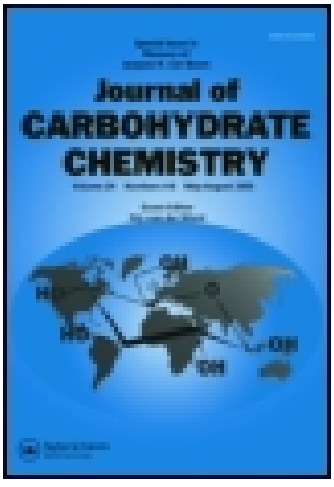

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Uwe Schmelzer [a] , Zhaojun Zhang [a] & Prof. Dr. Richard R. Schmidt [a]
[a] Fachbereich Chemie, Universität Konstanz , Konstanz, Germany
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Dichloro-cyanoacetimidates as Glycosyl Donors

Uwe Schmelzer, Zhaojun Zhang, and Richard R. Schmidt

Fachbereich Chemie, Universität Konstanz, Konstanz, Germany

Transformation of 1-*O*-unprotected glucose and galactose derivatives (**1a**–**d**) into *O*-glycosyl dichloro-cyanoacetimidates (**2a**–**d**) was performed with dichloro-cyanoacetonitrile in the presence of DBU as base. Reaction with different acceptors (**3a**–**d**) under TMSOTf catalysis afforded glycosides **4** in high yields. Competition experiments with *O*-glucopyranosyl trichloroacetimidate **10a**, bearing a 4-*tert*-butylbenzyl group at 6-*O*, and *O*-glucopyranosyl dichloro-cyanoacetimidate **10b**, bearing a 4-methylbenzyl group at 6-*O*, displayed similar reactivities for these two types of glycosyl donors.

Keywords Glycosyl donors, Glycosidation, Catalysis, Leaving group, Dichloromalonitrile, Imidates

INTRODUCTION

O-Glycosyl trichloroacetimidates have become popular because they are powerful glycosyl donors.[1–3] These donors can be readily obtained by base catalyzed addition of the anomeric hydroxy group to the nitrile group of trichloroacetonitrile. This addition is strongly supported by the electron-withdrawing trichloromethyl group. Once prepared, these glycosyl donors can be generally activated by catalytic amounts of (Lewis) acid, conditions that are orthogonal to their preparation. This way, they react with various nucleophiles to provide various types of glycosides generally in high yields and high anomeric stereocontrol.

This glycosidation principle consists of[1] generation of powerful glycosyl donors by catalyzed reversible addition of the anomeric hydroxy group to the activating group and[2] activation of this glycosyl donor by a promoter in

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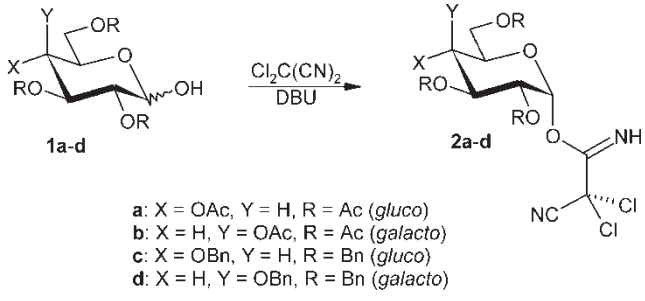
Address correspondence to Prof. Dr. Richard R. Schmidt, Fachbereich Chemie, Universität Konstanz, Fach M 725, D-78457, Konstanz, Germany. E-mail: richard.schmidt@uni-konstanz.de

catalytic amounts (i.e., an agent that is not consumed during the reaction course). Particularly in large-scale preparations, such methods are generally superior to methods that require replacement of the anomeric oxygen by other elements and activation of the glycosyl donor by equimolar amounts (often even big excess is employed) of a reaction promoter.[3,4] However, for various reasons, the last methods are still quite popular. For instance, thioglycosides can be generally stored at rt and they tolerate various protecting group manipulations. We initiated further investigations to provide efficient glycosyl donors, which follow the principle of *O*-glycosyl trichloroacetimidate formation and activation. Previously trifluoroacetonitrile,[5] ketenimines,[5,6] imide halides having electron-withdrawing carbon substituents,[5,7–10] and their heterocyclic equivalents[7,11–14] have been investigated. The last two systems have the disadvantage of furnishing equimolar amounts of salt on glycosyl donor generation. Additionally, glycosyl donor generation is not reversible; therefore, α/β-stereocontrol is much more difficult or impossible. Hence, surpassing the properties of O-glycosyl trichloroacetimidates is an interesting task.

We reasoned that replacement of one chlorine atom in trichloroacetonitrile by a cyano group, that is, using dichloromalonitrile (Sch. 1) as activating agent, may lead to increased glycosyl donor properties because the negative inductive effect of the cyano group is bigger than that of the chlorine atom. However, the influence of the different inductive effects could be modified by the different size, leading to different conformational preferences of the derived *O*-glycosyl dichloro-cyanoacetimidates, or by other effects.

RESULTS AND DISCUSSION

The investigation of the dichloro-cyanoacetimidate leaving group was based on readily available anomeric *O*-unprotected glucose and galactose derivatives **1a–d**[15–17] (Sch. 1). Reaction with dichloromalonitrile under catalysis with DBU as base for *O*-glycosyl trichloroacetimidate formation gave *O*-gluco- and



Scheme 1: Transformation of **1a–d** into *O*-glycosyl dichloro-cyanoacetimidates **2a–d**.

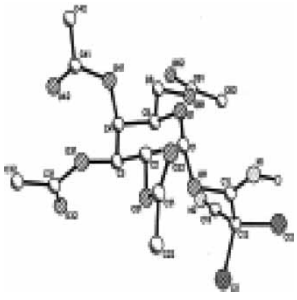
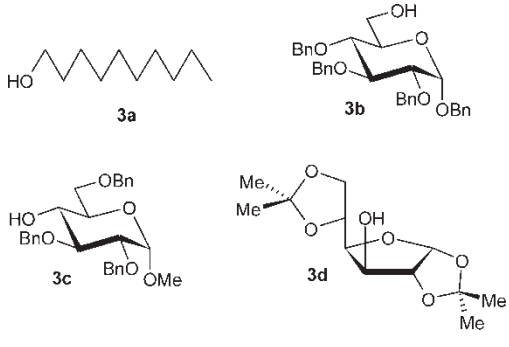


Figure 1: X-ray structure of **2b**.

