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Direct azidation of unprotected carbohydrates under Mitsunobu conditions using hydrazoic acid

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ABSTRACT

A single step procedure for the direct and regioselective synthesis of carbohydrate azides from unprotected sugars using hydrazoic acid under Mitsunobu conditions is reported. A series of mono-, di-, or triazido polyhydroxylated systems are described.

Azides are valuable intermediates in organic chemistry. Usually obtained by the replacement of hydroxyl groups, their chemical stability and their easy reduction make them attractive compounds for obtaining the corresponding amines. Azides have gained even more interest with the discovery of the mild and effective Cu(I)-catalysed 1,3-dipolar Huisgen cycloaddition of azides with alkynes[1] (belonging to 'click' chemistry[2]). This method has been used for the synthesis of a wide range of 1,2,3-triazoles and has also found some promising applications in polymer and material science.[3] In this context, carbohydrates bearing azido functions have emerged as attractive intermediates,[4] bringing to the obtained 'click' adducts their intrinsic properties (biological role, polarity, solubility, biocompatibility, biodegradability, etc.) or for serving as scaffolds in drug discovery studies.[5] Reduction of azido carbohydrates could also give access to new aminoglycosides, an important class of biologically active compounds. In the context of our studies concerning the direct and selective modification of unprotected carbohydrates,[6] we wished to exploit the multifunctionality of carbohydrates as well as their structural diversity for the rapid and efficient production of polyhydroxylated azides of defined structure.

Several methods for the azidation of unprotected carbohydrates have been reported. All are based on the synthesis of halogenated deoxysugars followed by their in situ substitution by azide anions as illustrated by the work of Hanessian et al. who first described the selective azidation of the 6-position of methyl pyranosides using a PPh_3/*N*-bromosuccinimide/NaN_3 system.[7] Later on, the azidation of the anomeric position of carbohydrates in a one-pot procedure was described using similar systems[8] and the direct azidation of mono- or oligosaccharides, using PPh_3/CBr_4 with sodium or lithium azide was also reported.[9,10] Reactions proceeded with good selectivity, but in some cases led to the formation of undesired brominated or anhydro side products arising from an incomplete substitution of intermediates or intramolecular cyclization, respectively.

These limitations led us to envisage an alternative route, exploring the direct azidations of unprotected carbohydrates using hydrazoic acid under Mitsunobu conditions. Hydrazoic acid has been shown to be very reactive under these conditions[11] and the Mitsunobu reactions have indeed been reported as very clean and effective even for the difficult substitution of allylic or homoallylic hydroxyl groups.[12] This approach was extended to the azidation of partially protected carbohydrates[13] and was also employed in nucleoside modification.[14] Moreover, hydrazoic acid (pK_a 4.7) is an ideal candidate for carbohydrate modification since the mild reaction conditions used are compatible with most glycosidic linkages.

Importantly, due to its well-documented toxicity and explosive properties,[15] precise and careful procedures have to be followed to avoid the risks linked to the use of this reagent.[16] Two different procedures were used for producing HN_3. The first was the production

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of a dry HN_3 solution in toluene according to a literature protocol,[17] this solution was then directly used in the Mitsunobu reactions (method A). The second was the direct treatment of an excess of NaN_3 by concentrated H_2SO_4 in DMF, the obtained mixture was dried using sodium sulfate before being added to the carbohydrate solution in DMF and Mitsunobu reactions were directly performed in this medium (method B). According to the literature,[17] a 5% solution is obtained in the case of method A while in method B the concentration of HN_3 is directly related to the amounts of sulfuric acid introduced in the solution. For safety concerns, using both methods, HN_3 concentrations were not evaluated and an excess of HN_3 was used while the stoichiometry of the reactions was controlled by the amounts of PPh_3 and DIAD employed.

