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Hydroxyl group deprotection reactions with $Pd(OH)_2/C$: a convenient alternative to hydrogenolysis of benzyl ethers and acid hydrolysis of ketals

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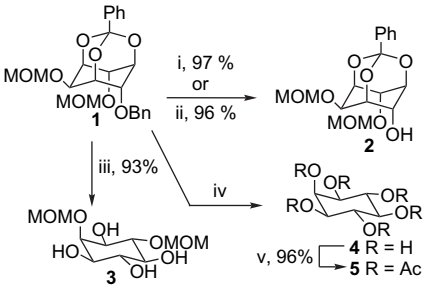
Abstract—Benzyl ethers, ketals and orthoformates were cleaved with $Pd(OH)_2/C$ in methanol, to generate the corresponding alcohol; carboxylic acid esters were stable under these reaction conditions. $Pd(OH)_2/C$ in methanol was used for the deprotection of hydroxyl groups during the preparation of sequoyitol via *myo*-inositol orthobenzoate. This method of deprotection has the potential to be useful in the synthesis of different classes of organic compounds since the reaction conditions do not involve strong acids, bases or hydrogen.

1. Introduction

The selective protection and deprotection of functional groups[1] are essential during the synthesis of complex organic molecules. New methods for the protection and deprotection of various functional groups are required to meet the emerging challenges in organic synthesis. Although the use of palladium derived catalysts for hydrogenolysis reactions is a matter of routine during organic synthetic transformations, utility of palladium compounds in other types of deprotection reactions of organic functional groups is relatively rare. Lipshutz et al.[2] first demonstrated the use of $PdCl_2$–acetonitrile complex for the deprotection of acetals and subsequently this reaction was utilized by Ley et al.,[3] Taylor et al.[4] and Schmeck and Hegedus[5] for significant synthetic transformations. Other instances of the use of palladium compounds for the deprotection of organic functional groups include the cleavage of allyl and propenyl ethers,[2,6] selective cleavage of silyl ethers,[2,7] cleavage of alkyl vinyl carbonate,[8] cleavage of *N*,*N*-dimethylhydrazone[9] and allyl ester.[10] We herein describe methods for the deprotection of benzyl ether, acetal and orthoester with $Pd(OH)_2/C$ in methanol, which have the potential to be significantly useful in the synthesis of different classes of compounds since benzyl ethers are cleaved under non-hydrogen conditions and acetals as well as orthoesters are cleaved in the absence of protic acids. Particularly, the cleavage of benzyl ethers and acetals is useful for the preparation of cyclitol[11] derivatives and preparation of naturally occurring sequoyitol is described as an example.

2. Results and discussion

During our investigations on the selective protection and deprotection of *myo*-inositol orthoester hydroxyl groups,[12] we observed some unexpected results with the *myo*-inositol orthobenzoate[13] derivative **1** (Scheme 1). The product of hydrogenolysis of the methoxymethyl ether **1** was dependent on both the amount of the catalyst used and the solvent used for the reaction. Selective cleavage of only the benzyl ether (to obtain **2**) or cleavage of the benzyl ether as well as the orthobenzoate (to obtain **3**) or complete cleavage of all the protecting groups (to obtain **4**, isolated as **5**) could be achieved by varying the conditions of the hydrogenolysis reaction and the amount of $Pd(OH)_2/C$ used (Scheme 1).



Scheme 1. Reagents and conditions: (i) H_2, $Pd(OH)_2/C$, EtOAc, 2 h; (ii) $Pd(OH)_2/C$, MeOH, rt, seven days or reflux, 32 h; (iii) H_2, $Pd(OH)_2/C$, MeOH, 13 h; (iv) H_2, excess $Pd(OH)_2/C$, MeOH, 13 h; (v) Ac_2O, pyr., rt, 40 h.

Keywords: Palladium hydroxide; Benzyl ether; Ketal; Acetal; Protective group.
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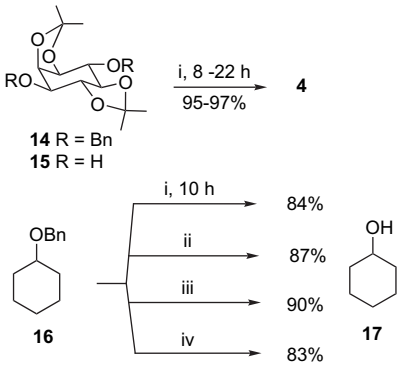
Since we observed the cleavage of methoxymethyl ethers under hydrogenolysis conditions, we wondered whether this was due to the complexation of palladium with **1**, which could aid the cleavage of the methoxymethyl ethers. Inositol derivatives are known to form complexes with metal ions in solution as well as in the solid state.[14] Hence we treated the orthobenzoate derivative **1** with $Pd(OH)_2/C$ in ethyl acetate or methanol at ambient as well as reflux temperatures (in the absence of hydrogen). This was also to investigate whether the methoxymethyl ethers were cleaved prior to or subsequent to the cleavage of the orthobenzoate in the hydrogenolysis reactions mentioned above. Reaction of the orthobenzoate derivative **1** with $Pd(OH)_2/C$ in methanol (Scheme 1) unexpectedly resulted in the cleavage of the benzyl ether alone (to give **2**). Since the reactions of the orthobenzoate **1** in the presence of $Pd(OH)_2/C$ gave unexpected results, we investigated in detail the reaction of *myo*-inositol orthoesters with $Pd(OH)_2/C$ under non-hydrogen conditions (Table 1).

