Tetrahedron Letters, Vol. 34, No. 52, pp. 8523-8526, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Dispiroketals in Synthesis (Part 5)[1]: A New Opportunity for Oligosaccharide Synthesis Using Differentially Activated Glycosyl Donors and Acceptors

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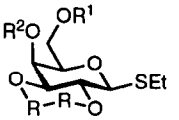
Abstract: The reactivity of dispiroketal protected thioglycosides makes them useful new precursors for oligosaccharide synthesis as is illustrated by the preparation of a protected pentasaccharide unit common to the variant surface glycoprotein of *Trypanosoma brucei*.

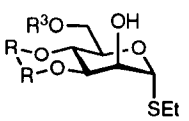
The important armed/disarmed glycosylation concept introduced by Fraser-Reid *et al.*[2] has proven to be a powerful tool in the concise preparation of complex oligosaccharides. Furthermore, recent modifications to this general process have proven to be equally valuable.[3] The process relies upon the fact that the reactivity of the anomeric centre can be regulated by either the nature of the flanking C-2 hydroxylated derivative (ether *vs* ester) or the presence of cyclic acetals.[4] For example, a donor having an ether protecting group at C-2 (armed - activated) can be chemoselectively coupled to an acceptor bearing a C-2 ester group (disarmed - deactivated).[2] Further glycosylation of the obtained disaccharide could be accomplished by using a more powerful activator of the anomeric leaving group or *via* functional group interconversion. Despite the versatility of this approach there remains an exciting opportunity to tune glycosyl donor leaving group ability further and thus realise a greater potential for these coupling sequences.

Here we wish to report the effect of dispiroketal substitution (dispoke protection[1]) on glycosyl reactivity whereby we have produced a new range of differentially reactive coupling substrates. The potential for these methods combined with other leaving group tuning processes[5] is enormous.

The dispoke protected galactoside **4** and mannoside **6** were prepared in order to examine the anomeric leaving group ability of these substrates.[6] Thus, regioselective silylation of the spiroketal derivative **1**[7] afforded compound **2**[8] in 67% yield. Benzylation of **2** with benzyl bromide, sodium hydride and catalytic tetra-*N*-butylammonium iodide in DMF gave fully protected **3**, the silicon protecting group of which was removed by treatment with tetra-*N*-butylammonium fluoride to yield the target compound **4** in 72% overall yield. The selectively protected manno-derivative **6**[9] was easily obtained by regioselective benzylation of **5** using benzyl bromide and sodium hydride in DMF (63%).



