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Thermal epimerization of inositol 1,3-benzylidene acetals in the molten state

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ABSTRACT

1,3-*O*-Benzylidene-2,4,5,6-tetra-*O*-substituted-*myo*-inositol derivatives obtained by the DIBAL-H reduction of the corresponding *myo*-inositol 1,3,5-*ortho*benzoate derivatives undergo epimerization at the acetal carbon on heating, in the molten state, just above their melting point. The same epimerization reaction does not proceed either in the crystalline state or in solution. DFT calculations suggest that the epimeric acetal obtained by this thermal process is relatively more stable than the starting acetal. Either of these acetals could not be obtained by the reaction of the corresponding inositol derived diol with benzaldehyde. These observations constitute a novel reaction solely in the molten state, which are rarely encountered in the literature. X-ray crystal structures of the epimeric acetals as well as their radical deoxygenation reaction are also reported.

1. Introduction

Chemical reactions, which proceed with high selectivity for product formation have attracted the attention of chemists for over a hundred years due to their significance in research and industry. Organic chemists invest time and effort in tailoring reactions to maximize the yield of the product of their interest; ideally, they would like every reaction that they carry out to yield a single product. Although a large majority of reactions reported in the contemporary literature pertains to reactions conducted in the presence of solvents, there is considerable interest in reactions, which proceed in the absence of solvents. This category includes reactions in (i) crystals,[1] (ii) non crystalline solids,[2] (iii) solventless reactions,[3] and (iv) reactions in the molten state.[4]

Although investigation of reactions in the absence of solvents was initially driven by curiosity, such reactions are gaining ground due to environment related issues as well as because often they proceed with high product (regio-, stereo-, enantio-) selectivity that cannot be achieved in analogous solution state reactions. We had earlier reported[5] very facile benzoyl group transfer reactions in crystalline inositol derivatives. Among solventless reactions, the least encountered are the reactions that proceed truly or solely in the molten state.[4e] We herein report epimerization of inositol 1,3-acetals, which proceed with high selectivity in the molten state. We also present results on DFT calculations and X-ray crystal structures of relevant compounds, which suggest that epimerization of these 1,3-acetals in the molten state provides the thermodynamically more stable product. Study of epimerization of organic compounds in condensed phases[6] is also of relevance and importance due to their potential to generate optically active compounds without the aid of other chiral compounds or auxiliaries. Much interest was generated in the chemistry of inositols due to the realization of their role in various biological phenomena and subsequent implication of the *myo*-inositol cycle in various diseases, such as cancer and diabetes.[7]

2. Results and discussion

myo-Inositol 1,3-benzylidene acetals can be prepared by the reduction of the corresponding *ortho*benzoate, with DIBAL-H.[8] The extent of regioselectivity of this reduction is known to depend on other substituents present in the *myo*-inositol *ortho*ester molecule.[9] The *ortho*benzoates **3** and **4** were prepared[8b,10] from *myo*-inositol and reduced with DIBAL-H to obtain a single diastereomer of the corresponding 1,3-acetal **5** and **6** (Scheme 1). The 1,3-acetals **5** and **6** were converted to the xanthates **7**, **8**, and **9** by adopting routine procedures.

The xanthates of these pentaprotected *myo*-inositol derivatives underwent novel radical deoxygenation reaction to provide the corresponding dideoxy *myo*-inositol derivatives.[11] The chemistry of these inositol derivatives were being investigated in our laboratory in order to prepare orthogonally protected inositol derivatives, which can be diversified to obtain a variety of cyclitol derivatives.[9b,11]

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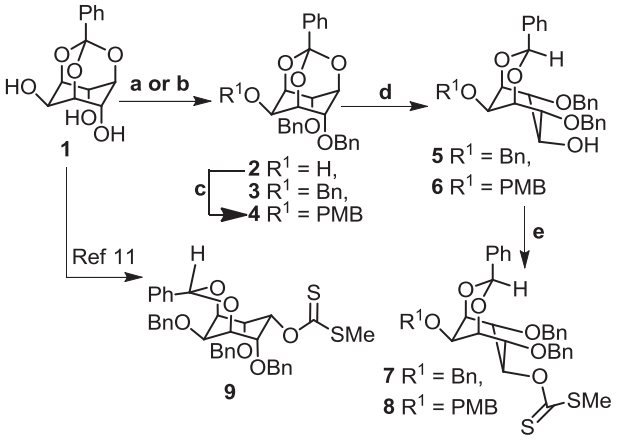
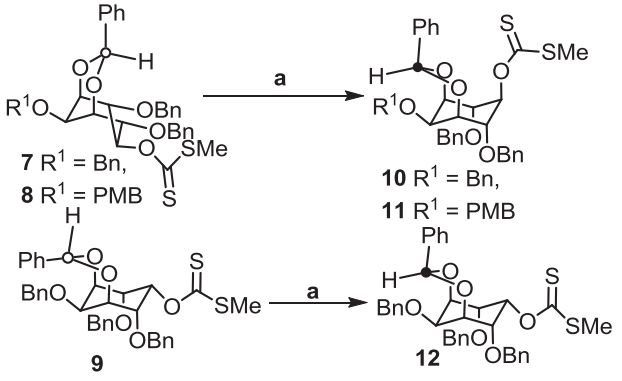


Scheme 1. Synthesis of xanthates: (a) DMF, LiH, BnBr, rt, 12 h, 81% (for **2**); (b) DMF, NaH, BnBr, rt, 3 h, 98% (for **3**); (c) DMF, NaH, PMBCl, rt, 96%; (d) DCM, DIBAL-H (2.2 equiv), 0 °C, 80–94%; (e) THF, NaH, CS_2, reflux, 1 h, MeI, rt, 16 h, 96–98%.

During the course of these investigations we observed that the PMB ether **8** was stable in the solid state (see below) but produced minor amounts of another organic compound while isolation from its solution (by evaporation of the solvent) or storage (as a gum) at ambient temperature. Isolation of this product and the scrutiny of its spectral characteristics showed it to be an isomer of the starting PMB ether **8**. We were intrigued to see that refluxing a toluene solution or heating a DMF solution (obtained by dissolving crystals of **8**) at 130 °C however did not produce the isomer of **8** that we had observed earlier. Hence we wondered whether the isomerization could be occurring in the solid state. But, heating crystals of **8** just below their melting point did not result in isomerization of **8**. Continued heating of the xanthate **8** beyond its melting point[12] resulted in its isomerization to **11** (Scheme 2, about 50% conversion) with concomitant formation of the corresponding diol (**14**, see Experimental section).



Scheme 2. Epimerization in the molten state: (a) 120 °C, 12 h for **7** and **9**, 30 h for **8**.

