Pergamon

Tetrahedron Letters 43 (2002) 9429–9431

TETRAHEDRON LETTERS

Chemoselective glycosylations of sterically hindered glycosyl acceptors

Richard Geurtsen and Geert-Jan Boons*

Complex Carbohydrate Research Center, University of Georgia, 220 Riverbend Road, Athens, GA 30602-4712, USA

Received 19 July 2002; accepted 11 October 2002

Abstract—Unexpected intermolecular aglycon transfer in chemoselective glycosylations between activated thioglycosyl donors and deactivated thioglycosyl acceptors could be avoided by employing a glycosyl acceptor that has a bulky anomeric dicyclohexylmethanethio group. The methodology was applied to the synthesis of a protected fragment of an oligosaccharide released from the jelly coat glycoprotein of *X. leavis*.

Carbohydrates are key to many of the events leading to fertilization[1–3] and examples include recognition of egg by sperm,[4] induction of the acrosome reaction, fusion of sperm and egg and the formation of the fertilization layer.

The South African clawed toad, *X. laevis*, is a useful model animal in which to study phenomena associated with fertilization and early development. In this organism, the interaction of the novel carbohydrate-binding protein XL35 with the *O*-glycans of a jelly coat protein (JCP) enrobing the egg, is considered key in the prevention of polyspermy.[5–7] *O*-Glycans released upon mild base treatment of JCP samples derived from the oocytes of six individual *X. laevis* toads have been found by NMR spectroscopy to comprise twenty three different structural motifs, eleven of which are unique.[8] Heptasaccharide **1** is one of the most complex oligosaccharides isolated from the jelly coat glycoprotein and is composed of an unusual dimeric H-antigen substituted by an α-galactoside (Fig. 1). The oligosaccharide is attached to the protein through an *O*-linked *N*-acetyl galactosamine moiety, which is further extended by a *N*-acetyl glucosamine residue.

Previously, we reported a polymer-supported synthesis of protected tetrasaccharide **1A** using a novel two directional glycosylation strategy.[9] It was expected that the synthesis of **1** could be completed by extension of this tetrasaccharide by a properly protected Gal-α-(1→4)-Gal glycosyl donor (**1B**) followed by fucosylation of the two internal galactosides.

Herein we report the synthesis of properly protected gallibiose donors **12** and **13** using a chemoselective glycosylation strategy, whereby the anomeric reactivity of thioglycosyl donors and acceptors is controlled by a combination of properly selected protecting groups and the use of either an anomeric thioethyl or bulky dicyclohexylmethanethio group.

An attractive feature of thioglycosyl donors and acceptors is that they can be assembled into oligosaccharides by a chemoselective glycosylation strategy.[10,11] This approach is based on the observation that protecting group patterns can control anomeric reactivities of thioglycosides. Thus, it is possible that a thioglycosyl donor can be coupled with a thioglycosyl acceptor of lower anomeric reactivity to give a well-defined product. In a subsequent glycosylation, the resulting

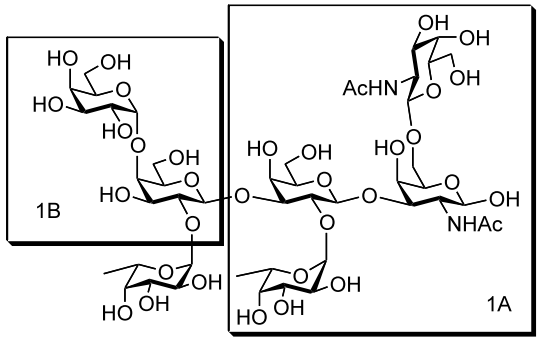


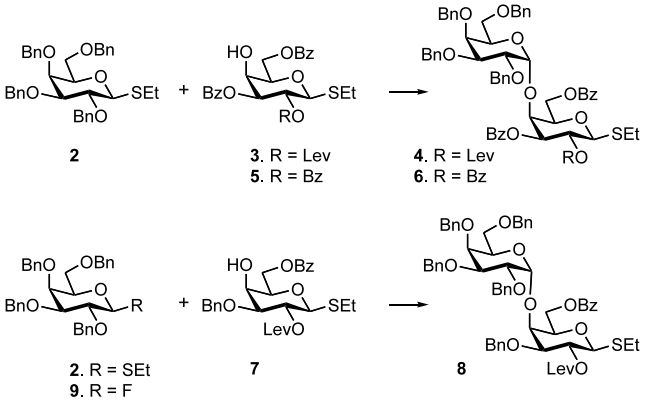
Figure 1. A heptasaccharide (**1**) isolated from the jelly coat glycoprotein of *X. laevis*.

