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First preparative synthesis of a 3-acetamido-3,6-dideoxy-D-galactopyranose glycosyl donor via intramolecular cyclization of an epoxytrichloroacetimidate

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Abstract—The preparative synthesis of a 3-acetamido-3,6-dideoxy-D-galactopyranose *N*-phenyl-trifluoroacetimidate donor has been accomplished using as key step a silica gel mediated cyclization of an epoxytrichloroacetimidate, while other more conventional routes to aminosugars failed. Test glycosylations with the *N*-phenyl-trifluoroacetimidate donor are also reported.

3-Acetamido-3,6-dideoxy-D-galactopyranose (D-Fuc*p*3NAc) is a sugar frequently found in the *O*-antigen moiety of lipopolysaccharides (LPS)[1] extracted almost exclusively from phytopathogenic Gram-negative bacteria.[2] The synthesis of several unusual aminodeoxyhexoses and some related oligosaccharides has already been accomplished,[3] as some of them are important constituents of various antibiotics[4] and play important biological roles. In contrast, the biological role of D-Fuc*p*3NAc has not yet been clearly elucidated, despite its wide distribution in nature.

Therefore, the synthesis of a suitable D-Fuc*p*3NAc building-block and its incorporation in biologically important oligosaccharide sequences would be useful for the purpose. Actually, the only to date reported synthesis of L-Fuc*p*3NAc, as a methyl glycoside,[5] is not practical for a preparative purpose, the overall yield being modest and the product obtained being in an unsuitable form for incorporation into more complex oligosaccharides. Therefore, a preparative new procedure for the synthesis of D-Fuc*p*3NAc donors was mandatory.

In an initial attempt, we planned a synthetic strategy from commercially available D-fucose entailing the conversion of the 3-OH group to an amino functionality via an S_N2 displacement of a triflate with sodium azide. Therefore the first steps of the synthesis required the regioselective protection of D-fucose to obtain a free alcoholic function exclusively on position 3 (Scheme 1). We firstly protected the anomeric position with an ethyl group by a sequence of reactions (Fischer glycosylation, acetylation, α-anomerization with $FeCl_3$;[6] 56% over three steps) that assured the enrichment of the anomeric mixture with the α-anomer **1**. This triacetylated compound was then deacylated under Zemplèn conditions (87%) to yield triol **2** that was then subjected to a one-pot sequence of three reactions (orthoesterification, allylation and orthoester regioselective opening; 51% over three steps) to afford the alcohol **3**. A direct displacement of the triflated derivative of **3** with sodium azide would give an azido-sugar with a configuration at C-3 opposite to that desired; therefore, alcohol **3** was epimerized in two steps by oxidation with DMSO/Ac_2O[7] and subsequent reduction of the ketone **4**. This sequence afforded alcohol **5** in 55% yield with excellent stereoselectivity, reasonably due to the steric hindrance of the axial ethyl group at the anomeric position.

Deoxygulose alcohol **5** was then converted into the corresponding triflated derivative that unfortunately did not afford the desired azidosugar **6** when treated with