These reactions clearly showed that benzyl ethers are cleaved by $Pd(OH)_2/C$ in refluxing methanol and that the orthoester moiety underwent solvolysis to give the corresponding ester. The orthobenzoate **6** and its benzyl ethers **7** and **8** gave *myo*-inositol 2-benzoate (**12**) on refluxing with $Pd(OH)_2/C$ in methanol while the orthoacetate **9** gave a mixture of acetates (**13**) due to migration of the acetyl group in *myo*-inositol 2-acetate initially formed. The orthoformate **10** and its tribenzyl ether **11** gave *myo*-inositol (**4**) as the product since the formate ester (of inositol) initially formed undergoes solvolysis with ease. *myo*-Inositol orthoesters are known[15] to give the corresponding *myo*-inositol monoester derivative on acid hydrolysis.

These reactions suggested that $Pd(OH)_2/C$ cleaved benzyl ether and orthoesters by different mechanisms and that ester groups were stable under the conditions of cleavage of the benzyl ether and orthoesters. In order to get a clue on the mechanism of cleavage of benzyl ethers by $Pd(OH)_2/C$ and to check the generality of the reaction, we subjected the diisopropylidene derivatives **14**, **15** and the benzyl ether **16**, to reaction with $Pd(OH)_2/C$ under a variety of conditions (Scheme 2).

$Pd(OH)_2/C$ in methanol deprotected the diisopropylidene derivative **14** completely to give *myo*-inositol; and

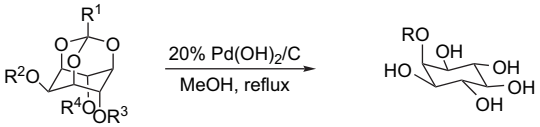


Scheme 2. Reagents and conditions: (i) 20% $Pd(OH)_2/C$, MeOH, reflux; (ii) 10% Pd/C (Aldrich), MeOH, reflux, 21 h; (iii) 10% Pd/C (Lancaster), MeOH, reflux, 25 h; (iv) $Pd(OAc)_2$ (50 mol %), MeOH, reflux, 40 h.

cyclohexanol (**17**) was obtained in very good yield from its benzyl ether **16**. Ethyl acetate or THF could also be used as solvents for the cleavage of protecting groups in **16**, but the reaction times were longer. Benzyl ether **16** could also be cleaved by palladium acetate, although relatively slowly as compared to $Pd(OH)_2/C$. GC–MS analysis of the reaction mixture during the cleavage of the ketal **15** showed the presence of acetone and 2,2-dimethoxy propane, which indicated that the ketal was cleaved by hydrolysis as well as methanolysis. A ^1H NMR spectrum of the mixture of products formed on cleavage of **16** with $Pd(OH)_2/C$ in methanol showed the presence of benzaldehyde and methyl benzoate, which suggested the oxidative cleavage of benzyl ethers. Instances of oxidative cleavage of ethers[1,16] and palladium catalyzed oxidation reactions[17] have been reported previously. However, cleavage of benzyl ethers by transfer hydrogenation[18] is a possible competing reaction, with methanol serving as the hydrogen donor and generating formaldehyde. Since formaldehyde is known to be a catalyst poison, this could explain the requirement of molar equivalents of $Pd(OH)_2/C$ for the cleavage of benzyl ethers.

In order to confirm the oxidative cleavage of benzyl ethers by $Pd(OH)_2/C$, we carried out a control reaction using Pd/C. Unexpectedly, benzyl ether **16** was cleaved by these 'samples of Pd/C' in the absence of hydrogen. We suspected this to be due to the presence of Pd(II) species in (supposedly)

Table 1. Cleavage of benzyl ether and orthoesters with $Pd(OH)_2/C$



Entry		Substrate				Reaction time (h)	Product, R	Yield (%)
		R^1	R^2	R^3	R^4			
1	**6**	Ph	H	H	H	9	**12**, Bz	94
2	**7**	Ph	H	H	Bn	12	**12**, Bz	92
3	**8**	Ph	Bn	Bn	Bn	40	**12**, Bz	84
4	**9**	Me	H	H	H	52	**13**, Ac[a]	93
5	**10**	H	H	H	H	32	**4**, H	96
6	**11**	H	Bn	Bn	Bn	72	**4**, H	96

[a] Mixture of isomeric monoacetates.

