JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

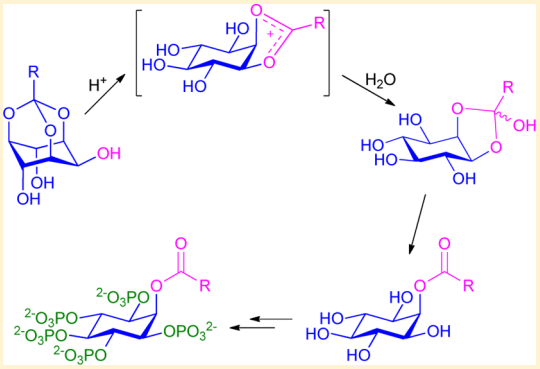
Regioselective Opening of *myo*-Inositol Orthoesters: Mechanism and Synthetic Utility

Himali Y. Godage,[†] Andrew M. Riley,[†] Timothy J. Woodman,[†] Mark P. Thomas,[†] Mary F. Mahon,[‡] and Barry V. L. Potter*[,†]

[†]Wolfson Laboratory of Medicinal Chemistry, Department of Pharmacy and Pharmacology, [‡]X-ray Crystallographic Suite, Department of Chemistry, University of Bath, Bath BA2 7AY, U.K.

Supporting Information

ABSTRACT: Acid hydrolysis of *myo*-inositol 1,3,5-orthoesters, apart from orthoformates, exclusively affords the corresponding 2-*O*-acyl *myo*-inositol products via a 1,2-bridged five-membered ring dioxolanylium ion intermediate observed by NMR spectroscopy. These C-2-substituted inositol derivatives provide valuable precursors for rapid and highly efficient routes to 2-*O*-acyl inositol 1,3,4,5,6-pentakisphosphates and *myo*-inositol 1,3,4,5,6-pentakisphosphate with biologically interesting and anticancer properties. Deuterium incorporation into the α-methylene group of such alkyl ester products (2-*O*-C(O)CD_2R), when the analogous alkyl orthoester is treated with deuterated acid, is established utilizing the novel orthoester *myo*-inositol 1,3,5-orthobutyrate as an example. Such deuterated ester products provide intermediates for deuterium-labeled synthetic analogues. Investigation into this selective formation of 2-*O*-ester products and the deuterium incorporation is presented with proposed mechanisms from NMR experiments.

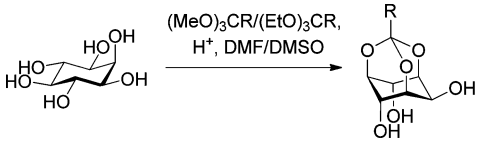


INTRODUCTION

Inositol phosphates are important intracellular messengers that play a vital role in many cellular functions including cell growth, migration, differentiation, apoptosis, and endocytosis.[1,2] To facilitate biochemical investigations, it is vital that efficient routes to these naturally occurring inositol phosphates are established.[3−7] As the demand for key synthetic intermediates increases, so does the need for differentially protected entities having free hydroxyl groups at specific positions. *myo*-Inositol 1,3,5-orthoesters have been extensively utilized as synthetic precursors for such inositol derivatives,[8−21] since the O-1, O-3, and O-5 atoms can be protected in a single step leaving O-2, O-4, and O-6 for further manipulation (Scheme 1). Also, varied patterns of hydroxyl group protection can be obtained by the cleavage of orthoesters with reducing agents,[11−15] and in the case of the alkyl orthoesters, acid hydrolysis can introduce an acyl ester at various positions on the inositol ring.[18,19] *myo*-Inositol orthoformate (**1**) has been extensively investigated over the years.[11−17] Acid hydrolysis partially or completely removes the orthoformate ester, since any intermediate formate ester produced is easily further cleaved under acidic conditions. *myo*-Inositol orthoacetate (**2**), which we[18] and others[19,20] have also explored, has the advantage that acid hydrolysis leaves an acetate ester on one of the oxygen atoms of the inositol ring, and this can be retained as a protecting group for further manipulation. However, such acetate esters are prone to migration under acid conditions, and therefore, we have recently investigated derivatives of *myo*-inositol orthobenzoate (**3**) as synthetic precursors.[21,22] Acid hydrolysis of the orthobenzoate **3** gives a much more stable benzoate ester, which can be directed to different positions on the ring, e.g., C-1 and C-3 by choosing suitable conditions and protection of other OH groups[21] and in concert with chiral desymmetrization can lead to optically active targets.

In contrast, apart from orthoformate **1**, acid hydrolysis of C-2 unprotected *myo*-inositol orthoesters **2**, **3**, and **4** unexpectedly affords the 2-*O*-acyl *myo*-inositol derivatives **5**, **6**, and **7**, respectively (Scheme 2). In a preliminary communication,[22] we reported the surprising regioselective conversion of orthobenzoate **3** to the 2-*O*-benzoyl derivative **6** and demonstrated that this proceeds via the intermediacy of a 1,2-bridged 2′-phenyl-

Scheme 1

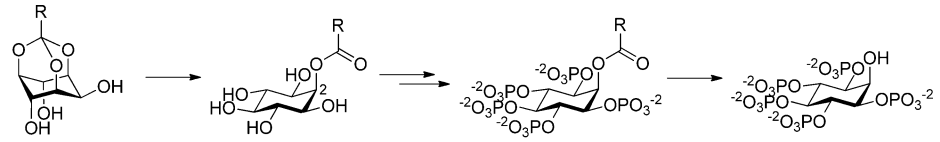


Myo-inositol

R = H (1)
R = CH_3 (2)
R = Ph (3)
R = $(CH_2)_2CH_3$ (4)

Received: December 27, 2012
Published: February 25, 2013

Scheme 2



1′,3′-dioxolan-2′-ylium ion. We now report full details and extension of this work including mechanistic NMR and labeling experiments and show that the resulting protected inositol can be used to provide a highly efficient route to two emerging anticancer agents.[23−25]

RESULTS AND DISCUSSION

Regioselective Synthesis of *myo*-Inositol 2-*O*-Acetate and Mechanistic Investigations. Orthoacetate **2** was prepared by treating *myo*-inositol with triethyl orthoacetate and PTSA in DMF under reflux as previously reported.[18] Treatment of **2** with aqueous TFA (10:1) gives 2-*O*-acetate **5** with complete selectivity in quantitative yield. This reaction is extremely fast and clean with no starting material observed by TLC even after 5 min of commencing the reaction.

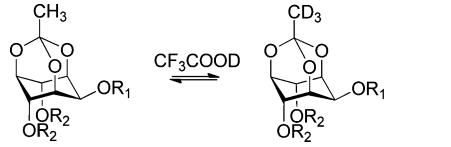
Our finding that acid hydrolysis of **2** leads to the selective formation of ester **5** was unexpected. Previous studies[21] on the hydrolysis of *myo*-inositol orthoesters have shown that the ester group is directed to the C-1 or C-3 position, although in these studies, the 2-OH group was protected. Interestingly, it was previously reported that acid hydrolysis of (±)-4-deoxy-*myo*-inositol 1,3,5-orthopentanoate gave the 2-*O*-pentanoate, although the authors attributed this to acyl migration.[26] We reasoned, however, that acyl migration could not explain the high regioselectivity in the formation of **5** from **2** and a series of NMR experiments was therefore undertaken in an attempt to observe intermediates in this hydrolysis reaction.

A ^{1}H NMR spectrum taken immediately after treatment of **2** with deuterated TFA and $CDCl_3$ showed only the starting material and some 2-*O*-acetate product **5**, the latter presumably arising from adventitious water. A small amount of $CDCl_3$ was used due to difficulty in attaining a lock signal in neat CF_3CO_2D. Although we were unable to observe any intermediates at this initial stage, a small change in the methyl peak of **5** was seen. Over time, the disappearance of the methyl singlet at 1.52 ppm and the appearance of new peaks next to it and their disappearance was observed by ^{1}H NMR (Supporting Information, Figure 1), leading us to believe that the methyl group was being deuterated giving a mixture of $-CH_3$, $-CH_2D$, and $-CHD_2$ peaks. The reaction was therefore repeated, and further ^{2}H and ^{13}C NMR spectra were taken at different times. Deuterium NMR spectra showed an increase in the deuterated methyl peaks ($-CH_2D$, $-CHD_2$, and $-CD_3$) at 1.52 ppm over time, complementary to the ^{1}H NMR decrease in the methyl singlet ($-CH_3$) proving that methyl group protons were exchanging (Supporting Information, Figure 2). This was further proven by ^{13}C NMR spectra taken on a different time scale. Splitting patterns were seen progressively in the ^{13}C NMR spectrum with initially a singlet ($-CH_3$) at δ 23 ppm, a mixture of the singlet and a triplet (indicating $-CH_2D$), a mixture along with a quintet showing some $-CHD_2$, and a septet showing $-CD_3$.

When acidic hydrolysis of orthoacetate **2** was carried out in other solvents such as ethanol, methanol, or acetonitrile, or with use of mineral acids such as HCl, the observed selectivity for **5** was reduced and longer reaction times were also needed. Furthermore, under the selective reaction conditions using 10:1 TFA/water (50%) but in the presence of another solvent such as methanol (50%), small amounts of 1/3-*O*-acetate were also obtained.

In order to further investigate this high regioselectivity and also to further understand the observed deuterium incorporation, both the C-2 hydroxyl-free and protected orthoacetates 4,6-di-*O*-benzyl orthoacetate (**12**) and 2,4,6-tri-*O*-benzyl orthoacetate (**13**) were synthesized (Scheme 3).

Scheme 3. Orthoacetates in Deuterated TFA



Metal alkoxide chelation-controlled regioselective protection of C-4 and C-6 hydroxyl groups was achieved in excellent yield when orthoacetate triol **2** was treated with lithium hydride and benzyl bromide in dry DMF. A higher yield was obtained when lithium hydride was used in comparison to that using *n*-butyllithium.[27] Observation of **12** in deuterated TFA and $CDCl_3$ by NMR spectroscopy (^{1}H, ^{2}H, and ^{13}C) again showed the disappearance of the signal corresponding to the methyl group of the orthoacetate at 1.56 ppm (^{1}H NMR) and an increase in the height of the deuterated methyl peaks over time by ^{2}H NMR spectra, once more confirming that the protons of the methyl group were exchanging with solvent deuterium. Although the major peaks seen were of the starting material which was being deuterated, there was a very small amount of hydrolyzed product, *myo*-inositol 4,6-di-*O*-benzyl 2-*O*-acetate, as well as a minute amount of some other broad peaks, perhaps corresponding to an intermediate species. This other species showed downfield broad signals at 5.91 and 5.72 ppm corresponding to one proton each and a multiplet around 4.21−4.27 ppm corresponding to four protons, along with a broad singlet at 2.67 ppm corresponding to three protons, perhaps representing a methyl group. However, since this species was observed only in trace amounts by ^{1}H NMR and not by ^{13}C NMR, identification of this potential intermediate was impossible.

Tribenzyl orthoacetate **13**, synthesized by conventional benzylation of **2**,[28] was treated with deuterated TFA, and after 15 min, only starting material was seen by NMR

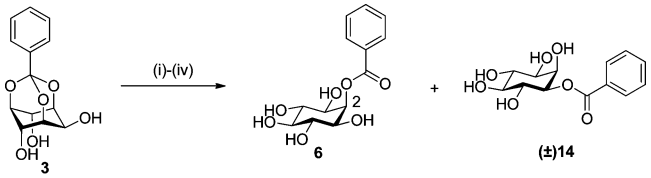
dx.doi.org/10.1021/jo3027774 | J. Org. Chem. 2013, 78, 2275−2288

spectroscopy, and no intermediates or changes to the methyl singlet were observed. Additionally, ^{2}H NMR spectra taken up to 5 days showed no peaks due to deuterium incorporation into the methyl group of starting material **13**.

Regioselective Synthesis of *myo*-Inositol 2-*O*-Benzoate (6). Orthobenzoate **3** was synthesized by transesterification of *myo*-inositol using DMSO as the solvent.[21,22] Distilling off the formed methanol (for example, by carrying out the reaction in a rotary evaporator) shortened the reaction time. Initial attempts to carry out the reaction in DMF at the usual temperatures for orthoformate **1** and orthoacetate **2** synthesis (100 °C) gave very low yields, and higher temperatures (>140 °C) were required.[21,22,29] When DMF was used a large excess of both the acid catalyst (*p*-toluenesulfonic acid) and trimethyl orthobenzoate was needed, perhaps due to thermal decomposition. Use of DMSO as the reaction solvent also gives a much cleaner reaction, making the purification easier.

Acid hydrolysis of **3** with aqueous TFA gave 2-*O*-benzoate **6**, once more with complete selectivity and in quantitative yield. Again, this reaction was extremely fast. However, when alcohols such as ethanol or methanol were used as the solvent, along with longer reaction times, selectivity was reduced and 1- or 3-*O*-benzoyl-*myo*-inositol (±**14**) was also obtained as a minor product (Scheme 4).

Scheme 4. Acid Hydrolysis of 3 under Various Conditions



(i) 1M HCl/EtOH, 1:2, 80 °C	88%	:	12%
(ii) 1M HCl/MeOH, 1:2, RT	91%	:	9%
(iii) TFA/MeOH, 1:5, RT	93%	:	7%
(iv) TFA/H_2O, 10:1	100%		

Investigation into the Possibility of Acyl Migration. While we believed that acyl migration could not be a result of the high regioselectivity in the formation of 2-*O*-ester products, further studies were undertaken to establish that **5** and **6** are not products of acyl migration of their 1- or 3-*O*-acyl *myo*-inositol regioisomers. We therefore tested the migratory abilities of the benzoyl group in both **6** and (±)-**14** under a variety of reaction conditions.

Both the (±)-**14** and **6** regioisomers were tested individually for the migratory ability of their benzoyl group under the same reaction conditions used for the acid hydrolysis of orthoesters **2** and **3** (i.e., TFA/H_2O 10:1). However, no products due to migration were obtained even after extended reaction times, proving that **6** is not a migratory product from (±)-**14**. Partial migration was observed only at elevated temperatures and with much longer reaction times. For example, when (±)-**14** was treated in 1 M HCl and ethanol at 80 °C for 10 h, a 6.5:1 mixture of (±)-**14** and **6** was obtained, while treatment of **6** under the same reaction conditions gave a 4:1 mixture of **6** and (±)-**14**, respectively. Therefore, since more of the ester **6** is converted to (±)-**14**, the equatorial benzoyl ester (±)-**14** may be the thermodynamically more stable product while the axial regioisomer **6** is the kinetic product.

Role of a 1,2-bridged Dioxolanylium Ion Intermediate in Orthoester Opening. After establishing that 2-*O*-benzoate **6** is not a migratory product of acid hydrolysis of orthobenzoate **3**, further NMR experiments were undertaken in an attempt to observe the intermediates involved in the hydrolysis reaction. To our surprise, the ^{1}H NMR spectrum taken immediately after the treatment of **3** with deuterated TFA showed a new species along with product **6**, the latter presumably arising from adventitious water. (See Figure 3 in the Supporting Information for a full spectrum. Expansions are shown in Figure 1.)

