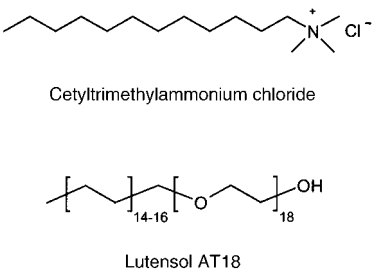

Figure 2. Successfully employed cationic and nonionic emulsifiers.

during the prepolymerization accounts for an insignificant amount of the sPS obtained with cationic and nonionic emulsifiers. Thus, the bulk of the polymer is produced in the aqueous environment in emulsion.

In attempts to further increase the shielding of the catalyst from water, the alkoxide substituent was varied. The original system contained methoxide ligands, which were subsequently replaced by more sterically demanding substituents (Figure 3). However, no improvement in terms of turnover or dispersion stability was observed.

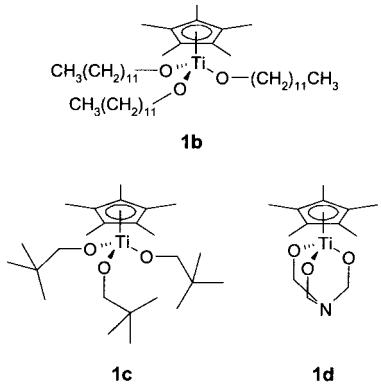

Figure 3. Monocyclopentadienyl complexes for the polymerization of styrene in aqueous emulsion.

The influence of other metal complexes and emulsifiers on the styrene polymerization is part of ongoing investigations as is the transfer to other monomers. In addition, particle size distribution as well as dispersion stability will be further optimized.

Experimental Section

The polymerizations were performed under the exclusion of air. All chemicals were obtained commercially.

Aqueous emulsion polymerization: In a 1 L flask styrene (75 g) was dissolved in toluene (300 g) and heated to 80 °C. Then a 25 % triisobutylaluminium solution in toluene (9.5 g) was added. A solution of of *N*,*N*-dimethylanilinium tetrakis(pentafluorophenyl) borate (0.385 g) and of pentamethylcyclopentadienyl titanium trimethoxide (**1a**; 0.135 g) in toluene (10 mL) was prepared seperately and added from a feed vessel. After 0.5 min the resulting mixture was added to a solution of 20 % Lutensol AT18 (18.75 g) in deionized water (300 g). The reaction was quenched with ethanol after 1 h. The suspension was dried at 80 °C in vacuo. Conversion: 66 %; tacticity: ^{13}C NMR rr = 99 %, mm = 0 %, rm = 1 % (r = racemic diad (syndotactic); m = meso diad (isotactic)); m. p. (DSC): 269 °C; average particle size (determined from scanning electron microscopy (SEM) pictures): ca. 500 μm.

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α(1-3)-Galactosyltransferase Inhibition Based on a New Type of Disubstrate Analogue**

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Oligosaccharides play an important role in various cellular recognition and signal transduction processes.[1] Therefore, control of the biosynthesis of the structurally diverse oligosaccharides is of great interest for biological studies. An important control mechanism is the specific inhibition of the various glycosyltransferases.[2] In enzymatic oligosaccharide synthesis, a glycosyl donor (commonly a nucleoside mono- or diphosphate) and an acceptor are generally coupled, with the

