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Dispiroketals in Synthesis (Part 2)[1]: A New Group for the Selective Protection of Diequatorial Vicinal Diols in Carbohydrates.

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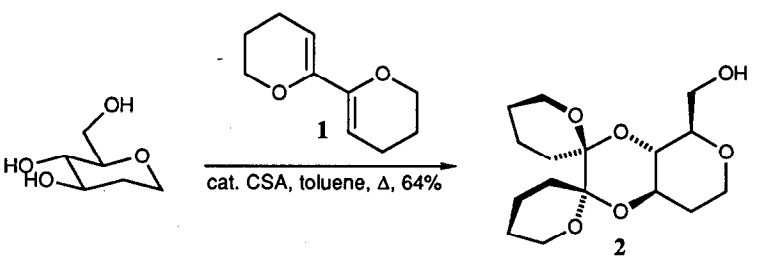
Abstract: Dispiroketal formation as a new method for the selective protection of *trans* diequatorial vicinal diols in carbohydrate systems is reported.

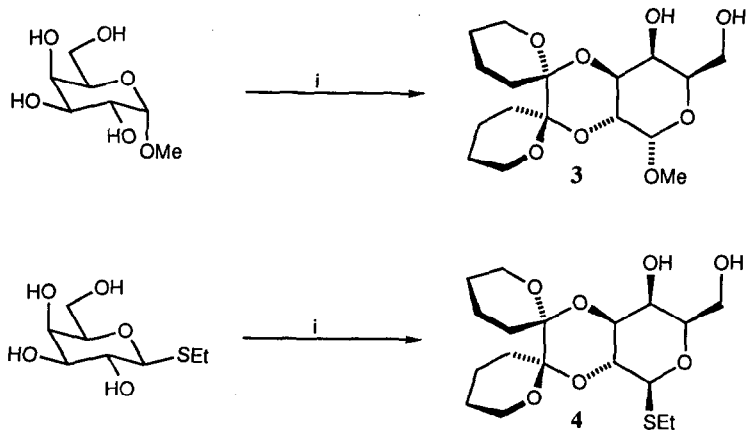
Keywords: Dispiroketal, carbohydrate, protection, glycoside.

We reported previously[1] on the protection of *(S)*-1,2,4-butanetriol with 3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran (bis-DHP) **1**[2] which demonstrates its inherent selectivity for vicinal diol protection over 1,3-diol protection. The formation of the 1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane (dispiroketal) unit is governed by the predictable stabilising influence of multiple anomeric effects, leading to a single diastereomeric derivative. The successful extension of this methodology to the preparation of the 1,2-dideoxy-D-glucose derivative **2**[3] indicates that vicinal diols in cyclic substrates are candidates for dispiroketal formation in the presence of other hydroxyl groups. *(Scheme 1)*



Scheme 1

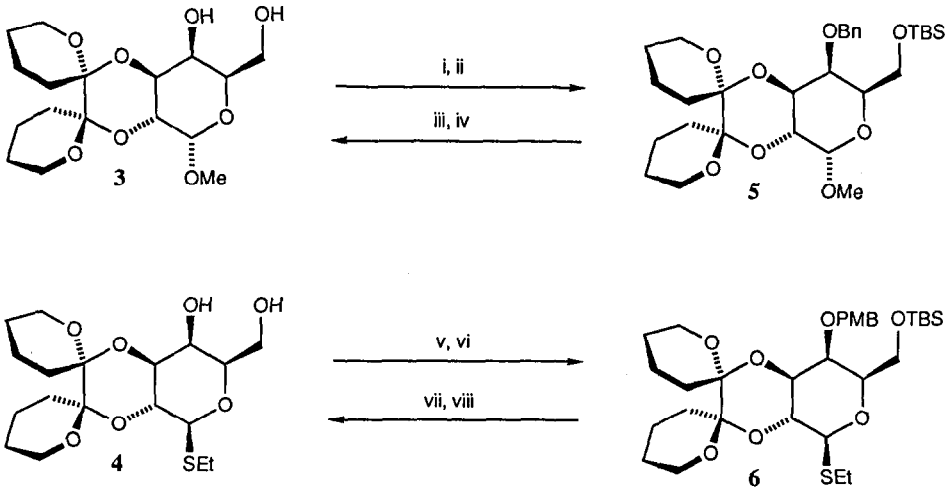
This observation led naturally to an investigation of simple carbohydrates in which the selective protection of *trans* diequatorial vicinal diols may be an attractive alternative to the existing range of ketal based methods which display *cis* selectivity. In this case the *cis* dispiroketal protected derivatives would suffer steric hinderance and a flattening of the central dioxane ring, reducing the magnitude of anomeric stabilisation at both spirocentres and thereby augmenting the unfavourable steric effects. Hence we expect to observe selectivity for the *trans* diequatorial diol under the thermodynamic conditions of the reaction. Indeed treatment of 1-*O*-methyl-α-D-galactopyranoside monohydrate with **1** in chloroform at reflux with catalytic camphorsulphonic acid[4] followed by treatment with ethylene glycol gave the 2,3-dispiroketal protected derivative **3** in 76% yield[5]. Similarly, 1-*S*-ethyl-β-D-thiogalactopyranoside[6] gave the corresponding 2,3-dispiroketal derivative **4** in 59% yield.