No residual starting material was observed, indicating complete conversion to this novel intermediate, later identified as the 1,2-bridged 2′-phenyl-1′,3′-dioxolan-2′-ylium ion (dioxolenium ion) (±)-**15** (Scheme 5) possessing characteristic downfield signals at 6.12 and 6.29 ppm, corresponding to H-1 and H-2 of the inositol ring protons. H-1 and H-2 are strongly deshielded relative to the other inositol ring protons, and the coupling constant between them is unusually large (J_{1-2} 9.0 Hz, while J_{1-2} 1.9 Hz for orthobenzoate **3**) owing to the incorporation of C-1 and C-2 into the five-membered dioxolanylium ring. The signals corresponding to the phenyl ring protons of the dioxolanylium ion are clearly distinguishable from those in the starting material or product, being more deshielded [δ_H 8.40−8.37 (2H/Ar-*ortho*), 8.19−8.15 (1H/Ar-*para*) and 7.82−7.78 (2H/Ar-*meta*)] compared to those in **3** [δ_H 7.68−7.66 (2H) and 7.40−7.38 (3H)] and product **6** [δ_H 8.03−8.01 (2H/Ar-*ortho*), 7.74−7.70 (1H/Ar-*para*) and 7.54−7.50 (2H/Ar-*meta*)]. In addition, fully in line with the values reported for similar dioxolanylium ions and α,α-dialkoxybenzyl cations,[30−32] the ^{13}C NMR spectrum of (±)-**15** also showed a signal attributable to C-2′ of the dioxolanylium ion at 183.3 ppm (Supporting Information, Figure 4).

It is likely that the dioxolanylium ion intermediate (±)-**15** formed from *myo*-inositol orthobenzoate (**3**) is more stable than the corresponding intermediate for opening of *myo*-inositol orthoacetate (**2**). This would account for our finding that (±)-**15** can readily be observed by ^{1}H and ^{13}C NMR. Therefore, we went on to synthesize the 4,6-di-*O*-methyl (**16**) and 4,6-di-*O*-benzyl (**19**) derivatives of **3**, keeping the C-2 hydroxyl group free to allow formation of 1,2-bridged intermediate for further studies.

Thus, protection of the C-2 hydroxyl group of **3** as its TBDMS ether followed by C-4 and C-6 methylation afforded the compound **23** in good yield (Scheme 6). Finally, removal of the TBDMS group gave the required 4,6-di-*O*-Me orthobenzoate **16**.

Treatment of **16** with deuterated TFA showed a similar dioxolanylium ion intermediate by ^{1}H NMR for a second time with immediate consumption of starting material to give the 1,2-bridged dioxolanylium ion **17** (Scheme 5) comprising downfield signals at 5.92 and 6.16 ppm, representing strongly deshielded inositol ring protons H-1 and H-2 with a large J_{1-2} value of 8.9 Hz (Supporting Information, Figure 5). ^{13}C NMR spectra further confirmed the structure of the intermediate ion (±)-**17** with a signal at 182.9 ppm corresponding to the carbocation (Supporting Information, Figure 6). A trace amount of 4,6-di-*O*-methyl 2-*O*-benzoate product **18** was also observed along with the dioxolanylium ion **17**.

Chelation-controlled regioselective protection of C-4 and C-6 hydroxyl groups of **3** was achieved using benzyl bromide to afford 4,6-di-*O*-benzyl orthobenzoate **19** in high yield. When **19** was treated with deuterated TFA, along with hydrolyzed product di-*O*-benzyl 2-*O*-benzoate **21**, a 1,2-bridged dioxola-

dx.doi.org/10.1021/jo3027774 | J. Org. Chem. 2013, 78, 2275−2288

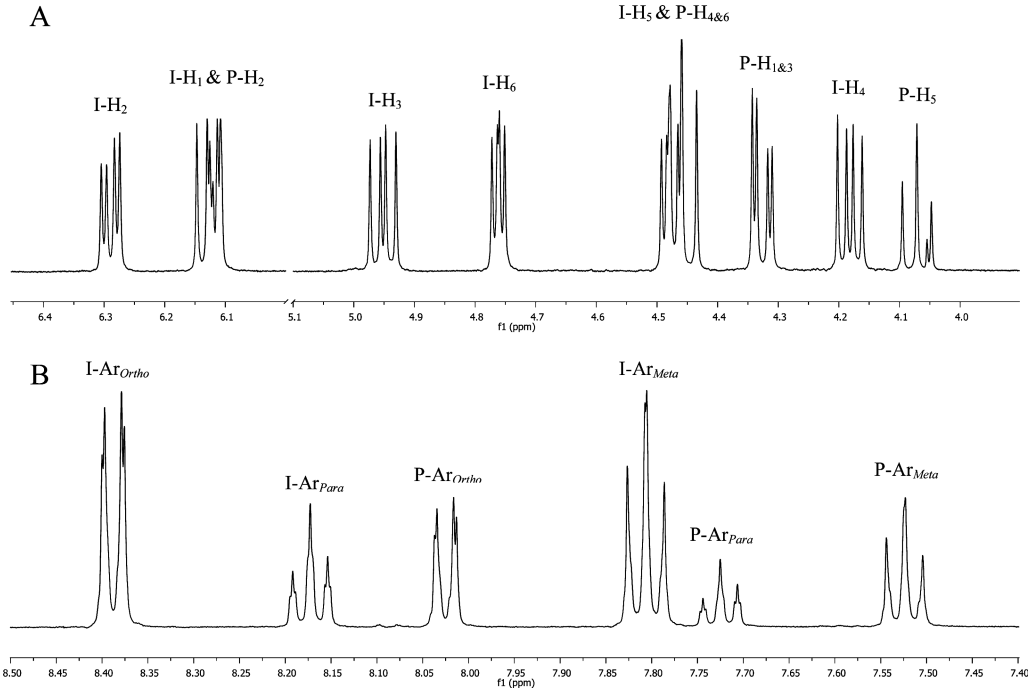
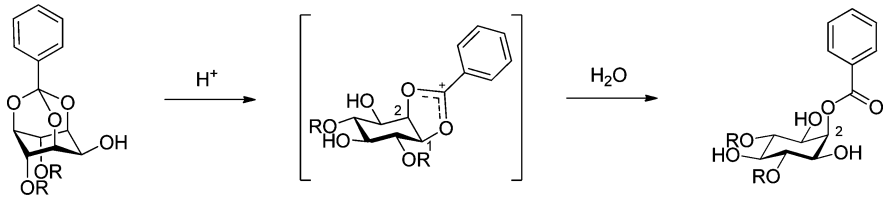
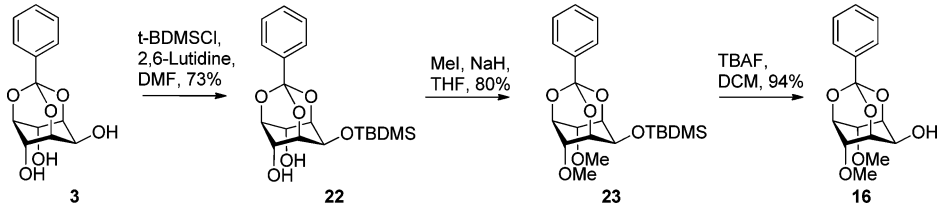


Figure 1. Proton NMR of the 1,2-bridged intermediate (±)-**15** (labeled as I) and product **6** (labeled as P): (A) expansion of 3.90−6.45 ppm; (B) expansion of 7.40−8.50 ppm.

Scheme 5. Acid Hydrolysis of Orthobenzoate Derivatives Proceeds Regioselectively via a 1,2-Bridged Intermediate



Scheme 6. Synthesis of *myo*-Inositol 4,6-Di-*O*-methyl 1,3,5-Orthobenzoate 16

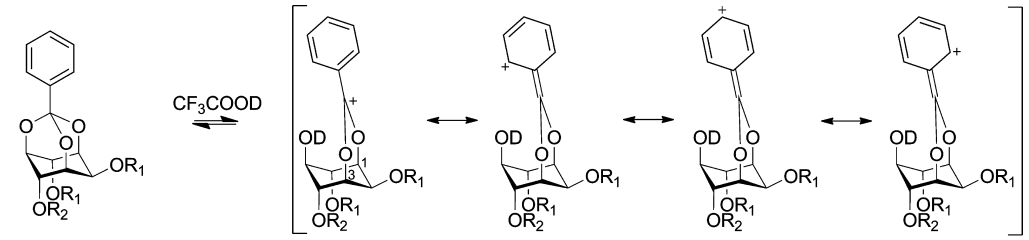


nylium ion intermediate **20** was also observed. Dioxolanylium ion **20** exhibited spectroscopic data analogous to **15** and **17** with ^{1}H NMR signals at 6.02 and 6.25 ppm and ^{13}C NMR signal at 182.3 ppm. The aromatic protons of the dioxolanylium ion were also clearly noticeable since they were more deshielded in comparison to those in the starting material or product. Vicinal proton proton coupling constants ($^{3}J_{H,H}$) are compatible with slightly twisted boat conformation (see the SI for a computational molecular dynamics study of dioxolanylium ion **20**).

Although it was not possible to observe the initial acid-catalyzed opening of the orthobenzoate cage owing to the rapidity of the reaction, it is most likely that the more stable 1,2-bridged dioxolanylium ion is produced by rearrangement of a 1,3-bridged dioxanylium (dioxenium) ion intermediate, when the 2-hydroxyl group in the starting material is free for instant rearrangement. Once the 2-hydroxyl group is protected, and there is therefore no possibility of rearrangement, only 1- or 3-*O*-subsituted product is obtained,[21] providing further evidence of the involvement of a 1,3-bridged dioxanylium intermediate in the initial stages of the acid hydrolysis. Therefore, 2,4,6-tri-*O*-methylated, 2,4,6-tri-*O*-benzylated, and 2,6-di-*O*-benzylated orthobenzoates were synthesized to facilitate NMR experiments, with the anticipation that the initial opening of the orthobenzoate cage might be observed due to the absence of a 2-hydroxyl, thus preventing the formation of any 1,2-bridged intermediates or even a potential transient 1,2,3-cage structure.

dx.doi.org/10.1021/jo3027774 | J. Org. Chem. 2013, 78, 2275−2288

Scheme 7. Reversible Opening of C-2 Hydroxyl-Protected Orthobenzoates

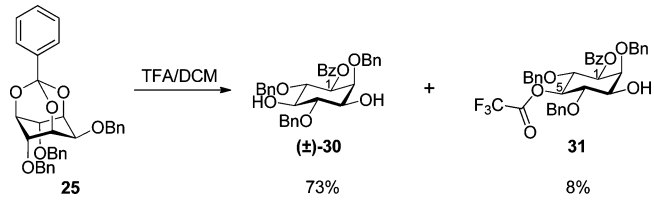


Conventional methylation of **3** afforded the 2,4,6-tri-*O*-methyl orthobenzoate **24**. However, when **24** was treated with deuterated TFA, signals in the ^{1}H NMR spectrum were broadened suggesting a rapid equilibration. Inositol ring signals [δ_H 5.47 (2H), 4.55−4.52 (2H), 4.37−4.36 (2H)] were more deshielded in comparison to those in the starting material [δ_H 4.58−4.56 (3H), 4.28−4.26 (2H), 3.67 (1H)] in just $CDCl_3$ (Supporting Information, Figure 7). The signals corresponding to the phenyl ring protons [δ_H 8.09 (2H/Ar-*ortho*), 7.87 (1H/Ar-*para*) and 7.63−7.59 (2H/Ar-*meta*)] were also more deshielded, with broadened peaks for *ortho* and *para* protons from those in the starting material **24** [δ_H 7.65−7.63 (2H) and 7.34−7.31 (3H)]. Broadening of the signals in the ^{13}C NMR spectrum was also significant, along with the disappearance of some signals corresponding to inositol ring carbons and aromatic *ortho* and *para* carbons as well as the orthoester carbon (O_3CPh), again consistent with a dynamic equilibrium (Supporting Information, Figure 8).

2,4,6-Tri-*O*-benzyl 1,3,5-orthobenzoate **25** was also obtained from **3**, and treatment of **25** with deuterated TFA again showed broad signals in the ^{1}H NMR spectrum with deshielded inositol and aromatic protons, especially H-1 and H-3 at 5.26 ppm instead of 4.52 ppm and *ortho* and *para* protons of orthobenzoate at 8.15 ppm and 8.00 ppm respectively instead of 7.23−7.69 ppm in the starting material **25**, indicative of a rapid equilibration (Supporting Information, Figure 9). Significant broadening and disappearance/reduction of some signals corresponding to inositol ring carbons and the aromatic region of the orthobenzoate were also clearly distinguishable in the ^{13}C NMR spectrum from those in **25**, again demonstrating a dynamic equilibrium (Supporting Information, Figure 10).