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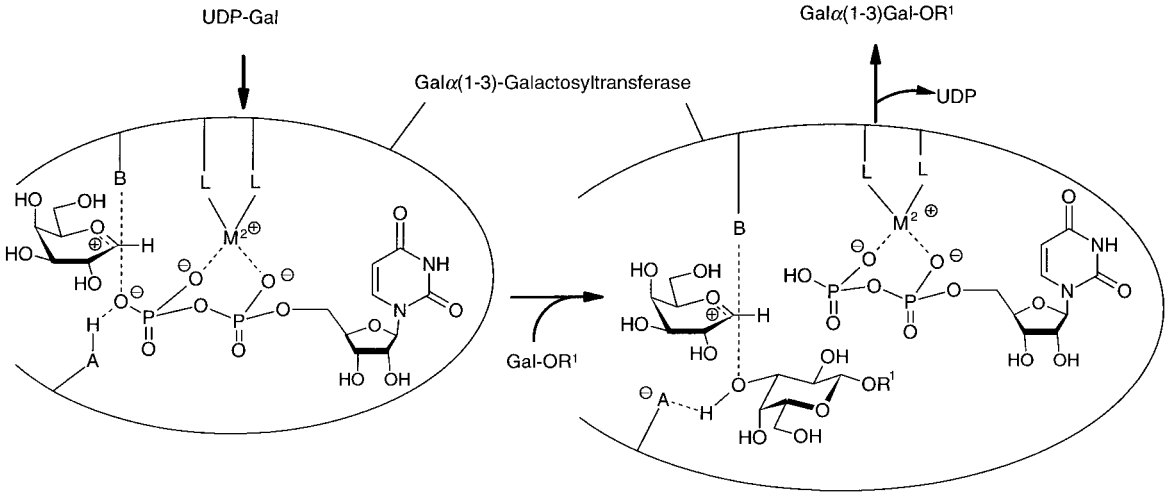
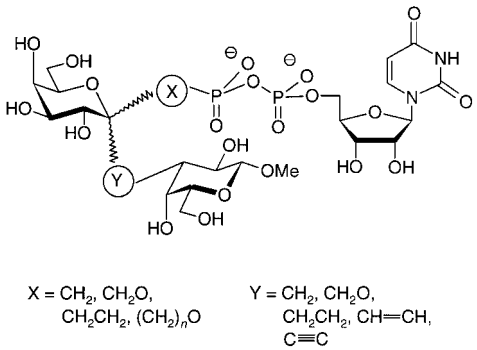


Scheme 1. Proposed course of the galactosyl transfer (B or UDP = catalytic nucleophile, A–H = acid).

loss of the nucleoside mono- or diphosphate residue. Substrate analogues of the donor and of the acceptor have been investigated as inhibitors, but with limited success.[3] Transition state analogues of the donor have also been constructed.[4] They are often derived from the corresponding glycals, because it is assumed that an oxocarbenium ion is structurally closely related to the geometry of the transition state (Scheme 1).[4–6] Disubstrate analogues[7, 8] that contain the glycosyl donor and acceptor in a steric arrangement that simulates the transition state may be of particular interest; for a retaining α(1-3)-galactosyltransferase reaction, see Scheme 1.[9] Such compounds are expected to have a high affinity for the active site, thus leading to a higher specificity.

Potential disubstrate analogues are shown in Scheme 2. In the target molecules, both the leaving group and the acceptor are connected to the glycosyl moiety through hydrolytically stable linkages, and thus the synthesis of C-ketoside derivatives is of interest[10]. The inhibition of α(1-3)-galactosyltransferase is a key to the prevention of hyperacute rejection in the xenotransplantation of organs from pigs to humans.[11] Similarly, inhibitors of galactosyltransferases, which are required for the synthesis of glycosylphosphatidylinositol (GPI) membrane anchors in trypanosomes[12–14] are interesting pharmacological targets. We focused on the synthesis of compounds **1*α*** and **1*β*** (in Scheme 2: X = CH_2O, Y = CH_2CH_2).[15, 16]

