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The behaviour of deoxyhexose trihaloacetimidates in selected glycosylations

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Abstract—Armed deoxyhexose glycosyl donors are very reactive and sometimes too uncontrollably activated in glycosylation reactions; yields can be thereby reduced, especially when unreactive glycosyl acceptors are involved. In this paper, the behaviour of a range of deoxyhexose trihaloacetimidate (trichloro- and *N*-phenyl trifluoro-) donors is compared in some selected glycosylations towards biologically relevant targets. The selected *N*-phenyl trifluoroacetimidates often afforded best results in terms of both donor synthesis and glycosylation yield.

Keywords: Glycosylations; Deoxysugars; Glycosyl *N*-phenyl trifluoroacetimidates; Glycosyl trichloroacetimidates

1. Introduction

Deoxyhexoses are commonly found as constituents of O-antigenic lipopolysaccharides[1] (they are the major constituents of O-chains from phytopathogenic bacteria),[2] as well as components of various glycoproteins, glycolipids and other glycoconjugates as cardioglycosides, natural antibiotics and anticancer agents.[3] Since the biological role of the deoxyhexose moiety in oligosaccharides seems important, the synthesis of deoxyhexose-containing oligosaccharides is a major target in carbohydrate chemistry.

The key reactions in oligosaccharide synthesis consist in glycosylations, which involve the coupling between a glycosyl acceptor and a glycosyl donor. Thioglycosides and trichloroacetimidates are frequently used as glycosyl donors in oligosaccharide synthesis. Recently, structural analogues of glycosyl trichloroacetimidates, namely glycosyl *N*-phenyl trifluoroacetimidates,[4] were successfully used as novel glycosyl donors and exploited in the synthesis of biologically relevant oligosaccharide sequences such as Lewis X,[5] a Globo H moiety,[6] saponins glycolipids,[4c,7] glycosylated antibiotics[8] and fragments of several lipopolysaccharides.[9] Interestingly, in some cases the installation of the *N*-phenyl trifluoroacetimidate leaving group at the anomeric position of the glycosyl donor was demonstrated to be preferable: for example, the N-glycosylation of the amide group of some asparagine building blocks was firstly performed in high yields with glycosyl *N*-phenyl trifluoroacetimidates, whereas analoguous trichloroacetimidate donors gave unsatisfactory yields.[10] Besides, the observation that also some O- and C-glycosylations proceed with better yields when conducted with glycosyl *N*-phenyl trifluoroacetimidates in place of glycosyl trichloroacetimidates[9,11] prompted us to explore this feature in the case of deoxyhexose glycosylations. These reactions are not always high-yielding due to the lower electron-withdrawing effect caused by the absence of one or more hydroxyls, which can sometimes increase too much the rate of leaving group release at the anomeric position. Actually, few scattered results were previously reported about this behaviour.[9a–c] A more accurate comparative study of deoxyhexose glycosylations with trichloro- and *N*-phenyl trifluoroacetimidates is now presented. The examples are

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restricted to the synthesis of building blocks of interest for the synthesis of biologically relevant probes. L-Fucose was the deoxyhexose on which we focused major attention, since it is the most relevant natural deoxyhexose and L-fucose containing oligosaccharides have potential application in many biomedical fields.[12] Other deoxyhexoses treated in this study were D-bacillosamine (2,4-diacetamido-2,4,6-trideoxy-D-glucose), 3-fucosamine (3-acetamido-3,6-dideoxy-D-galactose) and D-tyvelose (D-*arabino*-hexose), which are peculiar constituents of bacterial O-antigens.[13]

2. Results and discussion

The hemiacetal building blocks used as starting material for the synthesis of the trihaloacetimidates were functionalized with arming protecting groups. The choice of screening almost exclusively armed donors was dictated by the fact that biologically relevant oligosaccharides contain mainly α-linked deoxyhexoses: therefore, in the case of *galacto*- or *gluco*-configurated deoxyhexoses such as fucose, 3-fucosamine and bacillosamine, a non-participating protecting group at position C-2 was necessary. On the other hand, armed glycosyl donors are faster activated in glycosylation reactions; this feature, which is due to the decrease of the electron-withdrawing effect caused by the presence of one or more deoxy functions, often renders the glycosyl donor too uncontrollably reactive. This could be detrimental for glycosylation yields, especially when quite unreactive glycosyl acceptors are involved. Partially acylated 2-O-benzylated donors are routinely adopted to face this problem,[14] but their preparation entails longer synthetic sequences as compared with the synthesis of fully benzylated donors.[15]

