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Polycyclitols: Stereoselective Synthesis of Decalin and Diquinane Based Polyols as Potential Glycomimics

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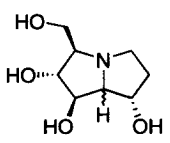
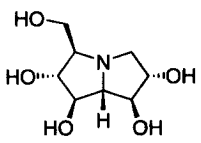
Abstract: Stereoselective syntheses of novel, polyhydroxylated decalins and diquinanes (enantiopure) bearing ten and eight stereogenic centres, respectively, from readily available starting materials is reported.

Keywords: Polyols; Polyquinane; Baeyer-Villiger reactions; Osmylation

Recent studies on polyhydroxylated pyrrolizidine, indolizidine and quinolizidine alkaloids have shown that these natural products are endowed with wide ranging biological activities.[1] Some of the more notable examples are the pyrrolizidine based alexine **1a**, australin **1b** and casuarine **2**, indolizidine based castanospermine **3** and a quinolizidine based synthetic analogue **4**.[1-3] While these alkaloids exhibit activities ranging from anti-viral, anti-cancer and anti-HIV to diabetes, a common trait of these compounds is the powerful and specific inhibitory action against glycosidases. This characteristic marks the compounds related to **1-4** as potent glycomimics and there is widespread interest in the synthesis and evaluation of various analogues and structural variants of these alkaloids.[3] The hydroxyl substitution pattern in the alkaloids **1-4**, as well as the presence of the hydroxymethyl moiety, is reminiscent of the structural and substitution pattern present in cyclitols and carbasugars. We therefore became interested in seeking the carbocyclic equivalents of the biologically active pyrrolizidine, indolozidine and quinolizidine alkaloids, with an enhanced array of hydroxyl functionalities, which may have potential as glycomimics like cyclitols and carbasugars. In the accompanying letter, we have reported the synthesis of hydrindane based polyols related to the indolizidine ring system. Herein, we describe stereoselective routes to polyhydroxylated decalins and diquinanes related to the pyrrolizidine and quinolizidine system, respectively. It is noteworthy that ten stereogenic centres and eight hydroxyl groups on the decalin frame and eight stereogenic centres and up to six hydroxyl groups on the diquinane frame are installed in relatively short sequences with complete stereocontrol. It is also to be noted that polyhydroxylated decalin derivatives occur in nature, exhibit considerable biological activity, and have aroused synthetic interest.[4]



1a α-H, **b** β-H



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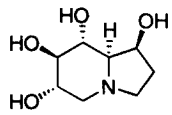

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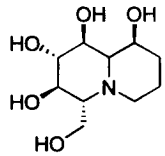

4

Our initial approach was targeted towards the dipolarofacial octahydroxy decalin **5** from the known tricyclic *endo*-diene **6**.[5] Exhaustive catalytic osmylation of **6** furnished the all *cis*-tetrol **7** with