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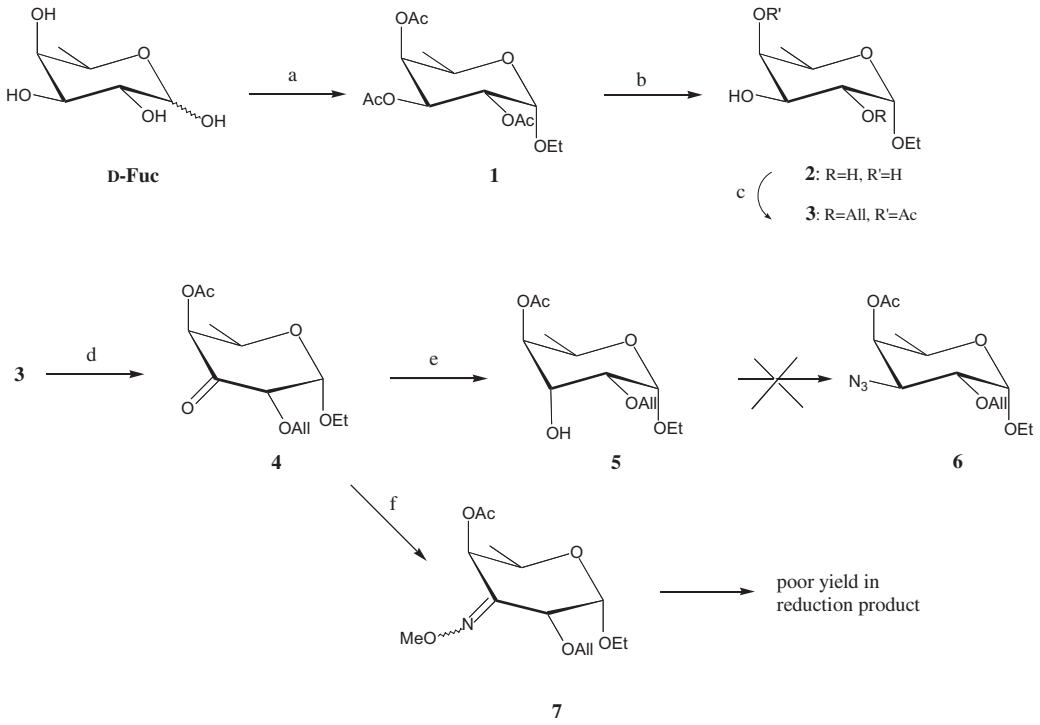


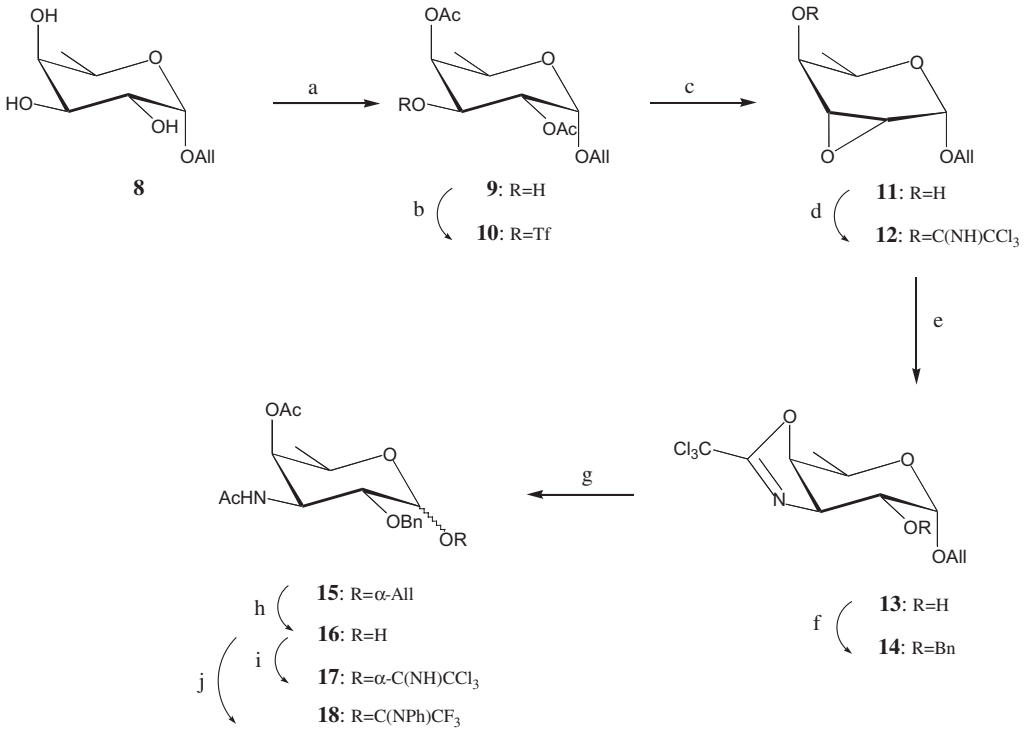
Scheme 1. Reagents and conditions: (a) (i) EtOH, Amberlist-15 (H^+), reflux, (ii) Ac_2O, pyridine, rt, (iii) $FeCl_3$, CH_2Cl_2, rt, 56% over three steps; (b) NaOMe, MeOH, rt, 87%; (c) (i) trimethyl-orthoacetate, CSA, DMF, 40 °C, (ii) NaH, AllBr, rt, (iii) 80% AcOH, rt, 51% over three steps; (d) 2:1 DMSO/Ac_2O, rt; (e) $NaBH_4$, 9:1 THF/MeOH, 0 °C, 55% over two steps from **3**; (f) $NH_2OMe{\cdot}HCl$, 64% over two steps from **3**.

