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A Single Route to Mammalian N-Glycans substituted with Core Fucose and Bisecting GlcNAc

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This work is dedicated to the 150th anniversary of TUM

Abstract:

The occurrence of α1,6-linked core-fucose on the N-glycans of mammalian glycoproteins is involved in tumor progression and reduces the bioactivity of antibodies in ADCC. Since core-fucosylated N-glycans are difficult to isolate from natural sources only chemical or enzymatic synthesis can provide the desired compounds for biological studies. A general drawback of chemical α-fucosylation is that the chemical assembly of α1,6-linked fucosides is not stereospecific. We have developed a robust and general method for the α-selective fucosylation of acceptors with primary hydroxyl groups in α/β ratios exceeding 99:1. The high selectivities result from the interplay of an optimized protecting group pattern of the fucosyl donors in combination with the activation principle and the reaction conditions. Selective deprotection yielded versatile azides of all mammalian complex-type core-fucosylated N-glycans with 2-4 antennae and optional bisecting GlcNAc.

Mammalian N-glycoproteins frequently display core fucose or bisecting GlcNAc in the core region of N-glycans.[1] These ubiquitous modifications are influencing the conformational behavior of the N-glycan[2] and the biological properties of the parent N-glycoprotein. Of high relevance is the lowered antibody-dependent cellular cytotoxicity (ADCC) of core fucosylated antibodies.[3] Furthermore core fucose and bisecting GlcNAc are frequently associated with cancer progression and serve as a tumor marker.[4]

The chemical synthesis of complex-type N-glycans is challenging and compounds with substitutions in the core require additional efforts. Thus, only a limited number of examples are reported with core fucose[5] or a bisecting GlcNAc[6] or even both modifications.[7] Chemoenzymatic approaches using recombinant α1,6-fucosyltransferases[8] or

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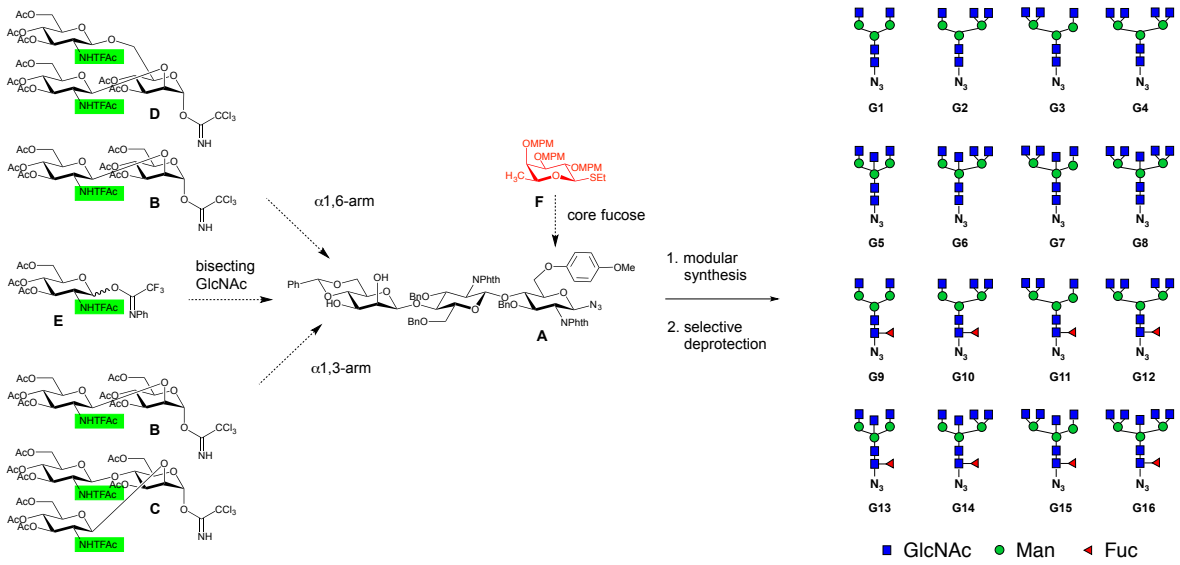
endoglycosidases[9] are simplifying the introduction of core fucose only for appropriate substrates. Recently, a mutated fucosidase was developed capable of adding a core fucose onto glycopeptides and glycoproteins.[10] Here we show that chemical α1,6-fucosylation of complex N-glycans can reliably be carried out with nearly exclusive α-selectivity using suitably protected fucosyl donors. The new approach is compatible with the modular one-pot introduction of a bisecting GlcNAc moiety and can furnish anomeric azides of all mammalian complex-type core-fucosylated N-glycans with an optional bisecting GlcNAc.



