Tetrahedron 65 (2009) 2703–2710

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regioselective O-acylation of *myo*-inositol 1,3,5-orthoesters: dependence of regioselectivity on the stoichiometry of the base

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ARTICLE INFO

Article history:
Received 18 April 2008
Received in revised form 29 December 2008
Accepted 13 January 2009
Available online 20 January 2009

Keywords:
Acylation
Cyclitol
Inositol
Orthoester
Regioselectivity
Transesterification

ABSTRACT

A metal mediated unusual 1–3 acyl migration from C4–O to C2–OH of *myo*-inositol 1,3,5-orthoformate was observed during the alkylation of racemic 4-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate. This has been exploited for the selective esterification of either the C4(6)–OH or the C2–OH of *myo*-inositol by varying the amount of the base used. While the use of 1 equiv of the base (sodium hydride or potassium *tert*-butoxide) for the acylation of *myo*-inositol orthoesters gives the corresponding *C*4-ester exclusively, the use of two or more equivalents of base for the same reaction gives the *C*2-ester exclusively. The relatively higher stability of the alkoxide of racemic 2-*O*-acyl-*myo*-inositol 1,3,5-orthoester as compared to the alkoxide of 4-*O*-acyl-*myo*-inositol 1,3,5-orthoester is suggested to be responsible for the observed isomerization.

1. Introduction

The chemistry and biology of phosphorylated inositols have become intense areas of research during the last two decades due to their involvement in various cellular signaling processes.[1] There are at least 26 different *myo*-inositol phosphates, 8 phosphoinositol lipids and several glycoconjugates known to occur in nature. Apart from well established roles of a few phosphoinositols in cellular signaling and protein anchoring, the biological functions of many of these phosphoinositols and glycoconjugates are far from well understood. Considering the facts that these derivatives occur in nature in very small quantities and their isolation is often tedious due to their transient nature (short half-life) and difficulty in purification, it is not surprising that these molecules have attracted the interest of synthetic chemists.[1a,2] Although methodologies for phosphoinositol synthesis starting from different starting materials have been reported,[2a,c,h,3] *myo*-inositol (**1**, Fig. 1) continues to be a frequently used starting material for the synthesis of phosphoinositols.

myo-Inositol being a cyclohexane hexol having six secondary hydroxyl groups with more or less similar chemical environment, the selective functionalization of these hydroxyl groups[4] is one of the main challenges in synthetic inositol chemistry. Often, partially protected ketals or orthoesters of inositol are used for further selective functionalization during phosphoinositol synthesis. Such a modification usually perturbs the chemical environment of different hydroxyl groups unevenly making them prone to better discrimination during synthetic manipulations. While the ketalization of *myo*-inositol gives a mixture of ketals (thus reducing the yield of the required ketal, often less than 35%), the orthoesterification provides a single product, *myo*-inositol 1,3,5-orthoester,[5] in high yield (>90%). The *myo*-inositol orthoesters (**2**–**5**, Fig. 1) have two axial hydroxyl groups and one equatorial hydroxyl group (with respect to the inositol ring) and this facilitates better discrimination among the hydroxyl groups of orthoesters. Also, the known strategies for the selective partial cleavage[4c] of the orthoester cage with reducing agents in protected *myo*-inositol orthoesters (to regenerate the C1(3)–OH or the C5–OH) make *myo*-inositol 1,3,5-orthoesters versatile intermediates for synthetic purposes. Consequently, orthoesters have become the preferred starting materials for the synthesis of phosphoinositols and their analogs in recent years.[5b,6] Several methodologies for regioselective protection of *myo*-inositol orthoester hydroxyl groups have been reported.[4c] Among various protecting groups, ester protecting groups have the advantage of mild reaction conditions for their introduction and removal, possibilities of resolution using enzymes or via diastereomeric derivatives.[5d,6] Due to these advantages, acylation of *myo*-inositol derivatives forms an important synthetic strategy. However, acyl migrations among the hydroxyl groups of *myo*-inositol are sometimes annoying during the synthesis of

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doi:10.1016/j.tet.2009.01.060

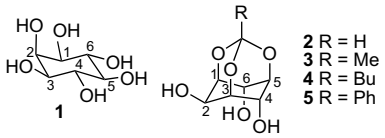
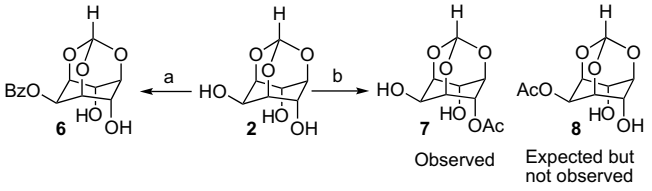


Figure 1. *myo*-Inositol and its known orthoesters.

phosphoinositols or their derivatives. Nevertheless, in a few instances, acyl migrations have been exploited for strategic and efficient synthesis of *myo*-inositol phosphates.[7]

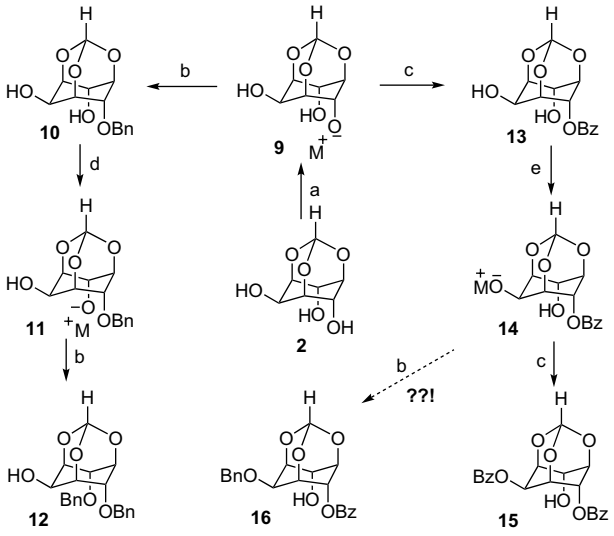
Considerable efforts have been made to understand and optimize selective acylation of the three hydroxyl groups of *myo*-inositol orthoesters.[5b,6g,8] Most of these reports deal with maximizing the yield of a particular *O*-acylated (e.g., *O*-benzoyl) derivative of a *myo*-inositol orthoester (e.g., orthoformate **2**) and hence there is no general method that could be used for the selective acylation of *C*2- or *C*4(6)-hydroxyl group in *myo*-inositol orthoesters. For instance, when we applied the reaction conditions reported for the 2-O-benzoylation[8d] of the orthoformate **2** for the preparation of the corresponding acetate, we obtained the *C*4-acetate **7** (Scheme 1). We have developed[9] simple and general methodologies for selective acylation either at the C2–OH or the C4–OH by varying the amount of the base used and the full details of this work are presented here.



Scheme 1. Acylation of **2** showing lack of generality. (a) Pyridine, benzoyl chloride;[8d] (b) pyridine, acetyl chloride.

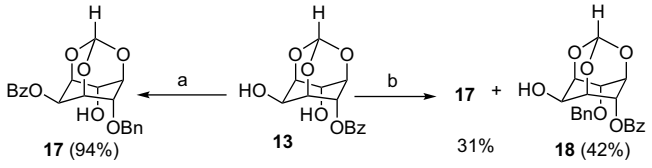
2. Results and discussion

In our efforts toward the development of simpler methods for the synthesis of inositol derivatives, we required to synthesize 2-*O*-benzyl-*myo*-inositol,[10] the precursor for *myo*-inositol 1,3,4,5,6-pentakisphosphate. Benzylation of triol **2** with 1 equiv of sodium hydride and benzyl bromide is known to give 4-*O*-benzyl ether **10** (Scheme 2) while dibenzylation gives 4,6-dibenzyl ether **12** as the major product.[6b] These results suggest that first deprotonation in **2** and **10** occurs at the *C*4- and *C*6-hydroxyl groups, respectively, on their reaction with sodium hydride. This has been attributed to the increased stability of the 4(6)-alkoxide due to chelation of the alkali metal ion.[6b] However, dibenzoylation of orthoformate **2** with potassium *tert*-butoxide and benzoyl chloride is reported to give the unsymmetrical dibenzoate **15** (in contrast to the corresponding benzylation reaction) although mono-benzoylation[11] occurs at the C4–OH (similar to mono-benzylation of **2**). A mechanism involving initial benzoylation at the C4–OH followed by the second benzoylation at the C2–OH has been proposed (Scheme 2).[11] These results imply that the treatment of the 4-benzyl ether **10** with a strong base generates *C*6-alkoxide **11** predominantly while the treatment of 4-benzoate **13** with a strong base generates *C*2-alkoxide **14** predominantly. If this is indeed the case, alkylation (benzylation) of **13** should in principle, give *C*2-*O*-alkylated product **16**. Prompted by this logic, we attempted benzylation of racemic 4-benzoate **13** in the presence of potassium *tert*-butoxide.



