugar/con-



Scheme 1. *Reagents and conditions*: (i) Acetone, amberlyst-15, 89%; (ii) $C_6H_5NO_2$, heat, 160°C, 50%; (iii) OsO_4 (cat.), NMMO, Me_2CO:H_2O:*t*-BuOH (5:5:2), 88%; (iv) aq. NaOH, 60%.



Scheme 2. *Reagents and conditions*: (i) Acetone, amberlyst-15, reflux, 81%; (ii) $C_6H_5NO_2$, heat, 160°C, 67%; (iii) $^1O_2$, *hv*, methylene blue, $CHCl_3$, 90%; (iv) $LiAlH_4$, THF, 54%; (v) OsO_4 (cat.), NMMO, Me_2CO:H_2O:*t*BuOH (5:5:2), 83%; (vi) acetone, amberlyst-15, followed by SiO_2-gel separation, 62% for **21** and 21% for **22**, from **18**; (vii) 30% CF_3COOH, 92% for **23** and 88% for **24**.



Scheme 3. *Reagents and conditions*: (i) OsO_4 (cat.), NMMO, Me_2CO:H_2O:*t*BuOH (5:5:2), 83%; (ii) 30% CF_3COOH, 89%.

duritol analogue, exhibits moderate and selective α-glucosidase inhibitory activity.

Acknowledgements

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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 spectral data. **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88–5.84 (m, 2H), 5.70–5.66 (m, 2H), 5.25 (t, 1H, $J=4.5$ Hz), 5.09–5.05 (m, 2H), 3.10 (br s, 2H), 2.09 (s, 3H), 2.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1 (2C), 170.0, 124.7 (2C), 122.4 (2C), 78.0 (2C), 69.5, 38.9 (2C), 20.7, 20.6. **11**: ^{1}H NMR (300 MHz, D_2O): δ 5.38 (t, 1H, $J=6.3$ Hz), 5.27 (dd, 1H, $J=6.3$, 18.0 Hz), 5.08 (t, 1H, $J=7.0$ Hz), 3.97 (br s, 1H), 3.90 (t, 1H, $J=4.0$ Hz), 3.78 (dd, 1H, $J=7.9$, 3.7 Hz), 3.66 (dd, 1H, $J=8.2$, 2.8 Hz), 2.52 (m, 1H), 2.40 (br s, 1H), 1.99 (s, 6H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, D_2O): δ 174.2, 174.1, 173.2, 75.0, 74.7, 71.7, 71.1, 70.0, 69.0, 68.6, 45.6, 43.5, 20.9, 20.8, 20.5. **12**: ^{1}H NMR (300 MHz, D_2O): δ 4.13 (t, 1H, $J=4.3$ Hz), 3.98–3.85 (m, 4H), 3.73 (dd, 1H, $J=7.3$, 4.0 Hz), 3.61 (dd, 1H, $J=7.6$, 2.8 Hz), 2.21–2.08 (m, 2H); ^{13}C NMR (100 MHz, D_2O): δ 76.4, 75.0, 74.6, 74.4, 73.1, 71.9, 71.8, 48.3, 47.2. **23**: ^{1}H NMR (300 MHz, D_2O): δ 4.05–4.01 (m, 1H), 3.89–3.85 (m, 2H), 3.74–3.70 (m, 3H), 3.63–3.61 (m, 1H), 2.46 (q, 1H, $J=7.0$ Hz), 2.15–2.09 (m, 1H); ^{13}C NMR (75 MHz, D_2O): δ 78.9, 77.6, 72.7, 72.2, 71.5, 70.8, 70.1, 47.5, 41.0. **24**: ^{1}H NMR (300 MHz, D_2O): δ 4.10 (t, 1H, $J=5.8$ Hz), 4.00 (t, 1H, $J=5.4$ Hz), 3.87–3.80 (m, 2H), 3.75–3.70 (m, 1H), 3.66–3.61 (m, 2H), 2.40–2.32 (q like m, 1H), 1.97–1.90 (q like m, 1H); ^{13}C NMR (75 MHz, D_2O): δ 77.8, 77.1, 74.0, 73.2, 72.3, 72.0, 68.8, 48.6, 44.2. **26**: ^{1}H NMR (300 MHz, D_2O): δ 4.19–4.15 (m, 1H), 4.01–3.81 (m, 4H), 3.68–3.64 (m, 1H), 3.61–3.56 (m, 1H), 2.40–2.33 (m, 1H), 2.13–2.07 (m, 1H); ^{13}C NMR (75 MHz, D_2O): δ 77.9, 77.2, 73.6, 72.9, 72.3, 68.4, 67.4, 45.9, 41.8.
7. Each enzymatic assay contained α- or β-glucosidase (0.1–1.0 U/ml), compounds **12**, **23**, **24** and **26** 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.
8. Stereostructure **26** is the most likely formulation and is derived on the basis of analogy with **11**, the inherent steric preference of the *cis*-hydrindane moiety and the directing influence of the α-hydroxy group in **16**.