Pd(0)/C samples that we used and recorded their X-ray photoelectron spectra (XPS). A comparison of the XPS (Fig. 1) of the Pd 3d core level of $Pd(OH)_2$/C (curve 1), Pd/C (curve 2) and the spent $Pd(OH)_2$/C-recovered after the cleavage of **16** (curve 3) clearly showed (i) that the spent palladium recovered after the reaction did not contain Pd(II) species and (ii) the presence of a considerable amount of Pd(II) species in the sample of Pd(0)/C that we used for control experiments. Pd(0) is known to undergo oxidation to Pd(II) on exposing to air.[19] The unexpected reactivity patterns of Pd/C during hydroxyl group deprotection have earlier been recorded in the literature.[7f]

We also carried out experiments wherein benzyl ether **16** (in 1 equiv portions) was added to the reaction mixture (when TLC indicated the absence of the starting material **16**) to see for how many cycles the same $Pd(OH)_2$/C could be used. These experiments showed that 1.0 mmol of $Pd(OH)_2$/C was able to cleave about 2.0 mmol of **16**. However, similar experiments on the cleavage of the ketal **15** with $Pd(OH)_2$/C showed that the same $Pd(OH)_2$/C was able to cleave up to 10.0 equiv of the ketal. Also, cleavage of the benzyl ether as well as ketals could be completely prevented by the addition of 0.5 equiv of triethylamine to the reaction mixture. This perhaps indicates that complexation of the benzyl ether or the ketal with palladium is essential for cleavage. Based on these observations a plausible mechanism for the cleavage of acetals by $Pd(OH)_2$/C is shown in Scheme 3; arrival at the definitive mechanism of cleavage of benzyl ethers requires further studies.

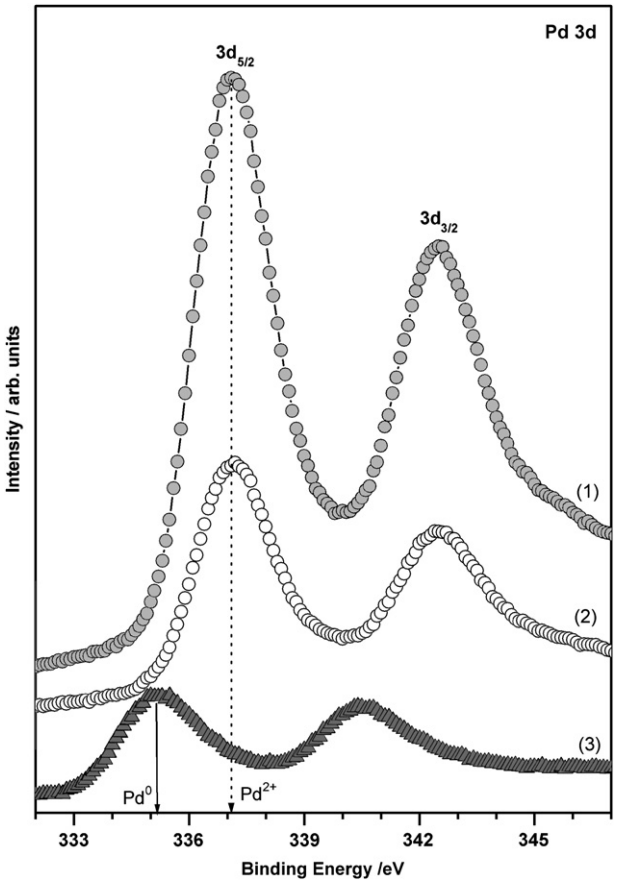
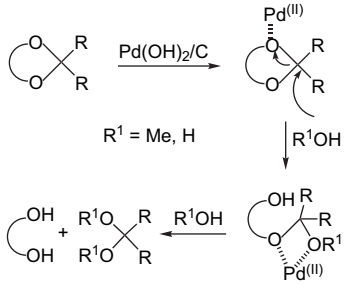
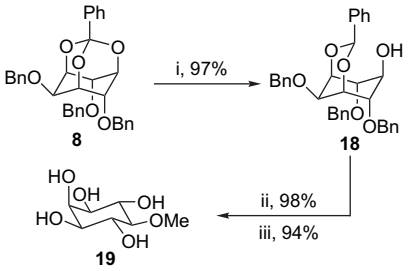


Figure 1. Comparison XPS spectra of palladium catalysts.



