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From aromatics to conjoined inositols: stereoselective oxyfunctionalization of anthracene

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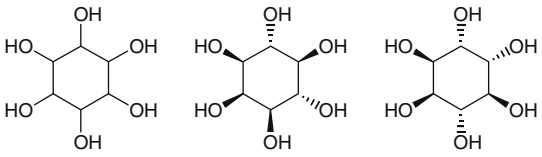
ABSTRACT

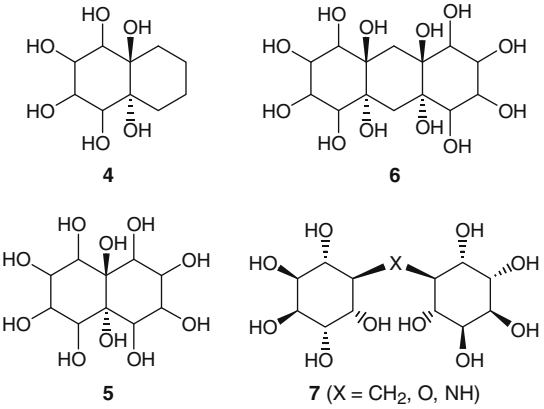
Novel 'conjoined' inositols are conceptualized as new structural motifs and an oxyfunctionalization protocol on anthracene is devised in quest for these entities.

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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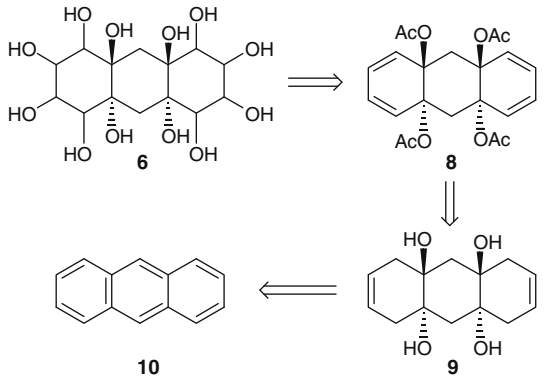
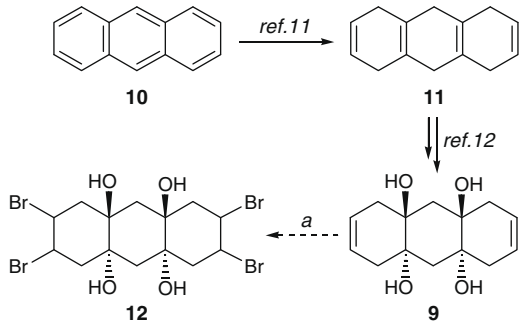


Scheme 1. Retrosynthetic analysis of conjoined inositols from anthracene.



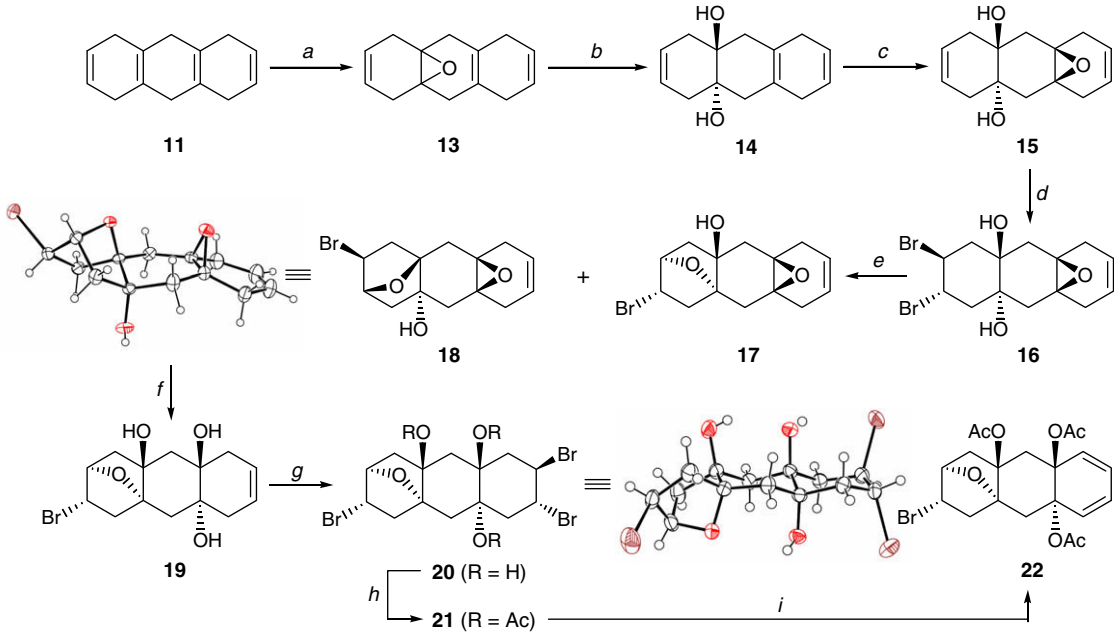
Scheme 2. Reagents and conditions: (a) $pyH^{+}Br_3^{-}$, CH_2Cl_2, rt.

