Pergamon

*Tetrahedron Letters*, Vol. 35, No. 5, pp. 777-780, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0304-3

# Dispiroketals in Synthesis (Part 8)[1]: Regioselective Protection of D-Glucopyranose Substrates.

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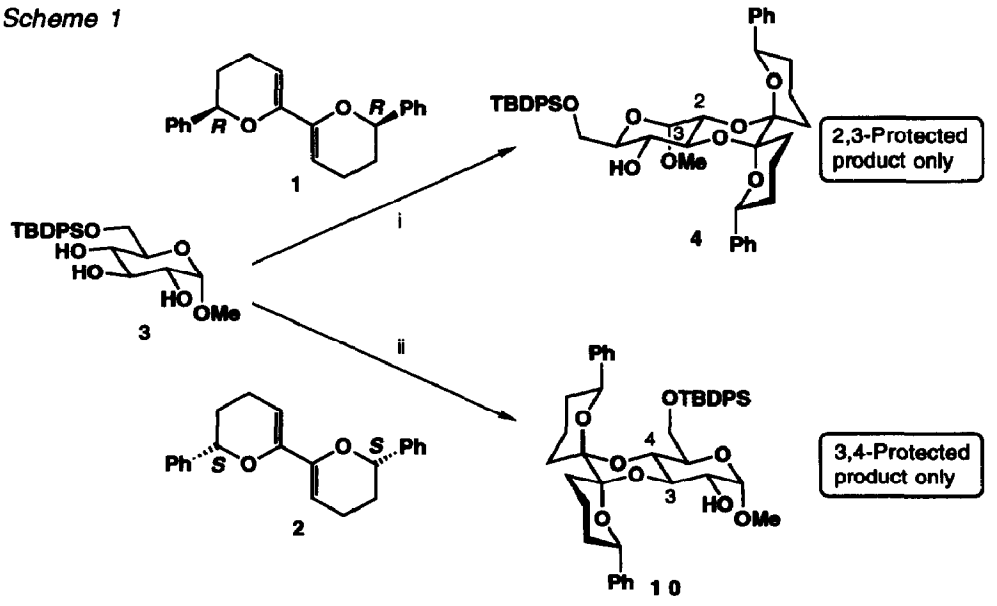
***Abstract:*** A new process for the efficient regioselective formation of 1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecanes (dispiroketals) of various D-glucopyranosyl substrates by the chiral recognition of enantiomeric *trans* 1,2-diol relationships is described. This was achieved using the novel enantiomerically pure 2,2'-disubstituted 3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyrans **1**, **2** and **11**. New conditions for the removal of dispiroketal protecting groups are presented.

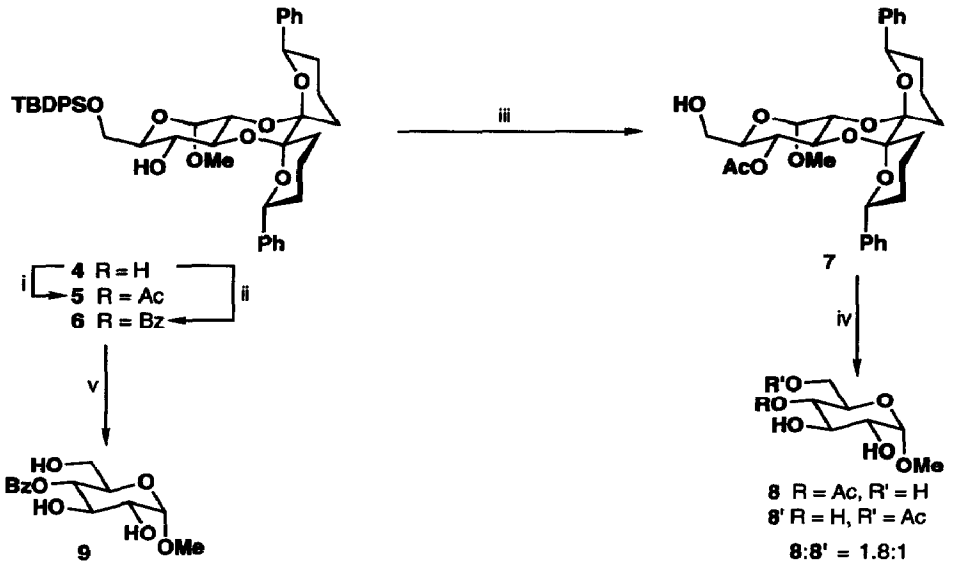
The dispoke protection of monosaccharides is hampered by their low solubility in preferred solvents for reaction.[1] In the previous communication[1] a high yielding method for the dispoke protection of D-glucopyranosyl substrates was developed. The efficiency of the strategy was, however, marred by the lack of regioselection predictably due to the presence of two relatively non-sterically differentiated enantiomeric *trans*-1,2-diol relationships in the gluco substrates.