Treatment of **26**[21] with deuterated TFA yet again showed broad signals in the ^{1}H NMR spectrum, with deshielded inositol and aromatic protons along with broadened or lost signals in the ^{13}C NMR spectrum, once more suggesting a rapid equilibration. This may be due to reversible opening of the orthobenzoate cage[33] giving a rapidly interconverting mixture of starting material (**24**, **25**, and **26**) and the respective 1,3-dioxan-2-ylium ion (**27**, **28**, and **29**) (Scheme 7). Nonetheless, addition of water to this equilibrium mixture did not give rise to the expected hydrolysis product, but instead resulted in ring closure to reform the starting material. This presumably results from destabilization of the dioxanylium intermediate due to dilution of the acid concentration, and demonstrates that hydrolysis is the rate limiting step of this reaction. Since the departing hydroxyl group remains in close proximity to the cationic center after ring-opening, the intramolecular ring closure will be much faster for a such 1,3-bridged dioxanylium ion intermediate than addition of water.[34,35] Although in principal, the orthobenzoate cage could also be opened to give dioxanylium ions bridged between O-5 and O-1/3 of the inositol ring in the initial stage of acid hydrolysis, only 1/3-*O*-benzoate ester products were obtained from acid hydrolysis of all 2,6-di and 2,4,6-tri-*O*-benzylated and 2,4,6-tri-*O*-methylated orthobenzoates **26**, **25**, and **24**, respectively. However, on one occasion acid hydrolysis of **25** in TFA and DCM, gave a minor product **31** in 8% yield where a trifluoro acetyl group was substituted at the C-5 position along with the 1- or 3-*O*-benzoyl major product **30** (Scheme 8). This unexpected acylation at the

Scheme 8. Acid Hydrolysis of 2,4,6-Tri-*O*-benzyl Orthobenzoate 25 in TFA/DCM; 1:1



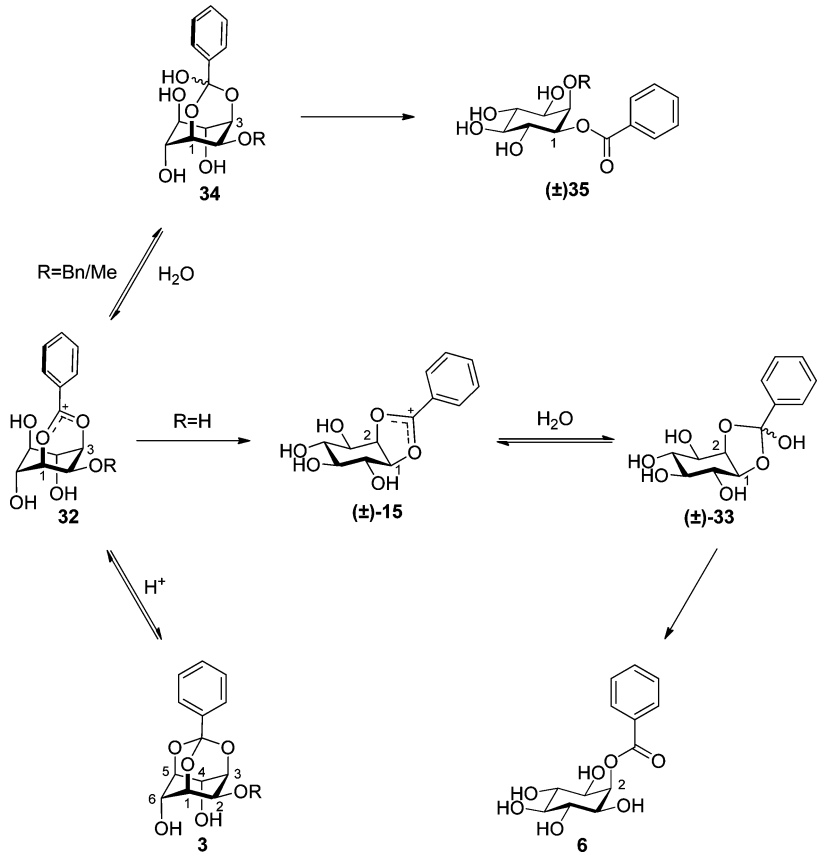
C-5 position and not on the C-1 or C-3 positions also implies that the orthobenzoate cage may only be opened to give a bridge between O-1 and O-3, leaving the 5-hydroxyl group free for esterification by solvent. It could be that O-5 may perhaps be more easily protonated since O-1 and O-3 are more hindered due to the equatorial C-2 substituent.

This may, in addition, be due to the fact that symmetrical 1,3-bridged 2′-phenyl-1′,3′-dioxan-2′-ylium ions **27**, **28**, and **29** are thermodynamically more stable, since conformationally all four hydroxyl groups of the twisted boat could attain a less-hindered equatorial orientation in comparison to an alternative 1,5- or 3,5-bridged dioxanylium ion intermediate that would possess two equatorial and two axial hydroxyl groups.

Therefore, from the above observations we can postulate that the mechanism of acid hydrolysis of orthobenzoate **3** takes place via initial reversible ring-opening giving the 1,3-bridged 2′-phenyl-1′,3′-dioxan-2′-ylium ion **32** (indirectly observed as broad signals in the ^{1}H and ^{13}C NMR spectra of compounds with the 2-OH protected). This symmetrical, six-membered intermediate then rearranges immediately to the more stable 1,2-bridged 2′-phenyl-1′,3′-dioxolan-2′-ylium ion (±)-**15**, which is then followed by the rate-determining attack by water, presumably from the less hindered face, to provide the hemiorthoester (±)-**33** (Scheme 9). Subsequent decomposition of (±)-**33**, under stereoelectronic control,[36−38] affords the product with an axial benzoate ester and equatorial hydroxyl groups (**6**). However, for substrates in which the 2-hydroxyl group is protected, rearrangement to the presumed five

dx.doi.org/10.1021/jo3027774 | J. Org. Chem. 2013, 78, 2275−2288

Scheme 9. Proposed Mechanism for the Acid Hydrolysis of Orthobenzoate 3



membered dioxolanylium intermediate is not possible and thus slow hydrolysis gives product (±)-**35** with the benzoate ester at O-1 or O-3, via a 1,3-bridged hemiorthoester intermediate **34**.

Acid Hydrolysis of *myo*-Inositol 1,3,5-Orthoformate (1). Orthoformate **1** was also explored under the selective conditions used in opening orthoesters **2** and **3** onto the C-2 position. Orthoformate **1** was prepared using literature procedures.[39] It should be noted that in the ^{1}H NMR spectrum of the orthoformate, the signal that corresponds to the methylidyne proton is a small doublet of 1.1 Hz due to a 5 bond long-range spin coupling with C-2-H.

An ^{1}H NMR spectrum taken immediately after treatment of **1** with deuterated TFA and $CDCl_3$ showed only the starting material and no intermediate species or hydrolyzed products. When the same NMR sample was analyzed after being at room temperature for 15 h mainly the starting material was seen, along with very small amounts of products. Also, no deuterated starting material or products were seen even after 3 days. However, when the reactions were carried out in deuterated TFA and $CDCl_3$ with a drop of D_2O, the spectrum taken 5 min after the addition of D_2O showed a 50:50 mixture of starting material and products, though no other intermediates were seen. Among the products, both the 2-*O*-formate and 1/3-*O*-formate products were present at a ratio of 2.8:1, the 2-*O*-formate product still being predominant. Analysis of the same NMR sample after 30 min showed a starting material to products ratio of 1: 9.3, with 2-*O*-formate product to 1/3-*O*-formate product corresponding to a ratio of 2.5:1.

Acid hydrolysis of **1** was carried out using 10:1 mixture of TFA:water at room temperature for 15 min until all starting material had been consumed and the resulting mixture was evaluated by NMR after evaporation to establish product ratios. The ^{1}H NMR spectrum showed the presence of inositol (arising due to hydrolysis of the formate ester group under the acidic conditions), 2-*O*-formate product and 1/3-*O*-formate product in a ratio of 1:1.7:1.2.

Regioselective Synthesis of *myo*-Inositol 2-*O*-Butanoate 9 and Mechanistic Investigations. Having studied orthoacetate **2**, orthobenzoate **3**, and orthoformate **1** opening under acid hydrolysis and seeing their similarities and differences, we synthesized another orthoester, this time with a longer alkyl chain to investigate further deuterium incorporation and intermediate cation formation. The novel orthoester, *myo*-inositol orthobutanoate (**4**), was prepared in high yield using analogous conditions for the synthesis of orthoacetate **1** by treatment of *myo*-inositol with trimethyl orthobutyrate and a catalytic amount of PTSA in DMF at 140 °C (this time due to shorter reaction time than for orthobenzoate synthesis under the same reaction conditions).

4 Was then treated with aqueous TFA to obtain *myo*-inositol 2-*O*-butanoate (**7**) in quantitative yield. Recrystallization of **7** in water and methanol afforded long thin crystals for which an X-ray crystal structure was obtained (Figures 2 and 3).

Therefore, from the above results, we can conclude that any 1,3,5-orthoester apart from orthoformate **1** should selectively open to give the axial 2-*O*-ester product under the above acidic hydrolysis conditions as already established for orthoacetate **2** and orthobenzoate **3**. This ties in well with the rationalization offered by King and Allbutt[36] based on the differences in steric strain among the possible transition states that fulfill the stereoelectronic requirements of dialkoxycarbonium ion formation.

dx.doi.org/10.1021/jo3027774 | J. Org. Chem. 2013, 78, 2275−2288

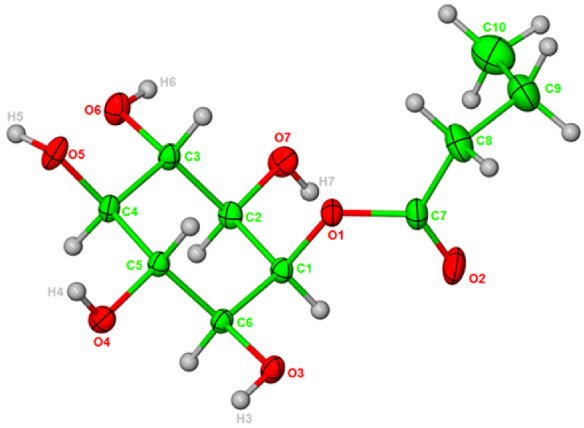


Figure 2. X-ray crystal structure of **7**. Ellipsoids are represented at 30% probability.

Mechanistic investigations of orthobutanoate **4** in deuterated TFA again showed deuterium incorporation at the α-position. However, unlike for orthobenzoate, only a minor species was seen by ^{1}H NMR, perhaps attributed to a 1,2-bridged 2′-butyl-1′,3′-dioxolan-2′-ylium ion intermediate akin to (±)-**15** which could not be fully identified due to the small amount present.

Hence, having observed α-methylene protons exchange for deuterium in orthobutanoate **4**, orthoacetate **2** and **12** using deuterated acid, we can postulate that the mechanism of exchange proceeds *via* a ketene acetal **38** or (±)-**40** or both (Scheme 10). Although, having observed only a small amount of deuterium exchanged product and no such exchange in the starting material when tri-*O*-Bn orthoacetate **13** was treated with deuterated acid, this suggests that when the C-2 hydroxyl group is protected, the equilibrium may lie quite far on the side of the 1,3-dioxan-2-ylium ion **37** due to the rapid interconvertion between the starting material **13** and the ion **37**. Thus, when the C-2 hydroxyl group is free, the equilibrium being rapidly established may lie greatly toward the side of the ketene acetal (±)-**40** due to the immediate rearrangement of 1,3-dioxan-2-ylium ion **37** to the1,2-bridged ion (±)-**39**.

Treatment of **4** in deuterated TFA for 24 h followed by the addition of water in the subsequent hydrolysis gave the 2-*O*-$C(O)CD_2CH_2CH_3$ *myo*-inositol as the major product (over 92%) with trace amounts of 2-*O*-butanoate **7** and 2-*O*-$C(O)CHDCH_2CH_3$ *myo*-inositol, perhaps arising due to adventitious water. Therefore, any such alkyl orthoesters **36** could be treated in deuterated acid under anhydrous conditions for the deuterium exchange to take place before hydrolysis to yield 2-*O*-$C(O)D_2R$ ester products **44** with deuterated methylene group at the α-position (Scheme 11). These deuterium incorporated products could provide valuable intermediates to many deuterium labeled synthetic analogues that could be used to study biologically important metabolic pathways or chemical reactions.

We have also proven that this deuterium incorporation only takes place before the hydrolysis step and thus before the formation of the hemiorthoester intermediate (±)-**46** (Scheme 12). Therefore, once the products are formed deuterium incorporation at the α-methylene position is not possible in deuterated acid. To confirm this, 2-*O*-acetate and butanoate products **5** and **7** were treated in both deuterated TFA and $CDCl_3$ and deuterated TFA and D_2O for 9 days and monitored by NMR spectroscopy for deuterium exchange. No deuterium exchange was observed by ^{2}H NMR spectroscopy over 9 days; only decomposition and migration products were seen by ^{1}H NMR spectroscopy, further proving that deuterium incorporation only takes place *via* the ketene acetal (±)-**40** and that no exchange takes place once products are formed through a mechanism similar to that occupy in migration of products involving a hemiorthoester intermediate (±)-**46**.

Synthesis of 2-*O*-Benzoyl *myo*-Inositol 1,3,4,5,6-Pentakisphosphate 9 and *myo*-Inositol 1,3,4,5,6-Pentakisphosphate 11. The efficient regioselective transformation observed also facilitates exploitation in the synthesis of inositol polyphosphates with 2-position substitutions that are of biological interest[23] as well as providing a proficient route to the anticancer agent inositol pentakisphosphate **11**.[24,25] Thus, 2-*O*-benzoyl *myo*-inositol **6** was phosphitylated using *N*,*N*-diethyl-1,5-dihydro-2,4,3-benzodioxaphosphepin-3-amine in the presence of 5-phenyltetrazole. The commonly used 1*H*-tetrazole, which has potential explosive properties at room temperature, has recently become difficult to obtain due to shipping restrictions and we found that 5-phenyltetrazole is equally effective as an activator in such phosphitylation reactions. The intermediate pentakisphosphite was subse-

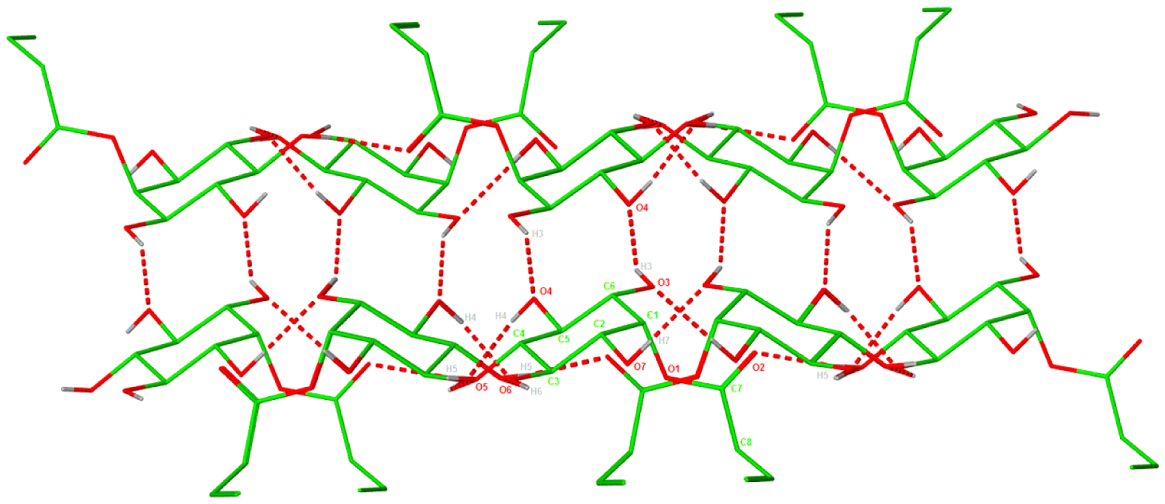
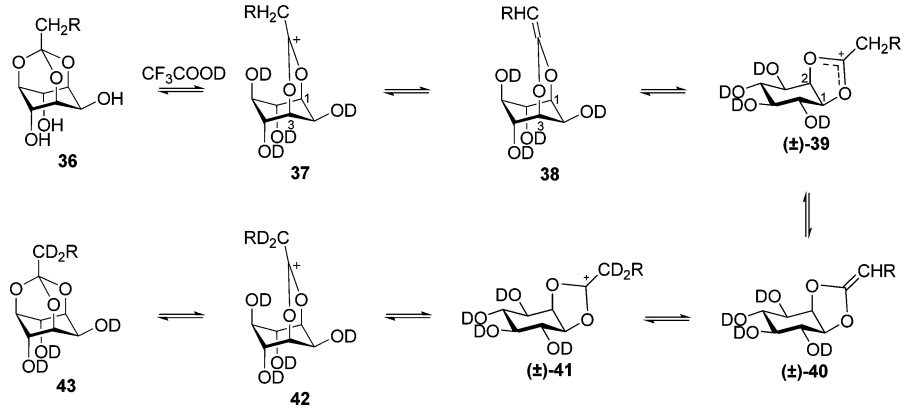