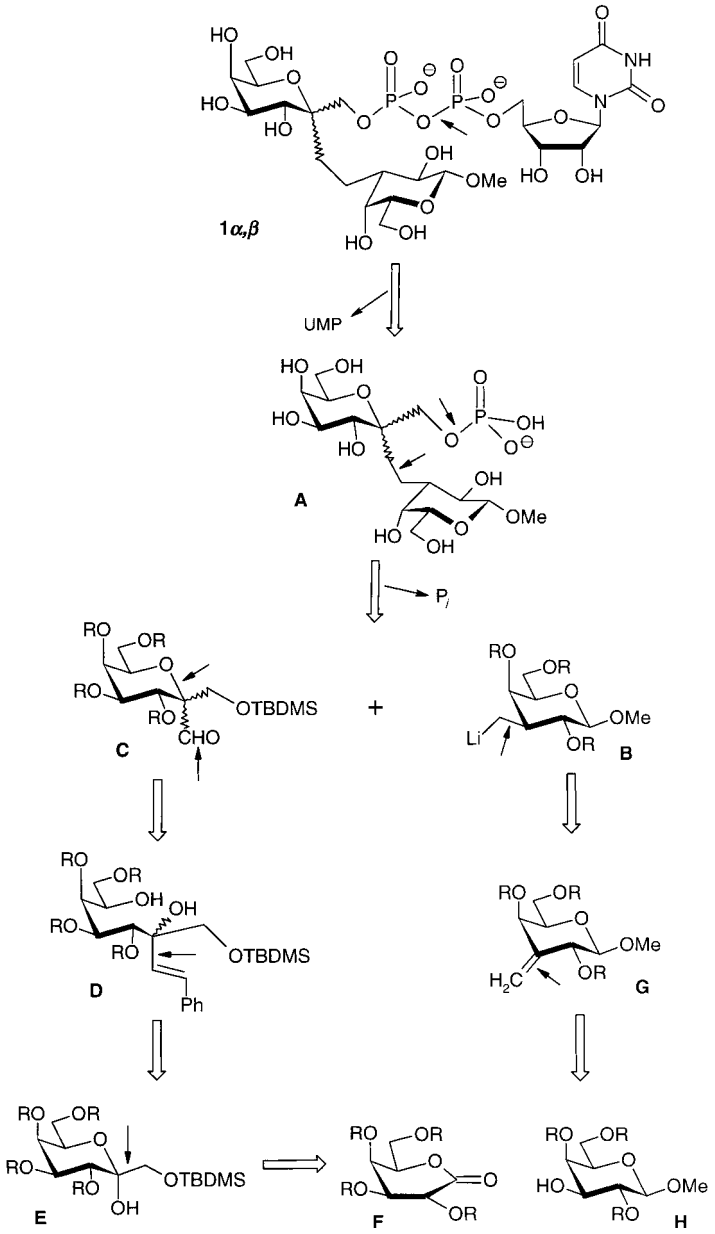
The retrosynthesis of target molecules **1*α*** and **1*β*** is shown in Scheme 3. Retrosynthetic cleavage of uridine-5′-monophosphate (UMP) gives synthetic equivalent **A**. Removal of the



X = CH_2, CH_2O, CH_2CH_2, $(CH_2)_nO$

Y = CH_2, CH_2O, CH_2CH_2, CH=CH, C≡C

Scheme 2. Proposed disubstrate analogues.



Scheme 3. Retrosynthetic scheme for the synthesis of disubstrate analogues **1*α*** and **1*β***.

