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Polycyclitols: Stereoselective Synthesis of Enantiopure Polyhydroxylated Hydrindanes (Annulated Carbasugars)

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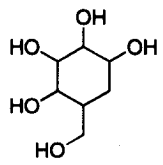
Abstract: Employing readily available 5,10-dioxygenated-tricyclo[5.2.1.$0^{2,6}$] decane derivatives, synthesis of several polyhydroxylated hydrindanes, constituting a new family of annulated carbasugars has been accomplished in a stereoselective manner.

Key Words: Cyclitols; Indanes/Hydrindanes; Osmylation

Design of new glycomimics that can competitively inhibit glycoside processing enzymes is one of the more actively pursued area of current research.[1] Such glycosidase inhibitors have considerable therapeutic potential in the management of diabetes, viral infections and cancer as well as many other disorders. A range of carbocyclic analogues of carbohydrates like **1** (carba- or pseudosugars) with diverse substitution patterns and stereochemical features that resemble monosaccharides in shape, size and functionalization but lacking the glycosidic linkage have been synthesised and their activities evaluated.[1,2] Similarly, a variety of aza analogues of carbasugars eg. deoxynojirimycins **2**,[3a]



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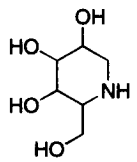

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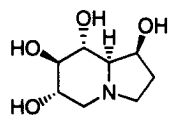

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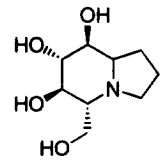

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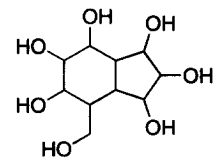

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bearing a piperidine ring system have been prepared and some of them have been found to be potent and specific glycosidase inhibitors.[1b] Several naturally occurring indolizidine alkaloids[3b] like castanospermine **3** as well as the synthetic analogue **4**, endowed with a bicyclic annulated piperidine skeleton, also exhibit wide ranging activity and have been targets of considerable synthetic interest. Recognising the structural relationship between the piperidine and the indolizidine alkaloids, both of which show a notable biological activity profile, we became interested in seeking the polyhydroxylated carbocyclic equivalent **5** of indolizidine alkaloids, which will have the same relationship with carbasugars **1** as indolizidines **3** and **4** have with piperidine based deoxynojirimycins **2** and related compounds. Novel, polyhydroxylated, hydrindane based bicyclic structures like **5**