Glycosyl *N*-phenyl trifluoroacetimidates were readily synthesized from the corresponding hemiacetals with $CF_3C(NPh)Cl$ and a stoichiometric amount of NaH in CH_2Cl_2,[4b] whereas trichloroacetimidate donors were obtained by applying the Schmidt protocol[16] with Cl_3CCN and catalytic DBU in CH_2Cl_2. Interestingly, in every case *N*-phenyl trifluoroacetimidate donors were obtained in higher or at least the same yield as compared with the trichloro-counterparts (Table 1). No tests with other bases were conducted to increase trichloroacetimidate yields, since such bases (NaH, K_2CO_3) were already employed in the synthesis of compound **1** with worse results.[†] Actually, one of the most relevant causes of this difference in yields was the higher lability of glycosyl trichloroacetimidates to the chromatographical process, even when it was conducted on a partially deactivated support such as Brockman grade 2 alumina immediately after the work-up of the reaction. The anomeric configuration of the *N*-phenyl trifluoroacetimidate group was strictly dependent on the nature of the reacting hemiacetal, whereas the trichloroacetimidate function was always α-configurated.[19]

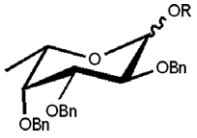
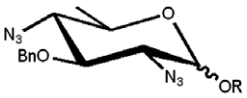
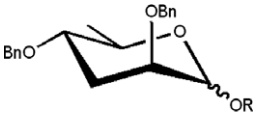
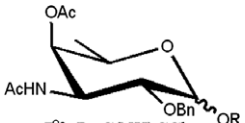
Glycosylation experiments were conducted, unless otherwise stated, by adding the promoter to a CH_2Cl_2 solution of donor and acceptor at −70 °C. The solution was then allowed to warm up spontaneously (see Section 3 for details). Preliminary screenings evidenced that less reactive *N*-phenyl trifluoroacetimidate donors are best activated with TMSOTf, whereas the milder $BF_3{\cdot}OEt_2$ worked better with armed trichloroacetimidate counterparts. The results are summarized in Table 2: in the case of fucosylations, *N*-phenyl trifluoroacetimidate donor **2** provided better or at least comparable yields with respect to trichloro-analogue **1**.[17] The difference in yield was particularly marked with an unreactive glycosyl acceptor such as glucosamine derivative **9** (entries 1 and 2), whose hydroxyl function at C-4, well known to be scarcely nucleophilic,[20] was even more unreactive in this case due to the presence of an adjacent electron-withdrawing Cbz group. The low reactivity of **9** did not match with the rapid activation of the fucosyl trichloroacetimidate donor; disaccharide **10** was thus obtained in low yield, together with perbenzylated fucose hemiacetal **11**, trichloroacetamide **12** and perbenzylated L-Fuc-(1→1)-L-Fuc disaccharide **13**. These byproducts resulted from the trapping of the fucosyl oxocarbenium ion with nucleophilic species, more reactive than **9**, which were in situ generated by the activation of the trichloroacetimidate donor (Scheme 1). Some yield improvements could be usually achieved with fucosyl trichloroacetimidate donors by applying the 'inverse procedure',[21] since the oxocarbenium ion is generated slowly in the presence of an excess of acceptor, which traps the intermediate before it can react with other species. We tested such protocol to ascertain if an improvement in yield was possible in glycosylations with donor **1** (entries 3–5). The best result was obtained by using TMSOTf as activating agent in Et_2O (entry 5), even though no significant yield improvement was observed, whereas α-stereoselectivity was strongly enhanced in Et_2O as well as in CH_2Cl_2.

Minor differences in efficiency between trichloro- and *N*-phenyl trifluoroacetimidate donors were observed with more nucleophilic acceptors, such as **14** and **16** (entries 6–9). Interestingly, the attempted coupling between **2** and **16** by TMSOTf activation surprisingly afforded no disaccharide **17**; actually, acceptor **16** gave acyl migration from the anomeric position to O-2.[‡] However, this problem was recently circumvented by

[†] Compound **1** was obtained in 65% yield using DBU as base,[17] whereas a 50% yield was reported with NaH[17] as well as K_2CO_3.[19]

[‡] This rearrangement occurred extensively also by treating **18** alone with TMSOTf (0.02 equiv) at −78 °C.

Table 1. Synthesis of trihaloacetimidate deoxyhexose donors from hemiacetals

Entry	Deoxyhexose	Donor	Trichloroacetimidate yield[a] (%) (α/β ratio)[c]	*N*-Phenyl trifuluoracetimidate yield[b] (%) (α/β ratio)[c]
1	L-Fucose	 **1**[17]: R=C(NH)CCl_3 **2**[6]: R=C(NPh)CF_3	65 (only α)	99 (only β)
2	D-Bacillosamine	 **3**: R=C(NH)CCl_3 **4**[18]: R=C(NPh)CF_3	75 (only α)	75 (1:2)[d]
3	D-Tyvelose	 **5**: R=C(NH)CCl_3 **6**: R=C(NPh)CF_3	64 (only α)	77 (only α)
4	D-Fucos-3-amine	 **7**[9a]: R=C(NH)CCl_3 **8**[9a]: R=C(NPh)CF_3	53 (only α)	74 (3:1)