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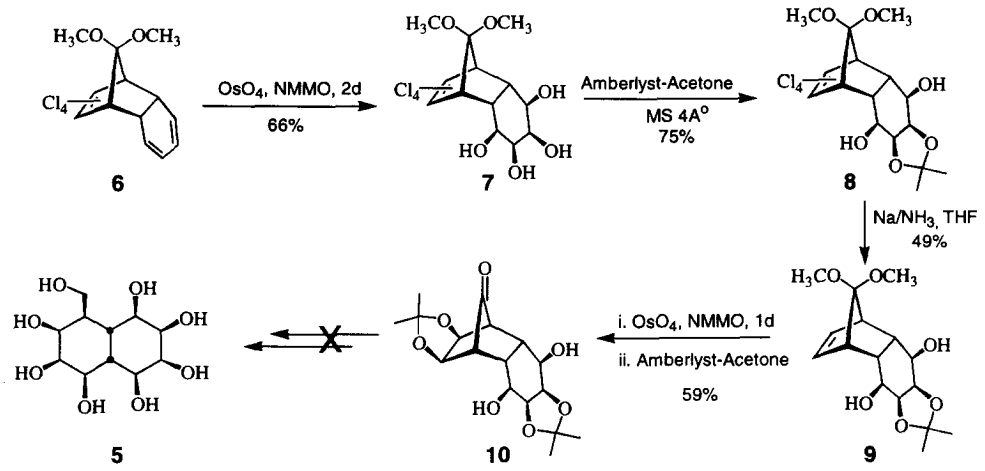
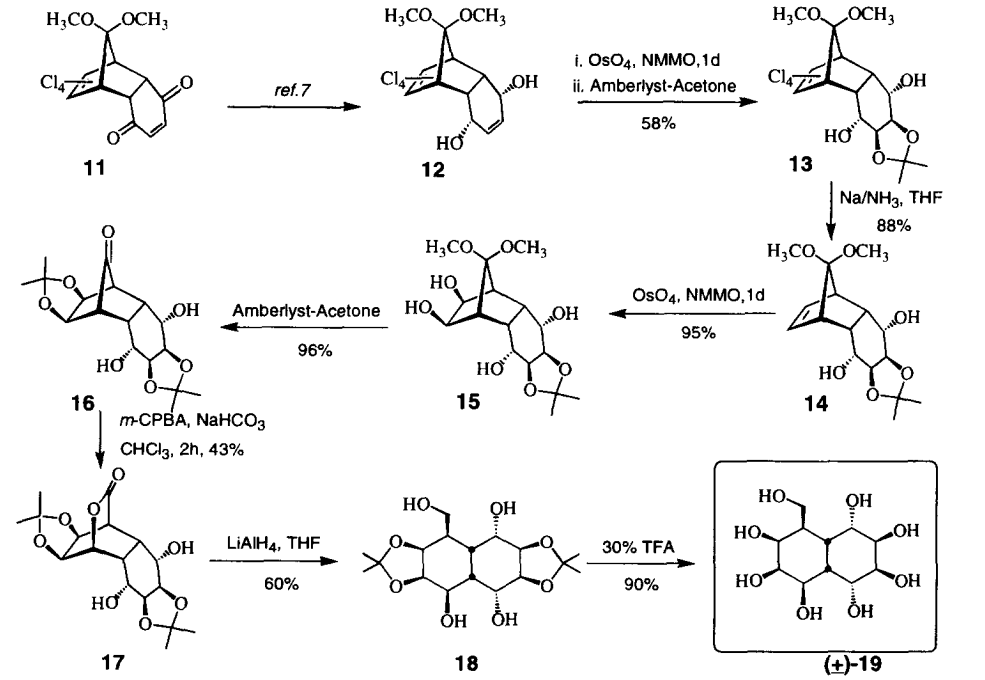


Scheme 1

exclusive addition from the exo face and further protection led to the symmetrical monoacetonide **8**.[6] Reductive dehalogenation in **8** gave **9** in which the norbornene double bond was again subjected to OsO_4 mediated dihydroxylation from the preferred *exo*-face. Further protection of the 1,2-diol moiety and acetal deprotection delivered the ketoacetonide **10**.[6] Baeyer-Villiger oxidation in **10** and $LiAlH_4$ reduction was expected to give the desired **5**, Scheme 1. However, **10**, with six hydroxyl groups directed on the *exo*-face proved to be totally unreactive towards Baeyer-Villiger oxidation under a variety of reaction regimes and forced us to abandon this short approach to bicyclitol **5**.

