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Quest for inosito-inositols: synthesis of novel, annulated and conformationally locked inositols

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Abstract—A new family of annulated inositols (inosito-inositols) has been conceptualized. Naphthalene has been elaborated into novel cyclohexa-annulated *neo*- and *chiro*-inositols, with two additional hydroxyl functionalities, through a series of stereoselective oxyfunctionalization protocols. The *trans*-ring fusion present in these new annulated inositols ensures conformational locking.
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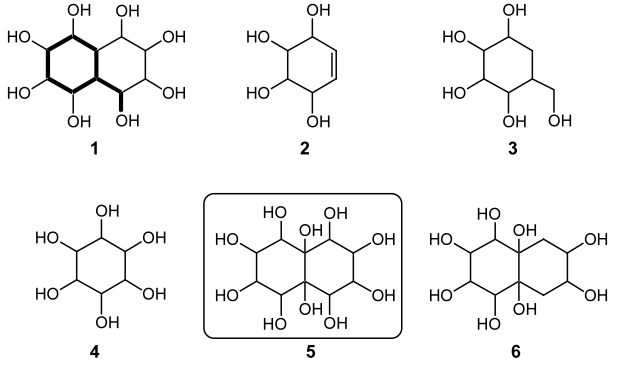
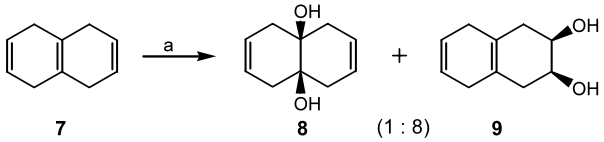
Recently, we have introduced polycylitols as new entities, which can be regarded as either fused (annulated) or hybrid variants of biologically important monocyclitols like conduritols and carbasugars.[1] For example, octahydroxy decalin **1** can be considered as a hybrid of two conduritol molecules **2**, constituted through a common, shared ring junction.[1c] Similarly, **1** can also be visualized as a hybrid of carbasugar **3** (see, bold portion in **1**). We have accomplished the synthesis of bicyclitols **1** and related compounds and found potent and selective α-glucosidase inhibitory activity in some of them.[1c,d] These observations spurred us to conceptualize novel polycyclitols (decahydroxy-decalins) based on inositols **4**, structurally similar to **2** and **3** but with an enhanced oxygenation level. Inositols **4** and their derivatives have been implicated in many diverse and important biological functions among which the ability of inositol triphosphate [Ins(1,4,5)P_3] to act as secondary messenger by binding to specific receptors on the endoplasmic reticulum and stimulating the release of calcium ions from the intracellular stores is most significant.[2] Recognising the importance of inositols **4**, we propose bicyclic inositols **5** (inosito-inositols) as new structural motifs that might exhibit unusual biological properties and metal binding characteristics. Our efforts en route to **5** have resulted in the synthesis of some new bicyclic inositols **6** with as many as eight hydroxyl groups on the decalin framework. The two additional hydroxyl groups in the annulated ring as in **6** can act as promoters of additional binding interactions along with the inositol core. In addition, the *trans*-ring fusion in **6** ensures conformational locking and these annulated inositols exist in 'un-natural' conformations (vide infra) as demonstrated by us recently for related systems.[3,4]



Our synthetic approach towards **6** commenced from tetrahydronaphthalene **7**, readily available from naphthalene via metal-ammonia reduction. Controlled OsO_4-mediated dihydroxylation of **7**, furnished the regioisomeric *cis*-diols **8** and **9** (1:8) in which the required isomer **9** predominated (Scheme 1). Epoxidation of **9** (R = H) with *m*CPBA furnished a mixture of *syn*-**10** and *anti*-epoxide **11** (2:1) (Scheme 2).[5,6] Interestingly, protecting groups on the diol moiety of **9** could



Scheme 1. *Reagents and conditions*: (a) OsO_4 (1 mol%), NMMO, acetone:water (4:1), 10°C, 60%.