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.]

romo derivative **20**, obtained smoothly through straightforward monobromination, Scheme 3.[16] The tribromide **20** underwent smooth acetylation in the presence of the mild Lewis acid, ferric chloride, to give the triacetate **21** in excellent yield, which on DBU-mediated double dehydrobromination afforded the diene **22**, Scheme 3.[15]

With the pivotal building block **22** in hand, it was simply a matter of sequencing the successive dihydroxylations (*cis* and/or *trans*) to generate the first inositol moiety of the desired stereochemistry. Despite its sluggish reactivity and the attendant decomposition of the reactant, *m*CPBA proved to be the reagent of choice in carrying out the monoepoxidation of the diene **22**. Of the four regio- and stereoisomeric products theoretically attainable in this reaction, only the monoepoxides **23** and **24** were obtained in equal amounts. The stereoselectivity observed during the epoxidation of **22** can be attributed to the attack of *m*CPBA *anti* to the acetate functionality proximal to the reacting double bond (Scheme 4). The epoxides (**23** and **24**) were separated and each on acid-mediated ring-opening furnished two products [(**25**+**26**) and (**27**+**28**), respectively] both in a 2:1 ratio, Scheme 4.[15] While the *trans*-diols **26** and **28** could arise from the corresponding epoxides **23** and **24** via a normal 1,2-epoxide ring opening, the formation of the major products **25** and **27**, having the two newly introduced hydroxy groups *syn* to each other, from **23** and **24**, respectively, required a deep-seated rearrangement involving both the bridgehead acetates.[6,17] In order to establish the relationship among the stereocentres of the two functionalized peripheral rings in **25–28**, it was necessary and sufficient to take the crystal structure of any one of these products, since the stereochemical disposition of the functional groups within each ring of **25–28** would be predetermined or could be extrapolated from literature precedence.[6] The crystal structure of the

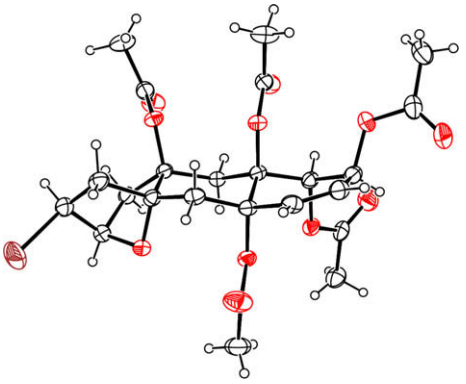
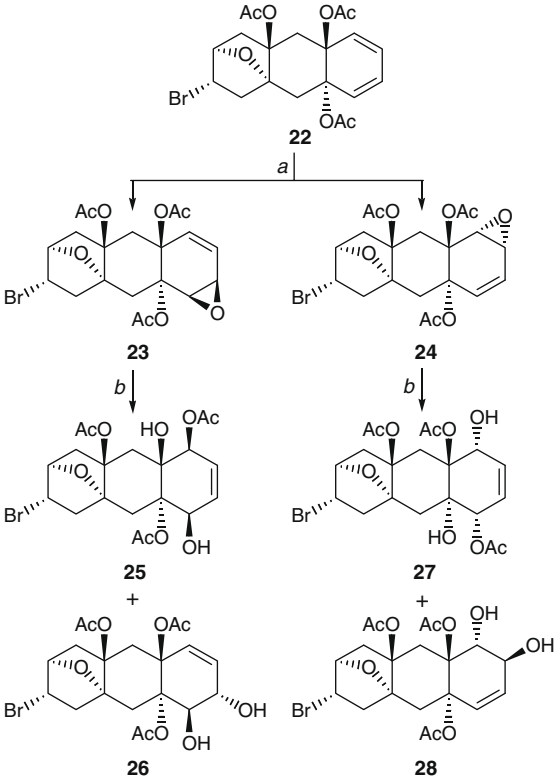


