Synthesis and Biological Evaluation of Novel Analogues and Prodrugs of the Cytotoxic Antibiotic CC-1065 for Selective Cancer Therapy

Lutz F. Tietze,*[a] Tobias Herzig,[a] Tim Feuerstein,[a] and Ingrid Schuberth[a]

Keywords: Antitumor agents / Cancer therapy / Enzymes / Glycosides / Prodrugs

This paper describes novel *seco*-analogues **25**–**27** of the cytotoxic antibiotic CC-1065 (**1**) and their prodrugs **5**, **6a**, and **6b**, for antibody-directed enzyme prodrug therapy (ADEPT). The partially hydrogenated *seco*-CCI-analogue **7** and the corresponding methyl-CCI analogues **8a** and **8b** were synthesized by alkylation of **9** with **15** and **16**, respectively, followed by radical cyclization and deprotection. Treatment of **7**, **8a**, and **8b** with the galactose trichloroacetimidate **21** and the bisindolyl-carboxylic acid **20** in the presence of EDC followed by solvolysis gave the desired prodrugs **5**, **6a**, and **6b**, respectively. Compounds **25**–**27** were prepared by treatment of **7**, **8a**, and **8b** with **20** after deprotection. In vitro tests showed a strong cytotoxicity for **25** and a fairly low toxicities for **26** and **27**. However, the selectivity of the prodrugs **5**, **6a**, and **6b** was not sufficient for ADEPT. Interestingly, **8a** and **8b** did not undergo Winstein cyclization to produce the spirocyclopropylcyclohexadienone moiety.

Introduction

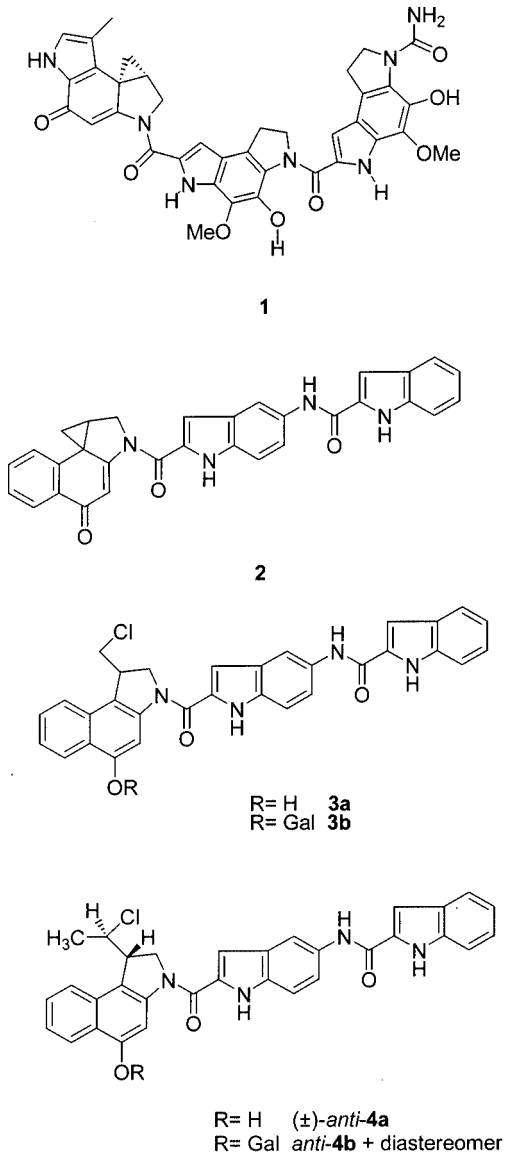
One of the main problems of anticancer therapy is insufficient differentiation between normal and malignant cells by the known antiproliferant agents, resulting in severe side effects. Approaches for more selective therapy might be based on the use of phenotypic differences[1–4] such as the increased rate of glycolysis and the expression of specific antigens, as well as on genetic[5] differences. This may result in a specific liberation of a toxin from a suitable nontoxic or little toxic prodrug.

A promising concept is *antibody-directed enzyme prodrug therapy* (ADEPT).[5–7] In this approach, the toxic effector is liberated from a prodrug by enzymatic cleavage by a conjugate of an appropriate enzyme and a monoclonal antibody that binds to tumor-associated antigens. A crucial requirement for this approach is high cytotoxicity in the corresponding drug, in the range of an ED_{50} value < 10 nM (ED_{50}, drug concentration required for 50% biological effect on target cells) and a high Q ED_{50} value (ED_{50} of prodrug/ED_{50} of prodrug + enzyme).

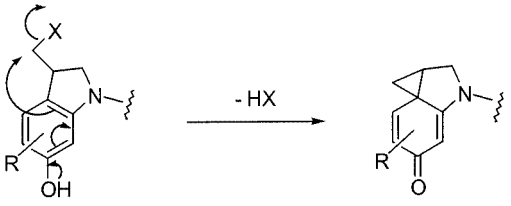
One class of compounds with extraordinarily high cytotoxicities, with ED_{50} values of about 0.03 nM (cell line L1210), are the natural occurring antibiotics CC-1065 (**1**) and the duocarmycins (Scheme 1).[8] However, CC-1065 (**1**) cannot be used for clinical treatment because of its delayed lethal hepatotoxicity. Synthetic analogues of **1**, such as CBI (**2**), are highly potent cytostatic agents but do not display this hepatotoxicity.[9] The antiproliferative effect of **1** and its analogues was shown to derive from a selective alkylation of *N*-3 of adenine in DNA by a nucleophilic attack at the spirocyclopropylcyclohexadienone moiety as the pharmacophoric group.[10]

Synthetically, the pharmacophoric group in **1** and **2** might be formed by a Winstein cyclization[11] of a corresponding phenol, such as **3a**, with a leaving group at the β-position (Scheme 2).[9] The cyclization, which also proceeds under physiological conditions, can be blocked by glycosylation of the phenolic hydroxyl group.[12–14] In order to employ this effect in ADEPT, we prepared the *seco*-CBI-galactoside **3b**. However, this compound surprisingly showed a decrease in cytotoxicity relative to **3a** by a factor of only 32, which is clearly not sufficient for selective therapy. Speculating that the comparably high cytoxicity of **3a** may derive from a direct attack of *N*-3 in adenine at the chloromethyl group in **3a** without formation of the spirocyclopropylcyclohexadiene moiety, we prepared the branched compound *anti*-**4b**, containing a secondary rather than a primary chloride as in **3b**. Enzymatic cleavage resulted in *anti*-**4a**, which cyclized to give the spirocyclopropylcyclohexadienone moiety. This indeed showed a much higher selectivity, with a Q $ED_{50} = 770$ with human bronchial carcinoma cells of line A549.[14] To obtain further information about the structure activity relationship of *seco*-CC-1065 analogues, we prepared a new class of antiproliferating agents containing a partially hydrogenated ring **A**. Here we describe the synthesis and the evaluation of the biological activity of compounds **5**, **6a**, and **6b**, and **25**–**27**.

[a] Georg-August-Universität Göttingen, Institut für Organische Chemie
Tammannstraße 2, 37077 Göttingen, Germany
Fax: (internat.) + 49-(0)551/399476
E-mail: ltietze@gwdg.de



Scheme 1. Structure of (+)-CC-1065 (**1**) and the analogues CBI (**2**), *seco*-CBI **3a**, and methyl-*seco*-CBI **4a**, and their prodrugs **3b** and **4b**



Scheme 2. Formation of the spirocyclopropylcyclohexadienone moiety of CC-1065 and its analogues by Winstein cyclization from the *seco*-compounds

Results

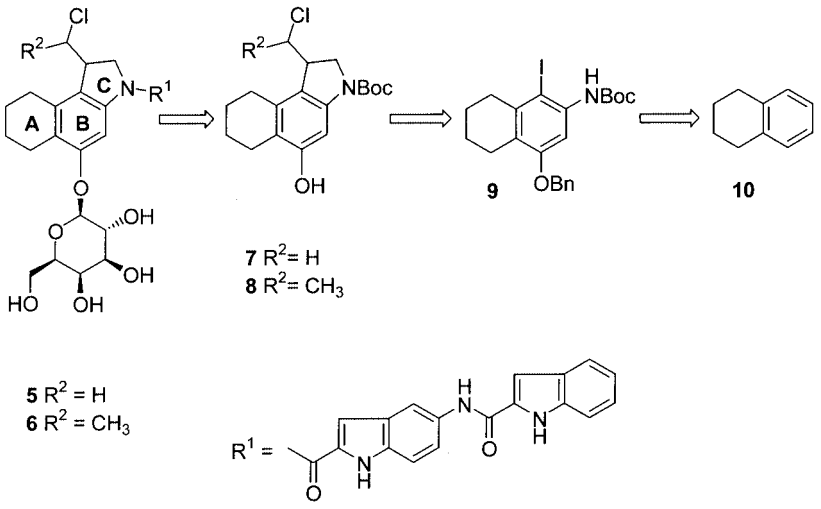
Synthesis

Retrosynthesis of the glycosidic prodrugs **5** and **6** suggested the tetralene derivative **9**, via **7** and **8**, respectively (Scheme 3). There are three possible approaches for the synthesis of **9**: selective hydrogenation of an aromatic ring in a naphthalene derivative, construction of a second alicyclic ring starting from a benzene derivative, or preparation from tetralene **10** by aromatic substitution reactions. The first way would involve the danger of incomplete reduction and hence potential contamination of the prodrugs **5** and **6** with traces of the CBI analogue, which could seriously falsify the results of biological tests. While exploring the second way, we observed that the final closure of the alicyclic ring required harsh conditions that were not compatible with the substituents already present in the aromatic ring.

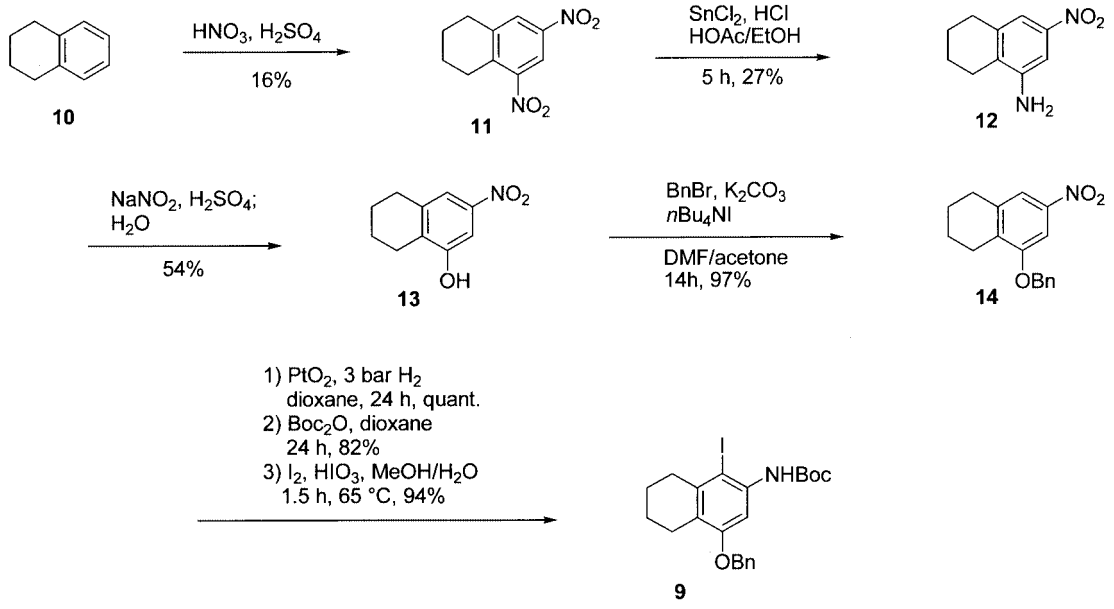
We therefore employed the commercially available tetralene **10** as starting material. Compound **10** was transformed into **12** via the dinitro derivative **11**, by use of a mixture of concentrated nitric and sulfuric acid with careful control over the reaction conditions, followed by reduction of the nitro group at position 1 with $SnCl_2$ to give the amine **12** (Scheme 4).[15] The yields of both reactions were poor and the workup procedure lengthy, but it was possible to work on mole scales and thus obtain sufficient amounts of material for the following conversions. Transformation of the amine **12** to give phenol **13** was performed by formation of a diazonium salt followed by addition of water. After protection of the phenolic hydroxyl group in **13** as its benzyl ether **14**, the remaining nitro group was reduced, and the amino group formed was protected as its BOC-carbamate. Regioselective iodination in the position *para* to the benzyl ether moiety was achieved by use of the Königstein procedure to give **9** in 75% yield based on **13**.[16]

Ring **C** in **5** was introduced by alkylation of the amide **9** with 1,3-dichloride **15** followed by radical cyclization with nBu$_3$SnH, which provided chloride **17** in a good overall yield of 77% based on **9** (Scheme 5).[17,18] Debenzylation of **17** to give **7** was achieved under mild conditions without dehalogenation in a transfer hydrogenation with Pd/C in the presence of ammonium formate.[19] The introduction of the sugar moiety and the side chain, which is important for binding to the minor groove of the DNA, was performed in one process, since we were able to remove the protecting group at the nitrogen simultaneously during the glycosidation. Thus, treatment of **7** with the trichloroacetimidate **21**[20] in the presence of $BF_3{\cdot}OEt_2$ gave the corresponding β-D-galactoside, containing a free secondary amino moiety. This was transformed into the desired prodrug **5** by addition of the bisindolyl-carboxylic acid **20** and *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDC), followed by solvolysis of the acetate moieties to give a 25% yield over three steps.

