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Asymmetric Synthesis and Biological Evaluation of Glycosidic Prodrugs for a Selective Cancer Therapy

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Dedicated to Professor Dieter E. Kaufmann on the occasion of his 60th birthday

*A severe limitation in cancer therapy is the often insufficient differentiation between malign and benign tissue using known chemotherapeutics. One approach to decrease side effects is antibody-directed enzyme prodrug therapy (ADEPT). We have developed new glycosidic prodrugs such as (−)-(1S)-**26b** based on the antibiotic (+)-duocarmycin SA ((+)-**1**) with a QIC_{50} value of 3500 ($QIC_{50} = IC_{50}$ of prodrug/IC_{50} of prodrug + enzyme) and an IC_{50} value for the corresponding drug (prodrug + enzyme) of 16 pM. The asymmetric synthesis of the precursor (−)-(1S)-**19** was performed by arylation of the enantiomerically pure epoxide (+)-(S)-**29** (≥ 98% ee).*

Introduction

Cancer chemotherapy is generally based on the different proliferation rates of normal and malignant cells. However, very often severe side effects are observed as the proliferation rates of several normal cells, such as those from the hematopoietic system and the intestinal tract, are similar to those of tumor cells. Thus, a new form of chemotherapy that selectively targets only malignant cells and avoids damage of healthy cell populations would be valuable. In this respect, the antibody-directed enzyme prodrug therapy (ADEPT), which has first been described by Bagshawe,[1] is a highly promising alternative.[2] The concept is based on the selective formation of a highly cytotoxic drug from a relatively nontoxic prodrug in the tumor tissue. The selectivity is achieved by employing conjugates of monoclonal antibodies which bind to tumor associated antigens. These antibodies are conjugated to enzymes which are capable of transforming the prodrug into the drug. In addition to ADEPT, other approaches for the selective treatment of cancer involve the application of immunoconjugates,[3] angiogenesis inhibitors,[4] antitumor vaccines,[5] kinase inhibitors, and conjugates of a peptide and an antitumor agent.[6,7]

We have previously established several main criteria for prodrugs and the corresponding drugs used in the ADEPT concept.[8] Thus, the prodrugs should have comparatively low cytotoxicity, should be water-soluble, and should not penetrate the cell membrane of either normal or malignant cells, whereas the liberated toxins should be able to penetrate the cell membrane and have high cytotoxicity ($IC_{50} < 10$ nM) resulting in a QIC_{50} value > 1000 ($QIC_{50} = IC_{50}$ of prodrug/IC_{50} of prodrug + enzyme).

The natural cytotoxic antibiotics duocarmycin SA ((+)-**1**), CC-1065 ((+)-**2**), and yatakemycin ((+)-**3**) seem to be especially suitable for the ADEPT approach because of their very high cytotoxicities with IC_{50} values of 10, 20, and 3–5 pM (L1210 tumor cell line), respectively.[9–11] They all share a structural element, namely the spirocyclopropylcyclohexadienone moiety, that causes sequence-selective alkylation of N3 of adenine in AT-rich sites of the minor groove of DNA. An artificial analogue of these compounds is (+)-*N*-Boc-CBI ((+)-**4**) with an IC_{50} value of 77 nM (L1210 tumor cell line) developed by Boger and coworkers,[12,13] which can be formed from the corresponding seco-compound (−)-(1*S*)-**5** by an intramolecular alkylation.

Recently we have shown that the in situ formation of **4** from **5** can be reversibly blocked by transforming the phenolic hydroxy group in **5** into a glycoside.[14] However, the biological assay of the diastereomeric prodrug mixture **7a**/**7b** led to a rather low QIC_{50} value of 32 which does not meet our criteria of a $QIC_{50} > 1000$ to have a sufficiently large therapeutic window. Moreover, using other leaving groups such as in seco-drug *rac*-**8** and prodrug **9a**/**9b** or employing partly hydrogenated seco-drugs and prodrugs such as *rac*-**10** and **11a**/**11b** did not change the picture.[15]

We therefore developed prodrugs based on the 10-methyl-seco-CBI skeleton bearing a secondary chloride to minimize possible direct alkylation reactions. This concept was very successful resulting in novel prodrugs such as (+)-(1*S*,10*R*)-**15a** containing the *N*,*N*-dimethylaminoethoxyindole (DMAI) DNA binding subunit developed by Denny, and (+)-(1*S*,10*R*)-**17a**

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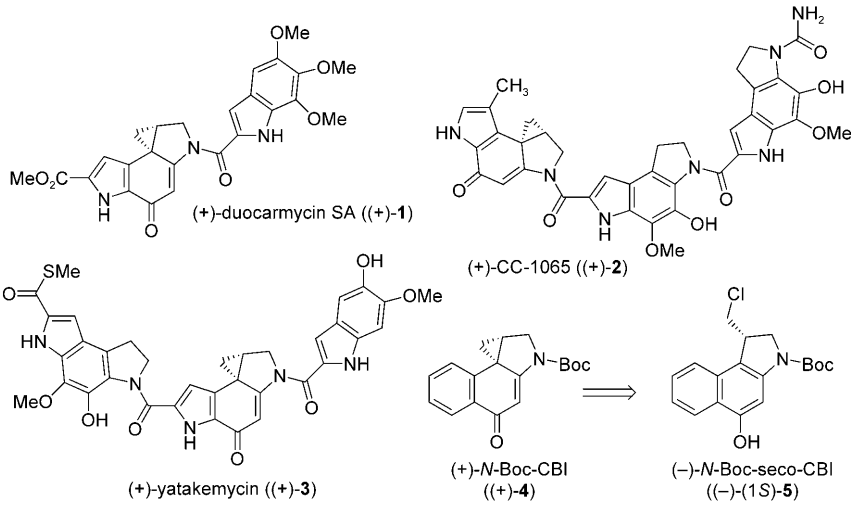
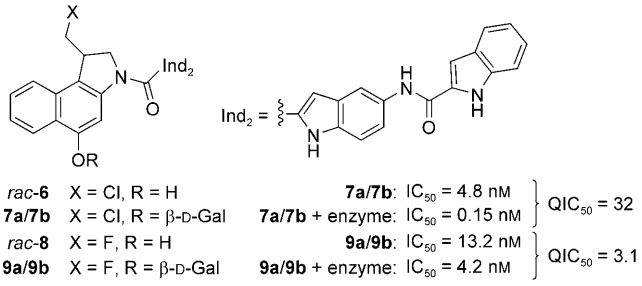
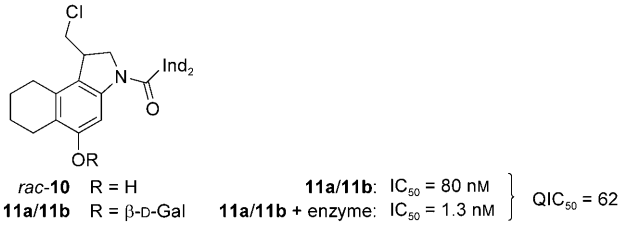
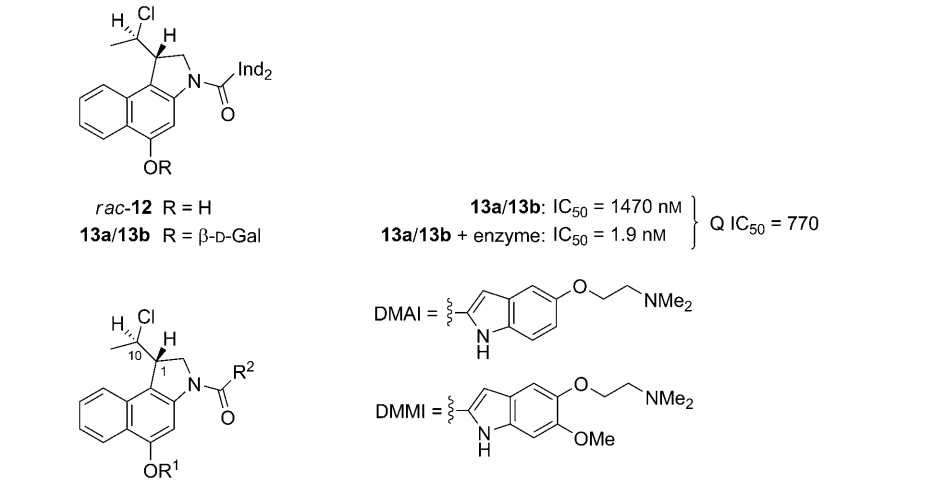








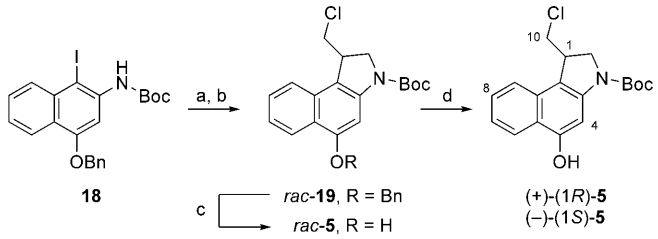
containing the related *N*,*N*-dimethylaminoethoxymethoxyindole (DMMI) DNA binding subunit developed by our group.[16,17] These prodrugs exhibit excellent QIC_{50} values up to approximately 5000; however, the compounds are rather sensitive and the IC_{50} values of the corresponding seco-drugs are only 0.75 nM and 0.22 nM, respectively.[18] Surprisingly, in the biological investigation of compounds **13a**/**13b** containing the 10-methyl-seco-CBI skeleton and a bisindole DNA binding subunit as in **7a**/**7b**, **9a**/**9b**, and **11a**/**11b** instead of DMAI or DMMI, a much lower QIC_{50} value of 770 was observed,[15] showing that the DNA binding subunit has a pronounced effect on the QIC_{50} value, which was not known so far. These results forced us to reinvestigate our work on the CBI skeleton connected to the DMAI and DMMI moiety. Thus, herein we describe the synthesis and biological evaluation of the prodrugs **26a**/**26b**, (−)-(1*R*)-**26a**, (−)-(1*S*)-**26b**, and (−)-(1*S*)-**27b** together with an asymmetric synthesis of the benzyl-protected (−)-(1*S*)-*N*-Boc-seco-CBI ((−)-(1*S*)-**19**).

