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Total Synthesis of the Chlorinated Indigo-*N*-Glycosides Akashin A, B and C

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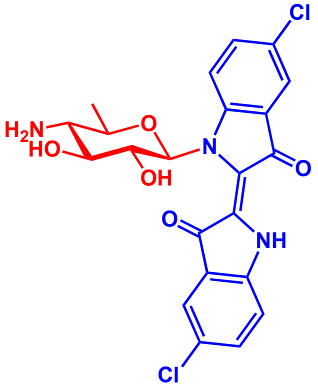
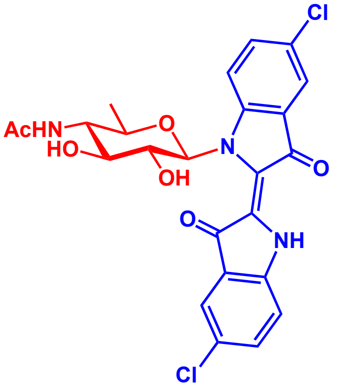
Abstract

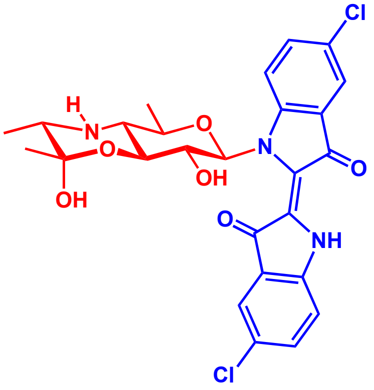
A total synthesis of the indigo-derived natural products akashin A-C was developed. The key step was the *N*-glycosylation of soluble *N*-benzylated-indigos with a suitably protected viosaminyl trichloroacetimidate. This donor was obtained from D-galactose. Unusual intermediates in the glycosylation reaction of *N*-benzylindigo (*O*-glycosides) were observed. The final transformations yielding akashin A required the adjustment of the reaction conditions to preserve the sensitive chlorinated indigo scaffold. Akashin A was converted to akashin B and C, all of which display an unusually high dextrarotatory optical rotation thus establishing the D-configuration in the sugar part of the natural akashins A-C.



Akashin A



Akashin B

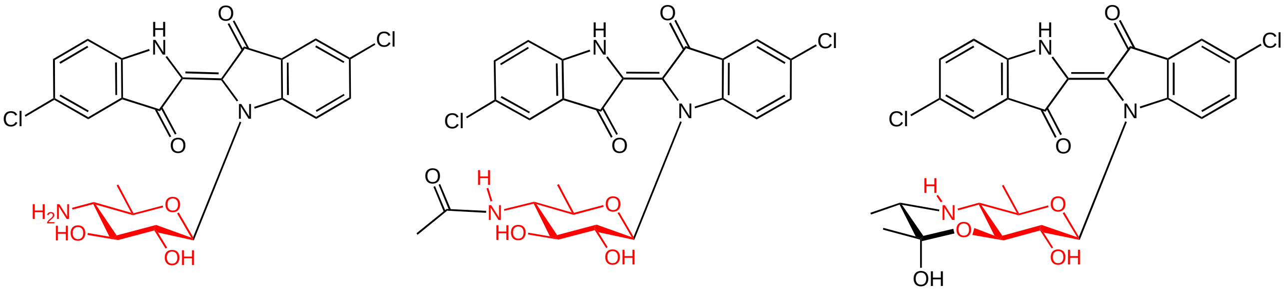


Akashin C

Keywords: Indigo, *N*-glycoside, glycosylation, protecting groups, natural products

Introduction

Heterocyclic *N*-glycosides are part of many natural products with pharmacological relevance. For example, the *N*-glyosylated natural products rebeccamycin, UCN-01, staurosporine and derivatives, all containing bisindole aglycons,[1-6] exhibit a strong cytotoxic activity. In the case of an N-glycosylated derivate of isoindigo named NATURA[7-8] and of *N*-(β-D-rhamnosyl)indirubin[9-10] anti-proliferative activities were found. No bioactive analogues of indigo were known until 2002, when *Laatsch et al*.[11-12] reported the isolation of akashin A (**1**), B (**2**) and C (**3**) from terrestric *Streptomyces* sp. GW 48/1497 (Figure 1). The akashins are colourful dyes with unusually high optical rotations. In contrast to pharmacologically inactive indigo the akashins show a remarkable cancerostatic activity against various human cancer cell lines. Akashin A was recently also discovered in the marine derived *Streptomyces* sp. strain F001.[13]



akashin A (**1**) akashin B (**2**) akashin C (**3**)

Scheme 1. The akashins A-C are natural products from *Streptomyces* containing a dichloroindigo aglycon *N*-glycosidically linked to the rare deoxy sugar viosamine (red).

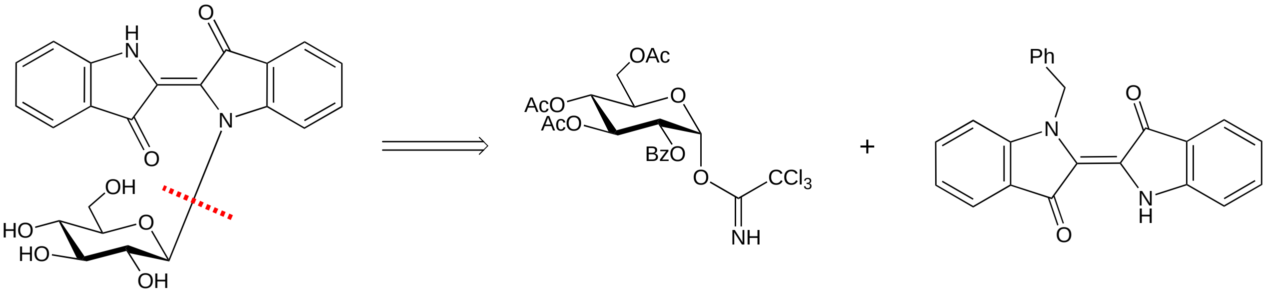
The akashins A-C were reported to be composed of dichloroindigo *N*-glycosidically linked to 4-amino-4,6-dideoxy-glucopyranose (viosamine)[14] with a hitherto undetermined absolute configuration. This rare carbohydrate is present as D-viosamine in the tetrasaccharide antigen of the *Bacillius anthracis* exosporium glycoprotein Bcl.[15] Additionally, also the enantiomer L-viosamine is part of natural products and antibiotics like amicetin,[16] norplicacetin,[17] tallysomicin[18] and the family of calicheamicins.[19]

Several approaches were developed for the synthesis of *N*-glycosylated indole derivatives comprising the indole-indolin-method by Preobrazhenskaya[13] and the direct acid-mediated glycosylation of substituted indoles[14]. For more than 100 years the preparation of synthetic indigo is known by dimerization of indoxyl in the presence of oxygen[15]. In analogy, a conceivable synthesis of akashins might be accomplished by the *N*-glycosylation of a chlorinated 3-indolyl acetate with suitable viosaminyldonor followed by a heterodimerization with chlorinated 3-indolyl acetate. Furthermore, a direct glycosylation of indigo or its derivatives could also be considered. Since the solubility of indigos is very low the use of derivatives for glycosylation has practical advantages. In particular *N*-benzylindigo[20] and also dehydroindigo[21] were shown by the Langer group to serve as suitable acceptors in glycosylation reactions.

Here we report the first total synthesis of akashin A and its subsequent derivatization to akashin B and C.

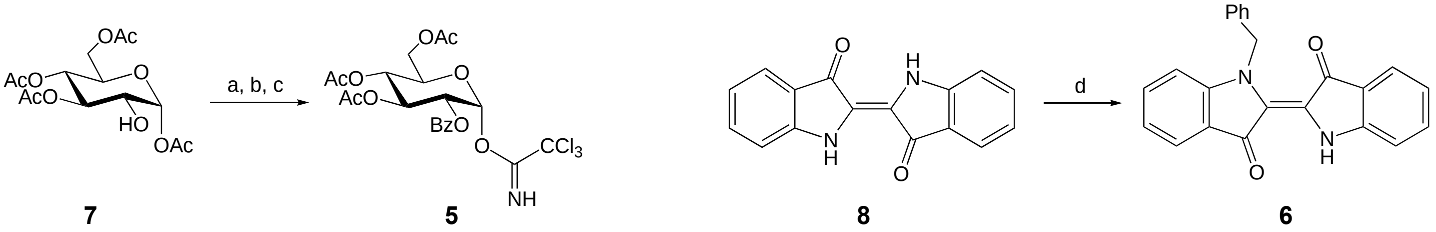
Results and Discussion

After a number of unsuccessful attempts to obtain soluble derivatives of indigo for glycosylation reactions we adopted the strategy developed by Langer[21] using *N*-benzylindigo **6** in combination with glycosyltrichloroacetimidates. The benzyl group of the corresponding indigo N-glycosides can be removed under oxidative conditions. However the formation of orthoester-like amide acetals in the glycosylation of **6** required the use of pivaloyl groups[22] in the glycosyl donor, which could not be removed without affecting the indigo scaffold.[21] As a model compound to demonstrate the *N*-glycosylation of *N*-benzylindigo **6** and the subsequent complete deprotection we selected the indigo glucoside **4** (Figure 2).



Scheme 2. Retrosynthesis of *N*-β-D-glucopyranosyl-indigo **4** as a model compound.

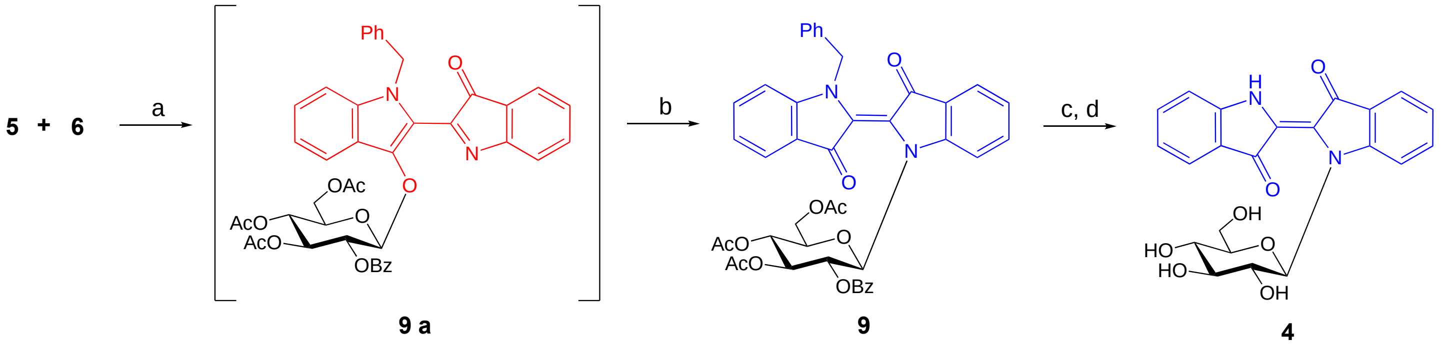
In view of the previous synthesis of tryptophan *N*-glucoside[23] we chose donor **5** with a benzoyl group at O-2. In analogy to 2-pivaloyl groups a benzoate should also reduce the amount of orthoester-like side products during glycosylation and permit cleavage under relatively mild conditions.[23]
The required trichloroacetimidate[24] building block **5** (Figure 3) was synthesized in three steps from 1,3,4,6-tetraacetyl-glucose **7**.[25] After benzoylation of OH-2 the anomeric acetate of compound **7a** was cleaved with hydrazine acetate and the intermediate hemiacetal **7b** was converted to the imidate **5** using DBU and trichloroacetonitrile in an overall yield of 75%. *N*-Benzylindigo **6** was obtained from indigo **8** in 48% yield accompanied by only small amounts of the green by-product *N,N'*-dibenzylindigo.



Scheme 3. Synthesis of **5** and **6**. Reagents and conditions: a) BzCl, pyridine, CH_2Cl_2 (99%); b) hydrazine acetate, DMF (80%); c) Cl_3CCN, DBU, CH_2Cl_2, 0°C (90%); d) NaH, DMF, BnBr (48%).

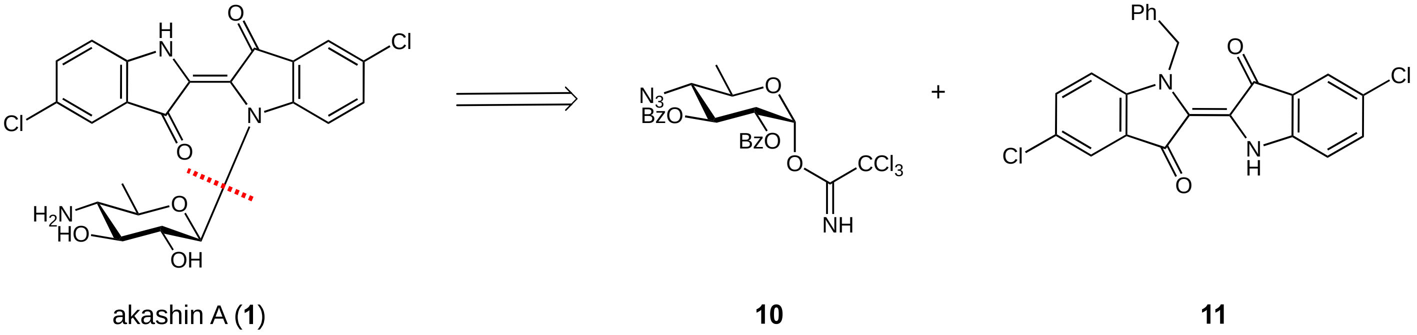
The glycosylation of *N*-benzylindigo **6** with the benzoylated donor **5** using TMSOTf furnished the desired indigo-*N*-glucoside **9** in 23% yield (Figure 4). Notably, the reaction proceeded in two steps accompanied by a colour change of the product spots on TLC. At low temperatures a red compound formed initially, which disappeared at higher temperatures and led to a new turquoise spot. As proposed by Langer[20] an *O*-glycoside

(**9a**, red) appeared first followed by rearrangement to the stable *N*-glycoside (**9**, turquoise). Variation of the glycosylation conditions did not increase the yield significantly. However, some of the starting material **6** could be recovered. The oxidative removal of the benzyl group was investigated next. Using a heated mixture of toluene/HOAc (1:1) in the presence of air led to the slow debenzylation of **9** over 12-18h and furnished the debenzylated intermediate **9b** (see supporting information) in a yield of 61%. Subsequently, the ester groups of **9a** were removed using dilute NaOMe/MeOH (c = 0.01 mol/l) furnishing the desired *N*-glycoside **4** in 51% yield. Higher concentrations of base or elevated temperatures resulted in the loss of the blue colour of the indigo core and led to inferior yields.



Scheme 4. Synthesis of N-glucosyl indigo **4**. Reagents and conditions: a) TMSOTf, 4 Å MS, CH_2Cl_2, -18 °C, 3 h; b) TMSOTf, 4 Å MS, CH_2Cl_2, RT, 10-12 h (23% over two steps); c) toluene/HOAc (1:1), 50 °C, air, 12-18 h, (61%); d) i. NaOMe/MeOH, 11 h; ii. Amberlyst 15 (H^+), (51%).

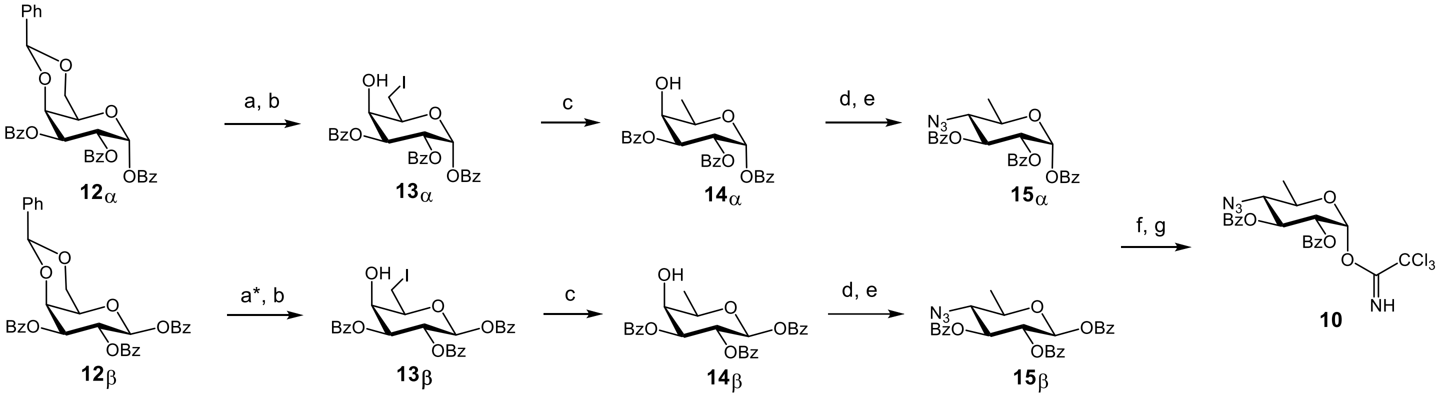
Following the synthetic route to *N*-glucosylated indigo **4** the synthesis of akashin A was planned based on the building blocks **10** and **11**. The viosaminyldonor **10** was conceived to contain benzoates, an azido group as a precursor for the free amine and an activation as a trichloroacetimidate. As an acceptor the benzylated 5,5´-dichloroindigo **11** was considered. The other akashins B (**2**) and C (**3)** should be accessible by chemical transformation of akashin A **1** (Scheme 5).