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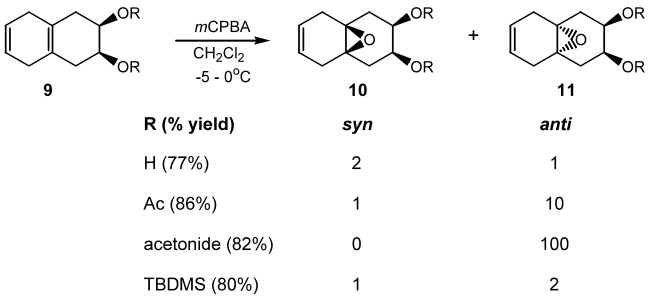
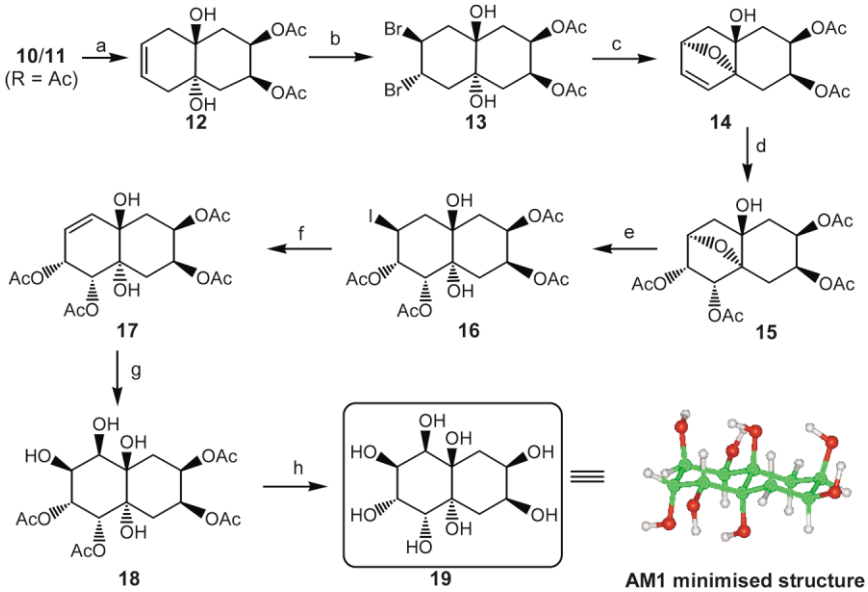


Scheme 2.

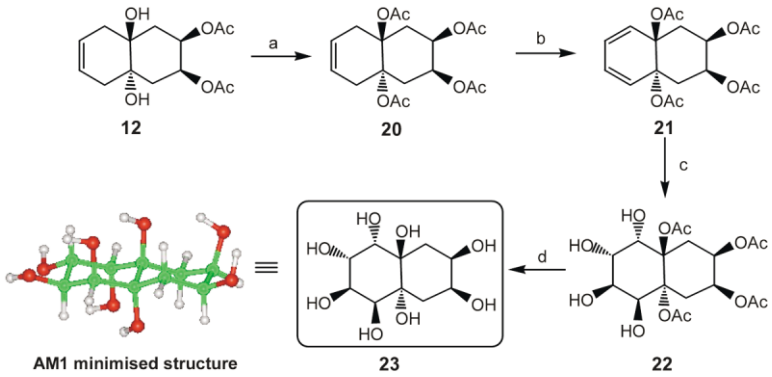
modulate the diastereoselectivity of the epoxidation in a profound way. Thus, simple acetylation of the diol to the diacetate and epoxidation reversed the selectivity (10:1) in favor of the *anti*-epoxide **11** (Scheme 2), while acetonide protection directed the epoxidation exclusively from the *anti*-face.[5,6] Interestingly, the bulky TBDMS group exhibited only moderate selectivity in favor of *anti*-addition (Scheme 2). While these studies were in progress, O'Brien et al.[7] published their detailed studies on the epoxidation of simple *cis*-4,5-dihydroxy cyclohexenes and explained the observed diastereoselectivities in terms of steric effects and/or directed hydrogen bonding interactions. The diastereoselection encountered during the epoxidation of **9** and its derivatives closely parallel the O'Brien findings and our observations can be rationalized in an analogous manner.[7]

