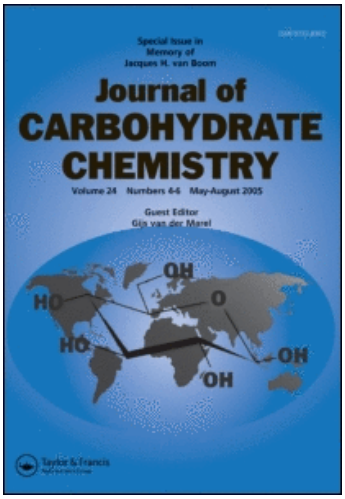


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis of Modified Di- and Trisaccharide Fragments of *N*-Glycoproteins

Nynke M. Spijker[a]; Jan-Willem Slief[a]; Constant A. A. Van Boeckel[a]
[a] Organon International B.V., Scientific Development Group, The Netherlands

To cite this Article Spijker, Nynke M. , Slief, Jan-Willem and Van Boeckel, Constant A. A.(1993) 'Synthesis of Modified Di- and Trisaccharide Fragments of *N*-Glycoproteins', Journal of Carbohydrate Chemistry, 12: 8, 1017 — 1041
To link to this Article: DOI: 10.1080/07328309308020115
URL: http://dx.doi.org/10.1080/07328309308020115

J. CARBOHYDRATE CHEMISTRY, 12(8), 1017-1041 (1993)

SYNTHESIS OF MODIFIED DI- AND TRISACCHARIDE FRAGMENTS OF *N*-GLYCOPROTEINS

Nynke M. Spijker, Jan-Willem Slief and Constant A. A. van Boeckel

Organon International B.V., Scientific Development Group,
P.O. Box 20, 5340 BH Oss, The Netherlands

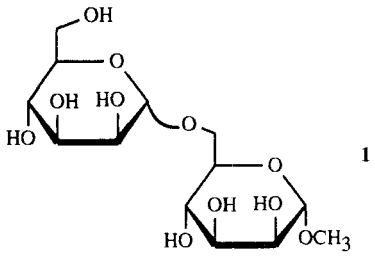
Received February 22, 1993 - Final Form May 24, 1993

ABSTRACT

The syntheses of several analogues of disaccharide Manα(1→6)Manα-OCH_3 (**1**) and of trisaccharide Manα(1→6)[Manα(1→3)]Manα-OCH_3 (**2**) are reported. The syntheses are described of the diastereomeric 6-methyl derivatives **9a** and **9b**, which are representatives of fixed conformations of disaccharide **1**. The syntheses of the 2-amino-2-deoxy analogues **15** and **17** and the synthesis of the 2-fluoro-2-deoxy analogue **28** are also reported.

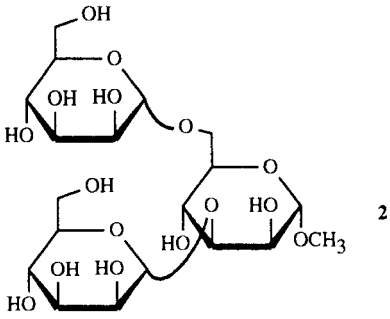
INTRODUCTION

The carbohydrate parts of *N*-glycoproteins are involved in a variety of biological recognition processes with proteins such as receptors,[1,2] lectins[3,4] and enzymes.[5] Because of the increasing biological interest in *N*-linked carbohydrates it is of paramount importance to get a better understanding of the carbohydrate-protein interaction. Several groups[6-9] have comprehensively studied the binding of carbohydrates with proteins by investigating chemically modified analogues of oligosaccharides. It was found that only a few hydroxyl groups (the key polar groups) of an oligosaccharide play a critical role in the binding with a particular protein, while



1

Manα(1→6)Manα-OCH_3



2

Manα(1→6)[Manα(1→3)]Manα-OCH_3

Figure 1

others may enhance the affinity of the binding. This phenomenon was revealed by study of synthetic analogues in which the key hydroxyl groups were replaced by halogens, hydrogen or amino groups. These analogues turned out to be inactive. Replacement of other hydroxyl groups, by for instance halogens or hydrogens, has relatively small effect, although at certain positions these modifications may lead to increased binding with the protein; apparently hydrophobic interactions also play a role in carbohydrate-protein interactions. There is much evidence[6,7] that hydrogen bonds are the main factors in conferring specificity and affinity to protein-carbohydrate interactions.

In order to gain more insight into the interaction between *N*-linked carbohydrates and proteins recognizing these carbohydrates (*e.g.*, the jack bean lectin Con A[3,4,10,11]), we synthesized modified fragments of disaccharide Manα(1→6)Manα-OCH_3 **1** and of trisaccharide Manα(1→6)[Manα(1→3)]Manα-OCH_3 **2** (Fig. 1), which are common structural components of all high-mannose *N*-glycoproteins.

First, the synthesis is presented of the diastereomeric 6-methyl analogues (**9a** and **9b**) of the Manα(1→6)Manα-OCH_3 disaccharide. Introduction of a 6-methyl group will make the flexible α(1→6) glycosidic bond more rigid, giving us better insight into the relationship between conformation and binding affinity. The synthesis of mannose di- and trisaccharides containing 2-amino-2-deoxy groups (compounds **15** and **17**) and 2-fluoro-2-deoxy groups (compound **28**) will also be presented. These modifications were selected since the (axial) 2-position, characteristic of mannopyranosides, might be involved in the specific interaction with a protein.

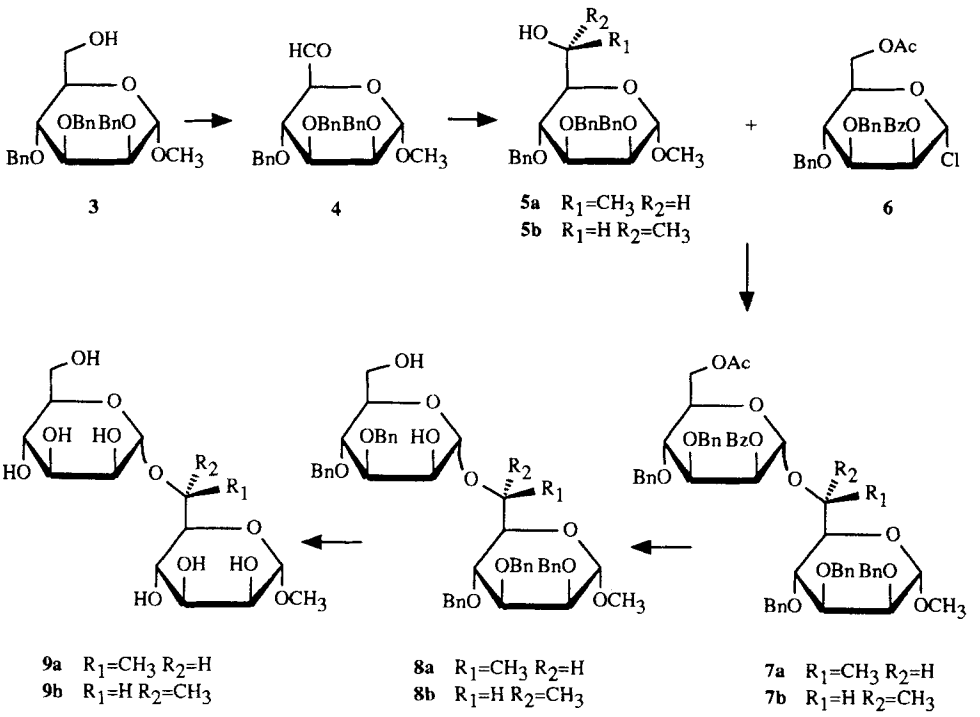
RESULTS AND DISCUSSION

*Synthesis of 6-methyl derivatives **9a** and **9b** (Scheme 1)*

Oligosaccharides such as Manα(1→6)Man and Manα(1→6)[Manα(1→3)]Man have much conformational freedom about the α(1→6) linkage and exist, in aqueous solution, as a mixture of the rapidly interconverting rotamers: gt (ω-angle (H-5,C-5,C-6,O-6) = -60°) and gg (ω = 180°).[12] It was demonstrated by Lemieux et al.[13] and Hindsgaul et al.[14] that substitution of a hydrogen for an alkyl group at the C-6 position of a glycopyranoside favours the occurrence of only one of the rotamers, depending on which H (pro-*S* or pro-*R*) is substituted. In order to examine the involvement of the hydroxymethyl group of the Manα(1→6)Man disaccharide in its complexation with a protein, the diastereomeric 6-methyl analogues **9a** and **9b** were prepared as representatives of fixed gg and gt conformations, respectively.

For the preparation of the diastereomeric disaccharides, the syntheses of methyl 2,3,4-tri-*O*-benzyl-7-deoxy-α-L-*glycero*-D-*manno*-heptopyranoside (*S*-configuration at C-6) (**5a**) and methyl 2,3,4-tri-*O*-benzyl-7-deoxy-α-D-*glycero*-D-*manno*-heptopyranoside (*R*-configuration at C-6) (**5b**) were first examined. Oxidation of starting compound **3**, methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside, was performed using chromium trioxide-pyridine complex in acetic anhydride[15] to give aldehyde **4**.[16] Treatment of crude **4** with methylmagnesium bromide in ether afforded, after fractionation of the stereoisomers by chromatography, the *S*-isomer **5a** in 45% yield and the *R*-isomer **5b** in 5% yield. The configurations at the new asymmetric carbon centres were established from ^{1}H NMR and nuclear Overhauser enhancement (NOE) studies. Saturation of the 6-methyl group of the major isomer led to a NOE on H-5 and on the anomeric methyl group. Furthermore, a coupling constant of 2.0 Hz was observed between H-5 and H-6. On the basis of these results we concluded that the major isomer was the *S*-isomer **5a**. On the other hand, the minor isomer was assigned to be the *R*-isomer **5b** since saturation of the 6-methyl group enhanced the signals for H-4 and H-5 and the coupling constant between H-5 and H-6 was 4.0 Hz.

The predominant formation of the *S*-isomer is in accordance with Cram's chelation rule.[17] However, we wished to increase the yield of the *R*-isomer for the preparation of compound **9b**. Since it has been documentated that in some cases reactions with organolithium reagents are less stereoselective,[17,18] we examined the reaction of aldehyde **4** with methyllithium. Reaction of **4** with methyllithium at -78 °C in THF indeed afforded a higher ratio between the *R*- and *S*-isomer (**5b/5a** : 1/1), but



Scheme 1

many side-products were formed and the yield of **5a** and **5b** was very low (yield **5a** + **5b** ≈ 25%).

Glycosylation of **5a** and **5b** with glycosyl chloride **6** in the presence of silver trifluoromethanesulfonate and 2,6-di-*tert*-butylpyridine afforded the α-linked disaccharides **7a** and **7b** in 90% and 77% yield, respectively. Deacylation of **7a** and **7b**, with potassium *tert*-butoxide in methanol, and subsequent hydrogenolysis in the presence of 10% Pd/C provided the deprotected disaccharides **9a** (*S*-configuration at C-6) and **9b** (*R*-configuration at C-6). The preferred conformations of **9a** and **9b** were established by the use of NOE techniques as follows. Saturation of H-6 of **9a** and **9b** caused a NOE on H-4, H-5 and H-1'. Moreover, saturation of the 6-methyl group of compound **9a** caused a NOE on H-5 and on H-1', while saturation of the 6-methyl of compound **9b** gave a NOE on H-4. These data, together with the coupling constants between H-5 and H-6 (1.2 Hz for **9a** and 3.0 Hz for **9b**) are in agreement with the expectation that the rotamer distribution about C-5,C-6 in compound **9a** is in favour of the gg conformation, while **9b** is biased towards the gt rotamer.

