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From aromatics to conjoined inositols: stereoselective oxyfunctionalization of anthracene

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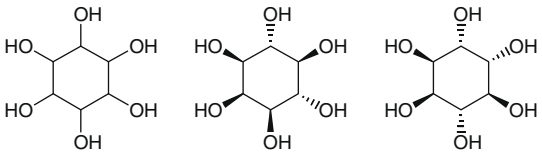
ABSTRACT

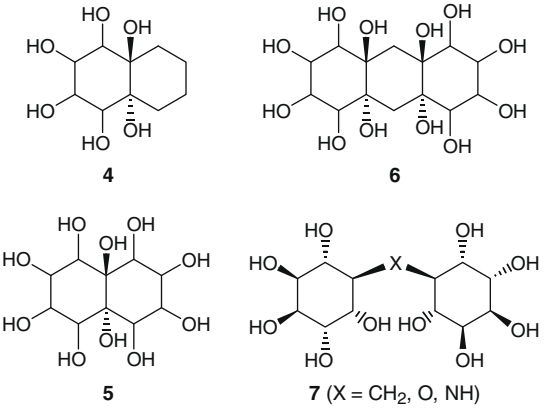
Novel 'conjoined' inositols are conceptualized as new structural motifs and an oxyfunctionalization protocol on anthracene is devised in quest for these entities.

Inositols **1** or cyclohexane-1,2,3,4,5,6-hexols constitute a biologically important class of cyclitols for which all the possible nine diastereomers, five natural (*myo*, *scyllo*, D-*chiro*, L-*chiro* and *neo*) and four synthetic (*cis*, *epi*, *allo* and *muco*), are known.[1] *Myo*-inositol **2**, the diastereomer most widely prevalent in Nature, forms the structural basis of a number of secondary messengers in eukaryotic cells and is therefore engaged in diverse biological processes. These include insulin signal transduction, control of intracellular calcium ion concentration, maintenance of cell membrane potential, modulation of serotonin activity and gene expression.[1,2] In addition, clinical studies have revealed that administration of *myo*-inositol forms a promising line of treatment in patients suffering from psychiatric disorders such as obsessive compulsive-disorder and bipolar depression.[3] Among the other naturally occurring inositol isomers, D-*chiro*-inositol **3** has been effectively employed in management of polycystic ovary syndrome.[4]



1 **2** **3**

The wide-ranging biological functions of inositols have, not surprisingly, generated contemporary interest in their chemistry and stimulated the search for novel analogues for therapeutic applications.[5] Our group has been actively involved in this quest and we have introduced a number of bicyclic inositol variants, such as annulated inositols **4**[6] and inosito-inositols **5**,[7] endowed with a unique structural commonality.[8] Constructed upon a conformationally locked *trans*-decalin scaffold, these inositol analogues exhibit a high-energy 'unnatural' axial-rich conformation of the cyclitol moiety while retaining its natural configuration. From a synthetic perspective, these structural attributes of **4** and **5** stemmed from the sequence of stereo-controlled oxyfunctionalization steps carried out on the respective aromatic precursors, namely tetralin/indane and naphthalene. The synthetic scheme, delineated in the elaboration of the aromatic nucleus into the inositol moiety in **4** and **5**, appeared amenable for diversification and encouraged us to look into the possibility of utilizing anthracene as a polycyclic carbon scaffold to obtain novel polycyclic entities that can be termed 'conjoined inositols' **6**. Our conceptualization of conjoined inositols was also inspired by the observation of calcium binding affinity and β-galactosidase inhibition activity in several linked inositols **7** (X = O, NH) reported by Hudlicky and co-workers.[9]



4 **6**

5 **7** (X = CH_2, O, NH)

Structurally, a conjoined inositol would consist of two or more inositol units fused by hydrocarbon annuli and would therefore provide a means of extending the *trans*-fusion strategy to lock the constituent inositols in novel conformations unattainable by a single methylene, imino or oxido linker (e.g., **7**). In addition to being potential candidates for metal chelating studies, conjoined inositols are expected to exhibit interesting supramolecular

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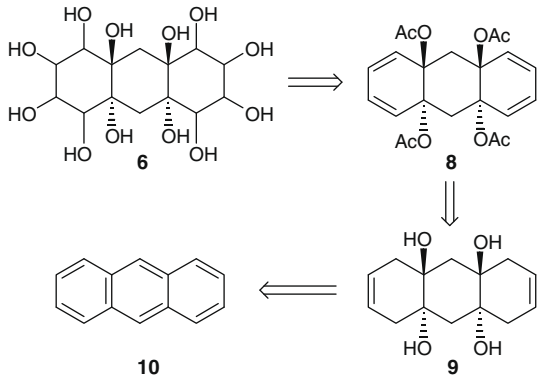
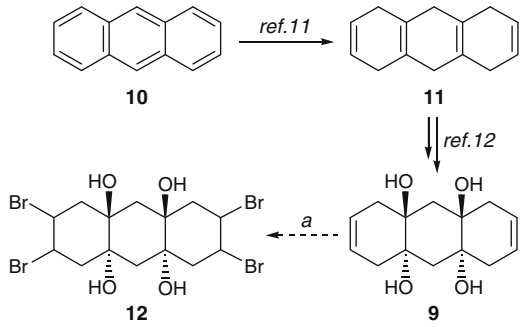


Scheme 1. Retrosynthetic analysis of conjoined inositols from anthracene.



