DOI: 10.1002/ejoc.201301198

Indoxylic Acid Esters as Convenient Intermediates Towards Indoxyl Glycosides

Stephan Böttcher[a] and Joachim Thiem*[a]

Dedicated to the memory of Professor Robert J. Ferrier

Keywords: Carbohydrates / Glycosides / Decarboxylation / Dyes/Pigments / Glycosylation / Nitrogen heterocycles

Indoxylic acid methyl and allyl esters with varied halide-substitution patterns were obtained in excellent yields using a scalable route. Phase-transfer glycosylation of these key intermediates was carried out with various glycosyl halides. Subsequent mild silver-mediated decarboxylation followed by Zemplén deacetylation led to indoxyl glycosides in good overall yields. Indoxyl glycosides are well-established and widely used tools for enzyme screening and enzyme-activity monitoring. In the past, their synthesis has been difficult, so this new approach has led to a variety of useful structures.

Introduction

Historically, indigo was extracted from plants, and economically, this was a very important process in ancient times. The indigo precursors were indicane, isatan A, and isatan B (Figure 1).[1] In these structures, indoxyl is linked to glucose (indicane) or modified glucose structures (isatans A and B). Hydrolysis of the glycosidic linkage releases free indoxyl, a slightly yellow, water-soluble compound, which is rapidly oxidized to give the indigo dye, for example by atmospheric oxygen.

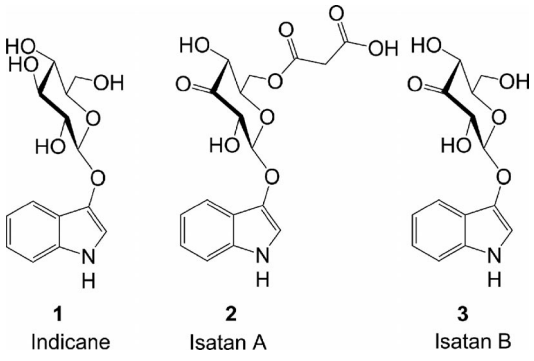


Figure 1. Natural indigo precursors from plants.[1]

This reaction is used in histochemistry, biochemistry, bacteriology, and molecular biology for monitoring enzyme activities, and these days, some substrates are commercially available (Figure 2). Different residues can be linked to the 3-hydroxy group of the indoxyl moiety, such as, for example, glycosides (Figure 3 top) to check for glycosidases, esters for esterases, or phosphates for phosphatases. The indoxyl part is normally decorated with halides, and the substitution pattern determines the colour (Figure 3 bottom) and physical properties of the resulting indigo dyes.[1,2] The most common substitution patterns are 5-bromo-, 5-

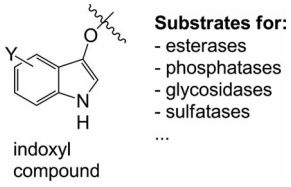


Figure 2. Indoxyl substrates.

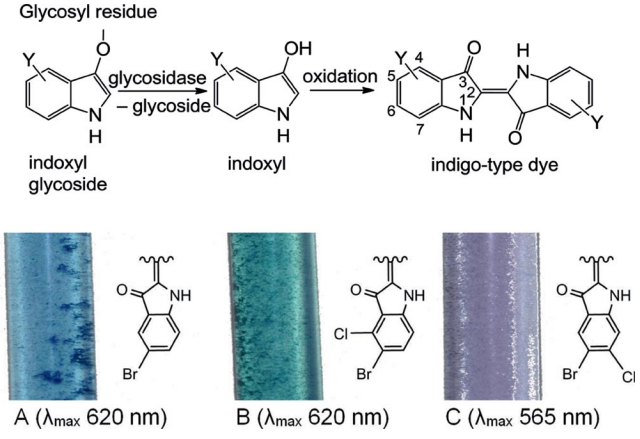


Figure 3. Top: monitoring of glycosidase activity: formation of indigo-type dye. Bottom: monitoring of glycosidase activity: indigo-type dyes and wavelengths.

[a] Department of Chemistry, Faculty of Science, University of Hamburg,
Martin-Luther-King-Platz 6, 20146 Hamburg, Germany
E-mail: thiem@chemie.uni-hamburg.de
http://www.chemie.uni-hamburg.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301198.

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

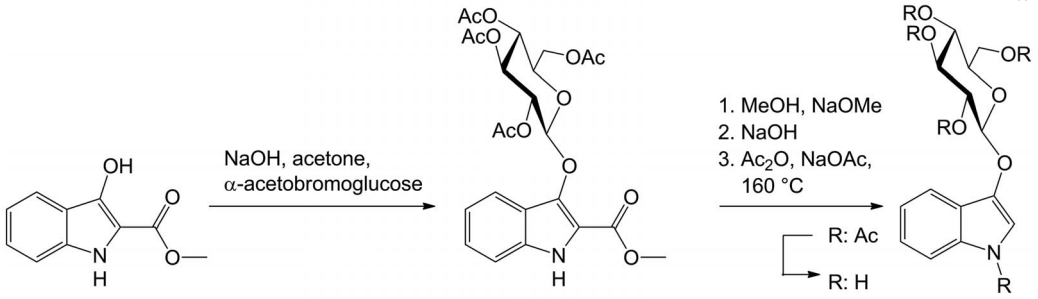


Figure 4. Synthesis of indicane by A. Robertson in 1927.[7]

bromo-6-chloro-, and 5-bromo-4-chloro-indoxyl (which is commonly abbreviated as X), because the resulting compounds show the least diffusion from the sites of hydrolysis, they give the smallest dye particles, and they do not form granules.[1]

The synthesis of complex oligosaccharides is a challenging task. It requires protracted protecting group chemistry, and also the regiochemical and stereochemical outcomes of glycosylation reactions must be controlled. These issues can be avoided by enzymes such as transferases and transglycosidases, which are important and powerful tools for the synthesis of complex oligosaccharides. Screening for new glycosidases as well as transglycosidases can be carried out using indoxyl glycosides (Figure 3 top and bottom). Thus, indoxyl glycosides are powerful tools with both in vivo and in vitro applications, that can be used in qualitative and quantitative approaches, e.g., blue/white screening.

Unfortunately, the synthesis of indoxyl glycosides is often problematic and low-yielding, especially for glucose derivatives (X-Glc 15%, X-GlcNAc 29%) or more complex glycosides.[3–6] Most commonly, a glycosylation of the sugar halide is carried out in acetone with sodium hydroxide, and with the respective indoxyl derivative as the acceptor. Indoxyl itself is quite reactive, and it can undergo a number of side-reactions, even in the absence of oxygen, which lowers the yield, and also causes problems during purification. Furthermore, elimination under the strongly basic conditions can decrease the yield drastically.

A. Robertson developed a synthesis of indicane in 1927, and of 6-bromoindicane in 1929.[7,8] Starting from indoxylic acid methyl ester, the glycosylation was carried out in acetone with sodium hydroxide. The resulting glycoside was deprotected (Zemplén deacetylation[9] followed by ester hydrolysis). Subsequent decarboxylation at temperatures up to 160 °C gave the protected compound in around 50% yield. Finally, Zemplén deacetylation[9] gave the free indicane (Figure 4).

Carrying out the complete deprotection of the glycoside followed by decarboxylation at temperatures up to 160 °C is unsuitable for sensitive sugar structures, as both of these steps favour side reactions and decomposition.

Results and Discussion

In this paper, we wish to report an improved synthesis of indoxyl glycosides based on indoxylic acid esters as key intermediates.[10] Indoxylic acid allyl and methyl esters were obtained in good yields using a scalable pathway. These compounds were compared and tested with different sugar halides in the glycosylation and decarboxylation reactions (Figure 5).

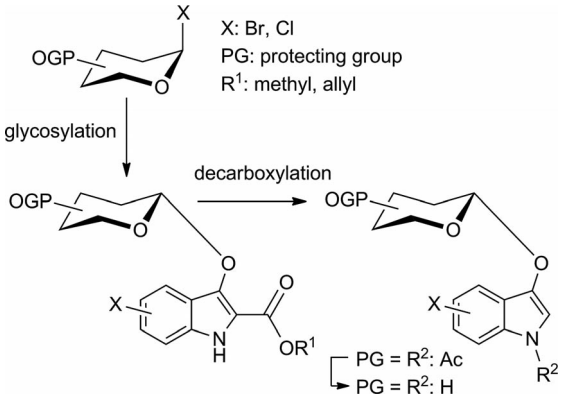
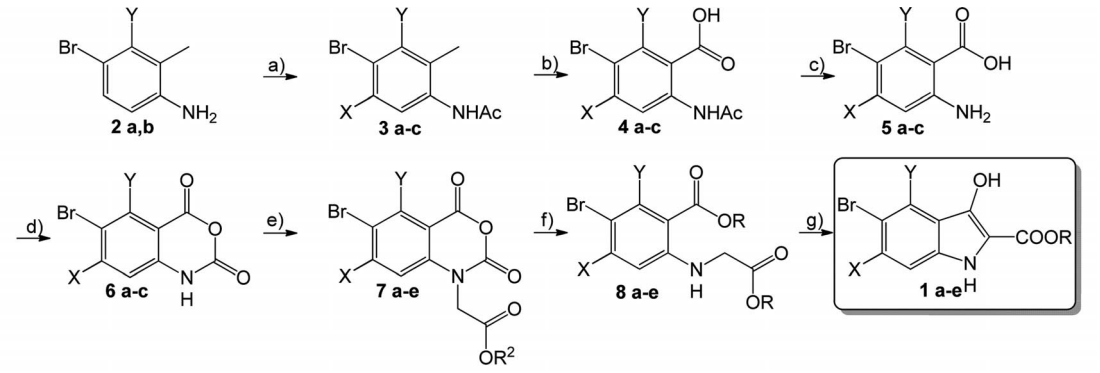


Figure 5. General synthetic pathway.

Glycosylation was carried out effectively under phase-transfer conditions. Then the protected indoxyl glycosides were obtained by using a mild silver-mediated decarboxylation. The allyl ester derivatives allowed a selective ester cleavage, but the methyl esters required a complete deprotection of the whole glycoside for decarboxylation, following the Robertson approach.

The synthetic route for preparation of indoxylic acid esters **1a**–**1f** is shown in Scheme 1. Starting by acetylation[11] of 4-bromo-2-methylaniline (**2a**) and 4-bromo-3-chloro-2-methylaniline (**2b**), *N*-acetylated compounds **3a** (97%) and **3b** (85%) were obtained. *N*-(4-Bromo-5-chloro-2-methylphenyl)acetamide (**3c**) was obtained by acetylation and subsequent bromination of 5-chloro-2-methylaniline.[12] Oxidation with $KMnO_4$[11] in water (to give **4a**, 70%; **4b**, 66%; and **4c**, 63%), followed by deacetylation under reflux in sodium hydroxide solution[13] gave free anthranilic acids **5a** (88%), **5b** (93%), and **5c** (94%). Treatment with triphosgene and pyridine in acetonitrile[14] led to isatoic anhydrides **6a** (80%), **6b** (94%), and **6c** (82%). *N*-Alkylation was achieved by treatment with sodium hydride[15] and allyl bromoacetate or methyl bromoacetate to give compounds **7a**–**7e** in excellent yields of 93% (**7a**), 99% (**7b**), 84% (**7c**), 99% (**7d**), and 98% (**7e**). Opening of the anhydrides was performed using the corresponding alcohol and a catalytic

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



								Y	X	R
2a	**3a** (97%)	**4a** (70%)	**5a** (88%)	**6a** (80%)	**7a** (93%)	**8a** (80%)	**1a** (84%)	Cl	H	Allyl
2b	**3b** (85%)	**4b** (66%)	**5b** (93%)	**6b** (94%)	**7b** (99%)	**8b** (75%)	**1b** (80%)	H	H	Allyl
	3c (96%)*	**4c** (63%)	**5c** (94%)	**6c** (82%)	**7c** (84%)	**8c** (84%)	**1c** (76%)	H	Cl	Allyl
					7d (99%)	**8d**(93%)	**1d** (95%)	Cl	H	Me
					7e (98%)	**8e** (88%)	**1e** (81%)	H	H	Me

Scheme 1. Synthesis of indoxylic acid esters **1a**–**1e**. Reagents and conditions: (a) CH_2Cl_2, Ac_2O, 0 °C – room temp., 5–16 h; (b) H_2O, $MgSO_4$, $KMnO_4$, reflux, 6 h; (c) NaOH, reflux, 5 h; (d) MeCN, pyridine, triphosgene, 50 °C, 4 h; (e) DMF, sodium hydride, allyl or methyl bromoacetate, room temp., 5–10 h; (f) allyl or methyl alcohol, sodium hydride, room temp., 2–7 h; (g) for allyl ester: Et_2O, KO*t*Bu, reflux, 2 h; for methyl ester: Et_2O, MeOH, NaOMe, reflux, 2 h. ***3c** was prepared by bromination of 5-chloro-2-methylacetamide.

amount of sodium hydride to give compounds **8a** (80%), **8b** (75%), **8c** (84%), **8d** (93%), and **8e** (88%). Finally, indoxylic acid allyl esters **1a** (84%), **1b** (80%), and **1c** (76%), as well as methyl esters **1d** (95%) and **1e** (81%) were obtained by Dieckmann condensation.[16]

Phase-transfer glycosylations of these six indoxyl acid esters (i.e., **1a**–**1e**) were carried out under standard conditions with three different sugar halides (i.e., **9**–**11**) (Figure 6). The results of the phase-transfer glycosylations and decarboxylations are summarized in Scheme 2. Glycosylations with 5-bromo-4-chloroindoxylic acid methyl ester **1d** gave the corresponding glucoside (i.e., **12a**, 83%), lactoside (i.e., **12b**, 73%), and galactoside (i.e., **12c**, 83%). Glycosylation of α-acetobromogalactose (**11**) with 5-bromoindoxylic acid methyl ester **1e** gave an 82% yield of **12d**. Glycosylations using 5-bromo-4-chloroindoxylic acid allyl ester **1a** led to the corresponding glucoside (i.e., **13a**, 77%), lactoside (i.e., **13b**, 74%), and galactoside (i.e., **13c**, 88%). Finally, glycosylation of α-acetobromogalactose (**11**) was performed with 5-bromoindoxylic acid allyl ester **1b** as well as with 5-bromo-6-chloroindoxylic acid allyl ester **1c** to give **13d** (75%) and **13e** (70%), respectively. All the glycosylation reactions gave good yields of 73–86%. The best yields were obtained with the galactose donor **9** (**12c**, 86%, and **13c**, 86%). The yields for the methyl ester and allyl ester derivatives were more or less the same.

