Highly Selective Glycosylated Prodrugs of Cytostatic CC-1065 Analogues for Antibody-Directed Enzyme Tumor Therapy

Lutz F. Tietze,* Tobias Herzig, Anja Fecher, Frank Haunert, and Ingrid Schuberth[a]

*Novel prodrugs of the cytotoxic antibiotic CC-1065 for an antibody-directed enzyme prodrug therapy (ADEPT) were prepared that show an excellent selectivity with a high toxicity of the corresponding drug. In particular, the seco-CBI analogue of CC-1065, 1-chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benz[e]indole, as well as the novel methyl-seco-CBI analogue 1-(1′-chloroethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[e]indole, were synthesized and transformed into their galactosides **10a** and **10b**, respectively. These galactosides can be cleaved with β-D-galactosidase to give the free cytotoxic compounds. They were tested in in vitro cytotoxicity assays by using human bronchial carcinoma cells of line A549 in the presence and in the absence of β-D-galactosidase. While the seco-CBI prodrugs revealed only modest selectivity, prodrugs of the methyl-seco-CBI analogue bearing an* anti *orientation of the substituents at the two stereogenic centers of the N-heterocycle displayed an excellent selectivity with an ED_{50} quotient of about 750. The cytotoxicity of the corresponding phenol was rather high, with an ED_{50} of 1.3 nM. The diastereomer with a* syn *orientation at the stereogenic centers was much less toxic.*

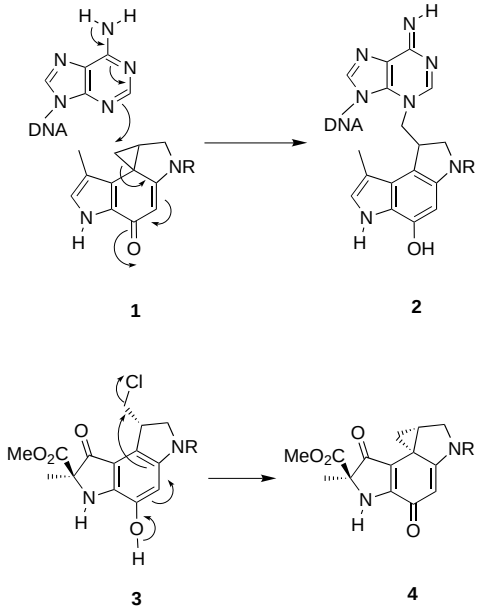
KEYWORDS:

ADEPT (antibody-directed enzyme prodrug therapy) · antitumor agents · glycosides · indoles · prodrugs

Introduction

Several promising approaches for a selective anticancer therapy exploit genetic and phenotypic differences between malignant and normal cells, such as the increased rate of glycolysis[1] and the expression of specific antigenes.[2] Based on the latter, the antibody-directed enzyme prodrug therapy (ADEPT)[2, 3] was developed which uses the transformation of prodrugs exhibiting little toxicity into a highly cytotoxic drug selectively at the surface of malignant cells. This chemical transformation is achieved by employing conjugates of enzymes cleaving the prodrug and monoclonal antibodies binding to tumor associated antigenes. However, the success of this concept depends on the difference in cytotoxicity between prodrug and drug as well as on a high biological activity of the drug.

Since the antibiotics CC-1065 and the duocarmycins are particularly potent cytotoxic compounds with an ED_{50} value of about 0.03 nM[4, 5] (ED_{50} = drug concentration required for 50% biological effect on target cells), they are suitable for this approach, providing that they can be reversibly detoxified. CC-1065 and also most of the duocarmycins contain a spirocyclopropylcyclohexadienone moiety as in **1** which reacts with N-3 of adenine to form an adduct with a covalent C–N bond (**2**) (Scheme 1). However, some natural seco compounds such as duocarmycin C_2 (**3**) are also known, which first undergo an intramolecular cyclization to build up the corresponding spirocyclopropane moiety as in **4** before reacting with the DNA. This process takes place quite fast even under physiological conditions, with a half-life of about 3.5 h in human plasma at 37 °C.[6]



Scheme 1. *Alkylation of DNA by CC-1065 and its analogues. Formation and opening of the cyclopropane ring are shown.*

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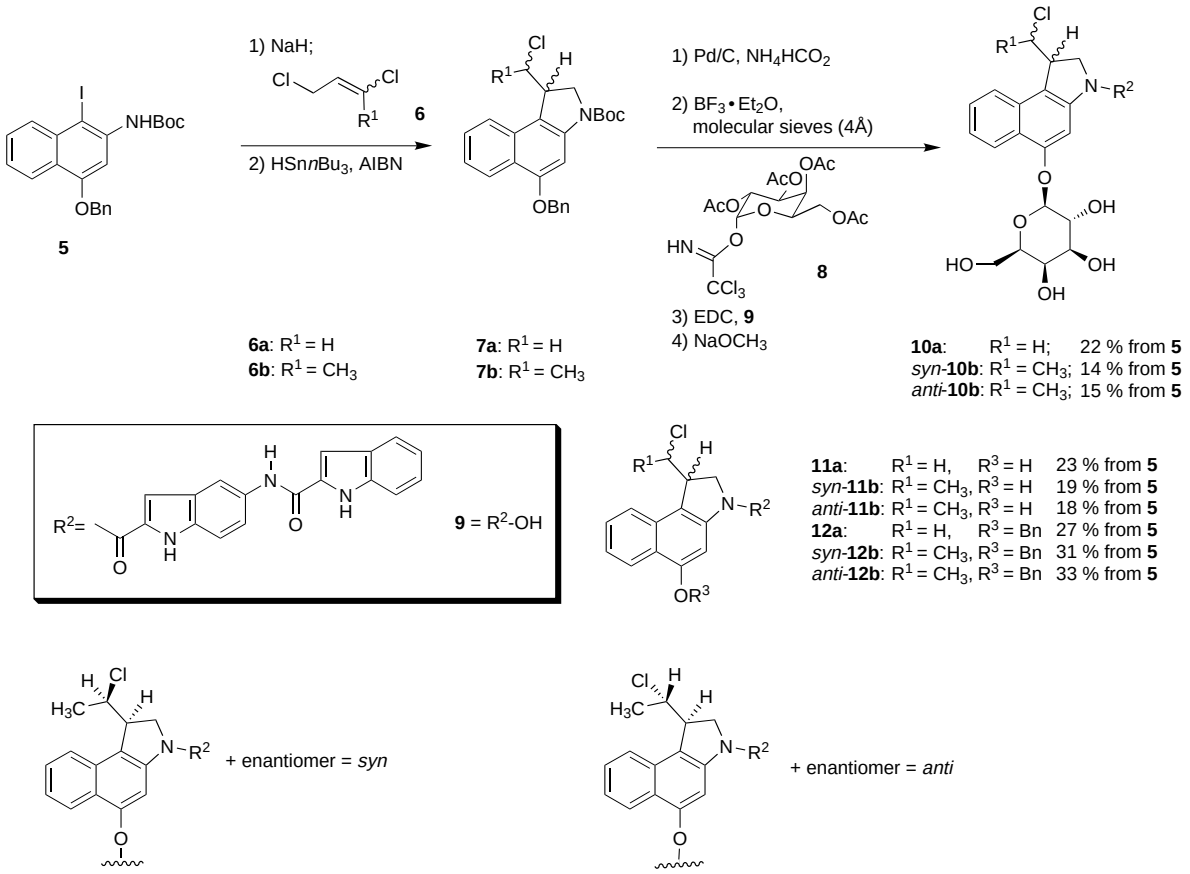
Our previous studies[7] and those of others[8] have demonstrated that the cytotoxicity of such a seco compound is significantly diminished by etherification of the phenolic hydroxy group since in this case the spirocyclopropane moiety cannot be formed. Based on these results, we developed prodrugs in which the phenolic hydroxy group is reversibly blocked by formation of a glycoside which can be cleaved by a glycohydrolase. Here we describe such glycosylated prodrugs of the novel methyl-seco-CBI analogue (1-(1′-chloroethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole) of CC-1065, which not only show an excellent selectivity, but also a high cytotoxicity of the corresponding drug. In addition, we have prepared a prodrug of seco-CBI (1-chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole) that displayed only a slightly diminished cytotoxicity compared to seco-CBI.

