Pergamon

Tetrahedron Letters 43 (2002) 8819–8822

TETRAHEDRON LETTERS

Semi-orthogonality of *O*-pentenyl and *S*-ethyl glycosides: application for the oligosaccharide synthesis

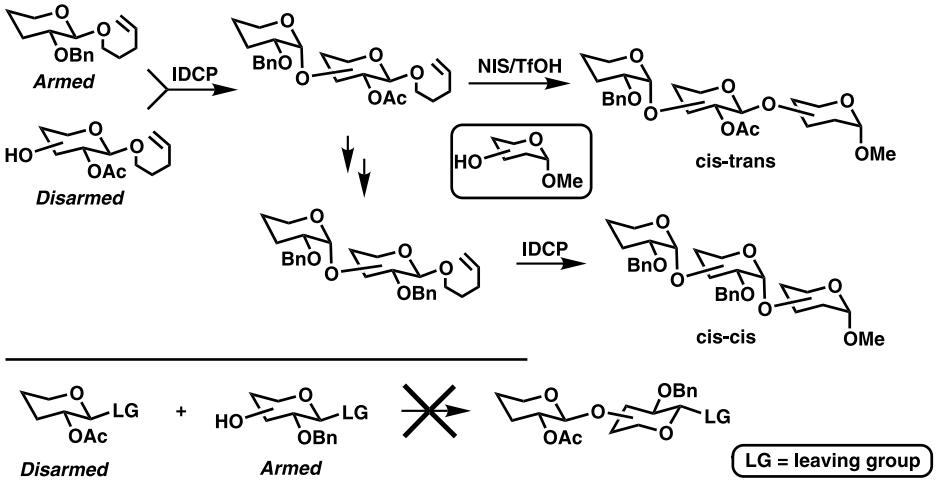
Alexei V. Demchenko* and Cristina De Meo

Department of Chemistry and Biochemistry, University of Missouri–St. Louis, 8001 Natural Bridge Road, St. Louis, MO 63121, USA

Received 4 September 2002; revised 4 October 2002; accepted 8 October 2002

Abstract—Novel semi-orthogonal glycosylation strategy with the use of *O*-pentenyl and thioglycosides has been developed. According to this technique both armed and disarmed thioglycosides can be selectively activated with MeOTf in the presence of either armed or disarmed *O*-pentenyl glycosides. The applicability of this novel strategy for the synthesis of a *trans–cis* glycosylation pattern, not accessible via conventional armed–disarmed approach, has been demonstrated for the synthesis of a linear tetrasaccharide derivative. © 2002 Elsevier Science Ltd. All rights reserved.

The 1,2-*cis* and 1,2-*trans* glycosyl residues are present as the components in a wide variety of natural glycosides, glycoconjugates, oligo-, and polysaccharides, the biological role and tremendous therapeutic potential of which has been revealed primarily during past decade.[1–3] One of the major drawbacks in the study of these derivatives is the low availability of pure samples from natural sources; clearly, in these cases chemical or enzymatic synthesis would allow access to considerably larger quantities of chirally pure material. Since the first attempts at the turn of the 20th century, enormous progress has been made in the area of the *O*-glycoside synthesis, however only last decade or two have witnessed a dramatic improvement in the methods used for the assembly of complex oligosaccharides and glycoconjugates.[4–9] Many new glycosyl donors, which can be synthesized under mild reaction conditions and are sufficiently stable to be purified, modified and stored for a considerable period of time, have been developed.[6,10] Methods for solid phase oligosaccharide syn-



Scheme 1. Armed–disarmed glycosylation strategy.

Keywords: chemoselectivity; glycosylation; novel synthetic strategy; glycosyl donors.

* Corresponding author. Tel.: +1-314-516-7995; fax: +1-314-516-5342; e-mail: demchenkoa@umsl.edu

