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First synthesis of an α-D-Fuc*p*3NAc containing oligosaccharide: a study on D-Fuc*p*3NAc glycosylation

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Abstract—3-Acetamido-3,6-dideoxy-D-galactopyranose (D-Fuc*p*3NAc) is an aminosugar almost exclusively found in phytopathogenic *O*-antigens. The glycosylation reaction involving D-Fuc*p*3NAc donors was studied with several rhamnosyl acceptors, revealing that the best yields and highest α-stereoselectivity were obtainable by coupling a *N*-phenyl trifluoroacetimidate glycosyl donor in a ternary mixture (dioxane/DME/toluene 4:1:1) as solvent. For the first time a synthetic access to α-D-Fuc*p*3NAc containing oligorhamnans, that are interesting molecules for studying the effects of *O*-antigen model oligosaccharides on the modulation of plant response to bacteria, was reported. An example is the pentasaccharide repeating unit of the major *O*-antigen component from *Pseudomonas syringae* pv. *holci* IMV 8300, which was synthesized as its methyl glycoside.

1. Introduction

Lipopolysaccharides (LPSs) are amphiphilic macromolecules that are located on the external membrane of Gram-negative bacteria.[1] They consist of three different domains:[2] a lipid part, named Lipid-A, an oligosaccharide region, named Core and a polysaccharide portion (*O*-specific chain, or simply *O*-chain), consisting of a 1–8 sugar residues repeating unit, and extends out from the bacterial membrane surface. The role of LPSs in bacterial interactions both with animals and plants is surely crucial, as they cover almost 80% of the cell surface; therefore, they have been the object of many studies, especially in relation to Gram-negative bacteria that are pathogenic to humans and mammals.[3] These studies elucidated that most of the biological activities of LPS are played by Lipid-A, nevertheless *O*-chain is also involved in interactions between bacterial cells and their eukaryotic hosts with its antigenic properties.

However, the effects of LPSs on plant cells have still been poorly elucidated. The only extensive study is on the ability of LPS to prevent the hypersensitive response (HR) caused in plants by avirulent bacteria.[4,5] Even if the molecular basis of the LPS-plant interaction is still very far from completely known, the *O*-chain should be highly involved in the interaction mechanism,[5] because of its extension out from the bacterial cell.

The *O*-chain from phytopathogenic bacteria is typically made of a repeating unit with a linear L- and/or D-rhamnosyl skeleton. This backbone usually bears, as a branch, a single monosaccharide, that can be a common monose (L- or D-Xyl*p*, L- or D-Rha*p*, D-Glc*p*NAc, D-Fuc*f*) or a peculiar aminosugar, 3-acetamido-3,6-dideoxy-D-galactopyranose (D-Fuc*p*3NAc), that is almost exclusively found in LPS from phytopathogenic bacteria.[6] Interestingly, the linkage between D-Fuc*p*3NAc and the rhamnosyl backbone occurs in natural oligosaccharides exclusively as the α-glycoside.

In a recent study, synthetic linear oligorhamnans, mimicking the common structure of the *O*-chain backbones from phytopathogenic bacteria, have been proved to be effective in preventing HR,[7] demonstrating in this way that oligosaccharides are also plant-recognizable pathogen-associated molecular patterns (PAMPs).[8] In order to investigate deeper the effects of oligosaccharides on the modulation of plant response to bacteria, the synthesis of model oligosaccharides, related to the repeating units of *O*-chain, has recently become a topic of interest in carbohydrate synthesis.[9]

In particular, in this paper we have studied the coupling reaction between D-Fuc*p*3NAc trihaloacetimidate donors and some L- and D-rhamnosyl acceptors, in order to open a

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synthetic access to α-D-Fuc*p*3NAc containing oligorhamnans, which are model oligosaccharides of the repeating units of *O*-chain from phytopathogenic bacteria. To demonstrate the effectiveness of this route, we have synthesized the methyl glycoside of the pentasaccharide repeating unit of the major *O*-antigen component from *Pseudomonas syringae* pv. *holci* IMV 8300[10] (Fig. 1). To the best of our knowledge, this is the first synthesis of an α-D-Fuc*p*3NAc containing oligosaccharide.

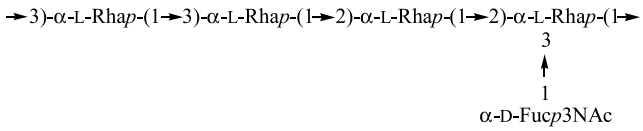
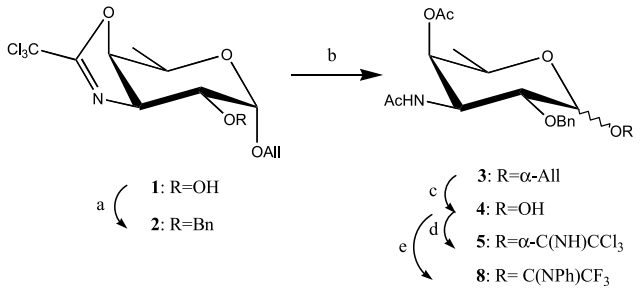


Figure 1. The repeating unit of the major *O*-antigen component from *P. syringae* pv. *holci* IMV 8300.

2. Results and discussion

2.1. Study on D-Fuc*p*3NAc glycosidation reaction

The preparative synthesis of the D-Fuc*p*3N building-block **1** from D-fucose has recently been reported.[11] This molecule could be further elaborated to afford D-Fuc*p*3N donors, firstly by protecting position *O*-2. Since D-Fuc*p*3NAc exclusively occurs in the natural polysaccharides as the α-glycoside, a non-participating protecting group, such as the benzyl group, was chosen. Thus, **1** was benzylated to give **2** (68%) that was then subjected to cleavage of the oxazoline ring by acid hydrolysis, and subsequent acetylation of the obtained amino-alcohol (63% over two steps) (Scheme 1). Also the use of an acyl group in position *O*-4 was in accordance with the required α-stereoselectivity in D-Fuc*p*3N glycosidations. Actually, a long range participation effect was firstly postulated[12] and then evidenced[13] to be active in glycosylations involving 4-*O*-acyl-galactose donors; nevertheless it has not been observed in two recent works regarding the coupling of 4-*O*-acyl-thioglycosides.[14,15] We therefore decided to activate D-Fuc*p*3N as trichloroacetimidate, since the use of this kind of glycosyl donor for performing fucosylations with high α-selectivities has been already reported.[16]



Scheme 1. Reagents and conditions: (a) BnBr, NaH, DMF, rt, 68%; (b) (i) 1 M HCl, THF, rt, (ii) Ac_2O, py, rt, 63% over two steps; (c) $PdCl_2$, 1:1 CH_2Cl_2/MeOH, rt, 84% (α/β=1:1.5 as determined by ^1H NMR analysis); (d) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 53%; (e) $CF_3C(NPh)Cl$, NaH, 4 Å molecular sieves, CH_2Cl_2, 0 °C, 74% (α/β=3:1 as determined by ^1H NMR analysis).

The anomeric allyl protecting group of **3** was removed with $PdCl_2$ (84%); the conversion of the resulting hemi-acetal **4** into the α-trichloroacetimidate **5** by treatment with Cl_3CCN and DBU proceeded with only moderate yield (53%). The coupling of **5** with the rhamnosyl acceptors **6**[17] and **7**[18] in CH_2Cl_2 using catalytic TMSOTf (0.01 equiv) as activator led to the consumption of the donor in few min, even working at −50 °C, affording only traces of the desired disaccharides (Fig. 2 and Table 1, entries 1 and 2). A milder activator ($BF_3\cdot OEt_2$), was unfortunately not able to activate **5**, even when used in a more than stoichiometric amount in CH_2Cl_2 at reflux (entry 3).

The rapid decomposition of a 4-*O*-acyl-2-benzylated fucosyl trichloroacetimidate with catalytic TMSOTf in CH_2Cl_2 has been recently reported;[19] moreover, a trimethylated fucosyl trichloroacetimidate revealed a high instability towards many activation conditions,[20] demonstrating in this way the difficulty, in some cases, in glycosylating armed fucosyl-trichloroacetimidates. The difficulty in coupling a D-Fuc*p*3N TCAI-donor as **5** and the not very satisfying yield in obtaining it from **4**, suggested the use of a different glycosyl donor.

Recently, a different trihaloacetimidate, the *N*-phenyl trifluoroacetimidate leaving group, has been installed on the anomeric position of carbohydrates to act as novel glycosyl donor.[21] Since fucosyl *N*-phenyl trifluoroacetimidates have been already successfully glycosylated,[22] the use of this donor also in the D-Fuc*p*3N case has been attempted. Thus, **4** was treated with $CF_3C(NPh)CCl$ and NaH[23] giving **8** in a better yield (74%; α/β 3:1) than **5**.

Gratifyingly, the coupling of **8** respectively with **6** and **7** in CH_2Cl_2 proceeded smoothly, giving disaccharides **9** and **10** in good yields but with moderate α-selectivity (Table 1, entries 4 and 5). Interestingly, 0.1 equiv of TMSOTf were necessary to perform the couplings, but the use of so much activator did not cause significant glycosyl donor decomposition. In order to enhance the α-selectivity of the couplings, we turned to different solvent systems. In particular, α-selectivity is generally favored in electron-donating solvents such as ethers, even if their use can sometimes decrease the total yield of the glycosylation;[24] nevertheless, the use of an 'ether-based' ternary mixture (dioxane/DME/toluene 4:1:1) as solvent for glycosylations involving armed *N*-phenyl trifluoroacetimidate donors, led to higher stereoselectivities of 1,2-*cis*-adducts without affecting the yield of the reactions.[22,25] Actually, performing the coupling between **8** and **7** in this solvent system, the α-stereoselectivity was highly enhanced without a noticeable decrease of the yield (entry 6).

