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Efficient regioselective protection of *myo*-inositol via facile protecting group migration

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ABSTRACT

A *cis*-1,2-cyclohexanediol, 1,4,5,6-tetra-*O*-benzyl-*myo*-inositol, was selectively protected at the axial C2-hydroxyl via acid-mediated rearrangement of the corresponding 1,2-orthoacetate, or via the base-induced migration of a protecting group that had previously been easily installed with complete regioselectivity at the adjacent equatorial hydroxyl. Esters **4a**–**6a** were synthesized in high yields (75–82%) while sulfonate **7a** and silyl ether **8a** were obtained in 85 and 31% yields, respectively. The migration of the esters induced by DBU results in equilibrium between regioisomers favouring the C2 protected isomer, but NaH induced migration of sulfonyl and silyl groups results in complete migration from equatorial to axial hydroxyl groups.

1. Introduction

As part of an on-going search for potential inhibitors of mycothiol (**MSH**),1D-*myo*-inosityl 2-(*N*-acetyl-L-cysteinyl)amido-2-deoxy-α-D-glucopyranoside, biosynthesis in the *Mycobacteria*, we have been interested in the synthesis of mimics of **MSH** or its biosynthetic precursors.[1] Mycothiol is produced by *Mycobacteria*, including the causative pathogen of tuberculosis (TB), *Mycobacterium tuberculosis*, in self-defence against the oxidative immune response to infection and also as part of a detoxification mechanism that might be responsible for the bacterium acquiring resistance to first-line anti-TB drugs.[2] The search for new, faster-acting drugs to combat tuberculosis, especially the new multi-drug resistant strains (MDR or XDR) of the pathogen, is an urgent challenge worldwide but critical in sub-Saharan Africa.

The *pseudo*-disaccharide intermediate 1-D-1-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol (α-**DGI**) and its structural analogues are needed as reference standards in the evaluation of potential inhibitors of the **MSH** biosynthetic enzymes. The chemical synthesis of α-**DGI** has attracted the attention of various groups who have used strategies that differ mainly in the preferred method of *myo*-inositol resolution and the selective, orthogonal protection schemes to leave only the C1 hydroxyl unprotected and available for glycosylation.[1,3] In most of these methods the resolution step is the most costly in terms of time (involving repeated crystallizations), material (expensive chiral auxiliaries) and efficiency (low yields of each resolved and protected enantiomer of *myo*-inositol). The most efficient method for the simultaneous preparation and dynamic resolution of *myo*-inositol appears to be that of Pietrusiewicz et al. as subsequently modified to incorporate in situ preparation of the desired camphor dimethyl acetal.[4] This produces the desired diastereomer of 1,2-protected *myo*-inositol, whose other hydroxyl groups can be easily protected before selective removal of the camphor acetal to form the 1,2-diol.

However, even when the single diastereomer of the 1,2-diol is efficiently prepared, differentiation of the two free hydroxyls remains a challenge. The selectively unprotected equatorial C1 hydroxyl is generally accomplished via circuitous routes involving selective temporary protection at C1, protection of the other hydroxyl groups, and finally removal of the C1 protection. The favoured route is via the traditional stannylene acetal protocol although Shashidhar et al. have recently reported high yields in the regiospecific protection of *myo*-inositol orthoester derivatives via metal chelation control and exploitation of the subtle differences in the rates of reaction of axial and equatorial hydroxyl groups.[5]

We report here on the exploration of two complementary strategies (Scheme 1) for preparation of selectively protected *myo*-

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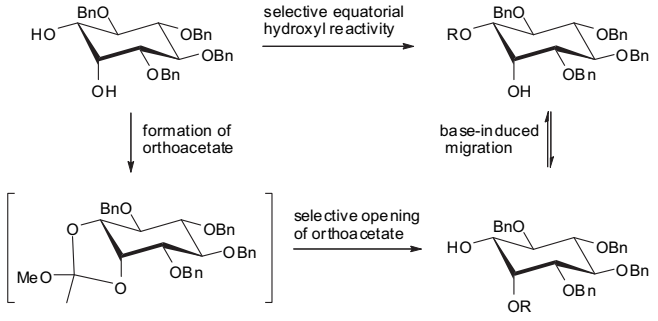
inositol. One involves acid-mediated opening of the 1,2-orthoacetate of *myo*-inositol to yield the axial mono-acetate, by analogy with work on carbohydrate 1,2-*cis*-orthoacetates. The other attempts to exploit differential hydroxyl and alkoxide reactivity in the conformationally-restricted environment of the inositols, that is, while equatorial hydroxyl groups are more nucleophilic compared to axial hydroxyl groups, axial alkoxides would be less stable and thus more reactive.



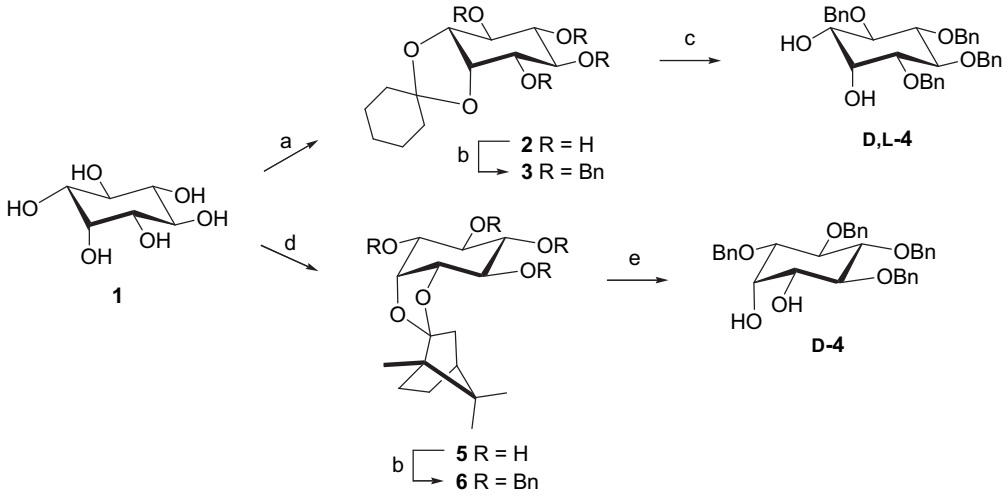
Scheme 1. Strategies for preparation of selectively protected *myo*-inositol derivatives.