Compound **5** contains a stereogenic center in the *seco*-CCI unit.[21] This was formed nonselectively, and so the compound, since it also contains a sugar moiety, was obtained as a 1:1 mixture of two diastereomers. However, no attempts were made to separate the stereoisomers, since (as shown by us for related compounds) both diastereomers could be cleaved by galactosidase at similar rates. In addition, we prepared the benzyl ether **22** and the phenol **25** as model substances for the cytotoxicity tests, by coupling of



Scheme 3. Retrosynthesis of the novel partially hydrogenated prodrugs **5** and **6**



Scheme 4. Synthesis of the key intermediate **9**

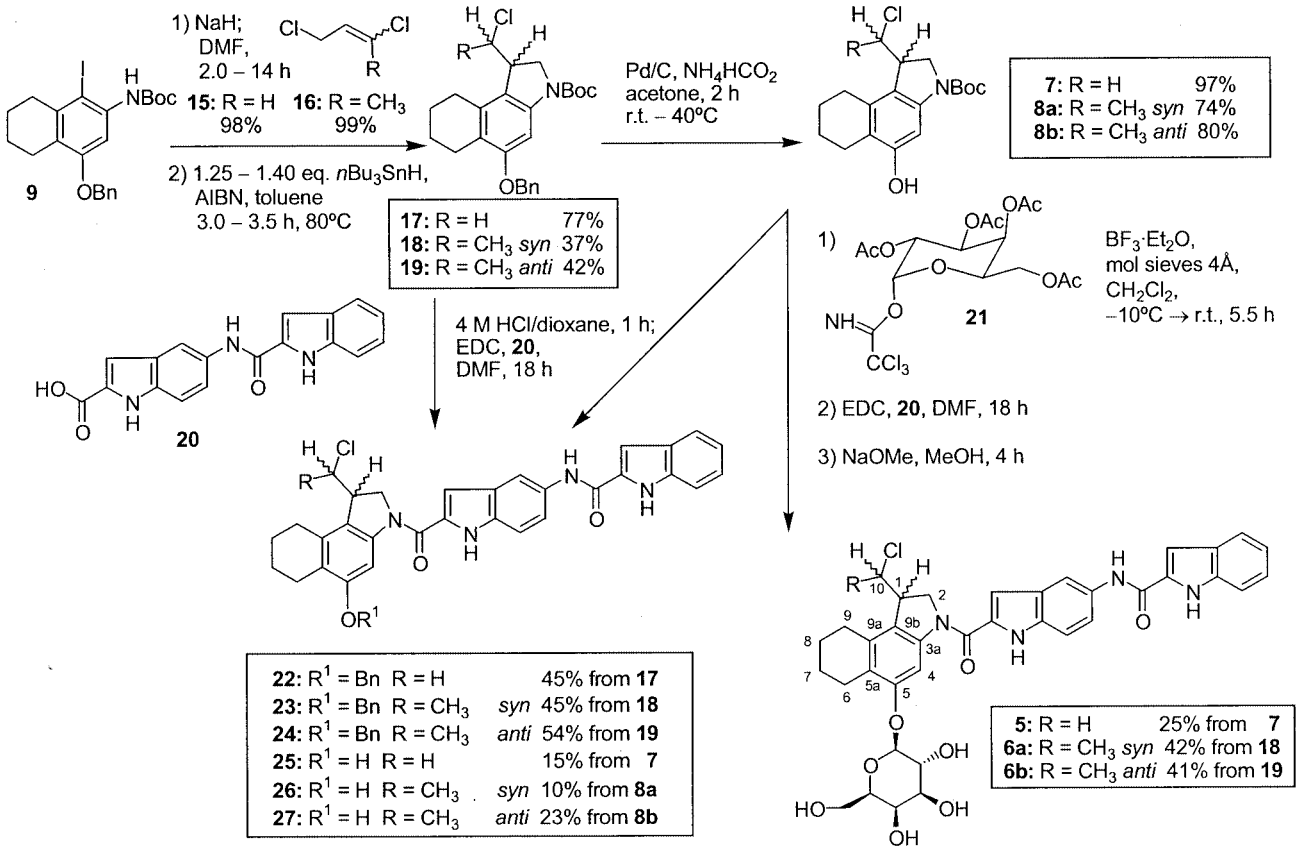
N-deprotected **7** and **17**, respectively, with acid **20** in the presence of EDC.

In a fashion similar to that described for the synthesis of **5**, we also synthesized the methyl-substituted prodrug **6**. Compound **6** contains two stereogenic centers in the *seco*-CCI unit, and thus can exist as four diastereomers. Here a pronounced difference in the biological activities had to be expected; we therefore prepared the diastereomers **6a** and **6b** (with a *syn* and an *anti* orientation of the hydrogens at C-1 and C-10) separately. Alkylation of **9** with **16** followed by radical cyclization gave a 1:1 mixture of the diastereomers **18** and **19**, which could be separated by column chromatography (**18**: 37%; **19**: 42%). For further transformations, the single diastereomers were used separately. Thus, debenzylation of **18** to give **8a** followed by glycosidation with **21** and introduction of the bisindolyl-carboxylic acid moiety **20** afforded **6a** in 42% yield after solvolysis, whereas the same procedure from **19**, via **8b**, gave nearly identical yields of **6b**. We also prepared the benzyl ethers **23** and **24** in this series, as well as the unprotected phenols **26** and **27**, all containing the bisindolyl-carboxylic acid for binding to the minor groove of the DNA.

Structure Determination

The structures of the newly prepared compounds were mainly determined by NMR spectroscopy. As examples, the ^{1}H NMR spectroscopic data of compounds **5**–**8** are discussed. It should be noted that the compounds were measured in different solvents.

The hydrogens 7-CH_2 and 8-CH_2 of the alicylic moiety of these compounds resonated as multiplets around δ = 1.65 and 1.80, and the corresponding benzylic hydrogens around δ = 2.60. For the aromatic hydrogens in **7**, **8a**, and **8b**, singlets were found at δ = 7.28–7.33, whereas for the



Scheme 5. Preparation of the *seco*-CCI derivatives for the biological tests; AIBN = α,α′-Azoisobutyronitrile, EDC = *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride

glycosidic compounds **5**, **6a**, and **6b**, singlets were observed, as expected, further downfield at δ = 8.00−8.06. For determination of the configurations of the glycosidic bonds in **5**, **6a**, and **6b**, the resonances of the hydrogens at the anomeric centers are of importance; the corresponding signals were found at δ = 4.90−4.92 as doublets with J = 7.5−8.0 Hz, clearly indicating a β configuration. The assignment of the relative configurations of the two pairs of diastereomers **6a** and **6b** and **8a** and **8b** was hampered by the fact that **8a** and **8b** could not be transformed into the spirocyclopropylcyclohexadienone moiety, as shown for the corresponding diastereomeric methyl-*seco*-CBI analogues *syn*- and *anti*-**4a**.[14] However, comparison of the chemical shift values for 1-H and the methyl groups at C-10 of *syn*- and *anti*-**4a**, and also their derivatives, with those of **8a** and **8b** allowed the structures to be assigned. Thus, 1-H of the *syn* compounds always resonated at lower field than 1-H of the *anti* compounds, while the opposite was true of the methyl groups at C-10. We therefore assumed that **8a**, with signals for 1-H at δ = 3.66 and for 11-CH_3 at δ = 1.18, had a *syn* orientation of the hydrogens at C-1 and C-10 (1*SR*, 10*SR*). Correspondingly, 1-H of **8b** resonated at δ = 3.40 and 11-CH_3 at δ = 1.54, and **8b** should therefore have an *anti* orientation. In accordance with this assignment, **6a** must have a *syn* and **6b** an *anti* orientation. In contrast to 1-H and 11-CH_3, the diastereotopic protons at C-2 in **7**, **8a**, and **8b** resonated at very similar fields, with δ = 3.85−3.90 and 4.10−4.18. The resonances for 10-H in **8a** and **8b**, as quadruplets of doublets at δ = 4.40 and 4.44 with J = 7.2/7.0 and 3.5/3.6 Hz, respectively, also did not allow differentiation.

In vitro Cytotoxicity Assays

The in vitro cytotoxicity assays were carried out with coherent cells of the bronchial carcinoma cell line A549 in triplicate in 6 multiwell plates of concentrations of 10^2, 10^3, 10^4, and 10^5 cells per cavity. Incubation with the phenolic compounds **25**, **26**, and **27**, the benzyl ethers **22**, **23**, and **24**, and the galactosides **5**, **6a**, and **6b**, both in the absence and in the presence of galactosidase, was performed in ultraculture medium of various concentrations for 24 h. An important criterion is the comparison of the ED_{50} value of the phenolic compound and the ED_{50} value of a mixture of the glycosidic compound and β-D-galactosidase. These values should be similar, otherwise a suicide mechanism must be assumed. In such a case the system is not suitable for ADEPT.

The *seco*-CCI derivative **25** showed very high cytotoxicity, with an ED_{50} of 0.14 nM (Figure 1 and Table 1) in our HTCFA (Human Tumor Colony Forming Ability) assay on A549 cells. Its biological activity was only less than that of CC-1065 (**1**) by a factor of five, and by a factor of fifteen relative to that of its CBI analogue **2**, according to the published data[22] for these compounds on L1210 cells. This

shows that the insertion of **25** into the minor groove of the DNA still takes place, even though it does not have the ideal flat aromatic ring system. Thus, partially hydrogenated derivatives of CC-1065 (**1**) are a novel, highly potent class of CC-1065 analogues.

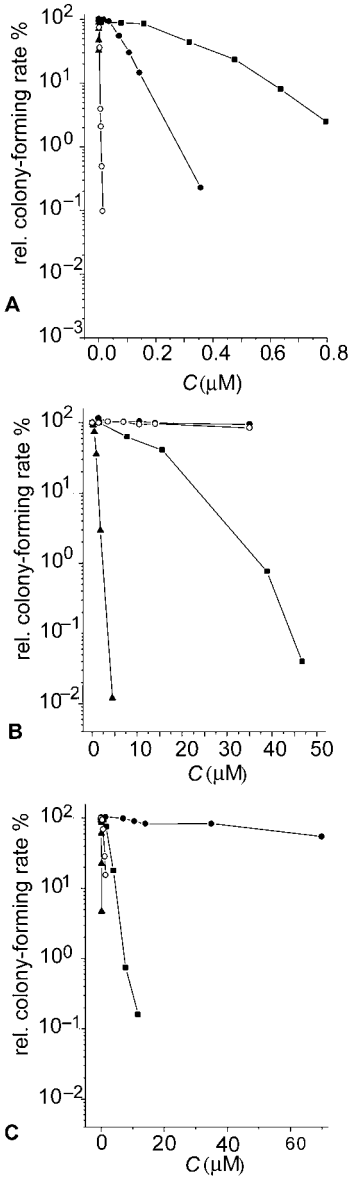


Figure 1. In vitro cytotoxicity of **5**, **6a**, **6b**, and **22**−**27** against human bronchial carcinoma cells of line A549; *A*, in vitro cytotoxicity of compound **22** (black square), **25** (black triangle), and **5** without (black circle) and with (white circle) addition of β-D-galactosidase (0.4 U/mL); *B*, in vitro cytotoxicity of *syn*-compounds **23** (black square), **26** (black triangle), and **6a** without (black circle) and with (white circle) addition of β-D-galactosidase (0.4 U/ml); *C*, in vitro cytotoxicity of *anti*-compounds **24** (black square), **27** (black triangle), and **6b** without (black circle) and with (white circle) addition of β-D-galactosidase (0.4 U/ml); 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

A cytotoxicity similar to that found for the phenol **25** was observed for the prodrug **5** in the presence of the enzyme β-D-galactosidase, with an ED_{50} = 1.3 nM, which indicated that the enzyme was not deactivated in the hydrolytic process. However the cytotoxicity of prodrug **5** was only slightly less than that of **25**, with a Q ED_{50} = 62.