*Scheme 1*



Here, we wish to introduce a new process for the dispoke protection of saccharides by chiral recognition of enantiomeric pairs of *trans* 1,2-diols. This regioselective protection strategy is achieved *via* the use of the enantiomerically pure dienes **1**, **2** and **11** and exploits the preference for substituents about anomerically stabilised spiroketals to adopt equatorial orientations.[2] Under ketalising reaction conditions this equatorial preference determines which compound is formed. In the case of a substrate having an enantiomeric pair of 1,2-diols, a particular diene will have a 'matching' relationship with only one diol that allows the substituents in the fully anomerically stabilised product to lie equatorially. The other diol will be 'mismatched', forcing substituents in the dispoke product to be axially configured which is obviously disfavoured. Furthermore, the choice of the dienes **1**, **2** and **11** was dictated by the desire to develop new, mild methods for the removal of dispiroketals and to enhance the stability of the dispiroketal precursors.

*Scheme 2*




i. $Ac_2O$, 4-*N,N*-dimethylamino-pyridine (DMAP), pyridine, RT, overnight, 88%; ii. BzCl, DMAP, pyridine, RT, overnight, 96%; iii. $FeCl_3$ (2.5 eq.), $CH_2Cl_2$, RT, overnight, 84%; iv. $FeCl_3$ (3 eq.), $CH_2Cl_2$, RT, overnight; v. $FeCl_3$ (5 eq.), $CH_2Cl_2$, RT, overnight, 50%.

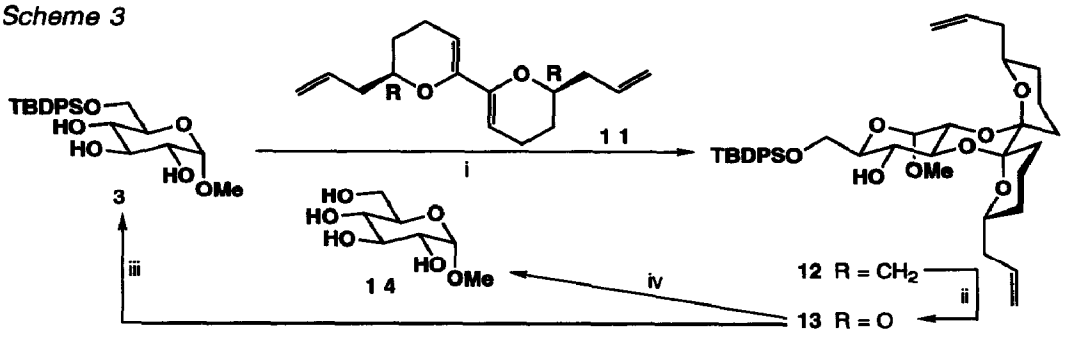
Complete regiocontrol of adduct formation was observed in reactions using the phenyl substituted dienes **1** and **2**. The *R,R*-configured diene **1** matches the enantiotopicity at C-2 and C-3 of D-gluco substrates. Reaction of the diene **1** with the gluco substrate **3** under standard acid catalysed conditions gave the 2,3-adduct **4**[3] in 88% yield (Scheme 1). The adduct was confirmed as the 2,3-regioisomer by formation of its acetate (Ac) **5** and its benzoate (Bz) **6** (Scheme 2) and examination of their respective $^1H$ NMR spectra. It was hoped that the dispiroketals formed from the phenyl substituted dienes could be removed by hydrogenolysis. In practice, however, the adduct **4** proved stable to hydrogenolytic procedures. Treatment of the acetate **5** with Lewis acid

($FeCl_3$) gave initially the desilylated compound **7** in good yield (84%). A larger excess of $FeCl_3$ resulted in removal of the dispoke protecting group, however, acetate migration also occurred and the mixture of acetates **8** was isolated. The ester migration was circumvented by employing the benzoate **6** which is less prone to migration in the deprotection reaction. Treatment of the benzoate **6** with 5 equivalents of $FeCl_3$ gave, after work-up, the 4-*O*-benzoate **9**[4] in 50% yield which is the result of desilylation and dispoke removal. Further experiments to optimise this cleavage reaction are underway.

