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Introduction

Myo-inositol has attracted considerable scientific attention primarily due to the involvement of phosphoinositols in various cellular signallings.¹ Phospholipase C mediated hydrolysis of the lipid, phosphatidylinositol-4,5-bisphosphate [PI(4,5)P₂], produces *D*-*myo*-inositol-1,4,5-trisphosphate (IP₃), which mediates calcium release from the endoplasmic reticulum through the activation of IP₃ receptor.^{1e,2} IP₃ will then be metabolized and finally recycled by the sequential action of several kinases and phosphatases resulting in the formation of several inositol phosphates (IPn), pyrophosphates (PPIPn) and phosphatidyl inositol phosphate is involved in Akt signalling,³ capacitative

Chemoselective alcoholysis/acetolysis of *trans*-ketals over *cis*-ketals and its application in the total synthesis of the cellular second messenger, *D-myo*-inositol-1,4,5-trisphosphate†

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The involvement of natural phosphoinositols in various cellular signalling processes and the use of synthetic inositol derivatives in catalysis, supramolecular chemistry, natural product synthesis *etc.* gave momentum to *myo*-inositol chemistry. The presence of six secondary hydroxyl groups necessitates efficient protection–deprotection strategies for the synthesis of inositol derivatives. An important strategy for the initial protection of *myo*-inositol is the di-ketalization, which gives a mixture of three diketals, each having both *cis*-fused and *trans*-fused ketals. It is important to have methodologies either to selectively hydrolyze one of the two ketals or to convert one of the two acid labile ketals to an orthogonal base labile protecting group. By exploiting the difference in strain between *trans*-ketals and *cis*-ketals, we developed two operationally simple, high yielding methodologies for the chemoselective hydrolysis/ acetolysis of *trans*-ketals (both isopropylidene and cyclohexylidene) of inositols, leaving the *cis*-ketal undisturbed, using cheap and easily preparable H₂SO₄-silica as the catalyst. Also, terminal ketal moieties of carbohydrates and acyclic polyols could be selectively hydrolyzed/acetolyzed leaving the internal ketals intact. The use of methanol as the solvent leads to chemoselective alcoholysis but the use of DCM and acetic anhydride leads to chemoselective acetolysis. Applying this methodology, a short synthesis of *p-myo*-inositol-1,4,5-trisphosphate has been achieved.

calcium influx⁴ and cell regulation.⁵ Also, pyrophosphorylated inositols are thought to be involved in several biological processes.⁶ At least 26 IPns, 8 PIPns and several glycosylated inositols are known to occur naturally (Fig. 1).⁷ Though the involvement of some of these phosphoinositols in various biological processes has been established,^{3–6} a clear picture of the



Fig. 1 Representative members of various phosphoinositols.

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[†]Electronic supplementary information (ESI) available: ¹H NMR, COSY, ¹³C NMR, DEPT and HMQC spectra of all new compounds, ¹H NMR and ³¹P NMR spectra of **35**, **36** and **5** and crystal structure of **24a**. CCDC 925397, 925398 and 925399. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c30b40789f

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Paper

cellular role played by many phosphoinositols is lacking.^{1d,f} The scarcity of these natural products and the necessity of large quantities of these substances and their unnatural analogues for biological studies demand the chemical synthesis of phosphoinositols⁸ and their analogues.⁹ Furthermore, the use of synthetic inositol derivatives in catalysis,¹⁰ supramolecular chemistry,¹¹ natural product synthesis¹² *etc.* gives additional impetus to the inositol chemistry.

Owing to the presence of six secondary hydroxyl groups of similar reactivities, synthesis of inositol derivatives necessitates efficient strategies for the protection and deprotection of specific hydroxyl groups. Hence, developing methodologies for selective protection and deprotection¹³ of inositol hydroxyl groups is an important area of research. Also, for the efficient synthesis of target products from polyols such as carbohydrates, inositol *etc.*, specific hydroxyl groups need to be selectively functionalized in a specific order in the synthetic sequence. For such regiotemporal control, it is important to use orthogonal protecting groups, so that any of these protecting groups (PGs) can be selectively removed without disturbing the others and hence the required hydroxyl group can be exposed. Acid labile ketals and base labile acetates constitute a pair of orthogonal protecting groups for hydroxyl groups.

One of the important strategies for the initial protection of myo-inositol is acid catalyzed di-ketalization,¹⁴ which gives a mixture of three diketals, each of which has a cis fused and a trans fused ketal moiety (Scheme 1).¹⁵ Both isopropylidene and cyclohexylidene ketals are used frequently. These diketals have been used in phosphoinositol synthesis,16 natural product synthesis^{12,16d} and the synthesis of myo-inositol based supramolecular entities.¹⁷ Though di-ketalization is an important early protection of inositol, protection of four hydroxyl groups with an acid labile ketal moiety is often disadvantageous (non-orthogonal) for further synthetic manipulations. Thus, it is important to have methodologies either to selectively hydrolyze one of the two ketals or to convert one of the two acid labile ketals to an orthogonal base labile PG (e.g. ester). Usually such transformations are done in two steps, the acid catalyzed cleavage of ketal to the diol followed by its base catalyzed esterification.^{12d,18} We herein report two operationally simple methodologies for the chemoselective alcoholysis/ acetolysis (one step conversion of ketal to diacetate) of transketals without disturbing the *cis*-ketals, using cheap and easily preparable H₂SO₄-silica as the catalyst under ambient conditions. Also, we illustrate the efficiency of this methodology by a short synthesis of the cellular second messenger, D-myoinositol-1,4,5-trisphosphate (IP₃).



Scheme 1 Di-ketalization of myo-inositol.