PII: S0040-4039(02)02235-9

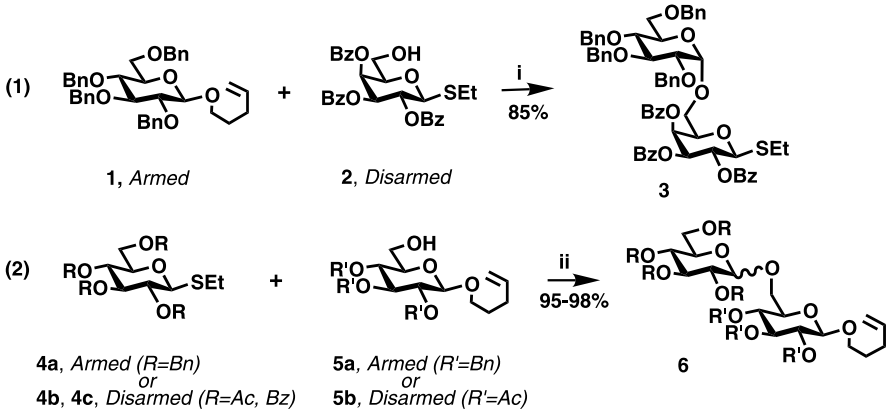
thesis have been reported and these procedures often shorten oligosaccharide synthesis by avoiding the necessity to purify intermediate derivatives.[11–14] The power of modern supercomputers has been applied for the conformational analysis in order to explain or even predict the reactivity of carbohydrate molecules.[15] Despite considerable progress and the extensive effort, there is a continuous need in new versatile synthetic methods for the oligosaccharide synthesis.

A number of synthetic strategies enabling the convenient assembly of oligosaccharides from properly protected building blocks have recently emerged.[16,17] These strategies offer more efficient route toward complex saccharides by reducing the number of synthetic steps in comparison to that of conventional linear glycosylation techniques. Many modern strategies for the oligosaccharide synthesis are based on the selective activation of a particular glycosyl donor over another. One of the most elegant strategies is based on the chemoselectivity principle, so-called armed–disarmed glycosylation approach, was rationalized by Fraser-Reid and co-workers (Scheme 1).[18,19] According to this strategy, a benzylated (armed) glycosyl donor can be chemoselectively activated in the presence of the acetylated (disarmed) derivative to afford a 1,2-*cis*-linked disaccharide. The latter can either be used for 1,2-*trans* glycosylation directly with the use of a more powerful promoter, or 1,2-*cis* glycosylation after appropriate protecting group manipulations. Similar concept was explored for the glycosylations with ethyl thioglycosides.[20] Overall, the armed–disarmed glycosylation strategy offers an efficient way to synthesize oligosaccharides with *cis–trans* or *cis–cis* glycosylation pattern. However, this method is not applicable for the synthesis of *trans–cis*, or *trans–trans*-linked saccharides in its pure fashion.

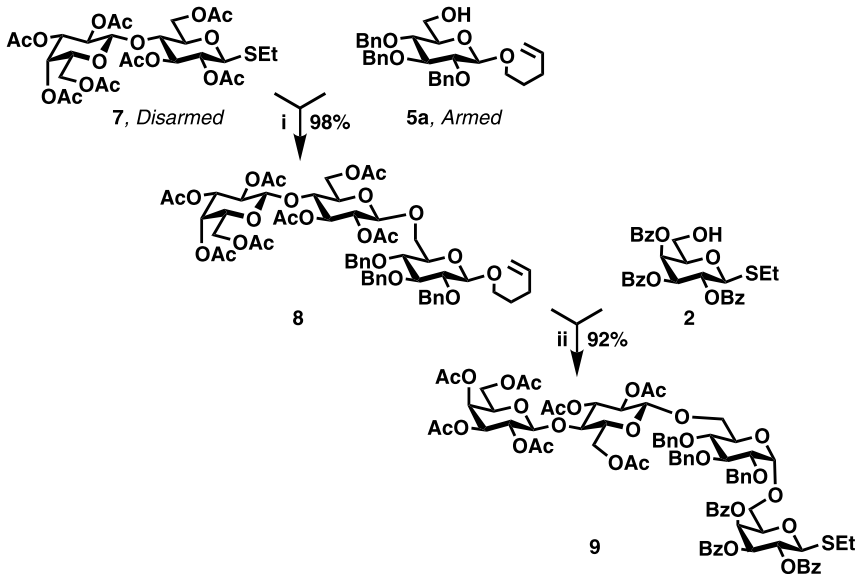
Combination of two chemically distinct glycosylation reactions, in which one of the leaving groups is activated while the other stays intact and vice versa, has led to the discovery of the orthogonal glycosylation strategy.[21] This unique and virtually one of the most advanced techniques for the oligosaccharides synthesis requires the use of orthogonal glycosyl donors, which can be independently activated in the reaction media, and therefore, at this point is limited to too few examples to become generally applicable.[17] Typically, phenyl thioglycosides are selectively activated over glycosyl fluorides and vice versa.[21]

As a part of a program to develop versatile and stereoselective methods for the oligosaccharide synthesis, we report here a novel semi-orthogonal glycosylation strategy with the use of *S*-ethyl[22,23] and *O*-pentenyl glycosides.[19,24] Both thio and *O*-pentenyl glycosides fulfill the requirements for a modern glycosyl donor (accessibility, high stability toward protecting group manipulations, mild activation conditions) and, therefore, occupy an important niche among the modern glycosylation methods, being especially useful for the oligosaccharide synthesis. Traditionally, these glycosyl donors are activated under similar reaction conditions and therefore, were considered to be unsuitable for the orthogonal synthesis when applied together. Typical electrophilic reagents used for their activation are NIS/TfOH, iodonium(di-γ-collidine)perchlorate (IDCP), or NBS.[6] Indeed, to fulfill the requirements for the orthogonality, each selected leaving group should be unaffected under the conditions used to activate the other.

