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A Strategy for Tumor-Selective Chemotherapy by Enzymatic Liberation of *seco*-duocarmycin SA-derivatives from Nontoxic Prodrugs

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Abstract—Immuno-conjugates obtained by linking enzymes with appropriate monoclonal antibodies, which bind to tumor-associated antigens, can be employed in a tumor-selective antibody directed enzyme prodrug therapy (ADEPT). For this strategy the glycosides **17a**–**c** were prepared as prodrugs of CI-TMI **14** which is a structurally simplified analogue of the highly potent antitumor agent duocarmycin SA **2**. Exposure of **17a**–**c** to cultured carcinoma cells of line A549 displayed a very low toxicity; however, after addition of the corresponding enzymes and exposure for 24 h at prodrug concentrations of <0.1 μM the proliferation of the carcinoma cells was inhibited almost completely with $ED_{50prodrug}/ED_{50drug}$ of up to 270 in the presence and in the absence of the enzyme. The synthesis of **17a**–**c** was achieved by transformation of nitroanisidine **6** into **12** which was glycosidated to give **16a**–**c**. Removal of the silyl groups, introduction of a chlorine atom and solvolysis of the acetal groups led to **17a**–**c**, of which **17a** and **17c** are promising candidates for further elaboration.

Introduction

Tumor-selective chemotherapy must be based on the exploitation of phenotypic or genetic differences of malignant cells from normal tissue. Several rather specific antigens of tumor cells have been identified in recent years[1] and monoclonal antibodies were raised against these domains. For therapeutic purposes, these antibodies have been linked to radioactive species,[2] natural toxines or cytotoxic agents.[3] Very promising is the ADEPT concept (antibody directed enzyme prodrug therapy)[3a,4] in which a little toxic prodrug is enzymatically converted into a toxic species selectively at the surface of malignant cells employing enzyme–immunoconjugates (Fig. 1). The success of this concept clearly depends on the difference of toxicity between the prodrugs and the corresponding drugs as well as on a high biological activity of the drug itself.

In various studies it was shown that the natural antibiotic CC-1065 **1**, which was first isolated from *Streptomyces zelensis*, is a very potent cytostatic agent (Scheme 1).[5] Recently, the duocarmycins as duocarmycin SA **2** have been identified which express a similar pharmacophoric group.

The cytotoxicity of CC-1065 and the duocarmycins is caused by an alkylation of *N*-3 of adenine in AT-rich parts of the minor groove of the DNA by reaction with the spirocyclopropylcyclohexadienone moiety in **1** or **2**.

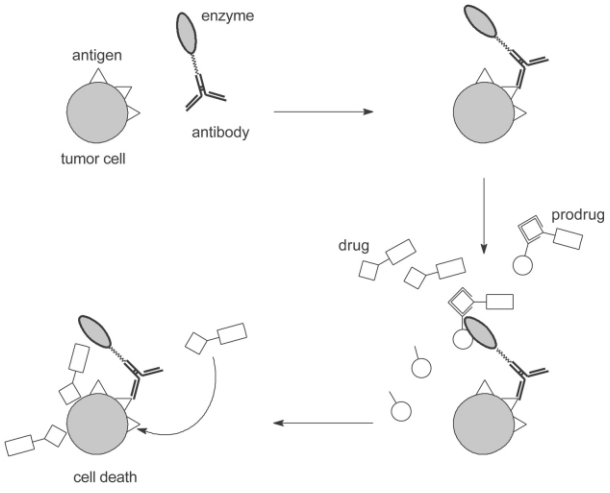

Figure 1. Model of the antibody directed enzyme prodrug therapy (ADEPT) concept.

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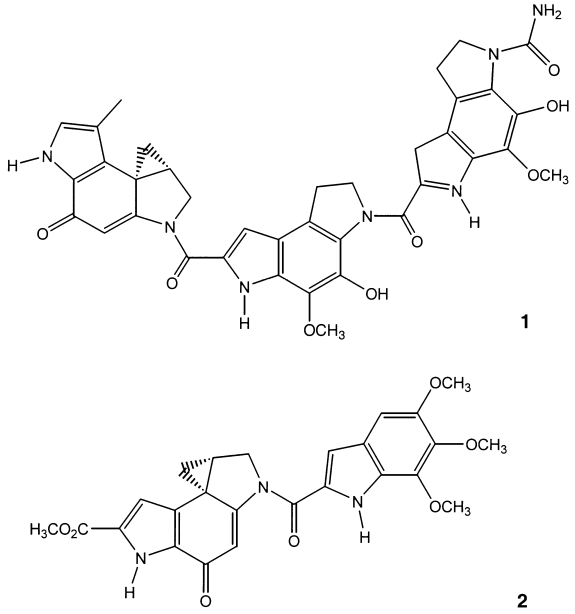
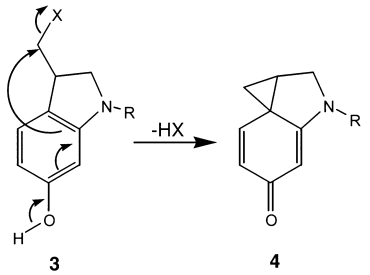
However, *seco*-compounds of **1** or **2** as **3** which cannot form the spirocyclopropyl moiety as in **4** have a drastically reduced cytotoxicity (Scheme 2).

Thus, we[6] and others[7] have shown that the formation of this structural element is halted by blocking the phenolic hydroxy group as an ether. However, ethers are very stable functionalities which can usually not be cleaved under physical conditions. We therefore introduced the glycosides which can be hydrolyzed by a glycohydrolase with liberation of the corresponding toxin. These compounds are now suitable for ADEPT as prodrugs. CC-1065 cannot be used in cancer therapy due to a delayed deadly liver toxicity. But structurally related simplified compounds as CI-TMI **5** (CI = 1,2,7,7a-tetrahydrocyclopropa[*c*]indol-4-one, TMI = 5,6,7-trimethoxyindole-2-carboxylate) are appropriate as anticancer agents.

Here, we present our results using different glycosides of *seco*-CI-TMI **5**[7a,8] (Scheme 3) containing the *seco*-CI-unit as a simplified pharmacophoric group of duocarmycin SA **2** with the trimethoxyindole moiety for binding to the minor groove of DNA. In a former short communication[6] we had already described glycosides of the *seco*-CI-unit without the TMI moiety; however, these compounds did not reveal a sufficient cytotoxicity after enzymatic cleavage.



Scheme 1. Structure of (+)-CC-1065 (**1**) and (+)-duocarmycin SA (**2**).



Scheme 2. Formation of the spirocyclopropylcyclohexadienone moiety (**4**) from a *seco*-compound (**3**).

Results

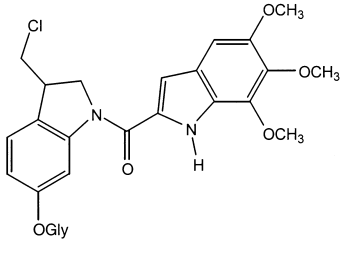
Synthesis of *seco*-CI-TMI 14 and the glycosides 17a–c

The synthesis of *seco*-CI-TMI **14** and the glycosides **17a–c** was accomplished by transformation of nitroanisidine **6** into the known *seco*-CI-methanesulfonamide **7** in eight steps with an overall yield of 27% (Scheme 4).[8a] Removal of the methanesulfonyl moiety was accomplished by reduction with an excess of bismethoxyethoxy sodium dihydroaluminate (RedAl®) in refluxing toluene and the resulting secondary amine **8** was immediately coupled without purification with 5,6,7-trimethoxy-indole-2-carboxylic acid **9**[8b] in DMF using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) as coupling reagent to give the amide **10** in 57% yield.

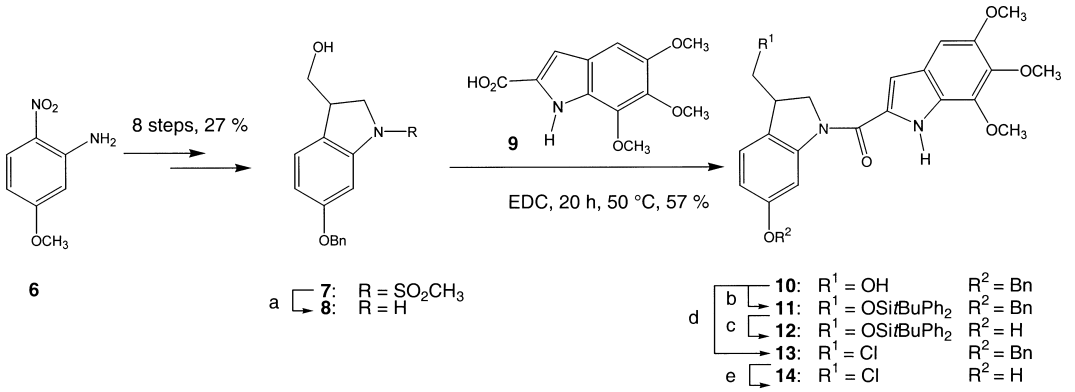
Compound **10** was employed as the key intermediate for the synthesis of the CI-TMI glycosides **17a–c**. On the other hand, it was also used to prepare the free *seco*-CI-TMI **14** as well as the benzyl-protected compound **13** for comparison in the cell tests. Substitution of the hydroxy group in **10** by chloride using the *Appel* procedure with triphenylphosphane in tetrachloromethane and dichloromethane for 5 h at 40 °C gave **13**. Hydrogenolytic removal of the benzyl group using palladium on carbon yielded *seco*-CI-TMI **14**.[8b]

For the synthesis of the *seco*-CI-TMI glycosides **17a–c**, the hydroxy group in **10** was protected as a *tert*-butyldiphenylsilyl ether to give **11**. Which was then deprotected at the phenolic hydroxy group by hydrogenation to yield **12**. Peracetylated trichloroacetimidates of galactose **15a,** glucose **15b** and mannose **15c** were used for the glycosidation of **12** in the presence of $BF_3 \cdot OEt_2$ in dichloromethane at room temperature (Scheme 5).[9] In all cases the 1,2-*trans*-glycosides were obtained in acceptable yields of 53–75%.

The configuration at the anomeric center was determined by ^1H NMR spectroscopy showing a coupling constant of $J_{1'',2''} = 8.0$ Hz for the β-galactoside **16a** and $J_{1'',\ 2''} = 3.5$ Hz for the α-mannoside **16c**. In the spectrum of glucoside **16b** the signal for 1″-H is hidden in a multiplet.



Scheme 3. Prodrugs of the *seco*-CI-TMI unit (**5**).



Scheme 4. Synthesis of *seco*-CI-TMI derivatives **13** and **14**: (a) RedAl, 3 h 110 °C, 94%; (b) tBuPh$_2$SiCl, 4-dimethylamino-pyridine, NEt$_3$, 16 h 40 °C, 92%; (c)Pd/C, 3 bar H_2, 16 h, 64%; (d) PPh$_3$, CCl$_4$, 20 h, 60 °C, 55%; (e) Pd/C, 3 bar H_2, 24 h, 55%.

The *tert*-butyldiphenylsilyl moiety was removed with silica gel coated with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran, and the deprotected primary hydroxy group transformed into the chloride in an *Appel* reaction with triphenylphosphane in tetrachloromethane and dichloromethane. Solvolysis of the acetyl groups using sodium methoxide in methanol completed the synthesis to give **17a**–**c** in 38–70% yield over three steps.