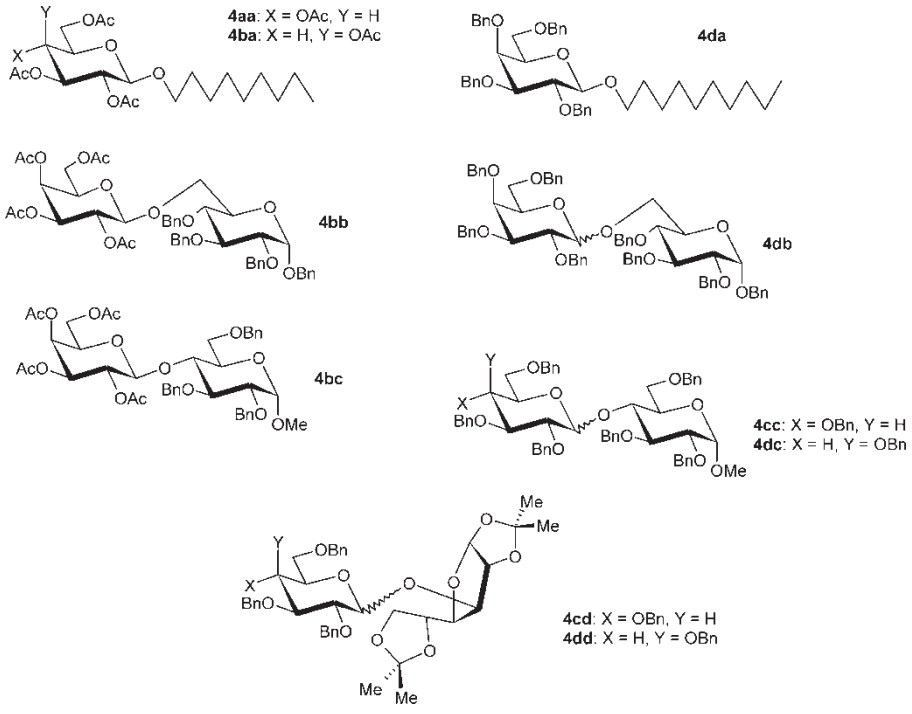
O-galactopyranosyl dichloro-cyanoacetimidates **2a**–**d** in excellent yields. Only the α-anomers could be isolated in pure form under these conditions. From compound **2b** crystals could be obtained, which were subjected to X-ray analysis (Fig. 1).[18] Interestingly, the smaller cyano group was below the sugar residue, thus exhibiting that the size of the chlorine atom may lead in *O*-glycosyl trichloroacetimidates to different conformational preferences.

Reaction of *O*-acetyl-protected *O*-glycosyl dichloro-cyanoacetimidates **2a**,**b** with readily available acceptors **3a**–**c**[19–22] (Sch. 2) led under TMSOTf catalysis to high yields of glycosides **4aa**,[23] **4ba**,[23] **4bb**, and **4bc,**[24] respectively (Sch. 3 and Table 1: entries 1–4). Due to anchimeric assistance, only the β-linked products were obtained. Investigations with the *O*-benzyl-protected glycosyl donors **2c**,**d** and **3a**–**d** as acceptors were also carried out under the same conditions; this led to glycoside bond formation in very good yields, even for low reactive acceptor **3d** (Table 1, entries 5–11: products **4cc**,[25] **4cd**,[26,27] **4da**, **4db**, **4dc**,[28] **4dd**[29]). Compared with results obtained for *O*-glycosyl trichloroacetimidates with typical acceptors, as, for example, **3b** and **3c**, a higher tendency for α-product formation was observed even at -40°C.[2]

To obtain further information on the reactivity of *O*-glycosyl dichloro-cyanoacetimidates, competition experiments with an *O*-glycosyl



Scheme 2: Acceptors **3a**–**d** for the glycosylation reactions.



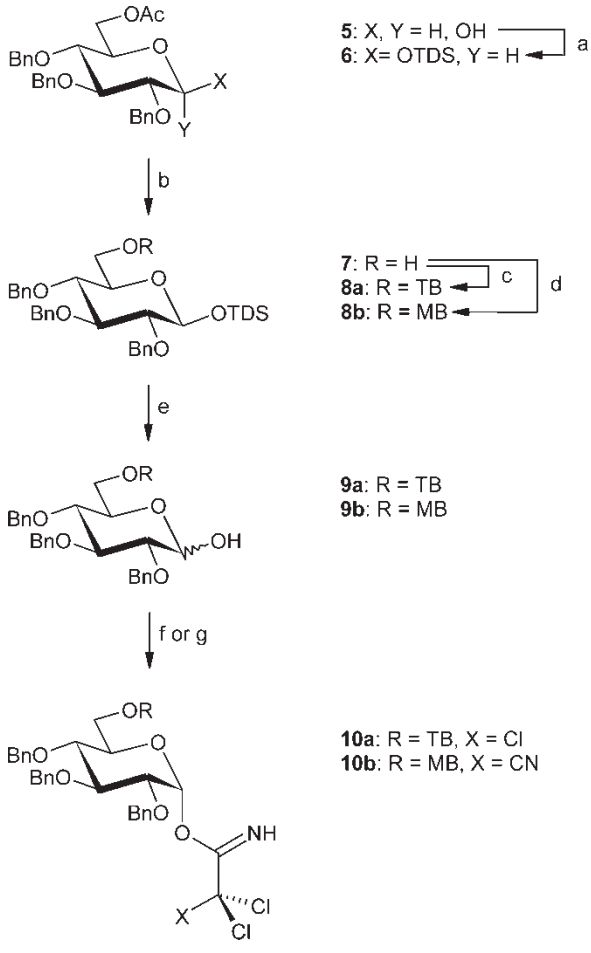
Scheme 3: Glycosylation products of donors **2a**–**d** with acceptors **3a**–**d**.

trichloroacetimidate were carried out. To this end, 6-*O*-(4-*tert*-butylbenzyl)- and 6-*O*-(4-methylbenzyl)-protected glucose derivatives **9a**,**b** were prepared (Sch. 4). Readily available glucose derivative **5**[30] was silylated with thexyldimethylsilyl (TDS) chloride in the presence of imidazole to furnish exclusively

Table 1: Glycosylation Results of acceptors **3a**–**d** with donors **2a**–**d**.

Entry	Donor	Acceptor	Reaction Temp.	Conditions[a] TMSOTf (eq)	Product	Yield (%)	α/β-Ratio
1	**2a**	**3a**	rt	0.05	**4aa**	71	β
2	**2b**	**3a**	rt	0.025	**4ba**	65	β
3	**2b**	**3b**	0°C	0.025	**4bb**	82	β
4	**2b**	**3c**	0°C	0.1	**4bc**	84	β
5	**2d**	**3a**	−40°C	0.02	**4da**	80	β
6	**2d**	**3b**	−40°C	0.03	**4db**	89	2:1
7	**2d**	**3c**	−40°C	0.07	**4dc**	73	α
8	**2c**	**3c**	−40°C	0.05	**4cc**	95	1:4
9	**2c**	**3d**	−40°C	0.02	**4cd**	90	1:2
10	**2d**	**3d**	−40°C	0.05	**4dd**	83	1:3
11	**2d**	**3d**	rt	0.05	**4dd**	57	10:1

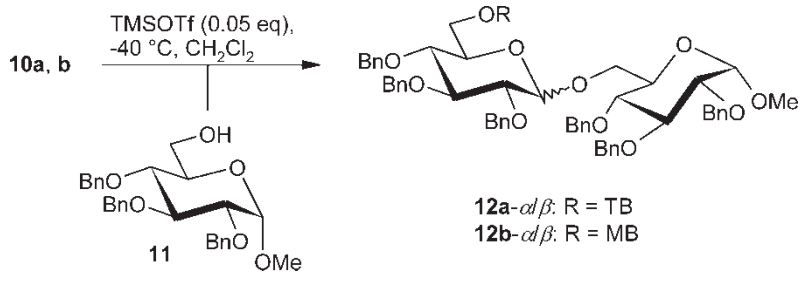
[a]Solvent: CH_2Cl_2/Hexane, 1:1.