It turns out that both *syn*-**10** and *anti*-**11** were serviceable for our projected sequence. Thus, the mixture of **10** and **11** was converted to their diacetates and exposure to mild acid led to a single *trans*-diol-*cis*-diacetate **12**.[6] Bromination furnished dibromide **13**, which on treatment with base underwent regio- and stereoselective transetherification as well as dehydrobromination in a single pot operation to furnish the tricyclic compound **14** with an embedded oxabicyclo[2.2.1]heptene moiety (Scheme 3).[6] The presence of the bridged oxanorbornyl moiety ensured that the catalytic OsO_4 dihydroxylation of **14** was stereoselective from the *exo*-face and acetylation furnished the tetra-acetate **15**. The ether linkage in the oxabicyclo[2.2.1]heptene moiety now needed to be cleaved and after some trials, we found that tetrabutylammonium iodide in the presence of BF_3-etherate[8] cleaved **15** to furnish the iodotetra-acetate **16** (Scheme 3).[9] Base mediated dehydroiodination in **16** led to **17**, an annulated conduritol derivative (cf. conduritol **2**). Dihydroxylation of **17** proceeded smoothly from the face opposite to the allylic acetate group to furnish the tetrahydroxy-tetraacetate **18** in a stereoselective manner. Finally, the hydrolysis of the acetate groups in **18** delivered the octahydroxydecalin, a bicyclic inositol derivative **19** having the *neo*-inositol configuration (Scheme 3). The energy minimized structure of **19** clearly showed that the inositol moiety exists in a (4a/2e) conformation with four axial and two equatorial hydroxyl groups. In contrast *neo*-inositol is known to have a 4e/2a conformation.[10] Thus, the annulation tactic can be employed in the case of inositols to access 'un-natural' conformations while retaining the 'natural' configuration as shown recently by us in related examples.[4]

In another sequence, diol-diacetate **12** was converted to the tetra-acetate **20** and subjected to a two-step allylic bromination–dehydrobromination sequence to furnish the bicyclic 1,3-cyclohexadiene derivative **21**.[11] Exhaustive OsO_4-mediated dihydroxylation of **21** led to the tetrol-tetraacetate **22**, and the stereochemical outcome



Scheme 3. *Reagents and conditions*: (a) 10% AcOH, 1 h, 85%; (b) $C_5H_5N^+HBr_3^-$, CH_2Cl_2, 3 h, 77%; (c) KO^{t}Bu, ^{t}BuOH:dioxane (1:2), rt (1 h) to 60°C (3 h), 45%; (d) i. OsO_4 (1 mol%), NMMO, acetone:water (4:1), 2 h; ii. Ac_2O, DMAP, CH_2Cl_2, 30 min, 75% (two steps); (e) $Bu_4N^+I^-$, $BF_3{\cdot}O(C_2H_5)_2$, $CHCl_3$, reflux, 4 h, 73%; (f) KO^{t}Bu, ^{t}BuOH:dioxane (1:2), 60°C, 2 h, 63%; (g) OsO_4 (1 mol%), NMMO, acetone:water (4:1), 3–4 h, 60%; (h) K_2CO_3, CH_3OH, rt, 1 h, 67%.



Scheme 4. *Reagents and conditions*: (a) Ac_2O, $BF_3{\cdot}O(C_2H_5)_2$, 3 h, 88%; (b) i. NBS, AIBN, CCl_4, reflux, 1 h, ii. DBU, DMSO, 3 h, 56% (two steps); (c) OsO_4, NMMO, acetone:water (4:1), 2 d, 52%; (d) K_2CO_3, CH_3OH, 1 h, 95%.

was predictable in view of our experience with related compounds.[4] Acetate hydrolysis in **22** led to the annulated *chiro*-inositol derivative **23** (Scheme 4). Once again the energy minimized structure of **23** revealed a 4a/2e conformation, whereas the crystal structure of the parent *chiro*-inositol showed it to be in a 4e/2a conformation.[12]

In short, we have accomplished the synthesis of novel cyclohexa-annulated *neo*- and *chiro*-inositols, bearing two additional hydroxyl groups, from naphthalene following short, stereoselective protocols. These new inositols are locked in conformations not present in natural inositols and pave the way for the evaluation of their physico-chemical and biological profiles.