We could improve the yield of the isomeric product to about 70% by heating molten **8** in an inert (argon) atmosphere. This isomer of **8** could be crystallized from a mixture of ethyl acetate and hexane; single crystal X-ray diffraction studies of these crystals established the structure of the isomer of **8** as **11** (Fig. 1 and Scheme 2; carbon atom undergoing a change in configuration is marked in **8** and **11**). We carried out the epimerization (in the molten state) of two other 1,3-acetals **7** and **9** having the *myo*- and the neo-configurations, which gave the epimerized products **10** and **12**, respectively.[12] All these epimerization reactions were not feasible in the crystalline state as well as in solution (DMF, 130 °C). It is interesting to note that epimerization of the acetals **7** and **8** having the *myo*-configuration leads to a change in the conformation of the inositol as well

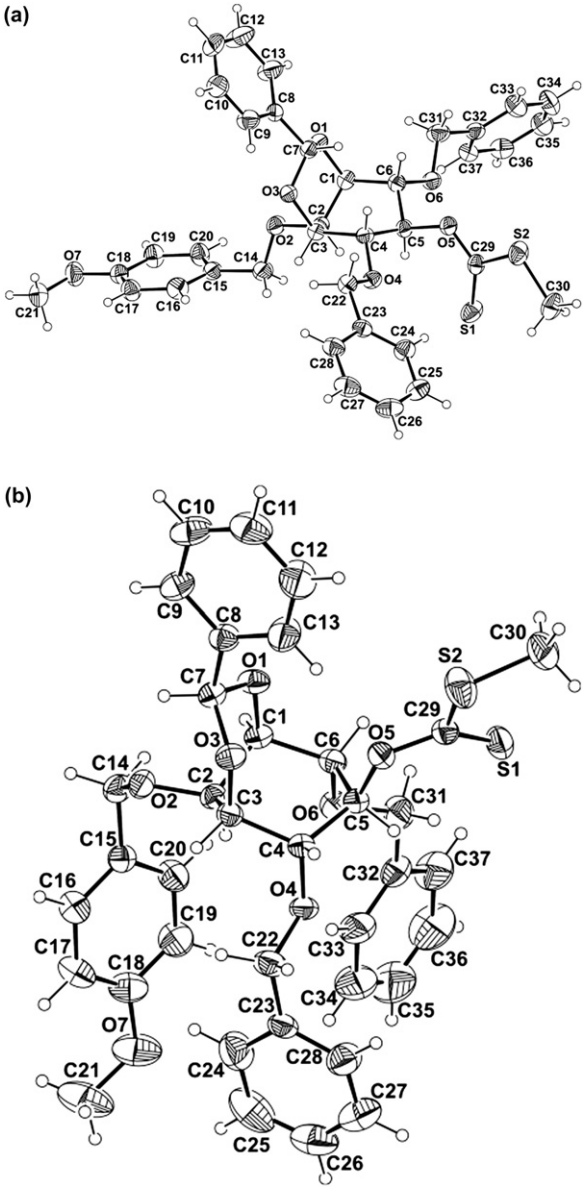


Fig. 1. ORTEP of xanthate **8** (a) and its epimer **11** (b). Thermal ellipsoids are drawn at 30% probability and hydrogen atoms are depicted as small spheres of arbitrary radii.

as the acetal ring, while in the acetal **9** with neo-configuration, the conformation of the two rings are retained (Figs. 2 and 3).

Additional support for the nonoccurrence of epimerization of the acetals **7**, **8**, and **9** in solution was obtained by subjecting their epimers (**10**, **11**, and **12**) to radical deoxygenation conditions and comparing the results that we had obtained earlier[11] for the deoxygenation of **7**, **8**, and **9**. The xanthates **10**, **11**, and **12** when subjected to radical deoxygenation conditions as reported earlier,[11] yielded the corresponding mono-deoxygenated derivatives exclusively (**18**, **19** Scheme 3), since intramolecular (acetal) hydrogen abstraction is sterically forbidden in these molecules.

The structure of the mono-deoxy derivative **19** was established by single crystal X-ray diffraction analysis (Fig. 4). The xanthates **7**, **8**, and **9** on the other hand had provided the dideoxy derivatives on subjecting to radical deoxygenation conditions, via intramolecular (acetal) hydrogen abstraction.[11] The contrasting results of these deoxygenation reactions with the two epimers supports our observation that the epimerization of the xanthates **7**, **8**, and **9** does not occur in the solution phase. If it did, we would have observed

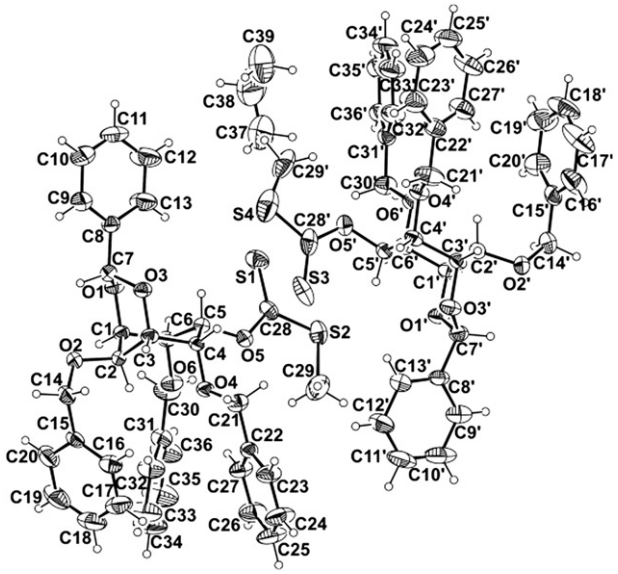


Fig. 2. ORTEP of hexane solvate of neo-xanthate **12** (epimer of **9**). Thermal ellipsoids are drawn at 30% probability and hydrogen atoms are depicted as small spheres of arbitrary radii.

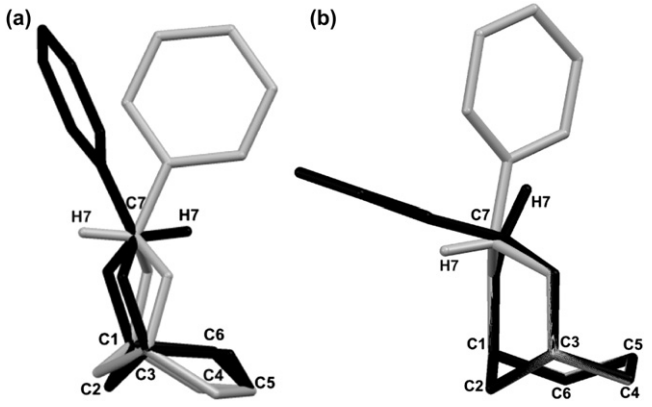
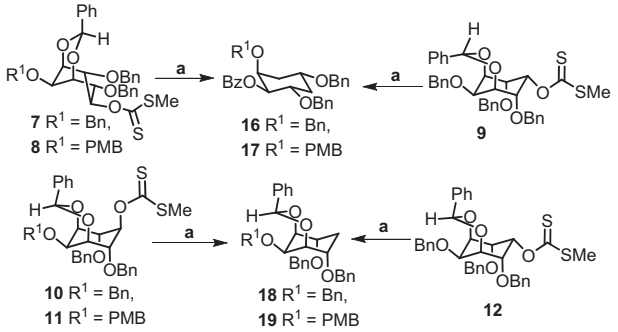


Fig. 3. (a) Molecular overlap of the xanthate **8** (black) with its epimer, the xanthate **11** (grey); (b) Molecular overlap of the xanthate **9** (black) with one of the two molecules in the asymmetric unit of its epimer, the xanthate **12** (grey). Some functional groups are omitted for the sake of clarity. For complete overlap of the two molecules see ESD.



Scheme 3. Deoxygenation of xanthates: (a) toluene, *n*-Bu_3SnH, AIBN, reflux, 1 h, 80–92%.

formation of a mixture of the mono and the dideoxy derivatives during the deoxygenation of the epimeric xanthates.

