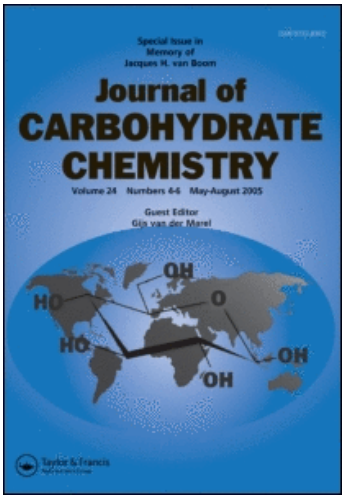

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IODONIUM-ION ASSISTED STEREOSPECIFIC GLYCOSYLATION: SYNTHESIS OF OLIGOSACCHARIDES CONTAINING α(1-4)-LINKED L-FUCOPYRANOSYL UNITS

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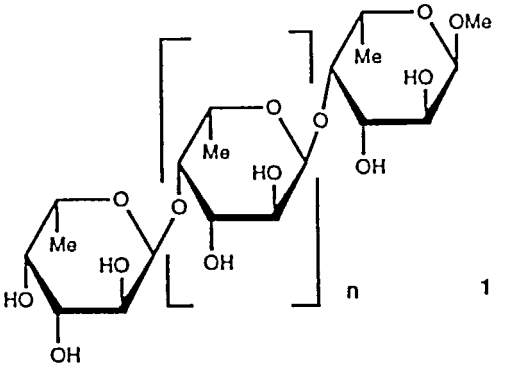
ABSTRACT

The terminal glycosyl acceptor methyl 2,3-di-*O*-benzyl-α-L-fucopyranoside (**6**) was extended three times with the non-terminal glycosyl donor ethyl 4-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-ß-L-fucopyranoside (**13**) via iodonium-ion assisted glycosylations and intermittent removal of the C-4 acetyl group in intermediate dimer **16** and trimer **18**. The 4-*O*-acetyl group in trimer **18** and tetramer **20** was highly resistant towards basic hydrolysis. The latter could be nullified by using dichloroacetyl instead of acetyl to protect the C-4-OH in the donor. The exclusive formation of 1,2-*cis*-linked oligomers could be explained by through-bond interactions exerted by the electron-withdrawing C-4 acyl group in the glycosyl donor.

INTRODUCTION

Contamination of stored grain, fruits and vegetables by mould species belonging to the order of *Mucorales*, some members of which may also cause mucormycosis in humans, is responsible for a considerable amount of food spoilage. Some years ago, Notermans *et al.*[1,2] proposed a method in which the immunochemical properties of the extracellular polysaccharides (EPS) of the *Mucorales* species could be used for their detection. Preliminairy structural studies[3,4] on the *Mucorales* EPS revealed *inter alia* the presence of D-glucuronic acid, D-mannopyranoside and L-fucopyranoside residues.

In addition, it was found[5] that the α(1-4)-linked L-fucopyranoside dimer **1** (n=0) was able to inhibit the immunological reaction between EPS of *Mucor racemosus* and antibodies raised against EPS of *Mucorales racemosus* using the inhibition ELISA. The latter indicates that α(1-4)-linked L-fucopyranoside units may be an essential part of the epitope. In order to assess the possible role of the L-fucose residues in the immunodominant part of the *Mucorales* EPS, longer oligosaccharides of α(1-4)-linked L-fucopyranosides were needed. We report here the synthesis of α(1-4)-linked L-fucopyranoside oligomers **1** (n=0,1,2), which were used to study the effect of increasing chain length on the outcome of the inhibition ELISA experiments.



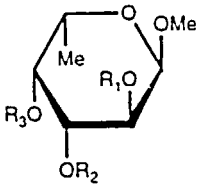
1 (n=0,1,2)

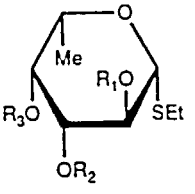
RESULTS AND DISCUSSION

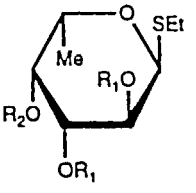
Recently,[6] we reported that iodonium dicollidine perchlorate (IDCP) mediated glycosylation of glycosyl acceptors by ethyl 1-thioglycosyl donors, having a non-participating ether group at C-2, proceeds in a high yield and with the predominant formation of 1,2-*cis* linkages. The presence in the target tetrasaccharide **1** (n=2) of solely α(1-4)-linked L-fucopyranosides urged us to follow a straightforward, stepwise elongation approach based on activation of thioglycosides with the promoter IDCP.[7] According to this concept, IDCP assisted coupling of the C-4-OH in a terminal acceptor (*i.e.* compound **6**) with a non-terminal thioglycoside donor, having a 4-*O*-acetyl group (*i.e.* compound **13**), will afford a fully protected dimer (*i.e.* compound **16**). Elongation of dimer **16** can then be accomplished by removal of the 4-*O*-acetyl group followed by condensation with the same non-terminal thioglycosyl donor.

The terminal acceptor, methyl 2,3-di-*O*-benzyl-α-L-fucopyranoside **6**[8-10] was synthesized in three steps from methyl 3,4-*O*-isopropylidene-α-L-fucopyranoside (**3**),

which was obtained by a slight modification of the method of Ok *et al.*[11] Thus, acetylation of methyl 3,4-*O*-isopropylidene-α(ß)-L-fucopyranoside,[12] followed by separation of the anomeric mixture by silica gel chromatography and Zemplèn deacetylation of **2** gave homogeneous **3** in 54% overall yield. Benzylation (**3**→**4**) followed by acidic hydrolysis of the acetonide function in **4** furnished **5**[10] in 85% yield. Regioselective benzylation of the equatorial C-3 hydroxyl group in **5** was executed by treating the stannylidene complex of compound **5** with benzyl bromide in the presence of tetrabutylammonium iodide[13] (0.5 eq.), which gave compound **6** in a better yield than reported earlier.[8] The non-terminal donor **13** was prepared in six steps starting from easily accessible[14] ethyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranoside **7**. Deacetylation (**7**→**8**) and subsequent acetonation of **8** afforded the 3,4-*O*-isopropylidene derivative **9** in 80% overall yield.







2 R_1=Ac; R_2,R_3=CMe_2
3 R_1=H; R_2,R_3=CMe_2
4 R_1=Bn; R_2,R_3=CMe_2
5 R_1=Bn; R_2=R_3=H
6 R_1=R_2=Bn; R_3=H

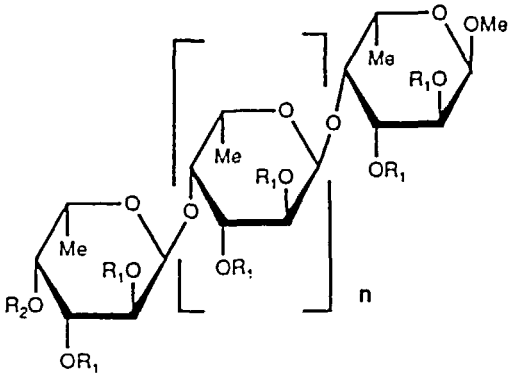
7 R_1=R_2=R_3=Ac
8 R_1=R_2=R_3=H
9 R_1=H; R_2,R_3=CMe_2
10 R_1=Bn; R_2,R_3=CMe_2
11 R_1=Bn; R_2=R_3=H
12 R_1=R_2=Bn; R_3=H
13 R_1=R_2=Bn; R_3=Ac
14 R_1=R_2=Bn; R_3=Cl_2Ac

15 R_1=Bn; R_2=Ac

Benzylation (**9**→**10**) followed by acidic hydrolysis of the acetonide function in **10** gave **11** in high yield. Regioselective benzylation of the stannylidene complex of compound **11** with benzyl bromide and cesium fluoride,[15] instead of tetrabutylammonium iodide (see benzylation of **5**→**6**), resulted in a higher yield of **12**. Finally, acetylation of **12** with acetic anhydride in pyridine afforded the non-terminal donor **13** in 80% overall yield (based on **11**).