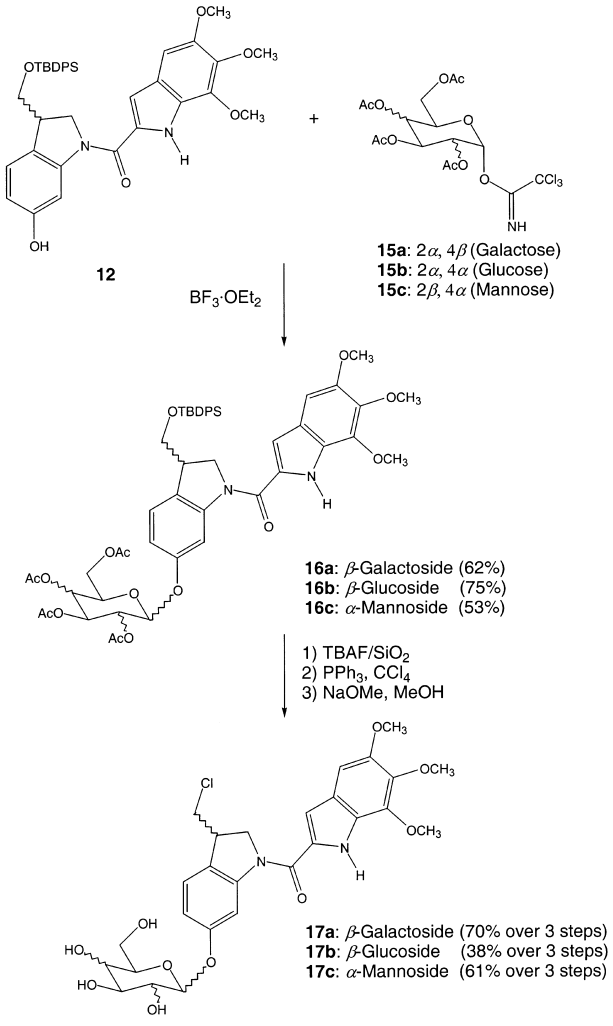
Determination of the cytotoxicity of *seco*-CI-TMI glycosides and *seco*-CI-TMI derivatives 13 and 14

The cytotoxic effect of the *seco*-CI-TMI glycosides and other *seco*-CI-TMI derivatives was evaluated in vitro by exposure of human bronchial carcinoma cells of line A549 to the substances for 24 h. As expected, the *seco*-CI-TMI **14** with a free phenolic hydroxy group exhibited a relatively high cytotoxicity with an $ED_{50} = 2.2$ nM for the relative clone formation, while the benzylated *seco*-CI-TMI **13** showed a much lower toxicity with an $ED_{50} = 650$ nM (Fig. 2A–C).

For the determination of the cytotoxicity of the *seco*-CI-TMI glycosides we used a serum free culture medium in order to avoid an enzymatic hydrolysis of the glycosides since we have shown that fetal calf serum and even the basal medium supplement contain some β-D-galactosidase and β-D-glucosidase.[6] The testing revealed that the cytotoxicity of the galactoside **17a** (Fig. 2A) with an $ED_{50} = 1050$ nM and of the mannoside **17c** (Fig. 2C) with an $ED_{50} = 2200$ nM is as low as found for the stable benzyl protected *seco*-CI-TMI **13**, whereas the glucoside **17b** (Fig. 2B) proved to be unexpectedly toxic with an $ED_{50} = 100$ nM.

In the presence of the corresponding enzyme, which removes the sugar moiety from the phenolic hydroxy group and thus releases the cytotoxic *seco*-CI-TMI, all glycosides displayed an ED_{50} in the range of the cytotoxicity of *seco*-CI-TMI **14**.

For the glycosidations racemic **12** was used and thus **16a**–**c** were obtained as mixtures of diastereomers. Since an enantiomer-differentiating reaction does not occur due to a large distance between the stereogenic centers in **12** and the sugar moieties, a 1:1 mixture is formed. In some cases it was possible to separate the diastereomers and prepare enantiopure **12** by enzymatic removal of the sugar moiety. However, in the described work the mixtures of diastereomers were used for the biological tests since a difference in the rate of enzymatic cleavage of the diastereomers was not observed and in addition, it was known that the enantiomers of **1** show comparable cytotoxicity.



Scheme 5. Synthesis of the glycosidic prodrugs **17a**–**c** of *seco*-CI-TMI (**14**).

The toxicity of the galactoside **17a** was also examined at a lower pH of 6.2 (Fig. 2D). These investigations were stimulated by our work on the design of new selective antitumor agents based on the difference of pH in normal and tumor cells under hyperglycemic conditions.[10] Thus, we developed compounds showing a 100 times higher cytotoxicity at pH 6.2, the mean pH value in the tissue of transplanted solid tumors of hygerglycemic hosts, compared to the cytotoxicity at pH 7.4, the pH value in normal cells of that host. However, a difference of cytotoxicity of **17a** at pH 6.2 was not observed since the galactoside is stable at these pH values.

Discussion

In spite of its simplified structure the *seco*-CI-TMI **14** shows a remarkable high cytotoxicity which is only diminished by a factor of less than 100 compared to CC-1065. It is easily accessible and can be detoxified by blocking the phenolic hydroxy group thus preventing the formation of the spirocyclopropyl moiety which causes alkylation at *N*-3 of adenine units in the DNA. The use of *seco*-CI-TMI in the ADEPT concept requires a blocking of the phenolic hydroxy group in a way that allows its release under physiological conditions by use of an enzyme. This is possible for the glycosides **17a–c** which can be cleaved by glycohydrolases in order to release the *seco*-CI-TMI unit. The difference of cytotoxicity of *seco*-CI-TMI galactoside **17a** and *seco*-CI-TMI mannoside **17c** is very high in comparison with *seco*-CI-TMI **14** and sufficient for a selective approach (Table 1).

Surprisingly, the difference of cytotoxicity between *seco*-CI-TMI glucoside **17b** and *seco*-CI-TMI **14** is rather low with an $ED_{50prodrug}/ED_{50drug}$ of 40. So far we do not have an explanation for the relatively high cytotoxicity of the *seco*-CI-TMI glucoside **17b**. However, the prodrug might penetrate the cell membrane by an active

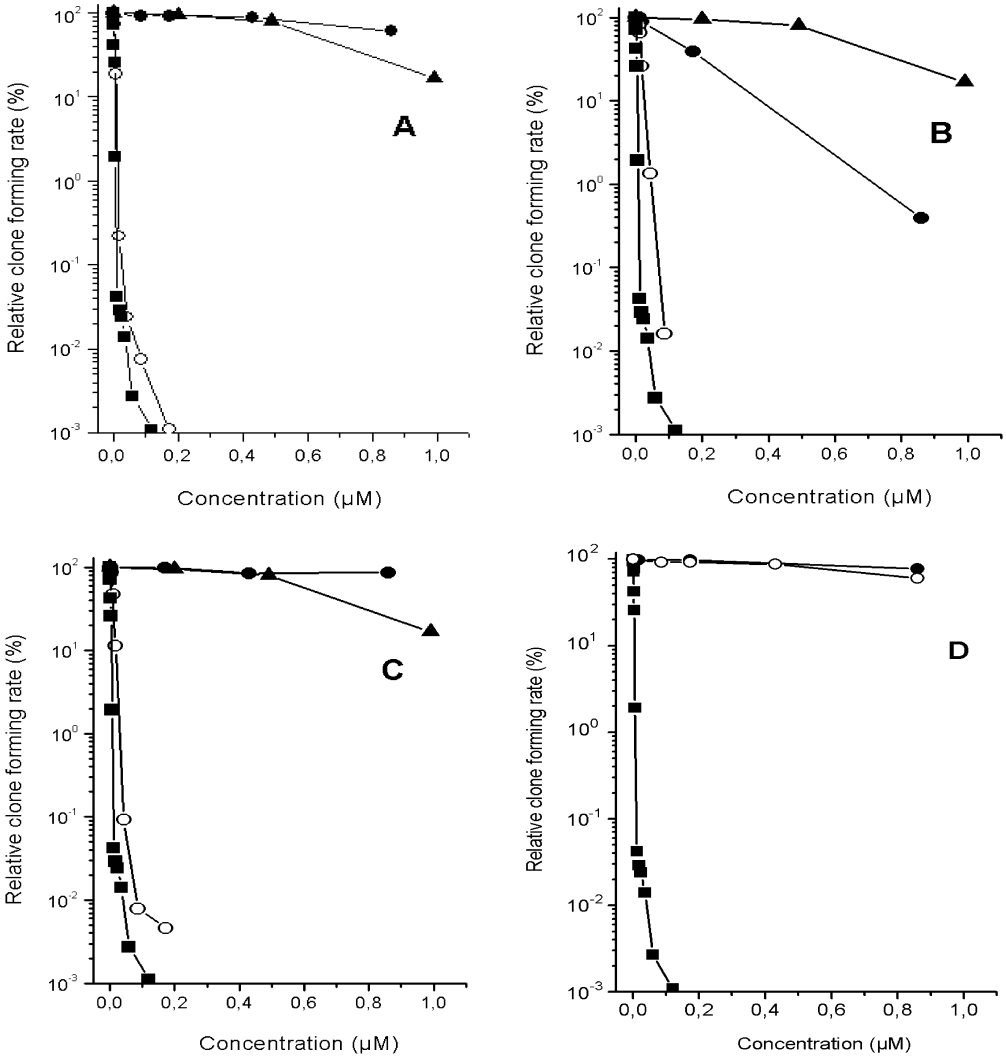


Figure 2. In vitro cytotoxicity of **13, 14** and **17a–c** against human bronchial carcinoma cells of line A549. (A) in vitro cytotoxicity of compound **13** (▲), **14** (■) and **17a** without (●) and with (○) addition of β-D-galactosidase (0.4 U/mL); (B) in vitro cytotoxicity of compound **13** (▲), **14** (■) and **17b** without (●) and with (○) addition of β-D-glucosidase (0.4 U/mL); (C) in vitro cytotoxicity of compound **13** (▲), **14** (■) and **17c** without (●) and with (○) addition of α-D-mannosidase (0.4 U/mL); (D) in vitro cytotoxicity of compound **17a** at pH 6.2 (●) and pH 7.4 (○) and compound **14** (■). Cells were exposed to various concentrations of the test substances for 24 h at 37 °C; after 12 days of incubation clone formation was compared to untreated control assay and the relative clone forming rate was determined.

Table 1. In vitro cytotoxicity of compounds **13**, **14** and **17a–c** against human bronchial carcinoma cells of line A549

Substituent at the phenolic oxygen[a]	Addition of glycohydrolase	ED_{50} (nM)[b]	Specifity factor[c]
H (**13**)	–	2.20	
Bn (**14**)	–	650	
β-D-Galactose (**17a**)	–	1050	180
β-D-Galactose (**17a**)	+	6.10	
β-D-Galactose (**17a**)	–[d]	1000	
β-D-Glucose (**17b**)	–	100	7
β-D-Glucose (**17b**)	+	14.2	
α-D-Mannose (**17c**)	–	2200	270
α-D-Mannose (**17c**)	+	8.20	

[a]Compounds **13** and **14** were used as racemic mixtures; compounds **17a–c** were used as mixtures of diastereomers.
[b]Cells were exposed to the compounds for 24 h at 37 °C; after 12 days of incubation the clone formation was compared to an untreated control assay.
[c]Specificity factor = ED_{50} in the absence of the enzyme/ED_{50} in the presence of the enzyme.
[d]Measured at pH 6.2; all other measurements were carried out at pH 7.4.

transport mechanism and then be cleaved in the lysosome which contains glycohydrolases. This effect may be of interest in designing novel selective anticancer agents which are not based on the ADEPT concept, since the glucose intake of cancer cells is much higher compared to normal cells.