Since we noticed the formation of 1,3-diols (**13**–**15**, see Experimental section) during the epimerization of the acetals **7**, **8**, and **9** we wondered whether they were intermediates during the process of epimerization. That is, whether epimerization of the

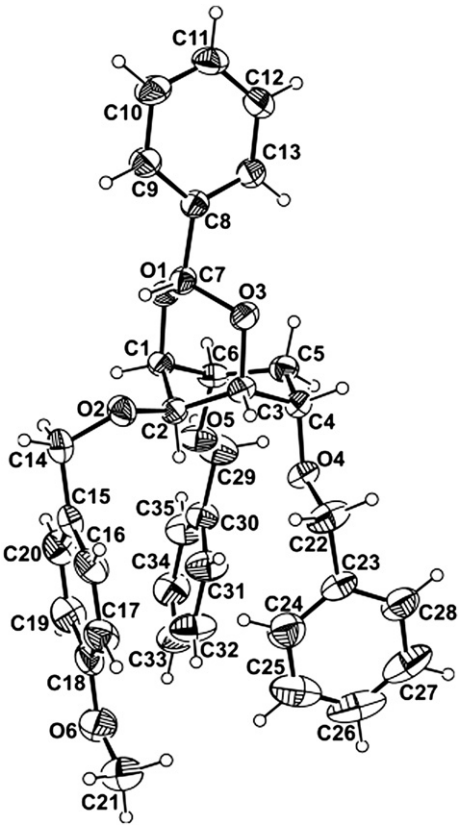


Fig. 4. ORTEP of **19**. Thermal ellipsoids are drawn at 30% probability and hydrogen atoms are depicted as small spheres of arbitrary radii.

acetals **7**, **8**, and **9** was occurring in two steps: (a) formation of the corresponding diol followed by (b) its reaction in situ with benzaldehyde produced. However, heating of the diols **13**–**15** with benzaldehyde under the conditions of epimerization did not result in the formation of the corresponding 1,3 acetal. This ruled out the epimerization of the acetal via the corresponding diol and suggested that the diols **13**–**15** were formed only as a bi-product during epimerization of the acetals **7**, **8**, and **9**, but did not function as intermediates. These experiments also led to an interesting observation. Although the two epimeric acetals (**7**, **10** or **8**, **11** or **9**, **12**) cannot be prepared from the parent diol (**13** or **14** or **15**), they can be accessed via the *ortho*benzoates and the relatively more stable acetal (**10** or **11** or **12**) can only be obtained by isomerization of its less stable epimer (see below), since reduction of the *ortho*-benzoate (**3** or **4**) is stereoselective to yield **7** and **8** exclusively!

We also estimated the relative stability of the epimeric acetals (**7** vs **10**; **8** vs **11**; **9** vs **12**) by DFT calculations. Geometry optimization for all the acetals was carried out with the input structures taken from the conformation of the two rings (inositol and the acetal) as observed in their crystals. The ^{1}H NMR spectra of these xanthates suggested that the conformations observed in their crystals are retained in their solution. Estimation of the relative energies (Fig. 5) suggested that the acetals **10**, **11**, and **12** are relatively more stable compared to their epimers **7**, **8**, and **9**, respectively. The relative difference in stability (3.9 kcal/mol) is slightly higher for the pair of acetals (**9**, **12**) with the neo-configuration as compared to those having the *myo*-configuration (**7**, **10**, and **8**, **11**, <1.4 kcal/mol). The differences in the stability of these 1,3-acetals could explain the facility of epimerization under thermal conditions.

Although the mechanism of epimerization of acetals **7**, **8**, and **9** is not clear, we can postulate that the reaction proceeds by cleavage of one of the acetal C–O bonds, rotation of the other C–O bond and re-formation of the broken C–O bond (Scheme 4). It is not unlikely

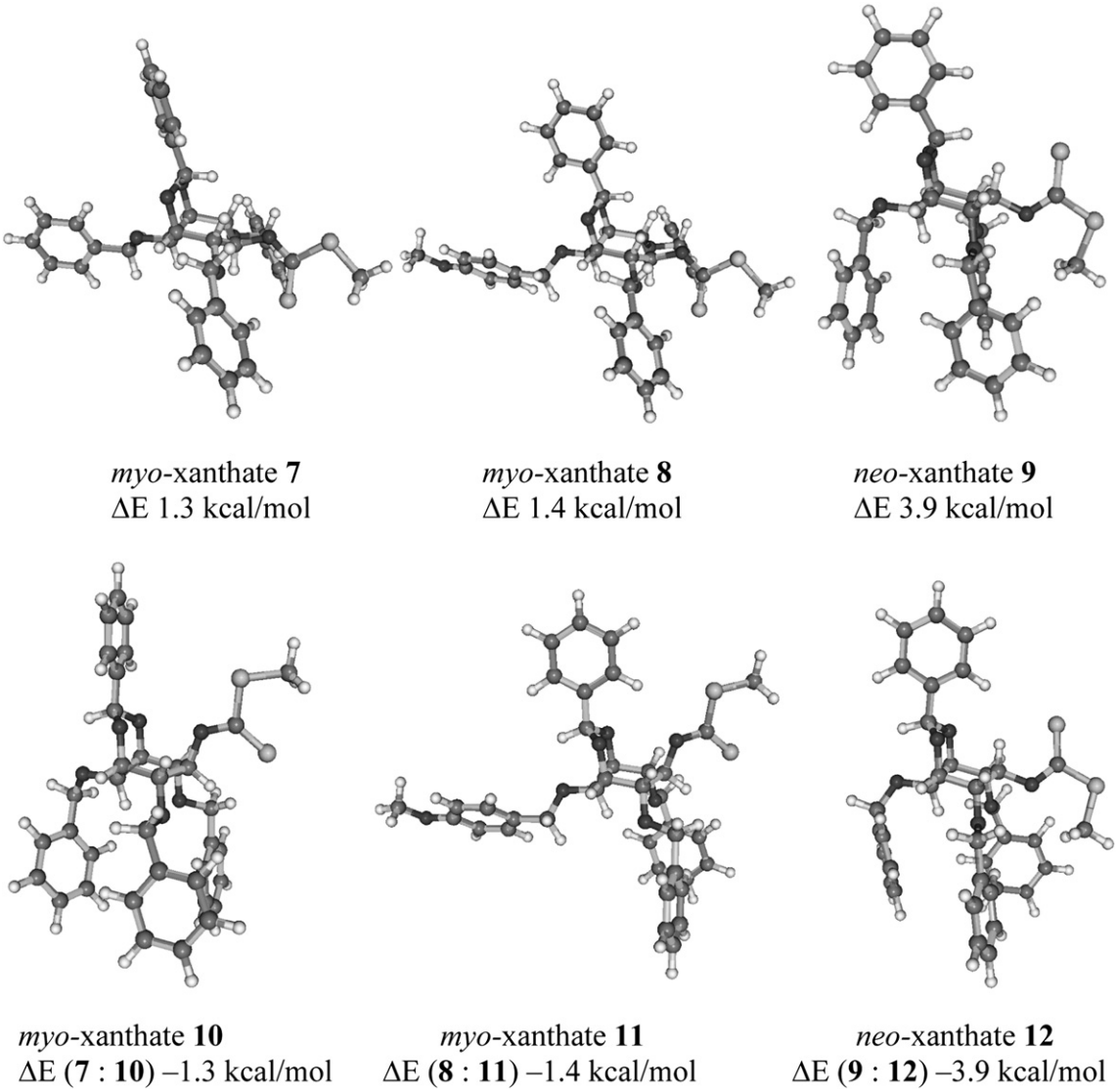
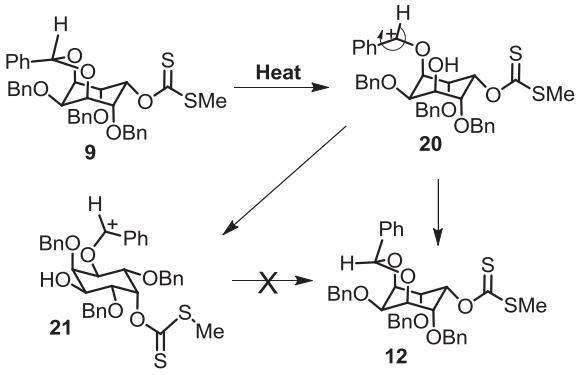


Fig. 5. Geometry optimized structures of xanthates **7**, **8**, **9**, and their epimers **10**, **11**, and **12**.