***Scheme 1**: Modular set of building blocks designed for the envisioned all-in-one-route to mammalian complex N-glycans **G1-G16** with optional bisecting GlcNAc and core fucose. Bn=benzyl, NPhth=phthalimido, Ac=acetyl, TFAc=trifluoracetyl, MPM=p-methoxybenzyl, MP=p-methoxyphenyl.*

The N-TFAc-protected building blocks **B-E** efficiently provide N-glycans with an optional bisecting modification (**G1-G8**).[6k] We thus intended to combine the latter approach with the core trisaccharide **A**[5i] functionalized for the late introduction of α1,6-linked fucose.[7c] This should consequently allow the synthesis of all the core variations of mammalian N-glycans (**G1-G16**) via a single pathway (Scheme 1). However, the low steroselectivity (α/β ratios around 10:1) observed for chemical α1,6-fucosylation of N-glycan acceptors posed an unresolved obstacle.[5g, 5i] The formation of β-fucoside side products can be determined by analytical HLPC-MS of the crude reaction mixture but is easily overlooked when relying only on NMR. Typically, the separation of α- and β-fucosylated N-glycans by flash chromatography is not possible. When purifying these mixtures by preparative RP-HPLC we experienced

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coelution of the anomers leading to significant loss of the valuable compounds after repetitive separations.[5i] The key for a general approach to core fucosylated N-glycans was thus to find a highly stereoselective and reliable method for chemical α1,6-fucosylation.

We initially pursued the modular approach outlined in Scheme 1 by using the analogous thioglycoside donors instead of the imidate donors **B**-**E**. Although the syntheses were successful we observed side reactions on the electron-rich p-methoxyphenyl (MP) protecting group of **A**. When activating aromatic thioglycosides with NIS/TfOH we found halogenations or aglycon transfer on the MP group affecting the purity of the reaction products (data not shown). In contrast, glycosylation of **A** with the imidates **B** or **C** and catalytic activation with BF_3-OEt_2 proceeded smoothly, in high yield and exclusive α1,3 regio- and stereoselectivity. Only minor amounts of double glycosylation products were formed, which could be removed by flash chromatography. The regioselectivity generally observed for **A** results from a higher reactivity of the equatorial OH-group and is assisted by the surrounding protecting groups. Pentasaccharide **1** (89 % yield) and hexasaccharide **2** (88 % yield) were routinely[6k] converted to the diols **3** and **4** followed by introduction of the 1,6-arm using the imidates **B** or **D** and activation with TMSOTf. Again α1,6 regio- and stereoselectivity was observed for compounds **5**-**8** (78-85 % yield) and confirmed by 2D-NMR analysis including ^{13}C-^{1}H coupling constants for the anomeric carbons.[11] The corresponding bisected N-glycans were synthesized in a one-pot procedure[6k] by first reacting the primary OH-group of the diols **3** or **4** with the donors **B** or **D** and subsequent addition of GlcNAc donor **E** (10 equiv.) and TfOH (4 equiv.) at -45 °C. Following a single protocol with two nearly quantitative conversions the four bisected N-glycans **9**-**12** were obtained in high yields (72-80 %). Even the pentaantennary bisected N-glycan **H** was obtained in 86 % yield by the one-pot approach whereas the early introduction of a bisecting GlcNAc gave the analogous pentaantennary intermediate in a far lower yield (19 %).[7c] The glycosylations proceeded without side reactions facilitating purification of the N-TFAc protected glycans by flash chromatography. Subsequently, the N-glycans **5**-**8** were acetylated and selectively deprotected with CAN giving the acceptors **13**-**16**. The bisected compounds **9**-**12** were directly oxidized to the acceptors **17**-**20**.