products were formed.[8] Notwithstanding Chung and Chang's later observation that the migration of benzoyl groups in *myo*-inositol dibenzoates did not proceed in a predictable or selective manner to be useful in a general synthetic strategy,[9] a systematic investigation of the migration of labile protecting groups on a *cis*-1,2-cyclohexanediol substrate was considered reasonable.

2. Results and discussion

Our starting point in most of the work described here was the readily accessible racemic diol D,L-**4**. This was synthesized as shown in Scheme 2 in 72% overall yield from *myo*-inositol according to the method of Massy and Wyss with minor modifications, namely the use of benzene instead of toluene in the cyclohexylidenation step and the benzylation of **2** by the Provelenghiou method.[10] The pure D-isomer of the diol (D-**4**) was also produced via camphor acetal **5**.[4]

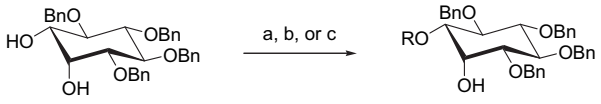
Protection of the equatorial hydroxyl group in diol **4** was achieved in variable yield (conversion), but with complete regioselectivity (Scheme 3). The regioisomers are easily distinguishable by the chemical shift of H-2, the only equatorial hydrogen on the *myo*-inosityl skeleton that has characteristic doublet of doublets splitting with small coupling constants (*J*) due to the two axial-equatorial dihedral angles. The chemical shift of this proton is



Scheme 2. Reagents and conditions: (a) Cyclohexanone, *p*-TsOH, DMF/PhH (1:1), reflux, 24 h (93%); (b) NaH (8 equiv), BnBr (6 equiv), TBAI (0.4 equiv), THF, 0 °C—rt, 24 h (84%); (c) HOAc (80% aq), reflux, 2 h (91%); (d) L-camphor dimethyl acetal, H_2SO_4, DMSO, 75 °C; (e) TFA, $CHCl_3$, reflux. (94% over two steps).

It was anticipated, as has been shown by others, that regioselective equatorial acylation, silylation, or sulfonylation of *cis*-1,2-cyclohexanediols would be readily accomplished based on the greater nucleophilicity of an equatorial hydroxyl compared to an axial hydroxyl.[6] The intention was to then investigate whether formation of an alkoxide at the axial hydroxyl would lead to the migration of the equatorial protecting group to the axial position (Scheme 1). Such a migration would be mildly disfavoured due to increased 1,3-diaxial steric interactions on derivatization of the axial hydroxyl, considering the free energies (−ΔGo) or A-values: OH (0.6 kcal/mol), $OCOCH_3$ (0.68 kcal/mol), $OCOC_6H_5$ (0.5 kcal/mol), $OSO_2C_6H_4CH_3$-*p* (0.5 kcal/mol) and $OSi(CH_3)_3$ (0.74 kcal/mol).[7] It was nonetheless reasonable to hypothesize that the more easily solvated and stabilized equatorial alkoxide would be less reactive and would lose its 'protection' to the more unstable and more reactive axial alkoxide. In 1988 Meek et al. reported that an equatorial benzoyl group in 1,4-dibenzoyl-*myo*-inositol migrated to an axial position to give 2,4-dibenzoyl-*myo*-inositol in pyridine-water (3:2) at 100 °C, although the conversion was poor (<50%) and other by-

~4.2–4.5 ppm when acylation or sulfonylation takes place at the equatorial hydroxyl group, but moves downfield by ~1.5 ppm when derivatization takes place at C2.



Scheme 3. Reagents and conditions: (a) Et_3N (1.2 equiv), DMAP (0.2 equiv), RCOCl (1 equiv), CH_2Cl_2, 0 °C—rt, 24 h; (b) Et_3N (1.2 equiv), Bu_2SnO (0.05 equiv), TsCl (2 equiv), CH_2Cl_2, reflux, 24 h; (c) TBSCl (1 equiv), imidazole (3 equiv), DMF, 60 °C, 48 h.

Esterification of **4** with 1 equiv of acid chloride under DMAP catalysis with triethylamine as a base gave selectively protected axial alcohols **7a**, **8a** and **9a** in good yields (Scheme 3). Tosylation of **4** using

Martinelli's protocol for catalytic organotin assisted selective sulfonylation of 1,2-diols occurred with poor conversion (45% recovered diol),[11] but gave good regioselectivity with a 12:1 ratio of monotosylate **10a** to ditosylate as determined from ^{1}H NMR spectroscopy. However, when the catalytic ratio of Bu_2SnO was increased from 2 to 5 mol %, the conversion was excellent (85%) and there was complete regioselectivity for **10a**. Unfortunately silylation of diol **4** to **11a**, using TBSCl, was poor (31%) under the classical conditions (imidazole as base, in DMF solvent) although diol **4** is easily recovered by column chromatography;[12] repeated attempts to improve these yields by varying solvents and conditions have met with failure.