sodium azide in DMF. Indeed, the reaction produced a complex mixture with predominant amounts of elimination products. Every attempt to achieve the predominance of the substitution process over elimination using crown-ethers and/or different solvents (DMSO, toluene) failed. Actually, difficulties in nucleophilic displacements of 3-OTf-gulose derivatives have been recently reported,[8,9] and they have been solved by using a 4,6-*O*-benzylidene ring[8] and/or a 2-*O*-acyl protecting group.[9] Both methods minimize elimination reactions, nevertheless they were unfortunately considered to be not very useful for our scope, due to the impossible installation of a 4,6-*O*-benzylidene on a 6-deoxysugar and the necessity of avoiding the use of 2-*O*-acyl protecting group in the synthesis of a D-Fuc*p*3NAc donor to be used for α-glycosidations (see below).

Thus, we decided to insert the amino functionality on C_3 by oxime reduction:[10] ketone **4** was transformed in its *O*-methyloxime derivative **7** by treatment with $NH_2OMe{\cdot}HCl$ (64% over two steps from **3**), but the subsequent reduction of **7** with either $BH_3{\cdot}THF$ or $LiAlH_4$ gave a complex mixture with only a small amount of the desired compound.

Since the most conventional strategies for converting a saccharidic alcohol to an amino group were uneffective on our compounds, we envisioned a different synthetic approach, based on the electrophile-induced cyclization of an epoxytrichloroacetimidate to a (trichloromethyl)oxazoline. In carbohydrate chemistry (trichloromethyl)oxazoline derivatives have already been used: their formation is usually accomplished by electrophile-induced cyclization of allylic trichloroacetimidate[11] or by intramolecular nucleophilic displacement of bis(trichloroacetimidate),[12] whereas here we report this achievement by an intramolecular cyclization of 2,3-epoxytrichloroacetimidates.

Starting from allyl α-D-fucopyranoside **8** (Scheme 2), readily available from D-galactose,[13] alcohol **9** was initially prepared by a one-pot sequence of three reactions (orthoesterification, acetylation and orthoester regioselective opening; 58% yield over three steps). Conversion of **9** into the corresponding triflate **10** and subsequent exposure to Zemplèn deacylation conditions, afforded, with high regio and stereoselectivity, the epoxyalcohol **11** that was in turn directly converted to the epoxytrichloroacetimidate **12** with trichloroacetonitrile and catalytic DBU. The intramolecular cyclization of 2,3-epoxytrichloroacetimidates to (trichloromethyl)oxazolines has been already applied on open-chain compounds,[14] whereas its application to cyclic saccharidic-like compounds is so far restricted to a single example.[15] Its mechanism requires the catalysis of Lewis acids (Et_2AlCl,[14a] $BF_3{\cdot}OEt_2$,[14b] $SnCl_4$,[14b] Et_3Al,[14c,15] $CoCl_2$[16]), most of which are quite poisonous and moisture sensitive; in contrast, the cyclization of the epoxytrichloroacetimidate **12** was simply performed by adsorption on silica gel at 45 °C and subsequent chromatography. It is also worthy of note that in the previously reported procedures the chromatographic purification of the intermediates is required. In this case the oxazoline **13** was instead obtained in a 64% yield over four steps from the

