Pergamon

Tetrahedron Letters, Vol. 35, No. 5, pp. 773-776, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0303-2

Dispiroketals in Synthesis (Part 7)[1]: Protection of D-Glucopyranose Substrates.

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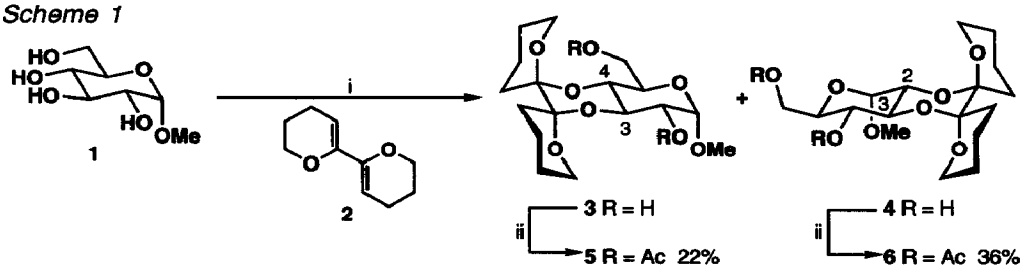
Abstract: The formation of 1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecanes (dispiroketals) of various D-glucopyranosyl substrates is described.

We have reported previously[2] on the dispiroketal (Dispoke)[3] protection of a representative selection of simple pyranosyl carbohydrates. In the course of those and related studies it was found that the dispiroketal moiety had an inherent preference for formation at 1,2-*trans* diequatorial diols in the presence of 1,2-*cis* and 1,3-diols. This regioselective reaction was controlled by the predictable stabilising influence of multiple anomeric effects leading to the thermodynamically most stable conformer.

In reactions with glucopyranose substrates, regioselectivity was not expected, due to the presence of two 1,2-*trans* diequatorial diol relationships. Here we wish to report the results of studies devoted to the efficient dispoke protection of a number of D-glucopyranose substrates as a preliminary to the following communication where we delineate a new enantioselective diol pair recognition and protection procedure.

Reaction of methyl α-D-glucopyranoside **1** under standard conditions [3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran, (*bis*-DHP, **2**[4]) and catalytic camphorsulfonic acid (CSA)] gave an inseparable mixture of the two dispiroketals **3** and **4** in a combined yield of only 39% (Scheme 1). Acetylation gave the separable diacetates **5** and **6**, the structures of which were assigned by examination of the ^{1}H and ^{13}C NMR spectra.[5,6] The diacetates **5** and **6** indicated the dispiroketals had formed in the ratio *ca.* 1.6:1 in favour of the 2,3-protected compound **6**. The poor regioselectivity was anticipated on steric grounds. The low conversion of **1** to *bis*-ketal protected material was attributed to its low solubility in chloroform and the instability of **2**.

Scheme 1

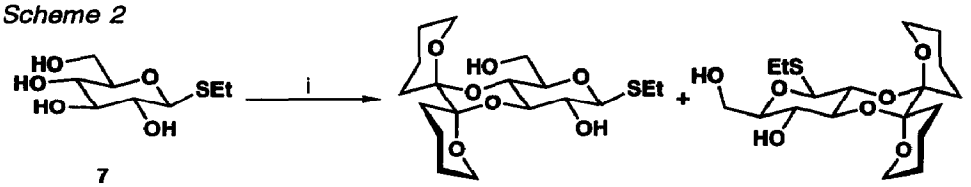


i. *bis*-DHP **2** 2.1 eq., CSA (cat.), $CHCl_3$, Δ, 1.5 h then ethylene glycol, Δ, 0.5 h, 39% or *bis*-DHP **2** 2.1 eq., PPh_3.HBr (cat.), DMF, 60 °C, 4 d, 68%; ii. Ac_2O (xs), pyridine (xs), 58%.

Two methods to circumvent this solubility problem were considered. Firstly, use of *N*,*N*-dimethylformamide (DMF) as solvent has previously been shown to be disadvantageous due to the greater rate of *bis*-DHP **2** decomposition relative to the rate of the desired ketalisation reaction.[4] However, in the presence of the mild acid catalyst, triphenylphosphine-hydrogen bromide complex,[7] methyl α-D-glucopyranoside **1** gave the regioisomeric dispiroketals **3** and **4** in a greatly improved 68% yield also as a 3:2 mixture (Scheme 1).