Scheme 2. Alkoxide mediated benzylation and benzoylation of **2**. (a) NaH or KO^{t}Bu; (b) benzyl bromide; (c) benzoyl chloride; (d) NaH (Ref. 6b); (e) KO^{t}Bu.

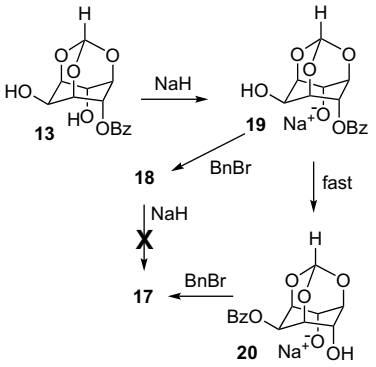
Benzoate **13** was treated with potassium *tert*-butoxide (or sodium hydride) for 5 min, and then allowed to react with benzyl bromide when racemic 2-*O*-benzoyl-4-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate[12] (**17**) was obtained as the only product (Scheme 3). The formation of **17** suggested migration of the benzoyl group from the C4–O to the C2–OH during benzylation. When the benzylation of **13** was carried out by the addition of sodium hydride to a previously mixed solution of benzoate **13** and benzyl bromide in DMF (the alkoxide was made to react as soon as it was formed), a mixture of racemic 4-*O*-benzoyl-6-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (**18**) and **17** were formed along with some amount of racemic **10**.[6b] Compound **18** was unambiguously characterized by its aminolysis to the known[6b] benzyl ether. No trace of the expected racemic **16** (Scheme 2) could be found in any of these experiments. These results suggested that after the generation of the alkoxide (in **13**) benzoyl migration competes with benzylation. It is interesting to note that the alkylation takes place only at the C4–OH no matter whether the acyl group has migrated or not. When **18** was treated with sodium hydride in DMF migration of the benzoyl group was not observed.



Scheme 3. Benzylation of **13**. (a) DMF, NaH, 5 min then benzyl bromide; (b) DMF, benzyl bromide, then NaH.

From these results, it was clear that the benzoyl migration occurred prior to O-alkylation, resulting in the formation of monoalkoxide **20** (Scheme 4), which underwent benzylation to give **17**. Treatment of 4-benzoate **13** with 1 equiv of sodium hydride in DMF gave 2-benzoate **6** as anticipated. Similar results were obtained when sodium hydride was replaced with potassium *tert*-butoxide for all the reactions presented above. Increasing the amount of sodium hydride or potassium *tert*-butoxide did not make any difference in the observed acyl migration. In some of the initial experiments, since the recovery of **6** was not good, it was isolated as its known[13] diacetate.

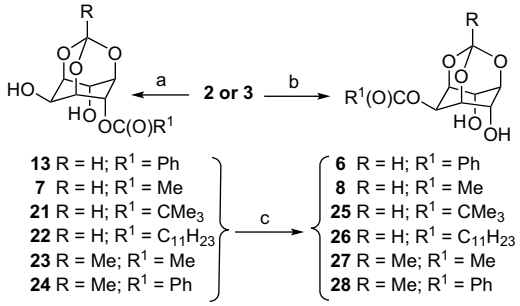
To examine the generality of this unusual 1,3-acyl migration, different racemic 4-*O*-acyl-*myo*-inositol orthoesters were required. But, there is no general method in the literature for the preparation of racemic 4-*O*-acyl-*myo*-inositol orthoesters. Based on the



Scheme 4. Pathways for benzylation of **13**.

chelation mediated 4-O-alkylation of triol **2** we anticipated 4-O-acylation of *myo*-inositol orthoesters on treatment with 1 equiv each of NaH and an acylating agent.

Accordingly different racemic 4-*O*-acyl-*myo*-inositol orthoesters (**7**, **13**, **21**–**24**) were prepared by the treatment of *myo*-inositol orthoesters with 1 equiv of sodium hydride and 1 equiv of the required acylating agent in DMF (Scheme 5 and Table 1). Interestingly, all these 4-*O*-acyl derivatives could be successfully converted to the corresponding 2-esters (**6**, **8**, **25**–**28**) by treatment with one or more equivalent(s) of sodium hydride in DMF (Scheme 5). In some initial experiments **8** was isolated as its dibenzoate, 2-*O*-acetyl-4,6-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (**29**).



Scheme 5. Acylation of triols **2** and **3** and isomerization of *C*4-esters to *C*2-esters. (a) DMF, NaH or KOBu^t (1 equiv), R^1COCl or $(R^1CO)_2O$ (1 equiv); (b) as in (a) with 2 equiv NaH; (c) DMF, NaH.

As the 4-*O*-acyl derivatives **7**, **13**, **21**–**24** on treatment with one or more equivalent(s) of sodium hydride gave the corresponding 2-*O*-acyl derivatives **6**, **8**, **25**–**28**, it was reasonable to expect that acylation of triol **2** or **3** in the presence of two or more equivalents of sodium hydride or potassium *tert*-butoxide, with 1 equivalent of an acylating agent would give the corresponding 2-*O*-acyl derivative directly. The first equivalent of sodium hydride would acylate the C4–OH (of a *myo*-inositol orthoester) while the excess of sodium hydride would effect the acyl migration to the C2–OH. If this is indeed the case, we can achieve two different selectivities for acylation of orthoesters of *myo*-inositol just by changing the stoichiometry of the base used. To explore these possibilities further, triol **2** was treated with 2 equiv of sodium hydride and 1 equiv of benzoyl chloride in DMF and as expected, 2-benzoate **6** was obtained as the sole product. Similarly treatment of triol **2** or **3** with different acylating agents with different electronic and steric features such as pivaloyl chloride (bulky), benzoyl chloride (aromatic), lauroyl chloride (fatty acyl) and acetic anhydride (small aliphatic acyl) in the presence of two or more equivalents of sodium hydride gave the corresponding *C*2-*O*-acyl derivatives (**6**, **8**, **25**–**28**) in very good yields (Table 1). Previously reported methods suffer from lack of such generality and in most methods a mixture of products is obtained where one isomer is predominantly present and requires separation from minor products. For instance, benzoylation of triol **2** using Et_3N as the base is reported to give 4-benzoate **13** while the use of pyridine as the base gives benzoate **6**.[8d] When these methodologies were adopted for acetylation of **2** we got a mixture of 4-acetate **7** and 4,6-di-*O*-acetyl-*myo*-inositol 1,3,5-orthoformate by both the methods. Similarly the use of triol **3** instead of triol **2** for benzoylation (in pyridine), gave a mixture of benzoate **28** and racemic 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoacetate. Thus previous reports are not generally applicable to either the orthoesters or the acylating agents.