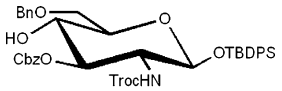
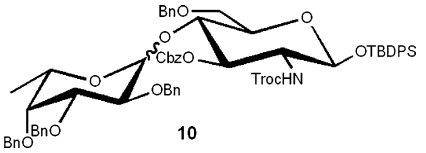
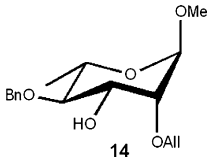
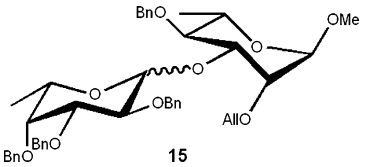
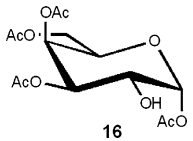
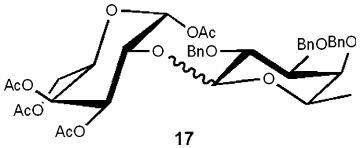
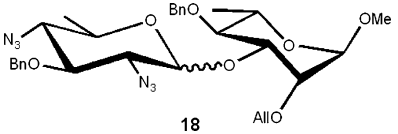
[a] Reaction conditions: Cl_3CCN, DBU, CH_2Cl_2, rt.
[b] Reaction conditions: $CF_3C(NPh)Cl$, NaH, CH_2Cl_2, 0 °C to rt.
[c] Measured by ^1H NMR, unless otherwise stated.
[d] Measured after separation of the two anomers.

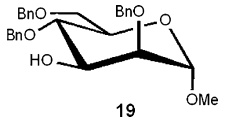
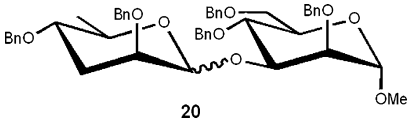
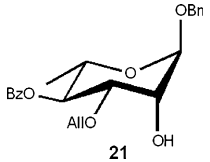
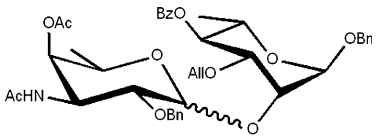
using a milder promoter, such as $Bi(OTf)_3$, which allowed the formation of disaccharide **17**[22] in high yield and stereoselectivity (75%, α/β >10).[23] Little differences in yields were obtained for glycosylations involving bacillosamine and tyvelose trichloro- or *N*-phenyl trifluoroacetimidate donors **3**–**6** (entries 10–14). The good outcome in tyvelose glycosylations is remarkable, since in the past the use of 3,6-dideoxyhexose thioglycosides was preferred with respect to trichloroacetimidates,[24] in spite of a more laborious preparation. The last two entries in Table 2 report previously published results concerning 3-fucosamine donors **7** and **8**:[9a] in this case only the glycosylation conducted with the *N*-phenyl trifluoroacetimidate donor proceeded.

The major α-stereoselectivity observed in glycosylations with glycosyl *N*-phenyl trifluoroacetimidates might be explained by taking into account that such donors require harsher conditions for their activation with respect to their trichloroacetimidate counterparts; this would favour a S_N1-type mechanism and therefore α-stereoselectivity, whichever the glycosyl acceptor is. Instead, the milder conditions ($BF_3{\cdot}OEt_2$ in CH_2Cl_2 at lower temperature), which are necessary for the activation of armed deoxyhexose α-trichloroacetimidate donors, would render the mechanism more dependent on the reactivity of the glycosyl acceptor. Indeed, with an armed acceptor such as **14**, β-disaccharides were predominantly obtained in agreement with a S_N2-type mechanism via a tight ion pair.[19] On the contrary, less reactive acceptors such as **9** or **16** favour a S_N1 type mechanism, affording predominantly α-products.