1 $R^1 = R^2 = H$
2 R^1 = TBDMS, $R^2 = H$
3 R^1 = TBDMS, R^2 = Bn
4 $R^1 = H$, R^2 = Bn



5 $R^3 = H$
6 R^3 = Bn

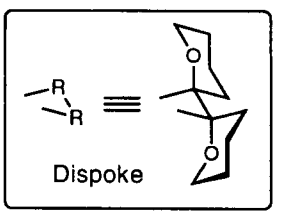
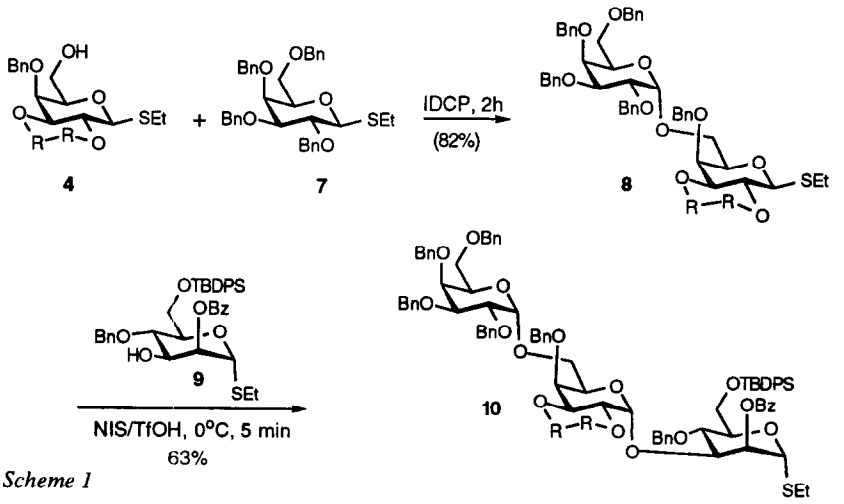
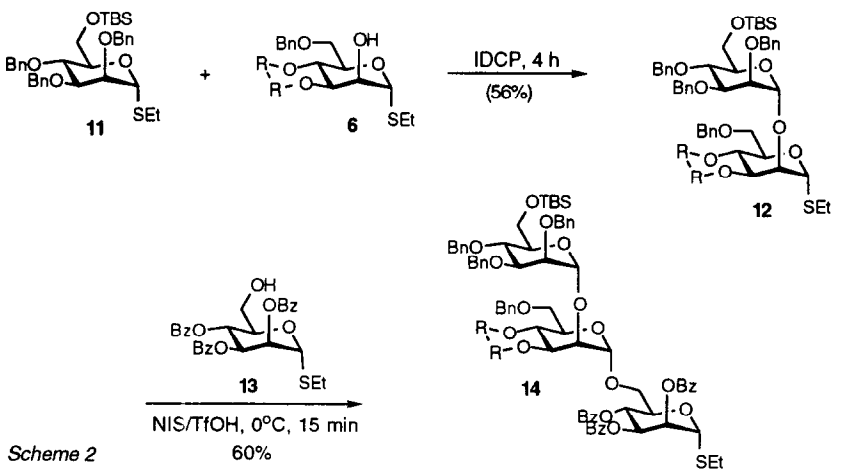


Figure 1



Scheme 1

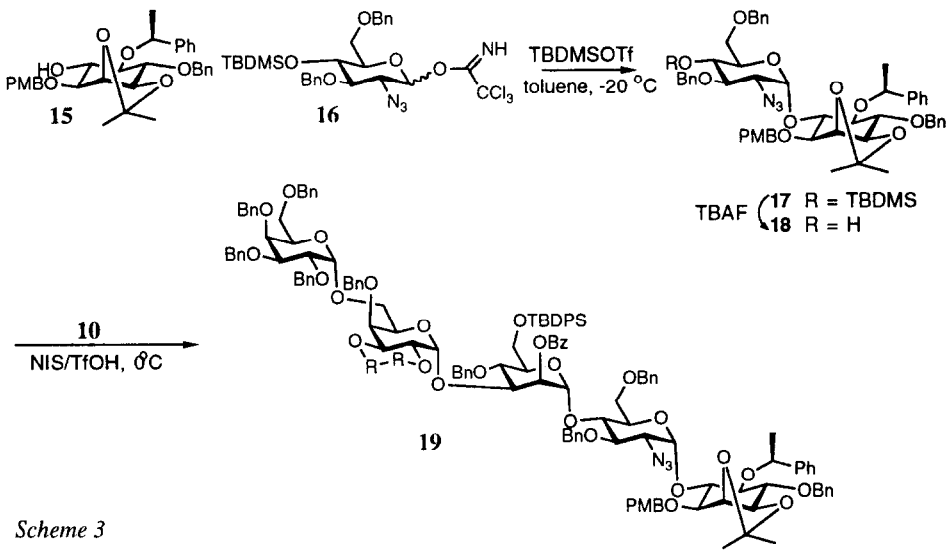
Iodonium dicollidine perchlorate (IDCP) mediated chemoselective glycosylation[3a] of glycoside donor **7** with dispoke protected acceptor **4** in ether/dichloroethane after 2 h, gave the disaccharide **8** in an excellent yield of 82% and α/β ratio of 5:2. No self condensed products were observed. Further chemoselective glycosylation of **8** with acceptor **9**[10] in the presence of the more powerful activating system, *N*-iodosuccinimide (NIS)/triflic acid (TfOH),[3b] after a reaction time of 5 min gave a 63% yield of trisaccharide **10** as essentially one anomer (Scheme 1). These coupling procedures are also suitable for the synthesis of mannosides. For example, coupling of thio-mannoglycoside **11** with dispoke protected derivative **6** gave dimer **12** in 51% yield which could be further coupled with glycosyl acceptor **13** to give manno trisaccharide **14** as a single anomer (Scheme 2). These examples clearly illustrate that a dispoke protecting group has a profound influence on the reactivity of the anomeric centre. Furthermore, the reactivity is of an order of magnitude between substrates having a fully arming ether or disarming ester protecting group on C-2 which implies that dispoke protected thioglycosides may be regarded as semi-disarmed substrates.