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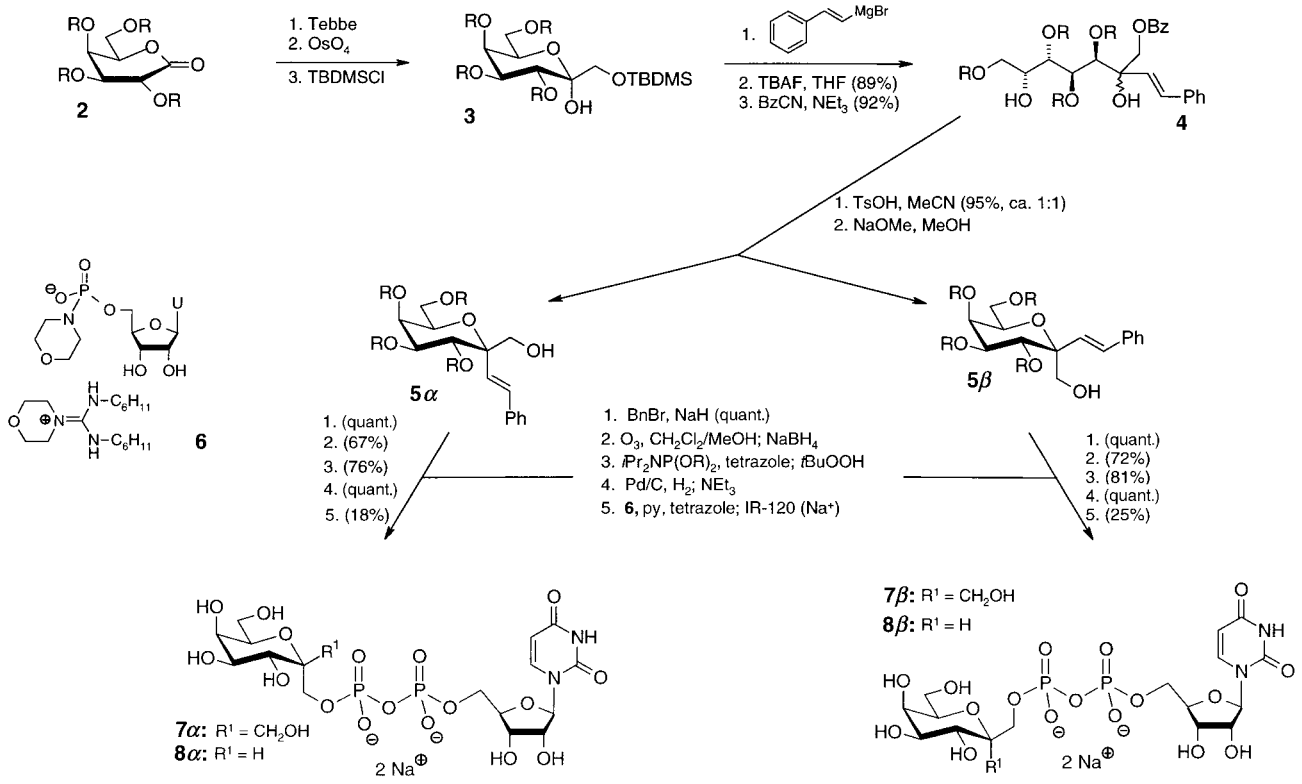
phosphate group (P_i) and further disconnection leads back to the two galactose residues **B** and **C**. Fragment **C** can be envisioned from the ring closure of precursor **D**, which is equipped with a latent functionality at C1. The two C_1 synthetic equivalents can be obtained from galactonolactone (**F**; R = H) via intermediate **E**. The 3-*C*-lithiomethylgalactoside fragment **B** is derived from 3-*C*-methylene derivative **G**, which can be obtained from 3-O-unprotected galactopyranoside **H**.