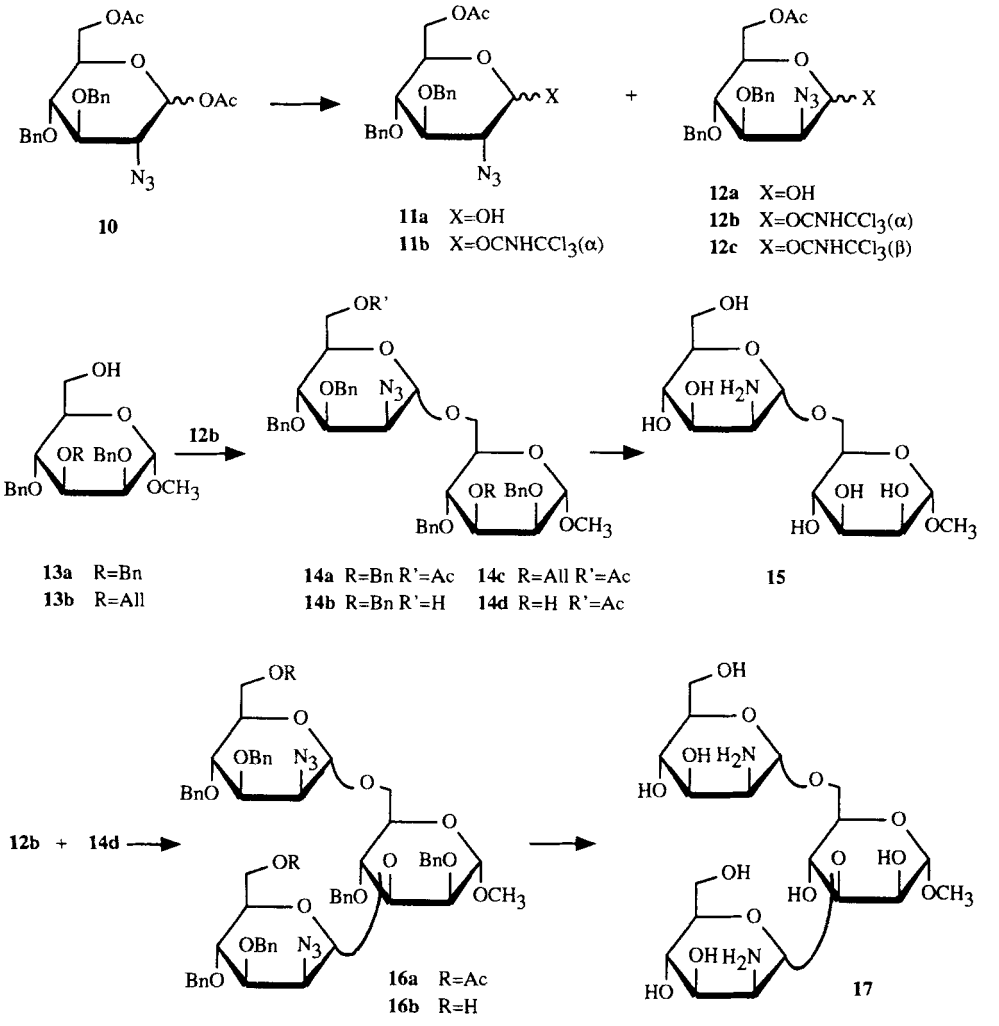
*Synthesis of the 2-amino-2-deoxy derivatives **15** and **17** (Scheme 2)*

In this section we describe the synthesis of the 2'-amino-2'-deoxy analogue (*i.e.*, compound **15**) of Manα(1→6)Manα-OMe and the 2'2''-diamino-2'2''-dideoxy analogue (*i.e.*, compound **17**) of Manα(1→6)[Manα(1→3)]Manα-OMe.

Several groups[9,19-21] have reported the synthesis and binding potential of oligosaccharides in which a hydroxyl group is substituted by an amino group. Even if the substituted hydroxyl group was not a key polar group, the binding activity for the protein could be influenced by the introduction of amino groups. In aqueous media at pH 7 these amino groups are mainly protonated and most likely serve as hydrogen bond donors, whereas hydroxyl groups can serve both as donors and as acceptors. Thus, by chemical synthesis of the target 2-amino-2-deoxy derivatives, more insight can be obtained concerning the role of the hydroxyl group at C-2 of the non-reducing mannose units.

For the synthesis of disaccharide **15** and for trisaccharide **17**, a 2-azido-2-deoxy-mannopyranosyl donor was selected. An easily accessible 2-azido-2-deoxy-mannopyranosyl donor turned out to be compound **12b**, obtained as a side-product in the synthesis of the corresponding glucopyranosyl imidate **11b**. During the anomeric saponification of compound **10**[22] with piperidine in tetrahydrofuran, some epimerization at C-2 took place resulting in the formation of a mixture of glucopyranoside **11a** and mannopyranoside **12a**. The mixture was subsequently treated with potassium carbonate and trichloroacetonitrile to give, after chromatography on silica gel, the glucopyranosyl α-imidate **11b** together with the mannopyranosyl α-imidate **12b**. The ratio of **11b** to **12b** appeared to be dependent on the reaction conditions and varied between 30:1 and 7:1. Since in our laboratory compound **11b** was synthesized on a large scale (~100 g), considerable amounts of **12b** became available. However, it is to be noted that 2-azido-2-deoxy-mannopyranosides can also be prepared via other routes, for instance by azidonitration of glycals.[23]

The synthesis of disaccharide **15** was then examined. Glycosylation of the primary hydroxyl group of acceptor **13a**[16] with α-imidate **12b** in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at -40 °C in ether afforded the disaccharide in a high yield (92%), but with a low stereoselectivity (α/β ≈ 1/1). However results from Schmidt et al.[24] indicated that much better α-selectivities should be obtained with β-imidates. Therefore the β-imidate **12c** was prepared from the α-imidate **12b** by the following two-step procedure. Hydrolysis of the anomeric imidate group with boron trifluoride etherate in a mixture of



Scheme 2

dichloromethane and water and subsequent treatment with trichloroacetonitrile and potassium carbonate for 20 minutes afforded a mixture of the α- and β-imidates. Chromatography of the mixture over silica gel afforded the pure β-imidate **12c** in 50% yield. Unfortunately, condensation of the β-imidate **12c** with acceptor **13a** in the presence of TMSOTf in ether at -40 °C afforded the disaccharide in the same poor α/β ratio of 1/1. Similar reactive intermediates are apparently involved in the glycosylation with the α-imidate and in the glycosylation with the β-imidate. It is important to note that glycosylations with a fully acetylated 2-azido-2-deoxy-mannopyranosyl imidate

will probably give rise to higher α/β ratios, as was experienced later in the synthesis of compound **28** (see next section).

The α-coupled disaccharide **14a** was then converted into the deprotected compound **15** in two steps. Saponification of the acetyl group with potassium *tert*-butoxide in methanol, followed by reduction of the azido group and simultaneous hydrogenolysis of the benzyl groups with palladium on charcoal provided the fully deprotected disaccharide **15** in 89% yield.

Next we turned our attention to the synthesis of trisaccharide **17**. We decided to introduce the 2-azido-2-deoxy-mannopyranosides stepwise, since we expected that simultaneous glycosylation of the 3- and 6-hydroxyl groups would lead to a very complex mixture of α- and β-coupled products. Thus, the α(1→6) linkage of the trisaccharide was first introduced by condensation of acceptor **13b**[25] (containing a temporary 3-*O*-allyl protective group) with the earlier-used donor **12b**. The glycosylation was performed under the same conditions as described above and afforded, after chromatography, the α-coupled disaccharide **14c** in 38% yield (α/β : 1/1.5).

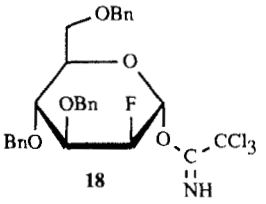
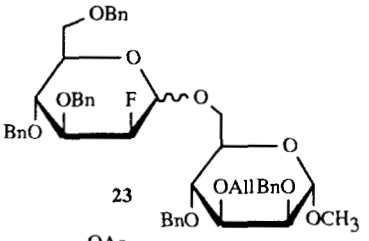
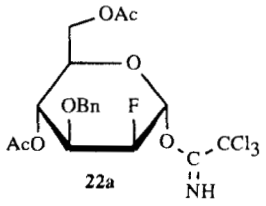
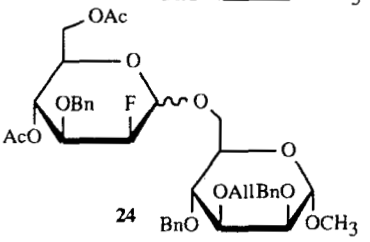
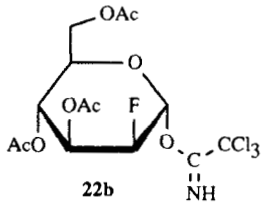
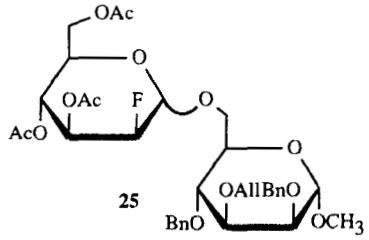
The allyl ether of **14c** was isomerised using 1,5-cyclooctadiene-*bis*[methyldiphenylphosphine]iridium hexafluorophosphate[26] as a catalyst to give the corresponding 1-propenyl ether, which was subsequently removed by treatment with *N*-iodosuccinimide in a mixture of tetrahydrofuran and water[27] to give the glycosyl acceptor **14d** in 54% yield. The acceptor thus obtained was condensed with glycosyl donor **12b** in the presence of TMSOTf at -20 °C to give the desired α-coupled trisaccharide **16a** in 35% yield together with the β-coupled isomer (15% yield). As expected, the α/β ratio (α/β : 2.3/1) of this coupling reaction was higher than the above-mentioned α/β ratios, because of the lower reactivity of the 3-hydroxyl group of **14d** compared to the primary 6-hydroxyl groups of **13a** and **13b**.

Deblocking of compound **16a** was effected by the same two-step procedure used for the conversion of **14a** into **15**, to give the fully deprotected trisaccharide **17** in quantitative yield. The identity of **17** was ascertained by ^{1}H NMR spectroscopy and FAB mass analysis.

Synthesis of the 2-fluoro-2-deoxy derivative (28) (Scheme 3)

Here we report the synthesis of the 2'2''-difluoro-2'2''-dideoxy analogue (*i.e.*, compound **28**) of Manα(1→6)[Manα(1→3)]Manα-OCH_3. The study of this compound may give additional information on the protein-carbohydrate interaction, since substitution of hydroxyl groups by fluorine atoms prevents hydrogen donation, without

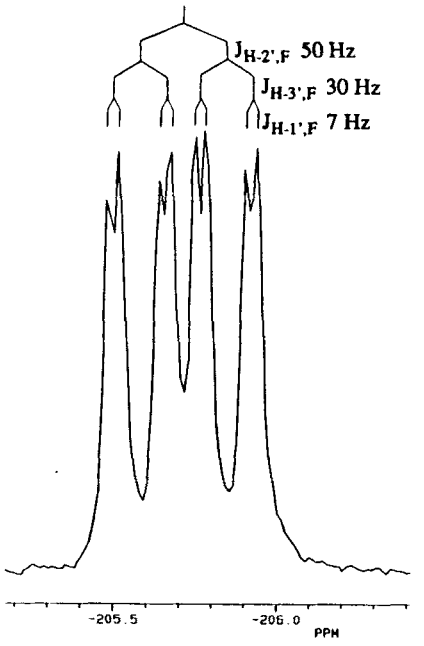
TABLE. Glycosylation of **13b** with several 2-fluoro-2-deoxy-mannopyranosyl donors.

