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Resolution of synthetically useful *myo*-inositol derivatives using the chiral auxiliary *O*-acetylmandelic acid

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Abstract—Efficient methods for the resolution of various *myo*-inositol derivatives have been developed using *O*-acetylmandelic acid (OAM) as the chiral auxiliary. Various methods of introduction of the chiral auxiliary have been compared. DCC mediated coupling between the inositol derivative and *O*-acetylmandelic acid resulted in substantial racemization even at 0 °C; while acylation with *O*-acetylmandeloyl chloride in the presence of pyridine gave the diastereomers without any racemization of the chiral auxiliary. The advantage of using OAM as a chiral auxiliary is that the absolute configuration of the resolved diastereomers can be determined by analyzing the ^{1}H NMR chemical shifts of various protons. The diastereomeric separation has been achieved either by fractional crystallization or column chromatography. The enantiomers of inositol derivatives could be obtained by the removal of chiral auxiliaries. By employing the known selective protection–deprotection strategies, various derivatives in optically active form could be synthesized.

1. Introduction

The realization that phosphorylated inositols play crucial roles in various biological processes such as cellular signal transduction,[1] anchoring of proteins to the cell membrane[2] etc. has accelerated the pace of research associated with the chemistry and biology of inositols over the last two decades. The increased interest in the biological role played by phosphoinositols necessitated better synthetic strategies for their preparation. In addition, the disclosed therapeutic potential[3] of inositol derivatives and the recent use of inositol as the synthon for the synthesis of many natural products[4] have given further impact to the *myo*-inositol chemistry. This multi-faceted importance of inositol demands better methods for the resolution and selective protection–deprotection for this *meso*-cyclohexane hexol. Many methods are known for the selective protection and deprotection of *myo*-inositol hydroxyl groups.[5] Still the search for efficient methodologies for its resolution continues. Although various chiral auxiliaries have been used to resolve *myo*-inositol derivatives, the absolute configuration of the resulting diastereomers are usually deduced by conversion to a derivative of known absolute stereochemistry, at times through a number of chemical transformations, which are time consuming and costly.

We have recently reported[6] a reliable method for the determination of the absolute configuration of inositol derivatives and other secondary alcohols using OAM esters as a chiral anisotropy reagent (CAR). Our study unambiguously established that OAM could be reliably used as a CAR in inositol and other cyclitol systems for the determination of their absolute configuration. The conformational model for OAM esters is similar to that of Trost's model[7] for MPA (methoxy phenyl acetate) derivatives. According to this, the OAM takes up a *syn*-periplanar conformation whereby the α-hydrogen, carbonyl carbon, and C–OAc align in a coplanar arrangement (Fig. 1). In this conformation, the phenyl group shields H_A and H_B in (*R*)-OAM ester and H_X and H_Y in (*S*)-OAM ester. Thus $\Delta\delta^{S-R}$ for H_A and H_B protons will be positive and for H_X and H_Y will be negative. Therefore by measuring $\Delta\delta$ of protons on both the sides of OAM plane, the absolute configuration can be determined. Due to this additional advantage, we chose

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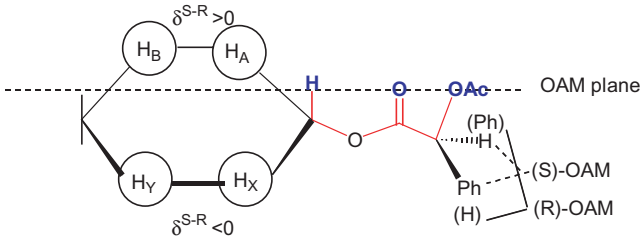
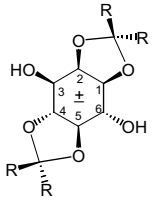
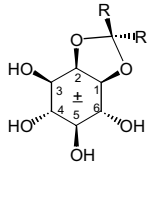


Figure 1. Conformational model for (*S*)-OAM and (*R*)-OAM esters of inositols.

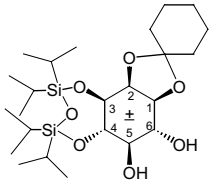
O-acetylmandelic acid as the chiral auxiliary for the resolution of various protected *myo*-inositol derivatives. We herein report methods for the resolution of synthetically useful partially protected *myo*-inositol derivatives **1**–**5** using *O*-acetylmandelic acid[4b,d,8] as the chiral auxiliary.



1. RR = $(CH_2)_5$
2. R = Me



3. RR = $(CH_2)_5$
4. R= Me



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2. Results and discussion

Ketalization of *myo*-inositol with excess ketal donor reagents is known to produce a mixture of ketals from which the diketal **1** or **2** can be crystallized in 20–25% yield. The relative reactivity of hydroxyl groups in 1,2:4,5-di-*O*-alkylidene-*myo*-inositols has been studied extensively.[9] It has been reported that phosphorylation,[10] acylation,[10,11] silylation[10,12] and alkylation[13] undergo selectively at the 3-*O*-position. Also, it is documented[13a,14] that the *trans*-ketal can be cleaved in the presence of the *cis*. These selectivities in diols **1** and **2** make them good synthons for many inositol phosphates and lipid derivatives. However, methodologies for efficient resolution of these diols are scarce in the literature. Thus, we have investigated resolution of these diols using OAM as the chiral auxiliary.

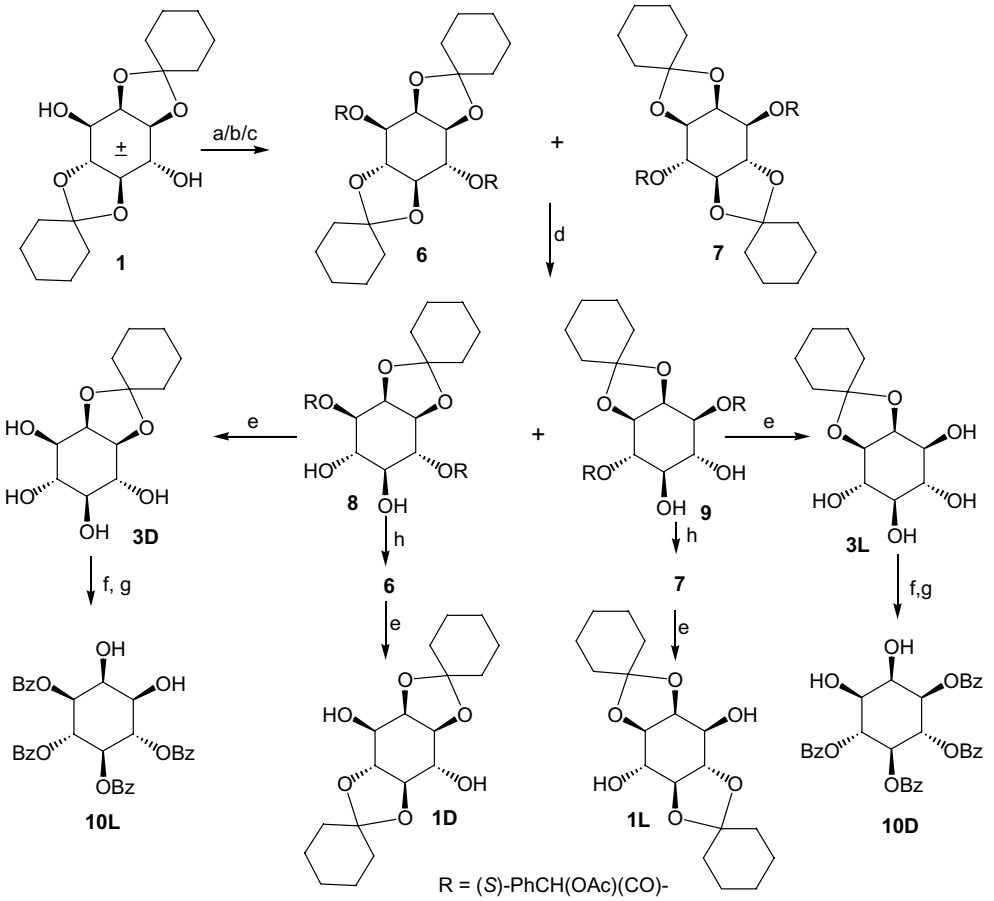
DCC mediated coupling of the racemic diol **1** with excess of (*S*)-*O*-acetylmandelic acid gave a chromatographically inseparable mixture of diastereomers **6** and **7** in moderate yield (Scheme 1). However, the selective cleavage of the more labile *trans*-cyclohexylidene using pyridinium polyhydrogenfluoride[15] resulted in the formation of diols **8** and **9**, which could be separated by column chromatography.