With selectively protected alcohols in hand we proceeded to investigate the optimal conditions (type of base and reaction time) for the C1→C2 protective group migration, starting with esters **7a** and **8a** (Table 1). The ratios of products, including the diol **4** arising from the total cleavage of a protecting group were determined from HPLC analyses of the organic phase from the reaction work-up. In most cases the hydrolysis of the esters during the migration and work-up could be minimized by ensuring strictly anhydrous conditions and a rapid work-up with cold, saturated NH_4Cl. The benzoyl and pivaloyl groups migrated readily at room temperature when the C1-*O*-acyl derivatives were treated with 2 equiv of DBU in CH_3CN. The reaction was monitored by TLC and within 5 min it was apparent by TLC that migration was taking place, due to the appearance of a new, more polar spot, but even after 48 h the spot for the starting material was persistent. The migration seemed to reach equilibrium within 4 h and extended time did not alter the ratio of products (Table 1, entries 1 and 2). Furthermore, the migration was assumed to be under thermodynamic control since addition of an acylation catalyst (DMAP) did not change the ratio of products (Table 1, entry 4).

Table 2
Protecting group migration in a *cis*-1,2-cyclohexanediol substrate

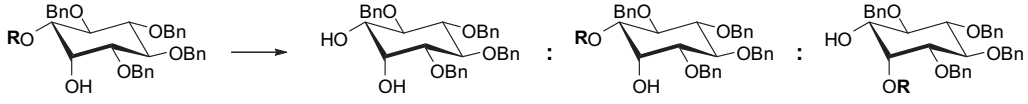
Entry	Substrate	Migration method	Ratio **4**:**Xa**:**Xb**
1	**7a**	DBU, 4 h, rt, CH_3CN	1:49:50[a]
2	**8a**	DBU, 4 h, rt, CH_3CN	0:36:64[a]
3	**9a**	DBU, 4 h, rt, CH_3CN	0:30:70[b]
4	**10a**	NaH, 30 min, 0 °C, DMF	0:0:100[b]
5	**11a**	NaH, 30 min, 0 °C, DMF	0:0:100[b]

[a] Ratio determined by HPLC and confirmed by isolated yield.
[b] Isolated yield; after purification by column chromatography.

amazingly it is the more bulky esters that favour the axial position (Table 2, entries 1–3) contrary to what might be expected from consideration of A-values. The sulfonyl and silyl protecting groups were more robust towards hydrolysis in the presence of NaH and showed complete C1→C2 migration from an equatorial hydroxyl to an axial position (Table 2, entries 4 and 5). These results support the hypothesis that axial alkoxides are more unstable and thus more reactive and will readily contest for the closest electrophile, in this case the sulfonyl or silyl group at C1.

Overall we have shown that the migration of protecting groups, which is sometimes a drawback in the selective protection of polyols, can be predictable and harnessed as an alternative to the use of transient, orthogonal protection schemes. Furthermore, the potential for simultaneous regioselective protection and resolution of diastereomers is illustrated in results for camphanate ester **9a**, derived from racemic diol **4** by incorporation of a chiral protecting group. The mixture of two diastereomers was unfortunately not easily separated by column chromatography. However, the diastereomers of **9b** derived as the major product of base-induced migration were easily separated by column chromatography using

Table 1
Equilibration of regioisomers during base-induced migration of esters



Entry	Substrate/method	Ratio of products (**4**:**7a**/**8a**:**7b**/**8b**) after given time intervals:				
		4 h	8 h	12 h	24 h	48 h
1	**7a**/DBU	1:49:50	1:49:51	2:49:49	4:51:45	8:44:48
2	**8a**/DBU	0:36:64	0:38:62	0:36:64	0:37:63	0:34:66
3	**8a**/*t*-BuOK	4:80:16	62:15:23	27:30:43	12:18:70	4:36:60
4	**8a**/DBU+DMAP	0:36:64				
5	**8a**/DBU/DBU	0:36:64				

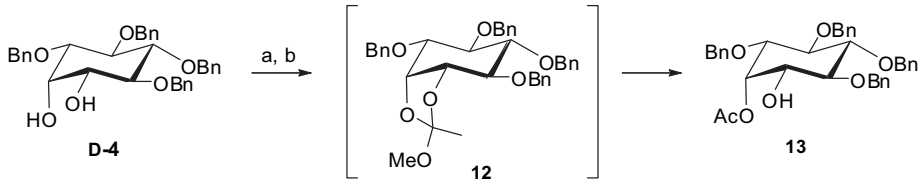
When sequential addition of DBU was investigated, where the substrate **8a** was treated with DBU for 4 h and then a further aliquot of DBU was added and the reaction allowed to proceed for a further 4 h (Table 1, entry 5), there was still no change to the ratio of regioisomers; this appears to confirm that the acyl group migration is a reversible reaction.

When *t*-BuOK was used as the base for migration (Table 1, entry 3), the results were inconsistent and it took longer (>24 h) to reach an equilibrium ratio for the regioisomers; appreciable hydrolysis was also observed during the butoxide induced migration of the pivaloyl group. When NaH was used as the base for migration (results not shown in Table 1), there was immediate (within 5 min) hydrolysis of the esters as observed by TLC.