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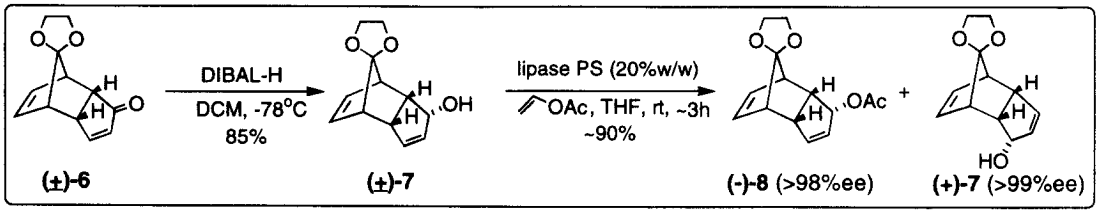
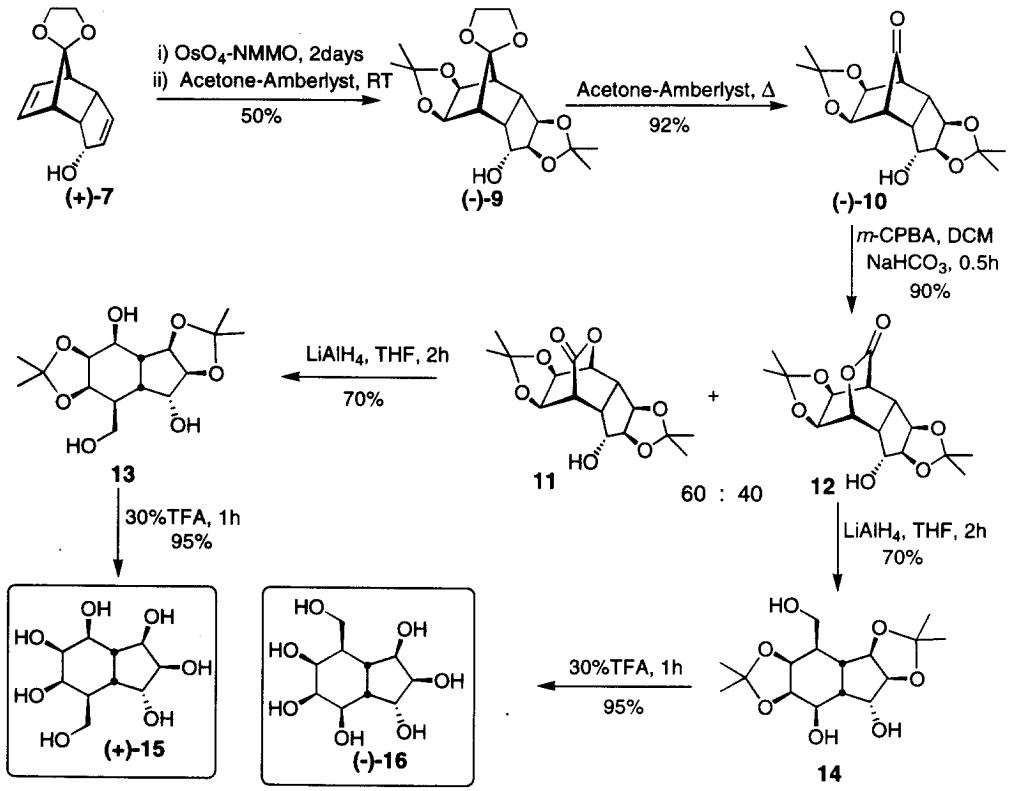
have remained unknown[4] and unexplored, despite the presence of promising carbasugar-like structural features in them. Herein, we report stereoselective routes to a new family of annulated carbasugars (polycyclitols) represented by **5**, with secured stereochemistry at all the nine stereogenic centres, from readily available dioxygenated dicyclopentadienes. In the accompanying letter, we further amplify this theme and describe synthetic routes to bicyclitols based on diquinane and decalin frameworks.



Scheme 1

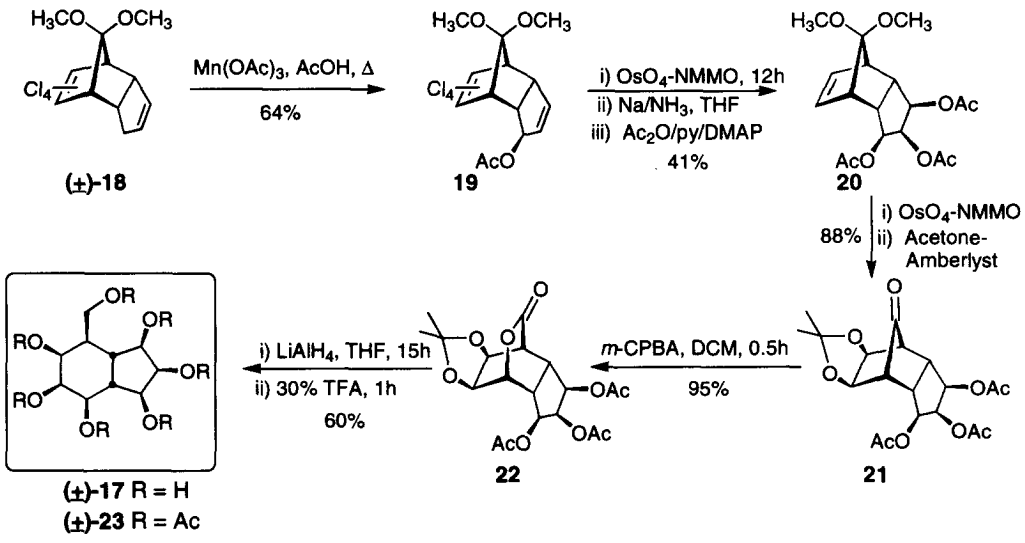
We have recently shown that kinetic enzymatic acylation of tricyclic *endo*-allylic alcohol **7**, readily available from the dicyclopentadiene enone **6**,[5] furnished the dioxygenated acetate **(-)-8** (>98% ee, 44% yield) and alcohol **(+)-7** (>99% ee, 46% yield), Scheme 1.[6] While both **(+)-7** and **(-)-8** were serviceable for our projected work, the present set of reactions were carried out with enantiomerically pure **(+)-7**. Catalytic dihydroxylation of the two double bonds in **(+)-7** proceeded with complete *exo*-face selectivity and protection of the two 1,2-diol functionalities furnished the