Scheme 5. Retrosynthesis of akashin A.

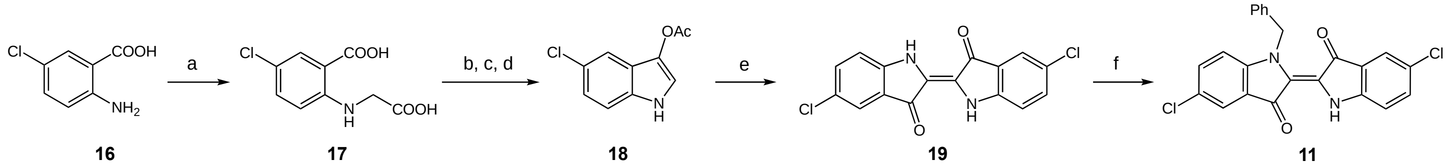
The synthesis of the D-*gluco*-configurated viosaminyldonor **10** required the introduction of an equatorial azide and deoxygenation of OH-6 when starting from D-galactose (Figure 6). After 4,6-benzylidenation of D-galactose and subsequent perbenzoylation it was found that the reactivity of tribenzoyl-4,6-benzylidene-D-galactose **12**[26] in the following reactions was depending on the anomeric configuration. Thus, both anomers were separated by flash chromatography (**12α**:**12**β = 87:13) and individual syntheses were carried out with each anomer.

After acidic removal of the benzylidene group (**12α–1**, **12β–1** the liberated primary alcohol was selectively converted to a halide. Reduction of the bromides using various methods was not successful. However, catalytic hydrogenation of the primary iodide **13α** gave fucoside **14α** in yields of up to 82% depending on the reaction volume. In contrast, the maximum yield of the corresponding beta anomer **14β** was only 35%. By recycling the recoverable starting material **13β** and the Pd-catalyst the overall yield could be improved. The equatorial azido function was introduced efficiently by formation of a triflate and subsequent nucleophilic substitution at C-4 using sodium azide in DMF. Both azides **15α,β** were selectively deprotected at the anomeric position with hydrazine hydrate (**10a**) and converted to the desired viosaminyl-trichloroacetimidate **10**.[27] The overall yields (9 steps) were 33% via the α-anomer **12α** vs. 17% from the β-anomer **12β**.



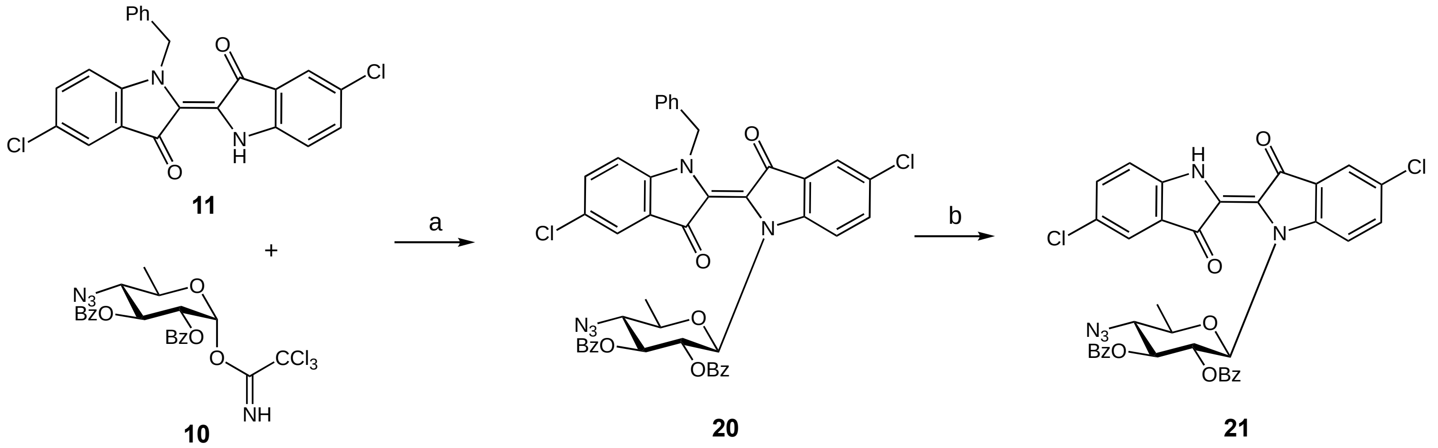
Scheme 6. Synthesis of donor **10**. Reagents and conditions: a) p-TsOH-H_2O, acetonitrile, MeOH, 1d (74%); a*) 2N HCl, acetonitrile, MeOH, 80 °C, 2 h (81%); b) NIS, PPh_3, DMF, 0-50 °C, 1d, **13α** (73%), **13β** (85%); c) H_2, Pd/C (10%), MeOH/HOAc (10:1), **14α** (56-83%), **14β** (35%); d) Tf_2O, pyridine, CH_2Cl_2, -18 °C, 2h; e) NaN_3, DMF, 30 min, **15α** (92%), **15β** (84%) over two steps; f) hydrazine acetate, DMF, RT, 3-6 h; g) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 2 h, (95% over two steps).

5,5'-Dichloroindigo **19**[28] was generated by the classic method via oxidative dimerization of indoxyl to indigo in basic solution (Figure 7).[29] The required 3-acetoxy-5-chloroindole **18**[30] was prepared by reacting 4-chloroanthranilic acid **16** and chloroacetic acid to 4-chlorophenylglycine-2-carboxylic acid **17**. Subsequent ring closure was effected by acetic anhydride giving 1,3-diacetyl-5-chloroindole. The cleavage of both acetyl groups in NaOH under argon followed by selective O-acetylation of the intermediate indoxyl provided **18** in 67% yield over two steps. The dichloroindigo **19** (73%) was obtained by oxidative dimerization of **18** under basic conditions. Due to the low solubility of **19** NMR analysis was carried out after reduction[31] to the corresponding vat indigo **19v**. *N*-Benzylation of **19** gave the selectively protected dichloroindigo derivative **11** 59%.



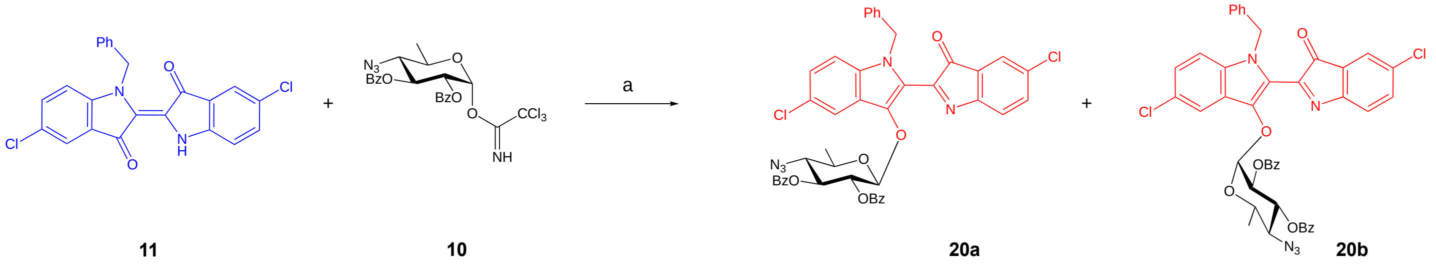
Scheme 7. Synthesis of *N*-benzyl-5,5'-dichloroindigo **11**. Reagents and conditions: a) chloroacetic acid, Na_2CO_3, reflux, 6 h (66%); b) Ac_2O, NaOAc, reflux, 3 h, (63%); c) NaOH, reflux, argon, 30 min; d) Ac_2O, 0°C, argon, 45 min, (67% over two steps); e) NaOH, MeOH, air, (73%); f) NaH, DMF, BnBr, 2 h, (59%).

N-benzyl-5,5'-dichloroindigo **11** was subsequently reacted with imidate **10** in the presence of TMSOTf as an activator (Scheme 8). By using less concentrated reaction conditions (18 mM **10** and **11**) the yield of the indigo-*N*-glycoside **20** was raised to 45%. Unreacted *N*-benzylindigo **11** (54%) was recovered and reused. The oxidative removal of the *N*-benzyl group of **20** proceeded smoothly over a period of 18 h. After purification by flash chromatography the indigo glycoside **21** was obtained in a yield of 60%.



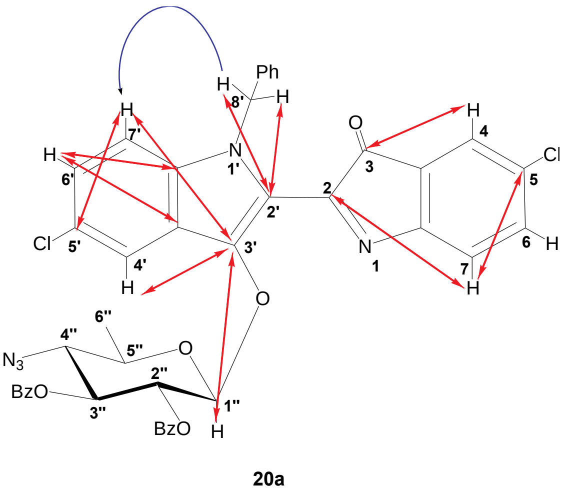
Scheme 8. Synthesis of the dichloroindigo-*N*-glycoside **21**. Reagents and conditions: a) TMSOTf, 4 Å MS, CH_2Cl_2, -18 °C to RT (15 h), (45%); b) toluene/HOAc (1:1), 60 °C, air, 12-18 h, (60%).

As observed before in the synthesis of **4** (Scheme 4) the *N*-glycosylation of the *N*-benzylated dichloroindigo **11** initially also gave a red intermediate at low temperatures (Scheme 9). Upon warming this intermediate disappeared and was converted to the *N*-glycoside **20** visible as a turquoise spot on TLC. We decided to isolate the red intermediate and determine its structure. Thus, a glycosylation reaction using **10** and **11** was kept at -18 °C and quenched with Et_3N after 2 h. Under slightly basic conditions the red intermediate **20a** was sufficiently stable for flash chromatography in the presence of Et_3N added to the solvents. In the course of this purification a second red compound (**20b**) was isolated, which nearly comigrated with the turquoise spot of the *N*-glycoside **21** on TLC.



Scheme 9. Synthesis of the reaction intermediates **20a** (β-*O*-glycoside) and **20b** (α-*O*-glycoside). Reagents and conditions: a) TMSOTf, 4 Å MS, CH_2Cl_2, -18 °C, 2 h.

The structures of the red indigo glycosides were determined by a set of 2D-NMR experiments (HH-COSY, HMQC, HMQC-COSY, NOESY, HMBC).[32] In the HMBC spectrum of **20a** (Scheme 10) the most relevant cross peaks were correlating C-3' with the anomeric proton H-1'' and C-2' with the benzylic H-8' thus localizing the glycoside at the oxygen of the benzylated half of the indigo. A strong NOESY cross peak was correlating H-8'a with H-7'. The *O*-glycoside was further supported by the ^{13}C-NMR signal for the anomeric carbon C-1'' of **21a** located at 101.4 ppm (N-glycoside **20**: C-1'': 85.3 ppm). The β-linkages of **20a** and **20** were deduced from the large coupling constants for H-1'' of **20a** ($J_{1'',2''}$ = 8.0 Hz at 5.3 ppm) and H-1'' of **20** ($J_{1'',2''}$ = 9.1 Hz at 6.0 ppm). The NMR results showed that **20a** is an *O*-glycoside thus confirming the mechanistic proposal that indigo *O*-glycosides occur as intermediates in the synthesis of benzylated indigo *N*-glycosides.[20]

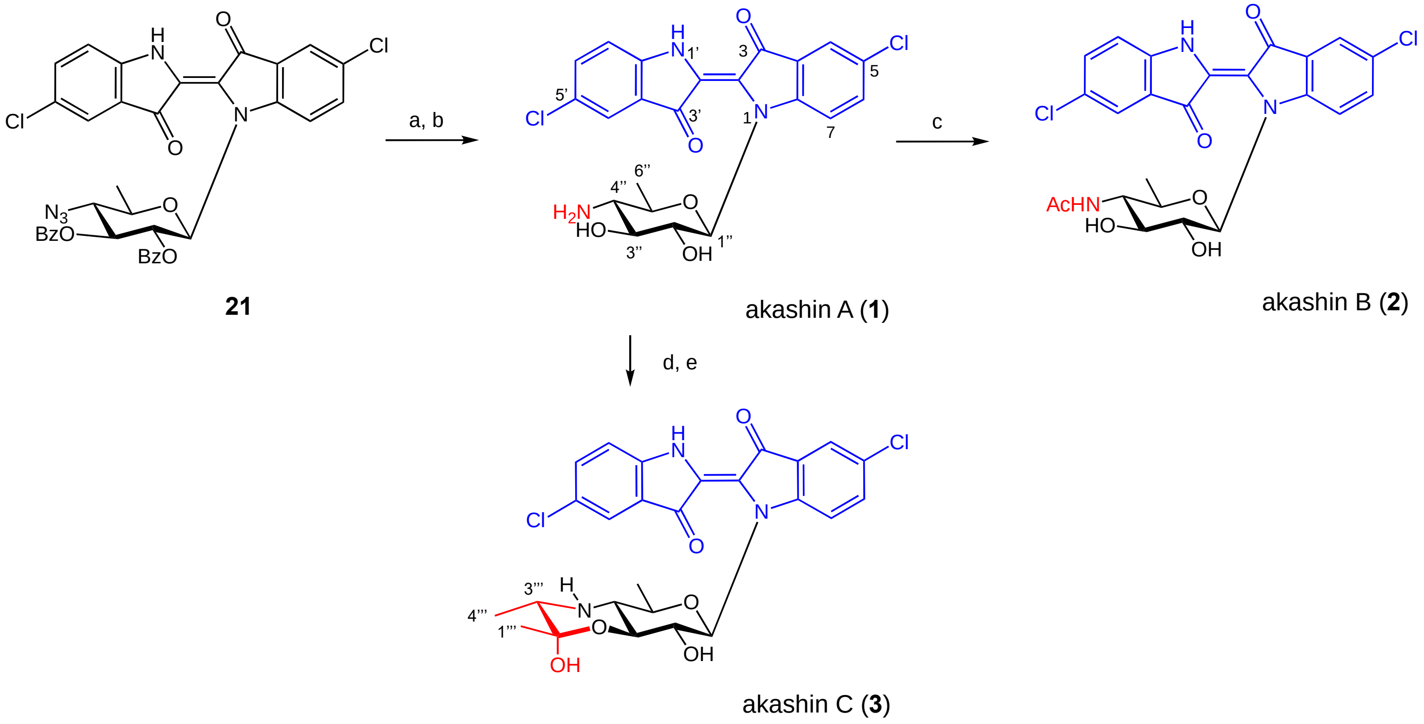


Scheme 10. HMBC (red)- and NOESY (blue)-correlations found for the red O-glycosidically linked indigo intermediate **20a.**

The ^{1}H-NMR spectra of **20b** also indicated an *O*-glycoside (^{13}C-NMR signal at 99.3 ppm for C-1''), however, with a small anomeric coupling constant ($J_{1'',2''}$ = 3.4 Hz for H-1'') corresponding to an α-glycoside. We first assumed an orthoester but in the ^{13}C-NMR spectrum of **20b** the carbonyl groups of both benzoates were present. Furthermore, the chemical shift of H-2 in **20b** was very similar to **20a** (**20a** H-2'': 5.38 ppm: **20b** H-2'': 5,35 ppm) thus ruling out an orthoester structure for **20b**.

The final steps in the synthesis of akashin A required the conversion of the azido function of **21** to a primary amine and the removal of the benzoates (Scheme 11). We found that both steps could be performed simultaneously using propanedithiol as a reductant under basic conditions. For best results thoroughly degassed and dried solvents were used under an argon atmosphere. When adding propanedithiol[33] to a methanolic solution of **21** containing DIPEA the blue colour of the starting material vanished immediately. The pale yellow colour of the solution indicated the formation of a leukoindigo. Under these conditions the combined reduction of the azide and the debenzoylation took about 4d until completion. At this point reoxidation of the indigo was initiated by acidification with 1% HOAc in dichloromethane accompanied by vigorous stirring of the reaction mixture in an open flask. The entire reaction sequence needed to be carried out under strict exclusion of light to prevent extensive radical dehalogenation of the reduced dichloroindigo.[31] In the presence of light the corresponding indigo *N*-glycosides with only one chloroatom or completely dehalogenated indigo were formed. After purification by solid phase extraction (C18) and size exclusion chromatography the intensely blue coloured akashin A (**1**) was isolated in yields up to 73%.