Next, these glycosides (i.e., **12a**–**12d** and **13a**–**13e**) were subjected to mild silver-mediated decarboxylation. Before decarboxylation could take place, ester cleavage was essential. For allyl ester derivatives **13a**–**13e**, the ester could be selectively cleaved by treatment with $Pd(PPh_3)_4$ and morpholine in THF.[17] The methyl esters in **12a**–**12d** were hydrolysed by treatment with sodium hydroxide after an initial Zemplén[9] deacetylation.

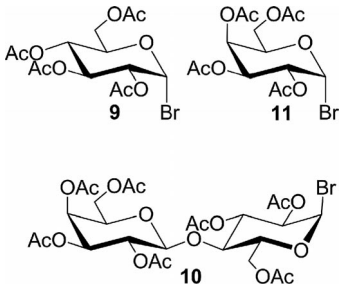
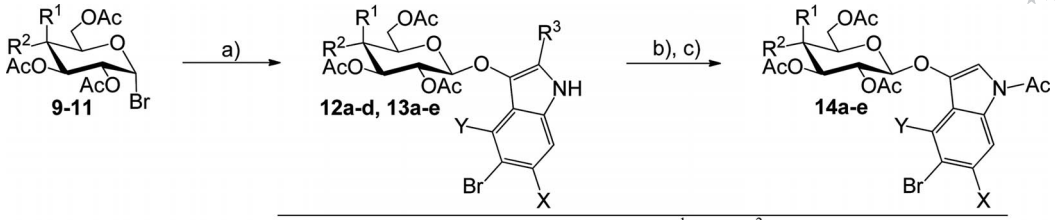


Figure 6. Sugar halides **9**–**10**.

For the decarboxylation step, a modification of a recently published method was used.[18] Instead of NMP (*N*-methylpyrrolidone) or DMF, acetic anhydride was used as the solvent, in combination with AgOAc and K_2CO_3.[10] Under these conditions, decarboxylations could take place at lower temperatures between 90–110 °C, and the reaction times required were shorter (20–40 min). Decarboxylation of glycosides **12a**–**12d**, after Zemplén[9] deacetylation and ester hydrolysis gave the protected 5-bromo-4-chloroindoxyl glucoside (i.e., **14a**, 63%), lactoside (i.e., **14b**, 42%), and galactoside (i.e., **14c**, 47%). Decarboxylation of compound **13d** led to peracetylated indoxyl glycoside **14d** in 43% yield. Compounds **13a**–**13e** were subjected to selective allyl ester cleavage,[17] and subsequent decarboxylation gave the peracetylated indoxyl glycosides of glucose (i.e., **14a**, 74%), lactose (i.e., **14b**, 76%), and galactose (i.e., **14c**, 88%). Protected 5-bromo and 5-bromo-6-chloroindoxyl derivatives **14d** and **14e** were obtained in 75 and 87% yields.

The route via the allyl ester derivatives gave much higher yields for the decarboxylation. An improvement of 11% for glucose (**12a** vs. **13a**), 34% for lactose (**12b** vs. **13b**), 41% for

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



			Glycoside	R^1	R^2	Y	X
9	**13a** (77%)	**14a** (74%)	Glc	H	OAc	Cl	H
10	**13b** (74%)	**14b** (76%)	Lac	H	β-Gal $(OAc)_4$(1-4)	Cl	H
11	**13c** (86%)	**14c** (88%)	Gal	OAc	H	Cl	H
	13d (80%)	**14d** (75%)	Gal	OAc	H	H	H
	13e (70%)	**14e** (87%)	Gal	OAc	H	H	Cl

13a-e, R^3:

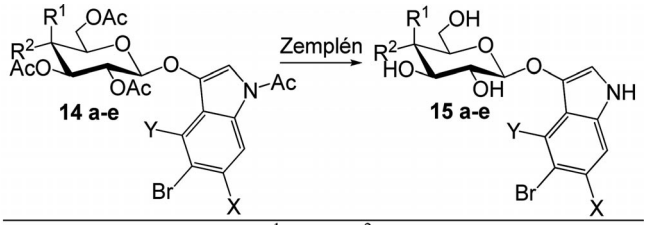
			Glycoside	R^1	R^2	Y	X
9	**12a** (83%)	**14a** (63%)	Glc	H	OAc	Cl	H
10	**12b** (73%)	**14b** (42%)	Lac	H	β-Gal $(OAc)_4$(1-4)	Cl	H
11	**12c** (86%)	**14c** (47%)	Gal	OAc	H	Cl	H
	12d (82%)	**14d** (43%)	Gal	OAc	H	H	H

12a-d, R^3:

Scheme 2. Synthesis of peracetylated indoxyl glycosides **14a**–**14e**. Reagents and conditions: (a) CH_2Cl_2, K_2CO_3 (1 M), TBAHS (tetrabutylammonium hydrogen sulfate), room temp., 2–5 h; (b) for allyl ester derivatives: THF, morpholine, $Pd(PPh_3)_4$, room temp., overnight; for methyl ester derivatives: 1. MeOH, NaOMe, room temp., 2–6 h; 2. NaOH (0.1 N), room temp., 1–4 h; (c) Ac_2O, AgOAc, K_2CO_3, 90–110 °C, 20–40 min.

galactose (**12c** vs. **13c**), and 32% for the 5-bromo galactose derivatives (**12d** vs. **13d**) was observed. In addition, longer reaction times were needed for the decarboxylation step on the methyl ester route, since here the unprotected glycosides first had to be acetylated for solubility reasons. Furthermore, it was noted that the yields (phase-transfer glycosylation and decarboxylation) for the 5-bromo-4-chloro derivatives (i.e., **12c** and **13c**) were slightly higher (by 4–13%) than those for the corresponding 5-bromo derivatives (i.e., **12d** and **13d**).

Finally, Zemplén deacetylation[9] gave the free indoxyl glycosides (i.e., **15a**–**15e**; Scheme 3). X-Glc (**15a**) was obtained in 75% yield, X-Lac (**15b**) in 75% yield, X-Gal (**15c**) in 87% yield, 5-bromoindoxyl galactoside (**15d**) in 80% yield, and finally 5-bromo-6-chloroindoxyl galactoside (**15e**) in 99% yield.



	Glycoside	R^1	R^2	Y	X
15a (75%)	Glc	H	OH	Cl	H
15b (75%)	Lac	H	β-Gal (1-4)	Cl	H
15c (87%)	Gal	OH	H	Cl	H
15d (80%)	Gal	OH	H	H	H
15e (99%)	Gal	OH	H	H	Cl

Scheme 3. Zemplén deacetylation of **14a**–**14e**.

Conclusions

A new synthetic route to indoxyl glycosides has been developed. Due to the poor yields and the limitations for complex saccharide structures of previous approaches, our aim was to establish a new general route. The use of cheap starting materials and a high-yielding scalable modular acceptor synthesis allow access to a variety of different indoxyl compounds.

The acceptor synthesis was tested with the three most common substitution patterns. After blocking the reactive position in the indoxyl moiety as an allyl or methyl ester, glycosylations were carried out under phase-transfer conditions between these acceptors and glycopyranosyl bromides of lactose, galactose, and glucose to give the glycosides in good yields. The key decarboxylation step was superior with the allyl esters, as these could be cleaved selectively. Activation of the carboxylic acid for decarboxylation using silver salts allowed lower temperatures and shorter reaction times. X-Gal (66% over three steps), X-Glc (43% over three steps), and X-Lac (42% over three steps) were obtained by this route in the best yields reported to date.

Further studies focussing on the synthetic scope of this route using complex biologically relevant aminosugars such as LacNAc and LNB (lacto-*N*-biose) are currently in progress, and the results will be reported in due course.

Experimental Section

General Remarks: All reagents were purchased from commercial suppliers, and were used as received. Sodium hydride (NaH) was used as a 60% suspension in paraffin. TLC was carried out on Merck silica gel 60 F_{254} plates. Compounds were detected using UV

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

light and/or by treatment with EtOH/H_2SO_4 (9:1) and subsequent heating. Column chromatography was performed with Merck/Fluka silica gel 60 (230–400 mesh). Solvents for column chromatography were distilled prior to use. ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-400 or Bruker AV-400 spectrometers (400 MHz for ^1H, 101 MHz for ^{13}C); spectra were calibrated using the residual solvent peak. In $CDCl_3$, tetramethylsilane was used for calibration. The abbreviation "v" before a multiplicity means virtual. Melting points were measured with a Büchi M-565 melting point apparatus. Optical rotations were obtained using a Krüss Optronic P8000 polarimeter (589 nm). HRMS (ESI) spectra were recorded with a Thermo Finnigan MAT 95XL mass spectrometer. The preparation and characterization of compounds **1a**,[10] **3a**–**8a**,[10] **3b**[19] were carried out as reported previously.

General Procedure 1. Oxidation with $KMnO_4$:[11] A mixture of the starting material (1.0 mmol) and $MgSO_4$ (2.0 mmol) in H_2O (5.0 mL) was heated to reflux in a three-necked round-bottomed flask. Then $KMnO_4$ (saturated aq. solution; 7.5 mL) was added dropwise over a period of 2 h. The reaction mixture was heated to reflux for a further 3.5 h. After cooling, the lukewarm reaction mixture was filtered to remove the manganese dioxide. The filtrate was acidified with hydrochloric acid (37%) to pH 1.0. The precipitate was collected by filtration and then dried at 45 °C under high vacuum.

General Procedure 2. Hydrolysis of Anthranilate Esters:[13] A suspension of the starting material (1.0 mmol) in sodium hydroxide (1 N aqueous; 5.0 mL) was heated at reflux for 4 h to give a clear solution. After cooling to room temperature, the mixture was treated with hydrochloric acid (37%, pH 1). The precipitate was collected by filtration and then dried at 45 °C under high vacuum.

General Procedure 3. Formation of Isatoic Anhydrides with Triphosgene:[14] The following reaction was carried out under an argon atmosphere using dry solvents. Pyridine (1.6 mL) and a solution of triphosgene (3.3 mmol) in CH_2Cl_2 (6.0 mL) were simultaneously added dropwise to a suspension of anthranilic acid (10 mmol) in MeCN (10 mL) over a period of 30 min. The reaction mixture was heated at 45 °C for 3 h. The reaction was quenched by the addition of water. The product was collected by filtration, then it was washed with water and chilled CH_2Cl_2, and dried at 45 °C under high vacuum.

General Procedure 4. *N*-Alkylation of Isatoic Anhydrides:[15] The following reaction was carried out under an argon atmosphere using dry solvents. The isatoic anhydride (1.0 mmol) was dissolved in DMF (4.0 mL), and the solution was cooled in an ice bath. Sodium hydride (1.15 equiv.) was added portionwise to the cooled solution. After 45 min, the ice bath was removed, and methyl bromoacetate/allyl bromoacetate (1.2 equiv.) was added. The reaction mixture was stirred overnight, and then it was quenched by the addition of water. The product was collected by filtration, then it was washed with water and dried at 45 °C under high vacuum.

General Procedure 5a. Opening of Isatoic Anhydrides; Formation of Methyl Esters: The following reaction was carried out under an argon atmosphere using dry solvents. A mixture of the starting material (1.0 mmol) in MeOH (4.0 mL) was treated with sodium methoxide (0.6 equiv.). The reaction mixture was stirred for 2 h at 40–45 °C to give a clear solution. The reaction was quenched by the addition of water, then the flask was kept at 5 °C for 2 h without stirring. The precipitate was collected by filtration, then it was washed with water and dried at 45 °C under high vacuum.

General Procedure 5b. Opening of Isatoic Anhydrides; Formation of Allyl Ester:[10] The following reaction was carried out under an argon atmosphere using dry solvents. A mixture of the starting material (1.0 mmol) and allyl alcohol (4.0 mL) was treated portionwise with sodium hydride (0.3 equiv.). The reaction mixture was stirred for 6.5 h at room temperature. The solvent was removed, and the crude product was purified by column chromatography (petroleum ether/EtOAc, 2:1).

General Procedure 6a. Dieckmann Condensation; Methyl Esters:[16] The following reaction was carried out under an argon atmosphere using dry solvents. The starting material (1.0 mmol) was dissolved in Et_2O (2.0 mL) and a solution of sodium methoxide (2.8 M in MeOH; 0.7 mL) was added dropwise. The resulting viscous mixture was heated to 40–45 °C for 2 h. The mixture was cooled to room temperature, then the reaction was quenched with dilute hydrochloric acid (0.5 M). The product was collected by filtration, then it was washed with dilute hydrochloric acid (0.5 M) and water, and dried at 45 °C under high vacuum.