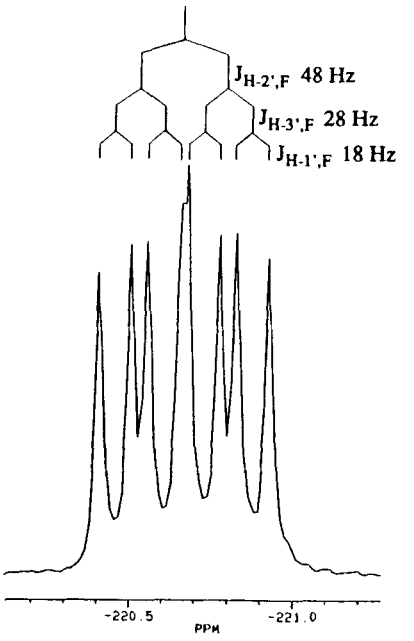
donor	acceptor	product	yield	α/β
 **18**	**13b**	 **23**	72%	1/1.5
 **22a**	**13b**	 **24**	68%	1/3
 **22b**	**13b**	 **25**	55%	α

repressing hydrogen bond acceptation.[28,29] Increased interactions can be found when the fluorine atom is involved in non-polar interactions with the protein. On the other hand, when the substituted hydroxyl group is a "key hydroxyl group",[6] the introduction of fluorine can result in complete loss of affinity by a protein.

In the first approach to the synthesis of trisaccharide **28**, we selected compound **18** (see Table) as 2-fluoro-2-deoxy-mannopyranosyl donor. Thus, treatment of known 3,4,6-tri-*O*-benzyl-2-deoxy-2-fluoro-D-mannopyranose[30] with trichloroacetonitrile and cesium carbonate[31] gave exclusively the α-imidate donor **18**. This compound was coupled with glycosyl acceptor **13b** (having a free primary hydroxyl group) in the presence of a catalytic amount of TMSOTf to afford the disaccharide **23** as a mixture of α- and β-coupled products (yield 72%, α/β : 1/1.5, see Table).

The stereochemistry of **23**-α and **23**-β could readily be assigned on the basis of the ^{1}H-coupled ^{19}F NMR spectra (Fig. 2), since the coupling constant between the axial fluoro and an equatorial H-1' (α-linkage) is distinct from the coupling constant





^{19}F NMR spectrum of compound **23-α** ^{19}F NMR spectrum of compound **23-β**

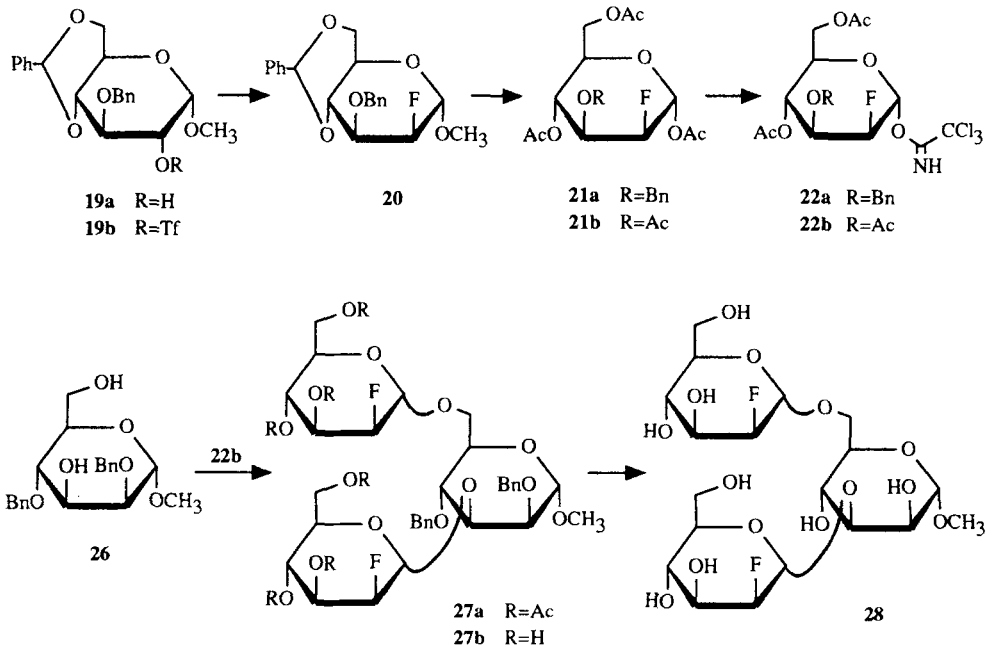
Figure 2

between the axial fluoro and an axial H-1' (β-linkage).[32] Thus, the $J_{H-1',F}$ value of 7 Hz is in agreement with the presence of an α-glycosidic linkage whereas the $J_{H-1',F}$ value of 18 Hz is in accordance with the β-glycosidic structure. It is important to note that the configuration of the anomeric centre cannot be assigned unambiguously on the basis of the coupling constants between H-1' and H-2', due to the small difference in $J_{1',2'}$ of α- and β-linked mannopyranosides.

The poor α/β ratio of the above-mentioned glycosylation might be caused by an unfavourable substituent pattern at the donor *(vide infra)* and by the high reactivity of both the donor and acceptor. A similar low stereoselectivity was described by Ogawa et al.[30] for the coupling reaction between a corresponding glycosyl chloride (with the same substitution pattern as **18**) and a reactive primary alcohol function. Since it has been reported[33] that α/β ratios of glycosylations can be increased by using less reactive donors and/or acceptors, we decided to prepare the less reactive glycosyl donors **22a** and **22b**, which contain (two and, respectively, three) acetyl groups instead of benzyl groups.

In a first attempt to synthesize the 2-fluoro-2-deoxy-mannopyranosides derivatives **22a** and **22b**, compound **19a** (see Scheme 3) was treated with (diethylamino)sulphur trifluoride (DAST) in dichloromethane at 40 °C. Under these conditions a complex mixture of products was obtained, although Dessinges et al.[34] reported that a mannopyranoside could be converted into a 2-fluoro-2-deoxy-*gluco*pyranoside under the same conditions in a high yield. Alternatively, the well-known 2-*O*-trifluoromethanesulfonate derivative[35] was prepared by treatment of **19a** with trifluoromethanesulfonic anhydride and 2,6-lutidine. Inversion of the triflate with tetrabutylammonium fluoride in THF at 50 °C afforded compound **20**[35] in an overall yield of 35%. In this respect it should be mentioned that, according to Haradahira et al.,[35] fluorination of the corresponding β-*O*-methyl derivative of **19b** gives a higher yield of the 2-deoxy-2-fluoro-mannopyranoside. However, due to the easier accessibility of the α-*O*-methyl analogue we used **19a** as starting material.

The next stage in the synthesis of **22a** and **22b** involved the acetolysis of **20** with 1% sulphuric acid in acetic anhydride[36] to give a mixture of compound **21a** and compound **21b**. The ratio of **21a** to **21b** was found to be dependent on the temperature and the reaction time. Thus, mainly the tri-*O*-acetyl-3-*O*-benzyl derivative **21a** (57% yield) was formed when the acetolysis was performed in 1% sulphuric acid in acetic



Scheme 3

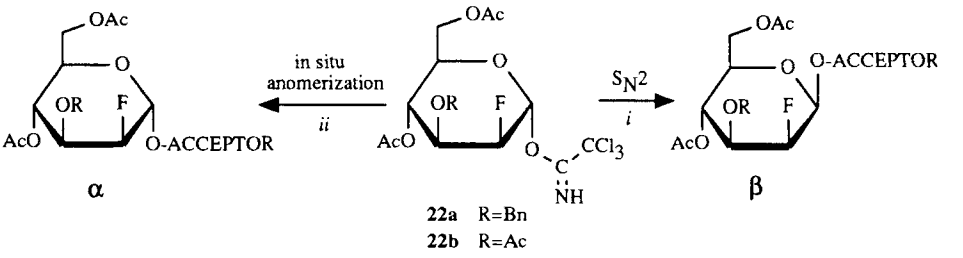


Fig. 3. In the presence of TMSOTf as promotor, pathway *i* (leading to the β-glycoside) is favoured when R=Bn, while pathway *ii* (leading to the α-glycoside) is favoured when R=Ac.

anhydride at 45 °C for 35 minutes. On the other hand, when the reaction was conducted at 50 °C for 5 hours, the tetra-*O*-acetyl derivative **21b** was obtained in 63% yield. Anomeric saponification of **21a** and **21b** with hydrazine acetate in DMF[37] and subsequent treatment with cesium carbonate and trichloroacetonitrile gave exclusively the α-imidates **22a** and **22b**.

First, glycosyl imidate **22a**, containing a 3-*O*-benzyl group, was coupled with acceptor **13b** at -5 °C using TMSOTf as promoter to give the disaccharide **24** in a yield of 68%, but in a very poor α/β ratio of 1/3 (Table). Unfortunately, this α/β ratio is even lower than the α/β ratio found in the glycosylation of **13b** with **18** (1/1.5), despite the introduction of deactivating acetyloxy groups at position 4 and 6 of the glycosyl donor.

As we found previously[38-41] in numerous glycosylations of reactive acceptors with α-glycosyl bromides in the presence of insoluble silver salts, the direct inversion at the anomeric centre (to give β-glycosides) improves when electron-withdrawing substituents at C-2 and C-4 and electron-donating substituents at C-3 and C-6 are present.

Taking into account these results, the predominant formation of the undesired β-coupled product (**24**-β) can be explained by a combination of similar factors (*i.e.*, coupling of the reactive acceptor **13b** with donor **22a**, containing electron-withdrawing groups at C-2 and C-4 and an electron-donating group at C-3) that stimulates a direct inversion (S_N2 like reaction, pathway *i* in Fig. 3) at the anomeric centre.

In order to increase the α/β ratio of the above-mentioned glycosylation, we reasoned that we had to suppress direct inversion (pathway *i*) and to stimulate the in situ anomerization (pathway *ii*). Therefore, we selected the low reactive donor **22b**, which contains an electron-withdrawing acetoxy group at C-3. Condensation of glycosyl imidate **22b** with acceptor **13b** in the presence of TMSOTf indeed provided

exclusively the α-coupled product in 55% yield (Table). The above-mentioned results suggest that the substituent effect that was described for glycosylations with glycosyl bromides in the presence of an insoluble silver salt also may apply to other types of coupling reactions.

Since the glycosylation of **22b** with the reactive acceptor **13b** proceeds stereoselectively, we decided to glycosylate the 6- and 3-hydroxyl groups simultaneously. To this end glycosyl acceptor **26**[42] was prepared and condensed with a small excess of **22b** to give 66% of fully α-coupled trisaccharide **27a**.

