A Highly Efficient Synthetic Strategy for Polymeric Support Synthesis of Le^x, Le^y, and H-type 2 Oligosaccharides

Tong Zhu and Geert-Jan Boons*[a]

Abstract: The O-protecting groups Levulinoyl (Lev) and 9-fluroenylmethoxycarbonyl (Fmoc) offer an attractive set of orthogonal protecting groups which are compatible with base sensitive *N*-trichloroethoxylcarbonyl (Troc) group. By exploiting these orthogonal protecting groups and a novel phenolic ester linker, a series of oligosaccharide of biological importance, Le^x, H-type 2, and Le^y, were synthesized on the polytheylene glycol resin MPEG (M_W 5000). The products bearing a *p*-hydroxybenzyl group could be easily converted into glycosyl donors for further synthesis. Using this strategy, a spacer containing tumor antigen Le^y-Lac hexasaccharide was described. The artificial spacer at the reducing end provides an opportunity for selective conjugation to an appropriate carrier protein for immunlogical studies.

Keywords: glycosylation · oligosaccharides · polymeric support · synthetic methods · tumor antigens

Introduction

Traditional methods of oligosaccharide synthesis involve the preparation of one target compound at the time. This approach is very time consuming and does not allow the synthesis of large collections of oligosaccharides for structure–function relationship studies. Recent developments[1] in oligosaccharide chemistry focus on the preparation of compound libraries either by parallel synthesis or by a mix and split approach.[2] In particular, the use of monosaccharide building blocks that are substituted with orthogonal protecting groups proved to be attractive for parallel synthesis of collections of oligosaccharides. For example, Wong and coworkers reported[3] that chloroacetyl (ClAc), *p*-methoxybenzyl (PMB), levulinoyl (Lev), and *tert*-butyldiphenylsilyl (TBDPS) are a set of orthogonal protecting groups that in conjunction with seven different glycosyl donors could, in principle, be used for the synthesis of 1176 different trisaccharides.

Recently, we reported[4, 5] that the Fmoc, Lev, and diethylisopropylsilyl (DEIPS) are an attractive set orthogonal hydroxyl protecting groups for amino sugars. The Fmoc group can be cleaved by β-elimination using the sterically hindered base triethylamine in CH_2Cl_2 and these mild conditions did not affecting the Lev or DEIPS group. On the other hand, the Lev ester could be removed with hydrazine acetate in THF. This reaction proceeds by a different mechanism than the cleavage of Fmoc and involves reaction of hydrazine acetate with the ketone moiety of Lev to give a hydrazone intermediate which cyclizes to give a deprotected alcohol. We found that hydrazine acetate did not remove an Fmoc or DEIPS protecting group. The DEIPS could be removed by treatment with TBAF that was buffered with acetic acid and these conditions did not affect the other two protecting group. In addition, the cleavage conditions for the three protecting groups did not affect base sensitive amino protecting group trichloroethoxycarbonyl (Troc).

Further speed of synthesis of oligosaccharides may be achieved by employing polymer-supported synthesis.[6] Several elegant syntheses of oligosaccharides on insoluble polymers have been reported.[7] These approaches were, however, hampered by the need to use large excesses of glycosyl donor or acceptor to drive reactions to completion. This represents a serious drawback since oligosaccharide chemistry requires elaborate and expensive synthesis of glycosyl donors and acceptors. In addition, the rate of reactions on a solid support is often considerably slower compared with similar reactions in solution. This feature makes it difficult to extrapolate solution phase conditions to solid-supported procedures.

These problems have been addressed by replacing insoluble cross-linked resins with soluble polymer supports.[8] In this way, reaction conditions typical for classical organic reactions can be employed while product purification can be facilitated by taking advantage of the macromolecular properties of the polymer. Polyethylene glycol methyl ether (MPEG) is the most widely used polymer for liquid phase oligosaccharide syntheses.[9] It is soluble under glycosylation and protecting

[a] Prof. G.-J. Boons, Dr. T. Zhu
Complex Carbohydrate Research Center
University of Georgia, 220 Riverbend Road
Athens, GA 30602-4712 (USA)
Fax: (+1)706-5424412
E-mail: gjboons@ccrc.uga.edu

  0947-6539/01/0711-2382 $ 17.50+.50/0

group manipulation conditions. However, MPEG is made insoluble during the work-up procedure by the simple addition of diethyl ether or *tert*-butylmethyl ether. Excess of reagents and other side products can thus be easily removed by washing the MPEG precipitate.

Recently, we described a highly efficient strategy for the MPEG-supported synthesis of the dimeric Lewis antigen Lewis^x–Lewis^x (Le^x–Le^x),[5] whereby a polymer bound Le^x trisaccharide was prepared which could be converted into a glycosyl acceptor by selective removal of a temporary protecting group or into a soluble glycosyl donor by cleavage from the polymeric support followed by activation of the anomeric center. Coupling of the resulting glycosyl donor and acceptor followed by cleavage from the solid support gave the target hexasaccharide. A novel phenolic ester linker was employed that attaches a saccharide to a polymeric support through the anomeric center of the reducing sugar (Figure 1).

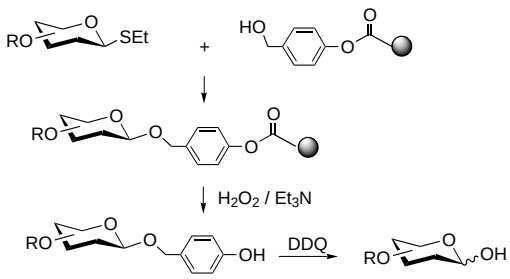


Figure 1. Concept of phenolic ester linker.

The new linker is stable towards Lewis acidic conditions used in glycosylations but could be cleaved within minutes by treatment with hydrogen peroxide/Et_3N. After detachment, a stable *p*-hydroxyl benzyl glycoside is obtained as a single anomer and this feature facilitates purification. Oxidative removal of the *p*-hydroxyl benzyl moiety with DDQ gives a lactol that can be easily converted into a glycosyl donor. The linker proved to be compatible with the base sensitive amino protecting group trichloroethoxycarbonyl (Troc) and the temporary hydroxyl protecting groups 9-fluorenylmethoxycarbonyl (Fmoc) and diethylisopropylsilyl (DEIPS).

The use of a set of orthogonal protecting groups in combination with polymer-supported synthesis should offer an exciting opportunity to obtain a range of well-defined structures in a fast and facile manner. Herein, we report such an approach whereby Fmoc and Lev are employed as orthogonal protecting groups for Troc protected amino sugars and a novel phenolic ester linker for facile temporary attachment of oligosaccharides to a polymeric support. The methodology was applied to the synthesis of the blood group oligosaccharides Le^x, Le^y and H-type 2 oligosaccharide.

Results and Discussion

The oligosaccharides Le^x, Le^y, and H-type 2 oligosaccharide have a common β-D-Gal-(1 $\rightarrow$ 4)-D-GlcNAc core structure but differ in their fucose substitution pattern. Le^y has fucosides at C-3 of the GlcNAc and C-2 of the Gal moiety whereas Le^x has only one fucose residue at C-3 of the GlcNAc and H-type 2 oligosaccharide has one fucose moiety at C-2 of Gal (Figure 2).