Results and Discussion

Synthesis of the prodrugs of seco-CBI and methyl-seco-CBI

N-Alkylation of the known iodonaphthylamine **5** with chloride **6a** and subsequent radical ring closure employing nBu$_3$SnH led to **7a**.[9] Hydrogenolytic cleavage of the benzylic ether moiety in **7a**, treatment of the resulting phenol with the trichloroacetimidate of tetraacetylgalactose (**8**)[10] in the presence of $BF_3 \cdot Et_2O$ followed by bisindolylcarboxylic acid (**9**)[11] in the presence of *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) in a one-pot procedure and removal of the acetyl groups by using sodium methoxide in methanol yielded **10a** in 22% overall yield based on **5**. In addition, **11a** and **12a** were prepared following standard protocols.[11]

For the synthesis of the novel methyl-seco-CBI and its prodrugs, **5** was alkylated with **6b** to give **7b** after radical cyclization. In the ring formation, two new stereogenic centers are formed, and since a facial differentiation does not occur, a 1:1 mixture of the two diastereomers *syn*-**7b** and *anti*-**7b** was obtained; they could easily be separated by chromatography on silica gel. Deprotection of *syn*-**7b** and *anti*-**7b** and treatment with **8** and **9** followed by solvolysis as described for **10a** afforded *syn*-**10b** and *anti*-**10b** in 14% and 15% yield, respectively, based on **5** (Scheme 2). In addition, the free phenolic and the benzyl-protected compounds *syn*- and *anti*-**11b** and **12b**, respectively, were also prepared; in the cytotoxicity tests the *syn* and *anti* diastereomers were used separately. In the reaction of **7a**, containing one stereogenic center, with the galactose derivative **8** as well as of *syn*-**7b** and *anti*-**7b**, containing two stereogenic centers, racemic mixtures were employed. Therefore, two diastereomers were formed in each case. An enantiomer differentiation did not take place since, as expected, a 1:1 mixture of **10a** as well as of *syn*-**10b** and *anti*-**10b** was obtained. A difference in the rate of the enzymatic hydrolysis of these compounds was not observed. Since the enantiomers of the free



Scheme 2. *Synthesis of the substrates for the in vitro cytotoxicity tests. AIBN = α,α′-azobisisobutyronitrile, EDC = N-ethyl-N′-(3-dimethylaminopropyl)carbodiimide hydrochloride.*

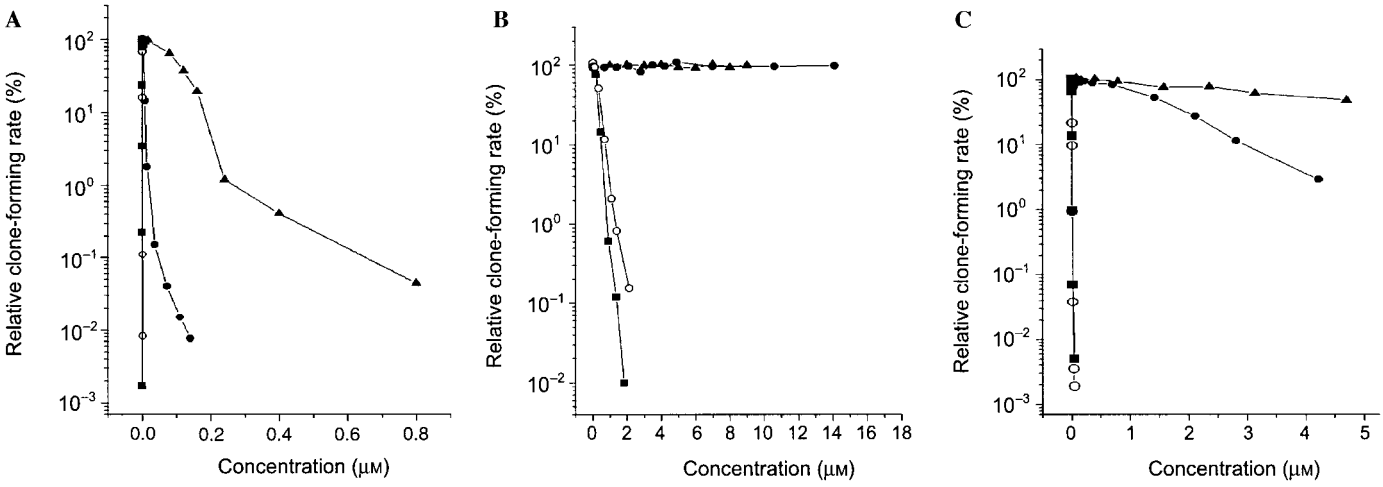


*Figure 1. In vitro cytotoxicity of **10** – **12** against human bronchial carcinoma cells of line A549. A) In vitro cytotoxicity of compounds **12a** (▲), **11a** (■), and **10a** without (●) and with (○) addition of β-D-galactosidase (0.4 U mL^{-1}). B) In vitro cytotoxicity of compounds* syn-***12b*** *(▲),* syn-***11b*** *(■), and* syn-***10b*** *without (●) and with (○) addition of β-D-galactosidase (0.4 U mL^{-1}). C) In vitro cytotoxicity of compounds* anti-***12b*** *(▲),* anti-***11b*** *(■), and* anti-***10b*** *without (●) and with (○) addition of β-D-galactosidase (0.4 U mL^{-1}). Cells were exposed to various concentrations of the test compounds for 24 h at 37 °C; after 12 days of incubation clone formation was compared to untreated control assays and the relative clone-forming rate was determined.*

drugs **11a**, as well as *syn*-**11b** and *anti*-**11b**, should have a similar cytotoxicity, as shown for the enantiomers of **1**, the biological tests were performed with the diastereomers.

In vitro cytotoxicity tests

In these tests, we employed the free phenolic compounds **11a** and **11b**, the benzylated compounds **12a** and **12b** as well as the glycosylated compounds **10a** and *syn*- and *anti*-**10b**. In addition, **10a** as well as *syn*- and *anti*-**10b** were also tested in the presence of β-D-galactosidase to confirm that they can be cleaved to give the cytotoxic phenols **11a** as well as *syn*- and *anti*-**11b**, and that a suicide mechanism does not occur. In such a case, the cytotoxicity of the prodrug in the presence of the enzyme and the cytotoxicity of the free phenolic drug would differ considerably. On the other hand, we expected the cytotoxicity of the benzylated phenols **12a** and **12b** and the glycosylated compounds **10a** and **10b** to be quite similar since in both cases formation of the spirocyclopropane moiety should be prohibited. Every single test was performed in triplicate, the accuracy of the results is therefore very high.

The seco-CBI derivative **11a** showed a very high cytotoxicity with an ED_{50} value of 0.06 nM (Figure 1 and Table 1) in our assay, which was in accordance with the results given in the literature.[4] In contrast, the benzyl analogue **12a** was less active by a factor of 1600. In the presence of the enzyme β-D-galactosidase, prodrug **10a** displayed a cytotoxicity of $ED_{50} = 0.15$ nM, which is close to that of the free phenol **11a** and thus indicates that the enzyme is not deactivated in the hydrolytic process. Quite unexpected, however, was the result that the cytotoxicity of the

Table 1. *In vitro cytotoxicity of compounds **10** – **12** against human bronchial carcinoma cells of line A549.*

Scaffold[a]	Substituent at the phenolic oxygen atom	Addition of β-D-galactosidase	ED_{50} [nM][b]	Specificity factor[c]
seco-N^3-bisindolyl-CBI	H (**11a**)	–	0.06	
	benzyl (**12a**)	–	100	
	β-D-galactose (**10a**)	–	4.8	32
	β-D-galactose (**10a**)	+	0.15	
syn-methyl-seco-N^3-bisindolyl-CBI	H (*syn*-**11b**)	–	280	
	benzyl (*syn*-**12b**)	–	> 11700	
	β-D-galactose (*syn*-**10b**)	–	> 14100	> 37
	β-D-galactose (*syn*-**10b**)	+	380	
anti-methyl-seco-N^3-bisindolyl-CBI	H (*anti*-**11b**)	–	1.3	
	benzyl (*anti*-**12b**)	–	4400	
	β-D-galactose (*anti*-**10b**)	–	1470	770
	β-D-galactose (*anti*-**10b**)	+	1.9	

[a] Compounds **10** – **12** were used as racemic mixtures with regard to their scaffolds. [b] Cells were exposed to the compounds for 24 h at 37 °C; after 12 days of incubation, clone formation was compared to that in untreated control assays. ED_{50} = drug concentration required for 50% biological effect on target cells. [c] Specificity factor = $\frac{ED_{50} \text{ in the absence of enzyme}}{ED_{50} \text{ in the presence of enzyme}}$.

prodrug **10a** was only slightly diminished in the absence of the enzyme, with an ED_{50} quotient of 32. The reason for the comparatively high cytotoxicity of the galactoside **10a** has not yet been understood completely. Since serum-free incubation medium was employed, any enzyme activity of the medium as observed in previous studies[7] with other media could be excluded. This phenomenon could therefore be explained by a nonenzymatic cleavage of the galactoside or by a direct alkylation of the DNA by the seco compound **10a** without formation of the spirocyclopropane moiety. However, this must be induced by the galactose moiety since the benzylated compound **12a** shows a rather low cytotoxicity.

In order to diminish the possibility of a direct alkylation of the DNA by reaction with a seco compound we have developed the seco-methyl-CBI analogues *syn*-**10b** and *anti*-**10b** of CC-1065. It was assumed that by introduction of a methyl group at the chloromethyl group as in **10b**, and thus a conversion of a primary into a secondary, sterically more hindered chloride, the intermolecular N-alkylation should be disfavored. This is indeed observable.

The two diastereomers of the methyl-seco-CBI analogue *syn*- and *anti*-**11b** showed a considerable difference in their biological activity: Compound *syn*-**11b** possesses only modest cytotoxicity with an $ED_{50} = 280$ nM, whereas a high cytotoxicity with $ED_{50} = 1.3$ nM was observed for *anti*-**11b**. The corresponding galactoside of *syn*-**11b**, *syn*-**10b**, was almost nontoxic in the investigated range of concentrations. Thus, an exact value of the ED_{50} quotient cannot be given. However, due to the low cytotoxicity of *syn*-**11b**, this prodrug would be less suitable for an application. In contrast, excellent results were obtained with the galactoside *anti*-**10b**. This compound displays a 770-fold lower cytotoxicity in the absence of β-D-galactosidase than in its presence, in which case the same degree of activity as found for the free drug **11b** was observed.

These results demonstrate that the galactoside *anti*-**10b** as a suitably modified derivative of the highly cytostatic CC-1065 is an excellent substrate for an application in ADEPT, since it possesses a pronounced difference in cytotoxicity in comparison with the corresponding free drug and a very high biological activity of the drug. Our continuing studies now focus on in vivo tests with conjugates of β-D-galactosidase and monoclonal antibodies.

Experimental Section

General: 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 & Co.). Silica gel 32 – 64 (0.032 – 0.064 mm) (Macherey-Nagel & Co.) was used for column chromatography.