Conversion of **27a** into the deprotected derivative **28** was accomplished in two steps. Saponification of the acetyl groups with potassium *tert*-butoxide in methanol, followed by hydrogenolysis in the presence of 10% Pd/C afforded **28** in quantitative yield. The structure and identity of **28** was confirmed by ^{1}H and ^{19}F NMR spectroscopy and FAB mass analysis.

In conclusion, the results presented in this paper show that the modified di- and trisaccharide fragments **9a**, **9b**, **15**, **17** and **28** of Manα(1→6)Manα-OCH_3 and Manα(1→6)[Manα(1→3)]Manα-OCH_3 could be prepared conveniently. However, in the synthesis of the 2-amino-2-deoxy derivatives **15** and **17**, low α/β ratios were obtained in the glycosylation of acceptors **13a** and **13b** with donor **12b**. Furthermore in the synthesis of the fluorinated trisaccharide **28**, it was found that the presence of an acetoxy group at C-3 of the glycosyl donor strongly increased the α/β ratio of the glycosidic bond formation.

EXPERIMENTAL

General procedures. Pyridine was dried by heating with CaH_2 under reflux and then distilled; *N,N*-dimethylformamide (DMF) was stirred with CaH_2 at room temperature and distilled under reduced pressure. Methanol was heated with magnesium and then distilled. Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Dichloromethane, ether and toluene were distilled from P_2O_5. Pyridine was stored over molecular sieves 4Å, toluene and ether over sodium wire and dichloromethane over basic alumina. Reactions were performed under strict anhydrous conditions unless noted otherwise. Optical rotations were recorded at ambient temperature with a Perkin Elmer 241 polarimeter. TLC analysis was performed on Merck-Fertigplatten (Kieselgel 60 F254, 5x10 cm) or on HPTLC Merck-Fertigplatten (Kieselgel 60 F254, 5x5 cm). Compounds were visualized by spraying with sulphuric acid/ethanol (1/4,

v/v) or by Usui (110 g of molybdate phosphoric acid dissolved in 2200 mL of ethanol and 110 mL of sulphuric acid). Column chromatography was performed on Kieselgel 60, 230-400 Mesh (Merck). ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker WM 360 spectrometer equipped with an ASPECT 3000 computer or a Bruker WM 200 spectrometer; chemical shifts are given in ppm (δ) relative to TMS as internal reference, or relative to D_2O. Fast Atom Bombardment (FAB) mass spectra were recorded on a Finnigan MAT 90 mass spectrometer equipped with a WATV Cs ion gun. Glycerol was used as the matrix.

Methyl 2,3,4-Tri-*O*-benzyl-7-deoxy-L-*glycero*-α-D-*manno*-heptopyranoside (5a) and Methyl 2,3,4-Tri-*O*-benzyl-7-deoxy-D-*glycero*-α-D-*manno*-heptopyranoside (5b). A solution of **4** (800 mg, 1.73 mmol) in ether (4.0 mL) was added dropwise to a solution of methylmagnesium bromide in ether (3 M, 1.15 mL). After stirring for 2.5 h at room temperature the reaction mixture was diluted with a mixture of ether and aqueous NH_4Cl. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. Purification of the crude product on silica gel (hexane/ethyl acetate 85/15 → 75/25) gave **5a** (370 mg, 45%) and **5b** (39 mg, 5%): R_f(**5a**) 0.54 (hexane/ethyl acetate 6/4); R_f(**5b**) 0.36 (hexane/ethyl acetate 6/4); ^{1}H NMR (360 MHz)($CDCl_3$) of **5a** δ 1.28 (d, 3H, (C-7)$\underline{H}_3$, $J_{6,CH3}$ 6.5 Hz), 3.29 (s, 3H, O$C\underline{H}_3$), 3.38 (dd, 1H, H-5, $J_{4,5}$ 9.5 Hz, $J_{5,6}$ 2.0 Hz), 3.79 (dd, 1H, H-2, $J_{1,2}$ 1.9 Hz, $J_{2,3}$ 3.0 Hz), 3.88 (dd, 1H, H-3, $J_{3,4}$ 9.5 Hz), 4.09 (t, 1H, H-4, $J_{3,4}$=$J_{4,5}$ 9.5 Hz), 4.09 (c, 1H, H-6), 4.74 (d, 1H, H-1, $J_{1,2}$ 1.9 Hz), 4.62-4.99 (m, 6H, 3x$C\underline{H}_2$Ph), 7.22-7.39 (m, 15H, H-arom); ^{1}H NMR (360 MHz)($CDCl_3$) of **5b** δ 1.24 (d, 3H, (C-7)$\underline{H}_3$, $J_{6,CH3}$ 6.5 Hz), 3.33 (s, 3H, O$C\underline{H}_3$), 3.53 (dd, 1H, H-5, $J_{5,6}$ 4.0 Hz), 3.80 (t, 1H, H-2, $J_{1,2}$=$J_{2,3}$ 2.0 Hz), 3.92-3.95 (m, 2H, H-3, H-4), 4.05 (m, 1H, H-6), 4.72 (d, 1H, H-1, $J_{1,2}$ 2.0 Hz), 4.57-4.79 (m, 6H, 3x$C\underline{H}_2$Ph), 7.21-7.41 (m, 15H, H-arom).

6-*O*-Acetyl-3,4-di-*O*-benzyl-2-*O*-benzoyl-α-D-mannopyranosyl Chloride (6). Glycosyl chloride **6** was prepared from 1,6-anhydro-3,4-di-*O*-benzyl-β-D-mannopyranoside[43] by successively benzoylation of the 2-hydroxyl group, acetolysis, anomeric saponification and chlorination of the anomeric centre. Thus, to a solution of 1,6-anhydro-3,4-di-*O*-benzyl-β-D-mannopyranoside (3.35 g, 0.79 mmol) in pyridine (35 mL) was added benzoyl chloride (1.25 mL). After stirring for 16 h at room temperature, a solution of 4-dimethylaminopyridine (5 mg) in aqueous $NaHCO_3$ was added. The mixture was stirred for another 30 min and then extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$) and concentrated to give crude 1,6-anhydro-3,4-di-*O*-benzyl-2-*O*-benzoyl-1,6-anhydro-β-D-mannopyranoside. The crude compound was dissolved in a mixture of acetic

anhydride (60 mL) and acetic acid (0.5 mL). Trifluoroacetic acid (4.0 mL) was added at 0 °C and the mixture was stirred for 2 h at room temperature. Next, toluene was added and the mixture was concentrated. Purification on silica gel (toluene/ethyl acetate 95/5 → 9/1) afforded 1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-benzoyl-α/β-D-mannopyranoside (4.32 g, 81%). Anomeric saponification of this compound was accomplished using hydrazine acetate in DMF as described for the synthesis of **22a** (yield 91%). The obtained 6-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-benzoyl-α/β-D-mannopyranoside (3.65 g, 7.21 mmol) was dissolved in a mixture of dichloromethane (54 mL) and DMF (8.0 mL). Next, a solution of oxalyl chloride in dichloromethane (1 M, 27 mL) was added and the reaction mixture was stirred for 45 min at room temperature. Cold aqueous $NaHCO_3$ was added and the organic layer was washed with cold brine, dried and concentrated to give compound **6** (3.55 g, 94%): R_f 0.68 (toluene/ethyl acetate 8/2); ^1H NMR (200 MHz)($CDCl_3$) δ 2.05 (s, 3H, $C\underline{H}_3CO$), 3.95 (t, 1H, H-4, $J_{3,4}=J_{4,5}$ 9.5 Hz), 4.10-4.45 (m, 4H, H-3, H-5, H-6a, H-6b), 4.56-4.95 (m, 4H, $2xC\underline{H}_2Ph$), 5.70 (dd, 1H, H-2, $J_{1,2}$ 2.2 Hz, $J_{2,3}$ 3.5 Hz), 6.12 (d, 1H, H-1, $J_{1,2}$ 2.2 Hz), 7.14-7.69 (m, 15H, H-arom).

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(6-*O*-acetyl-2-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl)-7-deoxy-L-*glycero*-α-D-*manno*-heptopyranoside (7a). A mixture of compound **5a** (40 mg, 0.083 mmol), silver trifluoromethanesulfonate (64 mg, 0.25 mmol), 2,6-di-*tert*-butylpyridine (14 μL, 0.062 mmol) and powdered molecular sieves 4Å in dichloromethane (1.4 mL) was stirred at 0 °C. A solution of glycosyl chloride **6** (50 mg, 0.096 mmol) in dichloromethane (0.5 mL) was added dropwise. After stirring for 1 h at 0 °C the mixture was diluted with aqueous $NaHCO_3$, filtered and the organic layer was washed with aqueous NaCl, dried and concentrated. The residue was purified on silica gel (toluene/ethyl acetate 95/5 → 8/2) to give **7a** (72 mg, 90%): R_f 0.69 (dichloromethane/acetone 95/5); ^1H NMR (360 MHz)($CDCl_3$) δ 1.39 (d, 3H, (C-7)$\underline{H}_3$, $J_{6,CH3}$ 6.4 Hz), 1.95 (s, 3H, $C\underline{H}_3CO$), 3.31 (s, 3H, $OC\underline{H}_3$), 3.48 (dd, 1H, H-5, $J_{4,5}$ 9.2 Hz, $J_{5,6}$ 2.0 Hz), 3.81 (dd, 1H, H-2, $J_{1,2}$ 2.1 Hz, $J_{2,3}$ 3.2 Hz), 3.84 (t, 1H, H-4', $J_{3',4'}=J_{4',5'}$ 9.1 Hz), 3.89 (dd, 1H, H-3, $J_{3,4}$ 9.2 Hz), 3.93 (m, 1H, H-5'), 4.09 (t, 1H, H-4, $J_{3,4}=J_{4,5}$ 9.2 Hz), 4.10 (m, 2H, H-6a', H-6b'), 4.15 (dd, 1H, H-3', $J_{2',3'}$ 3.2 Hz), 4.25 (dq, 1H, H-6), 4.41-4.99 (m, 10H, $5xC\underline{H}_2Ph$), 4.84 (d, 1H, H-1, $J_{1,2}$ 2.1 Hz), 5.21 (d, 1H, H-1', $J_{1',2'}$ 2.0 Hz), 5.71 (dd, 1H, H-2'), 7.06-8.13 (m, 30H, H-arom).

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(6-*O*-acetyl-2-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl)-7-deoxy-D-*glycero*-α-D-*manno*-heptopyranoside (7b). Compound **7b** was prepared by reacting together compound **5b** and glycosyl chloride **6** in the same way as described for the synthesis of **7a**: yield of **7b** 77%; R_f 0.73

(dichloromethane/acetone 95/5); ^{1}H NMR (360 MHz)($CDCl_3$) δ 1.21 (d, 3H, (C-7)$\underline{H}_3$, $J_{6,CH3}$ 6.5 Hz), 2.03 (s, 3H, $C\underline{H}_3CO$), 3.32 (s, 3H, $OC\underline{H}_3$), 3.74 (dd, 1H, H-5, $J_{4,5}$ 9.8 Hz, $J_{5,6}$ 1.8 Hz), 3.76 (dd, 1H, H-2, $J_{1,2}$ 2.0 Hz, $J_{2,3}$ 3.2 Hz), 3.79 (t, 1H, H-4, $J_{3,4}$=$J_{4,5}$ 9.8 Hz), 3.90 (dd, 1H, H-3), 3.91 (dd, 1H, H-4', $J_{3',4'}$ 9.2 Hz, $J_{4',5'}$ 9.8 Hz), 4.01 (m, 1H, H-5'), 4.14 (dq, 1H, H-6), 4.17 (dd, 1H, H-3', $J_{2',3'}$ 3.2 Hz), 4.35-4.38 (m, 2H, H-6a', H-6b'), 4.51-4.93 (m, 10H, 5x$C\underline{H}_2$Ph), 4.76 (d, 1H, H-1, $J_{1,2}$ 2.0 Hz), 5.14 (d, 1H, H-1', $J_{1',2'}$ 2.0 Hz), 5.62 (dd, 1H, H-2'), 7.18-8.12 (m, 30H, H-arom).