Scheme 3. A plausible mechanism for the cleavage of acetals by $Pd(OH)_2$/C.

We utilized this method of cleavage of benzyl ethers and acetals for the preparation of the naturally occurring sequoyitol[20] (**19**, Scheme 4). Partial cleavage of the orthobenzoate **8** with DIBAL-H[21] released the C5-hydroxyl group (**18**), which was methylated using sodium hydride and methyl iodide. All the benzyl ethers and benzaldehyde acetal were cleaved in one step with $Pd(OH)_2$/C in refluxing methanol to obtain sequoyitol (**19**) in an overall yield of 81% from *myo*-inositol. The yield in the previously reported[20c] methods for the preparation of sequoyitol (**19**) from naturally occurring pinitol did not exceed 8%.



Scheme 4. Synthesis of sequoyitol: reagents and conditions: (i) DIBAL-H, DCM, rt, 2 h; (ii) NaH, MeI, DMF, rt, 1 h; (iii) $Pd(OH)_2$/C, MeOH, reflux, 20 h.

3. Conclusions

We have discovered a new method for the cleavage of benzyl ethers and acetals and demonstrated its use in a short synthesis of sequoyitol. This method of cleavage could have applications in the synthesis of inositol-derived end-products wherein other functional groups present in the required products do not allow reductive cleavage of benzyl ethers and acid catalyzed hydrolysis of acetals and orthoesters. However, rather large amounts of $Pd(OH)_2$/C are required to bring about the cleavage of benzyl ethers and this could be a limitation for the large scale use of the method being reported. The present work also illustrates the potential of *myo*-inositol orthobenzoate for the preparation of inositol derivatives. We are currently investigating the selectivity aspects (with respect to other protecting groups) of the deprotection reactions reported here.

4. Experimental

4.1. General

All the solvents were purified according to the literature procedures[22] before use. A 60% dispersion of sodium hydride in

mineral oil was used for O-alkylation reactions. All the palladium compounds used were obtained from Aldrich chemical Co. or Lancaster Synthesis. Thin layer chromatography was performed on E. Merck pre-coated 60 F_{254} plates and the spots were rendered visible either by shining UV light or by charring the plates with concd H_2SO_4. Column chromatographic separations and flash column chromatographic separations were carried out on silica gel 60–120 mesh and 100–200 mesh, respectively, with solvent system as mentioned in experimental procedures. The compounds previously reported in the literature were characterized by comparison of their melting points and/or ^{1}H NMR spectra with reported data. All the asymmetrically substituted *myo*-inositol derivatives reported are racemic.

4.1.1. Racemic-2,4-di-*O*-methoxymethyl-6-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate (1). Sodium hydride (0.252 g, 6.30 mmol) was added to a cooled (0 °C) solution of the triol **6** (1.598 g, 6.0 mmol) in dry DMF (24 mL) and stirred for 15 min. Benzyl bromide (0.71 mL, 6.0 mmol) was added to this solution and stirring was continued for 1 h at rt. To the same reaction mixture, sodium hydride (0.72 g, 18.0 mmol) was added and stirring was continued for 15 min. Methoxymethyl chloride[23] (1.36 mL, 18.0 mmol) was then added and stirring was continued for 12 h. Solvents were then removed under reduced pressure and the residue was worked up with ethyl acetate. The crude product obtained was purified by flash column chromatography (eluent: 15% ethyl acetate in petroleum ether) to get **1** as a white solid (2.366 g, 89%). Mp 80–82 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60–7.75 (m, 2H, Ar H), 7.25–7.45 (m, 8H, Ar H), 4.78–4.88 (m, 3H, CH_2, Ins H), 4.70–4.77 (m, 2H, CH_2), 4.54–4.65 (m, 3H, CH_2, Ins H), 4.44–4.53 (m, 3H, Ins H), 4.23–4.26 (m, 1H, Ins H), 3.45 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 137.5 (C_{ipso}), 137.0 (C_{ipso}), 129.1 (C_{arom}), 128.2 (C_{arom}), 127.7 (C_{arom}), 127.5 (C_{arom}), 125.2 (C_{arom}), 107.6 ($PhCO_3$), 96.7 (CH_2), 95.5 (CH_2), 73.5 (Ins C), 73.3 (Ins C), 73.1 (Ins C), 72.4 (Ins C), 71.4 (CH_2), 69.1 (Ins C), 65.3 (Ins C), 55.6 (OCH_3), 55.3 (OCH_3). Anal. calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.95; H, 6.31.

4.1.2. Hydrogenolysis of racemic-2,4-di-*O*-methoxymethyl-6-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate (1).