At this stage, the fully protected tetramer **20** (R_2=Ac) was assembled by extending the terminal unit **6** three times with **13** and intermittent removal of the temporary protective group at C-4 from the intermediate dimer **16** and trimer **18**. Thus, conden-

sation of the terminal acceptor **6** with a slight excess of the non-terminal donor **13**, using IDCP as the promoter in a mixture of diethyl ether and 1,2-dichloroethane, resulted in the exclusive formation of the 1,2-*cis* linked glycosidation product **16** as evidenced by TLC analysis, ^{1}H- and ^{13}C NMR spectroscopy (H-1^b, $J_{1,2}$ 4.0 Hz; H-1^a, $J_{1,2}$ 3.6 Hz; C-1^b, $J_{C,H}$ 165.6 Hz; C-1^a, $J_{C,H}$ 167.0 Hz). Subsequent removal of the acetyl function in dimer **16** with a catalytic amount of potassium *tert*-butoxide (KOtBu) in methanol (15 h, 20 °C) furnished acceptor **17** in 74% overall yield (based on **6**). IDCP-mediated extension of dimer **17** with donor **13** gave, after purification on Sephadex LH-20, homogeneous trimer **18** (R_2=Ac), as ascertained by TLC analysis and NMR spectroscopy (C-1^c, $J_{C,H}$ 168.9 Hz).



16 R_1=Bn; R_2=Ac; n=0
17 R_1=Bn; R_2=H ; n=0
18 R_1=Bn ; R_2=Ac (Cl_2Ac); n=1
19 R_1=Bn ; R_2=H; n=1
20 R_1=Bn; R_2=Ac (Cl_2Ac); n=2
21 R_1=Bn; R_2=H; n=2

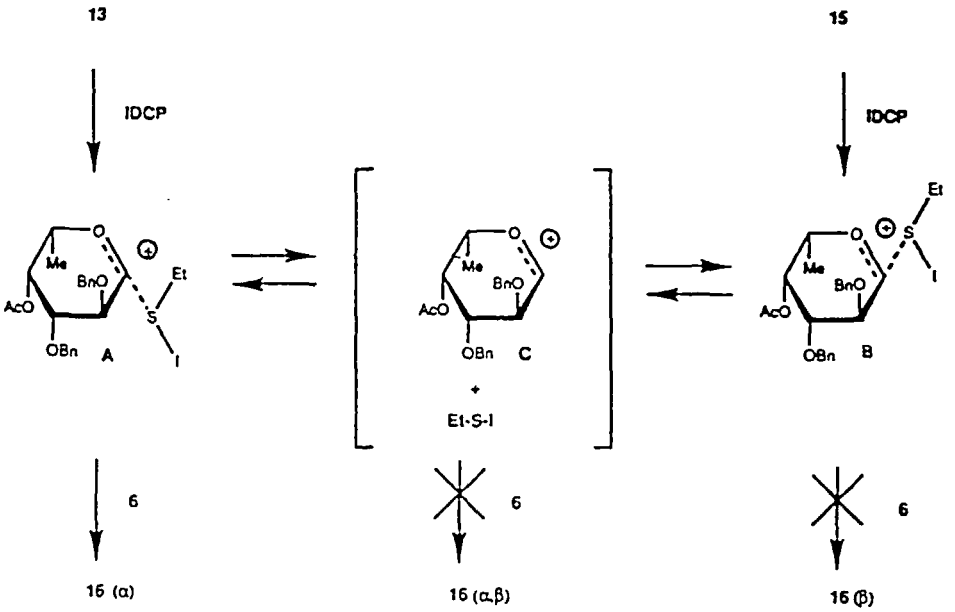
Surprisingly, deblocking of the acetyl group in trimer **18**, under the same conditions as described for dimer **16**, failed. However, complete removal of the acetyl group could be realized by treating **18** with an equimolar amount of KOtBu in methanol for 8 h at 70 °C. In this way, acceptor **19** could be isolated in 75% overall yield (based on **17**). Extension of **19** with **13** resulted, after purification on Sephadex LH-20, in the exclusive isolation of 1,2-*cis* linked tetramer **20** (R_2=Ac) as evidenced by TLC analysis and ^{13}C NMR spectroscopy (C-1^d, $J_{C,H}$ 167.8 Hz). However, KOtBu mediated hydrolysis of tetramer **20** (→**21**), as performed earlier for trimer **18** (→**19**), was extremely slow. Fortunately, deacetylation of **20** (→**21**) proceeded smoothly and in high yield with sodium hydroxide in dioxane-methanol. The slow deacetylation of **18** and **20** under the rather basic conditions, urged us to replace the acetyl in glycon **13**

by the more base labile dichloroacetyl group. The corresponding dichloroacetyl donor **14** was easy accessible by acylation of compound **12** with dichloroacetic anhydride in pyridine. Elongation of dimer **17** with donor **14** gave, after purification on Sephadex LH-20, homogeneous trimer **18** (R_2=Cl_2Ac) in 82% yield. Also in this case, the IDCP mediated elongation resulted as expected in the exclusive formation of the 1,2-*cis* linked product: no trace of the 1,2-*trans*-linked glycosylation product could be detected by TLC analysis and NMR spectroscopy. Removal of the dichloroacetyl group in **18** proceeded rapidly with a catalytic amount of KOtBu in methanol (15 min, 20 °C), to afford trimer **19** in high yield. In a similar fashion, the 1,2-*cis* linked tetramer **20** (R_2=Cl_2Ac) could be obtained and efficiently deacylated to give homogeneous **21** in 80% overall yield (based on **19**).

Finally, debenzylation of **17**, **19** and **21** via hydrogenolysis gave the fully deblocked dimer **1** (**n=0**)[9], trimer **1** (**n=1**) and tetramer **1** (**n=2**), respectively, the ^{1}H- and ^{13}C NMR data of which were in good accordance with the proposed structures ($J_{1,2}$ for each anomeric proton was in the order of 4 Hz: a characteristic value for 1,2-*cis*-linked L-fucopyranosyl units).

The successful synthetic conclusion of tetramer **1** (**n=2**) presented in this paper reveals two interesting features. The first one is the substantial decrease in the basic hydrolysis rate of *O*-4 acetyl groups with increasing chain length. The latter not well recognized phenomenon may be ascribed to an increasing lipophilicity of the substrate after each elongation step. In addition, it is of interest to note that several oligosaccharides containing *O*-4 acetylated L-fucopyranosyl moieties have been isolated[16] from natural sources: hence indicating that the relatively slow basic hydrolysis of the *O*-4 acetyl group is an intrinsic property of L-fucopyranosyl sugars.

