Fast and Efficient Preparation of an α-Fucosyl Building Block by Reductive 1,2-Benzylidene Ring-Opening Reaction

Daniel B. Werz,* Heiko J. Schuster, Lutz F. Tietze

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstraße 2, 37077 Göttingen, Germany
Fax +49(551)399476; E-mail: dwerz@gwdg.de

Received 8 May 2008

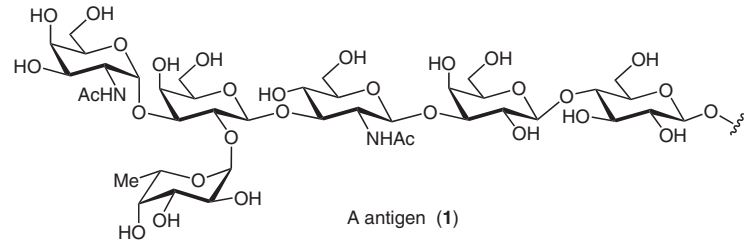
Abstract: 1,2-Benzylidene ring opening on fucose was promoted in the presence of different reducing agents and Lewis acids, providing a fast access to fucosyl building blocks.

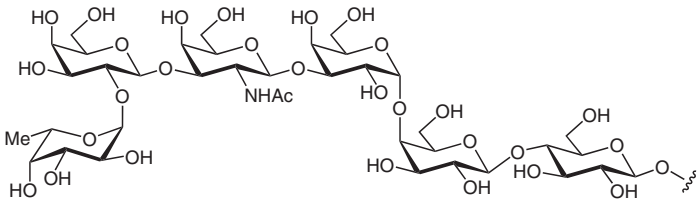
Key words: carbohydrates, fucose, building block, protecting group, benzylidene

Fucosylated oligosaccharides are crucial for a variety of biological processes including tissue development, angiogenesis, fertilization, inflammation, cell adhesion, and tumor metastasis.[1] Among fucosylated carbohydrates, Lewis X and Lewis Y,[2] the ABH-antigens,[3] and Globo-H[4] are the most prominent structures from the biological as well as the synthetic point of view. Figure 1 depicts two examples of fucose-containing oligosaccharides such as the A antigen (**1**),[3] being responsible for blood group A, and the tumor-associated antigen Globo-H (**2**).[4] But also antitumor agents such as the camptothecine derivative[5] (**3**) contain a fucosyl moiety. It is known that abnormal fucosylation occurs in many diseases[1] and recently it was shown that Gal-Fuc derivatives play also an important role in the nervous system.[6]

The fucosyl motif is found to be one of the most redundant monosaccharide units for the termination of mammalian oligosaccharides at their non-reducing end.[7] Commonly, it is linked by an α-glycosidic bond to the adjacent monosaccharide moiety (cf. Figure 1).[7]

To create such a linkage one cannot rely on neighboring-group participation at the C-2 hydroxyl due to the *cis* arrangement of the two C–O bonds. Thus, an efficient α-fucosyl building block requires a non-participating group such as a benzyl (Bn) ether at the C-2 hydroxyl. Recent studies have shown that ester groups such as pivaloyl (Piv) or benzoyl (Bz) at the C-4 hydroxyl increase the α/β selectivity during the glycosylation reaction.[8] It is assumed that the ester functionality acts as a remote participating group when the oxocarbenium intermediate is formed and the attack of the nucleophile occurs only from the upper (α) face (Figure 2).[8] To generate such a protecting-group pattern with an ester functionality in position 4 and an ether moiety in position 2 several synthetic routes have been developed.[9] However, all of them are quite lengthy and require at least seven steps starting from unprotected L-fucose.





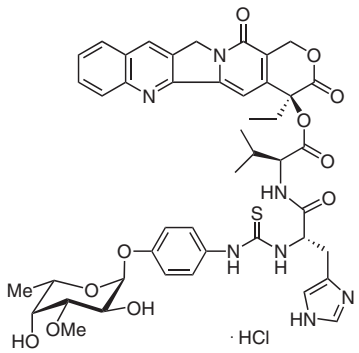


Figure 1 Fucose-containing antigens such as the blood-group-A antigen and the breast-cancer-associated antigen Globo-H; a fucosylated camptothecine derivative that is an excellent antitumor agent is also shown

SYNLETT 2008, No. 13, pp 1969–1972
Advanced online publication: 15.07.2008
DOI: 10.1055/s-2008-1077961; Art ID: G16308ST