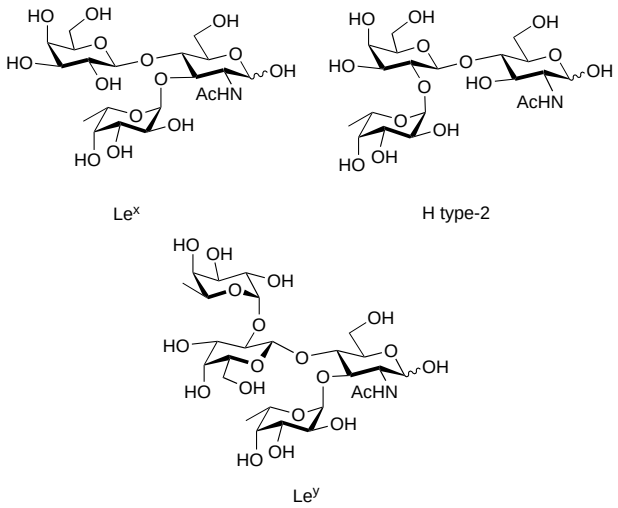
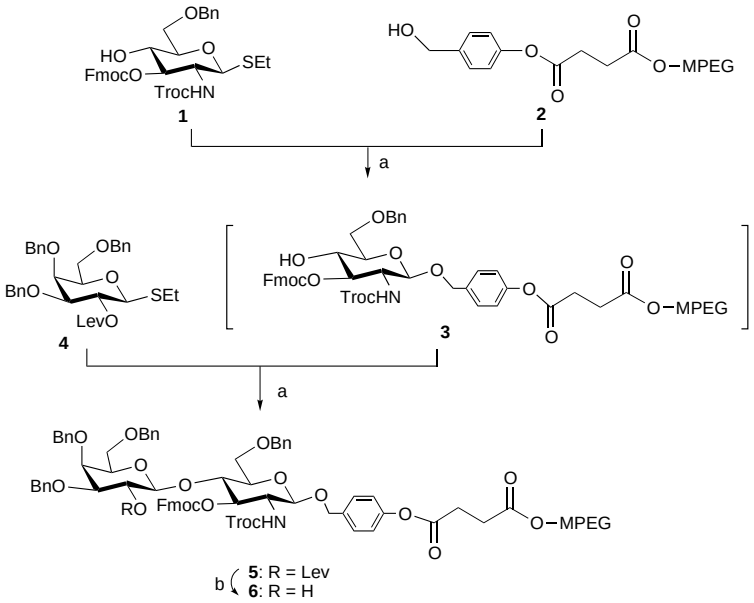


Figure 2. Structures Le^x, H type-2, and Le^y oligosaccharides.

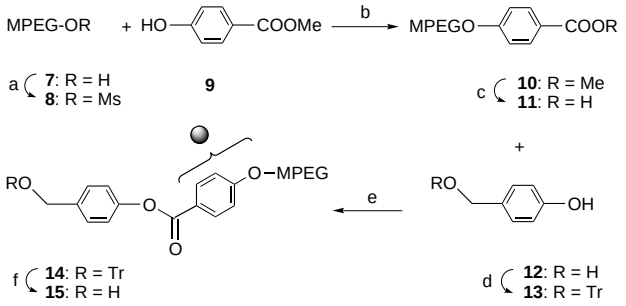
It was anticipated that the polymer-bound disaccharide **5** (see Scheme 1), which is functionalized with orthogonal Fmoc and Lev protecting groups, should be an appropriate precursor for the synthesis of the three oligosaccharides. Furthermore, the Troc protecting group of the glucosamine moiety should ensure high glycosyl accepting properties of its C-3 hydroxyl.[5, 10] This issue is important because several studies[5, 10] have shown that the C-3 hydroxyl can not be glycosylated when a phthaloyl is used as an amino protecting group. The oligosaccharides will be attached to MPEG by the versatile phenolic ester linker **2** (Scheme 1).



Scheme 1. Synthesis of a polymer bound disaccharide **6**.a) NIS, TMSOTf, MS 4 Å, 0 °C, CH_2Cl_2; b) $NH_2NH_2 \cdot HOAc$, MeOH, CH_2Cl_2.

Coupling of **1** with **2** in the presence of *N*-iodosuccinimide/trimethylsilyl trifluoromethanesulfonate (NIS/TMSOTf)[11] gave immobilized **3** (Scheme 1). Only 1.1 equivalent of glycosyl donor **1** was required to achieve complete conversion of the polymeric acceptor. No self-condensation of **1** was observed which was expected due to the much greater reactivity of the benzylic alcohol of **2** compared with the C-4 hydroxyl of **1**. The polymer bound monosaccharide **3**, bearing a free C-4 hydroxyl, was immediately used in a subsequent glycosylation without work-up and purification by precipitation. Thus, addition to the reaction mixture of another amount of NIS/TMSOTf and galactosyl donor **4** gave, after standard work-up and purification by precipitation, immobilized disaccharide **5**. The NMR spectrum indicated clean formation of **5** and no production of truncated or incomplete glycosylated structures. Furthermore, the Lev protecting group of **4** performed neighboring group participation during the glycosylation ensuring exclusive formation of a β-glycoside. Next, the Lev of **5** was removed by the treatment with hydrazine acetate in dichloromethane/methanol to give acceptor **6**. Unfortunately, this reaction resulted in partial cleavage of the disaccharide from the polymeric support.

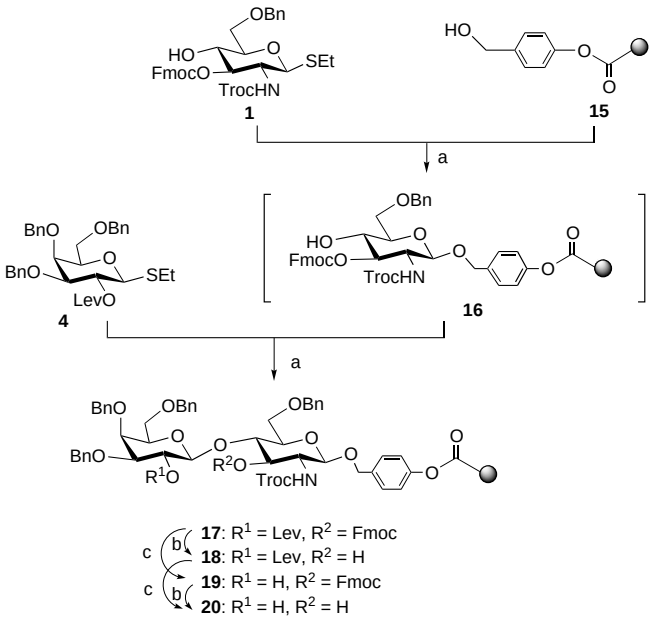
To address this problem, a new phenolic ester linker was developed. This new linker should be more stable towards basic and nucleophilic reaction conditions than the initial linker system **2**. However, it should be sensitive towards H_2O_2/Et_3N to allow selective cleavage from the polymeric support without affecting acyl and *N*-Troc protecting groups. It was anticipated that the polymer bound linker **15** would possess these properties (Scheme 2).



Scheme 2. Attachment of linker to MPEG. a) MsCl, Et_3N, CH_2Cl_2; b) Cs_2CO_3, DMF, 60 °C; c) NaOH, MeOH, H_2O; d) TrCl, py; e) DCC, DMAP, CH_2Cl_2; f) TFA, TESH, CH_2Cl_2.

The mesylate **8**,[12] which was obtained by reaction of MPEG (M_W 5000) with mesyl chloride, was treated with methyl 4-hydroxylbenzoate (**9**) and Cs_2CO_3 in DMF to give polymer bound ester **10** in an excellent yield (>95%).[13] Hydrolysis of this methyl ester of **10** with 2 M aqueous NaOH, followed by dicyclohexylcarbodimide/4-dimethylaminopyridine (DCC/DMAP) mediated coupling with phenol **13** gave the phenolic ester **14**. The trityl group of **14** was easily removed with 5% trifluoroacetic acid in dichloromethane using triethylsilane as a trityl cation scavenger to afford the linker modified MPEG **15** (Scheme 2).

Regioselective coupling of modified MPEG **15** with glycosyl donor **1** (1.1 equiv) in the presence of NIS/TMSOTf gave polymer bound **16** (see Scheme 3), which was immediately used in the next glycosylation step with thioglycosyl donor **4** to afford **17**. The immobilized disaccharide **17**, which is substituted with the orthogonal protecting groups, Fmoc and Lev, is an ideal precursor for the synthesis of the Le^x, Le^y, and H-type 2 oligosaccharides. Thus, the Fmoc[14] group of **17** was removed by the treatment with non-nucleophilic base triethylamine in dichloromethane to give acceptor **18**. On the other hand, removal of the Lev[15] group of **17** could easily be accomplished by treatment with hydrazine acetate in dichloromethane/methanol to give **19**. The polymer bound diol **20** was easily obtained by removal of the Fmoc group of **19** under standard conditions (Scheme 3).