General Procedure 6b. Dieckmann Condensation; Allyl Esters:[10] The following reaction was carried out under an argon atmosphere using dry solvents. A mixture of the starting material (1.0 mmol) and KO^{t}Bu (2.0 equiv.) in Et_2O (13 mL) was heated to 40–45 °C for 2 h. Then about half of the solvent was removed, and the reaction was quenched with dilute hydrochloric acid (1 M). The product was collected by filtration, then it was washed with dilute hydrochloric acid (0.5 M) and water, and dried at 40 °C under high vacuum.

General Procedure 7. Phase-Transfer Glycosylation: The donor (1.0 mmol), TBAHS (1.0 equiv.), and the respective acceptor (1.0–1.5 equiv.) were mixed in CH_2Cl_2 (12.5 mL). K_2CO_3 (1 M aq.; 12.5 mL) was added, then the reaction mixture was stirred at room temperature until TLC indicated complete consumption of the donor. The organic phase was separated, and the solvent was removed. The crude product was purified by column chromatography in the solvent stated.

General Procedure 8a. Decarboxylation of Methyl Esters:[10,18] A solution of the starting material (1.0 mmol) in MeOH (10–20 mL) was treated with a catalytic amount of sodium methoxide. After TLC indicated that deacetylation was complete, the solvent was removed, and sodium hydroxide (0.1 M aq.; 45 mL) was added. The mixture was heated to 40–45 °C and stirred until TLC indicated that the ester hydrolysis was complete. The mixture was freeze-dried, then silver acetate (3 equiv.), potassium carbonate (6–7 equiv.), and acetic anhydride (10 mL) were added. The mixture was heated to 110 °C for 1 h. Then the mixture was cooled to room temperature and diluted with water and CH_2Cl_2. The organic phase was washed twice with water and once with $NaHCO_3$ (dilute aq.). The organic phase was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the crude product was purified by column chromatography in the solvent stated.

General Procedure 8b. Decarboxylation of Allyl Esters:[10,17,18] The starting material (1.0 mmol) was dissolved in THF (15 mL), and morpholine (10 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.) were added. The solution was stirred overnight at room temperature. The solvent was removed, then silver acetate (3 equiv.), potassium carbonate (6–7 equiv.), and acetic anhydride (10 mL) were added. The resulting mixture was heated to 90–105 °C for 20–35 min. Work-up and purification were carried out as for general procedure 8a.

General Procedure 9. Zemplén Deacetylation:[9] A solution of the starting material (1.0 mmol) in MeOH (15–20 mL) was treated with a catalytic amount of sodium methoxide. The solution was stirred overnight. If the product had precipitated during this time it was collected by filtration, otherwise the solution was neutralized with

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Amberlite IR-120 (H^+) resin and concentrated. The product was dried at 40 °C under high vacuum.

Allyl 5-Bromoindoxylate (1b): Prepared according to general procedure 6b. Compound **8b** (5.00 g, 14.1 mmol), Et_2O (180 mL), KO*t*Bu (3.20 g, 28.5 mmol). Yield 80% (3.35 g, 11.3 mmol), slightly yellow solid. m.p. 130 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 11.08 (s, 1 H, H, -OH), 9.61 (s, 1 H, NH), 7.93 (s, 1 H, H_{arom}), 7.36–7.32 (m, 1 H, H_{arom}), 7.28–7.25 (m, 1 H, H_{arom}), 6.07 (dddd, $^3J_{CH=CH2a,CH=CH2a}$ = 17.2, $^3J_{CH=CH2b,CH=CH2b}$ = 10.5, $^3J_{CH2-CH=,CH2-CH}$ = 5.1 Hz, 1 H, -CH$_2$-CH=CH$_2$), 5.49–5.43 (m, 1 H, -CH=CH$_2$a), 5.29–5.25 (m, 1 H, -CH=CH$_2$b), 4.82–4.78 (m, 2 H, -CH$_2$-CH=CH$_2$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 161.0 [C(O)O-], 142.0, 133.3 (C_{quat}), 133.0, 128.2, 122.1 (CH_{arom}), 119.9 (C_{quat}), 117.5 (O-CH$_2$-CH=CH$_2$), 114.5 (O-CH$_2$-CH=CH$_2$), 110.5, 110.3 (C_{quat}), 66.4 (O-CH$_2$-CH=CH$_2$) ppm. $C_{12}H_{10}BrNO_3$ calcd. C 48.67, H 3.40, N 4.73; found C 47.65, H 3.36, N 4.76.

Allyl 5-Bromo-6-chloroindoxylate (1c): Prepared according to general procedure 6b. Compound **8c** (750 mg, 1.93 mmol), Et_2O (25 mL), KO*t*Bu (440 mg, 3.92 mmol). Yield 76% (488 mg, 1.48 mmol), slightly yellow solid. m.p. 185 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.15 (s, 1 H, H, -OH), 9.93 (br. s, 1 H, NH), 8.16 (s, 1 H, H_{arom}), 7.50 (s, 1 H, H_{arom}), 6.04 (dddd, $^3J_{CH=CH2a,CH=CH2a}$ = 17.2, $^3J_{CH=CH2b,CH=CH2b}$ = 10.5, $^3J_{CH2-CH=,CH2-CH}$ = 5.2 Hz, 1 H, -CH$_2$-CH=CH$_2$), 5.44 (dddd~vdq, 1 H, -CH=CH$_2$a), 5.26 (dddd~vdq, 1 H, -CH=CH$_2$a), 4.79 (ddd~vdt, 2 H, -CH$_2$-CH=CH$_2$) ppm. ^{13}C NMR (101 MHz, [D$_6$]-DMSO): δ = 160.6 [C(O)O-], 141.8, 133.7 (C_{quat}), 132.9 (O-CH$_2$-CH=CH$_2$), 129.5 (C_{quat}) 124.6, (CH_{arom}), 117.5 (O-CH$_2$-CH=CH$_2$), 113.6, (CH_{arom}), 110.9, 110.3 (C_{quat}), 64.2 (O-CH$_2$-CH=CH$_2$) ppm. HRMS (ESI): calcd. for $C_{12}H_9BrClNO_3K$ [M + K]$^+$ 369.9071; found 369.8973. $C_{12}H_9BrClNO_3$ calcd. C 43.60, H 2.74, N 4.24; found C 42.92, H 2.73, N 4.33.

Methyl 5-Bromo-4-chloroindoxylate (1d): Prepared according to general procedure 6a. Compound **8d** (2.00 g, 5.94 mmol), Et_2O (10 mL), solution of NaOMe (2.8 M in MeOH; 4.2 mL). Yield 95% (1.71 g, 5.61 mmol), colourless solid. m.p. 210 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.52 (s, 1 H, OH), 8.93 (s, 1 H, NH), 7.48 (d, $^3J_{arom-H,H}$ = 8.9 Hz, 1 H, H_{arom}), 7.20 (d, $^3J_{arom-H,H}$ = 8.9 Hz, 1 H, H_{arom}), 3.86 (s, 3 H, -O-CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 161.7 [C(O)O-CH$_3$], 142.1, 134.5 (C_{quat}), 129.7 (CH_{arom}), 125.2, 116.3 (C_{quat}), 113.0 (CH_{arom}), 111.8, 111.6 (C_{quat}), 51.3 (OCH_3) ppm. HRMS (ESI): calcd. for $C_{10}H_7BrClNO_3Na$ [M + Na]$^+$ 327.9175; found 327.9159.

Methyl 5-Bromoindoxylate (1e): Prepared according to general procedure 6a. Compound **8e** (2.00 g, 6.62 mmol), Et_2O (15 mL), solution of NaOMe (2.8 M in MeOH; 4.6 mL). Yield 81% (1.45 g, 5.37 mmol), colourless solid. m.p. 210 °C (decomp.), ref.[20] m.p. 196 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.07 (s, 1 H, OH), 9.50 (br. s, 1 H, NH), 7.9 (d, $^3J_{arom-H,H}$ = 1.8 Hz, 1 H, H_{arom}), 7.32 (dd, $^3J_{arom-H,H}$ = 8.9, and 1.8 Hz, 1 H, H_{arom}), 7.24 (d, $^3J_{arom-H,H}$ = 8.9 Hz, 1 H, H_{arom}), 3.83 (s, 3 H, -O-CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 161.7 [C(O)O-CH$_3$], 141.7, 132.3 (C_{quat}), 128.1, 122.0 (CH_{arom}), 119.9 (C_{quat}), 114.5 (CH_{arom}), 110.5, 110.4 (C_{quat}), 51.1 (-OCH_3) ppm. $C_{10}H_8BrNO_3$ calcd. C 44.47, H 2.99, N 5.19; found C 44.98, H 3.26, N 5.21.

***N*-(4-Bromo-5-chloro-2-methylphenyl)acetamide (3c):** A cooled (ice-bath) suspension of 5-chloro-2-methylaniline (10.0 g, 54.5 mmol) in AcOH (80 mL) was treated dropwise with bromine (8.50 mL, 166 mmol). After the addition was complete, the ice-bath was removed, and the reaction mixture was stirred for 5 h at room temperature. Then the mixture was poured into ice-water, and the product was collected by filtration, washed with water, and dried at 40 °C under high vacuum. Yield 96% (13.8 g, 52.4 mmol), colourless solid. m.p. 182–183 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.37 (s, 1 H, NH), 7.82 (s, 1 H, H_{arom}), 7.61 (s, 1 H, H_{arom}), 2.20 [s, 3 H, C(O)CH$_3$], 2.08 (s, 3 H, Ph-CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 168.7 [C(O)CH$_3$], 137.2 (C_{quat}), 134.6 (CH_{arom}), 129.7, 131.8 (C_{quat}), 125.1 (CH_{arom}), 116.0 (C_{quat}), 23.4 [C(O)CH$_3$], 17.0 (Ph-CH$_3$) ppm. HRMS (ESI): calcd. for $C_9H_{10}BrClNO$ [M + H]$^+$ 263.9634; found 263.9635.

***N*-Acetyl-5-bromoanthranilic Acid (4b):** Prepared according to general procedure 1. Compound **3b** (7.50 g, 32.9 mmol), water (150 mL), $MgSO_4$ (7.8 g, 65 mmol), $KMnO_4$ solution (saturated aq.; 180 mL). Yield 66% (5.62 g, 21.8 mmol), colourless solid. m.p. 219–221 °C, ref.[21] m.p. 222–223 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.00 (s, 1 H, -NH-Ac), 8.40 (d, $^3J_{arom-H,H}$ = 8.6 Hz, 1 H, H_{arom}), 8.03 (s, 1 H, H_{arom}), 7.74 (d, $^3J_{arom-H,H}$ = 8.6 Hz, 1 H, H_{arom}), 2.13 [s, 3 H, NH-C(O)-CH$_3$] ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 168.5, 168.0 [C(O)CH$_3$, COOH], 139.8 (C_{quat}), 136.2, 132.9, 122.0 (CH_{arom}), 118.8, 113.8 (C_{quat}), 24.8 (CH_3) ppm.

***N*-Acetyl-5-bromo-4-chloroanthranilic Acid (4c):** Prepared according to general procedure 1. Compound **3c** (10.0 g, 38.1 mmol), water (180 mL), $MgSO_4$ (9.0 g, 75 mmol), $KMnO_4$ solution (saturated aq.; 200 mL). Yield 65% (6.49 g, 22.1 mmol), colourless solid. m.p. 232–234 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.09 (s, 1 H, NH-Ac), 8.74 (s, 1 H, H_{arom}), 8.19 (s, 1 H, H_{arom}), 2.16 [s, 3 H, NH-C(O)-CH$_3$] ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 169.5, 168.0 [C(O)CH$_3$, COOH], 141.1, 138.6 (C_{quat}), 135.8 (CH_{arom}), 121.4 (CH_{arom}), 117.7, 114.2 (C_{quat}), 25.4 (CH_3) ppm.

5-Bromoanthranilic Acid (5b): Prepared according to general procedure 2. Compound **4b** (5.00 g, 19.4 mmol), NaOH solution (1 M aq.; 100 mL). Yield 93% (3.90 g, 18.0 mmol), slightly yellow solid. m.p. 219–220 °C, ref.[22] m.p. 220 °C. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 7.75 (d, $^3J_{arom-H,H}$ = 2.5 Hz, 1 H, H_{arom}), 7.34 (dd, $^3J_{arom-H,H}$ = 2.5 and 8.9 Hz, 1 H, H_{arom}), 6.72 (d, $^3J_{arom-H,H}$ = 8.9 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 168.8 [C(O)CH$_3$], 151.0 (C_{quat}), 136.6, 133.3, 119.1 (CH_{arom}), 111.6, 105.5 (C_{quat}) ppm.

5-Bromo-4-chloroanthranilic Acid (5c): Prepared according to general procedure 2. Compound **4c** (6.00 g, 20.5 mmol), NaOH solution (1 M aq.; 100 mL). Yield 94% (4.83 g, 19.3 mmol), colourless solid. m.p. 232–234 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.90 (s, 1 H, H_{arom}), 7.03 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (101 MHz, [D$_6$]-DMSO): δ = 167.7 [C(O)CH$_3$], 151.2, 137.8 (C_{quat}), 135.8, 117.2 (CH_{arom}), 110.4, 104.0 (C_{quat}) ppm.

5-Bromoisatoic Anhydride (6b): Prepared according to general procedure 3. Compound **5b** (2.50 g, 11.6 mmol), MeCN (12.5 mL), pyridine (1.9 mL), triphosgene (1.15 g, 3.87 mmol) in CH_2Cl_2 (7.0 mL). Yield 94% (2.65 g, 10.9 mmol), colourless solid. m.p. 289 °C (decomp.), ref.[23] m.p. 270–275 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.86 (s, 1 H, NH), 7.98 (d, $^3J_{arom-H,H}$ = 2.4 Hz, 1 H, H_{arom}), 7.89 (dd, $^3J_{arom-H,H}$ = 8.8 and 2.4 Hz, 1 H, H_{arom}), 7.09 (d, $^3J_{arom-H,H}$ = 8.8 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 158.9, 146.8, 140.7 (C_{quat}), 139.3, 130.6, 117.7 (CH_{arom}), 114.6, 112.5 (C_{quat}) ppm.