The azidation reactions were first performed on four different unprotected nonreducing di- and trisaccharides, namely sucrose (**1**), trehalose (**2**), melezitose (**3**), and raffinose (**4**) (Chart 1). When sucrose (up to 10 g) was treated in DMF overnight with PPh_3 and DIAD in the presence of an excess of hydrazoic acid using method A or method B, the known 6-azido-6-deoxysucrose (**5**) and 6,6′-diazido-6,6′-dideoxysucrose (**6**) were obtained in various ratios (Chart 1).[18] The influence of the amount of the PPh_3/DIAD system was studied (see Table 1, entries 1–5), showing that when 2 equiv of PPh_3/DIAD (compared to sucrose) were used, a 61% isolated yield of azide **5** was reached by taking advantage of the regioselectivity of the reaction for primary hydroxyl groups. Comparatively, the use of diphenylphosphoryl azide (DPPA), a substitute for HN_3, did not give

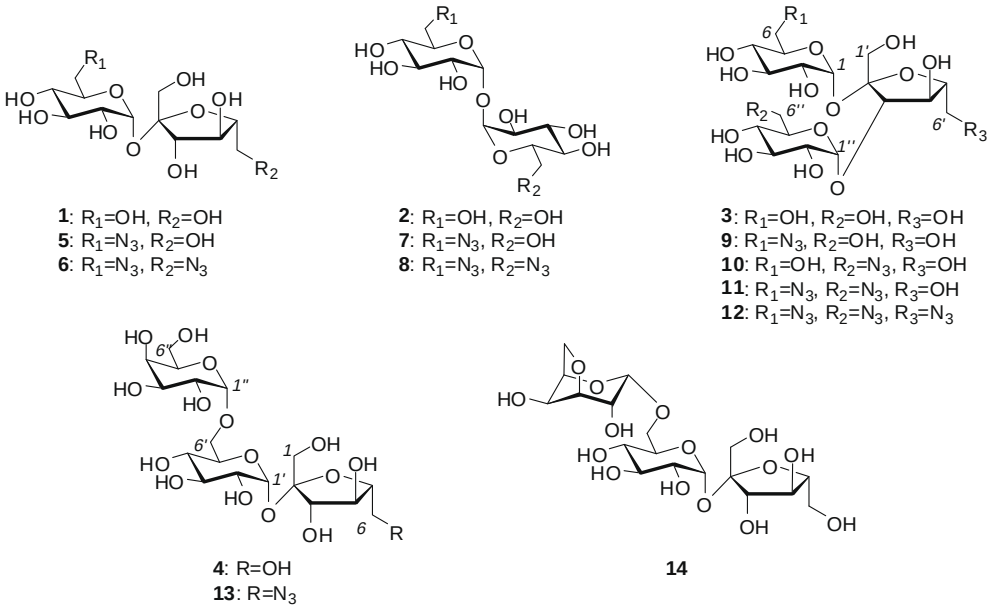

Chart 1. Structures of the nonreducing starting carbohydrates and of the corresponding obtained azides. Reagent and conditions: see Table 1.

Table 1
Azidation of unprotected nonreducing carbohydrates

Entry	Starting carbohydrate	Method[a]	PPh_3/DIAD (equiv)	Products and yields[b] (%)		
	1			**5**	**6**	
1		A	2	61	9	
2		B	2	59	12	
3		A	4	50	49	
4		B	4	55	30	
5		A	10	–	65	
	2			**7**	**8**	
6		A	4	49	16	
7		B	4	30	–	
8		A	10	–	89	
	3			**9**, **10** (**9**:**10**)	**11**	**12**
9		A	2	21 (1:4)	–	–
10		A	4	34 (1:4)	33	8
11		B	4	46 (1:4)	11	–
12		A	10	–	–	61
	4			13	14	
13		A	5.4	7	11	
14		A	10[c]	19	44	
15		A	10[d]		35	

Reagents and conditions: HN_3, DIAD, PPh_3, DMF, 0 °C to rt, 24 h (unless other indications).[19]
[a] A: HN_3 solution in toluene, B: in situ generated HN_3 in DMF, see in the text.
[b] Isolated yields.
[c] Reaction time 76 h.
[d] Reaction time 1 h.

