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Dispiroketals in Synthesis (Part 11)[1]: Concomitant Enantioselective and Regioselective Protection of 2,5-Dibenzoyl-*myo*-inositol.

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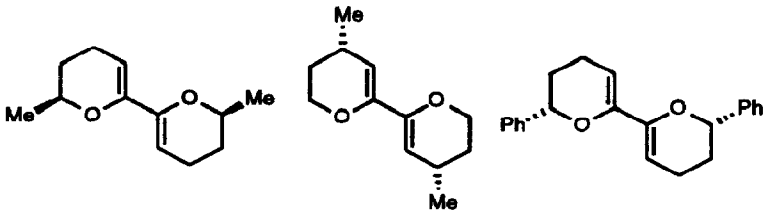
Abstract: 2,5-Dibenzoyl-*myo*-inositol, a symmetrical polyol, may be simultaneously enantioselectively and regioselectively protected using the chiral dienes (**1**), (**2**) and (**3**). Deprotection, to afford D or L-1,6-tetra-*O*-benzyl-*myo*-inositol (**8**) and (**12**) respectively, was achieved using trifluoroacetic acid.

There is a need for enantiomerically pure inositol derivatives which are important intermediates in the preparation of phosphoinositides and inositol phosphates. The latter are implicated as secondary messengers in intracellular signalling and as membrane protein anchors.[2] The preparation of enantiomerically pure materials usually involves the optical resolution of *myo*-inositol derivatives which requires tedious chromatographic separation or recrystallation procedures (for example via camphanic acid ester diastereoisomers)[3] generally with rather low overall efficiency.

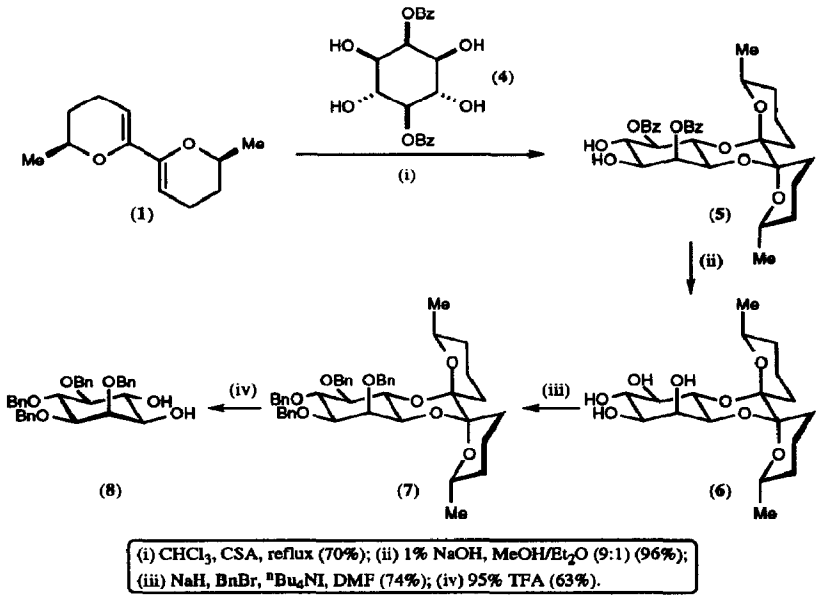
The utility of dispiroketal (Dispoke)[4] protection of carbohydrates,[5] in the synthesis of a stable glyceraldehyde equivalent,[4] as a rigid lactate protecting group,[6] and in the thermodynamic resolution of 1,2-diols[7] has been demonstrated previously. We have also recently shown that chiral recognition of *trans* 1,2-diols is possible in carbohydrates.[8]

Here we wish to report the enantioselective differentiation and regioselective protection of symmetrical 2,5-dibenzoyl-*myo*-inositol using (2*S*,2'*S*) 2,2'-dimethyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran (**1**) ((2*S*,2'*S*) MDHP), (4*S*,4'*S*) 2,2'-dimethyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran[9] (**2**) ((4*S*,4'*S*) MDHP) and (2*S*,2'*S*) 2,2'-diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran (**3**) ((2*S*,2'*S*) PDHP). This protocol should allow access, upon deprotection of the spiroketal moiety, to the D enantiomer of the inositol diol (**8**) with ((2*S*,2'*S*) MDHP) (**1**), and the L enantiomer (**12**) with either ((4*S*,4'*S*) MDHP) (**2**) or ((2*S*,2'*S*) PDHP) (**3**).