Results and Discussion

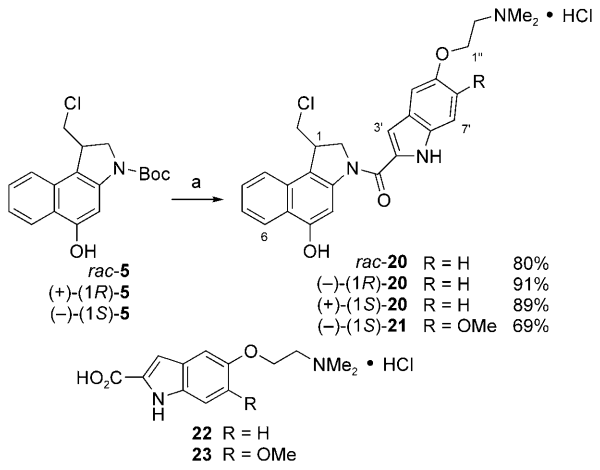
Synthesis of the seco-drugs and the prodrugs

The synthesis of the racemic and enantiomerically pure *N*-Boc-seco-CBI (**5**) derivatives started from precursor **18**, which is available in eight steps from benzaldehyde (Scheme 1).[19] Alkylation with 1,3-dichloropropene (*E*/*Z* mixture) and subsequent radical 5-*exo*-trig cyclization using TTMSS gave *rac*-**19** in 92% yield over two steps.[20] Preparative chromatographic resolution of *rac*-**19** was described with a Chiralcel® OD column,[21] but could be achieved in a much more efficient manner after reductive removal of the benzyl group using a Chiralpak® IA column to give (+)-(1*R*)-**5** and (−)-(1*S*)-**5** with >99.9% *ee*.

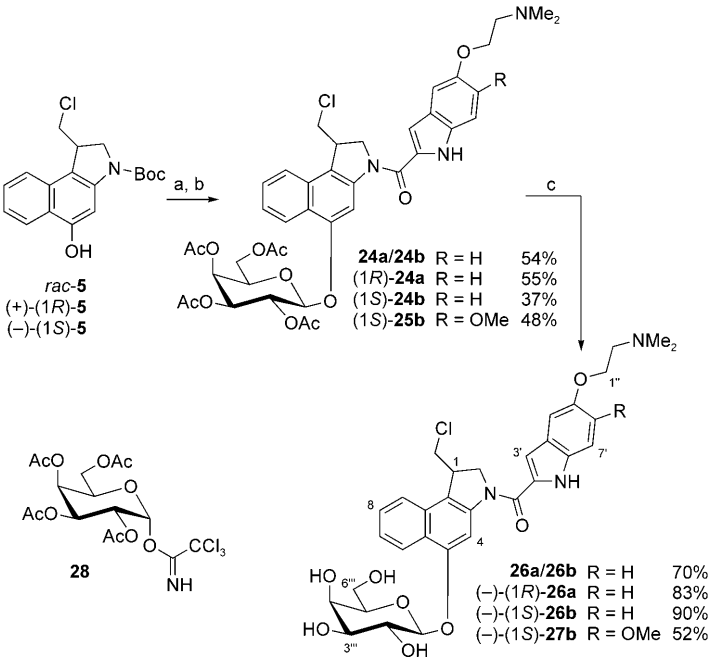
For the synthesis of the seco-drugs starting from racemic and enantiomerically pure *N*-Boc-seco-CBI **5** (Scheme 2), the Boc protecting group was cleaved using HCl in ethyl acetate. Then,



Scheme 1. Synthesis of the seco-drug and prodrug CBI precursors: a) NaH, DMF, RT, 1.5 h, then 1,3-dichloropropene, RT, 5.5 h, quant; b) AIBN, TTMSS, toluene, 80 °C, 4 h, 92%; c) Pd/C/NH_4HCO_2, THF, 35 °C, 30 min, 93%; d) Chiralpak® IA, *n*-hexane/*i*PrOH (97:3). Boc = *tert*-butyloxycarbonyl, Bn = benzyl, AIBN = 2,2′-azobis(2-methylpropionitrile), TTMSS = tris(trimethylsilyl)silane.



Scheme 2. Synthesis of the seco-drugs: a) 4 M HCl/EtOAc, RT, 3 h, then **22** or **23**, EDC·HCl, DMF, RT, 18–22 h, then 4 M HCl/EtOAc, conc. HCl. EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide.



Scheme 3. Synthesis of the glycosidic prodrugs: a) **28**, BF_3·OEt_2, CH_2Cl_2, molecular sieves (4 Å), −10 °C, 3.5 h, then BF_3·OEt_2, RT, 5 h; b) **22** or **23**, EDC·HCl, DMF, RT, 20 h; c) NaOMe/MeOH, RT, 2 h.

the resulting ammonium hydrochloride salts were coupled with the DNA binding subunits DMAI-CO_2H·HCl (**22**) and DMMI-CO_2H·HCl (**23**), respectively to give the seco-drugs *rac*-**20**, (−)-(1*R*)-**20**, (+)-(1*S*)-**20**, and (−)-(1*S*)-**21** in good to excellent yields of 69–91%. Formation of the hydrochloride salts, again using HCl in ethyl acetate, avoided cyclization to the corresponding drugs during the work-up procedures.

For the synthesis of the prodrugs (Scheme 3), glycosylation of the seco-CBI pharmacophores *rac*-**5**, (+)-(1*R*)-**5**, and (−)-(1*S*)-**5** using Schmidt's trichloracetimidate procedure was followed by cleavage of the Boc protecting group and coupling with DMAI-CO_2H·HCl (**22**) and DMMI-CO_2H·HCl (**23**), respectively.[22] Saponification of the obtained acetylated glycosides **24a**/**24b**, (1*R*)-**24a**, (1*S*)-**24b**, and (1*S*)-**25b** employing the Zemplén procedure yielded the prodrugs **26a**/**26b**, (−)-(1*R*)-**26a**, (−)-(1*S*)-**26b**, and (−)-(1*S*)-**27b** in 33–46% yield over three steps.[23]

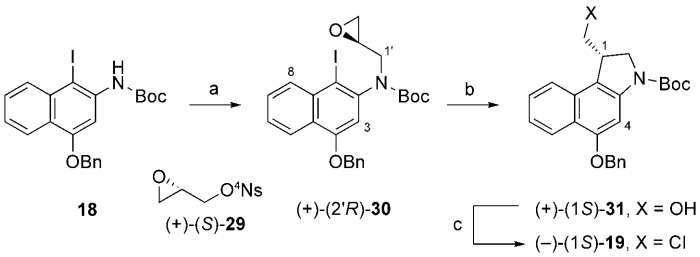
Asymmetric synthesis of seco-CBI precursor (−)-(1*S*)-19

To carry out clinical trials with the diastereomerically and enantiomerically pure prodrug (−)-(1*S*)-**26b**, which showed the best results in the biological assays (see below), access to larger quantities of the precursor (−)-(1*S*)-**19** was needed. Besides chromatographic resolution, there are several approaches described in the literature to provide enantiomerically pure or at least enriched CBI derivatives including enzymatic desymmetrization,[24] asymmetric hydroboration,[25] Jacobsen epoxidation, and Sharpless AD reaction.[25a,26] We previously reported a new asymmetric route to the related 10-methyl-seco-CBI which can also be employed in the synthesis of the seco-CBI pharmacophore.[27]

Alkylation reactions using a glycidyl-nosylate[28] had been shown to proceed regioselectively.[29] Thus, reaction of **18** with the nosylate (+)-(*S*)-**29** afforded (+)-(2′*R*)-**30** in 95% yield, which in the following metal mediated opening of the epoxide delivered the five-membered ring system (+)-(1*S*)-**31** as the main product in 58% yield in a stereoselective manner without any loss of stereo integrity. Transformation of (+)-(1*S*)-**31** employing an Appel reaction led to the benzyl protected seco-CBI precursor (−)-(1*S*)-**19** (Scheme 4).[24a]

In vitro cytotoxicity tests

The in vitro cytotoxicities of the newly synthesized compounds were tested on human tumor cells using a colony-forming test based on the HTCFA (human tumor colony-forming ability assay) that reflects the proliferation capacity of single cells. The assays were carried out in three to six replicates of duplicate experiments using adherent cells of the human bronchial carcinoma cell line A549 in six multi-well plates with concentrations of 10^2, 10^3, and 10^4 cells per cavity. Incubation with various concentrations of seco-drug hydrochlorides *rac*-**20**, (−)-(1*R*)-**20**, (+)-(1*S*)-**20**, and (−)-(1*S*)-**21** as well as of the β-D-galactosidic prodrugs **26a**/**26b**, (−)-(1*R*)-**26a**, (−)-(1*S*)-**26b**, and (−)-(1*S*)-



Scheme 4. Synthesis of the benzyl-protected seco-CBI precursor (−)-(1*S*)-**19**: a) NaH, DMF, RT, 30 min, then (+)-(*S*)-**29**, RT, 23 h, 95%; b) $ZnCl_2$, MeLi, THF, 0 °C, 30 min, addition of TMS-NCS at −78 °C followed by 30 min at 0 °C, then addition of a solution of (+)-(2′*R*)-**30** in THF at −78 °C, warming (−78 °C→ RT) over 3 h and then 14 h at RT, 58%; c) PPh_3, CCl_4, CH_2Cl_2, RT, 3 h, 93%. TMS-NCS = trimethylsilyl isothiocyanate.

27b in the absence and presence of β-D-galactosidase was performed in serum-free medium (Table 1). It should be pointed out that these assays also give information about the efficiency of drug formation from the prodrug and whether an undesired suicide mechanism that inactivates the enzyme takes place. Thus, when the IC_{50} value of the seco-drug and the IC_{50} value of the prodrug in the presence of the cleaving enzyme are almost identical, one can assume that the enzymatic cleavage is fast and the enzyme is not deactivated by the product formed.