UV/Vis spectra were recorded in CH_3CN on a Perkin – Elmer Lambda 2 or Lambda 9 spectrometer. IR spectra were recorded with the sample as a KBr pellet or as a film on a Bruker IFS 25 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-200, UNITY300 and INOVA-500 or a Bruker AM 300 with tetramethylsilane (TMS) as the internal standard in [D]chloroform, [D_6]acetone, [D_6]DMSO, or [D_7]DMF. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured at 70 eV (EI) or 200 eV (DCI) on a Varian MAT311A, high-resolution mass spectra on a Varian MAT731 instrument. Melting points were determined on a Mettler FR61 and are uncorrected.

(1*R*/*S*)-5-Benzyloxy-3-(*tert*-butyloxycarbonyl)-1-chloromethyl-1,2-dihydro-3*H*-benz[*e*]indole (7a): Amine **5**[10] (200 mg, 422 μmol) was dissolved in DMF (5.0 mL) and treated with NaH (60% in oil, 40 mg, 1.00 mmol). After stirring at room temperature for 30 min, chloride **6a** (94 mg, 844 μmol) was added. The mixture was quenched with saturated aq. NH_4Cl after 12 h at room temperature. It was then extracted with EtOAc (3 ×), and the extracts were washed with water (5 ×) and brine and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (petroleum ether [PE]/EtOAc = 20:1). (*E*/*Z*)-2-Amino-4-benzyloxy-*N*-(*tert*-butyloxycarbonyl)-*N*-(3′-chloroprop-2′-enyl)-1-iodonaphthalene (230 mg, 419 μmol, 99%) was obtained as a yellow oil as a mixture of rotamers. $R_f = 0.34$, 0.39 (PE/EtOAc = 10:1); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.33$, 1.58 (s, 9H, Boc-CH_3), 3.72 – 4.34 (m, 1H, NC*H*H), 4.47 – 4.63 (m, 1H, NCH*H*), 5.26 (br s, 2H, OCH_2), 5.93 – 6.18 (m, 2H, C*H* = C*H*Cl), 6.65 – 6.79 (m, 1H, 3-H), 7.31 – 7.63 (m, 7H, 6-H, 7-H, Ph-H), 8.10, 8.22 (d, $J = 8.0$ Hz, each 1H, 5-H, 8-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.3$, 28.5 (CH_3), 46.0, 49.1, 70.3, 70.4 (all CH_2), 80.7, 95.0, 95.1 (all C), 107.1, 107.7, 120.6, 120.8, 122.5 (all CH), 125.5 (C), 126.3, 126.4, 127.3 (all CH), 128.1, 128.2, 128.5, 128.6, 128.7, 132.7 (all CH), 135.3, 136.3, 136.4, 142.4, 142.8, 153.7, 153.9, 155.3 (all C).

A solution of (*E*/*Z*)-2-amino-4-benzyloxy-*N*-(*tert*-butyloxycarbonyl)-*N*-(3′-chloroprop-2′-enyl)-1-iodonaphthalene (230 mg, 419 μmol) in toluene (7.0 mL) was degassed thoroughly and treated with *n*Bu_3SnH (0.13 mL, 469 μmol) and AIBN (7.0 mg, 43 μmol). After 2.5 h of stirring at 80 °C, the volatiles were removed in vacuo and the residue was dissolved in Et_2O. The solution was washed with 10% (w/v) aq KF and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the residue purified by flash chromatography (PE/EtOAc = 20:1). **7a** (147 mg, 347 μmol, 83%) was obtained as a white solid. $R_f = 0.47$ (PE/EtOAc = 10:1); m.p. 155 °C; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.62$ (s, 9H, Boc-CH_3), 3.44 (dd, 2 × $J = 11.0$ Hz, 1H, 10-H_a), 3.91 – 4.02 (m, 2H, 1-H, 10-H_b), 4.14 (dd, 2 × $J = 11.0$ Hz, 1H, 2-H_a), 4.29 (br d, $J = 11.0$ Hz, 2-H_b), 5.17 (s, 2H, OCH_2), 7.29 – 7.57 (m, 7H, 7-H, 8-H, Ph-H), 7.65 (d, $J = 8.0$ Hz, 1H, 9-H), 7.84 (br s, 1H, 4-H), 8.29 (d, $J = 8.0$ Hz, 1H, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.5$ (CH_3), 41.6 (CH), 46.5, 53.0, 70.3 (all CH_2), 81.2 (C), 96.4 (CH), 114.0, 122.4 (all C), 121.7, 123.1, 123.6, 127.5, 127.6, 128.0, 128.5 (all CH), 130.2, 136.7, 143.4, 152.6, 156.0 (C).

(1,10)-*syn*-5-Benzyloxy-3-(*tert*-butyloxycarbonyl)-1-(10-chloroethyl)-1,2-dihydro-3*H*-benz[*e*]indole (*syn*-7b) and (1,10)-*anti*-5-Benzyloxy-3-(*tert*-butyloxycarbonyl)-1-(10-chloroethyl)-1,2-dihydro-3*H*-benz[*e*]indole (*anti*-7b): Amine **5**[10] (2.00 g, 4.21 mmol) was dissolved in DMF (50 mL) and treated with NaH (60% in oil, 400 mg, 10.0 mmol). After stirring at room temperature for 30 min, chloride **6b** (1.37 g, 10.9 mol) was added. The mixture was quenched with sat. aq NH_4Cl after 2 h at room temperature. It was then extracted with EtOAc (3 ×), and the extracts were washed with water (5 ×) and brine and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the residue purified by flash chromatography (PE/EtOAc = 20:1). (*E*/*Z*)-2-Amino-4-benzyloxy-*N*-(*tert*-butyloxycarbonyl)-*N*-(3′-chlorobut-2′-enyl)-1-iodonaphthalene (2.32 g, 4.12 mmol, 98%) was obtained as a yellow oil as a mixture of rotamers. $R_f = 0.33$, 0.40 (PE/EtOAc = 10:1). ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.30/1.60$ (s, 9H, Boc-CH_3), 1.82/2.03 (s, 3H, C = CCH_3), 3.79 – 4.26 (m, 1H, NC*H*H), 4.47 – 4.60 (m, 1H, NCH*H*), 5.26 (br s, 2H, OCH_2), 5.72 – 5.86 (m, 1H, C*H* = CClMe), 6.68 – 6.80 (m, 1H, 3-H), 7.32 – 7.60 (m, 7H,

6-H, 7-H, Ph-H), 8.10, 8.22 (d, $J = 8.0$ Hz, each 1H, 5-H, 8-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 20.9$, 26.2, 28.3, 28.5 (all CH_3), 46.5, 47.8, 70.4, 70.5 (all CH_2), 80.5, 94.9, 95.2 (all C), 107.1, 107.8, 121.6, 122.8, 122.5 (2 signals) (all CH), 125.4 (C), 126.2, 126.3, 127.3, 128.1, 128.2, 128.5 (2 signals), 128.7 (2 signals), 132.7, 132.8 (all CH), 134.0, 135.3, 135.3, 136.3, 136.4, 142.5, 143.1, 153.7, 153.9, 155.2, 155.3 (all C); MS (EI, 70 eV): *m/z* (%): 563 (3) $[M]^+$, 436 (48) $[M-I]^+$, 380 (100) $[M-I-C_4H_9+H]^+$, 318 (68) $[M-I-C_4H_9-C_2H_3Cl+H]^+$; HR-MS: calcd for $C_{26}H_{27}ClINO_3$: 563.0683, found 563.0724.

A solution of (*E*/*Z*)-2-amino-4-benzyloxy-*N*-(*tert*-butyloxycarbonyl)-*N*-(3′-chlorobut-2′-enyl)-1-iodonaphthalene (578 mg, 1.02 mmol) in toluene (17 mL) was degassed thoroughly and treated with nBu$_3$SnH (0.35 mL, 1.26 mmol) and AIBN (43.0 mg, 264 μmol). After 3.5 h of stirring at 80 °C, the volatiles were removed in vacuo and the residue was dissolved in Et_2O. The solution was washed with 10% (w/v) aq KF, dried over Na_2SO_4, concentrated under reduced pressure, and the two diastereomers separated by flash chromatography (PE/EtOAc = 20:1) to give *syn*-**7b** (191 mg, 437 μmol, 43%) and *anti*-**7b** (187 mg, 427 μmol, 42%) as white solids.

syn-**7b**: $R_f = 0.51$ (PE/EtOAc = 10:1); m.p. 177 °C (dec.); UV (CH_3CN): λ_{max} (lgε) = 208.5 (4.376), 217.0 (4.315), 254.5 (4.796), 302.5 (3.933), 314.0 (4.022), 340.0 nm (3.523); IR (KBr): $\tilde{\nu} = 3444$, 2980, 1701, 1625, 1580, 1455, 1408, 1366, 1339, 1325, 1146, 760 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.16$ (d, $J = 6.8$ Hz, 3H, 11-CH_3), 1.60 (s, 9H, Boc-CH_3), 4.07 (dd, $J = 11.1$, 10.8 Hz, 1H, 2-H_a), 4.16 (dd, $J = 10.7$, 3.0 Hz, 1H, 1-H), 4.38 (br d, $J = 11.1$ Hz, 2-H_b), 4.69 (dq, $J = 3.2$, 6.8 Hz, 1H, 10-H), 5.27 (s, 2H, OCH_2), 7.29 – 7.56 (m, 7H, 7-H, 8-H, Ph-H), 7.64 (d, $J = 8.2$ Hz, 1H, 9-H), 7.84 (br s, 1H, 4-H), 8.29 (d, $J = 8.0$ Hz, 1H, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 17.9$, 28.5 (all CH_3), 46.0 (CH), 49.4, 58.2, 70.3 (all CH_2), 81.1 (C), 96.5 (CH), 115.6, 122.4 (all C), 121.9, 123.1, 123.6, 127.6, 128.0, 128.5 (all CH), 130.2, 136.8, 141.9, 152.3, 156.0 (all C); MS (DCI, 200 eV): *m/z* (%): 455 (29) $[M+NH_4]^+$, 438 (10) $[M+H]^+$, 394 (27) $[M-C_2H_4Cl+H]^+$, 318 (31) $[M-C_2H_4Cl-C_4H_9+H]^+$; elemental analysis calcd (%) for $C_{26}H_{28}ClNO_3$ (437.970): C 71.30, H 6.44; found: C 71.16, H 6.38.