5-Bromo-4-chloroisatoic Anhydride (6c): Prepared according to general procedure 3. Compound **5c** (4.50 g, 18.0 mmol), MeCN (22.5 mL), pyridine (3.5 mL), triphosgene (2.0 g, 6.7 mmol) in CH_2Cl_2 (12.5 mL). Yield 82% (4.08 g, 14.7 mmol), colourless solid. m.p. 280–281 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.93 (s, 1 H, NH), 8.17 (s, 1 H, H_{arom}), 7.30 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 158.1, 146.6, 141.4, 140.9 (C_{quat}), 133.1, 116.7 (CH_{arom}), 114.8, 111.4 (C_{quat}) ppm.

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

5-Bromo-*N*-[(allyloxycarbonyl)methyl]isatoic Anhydride (7b): Prepared according to general procedure 4. Compound **6b** (6.48 g, 26.8 mmol), DMF (60 mL), allyl bromoacetate (3.31 mL, 26.9 mmol), sodium hydride (1.17 g, 29.3 mmol). Yield 99% (9.02 g, 26.5 mmol), colourless solid. m.p. 151–153 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.31 (d, $^3J_{\text{arom-H,H}}$ = 2.0 Hz, 1 H, H$_{\text{arom}}$), 8.02 (dd, $^3J_{\text{arom-H,H}}$ = 9.1 and 2.0 Hz, 1 H, H$_{\text{arom}}$), 7.45 (d, $^3J_{\text{arom-H,H}}$ = 9.1 Hz, 1 H, H$_{\text{arom}}$), 5.93 (dddd~vddd, 1 H, -CH$_2$-CH=CH$_2$), 5.37–5.31 (m, 1 H, -CH$_2$-CH=C*H*$_2$a), 5.27–5.22 (m, 1 H, -CH$_2$-CH=C*H*$_2$b), 4.97 (s, 2 H, N-CH$_2$-), 4.70–4.66 (m, 2 H, -C*H*$_2$-CH=CH$_2$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 167.0, 157.1, 147.3, 140.4 (C$_{\text{quat}}$), 139.5 (CH$_{\text{arom}}$), 131.8 (CH$_2$-*C*H=CH$_2$), 131.2 (CH$_{\text{arom}}$), 118.1 (CH$_2$-CH=*C*H$_2$), 117.2 (CH$_{\text{arom}}$), 115.6, 113.2 (C$_{\text{quat}}$), 65.6 (*C*H$_2$-CH=CH$_2$), 45.8 (N-CH$_2$-) ppm. HRMS (ESI): calcd. for C$_{13}$H$_{11}$BrNO$_5$ [M + H]$^+$ 339.9821; found 339.9813.

5-Bromo-4-chloro-*N*-[(allyloxycarbonyl)methyl]isatoic Anhydride (7c): Prepared according to general procedure 4. Compound **6c** (1.00 g, 3.62 mmol), DMF (15 mL), allyl bromoacetate (450 µL, 3.66 mmol), sodium hydride (160 mg, 4.00 mmol). Yield 84% (1.13 g, 3.02 mmol), slightly yellow solid. m.p. 209–211 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.29 (s, 1 H, H$_{\text{arom}}$), 7.93 (s, 1 H, H$_{\text{arom}}$), 5.94 (dddd~vddd, 1 H, -CH$_2$-C*H*=CH$_2$), 5.39–5.32 (m, 1 H, -CH$_2$-CH=C*H*$_2$a), 5.28–5.23 (m, 1 H, -CH$_2$-CH=C*H*$_2$b), 4.97 (s, 2 H, N-CH$_2$-), 4.71–4.67 (m, 2 H, -C*H*$_2$-CH=CH$_2$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 167.0, 156.6, 147.3, 142.0, 141.3 (C$_{\text{quat}}$), 133.7 (CH$_{\text{arom}}$), 131.2 (CH$_2$-*C*H=CH$_2$), 118.1 (CH$_2$-CH=*C*H$_2$), 117.0 (CH$_{\text{arom}}$), 116.1, 112.1 (C$_{\text{quat}}$), 65.7 (*C*H$_2$-CH=CH$_2$), 46.1 (N-CH$_2$-) ppm. HRMS (ESI): calcd. for C$_{13}$H$_{10}$BrClNO$_5$ [M + H]$^+$ 375.9410; found 375.9405.

5-Bromo-6-chloro-*N*-[(methoxycarbonyl)methyl]isatoic Anhydride (7d): Prepared according to general procedure 4. Compound **6a** (7.50 g, 27.1 mmol), DMF (100 mL), methyl bromoacetate (3.2 mL, 34 mmol), sodium hydride (1.20 g, 30.0 mmol). Yield 97% (9.18 g, 26.3 mmol), colourless solid. m.p. 219–221 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.16 (d, $^3J_{\text{arom-H,H}}$ = 9.1 Hz, 1 H, H$_{\text{arom}}$), 7.37 (d, $^3J_{\text{arom-H,H}}$ = 9.1 Hz, 1 H, H$_{\text{arom}}$), 4.92 [s, 2 H, N-C*H*$_2$-C(O)CH$_3$], 3.73 (s, 3 H, O-CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 167.6 [CH2-C(O)-CH$_3$], 154.1, 147.1, 142.7, 135.0, 119.0, 111.4 (C$_{\text{quat}}$), 139.8, 115.4 (CH$_{\text{arom}}$), 52.5 (O-CH$_3$), 46.2 [*C*H$_2$-C(O)-CH$_3$] ppm. HRMS (ESI): calcd. for C$_{11}$H$_7$BrClNO$_5$Na [M + Na]$^+$ 371.9073; found 371.9079.

5-Bromo-*N*-[(methoxycarbonyl)methyl]isatoic Anhydride (7e): Prepared according to general procedure 4. Compound **6b** (2.53 g, 10.4 mmol), DMF (30 mL), methyl bromoacetate (1.13 mL, 12.0 mmol), sodium hydride (460 mg, 11.5 mmol). Yield 98% (3.21 g, 10.2 mmol), colourless solid. m.p. 199–200 °C, ref.[24] 205–209 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.12 (d, $^3J_{\text{arom-H,H}}$ = 2.4 Hz, 1 H, H$_{\text{arom}}$), 8.01 (dd, $^3J_{\text{arom-H,H}}$ = 8.8 and 2.4 Hz, 1 H, H$_{\text{arom}}$), 7.43 (d, $^3J_{\text{arom-H,H}}$ = 8.8 Hz, 1 H, H$_{\text{arom}}$), 4.92 (s, 2 H, N-CH$_2$-), 3.73 (s, 3 H, O-CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 167.9 [-CH$_2$-*C*(O)-CH$_3$], 157.2, 147.4, 140.5 (C$_{\text{quat}}$), 139.6, 131.3, 117.3 (CH$_{\text{arom}}$), 115.7, 113.4 (C$_{\text{quat}}$), 52.6 (O-CH$_3$), 45.9 [-*C*H$_2$-C(O)-CH$_3$] ppm. HRMS (ESI): calcd. for C$_{11}$H$_8$BrNO$_5$Na [M + Na]$^+$ 337.9463; found 337.9489.

Allyl 5-Bromo-*N*-[(allyloxycarbonyl)methyl]anthranilate (8b): Prepared according to general procedure 5b. Compound **7b** (9.00 g, 26.5 mmol), allyl alcohol (100 mL), sodium hydride (350 mg, 8.75 mmol). Yield 75% (7.02 g, 19.8 mmol), slightly yellow solid. m.p. 69–70 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.21 (br. s, 1 H, NH), 8.07 (d, $^3J_{\text{arom-H,H}}$ = 8.9 Hz, 1 H, H$_{\text{arom}}$), 7.42 (dd, $^3J_{\text{arom-H,H}}$ = 8.9 and 2.5 Hz, 1 H, H$_{\text{arom}}$), 6.43 (d, $^3J_{\text{arom-H,H}}$ = 2.5 Hz, 1 H, H$_{\text{arom}}$), 6.03 (dddd, $^3J_{\text{CH=}CH\text{2a,}CH\text{=CH2a}}$ = 17.2, $^3J_{\text{CH=}CH\text{2b,}CH\text{=CH2b}}$ = 11.5, $^3J_{CH\text{2-CH=,CH2-}CH}$ = 5.7 Hz, 1 H, -CH$_2$-C*H*=CH$_2$), 5.92 (dddd, $^3J_{\text{CH=}CH\text{2a,}CH\text{=CH2a}}$ = 17.2, $^3J_{\text{CH=}CH\text{2b,}CH\text{=CH2b}}$ = 11.5, $^3J_{CH\text{2-CH=,CH2-}CH}$ = 5.7 Hz, 1 H, -CH$_2$-C*H*=CH$_2$), 5.40 (dddd~vdq, 1 H, -CH=C*H*$_2$a), 5.39–5.24 (m, 3 H, -CH=C*H*$_2$a′, -CH=C*H*$_2$b, -CH=C*H*$_2$b′), 4.79 (ddd~vdt, 2 H, -C*H*$_2$-CH=CH$_2$), 4.69 (ddd~vdt, 2 H, -C*H*$_2$-CH=CH$_2$), 4.01 (d, $^3J_{\text{NH,NH-}CH2}$ = 4.5 Hz, 2 H, NH-C*H*$_2$) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 169.7, 166.9 [C(O)O-], 148.8 (C$_{\text{quat}}$), 137.2, 133.9 (CH$_{\text{arom}}$), 132.1, 131.5 (O-CH$_2$-*C*H=CH$_2$), 119.1, 118.5 (O-CH$_2$-CH=*C*H$_2$), 113.0 (*C*H$_{\text{arom}}$), 112.3, 107.1 (C$_{\text{quat}}$), 66.0, 65.4 (O-*C*H$_2$-CH=CH$_2$), 44.9 (NH-CH$_2$-) ppm. HRMS (ESI): calcd. for C$_{15}$H$_{17}$BrNO$_4$ [M + H]$^+$ 354.0341; found 354.0339.

Allyl 5-Bromo-4-chloro-*N*-[(allyloxycarbonyl)methyl]anthranilate (8c): Prepared according to general procedure 5b. Compound **7c** (1.00 g, 3.6 mmol), allyl alcohol (10 mL), sodium hydride (35 mg, 8.7 mmol). Yield 84% (870 mg, 2.23 mmol), slightly red solid. m.p. 80–82 °C, R_f = 0.53 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.09 (t, $^3J_{\text{NH, CH2}}$ = 5.4 Hz, 1 H, NH), 8.04 (s, 1 H, H$_{\text{arom}}$), 7.42 (s, 1 H, H$_{\text{arom}}$), 6.05 (dddd, $^3J_{\text{CH=}CH\text{2a,}CH\text{=CH2a}}$ = 17.2, $^3J_{\text{CH=}CH\text{2b,}CH\text{=CH2b}}$ = 11.5, $^3J_{CH\text{2-CH=,CH2-}CH}$ = 5.7 Hz, 1 H, -CH$_2$-C*H*=CH$_2$), 5.93 (dddd, $^3J_{\text{CH=}CH\text{2a,}CH\text{=CH2a}}$ = 17.2, $^3J_{\text{CH=}CH\text{2b,}CH\text{=CH2b}}$ = 11.5, $^3J_{CH\text{2-CH=,CH2-}CH}$ = 5.7 Hz, 1 H, -CH$_2$-C*H*=CH$_2$), 5.42–5.20 (m, 4 H, 2 -CH=C*H*$_2$), 4.78 (ddd~vdt, 2 H, -C*H*$_2$-CH=CH$_2$), 4.65 (ddd~vdt, 2 H, -C*H*$_2$-CH=CH$_2$), 4.24 (d, $^3J_{\text{NH,NH-}CH2}$ = 5.4 Hz, 2 H, NH-C*H*$_2$) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 169.7, 165.4 [C(O)O-], 149.7, 139.9 (C$_{\text{quat}}$), 135.0, (CH$_{\text{arom}}$), 132.4, 132.3 (O-CH$_2$-*C*H=CH$_2$), 118.4, 117.9 (O-CH$_2$-CH=*C*H$_2$), 113.8 (*C*H$_{\text{arom}}$), 110.2, 105.2 (C$_{\text{quat}}$), 65.2, 65.1 (O-*C*H$_2$-CH=CH$_2$), 44.1 (NH-CH$_2$-) ppm. HRMS (ESI): calcd. for C$_{15}$H$_{17}$BrClNO$_4$ [M + H]$^+$ 389.9931; found 389.9930.

Methyl 5-Bromo-6-chloro-*N*-[(methoxycarbonyl)methyl]anthranilate (8d): Prepared according to general procedure 5a. Compound **7d** (9.10 g, 26.1 mmol), MeOH (100 mL), sodium methoxide (910 mg, 16.8 mmol). Yield 93% (8.18 g, 24.3 mmol), colourless solid. m.p. 73–75 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.54 (d, $^3J_{\text{arom-H,H}}$ = 9.1 Hz, 1 H, H$_{\text{arom}}$), 6.50 (d, $^3J_{\text{arom-H,H}}$ = 9.1 Hz, 1 H, H$_{\text{arom}}$), 6.18 (t, $^3J_{\text{NH, CH2}}$ = 6.1 Hz, 1 H, NH), 3.99 (d, $^3J_{\text{NH, CH2}}$ = 6.1 Hz, 2 H, NH-C*H*$_2$-), 3.87 [s, 3 H, C$_{\text{arom}}$-C(O)OCH$_3$], 3.65 (s, 3 H, -CH$_2$-COOC*H*$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.7 [CH$_2$-*C*(O)O-CH$_3$], 165.7 [C$_{\text{arom}}$-*C*(O)O-CH$_3$], 145.6, 130.2, 119.0, 107.2 (C$_{\text{quat}}$), 134.8, 111.9 (CH$_{\text{arom}}$), 52.7, 51.7 [C(O)O*C*H$_3$], 44.2 (NH-CH$_2$-) ppm. HRMS (ESI): calcd. for C$_{11}$H$_{11}$BrClNO$_4$Na [M + Na]$^+$ 357.9458; found 357.9452.