The second remarkable feature is that the coupling of the non-terminal ß-anomers **13** and **14** resulted in the exclusive formation of 1,2-*cis* interglycosidic linkages throughout the stepwise synthesis of tetramer **1** (**n=2**). Apart from this, we also established that the ß-anomer **13** could be rapidly converted with IDCP to the α-anomer **15**: short (15 min) or prolonged (1 h) treatment of **13** with IDCP (0.25 eq.) gave a mixture of **13** and **15** in a ratio of 1:2. Furthermore, IDCP-mediated condensation of α-anomer **15** with acceptor **6** gave also exclusively the 1,2-*cis* linked dimer **16**. Predominant formation of 1,2-*cis*-linkages was observed earlier by Flowers *et al.*[9,10,17,18] in the condensation of a similarly protected α-L-fucopyranosyl bromide with



SCHEME 1

an acceptor under Helferich conditions. Flowers *et al.*[10,17] proposed that the high stereoselectivity was due to participation of the 4-*O*-acyl group on the activated bromide resulting in a (1-4)-cyclic acyloxonium ion, which in turn can only be attacked from the α-side. Later on, van Boeckel *et al.*[19] reported that the high percentage of 1,2-*cis* linked products formed in the coupling of 4-*O*-acyl protected α-D-mannopyranosyl bromides with an acceptor, in the presence of insoluble silver catalysts, could be explained satisfactory by through-bond interactions. The latter process will suppress the occurrence of a glycosyloxycarbonium ion, but favour the formation of an α-intimate-ion pair which reacts via a SN-2 type mechanism with an incoming acceptor. The exclusive formation, based on the through-bond interaction principle, of an 1,2-*cis* interglycosidic bond in the IDCP-mediated glycosidation of the ß-(**13**) and α-(**15**) anomers with acceptor **6** is visualized in Scheme **1**. Thus, the ß-iodosulfenium intermediate **A** generated by the reaction of **13** with IDCP will react with **6** via a SN-2 type mechanism to give dimer **16**. On the other hand, the corresponding α-iodosulfenium intermediate **B**, derived from **15** and IDCP, will anomerize, via reassociation of the transient glycosyloxycarbonium ion **C** and

ethylsulfenyl iodide, to intermediate A which in turn reacts exclusively with **6** to give dimer **16**. Flowers *et al.*[10] reported partial formation (15%) of a 1,2-*trans* linked dimer in the glycosylation of 4-*O*-acetyl-2,3-di-*O*-benzyl-α-L-fucopyranosyl bromide with an acceptor, in the presence of $Hg(CN)_2$, a result which may be interpreted as follows. The transient intermediate C, formed during dissociation of the α-L-fucosyl bromide under the influence of the promoter, will be converted less effectively, due to possible complexation of the bromide ion with the promoter, in a similarly activated species A. Competitive attack of the acceptor on intermediate C may then account for the formation of the 1,2-*trans* linked product.

In conclusion, stereospecific introduction of α(1-4)-linked L-fucopyranosides can be performed in high yields by activation of properly protected ethyl 1-thio-α(ß)-L-fucopyranosides with the thiophillic promoter IDCP. The method presented here may be an attractive alternative for the *in situ* anomerization[20,21] approach of Lemieux, the Helferich method advocated by Flowers[9,10,17,18] and the trichloroacetimidate[22] or thiofucosyl[23,24] glycosylation reactions recently devised for the introduction of α-linked L-fucopyranosides. At present, we are studying in detail the influence of other thiophillic promoters and solvents on the stereochemical outcome of glycosylation reactions using protected 4-*O*-acyl alkyl(aryl)-1-thio-α(ß)-L-fucopyranosyl derivatives as the donor molecules.

EXPERIMENTAL

General Procedures. -Dioxane and pyridine were dried by refluxing with CaH_2 (5 g/L) for 6 h and then distilled. Dichloromethane, 1,2-dichloroethane and toluene were distilled from P_2O_5. DMF was stirred with CaH_2 at room temperature for 16 h and distilled under reduced pressure. Diethyl ether was distilled from $LiAlH_4$. Dioxane and pyridine were stored over molecular sieves 4 Å (Aldrich). Toluene and diethyl ether were stored over sodium wire, dichloromethane and 1,2-dichloroethane over Alumina. Schleicher and Schüll DC Fertigfolien F1500 LS 254 were used for TLC analysis. The following eluents were used: System A (ethyl acetate/n-hexane, 1/1, v/v), System B (dichloromethane/acetone, 97/3, v/v), System C (dichloromethane/methanol, 97/3, v/v), System D (diethyl ether/n-hexane, 1/1, v/v), System E (diethyl ether/n-hexane, 2/1, v/v) and System F (ethyl acetate/methanol/water, 5/3/2, v/v/v). Compounds were detected by charring with 20% sulfuric acid in methanol. Optical rotations were recorded at 20 °C with a Perkin-Elmer 241 polarimeter. Column chromatography was performed on silica gel 60, 70-230 mesh (Merck). Gel filtration was performed on Sephadex

LH-20 (Pharmacia). NMR spectra were recorded with a JEOL JNM-FX 200 (^{13}C, 50.1 MHz, internal standard chloroform or methanol) and a Bruker WM-300 spectrometer equipped with an Aspect-2000 computer (^1H, 300 MHz, internal standard Me_4Si).

Methyl 2-*O*-Acetyl-3,4-*O*-isopropylidene-α-L-fucopyranoside (2). Methyl 3,4-*O*-isopropylidene-α,ß-L-fucopyranoside[12] (2.8 g, 12.8 mmol) was dissolved in pyridine (30 mL) and acetic anhydride (15 mL). After stirring for 2 h at 20 °C, the reaction mixture was concentrated and the remaining oil was coevaporated with toluene (4x50 mL). Purification of the residue on silica gel (gradient elution: ethyl acetate/hexane, 1/3 v/v to 1/1, v/v) gave 2α (1.8 g, 54%), Rf 0.8 (System A), m.p. 100-102°, $[\alpha]_D^{20}$ -161° (c 1, $CHCl_3$) [lit.[11] m.p. 101-102° and $[\alpha]_D^{26}$ -176° (c 1, $CHCl_3$)] and 2ß (0.9 g, 27%); Rf 0.7 (System A); ^{13}C NMR data ($CDCl_3$) 2α: δ 170.1 (C-quat., acetyl); δ 108.9 (C-quat., isopropylidene); δ 96.9 (C-1, J_{CH} 170 Hz); δ 62.7, 71.6, 73.1, 75.8 (C-2, C-3, C-4, C-5); δ 55.0 (OCH_3); δ 26.1, 27.7 (2x CH_3, isopropylidene); δ 20.7 (CH_3, acetyl); δ 15.9 (C-6); 2ß: δ 103.0 (C-1, J_{CH} 156.8 Hz).

Methyl 2-*O*-Benzyl-3,4-*O*-isopropylidene-α-L-fucopyranoside (4). To a stirred solution of compound 2α (1.8 g, 6.9 mmol) in dry methanol (25 mL) was added potassium *tert*-butoxide (10 mg). After stirring for 2.5 h at 20 °C, TLC analysis (System A, Rf 3 0.2) revealed the reaction to be complete. The mixture was neutralized with Dowex 50W (H^+ form), filtered, concentrated and the residue was coevaporated with toluene (2x50 mL) to give crude 3 (1.5 g, 100%). Compound 3 was dissolved in DMF (20 mL) and at 0 °C sodium hydride (80% dispersion in mineral oil, 252 mg) was added. After stirring the mixture for 15 min, benzyl bromide (0.91 mL) was added. The reaction was left for 3 h at 20 °C, after which time TLC analysis (System B) revealed complete reaction. Methanol (6 mL) was added to destroy excess NaH and the mixture was neutralized with acetic acid, concentrated and redissolved in dichloromethane (75 mL). The solution was extracted with aq. $NaHCO_3$ (2x50 mL) and water (50 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (eluent: 3% acetone in dichloromethane) resulting in pure 4 (1.8 g, 85%) as a colourless oil; $[\alpha]_D^{20}$ -96.8° (c 1, $CHCl_3$) [lit.[17] $[\alpha]_D^{25}$ -98.5° (c 1.16, $CHCl_3$)]; Rf 0.6 (System B); ^{13}C NMR data ($CHCl_3$): δ 137.9 (C-quat., benzyl); δ 127.3-128.0 (C-arom.); δ 108.3 (C-quat., isopropylidene); δ 98.0 (C-1); δ 75.8 (2x), 75.7 (C-2, C-3, C-4); δ 71.9 (CH_2-benzyl); δ 62.5 (C-5); δ 55.0 (OCH_3); δ 26.1, 27.9 (2x CH_3, isopropylidene); δ 15.9 (C-6); ^1H NMR data : δ 7.2-7.4 (m, 5 H, H-arom.); δ 4.7-4.8 (AB, 2 H, CH_2-benzyl); δ 4.6 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1); δ 4.3 (dd, 1 H, $J_{2,3}$ 8 Hz, $J_{3,4}$ 5.1 Hz, H-3); δ 4.0 (m, 2 H, H-4, H-5); δ 3.5 (dd, 1 H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 8 Hz, H-2); δ 3.38 (s, 3 H, OCH_3); δ 1.3-1.4 (m, 9 H, 3x H-6 + 6x H, isopropylidene).