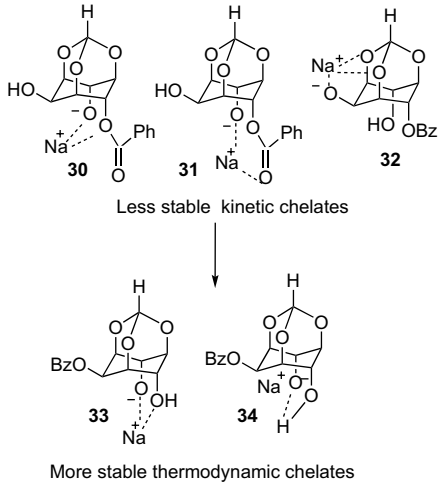
Table 1
Acylation of triols **2** and **3**

Entry	Reactant	Conditions	Product	Yield (%)
1	**2**	NaH (1 equiv), BzCl (1 equiv), DMF	**13**	89
2	**2**	NaH (1 equiv), Ac_2O (1 equiv), DMF	**7**	86
3	**2**	NaH (1 equiv), PivCl (1 equiv), DMF	**21**	84
4	**2**	NaH (1 equiv), LaurCl (1 equiv), DMF	**22**	84
5	**3**	NaH (1 equiv), Ac_2O (1 equiv), DMF	**23**	87
6	**3**	NaH (1 equiv), BzCl (1 equiv), DMF	**24**	88
7	**2**	NaH (2 equiv), BzCl (1 equiv), DMF	**6**	85
8	**2**	NaH (3 equiv), BzCl (1 equiv), DMF	**6**	87
9	**2**	NaH (7 equiv), BzCl (1 equiv), DMF	**6**	89
10	**2**	NaH (2 equiv), Ac_2O (1 equiv), DMF	**8**	91
11	**2**	NaH (2 equiv), PivCl (1 equiv), DMF	**25**	88
12	**2**	NaH (2 equiv), LaurCl (1 equiv), DMF	**26**	82
13	**3**	NaH (2 equiv), Ac_2O (1 equiv), DMF	**27**	91
14	**3**	NaH (2 equiv), BzCl (1 equiv), DMF	**28**	97

Recently, both synthetic and naturally occurring *O*-acylated inositols are being recognized as biologically active compounds with a wide spectrum of therapeutic potential. Interestingly, many of the naturally occurring *myo*-inositol esters are acylated at 2-OH and/or 6-OH of *myo*-inositol.[14] Lanceolitols, a group of 2-*O*-fatty-acylated *myo*-inositol derivatives isolated from *Solanum lanceolatum*, have shown anti-inflammatory activity as a result of COX-2 inhibition.[15] Various phosphatidylinositol mannosides, the important component of mycobacterial cell wall, contain fatty esters on inositol moiety.[16] The phosphatidylinositol component of GPI anchor of proteins are decorated with a variety of fatty acyl chains at 2-position of *myo*-inositol, which accounts for the stability of these anchors toward PIPLC action.[17] In addition, some of the synthetic *myo*-inositol esters have shown anti-oxidative[18] and anti-convulsant[19] properties. All these facts establish the importance of acylated *myo*-inositols and warrants efficient and selective methodologies for acylation of *myo*-inositol. In this context, the simple, general, and selective esterification methodology that we have developed is highly relevant and invaluable. Furthermore, recently inositols and their derivatives are increasingly being used as synthons for natural products,[20] ligands for metal complexing,[21] gelators,[22] catalysts for various organic transformations,[23] supramolecular assemblies,[24] etc. giving further impact for developing efficient methodologies for their selective derivatization.

In order to get some insight into the mechanism of the acyl migration reaction under discussion, we carried out additional experiments and made the following observations. The results of the crossover experiments[9] involving two different inositol orthoester derivatives suggested the acyl migration (Scheme 5) to be an intramolecular reaction.[25] Relatively weaker bases (Et_3N, *i*-Pr_2NEt, K_2CO_3), that cannot generate alkoxide anion (of a racemic 4-*O*-acyl-*myo*-inositol orthoester) were incapable of effecting the acyl migration suggesting that alkoxide generation is essential for this acyl migration. Hence it is reasonable to suggest that metal ion–inositol orthoester chelates may have a crucial role in this unusual acyl migration. This assumption was supported by the diminished rate of acyl migration in benzoate **13** when dibenzo-18-crown-6-ether was added to the reaction mixture or when the

reaction was conducted in THF (chelating solvent). Also, the time for completion of the reaction increased when lithium hydride was used as the base to isomerize benzoate **13**; while sodium hydride effected the acyl migration in less than 5 min, lithium hydride took about 20 min. The observed reduction in the rate of isomerization on changing the metal ion from sodium to lithium could be due to the differences in stability of the corresponding chelates. However, the lower reactivity of lithium hydride with alcohols (to generate the corresponding alkoxide) compared to sodium hydride as being responsible for an increase in the reaction time cannot be excluded. Structures of the chelates that could be involved during the acyl migration reaction are shown in Scheme 6.



Scheme 6. Chelates that could be involved during the isomerization shown in Scheme 5.

The driving force for the isomerization of the *C*4-esters to the corresponding *C*2-esters could be the formation of a relatively stable alkoxide (such as **33**, **34**) of a 1,3-diaxial diol from the chelate of a hydroxyl ester (such as **30**–**32**). We had observed earlier that the reaction of alkoxides of *myo*-inositol orthoesters (with alkyl halides) generated using different metal hydrides (sodium vs lithium) result in different regioselectivities due to variation in the stability of the chelates involved.[4d,e] Involvement of metal ion–*myo*-inositol orthoester chelates has been suggested to rationalize the observed regioselectivity during the O-alkylation of *myo*-inositol orthoesters.[6b]

3. Conclusion

We have described a novel and unusual 1(axial)→3(equatorial) acyl migration in orthoesters of *myo*-inositol. Generality of this isomerization has been illustrated by using different carboxylic acid esters. We have exploited this acyl migration to develop a convenient and efficient method to access 2-*O*- and 4-*O*-acyl-*myo*-inositol orthoesters irrespective of the nature of the acyl group, just by varying the amount of sodium hydride used for the reaction. To the best of our knowledge this is the first case of the dependence of regioselectivity on the stoichiometry of the base used in a reaction. Unlike previously reported methods of acylation of inositol orthoesters, our method is very general and can be applied to synthesize a variety of *myo*-inositol esters. These results are of interest not only to organic chemists dealing with phosphoinositol synthesis but also to a wider cross section of biological and medicinal chemists in the context of the use of inositols in various fields overlapping with organic chemistry.

4. Experimental section

4.1. General methods

All the deuterated solvents, *myo*-inositol, triethylorthoformate, trimethylorthoacetate, benzyl bromide, sodium hydride, pivaloyl chloride, and lauric acid were obtained from Aldrich Chemical Company, USA and were used as received. Benzoyl chloride, acetic anhydride, dimethylformamide, pyridine, chloroform, anhydrous sodium sulfate, sodium bicarbonate, potassium carbonate, triethylamine, potassium *tert*-butoxide, sodium chloride, and *p*-toluenesulfonic acid, were obtained from SD Fine Chemicals, India. All the solvents used, benzoyl chloride and *p*-toluenesulfonic acid were purified according to the literature procedures.[26] Silica gel for flash column chromatography (230–400 mesh) was obtained from Spectrochem India Ltd. Light petroleum refers to the 60–80 °C boiling fraction of petroleum ether. TLC 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 after spraying concd sulfuric acid. *myo*-Inositol 1,3,5-orthoesters were prepared as reported earlier.[5] Sodium hydride used in the reactions was a suspension in mineral oil (60%) and was washed with dry hexane and dried under vacuum before use. Column chromatographic separations were carried out by flash chromatography with light petroleum–ethyl acetate mixture, unless otherwise mentioned. IR spectra were recorded in the solid state as Nujol mull or as KBr pellets or in solution using an appropriate solvent (concd 1 μM) on an FTIR-8400 Shimadzu spectrophotometer. NMR spectra were recorded either on Bruker ACF 200 (200 MHz for ^{1}H) or MSL 300 (300 MHz for ^{1}H) spectrometers. Chemical shifts (δ) reported are referred to internal tetramethylsilane. Microanalytical data were obtained using a Carlo-Erba CHNS-0 EA 1108 Elemental Analyzer, at the National analytical facility, National Chemical Laboratory, Pune 411 008. All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus. All the compounds previously known in the literature were characterized by comparison of their R_f values on TLC, IR, and ^{1}H NMR spectra as well as melting point (in case of solids) with authentic samples.

4.2. Benzylation of (±)-4-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (13)

4.2.1. Procedure I

(±)-Benzoate **13**[8d] (0.300 g, 1.02 mmol) was dissolved in DMF (3 mL) and stirred with sodium hydride (0.024 g, 1 mmol) at room temperature for 5 min. Benzyl bromide (0.12 mL, 1 mmol) was added to the reaction mixture and the stirring continued for 24 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (25 mL×5) followed by brine (25 mL×2), dried over anhydrous sodium sulfate; the solvents were removed under reduced pressure using a rotary evaporator. The products were separated by column chromatography (eluent: gradient elution with 2–30% ethyl acetate in light petroleum) to obtain (±)-**17**[12] (0.360 g, 94%) as colorless solid (R_f=0.3, 20% ethyl acetate in light petroleum) and (±)-**10**[6b] (0.010 g, 4%) as a colorless gum (R_f=0.3, 30% ethyl acetate in light petroleum).

