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Dispiroketals in Synthesis (Part 4):[1] Enantioselective Desymmetrization of Glycerol Using a C_2-Symmetric Disubstituted *bis*-Dihydropyran.

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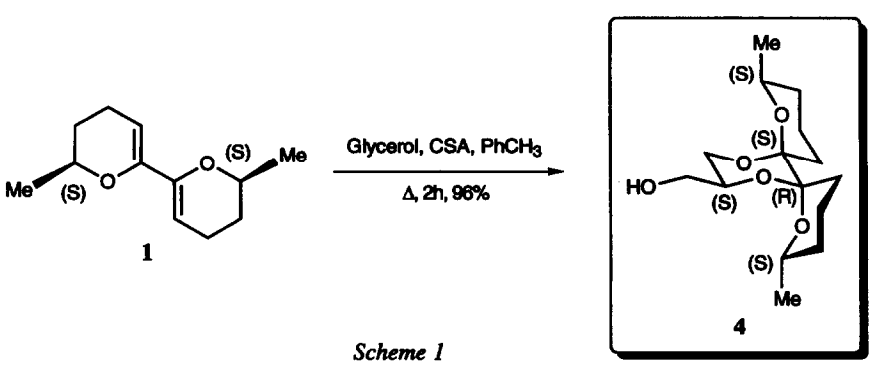
Abstract: Glycerol may be simultaneously protected and enantioselectively desymmetrised by dispiroketal formation with (*S,S*)-2,2'-dimethyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran **1**.

We wish to describe a new concept which accomplishes the simultaneous protection and enantioselective desymmetrization of *meso*-polyols. This process is illustrated here by the reaction of glycerol with the chiral C_2-symmetric dimethyl *bis*-dihydropyran derivative **1**.

Previously, we have demonstrated the power of multiple anomeric effects in the controlled formation of dispiroketals from vicinal diols and *bis*-dihydropyran. This work has led to new selective diol protection methods (Dispoke protection[2]), especially for carbohydrates and in the preparation of a new glyceraldehyde acetonide synthetic equivalent.[3] Glyceraldehyde acetonide and the related solketal (glycerol acetonide) are recognised as important three carbon synthons in organic synthesis.[4] Moreover, the new dispoke glyceraldehyde equivalent has improved configurational stability and has improved *anti* selectivity in addition reactions.

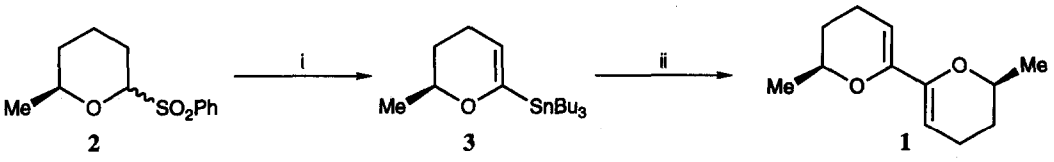
The incorporation of chirality in the *bis*-dihydropyran reagent will provide an additional control element for dispiroketal formation thereby extending the scope of this methodology. This is illustrated by the enantioselective desymmetrization and protection of glycerol in a single operation (*Scheme 1*). To accomplish this we have used the C_2-symmetric disubstituted dimethyl-*bis*-dihydropyran derivative, **1**, in enantiomerically pure form. The reaction of **1** with glycerol, in the presence of catalytic camphorsulphonic acid in boiling toluene, proceeded with complete diastereoselectivity, to give the dispiroketal **4**[7], which was confirmed by preparation of the corresponding Mosher's ester.[8]



Scheme 1

The enantioselective desymmetrisation of glycerol is explained as follows. The absolute stereochemistry of the spiro centres (*S,R*) is controlled by a combination of multiple anomeric effects and the absolute configuration at the site of substitution of the methyl groups, which adopt an equatorial orientation. Due to steric effects, the hydroxymethylene substituent on the dioxane ring adopts an equatorial orientation. These factors result in the exclusive formation of the glycerol derivative **4** with (*S*) stereochemistry at C-2 of the glycerol unit.

