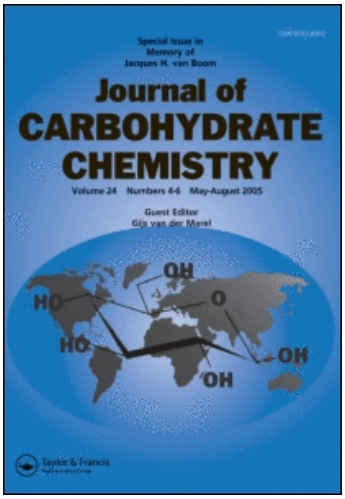



## Journal of Carbohydrate Chemistry

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

# Synthesis of A Novel Sialyl Lewis X Analogue Containing A Pyrrolidine in Place of *N*-Acetyl Glucosamine

Elsa Dechaux; Pascal Savy; Samule Bouyain; Claude Monneret; Jean-Claude Florent

**To cite this Article** Dechaux, Elsa , Savy, Pascal , Bouyain, Samule , Monneret, Claude and Florent, Jean-Claude(2000) 'Synthesis of A Novel Sialyl Lewis X Analogue Containing A Pyrrolidine in Place of *N*-Acetyl Glucosamine', Journal of Carbohydrate Chemistry, 19: 4, 485 — 501

**To link to this Article: DOI:** 10.1080/07328300008544095

**URL:** http://dx.doi.org/10.1080/07328300008544095

J. CARBOHYDRATE CHEMISTRY, 19(4&5), 485–501 (2000)

# SYNTHESIS OF A NOVEL SIALYL LEWIS X ANALOGUE CONTAINING A PYRROLIDINE IN PLACE OF *N*-ACETYL GLUCOSAMINE[1]

Elsa Dechaux, Pascal Savy, Samuel Bouyain, Claude Monneret and Jean-Claude Florent*

UMR 176, CNRS-Institut Curie, Section Recherche, 26, rue d'Ulm,
F-75248 Paris Cedex 05, France

*Received October 1, 1999 - Final Form March 14, 2000*



## ABSTRACT

The synthesis of the new sialyl Lewis X analogue, 4-*O*-(α-L-fucopyranosyl)-3-*O*-(3-*O*-sodium sulfonato-β-D-galactopyranosyl)-(2*S*,3*R*, 4*R*)-2-ethyl-3,4-dihydroxypyrrolidine **2** has been achieved. The *N*-acetyl glucosamine unit of natural Lewis X has been replaced by a rigid 3*R*/4*R*-dihydroxylated pyrrolidine **12**. This one has been synthezised from the methyl 4-*O*-benzoyl-2,3-di-*O*-benzyl-6-deoxy-6-iodo-α-D-altropyranoside sugar precursor **10** using the Ganem/Bernotas one-pot elimination-reductive amination ring contraction reaction. The (2*S*,3*R*,4*R*)-1-benzyloxycarbonyl-3,4-dihydroxy-2-ethylpyrrolidine **12** obtained was subsequently regioselectively glycosylated, using 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl fluoride and 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl bromide as glycosyl donors. Disaccharide containing pyrrolidine **21** was finally transformed into the target *O*-sulfated analog **2**, after regioselective sulfation and usual deprotection.

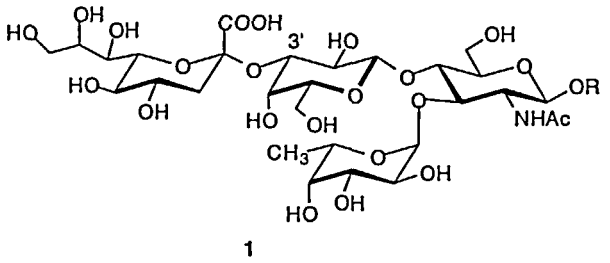
## INTRODUCTION

Carbohydrate-mediated cell adhesion is now widely recognized as being important in inflammation and infection and is also involved in tumour cell adhesion,[2] metastasis[3] and angiogenesis.[4] The selectins are a family of cell adhesion molecules which participate

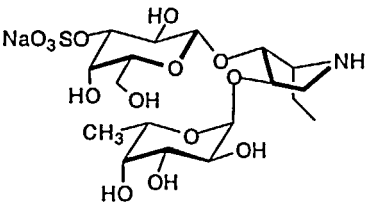
in the initial interaction of leucocyte homing, to the activated endothelium of blood vessels during inflammation response.[5] The E-, P-, and L-selectins recognize the sialyl Lewis X ($sLe^x$) tetrasaccharide determinant, α-Neu5Ac-(2→3)-β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-β-D-GlcNAc **1** (scheme1), which is found as the minimal recognition motif, as a terminal carbohydrate structure of both cell membrane glycolipids and glycoproteins. The oligosaccharides $sLe^x$, its isomer $sLe^a$ and the sulfated derivatives of $Le^x$ and $Le^a$ bind to E-selectin.[6] The glycoprotein receptors bearing these carbohydrates have been identified as ESL-1 and PSGL-1.[7] Blocking this interaction may therefore provide therapeutic opportunities for the treatment of acute and/or chronic diseases, in which excessive adherence of neutrophiles occurs at inflamed tissues sites. Although preliminary results with $sLe^x$ or analogs as selectin receptor antagonist, potent anti-adhesive and anti-inflammatory drugs in animal studies have been promising, improvement in potency and in pharmacological properties (bioavailability and serum half-life) are requisite for expanded chemical use.[8]

The identification of the minimal functional domain of $sLe^x$ required for selectin-binding allowed the design of various glycomimetics in recent years.[9] We are interested in elaborating some new sialyl Lewis A or X mimetics which would be able, through liposome technology, to assure an efficient presentation of ligand to cell surface receptors by multivalent contacts.[10] Moreover, we would like to take advantage of the selective recognition of these liposomal particles by activated endothelium for targeted delivery of drugs to this tissue.[11]






1




2

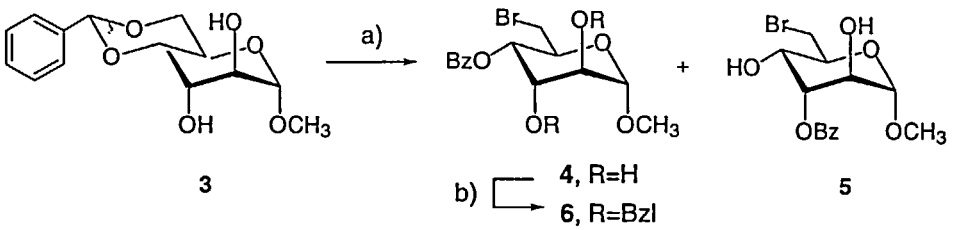
**Scheme 1**

Since 3"-*O*-sulfated Lewis A and Lewis X trisaccharides have been shown also to exibit high affinity binding to E-selectin through a common epitope,[12] we have elaborated a simpler mimetic **2**, which retains the important core for interaction with E-selectin: the *O*-α-fucose interacting with Glu 80, Asn 82, Asn 105 and Asp 108, the *O*-β-galactose for Tyr 94 interaction and the necessary anionic substituent 3-*O*-sulfate at the spatial position normally occupied by sialic acid in $sLe^x$, for binding with the Arg 97 residue of the

protein.[13] However, the GlcNAc residue has been substituted by a (3*R*,4*R*)-*trans*-diol pyrrolidine rigid core. The pyrrolidine nitrogen of the latter has the avantage of being able to be further linked to other spatial devices for multivalency purpose or even to lipids in order to make new $sLe^X$ analog graft liposomes.

## RESULTS AND DISCUSSION

The synthesis of the (3*R*,4*R*)-*trans*-diol pyrrolidine was based on the original work of Ganem, which consists in the elaboration of chiral pyrrolidine rings from 6-halopyranosides.[14] The synthesis started from methyl 4,6-*O*-benzylidene-α-D-altropyranoside **3**, itself readily obtained in 4 steps from methyl glucopyranoside.[15] The ring opening of the 4,6-*O*-benzylidene of **3** with *N*-bromosuccinimide[16] afforded the methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-altropyranoside **4** in 60% yield after column chromatography (Scheme 2), along with the regioisomer **5** (30%). This latter resulted from a 4-*O* →3-*O* -benzoyl transfer side-reaction occurring in part during the bromination step, but also during column chromatography.