* Corresponding author. Tel.: +1-706-542-9161; fax: +1-706-542-4412; e-mail: gjboons@ccrc.uga.edu

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02334-1

product can act as a glycosyl donor and react with a thioglycosyl acceptor that has even a lower reactivity. This process can be repeated to give rather complex structures without the need for intermediate protecting group chemistry. Recently, the usefulness of this approach was expanded by the creation of a database that makes it possible to predict the relative reactivities of a large number of *p*-methylphenyl thioglycosides.[12] In general, an electron-donating ether substituent at C-2 activates and an electron-withdrawing ester functionality deactivates the reactivity of an anomeric-leaving group.

It was expected that coupling of reactive ethyl thioglycoside **2**, which has an activating benzyl ether at C-2, with ethyl thioglycoside **3**, which has a deactivating levulinoyl ester (Lev) at C-2,[13–15] would give disaccharide **4** in high yield (Scheme 1). This disaccharide could then immediately be used as a glycosyl donor and furthermore the Lev ester at C-2 would allow incorporation of a fucoside. Surprisingly, coupling of **2** with **3** in the presence of *N*-iodosuccinimate/trimethylsilyl triflate (NIS/TMSOTf) as the promoter[16] gave apart from the expected disaccharide **4** (yield: 35%) substantial quantities of trehalose and a trisaccharide. The use of the mild activator iodonium dicollidine perchlorate (IDCP)[17] gave a somewhat higher yield but the product was still contaminated with side products and furthermore **4** was formed as an inseparable mixture of anomers. The best results were obtained by in situ conversion of thioglycoside **2** into the corresponding bromide followed by a silver triflate promoted glycosylation (Br_2, AgOTf, TMU, toluene)[18,19] with glycosyl acceptor **5**, which has a more deactivating benzoyl group at C-2, to give disaccharide **6** as only the α-anomer in a yield of 48%. However, this glycosylation gave also substantial quantities of trehalose and trisaccharide. Furthermore, mixtures of anomers were obtained when others solvents than toluene were used. In this respect, it is important to note that use of toluene is not compatible with IDCP due to insolubility of the activator.



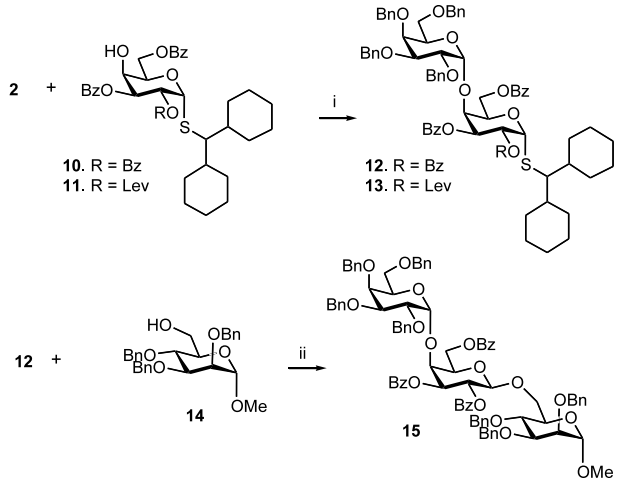
Scheme 1.

In order to reduce the formation of side products, glycosyl acceptor **7** was used in the coupling with **2**. The rationale of using this acceptor was that it has a benzyl ether at C-3, which should increase glycosyl accepting properties. Unfortunately, coupling of **2** with **7**, using Br_2/AgOTf as the activator gave disaccharide **8** in low yield and the product was contaminated with trisaccharide and trehalose.

Next, an orthogonal glycosylation between fluoride **9** and acceptor **7** was investigated. It is well known that an anomeric fluoride can be activated in the presence of a thioglycosyl acceptor to give a product that can immediately be used in a subsequent glycosylation.[20] Unfortunately, a $Zr(Cp)_2Cl_2$/AgOTf mediated coupling[21] of **9** with **7** gave a mixture of products. Interestingly, ethyl 2,3,4,6-tetra-*O*-benzylthiogalactoside (**2**) was isolated as a main product. Thus, it appears that after activation of **9**, the resulting oxacarbenium ion reacts with the anomeric ethyl thio group of **7** rather than with its alcohol.[22] In this particular case, this mode of reaction is prevalent because of the low reactivity of the C-4 hydroxyl of **7**. The activation of the anomeric center of **7** may subsequently lead to self-condensation. Probably, the trisaccharides observed in the glycosylations described above result from further glycosylation of the hydroxyl of the self-condensed disaccharide. Alternatively, it can not be excluded that trisaccharide formation arises from activation of disaccharides **4**, **6** and **8** by a sugar oxacarbenium ion followed by condensation with an acceptor. It is, however, unlikely that acceptors **3**, **5** and **7** or disaccharides **4**, **6** and **8** are directly activated by the promoter because of the much higher reactivity of glycosyl donor **2**.