Scheme 4. Plausible mechanism for the epimerization of 1,3-acetals in the molten state.

that the diol is formed as a result of flipping of the inositol ring (**20**→**21**), since in this 'equatorial rich' conformation (**21**), re-establishment of the broken C–O bond is not feasible. Since the major product obtained is the epimer of the starting acetal, it is plausible that re-formation of the broken acetal C–O bond is faster than flipping of the inositol ring. The relatively sluggish flipping of the inositol ring could be a result of closely packed molecules in the melt just above the melting point of the crystals. This is supported by the fact that epimerization of the acetals at higher temperatures resulted in increased yield of the corresponding diol, perhaps due to loosening of the molecules in the melt, resulting in faster ring flipping. These possibilities are schematically represented for the epimerization of the acetal **9** (for illustration) in Scheme 4.

The process of epimerization of the acetals (**7** and **8**) having the *myo*-configuration involve a change in the conformation of the acetal ring as well as the inositol ring. The data available to us is not sufficient to figure out whether these conformational changes precede or succeed epimerization of the acetal carbon. Perusal of the crystal structures of the acetals **7**–**9** as well as their epimers **11** and **12** shows that the close packing of molecules in the crystal lattice does not allow major conformational changes required for the epimerization reaction under discussion (Fig. 6).

A measurement of the unit cell parameters of the reactant crystal at (a) ambient temperature, (b) when heated up to 90 °C and then (c) cooled down to ambient temperature did not show significant variation, indicating that the reaction does not occur in the crystal. This is in line with our experimental observations that the epimerization of **7**–**9** sets in, subsequent to melting of the crystals. That the nonoccurrence of epimerization in the crystalline state is

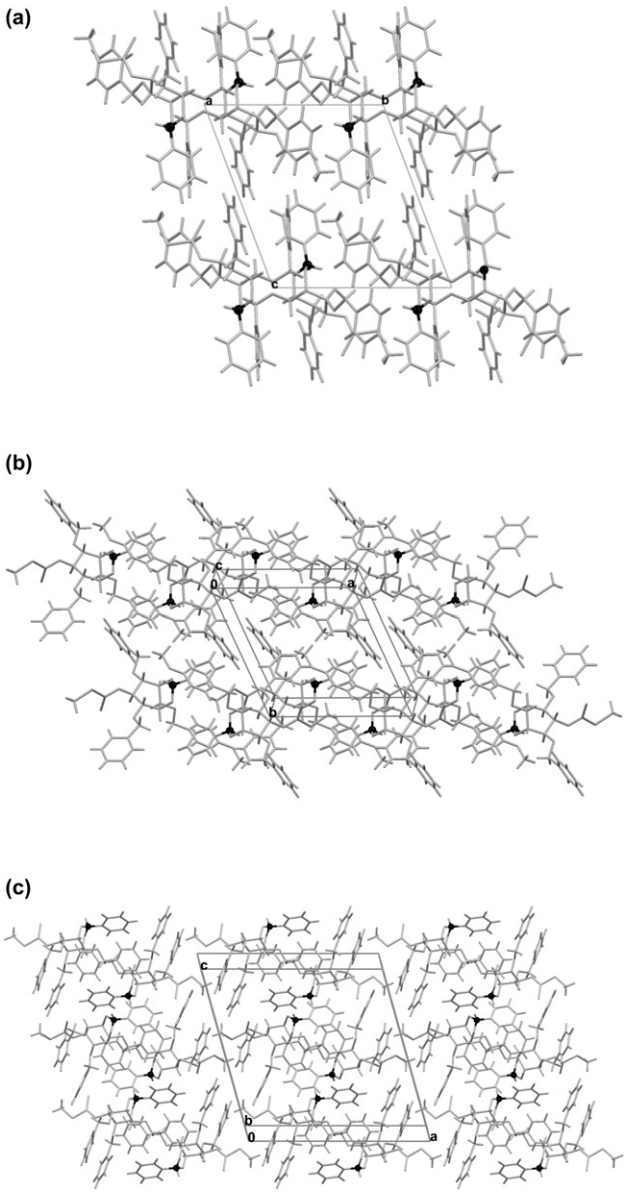


Fig. 6. Molecular packing in crystals of (a) **7**, (b) **8**, and (c) **9**. The carbon atom undergoing epimerization is shown as black filled circle.

not due to differences in temperature between the molten state and the crystalline state alone, is suggested by the fact that the epimerization in solution at temperatures higher than the melting point of **7**–**9** also did not occur.

3. Conclusions

We have presented a novel thermal epimerization of inositol derived 1,3-acetals, which occur only in the molten state wherein the molecules are free enough to go through the bond scission and conformational changes, which result in the formation of the relatively stable epimer. Interestingly, results presented here suggest that in the molten state (just above the melting point of crystals), molecules are not very free to undergo flipping of the inositol ring, which would sterically forbid the formation of the cyclic 1,3-acetal. Hence it is likely that in the molten state aggregated molecules achieve the fine balance between the rigidity of the matrix, and the molecular motion needed for their reaction to realize their epimerization.

This process of epimerization is perhaps augmented by the relative stabilities of the two epimers. In the solution state, which allows complete freedom of movement for the molecules, the acetal molecules may not achieve the required aggregation and rigidity necessary for fruitful epimerization. Encountering such unusual facile reactions in the molten state makes one wonder whether organic chemists should consider carrying out reactions in melt routinely, just as they carry out reactions in different solvents, to maximize the yield and selectivity. This is especially significant since reactions in melt are easy to carry out, do not need any specialized equipment, and are far less hazardous (in terms of generating waste) to our environment as compared to solution state reactions. The results presented here reiterates the importance of the phase (in which the reaction is carried out) on the facility and selectivity of a reaction, whether or not the phase of a substance can be defined and characterized by conventional methods and stresses the need for investigations aimed at deeper understanding of the phases other than solids, liquids, and vapor.

4. Experimental section

4.1. Computational details

All the density functional theory calculations were carried out using the Turbomole suite of programs.[13] The strategy adopted for the geometry optimizations is as follows: for a given geometry, a conformational search was first done using Molecular Mechanics (MM+force field) methods as implemented in the Hyperchem[14] software. The best five geometries obtained from the conformational analysis were then used as input structures for the DFT calculations. The conformation obtained with the lowest energy (i.e., the most stable conformation) has then been considered for the relative (ΔE) analysis as reported in the paper. The DFT Geometry optimizations were performed using the B-P 86 functional.[15] The electronic configuration of the atoms was described by a triple-zeta basis set augmented by a polarization function (TURBOMOLE basis set TZVP).[16] The resolution of identity (RI),[17] along with the multipole accelerated resolution of identity (marij)[18] approximations was employed for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations.