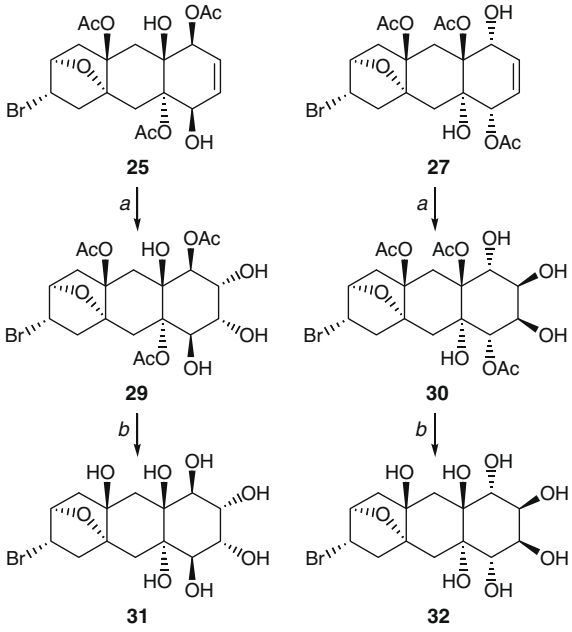
Figure 1. ORTEP diagram of the penta-acetate derivative of **28** drawn at 30% ellipsoidal probability (the derivative was prepared by reacting **28** with Ac_2O in the presence of DMAP as a catalyst).

penta-acetate derivative of **28** revealed it to be, as expected, the 'normal' hydrolysis product of the epoxide **24**, Figure 1.[16]

The stereochemical disposition of the oxyfunctionalities within the polyhydroxylated ring of each of the two diastereomeric pairs of diols, (**25** and **27**) and (**26** and **28**), was reminiscent of a conduritol F and B sub-structure, respectively.[18] Each of the two major diols, **25** and **27**, was subjected to OsO_4-mediated dihydroxylation to furnish the inositol derivatives **29** and **30**,[15] respectively. The stereospecificity observed in this dihydroxylation step was predictable from Kishi's rule for OsO_4-mediated dihydroxylation of allylic alcohols.[19] Transacetylation of the triacetates **29** and **30** in K_2CO_3/methanol gave the diastereomeric *chiro*-inositols **31** and **32**,[15] respectively, in quantitative yield, Scheme 5. The relative configuration and conformation of the inositol moiety in **31** and **32** could be established from the ^1H NMR coupling constants observed for the methine protons attached to the cyclitol framework in **31** and **32**, and also from the crystal structure of **32**, Figure 2.[16] In line with our expectations, the *chiro*-inositol moieties in **31** and **32** were locked in the high-energy axial-rich 4a/2e conformation.



Scheme 4. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, rt, 4 d, 70% overall at 60% conversion (**23**:**24** = 1:1); (b) 10% AcOH (aq), THF, 50 °C, 1 d, 94% overall, **25**:**26** = **27**:**28** = 2:1.



Scheme 5. Reagents and conditions: (a) OsO_4, NMMO, acetone–water (4:1), rt, 12 h, 83–86%; (b) K_2CO_3, MeOH, rt, 2 h, quantitative.

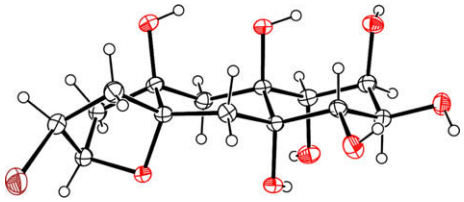


Figure 2. ORTEP diagram of **32** drawn at 30% ellipsoidal probability. The compound crystallizes as a dihydrate.