It was anticipated that a glycosyl acceptor that has an anomeric dicyclohexylmethanethio group would be less prone to be activated by a sugar oxacarbenium ion.[23,24] In this case, the bulky aglycon of the glycosyl acceptor would block attack by an oxacarbenium ion. Indeed, AgOTf/Br_2 mediated coupling of ethyl thiogalactoside **2** with dicyclohexylmethyl thiogalactoside **10** gave disaccharide **12**[25] in a good yield of 73% as only the α-anomer. As expected, coupling of **2** with acceptor **11**, which has a Lev ester at C-2, gave **13** in a good yield of 71% (Scheme 2). Finally, to demonstrate that **12** is an appropriate glycosyl donor, it was coupled with **14** using the promoter NIS/TMSOTf and trisaccharide **15**[26] was isolated in an excellent yield of 91%.

In conclusion, chemoselective glycosylations of ethyl thioglycosyl acceptors that have hydroxyls of low reactivity are prone to self-condensation. Employing a glycosyl acceptor that has a bulky dicyclohexylmethanethio group at its anomeric center can prevent this unwanted reaction. The new methodology was applied to the synthesis of properly protected gallibiose fragment **13**, which will be a key building block in the synthesis of heptasaccharide **1**.



Scheme 2. *Reagents and conditions*: (i) Br_2, AgOTf, TMU, 4 Å MS, toluene; (ii) NIS, TMSOTf toluene, 4 Å MS.

Acknowledgements

This work was supported by the NIH Resource Center for Biomedical Complex Carbohydrates (P41-RR05351).