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-7-deoxy-L-*glycero*-α-D-*manno*-heptopyranoside (8a). Compound **7a** (62 mg, 0.064 mmol) was dissolved in a mixture of dioxane and methanol (2.0 mL, 1/1) and potassium *tert*-butoxide (4 mg) was added. After stirring for 2.5 h at room temperature, the reaction mixture was neutralized with Dowex 50 (H^+) resin and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel (dichloromethane/methanol 99/1 → 9/1) to give **8a** (51 mg, 97%): R_f 0.41 (dichloromethane/methanol 95/5).

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-7-deoxy-D-*glycero*-α-D-*manno*-heptopyranoside (8b). Compound **7b** (35 mg, 0.036 mmol) was treated as described for the synthesis of compound **8a**, to give **8b** (34 mg, 98%): R_f 0.50 (dichloromethane/methanol 96/4).

Methyl 6-*O*-(α-D-Mannopyranosyl)-7-deoxy-L-*glycero*-α-D-*manno*-heptopyranoside (9a). A solution of compound **8a** (51 mg, 0.062 mmol) in a mixture of DMF (12 mL) and water (0.1 mL) was hydrogenolyzed in the presence of 10% Pd/C (48 mg) for 16 h. The reaction mixture was filtered, and the filtrate was concentrated to give **9a** (23 mg, 100%): R_f 0.57 (dichloromethane/methanol/water 5/4/1); $[\alpha]_D$ +68.2° (*c* 1.0, H_2O); FAB(+) 371.1 $(M+H)^+$; FAB(-) 369.1 $(M-H)^-$; ^{1}H NMR (360 MHz)(D_2O) δ 1.33 (d, 3H, (C-7)$\underline{H}_3$, $J_{6,CH3}$ 6.3 Hz), 3.41 (s, 3H, $OC\underline{H}_3$), 3.52 (dd, 1H, H-5, $J_{4,5}$ 9.6 Hz, $J_{5,6}$ 1.2 Hz), 3.68 (t, 1H, H-4', $J_{3',4'}$=$J_{4',5'}$ 9.2 Hz), 3.72 (dd, 1H, H-3, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 9.6 Hz), 3.74-3.80 (m, 2H, H-5', H-6a'), 3.87 (t, 1H, H-4, $J_{3,4}$=$J_{4,5}$ 9.6 Hz), 3.89 (dd, 1H, H-3', $J_{2',3'}$ 3.5 Hz, $J_{3',4'}$ 9.2 Hz), 3.93 (dd, 1H, H-2, $J_{1,2}$ 1.5 Hz, $J_{2,3}$ 3.5 Hz), 3.94 (m, 1H, H-6b'), 3.95 (dd, 1H, H-2', $J_{1',2'}$ 2.0 Hz, $J_{2',3'}$ 3.5 Hz), 4.29 (dq, 1H, H-6), 4.77 (d, 1H, H-1, $J_{1,2}$ 1.5 Hz), 5.02 (d, 1H, H-1', $J_{1',2'}$ 2.0 Hz); ^{13}C NMR (D_2O) δ 16.79 ($\underline{C}$-7(H_3)), 57.57 ($O\underline{C}H_3$), 63.73, 69.29, 69.53, 70.54, 72.79, 73.38, 73.42, 74.15, 76.08, 76.84 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-6'), 99.34 (C-1, $J_{C-1,H-1}$ 170.4 Hz), 103.99 (C-1', $J_{C-1',H-1'}$ 170.0 Hz).

Methyl 6-*O*-(α-D-Mannopyranosyl)-7-deoxy-D-*glycero*-α-D-*manno*-heptopyranoside (9b). Compound **8b** (24 mg, 0.029 mmol) was debenzylated as described

for the synthesis of **9a**, to afford **9b** (10.8 mg, 100%): R_f 0.61 (dichloromethane/methanol/water 5/4/1); $[\alpha]_D$ +98.6° (*c* 0.77, H_2O); FAB(+) 371.1 $(M+H)^+$; FAB(-) 369.1 $(M-H)^-$; ^1H NMR (360 MHz)(D_2O) δ 1.27 (d, 3H, (C-7)$\underline{H}_3$, $J_{6,CH3}$ 6.5 Hz), 3.36 (s, 3H, $OC\underline{H}_3$), 3.58 (t, 1H, H-4, $J_{3,4}$=$J_{4,5}$ 9.7 Hz), 3.62 (t, 1H, H-4', $J_{3',4'}$=$J_{4',5'}$ 9.2 Hz), 3.67-3.75 (m, 2H, H-5', H-6a'), 3.73 (dd, 1H, H-3, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 9.7 Hz), 3.78 (dd, 1H, H-5, $J_{4,5}$ 9.7 Hz, $J_{5,6}$ 3.0 Hz), 3.81 (dd, 1H, H-3', $J_{2',3'}$ 3.1 Hz, $J_{3',4'}$ 9.2 Hz), 3.87 (dd, 1H, H-2', $J_{1',2'}$ 1.7 Hz, $J_{2',3'}$ 3.1 Hz), 3.88 (c, 1H, H-6b'), 3.91 (dd, 1H, H-2, $J_{1,2}$ 1.5 Hz, $J_{2,3}$ 3.5 Hz), 4.22 (dq, 1H, H-6), 4.75 (d, 1H, H-1, $J_{1,2}$ 1.5 Hz), 5.00 (d, 1H, H-1', $J_{1',2'}$ 1.7 Hz); ^{13}C NMR (D_2O) δ 16.01 ($\underline{C}$-7(H_3)), 57.07 ($O\underline{C}H_3$), 63.45, 69.32, 69.68, 72.27, 72.87, 72.94, 73.25, 73.75, 73.76, 75.63 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-6'), 100.71 (C-1, $J_{C-1,H-1}$ 172.4 Hz), 103.45 (C-1', $J_{C-1',H-1'}$ 168.3 Hz).

6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl Trichloroacetimidate (11b) and 6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl Trichloroacetimidate (12b). To a stirred mixture of compound **10** (104 g, 0.22 mol) in tetrahydrofuran (1000 mL) was added dropwise piperidine (100 mL) at 0 °C. After stirring for 16 h at room temperature the mixture was neutralized with 2 M HCl and extracted with dichloromethane. The organic layer was washed with water, aqueous $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated to give a mixture of **11a** and **12a**. The crude mixture was dissolved in dichloromethane (1080 mL), and potassium carbonate (35.4 g) and trichloroacetonitrile (105 mL) were subsequently added at 0 °C. After stirring for 4 h, the mixture was filtered, and the filtrate was concentrated to dryness. Purification of the residue on silica gel (hexane/ethyl acetate 9/1 → 8/2) gave compound **11b** and **12b** (yield of **11b** and **12b** 80%): R_f (**12b**) 0.62 (dichloromethane/acetone 97/3); ^1H NMR (200 MHz)($CDCl_3$) of **12b** δ 2.04 (s, 3H, $C\underline{H}_3CO$), 3.90-3.95 (m, 3H, H-2, H-4, H-5), 4.11 (dd, 1H, H-3, $J_{2,3}$ 3.8 Hz, $J_{3,4}$ 9.5 Hz), 4.26-4.32 (m, 2H, H-6a, H-6b), 4.58-4.97 (m, 4H, 2x$OC\underline{H}_2Ph$), 6.18 (d, 1H, H-1, $J_{1,2}$ 2.0 Hz), 7.26-7.44 (m, 10H, H-arom), 8.63 (s, 1H, $OCN\underline{H}CCl_3$).

6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-mannopyranosyl Trichloroacetimidate (12c). To a stirred mixture of **12b** (50 mg, 0.087 mmol) in a mixture of dichloromethane (2.0 mL) and water (10 μL) was added boron trifluoride etherate (5 μL). After stirring for 30 min at room temperature the mixture was poured into aqueous $NaHCO_3$. The organic layer was washed with water, dried and concentrated to give **12a** (R_f 0.22 (dichloromethane/acetone 97/3)). The crude compound was dissolved in dichloromethane (0.40 mL) and trichloroacetonitrile (0.11 mL). Potassium carbonate (34 mg) was added at 0 °C and the mixture was stirred for 20 min at room

temperature. Purification of the reaction mixture on silica gel (dichloromethane/acetone 98/2) gave β-imidate **12c** (25 mg, 50%), together with α-imidate **12b** (10 mg, 20%) and compound **12a** (6 mg, 16%): R_f(**12c**) 0.57 (dichloromethane/acetone 97/3); ^{1}H NMR (200 MHz)($CDCl_3$) of **12c** δ 5.84 (d, 1H, H-1, $J_{1,2}$ 1.8 Hz), 8.69 (s, 1H, OCNHCCl$_3$).

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl)-α-D-mannopyranoside (14a). To a solution of **12b** (90 mg, 0.16 mmol) and **13a** (85 mg, 0.18 mmol) in ether (3.5 mL) containing spherical pearls molecular sieves 4Å was added trimethylsilyl trifluoromethanesulfonate (4.7 μL) in dichloromethane (120 μL) at -40 °C. After stirring for 30 min at -40 °C, the mixture was filtered, and the filtrate was washed with aqueous $NaHCO_3$ and water, dried and concentrated. The residue was purified on silica gel (toluene/ethyl acetate 95/5) to give **14a**-α (66 mg, 48%) together with the β-coupled disaccharide **14a**-β (60 mg, 44%): R_f(**14a**-α) 0.64 (dichloromethane/acetone 97/3); R_f(**14a**-β) 0.58 (dichloromethane/acetone 97/3); ^{1}H NMR (200 MHz)($CDCl_3$) of **14a**-α δ 2.00 (s, 3H, CH$_3$CO), 3.27 (s, 3H, OCH$_3$), 4.72 (d, 1H, H-1, $J_{1,2}$ 1.5 Hz), 5.01 (d, 1H, H-1', $J_{1',2'}$ 1.7 Hz); ^{1}H NMR (200 MHz)($CDCl_3$) of **14a**-β δ 1.99 (s, 3H, CH$_3$CO), 3.27 (s, 3H, OCH$_3$), 4.46 (d, 1H, H-1', $J_{1',2'}$ 1.2 Hz), 4.70 (d, 1H, H-1, $J_{1,2}$ 1.9 Hz).

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl)-α-D-mannopyranoside (14b). To a solution of compound **14a** (66 mg, 0.075 mmol) in a mixture of dioxane and methanol (3.0 mL, 2/1) was added a catalytic amount of potassium *tert*-butoxide. After stirring 30 min at room temperature, Dowex 50 (H^+) was added to the reaction mixture. The mixture was filtered, and the filtrate was concentrated. Purification of the residue on silica gel (dichloromethane/ethyl acetate 97/3 → 95/5) afforded **14b** (56 mg, 89%): R_f 0.26 (dichloromethane/acetone 97/3).