To check the enantiomeric excess of the individual diastereomers **8** and **9**, they were converted to the known[16] tetra-*O*-benzoyl-*myo*-inositols **10**L and **10**D. The acetylmandeloyl groups were removed by hydrazinolysis and the tetrols **3**D and **3**L obtained were benzoylated, under standard conditions, and finally the acid labile cyclohexylidene ketal was cleaved by treatment with aqueous acetic acid to afford the known tetrabenzoates **10**L and **10**D, respectively. Unfortunately, HPLC analysis (chiralcel OD column) of these tetrabenzoates revealed that they are not enantiomerically pure. This suggested that racemization of the chiral auxiliary occurred during its introduction. Hence, other methods for the introduction of chiral auxiliaries were sought (Table 1). DMC (2-chloro-1,3-dimethyl-imidazolinium chloride) mediated coupling of (*S*)-*O*-acetylmandelic acid and diol (±)-**1** also resulted in serious racemization at the chiral auxiliary giving four different diesters. However, the use of *O*-acetylmandeloyl chloride, in the presence of pyridine, for the acylation resulted in formation of **6** and **7** in very good yield compared to the other two methods. The conversion into enantiomers of tetrabenzoate **10** and their HPLC analysis revealed that they are enantiomerically pure. The acid chloride method gave the diesters **6** and **7** not only in very good yield but also without any racemization. Thus chloride method was taken as the optimum condition for the introduction of the chiral auxiliary.

The ^{1}H NMR spectra of both the diastereomers **8** and **9** were analyzed to assign the absolute configuration. According to the conformational model, H-1 and H-2 in L-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-isopropylidene-*myo*-inositol and H-4 and H-5 in the diastereomer D-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-isopropylidene-*myo*-inositol are expected to be shielded by the phenyl group of OAM and hence these proton signals are expected to appear at higher fields in the respective diastereomer compared to the other diastereomer. H-4 and H-5 in the less polar diastereomer (R_f = 0.55 AcOEt/benzene = 1/1) are shielded by 0.17 ppm and 0.25 ppm, respectively, and H-1 and H-2 in the more polar diastereomer (R_f = 0.35) are shielded by 0.24 ppm and 0.20 ppm, respectively. Thus the first (less polar) and the second (more polar) diastereomers were assigned to be D-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-isopropylidene-*myo*-inositol **8** and L-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-isopropylidene-*myo*-inositol **9**, respectively. The fact that **8** and **9** were converted to **10**L and **10**D, respectively, further substantiated the structural assignments of **8** and **9** based on ^{1}H NMR.

Diols **8** and **9** allow access to the 4-OH and 5-OH of inositol for phosphorylation or other derivatization. To have access to another pair of hydroxyl groups (3-OH and 6-OH), the diols **8** and **9** were re-protected again to di-cyclohexylidene derivatives **6** and **7**, respectively, in very good yields. Diol **8** on treatment with 1,1-dimethoxycyclohexane in the presence of catalytic amount of camphorsulfonic acid provided the diastereomerically pure diketal **6** in very good yield. Similarly, compound **9** was converted to **7**. Removal of the chiral auxiliary from **6** and **7** by hydrazinolysis provided diols **1**D[17] and **1**L in enantiomerically pure forms.

Next, we turned our attention to the resolution of di-isopropylidene-*myo*-inositol, (±)-**2** to see whether we can separate the diastereomers at the diketal stage itself. The acylation of the diketal (±)-**2** with (*S*)-*O*-acetyl-



Scheme 1. Reagents and conditions: (a) (*S*)-*O*-acetylmandeloyl chloride, pyr, DMAP, 0 °C; (b) (*S*)-*O*-acetylmandelic acid, DCC, CH_2Cl_2, 0 °C; (c) (*S*)-*O*-acetylmandelic acid, DMC, CH_2Cl_2, pyr, 0 °C; (d) pyr(HF)$_x$, ethylene glycol, MeCN; (e) $N_2H_4{\cdot}H_2O$, ethanol, rt; (f) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 21 h; (g) 80% AcOH, reflux, 3 h; (h) 1,1-dimethoxy cyclohexane, CSA, CH_2Cl_2, reflux.

Table 1. Comparison of different methods for *O*-acetylmandeloylation of (±)-**1**

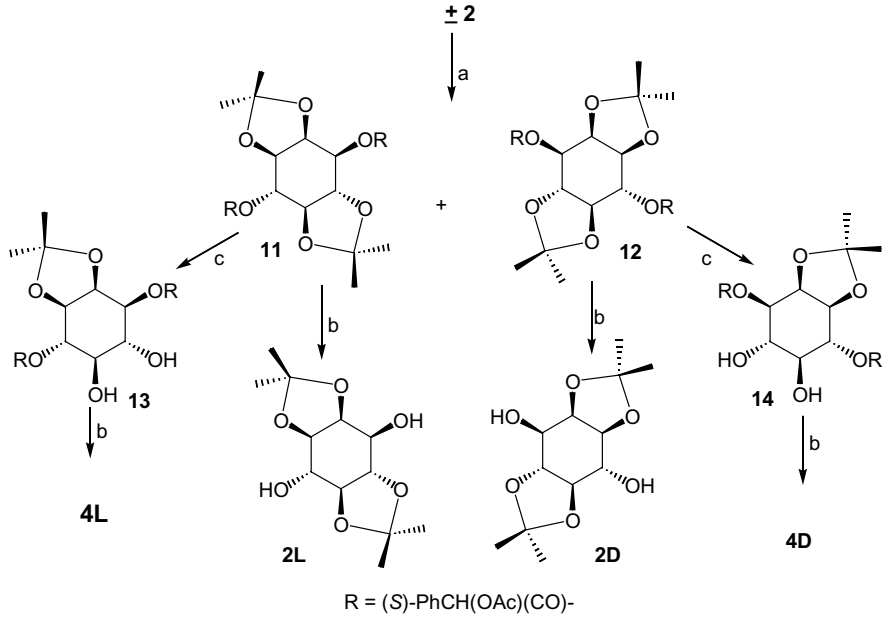
	Reagents and conditions	% Yield (**6** + **7**)	% Ee[a] **1**D, **1**L
1	*O*-Acetylmandelic acid, DCC, DMAP, CH_2Cl_2, 0 °C	60	72, 76
2	*O*-Acetylmandelic acid, DMC, pyr, CH_2Cl_2, 0 °C	71	Substantial racemization
3	*O*-Acetylmandeloyl chloride, pyr, DMAP, CH_2Cl_2, 0 °C	98	100, 100

[a] Determined by conversion to **10** and HPLC analysis.

mandeloyl chloride[18] in pyridine gave diastereomers **11** and **12** in good yield (Scheme 2). However, diesters **11** and **12** were inseparable by chromatography as in the case of their cyclohexylidene counterparts. However, crystallization from a mixture of ethyl acetate and hexane yielded one of the diastereomers in pure form (by ^{1}H NMR) in 46% yield (92% of the theoretical maximum) as cotton-like fluffy crystals. Further crystallization of the concentrated mother liquor from chloroform–hexane yielded the second diastereomer in very pure form in good yield (42%) as dense thick crystals. Thus both the diastereomers could be separated by sequential crystallizations.

The absolute configuration of **11** and **12** were determined by analyzing their ^{1}H NMR spectra. H-2 and H-3 in D-1,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol and H-5 and H-6 in the diastereomer L-1,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol are expected to be shielded by the phenyl group of OAM. H-5 and H-6 in the first diastereomer (crystallized from ethyl acetate–hexane) are shielded by 0.22 ppm and 0.02 ppm, respectively, and H-2 and H-3 in the second diastereomer (crystallized from chloroform–hexane) are shielded by 0.22 ppm and 0.37 ppm, respectively. Thus the first and the second diastereomers were assigned to be L-1,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol and D-1,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol, respectively. Later, these assignments were substantiated by solving the single crystal X-ray structure of the second diastereomer.[19]

The chiral auxiliaries could be removed by hydrazinolysis to yield enantiomers of diol **2** in quantitative yields. Also, to check the synthetic versatility of diastereomers **11** and **12**, we attempted cleavage of the *trans*-isopropylidene in presence of the *cis*. In general, the reported



Scheme 2. Reagents and conditions: (a) (*S*)-(+)-*O*-acetylmandeloyl chloride (2.1 equiv), pyr, 0 °C, 2 h; (b) $N_2H_4{\cdot}H_2O$, EtOH, rt, 3 h; (c) TFA (2 equiv), H_2O (1 equiv), CH_2Cl_2, 0 °C to rt, 50 min.