anti-**7b**: $R_f = 0.38$ (PE/EtOAc = 10:1); m.p. 169 °C (dec.); UV (CH_3CN): λ_{max} (lgε) = 207.0 (4.442), 217.5 (4.388), 255.0 (4.845), 302.5 (3.966), 314.0 (4.051), 341.0 nm (3.537); IR (KBr): $\tilde{\nu} = 3445$, 2977, 2928, 1698, 1626, 1580, 1455, 1410, 1367, 1338, 1272, 1147, 910, 846, 751 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.62$ (s, 9H, Boc-CH_3), 1.63 (d, $J = 6.8$ Hz, 3H, 11-CH_3), 3.86 (ddd, $J = 9.2$, 2 × 3.4 Hz, 1H, 1-H), 4.07 (dd, $J = 11.7$, 9.8 Hz, 1H, 2-H_a), 4.34 (br d, $J = 11.0$ Hz, 2-H_b), 4.60 (dq, $J = 3.7$, 6.4 Hz, 1H, 10-H), 5.27 (s, 2H, OCH_2), 7.28 – 7.50 (m, 5H, 7-H, 8-H, *m*-H, *p*-H), 7.56 (d, $J = 7.8$ Hz, 2H, *o*-H), 7.64 (d, $J = 8.0$ Hz, 1H, 9-H), 7.88 (br s, 1H, 4-H), 8.31 (d, $J = 8.0$ Hz, 1H, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 23.7$, 28.5 (CH_3), 46.0 (CH), 50.7, 60.2, 70.2 (all CH_2), 80.9 (C), 96.3 (CH), 115.2, 122.4 (all C), 122.1, 122.9, 123.6, 127.3, 127.6, 127.9, 128.5 (all CH), 130.4, 136.9, 142.0, 152.4, 155.8 (all C); MS (DCI, 200 eV): *m/z* (%): 455 (100) $[M+NH_4]^+$, 438 (66) $[M+H]^+$, 399 (56) $[M-C_4H_9+H]^+$.

(1*R*/*S*)-3-(*tert*-Butyloxycarbonyl)-1-chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (13a): A 25% (w/v) aq solution of NH_4HCO_2 (0.20 mL) as well as 10% Pd/C (19.6 mg, 18.4 μmol) were added to a solution of benzyl ether **7a** (41.4 mg, 97.7 μmol) in THF (1.5 mL) at 0 °C. After stirring for 4 h at 40 °C, the solid was removed by filtration through Celite, and the Celite was washed thoroughly with THF. The concentrated filtrate was purified by flash chromatography (PE/EtOAc = 5:1) to afford **13a** (29.2 mg, 87.4 μmol, 89%) as a white solid. $R_f = 0.23$ (PE/EtOAc = 10:1); m.p. 153 – 154 °C (dec.); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.62$ (s, 9H, Boc-CH_3), 3.41 (dd, 2 × $J = 11.0$ Hz, 10-H_a), 3.90 – 4.00 (m, 2H, 1-H, 10-H_b), 4.10 (dd, 2 × $J = 11.0$ Hz, 1H, 2-H_a), 4.26 (br d, $J = 11.0$ Hz, 2-H_b), 6.61 (br s, 1H, OH), 7.31 (dt, $J = 1.0$ Hz, 8.0 Hz, 7-H), 7.47 (dt, 1.0 Hz, 8.0 Hz, 1H, 8-H), 7.61 (d, $J = 8.0$ Hz, 1H, 9-H), 7.78 (br s, 1H, 4-H), 8.20 (d, $J = 8.0$ Hz, 1H, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.5$ (CH_3), 41.7 (CH), 46.5, 53.1 (all CH_2), 81.8 (C), 99.1 (CH), 114.0, 121.5 (all C), 121.7, 122.7, 123.6, 127.5 (all CH), 130.3, 141.1, 153.3, 154.1 (all C).

(1,10)-*syn*-3-(*tert*-Butyloxycarbonyl)-1-(10-chloroethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (*syn*-13b): A solution of benzyl ether *syn*-**7b** (148 mg, 338 μmol) in acetone (8.5 mL) was treated with 10% Pd/C (165 mg, 152 μmol) and NH_4HCO_2 (135 mg, 2.12 mmol). After stirring for 2 h at 40 °C, the solid was removed by filtration through Celite, the Celite was washed thoroughly with acetone, and the filtrate was concentrated. Flash chromatography (PE/EtOAc = 10:1) provided *syn*-**13b** (100 mg, 287 μmol, 85%) as a white solid. $R_f = 0.48$ (PE/EtOAc = 5:1); m.p. 190 – 192 °C (dec.); UV (CH_3CN): λ_{max} (lgε) = 209.5 (4.242), 220.5 (4.221), 255.0 (4.852), 304.0 (3.926), 315.0 (3.991), 342.0 (3.497); IR (KBr): $\tilde{\nu} = 3377$, 2976, 1680, 1629, 1589, 1419, 1346, 1231, 1146, 1040, 910, 856, 760 cm^{-1}; ^{1}H NMR (200 MHz, [D$_6$]acetone): $\delta = 1.09$ (d, $J = 7.4$ Hz, 3H, 11-CH_3), 1.60 (s, 9H, Boc-CH_3), 4.07 (dd, $J = 11.4$, 10.3 Hz, 1H, 2-H_a), 4.19 (dd, $J = 10.3$, 4.1 Hz, 1H, 1-H), 4.34 (d, $J = 11.5$ Hz, 2-H_b), 4.75 (dq, $J = 4.1$, 7.4 Hz, 1H, 10-H), 7.31 (dt, $J = 2.0$, 8.0 Hz, 1H, 7-H), 7.50 (dt, $J = 2.0$, 8.0 Hz, 1H, 8-H), 7.72 (br s, 1H, 4-H), 7.76 (d, $J = 8.0$ Hz, 1H, 9-H), 8.20 (d, $J = 8.0$ Hz, 1H, 6-H), 9.27 (br s, 1H, OH); ^{13}C NMR (50 MHz, [D$_6$]acetone): $\delta = 18.2$, 28.6 (all CH_3), 46.5 (CH), 50.6, 59.3 (all CH_2), 81.3 (C), 99.7 (CH), 114.6, 122.4 (all C), 123.1, 123.3, 124.2, 128.2 (all CH), 131.5, 142.7, 152.6, 155.4 (all C); MS (EI, 70 eV): *m/z* (%): 347 (16) $[M]^+$, 291 (15) $[M-C_4H_9+H]^+$, 228 (100) $[M-C_2H_4Cl-C_4H_9+H]^+$, 184 (29) $[M-Boc-C_2H_4Cl+H]^+$; elemental analysis calcd (%) for $C_{19}H_{22}ClNO_3$ (347.845): C 65.61, H 6.38, found: C 65.42, H 6.14.

(1,10)-*anti*-3-(*tert*-Butyloxycarbonyl)-1-(10-chloroethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (*anti*-13b): A solution of benzyl ether *anti*-**7b** (162 mg, 370 μmol) in acetone (10.0 mL) was treated with 10% Pd/C (178 mg, 167 μmol) and NH_4HCO_2 (146 mg, 2.32 mmol). After 2 h at 40 °C, the solid was removed by filtration through Celite, the Celite was washed thoroughly with acetone, and the filtrate was concentrated. Flash chromatography (PE/EtOAc = 10:1) provided *anti*-**13b** (103 mg, 296 μmol, 80%) as a white solid. $R_f = 0.37$ (PE/EtOAc = 5:1); m.p. 182 – 184 °C (dec.); UV (CH_3CN): λ_{max} (lgε) = 209.5 (4.242), 220.5 (4.221), 255.0 (4.852), 304.0 (3.926), 315.0 (3.991), 342.0 nm (3.497); IR (KBr): $\tilde{\nu} = 3377$, 2976, 1680, 1629, 1589, 1419, 1346, 1231, 1146, 1040, 910, 856, 760 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.62$ (s, 9H, Boc-CH_3), 1.63 (d, $J = 6.7$ Hz, 3H, 11-CH_3), 3.85 (ddd, $J = 9.2$, 2 × 3.4 Hz, 1H, 1-H), 4.06 (dd, $J = 11.7$, 9.8 Hz, 1H, 2-H_a), 4.31 (br d, $J = 11.0$ Hz, 2-H_b), 4.56 (dq, $J = 3.7$, 6.4 Hz, 1H, 10-H), 6.56 (br s, 1H, OH), 7.31 (dt, $J = 1.5$, 8.0 Hz, 1H, 7-H), 7.45 (t, $J = 8.0$ Hz, 1H, 8-H), 7.61 (d, $J = 8.0$ Hz, 1H, 9-H), 7.75 (br s, 1H, 4-H), 8.18 (d, $J = 8.0$ Hz, 1H, 6-H); ^{13}C NMR (50 MHz, [D$_6$]acetone): $\delta = 23.7$, 28.6 (all CH_3), 46.2 (CH), 50.7, 61.7 (all CH_2), 80.9 (C), 99.8 (CH), 114.8, 122.4 (all C), 123.0, 123.2, 124.2, 127.8 (all CH), 131.6, 142.0, 152.7, 155.1 (all C); MS (DCI, 200 eV): *m/z* (%): 365 (76) $[M+NH_4]^+$, 348 (65) $[M+H]^+$, 312 (53) $[M-HCl+H]^+$, 309 (100) $[M-C_4H_9+H]^+$; elemental analysis calcd (%) for $C_{19}H_{22}ClNO_3$ (347.845): C 65.61, H 6.38, found: C 65.58, H 6.25.