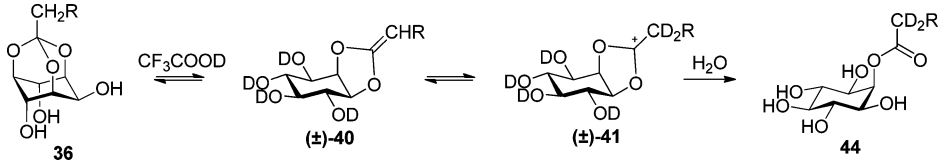
Figure 3. Crystal packing diagram for compound **7** showing the extensive H-bonding network.

dx.doi.org/10.1021/jo3027774 | *J. Org. Chem.* 2013, 78, 2275−2288

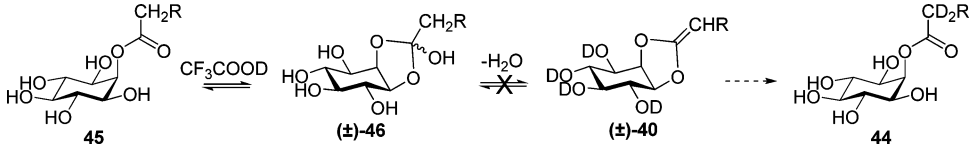
Scheme 10. Proposed Mechanism for the Deuterium Exchange



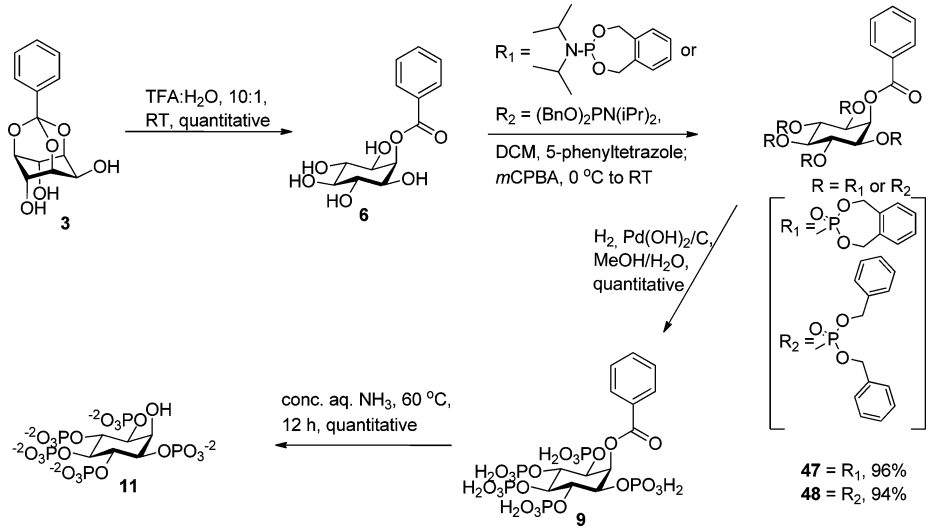
Scheme 11. Proposed Mechanism for the Formation of α-Methyl Deuterated Ester Products



Scheme 12. No Deuterium Incorporation after Formation of Product



Scheme 13. Synthesis of 2-*O*-Benzoyl *myo*-Inositol 1,3,4,5,6-Pentakisphosphate 9 and *myo*-Inositol 1,3,4,5,6-Pentakisphosphate 11



quently oxidized in situ by *m*-CPBA to afford the symmetrical pentakisphosphate **47** in 96% yield (Scheme 13). **6** could also be phosphorylated with the phosphitylating agent bis-(benzyloxy)diisopropylaminophosphine in good yield (94%) using 5-phenyltetrazole followed by oxidation. After purification of the product, the phosphate protection was removed by hydrogenolysis to afford pure 2-*O*-benzoyl pentakisphosphate **9**. Finally, the cleavage of benzoate ester in concentrated aqueous ammonia followed by simple removal of benzamide byproduct after aqueous work up with dichloromethane provided the Ins(1,3,4,5,6)P_5 **11** as the ammonium salt in 86% isolated overall yield from *myo*-inositol. Pentakisphosphate **11** could also be synthesized from 2-*O*-acetyl *myo*-inositol **5** or 2-*O*-butanoyl *myo*-inositol **7** in a similar method in high yield. This sequence greatly benefits from involving only a single chromatographic purification step thus, eliminating the need for the usual ion-exchange chromatography and also allows easy access to multigram scale quantities for in vivo studies. We

dx.doi.org/10.1021/jo3027774 | J. Org. Chem. 2013, 78, 2275−2288

anticipate that this route can give efficient synthetic access to a range of 2-substituted inositol phosphate derivatives of potential biological interest and such work is in progress.[23]

CONCLUSIONS

In summary, we show that acid hydrolysis of C-2 unprotected inositol-based orthoesters, apart from the orthoformate, can lead to exclusive formation of 2-*O*-acyl *myo*-inositol products. This interesting regioselectivity is rationalized through the intermediacy of a 1,2-bridged 2′-substituted-1′,3′-dioxolan-2′-ylium ion that is observed by NMR spectroscopy and preceded by a 1,3-bridged dioxanylium ion intermediate. Deuterium incorporation into the α-methylene group at inositol C-2 of an alkyl ester (2-*O*-C(O)D_2R) is possible when the corresponding alkyl orthoester is treated in deuterated acid under anhydrous conditions, with deuterium exchange taking place before hydrolysis. Furthermore, using these observations, we describe a most efficient route for gram-scale synthesis of Ins(1,3,4,5,6)P_5 **11** and 2-*O*-Benzoyl Ins(1,3,4,5,6)P_5 **9** via *myo*-inositol 1,3,5-orthobenzoate **3**.

EXPERIMENTAL SECTION

All reagents and solvents either were of commercial quality or were synthesized and purified in the laboratory using standard procedures. Some solvents were redistilled and dried where necessary using standard procedures or purchased in anhydrous form. Petroleum ether 40−60 °C is abbreviated as pet. ether. ^{1}H NMR and ^{13}C NMR chemical shifts were measured in ppm (δ) relative to internal tetramethylsilane (TMS), and ^{31}P NMR chemical shifts are measured in ppm (δ) relative to phosphoric acid as an external standard. Signals are expressed and abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), and app (apparent). All ^{1}H NMR and ^{13}C NMR assignments are based on gCOSY, gHMQC, gHMBC, and DEPT experiments. Coupling constants (J) are given in hertz. TLC was performed on precoated plates (aluminum sheets, silica gel 60 F_{254}) with detection by UV light or with phosphomolybdic acid in ethanol followed by heating. Flash chromatography was performed on silica gel (particle size 40−63 μm).

2-*O*-Acetyl *myo*-Inositol (5). A mixture of TFA (10 mL) and water (1 mL) was added to **2** (1.5 g, 7.3 mmol) prepared as described,[18] and the solution was stirred for 5 min after which time TLC (ethyl acetate) indicated the complete conversion of starting material (R_f 0.5) to a product (R_f 0.0). The reaction mixture was then coevaporated with water followed by DCM in vacuo to obtain **5** (1.63 g, quantitative) as a white solid: ^{1}H NMR (400 MHz, D_2O) δ 2.12 (3H, s, CH_3), 3.25 (1H, t, $J_{4,5} = J_{5,6}$ = 9.2 Hz, C-5-H), 3.57 (2H, t, $J_{1,6} = J_{3,4}$ = 10.2 Hz, C-4-H and C-6-H), 3.65 (2H, dd, $J_{1,2} = J_{2,3}$ = 2.7 Hz, C-1-H and C-3-H), 5.38 (1H, t, C-2-H); ^{13}C NMR (100.6 MHz, D_2O) δ_C 20.4 (q, CH_3), 69.6 (d, C-1 and C-3), 72.5 (d, C-4 and C-6), 74.1 (d, C-5), 74.3 (d, C-2), 173.8 (s, CO_2CH_3); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_8H_{15}O_7$ 223.0818, found 223.0812; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_8H_{14}O_7Na$ 245.0637, found 245.0632; ^{1}H NMR (400 MHz, CF_3CO_2D and $CDCl_3$) δ 2.25 (3H, s, CH_3), 3.85 (1H, m, J = 7.4 Hz, C-5-H), 4.06−4.13 (4H, m, C-1-H and C-3-H, C-4-H and C-6-H), 5.74 (1H, t, $J_{1,2} = J_{2,3}$ = 2.4 Hz, C-2-H), ^{13}C NMR (100.6 MHz, CF_3CO_2D and $CDCl_3$) δ_C 20.2 (q, CH_3), 70.4, 73.0 (2 × d, C-1 and C-3, C-4 and C-6), 73.8, 73.9 (2 × d, C-2 and C-5), 175.9 (s, CO_2CH_3).

4,6-Di-*O*-benzyl *myo*-Inositol 1,3,5-Orthoacetate (12). Lithium hydride (133.9 mg of 95%, 16 mmol) was added portionwise to a solution of **2** (816.7 mg, 4 mmol) in dry DMF (12 mL) under argon. The resulting mixture was stirred for 10 min, and benzyl bromide (1.05 mL, 8.8 mmol) in dry DMF (4 mL) was then added dropwise. Stirring was continued for a further 16 h, after which time TLC (2:1, pet. ether/ethyl acetate) showed the complete conversion of starting material (R_f 0.05) to a product (R_f 0.46). The reaction mixture was then diluted with ethyl acetate (80 mL), washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated in vacuo. The resulting compound was purified by column chromatography (pet. ether/ethyl acetate, 3:1) to afford **12** (1.37 g, 89%) as a white solid: mp 87.0−88.5 °C (ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (3H, s, CH_3), 3.41 (1H, d, J = 11.6 Hz, C-2-OH), 4.21 (1H, app br d, C-2-H), 4.30 (2H, m, $J_{1,2} = J_{2,3} = J_{1,5} = J_{3,5}$ = 1.8 Hz, $J_{1,6} = J_{3,4}$ = 3.6 Hz, C-1-H and C-3-H), 4.36 (2H, t, $J_{4,5} = J_{5,6}$ = 3.6 Hz, C-4-H and C-6-H), 4.43−4.45 (1H, m, C-5-H), 4.63 (4H, AB, J_{AB} = 11.6 Hz, CH_2Ph), 7.29−7.33 (10H, m, Ar-H); ^{13}C NMR (100.6 MHz, ($CDCl_3$) δ_C 24.2 (q, CH_3), 60.2 (d, C-2), 67.6 (d, C-5), 71.4 (t, CH_2Ph), 73.3 (d, C-1 and C-3), 73.4 (d, C-4 and C-6), 109.0 (s, O_3CCH_3), 127.5, 128.2 (2 × d, Ar-C_{ortho} and Ar-C_{meta}), 127.6 (d, Ar-C_{para}), 137.4 (s, Ar-C_{ipso}); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{25}O_6$ 385.1651, found 385.1646. Anal. Calcd for $C_{22}H_{24}O_6$ (384.42): C, 68.74; H, 6.29. Found: C, 68.7; H, 6.31.

2,4,6-Tri-*O*-benzyl *myo*-Inositol 1,3,5-Orthoacetate (13). Compound **13** was prepared as reported earlier:[28] mp 77.5−78.5 °C; ^{1}H NMR (400 MHz, CF_3CO_2D and $CDCl_3$) δ 1.54 (3H, s, CH_3), 4.28 (1H, t, $J_{1,2} = J_{2,3}$ = 1.6 Hz, C-2-H), 4.41 (2H, br s, Ins-H), 4.46−4.47 (3H, m, Ins-H), 4.64 (4H, AB, J_{AB} = 11.7 Hz, C-4 and C-6 CH_2Ph), 4.76 (2H, s, C-2 CH_2Ph), 7.29−7.32 (4H, m, Ar-H), 7.40−7.46 (11H, m, Ar-H); ^{13}C NMR (100.6 MHz, CF_3CO_2D and $CDCl_3$) δ_C 23.2 (q, CH_3), 67.6, 69.6, 72.1, 73.5 (2 × d, 2 × t, C-2, C-5, CH_2Ph), 74.0, 74.4 (2 × d, C-1 and C-3, C-4 and C-6), 105.7 (s, O_3CCH_3), 129.3, 129.6 (2 × d, C-4 and C-6 Ar-C_{ortho} and Ar-C_{meta}), 129.7, 129.7, 129.8, 130.1 (4 × d, Ar-C), 135.6 (s, C-2 Ar-C_{ipso}), 136.9 (s, C-4 and C-6 Ar-C_{ipso}); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{29}H_{31}O_6$ 475.2121, found 475.2115.

***myo*-Inositol 1,3,5-Orthobenzoate (3).** Trimethyl orthobenzoate (10 mL, 55 mmol) was added to a suspension of oven-dried *myo*-inositol (9.0 g, 50 mmol) and camphorsulfonic acid (232 mg, 1.00 mmol) in anhydrous DMSO (30 mL). The resulting mixture was then heated at 60−80 °C under a pressure of 260−280 mbar for 3 h on a rotary evaporator, after which time TLC (ethyl acetate) indicated the complete consumption of starting material (R_f 0.0) and the formation of a major product (R_f 0.4). The resulting clear solution was allowed to cool, and the catalyst was neutralized by addition of triethylamine (1.0 mL). The reaction mixture was concentrated under reduced pressure, redissolved in hot ethyl acetate (500 mL), filtered through a pad of silica gel, and washed further with hot ethyl acetate (2 × 250 mL). The resulting filtrate was concentrated under reduced pressure to about a volume of approximately 100 mL, and the solution was left in the refrigerator overnight. Concentration of the mother liquor and cooling gave a further crops of crystals to give a total yield of 12.2g (92%) of colorless crystals of **3**: mp 213-214 °C (ethyl acetate); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 4.11 (1H, dt, $J_{1,2} = J_{2,3}$ = 1.9 Hz and $J_{H,OH}$ = 6.3 Hz, C-2-H), 4.18−4.20 (2H, m, C-1-H and C-3-H), 4.23−4.25 (IH, m, C-5-H), 4.42−4.45 (2H, m, C-4-H and C-6-H), 5.38 (1H, d, C-2-OH), 5.57 (2H, d, $J_{H,OH}$ = 6.2 Hz, C-4-OH and C-6-OH), 7.34−7.41 (3H, m, Ar-H), 7.56−7.61 (2H, m, Ar-H); ^{13}C NMR (100.6 MHz, $(CD_3)_2SO$) δ_C 58.2 (d, C-2), 67.7 (d, C-4 and C-6), 70.6 (d, C-5), 76.3 (d, C-1 and C-3), 106.9 (s, O_3C-Ar), 126.0 (d, Ar-C), 128.0 (d, Ar-C), 129.5 (d, Ar-C), 138.3 (s, Ar-C); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{15}O_6$ 267.0869, found 267.0863. Anal. Calcd for $C_{13}H_{14}O_6$ (266.25): C, 58.64; H, 5.30. Found: C, 58.80 H, 5.33.