4.2.2. Procedure II

(±)-Benzoate **13** (0.300 g, 1.02 mmol) and benzyl bromide (0.12 mL, 1 mmol) were dissolved in DMF (3 mL) and sodium hydride (0.024 g, 1 mmol) was added and stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (25 mL×5) followed by brine (25 mL×2), dried over anhydrous sodium sulfate; the solvents were removed under reduced pressure using a rotary evaporator. The products were separated by column chromatography (eluent:

gradient elution with 2–30% ethyl acetate in light petroleum) to obtain (±)-**17**[12] (0.120 g, 31%) (20% ethyl acetate in light petroleum) and (±)-**18** (0.160 g, 42%) as colorless solids, and (±)-**10**[6b] (0.040 g, 14%) (20% ethyl acetate in light petroleum) as a colorless gum. Compound **18**: mp 107–110 °C; R_f=0.25 (20% ethyl acetate in light petroleum); Found: C, 64.91; H, 5.35. $C_{21}H_{20}O_7 \cdot 0.25H_2O$ requires: C, 64.84; H, 5.32%; HRMS: MH^+ found 385.1291, $C_{21}H_{21}O_7$ requires 385.1287; ν_{max}(Nujol) 1724 (C=O), 3200–3600 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.90 (2H, d, *J* 12 Hz, ArH), 7.10–7.65 (8H, m, ArH), 5.70–5.85 (1H, m, Ins H-6), 5.57 (1H, s, HCO_3), 4.65–4.75 (1H, m, Ins H), 4.50–4.65 (2H, s, $PhCH_2$), 4.40–4.50 (1H, m, Ins H), 4.30–4.40 (2H, m, Ins H), 4.25 (1H, m, Ins H), 3.00–3.55 (1H, br s, OH); δ_C (50.3 MHz, $CDCl_3$) 165.1 (O–*C*=O), 136.7 (Ar C), 133.1 (Ar C), 129.6 (Ar C), 128.8 (Ar C), 128.1 (Ar C), 127.6 (Ar C), 127.4 (Ar C), 103.0 (HCO_3), 73.4 (Ins *C*-6), 72.4 (BnCH_2), 71.9 (Ins C), 71.7 (Ins C), 67.9 (Ins C), 66.6 (Ins C), 61.1 (Ins C).

4.3. Aminolysis of (±)-18

(±)-Benzoate **18** (0.100 g, 0.26 mmol) was stirred with *iso*-butylamine (1 mL) and methanol at room temperature for 24 h. Solvent was evaporated and the residue purified by column chromatography to get benzyl ether (±)-**10**[6b] (0.070 g, 96%) as a colorless gum.

4.4. Preparation of *myo*-inositol 1,3,5-orthoacetate (3)

myo-Inositol (12 g, 66.7 mmol) was suspended in DMF (100 mL), trimethylorthoacetate (12 mL, 94.3 mmol), and *p*-toluenesulfonic acid (1 g, 5.8 mmol) were added and stirred at 90–100 °C for 1–2 h. The acid was neutralized by the addition of triethylamine (4 mL) and the reaction mixture was cooled to room temperature. The solvents were evaporated under reduced pressure and the residue obtained was chromatographed over silica gel with ethyl acetate as the eluent to obtain *myo*-inositol 1,3,5-orthoacetate (**3**, 12.38 g, 91%) as a colorless solid. R_f=0.5 (ethyl acetate); mp 186–187 °C; lit.[5b] mp 185–187 °C.

4.5. General procedure (A) for 4-O-acylation of *myo*-inositol 1,3,5-orthoesters

myo-Inositol 1,3,5-orthoester (1 mmol) was dissolved in DMF (3 mL). Sodium hydride (1 mmol) and the required acyl chloride or acid anhydride (1 mmol) were added and the mixture stirred for 5 min. Residual sodium hydride was destroyed by the addition of moist ethyl acetate (10 mL) or acetic acid (0.06 mL). The reaction mixture was diluted with ethyl acetate (60 mL), washed with water (30 mL×5) followed by brine (30 mL×2), dried over anhydrous sodium sulfate; the solvents were removed under reduced pressure using a rotary evaporator to obtain crude (±)-4-*O*-acyl-*myo*-inositol 1,3,5-orthoester. The product was isolated by column chromatography (eluent: gradient elution with 2–40% ethyl acetate in light petroleum).

4.6. Benzoylation of *myo*-inositol 1,3,5-orthoformate (2)

Orthoformate **2** (0.190 g, 1 mmol) was benzoylated with benzoyl chloride (0.12 mL) and sodium hydride (0.024 g, 1 mmol) as in the general procedure A to obtain (±)-4-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate[8d] (**13**, 0.260 g, 88%) as a colorless solid. Mp 149–152 °C; R_f=0.31 (30% ethyl acetate in light petroleum); ν_{max}-(Nujol) 1720 (C=O), 3200–3600 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) δ 7.90–8.05 (2H, d, *J* 12 Hz, Ar H), 7.30–7.70 (3H, m, Ar H), 5.75–5.85 (1H, m, Ins H-4), 5.55–5.60 (1H, s, HCO_3), 4.60–4.75 (1H, m, Ins H), 4.50–4.60 (1H, m, Ins H), 4.30–4.45 (1H, m, Ins H), 4.15–4.30 (2H, m, Ins H), 3.30 (1H, d, *J* 19 Hz, OH), 2.50 (1H, d, *J* 7 Hz, OH); δ_C (50.3 MHz, $CDCl_3$) 164.9 (O–*C*=O), 133.7 (Ar C), 129.7 (Ar C), 128.6 (Ar C), 103.0 (HCO_3), 74.2 (Ins C), 71.9 (Ins C), 68.5 (Ins C), 68.1 (Ins C), 67.3 (Ins C), 61.0 (Ins C).

4.7. Acetylation of *myo*-inositol 1,3,5-orthoformate (2)

Acetylation of **2** (0.190 g, 1 mmol) with acetic anhydride (0.1 mL) and sodium hydride (0.024 g, 1 mmol) following the general procedure A gave the racemic acetate **7** (0.200 g, 86%) as a colorless solid. Mp 156 °C; R_f=0.26 (40% ethyl acetate in light petroleum); Found: C, 46.18; H, 5.45. $C_9H_{12}O_7$ requires: C, 46.53; H, 5.21%; ν_{max}(Nujol) 1717 (C=O), 3300–3500 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.40–5.55 (2H, m, Ins H-4 and HCO_3), 4.55–4.65 (1H, m, Ins H), 4.40–4.50 (1H, m, Ins H), 4.15–4.25 (2H, m, Ins H), 4.00–4.10 (1H, m, Ins H), 3.56 (1H, br d, *J* 10 Hz, OH), 2.80 (1H, br d, *J* 7 Hz, OH), 2.11 (3H, s, CH_3); δ_C (50.3 MHz, DMSO-d_6) 170.3 (O–*C*=O), 102.6 (HCO_3), 74.2 (Ins *C*-4), 71.9 (Ins C), 68.9 (Ins C), 68.4 (Ins C), 66.6 (Ins C), 59.4 (Ins C), 21.0 (CH_3).

4.8. Pivaloylation of *myo*-inositol 1,3,5-orthoformate (2)

Triol **2** (0.190 g, 1 mmol) was allowed to react with pivaloyl chloride (0.12 mL, 1 mmol) and sodium hydride (0.024 g, 1 mmol) as in procedure A to obtain the racemic pivalate **21** (0.230 g, 84%) as a colorless solid. Mp 128 °C; R_f=0.31 (30% ethyl acetate in light petroleum); Found: C, 52.62; H, 6.55. $C_{12}H_{18}O_7$ requires: C, 52.53; H, 6.62%; ν_{max}(Nujol) 1717 (C=O), 3100–3600 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.50–5.60 (2H, m, Ins H-4 and HCO_3), 4.55–4.65 (1H, m, Ins H), 4.40 (1H, m, Ins H), 4.20–4.25 (2H, m, Ins H), 4.00–4.10 (1H, m, Ins H), 3.30 (1H, br d, *J* 10 Hz, OH), 2.50 (1H, br d, *J* 6 Hz, OH), 1.20 (9H, s, 3×CH_3); δ_C (50.3 MHz, $CDCl_3$) 176.7 (O–*C*=O), 102.7 (HCO_3), 74.1 (Ins *C*-4), 71.6 (Ins C), 68.2 (Ins C), 67.8 (Ins C), 67.1 (Ins C), 60.7 (Ins C), 38.7 (CMe_3), 26.8 (3×CH_3).