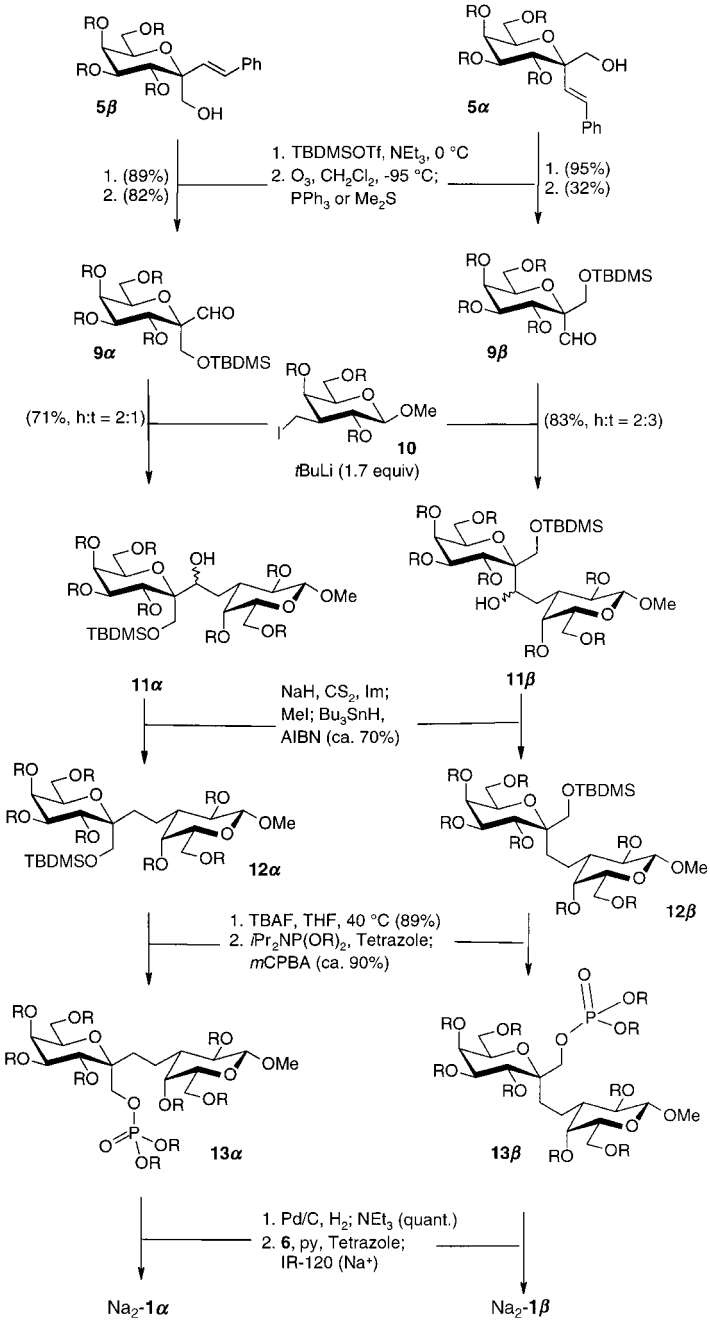
O-Benzyl-protected galactonolactone **2**[17] was selected as the precursor for the synthesis of **1*α*** and **1*β*** and other UDP-Gal mimetics (Scheme 4). The two C_1 nucleophiles that are required were introduced by Tebbe methylenation of **2**, dihydroxylation of the resulting C–C double bond, and selective protection of the primary hydroxy group with *tert*-butyldimethylsilyl (TBDMS) chloride to furnish the protected 2-heptulose **3**. Addition of styrylmagnesium bromide to **3** as the latent C_1 functionality and replacement of the TBDMS group by a benzoyl group afforded alcohol **4** as a 1:1 mixture of diastereomers. The protecting groups and the styryl group allowed the facile cyclization of **4** under acid catalysis to afford a 1:1 mixture of diastereomeric tetrahydropyran derivatives. Removal of the *O*-benzoyl group gave the important intermediates **5*α*** and **5*β*** in high overall yield. These compounds were subjected to O-benzylation, ozonolytic cleavage of the C–C double bond, and reduction of the resulting formyl group to form the hydroxymethyl derivatives. Subsequent phosphorylation of the primary hydroxy groups, complete hydrogenolytic O-debenzylation, coupling of UMP with the help of activated intermediate **6**, and ion exchange gave UDP-Gal mimetics **7*α*** and **7*β***, respectively, as disodium salts. As donor-substrate analogues, they are also potential galactosyltransferase inhibitors; as are the UDP homologues **8*α*** and **8*β***, which were obtained by following reported procedures.[4, 16, 18] All four compounds were investigated in the biological studies.