2.2. Synthesis of the pentasaccharide repeating unit of the major *O*-antigen component from *P. syringae* pv. *holci* IMV 8300

The optimization of the conditions for the α-stereoselective coupling between a D-Fuc*p*3N donor as **8** and rhamnosyl acceptors led us to perform the first synthesis of an α-Fuc*p*-3NAc containing repeating unit of *O*-chain from phytopathogenic bacteria, in order to demonstrate the effectiveness of this synthetic approach to this kind of

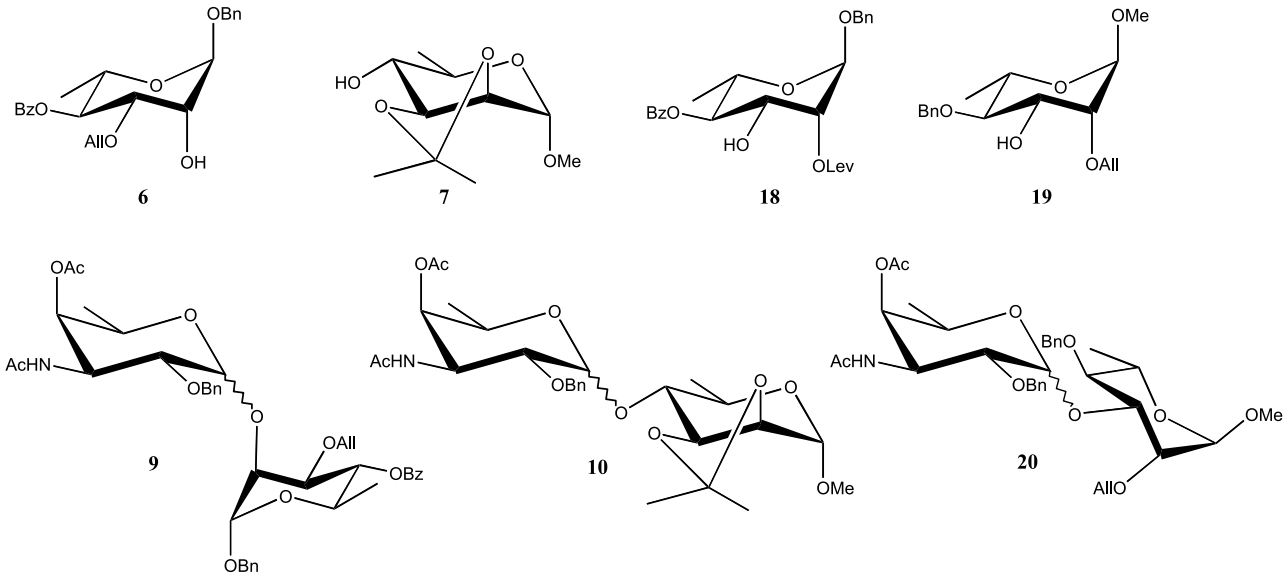


Figure 2. Glycosyl acceptors and products of Table 1 (reaction conditions of the glycosidations are described therein).

Table 1. Glycosylations with D-Fuc*p*3N trihaloacetimidate donors

Entry	Acceptor	Donor	Solvent	Activator	Yield[a] (α/β)	Product
1	**6**	**5** (2.0 equiv)	CH_2Cl_2	TMSOTf	Traces	**9**
2	**7**	**5** (2.0 equiv)	CH_2Cl_2	TMSOTf	Traces	**10**
3	**6**	**5** (2.0 equiv)	CH_2Cl_2	$BF_3 \cdot OEt_2$	No product	—
4	**6**	**8** (2.0 equiv)	CH_2Cl_2	TMSOTf	65% (62:38)[b]	**9**
5	**7**	**8** (2.0 equiv)	CH_2Cl_2	TMSOTf	61% (68:32)[b]	**10**
6	**7**	**8** (1.5 equiv)	Dioxane/DME/ toluene 4:1:1	TMSOTf	55% (88:12)[b]	**10**
7	**18**	**8** (1.5 equiv)	Dioxane/DME/ toluene 4:1:1	TMSOTf	No product	—
8	**19**	**8** (1.8 equiv)	CH_2Cl_2	TMSOTf	70% (82:18)[c]	**20**
9	**19**	**8** (1.5 equiv)	Dioxane/DME/ toluene 4:1:1	TMSOTf	63% (89:11)[c]	**20**

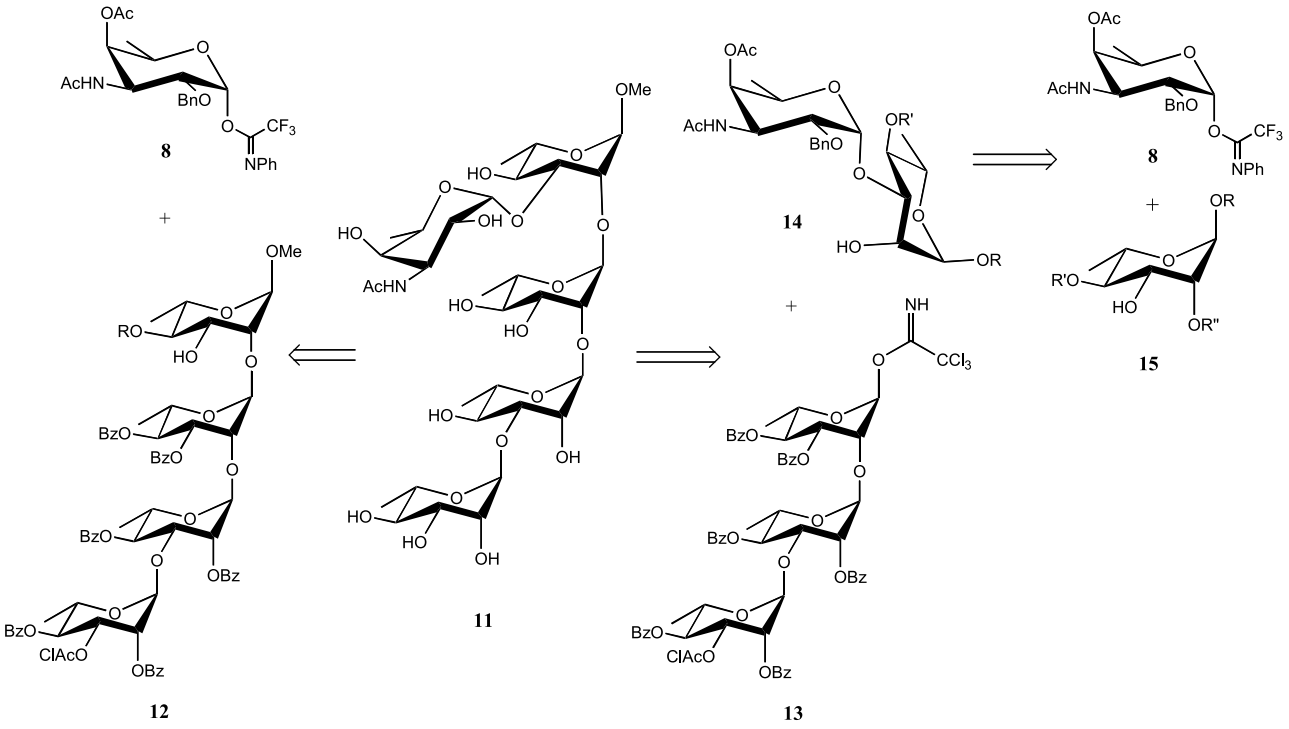
[a] Isolated yield.
[b] Measured by ^{1}H NMR.
[c] Measured after separation of the two anomers.

oligosaccharides. Among the several repeating units that characterise each serotype of phytopathogenic lipopolysaccharides, the pentasaccharide repeating unit of the major *O*-antigen component from *P. syringae* pv. *holci* IMV 8300[10] was chosen (Fig. 1).

For the synthesis of the branched pentasaccharide **11**, two paths could be planned: retrosynthetic analysis suggested either a (4+1) approach, involving the coupling between **8** and a linear rhamnosyl tetrasaccharide **12**,[17] or a (3+2) strategy, in, which the key-glycosylation regards the trisaccharide donor **13**[17] and the disaccharide acceptor **14**, which could be obtained by coupling **8** with a suitable rhamnosyl *O*-3 acceptor **15** (Scheme 2).