Anal. Calcd for $C_{17}H_{24}O_5$: C 66.21, H 7.84; Found: C 66.12, H 7.91%.

Methyl 2-*O*-Benzyl-α-L-fucopyranoside (5). Compound 4 (1.7 g, 5.5 mmol) was suspended in acetic acid-water, 1/1, v/v (40 mL) and stirred at 70 °C for 1 h. Evaporation of the solvent

and coevaporation with toluene (4x50 mL) gave crude **5**[10] (1.5 g, 100%), which was used in the next step without further purification; Rf 0.25 (System C); ^{13}C NMR data ($CDCl_3$): δ 138.6 (C-quat., benzyl); δ 127.2-129.0 (C-arom.); δ 98.3 (C-1); δ 76.7 (C-2); δ 72.9 (CH_2-benzyl); δ 72.1, 69.7, 65.7 (C-3, C-4, C-5); δ 55.1 (OCH_3); δ 16.3 (C-6); ^{1}H NMR data: δ 7.2-7.4 (m, 5 H, H-arom.); δ 4.6-4.8 (AB, 2 H, CH_2-benzyl); δ 4.6 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1); δ 3.9 (dd, 1 H, $J_{2,3}$ 10 Hz, $J_{3,4}$ 3.4 Hz, H-3); δ 3.8 (m, 1 H, H-5); δ 3.7 (dd, 1 H, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 1.1 Hz, H-4); δ 3.65 (dd, 1 H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10 Hz, H-2); δ 3.3 (s, 3 H, OCH_3); δ 1.24 (d, 3 H, $J_{5,6}$ 6.7 Hz, 3x H-6).

Methyl 2,3-Di-*O*-benzyl-α-L-fucopyranoside (6). A solution of compound **5** (1.5 g, 5.5 mmol) and dibutyltin oxide (1.5 g, 6.0 mmol) in methanol (40 mL) was refluxed for 3 h and subsequently concentrated. After coevaporation with toluene (4x75 mL), the residue was redissolved in toluene (25 mL). To this solution was added benzyl bromide (0.8 mL) and tetrabutylammonium iodide (1 g). The reaction mixture was stirred for 16 h at 85 °C, when TLC analysis (System B) indicated the formation of **6** to be complete. The mixture was concentrated in vacuo and redissolved in dichloromethane (100 mL), extracted with water (2x50 mL), dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (eluent: dichloromethane/acetone, 97/3, v/v) to give pure **6** (1.5 g, 75%); Rf 0.4 (System B); m.p. 80-82°C; $[\alpha]_D^{20}$ -62° (c 1, $CHCl_3$) [lit.[8] $[\alpha]_D^{20}$ -60° and m.p. 78-80°]; ^{13}C NMR data ($CDCl_3$): δ 137.7, 137.9 (2x C-quat., benzyl); δ 127.0-128.0 (C-arom.); δ 97.9 (C-1); δ 77.4, 75.1 (C-2, C-3); δ 72.7, 72.1 (2x CH_2-benzyl); δ 69.6 (C-4); δ 64.7 (C-5); δ 54.6 (OCH_3); δ 15.6 (C-6); ^{1}H NMR data: δ 7.2-7.4 (m, 10 H, H-arom.); δ 4.6-4.8 (2xAB, 4H, 2x CH_2, benzyl); δ 4.6 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1); δ 3.7-3.9 (m, 4 H, H-2, H-3, H-4, H-5); δ 3.36 (s, 3 H, OCH_3); δ 1.26 (d, 3 H, $J_{5,6}$ 6.67 Hz, 3x H-6).

Anal. Calcd for $C_{21}H_{26}O_5$: C 70.37, H 7.31; Found: C 70.21, H 7.40%.

Ethyl 3,4-*O*-isopropylidene-1-thio-β-L-fucopyranoside (9). Compound **7**[14] (9.8 g, 29.3 mmol) was dissolved in dry methanol (100 mL) and potassium *tert*-butoxide (550 mg, 5 mmol) was added. After stirring for 30 min, the mixture was neutralized with acetic acid and concentrated to give **8** as an oil. Crude **8** was dissolved in a mixture of DMF (100 mL) and 2,2-dimethoxypropane (45 mL). To the solution was added *p*-toluenesulphonic acid (100 mg) and the mixture was stirred for 3 h at 20 °C, when TLC analysis (System C) indicated the reaction to be complete. The reaction mixture was quenched with triethylamine (5 mL) and concentrated, redissolved in dichloromethane (150 mL), extracted with water (3x50 mL), dried ($MgSO_4$) and again concentrated. Purification by silica gel chromatography (3% methanol in dichloromethane) afforded pure **9** (5.8 g, 80%); Rf 0.75 (System C); ^{13}C NMR data ($CDCl_3$): δ 109.6 (C-quat., isopropylidene); δ 84.9 (C-1); δ 79.0, 76.2 (C-3, C-4); δ 72.6 (C-2); δ 71.8 (C-5); δ 28.1, 26.2 (2x CH_3, isopropylidene); δ 24.0 (CH_2, SEt); δ 16.7 (C-6); δ 15.0 (CH_3, SEt).

Ethyl 2-*O*-Benzyl-3,4-*O*-isopropylidene-1-thio-β-L-fucopyranoside (10). To a cooled (0 °C) solution of compound **9** (5 g, 20 mmol) in DMF (75 mL) was added sodium hydride (80% dispersion in mineral oil, 864 mg, 30 mmol) and benzyl bromide (3.1 mL, 26 mmol). After stirring for 1 h at 20 °C, TLC analysis (System D) revealed complete reaction. The reaction mixture was quenched with methanol (5 mL) to destroy excess NaH and the solution was neutralized with acetic acid. After concentration under reduced pressure, the residue was dissolved in dichloromethane (100 mL), extracted with aq. $NaHCO_3$ (2x50 mL) and water (50 mL) and dried ($MgSO_4$). Evaporation of the solvent gave a residue which was chromatographed on silica gel (diethyl ether/n-hexane, 1:1, v/v) to give pure **10** (6.1 g, 90%) as a colourless oil; Rf 0.8 (System D); $[\alpha]_D^{20}$ -8.1° (c 1.25, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 137.5 (C-quat., benzyl); δ 127.0-128.0 (C-arom.); δ 108.7 (C-quat., isopropylidene); δ 82.6 (C-1); δ 79.1, 78.5, 75.9 (C-2, C-3, C-4); δ 72.7 (CH_2-benzyl); δ 71.7 (C-5); δ 25.8, 27.4 (2x CH_3, isopropylidene); δ 23.6 (CH_2, SEt); δ 16.2 (C-6); δ 14.4 (CH_3, SEt); ^1H NMR data ($CDCl_3$): δ 7.20-7.35 (m, 5 H, H-arom.); δ 4.7-4.8 (AB, 2 H, CH_2, benzyl); δ 4.38 (d, 1 H, $J_{1,2}$ 9.8 Hz, H-1); δ 4.2 (dd, 1 H, $J_{2,3}$ 6.6 Hz, $J_{3,4}$ 5.7 Hz, H-3); δ 4.0 (dd, 1 H, $J_{3,4}$ 5.7 Hz, $J_{4,5}$ 2.3 Hz, H-4); δ 3.8 (m, 1 H, $J_{5,6}$ 6.7 Hz, H-5); δ 3.4 (dd, 1 H, $J_{2,3}$ 6.6 Hz, H-2); δ 2.65 (m, 2 H, CH_2, SEt); δ 1.2-1.4 (m, 12 H, 2x CH_3 isopropylidene + 3x H-6 + CH_3, SEt).