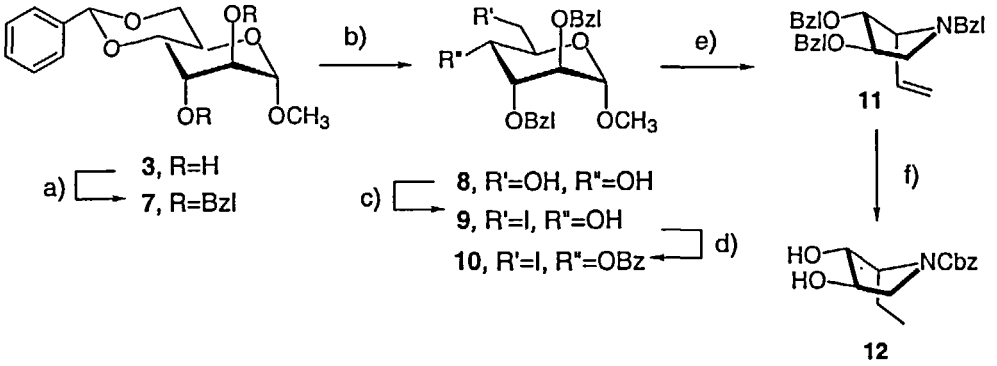



*Reagents and conditions* : a) NBS, $BaCO_3$, $CCl_4$, reflux, 1 h, 60%; b) $BzlOC(=NH)CCl_3$, $CH_2Cl_2$/cyclohexane, $CF_3SO_3H$ cat., rt, 16 h, 63%.

**Scheme 2**

Indeed, while the NMR spectrum of compound **4** exhibited a dd at 5.31 ppm, which could be attributed to H-4 ($J_{4,5}$ = 9 Hz and $J_{4,3}$ = 3 Hz), the corresponding deshielded signal for compound **5** was a dd at 5.36 ppm, unambiguously attributed to H-3, with $J_{3,4} = J_{3,2} = 3.0$ Hz. The very close polarity of the 3- and 4-*O*-benzoyl isomers **4** and **5** made their separation difficult. Benzylation of the major diol **4** was achieved using acidic conditions with benzyl trichloroacetimidate and triflic acid as catalyst,[17] affording the expected 2,3-*O*-benzylated compound **6**. The difficulties encountered in scaling up this reaction, and the modest yield obtained during the process, prompted us to investigate another route where the 2- and 3-OH were benzylated prior to introduction of the 6-halogen.

According to an alternative pathway, the diol 3 was treated with benzyl chloride and KOH in toluene at reflux to give compound **7**[18] in 91% yield (Scheme 3). Oxidative ring opening of the benzylidene group was not considered because of the known instability of the benzyl protecting groups under the Hanessian reaction conditions. Instead, the benzylidene ring was quantitatively hydrolysed by heating in the presence of iodine in MeOH,[19] to afford compound **8**[18] (98%). Selective substitution of the 6-OH by iodine was achieved following the Garegg-Samuelsson method of alkoxyphosphonium substitution,[20] ($I_2$, triphenylphosphine and imidazole) to afford the iodo compound **9**[18] (78%). Finally, the 4-OH of **9** was benzoylated by treatment with benzoyl chloride in pyridine at room temperature, giving the suitably functionalized compound **10** in 87% yield.




*Reagents and conditions* : a) BzlCl, KOH, toluene, reflux, 4 h, 91%; b) $I_2$, MeOH, reflux, 2 h, 98%; c) $I_2$, $PPh_3$, imidazole, toluene, 50 °C, 15 min, 78%; d) BzCl, pyridine, rt, 16 h, 87%; e) $NaBH_3CN$, $BzlNH_2$, activated Zn, $EtOH/H_2O$, reflux, 16 h, 80%; f) i: $H_2$, Pd/C 10%, MeOH.HCl, MeOH; ii: $BzlOC(O)Cl$, $Na_2CO_3$, $H_2O$, 0 °C, 30 min, 66%.

**Scheme 3**

Synthesis of the hydroxylated pyrrolidine was achieved under the conditions reported by Bernotas and Ganem in the *gluco* and *galacto* series.[21, 14] Thus, as depicted in Scheme 3, starting from compound **10**, reductive elimination-reductive amination ($Zn/NaBH_3CN/PhCH_2NH_2/i$ $PrOH/H_2O$, reflux, 2 h) afforded the pyrrolidine **11** in excellent yield (80%). The same product was also obtained when the bromo sugar **6** was submitted to these reaction conditions, but with a slightly lower yield (68%). Finally, the *O*- and *N*-benzyl protecting groups were removed by catalytic hydrogenolysis in MeOH with 10% Pd/C. The resulting intermediary free pyrrolidine was immediately protected as the N-benzyloxycarbonyl derivative **12** (66%).

Pyrrolidine **12** appeared to be a good scaffold for positioning, in the following steps, the L-fucosyl and the D-galactosyl residues in a similar orientation to that of the natural

ligand. Indeed, a selective glycosylation at the 4-position could be expected because of the steric hindrance generated at the corresponding 3-position by the presence of the *cis* vicinal ethyl group.

Therefore, fucose was first glycosylated and the fucosyl fluoride **13**[22] was chosen as the glycosyl donor. The glycosylation reaction was carried out in diethyl ether, using $SnCl_2/AgClO_4$[23] as the catalyst (Scheme 4). As we anticipated, compound **14** was obtained with both α-stereo-($J_{1',2'}$ = 2.5 Hz) and regioselectivity (proved by $^1H$ and $^{13}C$ spectra).

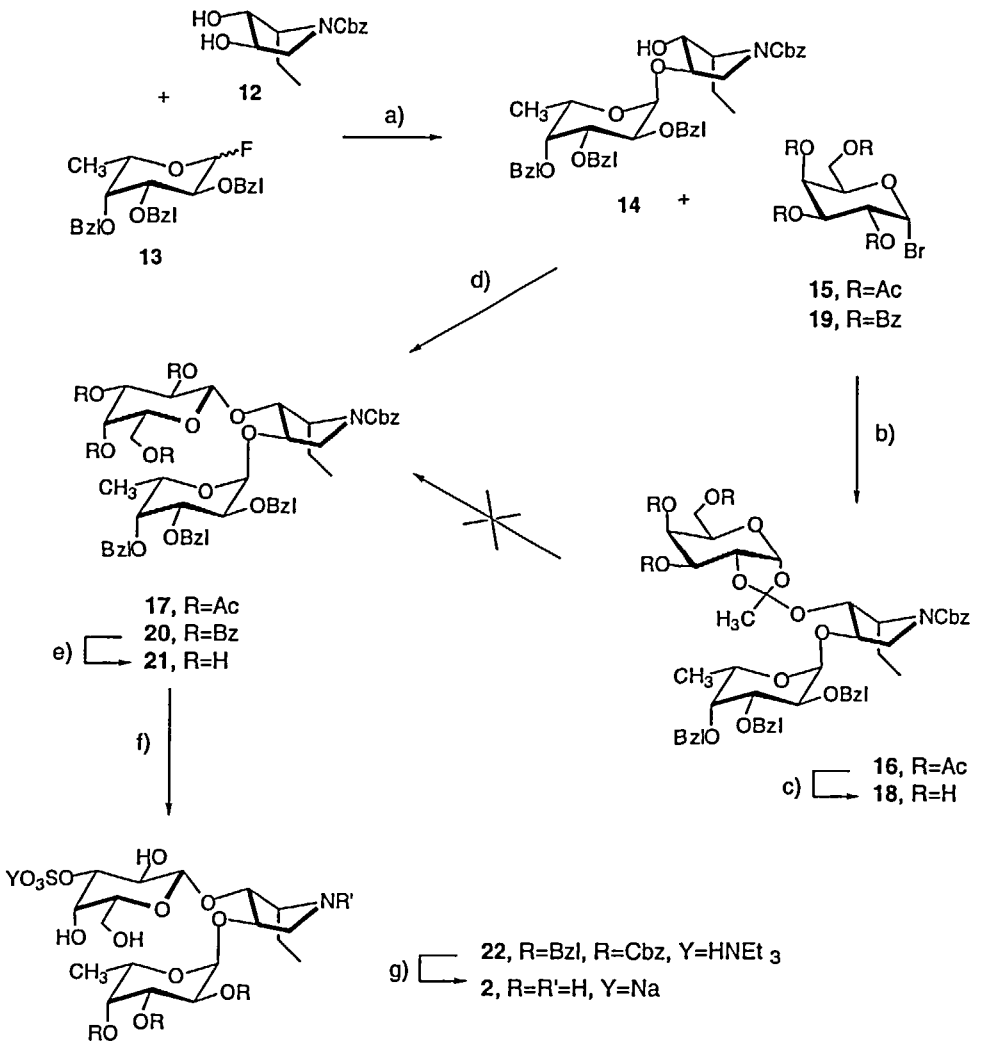
Koenigs-Knorr glycosylation of **14** with the galactosyl bromide **15**[24] was then performed, promoted by AgOTf and *sym*-collidine in dichloromethane.[25] However, it turned out that the 1,2-*ortho*-acetate **16** had been formed in 52% yield, instead of the corresponding 1,2-*trans*-glycoside **17**. The structure of **16** has been deduced from a panel of $^1H$ and $^{13}C$ NMR data: the coupling constant of the anomeric proton of galactose was too small ($J_{1,2}$ = 4 Hz) for the expected β-glycoside with H-1, H-2 axial/axial coupling; moreover, one of the four peaks corresponding to the methyl of the acetates was shielded in the $^1H$ NMR spectrum (δ = 1.66 ppm) and deshielded in the $^{13}C$ spectrum (δ = 25.9 ppm). As expected for an orthoester, the analytical data of the corresponding deacetyl compound **18**, obtained by treatment of **16** with MeONa/MeOH, removed any ambiguity, since we observed the persistency of the methyl signal of the orthoester (for $^1H$ at δ = 1.62 ppm and for $^{13}C$ at δ = 25.7 ppm), results confirmed by analysis of mass fragmentation.