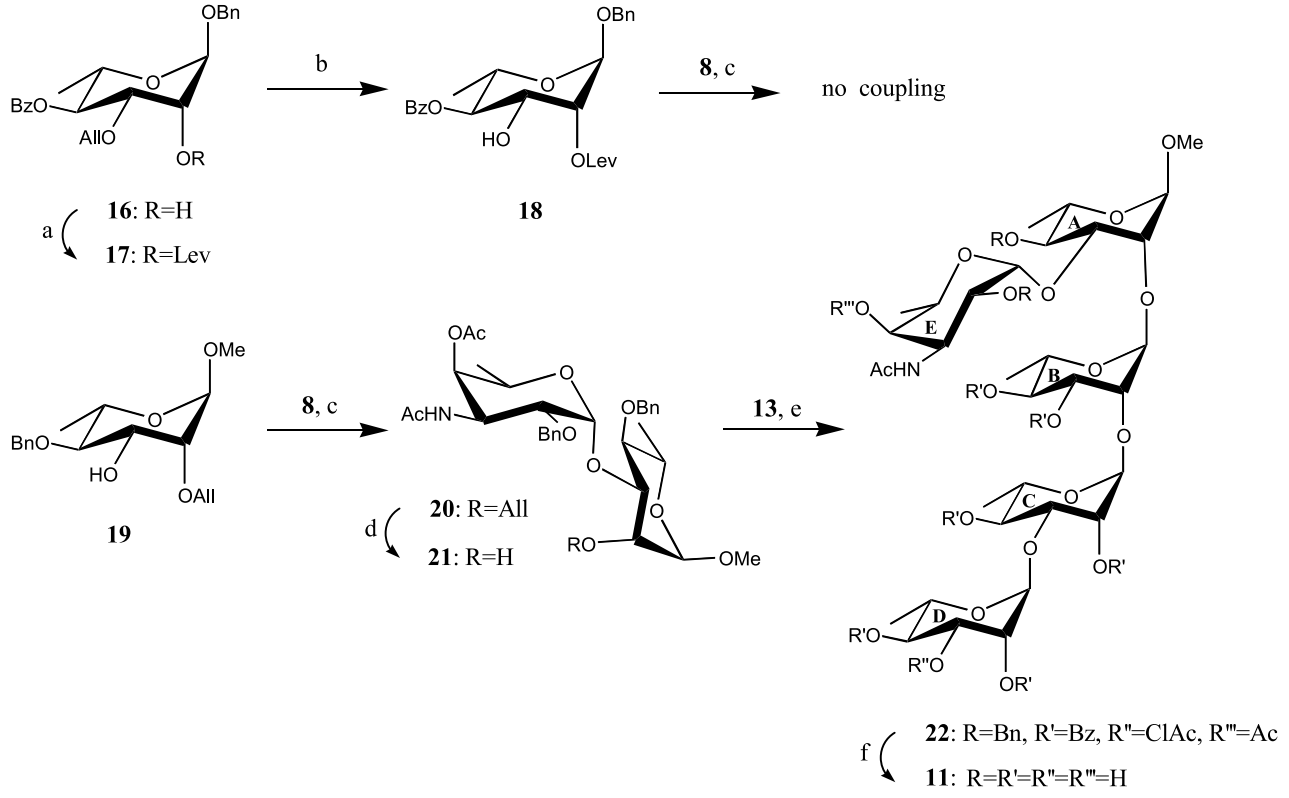
In the synthesis of an analogous pentasaccharide, the major component from *P. syringae* pv. *ribicola* NVPPB 1010, in which the D-Fuc*p*3N branch is replaced by a D-Glc*p*NAc unit,[26] a (4+1) strategy was chosen.[17] It revealed that the (4+1) key-coupling needed a large excess of the aminosugar donor, because of the very poor reactivity of the acceptor **12** (with R=Bz). Since donor **8** was quite 'precious', the other strategy, the (3+2) approach, was chosen for the synthesis of **11**. It required the synthesis of the rhamnosyl *O*-3 acceptor **15**, whose position 2 would be protected with an orthogonal protecting group. Firstly levulinoyl (Lev) was chosen as protecting group for this position. Thus, the known benzyl 3-*O*-allyl-4-*O*-benzoyl-α-L-rhamnopyranoside **16**[17] was subjected to levulination with LevOH in presence of *N*,*N*′-diisopropylcarbodiimide (DIPC) and 4-dimethylaminopyridine (DMAP) (99%) and subsequent de-*O*-allylation with $PdCl_2$ (78%): no acyl migration was observed during the allyl cleavage to obtain **18** (Scheme 3).[27] Unfortunately, the coupling between **8** and **18** was unsuccessful, revealing that the coupling of the D-Fuc*p*3NAc donor **8** probably works only with armed acceptors. Actually, when **8** was coupled with the armed 2-*O*-allylated rhamnosyl *O*-3 acceptor **19**,[28,29] disaccharide **20** was obtained in satisfying yield both in CH_2Cl_2 and in dioxane/DME/toluene 4:1:1 (Table 1, entries 8 and 9). In order to obtain a suitable disaccharide glycosyl acceptor, **20** was subjected to de-*O*-allylation to give **21** in high yield (93%).

The coupling between **21** and the trisaccharide trichloroacetimidate donor **13** was performed in CH_2Cl_2 with



Scheme 2. Retrosynthetic analysis of the methyl glycoside of the pentasaccharide repeating unit of the major *O*-antigen component from *P. syringae* pv. *holci* IMV 8300.

$BF_3 \cdot OEt_2$ as activator, giving **22** in 51% yield. As expected, the new glycosidic bond was formed with total α-stereoselectivity, as ascertained by the value of the heteronuclear $^1J_{C,H}$ coupling constant ($^1J_{C,H}$ = 173 Hz),[30] measured in a coupled HMQC-COSY experiment. Besides, even if the 2-OH group of the glycosyl acceptor **14** was considered to be poorly reactive due to its steric hindrance, and therefore susceptible to competition by the NHAc group as a



Scheme 3. Reagents and conditions: (a) LevOH, DIPC, DMAP, CH_2Cl_2, rt, 99%; (b) $PdCl_2$, 3:2 CH_2Cl_2/MeOH, rt, 78%; (c) see Table 1, entries 7–9; (d) $PdCl_2$, 1:1 CH_2Cl_2/MeOH, rt, 93%; (e) $BF_3 \cdot OEt_2$, AW-300 4 Å molecular sieves, CH_2Cl_2, −20 °C, 51%; (f) (i) Pd/C, 9:1 MeOH/HCOOH, ultrasound bath, rt, (ii) 1 M NaOMe, MeOH, rt, 78% over two steps.

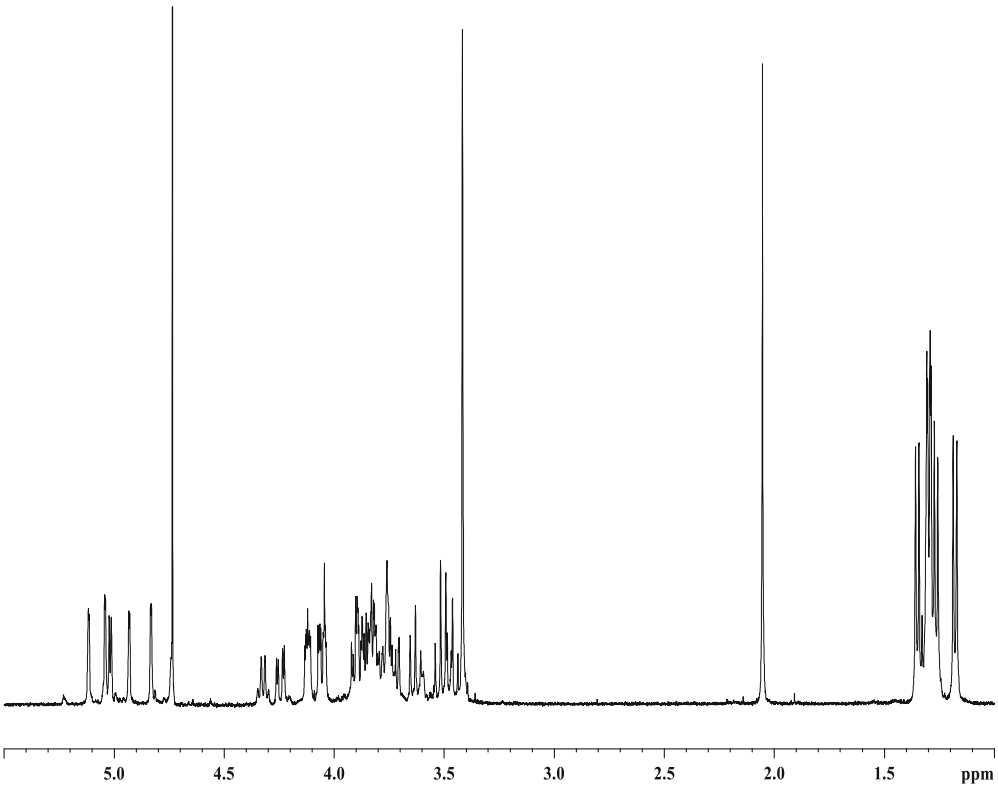


Figure 3. ^{1}H NMR spectrum (D_2O, 400 MHz) of the target pentasaccharide **11**.

nucleophile in the glycosylation,[31] no imidate adducts were detected during the reaction course. Finally, a two-step deprotection of **22** (debenzylation by transfer hydrogenation under Perlin's conditions,[32] and subsequent de-*O*-acylation with sodium methoxide) afforded the target pentasaccharide **11** in 78% yield (^{1}H NMR spectrum of **11** reported in Fig. 3).