In accordance with the results found for *anti*-**4b**, a much higher selectivity was expected for the methyl-CCI compounds **6a** and **6b**, since the direct attack of *N*-3 of adenine should be slower due to steric hindrance. We first investigated the cytotoxicity of the diastereomeric compounds **26** and **27**, containing free phenolic hydroxy groups. The *syn* isomer **26** displayed a modest cytotoxicity of ED_{50} = 600 nM, whereas the *anti* isomer **27** showed a cytotoxicity fifteen times higher, with an ED_{50} = 40 nM. The *syn*-galactoside **6a** was nontoxic in the investigated concentration range, even in the presence of β-D-galactosidase (ED_{50} > 35000 nM). The *anti*-galactoside **6b** showed a cytotoxicity of ED_{50} = 73000 nM, whereas the antiproliferative effect in the presence of β-D-galactosidase was increased to an ED_{50} = 800 nM, corresponding to a selectivity factor (Q ED_{50}) of 91.

Astoundingly, the decrease in the cytotoxicity of the benzylated compounds **23** and **24** compared to the free phenols **26** and **27**, respectively, was rather low, with a factor of 20−55.

Discussion

The reason for the comparatively high cytotoxicity of the galactoside **5** still remains unknown. Since serum-free incubation medium was employed, any enzyme activity of the medium (as observed in previous studies[12] with other media) could be ruled out. We must therefore assume either that nonenzymatic cleavage of the glycosidic bond in **5** occurs, or that direct alkylation of the DNA with **5** takes place without formation of the spirocyclopropane moiety. The latter effect must be caused by the galactose moiety, since the benzylated compound **22** shows a rather low cytotoxicity. Similar observations were made with the corresponding CBI prodrug, showing a selectivity factor of 32;[14] compared to this result, the partially hydrogenated prodrug **5** displays a slightly better selectivity, but this is not sufficient in our opinion for selective cancer therapy.

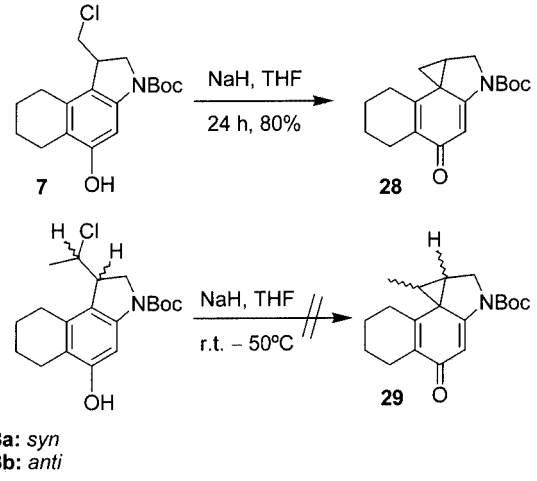
The lack of any cytotoxicity of the *syn*-galactoside **6a** in the presence of β-D-galactosidase − the corresponding phenolic compound **26** has an ED_{50} = 600 nM − might be due to the fact that **6a** is a poor substrate for galactosidase. The same might also be true for the *anti*-galactoside **6b**, since **6b** in the presence of galactosidase is 20 times less toxic than the phenolic compound **27**. We do not assume a suicide mechanism in these cases, since the activity of the enzyme is nearly unaltered for suitable substrates in the mixture. An important aspect is the low difference in the cytotoxicities of the benzyl ethers **23** and **24** relative to those of the corresponding phenols **26** and **27**, respectively, clearly indicating that direct alkylation of adenine or some other base in DNA takes place with the chloromethyl group in **23** and **24**. We therefore postulate that the formation of the spirocyclopropyl moiety is somehow hampered by the

Table 1. In vitro cytotoxicity of compounds **5**, **6a**, **6b**, and **22**−**27** against human bronchial carcinoma cells of line A549

Compound[a]	Substituent at the phenolic oxygen	ED_{50} [nM][b]	Selectivity factor[c] (Q ED_{50})
22	Benzyl	290	
25	H	0.14	
5	β-D-Galactose	80	62
5	β-D-Galactose[d]	1.3	
23	Benzyl	12400	
26	H	600	
6a	β-D-Galactose	>35000	−
6a	β-D-Galactose[d]	>35000	
24	Benzyl	2200	
27	H	40	
6b	β-D-Galactose	73000	91
6b	β-D-Galactose[d]	800	

[a] Compounds **5**, **6a**, and **6b** were used as mixtures of diastereomers and **22**−**27** as racemic mixtures of the respective diastereomer. [b] Cells were exposed to the compounds for 24 h at 37 °C; after 12 days of incubation clone formation was compared to untreated control assay. ED_{50} = drug concentration required for 50% biological effect on target cells. [c] Selectivity factor (Q ED_{50}) = ED_{50} of compound/ED_{50} of compound in the presence of β-D-galactosidase. [d] 0.4 U β-D-galactosidase/mL were added for 24 h.

cyclohexane moiety. To verify this assumption we investigated the Winstein cyclization of the phenols **7**, **8a**, and **8b** under basic conditions (Scheme 6). Treatment of **7** with sodium hydride in THF afforded the desired spirocyclopropyl compound **28** in 80% yield. In contrast, the phenols **8a** and **8b** did not react at all to give **29** under these conditions. Since the *seco*-methyl-CBI analogue *anti*-**4a** reacted smoothly, the observed behavior of **8a** and **8b** must arise from the combined steric bulk of the methyl group and the cyclohexene moiety. On the basis of these results, it is understandable that the introduction of a methyl group at the chloromethyl moiety in **7** does not improve the selectivity (Q ED_{50}), as found for methyl-*seco*-CBI. Further work will thus concentrate on this aspect, and so we intend to prepare the corresponding cyclobutano, cyclopentano, and cycloheptano compounds and compare their cytotoxicities and selectivities.



Scheme 6. Winstein cyclization of partially hydrogenated *seco*-CBI analogues

Conclusion

A new type of a *seco*-CC-1065 analogue with an annulated cyclohexane ring has been prepared. The antiproliferative activity was similar to that of CC-1065 (**1**) and CBI (**2**). The quotient of the ED_{50} of the corresponding glycosidated prodrug and the drug was slightly higher than that found for the glycosylated *seco*-CBI compound, but still not sufficient for use in ADEPT. Of interest is the observation that the methylated *seco*-CCI **8**, with a free phenolic hydroxy group, did not undergo cyclization under basic conditions to give the corresponding spirocyclopropylcyclohexadienone moiety. A possible explanation for this finding is the steric bulk of methyl *seco*-CCI **8** relative to methyl *seco*-CBI *anti*-**4a** and *seco*-CCI **7**.

Experimental Section

General: Reactions were performed under an inert gas atmosphere in flame-dried flasks. Solvents were dried by standard methods. 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 (PE: petroleum ether).

Elemental Analysis: Because of the high value of several prepared compounds, elemental analyses were not performed in these cases.

1-Hydroxy-3-nitro-5,6,7,8-tetrahydronaphthalene (13): Pulverized amine **12**[15] (6.48 g, 33.7 mmol), obtained from **10** by nitration and reduction, was suspended in 75% H_2SO_4 (100 mL) and treated at −5 °C with a solution of $NaNO_2$ (2.44 g, 35.4 mmol, 1.05 equiv.) in conc. H_2SO_4 (15 mL). After the mixture had been stirred for 1 h at this temperature, water (100 mL) was added and the mixture was warmed to 60 °C until the evolution of gas ceased. The dark brown solution was extracted twice with EtOAc, and the extracts were washed with water and brine and dried with Na_2SO_4. Evaporation

of the solvent and column chromatography (PE/EtOAc, 5:1) yielded phenol **13** (3.49 g, 18.1 mmol, 54%) as a brown solid. R_f = 0.45 (PE/EtOAc, 5:1), m.p. 100−101 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.84 (m_c, 4 H, 6-CH_2, 7-CH_2), 2.71, 2.84 (each t, J = 5.2 Hz, each 2 H, 5-CH_2, 8-CH_2), 5.59 (s, 1 H, OH), 7.46 (d, J = 2.0 Hz, 1 H, 2-H), 7.58 (s, 1 H, 4-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0, 22.3 (C-6, C-7), 23.4 (C-8), 29.8 (C-5), 106.6 (C-2), 116.5 (C-4), 132.0 (C-8a), 140.0 (C-4a), 145.9 (C-3), 153.9 (C-1). MS (EI, 70 eV): *m*/*z* (%) = 193 (100) $[M]^+$, 176 (22) $[M - OH]^+$, 147 (28) $[M - NO_2]^+$. $C_{10}H_{11}NO_3$ (193.205).

1-Benzyloxy-3-nitro-5,6,7,8-tetrahydronaphthalene (14): Phenol **13** (3.49 g, 18.1 mmol) was dissolved in an acetone/DMF mixture (2:1, 27 mL), and K_2CO_3 (3.48 g, 25.2 mmol, 1.5 equiv.), benzyl bromide (2.43 mL, 21.7 mmol, 1.2 equiv.), and tetrabutylammonium iodide (333 mg, 905 μmol, 0.05 equiv.) were added. After stirring for 14 h at room temperature, the solution was concentrated and taken up in EtOAc. The organic extract was washed five times with water, then with brine, dried with Na_2SO_4, and concentrated in vacuo. Benzyl ether **14** (4.96 g, 17.5 mmol, 97%) was isolated as a brown, amorphous solid. R_f = 0.56 (PE/EtOAc, 4:1), m.p. 96−98 °C. UV (CH_3CN): λ_{max} (lg ε) = 294.5 nm (3.852). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3425, 2927, 1523, 1340. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.82 (m_c, 4 H, 6-CH_2, 7-CH_2), 2.82 (m_c, 4 H, 5-CH_2, 8-CH_2), 5.14 (s, 2 H, OCH_2), 7.35−7.46 (m, 5 H, *o*-H, *m*-H, *p*-H), 7.56 (d, J = 2.1 Hz, 1 H, 2-H), 7.63 (s, 1 H, 4-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 22.3 (C-6, C-7), 23.9 (C-8), 29.8 (C-5), 70.2 (OCH_2), 102.8 (C-2), 116.9 (C-4), 127.2 (*o*-C), 128.1, (*p*-C), 128.7 (*m*-C), 134.5 (C-8a), 136.2 (*i*-C), 139.4 (C-4a), 146.1 (C-3), 156.6 (C-1). MS (EI, 70 eV): *m*/*z* (%) = 283 (18) $[M]^+$, 91 (100) $[C_7H_7]^+$. $C_{17}H_{17}NO_3$ (283.330).

3-Amino-1-benzyloxy-5,6,7,8-tetrahydronaphthalene (30): A mixture of benzyl ether **14** (4.61 g, 16.3 mmol) in 1,4-dioxane (22 mL) and $PtO_2 \cdot H_2O$ (20 mg, 0.86 mmol, 0.05 equiv.) was placed under an atmosphere of hydrogen (3 bar) and stirred for 24 h. After the catalyst had been removed by filtration through celite, the solution was evaporated to dryness. Amine **30** (4.12 g, 16.3 mmol, quantitative yield) was obtained as a brown solid and was used in the next step without further purification. R_f = 0.29 (PE/EtOAc, 5:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.74 (m_c, 4 H, 6-CH_2, 7-CH_2), 2.64 (m_c, 4 H, 5-CH_2, 8-CH_2), 3.32 (br. s, 2 H, NH_2), 5.01 (s, 2 H, OCH_2), 6.08, 6.14 (each s, each 1 H, 2-H, 4-H), 7.30−7.44 (m, 5 H, *o*-H, *m*-H, *p*-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.7, 23.0, 23.1 (C-6, C-7, C-8), 29.8 (C-5), 69.6 (OCH_2), 97.3 (C-2), 107.8 (C-4), 116.7 (C-8a), 126.9 (*o*-C), 127.6, (*p*-C), 128.4 (*m*-C), 137.6 (*i*-C), 139.2 (C-4a), 144.4 (C-3), 157.3 (C-1). MS (EI, 70 eV): *m*/*z* (%) = 253 (71) $[M]^+$, 162 (38) $[M - C_7H_7]^+$, 91 (100) $[C_7H_7]^+$. $C_{17}H_{19}NO$ (253.346).