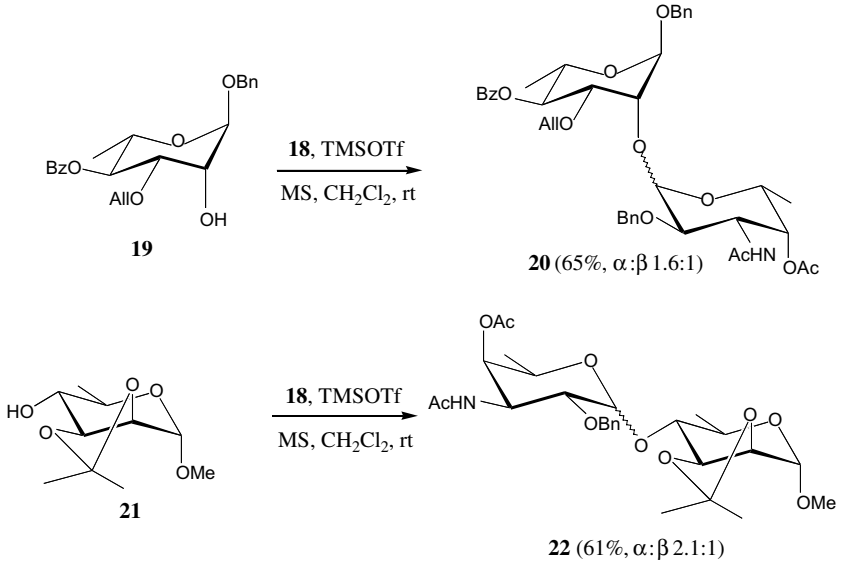


Scheme 2. Reagents and conditions: (a) (i) trimethyl-orthoacetate, CSA, DMF, 40 °C, (ii) Ac_2O, pyridine, rt, (iii) AcOH 80%, rt, 58% over three steps; (b) Tf_2O, 1:1 CH_2Cl_2/py, 0 °C; (c) NaOMe, MeOH, rt; (d) Cl_3CCN, DBU, CH_2Cl_2, 0 °C; (e) silica gel (0.063–0.200 mm), $CHCl_3$, 45 °C, in vacuo, 64% over four steps from **9**; (f) BnBr, NaH, DMF, rt, 68%; (g) (i) 1 M HCl, THF, rt, (ii) Ac_2O, py, rt, 63% over two steps; (h) $PdCl_2$, 1:1 CH_2Cl_2/MeOH, rt, 84% ($\alpha:\beta = 1:1.5$ as determined by ^1H NMR analysis); (i) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 53%; (j) $CF_3C(NPh)CCl$, NaH, molecular sieves 4 Å, CH_2Cl_2, 0 °C, 67% ($\alpha:\beta = 3:1$ as determined by ^1H NMR analysis).

alcohol **9** without any intermediate chromatography,[17] also by means of the excellent regio and stereoselectivity of the whole synthetic sequence.

Since D-Fuc*p*3N occurs in natural oligosaccharides almost exclusively as an α-glycoside, the preparation of its glycosyl donor required the installation of a nonparticipating protecting group at position 2. Moreover, a 4-*O*-acyl group was chosen in designing the most suitable glycosyl donor, as it is supposed to exalt the α-stereoselectivity in glycosidation reactions through a long range participation effect,[18] even though this effect has not been observed in a recent study regarding the coupling of various fucosyl donors with linear alcohols.[19]

Thus, **13** was benzylated to give **14** (68%) that was subsequently subjected to acid hydrolysis of the oxazoline cycle and acetylation to obtain **15** (63% over two



Scheme 3.

steps). Anomeric deallylation with $PdCl_2$ afforded **16** (84%) that was finally converted into two different glycosyl donors, namely trichloroacetimidate **17** (53%) by treatment with Cl_3CCN and DBU and *N*-phenyl-trifluoroacetimidate[20] **18** (67%) by treatment with $CF_3C(NPh)Cl$ and NaH.[21] Since **18** was obtained in a significantly better yield than **17** after chromatographical purification, we decided to test the former compound in two glycosylation reactions.