General procedure for the preparation of the β-D-galactoside prodrugs 10: The phenol was dissolved in dry CH_2Cl_2 (50 mL mmol^{-1}) and treated with molecular sieves (4 Å; 6.90 g mmol^{-1}) and 1.05 equiv of the tetraacetyl trichloroacetimidate **8**.[11] The mixture was stirred for 30 min at room temperature, and 7.7 equiv of $BF_3 \cdot OEt_2$ were added dropwise at −10 °C. Stirring was continued for 1 h at this temperature, then the mixture was allowed to reach room temperature and stirred for further 4.5 h. The solution was separated from the molecular sieves by a transfer cannula, and the molecular sieves were washed three times with CH_2Cl_2. The combined solutions were concentrated in vacuo, and the residue was thoroughly dried under vacuum (oil pump). It was then dissolved in dry degassed DMF

(17 mL mmol^{-1}) and treated with 2.2 equiv of EDC and 0.9 equiv of acid **9**.[10] After 18 h of stirring a small amount of silica gel was added, and the mixture was evaporated to dryness. Flash chromatography (PE/EtOAc = 2:1 → PE/EtOAc = 1:2 → PE/acetone/MeOH = 10:6:1) yielded the intermediate product which was dissolved in dry MeOH (40 mL mmol^{-1}) and treated with 2.0 equiv of a 5.4 M solution of NaOMe in MeOH. Water (20 mL mmol^{-1}) was added after 4 h of stirring, and the precipitate was collected by a glass frit and washed with water. Thorough drying provided **10**.

[(1*R*/*S*)-1-Chloromethyl-3-(5′-(1*H*-indol-2″-ylcarbonylamino)-1*H*-indol-2′-ylcarbonyl)-1,2-dihydro-3*H*-benz[*e*]indol-5-yl]-β-D-galactopyranoside (10a): Phenol **13a** (61 mg, 183 μmol) was treated with the tetraacetyl trichloroacetimidate **8** (95 mg, 192 μmol), $BF_3 \cdot OEt_2$ (0.19 mL, 1.41 mmol) and molecular sieves (4 Å, 1.26 g) according to the general procedure described above. EDC (105 mg, 549 μmol) and acid **9** (52 mg, 165 μmol) were added to the residue. The intermediate product obtained after chromatography (60 mg, 69 μmol) was treated with 5.4 M NaOMe/MeOH (26 μL, 138 μmol). **10a** (38 mg, 55 μmol, 30%) was obtained as a greyish powder as a mixture of diastereomers. R_f (intermediate product) = 0.63 (PE/EtOAc = 1:2); UV (CH_3CN): λ_{max} (lgε) = 207.0 (4.667), 301.5 nm (4.629); IR (KBr): $\tilde{\nu}$ = 3414, 3304, 2924, 1642, 1622, 1590, 1542, 1520, 1464, 1414, 1312, 1234, 1076, 748 cm^{-1}; ^{1}H NMR (500 MHz, [D$_7$]DMF): δ = 3.70 – 3.81 (m, 4H, OH), 4.00 – 4.06 (m, 2H, 6*-H), 4.03 (dd, J = 11.0, 7.5 Hz, 1H, 10-H$_a$), 4.16 (dd, J = 11.0, 2.5 Hz, 1H, 10-H$_b$), 4.38 (m$_c$, 1H, 1-H), 4.72 – 4.76 (m, 2H, 3*-H, 5*-H), 4.80 (dd, J = 10.4, 1.5 Hz, 1H, 2-H$_a$), 4.90 – 4.97 (m, 1H, 2*-H), 4.97 (dd, 2 × J = 10.0, 1H, 2-H$_b$), 5.13 (d, J = 8.0 Hz, 1H, 1*-H), 5.60 (d, J = 5.0 Hz, 1H, 4*-H), 7.11 (t, J = 7.9 Hz, 1H, 5″-H), 7.27 (t, J = 7.9 Hz, 1H, 6″-H), 7.31, 7.33 (s, total 1H, 3′-H), 7.44 (t, J = 8.1 Hz, 1H, 7-H), 7.54 (d, J = 1.0 Hz, 1H, 3″-H), 7.59 – 7.65 (m, 3H, 8-H, 7′-H, 7″-H), 7.71 (d, J = 8.0 Hz, 1H, 4″-H), 7.74 (d, J = 8.5 Hz, 1H, 6′-H), 8.00 (d, J = 8.0 Hz, 1H, 9-H), 8.43 (m$_c$, 3H, 4-H, 6-H, 4′-H), 10.31, 10.32 (s, 1H, CONH), 11.79 (br s, 1H, indole-NH), 11.85 (br s, 1H, indole-NH); ^{13}C NMR (125 MHz, [D$_7$]DMF): δ = 42.4, 42.7 (C-1), 48.0/48.1 (C-10), 56.0/56.1 (C-2), 61.4 (2 signals) (C-6*), 69.2/69.3 (C-4*), 71.9/72.0 (C-2*), 74.7/74.8 (C-3*), 76.5 (C-5*), 102.8/103.1 (C-1*), 103.4 (C-4), 103.9 (C-3″), 106.6 (2 signals) (C-3′), 113.0 (2 signals) (C-7′, C-7″), 113.5, 113.6 (C-4′), 118.9, 119.0 (C-9b), 119.9 (C-6′), 120.6 (C-5″), 122.4 (C-4″), 123.5, 124.1, 124.2 (2 signals), 124.3, 124.4 (C-5a, C-6, C-7, C-9, C-6″), 128.2 (2 signals) (C-8), 128.4, 128.5 (C-3a′, C-3a″), 130.7 (2 signals) (C-9a), 132.5 (2 signals) (C-2′), 133.1 (2 signals), 133.2 (C-5′, C-2″), 134.5 (2 signals) (C-7a′), 137.9 (C-7a″), 143.3 (C-3a), 155.0, 155.1 (C-5), 160.5 (CONH″), 161.3 (CONH′); MS (ESI): m/z (%): 1415 (32) [2M+Na]$^+$, 720 (100) [M+Na]$^+$; elemental analysis calcd (%) for $C_{37}H_{33}ClN_4O_8$ (697.087): C 63.79, H 4.78, found: C 63.48, H 4.97.

[(1,10)-*syn*-1-(10-Chloroethyl)-3-(5′-(1*H*-indol-2″-ylcarbonylamino)-1*H*-indol-2′-ylcarbonyl)-1,2-dihydro-3*H*-benz[*e*]indol-5-yl]-β-D-galactopyranoside (*syn*-10b): Phenol *syn*-**13b** (50 mg, 144 μmol) was treated with the tetraacetyl trichloroacetimidate **8** (74 mg, 148 μmol), $BF_3 \cdot OEt_2$ (146 μL, 1.11 mmol) and molecular sieves (4 Å, 1.00 g) according to the general procedure described above. EDC (62 mg, 320 μmol) and acid **9** (41 mg, 128 μmol) were added to the residue. The intermediate product obtained after chromatography (70 mg, 80 μmol) was treated with 5.4 M NaOMe/MeOH (36 μL, 160 μmol) to give *syn*-**10b** (19 mg, 27 μmol, 19%) as a greyish powder as a mixture of diastereomers. R_f (intermediate product) = 0.59 (PE/acetone/MeOH = 10:6:1); UV (CH_3CN): λ_{max} (lgε) = 207.5 (4.546), 301.5 nm (4.550); IR (KBr): $\tilde{\nu}$ = 3406, 3309, 2925, 1590, 1513, 1463, 1415, 1313, 1233, 1141, 1077, 807, 745 cm^{-1}; ^{1}H NMR (500 MHz, [D$_7$]DMF): δ = 1.18, 1.22 (d, J = 6.9 Hz, 3H, 11-CH$_3$), 3.68 – 3.89 (m, 4H, OH), 4.01 – 4.05 (m, 2H, 6*-H), 4.41 (m$_c$, 1H, 1-H), 4.62 – 4.66 (m, 2H, 3*-H, 5*-H), 4.86 – 4.92 (m, 4H, 2-CH$_2$, 10-H, 2*-H), 5.12 (d, J = 7.8 Hz, 1H, 1*-H), 5.52 (m$_c$, 1H, 4*-H), 7.11 (t, J = 8.0 Hz, 1H, 5″-H), 7.26 (t, J = 8.0 Hz, 1H, 6″-H), 7.33, 7.36 (s, 1H, 3′-H), 7.45 (t, J = 8.0 Hz, 1H, 7-H), 7.53 (s, 1H, 3″-H), 7.62 (t, J = 7.9 Hz, 1H, 8-H), 7.63 (d, J = 8.0 Hz, 1H, 7′-H), 7.65 (d, J = 8.0 Hz, 1H, 7″-H), 7.71 (d, J = 7.8 Hz, 1H, 4″-H), 7.74 (d, J = 8.0 Hz, 1H, 6′-H), 7.97, 7.99 (d, J = 8.0 Hz, 1H, 9-H), 8.38 (br s, 1H, 4-H), 8.40 – 8.44 (m, 2H, 6-H, 4′-H), 10.25 (s, 1H, CONH), 11.70 (s, 1H, indole-NH), 11.74, 11.80 (s, 1H, indole-NH); ^{13}C NMR (125 MHz, [D$_7$]DMF): δ = 18.7, 18.9 (C-11), 47.4, 47.6 (C-1), 53.7, 53.8 (C-2), 59.6, 59.7 (C-10), 61.4 (2 signals) (C-6*), 69.2, 69.3 (C-4*), 71.9, 72.0 (C-2*), 74.7, 74.8 (C-3*), 76.5 (C-5*), 102.8, 103.0 (C-1*), 103.4 (C-4), 103.9 (C-3″), 106.7, 106.8 (C-3′), 113.0 (2 signals) (C-7′, C-7″), 113.5, 113.6 (C-4′), 118.9, 119.0 (C-9b), 120.0 (C-6′), 120.6 (C-5″), 122.4 (C-4″), 123.8, 124.2 (2 signals), 124.3, 124.5, 124.6 (C-5a, C-6, C-7, C-9, C-6″), 128.3 (C-8), 128.3, 128.5 (C-3a′, C-3a″), 130.7 (2 signals) (C-9a), 132.3 (2 signals) (C-2′), 133.1, 133.2 (C-5′, C-2″), 134.6 (2 signals) (C-7a′), 137.9 (C-7a″), 143.3 (C-3a), 155.1, 155.2 (C-5), 160.5 (CONH″), 161.1, 161.2 (CONH′); MS (ESI): m/z (%): 709 (100) [M – H]$^-$.