((2*S*,2'*S*) MDHP) (**1**) ((4*S*,4'*S*) MDHP) (**2**) ((2*S*,2'*S*) PDHP) (**3**)

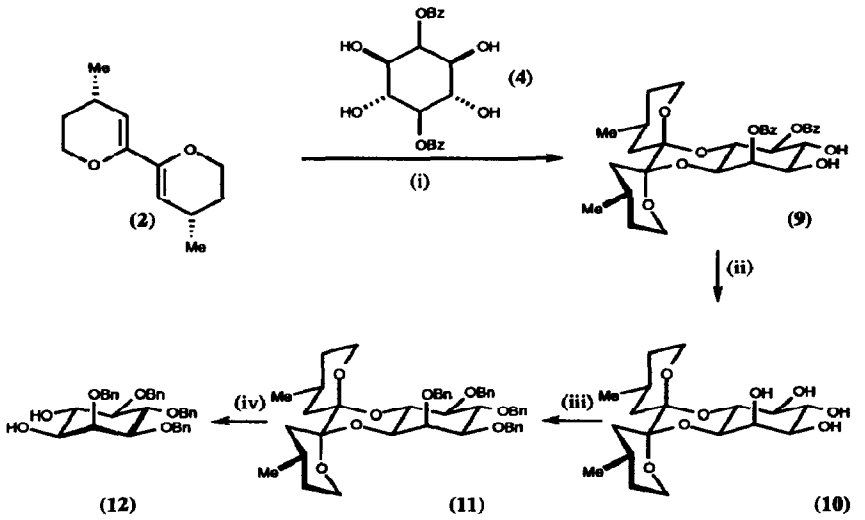
The symmetrical 2,5-dibenzoyl-*myo*-inositol (**4**) was prepared according to known procedures.[10] This was reacted firstly with ((2*S*,2'*S*) MDHP) (**1**) under standard conditions to give the 3,4-protected dispoke adduct, (**5**)[11] in 70% yield (Scheme 1). This dispoke adduct is fully anomerically stabilised due to the oxygen substituents at the spiro centres adopting axial orientations. Regioselectivity is achieved *via* the use of enantiomerically pure diene (**1**) which has the ability to selectively protect one pair of enantiomeric vicinal diols in the substrate (**4**), to give a "matched" dispoke adduct, with the side chain methyl substituents equatorial. Protection of the antipodial vicinal diol pair would lead to a "mismatched" dispoke adduct with axial side chain substituents, and therefore is disfavoured. It is important to note that the dibenzoyl inositol derivative (**4**) is a *meso* compound and therefore all the starting material is utilised in the step leading to the dissymmetric dispoke adduct (**5**). Debenzoylation was achieved using 1% sodium hydroxide in methanol/diethyl ether to give the tetrol (**6**) in 96% yield. This compound was then benzylated using sodium hydride/benzyl bromide in DMF with catalytic tetra-*n*-butyl ammonium iodide to give the fully protected dispoke adduct (**7**) in 74% yield. The diol was subsequently unmasked by treatment of (**7**) with 95% trifluoroacetic acid (TFA) to give the diol (**8**)[12] in 63% yield, $[\alpha]_D^{30}$=-15.8. [Literature values[3] $[\alpha]_D^{25}$=-13.2 and -15.5]



Scheme 1

The enantiomer of diol (**8**), namely (**12**), can been prepared from both ((4*S*,4'*S*) MDHP) (**2**), (Scheme 2) and ((2*S*,2'*S*) PDHP) (**3**) (Scheme 3). Enantioselective reaction of symmetrical 2,5-dibenzoyl-*myo*-inositol (**4**) using ((4*S*,4'*S*) MDHP) (**2**), under standard conditions, gave the dispoke adduct (**9**) in 63% yield where the 1,6-enantiomeric vicinal diol moiety has been regioselectively protected. Dispoke adduct (**9**) was isolated as a single isomer, with the two methyl side chain substituents in the stable equatorial positions. The stereochemical outcome can be rationalised again in terms of "matched"/"mismatched" chiral recognition process occuring during

spiroketalisation. The dispoke adduct (**9**) was then subjected to debenzoylation conditions to give the tetrol (**10**) in 91% yield. The tetrabenzyl derivative (**11**) being produced in 87% yield from the tetrol using sodium hydride/benzyl bromide and catalytic tetra-*n*-butyl ammonium iodide. The diol (**12**), $[\alpha]_D^{29}$=+14.3, was deprotected using 95% TFA in an unoptimised 18% yield. Diol (**12**) is a suitable intermediate in the synthesis of the glycosylphosphatidylinositol anchor of *Trypanosoma brucei* Varient Surface Glycoprotein.[13]