In the presence of the corresponding glycohydrolases, all three *seco*-CI-TMI glycosides **17a–c** displayed nearly the same cytotoxicity as found for *seco*-CI-TMI **14**. This shows that the glycosides are completely cleaved by the enzymes meaning that the enzyme is not destroyed by the formed toxin; thus, a suicide mechanism with regard to the enzymes does not occur. $ED_{50prodrug}/ED_{50drug}$ values of 270 and 170 were reached for the mannoside and the galactoside by comparing the cytotoxicity in the presence and in the absence of the enzyme.

Conclusion

The *seco*-CI-TMI galactoside **17a** and the *seco*-CI-TMI mannoside **17c** are both accessible by efficient synthetic routes. The compounds seem to be very suitable for ADEPT since they display a high difference of cytotoxicity in the presence and in the absence of β-D-galactosidase and α-D-mannosidase, respectively, and a high biological activity of the drug itself. In contrast, the *seco*-CI-TMI glucoside shows a relatively high cytotoxicity. Further investigations with different cell lines and other types of assays will now be undertaken. Appropriate immuno-conjugates of antibodies and enzymes will be employed for the in vivo cleavage of the prodrugs according to the concept of the ADEPT. The results of the these tests will be reported in due course.

Experimental

All reactions were performed under an inert gas atmosphere in flame-dried flasks. All solvents were dried by standard methods. All reagents obtained from commercial sources were used without further purification. Thin-layer chromatography was performed on precoated silica gel plates (SIL G/UV_{254}, Macherey-Nagel GmbH & Co. KG). Silica gel 32–63 (0.032–0.064 mm) (Macherey-Nagel GmbH & Co. KG) was used for column chromatography.

UV–vis spectra were recorded in CH_3CN on a Mettler Lambda 2 spectrometer. IR spectra were recorded as KBr pellets or as films on a Bruker IFS 25 or Vector 22 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian XL 200, VXR 200 and VXR 500 or a Bruker AM 300 with tetramethylsilane (TMS) as the internal standard in [D]chloroform or [D_4]methanol. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured at 70 eV on a Varian MAT311A, high-resolution mass spectra on a Varian MAT731 instrument. Melting points were determined on a Mettler FR 61 and are uncorrected.

(3*R*/*S*)-6-Benzyloxy-3-hydroxymethyl-1-(5′,6′,7′-trimethoxyindol-2′-yl-carbonyl)-2,3-dihydro-1*H*-indole (10). 6-Benzyloxy-3-hydroxymethyl-*N*-methanesulfonyl-2,3-dihydro-1*H*-indole (10.35 g, 31.04 mmol) **7**[8a] was dissolved in oxygen free toluene (140 mL), and sodium(bismethoxyethoxy)-dihydroaluminate (RedAl®) (46 mL, 0.155 mol, 5.0 equiv) was slowly added while stirring. After refluxing for 3 h the solution was cooled to 0 °C, poured into ice cold brine (200 mL), extracted with diethyl ether (3×200 mL) and dried over Na_2SO_4. Concentration in vacuo yielded 6-benzyloxy-3-hydroxymethyl-2,3-dihydro-1*H*-indole 8 (7.44 g, 29.14 mmol, 94%) as a light yellow oil. This was dissolved in DMF (200 mL) and 5,6,7-trimethoxyindole-2-carboxylic acid 9[8b] (5.98 g, 23.78 mmol, 1.0 equiv) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (9.12 g, 47.56 mmol, 3.0 equiv) were added. The solution was stirred for 20 h at 50 °C, cooled to rt and poured into water (200 mL). The organic layer was extracted with ethyl acetate (3×200 mL), washed with brine (200 mL) and dried over Na_2SO_4. Evaporation and purification by column chromatography (PE/EtOAc = 2:1) afforded **10** (6.62 g, 13.55 mmol, 57%) as a white solid. $R_f = 0.28$ (PE/EtOAc = 1:1); mp 149 °C; IR (pellet): $\tilde{\nu} = 3442$ (OH), 2928, 2854 (aliphat. C–H), 1626 (C=O, amide), 1592, 1494 (C=C), 1390 (CH_3), 1310 (OH), 1236, 1108 (C–O), 948, 836 cm^{-1} (1,3,4-trisubstitution); UV/vis (CH_3CN): λ_{max} (lg ε) = 207.0 (4.733), 324.0 nm (4.495); ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (s_b; 1H, OH), 3.62–3.67 (m; 1H, 3-H), 3.76–3.82 (m; 1H, 8-H_a), 3.85–3.89 (m; 1H, 8-H_b), 3.91 (s; 3H, OCH_3), 3.94 (s; 3H, OCH_3), 4.08 (s; 3H, OCH_3), 4.48 (dd, J = 4,5, 10.5 Hz; 1H, 2-H_a), 4.61 (dd, J = 9.5, 10.5 Hz; 1H, 2-H_b), 5.10 (s; 2H, OCH_2Ph), 6.73 (dd, J = 2.5, 8.0 Hz; 1H, 5-H), 6.83 (s; 1H, 4′-H), 6.96 (d, J = 2.5 Hz; 1H, 3′-H), 7.16 (dd, J = 1.0, 8.0 Hz; 1H, 4-H), 7.32 (t, J = 7.0 Hz; 1H, Ph–H), 7.39 (t, J = 7.0 Hz; 2H, Ph–H), 7.46 (d, J = 7.0 Hz; 2H, Ph–H), 8.13 (d, J = 2.5 Hz; 1H, 7-H), 9.40 (s_b; 1H, indole NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 42.79 (C-3), 53.85 (C-2), 56.26 (OCH_3), 61.09 (OCH_3), 61.45 (OCH_3), 65.25 (C-8), 70.20 (OCH_2Ph),

97.67 (C-3′), 104.7 (C-7), 106.5 (C-4′), 111.6 (C-5), 123.6 (C-6′), 123.7 (C-3a), 124.4 (C-4), 125.4 (C-7a′), 127.5 (Ph–C), 127.9 (Ph–C), 128.5 (Ph–C), 130.0 (C-3a′), 137.0 (C-1″), 138.8 (C-7′),140.6 (C-2′), 145.2 (C-7a), 150.1 (C-5′), 159.2 (C-6), 160.3 (NCO); MS (70 eV, EI): *m*/*z* (%) 488 (90) $[M]^+$, 457 (2) $[M–CH_2OH]^+$, 397 (5) $[M–Bn]^+$, 255 (15) $[M–(TMI–OH–H)]^+$, 234 (100) $[TMI–OH]^+$, 224 (30) $[M–(TMI–OH–H)–CH_2OH]^+$, 91 (55) $[Bn]^+$; $C_{28}H_{28}N_2O_6$ (488.54) calcd (%) C 68.84, H 5.78; found C 68.79, H 5.79; HRMS calcd 488.1947; found 488.1947.

(3*R*/*S*)-6-Benzyloxy-3-(*tert*-butyl-diphenyl-silyl)-oxymethyl-1-(5′,6′,7′-trimethoxyindol-2′-yl-carbonyl)-2,3-dihydro-1*H*-indole (11). To a solution of alcohol **10** (2.12 g, 4.34 mmol), triethylamine (10 mL) and 4-dimethylaminopyridine (DMAP) (50 mg, 0.87 mmol, 0.2 equiv) in dichloromethane (55 mL) was added dropwise *tert*-butyldiphenylsilyl chloride (2.26 mL, 2.39 g, 8.65 mmol, 2.0 equiv) at rt. The reaction mixture was stirred for 16 h at 60 °C, washed with brine (100 mL) and extracted with dichloromethane (3×100 mL). After drying of the extracts over Na_2SO_4 the solvents were removed in vacuo and the residue purified by column chromatography (PE/EtOAc = 3:1) to afford **11** (2.90 g, 3.99 mmol, 92%) as a colorless oil. R_f = 0.68 (PE/EtOAc = 3:1); IR (pellet): $\tilde{\nu}$ = 3458 (NH), 2934, 2858 (aliphat. C-H), 1628 (C=O, amide), 1598 (C=C), 1526 (NCO), 1428, 1412, 1388 (CH_3), 1230, 1194, 1160 (C–O), 950, 836 (1,3,4-trisubst.), 744, 706 cm^{-1} (Si–Ph); UV–vis (CH_3CN): λ_{max} (lg ε) = 324.5 nm (4.478); ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (s; 9H, $(CH_3)_3C$), 3.64 (m_c; 1H, 3-H), 3.69 (dd, *J* = 7.5, 9.5 Hz; 1H, 8-H_a), 3.99 (dd, *J* = 5.0, 9.5 Hz; 1H, 8-H_b), 3.94 (s; 3H, OCH_3), 3.96 (s; 3H, OCH_3), 4.09 (s; 3H, OCH_3), 4.43 (dd, *J* = 4.5, 10.5 Hz; 1H, 2-H_a), 4.55 (dd, *J* = 9.5, 10.5 Hz; 1H, 2-H_b), 5.11 (s; 2H, OCH_2Ph), 6.69 (dd, *J* = 2.5, 8.0 Hz; 1H, 5-H), 6.84 (s; 1H, 4′-H), 6.87 (d, *J* = 2.5 Hz; 1H, 3′-H), 7.07 (d, *J* = 8.0 Hz; 1H, 4-H), 7.28–7.50 (m; 11H, Ph–H), 7.54–7.63 (m; 4H, Ph–H), 8.12 (d, *J* = 2.5 Hz; 1H, 7-H), 9.40 (s_b; 1H, indole NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.20 ($(CH_3)_3C$), 26.77 ($(CH_3)_3C$), 42.96 (C-3), 53.93 (OCH_3), 61.06 (OCH_3), 61.43 (OCH_3), 66.78 (C-2), 70.12 (OCH_2Ph), 97.62 (C–2), 104.4 (C–4′), 106.1 (C–7), 111.4 (C–3′), 123.6 (C–3a), 124.4 (C–3a′), 124.7 (C–4), 125.3 (C–7a′), 127.4 (Ph–C, Bn), 127.7 (Ph–C, TBDPS), 127.8 (Ph–C, Bn), 128.4 (Ph–C, Bn), 129.7 (Ph–C, TBDPS), 130.1 (C-2′), 133.1 (C-1‴, TBDPS), 135.3 (Ph–C, TBDPS), 137.0 (C-1″, Bn), 138.8 (C-7′), 140.3 (C-6′), 144.9 (C-7a), 150.0 (C-5′), 159.0 (C-6), 160.0 (NCO); MS (70 eV, EI): *m*/*z* (%) 726.7 (30) $[M]^+$, 669.5 (55) $[M–(CH_3)_3C]^+$, 234 (100) $[TMI]^+$; $C_{44}H_{46}N_2O_6Si$ (726.95): calcd (%) C 72.70, H 6.38; found C 72.65, H 6.39; HR-MS calcd 726.3125; found 726.3125.