[(1,10)-*anti*-1-(10-Chloroethyl)-3-(5′-(1*H*-indol-2″-ylcarbonylamino)-1*H*-indol-2′-ylcarbonyl)-1,2-dihydro-3*H*-benz[*e*]indol-5-yl]-β-D-galactopyranoside (*anti*-10b): Phenol *anti*-**13b** (50 mg, 144 μmol) was treated with tetraacetyl trichloracetimidate **8** (74 mg, 148 μmol), $BF_3 \cdot OEt_2$ (146 μL, 1.11 mmol) and molecular sieves (4 Å, 1.00 g) according to the general procedure described above. EDC (62 mg, 320 μmol) and acid **9** (41 mg, 128 μmol) were added to the residue. The intermediate product obtained after chromatography (60 mg, 68 μmol) was treated with 5.4 M NaOMe/MeOH (29 μL, 136 μmol) to give *anti*-**10b** (23 mg, 32 μmol, 22%), which was obtained as a grey powder and as a mixture of diastereomers. R_f (intermediate product) = 0.67 (PE/acetone/MeOH = 10:6:1); UV (CH_3CN): λ_{max} (lgε) = 207.0 (4.564), 301.5 nm (4.547); IR (KBr): $\tilde{\nu}$ = 3405, 3292, 1624, 1516, 1466, 1415, 1313, 1232, 1141, 1074, 747 cm^{-1}; ^{1}H NMR (500 MHz, [D$_7$]DMF): δ = 1.75, 1.77 (d, J = 6.8 Hz, 3H, 11-CH$_3$), 3.71 – 3.84 (m, 4H, OH), 4.03 – 4.06 (m, 2H, 6*-H), 4.36 (br d, J = 8.5 Hz, 1H, 1-H), 4.74 (m, 2H, 3*-H, 5*-H), 4.85 – 4.93 (m, 3H, 2-CH$_2$, 10-H), 5.00 (m, 1H, 2*-H), 5.13 (d, J = 7.8 Hz, 1H, 1*-H), 5.62 (d, J = 5.5 Hz, 1H, 4*-H), 7.11 (t, J = 8.0 Hz, 1H, 5″-H), 7.27 (t, J = 8.0 Hz, 1H, 6″-H), 7.41 – 7.45 (m, 2H, 7-H, 3′-H), 7.55 (s, 1H, 3″-H), 7.58 – 7.65 (m, 3H, 8-H, 7′-H, 7″-H), 7.71 (d, J = 8.0 Hz, 1H, 4″-H), 7.73 (d, J = 8.1 Hz, 1H, 6′-H), 8.03, 8.04 (d, J = 8.0 Hz, 1H, 9-H), 8.40 – 8.46 (m, 3H, 4-H, 6-H, 4′-H), 10.31 (s, 1H, CONH), 11.78 (s, 1H, indole-NH), 11.83 (s, 1H, indole-NH); ^{13}C NMR (125 MHz, [D$_7$]DMF): δ = 23.8 (C-11), 47.3 (C-1), 53.1, 53.2 (C-2), 61.4 (C-10), 62.1, 62.2 (C-6*), 69.2 (C-4*), 71.9, 72.1 (C-2*), 74.7, 74.8 (C-3*), 76.5 (C-5*), 103.1, 103.5 (C-1*, C-4), 103.9 (C-3″), 106.8 (C-3′), 113.0 (2 signals) (C-7′, C-7″), 113.5 (C-4′), 119.8, 119.9 (2 signals) (C-9b, C-6′), 120.6 (C-5″), 122.4 (C-4″), 123.7, 124.1, 124.2, 124.3 (C-5a, C-6, C-7, C-9, C-6″), 128.0 (C-8), 128.5 (2 signals) (C-3a′, C-3a″), 130.6, 130.7 (C-9a), 132.4 (C-2′), 133.1 (2 signals) (C-5′, C-2″), 134.5 (2 signals) (C-7a′), 137.9 (C-7a″), 143.3 (C-3a), 154.8, 154.9 (C-5), 160.5 (CONH″), 161.1 (CONH′); MS (ESI): m/z (%): 733 (100) [M+Na]$^+$, 709 (100) [M – H]$^-$.

General procedure for the preparation of the model compounds 11 and 12: The substrate for the coupling reaction was dissolved in 4 M HCl/1,4-dioxane (prepared by diluting conc aq HCl [ca. 12 M] with 1,4-dioxane to a final HCl concentration of 4 M; 25 mL mmol^{-1}) and stirred at room temperature. The solution was concentrated in vacuo, and the residue was thoroughly dried under vacuum (oil pump). It was then dissolved in dry degassed DMF (17 mL mmol^{-1}) and treated with 3.0 equiv of EDC and 1.0 equiv of acid **9**.[10] After 18 h of stirring at room temperature, a small amount of silica gel was added and the mixture was evaporated to dryness. Flash chromatography (PE/acetone = 5:1 → PE/acetone = 5:3 → PE/acetone/MeOH = 10:6:1) provided the title compound, which was isolated by concentration of the eluate to a small volume and

subsequent addition of petroleum ether. The precipitate was then collected by filtration through a glass frit, washed with Et_2O and a small amount of acetone, and thoroughly dried.

(1*R*/*S*)-1-Chloromethyl-5-hydroxy-3-[5′-(1*H*-indol-2″-ylcarbonylamino)-1*H*-indol-2′-ylcarbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (11 a): According to the general procedure described above, phenol **13 a** (56 mg, 168 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The mixture was treated with EDC (97 mg, 504 μmol) and acid **9** (53 mg, 168 μmol). **11 a** (28 mg, 52 μmol, 31 %) was obtained as a brownish powder. $R_f = 0.68$ (PE/acetone/MeOH = 10:6:1); ^{1}H NMR (500 MHz, [D$_7$]DMF): $\delta = 3.97$ (dd, $J = 11.0$, 7.8 Hz, 1 H, 10-H$_a$), 4.15 (dd, $J = 11.0$, 3.0 Hz, 1 H, 10-H$_b$), 4.33 (m$_c$, 1 H, 1-H), 4.77 (d, $J = 10.4$ Hz, 1 H, 2-H$_a$), 4.90 (dd, 2 × $J = 10.4$, 1 H, 2-H$_b$), 7.11 (t, $J = 8.0$ Hz, 1 H, 5″-H), 7.26 (t, $J = 8.0$ Hz, 1 H, 6″-H), 7.31 (s, 1 H, 3′-H), 7.41 (t, $J = 8.0$ Hz, 1 H, 7-H), 7.54 (s, 1 H, 3″-H), 7.57 (t, $J = 8.0$ Hz, 1 H, 8-H), 7.59 (d, $J = 8.4$ Hz, 1 H, 7′-H), 7.61 (d, $J = 8.3$ Hz, 1 H, 7″-H), 7.70 (d, $J = 8.0$ Hz, 1 H, 4″-H), 7.73 (d, $J = 8.5$ Hz, 1 H, 6′-H), 7.94 (d, $J = 8.0$ Hz, 1 H, 9-H), 8.10 (br s, 1 H, 4-H), 8.23 (d, $J = 8.2$ Hz, 1 H, 6-H), 8.41 (s, 1 H, 4′-H), 10.32 (s, 1 H, CONH), 10.61 (s, 1 H, OH), 11.70 (s, 1 H, indole-NH), 11.80 (s, 1 H, indole-NH); ^{13}C NMR (125 MHz, [D$_7$]DMF): $\delta = 42.6$ (C-1), 48.1 (C-10), 55.9 (C-2), 101.3 (C-4), 103.9 (C-3″), 106.5 (C-3′), 112.9, 113.0 (C-7′, C-7″), 113.4 (C-4′), 116.0 (C-9b), 119.8 (C-6′), 120.6 (C-5″), 122.4 (C-4″), 123.3, 123.5, 123.8, 124.0 (C-5a, C-6, C-7, C-9), 124.3 (C-6″), 128.0 (C-8), 128.4, 128.5 (C-3a′, C-3a″), 131.0 (C-9a), 132.6 (C-2′), 133.1 (C-5′, C-2″), 134.4 (C-7a′), 137.9, (C-7a″), 143.5 (C-3a), 155.3 (C-5), 160.5 (CONH″), 161.1 (CONH′).