2-*O*-Benzoyl *myo*-Inositol (6). A mixture of TFA (10 mL) and water (1 mL) was added to **3** (1.5 g, 5.6 mmol), and the solution was stirred for 3 min after which time TLC (ethyl acetate) indicated the complete conversion of starting material (R_f 0.4) to a product (R_f 0.0). The reaction mixture was then coevaporated with water in vacuo to obtain **6** (1.6 g, quantitative) as a white solid: mp 240−242 °C (ethanol/water); ^{1}H NMR (400 MHz, D_2O) δ 3.26−3.30 (1H, m, C-5-H), 3.64−3.71 (4H, m, C-1-H, C-3-H, C-4-H and C-6-H), 5.57 (1H, t, $J_{1,2} = J_{2,3}$ = 2.7 Hz, C-2-H), 7.39−7.43 (2H, m, Ar-H_{meta}), 7.54−7.58 (1H, m, Ar-H_{para}), 7.92 (2H, m, $J_{ortho,meta}$ = 8.2 Hz, $J_{ortho,para}$ = 1.2 Hz, Ar-H_{ortho}); ^{13}C NMR (100.6 MHz, D_2O) δ_C 70.0, 73.0 (2 × d, C-1 and C-3, C-4 and C-6), 74.4 (d, C-5), 75.2 (d, C-2), 128.9 (d, Ar-C_{meta}), 128.9 (s, Ar-C_{ipso}), 129.8 (d, Ar-C_{ortho}), 134.2 (d, Ar-C_{para}), 168.1 (s, CO_2Ph); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{17}O_7$

dx.doi.org/10.1021/jo3027774 | J. Org. Chem. 2013, 78, 2275−2288

285.0974, found 285.0969. Anal. Calcd for $C_{13}H_{16}O_7$ (284.26): C, 54.93; H, 5.67. Found: C, 54.90; H, 5.75.

Data for 1,2-bridged 2′-phenyl-1′,3′-dioxolan-2′-ylium ion intermediate (±)-**15** observed by ^{1}H and ^{13}C NMR spectroscopy soon after the addition of deuterated trifluoroacetic acid (0.5 mL) into a NMR sample tube containing the dry *myo*-inositol 1,3,5-orthobenzoate **3** (50 mg, 0.19 mmol) and anhydrous deuterated chloroform (0.2 mL). A small amount of $CDCl_3$ was used due to the difficulty in attaining a lock signal in neat CF_3CO_2D: ^{1}H NMR (400 MHz, CF_3CO_2D and $CDCl_3$) δ 4.18 (1H, dd, $J_{4,5}$ = 5.9 Hz, $J_{5,6}$ = 10.2 Hz, C-5-H), 4.48 (1H, app t, $J_{3,4}$ = 5.1 Hz, C-4-H), 4.76 (1H, dd, $J_{2,3}$ = 3.5 Hz, C-3-H), 4.95 (1H, dd, $J_{1,6}$ = 6.7 Hz, C-6-H), 6.12 (1H, dd, $J_{1,2}$ = 9.0 Hz, C-1-H), 6.29 (1H, dd, C-2-H), 7.80 (2H, dd, $J_{meta,para}$ = 7.8 Hz, $J_{ortho,meta}$ = 8.6 Hz, Ar-H_{meta}), 8.17 (1H, t, Ar-H_{para}), 8.38 (2H, dd, $J_{ortho,para}$ = 1.2 Hz, Ar-H_{ortho}); ^{13}C NMR (100.6 MHz, CF_3CO_2D and $CDCl_3$) δ_C 69.6 (d, C-3), 71.5 (d, C-6), 73.9 (d, C-5), 74.9 (d, C-4), 87.1 (d, C-2), 90.2 (d, C-1), 115.9 (s, Ar-C_{ipso}), 131.2 (d, Ar-C_{meta}), 134.8 (d, Ar-C_{ortho}), 143.5 (d, Ar-C_{para}), 183.3 (s, C-2′).

2-*O*-Benzoyl *myo*-inositol (**6**) in CF_3CO_2D and $CDCl_3$: ^{1}H NMR (400 MHz) δ 4.08 (1H, t, $J_{4,5}$ = $J_{5,6}$ = 9.8 Hz, C-5-H), 4.33 (2H, dd, $J_{1,2}$ = $J_{2,3}$ = 2.7 Hz, $J_{1,6}$ = $J_{3,4}$ = 10.2 Hz, C-1-H and C-3-H), 4.46 (2H, t, C-4-H and C-6-H), 6.12 (1H, t, C-2-H), 7.52 (2H, dd, $J_{ortho,meta}$ = 8.2 Hz, $J_{meta,para}$ = 7.8 Hz, Ar-H_{meta}), 7.70−7.74 (1H, m, Ar-H_{para}), 8.02 (2H, dd, $J_{ortho,para}$ = 1.2 Hz, Ar-H_{ortho}); ^{13}C NMR (100.6 MHz) δ_C 71.0 (d, C-1 and C-3), 73.4 (d, C-4 and C-6), 74.3 (d, C-2 and C-5), 127.4 (s, Ar-C_{ipso}), 129.5 (d, Ar-C_{meta}), 130.3 (d, Ar-C_{ortho}), 136.0 (d, Ar-C_{para}), 170.0 (s, CO_2Ph).

2-*O*-*tert*-Butyldimethylsilyl *myo*-Inositol 1,3,5-Orthobenzoate (22). TBDMSCl (317 mg, 2.1 mmol) was added portionwise to a solution of **3** (532.5 mg, 2 mmol) in dry DMF (5 mL) and 2,6-lutidine (0.5 mL, 5 mmol) under argon and stirred for 2 days. The resulting mixture was evaporated in vacuo and purified by column chromatography (pet. ether/ethyl acetate, 8:1) to afford **22** (555 mg, 73%) as a white solid: mp 148.5−149.5 °C (Et_2O, hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (6H, s, 2 × CH_3), 0.96 (9H, s, 3 × CH_3), 3.84 (2H, br s, C-4-OH and C-6-OH), 4.11−4.12 (1H, m, J = 1.6 and 3.7 Hz, C-5-H), 4.19−4.20 (2H, m, J = 1.6 and 2.9 Hz, C-1-H and C-3-H), 4.23 (1H, t, $J_{1,2}$ = $J_{2,3}$ = 1.6 Hz, C-2-H), 4.45−4.47 (2H, m, J = 3.7 Hz, C-4-H and C-6-H), 7.36−7.39 (3H, m, Ar-H), 7.62−7.64 (2H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C −4.6 (q, 2 × CH_3), 18.3 (s, $C(CH_3)_3$), 25.8 (q, 3 × CH_3), 59.6 (d, C-2), 68.1 (d, C-4 and C-6), 69.3 (d, C-5), 75.9 (d, C-1 and C-3), 106.9 (s, O_3CPh), 125.3, 128.1 (2 × d, Ar-C_{ortho} and C_{meta}), 129.6 (d, Ar-C_{para}), 136.9 (s, Ar-C_{ipso}); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{29}O_6Si$ 381.1733, found 381.1728. Anal. Calcd for $C_{19}H_{28}O_6Si$ (380.51): C, 59.97; H, 7.42. Found: C, 59.80; H, 7.50.

2-*O*-*tert*-Butyldimethylsilyl 4,6-Di-*O*-methyl *myo*-Inositol 1,3,5-Orthobenzoate (23). Sodium hydride (240 mg of a 60% dispersion in oil, 6 mmol) was added portionwise to a solution of **22** (570.8 mg, 4 mmol) in dry THF (6 mL) at 0 °C. The resulting mixture was stirred for 10 min, and methyl iodide (0.37 mL, 6 mmol) was then added dropwise. Stirring was continued for a further 15 h, after which time TLC (2:1, pet. ether/ethyl acetate) showed the complete conversion of starting material (R_f 0.48) to a product (R_f 0.78). The reaction mixture was then diluted with ethyl acetate (50 mL), washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo. The resulting compound was purified by column chromatography (pet. ether/ethyl acetate, 8:1) to afford **23** (491 mg, 80%) as a white solid: mp 122.5−123.5 °C (ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (6H, s, 2 × CH_3), 0.95 (9H, s, 3 × CH_3), 3.48 (6H, s, 2 × OCH_3), 4.16 (1H, t, $J_{1,2}$ = $J_{2,3}$ = 1.8 Hz, C-2-H), 4.22 (2H, t, $J_{1,6}$ = $J_{3,4}$ = $J_{4,5}$ = $J_{5,6}$ = 3.6 Hz, C-4-H and C-6-H), 4.32−4.34 (2H, m, C-1-H and C-3-H), 4.55 (1H, septet, $J_{1,5}$ = $J_{3,5}$ = 1.8 Hz, C-5-H), 7.33−7.37 (3H, m, Ar-H), 7.64−7.66 (2H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C −4.6 (q, 2 × CH_3), 18.2 (s, $C(CH_3)_3$), 25.8 (q, 3 × CH_3), 57.9 (q, 2 × OCH_3), 60.3 (d, C-2), 68.3 (d, C-5), 74.0 (d, C-1 and C-3), 76.5 (d, C-4 and C-6), 107.7 (s, O_3CPh), 125.3, 128.0 (2 × d, Ar-C_{ortho} and C_{meta}), 129.3 (d, Ar-C_{para}), 137.5 (s, Ar-C_{ipso}); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{33}O_6Si$ 409.2046, found 409.2041. Anal. Calcd for $C_{21}H_{32}O_6Si$ (408.20): C, 61.73; H, 7.89. Found: C, 61.80; H, 7.93.

4,6-Di-*O*-methyl *myo*-Inositol 1,3,5-Orthobenzoate (16). TBAF (1.3 mL of a 1 M solution in THF, 1.3 mmol) was added dropwise to a stirred solution of **23** (350 mg, 0.86 mmol) in dry THF (2.5 mL) under argon. Stirring was continued for a further 15 h, after which time TLC (2:1, pet. ether/ethyl acetate) showed the complete conversion of starting material (R_f 0.70) to a product (R_f 0.16). The reaction mixture was then diluted with ethyl acetate (50 mL), washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo. The resulting compound was purified by column chromatography (pet. ether/ethyl acetate, 1.5:1) to afford **16** (236 mg, 94%) as a white solid: mp 121.0−122.5 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (1H, $J_{H,OH}$ = 12.0 Hz, C-2-OH), 3.49 (6H, s, 2 × OCH_3), 4.06 (1H, dt, $J_{1,2}$ = $J_{2,3}$ = 1.9 Hz, C-2-H), 4.28 (2H, t, $J_{1,6}$ = $J_{3,4}$ = $J_{4,5}$ = $J_{5,6}$ = 3.7 Hz, C-4-H and C-6-H), 4.45 (2H, quintet, $J_{1,5}$ = $J_{3,5}$ = 1.9 Hz, C-1-H and C-3-H), 4.56 (1H, septet, C-5-H), 7.37−7.39 (3H, m, Ar-H), 7.63−7.65 (2H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 57.9 (q, 2 × OCH_3), 60.5 (d, C-2), 68.4 (d, C-5), 73.8 (d, C-1 and C-3), 75.9 (d, C-4 and C-6), 108.0 (s, O_3CPh), 125.2, 128.1 (2 × d, Ar-C_{ortho} and C_{meta}), 129.7 (d, Ar-C_{para}), 136.9 (s, Ar-C_{ipso}); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{19}O_6$ 295.1182, found 295.1176. Anal. Calcd for $C_{15}H_{18}O_6$ (294.30): C, 61.22; H, 6.16. Found: C, 61.20; H, 6.17.

Data for 1,2-bridged 2′-phenyl-1′,3′-dioxolan-2′-ylium ion (±)-**17** from 4,6-di-*O*-methyl orthobenzoate **16**: ^{1}H NMR (400 MHz, CF_3CO_2D) δ_H 3.61 (3H, s, CH_3), 3.78 (3H, s, CH_3), 3.95 (1H, br t, H-4), 4.15 (1H, dd, $J_{4,5}$ = 3.6 Hz, $J_{5,6}$ = 9.0 Hz, H-5), 4.53 (1H, dd, $J_{1,6}$ = 6.1 Hz, H-6), 4.76 (1H, br t, H-3), 5.92 (1H, dd, $J_{1,2}$ = 8.9 Hz, H-1), 6.16 (1H, dd, $J_{2,3}$ = 2.7 Hz, H-2), 7.78 (2H, t, Ar-H$_{meta}$), 8.14 (1H, t, Ar-H$_{para}$), 8.34 (2H, d, Ar-H$_{ortho}$); ^{13}C NMR (400 MHz, CF_3CO_2D) δ_C 58.4, 59.7 (2 × q, 2 × CH_3), 66.7 (d, C-3), 72.3 (d, C-5), 79.1 (d, C-6), 84.0 (d, C-4), 87.0 (d, C-2), 89.6 (d, C-1), 115.6 (s, Ar-C_{ipso}), 131.0 (d, Ar-C_{meta}), 134.5 (d, Ar-C_{ortho}) 143.3 (d, Ar-C_{para}), 182.9 (s, C-2′).

4,6-Di-*O*-benzyl *myo*-Inositol 1,3,5-Orthobenzoate (19). Lithium hydride (133.9 mg of 95%, 16 mmol) was added portionwise to a solution of **3** (1.07 g, 4 mmol) in dry DMF (12 mL) under argon. The resulting mixture was stirred for 10 min, and benzyl bromide (1.05 mL, 8.8 mmol) in dry DMF (4 mL) was then added dropwise. Stirring was continued for a further 18 h, after which time TLC (2:1, pet. ether/ethyl acetate) showed the complete conversion of starting material (R_f 0.07) to a product (R_f 0.52). The reaction mixture was then diluted with ethyl acetate (80 mL), washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated in vacuo. The resulting compound was purified by column chromatography (pet. ether/ethyl acetate, 4:1) to afford **19** (1.57 g, 88%) as a white solid: mp 84.5−85.5 °C (ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (1H, d, J = 11.4 Hz, C-2-OH), 4.29 (1H, app br d, C-2-H), 4.45 (2H, quintet, $J_{1,2}$ = $J_{2,3}$ = $J_{1,5}$ = $J_{3,5}$ = 1.8 Hz, $J_{1,6}$ = $J_{3,4}$ = 3.8 Hz, C-1-H and C-3-H), 4.51 (2H, t, $J_{4,5}$ = $J_{5,6}$ = 3.8 Hz, C-4-H and C-6-H), 4.59 (1H, septet, C-5-H), 4.68 (4H, AB, J_{AB} = 11.5 Hz, CH_2Ph), 7.30−7.31 (10H, m, Bn-Ar-H), 7.37−7.38 (3H, m, Bz-Ar-H), 7.63−7.65 (2H, m, Bz-Ar-H); ^{13}C NMR (100.6 MHz, ($CDCl_3$) δ_C 60.7 (d, C-2), 68.7 (d, C-5), 71.8 (t, 2 × CH_2Ph), 73.7 (d, C-4 and C-6), 74.4 (d, C-1 and C-3), 108.0 (s, O_3CPh), 125.3, 127.9, 128.1 (3 × d, Bn-Ar-C_{para}, Bz-Ar-C_{ortho} and Bz-Ar-C_{meta}), 127.7, 128.5 (2 × d, Bn-Ar-C_{ortho} and Bn-Ar-C_{meta}), 129.7 (d, Bz-Ar-C_{para}), 137.0 (s, Bz-Ar-C_{ipso}), 137.6 (s, Bn-Ar-C_{ipso}); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{27}O_6$ 447.1808, found 447.1802. Anal. Calcd for $C_{27}H_{26}O_6$ (446.49): C, 72.63; H, 5.87. Found: C, 72.80; H, 5.93.