4.2. General methods

All the solvents were purified according to the literature procedures[19] before use. 60% dispersion of sodium hydride in mineral oil was used for O-alkylation reactions. Thin layer chromatography was performed on E. Merck pre-coated 60 F_{254} plates and the spots were rendered visible either by shining UV light or by charring the plates with concd H_2SO_4. Work up implies washing of the organic layer successively with water, dilute HCl ($\sim$2%), water, saturated sodium bicarbonate solution, water followed by brine. Column chromatographic separations were carried out on silica gel (60–120 mesh or 230–400 mesh) with solvent system as mentioned in individual procedures. The compounds previously reported in the literature were characterized by comparison of their melting points and/or ^{1}H NMR spectra with reported data. All the asymmetrically substituted racemic *myo*-inositol derivatives (numbered with the prefix *rac*-) are represented in schemes by one of the enantiomers without numbering of the inositol carbon atoms.

*4.2.1. 2-O-(4-Methoxy benzyl)-4,6-di-O-benzyl-myo-inositol-1,3,5-orthobenzoate (**4**).* To a solution of **2** (8.93 g, 20.00 mmol) in dry DMF (100 mL) sodium hydride (0.96 g, 24.00 mmol) was added and stirred for 10 min. *p*-Methoxybenzyl chloride (3.00 mL, 22.00 mmol) was then added drop-wise and the reaction mixture stirred for 4 h. Excess of sodium hydride was quenched by the

addition of cold water. The reaction mixture was concentrated under reduced pressure to get a gum, which was worked up with ethyl acetate; the organic extract was dried over anhyd sodium sulfate. The solvent was removed under reduced pressure to afford a gummy residue, which was purified by column chromatography (eluent: 20% ethyl acetate/light petroleum) to obtain **4** as a colorless solid (10.92 g, 96%). TLC R_f=0.5 (20% ethyl acetate/light petroleum); mp 89.4–92.0 °C (crystals from a hot mixture of 30% ethyl acetate/light petroleum); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.60–7.68 (m, 2H, Ar H), 7.17–7.38 (m, 15H, Ar H), 6.79–6.86 (m, 2H, Ar H), 4.40–4.70 (m, 11H, 3× CH_2, and 5 Ins H), 4.10 (t, 1H, J=1.5 Hz), 3.76 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 159.2 (C_{arom}), 137.6 (C_{arom}), 137.2 (C_{arom}), 130.0 (C_{arom}), 129.7 (C_{arom}), 129.3 (C_{arom}), 128.3 (C_{arom}), 127.9 (C_{arom}), 127.7 (C_{arom}), 127.5 (C_{arom}), 125.4 (C_{arom}), 113.7 (C_{arom}), 107.8 ($PhCO_3$), 74.0 (Ins C), 71.9 (Ins C), 71.5 (CH_2), 70.7 (CH_2), 69.0 (Ins C), 65.5 (Ins C), 55.1 (CH_3) ppm; elemental analysis calcd (%) for $C_{35}H_{34}O_7$ (566.64): C 74.19, H 6.05; found: C 74.11, H 6.43%.

*4.2.2. 1,3-O-Benzylidene-2-O-(4-methoxy benzyl)-4,6-di-O-benzyl myo-inositol (**6**).* DIBAL-H (1 M solution) in toluene (15.40 mL, 15.40 mmol) was added drop-wise over a period of 15 min to a solution of **4** (3.96 g, 7.00 mmol) in dry dichloromethane (60 mL) at 0 °C and stirred at room temperature for 2.5 h. The reaction mixture was poured into a stirred solution of sodium potassium tartrate (42 g in 70 mL water) and saturated ammonium chloride (70 mL) and stirred for 12 h. The mixture was extracted with dichloromethane (2×100 mL), washed with brine and dried over anhyd sodium sulfate. The solvent was removed under reduced pressure to obtain a gummy residue, which was purified by column chromatography (eluent: 25% ethyl acetate/light petroleum) to afford **6** as a colorless solid (3.78 g, 95%). R_f=0.4 (25% ethyl acetate/light petroleum); mp 122.8–124.6 °C (crystals from CH_2Cl_2); IR (neat): ν_{max}/cm^{-1} 3330–3510. ^{1}H NMR (CD_2Cl_2, 200 MHz): δ 7.42–7.51 (m, 2H, Ar H), 7.24–7.45 (m, 15H, Ar H), 6.83–6.91 (m, 2H, Ar H), 5.68 (s, 1H, $PhCHO_2$), 4.66 (q, 4H, 2× CH_2, J=11.6 Hz), 4.59 (s, 2H, CH_2), 4.33 (d, 2H, Ins H, J=2.4 Hz), 3.94 (d, 2H, Ins H, J=8.2 Hz), 3.72–3.80 (m, 1H, Ins H), 3.75 (s, 3H, CH_3), 3.57 (t, 1H, J=2.4 Hz, Ins H), 2.54 (d, 1H, J=2.9 Hz, OH) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 159.7 (C_{arom}), 138.8 (C_{arom}), 138.1 (C_{arom}), 130.4 (C_{arom}), 129.7 (C_{arom}), 128.8 (C_{arom}), 128.4 (C_{arom}), 126.8 (C_{arom}), 114.1 (C_{arom}), 92.8 ($PhCHO_2$), 82.1 (Ins C), 73.9 (Ins C), 72.0 (CH_2), 70.8 (CH_2), 68.5 (Ins C), 55.5 (CH_3) ppm; elemental analysis calcd (%) for $C_{35}H_{36}O_7$ (568.66): C 73.92, H 6.38; found: C 73.94, H 6.12%.

*4.2.3. O-((1R,3s,5S,6R,7R,8S,9R)-6,8-bis(benzyloxy)-9-((4-methoxybenzyl)oxy)-3-phenyl-2,4-dioxabicyclo[3.3.1]nonan-7-yl) S-methyl carbonodithioate (**8**).* To a cooled (0 °C) solution of the alcohol **6** (1.14 g, 2.00 mmol) in dry THF (10 mL), sodium hydride (0.40 g, 10.00 mmol) was added and stirred at ambient temperature for 30 min. Carbon disulfide (1.80 mL, 30.00 mmol) was added to the reaction mixture and refluxed for 1 h. The reaction mixture was allowed to cool to room temperature; methyl iodide (0.60 mL, 10.00 mmol) was added and stirred for 16 h. The reaction mixture was diluted with ethanol (4 mL), water (8 mL), and extracted with ethyl acetate. The organic layer was washed with saturated ammonium chloride solution followed by brine and dried over anhyd sodium sulfate. The gummy residue obtained after evaporation of the solvent was purified by column chromatography (eluent: 15% ethyl acetate/light petroleum) to obtain **8** as a colorless solid (1.29 g, 98%). R_f=0.4 (15% ethyl acetate/light petroleum); mp 93–93.8 °C (crystals from a hot mixture of 10% ethyl acetate in light petroleum); IR ($CHCl_3$): ν_{max}/cm^{-1} 1455, 1377. ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 7.20–7.48 (m, 17H, Ar H), 6.82–6.89 (m, 2H, Ar H), 6.20 (t, 1H, Ins H, J=7.5 Hz), 5.75 (s, 1H, $PhCHO_2$), 4.60 (s, 2H, CH_2), 4.58 (q, 4H, 2× CH_2, J=11.9 Hz), 4.38 (d, 2H, Ins H, J=2.3 Hz), 4.10 (d, 2H, Ins H, J=7.5 Hz), 3.76 (s, 3H, OCH_3), 3.72–3.74 (m, 1H, Ins H), 2.51 (s, 3H, SCH_3) ppm; ^{13}C NMR (CD_2Cl_2, 50.3 MHz): δ 216.0 (C=S), 159.7 (C_{arom}), 138.7 (C_{arom}), 137.6 (C_{arom}), 130.4 (C_{arom}), 129.7 (C_{arom}), 128.7 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 126.7 (C_{arom}), 114.1 (C_{arom}), 92.9 ($PhCO_2$), 82.4 (Ins C), 79.7 (Ins C), 73.8 (Ins C), 71.8 (CH_2), 70.9 (CH_2), 68.4 (Ins C), 55.5 (OCH_3), 19.5 (SCH_3) ppm; elemental analysis calcd (%) for $C_{37}H_{38}O_7S_2$ (658.82): C 67.45, H 5.81, S 9.73; found C 67.51, H 5.98, S 9.67%.