In all cases, the IC_{50} values of the prodrugs in the presence of β-D-galactosidase show no significant deviation from the IC_{50} values of the corresponding seco-drugs. The QIC_{50} values of all new CBI-based glycosidic prodrugs containing either the DMAI subunit as in **26a**/**26b**, (−)-(1*R*)-**26a** and (−)-(1*S*)-**26b** or the DMMI subunit as in (−)-(1*S*)-**27b** exceed the value of >1000 that is demanded for ADEPT. However, as expected (−)-(1*R*)-**26a** bearing the unnatural *R* configuration at C-1 is considerably less toxic in the presence of β-D-galactosidase with an IC_{50} value of only 12 nM compared to (−)-(1*S*)-**26b** with an IC_{50} of 16 pM in the presence of the cleaving enzyme; moreover, the QIC_{50} value of 3500 obtained for (−)-(1*S*)-**26b** is more favorable.

The seco-drug (−)-(1*S*)-**21** and the prodrug (−)-(1*S*)-**27b** (in the presence of β-D-galactosidase) both containing the DMMI DNA binding subunit have the highest cytotoxicity (IC_{50} = 9 and 4.5 pM, respectively); however, in comparison to (−)-(1*S*)-**26b** the corresponding glycosidic prodrug (−)-(1*S*)-**27b** also expresses rather high cytotoxicity resulting in a slightly lower QIC_{50} value of only 2100. This again shows the importance of the DNA binding subunit for cytotoxicity and selectivity.

The prodrug (−)-(1*S*)-**26b** shows the best chemical and biological results of all compounds developed by us and others so far for the treatment of cancer using the ADEPT approach, and it will be developed further. It should be mentioned that the prodrugs (+)-(1*S*,10*R*)-**15a** and (+)-(1*S*,10*R*)-**17a** have slightly higher QIC_{50} values, but the much better stability of (−)-(1*S*)-**26b** in serum-free medium and the much higher cytotoxicity of the corresponding drug make this compound superior.

For comparison, Figure 1 shows the HTCFA assays of currently used anticancer agents such as carmustine (**34**), melphalan (**33**), doxorubicin (**32**) and the new prodrug (−)-(1*S*)-**26b** in presence of the enzyme β-D-galactosidase. The difference in the biological activity is very pronounced and highlights again the potential of the prodrug (−)-(1*S*)-**26b** for a selective treatment of cancer using the ADEPT approach.

Table 1. In vitro cytotoxicities.[a]

Compound	Presence of β-D-galactosidase	IC_{50} [nM][b]	QIC_{50}[c]
rac-**20**	−	0.071	
26a/**26b**	+	0.043	1900
26a/**26b**	−	82	
(−)-(1*R*)-**20**	−	11.5	
(−)-(1*R*)-**26a**	+	12	1400
(−)-(1*R*)-**26a**	−	16700	
(+)-(1*S*)-**20**	−	0.026	
(−)-(1*S*)-**26b**	+	0.016	3500
(−)-(1*S*)-**26b**	−	56.3	
(−)-(1*S*)-**21**	−	0.009	
(−)-(1*S*)-**27b**	+	0.0045	2100
(−)-(1*S*)-**27b**	−	9.5	

[a] In vitro cytotoxicities in the HTCFA of β-D-galactosidic prodrugs in the presence and absence of β-D-galactosidase and of the corresponding seco-drugs against human bronchial carcinoma cells (A549). Cells were exposed to various concentrations of each compound for 24 h at 37 °C in serum-free medium and washed with incubation medium afterward; after cultivation in normal culture medium for 10 days, 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} from Sigma. [b] IC_{50} values were determined from three to six replicates of duplicate experiments. The coefficients of variation of all IC_{50} values were consistently below 10%. [c] QIC_{50} = (IC_{50} of prodrug)/(IC_{50} of prodrug in the presence of β-D-galactosidase).

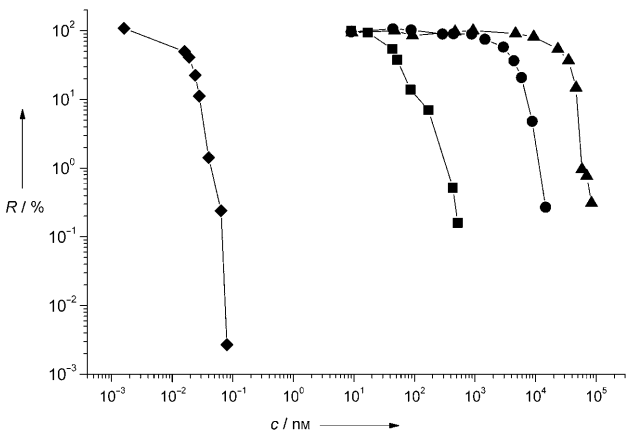
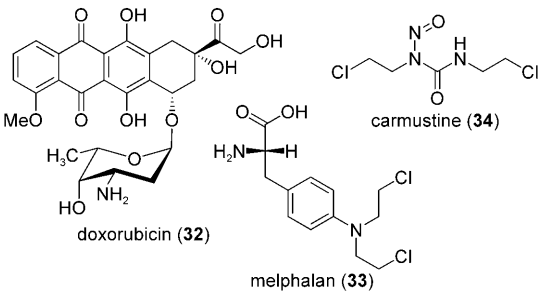


Figure 1. Comparison of the in vitro cytotoxicities of various anticancer agents against human bronchial carcinoma cells of line A549: (−)-(1*S*)-**26b** [◆] in the presence of β-D-galactosidase (4 U mL^{-1}) IC_{50} = 0.016 nM; doxorubicin (**32** [■]) IC_{50} = 45 nM; melphalan (**33** [●]) IC_{50} = 3.4×10^3 nM; carmustine (**34** [▲]) IC_{50} = 2.6×10^4 nM. *R* = relative clone-formation rate.



Conclusion

We have described the asymmetric synthesis and biological evaluation of new glycosidic prodrugs of duocarmycin analogues. All prodrugs meet the criteria for ADEPT with prodrug (−)-(1*S*)-**26b** showing an excellent QIC_{50} value of 3500 in combination with an IC_{50} value of 16 pM in the presence of the enzyme β-D-galactosidase. The compound has very good stability in serum-free medium, and is therefore a clinically relevant candidate and probably the best compound developed so far within the ADEPT approach for the selective treatment of cancer. Its potential is currently being evaluated in preclinical studies using mice and rat models.

Experimental Section

General

All reactions were carried out under argon in flame dried flasks. All solvents were distilled prior to use by common laboratory methods. All reagents purchased from commercial sources were used without further purification. Thin-layer chromatography (TLC) was performed on precoated silica gel SIL G/UV_{254} plates (Machery–Nagel), and silica gel 60 (0.032–0.063 mm, Merck) was used for column chromatography. Vanillin in methanolic sulfuric acid was used as the staining reagent for TLC. UV spectra were recorded in CH_3CN or MeOH using a PerkinElmer Lambda 2 spectrometer. IR spectra were recorded as KBr pellets or as films using a Bruker IFS 25 spectrometer. Optical rotations were measured on a PerkinElmer 241 polarimeter in the solvent indicated. ^1H and ^{13}C NMR spectra were recorded with Mercury 300, Unity 300, Inova 500, and Inova 600 (Varian) spectrometers. Chemical shifts are listed in δ (ppm) with tetramethylsilane (TMS) as internal standard. Multiplicity of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured with Finnigan MAT 95, TSQ 7000, and LCQ instruments. HRMS was performed with 7 T FTICR–MS APEX IV equipment (Bruker). The following abbreviations are used: P = *n*-pentane, EtOAc = ethyl acetate, *i*PrOH = 2-propanol, DMF = *N*,*N*-dimethylformamide, AIBN = 2,2′-azobisisobutyronitrile, Boc = *tert*-butyloxycarbonyl, EDC·HCl = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, TMS-NCS = trimethylsilyl isothiocyanate, THF = tetrahydrofuran. Melting points of the new seco-drug hydrochlorides and prodrugs cannot be provided because the compounds decompose before melting.

Synthesis of *N*-Boc-seco-CBI [*rac*-5, (+)-(1*R*)-5 and (−)-(1*S*)-5]

(*E*/*Z*)-2-amino-4-benzyloxy-*N*-(*tert*-butyloxycarbonyl)-*N*-(3-chloro-2-propenyl)-1-iodonaphthalene: A solution of amine **18** (2.00 g, 4.21 mmol) in DMF (20 mL) was added dropwise to a solution of NaH (60% in mineral oil, 589 mg, 14.7 mmol) and the mixture was stirred for 1.5 h at RT. Then, (*E*/*Z*)-1,3-dichloropropene (934 mg, 8.42 mmol) was added and the reaction mixture was stirred for another 5.5 h followed by addition of a saturated aqueous solution of NH_4Cl (50 mL), H_2O (50 mL), and EtOAc (100 mL), and extraction with EtOAc (3×100 mL). The combined organic layers were washed with H_2O (4×150 mL) and brine (200 mL), dried over $MgSO_4$, and the solvent was removed in vacuo. The resulting crude product was purified by column chromatography on silica gel (P/EtOAc = 10:1) to provide (*E*/*Z*)-2-amino-4-benzyloxy-*N*-(*tert*-butyloxycarbonyl)-*N*-(3-chloro-2-propenyl)-1-iodonaphthalene as yellow oil (2.31 g, 4.21 mmol, quant.). R_f = 0.42, 0.50 (P/EtOAc, 10:1); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.33/1.58 (s, 9H, $C(CH_3)_3$), 3.72–4.34 (m, 1H, 1′-H_a), 4.47–4.63 (m, 1H, 1′-H_b), 5.26 (br s, 2H, OCH_2Ph), 5.93–6.18 (m, 2H, 2′-H, 3′-H), 6.65–6.79 (m, 1H, 3-H), 7.31–7.63 (m, 7H, 6-H, 7-H, 5×Ph-H), 8.10/8.22 (2×d, $2J$ = 8.0 Hz, 2×1H, 5-H, 8-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3/28.5 ($C(CH_3)_3$), 46.0/49.1 (C-1′), 70.3/70.4 (OCH_2Ph), 80.7 ($C(CH_3)_3$), 95.0/95.1 (C-1), 107.1/107.7 (C-3), 120.6/120.8 (C-3′), 122.5 (C-5), 125.5 (C-4a), 126.3, 126.4, 127.3 (2 signals) (C-6, C-2′, 2×Ph-C_oH), 128.1/128.2 (Ph-C_pH), 128.5/128.6 (C-8), 128.7 (2 signals) (2×Ph-C_mH), 132.7 (C-7), 135.3 (C-8a), 136.3/136.4 (Ph-*C*), 142.4/142.8 (C-2), 153.7/153.9 (C=O), 155.3 (C-4).