Scheme 4: Synthesis of glycosyl donors **10a**,**b**. *Reagents and conditions*: a) TDS-Cl, imidazole, DMF, rt (97%); b) NaOMe, MeOH, rt (91%); c) TB-Br, NaH, DMF (95%); d) MB-Br, NaH, DMF (97%); e) TBAF, HOAc, THF (**9a**: qu, **9b**: 92%); f) CCl_3CN, DBU, CH_2Cl_2 (**10a**: 92%); g) $Cl_2C(CN)_2$, DBU, CH_2Cl_2, rt (**10b**: 90%).

β-glycoside **6**. Methanolysis of the 6-*O*-acetyl group ($\rightarrow$ **7**) and then alkylation with 4-*tert*-butylbenzyl (TB) bromide and 4-methylbenzyl (MB) bromide with NaH in DMF afforded 6-*O*-protected compounds **8a** and **8b**, respectively. 1-*O*-Desilylation with tetrabutylammonium fluoride (TBAF) in the presence of HOAc in THF gave the desired compounds **9a**,**b**. Reaction of **9a** with trichloroacetonitrile and of **9b** with dichloromalonitrile under standard conditions for imidate formation with electron-poor nitriles (i.e., catalysis with DBU as base) furnished *O*-glycosyl imidates **10a** and **10b**, respectively.

The 4-*tert*-butylbenzyl group in **10a** and the methyl group in **10b** are quite distant from the anomeric center; therefore, they should have



Scheme 5: Competition experiments with donors **10a**,**b** and acceptor **11**.

practically no influence on the glycosylation result with 6-*O*-unportected methyl glucopyranoside **11**[31] as acceptor. However, the **12a**/**12b** product ratios can be readily derived from the well-separated ^{1}H NMR signals of the *tert*-butyl and the methyl group (Sch. 5). Reaction of one equivalent each of **10a** and **10b** with subequivalent amounts of **11** (0.4, 1.0, 1.2 equivalents) under standard glycosylation conditions afforded in all cases a slight excess of disaccharide **12a**α,β over **12b**α,β in high yield (95%; **12a**:**12b**$\approx$6:5; α:$\beta\approx$1:4), thus exhibiting that imidates **10a** and **10b** possess similar reactivity. The difference in basicity of the imino group in **10a** and **10b**, due to the different electro-negativities of the chlorine atom and the cyano group, could lead to preferred catalyst attack and thus activation of **10a** and this way explain the experimental finding. It remains to be seen whether the lower steric demand of the dichloro-cyanomethyl group over the trichloromethyl group has advantages in sterically more demanding *O*-glycosyl imidate formations.

In conclusion, dichloromalonitrile is a suitable reagent for the base-catalyzed generation of *O*-glycosyl dichloro-cyanoacetimidates. These compounds exhibit glycosyl donor properties closely related to those of *O*-glycosyl trichloroacetimidates.

EXPERIMENTAL

General Methods

Solvents were purified according to the standard procedures, boiling range of petroleum ether 35–65°C. For flash chromatography, silica gel (J. T. Baker, particle size 40 μm) was employed. Thin-layer chromatography (TLC) was carried out using layer plastic foils coated with silica gel 60 F_{254} (Merck, layer thickness 0.2 mm). Melting points are reported uncorrected. Optical rotations were measured using a Perkin-Elmer 241 MC polarimeter 1-dm cell at 20°C. NMR spectra were recorded using Bruker AC 250 Cryospec or Bruker Avanca-DRX 600 spectrometers with teramethylsilane (TMS) or

residual H-signal in deuterated solvent as internal standard. MALDI-mass spectra were recorded on a Kratos Kompact Maldi 2, and 2,5-dihydroxybenzoic acid (DHB) or 6-aza-2-thiothymine (ATT) was used as the matrix. FAB mass spectra were measured on a Finnigan MAT 312/AMD 5000 spectrometer.

***O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl) Dichloro-cyanoacetimidate (2a).** To a solution of dichloromalonitrile (0.89 mL, 8.60 mmol) and three drops of DBU in 3 mL of dichloromethane, a solution of compound **1a** in 7 mL of dichloromethane was added dropwise. After 30 min the reaction mixture was worked up and purified as described for compound **2b**, which furnished **2a** (0.95 g, 68%) as colorless foam. The corresponding β-compound (12%) could not be obtained in pure form. TLC (toluene/acetone 4:1): $R_f = 0.44$. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.83 (s, 1H, NH), 6.59 (d, $J_{1,2} = 3.7$ Hz, 1H, 1-H), 5.55 (d, $J_{3,2} = 9.8$ Hz, 1H, 3-H), 5.19 (t, $J_t = 9.8$ Hz, 1H, 4-H), 5.15 (dd, $J_{2,1} = 3.7$, $J_{2,3} = 9.8$ Hz, 1H, 2-H), 4.32–4.11 (m, 3H, 5-H, 2 6-H), 2.09, 2.06, 2.04, 2.03 (4 s, 12H, 4 OAc). $C_{17}H_{20}Cl_2N_2O_{10}$ (483.3). Calcd.: C, 42.25; H, 4.17; N, 5.80. Found: C, 42.26; H, 4.20; N, 5.72.

***O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl) Dichloro-cyanoacetimidate (2b).** To a solution of dichloromalonitrile (888 μL, 8.60 mmol) and three drops of DBU in 3 mL of dichloromethane, a mixture of 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose in 7 mL of dichloromethane was slowly added dropwise. After 30 min stirring at rt the solvent was evaporated in vacuo. Purification by flash chromatography (toluene/acetone 8 : 1) furnished **2b** as an oily residue, which after recrystallization (petroleum ether/diethyl ether) furnished colorless crystals (1.21 g, 87%). m.p.: 113°C. TLC (toluene/acetone 4 : 1): $R_f = 0.41$. $[\alpha]_D = +106.2$ (*c* 2.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): (=8.76 (bs, 1H, NH), 6.58 (d, $J_{1,2} = 2.6$ Hz, 1H, 1-H), 5.54 (m, 1H, 4-H), 5.40–5.30 (m, 2H, 2-H, 3-H), 4.38 (t, $J_t = 6.8$ Hz, 1H, 5-H), 4.18–3.98 (m, 2H, 2 6-H), 2.14, 2.01, 2.00, 1.98 (4 s, 12H, 4 OAc). $C_{17}H_{20}Cl_2N_2O_{10}$ (483.3). Calcd.: C, 42.25; H, 4.17; N, 5.80. Found: C, 42.30; H, 4.21; N, 5.80.