The second method, relied on the increased lipophilicity of 1-ethylthio β-D-glucopyranoside **7**.[8] Treatment of this compound with *bis*-DHP **2** under standard conditions afforded, after flash chromatography, the regioisomeric dispiroketals **8** and **9** in 33% and 26% respectively (Scheme 2). Both strategies for increasing the overall conversion were therefore reasonably successful. However, the best reaction (Scheme 1), gave a moderate 68% yield after four days of reaction and this was deemed unsatisfactory. The solubility of the substrates in these reactions was still too low and *bis*-DHP decomposition was competing with ketalisation.

Scheme 2



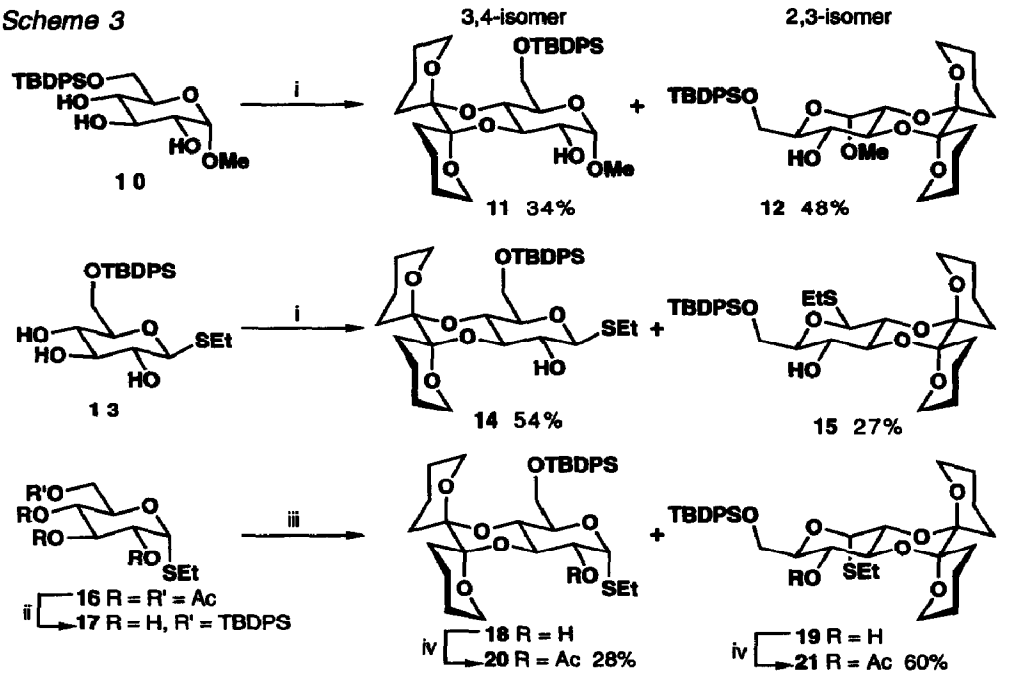
7 **8** 33% **9** 26%

i. *bis*-DHP **2** 2.1 eq., CSA (cat.), $CHCl_3$, Δ, 1.5 h then ethylene glycol, Δ, 0.5 h, 59%.

Many excellent, selective methods are available for the protection of a primary hydroxyl in the presence of secondary hydroxyls.[9] The protecting groups generally employed result in a considerably more lipophilic product. The primary hydroxyl of D-glucose does not compete in the formation of the desired dispiroketals and so the protection of this group prior to reaction with *bis*-DHP **2** was the next means investigated to improve the efficiency of ketalisation. Thus the *tert*-butyldiphenylsilyl (TBDPS) ether **10**[10] was treated with *bis*-DHP **2** under standard conditions to give the two dispiroketals **11** and **12** (separable by column chromatography) in a 1:1.4 ratio and combined yield of 82% (Scheme 3). Similarly, the 1-ethylthio β-D-glucoside **7** was converted to the silyl ether **13** which subsequently gave the dispiroketals **14** and **15** in a 2:1 ratio and combined 81% yield (Scheme 3).