4.9. Lauroylation of *myo*-inositol 1,3,5-orthoformate (2)

Triol **2** (0.190 g, 1 mmol) was allowed to react with lauroyl chloride (0.23 mL, 1 mmol) as in procedure A to obtain the racemic laurate **22** (0.310 g, 84%) as a colorless solid. Mp 82–84 °C; R_f=0.35 (30% ethyl acetate in light petroleum); Found: C, 61.20; H, 8.76. $C_{19}H_{32}O_7$ requires: C, 61.25; H, 8.67%; ν_{max}(Nujol) 1745 (C=O), 3200–3600 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.55 (1H, m, Ins H-4), 5.50 (1H, s, HCO_3), 4.60 (1H, m, Ins H), 4.40 (1H, m, Ins H), 4.20 (2H, m, Ins H), 4.05 (1H, m, Ins H), 3.50 (1H, br s, OH), 2.85 (1H, br s, OH), 2.30 (2H, t, *J* 9 Hz, $COCH_2$), 1.50–1.70 (2H, m, $COCH_2CH_2$), 1.15–1.45 (16H, m, 8×CH_2), 0.80–0.95 (3H, t, *J* 9 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 171.9 (O–*C*=O), 102.8 (HCO_3), 74.1 (Ins *C*-4), 71.6 (Ins C), 68.2 (Ins C), 67.7 (Ins C), 67.2 (Ins C), 60.6 (Ins C), 33.9 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.5 (CH_2), 22.5 (CH_2), 13.9 (CH_3).

4.10. Acetylation of *myo*-inositol 1,3,5-orthoacetate (3)

Triol **3** (0.204 g, 1 mmol) was acetylated with acetic anhydride (0.1 mL, 1 mmol) as in the general procedure A to obtain the racemic acetate **23** (0.215 g, 87%) as a colorless solid. Mp 181–183 °C; R_f=0.3 (40% ethyl acetate in light petroleum); Found: C, 46.66; H, 5.69. $C_{10}H_{14}O_7 \cdot 0.6H_2O$ requires: C, 46.71; H, 5.96%; ν_{max}(Nujol) 1728–1747 (C=O), 3261 (OH), 3458 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.40–5.55 (1H, m, Ins H-4), 4.50–4.60 (1H, m, Ins H), 4.35–4.45 (1H, m, Ins H), 4.15–4.30 (2H, m, Ins H), 3.95–4.10 (1H, m, Ins H), 3.60 (1H, br s, OH), 3.10 (1H, br s, OH), 2.10 (3H, s, $COCH_3$), 1.45 (3H, s, H_3CCO_3); δ_C (50.3 MHz, $CDCl_3$) 170.3 (O–*C*=O), 108.7 ($MeCO_3$), 75.2 (Ins *C*-4), 72.8 (Ins C), 69.1 (Ins C), 68.7 (Ins C), 66.7 (Ins C), 58.5 (Ins C), 24.8 (H_3CCO_3), 21.3 ($COCH_3$).

4.11. Benzoylation of *myo*-inositol 1,3,5-orthoacetate (3)

Triol **3** (0.204 g, 1 mmol) was benzoylated with benzoyl chloride (0.12 mL), as above (general procedure A) to obtain the racemic benzoate **24** (0.270 g, 88%) as a colorless solid. Mp 108 °C; R_f=0.33 (35% ethyl acetate in light petroleum); Found: C, 58.79; H, 5.52. $C_{15}H_{16}O_7$ requires: C, 58.42; H, 5.23%; ν_{max}(Nujol) 1717 (C=O), 3200–3600 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.90–8.10 (2H, m, Ar H), 7.55–7.65 (1H, m, Ar H), 7.35–7.50 (2H, m, Ar H), 5.65–5.70 (1H, m, Ins H-4), 4.55–4.65 (1H, m, Ins H), 4.45–4.50 (1H, m, Ins H), 4.30–4.35 (1H, m, Ins H), 4.15–4.25 (2H, m, Ins H), 3.6 (1H, br s, OH), 3.15 (1H, br s, OH), 1.50 (3H, s, CH_3); δ_C (50.3 MHz, CH_3OH with D_2O as external lock) 167.7 (O–*C*=O), 134.6 (Ar C), 131 (Ar C), 129.8 (Ar C), 109.8 (Me*C*O_3), 74.5 (Ins *C*-4), 71.2 (Ins C), 69.2 (Ins C), 64.7 (Ins C), 24.9 (*C*H_3).

4.12. General procedure (B) for the isomerization of (±)-4-*O*-acyl-*myo*-inositol 1,3,5-orthoesters to 2-*O*-acyl-*myo*-inositol 1,3,5-orthoesters

(±)-4-*O*-Acyl-*myo*-inositol 1,3,5-orthoester (1 mmol) was dissolved in DMF (3 mL) and stirred with sodium hydride or potassium *tert*-butoxide (1 mmol) for 5 min. The reaction mixture was then diluted with ethyl acetate (50 mL), washed with water (30 mL×5) followed by brine (30 mL×2) and dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to obtain 2-*O*-acyl-*myo*-inositol 1,3,5-orthoester. In some experiments, the product was isolated as its diacetate or dibenzoate derivative.

4.13. Isomerization of (±)-4-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (13)

4.13.1. Using sodium hydride

Benzoate **13** (0.294 g, 1 mmol) was isomerized to 2-benzoate **6** (0.265 g, 90%) as described in the general procedure B; mp 211 °C; lit.[8a] mp 210–213 °C.

4.13.2. Using potassium tert-butoxide

Benzoate **13** (0.294 g, 1 mmol) was treated with potassium *tert*-butoxide (0.112 g, 1 mmol) as above. After 5 min pyridine (5 mL) and acetic anhydride (1 mL) were added and the reaction mixture was stirred overnight, at room temperature. The reaction mixture was then diluted with chloroform (100 mL), washed successively with water (50 mL×5), cold dil HCl (30 mL×2), satd sodium bicarbonate solution (50 mL×2), and brine (50 mL×2). The organic layer was dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure to obtain 2-*O*-benzoyl-4,6-di-*O*-acetyl-*myo*-inositol 1,3,5-orthoformate (0.350 g, 93%) as a colorless solid. Mp 142 °C; lit.[13] mp 142–143 °C.

4.14. Isomerization of (±)-4-*O*-acetyl-*myo*-inositol 1,3,5-orthoformate (7)

4.14.1. Using sodium hydride

The racemic acetate **7** (0.232 g, 1 mmol) was treated with sodium hydride as in the general procedure B and benzoylated with benzoyl chloride (10 mmol) and pyridine (10 mL) to obtain 2-*O*-acetyl-4,6-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (**29**, 0.390 g, 89%) and 2,4,6-tri-O-benzoyl-*myo*-inositol 1,3,5-orthoformate[8b] (0.030 g, 6%) as colorless solids, after chromatography (eluent: gradient elution with 2–20% ethyl acetate in light petroleum). Compound **29**: mp 212 °C; R_f=0.27 (15% ethyl acetate in light petroleum); Found: C, 62.51; H, 4.11. $C_{23}H_{20}O_9$ requires: C, 62.72; H, 4.54%; ν_{max}(Nujol) 1730 (C=O) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.75–7.95 (4H, d, *J* 12 Hz, Ar H), 7.40–7.55 (2H, t, *J* 12 Hz, Ar H), 7.10–7.30 (4H, m, Ar H), 5.85 (2H, t, *J* 6 Hz, Ins H-4 and Ins H-6), 5.70 (1H, s, HCO_3), 5.5 (1H, m, Ins H-2), 4.90–5.00 (1H, m, Ins H-5), 4.50–4.60 (2H, m, Ins H-1 and Ins H-3), 2.25 (3H, s, $COCH_3$); δ_C (50.3 MHz, $CDCl_3$) 170.5 (O–*C*=O of Ac), 165.0 (2×O–*C*=O of Bz), 133.4 (Ar C), 129.3 (Ar C), 128.6 (Ar C), 128.3 (Ar C), 103.2 (*H*CO_3), 69.3 (Ins C), 68.4 (Ins C), 67.0 (Ins C), 63.4 (Ins C), 20.7 (*C*H_3).