A summary of the migration experiments on all the protective groups investigated is shown in Table 2. The equilibrium of ester migration is surprisingly dependent on the identity of the acyl group. The reason for such a discrepancy is not apparent, but

Et_2O/CH_2Cl_2 (1:13), giving camphanate diastereomers D-**9b** and L-**9b** in a ratio 54:46. These were assigned on the basis of their optical rotations ($[\alpha]_D^{24}$ −3.62 (*c* 1.25 $CHCl_3$) and $[\alpha]_D^{24}$ −12.8 (*c* 1.25 $CHCl_3$), respectively), and could also be distinguished from their ^{1}H NMR spectra where the camphanoyl methyl groups had distinctive chemical shifts: D-**9b** (δ 1.11, 0.94, 0.94 ppm) and L-**9b** (δ 1.11, 1.04, 0.84 ppm). This therefore represents a viable alternative route to the resolution and selective formation of a *myo*-inositol derivative with only the C1 hydroxyl available for further reactions, such as glycosylation.

While the results described above represent a synthetically useful approach, the most efficient and selective protection of the axial hydroxyl group in the *cis*-1,2-diol **4** was in the end achieved by formation and subsequent opening of an orthoacetate (Scheme 4). Orthoacetate **12** was easily formed from diol D-**4** (Scheme 3), and upon treatment with *p*-toluenesulfonic acid reverted to the axially-protected derivative **13** in excellent overall yield of 94% (Scheme 4).



Scheme 4. Reagents and conditions: (a) *p*-TsOH, $(CH_3O)_3CCH_3$, CH_3CN, rt, 2h; (b) H_2O, −40 °C, 94%.

This result seems consistent with our earlier observations, in that it implies initial preferential protonation of the equatorially-oriented oxygen in acetal **12** with the axially-oriented oxygen thus retaining the acetate after the hydrolytic opening of the dioxolane unit. This preparation of selectively unprotected D-*myo*-inositol derivative **13** in four steps, if one considers that the orthoacetate is not isolated, is thus the shortest and most efficient preparation to date of a suitable glycosyl acceptor for use in the synthesis of mycothiol and its analogues.

3. Experimental

3.1. General methods

All reactions were carried out under an inert N_2 atmosphere. Solvents were dried and distilled by the standard methods.[13] All commercially available reagents were used without further purification. Reactions were monitored by TLC using Silica gel 60 UV_{254} (Alugram) pre-coated silica gel plates; detection was by means of a UV lamp and by heating the plate after spraying with a solution of CAS [Preparation: 63 g Ceric ammonium sulfate dissolved in 500 mL of 6% H_2SO_4 and diluted to 1 L mark by distilled H_2O]. Organic layers were dried over anhydrous $MgSO_4$ or Na_2SO_4 prior to evaporation on a Büchi rotary evaporator B-490 with a bath temperature of ≤50 °C. Column chromatography was carried out on Machery Nagel silica gel 60 (70–230 mesh). IR spectra were recorded on a Nicolet Impact 400 FT-IR spectrophotometer as thin films on NaCl windows for oils or KBr pellets for solids. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 300 at ambient temperature in the specified solvent. The splitting patterns are reported as follows: singlet (s), doublet (d), triplet (t), doublet of doublets (dd), multiplet (m) and broad singlet (br s). Optical rotations were collected on a Perkin–Elmer 14 Polarimeter at ambient temperature and the concentration is calculated in g/100 mL. Melting points were recorded with a Stuart Melting Point Apparatus SMP10 and are reported uncorrected.

*3.1.1. 1,2-O-Cyclohexylidene-D/L-myo-inositol (**2**).* *myo*-Inositol (**1**) (4.707 g, 26.13 mmol) and cyclohexanone (40 mL, 385.9 mmol) were combined in DMF (50 mL) and benzene (50 mL) and heated to reflux in a Dean–Stark apparatus. To this refluxing mixture was added *p*-TsOH·H_2O (0.202 g, 1.06 mmol) in DMF (5 mL) in 1.25 mL aliquots at 2 h intervals. The mixture changed from cloudy to a clear pale yellow after 10 h and was heated to reflux for 24 h. The solvents were then removed by vacuum distillation to leave a viscous orange liquid that was taken up in hot EtOH (100 mL) and left to cool slowly to crystallize. The solid was filtered and re-crystallized from EtOH to give **2** as white needle-like crystals (6.34 g, 93%). Mp 180–181 °C (lit.[14] 179–180 °C); ^{13}C NMR (100 MHz, DMSO): δ 109.2, 79.5, 76.7, 75.7, 74.9, 73.5, 73.0, 72.6, 70.6, 38.3, 35.6, 25.3, 24.3, 24.0.

*3.1.2. (±)-3,4,5,6-Tetra-O-benzyl-1,2-O-cyclohexylidene-myo-inositol (**3**).* Tetraol **2** (6.411 g, 24.65 mmol) was dissolved in dry, freshly distilled THF (60 mL) in a 2-necked 100 mL round bottom flask and cooled to 0 °C. To this was added NaH (7 g, 145.8 mmol, 50% dispersion in mineral oil) and, after stirring for 30 min TBAI (4.51 g, 12.21 mmol) was added followed by slow addition of benzyl bromide (18 mL, 151.3 mmol) and the reaction mixture was heated to reflux for 16 h. The reaction was then quenched first with MeOH and then H_2O; the mixture was washed with EtOAc (2×80 mL) and the combined organic layers washed with brine (50 mL) and dried over Na_2SO_4. The crude product was purified by chromatography on SiO_2 using hexanes to remove excess benzyl bromide and EtOAc/PE (1:9) to isolate **3** as an oily product (14.27 g, 93%) that was determined to be sufficiently pure by NMR to use in the next step without further purification (lit.[15] mp 85–87 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.25 (20H, m), 4.94–4.74 (8H, m), 4.29 (1H, t, *J*=4 Hz), 4.1 (1H, t, *J*=5.2 Hz), 3.95 (1H, t, *J*=8.4 Hz), 3.82 (1H, t, *J*=9.6 Hz), 3.7 (1H, dd, *J*=4.0; 8.4 Hz), 3.42 (1H, dd, *J*=8.4; 9.6 Hz), 1.9–1.4 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.64,138.58, 138.57, 138.27, 128.34, 128.31, 128.28, 128.24, 128.12, 128.05, 127.99, 127.98, 127.95, 127.92, 127.75, 127.61, 127.57, 127.54, 127.48, 110.43, 82.93, 82.09, 80.91, 78.77, 77.28, 75.27, 75.12, 74.01, 73.98, 73.12, 37.4, 35.05, 25.04, 23.91, 23.65.