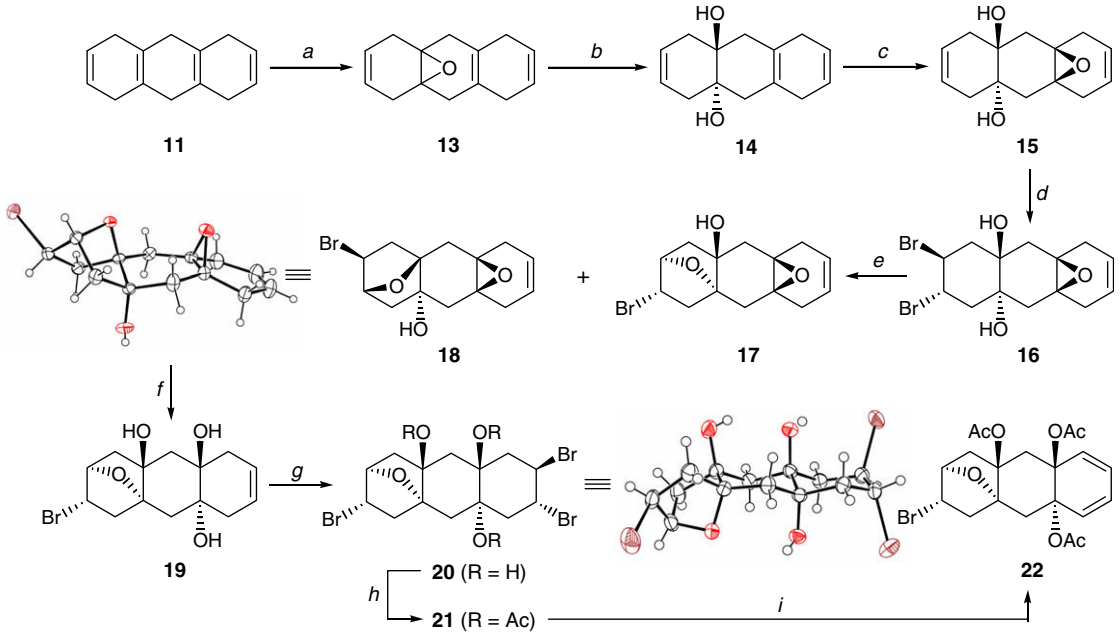
Scheme 2. Reagents and conditions: (a) $pyH^{+}Br_3^{-}$, CH_2Cl_2, rt.

architecture in the solid state on account of the extensive hydrogen-bonding network inevitably formed by the conformationally locked inositol units which lie in close proximity to each other.[10] In this paper, we report the details of our ongoing efforts en route to **6** which have resulted in the synthesis of some new polyhydroxylated frameworks and tricyclic inositol analogues, constructed on an anthracene platform and endowed with up to nine oxygenated carbon atoms and ten stereocentres.

Retrosynthetic analysis of **6** identified the C_{2h}-symmetric tricyclic tetra-acetoxytetraene **8** as the key intermediate for the symmetrical construction of the two inositol moieties. The tetraene **8** was to be accessed from the tetrol **9** through a bromination–dehydrobromination or an equivalent manoeuver, Scheme 1. A ready access to the tetrol **9** from anthracene **10** has already been described by us.[10a,d]

Exhaustive Birch reduction of **10** gave 1,4,5,8,9,10-hexahydroanthracene **11**.[10d,11] Regioselective epoxidation of **11**, followed by acid-mediated ring-opening, furnished the C_{2h}-symmetric tetrol **9**.[10d,12] Much to our disappointment, bromination of **9** to give **12** instead yielded a product that was too insoluble in any common solvent to be amenable for characterization or further reactions, Scheme 2. Taking recourse to an allylic bromination–dehydrobromination sequence as an alternative approach towards **8** from **9** was also unsuccessful.

Consequently, a redefined synthetic strategy was adopted which focused on a stepwise construction of the two inositol fragments present in **6**. Accordingly, controlled *m*CPBA mediated regioselective epoxidation of **11** afforded the monoepoxide **13**, which on acid-catalyzed ring-opening furnished the *trans*-diol **14**.[12a] Regioselective epoxidation of the tetrasubstituted double bond in **14** led to the epoxydiol **15**, Scheme 3. Epoxydiol **15** on monobromination yielded **16** in a stereo- and regioselective manner.[13,14] Attempted base-mediated double dehydrobromination of **16** afforded a diastereomeric mixture (3:1) of the bicyclic ethers **17**[15] and **18**. The stereostructures of the two 7-oxabicyclo[2.2.1]heptane bearing moieties **17** and **18** were secured on the basis of X-ray crystal structure determination of the latter.[16] Interestingly enough, both **17** and **18**, upon treatment with 10% aqueous acetic acid, attained stereochemical convergence to furnish the same triol **19** and thereby rendered the sequence stereoselective. The *trans–syn–trans* relationship of the two ring junctions in **19** was unambiguously settled in the next step from the crystal structure analysis of the trib-



Scheme 3. Reagents and conditions: (a) *m*CPBA (1 equiv), CH_2Cl_2, −40 °C, 5 min, 68%; (b) 10% AcOH (aq), 60 °C, 2 h, 95%; c) *m*CPBA (1 equiv), CH_2Cl_2, −30 °C, 5 min, 89%; (d) $pyH^{+}Br_3^{-}$, CH_2Cl_2, 0 °C, 5 min, 70%; (e) NaOH, moist THF, rt, 2 h, 95% overall (**17**:**18** = 3:1); (f) 10% AcOH, 50 °C, 12 h, 90% [over two steps, based on the amount of **16** used]; (g) $pyH^{+}Br_3^{-}$, CH_2Cl_2, rt, 2 h, 95%; (h) Ac_2O, $FeCl_3$ (cat.), rt, 2 h, 92%; (i) DBU, DMSO, rt, 60%. [Please note that the ORTEP diagrams are drawn at 30% ellipsoidal probability.]