4.14.2. Using potassium tert-butoxide

The racemic acetate **7** (0.232 g, 1 mmol) was isomerized with potassium *tert*-butoxide (0.112 g, 1 mmol) as in the general procedure B and benzoylated as in the procedure given in Section 4.14.1, to obtain **29** (0.420 g, 95%) as a colorless solid.

4.15. Isomerization of (±)-4-*O*-pivaloyl-*myo*-inositol 1,3,5-orthoformate (21) with sodium hydride

The racemic pivalate **21** (0.100 g, 0.36 mmol) was treated with sodium hydride (0.010 g, 0.4 mmol) in DMF (2 mL) as in the general procedure B to obtain 2-pivalate **25** (0.090 g, 90%) as a colorless solid. Mp 159 °C; R_f=0.28 (25% ethyl acetate in light petroleum); Found: C, 52.95; H, 6.46. $C_{12}H_{18}O_7$ requires: C, 52.55; H, 6.62%; ν_{max}(Nujol) 1721 (C=O), 3100–3500 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.50 (1H, s, HCO_3), 5.25 (1H, m, Ins H-2), 4.60 (2H, m, Ins H), 4.30 (3H, m, Ins H), 4.20 (2H, br, 2×OH), 1.30 (9H, s, 3×CH_3); δ_C (50.3 MHz, $CDCl_3$) 179.3 (O–*C*=O), 102.2 (*H*CO_3), 71.5 (2×Ins C), 68.5 (Ins *C*-2), 67.8 (2×Ins C), 63.0 (Ins *C*-5), 38.9 (*C*Me_3), 26.8 (3×*C*H_3).

4.16. Isomerization of (±)-4-*O*-lauroyl-*myo*-inositol 1,3,5-orthoformate (22) with sodium hydride

The racemic laurate **22** (0.100 g, 0.27 mmol) was treated with sodium hydride (0.010 g, 0.4 mmol) in DMF (2 mL) as in the general procedure B to obtain 2-laurate **26** (0.093 g, 93%) as a colorless solid. Mp 89 °C; R_f=0.3 (25% ethyl acetate in light petroleum); Found: C, 61.01; H, 8.73. $C_{19}H_{32}O_7$ requires: C, 61.25; H, 8.67%; ν_{max}(Nujol) 1747 (C=O), 3466 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.50 (1H, s, HCO_3), 5.30 (1H, m, Ins H-2), 4.55–4.65 (2H, m, Ins H), 4.20–4.40 (5H, m, 2×OH, 3×Ins H), 2.5 (2H, t, *J* 10 Hz, $COCH_2$), 1.55–1.75 (2H, m, $COCH_2CH_2$), 1.15–1.45 (16H, m, 8×CH_2), 0.80–0.95 (3H, t, *J* 11 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 174.3 (O–*C*=O), 102.2 (*H*CO_3), 71.6 (2×Ins C), 68.4 (Ins *C*-2), 67.7 (2×Ins C), 62.9 (Ins *C*-5), 34.1 (aliph C), 31.7 (aliph C), 29.3 (aliph C), 29.1 (aliph C), 28.8 (aliph C), 24.7 (aliph C), 22.4 (aliph C), 13.8 (*C*H_3).

4.17. Isomerization of (±)-4-*O*-acetyl-*myo*-inositol 1,3,5-orthoacetate (23)

4.17.1. Using sodium hydride

The racemic acetate **23** (0.246 g, 1 mmol) was treated with sodium hydride (0.024 g, 1 mmol) in DMF (3 mL) as in the general procedure B to get 2-acetate **27** (0.22 g, 89%) as a colorless solid. Mp 66–68 °C; R_f=0.25 (30% ethyl acetate in light petroleum); Found: C, 45.37; H, 5.88. $C_{10}H_{14}O_7 \cdot H_2O$ requires: C, 45.43; H, 6.10%; HRMS: MNa^+ found 269.0637, $C_{21}H_{21}O_7Na$ requires 269.0637; ν_{max}(Nujol) 1732 (C=O), 3100–3600 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.30 (1H, m, Ins H-2), 5.00 (2H, d, *J* 9 Hz, 2×OH), 4.40–4.60 (2H, m, 2×Ins H), 4.30 (2H, m, 2×Ins H), 4.10–4.25 (1H, m, Ins H-5), 2.20 (3H, s, $COCH_3$), 1.45 (3H, s, CCH_3); δ_C (50.3 MHz, $CDCl_3$) 170.1 (O–*C*=O), 107.6 (O_3CMe), 72.3 (2×Ins C), 68.5 (Ins *C*-2), 66.9 (2×Ins C), 61.9 (Ins *C*-5), 29.1 (*C*OCH_3), 23.6 (*C*CH_3).

4.17.2. Using potassium tert-butoxide

The racemic acetate **23** (0.246 g, 1 mmol) was treated with potassium *tert*-butoxide (0.112 g, 1 mmol) in DMF (3 mL) with stirring,

as in the general procedure B, to get **27** (0.21 g, 85%) as the only product.

4.18. Isomerization of (±)-4-*O*-benzoyl-*myo*-inositol 1,3,5-orthoacetate (24)

4.18.1. Using sodium hydride

The racemic benzoate **24** (0.20 g, 0.65 mmol) was treated with sodium hydride (0.156 g, 0.65 mmol) in DMF (2 mL) as in the general procedure B to obtain 2-benzoate **28** (0.190 g, 95%) as a colorless solid. Mp 160 °C; R_f=0.4 (35% ethyl acetate in light petroleum); Found: C, 58.07; H, 5.37. $C_{15}H_{16}O_7$ requires: C, 58.42; H, 5.23%; ν_{max}(Nujol) 1711 (C=O), 3100–3600 (OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.1–8.2 (2H, d, *J* 9 Hz, Ar H), 7.60 (1H, t, *J* 9 Hz, Ar H), 7.40–7.55 (2H, m, Ar H), 5.5 (1H, t, 3 Hz, Ins H-2), 4.55–4.65 (2H, m, 2×Ins H), 4.45–4.50 (2H, m, 2×Ins H), 4.3 (1H, m, Ins H-5), 4.25 (2H, d, *J* 6 Hz, 2×OH), 1.50 (3H, s, CH_3); δ_C (50.3 MHz, CH_3OH with D_2O as external lock) 167.7 (O–*C*=O), 134.6 (Ar C), 131 (Ar C), 129.8 (Ar C), 109.8 ($MeCO_3$), 74.5 (2×Ins C), 71.2 (Ins *C*-2), 69.2 (2×Ins C), 64.7 (Ins *C*-5), 24.9 (*C*H_3).

4.18.2. Using potassium tert-butoxide

The racemic benzoate **24** (0.100 g, 0.32 mmol) was treated with potassium *tert*-butoxide (0.037 g, 0.33 mmol) in DMF (1 mL) as in the general procedure B to obtain **28** (0.090 g, 90%) as the only product.

4.19. General procedure (C) for 2-O-acylation of *myo*-inositol 1,3,5-orthoesters

myo-Inositol 1,3,5-orthoester (1 mmol) was dissolved in DMF (3 mL). Sodium hydride (2 mmol) and acyl chloride (or acid anhydride) were added and the mixture stirred for 5 min. Residual sodium hydride was destroyed by the addition of moist ethyl acetate (10 mL) or acetic acid (0.06 mL). The reaction mixture was diluted with ethyl acetate (60 mL), washed with water (30 mL×5), saturated sodium bicarbonate (30 mL×2) followed by brine (30 mL×2) and dried over anhydrous sodium sulfate; the solvents were removed under reduced pressure using a rotary evaporator, to obtain 2-*O*-acyl-*myo*-inositol 1,3,5-orthoester. The products were isolated by column chromatography (eluent: gradient elution with 2–40% ethyl acetate in light petroleum).

4.20. Benzoylation of *myo*-inositol 1,3,5-orthoformate (2)

Triol **2** (0.190 g, 1 mmol) was benzoylated with benzoyl chloride (0.12 mL) and sodium hydride (0.048 g, 2 mmol) as in the general procedure C to obtain **6** (0.250 g, 85%) and (±)-dibenzoate **15** (0.030 g, 8%) as colorless solids.

4.21. Reaction of *myo*-inositol 1,3,5-orthoformate (2) with 3 equiv of sodium hydride and 1 equiv benzoyl chloride

Triol **2** (0.190 g, 1 mmol) was dissolved in DMF (3 mL). Sodium hydride (0.072 g, 3 mmol) and benzoyl chloride (0.12 mL) were added and stirred for 5 min. Work up of the reaction mixture (as in procedure C) followed by column chromatography gave **6** (0.256 g, 87%) as the only product.