It has been known that the ketals of *anti*-diols are more sterically strained than ketals of the *syn*-diols.¹⁹ This difference in energy has been exploited in the selective cleavage of the *trans*-acetonides of 1,3-diols.²⁰ Also selective cleavage of *trans*-acetonides in the presence of *cis* acetonides has been reported in *myo*-inositol derivatives using PTSA,²¹ acetyl chloride in methanol.^{16d} However, these methods are low yielding and less selective.^{21b} This is often due to the use of homogeneous catalysts which warrants workup to remove these acidic impurities. At times, lengthy workup leads to complete non-selective deprotection also. This limitation can be circumvented by the use of a solid supported catalyst which can be removed rapidly after the reaction by just a simple filtration.

Results and discussion

Recently, H₂SO₄-silica has gained attention as a mildly acidic heterogeneous catalyst for various transformations.²² We have recently demonstrated the utility of H₂SO₄-silica as an efficient catalyst for the ketalization and orthoesterification of myoinositol.²³ This prompted us to use this catalyst for selective deprotection of *trans* ketals. In order to test the efficiency of H₂SO₄-silica in ketal cleavage, (±)-1,2:5,6-di-O-isopropylidene*myo*-inositol (9) was treated with a catalytic amount of H_2SO_4 silica in MeOH at rt. To our satisfaction, the tetrol 15 was obtained in very good yield as a result of the selective deprotection of the trans-ketal (Table 1). Similarly, the trans-isopropylidene group of (±)-1,2:4,5-di-O-isopropylidene-myo-inositol (10) and (±)-1,2:3,4-di-O-isopropylidene-myo-inositol (11) could be selectively cleaved to get the tetrol 15 in good yields under these conditions. No appreciable amount of *cis*-ketal deprotection was observed in any of these diketals. A change of the solvent from methanol to ethanol slowed down the reaction and it took a longer time for complete reaction. On the other hand, the reaction was not facile in aprotic solvents like DCM as anticipated.

Our next target was to check the tolerability of different protecting groups under the reaction conditions. Thus various derivatives of diketals **9** and **10** were treated with H_2SO_4 -silica in methanol (Table 1). It was found that various common protecting groups such as benzyl ethers, PMB ethers, methyl ethers, esters and sulfonates tolerate the deprotection conditions. A remarkable selectivity for the *trans*-ketal was observed in the case of benzyl ethers, PMB ethers, esters and sulfonates. However, in the case of methyl ether derivatives of **9** and **10**, there was no selectivity and this resulted in complete deprotection of both *cis*- and *trans*-ketals. In general, the benzyl and PMB ether derivatives gave better yields than ester derivatives. Also, derivatives of **10** gave better yields than derivatives of **9**, presumably due to the difference in the strain.

Interestingly, treatment of 1,2:3,4:5,6-tri-*O*-isopropylidene-D-*chiro*-inositol (**17**) with H₂SO₄-silica in MeOH resulted in selective cleavage of only the *trans*-ketal giving the diketal **18** in 90% yield. Compound **18** was characterized by solving its crystal structure using single crystal XRD. Fig. 2 shows the

 Table 1
 Selective deprotection of trans-ketals over cis-ketals of inositol derivatives^a

Reactant		\mathbb{R}^1	R^2	Product	\mathbb{R}^1	R^2		Yield
	9 ⁴¹ 9a ²⁹ 9b ²⁹	H Bn Bz	H Bn Bz		$15^{43} \\ 15a^{30} \\ 15b^{16d}$	H Bn Bz	H Bn Bz	76 78 72
	10 ⁴¹ 10a ²⁹ 10b ²⁹ 10c ³¹	H Bn PMB Ts	H Bn PMB H	R ² O ^W OH OH	15 ⁴³ 16a ²⁵ 16b ³² 16c	H Bn PMB Ts	H Bn PMB H	74 81 86 70
	11 ⁴⁵	-	-	о он	15 ⁴³	-	-	75
	17 ³³	_	_		18 ³³	_	_	90
	19 ³⁴	_	_	но он	20 ³⁴	_	_	92
	12 ⁴² 12a	H Bz	H Bz		21 ⁴⁴ 21a	H Bz	H Bz	93 73
$R^{2}O^{W}$	13 ⁴² 13a ^{12a} 13b ³⁵ 13c	H Bn Me PMB	H Bn Me PMB	R O R ² O ^W OR ¹ OH	21 ⁴⁴ 22a ³⁶ 22b 22c	H Bn Me PMB	H Bn Me PMB	91 89 92 94
R $R \rightarrow 0$ $O \rightarrow O \rightarrow 0$ $H O = O \rightarrow O \rightarrow 0$ $H O = O \rightarrow O \rightarrow 0$	14 ⁴²	_	_		21 ⁴⁴	_	_	90

^{*a*} RR = -(CH₂)₅-. ^aH₂SO₄-silica, MeOH, rt.

ORTEP diagram of compound **18**. Also, the acyclic derivative 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (**19**) underwent selective hydrolysis of one of the terminal isopropylidene groups to give diol **20** in good yield. Diol **20** has been exploited for the total synthesis of several natural products.²⁴ These examples suggest that H_2SO_4 -silica is applicable not only for the deprotection of *trans*-ketal of *myo*-inositol but also that of other cyclitols and acyclic derivatives.

In order to check the generality of this *trans*-ketal deprotection, we have applied this methodology to various derivatives of cyclohexylidene ketals **12**, **13** and **14** (Scheme 1). In all these cases, the *trans*-cyclohexylidene group underwent cleavage selectively in excellent yields. Remarkably, in the case of cyclohexylidene ketals, the methyl derivatives also underwent selective hydrolysis of the *trans*-ketal in excellent yields. Also, it is noteworthy that the *trans*-cyclohexylidene cleavage is regiospecific and higher yielding than the isopropylidene cleavage. Even with prolonged reaction time, we could not observe any trace of product formed from *cis*-ketal cleavage in the case of cyclohexylidene ketals. Hence, it is advisable to use cyclohexylidene derivatives for better selectivity and better yields.