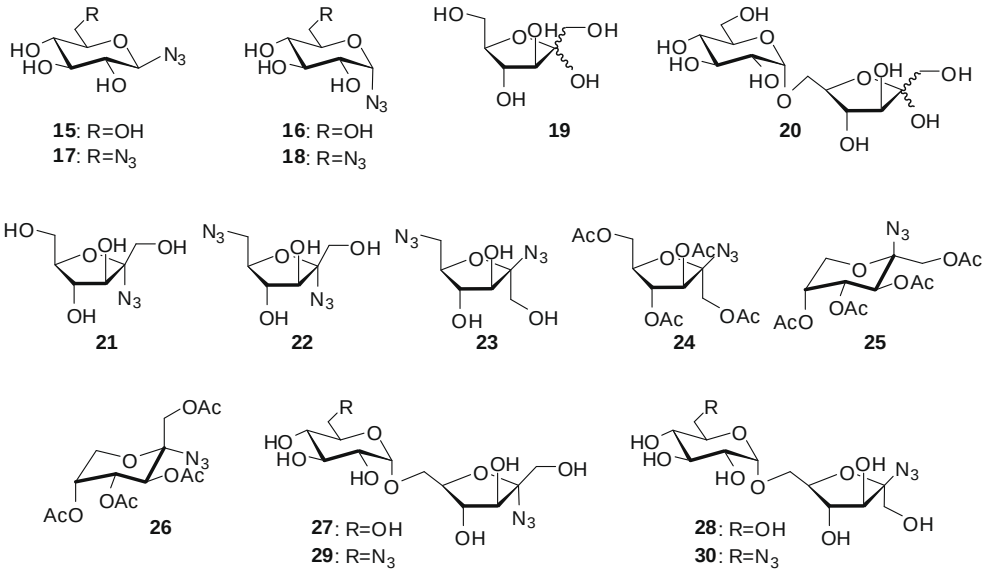

Chart 2. Structures of reducing sugars and of the obtained azides.

satisfactory results, leading to compounds **5** and **6** in only 20% and 5% yields, respectively. The products were also found to be more difficult to purify from side products arising from the use of DPPA. Diazide **6** was obtained as the major compound in 65% yield when 10 equiv of PPh_3/DIAD were used. When compared to previous reports on sucrose azidation,[9] the present method was found to give slightly better yields using a simpler purification protocol.

The same procedure was applied to trehalose (**2**) to furnish efficiently the known monoazide **7**[20] and diazide **8**[21] in maximum isolated yields of 49% and 89%, respectively (Table 1, entries 6–8). The direct azidations of melezitose (**3**) and raffinose (**4**), two commercially available nonreducing trisaccharides containing a sucrose scaffold, were then studied. When melezitose was treated with 2 equiv of PPh_3/DIAD, an inseparable mixture of the two monoazides **9** and **10** was obtained (Table 1, entry 9), in which the primary hydroxyl groups of the glucosyl moieties are transformed with faster reaction rates and the 6″ position reacted faster than the 6 position. Increasing the amounts of PPh_3/DIAD resulted in the formation of diazide **11** and triazide **12**, in up to 61% yield of the latter when 10 equiv was employed (Table 1; entries 10–12). The hydroxyl reactivity order, 6″ > 6 > 6′, is consistent with what was observed for esterification under Mitsunobu conditions.[6] The substitution position were assessed by an upfielded shift of the carbon atoms linked to the azide functions compared to the corresponding carbon shift on the starting carbohydrate.

In the case of raffinose (**4**), 3,6-anhydroraffinose (**14**) was observed as the main product,[6] but the known 6-azido-6-deoxyraffinose[22] (**13**) could be obtained in 35% yield when a tenfold excess of PPh_3/DIAD was used and the reaction was stopped after one hour in order to favor the azidation reaction versus the intramolecular cyclization (Table 1, entry 15).