The enantiomeric diene **2** was predicted to form a 3,4-dispiroketal adduct with D-gluco substrates. Indeed, under standard conditions the diene **2** and the 6-*O*-silylether **3** gave only the 3,4-adduct **10**[5] in 75% yield (Scheme 1). The two dienes **1** and **2** thus provide an efficient, complementary, regioselective protection strategy for D-gluco substrates and potentially for other compounds having enantiomeric 1,2-diol combinations.

The di-allyl substituted diene **11**[6,7] was prepared from 2-allylcyclopentanone[8] in an effort to determine the feasibility of a β-elimination process for the deprotection of dispoke compounds. The R,R-configuration of the diene **11** matches the enantiomeric arrangement of the hydroxyls at C-2 and C-3 of the D-gluco triol **3**[1,9] and so the 2,3-dispiroketal adduct was the predicted product of reaction of compounds **3** with **11**. Thus the 6-*O*-silyl D-glucoside **3** was heated to reflux in the presence of the di-allyl diene **11** and the mild acid catalyst pyridinium *p*-toluene sulfonate (PPTS). Work-up gave the expected 2,3-adduct **12**[10] in 76% yield (Scheme 3). The removal of the dispiroketal moiety was performed as a two step process. Firstly, the diene **12** was ozonolysed to give the dialdehyde **13**. Heating the dialdehyde **13** in toluene in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the 6-*O*-silyl ether **3** in moderate yield (54%). Alternatively, the dialdehyde **13** could be stirred with Schwesinger's base[11] ($P_4$-t-octyl) at 0 °C in tetrahydrofuran (THF) to give methyl α-D-glucopyranoside **14** (70%) which is the result of the desired β-elimination and concomitant desilylation.

*Scheme 3*




i. PPTS (cat.), **11** (1.16 eq.), $CHCl_3$, ↑↓, 2d, 76%; ii. $O_3$, $CH_2Cl_2$, -78 °C then $Ph_3P$ (1.4 eq.),7h, RT, 100%; iii. DBU (1eq.), $PhCH_3$, 80 °C, 21 h, 54%; iv. $P_4$-t-octyl (1 eq.), 0 °C, THF, 2h, 70%.

In conclusion we have developed a new and exciting opportunity for the selective protection of 1,2-diols in carbohydrates. These self-determining or "smart" protecting groups which are able to use chirality recognition processes open a multitude of potential applications in oligosaccharide and polyol research.

***Acknowledgements***

*We thank Shell Research Ltd for the Shell Research Fellowship (to ABH) and SmithKline Beecham for a C.A.S.E. Award (to DAE). We thank Farmitalia Carlo Erba for study leave (GV) and for generous support for this research. We also acknowledge financial support from Pfizer Central Research, Ciba Geigy (Basel) and the BP research endowment (to SVL).*