(3*R*/*S*)-3-(*tert*-Butyl-diphenyl-silyl)-oxymethyl-6-hydroxy-1-(5′,6′,7′-trimethoxyindol-2′-yl-carbonyl)-2,3-dihydro-1*H*-indole (12). Benzyl ether **11** (4.2 g, 5.53 mmol) was dissolved in ethyl acetate (30 mL) and palladium (10% on charcoal, 1.18 g, 1.11 mmol, 0.2 equiv) was added. The suspension was stirred in a hydrogen pressure apparatus (3 bar) at rt for 16 h. The solid was removed by filtration through Celite and the solution was concentrated in vacuo. Purification by column chromatography (PE/EtOAc = 3:1) yielded **12** (2.24 g, 3.52 mmol, 64%) as a white solid. R_f = 0.35 (PE/EtOAc = 3:1); IR (pellet): $\tilde{\nu}$ = 3458 (NH), 2934, 2858 (aliphat. C–H), 1624 (C=O, Amid), 1586, 1494 (C=C), 1528 (NCO), 1462, 1428, 1386 (CH_3), 1312 (OH), 1258, 1236, 1198, 1156 (C–O), 944, 860 cm^{-1} (1,3,4-trisubst.); UV–vis (CH_3CN): λ_{max} (lg ε) = 192.5 (4.992), 324.5 nm (4.457); ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (s; 9H, $(CH_3)_3C$), 3.62 (m_c; 1H, 3-H), 3.65 (dd, *J* = 7.5, 9.5 Hz; 1H, 8-H_a), 3.86 (dd, *J* = 5.0, 9.5 Hz; 1H, 8-H_b), 3.91 (s; 3H, OCH_3), 3.96 (s; 3H, OCH_3), 4.14 (s; 3H, OCH_3), 4.41 (dd, *J* = 4.5, 10.5 Hz; 1H, 2-H_a), 4.52 (dd, *J* = 9.5, 10.5 Hz; 1H, 2-H_b), 6.61 (dd, *J* = 2.5, 8.0 Hz; 1H, 5–H), 6.82 (s; 1H, 4′-H), 6.89 (d, *J* = 2.5 Hz; 1H, 3′-H), 7.03 (d, *J* = 8.0 Hz; 1H, 4-H), 7.26–7.43 (m; 6H, Ph–H), 7.52–7.60 (m; 4H, Ph–H), 7.95 (s_b; 1H, phenol OH), 8.21 (d, *J* = 2.5 Hz; 1H, 7-H), 9.51 (s_b; 1H, indole NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.23 ($(CH_3)_3C$), 26.80 ($(CH_3)_3C$), 43.00 (C-3), 54.33 (OCH_3), 61.26 (OCH_3), 61.57 (OCH_3), 66.86 (C-2), 97.71 (C-4′) 106.0 (C-7), 107.2 (C-3′), 111.7 (C-5), 123.3 (C-3a), 123.5 (C-3a′), 125.0 (C-4), 125.8 (C-7a′), 127.7 (Ph–C), 129.6 (C-2′), 129.7 (Ph–C), 133.2 (C-1″), 135.5 (Ph–C), 138.1 (C-7′), 140.7 (C-6′), 144.3 (C-7a), 150.0 (C-5′), 157.1 (C-6), 160.7 (NCO); MS (70 eV, EI): *m*/*z* (%) 636.2 (25) $[M]^+$, 579.1 (30) $[M–(CH3)C]^+$, 234.0 (35) $[TMI]^+$, 199.0 (100) $[Ph_2SiOH]^+$; $C_{37}H_{40}N_2O_6Si$ (636.82) calcd C 69.79, H 6.33; found C 69.62, H 6.36.

(3*R*/*S*)-6-Benzyloxy-3-chloromethyl-1-(5′,6′,7′-trimethoxyindol-2′-yl-carbonyl)-2,3-dihydro-1*H*-indole (13). To a solution of amide **7** (100 mg, 0.20 mmol) in dichloromethane (5 mL) and tetrachloromethane (5 mL) was added triphenylphosphane (161 mg, 0.61 mmol, 3.0 equiv), and the mixture was stirred for 5 h at 40 °C. Removal of the solvent and purification by column chromatography (PE/EtOAc = 3:1) afforded **13** (55 mg, 0.11 mmol, 55%) as a colorless solid. R_f = 0.50 (PE/EtOAc = 3:1); IR (pellet): $\tilde{\nu}$ = 936 (aliphat. C–H), 1628 (C=O, amide), 1600, 1494 cm^{-1} (C=C); UV–vis (CH_3CN): λ_{max} (lg ε) = 206.0 (4.743), 324.5 nm (4.449); ^1H NMR (300 MHz, C_6D_6): δ 3.10–3.22 (m; 2H, CH_2Cl), 3.55 (s; 3H, OCH_3), 3.70 (s; 3H, OCH_3), 3.73–3.78 (m_c; 1H, 3-H), 3.80 (s; 3H, OCH_3), 3.98–4.07 (m; 2H, 2-H_2), 4.92 s; 2H, OCH_2Ph), 6.69 (s; 1H, 4′-H), 6.72 (dd, *J* = 2.5, 8.0 Hz; 1H, 5-H), 7.00–7.44 (m; 7H, 5-H, 3′-H, Ph–H), 8.70 (d, *J* = 2.5 Hz; 1H, 7-H), 9.75 (s_b; 1H, indole NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 43.12 (C-3), 47.16 (C-2), 54.84 (C-8), 56.25 (OCH_3), 61.13 (OCH_3), 61.47 (OCH_3), 70.20 (OCH_2Ph), 97.61 (C-3′), 104.6 (C-7), 106.4 (C-4′), 111.7 (C-5), 123.3 (C-6′), 123.6 (C-3a), 124.5 (C-4), 125.5 (C-7a′), 127.5 (Ph–C), 128.0 (Ph–C), 128.6 (Ph–C), 129.8 (C-3a′), 136.8 (C-1″), 138.9 (C-7′), 140.5 (C-2′), 144.9 (C-7a), 150.1 (C-5′), 159.6 (C-6), 160.2 (NCO). MS (70 eV, EI): *m*/*z* (%) 506.5 (3) $[M]^+$, 234.2 (5) $[TMI]^+$, 223.2 (5) $[M–TMI–CH_2Cl]^+$, 91.1 (100) $[Bn]^+$.

(3*R*/*S*)-3-Chloromethyl-6-hydroxy-1-(5′,6′,7′-trimethoxyindol-2′-yl-carbonyl)-2,3-dihydro-1*H*-indole (14). Benzyl ether **13** (55 mg, 0.11 mmol) was dissolved in ethyl acetate (10 mL) and palladium (10% on charcoal, 17 mg, 0.02

mmol, 0.2 equiv) was added. The suspension was stirred in a hydrogen pressure apparatus (3 bar) at rt for 24 h. The solid was removed by filtration through Celite and washed with dichloromethane (50 mL) and methanol (50 mL). The filtrate was concentrated in vacuo to yield **14** (25 mg, 0.06 mmol, 55%). $R_f = 0.52$ (PE/EtOAc = 1:1); IR (pellet): $\tilde{\nu} = 3432$ (OH), 2934 (aliphat. C–H), 1622 (C=O, amide), 1492 (C=C), 1304 (OH), 1264 (CH_3), 1112 cm^{-1} (C–O); UV–vis (CH_3CN): λ_{max} (lg ε) 206.0 (4.554), 324.5 nm (4.328); ^1H NMR (300 MHz, 80% $CDCl_3$, 20% DMSO-d_6): δ 3.59 (dd, $J = 8.0$, 10.0 Hz; 1H, 8–H_a), 3.70–3.87 (m; 2H, 8-H_b, 3-H), 3.89 (s; 3H, OCH_3), 3.91 (s; 3H, OCH_3), 4.07 (s; 3H, OCH_3), 4.40 (dd, $J = 4.5$, 10.5 Hz; 1H, 2-H_a), 4.62 (dd, $J = 6.0$, 10.5 Hz; 1H, 2–H_b), 6.57 (dd, $J = 2.5$, 8.0 Hz; 1H, 5-H), 6.88 (s; 1H, 4′-H), 6.95 (d, $J = 2.0$ Hz; 3′-H), 7.10 (d, $J = 8.0$ Hz; 1H, 4 H), 7.78 (s_b; 1H, 7-H), 9.18 (s_b; 1H, indole NH), 10.28 (s_b; 1H, OH); ^{13}C NMR (50 MHz, 80% $CDCl_3$, 20% DMSO-d_6): δ 42.86 (C-3), 47.32 (C-8), 54.77 (C–2), 56.17 (OCH_3), 61.11 (OCH_3), 61.37 (OCH_3), 97.65 (C-3′), 105.6 (C-7), 106.2 (C–4′), 111.5 (C-5), 121.7 (C-6′), 123.5 (C-3a), 124.5 (C-4), 125.3 (C-7a′), 130.1 (C-3a′), 138.8 (C-7′), 140.2 (C-2′), 144.6 (C-7a), 149.9 (C-5′), 158.1 (C-6), 160.0 (NCO); MS (70 eV, EI): m/z 416.3 (69) $[M]^+$, 234.2 (100) $[TMI]^+$.

[(3*R*/*S*)-3-(*tert*-Butyl-diphenyl-silyl)-oxymethyl-1-(5,6,7-trimethoxyindol-2-yl-carbonyl)-2,3-dihydro-1*H*-indol-6-yl]-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (16a). To a mixture of phenol **12** (2.19 g, 3.44 mmol), molecular sieves (4 Å, 10 g) and trichloroacetimidate **15a** (1.80 g, 3.78 mmol, 1.1 equiv) in dichloromethane (140 mL) was added dropwise a solution of boron trifluoride diethyl ether complex (0.49 g, 3.44 mmol, 1.0 equiv) in dichloromethane (25 mL) at 0 °C and the mixture was stirred for 16 h at rt. The molecular sieves were filtered off, and the filtrate was washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (3×150 mL) and the combined organic phases were washed with brine and dried over Na_2SO_4. Evaporation and purification by column chromatography (PE/EtOAc = 3:1) afforded **16a** (2.062 g, 2.13 mmol, 62%) as a colorless foam. $R_f = 0.10$ (PE/EtOAc = 2:1); IR (pellet): $\tilde{\nu} = 3328$ (aromat. C–H), 2972, 2936, 2862 (aliphat. C–H), 1754 (C=O, ester), 1626 (C=O, amide), 1596, 1492 (C=C), 1526 (NCO), 1466, 1440, 1374 (CH_3), 1228, 1156, 1114, 1076 (C–O), 954, 824 (1,3,4-trisubst.), 744, 706 cm^{-1} (Si–Ph); UV–vis (CH_3CN): λ_{max} (lg ε) = 319.5 (4.086), 266.0 nm (3.797); ^1H NMR (300 MHz, $CDCl_3$)[11]: δ 1.02 (s; 9H, $(CH_3)_3C$), 2.01, 2.03, 2.09, 2.19 (s; each 3H, Ac–CH_3), 3.63 (m_c; 1H, 3-H), 3.70 (ddd, $J = 7.5$, 9.0, 9.5 Hz; 1H, 8-H_a), 3.86 (ddd, $J = 5.0$, 9.5, 11.5 Hz; 1H, 8-H_b), 3.92 (s; 3H, OCH_3), 3.95 (s; 3H, OCH_3), 4.08 (s; 3H, OCH_3), 4.09 (m_c; 1H, 5″-H), 4.20 (d, $J = 6.5$ Hz; 2H, 6″-H_2), 4.42 (ddd, $J = 4.5$, 10.5, 13.5 Hz; 1H, 2–H_a), 4.54 (ddd, $J = 7.5$, 9.5, 10.5 Hz; 1H, 2-H_b), 5.10 (t, $J = 8.0$ Hz; 1H, 2″-H), 5.11 (ddd, $J = 0.5$, 3.5, 10.5 Hz; 1H, 1″-H), 5.46 (dt, $J = 1.0$, 3.5 Hz; 1H, 4″-H), 5.50 (ddd, $J = 1.0$, 8.0, 10.5 Hz; 1H, 3″-H), 6.72 (dt, $J = 2.5$, 8.0 Hz; 1H, 5–H), 6.82 (s; 1H, 4′-H), 6.85 (dd, $J = 1.0$, 2.5 Hz; 1H, 3′-H), 7.08 (d, $J = 8.0$ Hz; 1H, 4-H), 7.28–7.36 (m_c; 4H, Ph–H), 7.36–7.44 (m_c; 2H, Ph–H), 7.52–7.61 (m; 4H, Ph–H), 8.06 (s_b; 1H, 7-H), 9.35 (s_b; 1H, indole NH); ^{13}C NMR (75 MHz, $CDCl_3$):[11] δ 19.13 ($(CH_3)_3C$), 20.50, 20.58, 20.67 (Ac–CH_3), 26.69 ($(CH_3)_3C$), 42.91 (C-3), 53.82 (C–2), 56.20 (OCH_3), 61.04 (OCH_3), 61.25 (C-6″), 61.31 (OCH_3), 66.61 (C-8), 66.84 (C-4″), 68.57 (C-3″), 70.81 (C-2″), 70.97 (C-5″), 97.57 (C-4′), 99.72 (C-1″), 106.3 (C-3′), 106.6/106.8 (C-7), 113.0/113.1 (C-5), 123.5 (C-3a′), 124.8 (C-4), 125.4 (C-7a′), 127.0 (C-3a), 127.7 (Ph–C), 129.7 (Ph–C), 129.9 (C-2′), 133.0 (C-1‴), 135.4 (Ph–C), 138.8 (C-7′), 140.4 (C-6′), 144.9 (C-7a), 150.0 (C-5′), 157.0 (C-6), 160.0 (NCO), 169.4, 170.0, 170.2, 170.4 (Ac–CO); MS (70 eV, DCI): m/z (%) 984.5 (100) $[M + NH_4]^+$, 967.5 (50) $[M + H]^+$.