After unsuccessful attempts to rearrange the orthoester with $SnCl_4$,[26] and considering the discouraging results obtained by Saunders *et al.*[27] in their synthesis of $Le^x$, our next efforts were turned towards alternative approaches.

It has been described that the formation of orthoesters is strongly influenced by the reaction conditions and, in particular, glycosylation catalysed by tetramethylurea instead of *sym*-collidine is supposed to avoid such side-reactions.[26] However, in our case, such a result was not observed.

It can be noted that the coupling with a galactose unit activated by a trichloroacetimidate, often used to avoid the formation of orthoesters,[28] was tried without any success in our case, the starting materials being completely recovered.

As benzoyl protecting groups are known to disfavor the formation of orthoesters,[29] the galactosyl bromide **19**[30] was chosen for coupling with **14**. The reaction was carried out under the same conditions as for **15**, and in this case, the desired compound **20** was finally obtained in acceptable yield (65%). Deprotection of **20** under Zemplen conditions afforded a product, whose mass spectrum was in agreement with the 1,2-*trans* glycoside **21**. The β-stereoselectivity of the galactose coupling in **20** and **21** could not be ascertained at these stages, since the NMR signal of the anomeric proton of galactose was part of a multiplet.




*Reagents and conditions* : a) $SnCl_2$, $AgClO_4$, DTBP, $Et_2O$, reflux, 16 h, 60%; b) AgOTf, *sym*-collidine, $CH_2Cl_2$, -78 °C, 1 h, 52%; c) MeONa/MeOH, 0 °C, 4 h, 84%; d) AgOTf, *sym*-collidine, $CH_2Cl_2$, -78 °C, 1 h, 65%; e) MeONa/MeOH, 0 °C, 24 h, 63%; f) i: $Bu_2SnO$, PhH, 120 °C; ii: $SO_3.NEt_3$, PhH, rt, 20 min, 70%; g) i: $H_2$, Pd/C 10%, MeOH, AcOH; ii: NaOH, 55%.

**Scheme 4**

Treatment of **21** with dibutyltin oxide gave an intermediate dibutyl stannane, which, upon sulfation with the $SO_3.NEt_3$ complex,[31] gave exclusively the 3″-*O*-sulfo compound **22** in 70% yield. Removal of the benzyl and benzyloxycarbonyl protecting groups in the presence of 10% Pd/C, followed by treatment with NaOH, afforded the final $sLe^x$ analog **2**, in 55% yield after purification and lyophilization. Fortunately, with compound **2**, the galactose glycosidic linkage could be rigorously confirmed to be β ($\delta = 4.50$, d, $J_{1'',2''} = 8.0$ Hz).

## CONCLUSION

In conclusion, we have prepared a new $sLe^x$ mimetic as E-selectin inhibitor. In this derivative, the natural neuraminic acid and the *N*-acetyl glucosamine residues have been replaced by a sulfate group and a pyrrolidine ring, respectively. The biological data for this new mimetic will be reported elsewhere.

Further elaborations of other nitrogenous heterocyclic scaffold analogues retaining both *O*-α-fucose and *O*-β-galactose core structures are currently under investigation.[32]



## EXPERIMENTAL

**General methods.** Melting points are uncorrected. IR spectra were recorded in chloroform solution using a Perkin-Elmer 1710 spectrophotometer, calibrated against a polystyrene film and are expressed in $cm^{-1}$. Optical rotations were determined with a Perkin-Elmer 241 polarimeter (589 nm), at 20 °C, with a concentration expressed in g/100 mL. $^1H$ NMR spectra were recorded using a Bruker AM250 (250 MHz), a Bruker AC300 (300 MHz) and a Bruker AM400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from internal $Me_4Si$ with the notations indicating the multiplicity of the signal. Assignments were aided by COSY and H/C correlations experiments. $^{13}C$ NMR spectra were recorded at 62.5 MHz using a Bruker AM250, at 75 MHZ using a Bruker AC300 or at 100 MHz using a Bruker AM400. For mass spectra, CI ($NH_3$) were recorded with a Nermag R10-10C and FAB ($M+ Na^+$) was recorded with a Jeol MS 700. TLC was performed on Silica gel $60F_{254}$ (Merck). Silica gel (Merck, particle size 0.040-0.063 nm) was used for flash chromatography. All reactions, except hydrogenation and those under aqueous conditions, were performed under an argon atmosphere. Anhydrous reaction solvents were distilled as follows: diethyl ether, tetrahydrofuran and toluene from sodium/benzophenone; benzene from calcium hydride; dichloromethane and carbon

tetrachloride from phosphorus pentoxide. For the NMR assignment of compounds **2** and **11-21**, the atoms of the pyrrolidine will be noted 1-7 (the nitrogen being 1), those of fucose 1'-6', those of galactose 1"-6" and for the orthoester C-7" and $CH_3$-8".

**Methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-altropyranoside (4) and methyl 3-*O*-benzoyl-6-bromo-6-deoxy-α-D-altropyranoside (5).** A solution of **3** (1.95 g, 6.9 mmol), *N*-bromosuccinimide (1.54 g, 8.6 mmol) and barium carbonate (3 g, 15.2 mmol) in dry $CCl_4$ was refluxed for 1 h. The mixture was filtered and the filtrate washed with water (2 x 100 mL). The combined aqueous phases were extracted with ethyl acetate (100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography (cyclohexane/ethyl acetate 2:1, v/v) afforded **4** (1.5 g, 60%) and **5** (0.75 g, 30%); data for **4**: $R_f$ 0.48 (cyclohexane/acetone 1:1, v/v); $[\alpha]_D^{20}$ +24 ° (*c* 0.8, chloroform); $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.04 (m, 2H, Ar), 7.58 (m, 1H, Ar), 7.48 (m, 1H, Ar), 5.31 (dd, 1H, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 4.86 (s, 1H, H-1), 4.41 (m, 1H, H-5), 4.26 (m, 1H, H-3), 4.03 (m, 1H, H-2), 3.75-3.52 (m, 2H, H-6), 3.55 (s, 3H, $OCH_3$); MS (DCI/$NH_3$): *m/z* 378 $[M + NH_4]^+$.