3. Summary

The study on the glycosylation reaction involving a D-Fuc*p*3N donor here reported revealed that the *N*-phenyl trifluoroacetimidate of D-Fuc*p*3N gives good yields with several armed rhamnosyl acceptors and a high α-stereoselectivity is achievable by using a ternary mixture (dioxane/DME/toluene 4:1:1) as solvent. This study opens a route to the synthesis of α-D-Fuc*p*3NAc containing oligorhamnans, that are interesting molecules for studying the effects of *O*-antigen model oligosaccharides on the modulation of plant response to bacteria. An example of the synthetic accessibility to these molecules is the first reported synthesis of an α-D-Fuc*p*3NAc containing oligosaccharide, the methyl glycoside of the pentasaccharide repeating unit of the major *O*-antigen component from *P. syringae* pv. *holci* IMV 8300.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on Varian XL-200 (^{1}H: 200 MHz, ^{13}C: 50 MHz) or Bruker DRX-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) instruments in $CDCl_3$ ($CHCl_3$ as internal standard, ^{1}H: C*H*Cl_3 at δ 7.26; ^{13}C: *C*DCl_3 at δ 77.0) and in D_2O (acetone as internal standard, ^{1}H: (CH_3)$_2$CO at δ 2.05; ^{13}C: (CH_3)$_2$CO at δ 31.5). Assignment of proton chemical shifts were based on 1D HOHAHA and COSY experiments. For pentasaccharides **11** and **22**, 2D NMR experiments such as TOCSY, NOESY, HSQC and HMQC-COSY were also performed to assign proton and carbon chemical shifts. Positive ESI-MS spectra were recorded on a Finnigan LCQ-DECA ion trap mass spectrometer. IR spectra were recorded on a JASCO-FT/IR-430 spectrometer. Optical rotations were measured on a JASCO P-1010 polarimeter. Analytical thin layer chromatographies (TLC) were performed on aluminium plates precoated with Merck Silica Gel 60 F_{254} as the adsorbent. The plates were developed with 5% H_2SO_4 ethanolic solution and then heating to 130 °C. Column chromatographies were performed on Merck Kieselgel 60 (63–200 mesh), except where differently specified. Gel-filtration chromatography was performed on a Sephadex G-10 column (1.0×20 cm) with water as eluant.

4.1.1. Allyl 2-*O*-benzyl-3-deoxy-4,3-(2-trichloromethyl-1-oxa-3-azaprop-2-eno)-α-D-fucopyranoside (2). A solution of **1** (903 mg, 2.74 mmol) in DMF (20 mL) was treated with BnBr (3.4 mL, 28.6 mmol) and NaH (60% oil suspension; 353 mg, 14.7 mmol). The solution was stirred at rt for 90 min, the solution was then diluted with CH_2Cl_2 (300 mL) and washed with water (300 mL). The organic layer was collected, dried and concentrated to give a residue that, after chromatography (11:1 petroleum ether/EtOAc), afforded pure **2** (840 mg, 68%) as a yellowish oil. $[\alpha]_D$

+70.2 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3035, 2944, 1677, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.36 (m, 5H, H-Ar), 5.91 (m, 1H, $OCH_2CH{=}CH_2$), 5.32 (dd, 1H, $J_{vic}=17.2$ Hz, $J_{gem}=1.6$ Hz, $OCH_2CH{=}CHH$ *trans*), 5.20 (dd, 1H, $J_{vic}=10.4$ Hz, $J_{gem}=1.6$ Hz, $OCH_2CH{=}CHH$ *cis*), 4.85 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.76–4.69 (m, 3H, H_1, H_4, OC*H*HPh), 4.55 (dd, 1H, $J_{3,4}=9.0$ Hz, $J_{3,2}=5.4$ Hz, H_3), 4.30 (m, 2H, H_5, OC*H*HCH=CH_2), 4.05 (m, 1H, OC*H*HCH=CH_2), 3.77 (dd, 1H, $J_{2,3}=5.4$ Hz, $J_{2,1}=4.0$ Hz, H_2), 1.33 (d, 3H, $J_{6,5}=6.6$ Hz, H_6); ($CDCl_3$, 50 MHz) δ 164.1 (*C*=N), 138.0 (C_{ipso}), 134.0 ($OCH_2CH{=}CH_2$), 128.5 (C-Ar), 117.2 ($OCH_2CH{=}CH_2$), 96.1 (C_1), 84.7 (C_4), 74.0, 73.8, 68.7, 66.8, 64.2 (C_2, C_3, C_5, $OCH_2CH{=}CH_2$, OCH_2Ph), 16.1 (C_6). ESI-MS for $C_{18}H_{20}Cl_3NO_4$ (*m*/*z*): M_r (calcd) 419.05, M_r (found) 442.28 $(M+Na)^+$. Anal. Calcd: C, 51.39; H, 4.79; N, 3.33. Found: C, 51.55; H, 4.70; N, 3.32.

4.1.2. Allyl 4-*O*-acetyl-3-acetamido-2-*O*-benzyl-α-D-fucopyranoside (3). To a solution of **2** (689 mg, 1.64 mmol) in THF (10 mL), 1 M HCl was added (1.57 mL). The mixture was vigorously stirred at rt for 30 min, after that 1 M $NaHCO_3$ (200 mL) was added. Stirring was continued for additional 10 min, then EtOAc (200 mL) was added. The organic layer was collected, dried and concentrated to afford an oily residue that was subsequently dissolved in pyridine (3 mL). The solution was treated with acetic anhydride (3 mL) and stirred at rt overnight. The solution was then concentrated and the residue dissolved in CH_2Cl_2 (100 mL) and extracted with 1 M HCl (100 mL) and water (100 mL). The organic layer was collected, dried and concentrated to afford a residue, that, after chromatography (3:2 petroleum ether/EtOAc), gave pure **3** (403 mg, 63%) as a white foam. $[\alpha]_D$ +126.8 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3055, 2951, 1735, 1664, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.36 (m, 5H, H-Ar), 5.897 (m, 1H, $OCH_2CH{=}CH_2$), 5.35–5.14 (m, 4H, H_4, NH, $OCH_2CH{=}CH_2$), 4.95 (d, 1H, $J_{1,2}=2.7$ Hz, H_1), 4.65 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.53 (m, 1H, H_3), 4.47 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.13 (m, 2H, H_5, $OCH_2CH{=}CH_2$), 3.97 (m, 2H, $OCH_2CH{=}CH_2$), 3.67 (dd, 1H, $J_{2,3}=11.4$ Hz, $J_{2,1}=2.7$ Hz, H_2), 2.06 (s, 3H, OAc), 1.79 (s, 3H, NAc), 1.03 (d, 3H, $J_{6,5}=6.6$ Hz, H_6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.0 (2 *C*OCH_3), 138.0 (C_{ipso}), 133.7 ($OCH_2CH{=}CH_2$), 128.5 (C-Ar), 117.8 ($OCH_2CH{=}CH_2$), 95.4 (C_1), 73.1, 72.7, 71.6, 68.4, 64.8 (C_2, C_4, C_5, $OCH_2CH{=}CH_2$, OCH_2Ph), 48.2 (C_3), 23.0, 20.6 (2 CO*C*H_3), 16.1 (C_6). ESI-MS for $C_{20}H_{27}NO_6$ (*m*/*z*): M_r (calcd) 377.18, M_r (found) 400.37 $(M+Na)^+$. Anal. Calcd: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.80; H, 7.00; N, 3.65.

4.1.3. 4-*O*-Acetyl-3-acetamido-2-*O*-benzyl-D-fucopyranose (4). A suspension of **3** (357 mg, 0.92 mmol) and $PdCl_2$ (27 mg, 0.15 mmol) in 1:1 CH_2Cl_2/MeOH (10 mL) was vigorously stirred at rt for 5 h. The mixture was filtered over a Celite pad, then diluted with CH_2Cl_2 (150 mL) and washed with 5 M NaCl (150 mL). The organic layer was collected, dried and concentrated. The resulting residue was chromatographed (1:1 petroleum ether/EtOAc) to afford **4** (270 mg, 84%; $\alpha/\beta=1{:}1.5$) as a yellowish oil. IR (thin film, NaCl) 3517, 3009, 1743, 1666, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.40 (d, 1H, $J_{1,2}=3.6$ Hz, H-1$^{\alpha}$), 5.27 (d, 1H, $J_{4,3}=2.8$ Hz, H-4$^{\alpha}$), 5.21 (d, 1H, $J_{4,3}=2.8$ Hz, H-4$^{\beta}$), 5.01–4.83 (m, 4H, H-1$^{\beta}$, NH$^{\alpha}$, NH$^{\beta}$, OC*H*HPh), 4.76 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.68 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.53 (m, 2H, H-3$^{\alpha}$, OC*H*HPh), 4.38 (q, 1H, $J_{5,6}=6.6$ Hz, H-5$^{\alpha}$), 4.17 (m, 1H, H-3$^{\beta}$), 3.84 (q, 1H, $J_{5,6}=6.6$ Hz, H-5$^{\beta}$), 3.63 (dd, 1H, $J_{2,3}=10.2$ Hz, $J_{2,1}=3.6$ Hz, H-2$^{\alpha}$), 3.33 (dd, 1H, $J_{2,3}=10.2$ Hz, $J_{2,1}=7.2$ Hz, H-2$^{\beta}$), 2.08 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.84 (s, 3H, NAc), 1.79 (s, 3H, NAc), 1.13 (d, 3H, $J_{6,5}=6.6$ Hz, H-5$^{\beta}$), 1.07 (d, 3H, $J_{6,5}=6.6$ Hz, H-5$^{\alpha}$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.0 (4 *C*OCH_3), 138.1 (C_{ipso}), 137.4 (C_{ipso}), 128.4 (C-Ar), 98.0 (C-1$^{\alpha}$), 90.5 (C-1$^{\beta}$), 76.0, 73.7, 72.8, 72.1, 71.9, 70.2, 65.0, 60.4 (C-2$^{\alpha}$, C-2$^{\beta}$, C-4$^{\alpha}$, C-4$^{\beta}$, C-5$^{\alpha}$, C-5$^{\beta}$, 2 OCH_2Ph), 52.0, 47.8 (C-3$^{\alpha}$, C-3$^{\beta}$), 23.2 (2 *C*OCH_3), 21.0, 20.7 (2 CO*C*H_3), 16.5, 16.3 (C-6$^{\alpha}$, C-6$^{\beta}$). ESI-MS for $C_{17}H_{23}NO_6$ (*m*/*z*): M_r (calcd) 337.15, M_r (found) 360.22 $(M+Na)^+$. Anal. Calcd: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.89; H, 6.80; N, 4.00.

4.1.4. 4-*O*-Acetyl-3-acetamido-2-*O*-benzyl-α-D-fucopyranosyl trichloroacetimidate (5). Compound **4** (77 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (3.0 mL) under an argon atmosphere and to the 0 °C cooled solution Cl_3CCN (115 μL, 1.21 mmol) and DBU (3.3 μL, 6.6 μmol) were added. The solution was stirred at 0 °C for 4 h and then concentrated. The resulting residue was chromatographed (1:1 petroleum ether/EtOAc) over neutral alumina gel to afford **5** (57 mg, 53%) as a white foam. $[\alpha]_D$ +99.2 (*c* 0.8, CH_2Cl_2). IR (thin film, NaCl) 3022, 2979, 1739, 1671 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.60 (s, 1H, N*H*CCl_3), 7.36 (m, 5H, H-Ar), 6.60 (d, 1H, $J_{1,2}=3.4$ Hz, H_1), 5.41 (d, 1H, $J_{4,3}=2.4$ Hz, H_4), 5.02 (d, 1H, $J_{H,NH}=6.6$ Hz, NH), 4.75 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.55 (m, 1H, H_3), 4.46 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.33 (q, 1H, $J_{5,6}=6.6$ Hz, H_5), 3.81 (dd, 1H, $J_{2,3}=11.4$ Hz, $J_{2,1}=3.4$ Hz), 2.08 (s, 3H, OAc), 1.84 (s, 3H, NAc), 1.09 (d, 3H, $J_{6,5}=6.6$ Hz, H_6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.1, 169.9 (2 *C*OCH_3), 161.4 (Cl_3CC=NH), 137.4 (C_{ipso}), 128.3 (C-Ar), 93.5 (C-1), 72.0, 71.9, 71.8, 67.8 (C_2, C_4, C_5, OCH_2Ph), 48.7 (C_3), 23.1, 20.6 (2 CO*C*H_3), 16.3 (C_6). ESI-MS for $C_{19}H_{23}Cl_3N_2O_6$ (*m*/*z*): M_r (calcd) 480.06, M_r (found) 513.30 $(M+Na)^+$. Anal. Calcd: C, 47.37; H, 4.81; N, 5.81. Found: C, 47.60; H, 4.89; N, 5.75.

4.1.5. 4-*O*-Acetyl-3-acetamido-2-*O*-benzyl-D-fucopyranosyl *N*-phenyl-trifluoroacetimidate (8). A mixture of **4** (251 mg, 0.72 mmol) and freshly powdered 4 Å molecular sieves was suspended under argon in CH_2Cl_2 (5 mL) and cooled to 0 °C under stirring. CF_3C(NPh)Cl (53 μL, 0.42 mmol) and NaH (60% oil suspension; 17 mg, 0.42 mmol) were added and stirred was continued at 0 °C for 3 h, after that the mixture was filtered over Celite and the filtrate concentrated. Neutral alumina (Brockman grade 1) column chromatography (3:2 petroleum ether/EtOAc) on the residue, afforded **8** (277 mg, 74%; $\alpha/\beta=3{:}1$) as a colourless oil. IR (thin film, NaCl) 3040, 1738, 1670, 1656, 1260 cm^{-1}; ^1H NMR NMR ($CDCl_3$, 200 MHz) (α-anomer) δ 7.42–6.73 (H-Ar), 6.60 (m, 1H, H-1), 5.38 (d, 1H, $J_{4,3}=2.4$ Hz, H-4), 4.83 (m, 2H, NH, OC*H*HPh), 4.50 (m, 2H, H_3, OC*H*HPh), 4.28 (q, 1H, $J_{5,6}=6.6$ Hz, H-5), 3.75 (dd, 1H, $J_{2,3}=10.2$ Hz, $J_{2,1}=3.4$ Hz, H-2), 2.07 (s, 3H, OAc), 1.84 (s, 3H, NAc), 1.11 (dd, 3H, $J_{6,5}=6.6$ Hz, H-6); ^{13}C NMR ($CDCl_3$, 50 MHz) (α-anomer) δ 170.1, 169.9 (2 *C*OCH_3),

143.5, 137.4 (2 C_{ipso}), 129.3–119.4 (C-Ar), 92.5 (C-1), 72.3, 71.9, 71.8, 67.9 (C_2, C_4 C_5, OCH_2Ph), 48.5 (C_3), 23.2, 20.6 (2 COCH_3), 16.4 (C_6). ESI-MS for $C_{25}H_{27}F_3N_2O_6$ (*m/z*): M_r (calcd) 508.18, M_r (found) 531.38 $(M+Na)^+$. Anal. Calcd: C, 59.05; H, 5, 35; N, 5.51. Found: C, 59.10; H, 5.45; N, 5.43.

4.2. General procedure for D-Fuc*p*3NAc couplings in CH_2Cl_2

A mixture of donor **8** (37 mg, 0.074 mmol) and rhamnosyl acceptor (0.037 mmol) was co-evaporated three times with toluene, the residue was then mixed with freshly powdered AW-300 4 Å molecular sieves and suspended under argon in CH_2Cl_2 (1.0 mL). The mixture was cooled and stirred at 0 °C, TMSOTf (1.2 μL, 7.4 μmol) was added and the temperature was allowed to gradually rise to rt. After completion of the reaction (TLC analysis), the mixture was neutralized by adding pyridine. The mixture was then filtered over Celite and concentrated to give a residue, that was purified by column chromatography.

4.3. General procedure for D-Fuc*p*3NAc couplings in dioxane/toluene/DME 4:1:1 v/v/v

A mixture of donor **8** (37 mg, 0.074 mmol) and rhamnosyl acceptor (0.049 mmol) was co-evaporated three times with toluene, the residue was then mixed with freshly powdered AW-300 4 Å molecular sieves and suspended under argon in 4:1 dioxane/toluene (1.5 mL). The mixture was cooled and stirred at 0 °C, a 0.025 M DME solution of TMSOTf (0.3 mL, 7.4 μmol) was added and the temperature was allowed to gradually raise to rt After completion of the reaction (TLC analysis), the mixture was neutralized by adding pyridine. The mixture was then filtered over Celite and concentrated to give a residue, that was purified by column chromatography.

4.3.1. Benzyl(4-*O*-acetyl-3-acetamido-2-*O*-benzyl-D-fucopyranosyl)-(1→3)-3-*O*-allyl-4-*O*-benzoyl-α-L-rhamnopyranoside (9).

See the general procedure for D-Fuc*p*3-NAc couplings in CH_2Cl_2 and in dioxane/toluene/DME 4:1:1 v/v/v. IR (thin film, NaCl) 3025, 2980, 2933, 1744, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11–7.26 (m, 30H, H-Ar), 5.73 (m, 2H, 2 OCH$_2$C*H*=CH$_2$), 5.50 (t, 1H, $J_{4,3}=J_{4,5}=10.0$ Hz, H-4$^{\beta}_{A}$), 5.41 (d, 1H, $J_{4,3}=1.8$ Hz, H-4$^{\alpha}_{B}$), 5.35 (t, 1H, $J_{4,3}=J_{4,5}=10.0$ Hz, H-4$^{\alpha}_{A}$), 5.20–5.10 (m, 5H, H-1$^{\beta}_{A}$, H-4$^{\beta}_{B}$, OC*H*HPh, 2 OCH$_2$CH=C*H*H *trans*), 5.08–4.97 (m, 4H, H-1$^{\alpha}_{B}$, NH$^{\alpha}$, 2 OCH$_2$CH=C*H*H *cis*), 4.91 (bs, 1H, H-1$^{\alpha}_{A}$), 4.77 (m, 4H, NH$^{\beta}$, 3 OC*H*HPh), 4.65 (d, 1H, $J_{1,2}=7.4$ Hz, H-1$^{\beta}_{B}$), 4.61–4.50 (m, 6H, H-3$^{\alpha}_{B}$, H-5$^{\alpha}_{A}$, 4 OC*H*HPh), 4.12–4.03 (m, 5H, H-2$^{\alpha}_{A}$, H-2$^{\beta}_{A}$, H-3$^{\beta}_{B}$, 2 OC*H*HCH=CH$_2$), 4.01–3.94 (m, 6H, H-3$^{\alpha}_{A}$, H-3$^{\beta}_{A}$, H-5$^{\alpha}_{A}$, H-5$^{\beta}_{A}$, 2 OC*H*HCH=CH$_2$), 3.78 (dd, 1H, $J_{2,3}=10.3$ Hz, $J_{2,1}=3.4$ Hz, H-2$^{\alpha}_{B}$), 3.69 (q, 1H, $J_{5,6}=6.4$ Hz, H-5$^{\beta}_{B}$), 3.34 (dd, 1H, $J_{2,3}=10.7$ Hz, $J_{2,1}=7.4$ Hz, H-2$^{\beta}_{B}$), 2.078 (s, 3H, OAc) 2.05 (s, 3H, OAc), 1.84 (s, 3H, NAc), 1.79 (s, 3H, NAc), 1.29 (m, 6H, H-6$^{\alpha}_{A}$, H-6$^{\beta}_{A}$), 1.01 (d, 3H, $J_{6,5}=6.4$ Hz, H-6$^{\alpha}_{B}$), 0.98 (m, 6H, $J_{6,5}=6.4$ Hz, H-6$^{\beta}_{B}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 169.9 (4 *C*OCH$_3$), 165.5, 165.4 (*C*OPh), 134.4–128.1 (2 OCH$_2$*C*H=CH$_2$, C-Ar), 116.7, 116.6 (2 OCH$_2$CH=*C*H$_2$), 105.8 (C-1$^{\beta}_{B}$), 98.7, 96.6, 96.4 (C-1$^{\alpha}_{A}$, C-1$^{\beta}_{A}$, C-1$^{\alpha}_{B}$), 76.9, 76.0, 75.8, 74.4, 74.2, 73.6, 73.5, 73.4, 72.6, 71.5, 71.3, 71.2, 70.9, 70.5, 69.1, 69.0, 68.9, 67.3, 66.7, 65.1 (C-2$^{\alpha}_{A}$, C-2$^{\beta}_{A}$, C-2$^{\beta}_{B}$, C-2$^{\beta}_{B}$, C-3$^{\alpha}_{A}$, C-3$^{\beta}_{A}$, C-4$^{\alpha}_{A}$, C-4$^{\beta}_{A}$, C-4$^{\alpha}_{B}$, C-4$^{\beta}_{B}$, C-5$^{\alpha}_{A}$, C-5$^{\beta}_{A}$, C-5$^{\alpha}_{B}$, C-5$^{\beta}_{B}$, 2 OC*H*$_2$CH=CH$_2$, 4 OC*H*$_2$Ph,), 23.0, 22.9, 20.6, 20.4 (4 CO*C*H$_3$), 17.6, 17.5, 16.3, 16.1 (C-6$^{\alpha}_{A}$, C-6$^{\beta}_{A}$, C-6$^{\alpha}_{B}$, C-6$^{\beta}_{B}$). ESI-MS for $C_{40}H_{47}NO_{11}$ (*m/z*): M_r (calcd) 717.31, M_r (found) 740.51 $(M+Na)^+$. Anal. Calcd: C, 66.93; H, 6.60; N, 1.95. Found: C, 67.10; H, 6.47; N, 1.99.

4.3.2. Methyl(4-*O*-acetyl-3-acetamido-2-*O*-benzyl-D-fucopyranosyl)-(1→3)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (10).

See the general procedure for D-Fuc*p*3-NAc couplings in CH_2Cl_2 and in dioxane/toluene/DME 4:1:1 v/v/v. IR (thin film, NaCl) 3042, 1748, 1680, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.26 (m, 10H, H-Ar$^{\alpha,\beta}$), δ 5.73 (d, 1H, $J_{1,2}=3.5$ Hz, H-1$^{\alpha}_{B}$), 5.33 (d, 1H, $J_{4,3}=2.2$ Hz, H-4$^{\alpha}_{B}$), 5.14 (d, 1H, $J_{4,3}=2.2$ Hz, H-4$^{\beta}_{B}$), 4.86 (m, 5H, H-1$^{\alpha}_{A}$, H-1$^{\beta}_{B}$, NH$^{\alpha}$, 2 OC*H*HPh), 4.67–4.54 (m, 4H, H-1$^{\beta}_{B}$, H-5$^{\beta}_{B}$, NH$^{\beta}$, OC*H*HPh), 4.44 (d, 1H, $J_{gem}=$ 12.0 Hz, OC*H*HPh), 4.40 (m, 1H, H-3$^{\alpha}_{B}$), 4.31 (t, 1H, $J_{4,3}=J_{4,5}=7.1$ Hz, H-3$^{\beta}_{A}$), 4.24 (t, 1H, $J_{4,3}=J_{4,5}=7.1$ Hz, H-3$^{\alpha}_{A}$), 4.20–4.07 (m, 4H, H-2$^{\alpha}_{A}$, H-2$^{\beta}_{A}$, H-3$^{\beta}_{B}$, H-5$^{\alpha}_{B}$), 3.72 (m, 2H, H-5$^{\alpha}_{A}$, H-5$^{\beta}_{A}$), 3.65 (dd, 1H, $J_{2,3}=11.4$ Hz, $J_{2,1}=3.5$ Hz, H-2$^{\alpha}_{B}$), 3.56 (dd, 1H, $J_{4,5}=9.9$ Hz, $J_{4,3}=7.1$ Hz, H-4$^{\alpha}_{A}$), 3.51 (dd, 1H, $J_{4,5}=9.9$ Hz, $J_{4,3}=7.1$ Hz, H-4$^{\beta}_{A}$), 3.36 (m, 7H, H-2$^{\beta}_{B}$ OMe$^{\alpha}$, OMe$^{\beta}$), 2.08 (2 s, 6H, 2 OAc), 1.85 (s, 3H, NAc), 1.76 (s, 3H, NAc), 1.57 (s, 6H, 2 CH_3), 1.36 (s, 6H, 2 CH_3), 1.34 (d, 3H, $J_{6,5}=6.2$ Hz, H-6$^{\alpha}_{A}$), 1.24 (d, 3H, $J_{6,5}=$ 6.6 Hz, H-6$^{\beta}_{B}$), 1.15 (d, 3H, $J_{6,5}=6.2$ Hz, H-6$^{\beta}_{A}$), 1.09 (d, 3H, $J_{6,5}=6.6$ Hz, H-6$^{\alpha}_{B}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8 (*C*OCH$_3$), 137.6 (C_{ipso}), 126.5–125.7 (C-Ar), 104.2 (C-1$^{\beta}_{B}$), 97.9 C-1$^{\alpha}_{A}$, C-1$^{\beta}_{A}$), 94.5 (C-1$^{\alpha}_{B}$), 82.2, 78.4, 78.2, 76.4, 76.0, 75.8, 75.2, 73.8, 72.3, 72.1, 71.2, 70.5, 67.3, 65.0, 63.7 (C-2$^{\alpha}_{A}$, C-2$^{\beta}_{A}$, C-2$^{\alpha}_{B}$, C-2$^{\beta}_{B}$, C-3$^{\alpha}_{A}$, C-3$^{\beta}_{A}$, C-4$^{\alpha}_{A}$, C-4$^{\beta}_{A}$, C-4$^{\alpha}_{B}$, C-4$^{\beta}_{B}$, C-5$^{\alpha}_{A}$, C-5$^{\beta}_{A}$, C-5$^{\alpha}_{B}$, C-5$^{\beta}_{B}$, OC*H*HPh), 54.5 (OMe), 51.8 (C-3$^{\beta}_{B}$), 47.9 (C-3$^{\alpha}_{B}$), 27.8 (CH_3), 26.1 (CH_3), 22.9, 22.8, 20.6, 20.5 (4 CO*C*H$_3$), 17.8, 17.5, 16.3, 15.9 (C-6$^{\alpha}_{A}$, C-6$^{\beta}_{A}$, C-6$^{\alpha}_{B}$, C-6$^{\beta}_{B}$). ESI-MS for $C_{27}H_{39}NO_{10}$ (*m/z*): M_r (calcd) 537.26, M_r (found) 538.20 $(M+H)^+$. Anal. Calcd: C, 60.32; H, 7.31; N, 2.61. Found: C, 60.40; H, 7.19; N, 2.51.

4.3.3. Benzyl 3-*O*-allyl-4-*O*-benzoyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (17).

To a solution of **16** (152 mg, 0.382 mmol) in CH_2Cl_2 (3.0 mL), levulinic acid (245 μL, 2.28 mmol), DMAP (23 mg, 0.190 mmol) and then DIPC (220 μL, 2.48 mmol) were added. After 4 h stirring at rt, the mixture was filtered over a Celite pad, diluted with CH_2Cl_2 (50 mL) and washed with water (50 mL). The organic layer was collected, dried and concentrated to give a residue, which after chromatography (8:1 petroleum ether/EtOAc) afforded **17** (187 mg, 99%) as an oil. $[\alpha]_D$ −12.7 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3028, 2935, 1749, 1725, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.05–7.36 (m, 10H, H-Ar), 5.67 (m, 1H, OCH$_2$C*H*=CH$_2$), 5.36 (dd, 1H, $J_{2,3}=3.4$ Hz, $J_{2,1}=1.6$ Hz, H$_2$), 5.24 (t, 1H, $J_{4,3}=J_{4,5}=$ 9.8 Hz, H$_4$), 5.14 (d, 1H, $J_{vic}=17.2$ Hz, $J_{gem}=1.8$ Hz, OCH$_2$CH=C*H*H *trans*), 5.01 (d, 1H, $J_{vic}=10.4$ Hz, $J_{gem}=$ 1.8 Hz, OCH$_2$CH=C*H*H *cis*), 4.88 (d, 1H, $J_{1,2}=1.6$ Hz, H$_1$), 4.72 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.54 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.07–3.76 (m, 4H, H$_3$, H$_5$, OC*H*$_2$CH=CH$_2$), 2.84–2.68 (m, 4H, C*H*$_2$C*H*$_2$), 2.20 (s, 3H, C*H*$_3$CO), 1.24 (d, 3H, $J_{6,5}=6.4$ Hz, H$_6$); ^{13}C NMR

($CDCl_3$, 50 MHz) δ 206.1 (CH_3C=O), 171.7 (C=O Lev), 166.5 (C=O Bz), 136.4 (C_{ipso}), 134.1 (OCH_2CH=CH_2), 133.2 (C_{ipso}), 130.0–127.5 (C-Ar), 117.5 (OCH_2CH=CH_2), 97.6 (C-1), 74.8, 73.2, 70.9, 69.0, 68.9, 66.6 (C-2, C-3, C-4, C-5, OCH_2CH=CH_2, OCH_2Ph), 37.9, 29.8, 28.2 (CH_2CH_2, CH_3C=O), 17.5 (C-6). ESI-MS for $C_{28}H_{32}O_8$ (*m*/*z*): M_r (calcd) 496.21, M_r (found) 519.22 $(M+Na)^+$. Anal. Calcd: C, 67.73; H, 6.50. Found: C, 67.60; H, 6.65.