Methyl 3-*O*-Allyl-2,4-di-*O*-benzyl-6-*O*-(6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl)-α-D-mannopyranoside (14c). Compound **14c** was obtained in the same way as described for the synthesis of **14a**, starting from glycosyl donor **12b** and glycosyl acceptor **13b**: yield of **14c**-α 38%; yield of **14c**-β 54%; R_f(**14c**-α) 0.52 (dichloromethane/acetone 97/3); R_f(**14c**-β) 0.47 (dichloromethane/acetone 97/3); ^{1}H NMR (360 MHz)($CDCl_3$) of **14c**-α δ 2.00 (s, 3H, CH$_3$CO), 3.28 (s, 3H, OCH$_3$), 3.61 (m, 1H, H-5), 3.67 (dd, 1H, H-6a, $J_{5,6a}$ 2.0 Hz, $J_{6a,6b}$ 11.6 Hz), 3.74-3.81 (m, 4H, H-2, H-3, H-4', H-5'), 3.86 (c, 1H, H-4), 3.87 (dd, 1H, H-6b, $J_{5,6b}$ 4.1 Hz), 4.00 (dd, 1H, H-3', $J_{2',3'}$ 3.9 Hz, $J_{3',4'}$ 9.4 Hz), 4.05 (dd, 1H, H-2', $J_{1',2'}$ 1.7 Hz), 4.09 (m, 2H, CH$_2$-CH=CH$_2$), 4.12-4.25 (m, 2H, H-6a', H-6b'), 4.43-4.94 (m, 8H,

4xC<u>H</u>$_2$Ph), 4.71 (d, 1H, H-1, $J_{1,2}$ 1.5 Hz), 5.00 (d, 1H, H-1', $J_{1',2'}$ 1.7 Hz), 5.25 (m, 2H, CH_2-CH=C<u>H</u>$_2$), 5.95 (m, 1H, CH_2-C<u>H</u>=CH_2), 7.21-7.46 (m, 20H, H-arom); ^{1}H NMR (360 MHz)($CDCl_3$) of **14c-β** δ 4.47 (d, 1H, H-1', $J_{1',2'}$ 1.2 Hz), 4.68 (d, 1H, H-1, $J_{1,2}$ 1.9 Hz); ^{13}C NMR ($CDCl_3$) of **14c-β** δ 98.93 (d, C-1, $J_{C\text{-}1,H\text{-}1}$ 168 Hz), 100.19 (d, C-1', $J_{C\text{-}1',H\text{-}1'}$ 160 Hz).

Methyl 2,4-Di-*O*-benzyl-6-*O*-(6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl)-α-D-mannopyranoside (14d). To a solution of **14c** (60 mg, 0.073 mmol) in THF (25 mL) was added a catalytic amount of 1,5-cyclooctadiene-*bis*[methyldiphenylphosphine]iridium hexafluorophosphate. The stirred mixture was degassed, placed under hydrogen for 2 min, degassed and placed under nitrogen. After stirring for 2 h at room temperature, the mixture was diluted with water (2.5 mL) and *N*-iodosuccinimide (14 mg) was added. After stirring for 1 h at room temperature, the mixture was concentrated and the residue was purified on silica gel (toluene/ethyl acetate 9/1 → 1/1) to give **14d** (31 mg, 54%) and 27% of starting compound **14c**, R_f 0.23 (toluene/ethyl acetate 8/2).

Methyl 6-*O*-(2-Amino-2-deoxy-α-D-mannopyranosyl)-α-D-mannopyranoside (15). A mixture of compound **14b** (56 mg, 0.067 mmol) and palladium on activated charcoal (10%, 56 mg) in DMF (10 mL) and acetic acid (1.0 mL) was stirred under an atmosphere of hydrogen for 16 h. The mixture was filtered, and the filtrate was concentrated and redissolved in a mixture of *tert*-butyl alcohol, water and acetic acid (11 mL, 5/5/1). Palladium on carbon (10%, 25 mg) was added and the mixture was stirred under an atmosphere of hydrogen. After 16 h the mixture was filtered, and the filtrate was concentrated to give **15** (24 mg, 100%): R_f 0.08 (dichloromethane/methanol/water 13/6/1); $[\alpha]_D$ +60.2° (*c* 1.0, H_2O); FAB(+) 356.1 $(M+H)^+$; FAB(-) 354.2 $(M-H)^-$; ^{1}H NMR (360 MHz)(D_2O) δ 3.40 (s, 3H, OC<u>H</u>$_3$), 3.61 (c, 1H, H-2'), 3.66 (c, 1H, H-4'), 3.95 (c, 1H, H-2), 4.12 (dd, 1H, H-3', $J_{2',3'}$ 4.3 Hz, $J_{3',4'}$ 9.8 Hz), 4.76 (d, 1H, H-1, $J_{1,2}$ 1.7 Hz), 5.07 (bs, 1H, H-1'); ^{13}C NMR (D_2O) δ 56.41 (C-2'), 57.50 (O<u>C</u>H$_3$), 63.09, 68.55 (C-6, C-6'), 68.72, 69.06, 70.70, 72.58, 73.45, 73.45, 75.05 (C-2, C-3, C-4, C-5, C-3', C-4', C-5'), 99.82, 103.81 (C-1, C-1').

Methyl 2,4-Di-*O*-benzyl-3-*O*-(6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl)-6-*O*-(6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl)-α-D-mannopyranoside (16a). Compound **12b** and compound **14d** were coupled at -20 °C to give trisaccharide **16a**, using the procedure described for the preparation of **14a**: yield **16a-α** 35%; yield **16a-β** 15%; R_f(**16a-α**) 0.59 (dichloromethane/acetone 95/5); R_f(**16a-β**) 0.44 (dichloromethane/acetone 95/5); ^{1}H NMR (360 MHz)($CDCl_3$) of **16a-α** δ 2.00, 2.01 (2xs, 6H, 2xC<u>H</u>$_3$CO), 3.27 (s, 3H, OC<u>H</u>$_3$),

3.61 (dd, 1H, H-2', $J_{1',2'}$ 1.8 Hz, $J_{2',3'}$ 3.9 Hz), 3.62 (m, 1H, H-5), 3.68-3.74 (m, 3H, H-2, H-6a, H-4'), 3.78-3.86 (m, 4H, H-6b, H-5', H-4'', H-5''), 3.87 (t, 1H, H-4, $J_{3,4}$=$J_{4,5}$ 10.0 Hz), 4.00 (dd, 1H, H-3', $J_{2',3'}$ 3.9 Hz, $J_{3',4'}$ 9.4 Hz), 4.00-4.02 (m, 2H, H-2'', H-3''), 4.03 (dd, 1H, H-3, $J_{2,3}$ 3.4 Hz, $J_{3,4}$ 10.0 Hz), 4.14 (dd, 1H, H-6a', $J_{5',6a'}$ 5.7 Hz, $J_{6a',6b'}$ 11.4 Hz), 4.18-4.24 (m, 2H, H-6b', H-6a''), 4.27 (dd, 1H, H-6b'', $J_{5'',6b''}$ 1.2 Hz, $J_{6a'',6b''}$ 10.0 Hz), 4.53-4.91 (m, 12H, 6x$C\underline{H}_2$Ph), 4.71 (d, 1H, H-1, $J_{1,2}$ 1.5 Hz), 5.02 (c, 2H, H-1', H-1''), 7.18-7.45 (m, 30H, H-arom). The signals for the 2-amino-2-deoxy-mannopyranoside units might be interchanged.

Methyl 2,4-Di-*O*-benzyl-3-*O*-(2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl)-6-*O*-(2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl)-α-D-mannopyranoside (16b). Compound **16a** (13 mg, 0.011 mmol) was deacetylated as described above for the synthesis of **14b**, to give compound **16b** (12 mg, 100%): R_f 0.03 (dichloromethane/acetone 95/5).

Methyl 3-*O*-(2-Amino-2-deoxy-α-D-mannopyranosyl)-6-*O*-(2-amino-2-deoxy-α-D-mannopyranosyl)-α-D-mannopyranoside (17). Reduction of the azide groups and hydrogenolytic cleavage of the benzyl groups of **16b** (12 mg, 0.011 mmol) was performed as described for the synthesis of **15**, to give the fully deprotected trisaccharide **17** (7 mg, 100%): $[\alpha]_D$ +64.8° (*c* 0.5, H_2O); FAB(+) 517 $(M+H)^+$; FAB(-) 515 $(M-H)^-$; ^1H NMR (360 MHz)(D_2O) δ 3.38 (s, 3H, $OC\underline{H}_3$), 3.67 (dd, 1H, H-2', $J_{1',2'}$ 0.9 Hz, $J_{2',3'}$ 4.6 Hz), 3.72 (c, 1H, H-2''), 4.09 (dd, 1H, H-2, $J_{1,2}$ 1.7 Hz, $J_{2,3}$ 4.9 Hz), 4.12 (dd, 1H, H-3', $J_{3',4'}$ 10.0 Hz), 4.15 (dd, 1H, H-3'', $J_{2'',3''}$ 4.2 Hz, $J_{3'',4''}$ 10.0 Hz), 4.71 (d, 1H, H-1, $J_{1,2}$ 1.7 Hz), 5.08 (d, 1H, H-1', $J_{1',2'}$ 0.9 Hz), 5.29 (d, 1H, H-1'', $J_{1'',2''}$ 0.9 Hz); ^{13}C NMR (D_2O) δ 100.97 (C-1), 103.46 (C-1'), 103.48 (C-1''). The signals for the 2-amino-2-deoxy-mannopyranoside units might be interchanged.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-fluoro-α-D-mannopyranosyl Trichloroacetimidate (18). To a solution of 3,4,6-tri-*O*-benzyl-2-deoxy-2-fluoro-D-mannopyranose (43 mg, 0.095 mmol) in a mixture of dichloromethane (0.75 mL) and trichloroacetonitrile (0.14 mL) was added cesium carbonate (5 mg). After stirring for 45 min at room temperature, the mixture was filtered, and the filtrate was concentrated. Purification of the residue on silica gel (toluene → toluene/ethyl acetate 95/5) afforded compound **18** (45 mg, 79%): R_f 0.34 (toluene/ethyl acetate 95/5).