Coupling **18** with the rhamnosyl acceptors **19**[22] and **21**[23] (Scheme 3) under the agency of TMSOTf gave **20** and **22** in 65% and 61% yield, respectively, and a fairly good α-selectivity. Notably, both **20** and **22** are useful building-blocks for the synthesis of many D-Fuc*p*3NAc containing repeating unit of LPS from phytopathogenic bacteria. Work is in progress in order to further enhance α-selectivity of the couplings; the results will be published at due time.

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References and notes

1. (a) Knirel, Y.; Kochetkov, N. K. *Biochemistry* (*Moscow*) **1994**, *59*, 1325–1383; (b) Jansson, P.-E. In *Endotoxins in Health and Disease*; Brade, H., Opal, S. M., Vogel, S., Morrison, D. C., Eds.; Marcel Dekker: New York, 1999; pp 155–178; (c) Raetz, C. R. H.; Whitfield, C. *Ann. Rev. Biochem.* **2002**, *71*, 535–700.
2. Corsaro, M. M.; De Castro, C.; Molinaro, A.; Parrilli, M. *Recent Res. Dev. Phytochem.* **2001**, *5*, 119–138.
3. Some recent examples: (a) Langner, M.; Laschat, S.; Grunenberg, J. *Eur. J. Org. Chem.* **2003**, 1494–1499; (b) Nicolaou, K. C.; Baran, P. S.; Zhang, Y.-L.; Barluenga, S.; Hunt, W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233–2244; (c) Varga, Z.; Bajza, I.; Batta, G.; Lipták, A. *Tetrahedron Lett.* **2002**, *43*, 3145–3148; (d) Kirkpatrick, P. N.; Scafe, W.; Hallis, T. M.; Liu, H.-W.; Spencer, J. B.; Williams, D. H. *Chem. Commun.* **2000**, 1565–1566; (e) Tsvetkov, Y. E.; Shashkov, A. S.; Knirel, Y.; Backinowsky, L.; Zähringer, U. *Mendeleev Commun.* **2000**, 90–92; (f) Franck-Neumann, M.; Miesch-Gross, L.; Gateau, C. *Tetrahedron Lett.* **1999**, *40*, 2829–2832.
4. Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624.
5. Adinolfi, M.; Barone, G.; Corsaro, M. M.; Lanzetta, R.; Mangoni, L.; Monaco, P. *J. Carbohydr. Chem.* **1995**, *14*, 913–928.
6. Chatterjee, S. K.; Nuhn, P. *Chem. Commun.* **1998**, 1729–1730.
7. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
8. Liakatos, A.; Kiefel, M. J.; von Itzstein, M. *Org. Lett.* **2003**, *5*, 4365–4368.
9. Rich, J. R.; Bundle, D. R. *Org. Lett.* **2004**, *6*, 897–900.
10. Tsuda, Y.; Okuno, Y.; Iwaki, M.; Kanemitsu, K. *Chem. Pharm. Bull.* **1989**, *37*, 2673–2678.
11. (a) Pauls, H. W.; Fraser-Reid, B. *J. Org. Chem.* **1983**, *48*, 1392–1393; (b) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1983**, *39*, 3801–3806.
12. Link, T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552–553.
13. Liu, M.; Yu, B.; Wu, X.; Hui, Y.; Fung, K.-P. *Carbohydr. Res.* **2000**, *329*, 745–754.
14. (a) Hatakeyama, S.; Matsumoto, H.; Fukuyama, H.; Mukugi, Y.; Irie, H. *J. Org. Chem.* **1997**, *62*, 2275–2279; (b) Schmidt, U.; Respondek, M.; Lieberknecht, A.; Werner, J.; Fischer, P. *Synthesis* **1989**, 256–261; (c) Bernet, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *49*, 5491–5494.