Methyl 5-Bromo-*N*-[(methoxycarbonyl)methyl]anthranilate (8e): Prepared according to general procedure 5a. Compound **7e** (3.10 g, 9.87 mmol), MeOH (40 mL), sodium methoxide (338 mg, 6.25 mmol). Yield 88% (2.62 g, 8.67 mmol), colourless solid. m.p. 80–81 °C, ref.[20] 88–91 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.00 (t, $^3J_{\text{NH, CH2}}$ = 5.6 Hz, 1 H, NH), 7.88 (d, $^3J_{\text{arom-H,H}}$ = 2.5 Hz, 1 H, H$_{\text{arom}}$), 7.52 (dd, $^3J_{\text{arom-H,H}}$ = 2.5, $^3J_{\text{arom-H,H}}$ = 9.1 Hz, 1 H, H$_{\text{arom}}$), 6.65 (d, $^3J_{\text{arom-H,H}}$ = 9.1 Hz, 1 H, H$_{\text{arom}}$), 4.15 (d, $^3J_{\text{NH, CH2}}$ = 5.6 Hz, 2 H, NH-C*H*$_2$-), 3.82 [s, 3 H, C$_{\text{arom}}$-C(O)-OCH$_3$], 3.68 (s, 3 H, -CH$_2$-COOC*H*$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.6 [CH$_2$-*C*(O)O-CH$_3$], 166.7 [C$_{\text{arom}}$-*C*(O)O-CH$_3$], 148.8 (C$_{\text{quat}}$), 137.0, 132.8, 114.4 (CH$_{\text{arom}}$), 111.3, 105.6 (C$_{\text{quat}}$), 51.9, 51.9 [C(O)O*C*H$_3$], 44.0 (NH-CH$_2$-) ppm. HRMS (ESI): calcd. for C$_{11}$H$_{14}$BrNO$_4$ [M + H]$^+$ 302.0028; found 302.0020.

(Methyl 5-Bromo-4-chloroindox-3-ylate) 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (12a): Prepared according to general procedure 7. Compound **1d** (500 mg, 1.64 mmol), compound **9** (710 mg,

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

1.73 mmol), TBAHS (360 mg, 1.06 mmol), CH_2Cl_2 (25 mL), K_2CO_3 solution (1 M aq.; 25 mL). Yield 83% (865 mg, 1.34 mmol), yellow syrup. R_f = 0.19 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{29}$ = –8.6 (c = 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, 1 H, NH), 7.49 (d, $^3J_{arom\text{-}H,H}$ = 8.9 Hz, 1 H, CH_{arom}), 7.12 (d, $^3J_{arom\text{-}H,H}$ = 8.9 Hz, 1 H, CH_{arom}), 5.40 (dd, $^3J_{1,2}$ = 7.8, $^3J_{2,3}$ = 9.4 Hz, 1 H, 2-H), 5.33 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 5.30 (dd~vt, 1 H, 3-H), 5.20 (dd~vt, 1 H, 4-H), 4.16 (dd, $^3J_{5,6a}$ = 4.6, $^3J_{6a,6b}$ = 12.3 Hz, 1 H, 6a-H), 3.98 (dd, $^3J_{5,6b}$ = 2.6, $^3J_{6a,6b}$ = 12.3 Hz, 1 H, 6b-H), 3.96 (s, 3 H, -OCH_3), 3.65–3.59 (m, 1 H, 5-H), 2.09, 2.04, 2.02, 1.97 [4 s, each 3 H, C(O)CH_3] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 170.3, 169.3 [C(O)CH_3], 161.0 [C(O)O-], 133.3 (C_{quat}), 130.5 (CH_{arom}), 126.6, 120.3, 118.5, 115.4 (C_{quat}), 111.7 (CH_{arom}), 101.4 (C-1), 73.0 (C-3), 71.9 (C-2), 71.7 (C-5), 68.5 (C-4), 61.5 (C-6), 52.1 (-OCH_3), 20.7, 20.6, 20.6, 20.5 [C(O)CH_3] ppm. HRMS (ESI): calcd. for $C_{24}H_{25}BrClNO_{12}Na$ [M + Na]$^+$ 656.0146; found 656.00153.

(Methyl 5-Bromo-4-chloroindox-3-ylate) (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (12b): Prepared according to general procedure 7. Compound **1d** (30 mg, 98 μmol), compound **10** (69 mg, 98 μmol), TBAHS (33 mg, 97 μmol), CH_2Cl_2 (2.5 mL), K_2CO_3 solution (1 M aq.; 2.5 mL). Yield 73% (66 mg, 71 μmol), colourless solid. R_f = 0.12 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{25}$ = +20.6 (c = 0.5, $CHCl_3$). m.p. 81–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (s, 1 H, NH), 7.48 (d, $^3J_{arom\text{-}H,H}$ = 8.6 Hz, 1 H, H_{arom}), 7.10 (d, $^3J_{arom\text{-}H,H}$ = 8.6 Hz, 1 H, H_{arom}), 5.37–5.34 (m, 1 H, 4′-H), 5.33–5.28 (m, 3 H, 1-H, 2-H, 3-H), 5.10 (dd, $^3J_{1',2'}$ = 7.8, $^3J_{2',3'}$ = 10.1 Hz, 1 H, 2′-H), 4.97 (dd, $^3J_{2',3'}$ = 10.1, $^3J_{3',4'}$ = 3.5 Hz, 1 H, 3′-H), 4.52 (d, $^3J_{1',2'}$ = 7.8 Hz, 1 H, 1′-H), 4.33 (dd, $^3J_{5,6a}$ = 2.5, $^3J_{6a,6b}$ = 12.1 Hz, 1 H, 6a-H), 4.15–4.08 (m, 2 H, 6′a-H, 6′b-H), 4.01 (dd, $^3J_{5,6b}$ = 4.8, $^3J_{6a,6b}$ = 12.1 Hz, 1 H, 6b-H), 3.97 (dd, $^3J_{3,4}$ = 4.0, $^3J_{4,5}$ = 9.8 Hz, 1 H, 4-H), 3.95 (s, 3 H, OCH_3), 3.89 (ddd~vt, 1 H, 5′-H), 3.53 (ddd, $^3J_{4,5}$ = 9.8, $^3J_{5,6a}$ = 2.5, $^3J_{5,6b}$ = 4.8 Hz, 1 H, 5-H), 2.15, 2.09, 2.08, 2.06, 1.99, 1.98, 1.95 [7 s, each 3 H, C(O)CH_3] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 170.1, 170.0, 169.8, 169.7 [C(O)-CH_3], 133.3 (C_{quat}), 130.5, 111.7 (CH_{arom}), 101.4 (C-1), 101.1 (C-1′), 76.2 (C-4), 73.1, 72.6, 72.3 (C-2, C-3, C-5), 70.9 (C-3′), 70.7 (C-5′), 69.1 (C-2′), 66.6 (C-4′), 61.1 (C-6), 60.8 (C-6′), 52.1 (OCH_3), 20.8, 20.8, 20.7, 20.6, 20.6, 20.5 [C(O)CH_3] ppm. HRMS (ESI): calcd. for $C_{36}H_{41}BrClNO_{20}Na$ [M + Na]$^+$ 944.0992; found 944.1000.

(Methyl 5-Bromo-4-chloroindox-3-ylate) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (12c): Prepared according to general procedure 7. Compound **1d** (370 mg, 1.21 mmol), compound **11** (520 mg, 1.26 mmol), TBAHS (410 mg, 121 mmol), CH_2Cl_2 (10 mL), K_2CO_3 solution (1 M aq.; 10 mL). Yield 86% (660 mg, 1.02 mmol), slightly yellow solid. R_f = 0.29 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{25}$ = –28.2 (c = 0.5, $CHCl_3$). m.p. 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (s, 1 H, NH), 7.49 (d, $^3J_{arom\text{-}H,H}$ = 8.6 Hz, 1 H, CH_{arom}), 7.12 (d, $^3J_{arom\text{-}H,H}$ = 8.6 Hz, 1 H, CH_{arom}), 5.58 (dd, $^3J_{1,2}$ = 7.8, $^3J_{2,3}$ = 10.3 Hz, 1 H, 2-H), 5.42–5.39 (m, 1 H, 4-H), 5.32 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 5.13 (dd, $^3J_{2,3}$ = 10.3, $^3J_{3,4}$ = 3.3 Hz, 1 H, 3-H), 4.08–3.98 (m, 2 H, 6a-H, 6b-H), 3.97 (s, 3 H, -OCH_3), 3.86–3.81 (m, 1 H, 5-H), 2.20, 2.11, 2.02, 1.89 [4 s, each 3 H, C(O)CH_3] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 170.2, 170.2, 169.5 [C(O)CH_3], 161.0 [C(O)O-], 133.3, 126.7, 120.4, 118.4, 115.4 (C_{quat}), 130.5 (CH_{arom}), 111.6 (CH_{arom}), 101.8 (C-1), 71.0 (C-3), 70.7 (C-5), 69.4 (C-2), 66.9 (C-4), 60.7 (C-6), 52.0 (-OCH_3), 20.9, 20.7, 20.6, 20.4 [C(O)CH_3] ppm. HRMS (ESI): calcd. for $C_{24}H_{25}BrClNO_{12}Na$ [M + Na]$^+$ 658.0126; found 658.0121.

(Methyl 5-Bromoindox-3-ylate) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (12d): Prepared according to general procedure 7. Compound **1e** (327 mg, 1.21 mmol), compound **11** (520 mg, 1.26 mmol), TBAHS (410 mg, 121 mmol), CH_2Cl_2 (10 mL), K_2CO_3 solution (1 M aq.; 10 mL). Yield 82% (597 mg, 0.997 mmol), slightly yellow solid. R_f = 0.33 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{25}$ = 5.6 (c = 0.5, $CHCl_3$). m.p. 94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (br. s, 1 H, NH), 7.95 (d, $^3J_{arom\text{-}H,H}$ = 2.0 Hz, 1 H, H_{arom}), 7.39 (dd, $^3J_{arom\text{-}H,H}$ = 2.0, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, H_{arom}), 7.20 (d, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, H_{arom}), 5.57 (dd, $^3J_{1,2}$ = 7.9, $^3J_{2,3}$ = 10.5 Hz, 1 H, 2-H), 5.44 (dd, $^3J_{3,4}$ = 3.5, $^3J_{4,5}$ = 1.0 Hz, 1 H, 4-H), 5.11 (d, $^3J_{1,2}$ = 7.9 Hz, 1 H, 1-H), 5.11 (dd, $^3J_{2,3}$ = 10.5, $^3J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 4.20–4.10 (m, 2 H, 6a-H, 6b-H), 4.00–3.94 (m, 1 H, 5-H), 3.93 (s, 3 H, OCH_3), 2.23, 2.13, 2.02, 1.94 [4 s, each 3 H, C(O)CH_3] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4, 170.3, 170.1, 169.6 [C(O)CH_3], 160.7 [C(O)OCH_3], 139.7, 132.1, 122.9, 115.9, 113.8 (C_{quat}), 129.3, 123.4, 113.3 (CH_{arom}),102.8 (C-1), 71.1 (C-5), 70.8 (C-3), 68.8 (C-2), 67.0 (C-4), 61.4 (C-6), 51.9 [C(O)-OCH_3], 20.9, 20.7, 20.6 [C(O)CH_3] ppm. HRMS (ESI): calcd. for $C_{24}H_{26}BrNO_{12}Na$ [M + Na]$^+$ 622.0536; found 622.0530.

(Allyl 5-Bromo-4-chloroindox-3-ylate) 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (13a): Prepared according to general procedure 7. Compound **1a** (50 mg, 0.15 mmol), compound **9** (70 mg, 0.17 mmol), TBAHS (51 mg, 0.15 mmol), CH_2Cl_2 (5 mL), K_2CO_3 solution (1 M aq.; 5 mL). Yield 77% (76.0 mg, 0.115 mmol), colourless solid. R_f = 0.30 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{25}$ = –7.5 (c = 0.55, $CHCl_3$). m.p. 82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (s, 1 H, NH), 7.49 (d, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, H_{arom}), 7.12 (d, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, H_{arom}), 6.08 (dddd, $^3J_{CH=CH2a,CH=CH2}$ = 17.1, $^3J_{CH=CH2b,CH=CH2}$ = 11.5, $^3J_{CH2\text{-}CH=,CH2\text{-}CH}$ = 5.6 Hz, 1 H, -CH_2-CH=CH_2), 5.53–5.47 (m, 1 H, -CH=CH_2a), 5.42–5.33 (m, 3 H, 1-H, 2-H, -CH=CH_2b), 5.29 (dd~vt, 1 H, 3-H), 5.16 (dd~vt, 1 H, 4-H), 4.87–4.84 (m, 2 H, O-CH_2-), 4.16 (dd, $^3J_{5,6a}$ = 4.7, $^3J_{6a,6b}$ = 12.2 Hz, 1 H, 6a-H), 3.96 (dd, $^3J_{5,6b}$ = 2.5, $^3J_{6a,6b}$ = 12.2 Hz, 1 H, 6b-H), 3.62 (ddd, $^3J_{4,5}$ = 10.0, $^3J_{5,6a}$ = 4.7, $^3J_{5,6b}$ = 2.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4, 170.3, 169.4 [C(O)CH_3], 160.2 [-C(O)O-], 137.1, 133.4, 126.6, 120.2, 118.6, 115.3 (C_{quat}), 131.6 (-CH=CH_2), 130.5 (CH_{arom}), 119.3 (-CH=CH2),111.7 (CH_{arom}), 101.3 (C-1), 72.9 (C-3), 71.8 (C-2), 71.8 (C-5), 68.5 (C-4), 65.9 (O-CH_2-), 61.5 (C-6), 20.7, 20.6, 20.6, 20.5 [C(O)CH_3] ppm. HRMS (ESI): calcd. for $C_{26}H_{27}BrClNO_{12}Na$ [M + Na]$^+$ 684.0303; found 684.0292.