4.1.2.1. Method A. The benzyl ether **1** (0.222 g, 0.50 mmol) was hydrogenolyzed in ethyl acetate (2.5 mL) in the presence of 20% $Pd(OH)_2$/C (0.06 g) at 55 psi. After 2 h, the reaction mixture was filtered over a short bed of Celite and the solution was evaporated under reduced pressure to get racemic **2** as a gum (0.172 g, 97%). IR (Nujol): ν 3350–3600 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.60–7.72 (m, 2H, Ar H), 7.30–7.42 (m, 3H, Ar H), 4.86–4.95 (m, 2H, CH_2), 4.79 (q, 2H, J=9.9 Hz, CH_2), 4.58–4.72 (m, 3H, Ins H), 4.50–4.56 (m, 1H, Ins H), 4.39–4.47 (m, 1H, Ins H), 4.19 (t, 1H, J=1.6 Hz, Ins H), 3.56 (s, 1H, OH), 3.47 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 136.7 (C_{ipso}), 129.4 (C_{arom}), 127.9 (C_{arom}), 125.3 (C_{arom}), 107.2 ($PhCO_3$), 97.5 (CH_2), 95.3 (CH_2), 74.2 (Ins C), 72.5 (Ins C), 69.1 (Ins C), 67.9, 64.2 (Ins C), 56.4 (OCH_3), 55.6 (OCH_3). Anal. calcd for $C_{17}H_{22}O_8$: C, 57.62; H, 6.26. Found: C, 57.44; H, 5.95.

4.1.2.2. Method B. The compound **1** (0.51 g, 1.15 mmol) was hydrogenolyzed in methanol (6 mL) in the presence of 20% $Pd(OH)_2$/C (0.161 g) at 55 psi at rt. After 13 h, the reaction mixture was filtered over a short bed of Celite and Celite was washed with methanol (10 mL). The combined methanol solution was evaporated under reduced pressure and the gummy residue obtained was purified by flash column chromatography (eluent: 10% methanol in ethyl acetate) to get the tetrol **3** as a white solid (0.285 g, 93%). Mp 117–118 °C; IR (Nujol) ν: 3200–3500 (OH) cm^{-1}; ^{1}H NMR (Acetone-d_6, 200 MHz): δ 4.77–4.84 (m, 4H, CH_2), 3.97 (t, 1H, J=2 Hz, Ins H), 3.52–3.70 (m, 3H, Ins H), 3.43–3.46 (m, 1H, Ins H), 3.41 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.26 (m, 1H, Ins H), 2.09 (s, 4H, OH). ^{13}C NMR (Acetone-d_6, 50.32 MHz): δ 98.8 (CH_2), 98.4 (CH_2), 82.0 (Ins C), 81.5 (Ins C), 75.0 (Ins C), 74.0 (Ins C), 71.9 (Ins C), 71.5 (Ins C), 56.0 (OCH_3), 55.9 (OCH_3). Anal. calcd for $C_{10}H_{20}O_8$: C, 44.77; H, 7.51. Found: C, 44.42; H, 7.27.

4.1.2.3. Method C. Hydrogenolysis of the compound **1** (0.51 g, 1.15 mmol) using excess of 20% $Pd(OH)_2$/C (0.64 g) as above gave **4** (0.204 g), which was characterized as its hexa-acetate: the crude **4** was suspended in pyridine (6 mL) and acetic anhydride (1.95 mL, 20.667 mmol) was added at 0 °C over 15 min and stirring was continued for 40 h at rt. The solvents were removed under reduced pressure and usual workup of the residue followed by column chromatography afforded **5** as a white solid (0.469 g, 96%). Mp 210–212 °C (lit.[24] mp 211–212 °C).

4.1.3. Reaction of racemic-2,4-di-*O*-methoxymethyl-6-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate (1) with 20% $Pd(OH)_2$/C in methanol. A mixture of racemic **1** (0.222 g, 0.50 mmol) and 20% $Pd(OH)_2$/C (0.281 g) in methanol (3 mL) was stirred at rt for seven days. The reaction mixture was filtered over a short bed of Celite and Celite was washed with methanol (10 mL). The combined methanol solution was evaporated under reduced pressure. The residue obtained was purified by column chromatography (eluent: 40% ethyl acetate in petroleum ether) to get racemic **2** as a gum (0.17 g, 96%). This reaction could be carried out in shorter time (32 h) in refluxing methanol to afford racemic **2** (0.172 g, 97%).