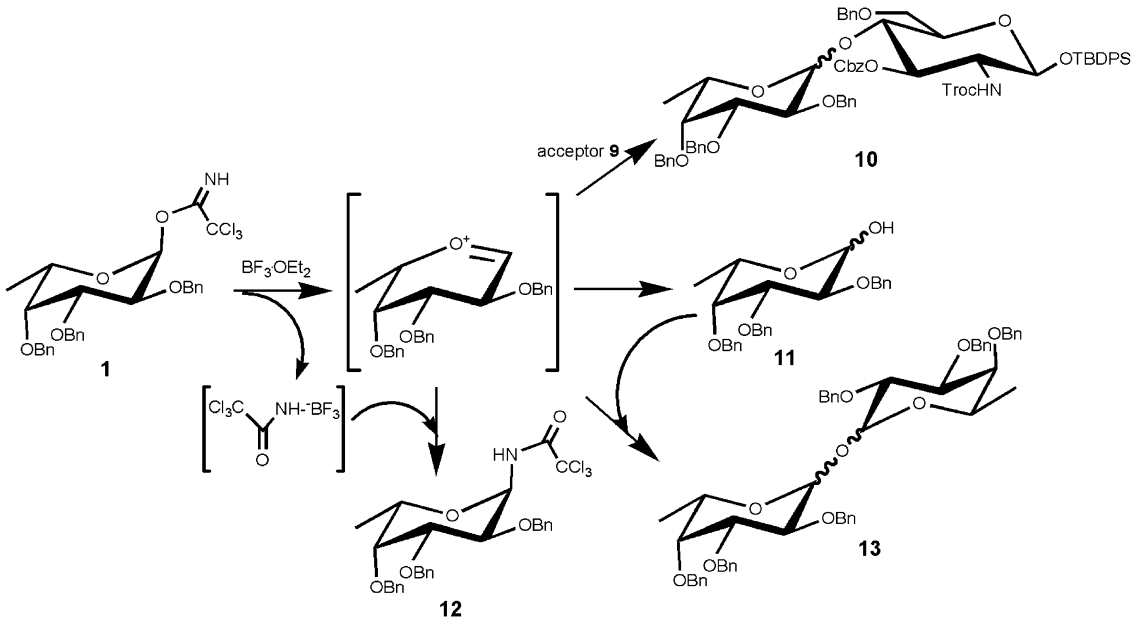
Conclusively, in Table 2 some selected glycosylations involving deoxyhexoses are reported. Good yields were obtained with *N*-phenyl trifluoroacetimidate glycosyl donors, which gave in some cases even better results with respect to trichloroacetimidate donors. This could be ascribed to a slower formation of the oxocarbenium ion, which can be therefore trapped with more efficiency even by a low reactive glycosyl acceptor. Actually, the conditions (temperature, acidity of the activator: see Table 2 for details) necessary for the activation of *N*-phenyl trifluoroacetimidate donors were relatively harsher than for trichloro-ones. This would favour the formation of the thermodynamic α-configurated

Table 2. Glycosylation reactions of deoxyhexosyl trihaloacetimidate donors

Entry	Acceptor	Donor[a]	Solvent	Promoter	*T* (°C)	Yield[d] (%) (α/β ratio)[e]	Product	Natural target
1	 **9**	**1**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	−70 to −30 °C	28 (4:3)[f]	 **10**	Lewis A
2	**9**	**2**	CH_2Cl_2	TMSOTf	−50 to −30 °C	71 (only α)	**10α**	Lewis A
3	**9**	**1**	CH_2Cl_2	TMSOTf (inverse procedure)	−70 °C to rt	No product	—	
4	**9**	**1**	CH_2Cl_2	$BF_3{\cdot}OEt_2$ (inverse procedure)	−70 °C to rt	17 (>10:1)[f]	**10**	Lewis A
5	**9**	**1**	Et_2O	TMSOTf (inverse procedure)	−70 °C to rt	30 (only α)	**10α**	Lewis A
6	 **14**	**1**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	−70 to −50 °C	69 (2:3)	 **15**	O-Antigen from *Pseudomonas fluorescens* IMV472
7	**14**	**2**	CH_2Cl_2	TMSOTf	−50 to −30 °C	85 (3:2)	**15α**	O-Antigen from *Pseudomonas fluorescens* IMV472
8	 **16**	**1**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	−70 to −50 °C	68 (6:1)[f]	 **17**	Lewis A, B
9	**16**	**2**	CH_2Cl_2	TMSOTf	−70 °C to rt	No product	—	
10	**14**	**3**	CH_2Cl_2	$BF_3{\cdot}OEt_2$	−70 to −50 °C	85 (1:1)[f]	 **18**	O-Antigens from *Pseudomonas aeruginosa* O1, O3, O13, O14 *Pseudomonas aeruginosa* NCTC 8505 *Shewanella algae* BrY

11[18]	**14**	**4α**	CH_2Cl_2	TMSOTf	0 °C	75 (only α)	**18α**	O-Antigens from *Pseudomonas aeruginosa* O1, O3, O13, O14 *Pseudomonas aeruginosa* NCTC 8505 *Shewanella algae* BrY
12[18]	**14**	**4β**	CH_2Cl_2	TMSOTf	0 °C	86 (only α)	**18α**	O-Antigens from *Pseudomonas aeruginosa* O1, O3, O13, O14 *Pseudomonas aeruginosa* NCTC 8505 *Shewanella algae* BrY
13	 **19**	**5**[b]	CH_2Cl_2	$BF_3{\cdot}OEt_2$	−70 to −20 °C	89 (3:2)	 **20**	O-Antigen from *Salmonella enterica* sv. *enteritidis*
14	**19**	**6**[b]	CH_2Cl_2	TMSOTf	−70 °C to rt	79 (5:2)	**20**	O-Antigen from *Salmonella enterica* sv. *enteritidis*
15[9a]	 **21**	**7**[c]	CH_2Cl_2	$BF_3{\cdot}OEt_2$	−70 °C to rt	No product	—	
16[9a]	**21**	**8**[c]	CH_2Cl_2	TMSOTf	0 °C to rt	65 (62:38)[f]	 **22**	O-Antigens from *Pseudomonas fluorescens* ATCC49271 *Pseudomonas syringae pv. tabaci* MV 223 *Pseudomonas syringae pv. coriandricola* GFPB2028

[a] 1.4 equiv in respect to the acceptor, unless otherwise stated.
[b] 1.8 equiv in respect to **19**.
[c] 1.1 equiv in respect to **21**.
[d] Isolated yield.
[e] Measured after separation of the two anomers unless otherwise stated.
[f] Measured by ^1H NMR.