1-Benzyloxy-3-(*tert*-butyloxycarbonylamino)-5,6,7,8-tetrahydronaphthalene (31): Di-*tert*-butyl dicarbonate (4.44 g, 20.3 mmol, 1.25 equiv.) was added to a solution of amine **30** (4.10 g, 16.2 mmol) in 1,4-dioxane (90 mL). After the mixture had been stirred for 24 h at room temperature, the solvent was evaporated and the residue was recrystallized from ethanol/water (1:1) to give amide **31** (4.70 g, 13.3 mmol, 82%) as light brown needles. R_f = 0.74 (PE/EtOAc, 5:1), m.p. 123 °C. UV (CH_3CN): λ_{max} (lg ε) = 215.5 nm (4.686), 244.5 (4.151), 281.5 (3.324), 287.5 (3.321). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3295, 2928, 1686, 1612, 1536. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.52 (s, 9 H, Boc-CH_3), 1.76 (m_c, 4 H, 6-CH_2, 7-CH_2), 2.68 (m_c, 4 H, 5-CH_2, 8-CH_2), 5.05 (s, 2 H, OCH_2), 6.36 (br. s, 1 H, NH), 6.60, 6.95 (each s, each 1 H, 2-H, 4-H), 7.30−7.46 (m, 5 H, *o*-H, *m*-H, *p*-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.8, 22.9 (C-6, C-7, C-8), 28.3 (Boc-CH_3), 29.8 (C-5), 69.6 (OCH_2), 80.2 (Boc-C), 99.9 (C-2), 111.1 (C-4), 121.1 (C-8a), 127.1 (*o*-C), 127.6, (*p*-C), 128.4 (*m*-C), 136.2 (C-3), 137.6 (*i*-C), 138.8 (C-4a), 152.8 (C=O), 156.8 (C-1). MS (EI, 70 eV): *m*/*z* (%) = 353 (4) $[M]^+$, 297 (15) $[M - C_4H_9 + H]^+$, 91 (100) $[C_7H_7]^+$. $C_{22}H_{27}NO_3$ (353.465).

4-Benzyloxy-2-(*tert*-butyloxycarbonylamino)-1-iodo-5,6,7,8-tetrahydronaphthalene (9): A solution of amide **31** (4.65 g, 13.3 mmol) in methanol/water (4:1, 350 mL) was treated with HIO_3 (492 mg, 2.79 mmol, 0.21 equiv.) and iodine (1.38 g, 5.45 mmol, 0.41 equiv.) and heated under reflux with vigorous stirring for 1.5 h. Cooling of the mixture in an ice bath gave a white, voluminous precipitate, which was filtered off and washed with water. Thorough drying provided iodide **9** (6.00 g, 12.5 mmol, 94%) as white flakes. R_f = 0.64 (PE/EtOAc, 10:1), m.p. 135−137 °C. UV (CH_3CN): λ_{max} (lg ε) = 219.5 nm (4.664), 242.0 (4.194), 286.0 (3.289). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3388, 2937, 1730, 1595−^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.56 (s, 9 H, Boc-CH_3), 1.75 (m_c, 4 H, 6-CH_2, 7-CH_2), 2.67 (m_c, 4 H, 5-CH_2, 8-CH_2), 5.09 (s, 2 H, OCH_2), 7.04 (br. s, 1 H, NH), 7.30−7.46 (m, 5 H, *o*-H, *m*-H, *p*-H), 7.72 (s, 1 H, 3-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.3, 23.7, 24.0 (C-5, C-6, C-7), 28.4 (Boc-CH_3), 37.4 (C-8), 69.8 (OCH_2), 80.7 (Boc-C), 87.3 (C-1), 101.5 (C-3), 123.7 (C-4a), 127.3 (*o*-C), 127.7, (*p*-C), 128.4 (*m*-C), 136.7 (C-2), 137.1 (*i*-C), 139.9 (C-8a), 152.8 (C=O), 156.9 (C-1). MS (EI, 70 eV): *m*/*z* (%) = 479 (20) $[M]^+$, 423 (40) $[M - C_4H_9 + H]^+$, 296 (21) $[M - I - C_4H_9 + H]^+$, 91 (100) $[C_7H_7]^+$. $C_{22}H_{26}INO_3$ (479.357): calcd. (%) C 55.12, H 5.47; found C 55.18, H 5.32.

5-Benzyloxy-3-(*tert*-butyloxycarbonyl)-1-chloromethyl-1,2,6,7,8,9-hexahydro-3*H*-benz[*e*]indole (17). Alkylation: Amide **9** (500 mg, 1.04 mmol) was dissolved in DMF (12 mL) and treated with NaH (60% in oil, 100 mg, 2.50 mmol, 2.5 equiv.). After the mixture had been stirred at room temperature for 30 min, chloride **15** (231 mg, 2.08 mmol, 2.0 equiv.) was added, and after 14 h the reaction was quenched with saturated aq. NH_4Cl. After extraction with EtOAc, the extracts were washed with water and brine and dried with Na_2SO_4. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (PE/EtOAc, 20:1) to give 564 mg (11.02 mmol, 98%) of a yellow oil as a mixture of stable rotamers. R_f = 0.49, 0.59 (PE/EtOAc, 10:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.34/1.58 (each s, together 9 H, Boc-CH_3), 1.76 (m_c, 4 H, 6-CH_2, 7-CH_2), 2.70 (m_c, 4 H, 5-CH_2, 8-CH_2), 3.55−4.10 (m, 1 H, 1′-H_a), 4.43−4.51 (m, 1 H, 1′-H_b), 4.96−5.12 (m, 2 H, OCH_2), 5.93−6.05 (m, 2 H, 2′-H, 3′-H), 6.52−6.66 (m, 1 H, 3-H), 7.30−7.49 (m, 5 H, *o*-H, *m*-H, *p*-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0, 23.7, 23.9 (C-5, C-6, C-7), 28.3/28.4 (Boc-CH_3), 37.1 (C-8), 46.0/49.0 (C-1′), 69.7 (OCH_2), 80.3/80.8 (Boc-C), 98.5/98.6 (C-1), 109.9/110.5 (C-3), 119.9/120.0 (C-3′), 121.1/121.4 (C-4a), 126.9/127.0 (*o*-C), 127.8 (2 signals) (*p*-C), 128.5 (2 signals) (*m*-C), 128.8/129.1 (C-2′), 136.7/136.8 (*i*-C), 141.0, 141.2, 141.4, 141.8 (C-2, C-8a), 153.8/154.0 (C=O), 156.2/156.3 (C-4). MS (EI, 70 eV): *m*/*z* (%) = 553 (2) $[M]^+$, 497 (9) $[M - C_4H_9 + H]^+$, 426 (8) $[M - I]^+$, 370 (98) $[M - I - C_4H_9 + H]^+$, 91 (100) $[C_7H_7]^+$. HRMS calcd. for $C_{25}H_{29}ClINO_3$ (553.167): 553.0840; found 553.0880.

Cyclization: A solution of the alkylated product (564 mg, 1.02 mmol) in toluene (17.0 mL) was degassed thoroughly and treated with nBu$_3$SnH (0.36 mL, 1.28 mmol, 1.25 equiv.) and AIBN (18 mg, 101 μmol, 0.1 equiv.) After the mixture had been stirred for 2.5 h at 80 °C, the volatiles were removed in vacuo and the residue was dissolved in Et_2O. The solution was washed with 10% aq. KF and dried with Na_2SO_4. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (PE/EtOAc, 20:1). Benzyl ether **17** (336 mg, 786 μmol, 77%) was obtained as a white solid. R_f = 0.38 (PE/EtOAc, 20:1),

m.p. 157 °C. UV (CH_3CN): λ_{max} (lg ε) = 220.5 nm (4.596), 254.5 (4.101), 297.5 (3.638). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3445, 2939, 1693, 1595, 1480. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.57 (s, 9 H, Boc-CH_3), 1.68, 1.88 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 2.55−2.83 (m, 4 H, 6-CH_2, 9-CH_2), 3.34 (dd, *J* = 11.1, 10.5 Hz, 1 H, 10-H_a), 3.50 (dddd, *J* = 9.1, 10.5, 2.0, 2.1 Hz, 1 H, 1-H), 3.70 (dd, *J* = 11.1, 2.1 Hz, 1 H, 10-H_b), 3.93 (dd, *J* = 11.8, 9.1 Hz, 1 H, 2-H_a), 4.14 (br. d, *J* = 11.8 Hz, 2-H_b), 5.07 (s, 2 H, OCH_2), 7.31−7.47 (m, 6 H, 4-H, *o*-H, *m*-H, *p*-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.5, 22.6, 23.2 (C-6, C-7, C-8), 26.7 (C-9), 28.4 (Boc-CH_3), 41.5 (C-1), 45.8 (C-10), 52.5 (C-2), 69.7 (OCH_2), 80.7 (Boc-C), 97.1 (C-4), 119.6 (C-9b), 120.3 (C-5a), 127.1 (*o*-C), 127.6 (*p*-C), 128.4 (*m*-C), 134.4 (C-9a), 137.4 (*i*-C), 141.2 (C-3a), 152.5 (C=O), 157.1 (C-5). MS (DCI, 200 eV): *m*/*z* (%) = 445 (100) $[M + NH_4]^+$, 389 (9) $[M - C_4H_9 + NH_4]^+$. $C_{25}H_{30}ClNO_3$ (427.975).

***syn*-Benzyl Ether 18 and *anti*-Benzyl Ether 19. Alkylation:** In accordance with the procedure given above, amide **9** (500 mg, 1.04 mmol) was treated with NaH (60% in oil, 100 mg, 2.50 mmol, 2.5 equiv.) and chloride **16** (261 mg, 2.09 mmol, 2.0 equiv.) to give 590 mg (1.04 mmol, 99%) of a yellow oil as a mixture of stable rotamers. R_f = 0.40, 0.48 (PE/EtOAc, 10:1). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.34/1.55 (each s, together 9 H, Boc-CH_3), 1.76 (m_c, 4 H, 6-CH_2, 7-CH_2), 1.88/2.05 (each s, together 3 H, 4′-CH_3), 2.70 (m, 4 H, 5-CH_2, 8-CH_2), 3.64−4.05 (m, 1 H, 1′-H_a), 4.43−4.49 (m, 1 H, 1′-H_b), 4.95−5.12 (m, 2 H, OCH_2), 5.68−5.75 (m, 1 H, 2′-H), 6.54−6.66 (m, 1 H, 3-H), 7.27−7.44 (m, 5 H, *o*-H, *m*-H, *p*-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0, 23.7, 23.8 (C-5, C-6, C-7), 20.9/26.1 (C-4′), 28.2/28.4 (Boc-CH_3), 37.1 (C-8), 46.4/47.9//48.8 (C-1′), 69.7 (OCH_2), 80.0/80.5 (Boc-C), 98.6 (C-1), 109.8/110.4 (C-3), 121.9/122.1 (C-4a), 123.0 (C-2′), 126.8 (*o*-C), 127.7 (2 signals) (*p*-C), 128.4 (2 signals) (*m*-C), 132.0 (C-3′), 136.7 (2 signals) (*i*-C), 140.9, 141.0, 141.3, 142.1 (C-2, C-8a), 153.7/153.9 (C=O), 156.2/156.7 (C-4). MS (DCI, 200 eV): *m*/*z* (%) = 585 (100) $[M + NH_4]^+$, 529 (22) $[M - C_4H_9 + H]^+$. $C_{26}H_{31}ClINO_3$ (567.894).

Cyclization: A solution of the alkylated product (590 mg, 1.04 mmol) in toluene (17 mL) was degassed thoroughly and treated with *n*Bu_3SnH (0.40 mL, 1.44 mmol, 1.39 equiv.) and AIBN (45 mg, 276 μmol, 0.25 equiv.). After the mixture had been stirred for 3.5 h at 80 °C, all volatile components were removed in vacuo and the residue was dissolved in Et_2O. The solution was washed with 10% equiv. KF and dried with Na_2SO_4. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (PE/EtOAc, 20:1). The *syn*-benzyl ether **18** (171 mg, 387 μmol, 37%) and *anti*-benzyl ether **19** (193 mg, 437 μmol, 42%) were both obtained as white solids containing traces of *n*Bu_3Sn-compounds.