[(3*R*/*S*)-3-(*tert*-Butyl-diphenyl-silyl)-oxymethyl-1-(5,6,7-trimethoxyindol-2-yl-carbonyl)-2,3-dihydro-1*H*-indol-6-yl]-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (16b). To a solution of phenol **12** (1.14 g, 1.78 mmol), molecular sieves (4 Å, 12 g) and trichloroacetimidate **15b** (0.91 g, 1.78 mmol, 1.07 equiv) in dichloromethane (80 mL) was added dropwise a solution of boron trifluoride diethyl ether complex (0.253 g, 1.78 mmol, 1.0 equiv) in dichloromethane (1.78 mL) at 0 °C and the mixture was stirred for 16 h at rt. The molecular sieves were filtered off, and the filtrate was washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (3×100 mL) and the combined organic phases were washed with brine and dried over Na_2SO_4. Evaporation and purification by column chromatography (PE/EtOAc = 3:1) afforded **16b** (1.30 g, 1.34 mmol, 75%) as a colorless foam. $R_f = 0.09$ (PE/EtOAc = 2:1); IR (pellet): $\tilde{\nu} = 3464$ (NH), 3076, 3048 (aromat. C–H), 2934, 2858 (aliphat. C–H), 1758 (C=O, ester), 1630 (C=O, amide), 1598, 1490 (C=C), 1526 (NCO), 1440, 1430, 1376 (CH_3), 1228, 1162, 1112, 1070 (C–O), 942, 852 (1,3,4-trisubst.), 744, 706 cm^{-1} (Si–Ph); UV–vis (CH_3CN): λ_{max} (lg ε) = 266.0 (3.854), 321.0 nm (4.463); ^1H NMR (200 MHz, $CDCl_3$):[11] δ 1.04 (s; 9H, $(CH_3)_3C$), 2.04, 2.05, 2.07, 2.08 (s; each 3H, Ac–CH_3), 3.63 (m_c; 1H, 3-H), 3.69 (m; 1H, 8-H_a), 3.82 (m; 1H, 5″-H), 3.88 (m; 1H, 8-H_b), 3.92 (s; 3H, OCH_3), 3.96 (s; 3H, OCH_3), 4.08 (s; 3H, OCH_3), 4.18 (m_c; 1H, 6″-H_a), 4.30 (m_c; 1H, 6″-H_b), 4.42 (m_c; 1H, 2-H_a), 4.54 (m_c; 1H, 2-H_b), 5.16 (m; 2H, 1″-H, 2″-H), 5.29 (m; 2H, 3″–H, 4″-H), 6.70 (dt, $J = 2.5$, 8.0 Hz; 1H, 5–H), 6.83 (s; 1H, 4′-H), 6.85 (d, $J = 2.0$ Hz; 1H, 3′-H), 7.08 (d, $J = 8.0$ Hz; 1H, 4-H), 7.30–7.42 (m_c; 6H, Ph–H), 7.53–7.61 (m_c; 4H, Ph–H), 8.05 (s_b; 1H, 7-H), 9.29 (s_b; 1H, indole NH); ^{13}C NMR (75 MHz, $CDCl_3$)[11]: δ ($(CH_3)_3C$), 20.54, 20.55, 20.60, 20.64 (Ac–CH_3), 26.81 ($(CH_3)_3C$), 43.01 (C-3), 53.93 (C-2), 56.31 (OCH_3), 61.07 (OCH_3), 61.47 (OCH_3), 61.74 (C6″), 66.71 (C-8), 68.16 (C-4″), 71.13 (C-3″), 72.01 (C-2″), 72.90 (C-5″), 97.72 (C-4′), 99.17 (C-1″), 106.3 (C-3′), 106.6 (C-7), 113.2 (C-5), 123.6 (C-3a′), 124.9 (C-4), 125.5 (C-7a′), 127.0 (C-3a), 127.8 (Ph–C), 129.8 (Ph–C), 133.1 (C-2′), 134.8 (C-1‴), 135.5 (Ph–C), 138.9 (C-7′), 140.5 (C-6′), 145.0 (C-7a), 150.1 (C-5′), 157.0 (C-6), 160.2 (NCO), 169.3, 169.4, 170.2, 170.7 (Ac–CO); MS (70 eV, DCI): m/z (%) 985.0 (95) $[M + NH_4]^+$, 967.9 (100) $[M + H]^+$.

[(3*R*/*S*)-3-(*tert*-Butyl-diphenyl-silyl)-oxymethyl-1-(5,6,7-trimethoxyindol-2-yl-carbonyl)-2,3-dihydro-1*H*-indol-6-yl]-2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (16c). To a solution of phenol **12** (200 mg, 0.31 mmol), molecular sieves (4 Å, 2 g) and trichloroacetimidate **15c** (106 mg, 0.38 mmol, 1.2 equiv) in dichloromethane (20 mL) was added dropwise a solution of boron trifluoride diethyl ether complex (26 mg, 0.31 mmol, 1.0 equiv) in dichloromethane (2.0 mL) at 0 °C and the mixture was stirred for 24 h at rt. The molecular sieves were filtered off, and the filtrate was washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (3×100 mL) and the combined organic phases were washed with brine and dried over Na_2SO_4. Evaporation and purification by column chromatography (PE/EtOAc = 3:1) afforded **16c** (161 mg, 0.166 mmol, 53%) as a colorless foam. R_f = 0.13 (PE/EtOAc = 2:1); IR (pellet): $\tilde{\nu}$ = 3462 (NH), 2936 (aliphat. C-H), 1754 (C=O, ester), 1630 (C=O, amide), 1602, 1490 (C=C), 1526 (NCO), 1468, 1440, 1430, 1412, 1386 (CH_3), 1228, 1162, 1112, 1074 (C–O), 956, 856 (1,3,4-trisubst.), 744, 706 cm^{-1} (Si–O); UV–vis (CH_3CN): λ_{max} (lg ε) = 321.0 nm (4.379); ^1H NMR (500 MHz, $CDCl_3$):[11] δ 1.00/1.01 (s; 9H, $(CH_3)_3C$), 1.97/1.98, 2.01, 2.02, 2.03 (s; each 3H, Ac–CH_3), 3.64 (m_c; 1H, 3-H), 3.67/3.68 (dd, *J* = 8.0, 10.0 Hz; 1H, 8–H_a), 3.85/3.86 (dd, *J* = 5.5, 10.0 Hz; 1H, 8–H_b), 3.90 (s; 3H, OCH_3), 3.93 (s; 3H, OCH_3), 4.03/4.05 (dd, *J* = 2.0, 12.5 Hz; 1H, 6″-H_a), 4.05 (s; 3H, OCH_3), 4.11 (m; 1H, 5″-H), 4.32–4.34 (dd, *J* = 3.5, 12.5 Hz; 1H, 6″-H_b), 4.39/4.41 (dd, *J* = 4.5, 10.5 Hz; 1H, 2-H_a), 4.51/4.53 (dd, *J* = 4.5, 9.5 Hz; 1H, 2-H_b), 5.36 (t, *J* = 10.0 Hz; 1H, 4″-H), 5.43 (dd, *J* = 2.0, 3.5 Hz; 1H, 2″-H), 5.54 (m; 2H, 1″-H, 3″-H), 6.74 (2 dd, *J* = 2.5, 8.0 Hz; 1H, 5-H), 6.81 (s; 1H, 4′-H), 6.83 (2 d, *J* = 2.0 Hz; 1H, 3′-H), 7.07 (d, *J* = 8.0 Hz; 1H, 4-H), 7.25–7.35 (m_c; 4H, Ph–H), 6.35–7.42 (m_c; 2H, Ph–H), 7.53–7.60 (m_c; 4H, Ph–H), 8.13 (2 d, *J* = 2.5 Hz; 1H, 7-H), 9.37 (s_b; 1H, indole NH); ^{13}C NMR (75 MHz, $CDCl_3$):[11] δ 19.21 ($(CH_3)_3C$), 20.63, 20.69, 20.85, 21.00 (Ac–CH_3), 26.78 ($(CH_3)_3C$), 43.00 (C-3), 53.78 (C-2), 56.26 (OCH_3), 61.08 (OCH_3), 61.44 (OCH_3), 62.16 (C-6‘‘), 66.02 (C-4″), 66.65 (C-8), 68.92 (C-3″), 69.08 (C-2″), 69.42 (C-5″), 95.96/96.05 (C-4′), 97.67 (C-1″), 106.2 (C-3′), 107.0/107.1 (C-7), 112.0/112.2 (C-5), 123.7 (C-3a′), 124.8/124.9 (C-4), 125.4 (C-3a), 126.8 (C-7a′), 127.8 (Ph–C), 129.8/130.0 (Ph–C), 133.0 (C-2′), 133.1 (C-1‴), 133.5 (Ph–C), 138.9 (C-7′), 140.5 (C-6′), 145.1 (C-7a), 150.0 (C-5′), 155.7 (C-6), 160.0 (NCO), 169.7, 169.8, 170.0, 170.1 (Ac–CO); MS (70 eV, DCI): *m*/*z* 984.5 (100) $[M + NH_3]^+$, 967.5 (35) $[M]^+$.