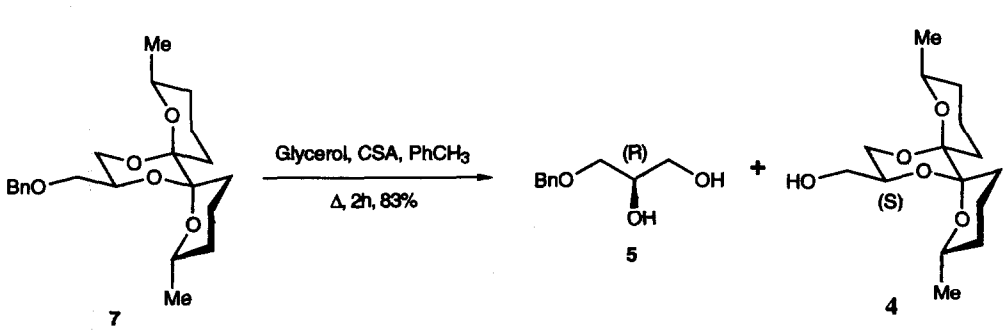
The (*S,S*)-dimethyl *bis*-dihydropyran derivative **1** was prepared[5] from the readily available sulphone **2** (*Scheme 2*). Thus, treatment of the sulphone **2** with butyl lithium followed by quench of the corresponding anion with tributyltin chloride and elimination of phenylsulphinic acid, with Hünig's base, afforded the stannane **3** in good yield. Transmetallation[6] of **3** with butyl lithium followed by palladium catalysed homo-coupling gave the required *bis*-dihydropyran **1**.[7] Direct coupling of the stannane **3** with catalytic palladium (II) chloride bis-acetonitrile complex in *N,N*-dimethylformamide also gave **1**, however, this process was lower yielding.



i. BuLi, THF, -78° C followed by Bu_3SnCl, -20° C, aqueous work-up then Hunig's base, $CHCl_3$, Δ, 2h, 75%.
ii. BuLi, THF, -78° C then addition of 2% $PdCl_2(MeCN)_2$, $CuCl_2$, -78 to 0° C, 2h, then NH_4Cl/NH_3 (aq), 60%.

Scheme 2

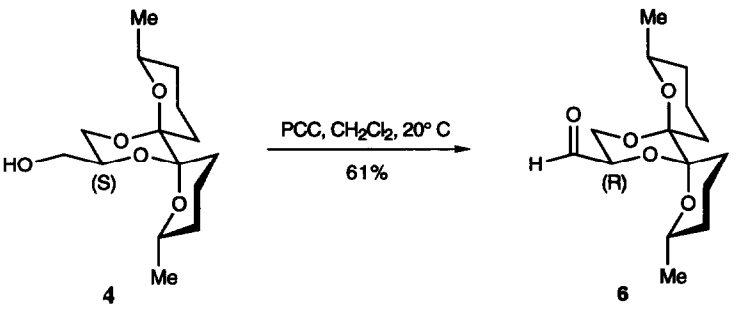
Next, we focused our attention on converting **4** into the useful building blocks **5** and **6**. Thus, treatment of **4** with sodium hydride and benzyl bromide afforded benzyl ether **7**. Treatment of **7** with neat glycerol and catalytic camphorsulphonic acid gave (*R*)-1-*O*-benzyl glycerol **5** together with the returned dispiroketal protected glycerol derivative **4** (*Scheme 3*). As expected compound **4** was again obtained as a single diastereoisomer thereby providing an extremely efficient recycling process. Thus, during the deprotection step the chiral protecting group is preserved. Compound **5** was converted into the analogous isopropylidene derivative, the optical rotation and NMR data of which were in full agreement with literature values.[9,10]



Scheme 3

Furthermore, it should be noted that **5** is a key compound in the preparation of glyco-, phospho- and ether lipids, some of which show remarkable biological activities.

Finally, oxidation of **4** with pyridinium chlorochromate in dichloromethane gave, after silica gel column chromatography, the aldehyde **6** together with some of the corresponding hydrate. Stirring the mixture of compounds for 16 hours in chloroform, at room temperature, gave a clean sample of the aldehyde **6**[7] upon evaporation of the solvent (*Scheme 4*).



Scheme 4

In conclusion, this work presents a potentially powerful new method and concept for the desymmetrization of *meso*-polyols using asymmetric dispoke protection methods. This process could have considerable synthetic application and further examples are under investigation. Furthermore, the use of various C_2-substituted *bis*-dihydropyran derivatives with different reactivities; especially towards deprotection, will be reported in due course.