4.1.4. Reaction of *myo*-inositol 1,3,5-orthobenzoate (6) with $Pd(OH)_2$/C in methanol. A solution of **6** (0.133 g, 0.50 mmol) in methanol (3 mL) and 20% $Pd(OH)_2$/C (0.281 g) were stirred at rt for eight days. The reaction mixture was filtered over a short bed of Celite and Celite was washed with methanol (10 mL). The combined methanol solution was evaporated under reduced pressure. The residue obtained was purified by column chromatography (eluent: 10% methanol in ethyl acetate) to get **12** as a white solid (0.132 g, 93%). Mp 236–239 °C (lit.[25] mp 240–242 °C). Refluxing a solution of **6** (0.267 g, 1.0 mmol) in methanol (5 mL) for 9 h in the presence of 20% $Pd(OH)_2$/C (0.562 g) also afforded **12** (0.266 g, 94%).

4.1.5. Racemic 4-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate (7). Sodium hydride (0.168 g, 4.2 mmol) was added to a cooled (0 °C) solution of the triol **6** (1.065 g, 4.0 mmol) in dry DMF (16 mL) and stirred for 15 min. To this solution, benzyl bromide (0.5 mL, 4.2 mmol) was added and stirring was continued for 30 min at rt. Solvents were removed under reduced pressure and the residue was worked

up with ethyl acetate. The gummy product obtained was purified by column chromatography (eluent: 40% ethyl acetate in petroleum ether) to get the monobenzyl ether **7** as a white solid (1.363 g, 96%). Mp 86–88 °C; IR ($CHCl_3$): ν 3300–3600 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.54–7.68 (m, 2H, Ar H), 7.25–7.49 (m, 8H, Ar H), 4.69 (q, 2H, J=12 Hz, CH_2), 4.50–4.62 (m, 2H, Ins H), 4.35–4.46 (m, 3H, Ins H), 4.15 (d, 1H, J=10 Hz, Ins H), 3.75 (d, 1H, J=10 Hz, OH), 3.23 (d, 1H, J=11 Hz, OH). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 136.5 (C_{ipso}), 135.8 (C_{ipso}), 129.4 (C_{arom}), 128.6 (C_{arom}), 128.5 (C_{arom}), 127.8 (C_{arom}), 125.1 (C_{arom}), 107.1 ($PhCO_3$), 75.8 (Ins C), 73.7 (Ins C), 73.3 (Ins C), 72.6 (CH_2), 68.0 (Ins C), 67.5 (Ins C), 59.5 (Ins C). Anal. calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.10; H, 5.72.

4.1.6. Reaction of racemic 4-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate (7) with $Pd(OH)_2$/C in methanol. A solution of the monobenzyl ether **7** (0.267 g, 0.75 mmol) in methanol (4 mL) and 20% $Pd(OH)_2$/C (0.420 g) were stirred at rt for six days. The reaction mixture was filtered over a short bed of Celite and Celite was washed with methanol (10 mL). The combined methanol solution was evaporated under reduced pressure and the residue obtained was purified by column chromatography (eluent: 10% methanol in ethyl acetate) to get **12** as a white solid (0.196 g, 92%). Mp 236–239 °C. When the above reaction of the monobenzyl ether **7** (0.179 g, 0.50 mmol) with 20% $Pd(OH)_2$/C (0.281 g) was carried out in refluxing methanol (3.5 mL), the reaction was complete in 12 h to afford **12** (0.133 g, 93%).

4.1.7. 2,4,6 Tri-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate (8). Sodium hydride (1.92 g, 48.0 mmol) was added to a cooled (0 °C) solution of **6** (3.195 g, 12.0 mmol) in dry DMF (60 mL) and stirred for 15 min. To this solution, benzyl bromide (7.1 mL, 60.0 mmol) was added and stirring was continued for 1 h at rt. The solvents were removed under reduced pressure and the residue was worked up with ethyl acetate. The gummy residue obtained was purified by column chromatography (eluent: 10% ethyl acetate in petroleum ether) to get **8** as a white solid (6.288 g, 98%). Mp 83–85 °C; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.60–7.71 (m, 2H, Ar H), 7.15–7.50 (m, 18H, Ar H), 4.37–4.80 (m, 11H, Ins H+CH_2), 4.11 (t, 1H, J=2 Hz, Ins H). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 137.9 (C_{ipso}), 137.5 (C_{ipso}), 137.1 (C_{ipso}), 129.2 (C_{arom}), 128.2 (C_{arom}), 127.9 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 127.4 (C_{arom}), 125.3 (C_{arom}), 107.7 ($PhCO_3$), 73.9 (Ins C), 71.7 (Ins C), 71.4 (CH_2), 71.0 (CH_2), 68.8 (Ins C), 66.0 (Ins C). Anal. calcd for $C_{34}H_{32}O_6$: C, 76.10; H, 6.00. Found: C, 75.76; H, 6.36.