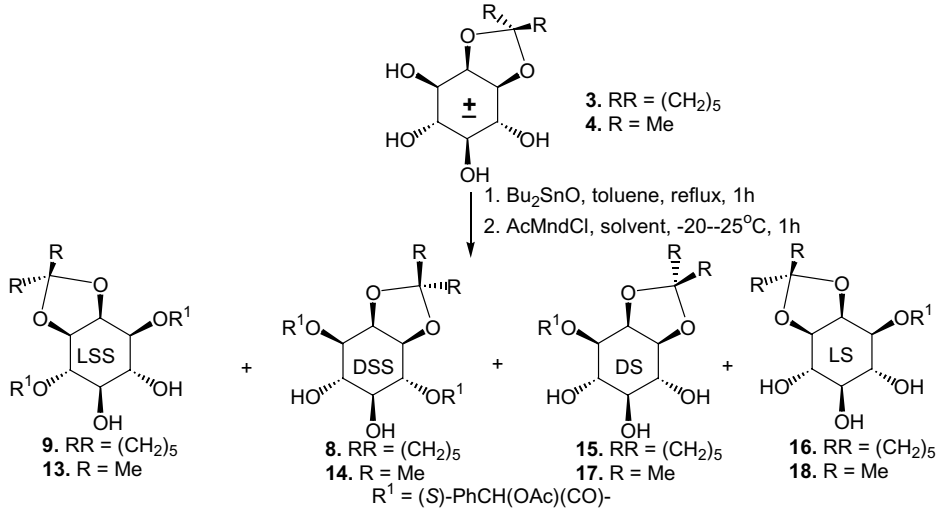
methods for the selective *trans*-ketal cleavage are low yielding (around 60%). Recently a high yielding method using ion exchange resin has been reported.[14b] Unfortunately, we were unable to cleave the *trans*-ketal from the diester **11** or **12** by this method. After some experimentation we arrived at an optimum condition for the selective cleavage of the *trans*-ketal from **11** or **12** using a limited amount of TFA and water (2 and 1 equiv, respectively) in CH_2Cl_2 to get diols **13** and **14** in good yields (82–87%). Since **11** and **12** were separated by crystallization, the enantiomeric purity of the diols **2D** and **2L** alone does not rule out the possible racemization at the chiral auxiliary during its introduction. For this reason, the inseparable mixture of **11** and **12** obtained was subjected to *trans*-isopropylidene cleavage to obtain chromatographically separable diols **13** and **14**, which were individually converted to enantiomers of tetrabenzoate and their enantiomeric excesses established by HPLC analysis. This ruled out racemization of the chiral auxiliary. Since diketals **1** and **2** and their derivatives are identical in terms of reactivity and selectivity, resolution of (±)-**2** is more appealing as both the resulting diastereomers **11** and **12** can be separated by sequential crystallization.

Although diketal derivatives are synthetically versatile, the major disadvantage of using the diketal **1** or **2** as starting material is that the diketalization of inositol yields a mixture of ketals, where the yield of the required diketal **1** or **2** is only about 20–25%. On the other hand, monoketalization of *myo*-inositol gives only a single monoketal **3** or **4** in very good yield (>90%).[5] Unfortunately, few attempts[16,20] have been made in the past either to resolve this tetrol or to use this tetrol for phosphoinositol synthesis. It is known that diacylation and disilylation of tetrol **3** gives 3,6-di-*O*-silylated derivatives.[5] However, our treatment of (±)-**3** with two equivalents of *O*-acetylmandeloyl chloride in pyridine gave a mixture of many products. Stannylene mediated reactions have often been employed for regioselective functionalization of polyol derivatives.[21] Gigg et al. reported[22] that tin mediated benzylation of 1,2-*O*-isopropylidene-*myo*-inositol **4** yields 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol predominantly. By analogy, we anticipated similar selectivity during acylation also. Thus the tetrol (±)-**3** was converted into the stannylene acetals by treatment with Bu_2SnO in refluxing toluene in a Dean–Stark apparatus. Subsequent treatment with excess (more than 2 equiv) of *O*-acetylmandeloyl chloride at low temperature (−20 °C) gave both D- and L-3,6-di-*O*-acetylmandelate derivatives (1:1) as expected with minor amounts of 3-*O*-monoesters (D/L = 1:1). The diesters could be separated by column chromatography, but not the monoesters. NMR analysis revealed that the diesters were contaminated with other positional isomers. At relatively higher temperature (0 °C) no monoester was isolated but a mixture of triacylated derivatives were formed. When the solvent for the acylation was changed to dichloromethane, interestingly, both the diastereomers **8** and **9** (Scheme 3) were obtained without any contaminated regioisomers. Also, one of the diastereomers has been found to form predominantly over the other. In all the attempts, the L-diastereomer, **9** was obtained in higher yield than the corresponding D-diastereomer, **8**. In addition, the ratio of monoester was found to be in the reverse order as expected. By using 2.5 equiv of acyl chloride we obtained 42% of **9**, 10% of **8** and 20% of **15** without any contamination of **16**. Similar results were obtained when a structurally similar isopropylidene derivative (±)-**4** was used (Table 2). Irrespective of the amount of acyl chloride used, only 1.2–1.5 equiv of acyl chloride were consumed in the reaction. From these results, it is obvious that the first acylation is at the 3-

O-position in both the D- and L-forms of tetrol **3** or **4**. It is also evident that the 6-OH of monoester **16/18** is more reactive toward the second acylation (in DCM), than that of **15/17**. These product ratios are very appealing, since optically active and differently protected derivatives can be obtained in high yields taking into consideration the very high yield of monoketals **3** and **4** from *myo*-inositol.

Diol **5** is another important protected derivative, which can be obtained in very good yield (>90%) from *myo*-inositol.[23] Efficient methods for the resolution of such a derivative are essential for the economical synthesis of various phosphoinositols and other derivatives. We have previously attempted the resolution of this diol using OAM as the chiral auxiliary. Acylation of the diol (±)-**5** with 1 equiv of *O*-acetylmandeloyl chloride gave the D- and L-1,2-*O*-cyclohexylidene-3,4-*O*-(tetraisopropyl-disiloxane-1,3-diyl)-6-*O*-[*O*-acetylmandeloyl]-*myo*-inositol as a mixture of inseparable diastereomers **19**. Silylation of the remaining hydroxyl group, with TES-Cl, gave the fully protected diastereomers, which could easily be separated by column chromatography. The usefulness of this method has been exemplified by the efficient syntheses of various phosphoinositols.[24]

Many of the important biologically active inositol phosphates ($InsP_n$s: Ins(5)P, Ins(1,5)P_2, Ins(1,4,5)P_3 Ins(1,3,4,5)P_4, Ins(1,4,5,6)P_4, Ins(1,3,4,5,6)P_5) and phosphatidylinositolphosphates (PtdInsPns: PtdIns(5)P, PtdIns(3,5)P_2, PtdIns(4,5)P_2, PtdIns(3,4,5)P_3) contain a phosphate group at the 5-*O*-position of *myo*-inositol. Efficient syntheses of 5-*O*-phosphorylated inositol phospholipids and phosphates are challenging since the introduction of a phosphate group, selectively, at *O*-5 is not trivial in inositol derivatives with two or more hydroxyl groups. Although 5-OH can be selectively exposed (for subsequent phosphorylation) from **20** or **21**, this involves two additional steps (silylation and selective desilylation) in the synthesis. The synthesis of 5-*O*-phosphorylated phosphoinositols can be improved if the diastereomers after phosphitylation/phosphorylation of DL-**19** are separable. Phosphitylation of DL-**19** with dibenzyl *N*,*N*-diisopropylphosphoramidite yielded diastereomeric phosphites **22** and **23** (Scheme 4), which were separated by column chromatography. The absolute configurations of **22** and **23** were confirmed by analyzing their NMR spectra. Further confirmation of their absolute configurations was made by unambiguous syntheses of phosphites **22** and **23** from enantiomerically pure L-**19** and D-**19**, respectively. Phosphites **22** and **23** were separately oxidized, using *m*-CPBA, to the phosphates **24** and **25**, respectively. Use of these two compounds is advantageous in the comprehensive synthesis of 5-*O*-phosphorylated PtdInsP_ns and InsP_ns in terms of the number of steps and yield. Either 1,2-diols or 3,4-diols can be exposed from **24** and **25** by selective cleavage of TIPDS or cyclohexylidene groups as necessary. Since selectivity

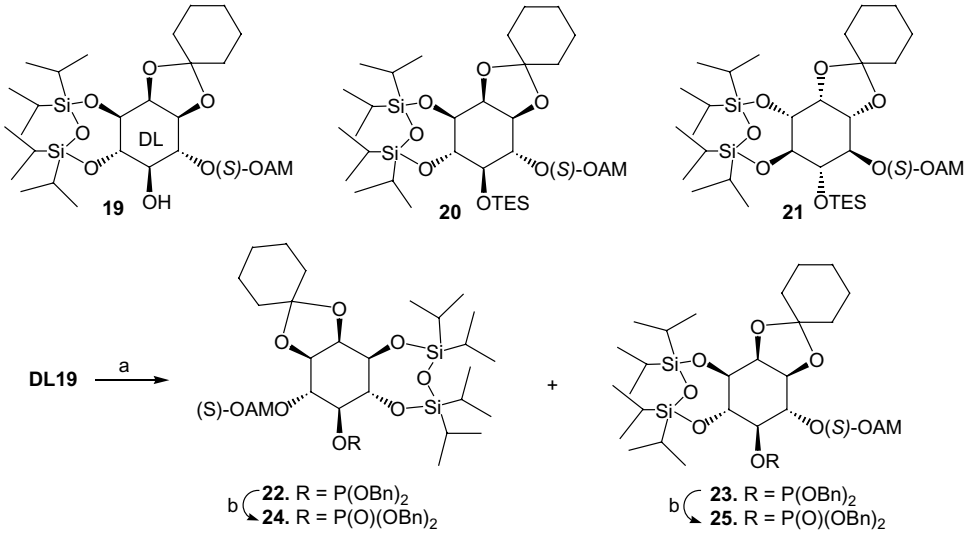


Scheme 3.