Anal. Calcd for $C_{18}H_{26}O_4S$: C 63.88, H 7.74; Found: C 63.71, H 7.63%.

Ethyl 2-*O*-Benzyl-1-thio-ß-L-fucopyranoside (11). Compound **10** (4.8 g, 14.2 mmol) was suspended in acetic acid-water, 7/3, v/v (50 mL) and stirred at 80 °C for 2 h. The mixture was concentrated followed by coevaporation of the remaining residue with toluene (4x75 mL) to give compound **10** (4.2 g, 100%) as an yellow oil, which was used in the next step without further purification; Rf 0.6 (System C); ^{13}C NMR data ($CDCl_3$): δ 138.0 (C-quat., benzyl); δ 127.1-128.2 (C-arom.); δ 84.3 (C-1); δ 71.5-78.6 (C-2, C-3, C-4, C-5, CH_2-benzyl); δ 24.6 (CH_2, SEt); δ 16.3 (C-6); δ 14.7 (CH_3, SEt).

Ethyl 2,3-Di-*O*-benzyl-1-thio-ß-L-fucopyranoside (12). A solution of compound **11** (4.2 g, 14 mmol) and dibutyltin oxide (3.8 g, 15.4 mmol) in dry methanol (100 mL) was refluxed for 3 h and subsequently concentrated. The resulting oil was coevaporated with toluene (3x50 mL) and redissolved in DMF (60 mL). To this solution was added cesium fluoride[15] (4.1 g, 27 mmol) and benzyl bromide (2.1 mL). The reaction mixture was stirred for 16 h at 40 °C, when TLC analysis (System D) indicated the formation of **12** to be complete. The solution was concentrated in vacuo and the residue was redissolved in dichloromethane (100 mL), extracted with water (2x50 mL), dried ($MgSO_4$) and concentrated to give crude **12**. Purification on silica gel (diethyl ether/n-hexane, 1/1, v/v) gave pure **12** (4.6 g, 85%) as an oil; Rf 0.35 (System D); ^{13}C NMR data ($CDCl_3$): δ 137.9, 138.3 (2x C-quat., benzyl); δ 127.8-128.5 (C-arom.); δ 84.7 (C-1, $J_{C,H}$ 151 Hz); δ 82.7, 77.8 (C-2, C-3); δ 75.6, 71.9 (2x CH_2-benzyl); δ 74.1 (C-4); δ 69.3 (C-5); δ 24.6 (CH_2, SEt); δ 16.8 (C-6); δ 15.1 (CH_3, SEt).

Anal. Calcd for $C_{22}H_{28}O_4S$: C 68.01, H 7.26; Found: C 67.84, H 7.12%.

Ethyl 4-*O*-Acetyl-2,3-di-*O*-benzyl-ß-1-thio-L-fucopyranoside (13). Compound **12** (4.0 g, 10.3 mmol) was dissolved in pyridine (30 mL) and acetic anhydride (15 mL). After stirring for 2 h at 20 °C, toluene was added 50 mL and the solution was concentrated. The remaining oil was coevaperated with toluene (3x50 mL and chromatographed on silica gel (diethyl ether/n-hexane, 1/1, v/v) to give pure **13** (4.2 g, 94%); Rf 0.7 (System D); $[\alpha]_D^{20}$ -12.9° (c 1, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 170.4 (C-quat., acetyl); δ 137.4, 137.9 (2x C-quat., benzyl); δ 127.3-128.0 (C-arom.); δ 84.5 (C-1, $J_{C,H}$ 154 Hz); δ 80.7, 77.4 (C-2, C-3); δ 75.4, 71.4 (2x CH_2, benzyl); δ 72.5, 69.5 (C-4, C-5); δ 24.4 (CH_2, SEt); δ 20.5 (CH_3, acetyl); δ 16.4 (C-6); δ 14.7 (CH_3, SEt); ^1H NMR data: δ 7.25-7.4 (m, 10 H, H-arom.); δ 5.38 (dd, 1 H, $J_{3,4}$ 3.1 Hz, $J_{4,5}$ 0.8 Hz, H-4); δ 4.5-4.85 (2x AB, 4 H, 2x CH_2, benzyl); δ 4.4 (d, 1 H, $J_{1,2}$ 9.4 Hz, H-1); δ 3.7 (m, 1 H, H-5); δ 3.55 (m, 2 H, H-2, H-3); δ 2.8 (m, 2 H, CH_2, SEt); δ 2.2 (s, 3 H, acetyl); δ 1.3 (t, 3 H, CH_3, SEt); δ 1.2 (d, 3 H, $J_{5,6}$ 6.4 Hz, 3x H-6).

Anal. Calcd for $C_{24}H_{30}O_5S$: C 66.95, H 7.02; Found: C 66.68, H 6.88%.

Ethyl 2,3-Di-*O*-benzyl-4-*O*-dichloroacetyl-ß-1-thio-L-fucopyranoside (14). To a solution of **12** (2 g, 5.1 mmol) in pyridine (20 mL) was added 0.5 M dichloroacetic anhydride in toluene (13 mL). After stirring the mixture for 0.5 h, compound **14** (2.4 g, 94%) was obtained after the same work-up procedure as used for compound **13**; Rf 0.75 (System D); ^{13}C NMR data ($CDCl_3$): δ 164.0 (C-quat., dichloroacetyl); δ 137.6, 137.1 (2x C-quat., benzyl); δ 127.2-127.8 (C-arom.); δ 84.1 (C-1); δ 80.2, 76.6 (C-2, C-3); δ 75.1, 71.5 (2x CH_2, benzyl); δ 72.9, 71.9 (C-4, C-5); δ 63.9 (CH, dichloroacetyl); δ 23.9 (CH_2, SEt); δ 16.0 (C-6); δ 14.6 (CH_3, SEt); ^1H NMR data : δ 7.2-7.4 (m, 10 H, H-arom.); δ 6.1 (s, 1 H, CH, dichloroacetyl); δ 5.38 (dd, 1 H, $J_{3,4}$ 3.2 Hz, $J_{4,5}$ 1 Hz, H-4); δ 4.5-4.85 (2x AB, 4 H, 2x CH_2-benzyl); δ 4.44 (d, 1 H, $J_{1,2}$ 9.4 Hz, H-1); δ 3.7 (m, 1 H, H-5); δ 3.5-3.65 (m, 2 H, H-2, H-3); δ 2.8 (m, 2 H, CH_2, SEt); δ 1.3 (t, 3 H, CH_3, SEt); δ 1.3 (d, 3 H, $J_{5,6}$ 6.4 Hz, 3x H-6).

Anal. Calcd for $C_{24}H_{28}O_5Cl_2S$: C 57.72, H 5.65; Found: C 57.61, H 5.56%.