***rac*-19**: Tris(trimethylsilyl)silane (1.15 g, 4.63 mmol) and AIBN (173 mg, 1.05 mmol) were added to a thoroughly degassed solution of (*E*/*Z*)-2-amino-4-benzyloxy-*N*-(*tert*-butyloxycarbonyl)-*N*-(3-chloro-2-propenyl)-1-iodonaphthalene (2.31 g, 4.21 mmol) in toluene (50 mL). The reaction mixture was then heated at 80 °C using a preheated oil bath and stirred for 2.5 h. After cooling to RT, a 10% (*w*/*w*) aqueous solution of KF (50 mL) was added and stirring was continued for 1 h. The organic layer was then dried over $MgSO_4$ and the solvent was removed in vacuo. Column chromatography on silica gel (P/EtOAC = 50:1→20:1) gave *rac*-**19** (1.64 g, 3.86 mmol, 92%) as a white solid. R_f = 0.50 (P/EtOAc, 10:1); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62 (s, 9H, $C(CH_3)_3$), 3.44 (t, J = 10.9 Hz, 1H, 10-H_a), 3.92–4.01 (m, 2H, 1-H, 10-H_b), 4.13 (t, J = 10.7 Hz, 1H, 2-H_a), 4.28 (d, J = 11.1 Hz, 1H, 2-H_b), 5.27 (s, 2H, OCH_2Ph), 7.31–7.56 (m, 7H, 7-H, 8-H, 5×Ph-H), 7.65 (d, J = 8.4 Hz, 1H, 9-H), 7.87 (br s, 1H, 4-H), 8.30 (d, J = 8.4 Hz, 1H, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.5 ($C(CH_3)_3$), 41.6 (C-1), 46.5 (C-10), 53.0 (C-2), 70.3 (OCH_2Ph), 81.2 (*C*-$(CH_3)_3$), 96.4 (C-4), 114.0 (C-9b), 122.4 (C-5a), 121.7, 123.1, 123.6 (C-6, C-7, C-9), 127.5 (Ph-C_o), 127.6 (C-8), 128.0 (Ph-C_p), 128.5 (Ph-C_m), 130.2 (C-9a), 136.7 (Ph-Ci), 143.4 (C-3a), 152.6 (C=O), 156.0 (C-5); MS (ESI): *m*/*z* (%): 446.15 (100) $[M+Na]^+$; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{25}H_{26}ClNNaO_3$: 446.1493, found: 446.1491.

***rac*-5**: *rac*-**19** (200 mg, 472 μmol) was dissolved in freshly distilled THF (20 mL) and the solution was warmed to 35 °C. Then, Pd/C (10%, 100 mg) was added under stirring and a 25% (*w*/*w*) aqueous solution of ammonium formate (1 mL) was added dropwise. After stirring for 30 min at 35 °C, solids were remove by filtration through celite which was washed thoroughly with acetone (400 mL). After removal of the solvents in vacuo, the concentrated filtrate was purified by column chromatography on silica gel (P/EtOAc = 5:1) to yield *rac*-**5** (147 mg, 440 μmol, 93%) as a white solid. R_f = 0.54 (P/EtOAc, 5:1); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 9H, $C(CH_3)_3$), 3.42 (t, J = 10.8 Hz, 1H, 10-H_a), 3.90–4.00 (m, 2H, 1-H, 10-H_b), 4.11 (t, J = 10.7 Hz, 1H, 2-H_a), 4.24 (d, J = 11.7 Hz, 1H, 2-H_b), 6.14 (br s, 1H, OH), 7.34 (dt, J = 7.7, 1.1 Hz, 1H, 7-H), 7.50 (dt, J = 7.6, 1.2 Hz, 1H, 8-H), 7.64 (d, J = 8.4 Hz, 1H, 9-H), 7.71 (br s, 1H, 4-H), 8.17 (d, J = 8.4 Hz, 1H, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.5 ($C(CH_3)_3$), 41.7 (C-1), 46.5 (C-10), 53.1 (C-2), 81.8 ($C(CH_3)_3$), 99.1 (C-4), 114.0 (C-9b*), 121.5 (C-5a*), 121.7, 122.7, 123.6 (C-6, C-7, C-9), 127.5

(C-8), 130.3 (C-9a), 141.1 (C-3a), 153.3 (C=O), 154.1 (C-5); MS (ESI): *m/z* (%): 356.1 (100) $[M+Na]^+$; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{20}ClNNaO_3$: 356.1076, found: 356.1080.

Chromatographic resolution of *rac*-5: A solution of *rac*-**5** in a 1:1 mixture of *n*-hexane and *i*PrOH ($c = 25\ mg\ mL^{-1}$) was separated consecutively (injection volume: 1 mL) by semipreparative HPLC (Chiralpak® IA, 250×20 mm, particle size: 5 μm; *n*-hexane/*i*PrOH = 97:3; flow: 18 $mL\ min^{-1}$; UV detector: $\lambda = 254$ nm) to provide (+)-(1*R*)-**5** ($t_R = 8.6$ min) and (−)-(1*S*)-**5** ($t_R = 10.8$ min). The optical purity was determined by analytical HPLC (Chiralcel® OD, 250×4.6 mm, particle size: 10 μm; *n*-hexane/*i*PrOH = 98:2; flow: 0.8 $mL\ min^{-1}$; UV detector: $\lambda = 254$ nm): (+)-(1*R*)-**5**, 99.9% *ee* ($t_R = 11.4$ min); $[\alpha]_D^{20} = +48.6$ ($c = 0.28$ in $CHCl_3$); (−)-(1*S*)-**5**, 99.9% *ee* ($t_R = 15.2$ min); $[\alpha]_D^{20} = -45.8$ ($c = 0.24$ in $CHCl_3$).

General procedure 1 for the preparation of the seco-drug hydrochlorides *rac*-20, (−)-(1*R*)-20, (+)-(1*S*)-20, and (−)-(1*S*)-21

Rac-**5**, (+)-(1*R*)-**5**, or (−)-(1*S*)-**5** were treated with 4 M HCl/EtOAc (5.0 mL) and stirred at RT for 3 h. The solvents were removed in vacuo and the residues were thoroughly dried under vacuum for 1 h. Then, the residues were dissolved in dry DMF (3.5 mL) and the solutions cooled to 0 °C. EDC·HCl (3 equiv) and DMAI-CO_2H·HCl (**22**, 1.3 equiv) or DMMI-CO_2H·HCl (**23**, 1.3 equiv) were added and the reaction mixture was allowed to warm to RT. After stirring for 18–22 h at this temperature, concentrated HCl (1.0 mL) was added and the solvents were removed in vacuo. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH = 5:1, 1% conc. HCl) and in an exceptional case preparative HPLC (Kromasil® 100 C_{18}, 250×20 mm, particle size: 7 μm; solvent A: H_2O with 0.06% (*v/v*) conc. HCl, solvent B: MeOH; gradient: A/B = 70:30→0:100 in 15 min) provided the seco-drugs *rac*-**20**, (−)-(1*R*)-**20**, (+)-(1*S*)-**20**, and (−)-(1*S*)-**21**, respectively.

(*rac*)-{1-Chloromethyl-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)indol-2-yl)-carbonyl]-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole hydrochloride} [*rac*-20]: According to general procedure 1, *rac*-**5** (74 mg, 222 μmol) was stirred in 4 M HCl/EtOAc. After that, a suspension of the residue in DMF was treated with EDC·HCl (128 mg, 666 μmol) and DMAI-CO_2H·HCl (**22**, 82.0 mg, 289 μmol) and the reaction mixture was stirred for 18 h at RT. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH = 5:1, 1% conc. HCl) provided seco-drug hydrochloride *rac*-**20** (89.3 mg, 178 μmol, 80%) as a pale-yellow solid. $R_f = 0.38$ (CH_2Cl_2/MeOH, 5:1, 1% conc. HCl); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 2.98$ (s, 6H, NMe_2), 3.51–3.65 (m, 3H, 2″-H_2, 10-H_a), 3.93 (dd, $J = 11.2$, 3.0 Hz, 1H, 10-H_b), 4.03–4.12 (m, 1H, 1-H), 4.32 (t, $J = 4.8$ Hz, 2H, 1″-H_2), 4.52–4.66 (m, 2H, 2-H_2), 6.99–7.06 (m, 2H, 3′-H, 6′-H), 7.24 (d, $J = 2.4$ Hz, 1H, 4′-H), 7.33 (t, $J = 7.6$ Hz, 1H, 7-H), 7.43 (d, $J = 8.9$ Hz, 1H, 7′-H), 7.49 (t, $J = 7.6$ Hz, 1H, 8-H), 7.72 (d, $J = 8.4$ Hz, 1H, 9-H), 7.81 (br s, 1H, 4-H), 8.18 (d, $J = 8.4$ Hz, 1H, 6-H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 43.5$ (C-1), 43.9 (NMe_2), 47.5 (C-10), 56.8 (C-2), 57.8 (C-2″), 63.7 (C-1″), 101.4 (C-4), 105.2 (C-4′), 107.2 (C-3′), 114.2 (C-7′), 117.1, 117.2 (C-5a, C-6), 123.5 (C-9), 124.3, 124.5, 124.6 (C-6, C-7, C-9a), 128.6 (C-8), 129.2, 131.5, 132.5, 133.9 (C-2, C-3a′, C-7a, C-9b), 143.1 (C-3a), 153.8 (C-5′), 155.8 (C-5), 162.6 (C=O); IR (KBr): $\tilde{\nu} = 3416$, 1626, 1518, 1471, 1413, 1284, 1233, 1178 cm^{-1}; UV/Vis (MeOH): $\lambda_{max}(\log \varepsilon) = 207.0$ (4.361), 247.5 (4.127), 302.5 (4.162), 336.0 nm (4.082); MS (ESI): *m/z* (%): 464.2 (100) $[M-Cl]^+$; HRMS (ESI): *m/z* $[M-Cl]^+$ calcd for $C_{26}H_{27}ClN_3O_3$: 464.1741 found: 464.1736.