Table 2. Comparison of different conditions of *O*-acetylmandeloylation of (±)-**3**

Tetrol	Solvent, temp	Equiv of AcMnd-Cl	% Yield **9/13**	% Yield **8/14**	% Yield **15** + **16/17** + **18** (D*S*/L*S*)
3	Toluene, −20 °C	3.0	38	34	12 (1/1)
3	Toluene, 0 °C[a]	3.0	31	31	—
3	CH_2Cl_2, −20 °C	1.8	21	7	60 (2/1)
3	CH_2Cl_2, −20 °C	2.5	42	10	20 (D only)
4	Toluene, −20 °C	4.0	27	27	26 (3/2)
4	Toluene, −20 °C	3.0	27	27	23 (1/1)
4	CH_2Cl_2, −20 °C	2.5	40	7	44 (6/1)

[a] At 0 °C mixture of triacylated derivatives were isolated but not monoesters.



Scheme 4. Reagents and conditions: (a) dibenzyl *N*,*N*-diisopropylphosphoramidite (1.6 equiv), tetrazole (2.0 equiv), CH_2Cl_2, 0 °C to rt, 1 h, 96%; (b) *m*-CPBA (1.4 equiv), CH_2Cl_2, −78 °C–rt, 1 h.

can be achieved between two hydroxyl groups of these two gem diols, many important inositol phosphates and phosphatidylinositol phosphates can be synthesized in economical routes. Unlike most of the resolved diastereomers, both **24** and **25** can be used for phosphoinositol syntheses. The practical use of these two compounds for the comprehensive syntheses of $PtdIns P_n$s and $Ins P_n$s is underway.

3. Conclusion

In conclusion, we have achieved efficient methods for the optical resolution of important *myo*-inositol derivatives using OAM as the chiral auxiliary. The advantage of this method is that the absolute configuration can be determined by analyzing the ^1H NMR of both the diastereomers. UV activity of the products (advantageous for chromatographic separation) and low cost of mandelic acid (both *R* and *S*) are added advantages of using acetylmandelic acid over other frequently used chiral auxiliaries, like camphanic acid, menthoxy acetic acid etc. By applying the known selective reactions, many optically active inositol derivatives can be synthesized in an economical way. We hope that these resolution methods will be useful, not only to the inositol chemists but also to a wider cross section of organic chemists, as inositols are increasingly being used as synthons for many natural products,[4] metal complexing agents,[25] gelators,[26] catalysts,[27] supramolecular assemblies,[28] chiral auxiliary,[29] etc.

4. Experimental

4.1. General

All experiments were conducted under nitrogen atmosphere. Melting points were determined with a Yanaco Micro Melting Point Apparatus and are uncorrected. Flash column chromatography was performed using silica gel (Fuji Silysia, Silica gel BW-300). ^1H, ^{31}P and ^{13}C NMR spectra were recorded on a Bruker-DPX-400 instrument or JEOL JNM-GSX270 instrument. Chemical shifts (δ_H values relative to tetramethylsilane, δ_C values relative to $CDCl_3$ and δ_P values relative to H_3PO_4) and coupling constants (*J* values) are given in parts per million and hertz, respectively. Optical rotations were recorded in a JASCO P-1010 Polarimeter. Elemental analyses were carried out on a YANACO MT-5 elemental analyzer. Usual work-up refers to evaporation of the reaction solvent followed by dissolution of the residue in ethyl acetate and washing successively with water, dil HCl, satd $NaHCO_3$ solution and brine followed by drying over anhydrous $MgSO_4$ and concentration under reduced pressure.

4.2. Preparation of *O*-acetylmandeloyl chloride

To an ice cooled solution of DMF (316 mg, 1.43 mmol) and oxalyl chloride (402 mg, 3.17 mmol) in dichloromethane (5 mL) was added dropwise a solution of (*S*)-*O*-acetylmandelic acid (560 mg, 2.88 mmol) in dichloromethane (5 mL), and the mixture was stirred at 0 °C for 15 min. When the effervescence was ceased (about 15 min), the volatile materials were evaporated off under reduced pressure and the residual DMF solution was extracted with hexane (6 × 3 mL). The combined hexane extracts were evaporated under reduced pressure, to obtain (*S*)-*O*-acetylmandeloyl chloride.

4.3. DL-3,6-Di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol 6 and 7

To a cooled (−5 to −10 °C; ice–salt bath) solution of (±)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (1.00 g, 2.94 mmol) in dry pyridine (15 mL) was added a solution of (*S*)-*O*-acetylmandeloyl chloride (1.87 g, 8.82 mmol) in dichloromethane (15 mL). The mixture was stirred for 2.5 h at −5 °C under nitrogen atmo-

sphere and then quenched by the addition of water. After being stirred for 30 min, usual work-up followed by purification of the residue thus obtained by chromatography (AcOEt/hexane, 1:4) yielded D- and L-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol **6** and **7**, 2.00 g, 98%) as an inseparable mixture of diastereomers. ^{1}H NMR (270 MHz, $CDCl_3$): 1.23–1.77 (40H, complex, cyclohexylidene H), 2.17 (s, 6H, Me), 2.19 (s, 3H, Me), 2.20 (s, 3H, Me), 3.24 (dd, 1H, J = 9.8, 11.2 Hz, Ins H-5), 3.45 (dd, 1H, J = 9.8, 11.2 Hz, Ins H-5), 3.82 (dd, 1H, J = 6.8, 4.9 Hz, Ins H-1), 4.05 (dd, 2H, J = 10.7, 9.3 Hz, Ins H-4), 4.14 (dd, 1H, J = 4.4, 6.8 Hz, Ins H-1), 4.39 (t, 1H, J = 4.4 Hz, Ins H-2), 4.57 (t, 1H, J = 4.4 Hz, Ins H-2), 5.02 (dd, 1H, J = 4.4, 10.7 Hz, Ins H-3), 5.06 (dd, 1H, dd, J = 4.4, 10.7 Hz, Ins H-3), 5.20 (dd, 1H, J = 6.8, 11.2 Hz, Ins H-6), 5.22 (dd, 1H, J = 6.84, 11.2 Hz, Ins H-6), 6.00 (s, 1H, benzylic-H), 6.08 (s, 1H, benzylic-H), 6.11 (s, 2H, benzylic-H), 7.33–7.54 (m, 20H, aromatic-H); ^{13}C NMR (67.9 MHz, $CDCl_3$): 20.57, 20.64, 20.72, 23.21, 23.34, 23.61, 23.76, 24.81, 34.62, 34.77, 35.99, 36.17, 36.25, 37.15, 37.40, 71.80, 74.08, 74.14, 74.40, 74.57, 75.18, 75.72, 75.95, 76.04, 78.23, 78.56, 110.99, 111.43, 113.35, 113.86, 127.82, 128.13, 128.17, 128.57, 128.64, 129.08, 129.17, 133.28, 133.43, 133.96, 167.70, 167.74, 168.12, 168.34, 169.88, 170.04, 170.19.

4.4. Selective cleavage of *trans*-cyclohexylidene from DL-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol

To a solution of **6** and **7** (1.19 g, 1.72 mmol) and ethylene glycol (106 μL, 1.89 mmol) in anhydrous acetonitrile (7 mL) was added pyridinium poly(hydrogen fluoride) (1.03 mL, 36.16 mmol) at 0 °C, and the mixture was stirred at the same temperature for 10 min and then at room temperature for another 4 h. When the starting material was disappeared (TLC), solid $NaHCO_3$ was added and stirred for another 30 min to neutralize the acid and then worked-up as usual. Purification by chromatography (AcOEt/benzene, 4:7) yielded the less polar D-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-cyclohexylidene-*myo*-inositol **8** (358 mg, 34% yield, R_f = 0.55, AcOEt/benzene, 1:1) and further elution gave L-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-cyclohexylidene-*myo*-inositol **9** (505 mg, 48% yield, R_f = 0.35, AcOEt/benzene, 1:1).