Compound 18: R_f = 0.55 (PE/EtOAc, 10:1), m.p. 179−180 °C, dec. UV (CH_3CN): λ_{max} (lg ε) = 221.0 nm (4.641), 255.5 (4.143), 298.0 (3.685). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3442, 2935, 1692, 1593, 1452. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 7.4 Hz, 3 H, 11-CH_3), 1.57 (s, 9 H, Boc-CH_3), 1.58−1.95 (m, 4 H, 7-CH_2, 8-CH_2), 2.50−2.86 (m, 4 H, 6-CH_2, 9-CH_2), 3.69 (br. d, *J* = 9.5 Hz, 1 H, 1-H), 3.89 (dd, *J* = 11.8, 9.9 Hz, 1 H, 2-H_a), 4.22 (br. d, *J* = 11.8 Hz, 2-H_b), 4.42 (dq, *J* = 4.0, 7.0 Hz, 1 H, 10-H), 5.07 (s, 2 H, OCH_2), 7.31−7.48 (m, 6 H, 4-H, *o*-H, *m*-H, *p*-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.9 (C-11), 22.6, 23.2 (C-6, C-7, C-8), 27.0 (C-9), 28.5 (Boc-CH_3), 45.9 (C-1), 49.4 (C-2), 57.8 (C-10), 69.7 (OCH_2), 80.5 (Boc-C), 97.0 (C-4), 119.8, 120.2 (C-5a, C-9b), 127.1 (*o*-C), 127.6 (*p*-C), 128.4 (*m*-C), 134.2 (C-9a), 137.4 (*i*-C), 141.5 (C-3a), 152.2 (C=O), 157.0 (C-5). MS (EI, 70 eV): *m*/*z* (%) = 441 (18) $[M]^+$, 385 (36) $[M - C_4H_9 + H]^+$, 322 (38) $[M - C_4H_9 - C_2H_4Cl + H]^+$, 91 (100) $[C_7H_7]^+$.

Compound 19: R_f = 0.42 (PE/EtOAc, 10:1), m.p. 186−188 °C, dec. UV (CH_3CN): λ_{max} (lg ε) = 219.0 nm (4.651), 252.0 (4.172), 298.0 (3.718). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3443, 2934, 1688, 1593, 1483. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.56 (s, 9 H, Boc-CH_3), 1.57 (d, *J* = 7.0 Hz, 3 H, 11-CH_3), 1.70, 1.92 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 2.49−2.88 (m, 4 H, 6-CH_2, 9-CH_2), 3.44 (ddd, *J* = 10.1, 2 × 3.5 Hz, 1 H, 1-H), 3.90 (dd, *J* = 10.1, 10.5 Hz, 1 H, 2-H_a), 4.13 (br. d, *J* = 10.5 Hz, 2-H_b), 4.47 (dq, *J* = 3.5, 7.0 Hz, 1 H, 10-H), 5.07 (s, 2 H, OCH_2), 7.30−7.54 (m, 6 H, 4-H, *o*-H, *m*-H, *p*-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.5, 22.6, 23.3 (C-6, C-7, C-8), 23.4 (C-11), 27.3 (C-9), 28.5 (Boc-CH_3), 45.9 (C-1), 49.5 (C-2), 59.4 (C-10), 69.6 (OCH_2), 80.4 (Boc-C), 96.7 (C-4), 120.0 (C-9b), 121.2 (C-5a), 127.1 (*o*-C), 127.5 (*p*-C), 128.4 (*m*-C), 134.2 (C-9a), 137.5 (*i*-C), 141.5 (C-3a), 152.2 (C=O), 156.8 (C-5). MS (EI, 70 eV): *m*/*z* (%) = 441 (20) $[M]^+$, 385 (35) $[M - C_4H_9 + H]^+$, 322 (100) $[M - C_4H_9 - C_2H_4Cl + H]^+$, 91 (65) $[C_7H_7]^+$ − $C_{26}H_{32}ClNO_3$ (442.002).

General Procedure 1. Cleavage of the Benzyl Ether 17−19: Pd/C (10%, 1.1 weight-equiv.) and ammonium formate (0.9 weight-equiv.) were added to a solution of the benzyl ether in acetone (25 mL/mmol). The mixture was stirred for the specified time (1−24 h) at the specified temperature (25−56 °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 the product.

3-(*tert*-Butyloxycarbonyl)-1-chloromethyl-5-hydroxy-1,2,6,7,8,9-hexahydro-3*H*-benz[*e*]indole (7): According to General Procedure 1, benzyl ether **17** (135 mg, 315 μmol) was treated with 10% Pd/C (150 mg, 141 μmol) and NH_4HCO_2 (122 mg, 1.93 mmol) for 2.5 h at room temperature. Phenol **7** (104 mg, 308 μmol, 97%) was isolated as a brownish solid. R_f = 0.16 (PE/EtOAc, 10:1), m.p. 137−140 °C. UV (CH_3CN): λ_{max} (lg ε) = 219.5 nm (4.585), 252.0 (4.137), 298.0 (3.670). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3394, 2936, 1675, 1601, 1416. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.55 (s, 9 H, Boc-CH_3), 1.67, 1.88 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 2.48−2.72 (m, 4 H, 6-CH_2, 9-CH_2), 3.31 (dd, *J* = 11.1, 10.5 Hz, 1 H, 10-H_a), 3.47 (dddd, *J* = 9.0, 10.5, 2 × 2.0 Hz, 1 H, 1-H), 3.68 (dd, *J* = 11.1, 2.0 Hz, 1 H, 10-H_b), 3.90 (dd, *J* = 11.8, 9.0 Hz, 1 H, 2-H_a), 4.10 (br. d, *J* = 11.8 Hz, 2-H_b), 6.11 (s, 1 H, OH), 7.33 (br. s, 1 H, 4-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.5, 22.7 (C-6, C-7, C-8), 26.7 (C-9), 28.4 (Boc-CH_3), 41.5 (C-1), 45.8 (C-10), 52.5 (C-2), 81.2 (Boc-C), 100.2 (C-4), 118.0 (C-9b), 119.5 (C-5a), 134.6 (C-9a), 140.7 (C-3a), 152.7 (C=O), 154.4 (C-5). MS (EI, 70 eV): *m*/*z* (%) = 337 (26) $[M]^+$, 281 (77) $[M - C_4H_9 + H]^+$, 232 (100) $[M - C_4H_9 - CH_2Cl + H]^+$, 188 (42) $[M - Boc - CH_2Cl]^+$. $C_{18}H_{24}ClNO_3$ (337.850): calcd. (%)C 63.99, H 7.16; found C 63.76, H 6.97.

***syn*-Phenol 8a:** According to General Procedure 1, benzyl ether **18** (144 mg, 326 μmol) was treated with 10% Pd/C (158 mg, 148 μmol) and NH_4HCO_2 (130 mg, 2.06 mmol) for 1.5 h at 50 °C. Phenol **8a** (85 mg, 242 μmol, 74%) was isolated as a white solid. R_f = 0.43 (PE/EtOAc, 5:1), m.p. 193−196 °C, dec. UV (CH_3CN): λ_{max} (lg ε) = 220.0 nm (4.553), 252.5 (4.084), 298.5 (3.622). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3383, 2970, 1683, 1603, 1487. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 7.2 Hz, 3 H, 11-CH_3), 1.57 (s, 9 H, Boc-CH_3), 1.66, 1.91 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 2.43−2.74 (m, 4 H, 6-CH_2, 9-CH_2), 3.66 (ddd, *J* = 9.8, 2 × 3.5 Hz, 1 H, 1-H), 3.85 (dd, *J* = 11.9, 9.8 Hz, 1 H, 2-H_a), 4.18 (br. d, *J* = 11.9 Hz, 1 H, 2-H_b), 4.40 (dq, *J* = 3.5, 7.2 Hz, 1 H, 10-H), 5.51 (br. s, 1 H, OH), 7.28 (br. s, 1 H, 4-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.8 (C-11), 22.6, 22.8 (C-6, C-7, C-8), 26.9 (C-9), 28.5 (Boc-CH_3), 45.9 (C-1), 49.4 (C-2), 57.8 (C-10), 81.1 (Boc-C), 100.3 (C-4), 117.9 (C-5a), 119.8 (C-9b), 134.5 (C-9a), 141.1 (C-3a), 152.4 (C=O), 154.3

(C-5). MS (DCI, 200 eV): *m/z* (%) = 369 (100) $[M + NH_4]^+$. $C_{19}H_{26}ClNO_3$ (351.877): calcd. C 64.85, H 7.45; found C 64.64, H 7.15.

***anti*-Phenol 8b:** According to General Procedure 1, benzyl ether **19** (183 mg, 414 μmol) was treated with 10% Pd/C (201 mg, 189 μmol) and NH_4HCO_2 (165 mg, 2.62 mmol) for 2 h at 50 °C. Phenol **8b** (117 mg, 333 μmol, 80%) was isolated as a brownish solid. R_f = 0.35 (PE/EtOAc, 5:1), m.p. 168−171 °C, dec. UV (CH_3CN): λ_{max} (lg ε) = 217.5 nm (4.537), 250.0 (4.113), 298.5 (3.647). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3379, 2974, 1674, 1602, 1487. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.54−1.76 (m, 14 H, 7-CH_2/8-CH_2, 11-CH_3, Boc-CH_3), 1.98 (m_c, 2 H, 7-CH_2/8-CH_2), 2.43−2.76 (m, 4 H, 6-CH_2, 9-CH_2), 3.40 (m_c, 1 H, 1-H), 3.86 (dd, *J* = 11.3, 9.5 Hz, 1 H, 2-H_a), 4.11 (br. d, *J* = 11.3 Hz, 1 H, 2-H_b), 4.44 (dq, *J* = 3.6, 7.0 Hz, 1 H, 10-H), 5.05 (br. s, 1 H, OH), 7.32 (br. s, 1 H, 4-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.5, 22.6, 22.8 (C-6, C-7, C-8), 23.4 (C-11), 27.2 (C-9), 28.5 (Boc-CH_3), 45.9 (C-1), 49.5 (C-2), 59.4 (C-10), 80.7 (Boc-C), 100.1 (C-4), 117.8 (C-5a), 120.3 (C-9b), 134.4 (C-9a), 141.1 (C-3a), 152.4 (C=O), 154.1 (C-5). MS (DCI, 200 eV): *m/z* (%) = 369 (100) $[M + NH_4]^+$, 313 (92) $[M - C_4H_9 + NH_4]^+$. $C_{19}H_{26}ClNO_3$ (351.877): calcd. (%) C 64.85, H 7.45; found C 64.98, H 7.29.

General Procedure 2: Coupling of **7**, **8**, **17**−**19** with **20**: The substrates were dissolved in 4 M HCl/1,4-dioxane (25 mL/mmol) and stirred at room temperature for the specified time. The solution was concentrated in vacuo, and the residue was thoroughly dried in vacuo. It was then dissolved in dry degassed DMF (17 mL/mmol) and treated with 3.0 equiv. of EDC and 1.0 equiv. of bisindolylcarboxylic acid **20**.[9] After the mixture had been stirred for 18 h at room temperature, a small amount of silica gel was added, and the solvents were evaporated to dryness. Flash chromatography (solvent gradient 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 addition of petroleum ether. The precipitate was collected by a glass frit, washed with Et_2O and a small amount of acetone, and thoroughly dried.