[(3*R*/*S*)-3-Hydroxymethyl-1-(5,6,7-trimethoxyindol-2-yl-carbonyl)-2,3-dihydro-1*H*-indol-6-yl]-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (18a). To a solution of galactoside **16a** (1.50 g, 1.55 mmol) in tetrahydrofuran (100 mL) was added tetrabutylammonium fluoride on silica gel (1.1 mmol/1 g, 2.82 g, 3.10 mmol, 2.0 equiv) at 0 °C. The reaction mixture was warmed to 40 °C and stirred for 5 h. After removal of the solvents in vacuo the residue was purified by column chromatography (PE/EtOAc = 1:1) to yield **18a** (1.05 g, 1.44 mmol, 93%) as a colorless foam. R_f = 0.15 (PE/EtOAc = 1:2); IR (pellet): $\tilde{\nu}$ = 3464 (OH), 2938 (aliphat. C-H), 1752 (C=O, ester), 1628 (C=O, amide), 1604, 1490 (C=C), 1526 (NCO), 1440, 1384 (CH_3), 1308 (OH), 1232, 1160, 1108, 1076 (C–O), 954, 874 cm^{-1} (1,3,4-trisubst.); UV–vis (CH_3CN): λ_{max} (lg ε) = 206.0 (4.641), 320.5 nm (4.443); ^1H NMR (300 MHz, $CDCl_3$):[11] δ 0.79 (s_b; 1H, OH), 1.92, 1.95, 2.00, 2.10 (s; each 3H, Ac–CH_3), 3.56 (m_c; 1H, 3-H), 3.72 (m_c; 2H, 8-H_2), 3.82 (s; 3H, OCH_3), 3.87 (s; 3H, OCH_3), 3.95 (s; 2H, 6″-H_2), 4.00 (s; 3H, OCH_3), 4.08 (t, *J* = 6.5 Hz; 1H, 5″-H), 4.49 (m; 2H, 2-H_2), 5.03 (m; 2H, 1″-H, 2″-H), 5.38 (m; 2H, 3″-H, 4″-H), 6.67 (dd, *J* = 2.5, 8.0 Hz; 1H, 5-H), 6.74 (s; 1H, 4′-H), 6.87 (s; 1H, 3′-H), 7.08 (d, *J* = 8.0 Hz; 1H, 4-H), 8.02/8.04 (d, *J* = 2.5 Hz; 1H, 7-H), 9.46/9.82 (s_b; 1H, indole NH); ^{13}C NMR (75 MHz, $CDCl_3$):[11] δ 20.47, 20.54, 20.63, 20.78 (Ac–CH_3), 42.82/43.01 (C-3), 53.84/53.98 (C-2), 56.20 (OCH_3), 61.02 (OCH_3), 61.19/61.23 (C-6″), 61.36 (OCH_3), 64.89 (C-8), 66.84/66.92 (C-4″), 68.60 (C-3″), 70.74/70.79 (C-2″), 70.81/70.93 (C-5″), 97.68/97.72 (C-4′), 99.55/99.59 (C-1″), 106.5 (C-7), 106.6 (C-3′), 113.3 (C-5), 123.5 (C-3a′), 124.5 (C-4), 125.5/125.6 (C-7a′), 126.6 (C-3a), 129.8/129.9 (C-2′), 138.7 (C-7′), 140.4/140.6 (C-6′), 144.9/145.0 (C-7a), 150.0 (C-5′), 157.0/157.1 (C-6), 160.3/160.5 (NCO), 169.4, 170.0, 170.2, 170.4 (Ac–CO); MS (70 eV, DCI): *m*/*z* (%) 746.6 (100) $[M + NH_4]^+$, 729.6 (65) $[M + H]^+$.

[(3*R*/*S*)-3-Hydroxymethyl-1-(5,6,7-trimethoxyindol-2-yl-carbonyl)-2,3-dihydro-1*H*-indol-6-yl]-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (18b). To a solution of glucoside **16b** (1.30 g, 1.34 mmol) in tetrahydrofuran (100 mL) was added tetrabutylammonium fluoride on silica gel (1.1 mmol/1 g, 2.45 g, 2.69 mmol, 2.0 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h. After removal of the solvents in vacuo the residue was purified by column chromatography (PE/EtOAc = 1:1) to yield **18b** (596 mg, 0.82 mmol, 61%) as a colorless foam. R_f = 0.13 (PE/EtOAc = 1:2); IR (pellet): $\tilde{\nu}$ = 3468 (NH), 2940 (aliphat. C-H), 1756 (C=O, ester), 1626 (C=O, amide), 1600, 1492 (C=C), 1526 (NCO), 1468, 1440, 1414, 1378 (CH_3), 1308 (OH), 1232, 1162, 1110, 1044 (C–O), 958, 878 cm^{-1} (1,3,4-trisubst.); UV–vis (CH_3CN): λ_{max} (lg ε) = 207.5 (4.614), 320.5 nm (4.458); ^1H NMR (500 MHz, $CDCl_3$):[11] δ 2.01/2.02, 2.04/2.05, 2.06, 2.07/2.08 (s; each 3H, Ac–CH_3), 3.64 (m_c; 1H, 3-H), 3.78 (dd, *J* = 7.0, 10.5 Hz; 1H, 8-H_a), 3.80 (m; 2H, 5″-H), 3.86 (dd, *J* = 5.0, 10.5 Hz; 1H, 8-H_b), 3.89/3.90 (s; 3H, OCH_3), 3.94/3.96 (s; 3H, OCH_3), 3.99/4.07 (s; 3H, OCH_3), 4.18 (dd, *J* = 1.5, 12.5 Hz; 1H, 6″-H_a), 4.26 (dd, *J* = 4.5, 12.5 Hz; 1H, 6″-H_b), 4,48 (dd, *J* = 4.5, 10.5 Hz; 1H, 2-H_a), 4.61 (dd, *J* = 2.5, 10.5 Hz; 1H 2-H_b), 5.17 (m; 2H, 1″-H, 2″-H), 5.28 (m; 2H, 3″-H, 4″-H), 6.74/6.75 (dd, *J* = 2.5, 8.0 Hz; 1H, 5–H), 6.84 (s; 1H, 4′-H), 6.96/6.99 (s; 1H, 3′-H), 7.17/7.18 (d, *J* = 8.0 Hz; 1H, 4-H), 8.09/8.14 (s_b; 1H, 7-H), 9.43/10.23 (s_b; 1H, indole NH); ^{13}C NMR (125 MHz, $CDCl_3$):[11] δ 20.21, 20.47, 20.54/20,59, 20.61/20.63, (Ac–CH_3), 42.89/43.85 (C-3), 53.19/54.22 (C-2), 56.29/56.32 (OCH_3), 60.96/61.57 (C-6″), 61.04/61.08 (OCH_3), 61.52/61.69 (OCH_3), 64.75/64.92 (C-8), 67.40/67.97 (C-4″), 70.85/71.06 (C-3″), 71.29/71.81 (C-2″), 72.86 (C-5″), 97.82/98.14 (C-4′), 98.49/98.82 (C-1″), 105.3/106.3 (C-7), 106.7/106.9 (C-3′),

113.4/113.6 (C-5), 123.4/123.6 (C-3a′), 124.5/124.7 (C-4), 125.7 (C-7a′), 126.3/126.5 (C-3a), 130.0/130.4 (C-2′), 138.6/138.8 (C-7′), 140.7/141.3 (C-6′), 144.7/145.1 (C-7a), 150.1 (C-5′), 157.0 (C-6), 160.6/161.2 (NCO), 169.0/169.3, 169.4, 170.1/170.2, 171.1/172.0 (Ac–CO); MS (70 eV, DCI): *m*/*z* (%) 746.4 (100) $[M+NH_4]^+$, 729.4 (25) $[M+H]^+$, 704.4 (20) $[M-OAc]^+$.

[(3*R*/*S*)-3-Hydroxymethyl-1-(5,6,7-trimethoxyindol-2-yl-carbonyl)-2,3-dihydro-1*H*-indol-6-yl]-2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosid (18c). To a solution of mannoside **16c** (572 mg, 0.59 mmol) in tetrahydrofuran (20 mL) was added tetrabutylammonium fluoride on silica gel (1.1 mmol/1 g, 1.14 g, 1.20 mmol, 2.0 equiv) at 0 °C. The reaction mixture was stirred at rt for 2 h. After removal of the solvents in vacuo the residue was purified by column chromatography (PE/EtOAc = 1:1) to yield **18c** (268 mg, 0.37 mmol, 62%) as a colorless foam. R_f = 0.19 (PE/EtOAc = 1:2); IR (pellet): $\tilde{\nu}$ = 3466 (OH), 2938 (aliphat. C–H), 1752 (C=O, ester), 1630 (C=O, amide), 1602, 1490 (C=C), 1526 (NCO), 1468, 1440, 1412, 1372 (CH_3), 1230, 1162, 1110, 1084 (C–O), 950, 870 cm^{-1} (1,3,4-trisubst.); UV–vis (CH_3CN): λ_{max} (lg ε) = 207.5 (4.624), 321.0 nm (4.479); ^{1}H NMR (300 MHz, $CDCl_3$):[11] δ 2.03, 2.04, 2.06, 2.20 (s; each 3H, Ac–CH_3), 3.66 (m_c; 1H, 3-H), 3.78 (m_c; 1H, 8-H_a), 3.80 (m_c; 1H, 8-H_b), 3.90 (s; 3H, OCH_3), 3.94 (s; 3H, OCH_3), 4.07 (s; 3H, OCH_3), 4.08 (m_c; 1H, 6″-H_a), 4.13 (m_c; 1H, 5″-H), 4.30 (dd, *J* = 4.5, 12.5 Hz; 1H, 6″-H_b), 4,49 (m; 1H, 2-H_a), 4.61 (m; 1H 2-H_b), 5.39 (t, *J* = 10.0 Hz; 1H, 4″-H), 5.45 (dd, *J* = 2.0, 3.5 Hz; 1H, 2″-H), 5.57 (m; 2H, 1″-H, 3″-H), 6.79/6.81 (dd, *J* = 2.5, 8.0 Hz; 1H, 5-H), 6.83 (s; 1H, 4′-H), 6.96 (d, *J* = 2.0 Hz; 1H, 3′-H), 7.18 (d, *J* = 8.0 Hz; 1H, 4-H), 8.17 (d, *J* = 2.5 Hz; 1H, 7-H), 9.42 (s_b; 1H, indole NH); ^{13}C NMR (75 MHz, $CDCl_3$):[11] δ 20.61, 20.66, 20.84, 21.01 (Ac–CH_3), 42.74/43.82 (C-3), 53.66/53.69 (C-2), 56.20 (OCH_3), 61.06 (OCH_3), 61.42 (OCH_3), 62.12 (C-6″), 65.06/65.14 (C-8), 65.95 (C-4″), 66.86 (C-3″), 69.01 (C-2″), 69.34 (C-5″), 95.71 (C-4′), 97.57 (C-1″), 106.4 (C-3′), 107.1 (C-7), 112.1/112.2 (C-5), 123.6 (C-3a′), 124.4/124.5 (C-4), 125.4 (C-3a), 126.1 (C-7a′), 129.8 (C-2′), 136.8 (C-7′), 140.4 (C-6′), 145.1/145.2 (C-7a), 150.0 (C-5′), 155.8 (C-6), 160.1 (NCO), 169.7, 169.9, 170.0, 170.6 (Ac–CO); MS (70 eV, DCI): *m*/*z* (%) 746.6 (100) $[M+NH_4]^+$, 729.6 (25) $[M+H]^+$.