Ethyl 4-*O*-Acetyl-2,3-di-*O*-benzyl-α-1-thio-L-fucopyranoside (15). To a solution of compound **13** (2.15 g, 5 mmol) in diethyl ether (7 m) and 1,2-dichloroethane (7 mL) was added molecular sieves 4 Å (3 g) and IDCP[7] (570 mg, 1.25 mmol). The mixture was stirred for 15 min at 20 °C. The solution was diluted with diethyl ether (40 mL), filtered, extracted with 10% aq. $Na_2S_2O_3$ (2x25 mL), 10% aq. $NaHCO_3$ (25 mL) and water (2x50 mL). The organic layer was dried ($MgSO_4$), concentrated and the residue was purified by silica gel chromatography (diethyl ether/n-hexane, 1/1, v/v) to yield pure **15** (1.18 g, 55%) and **13** (630 mg, 29%); compound **15**: Rf 0.8 (System D); $[\alpha]_D^{20}$ -111.0° (c 1, $CHCl_3$); mp 74-76°C; ^{13}C NMR data ($CDCl_3$): δ 170.3 (C-quat., acetyl); δ 138.0, 138.1 (2x C-quat., benzyl); δ 127.3-128.0 (C-arom.); δ 83.2 (C-1, $J_{C,H}$ 164 Hz); δ 76.4, 74.9 (C-2, C-3); δ 72.3, 71.9 (2x CH_2-benzyl); δ 70.6, 64.7 (C-4, C-5); δ 23.5 (CH_2, SEt); δ 20.6 (CH_3, acetyl); δ 16.0 (C-6); δ 14.6 (CH_3, SEt); ^1H NMR data: δ 7.25-7.4 (m, 10 H, H-arom.); δ 5.44 (d, 1 H, $J_{1,2}$ 5.7 Hz,

H-1); δ 5.38 (dd, 1 H, $J_{3,4}$ 3.5 Hz, $J_{4,5}$ 1.2 Hz, H-4); δ 4.5-4.7 (2x AB, 4 H, 2x CH_2, benzyl); δ 4.39 (m, 1 H, $J_{5,6}$ 6.5 Hz, H-5); δ 4.05 (dd, 1 H, $J_{1,2}$ 5.6 Hz, $J_{2,3}$ 10 Hz, H-2); δ 3.8 (dd, 1 H, $J_{2,3}$ 10 Hz, $J_{3,4}$ 3.5 Hz, H-3); δ 2.4-2.6 (m, 2 H, CH_2-SEt); δ 2.14 (s, 3 H, acetyl); δ 1.27 (t, 3 H, CH_3, SEt); δ 1.2 (d, 3 H, $J_{5,6}$ 6.5 Hz, 3x H-6).

Anal. Calcd for $C_{24}H_{30}O_5S$: C 66.95, H 7.02; Found: C 66.89, H 7.96%.

Methyl 4-*O*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranoside (16). To a solution of compound **6** (644 mg, 1.8 mmol) and **13** (1.1 g, 2.5 mmol) in diethyl ether (16 mL) and 1,2-dichloroethane (4 mL) was added molecular sieves 4 Å (2 g). After the mixture was stirred for 1 h, IDCP (1.7 g, 3.7 mmol) was added. The mixture was stirred for 3 h at 20 °C, when TLC analysis (System D) indicated the reaction to be complete. The solution was diluted with diethyl ether (50 mL) and filtered, extracted with 10% aq. $Na_2S_2O_3$ (2x25 mL), 10% aq. $NaHCO_3$ (25 mL) and water (2x50 mL). The organic layer was dried ($MgSO_4$), concentrated and the residue was purified by silica gel chromatography (diethyl ether/n-hexane, 1/1, v/v) to yield pure **16** (1.03 g, 80%); Rf 0.4 (System D); $[\alpha]_D^{20}$ -79.1° (c 1, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 170.0 (C-quat., acetyl); δ 137.8-138.4 (4x C-quat., benzyl); δ 127.0-127.8 (C-arom.); δ 99.6, 97.9 (C-1^b, J_{C_1,H_1} 165.6 Hz; C-1^a, J_{C_1,H_1} 167 Hz;); δ 78.6, 76.7, 75.9, 75.1, 74.5 (C-2^b, C-3^b, C-2^a, C-3^a, C-4^a); δ 73.4, 72.4, 72.2, 71.1 (4x CH_2-benzyl); δ 70.5, 66.1, 64.6 (C-4^b, C-5^b, C-5^a); δ 54.6 (OCH_3); δ 20.3 (CH_3, acetyl); δ 15.9, 15.4 (C-6^b, C-6^a); ^1H NMR data: δ 7.1-7.4 (m, 20 H, H-arom.); δ 5.3 (dd, 1 H, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 1.5 Hz, H-4^b); δ 4.9 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1^b); δ 4.75 (d, 1 H, $J_{1,2}$ 3 Hz, H-1^a); δ 4.45-4.85 (m, 8H, 4xCH_2-benzyl); δ 4.4 (m, 1H, $J_{4,5}$ 1.5 Hz, $J_{5,6}$ 6.4 Hz, H-5^a); δ 3.95 (dd, 1 H, H-3^b); δ 3.9 (1 H, H-3^a); δ 3.85 (dd, 1 H, $J_{1,2}$ 3 Hz, $J_{2,3}$ 6 Hz, H-2^a); δ 3.74-3.84 (m, 3 H, H-2^b, H-5^b, H-4^a); δ 3.3 (s, 3 H, OCH_3); δ 2.2 (s, 3H, CH_3 acetyl); δ 1.3 (d, 3 H, $J_{5,6}$ 6.6 Hz, 3x H-6); δ 0.9 (d, 3 H, $J_{5,6}$ 6.6 Hz, 3x H-6).

Anal. Calcd for $C_{43}H_{50}O_{10}$: C 71.06, H 6.93; Found: C 70.86, H 6.81%.

Methyl 4-*O*-(2,3-Di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranoside (17). To a solution of compound **16** (1.15 g, 1.6 mmol) in dry methanol (30 mL) was added a catalytic amount (10 mg) of potassium *tert*-butoxide. The mixture was stirred for 16 h at 20 °C, when TLC analysis (System E) indicated complete conversion of **16** into **17**. The solution was neutralized with Dowex 50W (H^+ form), filtered, concentrated and coevaporated with toluene (2x 60 mL). The residue was purified on silica gel (diethyl ether/n-hexane, 2/1, v/v) to give pure **17** (1.0 g, 92%); Rf 0.4 (System E); $[\alpha]_D^{20}$ -78.0° (c 1, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 137.9-138.6 (4 x C-quat., benzyl); δ 127.0-128.1 (C-arom.); δ 99.6, 98.1 (C-1^b, C-1^a); δ 78.6, 77.9, 77.1, 75.5, 74.5 (C-2^a, C-3^a, C-4^a, C-2^b, C-3^b); δ 73.5, 72.5, 72.4, 71.7 (4x CH_2-benzyl); δ 69.7 (C-4^b) δ 66.3, 65.5 (C-5^b, C-5^a); δ 54.8 (OCH_3); δ 16.1, 15.7 (C-6^a, C-6^b).