Once achieved on nonreducing carbohydrates, we wished to extend the study to aldoses and ketoses. As an example of aldose, glucose was studied first. Subjected to the same direct azidation conditions, it gave access to four different known glucosyl mono- and diazides **15**–**18** (Chart 2).[23] The reaction showed a higher reactivity of the anomeric position as well as a stereoselectivity for the formation of β anomers. When performed using 2 equiv of PPh_3/DIAD (Table 2, entry 1) the reaction gave monoazides **15** and **16** in 88% yield. When 4 equiv of PPh_3/DIAD were used, diazides **17** and **18** could be obtained in 91% yield (Table 2, entry 2) and higher amounts of reagents did not promote further increase of the yield.

Table 2
Azidation of glucose

Entry	Starting carbohydrate	Method[a]	PPh_3/DIAD (equiv)	Products and yields[b] (%)	
	Glucose			**15**, **16** (**15**:**16**)	**17**, **18** (**17**:**18**)
1		A	2	88 (5:2)	—
2		A	4	—	91 (3:1)
3		B	4	—	71 (3:1)
4		A	10	—	81 (3:1)

Reagents and conditions: HN_3, DIAD, PPh_3, DMF, 0 °C to rt, 24 h.[19]
[a] A: HN_3 solution in toluene, B: in situ generated HN_3 in DMF, see in the text.
[b] Isolated yields.

During the course of this study, some elegant works focusing on anomeric modifications of unprotected aldoses for the synthesis of β-glycosyl azides were reported;[24,25] we thus concentrated our efforts toward the modification of ketoses. Two sugars were selected for this purpose: fructose (**19**) and isomaltulose (**20**), a readily available disaccharide. Azidation of fructose using method A or B led to complex mixtures of azido carbohydrates and four fractions were isolated after the regular workup and column chromatography. Three fractions contained the new monoazide **21** and diazides **22** and **23,** the structures of which were assessed by NOESY NMR experiments. C-2 ^{13}C NMR chemical shifts possessing α configurations of compounds **21** and **22** were found at 100.2 and 100.5 ppm, respectively. On the other hand, the chemical shift of the quaternary carbon was found at 98.0 ppm for diazide **23** bearing a β configuration. The fourth fraction was an inseparable mixture of different monoazidosaccharides[26] and was thus subjected to acetylation conditions in order to identify the structures: three acetylated monoazides **24**–**26** were characterized. An inseparable mixture of fructopyranosides **25** and **26** was isolated, their structures were confirmed by comparison with the NMR spectra of structurally related thio-analogs.[27] Different reaction conditions were employed for reacting fructose (**19**). For example, when fructose was treated with 2 equiv of PPh_3/DIAD (Table 3, entry 1) only monoazides were obtained, diazides **22** and **23** were observed when 4 equiv of the same reagents were employed (Table 3, entry 2). These results showed a higher reactivity of the hemiacetalic hydroxyl group compared to the primary alcohol functions of fructose.

Table 3
Azidation of ketoses

Entry	Starting carbohydrate	Method[a]	PPh_3/DIAD (equiv)	Products and yields[b] (%)			
	19			**21**	**22**	**23**	Other monoazides[c]
1		A	2	24	—	—	70
2		A	4	4	19	19	50
3		B	4	5	18	15	45
	20			**27**	**28**	**29**	**30**
4		A	2	20	33	—	—
5		A	2.7	33	48	7	7
6		A	4	8	11	34	35
7		B	4	35	47	5	6
8		A	10	—	—	3	15

Reagents and conditions: HN_3, DIAD, PPh_3, DMF, 0 °C to rt, 24 h.[19]
[a] A: HN_3 solution in toluene, B: in situ generated HN_3 in DMF, see in the text.
[b] Isolated yields.
[c] Precursors of acetylated compounds **24**–**26**.