(1,10)-*syn*-1-(10-Chloroethyl)-5-hydroxy-3-[5′-(1*H*-indol-2″-ylcarbonylamino)-1*H*-indol-2′-ylcarbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (*syn*-11 b): According to the general procedure described above, phenol *syn*-**13 b** (40 mg, 115 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The mixture was treated with EDC (66 mg, 345 μmol) and acid **9** (37 mg, 115 μmol). *syn*-**11 b** (25 mg, 46 μmol, 40 %) was obtained as a brownish powder. $R_f = 0.60$ (PE/acetone/MeOH = 10:6:1); UV (CH_3CN): λ_{max} (lgε) = 206.0 (4.165), 247.0 (3.976), 304.0 nm (4.077); IR (KBr): $\tilde{\nu} = 3430$, 3291, 1655, 1585, 1548, 1518, 1416, 1314, 1240, 1140, 746 cm^{-1}; ^{1}H NMR (500 MHz, [D$_7$]DMF): $\delta = 1.18$ (d, $J = 7.1$ Hz, 3 H, 11-CH$_3$), 4.39 (d, $J = 6.9$, 1 H, 1-H), 4.82 – 4.91 (m, 3 H, C-H$_2$, C-10), 7.11 (t, $J = 8.0$ Hz, 1 H, 5″-H), 7.27 (t, $J = 8.0$ Hz, 1 H, 6″-H), 7.35 (s, 1 H, 3′-H), 7.42 (t, $J = 8.1$ Hz, 1 H, 7-H), 7.53 (s, 1 H, 3″-H), 7.55 – 7.62 (m, 3 H, 8-H, 7′-H, 7″-H), 7.70 (d, $J = 8.1$ Hz, 1 H, 4″-H), 7.73 (d, $J = 8.1$ Hz, 1 H, 6′-H), 7.93 (d, $J = 8.0$ Hz, 1 H, 9-H), 8.08 (br s, 1 H, 4-H), 8.23 (d, $J = 8.0$ Hz, 1 H, 6-H), 8.42 (s, 1 H, 4′-H), 10.34 (s, 1 H, CONH), 10.67 (s, 1 H, OH), 11.73 (s, 1 H, indole-NH), 11.81 (s, 1 H, indole-NH); ^{13}C NMR (125 MHz, [D$_7$]DMF): $\delta = 18.6$ (C-11), 47.5 (C-1), 53.5 (C-2), 59.7 (C-10), 101.3 (C-4), 103.9 (C-3″), 106.6 (C-3′), 112.9, 113.0 (C-7′, C-7″), 113.5 (C-4′), 115.9 (C-9b), 119.9 (C-6′), 120.5 (C-5″), 122.4 (C-4″), 123.3, 123.7, 123.9, 124.0 (C-5a, C-6, C-7, C-9), 124.3 (C-6″), 128.1 (C-8), 128.4, 128.5 (C-3a′, C-3a″), 131.0 (C-9a), 132.4 (C-2′), 133.1, 133.2 (C-5′, C-2″), 134.5 (C-7a′), 137.9, (C-7a″), 143.5 (C-3a), 155.5 (C-5), 160.5 (CONH″), 160.9 (CONH′); MS (ESI): *m*/*z* (%): 1119 (97) [2*M*+Na]$^+$, 571 (100) [*M*+Na]$^+$.

(1,10)-*anti*-1-(10-Chloroethyl)-5-hydroxy-3-[5′-(1*H*-indol-2″-ylcarbonylamino)-1*H*-indol-2′-ylcarbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (*anti*-11 b): According to the general procedure described above, phenol *anti*-**13 b** (27 mg, 78 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The mixture was treated with EDC (45 mg, 233 μmol) and acid **9** (23 mg, 72 μmol). *anti*-**11 b** (6.0 mg, 11 μmol, 14 %) was obtained as a beige powder. $R_f = 0.59$ (PE/acetone/MeOH = 10:6:1); UV (CH_3CN): λ_{max} (lgε) = 206.0 (4.124), 247.0 (3.951), 304.5 nm (4.105); IR (KBr): $\tilde{\nu} = 3430$, 3292, 1655, 1583, 1549, 1518, 1415, 1315, 1240, 1138, 746 cm^{-1}; ^{1}H NMR (500 MHz, [D$_7$]DMF): $\delta = 1.74$ (d, $J = 6.8$ Hz, 3 H, 11-CH$_3$), 4.30 (d, $J = 8.5$, 1 H, 1-H), 4.81 – 4.90 (m, 3 H, C-H$_2$, C-10), 7.11 (t, $J = 7.7$ Hz, 1 H, 5″-H), 7.26 (t, $J = 7.6$ Hz, 1 H, 6″-H), 7.39 (s, 1 H, 3′-H), 7.41 (t, $J = 8.1$ Hz, 1 H, 7-H), 7.53 (s, 1 H, 3″-H), 7.55 (t, $J = 8.1$ Hz, 1 H, 8-H), 7.59 (d, $J = 7.6$ Hz, 1 H, 7′-H), 7.61 (d, $J = 7.6$ Hz, 1 H, 7″-H), 7.70 (d, $J = 7.8$ Hz, 1 H, 4″-H), 7.72 (dd, $J = 8.0$, 1.7 Hz, 1 H, 6′-H), 7.97 (d, $J = 8.0$ Hz, 1 H, 9-H), 8.14 (br s, 1 H, 4-H), 8.25 (d, $J = 8.0$ Hz, 1 H, 6-H), 8.42 (d, $J = 1.0$, 1 H, 4′-H), 10.31 (s, 1 H, CONH), 10.57 (s, 1 H, OH), 11.70 (s, 1 H, indole-NH), 11.79 (s, 1 H, indole-NH); ^{13}C NMR (125 MHz, [D$_7$]DMF): $\delta = 23.8$ (C-11), 47.2 (C-1), 53.1 (C-2), 62.3 (C-10), 101.4 (C-4), 103.9 (C-3″), 106.7 (C-3′), 112.9, 113.0 (C-7′, C-7″), 113.5 (C-4′), 117.0 (C-9b), 119.7 (C-6′), 120.6 (C-5″), 122.4 (C-4″), 123.4, 123.6, 123.7, 124.0 (C-5a, C-6, C-7, C-9), 124.3 (C-6″), 127.7 (C-8), 128.5 (C-3a′, C-3a″), 131.0 (C-9a), 132.6 (C-2′), 133.1 (2 signals) (C-5′, C-2″), 134.4 (C-7a′), 137.9, (C-7a″), 143.5 (C-3a), 155.1 (C-5), 160.5 (CONH″), 160.8 (CONH′); MS (ESI): *m*/*z* (%): 547 (42) [*M* − H]$^-$, 511 (100) [*M* − HCl − H]$^-$.

5-Benzyloxy-1-chloromethyl-3-[5′-(1*H*-indol-2″-ylcarbonylamino)-1*H*-indol-2′-ylcarbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (12 a): According to the general procedure described above, benzyl ether **7 a** (47 mg, 168 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The mixture was treated with EDC (64 mg, 333 μmol) and acid **9** (35 mg, 111 μmol). **12 a** (23 mg, 37 μmol, 33 %) was obtained as a yellowish powder. $R_f = 0.31$ (PE/EtOAc = 3:2); UV (CH_3CN): λ_{max} (lgε) = 207.5 (4.646), 302.5 (4.549), 334.5 nm (4.388); IR (KBr): $\tilde{\nu} = 3415$, 3289, 2924, 1624, 1524, 1460, 1407, 1312, 1232, 1140, 746 cm^{-1}; ^{1}H NMR (500 MHz, [D$_7$]DMF): $\delta = 4.03$ (dd, $J = 11.3$, 7.5 Hz, 1 H, 10-H$_a$), 4.16 (dd, $J = 11.2$, 3.1 Hz, 1 H, 10-H$_b$), 4.36 – 4.40 (m, 1 H, 1-H), 4.80 (dd, $J = 10.8$, 2.0 Hz, 1 H, 2-H$_a$), 4.95 (dd, $J = 10.5$, 9.4 Hz, 1 H, 2-H$_b$), 5.38 (s, 2 H, OCH$_2$), 7.11 (dt, $J = 1.0$, 8.0 Hz, 1 H, 5″-H), 7.27 (dt, $J = 1.0$, 8.0 Hz, 1 H, 6″-H), 7.34 (d, $J = 2.0$ Hz, 1 H, 3′-H), 7.41 (t, $J = 7.5$ Hz, 1 H, 7-H), 7.45 – 7.50 (m, 3 H, *m*-H, *p*-H), 7.55 (s, 1 H, 3″-H), 7.60 – 7.64 (m, 3 H, 8-H, 7′-H, 7″-H), 7.68 (d, $J = 7.5$ Hz, 2 H, *o*-H), 7.71 (d, $J = 7.5$ Hz, 1 H, 4″-H), 7.76 (dd, $J = 8.0$, 2.0 Hz, 1 H, 6′-H), 8.00 (d, $J = 8.0$ Hz, 1 H, 9-H), 8.25 (br s, 1 H, 4-H), 8.29 (d, $J = 8.0$ Hz, 1 H, 6-H), 8.45 (s, 1 H, 4′-H), 10.32 (s, 1 H, CONH), 11.77 (s, 1 H, indole-NH), 11.80 (s, 1 H, indole-NH); ^{13}C NMR (125 MHz, [D$_7$]DMF): $\delta = 42.6$ (C-1), 48.2 (C-10), 56.0 (C-2), 70.7 (OCH$_2$), 99.2 (C-4), 103.9 (C-3″), 106.7 (C-3′), 112.9, 113.0 (C-7′, C-7″), 113.5 (C-4′), 117.6 (C-9b), 119.9 (C-6′), 120.6 (C-5″), 122.4 (C-4″), 123.6 (2 signals), 123.8, 124.6 (C-5a, C-6, C-7, C-9), 124.3 (C-6″), 128.3 (C-8), 128.4, 128.5 (C-3a′, C-3a″), 128.5 (*o*-C), 128.7 (*p*-C), 129.2 (*m*-C), 130.8 (C-9a), 132.4 (C-2′), 133.1, 133.2 (C-5′, C-2″), 134.5 (C-7a′), 137.9 (2 signals) (C-7a″, *ipso*-C), 143.4 (C-3a), 155.7 (C-5), 160.5 (CONH″), 161.2 (CONH′); MS (DCI, 200 eV): *m*/*z* (%): 642 (100) [*M*+NH$_4$]$^+$, 625 (20) [*M*+H]$^+$, 606 (16) [*M* − HCl+NH$_4$]$^+$, 589 (10) [*M* − HCl+H]$^+$.