***O*-(2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl) Dichloro-cyanoacetimidate (2c).** To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **1c** (1.55 g, 2.87 mmol) in dichloromethane (10 mL) was added dichloromalonitrile (0.8 mL, 7.78 mmol) and three drops of DBU. After 30 min the reaction mixture was worked up and purified as described for compound **2d,** furnishing essentially only α-product **2c** (1.26 g, 68%) as colorless oil. TLC (petroleum ether/diethyl ether 3:2): $R_f = 0.36$. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.62 (s, 1H, NH), 7.07–7.31 (m, 20H, Ph), 6.51 (dd, $J_{1,2} = 3.4$ Hz, 1H, 1-H), 5.33–4.36 (m, 8H, 4 CH_2Ph), 4.01 (dd, $J_{3,2} = J_{3,4} = 9.4$ Hz, 1H, 3-H), 3.94 (m, 1H, 4-H), 3.73 (dd, $J_{2,1} = 3.4$, $J_{2,3} = 9.4$ Hz, 1H, 2-H), 3.79–3.56 (m, 2H, 5-H, 2 6-H).

***O*-(2,3,4,6-Tetra-*O*-benzyl-D-galactopyranosyl) Dichloro-cyanoacetimidate (2d).** To a solution of **1d** (1.55 g, 2.87 mmol) in dichloromethane were added dichloromalonitrile (0.8 mL, 7.78 mmol) and three drops of DBU. After stirring for 30 min the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/diethyl ether 3:2) furnished essentially only α-product **2d** (1.17 g, 60%) as a colorless oil. TLC (petroleum ether/diethyl ether 3:2): $R_f = 0.45$. $[\alpha]_D = +39.4$ (c 2.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.58 (bs, 1H, NH), 7.38–7.19 (m, 10H, Ph), 6.54 (d, $J_{1,2} = 3.4$ Hz, 1H, 1-H), 4.98–4.36 (m, 8H, 4 CH_2Ph), 4.23 (dd, $J_{2,1} = 3.4$, $J_{2,3} = 9.6$ Hz, 1H, 2-H), 4.14 (t, $J_t = 6.6$ Hz, 1H, 5-H), 4.03–3.92 (m, 2H, 3-H, 4-H), 3.61–3.47 (m, 2H, 2 6-H).

Decyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (4aa). Donor **2a** (230 mg, 476 μmol) and 1-decanol (109 μL, 572 μmol) were dissolved in dichloromethane/hexane (1:1) at 0°C. A 0.1 M solution of TMSOTf (115 μL, 11.5 μmol, 0.025 eq) in dichloromethane was added dropwise. After 1 h stirring at 0°C the reaction was terminated by adding triethylamine and the reaction mixture concentrated under reduced pressure. Purification by flash chromatography (toluene/acetone 20:1) furnished **4aa** (156 mg, 65%) as a colorless oil. The physical data correspond with those in ref. 23.

Decyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside (4ba). 2b (100 mg, 0.21 mmol) and 1-decanol (48 μL, 0.25 mmol) were dissolved in dichloromethane/hexane (1:1) (2 mL) and the glycosidation initiated by adding a 0.1 M solution of TMSOTf (50 μL, 5 μmol, 0.025 eq) in dichloromethane at rt. After 1 h the reaction mixture was quenched with one drop of triethylamine and concentrated under reduced pressure. Purification by flash chromatography furnished **4ba** (72 mg, 71%) as a colorless oil. The physical data correspond with those in ref. 23.

Benzyl 2,3,4-Tri-*O*-benzyl-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1-6)-α-D-glucopyranoside (4bb). A solution of **2b** (200 mg, 414 μmol) and **3b**[20] (269 mg, 497 μmol) in dichloromethane/hexane (1 : 2) (3 mL) was cooled down to 0°C and then TMSOTf (10 μmol, 0.025 eq) in dichloromethane added. After 1 h the reaction mixture was quenched with one drop of triethylamine and concentrated under reduced pressure. Purification by flash chromatography furnished **4bb** (296 mg, 82%) as a colorless oil. TLC (petroleum ether/ethyl acetate 2:1): $R_f = 0.27$. $[\alpha]_D = +29.9$ (c 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.38–5.37 (dd, 1H, 4b-H), 5.29 (dd, $J_{2b,1b} = 8.1$, $J_{2b,3b} = 10.4$ Hz, 1H, 2b-H), 5.00 (dd, $J_{3b,2b} = 10.4$, $J_{3b,4b} = 4.5$ Hz, 1H, 3b-H), 4.81 (d, $J_{1a,2a} = 4.0$ Hz, 1H, 1a-H), 5.03–4.51 (m, 8H, 4 CH_2Ph), 4.49 (d, $J_{1b,2b} = 8.1$ Hz, 1H, 1b-H), 4.18–4.12 (m, 2H, 2 6b-H), 4.08–4.01 (m, 2H, 6a-H, 5b-H), 3.89–3.82 (m, 2H, 4a-H, 5a-H), 3.66 (dd, $J_{gem} = 10.6$, $J_{6a,5a} = 4.6$ Hz, 1H, 6a-H), 3.51 (dd, $J_{2a,1a} = 4.0$,

$J_{2a,3a} = 9.8$ Hz, 1H, 2a-H), 3.45 (dd, $J_{3a,2a} = J_{3a,4a} = 9.8$ Hz, 1H, 3a-H), 2.12, 2.03, 1.97, 1.95 (4 s, 12H, 4 OAc).

Methyl 2,3,6-Tri-*O*-benzyl-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1-4)-α-D-glucopyranoside (4bc). A solution of **2b** (200 mg, 414 μmol) and **3c**[21] (231 mg, 497 μmol) in dichloromethane/hexane (1:1) (4 mL) was cooled down to 0°C. After addition of 400 μL of a solution of TMSOTf (10 μmol, 0.025 eq) in dichloromethane, immediately one drop of triethylamine was added and the reaction mixture concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate 2:1) furnished **4bc** (275 mg, 84%) as a colorless foam. The physical data correspond with those in ref. 24.

Decyl 2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranoside (4da). A solution of **2d** (300 mg, 444 μmol) and 1-decanol (110 μL, 577 μmol) in dichloromethane/hexane (1:1, 5 mL) was cooled to −40°C. Then a 0.1 M solution of TMSOTf (100 μL, 10 μmol, 0.02 eq) in dichloromethane was added followed by one drop of triethylamine. The reaction mixture was then concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate 2:1) furnished **4da** (275 mg, 84%) as a colorless oil. The structure of the compound was secured by debenzylation, peracetylation, and comparison with **4ba**. **4da**: TLC (petroleum ether/ethyl acetate 4:1): $R_f = 0.62$. $[\alpha]_D = -1.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.23 (m, 20H, Ph), 4.96–4.37 (m, 8H, 4 CH_2Ph), 4.34 (d, $J_{1,2} = 7.7$ Hz, 1H, 1-H), 3.96–3.90 (m, 1H, 5-H), CH_3), 3.88–3.88 (m, 1H, 4-H), 3.81 (d, $J_{2,1} = 7.7$, $J_{2,3} = 9.7$ Hz, 1H, 2-H), 3.61–3.43 (m, 5H, 3-H, 2 6-H, CH_2), 1.66–1.57 (m, 2H, CH_2), 1.25 (bs, 14H, 7 CH_2), 0.87 (t, $J_t = 6.5$ Hz, 3H, CH_3). $C_{44}H_{56}O_6 \cdot H_2O$ (699.0). Calcd.: C, 75.61; H, 8.36. Found: C, 75.79; H 8.17.

Benzyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-(1-6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (4db-α) and Benzyl *O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-(1-6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (4db-β). A solution of **2d** (200 mg, 296 μmol) and **3b**[20] (192 mg, 355 μmol) in dichloromethane/hexane (1:1, 3 mL) was cooled to −40°C. Then a 0.1 M solution of TMSOTf (100 μL, 10 μmol, 0.03 eq) in dichloromethane was added and stirred for 30 min. The reaction mixture was quenched with triethylamine and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate 2:1) furnished **4db-α** (184 mg, 59%) and **4db-β** (96 mg, 30%).

4db-α: TLC (petroleum ether/ethyl acetate 4:1): $R_f = 0.36$. $[\alpha]_D = +86.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.13 (m, 40H, Ph), 5.01 (d, $J_{1b,2b} = 3.4$ Hz, 1H, 1b-H), 4.73 (d, $J_{1a,2a} = 3.7$ Hz, 1H, 1a-H), 5.00–4.33 (m, 16H, 8 CH_2Ph), 4.05–3.50 (m, 11H, 2b-H, 3a-H, 3b-H, 4a-H, 4b-H, 5a-H, 5b-H, 2 6a-H, 2 6b-H), 3.49 (dd, $J_{2a,1a} = 3.7$, $J_{2a,3a} = 9.6$ Hz, 1H, 2a-H).

4db-β: TLC (petroleum ether/ethyl acetate 4:1): $R_f = 0.28$. ^{1}H NMR (250 MHz, $CDCl_3$): (7.33–7.13 (m, 40H, Ph), 5.00–4.35 (m, 17H, 1a-H, 8 CH_2Ph), 4.33 (d, $J_{1a,2a} = 7.7$ Hz, 1H, 1b-H), 4.13–3.83 (m, 5H, 3b-H, 4a-H, 4b-H, 5a-H, 5b-H), 3.66–3.35 (m, 7H, 2a-H, 2b-H, 3a-H, 2 6a-H, 2 6b-H).

Methyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-(1-4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (4dc). A solution of **2d** (280 mg, 414 μmol) and **3d**[22] (130 mg, 497 μmol) in dichloromethane/hexane (1:1, 4 mL) was cooled down to −40°C. Then a 0.1 M solution of TMSOTf (300 μL, 30 μmol, 0.07 eq) in dichloromethane was added. One drop of triethylamine was added and the reaction mixture concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate 4:1) furnished **4dc** (318 mg, 73%) as colorless oil. The physical data are in accordance with the literature.[28]

Methyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl)-(1-4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (4cc). A solution of **2c** (300 mg, 444 μmol) and **3c**[21] (248 mg, 533 μmol) in dichloromethane/hexane (1:1, 4 mL) was cooled down to −40°C. Then 200 μL of a solution of TMSOTf (20 μmol, 0.05 eq) in dichloromethane was added. After 30 min two drops of triethylamine were added and the reaction mixture concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate 4:1) furnished **4cc** (535 mg, 95%) as colorless oil; anomeric mixture ($\alpha/\beta = 4:1$). The physical data are in accordance with the literature.[25]

1,2:5,6-Di-*O*-isopropylidene-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1-3)-α-D-glucofuranose (4cd-α) and 1,2:5,6-Di-*O*-isopropylidene-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-(1-3)-α-D-glucofuranose (4cd-β). A solution of **2c** (300 mg, 444 μmol) and **3d**[22] (130 mg, 497 μmol) in dichloromethane/hexane (1 : 1, 6 mL) was cooled down to −40°C. Then a 0.1 M solution of TMSOTf (100 μL, 10 μmol, 0.02 eq) in dichloromethane was added dropwise. After adding three drops of triethylamine, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate 4:1) furnished **4cd-α** (104 mg, 30%) and **4cd-β** (207 mg, 60%). The physical data are in accordance with the literature.[26,27]

3-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-(1-3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (4dd-α) and 3-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-(1-3)-1,2:5,6-di-*O*-isopropyliden-α-D-glucofuranose (4dd-β). A solution of **2d** (280 mg, 414 μmol) and **3d**[22] (130 mg, 497 μmol) in dichloromethane/hexane (1:1, 6 mL) was cooled down to −40°C. Then 200 μL of a solution of TMSOTf (20 μmol, 0.05 eq)

in dichloromethane was added dropwise. The reaction mixture was quenched with triethylamine and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate 4:1) furnished **4dd-α** (69 mg, 21%) and **4dd-β** (202 mg, 62%) as colorless oils (α/β ratio = 1:3). The physical data are in accordance with the literature.[29]

Dimethylthexylsilyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (6). To a stirred solution of hemiacetal **5**[30] (13.00 g, 26.42 mmol) and imidazole (2.70 g, 39.63 mmol) in dry DMF (60 mL) was slowly added dimethylthexylsilyl chloride (6.16 mL, 31.70 mmol) at rt and the mixture was continuously stirred for 17 h. The mixture was then poured into ice water (200 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography on silica gel (petroleum ether/:EtOAc 9 : 1) to afford compound **6** (16.17 g) in 97% yield as a colorless syrup. R_f 0.76 (PE/EtOAc 3:1); $[\alpha]_D = +27.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.25 (m, 15H, ArH), 5.03–4.74 (m, 5H, 2.5 $PhCH_2$), 4.68 (d, $J_{1,2} = 7.5$ Hz, 1H, 1-H), 4.60 (d, $J = 10.8$ Hz, 1H, 0.5 $PhCH_2$), 4.39 (dd, $J_{6A,6B} = 11.8$, $J_{6A,5} = 1.8$ Hz, 1H, H-6_A), 4.17 (dd, $J_{6B,6A} = 11.8$, $J_{6B,5} = 5.8$ Hz,1H, H-6_B), 3.69 (t, $J_{3,2} = J_{3,4} = 9.0$ Hz, 1H, H-3), 3.55–3.50 (m, 2H, H-4,5), 3.42 (dd, $J_{2,3} = 9.3$ Hz, $J_{2,1} = 7.5$ Hz, 1H, 2-H), 2.06 (s, 3H, Ac), 1.76–1.65 (m, 1H, Me_2CH), 0.93, 0.92, 0.90 (3 s, 12H, 4 Me), 0.22, 0.20 (2 s, 6H, 2 Me) ppm; MALDI-MS (positive mode, matrix: DHB) for $C_{37}H_{50}O_7Si$ (*m*/*z*): $[M + Na]^+ = 657.7$; Anal. Calcd for $C_{37}H_{50}O_7Si$ (634.9): C, 70.00; H, 7.94. Found: C, 69.69; H, 7.49.