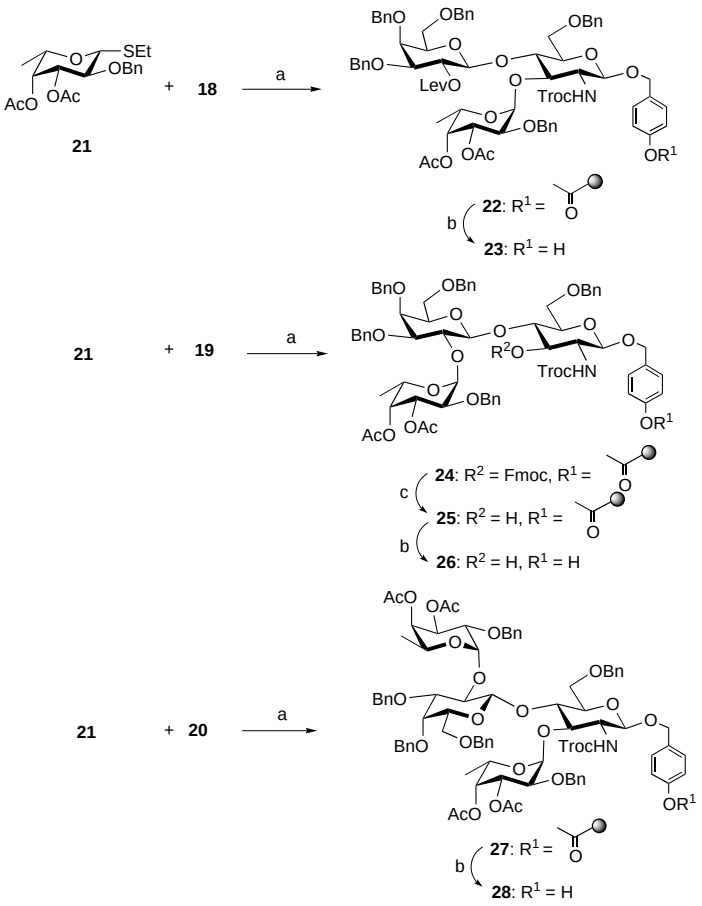


Scheme 3. Synthesis of disaccharide building blocks. a) NIS, TMSOTf, MS 4 Å, 0 °C, CH_2Cl_2; b) Et_3N, CH_2Cl_2; c) NH_2NH_2.HOAc, MeOH, CH_2Cl_2.

In each reaction, complete orthogonality of Lev and Fmoc and no cleavage of the phenolic ester and *N*-Troc group was found; this demonstrates that linker system **15** is more appropriate for the synthesis of the target structures. Fucosylation of **18**, **19**, and **20** was performed with thioglycosyl donor **21** and NIS/TMSOTf as the promoter system to produce polymer bound **22**, **24**, and tetrasaccharide **27**, respectively. The Le^y tetrasaccharide **27** could also be synthesized in a stepwise manner whereby the Fmoc of **24** was removed to give **25**, which was coupled with **21** (Scheme 4). Interestingly only a very small amount of fucosylated product was formed when the amino function of the glycosamine moiety was protected by a phthaloyl instead of trichloroethoxycarbonyl group.

The compounds **23, 26**, and **28** were cleaved from the polymeric support by treatment with H_2O_2/Et_3N in THF for 18 h to give the protected Le^x trisaccharide **23**, H-type 2 trisaccharide **26**, and Le^y tetrasaccharide **28** in overall yields of

0947-6539/01/0711-2384 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 11

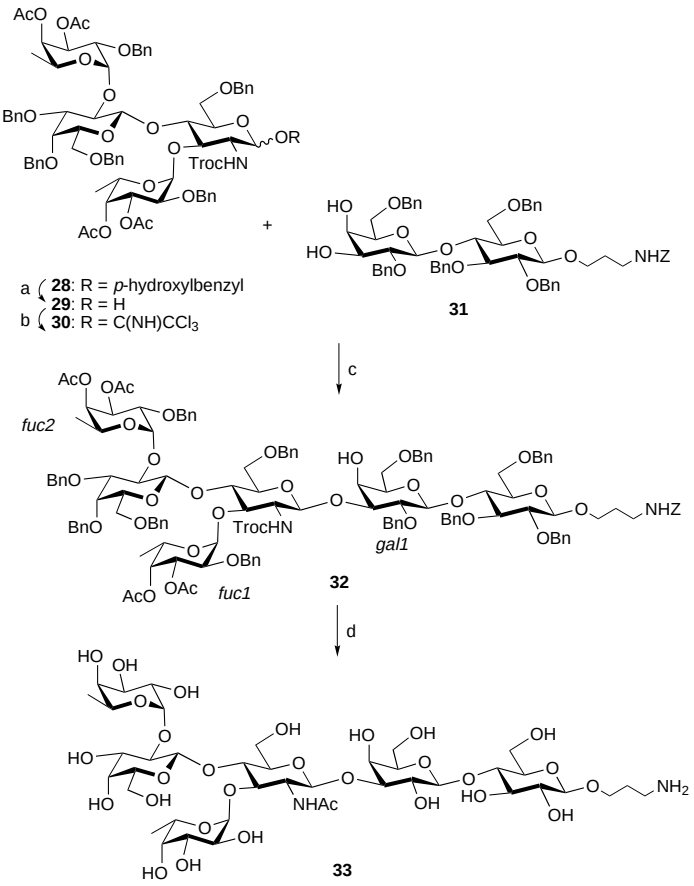


Scheme 4. Syntheses of Le^x, H-type 2, and Le^y oligosaccharides. a) NIS, TMSOTf, MS 4 Å, 0 °C, CH_2Cl_2; b) H_2O_2, Et_3N, THF; c) Et_3N, CH_2Cl_2.

30–35 % (based on the loading of MPEG 5000, 0.2 mmol per g) (Scheme 4). Under similar conditions, cleavage of linker **2** was completed within 30 min, demonstrating the difference in stability between **2** and **15**.

In conjunction with a research program[5, 16] to develop synthetic carbohydrate-based anticancer vaccines, we required tumor-associated saccharides that are substituted with an artificial spacer for selective conjugation to an appropriate carrier protein.[17] In particular, the Le^y determinant was important because it is over-expressed on human gastrointestinal, colorectal, breast, and lung cancer cells and has been identified as an important epitope that can elicit selective antibodies against colon and liver carcinomas.[18] The protected Le^y tetrasaccharide **28** was converted into glycosyl donor **30** which was coupled with the spacer modified lactosyl acceptor **31** and the resulting hexasaccharide **32** was deprotected to give compound **33** which is a suitable derivative for selective conjugation to carrier proteins.

Thus, oxidative removal of the anomeric *p*-hydroxylbenzyl group of compound **28** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[19] gave hemiacetal **29** (82 %), which was subsequently treated with trichloroacetonitrile in the presence of catalytic amount of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU)[20] to give trichloroacetimidate **30** in 85 % yield. Next, $BF_3 \cdot Et_2O$[20] mediated coupling of **30** with acceptor **31**[21] gave the desired hexasaccharide **32** in 54 % yield. Compound **32** was deprotected by a four-step procedure. The Troc group was removed by treatment with activated zinc in acetic acid[22] and the revealed amino function was acetylated with acetic anhydride in pyridine. The *O*-acetyl groups were removed under Zemplén conditions and finally, the benzyloxylcarbonyl and benzyl groups were removed by catalytic hydrogenation over palladium to give the target compound **33** in an overall 85 % yield (Scheme 5).



Scheme 5. Synthesis of hexasaccharide **33**. a) DDQ, CH_2Cl_2/H_2O 19:1 *v/v*, 82 %; b) CCl_3CN, DBU, CH_2Cl_2, 85 %; c) $BF_3 \cdot Et_2O$, CH_2Cl_2, MS 4 Å, 54 %; d) 1) Zn, HOAc; 2) Ac_2O, py; 3) MeONa, MeOH; 4) Pd/C, EtOH, HOAc, H_2. Z = Benzyloxycarbonyl.