*4.2.4. S-Methyl O-((1R,3r,5S,6R,7R,8S,9R)-6,8,9-tris(benzyloxy)-3-phenyl-2,4-dioxabicyclo[3.3.1]nonan-7-yl) carbonodithioate (**10**, epimer of **7**).* The solid xanthate **7** (0.20 g, 0.32 mmol) was heated at 120 °C (mp of **7** is 112–114 °C lit.[11]) under argon for 12 h and the products were separated by column chromatography (eluent: 5–7% ethyl acetate in light petroleum) to afford **10** (0.14 g, 70%; R_f=0.4 in 10% ethyl acetate/light petroleum) and **13**[11] as gums (0.04 g, 25%; R_f=0.3 in 40% ethyl acetate/light petroleum). Data for **10**: ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 7.45–7.58 (m, 2H, Ar H), 7.10–7.40 (m, 18H, Ar H), 6.45 (s, 1H, $PhCHO_2$), 6.06 (br s, 1H, Ins H), 4.69 (s, 2H, CH_2), 4.69 (q, 4H, 2× CH_2, J=12.1 Hz), 4.50–4.64 (m, 2H, Ins H), 4.39 (t, 1H, Ins H, J=1.4 Hz), 4.05 (dd, 2H, Ins H, J_1=1.3 Hz and J_2=3.5 Hz), 2.41 (s, 3H, CH_3) ppm; ^{13}C NMR (CD_2Cl_2, 125.76 MHz): δ 216.2 (C=S), 139.2 (C_{arom}), 138.3 (C_{arom}), 138.2 (C_{arom}), 129.1 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.31 (C_{arom}), 128.29 (C_{arom}), 128.2 (C_{arom}), 128.1 (C_{arom}), 128.0 (C_{arom}), 127.4 (C_{arom}), 92.7 ($PhCO_2$), 80.0 (Ins C), 78.6 (Ins C), 72.8 (CH_2), 72.4 (Ins C), 71.0 (CH_2), 70.5 (Ins C), 19.7 (CH_3) ppm; elemental analysis calcd (%) for $C_{36}H_{36}O_6S_2$ (628.80): C 68.76, H 5.77; found C 68.51, H 6.03%.

4.2.5. Attempted epimerization of xanthate 7 in the presence of solvents. In toluene: A solution of the xanthate **7** (0.10 g, 0.16 mmol) in dry toluene (2 mL) was refluxed for 24 h in an atmosphere of argon. The solvent was removed under reduced pressure to obtain **7** (0.10 g, 100%) as a solid. The same result was obtained on repeating the reaction (for 12 h) in the presence of water (0.1 mL).

In DMF: a solution of the xanthate **7** (0.10 g, 0.16 mmol) in dry DMF (2 mL) was heated at 130 °C for 24 h in an atmosphere of argon. The solvent was removed under reduced pressure and the residue column chromatographed to obtain **7** (0.095 g, 95%) as a solid. The same result was obtained on repeating the reaction (for 12 h) in the presence of water (0.1 mL).

*4.2.6. O-((1R,3r,5S,6R,7R,8S,9R)-6,8-bis(benzyloxy)-9-((4-methoxybenzyl)oxy)-3-phenyl-2,4-dioxabicyclo[3.3.1]nonan-7-yl) S-methyl carbonodithioate (**11**, epimer of **8**).* The solid xanthate **8** (0.20 g, 0.30 mmol) was heated at 120 °C (mp of **8** is 93–93.8 °C) under argon for 30 h and the products separated by column chromatography (eluent: 10% ethyl acetate in light petroleum) to afford **11** as gum (0.14 g, 72%; R_f=0.6 in 20% ethyl acetate/light petroleum) and **14** as a solid (0.04 g, 24%; R_f=0.3 in 40% ethyl acetate/light petroleum). The gummy xanthate **11** was stored under *n*-pentane at −20 °C for 12 h when it turned into a colorless solid. Mp 77–79.2 °C (crystals from a hot mixture of 10% ethyl acetate in light petroleum); ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 7.45–7.60 (m, 2H, Ar H), 7.16–7.43 (m, 15H, Ar H), 6.75–6.88 (m, 2H, Ar H), 6.44 (s, 1H, $PhCHO_2$), 6.06 (br s, 1H, Ins H), 4.69 (q, 4H, 2× CH_2, J=11.9 Hz), 4.63 (s, 2H, CH_2), 4.49–4.55 (m, 2H, Ins H), 4.38 (t, 1H, Ins H, J=1.3 Hz), 4.01–4.09 (m, 2H, Ins H), 3.75 (s, 3H, OCH_3), 2.42 (s, 3H, SCH_3) ppm; ^{13}C NMR (CD_2Cl_2, 125.76 MHz): δ 216.2 (C=S), 159.8 (C_{arom}), 139.2 (C_{arom}), 138.3 (C_{arom}), 130.2 (C_{arom}), 130.0 (C_{arom}), 129.1 (C_{arom}), 128.7 (C_{arom}), 128.3 (C_{arom}), 128.1 (C_{arom}), 128.0 (C_{arom}), 127.4 (C_{arom}), 114.1 (C_{arom}), 92.7 ($PhCO_2$), 80.0 (Ins C), 78.5 (Ins C), 72.7 (CH_2), 72.4 (Ins C), 70.5 (CH_2), 69.9 (Ins C), 55.5 (OCH_3), 19.6 (SCH_3) ppm; elemental analysis calcd (%) for $C_{37}H_{38}O_7S_2$ (658.82): C 67.45, H 5.81; found C

67.51, H 5.98%. Data for **14**: mp 83.3–83.6 °C (crystals from CH_2Cl_2); IR ($CHCl_3$): ν_{max}/cm^{-1} 3300–3500. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.24–7.40 (m, 12H, Ar H), 6.87–6.95 (m, 2H, Ar H), 6.15 (t, 1H, Ins H, J=9.3 Hz), 4.75 (s, 2H, CH_2), 4.67 (q, 4H, 2× CH_2, J=11.2 Hz), 4.01 (t, 1H, Ins H, J=2.7 Hz), 3.87–3.97 (m, 2H, Ins H), 3.83 (s, 3H, OCH_3), 3.65 (dd, 2H, Ins H, J_1=9.6 Hz, J_2=2.6 Hz), 2.60 (s, 3H, SCH_3), 2.36 (br s, 2H, 2× OH) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 215.7 (C═S), 159.2 (C_{arom}), 137.7 (C_{arom}), 130.4 (C_{arom}), 129.6 (C_{arom}), 128.3 (C_{arom}), 128.1 (C_{arom}), 127.8 (C_{arom}), 113.7 (C_{arom}), 83.6 (Ins C), 80.0 (Ins C), 78.3 (Ins C), 74.9 (CH_2), 74.8 (CH_2), 71.8 (Ins C), 55.1 (CH_3), 19.3 (CH_3) ppm; elemental analysis calcd (%) for $C_{30}H_{34}O_7S_2$ (570.72): C 63.13, H 6.00; found C 63.09, H 6.11%.