Scheme 1. Disaccharide product and byproducts formation in glycosylation of **1** with **9**.

disaccharide, which is very often required in biological-targeted glycosylations involving deoxyhexoses, what might be the glycosyl acceptor. Although generalization of these results would still require a larger panel of examples, we feel that they could be of interest in selected glycosylations involving deoxyhexose donors and unreactive glycosyl acceptors.

3. Experimental

3.1. General methods

^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Gemini-300 NMR equipment, in $CDCl_3$ (internal standard, for ^{1}H: $CHCl_3$ at δ 7.26; for ^{13}C: $CDCl_3$ at δ 77.0). Positive MALDIMS spectra were recorded on an Applied Biosystem Voyager DE-PRO MALDI-TOF mass spectrometer in the positive mode: compounds were dissolved in MeCN at a concentration of 0.1 mg/mL and 1 μL of this soln was mixed with 1 μL of a 20 mg/mL soln of 2,5-dihydroxybenzoic acid in 7:3 MeCN–water. Optical rotations were measured on a JASCO P-1010 polarimeter. Elemental analysis was performed on a Carlo Erba 1108 instrument. Analytical thin layer chromatography (TLC) was performed on aluminium plates precoated with E. Merck Silica Gel 60 F_{254} as the adsorbent. The plates were developed with 5% H_2SO_4 ethanolic soln and then heated to 130 °C. Column chromatography was performed on Kieselgel 60 (63–200 mesh) unless otherwise stated. Solvents used were purchased from Fluka and not further purified before use.

3.2. General procedure for trichloroacetimidate formation

The hemiacetal (0.50 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and to the 0 °C cooled soln, Cl_3CCN (2.50 mmol) and DBU (0.10 mmol) were added. The soln was stirred at rt until the reaction finished (TLC analysis) and then concentrated. The resulting residue was then immediately chromatographed over neutral alumina (Brockman grade 2) gel.

3.3. General procedure for *N*-phenyl trifluoroacetimidate formation

The hemiacetal (0.50 mmol) was dissolved in CH_2Cl_2 (2.0 mL) under an argon atmosphere and then cooled to 0 °C under stirring. $CF_3C(NPh)Cl$ (0.65 mmol) and NaH (60% oil suspension; 0.75 mmol) were added and stirring was continued at 0 °C and eventually at rt until the reaction finished (TLC analysis), after that the soln was concentrated. Neutral alumina (Brockman grade 2) column chromatography afforded the pure *N*-phenyl trifluoroacetimidate donor.

3.4. General procedure for glycosylation

A mixture of acceptor (0.050 mmol) and donor (0.055–0.100 mmol: see Table 2 for details) was coevaporated three times with toluene, the residue was then mixed with freshly activated AW-300 4 Å molecular sieves, cooled to −70 °C and then suspended under argon in the solvent (1.0 mL). Upon stirring, a soln of $BF_3{\cdot}OEt_2$ or TMSOTf in CH_2Cl_2 (0.02 equiv of the activator in respect to the donor) was added and the temperature

was allowed to rise spontaneously. After completion of the reaction (TLC analysis), the mixture was neutralized by adding Et_3N. The mixture was then filtered over Celite and concentrated to give a residue that was purified by chromatography.

3.4.1. 3-*O*-Benzyl-2,4-diazido-α-D-glucopyranosyl trichloroacetimidate (3). $[\alpha]_D$ +55.3 (*c* 1.4, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.50–7.33 (m, 5H), 6.36 (d, $J = 3.4$ Hz, 1H), 4.92 (s, 2H), 3.85 (m, 2H), 3.66 (dd, $J = 10.0$, 3.4 Hz, 1H), 3.24 (t, $J = 10.0$ Hz, 1H), 1.36 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7 (C=N), 136.9 (C_{ipso}), 128.6–128.2 (C–Ar), 94.5 (C-1), 78.3, 75.5, 69.4, 68.0, 63.2 (C-2, C-3, C-4, C-5, O*C*H_2Ph), 18.4 (C-6). Anal. Calcd: C, 40.15; H, 3.59; N, 21.85. Found: C, 40.29; H, 3.56; N, 21.68.