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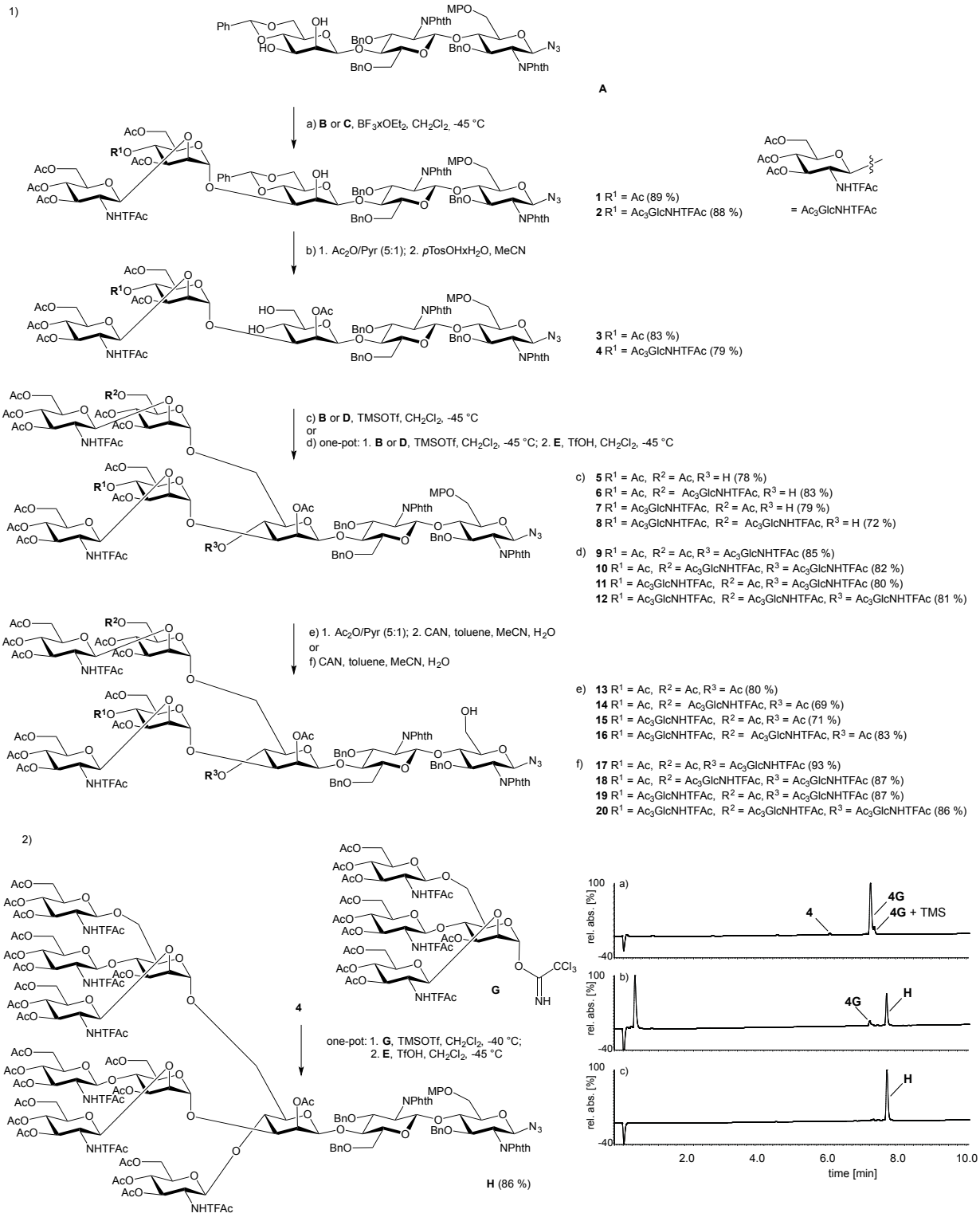