Acknowledgements

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References

1. (a) Mehta, G.; Reddy, D. S. *Tetrahedron Lett*. **1999**, *40*, 9137; (b) Mehta, G.; Reddy, D. S.; Ramesh, S. S.; Tatu, U. *Tetrahedron Lett*. **1999**, *40*, 9141; (c) Mehta, G.; Ramesh, S. S. *Chem. Commun*. **2000**, 2429; (d) Mehta, G.; Ramesh, S. S. *Tetrahedron Lett*. **2001**, *42*, 1987.
2. For some important references dealing with the chemistry and biology of inositols, see: (a) Berridge, M. J.; Irvine, R. F. *Nature* **1984**, *312*, 315; (b) Berridge, M. J.; Irvine, R. F. *Nature* **1989**, *341*, 197; (c) Potter, B. V. L. *Nat. Prod. Rep*. **1990**, 1; (d) Berridge, M. J. *Nature* **1993**, *361*, 315; (e) Potter, B. V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1933; (f) Hinterding, K.; Díaz, D. A.; Waldmann, H. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 688; (g) Chang, Y.-T.; Rosania, G. R.; Chung, S.-K. *Exp. Opin. Ther. Patents* **2001**, *11*, 1.
3. Selected references on efforts to prepare new inositol analogues: (a) Kozikowski, A. P.; Fauq, A.H.; Powis, G.; Melder, D. C. *J. Am. Chem. Soc*. **1990**, *112*, 4528; (b) Riley, A. M.; Potter, B. V. L. *J. Org. Chem*. **1995**, *60*, 4970; (c) Liu, C.; Potter, B. V. L. *J. Org. Chem*. **1997**, *62*, 8335; (d) Riley, A. M.; Potter, B. V. L. *Tetrahedron Lett*. **1999**, *40*, 2213; (e) Sun, H.; Reddy, G. B.; George, C.; Meuillet, E. J.; Berggren, M.; Powis, G.; Kozikowski, A. P. *Tetrahedron Lett*. **2002**, *43*, 2835; (f) Cheikh, A. B.; Craine, L. E.; Zemlicka, J.; Heeg, M. H. *Carbohydr. Res*. **1990**, *199*, 19; (g) Schnaars, A.; Schultz, C. *Tetrahedron* **2001**, *57*, 519; (h) Paul, B. J.; Willis, J.; Martinot, T. A.; Ghivriga, I.; Abboud, K. A.; Hudlicky, T. *J. Am. Chem. Soc*. **2002**, *124*, 10416.
4. Mehta, G.; Ramesh, S. S.; Bera, M. K. *Chem. Eur. J*. in press.
5. The stereochemistry of the *syn*- and *anti*-epoxides in each case was secured on the basis of X-ray crystal structure determination of *anti*-diacetate **11** (Fig. 1) and employing it as the point of reference for chemical correlation with other epoxides through routine transformations. **Crystal data for 11**: The structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. Crystal system: monoclinic, space group: $P21/c$, cell parameters: $a=9.0549(18)$ Å, $b=15.074(3)$ Å, $c=9.9022(19)$ Å, $\beta=92.312(3)°$, $V=1350.5(4)$ Å^3, $Z=4$, $\rho(\text{calcd})=1.31$ g cm^{-3}, $F(000)=568$, $\mu=0.099$ mm^{-1}, $\lambda=0.71073$ Å. Total number of l.s. parameters = 244. $R_1=0.0551$ for $F_o>4\sigma(F_o)$ and 0.0751 for all 2970 data. $wR_2=0.1416$, GooF = 1.024, Restrained GooF = 1.024 for all data. An ORTEP drawing of compound **11** with 50% ellipsoidal probability has been shown below. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre [CCDC 200363].
6. All new compounds were characterized on the basis of their IR, ^{1}H and ^{13}C NMR and mass spectral data.

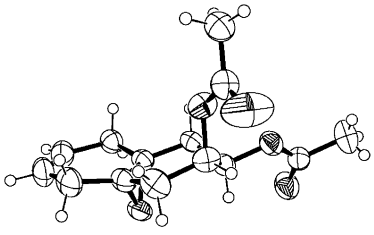

Figure 1. ORTEP diagram of **11**.

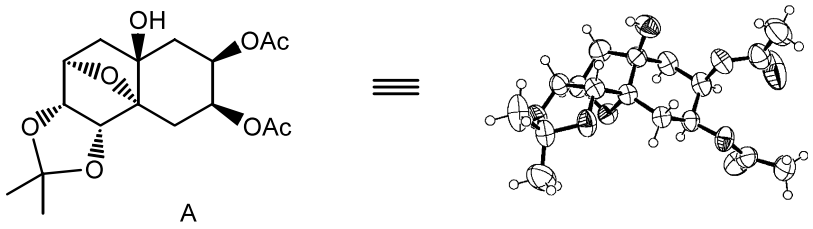

Figure 2. ORTEP diagram of A.