4.1.8. Reaction of 2,4,6-tri-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate (8) with $Pd(OH)_2$/C in methanol. A solution of **8** (0.268 g, 0.50 mmol) in methanol (3 mL) and 20% $Pd(OH)_2$/C (0.526 g) were refluxed for 40 h. The reaction mixture was filtered over a short bed of Celite and Celite was washed with methanol (10 mL). The combined methanol solution was evaporated under reduced pressure and the residue obtained was purified by column chromatography (eluent: 10% methanol in ethyl acetate) to get **12** as a white solid (0.121 g, 84%). Mp 235–238 °C (lit.[25] mp 240–242 °C).

4.1.9. Reaction of *myo*-inositol 1,3,5-orthoacetate (9) with $Pd(OH)_2$/C in methanol. A solution of the triol **9**[15a] (0.204 g, 1.0 mmol) in methanol (5 mL) and 20% $Pd(OH)_2$/C (0.562 g) were refluxed for 52 h. The reaction mixture was filtered over a short bed of Celite and Celite was washed with methanol (10 mL). The combined methanol solution was evaporated under reduced pressure and the residue obtained was chromatographed (eluent: 10% methanol in ethyl acetate) to get a mixture of *myo*-inositol monoacetates **13** (0.206 g, 93%) as revealed by the ^1H NMR spectrum; no attempt was made to separate the *myo*-inositol acetates obtained.

4.1.10. Reaction of *myo*-inositol 1,3,5-orthoformate (10) with $Pd(OH)_2$/C in methanol. A solution of the triol **10**[26] (0.19 g, 1.0 mmol) in methanol (5 mL) and 20% $Pd(OH)_2$/C (0.562 g) were refluxed for 32 h. The reaction mixture was diluted with distilled water (10 mL) and the catalyst was removed by filtration using a Whatman filter paper. The filtrate was evaporated under reduced pressure and the residue obtained was acetylated with acetic anhydride (1.9 mL, 2.055 g, 20.14 mmol) in dry pyridine (5 mL) for 40 h. The solvents were removed under reduced pressure; usual workup of the residue followed by column chromatography (eluent: 35% ethyl acetate in petroleum ether) gave the hexa-acetate **5** as a white solid (0.41 g, 96%). Mp 210–212 °C (lit.[24] mp 211–212 °C).

4.1.11. Reaction of 2,4,6-tri-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (11) with $Pd(OH)_2$/C in methanol. A solution of **11**[27] (0.231 g, 0.50 mmol) in methanol (3 mL) and 20% $Pd(OH)_2$/C (0.528 g) were refluxed for 72 h. The reaction mixture was diluted with distilled water (10 mL) and the catalyst was removed by filtration using a short bed of Celite and Celite was washed with distilled water (10 mL). The solvents were removed under reduced pressure to obtain **4** as a white solid (0.087 g, 96%). Mp 222–224 °C (lit.[28] mp 224–225 °C).

4.1.12. Reaction of racemic 1,2:4,5-di-isopropylidine-3,6-di-*O*-benzyl-*myo*-inositol (14) with $Pd(OH)_2$/C in methanol. A solution of **14**[29] (0.049 g, 0.11 mmol) in methanol (1 mL) and 20% $Pd(OH)_2$/C (0.078 g) were refluxed for 22 h. The reaction mixture was diluted with water (2 mL) and filtered over a short bed of Celite and Celite was washed with water (5 mL). The solvents were evaporated under reduced pressure to get **4** as a white solid (0.019 g, 95%).

4.1.13. Reaction of racemic 1,2:4,5-di-isopropylidine-*myo*-inositol (15) with $Pd(OH)_2$/C in methanol. A mixture of **15**[30] (0.065 g, 0.25 mmol) and 20% $Pd(OH)_2$/C (0.175 g) in methanol (3 mL) was refluxed for 8 h, when TLC analysis of the reaction mixture showed the absence of **15**. The ketal **15** was added (0.065 g for every 8 h) to the same reaction mixture and the refluxing was continued. This addition of **15** was repeated 10 times at the end of which the reaction mixture was diluted with distilled water (5 mL) and the catalyst was filtered using a short bed of Celite. The solvents were removed under reduced pressure to get **4** as a white solid (0.436 g, 97%). Mp 223–224 °C.

4.1.14. Reaction of cyclohexyl benzyl ether (16) with 20% $Pd(OH)_2$/C in methanol. The benzyl ether **16** (0.195 g,

1.03 mmol) and 20% $Pd(OH)_2/C$ (0.359 g) were refluxed in methanol (5 mmol) for 10 h under argon atmosphere. The reaction mixture was allowed to cool to room temperature and the catalyst was filtered using a short bed of Celite. The catalyst was washed with methanol (2×5 mL). The crude product obtained was purified by column chromatography (10% ethyl acetate in petroleum ether) to get cyclohexanol (**17**) as a colourless liquid (0.086 g, 84%).