[(3*R*/*S*)-3-Chloromethyl-1-(5,6,7-trimethoxyindol-2-yl-carbonyl)-2,3-dihydro-1*H*-indol-6-yl)-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (19a). The primary alcohol **18a** (122 mg, 0.167 mmol) was dissolved in a mixture of dichloromethane (2 mL) and tetrachloromethane (5 mL), and triphenylphosphane (101 mg, 0.501 mmol, 3.0 equiv) was added. After stirring for 8 h at 50 °C the solvents were removed in vacuo and the residue was purified by column chromatography (PE/EtOAc = 1:1) to afford **19a** (103 mg, 0.138 mmol, 82%) as a white solid. R_f = 0.30 (PE/EtOAc = 1:1); IR (pellet): $\tilde{\nu}$ = 3460 (NH), 2992, 2936, 2836 (aliphat. C–H), 1728 (C=O, ester), 1624 (C=O, amide), 1598, 1492 (C=C), 1526 (NCO), 1464, 1442, 1412, 1388 (CH_3), 1234, 1196, 1176, 1110, 1084 (C–O), 946, 826 (1,3,4-trisubst.), 748 cm^{-1}(Cl); UV–vis (CH_3CN): λ_{max} (lg ε) = 207.0 (4.898), 321.5 nm (4.649); ^{1}H NMR (300 MHz, $CDCl_3$):[11] δ 1.94, 1.96/1.99, 2.01/2.02, 2.11 (s; each 3H, Ac–CH_3), 3.50 (m_c; 1H, 3-H), 3.74 (m; 2H, 8-H_2), 3.83 (s; 3H, OCH_3), 3.87 (s; 3H, OCH_3), 4.01 (s; 3H, OCH_3), 4.04 (m_c; 1H, 5″-H), 4.12 (dd, *J* = 1.0, 6.0 Hz; 2H, 6″-H_2), 4.41 (dt, *J* = 5.0, 6.0 Hz; 1H, 2-H_a), 4.54 (dt, *J* = 5.0, 10.0 Hz; 1H, 2-H_b), 5.05 (m; 2H, 1″-H, 2″-H), 5.40 (d, *J* = 3.5 Hz; 1H, 4″-H), 5.43 (dd, *J* = 8.0, 10.5 Hz; 1H, 3″-H), 6.70 (dd, *J* = 2.5, 8.0 Hz; 1H, 5-H), 6.80 (s; 1H, 4′-H), 6.83 (d, *J* = 1.5, Hz; 1H, 3′-H), 7.10 (d, *J* = 8.0 Hz; 1H, 4-H), 8.00 (d, *J* = 2.5 Hz; 1H, 7-H), 9.31 (s_b; 1H, indole NH); ^{13}C NMR (75 MHz, $CDCl_3$):[11] δ 20.58, 20.65, 20.77 (Ac–CH_3), 43.03 (C-3), 46.95 (C-2), 54.77 (C-6″), 56.28 (OCH_3), 61.12 (OCH_3), 61.35 (C-8), 61.47 (OCH_3), 66.93 (C-4″), 68.62 (C-3″), 70.87 (C-2″), 71.14 (C-5″), 97.62 (C-4′), 99.64/99.74 (C-1″), 106.5 (C-3′), 106.8/107.1 (C-7), 113.4/113.5 (C-5), 123.6 (C-3a′), 124.5/124.6 (C–4), 125.6 (C-3a), 125.7/125.8 (C-7a′), 129.6 (C-2′), 133.0 (C-1″), 139.0 (C-7′), 140.5 (C-6′), 144.9 (C-7a), 150.3 (C-5′), 157.6 (C-6), 160.2 (NCO), 169.4, 170.1, 170.3, 170.4 (Ac–CO); MS (70 eV, DCI): *m*/*z* (%) 764.4 (100) $[M+NH_4]^+$, 747.4 (45) $[M+H]^+$.

[(3*R*/*S*)-3-Chloromethyl-1-(5,6,7-trimethoxyindol-2-yl-carbonyl)-2,3-dihydro-1*H*-indol-6-yl]-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (19b). The primary alcohol **18b** (500 mg, 0.69 mmol) was dissolved in a mixture of dichloromethane (5 mL) and tetrachloromethane (25 mL), and triphenylphosphane (277 mg, 1.37 mmol, 2.0 equiv) was added. After stirring for 24 h at 50 °C the solvents were removed in vacuo and the residue was purified by column chromatography (PE/EtOAc = 1:1) to afford **19b** (475 mg, contaminated with triphenylphosphane) as a white solid. R_f = 0.25 (PE/EtOAc = 1:1); IR (pellet): $\tilde{\nu}$ = 3464 (NH), 3056 (aromat. C–H), 2936, 2854 (aliphat. C-H), 1756 (C=O, ester), 1628 (C=O, amide), 1594, 1492 (C=C), 1526 (NCO), 1468, 1440, 1386 (CH_3), 1232, 1114, 1068 (C–O), 960, 878 (1,3,4-trisubst.), 752 cm^{-1} (Cl); UV–vis (CH_3CN): λ_{max} (lg ε) = 195.0 (4.786), 265.0 (3.809), 320.0 nm (4.400); ^{1}H NMR (500 MHz, $CDCl_3$):[11] δ 2.03, 2.04, 2.07, 2.08 (s; each 3H, Ac–CH_3), 3.57 (dd, *J* = 8.5, 10.5 Hz; 1H, 8-H_a), 3.81 (dd, *J* = 4.5, 8.5 Hz; 1H, 8-H_b), 3.88 (m; 2H, 3-H, 5″-H), 3.91 (s; 3H, OCH_3), 3.95 (s; 3H, OCH_3), 4.08 (s; 3H, OCH_3), 4.18 (dd, *J* = 2.0, 12.5 Hz; 1H, 6″-H_a), 4.28 (dd, *J* = 5.0, 12.5 Hz; 1H, 6″-H_b), 4.48 (dd, *J* = 4.5, 10.5 Hz; 1H, 2-H_a), 4.66 (dd, *J* = 9.5, 10.5 Hz; 1H, 2-H_b), 5.17 (m; 2H, 1″-H, 2″-H), 5.29 (m; 1H, 3″-H, 4″-H), 6.76 (dd, *J* = 2.5, 8.0 Hz; 1H, 5-H), 6.87 (s; 1H, 4′-H), 6.96 (d, *J* = 2.0 Hz; 1H, 3′-H), 7.18 (d, *J* = 8.0 Hz; 1H, 4-H), 8.07 (s_b; 1H, 7-H), 9.42 (s_b; 1H, indole NH); ^{13}C NMR (75 MHz, $CDCl_3$):[11] δ 20.50, 20.60, 20.64, 21.04 (Ac–CH_3), 42.90/43.03 (C-3), 46.88/47.02 (C-2), 54.81/54.87 (C-6″), 56.25 (OCH_3), 61.08 (OCH_3), 61.45 (C-8), 61.54 (OCH_3), 67.94 (C-4″), 70.97 (C-3″), 71.86 (C-2″), 71.91 (C-5″), 97.72 (C-4′), 98.67 (C-1″), 106.2/106.3 (C-7), 106.6 (C-3′), 113.4 (C-5), 123.5/123.6 (C-3a′), 124.5/124.7 (C-4), 125.7/125.8 (C-7a′), 129.6 (C-3a), 133.2 (C-2′), 138.0 (C-7′), 140.7/140.8 (C-6′), 144.9 (C-7a), 150.2 (C-5′), 157.4 (C-6), 160.4 (NCO), 169.3, 170.1, 170.7, 171.1 (Ac–CO); MS (70 eV, DCI): *m*/*z* (%) 764.4 (100) $[M+NH_4]^+$, 747.4 (10) $[M+H]^+$.

[(3*R*/*S*)-3-Chloromethyl-1-(5,6,7-trimethoxyindol-2-ylcarbonyl)-2,3-dihydro-1*H*-indol-6-yl]-2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (19c). The primary alcohol **18c** (200 mg, 0.28 mmol) was dissolved in a mixture of dichloromethane (2 mL) and tetrachloromethane (10 mL), and triphenylphosphane (112 mg, 0.55 mmol, 2.0 equiv) was added. After stirring for 8 h at 50 °C the solvents were removed in vacuo and the residue was purified by column chromatography (PE/EtOAc = 1:1) to afford **19c** (202 mg, 0.27 mmol, 98%) as a white solid. R_f = 0.29 (PE/EtOAc = 1:1); IR (pellet): $\tilde{\nu}$ = 3466 (NH), 2940 (aliphat. C–H), 1752 (C=O, ester), 1630 (C=O, amide), 1604, 1490 (C=C), 1526 (NCO), 1468, 1442, 1412, 1388 (CH_3), 1232, 1126, 1110, 1084 (C–O), 944, 870 (1,3,4-trisubst.), 750 cm^{-1} (Cl); UV–vis (CH_3CN): λ_{max} (lg ε) = 207.0 (4.612), 319.5 nm (4.407); ^{1}H NMR (300 MHz, $CDCl_3$):[11] δ 2.00/2.01, 2.02, 2.04, 2.18, (s; each 3H, Ac–CH_3), 3.54 (m_c; 1H, 3-H), 3.80 (m_c; 2H, 8-H_2), 3.88 (s; 3H, OCH_3), 3.91 (s; 3H, OCH_3), 4.03 (m_c; 1H, 6″-H_a), 4.04 (s; 3H, OCH_3), 4.10 (m_c; 1H, 5″-H), 4.27 (dd, J = 4.5, 12.5 Hz; 1H, 6″-H_b), 4,45 (m; 1H, 2-H_a), 4.63 (m; 1H 2-H_b), 5.27 (t, J = 10.0 Hz; 1H, 4″-H), 5.42 (dd, J = 2.0, 3.5 Hz; 1H, 2″-H), 5.54 (m; 2H, 1″-H, 3″-H), 6.81 (dd, J = 2.5, 8.0 Hz; 1H, 5-H), 6.83 (s; 1H, 4′-H), 6.92 (d, J = 2.0 Hz; 1H, 3′-H), 7.15 (d, J = 8.0 Hz; 1H, 4-H), 8.14 (s_b; 1H, 7-H), 9.39 (s_b; 1H, indole NH); ^{13}C NMR (75 MHz, $CDCl_3$):[11] δ 20.56, 20.59, 20.76, 20.93 (Ac–CH_3), 42.93 (C-3), 46.66 (C-2), 54.59 (C-6″), 56.13 (OCH_3), 61.02 (OCH_3), 61.35 (OCH_3), 62.04 (C-8), 65.87 (C-4″), 68.74 (C-3″), 69.02 (C-2″), 69.24 (C-5″), 95.79/95.64 (C-4′), 97.51 (C-1″), 106.4 (C-3′), 107.0/107.1 (C-7), 112.2/112.3 (C-5), 123.5 (C-3a′), 124.5 (C-3a), 125.2/125.5 (C-4), 126.9 (C-7a′), 129.5 (C-2′), 136.8 (C-7′), 140.5 (C-6′), 144.8/144.9 (C-7a), 150.0 (C-5′), 156.1 (C-6), 160.1 (NCO), 169.6, 169.8, 169.9, 170.5 (Ac–CO); MS (70 eV, DCI): m/z (%) 764.4 (100) $[M + NH_4]^+$.