Dimethylthexylsilyl 2,3,4-Tri-*O*-benzyl-β-D-glucopyranoside (7). To a stirred solution of compound **6** (15.95 g, 26.16 mmol) in dry methanol (90 mL) and CH_2Cl_2 (10 mL) was added NaOMe (68 mg, 1.26 mmol) at rt and the mixture was continuously stirred for 23 h. The mixture was then neutralized with Amberlyst 15 ion exchange resin, filtered, concentrated in vacuo, and purified by flash column chromatography on silica gel (PE/EtOAc 18:1 → 12:1) to afford compound **7** (14.89 g) in 91% yield as a colorless syrup. R_f 0.19 (PE/EtOAc 12:1); $[\alpha]_D = +10.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30–7.25 (m, 15H, ArH), 4.96–4.59 (m, 7H, 3 $PhCH_2$, 1-H), 3.82 (dd, $J_{6A,6B} = 12.0$, $J_{6A,5} = 3.0$ Hz,1H, H-6_A), 3.69–3.61 (m, 2 H), 3.54 (t, $J = 9.3$ Hz, 1 H), 3.38–3.32 (m, 2 H), 1.75–1.60 (m, 1H, Me_2CH), 0.89, 0.88, 0.87 (3 s, 12H, 4 Me), 0.18, 0.17 (2 s, 6H, 2 Me) ppm; MALDI-MS (positive mode, matrix: DHB) for $C_{35}H_{48}O_6Si$ (*m*/*z*): $[M + Na]^+ = 615.7$, $[M + K]^+ = 631.6$; Anal. Calcd for $C_{35}H_{48}O_6Si$ (592.8): C, 70.91; H, 8.16. Found: C, 70.66; H, 7.67.

Dimethylthexylsilyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4-*tert*-butylbenzyl)-β-D-glucopyranoside (8a). To a stirred suspension of compound **7** (1.10 g, 1.86 mmol) and molecular sieves (4 Å MS, 1.50 g) in dry DMF (10 mL) was added NaH (89 mg, 2.23 mmol, 60% dispersion in mineral oil) at 0°C. Five minutes later, 4-*tert*-butylbenzyl bromide (0.41 mL, 2.23 mmol) was added dropwise and the mixture was continuously stirred for 17 h at rt. The mixture was then diluted with sat. $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography on silica gel (PE/EtOAc 30:1 → 20:1) to afford compound **8a** (1.31 g) in 95% yield as a colorless syrup. R_f 0.59 (PE/EtOAc 12:1); $[\alpha]_D = +17.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.21 (m, 19H, ArH), 5.02–4.51 (m, 9H, 4 $ArCH_2$, H-1), 3.71–3.60 (m, 4 H), 3.47–3.38 (m, 2 H), 1.78–1.65 (m, 1H, Me_2CH), 1.32 (s, 9H, Me_3C), 0.93, 0.92, 0.91, 0.90, 0.89 (5 s, 12H, 4Me), 0.24, 0.21 (2 s, 6H, 2 Me) ppm; MALDI-MS (positive mode, matrix: DHB) for $C_{46}H_{62}O_6Si$ (*m*/*z*): $[M + Na]^+ = 761.7$, $[M + K]^+ = 777.7$; Anal. Calcd for $C_{46}H_{62}O_6Si$ (739.1): C, 74.76; H, 8.46. Found: C, 74.79; H, 8.25.

Dimethylthexylsilyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4-methylbenzyl)-β-D-glucopyranoside (8b). Compound **8b** was prepared using the same protocol as that for preparing compound **8a**. **8b**: 1.37 g (97%), colorless syrup. R_f 0.69 (PE/EtOAc 12 : 1); $[\alpha]_D = +14.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.21 (m, 19H, ArH), 5.02–4.51 (m, 9H, 4 $ArCH_2$, 1-H), 3.71–3.60 (m, 4H), 3.47–3.38 (m, 2H), 1.78–1.65 (m, 1H, Me_2CH), 1.32 (s, 9H, Me_3C), 0.93, 0.92, 0.91, 0.90, 0.89 (5 s, 12H, 4 Me), 0.24, 0.21 (2 s, 6H, 2 Me) ppm; MALDI-MS (positive mode, matrix: DHB) for $C_{43}H_{56}O_6Si$ (*m*/*z*): $[M + Na]^+ = 719.9$; Anal. Calcd for $C_{43}H_{56}O_6Si$ (697.0): C, 74.10; H, 8.10. Found: C, 73.99; H, 7.82.

2,3,4-Tri-*O*-benzyl-6-*O*-(4-*tert*-butylbenzyl)-D-glucopyranose (9a). To a stirred solution of compound **8a** (790 mg, 1.07 mmol) and AcOH (240 μL, 4.19 mmol) in dry THF (6 mL) in a Teflon flask was added TBAF · 3 H_2O (4 mL, 1 mmol/mL THF solution) at 0°C and the mixture was continuously stirred for 24 h at rt. The mixture was then diluted with sat. $NaHCO_3$ (60 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography on silica gel (PE/EtOAc 4:1) to afford compound **9a** (637 mg) in quant. yield as a white solid. R_f 0.21 (PE/EtOAc 4 : 1); $\alpha/\beta = 37 : 10$; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.34–7.13 (m, 19H, ArH), 5.26 (t, $J = 2.5$ Hz, 0.79H, H-1α), 4.97–4.42 (m, 8.21H, 4 $ArCH_2$, H-1β), 4.05–3.36 (m, 6H, H-2,3,4,5,6), 3.13, 2.88 (2 br s, 1H, OH), 1.29, 1.27 (2 s, 9H, Me_3C) ppm; MALDI-MS (positive mode, matrix: DHB) for $C_{38}H_{44}O_6$ (*m*/*z*): $[M + Na]^+ = 619.8$, $[M + K]^+ = 635.8$; Anal. Calcd for $C_{38}H_{44}O_6$ (596.8): C, 76.48; H, 7.43. Found: C, 76.25; H, 7.22.

2,3,4-Tri-*O*-benzyl-6-*O*-(4-methylbenzyl)-D-glucopyranoside (9b). Compound **9b** was prepared using the same protocol as that for preparing compound **9a. 9b**: 952 mg (92%), white solid. R_f 0.50 (PE/EtOAc 4:1); $\alpha/\beta = 8{:}5$; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.42–7.10 (m, 19H, ArH), 5.24 (d, $J = 3.5$ Hz, 0.62H, H-1α), 4.98–4.41 (m, 8.38H, 4 $ArCH_2$, H-1β), 4.06–3.37 (m, 6H, H-2,3,4,5,6), 3.13, 2.86 (2 br s, 1H, OH), 2.34, 2.32 (2 s, 3H, Me) ppm; MALDI-MS (positive mode, matrix: DHB) for $C_{35}H_{38}O_6$ (m/z): $[M + Na]^+ = 578.2$; Anal. Calcd for $C_{35}H_{38}O_6$ (554.7): C, 75.79; H, 6.91. Found: C, 75.84; H, 7.08.