Scheme 2

The potential of this new glycosylation sequence was illustrated by the preparation of suitably protected pentasaccharide **19** which forms part of the variant surface glycoprotein of *Trypanosoma brucei.*[11]

The pseudo-disaccharide **17** was obtained by TBDMSOTf promoted coupling[12] of glucosylimidate **16**[13,14] with known inositol derivative **15**[15] in toluene (72%, α:β 2/1). It is of interest to note that the β anomer predominated when this glycosylation was performed in dichloromethane or if the TBDMS protecting group on the glycosyl donor was replaced by an electron withdrawing acetate functionality. Treatment of **17** with TBAF in THF gave the acceptor **18** which was coupled with trisaccharide **10** in the presence of NIS and catalytic TfOH to give pseudopentasaccharide **19**[16] as a single anomer in an unoptimized yield of 41%. Compound **19** has the appropriate protection pattern for further processing to the GPI anchor of *Trypanosoma brucei.*



Scheme 3

In summary, we have demonstrated that the dispoke protecting group has a marked effect on the reactivity of the anomeric centre and may be regarded as a semi-disarmed substrate. This allows the preparation of complex oligosaccharides in a concise manner thus avoiding tedious functional group manipulation that often accompanies other syntheses.

Acknowledgement

We thank the S.E.R.C. for financial support, the Ramsay Memorial Fund (Fellowship to G.-J. B.) and Zeneca Pharmaceuticals (C.A.S.E. Award to R.L.) for additional support. We also acknowledge the B.P.endowment (to S.V.L.) at Cambridge and Dr D. M. Hollinshead (Zeneca Pharmaceuticals) for useful discussions.

References and notes

1. For part 4 see Boons G.J., Entwistle D.A., Ley S.V., *Tetrahedron Lett.*, in press.

2. Fraser-Reid B., Udodong. U. E.,Wu Z., Ottoson H., Merritt. R.,Rao C.S., Roberts C., *Synlett*, **1992**, 927.

3a) Veeneman G.H., Van Boom J.H., *Tetrahedron Lett.*, **1990**, *31*, 274; b) Veeneman G.H., Van Leeuwen S.H., Van Boom J.H., *Tetrahedron Lett.*, **1990**, *31*, 1331; c) Toshima K., Nozaki Y., Innokuchi H., Nakata M., Tatsuta K., Kinoshita M., *Tetrahedron Lett.*, **1993**, *34*, 1911; d) Friesen R.W., Danishefsky S.J., *J. Am. Chem. Soc.*, **1989**, *31*, 2365.

4a) Fraser-Reid B., Zugan W., Andrews W., Skowronski E., *J. Am. Chem. Soc.*, **1991**, *113*, 1434; b) Toshima K., Nozaki Y., Tatsuta K., *Tetrahedron Lett.*, **1991**, 32, 6887; c) Veeneman G.H. *Ph.D. Thesis*, Leiden, **1991**, p103.

5a) Zuurmond H.M., Van der Klein P.A.M., Van der Meer P.H., Van der Marel G.A., Van Boom J.H., *Recl. Trav. Chim. Pays-Bas*, **1992**, *111*, 365;.b) Raghavan S., Kahne D., *J. Am. Chem. Soc.*, **1993**, *115*, 1580.