Anal. Calcd for $C_{14}H_{17}BrO_6$: C, 46.56; H, 4.74. Found: C, 46.74; H, 4.49.

Data for **5**: $R_f$ 0.50 (cyclohexane/acetone 1:1 v/v); $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.05 (d, 2H, Ar), 7.60 (dd, 1H, Ar), 7.47 (dd, 1H, Ar), 5.36 (dd, 1H, $J_{2,3} = J_{3,4}$ = 3.0 Hz, H-3), 4.73 (s, 1H, H-1), 4.23 (m, 1H, H-5), 4.14 (dd, 1H, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 6.0 Hz, H-4), 4.09 (d, 1H, $J_{2,3}$ = 3.0 Hz, H-2), 3.83 (dd, 1H, $J_{5,6a}$ = 2.0 Hz, $J_{6a,6b}$ = 11.0 Hz, H-6a), 3.64 (dd, 1H, $J_{5,6b}$ = 7.0 Hz, $J_{6a,6b}$ = 11.0 Hz, H-6b), 3.52 (s, 3H, $OCH_3$); MS (DCI/$NH_3$): *m/z* 378 $[M + NH_4]^+$.

**Methyl 4-*O*-benzoyl-2,3-di-*O*-benzyl-6-bromo-6-deoxy-α-D-altropyranoside (6).** To a solution of **5** (1.2 g, 3.3 mmol) in dichloromethane/cyclohexane (1:2, v/v) were added benzyl trichloroacetimidate (2.5 mL, 13.2 mmol) and trifluoromethanesulfonic acid (60 µL). The mixture was stirred overnight at room temperature. The precipitate was filtered, and the filtrate was washed with saturated $NaHCO_3$ solution (30 mL) and water (30 mL). The combined aqueous layers were extracted with cyclohexane, and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography (cyclohexane/acetone 1:1, v/v) afforded **6** (1.1 g, 63%); $R_f$ 0.75 (cyclohexane/acetone 1:1, v/v); $[\alpha]_D^{20}$ +18 ° (*c* 0.7, chloroform); $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.05-8.00 (m, 2H, Ar), 7.58-7.11 (m, 13H, Ar), 5.34 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 4.90-4.41 (m, 7H, $PhC\underline{H}_2$, H-1, H-3, H-5), 4.07 (dd, 1H, J = 3.0 Hz, J' = 7.0 Hz, H-2), 3.70 (m, 2H, H-6), 3.49 (s, 3H, $OCH_3$); MS (DCI/$NH_3$): *m/z* 558 $[M + NH_4]^+$.

Anal. Calcd for $C_{28}H_{29}BrO_6$: C, 62.11; H, 5.40. Found: C, 61.98; H, 5.29.

**Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-altropyranoside (7).** To a solution of **3** (10.4 g, 36.9 mmol) in dry toluene (150 mL) were added benzyl chloride (30.5 mL, 265 mmol) and potassium hydroxide (13.05 g, 232 mmol), and the mixture was refluxed for 4 h, then cooled to room temperature. After dilution with toluene (700 mL), the mixture was washed with water, and the organic layer was coevaporated with water to remove the benzyl chloride and ether. The resulting oil was coevaporated twice with toluene and chromatographed on silica gel (cyclohexane/acetone 9:1, v/v) to give **7** as a white solid (15.5 g, 91%); $R_f$ 0.7 (cyclohexane/acetone 1:1, v/v); mp 89 °C; lit[18]: 86-87.5 °C; $[\alpha]_D^{20}$ +2 ° (*c* 0.975, chloroform); lit[18]: -1 ° (*c* 2.5, chloroform); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.52 (m, 2H, Ar), 7.41-7.26 (m, 13H, Ar), 5.60 (s, 1H, PhC<u>H</u>), 4.85-4.71 (m, 2H, PhC<u>H</u>$_2$), 4.69 (s, 1H, H-1), 4.50 (m, 2H, PhC<u>H</u>$_2$), 4.46-4.41 (m, 1H, H-6a), 4.38-4.33 (m, 1H, H-6b), 4.06-4.02 (dd, 1H, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.97 (dd, 1H, $J_{2,3} = J_{3,4}$ = 3.0 Hz, H-3), 3.85 (dd, 1H, $J_{4,5} = J_{5,6}$ = 9.5 Hz, H-5), 3.69 (d, 1H, $J_{2,3}$ = 3.0 Hz, H-2), 3.43 (s, 3H, $OCH_3$); MS (DCI/$NH_3$): *m/z* 480 $[M + NH_4]^+$.

Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.74; H, 6.56.

**Methyl 2,3-di-*O*-benzyl-α-D-altropyranoside (8).** A solution of **7** (15.2 g, 32.9 mmol) and iodine (3.1 g, 12.2 mmol) in MeOH (300 mL) was refluxed for 2 h. After cooling, the mixture was treated with a 10% sodium thiosulfate solution, then concentrated under reduced pressure. Water was added, and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by flash chromatography (dichloromethane/methanol 98:2, v/v) to give **8** (12.12 g, 98 %) as an oil; $R_f$ 0.6 (cyclohexane/acetone 1:1, v/v); IR ($CHCl_3$): 3359 $cm^{-1}$ ($\nu_{OH}$); $[\alpha]_D^{20}$ +64 ° (*c* 1.18, chloroform); lit[18]: +59 ° (*c* 1.6, chloroform); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.40 (m, 10H, Ar), 4.70 (s, 1H, H-1), 4.66-4.40 (m, 4H, PhC<u>H</u>$_2$), 3.90-3.73 (m, 6H, H-2, H-3, H-4, H-5, H-6), 3.49 (s, 3H, $OCH_3$), 2.42 (d, 1H, J = 9.5 Hz, OH), 2.09 (s, 1H, OH); MS (DCI/$NH_3$): *m/z* 392 $[M + NH_4]^+$.

Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.23; H, 6.81.

**Methyl 2,3-di-*O*-benzyl-6-deoxy-6-iodo-α-D-altropyranoside (9).** To a solution of **8** (12.12 g, 32.4 mmol) in dry toluene were added triphenylphosphine (11.9 g, 45.4 mmol), imidazole (6.43 g, 97.2 mmol) and iodine (12.4 g, 48.6 mmol). The mixture was stirred at 50 °C for 15 min, then quenched with MeOH (30 mL). After concentration under reduced pressure to remove the resulting methyl iodide, a 10% sodium thiosulfate solution was added. The aqueous layer was extracted with $CH_2Cl_2$ (2 x 200 mL), and the combined organic phases were dried ($MgSO_4$), filtered and evaporated. Diethyl ether was added to precipitate the triphenylphosphine oxide. The

mixture was filtered, and the filtrate was concentrated to an oily residue. After purification by flash chromatography (cyclohexane/ethyl acetate 6:1, v/v) **9** was obtained as an oil (12.2 g, 78%); $R_f$ 0.55 (cyclohexane/acetone 1:1, v/v); IR ($CHCl_3$): 3352 $cm^{-1}$ ($\nu_{OH}$); $[\alpha]_D^{20}$ +52 ° (*c* 1.1, chloroform); lit[18]: +51 ° (*c* 1, chloroform); $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.40-7.27 (m, 10H, Ar), 4.74 (s, 1H, H-1), 4.66 and 4.64 (2d, 2H, J = 11.0 Hz, PhC$\underline{H}_2$), 4.52 and 4.34 (2d, 2H, J = 11.5 Hz, PhC$\underline{H}_2$), 3.81 (ddd, 1H, $J_{5,6a}$ = 2.0 Hz, $J_{4,5}$ = $J_{5,6b}$ = 9.0 Hz, H-5), 3.74 (m, 2H, H-2, H-3), 3.65 (m, 2H, H-4, H-6a), 3.49 (s, 3H, $OCH_3$), 3.25 (dd, 1H, $J_{5,6b}$ = 9.0 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6b), 2.40 (d, 1H, $J_{4,OH}$ = 10.5 Hz, OH); MS (DCI/$NH_3$): *m/z* 502 $[M + NH_4]^+$.

Anal. Calcd for $C_{21}H_{25}IO_5$: C, 52.08; H, 5.20. Found: C, 52.43; H, 5.40.