Lastly, the 1-ethylthio α-D-glucopyranoside **16** was produced as a by-product in the formation of 1-ethylthio 2,3,4,6-tetraacetoxy β-D-glucopyranoside. The tetraacetate **16** was methanolysed and the resulting tetrol was silylated to give the silyl ether **17**. It is hoped in later studies to examine not only the influence of the dispiroketal on glycosidation reactions but also the effect of the anomeric configuration of the glycosyl donor. The silyl ether **17** was then ketalised under standard conditions to give an inseparable mixture of the dispiroketals **18** and **19** in 51% yield. Acetylation of this mixture gave the two acetates **20** and **21** in 28% and 60% yields respectively. These were separable and the structures were assigned by examination of the ^1H and ^{13}C NMR spectra.[11] The low conversion of the α-anomer **17** to the dispiroketals **18** and **19** was attributed to the observed normal reduced stability of the α-thio compound compared to the analogous β-thio anomer.

Scheme 3



i. *bis*-DHP **2** 2.1 eq., CSA (cat.), $CHCl_3$, Δ, overnight; ii. KO^{t}Bu (cat.), MeOH then TBDPSCl, pyridine, 53%; iii. *bis*-DHP **2** 2.1 eq., CSA (cat.), $CHCl_3$, Δ, overnight, 51%; iv. Ac_2O (xs), pyridine (xs).

In summary, this work demonstrates that a high chemical conversion of the glucopyranosyl substrates **10** and **13** to the dispiroketals **11**, **12**, **14** and **15** is possible by preliminary protection of the C-6 hydroxyl group. The formation of the dispiroketals gives under standard thermodynamic conditions the anomerically stabilised conformers. The results of further studies aimed at the regioselective protection by chiral recognition of these glucopyranosyl substrates are reported in the following communication.

Acknowledgements

We thank Shell Research Ltd for the Shell Research Fellowship (to ABH) and Schering Agrochemicals Ltd for the award of the Schering Fellowship of Bio-Organic Chemistry (to HWMP). We also acknowledge financial support from Pfizer Central Research, Glaxo Group Research and the BP research endowment (to SVL).

References and footnotes

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5. All new compounds gave satisfactory analytical and/or accurate mass spectral data.