5-Benzyloxy-1-chloromethyl-3-[(5′-{[(1*H*-indol-2′′-yl)carbonyl]-amino}-1*H*-indol-2′-yl)carbonyl]-1,2,6,7,8,9-hexahydro-3*H*-benz-[*e*]indole (22): According to General Procedure 2, benzyl ether 17 (70 mg, 160 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The residue was treated with EDC (93 mg, 480 μmol) and acid 20 (51 mg, 160 μmol). Indole derivative 22 (45 mg, 72 μmol, 45%) was obtained as a yellowish powder. R_f = 0.68 (PE/acetone/MeOH, 10:6:1). UV (CH_3CN): λ_{max} (lg ε) = 207.0 nm (4.810), 319.0 (4.666). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3417, 3282, 2930, 1618, 1523. ^1H NMR (500 MHz, [D_6]DMSO): δ = 1.60, 1.83 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 2.51 (m_c, 1 H, 9-H_a), 2.63−2.72 (m, 3 H, 6-CH_2, 9-H_b), 3.67 (dd, *J* = 11.2, 9.5 Hz, 1 H, 10-H_a), 3.76 (m_c, 1 H, 1-H), 3.87 (dd, *J* = 11.2, 2.6 Hz, 1 H, 10-H_b), 4.45 (d, *J* = 11.5 Hz, 1 H, 2-H_a), 4.58 (dd, 2 × *J* = 11.5 Hz, 2-H_b), 5.06 (s, 2 H, OCH_2), 7.06 (t, *J* = 7.9 Hz, 1 H, 5′′-H), 7.13 (s, 1 H, 3′-H), 7.22 (t, *J* = 7.9 Hz, 1 H, 6′′-H), 7.31 (t, *J* = 8.1 Hz, 1 H, *p*-H), 7.38 (t, *J* = 8.0 Hz, 2 H, *m*-H), 7.41 (s, 1 H, 3′′-H), 7.44 (d, *J* = 7.8 Hz, 2 H, *o*-H), 7.49 (d, *J* = 7.8 Hz, 2 H, 6′-H, 7′′-H), 7.57 (d, *J* = 7.8 Hz, 1 H, 7′-H), 7.66 (d, *J* = 7.9 Hz, 1 H, 4′′-H), 7.77 (br. s, 1 H, 4-H), 8.19 (s, 1 H, 4′-H), 10.14 (s, 1 H, CONH), 11.65 (s, 2 H, indole-NH). ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 22.1, 23.2 (C-6, C-7, C-8), 25.9 (C-9), 41.1 (C-1), 46.8 (C-10), 54.5 (C-2), 69.3 (OCH_2), 99.4 (C-4), 103.5 (C-3′′), 105.5 (C-3′), 112.3, 112.4 (C-7′, C-7′′), 113.1 (C-6′′), 119.4, 119.9 (C-4′, C-6′), 121.3, 121.4, 121.7 (C-5a, C-9b, C-4′′), 123.7 (C-5′′), 127.2 (C-3a′, C-3a′′), 127.2 (*o*-C), 127.8 (*p*-C), 128.5 (*m*-C), 131.4 (C-2′′), 131.7, 131.9 (C-2′, C-5′), 133.4 (C-7a′), 134.4 (C-9a), 136.8 (C-7a′′), 137.4 (*i*-C), 141.9 (C-3a), 155.9 (C-5), 159.7 (CONH′′), 159.9 (CONH′). MS (DCI, 200 eV): *m/z* (%) = 646 (100) $[M + NH_4]^+$, 629 (16) $[M + H]^+$, 610 (19) $[M - HCl + NH_4]^+$. $C_{38}H_{33}ClN_4O_3$ (629.163).

***syn*-Benzyl Ether 23:** According to General Procedure 2, *syn*-benzyl ether **18** (70 mg, 158 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The residue was treated with EDC (93 mg, 480 μmol) and acid **20** (50 mg, 160 μmol). Indole derivative **23** (46 mg, 72 μmol, 45%) was obtained as a white powder. R_f = 0.93 (PE/acetone/MeOH, 10:6:1). UV (CH_3CN): λ_{max} (lg ε) = 207.5 nm (4.852), 319.0 (4.705). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3419, 3282, 2930, 1615, 1523. ^1H NMR (500 MHz, [D_6]DMSO): δ = 1.09 (d, *J* = 7.0 Hz, 3 H, 11-CH_3), 1.61, 1.83 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 2.50−2.57 (m, 1 H, 9-H_a), 2.64−2.74 (m, 3 H, 6-CH_2, 9-H_b), 3.86 (m_c, 1 H, 1-H), 4.57 (m_c, 3 H, 2-CH_2, 10-H), 5.08 (s, 2 H, OCH_2), 7.07 (t, *J* = 8.0 Hz, 1 H, 5′′-H), 7.17 (s, 1 H, 3′-H), 7.21 (t, *J* = 8.0 Hz, 1 H, 6′′-H), 7.32 (t, *J* = 7.5 Hz, 1 H, *p*-H), 7.38 (t, *J* = 8.0 Hz, 2 H, *m*-H), 7.42 (s, 1 H, 3′′-H), 7.45 (d, *J* = 7.5 Hz, 2 H, *o*-H), 7.49 (d, *J* = 8.1 Hz, 2 H, 6′-H, 7′′-H), 7.59 (d, *J* = 8.1 Hz, 1 H, 7′-H), 7.67 (d, *J* = 8.0 Hz, 1 H, 4′′-H), 7.78 (br. s, 1 H, 4-H), 8.24 (s, 1 H, 4′-H), 10.15 (s, 1 H, CONH), 11.69 (s, 2 H, indole-NH). ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 17.9 (C-11), 22.0 (2 signals), 23.0 (C-6, C-7, C-8), 26.0 (C-9), 46.1 (C-1), 51.7 (C-2), 58.1 (C-10), 69.2 (OCH_2), 99.4 (C-4), 103.4 (C-3′′), 105.4 (C-3′), 112.1, 112.3 (C-7′, C-7′′), 113.0 (C-6′′), 119.3, 119.8 (C-4′, C-6′), 121.1, 121.4, 121.5 (C-5a, C-9b, C-4′′), 123.5 (C-5′′), 127.0, 127.1 (C-3a′, C-3a′′), 127.1 (*o*-C), 127.6 (*p*-C), 128.4 (*m*-C), 131.2 (C-2′′), 131.7, 131.9 (C-2′, C-5′), 133.3 (C-7a′), 134.3 (C-9a), 136.7 (C-7a′′), 137.2 (*i*-C), 141.7 (C-3a), 155.9 (C-5), 159.5 (CONH′′), 159.7 (CONH′). MS (DCI, 200 eV): *m/z* (%) = 660 (100) $[M + NH_4]^+$, 624 (9) $[M - HCl + NH_4]^+$. $C_{39}H_{35}ClN_4O_3$ (643.190).

***anti*-Benzyl Ether 24:** According to General Procedure 2, *anti*-benzyl ether **19** (70 mg, 158 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The residue was treated with EDC (93 mg, 480 μmol) and acid **20** (50 mg, 160 μmol). Indole derivative **24** (55 mg, 86 μmol, 54%) was obtained as a beige powder. R_f = 0.94 (PE/acetone/MeOH, 10:6:1). UV (CH_3CN): λ_{max} (lg ε) = 205.5 nm (4.796), 317.5 (4.624). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3410, 3286, 2930, 1619, 1543. ^1H NMR (500 MHz, [D_6]DMSO): δ = 1.58 (d, *J* = 6.9 Hz, 3 H, 11-CH_3), 1.59, 1.87 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 2.54 (m_c, 1 H, 9-H_a), 2.66−2.77 (m, 3 H, 6-CH_2, 9-H_b), 3.77 (d, *J* = 9.2 Hz, 1 H, 1-H), 4.49−4.56 (m, 2 H, 2-CH_2), 4.61 (dq, *J* = 2.3, 6.8 Hz, 1 H, 10-H), 5.08 (s, 2 H, OCH_2), 7.07 (t, *J* = 8.1 Hz, 1 H, 5′′-H), 7.22 (t, *J* = 8.1 Hz, 1 H, 6′′-H), 7.23 (s, 1 H, 3′-H), 7.31 (t, *J* = 7.8 Hz, 1 H, *p*-H), 7.39 (t, *J* = 7.8 Hz, 2 H, *m*-H), 7.42 (s, 1 H, 3′′-H), 7.44−7.48 (m, 4 H, 6′-H, 7′′-H, *o*-H), 7.57 (d, *J* = 7.9 Hz, 1 H, 7′-H), 7.67 (d, *J* = 8.0 Hz, 1 H, 4′′-H), 7.85 (br. s, 1 H, 4-H), 8.25 (s, 1 H, 4′-H), 10.14 (s, 1 H, CONH), 11.66 (s, 1 H, indole-NH), 11.68 (s, 1 H, indole-NH). ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 22.0, 22.1, 23.1 (C-6, C-7, C-8), 23.4 (C-11), 26.1 (C-9), 45.7 (C-1), 51.2 (C-2), 60.7 (C-10), 69.2 (OCH_2), 99.2 (C-4), 103.4 (C-3′′), 105.5 (C-3′), 112.1, 112.3 (C-7′, C-7′′), 113.0 (C-6′′), 119.2, 119.8 (C-4′, C-6′), 121.1, 121.5, 122.2 (C-5a, C-9b, C-4′′), 123.5 (C-5′′), 127.1, 127.2 (C-3a′, C-3a′′), 127.1 (*o*-C), 127.6 (*p*-C), 128.4 (*m*-C), 131.3 (C-2′′), 131.6, 131.9 (C-2′, C-5′), 133.3 (C-7a′), 134.0 (C-9a), 136.7 (C-7a′′), 137.3 (i-C), 141.9 (C-3a), 155.6 (C-5), 159.5, 159.6 (CONH′, CONH′′). MS (DCI, 200 eV): *m/z* (%) = 660 (59) $[M + NH_4]^+$, 643 (18) $[M + H]^+$, 624 (100) $[M - HCl + NH_4]^+$, 607 (24) $[M - HCl + H]^+$. $C_{39}H_{35}ClN_4O_3$ (643.190).

Phenol 25: According to General Procedure 2, amide **7** (65 mg, 192 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The residue was

treated with EDC (111 mg, 577 μmol) and acid **20** (61 mg, 192 μmol). Phenol **25** (16 mg, 30 μmol, 15%) was obtained as a grayish powder. R_f = 0.69 (PE/acetone/MeOH, 10:6:1). UV (CH_3CN): λ_{max} (lg ε) = 205.0 nm (4.534), 316.5 (4.390). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3428, 3275, 2932, 1658, 1521. ^1H NMR (500 MHz, [D_7]DMF): δ = 1.66, 1.88 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 2.55 (m_c, 1 H, 9-H_a), 2.68−2.78 (m, 3 H, 6-CH_2, 9-H_b), 3.70 (dd, *J* = 11.2, 9.7 Hz, 1 H, 10-H_a), 3.79 (m_c, 1 H, 1-H), 3.94 (dd, *J* = 11.2, 2.6 Hz, 1 H, 10-H_b), 4.59 (d, *J* = 11.5 Hz, 1 H, 2-H_a), 4.65 (dd, *J* = 11.5, 10.3 Hz, 2-H_b), 7.10 (t, *J* = 8.0 Hz, 1 H, 5′′-H), 7.20 (s, 1 H, 3′-H), 7.25 (t, *J* = 8.0 Hz, 1 H, 6′′-H), 7.51 (s, 1 H, 3′′-H), 7.58 (d, *J* = 8.2 Hz, 1 H, 7′-H), 7.61 (d, *J* = 8.2 Hz, 1 H, 7′′-H), 7.69 (d, *J* = 8.0 Hz, 1 H, 6′-H), 7.71 (d, *J* = 8.0 Hz, 1 H, 4′′-H), 7.72 (br. s, 1 H, 4-H), 8.36 (s, 1 H, 4′-H), 10.24 (s, 1 H, CONH), 11.55 (s, 1 H, indole-NH), 11.70 (s, 1 H, indole-NH). ^{13}C NMR (125 MHz, [D_7]DMF): δ = 23.2 (2 signals), 23.4 (C-6, C-7, C-8), 26.7 (C-9), 42.6 (C-1), 47.2 (C-10), 55.4 (C-2), 102.8 (C-4), 103.9 (C-3′′), 106.1 (C-3′), 112.8, 113.0 (C-7′, C-7′′), 113.4 (C-4′), 119.6 (C-6′), 120.3, 120.4 (C-5a, C-9b), 120.6 (C-5′′), 122.4 (C-4′′), 124.3 (C-6′′), 128.4, 128.5 (C-3a′, C-3a′′), 132.7 (C-2′), 133.0, 133.1 (C-5′, C-2′′), 134.3, 134.9 (C-9a, C-7a′), 137.9 (C-7a′′), 142.5 (C-3a), 156.2 (C-5), 160.5, 160.6 (CONH′, CONH′′). MS (ESI): *m*/*z* (%) = 537 (100) $[M - H]^-$, 501 (71) $[M - HCl - H]^+$. $C_{31}H_{27}ClN_4O_3$ (539.038).