We performed a number of experiments of selective and chemoselective activation reactions with the use of a number of glycosyl donors. Some of these experiments are summarized in Scheme 2. For example, we established that armed *O*-pentenyl glycoside **1** can be selectively activated over the disarmed ethyl thioglycoside **2** (Eq. (1)), which is presumably attributed to the general chemoselectivity considerations. These glycosylations were effectively promoted by IDCP[25] in the presence of molecular sieves (MS) 4 Å.[26] In this context, selective activation of armed *O*-pentenyl glycosides over the armed ethyl thioglycosides have been previously investigated, however, has failed.[20] Similarly, armed thioglycoside **4a** can be chemoselectively activated in the presence of disarmed pentenyl glycoside **5b** (IDCP). Interestingly, we have shown that armed thioglycoside **4a** can be also activated over armed *O*-pentenyl glycosides in the presence of MeOTf[27] and MS 3 Å in CH_2Cl_2. Most importantly, similar reaction conditions allowed the glycosylation of either armed or disarmed



Scheme 2. *Reagents and conditions*: (i) IDCP, MS 4 Å, toluene–dioxane, 1/3, v/v; (ii) MeOTf, MS 3 Å, CH_2Cl_2.



Scheme 3. *Reagents and conditions*: (i) MeOTf, MS 3 Å, CH_2Cl_2; (ii) IDCP, MS 4 Å, toluene–dioxane, 1/3, v/v.

O-pentenyl glycosides **5a** or **5b** with the disarmed (R = Ac or Bz) ethyl thioglycosides **4b** or **4c**. It should be noted that this result is supported by the evidence of the selective activation of a disarmed thioglycoside (OAc) over a disarmed *O*-pentenyl glycoside (NPhth).[28]

These findings have created the firm basis for the development of a novel efficient route toward the synthesis of complex oligosaccharides. To support the credibility of this statement, we performed the two-step synthesis of a complex linear tetraasaccharide **9** of the core structure β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1→6)-α-D-Gal*p* starting from common building blocks **2**, **5a**, and **7** (Scheme 3). According to the novel approach, the first synthetic step involved selective activation of the fully acetylated (disarmed, glycosyl donor) ethyl thiolactoside **7** in the presence of the pent-4-enyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside **5a** (armed, glycosyl acceptor) to afford the trisaccharide derivative **8** in a high yield of 98%.[29] The latter was coupled with **2** in the 'armed–disarmed' fashion in the presence of IDCP and molecular sieves 4 Å. It is noteworthy that in order to improve the stereochemical outcome, the glycosylation was performed in the toluene–dioxane mixture (1/3 v/v).[30] Indeed, the tetrasaccharide derivative **9** was obtained with complete 1,2-*cis* stereoselectivity in 92% yield. In principle, this synthetic sequence can be repeated if needed, thus, according to the novel strategy, synthesized tetrasaccharide can be explored as a glycosyl donor for 1,2-*trans* glycosylation.

In summary, we demonstrated that even disarmed thioglycosides could be activated with MeOTf in the presence of armed *O*-pentenyl glycosides, which could be subsequently activated with IDCP and so on. This, so-called semi-orthogonal glycosylation approach, allows a flexible synthetic method for the introduction of a 1,2-*trans*-glycosidic linkage prior to 1,2-*cis* glycosylation. As it can be envisaged, two sequential 1,2-*trans* linkages without protecting group manipulations can be also formed via this technique. The advantageous features of this approach have been explored for the convergent synthesis of a tetrasaccharide derivative. Further investigation of the novel glycosylation strategy as well as application for the synthesis of biologically important molecules is on the way.

Acknowledgements

This work was supported by the University of Missouri–St. Louis and 'The Foundation BLANCEFLOR Boncompagni-Ludovisi, née Bildt'

References

1. Varki, A. *Glycobiology* **1993**, *3*, 97–130.
2. Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720.
3. Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science* **2001**, *291*, 2370–2376.
4. Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155–173.
5. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235.
6. Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531.
7. Whitfield, D. M.; Douglas, S. P. *Glycoconjugate J.* **1996**, *13*, 5–17.
8. Boons, G. J. *Contemp. Org. Synth.* **1996**, *3*, 173–200.
9. Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137–2160.
10. Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624.
11. Osborn, H. M. I.; Khan, T. H. *Tetrahedron* **1999**, *55*, 1807–1850.
12. Kochetkov, N. K. *Uspekhi Khim.* **2000**, *69*, 869–896.
13. Seeberger, P. H.; Haase, W. C. *Chem. Rev.* **2000**, *100*, 4349–4393.