(−)-{(1*R*)-1-Chloromethyl-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)indol-2-yl)-carbonyl]-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole hydrochloride} [(−)-(1*R*)-20]: According to general procedure 1, (+)-(1*R*)-**5** (70 mg, 210 μmol) was stirred in 4 M HCl/EtOAc. After that, a suspension of the residue was treated with EDC·HCl (121 mg, 630 μmol) and DMAI-CO_2H·HCl (**22**, 77.5 mg, 273 μmol) and the reaction mixture was stirred for 20 h at RT. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH, 5:1, 1% conc. HCl) provided seco-drug hydrochloride (−)-(1*R*)-**20** (95.4 mg, 191 μmol, 91%) as a pale-yellow solid. $R_f = 0.36$ (CH_2Cl_2/MeOH, 5:1, 1% conc. HCl); $[\alpha]_D^{20} = -18.0$ ($c = 0.2$ in MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 2.83$ (s, 6H, NMe_2), 3.48 (t, $J = 5.0$ Hz, 2H, 2″-H_2), 3.84 (dd, $J = 11.0$, 7.6 Hz, 1H, 10-H_a), 4.03 (dd, $J = 11.0$, 3.0 Hz, 1H, 10-H_b), 4.22 (m_c, 1H, 1-H), 4.39 (t, $J = 5.0$ Hz, 2H, 1″-H_2), 4.54 (dd, $J = 11.0$, 1.8 Hz, 1H, 2-H_a), 4.79 (dd, $J = 11.0$, 9.4 Hz, 1H, 2-H_b), 7.00 (dd, $J = 8.8$, 2.2 Hz, 1H, 6′-H), 7.11 (d, $J = 1.4$ Hz, 3′-H), 7.26 (d, $J = 2.2$ Hz, 1H, 4′-H), 7.36 (t, $J = 7.6$ Hz, 1H, 7-H), 7.45 (d, $J = 8.9$ Hz, 1H, 7′-H), 7.52 (t, $J = 7.6$ Hz, 1H, 8-H), 7.84 (d, $J = 8.4$ Hz, 1H, 9-H), 7.97 (s, 1H, 4-H), 8.13 (d, $J = 8.4$ Hz, 1H, 6-H), 10.43 (s, 1H, OH), 10.93 (br s, 1H, NH^+), 11.64 (s, 1H, NH); ^{13}C NMR (150 MHz, CD_3OD): $\delta = 43.5$ (C-1), 43.9 (NMe_2), 47.5 (C-10), 56.8 (C-2), 57.8 (C-2″), 63.7 (C-1″), 101.4 (C-4), 105.2 (C-4′), 107.2 (C-3′), 114.2 (C-7′), 117.1, 117.2 (C-5a, C-6), 123.5 (C-9), 124.3, 124.5, 124.6 (C-6, C-7, C-9a), 128.6 (C-8), 129.2, 131.5, 132.5, 133.9 (C-2, C-3a′, C-7a, C-9b), 143.1 (C-3a), 153.8 (C-5′), 155.8 (C-5), 162.6 (C=O); IR (KBr): $\tilde{\nu} = 3416$, 1626, 1518, 1471, 1413, 1284, 1233, 1178 cm^{-1}; UV/Vis (MeOH): $\lambda_{max}(\log \varepsilon) = 207.0$ (4.361), 247.5 (4.127), 302.5 (4.162), 336.0 nm (4.082); MS (ESI): *m/z* (%): 464.2 (100) $[M-Cl]^+$; HRMS (ESI): *m/z* $[M-Cl]^+$ calcd for $C_{26}H_{27}ClN_3O_3$: 464.1741, found: 464.1736.

(+)-{(1*S*)-Chloromethyl-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)indol-2-yl)-carbonyl]-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole hydrochloride} [(+)-(1*S*)-20]: According to general procedure 1, (−)-(1*S*)-**5** (70 mg, 210 μmol) was stirred in 4 M HCl/EtOAc. After that, a suspension of the residue was treated with EDC·HCl (121 mg, 630 μmol) and DMAI-CO_2H·HCl (**22**, 77.5 mg, 273 μmol) and the reaction mixture was stirred for 20 h at RT. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/MeOH, 5:1, 1% conc. HCl) provided seco-drug hydrochloride (+)-(1*S*)-**20** (93.2 mg, 186 μmol, 89%) as a pale-yellow solid. $R_f = 0.40$ (CH_2Cl_2/MeOH, 5:1, 1% conc. HCl); $[\alpha]_D^{20} = +20.2$ ($c = 0.213$ in MeOH); ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta = 2.86$ (s, 6H, NMe_2), 3.52 (t, $J = 5.0$ Hz, 2H, 2″-H_2), 3.85 (dd, $J = 11.2$, 8.0 Hz, 1H, 10-H_a), 4.03 (dd, $J = 11.2$, 3.0 Hz, 1H, 10-H_b), 4.22 (m_c, 1H, 1-H), 4.38 (t, $J = 5.0$ Hz, 2H, 1″-H_2), 4.55 (dd, $J = 11.2$, 1.6 Hz, 1H, 2-H_a), 4.79 (dd, $J = 11.2$, 9.6 Hz, 1H, 2-H_b), 7.01 (dd, $J = 9.0$, 2.2 Hz, 1H, 6′-H), 7.11 (d, $J = 1.4$ Hz, 3′-H), 7.27 (d, $J = 2.2$ Hz, 1H, 4′-H), 7.37 (t, $J = 7.6$ Hz, 1H, 7-H), 7.45 (d, $J = 9.0$ Hz, 1H, 7′-H), 7.53 (t, $J = 7.6$ Hz, 1H, 8-H), 7.85 (d, $J = 8.4$ Hz, 1H, 9-H), 7.97 (s, 1H, 4-H), 8.13 (d, $J = 8.4$ Hz, 1H, 6-H), 10.41 (s, 1H, OH), 10.45 (br s, 1H, NH^+), 11.65 (s, 1H, NH); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta = 41.2$ (C-1), 42.8 (NMe_2), 47.5 (C-10), 54.9 (C-2), 55.4 (C-2″), 62.9 (C-1″), 100.3 (C-4), 104.0 (C-4′), 105.1 (C-3′), 113.2 (C-7′), 114.9 (C-5a), 115.5 (C-6), 122.1 (C-9a), 122.7 (C-9), 123.0 (C-7), 123.1 (C-6), 127.2 (C-8), 127.3, 129.8, 131.3, 131.9 (C-2, C-3a′, C-7a, C-9b), 142.2 (C-3a), 152.0 (C-5′), 154.1 (C-5), 160.0 (C=O); IR (KBr): $\tilde{\nu} = 3416$, 1626, 1518, 1471, 1413, 1284, 1233, 1178 cm^{-1}; UV/Vis (MeOH): $\lambda_{max}(\log \varepsilon) = 207.0$ (4.361), 247.5 (4.127), 302.5 (4.162), 336.0 nm (4.082); MS (ESI): *m/z* (%): 464.2 (100) $[M-Cl]^+$; HRMS (ESI): *m/z* $[M-Cl]^+$ calcd for $C_{26}H_{27}ClN_3O_3$: 464.1741, found: 464.1736.

(−)-{(1*S*)-1-Chloromethyl-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)-6-methoxyindol-2-yl)-carbonyl]-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole hydrochloride} [(−)-(1*S*)-21]: According to general

procedure 1, (−)-(1*S*)-**5** (72.0 mg, 216 μmol) was stirred in 4 M HCl/EtOAc. After that, a suspension of the residue was treated with EDC·HCl (124 mg, 647 μmol) and DMMI-CO_2H·HCl (**23**, 88.3 mg, 280 μmol) and the reaction mixture was stirred for 22 h at RT. Purification of the crude product by preparative HPLC (consecutive injections of 1 mL of a solution of the crude product in MeOH with 0.06% (*v*/*v*) HCl; $c = 20$ mg mL^{-1}) provided seco-drug hydrochloride (−)-(1*S*)-**21** ($t_R = 11.2$ min, 78.6 mg, 148 μmol, 69%) as a pale-yellow solid. $R_f = 0.60$ (CH_2Cl_2/MeOH, 5:1, 1% conc. HCl); $[\alpha]_D^{20} = -2.5$ ($c = 0.201$ in MeOH); ^{1}H NMR (600 MHz, [D_6]DMSO): $\delta = 2.90$ (d, $J = 3.7$ Hz, 6H, NMe_2), 3.52 (m_c, 2H, 2″-H_2), 3.82–3.85 (m, 4H, 10-H_a, OCH_3), 4.03 (dd, $J = 11.2$, 3.1 Hz, 1H, 10-H_b), 4.22 (m_c, 1H, 1-H), 4.36 (t, $J = 10.1$ Hz, 2H, 1″-H_2), 4.54 (dd, $J = 10.8$, 2.1 Hz, 1H, 2-H_a), 4.77 (t, $J = 10.0$ Hz, 1H, 2-H_b), 7.04 (s, 1H, 7′-H), 7.08 (d, $J = 1.9$ Hz, 3′-H), 7.32 (s, 1H, 4′-H), 7.36 (ddd, $J = 2 \times 8.3$, 1.0 Hz, 1H, 7-H), 7.52 (ddd, $J = 2 \times 8.3$, 1.2 Hz, 1H, 8-H), 7.84 (d, $J = 8.3$ Hz, 1H, 9-H), 7.99 (s, 1H, 4-H), 8.13 (d, $J = 8.3$ Hz, 1H, 6-H), 10.40 (s, 1H, OH), 10.60 (br s, 1H, NH^+), 11.51 (s, 1H, NH); ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta = 41.2$ (C-1), 42.9 (NMe_2), 47.5 (C-10), 54.9 (C-2), 55.5 (C-2″), 55.6 (OCH_3), 64.7 (C-1″), 94.7 (C-7′), 100.3 (C-4), 105.8 (C-3′), 106.9 (C-4′), 114.7 (C-5a), 120.1 (C-3a′), 122.0 (C-9b), 122.6 (C-9), 122.9 (C-7), 123.1 (C-6), 127.2 (C-8), 129.5, 129.8 (C-2′, C-9a), 132.3 (C-7a′), 142.4 (C-3a), 143.3 (C-5′), 149.4 (C-6′), 154.1 (C-5), 159.9 (C=O); IR (KBr): $\tilde{\nu} = 3407$, 1627, 1587, 1516, 1469, 1414, 1312, 1236, 1200, 1149, 754, 540 cm^{-1}; UV/Vis (MeOH): $\lambda_{max}(\log \varepsilon) = 205.5$ (4.702), 245.5 (4.401), 349.0 nm (4.561); MS (ESI): *m*/*z* (%): 494.3 (100) [*M*−Cl]$^+$; HRMS (ESI): *m*/*z* [*M*−Cl]$^+$ calcd for $C_{27}H_{29}ClN_3O_4$: 494.1841; found: 494.1841.