To construct the target molecules **1*α*** and **1*β***, the primary hydroxy groups of **5*α*** and **5*β*** were protected with the TBDMS group (Scheme 5), and the styryl groups were then treated with ozone to generate the formyl groups in **9*α*** and **9*β***, respectively. The aldehyde groups were used to attach the galactosyl moiety, which is the acceptor part of the disubstrate analogues **1*α*** and **1*β***: 3-*C*-iodomethylgalactoside **10**, which was readily obtained from methyl 2,3,6-tri-*O*-benzyl-*β*-D-galactopyranoside,[19] was transformed with *tert*-butyllithium into the 3-*C*-lithiomethyl derivative, and then treated with **9*α*** and **9*β*** to furnish *C*-disaccharides **11*α*** and **11*β***, respectively, both as mixtures of diastereomers. Removal of the hydroxy groups under Barton conditions led to **12*α*** and **12*β*** as single isomers. The TBDMS protecting group was replaced with the phosphate group under standard conditions in high yield, thus affording O-benzyl-protected phosphates **13*α*** and **13*β***. Complete O-debenzylation by means of hydrogenolysis was followed by the reaction with activated UMP derivative **6** to furnish target molecules **1*α*** and **1*β*** as disodium salts after ion exchange. Compounds **1*α*** and **1*β*** and all intermediates were characterized by means of NMR spectroscopy (Table 1).

The compounds **1*α***, **1*β***, **7*α***, **7*β***, **8*α***, and **8*β*** were tested in vitro for the inhibition of purified recombinant pig α(1-3)-galactosyltransferase (pα(1-3)GalT) by using radiolabeled UDP-Gal as donor and LacNAc-R as acceptor (for details see Experimental Section). At a concentration of 50 μM, only **1*β***



Scheme 4. Synthesis of UDP-Gal homologues **7*α*,*β*** and **8*α*,*β***. R = $PhCH_2$ (Bn), TBAF = Bu_4NF, Bz = PhCO, Ts = *para*-toluenesulfonyl, py = pyridine, IR-120(Na^+) = ion exchange resin in the Na^+ form.



Scheme 5. Assembly of the target molecules **1α**,**β**. R = Bn, Tf = CF_3SO_2, Im = imidazole, AIBN = azobisisobutyronitrile, *m*CPBA = *meta*-chloroperbenzoic acid

Table 1. Physical data for **1α**, **1β**, **7α**, and **7β**.[a]

1α: ^{1}H NMR: $\delta = 1.39-1.44$ (m, 2H; 7a-H, 8a-H), 1.52 (m, 1H; 3-H), 1.59 (m, 1H; 8a′-H), 1.86 (m, 1H; 7a′-H), 3.24 (dd, $^3J_{2,1} = 8.0$, $^3J_{2,3} = 10.8$ Hz, 1H; 2-H), 3.49 (s, 3H; OCH_3), 3.60–3.67 (m, 6H; 1a-H, 1a′-H, 2a-H, 5-H, 6-H, 6′-H), 3.77 (dd, $^3J_{4a,5a} = 10.3$, $^3J_{4a,3a} = 3.4$ Hz, 1H; 4a-H), 3.79 (d, $^3J_{4,3} \approx 2.1$, $^3J_{4,5} \leq 1$ Hz, 1H; 4-H), 3.86 (d, $^3J_{3a,4a} = 3.4$, $^3J_{3a,2a} \leq 1$ Hz, 1H; 3a-H), 3.97–4.00 (m, 3H; 1b-H, 1b′-H, 5a-H), 4.10–4.20 (m, 3H; 4c-H, 5c-H, 5c′-H) 4.24 (d, $^3J_{1,2} = 8.0$ Hz, 1H; 1-H), 4.25–4.30 (m, 2H; 2c-H, 3c-H), 5.82 (d, $^3J_{5d,6d} = 7.7$ Hz, 1H; 5d-H), 5.94 (d, $^3J_{1c,2c} = 5.0$ Hz, 1H; 1c-H), 7.76 (d, $^3J_{6d,5d} = 7.7$ Hz, 1H; 6d-H); ^{31}P NMR: $\delta = -12.31 - -12.90$ (2 × d, $^3J_{P,P} \approx 21$ Hz; 2P)