Conclusion

A range of biologically important oligosaccharides (Le^x, H type-2, and Le^y) have been prepared by employing solvent soluble polymeric support synthesis in combination with the orthogonal protecting group Lev and Fmoc. The Troc was used as an amino protecting group to ensure high glycosylating properties of a C-3 hydroxyl of a glucosamine unit. The neutral or mild basic conditions used to remove Lev and Fmoc were compatible with base sensitive Troc moiety. Another key feature of this synthetic strategy was the use of a novel phenolic ester linker which is stable under the protecting group manipulation and glycosylation conditions but can easily be cleaved under mild conditions using H_2O_2/Et_3N. This cleavage reaction gives a product with an anomeric *p*-

hydroxybenzyl group, which can be removed by oxidation with DDQ. The resulting lactol can be converted into a corresponding trichloroacetimidate for further glycosylations. The latter sequence of manipulations was employed for the synthesis of the tumor-associated hexasaccharide "Le^y-Lac" bearing an artificial aminopropyl spacer for controlled conjugation to proteins.

The synthetic strategy described here allows the facile synthesis of many other biologically important oligosaccharides from a small set of common monosaccharide precursors. For example, the Lewis antigens Le^a and Le^b can also be prepared from building blocks **1**, **4**, and **21** by different sequence of glycosylation and furthermore, a wide range of dimeric Lewis antigens can be obtained by incorporating a DEIPS protecting group at the C-3 hydroxyl of a galactosyl moiety. This silyl ether is also compatible with the linker and orthogonal with the Lev and Fmoc protecting groups.

Experimental Section

General: Chemicals were purchased from Aldrich, Acros, and Fluka and used without further purification. Molecular sieves were activated at 350 °C in vacuo for 3 h. All solvents were distilled from the appropriate drying agents. All the reactions were performed under anhydrous conditions and monitored by TLC on aluminum Kieselgel 60 F_{254} (Merck). Detection was done under UV light (254 nm) and by charring with 10 % sulfuric acid in methanol. Column chromatography was performed on silica gel (Merck, 70 – 230 mesh). Size-exclusion column chromatography was performed on Sephadex LH-20 (Pharmacia Biotech AB, Uppsala Sweden) and dichloromethane/methanol 1:1 (*v*/*v*) was used as eluent. Organoc extracts were concentrated under reduced pressure at <40 °C (bath). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova500 spectrometer and a Varian Inova600 spectrometer equipped with Sun workstations. ^{1}H NMR spectra recorded in $CDCl_3$ were referenced to residue $CHCl_3$ at $\delta = 7.26$, and ^{13}C NMR spectra to the central peak of $CDCl_3$ at $\delta = 77.0$. Assignments were made by standard gCOSY, gHSQC, TOCSY, and gHMBC experiments. For polymer bound samples, the glycol peak of MPEG was suppressed by saturation at $\delta = 3.64$ and the terminal methyl signal of MPEG ($\delta = 3.38$) was used as internal standard for quantitation. Negative ion matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectra were recorded using an HP-MALDI instrument using gentisic acid as a matrix.

***p*-MPEG-oxy-benzoic acid (11)**: Cs_2CO_3 (2.61 g, 8.0 mmol) was added to a solution of MPEG mesylate **8** (10 g, 2.0 mmol) and methyl *p*-hydroxybenzoate (**9**, 1.22 g, 8.0 mmol) in DMF (80 mL) and the mixture was stirred at 60 °C under nitrogen for 24 h. After the reaction mixture was cooled to room temperature, excess of DOWEX-50 H^+ resin was added and the stirring was continued for an additional 0.5 h. The resin was removed by filtration, the filtrate was concentrated to dryness under reduced pressure, and redissolved in dichloromethane (250 mL). The mixture was filtered through celite and washed with dichloromethane (60 mL). The combined filtrate/washings were concentrated to a small volume (20 mL), which was cooled (0 °C), followed by the addition of anhydrous diethyl ether (1500 mL) with vigorous stirring. The precipitated material was collected by filtration, washed with diethyl ether (150 mL). The obtained MPEG bound compound **10** was dissolved in THF/MeOH (300 mL, 1:1 *v*/*v*) and 2 M aqueous NaOH solution (150 mL) was added. The reaction mixture was stirred at room temperature for 18 h after which 3 M HCl aqueous solution (100 mL) was added. The mixture was concentrated to dryness under reduced pressure, diluted with dichloromethane (250 mL) and filtered. The filtrate was concentrated under reduced pressure to a small volume (20 mL), and triturated with diethyl ether (1500 mL). The resulting solid was filtered-off, washed with diethyl ether and dried in vacuo to give **11** (10.1 g) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.00$ (d, $J =$ 8.8 Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 4.20 (t, $J = 4.8$ Hz, 2H), 3.90 – 3.48 (m, PEGCH_2), 3.38 (s, 3H, OCH_3).

***p*-Hydroxymethylphenyl *p*-MPEG-oxy-benzoate (15)**: A mixture of MPEG derivative **11** (10 g, 2.0 mmol) and compound **13** (1.40 g, 4.0 mmol) was dried over P_2O_5 at high vacuum for 12 h. This mixture was dissolved in dichloromethane (100 mL), and a catalytic amount of DMAP (25 mg), followed by DCC (1.66 g, 8.0 mmol) was added. The solution turned cloudy within 15 min and was stirred for 18 h at room temperature. The precipitated urea was removed by filtration, washed with dichloromethane and the combined filtrates were concentrated to dryness. The residue was dissolved in dichloromethane (30 mL), cooled (0 °C) and diethyl ether (1500 mL) was added with vigorous stirring. The precipitate was filtered-off and washed with diethyl ether (2×40 mL) and cold ethanol (2×40 mL) and dried in vacuo. The obtained compound **14** was dissolved in dichloromethane (150 mL), and triethylsilane (6.0 mL), followed by trifluoroacetic acid (6.0 mL), was added. The reaction mixture was stirred at room temperature for 30 min and was then diluted with toluene (200 mL). The resulting solution was concentrated to dryness and the residue was redissolved in dichloromethane (30 mL), and triturated with diethyl ether (1500 mL). The precipitate was recovered by filtration and washed with diethyl ether (100 mL) to give **15** after drying under high vacuum as a white solid (9.6 g). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.14$ (d, $J = 8.8$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.01 (d, $J = 8.8$ Hz, 2H), 4.72 (s, 2H; OPhCH_2OH), 4.23 (t, $J = 4.8$ Hz, 2H), 3.92 – 3.48 (m, PEGCH_2), 3.38 (s, 3H; OCH_3).

***p*-(*p*-MPEG-oxy-benzoyloxy)-benzyl 6-*O*-benzyl-2-deoxy-2-[[(2,2,2-trichloroethoxy)carbonyl]amino]-3-*O*-(9-fluorenylmethoxycarbonyl)-4-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-levulinoyl-*β*-D-galatopyranosyl)-*β*-D-glucopyranoside (17)**: A solution of thioglycoside **1** (78 mg, 0.11 mmol) and MPEG-bound compound **15** (523 mg, 0.10 mmol) was stirred at room temperature under Ar in the presence of activated molecular sieves 4 Å for 30 min. The mixture was cooled in an ice bath and NIS (27 mg, 0.12 mmol) was added followed by TMSOTf (1 μL). After the donor was consumed (monitored by TLC, ethyl acetate/hexanes 1:2 *v*/*v*), compound **4** (118 mg, 0.20 mmol) and NIS (49 mg, 0.22 mmol) were added to the reaction mixture followed by TMSOTf (2 μL) and the reaction mixture was stirred at 0 °C for 0.5 h. The reaction mixture was diluted with dichloromethane (100 mL) and molecular sieves were removed by filtration. Aqueous $Na_2S_2O_3$ (15 %, 4 mL) was added to the filtrate and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to the volume of 4 mL. Diethyl ether (100 mL) was added at 0 °C with vigorous stirring. The precipitate was recovered by filtration, washed with diethyl ether (20 mL) and dried under high vacuum to give compound **17** as a white solid (583 mg). Selected ^{1}H NMR data (600 MHz, $CDCl_3$): $\delta = 8.13$ (d, $J = 8.8$ Hz, 2H, Ar-H), 7.74 (t, $J = 8.5$ Hz, 2H; Ar-H, Fmoc), 7.53 – 7.09 (m, Ar-H), 7.00 (d, $J = 8.8$ Hz, 2H; Ar-H), 5.26 (t, $J = 9.3$ Hz, 1H; H-2′), 5.16 (d, $J = 8.3$ Hz, 1H; N*H*), 4.96 (t, $J = 9.3$ Hz, 1H; H-3), 2.71 – 2.32 (m, 4H; CH_2CH_2, Lev), 2.12 (s, 3H; $COCH_3$, Lev).