General procedure 2 for the preparation of the β-D-galactosidic prodrugs 26a/26b, (−)-(1*R*)-26a, (−)-(1*S*)-26b, and (−)-(1*S*)-27b

Molecular sieves (4 Å; 0.44 mg mL^{-1}) were added to a solution of *rac*-**5**, (+)-(1*R*)-**5**, or (−)-(1*S*)-**5** in dry CH_2Cl_2 ($c = 0.02$ M) and the mixture was stirred for 30 min at RT. After addition of trichloroacetimidate **28** (1.05 equiv), the reaction mixture was cooled to −10 °C and a solution of BF_3·OEt_2 (0.5 equiv) in dry CH_2Cl_2 ($c = 0.01$ M) was added dropwise. Stirring was continued for 3.5 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 RT and was stirred for another 5 h. Separation of the solution from the molecular sieves was performed under argon using a transfer cannula and the molecular sieves were washed with CH_2Cl_2 (2×10 mL). The combined solutions were concentrated and the residue was dried in vacuo for 1 h.

The residue was then dissolved in dry DMF ($c = 0.02$ M) and cooled to 0 °C. After addition of EDC·HCl (3.0 equiv) and either DMAI-CO_2H·HCl (**22**, 1.5 equiv) or DMMI-CO_2H·HCl (**23**, 1.5 equiv) the reaction mixture was allowed to warm to RT and stirred at this temperature for 20 h. The solution was then diluted with EtOAc (25 mL), H_2O (25 mL), and a saturated aqueous solution of $NaHCO_3$ (25 mL) followed by extraction with EtOAc (4×50 mL). The combined organic layers were washed with brine (4×100 mL), dried over $MgSO_4$, and the solvent was removed in vacuo. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH = 10:1) provided tetraacetylglycosides **24a**/**24b**, (1*R*)-**24a**, (1*S*)-**24b**, and (1*S*)-**25b**, respectively.

A solution of **24a**/**24b**, (1*R*)-**24a**, (1*S*)-**24b**, or (1*S*)-**25b** in dry MeOH ($c = 0.01$–0.03 M) was treated with a 5.4 M solution of NaOMe in MeOH (2.0 equiv) at 0 °C and was then allowed to warm to RT. After stirring for 2 h at this temperature, the solution was diluted with MeOH (13 mL mmol^{-1}) and H_2O (~8 mL mmol^{-1}) 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 purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 1:1) or in an exceptional case by preparative HPLC (Kromasil® 100 C_{18}, 250×20 mm, particle size: 7 μm; solvent A: H_2O with 0.05% (*v*/*v*) conc. acetic acid, solvent B: MeOH with 0.05% (*v*/*v*) conc. acetic acid; gradient: A/B = 70:30→0:100 in 15 min) to provide β-D-galactosidic prodrugs **26a**/**26b**, (−)-(1*R*)-**26a**, (−)-(1*S*)-**26b**, and (−)-(1*S*)-**27b**, respectively.

Diastereomeric mixture of (−)-{[(1*R*)-1-Chloromethyl-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)indol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indol-5-yl] β-D-galactopyranoside} and (−)-{[(1*S*)-1-Chloromethyl-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)indol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indol-5-yl] β-D-galactopyranoside}-[26a/26b]: According to general procedure 2 for the preparation of the β-D-galactosidic prodrugs, *rac*-**5** (136 mg, 407 μmol) in dry CH_2Cl_2 (18 mL) was glycosylated with **28** (211 mg, 428 μmol) and BF_3·OEt_2 (26 μL, 205 μmol) in dry CH_2Cl_2 (2.1 mL). For Boc deprotection, additional BF_3·OEt_2 (155 μL, 1.22 mmol) in dry CH_2Cl_2 (1.8 mL) was added and the residue was then treated with EDC·HCl (234 mg, 1.22 mmol) and indole carboxylic acid **22** (174 mg, 611 μmol) in DMF (19 mL) to give the mixture of diastereomers **24a**/**24b** (173 mg, 218 μmol, 54%) as a yellow solid after purification by column chromatography. $R_f = 0.38$ (CH_2Cl_2/MeOH, 10:1); HRMS (ESI): *m*/*z* [*M*+H]$^+$ calcd for $C_{40}H_{45}ClN_3O_{12}$: 794.2692, found: 794.2686.

Saponification of **24a**/**24b** (170 mg, 214 μmol) in MeOH (9 mL) was performed in 2 h by addition of a 5.4 M solution of NaOMe in MeOH (79 μL, 428 μmol). After purification by column chromatography **26a**/**26b** (94 mg, 150 μmol, 70%) was obtained as a pale-yellow solid. $R_f = 0.26$ (CH_2Cl_2/MeOH, 1:1); ^{1}H NMR (600 MHz, [D_6]DMSO): $\delta = 2.24$ (s, 6H, NMe_2), 2.66 (t, $J = 5.9$ Hz, 2H, 2″-H_2), 3.35–3.86 (m, 6H, 2‴-H, 3‴-H, 4‴-H, 5‴-H, 6‴-H_2,), 3.89–3.95 (m, 1H, 10-H_a), 4.02–4.09 (m, 3H, 1″-H_2, 10-H_b), 4.25–4.32 (m, 1H, 1-H), 4.53–4.63 (m, 3H, 2-H_2, OH), 4.71–4.97 (m, 3H, 1‴-H, 2×OH), 5.27–5.36 (m, 1H, OH), 6.91 (dd, $J = 8.9$, 2.3 Hz, 1H, 6′-H), 7.06–7.11 (m, 1H, 3′-H), 7.17–7.19 (m, 1H, 4′-H), 7.38–7.45 (m, 2H, 7-H, 7′-H), 7.57 (m, 1H, 8-H), 7.91 (d, $J = 8.6$ Hz, 1H, 9-H), 7.98–8.28 (m, 1H, 4-H), 8.33, 8.35 (2×d, $J = 8.6$ Hz, 1H, 6-H), 11.62, 11.64 (2×br s, 1H, NH); ^{13}C NMR (150 MHz, [D_6]DMSO): $\delta = 41.0/41.2$ (C-1), 45.5 (NMe_2), 47.5 (C-10), 54.9/55.0 (C-2), 57.8 (C-2″), 59.6/59.7 (C-6‴), 66.3 (C-1″), 67.5/67.7 (C-4‴), 70.4/70.5 (C-2‴), 73.2 (2 signals) (C-3‴), 75.2 (C-5‴), 101.8 (C-4), 102.1/102.3 (C-1‴), 103.2/103.3 (C-4′), 105.2/105.3 (C-3′), 113.1/113.2 (C-7′), 115.8/115.9 (C-6′), 117.9/118.0 (C-5a), 122.7 (C-9), 122.9/123.0 (C-9b), 123.3/123.4 (C-6), 123.7/123.8 (C-7), 127.5 (C-3a′, C-8), 129.5 (2 signals) (C-9a), 130.9 (2 signals), 131.6/131.7 (C-2′, C-7a′), 142.1 (C-3a), 153.0 (2 signals) (C-5′), 153.7 (2 signals) (C-5), 160.3 (2 signals) (C=O); IR (KBr): $\tilde{\nu} = 3406$ cm^{-1}, 2873, 1622, 1590, 1517, 1462, 1413, 1266, 1231, 1076, 759 cm^{-1}; UV/Vis (CH_3CN): $\lambda_{max}(\log \varepsilon) = 206.5$ (4.615), 245.0 (4.329), 298.5 (4.463), 334.5 nm (4.406); MS (ESI): *m*/*z* (%): 626.4 (100) [*M*+H]$^+$; HRMS (ESI): *m*/*z* [*M*+H]$^+$) calcd for $C_{32}H_{37}ClN_3O_8$: 626.2269, found: 626.2264.

(−)-{[(1*R*)-1-Chloromethyl-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)indol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indol-5-yl] β-D-galactopyranoside} [(−)-(1*R*)-26a]: According to general procedure 2 for the preparation of the β-D-galactosidic prodrugs, (+)-(1*R*)-**5** (170 mg, 509 μmol) in dry CH_2Cl_2 (22 mL) was glycosylated with **28** (258 mg, 525 μmol) and BF_3·OEt_2 (32 μL, 255 μmol) in dry CH_2Cl_2

(2.6 mL). For Boc deprotection, additional $BF_3{\cdot}OEt_2$ (194 μL, 1.53 mmol) in dry CH_2Cl_2 (2.3 mL) was added and the residue was then treated with EDC·HCl (293 mg, 1.53 mmol) and indole carboxylic acid **22** (218 mg, 611 μmol) in DMF (23 mL) to give (1*R*)-**24 a** (221 mg, 279 μmol, 55%) as a yellow solid after purification by column chromatography. $R_f = 0.38$ (CH_2Cl_2/MeOH, 10:1); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{45}ClN_3O_{12}$: 794.2686, found: 794.2689.