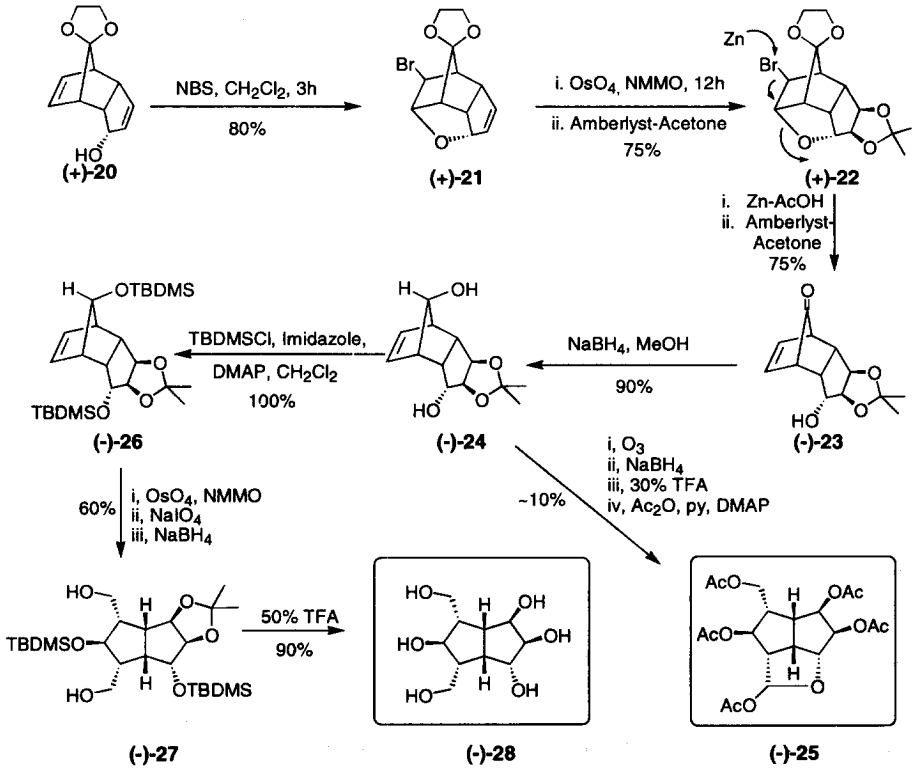


Scheme 2

Our alternate approach to a decalin based polyol originated from the Diels-Alder *endo*-adduct **11** of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and benzoquinone, which was conveniently

transformed to the *endo,endo*-diol **12**.[7] Osmylation of the cyclohexene double bond in **12** proceeded smoothly from the *exo*-face and the 1,2-diol moiety was protected to furnish the acetonide **13**. Reductive dehalogenation in **13** led to **14** in which the norbornene double was ready for further functionalization. Catalytic dihydroxylation in **14** from the *exo*-face gave the diol **15**. A one-pot acid catalysed acetal-deprotection and 1,2-diol protection in **15** furnished the keto-diacetonide **16**[6] quite satisfactorily, Scheme 2. Baeyer-Villiger oxidation in **16** proved to be problematic but after some trial and error, lactone **17** could be realized in a modest yield. $LiAlH_4$ reduction of **17** revealed the decalin framework and tetrol-*bis*-acetonide **18** was fully characterized.[6] Deprotection of **18** led to the polar, water soluble polyol **19** having eight hydroxy groups, Scheme 2. The ^1H NMR spectral signals of **19**, while in agreement with the structure,[6] showed considerable line broadening due to the involvement of exchange processes.

The approach to diquinane based polyols emanated from the enantiomerically pure *endo*-tricyclic allylic alcohol (+)-**20** recently described by us.[8] The norbornene double bond in **20** was protected through intramolecular etherification to (+)-**21**.[6] Osmylation of the cyclopentene double bond from the *exo*-face and protection of the 1,2-diol moiety furnished acetonide (+)-**22**. The norbornene double bond was now unmasked with Zn metal and acetal deprotection gave (-)-**23**. Hydride reduction of the carbonyl group in **23** was exclusively from the norbornene face. The



Scheme 3

resulting diol **24** was subjected to ozonolysis, reductive work-up, acetal deprotection and acetylation steps to furnish penta-acetate **25**. While **25** had the requisite level of functionalization and could be fully characterized, the yield from **24**[6] after four steps was a paltry 10%. To overcome this limitation, the diol functionality in **24** was protected as TBDMS-ether **26**. A three step sequence involving

dihydroxylation, periodate cleavage and hydride reduction was now efficiently executed on **26** to furnish **27**. Removal of protective groups in **27** gave chiral hexahydroxy diquinane (-)-**28**.[6] Besides its solubility in water, eight stereogenic centres and six hydroxy groups, it is the branching in the form of two hydroxymethyl bearing side arms in **28** that mark it out as a potential substrate for further functional group manoeuvres. Indeed, the protected derivative (-)-**27** is well suited for such pursuits. It is to be noted that branched carbasugars bearing additional hydroxymethyl/aminomethyl side arms have been recently considered as promising lead compounds for drug discovery.[9]