Compound **8**: mp = 100.0–103.0 °C (from AcOEt/hexane); $[\alpha]_D^{26}$ = +67.0 (*c* 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 1.36–1.80 (m, 10H, cyclohexylidene), 2.18 (s, 3H, Me) 2.20 (s, 3H, Me), 3.26 (t, 1H, J = 9.8 Hz, Ins H-5), 3.90 (t, 1H, J = 9.8 Hz, Ins H-4), 4.13 (dd, 1H, J = 7.8, 4.9 Hz, Ins H-1), 4.43 (t, 1H, J = 4.9 Hz, Ins H-2), 4.95 (dd, 1H, J = 4.9, 9.8 Hz, Ins H-3), 5.10 (dd, 1H, J = 9.8, 7.8 Hz, Ins H-6), 5.98 (s, 1H, benzylic-H), 6.00 (s, 1H, benzylic-H), 7.30–7.53 (m, 10H, aromatic-H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.68, 20.76, 23.45, 23.75, 24.86, 34.94, 37.32, 70.43, 71.95, 72.75, 72.30, 74.70, 74.81, 75.46, 77.00, 111.63, 127.81, 127.91, 128.82, 129.38, 129.50, 133.46, 133.74, 168.13, 168.38, 170.67, 170.77; FABMS (*m*/*z*): 613 $(M+H)^+$, 635 $(M+Na)^+$. Anal. Calcd for $C_{32}H_{36}O_{12}$: C, 62.74; H, 5.92. Found C, 62.45; H, 6.11.

Compound **9**: mp = 118.0–120.0 °C (from AcOEt/hexane); $[\alpha]_D^{26}$ = +45.6 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 1.20–1.63 (m, 10H, cyclohexylidene), 2.18 (s, 3H, Me) 2.20 (s, 3H, Me), 3.51 (t, 1H, J = 9.3 Hz, Ins H-5), 3.89 (dd, 1H, J = 7.8, 4.9 Hz, Ins H-1), 4.07 (t, 1H, J = 9.3 Hz, Ins H-4), 4.23 (t, 1H, J = 4.4 Hz, Ins H-2), 5.03 (dd, 1H, J = 4.4, 9.3 Hz, Ins H-3), 5.13 (t, 1H, J = 10.3, 7.8 Hz, Ins H-6), 5.93 (s, 1H, benzylic-H), 6.00 (s, 1H, benzylic-H), 7.30–7.53 (m, 10H, aromatic-H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.62, 20.66, 23.29, 23.66, 24.79, 34.81, 37.24, 70.50, 71.56, 72.62, 74.49, 74.79, 75.46, 76.68, 77.07, 111.10, 127.50, 127.91, 128.65, 128.72, 129.14, 133.20, 168.48, 168.59, 170.63, 170.92; FABMS (*m*/*z*): 636 $(M+H+Na)^+$. Anal. Calcd for $C_{32}H_{36}O_{12}\cdot 1/2\ H_2O$: C, 61.83; H, 6.00. Found: C, 61.84; H, 6.18.

4.5. D-1,2-*O*-Cyclohexylidene-*myo*-inositol 3D

A solution of D-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-cyclohexylidene-*myo*-inositol, **8** (117 mg, 0.20 mmol, 1.0 equiv) and hydrazine monohydrate (50 mg, 1.0 mmol) in EtOH (2 mL) was stirred at room temperature for 3 h. Volatile materials were removed under reduced pressure and the residue was chromatographed (MeOH–$CHCl_3$, 1:3) to afford **3D** (47 mg, 96%). Mp = 175–177 °C; $[\alpha]_D^{26}$ = −27.1 (*c* 0.70, MeOH).

4.6. L-1,2-*O*-Cyclohexylidene-*myo*-inositol 3L

Compound **3L** was prepared by hydrazinolysis of **9** by following the procedure described for the preparation of **3D** (Section 4.5). Mp 180–181 °C; $[\alpha]_D^{26}$ = +26.9 (*c* 0.78, MeOH).

4.7. L-1,4,5,6-Tetra-*O*-benzoyl-*myo*-inositol 10L

To a solution of **3D** (36 mg, 0.14 mmol), Et_3N (308 μL, 2.2 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (1.0 mL) was added, BzCl (128 μL, 1.10 mmol) at 0 °C and the mixture was stirred for 2 h at rt and worked-up as usual. The residue thus obtained was dissolved in 80% aqueous AcOH and the solution was refluxed for 3 h. Acetic acid was evaporated off and the residue was dissolved in ethyl acetate and worked-up as usual. The crude product was chromatographed (AcOEt/hexane, 1:2) to obtain L-1,4,5,6-tetra-*O*-benzoyl-*myo*-inositol **10L** (80 mg, 97%). The optical purity was checked by HPLC on a Chiralcel OD column. Compound **10L** >99% ee, 29 min (*i*-PrOH/hexane, 1:5).

4.8. D-1,4,5,6-Tetra-*O*-benzoyl-*myo*-inositol 10D

Compound **10D** was similarly obtained in 65% overall yield starting from **9** following the procedure described in Section 4.7. Compound **10D** >99% ee, 18 min (*i*-PrOH/hexane, 1:5).

4.9. D-3,6-Di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol 6

A solution of diol **8** (83.7 mg, 0.14 mmol), 1,1-dimethoxycyclohexane (82.4 μL, 0.547 mmol), and

camphorsulfonic acid (3.2 mg, 0.014 mmol) in CH_2Cl_2 (1 mL) was stirred under reflux for 8 h. Usual work-up followed by chromatographic purification (AcOEt/hexane, 2:7) yielded **6** (86 mg, 91%) as white crystalline powder. Mp = 162.0–162.4 °C (from AcOEt/hexane); $[\alpha]_D^{23} = +65.0$ (*c* 0.846, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 1.25–1.76 (m, 20H, cyclohexylidene-H), 2.17 (s, 3H, Me), 2.19 (s, 3H, Me), 3.24 (dd, 1H, *J* = 9.8, 11.2 Hz, Ins H-5), 4.05 (t, 1H, *J* = 9.8 Hz, Ins H-4), 4.14 (dd, 1H, *J* = 6.8, 4.9 Hz, Ins H-1), 4.53 (t, 1H, *J* = 4.9 Hz, Ins H-2), 5.02 (dd, 1H, *J* = 4.9, 9.8 Hz, Ins H-3), 5.22 (dd, 1H, *J* = 6.8, 11.2 Hz, Ins H-6), 6.00 (s, 1H, benzylic-H), 6.11 (s, 1H, benzylic-H), 7.26–7.53 (m, 10H, aromatic-H); ^{13}C NMR (67.9 MHz, $CDCl_3$): 20.53, 20.67, 20.96, 23.33, 23.43, 23.49, 23.75, 24.80, 34.77, 35.98, 36.11, 37.39, 71.75, 74.05, 74.14, 74.56, 74.61, 75.72, 76.05, 78.25, 111.4, 113.4, 127.8, 128.1, 128.3, 128.5, 128.6, 129.0, 129.1, 133.3, 134.0, 167.7, 168.3, 169.8, 170.2.

4.10. L-3,6-Di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol 7

Compound **7** was obtained in 93% from L-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-cyclohexylidene-*myo*-inositol **9** by following the procedure described in Section 4.9. Mp = 165.2–165.7 °C (from AcOEt/hexane); $[\alpha]_D^{24} = +27.1$ (*c* 0.258, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 1.25–1.64 (m, 20H, cyclohexylidene-H), 2.17 (s, 3H, Me), 2.19 (s, 3H, Me), 3.45 (dd, 1H, *J* = 10.3, 11.2 Hz, Ins H-5), 3.82 (dd, 1H, *J* = 6.8, 4.9 Hz, Ins H-1), 4.08 (t, 1H, *J* = 10.3 Hz, Ins H-4), 4.39 (t, 1H, *J* = 4.4 Hz, Ins H-2), 5.06 (dd, 1H, *J* = 4.9, 10.3 Hz, Ins H-3), 5.20 (dd, 1H, *J* = 6.8, 11.2 Hz, Ins H-6), 6.00, (s, 1H, benzylic-H), 6.11 (s, 1H, benzylic-H), 7.34–7.53 (m, 10H, aromatic-H); ^{13}C NMR (67.9 MHz, $CDCl_3$): 20.63, 20.70, 23.22, 23.55, 23.61, 24.71, 24.88, 34.64, 36.25, 37.15, 71.81, 74.10, 74.17, 74.18, 74.42, 75.21, 75.98, 78.58, 111.0, 113.9, 127.8, 128.2, 128.57, 128.64, 129.1, 129.2, 133.5, 134.0, 167.7, 168.1, 170.0, 170.07.