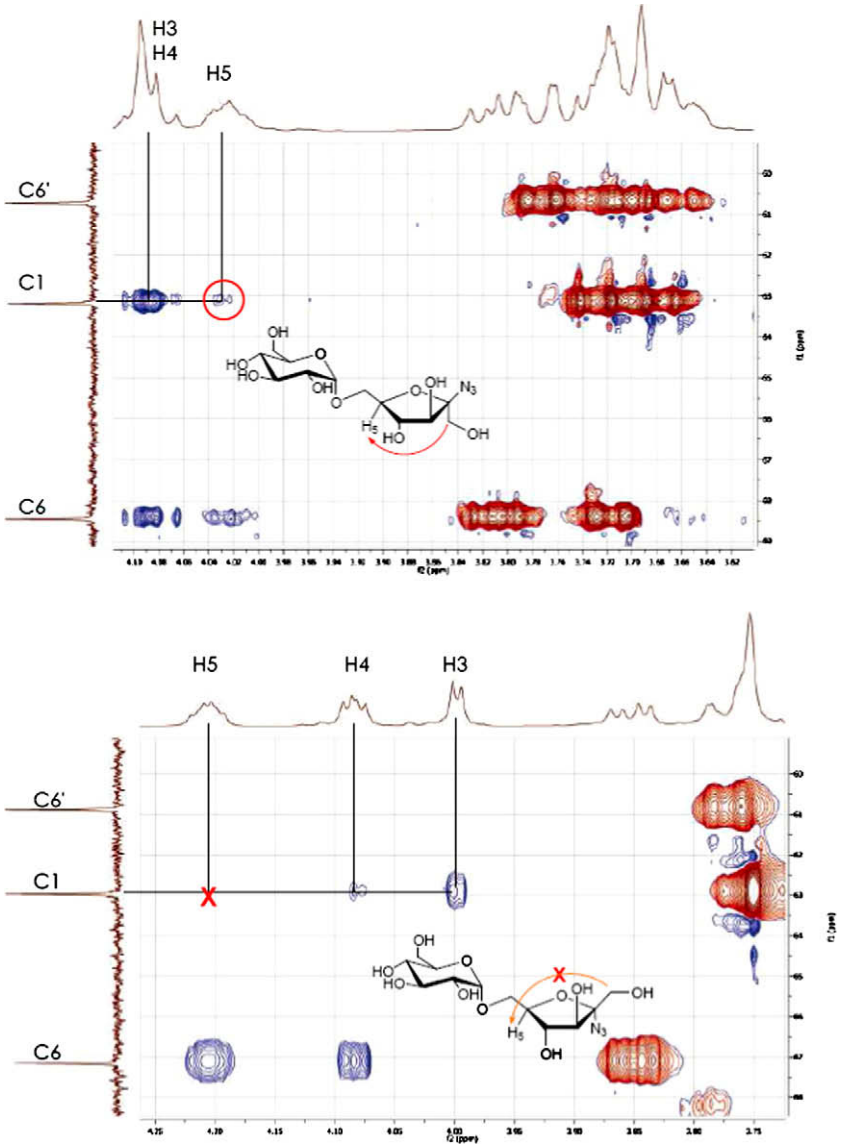

Figure 1. 2D NMR HSQC-NOESY spectra of compounds **28** (top) and **27** (bottom). 2D spectra where acquired at 500 MHz on a Bruker DRX500 spectrometer. Direct HSQC peaks are in red, relayed NOESY peaks in blue. Only the β configuration of compound **28** led NOESY cross peak between protons H-1 and H-5.

The direct azidation of isomaltulose (**20**) gave monoazides **27** and **28** when 2 equiv of PPh_3/DIAD (Table 2, entry 4) were used, hence showing the regioselectivity of the reaction for the hemiacetalic hydroxyl group. The use of greater amounts such as 4 equiv of the same reagents resulted in the observation of a total of four compounds on the TLC (Table 3, entry 6). These four compounds

could be separated by column chromatography and besides monoazides **27** and **28**, diazides **29** and **30** were isolated and characterized. However, the attribution of the configuration at the anomeric center of the fructosyl moiety was complicated due to the very small chemical shift range of the protons involved. To overcome this problem, 2D NMR HSQC-NOESY experiments were employed for spreading proton signals onto the carbon dimension. In spite of the low sensitivity of the method, the configurations of the fructofuranosyl moieties were identified easily by visualizing the nOe correlation between H-1 and H-5. As shown in Figure 1, this correlation was detected in the case of compound **28** while the same correlation is absent on the spectrum of azide **27**. When larger amounts of PPh_3/DIAD were used (10 equiv, see Table 3, entry 8) no monoazide could be detected by TLC and only diazides **29** and **30** were isolated, but in poor yields (the TLC indicated the formation of a great number of less polar compounds).