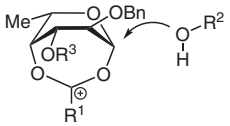


Figure 2 α-Selectivity in fucosylation by remote participation

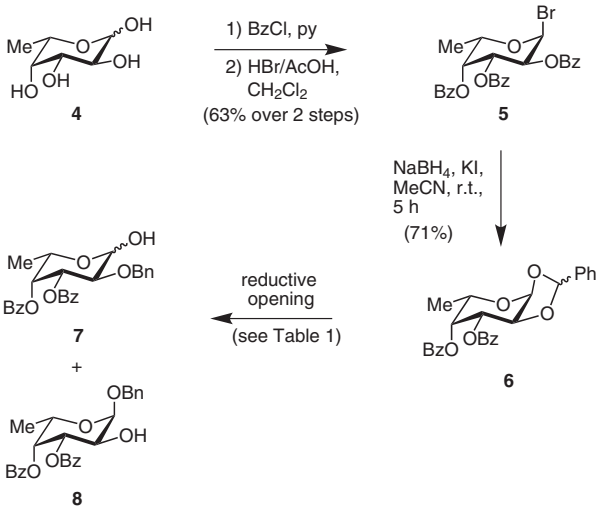
Recent investigations of 1,2-*O*-benzylidene hexopyranoses have shown that this group has the potential for a carbohydrate protecting group that can be reductively ring-opened in a regioselective manner to afford either 1-O- or 2-O-substituted monosaccharide units.[10,11] Whereas the behavior of 4,6-benzylidene acetals in reductive ring-opening reactions is known since decades and has been used as one of the most frequent manipulations for the syntheses of carbohydrate building-blocks,[12] the nature of the analogous 1,2-benzylidenes is not well investigated. In the cases described so far, the regioselectivity of the reductive ring opening strongly depends on the reducing agent, the Lewis acid that is used to activate the system, the solvent, and the reaction temperature.[10,11] However, in some cases good regioselectivities could be achieved.

Encouraged by these results, we investigated the reductive ring-opening reaction of 1,2-benzylidene fucopyranose in order to design a short and efficient access to α-fucosyl building blocks.

The 1,2-benzylidene group can be constructed in several ways, either by acetal-exchange reactions of the corresponding isopropylidene[13] or orthoester[14] derivatives under acidic conditions or by reaction of a glycosyl halide with an adjacent *trans*-configured benzoate under reductive conditions.[15] Of course, for the construction of 1,2-benzylidene fucose the latter method is the best choice.

Extensive benzoylation of the unprotected fucose **4** in the presence of pyridine afforded the tetra-*O*-benzoylfucose which can be easily converted into the corresponding bromide **5** by the action of hydrobromic acid in acetic acid.[16] The benzylidene acetal formation to afford **6** was accomplished in 71% yield using $NaBH_4$ as reducing agent in the presence of KI with acetonitrile as solvent.[17] The use of KI in the reaction is necessary to allow an isomerization of the anomerically favored α-bromide **5** that is unfavorable for the course of the transformation. Thus, reaction of α-bromide with the iodide affords the β-iodide that is prone to be substituted by the *trans*-orientated benzoate (Scheme 1).

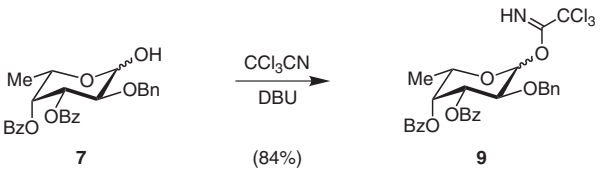
With 1,2-benzylidene acetal **6** in hand, we attempted several procedures for a selective ring opening under reductive conditions to afford either the 2-O-benzylated fucose hemiacetal **7** or the 1-O-benzylated fucose **8** (Table 1) When Et_3SiH was used as reducing agent in the presence of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) in dichloromethane at 0 °C to room temperature fucose derivative **8** was obtained as the major product (82%). The use of DIBAL-H in dichloromethane



Scheme 1 Access to the hemiacetal of fucose with the appropriate protecting-group pattern via reductive 1,2-benzylidene ring opening

also yielded **8** as the major product (44%); however, several further side products were observed. With the mild reducing agent $NaBH(OAc)_3$ in acetonitrile no conversion was found. The best results in favor of the desired fucose **7** were obtained using BH_3·THF complex. A variety of different conditions was tested using this system. The use of BH_3·THF (1.5 equiv) in THF as solvent and a catalytic amount (0.15 equiv) of the Lewis acid Bu_2BOTf afforded the highest amount of isomer **7** (45%) together with **8** (43%) which could easily be separated by column chromatography on silica gel.[18] Dichloromethane as solvent showed a slight preference for isomer **8**. With decreasing temperature the regioselectivity of the ring opening could not be increased, but the total yields became smaller. A larger amount of Lewis acid did result in significant loss of the benzylidene moiety leading to the 1,2-diol. In THF also polymerization of the solvent was observed when using a high concentration (2.0 equiv) of Bu_2BOTf. The use of the more bulky Lewis acid $PhBCl_2$ gave similar results in comparison with Bu_2BOTf. Finally, we tested silica gel as Lewis acid, but no conversion at all was observed. With use of 1,2-bis(trimethylsiloxy)benzene and BF_3·OEt_2 we envisioned the formation of a chelating bifunctional Lewis acid system being more selective. However, the reaction resulted in a complex mixture.