**Methyl 4-*O*-benzoyl-2,3-di-*O*-benzyl-6-deoxy-6-iodo-α-D-altropyranoside (10).** To a solution of **9** (11.4 g, 23.5 mmol) in dry pyridine (150 mL) cooled at 0 °C, was gradually added benzoyl chloride (4 mL, 35.3 mmol). The mixture was stirred at room temperature for 16 h, then poured onto ice. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 250 mL), and the combined organic layers were washed with 6N HCl at 0 °C (2 x 200 mL), saturated $Na_2CO_3$ solution (150 mL) and water (4 x 150 mL). After drying ($MgSO_4$), the residue was filtered, concentrated and purified by flash chromatography (cyclohexane/ethyl acetate 15:1, v/v) to yield **10** as an oil (12.1 g, 87%); $R_f$ 0.53 (cyclohexane/acetone 5:1, v/v); IR ($CHCl_3$): 1720 $cm^{-1}$ ($\nu_{C=O}$); $[\alpha]_D^{20}$ +31 ° (*c* 1, chloroform); $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.03 (d, 2H, J = 7.0 Hz, Ar), 7.61 (t, 1H, J = 7.5 Hz, Ar), 7.47 (t, 2H, J = 7.5 Hz, Ar), 7.38-7.13 (m, 10H, Ar), 5.25 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 4.77 (bs, 1H, H-1), 4.63-4.47 (m, 4H, PhC$\underline{H}_2$), 4.32 (dt, 1H, $J_{5,6a}$ = 2.5 Hz, $J_{4,5}$ = $J_{5,6b}$ = 9.0 Hz, H-5), 4.03 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{2,3}$ = 4.5 Hz, H-3), 3.70 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 4.5 Hz, H-2), 3.53 (s, 3H, $OCH_3$), 3.46 (dd, 1H, $J_{5,6a}$ = 2.5 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6a), 3.28 (dd, 1H, $J_{5,6b}$ = 9.0 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6b); MS (DCI/$NH_3$): *m/z* 606 $[M + NH_4]^+$.

Anal. Calcd for $C_{28}H_{29}IO_6$: C, 57.15; H, 4.97. Found: C, 57.42; H, 5.09.

**(2*S*,3*R*,4*R*)-1-Benzyl-3,4-dibenzyloxy-2-vinylpyrrolidine (11).** To a solution of **10** (12.5 g, 21.2 mmol), $NaBH_3CN$ (4.35 g, 69.2 mmol) and benzylamine (65 mL, 595.6 mmol) in EtOH/$H_2O$ (500 mL, 19/1) was added activated zinc powder (58.5 g, 892.4 mmol) [prepared as follows: powdered zinc metal (130 g) was vigorously stirred for 5 min with 1N HCl (780 mL), then washed successively with water (780 mL), ethanol (380 mL), acetone (780 mL) and $Et_2O$ (780 mL). The powder was finally dried for 15 min at 90 °C under 10 mm Hg, and used immediately]. The suspension was refluxed overnight. After cooling to room temperature, the mixture was filtered through Celite and the residue was washed with MeOH. The filtrate was concentrated to dryness, and the resulting oil was dissolved in MeOH/$CH_2Cl_2$/1N HCl (840 mL, 6/4/11).

Saturated $Na_2CO_3$ solution (150 mL) was then added, as well as $CH_2Cl_2$. The aqueous phase was extracted (4 x 250 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chomatography (cyclohexane/ethyl acetate 10:1, v/v) afforded **11** (6.8 g, 80 %); $R_f$ 0.7 (cyclohexane/ethyl acetate 3:1, v/v); $[\alpha]_D^{20}$ +67 ° (*c* 0.84, chloroform); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.40-7.25 (m, 15H, Ar), 6.05 (ddd, 1H, $J_{2,6}$ = 9.0 Hz, $J_{6,7b}$ = 10.0 Hz, $J_{6,7a}$ = 17.0 Hz, H-6), 5.35 (dd, 1H, $J_{7a,7b}$ = 2.0 Hz, $J_{6,7b}$ = 10.0 Hz, H-7b), 5.34 (dd, 1H, $J_{7a,7b}$ = 2.0 Hz, $J_{6,7a}$ = 17.0 Hz, H-7a), 4.55 and 4.53 (2d, 2H, J = 12.0 Hz, PhC$\underline{H}_2$O), 4.41 (s, 2H, PhC$\underline{H}_2$O), 4.09 (m, 1H, H-4), 3.99 (m, 1H, H-3), 3.24 and 3.22 (2d, 2H, J = 8.0 Hz, PhC$\underline{H}_2$N), 3.30 (dd, 1H, $J_{2,3}$ = 7.0 Hz, $J_{2,6}$ = 9.0 Hz, H-2), 3.25 (dd, 1H, $J_{4,5a}$ = 6.5 Hz, $J_{5a,5b}$ = 10.0 Hz, H-5a), 2.23 (dd, 1H, $J_{4,5b}$ = 6.5 Hz, $J_{5a,5b}$ = 10.0 Hz, H-5b); MS (DCI/$NH_3$): *m/z* 400 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{29}NO_6$: C, 81.17; H, 7.32; N, 3.51. Found: C, 80.96; H, 7.73; N, 3.18.

**(2*S*, 3*R*, 4*R*)-1-Benzyloxycarbonyl-3,4-dihydroxy-2-ethylpyrrolidine (12).** A mixture of **11** (2.05 g, 5.14 mmol), methanolic hydrochloric acid (1.3 eq) and 10% Pd/C (500 mg) in MeOH (50 mL) was stirred overnight under hydrogen atmosphere. After filtration through Celite, the filtrate was concentrated to dryness, and the residue was dissolved in water (25 mL) and cooled to 0 °C. A 10% solution of $Na_2CO_3$ (25 mL) was added dropwise as well as benzyl chloroformate (1 mL, 7 mmol). After 30 min of stirring, the aqueous layer was extracted with EtOAc (5 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to an oil, which was purified by flash chromatography (cyclohexane/ethyl acetate 1:2, v/v) to yield **12** as a white solid (0.9 g, 66%); $R_f$ 0.5 (cyclohexane/acetone 1:1, v/v); $[\alpha]_D^{20}$ +21 ° (*c* 0.935, chloroform); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H, Ar), 5.10 (s, 2H, PhC$\underline{H}_2$), 4.16-4.07 (m, 2H, H-3, H-4), 3.87 (dd, 1H, $J_{2,3}$ = 6.5 Hz, $J_{2,6}$ = 12.5 Hz, H-2), 3.64 (dd, 1H, $J_{4,5a}$ = 5.5 Hz, $J_{5a,5b}$ = 10.5 Hz, H-5a), 3.39 (br d, 1H, $J_{5a,5b}$ = 10.5 Hz, H-5b), 1.80-1.67 (m, 3H, OH, H-6), 0.96-0.89 (m, 3H, H-7); $^{13}$C NMR (62.5 MHz, $CDCl_3$): δ 156.2 (C=O), 136.6,128.6,128.1,127.8 (Ar), 76.0,74.0 (C-3, C-4), 67.2 (Ph$\underline{C}H_2$), 60.8 (C-2), 51.0 (C-5), 21.7 (C-6), 10.8 (C-7); MS (DCI/$NH_3$): *m/z* 283 $[M + NH_4]^+$, 266 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.56; H, 7.53; N, 5.18.