***Scheme 2**: 1.) Modular synthesis of eight N-glycan acceptors with **(17-20)** and without bisecting GlcNAc **(13-16)** using acceptor **A** and imidate donors **B-E**. The introduction of the 1,6-arm and the bisecting GlcNAc moiety was carried out in a one-pot procedure (step d); 2.) One-pot synthesis of pentaantennary bisected N-glycan **H** and HPLC-chromatograms: a) crude reaction mixture of **4** with **G** and resulting decasaccharide **4G**, b) crude reaction mixture after addition of **E**, c) product **H** after flash chromatography.*

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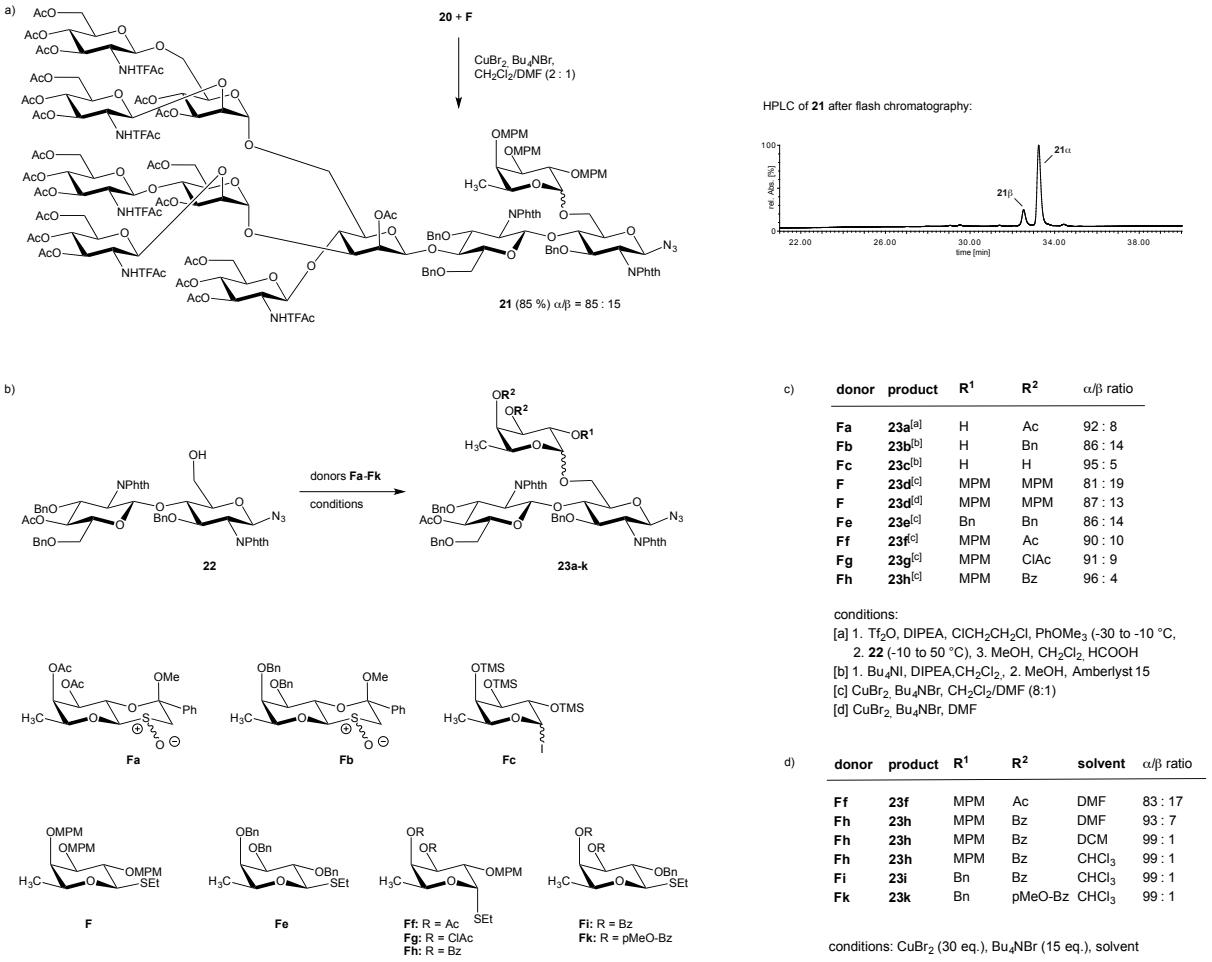
An exploratory α-fucosylation of acceptor **20** with donor **F** under the in-situ anomerization conditions used previously[5a, 5i, 7b, 7c] gave only moderate α-selectivity. For undecasaccharide **21** an α/β ratio of 85:15 was determined by HPLC after flash chromatography (Scheme 3). At this point we set out for a more selective α1,6-fucosylation method. There is a broad knowledge on influencing the selectivity of 1,2-cis-glycosylations.[12] For α-fucosylations a non-participating protecting group at O-2 is required.[13] Despite many examples of α-fucosylations, there are only few reports where α-fucosylations of acceptors with primary alcohol groups[14] were studied systematically. It was found that the α-selectivity with primary alcohols is generally lower compared to secondary alcohols and susceptible mainly to the protecting groups in the donor in conjunction with the particular reaction conditions.