Scheme 2

i. bis-DHP, CSA, $CHCl_3$, Δ, 1.5h, then ethylene glycol, Δ, 0.5h.

For these systems to be useful to oligosaccharide synthesis we need to demonstrate that they are stable to functional group manipulation, glycosidation and are easily removed at the end of a synthetic sequence. The compatibility of the dispiroketal unit with some protection/deprotection conditions has been investigated. Silylation of **3** followed by benzylation gave the fully protected derivative **5** which was sequentially deprotected to **3** in good yield. Similarly, **4** was silylated and *p*-methoxybenzylated to give **6** which was then sequentially deprotected to give **4** in good yield. These reactions demonstrate the stability of the dispiroketal group towards a variety of reaction conditions. Of particular note is its stability towards mild acidic conditions employed in the removal of the *p*-methoxybenzylidene formed by the DDQ oxidation of the corresponding *p*-methoxybenzyl group[7].*(Scheme 3).*

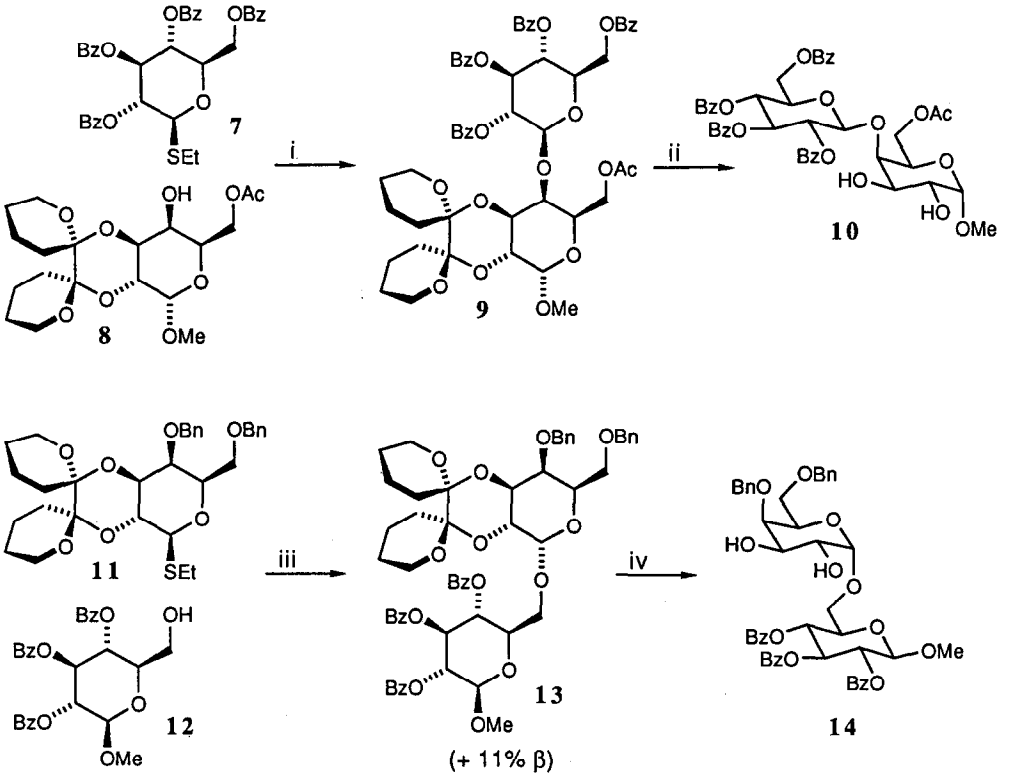


Scheme 3

i. TBSCl, Py, 86%; ii. NaH, BnBr, 83%; iii. TBAF, THF, 100%; iv. H_2, Pd/C, 91%; v. TBSCl, TEA, DMAP, 56%; vi. NaH, pMeOBnCl, 84%; vii. TBAF, THF, 100%; viii. DDQ then AcOH/H2O, 100%

We then turned our attention to glycosidation, initially using the versatile thioglycoside methodology.[8] Thus, reaction of the dispiroketal protected acceptor **8** with glycosyl donor **7** in the presence of *N*-iodosuccinimide and triflic[9] acid gave the disaccharide **9**. Moreover, reaction of dispiroketal protected glycosyl donor **11** with the benzoylated derivative **12** gave a respectable yield of the disaccharide **13** as a α:β (4:1) mixture. *(Scheme 4)*

These results demonstrate clearly that the dispiroketal protecting group is compatible with glycosidic coupling whether present on the donor or acceptor moiety. Finally, the facile cleavage of the dispiroketal unit was accomplished with 95% trifluoroacetic acid at room temperature.[10] Thus, compounds **9** and **13** afforded the diols **10** and **14** respectively. *(Scheme 4)* It is notable that there does not appear to be any migration of secondary protecting groups such as benzoate and acetate.



Scheme 4

i. NIS, triflic acid, $ClCH_2CH_2Cl/Et_2O$, 53%; ii. TFA/H_2O (19:1), 58%;
iii. NIS, triflic acid, $ClCH_2CH_2C/Et_2O$, 42%; iv. TFA/H_2O (19:1), 59%.