**4-*O*-(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-(2*S*,3*R*,4*R*)-1-benzyloxycarbonyl-2-ethyl-3,4-dihydroxypyrrolidine (14).** To a mixture of dry $SnCl_2$ (220 mg, 1.14 mmol), dry $AgClO_4$ (240 mg, 1.14 mmol), di-*tert*-butylpyridine (385 µL, 1.71 mmol) and 4 Å molecular sieves (520 mg) was added a solution of **13** (279 mg,

0.64 mmol) and **12** (153 mg, 0.57 mmol) in dry $Et_2O$ (15 mL). The mixture was refluxed for 48 h in the dark, then cooled to room temperature and filtered through Celite. The filtrate was concentrated and chromatographed over silica gel (cyclohexane/ethyl acetate 4:1, v/v) to afford **14** as an oil (231 mg, 60%); $R_f$ 0.5 (cyclohexane/acetone 2/1, v/v); $[\alpha]_D^{20}$ -41 ° (*c* 1.05, chloroform); $^1H$ NMR (250 MHz, $CDCl_3$): δ 7.42-7.30 (m, 20H, Ar), 5.14 (s, 2H, PhC$\underline{H}_2$), 5.08-4.82 (m, 2H, PhC$\underline{H}_2$), 4.78 (d, 1H, $J_{1',2'}$ = 2.5 Hz, H-1'), 4.76-4.58 (m, 4H, PhC$\underline{H}_2$), 4.10-3.99 (m, 4H, H-2, H-3, H-2', H-5'), 3.91-3.76 (m, 3H, H-4, H-5a, H-3'), 3.68 (s, 1H, H-4'), 3.49-3.46 (m, 2H, H-5b, OH), 1.70-1.50 (m, 2H, H-6), 1.14 (d, 3H, $J_{5',6'}$ = 6.5 Hz, H-6'), 0.98-0.90 (m, 3H, H-7); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 155.7 (C=O), 138.8-127.5 (Ar), 83.5 (C-4), 78.9 (C-3'), 78.7,78.5 (C-3, C-2'), 77.6 (C-4'), 75.1-73.5 (Ph$\underline{C}H_2$), 67.6 (C-5'), 66.8 (C-8), 60.4 (C-2), 48.2 (C-5), 22.1 (C-6), 16.6 (C-6'), 10.9 (C-7); MS (DCI/$NH_3$): *m/z* 699 $[M + NH_4]^+$.

Anal. Calcd for $C_{41}H_{47}NO_8$: C, 72.22; H, 6.95; N, 2.05. Found: C, 72.07; H, 7.13; N, 2.18.

**3,4,6-Tri-*O*-acetyl-1,2-*O*-[1-*exo*-[(2*S*,3*R*,4*R*)-4-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-*N*-benzyloxycarbonyl-2-ethyl-3,4-dihydroxy-3-yl-pyrrolidine]ethylidene]-β-D-galactopyranose (16).** To a mixture of dry AgOTf (414 mg, 1.61 mmol), *sym*-collidine (50 µL, 0.37 mmol) and 4 Å molecular sieves (2 g) was added a solution of **14** (368 mg, 0.54 mmol) in dry $CH_2Cl_2$ (5 mL). The mixture was cooled to -78 °C, and a solution of **15** (378 mg, 0.92 mmol) in dry $CH_2Cl_2$ (5 mL) was added. After 1 h at -78 °C, stirring was pursued at 0 °C for another hour. Dichloromethane (100 mL) was then added and, after filtration through Celite, the residue was rinsed with ethyl acetate, then successively washed with saturated $NaHCO_3$ solution (2 x 50 mL) and water (2 x 50 mL). The combined aqueous phases were extracted with $CH_2Cl_2$ (50 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. After flash chromatography (cyclohexane/ethyl acetate 5:1, v/v), **16** was obtained as a white foam (286 mg, 52%); $R_f$ 0.27 (cyclohexane/acetone 2:1, v/v); $[\alpha]_D^{20}$ +3.5 ° (*c* 0.5, chloroform); $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.40-7.25 (m, 20H, Ar), 5.84 (d, 1H, $J_{1'',2''}$ = 4.0 Hz, H-1''), 5.42 (dd, 1H, $J_{3'',4''} = J_{4'',5''}$ = 2.5 Hz, H-4''), 5.12 (s, 2H, PhC$\underline{H}_2$), 5.01 (m, 1H, H-2''), 4.97 (d, 1H, J = 11.5 Hz, PhC$\underline{H}_2$), 4.85-4.58 (m, 5H, PhC$\underline{H}_2$), 4.36 (m, 1H, H-3''), 4.30-4.25 (m, 2H, H-4, H-5''), 4.18-4.10 (m, 3H, H-3, H-6''), 4.02-3.95 (m, 2H, H-2', H-5'), 3.90-3.84 (m, 2H, H-2, H-3'), 3.67-3.56 (m, 3H, H-4', H-5), 2.12-2.03 (m, 9H, $COCH_3$), 1.66 (m, 5H, H-6, $CH_3$-orthoester), 1.10 (d, 3H, $J_{5',6'}$ = 6.0 Hz, H-6'), 0.90 (m, 3H, H-7); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 170.4-169.8 (CO), 138.6-136.7 (Ar Cq), 128.5-127.4 (Ar CH), 122.3 (C-7''), 98.1 (C-1'), 97.3 (C-1''), 79.0 (C-3', C-3), 77.3 (C-4'), 76.1, (C-2'), 75.6,74.8

(C-4, C-2"), 75.1-73.2 (PhCH$_2$), 71.7 (C-3"), 69.4 (C-5"), 66.7 (C-5', PhCH$_2$), 65.9 (C-4"), 61.0 (C-6"), 60.6 (C-2), 49.3 (C-5), 25.9 (C-8"), 21.5 (C-6), 20.6 (3 x $COCH_3$), 16.5 (C-6'), 10.3 (C-7); MS (DCI/$NH_3$): *m/z* 1029 $[M + NH_4]^+$, 1012 $[M + H]^+$. HRMS (FAB positive mode, NBA + LiI) calcd for $C_{55}H_{65}LiNO_{17}$ $[M + Li]^+$: 1018.4413. Found: 1018.4416.

**1,2-*O*-[1-*Exo*-[(2*S*,3*R*,4*R*)-4-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-1-benzyloxycarbonyl-2-ethyl-3,4-dihydroxy-3-yl-pyrrolidine]ethylidene]-β-D-galactopyranose (18).** Compound **16** (103 mg, 0.1 mmol) was coevaporated with toluene, then cooled to 0 °C and dissolved in a 1M sodium methanolate solution. The solution was stirred for 24 h, then neutralized with Amberlite IRC 50-S and filtered. The filtrate was concentrated to an oily residue and purified by chromatography (cyclohexane/ethyl acetate 1:2, v/v) to give **18** (74 mg, 84%) as a white foam; $R_f$ 0.18 (cyclohexane/ethyl acetate 1:2 v/v); $[\alpha]_D^{20}$ -19 ° (*c* 0.5, chloroform); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.38-7.25 (m, 20H, Ar), 5.81 (m, 1H, H-1"), 5.04 (s, 2H, PhCH$_2$), 4.86-4.56 (m, 6H, 3 x PhCH$_2$), 4.75 (s, 1H, H-1'), 4.30 (m, 1H, H-3"), 4.23 (m, 1H, H-3), 4.17 (m, 1H, H-4), 3.89 (m, 3H, H-2', H-5', H-4"), 3.86-3.80 (m, 2H, H-2, H-3'), 3.78 -3.74 (m, 3H, H-5", H-6"), 3.73-3.69 (m, 2H, H-4', H-2"), 3.63-3.45 (m, 2H, H-5), 1.80-1.62 (m, 5H, H-6, H-8"), 1.16 (d, 3H, $J_{5',6'}$ = 6.0 Hz, H-6'), 0.86 (m, 3H, H-7); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 155.6 (CO), 138.8-136.7 (Ar Cq), 128.6-127.5 (Ar CH), 121.8 (C-7"), 97.8 (C-1', C-1"), 79.2-78.6 (C-2", C-3, C-3'), 77.7 (C-4'), 76.3 (C-2'), 75.1-73.2 (PhCH$_2$), 74.7 (C-4), 72.3 (C-3"), 71.2 (C-5"), 68.1 (C-4"), 67.0 (C-8), 66.8 (C-5'), 62.3 (C-6"), 60.7 (C-2), 49.3 (C-5), 25.7 (C-8"), 21.0 (C-6), 16.6 (C-6'), 10.4 (C-7); MS (DCI/$NH_3$): *m/z* 903 $[M + NH_4]^+$. HRMS (FAB positive mode, NBA + LiI) calcd for $C_{49}H_{59}LiNO_{14}$ $[M + Li]^+$: 892.4096. Found: 892.4100.

**4-*O* -(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(2*S*,3*R*,4*R*)-1-benzyloxycarbonyl-2-ethyl-3,4-dihydroxypyrrolidine (20).** To a mixture of dry AgOTf (474 mg, 1.84 mmol), *sym*-collidine (220 µL, 1.66 mmol) and 4 Å molecular sieves (3 g) was added a solution of **14** (1.07 g, 1.61 mmol) in dry $CH_2Cl_2$ (10 mL). The mixture was cooled to -78 °C and a solution of **19** (730 mg, 1.07 mmol) in dry $CH_2Cl_2$ (7 mL) was added. After 1 h at -78 °C, stirring was continued at -10 °C for another hour. $CH_2Cl_2$ (100 mL) was then added and, after filtration through Celite, the residue was rinsed with acetone, then successively washed with saturated $NaHCO_3$ solution (50 mL) and water (50 mL). The combined aqueous phases were extracted with $CH_2Cl_2$ (50 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. After flash chromatography (cyclohexane/ethyl acetate 5:1, v/v), **20** was obtained as a white foam (890 mg, 65%); $R_f$ 0.4 (cyclohexane/ethyl acetate 2:1, v/v); IR ($CDCl_3$): 1732

$cm^{-1}$ ($\nu_{C=O}$); $[\alpha]_D^{20}$ +25.4 °(*c* 0.7, chloroform); $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.06-7.20 (m, 40H, Ar), 5.96 (d, 1H, $J_{3",4"}$ = 3.0 Hz, H-4"), 5.79 (m, 1H, H-2"), 5.57 (dd, 1H, $J_{3",4"}$ = 3.0 Hz, $J_{2",3"}$ = 10.0 Hz, H-3"), 5.07 (m, 2H, PhC$\underline{H}_2$), 4.96 (d, 2H, J = 11.5 Hz, PhC$\underline{H}_2$), 4.90-4.81 (m, 2H, H-1', H-1"), 4.67 and 4.60 (2d, 2H, J = 11.5 Hz, PhC$\underline{H}_2$), 4.43-4.38 (m, 3H, H-3, H-6"), 4.31 (m, 2H, H-4, H-5"), 4.02 (q, 1H, $J_{5',6'}$ = 6.5 Hz, H-5'), 3.85 (m, 4H, H-2, H-2', H-3', H-5a), 3.64 (m, 2H, H-4', H-5b), 1.60-1.40 (m, 2H, H-6), 1.23 (d, 3H, $J_{5',6'}$ = 6.5 Hz, H-6'), 0.52 (t, 3H, $J_{6,7}$ = 7.0 Hz, H-7); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 127.2-113.6 (Ar), 112.5 (C-1"), 97.8 (C-1'), 82.5 (C-4), 80.0 (C-3'), 78.9 (C-3), 77.9 (C-4'), 76.4 (C-2'), 75.0-73.0 (Ph$\underline{C}H_2$), 71.5,71.4 (C-3", C-5"), 69.5 (C-2"), 68.1 (C-4"), 66.6 (C-5'), 66.5 (C-8), 62.3 (C-6"), 50.0 (C-5), 26.8 (C-6), 16.7 (C-6'), 10.4 (C-7); HRMS (DCI/$CH_4$) calcd for $C_{75}H_{74}NO_{17}$ $[M + H]^+$: 1260.4957. Found: 1260.5000.

**4-*O*-(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-3-*O*-(β-D-galactopyranosyl)-(2*S*, 3*R*, 4*R*)-1-benzyloxycarbonyl-2-ethyl-3,4-dihydroxypyrrolidine (21).** Compound **20** (126 mg, 0.1 mmol) was coevaporated with toluene, then cooled to 0 °C and dissolved in a 1M sodium methanolate solution. The solution was stirred for 4 h, then neutralized with Amberlite IRC 50-S and filtered. The filtrate was concentrated to an oily residue and purified by chromatography (cyclohexane/acetone 1:1, v/v) to give **21** (53 mg, 63%) as a white solid; $R_f$ 0.35 (ethyl acetate); mp: 98-99 °C (chloroform/hexane); $[\alpha]_D^{20}$ -36.4 ° (*c* 1, chloroform); $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.40-7.27 (m, 40H, Ar), 5.09 (s, 2H, PhC$\underline{H}_2$), 4.93 (m, 1H, H-1'), 4.98-4.59 (3d, 6H, J = 11.5 Hz, 3 x PhC$\underline{H}_2$), 4.32-4.23 (m, 3H, H-3, H-4, H-1"), 4.00 (m, 1H, H-5'), 3.87-3.82 (m, 2H, H-3', H-4"), 3.74 (m, 3H, H-2, H-6"), 3.65-3.61 (m, 4H, H-5, H-4', H-2"), 3.48 (m, 1H, H-3"), 3.38 (m, 1H, H-5"), 1.79-1.71 (br m, 1H, OH), 1.28 (m, 2H, H-6), 1.11 (d, 3H, $J_{5',6'}$ = 6.5 Hz, H-6'), 0.88 (m, 3H, H-7); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 128.5-127.5 (Ar), 103.9 (C-1', C-1"), 81.5 (C-4), 80.5 (C-3), 79.0 (C-3'), 77.5 (C-4'), 76.2 (C-2'), 74.8 (C-5"), 75.0-73.1 (Ph$\underline{C}H_2$), 73.2 (C-3"), 71.5 (C-2"), 69.2 (C-4"), 67.2 (C-5'), 67.0 (C-8), 62.4 (C-6"), 60.9 (C-2), 50.1 (C-5), 29.8 (C-6), 16.7 (C-6'), 10.7 (C-7); MS (DCI/$NH_3$): *m/z* 861 $[M + NH_4]^+$.

Anal. Calcd for $C_{47}H_{57}NO_{13}$: C, 66.89; H, 6.81; N, 1.66. Found: C, 66.81; H, 6.97; N, 1.90.

**4-*O*-(α-L-Fucopyranosyl)-3-*O*-(3-*O*-sodium sulfonato-β-D-galactopyranosyl)-(2*S*, 3*R*, 4*R*)-2-ethyl-3,4-dihydroxypyrrolidine (2).** A mixture of **21** (207 mg, 0.245 mmol) and dibutyltin oxide (62.5 mg, 0.245 mmol) in dry benzene (20 mL) was fitted with a Dean-Stark apparatus, and the solvent was concentrated to 5 mL by distillation. Benzene (20 mL) was then added and evaporated again to 5 mL. The solution was cooled to room temperature, and triethylamine-sulfur trioxide complex (57.8 mg,

0.319 mmol) was added. After stirring for 15 min, methanol (7 mL) was added, and the solvents were evaporated under reduced pressure. The residue was purified by chromatography (cyclohexane/acetone 1:3, v/v) to yield **22** (175 mg, 70%) as a white foam; $R_f$ 0.15 (cyclohexane/acetone 1:2, v/v); mp 163-164 °C (chloroform/cyclohexane); $[\alpha]_D^{20}$ -34.9 ° (*c* 1, chloroform); FAB (negative mode): *m/z* 922.4 $[M - NEt_3]^-$.