The 2-O-benzylated fucose hemiacetal **7** was converted to building block **9** suitable for oligosaccharide synthesis. Using conditions reported by Schmidt[19] compound **7** was reacted with trichloroacetonitrile and catalytic amounts of DBU to yield the corresponding trichloroacetimidate **9**



Scheme 2 Transformation of the fucose hemiacetal **7** into the fucosyl trichloroacetimidate **9**

Table 1 Different Conditions Tested for the Reductive Ring-Opening Reaction of 1,2-Benzylidene Fucose **6** into **7** and **8**[a]

Entry	Conditions	Temp (°C)	**7** (%)	**8** (%)
1	Et_3SiH, TFA, TFAA, CH_2Cl_2	0 to 25	11	82
2	DIBAL-H, CH_2Cl_2	0	10	44
3	$NaBH(OAc)_3$, MeCN	25	no conversion	
4	BH_3·THF, Bu_2BOTf, THF	–30	16	30
5	BH_3·THF, Bu_2BOTf, THF	0	33	38
6	BH_3·THF, Bu_2BOTf, THF	25	45	43
7	BH_3·THF, Bu_2BOTf, CH_2Cl_2	0 to 25	44	46
8	BH_3·THF, Bu_2BOTf, CH_2Cl_2	25	42	47
9	BH_3·THF, TMSOTf, CH_2Cl_2	25	35	38
10	BH_3·THF, $PhBCl_2$, CH_2Cl_2	0	39	41
11	BH_3·THF, $PhBCl_2$, CH_2Cl_2	25	41	43
12	BH_3·THF, SiO_2, CH_2Cl_2	25	no conversion	
13	BH_3·THF, BF_3·OEt_2, 1,2-bis-(trimethylsiloxy)benzene, CH_2Cl_2	0 to 25	complex mixture	

[a] Isolated yields.

(Scheme 2).[20] Recent investigations have already shown that this fucosyl trichloroacetimidate is a useful building block for oligosaccharide assembly.[21]

In conclusion, we present a fast and efficient protocol for the preparation of α-fucosyl building blocks in only five steps. The key step is a reductive 1,2-benzylidene ring-opening reaction, rendering this route shorter than the common syntheses of fucosyl building blocks.

Acknowledgment

We thank the Deutsche Forschungsgemeinschaft (Emmy Noether Fellowship to D.B.W.) and the Fonds der Chemischen Industrie (Liebig Fellowship to D.B.W.) for financial support. H.J.S. thanks the Friedrich-Ebert-Stiftung for a Ph.D. fellowship.

References and Notes

(1) (a) Ma, B.; Simala-Grant, J. L.; Taylor, D. E. *Glycobiology* **2006**, *16*, 158R. (b) Sharon, N.; Lis, H. *Science* **1989**, *246*, 227.

(2) (a) Watkins, W. M. *Trends Glycosci. Glycotechnol.* **1999**, *11*, 391. (b) Hakomori, S.; Zhang, Y. *Chem. Biol.* **1997**, *4*, 97. (c) Brocke, C.; Kunz, H. *Bioorg. Med. Chem.* **2002**, *10*, 3085. (d) Deshpande, P. P.; Danishefsky, S. J. *Nature (London)* **1997**, *387*, 164. (e) Love, K. R.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2004**, *43*, 602.

(3) Watkins, W. M.; Morgan, W. J. M. *Vox Sang.* **1955**, *5*, 1.

(4) (a) Clausen, H.; Levery, S. B.; Kannagi, R.; Hakomori, S. *J. Biol. Chem.* **1986**, *261*, 1380. (b) Lassaletta, J. M.; Schmidt, R. R. *Liebigs Ann.* **1996**, 1417. (c) Zhu, T.; Boons, G.-J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3495. (d) Allen, J. R.; Allen, J. G.; Zhang, X. F.; Williams, L. J.; Zatorski, A.; Ragupathi, G.; Livingston, P. O.; Danishefsky, S. J. *Chem. Eur. J.* **2000**, *6*, 1366. (e) Burkhart, F.; Zhang, Z.; Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1274. (f) Werz, D. B.; Castagner, B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2007**, *129*, 2770.