4.1.15. Reaction of cyclohexyl benzyl ether (16) with $Pd(OAc)_2$ in methanol. A mixture of the benzyl ether **16** (0.048 g, 0.25 mmol) and $Pd(OAc)_2$ (0.028 g, 0.13 mmol) in methanol (5 mL) was refluxed for 40 h under argon atmosphere. The product, cyclohexanol (**17**, 0.021 g, 83%) was isolated as above.

4.1.16. Reduction of 2,4,6-tri-*O*-benzyl-*myo*-inositol 1,3,5-orthobenzoate (8) with DIBAL-H.[21] Solution of DIBAL-H (1 M) in toluene (4 mL, 4.0 mmol) was added drop wise over a period of 15 min to a solution of **8** (1.073 g, 2.0 mmol) in dry dichloromethane (16 mL) at 0 °C and stirred at rt for 2 h. The reaction mixture was poured into a stirred solution of saturated Na/K tartrate (10 mL) and ammonium chloride (10 mL) and stirred for 2 h. The mixture was extracted with ethyl acetate (2×100 mL) and usual workup followed by column chromatography (ethyl acetate:dichloromethane:petroleumether=1:1:8) afforded **18** as a solid (1.05 g, 97%). Mp 102–104 °C (crystallized from a solution of dichloromethane and light petroleum ether cooled to 0 °C), IR (neat) υ=3452 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.50–7.60 (m, 2H, Ar H), 7.27–7.45 (m, 18H, Ar H), 5.72 (s, 1H, PhCH), 4.58–4.81 (m, 6H, CH_2), 4.41 (d, 2H, J=2 Hz, Ins H), 3.96–4.15 (m, 2H, Ins H), 3.79 (t, 1H, J=8.64 Hz, Ins H), 3.62 (t, 1H, J=2.44 Hz, Ins H), 2.57 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 137.9 (C_{ipso}), 137.8 (C_{ipso}), 137.3 (C_{ipso}), 129.3 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 127.9 (C_{arom}), 127.8 (C_{arom}), 127.6 (C_{arom}), 126.5 (C_{arom}), 92.7 (PhCH), 81.5 (Ins C), 73.5 (Ins C), 73.4 (Ins C), 71.6 (CH_2), 70.6 (CH_2), 68.1 (Ins C). Anal. calcd for $C_{34}H_{34}O_6$: C, 75.82; H, 6.36. Found: C, 75.80; H, 6.40.

4.1.17. Preparation of sequoyitol (19). Sodium hydride (0.040 g, 0.10 mmol) was added to a solution of **18** (0.480 g, 0.89 mmol) in dry DMF (3 mL) and stirred for 30 min. The mixture was cooled to 0 °C and methyl iodide (0.182 g, 1.28 mmol) was added drop wise and the mixture stirred for 1 h at rt. The reaction mixture was concentrated under reduced pressure and worked up with chloroform. Column chromatography (10% ethyl acetate in petroleum ether) of the residue obtained after evaporation of chloroform afforded the methyl ether of **18** as a solid (0.481 g, 98%). Mp=85–88 °C, ^1H NMR ($CDCl_3$, 200 MHz): δ 7.50–7.55 (m, 2H, Ar H), 7.25–7.45 (m, 18H, Ar H), 5.74 (s, 1H, PhCH), 4.56–4.76 (m, 6H, CH_2), 4.37 (d, 2H, J=2 Hz, Ins H), 4.02 (d, 2H, J=7 Hz, Ins H), 3.56–3.63 (m, 1H, Ins H), 3.59 (s, 3H, OCH_3), 3.44 (t, 1H, J=7 Hz, Ins H). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 138.0 (C_{ipso}), 137.8 (C_{ipso}), 137.5 (C_{ipso}), 129.2 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 126.4 (C_{arom}), 92.8 (PhCH), 83.5 (Ins C), 82.3 (Ins C), 73.2 (Ins C), 71.4 (CH_2), 70.6 (CH_2), 68.2 (Ins C), 59.7 (OCH_3). Anal. calcd for $C_{35}H_{36}O_6$: C, 76.06; H, 6.56. Found: C, 76.21; H, 6.43.

A mixture of the methyl ether of **18** (0.280 g, 0.53 mmol) obtained above and 20% $Pd(OH)_2/C$ (0.554 g) in methanol (5 mL) was refluxed under argon atmosphere for 20 h. The reaction mixture was allowed to cool to rt and diluted with 3 mL of water. The catalyst was filtered using a short bed of Celite and was washed with water (2×3 mL). The crude product obtained by evaporation of the filtrate, was dissolved in methanol and water mixture (3:1) and cooled in a freezer to get colourless crystals of **19** (0.096 g, 94%). Mp 237–239 °C (lit.[31] mp 238–239 °C).

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