Acknowledgements

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References and notes

1. For part 3 see S. V. Ley, G.-J. P. H. Boons, R. A. Leslie, and M. Woods, D. M. Hollinshead *Synthesis* 1993, *in press.*
2. As this process of dispiroketal formation for the protection of unusual diols is becoming a general concept we propose to use the name Dispoke for this type of diol protection.
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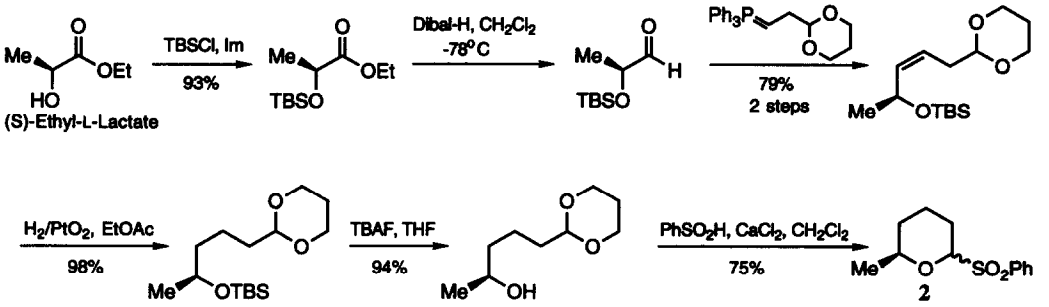
5. Preparation of sulphone 2:- Ethyl-L-lactate was protected as its TBS ether which was reduced with Dibal-H in dichloromethane to give the lactaldehyde derivative. Wittig reaction of the aldehyde with the dioxanylethyl phosphorane afforded the chain extended alkene which was hydrogenated over platinum oxide to give the saturated material. Desilylation and reaction with phenylsulphinic acid gave the sulphone 2, as a separable mixture of anomers, in good overall yield.



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7. **[2S,2'S]-2,2'-dimethyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran (1)** $[\alpha]_D^{28}$ -94.9 (c = 1, $CHCl_3$); δ_H(270MHz, $CDCl_3$) 5.22 (2H, t, *J* 3.8, 5-H and 5'-H), 4.0-3.87 (2H, m, 2-H and 2'-H), 2.22-2.04 (4H, m, 3-CH_2 and 3'-CH_2), 1.88-1.77 (2H, m, 4-H and 4'-H), 1.61-1.45 (2H, m, 4-H and 4'-H), 1.32 (6H, d, *J* 6.4, 6-Me and 6'-Me); *m/z* 194 (M^+), 125, 97 ($C_6H_9O^+$), 91, 69, 57, 55; HRMS: Found (M^+, 194.1307), $C_{12}H_{18}O_2$ requires (M^+, 194.1307).
[2S, 6S, 7R, 9S, 14S]-2,9-dimethyl-14-hydroxymethyl-1,8,13,16-tetraoxadispiro-[5.0.5.4]hexadecane (4) $[\alpha]_D^{22}$ - 48.7 (c = 1, $CHCl_3$); δ_H(400MHz, $CDCl_3$), 4.06-4.00 (1H, m, 14-H), 3.80-3.71 (2H, m, 2-H and 9-H), 3.75 (1H, t, *J* 11.1, 15-H_{ax}), 3.65-3.54 (2H, m, 17-CH_2), 3.47 (1H, dd, *J* 11.2 and 2.95, 15-H_{eq}), 1.85 (1H, br, OH), 1.83-1.68 (4H, m, 5-CH_2 and 12-CH_2), 1.59-1.50 and 1.49-1.38 (8H, 2 x m, 3-CH_2, 4-CH_2, 10-CH_2 and 11-CH_2), 1.14 and 1.12 (6H, 2 x d, *J* 6.2, 2-Me and 9-Me); HRMS: Found (MH^+, 287.1858), $C_{15}H_{26}O_5$ requires (MH^+, 287.1858).
[2S, 6S, 7R, 9S, 14R]-2,9-dimethyl-14-formyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecane (6) $[\alpha]_D^{28}$ - 57.5 (c = 1, $CHCl_3$); δ_H(400MHz, $CDCl_3$) 9.67 (1H, s, CHO), 4.35 (1H, dd, *J* 10.6 and 4, 14H), 3.80-3.70 (2H, m, 2-H and 9-H), 3.73 (1H, t, *J* 11.2, 15-H_{ax}), 3.67 (1H, dd, *J* 11.2 and 4.0, 15-H_{eq}), 1.93-1.36 (12H, m, 3-CH_2, 4-CH_2, 5-CH_2, 10-CH_2, 11-CH_2 and 12-CH_2), 1.14 and 1.12 (6H, 2 x d, *J* 6.3, 2-Me and 9-Me).

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