1,4,6-Tri-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-α-D-mannopyranoside (21a) and 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-α-D-mannopyranoside (21b). Compound **20** (105 mg, 0.281 mmol) was dissolved in a solution of sulphuric acid in acetic anhydride (1%, 2.0 mL). After stirring for 35 min at 45 °C, solid $NaHCO_3$ was added and the mixture was diluted with ethyl acetate and water. The organic layer was

washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. Purification on silica gel (hexane/ethyl acetate 8/2 → 6/4) afforded **21a** (64 mg, 57%) and **21b** (15 mg, 15%). If the reaction mixture was stirred for 5 h at 50 °C, 5% of **21a** and 63% of **21b** were isolated: R_f(**21a**) 0.28 (hexane/ethyl acetate 8/2); R_f(**21b**) 0.25 (hexane/ethyl acetate 8/2); ^1H NMR (200 MHz)($CDCl_3$) of **21a** δ 2.04, 2.08, 2.11 (3xs, 9H, 3xCH_3CO), 3.82 (ddd, 1H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 10.0 Hz, $J_{H\text{-}3,F}$ 28.3 Hz), 3.96 (m, 1H, H-5), 4.10 (dd, 1H, H-6a, $J_{5,6a}$ 2.3 Hz, $J_{6a,6b}$ 12.4 Hz), 4.24 (dd, 1H, H-6b, $J_{5,6b}$ 4.6 Hz), 4.67 (AB, 2H, CH_2Ph), 4.70 (dt, 1H, H-2, $J_{1,2}$=$J_{2,3}$ 2.3 Hz, $J_{H\text{-}2,F}$ 48.4 Hz), 5.40 (dt, 1H, H-4, $J_{3,4}$=$J_{4,5}$ 10.0 Hz, $J_{H\text{-}4,F}$ 0.9 Hz), 6.26 (dd, 1H, H-1, $J_{1,2}$ 2.3 Hz, $J_{H\text{-}1,F}$ 6.5 Hz), 7.26-7.44 (m, 5H, H-arom); ^1H NMR (200 MHz)($CDCl_3$) of **21b** δ 2.06, 2.10, 2.12, 2.17 (4xs, 12H, 4xCH_3CO), 4.06 (m, 1H, H-5), 4.12 (dd, 1H, H-6a, $J_{5,6a}$ 2.3 Hz, $J_{6a,6b}$ 12.5 Hz), 4.30 (dd, 1H, H-6b, $J_{5,6b}$ 4.5 Hz), 4.78 (dt, 1H, H-2, $J_{1,2}$=$J_{2,3}$ 2.4 Hz, $J_{H\text{-}2,F}$ 48.6 Hz), 5.30 (ddd, 1H, H-3, $J_{3,4}$ 10.0 Hz, $J_{H\text{-}3,F}$ 27.8 Hz), 5.43 (dt, 1H, H-4, $J_{3,4}$=$J_{4,5}$ 10.0 Hz, $J_{H\text{-}4,F}$ 1.5 Hz), 6.19 (dd, 1H, H-1, $J_{1,2}$ 2.4 Hz, $J_{H\text{-}1,F}$ 6.8 Hz).

4,6-Di-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-α-D-mannopyranosyl Trichloroacetimidate (22a). Compound **21a** (68 mg, 0.171 mmol) was dissolved in a solution of hydrazine acetate in DMF (0.1 M, 1.8 mL) and stirred for 1 h at room temperature. Next, the reaction mixture was diluted with dichloromethane and acetic acid and washed with water, aqueous $NaHCO_3$ and brine. The organic layer was dried and concentrated to give 4,6-di-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-α-D-mannopyranoside (61 mg, 100%, R_f 0.22 (hexane/ethyl acetate 6/4)). The crude compound was then converted to **22a** using the procedure described for **18**. Purification on silica gel (hexane/ethyl acetate 8/2 → 6/4) afforded **22a** (49%): R_f 0.59 (hexane/ethyl acetate 6/4); ^1H NMR (200 MHz)($CDCl_3$) δ 2.06, 2.07 (2xs, 6H, 2xCH_3CO), 3.88 (ddd, 1H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 10.0 Hz, $J_{H\text{-}3,F}$ 28.4 Hz), 3.99-4.28 (m, 3H, H-5, H-6a, H-6b), 4.69 (AB, 2H, CH_2Ph), 4.78 (dt, 1H, H-2, $J_{1,2}$=$J_{2,3}$ 2.4 Hz, $J_{H\text{-}2,F}$ 48.0 Hz), 5.45 (t, 1H, H-4, $J_{3,4}$=$J_{4,5}$ 10.0 Hz), 6.42 (dd, 1H, H-1, $J_{1,2}$ 2.4 Hz, $J_{H\text{-}1,F}$ 6.1 Hz), 7.28-7.39 (m, 5H, H-arom), 9.76 (s, 1H, OCNHCCl_3).

3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-mannopyranosyl Trichloroacetimidate (22b). Compound **21b** was converted to **22b** as described for the synthesis of **22a**. Purification on silica gel (toluene/ethyl acetate 9/1 → 1/1) afforded compound **22b** in 87% yield: R_f 0.39 (toluene/ethyl acetate 8/2); ^1H NMR (200 MHz)($CDCl_3$) δ 2.07, 2.09, 2.12 (3xs, 9H, 3xCH_3CO), 4.07-4.35 (m, 3H, H-5, H-6a, H-6b), 4.98 (dt, 1H, H-2, $J_{1,2}$=$J_{2,3}$ 2.2 Hz, $J_{H\text{-}2,F}$ 48.9 Hz), 5.35 (ddd, 1H, H-3, $J_{3,4}$ 10.0 Hz, $J_{H\text{-}3,F}$ 27.8 Hz), 5.48 (t, 1H, H-4, $J_{3,4}$=$J_{4,5}$ 10.0 Hz), 6.47 (dd, 1H, H-1, $J_{1,2}$ 2.2 Hz, $J_{H\text{-}1,F}$ 6.3 Hz), 9.82 (s, 1H, OCNHCCl_3).

Methyl 3-*O*-Allyl-2,4-di-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-fluoro-α/β-D-mannopyranosyl)-α-D-mannopyranoside (23). A mixture of glycosyl donor **18** (44 mg, 0.074 mmol), glycosyl acceptor **13b** (31 mg, 0.074 mmol) and spherical pearls molecular sieves 4Å in ether (1.0 mL) was stirred at -20 °C. A solution of trimethylsilyl trifluoromethanesulfonate (2 μL) in dichloromethane (18 μL) was added dropwise to the mixture. After stirring for 30 min at -20 °C, the mixture was diluted with aqueous $NaHCO_3$. The organic layer was washed with water, dried and concentrated. The residue was purified on silica gel (hexane/ethyl acetate 8/2) to give **23-α** (18 mg, 29%)(R_f 0.33 (hexane/ethyl acetate 8/2) and **23-β** (27 mg, 43%)(R_f 0.27 (hexane/ethyl acetate 8/2): ^1H NMR (200 MHz)($CDCl_3$) of **23-α** δ 4.87 (dt, 1H, H-2', $J_{1',2'}=J_{2',3}$ 1.8 Hz, $J_{H\text{-}2',F}$ 50.0 Hz), 5.18 (dd, 1H, H-1', $J_{1',2'}$ 1.8 Hz, $J_{H\text{-}1',F}$ 7.0 Hz); ^{19}F NMR ($CDCl_3$) of **23-α** δ -205.71 (ddd, F, $J_{H\text{-}1',F}$ 7.0 Hz, $J_{H\text{-}2',F}$ 50.0 Hz, $J_{H\text{-}3',F}$ 30.0 Hz); ^{19}F NMR ($CDCl_3$) of **23-β** δ -220.70 (ddd, F, $J_{H\text{-}1',F}$ 18.0 Hz, $J_{H\text{-}2',F}$ 48.0 Hz, $J_{H\text{-}3',F}$ 28.0 Hz).

Methyl 3-*O*-Allyl-2,4-di-*O*-benzyl-6-*O*-(4,6-di-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-α/β-D-mannopyranosyl)-α-D-mannopyranoside (24). Glycosyl donor **22a** and glycosyl acceptor **13b** were coupled at -5 °C using the procedure described for the synthesis of compound **23**, to give **24-α** (yield 17%, R_f 0.31 (hexane/ether 4/6)) and **24-β** (yield 51%, R_f 0.18 (hexane/ether 4/6)): ^1H NMR (200 MHz)($CDCl_3$) of **24-α** δ 4.85 (dt, 1H, H-2', $J_{1',2'}=J_{2',3}$ 2.0 Hz, $J_{H\text{-}2',F}$ 50 Hz), 5.22 (dd, 1H, H-1', $J_{1',2'}$ 2.0 Hz, $J_{H\text{-}1',F}$ 7.0 Hz), 5.29 (t, 1H, H-4', $J_{3',4'}=J_{4',5'}$ 9.8 Hz); ^{19}F NMR ($CDCl_3$) of **24-α** δ -206.03 (ddd, F, $J_{H\text{-}1',F}$ 7.0 Hz, $J_{H\text{-}2',F}$ 50.0 Hz, $J_{H\text{-}3',F}$ 28.2 Hz); ^{19}F NMR ($CDCl_3$) of **24-β** δ -220.80 (ddd, F, $J_{H\text{-}1',F}$ 19.0 Hz, $J_{H\text{-}2',F}$ 49.8 Hz, $J_{H\text{-}3',F}$ 28.0 Hz).

Methyl 3-*O*-Allyl-2,4-di-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-mannopyranosyl)-α-D-mannopyranoside (25). Glycosyl donor **22b** and glycosyl acceptor **13b** were coupled at -5 °C using the procedure described for the synthesis of compound **23**, to give compound **25** (yield 55%, R_f 0.30 (dichloromethane/ethyl acetate 95/5)): ^1H NMR (360 MHz)($CDCl_3$) δ 2.02, 2.04, 2.07 (3xs, 9H, 3x$C\underline{H}_3CO$), 3.20 (s, 3H, $OC\underline{H}_3$), 3.74-3.86 (m, 3H, H-3, H-4, H-6a), 3.75 (c, 1H, H-2), 3.68 (m, 1H, H-5), 3.88 (dd, 1H, H-6b), 4.03 (m, 1H, H-5'), 4.10 (m, 2H, $C\underline{H}_2$-CH=CH_2), 4.11 (c, 1H, H-6a'), 4.20 (dd, 1H, H-6b'), 4.58-5.02 (m, 4H, 2x$C\underline{H}_2Ph$), 4.67 (d, 1H, H-1, $J_{1,2}$ 1.7 Hz), 4.77 (dt, 1H, H-2', $J_{1',2'}=J_{2',3'}$ 2.5 Hz, $J_{H\text{-}2',F}$ 49.0 Hz), 5.21 (dd, 1H, H-1', $J_{1',2'}$ 2.5 Hz, $J_{H\text{-}1',F}$ 7.5 Hz), 5.23 (m, 2H, CH_2-CH=$C\underline{H}_2$), 5.26 (ddd, 1H, H-3', $J_{3',4'}$ 10.0 Hz, $J_{H\text{-}3',F}$ 30.5 Hz), 5.32 (c, 1H, H-4'), 5.92 (m, 1H, CH_2-$C\underline{H}$=CH_2), 7.22-7.42 (m, 10H, H-arom); ^{19}F NMR ($CDCl_3$) δ -205.5 (ddd, F, $J_{H\text{-}1',F}$ 7.5 Hz, $J_{H\text{-}2',F}$ 49.0 Hz, $J_{H\text{-}3',F}$ 30.5 Hz).