To summarize, in **31** and **32**, we have installed one inositol moiety within the tricyclic framework of anthracene in the quest for the conjoined inositol architecture **6**. More importantly, the 7-oxabicyclo[2.2.1]heptane, embedded in them, was crafted to serve as an inositol surrogate ('*latent inositol*') for positioning the second inositol moiety as demonstrated by us earlier.[7] Efforts towards this objective are currently underway. Nonetheless, the results described here provide an efficacious strategy for the installation of 10 stereogenic centres and eight oxygens on the aromatic hydrocarbon platform of anthracene in a controlled manner and sets the stage for further evolution to the novel conjoined inositol entities.

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13. While the stereoselectivity noted during the bromination of **15** may be regarded as an extension of the well-known Fürst-Plattner rule for epoxide ring opening (see Ref. 14), an explanation for the regioselectivity observed in the same reaction is far less obvious. Putatively, the regioselectivity observed here may be attributed to a greater through-space electronic stabilization of the incipient bromonium ion by one or other of the two homoallylic hydroxy groups present in **15**. See: (a) Chiappe, C.; De Rubertis, A.; Jaber, A.; Lenoir, D.; Wattenbach, C.; Pomelli, C. S. *J. Org. Chem.* **2002**, *67*, 7066–7074; (b) Teberekidis, V. I.; Sigalas, M. P. *Tetrahedron* **2002**, *58*, 6171–6178.
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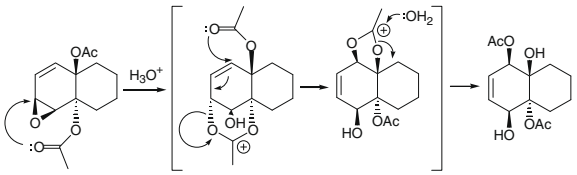
15. All new compounds were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. Spectral data of selected compounds: **17** mp 125–126 °C; IR (KBr) 3486, 3453, 3035, 3008 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.48 (s, 2H), 4.41 (d, J = 6 Hz, 1H), 4.12 (d, J = 7 Hz, 1H), 3.64 (s, 1H), 3.25 (dd, J = 14, 8 Hz, 1H), 2.58–2.11 (m, 8H), 1.97–1.84 (m, 2H), 1.42 (d, J = 13 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 122.12, 121.84, 84.76, 83.00, 75.73, 62.85, 61.08, 50.70, 43.95, 43.28, 39.51, 33.38, 30.60, 29.77 ppm; HRMS (ES) m/z calcd for $C_{14}H_{17}BrO_3Na$ (M+Na)$^+$: 335.0259; found: 335.0297; **22** mp 230–231 °C (decomp.); IR (KBr) 3053, 3015, 1739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.22 (d, J = 10 Hz, 1H), 6.03–5.92 (m, 3H), 4.51 (d, J = 6 Hz, 1H), 4.01 (d, J = 8 Hz, 1H), 3.63 (d, J = 16 Hz, 1H), 3.21 (d, J = 16 Hz, 1H), 3.02 (dd, J = 14, 8 Hz, 1H), 2.38 (d, J = 16 Hz, 1H), 2.32 (dd, J = 15, 7 Hz, 1H), 2.21 (d, J = 16 Hz, 1H), 2.11–1.90 (m, 11H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.02, 169.58, 169.45, 130.40, 129.61, 125.02, 123.85, 86.26, 83.51, 82.49, 76.34, 48.62, 44.92, 43.41, 32.82, 28.95, 22.19, 21.96, 21.66 ppm; HRMS (ES) m/z calcd for $C_{20}H_{23}BrO_7Na$ (M+Na)$^+$: 477.0525; found: 477.0523; **25** IR (neat) 3468, 1732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.98 (ddd, J = 10, 5, 2 Hz, 1H), 5.52 (dd, J = 10, 2 Hz, 1H), 5.41 (d, J = 2 Hz, 1H), 4.83–4.79 (m, 1H), 4.52 (d, J = 6 Hz, 1H), 4.01 (dd, J = 8, 2 Hz, 1H), 3.33 (d, J = 16 Hz, 1H), 3.06–2.96 (m, 2H), 2.79 (d, J = 17 Hz, 1H), 2.67 (d, J = 16 Hz, 1H), 2.43 (s, 1H), 2.37–2.20 (m, 1H), 2.16 (s, 3H), 2.04-1.92 (m, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.42, 170.04, 169.97, 129.52, 124.46, 85.19, 83.93, 81.01, 80.57, 73.10, 72.76, 64.78, 48.76, 43.51, 43.15, 35.35, 25.40, 22.65, 22.06, 21.09 ppm; HRMS (ES) m/z calcd. for $C_{20}H_{25}BrO_9Na$ (M+Na)$^+$: 511.0580; found: 511.0617; **26** mp 235–236 °C (decomp.); IR (KBr) 3438, 1739 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ = 5.96 (dd, J = 10, 2 Hz, 1H), 5.82 (dd, J = 9, 3 Hz, 1H), 4.47 (d, J = 6 Hz, 1H), 4.42 (d, J = 3 Hz, 1H), 4.20 (dd, J = 8, 3 Hz, 1H), 4.16 (br s, 1H), 3.61 (d, J = 15 Hz, 1H), 3.10 (dd, J = 14, 8 Hz, 1H), 2.69 (d, J = 16 Hz, 1H), 2.26-1.85 (m, 14H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ = 172.29, 171.65, 171.09, 133.26, 130.56, 87.76, 85.35, 83.31, 82.13, 78.53, 75.75, 72.64, 50.52, 45.20, 44.77, 35.10, 27.53, 22.81, 22.07, 21.84 ppm; HRMS (ES) m/z calcd. for $C_{20}H_{25}BrO_9Na$ (M+Na)$^+$: 511.0580; found: 511.0614; **28** mp 237–238 °C (decomp.); IR (KBr) 3463, 1738 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ = 6.18 (d, J = 10 Hz, 1H), 5.83 (dd, J = 10, 2 Hz, 1H), 4.48 (d, J = 6 Hz, 1H), 4.34 (s, 1H), 4.20 (dd, J = 7, 3 Hz, 1H), 4.13 (s, 1H), 3.67 (d, J = 16 Hz, 1H), 3.16–3.04 (m, 2H), 2.48 (d, J = 16 Hz, 1H), 2.36–2.25 (m, 2H), 2.03–1.80 (m, 13H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ = 172.14, 171.70, 171.57, 131.43, 130.11, 87.38, 85.24, 83.89, 81.42, 77.57, 73.82, 71.93, 50.04, 45.64, 44.62, 32.02, 31.28, 23.03, 22.10, 21.92 ppm; HRMS (ES) m/z calcd for $C_{20}H_{25}BrO_9Na$ (M+Na)$^+$: 511.0580; found: 511.0610; **30** (characterized as acetonide derivative) IR (neat) 3496, 1743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.47 (d, J = 8 Hz, 1H), 4.77 (d, J = 12 Hz, 1H), 4.64 (d, J = 6 Hz, 1H), 4.46–4.39 (m, 2H), 4.13–4.04 (m, 2H), 3.81 (d, J = 17 Hz, 1H), 3.72 (d, J = 12 Hz, 1H), 2.53–2.20 (m, 6H), 2.05–1.80 (m, 9H), 1.49 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.11, 169.68, 169.20, 109.39, 85.50, 84.35, 81.16, 80.39, 78.76, 76.88, 74.01, 73.50, 66.80,