Saponification of (1*R*)-**24 a** (215 mg, 271 μmol) in MeOH (10 mL) was performed in 2 h by addition of a 5.4 M solution of NaOMe in MeOH (100 μL, 541 μmol). After purification by column chromatography (−)-(1*R*)-**26 a** (140 mg, 224 μmol, 83%) was obtained as a pale-yellow solid. $R_f = 0.24$ (CH_2Cl_2/MeOH, 1:1); $[\alpha]_D^{20} = -42.4$ (*c* = 0.28 in DMSO); ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta = 2.24$ (s, 6H, NMe_2), 2.66 (t, $J = 5.9$ Hz, 2H, 2″-H_2), 3.39–3.48 (m, 3H, 3‴-H, 5‴-H, 6‴-H_a), 3.59–3.61 (m, 1H, 6‴-H_a), 3.75–3.79 (m, 2H, 2‴-H, 4‴-H), 3.92 (dd, $J = 11.4$, 7.2 Hz, 1H, 10-H_a), 4.04–4.08 (m, 3H, 10-H_b, 1″-H_2), 4.27–4.31 (m, 1H, 1-H), 4.57–4.66 (m, 3H, 2-H_a, 2×OH), 4.76–4.95 (m, 3H, 2-H_b, 1‴-H, OH), 5.33 (br s, 1H, OH), 6.92 (dd, $J = 8.4$, 2.4 Hz, 1H, 6′-H), 7.08 (s, 1H, 3′-H), 7.18 (d, $J = 1.8$ Hz, 1H, 4′-H), 7.39 (d, $J = 9.0$ Hz, 1H, 7′-H), 7.43 (dd, $2J = 7.5$ Hz, 1H, 7-H), 7.57 (dd, $2J = 7.5$ Hz, 1H, 8-H), 7.91 (d, $J = 9.0$ Hz, 1H, 9-H), 8.08 (br s, 1H, 4-H), 8.32 (d, $J = 8.4$ Hz, 1H, 6-H), 11.62 (br s, 1H, NH); ^{13}C NMR (150 MHz, [D$_6$]DMSO): $\delta = 41.0$ (C-1), 45.5 (NMe_2), 47.4 (C-10), 54.8 (C-2), 57.8 (C-2″), 59.6 (C-6‴), 66.3 (C-1″), 67.6 (C-4‴), 70.4 (C-2‴), 73.2 (C-3‴), 75.1 (C-5‴), 101.5 (C-4), 102.1 (C-1‴), 103.2 (C-4′), 105.2 (C-3′), 113.1 (C-7′), 115.8 (C-6′), 118.0 (C-5a), 122.7 (C-9), 122.8 (C-9b), 123.3 (C-6), 123.7 (C-7), 127.4 (C-8, C-3a′), 129.5 (C-9a), 130.9 (C-2′), 131.6 (C-7a′), 141.9 (C-3a), 153.0 (C-5′), 153.7 (C-5), 160.2 (C=O); IR (KBr): $\tilde{\nu} = 3385$, 1621, 1589, 1516, 1462, 1413, 1266, 1231, 1178, 1074, 758 cm^{-1}; UV/Vis (CH_3CN): $\lambda_{max}(\log\varepsilon) = 207.0$ (4.600), 244.5 (4.330), 298.5 (4.440), 334.0 nm (4.389); MS (ESI): *m/z* (%): 626.3 (100) $[M+H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{37}ClN_3O_8$: 626.2264, found: 626.2263.

(−)-{[(1*S*)-1-Chloromethyl-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*)-26b]: According to general procedure 2 for the preparation of the β-D-galactosidic prodrugs, (−)-(1*S*)-**5** (180 mg, 539 μmol) in dry CH_2Cl_2 (23 mL) was glycosylated with **28** (274 mg, 555 μmol) and $BF_3{\cdot}OEt_2$ (34 μL, 270 μmol) in dry CH_2Cl_2 (2.7 mL). For Boc deprotection, additional $BF_3{\cdot}OEt_2$ (205 μL, 1.62 mmol) in dry CH_2Cl_2 (2.5 mL) was added and the residue was then treated with EDC·HCl (310 mg, 1.62 mmol) and indole carboxylic acid **22** (230 mg, 809 μmol) in DMF (24 mL) to give (1*S*)-**24 b** (159 mg, 200 μmol, 37%) as a yellow solid after purification by column chromatography. $R_f = 0.38$ (CH_2Cl_2/MeOH, 10:1); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{45}ClN_3O_{12}$: 794.2686, found: 794.2688.

Saponification of (1*S*)-**24 b** (159 mg, 200 μmol) in MeOH (7.3 mL) was performed in 2 h by addition of a 5.4 M solution of NaOMe in MeOH (74 μL, 400 μmol). After purification by column chromatography (−)-(1*S*)-**26 b** (113 mg, 180 μmol, 90%) was obtained as a pale-yellow solid. $R_f = 0.24$ (CH_2Cl_2/MeOH, 1:1); $[\alpha]_D^{20} = -6.1$ (*c* = 0.28 in DMSO); ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta = 2.24$ (s, 6H, NMe_2), 2.65 (t, $J = 5.9$ Hz, 2H, 2″-H_2), 3.47–3.50 (m, 1H, 3‴-H), 3.55–3.57 (m, 2H, 5‴-H, 6‴-H_a), 3.65–3.69 (m, 1H, 6‴-H_b), 3.78–3.83 (m, 2H, 2‴-H, 4‴-H), 3.92 (dd, $J = 11.2$, 7.3 Hz, 1H, 10-H_a), 4.04–4.08 (m, 3H, 10-H_b, 1″-H_2), 4.28–4.31 (m, 1H, 1-H) 4.53 (d, $J = 4.6$ Hz, 1H, OH), 4.56–4.60 (m, 2H, 2-H_a, OH), 4.82 (dd, $2J = 10.1$ Hz, 1H, 2-H_b), 4.84 (d, $J = 5.5$ Hz, 1H, OH), 4.93 (d, $J = 7.6$ Hz, 1H, 1‴-H) 5.30 (d, $J = 5.4$ Hz, 1H, OH), 6.92 (dd, $J = 8.9$, 2.4 Hz, 1H, 6′-H), 7.10 (d, $J = 1.8$ Hz 1H, 3′-H), 7.18 (d, $J = 2.4$ Hz, 1H, 4′-H), 7.40 (d, $J = 9.0$ Hz, 1H, 7′-H), 7.43 (dd, $2J = 7.7$ Hz, 1H, 7-H), 7.58 (dd, $2J = 7.7$ Hz, 1H, 8-H), 7.92 (d, $J = 8.4$ Hz, 1H, 9-H), 8.23 (br s, 1H, 4-H), 8.35 (d, $J = 8.5$ Hz, 1H, 6-H), 11.63 (s, 1H, NH); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta = 41.2$ (C-1), 45.5 (NMe_2), 47.4 (C-10), 55.0 (C-2), 57.8 (C-2″), 59.5 (C-6‴), 66.3 (C-1″), 67.5 (C-4‴), 70.5 (C-2‴), 73.2 (C-3‴), 75.1 (C-5‴), 101.8 (C-4), 102.1 (C-1‴), 103.2 (C-4′), 105.2 (C-3′), 113.1 (C-7′), 115.8 (C-6′), 117.9 (C-5a), 122.7 (C-9), 122.9 (C-9b), 123.3 (C-6), 123.7 (C-7), 127.4 (2 signals) (C-8, C-3a′), 129.5 (C-9a), 130.9 (C-2′), 131.6 (C-7a′), 142.0 (C-3a), 153.0 (C-5′), 153.7 (C-5), 160.2 (C=O); IR (KBr): $\tilde{\nu} = 3385$, 1621, 1589, 1516, 1462, 1413, 1266, 1231, 1178, 1074, 758 cm^{-1}; UV/Vis (CH_3CN): $\lambda_{max}(\log\varepsilon) = 207.0$ (4.600), 244.5 (4.330), 298.5 (4.440), 334.0 nm (4.389); MS (ESI): *m/z* (%): 626.3 (100) $[M+H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{37}ClN_3O_8$: 626.2264, found: 626.2263.

(−)-{[(1*S*)-1-Chloromethyl-3-[(5-(2-*N*,*N*-dimethylaminoethoxy)-6-methoxyindol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indol-5-yl] β-D-galactopyranoside} [(−)-(1*S*)-27b]: According to general procedure 2 for the preparation of the β-D-galactosidic prodrugs, (−)-(1*S*)-**5** (165 mg, 494 μmol) in dry CH_2Cl_2 (21 mL) was glycosylated with **28** (251 mg, 509 μmol) and $BF_3{\cdot}OEt_2$ (31 μL, 247 μmol) in dry CH_2Cl_2 (2.5 mL). For Boc deprotection, additional $BF_3{\cdot}OEt_2$ (188 μL, 1.48 mmol) in dry CH_2Cl_2 (2.3 mL) was added and the residue was then treated with EDC·HCl (284 mg, 1.48 mmol) and indole carboxylic acid **23** (233 mg, 741 μmol) in DMF (22 mL) to give (1*S*)-**25 b** (197 mg, 239 μmol, 48%) as a yellow solid after purification by column chromatography. $R_f = 0.35$ (CH_2Cl_2/MeOH, 10:1); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{47}ClN_3O_{13}$: 824.2791, found: 824.2788.