Having succeeded in the chemoselective hydrolysis of the *trans*-ketal without disturbing the *cis*-ketal, we were curious to know whether H_2SO_4 -silica can affect chemoselective acetolysis of the *trans*-ketal, the one step conversion of the *trans*-ketal to diacetates. Such a direct and one pot conversion of an acid

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Fig. 2 ORTEP diagram of compound 18

Selective acetolysis of trans-ketals over cis-ketals of inositol derivatives^a

labile protecting group to a base labile protecting group will be advantageous. In order to check this, the model diketal 9a was treated with H₂SO₄-silica in the presence of acetic anhydride in dry DCM. Gratifyingly, the trans-isopropylidene very selectively underwent acetolysis under this condition giving the diacetate 23a in very good yield (Table 2). Similar selectivity and reactivity was observed when dry CHCl₃ was used as the solvent. However, the use of wet DCM (not dried) resulted in the formation of a mixture of the expected diacetate 23a and diol 16a in poor vields.

In order to understand whether the observed acetolysis is a two-step reaction involving the initial acid catalyzed cleavage of the ketal followed by acid catalyzed acetylation, diketal 9a was treated with H_2SO_4 -silica alone (in the absence of Ac_2O) in dry DCM. Interestingly, no ketal cleavage was observed and the starting material could be recovered almost quantitatively suggesting that the reaction is not a stepwise process and the acetic anhydride has a role in the cleavage step itself. Similarly,



^{*a*} RR = $-(CH_2)_5$ -. ^{*a*}H₂SO₄-silica, Ac₂O, dry DCM, Ar, rt.



Scheme 2 Plausible mechanism for acetolysis.

when the diketal 9a was treated with Ac_2O alone (absence of H_2SO_4 -silica), there was no reaction. Also the reaction was not facile when normal silica was used in the place of H_2SO_4 -silica.

A plausible mechanism is given in Scheme 2. The catalyst H_2SO_4 -silica might activate the ketal **A** by protonation. The oxonium ion (I) on C–O bond cleavage would give oxocarbenium ion (II). The hydroxyl group would then undergo acid catalyzed acetylation and the nucleophilic attack by the liberated acetate ion on the oxocarbenium ion (III) would lead to acetylated hemiacetal (IV). The relatively more nucleophilic oxygen of this acetylated hemiacetal could attack another molecule of protonated acetic anhydride leading to the intermediate (V). Finally, the attack of the released acetic acid on the intermediate (VI) will generate a molecule of Ac_2O , acetone and the diacetate **B**. However, the possible hydrolysis of acetic anhydride by acidic silica to acetic acid and subsequent catalysis by this acid can also not be ruled out.

Next, we have studied the generality of this highly chemoselective acetolysis. Interestingly, the *trans*-ketal of several derivatives of both 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol (**9–9b**) and 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**10–10b**) underwent acetolysis in very good yields (Table 2). In general, benzoates and benzyl ether derivatives gave very good yields of the products. Interestingly, *chiro*-inositol triketal (**17**) having two *cis*-ketal and one *trans*-ketal also underwent selective acetolysis of the *trans*-ketal at 0 °C.

In order to investigate the utility of this methodology in selective acetolysis of other ketals, we have attempted the acetolysis of various di-O-cyclohexylidene derivatives of *myo*-inositol prepared from different parent diketals (12–14). In all these cases (Table 2, six examples), the *trans*-cyclohexylidene motif underwent acetolysis very selectively in high yields (Fig. 3). In general, the yields of acetolysis of cyclohexylidene derivatives were better than that of the isopropylidene



Fig. 3 ORTEP diagram of compound **26**.



Scheme 3 Acetolysis of terminal ketals of sugars and acyclic polyols. a: $\rm H_2SO_4-$ silica, Ac_2O, dry DCM, Ar, rt.

derivatives. Notably, the dimethyl derivative **13b** also underwent smooth selective acetolysis at rt.

Having established the generality of the *trans*-ketal acetolysis in inositol derivatives, we have explored the utility of this method in other ketal protected polyols (Scheme 3). In these cases also, we could find selectivity between different ketal groups. For instance, 1,2:3,4:5,6-tri-*O*-isopropyledene-*b*-mannitol (**19**) underwent acetolysis of both the terminal ketal selectively giving the tetra-acetate (**30**)⁴⁰ in very good yield. Similarly, di-isopropylidene-*b*-glucose (**28**)³⁹ underwent selective acetolysis of the terminal ketal giving the triacetate **29** in very good yield. When only one *cis*-ketal was present (**31**), its acetolysis took a very long time. Though *cis*-ketal underwent acetolysis after prolonged reaction, interestingly the acid labile BDA group (**33**) was stable to acetolysis even at reflux conditions.

Having established two simple, efficient and reliable methodologies for chemoselective discrimination of *trans*-ketals from *cis*-ketals, we decided to illustrate the applicability of these methodologies. We have used chemoselective hydrolysis for the total synthesis of the cellular second messenger D-*myo*-inositol 1,4,5-trisphosphate. Optically pure diketal (+)-10^{8c} was benzylated using NaH/BnBr to get the dibenzyl ether (+)-10a. The *trans*-isopropylidene group was selectively hydrolyzed using H₂SO₄-silica to get the diol (+)-16a. This intermediate



Scheme 4 Synthesis of *myo*-inositol 1,4,5-trisphosphate: (i) NaH, BnBr, DMF, 0 °C, 95%, (ii) H_2SO_4 silica, MeOH, 84%, (iii) dibenzyl-*N*,*N*-diisopropylphosphora-midate, DCM, rt and then *m*-CPBA at -78 °C, 79%, (iv) aq. HCl, 95%, (v) POCl₃ in DCM, (vi) Pd(OH)₂/C, cyclohexene, MeOH–H₂O, 60% for two steps.