***p*-(*p*-MPEG-oxy-benzoyloxy)-benzyl 6-*O*-benzyl-2-deoxy-2-[[(2,2,2-trichloroethoxy)carbonyl]amino]-4-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-levulinoyl-*β*-D-galatopyranosyl)-*β*-D-glucopyranoside (18)**: MPEG bound compound **17** (200 mg) was dissolved in dichloromethane (4 mL) and triethylamine (1.0 mL) was added. The reaction mixture was stirred at room temperature for 18 h and then concentrated to dryness under reduced pressure. The residue was redissolved in dichloromethane (3 mL) and diethyl ether (80 mL) was added at 0 °C with vigorous stirring for 0.5 h. The precipitated solid was collected by filtration and washed with diethyl ether (10 mL) to give, after drying under high vacuum, compound **18** (176 mg) as a white solid. Selected ^{1}H NMR data (500 MHz, $CDCl_3$): $\delta = 8.15$ (d, $J = 8.8$ Hz, 2H; Ar-H), 7.39 – 7.22 (m, Ar-H), 7.14 (d, $J = 8.4$ Hz, 2H; Ar-H), 6.98 (d, $J = 8.8$ Hz, 2H; Ar-H), 5.32 (dd, $J = 10.1$, 8.2 Hz, 1H; H-2′), 5.04 (br s, 1H; N*H*), 4.58 (d, $J = 8.2$ Hz, 1H; H-1), 4.35 (d, $J = 7.7$ Hz, 1H; H-1′), 3.42 (dd, $J = 10.1$, 2.4 Hz, 1H; H-3′), 2.76 – 2.40 (m, 4H; CH_2CH_2, Lev), 2.12 (s, 3H; $COCH_3$, Lev).

***p*-(*p*-MPEG-oxy-benzoyloxy)-benzyl 6-*O*-benzyl-2-deoxy-2-[[(2,2,2-trichloroethoxy)carbonyl]amino]-3-*O*-(9-fluorenylmethoxycarbonyl)-4-*O*-(3,4,6-tri-*O*-benzyl-*β*-D-galatopyranosyl)-*β*-D-glucopyranoside (19)**: A solution of hydrazine acetate (7 mg) in methanol (0.2 mL) was added to a stirred solution of compound **17** (200 mg) in dichloromethane (4 mL) and the reaction mixture was kept stirring at room temperature for 2 h. Acetonylacetone (0.1 mL) was added to quench the reaction and the solvents were evaporated in vacuo. The residue was redissolved in dichloromethane (3 mL) and diethyl ether (80 mL) was added at 0 °C with

0947-6539/01/0711-2386 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 11

vigorous stirring for 0.5 h. The precipitated solid was collected by filtration and washed with diethyl ether (10 mL) and dried under high vacuum to give compound **19** (183 mg) as a white solid. Selected ^{1}H NMR (600 MHz, $CDCl_3$) data: $\delta = 8.11$ (d, $J = 7.7$ Hz, 2H; Ar-H), 7.72 (t, $J = 8.5$ Hz, 2H; Ar-H, Fmoc), 7.51–7.04 (m, Ar-H), 6.98 (d, $J = 7.7$ Hz, 2H; Ar-H), 5.12 (d, $J = 8.4$ Hz, 1H; N*H*), 5.01 (dd, $J = 10.5$, 8.5 Hz, 1H; H-3), 4.08 (t, $J = 8.4$ Hz, 1H; H-4), 4.02 (t, $J = 8.4$ Hz, 1H; H-3), 3.28 (dd, $J = 10.0$, 2.4 Hz, 1H; H-3′).

***p*-(*p*-MPEG-oxy-benzoyloxy)-benzyl 6-*O*-benzyl-2-deoxy-2-[[(2,2,2-trichloroethoxy)carbonyl]amino]-4-*O*-(3,4,6-tri-*O*-benzyl-β-D-galatopyranosyl)-β-D-glucopyranoside (20)**

Method A: The Fmoc group of compound **19** (200 mg) was removed by treatment with 20% triethylamine in dichloromethane as described for the preparation of compound **18**. Compound **20** was obtained as a white solid (178 mg).

Method B: The MPEG bound compound **18** (200 mg) was treated with hydrazine acetate in methanol/dichloromethane as described for the preparation of compound **19** to give the title product as a white solid (184 mg).

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.13$ (d, $J = 8.8$ Hz, 2H; Ar-H), 7.39–7.24 (m, Ar-H), 7.14 (d, $J = 8.4$ Hz, 2H; Ar-H), 6.98 (d, $J = 7.7$ Hz, 2H; Ar-H), 5.11 (br s, 1H; N*H*), 4.27 (d, $J = 7.8$ Hz, 1H; H-1′), 3.36 (dd, $J = 10.1$, 2.4 Hz, 1H; H-3′).

General procedure for the cleavage of product from MPEG: The MPEG bound compound (0.02 mmol) was dissolved in THF (2 mL) and Et_3N (0.1 mL) and H_2O_2 (50% in water, 0.03 mL) were added. After being stirred at room temperature for 18 h, the reaction mixture was diluted with toluene (5 mL) and concentrated to a small volume (0.5 mL) under reduced pressure. The residue was diluted with dichloromethane (1 mL) and diethyl ether (40 mL) was added. The solid was filtered off and the filtrate was concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography or size-exclusion chromatography.