3.4.2. 3-*O*-Benzyl-2,4-diazido-α-D-glucopyranosyl *N*-phenyltrifluoroacetimidate (4α). $[\alpha]_D$ +126.2 (*c* 1.4, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.46–6.84 (m, 10H, H–Ar), 6.34 (br s, 1H, H-1), 4.92 (s, 2H, C*H*$_2$Ph), 3.84–3.58 (m, 3H, H-2, H-3, H-5), 3.22 (t, 1H, 1H, $J_{4,3} = J_{4,5} = 9.6$ Hz, H-4), 1.37 (d, 3H, $J_{6,5} = 6.0$ Hz, H-6); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.1, 136.8 (2C_{ipso}), 128.7–118.2 (C–Ar), 93.4 (C-1), 78.5 (C-3), 75.7, 69.3, 67.9, 63.1 (C-2, C-4, C-5, O*C*H_2Ph), 18.4 (C-6). MALDIMS for $C_{21}H_{20}F_3N_7O_3$ (*m*/*z*): M_r(calcd) 475.16, M_r(found) 498.03 $(M+Na)^+$. Anal. Calcd: C, 53.05; H, 4.24; N, 20.62. Found: C, 53.00; H, 4.26; N, 20.74.

3.4.3. 3-*O*-Benzyl-2,4-diazido-β-D-glucopyranosyl *N*-phenyltrifluoroacetimidate (4β). $[\alpha]_D$ +98.9 (*c* 1.4, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.45–6.87 (m, 10H), 5.49 (br m, 1H), 4.93 (d, $J_{gem} = 10.8$ Hz, 1H), 4.87 (d, $J_{gem} = 10.8$ Hz, 1H), 3.65 (t, $J_{3,2} = J_{3,4} = 9.0$ Hz, 1H), 3.34–3.15 (m, 3H), 1.39 (d, $J_{6,5} = 6.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.0, 136.9 (2C_{ipso}), 128.7–119.2 (C–Ar), 95.3 (C-1), 81.2 (C-3), 75.6, 71.8, 67.2, 65.4 (C-2, C-4, C-5, *C*H_2Ph), 18.2 (C-6). MALDIMS for $C_{21}H_{20}F_3N_7O_3$ (*m*/*z*): M_r(calcd) 475.16, M_r(found) 497.94 $(M+Na)^+$. Anal. Calcd: C, 53.05; H, 4.24; N, 20.62. Found: C, 52.89; H, 4.30; N, 20.86.

3.4.4. 2,4-Di-*O*-benzyl-α-D-tyvelopyranosyl trichloroacetimidate (5). $[\alpha]_D$ +58.0 (*c* 0.9, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.24 (m, 10H), 6.19 (br s, 1H), 4.74–4.41 (m, 4H), 3.92 (m, 1H), 3.78 (br s, 1H), 3.53 (dq, $J = 9.8$, 6.0 Hz, 1H), 2.28 (dt, $J = 13.2$, 3.0 Hz, 1H), 1.82 (ddd, $J = 13.2$, 10.2, 3.0 Hz, 1H), 1.19 (d, $J = 6.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5 (C=N), 138.0, 137.7 (2C_{ipso}), 94.9 (C-1), 74.6, 73.4, 71.2, 71.1, 70.8 (C-2, C-4, C-5, 2O*C*H_2Ph), 29.6 (C-3), 17.9 (C-6). Anal. Calcd: C, 55.89; H, 5.12; N, 2.96. Found: C, 55.99; H, 5.10; N, 2.88.

3.4.5. 2,4-Di-*O*-benzyl-α-D-tyvelopyranosyl *N*-phenyltrifluoroacetimidate (6). $[\alpha]_D$ +15.6 (*c* 0.8, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.44–6.73 (m, 15H), 6.00 (br s, 1H), 4.70 (d, $J_{gem} = 12.6$ Hz, 1H), 4.63 (d, $J_{gem} = 12.6$ Hz, 1H), 4.53 (d, $J_{gem} = 11.7$ Hz, 1H), 4.48 (d, $J_{gem} = 11.7$ Hz, 1H), 3.91 (br s, 1H), 3.58 (m, 2H), 2.67 (br s, 1H), 2.32 (m, 1H), 1.37 (d, $J_{6,5} = 6.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.1, 135.8 (2C_{ipso}), 128.5–119.3 (C–Ar), 95.9 (C-1), 75.0, 74.9, 71.8, 71.3 (C-2, C-4, C-5, *C*H_2Ph), 29.9 (C-3), 18.6 (C-6). MALDIMS for $C_{28}H_{28}F_3NO_4$ (*m*/*z*): M_r(calcd) 499.20, M_r(found) 522.26 $(M+Na)^+$. Anal. Calcd: C, 67.32; H, 5.65; N, 2.80. Found: C, 67.45; H, 5.75; N, 2.86.