4.22. Reaction of *myo*-inositol 1,3,5-orthoformate (2) with excess sodium hydride and 1 equiv benzoyl chloride

Triol **2** (0.190 g, 1 mmol) was dissolved in DMF (3 mL) and benzoylated with benzoyl chloride (0.12 mL) in the presence of sodium hydride (0.170 g, 7 mmol) as above to get **6** as the sole product.

4.23. Acetylation of *myo*-inositol 1,3,5-orthoformate (2)

Triol **2** (0.190 g, 1 mmol) was acetylated with sodium hydride (0.048 g, 2 mmol) and acetic anhydride (0.1 mL, 1 mmol) as in the general procedure C to obtain **8** (0.210 g, 91%) as a colorless solid.[6c]

4.24. Pivaloylation of *myo*-inositol 1,3,5-orthoformate (2)

Triol **2** (0.190 g, 1 mmol) was allowed to react with pivaloyl chloride (0.12 mL, 1 mmol) as in procedure C, in the presence of sodium hydride (0.048 g, 2 mmol) to obtain **25** (0.241 g, 88%) as a colorless solid.

4.25. Lauroylation of *myo*-inositol 1,3,5-orthoformate (2)

Triol **2** (0.190 g, 1 mmol) was allowed to react with lauroyl chloride (0.23 mL, 1 mmol) in the presence of sodium hydride (0.048 g, 2 mmol) as in procedure C to obtain **26** (0.303 g, 82%) as a colorless solid.

4.26. Acetylation of *myo*-inositol 1,3,5-orthoacetate (3)

Triol **3** (0.204 g, 1 mmol) was acetylated with acetic anhydride (0.1 mL, 1 mmol) as in procedure C to obtain **27** (0.225 g, 91%) as a colorless solid.

4.27. Benzoylation of *myo*-inositol 1,3,5-orthoacetate (3)

Triol **3** (0.204 g, 1 mmol) was benzoylated with benzoyl chloride (0.12 mL) as above to obtain **28** (0.300 g, 97%) as a colorless solid.

Acknowledgements

K.M.S. and S.D. thank CSIR for research fellowships. This work was funded by the Department of Science and Technology, New Delhi, India. Technical assistance by Madhuri Patil and Rajendra Jagdhane is much appreciated.

References and notes

1. (a) Potter, B. V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933; (b) Hancock, J.T. *Cell Signaling,*; Oxford University: New York, NY, 2005.
2. (a) Prestwich, G. D. *Acc. Chem. Res.* **1996**, *29*, 503; (b) Gu, Q.-M.; Prestwich, G. D. *J. Org. Chem.* **1996**, *61*, 8642; (c) Chen, J.; Dorman, G.; Prestwich, G. D. *J. Org. Chem.* **1996**, *61*, 393; (d) Reddy, K. K.; Ye, J.; Falck, J. R.; Capdevila, J. H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2115; (e) Reddy, K. M.; Reddy, K. K.; Falck, J. R. *Tetrahedron Lett.* **1997**, *38*, 4951; (f) Reddy, K. K.; Rizo, J.; Falck, J. R. *Tetrahedron Lett.* **1997**, *38*, 4729; (g) Chung, S.-K.; Chang, Y. T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2715; (h) Chen, J.; Feng, L.; Prestwich, G. D. *J. Org. Chem.* **1998**, *63*, 6511; (i) Chung, S.-K.; Chang, Y. T.; Lee, E. L.; Shin, B.-G.; Kwon, Y.-U.; Kim, K.-C.; Lee, D. H.; Kim, M. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1503; (j) Chung, S.-K.; Shin, B.-G.; Chang, Y. T.; Suh, B.-C.; Kim, K.-T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 659; (k) Chung, S.-K.; Chang, Y. T.; Kwon, Y.-K. *J. Carbohydr. Chem.* **1998**, *17*, 369; (l) Solomons, K. R. H.; Freeman, S.; Schwalbe, C. H.; Shears, S. B.; Nelson, D. J.; Xie, W.; Bruzik, K. S.; Kaetzel, M. A. *Carbohydr. Res.* **1998**, *309*, 337; (m) Watanabe, Y.; Nakatomi, M. *Tetrahedron* **1999**, *55*, 9743; (n) Watanabe, Y.; Ishikawa, H. *Tetrahedron Lett.* **2000**, *41*, 8509; (o) Kubiak, R. J.; Bruzik, K. S. *J. Org. Chem.* **2002**, *68*, 960; (p) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 11653; (q) Chung, S.-K.; Kwon, Y. U.; Shin, J.-H.; Chang, Y.-T.; Lee, C.; Shin, B. G.; Kim, K.-C.; Kim, M.-J. *J. Org. Chem.* **2002**, *67*, 5626; (r) Han, F.; Hayashi, M.; Watanabe, Y. *Tetrahedron* **2003**, *59*, 7703; (s) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *Chem. Commun.* **2003**, 1781; (t) Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 13182; (u) Xu, Y.; Lee, S. A.; Kutateladze, T. G.; Sbrissa, D.; Shisheva, A.; Prestwich, G. D. *J. Am. Chem. Soc.* **2005**, *128*, 885; (v) Zhang, H.; Markadieu, N.; Beauwens, R.; Erneax, C.; Prestwich, G. D. *J. Am. Chem. Soc.* **2006**, *128*, 16464; (w) Gajewiak, J.; Xu, Y.; Lee, S. A.; Kutateladze, T. G.; Prestwich, G. D. *Org. Lett.* **2006**, *8*, 2811; (x) Xu, Y.; Sculimbrene, B. R.; Miller, S. J. *J. Org. Chem.* **2006**, *71*, 4919; (y) Liu, Y.; Mihai, C.; Kubiak, R. J.; Rebecchi, M.; Bruzik, K. S. *ChemBioChem* **2007**, *8*, 1430; (z) Seo, K.-C.; Yu, S.-H.; Chung, S.-K. *J. Carbohydr. Chem.* **2007**, *26*, 305.
3. (a) Falck, J. R.; Abdali, A.; Wittenberger, S. J. *J. Chem. Soc., Chem. Commun.* **1990**, 953; (b) Reddy, K. K.; Saady, M.; Falck, J. R.; Whited, G. *J. Org. Chem.* **1995**, *60*, 3385; (c) Falck, J. R.; Krishnan, U. M.; Capdevila, J. H. *Tetrahedron Lett.* **1999**, *40*, 8771.
4. (a) Bruzik, K. S.; Tsai, M. W. *J. Am. Chem. Soc.* **1992**, *114*, 6361; (b) Watanabe, Y. *Studies in Natural Products Chemistry*. Stereoselective Synthesis (Part K); Elsevier:

Oxford, UK, 1996; Vol. 18, p 391; (c) Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. *Chem. Rev.* **2003**, *103*, 4477; (d) Devaraj, S.; Shashidhar, M. S.; Dixit, S. S. *Tetrahedron* **2005**, *61*, 529; (e) Dixit, S. S.; Shashidhar, M. S.; Devaraj, S. *Tetrahedron* **2006**, *62*, 4360.