*4.2.7. S-Methyl O-((1R,3r,5S,6R,7S,8S,9R)-6,8,9-tris(benzyloxy)-3-phenyl-2,4-dioxabicyclo[3.3.1]nonan-7-yl) carbonodithioate (**12**, epimer of **9**).* The solid xanthate **9** (0.20 g, 0.32 mmol) was heated at 110 °C (mp of **9** is 100–102 °C lit.[11]) under argon for 12 h and the products separated by column chromatography (eluent: 5–7% ethyl acetate in light petroleum) to afford **12** (0.14 g, 72%; R_f=0.4 in 10% ethyl acetate/light petroleum) and **15** (0.04 g, 24%; R_f=0.3 in 40% ethyl acetate/light petroleum) as gums. Solid **12** could be obtained by storing the gummy **12** in *n*-pentane at −20 °C for 12 h. Data for **12**: mp 68.8–69.4 °C (crystals from a hot mixture of 5% ethyl acetate in light petroleum); ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.40–7.52 (m, 2H, Ar H), 7.22–7.40 (m, 18H, Ar H), 6.66 (t, 1H, Ins H, J=4.2 Hz), 6.42 (s, 1H, $PhCHO_2$), 4.66 (s, 2H, CH_2), 4.63 (q, 4H, 2× CH_2, J=11.9 Hz), 4.48–4.55 (m, 3H, Ins H), 4.30 (t, 2H, Ins H, J=4.2 Hz), 2.56 (s, 3H, CH_3) ppm; ^{13}C NMR (CD_2Cl_2, 125.76 MHz) δ 216.0 (C═S), 139.1 (C_{arom}), 138.8 (C_{arom}), 138.3 (C_{arom}), 129.5 (C_{arom}), 128.8 (C_{arom}), 128.65 (C_{arom}), 128.61 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 128.1 (C_{arom}), 128.0 (C_{arom}), 127.2 (C_{arom}), 93.3 ($PhCO_2$), 78.2 (Ins C), 77.6 (Ins C), 74.1 (CH_2), 72.9 (Ins C), 71.3 (CH_2), 69.9 (Ins C), 19.5 (CH_3) ppm; elemental analysis calcd (%) for $C_{36}H_{36}O_6S_2$ (628.80): C 68.76, H 5.77; found C 68.78, H 6.11%. Data for **15**: IR ($CHCl_3$): ν_{max}/cm^{-1} 3360–3550. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.25–7.45 (m, 15H, ArH), 6.88 (t, 1H, Ins H, J=2.65 Hz), 4.84 (s, 2H, CH_2), 4.68 (q, 4H, 2× CH_2, J=11.0 Hz), 4.12–4.20 (m, 1H, Ins H), 3.98 (dd, 2H, Ins H, J_1=2.7 Hz, J_2=10.1 Hz), 3.85 (dd, 2H, Ins H, J_1=2.8 Hz, J_2=10.1 Hz), 2.57 (s, 3H, SCH_3), 2.20–2.48 (br s, 2H, 2× OH) ppm; ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ 216.7 (C═S), 138.6 (C_{arom}), 137.3 (C_{arom}), 128.5 (C_{arom}), 128.4 (C_{arom}), 128.2 (C_{arom}), 128.0 (C_{arom}), 127.73 (C_{arom}), 127.68 (C_{arom}), 78.4 (Ins C), 77.4 (Ins C), 75.5 (CH_2), 74.9 (Ins C), 72.5 (CH_2), 70.8 (Ins C), 19.0 (CH_3) ppm; elemental analysis calcd (%) for $C_{29}H_{32}O_6S_2$ (540.69): C 64.42, H 5.97; found C 64.84, H 6.30%.

*4.2.8. Racemic-1-O-benzoyl-2-O-(4-methoxybenzyl)-3,5-dideoxy-4,6-di-O-benzyl myo-inositol (**17**).* To a solution of the xanthate **8** (1.05 g, 1.60 mmol) in dry toluene (10 mL), tri-*n*-butyltin hydride (0.70 mL, 2.50 mmol), and AIBN (0.02 g, 0.15 mmol) were added and heated at 100 °C for 1 h. The solvents were removed under reduced pressure and the residue obtained was purified by column chromatography (eluent: 15% ethyl acetate in light petroleum) to obtain **17** as a gum (0.82 g, 93%). R_f=0.4 (15% ethyl acetate/light petroleum); IR (neat): ν_{max}/cm^{-1} 1716. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.0–8.01 (m, 2H, Ar H), 7.09–7.63 (m, 15H, Ar H), 6.67–6.75 (m, 2H, Ar H), 5.11 (dd, 1H, Ins H, J=9.4, 3.0 Hz), 4.61–4.65 (m, 2H, CH_2), 4.52–4.56 (m, 2H, CH_2), 4.44 (s, 2H, CH_2), 3.95–4.13 (m, 2H, Ins H), 3.79–3.90 (m, 1H, Ins H), 3.74 (s, 3H, CH_3), 2.49–2.64 (m, 1H, Ins H), 2.27–2.43 (m, 1H, Ins H), 1.45–1.7 (m, 2H, Ins H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 165.9 (C═O), 159.0 (C_{arom}), 138.5 (C_{arom}), 132.9 (C_{arom}), 130.3 (C_{arom}), 129.7 (C_{arom}), 129.1 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 127.6 (C_{arom}), 127.5 (C_{arom}), 127.4 (C_{arom}), 113.6 (C_{arom}), 77.4 (Ins C), 74.0 (Ins C), 73.7 (Ins C), 71.9 (CH_2), 71.7 (CH_2), 71.4 (Ins C), 70.6 (CH_2), 55.1 (CH_3), 36.0 (Ins CH_2), 34.2 (Ins CH_2) ppm; elemental analysis calcd (%) for $C_{35}H_{36}O_6$ (552.66′) C 76.06, H 6.57; found C 75.66, H 6.48%.

*4.2.9. 1,3-O-Benzylidene-2,4,6-tri-O-benzyl-5-deoxy myo-inositol (**18**). Method A*: To a solution of the xanthate **10** (0.09 g, 0.14 mmol) in dry toluene (4 mL), tri-*n*-butyltin hydride (0.20 mL, 0.50 mmol), and AIBN (0.01 g) were added and heated at 100 °C for 1 h. The solvents were removed under reduced pressure and the residue obtained was purified by column chromatography (eluent: 7% ethyl acetate in light petroleum) to obtain **18** as a gum (0.06 g, 82%). The gummy compound **18** was stored under *n*-pentane at −20 °C for 12 h to afford a colorless solid. R_f=0.4 (10% ethyl acetate/light petroleum); mp 69.5–72.2 °C (crystals from a hot mixture of 5% ethyl acetate in light petroleum); ^1H NMR (CD_2Cl_2, 500 MHz) δ 7.20–7.50 (m, 20H, Ar H), 6.47 (s, 1H, $PhCHO_2$), 4.66 (s, 2H, CH_2), 4.55 (q, 4H, 2× CH_2, J=11.9 Hz), 4.52 (d, 2H, Ins H, J=3.3 Hz), 4.46–4.48 (m, 1H, Ins H), 3.91–3.97 (m, 2H, Ins H), 2.27–2.38 (m, 1H, Ins H), 2.05–2.11 (m, 1H, Ins H) ppm; ^{13}C NMR (CD_2Cl_2, 125.76 MHz) δ 139.8 (C_{arom}), 139.1 (C_{arom}), 138.6 (C_{arom}), 129.1 (C_{arom}), 128.7 (C_{arom}), 128.6 (C_{arom}), 128.5 (C_{arom}), 128.3 (C_{arom}), 128.0 (C_{arom}), 127.9 (C_{arom}), 127.8 (C_{arom}), 126.9 (C_{arom}), 92.8 ($PhCO_2$), 78.1 (Ins C), 72.9 (Ins C), 71.7 (CH_2), 70.8 (CH_2), 70.6 (Ins C), 24.2 (Ins CH_2) ppm; elemental analysis calcd (%) for $C_{34}H_{34}O_5$ (522.63): C 78.14, H 6.56; found C 77.83, H 6.71%.