has been used in the synthesis of many phosphoinositols.²⁵ The diol (+)-16a was phosphorylated to get the bis-phosphate (+)-35 in 79% yield. Deprotection of the remaining isopropylidene group using aqueous HCl in MeOH gave the diol (+)-36. Phosphorylation of the diol (+)-36 using POCl₃ as the phosphorylating agent gave an inseparable mixture of two compounds, whose ³¹P NMR revealed that one of the products is a cyclic phosphate (ESI). This mixture on debenzylation using transfer hydrogenolysis (Pd(OH)2/C in cyclohexene) vielded D-myo-inositol 1,4,5-trisphosphate [(+)-5] as the only product (Scheme 4).²⁶ This result suggests that the cyclic phosphate undergoes regioselective opening to form (+)-5 during the hydrogenolysis. To the best of our knowledge, this is the first example of the use of POCl₃ for the regioselective phosphorylation of inositol hydroxyl groups. The fact that the intermediate (+)-29 has been used for the synthesis of D-myo-inositol 2,4,5-trisphosphate and D-myo-inositol 1,2-cyclic-4,5-trisphosphate²⁷ shows the utility of our method for the synthesis of other inositol phosphates too.

Conclusions

In conclusion, we report two simple methodologies for chemoselective hydrolysis/acetolysis of trans-ketals in the presence of cis-ketals of cyclitols in good yields using the cheaply available and easily preparable H₂SO₄-silica as the catalyst. The use of a cheap and easy-to-prepare catalyst, milder reaction conditions, a simple work-up procedure, excellent chemoselectivity, high yield and wide applicability make these methods practically usable. Our one step conversion of a trans-ketal to diacetate is synthetically very important and economical, as such transformations are traditionally done in a two step process. Most of the common protecting groups tolerate the acetolysis condition. To the best of our knowledge, this is the first report on selective acetolysis between cis- and trans-ketals. We have illustrated the utility of this selective acetolysis not only in inositol chemistry but also in sugars and other acyclic polyols. In the case of sugars and acyclic polyols, the terminal ketal groups

could be selectively acetolyzed leaving the internal ketals untouched. We believe that these two methodologies will find applications in natural product synthesis, carbohydrate chemistry and phosphoinositol synthesis. The importance of the chemoselective hydrolysis has been demonstrated by the total synthesis of a representative phosphoinositol, *D-myo*-inositol 1,4,5-trisphosphate (5).

Experimental section

Materials and methods

Thin layer chromatography was carried out using pre-coated silica gel plates. Chromatograms were visualized under UV light and by dipping plates into either phosphomolybdic acid in MeOH or anisaldehyde in ethanol, followed by heating with a hot air gun. IR spectra were recorded by preparing KBr pellets, using an IR spectrometer. The ¹H NMR, COSY, DEPT, ¹³C NMR and HMQC spectra were recorded on a 500 MHz NMR spectrometer. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.0 ppm) or with the solvent reference relative to TMS employed as the internal standard (CDCl₃, δ 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). All NMR signals were assigned on the basis of ¹H NMR, ¹³C NMR, COSY and HMQC experiments. ¹³C spectra were recorded with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard. All NMR data were collected at 25 °C. Melting points were determined using a Stuart SMP30 melting point apparatus and are uncorrected. Elemental analyses were performed using an elemental analyzer. Flash column chromatography was performed using silica gel (200-400 mesh). H₂SO₄-silica was prepared as reported.^{22g} X-ray intensity data measurements of freshly grown crystals of 18 and 26 were carried out at 298 K on a single crystal X-ray diffractometer with graphite-monochromatized (MoK = 0.71073 Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with a scan width of 0.3° at different settings of φ (0°, 90° and 180°) keeping the sample to detector distance fixed at 40 mm and the detector position (2θ) fixed at 24°. The X-ray data collection was monitored by SMART program (Bruker, 2003). All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2003). SHELX-97 was used for structure solution and full matrix leastsquares refinement on F^2 . All the hydrogen atoms were placed in a geometrically idealized position (C-H = 0.95 Å for the phenyl and the acetylene H atoms, C-H = 0.99 Å for the methylene H-atoms and C-H = 1.0 Å for the central sugar ring H-atoms) and constrained to ride on their parent atoms $[U_{iso} (H) = 1.2U_{eq.} (C)]$. Molecular and packing diagrams were generated using ORTEP-3 and Mercury-3.0. Geometrical calculations were performed using SHELXTL (Bruker, 2003) and PLATON.

Crystal data of 18. CCDC 925397. C₁₂H₂₀O₆, *M* = 260.28, colorless hexagonal blocks, 0.2 × 0.15 × 0.1 mm³, orthorhombic, space group *P*2(1)2(1)2(1), *a* = 5.6971(2), *b* = 11.5145(3), *c* = 19.4201(5) Å, *V* = 1273.94(6) Å³, *Z* = 4, *T* = 293(2) K, 2θ_{max} = 50.00°, *D*_{calc} (g cm⁻³) = 1.355, *F*(000) = 560.0, μ (mm⁻¹) = 0.108, 5497 reflections collected, 2187 unique reflections (*R*_{int} = 0.0292), multi-scan absorption correction, *T*_{min} = 0.9786, *T*_{max} = 0.9892, the number of parameters = 163, the number of restraints = 0, GoF = 1.059, *R*₁ = 0.0285, w*R*₂ = 0.0823, *R* indices based on 2133 reflections with *I* > 2*σ*(*I*) (refinement on *F*²). $\Delta \rho_{max} = 0.195$, $\Delta \rho_{min} = -0.173$ (e Å⁻³).

Crystal data of 24a. CCDC 925399. $C_{27}H_{32}O_8$, M = 484.54, colorless needle, $0.25 \times 0.2 \times 0.15 \text{ mm}^3$, orthorhombic, space group *Pca* 21, a = 10.298(4), b = 11.735(5), c = 22.178(9) Å, V = 2680.2(18) Å³, Z = 4, T = 110(2) K, $2\theta_{\text{max}} = 46.00^{\circ}$, D_{calc} (g cm⁻³) = 1.193, F(000) = 1020.0, μ (mm⁻¹) = 0.088, 3318 reflections collected, 2798 unique reflections ($R_{\text{int}} = 0.1305$), multi-scan absorption correction, $T_{\text{min}} = 0.9801$, $T_{\text{max}} = 0.9965$, the number of parameters = 284, the number of restraints = 1, GoF = 1.196, $R_1 = 0.1150$, $wR_2 = 0.1117$, R indices based on 2798 reflections with $I > 2\sigma(I)$ (refinement on F^2). $\Delta \rho_{\text{max}} = 0.384$, $\Delta \rho_{\text{min}} = -0.237$ (e Å⁻³).