2,3,4-Tri-*O*-benzyl-6-*O*-(4-*tert*-butylbenzyl)-D-glucopyranosyl Trichloroacetimidate (10a). To a stirred solution of hemiacetal **9a** (413 mg, 0.69 mmol) and CCl_3CN (510 μL, 5.10 mmol) in dry CH_2Cl_2 (3 mL) were added three drops of DBU at rt. After 30 min the mixture was concentrated in vacuo and purified by flash column chromatography on silica gel (toluene/EtOAc/Et_3N 200:5:2 → 100:4:1) to afford **10a** (472 mg) in 92% yield as a slightly yellow syrup. R_f 0.59 (toluene/EtOAc 10:1); $\alpha/\beta = 23{:}1$; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.72, 8.57 (2 s, 1H, NH), 7.35–7.13 (m, 19H, ArH), 6.52, 5.83 (2 d, $J_{1\alpha,2} = 3.3$, $J_{1\beta,2} = 7.5$ Hz, 1H, H-1α,β), 4.98–4.40 (m, 8H, 4 $ArCH_2$), 4.08–3.62 (m, 6H, H-2,3,4,5,6), 1.29, 1.27 (2 s, 9H, Me_3C) ppm; MALDI-MS (positive mode, matrix: DHB) for $C_{40}H_{44}Cl_3NO_6$ (m/z): $[M - CCl_3CN + Na]^+ = 619.6$, $[M - CCl_3CN + K]^+ = 635.8$.

2,3,4-Tri-*O*-benzyl-6-*O*-(4-methylbenzyl)-D-glucopyranosyl Dichlorocyanoacetimidate (10b). To a stirred solution of hemiacetal **9b** (295 mg, 0.53 mmol) and $Cl_2C(CN)_2$ (140 μL, 1.33 mmol) in dry CH_2Cl_2 (3 mL) were added two drops of DBU at rt. After 30 min the mixture was concentrated under vacuo and purified by flash column chromatography on silica gel (toluene/EtOAc/Et_3N 200:5:2 → 100:4:1) to afford **10b** (330 mg) in 90% yield as a colorless syrup. R_f 0.56 (toluene/EtOAc 10:1); $\alpha/\beta = 27:1$; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.64, 8.27 (2 s, 1H, NH), 7.43–7.10 (m, 19H, ArH), 6.54, 5.79 (2d, $J_{1\alpha,2} = 3.5$, $J_{1\beta,2} = 7.5$ Hz, 1H, H-1α,β), 5.02–4.35 (m, 8H, 4 $ArCH_2$), 4.06–3.55 (m, 6H, H-2,3,4,5,6), 2.30, 2.32 (2 s, 3H, Me) ppm; MALDI-MS (positive mode, matrix: DHB) for $C_{38}H_{38}Cl_2N_2O_6$ (m/z): $[M + Na]^+ = 711.2$, $[M + K]^+ = 727.1$.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4-*tert*-butylbenzyl)-α-D-glucopyranosyl-(1-6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (12aα) and Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4-*tert*-butylbenzyl)-β-D-glucopyranosyl-(1-6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (12aβ). *General procedure for glycosylations:* Trichloroacetimidate **10a** (89 mg, 0.12 mmol), acceptor **11**[31] (46 mg, 0.10 mmol), and a stirrer were combined in a flask (10 mL) and then dried in high vacuo while the flask was being kept in a 45°C oil bath. Two

hours later, the flask was cooled by air to ambient temperature and filled with argon, and anhydrous CH_2Cl_2 (1.0 mL) was added. Then the mixture was cooled to $-40^{\circ}C$ and TMSOTf (94 μL, 0.05 eq) was slowly added. Thirty minutes later, TLC showed the completion of the glycosylation. The reaction was quenched with one drop of Et_3N and concentrated. The residue was purified by flash column chromatography on silica gel (toluene/EtOAc 30:1 → 20:1 → 10:1) to afford a mixture of **12aα** and **12aβ** (84 mg **12aα**/**12aβ** ≈ 1 : 4 as estimated by ^1H NMR) in 82% yield as a colorless syrup. The mixture of **12aα** and **12aβ** was subjected again to flash column chromatography on silica gel (hexane/EtOAc 5:1 → 4:1) to afford a little pure **12aβ** (15 mg). Pure **12aα** could not be obtained. **12aβ**: R_f 0.15 (toluene/EtOAc 10:1); $[\alpha]_D = +16.7$ (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.38–7.19 (m, 34H, ArH), 5.02–4.48 (m, 15H, 7 $ArCH_2$, H-1a), 4.37 (d, $J_{1b,2b} = 7.8$ Hz, 1H, H-1b), 4.21 (dd, $J_{gem} = 10.8$, $J_{6a,5a} = 1.5$ Hz, 1H, H-6a), 4.02 (t, $J = 9.3$ Hz), 3.88–3.81 (m, 1H, H-5a), 3.78–3.42 (m, 9 H), 3.35 (s, 3H, MeO), 1.31 (s, 3H, Me_3C) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 150.5, 138.8, 138.6, 138.3, 138.1, 135.2, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 125.2, 103.8, 98.0, 84.8, 82.1, 82.0, 79.9, 78.0, 77.9, 77.2, 75.6, 75.1, 74.9, 74.8, 73.3, 69.9, 69.0, 68.5, 55.2, 34.5, 31.3; MALDI-MS (positive mode, matrix: DHB) for $C_{66}H_{74}O_{11}$ (*m*/*z*): $[M + Na]^+ = 1065.0$, $[M + K]^+ = 1081.0$; Anal. Calcd for $C_{66}H_{74}O_{11} \cdot H_2O$ (1061.3): C, 74.24; H, 7.05. Found: C, 74.54; H, 6.92.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4-methylbenzyl)-α-D-glucopyranosyl-(1-6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (12bα) and Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4-methylbenzyl)-β-D-glucopyranosyl-(1-6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (12bβ). As described for **12a,** dichloro-cyanoacetimidate **10b** (128 mg, 0.19 mmol) reacted with acceptor **11**[31] (72 mg, 0.16 mmol) in the presence of catalyst TMSOTf (150 μL, 0.05 eq) to afford a mixture of **12bα** and **12bβ** (131 mg, **12bα**/**12bβ** ≈ 1:4 as estimated by ^1H NMR) in 84% yield as a white solid. The mixture of **12bα** and **12bβ** was subjected again to flash column chromatography on silica gel (hexane/EtOAc 5:1 → 4:1) to afford some pure **12bβ** (21 mg). **12bβ**: R_f 0.14 (toluene/EtOAc 10:1); $[\alpha]_D = +19.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.33–7.10 (m, 34H, ArH), 5.00–4.46 (m, 15H, 7 $ArCH_2$, H-1a), 4.35 (d, $J_{1b,2b} = 7.8$ Hz, 1H, H-1b), 4.19 (dd, $J_{gem} = 10.5$, $J_{6a,5a} = 1.5$ Hz, 1H, H-6a), 4.00 (t, $J = 9.3$ Hz), 3.86–3.81 (m, 1H, H-5a), 3.76–3.42 (m, 9 H), 3.33 (s, 3H, MeO), 2.31 (s, 3H, Me) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.8, 138.5, 138.4, 138.1, 137.1, 135.1, 129.0, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.4, 103.8, 98.0, 84.8, 82.0, 81.9, 79.8, 78.0, 77.9, 75.6, 75.0, 74.9, 74.8, 73.3, 69.8, 68.7, 55.1, 21.1; MALDI-MS (positive mode, matrix: DHB) for $C_{63}H_{68}O_{11}$ (*m*/*z*): $[M + Na]^+ = 1023.3$; Anal. Calcd for $C_{63}H_{68}O_{11}$ (1001.2): C, 75.58; H, 6.85. Found: C, 75.42; H, 6.85.