Method B: To a solution of the xanthate **12** (0.10 g, 0.16 mmol) in dry toluene (4 mL), tri-*n*-butyltin hydride (0.20 mL, 0.50 mmol), and AIBN (0.01 g) were added and the reaction was carried out as in method A to afford **18** as a gum (0.07 g, 84%).

*4.2.10. 1,3-O-Benzylidene-2-O-(4-methoxybenzyl)-4,6-di-O-benzyl-5-deoxy myo-inositol (**19**).* To a solution of the xanthate **11** (0.10 g, 0.15 mmol) in dry toluene (4 mL), tri-*n*-butyltin hydride (0.20 mL, 0.50 mmol), and AIBN (0.01 g) were added and heated at 100 °C for 1 h. The solvents were removed under reduced pressure and the residue obtained was purified by column chromatography (eluent: 10% ethyl acetate in light petroleum) to obtain **19** as a colorless solid (0.07 g, 85%). R_f=0.6 (20% ethyl acetate/light petroleum); mp 99.5–101.2 °C (crystals from a hot mixture of 10% ethyl acetate in light petroleum); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.24–7.50 (m, 17H, Ar H), 6.80–6.90 (m, 2H, Ar H), 6.52 (s, 1H, $PhCHO_2$), 4.61 (s, 2H, CH_2), 4.55 (q, 4H, 2× CH_2, J=11.9 Hz), 4.51–4.58 (m, 3H, Ins H), 3.95–4.01 (m, 2H, Ins H), 3.78 (s, 3H, OCH_3), 2.30–3.42 (m, 1H, Ins H), 2.03–2.30 (m, 1H, Ins H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 159.2 (C_{arom}), 139.0 (C_{arom}), 138.5 (C_{arom}), 130.0 (C_{arom}), 129.6 (C_{arom}), 128.9 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 127.4 (C_{arom}), 126.5 (C_{arom}), 113.8 (C_{arom}), 92.5 ($PhCO_2$), 77.4 (Ins C), 72.7 (Ins C), 71.1 (CH_2), 70.0 (CH_2), 69.5 (Ins C), 55.2 (CH_3), 23.8 (Ins CH_2) ppm; elemental analysis calcd (%) for $C_{35}H_{36}O_6$ (552.66): C 76.06, H 6.57; found C 75.73, H 6.34%.

4.3. X-ray crystallography

Single-crystal X-ray structures were determined for crystals of **8**, **11**, **12**, and **19**. All the crystals were stable at room temperature and the intensity data measurements were carried out at room temperature (297 K) on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo Kα=0.71073 Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with a ω scan width of 0.3° at four different settings of φ (0, 90, 180, and 270°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2θ) fixed at −28°. X-ray data collection was monitored by the SMART program (Bruker, 2003).[20] A semi-empirical absorption correction (multi-scan) based on symmetry equivalent reflections was applied using the SADABS program (Bruker, 2003).[20] Lattice parameters were determined

Table 1
Summary of crystal data, data collection, structure solution and refinement details

	8	**11**	**12**	**19**
Chemical formula	$C_{37}H_{38}O_7S_2$	$C_{37}H_{38}O_7S_2$	$2(C_{36}H_{36}O_6S_2)0.5(C_6H_{14})$	$C_{35}H_{36}O_6$
M_r	658.79	658.79	628.77	552.64
Temp/K	297(2) K	297(2) K	297(2) K	297(2)
Morphology	Plate	Plate	Plate	Plate
Crystal size	0.41×0.22×0.08	0.16×0.12×0.11	0.21×0.17×0.08	0.47×0.17×0.07
Crystal system	Triclinic	Monoclinic	Triclinic	Triclinic
Space group	*P*−1	$P2_1/c$	*P*−1	*P*−1
a (Å)	12.1038(12)	15.220(2)	13.968(8)	10.3094(12)
b (Å)	12.1371(12)	26.472(4)	15.223(9)	10.3163(12)
c (Å)	12.8640(13)	8.8065(13)	18.645(11)	14.0511(16)
α (°)	82.429(2)	90	79.963(11)	94.350(2)
β (°)	77.934(2)	104.498(10)	71.362(10)	92.309(2)
γ (°)	64.037(2)	90	67.525(9)	97.547(2)
V (Å^3)	1659.8(3)	3435.2(9)	3465(4)	1475.3(3)
Z	2	4	2	2
D_{calcd} (g cm^{-3})	1.318	1.274	1.247	1.244
μ (mm^{-1})	0.210	0.203	0.198	0.084
F(000)	696	1392	1378	588
Ab.correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan
T_{min}	0.9199	0.9685	0.9604	0.9617
T_{max}	0.9828	0.9775	0.9841	0.9946
θ_{max} (°)	25.00	25.00	25.00	25.00
h, *k*, *l* (min, max)	(−14,14), (−14,14), (−15,15)	(−18,18), (−31,31), (−10,10)	(−16,16), (−18,18), (−22,22)	(−12,12), (−12,12), (−16,16)
Reflns collected	16,279	32,897	33,588	14,376
Unique reflns	5833	6045	12,169	5181
Observed reflns	4564	4898	8454	3672
R_{int}	0.0246	0.0282	0.0428	0.0293
No. of parameters	417	417	823	371
GOF	1.020	1.041	1.156	1.019
$R_1[I>2\sigma(I)]$	0.0415	0.0614	0.0927	0.0523
$wR_2[I>2\sigma(I)]$	0.0965	0.1270	0.2014	0.1175
R_1_all data	0.0558	0.0614	0.1301	0.0785
wR_2_all data	0.1065	0.1270	0.2178	0.1297
$\Delta\rho_{max}$,$\Delta\rho_{min}$(eÅ^{-3})	0.23,−0.22	0.28,−0.18	0.47,−0.50	0.28, −0.19
CCDC No.	817427	817424	817425	817426

from least-squares analysis of all reflections. The structures were solved by direct methods and refined by full matrix least squares, based on F^2, using SHELX-97 software package.[21] All the hydrogen atoms were placed in geometrically idealized positions and refined isotropically. Molecular and packing diagrams were generated using ORTEP-32[22] and Mercury CSD 2.3,[23] respectively. Geometrical calculations were performed using SHELXTL (Bruker, 2003) and PLATON.[24] The crystallographic data are summarized in Table 1. CCDC-817424 to CCDC-817427 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

Electronic Supplementary Data (ESD) available: spectral data for all new compounds, crystallographic and geometry optimized colored diagrams for compounds **7**–**9**, **11**, **12** and **19** and Cartesian co-ordinates (DFT data) for compounds **7**–**12**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.07.044.

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