Crystal data of 26. CCDC 925398. C₂₀H₂₈O₁₀, *M* = 428.42, colorless needle, 0.2 × 0.15 × 0.1 mm³, monoclinic, space group *Cc*, *a* = 12.681(4), *b* = 18.138(5), *c* = 9.663(3) Å, *V* = 2208.1(11) Å³, *Z* = 4, *T* = 296(2) K, 2θ_{max} = 50.00°, *D*_{calc} (g cm⁻³) = 1.284, *F*(000) = 912.0, μ (mm⁻¹) = 0.104, 3430 reflections collected, 2729 unique reflections (*R*_{int} = 0.0246), multi-scan absorption correction, *T*_{min} = 0.9796, *T*_{max} = 0.9897, the number of parameters = 271, the number of restraints = 2, GoF = 1.031, *R*₁ = 0.0411, w*R*₂ = 0.1117, *R* indices based on 2744 reflections with *I* > 2 σ (*I*) (refinement on *F*²). $\Delta \rho_{max}$ = 0.211, $\Delta \rho_{min}$ = -0.141 (e Å⁻³).

Generalprocedureforselectivetrans-ketalhydrolysis.1mmol of diketal in MeOH (8 mL) treated with H_2SO_4 -silica (8 mg) at rt.When the TLC showed almost completion of the starting material, the reaction mixture wasquenched with solid NaHCO3, filtered, concentrated and purified by column chromatography.

General procedure for acetolysis of ketals. To a solution of diketal (1 mmol) and Ac_2O (3 mmol; if hydroxyl groups were in the starting material, an additional equivalent of Ac_2O per hydroxyl group was added) in dry DCM (5 mL), 25 mg of freshly prepared H_2SO_4 -silica was added. The reaction mixture was stirred at room temperature under an inert atmosphere and the reaction was monitored using TLC. When the starting material disappeared (2–6 h), the reaction mixture was filtered off and the organic layer was washed with a saturated aq. NaHCO₃ solution. The organic layer was dried over Na_2SO_4 and evaporated on a rotary evaporator. The crude product thus obtained was purified using flash column chromatography.

(±)-1,2:5,6-Di-O-cyclohexylidene-3,4-di-O-benzoyl-*myo*-inositol (12a). To a solution of compound 12 (500 mg, 1.47 mmol) in dry pyridine (10 mL), benzoylchloride (520 μ L, 4.42 mmol) and dimethylaminopyridine (9 mg, 0.07 mmol) (DMAP) were added at 0 °C. The reaction was monitored using TLC. After

completion of the reaction (1 h), pyridine was removed under reduced pressure. The crude material was dissolved in ethylacetate and washed with 1 M aq. citric acid. The organic layer was dried over Na₂SO₄ and concentrated. The crude was purified by column chromatography using 1:19 (v/v) ethylacetate and petroleum ether as an eluent to yield the colourless solid 12a (765 mg, 95%). MP: 187-189 °C. IR (KBr) 3057, 2977, 2909, 1728, 1454, 1328, 1236 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ : 8.01(d, J = 7.6 Hz, 2H), 7.97 (d, J = 7.5 Hz, 2H), 7.67-7.71 (m, 2H), 7.56 (t, J = 7.3 Hz, 4H), 5.54 (dd, J = 3.5, 3.8 Hz, 1H), 5.45 (dd, J = 3.5, 9 Hz, 1H), 4.79 (dd, J = 3.8, 6.3 Hz, 1H), 4.58 (dd, *J* = 6.3, 7.3 Hz, 1H), 4.16 (dd, *J* = 7.3, 10.3 Hz, 1H), 4.08 (dd, *J* = 9, 10.3 Hz, 1H), 1.7-1.3 (m, 20H). ¹³C NMR (125 MHz, Acetone d_6) δ : 164.8, 164.3, 133.5, 133.4, 129.7, 129.6, 129.5, 128.6, 128.5, 112.9, 111.1, 78, 76.2, 75.5, 73.9, 73.8, 73.0, 36.4, 36.3, 36.2, 34.0, 24.8, 24.7. Anal. Calcd for C₃₂H₃₆O₈: C, 70.06; H, 6.61. Found: C, 69.95; H, 6.72.

(±)-1,2:4,5-Di-O-cyclohexylidene-3,6-di-O-para-methoxybenzylmyo-inositol (13c). Compound 12 (500 mg, 1.47 mmol) in dry DMF (10 mL) was cooled to 0 °C. To this cooled solution, sodium hydride (60% in paraffin oil) (176 mg, 4.41 mmol), followed by p-methoxybenzylchloride (600 µL, 4.41 mmol) were added. The reaction mixture was allowed to warm to room temperature. The reaction was monitored using TLC. After completion of the reaction (4 h), the reaction mixture was quenched with ice cold water and evaporated under reduced pressure. The crude material was dissolved in ethylacetate and washed with water. The organic layer was dried over Na₂SO₄ and concentrated. The crude was purified by column chromatography using 1:9 (v/v) ethylacetate and petroleum ether as an eluent to yield the colourless solid 13c (758 mg, 89%). MP: 96–98 °C. IR (KBr): 3045, 2920, 2877, 1478, 1369, 1250 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ: 7.22–7.18 (m, 4H), 6.84–6.81 (m, 4H), 4.58 (q, J = 11.9, 17.1 Hz, 2H), 4.51 (s, 2H), 4.36 (t, J = 4.4 Hz, 1H), 3.99 (dd, J = 4.1, 10.2 Hz, 1H), 3.72 (t, J = 9.4 Hz, 1H), 3.67 (s, 3H), 3.66 (s, 3H) 1.55–1.27 (m, 20H). ¹³C NMR (125 MHz, DMSO-d₆) δ: 158.7, 158.6, 130.2, 129.39, 129.37, 129.2, 113.59, 113.50, 111.4, 109.0, 79.9, 77.7, 76.3, 75.1, 74.6, 70.7, 69.8, 55.0, 37.1, 36.0, 34.6, 24.4, 23.6, 23.5, 23.4. Anal. Calcd for C₃₄H₄₄O₈: C, 70.32; H, 7.64. Found: C, 70.41; H, 7.69.