A mixture of **22** (120 mg, 0.117 mmol), acetic acid (2 mL) and 10% Pd/C (44 mg) in MeOH (10 mL) was stirred under an atmosphere of hydrogen until completion of the reaction. After filtration through Celite, the filtrate was concentrated to dryness, and the residue was dissolved in a 1N sodium hydroxide solution. The residue was concentrated, purified by chromatography (ethyl acetate/2-propanol/water 3:3:2, v/v/v) and lyophilized to afford **2** (35 mg, 55%) as a white solid; $R_f$ 0.22 (ethyl acetate/2-propanol/water 3:3:2 v/v/v); $[\alpha]_D^{20}$ -62.4 ° (*c* 0.55, $H_2O$); $^1H$ NMR (400 MHz, $D_2O$): 4.90 (d, 1H, $J_{1',2'}$ = 3.0 v/v/v); $[\alpha]_D^{20}$ -62.4 ° (*c* 0.55, $H_2O$); $^1H$ NMR (400 MHz, $D_2O$): 4.90 (d, 1H, $J_{1',2'}$ = 3.0 Hz, H-1'), 4.53 (br d, 1H, $J_{4,5}$ = 4.5 Hz, H-4), 4.50 (d, 1H, $J_{1'',2''}$ = 8.0 Hz, H-1''), 4.30 (br d, 1H, $J_{2,3}$ = 3.0 Hz, H-3), 4.16 (m, 2H, H-3'', H-4''), 3.91 (q, 1H, $J_{5',6'}$ = 6.5 Hz, H-5'), 3.65 (m, 6H, H-2, H-2', H-3', H-5'', H-6''), 3.50 (m, 2H, H-5a, H-2''), 3.36 (d, 1H, $J_{5a,5b}$ = 13.5 Hz, H-5b), 3.05 (m, 1H, H-4'), 1.76 (m, 2H, H-6), 1.09 (d, 3H, $J_{5',6'}$ = 6.5 Hz, H-6'), 0.91 (t, 3H, $J_{6,7}$ = 7.5 Hz, H-7); $^{13}C$ NMR (100 MHz, $D_2O$): 105.2 (C-1''), 100.2 (C-1'), 81.8 (C-3), 81.5 (C-3''), 80.3 (C-4), 70.6 (C-2''), 76.0-69.2 (C-2', C-3', C-4', C-5''), 69.0 (C-5'), 68.1 (C-4''), 65.3 (C-2), 62.1 (C-6''), 50.2 (C-5), 24.8 (C-6), 16.9 (C-6'), 11.7 (C-7); FAB: *m/z* 542.2 $[M + H]^+$, 564.2 $[M + Na]^+$.



## ACKNOWLEDGEMENTS

We wish to thank Ms Geneviève Flad for her excellent assistance and helpful comments regarding NMR spectroscopy. Thanks are also due to CNRS and Institut Curie for financial support and to MENRT for a fellowship (Elsa Dechaux).

## REFERENCES AND NOTES

1. Presented as a poster at the *First Euroconference on Carbohydrates in Drug Research*, Sardinia, September 16-19, 1999.
2. a) T. A. Springer, *Nature*, **346**, 425 (1990); b) L. Osborn and L. A. Lasky, *Science*, **258**, 964 (1992).
3. R. Kannagi, *Glycoconjugate J.*, **14**, 577(1997).

4. H. Nguyen, F. R. Eilber and S. A. Defrees, *Biochem. Biophys. Res. Commun*, **228**, 716 (1996).
5. a) T. A. Springer, *Ann. Rev. Physiol.*, **57**, 827 (1995); b) T. A. Springer, *Cell*, **76**, 301 (1994); c) P. S. Frenette and D. D. Wagner, *New Engl. J. Med.*, **43**, 335 (1996); d) S. D. Rosen and C. R. Bertozzi, *Curr. Opin. Cell Biol.*, **6**, 663 (1994); e) D. M. Lewinsohn, R. F. Bargatze and E. C. Butcher, *J. Immunol.*, **137**, 4343 (1987).
6. a) E. L. Berg, M. K. Robinson, O. Mansson, E. C. Butcher and J. L. Magnani, *J. Biol. Chem.*, **266**, 14869 (1991); b) M. L. Phillips, E. Nudelman, F. C. A. Grota, M. Perez, A. K. Singhal, S.-I. Hakomori and J. C. Paulson, *Science*, **250**, 1130 (1990).
7. a) D. Tyrell, P. James, N. Rao, C. Fowall, S. Abbas, F. Daasgupta, M. Nashed, A. Hasegawa, H. Kiso, D. Asa, J. Kidd and B. K. Brandley, *Proc. Natl. Acad. Sci. U.S.A.*, **88**, 10372 (1991); b) M. Lenter, A. Levinovitz, S. Isenmann and D. Vestweber, *J. Cell. Biol.*, **125**, 471 (1994).
8. J. B. Lowe, P. X. Ward, *J. Clin. Invest.*, **29**, 822 (1997).
9. a) *Carbohydrates in Drug Design*, W. J. Zbigniew, K. A. Nieforth, Chap. 3; b) E. Simanek, G. J. McGarvey, J. A. Jablonowski and C.-H. Wong, *Chem. Rev.*, **98**, 833 (1998).
10. a) W. Spevak, C. Foxall, D. H. Charych, F. Dasgupta and J. C. Nagy, *J. Med. Chem.*, **39**, 1018 (1996); b) D. D. Manning, L. E. Strong, X. Hu, P. J. Beck and L. L. Kiessling, *Tetrahedron*, **53**, 11937 (1997); c) S. A. Defrees, L. Philips, L. Guo, S. Zalipsky, *J. Am. Chem. Soc.*, **118**, 610 (1996); d) I. Saiki, C. Koike, A. Ebata, H. Fujii, J. Murata, M. Kiso, A. Hasegawa and H. Komesawa, *Int. J. Cancer*, **65**, 833 (1996).
11. M. Sakagami, K. Horie, K. Nakamoto, T. Kawaguchi and H. Hamana, *Bioorg. Med. Chem. Lett.*, **8**, 2783 (1998).
12. C. T. Yuen, A. M. Lawson, W. Chai, M. Larkin, M. S. Stoll, A. C. Stuart, F. X. Sullivan, T. J. Ahern and T. Feizi, *Biochemistry*, **31**, 9126 (1992); b) C. T. Yuen, K. Bezouska, J. O'Brien, M. Stoll, R. Lemoine, K. C. Nicolaou and T. Feizi, *J. Biol. Chem.*, **269**, 1595 (1994).
13. T. P. Kogan, B. H. Revelle, S. Japp, D. Scott and P. J. A. Beck, *J. Biol. Chem.*, **270**, 14047 (1995); b) H. Tsujushita, V. Hiramatsu, N. Kondo, H. Ohmoto, H. Kondo, M. Kiso and A. Hasegawa, *J. Med. Chem.*, **40**, 362 (1997).
14. L. J. Liotta and B. Ganem, *Synlett*, **9**, 503 (1990).
15. N. K. Richtmyer, *Methods in Carbohydr. Chem .*, **1**, 107 (1962).
16. S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 503 (1990).
17. H. P. Wessel, T. Iversen and D. R. Bundle, *J. Chem. Soc., Perkin Trans. 1*, 2247 (1985).
18. N. Chida, M. Ohtsuda, K. Nakazawa and S. Ogawa, *J. Org. Chem.*, **56**, 2976 (1991).
19. W. A. Szarek, A. Zamojski, K. N. Tiwari and E. R. Ison, *Tetrahedron Lett.*, **33**, 3827 (1986).
20. P. J. Garegg and B. J. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, 2866 (1980).
21. R. C. Bernotas, *Tetrahedron Lett.*, **31**, 469 (1990).
22 M. Dejter-Juszynsky and H. M. Flowers, *Carbohydr. Res.*, **18**, 219 (1971).
23. S. J. Danishefsky, J. Gervay, J. M. Peterson, F. E. McDonald, K. Koseki, D. A. Griffith, T. Oriyama and S. P. Mardsen, *J. Am. Chem. Soc.*, **117**, 1940 (1995).
24. S. Jacobsen and O. Mols, *Acta Chem. Scand. Ser. B*, **35**, 163 (1981).
25. U. Spohr, M. Bach and R. G. Spiro, *Can J. Chem.*, **71**, 1928 (1993).
26. J. Banoub and D. R. Bundle, *Can. J. Chem.*, **57**, 2091 (1979).
27. W. J. Saunders, D. D. Manning, K. M. Koeller and L. L. Kiessling, *Tetrahedron*, **53**, 16391 (1997).
28. R. R. Schmidt and W. Kinzy, *Adv. Carbohydr. Chem. Biochem.*, **50**, 19 (1994).
29. B. Classon, P. J. Garegg and A.-C. Helland, *J. Carbohydr. Chem.*, **8**, 543 (1989).

30. I. Lundt and C. Pedersen, *Acta Chem. Scand., Ser. B*, **30**, 680 (1976).
31. G. Rubinstein, PhD Thesis, University of Paris 6, 1996.
32. For previously reported replacement of the *N*-acetylglucosamine scaffold by a nitrogenous heterocycle (*N*-methyl-1-deoxynojirimycin), see: M. Kiso, H. Furui, H. Ishida and A. Hasegawa, *J. Carbohydr. Chem.*, **15**, 1 (1996).