Data for 1,2-bridged 2′-phenyl-1′,3′-dioxolan-2′-ylium ion **20** from 4,6-di-*O*-benzyl orthobenzoate **19**: ^{1}H NMR (400 MHz, CF_3CO_2D) δ_H 4.25 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 3.7 Hz, H-4), 4.33 (1H, dd, $J_{5,6}$ = 8.9 Hz, H-5), 4.79 (1H, dd, $J_{1,6}$ = 6.0 Hz, H-6), 4.84 (1H, br t, H-3), 4.89 (2H, s, CH_2Ph), 5.02 (2H, AB, J_{AB} = 12.1 Hz, CH_2Ph), 6.02 (1H, dd, $J_{1,2}$ = 9.0 Hz, H-1), 6.25 (1H, dd, $J_{2,3}$ 2.9 Hz, H-2), 7.38−7.46 (10H, m, Bn-Ar-H), 7.81 (2H, t, $J_{ortho,meta}$ = $J_{meta,para}$ = 7.9 Hz, Bz-Ar-H$_{meta}$), 8.18 (1H, t, Bz-Ar-H$_{para}$), 8.24 (2H, d, Bz-Ar-H$_{ortho}$); ^{13}C NMR (400 MHz, CF_3CO_2D) δ_C 67.0 (d, C-3), 73.0 (d, C-5), 76.2 (d, C-6), 80.1 (d, C-

dx.doi.org/10.1021/jo3027774 | J. Org. Chem. 2013, 78, 2275−2288

4), 86.7 (d, C-2), 89.0 (d, C-1), 115.1 (s, Ar-C_{ipso}), (Bn-Ar-C) (*see below), 130.4 (d, Ar-C_{meta}), 133.9 (d, Ar-C_{ortho}) 142.7 (d, Ar-C_{para}), 182.3 (s, C-2′); *^{13}C NMR (400 MHz, CF_3CO_2D) 128.4, 128.7, 128.7, 128.8, 128.8, 129.0, 129.1, 129.1, 129.3, 134.6, 134.8 (11 × d, Bn-Ar-C of both intermediate **20** and product **21** and Bz-Ar-C_{meta} of Product **21**).

4,6-Di-*O*-benzyl 2-*O*-benzoyl *myo*-Inositol (21): ^{1}H NMR (400 MHz, CF_3CO_2D and $CDCl_3$) δ 4.28 (1H, t, $J_{4,5} = J_{5,6} = 9.2$ Hz, C-5-H), 4.42 (2H, dd, $J_{1,2} = J_{2,3} = 2.7$ Hz, $J_{1,6} = J_{3,4} = 10.1$ Hz, C-1-H and C-3-H), 4.48 (2H, t, C-4-H and C-6-H), 5.10 (4H, AB, $J_{A,B} = 11.0$ Hz, CH_2Ph), 6.16 (1H, t, C-2-H), 7.38−7.46 (10H, m, Bn-Ar-*H*), 7.63 (2H, t, $J_{ortho,meta} = J_{meta,para} = 7.9$ Hz, Bz-Ar-H_{meta}), 7.81 (1H, t, Bz-Ar-H_{para}), 8.14 (2H, dd, $J_{ortho,para} = 1.2$ Hz, Bz-Ar-H_{ortho}); ^{13}C NMR (100.6 MHz, CF_3CO_2D and $CDCl_3$) δ_C 70.3 (d, C-1 and C-3), 73.8 (d, C-2), 74.2 (d, C-5), 76.2 (t, 2 × CH_2Ph), 80.0 (d, C-4 and C-6), 127.1 (s, Bz-Ar-C_{ipso}), (Bn-Ar-C and Bz-Ar-C_{meta}) *(see above), 129.9 (d, Bz-Ar-C_{ortho}), 135.2 (d, Bz-Ar-C_{para}), 169.4 (s, CO_2Ph).

2,4,6-Tri-*O*-methyl 1,3,5-Orthobenzoate 24. Sodium hydride (451 mg of a 60% dispersion in oil, 11.3 mmol) was added portionwise to a solution of **3** (500 mg, 1.9 mmol) in dry THF (6 mL) at 0 °C. The resulting mixture was stirred for 10 min, and methyl iodide (0.70 mL, 11.3 mmol) was then added dropwise. Stirring was continued for a further 16 h, after which time TLC (1:1, pet. ether/ethyl acetate) showed the complete conversion of starting material (R_f 0.10) to a product (R_f 0.45). The reaction mixture was then diluted with ethyl acetate (50 mL), washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo. The resulting compound was purified by column chromatography (pet. ether/ethyl acetate, 2:1) to afford **24** (562 mg, 97%) as a white solid: mp 121.5−122.8 °C (ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.48 (6H, s, C-4-OCH_3 and C-6-OCH_3), 3.53 (3H, s, C-2-OCH_3), 3.67 (1H, br s, C-2-H), 4.26−4.28 (2H, m, C-4-H and C-6-H), 4.56−4.58 (3H, m, C-1-H, C-3-H and C-5-H), 7.31−7.34 (3H, m, Ar-H), 7.63−7.65 (2H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 56.8 (q, C-2-OCH_3), 57.8 (q, C-4-OCH_3 and C-6-OCH_3), 68.3, 68.3 (2 × d, C-2 and C-5), 70.6, 76.0 (2 × d, C-1 and C-3, C-4 and C-6), 107.8 (s, O_3CPh), 125.3, 127.9 (2 × d, Ar-C_{ortho} and Ar-C_{meta}), 129.3 (d, Ar-C_{para}), 136.9 (s, Ar-C_{ipso}); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{21}O_6$ 309.1338, found 309.1333. Anal. Calcd for $C_{16}H_{20}O_6$ (308.33): C, 62.33; H, 6.54. Found C, 62.30; H, 6.43. ^{1}H NMR (400 MHz, CF_3CO_2D and $CDCl_3$) δ_H 3.62 (6H, s, C-4-OCH_3 and C-6-OCH_3), 3.63 (3H, s, C-2-OCH_3), 4.36 (2H, br s, Ins-H), 4.53 (1H, br d, Ins-H), 5.47 (2H, br s, Ins-H), 7.61 (2H, br t, Ar-H_{meta}), 7.87 (1H, br s, Ar-H_{para}), 8.09 (2H, br s, Ar-H_{ortho}).

2,4,6-Tri-*O*-benzyl *myo*-Inositol 1,3,5-Orthobenzoate (25). Sodium hydride (3.15 g of a 60% dispersion in oil, 78.9 mmol) was added portionwise to a solution of **3** (3.5 g, 13.1 mmol) in dry DMF (20 mL) at 0 °C. The resulting suspension was stirred for 10 min, and benzyl bromide (9.4 mL, 78.9 mmol) was added. Stirring was continued for a further 2 h, after which time TLC (ethyl acetate) showed the complete conversion of starting material (R_f 0.4) to a product (R_f 0.7), and the excess sodium hydride was destroyed by the dropwise addition of methanol. The solvents were removed under reduced pressure and the residue was dissolved in dichloromethane (200 mL), washed with water (200 mL) and brine (200 mL), dried ($MgSO_4$), and evaporated in vacuo. The resulting compound was purified by column chromatography (hexane/ethyl acetate, 4:1) to afford **25** (6.7 g, 95%) as a white solid: mp 84−85 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (1H, t, $J_{1,2} = J_{2,3} = 1.6$ Hz, C-2-H), 4.48 (2H, t, $J_{1,6} = J_{3,4} = J_{4,5} = J_{5,6} = 3.9$ Hz, C-4-H and C-6-H), 4.52 (2H, dd, $J_{1,5} = J_{3,5} = 1.6$ Hz, C-1-H and C-3-H), 4.53 (2H, d, $J_{AB} = 11.5$ Hz, part of a AB system of C-4 and C-6 CH_2Ph), 4.57−4.59 (1H, m, C-5-H), 4.66 (2H, d, $J_{AB} = 11.5$ Hz, part of a AB system of C-4 and C-6 CH_2Ph), 4.70 (2H, s, C-2 CH_2Ph), 7.23−7.38 (16H, m, Ar-H), 7.41−7.43 (2H, m, Ar-H), 7.67−7.69 (2H, m, Ar-H); ^{13}C NMR (100.6 MHz, ($CDCl_3$) δ_C 66.1 (d, C-2), 69.0 (d, C-5), 71.2 (t, C-2 CH_2Ph) 71.6 (t, C-4 and C-6 CH_2Ph), 71.9 (d, C-1 and C-3), 74.0 (d, C-4 and C-6), 107.8 (s, O_3CAr), 125.3 (d, O_3CAr-C_{meta}), 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4 (7 × d, Ar-*C*), 129.4 (d, O_3CAr-C_{para}), 137.1 (s, C-2 Ar-C_{ipso}), 137.6 (s, C-4 and C-6 Ar-C_{ipso}), 138.0 (s, O_3CAr-C_{ipso}); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{34}H_{33}O_6$ 537.2277, found 537.2272.

2,4,6-Tri-*O*-benzyl 1-*O*-benzoyl 5-*O*-trifluoroacetyl *myo*-Inositol 1,3,5-Orthobenzoate (31): mp 138−139 °C (ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (1H, br s, C-3-OH), 3.81 (1H, br d, $J_{3,4} = 9.7$ Hz, C-3-H), 4.00 (1H, t, $J_{4,5} = 9.7$ Hz, C-4-H), 4.22 (1H, t, $J_{1,2} = J_{2,3} = 2.6$ Hz, C-2-H), 4.33 (1H, t, $J_{1,6} = J_{5,6} = 10.0$ Hz, C-6-H), 4.66 (2H, AB, $J = 10.8$ Hz, CH_2Ph), 4.73 (2H, s, CH_2Ph), 4.74 (2H, AB, $J = 11.8$ Hz, CH_2Ph), 5.18 (1H, dd, C-1-H), 5.29 (1H, t, C-5-H), 7.07−7.10 (2H, m, Ar-H), 7.16−7.20 (3H, m, Ar-H), 7.21−7.39 (10H, m, Ar-H), 7.47 (2H, t, $J = 7.9$ Hz, Bz-H_{ortho}), 7.60−7.64 (1H, m, Bz-H_{para}), 8.00−8.02 (2H, m, Bz-H_{meta}); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 72.1 (d, C-3), 74.0 (d, C-1), 75.2, 75.4, 75.6 (3 × t, CH_2Ph), 76.9 (d, C-6), 77.5 (d, C-2), 78.6 (d, C-5), 79.0 (d, C-4), 114.7 (quartet, $^2J_{C,F} = 286.0$ Hz, CO_2CF_3), 127.8, 127.9, 128.0, 128.0, 128.2, 128.3, 128.5, 128.6, 128.6 (9 × d, Bz-C_{ortho}, Ar-*C*), 129.2 (s, Bz-C_{ipso}), 129.7 (d, Bz-C_{meta}), 133.5 (d, Bz-C_{para}), 137.0, 137.4, 137.8 (3 × s, Ar-C_{ipso}), 156.5 (quartet, $^3J_{C,F} = 42.9$ Hz, CO_2CF_3), 165.4 (s, CO_2Ph); ^{19}F NMR (376.4 MHz, $CDCl_3$) δ_F −74.9 (3F, s, CO_2CF_3). Anal. Calcd for $C_{36}H_{33}F_3O_8$ (650.64): C, 66.46; H, 5.11. Found: C, 66.45; H, 5.00.

***myo*-Inositol 1,3,5-Orthoformate (1):** ^{1}H NMR (270 MHz, CF_3CO_2D and $CDCl_3$) δ 4.47−4.49 (3H, m, C-1-H, C-3-H and C-5-H), 4.51−4.54 (1H, m, C-2-H), 4.80 (2H, dd, $J = 3.8$ and 4.2 Hz, C-4-H and C-6-H), 5.64 (1H, d, $J = 1.1$ Hz, O_3CH); ^{13}C NMR (100.6 MHz, CF_3CO_2D and $CDCl_3$; peaks referenced to $CDCl_3$) δ_C 61.4, 67.7 (2 × d, C-2 and C-5) 67.7, 73.6 (2 × d, C-1 and C-3, C-4 and C-6), 102.7 (d, O_3CH); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_7H_{11}O_6$ 191.0556, found 191.0550; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_7H_{10}O_6Na$ 213.0375, found 213.0370.

Acid Hydrolysis of *myo*-Inositol 1,3,5-Orthoformate (1). A mixture of TFA (2 mL) and water (0.2 mL) was added to **1** (100 mg, 0.53 mmol), and the solution was stirred for 15 min after which time TLC (ethyl acetate) indicated the complete conversion of starting material (R_f 0.5) to products (R_f 0.0). The reaction mixture was then coevaporated with water in vacuo to obtain a white solid containing a mixture of 2-*O*-formyl *myo*-inositol, 1/3-*O*-formyl *myo*-inositol, and *myo*-inositol in a ratio of 1.7:1.2:1, respectively: ^{1}H NMR (400 MHz, D_2O) δ 3.11 (1H, t, $J_{4,5} = J_{5,6} = 9.4$ Hz, inositol C-5-H), 3.17 (1H, t, $J_{4,5} = J_{5,6} = 9.4$ Hz, 2-*O*-formyl inositol C-5-H), 3.22 (1H, t, $J_{4,5} = J_{5,6} = 9.4$ Hz, 1/3-*O*-formyl inositol C-5-H), 3.36 (2H, dd, $J_{1,2} = J_{2,3} = 2.7$ Hz, $J_{1,6} = J_{3,4} = 9.8$ Hz, inositol C-1-H and C-3-H), 3.43−3.53 (6H, m, inositol C-4-H and C-6-H, 2-*O*-formyl inositol C-4-H and C-6-H, 1/3-*O*-formyl inositol C-1/3-H and C-4/6-H), 3.59 (2H, dd, $J_{1,2} = J_{2,3} = 2.8$ Hz, $J_{1,6} = J_{3,4} = 10.2$ Hz, 2-*O*-formyl inositol C-1-H and C-3-H), 3.70 (1H, t, $J = 9.4$ Hz, 1/3-*O*-formyl inositol C-4/6-H), 3.89 (1H, t, inositol C-2-H), 4.03 (1H, t, $J_{1,2} = J_{2,3} = 2.2$ Hz, 1/3-*O*-formyl inositol C-2-H), 4.71 (1H, dd, $J = 2.2$ Hz and $J = 10.2$ Hz, 1/3-*O*-formyl inositol C-1/3-H), 5.28 (1H, app s, 2-*O*-formyl inositol C-2-H); ^{13}C NMR (100.6 MHz, D_2O) δ_C 69.3 (d, 2-*O*-formyl inositol C-1 and C-3), 69.8 (d, 1/3-*O*-formyl inositol C-2), 70.0 (d, 1/3-*O*-formyl inositol C-4/6), 70.5 (d, 1/3-*O*-formyl inositol C-3/4 or C-1/6), 71.0 (d, inositol C-1 and C-3), 72.0, 72.1 (2 × d, inositol C-2 and 1/3-*O*-formyl inositol C-3/4 or C-1/6), 72.3 (d, inositol C-4 and C-6), 72.4 (d, 2-*O*-formyl inositol C-4 and C-6), 73.7 (d, 1/3-*O*-formyl inositol C-1/3), 73.8 (d, inositol C-5), 74.0 (d, 2-*O*-formyl inositol C-5), 74.2 (d, 1/3-*O*-formyl inositol C-5), 74.9 (d, 2-*O*-formyl inositol C-2), 162.9, 163.5 (2 × s, 2-*O*-formyl inositol CO_2H and 1/3-*O*-formyl inositol CO_2H); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for 1/3/2-*O*-formyl *myo*-inositol, $C_7H_{13}O_7$ 209.0661, found 209.0656; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_7H_{12}O_7Na$ 231.0481, found 231.0475.