5. (a) Lee, H. W.; Kishi, Y. *J. Org. Chem.* **1985**, *50*, 4402; (b) Garret, S. W.; Liu, C.; Riley, A. M.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1367; (c) Biamonte, M. A.; Vasella, A. *Helv. Chem. Acta* **1998**, *81*, 688; (d) Riley, A. M.; Godage, H. Y.; Mahon, M. F.; Potter, B. V. L. *Tetrahedron: Asymmetry* **2006**, *17*, 171.
6. (a) Baudin, G.; Glanzer, B. I.; Swaminathan, K. S.; Vasella, S. *Helv. Chim. Acta* **1988**, *71*, 1367; (b) Billington, D. C.; Baker, R.; Kulagowski, J. J.; Mawer, I. M.; Vacca, J. P.; deSolms, S. J.; Huff, R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1423; (c) Andersch, P.; Schneider, M. P. *Tetrahedron: Asymmetry* **1993**, *4*, 2135; (d) Laumen, K.; Ghisalba, O. *Biosci. Biotechol. Biochem.* **1994**, *58*, 2046; (e) Lampe, D.; Liu, C.; Potter, B. V. L. *J. Med. Chem.* **1994**, *37*, 907; (f) Riley, A. M.; Murphy, C. T.; Lindley, C. J.; Westwick, J.; Potter, B. V. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2197; (g) Riley, A. M.; Mahon, M. F.; Potter, B. V. L. *Angew. Chem., Int. Ed.* **1997**, *36*, 1472; (h) Ballereau, S.; Poirier, S. N.; Guillemette, G.; Spiess, B.; Schlewer, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1859; (i) Laumen, K.; Ghisalba, O. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1374; (j) Falck, J. R.; Murali Krishna, U.; Kattipally, K. R.; Capdevila, J. H.; Ulug, E. T. *Tetrahedron Lett.* **2000**, *41*, 4271; (k) Falck, J. R.; Krishna, U. M.; Capdevila, J. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1711; (l) Sculimbrene, B. C.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125; (m) Hosoda, A.; Ozaki, Y.; Kashiwada, A.; Mutoh, M.; Wakabayashi, K.; Mizuno, K.; Nomura, E.; Taniguchi, H. *Bioorg. Med. Chem.* **2002**, *10*, 1189; (n) Sureshan, K. M.; Das, T.; Shashidhar, M. S.; Gonnade, R. G.; Bhadbhade, M. M. *Eur. J. Org. Chem.* **2003**, 1035; (o) Sureshan, K. M.; Watanabe, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1193; (p) Morgan, A. J.; Komiya, S.; Xu, Y.; Miller, S. J. *J. Org. Chem.* **2006**, *71*, 6923; (q) Kadrivel, M.; Bichenkova, E. V.; D′,Emanuele, A.; Freeman, S. *Chem. Lett.* **2006**, *35*, 868; (r) Sureshan, K. M.; Riley, A. M.; Potter, B. V. L. *Tetrahedron Lett.* **2007**, *48*, 1923.
7. (a) Meek, J. L.; Davidson, F.; Hobbs, F. W., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 2317; (b) Chung, S.-K.; Chang, Y.-T.; Sohn, K.-W. *Chem. Commun.* **1996**, 163; (c) Chung, S.-K.; Chang, Y.-T.; Ryu, Y. *Pure Appl. Chem.* **1996**, *68*, 931.
8. (a) Ozaki, S.; Koga, Y.; Ling, L.; Watanabe, Y.; Kimura, Y.; Hirata, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1058; (b) Banerjee, T.; Srikantiah, S. M. *Tetrahedron Lett.* **1994**, *35*, 8053; (c) Ozaki, S.; Lei, L. Chemoenzymatic Synthesis of Optically Active *myo*-Inositol Polyphosphate. In *Carbohydrates in Drug Design*; Witczak, Z. J., Neiforth, K. A., Eds.; Marcel Dekker: New York, NY 1997; p 343; (d) Flores-Mosquera, M.; Martín-Lomas, M.; Chiara, J. L. *Tetrahedron Lett.* **1998**, *39*, 5085.
9. Sureshan, K. M.; Shashidhar, M. S. *Tetrahedron Lett.* **2000**, *41*, 4185.
10. Lu, P.-J.; Gou, D.-M.; Shieh, W.-R.; Chen, C.-S. *Biochemistry* **1994**, *33*, 11586.
11. Chung, S.-K.; Chang, Y.-T.; Lee, J. W.; Ji, Y.-K. *Korean J. Med. Chem.* **1997**, *7*, 82.
12. Das, T.; Praveen, T.; Shashidhar, M. S. *Carbohydr. Res.* **1998**, *313*, 55.
13. Das, T.; Shashidhar, M. S. *Carbohydr. Res.* **1997**, *297*, 243.
14. (a) Da costa, F. B.; Schorr, K.; Arakawa, N. S.; Schilling, E. E.; Spring, O. *J. Braz. Chem. Soc.* **2001**, *12*, 403; (b) Spring, O.; Zipper, R.; Reeb, S.; Vogler, B.; Da Costa, F. B. *Phytochemistry* **2001**, *57*, 267.
15. Herrera-Salgado, Y.; Garduno-Ramirez, M. L.; Vazquez, L.; Rios, M. Y.; Alvarez, L. *J. Nat. Prod.* **2005**, *68*, 1031.
16. Alexander, D. C.; Jones, J. R. W.; Tan, T.; Chen, J. M.; Liu, J. *J. Biol. Chem.* **2004**, *279*, 18824.
17. Treumann, A.; Zitzmann, N.; Hulsmeier, A.; Prescott, A. R.; Almond, A.; Sheehan, J.; Ferguson, M. A. J. *J. Mol. Biol.* **1997**, *269*, 529.
18. (a) Hosoda, A.; Nomura, E.; Murakami, A.; Koshimizu, K.; Ohigashi, H.; Mizuno, K.; Taniguchi, H. *Bioorg. Med. Chem.* **2000**, *10*, 1439; (b) Hosoda, A.; Nomura, E.; Mizuno, K.; Taniguchi, H. *J. Org. Chem.* **2001**, *66*, 7199; (c) Hosoda, A.; Nomura, E.; Murakami, A.; Koshimizu, K.; Ohigashi, H.; Mizuno, K.; Taniguchi, H. *Bioorg. Med. Chem.* **2002**, *10*, 1855.
19. (a) Bodor, N.; Moon, S. C.; Bruno-Blanch, L. *Pharmazie* **2000**, *55*, 184; (b) Moon, S. C.; Echeverria, G. A.; Punte, G.; Ellena, J.; Bruno-Blanch, L. E. *Carbohydr. Res.* **2007**, *342*, 1456.
20. (a) Chida, N.; Ogawa, S. *Chem. Commun.* **1997**, 807 and references cited therein; (b) Chida, N.; Yoshinaga, M.; Tobe, T.; Ogawa, S. *Chem. Commun.* **1997**, 1043; (c) Suzuki, T.; Tanaka, S.; Yamada, I.; Koashi, Y.; Yamada, K.; Chida, N. *Org. Lett.* **2000**, *2*, 1137; (d) Kwon, Y.-K.; Lee, C.; Chung, S.-K. *J. Org. Chem.* **2002**, *67*, 3327; (e) Suzuki, T.; Suzuki, S. T.; Yamada, I.; Koashi, Y.; Yamada, K.; Chida, N. *J. Org. Chem.* **2002**, *67*, 2874; (f) Sureshan, K. M.; Miyasou, T.; Watanabe, Y. *Tetrahedron Lett.* **2004**, *45*, 3197; (g) Sato, K.; Akai, S.; Sugita, N.; Ohsawa, T.; Kogure, T.; Shoji, H.; Yoshimura, J. *J. Org. Chem.* **2005**, *70*, 7496; (h) Sureshan, K. M.; Murakami, T.; Watanabe, Y. *Synlett* **2005**, 769.
21. Dixit, S. S.; Shashidhar, M. S. *Tetrahedron* **2008**, *64*, 2160 and references cited therein.
22. Hosoda, A.; Miyake, Y.; Nomura, E.; Taniguchi, H. *Chem. Lett.* **2003**, *32*, 1042.
23. (a) Akiyama, T.; Hara, M.; Fuchibe, K.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2003**, 1734; (b) Hoberg, J. Chiral ligands, Auxiliaries and Functionalized Materials from Carbohydrates. Abstracts, 19th Rocky Mountain Regional Meeting of the American Chemical Society, 2006; RM-120; (c) Falshaw, A.; Gainsford, G. J.; Lensink, C.; Slade, A. T.; Wright, L. J. *Polyhedron* **2007**, *26*, 329; (d) Singleton, J. A.; Hoberg, J. D. *chiro*-Inositol as Chiral Ligand in AAA Reaction. Abstracts, 20th Rocky Mountain Regional Meeting of the American Chemical Society, 2007; RM-016.
24. Sureshan, K. M.; Gonnade, R. G.; Shashidhar, M. S.; Puranik, V. G.; Bhadbhade, M. M. *Chem. Commun.* **2001**, 881.
25. Although intramolecular acyl migration by addition–elimination at the *C*4-ester carbonyl group seems unlikely based on the inherent rigidity of *myo*-inositol orthoester framework, occurrence of intramolecular acyl migration by direct substitution on the acyl carbon cannot be ruled out. Also, intermolecular mutual acyl transfer in a homodimer (or homo-aggregates) formed as a result of self-assembly can also be invoked to rationalize the experimental observation.
26. Perrin, D. D.; Armarego, L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, UK, 1992.