*3.1.3. (±)-1,4,5,6-Tetra-O-benzyl-myo-inositol (D,L-**4**).* Acetal **3** (14.27 g, 24.65 mmol) was dissolved in 80% aq acetic acid (150 mL) and heated to a gentle reflux for 2 h. The solvent was evaporated under reduced pressure and the crude product crystallized at 0 °C from a mixture of toluene/PE (1:3) to give D,L-**4** as a white solid (10.28 g, 78%) that was re-crystallized from EtOAc/PE (1:4). Mp 145–147 °C (lit.[16] 141–143 °C); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.26 (20H, m), 4.94–4.72 (8H, m), 4.21 (1H, dd, *J*=2.4, 2.7 Hz), 3.97 (1H, dd, *J*=9.6, 9.3 Hz), 3.84 (1H, dd, *J*=9.6, 9.3 Hz), 3.51–3.45 (3H, m), 2.49 (1H, s), 2.41 (1H, d, *J*=4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.66, 138.54, 137.82, 128.57, 128.53, 128.39, 128.37, 127.95, 127.94, 127.88, 127.81, 127.60, 83.24, 81.67, 81.34, 80.05, 75.92, 75.69, 75.59, 72.77, 71.79, 69.21.

*3.1.4. (±)-1-Benzoyl-3,4,5,6-tetra-O-benzyl-myo-inositol (**7a**).* A mixture of diol D,L-**4** (0.5 g, 0.925 mmol), Et_3N (0.15 mL, 1.01 mmol) and a catalytic amount of DMAP was dissolved in CH_2Cl_2 (5 mL) followed by the addition of benzoyl chloride (0.12 mL, 1.03 mmol). The reaction was monitored by TLC and stirred at room temperature for 24 h then taken up with CH_2Cl_2 (50 mL) and quenched with saturated aq NH_4Cl (30 mL). The organic layer was dried over Na_2SO_4 and the crude product was purified by column chromatography using EtOAc/PE (1:4) to give **7a** as a white solid (0.486 g, 82%), R_f 0.33, mp 127–131 °C (lit.[17] 144–145 °C); IR (KBr): 3520, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (2H, d, *J*=7.8 Hz), 7.61–7.15 (23H, m), 5.14 (1H, dd, *J*=2.1, 10.2 Hz), 4.95–4.71 (8H, m), 4.43 (1H, d, *J*=2.1 Hz), 4.27 (1H, dd, *J*=9.3, 10.2 Hz), 4.04 (1H, dd, *J*=9.3, 9.6 Hz), 3.63 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.93, 138.48, 138.4, 138.02, 137.36, 133.58, 133.24, 130.1, 129.78, 129.65, 128.52, 128.43, 128.37, 128.21, 128.04, 127.92, 127.87, 127.62, 127.55, 83.14, 81.14, 79.98, 78.98, 76.0, 75.77, 73.74, 72.88, 67.88. $[M+H]^+$ calcd for $C_{41}H_{40}O_7$ 645.2852, found 645.2866.

*3.1.5. (±)-1-Pivaloyl-3,4,5,6-tetra-O-benzyl-myo-inositol (**8a**).* A mixture of diol D,L-**4** (0.513 g, 0.949 mmol), Et_3N (0.15 mL, 1.08 mmol) and a catalytic amount of DMAP was dissolved in CH_2Cl_2 (5 mL) followed by the addition of pivaloyl chloride (0.12 mL, 0.974 mmol). The reaction was monitored by TLC and stirred at room temperature for

24 h then taken up in CH_2Cl_2 (50 mL) and extracted with saturated NH_4Cl (30 mL). The organic layer was dried over Na_2SO_4 and the crude product was purified by SiO_2 using EtOAc/PE (1:4) to give **8a** as a white solid (0.494 g, 83%), mp 138–140 °C.

IR (KBr): 3469, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.28 (20H, m), 4.89–4.69 (9H, m), 4.21 (1H, t, J=2.6 Hz), 4.02 (1H, dd, J=9.6; 10.1 Hz), 3.88 (1H, t, J=9.6 Hz), 3.49–3.43 (2H, m), 2.3 (1H, br s), 1.18 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.97, 138.61, 138.5, 138.44, 137.56, 128.49, 128.27, 128.25, 127.95, 127.83, 127.77, 127.53, 127.50, 127.43, 127.30, 83.16, 81.16, 80.04, 78.87, 75.86, 75.41, 73.33, 72.81, 67.65, 38.88, 27.14. $[M+H]^+$ calcd for $C_{39}H_{44}O_7$ 625.3165, found 625.3182.