Methyl 4-*O*-(α-L-fucopyranosyl)-α-L-fucopyranoside (1, n=0). To a solution of compound **17** (210 mg, 0.3 mmol) in ethanol (10 mL) was added palladium on charcoal (210 mg). The mixture was stirred under a gentle stream of hydrogen for 16 h at 40 °C, when TLC analysis (System F) revealed the reaction to be complete. The reaction mixture was filtered over Celite, concentrated and the residue was purified by LH-20 chromatography (eluent: methanol) to yield pure **1, n=0** (84 mg, 84%); Rf 0.45 (System F); mp 100-103°C; $[\alpha]_D^{20}$ -228.0° (c 0.5, H_2O) [lit.[9] $[\alpha]_D^{25}$ -240° (c 0.95, H_2O), m.p. 102-104° (from methanol/diisopropyl ether)]; ^{13}C NMR data (CD_3OD): δ 102.1 (C-1^b); δ 101.2 (C-1^a); δ 81.5 (C-4^a); δ 73.4, 71.0, 70.6, 70.2, 69.7 (C-2^b, C-3^b, C-4^b, C-2^a, C-3^a); δ 68.1 (C-5^a, C-5^b); δ 56.0 (OCH_3); δ 16.6, 16.5 (C-6^a, C-6^b); ^1H NMR data (D_2O): δ 4.93 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-1^b); δ 4.8 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1^a); δ 4.5 (m, 1 H, $J_{5,6}$ 6.8 Hz, H-5^a); δ 4.07 (m, 1 H, $J_{5,6}$ 6.7 Hz, H-5^b); δ 3.75-3.93 (m, 6 H, H-2^a, H-3^a, H-4^a, H-2^b, H-3^b, H-4^b); δ 3.4 (s, 3 H, OCH_3); δ 1.3 (d, 3 H, $J_{5,6}$ 6.7 Hz, 3x H-6^b); δ 1.15 (d, 3 H, $J_{5,6}$ 6.7 Hz, 3x H-6^a).

Anal. Calcd for $C_{13}H_{24}O_9$: C 48.14, H 7.46; Found: C 47.91, H 7.73%.

Methyl 4-*O*-(4-*O*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranoside (18, R_2=Ac). To a solution of compound **17** (1.0 g, 1.46 mmol) and **13** (780 mg, 1.8 mmol) in diethyl ether (16 mL) and 1,2-dichloroethane (4 mL) was added molecular sieves 4 Å (2 g). After stirring the mixture for 1 h, IDCP (1.2 g, 2.7 mmol) was added. Work-up, after 3 h, as described for compound **16** and purification on a Sephadex LH-20 column (eluent: dichloromethane/methanol, 1/1, v/v) gave **18** (R_2=Ac) (1.2 g, 78%); Rf 0.35 (System D); $[\alpha]_D^{20}$ -93.3° (c 1, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 170.7 (C-quat., acetyl); δ 138.0-139.0 (C-quat., benzyl); δ 127.0-128.3 (C-arom.); δ 100.1, 99.4, 98.4 (C-1^c, $J_{C,H}$ 168.9 Hz; C-1^b, C-1^a); δ 79.4, 78.2, 77.4, 77.1, 76.2, 75.5, 75.3, 74.9 (C-2^c, C-3^c, C-2^b, C-3^b, C-4^b, C-2^a, C-3^a, C-4^a); δ 72.5-73.8 (6x CH_2-benzyl); δ 71.1 (C-4^c); δ 67.4, 66.6, 65.1 (C-5^a, C-5^b, C-5^c); δ 55.1 (OCH_3); δ 20.9 (CH_3, acetyl); δ 15.8-16.4 (3x C-6).

Anal. Calcd for $C_{63}H_{72}O_{14}$: C 71.84, H 6.89; Found: C 71.65, H 6.59%.

Methyl 4-*O*-(4-*O*-(2,3-Di-*O*-benzyl-4-*O*-dichloroacetyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranoside (18, R_2=Cl_2Ac). IDCP (344 mg, 0.75 mmol) mediated condensation of **14** (250 mg, 0.5 mmol) and **17** (290 mg, 0.42 mmol) in a mixture of 1,2-dichloroethane (1 mL) and diethyl ether (4 mL) was accomplished via the same procedure as described for the synthesis of **16**. After purification on Sephadex LH-20 (eluent: dichloromethane/methanol, 1/1, v/v) pure compound **18** (R_2=Cl_2Ac) (388 mg, 82%) was obtained; Rf 0.5 (System D); $[\alpha]_D^{20}$ -98.3° (c 1, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 164.6 (C-quat., dichloroacetyl); δ 138.4-139.4 (C-quat., benzyl); δ 127.0-128.8 (C-arom.); δ 100.3, 99.6, 98.8 (C-1^c, $J_{C,H}$ 169.1 Hz; C-1^b, C-1^a); δ 75.0-79.9 (C-2^a, C-3^a, C-4^a, C-2^b, C-3^b, C-4^b,

C-2^c, C-3^c); δ 72.4-74.2 (6x CH_2-benzyl); δ 64.4-67.7 (CH-dichloroacetyl, C-4^c, C-5^a, C-5^b, C-5^c); δ 55.5 (OCH_3); δ 16.0, 16.6, 16.8 (3x C-6).

Anal. Calcd or $C_{63}H_{70}O_{14}Cl_2$: C 67.43, H 6.29; Found: C 67.10, H 6.43%.

Methyl 4-*O*-(4-*O*-(-2,3-Di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranoside (19). Method A To a solution of compound **18** (R_2=Ac, 1.0 g, 0.95 mmol) in dry methanol (25 mL) was added potassium *tert*-butoxide (110 mg, 1 mmol). The mixture was stirred for 8 h at 70 °C, when TLC analysis (System D) revealed complete conversion of **18** (R_2=Ac) into **19**. The solution was neutralized with Dowex 50W (H^+ form), filtered, concentrated and coevaperated with toluene (2x50 mL). The residue was redissolved in dichloromethane (25 mL) and extracted with water (2x25 mL), dried ($MgSO_4$) and concentrated. The remaining oil was purified on silica gel (3% acetone in dichloromethane) to yield pure **19** (920 mg, 96%); Rf 0.2 (System D);

Method B Compound **18** (R_2=Cl_2Ac, 280 mg, 0.25 mmol) was dissolved in methanol (5 mL) and a catalytic amount (5 mg) of potassium *tert*-butoxide was added. The mixture was vigourously stirred for 15 minutes, when TLC analysis (System D) revealed the formation of the same product as described under method A. The same work-up procedure was followed to afford pure **19** (240 mg, 95%) as a white foam; $[\alpha]_D^{20}$ -85.3° (c 1, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 137.9-138.6 (6x C-quat., benzyl); δ 127.0-128.0 (C-arom.); δ 99.4, 99.2 (C-1^b, C-1^c); δ 98.1 (C-1^a); δ 78.7, 77.8 (2x), 77.2, 76.8, 75.5, 74.8, 74.5 (C-2^a, C-3^a, C-4^a, C-2^b, C-3^b, C-4^b, C-2^c, C-3^c); δ 73.4, 72.6 (2x), 72.3, 71.9, 71.7 (6x CH_2-benzyl); δ 69.7 (C-4^c); δ 67.1, 66.2, 65.4 (C-5^a, C-5^b, C-5^c); δ 54.8 (OCH_3); δ 16.1, 15.9, 15.6 (3x C-6).

Methyl 4-*O*-(4-*O*-(α-L-fucopyranosyl)-α-L-fucopyranosyl)-α-L-fucopyranoside (1, n=1). To a solution of compound **19** (100 mg, 0.1 mmol) in ethanol (10 mL) was added palladium on charcoal (110 mg). The mixture was stirred under a gentle stream of hydrogen at 40 °C for 16 h, when TLC analysis (System F) revealed complete conversion of **19** to one product. The mixture was filtered over Celite and concentrated in vacuo. The residue was purified by LH-20 chromatography (eluent: methanol) to give pure **1, n=1** (38 mg, 80%); Rf 0.35 (System F); $[\alpha]_D^{20}$ -149 (c 0.2, H_2O); ^{13}C NMR data (CD_3OD): δ 102.4, 101.8, 101.6 (C-1^c, C-1^b, C-1^a); δ 82.0, 81.9 (C-4^a, C-4^b); δ 68.1-73.7 (C-2^a, C-3^a, C-5^a, C-2^b, C-3^b, C-5^b, C-2^c, C-3^c, C-4^c, C-5^c); δ 55.8 (OCH_3); δ 16.6 (3x C-6); ^1H NMR data (D_2O): δ 4.9 (d, 1 H, $J_{1,2}$ 4 Hz, H-1^b); δ 4.85 (d, 1 H, $J_{1,2}$ 4 Hz, H-1^c); δ 4.7 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1^a); δ 4.45 (m, 2 H, H-5^b, H-5^a); δ 3.6-4.0 (m, 10 H, H-2^a, H-3^a, H-4^a, H-2^b, H-3^b, H-4^b, H-2^c, H-3^c, H-4^c, H-5^c); δ 3.3 (s, 3 H, OCH_3); δ 1.1-1.3 (3x d, 9 H, 9x H-6).