4.11. D-1,2:4,5-Di-*O*-cyclohexylidene-*myo*-inositol 1D

4.11.1. By hydrazinolysis route. A mixture of **6** (174 mg, 0.25 mmol) and hydrazine hydrate (122 mg, 2.51 mmol) in DMF (3 mL) was stirred for 1.5 h at room temperature. The mixture was taken in ethyl acetate and washed several times with water to remove DMF completely, and then with brine, dried, concentrated, and flash-chromatographed (AcOEt/$CHCl_3$/hexane 5:5:1) to get **1D** (64 mg, 74%).

4.11.2. By alkaline hydrolysis route. To an ice cooled solution of **6** (95 mg, 0.136 mmol) in dioxane/H_2O (10:1, 1 mL) added powdered KOH (153 mg, 2.73 mmol), and the mixture was stirred for 2 h at room temperature. CH_2Cl_2 was added and the organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from AcOEt/hexane to give crystals of diketal **1D** (29.5 mg, 63%). The mother liquor was chromatographed (AcOEt/hexane 1:1) to get an additional amount of **1D** (17 mg, 36%). Mp = 175.1–175.4 °C (from AcOEt/hexane); $[\alpha]_D^{23} = -26.0$ (*c* 0.562, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 1.42–1.70 (m, 22H, cyclohexylidene-H, –OH), 3.31 (dd, 1H, *J* = 9.8, 10.7 Hz, Ins H-5), 3.82 (t, 1H, *J* = 9.8 Hz, Ins H-4), 3.88 (dd, 1H, *J* = 10.7, 6.3 Hz, Ins H-6), 4.02 (dd, 1H, *J* = 4.9, 9.8 Hz, Ins H-3), 4.07 (dd, 1H, *J* = 4.9, 6.3 Hz, Ins H-1), 4.48 (t, 1H, *J* = 4.9 Hz, Ins H-2).

4.12. L-1,2:4,5-Di-*O*-cyclohexylidene-*myo*-inositol 1L

Diol **1L** was obtained by hydrazinolysis (74%) or alkaline hydrolysis (99%) of **7** by following the procedure described in Section 4.11. Mp = 179.5–180.1 °C (from AcOEt/hexane); $[\alpha]_D^{23} = +25.5$ (*c* 0.548, $CHCl_3$).

4.13. L-3,6-Di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol 11 and D-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol 12

To a solution of diol (±)-**2** (520 mg, 2 mmol) in pyridine (10 mL), a solution of (*S*)-*O*-acetyl mandeloyl chloride (893 mg, 4.2 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C and stirred for 3 h gradually allowing the reaction mixture to attain room temperature. After 3 h, ethyl acetate was added and washed successively with water, dil HCl, satd solution of $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain a solid (1.23 g). Crystallization from a mixture of ethyl acetate and hexane (1:3 v/v) yielded diastereomer **12** (563 mg, 46%) in pure form. The concentrated mother liquor was recrystallized from a mixture of $CHCl_3$ (10 mL) and hexane (20 mL) to get **11** (514 mg, 42%) as dense crystals. Compound **11**: mp = 177 °C; $[\alpha]_D^{26} = +53.2$ (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 1.00 (s, 3H, Me), 1.35 (s, 3H, Me), 1.41 (s, 3H, Me), 1.44 (s, 3H, Me), 2.16 (s, 3H, OAc), 2.18 (s, 3H, OAc), 3.45 (dd, 1H, *J* = 11.2, 10.3 Hz, Ins H-5), 3.79 (dd, 1H, *J* = 6.8, 4.4 Hz, Ins H-1), 4.06 (dd, 1H, *J* = 9.8, 10.5 Hz, Ins H-4), 4.33 (t, 1H, *J* = 4.4 Hz, Ins H-2), 5.07 (dd, 1H, *J* = 4.4, 10.5 Hz, Ins H-3), 5.22 (dd, 1H, *J* = 11.2, 6.8 Hz, Ins H-6), 6.05 (s, 1H, PhC*H*OAc), 6.11 (s, 1H, PhC*H*OAc), 7.34–7.47 (m, 10H, aromatic-H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.5, 20.6, 25.3, 26.7, 26.8, 27.2, 71.4, 73.97, 74.02, 74.2, 74.5, 75.4, 75.5, 79.0, 110.0, 113.1, 127.8, 128.1, 128.4, 128.6, 129.0, 129.1, 133.3, 133.8, 167.6, 168.2, 169.8, 169.9. Anal. Calcd for $C_{32}H_{36}O_{12}$: C, 62.74; H, 5.92%. Found C, 62.69; H, 5.96. Compound **12**: mp = 215–217 °C; $[\alpha]_D^{26} = +64.4$ (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (s, 3H, Me), 1.29 (s, 3H, Me), 1.31 (s, 3H, Me), 1.57 (s, 3H, Me), 2.17 (2s, 2 × 3H, 2 × OAc), 3.24 (dd, 1H, *J* = 11, 9.3 Hz, Ins H-5), 4.03 (dd, 1H, *J* = 9.3, 10.5 Hz, Ins H-4), 4.15 (dd, 1H, *J* = 6.8, 4.9 Hz, Ins H-1), 4.53 (dd, 1H, *J* = 4.4, 4.9 Hz, Ins H-2), 5.08 (dd, 1H, *J* = 4.4, 10.5 Hz, Ins H-3), 5.21 (dd, 1H, *J* = 11, 6.8 Hz, Ins H-6), 6.00 (s, 1H, PhC*H*OAc), 6.11 (s, 1H, PhC*H*OAc), 7.33–7.50 (m, 10 H, aromatic-H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.6, 20.7, 25.7, 26.5, 26.7, 27.7, 71.3, 74.0, 74.3, 74.5, 75.0, 75.6, 76.4, 78.6, 110.7, 112.6, 127.9, 128.2, 128.5,

128.6, 129.1, 129.2, 133.3, 133.9, 167.7, 168.4, 169.9, 170.2. Anal. Calcd for $C_{32}H_{36}O_{12}$: C, 62.74; H, 5.92. Found C, 62.39; H, 6.21.

4.14. L- and D-1,2:4,5-Di-*O*-isopropylidene-*myo*-inositol

Compound **2L** and **2D** were obtained by hydrazinolysis of **11** and **12**, respectively, by following the procedure described in Section 4.5. **2L**: yield 93%, mp = 160–162 °C, $[\alpha]_D^{25} = +22.3$ (*c* 1, CH_3CN). Lit.[30] mp 159–161 °C, $[\alpha]_D^{25} = +22$ (*c* 1.08, CH_3CN). Compound **2D**: yield 89%, mp = 159–161 °C, $[\alpha]_D^{25} = -21.8$ (*c* 1, CH_3CN).

4.15. D-3,6-Di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-isopropylidene-*myo*-inositol 14

To a solution of **12** (612 mg, 1 mmol) in CH_2Cl_2 (5 mL), was added water (18 μL, 1 mmol) and TFA (140 μL, 2 mmol) at 0 °C and stirred under nitrogen atmosphere. The reaction was followed by TLC and when the reaction was complete (50 min to 1 h), the mixture was dissolved in ethyl acetate, washed with satd $NaHCO_3$ and brine. The organic layer was dried over anhyd Na_2SO_4 and evaporated under reduced pressure. The resulting residue was chromatographed over silica gel (ethyl acetate/benzene, 1:3) to get the diol **14** (469 mg, 82%, R_f 0.48; AcOEt–benzene, 1:1). mp = 119–120 °C; $[\alpha]_D^{24} = +71$ (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 1.33 (s, 3H, Me), 1.56 (s, 3H, Me), 2.04 (d, *J* = 2.9 Hz, 4-OH), 2.19 (s, 3H, OAc), 2.21 (s, 3H, OAc), 2.24 (d, 1H, *J* = 3.9 Hz, 5-OH), 3.26 (dt, 1H, *J* = 9.8, 3.9 Hz, Ins H-5), 3.88 (dt, 1H, *J* = 9.8, 2.9 Hz, Ins H-4), 4.15 (dd, 1H, *J* = 7.3, 4.4 Hz, Ins H-1), 4.43 (t, 1H, *J* = 4.4 Hz, Ins H-2), 4.98 (dd, 1H, *J* = 4.4, 9.8 Hz, Ins H-3), 5.11 (dd, 1H, *J* = 9.8, 7.3 Hz, Ins H-6), 5.99 (s, 1H, PhCHOAc), 6.10 (s, 1H, PhCHOAc), 7.26–7.52 (m, 10H, aromatic-H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.70, 20.78, 25.87, 27.64, 70.23, 72.05, 72.42, 73.54, 74.64, 74.66, 75.89, 76.77, 110.98, 127.81, 127.88, 128.83, 128.85, 129.41, 129.49, 133.43, 133.68, 168.10, 168.45, 170.69, 170.74. Anal. Calcd for $C_{29}H_{32}O_{12}$: C, 60.83; H, 5.63. Found C, 61.13; H, 5.74.