(±)-1,2-O-Isopropylidene-3-O-tosyl-myo-inositol (16c). Yield: (262 mg, 70%). MP: 155–158 °C, IR (KBr): 3404, 3050, 2988, 2846, 1350, 1224 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ : 7.80 (d, J = 8.25 Hz, 2H), 7.44 (d, J = 8.05, 2H), 5.27 (d, J = 5.0 Hz, 1H), 5.04 (d, J = 4.7 Hz, 1H), 4.98 (d, J = 4.7 Hz, 1H), 4.08 (t, J = 5.15 Hz, 1H), 3.87 (t, J = 6.9 Hz, 1H), 3.50–3.45 (m, 1H), 3.02–2.97 (m, 1H), 2.41 (s, 3H), 1.34 (s, 3H), 1.05 (s, 3H); ¹³C NMR (125 MHz, DMSO-d₆) δ : 145.0, 134.3, 130.2, 128.1, 109.0, 81.0, 80.9, 79.2, 74.0, 73.8, 73.7, 70.4, 46.1, 28.1, 26.0, 21.5. Anal. Calcd for C₁₆H₂₂O₈S: C, 51.33; H, 5.92; S, 8.56. Found: C, 51.11; H, 6.09; S, 8.38.

(±)-1,2-O-Cyclohexylidene-3,4-di-O-benzoyl-*myo*-inositol (21a). Yield: (342 mg, 73%). MP: 164–166 °C, IR (KBr): 3479, 3035, 2960, 2870, 1737, 1462, 1344, 1225 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ : 8.13 (d, *J* = 7.35 Hz, 2H), 8.10 (d, *J* = 7.35 Hz, 2H), 7.75 (t, *J* = 7.25 Hz, 1H), 7.67–7.61 (m, 4H), 5.78 (m, 1H), 5.54–5.52 (m, 2H), 5.34 (t, J = 9.75 Hz, 1H), 4.25 (t, J = 10 Hz, 1H), 4.09–4.07 (m, 1H), 3.91–3.85 (m, 2H), 1.66–1.33 (m, 10H). ¹³C NMR (125 MHz, DMSO-d₆) δ : 165.09, 165.06, 133.3, 129.8, 129.5, 129.2, 128.8, 128.6, 111.7, 74.4, 73.9, 73.7, 73.1, 70.9, 69.4, 35.8, 35.5, 24.2, 23.0. Anal. Calcd for C₂₆H₂₈O₈: C, 66.66; H, 6.02. Found: C, 66.49; H, 6.27.

(±)-1,2-O-Cyclohexylidene-3,6-di-O-methyl-*myo*-inositol (22b). Yield: (264 mg, 92%). MP: 147–149 °C. IR (KBr): 3470, 2970, 2841, 1340, 1219 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ : 4.89 (d, *J* = 4.5 Hz, 1H –OH), 4.82 (d, *J* = 4.3 Hz, –OH), 4.36 (t, *J* = 4.9 Hz, 1H), 3.92 (t, *J* = 6.4, 1H), 3.47–3.44 (m, 1H), 3.43 (s, 3H), 3.37 (s, 3H), 3.23 (dd, *J* = 3.8, 9.0 Hz, 1H), 3.10–3.06 (m, 1H), 1.65–1.35 (m, 10H); ¹³C NMR (125 MHz, DMSO-d₆) δ : 108.7, 84.8, 78.9, 77.9, 73.0, 72.8, 71.4, 59.2, 57.2, 37.4, 34.8, 24.5, 23.5, 23.3. Anal. Calcd for C₁₄H₂₄O₆: C, 58.32; H, 8.39. Found: C; 58.02; H, 8.61.

(±)-1,2-O-Cyclohexylidene-3,6-di-O-para-methoxybenzyl-myoinositol (22c). Yield: (470 mg, 94%). MP: 146–148 °C, IR (KBr): 3420, 3021, 2927, 2869, 1511, 1457, 1238 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ : 7.31–7.30 (m, 4H), 6.89 (t, J = 6.6 Hz, 4H), 4.98 (d, J = 4.3 Hz, 1H –OH), 4.90 (d, J = 4.7 Hz, 1H, –OH), 4.7–4.65 (m, 2H), 4.59 (q, J = 11.6, 17.3 Hz, 2H), 4.33 (t, J = 3.9 Hz, 1H), 3.99 (t, J = 5.4 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.53–3.52 (m, 1H), 3.47 (dd, J = 3.5, 8.9 Hz, 1H), 3.17–3.14 (m, 1H), 1.57–1.35 (m, 10H). ¹³C NMR (125 MHz, DMSO-d₆) δ : 158.5, 158.4, 131.0, 130.9, 129.1, 129.0, 113.4, 113.3, 108.7, 82.3, 78.0, 77.1, 73.4, 72.2, 71.6, 70.8, 55.02, 55.01, 37.3, 34.7, 24.5, 23.6, 23.3. Anal. Calcd for C₂₈H₃₆O₈: C, 67.18; H, 7.25. Found: C, 67.10; H, 7.229.