***syn*-Phenol 26:** According to General Procedure 2, *syn*-amide **8a** (64 mg, 182 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The residue was treated with EDC (111 mg, 577 μmol) and acid **20** (58 mg, 182 μmol). *syn*-Phenol **26** (10 mg, 18 μmol, 10%) was obtained as a beige powder. R_f = 0.76 (PE/acetone/MeOH, 10:6:1). UV (CH_3CN): λ_{max} (lg ε) = 206.0 nm (4.453), 318.5 (4.363). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3426, 3291, 2932, 1621. ^1H NMR (500 MHz, [D_7]DMF): δ = 1.16 (d, *J* = 7.2 Hz, 3 H, 11-CH_3), 1.65, 1.88 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 2.51−2.57 (m, 1 H, 9-H_a), 2.69−2.76 (m, 3 H, 6-CH_2, 9-H_b), 3.88 (d, *J* = 10.1 Hz, 1 H, 1-H), 4.60−4.64 (m, 2 H, 2-H_a, 10-H), 4.70 (d, *J* = 10.8 Hz, 1 H, 2-H_b), 7.10 (t, *J* = 8.0 Hz, 1 H, 5′′-H), 7.23 (s, 1 H, 3′-H), 7.25 (t, *J* = 8.0 Hz, 1 H, 6′′-H), 7.51 (s, 1 H, 3′′-H), 7.56 (d, *J* = 8.0 Hz, 1 H, 7′-H), 7.59 (d, *J* = 8.0 Hz, 1 H, 7′′-H), 7.68 (d, *J* = 8.1 Hz, 1 H, 4′′-H), 7.71 (d, *J* = 8.0 Hz, 1 H, 6′-H), 7.72 (br. s, 1 H, 4-H), 8.39 (s, 1 H, 4′-H), 10.22 (s, 1 H, CONH), 11.57 (s, 1 H, indole-NH), 11.67 (s, 1 H, indole-NH). ^{13}C NMR (125 MHz, [D_7]DMF): δ = 18.2 (C-11), 23.2 (2 signals), 23.9 (C-6, C-7, C-8), 27.0 (C-9), 47.4 (C-1), 52.5 (C-2), 58.9 (C-10), 103.0 (C-4), 103.9 (C-3′′), 106.1 (C-3′), 112.8, 113.0 (C-7′, C-7′′), 113.5 (C-4′), 119.8 (C-6′), 120.4, 120.5 (2 signals) (C-5a, C-9b, C-5′′), 122.3 (C-4′′), 124.2 (C-6′′), 128.4, 128.5 (C-3a′, C-3a′′), 132.5 (C-2′), 133.0, 133.1 (C-5′, C-2′′), 134.3, 134.9 (C-9a, C-7a′), 137.9 (C-7a′′), 142.6 (C-3a), 156.2 (C-5), 160.4, 160.5 (CONH′, CONH′′). MS (ESI): *m*/*z* (%) = 1104 (33) $[2\,M - 2H]^{2-}$, 552 (100) $[M - H]^-$, 516 (54) $[M - HCl - H]^+$. $C_{32}H_{29}ClN_4O_3$ (553.065).

***anti*-Phenol 27:** According to General Procedure 2, *anti*-amide **8b** (64 mg, 182 μmol) was stirred in 4 M HCl/1,4-dioxane for 1 h. The residue was treated with EDC (111 mg, 577 μmol) and acid **20** (58 mg, 182 μmol). *anti*-Phenol **27** (23 mg, 42 μmol, 23%) was obtained as a beige powder. R_f = 0.77 (PE/acetone/MeOH, 10:6:1). UV (CH_3CN): λ_{max} (lg ε) = 205.0 nm (4.741), 318.0 (4.646). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3428, 3279, 2930, 1655, 1521. ^1H NMR (500 MHz, [D_7]DMF): δ = 1.63, 1.90 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 1.66 (d, *J* = 6.9 Hz, 3 H, 11-CH_3), 2.51−2.57 (m, 1 H, 9-H_a), 2.71−2.75 (m, 3 H, 6-CH_2, 9-H_b), 3.80 (d, *J* = 10.0 Hz, 1 H, 1-H), 4.59−4.68 (m, 3 H, 2-CH_2, 10-H), 7.10 (t, *J* = 7.9 Hz, 1 H, 5′′-H), 7.25 (t, *J* = 8.0 Hz, 1 H, 6′′-H), 7.28 (s, 1 H, 3′-H), 7.52 (s, 1 H, 3′′-H), 7.57 (d, *J* = 8.1 Hz, 1 H, 7′-H), 7.60 (d, *J* = 8.1 Hz, 1 H, 7′′-H), 7.67 (d, *J* = 8.0 Hz, 2 H, 6′-H, 4′′-H), 7.78 (br. s, 1 H, 4-H), 8.38 (s, 1 H, 4′-H), 10.22 (s, 1 H, CONH), 11.52 (s, 1 H, indole-NH), 11.68 (s, 1 H, indole-NH). ^{13}C NMR (125 MHz, [D_7]DMF): δ = 23.2, 23.3, 23.8, 23.9 (C-6, C-7, C-8, C-11), 27.2 (C-9), 47.0 (C-1), 52.2 (C-2), 61.5 (C-10), 102.8 (C-4), 103.9 (C-3′′), 106.2 (C-3′), 112.7, 113.0 (C-7′, C-7′′), 113.5 (C-4′), 119.6 (C-6′), 120.1 (C-5a), 120.5 (C-5′′), 121.4 (C-9b), 122.3 (C-4′′), 124.2 (C-6′′), 128.5 (2 signals) (C-3a′, C-3a′′), 132.7 (C-2′), 132.9, 133.1 (C-5′, C-2′′), 134.3, 134.7 (C-9a, C-7a′), 137.8 (C-7a′′), 142.7 (C-3a), 155.9 (C-5), 160.3, 160.5 (CONH′, CONH′′). MS (ESI): *m*/*z* (%) = 552 (100) $[M - H]^-$, 516 (41) $[M - HCl - H]^+$. $C_{32}H_{29}ClN_4O_3$ (553.065).

General Procedure 3: Glycosidation and coupling of phenols **7**, **8a**, and **8b** with **20**. The phenol was dissolved in dry CH_2Cl_2 (50 mL/mmol) and treated with molecular sieves (4Å, 6.90 g/mmol) and tetraacetyl trichloroacetimidate **21** (1.05 equiv.).[20] The mixture was stirred for 30 min at room temperature, and $BF_3{\cdot}OEt_2$ (7.7 equiv.) was added dropwise at −10 °C. Stirring was continued for 1 h at this temperature, and the mixture was then 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 in vacuo. The residue was dissolved in dry degassed DMF (17 mL/mmol) and treated with EDC (2.2 equiv.) and acid **20** (0.9 equiv.).[9] After the mixture had been stirred for 18 h, a small amount of silica gel was added, and the solvents were evaporated to dryness. Flash chromatography (PE/EtOAc, 2:1 // PE/EtOAc, 1:2 // PE/acetone/MeOH, 10:6:1) gave the peracetylated galactosides, which were dissolved in dry MeOH (40 mL/mmol) and treated with a solution of NaOMe in MeOH (5.4 M, 2.0 equiv.). Water (20 mL/mmol) was added after 4 h of stirring, and the precipitate was collected with a glass frit, washed with water, and thoroughly dried to provide the desired prodrugs.

Galactoside 5: According to General Procedure 3, phenol **7** (100 mg, 296 μmol) was treated with tetraacetyl trichloroacetimidate **21** (152 mg, 304 μmol), $BF_3{\cdot}OEt_2$ (0.30 mL, 2.28 mmol), and molecular sieves (2.06 g), followed by EDC (128 mg, 658 μmol) and acid **20** (83 mg, 263 μmol) to give 116 mg of the peracetylated galactoside (133 μmol), which was treated with NaOMe/MeOH (5.4 M, 49 μL, 266 μmol). Galactoside **5** (51 mg, 73 μmol, 25%) was obtained as a beige powder, as a mixture of diastereomers. R_f (intermediate product) = 0.65 (PE/acetone/MeOH, 10:6:1). UV (CH_3CN): λ_{max} (lg ε) = 206.5 nm (4.694), 317.0 (4.619). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3405, 3289, 2929, 1616, 1519. ^1H NMR (500 MHz, [D_7]DMF): δ = 1.64, 1.86 (each m_c, each 2 H, 7-CH_2, 8-CH_2), 2.53−2.58 (m, 1 H, 9-H_a), 2.71−2.79 (m, 3 H, 6-CH_2, 9-H_b), 3.58−3.63 (m, 1 H, 6*-H_a), 3.69 (m_c, 1 H, 6*-H_b), 3.75−3.79 (m, 2 H, 1-H, 10-H_a), 3.82 (m, 2 H, 3*-H, 5*-H), 3.95−4.00 (m, 2 H, 10-H_b, 2*-H), 4.60−4.75 (m, 3 H, 2-CH_2, 4*-H), 4.90 (d, *J* = 8.0 Hz, 1 H, 1*-H), 7.10 (t, *J* = 8.1 Hz, 1 H, 5′′-H), 7.20/7.22 (each s, together 1 H, 3′-H), 7.26 (t, *J* = 8.1 Hz, 1 H, 6′′-H), 7.52 (s, 1 H, 3′′-H), 7.59−7.63 (m, 2 H, 7′-H, 7′′-H), 7.71 (m_c, 2 H, 6′-H, 4′′-H), 8.00 (br. s, 1 H, 4-H), 8.38 (s, 1 H, 4′-H), 10.22 (s, 1 H, CONH), 11.63 (s, 1 H, indole-NH), 11.67 (s, 1 H, indole-NH). ^{13}C NMR (125 MHz, [D_7]DMF): δ = 23.0 (2 signals), 23.8, 23.9 (C-6, C-7, C-8), 26.8 (C-9), 42.4/42.6 (C-1), 47.0 (C-10), 55.3/55.5 (C-2), 61.4 (C-6*), 69.2/69.3 (C-4*), 71.9/72.0 (C-2*), 74.8/74.9 (C-3*), 76.3 (C-5*), 102.9/103.1 (C-1*), 103.3 (C-4), 103.9 (C-3′′), 106.1 (C-3′), 112.8, 113.0 (C-7′, C-7′′), 113.5 (2 signals) (C-4′), 119.7 (C-6′), 120.5 (C-5′′), 122.3 (C-4′′), 123.2 (2 signals) (C-5a, C-9b),

124.2 (C-6′′), 128.3, 128.5 (C-3a′, C-3a′′), 132.6 (2 signals) (C-2′), 133.0, 133.1 (C-5′, C-2′′), 134.3, 134.9 (C-9a, C-7a′), 137.9 (C-7a′′), 142.7 (C-3a), 156.4/156.5 (C-5), 160.5, 160.8 (CONH′, CONH′′). MS (ESI): *m*/*z* (%) = 724 (100) $[M + Na]^+$, 700 (100) $[M - H]^-$. $C_{37}H_{37}ClN_4O_8$ (701.184).

***syn*-Galactoside 6a:** According to General Procedure 3, phenol **8a** (105 mg, 299 μmol) was treated with tetraacetyl trichloroacetimidate **21** (154 mg, 306 μmol), $BF_3{\cdot}OEt_2$ (304 μL, 2.30 mmol), and molecular sieves (2.07 g), followed by EDC (129 mg, 663 μmol) and acid **20** (83 mg, 264 μmol) to give 190 mg of the peracetylated galactoside (215 μmol), which was treated with NaOMe/MeOH (5.4 M, 79 μL, 430 μmol). *syn*-Galactoside **6a** (65 mg, 91 μmol, 42%) was obtained as a gray powder, as a mixture of diastereomers. R_f (intermediate product) = 0.41 (PE/EtOAc, 1:1). UV (CH_3CN): λ_{max} (lg ε) = 207.0 nm (4.643), 316.5 (4.569). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3406, 2931, 1619, 1525, 1464. ^1H NMR (500 MHz, [D$_7$]DMF): δ = 1.16/1.19 (each d, *J* = 7.3 Hz, together 3 H, 11-CH_3), 1.64, 1.86 (each m$_c$, each 2 H, 7-CH_2, 8-CH_2), 2.53−2.59 (m, 1 H, 9-H_a), 2.70−2.80 (m, 3 H, 6-CH_2, 9-H_b), 3.63 (m$_c$, 1 H, 6*-H_a), 3.68−3.72 (m, 1 H, 6*-H_b), 3.77 (m$_c$, 1 H, 1-H), 3.82−3.86 (m, 2 H, 3*-H, 5*-H), 3.96−4.00 (m, 1 H, 2*-H), 4.63−4.75 (m, 4 H, 2-CH_2, 10-H, 4*-H), 4.92 (d, *J* = 7.5 Hz, 1 H, 1*-H), 7.11 (t, *J* = 8.1 Hz, 1 H, 5′′-H), 7.25−7.28 (m, 2 H, 3′-H, 6′′-H), 7.54 (s, 1 H, 3′′-H), 7.61−7.64 (m, 2 H, 7′-H, 7′′-H), 7.69 (d, *J* = 8.0 Hz, 1 H, 4′′-H), 7.72 (d, *J* = 8.1 Hz, 1 H, 6′-H), 8.02 (br. s, 1 H, 4-H), 8.39 (d, *J* = 2.0 Hz, 1 H, 4′-H), 10.24 (s, 1 H, CONH), 11.66−11.70 (m, 2 H, indole-NH). ^{13}C NMR (125 MHz, [D$_7$]DMF): δ = 18.2/18.3 (C-11), 23.0 (2 signals), 23.8, 23.9 (C-6, C-7, C-8), 27.0 (C-9), 47.4 (C-1), 52.7 (C-2), 58.7 (2 signals) (C-10), 61.4 (C-6*), 69.2 (2 signals) (C-4*), 71.8/72.0 (C-2*), 74.8 (2 signals) (C-3*), 76.3 (C-5*), 102.9/103.0 (C-1*), 103.4 (C-4), 103.9 (C-3′′), 106.3 (C-3′), 112.9, 113.0 (C-7′, C-7′′), 113.5/113.6 (C-4′), 119.8 (C-6′), 120.5 (C-5′′), 122.3 (C-4′′), 123.2 (2 signals), 123.4 (C-5a, C-9b), 124.2 (C-6′′), 128.3, 128.4 (C-3a′, C-3a′′), 132.4 (2 signals) (C-2′), 133.0 (2 signals) (C-5′, C-2′′), 134.4, 134.5, 134.9 (C-9a, C-7a′), 137.8 (C-7a′′), 142.7 (C-3a), 156.5 (2 signals) (C-5), 160.5, 160.6, 160.7 (CONH′, CONH′′). MS (ESI): *m*/*z* (%) = 1451 (10) $[2 M + Na]^+$, 737 (100) $[M + Na]^+$. $C_{38}H_{39}ClN_4O_8$ (715.211).

***anti*-Galactoside 6b:** According to General Procedure 3, phenol **8b** (58 mg, 165 μmol) was treated with tetraacetyl trichloroacetimidate **21** (85 mg, 169 μmol), $BF_3{\cdot}OEt_2$ (168 μL, 1.27 mmol), and molecular sieves (1.14 g), followed by EDC (71 mg, 366 μmol) and acid **20** (46 mg, 146 μmol) to give 132 mg of the peracetylated galactoside (149 μmol), which was treated with NaOMe/MeOH (5.4 M, 55 μL, 299 μmol). *anti*-Galactoside **29** (48 mg, 67 μmol, 41%) was obtained as a gray powder, as a mixture of diastereomers. R_f (peracetylated galactoside) = 0.77 (PE/EtOAc, 1:2). UV (CH_3CN): λ_{max} (lg ε) = 206.0 nm (4.698), 311.5 (4.630). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3406, 3330, 2930, 1620, 1531. ^1H NMR (500 MHz, [D$_7$]DMF): δ = 1.60, 1.89 (each m$_c$, each 2 H, 7-CH_2, 8-CH_2), 1.65/1.67 (each d, *J* = 7.0 Hz, 3 H, 11-CH_3), 2.51−2.56 (m, 1 H, 9-H_a), 2.68−2.80 (m, 3 H, 6-CH_2, 9-H_b), 3.62 (m$_c$, 1 H, 6*-H_a), 3.68−3.72 (m, 1 H, 6*-H_b), 3.76 (m$_c$, 1 H, 1-H), 3.81−3.85 (m, 2 H, 3*-H, 5*-H), 3.98−4.00 (m, 1 H, 2*-H), 4.63−4.71 (m, 4 H, 2-CH_2, 10-H, 4*-H), 4.91 (d, *J* = 7.5 Hz, 1 H, 1*-H), 7.10 (t, *J* = 8.0 Hz, 1 H, 5′′-H), 7.21/7.30 (each s, together 1 H, 3′-H), 7.26 (t, *J* = 8.0, 1 H, 6′′-H), 7.53 (s, 1 H, 3′′-H), 7.61 (d, *J* = 8.2 Hz, 1 H, 7′′-H), 7.56/7.62 (each d, *J* = 8.0 Hz, together 1 H, 7′-H), 7.70 (d, *J* = 8.1 Hz, 1 H, 4′′-H), 7.70/7.75 (each d, *J* = 8.0 Hz, together 1 H, 6′-H), 8.06 (br. s, 1 H, 4-H), 8.33/8.40 (each s, together 1 H, 4′-H), 10.23 (s, 1 H, CONH), 11.62/11.65/11.68/11.82 (each s, together 2 H, indole-NH). ^{13}C NMR (125 MHz, [D$_7$]DMF): δ = 23.0, 23.2, 24.0 (C-6, C-7, C-8), 24.3 (C-11), 27.2 (C-9), 46.2 (C-1), 51.4/52.5 (C-2), 60.4 (C-10), 61.4 (C-6*), 69.8 (2 signals) (C-4*), 71.8/72.0 (C-2*), 74.1 (2 signals) (C-3*), 75.4 (C-5*), 102.9/103.2 (C-1*), 104.5 (C-4), 104.6 (C-3′′), 105.6 (C-3′), 112.9, 113.0 (C-7′, C-7′′), 113.5/113.6 (C-4′), 119.9 (2 signals) (C-6′), 120.3 (C-5′′), 121.2 (C-4′′), 121.6, 121.7, 122.9 (C-5a, C-9b), 124.3 (C-6′′), 128.5 (C-3a′, C-3a′′), 132.5, 132.6 (C-2′), 133.0 (2 signals), 133.1 (C-5′, C-2′′), 134.3, 134.6 (C-9a, C-7a′), 137.8 (C-7a′′), 142.9 (C-3a), 156.2 (2 signals) (C-5), 160.5 (2 signals) (CONH′, CONH′′). MS (ESI): *m*/*z* (%) = 737 (100) $[M + Na]^+$. $C_{38}H_{39}ClN_4O_8$ (715.211).

2-(*tert*-Butyloxycarbonyl)-1,2,5,6,7,8,9,10-octahydrocyclopropa[*c*]benz[*e*]indol-4-one (28): Phenol **7** (10 mg, 30 μmol) was dissolved in THF (0.75 mL) and treated with NaH (60% in oil, 3.0 mg, 75 μmol, 2.5 equiv.). After 24 h at room temperature the mixture was concentrated, and the residue was purified by column chromatography. Compound **28** (7.2 mg, 24 μmol, 80%) was obtained as a yellow oil. R_f = 0.33 (PE/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (dd, 2 × *J* = 5.5 Hz, 1 H, 9-H_a), 1.46 (s, 9 H, Boc-CH_3), 1.61 (dd, *J* = 8.0, 5.4 Hz, 1 H, 9-H_b), 1.55−1.66 (m, 4 H, 6-CH_2, 7-CH_2), 1.78−1.86, 2.20−2.41 (each m, each 2 H, 5-CH_2, 8-CH_2), 2.37 (ddd, *J* = 8.0, 2 × 5.5 Hz, 1 H, 10-H), 3.75 (dd, *J* = 5.5, 12.0 Hz, 1 H, 1-H_a), 3.86 (d, *J* = 12.0 Hz, 1 H, 1-H_b), 6.45 (br. s, 1 H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 22.0, 22.1 (C-5, C-6, C-7), 22.7, 23.2, 24.3 (C-8, C-9, C-10), 28.2 (Boc-CH_3), 36.6 (C-8b), 52.3 (C-1), 83.0 (Boc-C), 108.8 (C-3), 134.4 (C-4a), 145.4 (C-8a), 151.8 (C=O), 158.8 (C-2a), 187.8 (C-4) − $C_{18}H_{23}NO_3$ (301.389).

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 Dulbecco's modified Eagle's medium (DMEM) (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 6 multiwell plates at concentrations of 10^2, 10^3, 10^4, and 10^5 cells per cavity. Culture medium was removed (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 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 performed 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:

relative clone-forming rate [%] = 100 × (number of clones counted after exposure)/(number of clones counted in the control)

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, purchased from Sigma Germany, Deisenhofen, Germany) to the cells during incubation with the substances.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 416) and the Fonds der Chemischen Industrie. The authors would like to thank Stefanie Heidrich for her excellent work in the cytotoxicity tests. We are also indebted to BASF AG, Bayer AG, Degussa AG, Dragoco Gerberding & Co. AG, and Wacker-Chemie GmbH for generous gifts of chemicals.

[1] L. F. Tietze, in: *Molecular Aspects of Chemotherapy* (Ed.: E. Borowski, D. Shugar), Pergamon Press, New York **1990**.
[2] L. F. Tietze, M. Neumann, T. Möllers, R. Fischer, K.-H. Glüsenkamp, M. F. Rajewsky, E. Jähde, *Cancer Res.* **1989**, *49*, 4179−4184.
[3] L. F. Tietze, M. Beller, R. Fischer, M. Lögers, E. Jähde, K.-H. Glüsenkamp, M. F. Rajewsky, *Angew. Chem.* **1990**, *102*, 812−813; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 782−783.
[4] I. F. Tannock, D. Rotin, *Cancer Res.* **1989**, *49*, 4373−4384.
[5] G. M. Dubowchik, M. A. Walker, *Pharmacology & Therapeutics* **1999**, *83*, 67−123.
[6] K. N. Syrigos, A. A. Epenetos, *Anticancer Res.* **1999**, *19*, 605−613.
[7] C. J. Springer, I. Niculescu-Duvaz, *Adv. Drug Deliv. Rev.* **1997**, *26*, 151−172.
[8] D. L. Boger, D. S. Johnson, *Angew. Chem.* **1996**, *108*, 1542−1580; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1438−1474.
[9] D. L. Boger, C. W. Boyce, R. M. Garbaccio, J. A. Goldberg, *Chem. Rev.* **1997**, *97*, 787−828.
[10] D. L. Boger, R. M. Garbaccio, *Acc. Chem. Res.* **1999**, *32*, 1043−1052.
[11] R. Baird, S. Winstein, *J. Am. Chem. Soc.* **1963**, *85*, 567−578.
[12] L. F. Tietze, R. Hannemann, W. Buhr, M. Lögers, P. Menningen, M. Lieb, D. Starck, T. Grote, A. Döring, I. Schuberth, *Angew. Chem.* **1996**, *108*, 2840−2842; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2674−2677.
[13] L. F. Tietze, M. Lieb, T. Herzig, F. Haunert, I. Schuberth, *Bioorg. Med. Chem.* **2001**, *9*, 1929−1939.
[14] L. F. Tietze, T. Herzig, A. Fecher, F. Haunert, I. Schuberth, *ChemBioChem* **2001**, *2*, 758−765.
[15] G. Schroeter, *Justus Liebigs Ann. Chem.* **1922**, *426*, 1−160.
[16] H. O. Wirth, O. Königstein, W. Kern, *Justus Liebigs Ann. Chem.* **1960**, *643*, 84−104.
[17] V. F. Patel, S. L. Andis, J. K. Endema, D. A. Johnson, J. H. Kennedy, F. Mohamadi, R. M. Schultz, D. J. Soose, M. M. Spees, *J. Org. Chem.* **1997**, *62*, 8868−8874.
[18] D. L. Boger, C. W. Boyce, R. M. Garbaccio, M. Searcey, *Tetrahedron Lett.* **1998**, *39*, 2227−2230.
[19] T. Bieg, W. Szeja, *Synthesis* **1985**, 76−77.
[20] P. Zimmermann, R. Bommer, T. Bär, R. R. Schmidt, *J. Carbohy. Chem.* **1988**, *7*, 435−452.
[21] We call the new pharmacophoric group formed after nucleophilic substitution cyclopropylcyclohexadienone indoline ≡ CCI.
[22] D. L. Boger, C. W. Boyce, R. M. Garbaccio, M. Searcey, Q. Jin, *Synthesis* **1999**, 1505−1509.

Received November 27, 2001
[O01564]