(1,10)-*syn*-5-Benzyloxy-1-(10-chloroethyl)-3-[5′-(1*H*-indol-2″-ylcarbonylamino)-1*H*-indol-2′-ylcarbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (*syn*-12 b): According to the general procedure described above, benzyl ether *syn*-**7 b** (60 mg, 137 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The mixture was treated with EDC (79 mg, 411 μmol) and acid **9** (43 mg, 137 μmol). *syn*-**12 b** (16 mg, 26 μmol, 19 %) was obtained as a yellowish powder. $R_f = 0.87$ (PE/acetone/MeOH = 10:6:1); UV (CH_3CN): λ_{max} (lgε) = 207.5 (4.655), 303.0 (4.596), 336.5 nm (4.431); IR (KBr): $\tilde{\nu} = 3417$, 3285, 3060, 2925, 1624, 1587, 1524, 1460, 1405, 1312, 1230, 1140, 803, 745, 697 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.11$ (d, $J = 6.7$ Hz, 3 H, 11-CH$_3$), 4.33 (br d, $J = 9.8$ Hz, 1 H, 1-H), 4.70 (d, $J = 11.1$ Hz, 1 H, 2-H$_a$), 4.81 – 4.84 (m, 2 H, 2-H$_b$, 10-H), 5.32 (m$_c$, 2 H, OCH$_2$), 7.07 (t, $J = 7.8$ Hz, 1 H, 5″-H), 7.21 (t, $J = 8.1$ Hz, 1 H, 6″-H), 7.26 (d, $J = 1.5$ Hz, 1 H, 3′-H), 7.36 (t, $J = 8.0$ Hz, 1 H, 7-H), 7.42 – 7.47 (m, 4 H, *m*-H, *p*-H, 3″-H), 7.48 (d, $J = 8.1$ Hz, 1 H, 7″-H), 7.50 (d, $J = 8.0$ Hz, 1 H, 6′-H), 7.56 – 7.60 (m, 4 H, 8-H, 7′-H, *o*-H), 7.67 (d, $J = 7.8$ Hz, 1 H, 4″-H), 7.92 (d, $J = 8.0$ Hz, 1 H, 9-H), 8.09 (br s, 1 H, 4-H), 8.12 (d, $J = 8.0$ Hz, 1 H, 6-H), 8.15 (s, 1 H, 4′-H), 10.15 (s, 1 H, CONH), 11.68 (s, 1 H, indole-NH), 11.76 (s, 1 H, indole-NH); ^{13}C NMR (125 MHz, [D$_7$]DMF): $\delta = 18.8$ (C-11), 47.5 (C-1), 53.7 (C-2), 59.7 (C-10), 70.8 (OCH$_2$), 99.2 (C-4), 103.9 (C-3″), 106.8 (C-3′), 113.0 (2 signals) (C-7′, C-7″), 113.5 (C-4′), 117.6 (C-9b), 120.0 (C-6′), 120.6 (C-5″), 122.4 (C-4″), 123.6, 123.9, 124.0, 124.7 (C-5a, C-6, C-7, C-9), 124.3 (C-6″), 128.4

(2 signals), 128.5 (2 signals) (C-8, C-3a′, C-3a″, *o*-C), 128.7 (*p*-C), 129.3 (*m*-C), 130.8 (C-9a), 132.2 (C-2′), 133.1, 133.2 (C-5′, C-2″), 134.6 (C-7a′), 137.8, 137.9 (C-7a″, *ipso*-C), 143.5 (C-3a), 155.9 (C-5), 160.5 (CONH″), 161.2 (CONH′); MS (DCI, 200 eV): *m/z* (%): 656 (52) $[M+NH_4]^+$, 639 (63) $[M+H]^+$, 622 (63) $[M-HCl+NH_4+2H]^+$, 605 (100) $[M-HCl+3H]^+$.

(1,10)-*anti*-5-Benzyloxy-1-(10-chloroethyl)-3-[5′-(1*H*-indol-2″-ylcarbonylamino)-1*H*-indol-2′-ylcarbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (*anti*-12b): According to the general procedure described above, benzyl ether *anti*-**7b** (150 mg, 343 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The mixture was treated with EDC (197 mg, 1.03 mmol) and acid **9** (108 mg, 343 μmol). *anti*-**12b** (76 mg, 119 μmol, 35 %) was obtained as a yellowish powder. $R_f = 0.74$ (PE/acetone = 5:3); UV (CH_3CN): λ_{max} (lgε) = 207.5 (4.596), 303.0 (4.502), 336.5 nm (4.335); IR (KBr): $\tilde{\nu} = 3415$, 3290, 3060, 1624, 1587, 1524, 1459, 1407, 1312, 1231, 1142, 804, 746, 697 cm^{-1}; ^1H NMR (300 MHz, [D_6]DMSO): $\delta = 1.67$ (d, $J = 6.7$ Hz, 3H, 11-CH_3), 4.25 (d, $J = 9.3$ Hz, 1H, 1-H), 4.65 (dd, $J = 10.4$, 3.0 Hz, 1H, 2-H_a), 4.78 (dd, $2 \times J = 10.0$ Hz, 1H, 2-H_b), 4.80 (m_c, 1H, 10-H), 5.32 (m_c, 2H, OCH_2), 7.07 (t, $J = 7.8$ Hz, 1H, 5″-H), 7.22 (t, $J = 8.1$ Hz, 1H, 6″-H), 7.32 (s, 1H, 3′-H), 7.37 (t, $J = 8.0$ Hz, 1H, 7-H), 7.43 (s, 1H, 3″-H), 7.45 (t, $J = 7.9$ Hz, 3H, *m*-H, *p*-H), 7.49 (d, $J = 7.9$ Hz, 1H, 7″-H), 7.51 (d, $J = 8.0$ Hz, 1H, 6′-H), 7.56 – 7.60 (m, 4H, 8-H, 7′-H, *o*-H), 7.67 (d, $J = 7.8$ Hz, 1H, 4″-H), 7.97 (d, $J = 7.9$ Hz, 1H, 9-H), 8.15 (br s, 1H, 4-H), 8.23 (d, $J = 8.1$ Hz, 1H, 6-H), 8.26 (s, 1H, 4′-H), 10.15 (s, 1H, CONH), 11.68 (s, 1H, indole-NH), 11.73 (s, 1H, indole-NH); ^{13}C NMR (125 MHz, [D_7]DMF): $\delta = 23.8$ (C-11), 47.2 (C-1), 53.1 (C-2), 62.2 (C-10), 70.7 (OCH_2), 99.2 (C-4), 103.9 (C-3″), 106.9 (C-3′), 112.9, 113.0 (C-7′, C-7″), 113.5 (C-4′), 118.6 (C-9b), 119.9 (C-6′), 120.6 (C-5″), 122.4 (C-4″), 123.6, 123.8, 123.9, 124.4 (C-5a, C-6, C-7, C-9), 124.3 (C-6″), 128.1 (C-8), 128.5 (2 signals) (C-3a′, C-3a″), 128.6 (*o*-C), 128.7 (*p*-C), 129.2 (*m*-C), 130.8 (C-9a), 132.4 (C-2′), 133.2 (C-5′, C-2″), 134.5 (C-7a′), 137.9 (2 signals) (C-7a″, *ipso*-C), 143.5 (C-3a), 155.6 (C-5), 160.5 (CONH″), 161.0 (CONH′); MS (DCI, 200 eV): *m/z* (%): 656 (15) $[M+NH_4]^+$, 639 (7) $[M+H]^+$, 620 (73) $[M-HCl+NH_4]^+$, 603 (68) $[M-HCl+H]^+$.

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 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).

In vitro cytotoxicity assays: 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 removed by suction 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 compounds **10** – **12** was then performed in Ultraculture medium at various concentrations for 24 h. All compounds were used as freshly prepared solutions in DMSO (Merck, Darmstadt, Germany) diluted with incubation medium to a final DMSO concentration of 1 % in the wells. After 24 h of exposure, the test compound 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:

$$\text{relativ clone-forming rate [\%]} = \frac{\text{number of clones counted after exposure}}{\text{number of clones counted in the control}} \times 100$$

Liberation of the drugs from their glycosidic prodrugs was achieved by addition of 0.4 U mL^{-1} β-D-galactosidase (EC 3.2.1.23, Grade X, purchased from Sigma Germany, Deisenhofen, Germany) to the cells during incubation with the compounds.

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