Anal. Calcd or $C_{19}H_{34}O_{13}$: C 48.51, H 7.28; Found: C 48.32, H 7.55%.

Methyl 4-*O*-(4-*O*-(4-*O*-(4-*O*-Acetyl-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranoside (20 R_2=Ac). Trimer **19** (650 mg, 0.64 mmol) was coupled, in the same way as mentioned

before, with compound **13** (357 mg, 0.83 mmol) using IDCP (560 mg, 1.21 mmol) in diethyl ether (8 mL) and 1,2-dichloroethane (2 mL). The crude product was purified on Sephadex LH-20 (eluent: dichloromethane/methanol, 1/1, v/v) to yield homogeneous **20** (R_2=Ac) (650 mg, 73%); Rf 0.6 (System B); $[\alpha]_D^{20}$ -103.2° (c 1, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 170.1 (C-quat., acetyl); δ 137.8-138.5 (8x C-quat., benzyl); δ 126.8-127.9 (C-arom.); δ 99.6, 99.0, 98.9 (C-1^b, C-1^c, C-1^d, $J_{C,H}$ 167.8 Hz); δ 98.0 (C-1^a); δ 79.8-65.4 (C-2^a, C-3^a, C-4^a, C-5^a); δ 72.0-74.0 (8x CH_2-benzyl); δ 54.6 (OCH_3); δ 20.3 (CH_3, acetyl); δ 15.4-16.0 (4x C-6).

Anal. Calcd for $C_{83}H_{94}O_{18}$: C 72.76, H 6.87; Found: C 72.61, H 6.75%.

Methyl 4-*O*-(4-*O*-(4-*O*-(4-*O*-Dichloroacetyl-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranoside (20, R_2=Cl_2Ac). The IDCP (414 mg, 0.9 mmol) mediated glycosylation of trimer **19** (470 mg, 0.46 mmol) and compound **14** (300 mg, 0.6 mmol) was performed in the same way as described above. After the standard work-up procedure and purification on a Sephadex LH 20 column (eluent: dichloromethane/methanol, 1/1, v/v), compound **20** (R_2=Cl_2Ac) was obtained as a white foam (590 mg, 89%); Rf 0.7 (System B); $[\alpha]_D^{20}$ -109.8 (c 0.5, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 164.7 (C-quat., dichloroacetyl); δ 138.4-139.5 (8x C-quat., benzyl); δ 125.7-129.4 (C-arom.); δ 100.4, 99.9, 99.6, 98.9 (4x C-1); δ 64.9-80.0 (C-2^a, C-3^a, C-4^a, C-5^a, 8x CH_2, benzyl); δ 64.8 (CH-dichloroacetyl); δ 55.6 (OCH_3); δ 16.0, 16.6, 16.7, 16.9 (4x C-6); ^1H NMR data: δ 7.2-7.4 (m, 40 H, H-arom.); δ 5.9 (s, 1 H, dichloroacetyl); δ 5.2 (dd, 1H, $J_{3,4}$ 2.7 Hz, $J_{4,5}$ 1 Hz, H-4^d); δ 4.95 (t, 2 H, 2x H-1); δ 4.5-4.85 (m, 18 H, 8x CH_2-benzyl, 2x H-1); δ 3.6-4.4 (m, 15H, H-2^a, H-3^a, H-4^a, H-4^b, H-4^c, H-5^a); δ 3.34 (s, 3 H, OCH_3); δ 0.7-1.3 (4x d, 12 H, $J_{5,6}$ 6.7 Hz, 12x H-6).

Anal. Calcd for $C_{83}H_{92}O_{18}Cl_2$: C 68.82, H 6.40; Found: C 68.68, H 6.32%.

Methyl 4-*O*-(4-*O*-(4-*O*-(2,3-Di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-2,3-di-*O*-benzyl-α-L-fucopyranoside (21). Method A. Compound **20** (R_2=Ac, 700 mg, 0.5 mmol) was suspended in a mixture of dioxane/methanol/4 N NaOH (29/9/2, v/v/v, 8 mL) and the suspension was stirred for 8 h at 70 °C, when TLC analysis (System B) revealed the reaction to be complete. The mixture was neutralized with Dowex 50W (H^+ form), filtered and evaporated in vacuo. The residue was purified on silica gel (dichloromethane/acetone, 97/3, v/v) to give pure **21** (540 mg, 81%) as a white foam; Rf 0.3 (System B); $[\alpha]_D^{20}$ -109.7 (c 1.9, $CHCl_3$).

Method B. Compound **20** (R_2=Cl_2Ac, 440 mg, 0.3 mmol) was dissolved in a mixture of dry dichloromethane (4 mL) and dry methanol (10 mL). To this solution was added a catalytic amount (5 mg) of potassium *tert*-butoxide and the mixture was stirred for 30 minutes at 20 °C, when TLC analysis (System B) revealed the formation of the same product as described under Method A. Work-up and purification as mentioned before gave pure **21** (370 mg, 91%) as a white foam; Rf 0.3 (System B); $[\alpha]_D^{20}$ -109.8 (c 1.9, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ

138.3-138.9 (8x C-quat., benzyl); δ 127.0-128.0 (C-arom.); δ 99.5, 99.2 (2x), 98.2 (C-1^n); δ 65.5-79.0 (C-2^n, C-3^n, C-4^n, C-5^n); δ 71.9-73.6 (8x CH_2-benzyl); δ 54.9 (OCH_3); δ 15.7-16.0 (C-6^n).

Methyl 4-*O*-(4-*O*-(4-*O*-(-α-L-fucopyranosyl)-α-L-fucopyranosyl)-α-L-fucopyranosyl)-α-L-fucopyranoside (1, n=2). To solution of compound **21** (100 mg, 0.075 mmol) in ethanol (6 mL) was added palladium on charcoal (100 mg) and the mixture was stirred under a gentle stream of hydrogen. TLC analysis (System F), after 16 h at 50 °C, revealed the complete conversion of **21** to one product, which was isolated and purified in the same way as described before, to give **1, (n=2)** (40 mg, 87%) as a white foam; $[\alpha]_D^{20}$ -168.0 (c 0.2, H_2O); ^{13}C NMR data (CD_3OD): δ 101.6 (2x C-1); δ 100.6 (2x C-1); δ 81.2 (2x), 81.0 (C-4^a, C-4^b, C-4^c); δ 67.9-73.0 (C-2^n, C-3^n, C-4^d, C-5^n); δ 56.1 (OCH_3); δ 16.2-16.5 (C-6^n); ^1H NMR data (D_2O): δ 4.98 (2x d, 2 H, $J_{1,2}$ 4.0 Hz, 2x H-1); δ 4.95 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-1); δ 4.8 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1); δ 4.5 (m, 3 H, 3x H-5); δ 4.1 (m, 1 H, $J_{5,6}$ 6.8 Hz, H-5); δ 3.70-4.1 (m, 12H, H-2^n, H-3^n, H-4^n); δ 3.4 (s, 3 H, OCH_3); δ 1.17-1.33 (4x d, 12 H, 12x H-6).

Anal. Calcd for $C_{25}H_{44}O_{17}$: C 48.70, H 7.19; Found: C 48.55, H 7.25%.

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