***myo*-Inositol 1,3,5-Orthobutanoate (4).** Trimethyl orthobutyrate (1.0 mL, 6.11 mmol) was added to a suspension of oven-dried *myo*-inositol (1.0 g, 5.55 mmol) and PTSA (316.7 mg, 1.67 mmol) in anhydrous DMF (10 mL), and the resulting mixture was heated at 140 °C for 3 h. Extra trimethyl orthobutyrate (0.5 mL, 3.05 mmol) was then added and heated for a further 15 min at 140 °C, after which time TLC (ethyl acetate) indicated the complete consumption of starting material (R_f 0.0) and the formation of a major product (R_f 0.5). The

dx.doi.org/10.1021/jo3027774 | J. Org. Chem. 2013, 78, 2275−2288

resulting solution was allowed to cool and the catalyst was neutralized by addition of triethylamine (0.22 mL). The reaction mixture was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography (ethyl acetate) to afford **4** (1.12 g, 87%) as a white crystalline solid: mp 139−140 °C (ethyl acetate); ^{1}H NMR (400 MHz, CD_3OD) δ 0.88 (3H, t, J = 7.4 Hz, $O_3C(CH_2)_2CH_3$), 1.41−1.51 (2H, m, $O_3CCH_2CH_2CH_2CH_3$), 1.58−1.62 (2H, m, $O_3CCH_2CH_2CH_3$), 4.08−4.11 (4H, m, C-1-H, C-2-H, C-3-H and C-5-H), 4.35−4.37 (2H, m, C-4-H and C-6-H); ^{13}C NMR (100.6 MHz, CD_3OD) δ_C 14.4 (q, $O_3C(CH_2)_2CH_3$), 17.0 (t, $O_3CCH_2CH_2CH_3$), 40.4 (t, $O_3CCH_2CH_2CH_3$), 60.3 (d, C-2/C-5), 69.0 (d, C-4 and C-6), 70.7 (d, C-2/C-5), 76.5 (d, C-1 and C-3), 110.2 (s, $O_3C(CH_2)_2CH_3$); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{10}H_{16}O_6Na$ 255.0845, found 255.0839; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{17}O_6$ 233.1025, found 233.1020. Anal. Calcd for $C_{10}H_{16}O_6$ (232.23): C, 51.72; H, 6.94. Found: C, 51.70; H, 7.01.

2-*O*-Butanoyl *myo*-Inositol (7). A mixture of TFA (5 mL) and water (0.5 mL) was added to orthobutanoate **4** (300 mg, 1.29 mmol), and the solution was stirred for 5 min after which time TLC (ethyl acetate) indicated the complete conversion of starting material (R_f 0.6) to a product (R_f 0.0). The reaction mixture was then coevaporated with water in vacuo to obtain **7** (323 mg, quantitative) as a white solid: mp 143−161 °C (methanol and water); ^{1}H NMR (400 MHz, D_2O) δ 0.72 (3H, t, J = 7.4 Hz, $CO_2(CH_2)_2CH_3$), 1.42 (2H, sextet, J = 7.4 Hz, $CO_2CH_2CH_2CH_3$), 2.24 (2H, t, J = 7.4 Hz, $CO_2CH_2CH_2CH_3$), 3.10 (1H, t, $J_{4,5} = J_{5,6}$ = 9.4 Hz, C-5-H), 3.41 (2H, t, $J_{1,6} = J_{3,4}$ = 9.8 Hz, C-4-H and C-6-H), 3.49 (2H, dd, $J_{1,2} = J_{2,3}$ = 2.7 Hz, C-1-H and C-3-H), 5.22 (1H, t, C-2-H); ^{13}C NMR (100.6 MHz, D_2O) δ_C 12.8 (q, $CO_2(CH_2)_2CH_3$), 17.8 (t, $CO_2CH_2CH_2CH_3$), 35.7 (t, $CO_2CH_2CH_2CH_3$), 69.6 (d, C-1 and C-3), 72.5 (d, C-4 and C-6), 74.0 (d, C-2), 74.2 (d, C-5), 176.3 (s, $CO_2(CH_2)_2CH_3$); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{19}O_7$ 251.1131, found 251.1125; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{10}H_{18}O_7Na$ 273.0950, found 273.0945. Anal. Calcd for $C_{10}H_{18}O_7$ (250.25): C, 48.00; H, 7.25. Found: C, 47.90; H, 7.31.

2-*O*-Butanoyl ($COCD_2CH_2CH_3$) *myo*-Inositol (44): ^{1}H NMR (400 MHz, D_2O) δ 0.75 (3H, t, J = 7.4 Hz, $CO_2CD_2CH_2CH_3$), 1.45 (2H, q, J = 7.1 and 14.5 Hz, $CO_2CD_2CH_2CH_3$), 3.14 (1H, t, $J_{4,5} = J_{5,6}$ = 9.3 Hz, C-5-H), 3.44 (2H, t, $J_{1,6} = J_{3,4}$ = 9.8 Hz, C-4-H and C-6-H), 3.53 (2H, dd, $J_{1,2} = J_{2,3}$ = 2.7 Hz, C-1-H and C-3-H), 5.26 (1H, t, C-2-H); ^{2}H NMR (400 MHz, D_2O) δ 2.26 (br s, $CO_2CD_2CH_2CH_3$); ^{13}C NMR (100.6 MHz, D_2O) δ_C 12.7 (q, $CO_2CD_2CH_2CH_3$), 17.6 (t, $CO_2CD_2CH_2CH_3$), 35.2−35.7 (t, $CO_2CD_2CH_2CH_3$), 69.6 (d, C-1 and C-3), 72.5 (d, C-4 and C-6), 74.0 (d, C-2), 74.2 (d, C-5), 176.3 (s, $CO_2CD_2CH_2CH_3$); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{17}D_2O_7$ 253.1256, found 253.1251; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{10}H_{16}D_2O_7Na$ 275.1076, found 275.1070.

2-*O*-Benzoyl 1,3,4,5,6-Pentakis-*O*-[(*O*-xylene-α,α-diyldioxy)-phosphoryl]-*myo*-Inositol (47).[39] To a solution of **6** (200 mg, 0.7 mmol) and 5-phenyltetrazole (1.03 g, 7.0 mmol) in dry dichloromethane (5 mL) under an atmosphere of argon was added *N*,*N*-diethyl-1,5-dihydro-2,4,3-benzodioxaphosphepin-3-amine (1.14 mL, 5.3 mmol). Stirring was continued for 2 h at room temperature, after which time TLC confirmed the complete consumption of starting material and ^{31}P NMR (109.4 MHz, H-decoupled, $CDCl_3$) showed signals at δ 133.59 (2P, s), 133.94 (2P, s), 134.13 (1P, s, phosphite at C-5). The reaction mixture was cooled to −40 °C, and *m*-CPBA (2.13 g, 7.0 mmol) was added portionwise while stirring. The cooling bath was removed, and the mixture was allowed to reach room temperature and diluted with dichloromethane (50 mL), washed with 10% sodium sulfite solution (2 × 100 mL), dried and solvent evaporated in *vacuo*. The residue was purified by column chromatography (chloroform/acetone, 4:1→1:1) to afford **47** (806 mg, 96%) as a white crystalline solid: mp 239−240 °C (chloroform/methanol); ^{31}P NMR (161.9 MHz, H-decoupled, $CDCl_3$) δ −4.99 (2P, s), −4.30 (1P, s, phosphate at C-5), −3.37 (2P, s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92−5.23, 5.30−5.37, 5.45−5.61 (m, 15H:4H:6H, C-1-H, C-3-H, C-4-H, C-5-H, C-6-H and 10 × CH_2Ar), 6.34 (br s, 1H, C-2-H), 7.17−7.36 (m, 20H, Ar-H), 7.38−7.42 (m, 2H, Bz-H$_{meta}$), 7.51 (t, 1H, J = 7.4 Hz, Bz-H$_{para}$), 7.99−8.00 (m, 2H, Bz-H$_{ortho}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 68.9, 69.0, 69.4, 69.5, 69.5 (5 × t, 10 × CH_2Ar), 70.4, 74.0 (2 × d, C-1 and C-3, C-4 and C-6), 74.1 (d, C-5), 77.2 (d, C-2), 128.3, 128.9, 129.1, 129.2, 129.3, 129.3, 129.3, 129.3, 129.9, 134.1, 135.0, 135.1, 135.6, 135.7 (14 × d, 36 × Ar-C), 165.1 (s, CO_2Ph); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{53}H_{52}O_{22}P_5$ 1195.1638, found 1195.1633.

2-*O*-Benzoyl 1,3,4,5,6-Pentakis-*O*-[bis(benzyloxy)-phosphoryl]-*myo*-Inositol (48). To a solution of **6** (950 mg, 3.3 mmol) and 5-phenyltetrazole (4.88 g, 33.4 mmol) in dry dichloromethane (10 mL) under an atmosphere of argon was added bis(benzyloxy)(*N*,*N*-diisopropylamino)phosphine (7.86 mL, 23.4 mmol). Stirring was continued for 1.5 h at room temperature, after which time TLC (1:1, ethyl acetate/pet. ether) confirmed the complete consumption of starting material (R_f 0.0) to product (R_f 0.8) of which ^{31}P NMR (109.4 MHz, $CDCl_3$) showed signals at δ 140.54 (2P, d, $J_{P1,P6} = J_{P3,P4}$ = 17.4 Hz, phosphite at C-1 and C-3) 142.44 (2P, t, $J_{P4,P5} = J_{P5,P6}$ = 29.0 Hz, phosphite at C-4 and C-6), 143.74 (1P, t, phosphite at C-5). The reaction mixture was cooled to −40 °C and 77% *m*-CPBA (7.49 g, 33.4 mmol) was added portionwise while stirring. The cooling bath was removed, and the mixture was allowed to reach room temperature. After 15 min, TLC (1:1, ethyl acetate/pet. ether) showed complete oxidation of pentaphosphite to pentaphosphate (R_f 0.3), the reaction mixture was diluted with dichloromethane (150 mL), washed with 10% sodium sulfite solution (2 × 150 mL), and dried, and solvent was evaporated in vacuo. The residue was purified by column chromatography (chloroform/acetone, 6:1) to afford **48** (4.98 g, 94%) as a colorless oil: ^{31}P NMR (161.9 MHz, H-decoupled, $CDCl_3$) δ −1.70 (2P, s), −1.39 (2P, s), −0.92 (1P, s, phosphate at C-5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73−4.99, 5.01−5.28 (3H:22H, m, C-1-H, C-3-H, C-4-H, C-5-H, C-6-H and 10 × CH_2Ar), 6.38 (1H, br s, C-2-H), 7.16−7.29 (50H, m, Ar), 7.44−7.47 (2H, m, Bz-H$_{meta}$), 7.59−7.63 (1H, m, Bz-H$_{para}$), 8.13−8.16 (2H, m, Bz-H$_{ortho}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 68.3 (d, C-2), 69.3, 69.3, 69.4, 69.4, 69.4, 69.4, 69.5, 69.5 (8 × t, 10 × CH_2Ar), 72.7, 74.6 (2 × d, C-1, C-3, C-4 and C-6), 74.1 (d, C-5), 127.6, 127.6, 127.7, 127.8, 127.9, 127.9, 128.0, 128.0, 128.0, 128.1, 128.1, 128.3, 128.4, 128.5, 129.7, 133.3, 135.2, 135.2, 135.2, 135.3, 135.4, 135.4, 135.5, 135.5, 135.6 (25 × d, 66 × Ar-*C*) 164.6 (s, CO_2Ph); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{83}H_{82}O_{22}P_5$ 1585.3986, found 1585.3980. Anal. Calcd for $C_{83}H_{81}O_{22}P_5$ (1585.39): C, 62.88; H, 5.15. Found: C, 62.80; H, 5.28.

2-*O*-Benzoyl *myo*-Inositol 1,3,4,5,6-Pentakisphosphate (9). Compound **47** (800 mg, 0.67 mmol) was dissolved in methanol (60 mL), and water (15 mL) and 10% palladium hydroxide on activated charcoal (400 mg) were added. The resulting suspension was stirred at room temperature overnight under an atmosphere of hydrogen in a hydrogenator. The catalyst was filtered through a PTFE syringe filter, and the filtrate was evaporated under reduced pressure to give **9** (460 mg, quantitative) as a hygroscopic white foam: ^{31}P NMR (109.4 MHz, H-decoupled, D_2O) δ −0.02 (2P, s), 0.79 (2P, s), 1.09 (1P, s, phosphate at C-5); ^{1}H NMR (270 MHz, D_2O) δ 4.34 (1H, ap. quartet, dt, $J_{4,5} = J_{5,6} = J_{H,P}$ = 9.4 Hz, C-5-H), 4.44 (2H, ddd, $J_{1,2} = J_{2,3}$ = 2.7 Hz, $J_{1,6} = J_{3,4} = J_{H,P}$ = 9.4 Hz, C-1-H and C-3-H), 4.57 (2H, ap. quartet, ddd, $J_{H,P}$ = 9.4 Hz, C-4-H and C-6-H), 5.90 (1H, t, C-2-H), 7.32−7.37 (2H, m, Ar-H$_{meta}$), 7.47−7.53 (1H, m, Ar-H$_{para}$), 7.86−7.88 (2H, m, Ar-H$_{ortho}$); ^{13}C NMR (100.6 MHz, D_2O) δ_C 71.5 (d, C-2), 72.5 (m, C-1 and C-3), 76.6 (m, C-4 and C-6), 76.9 (m, C-5), 128.5 (s, Ar-C$_{ipso}$), 128.8 (d, Ar-C$_{meta}$), 129.9 (d, Ar-C$_{ortho}$), 134.2 (d, Ar-C$_{para}$), 166.9 (s, CO_2Ph); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{22}O_{22}P_5$ 684.9291, found 684.9285.