(5) Lerchen, H. G.; Baumgarten, J.; von dem Bruch, K.; Lehmann, T. E.; Sperzel, M.; Kempka, G.; Fiebig, H.-H. *J. Med. Chem.* **2001**, *44*, 4186.

(6) Kalovidouris, S.; Gama, C.; Lee, L.; Hsieh-Wilson, L. C. *J. Am. Chem. Soc.* **2005**, *127*, 1340.

(7) Werz, D. B.; Ranzinger, R.; Herget, S.; Adibekian, A.; von der Lieth, C.-W.; Seeberger, P. H. *ACS Chem. Biol.* **2007**, *2*, 685.

(8) (a) Demchenko, A. V.; Rousson, E.; Boons, G.-J. *Tetrahedron Lett.* **1999**, *40*, 6523. (b) Gerbst, A. G.; Ustuzhanina, N. E.; Grachev, A. A.; Khatuntseva, E. A.; Tsvetkov, D. E.; Whitfield, D. M.; Berces, A.; Nifantiev, N. E. *J. Carbohydr. Chem.* **2001**, *20*, 821.

(9) (a) Windmüller, R. *Diplomarbeit*; Universität Konstanz: Germany, **1990**. (b) Windmüller, R.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *35*, 7927. (c) Rencoursi, A.; Poletti, L.; Russo, G.; Lay, L. *Eur. J. Org. Chem.* **2003**, 1672. (d) Love, K. R.; Andrade, R. B.; Seeberger, P. H. *J. Org. Chem.* **2001**, *66*, 8165.

(10) (a) Suzuki, K.; Nonaka, H.; Yamaura, M. *Tetrahedron Lett.* **2003**, *44*, 1975. (b) Suzuki, K.; Nonaka, H.; Yamaura, M. *J. Carbohydr. Chem.* **2004**, *23*, 253.

(11) Sakagami, M.; Hamana, H. *Tetrahedron Lett.* **2000**, *41*, 5547.

(12) (a) Liptak, A.; Imure, J.; Harangi, J.; Nanasi, P. *Tetrahedron* **1982**, *38*, 3721. (b) Galas, J. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 71. (c) Garreg, P. J. *Pure Appl. Chem.* **1984**, *56*, 845. (d) Garreg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97. (e) Oikawa, M.; Liu, W. C.; Nakai, Y.; Koshida, S.; Fukase, K.; Kusumoto, S. *Synlett* **1996**, 1179. (f) Jiang, L.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 355.

(13) Ress, R. G.; Tatchell, A. R.; Wells, R. D. *J. Chem. Soc. C* **1967**, 1768.

(14) Dick, W. E. Jr.; Weisleder, D.; Hodge, J. E. *Carbohydr. Res.* **1972**, *23*, 229.