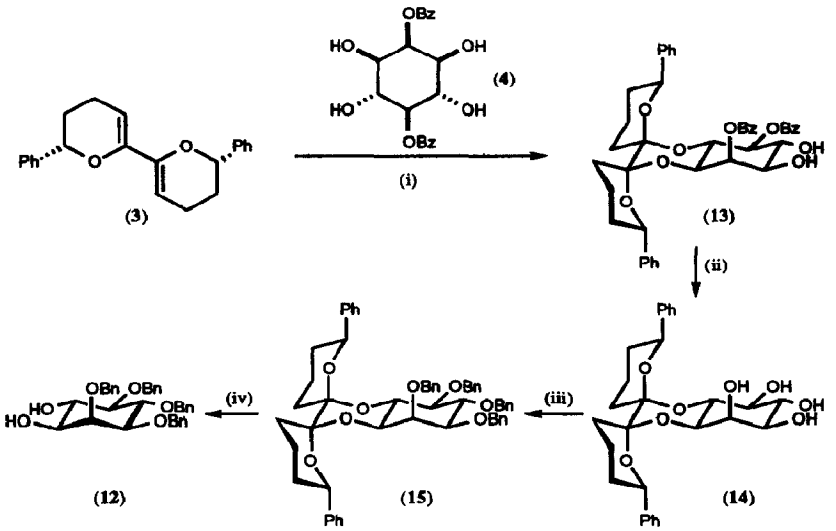


(i) $CHCl_3$, CSA, reflux (63%); (ii) 1% NaOH, MeOH/Et_2O (9:1) (91%); (iii) NaH, BnBr, $^nBu_4NI$, DMF (87%); (iv) 95% TFA (18%).

Scheme 2

The same diol (**12**) can also be formed from enantioselective reaction of the *myo*-inositol derivative (**4**) with ((2*S*,2'*S*) PDHP) (**3**). Reaction under standard conditions gave the dispoke adduct (**13**) in 52% yield, isolated as a single isomer (Scheme 3) (over page). Here, regioselective 1,6-diol protection has been achieved with the optically pure diene (**3**). Dispoke adduct (**13**) was converted into the tetrabenzyl intermediate (**15**) under similar conditions to those stated above. Deprotection of the dispiroketal moiety was achieved using 95% TFA to give the enantiopure diol (**12**) which was identical to that obtained previously from (**2**).

In conclusion we have demonstrated the ability of enantiomerically pure chiral dienes ((2*S*,2'*S*) MDHP) (**1**), ((4*S*,4'*S*) MDHP) (**2**) and ((2*S*,2'*S*) PDHP) (**3**) to selectively protect one pair of enantiomeric 1,2-diols in a *meso* polyol, leading to a dissymmetric product. The use of these protected chiral inositols is presently being studied towards the synthesis of a GPI anchor.



Scheme 3

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11. All new compounds gave satisfactory analytical and/or accurate mass spectral data.
12. (**8**): $[\alpha]_D^{30}$=-15.8 (c=0.13, $CHCl_3$); ^1H NMR (400MHz, $CDCl_3$): δ 2.50 (2H, brS, 2xO*H*), 3.32 (1H, apparent triplet, *J*9.2Hz, H_5), 3.38 (1H,dd, *J*9.6,2.0Hz, H_2), 3.48 (1H, dd, H_1, *J*9.8,2.0Hz), 3.83 (1H, apparent triplet, *J*9.4Hz, H_6), 4.02 (2H, apparent triplet, *J*9.2Hz, H_3 and H_4), 4.69, 4.76, 4.83, 4.94, 5.04 (8H, m, 4xCH_2Ph), 7.25-7.34 (20H, m, 4x*Ph*).
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