Selected spectral data: **14**, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.61 (dd, $J=5.7$, 1.6 Hz, 1H), 6.22 (d, $J=5.7$ Hz, 1H), 5.53 (d, $J=3$ Hz, 1H), 5.10 (ddd, $J=12.6$, 5.2, 2.5 Hz, 1H), 4.90 (dd, $J=4.5$, 1.2 Hz, 1H), 2.58–2.49 (m, 2H), 2.38 (dd, $J=15.6$, 3.9 Hz, 1H), 2.27 (dd, $J=14$, 5.4 Hz, 1H), 2.15 (s, 3H), 2.15–2.03 (m, 2H), 2.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 169.3, 138.4, 135.6, 88.2, 79.5, 74.2, 70.2, 68.7, 44.5, 39.3, 26.0, 21.1, 20.9; Mass (EI, 70 eV): m/z 180 (M^+–2Ac–H_2O). **19**, ^{1}H NMR (300 MHz, D_2O): δ 4.74 (d, $J=6.3$ Hz, 1H), 4.31 (d, $J=3.6$ Hz, 1H) 4.18 (d, $J=6$ Hz, 1H), 4.05 (br s, 1H), 4.92 (d, $J=6.3$ Hz, 1H), 3.61, (t, $J=3.6$ Hz, 1H), 2.15 (dd, $J=15.4$, 4.2 Hz, 1H), 1.88–1.80 (m, 2H), 1.27 (d, $J=12.9$ Hz, 1H); ^{13}C NMR (75 MHz, D_2O): δ 89.8, 83.8, 76.5, 75.2, 73.3, 71.2, 70.6, 70.4, 43.3, 43.1. **23**, ^{1}H NMR (300 MHz, D_2O): δ 3.95–3.87 (m, 3H), 3.79 (dd, $J=10.6$, 3.3 Hz, 1H), 3.60 (d, $J=3.3$ Hz, 1H) 3.55 (d, $J=3.3$ Hz, 1H), 2.20 (d, $J=13.5$ Hz, 1H), 2.18 (d, $J=14.6$ Hz, 1H), 1.57 (d, $J=14.6$ Hz, 1H), 1.42 (dd, $J=13.7$, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, D_2O): δ 77.9, 76.6, 75.4, 74.9, 70.1, 68.3, 68.1, 67.4, 33.9. 32.9; Mass (EI, 70 eV): m/z 267 (M^++1).

7. (a) de Souza, S. E.; Kee, A.; O'Brien, P.; Watson, S. T. *Tetrahedron Lett*. **1999**, *40*, 387; (b) de Souza, S. E.; O'Brien, P.; Pilgram, P.; Roder, D.; Towers, T. D. *Tetrahedron Lett*. **1999**, *40*, 391.
8. Mandal, A. K.; Soni, N. R.; Ratnam, K. R. *Synthesis* **1985**, 274.
9. Stereostructures of compounds **14–17** were secured through the X-ray crystal structure determination of the acetonide (**A**) derived from the diol derived from **14** (Fig. 2). **Crystal data for A**: The structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. Crystal system: monoclinic, space group: $C2/c$, cell parameters: $a=26.595(3)$ Å, $b=10.7892(11)$ Å, $c=14.1564(15)$ Å, $\beta=116.171(2)°$, $V=3645.6(7)$ Å^3, $Z=26$, ρ(calcd)$=1.357$ g cm^{-3}, $F(000)=1584$, $\mu=0.11$ mm^{-1}, $\lambda=0.71073$ Å. Total number of l.s. parameters$=239$. $R_1=0.0787$ for $F_o>2\sigma(F_o)$ and 0.1633 for all 2619 data. $wR_2=0.1828$, GooF$=1.179$, restrained GooF$=1.179$ for all data. An ORTEP drawing of compound **A** with 50% ellipsoidal probability is shown above. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre [CCDC 200362].
10. Angyal, S. J.; Craig, D. C. *Carbohydr. Res*. **1994**, *263*, 149.
11. Bicyclic cyclohexadiene **21** is an annulated cyclohexadiene *trans*-diol derivative related to those derived from the aromatics employing recombinant *E. coli* cells and can be a versatile substrate in the synthesis. See Franke, D.; Sprenger, G. A.; Muller, M. *Angew. Chem., Int. Ed. Engl*. **2001**, *40*, 555.
12. Jeffrey, G. A.; Yeon, Y. *Carbohydr. Res*. **1987**, *159*, 211.