(Allyl 5-Bromo-4-chloroindox-3-ylate) (2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (13b): Prepared according to general procedure 7. Compound **1a** (470 mg, 1.42 mmol), compound **10** (1.00 g, 1.43 mmol), TBAHS (485 mg, 1.43 mmol), CH_2Cl_2 (15 mL), K_2CO_3 solution (1 M aq.; 15 mL). Yield 74% (1.01 g, 1.06 mmol), colourless solid. R_f = 0.32 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{25}$ = –5.5 (c = 0.75, $CHCl_3$). m.p. 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (s, 1 H, NH), 7.47 (d, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, H_{arom}), 7.09 (d, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, H_{arom}), 6.06 (dddd~vddd, 1 H, O-CH_2-CH=CH_2), 5.50–5.44 (m, 1 H, CH_2-CH=CH_2a), 5.38–5.25 (m, 5 H, 1-H, 2-H, 3-H, 4′-H, CH_2-CH=CH_2b), 5.10 (dd, $^3J_{1',2'}$ = 8.2, $^3J_{2',3'}$ = 10.4 Hz, 1 H, 2′-H), 4.96 (dd, $^3J_{2',3'}$ = 10.4, $^3J_{3'4}$ = 3.5 Hz, 1 H, 3′-H), 4.86–4.83 (m, 2 H, CH_2-CH=CH_2), 4.51 (d, $^3J_{1',2'}$ = 8.2 Hz, 1 H, 1′-H), 4.33 (dd, $^3J_{5,6a}$ = 2.2, $^3J_{6a,6b}$ = 12.0 Hz, 1 H, 6a-H), 4.17–4.07 (m, 2 H, 6′a-H, 6′b-H), 4.00 (dd, $^3J_{5,6b}$ = 4.7, $^3J_{6a,6b}$ = 12.0 Hz, 1 H, 6b-H), 3.93 (dd~vt, 1 H, 4-H), 3.91–3.87 (m, 1 H, 5′-H), 3.53 (ddd, $^3J_{4,5}$ = 9.8, $^3J_{5,6a}$ = 2.2, $^3J_{5,6b}$ = 4.7 Hz, 1 H, 5-H), 2.15, 2.08, 2.07, 2.06, 1.99, 1.97, 1.95 [7 s, each 3 H, C(O)CH_3] ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 170.3, 170.1, 170.1, 169.8, 169.7, 169.0 [C(O)CH_3], 159.9 [C(O)O-Allyl], 137.5, 133.3 (C_{quat}), 131.7 (CH_2-CH=CH_2), 130.5 (CH_{arom}), 126.6, 120.4 (C_{quat}), 119.2 (CH_2-CH=CH_2), 118.0, 115.3 (C_{quat}), 111.7 (CH_{arom}), 101.2 (C-1′),

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

101.0 (C-1), 76.2 (C-4), 73.0, 72.2 (C-2, C-3), 72.6 (C-5), 70.9 (C-3′), 70.7 (C-5′), 69.1 (C-2′), 66.6 (C-4′), 65.9 (*C*H_2-CH=CH_2), 61.1 (C-6), 60.8 (C-6′), 20.8, 20.8, 20.7, 20.6, 20.6, 20.5 [C(O)*C*H_3] ppm. HRMS (ESI): calcd. for $C_{38}H_{43}BrClNO_{20}Na$ [M + Na]$^+$ 967.1148; found 967.1570.

(Allyl 5-Bromo-4-chloroindox-3-ylate) 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside (13c): Prepared according to general procedure 7. Compound **1a** (400 mg, 1.21 mmol), compound **11** (500 mg, 1.21 mmol), TBAHS (410 mg, 1.21 mmol), CH_2Cl_2 (10 mL), K_2CO_3 solution (1 M aq.; 10 mL). Yield 86% (690 mg, 1.04 mmol), colourless solid. R_f = 0.33 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{26}$ = –39.6 (*c* = 0.25, $CHCl_3$). m.p. 115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1 H, NH), 7.50 (d, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, CH_{arom}), 7.13 (d, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, CH_{arom}), 6.10 (dddd, $^3J_{CH=CH2a,CH=CH2}$ = 17.2, $^3J_{CH=CH2b,CH=CH2}$ = 10.5, $^3J_{CH2\text{-}CH=,CH2\text{-}CH}$ = 5.6 Hz, 1 H, -CH_2-C*H*=CH_2), 5.58 (dd, $^3J_{1,2}$ = 7.8, $^3J_{2,3}$ = 10.5 Hz, 1 H, 2-H), 5.52 (dddd~vdd, 1 H, -CH=CH_2a), 5.40 (dd, $^3J_{3,4}$ = 3.5, $^3J_{4,5}$ = 0.8 Hz, 1 H, 4-H), 5.36 (dddd~vdd, 1 H, -CH=CH_2b), 5.32 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 5.12 (dd, $^3J_{2,3}$ = 10.5, $^3J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 4.86–4.81 (m, 1 H, -CH_2-CH=CH_2), 4.04 (dd, $^3J_{5,6a}$ = 6.5, $^3J_{6a,6b}$ = 11.1 Hz, 1 H, 6a-H), 3.97 (dd, $^3J_{5,6b}$ = 7.1, $^3J_{6a,6b}$ = 11.1 Hz, 1 H, 6b-H), 3.85–3.79 (m, 1 H, 5-H), 2.19, 2.11, 2.02, 1.90 [4 s, each 3 H, C(O)CH_3] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5, 170.5, 170.4, 169.8 [*C*(O)-CH_3], 160.6 [C(O)O-], 137.3, 133.7, 126.8, 120.5, 115.6 (C_{quat}), 131.9 (-*C*H=CH_2), 130.7 (CH_{arom}), 119.2 (-CH=*C*H_2) 112.0 (CH_{arom}), 102.0 (C-1), 71.2 (C-3), 71.0 (C-5), 69.5 (C-2), 67.2 (C-4), 66.1 (*C*H_2-CH=CH_2), 60.9 (C-6), 21.1, 20.9, 20.8, 20.7 [C(O)*C*H_3] ppm. HRMS (ESI): calcd. for $C_{26}H_{27}BrClNO_{12}Na$ [M + Na]$^+$ 684.0303; found 684.02911.

(Allyl 5-Bromoindox-3-ylate) 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside (13d): Prepared according to general procedure 7. Compound **1b** (360 mg, 1.21 mmol), compound **11** (520 mg, 1.26 mmol), TBAHS (410 mg, 1.21 mmol), CH_2Cl_2 (10 mL), K_2CO_3 solution (1 M aq.; 10 mL). Yield 80% (605 mg, 0.966 mmol), colourless solid. R_f = 0.53 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{25}$ = –2.3 (*c* = 0.5, $CHCl_3$). m.p. 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (br. s, 1 H, NH), 7.94 (d, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, H_{arom}), 7.39 (dd, $^3J_{arom\text{-}H,H}$ = 8.8, $^3J_{arom\text{-}H,H}$ = 1.9 Hz, 1 H, H_{arom}), 7.20 (d, $^3J_{arom\text{-}H,H}$ = 1.9 Hz, 1 H, H_{arom}), 6.10–5.98 (m, CH_2-C*H*=CH_2), 5.56 (dd, $^3J_{1,2}$ = 7.9, $^3J_{2,3}$ = 10.5 Hz, 1 H, 2-H), 5.47–5.40 (m, 2 H, 4-H, CH_2-CH=CH_2a), 5.32 (ddd~vdd, 1 H, CH_2-CH=CH_2b), 5.13 (d, $^3J_{1,2}$ = 7.9 Hz, 1 H, 1-H), 5.11 (dd, $^3J_{2,3}$ = 10.5, $^3J_{3,4}$ = 3.4 Hz,1 H, 3-H), 4.86–4.82 (m, 2 H, -O-CH_2-CH=CH_2), 4.20–4.07 (m, 2 H, 6a-H, 6b-H), 3.97–3.90 (m, 1 H, 5-H), 2.23, 2.14, 2.02, 1.93 [4 s, each 3 H, C(O)CH_3] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 170.1, 169.7 [C(O)CH_3], 132.0 (C_{quat}), 131.8 (CH2-*C*H=CH_2), 129.4 (CH_{arom}), 123.3 (CH_{arom}), 123.1 (C_{quat}), 119.0 (CH_2-CH=*C*H_2), 116.1 (C_{quat}), 113.8 (C_{quat}), 113.3 (CH_{arom}), 102.8 (C-1), 71.0 (C-5), 70.9 (C-3), 68.8 (C-2), 67.0 (C-4), 65.6 (*C*H_2-CH=CH_2), 61.3 (C-6), 20.9, 20.7, 20.6 [C(O)*C*H_3] ppm. HRMS (ESI): calcd. for $C_{26}H_{28}BrNO_{12}Na$ [M + Na]$^+$ 648.0693; found 648.0688.

(Allyl 5-Bromo-6-chloroindox-3-ylate) 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside (13e): Prepared according to general procedure 7. Compound **1c** (110 mg, 0.333 mmol), compound **11** (150 mg, 0.363 mmol), TBAHS (113 mg, 0.333 mmol), CH_2Cl_2 (5 mL), K_2CO_3 solution (1 M aq.; 5 mL). Yield 70% (154 mg, 0.233 mmol), slightly yellow solid. R_f = 0.40 (hexane/EtOAc, 1:1). $[\alpha]_D^{29}$ = 2.8 (*c* = 0.35, $CHCl_3$). m.p. 89–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (br. s, 1 H, NH), 8.08 (s, 1 H, H_{arom}), 7.46 (s, 1 H, H_{arom}), 6.09–5.99 (m, CH_2-C*H*=CH_2), 5.55 (dd, $^3J_{1,2}$ = 7.9, $^3J_{2,3}$ = 10.7 Hz, 1 H, 2-H), 5.47–5.40 (m, 2 H, 4-H, CH_2-CH=CH_2a), 5.35–5.31 (ddd~vdd, 1 H, CH_2-CH=CH_2b), 5.11 (d, $^3J_{1,2}$ = 7.9 Hz, 1 H, 1-H), 5.11 (dd, $^3J_{2,3}$ = 10.7, $^3J_{3,4}$ = 3.3 Hz,1 H, 3-H), 4.86–4.82 (m, 2 H, -O-CH_2-CH=CH_2), 4.18–4.13 (m, 2 H, 6a-H, 6b-H), 3.95–3.90 (m, 1 H, 5-H), 2.23, 2.14, 2.02, 1.92 [4 s, each 3 H, C(O)CH_3] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 131.8 (CH2-*C*H=CH_2), 125.5 (CH_{arom}), 119.0 (CH_2-CH=*C*H_2), 113.9 (CH_{arom}), 102.9 (C-1), 71.1 (C-5), 70.8 (C-3), 68.7 (C-2), 66.9 (C-4), 65.7 (*C*H_2-CH=CH_2), 61.2 (C-6), 20.9, 20.7, 20.6, 20.6 [C(O)*C*H_3] ppm. HRMS (ESI): calcd. for $C_{26}H_{27}BrClNO_{12}Na$ [M + Na]$^+$ 682.0303; found 682.0306.

(*N*-Acetyl-5-bromo-4-chloroindol-3-yl) 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (14a)

Prepared According to General Procedure 8a: I) Compound **12a** (695 mg, 1.08 mmol), MeOH (20 mL), cat. NaOMe; II) sodium hydroxide solution (0.1 M aq.; 45 mL); III) AgOAc (500 mg, 3.00 mmol), K_2CO_3 (1.03 g, 7.45 mmol), Ac_2O (8.0 mL). Yield 63% (422 mg, 0.682 mmol).

Prepared According to General Procedure 8b: I) Compound **13a** (40 mg, 0.060 mmol), THF (8 mL), morpholine (60 μL), Pd(PPh_3)$_4$ (9.0 mg, 0.79 μmol); II) acetic anhydride (5.0 mL), potassium carbonate (60 mg, 0.43 mmol), silver acetate (30 mg, 0.18 mmol), 35 min, 105 °C. Yield 74% (24 mg, 0.039 mmol).