We started the search for highly α-selective fucosyl donors with the bicyclic fucosyl-oxathianes **Fa** and **Fb**[15] and the readily available chitobiose **22** as a model acceptor. LC-MS analysis revealed low reactivity towards **22** and product α/β-ratios of 92:8 (**Fa**) and 86:14 (**Fb**). The use of TMS-protected fucosyl iodide **Fc**[16] gave an α/β ratio of 95:5.



c)

donor	product	R^1	R^2	α/β ratio
Fa	**23a**[a]	H	Ac	92 : 8
Fb	**23b**[b]	H	Bn	86 : 14
Fc	**23c**[b]	H	H	95 : 5
F	**23d**[c]	MPM	MPM	81 : 19
F	**23d**[d]	MPM	MPM	87 : 13
Fe	**23e**[c]	Bn	Bn	86 : 14
Ff	**23f**[c]	MPM	Ac	90 : 10
Fg	**23g**[c]	MPM	ClAc	91 : 9
Fh	**23h**[c]	MPM	Bz	96 : 4

conditions:
[a] 1. Tf_2O, DIPEA, $ClCH_2CH_2Cl$, $PhOMe_3$ (-30 to -10 °C, 2. **22** (-10 to 50 °C), 3. MeOH, CH_2Cl_2, HCOOH
[b] 1. Bu_4NI, DIPEA,CH_2Cl_2, 2. MeOH, Amberlyst 15
[c] $CuBr_2$, Bu_4NBr, CH_2Cl_2/DMF (8:1)
[d] $CuBr_2$, Bu_4NBr, DMF

d)

donor	product	R^1	R^2	solvent	α/β ratio
Ff	**23f**	MPM	Ac	DMF	83 : 17
Fh	**23h**	MPM	Bz	DMF	93 : 7
Fh	**23h**	MPM	Bz	DCM	99 : 1
Fh	**23h**	MPM	Bz	$CHCl_3$	99 : 1
Fi	**23i**	Bn	Bz	$CHCl_3$	99 : 1
Fk	**23k**	Bn	pMeO-Bz	$CHCl_3$	99 : 1

conditions: $CuBr_2$ (30 eq.), Bu_4NBr (15 eq.), solvent

***Scheme 3**: a) fucosylation of N-glycan acceptor **20** with donor **F** was accompanied by β-linked fucoside **21**β, which can only be removed by HPLC; b) 1,6-fucosylations of chitobiosyl acceptor **22** using donors **Fa-Fk**. c) α/β-selectivities observed under established conditions. d) α/β-selectivities observed in neat solvents.*

Since we could not improve the α-selectivity with donors **Fa-Fc** any further we returned to donor **F**. The selectivity under in-situ-anomerization conditions ($CuBr_2$/Bu_4NBr) increased slightly by replacing the solvent DCM/DMF (α/β 81:19) by DMF (α/β 87:13). However, varying the amounts of promotor reagents in neat DMF showed nearly no effect (data not shown). We thus compared a series of fucosyl donors with different protecting groups (**F**, **Fe-Fh**) under identical reaction conditions. The α/β ratio increased to 86:14 with the perbenzylated donor **Fe**. The fucosyl donor (**Ff**) with two acetates improved the selectivity further (α/β 90:10). Best results were obtained with the 3,4-benzoylated donor **Fh** (α/β 96:4). However, when using neat DMF instead of DCM/DMF the selectivity for donors **Ff** and **Fh** dropped. Gratifyingly, the α/β-ratio of all 3,4-benzoylated donors **Fh-Fk** was exceeding 99:1 when utilizing pure DCM or $CHCl_3$ as a solvent (Scheme 3d).