15. Schürrle, K.; Beier, B.; Piepersberg, W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2407–2412.
16. Schmidt, U.; Zäh, M.; Lieberknecht, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1002–1004.
17. Compound **13**: A solution of **9** (1.34 g, 4.61 mmol) in 1:1 CH_2Cl_2/pyridine (10 mL) was cooled at 0 °C and then Tf_2O (1.6 mL, 9.7 mmol) was slowly added. The solution was stirred at 0 °C for 40′, after that the solution was diluted with CH_2Cl_2 (300 mL) and washed with 1 M HCl (300 mL), 1 M $NaHCO_3$ (300 mL) and water (300 mL). The organic layer was collected, dried and concentrated to afford an oily residue that was dissolved in 2:1 MeOH/CH_2Cl_2 (21 mL) and treated with a 0.6 M solution of NaOMe in MeOH (12 mL) at rt. After 2 h, the solution was diluted with CH_2Cl_2 (350 mL) and washed with water (350 mL). The organic layer was collected, dried and concentrated to afford an oily residue that was then dissolved in CH_2Cl_2 (13 mL). The solution was cooled at 0 °C and then treated with Cl_3CCN (4.5 mL, 44.8 mmol) and DBU (360 μL, 0.72 mmol). After 60′ under stirring at 0 °C, the solution was concentrated. Silica gel (0.063–0.200 mm) (5.6 g) was then added to the residue, the mixture was suspended in $CHCl_3$ (20 mL) and immediately concentrated in vacuo at 45 °C. After 10′ the solvent was completely evaporated and the solid residue was chromatographed (8:1 petroleum ether/EtOAc) to give **13** (965 mg, 64%) as a yellowish oil. $[\alpha]_D$ +31.7 (*c* 0.7, CH_2Cl_2). ^1H NMR ($CDCl_3$, 200 MHz): δ 5.90 (m, 1H, OCH_2CH=CH_2), 5.28 (dd, 1H, $J_{vic} = 17.2$ Hz, $J_{gem} = 1.6$ Hz, OCH_2CH=CH_2 *trans*), 5.21 (dd, 1H, $J_{vic} = 10.4$ Hz, $J_{gem} = 1.6$ Hz, OCH_2CH=CH_2 *cis*), 4.85 (dd, 1H, $J_{4,3} = 9.8$ Hz, $J_{4,5} = 1.6$ Hz, H_4), 4.76 (d, 1H, $J_{1,2} = 4.4$ Hz, H_1), 4.72 (dd, 1H, $J_{3,4} = 9.8$ Hz, $J_{3,2} = 3.8$ Hz, H_3), 4.40–4.28 (m, 3H, H_2, H_5, OCH_2CH=CH_2), 4.13 (m, 1H, OCH_2CH=CH_2), 3.08 (b s, 1H, OH), 1.29 (d, 3H, $J_{6,5} = 6.6$ Hz, H_6); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 164.2 (*C*=N), 133.8 (OCH_2CH=CH_2), 117.5 (OCH_2CH=CH_2), 94.6 (C_1), 83.5 (C_4), 68.3, 66.9, 65.7, 64.8 (C_2, C_3, C_5, OCH_2CH=CH_2), 15.9 (C_6). ESI-MS for $C_{11}H_{14}Cl_3NO_4$ (*m*/*z*): M_r (calcd) 329.00, M_r (found) 351.88 $(M+Na)^+$.
18. Dejter-Juszynski, M.; Flowers, H. M. *Carbohydr. Res.* **1972**, *23*, 41–45.
19. Vermeer, H. J.; van Dijk, C. M.; Kamerling, J. P.; Vliegenthart, J. F. G. *Eur. J. Org. Chem.* **2001**, 193–203.
20. Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405–2407.
21. Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Tetrahedron Lett.* **2002**, *43*, 5573–5577.
22. Bedini, E.; Barone, G.; Unverzagt, C.; Parrilli, M. *Carbohydr. Res.* **2004**, *339*, 393–400.
23. Zou, W.; Sen, A. K.; Szarek, W.; MacLean, D. B. *Can. J. Chem.* **1993**, *71*, 2194–2200.