(±)-1,2-O-Isopropylidene-3,4-di-O-benzoyl-5,6-di-O-acetyl-myoinositol (23b). Yield: (471 mg, 92%). MP: 221–222 °C, IR (KBr): 3075, 2987, 2920, 1749, 1727, 1450, 1373, 1275, 1238 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ : 7.87–7.81 (m, 4H), 7.66–7.61 (m, 2H), 7.52–7.47 (m, 4H), 5.89 (dd, J = 3.95 Hz, 9.8 Hz, 1H), 5.71 (t, J = 9.55 Hz, 1H), 5.53 (t, J = 9.95 Hz, 1 H), 5.34 (dd, J = 7.55 Hz, 10.1 Hz, 1H), 4.68 (t, J = 4.65 Hz, 1H), 4.53 (dd, J = 5.05 Hz, 7.4 Hz, 1H), 2.09 (s, 3H), 1.87 (s, 3H), 1.54 (s, 3H), 1.31 (s, 3H). ¹³C NMR (125 MHz, DMSO-d₆) δ : 169.40, 169.26, 164.96, 164.73, 133.85, 133.82, 129.21, 129.03, 128.85, 128.54, 128.50, 110.14, 75.61, 73.50, 72.24, 70.37, 69.62, 69.38, 27.43, 25.82, 20.46, 20.10. Anal. Calcd for C₂₇H₂₈O₁₀: C, 63.28; H, 5.51. Found: C, 63.51; H, 5.75.

(±)-1,2-O-Isopropylidene-3,6-di-*O-para*-methoxybenzyl-4,5-di-O-acetyl-*myo*-inositol (24b). Yield: (435 mg, 80%) gum. IR (KBr) 3050, 2980, 2854, 1745, 1490, 1383, 1265 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ : 7.15–7.09 (m, 4H), 6.85–6.82 (m, 4H), 5.07 (t, J = 9.5 Hz, 1H), 4.87 (t, J = 9.5 Hz, 1H), 4.50 (ABq, J = 12 Hz, 52.5 Hz, 2H), 4.44 (ABq, J = 11.5 Hz, 46.5 Hz, 2H), 4.43–4.42 (m, 1H), 4.15 (m, 1H), 3.85 (dd, J = 4 Hz, 10 Hz, 1H), 3.673 (s, 3H), 3.67 (s, 3H), 3.52 (dd, J = 7 Hz, 9.5 Hz, 1H), 1.89 (s, 3H), 1.88 (s, 3H), 1.38 (s, 3H), 1.24 (s, 3H). ¹³C NMR (125 MHz, DMSO-d₆) δ : 169.37, 169.24, 158.79, 158.76, 130.11, 129.13, 129.05, 113.62, 113.58, 109.06, 79.06, 77.88, 73.89, 73.20, 72.04, 71.53, 70.83, 70.65, 55.07, 55.04, 27.64, 26.33, 25.69, 20.48, 20.47. Anal. Calcd for C₂₉H₃₆O₁₀: C, 63.96; H, 6.66. Found: C, 64.10; H, 6.81. (±)-1,2-O-Cyclohexylidene-3,4-di-O-benzoyl-5,6-di-O-acetyl-myoinositol (26a). Yield: (524 mg, 95%). MP: 180–181 °C. IR (KBr): 3066, 2979, 2916, 1754, 1730, 1480, 1357, 1240 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) &: 7.98–7.95 (m, 2H), 7.74–7.71 (m, 1H), 7.61–7.57 (m, 2H), 5.75–5.73 (m, 1H), 5.57–5.50 (m, 3H), 4.69 (t, J = 4.1 Hz, 1H), 4.66–4.63 (m, 1H), 1.94 (s, 3H), 1.84 (s, 3H), 1.81 (br, 2H), 1.59–1.5 (m, 6H), 1.42 (br, 2H). ¹³C NMR (125 MHz, DMSO-d₆) &: 169.50, 169.20, 164.83, 164.77, 133.88, 133.80, 129.26, 129.24, 128.97, 128.90, 128.85, 128.80, 110.63, 75.26, 73.70, 73.04, 69.66, 69.57, 69.33, 36.82, 34.59, 24.24, 23.55, 23.15, 20.22, 20.07. Anal. Calcd for C₃₀H₃₂O₁₀: C, 65.21; H, 5.84. Found: C, 65.38; H, 5.82.

(±)-1,2-O-Cyclohexylidene-3,6-di-O-benzyl-4,5-di-O-acetyl-myoinositol (27a). Yield: (513 mg, 98%) Semi-solid. IR (KBr): 3018, 2987, 2851, 1748, 1457, 1222 cm⁻¹. ¹H NMR (500 MHz, DMSOd₆) δ : 7.39–7.27 (m, 10H), 5.19 (t, J = 9.5 Hz, 1H), 4.99 (t, J = 9.5 Hz, 1H), 4.66 (ABq, J = 12 Hz, 86 Hz, 2H), 4.64 (t, J = 13 Hz, 2H), 4.52 (t, J = 5 Hz, 1H), 4.27–4.24 (m, 1H), 3.99 (dd, J = 3.5 Hz, 9.5 Hz, 1H), 3.65 (dd, J = 7 Hz, 9.5 Hz, 1H), 1.99 (s, 3H), 1.96 (s, 3H), 1.71–1.69 (m, 2H), 1.61–1.54 (m, 6H), 1.39 (br, 2H). ¹³C NMR (125 MHz, DMSO-d₆) δ : 169.40, 169.24, 138.29, 138.24, 128.18, 128.15, 127.49, 127.45, 127.40, 109.67, 79.92, 77.58, 74.41, 72.89, 72.58, 71.39, 71.10, 70.65, 37.17, 34.53, 24.46, 23.65, 23.33, 20.46, 20.44. Anal. Calcd for C₃₀H₃₆O₈: C, 68.68; H, 6.92. Found: C, 68.71; H, 6.80.