4.16. L-3,6-Di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-isopropylidene-*myo*-inositol 13

To a solution of **11** (612 mg, 1 mmol) in CH_2Cl_2 (5 mL), was added water (18 μL, 1 mmol) and TFA (140 μL, 2 mmol) at 0 °C and stirred under nitrogen atmosphere. The reaction was followed by TLC and when the reaction was complete (50 min to 1 h), the mixture was dissolved in ethyl acetate, washed with satd $NaHCO_3$ and brine. The organic layer was dried over anhyd Na_2SO_4 and evaporated under reduced pressure. The resulting residue was chromatographed over silica gel to get the diol **13** (498 mg, 87%, R_f = 0.39; AcOEt–benzene, 1:1). Mp = 100–101 °C; $[\alpha]_D^{24} = +53$ (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 1.10 (s, 3H, Me), 1.44 (s, 3H, Me), 2.19 (s, 3H, OAc), 2.20 (s, 3H, OAc), 2.91 (d, 1H, *J* = 2.4 Hz, C4-OH), 3.02 (d, 1H, *J* = 2.9 Hz, C5-OH), 3.54 (dt, 1H, *J* = 9.8, 2.9 Hz, Ins H-5), 3.93 (dd, 1H, *J* = 7.3, 4.4 Hz, Ins H-1), 4.08 (dt, 1H, *J* = 9.8, 2.4 Hz, Ins H-4), 4.17 (t, 1H, *J* = 4.4 Hz, Ins H-2), 5.09 (dd, 1H, *J* = 4.4, 9.8 Hz, Ins H-3), 5.16 (dd, 1H, *J* = 9.8, 7.3 Hz, Ins H-6), 5.91 (s, 1H, PhC*H*OAc), 5.96 (s, 1H, PhC*H*OAc), 7.31–7.54 (m, 10H, aromatic-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.62, 20.69, 25.71, 27.53, 70.30, 71.78, 72.24, 73.25, 74.65, 74.88, 75.88, 76.83, 110.41, 127.56, 127.86, 128.66, 128.80, 129.24, 129.37, 133.01, 133.04, 168.56, 168.57, 170.75, 170.99. Anal. Calcd for $C_{29}H_{32}O_{12}\cdot H_2O$: C, 58.97; H, 5.80. Found C, 59.00; H, 5.77.

4.17. D-1,2-*O*-Isopropylidene-*myo*-inositol 4D

A solution of **14** (41 mg, 0.072 mmol) and hydrazine monohydrate (17 mg, 0.36 mmol) in EtOH (2 mL) was stirred at room temperature for 3 h. Volatile materials were removed under reduced pressure and the residue was chromatographed (MeOH–$CHCl_3$, 1:3) to afford **4D** (11 mg, 70%). Mp = 178–180 °C; $[\alpha]_D^{27} = -50.0$ (*c* 0.08, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.48 (s, 3H, Me), 1.62 (s, 3H, Me), 3.34 (t, 1H, *J* = 9.8 Hz, Ins H-5), 3.66 (dd, 1H, *J* = 7.8, 9.8 Hz, Ins H-4), 3.71 (t, 1H, *J* = 9.8 Hz, Ins H-6), 3.93 (dd, 1H, *J* = 9.8, 4.4 Hz, Ins H-1), 4.15 (dd, 1H, *J* = 4.4, 7.8 Hz, Ins H-3), 4.57 (t, 1H, *J* = 4.4 Hz, Ins H-2).

4.18. L-1,2-*O*-Isopropylidene-*myo*-inositol 4L

Tetrol **4L** was prepared from **13** by following the procedure described for **4D** (Section 4.17); mp = 180–181 °C; $[\alpha]_D^{27} = +56.0$ (*c* 0.25, MeOH).

4.19. Resolution of (±)-1,2-*O*-cyclohexylidene-*myo*-inositol via stannylene mediated *O*-acetylmandeloylation

Racemic 1,2-*O*-cyclohexylidene-*myo*-inositol ((±)-**3**, 300 mg, 1.15 mmol) and dibutyltin oxide (631 mg, 2.54 mmol) were suspended in 20 mL of dry toluene in a 50 mL two-necked round-bottomed flask, fitted with a Dean–Stark apparatus. The mixture was refluxed for 1 h, during which the water generated was removed. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane (15 mL). To this solution, a solution of (*S*)-*O*-acetylmandeloyl chloride (2.88 mmol) in dichloromethane (10 mL) was added slowly at −20 °C, and the mixture was stirred at the same temperature for 1 h. A solution of *N*,*N*-dimethyl-1,3-propanediamine (236 mg, 2.31 mmol) in dichloromethane (4 mL) was added to quench the excess acid chloride and stirred for 30 min and then acetic acid (264 μL, 4.62 mmol) in dichloromethane (4 mL) was added and stirred at the same temperature, for 10 min. The mixture was taken in a separating funnel and was washed with water (3 times) and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (AcOEt/benzene, 2:3) and recrystallized from AcOEt/hexane to give **8** (71 mg, 10%), **9** (296 mg, 42%), and D-3-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-cyclohexylidene-*myo*-inositol, **15** (100 mg, 20%, R_f = 0.10, AcOEt/benzene, 1:1). Compound **15**: mp = 150.0–152.0 °C (from AcOEt/hexane); $[\alpha]_D^{26} = +57.4$ (*c* 1.22, $CHCl_3$); ^{1}H NMR (270 MHz,

$CDCl_3$): 1.33–1.73 (m, 10H, cyclohexylidene-H), 2.22 (s, 3H, Me), 2.35 (d, 1H, $J = 3.4$ Hz, –OH), 2.80 (br s, 1H, –OH), 3.02 (br s, 1H, –OH), 3.32 (dt, 1H, $J = 9.8$, 2.4 Hz, Ins H-5), 3.64 (ddd, 1H, $J = 9.8$, 2.9 Hz, Ins H-4), 3.83 (dt, 1H, $J = 9.8$, 3.4 Hz, Ins H-6), 4.02 (dd, 1H, $J = 9.8$, 4.9 Hz, Ins H-1), 4.42 (dd, 1H, $J = 4.9$, 4.4 Hz, Ins H-2), 4.98 (dd, 1H, $J = 4.4$, 9.8 Hz, Ins H-3), 5.98 (s, 1H, benzylic-H), 7.35–7.55 (m, 5H, aromatic-H); ^{13}C NMR (100 MHz, CD_3OD): 21.35, 25.40, 25.82, 26.89, 36.72, 39.67, 72.65, 75.00, 75.84, 75.95, 77.03, 77.14, 80.90, 112.45, 129.86, 130.51, 131.05, 135.96, 170.94, 172.77; FABMS (*m*/*z*): 459 $(M+Na)^+$.

4.20. Resolution of (±)-1,2-*O*-isopropylidene-*myo*-inositol via stannylene mediated *O*-acetylmandeloylation

A mixture of 1,2-*O*-isopropylidene-*myo*-inositol (108 mg, 0.49 mmol) and dibutyltin oxide (268 mg, 1.08 mmol) in dry toluene was refluxed for 1 h in a flask equipped with a Dean–Stark apparatus, and then the toluene was distilled off. The residue was re-dissolved in toluene (3.0 mL) and a solution of *O*-acetylmandeloyl chloride in toluene (2.5 mL) was added at −20 °C and the solution was stirred at this temperature for 1.5 h. A solution of *N*,*N*-dimethyl-1,3-propanediamine (100 mg, 123 μL, 0.98 mmol) in dichloromethane (2 mL) was added to quench the excess acid chloride and stirred for 30 min and then acetic acid (58.8 mg, 56 μL, 0.98 mmol) in dichloromethane (2 mL) was added and stirred at the same temperature, for 10 min. After addition of $CHCl_3$, the organic layer was washed with brine (twice), dried, and evaporated. The residue was chromatographed on SiO_2 (AcOEt/benzene, 1:1) to give **13** (75.7 mg, 27%, $R_f = 0.40$), **14** (75.8 mg, 27%, $R_f = 0.48$), and a mixture of monomandelates (44.7 mg, 23%, $R_f = 0.10$).