(15) Suzuki, K.; Mizuta, T.; Yamaura, M. *J. Carbohydr. Chem.* **2003**, *22*, 143.
(16) Ichikawa, Y.; Sim, M. M.; Wong, C.-H. *J. Org. Chem.* **1992**, *57*, 2943.
(17) **3,4-Di-*O*-benzoyl-1,2-*O*-benzylidene-α-L-fucopyranose (6)**
To a stirred solution of fucosyl bromide **5** (16.9 g, 31.3 mmol, 1.00 equiv) in abs. MeCN (106 mL) was added dry KI (7.46 g, 44.9 mmol, 1.43 equiv) and $NaBH_4$ (1.13 g, 29.9 mmol, 0.96 equiv). The mixture was stirred for 2.5 h. Then more $NaBH_4$ (1.13 g, 29.9 mmol, 0.96 equiv) was added. After a total reaction time of 5 h, the solvent was removed. The residue was dissolved in EtOAc, washed with ice water, cold sat. $NaHCO_3$ solution, and twice with brine. The mixture was dried (Na_2SO_4), concentrated, and the residue purified by column chromatography (SiO_2; pentane–EtOAc, 5:1) to afford 10.2 g (71%) of **6** as a colorless foam.
Analytical Data of the *exo*-Product
IR (KBr): 2985, 1727, 1602, 1452, 1280 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 6.2 Hz, 3 H), 4.51 (dd, *J* = 6.9, 5.2 Hz, 1 H), 4.53 (m, 1 H), 5.51 (dd, *J* = 6.8, 3.5 Hz, 1 H), 5.64 (dd, *J* = 3.4, 1.6 Hz, 1 H), 5.91 (d, *J* = 5.1 Hz, 1 H), 6.04 (s, 1 H), 7.31–7.65 (m, 11 H), 7.93 (m, 2 H), 8.03 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 67.8, 69.5, 71.9, 72.9, 98.8, 101.9, 126.3, 128.2, 128.6, 129.4, 129.6, 129.7, 133.2, 133.4, 137.7, 165.6, 165.7. ESI-HRMS: *m/z* calcd for $C_{27}H_{24}O_7Na$: 483.14142; found: 483.14160.
(18) **3,4-Di-*O*-benzoyl-2-*O*-benzyl-α/β-L-fucopyranose (7)**
To a stirred solution of benzylidene fucose **6** (161 mg, 0.35 mmol, 1.0 equiv) in abs. THF (2 mL) BH_3·THF (0.53 mL, 0.53 mmol, 1.5 equiv) was added at r.t., then Bu_2BOTf (52 μL, 0.053 mmol, 0.15 equiv). The mixture was stirred for 1–2 h. Water was added and the reaction mixture was extracted with EtOAc. The organic phase was dried (Na_2SO_4), concentrated, and the residue purified by column chromatography (SiO_2; pentane–EtOAc, 3:1 to 2:1) to afford 72 mg (45%) of **7** and 70 mg (43%) of **8** as a colorless foam. The two products were easily separable (**7** is much more polar than **8**).
Analytical Data of the Anomeric Mixture (1:1) of 7
IR (film): 3434, 2936, 1726, 1602, 1453, 1283 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.1 Hz, 3 H), 1.27 (d, *J* = 6.1 Hz, 3 H), 3.38 (br s, 1 H), 3.84 (m, 2 H), 3.98 (q, *J* = 6.1 Hz, 1 H), 4.11 (dd, *J* = 7.4, 3.3 Hz, 1 H), 4.55 (q, *J* = 6.1 Hz, 1 H), 4.72 (d, *J* = 7.4 Hz, 1 H), 4.86 (d, *J* = 7.4 Hz, 1 H), 4.90 (m, 1 H), 5.39 (dd, *J* = 7.4, 3.3 Hz, 1 H), 5.43 (m, 1 H), 5.58 (m, 1 H), 5.64 (m, 1 H), 5.75 (dd, *J* = 7.4, 3.3 Hz, 1 H), 7.11–7.37 (m, 14 H), 7.40–7.55 (m, 6 H), 7.60 (m, 2 H), 7.81 (m, 4 H), 7.99 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1, 16.3, 65.1, 69.5, 70.5, 71.5, 72.3, 73.1, 73.7, 74.6, 77.4, 91.7, 97.5, 127.6, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4, 128.5, 129.6, 129.7, 129.8, 129.9, 133.0, 133.0, 133.2, 133.3, 137.3, 137.8, 165.6, 165.9, 165.9. ESI-HRMS: *m/z* calcd for $C_{27}H_{26}O_7Na$: 485.15707; found: 485.15705.
(19) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.
(20) **Analytical Data of the α-Anomer**
$[\alpha]_D^{20}$ –148.4 (*c* 1.90, $CDCl_3$). IR (film): 2943, 2867, 1733, 1672, 1464, 1278 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.1 Hz, 3 H), 4.29 (dd, *J* = 7.8, 3.4 Hz, 1 H), 4.55 (m, 1 H), 4.61 (d, *J* = 7.8 Hz, 1 H), 4.69 (d, *J* = 7.8 Hz, 1 H), 4.75–5.81 (m, 2 H), 6.68 (d, *J* = 3.4 Hz, 1 H), 7.23–7.33 (m, 7 H), 7.43–7.49 (m, 3 H), 7.62 (m, 1 H), 7.80 (m, 2 H), 7.94 (m, 2 H), 8.66 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2, 67.8, 70.3, 71.7, 72.3, 72.6, 91.2, 94.5, 127.8, 127.9, 127.9, 128.0, 128.2, 128.3, 128.5, 129.4, 129.5, 129.6, 129.7, 133.0, 133.3, 137.4, 161.4, 165.5, 165.7. ESI-HRMS: *m/z* calcd for $C_{29}H_{26}Cl_3NO_7Na$: 628.06725; found: 628.06734.
(21) Gerbst, A. G.; Grachev, A. A.; Ustyuzhanina, N. E.; Khatuntseva, E. A.; Tsvetkov, D. E.; Usov, A. I.; Shaskov, A. S.; Preobrazhenskaya, M. E.; Ushakova, N. A.; Nifantiev, N. E. *Russ. J. Bioorg. Chem.* **2004**, *30*, 137.