References

1. Mengerink, K. J.; Vacquier, V. D. *Glycobiology* **2001**, *11*, 37R–43R.
2. Takasaki, S.; Mori, E.; Mori, T. *Biochim. Biophys. Acta Gen. Subj.* **1999**, *1473*, 206–215.
3. Dell, A.; Morris, H. R.; Easton, R. L.; Patankar, M.; Clark, G. F. *Biochim Biophys. Acta Gen. Subj.* **1999**, *1473*, 196–205.
4. Vo, L. H.; Hedrick, J. L. *Biol. Reproduct.* **2000**, *62*, 766–774.
5. Roberson, M. M.; Barondes, S. H. *J. Biol. Chem.* **1982**, *257*, 7520–7524.
6. Lee, J. K.; Buckhaults, P.; Wilkes, C.; Teilhet, M.; King, M. L.; Moremen, K. W.; Pierce, M. *Glycobiology* **1997**, *7*, 367–372.
7. Nishihara, T.; Wyrick, R. E.; Working, P. K.; Chen, Y. H.; Hedrick, J. L. *Biochemistry* **1986**, *25*, 6013–6020.
8. Strecker, G.; Wieruszeski, J. M.; Plancke, Y.; Boilly, B. *Glycobiology* **1995**, *5*, 137–146.
9. Geurtsen, R.; Boons, G. J. *Eur. J. Org. Chem.* **2002**, 1473–1477.
10. Boons, G. J. *Tetrahedron* **1996**, *52*, 1095–1121.
11. Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179–205.
12. Zhang, Z.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753.
13. Hassner, A.; Strand, G.; Rubinstein, M. *J. Am. Chem. Soc.* **1975**, *97*, 1614–1615.
14. Zhu, T.; Boons, G. J. *Chem. Eur. J.* **2001**, *7*, 2382–2389.
15. Zhu, T.; Boons, G. J. *Tetrahedron: Asymmetry* **2000**, *11*, 199–205.
16. Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334.
17. Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275–278.
18. Sato, S.; Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, *155*, C6–C10.
19. Kihlberg, J. O.; Leigh, D. A.; Bundle, D. R. *J. Org. Chem.* **1990**, *55*, 2860–2863.
20. Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073–12074.
21. Suzuki, K.; Maeta, H.; Suzuki, T.; Matsumoto, T. *Tetrahedron Lett.* **1989**, *30*, 6879–6882.
22. Yu, H.; Yu, B.; Wu, X. Y.; Hui, Y. Z.; Han, X. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, *9*, 1445–1453.
23. Geurtsen, R.; Côté, F.; Hahn, M. G.; Boons, G. J. *J. Org. Chem.* **1999**, *64*, 7828–7835.
24. Geurtsen, R.; Holmes, C. S.; Boons, G. J. *J. Org. Chem.* **1997**, *62*, 8145–8154.
25. All new compounds gave satisfactory NMR spectroscopic, mass spectroscopic and elemental analytical data. Selected data for **12**: $[\alpha]_D^{24}$ +115.30 (*c* 1); MALDI-TOF MS: m/z = 1231.2 [M+Na], 1247.5 [M+K]; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.31, 165.84, 165.79 (3 C_6H_5CO), 138.82, 138.73, 138.50, 138.12, 133.13, 133.02, 129.89, 129.81, 129.75, 128.38–127.39 (4 $C_6H_5CH_2$, 3 C_6H_5CO), 129.53, 129.48 (2 C_6H_5CO), 100.80 (C-1′), 85.66 (C-1), 79.06 (C-3′), 76.50 (C-4), 75.89 (C-2′/C-4′), 74.85 (C-2′/C-4′), 71.53 (C-3), 69.82, 69.41, 68.92 (C-2, C-5, C-5′), 74.94, 74.22, 72.86, 72.56 (4 $C_6H_5CH_2$), 67.62 (C-6′), 62.32 (C-6), 60.07 ($SCH(C_6H_{11})_2$), 41.26, 39.52, 32.05, 31.57, 30.04, 29.38, 26.46, 26.46, 26.32, 26.21 ($SCH(C_6H_{11})_2$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99 (d, 2H, 1 C_6H_5CO, J = 7.2 Hz), 7.99 (d, 4H, 2 C_6H_5CO, J = 7.8 Hz), 7.62–7.10 (m, 29H, 4 $C_6H_5CH_2$, 3 C_6H_5CO), 5.77 (d, 1H, H-1), 5.52 (dd, 1H, H-3, $J_{3,4}$ = 2.4 Hz), 4.96 (d, 1H, H-1′, $J_{1',2'}$ = 3.3 Hz), 4.90–4.62 (m, 8H, 3 $C_6H_5CH_2$, H-6a, H-5, H-6b), 4.50 (d, 1H, H-4), 4.46 (d, 1H, $C_6H_5CH_2$, J_{gem} = −11.1 Hz), (dd, 1H, H-5′, J = 8.6, J = 5.3 Hz), 4.17 (dd, 1H, H-3′, $J_{2',3'}$ = 10.2, $J_{3',4'}$ = 2.4 Hz), 4.10 (s br, 1H, H-4′), 4.07 (dd, 1H, H-2′), 3.97 (s, 2H, $C_6H_5CH_2$), 3.37 (t, 1H, H-6′a, J = 8.7 Hz), 2.88 (dd, 1H, H-6′b, $J_{5',6'b}$ = 5.1 Hz), 2.41 (t, 1H, $SCH(C_6H_{11})_2$, J = 5.4 Hz), 2.0–0.7 (m, 22H, $SCH(C_6H_{11})_2$).
26. Selected data for **15**: MALDI-TOF MS m/z = 1483 [M+Na]; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.01–8.00 (m, 50H, 7 $C_6H_5CH_2$, 3 C_6H_5CO, aromatic), 5.80 (t, 1H, $J_{2',3'}$ = 7.7 Hz, H-2′), 5.20 (dd, 1H, $J_{3',4'}$ = 2.8 Hz, H-3′), 4.91 (d, 1H, $J_{1'',2''}$ = 3.4 Hz, H-1′), 4.87–4.69 (m, 11H, 5 $C_6H_5CH_2$), 4.77(q, 2H, H-6a′, H-6b′), 4.63 (s, 2H, $C_6H_5CH_2$), 4.50 (s, 2H, $C_6H_5CH_2$), 4.47 (s, 1H, H-1), 4.39 (d, 1H, $J_{4',5'}$ = 2.56 Hz, H-4′), 4.34 (m, 1H, H-5″), 4.24 (d, 2H, J = 10.2 Hz, H-6a,b), 4.19 (dd, 1H, $J_{3'',4''}$ = 2.8 Hz, H-3″), 4.10 (s, 1H, H-4″), 4.04 (dd, 1H, $J_{2'',3''}$ = 10.6 Hz, H-2″), 4.02 (m, 1H, J = 7.9 Hz, H-5′), 3.76 (dd, 1H, J = 9.1 Hz, J = 2.8 Hz, H-3), 3.71(m, 1H, H-5), 3.66 (t, 1H, $J_{2,3}$ = 9.1 Hz, H-2), 3.33 (m, 1H, J = 8.8 Hz, H-6a″), 2.82 (q, 1H, H-6b″).