Scheme 2

bis-acetonide **9**.[7] Controlled transacetalisation in **9** furnished the ketoacetonide **(-)-10**. The bridging carbonyl carbon in the tricyclic compound **10**, was advantageously disengaged through a Baeyer-Villiger oxidation sequence and exposure to peracid resulted in the formation of regioisomeric mixture of lactones **11** and **12** (60:40). $LiAlH_4$ reduction of the lactone mixture unravelled the hydrindane skeleton to furnish readily separable (SiO_2 gel) polyhydroxy *bis*-acetonides **13**[7] and **14**.[7] A detailed high field ^1H NMR analysis based on ^1H-^1H COSY enabled firm structural assignment to the two regioisomeric compounds **13** and **14**. Acetonide deprotection in **13** and **14** led to the polycyclitols (+)-**15** and (-)-**16**, respectively, Scheme 2. The polar, water soluble polyhydroxy hydrindanes (+)-**15**[7] and (-)-**16**[7] having a talopyranose-type stereochemical pattern in the six-membered ring were fully characterized on the basis of their spectroscopic characteristics.

At this stage, we also considered the possibility of synthesizing a hydrindane in which all the seven hydroxy groups on the bicyclic frame would be on the same face to impart on the molecule a bipolarofacial character. The structure (Fig) generated through AM1 calculations clearly indicated that in *cis*-fused **17**, all the polar substituents were on the convex surface while hydrogens were on the hydrophobic concave face. Our synthesis of **17** originated from the readily available Diels-Alder adduct **18** of 5,5-dimethoxy-tetrachlorocyclopentadiene and cyclopentadiene. Manganese acetate oxidation gave the *exo*-acetate **19** which was subjected to catalytic OsO_4-dihydroxylation, reductive dehalogenation and acetylation to furnish the triacetate **20**.[7] All the three acetate functionalities in **20** were *cis* disposed, through additions from the open *exo*-face of the *endo*-dicyclopentadiene system. Further dihydroxylation in **20** of the norbornene double bond and acetal deprotection-diol protection sequence led to the keto-acetonide **21**.[7] Bridge scission in **21** was again accomplished through Baeyer-Villiger oxidation which in this case furnished a single lactone **22** (because **21** is meso) in good yield. $LiAlH_4$ reduction in **22** and acetonide deprotection led to the desired bicyclitol **17**, Scheme 3. The water soluble **17** was best characterized as its hepta-acetate **23**.[7]



Scheme 3

Preliminary screening of the three bicyclitols **15-17** was carried out against three common glycosidases (α-galactosidase, β-galactosidase and β-mannosidase) that accept *p*- and *o*-nitrophenyl glycosides as substrate. However, **15-17** at μM concentration exhibited no significant inhibition. The absence of activity can perhaps be attributed to the mismatch in the stereochemical disposition between the carbasugar portion of **15-17** (talopyranose-type) and the three glycosidases that were tested. This suggests further screening against a wider range of glycosidases and also tactical manipulation of our synthetic route to provide access to polyhydroxylated hydrindanes having the stereochemical pattern present in the commonly encountered glycosidases. Efforts along this direction are currently underway.

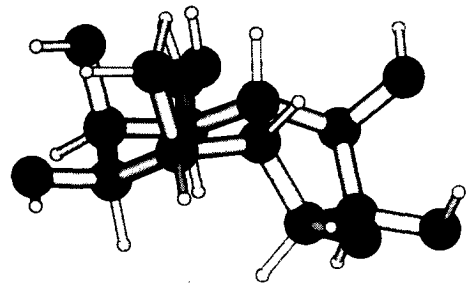


Fig. AM1 minimised structure of 17

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References:

[1] (a) Ganem, B. *Acc. Chem. Res.* **1996,** *29*, 340. (b) Martinez-Grau, A.; Marco-Contelles, J. *Chem. Soc. Rev.* **1998,** *27*, 155. (c) Bols, M. *Acc. Chem. Res.* **1998,** *31*, 1.