*3.1.6. (±)-1-(S)-Camphanoyl-3,4,5,6-tetra-O-benzyl-myo-inositol (**9a**).* A mixture of diol D,L-**4** (100 mg, 0.15 mmol), Et_3N (0.03 mL, 0.215 mmol) and a catalytic amount of DMAP was dissolved in CH_2Cl_2 (1.0 mL) followed by the addition of (*S*)-(−)-camphanic acid chloride (48 mg, 0.222 mmol). The reaction was monitored by TLC and stirred at room temperature for 24 h then taken up with CH_2Cl_2 (50 mL) and quenched with saturated NH_4Cl (30 mL). The organic layer was dried over Na_2SO_4 and the crude was purified by SiO_2 using EtOAc/PE (1:4) to give a mixture of diastereomers D-**9a** and L-**9a** as a white gum (97 mg, 75%). IR (neat): 3550, 1780, 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.17 (20H, m, 4×Ph), 4.97–4.65 (9H, m, H-1 and 4×CH_2Ph), 4.32 (0.5H, t, J=2.7 Hz, H-2 of D-**9a**), 4.29 (0.5H, t, J=2.7 Hz, H-2 of L-**9a**), 4.15 (0.5H, t, J=9.8 Hz, H-6 of D-**9a**), 4.13 (0.5H, t, J=9.8 Hz, H-6 of L-**9a**), 3.97 (0.5H, t, J=9.6 Hz, H-4 of D-**9a**), 3.96 (0.5H, t, J=9.4 Hz, H-4 of L-**9a**), 3.61–3.51 (2H, m, H-3 and H-5), 2.47–2.24 (1H, m, H-1′$_a$), 2.04 (2H, m, H-1′$_b$ and H-2′$_a$), 1.73–1.63 (1H, m, H-2′$_b$), 1.60 (1H, br s, OH), 1.11, 1.10, 1.08, 1.01, 0.98, 0.90 (9H, 6s, CH_3 of camphanoyl group); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.1, 177.8, 167.2, 167.0 (4×C=O of camphanoyl), 138.5, 138.4, 138.2, 137.6, 137.5, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 127.3, 91.0, 83.02, 83.0, 81.12, 81.08, 80.0, 79.9, 78.5, 78.4, 75.96, 75.93, 75.9, 75.5, 75.4, 74.8, 74.7, 73.1, 73.0, 67.7, 67.4, 54.8, 54.7, 54.3, 54.2, 30.6, 30.5, 29.1, 28.8, 16.7, 16.6, 16.56, 16.47, 9.7, 9.6. Anal. Calcd for $C_{44}H_{48}O_9$: C, 73.31; H, 6.71. Found: C, 73.32; H, 6.67.

*3.1.7. (±)-1-p-Toluenesulfonyl-3,4,5,6-tetra-O-benzyl-myo-inositol (**10a**).* In a 100 mL two-neck round bottom flask was added diol D,L-**4** (0.2 g, 0.370 mmol), *p*-toluenesulfonyl chloride (0.14 g, 0.734 mmol), dibutyltin oxide (0.005 g, 0.02 mmol) and Et_3N (0.05 mL, 0.359 mmol), CH_2Cl_2 (4 mL) and the mixture was heated to reflux for 24 h. The reaction mixture was taken up in CH_2Cl_2 (100 mL) and extracted with saturated aq NH_4Cl (50 mL). The organic layer was dried over Na_2SO_4 and the crude product was purified by column chromatography on silica gel using EtOAc/PE (1:2) to give a white solid product (0.219 g, 85%). The solid product was re-crystallized from EtOAc/PE (1:4) to give **10a** as cotton-like crystals; mp 115–116 °C (lit.[18] 115–117 °C); IR (KBr): 3522 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32 (2H, d, J=12.0 Hz), 7.24–7.05 (22H, m), 4.88–4.44 (10H, m), 4.01 (2H, t, J=9.45 Hz), 3.92 (2H, t, J=9.6 Hz), 2.34 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 138.4, 138.1, 138.0, 137.3, 133.6, 129.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 82.6, 81.1, 80.7, 79.2, 78.4, 76.0, 75.9, 75.4, 72.8, 68.6, 21.6. $[M+Na]^+$ calcd for $C_{41}H_{42}O_8S$ 717.2498, found 717.2473.

*3.1.8. (±)-1-tert-Butyldimethylsilanyloxy-3,4,5,6-tetra-O-benzyl-myo-inositol (**11a**).* A mixture of D,L-**4** (0.539 g, 0.997 mmol), imidazole (0.216 g, 3.17 mmol) and TBSCl (0.166 g, 1.1 mmol) was dissolved in DMF (5 mL). The mixture was heated at 60 °C and the progress was monitored by TLC; after 24 h there was still plenty of starting material and the reaction was allowed to continue heating for up to 48 h. Then the reaction was taken up in EtOAc (100 mL) and extracted successively with 2 M HCl (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$; the solvent was removed and the crude product was purified by column chromatography on silica gel using EtOAc/PE (1:4) to give **11a** as an oil (0.204 g, 31%) and recovered D,L-**4** (0.297 g, 55%); IR (neat) 3461 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.22 (20H, m), 4.91–4.63 (8H, m), 4.15 (1H, dd, J=2, 2.4 Hz), 3.93 (1H, t, J=9.6 Hz), 3.72 (1H, dd, J=9.2, 9.6 Hz), 3.47 (1H, t, J=9.2 Hz), 3.35 (1H, dd, J=2.0, 9.6 Hz), 3.30 (1H, dd, J=2.4, 9.6 Hz), 1.98 (1H, br s), 0.86 (9H, s), 0.06 (3H, s), 0 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.5, 138.4, 138.2, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.7, 127.7, 127.5, 83.8, 81.7, 81.4, 80.7, 75.9, 75.7, 75.3, 72.9, 72.2, 71.3, 26.0, 18.5, −4.6, −4.9. $[M+H]^+$ calcd for $C_{40}H_{50}O_6Si$ 655.3455, found: 655.3455.