48.20, 43.57, 42.60, 31.38, 29.86, 27.93, 26.06, 22.62, 21.37, 21.15 ppm; HRMS (ES) *m/z* calcd for $C_{23}H_{31}BrO_{11}Na$ $(M+Na)^+$: 585.0947; found: 585.0950; **31** mp 210 °C (chars before melting); IR (KBr) 3397 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ = 4.44 (d, *J* = 6 Hz, 1H), 4.15 (d, *J* = 8 Hz, 1H), 3.98 (br s, 1H), 3.80 (dd, *J* = 10, 3 Hz, 1H), 3.67 (br s, 1H), 3.58 (d, *J* = 10 Hz, 1H), 3.01 (dd, *J* = 14, 8 Hz, 1H), 2.52 (d, *J* = 16 Hz, 1H), 1.99–1.76 (m, 5H), 1.34 (d, *J* = 14 Hz, 1H) ppm; ^{13}C NMR (75 MHz, D_2O) δ = 88.08, 85.40, 79.15, 76.55, 74.47 (2C), 74.21, 71.22, 69.04, 50.62, 44.50, 43.55, 38.51, 32.49 ppm; HRMS (ES) *m/z* calcd for $C_{14}H_{21}BrO_8Na$ $(M+Na)^+$: 419.0317; found: 419.0353; **32** mp 220 °C (chars before melting); IR (KBr) 3437 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ = 4.47 (d, *J* = 5 Hz, 1H), 4.15 (d, *J* = 6 Hz, 1H), 3.96 (br s, 1H), 3.84 (dd, *J* = 10, 3 Hz, 1H), 3.69 (d, *J* = 10 Hz, 1H), 3.59 (br s, 1H), 3.00 (dd, *J* = 15, 7 Hz, 1H), 2.24 (d, *J* = 15 Hz, 1H), 2.09 (s, 2H), 1.98–1.60 (m, 3H), 1.36 (d, *J* = 14 Hz, 1H) ppm; ^{13}C NMR (75 MHz, D_2O) δ = 87.78, 85.44, 77.78, 77.10, 75.25, 75.21, 74.64, 72.06, 69.11, 50.60, 45.06, 43.58, 39.72, 32.67; HRMS (ES) *m/z* calcd for $C_{14}H_{21}BrO_8Na$ $(M+Na)^+$: 419.0317; found: 419.0330.

16. Single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 291 K using graphite monochromated MoK_α radiation (λ = 0.7107 Å). The X-ray generator was operated at 50 KV and 35 mA. The data were collected with a ω scan width of 0.3°. A total of 606 frames per set were collected using SMART in three different settings of φ (0°, 90° and 180°) keeping the sample to detector distance of 6.062 cm and the 2θ value fixed at −28°. The data were reduced by SAINTPLUS; an empirical absorption correction was applied using the package SADABS and XPREP was used to determine the space group. The crystal structures were solved by direct methods using SIR92 and refined by full-matrix least-squares method on F^2 using SHELXL97. CCDC 752350–752353 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystal data for **18** $C_{14}H_{17}BrO_3$, *M* = 313.18, monoclinic, $P2_1/n$, *a* = 12.750(3), *b* = 5.8615(14), *c* = 17.202(4) Å, β = 92.174(4)°, *V* = 1284.6(5) $Å^3$, *Z* = 4, ρ_{calcd} = 1.619 g/cm^3, 9655 reflections measured, 2620 unique (R_{int} = 0.028), R_1 = 0.0281 and wR_2 = 0.0715 for 2321 observed reflections, CCDC 752352; **20** $C_{14}H_{19}Br_3O_4$, *M* = 490.99, monoclinic, $P2_1/c$, *a* = 11.141(8), *b* = 12.253(8), *c* = 11.484(8) Å, β = 90.678(12)°, *V* = 1567.6(18) $Å^3$, *Z* = 4, ρ_{calcd} = 2.081 g/cm^3, 12508 reflections measured, 2259 unique (R_{int} = 0.022), R_1 = 0.0243 and wR_2 = 0.0587 for 2057 unique reflections, CCDC 752353; **28** (as its penta-acetate derivative) $C_{24}H_{29}BrO_{11}$, *M* = 573.37, monoclinic, $P2_1/c$, *a* = 16.751(3), *b* = 7.5985(15), *c* = 19.787(4) Å, β = 94.243(4)°, *V* = 2511.6(8) $Å^3$, *Z* = 4, ρ_{calcd} = 1.516 g/cm^3, 18232 reflections measured, 4639 unique (R_{int} = 0.0483), R_1 = 0.0541 and wR_2 = 0.1168 for 2995 observed reflections, CCDC 752350; **32** $C_{14}H_{21}BrO_8{\cdot}2H_2O$, *M* = 433.24, monoclinic, $P2_1/c$, *a* = 7.567(4), *b* = 13.777(7), *c* = 17.276(8) Å, β = 106.715(18)°, *V* = 1725.0(14) $Å^3$, *Z* = 4, ρ_{calcd} = 1.668 g/cm^3, 13069 reflections measured, 3473 unique (R_{int} = 0.0247), R_1 = 0.0288 and wR_2 = 0.0758 for 3045 observed reflections, CCDC 752351.
17. The mechanism for the acid-catalyzed rearrangement ('acetate dance') is shown below:



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