Colourless solid. R_f = 0.20 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{25}$ = –29.3 (*c* = 0.15, $CHCl_3$). m.p. 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, $^3J_{arom\text{-}H,H}$ = 8.9 Hz, 1 H, CH_{arom}), 7.56 (d, $^3J_{arom\text{-}H,H}$ = 8.9 Hz, 1 H, CH_{arom}), 7.29 (s, 1 H, 1 H, =CH-N), 5.37 (dd, $^3J_{1,2}$ = 7.5, $^3J_{2,3}$ = 7.9 Hz, 1 H, 2-H), 5.30 (dd~vt, 1 H, 3-H), 5.20 (dd~vt, 1 H, 4-H), 5.02 (d, $^3J_{1,2}$ = 7.5 Hz, 1 H, 1-H), 4.40 (dd, $^3J_{5,6a}$ = 4.9, $^3J_{6a,6b}$ = 12.4 Hz, 1 H, 6a-H), 4.18 (dd, $^3J_{5,6b}$ = 2.5, $^3J_{6a,6b}$ = 12.4 Hz, 1 H, 6b-H), 3.85 (ddd, $^3J_{4,5}$ = 10.1, $^3J_{5,6a}$ = 4.9, $^3J_{5,6b}$ = 2.5 Hz, 1 H, 5-H), 2.62 (s, 3 H, NC(O)CH_3), 2.11, 2.09, 2.07, 2.05 (4 s, each 3 H, C(O)CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.4, 169.2 (*C*(O)CH_3), 133.3, 118.5 (C_{quat}), 130.5 (CH_{arom}), 116.1 (CH_{arom}), 112.9 (=CH-N), 100.4 (C-1), 72.5 (C-3), 72.5 (C-5), 70.7 (C-2), 68.2 (C-4), 61.7 (C-6), 23.8 (N*C*(O)CH_3), 20.8, 20.7, 20.6 (C(O)*C*H_3) ppm. HRMS (ESI): calcd. for $C_{24}H_{25}BrClNO_{11}Na$ [M + Na]$^+$ 640.0197; found 640.0204.

(*N*-Acetyl-5-bromo-4-chloroindol-3-yl) (2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (14b)

Prepared According to General Procedure 8a: I) Compound **12b** (118 mg, 0.128 mmol), MeOH (5 mL), cat. NaOMe; II) sodium hydroxide solution (0.1 M aq.; 10 mL); III) AgOAc (60 mg, 0.36 mmol), K_2CO_3 (120 mg, 0.868 mmol), Ac_2O (5.0 mL). Yield 42% (49 mg, 54 μmol).

Prepared According to General Procedure 8b: I) Compound **13b** (700 mg, 0.737 mmol), THF (12.5 mL), morpholine (650 μL, 7.32), Pd(PPh_3)$_4$ 85.0 mg, 7.39 μmol); II) acetic anhydride (10 mL), potassium carbonate (700 mg, 5.06 mmol), silver acetate (365 mg, 2.19 mmol), 15 min, 100 °C. Yield 76% (510 mg, 0.562 mmol).

Colourless solid. R_f = 0.20 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{25}$ = –46.0 (*c* = 0.55, $CHCl_3$). m.p. 98–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (bd, 1 H, H_{arom}), 7.55 (d, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, CH_{arom}), 7.26 (s, 1 H, =CH-N), 5.38–5.38 (m, 1 H, 4′-H), 5.30–5.22 (m, 2 H, 2-H, 3-H), 5.14 (dd, $^3J_{1',2'}$ = 7.8, $^3J_{2',3'}$ = 10.4 Hz, 1 H, 2′-H), 5.01 (d, $^3J_{1,2}$ = 6.8 Hz, 1 H, 1-H), 5.00 (dd, $^3J_{2',3'}$ = 10.4, $^3J_{3',4'}$ = 3.3 Hz, 1 H, 3′-H), 4.80 (dd, $^3J_{5,6a}$ = 1.8, $^3J_{6a,6b}$ = 12.1 Hz, 1 H, 6a-H), 4.60 (d, $^3J_{1',2'}$ = 7.8 Hz, 1 H, 1′-H), 4.18–3.96 (m, 3 H, 6′a-H, 6′b-H, 6b-H), 3.91 (dd~vt, 1 H, 4-H), 3.80–3.74 (m, 1

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

H, 5′-H), 3.71 (ddd, $^3J_{4,5}$ = 10.0, $^3J_{5,6b}$ = 4.2, $^3J_{5,6a}$ = 1.8 Hz, 1 H, 5-H), 2.63 (s, 3 H, N-C(O)*C*H$_3$), 2.16, 2.11, 2.10, 2.07, 1.97 (5 s, each 3 H, -C(O)CH$_3$), 2.04 (s, 6 H, 2 C(O)CH$_3$) ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 171.4, 170.1 (-*C*(O)CH$_3$), 130.5, 112.9 (CH$_{arom}$), 101.2 (C-1′), 99.7 (C-1), 75.7 (C-4), 73.0, 72.9 (C-3, C-5), 71.3 (C-2), 70.9, 70.8 (C-3′, C-5′), 69.2 (C-2′), 66.6 (C-4′), 70.0, 60.8 (C-6, C-6′), 23.8 (N-*C*(O)CH$_3$), 20.8, 20.8, 20.6, 20.5, 20.5 (-*C*(O)CH$_3$) ppm. HRMS (ESI): calcd. for $C_{36}H_{41}BrClNO_{19}Na$ [M + Na]$^+$ 928.1042; found 928.1044.

(*N*-Acetyl-5-bromo-4-chloroindol-3-yl) 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside (14c)

Prepared According to General Procedure 8a: I) Compound **12c** (575 mg, 0.906 mmol), MeOH (10 mL), cat. NaOMe; II) sodium hydroxide solution (0.1 M aq.; 25 mL); III) AgOAc (450 mg, 2.70 mmol), K_2CO_3 (800 mg, 5.79 mmol), Ac_2O (10 mL). Yield 47% (263 mg, 0.425 mmol).

Prepared According to General Procedure 8b: I) Compound **13c** (600 mg, 0.908 mmol), THF (15 mL), morpholine (800 μL, 9.2 mmol), Pd(PPh$_3$)$_4$ (105 mg, 9.09 μmol); II) acetic anhydride (10 mL), potassium carbonate (800 mg, 5.79 mmol), silver acetate (400 mg, 2.40 mmol), 20 min, 90–100 °C. Yield 88% (495 mg, 0.800 mmol).

Colourless solid. R_f = 0.24 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{25}$ = –40 (*c* = 0.5, CHCl$_3$). m.p. 184–186 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.27–8.20 (m, 1 H, CH$_{arom}$), 7.57 (d, $^3J_{aromH,H}$ = 8.8 Hz, 1 H, CH$_{arom}$), 7.26 (s, 1 H, C=C*H*-N), 5.61 (dd, $^3J_{1,2}$ = 7.8, $^3J_{2,3}$ = 10.8 Hz, 1 H, 2-H), 5.50–5.48 (m, 1 H, 4-H), 5.11 (dd, $^3J_{2,3}$ = 10.8, $^3J_{3,4}$ = 3.1 Hz, 1 H, 3-H), 5.00 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 4.27–4.23 (m, 2 H, 6a-H, 6b-H), 4.09–4.05 (m, 1 H, 5-H), 2.60 (s, 3 H, N-C(O)CH$_3$), 2.20, 2.12, 2.07, 2.02 (4 s, each 3 H, C(O)-CH$_3$) ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 170.3, 170.2, 170.1, 169.3 (*C*(O)CH$_3$), 167.9 (N-*C*(O)CH$_3$), 140.0 (C$_{quat}$), 130.6 (CH$_{arom}$), 118.5 (C$_{quat}$), 116.1 (CH$_{arom}$), 111.9 (C=*C*H-N), 101.1 (C-1), 71.7 (C-5), 70.7 (C-3), 68.0 (C-2), 67.1 (C-4), 62.0 (C-6), 23.9 (N-C(O)*C*H$_3$), 20.9, 20.7, 20.7, 20.6 (C(O)*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{36}H_{41}BrClNO_{19}Na$ [M + Na]$^+$ 640.0197; found 640.0203.

(*N*-Acetyl-5-bromoindol-3-yl) 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside (14d)

Prepared According to General Procedure 8a: I) Compound **12d** (510 mg, 0.849 mmol), MeOH (10 mL), cat. NaOMe; II) sodium hydroxide solution (0.1 M aq.; 40 mL); III) AgOAc (400 mg, 2.40 mmol), K_2CO_3 (800 mg, 5.79 mmol), Ac_2O (10 mL). Yield 43% (213 mg, 0.364 mmol).

Prepared According to General Procedure 8b: I) Compound **13d** (550 mg, 0.878 mmol), THF (15 mL), morpholine (800 μL, 9.2 mmol), Pd(PPh$_3$)$_4$ (105 mg, 9.09 μmol); II) acetic anhydride (10 mL), potassium carbonate (800 mg, 5.79 mmol), silver acetate (400 mg, 2.40 mmol), 20 min, 90–100 °C. Yield 75% (355 mg, 0.607 mmol).

Colourless solid. R_f = 0.63 (Et$_2$O). $[\alpha]_D^{25}$ = –20.4 (*c* = 0.5, CHCl$_3$), ref.[4] $[\alpha]_D^{20}$ = –26 (*c* = 1.0, CHCl$_3$). m.p. 179–180 °C, ref.[4] 175–176 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.31–8.21 (m, 1 H, CH$_{arom}$), 7.62 (d, $^3J_{arom\text{-}H,H}$ = 2.0 Hz, 1 H, CH$_{arom}$), 7.47 (dd, $^3J_{arom\text{-}H,H}$ = 2.0, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, CH$_{arom}$), 7.16 (br. s, 1 H, C=CH-N), 5.53 (dd, $^3J_{1,2}$ = 8.0, $^3J_{2,3}$ = 10.3 Hz, 1 H, 2-H), 5.48 (dd, $^3J_{3,4}$ = 3.5, $^3J_{4,5}$ = 1.0 Hz, 1 H, 4-H), 5.12 (dd, $^3J_{2,3}$ = 10.3, $^3J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 4.97 (d, $^3J_{1,2}$ = 8.0 Hz, 1 H, 1-H), 4.25–4.21 (m, 2 H, 6a-H, 6b-H), 4.08–4.04 (m, 1 H, 5-H), 2.59 (s, 3 H, NC(O)CH$_3$), 2.20, 2.15, 2.07, 2.03 (4 s, each 3 H, C(O)CH$_3$) ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 170.3, 170.1, 170.1, 169.3 (*C*(O)-CH$_3$), 140.5 (C$_{quat}$), 129.2 (CH$_{arom}$), 120.5 (CH$_{arom}$), 118.0 (CH$_{arom}$), 117.1 (C$_{quat}$), 110.7 (C=*C*H-N), 101.4 (C-1), 71.6 (C-5), 70.6 (C-3), 68.4 (C-2), 66.9 (C-4), 61.7 (C-6), 20.8, 20.7, 20.6, 20.6 (C(O)*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{24}H_{26}BrNO_{11}Na$ [M + Na]$^+$ 606.0587; found 606.0574.

(*N*-Acetyl-5-bromo-6-chloroindol-3-yl) 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside (14e): Prepared according to general procedure 8b. Compound **13e** (110 mg, 0.166 mmol), THF (5 mL), morpholine (150 μL, 1.72 mmol), Pd(PPh$_3$)$_4$ (20 mg, 1.7 μmol); II) acetic anhydride (6 mL), potassium carbonate (150 mg, 1.08 mmol), silver acetate (75 mg, 0.45 mmol), 20 min, 90–95 °C. Yield 87% (90 mg, 0.145 mmol), colourless amorphous solid. R_f = 0.57 (Et$_2$O). $[\alpha]_D^{29}$ = –11.4 (*c* = 0.28, CHCl$_3$), ref.[3] $[\alpha]_D^{23}$ = –20 (*c* = 1.0, acetone). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.62–8.54 (br. s, 1 H, CH$_{arom}$), 7.73 (s, 1 H, CH$_{arom}$), 7.14 (br. s, 1 H, C=C*H*-N), 5.61 (dd, $^3J_{1,2}$ = 7.8, $^3J_{2,3}$ = 10.4 Hz, 1 H, 2-H), 5.48–5.46 (m, 1 H, 4-H), 5.12 (dd, $^3J_{2,3}$ = 10.4, $^3J_{3,4}$ = 3.4 Hz, 1 H, 3-H), 4.96 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 4.25–4.20 (m, 2 H, 6a-H, 6b-H), 4.08–4.04 (m, 1 H, 5-H), 2.58 (s, 3 H, N-C(O)CH$_3$), 2.20, 2.14, 2.07, 2.03 (4 s, each 3 H, C(O)-CH$_3$) ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 170.1, 170.1, 169.3 (*C*(O)CH$_3$), 140.1 (C$_{quat}$), 122.1, 118.9 (CH$_{arom}$), 117.5 (C$_{quat}$), 110.9 (C=*C*H-N), 101.4 (C-1), 71.7 (C-5), 70.6 (C-3), 68.4 (C-2), 66.9 (C-4), 61.7 (C-6), 20.8, 20.7, 20.6, 20.5 (C(O)*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{24}H_{25}BrClNO_{11}Na$ [M + Na]$^+$ 642.0177; found 642.0173.

(5-Bromo-4-chloroindol-3-yl) β-D-Glucopyranoside (15a): Prepared according to general procedure 9. Compound **14a** (370 mg, 0.598 mmol), MeOH (10 mL), cat. NaOMe. Yield 75% (185 mg, 0.453 mmol), colourless solid. $[\alpha]_D^{29}$ = –85.0 [*c* = 0.5, DMF (50% in H$_2$O)], $[\alpha]_D^{25}$ = –10.0 (*c* = 0.5, DMSO), ref.[3] $[\alpha]_D^{23}$ = –89.0 [*c* = 1.0, DMF (50% in H$_2$O)]. m.p. 230 °C (decomp.), ref.[3] 240–243 (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.08 (br. s, 1 H, NH), 7.31 (d, $^3J_{arom\text{-}H,H}$ = 8.5 Hz, 1 H, H$_{arom}$), 7.25–7.19 (m, 2 H, =C*H*-NH, H$_{arom}$), 5.08 (d, ^3J = 5.2 Hz, 1 H, OH), 5.02 (d, ^3J = 4.7 Hz, 1 H, OH), 4.98 (d, ^3J = 5.3 Hz, 1 H, OH), 4.64 (d, $^3J_{1,2}$ = 7.6 Hz, 1 H, 1-H), 4.58 (dd~vt, 1 H, 6-OH), 3.77–3.69 (m, 1 H, 6a-H), 3.51–3.43 (m, 1 H, 6b-H), 3.31–3.21 (m, 3 H, 2-H, 3-H, 5-H), 3.18–3.11 (m, 1 H, 4-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 136.6, 130.0, 125.3, 117.5, 111.4 (C$_{quat}$), 125.3 (CH$_{arom}$), 112.8 (=CH-NH), 112.1 (CH$_{arom}$), 103.5 (C-1), 69.9 (C-4), 77.1, 76.7 (C-3, C-5), 73.4 (C-2), 60.8 (C-6) ppm.