Methyl 2,4-Di-*O*-benzyl-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-mannopyranosyl)-6-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-mannopyranosyl)-α-D-mannopyranoside (27a). A solution of trimethylsilyl trifluoromethanesulfonate (4.3 μL) in dichloromethane (40 μL) was added at room temperature to a mixture of compound **22b** (76 mg, 0.168 mmol), compound **26** (25 mg, 0.067 mmol) and spherical pearls molecular sieves 4Å. After stirring for 1 h at room temperature the mixture was diluted with a mixture of dichloromethane and aqueous $NaHCO_3$. The organic layer was washed with water, dried and concentrated. Purification on silica gel (hexane/ethyl acetate 65/35 → 6/4) afforded **27a** (42 mg, 66%): R_f 0.19 (hexane/ethyl acetate 6/4); ^1H NMR (360 MHz)($CDCl_3$) δ 2.02-2.14 (6xs, 18H, 6x$C\underline{H}_3CO$), 3.33 (s, 3H, $OC\underline{H}_3$), 3.68 (m, 1H, H-5), 3.75 (dd, 1H, H-2, $J_{1,2}$ 3.2 Hz, $J_{2,3}$ 2.0 Hz), 3.81 (dd, 1H, H-6a, $J_{5,6a}$ 2.0 Hz, $J_{6a,6b}$ 12.0 Hz), 3.86 (c, 1H, H-6b), 3.87 (c, 1H, H-6a'), 3.89 (m, 1H, H-5'), 3.97 (c, 1H, H-4), 4.02 (m, 1H, H-5''), 4.11 (c, 1H, H-3), 4.11 (c, 1H, H-6b'), 4.14 (dd, 1H, H-6a''), 4.22 (dd, 1H, H-6b'', $J_{5'',6b''}$ 4.5 Hz, $J_{6a'',6b''}$ 12.3 Hz), 4.59-4.78 (m, 4H, 2x$C\underline{H}_2$Ph), 4.61 (dt, 1H, H-2'', $J_{1'',2''}$ 2.4 Hz, $J_{H\text{-}2'',F}$ 49.8 Hz), 4.74 (d, 1H, H-1, $J_{1,2}$ 3.2 Hz), 4.78 (dt, 1H, H-2', $J_{1',2'}$ 2.4 Hz, $J_{H\text{-}2',F}$ 49.8 Hz), 5.23 (dd, 1H, H-1', $J_{1',2'}$ 2.4 Hz), 5.26 (c, 1H, H-1''), 5.24 (c, 1H, H-4'), 5.29 (c, 1H, H-3'), 5.32 (c, 1H, H-3''), 5.34 (c, 1H, H-4''), 7.26-7.44 (m, 10H, H-arom); ^{19}F NMR ($CDCl_3$) δ -205.3 (ddd, F, $J_{H\text{-}1',F}$ 7.0 Hz, $J_{H\text{-}2',F}$ 49.8 Hz, $J_{H\text{-}3',F}$ 30.0 Hz), -204.5 (ddd, F, $J_{H\text{-}1'',F}$ 7.0 Hz, $J_{H\text{-}2'',F}$ 49.8 Hz, $J_{H\text{-}3'',F}$ 30.0 Hz). The signals for the 2-deoxy-2-fluoro-mannopyranoside units might be interchanged.

Methyl 2,4-Di-*O*-benzyl-3-*O*-(2-deoxy-2-fluoro-α-D-mannopyranosyl)-6-*O*-(2-deoxy-2-fluoro-α-D-mannopyranosyl)-α-D-mannopyranoside (27b). To a solution of **27a** (21 mg, 0.022 mmol) in a mixture of dioxane and methanol (2.0 mL, 1/1) was added potassium *tert*-butoxide (4 mg). After stirring for 1 h at room temperature, the mixture was neutralized with Dowex 50 (H^+) resin. The mixture was filtered and the filtrate was concentrated to give **27b** (15 mg, 100%): R_f 0.20 (dichloromethane/methanol 9/1).

Methyl 3-*O*-(2-Deoxy-2-fluoro-α-D-mannopyranosyl)-6-*O*-(2-deoxy-2-fluoro-α-D-mannopyranosyl)-α-D-mannopyranoside (28). Compound **27b** (15 mg, 0.022 mmol) was dissolved in a mixture of *tert*-butyl alcohol (5.0 mL) and water (2.0 mL) and was hydrogenolyzed in the presence of 10% Pd/C (15 mg) for 15 h. The reaction mixture was filtered and the filtrate was concentrated to give **28** (11.5 mg, 100%): R_f 0.45 (ethyl acetate/pyridine/acetic acid/water 20/7/1.6/4); $[\alpha]_D$ +84.5° (*c* 1.0, H_2O); FAB(+) 523.1 $(M+H)^+$; FAB(-) 521.1 $(M-H)^-$; ^1H NMR (360 MHz)(D_2O) δ 3.25 (s, 3H, $OC\underline{H}_3$), 3.52-3.94 (m, 12H, H-4, H-4', H-4'', H-5, H-5', H-5'', H-6a,

H-6a', H-6a'', H-6b, H-6b', H-6b''), 3.74 (c, 1H, H-3), 3.75 (c, 1H, H-3'), 3.80 (c, 1H, H-3''), 3.94 (t, 1H, H-2, $J_{1,2}$=$J_{2,3}$ 1.9 Hz), 4.57 (d, 1H, H-1, $J_{1,2}$ 1.9 Hz), 4.66 (dt, 1H, H-2', $J_{1',2'}$=$J_{2',3'}$ 2.0 Hz, $J_{H\text{-}2',F}$ 49.7 Hz), 4.71 (dt, 1H, H-2'', $J_{1'',2''}$=$J_{2'',3''}$ 2.0 Hz, $J_{H\text{-}2'',F}$ 49.7 Hz), 4.98 (dd, 1H, H-1', $J_{1',2'}$ 2.0 Hz, $J_{H\text{-}1',F}$ 7.4 Hz), 5.16 (dd, 1H, H-1'', $J_{1'',2''}$ 2.0 Hz, $J_{H\text{-}1'',F}$ 8.0 Hz); ^{19}F NMR (D_2O) δ -210.0 (ddd, F, $J_{H\text{-}1',F}$ 7.4 Hz, $J_{H\text{-}2',F}$ 49.7 Hz, $J_{H\text{-}3',F}$ 30.4 Hz), -208.6 (ddd, F, $J_{H\text{-}1'',F}$ 8.0 Hz, $J_{H\text{-}2'',F}$ 49.7 Hz, $J_{H\text{-}3'',F}$ 30.8 Hz). The signals for the 2-deoxy-2-fluoro-mannopyranoside units might be interchanged.

ACKNOWLEDGEMENTS

We wish to thank Y. M. Diepeveen and G. N. Wagenaars (Organon analytical R&D laboratories) for recording the NMR spectra.

REFERENCES

1. F. Dall'Olio, M. Chiricolo, N. Malagolini, C. Franceschi and F. Serafini-Cessi, *Cell. Immunol.*, **137**, 303 (1991).

2. A. P. Sherblom, J. M. Decker and A. V. Muchmore, *J. Biol. Chem.*, **263**, 5418 (1988).

3. N. Sharon and H. Lis, *Lectins*; Chapman and Hall, London, 1989.

4. I. J. Goldstein and C. E. Hayes, *Adv. Carbohydr. Chem. Biochem.*, **35**, 127 (1978).

5. H. Schachter, *Biochem. Cell. Biol.*, **64**, 163 (1986).

6. R. U. Lemieux, *Chem. Soc. Rev.*, **18**, 347 (1989).

7. F. A. Quiocho, *Pure Appl. Chem.*, **61**, 1293 (1989).

8. D. R. Bundle, *Pure Appl. Chem.*, **61**, 1171 (1989).

9. K. Bock, *NMR Spectroscopy in Drug Research*, Alfred Benzon Symposium **26**, 119 (1988).

10. C. F. Brewer and L. Bhattacharyya, *J. Biol. Chem.*, **261**, 7306 (1986)

11. J. P. Carver, A. E. Mackenzie and K. D. Hardman, *Biopolymers*, **24**, 49 (1985).

12. J.-R. Brisson and J. P. Carver, *Biochem.*, **22**, 1362 (1983).

13. R. U. Lemieux, T. C. Wong and H. Thøgerson, *Can. J. Chem.*, **60**, 81 (1982).

14. O. P. Srivastava, O. Hindsgaul, M. Shoreibah and M. Pierce, *Carbohydr. Res.*, **179**, 137 (1988).

15. P. J. Garegg and B. Samuelsson, *Carbohydr. Res.*, **67**, 267 (1978).

16. H. B. Borén, K. Eklind, P. J. Garegg, B. Lindberg and A. Pilotti, *Acta Chim. Scand.*, **26**, 4143 (1972).

17. D. J. Cram, K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959).

18. G. J. Boons, Ph.D. Dissertation, University of Leiden, 1991.

19. R. U. Lemieux, P. H. Boullanger, D. R. Bundle, D. A. Baker, A. Nagpurkar and A. Venot, *Nouv. J. Chim.*, **2**, 321 (1978).

20. T. Peters, J. R. Brisson and D. R. Bundle, *Can. J. Chem.*, **68**, 979 (1990).

21. R. U. Lemieux, R. Szweda, E. Paskiewicz-Hnatiw and U. Spohr, *Carbohydr. Res.*, **205**, C12 (1990).

22. H. Paulsen and W. Stenzel, *Chem. Ber.*, **111**, 2334 (1978).

23. R. U. Lemieux and R. M. Ratcliffe, *Can. J. Chem.*, **57**, 1244 (1979).

24. G. Grundler and R. R. Schmidt, *Liebigs Ann. Chem.*, 1826 (1984).

25. T. S. Hasan and O. Hindsgaul, *Can. J. Chem.*, **64**, 1771 (1986).

26. J. J. Oltvoort, C. A. A. van Boeckel, J. H. de Koning and J. H. van Boom, *Synthesis*, 308 (1981).

27. T. Nukada, H. Lucas, P. Konradsson and C. A. A. van Boeckel, *Synlett*, **5**, 365 (1991).

28. N. F. Taylor, *Fluorinated Carbohydrates*, *ACS Symp. Series*, 374 (1988).

29. C. P. J. Glaudemans, *Chem. Rev.*, **91**, 25 (1991).

30. T. Ogawa and Y. Takahashi, *J. Carbohydr. Chem.*, **2**, 461 (1983).

31. F. J. Urban, B. S. Moore and R. Breitenbach, *Tetrahedron Lett.*, **31**, 4421 (1990).

32. H. Günther, *NMR Spectroscopy*; Wiley, New York, 1987, p 351.

33. H. Paulsen, *Angew. Chem. Int. Ed. Engl.* **21**, 155 (1982).

34. A. Dessinges, A. Olesker, G. Lukacs and T. That Thang, *Carbohydr. Res.*, **126**, C6 (1984).

35. T. Haradahira, M. Maeda, H. Omae, Y. Yano and M. Kojima, *Chem. Pharm. Bull.*, **32**, 4758 (1984).

36. H. Paulsen and H. Bunsch, *Chem. Ber.*, **32**, 4758 (1984).

37. G. Excoffier, D. Gagnaire and J. P. Utille, *Carbohydr. Res.*, **39**, 368 (1975).

38. C. A. A. van Boeckel, T. Beetz and S. F. van Aelst, *Tetrahedron*, **40**, 4097 (1984).

39. C. A. A. van Boeckel and T. Beetz, *Recl. Trav. Chim. Pays-Bas*, **104**, 171 (1985).

40. C. A. A. van Boeckel and T. Beetz, *Recl. Trav. Chim. Pays-Bas*, **104**, 174 (1985).

41. N. M. Spijker, H. Zuurmond, P. Westerduin, C. A. A. van Boeckel, *Recl. Trav. Chim. Pays-Bas*, **108**, 360 (1989)

42. T. Ogawa and M. Matsui, *Carbohydr. Res.*, **62**, C1 (1978).

43. H. Hori, Y. Nishida, H. Ohrui and H. Meguro, *J. Org. Chem.*, **54**, 1346 (1989).