[(3*R*/*S*)-3-Chloromethyl-1-(5,6,7-trimethoxyindol-2-ylcarbonyl)-2,3-dihydro-1*H*-indol-6-yl]-β-D-galactopyranoside (17a). Galactoside **19a** (93 mg, 0.13 mmol) was dissolved in methanol (2 mL) and treated with a solution of sodium methoxide in methanol (5.4 M, 5 μL, 0.025 mmol, 0.2 equiv). The mixture was stirred for 2 h at rt before methanol (2 mL) was added, and the solution was neutralized with acidic duolite. Evaporation and purification by column chromatography (EtOAc/MeOH = 12:1) afforded **17a** (69 mg, 0.12 mmol, 95%) as a white powder. R_f = 0.48 (EtOAc/MeOH = 12:1); IR (pellet): $\tilde{\nu}$ = 3420 (OH), 2936 (aliphat. C–H), 1628 (C=O, amide), 1526 (NCO), 1492 (C=C), 1466, 1442, 1414, 1392 (CH_3), 1236, 1196, 1106, 1076 (C–O), 950, 868 (1,3,4-trisubst.), 750 cm^{-1} (Cl); UV–vis (CH_3CN): λ_{max} (lg ε) = 207.0 (4.596), 320.0 nm (4.421); ^{1}H NMR (300 MHz, CD_3OD):[11] δ 3.39–3.76 (m; 9H, 3-H, 8-H_2, 2″-H, 3″-H, 4″-H, 5″-H, 6″-H), 3.76/3.77 (s; 3H, OCH_3), 3.78 (s; 3H, OCH_3), 3.93 (s; 3H, OCH_3), 4.29 (m_c; 1H, 2-H_a), 4.50 (m_c; 1H, 2-H_b), 4.69 (m_c; 1H, 1″-H), 6.75/6.76 (dd, J = 2.5, 8.0 Hz; 1H, 5-H), 6.86/6.87 (s; 1H, 4′-H), 6.90/6.91 (s; 1H, 3′-H), 7.16 (d, J = 8.0 Hz; 1H, 4-H), 7.72 (s_b; 1H, 7-H); ^{13}C NMR (125 MHz, CD_3OD):[11] δ 43.67 (C-3), 56.20 (C-2), 56.74 (OCH_3), 61.72 (OCH_3), 61.88 (OCH_3), 62.39 (C-6″, C-8), 70.41 (C-4″), 72.21 (C-3″), 74.81 (C-2″), 76.75 (C-5″), 99.26 (C-4′), 102.9 (C-1″), 107.7 (C-7), 108.1 (C-3′), 113.6/113.7 (C-5), 125.1 (C-3a′), 125.8 (C-4), 126.7 (C-7a′), 127.0 (C-3a), 131.4 (C-2′), 140.2 (C-7′), 141.5 (C-6′), 145.6/145.7 (C-7a), 151.0 (C-5′), 159.3 (C-6), 162.3 (NCO); MS (70 eV, DCI): m/z (%) 596.3 (100) $[M + NH_4]^+$, 560.3 (50) $[M + 2H]^+$.

[(3*R*/*S*)-3-Chloromethyl-1-(5,6,7-trimethoxyindol-2-ylcarbonyl)-2,3-dihydro-1*H*-indol-6-yl]-β-D-glucopyranoside (17b). Glucoside **19b** (475 mg, max. 0.63 mmol, slightly contaminated with triphenylphosphane) was dissolved in methanol (10 mL) and treated with a solution of sodium methoxide in methanol (5.4 M, 22 μL, 0.12 mmol, 0.2 equiv). The mixture was stirred for 2 h at rt before methanol (10 mL) was added, and the solution was neutralized with acidic duolite. Evaporation and purification by column chromatography (EtOAc/MeOH = 12:1) afforded **17b** (209 mg, 0.36 mmol, 60% from **18b**) as a white powder. R_f = 0.59 (EtOAc/MeOH = 12:1); IR (pellet): $\tilde{\nu}$ = 3404 (OH), 3060 (aromat. C–H), 2928 (aliphat. C–H), 1628 (C=O, amide), 1602, 1490 (C=C), 1526 (NCO), 1464, 1440, 1414, 1390 (CH_3), 1308 (OH), 1236, 1192, 1116, 1074 (C–O), 904, 826 (1,3,4-trisubst.), 750 cm^{-1} (Cl); UV–vis (CH_3CN): λ_{max} (lg ε) = 195.0 (4.773), 265.5 (3.690), 320.0 (4.250), 272.5 nm (3.721); ^{1}H NMR (300 MHz, DMSO-d_6):[11] δ 3.13–3.25 (m; 4H, 3-H, 2″-H, 3″-H, 4″-H), 3.49 (m_c; 1H, 8-H_a), 3.65 (m_c; 1H, 8-H_b), 3.78 (s; 3H, OCH_3), 3.79 (s; 3H, OCH_3), 3.81 (m; 2H, 6″-H_2), 3.92 (s; 3H, OCH_3), 3.94 (m; 1H, 5″-H), 4.27 (m_c; 1H, 2-H_a), 4.58 (m_c; 1H, 2-H_b), 5.74 (m_c; 1H, 1″-H), 6.76/6.77 (dd, J = 2.5, 8.0 Hz; 1H, 5-H), 6.93 (s; 1H, 4′-H), 6.98 (d, J = 2.0 Hz; 1H, 3′-H), 7.31 (d, J = 8.0 Hz; 1H, 4-H), 7.71 (s_b; 1H, 7-H); ^{13}C NMR (125 MHz, CD_3OD):[11] δ 43.66 (C-3), 56.07/56.18 (C-2), 56.67/56.69 (OCH_3), 61.72 (OCH_3), 61.88 (OCH_3), 62.48 (C6″, C-8), 71.13 (C-4″, C-3″), 74.81 (C-2″), 77.90 (C-5″), 99.18 (C-4′), 102.3 (C-1″), 107.7 (C-7), 108.1 (C-3′), 113.5/113.6 (C-5), 125.0 (C-3a′), 125.8/125.9 (C-4), 127.0 (C-7a′), 127.1/127.2 (C-3a), 131.4 (C-2′), 140.2 (C-7′), 141.5 (C-6′), 145.6/145.7 (C-7a), 151.0 (C-5′), 159.2 (C-6), 162.3 (NCO); MS (70 eV, DCI): m/z (%) 596.5 (100) $[M + NH_4]^+$, 560.5 (50) $[M + 2H]^+$, 180.1 (65) $[Glc]^+$.

[(3*R*/*S*)-3-Chloromethyl-1-(5′,6′,7′-trimethoxyindol-2′-ylcarbonyl)-2,3-dihydro-1*H*-indol-6-yl]-α-D-mannopyranoside (17c). Mannoside **19c** (151 mg, 0.20 mmol) was dissolved in methanol (5 mL) and treated with a solution of sodium methoxide in methanol (5.4 M, 8 μL, 0.04 mmol, 0.2 equiv). The mixture was stirred for 2 h at rt before methanol (5 mL) was added, and the solution was neutralized with acidic duolite. Evaporation and purification by column chromatography (EtOAc/MeOH = 12:1) afforded **17c** (116 mg, 0.20 mmol, 99%) as a white powder. R_f = 0.52 (EtOAc/MeOH = 12:1); IR (pellet): $\tilde{\nu}$ = 3422 (OH), 2936, 2840 (aliphat. C–H), 1628 (C=O, amide), 1528 (NCO), 1492 (C=C), 1466, 1442, 1414, 1392 (CH_3), 1308 (OH), 1236, 1196, 1110, 1086 (C–O), 912, 824 (1,3,4-trisubst.), 750 cm^{-1} (Cl); UV–vis (CH_3CN): λ_{max} (lg ε) = 207.0 (4.400), 320.5 nm (4.365); ^{1}H NMR (500 MHz, CD_3OD):[11] δ 3.58–3.68 (m_c; 2H, 3-H, 8-H_a), 3.71–3.80 (m_c; 4H, 8-H_b, 6″-H_2, 5″-H), 3.84

(s; 3H, OCH_3), 3.85 (m; 1H, 4″-H), 3.86 (s; 3H, OCH_3), 3.90 (dd, $J=2.0$, 10.0 Hz; 1H, 3″-H), 4.00 (m; 1H, 2″-H), 4.35 (m_c; 1H, 2-H_a), 4.56 (m_c; 1H, 2-H_b), 5.47 (d, $J=1.5$ Hz; 1H, 1″-H), 6.86 (dd, $J=1.5$, 8.0 Hz; 1H, 5-H), 6.90 (s; 1H, 4′-H), 6.97 (s; 1H, 3′-H), 7.24 (d, $J=8.0$ Hz; 1H, 4-H), 7.91 (s_b; 1H, 7-H); ^{13}C NMR (125 MHz, CD_3OD): δ 43.67 (C-3), 56.20 (C-2), 56.74 (OCH_3), 61.72 (OCH_3), 61.88 (OCH_3), 62.39 (C-6″, C-8), 70.41 (C-4″), 72.21 (C-3″), 74.81 (C-2″), 76.75 (C-5″), 99.26 (C-4′), 102.9 (C-1″), 107.7 (C-7), 108.1 (C-3′), 113.6/113.7 (C-5), 125.1 (C-3a′), 125.8 (C-4), 126.7 (C-7a′), 127.0 (C-3a), 131.4 (C-2′), 140.2 (C-7′), 141.5 (C-6′), 145.6/145.7 (C-7a), 151.0 (C-5′), 159.3 (C-6), 162.3 (NCO); MS (70 eV, DCI): *m/z* (%) 596.3 (100) $[M+NH_4]^+$, 560.3 (50) $[M+2H]^+$.

Cell culture

Human bronchial carcinoma cells of line A549 (ATCC CCL 185) were kindly provided by the Institut für Zellbiologie, Universität Essen, and were maintained as exponentially growing cultures at 37 °C and 7.5% CO_2 in air in DMEM (Dulbecco's modified Eagle's medium, Biochrom, Berlin, Germany) supplemented with 10% fetal calf serum (heat-inactivated for 30 min at 56 °C, GibcoBRL, Karlsruhe, Germany), 44 mM $NaHCO_3$ (Biochrom, Berlin, Germany) and 4 mM L-Glutamine (GibcoBRL, Karlsruhe, Germany).

Drug exposure and plating

Adherent cells of line A549 were sown in triplicate in six multiwell plates at concentrations of 10^2, 10^3, 10^4, and 10^5 cells per cavity. Culture medium was sucked off after 24 h and cells were washed in the incubation medium Ultraculture (UC, serum-free special medium, purchased from BioWhittaker Europe, Verviers, Belgium). Incubation with test compounds was then performed in Ultraculture medium at various concentrations for 24 h. All substances were used as freshly prepared solutions in DMSO (Merck, Darmstadt, Germany) diluted with incubation medium to a final concentration of DMSO of 1% in the wells. After 24 h of exposure, the test substance was removed and the cells were washed with fresh medium. Cultivation was done at 37 °C and 7.5% CO_2 in air for 12 days. The medium was removed and the clones were dried and stained with Löffler's methylene blue (Merck, Darmstadt, Germany). They were then counted macroscopically.

The relative clone forming rate was determined according to the following formula:

$$\text{relative clone forming rate (\%)} = \frac{\text{number of clones counted after exposure}}{\text{number of clones counted in the control}} \times 100$$

Liberation of the drugs from their glycosidic prodrugs was achieved by addition of 0.4 U/mL β-D-galactosidase (EC 3.2.1.23, Grade X), β-D-glucosidase (EC 3.2.1.21) or α-D-mannosidase (EC 3.2.1.25) (all purchased from Sigma Germany, Deisenhofen, Germany) to the cells during incubation with the substances.

Results are presented as means of at least three separate experiments.

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11. Compounds **16**–**19** were obtained as mixtures of diastereomers. The NMR spectroscopical data refer to these mixtures.