(5-Bromo-4-chloroindol-3-yl) (β-D-Galactopyranosyl)-(1→4)-β-D-glucopyranoside (15b): Prepared according to general procedure 9. Compound **14b** (396 mg, 0.436 mmol), MeOH (10 mL), cat. NaOMe. Yield 75% (186 mg, 0.326 mmol), colourless solid. $[\alpha]_D^{25}$ = –37.3 (*c* = 0.6, DMSO). m.p. 188 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.10 (s, 1 H, NH), 7.31 (d, $^3J_{arom\text{-}H,H}$ = 8.6 Hz, 1 H, H$_{arom}$), 7.26–7.18 (m, 2 H, H$_{arom}$, =CH-N), 5.25 (br. s, 1 H, OH), 5.08 (br. s, 1 H, OH), 4.76 (br. s, 2 H, OH), 4.73 (d, $^3J_{1,2}$ = 7.8 Hz,1 H, 1-H), 4.65 (br. s, 2 H, O*H*), 4.52 (br. s, 1 H, O*H*), 4.24 (d, $^3J_{1',2'}$ = 6.8 Hz, 1 H, 1′-H), 3.85–3.30 (m, 12 H, 2-H, 2′-H, 3-H, 3′-H, 4-H, 4′-H, 5-H, 5′-H, 6a-H, 6b-H, 6′a-H, 6′b-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 136.4, 133.0 (C$_{quat}$), 125.3 (CH$_{arom}$), 123.0, 117.5 (C$_{quat}$), 113.0 (=CH-N), 112.1 (CH$_{arom}$), 111.5 (C$_{quat}$), 103.7 (C-1′), 103.1 (C-1), 80.4 (C-4), 75.4, 75.0, 75.0, 73.2, 73.0, 70.4 (C-2, C-2′, C-3, C-3′, C-5, C-5′), 68.1 (C-4′), 60.3, 60.3 (C-6, C-6′) ppm. HRMS (ESI): calcd. for $C_{14}H_{15}BrClNO_6Na$ [M + Na]$^+$ 594.0177; found 594.0164. calcd. C 42.09, H 4.41, N 2.45; found C 40.32, H 4.39, N 2.39.

(5-Bromo-4-chloroindol-3-yl) β-D-Galactopyranoside (15c): Prepared according to general procedure 9. Compound **14c** (295 mg,

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

0.477 mmol), MeOH (6 mL), cat. NaOMe. Yield 87% (170 mg, 0.416 mmol), colourless solid. $[\alpha]_D^{29}$ = –60 (*c* = 0.25, 50%DMF), ref.[3] $[\alpha]_D^{24}$ = –69 [*c* = 1.0, DMF (50% in H_2O)]. m.p. 177 °C (decomp.), ref.[3] 237–239 °C (decomp.). ^{1}H NMR (400 MHz, [D_6]-DMSO): δ = 11.05 (br. s, 1 H, NH), 7.30 (d, $^3J_{arom\text{-}H,H}$ = 8.6 Hz, 1 H, H_{arom}), 7.21 (d, $^3J_{arom\text{-}H,H}$ = 8.6 Hz, 1 H, H_{arom}), 7.18 (d, $^3J_{NH,=CH\text{-}N}$ = 1.8 Hz, 1 H, C=C*H*-NH), 4.90 (d, $^3J_{2,OH}$ = 5.6 Hz, 1 H, 2-OH), 4.79 (d, $^3J_{3,OH}$ = 5.8 Hz, 1 H, 3-OH), 4.64 (dd~vt, 1 H, 6-OH), 4.62 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 4.48 (d, $^3J_{4,OH}$ = 4.6 Hz, 1 H, 4-OH), 3.71–3.67 (m, 1 H, 4-H), 3.62 (ddd, $^3J_{1,1}$ = 7.8, $^3J_{2,OH}$ = 5.6, $^3J_{2,3}$ = 10.1 Hz, 1 H, 2-H), 3.58–3.48 (m, 3 H, 5-H, 6a-H, 6b-H), 3.38 (dd, $^3J_{2,3}$ = 10.1, $^3J_{3,4}$ = 3.2 Hz, 1 H, 3-H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 136.6, 133.0, 123.0, 117.5, 111.4 (C_{quat}), 125.3 (CH_{arom}), 112.6 (=CH-N), 112.1 (CH_{arom}), 104.0 (C-1), 75.6 (C-5), 73.4 (C-3), 70.3 (C-2), 68.1 (C-4), 60.4 (C-6) ppm. HRMS (ESI): calcd. for $C_{14}H_{15}BrClNO_6Na$ [M + Na]$^+$ 429.9669; found 429.9660.

(5-Bromoindol-3-yl) β-D-Galactopyranoside (15d): Prepared according to general procedure 9. Compound **14d** (250 mg, 0.428 mmol), MeOH (6 mL), cat. NaOMe. Yield 80% (128 mg, 0.342 mmol), colourless solid. $[\alpha]_D^{23}$ = –30.3 (*c* = 0.3, DMSO), ref.[4] $[\alpha]_D^{19}$ = –70 (*c* = 0.4, EtOH). m.p. 189 °C (decomp.), ref.[4] 195 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 10.77 (br. s, 1 H, NH), 7.77 (d, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, H_{arom}), 7.27 (d, $^3J_{arom\text{-}H,H}$ = 1.8 Hz, 1 H, H_{arom}), 7.16 (dd, $^3J_{arom\text{-}H,H}$ = 1.8, $^3J_{arom\text{-}H,H}$ = 8.8 Hz, 1 H, H_{arom}), 7.13 (d, $^3J_{NH,=CH\text{-}N}$ = 2.5 Hz, 1 H, C=C*H*-NH), 5.23 (d, $^3J_{2,OH}$ = 4.8 Hz, 1 H, 2-OH), 4.80 (d, $^3J_{3,OH}$ = 5.8 Hz, 1 H, 3-OH), 4.62 (dd~vt, 1 H, 6-OH), 4.49 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 4.46 (d, $^3J_{4,OH}$ = 4.5 Hz, 1 H, 4-OH), 3.69–3.66 (m, 1 H, 4-H), 3.62–3.52 (m, 3 H, 2-H, 6a-H, 6b-H), 3.48–3.43 (m, 1 H, 5-H), 3.40–3.34 (m, 1 H, 3-H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 136.4, 131.7 (C_{quat}), 123.7 (CH_{arom}), 121.4 (C_{quat}), 119.7 (CH_{arom}), 113.5 (CH_{arom}), 113.2 (=CH-N), 110.6 (C_{quat}), 105.0 (C-1), 75.5 (C-5), 73.1 (C-3), 70.4 (C-2), 68.1 (C-4), 60.4 (C-6) ppm. HRMS (ESI): calcd. for $C_{14}H_{16}BrNO_6Na$ [M + Na]$^+$ 396.0059; found 396.0046. $C_{14}H_{16}BrNO_6$ calcd. C 44.94, H 4.31, N 3.74; found C 44.87, H 4.33, N 3.90.

(5-Bromo-6-chloroindol-3-yl) β-D-Galactopyranoside (15e): Prepared according to general procedure 9. Compound **14e** (67 mg, 0.108 mmol), MeOH (5 mL), cat. NaOMe. Yield 99% (48.0 mg, 0.106 mmol), amorphous solid. $[\alpha]_D^{29}$ = –34 (*c* = 0.125, MeOH), ref.[3] $[\alpha]_D^{24}$ = –41 (*c* = 1.3, EtOH). ^{1}H NMR (400 MHz, [D_4]methanol): δ = 8.04 (s, 1 H, H_{arom}), 7.48 (s, 1 H, H_{arom}), 7.18 (d, $^3J_{NH,=CH\text{-}N}$ = 1.8 Hz, 1 H, C=C*H*-NH), 4.65 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 3.93–3.91 (m, 1 H, 4-H), 3.87–3.80 (m, 3 H, 2-H, 6a-H, 6b-H), 3.65–3.62 (m, 1 H, 5-H), 3.59 (dd, $^3J_{2,3}$ = 9.8, $^3J_{3,4}$ = 3.4 Hz, 1 H, 3-H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 138.3, 134.4, 127.9 (C_{quat}), 123.4 (CH_{arom}), 121.9 (C_{quat}) 114.8 (=CH-N), 113.8 (CH_{arom}), 112.3 (C_{quat}), 106.6 (C-1), 77.0 (C-5), 74.9 (C-3), 72.4 (C-2), 70.2 (C-4), 62.5 (C-6) ppm. HRMS (ESI): calcd. for $C_{14}H_{15}BrClNO_6Na$ [M + Na]$^+$ 429.9669; found 429.9664. $C_{14}H_{15}BrClNO_6$ calcd. C 41.15, H 3.70, N 3.43; found C 41.10, H 3.78, N 3.48.

Supporting Information (see footnote on the first page of this article): NMR spectra of all new compounds.

Acknowledgments

Support of this work by Glycom A/S, Copenhagen, Denmark is gratefully acknowledged.

[1] J. A. Kiernan, *Biotechn. Histochem.* **2007**, *82*, 73–103.
[2] J. Formanek, *Angew. Chem.* **1928**, *41*, 1133–1146.
[3] J. P. Horwitz, J. Chua, R. J. Curby, A. J. Tomson, M. A. Da Rooge, B. E. Fisher, J. Mauricio, I. Klundt, *J. Med. Chem.* **1964**, *7*, 574–575.
[4] F. B. Anderson, D. H. Leaback, *Tetrahedron* **1961**, *12*, 236–239.
[5] S. Kaneko, M. Kitaoka, A. Kuno, K. Hayashi, *Biosci. Biotechnol. Biochem.* **2000**, *64*, 741–745.
[6] V. Eschenfelder, R. Brossmer, *Glycoconjugate J.* **1987**, *4*, 171–178.
[7] A. Robertson, *J. Chem. Soc.* **1927**, 1937–1943.
[8] A. Robertson, R. B. Waters, *J. Chem. Soc.* **1929**, 2239–2243.
[9] G. Zemplén, *Ber. Dtsch. Chem. Ges.* **1926**, *59B*, 1254–1266.
[10] S. Böttcher, M. Hederos, E. Champion, G. Dékány, J. Thiem, *Org. Lett.* **2013**, *15*, 3766–3769.
[11] Y. Jin, H. Li, L. Lin, J. Tan, J. Ding, X. Luoc, Y. Longa, *Bioorg. Med. Chem.* **2005**, *13*, 5613–5622.
[12] J. J. Li, J. C. Sutton, A. Nirschl, Y. Zou, H. Wang, C. Sun, Z. Pi, R. Johnson, S. R. Krystek, R. Seethala, R. Golla, P. G. Sleph, B. C. Beehler, G. J. Grover, A. Fura, V. P. Vyas, C. Y. Li, J. Z. Gougoutas, M. A. Galella, R. Zahler, J. Ostrowski, L. G. Hamann, *J. Med. Chem.* **2007**, *50*, 3015–3025.
[13] F. Rogister, D. Laeckmann, P. O. Plasman, F. van Eylen, M. Ghyoot, C. Maggetto, J. F. Liégeois, J. Géczy, A. Herchuelz, J. Delarge, B. Masereel, *Eur. J. Med. Chem.* **2001**, *36*, 597–614.
[14] J. M. Huang, H. Chen, R. Y. Chen, *Synth. Commun.* **2002**, *14*, 2215–2225.
[15] M. S. Malamas, J. Millen, *J. Med. Chem.* **1991**, *34*, 1492–1503.
[16] J. F. Dropinski, T. Akiyama, M. Einstein, B. Habulihaz, T. Doebber, J. P. Berger, P. T. Meinke, G. Q. Shi, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5035–5038.
[17] H. Kunz, H. Waldmann, *Angew. Chem.* **1984**, *96*, 49–50; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 71–72.
[18] L. J. Gooßen, C. Linder, N. Rodríguez, P. P. Lange, A. Fromm, *Chem. Commun.* **2009**, 7173–7175.
[19] A. L. Borror, E. Chinoporos, M. P. Filosa, S. R. Herchen, C. P. Petersen, C. A. Stern, *J. Org. Chem.* **1988**, *53*, 2047–2052.
[20] P. C. Unangst, D. T. Connor, S. R. Stabler, R. J. Weikert, *J. Heterocycl. Chem.* **1987**, *24*, 811–815.
[21] U. M. Teotino, G. Cinarella, *J. Am. Chem. Soc.* **1959**, *81*, 4935–4939.
[22] S. Sharma, V. K. Srivastava, A. Kumar, *Eur. J. Med. Chem.* **2002**, *37*, 689–697.
[23] G. Reissenweber, D. Mangold, *Angew. Chem.* **1981**, *93*, 914–915; *Angew. Chem. Int. Ed. Engl.* **1981**, *10*, 882–883.
[24] M. Süsse, S. Johne, *Monatsh. Chem.* **1986**, *117*, 499–509.

Received: August 8, 2013
Published Online: November 14, 2013

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim