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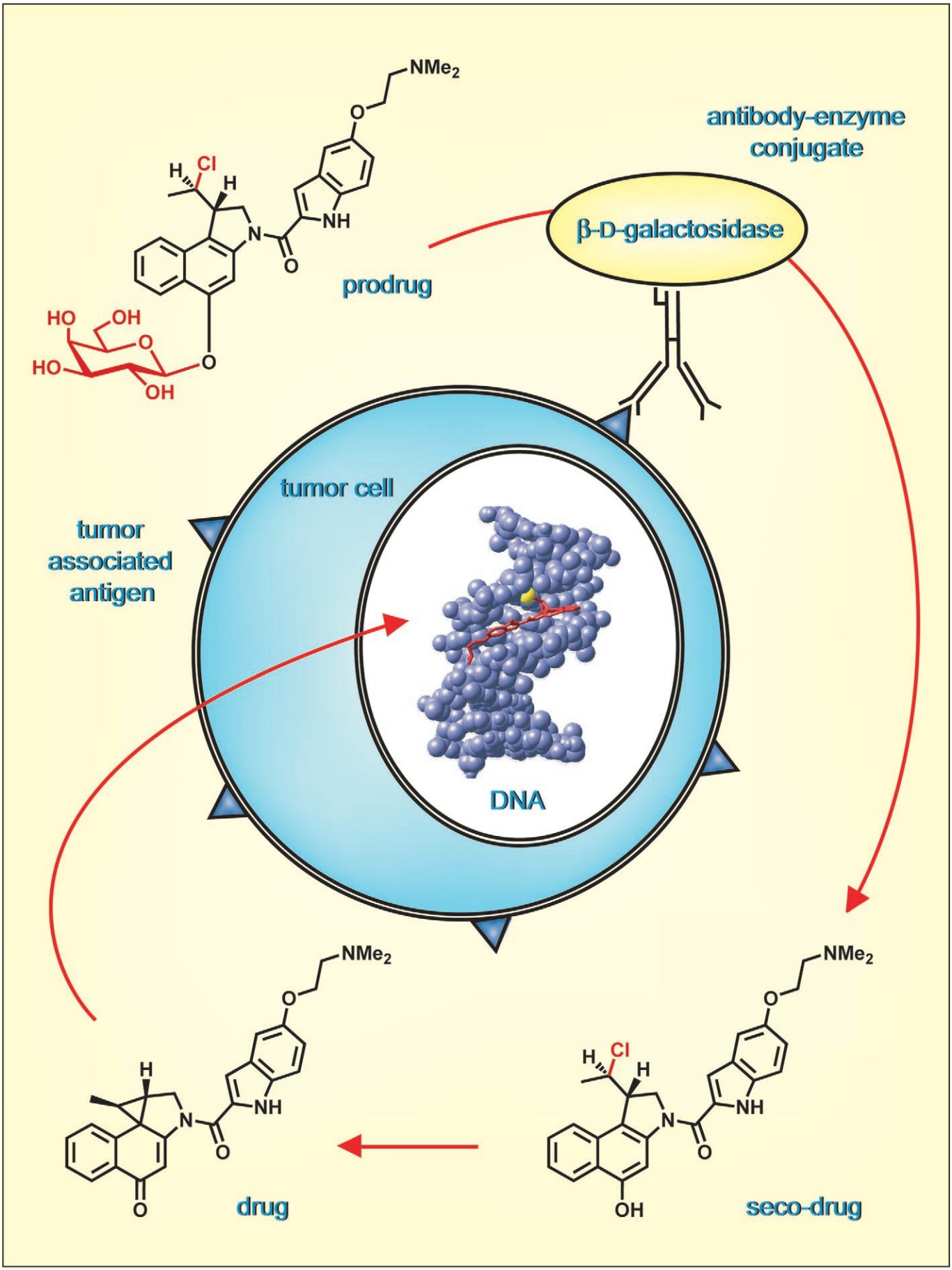

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Selective Treatment of Cancer: Synthesis, Biological Evaluation and Structural Elucidation of Novel Analogues of the Antibiotic CC-1065 and the Duocarmycins

Lutz F. Tietze,*[a] Felix Major,[a] Ingrid Schuberth,[a] Dirk A. Spiegl,[a] Birgit Krewer,[a] Katja Maksimenka,[b] Gerhard Bringmann,[b] and Jörg Magull[c]

Dedicated to Professor Burchard Franck on the occasion of his 80th birthday

Abstract: Novel diastereomerically pure β-D-galactosidic prodrugs (+)-**12a–e** of the cytotoxic antibiotics CC-1065 and the duocarmycins were prepared for an antibody directed enzyme prodrug therapy (ADEPT) using **4** as a substrate via a radical cyclization to give *rac*-**5** and *rac*-**6** followed by a chromatographic resolution of the enantiomers of *rac*-**5**, glycosidation and linkage to the DNA-binding units **10a–e**. These only slightly toxic compounds can be toxified enzymatically by an antibody–β-D-galactosidase conjugate at the surface of malignant cells to give the cytotoxic drugs, which then alkylate DNA. The new prodrugs were tested in in vitro cytotoxicity assays showing excellent QIC_{50} values of 4800 and 4300 for (+)-**12a** and (+)-**12b**, respectively. The absolute configuration of precursor (+)-**5** was determined by comparison of the experimental CD spectrum with the theoretically predicted CD spectra and by X-ray structure analysis.

Keywords: antitumor agents · cancer therapy · circular dichroism · prodrugs

Introduction

The antibody directed enzyme prodrug therapy (ADEPT)[1,2] is a promising concept for a selective treatment of cancer, in which a prodrug is enzymatically converted into a cytotoxic compound at the surface of malignant cells by employing an antibody–enzyme conjugate. It is a prerequisite that the prodrug has a relatively low toxicity whereas the corresponding drug selectively formed from the prodrug at the cancer cells should have a very high cytotoxicity. For a successful application of ADEPT in the treatment of cancer we propose the following requirements: The drug should have a high cytotoxicity with an IC_{50}[1] value of less than 10 nM and the QIC_{50} should be above 1000 [$QIC_{50} = IC_{50}$ (prodrug)/IC_{50} (prodrug + corresponding enzyme)].[3]

A class of compounds which is very appropriate for ADEPT is characterized by the antibiotic CC-1065 (**1**) and the duocarmycins such as **2**, which belong to the most potent antitumor agents discovered so far.[4] CC-1065 (**1**) and duocarmycin SA (**2**) specifically bind to double-stranded DNA within AT-rich minor grooves and alkylate *N*-3 of particular adenine moieties.[5] CC-1065 (**1**) itself, however, is less suitable due to a delayed lethal liver toxicity,[6] whereas other compounds of this type such as **2** having a similar cytotoxicity do not show this effect.

Some time ago we have demonstrated that the formation of the spirocyclopropane moiety as the pharmacophoric group of CC-1065 (**1**) and duocarmycin SA (**2**) from a corre-

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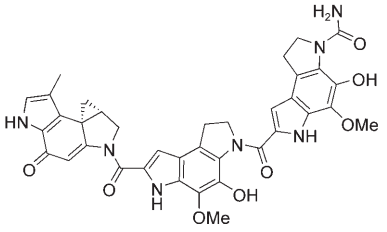
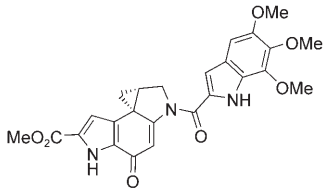
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author: CD spectra of (+)-**5** in different solvents (Figure S1), defined dihedral angles and heats of formation of the 16 minimum conformers of (1*S*,10*R*)-**5** (Table S1), CD spectra predicted by OM2 and TDDFT calculations.

[1] IC_{50} refers to the drug concentration required for 50% inhibition of target cells.

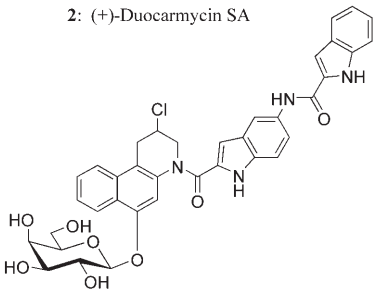
sponding seco-compound can be halted by transforming its phenolic hydroxyl group into a glycoside as shown in **3** (Scheme 1).[7] Such a derivative can be hydrolyzed enzymatically using a glycohydrolase which liberates the drug. In this way, glycosidic seco-CBI-Q **3** and similar compounds bearing a bisindolyl carboxylic acid moiety as a DNA-binding subunit were developed by us for ADEPT.[8,9] However, major drawbacks in their application are their poor water solubility and difficulties in the preparation of sufficient amounts of especially **3** due to low yields in the last steps of the synthesis. Moreover, the compounds have been employed so far as diastereomeric mixtures since the chiral core was used as a racemic mixture in the glycosidation.



1: (+)-CC-1065



2: (+)-Duocarmycin SA



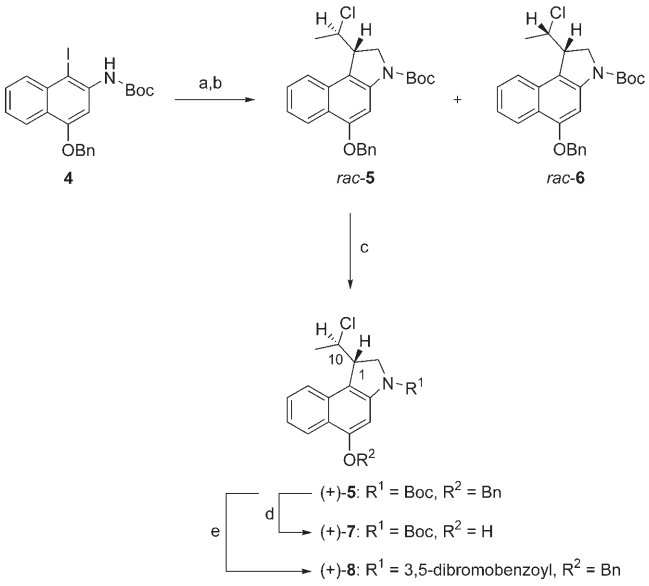
3: Prodrug

Scheme 1. Structures of (+)-CC-1065 (**1**), (+)-duocarmycin SA (**2**), and glycosidic prodrug **3**.

Here we describe a new type of prodrugs which are easily accessible, have a much better water solubility, can be prepared in diastereomerically pure form, and moreover show higher QIC_{50} values, which make these prodrugs superior to all other compounds described so far for the use in ADEPT. A short communication of parts of this work has recently been published.[10]

Results and Discussion

Synthesis and chromatographic resolution of the *N*-Boc-methyl-seco-CBI compound 5: *N*-Alkylation of the known iodonaphthylamine **4**[11] with (*E*/*Z*)-1,3-dichloro-2-butene and subsequent radical cyclization employing nontoxic tris-trimethylsilylsilane (TTMSS) and AIBN led to *N*-Boc-methyl-seco-CBI **5**/**6** (Scheme 2). In the ring formation, two stereogenic centers are formed, and since a facial differentiation does not occur, a 1:1 mixture of the diastereomers **5** and **6** was obtained as a racemic mixture. In vitro cytotoxicity tests showed that the diastereomers possess a considerable difference in their biological activity. Thus, compounds with a *syn*-orientation of the two hydrogens at the two stereogenic centers such as **6** (1*S*/*R*,10*S*/*R*) are not suitable for the development of prodrugs due to a rather low cytotoxicity of the corresponding seco-drugs, whereas compounds with the *anti*-orientation such as **5** (1*S*/*R*,10*R*/*S*) show appropriate properties.[8] The *syn*- and *anti*-diastereomers could be easily separated by chromatography on silica gel. For the synthesis of enantiopure (+)-**5** the use of classical resolution methods was investigated. However, differential crystallization of diastereomeric salts with enantiopure acids such as tartaric acid or camphorsulfonic acid and preparation of diastereomeric compounds using enantiopure reagents were not successful due to the low stability of the corresponding free amine of *rac*-**5**. Therefore, we employed an effective chromatographic resolution on a semipreparative Chiralpak IA column, which allowed the separation of 50 mg racemic **5** per injection within 10 min. By this method (+)-**5** and (−)-**5** could be obtained with *ee* values of 99.9%. Finally, the benzylic ether moiety in (+)-**5** was cleaved by catalytic transfer hydrogenation[12] to provide phenol (+)-**7** as a precursor of diastereopure glycosidic prodrugs.



Scheme 2. a) NaH, DMF, RT, 1 h, then (*E*/*Z*)-1,3-dichloro-2-butene, DMF, RT, 2 h, 98%; b) TTMSS, AIBN, toluene, 80 °C, 5 h, *rac*-**5**: 44%, *rac*-**6**: 42%; c) resolution of *rac*-**5**: Chiralpak IA (250×20 mm, particle size: 5 μm), CH_2Cl_2/*n*-heptane 4:1, flow: 18 mL min^{-1}, $\alpha = 2.05$, (+)-**5**: 99.9% *ee*, (−)-**5**: 99.9% *ee*; d) Pd/C/NH_4HCO_2, THF, 40 °C, 15 min, 93%; e) 4 M HCl/EtOAc, RT, 3 h, then 3,5-dibromobenzoic acid, EDC·HCl, DMF, RT, 19 h, 63%.

Determination of the absolute configuration of (+)-5 and (−)-5: The absolute configurations of the two enantiomers of **5** were independently determined by quantum chemical circular dichroism (CD) computations[13–15] and X-ray structure analysis. For the prediction of a reliable theoretical CD spectrum, in principle all possible conformational species that may influence the overall CD behavior had to be taken into consideration. For this purpose, two different approaches were applied: a comprehensive conformational analysis and, taking into account the high flexibility of the molecule, molecular dynamics (MD) simulations. Both calculations were arbitrarily started with the (1*S*,10*R*)-enantiomer of **5**. The conformational analysis was performed on the semiempirical AM1 level,[16] revealing the existence of 15 conformers with energies not higher than 3 kcal mol^{-1} above the global minimum (Figure 1 and Table S1 in the Supporting Information). In the case of the molecular dynamics simulation,[17] 1000 structures were extracted in 0.5 ps intervals over a total MD time of 500 ps.

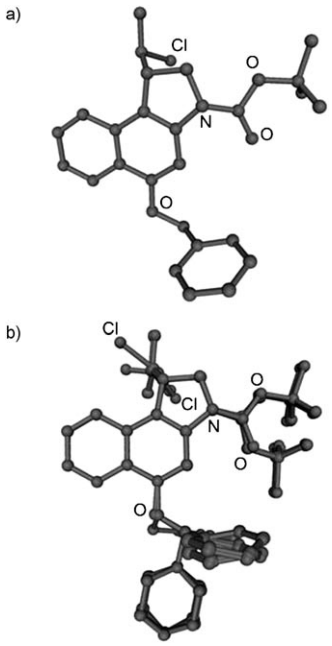


Figure 1. Results of the AM1 based conformational analysis of (1*S*,10*R*)-**5**; a) global minimum geometry; b) set of 15 conformers within a range of 3 kcal mol^{-1} above that global minimum.

Since halogen atoms are not parametrized within the semiempirical CNDO/S,[18] INDO/S,[19] and OM2 methods,[20] the chlorine atom in **5** had to be replaced by other appropriate groups. On the one hand an ethyl group as the closest no lone-pair electrons containing substituent and on the other hand a hydroxy group, which does possess an electron pair, were chosen. Based on the geometries found during the conformational analysis and the MD simulation, the chlorine atom was replaced by an ethyl substituent (to give structure **5a**) and, in a second approach, by a hydroxy group (i.e., structure **5b**). The geometries thus obtained were submitted to CD calculations at the semiempirical CNDO/S[18] level. For the 16 conformers obtained from the conformational analysis, CD calculations were also performed by the OM2[20] approach (Figure S2a, Supporting Information). Despite their identical absolute configuration, those two single conformers (Figure 2) that differed only in the position of the "freely" rotating phenyl ring, provided almost opposite CD spectra, once again demonstrating the necessity of considering all sufficiently populated conformational species and not only the global minimum structure.

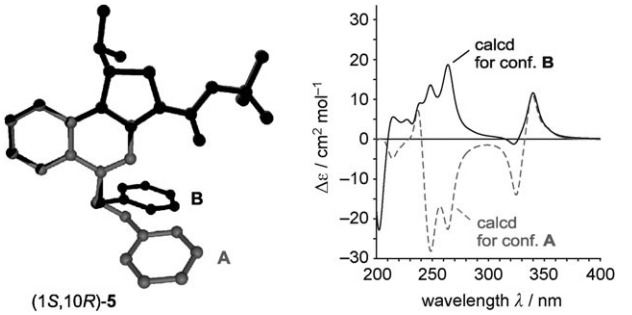


Figure 2. Two single conformers, **A** and **B**, of (1*S*,10*R*)-**5** that differ only in the orientation of the phenyl ring, and the corresponding CNDO/S based CD spectra.

The overall calculated CD curves were obtained by means of Boltzmann weighting of the single CD spectra, that is, according to the heat of formation of the respective conformer obtained during the conformational analysis (Figure 3a), while for the MD simulated structures the respective single spectra were just arithmetically added up (Figure 3b). Reflection of these calculated CD spectra at the zero line generated the theoretical spectra predicted for the enantiomeric compounds (1*R*,10*S*)-**5a** and (1*R*,10*S*)-**5b**. The comparison of the calculated CD spectra of both, (1*S*,10*R*)-**5a** and (1*S*,10*R*)-**5b**, with the measured CD curve of (+)-**5** showed a good agreement in the decisive region of 200–290 nm, while the broad doubled band between 300 and 380 nm was not entirely reproduced (Figure 3a, left). On the other hand, the respective MD based CD spectra reflected this region correctly (Figure 3b, left). Expectedly, the CD curves predicted for (1*R*,10*S*)-**5a** and (1*R*,10*S*)-**5b** behaved almost oppositely (Figure 3a, b, right). By this way, the absolute configuration of (+)-**5** was assigned to be (1*S*,10*R*). Unexpectedly, CD calculations at the TDDFT/B3LYP/TZVP[21–23] level gave less clear results (Figure S2b, Supporting Information).

These results were confirmed independently by structure elucidation using anomalous X-ray scattering of (+)-(1*S*,10*R*)-**8**, which was obtained from (+)-(1*S*,10*R*)-**5** by acid-catalyzed amine deprotection and subsequent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) mediated coupling with 3,5-dibromobenzoic acid.[24]

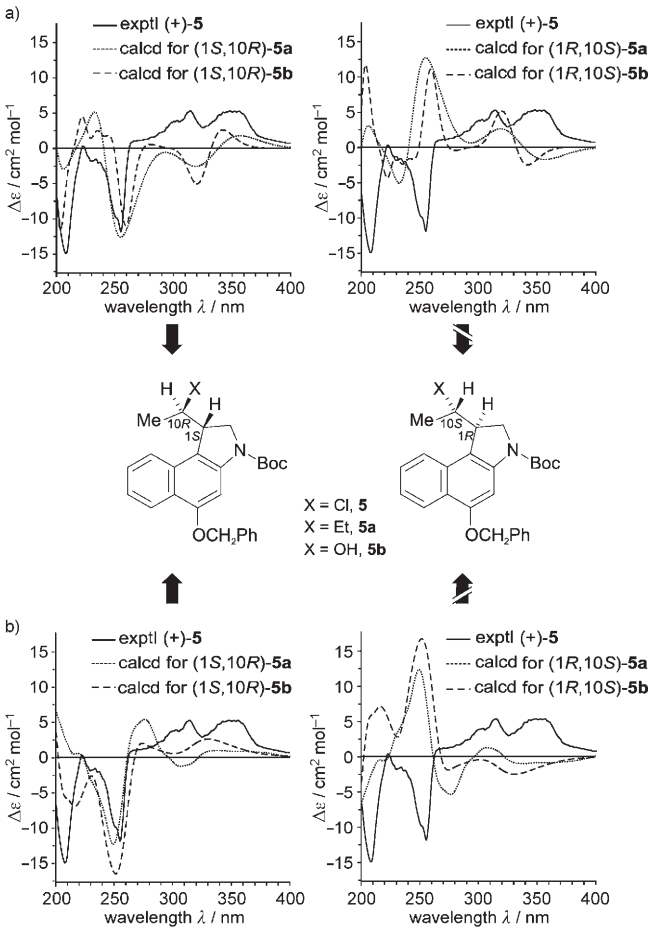
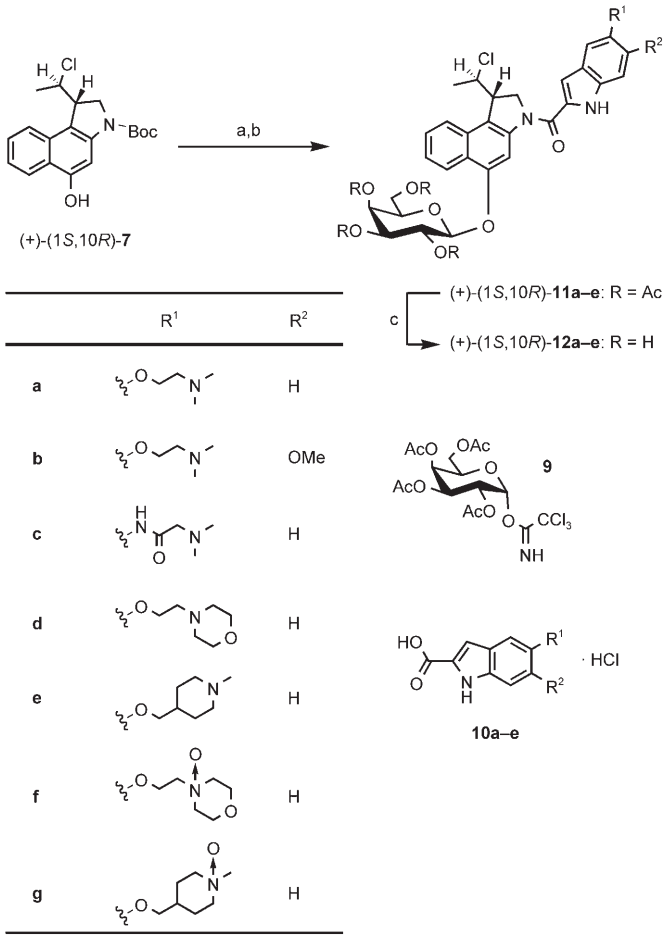


Figure 3. Determination of the absolute configuration of (+)-**5** as (1*S*,10*R*) by comparison of the experimental CD curve (in acetonitrile) with the theoretically predicted CD spectra (CNDO/S) of **5a** and **5b**; a) according to the conformational analysis; b) by using the MD method.

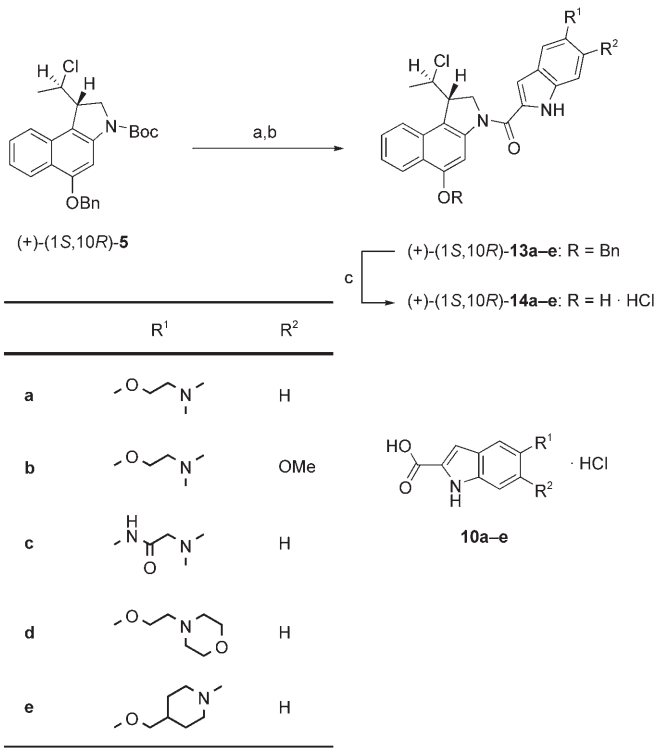


Scheme 3. Synthesis of β-D-galactosidic prodrugs (+)-(1*S*,10*R*)-**12a–e**: a) **9**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 4 Å MS, −10 °C → RT, 9 h; b) **10a–c**, EDC·HCl, DMF, RT, 20–22 h; **10d,e**, EDC·HCl, DMF, RT, 20–22 h, then $PtO_2{\cdot}H_2O$/H_2, EtOH, RT, 5–16 h; c) NaOMe/MeOH, RT, 20–120 min; yields from (+)-**7**: (+)-**12a**: 46%, (+)-**12b**: 43%, (+)-**12c**: 39%, (+)-**12d**: 29%, (+)-**12e**: 36%.

Synthesis of β-D-galactosidic prodrugs (+)-(1*S*,10*R*)-12a–e: As already mentioned, it has been shown for CC-1065 (**1**) that the type of the DNA-binding unit connected to the pharmacophoric group has a considerable influence on the toxicity of the drug and on the water solubility. Moreover, we expected that this unit might also affect the QIC_{50} values. We therefore prepared five novel glycosidic prodrugs **12a–e** which differ in the side chain of the indole carboxylic acids **10a–e**.[27,28]

For the synthesis of the β-D-galactosides (+)-(1*S*,10*R*)-**12a–c**, phenol (+)-(1*S*,10*R*)-**7** was treated with the trichloroacetimidate **9** of tetraacetylgalactose in the presence of $BF_3{\cdot}OEt_2$ using the Schmidt procedure (Scheme 3).[29] Since we were able to remove the protecting group at the nitrogen simultaneously during the glycosidation, a subsequent EDC·HCl-mediated addition of indole carboxylic acid hydrochlorides **10a–c** was performed providing **11a–c**. Finally, the acetate groups in **11a–c** were removed by solvolysis with sodium methoxide in methanol to give the desired β-D-galactoside prodrugs (+)-(1*S*,10*R*)-**12a–c** in 39–46% overall yield based on (+)-(1*S*,10*R*)-**7**. Surprisingly, the use of the indole carboxylic acid hydrochlorides **10d** and **e** in the protocol described above provided exclusively the *N*-oxide **11f** and a mixture of **11e** and **g**, respectively. However, reduction of the *N*-oxides using hydrogen in the presence of catalytic amounts of $PtO_2{\cdot}H_2O$ followed by solvolysis of the acetate groups yielded the desired β-D-galactosidic compounds (+)-(1*S*,10*R*)-**12d** in 29% and (+)-(1*S*,10*R*)-**12e** in 36% yield over four steps.

Synthesis of seco-drug hydrochlorides (+)-(1*S*,10*R*)-14a–e: For a comparison of the cytotoxicity of the β-D-galactosidic prodrugs (+)-(1*S*,10*R*)-**12a–e** in the presence of the enzyme β-D-galactosidase with the seco-drugs (+)-(1*S*,10*R*)-**14a–e** containing a free phenolic hydroxy group, we synthesized the corresponding unstable indoline hydrochloride salt, which was subsequently reacted in an EDC-mediated coupling with indole carboxylic acid hydrochlorides **10a–e** to give (+)-(1*S*,10*R*)-**13a–e** (Scheme 4). These compounds were converted into their hydrochlorides using again 4 M HCl/EtOAc. The debenzylation was then achieved under mild conditions using 10% Pd/C in the presence of ammoni-



Scheme 4. Synthesis of seco-drug hydrochlorides (+)-(1*S*,10*R*)-**14a–e**: a) 4 M HCl/EtOAc, RT, 3–3.5 h; b) **10a–e**, EDC·HCl, DMF, RT, 19–24 h; c) 4 M HCl/EtOAc, RT, 2 h, then Pd/C/NH_4HCO_2, THF, 40 °C, 20–120 min; yields from (+)-**5**: (+)-**14a**: 65%, (+)-**14b**: 57%, (+)-**14c**: 66%, (+)-**14d**: 69%, (+)-**14e**: 62%.

um formate[12] to yield the seco-drug hydrochlorides (+)-**14a–e** in a yield of 57–69% based on (+)-**5**. Direct debenzylation of (+)-**13a** to the corresponding phenol, by contrast, led to decomposition, which is probably due to deprotonation of the phenol moiety by the tertiary amine followed by cyclization and other unwanted side reactions. It is also noteworthy that the direct glycosidation of the seco-drug hydrochlorides, for example, (+)-**14a** using the Schmidt procedure was not successful. In contrast to the reaction of the galactoside of (+)-**7** with **10d** and **e**, the formation of *N*-oxides was not observed in the synthesis of **14d** and **e**.

In vitro cytotoxicity tests: The in vitro cytotoxicity assays were carried out in triplicate with coherent cells of the human bronchial carcinoma cell line A549 in six multiwell plates with concentrations of 10^2, 10^3, 10^4, and 10^5 cells per cavity. Incubation with various concentrations of seco-drug hydrochlorides (+)-**14a–e** and β-D-galactosidic prodrugs (+)-**12a–e** in the absence or in the presence of β-D-galactosidase was performed in ultraculture medium (Table 1). An important criterion is the comparison of the IC_{50} value of the seco-drug hydrochloride and the IC_{50} value of the galactosidic prodrug in the presence of β-D-galactosidase. If the IC_{50} values are similar one can assume that the seco-drug is formed from the prodrug and that the activity of the enzyme is not affected by the liberation of the seco-drug.

Table 1. In vitro cytotoxicity of β-D-galactosidic prodrugs (+)-**12a–e** in the presence or absence of β-D-galactosidase and of the seco-drug hydrochlorides (+)-**14a–e** against human bronchial carcinoma cells (A549).[a]

Compound	Addition of β-D-galactosidase	IC_{50} [nM]	QIC_{50}
(+)-**12a**	–	3.6×10^3	4800
(+)-**12a**	+	0.75	
(+)-**14a**	–	0.75	
(+)-**12b**	–	9.4×10^2	4300
(+)-**12b**	+	0.22	
(+)-**14b**	–	0.20	
(+)-**12c**	–	7.7×10^3	1300
(+)-**12c**	+	5.9	
(+)-**14c**	–	3.8	
(+)-**12d**	–	1.5×10^3	600
(+)-**12d**	+	2.5	
(+)-**14d**	–	3.7	
(+)-**12e**	–	8.3×10^2	1100
(+)-**12e**	+	0.75	
(+)-**14e**	–	0.80	

[a] Cells were exposed to various concentrations of the test substance for 24 h at 37 °C; after 12 days of incubation the clone formation was compared with an untreated control assay and the relative clone forming rate was determined. β-D-galactosidase: *Escherichia coli*, 4 U mL^{-1}.

The cytotoxicities found for all seco-drug hydrochlorides (+)-**14a–e** were similar to those observed for the corresponding glycosidic prodrugs (+)-**12a–e** in the presence of the enzyme β-D-galactosidase, which indicates that the enzyme is not deactivated in the hydrolytic process. Except for (+)-**12d**, all prodrugs fortunately met the requirements for a successful use in ADEPT ($QIC_{50} > 1000$; IC_{50} (prodrug + enzyme) < 10 nM). Prodrug (+)-**12a** is the most potent one with an excellent QIC_{50} of 4800 and a high cytotoxicity of the corresponding seco-drug (+)-**14a** (IC_{50} = 0.75 nM) as well as of the prodrug in presence of β-D-galactosidase (IC_{50} = 0.75 nM). Compound (+)-**12b** bearing an additional methoxy substituent at C-6 of the DNA-binding subunit is four times more toxic than (+)-**12a** but has a slightly lower QIC_{50} of 4300. By contrast, prodrug (+)-**12c**, which has no longer an *N*,*N*-dimethylaminoethoxy but an *N*,*N*-dimethylglycine substituent at C-5 of the indole moiety, shows a twofold decreased cytotoxicity compared with (+)-**12a**, also a decreased cytotoxicity of the corresponding seco-drug and a moderate QIC_{50} of 1300. Surprisingly, prodrug (+)-**12e** with a sterically demanding *N*-methylpiperidinyl-methoxy substituent is four times more toxic than (+)-**12a**. In addition, (+)-**12e** shows the same cytotoxicity in the presence of the enzyme as it was found for (+)-**12a** in the presence of the enzyme resulting in a moderate QIC_{50} of 1100. Finally, prodrug (+)-**12d** bearing a morpholinoethoxy substituent, which is also sterically demanding, is two times more toxic than (+)-**12a** whereas prodrug (+)-**12d** in the presence of the enzyme shows a three times lower cytotoxicity. This is the reason for the low QIC_{50} of 600, which is in our opinion not sufficient for an application of (+)-**12d** in ADEPT.

As expected, the different QIC_{50} values of our β-D-galactosidic prodrugs (+)-**12a–e** and the different cytotoxicity of

the seco-drug hydrochlorides (+)-**14a–e** are due to the nature of the DNA-binding indole subunit. In this context, Boger et al. have reported previously that substituents at C-5 of the DNA binding subunit have a pronounced effect on the rate and efficiency of DNA alkylation and the resulting biological potency of CC-1065 analogues, which is largely insensitive to the electronic character of the substituent but is sensitive to its size, rigid length, and shape.[30] This would explain why the different seco-drugs **14a–e** have such a different cytotoxicity, but it does not explain the different QIC_{50} values ranging from 4800 to 600. Further work will thus concentrate on this aspect; we intend to investigate the mode of action of these compounds employing our newly developed ESI-HRMS based method[31] for the determination of the DNA alkylation activity and selectivity.

Conclusion

Ten enantio- and diastereopure (+)-*anti*-methyl-seco-CBI compounds [(+)-**12a–e** and (+)-**14a–e**] bearing the DNA-binding subunits **10a–e** were prepared. In vitro cytotoxicity tests of these compounds against the human bronchial carcinoma cell line A549 revealed that all prodrugs except (+)-**12d** meet the requirements for a successful use in ADEPT. Moreover, β-D-galactosidic prodrugs (+)-**12a** and (+)-**12b** show excellent QIC_{50} values of 4800 and 4300, respectively; thus, these substances are superior to all compounds described so far for the use in ADEPT. Besides this, the cytotoxicities found for all seco-drug hydrochlorides (+)-**14a–e** were similar to those observed for the corresponding glycosidic prodrugs (+)-**12a–e** in the presence of the enzyme β-D-galactosidase, which indicates that the enzyme is not deactivated in the hydrolytic process. In addition, an advantage of all new compounds is their improved water solubility due to their solubilizing tertiary amino functionality as part of their DNA-binding subunit. Furthermore, resolution of precursor *rac*-**5** and determination of the absolute configuration of (+)-(1*S*,10*R*)-**5** by comparison of the experimental CD curve with the theoretically predicted CD spectra were reported. These results were confirmed independently by an X-ray structure analysis using anomalous scattering of the 3,5-dibromobenzoic acid amide (+)-(1*S*,10*R*)-**8**.

Experimental Section

General: All reactions were performed under argon in flame-dried flasks. All solvents were dried and distilled prior to use by usual laboratory methods. All reagents obtained from commercial sources were used without further purification. Thin-layer chromatography (TLC) was performed on precoated silica gel SIL G/UV_{254} plates (Macherey–Nagel) and silica gel 60 (0.032–0.063 mm, Merck) was used for column chromatography. Phosphomolybdic acid in MeOH (PMA) or vanillin in methanolic sulphuric acid were used as staining reagents for TLC. UV spectra were taken in CH_3CN or MeOH with a Perkin–Elmer Lambda 2 spectrometer. IR spectra were recorded as KBr pellets or as films with a Bruker IFS 25 spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in the solvent indicated. ^1H and ^{13}C NMR spectra were recorded with Mercury-200, VXR-200, Unity 300, Inova 500, Unity Inova-600 (Varian) or AMX 300 (Bruker) spectrometers. Chemical shifts are reported in δ (ppm) with tetramethylsilane (TMS) as internal standard. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured with a Finnigan MAT 95, TSQ 7000 and LCQ instrument. HRMS was performed with a 7 T FTICR-MS APEX IV (Bruker). The following abbreviations are used in the text: EtOAc = ethyl acetate, PE = petroleum ether (b.p. 35–60 °C).

CD measurements: CD spectra of (+)-(1*S*,10*R*)-**5** were obtained on a J-715 spectrometer (Jasco) in a 0.2 mm quartz cuvette at room temperature within the range of 200–400 nm.

Computational methods: The conformational analysis of **5** was performed on a Linux AMD MP 2800+ workstation using the semiempirical AM1[16] method as implemented in the program package Gaussian 98.[32] The molecular dynamics (MD) simulation was performed at a virtual temperature of 500 K using the TRIPOS[17] force field, as implemented in the molecular modeling package SYBYL. The overall simulation time was 500 ps.

The single structures of **5a** and **b** were created by the replacement of the chlorine atom of **5** by an ethyl and by a hydroxy group, respectively, using the program package Molden 4.2.[33] The wave functions for the calculation of the rotational strengths for the electronic transitions from the ground state to the excited states were obtained by CNDO/S-CI[18] and OM2-CI[20] computations with a CI expansion including 576 and 900 singly occupied configurations, respectively, and the ground state determinant. These calculations were carried out on a Linux Pentium III workstation by the use of the BDZDO/MCDSPD[34] and MNDO99[35] program packages. The calculated rotational strengths were transformed into $\Delta\varepsilon$ values and superimposed with a Gaussian band shape function. The CD spectra thus obtained were then UV-corrected[36] by 15 nm in the case of the conformational analysis, and by 5 nm for the MD based approach. Time-dependent DFT calculations of 35 excited states being lowest in energy were performed using the B3LYP[21,22] functional and a TZVP[23] basis set within the TURBOMOLE[37] suite of programs.

***rac*-(1*S*,10*R*)-5-Benzyloxy-3-(*tert*-butyloxycarbonyl)-1-(10-chloroethyl)-1,2-dihydro-3*H*-benz[*e*]indole (*rac*-5)**: A solution of amine **4** (9.51 g, 20.0 mmol) in DMF (100 mL) was added to a suspension of NaH (60% in oil, 2.00 g, 50.0 mmol) in DMF (150 mL) and the resulting mixture was stirred for 1 h at room temperature. Then, (*E*/*Z*)-1,3-dichloro-2-butene (4.31 mL, 5.00 g, 38.4 mmol) was added and the reaction mixture stirred for further 2 h followed by addition of a saturated aqueous solution of NH_4Cl (200 mL) and extraction with EtOAc (3×250 mL). The combined organic layers were washed with water (3×250 mL) and brine (250 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The resulting crude product was purified by column chromatography on silica gel (PE/EtOAc 20:1) to provide (*E*/*Z*)-2-amino-4-benzyloxy-*N*-(*tert*-butyloxycarbonyl)-*N*-(3-chloro-2-butenyl)-1-iodonaphthalene as a white solid (11.0 g, 19.5 mmol, 98%). R_f = 0.33, 0.40 (PE/EtOAc 10:1); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32/1.58 (s, 9H, $C(CH_3)_3$), 1.81/2.03 (s, 3H, 4′-CH_3), 3.77–4.31 (m, 1H, 1′-H_a), 4.41–4.64 (m, 1H, 1′-H_b), 5.25 (br s, 2H, OCH_2Ph), 5.65–5.90 (m, 1H, 2′-H), 6.65–6.88 (m, 1H, 3-H), 7.34–7.68 (m, 7H, 6-H, 7-H, 5×Ph-H), 8.15–8.37 ppm (m, 2H, 5-H, 8-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.9/26.2 (C-4′), 28.3/28.5 ($C(CH_3)_3$), 46.5/47.8 (C-1′), 70.4/70.5 (OCH_2), 80.5 ($C(CH_3)_3$), 94.9/95.2 (C-1), 107.1/107.8 (C-3), 121.6/122.8 (C-2′), 122.5 (2 signals) (C-5), 125.4 (C-4a), 126.2, 126.3, 127.3, (C-6, C-8), 128.1, 128.2, 128.5 (2 signals), 128.7 (2 signals) (5×Bn-*C*H), 132.7/132.8 (C-7), 134.0/135.3 (C-3′), 135.3 (C-8a), 136.3/136.4 (Bn-C), 142.5/143.1 (C-2), 153.7/153.9 (C=O), 155.2/155.3 ppm (C-4); MS (DCI, 200 eV): *m*/*z* (%): 581.5 (100) [M^++NH_4]; HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{27}ClINO_3Na$: 586.0622; found: 586.0616 [M^++Na].

A thoroughly degassed solution of (*E*/*Z*)-2-amino-4-benzyloxy-*N*-(*tert*-butyloxycarbonyl)-*N*-(3-chloro-2-butenyl)-1-iodonaphthalene (4.00 g, 7.09 mmol) in toluene (120 mL) was treated with tris(trimethylsilyl)silane (2.41 mL, 7.80 mmol) and AIBN (291 mg, 1.77 mmol). Then, the stirred reaction mixture was heated to 80 °C using a preheated oil bath and stirring was continued for 5 h. After cooling to room temperature the solvent was removed in vacuo and the two diastereomers were separated by

column chromatography on silica gel (PE/EtOAc 40:1 → 10:1) to give the desired diastereomer *rac*-**5** (1.37 g, 3.12 mmol, 44%) as a white solid. R_f=0.32 (PE/EtOAc 10:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.58–1.65 (m, 12H, $C(CH_3)_3$, 11-H_3), 3.86 (ddd, J=9.4, 2×3.1 Hz, 1H, 1-H), 4.07 (m, 1H, 2-H_a), 4.34 (m, 1H, 2-H_b), 4.60 (m, 1H, 10-H), 5.26 (s, 2H, OCH_2Ph), 7.27–7.69 (m, 8H, 7-H, 8-H, 9-H, 5×Ph-H), 7.87 (brs, 1H, 4-H), 8.30 ppm (d, J=8.0 Hz, 1H, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 23.7 (C-11), 28.5 ($C(CH_3)_3$), 46.0 (C-1), 50.7 (C-2), 60.2 (C-10), 70.2 (OCH_2), 80.9 ($C(CH_3)_3$), 96.3 (C-4), 115.2 (C-9b), 122.4 (C-5a), 122.1, 122.9, 123.6 (C-6, C-7, C-9), 127.3 (C-8), 127.6, 127.9, 128.5 (5×Bn-*C*H), 130.4 (C-9a), 136.9 (Bn-C), 142.0 (C-3a), 152.4 (C=O), 155.8 ppm (C-5); IR (KBr): $\tilde{\nu}$=3445, 2977, 2928, 1698, 1626, 1580, 1455, 1410, 1367, 1338, 1272, 1147, 910, 846, 751 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=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); MS (DCI, 200 eV): *m*/*z* (%): 455.5 (100) [M^++NH_4], 438.5 (47) [M^++H]; HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{28}ClNO_3Na$: 460.1655; found: 460.1650 [M^++Na].

Chromatographic resolution of *rac*-5: A solution of *rac*-**5** (1.10 g, 2.51 mmol) in a 1:1 mixture of *n*-heptane and CH_2Cl_2 (22 mL) was separated consecutively (injection volume: 1 mL) by semipreparative HPLC (Chiralpak IA, 250×20 mm, particle size: 5 μm; *n*-heptane/CH_2Cl_2 4:1; flow: 18 mL min^{-1}; UV detector: λ=250 nm) to provide (+)-(1*S*,10*R*)-**5** (t_R=5.2 min) and (−)-(1*R*,10*S*)-**5** (t_R=7.1 min). The optical purity was determined by analytical HPLC (Chiralcel OD, 250×4.6 mm, particle size: 10 μm; *n*-hexane/*i*PrOH 99:1; flow: 0.8 mL min^{-1}; UV detector: λ= 254 nm): (+)-(1*S*,10*R*)-**5**: 99.9% *ee* (t_R=13.6 min); $[\alpha]_D^{20}$ = +28.0 (c=0.8 in $CHCl_3$); (−)-(1*R*,10*S*)-**5**: 99.9% *ee* (t_R=17.4 min); $[\alpha]_D^{20}$ = −27.0 (c= 0.8 in $CHCl_3$).

(+)-{(1*S*,10*R*)-3-(*tert*-Butyloxycarbonyl)-1-(10-chloroethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole} [(+)-(1*S*,10*R*)-7]: (+)-(1*S*,10*R*)-**5** (197 mg, 450 μmol) was dissolved in freshly distilled THF (15 mL) and the resulting solution was warmed to 40°C. Then, Pd/C (10%, 96 mg) was added under stirring and a 25% (w/w) aqueous solution of NH_4HCO_2 (0.96 mL) was added dropwise. After stirring for 15 min at 40°C, the solid was removed by filtration through Celite which was washed thoroughly with acetone (250 mL). The concentrated filtrate was purified by column chromatography (PE/EtOAc 30:1 → 10:1) to give (+)-**7** (146 mg, 420 μmol, 93%) as a white solid. R_f=0.30 (PE/EtOAc 5:1); $[\alpha]_D^{20}$ = +11.4 (c=0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.55–1.64 (m, 12H, $C(CH_3)_3$, 11-H_3), 3.80 (m, 1H, 1-H), 4.00 (m, 1H, 2-H_a), 4.30 (m, 1H, 2-H_b), 4.54 (m, 1H, 10-H), 7.30 (m, 1H, 7-H), 7.44 (m, 1H, 8-H), 7.59 (d, J=8.3 Hz, 1H, 9-H), 7.70–7.92 (2×brs, 2H, 4-H, OH), 8.12 ppm (d, J=8.3 Hz, 1H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.8 (C-11), 28.5 ($C(CH_3)_3$), 46.1 (C-1), 51.2 (C-2), 60.3 (C-10), 81.5 ($C(CH_3)_3$), 99.1 (C-4), 114.9 (C-9b), 121.7 (C-5a), 122.1, 122.6, 123.6 (C-6, C-7, C-9), 127.1 (C-8), 130.5 (C-9a), 141.4 (C-3a), 152.8 (C=O), 153.9 ppm (C-5); IR (KBr): $\tilde{\nu}$=3380, 2976, 1686, 1629, 1585, 1412, 1342, 1249, 1147, 1044, 911, 853, 751 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=207.5 (4.245), 219.0 (4.216), 255.5 (4.869), 304.5 (3.908), 315.5 (3.973), 342.5 nm (3.485); MS (ESI): *m*/*z* (%): 717 (12) [2M^++Na], 370 (21) [M^++Na]; HRMS (ESI): *m*/*z*: calcd for $C_{19}H_{22}ClNO_3H$: 348.1366; found: 348.1361 [M^++H].

(+)-{(1*S*,10*R*)-5-Benzyloxy-1-(10-chloroethyl)-3-[(3,5-dibromophenyl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole} [(+)-8]: Benzyl ether (+)-**5** (70.0 mg, 160 μmol) was treated with 4 M HCl/EtOAc (10 mL) and stirred at room temperature for 3 h. The resulting solution was concentrated in vacuo and the residue was thoroughly dried under vacuum. Then, the residue was dissolved in dry DMF (10 mL) and the solution cooled to 0°C. EDC·HCl (92.0 mg, 480 μmol) and 3,5-dibromobenzoic acid (58.0 mg, 208 μmol) were added and the reaction mixture was allowed to warm to room temperature. After stirring for 19 h at this temperature, the solution was diluted with water (25 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3×50 mL), the combined organic fractions were washed with brine (4×100 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. Purification by column chromatography on silica gel (PE/EtOAc 5:1) provided (+)-**8** as pale yellow needles (60 mg, 100 μmol, 63%). R_f=0.35 (PE/EtOAc 5:1); $[\alpha]_D^{20}$ = +13.7 (c=0.35, $CHCl_3$); ^{1}H NMR (300 MHz, [D_6]DMSO, 100°C): δ=1.58 (d, J=6.7 Hz, 3H, 11-H_3), 4.08 (m, 1H, 1-H), 4.15 (m, 1H, 2-H_a), 4.34 (dd, J=11.5, 9.2 Hz, 1H, 2-H_b), 4.75 (dq, J=6.7, 3.0 Hz, 1H, 10-H), 5.19 (brs, 2H, OCH_2), 7.31–7.62 (m, 8H, 4′-H, 7-H, 8-H, 5× Bn-H), 7.79 (d, J=1.8 Hz, 2H, 2′-H, 6′-H), 7.92 (d, J=8.3 Hz, 1H, 9-H), 8.00 (m, 1H, 4-H), 8.23 ppm (d, J=8.3 Hz, 1H, 6-H); ^{13}C NMR (75 MHz, [D_6]DMSO, 100°C): δ=22.9 (C-11), 45.1 (C-1), 52.0 (C-2), 60.6 (C-10), 69.8 (OCH_2), 97.7 (C-5a*), 118.0, 122.3, 122.7, 123.5 (C-4′, C-6, C-7, C-9, C-9a, C-9b*), 126.8, 127.1, 127.4, 128.0 (C-8, 5×Bn-*C*H), 128.3 (C-2′, C-6′), 129.5 (C-3′, C-5′), 134.7 (C-4), 136.2 (Bn-*C*), 139.9, 140.3 (C-1′, C-3a), 154.2 (C-5), 163.8 ppm (C=O); IR (KBr): $\tilde{\nu}$=3064, 2918, 1642, 1579, 1551, 1454, 1404 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=208.5 (4.750), 252.0 (4.584), 324.5 nm (4.113); MS (EI, 70 eV): *m*/*z* (%): 599 (14) [M^+], 536 (33) [M^+−$CHClCH_3$]; HRMS (EI): *m*/*z*: calcd for $C_{28}H_{22}Br_2ClNO_2$: 596.9706; found: 596.9706.

General procedure 1

Preparation of β-D-galactosidic prodrugs [(+)-(1*S*,10*R*)-12a–c]: A solution of phenol (+)-(1*S*,10*R*)-**7** in dry CH_2Cl_2 (c=0.02 M) was treated with molecular sieves (4 Å; 0.8 g) and stirred for 30 min at room temperature. Then trichloroacetimidate **9** (1.03 equiv) was added, the reaction mixture cooled to −10°C and a solution of BF_3·OEt_2 (0.5 equiv) in dry CH_2Cl_2 (c=0.10 M) added dropwise. Stirring was continued for 4 h at this temperature followed by dropwise addition of additional BF_3·OEt_2 (3.0 equiv) in dry CH_2Cl_2 (c=0.66 M). The reaction mixture was allowed to warm to room temperature and was stirred for further 5 h. The solution was separated from the molecular sieves under argon by transfer cannula and the molecular sieves were washed with CH_2Cl_2 (2×10 mL). The combined solutions were concentrated and the residue was thoroughly dried in vacuo.

The residue was dissolved in dry DMF (c=0.02 M) and the solution cooled to 0°C. EDC·HCl (3.0 equiv) and indole **10a–c** (1.5 equiv) were added and the reaction mixture was allowed to warm to room temperature. After stirring for 20–22 h at this temperature, the solution was diluted with EtOAc (25 mL), water (25 mL) and a saturated aqueous solution of $NaHCO_3$ (25 mL). The mixture was extracted with EtOAc (4×50 mL), the combined organic fractions were washed with brine (4×100 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH) provided tetraacetylglycosides (+)-**11a–c**.

A solution of (+)-**11a–c** in dry MeOH (c=0.02 M) was treated with a 5.4 M solution of NaOMe in MeOH (2.0 equiv) at 0°C and the reaction mixture was allowed to warm to room temperature. After stirring for 30–120 min at this temperature, the solution was diluted with MeOH (2 mL) and water (2 mL) and the mixture was adjusted to neutral pH by addition of ion-exchange resin (Amberlite-IR 120). The solution was separated from the ion-exchange resin by filtration and the ion-exchange resin was washed with MeOH (10 mL). The combined solutions were concentrated and the residue was purified by column chromatography (CH_2Cl_2/MeOH) to provide galactosides (+)-**12a–c**.

(+)-{[(1*S*,10*R*)-1-(10-Chloroethyl)-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)-indol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indol-5-yl] β-D-galactopyranoside} [(+)-(1*S*,10*R*)-12a]: According to GP 1 phenol (+)-**7** (130 mg, 374 μmol) in dry CH_2Cl_2 (16 mL) was glycosylated with **9** (190 mg, 386 μmol) and BF_3·OEt_2 (24 μL, 189 μmol) in dry CH_2Cl_2 (1.9 mL). Additional BF_3·OEt_2 (142 μL, 1.12 mmol) in dry CH_2Cl_2 (1.7 mL) was added for *N*-Boc deprotection and the residue was then treated with EDC·HCl (215 mg, 1.12 mmol) and indole **10a** (160 mg, 561 μmol) in DMF (17 mL) for 20 h to give (+)-**11a** (168 mg, 208 μmol, 56%) after purification by column chromatography (CH_2Cl_2/MeOH 10:1) as a brown solid. R_f=0.43 (CH_2Cl_2/MeOH 10:1); HRMS (ESI): *m*/*z*: calcd for $C_{41}H_{46}ClN_3O_{12}H$: 808.2843; found: 808.2843 [M^++H].

Solvolysis of (+)-**11a** (164 mg, 203 μmol) in MeOH (9 mL) was performed in 2 h with a 5.4 M solution of NaOMe in MeOH (75 μL, 406 μmol). Purification by column chromatography on silica gel (CH_2Cl_2/MeOH 1:1) provided (+)-**12a** (106 mg, 166 μmol, 82%) as a pale yellow solid. R_f=0.26 (CH_2Cl_2/MeOH 1:1); $[\alpha]_D^{20}$ = +10.0 (c=0.2 in DMSO); ^{1}H NMR (600 MHz, [D_6]DMSO): δ=1.65 (d, J=6.6 Hz, 3H, 11-H_3), 2.24 (s, 6H, NMe_2), 2.66 (t, J=5.9 Hz, 2H, 2′′-H_2), 3.44–3.61 (m, 3H, 3′′′-H, 5′′′-H, 6′′′-H_a), 3.63–3.72 (m, 1-H, 6′′′-H_b), 3.76–3.86 (m, 2H, 2′′′-H, 4′′′-H), 4.07 (t, J=5.9 Hz, 2H, 1′′-H_2), 4.24 (m, 1H, 1-H), 4.58–4.71 (m, 3H,

2×OH, 2-H_a), 4.75 (m, 1H, 2-H_b), 4.82 (m, 1H, 10-H), 4.93 (m, 2H, 1‴-H, OH), 5.36 (brs, 1H, OH), 6.92 (dd, J=9.0, 2.2 Hz, 1H, 6′-H), 7.13–7.19 (m, 2H, 3′-H, 4′-H), 7.37–7.46 (m, 2H, 7-H, 7′-H), 7.56 (m, 1H, 8-H), 7.95 (d, J=8.4 Hz, 1H, 9-H), 8.23 (brs, 1H, 4-H), 8.36 (d, J=8.4 Hz, 1H, 6-H), 11.64 ppm (brs, 1H, NH); ^{13}C NMR (150 MHz, [D_6]DMSO): δ=23.4 (C-11), 45.5 (NMe_2), 45.9 (C-1), 52.1 (C-2), 57.8 (C-2″), 59.6 (C-6‴), 61.3 (C-10), 66.3 (C-1″), 67.5, 70.4, 73.2, 75.2 (C-2‴, C-3‴, C-4‴, C-5‴), 101.9 (C-4), 102.3 (C-1‴), 103.2 (C-4′), 105.4 (C-3′), 113.1 (C-7′), 115.8 (C-6′), 118.8 (C-5a), 123.0, 123.4, 123.6 (C-6, C-7, C-9, C-9b), 127.2 (C-8), 127.5 (C-3a′), 129.4, 130.9, 131.7 (C-2′, C-7a′, C-9a), 142.0 (C-3a), 153.0 (C-5′), 153.6 (C-5), 160.1 ppm (C=O); IR (KBr): $\tilde{\nu}$=3386, 1624, 1590, 1515, 1464, 1415, 1267, 1232, 1075, 760 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=206.0 (4.644), 246.0 (4.322), 299.0 (4.487), 336.5 nm (4.424); MS (ESI): m/z (%): 1280.9 (14) [2M^++H], 640.2 (100) [M^++H]; HRMS (ESI): m/z: calcd for $C_{33}H_{38}ClN_3O_8H$: 640.2420; found: 640.2420 [M^++H].

(+)-{[(1*S*,10*R*)-1-(10-Chloroethyl)-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)-6-methoxy-indol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indol-5-yl] β-D-galactopyranoside} [(+)-(1*S*,10*R*)-12b]: According to GP 1, phenol (+)-**7** (106 mg, 305 μmol) in dry CH_2Cl_2 (14 mL) was glycosylated with **9** (155 mg, 314 μmol) and BF_3·OEt_2 (19 μL, 152 μmol) in dry CH_2Cl_2 (1.5 mL). Additional BF_3·OEt_2 (116 μL, 914 μmol) in dry CH_2Cl_2 (1.4 mL) was added for N-Boc deprotection and the residue was then treated with EDC·HCl (175 mg, 914 μmol) and indole **10b** (144 mg, 457 μmol) in DMF (14 mL) for 22 h to give (+)-**11b** (128 mg, 153 μmol, 50%) after purification by column chromatography (CH_2Cl_2/MeOH 10:1) as a brown solid. R_f=0.53 (CH_2Cl_2/MeOH 5:1); HRMS (ESI): m/z: calcd for $C_{42}H_{48}ClN_3O_{13}H$: 838.2957; found: 838.2948 [M^++H].

Solvolysis of (+)-**11b** (125 mg, 149 μmol) in MeOH (7 mL) was performed in 30 min with a 5.4 M solution of NaOMe in MeOH (55 μL, 298 μmol). Purification by column chromatography on silica gel (CH_2Cl_2/MeOH 1:1) provided (+)-**12b** (86 mg, 128 μmol, 86%) as a pale yellow solid. R_f=0.27 (CH_2Cl_2/MeOH 1:1, 1% NEt_3); $[\alpha]_D^{20}$ = +2.0 (c=0.4 in DMSO); ^{1}H NMR (600 MHz, [D_6]DMSO): δ=1.66 (d, J=6.7 Hz, 3H, 11-H_3), 2.25 (s, 6H, NMe_2), 2.66 (t, J=6.0 Hz, 2H, 2″-H_2), 3.47 (m, 1H, 3‴-H), 3.53–3.59 (m, 2H, 5‴-H, 6‴-H_a), 3.67 (m, 1-H, 6‴-H_b), 3.77–3.83 (m, 5H, 2‴-H, 4‴-H, OCH_3), 4.05 (t, J=6.0 Hz, 2H, 1″-H_2), 4.24 (m, 1H, 1-H), 4.54–4.77 (m, 4H, 2×OH, 2-H_2), 4.82 (m, 1H, 10-H), 4.85–4.99 (m, 2H, 1‴-H, OH), 5.32 (brs, 1H, OH), 6.98 (s, 1H, 7′-H), 7.14 (brs, 1H, 3′-H), 7.18 (s, 1H, 4′-H), 7.42 (t, J=7.7 Hz, 1H, 7-H), 7.56 (t, J=7.6 Hz, 1H, 8-H), 7.95 (d, J=8.6 Hz, 1H, 9-H), 8.23 (brs, 1H, 4-H), 8.35 (d, J=8.6 Hz, 1H, 6-H), 11.48 ppm (s, 1H, NH); ^{13}C NMR (150 MHz, [D_6]DMSO): δ=23.4 (C-11), 45.6 (NMe_2), 46.0 (C-1), 52.0 (C-2), 55.6 (OCH_3), 57.8 (C-2″), 59.6 (C-6‴), 61.3 (C-10), 67.2 (C-1″), 67.5 (C-4‴), 70.6 (C-2‴), 73.3 (C-3‴), 75.2 (C-5‴), 94.7 (C-7′), 101.9 (C-4), 102.3 (C-1‴), 104.7 (C-4′), 106.1 (C-3′), 118.6 (C-5a), 120.3 (C-3a′), 122.8 (C-9), 122.9 (C-9b), 123.4 (C-6), 123.5 (C-7), 127.2 (C-8), 128.9, 129.5 (C-2′, C-9a), 131.8 (C-7a′), 142.2 (C-3a), 144.6 (C-5′), 149.4 (C-6′), 153.6 (C-5), 160.1 ppm (C=O); IR (KBr): $\tilde{\nu}$=3386, 2929, 1614, 1590, 1514, 1464, 1417, 1307, 1267, 1202, 1153, 1076 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=205.5 (4.666), 305.5 (4.265), 346.5 nm (4.539); MS (ESI): m/z (%): 670.3 (100) [M^++H]; HRMS (ESI): m/z: calcd for $C_{34}H_{40}ClN_3O_9H$: 670.2531; found: 670.2526 [M^++H].

(+)-{[(1*S*,10*R*)-1-(10-Chloroethyl)-3-[(5-(2-*N*,*N*-dimethylaminoacetylamino)-indol-2-yl)-carbonyl]-1,2-dihydro-3*H*-benz[*e*]indol-5-yl] β-D-galactopyranoside} [(+)-(1*S*,10*R*)-12c]: According to GP 1 phenol (+)-**7** (137 mg, 394 μmol) in dry CH_2Cl_2 (17 mL) was glycosylated with **9** (200 mg, 406 μmol) and BF_3·OEt_2 (25 μL, 197 μmol) in dry CH_2Cl_2 (1.9 mL). Additional BF_3·OEt_2 (150 μL, 1.18 mmol) in dry CH_2Cl_2 (1.8 mL) was added for N-Boc deprotection and the residue was then treated with EDC·HCl (227 mg, 1.18 mmol) and indole **10c** (176 mg, 591 μmol) in DMF (18 mL) for 21 h to give (+)-**11c** (155 mg, 189 μmol, 48%) after purification by column chromatography (CH_2Cl_2/MeOH 25:1) as a pale brown solid. R_f=0.57 (CH_2Cl_2/MeOH 10:1); HRMS (ESI): m/z: calcd for $C_{41}H_{45}ClN_4O_{12}H$: 821.2801; found: 821.2795 [M^++H].

Solvolysis of (+)-**11c** (142 mg, 173 μmol) in MeOH (6 mL) was performed in 30 min with a 5.4 M solution of NaOMe in MeOH (64 μL, 346 μmol). Purification by column chromatography on silica gel (CH_2Cl_2/MeOH 7:1 → 3:1) and washing with *n*-pentane (5×15 mL) provided (+)-**12c** (93 mg, 142 μmol, 82%) as a yellow solid. R_f=0.32 (CH_2Cl_2/MeOH 5:1); $[\alpha]_D^{20}$ = +19.1 (c=0.35 in DMSO); ^{1}H NMR (600 MHz, [D_6]DMSO): δ=1.65 (d, J=6.7 Hz, 3H, 11-H_3), 2.31 (s, 6H, NMe_2), 3.08 (s, 2H, 1″-H_2), 3.45–3.52 (m, 1H, 3‴-H), 3.53–3.61 (m, 2H, 5‴-H, 6‴-H_a), 3.64–3.71 (m, 1H, 6‴-H_b), 3.77–3.85 (m, 2H, 2‴-H, 4‴-H), 4.25 (m, 1H, 1-H), 4.55–4.66 (m, 3H, 2-H_a, 2×OH), 4.72–4.90 (m, 3H, 2-H_b, 10-H, OH), 4.93 (m, 1H, 1‴-H), 5.31 (brs, 1H, OH), 7.25 (brs, 1H, 3′-H), 7.37–7.46 (m, 3H, 6′-H, 7′-H, 7-H), 7.57 (m, 1H, 8-H), 7.96 (d, J=8.4 Hz, 1H, 9-H), 8.13 (brs, 1H, 4′-H), 8.24 (brs, 1H, 4-H), 8.36 (d, J=8.6 Hz, 1H, 6-H), 9.60 (s, 1H, NH), 11.70 ppm (s, 1H, NH); ^{13}C NMR (150 MHz, [D_6]DMSO): δ=23.4 (C-11), 45.3 (NMe_2), 46.0 (C-1), 52.1 (C-2), 59.6 (C-6‴), 61.4 (C-10), 63.2 (C-1″), 67.5 (C-4‴), 70.6 (C-2‴), 73.3 (C-3‴), 75.2 (C-5‴), 101.9 (C-4), 102.3 (C-1‴), 105.8 (C-3′), 112.1 (C-4′), 112.2 (C-7′), 118.6 (C-6′), 119.0 (C-5a), 122.9, 123.1, 123.4, 123.7 (C-6, C-7, C-9, C-9b), 127.1 (C-3a′), 127.3 (C-8), 129.5, 131.1, 131.5, 133.3 (C-2′, C-5′, C-7a′, C-9a), 142.0 (C-3a), 153.6 (C-5), 160.1 (C=O), 168.2 ppm (C=O); IR (KBr): $\tilde{\nu}$=3386, 2928, 1625, 1591, 1525, 1467, 1416, 1335, 1313, 1267, 1232 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=206.0 (4.505), 233.0 (4.470), 259.0 (4.488), 299.5 (4.424), 336.5 nm (4.382); MS (ESI): m/z (%): 653.2 (100) [M^++H]; HRMS (ESI): m/z: calcd for $C_{33}H_{37}ClN_4O_8H$: 653.2378; found: 653.2373 [M^++H].

(+)-{[(1*S*,10*R*)-1-(10-Chloroethyl)-3-[(5-(2-morpholin-4-yl-ethoxy)-indol-2-yl)-carbonyl]1,2-dihydro-3*H*-benz[*e*]indol-5-yl] β-D-galactopyranoside} [(+)-(1*S*,10*R*)-12d]: A solution of phenol (+)-**7** (142 mg, 408 μmol) in dry CH_2Cl_2 (18 mL) was treated with molecular sieves (4 Å; 0.8 g) and stirred for 30 min at room temperature. After that, trichloroacetimidate **9** (207 mg, 420 μmol) was added and the reaction mixture was cooled to −10 °C. Then, a solution of BF_3·OEt_2 (26 μL, 205 μmol) in dry CH_2Cl_2 (2.0 mL) was added dropwise and stirring was continued for 4 h at this temperature. After dropwise addition of additional BF_3·OEt_2 (155 μL, 1.22 mmol) in dry CH_2Cl_2 (1.9 mL) the reaction mixture was allowed to warm to room temperature and was stirred for further 5 h at room temperature. The solution was separated from the molecular sieves under argon by transfer cannula and the molecular sieves were washed with CH_2Cl_2 (2×10 mL). The combined solutions were concentrated and the residue was thoroughly dried in vacuo.

The residue was then dissolved in dry DMF (19 mL) and the solution cooled to 0 °C. EDC·HCl (235 mg, 1.23 mmol) and indole **10d** (200 mg, 612 μmol) were added and the reaction mixture was allowed to warm to room temperature. After stirring for 20 h at this temperature, the solution was diluted with EtOAc (25 mL), water (25 mL) and a saturated aqueous solution of $NaHCO_3$ (25 mL). The mixture was extracted with EtOAc (4×50 mL), the combined organic fractions were washed with brine (4×100 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH 10:1) provided *N*-oxide (+)-**11f** (142 mg, 164 μmol, 40%) as a pale brown solid. R_f=0.15 (CH_2Cl_2/MeOH 10:1); HRMS (ESI): m/z: calcd for $C_{43}H_{48}ClN_3O_{14}H$: 866.2903; found: 866.2898 [M^++H].

A solution of *N*-oxide (+)-**11f** (67 mg, 77 μmol) was then dissolved in dry EtOH (15 mL) and hydrogenated (balloon) over PtO_2·H_2O (81%, 6 mg) for 5 h at room temperature. The solid was removed by filtration through Celite which was washed thoroughly with MeOH (50 mL) and the concentrated filtrate was purified by column chromatography (CH_2Cl_2/MeOH 10:1) to provide (+)-**11d** (53 mg, 62 μmol, 81%) as a yellow solid. R_f=0.69 (CH_2Cl_2/MeOH 10:1); HRMS (ESI): m/z: calcd for $C_{43}H_{48}ClN_3O_{13}H$: 850.2954; found: 850.2948 [M^++H].

Then, a solution of (+)-**11d** (51 mg, 60 μmol) in dry MeOH (6 mL) was treated with a 5.4 M solution of NaOMe in MeOH (22 μL, 120 μmol) at 0 °C and the reaction mixture was allowed to warm to room temperature. After stirring for 20 min at this temperature, the solution was diluted with MeOH (2 mL) and water (2 mL) and the mixture was adjusted to neutral pH by addition of ion-exchange resin (Amberlite-IR 120). The solution was separated from the ion-exchange resin by filtration and the ion-exchange resin was washed with MeOH (10 mL). The combined solutions were concentrated and the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 10:1 → 4:1). The obtained solid

was washed with *n*-pentane (4×15 mL) to provide galactoside (+)-**12d** (37 mg, 54 μmol, 90%) as a yellow solid. R_f=0.19 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D^{20}$ = +4.4 (*c*=0.25 in DMSO); ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ= 1.65 (d, *J*=6.6 Hz, 3H, 11-H$_3$), 2.48–2.52 (m, 4H, 3‴-H$_2$, 5‴-H$_2$), 2.73 (t, *J*=5.8 Hz, 2H, 2″-H$_2$), 3.45–3.70 (m, 8H, 2‴-H$_2$, 6‴-H$_2$, 3⁗-H, 5⁗-H, 6⁗-H$_2$), 3.76–3.85 (m, 2H, 2⁗-H, 4⁗-H), 4.11 (t, *J*=5.8 Hz, 2H, 1″-H$_2$), 4.25 (m, 1H, 1-H), 4.52–4.65 (m, 3H, 2-H$_a$, 2×OH), 4.72–4.79 (m, 1H, 2-H$_b$), 4.79–4.88 (m, 2H, 10-H, OH), 4.92 (m, 1H, 1‴-H), 5.30 (brs, 1H, OH), 6.92 (dd, *J*=8.9, 2.4 Hz, 1H, 6′-H), 7.14–7.20 (m, 2H, 3′-H, 4′-H), 7.40 (d, *J*=8.8 Hz, 1H, 7′-H), 7.43 (m, 1H, 7-H), 7.57 (m, 1H, 8-H), 7.96 (d, *J*=8.4 Hz, 1H, 9-H), 8.22 (brs, 1H, 4-H), 8.36 (d, *J*=8.5 Hz, 1H, 6-H), 11.63 ppm (s, 1H, NH); ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ=23.4 (C-11), 46.0 (C-1), 52.1 (C-2), 53.6 (C-3‴, C-5‴), 57.1 (C-2″), 59.5 (C-6⁗), 61.3 (C-10), 65.9 (C-1″), 66.2 (C-2⁗, C-6‴), 67.5 (C-4⁗), 70.6 (C-2⁗), 73.2 (C-3⁗), 75.1 (C-5⁗), 101.9 (C-4), 102.3 (C-1⁗), 103.4 (C-4′), 105.4 (C-3′), 113.2 (C-7′), 115.9 (C-6′), 118.9 (C-5a), 122.9, 123.0, 123.4, 123.7 (C-6, C-7, C-9, C-9b), 127.3, 127.5 (C-3a′, C-8), 129.5, 130.9, 131.7 (C-2′, C-7a′, C-9a), 142.0 (C-3a), 152.9 (C-5′), 153.6 (C-5), 160.1 ppm (C=O); IR (KBr): $\tilde{\nu}$=3385, 2924, 1624, 1590, 1516, 1462, 1416, 1290, 1267, 1233, 1071 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=205.5 (4.665), 246.5 (4.336), 299.0 (4.496), 336.0 nm (4.433); MS (ESI): *m*/*z* (%): 1385.1 (13) [2*M*$^+$+Na], 704.3 (100) [*M*$^+$+Na], 682.3 (32) [*M*$^+$+H]; HRMS (ESI): *m*/*z*: calcd for $C_{35}H_{40}ClN_3O_9H$: 682.2531; found: 682.2526 [*M*$^+$+H].

(+)-{[(1*S*,10*R*)-1-(10-Chloroethyl)-3-[(5-(1-methylpiperidin-4-yl-methoxy)-indol-2-yl)-carbonyl]-1,2-dihydro-3-benz[*e*]indol-5-yl] β-D-galactopyranoside} [(+)-(1*S*,10*R*)-12e]: A solution of phenol (+)-**7** (134 mg, 385 μmol) in dry CH_2Cl_2 (17 mL) was treated with molecular sieves (4 Å; 0.8 g) and stirred for 30 min at room temperature. Trichloroacetimidate **9** (196 mg, 398 μmol) was added and the reaction mixture was cooled to −10°C. Then, a solution of BF_3·OEt_2 (25 μL, 197 μmol) in dry CH_2Cl_2 (1.9 mL) was added dropwise and stirring was continued for 4 h at this temperature. After dropwise addition of additional BF_3·OEt_2 (146 μL, 1.15 mmol) in dry CH_2Cl_2 (1.8 mL) the reaction mixture was allowed to warm to room temperature and was stirred for further 5 h at room temperature. The solution was separated from the molecular sieves under argon by transfer cannula and the molecular sieves were washed with CH_2Cl_2 (2×10 mL). The combined solutions were concentrated and the residue was thoroughly dried in vacuo.

The residue was then dissolved in dry DMF (18 mL) and the solution cooled to 0°C. EDC·HCl (222 mg, 1.16 mmol) and indole **10e** (188 mg, 579 μmol) were added and the reaction mixture was allowed to warm to room temperature. After stirring for 20 h at this temperature, the solution was diluted with EtOAc (50 mL), water (50 mL) and a saturated aqueous solution of $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (4×50 mL), the combined organic fractions were washed with brine (4×100 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH 10:1 → 5:1) provided (+)-**11e** (65 mg, 77 μmol, 20%) as a pale brown solid and *N*-oxide (+)-**11g** (110 mg, 127 μmol, 33%) as a pale brown solid. (+)-**11e**: R_f=0.27 (CH_2Cl_2/MeOH 10:1); HRMS (ESI): *m*/*z*: calcd for $C_{44}H_{50}ClN_3O_{12}H$: 848.3161; found: 848.3156 [*M*$^+$+H]; *N*-oxide (+)-**11g**: R_f=0.13 (CH_2Cl_2/MeOH 10:1); HRMS (ESI): *m*/*z*: calcd for $C_{44}H_{50}ClN_3O_{13}H$: 864.3110; found: 864.3105 [*M*$^+$+H].

A solution of *N*-oxide (+)-**11g** (40 mg, 46 μmol) was then dissolved in dry EtOH (6 mL) and hydrogenated (balloon) over PtO_2·H_2O (81%, 6 mg) for 16 h at room temperature. The solid was removed by filtration through Celite which was washed thoroughly with MeOH (50 mL) and the concentrated filtrate was purified by column chromatography (CH_2Cl_2/MeOH 10:1) to provide (+)-**11e** (24 mg, 28 μmol, 61%) as a yellow solid.

Then, a solution of (+)-**11e** (74 mg, 87 μmol) in dry MeOH (6 mL) was treated with a 5.4 M solution of NaOMe in MeOH (32 μL, 120 μmol) at 0°C and the reaction mixture was allowed to warm to room temperature. After stirring for 30 min at this temperature, the solution was diluted with MeOH (2 mL) and water (2 mL) and the mixture was adjusted to neutral pH by addition of ion-exchange resin (Amberlite-IR 120). The solution was separated from the ion-exchange resin by filtration and the ion-exchange resin was washed with MeOH (10 mL). The combined solutions were concentrated and the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 5:1). The obtained solid was washed with *n*-pentane (5×15 mL) to provide galactoside (+)-**12d** (53 mg, 78 μmol, 90%) as a pale yellow solid. R_f=0.22 (CH_2Cl_2/MeOH 5:1, 1% NEt_3); $[\alpha]_D^{20}$ = +4.8 (*c*=0.25 in DMSO); ^{1}H NMR (600 MHz, [D$_6$]DMSO, 100°C): δ=1.40–1.50 (m, 2H, 3‴-H$_{ax}$, 5‴-H$_{ax}$), 1.65 (d, *J*= 6.7 Hz, 3H, 11-H$_3$), 1.77–1.86 (m, 3H, 3‴-H$_{eq}$, 4‴-H, 5‴-H$_{eq}$), 2.14 (m, 2H, 2‴-H$_{ax}$, 6‴-H$_{ax}$), 2.29 (s, 3H, NCH_3), 2.87–2.93 (m, 2H, 2‴-H$_{eq}$, 6‴-H$_{eq}$), 3.15 (brs, H_2O, 4×OH), 3.47–3.51, 3.52–3.56, 3.60–3.64, 3.68–3.73 (4×m, 4H, 3⁗-H, 5⁗-H, 6⁗-H$_2$), 3.81–3.92 (m, 4H, 1″-H$_2$, 2⁗-H, 4⁗-H), 4.22 (m, 1H, 1-H), 4.63–4.73 (m, 2H, 2-H$_2$), 4.81 (m, 1H, 10-H), 4.92 (d, *J*=7.6 Hz, 1H, 1⁗-H), 6.93 (m, 1H, 6′-H), 7.09, 7.18 (2×brs, 2H, 3′-H, 4′-H), 7.40–7.45 (m, 2H, 7-H, 7′-H), 7.56 (m, 1H, 8-H), 7.93 (d, *J*= 8.4 Hz, 1H, 9-H), 8.17 (brs, 1H, 4-H), 8.37 (d, *J*=8.6 Hz, 1H, 6-H), 11.31 ppm (s, 1H, NH); ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ=23.4 (C-11), 28.1 (C-3‴, C-5‴), 34.5 (C-4‴), 45.5 (NCH_3), 46.0 (C-1), 52.1 (C-2), 54.5 (C-2‴, C-6‴), 59.6 (C-6⁗), 61.3 (C-10), 67.5 (C-4⁗), 70.6 (C-2⁗), 72.5 (C-1″), 73.3 (C-3⁗), 75.2 (C-5⁗), 101.9 (C-4), 102.3 (C-1⁗), 103.4 (C-4′), 105.4 (C-3′), 113.2 (C-7′), 115.8 (C-6′), 118.9 (C-5a), 122.9, 123.0, 123.4, 123.7 (C-6, C-7, C-9, C-9b), 127.3, 127.5 (C-3a′, C-8), 129.5, 130.9, 131.7 (C-2′, C-7a′, C-9a), 142.0 (C-3a), 153.2 (C-5′), 153.6 (C-5), 160.2 ppm (C=O); IR (KBr): $\tilde{\nu}$=3384, 2926, 1624, 1590, 1515, 1466, 1413, 1267, 1234 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=205.0 (4.618), 245.5 (4.270), 299.0 (4.434), 337.0 nm (4.368); MS (ESI): *m*/*z* (%): 702.3 (12) [*M*$^+$+Na], 680.3 (100) [*M*$^+$+H]; HRMS (ESI): *m*/*z*: calcd for $C_{36}H_{42}ClN_3O_8H$: 680.2739, found: 680.2733 [*M*$^+$+H].

General procedure 2

Preparation of (+)-(1*S*,10*R*)-13a–e: Benzyl ether (+)-**5** was treated with 4 M HCl/EtOAc (14 mL) and stirred at room temperature for 3–3.5 h. The resulting solution was concentrated in vacuo and the residue was thoroughly dried under vacuum. Then, the residue was dissolved in dry DMF (10 mL) and the solution cooled to 0°C. EDC·HCl (3.0 equiv) and indole **10** (1.3 equiv) were added and the reaction mixture was allowed to warm to room temperature. After stirring for 19–24 h at this temperature, the solution was diluted with EtOAc (50 mL), water (50 mL) and a saturated aqueous solution of $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (4×50 mL), the combined organic fractions were washed with brine (4×100 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH) provided (+)-**13**.

(+)-{(1*S*,10*R*)-5-Benzyloxy-1-(10-chloroethyl)-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)-indol-2-yl)-carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole} [(+)-(1*S*,10*R*)-13a]: According to GP 2 benzyl ether (+)-**5** (200 mg, 457 μmol) was stirred in 4 M HCl/EtOAc for 3.5 h at room temperature. The residue was then treated with EDC·HCl (263 mg, 1.37 mmol) and indole **10a** (169 mg, 594 μmol) in DMF for 19 h at room temperature. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH 10:1) provided (+)-**13a** (196 mg, 345 μmol, 76%) as a pale brown solid. R_f=0.40 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D^{20}$ = +43.2 (*c*=0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.62 (d, *J*=6.8 Hz, 3H, 11-H$_3$), 2.37 (s, 6H, NMe_2), 2.77 (t, *J*=5.7 Hz, 2H, 2″-H$_2$), 3.88–3.97 (m, 1H, 1-H), 4.10 (t, *J*=5.7 Hz, 2H, 1″-H$_2$), 4.46–4.60 (m, 2H, 2-H$_a$, 10-H), 4.84 (m, 1H, 2-H$_b$), 5.24 (m, 2H, OCH_2Ph), 6.94–7.04 (m, 2H, 3′-H, 6′-H), 7.12 (d, *J*= 2.2 Hz, 1H, 4′-H), 7.28–7.44, 7.45–7.55 (2×m, 8H, 7-H, 7′-H, 8-H, 5×Ph-H), 7.67 (d, *J*=8.3 Hz, 1H, 9-H), 8.18 (brs, 1H, 4-H), 8.35 (d, *J*=8.3 Hz, 1H, 6-H), 9.81 ppm (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.0 (C-11), 45.8 (NMe_2), 47.5 (C-1), 53.6 (C-2), 58.3 (C-2″), 59.9 (C-10), 66.5 (C-1″), 70.3 (OCH_2Ph), 98.2 (C-4), 103.5 (C-4′), 105.9 (C-3′), 112.7 (C-7′), 117.1, 117.2 (C-6′, C-5a), 122.5, 123.7, 123.7, 123.8 (C-6, C-7, C-9, C-9b), 127.4, 127.6, 127.9, 128.1, 128.5 (C-3a′, C-8, 5×Bn-*C*H), 130.0, 130.8, 131.4 (C-2′, C-7a′, C-9a), 136.7 (Bn-C), 142.4 (C-3a), 153.8 (C-5′), 155.6 (C-5), 160.5 ppm (C=O); IR (KBr): $\tilde{\nu}$=3452, 2937, 1621, 1518, 1456, 1414 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=207.0 (4.826), 249.5 (4.434), 290.0 (4.446), 300.0 (4.606), 339.5 nm (4.519); MS (EI, 70 eV): *m*/*z* (%): 567.4 (11) [*M*$^+$]; HRMS (EI): *m*/*z*: calcd for $C_{34}H_{34}ClN_3O_3$: 567.2289; found: 567.2289.

(+)-{(1*S*,10*R*)-5-Benzyloxy-1-(10-chloroethyl)-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)-6-methoxy-indol-2-yl)-carbonyl]-1,2-dihydro-3*H*-benz[*e*]in-

dole} [(+)-(1*S*,10*R*)-13b]: According to GP 2, benzyl ether (+)-**5** (150 mg, 342 μmol) was stirred in 4 M HCl/EtOAc for 3 h at room temperature. The residue was then reacted with EDC·HCl (197 mg, 1.03 mmol) and indole **10b** (140 mg, 445 μmol) in DMF for 20 h at room temperature. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH 10:1) provided (+)-**13b** (134 mg, 224 μmol, 66%) as a pale brown solid. R_f=0.46 (CH_2Cl_2/MeOH 5:1); $[\alpha]_D^{20}$ = +61.7 (c=0.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.60 (d, J=6.7 Hz, 3H, 11-H_3), 2.35 (s, 6H, NMe_2), 2.80 (t, J=6.1 Hz, 2H, 2″-H_2), 3.28 (s, 3H, OCH_3), 3.89–3.98 (m, 1H, 1-H), 4.09 (t, J=6.1 Hz, 2H, 1″-H_2), 4.48–4.65 (m, 2H, 2-H_a, 10-H), 4.78–4.88 (m, 1H, 2-H_b), 5.26 (m, 2H, OCH_2Ph), 6.71 (s, 1H, 7′-H), 6.98 (d, J=1.5 Hz, 1H, 3′-H), 7.07 (s, 1H, 4′-H), 7.22–7.43, 7.45–7.56 (2×m, 7H, 7-H, 8-H, 5×Ph-H), 7.67 (d, J=8.2 Hz, 1H, 9-H), 8.35 (d, J=8.3 Hz, 1H, 6-H), 8.39 (brs, 1H, 4-H), 10.68 ppm (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.8 (C-11), 45.8 (NMe_2), 47.4 (C-1), 53.5 (C-2), 55.2 (OCH_3), 58.0 (C-2″), 59.7 (C-10), 67.4 (C-1″), 70.4 (OCH_2Ph), 93.9 (C-7′), 98.5 (C-4), 104.8 (C-4′), 106.5 (C-3′), 117.3 (C-5a), 120.5 (C-3a′), 122.4 (C-9), 123.5, 123.6, 123.9 (C-6, C-7, C-9b), 127.5 (2 signals), 127.9, 128.5, (C-8, 5×Bn-*C*H), 128.7, 129.9, 132.3 (C-2′, C-7a′, C-9a), 136.6 (Bn-C), 142.7 (C-3a), 145.0 (C-5′), 150.4 (C-6′), 155.5 (C-5), 160.5 ppm (C=O); IR (KBr): $\tilde{\nu}$=3256, 2938, 1625, 1585, 1514, 1459, 1405, 1306 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=206.5 (4.802), 245.0 (4.340), 307.0 (4.350), 349.0 nm (4.608); MS (ESI): m/z (%): 1217.0 (19) [2M^++Na], 598.2 (100) [M^++H]; HRMS (ESI): m/z: calcd for $C_{35}H_{36}ClN_3O_4H$: 598.2473; found: 598.2467 [M^++H].

(+)-{(1*S*,10*R*)-5-Benzyloxy-1-(10-chloroethyl)-3-[(5-(2-*N*,*N*-dimethylaminoacetylamino)-indol-2-yl)-carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole} [(+)-(1*S*,10*R*)-13c]: According to GP 2, benzyl ether (+)-**5** (150 mg, 342 μmol) was stirred in 4 M HCl/EtOAc for 3.5 h at room temperature. The residue was then reacted with EDC·HCl (197 mg, 1.03 mmol) and indole **10c** (133 mg, 445 μmol) in DMF for 24 h at room temperature. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH 30:1) provided (+)-**13c** (155 mg, 267 μmol, 78%) as a pale green foam. R_f=0.31 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D^{20}$ = +66.0 (c=0.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.63 (d, J=6.8 Hz, 3H, 11-H_3), 2.39 (s, 6H, NMe_2), 3.11 (s, 2H, 1″-H_2), 3.88–4.02 (m, 1H, 1-H), 4.47–4.63 (m, 2H, 2-H_a, 10-H), 4.84 (dd, J=10.8, 1.5 Hz, 1H, 2-H_b), 5.24 (m, 2H, OCH_2Ph), 7.06 (d, J=1.4 Hz, 1H, 3′-H), 7.20 (dd, J=8.8, 1.9 Hz, 1H, 6′-H), 7.28–7.56 (m, 8H, 7-H, 7′-H, 8-H, 5×Ph-H), 7.68 (d, J=8.2 Hz, 1H, 9-H), 8.13–8.28 (m, 2H, 4-H, 4′-H), 8.35 (d, J=8.3 Hz, 1H, 6-H), 9.11 (s, 1H, NH), 10.03 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.9 (C-11), 46.0 (NMe_2), 47.4 (C-1), 53.5 (C-2), 59.9 (C-10), 63.6 (C-1″), 70.3 (OCH_2Ph), 98.2 (C-4), 106.4 (C-3′), 112.1 (C-7′), 112.6 (C-4′), 117.3 (C-5a), 118.8 (C-6′), 122.5 (C-9), 123.7, 123.8, 123.9 (C-6, C-7, C-9b), 127.4, 127.6, 127.9, 128.0, 128.5 (C-3a′, C-8, 5×Bn-*C*H), 129.9 (C-5′), 131.1, 131.2, 133.2 (C-2′, C-7a′, C-9a), 136.7 (Bn-C), 142.3 (C-3a), 155.5 (C-5), 160.4 (C=O), 168.6 ppm (C=O); IR (KBr): $\tilde{\nu}$=3417, 3298, 2945, 1679, 1625, 1587, 1523, 1459, 1405, 1333, 1267 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=207.5 (4.688), 233.5 (4.558), 260.0 (4.603), 301.0 (4.549), 339.5 nm (4.479); MS (EI, 70 eV): m/z (%): 580.0 (10) [M^+], 544.0 (7) [M^+−Cl−H]; HRMS (ESI): m/z: calcd for $C_{34}H_{33}ClN_4O_3H$: 580.2319; found: 581.2314 [M^++H].

(+)-{(1*S*,10*R*)-5-Benzyloxy-1-(10-chloroethyl)-3-[(5-(2-morpholin-4-yl-ethoxy)-indol-2-yl)-carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole} [(+)-(1*S*,10*R*)-13d]: According to GP 2, benzyl ether (+)-**5** (150 mg, 342 μmol) was stirred in 4 M HCl/EtOAc for 3 h at room temperature. The residue was then reacted with EDC·HCl (197 mg, 1.03 mmol) and indole **10d** (146 mg, 445 μmol) in DMF for 21 h at room temperature. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH 30:1) provided (+)-**13d** (156 mg, 256 μmol, 75%) as a pale brown solid. R_f=0.25 (CH_2Cl_2/MeOH 30:1); $[\alpha]_D^{20}$ = +42.7 (c=0.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.62 (d, J=6.7 Hz, 3H, 11-H_3), 2.61 (m, 4H, 3‴-H_2, 5‴-H_2), 2.83 (t, J=5.8 Hz, 2H, 2″-H_2), 3.76 (m, 4H, 2‴-H_2, 6‴-H_2), 3.89–3.98 (m, 1H, 1-H), 4.15 (t, J=5.8 Hz, 2H, 1″-H_2), 4.47–4.61 (m, 2H, 2-H_a, 10-H), 4.85 (m, 1H, 2-H_b), 5.25 (m, 2H, OCH_2Ph), 6.94–7.02 (m, 2H, 3′-H, 6′-H), 7.12 (d, J=2.3 Hz, 1H, 4′-H), 7.29–7.57 (m, 8H, 7-H, 7′-H, 8-H, 5×Ph-H), 7.68 (d, J=8.2 Hz, 1H, 9-H), 8.19 (brs, 1H, 4-H), 8.34 (d, J=8.2 Hz, 1H, 6-H), 9.88 ppm (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.0 (C-11), 47.5 (C-1), 53.6 (C-2), 54.1 (C-3‴, C-5‴), 57.8 (C-2″), 59.9 (C-10), 66.3 (C-1″), 66.9 (C-2‴, C-6‴), 70.3 (OCH_2Ph), 98.2 (C-4), 103.7 (C-4′), 105.8 (C-3′), 112.8 (C-7′), 117.0, 117.2 (C-6′, C-5a), 122.6 (C-9), 123.7, 123.7, 123.9 (C-6, C-7, C-9b), 127.4, 127.6, 127.9, 128.1, 128.5 (C-3a′, C-8, 5×Bn-*C*H), 130.0, 130.8, 131.5 (C-2′, C-7a′, C-9a), 136.7 (Bn-C), 142.4 (C-3a), 153.7 (C-5′), 155.6 (C-5), 160.5 ppm (C=O); IR (KBr): $\tilde{\nu}$=3444, 2856, 1625, 1579, 1518, 1453, 1406, 1288, 1266 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=207.0 (4.783), 249.5 (4.391), 291.0 (4.405), 300.0 (4.566), 339.5 nm (4.477); MS (EI, 70 eV): m/z (%): 609.2 (1) [M^+], 573.1 (3) [M^+−Cl−H], 100.0 (100) [$CH_2(CH_2)_4O^+$]; HRMS (EI): m/z: calcd for $C_{36}H_{36}ClN_3O_4$: 609.2394; found: 609.2394.

(+)-{(1*S*,10*R*)-5-Benzyloxy-1-(10-chloroethyl)-3-[(5-(1-methylpiperidin-4-yl-methoxy)-indol-2-yl)-carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole} [(+)-(1*S*,10*R*)-13e]: According to GP 2, benzyl ether (+)-**5** (150 mg, 342 μmol) was stirred in 4 M HCl/EtOAc for 3.5 h at room temperature. The residue was then treated with EDC·HCl (197 mg, 1.03 mmol) and indole **10e** (144 mg, 445 μmol) in DMF for 23 h at room temperature. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH 10:1) provided (+)-**13e** (158 mg, 260 μmol, 76%) as a beige solid. R_f=0.29 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D^{20}$ = +36.3 (c=0.35 in DMSO); ^{1}H NMR (300 MHz, [D_6]DMSO): δ=1.32–1.51 (m, 2H, 3‴-H_{ax}, 5‴-H_{ax}), 1.63 (d, J=6.7 Hz, 3H, 11-H_3), 1.71–1.88 (m, 3H, 3‴-H_{eq}, 4‴-H, 5‴-H_{eq}), 2.07–2.22 (m, 2H, 2‴-H_{ax}, 6‴-H_{ax}), 2.30 (s, 3H, NCH_3), 2.85–3.01 (m, 2H, 2‴-H_{eq}, 6‴-H_{eq}), 3.85 (d, J=5.7 Hz, 2H, 1″-H_2), 4.16–4.27 (m, 1H, 1-H), 4.56–4.86 (m, 3H, 2-H_2, 10-H), 5.30 (m, 2H, OCH_2Ph), 6.93 (d, J=8.9, 2.3 Hz, 1H, 6′-H), 7.13–7.20 (m, 2H, 3′-H, 4′-H), 7.32–7.49, 7.51–7.62 (2×m, 8H, 7-H, 7′-H, 8-H, 5×Ph-H), 7.96 (d, J=8.3 Hz, 1H, 9-H), 8.12 (brs, 1H, 4-H), 8.23 (d, J=8.4 Hz, 1H, 6-H), 11.62 ppm (brs, 1H, NH); ^{13}C NMR (75 MHz, [D_6]DMSO): δ=23.3 (C-11), 27.8 (C-3‴, C-5‴), 34.2 (C-4‴), 45.1 (NCH_3), 45.9 (C-1), 52.0 (C-2), 54.3 (C-2‴, C-6‴), 61.3 (C-10), 69.6 (OCH_2Ph), 72.3 (C-1″), 98.4 (C-4), 103.4 (C-4′), 105.3 (C-3′), 113.1 (C-7′), 115.8 (C-6′), 117.5 (C-5a), 122.6 (2 signals), 123.0, 123.7 (C-6, C-7, C-9, C-9b), 127.3, 127.4, 127.5, 127.8, 128.4 (C-3a′, C-8, 5×Bn-*C*H), 129.6, 130.9, 131.6 (C-2′, C-7a′, C-9a), 136.8 (Bn-C), 142.1 (C-3a), 153.1 (C-5′), 154.2 (C-5), 160.1 ppm (C=O); UV (CH_3CN): λ_{max} (lg ε)=206.5 (4.768), 249.5 (4.369), 290.0 (4.385), 300.0 (4.546), 340.0 nm (4.457); IR (KBr): $\tilde{\nu}$=3423, 2933, 2785, 1624, 1582, 1516, 1455, 1406, 1267, 1232 cm^{-1}; MS (EI, 70 eV): m/z (%): 607.0 (4) [M^+], 571.0 (23) [M^+−Cl−H]; HRMS (ESI): m/z: calcd for $C_{37}H_{38}ClN_3O_3H$: 608.2680 [M^++H]; found: 608.2675.

General procedure 3

Preparation of seco-drug hydrochlorides (+)-(1*S*,10*R*)-14a–e: Benzyl ether (+)-**13** was dissolved in 4 M HCl/EtOAc (10 mL) and stirred for 2 h at room temperature. The resulting solution was concentrated in vacuo and the residue was thoroughly dried under vacuum. Then, the residue was suspended in freshly distilled THF (8 mL) and 10% Pd/C and a 25% (w/w) aqueous solution of NH_4HCO_2 were added. After stirring for 20–120 min at 40 °C, the solid was removed by filtration through Celite which was washed thoroughly with MeOH (150 mL). The concentrated filtrate was purified by column chromatography (CH_2Cl_2/MeOH/conc. HCl) to give seco-drug hydrochloride (+)-**14**.

(+)-{(1*S*,10*R*)-1-(10-Chloroethyl)-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)-indol-2-yl)-carbonyl]-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole hydrochloride} [(+)-(1*S*,10)-14a]: According to GP 3, benzyl ether (+)-**13a** (100 mg, 176 μmol) was stirred in 4 M HCl/EtOAc. After that, a suspension of the residue was treated with Pd/C (10%, 38 mg) and a 25% (w/w) aqueous solution of NH_4HCO_2 (0.38 mL), and the resulting mixture was stirred for 2 h at 40 °C. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH 5:1, 1% conc. HCl) provided seco-drug hydrochloride (+)-**14a** (78 mg, 152 μmol, 86%) as a green solid. R_f=0.43 (CH_2Cl_2/MeOH 5:1); $[\alpha]_D^{20}$ = +27.4 (c=0.5 in MeOH); ^{1}H NMR (300 MHz, [D_6]DMSO): δ=1.62 (d, J=6.6 Hz, 3H, 11-H_3), 2.81 (s, 6H, NMe_2), 3.47 (t, J=5.0 Hz, 2H, 2″-H_2), 4.16 (m, 1H, 1-H), 4.39 (t, J=5.0 Hz, 2H, 1″-H_2), 4.57 (m, 1H, 2-H_a), 4.66–4.81 (m, 2H, 2-H_b, 10-H), 7.00 (dd, J=8.9, 2.2 Hz, 1H, 6′-H), 7.16 (brs, 1H, 3′-H), 7.25 (d, J=2.0 Hz, 1H, 4′-H), 7.35 (t, J=7.6 Hz, 1H, 7-H), 7.45 (d, J=8.9 Hz, 1H, 7′-H), 7.51 (t, J=7.5 Hz, 1H, 8-H), 7.88 (d, J=8.3 Hz, 1H, 9-H), 7.97 (brs, 1H, 4-H), 8.14 (d, J=8.3 Hz, 1H, 6-H), 10.42 (s, 1H, OH),

11.00 (brs, 1H, NH^+), 11.65 ppm (brs, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.4 (C-11), 42.8 (NMe_2), 45.9 (C-1), 52.1 (C-2), 55.4 (C-2″), 61.5 (C-10), 63.1 (C-1″), 100.4 (C-4), 104.0 (C-4′), 105.2 (C-3′), 113.2 (C-7′), 115.6, 115.9 (C-6′, C-5a), 122.2, 122.9, 122.9, 123.1 (C-6, C-7, C-9, C-9b), 127.0 (C-8), 127.4 (C-3a′), 129.8, 131.3, 131.9 (C-2′, C-7a′, C-9a), 142.1 (C-3a), 152.0 (C-5′), 153.9 (C-5), 159.8 ppm (C=O); IR (KBr): $\tilde{\nu}$ = 3318, 2227, 1614, 1589, 1516, 1417, 1236, 1023 cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 207.5 (4.385), 248.5 (4.123), 303.0 (4.203), 337.5 nm (4.115); MS (EI, 70 eV): *m/z* (%): 441.3 (9) [M^+−2HCl]; HRMS (ESI): *m/z*: calcd for $C_{27}H_{29}ClN_3O_3$: 478.1892; found: 478.1892 [M^+].

(+)-{(1*S*,10*R*)-1-(10-Chloroethyl)-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)-6-methoxy-indol-2-yl)-carbonyl]-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole hydrochloride} [(+)-(1*S*,10*R*)-14b]: According to GP 3, benzyl ether (+)-**13b** (80 mg, 134 μmol) was stirred in 4 M HCl/EtOAc. After that, a suspension of the residue was treated with Pd/C (10%, 29 mg) and a 25% (w/w) aqueous solution of NH_4HCO_2 (0.29 mL), and the resulting mixture was stirred for 20 min at 40 °C. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH 5:1, 0.1% conc. HCl) provided seco-drug hydrochloride (+)-**14b** (63 mg, 116 μmol, 86%) as a green-yellow solid. R_f = 0.35 (CH_2Cl_2/MeOH 5:1, 1% conc. HCl); $[\alpha]_D^{20}$ = +29.3 (*c* = 0.4 in MeOH); ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 1.63 (d, *J* = 6.6 Hz, 3H, 11-H$_3$), 2.89 (s, 6H, NMe_2), 3.51 (m, 2H, 2″-H$_2$), 3.84 (s, 3H, OCH_3), 4.11–4.20 (m, 1H, 1-H), 4.39 (m, 2H, 1″-H$_2$), 4.50–4.82 (m, 3H, 2-H$_2$, 10-H), 7.04 (s, 1H, 7′-H), 7.14 (d, *J* = 1.5 Hz, 1H, 3′-H), 7.30 (s, 1H, 4′-H), 7.34 (m, 1H, 7-H), 7.50 (m, 1H, 8-H), 7.87 (d, *J* = 8.2 Hz, 1H, 9-H), 7.99 (s, 1H, 4-H), 8.13 (d, *J* = 8.2 Hz, 1H, 6-H), 10.40 (s, 1H, OH), 11.18 (brs, 1H, NH^+), 11.51 ppm (brs, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.4 (C-11), 42.8 (NMe_2), 45.9 (C-1), 52.1 (C-2), 55.3 (C-2″), 55.6 (OCH_3), 61.5 (C-10), 64.6 (C-1″), 94.7 (C-7′), 100.4 (C-4), 105.9 (C-3′), 106.6 (C-4′), 115.6 (C-5a), 120.1 (C-3a′), 122.1 (C-9b), 122.7, 122.8 (C-7, C-9), 123.1 (C-6), 126.9 (C-8), 129.4, 129.8 (C-2′, C-9a), 132.3 (C-7a′), 142.3 (C-3a), 143.4 (C-5′), 149.3 (C-6′), 153.8 (C-5), 159.7 ppm (C=O); IR (KBr): $\tilde{\nu}$ = 3385, 1612, 1587, 1516, 1471, 1415, 1313, 1201, 1153 cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 206.0 (4.653), 245.5 (4.321), 349.5 nm (4.492); MS (ESI): *m/z* (%): 508.2 (100) [M^+−Cl]; HRMS (ESI): *m/z*: calcd for $C_{28}H_{31}ClN_3O_4$: 508.2003; found: 508.1998 [M^+].

(+)-{(1*S*,10*R*)-1-(10-Chloroethyl)-3-[(5-(2-*N*,*N*-dimethylaminoacetylamino)-indol-2-yl)-carbonyl]-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole hydrochloride} [(+)-(1*S*,10*R*)-14c]: According to GP 3, benzyl ether (+)-**13c** (80 mg, 138 μmol) was stirred in 4 M HCl/EtOAc. After that, a suspension of the residue was treated with Pd/C (10%, 30 mg) and a 25% (w/w) aqueous solution of NH_4HCO_2 (0.30 mL), and the resulting mixture was stirred for 40 min at 40 °C. Purification of the crude product by column chromatography on silica gel (MeOH, 0.1% conc. HCl) provided a solid which was then dissolved in MeOH, 0.1% conc. HCl. Unsoluble silica gel was removed by filtration and the filtrate was concentrated in vacuo to give seco-drug hydrochloride (+)-**14c** (78 mg, 116 μmol, 84%) as a green solid. R_f = 0.62 (MeOH, 0.1% conc. HCl); $[\alpha]_D^{20}$ = +68.3 (*c* = 0.3 in MeOH); ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 1.63 (d, *J* = 6.3 Hz, 3H, 11-H$_3$), 2.90 (s, 6H, NMe_2), 4.11–4–25 (m, 3H, 1-H, 1″-H$_2$), 4.53–4.64 (m, 1H, 2-H$_a$), 4.65–4.81 (m, 2H, 2-H$_b$, 10-H), 7.21–7.55 (m, 5H, 3′-H, 6′-H, 7-H, 7′-H, 8-H), 7.88 (d, *J* = 8.3 Hz, 1H, 9-H), 7.99 (brs, 1H, 4-H), 8.07–8.19 (m, 2H, 4′-H, 6-H), 10.30 (brs, 1H, OH), 10.43, 11.03, 11.73 ppm (3×s, 3H, 2×NH, NH^+); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.3 (C-11), 43.1 (NMe_2), 45.8 (C-1), 52.1 (C-2), 57.9 (C-1″), 61.5 (C-10), 100.3 (C-4), 105.6 (C-3′), 112.1, 112.3 (C-4′, C-7′), 115.9 (C-5a), 118.0 (C-6′), 122.2, 122.9 (2 signals), 123.1 (C-6, C-7, C-9, C-9b), 126.9, 127.0 (C-3a′, C-8), 129.7, 130.8, 131.4, 133.3 (C-2′, C-5′, C-7a′, C-9a), 142.1 (C-3a), 153.8 (C-5), 159.7 (C=O), 162.4 ppm (C=O); IR (KBr): $\tilde{\nu}$ = 3206, 1682, 1589, 1518, 1473, 1412, 1252 cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 207.5 (4.484), 257.0 (4.499), 303.5 (4.409), 337.5 nm (4.328); MS (ESI): *m/z* (%): 981.0 (11) [2M^++H], 491.1 (100) [M^+−Cl]; HRMS (ESI): *m/z*: calcd for $C_{27}H_{28}ClN_4O_3$: 491.1850; found 491.1844 [M^+].

(+)-{(1*S*,10*R*)-1-(10-Chloroethyl)-5-hydroxy-3-[(5-(2-morpholin-4-yl-ethoxy)-indol-2-yl)-carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole hydrochloride} [(+)-(1*S*,10*R*)-14d]: According to GP 3, benzyl ether (+)-**13d** (80 mg, 131 μmol) was stirred in 4 M HCl/EtOAc. After that, a suspension of the residue was treated with Pd/C (10%, 28 mg) and a 25% (w/w) aqueous solution of NH_4HCO_2 (0.28 mL), and the resulting mixture was stirred for 1 h at 40 °C. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH 5:1, 0.1% conc. HCl) provided seco-drug hydrochloride (+)-**14d** (67 mg, 120 μmol, 82%) as a yellow solid. R_f = 0.30 (CH_2Cl_2/MeOH 10:1, 1% conc. HCl); $[\alpha]_D^{20}$ = +21.3 (*c* = 0.3 in DMSO); ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 1.62 (d, *J* = 6.5 Hz, 3H, 11-H$_3$), 3.14–3.63 (m, 6H, 2″-H$_2$, 3‴-H$_2$, 5‴-H$_2$), 3.83–4.03 (m, 4H, 2‴-H$_2$, 6‴-H$_2$), 4.12–4.21 (m, 1H, 1-H), 4.41–4.64 (m, 3H, 1″-H$_2$, 2-H$_a$), 4.64–4.82 (m, 2H, 2-H$_b$, 10-H), 7.00 (dd, *J* = 9.0, 1.8 Hz, 1H, 6′-H), 7.16 (brs, 1H, 3′-H), 7.25 (m, 1H, 4′-H), 7.35 (m, 1H, 7-H), 7.41–7.55 (m, 2H, 7′-H, 8-H), 7.88 (d, *J* = 8.4 Hz, 1H, 9-H), 7.98 (brs, 1H, 4-H), 8.14 (d, *J* = 8.3 Hz, 1H, 6-H), 10.42 (s, 1H, OH), 11.65 (s, 1H, NH), 11.93 ppm (brs, 1H, NH^+); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.4 (C-11), 45.9 (C-1), 51.6 (C-3‴, C-5‴), 52.1 (C-2), 54.9 (C-2″), 61.5 (C-10), 62.8 (C-1″), 63.0 (C-2‴, C-6‴), 100.4 (C-4), 104.0 (C-4′), 105.2 (C-3′), 113.2 (C-7′), 115.6, 115.9 (C-6′, C-5a), 122.2 (C-9b), 122.8, 122.9, 123.1 (C-6, C-7, C-9), 126.9 (C-8), 127.4 (C-3a′), 129.8, 131.3, 131.9 (C-2′, C-7a′, C-9a), 142.1 (C-3a), 151.9 (C-5′), 153.9 (C-5), 159.8 ppm (C=O); IR (KBr): $\tilde{\nu}$ = 3406, 3204, 2594, 1629, 1610, 1589, 1518, 1445, 1415, 1236 cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 206.5 (4.627), 249.0 (4.360), 303.0 (4.439), 336.0 nm (4.364); MS (ESI): *m/z* (%): 520.1 (100) [M^+−Cl]; HRMS (ESI): *m/z*: calcd for $C_{29}H_{31}ClN_3O_4$: 520.2003; found: 520.1998 [M^+].

(+)-{(1*S*,10*R*)-1-(10-Chloroethyl)-5-hydroxy-3-[(5-(1-methylpiperidin-4-yl-methoxy)-indol-2-yl)-carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole hydrochloride} [(+)-(1*S*,10*R*)-14e]: According to GP 3, benzyl ether (+)-**13e** (90 mg, 148 μmol) was stirred in 4 M HCl/EtOAc. After that, a suspension of the residue was treated with Pd/C (10%, 32 mg) and a 25% (w/w) aqueous solution of NH_4HCO_2 (0.32 mL), and the resulting mixture was stirred for 75 min at 40 °C. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH 5:1, 0.1% conc. HCl) provided seco-drug hydrochloride (+)-**14e** (67 mg, 121 μmol, 82%) as a yellow solid. R_f = 0.33 (CH_2Cl_2/MeOH 5:1, 1% conc. HCl); $[\alpha]_D^{20}$ = +44.2 (*c* = 0.33, MeOH); ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 1.60 (d, *J* = 6.5 Hz, 3H, 11-H$_3$), 1.64–1.82 (m, 2H, 3‴-H$_{ax}$, 5‴-H$_{ax}$), 1.87–2.09 (m, 3H, 3‴-H$_{eq}$, 4‴-H, 5‴-H$_{eq}$), 2.67 (s, 3H, NCH_3), 2.85–3.04 (m, 2H, 2‴-H$_{ax}$, 6‴-H$_{ax}$), 3.26–3.45 (m, 2H, 2‴-H$_{eq}$, 6‴-H$_{eq}$), 3.85 (m, 2H, 1″-H$_2$), 4.14 (m, 1H, 1-H), 4.47–4.79 (m, 3H, 2-H$_2$, 10-H), 6.91 (m, 1H, 6′-H), 7.11, 7.16 (2×brs, 2H, 3′-H, 4′-H), 7.28–7.44 (m, 2H, 7-H, 7′-H), 7.48 (m, 1H, 8-H), 7.86 (d, *J* = 8.3 Hz, 1H, 9-H), 7.96 (brs, 1H, 4-H), 8.12 (d, *J* = 8.3 Hz, 1H, 6-H), 10.43 (s, 1H, OH), 10.97 (brs, 1H, NH^+), 11.59 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.4 (C-11), 25.8 (C-3‴, C-5‴), 32.8 (C-4‴), 42.5 (NCH_3), 45.8 (C-1), 52.1 (C-2), 52.8 (C-2‴, C-6‴), 61.5 (C-10), 71.7 (C-1″), 100.4 (C-4), 103.6, 105.2 (C-3′, C-4′), 113.1 (C-7′), 115.6, 115.8 (C-6′, C-5a), 122.2, 122.8, 122.9, 123.1 (C-6, C-7, C-9, C-9b), 126.9 (C-8), 127.5 (C-3a′), 129.8, 131.1, 131.7 (C-2′, C-7a′, C-9a), 142.1 (C-3a), 152.9 (C-5′), 153.9 (C-5), 159.8 ppm (C=O); IR (KBr): $\tilde{\nu}$ = 3405, 2672, 1625, 1587, 1517, 1469, 1411, 1280 cm^{-1}; UV (MeOH): λ_{max} (lg ε) = 202.0 (4.676), 248.0 (4.356), 303.0 (4.450), 339.5 nm (4.362); MS (ESI): *m/z* (%): 518.0 (100) [M^+−Cl]; HRMS (ESI): *m/z*: calcd for $C_{30}H_{33}ClN_3O_3$: 518.2210; found: 518.2205 [M^+−Cl].

Cell culture: Human bronchial carcinoma cells of line A549 (ATCC CCL 185) were kindly provided by the Institut für Zellbiologie, Universität Essen (Germany), 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 six multiwell plates at concentrations of 10^2, 10^3, 10^4 and 10^5 cells per cavity. Culture medium was sucked off after 24 h and cells were washed in the incubation medium Ultraculture (UC, serum-free special medium, purchased from BioWhittaker Europe, Verviers, Belgium). Incubation with compounds (+)-**12a–e** and (+)-**14a–e** was then performed in Ultraculture medium at various concentrations for 24 h. All substances were used as freshly prepared solutions in DMSO (Merck, Darmstadt, Germany) diluted with incubation medium to a final concentration of DMSO of 1% in the wells. After 24 h of exposure the test substance was

removed and the cells were washed with fresh medium. Cultivation was done at 37 °C and 7.5 % CO_2 in air for 12 d. 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 IC_{50} values were based on the relative clone forming rate, which 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 seco-drugs from their glycosidic prodrugs was achieved by addition of 4.0 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 substances.

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