Catalytic hydrogenolysis of compound **48** (4.0g, 2.52 mmol) was also carried out as above in methanol (110 mL) and water (10 mL) with 10% palladium hydroxide on activated charcoal (400 mg) to afford **9** (1.75 g) in quantitative yield. The free acid **9** was then converted to the triethyl ammonium salt by neutralization with 1 M triethylammonium bicarbonate buffer followed by coevaporation with methanol to remove excess buffer.

***myo*-Inositol 1,3,4,5,6-Pentakisphosphate (11).** Compound **9** (600 mg, 0.88 mmol) was dissolved in concentrated aqueous ammonia solution (30 mL) and heated at 60 °C overnight in a Pyrex pressure

dx.doi.org/10.1021/jo3027774 | J. Org. Chem. 2013, 78, 2275−2288

tube. After evaporation of solution under vacuum, the residue was dissolved in water and the benzamide byproduct was removed by washing with dichloromethane to afford the pure ammonium salt of **11** (600 mg) as a hygroscopic white solid: ^{31}P NMR (109.4 MHz, H-decoupled, D_2O) δ 1.93 (2P, s), 2.98 (1P, s, phosphate at C-5), 3.69 (2P, s); ^{1}H NMR (270 MHz, D_2O) δ 3.87−4.04 (3H, m, J = 9.4 Hz, C-1-H, C-3-H and C-5-H), 4.26 (2H, app quartet, ddd, J = 9.4 Hz, C-4-H and C-6-H), 4.51 (1H, br s, C-2-H); HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_6H_{16}O_{21}P_5$ 578.8872, found 578.8878. Anal. Calcd for hexaammonium salt of **11** $C_6H_{35}N_6O_{21}P_5$ (682.24): C, 10.56; H, 5.17; N, 12.32. Found: C, 10.30; H, 5.38; N, 12.40.

The ammonium salt of **11** was converted into the free acid by quick filtration [since prolonged exposure causes migration] through Dowex H^+ resin (10-fold excess, previously washed with miliQ water) and then to its hexasodium salt by titration to pH 7.42 with 0.1 M sodium hydroxide followed by lyophilization: ^{31}P NMR (161.9 MHz, H-decoupled, D_2O) δ 1.05 (2P, s), 1.18 (2P, s), 1.46 (1P, s, phosphate at C-5); ^{1}H NMR (400 MHz, D_2O) δ 3.93−3.97, 4.22−4.26 (6H, 2 × m, C-1-H, C-2-H, C-3-H, C-4-H, C-5-H and C-6-H).

■ ASSOCIATED CONTENT

Supporting Information

Supporting figures; ^{1}H, ^{13}C, and ^{31}P NMR spectra for compounds **4**, **6**, **7**, **9**, **15**−**25**, **31**, **44**, **47**, and **48**; computational data for compound **20**; and crystallographic data for compound **7** (CIF) (CCDC deposition no. 921722). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: b.v.l.potter@bath.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Wellcome Trust for financial support (Programme Grant No. 082837) to B.V.L.P. and A.M.R. and Dr. A. Nathubhai for proofreading this manuscript.

■ REFERENCES

(1) Irvine, R. F.; Schell, M. J. Back in the Water: The Return of the Inositol Phosphates. *Nature Rev. Mol. Cell Biol.* **2001**, *2*, 327−338.

(2) Shi, Y.; Azab, A. N.; Thompson, M. N.; Greenberg, M. L. Inositol Phosphates and Phosphoinositides in Health and Disease. Biology of Inositols and Phosphoinositides. *Subcell. Biochem.* **2006**, *39*, 265−292.

(3) Conway, S. J.; Miller, G. J. Biology-Enabling Inositol Phosphates, Phosphatidylinositol Phosphates and Derivatives. *Nat. Prod. Rep.* **2007**, *24*, 687−707.

(4) Kilbaş, B.; Balci, M. Recent Advances in Inositol Chemistry: Synthesis and Applications. *Tetrahedron* **2011**, *67*, 2355−2389.

(5) Potter, B. V. L.; Lampe, D. Chemistry of Inositol Lipid-Mediated Cellular Signaling. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933−1972.

(6) Lu, P. J.; Gou, D. M.; Shieh, W. R.; Chen, C. S. Molecular-Interactions of Endogenous D-*myo*-Inositol Phosphates with the Intracellular D-*myo*-Inositol 1,4,5-Trisphosphate Recognition site. *Biochemistry* **1994**, *33*, 11586−11597.

(7) Podeschwa, M. A. L.; Plettenburg, O.; Altenbach, H. J. Flexible Stereo- and Regioselective Synthesis of *myo*-Inositol Phosphates (Part 1): Via Symmetrical Conduritol B Derivatives. *Eur. J. Org. Chem.* **2005**, 3101−3115.

(8) Shashidhar, M. S. Regioselective Protection of *myo*-Inositol Orthoesters - Recent Developments. *ARKIVOC* **2002**, *VII*, 63−75.

(9) Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. Regioselective Protection and Deprotection of Inositol Hydroxyl Groups. *Chem. Rev.* **2003**, *103*, 4477−4503.

(10) Sureshan, K. M.; Shashidhar, M. S. Sulfonate Protecting Groups. Regioselective *O*-Sulfonylation of *myo*-Inositol Orthoesters. *Tetrahedron Lett.* **2001**, *42*, 3037−3039.

(11) Gilbert, I. H.; Holmes, A. B.; Young, R. C. Synthesis of Protected *myo*-Inositols. *Tetrahedron Lett.* **1990**, *31*, 2633−2634.

(12) Gilbert, I. H.; Holmes, A. B.; Pestchanker, M. J.; Young, R. C. Lewis Acid Catalysed Rearrangements of *myo*-Inositol Orthoformate Derivatives. *Carbohydr. Res.* **1992**, *234*, 117−130.

(13) Conway, S. J.; Gardiner, J.; Grove, S. J. A.; Johns, M. K.; Lim, Z.-Y.; Painter, G. F.; Robinson, D. E. J. E.; Schieber, C.; Thuring, J. W.; Wong, L. S.-M.; Yin, M.-X.; Burgess, A. W.; Catimel, B.; Hawkins, P. T.; Ktistakis, N. T.; Stephens, L. R.; Holmes, A. B. Synthesis and Biological Evaluation of Phosphatidylinositol Phosphate Affinity Probes. *Org. Biomol. Chem.* **2010**, *8*, 66−76.

(14) Painter, G. F.; Grove, S. J. A.; Gilbert, I. H.; Holmes, A. B.; Raithby, P. R.; Hill, M. L.; Hawkins, P. T.; Stephens, L. R. General Synthesis of 3-Phosphorylated *myo*-Inositol Phospholipids and Their Derivatives. *J. Chem. Soc., Perkin Trans. 1* **1999**, 923−936.

(15) Yeh, S. M.; Lee, G. H.; Wang, Y.; Luh, T. Y. Chelation-Assisted C−O Bond Cleavage of Ortho Esters. A Convenient Synthesis of *myo*-Inositol Derivatives Having Free Hydroxy Group(s) at Specific Position(s). *J. Org. Chem.* **1997**, *62*, 8315−8318.

(16) Riley, A. M.; Mahon, M. F.; Potter, B. V. L. Rapid Synthesis of the Enantiomers of *myo*-Inositol-1,3,4,5-Tetrakisphosphate by Direct Chiral Desymmetrization of *myo*-Inositol Orthoformate. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1472−1474.

(17) Lee, H. W.; Kishi, Y. Synthesis of Mono and Unsymmetrical Bis Ortho-esters of *scyllo*-Inositol. *J. Org. Chem.* **1985**, *50*, 4402−4404.

(18) Garrett, S. W.; Liu, C. S.; Riley, A. M.; Potter, B. V. L. Rapid and Practical Synthesis of D-*myo*-Inositol 1,4,5-Trisphosphate. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1367−1368.

(19) Praveen, T.; Shashidhar, M. S. Convenient Synthesis of 4,6-Di-*O*-benzyl-*myo*-Inositol and *myo*-Inositol 1,3,5-Orthoesters. *Carbohydr. Res.* **2001**, *330*, 409−411.

(20) Sureshan, K. M.; Shashidhar, M. S. Sulfonate Protecting Groups. Regioselective *O*-Acylation of *myo*-Inositol 1,3,5-Orthoesters: The Role of Acyl Migration. *Tetrahedron Lett.* **2000**, *41*, 4185−4188.

(21) Riley, A. M.; Godage, H. Y.; Mahon, M. F.; Potter, B. V. L. Chiral Desymmetrisation of *myo*-Inositol 1,3,5-Orthobenzoate Gives Rapid Access to Precursors for Second Messenger Analogues. *Tetrahedron Asymm.* **2006**, *17*, 171−174.

(22) Godage, H. Y.; Riley, A. M.; Woodman, T. J.; Potter, B. V. L. Regioselective Hydrolysis of *myo*-Inositol 1,3,5-Orthobenzoate *via* a 1,2-Bridged 2′-Phenyl-1′,3′-dioxolan-2′-ylium Ion Provides a Rapid Route to the Anticancer Agent Ins(1,3,4,5,6)P_5. *Chem. Commun.* **2006**, *28*, 2989−2991.

(23) Falasca, M.; Chiozzoto, D.; Godage, H. Y.; Mazzoletti, M.; Riley, A. M.; Previdi, S.; Potter, B. V. L.; Broggini, M.; Maffucci, T. A Novel Inhibitor of the PI3K/Akt Pathway Based on the Structure of Inositol 1,3,4,5,6-Pentakisphosphate. *Br. J. Cancer* **2010**, *102*, 104−114.

(24) Piccolo, E.; Vignati, S.; Maffucci, T.; Innominato, P. F.; Riley, A. M.; Potter, B. V. L.; Pandolfi, P. P.; Broggini, M.; Iacobelli, S.; Innocenti, P.; Falasca, M. Inositol Pentakisphosphate Promotes Apoptosis through the PI3-K/Akt Pathway. *Oncogene* **2004**, *23*, 1754−1765.

(25) Maffucci, T.; Piccolo, E.; Cumashi, A.; Iezzi, M.; Riley, A. M.; Saiardi, A.; Godage, H. Y.; Rossi, C.; Broggini, M.; Iacobelli, S.; Potter, B. V. L.; Innocenti, P.; Falasca, M. Inhibition of the Phosphatidylinositol 3-Kinase/Akt Pathway by Inositol Pentakisphosphate Results in Antiangiogenic and Antitumor Effects. *Cancer Res.* **2005**, *65*, 8339−8349.

(26) Biamonte, M. A.; Vasella, A. An Advantageous Synthesis of 1D- and 1L-1,2,3,5/4-Cyclohexanepentol. *Helv. Chim. Acta* **1998**, *81*, 688−694.

(27) Devaraj, S.; Shashidhar, M. S.; Dixit, S. S. Chelation Controlled Regiospecific *O*-Substitution of *myo*-Inositol Orthoesters: Convenient Access to Orthogonally Protected *myo*-Inositol Derivatives. *Tetrahedron* **2005**, *61*, 529−536.

(28) Riley, A. M.; Potter, B. V. L. L-α-Phosphatidyl-D-*myo*-Inositol 3,5-Bisphosphate: Total Synthesis of a New Inositol Phospholipid via *myo*-Inositol Orthoacetate. *Tetrahedron Lett.* **1998**, *39*, 6769−6772.
(29) Bhosekar, G.; Murali, C.; Gonnade, R. G.; Shashidhar, M. S.; Bhadbhade, M. M. Identical Molecular Strings Woven Differently by Intermolecular Interactions in Dimorphs of *myo*-Inositol 1,3,5-Orthobenzoate. *Cryst. Growth Des.* **2005**, *5*, 1977−1982.
(30) Pindur, U.; Müller, J.; Flo, C.; Witzel, H. Ortho Esters and Dialkoxycarbenium Ions-Reactivity, Stability, Structure, and New Synthetic Applications. *Chem. Soc. Rev.* **1987**, *16*, 75−87.
(31) Childs, R. F.; Frampton, C. S.; Kang, G. J.; Wark, T. A. Structures of Some Dialkoxyphenylmethylium Ions − Steric Inhibition of Resonance. *J. Am. Chem. Soc.* **1994**, *116*, 8499−8505.
(32) Crich, D.; Dai, Z. M.; Gastaldi, S. On the role of Neighboring Group Participation and Ortho Esters in Beta-Xylosylation: C-13 NMR Observation of a Bridging 2-Phenyl-1,3-dioxalenium Ion. *J. Org. Chem.* **1999**, *64*, 5224−5229.
(33) Lam, P. W. K.; McClelland, R. A. Direct Observation of the Reversible Ring-Opening of the Hydrolysis of 3-Phenyl-2,4,10-trioxa-adamantane. *J. Chem. Soc., Chem. Commun.* **1980**, 883−884.
(34) McClelland, R. A.; Lam, P. W. K. Hydrolysis of Trioxaadamantane Ortho Esters. 1. Dialkoxycarbocation − Ortho Ester Equilibrium and Acidity Function. *Can. J. Chem.* **1984**, *62*, 1068−1073.
(35) McClelland, R. A.; Lam, P. W. K. Hydrolysis of Trioxaadamantane Ortho Esters. 2. Kinetic-Analysis and the Nature of the Rate-Determining Step. *Can. J. Chem.* **1984**, *62*, 1074−1080.
(36) King, J. F.; Allbutt, A. D. Remarkable Stereoselectivity in Hydrolysis of Dioxolenium Ions and Orthoesters Fused to Anchored 6-Membered Rings. *Can. J. Chem.* **1970**, *48*, 1754−1769.
(37) Li, S. G.; Dory, Y. L.; Deslongchamps, P. Hydrolysis of Cyclic Orthoesters: Experimental Observations and Theoretical Rationalization. *Tetrahedron* **1996**, *52*, 14841−14854.
(38) Deslongchamps, P. Stereoelectronic Effects in Organic Chemistry. In *Organic Chemistry Series*, 1st ed.; Baldwin, J. E., Eds.; Pergamon Press: Oxford, 1983; Vol. *1*, pp 82−85.
(39) Ozaki, S.; Koga, Y.; Ling, L.; Watanabe, Y.; Kimura, Y.; Hirata, M. Synthesis of 2-Substituted *myo*-Inositol 1,3,4,5-Tetrakis-(phosphate) and 1,3,4,5,6-Pentakis(phosphate) Analogs. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1058−1063.