4.3.4. Benzyl 4-*O*-benzoyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (18). Compound **17** (189 mg, 0.381 mmol) was dissolved in 3:2 MeOH/CH_2Cl_2 (5.0 mL), $PdCl_2$ (27 mg, 0.30 mmol) was then added and the mixture was vigorously stirred at rt overnight, after that it was filtered over a Celite pad, diluted with CH_2Cl_2 (50 mL) and washed with 5 M NaCl (50 mL). The organic layer was collected, dried and concentrated to give a residue, which, after chromatography (4:1 petroleum ether/EtOAc), afforded **18** (135 mg, 78%) as an oil. $[\alpha]_D$ −41.4 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3517, 3039, 1731, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.05–7.34 (m, 10H, H-Ar), 5.26 (dd, 1H, $J_{2,3}$=3.6 Hz, $J_{2,1}$=1.8 Hz, H_2), 5.12 (t, 1H, $J_{4,3}$=$J_{4,5}$=9.8 Hz, H_4), 4.91 (d, 1H, $J_{1,2}$=1.8 Hz, H_1), 4.74 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.55 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.22 (dd, 1H, $J_{3,4}$=9.8 Hz, $J_{2,1}$=3.6 Hz, H_3), 4.04 (dq, 1H, $J_{5,4}$=9.8 Hz, $J_{5,6}$=6.2 Hz, H_5), 2.87–2.63 (m, 4H, CH_2CH_2), 2.22 (s, 3H, CH_3CO), 1.27 (d, 3H, $J_{6,5}$=6.2 Hz, H_6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 207.2 (CH_3C=O), 172.2 (C=O Lev), 166.7 (C=O Bz), 136.8, 133.4 (2 C_{ipso}), 129.8–127.8 (C-Ar), 96.9 (C-1), 75.1, 72.7, 69.6, 68.9, 66.4 (C-2, C-3, C-4, C-5, OCH_2Ph), 38.2, 29.7, 28.2 (CH_2CH_2, CH_3C=O), 17.5 (C-6). ESI-MS for $C_{25}H_{28}O_8$ (*m*/*z*): M_r (calcd) 456.18, M_r (found) 479.49 $(M+Na)^+$. Anal. Calcd: C, 65.78; H, 6.18. Found: C, 65.78; H, 6.25.

4.3.5. Methyl(4-*O*-acetyl-3-acetamido-2-*O*-benzyl-α-D-fucopyranosyl)-(1→3)-2-*O*-allyl-4-*O*-benzyl-α-L-rhamnopyranoside (20). See the general procedure for D-Fuc*p*3-NAc couplings in CH_2Cl_2 and in dioxane/toluene/DME 4:1:1 v/v/v. (α-anomer). $[\alpha]_D$ +20.4 (*c* 0.6, CH_2Cl_2). IR (thin film, NaCl) 3019, 2956, 1747, 1665, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.27 (m, 10H, H-Ar), 5.87 (m, 1H, OCH_2CH=CH_2), 5.24 (dd, 1H, J_{vic}=17.3 Hz, J_{gem}=1.7 Hz, OCH_2CH=C*H*H *trans*), 5.21 (d, 1H, $J_{1,2}$=3.4 Hz, H-1_B), 5.14 (dd, 1H, J_{vic}=10.2 Hz, J_{gem}=1.7 Hz, OCH_2CH=C*H*H *cis*), 5.07 (d, 1H, $J_{4,3}$=3.0 Hz, H-4_B), 4.86 (d, 1H, J_{gem}=10.5 Hz, OC*H*HPh), 4.81–4.60 (m, 5H, H-1_A, H-3_B, NH, 2 OC*H*HPh), 4.43 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.27–4.09 (m, 3H, H-5_B, OCH_2CH=CH_2), 4.05 (dd, 1H, $J_{3,4}$=8.7 Hz, $J_{3,2}$=2.7 Hz, H-3_A), 3.79 (bs, 1H, H-2_A), 3.71 (m, 2H, H-2_B, H-5_A), 3.61 (t, 1H, $J_{4,3}$=$J_{4,5}$=9.3 Hz, H-4_A), 3.33 (m, 3H, OMe), 2.04 (s, 3H, OAc), 1.79 (s, 3H, NAc), 1.37 (d, 3H, $J_{6,5}$=6.0 Hz, H-6_A), 0.78 (d, 3H, $J_{6,5}$=6.6 Hz, H-6_B); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9 ($COCH_3$), 138.1, 138.0 (2 C_{ipso}), 134.9 (OCH_2CH=CH_2), 129.6–127.7 (C-Ar), 117.2 (OCH_2CH=CH_2), 98.9 (C-1_A), 93.6 (C-1_B), 79.8, 75.5, 74.4, 72.9, 72.8, 72.2, 71.6, 68.1, 68.0, 65.1 (C-2_A, C-2_B, C-3_A, C-4_A, C-4_B, C-5_A, C-5_B, OCH_2Ph, OCH_2CH=CH_2), 54.7 (OMe), 48.1 (C-3_B), 23.1, 20.6 (2 $COCH_3$), 18.1, 15.9 (C-6_A, C-6_B). ESI-MS for $C_{34}H_{45}NO_{10}$ (*m*/*z*): M_r (calcd) 627.72, M_r (found) 650.50 $(M+Na)^+$. Anal. Calcd: C, 65.05; H, 7.23; N, 2.23. Found: C, 65.20; H, 7.19; N, 2.32.

4.3.6. Methyl(4-*O*-acetyl-3-acetamido-2-*O*-benzyl-α-D-fucopyranosyl)-(1→3)-4-*O*-benzyl-α-L-rhamnopyranoside (21). A mixture of compound **20**-α (56 mg, 0.089 mmol) and $PdCl_2$ (7.8 mg, 44 μmol) was suspended in 1:1 CH_2Cl_2/MeOH (2.0 mL) under vigorous stirring. After 4 h the mixture was filtered on a Celite pad, then diluted with CH_2Cl_2 (25 mL) and washed with 5 M NaCl (30 mL). The organic layer was collected, dried and concentrated to give an oily residue that, after column chromatography (1:2 petroleum ether/EtOAc) afforded **21** (49 mg, 93%) as an oil. $[\alpha]_D$ +32.3 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3509, 3030, 1741, 1669, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49–7.29 (m, 10H, H-Ar), 5.07 (d, 1H, $J_{4,3}$=3.0 Hz, H-4_B), 5.04 (bs, 1H, H-1_A), 4.80–4.71 (m, 4H, H-1_B, 3 OC*H*HPh), 4.53 (m, 1H, H-3_B), 4.44 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.06 (q, 1H, $J_{5,6}$=6.6 Hz, H-5_B), 3.99 (m, 2H, H-2_A, H-3_A), 3.75 (dq, 1H, $J_{5,4}$=9.3 Hz, $J_{5,6}$=6.0 Hz, H-5_A), 3.63 (dd, 1H, $J_{2,3}$=11.4 Hz, $J_{2,1}$=3.3 Hz, H-2_B), 3.52 (t, 1H, $J_{4,3}$=$J_{4,5}$=9.3 Hz, H-4_A), 3.36 (s, 3H, OMe), 2.05 (s, 3H, OAc), 1.79 (s, 3H, NAc), 1.38 (d, 3H, $J_{6,5}$=6.0 Hz, H-6_A), 0.73 (d, 3H, $J_{6,5}$=6.6 Hz, H-6_B); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9 ($COCH_3$), 138.1, 137.1 (2 C_{ipso}), 128.7–127.5 (C-Ar), 99.9 (C-1_A), 93.3 (C-1_B), 79.3, 77.1, 75.5, 73.1, 73.0, 72.7, 67.6, 67.2 (C-2_A, C-2_B, C-3_A, C-4_A, C-4_B, C-5_A, C-5_B, 2 OCH_2Ph), 54.6 (OMe), 48.1 (C-3_B), 23.1, 20.5 (2 $COCH_3$), 17.9 (C-6_A), 15.8 (C-6_B). ESI-MS for $C_{31}H_{41}NO_{10}$ (*m*/*z*): M_r (calcd) 587.27, M_r (found) 610.00 $(M+Na)^+$. Anal. Calcd: C, 63.36; H, 7.03; N, 2.38. Found: C, 63.55; H, 6.96; N, 2.34.