***p*-Hydroxybenzyl 6-*O*-benzyl-2-deoxy-2-[[(2,2,2-trichloroethoxy)carbonyl]-amino]-3-*O*-(3,4-di-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-levulinoyl-β-D-galatopyranosyl)-β-D-glucopyranoside (23)**: A solution of compound **21** (38 mg, 0.1 mmol) and polymer bound compound **18** (100 mg) in dichloromethane (4 mL) was stirred in the presence of molecular sieves 4 Å for 30 min. The mixture was cooled (0 °C, ice bath) and NIS (25 mg, 0.11 mmol) and TMSOTf (1 μL) were added. After 30 minutes, TLC analysis (ethyl acetate/hexanes 1:3 *v*/*v*) indicated that all the thioglycoside **21** had been consumed. The reaction mixture was diluted with dichloromethane (60 mL) and the molecular sieves were removed by filtration. The filtrate was washed with aqueous sodium thiosulfate (15%, 4 mL) and concentrated to a small volume (3 mL). Diethyl ether (80 mL) was added at 0 °C with vigorous stirring. The precipitated white solid was collected by filtration and washed with diethyl ether (10 mL) to give compound **22** (97 mg) as a white solid. The crude product was cleaved from the polymeric support as described in the general procedure, followed by purification on an LH-20 size exclusion column (eluent: methanol/dichloromethane 1:1 *v*/*v*) to give the title product **23** as a colorless syrup (8 mg). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.35$–7.16 (m, 25H; Ar-H, 5 × Bn), 7.14 (d, 2H; Ar-H, *p*-hydroxybenzyl), 6.75 (d, 2H; Ar-H, *p*-hydroxybenzyl), 5.30 (d, $J = 8.0$ Hz, 1H; N*H*), 5.25 (dd, $J = 10.5$, 3.5 Hz, 1H; H-3″), 5.22 (d, $J = 2.5$ Hz, 1H; H-4″), 5.18–5.13 (m, 2H, H-1″; H-2′), 4.96 (q, $J = 6.0$ Hz, 1H; H-5″), 4.94 (d, $J = 11.0$ Hz, 1H; H-1), 4.76–4.32 (m, 15H; 5 × OC*H*$_2$Ph, OC*H*$_2$PhOH, OC*H*$_2$CCl$_3$, H-1′), 4.14 (t, $J =$ 9,5 Hz, 1H; H-3), 3.98 (t, 1H; H-4), 3.90 (d, $J = 2.5$ Hz, 1H; H-4′), 3.88–3.73 (m, 5H; H-6′a, H-6a, H-2″, H-6′b, H-6b), 3.43 (d, $J = 9.0$ Hz, 1H; H-5), 3.26 (dd, $J = 8.5$, 5.0 Hz, 1H; H-5′), 3.23 (dd, $J = 10.0$, 2.5 Hz, 1H; H-3′), 3.16 (dt, 1H; H-2), 2.81–2.40 (m, 4H; OCOCH_2CH_2CO), 2.17, 2.08, 1.96 (3s, 9H; 2 × CH_3CO, CH_3COCH$_2$), 0.95 (d, $J = 6.0$ Hz, 3H; H-6″); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 206.8$ (CH$_3$*C*OCH$_2$), 171.6 (CH$_2$CH$_2$*C*OO), 170.6, 169.6 (2C; 2 × CH$_3$*C*O), 155.7 (Ar-C), 153.5 (NH*C*O), 99.7 (C-1′), 98.4 (C-1), 97.6 (C-1″), 95.5 (CCl$_3$), 80.5 (C-3′), 75.2 (C-5), 75.0 (C-3), 74.5, 74.6, 73.5, 73.4, 73.2, 71.8, 70.8 (7C; 5 × O*C*H$_2$Ph, O*C*H$_2$CCl$_3$, O*C*H$_2$PhOH), 74.2 (C-2″), 73.6 (C-4), 73.5 (C-5′), 72.5 (C-4″), 72.2 (C-2′), 71.6 (C-4′), 70.6 (C-3″), 68.2 (C-6), 68.0 (C-6′), 64.8 (C-5″), 59.3 (C-2), 38.0 (*C*H$_2$COCH$_3$), 30.1 (CH$_2$CO*C*H$_3$), 28.0 (OCO*C*H$_2$CH$_2$), 21.1, 20.8 (2C; 2 × CO*C*H$_3$), 15.3 (C-6″); MALDI-TOF MS: *m*/*z* (%): 1424 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{72}H_{80}Cl_3NO_{21}$: C 61.69, H 5.75, N 1.00; found: C 61.77, H 5.68, N 1.05.

***p*-Hydroxybenzyl 6-*O*-benzyl-2-deoxy-2-[[(2,2,2-trichloroethoxy)carbonyl]-amino]-4-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-(3,4-di-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl)-β-D-galatopyranosyl)-β-D-glucopyranoside (26)**: The polymer bound compound **19** (100 mg) was coupled with fucosyl thioglycoside **21** (38 mg, 0.10 mmol) in the presence of NIS (25 mg, 0.11 mmol) and TMSOTf (1 μL) as described for the preparation of compound **22**. The resulting polymer **24** was treated with triethylamine to remove the Fmoc group as described for the preparation of compound **18**, followed by H_2O_2 as described in the general procedure. After being purified by LH-20 size exclusion chromatography (eluent: methanol/dichloromethane 1:1 *v*/*v*), compound **26** was obtained as a white foam (7 mg). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.41$–6.78 (m, Ar-H, 29H; 5 × OCH$_2$Ph, OCH$_2$PhOH), 5.73 (d, $J = 4.0$ Hz, 1H; H-1″), 5.37 (dd, $J = 10.5$, 3.0 Hz, 1H; H-3″), 5.20 (d, $J =$ 3.0 Hz, 1H; H-4″), 4.82–4.27 (m, 16H; 5 × OC*H*$_2$Ph, OC*H*$_2$PhOH, OC*H*$_2$CCl$_3$, H-1, H-5″), 4.17 (d, $J = 8.5$ Hz, 1H; H-1′), 4.09 (dd, $J = 8.5$, 8.0 Hz, 1H; H-2′), 3.94 (d, $J = 2.5$ Hz, 2H; H-6a, H-6b), 3.88 (d, $J = 3.5$ Hz, 1H; H-4′), 3.78 (dd, $J = 10.5$, 3.0 Hz, 1H; H-2″), 3.74 (dd, $J = 9.5$, 8.5 Hz, 1H; H-4), 3.66 (dd, $J = 9.0$, 8.5 Hz, 1H; H-3), 3.56 (d, $J = 6.5$ Hz, 2H; H-6′a, H-6′b), 3.47–3.41 (m, 3H; H-5′, H-2, H-3′), 3.25–3.21 (m, 1H; H-5), 2.11, 1.97 (2s, 6H; 2 × C*H*$_3$CO), 1.04 (d, $J = 6.5$ Hz, 3H; H-6″); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.4$, 170.2 (2C; 2 × CH$_3$*C*O), 155.6 (1C; Ar-C), 153.5 (NH*C*O), 139.0–115.5 (35C; Ar-C), 101.4 (C-1′), 98.7 (C-1), 97.2 (C-1″), 95.5 (CCl$_3$), 83.7 (C-3′), 78.9 (C-4), 74.9, 74.6, 73.8, 73.5, 72.3, 71.3, 70.4 (7C; 5 × O*C*H$_2$Ph, O*C*H$_2$PhOH, O*C*H$_2$CCl$_3$), 74.6 (C-5), 73.5 (C-5′), 73.1 (C-2″), 72.5 (C-2′), 72.3 (C-4′), 72.2 (C-3), 72.0 (C-4‴), 69.8 (C-3‴), 68.0 (C-6), 67.9 (C-6′), 64.3 (C-5‴), 57.7 (C-2), 20.8, 20.7 (2C; 2 × *C*H$_3$CO), 15.7 (C-6″); MALDI-TOF MS: *m*/*z* (%): 1326 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{67}H_{74}Cl_3NO_{19}$: C 61.73, H 5.72, N 1.07; found: C 61.49, H 5.61, N 1.09.

***p*-Hydroxybenzyl 6-*O*-benzyl-2-deoxy-2-[[(2,2,2-trichloroethoxy)carbonyl]-amino]-3-*O*-(3,4-di-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-(3,4-di-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl)-β-D-galatopyranosyl)-β-D-glucopyranoside (28)**: The polymer bound compound **20** (300 mg) was coupled with fucosyl thioglycoside **21** (229 mg, 0.60 mmol) in the presence of NIS (150 mg, 0.66 mmol) and TMSOTf (3 μL) as described for the preparation of compound **22**. The resulting solid was treated with H_2O_2 as described in the general procedure to release the crude product which was purified by size exclusion column chromatography (LH-20, eluent: methanol/dichloromethane 1:1 *v*/*v*) to give compound **28** as a white foam (31 mg). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.41$–6.78 (m, Ar-H, 34H; 6 × OCH$_2$Ph, OCH$_2$PhOH), 5.66 (d, $J = 2.9$ Hz, 1H; H-1‴), 5.26 (dd, $J =$ 10.6, 2.9 Hz, 1H; H-3″), 5.23 (dd, $J = 11.0$, 2.9 Hz, 1H; H-3‴), 5.22–5.16 (m, 3H; H-4″, H-4‴, N*H*), 5.10 (d, $J = 3.8$ Hz, 1H; H-1″), 5.02 (q, $J =$ 6.2 Hz, 1H; H-5″), 4.78 (d, $J = 8.2$ Hz, 1H; H-1), 4.76–4.12 (m, 20H; 6 × OC*H*$_2$Ph, OC*H*$_2$PhOH, OC*H*$_2$CCl$_3$, H-5‴, H-1′, H-4, H-3), 4.05 (dd, $J =$ 10.1, 10.0 Hz, 1H; H-6a), 3.96 (dd, $J = 10.1$, 8.2 Hz, 1H; H-2′), 3.90 (d, $J =$ 2.4 Hz, 1H; H-4′), 3.88–3.84 (m, 2H; H-6′a, H-6b), 3.82 (dd, $J = 11.0$, 2.9 Hz, 1H; H-2‴), 3.78 (dd, $J = 10.6$, 3.8 Hz, 1H; H-2″), 3.74 (dd, $J = 9.1$, 5.3 Hz, 1H; H-6′b), 3.36 (dd, $J = 10.1$, 2.4 Hz, 1H; H-3′), 3.24 (dd, $J = 8.6$, 5.3 Hz, 1H; H-5′), 3.18 (br d, $J = 9.6$ Hz, 1H; H-5), 3.06 (ddd, 1H; H-2), 2.09 (s, 3H; C*H*$_3$CO), 2.07 (s, 3H; C*H*$_3$CO), 1.99 (s, 6H; 2 × C*H*$_3$CO), 1.12 (d, $J = 6.7$ Hz, 3H; H-6‴), 0.90 (d, $J = 6.2$ Hz, 3H; H-6″); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.3$, 170.6, 170.5, 169.6 (4C; 4 × CH$_3$*C*O), 156.2 (1C; Ar-C), 153.5 (NH*C*O), 138.6–115.7 (41C; Ar-C), 99.5 (C-1′), 98.0 (C-1), 97.4 (C-1‴), 97.2 (C-1), 95.5 (CCl$_3$), 83.6 (C-3′), 75.4 (C-5), 75.2 (C-3), 74.5, 73.7, 73.4, 73.3, 72.7, 71.8, 70.9, 70.7 (8C; 6 × O*C*H$_2$Ph, O*C*H$_2$PhOH, O*C*H$_2$CCl$_3$), 73.8 (C-2‴), 73.6 (C-2′), 73.1 (C-5′), 72.7 (C-4), 72.6 (C-2″), 72.4 (2C; C-4″, C-4‴), 71.1 (C-4′), 70.6 (C-3‴), 70.0 (C-3″), 68.0 (2C; C-6, C-6′), 64.8 (C-5″), 64.6 (C-5‴), 59.4 (C-2), 21.0, 20.7 (4C; 4 × *C*H$_3$CO), 15.4 (C-6‴), 15.3 (C-6″); MALDI-TOF MS: *m*/*z* (%): 1646 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{84}H_{94}Cl_3NO_{25}$: C 62.12, H 5.83, N 0.86; found: C 62.37, H 5.66, N 0.78.

Benzyloxycarbonylaminopropyl hexasaccharide 32: DDQ (8 mg, 0.036 mmol) was added to a stirred mixture of compound **28** (30 mg, 0.018 mmol) in dichloromethane (2 mL) containing 5% water and the mixture was stirred vigorously in dark for 1 h. The reaction mixture was diluted with dichloromethane (30 mL) and was washed successively with aqueous sodium hydrogen carbonate (15%, 20 mL) and brine (15 mL). The organic phase was dried ($MgSO_4$) and concentrated to dryness under

reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexanes 2:3 *v*/*v*) to give compound **29** as a colorless syrup (22 mg, 82%).

CCl_3CN (0.1 mL) and DBU (1 μL) was added to a solution of **29** in dichloromethane (2 mL). After 5 min, the solution was concentrated under reduced pressure. Silica gel column chromatography (eluent: ethyl acetate/hexanes/triethylamine 1.1:0.01 *v*/*v*/*v*) yielded **30** as a colorless syrup (20 mg, 85%), which was dissolved in dry dichloromethane (2 mL) and stirred at room temperature in the presence of compound **31** (13 mg, 0.013 mmol) and molecular sieves (4 Å, 50 mg). $BF_3 \cdot Et_2O$ (1 μL) was added and after 10 min the reaction mixture was neutralized with triethylamine (50 μL). The reaction mixture was diluted with dichloromethane (30 mL) and the molecular sieves were removed by filtration. The filtrate was concentrated to dryness under reduced pressure and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexanes 2:3 *v*/*v*) to give compound **32** as a colorless syrup (16 mg, 54%). Selected ^1H and ^{13}C NMR data (Table 1, Table 2); MALDI-TOF MS: *m*/*z* (%): 2507 (100) $[M+Na]^+$.

Table 1. Selected ^1H NMR (500 MHz, $CDCl_3$) data.

	Fuc2	Gal2	Fuc1	GlcN	Gal1	Glc
H-1	5.67	4.52	5.02	5.21	4.37	4.28
H-2	3.78	4.00	3.81	3.06	3.52	3.31
H-3	5.25	3.42	5.27	3.99	3.56	3.48
H-4	5.24	3.91	5.21	4.07	4.06	3.87
H-5	4.62	3.30	4.98	3.42	3.44	3.23
H-6a	1.16	3.83	0.93	4.00	3.66	3.62
H-6b		3.75		3.78	3.52	3.60
spacer: $\delta = 3.86$, 3.63 (OCH_2), 3.29 (NCH_2), 1.78 (CH_2CH_2N)						

Table 2. Selected ^{13}C NMR (125 MHz, $CDCl_3$) data.

Fuc2	Gal2	Fuc1	GlcN	Gal1	Glc
C-1	97.3	99.4	98.1	99.2	101.8	103.2
C-2	72.5	75.5	73.7	59.7	82.8	81.5
C-3	69.5	83.3	70.4	73.3	68.0	82.6
C-4	71.8	70.8	72.1	72.1	67.6	76.1
C-5	64.5	74.6	64.6	74.8	72.9	74.6
C-6	15.3	67.8	15.1	67.8	68.7	67.9
spacer: $\delta = 67.2$ (OCH_2), 38.0 (NCH_2), 29.4 (CH_2CH_2N)						

Aminopropyl hexasaccharide 33: Hexasaccharide **32** (16 mg, 6.5 μmol) was dissolved in acetic acid (3 mL) and zinc (nanosize powder, Aldrich, 50 mg) was added. After 10 min, the reaction mixture was filtered and the filtrated was concentrated to dryness in vacuo. The residue was dissolved in pyridine (2 mL) and acetic anhydride (1 mL) was added. After 30 min, the reaction was quenched by addition of methanol (2 mL) and the mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (30 mL), washed successively with 1M HCl solution (5 mL), aqueous sodium hydrogencarbonate (15%, 5 mL), and brine (5 mL). The organic phase was concentrated to dryness and the obtained residue was dissolved in methanol (2 mL) and sodium methoxide (1M solution in methanol) was added to pH 10. The mixture was stirred at room temperature. After 24 h, the mixture was neutralized by Dowex 50 H^+ resin. The resin was removed by filtration and the filtrate was concentrated to dryness. The residue was purified by size exclusion column chromatography (LH-20, eluent: methanol/dichloromethane 1:1 *v*/*v*). The obtained product was dissolved in acetic acid/ethanol (1:5 *v*/*v*) and Pd/C (20 mg) was added. The mixture was stirred under the atmosphere of H_2 for 18 h. The catalyst was removed by filtration and the filtrate was concentrated to dryness in vacuo to give compound **33** as a white solid (6 mg, 85% overall yield). ^1H NMR (500 MHz, D_2O): $\delta = 5.16$ (d, $J =$ 3.1 Hz, 1H), 5.00 (d, $J = 4.0$ Hz, 1H), 4.76 (q, $J = 6.4$ Hz, 1H), 4.60 (d, $J = 8.3$ Hz, 1H), 4.40 (d, $J = 7.9$ Hz, 2H), 4.32 (d, $J = 7.9$ Hz, 1H), 4.14 (q, $J = 6.4$ Hz, 1H), 4.03 (d, $J = 3.1$ Hz, 1H), 3.97–3.44 (m, 29H), 3.34 (br s, 1H), 3.21 (t, 1H), 3.08–3.03 (m, 2H, NCH_2), 1.95–1.85 (m, 5H, CH_2CH_2N, $NHCOCH_3$), 1.15 (d, $J = 6.4$ Hz, 3H), 1.12 (d, $J = 6.4$ Hz, 3H); ^{13}C data of anomeric carbons (125 MHz, D_2O): $\delta = 103.2$, 102.8, 102.3, 100.4, 99.5, 98.7; MALDI-TOF MS: *m*/*z* (%): 1079 (100) $[M+Na]^+$.