6. Owing to the ease of preparation of ethyl 1-thio-β-galactoside and ethyl 1-thio-α-mannoside they were selected as starting materials. We are also investigating the effect of the anomeric configuration of the thioglycoside on the anomeric leaving group ability.

7. Ley S.V., Leslie R., Tiffen P.D., Woods M., *Tetrahedron Lett.*, **1992**, *33*, 4767.

8. All new compounds gave satisfactory spectroscopic and analytical data.

9. Ley S.V. , Boons G.J., Leslie R., Woods M., Hollinshead D.M., *Synthesis*, in press.

10. Preparation of compound **9**: Regioselective silylation of 1-thio-α-D-mannopyranoside with *tert*-butyldiphenylsilyl chloride (TBDPSCl), triethylamine and catalytic dimethylaminopyridine in DMF followed by protection of the *cis* diol as an isopropylidene functionality and benzylation with benzyl bromide and sodium hydride in DMF gave fully protected 1-thio-4-*O*-benzyl-2,3-di-*O*-isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranoside. Cleavage of the isopropylidene group of the fully protected compound with acetic acid/water followed by regioselective benzoylation under phase transfer conditions gave target compound **9**.

11. Ferguson M.A.J., Homans S.W., Rademacher T.W., *Science*, **1988**, *240*, 509.

12. Schmidt R.R., *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 212.

13. Compound **16** was prepared from known *tert*-butyldimethylsilyl 2-azido-3,6-di-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-2-deoxy-β-D-glucopyranoside[14] by silylation with TBDMSCl in pyridine followed by regioselective desilylation of the TBDMS group at the anomeric centre with TBAF in THF/acetic acid and conversion of the resulting anomeric alcohol into the trichloroacetimidate by treatment with trichloroacetonitrile and potassium carbonate.

14. Schmidt R.R., *Liebigs Ann. Chem.*, **1989**, 789.

15. Ley S.V., Yeung L.L., *Synlett*, **1992**, 997.

16. ^{1}H NMR data of compound **19** ($CDCl_3$): δ 8.05 (1H, d, J 11.2 Hz, H-Ar), 7.62 - 6.89 (68H, m, Ar-H), 5.75 (1H, s, H-2"), 5.68 (1H, s, H-1"), 5.43 (1H, d, J 1.5 Hz, H-1'), 5.38 (1H, d, J 12.5 Hz, C*H*HPh), 5.08 (1H, J 7.5 Hz, C*H*HPh), 5.04 (1H, s, H-1'"), 4.90 (2H, J 5.8 Hz, CH_2Ph), 4.82 - 4.84 (4H, m, CH_2Ph), 4.73 (2H, m, CH_2Ph), 4.70 (1H, d, J 12.5 Hz, C*H*HPh), 4.66 - 4.62 (2H, m, CH_2Ph), 4.59 (4H, m, H-1"", H-3", C*H*HPh, C*H*H*p*MeOPh), 4.47 - 4.36 (4H, m, CH_2Ph, C*H*H*p*MeOPh), 4.32 (3H, m, H-3"', H-3", H-5'), 4.26 (6H, m, H-5", H-2"', H-2, H-6a,b"', H-4"), 3.96 - 3.33 (5H, m, H-6a,b", H-3', H-4', H-4), 3.79 (3H, s, OCH_3), 3.76 - 3.41 (16 H, m, H-1, H-3, H-6a,b', H-3"', H-4"', H-5"', H-2, H-3"", H-4"", H-5"", H-6"", CH_2O spiroketal), 3.18 (1H, m, H-2'), 1.78 - 1.42 (12H, m, CH_2, spiroketal), 1.53 and 1.34 (6H, 2x s, CH_3, isoprop), 1.32 (3H, d, J 7.5, CH(C*H*$_3$)Ph), 0.94 (9H, s, $(CH_3)_3C$).

(Received in UK 10 August 1993; accepted 22 October 1993)