In summary, the straightforward regioselective azidation of unprotected carbohydrates using hydrazoic acid under Mitsunobu conditions offers a new access to complex polyhydroxylated azido structures readily available for further modifications by taking advantage of the different reactivity of the hydroxyl groups present on the sugar backbones. The reactions, easy to set up, proceeded in moderate to good yields and could be performed on a multi-gram scale without the production of undesired halogenated derivatives usually observed in the protocols involving halogen displacements for achieving the same transformations. The use of a HN_3 solution in toluene (method A) gave better yields than the in situ generation of HN_3 in DMF (method B). We are currently using this azidation strategy for the production of gram quantities of pure azido carbohydrates.

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Supplementary data

Supplementary data (characterization data for new compounds **9**–**12**, **21**–**30**, are available as well as their ^1H NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.173.

References and notes

1. (a) Rostovtsev, V. V.; Green, L. G.; Folkin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064; for recent review, see: (c) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015.
2. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
3. (a) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025; (b) Qiu, X. P.; Tanaka, F.; Winnik, F. M. *Macromolecules* **2007**, *40*, 7069–7071; (c) Bernard, J.; Save, M.; Arathoon, B.; Charleux, B. *J. Polym. Sci., Part A* **2008**, *46*, 2845–2857; (d) Binauld, S.; Damiron, D.; Hamaide, T.; Drockenmüller, E.; Pascault, J.-P.; Fleury, E. *Chem. Commun.* **2008**, 4138–4141; (e) Nagao, Y.; Takasu, A. *Macromol. Rapid. Commun.* **2009**, *30*, 199–203.
4. Dedola, S.; Nepogodiev, S. A.; Field, R. A. *Org. Biomol. Chem.* **2007**, *5*, 1006–1017.
5. For recent reviews, see: (a) Meutermans, W.; Le, G. T.; Becker, B. *ChemMedChem* **2006**, *1*, 1164–1194; (b) Murphy, P. V. *Eur. J. Org. Chem.* **2007**, 4177–4187.
6. (a) Molinier, V.; Fitremann, J.; Bouchu, A.; Queneau, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1753–1762; (b) Queneau, Y.; Jarosz, S.; Lewandowski, B.; Fitremann, J. *Adv. Carbohydr. Chem. Biochem.* **2007**, *61*, 217–292; (c) Besset, C.; Chambert, S.; Queneau, Y.; Kerverdo, S.; Rolland, H.; Guilbot, J. *Crabohydr. Res.* **2008**, *343*, 929–935.
7. Hanessian, S.; Ducharme, D.; Massé, R.; Capmau, M. L. *Carbohydr. Res.* **1978**, *63*, 265–269.
8. Moulay-Larbi, L.; Fréchou, C.; Demailly, G. *Tetrahedron Lett.* **1994**, *35*, 2175–2178.
9. Jiménez Blanco, J. L.; García Fernández, J. M.; Defaye, J. *Carbohydr. Res.* **1997**, *303*, 367–372.
10. Gouin, S. G.; Kovensky, J. *Tetrahedron Lett.* **2007**, *48*, 2875–2879.
11. Mitsunobu, O. *Synthesis* **1981**, 1–28.
12. For example, see: (a) Kan, C.-C.; Bittman, Y. J. *Biochemistry* **1992**, *31*, 1866–1874; (b) Keppler, F.; Jahn, E. M.; Hickman, V.; Carell, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 2325–2327.