3.4.6. *tert*-Butyldiphenylsilyl (2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→4)-6-*O*-benzyl-3-*O*-benzyloxycarbonyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside (10α). $[\alpha]_D$ −35.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.12 (m, 35H), 5.13 (d, $J = 12.0$ Hz, 1H), 5.06–5.00 (m, 3H), 4.88 (d, $J = 11.6$ Hz, 1H), 4.75 (d, $J = 11.6$ Hz, 1H), 4.72–4.62 (m, 4H), 4.59 (d, $J = 11.6$ Hz, 1H), 4.56 (d, $J = 11.6$ Hz, 1H), 4.51 (d, $J = 12.0$ Hz, 1H), 4.45 (d, $J = 8.0$ Hz, 1H), 4.32 (d, $J = 12.3$ Hz, 1H), 4.25 (d, $J = 12.3$ Hz, 1H), 3.97 (dd, $J = 9.9$, 3.6 Hz, 1H), 3.92–3.83 (m, 2H), 3.72–3.65 (m, 3H), 3.43 (br d, $J = 6.4$ Hz, 1H), 3.37 (br s, 1H), 3.12 (dd, $J = 9.6$, 2.0 Hz, 1H), 1.01 (s, 9H), 0.96 (d, $J = 6.4$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 153.8 (2C=O), 138.1–127.3 (C–Ar), 98.7, 96.1 (C-1_A, C-1_B), 95.4 (*C*$(CH_3)_3$) 79.5, 78.0, 75.9, 75.2, 74.6, 74.5, 74.2, 74.1, 73.4, 72.7, 69.8, 67.7, 67.2, 60.4, 58.5 (C-2_A, C-2_B, C-3_A, C-3_B, C-4_A, C-4_B, C-5_A, C-5_B, C-6_A, 5O*C*H_2Ph, O*C*H_2CCl_3), 26.7 (C(*C*$H_3)_3$), 16.4 (C-6_B). MALDIMS for $C_{67}H_{72}Cl_3NO_{13}Si$ (*m*/*z*): M_r(calcd) 1231.38, M_r(found) 1254.58 $(M+Na)^+$. Anal. Calcd: C, 65.23; H, 5.88; N, 1.14. Found: C, 65.35; H, 5.68; N, 1.16.

3.4.7. Methyl (2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-2-*O*-allyl-4-*O*-benzyl-α-L-rhamnopyranoside (15α). $[\alpha]_D$ −38.6 (*c* 0.7, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.10 (m, 20H), 5.91 (m, 1H), 5.29 (dd, $J = 17.0$, 2.1 Hz, 1H), 5.17–5.08 (m, 2H), 5.00 (d, $J = 11.6$ Hz, 1H), 4.85 (d, $J = 12.2$ Hz, 1H), 4.77–4.63 (m, 7H), 4.53 (d, $J = 11.8$ Hz, 1H), 4.14–3.97 (m, 4H), 3.72–3.63 (m, 3H), 3.52 (t, $J = 9.6$ Hz, 1H), 3.34 (m, 4H), 1.27 (d, $J = 6.2$ Hz, 3H), 1.13 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0, 138.9, 138.8, 138.6 (4C_{ipso}), 135.1 (OCH_2*C*H=CH_2), 128.3–127.2 (C–Ar), 116.7 (OCH_2CH=*C*H_2), 99.7, 98.0 (C-1_A, C-1_B), 79.9, 79.3, 78.9, 78.3, 78.0, 76.2, 74.8, 74.7, 73.0, 72.9, 71.5, 67.8, 66.9 (C-2_A, C-2_B, C-3_A, C-3_B, C-4_A, C-4_B, C-5_A, C-5_B, 4O*C*H_2Ph, O*C*H_2CH=CH_2), 54.7 (O*C*H_3), 18.0, 16.8 (C-6_A, C-6_B). MALDIMS for $C_{44}H_{52}O_9$ (*m*/*z*): M_r(calcd) 724.36, M_r(found) 747.50

$(M+Na)^+$. Anal. Calcd: C, 72.90; H, 7.23. Found: C, 73.15; H, 7.07.

3.4.8. Methyl (2,3,4-tri-*O*-benzyl-β-L-fucopyranosyl)-(1→3)-2-*O*-allyl-4-*O*-benzyl-α-L-rhamnopyranoside (15β) $[\alpha]_D$ −26.2 (*c* 0.7, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.10 (m, 20H), 5.78 (m, 1H), 5.16 (dd, $J = 17.0$, 2.1 Hz, 1H), 5.09–4.99 (m, 4H), 4.86 (d, $J = 11.8$ Hz, 1H), 4.76 (s, 2H), 4.66 (d, $J = 2.0$ Hz, 1H), 4.64 (d, $J = 11.6$ Hz, 1H), 4.54 (d, $J = 7.6$ Hz, 1H), 4.53 (d, $J = 12.0$ Hz, 1H), 4.27 (dd, $J = 9.6$, 3.2 Hz, 1H), 4.09 (m, 2H), 3.86 (dd, $J = 9.4$, 7.6 Hz, 1H), 3.72 (dd, $J = 3.2$, 2.0 Hz, 1H), 3.67–3.55 (m, 4H), 3.47 (q, $J = 6.6$ Hz, 1H), 3.32 (s, 3H), 1.33 (d, $J = 6.2$ Hz, 3H), 1.17 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0, 138.8, 138.7, 138.5 ($4C_{ipso}$), 135.1 ($OCH_2CH{=}CH_2$), 128.5–127.0 (C–Ar), 116.9 ($OCH_2CH{=}CH_2$), 100.8, 99.0 (C-1_A, C-1_B), 82.9, 79.6, 79.5, 76.8, 76.6, 75.0, 74.8, 74.7, 72.9, 72.1, 72.0, 70.4, 67.6 (C-2_A, C-2_B, C-3_A, C-3_B, C-4_A, C-4_B, C-5_A, C-5_B, $4OCH_2Ph$, $OCH_2CH{=}CH_2$), 54.5 (OCH_3), 18.0, 16.8 (C-6_A, C-6_B). MALDIMS for $C_{44}H_{52}O_9$ (*m*/*z*): M_r(calcd) 724.36, M_r(found) 747.38 $(M+Na)^+$. Anal. Calcd: C, 72.90; H, 7.23. Found: C, 73.09; H, 7.16.