4.3.7. Methyl(2,4-di-*O*-benzoyl-3-*O*-chloroacetyl-α-L-rhamnopyranosyl)-(1→3)-(2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→2)-[4-*O*-acetyl-3-acetylamino-2-*O*-benzyl-α-D-fucopyranosyl-(1→3)]-4-*O*-benzyl-α-L-rhamnopyranoside (22). A mixture of **21** (20 mg, 34.1 μmol) and **13** (66 mg, 50.8 μmol) was co-evaporated three times with toluene, the residue was then mixed with freshly powdered AW-300 4 Å molecular sieves, suspended under argon in CH_2Cl_2 (2.0 mL) and stirred at −20 °C. $BF_3{\cdot}OEt_2$ (3.2 μL, 25.4 μmol) was then added. After 24 h, an additional aliquot of **13** (44 mg, 33.9 μmol) and $BF_3{\cdot}OEt_2$ (2.1 μL, 16.9 μmol) was added. After an additional day the reaction was quenched with a drop of Et_3N. After filtration over a Celite pad, the mixture was concentrated to give a residue, that, after column chromatography (1:1 petroleum ether/EtOAc), afforded **22** (30 mg, 51%) as a white foam. $[\alpha]_D$ +113.3 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3052, 3028, 1739, 1656, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18–7.10 (m, 40H), 5.83 (dd, 1H, $J_{3,4}$=9.6 Hz, $J_{3,2}$=2.8 Hz, H-3_B), 5.72 (d, 1H, $J_{2,3}$=3.0 Hz, H-2_C), 5.59 (t, 1H, $J_{4,3}$=$J_{4,5}$=10.0 Hz, H-4_B), 5.56 (t, 1H, $J_{4,3}$=$J_{4,5}$=9.6 Hz, H-4_C), 5.44 (dd, 1H, $J_{3,4}$=9.8 Hz, $J_{3,2}$=2.8 Hz, H-3_D), 5.34 (m, 2H, H-1_B, H-4_D), 5.18 (m, 3H, H-1_D, H-1_E, H-2_D), 5.11 (d, 1H, $J_{4,3}$=2.8 Hz, H-4_E), 5.06 (bs, 1H, H-1_C), 4.90 (d, 1H, J_{gem}=10.8 Hz, OC*H*HPh), 4.87 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.84 (bs, 1H, H-1_A), 4.76 (d, 1H, J_{gem}=10.8 Hz, OC*H*HPh), 4.63 (m, 2H, H-3_C, NH), 4.50 (m, 1H, H-3_E), 4.42 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.34 (bs, 1H, H-2_B),

4.30–4.20 (m, 4H, H-5_B, H-5_C, H-5_D, H-5_E), 4.13 (dd, 1H, $J_{3,4}=9.6$ Hz, $J_{3,2}=2.8$ Hz, H-3_A), 4.08 (bs, 1H, H-2_A), 3.79–3.64 (m, 5H, H-2_E, H-4_A, H-5_A, CH_2Cl), 3.37 (s, 3H, OMe), 1.96 (s, 3H, OAc), 1.54 (s, 3H, NAc), 1.42 (d, 3H, $J_{6,5}=6.0$ Hz, H-6_A), 1.33 (m, 6H, H-6_B, H-6_C), 1.18 (d, 3H, $J_{6,5}=6.2$ Hz, H-6_D), 0.77 (d, 3H, $J_{6,5}=6.6$ Hz, H-6_E); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9 (*C*OCH$_2$Cl), 165.4–164.5 (*C*OCH$_3$, *C*OPh), 138.2, 137.1 (2 C_{ipso}), 133.4–128.0 (C-Ar), 100.5 (C-1_B), 99.8 (C-1_C, $^1J_{C,H}=173$ Hz), 99.6 (C-1_A), 98.9 (C-1_E), 94.2 (C-1_E), 79.8 (C-4_A), 78.7 (C-2_B), 76.6 (C-2_A), 75.7 (C-3_A), 75.5 (O*C*H$_2$Ph), 74.4 (C-3_C), 73.5 (C-4_C), 72.7 (C-4_E), 72.2 (C-2_E), 72.0 (C-4_B), 71.8 (C-2_C), 71.5 (C-4_D, O*C*H$_2$Ph), 70.4 (C-3_B), 70.3 (C-3_D), 68.2 (C-5_A), 67.8–67.2 (C-5_B, C-5_C, C-5_D, C-5_E), 55.0 (OMe), 48.1 (C-3_E), 40.2 (CO*C*H$_2$Cl), 22.9, 20.4 (2 CO*C*H$_3$), 18.1 (C-6_A), 17.7 (C-6_B, C-6_C), 17.3 (C-6_D), 15.8 (C-6_E). ESI-MS for $C_{93}H_{96}ClNO_{29}$ (*m*/*z*): M_r (calcd) 1725.58, M_r (found) 1748.05 $(M+Na)^+$. Anal. Calcd: C, 64.67; H, 5.60; N, 0.81. Found: C, 64.57; H, 5.80; N, 0.75.

4.3.8. Methyl α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-[3-acetamido-α-D-fucopyranosyl-(1→3)]-α-L-rhamnopyranoside (11). Compound **22** (13.0 mg, 7.54 μmol) was dissolved in 9:1 MeOH/HCOOH (2.0 mL) under argon. Pd/C (8 mg) was added and the mixture was kept in an ultrasound bath for 1 h, after that it was filtered on a Celite pad and concentrated. The residue was dissolved in MeOH (2.0 mL) and NaOMe 1 M in MeOH (250 μL) was added. After 48 h the solution was neutralized with Amberlist-15 H^+, filtered and concentrated. The residue was purified by gel filtration to obtain **11** (4.7 mg, 78%) as a white wax. $[\alpha]_D$ +11 (*c* 0.3, D_2O); ^{1}H NMR (D_2O, 400 MHz) δ 5.12 (d, 1H, $J_{1,2}=1.6$ Hz, H-1_B), 5.04 (d, 1H, $J_{1,2}=1.6$ Hz, H-1_D), 5.02 (d, 1H, $J_{1,2}=4.0$ Hz, H-1_E), 4.93 (d, 1H, $J_{1,2}=1.6$ Hz, H-1_C), 4.83 (d, 1H, $J_{1,2}=1.6$ Hz, H-1_A), 4.33 (q, 1H, $J_{5,6}=6.5$ Hz, H-5_E), 4.25 (dd, 1H, $J_{3,2}=11.1$ Hz, $J_{3,4}=2.9$ Hz, H-3_E), 4.12 (m, 2H, H-2_A, H-2_C), 4.07 (dd, 1H, $J_{2,3}=3.6$ Hz, $J_{2,1}=1.6$ Hz, H-2_D), 4.04 (dd, 1H, $J_{2,3}=3.6$ Hz, $J_{2,1}=1.6$ Hz, H-2_B), 3.92–3.73 (m, 10H, H-2_E, H-3_A, H-3_B, H-3_C, H-3_D, H-4_E, H-5_A, H-5_B, H-5_C, H-5_D), 3.63 (t, 1H, $J_{4,3}=J_{4,5}=9.6$ Hz, H-4_A), 3.52 (t, 1H, $J_{4,3}=J_{4,5}=9.5$ Hz, H-4_C), 3.49 (t, 1H, $J_{4,3}=J_{4,5}=9.8$ Hz, H-4_B), 3.46 (t, 1H, $J_{4,3}=J_{4,5}=9.8$ Hz, H-4_D), 3.42 (s, 3H, OMe), 2.05 (s, 3H, Ac), 1.35 (d, 3H, $J_{6,5}=6.2$ Hz, H-6_A), 1.29 (2d, 6H, $J_{6,5}=6.2$ Hz, H-6_B, H-6_D), 1.26 (d, 3H, $J_{6,5}=6.2$ Hz, H-6_C), 1.18 (d, 3H, $J_{6,5}=6.6$ Hz, H-6_E); ^{13}C NMR (D_2O, 100 MHz) δ 165.5 (CO*C*H$_3$), 102.4 (C-1_D), 101.8 (C-1_C), 100.5 (C-1_B), 99.4 (C-1_A), 94.5 (C-1_E), 78.5 (C-2_B), 78.0 (C-3_C), 75.0 (C-2_A), 74.0 (C-3_A), 72.1 (C-4_B), 72.0 (C-4_D), 71.3 (C-4_C), 70.4 (C-4_A), 70.3 (C-4_E), 70.1 (C-2_D), 70.0 (C-3_D), 69.9 (C-2_C), 69.8 (C-3_B), 69.2 (C-5_B), 69.0 (C-5_C), 68.9 (C-5_D), 68.3 (C-5_A), 66.8 (C-5_E), 65.5 (C-2_E), 54.9 (OMe), 51.1 (C-3_E), 22.0 (CO*C*H$_3$), 16.7–16.6 (C-6_A, C-6_B, C-6_C, C-6_D), 15.1 (C-6_E). ESI-MS for $C_{33}H_{57}NO_{21}$ (*m*/*z*): M_r (calcd) 803.34, M_r (found) 826.53 $(M+Na)^+$. Anal. Calcd: C, 49.31; H, 7.15; N, 1.74. Found: C, 49.49; H, 7.10; N, 1.85.

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