4.21. Phosphitylation of DL-6-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-cyclohexylidene-3,4-*O*-(tetraisopropyldisiloxan-1,3-diyl)-*myo*-inositol DL-19

To a solution of DL-**19** (120 mg, 0.18 mmol) and tetrazole (25.5 mg, 0.36 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added a solution of $(BnO)_2PN$*i*-Pr_2 (100 mg, 0.29 mmol) in CH_2Cl_2 (0.4 mL) and stirred for 30 min at rt. Usual work-up followed by chromatography (AcOEt/hexane, 1:10) yielded phosphites **22** [71.8 mg, 44%, $R_f = 0.41$ (AcOEt/hexane, 1:10), colorless oil] and **23** [64.2 mg, 39%, $R_f = 0.32$ (AcOEt/hexane, 1:10), colorless oil]. Compound **22**: $[\alpha]_D^{25} = +24.3$ (*c* 1.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 0.97–1.13 (m, 28H, *i*-Pr), 1.33–1.88 (m, 10H, cyclohexylidene-H), 2.03 (s, 3H, –C(O)CH_3), 3.67 (dd, $J = 4.4$, 7.6 Hz, 1H, Ins H-1), 3.76 (td, 1H, $J = 9.2$ Hz, Ins H-5), 3.82 (dd, $J = 4.4$, 9.8 Hz, 1H, Ins H-3), 4.11 (t, $J = 9.2$ Hz, 1H, Ins H-4), 4.18 (t, $J = 4.4$ Hz, 1H, Ins H-2), 4.79 (q, $J = 6.2$ Hz, 1H, ArCH_2), 4.82 (dd, $J = 7.0$, 12.4 Hz, 1H, ArCH_2), 4.89 (1H, dd, $J = 7.2$, 12.4 Hz, ArCH_2), 4.98 (1H, dd, $J = 9.2$, 12.4 Hz, ArCH_2), 5.30 (dd, $J = 7.6$, 9.2 Hz, 1H, Ins H-6), 6.17 (s, 1H, benzylic-H), 7.28–7.40 (m, 15H, aromatic-H); ^{31}P NMR (162 MHz, $CDCl_3$): 140.13; ^{13}C NMR (100 MHz, $CDCl_3$): 12.09, 12.58, 12.60, 12.87, 17.16, 17.23, 17.25, 17.27, 17.31, 17.54, 20.68, 23.63, 23.91, 25.04, 35.06, 37.40, 63.32, 63.80, 73.40, 73.84, 73.87, 74.97, 75.51, 75.90, 76.01, 110.63, 127.26, 127.33, 127.42, 127.53, 127.61, 128.07, 128.14, 128.28, 128.32, 128.47, 128.89, 134.52, 138.39, 138.70, 167.92, 169.43; FABMS (*m*/*z*): 924 $(M+H)^+$, 945 $(M+Na)^+$. Compound **23**: $[\alpha]_D^{23} = +27.4$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00–1.13 (m, 28H, *i*-Pr), 1.37 (br, 2H, cyclohexylidene-H), 1.57 (br, 6H, cyclohexylidene-H), 1.64 (br, 2H, cyclohexylidene-H), 2.13 (s, 3H, C(O)CH_3), 3.76 (td, 1H, $J = 8.4$Hz, Ins H-5), 3.84 (dd, $J = 4.0$, 8.4 Hz, 1H, Ins H-3), 4.13 (dd, 1H, $J = 6.8$, 4.0 Hz, Ins H-1), 4.15 (t, 1H, $J = 8.4$ Hz, Ins H-4), 4.33 (t, $J = 4.0$ Hz, Ins H-2), 4.60–4.68 (m, 3H, ArCH_2), 4.78 (dd, $J = 8.4$, 12.6 Hz, 1H, ArCH_2), 5.29 (dd, $J = 6.8$, 8.4 Hz, 1H, Ins H-6), 6.11 (s, 1H, benzylic-H), 7.20–7.41 (m, 15H, aromatic-H); ^{31}P NMR (162 MHz, $CDCl_3$): δ 140.79; ^{13}C NMR (100 MHz, $CDCl_3$): 12.00, 12.54, 12.58, 12.83, 17.17, 17.24, 17.28, 17.34, 17.54, 20.69, 23.63, 23.73, 25.01, 34.68, 37.04, 63.39, 63.62, 73.02, 74.19, 75.07, 75.12, 75.38, 75.96, 76.05, 110.70, 127.36, 127.39, 127.47, 127.51, 128.01, 128.13, 128.19, 128.26, 128.30, 128.51, 128.96, 133.91, 138.27, 138.52, 167.76, 169.60; FABMS (*m*/*z*): 924 $(M+H)^+$, 946 $(M+Na)^+$.

4.22. Dibenzyl {L-6-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-cyclohexylidene-3,4-*O*-(tetraisopropyldisiloxan-1,3-diyl)-*myo*-inositol-5}-phosphate 24

To a solution of phosphite **22** (78.1 mg, 0.085 mmol) in dry CH_2Cl_2 (1.1 mL) was added *m*-CPBA (20.8 mg, 0.12 mmol) at −78 °C and the mixture was stirred for 5 min at −78 °C and then the temperature was raised to rt and stirring was continued for another 30 min. The reaction was quenched by stirring with 10% aq Na_2SO_3 for 30 min. Usual work-up followed by chromatography (AcOEt/hexane, 1:3) yielded the phosphate **24** (75.5 mg, 95%, $R_f = 0.35$) as a colorless oil. $[\alpha]_D^{25} = +41.7$ (*c* 1.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97–1.13 (m, 28H, *i*-Pr), 1.35–1.87 (m, 10H, cyclohexylidene-H), 2.09 (s, 3H, C(O)CH_3), 3.66 (dd, 1H, $J = 7.6$, 5.2 Hz, Ins H-1), 3.82 (dd, 1H, $J = 9.6$, 4.2 Hz, Ins H-3), 4.10–4.18 (m, 2H, Ins H-2 and H-4), 4.24 (td, 1H, $J = 9.6$ Hz, Ins H-5), 5.00–5.06 (q, 4H, $J = 7.6$, 8.0 Hz, benzylic-H), 5.32 (dd, 1H, $J = 9.6$, 7.6 Hz, Ins H-6), 6.22 (s, 1H, benzylic-H), 7.25–7.44 (m, 15H, aromatic-H); ^{31}P NMR: δ −0.50; ^{13}C NMR (100 MHz, $CDCl_3$): 11.83, 12.50, 12.52, 12.79, 16.99, 17.03, 17.11, 17.17, 17.21, 17.26, 17.45, 20.70, 23.55, 23.87, 24.99, 34.93, 37.27, 69.12, 69.18, 73.09, 73.86, 73.97, 75.12, 75.27, 75.76, 77.61, 110.72, 127.85, 127.97, 128.16, 128.19, 128.29, 128.33, 128.35, 128.47, 128.91, 134.39, 135.86, 136.12, 167.98, 169.34; FABMS (*m*/*z*): 939 $(M+H)^+$, 961 $(M+Na)^+$.

4.23. Dibenzyl {D-6-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2-*O*-cyclohexylidene-3,4-*O*-(tetraisopropyldisiloxan-1,3-diyl)-*myo*-inositol-5}-phosphate 25

Oxidation of the phosphite **23** (58.8 mg, 0.064 mmol, 1.0 equiv) with *m*-CPBA (15.6 mg, 0.091 mmol, 1.4 equiv) as in the above procedure gave the phosphate **25** (57.6 mg, 96%, $R_f = 0.32$, AcOEt/hexane, 1:3) as

colorless oil. $[\alpha]_D^{24} = +12.0$ (*c* 1.34, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 0.98–1.14 (m, 28H, *i*-Pr), 1.29 (br, 2H, cyclohexylidene-H), 1.53 (br, 6H, cyclohexylidene-H), 1.73 (br, 2H, cyclohexylidene-H), 2.17 (s, 3H, C(O)CH_3), 3.88 (dd, 1H, $J = 9.8$, 3.6 Hz, Ins H-3), 4.18–4.22 (m, 2H, Ins H-4 & H-1), 4.30 (td, 1H, $J = 7.6$ Hz, Ins H-5), 4.36 (t, 1H, $J = 3.6$ Hz, Ins H-2), 4.82–4.99 (m, 4H, benzylic-H), 5.35 (t, 1H, $J = 7.6$ Hz, Ins H-6), 6.12 (s, 1H, PhC*H*(OAc)), 7.20–7.45 (m, 15H, aromatic-H); ^{31}P NMR: δ −1.37; ^{13}C NMR (100 MHz, $CDCl_3$): 11.84, 12.57, 12.60, 12.85, 17.11, 17.15, 17.21, 17.22, 17.30, 17.33, 17.36, 17.57, 20.79, 23.62, 23.78, 25.06, 34.46, 36.79, 69.02, 69.14, 72.66, 74.08, 74.24, 74.83, 75.21, 75.79, 79.48, 110.83, 127.83, 127.85, 127.97, 128.21, 128.26, 128.29, 128.38, 128.42, 128.66, 129.09, 134.04, 135.87, 135.98, 167.87, 169.80; FABMS (*m*/*z*): 939 $(M+H)^+$, 961 $(M+Na)^+$.

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