6. **5:** $[\alpha]_D^{28}$ +163 (*c* = 0.1, $CHCl_3$); IR (thin film) 3046-2800, 1745, 1440, 1370, 1237, 1072, 1045 cm^{-1}; FABMS *m/z* (relative intensity) 467 (M+Na, 2%), 445 (M+H, 6), 413 (6), 307 (13), 289 (9), 261 (9), 184 (18), 167 (100); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.38-1.75 (12 H, m, methylene envelope), 2.05 and 2.10 (each 3 H, s, OMe), 3.36 (3 H, s, OMe), 3.53-3.82 (4 H, m), 3.95 (1 H, ddd, *J* = 10.1, 4.8, 2.1 Hz, 5-H), 4.14-4.26 (2 H, m, 6-H and 3 or 4-H), 4.39 (1 H, dd, *J* = 12.0, 2.0 Hz, 6-H), 4.85-4.94 (2 H, m, 1-H and 2-H); ^{13}C NMR ($CDCl_3$, 50 MHz) 17.94 (t), 18.09 (t), 20.75 × 2 (q), 24.73 (t), 24.85 (t), 28.34 (t), 28.42 (t), 55.03 (q), 60.66 (t), 60.81 (t), 62.23 (t), 65.53 (d), 66.06 (d), 67.33 (d), 70.59 (d), 96.93 (s), 97.04 (s), 97.28 (d), 170.25 (s), 170.78 (s).
6: $[\alpha]_D^{20}$ +0.04 (*c* = 1.0, $CHCl_3$); IR (thin film) 3040-2790, 1746, 1440, 1370, 1238, 1166, 1090, 989, 734 cm^{-1}; FABMS *m/z* (relative intensity) 445 (M+H, 100), 413 (40), 394 (24), 331 (43); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.4-1.9 (12 H, m), 2.05 (3 H, s), 2.08 (3 H, s), 3.42 (3 H, s), 3.5-3.72 (4 H, m), 3.88 (1 H, dd, *J* = 10.2, 3.6 Hz), 3.84-3.96 (1 H, m), 4.04-4.28 (4 H, m), 4.78 (1 H, d, *J* = 3.6 Hz), 5.09 (1 H, apparent t, *J* 9.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) 17.87 (t), 18.13 (t), 20.60 (q), 20.72 (q), 24.75 (t), 24.68 (t), 28.12 (t), 28.39 (t), 55.23 (q), 60.47 (t), 60.59 (t), 62.29 (t), 66.36 (d), 67.41 (d), 68.02 × 2, (d), 96.64 (s), 97.22 (s), 98.07 (d), 169.33 (s), 170.75 (s).
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10. Hanessian, S., and Lavallee, P., *Can. J. Chem.*, **1975**, *53*, 2975.
11. **20**: $C_{36}H_{49}O_8SSi$ [*m/z* 669.2940 (M-H), Δ +2.28 mmu]; $[\alpha]_D^{20}$ +120.5 (*c* = 1.15, $CHCl_3$); IR (thin film) 3070, 3050, 3005-2790, 1744, 1590, 1471, 1428, 1368, 1267, 1231, 1189, 1146, 1103, 1073, 1046, 982, 897 cm^{-1}; FABMS *m/z* (relative intensity) 670 (M^+, 2), 609 (6), 409 (2), 365 (2), 349 (4), 271 (2), 241 (12), 197 (20), 167 (100); ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (9 H, s), 1.26 (3 H, t, *J* = 7.4), 1.51-1.78 (12 H, m), 1.93 (3 H, s), 2.58-2.69 (2 H, m), 3.63-3.72 (3 H, m), 3.74 (1 H, dd, *J* = 11.7, 6.2 Hz), 4.07-4.10 (1 H, m), 4.15-4.20 (1 H, m), 4.32-4.35 (1 H, m), 4.35 (1 H, apparent t, *J* = 7.5 Hz), 4.48 (1 H, dd, *J* = 11.1, 5.1 Hz), 4.98 (1 H, apparent t, *J* = 9.7 Hz), 5.46 (1 H, d, *J* = 5.1Hz), 7.34-7.43 (6 H, m), 7.64-7.67 (4 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.66 (q), 17.90 (t), 17.96 (t), 19.15 (s), 20.78 (q), 23.97 (t), 25.18 (t), 25.27 (t), 26.66 (q), 29.84 (t), 29.91 (t), 61.11 (t), 61.60 (t), 62.87 (t), 70.15 (d), 71.00 (d), 82.91 (d), 98.62 (s), 98.92 (s), 127.57 (d), 129.58 (d), 133.28 (s), 135.61 (d), 135.70 (d), 169.63 (s).
21: $C_{36}H_{49}O_8SSi$ [*m/z* 669.2928 (M-H), Δ +1.08 mmu]; $[\alpha]_D^{30}$ +44.6 (*c* = 1.45, $CHCl_3$); IR (thin film) 3070, 3046, 3005-2820, 1747, 1589, 1428, 1370, 1270, 1230, 1160, 1112, 1073, 1036, 988, 965, 936, 900 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.04 (9 H, s), 1.29 (3 H, t, *J* = 7.4 Hz), 1.40-1.84 (12 H, m), 1.92 (3 H, s), 2.65 (2 H, m), 3.54-3.68 (5 H, m), 3.74 (1 H, dd, *J* = 11.4, 6.2 Hz), 4.07 (1 H, dd, *J* = 19.2, 10 Hz), 4.12 (1 H, dd, *J* = 10, 5.2 Hz), 4.26 (1 H, m), 4.98 (1 H, apparent t, *J* = 9.6 Hz), 5.41 (1 H, d, *J* = 5.2 Hz), 7.35-7.43 (6 H, m), 7.65-7.68 (4 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.30 (q), 17.90 (t), 18.06 (t), 19.00 (s), 20.42 (q), 23.54 (t), 24.69 (t), 24.82 (t), 26.54 (q), 28.09 (t), 28.33 (t), 60.35 (t), 60.51 (t), 63.00 (t), 67.06 (d), 67.69 (d), 68.33 (d), 71.23 (d), 81.60 (d), 96.49 (s), 96.89 (s), 127.43 (d), 127.48 (d), 129.47 (d), 133.07 (s), 135.43 (d), 135.52 (d), 169.03 (s).

(*Received in UK* 1 *November* 1993; *accepted* 26 *November* 1993)