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REFERENCES

[1] Schmidt, R.R. New methods for the synthesis of glycosides oligosaccharides – Are there alternatives to the Koenigs-Knorr method? Angew. Chem. Int. Ed. Engl. **1986**, *25*, 212–235.

[2] Schmidt, R.R.; Kinzy, W. Anomeric oxygen activation for glycoside synthesis. The trichloroacetimidate method. Adv. Carbohydr. Chem. Biochem. **1994**, *50*, 21–123.

[3] Schmidt, R.R.; Jung, K.-H. Trichloroacetimidates. In *Carbohydrates in Chemistry and Biology, Part I: Chemistry of Saccharides*; Ernst, B., Hart, G.W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, 5–59.

[4] Toshima, K.; Tatsuta, K. Recent progress in *O*-glycosylation methods and its application to natural products synthesis. Chem. Rev. **1993**, *93*, 1503–1531.

[5] Michel, J. α- und β-Glycosylimidate: Ihre Herstellung und Anwendung in der Glycosid- und Oligosaccharidsynthese. Dissertation, Universität Konstanz, Verlag Wolfgang Hartung-Gorre: Konstanz, 1983.

[6] Schmidt, R.R.; Michel, J. Einfache Synthese von α- und β-*O*-Glycosylimidaten. Herstellung von Glykosiden und Disacchariden. Angew. Chem. Int. Ed. Engl. **1980**, *92*, 763–764.

[7] Huchel, U. Neue Methoden zur diastereoselektiven Glycosylierung. Dissertation, Universität Konstanz, Verlag Papierflieger, Clausthal-Zellerfeld: New York, 1998.

[8] Yu, B.; Tao, H. Glycosyl trifluoroacetimidates. Part 1: preparation and application as new glycosyl donors. Tetrahedron Lett. **2001**, *42*, 2405–2408.

[9] Yu, B.; Tao, H. Glycosyl trifluoroacetimidates. 2. Synthesis of dioscin and xiebai saponin I. J. Org. Chem. **2002**, *67*, 9099–9102.

[10] Adinolfi, M.; Barone, G.; Iademisi, A.; Schiattarella, M. Iodine/Triethylsilane as a convenient promoter system for the activation of disarmed glycosyl trichloro- and *N*-(phenyl)trifluoroacetimidates. Synlett **2002**, 269–272.

[11] Huchel, U.; Schmidt, C.; Schmidt, R.R. Direct anomeric *O*-arylation and *O*-hetarylation of glucose — electron deficient aromatic and heteroaromatic compounds in aryl and hetaryl glycoside synthesis. Tetrahedron Lett. **1995**, *36*, 9457–9460.

[12] Huchel, U.; Schmidt, C.; Schmidt, R.R. Synthesis of hetaryl glycosides and their glycosyl donor properties. Eur. J. Org. Chem. **1998**, 1353–1360; and references therein.

[13] Hanessian, S.; Condé, J.J.; Lion, B. The stereocontrolled synthesis of 1,2-cis furanosyl nucleosides via a novel anomeric activation. Tetrahedron Lett. **1995**, *36*, 5865–5868.

[14] Hanessian, S. *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker Inc: New York, 1997, 381–388and references therein.

[15] Glaudemans, P.J.; Fletcher, H.G., Jr. 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranose. In *Methods in Carbohydrate Chemistry*; Whistler, R.L., BeMiller, J.N., Eds.; Academic Press: New York, 1972; Vol. VI, 373–376.

[16] Gigg, J.; Gigg, R. The allyl ether as a protecting group in carbohydrate chemistry. J. Chem. Soc. (C) **1966**, 82.

[17] Excoffier, G.; Gagnaire, D.; Utille, J.P. Coupure sélective par l'hydrazine des groupements acétyles anomères de résidus glycosyles acetyls. Carbohydr. Res. **1975**, *39*, 368–373.

[18] Schmelzer, U. Synthesen und Eigenschaften von Nucleosidphosphatzucker-Analoga und neuen Glycosyldonoren. Dissertation, Universität Konstanz, Verlag Hartung-Gorre: Konstanz, 1997.

[19] Compound **3a** is commercially available.

[20] For compound **3b** see: Adams, P.R.; Harrison, R.; Inch, T.D.; Rich, P. Dehydrogenation of the phosphonate analogue of glucose 6-phosphate by glucose 6-phosphate dehydrogenase. Biochem. J. **1976**, *155*, 1–4.

[21] For compound **3c** see: Garegg, P.J.; Hultberg, H.; Wallin, S. A novel reductive ring-opening of carbohydrate benzylidene acetals. Carbohydr. Res. **1982**, *108*, 97–101.

[22] For compound **3d** see: Schmidt, O.T. Isopropylidene derivatives. In *Methods in Carbohydrate Chemistry*; Whistler, R.L., Wolfram, L., Eds.; Academic Press: New York, 1963; Vol. II, 320–321.

[23] Klotz, W. Untersuchungen zur anomeren *O*-Alkylierung von Hexosen und Pentosen – Reaktivität und Regioselektivität. Dissertation, Universität Konstanz, Verlag Hartung-Gorre: Konstanz, 1994.

[24] Kondo, H.; Aoki, S.; Ichikawa, Y.; Halcomb, R.L.; Ritzen, H.; Wong, C.H. Glycosyl phosphites as glycosylation reagents: scope and mechanism. J. Org. Chem. **1994**, *59*, 864–877.

[25] Sinaÿ, P.; Pougny, J.R.; Jacquinet, J.C.; Nassr, M.; Duchet, D. A novel synthesis of 1,2-*cis*-disaccharides. J. Am. Chem. Soc. **1977**, *99*, 6762–6763.

[26] Schmidt, R.R.; Michel, J. *O*-(α-D-Glucopyranosyl)-trichloracetimidate as glycosyl donor. J. Carbohydr. Chem. **1985**, *4*, 141–169.

[27] Schmidt, R.R.; Behrendt, M.; Töpfer, A. Nitriles as solvents in glycosylation reactions - highly selective β-glycoside synthesis. Synlett **1990**, 694–697.

[28] Wegmann, B.; Schmidt, R.R. The application of the trichloroacetimidate method to the synthesis of α-D-gluco- and α-D-galactopyranosides. J. Carbohydr. Chem. **1987**, *6*, 357–375.

[29] Tsvetkov, Y.E.; Klotz, W.; Schmidt, R.R. Disaccharide synthesis via anomeric *O*-alkylation. Liebigs Ann. Chem. **1992**, 371–375.

[30] McDevitt, J.P.; Lansbury, P.T., Jr. Glycosamino acids: new building blocks for combinatorial synthesis. J. Am. Chem. Soc. **1996**, *118*, 3818–3828.

[31] Liptak, A.; Jodal, I.; Nanasi, P. Stereoselective ring-cleavage of 3-*O*-benzyl- and 2,3-di-*O*-benzyl-4,6-*O*-benzylidenehexopyranoside derivatives with the $LiAlH_4$–$AlCl_3$, reagent. Carbohydr. Res. **1975**, *44*, 1–11.