3.2. General method for DBU induced migration of acyl groups

To a solution of the substrate (**7a**–**9a**) in freshly distilled CH_3CN (0.1 M) was added DBU (2 equiv) and the reaction stirred at room temperature for 4 h. The reaction mixture was quenched with ice-cold saturated aq NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed.

A sample of the crude product (**7a**/**7b** and **8a**/**8b**) was dissolved in CH_3CN and analyzed by RP-HPLC on a Varian Prostar Dynamic Model 210. The volume injected was 25 μL, which was separated by a C-18 reversed phase inertsil ODS-3 column (250 mm, 4.6 mm inner diameter, 5 μm particle size) with an integrated guard column (Variant Walnut Creek, California). The mobile phase was CH_3CN/MeOH (1:4) for **7a**/**7b** and H_2O/MeOH (1:19) for 8a/8b and the flow rate set at 1 mL/min. The detector was a Prostar 335 photodiode array and the results were analyzed by Varian Prostar Software.

The regioisomers in the crude mixtures were separated by column chromatography and the compounds **7b** and **8b** were characterized.

*3.2.1. (±)-2-O-Benzoyl-3,4,5,6-tetra-O-benzyl-myo-inositol (**7b**).* R_f 0.2 in EtOAc/PE (1:4), mp 112–114 °C; IR (Nujol) 3394, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (2H, d, J=7.5 Hz), 7.71–7.02 (23H, m), 5.95 (1H, br s), 5.02–4.46 (9H, m), 3.98 (1H, dd, J=8.7, 9.6 Hz), 3.88 (1H, t, J=8.7 Hz), 3.74–3.54 (2H, m), 2.44 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.08, 138.50, 138.18, 137.56, 133.17, 129.91, 128.62, 128.54, 128.42, 128.34, 128.22, 128.15, 128.01, 127.95, 127.73, 127.61, 83.2, 82.01, 81.36, 78.4, 76.18, 75.96, 75.62, 70.4, 69.81. $[M+H]^+$ calcd for $C_{41}H_{40}O_7$ 645.2852, found 645.2838.

*3.2.2. (±)-2-Pivaloyl-3,4,5,6-tetra-O-benzyl-myo-inositol (**8b**).* R_f 0.3 in EtOAc/PE (1:4); mp 103–105 °C; IR (Nujol) 3423, 1722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.63–7.31 (20H, m), 5.88 (1H, br s), 5.21–4.61 (8H, m), 4.45 (1H, d, J=9.3 Hz), 3.80 (1H, t, J=9.3 Hz), 3.68 (1H, t, J=9.3 Hz), 3.58–3.48 (2H, m), 2.40 (1H, br s), 1.40 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 138.4, 138.2, 138.1, 137.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5, 83.0, 81.8, 80.8, 78.5, 76.0, 75.8, 74.8, 71.7, 70.1, 65.5, 39.0, 27.2. $[M+H]^+$ calcd for $C_{39}H_{44}O_7$ 625.3165, found 625.3171.

The crude mixture of **9a**/**9b** was purified by column chromatography using EtOAc/PE and the mixture of the diastereomers of **9b** was separated by column chromatography using Et_2O/CH_2Cl_2 (1:13).

*3.2.3. 2-(S)-Camphanoyl-3,4,5,6-tetra-O-benzyl-D-myo-inositol (D-**9b**).* R_f 0.31 in EtOAc/PE (1:4); $[\alpha]_D^{24}$ −3.62 (*c* 1.25, $CHCl_3$); IR (neat) 3317, 1787, 1753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.24 (20H, m), 5.84 (1H, t, J=2.8 Hz), 5.01–4.51 (8H, m), 3.78 (1H, t, J=9.6 Hz), 3.76 (1H, t, J=9.6 Hz), 3.63 (1H, dd, J=2.2, 10.2 Hz), 3.57 (1H, dd, J=2.6, 9.8 Hz), 3.52 (1H, t, J=9.4 Hz), 2.46–2.36 (1H, m), 2.05–1.97 (1H, m), 1.94–1.84 (1H, m), 1.72–1.63 (1H, m), 1.59

(1H, br s), 1.11 (3H, s), 0.94 (3H, s), 0.94 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.2, 166.7, 138.2, 137.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 127.3, 91.2, 82.9, 81.4, 80.9, 78.1, 75.7, 75.66, 75.3, 72.2, 70.5, 69.0, 54.8, 54.2, 30.6, 28.8, 16.40, 16.36, 9.6. Anal. Calcd for $C_{44}H_{48}O_9$: C, 73.31; H, 6.71. Found: C, 73.37; H, 6.70.