We then tested the donors **Fi** and **Fk** under the most promising conditions with N-glycan acceptor **16**. Due a highly viscous reaction mixture the amounts of $CuBr_2$ and TBAB were reduced to 10 equiv. each. Surprisingly, the α-selectivity of donors **Fi** and **Fk** decreased (Scheme 4a) relative to the reaction with the disaccharide **22** (compounds **23i** and **23k**). By doubling the amount of TBAB relative to $CuBr_2$ the targeted α/β-ratio of 99:1 could be restored for the coupling of the systematically varied donors **Fi-Fn** with acceptor **15**. When omitting the TBAB completely from the reaction mixtures the α/β-ratio was lowered depending on the p-substituent (Scheme 4b,c). Notably, in the absence of TBAB the unsubstituted benzoate (**Fi**) showed the strongest loss of α-selectivity whereas the p-fluoro derivative **Fn** was barely affected. The p-fluorobenzoylated donor **Fn** was chosen for the further syntheses since the α/β-ratio even under non-optimal conditions (no TBAB) was already high (97:3). Under optimal starting conditions donor **Fn** should provide α/β-ratios of 99:1 even after solvent loss during preparative fucosylations (2-4 d).

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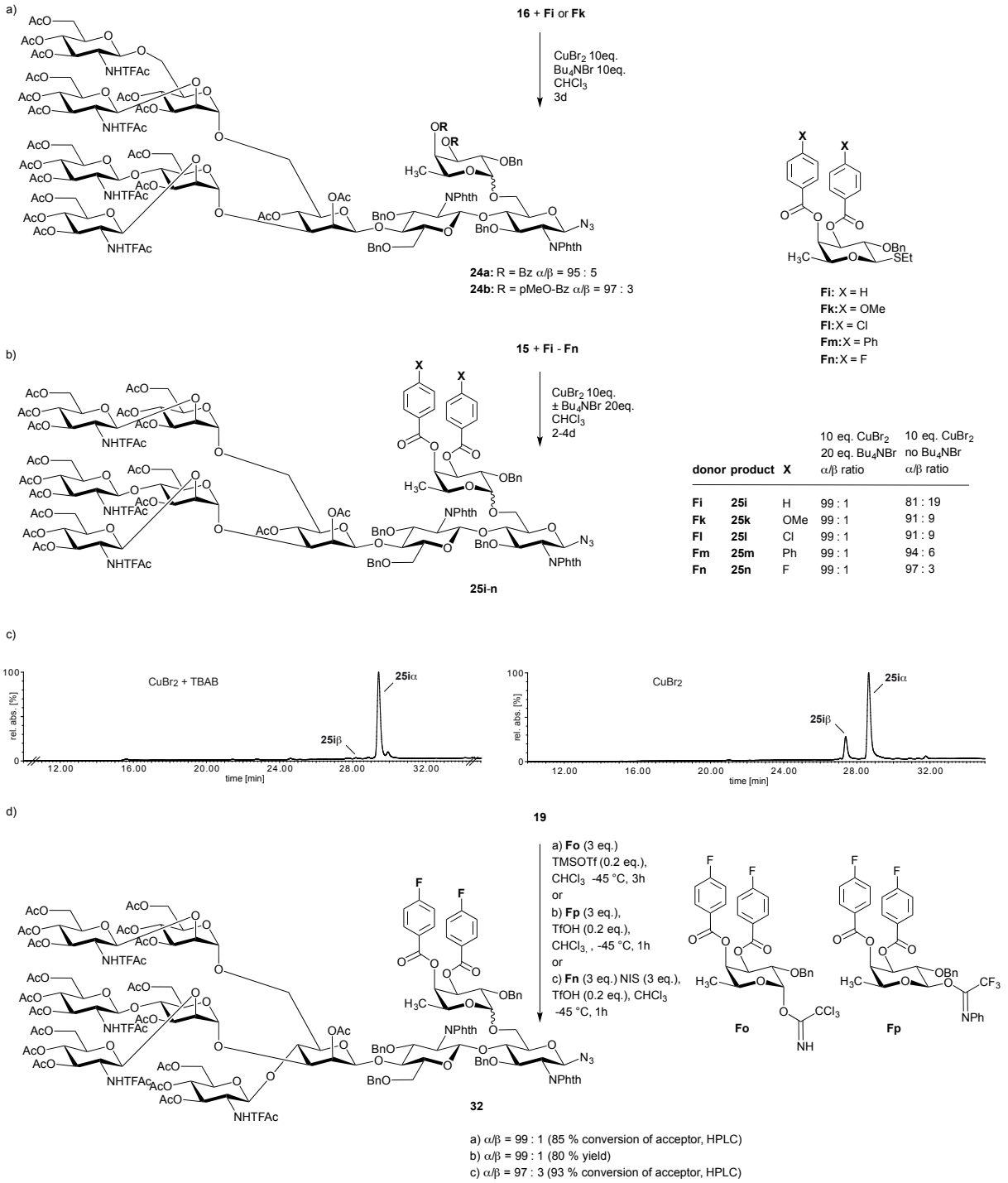