(±)-1,2-O-Cyclohexylidene-3,6-di-O-methyl-4,5-di-O-acetyl-myoinositol (27b). Yield: (323 mg, 87%). MP: 92–93 °C. IR (KBr): 2927, 2841, 1366, 1228 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ : 5.13 (t, J = 9.55 Hz, 1H), 4.90 (t, J = 9.55 Hz, 1H), 4.51–4.49 (m, 1H), 4.16–4.14 (m, 1H), 3.73 (dd, J = 3.85 Hz, 9.45, 1H), 3.41 (s, 3H), 3.41–3.37 (m, 1H), 3.42 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.75–1.71 (m, 2H), 1.62–1.50 (m, 6H), 1.38 (br, 2H). ¹³C NMR (125 MHz, DMSO-d₆) δ : 169.41, 169.28, 109.57, 81.85, 77.10, 75.81, 72.30, 71.54, 70.74, 59.19, 57.24, 37.16, 34.54, 24.44, 23.57, 23.30, 20.52, 20.46. Anal. Calcd for C₁₈H₂₈O₈: C, 58.05; H, 7.58. Found: C, 58.22; H, 7.75.

(+)-1,2-O-Isopropylidene-3,6-di-O-benzyl-myo-inositol (16a). To a solution of (+)-10 (800 mg, 3.076 mmol) in dry DMF was added NaH (184 mg, 7.69 mmol) and BnBr (1.3 g, 7.69 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was diluted with ethylacetate, washed with water and brine. The organic layer was dried over Na₂SO₄ and concentrated to get the corresponding dibenzyl ether (+)-10a (1.285 g, 95%) as a syrupy liquid. A solution of (+)-10a (800 mg, 1.818 mmol) in methanol (20 mL) was stirred with H₂SO₄-silica (25 mg) at room temperature for 2 h. The mixture was quenched by adding solid sodium bicarbonate, filtered through a filter paper, concentrated and purified by column chromatography to yield known (+)-16a²⁵ (610 mg, 84%) as a white solid.

(+)-1,2-O-Isopropylidene-3,6-di-O-benzyl-4,5-bis-O-(di-O-benzyl-phospho)-*myo*-inositol (35). To a solution of (+)-16a (500 mg, 1.25 mmol) in dry DCM, tetrazole (193 mg, 2.75 mmol) and bis(benzyloxy)(*N*,*N*-diisopropylamino)phosphine (948 mg, 2.75 mmol) were added. The resulting reaction mixture was stirred at rt for 1 h and cooled to -78 °C, and then m-CPBA

(429 mg, 2.75 mmol) was added and stirred for another hour. The mixture was warmed to room temperature and then diluted with EtOAc. The solution was washed with a Na₂SO₃ solution, saturated NaHCO₃, and brine. The organic layer was dried over MgSO₄, and concentrated to give an oily residue. This was further purified by column chromatography using ethyl acetate–petroleum ether (2:3 v/v) to yield known (+)-35^{21b} (910 mg, 79%) as an oil. ¹H NMR (500 MHz, CDCl₃) δ : 7.38–7.19 (m, 30H), 5.09–4.97 (m, 8H), 4.92–4.88 (m, 1H), 4.76–4.68 (m, 5H), 4.37 (dd, J = 3.4, 6.8 Hz, 1H), 4.28 (t, J = 6 Hz, 1H), 4.08 (t, J = 6.1 Hz, 1H), 3.97 (dd, J = 3.3, 7.6 Hz, 1H), 1.50 (s, 3H), 1.33 (s, 3H).

(+)-3,6-Di-O-benzyl-4,5-bis-O-(di-O-benzylphospho)-*myo*-inositol (36). To a solution of ketal (+)-35 (800 mg, 0.869 mmol) in methanol (10 mL), 1 N aq. HCl (1 mL) was added and the mixture was stirred at room temperature for 1 h. The solvents were evaporated and the residue was chromatographed using ethylacetate-petroleum ether (4 : 1 v/v) as an eluent to get the known diol (+)-36²⁶ (725 mg, 95%) as a white solid. MP: 91–93 °C, ¹H NMR (500 MHz, CDCl₃) δ : 7.25–7.02 (m, 30H), 5.00–4.96 (m, 2H), 4.89–4.73 (m, 8H), 4.60 (t, *J* = 11 Hz, 2H), 4.46–4.41 (m, 2H), 3.98 (br, 1H), 3.80 (t, *J* = 9 Hz, 1H), 3.47 (d, *J* = 7.3 Hz, 1H), 3.41 (d, *J* = 8.5 Hz, 1H).

myo-Inositol-1,4,5-trisphosphate (+)-5. To a solution of (+)-36 (125 mg, 0.142 mmol) in pyridine (3 mL) at 0 °C, POCl₃ (20 µL, 0.1562 mmol) was added and the reaction mixture was stirred at the same temperature. The consumption of starting material was confirmed by TLC analysis after 30 min. Pyridine was evaporated, the residue was diluted with ethylacetate, washed with dil. HCl and the organic layer was dried over sodium sulphate and concentrated. To the crude product (120 mg) thus obtained, Pd(OH)₂/C (150 mg), cyclohexene (4 mL), H₂O (0.75 mL) and MeOH (10 mL) were added and heated at 80 °C for 8 hours. The reaction mixture was filtered through a filter paper, and the crude debenzylated product was purified by ion exchange chromatography in Bio-Rad FPLC using triethylammonium bicarbonate as the eluent buffer (gradient elution) to get pure phosphate (+)-5²⁸ (35.8 mg, 60% for two steps). $[\alpha]_{D}^{25} = -25^{\circ}(C = 0.11, H_2O, pH)$ 8.5), ¹H NMR (500 MHz, D_2O) δ : 4.16–4.13 (m, 2H), 3.88 (br, 2H), 3.78 (d, J = 8.4 Hz, 1H), 3.58 (d, J = 9.2 Hz, 1H). ³¹P NMR (200 MHz, D₂O, a drop of TEA) δ: 4.57, 4.46, 2.68.

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