Polyols **19** and **(-)-28** were screened against α- and β–galactosidase and β–mannosidase that accept *o*- and *p*-nitrophenylglycosides, at μM concentration but no significant inhibition was observed. Also, using a well studied *N*-glycoprotein, Influenza hemaglutinin (HA) as a model, the ability of **19** and **(-)-28** to inhibit glucosidase I and II in animal cells was studied with deoxynojirimycin (DNM) as positive control.[10] Again at concentrations at which DNM blocks glucosidase action, our compounds were not effective in inhibiting these enzymes.

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[6] All compounds reported here were characterized on the basis of analytical and spectral data. Selected data: **18**: ^{1}H NMR (300MHz, $CDCl_3$): δ 4.73-4.44 (m, 4H), 4.14-3.90 (m, 3H), 3.80 (d, 2H, J=5.1Hz), 2.45 (dt, 1H, J=12, 3.6Hz), 2.26 (dt, 1H, J=11.4, 3.6Hz), 1.96-1.91(m, 1H), 1.45 (s, 3H), 1.44 (s, 3H), 1.36 (s, 6H); ^{13}C NMR (75MHz, $CDCl_3$) : δ 109.0, 108.2, 76.4, 75.9, 75.1, 75.0, 67.4, 67.1, 66.9, 63.9(CH_2), 36.6, 32.5, 28.9, 26.3, 25.8, 24.1, 23.8; MS(70 eV, EI): *m/z* (M^+) 360. **19**: ^{1}H NMR (300MHz, D_2O): δ 4.13 (brs, 1H), 3.80-3.55 (m, 8H), 2.26 (brs, 1H), 2.13 (brs, 1H), 1.87 (brs, 1H); MS(70 eV, EI): *m/z* (M^++1) 281. **(-)-25**: $[\alpha]_D^{25}$ = -16.2° (c, 0.8, $CHCl_3$) ^{1}H NMR (300MHz, $CDCl_3$): δ 6.53 (s, 1H), 5.41 (d, 1H, J=3.9 Hz), 5.13 (dd, 1H, J=9.6, 3.5Hz), 4.86 (dd, 1H, J=9.5, 4.5), 4.39(d, 1H, J=6.6Hz), 4.15-4.04 (m, 2H), 3.48(q, 1H, J= 6Hz), 2.90 (q, 1H, J=5.8Hz), 2.65-1.50(m, 2H), 2.05 (s, 3H), 2.04 (s, 3H), 1.99 (s, 6H), 1.93 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) : δ 170.7, 170.5, 169.5(2C), 169.3, 101.9, 84.0, 76.1, 75.5, 72.7, 61.2, 55.6, 46.1, 45.7, 44.3, 21.1, 20.8, 20.7(2C), 20.4; MS(70 eV, EI): *m/z* (M^++1+Na) 466 **(-)-28**: $[\alpha]_D^{25}$ = -45° (c, 0.4, H_2O) ^{1}H NMR (500MHz, D_2O): δ 4.15 (dd, 1H, J=7.1, 4.1Hz), 4.05 (dd, 1H, J=5.6, 2.4Hz), 3.88 (dd, 1H, J=11.3, 7Hz), 3.81-3.74(m, 4H), 3.61 (t, 1H, J=10.5Hz), 2.84 (q, 1H, J=5.7Hz), 2.51(q, 1H, J=7.4Hz), 2.11-1.96 (m, 2H); ^{13}C NMR (125MHz, D_2O) : δ 77.9, 75.2, 75.0, 72.4, 60.9(CH_2), 59.4(CH_2), 49.4, 48.1, 43.8, 42.6; HRMS calcd for $C_{10}H_{18}O_6$ (M^++1) 235.11816 found 235.11719.

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