[2] (a) Suami, T. *Top. Curr. Chem.* **1990**, *154*, 257. (b) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *95*, 2779. (c) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195. (d) Johnson, C. R. *Acc. Chem. Res.* **1998,** *31*, 333.

[3] (a) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994,** *11*, 135. (b) Michael, J. P. *Nat. Prod. Rep.* **1998,** *15*, 571 and earlier reports in the series.

[4] For a few related examples, see: (a) Billington, D. C.; Perron-Sierra, F.; Picard, I.; Beaubras, S.; Duhault, J.; Espinal, J.; Challal, S. *Bioorg. Med. Chem. Lett.* **1994,** *4*, 2307. (b) Kara, B.; Balci, M.; Bourne, S. A.; Watson, W. H. *Tetrahedron Lett.* **1994,** *35*, 3349. (c) Desjardins, M.; Lallemand, M. C.; Hudlicky, T.; Abboud, K. A. *Synlett.* **1997**, *38*, 7693.

[5] Schuda, P. F.; Ammon, H. L.; Heimann, M. R.; Bhattacharjee, S. *J. Org. Chem.* **1982,** *47*, 3434.

[6] Mehta, G.; Reddy, D. S. *Tetrahedron Lett.* **1999,** *40*, 991.

[7] All compounds reported here were characterized on the basis of analytical and spectroscopic data. Selected data: **(+)-15**: $[\alpha]_D^{25}$ = +25° (c, 0.4, H_2O) ^1H NMR (400MHz, D_2O): δ 4.12-4.04 (m, 3H), 3.97 (t, 1H, J= 5.6Hz), 3.85 (dd, 1H, J= 11.2, 5.3Hz), 3.82-3.73 (m, 2H), 3.66 (dd, 1H, J= 11.2, 5.9 Hz), 2.43 (q, 1H, J= 7.2Hz), 2.16 (q, 1H, J=5.8Hz), 1.88 (quintet, 1H, J=5.7Hz); ^{13}C NMR (75MHz, D_2O): δ 79.3, 77.2, 72.6, 71.7, 71.2, 70.5, 62.4 (CH_2), 48.4, 40.3, 37.1; HRMS calcd for $C_{10}H_{18}O_7$ (M^++1): 251.11307 found: 251.11374; **(-)-16**: $[\alpha]_D^{25}$ = -33.3° (c, 0.9, H_2O); ^1H NMR (300MHz, D_2O): δ 4.06-4.03 (m, 1H), 3.92-3.84 (m, 2H), 3.79-3.76 (m, 2H), 3.69 (t, 1H, J=3.3Hz), 3.60 (dq, 2H, J=10.8, 4.8Hz), 2.42 (q, 1H, J=6.9Hz), 1.86 (q, 1H, J=7.5Hz), 1.69 (quintet, 1H, J=6.6Hz); ^{13}C NMR (75MHz, D_2O): δ 79.2, 77.6, 74.5, 71.8, 70.5, 69.8, 61.5 (CH_2), 43.6, 42.7, 41.5; HRMS calcd. for $C_{10}H_{18}O_7$ (M^++1): 251.11307 found: 251.11236; **23**: ^1H NMR (400MHz, $CDCl_3$) : δ 5.48(t, 1H, J=5.8), 5.31(t, 1H, J=3.4), 5.25 (t, 1H, J=3.3), 5.13 (dt, 2H, J=12.8, 6.1Hz), 5.05 (dd, 1H, J=10.6, 3.4Hz), 4.22 (dd, 1H, J=11.4, 6.6Hz), 4.10(dd, 1H, J=11.4, 6.8Hz), 2.69 (q, 1H, J=7.3Hz), 2.56 (q, 1H, J=8Hz), 2.24-2.17 (m, 1H), 2.10-2.04 (series of s, 21H); ^{13}C NMR (100MHz, $CDCl_3$) : δ 171.6, 171.1, 170.6, 170.5(2C), 170.3, 169.9, 74.1, 72.6, 70.3, 69.0, 68.5, 67.5, 63.3, 42.9, 39.5, 38.2, 21.6, 21.5, 21.4(2C), 21.3(2), 21.1; MS(70 eV, EI): *m/z* (M^+) 568.