The selective *N*-acetylation of **1** was performed using a mixture of acetic anhydride and water[34] in methanol (Scheme 11). After purification by solid phase extraction akashin B (**2**) was obtained in nearly quantitative yield. The conversion of **1** to akashin C (**3**) was achieved by condensing diacetyl[35] (butane-2,3-dione) with **1** to a cyclic imine/hemiketal intermediate followed by a selective reduction of the imine with $NaCNBH_3$. Both steps were carried out in a one-pot procedure and gave akashin C (**3**) in 59% yield after flash chromatography. The axial orientation of the OH-group of the cyclic hemiketal in the final product **3** is stabilized by the anomeric effect. In the reductive amination step the formation of the sterically less hindered equatorial methyl group is favored.



Scheme 11. Final steps in the synthesis of akashin A, B and C. Reagents and conditions: a) propanedithiol, DIPEA, MeOH, exclusion of light, 3-4 d, argon; b) CH_2Cl_2/AcOH (99:1), air, 60-90 min, (39-73% over two steps); c) Ac_2O, MeOH, H_2O, 30-90 min, (quantitative); d) diacetyl, camphorsulfonic acid (CSA), trimethylorthoformate, MeOH, RT, 2-3 h; e) $NaCNBH_3$; MeOH, RT, 20-30 min, (59% over two steps).

The NMR signals of the synthetic akashins A-C (**1**-**3**) were assigned by an extensive set of NMR experiments (^{1}H, JMOD, (HH-COSY, HMQC, HMQC-COSY) and compared with the data reported for the isolated natural compounds.[11] The assignment of the resonances was in line with the data reported previously. Only minor differences were found for the neutral akashin B (**2**) where the position of the reported ^{1}H-signals were deviating only up to ($\Delta\delta^{max}$) 0.06 ppm and the ^{13}C signals up to 0.7 ppm in DMSO-D$_6$. The chemical shifts of akashin A (**1**) containing a primary amino group were less consistent with the reported data of the ^{1}H-spectra ($\Delta\delta^{max}$ = -0.5 ppm for H-4'' of **1**) and the ^{13}C-spectra ($\Delta\delta^{max}$ = +4.2 ppm for C-5'' of **1**). In contrast, for akashin C (**3**) with a secondary amine the comparison of the NMR data was quite satisfactory for protons (^{1}H: $\Delta\delta^{max}$ = -0.15 ppm for H-3'' of **3**) and ^{13}C ($\Delta\delta$ = -1.7 $\pm$ 0.4 ppm for all signals of **3**). The ^{1}H-NMR shifts of the sugar part of **1** were significantly affected by adding some hydrochloric acid to the NMR sample of synthetic **1**. Under these conditions the deviation ($\Delta\delta$) of the most affected sugar signal (H-4'' of **1**) was lowered from -0.5ppm to +0.11 ppm. The higher similarity of the ^{1}H-NMR spectra of isolated akashin A and synthetic akashin A (**1**) + HCl indicated that the isolated natural product **1** was presumably measured as an ammonium salt.

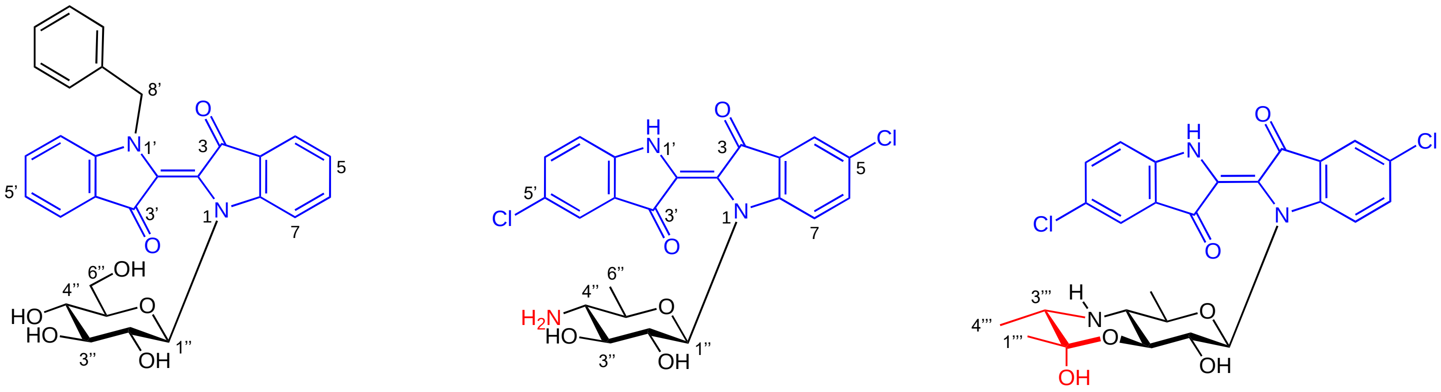
The isolated akashins A-C have in common an unusually high specific optical rotation with values of several thousand degrees (+2560° to +3100°) requiring the measurement at very low concentrations (~10 μg/mL). We also found very high positive values (+1143° to +4138°) for the synthetic akashins A-C (**1**-**3**). It can be assumed that the chiral properties of the akashins are depending on the stereochemistry of the sugar part. Vice versa the very high positive optical rotations of both the synthetic and the isolated akashins indicate that the absolute configuration of the sugar moiety is identical. Thus, the viosamine part of the natural akashins is D-configurated.

Conclusions

In conclusion we have developed a short synthesis for the natural dichloroindigo *N*-glycosides akashin A-C. The key building blocks were a benzyl-protected dichloroindigo and a suitably protected D-viosaminyl donor. Surprisingly an α- and a β-linked O-glycoside were isolated as intermediates of the *N*-glycosylation reaction. The identity of the synthetic and the isolated akashins was confirmed by NMR. Furthermore, the D-configuration of the dideoxy sugar viosamine in the natural products was established by optical rotation.

Experimental Section

General. Unless otherwise noted, chemicals were obtained from commercial suppliers and used without further purification. Methanol was dried with Mg-turnings (5 g / L) and distilled under argon. Dichloromethane was dried over phosphorous pentoxide, distilled and kept over 3 Å molecular sieves. Dimethylformamide and pyridine were p.a. quality, acetonitrile was HPLC grade (>99.9%). TLC was performed on precoated silica gel plates (Macherey-Nagel, Alugram Sil G/UV254, silica layer thickness: 0.25 mm). Fluorescent compounds were detected using a UV illuminator (254 nm). Glycosylated compounds were detected using a 1:1 solution of 0.2% of resorcinol monomethyl ether (3-methoxyphenol) and 2 M sulfuric acid in ethanol followed by heating. Flash chromatography was carried out on Merck silica gel (0.040-0.063 mm). For solid phase extraction Waters Sep-Pak Vac C18 cartridges were used. Optical rotations were determined in 1 dm cells (1 mL) in a Perkin-Elmer 241 polarimeter at 589 nm. UV measurements were performed with a Specord 200 Jena Analytik spectrophotometer. ESI-mass spectra were recorded on a Micromass LCT ESI-TOF mass spectrometer coupled to an Agilent HP 1100 HPLC with a photodiode array UV detector. The following reversed phase columns were used for LC-MS: YMC-Pack Pro C8, S-3 µm (50 x 2.1 mm), YMC-Pack Pro C18, S-3 µm (50 x 2.1 mm). Eluent A, water (0.1% formic acid); eluent B, acetonitrile (0.1% formic acid). EI-mass spectra were recorded on a Finnigan MS 8500 mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Jeol JNM-EX-270, Bruker Avance-360 and on Bruker Avance DRX-500 spectrometers. [D$_6$]-DMSO (δ (^{1}H) = 2.49 ppm, δ (^{13}C) = 39.5 ppm), CD_3OD (δ (^{1}H) = 3.35 ppm, δ (^{13}C) = 49.3 ppm) and D_2O were used as solvents, the internal standard was [D$_6$]-DMSO. Chemical shifts are given in ppm relative to $SiMe_4$ (δ (^{1}H) = 0 ppm), coupling constants are given in Hertz. ^{1}H, Jmod, HH-COSY, HMQC-COSY, NOESY and HMBC experiments were used for assignment. Proton and carbon atoms of the indigo glycosides are assigned as shown below:



4 akashin A (**1**) akashin C (**3**)

Scheme 12. NMR assignment of indigo glycosides.

3,4,6-Tri-*O*-acetyl-2-*O*-benzoyl-α-D-glucopyranosyl-trichloroacetimidate (5). 20 g of 1,3,4,6-tetraacetyl-glucose **7** (57.5 mmol, 1.0 eq) were dissolved in dichloromethane (200 mL) and pyridine (24 mL). The solution was cooled to 0°C followed by dropwise addition of of benzoylchloride (17 mL, 146 mmol) and subsequent stirring for 2.5 h at room temperature. The reaction was stopped by adding saturated potassium hydrogen carbonate (100 mL) and crushed ice (350 g). The mixture was stirred for further 1.5 h. The aqueous phase was extracted with dichloromethane (2x200 mL) and the combined organic layers were extracted with 2 N hydrochloric acid (2x200 mL) and saturated potassium hydrogen carbonate (200 mL). The organic phase was dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography (7 x 18 cm, eluent: cyclohexane/ethyl acetate 9:1 → 5:1 → 2:1 → 1:1). Yield of 1,3,4,6-tetra-*O*-acetyl-2-*O*-benzoyl-α-D-glucopyranoside **7a**: 25.9 g (99%, α:β = 9:1). R_f = 0.49 (cyclohexane/ethyl acetate 2:1). $[\alpha]_D^{22}$= + 113.5° (c = 1.02, dichloromethane). ESI/MS: *m/z* 475.24 [M+Na]$^+$, (calcd for $C_{19}H_{24}O_{11}Na$, 475.12). ^{1}H-NMR (270 MHz, [D$_6$]-DMSO) α-*anomer*: δ = 7.86 (d, 2H, *J* = 7.6 Hz, H_o-Ar), 7.69 (dd, 1H, *J* = 7.6 Hz, H_p-Ar), 7.54 (dd, 2H, *J* = 7.6 Hz, H_m-Ar), 6.35 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.53 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.9 Hz, H-3), 5.28 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.9 Hz, H-2), 5.20 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.9 Hz, H-4), 4.25-4.18 (m, 2H, H-5, H-6a), 4.07-4.01 (m, 1H, H-6b), 2.17 (s, 3H, Ac), 2.03 (s, 6H, 2Ac), 1.93 (s, 3H, Ac). ^{13}C-NMR (68 MHz, [D$_6$]-DMSO): δ = 170.6, 170.3, 169.7, 169.5 (*C*O-Ac), 165.2 (*C*O-Bz), 134.5 (C_p-Ar), 129.8 (C_m-Ar), 129.5 (C_o-Ar), 128.9 (C_i-Ar), 88.9 (C-1), 70.3 (C-5), 69.9 (C-2), 69.8 (C-3), 67.7 (C-4), 61.9 (C-6), 21.1, 20.9, 20.8 (Ac).

To a stirred solution of tetraacetyl-2-benzoyl-α-D-glucose **7a** (8.70 g, 19.4 mmol, 1.0 eq) in *N,N*-dimethylformamide (25 mL) was added hydrazine acetate (2.67 g, 29 mmol, 1.5 eq) of over 15 minutes. After 90 minutes the reaction was stopped by addition of acetone (12 mL) and stirred until the excess of hydrazine acetate was dissolved. The solution was diluted with dichloromethane (400 mL) and extracted with water and saturated potassium hydrogen carbonate. The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography (5 x 18 cm, eluent: cyclohexane/acetone 3:1 $\rightarrow$ 2:1). Yield of 3,4,6-tri-*O*-acetyl-2-*O*-benzoyl-D-glucopyranose **7b**: 6.22 g (80%). R_f = 0.40 (cyclohexane/acetone 2:1). $[\alpha]_D^{26}$ = + 115.3° (c = 0.52, dichloromethane). ESI/MS: *m/z* 433.20 $[M+Na]^+$ (calcd for $C_{19}H_{22}O_{10}Na$, 433.11). ^1H NMR (270 MHz, $[D_6]$-DMSO) α-*anomer:* δ = 7.90 (d, 2H, *J* = 7.6 Hz, H_o-Ar), 7.69 (dd, 1H, *J* = 7.6 Hz, H_p-Ar), 7.54 (dd, 2H, *J* = 7.6 Hz, H_m-Ar), 7.38 (d, 1H, $J_{OH,1}$ = 4.9 Hz, OH), 5.57 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.9 Hz, H-3), 5.43-5.39 (m, 1H, H-1), 5.02 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.9 Hz, H-4), 4.93 (dd, 1H, $J_{1,2}$ = 4.9 Hz, $J_{2,3}$ = 9.9 Hz, H-2), 4.25-4.11 (m, 2H, H-5, H-6a), 4.10-4.00 (m, 1H, H-6b), 2.02 (s, 6H, 2Ac), 1.91 (s, 3H, Ac). ^{13}C NMR (68 MHz, $[D_6]$-DMSO): δ = 170.7, 170.3, 169.9 (*C*O-Ac), 165.5 (*C*O-Bz), 134.4 (C_p-Ar), 129.8 (C_m-Ar), 129.4 (C_o-Ar), 129.4 (C_i-Ar), 88.6 (C-1), 72.5 (C-2), 69.9 (C-3), 68.8 (C-4), 67.0 (C-5), 62.7 (C-6), 21.1, 21.0, 20.9 (Ac).

Hemiacetal **7b** (11.65 g, 28.4 mmol, 1.0 eq) was dissolved in absolute dichloromethane (160 mL) and cooled to 0°C. Trichloroacetonitrile (28.5 mL, 283.9 mmol, 10 eq) was added followed by DBU (0.85 mL, 5.68 mmol, 0.2 eq). After 60 minutes the solvent was concentrated in vacuo (20°C) and the residue was purified by flash chromatography (7.5 x 11 cm, eluent: cyclohexane/acetone 5:1). Yield of imidate **5**: 14.20 g (90.3%).

R_f = 0.52 (cyclohexane/ethyl acetate 2:1). $[\alpha]_D^{28}$ = - 5.5° (c = 0.53, dichloromethane). ESI/MS: *m/z* 576.14 $[(^{35}Cl)M+Na]^+$, 578.14 $[(^{37}Cl)M+Na]^+$ (calcd for $C_{21}H_{22}Cl_3NO_{10}Na$, 576.02). ^1H-NMR (270 MHz, $[D_6]$-DMSO): δ = 9.96 (s, 1H, N*H*), 7.88 (d, 2H, *J* = 7.4 Hz, H_o-Ar), 7.67 (dd, 1H, *J* = 7.4 Hz, H_p-Ar), 7.52 (dd, 2H, *J* = 7.4 Hz, H_m-Ar), 6.62 (bs, 1H, H-1), 5.62 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.9 Hz, H-3), 5.40 (dd, 1H, $J_{1,2}$ = 2.3 Hz, $J_{2,3}$ = 9.9 Hz, H-2), 5.26 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.9 Hz, H-4), 4.27-4.08 (m, 3H, H-5, H-6a, H-6b), 2.03 (s, 6H, 2xAc), 1.93 (s, 3H, Ac). ^{13}C-NMR (68 MHz, $[D_6]$-DMSO): δ = 170.5, 170.2, 169.8 (*C*O-Ac), 165.1 (*C*O-Bz), 134.6 (C_p-Ar), 129.8 (C_m-Ar), 129.5 (C_o-Ar), 128.8 (C_i-Ar), 92.5 (C-1), 70.5 (C-2, C-5), 69.7 (C-3), 67.7 (C-4), 61.9 (C-6), 21.1, 20.8 (Ac).