***References and footnotes***

1. Ley, S.V., Hughes, A.B., Priepke, H.W.M., and Woods, M., preceding communication.
2. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Ch. 1, 1983, Pergamon Press: Oxford.
3. **4**: $C_{45}H_{55}O_8Si$ [*m/z* 751.3663 (M+H), Δ -0.29 mmu]; $[\alpha]_D^{26}$ +36.2 (*c* = 1.0, $CHCl_3$); IR (thin film) 3494, 2930, 2856, 1604, 1453, 1428, 1362, 1202, 1168, 1113, 1047, 982, 873, 823, 741, 699 $cm^{-1}$; FABMS *m/z* (relative intensity) 751 (M+H, 1%), 719 (1), 661 (2), 501 (2), 319 (75), 241 (20), 197 (48), 163 (35), 135 (100); $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.05 (9 H, s, $^t$Bu), 1.5-2.3 (12 H, m, methylene envelope), 2.60 (1 H, br s, OH), 3.42 (3 H, s, OMe), 3.67 (2 H, m, 4- and 5-H), 3.80 (3 H, m, 2-H and 6-H), 4.12 (1 H, m, 3-H), 4.68 (1 H, dd, *J* = 11.6, 2.3 Hz, PhC*H*O), 4.72 (1 H, d, *J* = 3.5, 1-H), 4.85 (1 H, dd, *J* = 11.6, 2.2 Hz, PhC*H*O), 7.3-7.5 (16 H, m, ArH), 7.65-7.8 (4 H, m, ArH).
4. Bollenback, G.N., and Parrish, F.W., *Carbohydrate Res.*, **1971**, *17*, 431.
5. **10**: $C_{45}H_{55}O_8Si$ [*m/z* 751.3680 (M+H), Δ +1.41 mmu]; $[\alpha]_D^{25}$ +63 (*c* = 1.0, $CHCl_3$); IR (thin film) 3474, 2931, 1157, 1112, 1046, 966, 740, 699 $cm^{-1}$; FABMS *m/z* (relative intensity) 773 (M+Na, 23%), 751 (M+H, 29), 319 (92), 241 (20), 197 (76), 163 (28), 135 (100); $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.01 (9 H, s, $^t$Bu), 1.3-2.1 (12 H, m, methylene envelope), 3.40 (3 H, s, OMe), 3.57 (1 H, m, 5-H), 3.5-3.7 (2 H, m), 3.69 (1 H, dd, *J* = 9.2, 4.0 Hz, 2-H), 3.80 (2 H, m, 6-H), 3.96 (2 H, apparent t, *J* = 9.9, 3- and 4-H), 4.45 (1 H, br s, 6'-H), 4.76 (1 H, d, *J* = 4.0, 1-H), 4.82 (1 H, dd, *J* = 11.5, 2.1 Hz, 6''-H), 7.1-7.4 (16 H, m, ArH), 7.66-7.76 (4 H, m, ArH).
6. Full experimental details of the preparations of the dienes **1**, **2** and **11** will be presented in due course.
7. All new compounds gave satisfactory analytical and/or accurate mass spectral data.
8. Lorette, N.B., and Howard, W.L., *J. Org. Chem.*, **1961**, *26*, 3112.
9. Hanessian, S., and Lavallee, P., *Can. J. Chem.*, **1975**, *53*, 2975.
10. **12**: $[\alpha]_D^{23}$ -8.75 (*c* = 1.2, $CHCl_3$); IR (thin film) 3518, 3080-2800, 1641, 1428, 1202, 1113, 1045 $cm^{-1}$; Found: C, 69.05; H, 8.25%. $C_{39}H_{54}O_8Si$ requires C, 68.99; H, 8.02%. $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.06 (9 H, s, $^t$Bu), 1.11-1.94 (12 H, m, methylene envelope), 2.16-2.30 (4 H, m, allyl $CH_2$), 2.44 (1 H, d, *J* = 1.9 Hz, OH), 3.38 (3 H, s, OMe), 3.62 (1 H, m, spiro-H), 3.69-3.77 (4 H, m, 2-, 4-, 5-, spiro-H), 3.90 (2 H, m, 6-H), 4.04 (1 H, dd, *J* = 10.0, 8.6 Hz, 3-H), 4.71 (1 H, d, *J* = 3.5 Hz), 4.90-5.08 (4 H, m), 5.84 (2 H, m), 7.35-7.44 (6 H, m), 7.69-7.72 (4 H, m); $^{13}C$ NMR (60 MHz, $CDCl_3$) δ 18.24 (t), 18.37 (t), 19.25 (s), 26.82 (q), 27.91 (t), 28.19 (t), 29.74 (t), 28.98 (t), 40.36 (t), 40.42 (t), 54.82 (q), 64.20 (t), 67.51 (d), 68.49 (d), 69.18 (d), 69.45 (d), 69.59 (d), 71.61 (d), 97.28 (s), 97.68 (s), 98.03 (d), 116.64 (t), 116.81 (t), 127.65 (d), 129.68 (d), 133.20 (s), 133.33 (s), 134.79 (d), 134.92 (d), 135.64 (d), 135.70 (d).
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(*Received in UK* 1 *November* 1993; *accepted* 26 *November* 1993)