*3.2.4. 2-(S)-Camphanoyl-3,4,5,6-tetra-O-benzyl-L-myo-inositol (L-**9b**).* R_f 0.22 in EtOAc/PE (1:4), $[\alpha]_D^{24}$ −12.8 (*c* 1.25, $CHCl_3$); IR (neat) 3316, 1787, 1755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.24 (20H, m) 5.82 (1H, t, *J*=2.8 Hz), 5.01–4.51 (8H, m), 3.83 (1H, t, *J*=9.4 Hz), 3.72–3.48 (4H, m), 2.36–2.26 (1H, m), 2.06–1.95 (1H, m), 1.94–1.84 (1H, m), 1.74–1.62 (1H, m), 1.57 (1H, br s), 1.11 (3H, s), 1.04 (3H, s), 0.84 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.1, 166.6, 138.3, 138.2, 138.1, 137.3, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 91.2, 82.9, 81.7, 80.3, 77.9, 75.8, 75.7, 72.2, 70.4, 69.5, 54.7, 54.1, 30.5, 28.8, 16.6, 16.3, 9.6. Anal. Calcd for $C_{44}H_{48}O_9$: C, 73.31; H, 6.71. Found: C, 73.19; H, 6.74.

3.3. General method for NaH induced migration of tosyl and *tert*-butyldimethylsilyl groups

To a cooled solution (0 °C) of compound **10a** or **11a** in DMF (0.2 M) was added NaH (1 equiv 60% dispersion in mineral oil). TLC analysis showed no starting material remained after 30 min and the reaction was quenched first with MeOH followed by H_2O. The mixture was taken up in EtOAc and washed successively with 2 M HCl, then brine, and the organic layer was dried over $MgSO_4$. The crude mixtures were analyzed by HPLC before the pure isomers **10b** and **11b** were isolated by column chromatography purification.

*3.3.1. (±)-2-p-Toluenesulfonyl-3,4,5,6-tetra-O-benzyl-myo-inositol (**10b**).* R_f 0.3 in EtOAc/PE (1:1); mp 106–109 °C; IR (CH_2Cl_2) 3523 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98–7.95 (2H, d, *J*=9 Hz), 7.61–7.45 (22H, m), 5.62 (1H, s), 5.27–4.69 (9H, m), 4.28–4.14 (2H, m), 3.72–3.64 (2H, m), 2.96 (1H, s), 2.57 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.78, 138.39, 139.12, 137.99, 137.35, 129.70, 128.67, 128.52, 128.49, 128.34, 128.30, 128.07, 127.99, 127.87, 127.81, 127.79, 127.67, 127.62, 127.56, 127.53, 127.38, 127.34, 126.93, 82.62, 81.23, 80.65, 79.21, 78.42, 76.01, 75.93, 75.39, 72.76, 68.59, 65.24, 21.62. $[M+Na]^+$ calcd for $C_{41}H_{42}O_8S$ 717.2498, found 717.2471.

*3.3.2. (±)-2-tert-Butyldimethylsilyloxy-3,4,5,6-tetra-O-benzyl-myo-inositol (**11b**).* R_f 0.56 in EtOAc/PE (1:2); IR (neat) 3449 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$): δ 7.39–7.19 (20H, m), 4.95–4.69 (8H, m), 4.02 (1H, t, *J*=9.6 Hz), 3.93 (1H, dd, *J*=2.4, 2.8 Hz), 3.79 (1H, dd, *J*=9.2, 9.6 Hz), 3.52 (1H, dd, *J*=2.4, 9.2 Hz), 3.42 (1H, dd, *J*=9.2, 9.6 Hz), 3.39 (1H, dd, *J*=2.8, 9.6 Hz), 2.5 (1H, br s), 0.9 (9H, s), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.5, 138, 128.4, 128.3, 128.2, 128.1, 127.93, 127.8, 127.7, 127.5, 127.4, 127.3, 127.2, 83.1, 81.6, 81.1, 79.3, 75.8, 75.8, 75.6, 73.4, 72.8, 70.9, 29.6, 25.8, −4.6, −4.9. $[M+H]^+$ calcd for $C_{40}H_{50}O_6Si$ 655.3455, found: 655.3455.

*3.3.3. 2-O-Acetyl-3,4,5,6-tetra-O-benzyl-D-myo-inositol (**13**).* To a solution of 3,4,5,6-tetra-*O*-benzyl-D-*myo*-inositol (0.90 g, 1.66 mmol) in acetonitrile (50 mL) were added *p*-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol) and trimethyl orthoacetate (0.90 mL, 0.85 g, 7.07 mmol). After stirring for 2 h at room temperature the starting material had been converted to the cyclic orthoester **12** (TLC, toluene/EtOAc 2:1). The reaction mixture was then cooled to −40 °C and water (0.90 mL, 49.7 mmol) was added. After stirring for 4 h at −40 °C the reaction mixture was neutralized with pyridine and concentrated. The residue was dissolved in EtOAc (20 mL), washed with water (2×20 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (toluene/EtOAc 10:1 to 5:1) gave **13** (0.91 g, 94%); IR ($CDCl_3$) 3463, 1745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.45 (20H, m), 5.74 (1H, t, *J*=2.7 Hz), 4.7–5.1 (7H, m, CH_2Ph), 4.54 (1H, d, *J*=11.3 Hz, CH_2Ph), 3.93 (1H, t, *J*=9.5 Hz), 3.82 (1H, t, *J*=9.6 Hz), 3.62 (1H, dd, *J*=2.7, 9.6 Hz), 3.57 (1H, t, *J*=9.6 Hz), 3.56 (1H, dd, *J*=2.7, 9.5 Hz), 2.20 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7 (C=O), 138.8, 138.5, 138.5, 137.8, 127.8–128.8 (Ph), 83.4, 82.1, 81.6, 78.6, 76.1, 76.1, 75.8, 72.3, 70.3, 69.6 (CH_2Ph, inositol), 21.2 (CH_3–COO–). $[M+Na]^+$ calcd for $C_{36}H_{38}O_7Na$ 602.2515, found 605.2501.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.063.

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