In conclusion we have shown that dispiroketal formation is a selective method for the protection of *trans* diequatorial vicinal diols in carbohydrate systems and we hope that this new methodology may give important strategic advantages in the rapid and concise preparation of oligosaccharides. Applications to other carbohydrates will be reported in due course.

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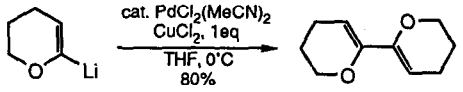
References and footnotes:

1. Ley, S.V., Woods, M., and Zanotti-Gerosa, A., *Synthesis*, 1992, 52.
2. The previously reported synthesis of bis-DHP proved to be unsuitable on a large scale, we have developed an efficient and direct synthesis using a palladium catalysed oxidative dimerisation reaction. This has proven reliable and simple to perform on a 30g scale.



Preparation of 3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran (bis-DHP) **1**. *tert*-Butyllithium (1.7M solution in pentanes, 200ml, 340mmol) was added dropwise to a stirred solution of dry distilled 3,4-dihydro-2*H*-pyran (30ml, 330mmol) in THF (60ml) at -78°C under argon. The cloudy mixture was then stirred at 0°C (ice/water bath) for 1h, giving a clear pale yellow solution. This was added (at 0°C), *via* cannula, to a cooled (0°C), rapidly stirred, slurry of palladium(II)chloride bis-acetonitrile complex (2g, 7,7mmol, 2.2%) and anhydrous copper(II)chloride (46.3g, 343mmol) in THF (300ml). The orange brown slurry became black and the resultant mixture was stirred at 0°C for 1h. The reaction was quenched by addition of saturated ammonium chloride/0.880 ammonia solution (4:1, pH 10) and extracted into ether (3x), with vigorous stirring. The combined ether extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow solid. Purification by column chromatography on silica gel (Merck 9385, 6cm x 20cm) eluting with 5% ether/petroleum ether gave 3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran (bis-DHP) **1** as a white crystalline solid (22.1g, 80%). m.p. 49-50°C (petroleum ether); ν_{max}(film)/cm^{-1} δ_H(270MHz, $CDCl_3$), 5.16 (2H, t, *J* 3.8, 5-H and 5'-H), 4.05-4.01 (4H, m, 2-CH_2 and 2'-CH_2), 2.14-2.08 (4H, m, 4-CH_2 and 4'-CH_2), 1.87-1.78 (4H, m, 3-CH_2 and 3'-CH_2); δ_C(68MHz, $CDCl_3$) 147.58, 96.79, 66.22, 22.42, 20.17; *m/z* 166 (M^+), 138, 111, 83, 55; Found: C, 72.24; H, 8.56. $C_{10}H_{14}O_2$ requires C, 72.26; H ,8.49.