1β: ^{1}H NMR: $\delta = 1.46$ (m, 3H; 3-H, 7a-H, 8a-H), 1.74 (pt, $J \approx 9.0$ Hz, 1H; 8a′-H), 1.89 (pt, $J \approx 9.4$ Hz, 1H; 7a′-H), 3.24 (pt, $^3J_{2,1} \approx {}^3J_{2,3} \approx 9.0$ Hz, 1H; 2-H), 3.49 (s, 3H, OCH_3), 3.59–3.62 (m, 4H; 1a-H, 1a′-H, 5-H, 6-H), 3.67–3.68 (m, 1H; 6′-H), 3.75 (d, $^3J_{5a,4a} = 10.0$ Hz, 1H; 5a-H), 3.84 (br s, 1H; 4-H), 3.89–3.93 (m, 4H; 1b-H, 2a-H, 3a-H, 4a-H), 4.10 (m, 1H; 5c-H), 4.16 (m, 1H; 5c′-H), 4.18 (m, 1H; 4c-H), 4.22 (d, $^3J_{1,2} = 7.9$ Hz, 1H; 1-H), 4.26–4.67 (m, 3H; 1b′-H, 2c-H, 3c-H), 5.85 (d, $^3J_{5d,6d} = 7.8$ Hz, 1H; 5d-H), 5.93 (d, $^3J_{1c,2c} = 4.7$ Hz, 1H; 1c-H), 7.81 (d, $^3J_{6d,5d} = 7.8$ Hz, 1H; 6d-H); ^{13}P NMR: $\delta = -11.86 - -12.33$ (2 × d, $^3J_{P,P} \approx 21$ Hz, 2P)

7α: ^{1}H NMR: $\delta = 3.40-3.70$ (m, 6H; 1-H, 4-H, 5-H, 6-H, 7-H, 7′-H), 3.71–4.03 (m, 4H; 1a-H, 1a′-H, 1′-H, 3-H), 4.04–4.25 (m, 5H; 2b-H, 3b-H, 4b-H, 5b-H, 5b′-H), 5.89 (d, $^3J_{5c,6c} = 8.1$ Hz, 1H; 5c-H), 5.91 (d, $^3J_{1b,2b} = 3.9$ Hz, 1H; 1b-H), 7.87 (d, $^3J_{6c,5c} = 8.1$ Hz, 1H; 6c-H)

7β: ^{1}H NMR: $\delta = 3.60$, (dd, $^2J_{7,7'} = 11.6$, $^3J_{7,6} = 4.7$ Hz, 1H; 7-H), 3.65–3.69 (m, 2H; 1-H, 7′-H), 3.71 (dd, $^3J_{4,3} = 10.4$, $^3J_{4,5} = 3.3$ Hz, 1H; 4-H), 3.79 (pt, $^3J_{6,7} \approx {}^3J_{6,7'} \approx 6.0$ Hz, 1H; 6-H), 3.85 (d, $^3J_{5,4} = 3.3$, $^3J_{5,6} \leq 1$ Hz, 1H; 5-H), 3.93 (d, $^2J_{1',1} = 12.9$ Hz, 1H; 1′-H), 3.95 (d, $^3J_{3,4} = {}^3J_{4,3} = 10.4$ Hz, 1H; 3-H), 3.98 (dd, $^2J_{1a,1a'} = 10.8$, $^3J_{1a,P} = 4{,}2$ Hz, 1H; 1a-H), 4.02 (dd, $^2J_{1a',1a} = 10.8$, $^3J_{1a',P} = 5.9$ Hz, 1H; 1a′-H), 4.05–4.19 (m, 3H; 4b-H, 5b-H, 5b′-H), 4.23–4.27 (m, 2H; 2b-H, 3b-H), 5.82 (d, $^3J_{5c,6c} = 7.9$ Hz, 1H; 5c-H), 5.90 (d, $^3J_{1b,2b} = 4.8$ Hz, 1H; 1b-H), 7.77 (d, $^3J_{6c,5c} = 7.9$ Hz, 1H; 6c-H); ^{13}P NMR: $\delta = -12.13 - -12.60$ (2 × d, $^3J_{P,P} \approx 21$ Hz, 2P)

[a] ^{1}H NMR (600 MHz) and ^{31}P NMR (242 MHz) spectra were measured in D_2O (pt = pseudo triplet).