13. For a review, see: Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 1651–2551.
14. For a review, see: Pathak, T. *Chem. Rev.* **2002**, *102*, 1623–1668.
15. See: Bertterton, E. A. *Crit. Rev. Environ. Sci. Technol.* **2003**, *33*, 423–458. and references therein.
16. One can notably mention: (i) only diluted HN_3 solution was used, (ii) for avoiding any leak problems, the reactions were performed in septa-plugged flasks and the HN_3 solution was transferred through the use of cannulas using a nitrogen flux, (iii) neutralizations were performed to stop the reactions and the extractions were thus run in basic media, (iv) all glassware were kept in a sodium hydroxide solution before cleaning.
17. Wolff, H.. In *Organic Reactions*; Adams, R., Bachmann, W. E., Fieser, L. F., Johnson, J. R., Snyder, H. R., Eds.; John Wiley & Sons: New York, 1959; Vol. III, p 327.
18. (a) Hough, L.; Mufti, K. S. *Carbohydr. Res.* **1972**, *25*, 497–503; (b) Khan, R.; Bhardwaj, C. L.; Mufti, K. S.; Jenner, M. R. *Carbohydr. Res.* **1980**, *78*, 185–189.
19. *Typical procedure (method A)*: A solution of sucrose (**1**, 2.04 g, 5.96 mmol) in DMF (70 mL) was first dried by concentrating under vacuum to a 50 mL volume. PPh_3 (3.13 g, 2 equiv) was added and the obtained solution was then cooled to 0 °C and placed under N_2. A 5% HN_3 solution in toluene (9.0 mL), prepared under N_2 according to a literature protocol (see Ref. 17), was added to the solution through the use of a cannula. DIAD (2.35 mL, 2 equiv) was then added and the reaction was let to warm up to room temperature over 1 h, then it was further stirred for 24 h. Water (50 mL) was then added and the solution was neutralized using a 28% ammonia solution. The obtained solution was extracted with CH_2Cl_2 (3×50 mL), the aqueous layer was concentrated and directly subjected to silica gel chromatography using a CH_2Cl_2/acetone/methanol/water gradient (three different ratios were employed: 78/10/10/2, 67/15/15/3 and 56/20/20/4) and gave monoazide **5** (1.35 g, 61%) and diazide **6** (0.21 g, 9%) as well as unreacted sucrose (**1**, 0.61 g, 29%).
20. Wang, M.; Tu, P. F.; Xu, Z. D.; Yang, M. *Helv. Chim. Acta* **2003**, *86*, 2637–2644.
21. Rose, J. D.; Maddry, J. A.; Comber, R. N.; Suling, W. J.; Wilson, L. N.; Reynolds, R. C. *Carbohydr. Res.* **2002**, *337*, 105–120.
22. Hough, L.; Richardson, A. C.; Salam, M. A. *Carbohydr. Res.* **1980**, *80*, 117–122.
23. (a) Szarek, W. A.; Achmatowicz, O.; Plenkiewicz, J.; Radatus, B. K. *Tetrahedron* **1978**, *34*, 1427–1433; (b) Gyorgydeak, Z.; Szilagyi, L. *Liebigs Ann. Chem.* **1987**, *3*, 235–241; (c) Szilagyi, L.; Gyorgydeak, Z. *Carbohydr. Res.* **1985**, *143*, 21–41.
24. Gudmundsdottir, A. V.; Nitz, M. *Org. Lett.* **2008**, *10*, 3461–3463.
25. Tanaka, T.; Nagai, H.; Noguchi, M.; Kobayashi, A.; Shoda, S. *Chem. Commun.* **2009**, 3378–3379.
26. Microanlaysis: Anal. Calcd for $C_6H_{11}N_3O_5$: C, 35.12; H, 5.40; N, 20.48. Found: C, 35.41; H, 5.47; N, 20.25.
27. Goursaud, F.; Peyrane, F.; Veyrieres, A. *Tetrahedron* **2002**, *58*, 3629–3637.