3. All new compounds display satisfactory spectroscopic and analytical data.
4. Similar conditions were used for the benzylidination of methyl galactosides: Ferro, V., Mocerino, M., Stick, R.V., and Tilbrook, D.M.G., *Aust. J. Chem.* **1988**, *41*, 813.
5. Preparation of **3**. *dl*-Camphorsulphonic acid (15mg, $6x10^{-5}$mol) was added to a stirred solution of finely powdered 1-*O*-Me-α-D-galactopyranoside monohydrate (301mg, 1.42mmol) and bis-DHP **1** (540mg, 3.12mmol) in dry chloroform (5ml) and the mixture heated under reflux for 1.5h. Anhydrous ethylene glycol (0.5ml, 9mmol) was added and heating continued for a further 0.5h. The resultant brown solution was diluted with dichloromethane and basified by addition of potassium carbonate (50mg), filtered and concentrated *in vacuo* to give a brown oil. Purification by column chromatography on silica gel (Merck 9385,) eluting with 80-100% ethyl acetate/petroleum ether gave **3** (390mg, 76%) as an off-white foam. $[\alpha]_D$ 8.1 (c = 1.05, $CHCl_3$), ν_{max}(film)/cm^{-1}, 3463 (br OH), 2944, 1440, 1536, 1273, 1195, 1158, 1073, 1046, 991, 939; δ_H(270MHz, $CDCl_3$), 4.85 (1H, d, *J* 3.4, 1-H), 4.23 (1H, dd, *J* 10.3 and 3.4, 2-H), 4.15-4.05 (2H, m, 3-H and 5-H), 4.0-3.8 (3H, m, 4-H and 6-CH_2), 3.75-3.55 (4H, m, 2'-CH_2 and 9'-CH_2), 3.42 (3H, s, OMe), 2.84 (1H, br s, OH), 2.59 (1H, br s, OH), 1.85-1.65 (4H, m, 5'-CH_2 and 12'-CH_2), 1.62-1.42 (8H, m, 3'-CH_2, 4'-CH_2, 10'-CH_2 and 11'-CH_2); *m/z* 360 (M^+), 200, 167 ($C_{10}H_{15}O_2^+$), 149, 111, 100; Found: C, 56.42; H, 8.01. $C_{17}H_{28}O_8$ requires C, 56.65; H, 7.83.
6. Veeneman, G.H., Brugge, H.F., Hoogerhout, P., Van Der Marel, G.A., and van Boom, J.H., *Recl. Trav. Chim. Pays-Bas*, **1988**, *107*, 610.
7. Oikawa, Y., Nishi, T., and Yonemitsu, O., *Tetrahedron Lett* , **1983**, *24*, 4037.
8. For a review on thioglycoside methodology see: Fügedi, P., Garegg, P.J., Lönn, H., and Norberg, T., *Glycoconj. J.*, **1987**, *4*, 97.
9. Veeneman, G.H., and van Boom, J.H., *Tetrahedron Lett* , **1990**, *31*, 275.
10. The dispiroketal moiety can be efficiently removed in other systems, not reported here, by exchange with ethylene glycol at 50°C with catalytic camphorsulphonic acid.

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