***Scheme 4**: a) Promotor ratio affects α-selectivity in fucosylations of N-glycan acceptor **16** with donors **Fi** and **Fk**; b) α1,6-fucosylations of acceptor **15** using fucosyl donors **Fi-Fn** are affected by the p-substituents X of the benzoyl groups and by omitting Bu_4NBr; c) RP-HPLC chromatograms of the synthesis of **25i** with (left) and without TBAB (right) d) rapid α1,6-fucosylation of **19** with imidates **Fo**, **Fp** and thioglycoside **Fn**.*

The donors **Fi-Fn** can be regarded as superdisarmed[12] requiring large excess of donor and long reaction times. Most likely the corresponding α-bromide generated after activation with $CuBr_2$/TBAB is not reactive enough to give a glycoside whereas the small amounts of more reactive β-bromide generated via in-situ-anomerization[17] lead to the desired α-glycoside[18] under the conditions found to be optimal for α1,6-selective fucosylation (halogenated solvent, no DMF, excess TBAB). Under less optimal conditions (e.g. $CuBr_2$ without TBAB) other pathways may operate and compromise the otherwise nearly exclusive α-selectivity. In those cases the p-substituted benzoyl groups[19] of the donors **Fi-Fn** may provide a valuable tool for tuning the α-selectivity in glycosylations lacking in-situ-anomerization. This assumption was tested with the trichloacetimidate[20] of the p-fluorobenzoylated fucose (**Fo**) and the acceptor **19** (Scheme 4d). Using 0.2 equiv of TMSOTf the decasaccharide **32** was obtained with an excellent α/β-ratio (99:1) and a much shorter reaction time (3 h, -45 °C). Since the imidate **Fo** gave only 85 % conversion we also tested the corresponding N-phenylimidate[21] **Fp**. Here full conversion was observed with identical α/β-ratio (99:1). Thus in-situ anomerization conditions are not essential for high α-selectivity in the fucosylation of primary acceptors. The fucosylation of acceptor **19** with thioglycoside **Fn** in $CHCl_3$ and activation with NIS/TfOH at -45° C gave a slightly lower α/β-ratio (97:3).

The preparative fucosylations were carried out using donor **Fn** under the robust in-situ-anomerization conditions established above. The N-glycan acceptors **13**-**20** were reacted with 10 equiv. of **F**, 10 equiv. of $CuBr_2$ and 12 equiv. of TBAB in $CHCl_3$ for 2-7 days. After purification by flash chromatography the yields for the core fucosylated compounds **26**-**33** were generally high (76-83 %) and the observed α/β-ratio was exceeding 99:1. For selective removal of the benzyl groups in the presence of an azide an oxidative debenzylation was carried out by using either $Na_2S_2O_4$/$NaBrO_3$[22] or the recently established NBS[23] as a more controllable source for bromine radicals. After cleavage of the base-labile protecting groups and acetylation the core fucosylated N-glycan azides **G9**-**G16** were obtained in good yields. The final products can be purified by RP-HPLC since the presence of 1,6-linked fucose leads to stronger retention on the column. The NMR spectra of the N-glycans **G9**-**G16** were fully assigned confirming the regio- and stereoselectivity. The core fucosylated N-glycans showed the typical ^{13}C signal for C-6^1 at 67.8 ppm. By applying the deprotection sequence to the non-fucosylated precursors **13**-**20** the synthesis of all mammalian type N-glycan cores **G1**-**G16** through a single pathway can be formally completed.