[1] a) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531; b) G. J. Boons, *Tetrahedron* **1996**, *52*, 1095–1121; c) G. J. Boons, *Contemp. Org. Chem.* **1996**, 173–200; d) B. G. Davis, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2137–2160.

[2] a) P. Arya, R. N. Ben, *Angew. Chem.* **1997**, *109*, 1335–1337; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1280–1282; b) F. Schweizer, O. Hindsgaul, *Curr. Opin. Chem. Biol.* **1999**, *2*, 291–298; c) P. M. St. Hilaire, M. Meldal, *Angew. Chem.* **2000**, *112*, 1210–1228; *Angew. Chem. Int. Ed.* **2000**, *39*, 1162–1179; d) W. H. Haase, P. H. Seeberger, *Curr. Org. Chem.* **2000**, *4*, 481–511.

[3] C. H. Wong, X. Ye, Z. Zhang, *J. Am. Chem. Soc.* **1998**, *120*, 7137–7138.

[4] T. Zhu, G. J. Boons, *Tetrahedron*: *Asymmetry* **2000**, *11*, 199–205.

[5] T. Zhu, G. J. Boons, *J. Am. Chem. Soc.* **2000**, *122*, 10222–10223.

[6] For a review, see H. M. I. Osborn, T. H. Khan, *Tetrahedron* **1999**, *55*, 1807–1850.

[7] For the recent advances in solid-support oligosaccharide synthesis, see: a) G. H. Veeneman, S. Notemans, R. M. J. Liskamp, G. A. van der Marel, J. H. van Boom, *Tetrahedron Lett.* **1987**, *28*, 6695–6698; b) S. J. Danishefsky, K. F. McClure, J. T. Randolph, R. B. Ruggeri, *Science* **1993**, *260*, 1307–1309; c) J. T. Randolph, S. J. Danishefsky, *Angew. Chem.* **1994**, *106*, 1538–1541; *Angew. Chem. Int. Ed. Engl.* **1994**, 1470–1473; d) M. Schulster, P. Wang, J. C. Paulson, C. H. Wong, *J. Am. Chem. Soc.* **1994**, *116*, 1135–1136; e) L. Yan, C. M. Taylor, R. Goodnow, Jr., D. Kahne, *J. Am. Chem. Soc.* **1994**, *116*, 6593–6594; f) J. T. Randolph, K. F. McClure, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 5712–5719; g) R. Liang, L. Yan, J. Loibach, M. Ge, Y. Uozumi, K. Sekanina, N. Horan, J. Gildersleeve, C. Thompson, A. Smith, K. Biswas, W. C. Still, D. Kahne, *Science* **1996**, *274*, 1520–1522; h) J. Rademann, R. R. Schmidt, *Tetrahedron Lett.* **1996**, *37*, 3989–3990; i) J. A. Hunt, W. R. Roush, *J. Am. Chem. Soc.* **1996**, *118*, 9998–9999; j) K. C. Nicolaou, N. Winssinger, J. Pastor, F. DeRoose, *J. Am. Chem. Soc.* **1997**, *119*, 449–450; k) R. Rodebaugh, B. Fraser-Reid, H. M. Geysen, *Tetrahedron Lett.* **1997**, *38*, 7653–7656; l) J. Rademann, R. R. Schmidt, *J. Org. Chem.* **1997**, *62*, 3650–3653; m) A. Heckel, E. Mross, K. Jung, J. Rademann, R. R. Schmidt, *Synlett* **1998**, 171–173; n) K. C. Nicolaou, N. Watanabe, J. Li, J. Pastor, N. Winssinger, *Angew. Chem.* **1998**, *110*, 1636–1638; *Angew. Chem. Int. Ed.* **1998**, *37*, 1559–1561; o) T. Kanemitsu, O. Kanie, C. H. Wong, *Angew. Chem.* **1998**, *110*, 3574–3577; *Angew. Chem. Int. Ed*. **1998**, *37*, 3415–3418; p) Y. Ito, S. Manabe, *Curr. Opin. Chem. Bio.* **1998**, *2*, 701–708; q) T. Zhu, G. J. Boons, *Angew. Chem.* **1998**, *110*, 2000–2003; *Angew. Chem. Int. Ed.* **1998**, *37*, 1898–1900; r) L. Rnerr, R. R. Schmidt, *Synlett* **1999**, 1802–1804; s) R. B. Andrade, O. J. Plante, L. G. Melean, P. H. Seeberger, *Org. Lett.* **1999**, *1*, 1811–1814; t) L. G. Melean, W. Haase, P. H. Seeberger, *Tetrahedron Lett.* **2000**, *41*, 4329–4333; u) G. Belogi, T. Zhu, G. J. Boons, *Tetrahedron Lett.* **2000**, *41*, 6965–6968; v) G. Belogi, T. Zhu, G. J. Boons, *Tetrahedron Lett.* **2000**, *41*, 6969–6972.

[8] D. J. Gravert, K. D. Janda, *Chem. Rev.* **1997**, *97*, 489–509.

[9] a) S. P. Douglas, D. M. Whitfield, J. T. Krepinsky, *J. Am. Chem. Soc.* **1991**, *113*, 5095–5097; b) R. Verduyn, P. A. M. van der Klein, G. A. van der Marel, J. H. van Boom, *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 464–465; c) S. P. Douglas, D. M. Whitfield, J. T. Krepinsky, *J. Am. Chem. Soc.* **1995**, *117*, 2116–2117.

[10] U. Ellervik, G. Magnusson, *J. Org. Chem.* **1998**, *63*, 9314–9322.

[11] a) P. Konradsson, U. E. Udodong, B. Fraser-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313–4316; b) G. H. Veeneman, S. H. van Leeuwen, J. H. van Boom, *Tetrahedron Lett*. **1990**, *31*, 1331–1334.

[12] X. Zhao, K. D. Janda, *Tetrahedron Lett.* **1997**, *38*, 5437–5440.

[13] M. Benaglia, R. Annunziata, M. Cinquini, F. Cozzi, S. Ressel, *J. Org. Chem.* **1998**, *63*, 8628–8629.

[14] C. Gioeli, J. B. Chattopadhyaya, *J. Chem. Soc. Chem. Commun.* **1982**, 672–674.

0947-6539/01/0711-2388 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 11

[15] a) A. Hassner, G. Strand, M. Rubinstein, *J. Am. Chem. Soc.* **1975**, *97*, 1614–1615; b) J. H. van Boom, P. M. J. Burgers, *Tetrahedron Lett.* **1976**, 4875–4878.
[16] T. Zhu, G. J. Boons, *Angew. Chem.* **1999**, *111*, 3704–3707; *Angew. Chem. Int. Ed.* **1999**, *38*, 3495–3497.
[17] S. J. Danishefsky, J. R. Allen, *Angew. Chem.* **2000**, *112*, 882–912; *Angew. Chem. Int. Ed.* **2000**, *39*, 836–863.
[18] a) S. Hakomori, *Acta. Anat.* **1998**, *161*, 79–90; b) P. W. Glunz, S. Hintermann, L. J. Williams, J. B. Schwarz, S. D. Kuduk, V. Kudryashov, K. O. Lloyd, S. J. Danishefsky, *J. Am. Chem. Soc*. **2000**, *122*, 7273–7279.
[19] L. Jobron, O. Hindsgaul, *J. Am. Chem. Soc.* **1999**, *121*, 5835–5836.
[20] a) R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213–236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212–235; b) L. Manzoni, L. Lay, R. R. Schmidt, *J. Carbohydr. Chem.* **1998**, 739–758.
[21] A. V. Demchenko, G. J. Boons, *J. Org. Chem.* **2001**, *66*, in press.
[22] T. B. Windholz, D. B. R. Johnston, M. Sharp, *Tetrahedron Lett.* **1967**, 2555–2557.

Received: December 11, 2000 [F2925]