3.4.9. Methyl (2,4-di-*O*-benzyl-α-D-tyvelopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (20α). $[\alpha]_D$ +3.1 (*c* 0.6, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.09 (m, 25H), 5.07 (br s, 1H), 4.75 (m, 3H), 4.67 (d, $J = 12.3$ Hz, 1H), 4.65 (d, $J = 11.4$ Hz, 1H), 4.58 (d, $J = 12.0$ Hz, 1H), 4.51 (d, $J = 12.0$ Hz, 1H), 4.48 (d, $J = 11.1$ Hz, 1H), 4.46 (d, $J = 11.4$ Hz, 1H), 4.34 (d, $J = 12.0$ Hz, 1H), 4.23 (d, $J = 12.0$ Hz, 1H), 4.17 (dd, $J = 9.3$, 3.0 Hz, 1H), 3.98 (t, $J = 9.3$ Hz, 1H), 3.86 (dq, $J = 9.0$, 6.3 Hz, 1H), 3.78–3.60 (m, 4H), 3.45 (td, $J = 8.2$, 3.6 Hz, 1H), 3.34 (m, 4H), 2.22 (dt, $J = 13.2$, 3.0 Hz, 1H), 1.78 (ddd, $J = 13.2$, 10.2, 3.0 Hz, 1H), 1.26 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5–138.2 ($5C_{ipso}$), 129.3–127.5 (C–Ar), 98.7 (C-1_A, C-1_B), 77.8, 77.1, 75.5, 75.3, 75.2, 74.4, 73.3, 72.6, 71.8, 70.9, 70.8, 69.1, 68.7 (C-2_A, C-2_B, C-3_A, C-4_A, C-4_B, C-5_A, C-5_B, C-6_A, $5OCH_2Ph$), 54.7 (OCH_3), 29.6 (C-3_B), 18.1 (C-6_B). MALDIMS for $C_{48}H_{54}O_9$ (*m*/*z*): M_r(calcd) 774.38, M_r(found) 797.49 $(M+Na)^+$. Anal. Calcd: C, 74.39; H, 7.02. Found: C, 74.25; H, 7.09.

3.4.10. Methyl (2,4-di-*O*-benzyl-β-D-tyvelopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (20β). $[\alpha]_D$ +4.1 (*c* 0.6, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.09 (m, 25H), 5.05 (d, $J = 10.2$ Hz, 1H), 4.81 (m, 2H), 4.71 (d, $J = 12.3$ Hz, 1H), 4.65–4.52 (m, 5H), 4.47 (br s, 1H), 4.43 (d, $J = 11.2$ Hz, 1H), 4.38 (d, $J = 10.5$ Hz, 1H), 4.21 (dd, $J = 8.1$, 3.3 Hz, 1H), 3.86 (t, $J = 8.1$ Hz, 1H), 3.76–3.54 (m, 5H), 3.47 (td, $J = 10.2$, 3.9 Hz, 1H), 3.36 (m, 4H), 2.29 (dt, $J = 13.5$, 3.9 Hz, 1H), 1.36 (ddd, $J = 13.5$, 9.9, 3.0 Hz, 1H), 1.30 (d, $J = 6.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 138.8, 138.5, 138.4, 138.2 ($5C_{ipso}$), 129.7–127.2 (C–Ar), 99.4, 98.9 (C-1_A, C-1_B), 76.9, 76.6, 75.5, 75.1, 74.9, 74.3, 74.2, 73.3, 72.7, 72.6, 71.7, 71.3, 69.6 (C-2_A, C-2_B, C-3_A, C-4_A, C-4_B, C-5_A, C-5_B, C-6_A, $5OCH_2Ph$), 54.7 (OCH_3), 33.7 (C-3_B), 18.4 (C-6_B). MALDIMS for $C_{48}H_{54}O_9$ (*m*/*z*): M_r(calcd) 774.38, M_r(found) 797.45 $(M+Na)^+$. Anal. Calcd: C, 74.39; H, 7.02. Found: C, 74.28; H, 7.10.

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