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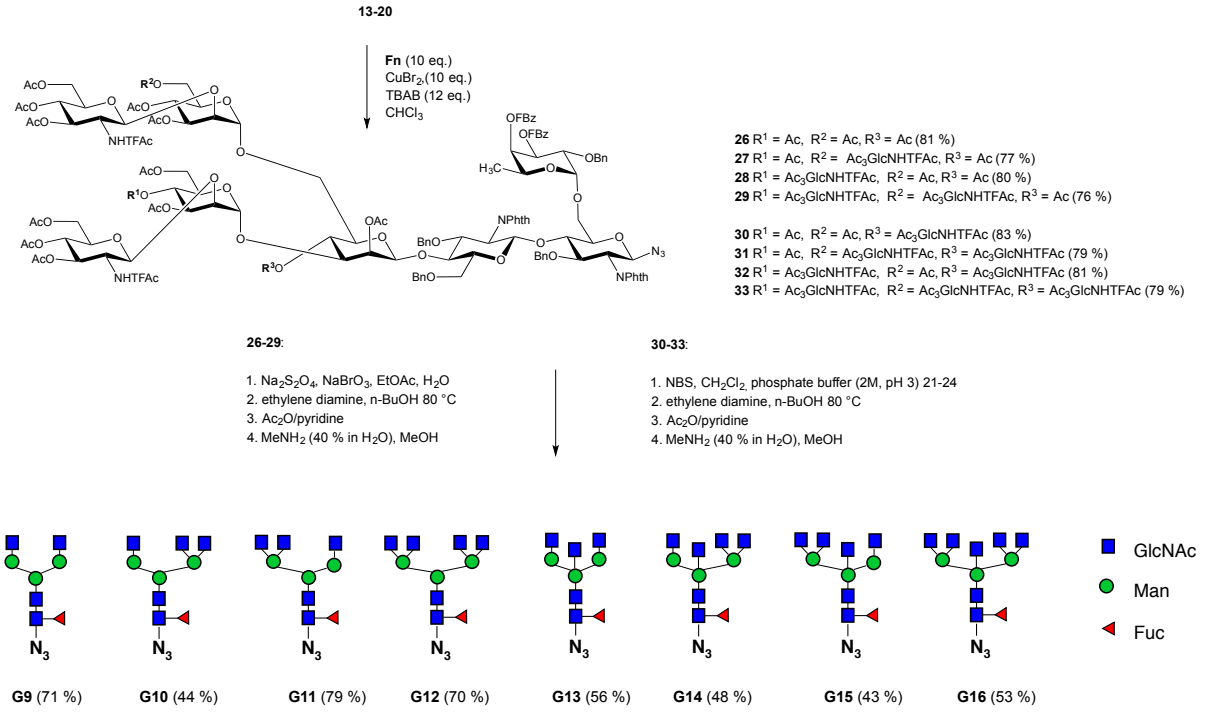

***Scheme 5**: optimized α-selective synthesis of core-fucosylated and bisected N-glycans **27-34** using donor **Fn** followed by deprotection to N-glycan azides **G9-G16**.*

In summary, a modular synthesis of all the 16 cores of mammalian complex-type N-glycans with optional core fucose and bisecting GlcNAc was established following a single approach. Key features for highly α-selective 1,6-fucosylations of N-glycans were superdisarmed donors and mild activation in halogenated solvents. By integrating a one-pot protocol even the most demanding core fucosylated and bisected N-glycans were synthesized with unprecedented efficiency and purity. Enzymatic elongation of these glycans can provide the tools needed for the investigation of the biological interplay of the ubiquitous bisecting GlcNAc and core fucose modifications.

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