14. Krepinsky, J. J.; Douglas, S. P. In *Carbohydrates in Chemistry and Biology*; Ernst, B.; Hart, G. W.; Sinay, P., Eds.; Wiley-VCH: New York, 2000; Vol. 1, pp. 239–265.
15. Imberty, A.; Perez, S. *Chem. Rev.* **2000**, *100*, 4567–4588.
16. Boons, G. J. *Tetrahedron* **1996**, *52*, 1095–1121.
17. Kanie, O. In *Carbohydrates in Chemistry and Biology*; Ernst, B.; Hart, G. W.; Sinay, P., Eds.; Wiley-VCH: New York, 2000; Vol. 1, pp. 407–426.
18. Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583–5584.
19. Fraser-Reid, B.; Udodong, U. E.; Wu, Z. F.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927–942 and references cited therein.
20. Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275–278.
21. Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073–12074.
22. Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179–205.
23. Oscarson, S. In *Carbohydrates in Chemistry and Biology*; Ernst, B.; Hart, G. W.; Sinay, P., Eds.; Wiley-VCH: New York, 2000; Vol. 1, pp. 93–116.
24. Fraser-Reid, B.; Anilkumar, G.; Gilbert, M. B.; Joshi, S.; Kraehmer, R. In *Carbohydrates in Chemistry and Biology*; Ernst, B.; Hart, G. W.; Sinay, P., Eds.; Wiley-VCH: New York, 2000; Vol. 1, pp. 135–154.
25. Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190–2198.
26. Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *J. Chem. Soc., Chem. Commun.* **1988**, 823–825.
27. Lonn, H. *Carbohydr. Res.* **1985**, *139*, 105–113.
28. Demchenko, A.; Boons, G. J. *Tetrahedron Lett.* **1997**, *38*, 1629–1632.
29. Major building blocks were obtained as follows. Ethyl thiolactoside **7** was obtained from the corresponding octaactetate and ethane thiol in the presence of $BF_3{\cdot}Et_2O$. The 6-hydroxyl derivatives of glucose **5a**,**b** and galactose **2** were obtained from the corresponding fully acetylated glycosides via sequential deacetylation (MeONa/MeOH), triphenylmethylation ($TrCl/C_6H_5N$), benzylation (BnBr/NaH/DMF) or benzoylation ($BzCl/C_6H_5N$) followed by acetic hydrolysis ($TFA/CH_2Cl_2/H_2O$ 20/78/2 v/v/v) without purification of the intermediates. Full experimental details of their synthesis will be published elsewhere.
Typical MeOTf-promoted glycosylation procedure: A mixture the glycosyl donor (0.22 mmol), glycosyl acceptor (0.20 mmol), and freshly activated molecular sieves (3 Å, 300 mg) in DCM (2 mL) was stirred for 2 h under an atmosphere of argon. MeOTf (0.66 mmol) was added and the reaction mixture was stirred for 2–24 h at room temperature; then Et_3N (1 mL) was added, mixture was diluted with CH_2Cl_2 (30 mL), the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate was washed with water, the organic phase was separated, dried, filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography.
Typical IDCP-promoted glycosylation procedure: A mixture the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 100 mg) in toluene–dioxane (4 mL) was stirred for 1.5 h under an atmosphere of argon. IDCP (0.22 mmol) was added and the reaction mixture was stirred for 24 h at room temperature; then mixture was diluted with CH_2Cl_2, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate was washed with 20% aq. $Na_2S_2O_3$ and water, the organic phase was separated, dried, filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography. All synthesized compounds have adequate ^1H, ^{13}C NMR, and HRMS data.
Selected analytical data: Compound **8**: ^{13}C NMR: 103.52, 101.11, 100.52 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{58}H_{72}NaO_{23}$: 1159.4362, found: 1159.4360. Compound **9**: ^{13}C NMR: 101.03, 100.82, 97.28, 83.91 ppm; HR-FAB MS $[M+Na]^+$ calcd for $C_{82}H_{90}NaO_{30}S$: 1609.5135, found: 1609.5140.
30. Demchenko, A.; Stauch, T.; Boons, G. J. *Synlett* **1997**, 818–820.