***N*-Benzylindigo (6).** Indigo **8** (1 g, 3.81 mmol, 1.0 eq) was suspended in absolute *N,N*-dimethylformamide (25 mL), NaH (60% in oil suspension, 100 mg, 2.5 mmol, 0.66 eq.) was added and the suspension stirred at room temperature. After 30 minutes further NaH (60% in oil suspension, 100 mg, 2.5 mmol, 0.66 eq.) was added. After 2 h benzylbromide (540 μL, 4.55 mmol, 1.2 eq) was added dropwise, and the reaction was stirred for 1 h at room temperature. Subsequently, the reaction mixture was concentrated in vacuo (60°C), the residue was dissolved in dichloromethane (200 mL) and extracted with water (3 x). The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography (3.5 cm x 28 cm, eluent: toluene). Yield of **6**: 641 mg (48%), blue solid. R_f = 0.57 (toluene/ethyl acetate 15:1). UV/VIS: λ_{max} (lg ε) = 626 nm (3.89) in dichloromethane. EI/MS (70 eV): *m/z* (%) = 352 (54) $[M]^+$, (calcd for $C_{23}H_{16}N_2O_2$, 352.12). ^1H-NMR (270 MHz, $[D_6]$-DMSO): δ = 7.68 (d, 1H, $J_{4,5}$ = 7.7 Hz, H-4), 7.59 (dd, 1H, $J_{5,6}$ = $J_{6,7}$ = 7.7 Hz, H-6), 7.55 (d, 1H, $J_{4',5'}$ = 7.7 Hz, H-4'), 7.50 (dd, 1H, $J_{5',6'}$ = $J_{6',7'}$ = 7.7 Hz, H-6'), 7.37 (d, 1H, $J_{6,7}$ = 7.7 Hz, H-7), 7.35 (d, 1H, $J_{6',7'}$ = 7.7 Hz, H-7'), 7.26-7.16 (m, 3H, H_m-Ar, H_p-Ar), 7.12-7.07 (m, 2H, H_o-Ar), 7.06 (dd, 1H, $J_{4,5}$ = 7.7 Hz, H-5), 6.94 (dd, 1H, $J_{4',5'}$ = 7.7 Hz, H-5'), 5.78 (s, 2H, H-8'). ^{13}C-NMR (68 MHz, $[D_6]$-DMSO): δ = 188.8 (C_q-3'), 187.2 (C_q-3), 153.3, 152.5 (C_q-7a, C_q-7a'), 138.3 (C_i-Ar), 136.7, 136.5 (C-6, C-6'), 129.1, 127.7, 127.3 (C-Ar), 125.0 (C_q-2'), 124.4, 124.0 (C-4, C-4'), 123.3 (C_q-2), 121.7, 121.0 (C-5, C-5'), 121.2 (C_q-3a'), 119.6 (C_q-3a), 113.8 (C-7'), 112.7 (C-7), 50.3 (*C*H_2-8').

***N*-[(2,3,4-Tri-*O*-acetyl-2-O-benzoyl-β-D-glucopyranosyl)-*N'*-benzyl]-indigo (9).** Under an inert gas imidate **5** (764 mg, 1.38 mmol, 1.0 eq), *N*-benzylindigo **6** (500 mg, 1.42 mmol, 1.03 eq) and molecular sieves 4 Å (1.0 g) were suspended in absolute dichloromethane (10 mL), stirred for 30 minutes at room temperature and cooled to -18 °C. The reaction was started by adding TMSOTf (100 μL, 0.55 mmol, 0.4 eq). After 3 h at – 18 °C the suspension was slowly warmed to room temperature over 12 h. The reaction was quenched by adding saturated potassium hydrogen carbonate (10 mL). After 10 minutes the mixture was filtered over Celite and washed with dichloromethane. The organic filtrate was extracted with water, saturated potassium hydrogen carbonate and brine. The organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (5 x 20 cm, solvent: toluene/ethyl acetate 15:1 → 12:1 → 9:1). Unreacted *N*-benzylindigo **6** was recovered 124 mg (0.35 mmol, 25%). Yield of **9**: 232 mg (22.6%), blue solid. R_f = 0.27 (cyclohexane/ethyl acetate 1.5:1). UV/VIS: λ_{max} (lg ε) = 630 nm (3.80) in dichloromethane. $[\alpha]_D^{23}$ = + 5428.6° (c = 7.0 μg/mL, dichloromethane). ESI/MS: *m/z* 745.76 $[M+H]^+$ (calcd for $C_{42}H_{37}N_2O_{11}$, 745.24). ^{1}H-NMR (360 MHz, [D_6]-DMSO): δ = 7.73 (d, 1H, $J_{6,7}$ = 7.9 Hz, H-7), 7.69 (d, 1H, $J_{4',5'}$ = 7.6 Hz, H-4'), 7.69 (dd, 2H, *J* = 7.9 Hz, H-6, H_p-Ar), 7.54 (dd, 2H, *J* = 8.0 Hz, H_m-Ar), 7.47 (d, 1H, $J_{4,5}$ = 7.3 Hz, H-4), 7.40 (dd, 2H, *J* = 8.0 Hz, H-6', H_p-Ar), 7.35-7.32 (m, 4H, H_o-Ar), 7.11 (dd, 1H, $J_{4,5}$ = 7.3 Hz, $J_{5,6}$ = 7.9 Hz, H-5), 7.03 (dd, 1H, $J_{4',5'}$ = 7.6 Hz, $J_{5',6'}$ = 8.0 Hz, H-5'), 6.92 (dd, 2H, *J* = 7.7 Hz, H_m-Ar), 6.66 (d, 1H, $J_{6',7'}$ = 8.0 Hz, H-7'), 6.01 (d, 1H, $J_{1'',2''}$ = 8.7 Hz, H-1''), 5.74-5.68 (m, 2H, H-2'', H-3''), 5.33 (dd, 1H, $J_{3'',4''}$ = $J_{4'',5''}$ = 9.4 Hz, H-4''), 5.02 (d, 1H, J_{gem} = 16.8 Hz, H-8'), 4.71 (d, 1H, J_{gem} = 16.8 Hz, H-8'), 4.31-4.26 (m, 1H, H-5''), 4.23-4.14 (m, 1H, H-6a''), 4.08-4.02 (m, 1H, H-6b''), 2.22 (s, 3H, Ac), 2.03 (s, 3H, Ac), 1.74 (s, 3H, Ac). ^{13}C-NMR (90 MHz, [D_6]-DMSO): δ = 185.1 (C_q-3'), 183.3 (C_q-3), 170.3, 169.9, 169.4 (*C*O-Ac), 163.9 (*C*O-Bz), 151.8 (C_q-7a'), 149.5 (C_q-7a), 135.1 (C-6'), 135.0 (C-6), 133.6, 133.4 (C_p-Ar), 128.5, 128.1 (C_m-Ar), 128.0 (C_o-Ar), 127.8 (C_i-Ar), 123.7 (C-4), 123.4 (C_q-2'), 123.1 (C-4'), 122.2 (C-5), 121.7 (C_q-2), 121.4 (C-5'), 119.0 (C-3a, C-3a'), 115.7 (C-7), 112.7 (C-7'), 87.5 (C-1''), 74.1 (C-5''), 73.1 (C-3''), 68.1 (C-2''), 68.6 (C-4''), 61.4 (C-6''), 53.5 (CH_2-8'), 20.6, 20.4, 20.2 (Ac).

***N*-(2,3,4-Tri-*O*-acetyl-2-*O*-benzoyl-β-D-glucopyranosyl)-indigo (9b).** Glycoside **9** (320 mg, 0.43 mmol, 1.0 eq) was dissolved in toluene/acetic acid (8 mL, 1:1) and stirred in an open flask for 28 h at 50°C. The solution was diluted with dichloromethane (150 mL) and extracted with water and saturated potassium hydrogen carbonate. The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography (5 x 18 cm, eluent: toluene/ethyl acetate 15:1 → 12:1). Yield: 173 mg (61.4%), blue solid. R_f = 0.41 (toluene/ethyl acetate 5:1). UV/VIS: λ_{max} (lg ε) = 600 nm (4.04) in dichloromethane. $[\alpha]_D^{23}$ = + 2328.2° (c = 3.9 μg/mL, dichloromethane). ESI/MS: *m/z* 655.30 $[M+H]^+$ (calcd for $C_{35}H_{31}N_2O_{11}$, 655.19). ^{1}H-NMR (360 MHz, [D_6]-DMSO): δ = 10.75 (s, 1H, N'*H*), 7.76 (d, 1H, $J_{6,7}$ = 7.5 Hz, H-7), 7.68 (dd, 1H, $J_{5,6}$ = $J_{6,7}$ = 7.5 Hz, H-6), 7.67 (d, 1H, $J_{4',5'}$ = 7.5 Hz, H-4'), 7.57-7.50 (m, 5H, H-4, H-6', H_o-Ar, H_p-Ar), 7.34 (d, 1H, $J_{6',7'}$ = 7.6 Hz, H-7'), 7.30 (dd, 1H, *J* = 7.6 Hz, H_m-Ar), 7.14 (dd, 1H, $J_{4,5}$ = $J_{5,6}$ = 7.5 Hz, H-5), 7.00 (dd, 1H, $J_{4',5'}$ = $J_{5',6'}$ = 7.6 Hz, H-5'), 6.56 (d, 1H, $J_{1'',2''}$ = 9.1 Hz, H-1''), 5.60 (dd, 1H, $J_{1'',2''}$ = $J_{2'',3''}$ = 9.1 Hz, H-2''), 5.52 (dd, 1H, $J_{2'',3''}$ = $J_{3'',4''}$ = 9.1 Hz, H-3''), 5.36 (dd, 1H, $J_{3'',4''}$ = $J_{4'',5''}$ = 9.1 Hz, H-4''), 4.34-4.28 (m, 2H, H-6a'', H-6b''), 4.23-4.17 (m, 1H, H-5''), 2.13 (s, 3H, Ac), 2.04 (s, 3H, Ac), 1.78 (s, 3H, Ac). ^{13}C-NMR (90 MHz, [D_6]-DMSO): δ = 186.9 (C_q-3'), 186.8 (C_q-3), 170.1, 169.4 (*C*O-Ac), 163.9 (*C*O-Bz), 152.4 (C_q-7a'), 149.8 (C_q-7a), 136.5 (C-6'), 135.7 (C-6), 133.6 (C_p-Ar), 129.0 (C_m-Ar), 128.6 (C_o-Ar), 127.9 (C_i-Ar), 124.6 (C_q-2'), 124.2 (C-4'), 123.3 (C-4), 122.6 (C-5), 122.1 (C_q-2), 120.8 (C-5'), 119.0 (C-3a, C-3a'), 116.2 (C-7), 113.3 (C-7'), 85.1 (C-1''), 74.2 (C-5''), 73.0 (C-3''), 68.7 (C-2''), 68.0 (C-4''), 61.9 (C-6''), 20.6, 20.4, 20.2 (Ac).

***N*-β-D-Glucopyranosyl)-indigo (4).** Under an argon atmosphere indigo **9b** (179 mg, 0.27 mmol, 1.0 eq) was dissolved in absolute methanol (9 mL). NaOMe in MeOH (9 mL, c = 0.01 mol/L) was added and the reaction was stirred for 11 h at room temperature. The reaction was stopped by neutralization with Amberlyst 15 (H^+). The ion exchange resin was removed by filtration over Celite and washed with methanol. The filtrate was concentrated and purified in three aliquots by solid phase extraction (SepPak-C_{18}, 2 g) with a gradient of 5-15% acetonitrile in water in 1%-steps. The product eluted between 12-15% acetonitrile and was lyophilized. Yield: 58 mg (50.7%), blue solid. R_f: 0.25 (dichloromethane/methanol 10:1). UV/VIS: λ_{max} (lg ε) = 606 nm (4.08) in methanol. $[\alpha]_D^{27}$ = + 2258° (c = 6.2 μg/mL, methanol). ESI/MS: *m/z* 425.07 $[M+H]^+$ (calcd for $C_{22}H_{21}N_2O_7$, 425.13). ^{1}H-NMR (500 MHz, [D_6]-DMSO with D_2O): δ = 7.68 (d, 1H, $J_{4,5}$ = 7.5 Hz, H-4), 7.59 (d, 1H, $J_{6,7}$ = 7.5 Hz, H-7), 7.56 (d, 1H, $J_{4',5'}$ = 7.7 Hz, H-4'), 7.55 (dd, 1H, $J_{5,6}$ = $J_{6,7}$ = 7.5 Hz, H-6), 7.51 (d, 1H, $J_{5',6'}$ = $J_{6',7'}$ = 7.7 Hz, H-6'), 7.33 (d, 1H, $J_{6',7'}$ = 7.7 Hz, H-7'), 7.12 (dd, 1H, $J_{4,5}$ = $J_{5,6}$ = 7.5 Hz, H-5), 6.95 (dd, 1H, $J_{4',5'}$ = $J_{5',6'}$ = 7.7 Hz, H-5'), 5.87 (d, 1H, $J_{1'',2''}$ = 9.1 Hz, H-1''), 3.80 (dd, 1H, $J_{5'',6a''}$ < 1.0 Hz, $J_{6a'',6b''}$ = 11.3 Hz, H-6a''), 3.66 (dd, 1H,

$J_{5'',6b''}$ = 4.9 Hz, $J_{6a'',6b''}$ = 11.3 Hz, H-6b''), 3.51 (dd, 1H, $J_{1'',2''} = J_{2'',3''}$ = 9.1 Hz, H-2''), 3.47-3.39 (m, 1H, H-5''), 3.31 (dd, 1H, $J_{3'',4''} = J_{4'',5''}$ = 9.1 Hz, H-4''), 3.19 (dd, 1H, $J_{2'',3''} = J_{3'',4''}$ = 9.1 Hz, H-3''). ^{1}H-NMR (360 MHz, [D$_6$]-DMSO: δ = 10.85 (bs, 1H, N'*H*), 4.98 (d, 1H, $J_{OH\text{-}3'',3''}$ = 5.8 Hz, OH-3''), 4.96 (d, 1H, $J_{OH\text{-}4'',4''}$ = 5.2 Hz, OH-4''), 4.82 (d, 1H, $J_{OH\text{-}2'',2''}$ = 6.8 Hz, OH-2''), 4.68 (t, 1H, $J_{OH\text{-}6'',6''}$ = 5.7 Hz, OH-6''). ^{13}C-NMR (126 MHz, [D$_6$]-DMSO with D$_2$O): δ = 188.2 (C$_q$-3'), 186.5 (C$_q$-3), 152.1 (C$_q$-7a'), 150.8 (C$_q$-7a), 136.0 (C-6'), 135.1 (C-6), 124.0 (C-4'), 123.9 (C$_q$-2), 123.6 (C$_q$-2'), 123.2 (C-4), 122.7 (C$_q$-3a), 121.7 (C-5), 120.3 (C-5'), 119.1 (C$_q$-3a'), 116.6 (C-7), 113.1 (C-7'), 88.5 (C-1''), 80.7 (C-5''), 78.0 (C-3''), 70.2, 70.1 (C-2'', C-4''), 61.4 (C-6'').

1,2,3-Tri-*O*-benzoyl-4,6-*O*-benzylidene-D-galactopyranose (12). The synthesis of **12** was carried out following the procedure of *Gros* and *Deulofeu*.[26] The anomers obtained after benzoylation of 4,6-benzylidene-D-galactose (10g) were separated by flash chromatography (7.5 x 12 cm, eluent: cyclohexane/ethyl acetate 9:1 → 6:1 → 5:1 → 3:1 → 2:1 → 1:1). α-*anomer* **12α**: yield: 18.88 g (87%). R$_f$ = 0.62 (dichloromethane/methanol 2:1). $[\alpha]_D^{24}$ = - 79.2° (c = 0.50, dichloromethane). ESI/MS: *m/z* 603.21 [M+Na]$^+$ (calcd for $C_{34}H_{28}O_9Na$, 603.16). ^{1}H-NMR (270 MHz, [D$_6$]-DMSO): δ = 8.14 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.88 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.74 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.62 (dd, 3H, *J* = 7.7 Hz, H-Ar), 7.57-7.33 (m, 10H, H-Ar), 6.79 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 6.01 (dd, 1H, $J_{2,3}$ = 10.9 Hz, $J_{3,4}$ = 3.1 Hz, H-3), 5.80 (dd, 1H, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 10.9 Hz, H-2), 5.78 (s, 1H, H-7), 4.87 (dd, 1H, $J_{3,4} = J_{4,5}$ = 3.1 Hz, H-4), 4.41-4.39 (m, 1H, H-5), 4.22-4.14 (m, 2H, H-6a, H-6b). ^{13}C-NMR (68 MHz, [D$_6$]-DMSO): δ = 165.6, 165.4, 164.9 (*C*O-Bz), 138.6 (C$_i$-benzylidene), 134.7, 134.4, 133.8 (C$_p$-Ar), 130.2, 129.8, 129.7, 129.6, 129.5 (C-Ar), 129.4 (C$_i$-Ar), 129.3 (C-Ar), 129.2 (C$_i$-Ar), 129.1 (C-Ar), 129.0 (C$_i$-Ar), 128.8, 126.6 (C-Ar), 100.1 (C-7), 91.4 (C-1), 74.0 (C-4), 69.3 (C-3), 68.8 (C-6), 68.0 (C-2), 65.5 (C-5).

β-*anomer* **12β**: yield: 2.72 g (13%). R$_f$ = 0.49 (dichloromethane/methanol 2:1). $[\alpha]_D^{24}$ = - 14.2° (c = 0.50, dichloromethane). ^{1}H-NMR (270 MHz, [D$_6$]-DMSO): δ = 8.00-7.80 (m, 6H, H-Ar), 7.70-7.32 (m, 14H, H-Ar), 6.45 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 5.92 (dd, 1H, $J_{3,2}$ = 10.5 Hz, $J_{3,4}$ = 2.9 Hz, H-3), 5.84 (dd, 1H, $J_{1,2}$ = 7.5 Hz, $J_{2,3}$ = 10.5 Hz, H-2), 5.76 (s, 1H, H-7), 4.79 (dd, 1H, $J_{3,4} = J_{4,5}$ = 2.9 Hz, H-4), 4.27-4.18 (m, 3H, H-5, H-6a, H-6b). ^{13}C-NMR (68 MHz, [D$_6$]-DMSO): δ = 165.6, 165.5, 164.7 (*C*O-Bz), 138.6 (C$_i$-benzylidene), 134.8, 134.4, 133.4 (C$_p$-Ar), 129.9, 129.8, 129.7, 129.6, 129.4, (C-Ar), 129.3 (C$_i$-Ar), 129.2 (C-Ar), 129.1 (C$_i$-Ar), 128.7 (C-Ar), 128.6 (C$_i$-Ar), 126.5 (C-Ar), 100.1 (C-7), 92.9 (C-1), 73.6 (C-4), 72.1 (C-3), 69.3 (C-2), 68.5 (C-6), 67.6 (C-5).

1,2,3-Tri-*O*-benzoyl-6-deoxy-6-iodo-α-D-galactopyranose (13α). Tribenzoyl-4,6-*O*-benzylidene-α-D-galactose **12α** (16.45 g, 28.4 mmol, 1.0 eq) was dissolved in dry acetonitrile (165 mL) and absolute methanol (107 mL). 3.34 g (17.6 mmol, 0.62 eq) of *p*-toluenesulfonic acid monohydrate in 34 mL of absolute methanol were added over 10 minutes. After 3 h of stirring 1.67 g (8.8 mmol, 0.31 eq) of *p*-toluenesulfonic acid monohydrate in 17 mL of absolute methanol were added. After 21 h the reaction was quenched by adding 4.2 mL of triethylamine. The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (7.5 x 16 cm, eluent: cyclohexane/ethyl acetate 6:1 → 5:1 → 3:1 → 1:1 → 1:2). Yield of 1,2,3-tri-O-benzoyl-α-D-galactopyranose (**12α–1**): 10.35 g (74.1%). R$_f$ = 0.24 (cyclohexane/ethyl acetate 1.5:1). $[\alpha]_D^{26}$ = + 27° (c = 0.50, dichloromethane). ESI/MS: *m/z* 515.29 [M+Na]$^+$ (calcd for $C_{27}H_{24}O_9Na$, 515.13). ^{1}H-NMR (270 MHz, [D$_6$]-DMSO): δ = 8.09 (d, 2H, *J* = 7.9 Hz, H-Ar), 8.01 (d, 2H, *J* = 7.9 Hz, H-Ar), 7.77-7.69 (m, 3H, H-Ar), 7.66-7.43 (m, 6H, H-Ar), 7.37 (dd, 2H, *J* = 7.7 Hz, H-Ar), 6.65 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 5.81 (dd, 1H, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 10.5 Hz, H-2), 5.70-5.73 (m, 1H, OH-4), 5.68 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 2.4 Hz, H-3), 4.81 (t, 1H, $J_{OH\text{-}6,6}$ = 5.6 Hz, OH-6), 4.44-4.33 (m, 1H, H-4), 4.21 (dd, 1H, $J_{4,5} = J_{5,6}$ = 6.0 Hz, H-5), 3.69-3.52 (m, 2H, H-6a, H-6b). ^{13}C-NMR (68 MHz, [D$_6$]-DMSO): δ = 165.8, 165.6, 164.9 (*C*O-Bz), 134.7, 134.3, 134.1 (C$_p$-Ar), 130.1 (C-Ar), 130.0 (C$_i$-Ar), 129.9, 129.6, 129.5 (C-Ar), 129.4 (C$_i$-Ar), 129.3, 129.2 (C-Ar), 129.2 (C$_i$-Ar), 91.1 (C-1), 74.8 (C-5), 71.9 (C-3), 68.5 (C-2), 66.5 (C-4), 60.4 (C-6).

3.0 g (6.09 mmol, 1.0 eq) of tribenzoyl-α-D-galactose (**12α–1**) and 4.11 g (18.27 mmol, 3.0 eq) of *N*-iodosuccinimide were dissolved in 60 mL of absolute *N,N*-dimethylformamide and cooled to 0°C. 6.39 g

(24.36 mmol, 4.0 eq) of triphenylphosphine were added over 20 minutes, and the reaction mixture was heated to 55°C. After stirring for 24 h the reaction was stopped by adding of 15 mL of methanol. The organic layer was concentrated in vacuo (60°C), diluted with dichloromethane, washed with water, dried ($MgSO_4$) and filtered. The filtrate was concentrated and the residue purified by flash chromatography (5 x 20 cm, eluent: cyclohexane/ethyl acetate 9:1 → 6:1). Yield of **13α**: 2.69 g (73.3%). R_f = 0.40 (cyclohexane/ethyl acetate 3:1). $[\alpha]_D^{24}$ = - 142.9° (c = 0.50, dichloromethane). ESI/MS: *m/z* 602.79 $[M+H]^+$, (calcd for $C_{27}H_{24}IO_8$, 603.05). ^{1}H-NMR (270 MHz, [D_6]-DMSO): δ = 8.11 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.95 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.79-7.71 (m, 3H, H-Ar), 7.60 (dd, 3H, *J* = 7.5 Hz, H-Ar), 7.58-7.52 (m, 1H, H-Ar), 7.47 (dd, 2H, *J* = 7.5 Hz, H-Ar), 7.37 (dd, 2H, *J* = 7.7 Hz, H-Ar), 6.64 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 5.97 (d, 1H, $J_{OH\text{-}4,4}$ = 5.6 Hz, OH-4), 5.80 (dd, 1H, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 10.6 Hz, H-2), 5.73 (dd, 1H, $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 1.9 Hz, H-3), 4.53 (ddd, 1H, $J_{3,4}$ = 1.9 Hz, $J_{4,5}$ = $J_{OH\text{-}4,4}$ = 5.5 Hz, H-4), 4.45-4.41 (m, 1H, H-5), 3.43 (dd, 1H, $J_{5,6a}$ = 6.1 Hz, $J_{6a,6b}$ = 10.0 Hz, H-6a), 3.32 (dd, 1H, $J_{5,6b}$ = 7.7 Hz, $J_{6a,6b}$ = 10.0 Hz, H-6b). ^{13}C-NMR (68 MHz, [D_6]-DMSO): δ = 165.8, 165.5, 164.8 (*C*O-Bz), 134.7, 134.3. 134.1 (C_p-Ar), 130.2, 129.9 (C-Ar), 129.8 (C_i-Ar), 129.6, 129.5, 129.3 (C-Ar), 129.2 (C_i-Ar), 90.8 (C-1), 74.7 (C-5), 71.6 (C-3), 68.0 (C-2), 67.5 (C-4), 3.8 (C-6).

1,2,3-Tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-galactopyranose (13β). Tribenzoyl-4,6-O-benzylidene-β-D-galactose **12β** (5.0 g, 8.6 mmol, 1.0 eq) was dissolved in acetonitrile (50 mL) and methanol (50 mL) and heated to 80 °C. Hydrochloric acid (5.0 mL, 2 N) was added dropwise and the reaction was stirred under reflux for 2 h. The reaction was stopped by adding triethylamine (4.2 mL). The organic layer was concentrated in vacuo, diluted with dichloromethane, washed with water, dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (5 x 25 cm, eluent: cyclohexane/ethyl acetate 6:1 → 1:1). Yield of 1,2,3-tri-*O*-benzoyl-β-D-galactopyranose (**12β-1**): 3.44 g (81.2%). R_f = 0.57 (cyclohexane/acetone 1:1). $[\alpha]_D^{26}$ = - 247.2° (c = 0.54, dichloromethane). ^{1}H-NMR (270 MHz, [D_6]-DMSO): δ = 7.91-7.82 (m, 6H, H-Ar), 7.70-7.38 (m, 9H, H-Ar), 6.28 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1), 5.84 (dd, 1H, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 5.59 (d, 1H, $J_{OH\text{-}4,4}$ = 5.5 Hz, OH-4), 5.53 (dd, 1H, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 4.88 (t, 1H, $J_{OH\text{-}6,6}$ = 5.7 Hz, OH-6), 4.27 (dd, 1H, $J_{OH\text{-}4,4}$ = 5.5 Hz, $J_{3,4}$ = 3.0 Hz, H-4), 4.05 (dd, 1H, $J_{5,6}$ = 8.6 Hz, H-5), 3.70-3.52 (m, 2H, H-6a, H-6b). ^{13}C-NMR (68 MHz, [D_6]-DMSO): δ = 165.7, 164.6 (*C*O-Bz), 134.7, 134.3, 134.1 (C_p-Ar), 129.9, 129.8, 129.6, 129.4 (C-Ar), 129.3 (C_i-Ar), 129.2 (C-Ar), 128.8 (C_i-Ar), 93.2 (C-1), 76.7 (C-5), 74.8 (C-3), 69.9 (C-2), 65.9 (C-4), 60.1 (C-6).

Tribenzoyl-β-D-galactose (**12β-1**) (6.88 g, 14.0 mmol, 1.0 eq) and *N*-iodosuccinimide (9.53 g, 42.3 mmol, 3.0 eq) were dissolved in absolute *N,N*-dimethylformamide (140 mL) and cooled to 0°C. Triphenylphosphine (11.0 g, 41.9 mmol, 3.0 eq) was added over 20 minutes and the reaction mixture was heated to 65°C. After stirring for 18h the reaction was stopped by adding methanol (15 mL). The organic layer was concentrated in vacuo (60°C), the residue diluted with dichloromethane, washed with water, dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (7.5 x 18 cm, eluent: cyclohexane/ethyl acetate 9:1 → 3:1). Yield of **13β**: 7.12 g (85%). R_f = 0.50 (cyclohexane/ethyl acetate 3:1). $[\alpha]_D^{28}$ = - 238.3° (c = 0.50, dichloromethane). ^{1}H-NMR (270 MHz, [D_6]-DMSO): δ = 7.93-7.80 (m, 6H, H-Ar), 7.70-7.39 (m, 9H, H-Ar), 6.31 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1), 5.88 (d, 1H, $J_{OH\text{-}4,4}$ = 5.5 Hz, OH-4), 5.81 (dd, 1H, $J_{1,2}$ = 8.2 Hz, $J_{2,3}$ = 10.3 Hz, H-2), 5.57 (dd, 1H, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 2.8 Hz, H-3), 4.41 (ddd, 1H, $J_{3,4}$ = 2.8 Hz, $J_{OH\text{-}4,4}$ = $J_{4,5}$ = 5.5 Hz, H-4), 4.35 (m, 1H, H-5), 3.47 (dd, 1H, $J_{5,6a}$ = 6.6 Hz, $J_{6a,6b}$ = 10.1 Hz, H-6a), 3.30 (dd, 1H, $J_{5,6b}$ = 7.3 Hz, $J_{6a,6b}$ = 10.1 Hz, H-6b). ^{13}C-NMR (68 MHz, [D_6]-DMSO): δ = 165.7, 164.5 (*C*O-Bz), 134.8, 134.3, 134.1 (C_p-Ar), 129.9, 129.8 (C-Ar), 129.7 (C_i-Ar), 129.6, 129.4, 129.2 (C-Ar), 129.2 (C_i-Ar), 92.9 (C-1), 76.4 (C-5), 74.5 (C-3), 69.5 (C-2), 66.8 (C-4), 3.5 (C-6).

1,2,3-Tri-*O*-benzoyl-6-deoxy-α-D-galactopyranose (14α). Pd/C (10% Pd, 8.73 g, 8.22 mmol) was suspended in absolute methanol (150 mL) containing acetic acid (98%, 17 mL) and stirred for 2 h under a hydrogen atmosphere. Iodide **13α** (3.42 g, 5.68 mmol) dissolved in absolute methanol (20 mL) was added and the reaction mixture was stirred for 2 d under a hydrogen atmosphere. Subsequently, the catalyst was removed by filtration over Celite and washed extensively with dichloromethane. The combined organic layers were extracted with saturated potassium hydrogen carbonate and water, dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (5 x 18 cm, eluent: cyclohexane/ethyl acetate 8:1 → 7:1 → 6:1 → 4:1). 1.02 g (29.8%) of the starting material **13α** were recovered. Yield: 1.51 g (55.9%). R_f = 0.22 (cyclohexane/ethyl acetate 4:1). $[\alpha]_D^{24}$ = + 155.0° (c = 0.50, dichloromethane). ESI/MS: *m/z* 477.12 $[M+H]^+$ (calcd for $C_{27}H_{25}O_8$, 477.15). ^{1}H-NMR (360 MHz, [D$_6$]-DMSO): δ = 8.07 (d, 2H, *J* = 7.5 Hz, H-Ar), 7.93 (d, 2H, *J* = 7.5 Hz, H-Ar), 7.75-7.70 (m, 3H, H-Ar), 7.65-7.57 (m, 3H, H-Ar), 7.53 (dd, 2H, *J* = 7.5 Hz, H-Ar), 7.47 (dd, 2H, *J* = 7.9 Hz, H-Ar), 7.36 (dd, 2H, *J* = 7.9 Hz, H-Ar), 6.58 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1), 5.78-5.70 (m, 3H, H-2, H-3, OH-4), 4.43 (dq, 1H, $J_{4,5}$ < 1.0 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 4.15-4.12 (m, 1H, H-4), 1.22 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6). ^{13}C-NMR (90 MHz, [D$_6$]-DMSO): δ = 165.3, 165.0, 164.4 (*C*O-Bz), 134.0, 133.7, 133.5 (C_p-Ar), 129.5 (C-Ar), 129.3 (C_i-Ar), 129.0 (C-Ar), 129.0 (C_i-Ar), 128.7 (C-Ar), 128.6 (C_i-Ar), 90.7 (C-1), 71.2 (C-3), 69.5 (C-5), 68.7 (C-4), 67.7 (C-2), 16.2 (C-6).

1,2,3-Tri-*O*-benzoyl-6-deoxy-β-D-galactopyranose (14β). Pd/C-catalyst (10% Pd, 11.2 g, 10.6 mmol) was suspended in absolute methanol (155 mL) and acetic acid (98%, 16 mL) and stirred for 2 h under a hydrogen atmosphere. A solution of iodide **13β** (3.1 g, 5.15 mmol) in absolute methanol (20 mL) was added. After 2 d the catalyst was removed by filtration over Celite and repeatedly washed with dichloromethane. The combined organic layer was extracted with saturated potassium hydrogen carbonate and water, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (5 x 20 cm, eluent: cyclohexane/ethyl acetate 8:1 → 5:1). 1.9 g (61.3%) of the starting material **13β** were recovered. Yield: 867 mg (35.3%). R_f = 0.34 (cyclohexane/ethyl acetate 4:1). ^{1}H-NMR (270 MHz, [D$_6$]-DMSO): δ = 7.91-7.82 (m, 5H, H-Ar), 7.70-7.35 (m, 10H, H-Ar), 6.22 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 5.79 (dd, 1H, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 10.3 Hz, H-2), 5.62 (d, 1H, $J_{OH\text{-}4,4}$ = 5.8 Hz, OH-4), 5.53 (dd, 1H, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 4.21 (dq, 1H, $J_{4,5}$ < 1.0 Hz, $_{5,6}$ = 6.2 Hz, H-5), 4.03-4.00 (m, 1H, H-4), 1.25 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6). ^{13}C-NMR (68 MHz, [D$_6$]-DMSO): δ = 165.7, 165.6, 164.7 (*C*O-Bz), 134.7, 134.3, 134.1 (C_p-Ar), 129.9, 129.8 (C-Ar), 129.6 (C_i-Ar), 129.4 (C-Ar), 129.0 (C_i-Ar), 93.2 (C-1), 74.8 (C-3), 71.8 (C-5), 69.6 (C-2), 68.8 (C-4), 16.7 (C-6).

4-Azido-1,2,3-tri-*O*-benzoyl-4,6-dideoxy-α-D-glucopyranose (15α). 6-Deoxysugar **14α** (7.3 g, 15.3 mmol, 1.0 eq) was dissolved in absolute dichloromethane (112 mL) and absolute pyridine (19 mL, 236 mmol) and cooled to -18 °C. Trifluoromethanesulfonic anhydride (6.2 mL, 37.6 mmol, 2.4 eq) was added. After stirring for 110 minutes the solution was extracted with water, saturated potassium hydrogen carbonate (2 x) and 2 N hydrochloric acid. The organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated and dried in high vacuum. Subsequently, sodium azide (9.0 g, 138 mmol, 8.5 eq) was added to the crude triflate. The mixture was suspended in absolute *N,N*-dimethylformamide (240 mL) and stirred for 30 minutes at room temperature. The organic layer was concentrated in vacuo (60 °C) and the residue was diluted with dichloromethane (300 mL). The solution was extracted with water, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (7.5 x 17 cm, eluent: cyclohexane/ethyl acetate 12:1 → 9:1). Yield: 7.05 g (92% over 2 steps). R_f = 0.47 (cyclohexane/acetone 3:1). $[\alpha]_D^{25}$ = + 213.2° (c = 0.55, dichloromethane). ESI-MS *m/z* 523.73 $[M+Na]^+$ (calcd for $C_{27}H_{23}N_3O_7Na$, 524.14). ^{1}H-NMR (270 MHz, [D$_6$]-DMSO): δ = 8.06 (d, 2H, *J* = 7.1 Hz, H-Ar), 7.97 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.79-7.49 (m, 9H, H-Ar), 7.39 (dd, 2H, *J* = 7.7 Hz, H-Ar), 6.64 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.87 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 10.1 Hz, H-3), 5.54 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 10.1 Hz, H-2), 4.27 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 10.1 Hz, H-4), 4.14-4.06 (m, 1H, H-5), 1.38 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6). ^{13}C-NMR (68 MHz, [D$_6$]-DMSO): δ = 165.7, 165.2, 164.2 (*C*O-Bz), 134.8, 134.6, 134.5 (C_p-Ar), 130.1, 129.9, 129.7, 129.6, 129.5, 129.4 (C-Ar), 129.1, 129.0, 128.7 (C_i-Ar), 90.3 (C-1), 71.5 (C-3), 71.0 (C-2), 69.5 (C-5), 64.4 (C-4), 18.5 (C-6).

4-Azido-1,2,3-tri-*O*-benzoyl-4,6-dideoxy-β-D-glucopyranose (15β). Under an inert gas 6-deoxysugar **14β** (3.86 g, 8.1 mmol, 1.0 eq) was dissolved in absolute dichloromethane (60 mL) and absolute pyridine (10 mL, 124 mmol) and cooled to – 18 °C. Trifluoromethanesulfonic anhydride (3.0 mL, 24.3 mmol, 2.2 eq) was added. After stirring for 60 minutes the solution was extracted with water, saturated potassium hydrogen carbonate (2 x) and hydrochloric acid (2 N). The organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated and dried in high vacuum. Subsequently, sodium azide (5.26 g, 81 mmol, 10 eq) was added to the crude triflate. The mixture was suspended in absolute *N,N*-dimethylformamide (116 mL) and stirred for 30 minutes at room temperature. The organic layer was concentrated in vacuo (60 °C) and the residue was diluted with 300 mL of dichloromethane. The solution was extracted with water, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (5 x 16 cm, eluent: cyclohexane/ethyl acetate 12:1 → 9:1). Yield: 3.41 g (84% over 2 steps). R$_f$ = 0.34 (cyclohexane/acetone 3:1). $[\alpha]_D^{26}$ = - 27.4° (c = 0.48, dichloromethane). ^{1}H-NMR (270 MHz, [D$_6$]-DMSO): δ = 7.96-7.87 (m, 4H, H-Ar), 7.79 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.70-7.40 (m, 9H, H-Ar), 6.37 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 5.94 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3), 5.54 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 8.1 Hz, H-2), 4.10-4.05 (m, 2H, H-4, H-5), 1.36 (d, 3H, $J_{5,6}$ = 5.1 Hz, H-6). ^{13}C-NMR (68 MHz, [D$_6$]-DMSO): δ = 165.6, 165.4, 164.5 (*C*O-Bz), 134.5, 134.4, 134.3 (C$_p$-Ar), 129.9, 129.8, 129.6, 129.5, 129.4 (C-Ar), 129.1, 128.9, 128.6 (C$_i$-Ar), 92.5 (C-1), 73.4 (C-3), 72.0 (C-2), 71.3 (C-5), 64.9 (C-4), 18.4 (C-6).

4-Azido-2,3-di-*O*-benzoyl-4,6-dideoxy-D-glucopyranose (10a) and 4-azido-2,3-di-*O*-benzoyl-4,6-dideoxy-α-D-glucopyranosyl-trichloroacetimidate (10) from 15α. Azide **15α** (1.32 g, 2.63 mmol, 1.0 eq) was dissolved in absolute *N,N*-dimethylformamide (12 mL). Hydrazine acetate (2.42 g, 26.3 mmol, 10 eq) was added and the suspension was stirred at room temperature. After 5.5 h the reaction was stopped by adding acetone (10 mL) and stirring was continued until the remaining solid hydrazine acetate was completely dissolved. The solution was diluted with dichloromethane (200 mL) and extracted with water and saturated potassium hydrogen carbonate. The organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and purified by flash chromatography (3.5 x 28 cm, eluent: cyclohexane/acetone 10:1). Yield of hemiacetal **10a**: 886 mg (84.8%, α:β = 2:1). R$_f$ = 0.26 (cyclohexane/acetone 2:1).

from **15β**: Azide **15β** (3.40 g, 6.8 mmol, 1.0 eq) was dissolved in absolute *N,N*-dimethylformamide (18 mL). Hydrazine acetate (4.70 g, 50.9 mmol, 7.5 eq) was added and the suspension was stirred at room temperature. After 3.5 h the reaction was stopped by adding acetone (20 mL) and stirring was continued until the remaining solid hydrazine acetate was completely dissolved. The solution was diluted with dichloromethane (400 mL) and extracted with water and saturated potassium hydrogen carbonate. The organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and purified by flash chromatography (5 x 20 cm, eluent: cyclohexane/acetone 10:1). Yield of hemiacetal **10a**: 2.38 g (88.6%, α:β = 2:1). ^{1}H-NMR (270 MHz, [D$_6$]-DMSO): δ = 7.96 (d, 2H, *J* = 7.1 Hz, H-Ar), 7.90 (d, 1H, *J* = 7.1 Hz, H-Ar), 7.83 (d, 3H, *J* = 7.1 Hz, H-Ar), 7.66-7.57 (m, 3H, H-Ar), 7.51-7.43 (m, 6H, H-Ar), 7.28 (d, 1H, $J_{OH\text{-}1\beta,1}$ = 6.2 Hz, OH-1β), 7.24 (d, 1H, $J_{OH\text{-}1\alpha,1}$ = 3.9 Hz, OH-1α), 5.75 (dd, 1H, $J_{2\alpha,3\alpha}$ = $J_{3\alpha,4\alpha}$ = 9.6 Hz, H-3α), 5.61 (dd, 1H, $J_{2\beta,3\beta}$ = $J_{3\beta,4\beta}$ = 9.5 Hz, H-3β), 5.39 (dd, 1H, $J_{OH\text{-}1\alpha,1}$ = $J_{1,2}$ = 3.6 Hz, H-1α), 5.11 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.6 Hz, H-2α), 5.12 (dd, 1H, $J_{1,2}$ = 7.6 Hz, $J_{2,3}$ = 9.6 Hz, H-2β), 5.02 (dd, 1H, $J_{1,2}$ = 7.6 Hz, $J_{OH\text{-}1\beta,1}$ = 6.2 Hz, H-1β), 4.01-3.83 (m, 3H, H-5α, H-4α, H-4β), 3.80-3.70 (m, 1H, H-5β), 1.32 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6β), 1.31 (d, 3H, $J_{5,6}$ = 5.6 Hz, H-6α). ^{13}C-NMR (68 MHz, [D$_6$]-DMSO): δ = 165.9, 165.6 (*C*O-Bz$_\alpha$), 165.7, 165.3 (*C*O-Bz$_\beta$), 134.3 (C$_p$-Ar$_\alpha$), 134.1 (C$_p$-Ar$_\beta$), 129.8, 129.7, 129.4 (C-Ar$_\alpha$), 129.6, 129.3, 129.2 (C-Ar$_\beta$), 94.3 (C-1β), 89.7 (C-1α), 74.5 (C-2β), 74.3 (C-3β), 73.0 (C-2α), 71.5 (C-3α), 69.8 (C-5β), 65.5 (C-4α, C-5α), 65.3 (C-4β), 18.5 (C-6α, C-6β).

Hemiacetal **10a** (1.08 g, 2.7 mmol, 1.0 eq) was dissolved in absolute dichloromethane (25 mL) and cooled to 0°C. Trichloroacetonitrile (2.8 mL, 27.9 mmol, 10.3 eq) followed by DBU (110 µL, 0.74 mmol, 0.35 eq) was added. After 2 h the solvent was concentrated in vacuo (20 °C) and the residue purified by flash chromatography (3 x 20 cm, eluent: cyclohexane/acetone 15:1). Yield of imidate **10**: 1.38 g (94.7%). R_f = 0.47 (cyclohexane/acetone 3:1). $[\alpha]_D^{26}$ = + 55.7° (c = 0.52, dichloromethane). ESI-MS *m/z* 562.92 $[M+Na]^+$ (calcd for $C_{22}H_{19}Cl_3N_4O_6Na$, (563.03). ^1H-NMR (270 MHz, $[D_6]$-DMSO): δ = 9.91 (s, 1H, N*H*), 7.96 (d, 2H, *J* = 7.5 Hz, H-Ar), 7.82 (d, 2H, *J* = 7.5 Hz, H-Ar), 7.70-7.57 (m, 2H, H-Ar), 7.55-7.42 (m, 4H, H-Ar), 6.60 (bs, 1H, H-1), 5.81 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz, H-3), 5.51 (dd, 1H, $J_{1,2}$ = 3.0 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 4.23 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, H-4), 3.94 (dq, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 1.38 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6). ^{13}C-NMR (68 MHz, $[D_6]$-DMSO): δ = 165.6, 165.2 (*C*O-Bz), 134.5, 134.3 (C_p-Ar), 129.9, 129.8, 129.4 (C-Ar), 129.0, 128.7 (C_o-Ar), 94.3 (C_q-CCl_3), 92.9 (C-1), 71.2 (C-3), 70.9 (C-2), 69.4 (C-5), 64.3 (C-4), 18.2 (C-6).

5-Chloro-2-carboxymethylamino-benzoic acid (17). 4-Chloroanthranilic acid **16** (10.0 g, 58.3 mmol, 1.0 eq) was dissolved in 1 N sodium carbonate (50 mL) and the pH of the solution was adjusted to 8.5 with 1 N sodium carbonate. Chloroacetic acid (7.2 g, 76.2 mmol, 1.3 eq) was dissolved in 1 N sodium carbonate (15 mL) and adjusted to pH 3 with 1 N sodium carbonate. Both solutions were united and adjusted to pH 9 with 1 N sodium carbonate. The reaction was stirred under reflux and a pH of 9 was kept by periodical addition of 1 N sodium carbonate. After 6 h the reaction was cooled to room temperature and the solution was acidified to pH 4 with 2N hydrochloric acid. The resulting precipitate was left for 12 h at 3°C and filtered. The precipitate was briefly washed with a small amount of water and dried by lyophilization. The product was used for the next reaction without any purification. An aliquot was purified by flash chromatography for analytical purposes (eluent: toluene/ethyl acetate containing 1% HOAc 7:1 → 5:1). Yield of **17**: 8.77 g (65.5%). R_f = 0.34 (cyclohexane/ethyl acetate 1:1 with 1.0% HOAc (98%). EI/MS (70 eV): *m/z* (%) = 231 (9) $[(^{37}Cl)M]^+$, 229 (27) $[(^{35}Cl)M]^+$ (calcd for $C_9H_8ClNO_4$, 229.01). ^1H-NMR (270 MHz, $[D_6]$-DMSO): δ = 13.06 (bs, 2H, COO*H*), 8.12 (bs, 1H, N*H*), 7.73 (d, 1H, $J_{4,6}$ = 2.6 Hz, H-6), 7.38 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,6}$ = 2.6 Hz, H-4), 6.64 (d, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 4.00 (s, 2H, H-7). ^{13}C-NMR (68 MHz, $[D_6]$-DMSO): δ = 172.0, 169.1 (*C*OOH), 149.3 (C_q-NH), 134.5 (C-4), 131.0 (C-6), 118.6 (C_q-Cl), 114.2 (C-3), 112.1 (C_q-COOH), 44.8 (C-7).

3-Acetoxy-5-chloroindol (18) via **1,3-diacetyl-5-chloroindol (17a).** Compound **17** (8.77 g, 38.2 mmol, 1.0 eq) was stirred in a mixture of acetic anhydride (88 mL, 0.9 mmol) and sodium acetate (9.39 g, 0.1 mmol) at 85 °C. After 3h the reaction was cooled to room temperature and the precipitate was removed by filtration. The precipitate was washed with ethyl acetate (300 mL) and the combined filtrate was extracted with water (3 x) and saturated potassium hydrogen carbonate (2 x). The organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (5 x 20 cm, eluent: cyclohexane/ethyl acetate 7:1 → 5:1). Yield of 1,3-diacetyl-5-chloroindol (**17a**): 6.09 g (63%). R_f = 0.64 (toluene/ethyl acetate 5:1 with 1% HOAc (98%). EI/MS (70 eV): *m/z* (%) = 253 (7) $[(^{37}Cl)M]^+$, 251 (20) $[(^{35}Cl)M]^+$ (calcd for $C_{12}H_{10}ClNO_3$, 251.03). ^1H-NMR (360 MHz, $[D_6]$-DMSO): δ = 8.33 (d, 1H, $J_{6,7}$ = 8.5 Hz, H-7), 7.96 (s, 1H, H-2), 7.63 (d, 1H, $J_{4,6}$ = 2.1 Hz, H-4), 7.40 (dd, 1H, $J_{4,6}$ = 2.1 Hz, $J_{6,7}$ = 8.5 Hz, H-6), 2.60 (s, 3H, NAc), 2.37 (s, 3H, OAc). ^{13}C-NMR (90 MHz, $[D_6]$-DMSO): δ = 169.5, 168.4 (*C*O-Ac), 132.6 (C_q-7a), 131.1 (C_q-3), 128.0 (C_q-5), 125.5 (C-7), 125.2 (C_q-3a), 117.6, 117.5 (C-2, C-4, C-6), 23.6 (NAc), 20.5 (OAc).

Under an inert gas 1,3-diacetyl-5-chloroindole **17a** (1.0 g, 4.0 mmol, 1.0 eq) was dissolved in sodium hydroxide (50 mL, 5%) and stirred under reflux. After 30 minutes the reaction was cooled to 0°C and 7 mL (74 mmol, 18.5 eq) of acetic anhydride were added dropwise. The reaction was stirred for 30 minutes. The resulting white-blue precipitate was filtered and washed with water. The precipitate was dissolved in dichloromethane and the insoluble blue material was removed by filtration. The filtrate was concentrated and dried in high vacuo. Yield of **18**: 0.73 g (87.1%). R_f = 0.40 (toluene/ethyl acetate 7:1). EI/MS (70 eV): *m/z* (%) = 211 (7) $[(^{37}Cl)M]^+$, 209 (22) $[(^{35}Cl)M]^+$ (calcd for $C_{10}H_8ClNO_2$, 209.02). ^1H-NMR (270 MHz, $[D_6]$-DMSO): δ = 11.18 (bs, 1H, N*H*), 7.44 (d, 1H, $J_{4,6}$ = 1.7 Hz, H-4), 7.41 (s, 1H, H-2), 7.38 (d, 1H, $J_{6,7}$ = 8.8 Hz, H-7), 7.11 (dd, 1H, $J_{4,6}$ = 1.7 Hz, $J_{6,7}$ = 8.8 Hz, H-6), 2.31 (s, 3H, Ac). ^{13}C-NMR (68 MHz, [D$_6$]-DMSO): δ = 169.3 (*C*O-Ac), 132.3 (C$_q$-7a), 129.1 (C$_q$-3), 124.2 (C$_q$-5), 122.3 (C-6), 121.3 (C$_q$-3a), 117.1, 116.9 (C-2, C-4), 114.1 (C-7), 21.1 (Ac).

5,5'-Dichloroindigo (19). Compound **18** (294 mg, 1.40 mmol, 0.5 eq) was dissolved in methanol (15 mL) and sodium hydroxide (1 mL, 1N) was added. Immediately, compressed air was bubbled through the solution. After 15 minutes the blue precipitate was filtered, washed with water (250 mL), methanol (200 mL) and diethyl ether (200 mL). The residue was dried in a compartment dryer at 70°C. Yield: 168 mg (72.9%), blue solid. EI/MS (70 eV): *m/z* (%) = 332 (67) [(^{37}Cl)M]$^+$, 330 (100) [(^{35}Cl)M]$^+$ (calcd for $C_{16}H_8Cl_2N_2O_2$, 330.00). For solution NMR 5,5'-dichloroindigo **19** was converted to its vat indigo[31] form **19v** by heating a mixture of **19**, sodium dithionite and potassium hydroxide in D$_2$O. NMR of vat indigo **19v**: ^{1}H-NMR (270 MHz, D$_2$O): δ = 7.53 (d, 2H, $J_{4,6}$ = 1.9 Hz, H-4), 7.26 (d, 2H, $J_{6,7}$ = 8.6 Hz, H-7), 6.99 (dd, 2H, $J_{4,6}$ = 1.9 Hz, $J_{6,7}$ = 8.6 Hz, H-6). ^{13}C-NMR (68 MHz, D$_2$O): δ = 138.9 (C$_q$-7a), 132.7 (C$_q$-3a), 124.3 (C$_q$-2), 122.8 (C$_q$-5), 120.3 (C-6), 116.5 (C-4), 116.3 (C$_q$-3), 112.1 (C-7).

***N*-Benzyl-5,5'-dichloroindigo (11).** 5,5'-Dichloroindigo **19** (2.06 g, 6.21 mmol, 1.0 eq) was suspended in absolute *N,N*-dimethylformamide (50 mL), NaH (60% in oil suspension, 273 mg, 6.83 mmol, 1.1 eq) was added and the suspension was stirred at room temperature. After 30 minutes a second portion of NaH (60% in oil suspension, 273 mg, 6.83 mmol, 1.1 eq) was added. After 2 h benzylbromide (0.9 mL, 7.57 mmol, 1.2 eq) was added dropwise. The reaction was stirred for 1 h at room temperature and was subsequently concentrated in vacuo (60 °C). The oily residue was dissolved in dichloromethane (150 mL) and extracted with water (3 x). The organic layer was dried (MgSO$_4$) and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (6 x 16 cm, eluent: toluene). Yield: 1.53 g (59%), blue solid. R$_f$ = 0.68 (toluene/ethyl acetate 15:1). UV/VIS: λ_{max} (lgε) = 642 nm (4.11) in dichloromethane. EI/MS (70 eV): *m/z* (%) = 422 (67) [(^{37}Cl)M]$^+$, 420 (100) [(^{35}Cl)M]$^+$ (calcd for $C_{23}H_{14}Cl_2N_2O_2$, 420.04). ^{1}H-NMR (360 MHz, [D$_6$]-DMSO): δ = 7.69 (d, 1H, $J_{4,6}$ = 2.0 Hz, H-4), 7.62 (dd, 1H, $J_{4,6}$ = 2.0 Hz, $J_{6,7}$ = 8.7 Hz, H-6), 7.55 (d, 1H, $J_{4',6'}$ = 2.0 Hz, H-4'), 7.54 (d, 1H, $J_{4',6'}$ = 2.0 Hz, $J_{6',7'}$ = 8.7 Hz, H-6'), 7.39 (d, 2H, *J* = 8.7 Hz, H-7, H-7'), 7.22-7.18 (m, 3H, H$_p$-Ar, H$_m$-Ar), 7.08 (d, 2H, *J* = 7.2 Hz, H$_o$-Ar), 5.74 (s, 2H, C*H*$_2$). ^{13}C-NMR (90 MHz, [D$_6$]-DMSO): δ = 186.8 (C$_q$-3), 184.4 (C$_q$-3'), 151.1 (C$_q$-7a'), 150.4 (C$_q$-7a), 137.3 (C$_i$-Ar), 135.6, 135.4 (C-6, C-6'), 128.6 (C$_o$-Ar), 127.3 (C$_p$-Ar), 126.7 (C$_m$-Ar), 125.6 (C$_q$-5), 124.7 (C$_q$-5'), 124.6 (C$_q$-2), 123.3 (C$_q$-2'), 123.1 (C-4'), 122.7 (C-4), 121.7 (C$_q$-3a'), 120.1 (C$_q$-3a), 115.1 (C-7), 114.1 (C-7'), 50.1 (*C*H$_2$).

***N*-[(4''-Azido-2'',3''-di-*O*-benzoyl-4'',6''-dideoxy-β-D-glucopyranosyl)-*N*'-benzyl]-5,5'-dichloroindigo (20).** Imidate **10** (213 mg, 0.39 mmol, 1.0 eq), *N*-benzyl-5,5'-dichloroindigo **11** (165 mg, 0.39 mmol, 1.0 eq) and molecular sieves (4 Å, 400 mg) were suspended in absolute dichloromethane (22 mL), stirred for 30 minutes at room temperature followed by cooling to -18 °C. The reaction was started by adding TMSOTf (23 µL, 0.127 mmol, 0.33 eq). The reaction was stirred for 2 h at -18 °C and slowly warmed to room temperature over 12 h. The reaction was stopped by adding saturated potassium hydrogen carbonate (10 mL). After 10 minutes the suspension was filtered through Celite and washed with dichloromethane. The filtrate was extracted with water, saturated potassium hydrogen carbonate and brine. The organic layer was dried (MgSO$_4$) and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (5 x 18 cm, eluent: cyclohexane/ethyl acetate 30:1 → 20:1 → 15:1 → 10:1). 89 mg (54%) of *N*-benzyl-5,5'-dichloroindigo **11** were recovered. Yield: 139 mg **20** (44.6%), turquoise solid. R$_f$ = 0.33 (cyclohexane/ethyl acetate 4:1). UV/VIS: λ_{max} (lgε) = 646 nm (4.04) in dichloromethane. $[\alpha]_D^{23}$ = + 5378.2° (c = 5.8 µg/mL, dichloromethane). ESI/MS: *m/z* = 800.39 [($^{35/35}$Cl)M+H]$^+$, 802.39 [($^{35/37}$Cl)M+H]$^+$, 804.39 [($^{37/37}$Cl)M+H]$^+$ (calcd for $C_{43}H_{32}Cl_2N_5O_7$, 800.17). ^{1}H-NMR (360 MHz, [D$_6$]-DMSO): δ = 7.82-7.78 (m, 3H, H-7, H-4, H-Ar), 7.73 (dd, 1H, $J_{4,6}$ = 2.1 Hz, $J_{6,7}$ = 8.7 Hz, H-6), 7.57 (dd, 1H, *J* = 7.5 Hz, H-Ar), 7.52 (d, 1H, $J_{4',6'}$ = 2.1 Hz, H-4'), 7.47 (dd, 1H, $J_{4',6'}$ = 2.1 Hz, $J_{6',7'}$ = 8.6 Hz, H-6'), 7.45-

7.40 (m, 5H, H-Ar), 7.38-7.27 (m, 6H, H-Ar), 6.86 (dd, 2H, *J* = 7.8 Hz, H-Ar), 6.64 (d, 1H, $J_{6',7'}$ = 8.6 Hz, H-7'), 6.00 (d, 1H, $J_{1'',2''}$ = 9.1 Hz, H-1''), 5.89 (dd, 1H, $J_{2'',3''} = J_{3'',4''}$ = 9.3 Hz, H-3''), 5.76 (dd, 1H, $J_{1'',2''} = J_{2'',3''}$ = 9.3 Hz, H-2''), 4.97 (d, 1H, J_{gem} = 16.9 Hz, H-8'), 4.59 (d, 1H, J_{gem} = 16.9 Hz, H-8'), 4.23 (dd, 1H, $J_{3'',4''} = J_{4'',5''}$ = 9.2 Hz, H-4''), 4.05-3.90 (m, 1H, H-5''), 1.59 (d, 3H, $J_{5'',6''}$ = 6.0 Hz, H-6''). ^{13}C-NMR (90 MHz, [D$_6$]-DMSO): δ = 185.6 (C$_q$-3), 185.3 (C$_q$-3'), 164.9, 164.0 (*C*O-Bz), 150.9 (C$_q$-7a'), 148.5 (C$_q$-7a), 136.2 (C$_i$-9'), 135.8 (C-6'), 135.0 (C-6), 134.6, 133.7, 133.8 (C$_p$-Ar), 129.5, 129.1, 128.8 (C-Ar), 128.6, 128.4 (C$_i$-Ar), 128.3 (C-Ar), 127.6 (C$_q$-5), 127.1 (C$_q$-5'), 127.0, 126.3 (C-Ar), 125.1 (C$_q$-2), 124.0 (C$_q$-2'), 123.6 (C-4), 122.6 (C-4'), 122.7 (C$_q$-3a), 120.2 (C$_q$-3a'), 117.9 (C-7), 115.2 (C-7'), 85.3 (C-1''), 74.4 (C-3''), 73.4 (C-5''), 69.1 (C-3''), 65.3 (C-4''), 54.5 (*C*H$_2$-8'), 18.2 (C-6'').

***N*-(4''-Azido-2'',3''-di-*O*-benzoyl-4'',6''-dideoxy-β-D-glucopyranosyl)-5,5'-dichloroindigo (21).** Glycoside **20** (184 mg, 0.23 mmol, 1.0 eq) was dissolved in toluene/acetic acid (52 mL, 1:1) and stirred in an open flask for 28 h at 50 °C. The solution was diluted with dichloromethane (200 mL), extracted with water and saturated potassium hydrogen carbonate. The organic layer was dried (MgSO$_4$) and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (5 x 18 cm, eluent: cyclohexane/ethyl acetate 20:1 $\rightarrow$ 15:1). Yield: 98 mg (60%), blue solid. R$_f$ = 0.53 (toluene). UV/VIS: λ_{max} (lgε) = 618 nm (3.35) in dichloromethane. $[\alpha]_D^{23}$ = + 4929.0° (c = 5.1 μg/mL, dichloromethane). ESI/MS: *m/z* = 709.99 [($^{35/35}$Cl)M+H]$^+$, 712.01 [($^{35/37}$Cl)M+H]$^+$, 713.99 [($^{37/37}$Cl)M+H]$^+$ (calcd for C$_{36}$H$_{26}$Cl$_2$N$_5$O$_7$, 710.12), ^{1}H NMR (270 MHz, [D$_6$]-DMSO): δ = 10.91 (s, 1H, N*H*), 7.84-7.80 (m, 3H, H-7, H$_o$-Ar), 7.77-7.71 (m, 2H, H-4, H-6), 7.64-7.56 (m, 3H, H-4', H-6', H$_p$-Ar), 7.53-7.43 (m, 5H, H$_o$-Ar, H$_p$-Ar), 7.40 (d, 2H, *J* = 8.6 Hz, H-7'), 7.29 (dd, 2H, *J* = 7.7 Hz, H$_m$-Ar), 6.38 (d, 1H, $J_{1'',2''}$ = 8.6 Hz, H-1''), 5.75-5.65 (m, 2H, H-2'', H-3''), 4.28 (dd, 1H, $J_{3'',4''} = J_{4'',5''}$ = 9.6 Hz, H-4''), 4.02-3.90 (m, 1H, H-5''), 1.55 (d, 3H, $J_{5'',6''}$ = 6.0 Hz, H-6''). ^{13}C NMR (90 MHz, [D$_6$]-DMSO): δ = 186.1 (C$_q$-3), 185.8 (C$_q$-3'), 165.5, 164.6 (*C*O-Bz), 151.4 (C$_q$-7a'), 149.1 (C$_q$-7a), 136.4 (C-6'), 135.6 (C-6), 134.4, 134.3 (C$_p$-Ar), 129.8, 129.6, 129.5, 129.4, 129.2 (C-Ar), 129.0 (C$_i$-Ar), 128.2 (C$_q$-5), 127.7 (C$_q$-5'), 125.9 (C$_q$-2), 125.6 (C$_q$-2'), 124.6 (C$_q$-3a), 124.2 (C-4), 123.2 (C-4'), 120.7 (C$_q$-3a'), 118.5 (C-7), 115.8 (C-7'), 86.1 (C-1''), 75.0, 69.7 (C-2'', C-3''), 74.4 (C-5''), 64.9 (C-4''), 18.7 (C-6'').

***O*'-[(4''-Azido-2'',3''-di-*O*-benzoyl-4'',6''-dideoxy-β-D-glucopyranosyl)-*N'*-benzyl]-5,5'-dichloroindigo (20a)**
and
***O'*-[(4''-azido-2'',3''-di-*O*-benzoyl-4'',6''-dideoxy-β-D-glucopyranosyl)-*N'*-benzyl]-5,5'-dichloroindigo (20b).** Imidate **10** (100 mg, 0.185 mmol, 1.0 eq), *N*-benzyl-5,5'-dichloroindigo **11** (78 mg, 0. 185 mmol, 1.0 eq) and molecular sieves (4 Å, 200 mg) were suspended in absolute dichloromethane (11 mL), stirred for 30 minutes at room temperature and subsequently cooled to -18 °C. The reaction was started by addition of TMSOTf (11 μL, 0.062 mmol, 0.33 eq). After stirring for 2 h at -18 °C the reaction was quenched by adding Et$_3$N in dichloromethane (200 μL, 0.5%). On TLC in cyclohexane/ethyl acetate 4:1 three colored spots were obtained: R$_f$ = 0.64 (blue), R$_f$ = 0.51 (green), R$_f$ = 0.44 (red). The reaction mixture was filtered over Celite and the filtrate was extracted with saturated sodium hydrogen carbonate solution. The organic layer was dried (MgSO$_4$) and filtered. After adding Et$_3$N in dichloromethane (7 mL, 0.5%) the filtrate was concentrated in vacuo and the residue purified by flash chromatography (2.5 x 14 cm, eluent: cyclohexane/ethyl acetate 30:1 containing 0.5% Et$_3$N). Four fractions were obtained: fraction 1: indigo **11** (blue) R$_f$ = 0.64; fraction 2: *N*-glycoside **20** (green) R$_f$ = 0.51); fraction 3: *N*-glycoside **20** and α-*O*-glycoside **20b** (red) R$_f$ = 0.48; fraction 4: β-*O*-glycoside **20a** (red) R$_f$ = 0.44 (R$_f$ values in cyclohexane/ethyl acetate 4:1).

β-*O*-Glycoside (20a). Yield: 6.6 mg (4.5%). UV/VIS: λ_{max} (lgε) = 488 nm (2.41) in dichloromethane. $[\alpha]_D^{23}$ = + 1579° (c = 9.5 μg/mL, dichloromethane). ESI/MS: *m/z* = 822.37 [($^{35/35}$Cl)M+Na]$^+$, 824.36 [($^{35/37}$Cl)M+Na]$^+$, 826.34 [($^{37/37}$Cl)M+Na]$^+$ (calcd for C$_{43}$H$_{31}$Cl$_2$N$_5$O$_7$Na, (822.15). ^{1}H-NMR (360 MHz, [D$_6$]-DMSO): δ = 7.86 (d, 2H, *J* = 7.4 Hz, H-Ar), 7.80 (d, 2H, *J* = 7.5 Hz, H-Ar), 7.63-7.59 (m, 3 H, H-6, H-Ar), 7.55 (d, 1H, $J_{6',7'}$ = 9.0 Hz, H-7'), 7.49-7.42 (m, 4H, H-Ar), 7.41 (bs, 1H, H-4'), 7.38 (d, 1H, $J_{6,7}$ = 7.1 Hz, H-7), 7.35 (d, 1H, $J_{4,6}$ = 1.7 Hz, H-4), 7.26 (dd, 1H, $J_{6',7'}$ = 8.9 Hz, $J_{4',6'}$ = 1.7 Hz, H-6'), 7.19-7.11 (m, 3H, H-benzyl), 6.93 (d, 2H, *J* = 7.0 Hz, H-benzyl), 5.71 (d, 1H, J_{gem} = 16.2 Hz, H-8'a), 5.64 (d, 1H, J_{gem} = 16.2 Hz, H-8'b), 5.62 (dd, 1H, $J_{2'',3''}$ = $J_{3'',4''}$ = 9.3 Hz, H-3''), 5.38 (dd, 1H, $J_{1'',2''}$ = $J_{2'',3''}$ = 9.3 Hz, H-2''), 5.29 (d, 1H, $J_{1'',2''}$ = 8.0 Hz, H-1''), 3.96 (dd, 1H, $J_{3'',4''}$ = $J_{4'',5''}$ = 9.3 Hz, H-4''), 3.67 (td, 1H, $J_{4'',5''}$ = 9.3, $J_{5'',6''}$ = 6.1 Hz H-5''), 0.99 (d, 3H, $J_{5'',6''}$ = 6.1 Hz, H-6''). ^{13}C-NMR (90 MHz, [D$_6$]-DMSO): δ = 187.8 (C_q-3), 164.9, 164.4 (*C*O-Bz), 157.8 (C_q-3a), 157.4 (C_q-7a), 139.3 (C_q-3'), 137.7 (C_{ipso}-9'), 135.7 (C-6), 135.3 (C_q-7a'), 133.9, 133.8 (C_p-Ar), 133.1 (C_q-2), 129.3, 129.0, 128.9 (C-Ar), 128.5 (C_m-benzyl), 128.4, 128.3 (C_q-Ar), 127.2 (C_p-benzyl), 126.4 (C_o-benzyl),125.6 (C-6'), 125.3 (C_q-3a'), 124.5 (C-4), 123.3 (C-7), 123.0 (C_q-5), 120.9 (C_q-2'), 120.5 (C_q-5'), 117.8 (C-4'), 113.4 (C-7'), 101.4 (C-1''), 73.4 (C-3''), 72.0 (C-2''), 69.7 (C-5''), 63.9 (C-4''), 47.2 (*C*H$_2$-8'), 17.2 (C-6'').

α-*O*-Glycoside (20b). The α-*O*-glycoside **20b** was isolated from fraction 3 by flash chromatography (5 x 17 cm, eluent: cyclohexane/ethyl acetate 30:1+0.5% NEt$_3$ → 25:1+0.5% NEt$_3$). Yield: 2.4 mg (1.6%). ESI/MS: *m/z* = 800.93 [($^{35/35}$Cl)M+H]$^+$, 802.93 [($^{35/37}$Cl)M+H]$^+$, 804.93 [($^{37/37}$Cl)M+H]$^+$ (calcd for $C_{43}H_{32}Cl_2N_5O_7$, 800.17). ^{1}H NMR (360 MHz, [D$_6$]-DMSO): δ = 7.93 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.71 (dd, 1H, $J_{4.6}$ = 1.9 Hz, $J_{6,7}$ = 8.2 Hz, H-6), 7.67 (d, 2H, *J* = 7.4 Hz, H-Ar), 7.61 (d, 1H, $J_{4',6'}$ = 2.0 Hz, H-4'), 7.59 (d, 1H, $^4J_{4,6}$ = 1.9 Hz, H-4), 7.56-7.46 (m, 4H, H-7', H-Ar), 7.44 (d, 1H, dd, 1H, $J_{6,7}$ = 8.1 Hz, H-7), 7.28 (dd, 2H, *J* = 7.7 Hz, H-Ar), 7.25 (dd, 1H, $J_{6',7'}$ = 2.0 Hz, *J* = 6.6 Hz H-6'), 7.20-7.13 (m, 3H, H-benzyl), 6.92 (d, 2H, *J* = 7.3 Hz, H_o-benzyl), 5.82 (dd, 1H, $J_{2'',3''}$ = $J_{3'',4''}$ = 9.9 Hz, H-3''), 5.81 (d, 1H, $J_{1'',2''}$ = 3.4 Hz, H-1''), 5.66 (d, 1H, J_{gem} = 16.5 Hz, H-8'), 5.58 (d, 1H, J_{gem} = 16.5 Hz, H-8'), 5.35 (dd, 1H, $J_{1'',2''}$ = 3.4 Hz, $J_{2'',3''}$ = 9.9 Hz, H-2''), 4.13 (dd, 1H, $J_{3'',4''}$ = $J_{4'',5''}$ = 9.9 Hz, H-4''), 4.05 (td, 1H, $J_{4'',5''}$ = 9.9 Hz, $J_{5'',6''}$ = 5.9 Hz, H-5''), 1.19 (d, 3H, $J_{5'',6''}$ = 5.9 Hz, H-6''). ^{13}C NMR (90 MHz, [D$_6$]-DMSO): δ = 188.7 (C_q-3), 165.1, 164.9 (*C*O-Bz), 157.5 (C_q-3a), 157.0 (C_q-7a), 140.2 (C_q-3'), 137.7 (C_i-9'), 136.1 (C-6), 135.4 (C_q-7a'), 133.9, 133.8 (C_p-Ar), 133.2 (C_q-2), 129.3, 129.1, 128.9, 128.7 (C-Ar), 128.6 (C_qAr), 128.4 (C_m-benzyl), 128.1 (C_q-Ar), 127.3 (C_p-benzyl), 126.5 (C_o-benzyl), 125.7 (C-6'), 125.3 (C_q3a'), 124.9 (C-4), 123.5 (C-7), 123.1 (C_q-5), 119.8 (C_q-2'), 119.6 (C_q-5'), 117.9 (C-4'), 113.6 (C-7'), 99.3 (C-1''), 71.5 (C-2''), 70.7 (C-3''), 67.8 (C-5''), 63.9 (C-4''), 47.6 (*C*H$_2$-8'), 17.6 (C-6'').

Akashin A (1). Under an argon atmosphere **21** was dissolved in thoroughly degassed and dried methanol (0.8 mL/mg starting material) followed by addition of propanedithiol (30 eq) and diisopropylethylamine (15 eq). Upon addition of the amine the color of the solution changed from blue to pale yellow. After 3-4 d at room temperature under strict exclusion of light the reaction was transferred into dichloromethane/acetic acid (99:1, 2 mL/mg starting material) and stirred in an open flask for 60-90 minutes. Within this time the yellowish vat indigo was reoxidised to the desired blue indigo. The organic phase was extracted with hydrochloric acid (25 mM). The blue aqueous phase was submitted to solid phase extraction using SepPak-C$_{18}$ material. Elution was carried out with acetonitrile in water (1% acetic acid) in steps of 2.5% from 0-30% acetonitrile. The product eluted from 17.5-25% acetonitrile and was lyophilized. For removal of the acetic acid the product was chromatographed by a Sephadex LH 20 column using dichloromethane/methanol (6:4) for elution. Yield: 39-73% of **1**, blue solid. R_f = 0.10 (dichloromethane/methanol 15:1). UV/VIS: $\lambda_{\max}$ (lgε) = 620 nm (4.15) in methanol. $[\alpha]_D^{24}$ = + 2591.0° (c = 6.9 μg/mL, methanol). ESI/MS: *m/z* = 476.12 [($^{35/35}$Cl)M+H]$^+$, 478.14 [($^{35/37}$Cl)M+H]$^+$, 480.13 [($^{37/37}$Cl)M+H]$^+$ (calcd for $C_{22}H_{20}Cl_2N_3O_5$, (476.08). ^{1}H-NMR (360 MHz, [D$_6$]-DMSO): δ = 11.00 (bs, 1H, N'*H*), 7.71 (d, 1H, $J_{4,6}$ = 1.4 Hz, H-4), 7.64 (dd, 1H, $J_{4,6}$ = 1.4 Hz, $J_{6,7}$ = 9.0 Hz, H-6), 7.63 (d, 1H, $J_{4',6'}$ = 1.6 Hz, H-4'), 7.55 (dd, 1H, $J_{4',6'}$ = 1.6 Hz, $J_{6',7'}$ = 8.6 Hz, H-6'), 7.50 (d, 1H, $J_{6,7}$ = 9.0 Hz, H-7), 7.41 (d, 1H, $J_{6',7'}$ = 8.6 Hz, H-7'), 5.69 (d, 1H, $J_{1'',2''}$ = 9.1 Hz, H-1''), 5.05 (d, 1H, $J_{\mathrm{OH}\text{-}3'',3''}$ = 5.0 Hz, OH-3''), 4.87 (d, 1H, $J_{\mathrm{OH}\text{-}2'',2''}$ = 6.9 Hz, OH-2''), 3.52-3.42 (m, 2H, H-2'', H-5''), 2.95 (ddd, 1H, $J_{2'',3''}$ = $J_{3'',4''}$ = 9.0 Hz, $J_{\mathrm{OH}\text{-}3'',3''}$ = 5.0 Hz, H-3''), 2.31 (dd, 1H, $J_{3'',4''}$ = $J_{4'',5''}$ = 9.0 Hz, H-4''), 1.34 (d, 3H, $J_{5'',6''}$ = 5.8 Hz, H-6''). ^{13}C-NMR (90 MHz, [D$_6$]-DMSO): δ = 185.2 (C_q-3'), 184.1 (C_q-3), 150.7 (C_q-7a'), 149.2 (C_q-7a), 135.6 (C-6'), 134.7 (C-6), 126.6 (C_q-5), 124.6 (C_q-5'), 124.2 (C_q-2), 124.0 (C_q-2'), 123.9 (C_q-3a), 123.2 (C-4'), 122.6 (C-4), 120.2 (C_q-3a'), 117.9 (C-7), 115.1 (C-7'), 88.0 (C-1''), 77.2 (C-3''), 76.3 (C-5''), 70.0 (C-2''), 59.2 (C-4''), 18.5 (C-6''). ^{1}H NMR (360 MHz, [D$_6$]-DMSO acidified with HCl): δ = 8.46-8.38 (bs, 1H, N'H_3^+), 7.71 (bs, 1H, H-4), 7.61 (m, 1H, H-6), 7.61 (m, 1H, H-4'), 7.56 (dd, 1H, $J_{4',6'}$ = 1.7 Hz, $J_{6',7'}$ = 8.1 Hz, H-6'), 7.57-7.50 (m, 1H, H-7), 7.39 (d, 1H, $J_{6',7'}$ = 8.5 Hz, H-7'), 5.74-5.69 (m, 1H, H-1''), 3.61 (dd, 1H, $J_{1'',2''}$ = $J_{2'',3''}$ = 9.0 Hz, H-2''), 2.95 (dd, 1H, $J_{2'',3''}$ = $J_{3'',4''}$ = 9.0 Hz, H-3''), 3.00-2.86 (m, 1H, H-4''), 3.96 (dq, 1H, $J_{5'',4''}$ = 9.9 Hz, $J_{5'',6''}$ = 6.0 Hz, H-5''), 1.43 (d, 3H, $J_{5'',6''}$ = 6.0 Hz, H-6''). ^{13}C NMR (90 MHz, [D$_6$]-DMSO acidified with HCl; ^{13}C-signals taken from HMQC-COSY): δ = 135.5 (C-6'), 134.0 (C-6), 123.4 (C-4'), 122.1 (C-4), 117.1 (C-7), 114.5 (C-7'), 87.1 (C-1''), 72.6 (C-3''), 71.5 (C-5''), 69.4 (C-2''), 57.0 (C-4''), 18.2 (C-6'').

Akashin B (2). Akashin A **1** (9.6 mg, 20 μmol, 1.0 eq) was dissolved in methanol (9.6 mL). Acetic anhydride (192 μL, 2.0 mmol, 100 eq) and water (288 μL, 16 mmol, 800 eq) were added and mixture was stirred for 30 minutes at room temperature. The crude product was concentrated in vacuo after addition of toluene. The remainder was purified by solid phase extraction over SepPak-C_{18} material using a step gradient of acetonitrile in water (20-100% in 10%-steps). The product eluted from 40-70% acetonitrile and was lyophilized. Yield: 10.3 mg **2** (99.4%), blue solid. R_f = 0.24 (dichloromethane/methanol 15:1). UV/VIS: λ_{max} (lgε) = 620 nm (4.18) in methanol. $[\alpha]_D^{27}$ = + 4137.9° (c = 5.8 μg/mL, methanol). ESI/MS: *m/z* = 518.20 [($^{35/35}$Cl)M+H]$^+$, 520.19 [($^{35/37}$Cl)M+H]$^+$, 522.19 [($^{37/37}$Cl)M+H]$^+$ (calcd for $C_{24}H_{22}Cl_2N_3O_6$, 518.09). ^{1}H-NMR (360 MHz, [D$_6$]-DMSO): δ = 11.01 (s, 1H, N*H'*), 7.77 (d, 1H, $J_{NH'',4''}$ = 8.9 Hz, N*H''*), 7.72 (s, 1H, H-4), 7.67 (d, 1H, $J_{6,7}$ = 8.2 Hz, H-6), 7.62 (s, 1H, H-4'), 7.60-7.54 (m, 2H, H-6', H-7), 7.41 (d, 1H, $J_{6',7'}$ = 8.2 Hz, H-7'), 5.71 (d, 1H, $J_{1'',2''}$ = 9.0 Hz, H-1''), 5.0-4.95 (m, 2H, OH-2'', OH-3''), 3.68-3.59 (m, 1H, H-5''), 3.60-3.49 (m, 2H, H-2'', H-4''), 3.24 (ddd, 1H, $J_{2'',3''}$ = $J_{3'',4''}$ = 9.1 Hz, $J_{OH-3'',3''}$ = 5.9 Hz, H-3''), 1.84 (s, 3H, NH-Ac), 1.23 (d, 3H, $J_{5'',6''}$ = 5.1 Hz, H-6''). ^{13}C-NMR (90 MHz, [D$_6$]-DMSO): δ = 187.4 (C_q-3), 186.0 (C_q-3'), 170.1 (*C*O-Ac), 151.5 (C_q-7a'), 149.9 (C_q-7a), 136.4 (C-6'), 135.6 (C-6), 127.1 (C_q-5), 125.4 (C_q-5'), 125.0 (C_q-2'), 124.8 (C_q-2), 124.7 (C_q-3a), 120.9 (C_q-3a'), 123.9 (C-4'), 123.4 (C-4), 118.7 (C-7), 115.9 (C-7'), 88.6 (C-1''), 75.1 (C-3'', C-5''), 71.0 (C-2''), 59.2 (C-4''), 23.8 (NAc), 19.1 (C-6'').

Akashin C (3). Akashin A **1** (4 mg, 8.4 μmol, 1.0 eq) was dissolved in absolute methanol (4.3 mL). Diacetyl (4.4 μL, 50.3 μmol, 6.0 eq) in absolute methanol (200 μL), trimethylorthoformate (12 μL, 110 μmol, 13 eq) in absolute methanol (200 μL) and camphorsulfonic acid (0.39 mg, 1.7 μmol, 0.2 eq) in absolute methanol (200 μL) were added. After stirring for 2-3 h at room temperature sodium cyanoborhydride (5.3 mg, 84 μmol, 10 eq) in absolute methanol (200 μL) was added. After 25 minutes the reaction was concentrated in vacuo and purified by flash chromatography (2 x 10 cm, solvent: dichloromethane/methanol 40:1 → 30:1 → 25:1 containing 0.1% formic acid). Yield: 2.7 mg **3** (59%), blue solid. R_f = 0.54 (dichloromethane/methanol 15:1). UV/VIS: λ_{max} (lgε) = 618 nm (3.71) in methanol. $[\alpha]_D^{27}$ = + 1143° (c = 14 μg/mL, methanol). ESI/MS: *m/z* = 546.75 [($^{35/35}$Cl)M+H]$^+$, 548.73 [($^{35/37}$Cl)M+H]$^+$, 550.74 [($^{37/37}$Cl)M+H]$^+$ (calcd for $C_{26}H_{26}Cl_2N_3O_6$, 546.12). ^{1}H-NMR (360 MHz, CD_3OD): δ = 7.72 (s, 1H, H-4), 7.62-7.58 (m, 3H, H-4', H-6, H-7), 7.50 (d, 1H, $J_{6',7'}$ = 8.7 Hz, H-6'), 7.22 (d, 1H, $J_{6',7'}$ = 8.7 Hz, H-7'), 6.05 (d, 1H, $J_{1'',2''}$ = 9.3 Hz, H-1''), 3.91-3.82 (m, 2H, H-2'', H-5''), 3.77 (dd, 1H, $J_{2'',3''}$ = $J_{3'',4''}$ = 9.3 Hz, H-3''), 2.81 (q, 1H, $J_{3''',4'''}$ = 6.3 Hz, H-3'''), 2.54 (dd, 1H, $J_{3'',4''}$ = 9.3 Hz, H-4''), 1.45 (d, 3H, $J_{5'',6''}$ = 6.0 Hz, H-6''), 1.30 (s, 3H, Me-1'''), 1.13 (d, 3H, $J_{3''',4'''}$ = 6.3 Hz, Me-4'''). ^{13}C NMR (90 MHz, CD_3OD; ^{13}C-signals taken from HMQC-COSY): δ = 135.0 (C-6'), 133.9 (C-6), 122.7 (C-4'), 121.9 (C-4), 116.9 (C-7), 113.3 (C-7'), 87.7 (C-1''), 73.7 (C-3'', C-5''), 67.3 (C-2''), 61.6 (C-4''), 57.1 (C-3'''), 23.8 (C-1'''), 15.9 (C-6''), 14.7 (C-4'''). ^{1}H-NMR (360 MHz, [D$_6$]-DMSO): δ = 11.00 (s, 1H, N*H'*), 7.72 (s, 1H, H-4), 7.65-7.60 (m, 2H, H-4', H-6'), 7.59-7.51 (m, 2H, H-6, H-7), 7.40 (d, 1H, $J_{6',7'}$ = 8.5 Hz, H-7'), 5.80 (d, 1H, $J_{1'',2''}$ = 8.4 Hz, H-1''), 5.67 (s, 1H, OH-2'''), 4.88 (d, 1H, $J_{OH-2'',2''}$ = 5.0 Hz, OH-2''), 3.73-3.46 (m, 3H, H-2'', H-4'', H-5''), 2.65-2.57 (m, 1H, H-3'''), 2.45-2.40 (m, 1H, H-3''), 1.32 (d, 3H, $J_{5'',6''}$ = 5.2 Hz, H-6''), 1.14 (s, 3H, Me-1'''), 0.95 (d, 3H, $J_{3''',4'''}$ = 6.1 Hz, Me-4'''). ^{13}C-NMR (90 MHz, [D$_6$]-DMSO; ^{13}C-signals taken from HMQC-COSY): δ = 135.5 (C-6'), 134.5 (C-6), 122.9 (C-4'), 122.5 (C-4), 117.5 (C-7), 114.9 (C-7'), 88.1 (C-1''), 74.1 (C-2''), 73.8 (C-5''), 67.1 (C-4''), 61.9 (C-3''), 57.5 (C-3'''), 25.3 (C-1'''), 17.8 (C-6''), 16.6 (C-4''').

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Supplementary Material

LC-MS and ^{1}H NMR Spectra of compounds **4, 20, 20a, 20b, 1, 2, 3** are given in the supplementary material file associated with this paper.

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