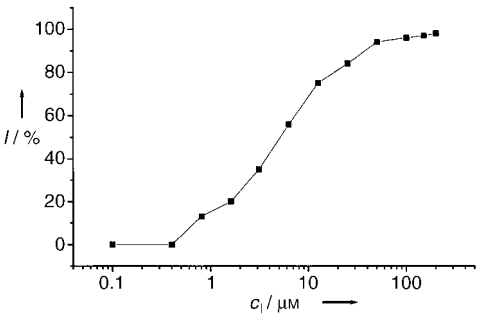


Figure 1. Inhibition of pα(1-3)GalT by **1β**: The transferase assay was performed in the presence of **1β** (200–0 μM), UDP-Gal (50 μM), and LacNAcR (360 μM). *I* = inhibition, c_I = concentration of inhibitor.

inhibited the enzyme. An IC_{50} of about 5 μM was found for **1β** (Figure 1).

In summary, disubstrate analogue **1β** was found to be a good inhibitor of the retaining pig α(1-3)-galactosyltransferase. The presence of UDP on the β-side of the galactose moiety leads to a higher affinity for the enzyme than when UDP is found on the α-side, as is the case in the natural galactosyl donor and in disubstrate analogue **1α**. This result is at first rather surprising and hints at the catalytic nucleophile within the active site which seems to be necessary for retaining glycosyltransferases, but yet could not be found for the retaining galactosyltransferase LgtC from *Neisseria meningitidis*:[9] therefore, UDP is not only the leaving group but also the catalytic nucleophile, that is, in retaining glycosyltransferases, UDP-Gal is first transformed into the corresponding β-anomer or perhaps its tight ion pair and then the acceptor is glycosylated at the α-side. Thus, it is proposed that arbitrarily chosen nucleophile B in Scheme 1 is UDP.

Experimental Section

Pig α(1-3)-galactosyltransferase (pα(1-3)GalT) and activity assay: The pα(1-3)GalT was cloned and expressed as soluble transferase in Baculovirus-infected Sf9 insect cells. The enzyme was purified by means of ion exchange and affinity chromatography. The assay used to assess the inhibitory potential of compounds is based on the transfer of radiolabeled

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[^{3}H]galactose from the donor UDP-Gal (50 μM) to the acceptor molecule LacNAc$(CH_2)_8CO_2CH_3$ (0.36 mM) by the pα(1-3)GalT (10 μM) in an assay buffer system consisting of sodium cacodylate (100 mM; pH 6.5), 15 mM $MnCl_2$, and BSA (bovine serum albumin; 50 $\mu g\,mL^{-1}$) at 37 °C for 30 min. The radiolabeled product, [^{3}H]Galα(1-3)LacNAc$(CH_2)_8CO_2CH_3$, was separated from unincorporated label by adsorption onto a SepPac C_{18} column[20]. The ratio of incorporated to total radioactivity is proportional to the activity of pα(1-3)GalT. We took precautions to ensure that the enzyme was the limiting reagent and that all other cofactors were close to the saturation point. Strictly speaking, the reported inhibition is an IC_{50} value because we have not carried out the assays with different concentrations of cofactors.

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Polyphenylene Dendrimers as Sensitive and Selective Sensor Layers**

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Polyphenylene dendrimers (PDs) are monodisperse macromolecules, which—because of their rigid framework—contain internal voids. This property differentiates them from other dendrimers, which consist of flexible, aliphatic groups, and makes them attractive as selective layers for gravimetric sensors. Such sensors based upon the quartz microbalance (QMB)[1] are widely used to monitor the concentration of various volatile organic compounds (VOCs) in different environments. These types of sensors are of increasing significance in many aspects of daily life, be it monitoring the manufacture or storage of foodstuff,[2] controlling chem-

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