Saponification of (1*S*)-**25 b** (190 mg, 231 μmol) in MeOH (17 mL) was performed in 2 h by addition of a 5.4 M solution of NaOMe in MeOH (85 μL, 461 μmol). Purification by preparative HPLC (consecutive injections of 1 mL of a solution of the crude product in DMSO; $c = 15$ mg mL^{-1}) provided (−)-(1*S*)-**27 b** ($t_R = 7.1$ min, 78.6 mg, 120 μmol, 52%) as a pale-yellow solid. $R_f = 0.41$ (CH_2Cl_2/MeOH, 1:1, 1% NEt_3); $[\alpha]_D^{20} = -18.7$ (*c* = 0.283 in DMSO); ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta = 2.28$ (s, 6H, NMe_2), 2.71 (t, $J = 5.9$ Hz, 2H, 2″-H_2), 3.49 (dd, $J = 9.5$, 3.0 Hz 1H, 3‴-H), 3.55–3.59 (m, 2H, 5‴-H, 6‴-H_a), 3.66–3.70 (m, 1H, 6‴-H_b), 3.79–3.83 (m, 5H, 2‴-H, 4‴-H, OCH_3), 3.91 (dd, $J = 11.1$, 7.4 Hz, 1H, 10-H_a), 4.06 (m_c, 3H, 10-H_b, 1″-H_2), 4.29 (m_c, 1H, 1-H) 4.54 (br s, 2H, 2×OH), 4.58 (dd, $J = 10.8$, 1.8 Hz 1H, 2-H_a), 4.79 (dd, $2J = 10.0$ Hz, 1H, 2-H_b), 4.85 (br s, 1H, OH), 4.95 (d, $J = 7.7$ Hz, 1H, 1‴-H), 5.31 (br s, 1H, OH), 6.99 (s, 1H, 7′-H), 7.07 (d, $J = 1.8$ Hz 1H, 3′-H), 7.19 (s, 1H, 4′-H), 7.42 (dd, $2J = 7.6$ Hz, 1H, 7-H), 7.57 (dd, $2J = 7.6$ Hz, 1H, 8-H), 7.90 (d, $J = 8.4$ Hz, 1H, 9-H), 8.25 (br s, 1H, 4-H), 8.34 (d, $J = 8.4$ Hz, 1H, 6-H), 11.50 (s, 1H, NH); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta = 41.2$ (C-1), 45.5 (NMe_2), 47.5 (C-10), 54.9 (C-2), 55.5 (OCH_3), 57.7 (C-2″), 59.6 (C-6‴), 67.1 (C-1″), 67.5 (C-4‴), 70.5 (C-2‴), 73.2 (C-3‴), 75.1 (C-5‴), 94.6 (C-7′), 101.9 (C-4), 102.1 (C-1‴), 104.7 (C-4′), 106.0 (C-3′), 117.7 (C-5a), 120.2 (C-3a′), 122.6 (C-9), 122.9 (C-9b), 123.3 (C-6), 123.6 (C-7), 127.4 (C-8), 128.9 (C-2′), 129.5 (C-9a), 131.8 (C-7a′), 142.3 (C-3a), 144.5 (C-5′), 149.4 (C-6′), 153.7 (C-5), 160.2 (C=O); IR (KBr): $\tilde{\nu} = 3406$, 1610, 1589, 1514, 1462; 1415, 1308, 1267, 1238, 1203, 1146, 1078, 759 cm^{-1}; UV/Vis (CH_3CN): $\lambda_{max}(\log\varepsilon) = 204.5$ (4.126), 306.0 (3.701), 346.5 nm (3.654); MS (ESI): *m/z* (%): 656.2 (100) $[M+H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{37}ClN_3O_8$: 656.2369, found: 626.2367.

Asymmetric synthesis of (−)-(1*S*)-19

(+)-(2′*R*)-2-Amino-4-benzyloxy-*N*-(2,3-epoxypropyl)-1-iodo-*N*-(*tert*-butyloxycarbonyl)-naphthaline [(+)-(2′*R*)-30]: NaH (60% sus-

pension in mineral oil, 168 mg, 4.2 mmol) was added to a solution of carbamate **18** (500 mg, 1.05 mmol) in DMF (5 mL) and the suspension was stirred at RT for 30 min. Then, (+)-(*S*)-**29** (435 mg, 1.68 mmol) was added and the mixture was stirred at RT for 23 h. The reaction was stopped by addition of a saturated aqueous solution of $NaHCO_3$ (50 mL), followed by addition of brine (50 mL), and extraction with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. Column chromatography on silica gel (P/EtOAc = 4:1) provided (+)-(2′*R*)-**30** as a mixture of rotamers in form of a yellow oil (531 mg, 1.0 mmol, 95%). R_f = 0.53 (P/EtOAc, 7:3); $[\alpha]_D^{20}$ = +8.0 (*c* = 0.6 in CH_2Cl_2); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C, the signals of the different rotamers are signed with (a) and (b)): δ = 1.46 (s, 18H, 2×C(CH_3)$_3$), 2.46 (apparent dt, *J* = 4.7, 2.6 Hz, 2H, 3′-H_a(a) and 3′-H_a(b)), 2.73 (apparent dt, *J* = 4.8, 9.0 Hz, 2H, 3′-H_b(a) and 3′-H_b(b)), 3.12–3.19 (m, 1H, 2′-H(a)), 3.28 (dd, *J* = 14.4, 6.6 Hz, 1H, 1′-H_a(a)), 3.35–3.42 (m, 1H, 2′-H(b)); 3.49 (dd, *J* = 14.7, 4.9 Hz, 1H, 1′-H_a(b)), 4.09–4.17 (m, 2H, 1′-H_b(a) and 1′-H_b(b)), 5.32, 5.33 (2 s, 4H, OCH_2Ph(a) and OCH_2Ph(b)), 6.89, 6.99 (2 s, 2H, 3-H(a) and 3-H(b)), 7.34–7.67 (m, 14H, 6-H(a), 6-H(b), 7-H(a), 7-H(b), 5×Ph-H(a) and 5×Ph-H(b)), 8.25 (2 m, 2H, 8-H(a) and 8-H(b)), 8.36 (2 m, 2H, 5-H(a) and 5-H(b)); ^{13}C NMR (75 MHz, $C_2D_2Cl_4$, 100 °C, the signals of the different rotamers are signed with (a) and (b)): δ = 29.8 (2 signals) (2×C(CH_3)$_3$), 47.3, 47.5 (C-3′), 51.0 (C-2′(a)), 51.5 (C-2′(b)), 52.9 (C-1′(b)), 54.5 (C-1′(a)), 72.2, 72.3 (2×OCH_2Ph), 82.1 (2 signals) (2×*C*(CH_3)$_3$), 96.2, 96.3 (C-1), 109.6, 109.7 (C-3), 123.9 (C-5), 127.2 (C-4a), 127.7 (2 signals), 128.6, 128.8, 129.4, 129.8, 129.9, 130.0 (2 signals) (C-6, C-7, C-8, 2×Ph-C_o, 2×Ph-C_m, Ph-C_p), 136.9 (2 signals) (C-8a), 137.9, 138.0 (Ph-Ci), 144.8, 145.3 (C-2), 155.0, 155.2 (C=O), 157.0, 157.1 (C-4); IR (film): $\tilde{\nu}$ = 2977, 1701, 1590, 1503, 1370, 1260, 1155, 1028, 761 cm^{-1}; UV/Vis (CH_3CN): λ_{max}(log ε) = 216.0 (4.686), 244 (4.442), 304.5 nm (3.960); MS (ESI): *m/z* (%): 554.0 (20) [*M*+Na]$^+$, 1085.6 (100) [2*M*+Na]$^+$; HRMS (ESI): *m/z* [*M*+H]$^+$ calcd for $C_{25}H_{27}NO_4I$: 532.0979, found: 532.0978.

(+)-(1*S*)-5-Benzyloxy-3-(*tert*-butyloxycarbonyl-1-(10-hydroxymethyl)1,2-dihydro-3*H*-benz[*e*]indole [(+)-(1*S*)-31]: MeLi (1.6 mL of a 1.6 M solution in Et_2O, 2.58 mmol) was added dropwise to a stirred suspension of freshly fused $ZnCl_2$ (88.1 mg, 646 μmol) in THF (5 mL) at 0 °C and stirring was continued for 30 min at that temperature. After cooling to −78 °C and dropwise addition of TMS-NCS (93 μL, 646 μmol), the reaction mixture was warmed to 0 °C and stirred for 30 min at that temperature. After cooling again to −78 °C, a solution of (+)-(2′*R*)-**30** (158 mg, 297 μmol) in THF (5 mL) was added dropwise. The solution was allowed to warm to RT within 3 h and stirring was continued at that temperature for 14 h. Afterward, a saturated aqueous solution of NH_4Cl (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3×75 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. Column chromatography (P/EtOAc = 5:1) gave primary alcohol (+)-(1*S*)-**31** as a yellow solid (70.2 mg, 173 μmol, 58%, 98% *ee*). R_f = 0.34 (P/EtOAc, 3:1); $[\alpha]_D^{20}$ = +5.0 (*c* = 0.8 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 9H, C(CH_3)$_3$), 3.66–3.76 (m, 1H, 10-H_a), 3.77–3.87 (m, 1H, 1-H), 3.88–3.98 (m, 1H, 10-H_b), 4.05–4.16 (m, 1H, 2-H_a), 4.17–4.26 (m, 1H, 2-H_b); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.5 (C(CH_3)$_3$), 41.3 (C-1), 52.4 (C-2), 64.7 (C-10), 70.3 (OCH_2Ph), 80.7 (*C*(CH_3)$_3$), 96.5 (C-4), 114.4 (C-9b), 122.3 (C-5a), 122.2, 122.9, 123.4 (C-6, C-7, C-9), 127.3 (C-8), 127.5, 127.9, 128.5 (5×Ph-CH), 130.6 (C-9a), 136.9 (Ph-Ci), 141.9 (C-3a), 152.7 (C=O), 155.6 (C-5); IR (KBr): $\tilde{\nu}$ = 3316, 2971, 1701, 1625, 1580, 1458, 1406, 1330, 1268, 1140, 1023, 905, 758 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (log ε) = 208.0 (4.463), 217.0 (4.419), 255.0 (4.799), 315.0 (4.048), 341.0 (3.512), 304 nm (3.972); HRMS (ESI): *m/z* [*M*+H]$^+$ calcd for $C_{25}H_{28}NO_4$: 406.2013, found: 406.2013. The optical purity was determined by analytical HPLC (Chiralcel® OD, 250×4.6 mm, particle size: 10 μm; *n*-hexane/*i*PrOH = 95:5; flow: 0.8 mL min^{-1}; UV detector: λ = 254 nm): (−)-(1*R*)-**24** (t_R = 21.9 min); (+)-(1*S*)-**24** (t_R = 27.1 min).

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[1] K. D. Bagshawe, *Br. J. Cancer* **1987**, *56*, 531–532.
[2] Reviews: a) K. D. Bagshawe, *Expert Rev. Anticancer Ther.* **2006**, *6*, 1421–1431; b) W. A. Denny, *Cancer Invest.* **2004**, *22*, 604–619; c) L. F. Tietze, T. Feuerstein, *Curr. Pharm. Des.* **2003**, *9*, 2155–2175; d) L. F. Tietze, T. Feuerstein, *Aust. J. Chem.* **2003**, *56*, 841–854; e) W. A. Denny, *Eur. J. Med. Chem.* **2001**, *36*, 577–595; f) M. Jung, *Mini-Rev. Med. Chem.* **2001**, *1*, 399–407; g) G. Xu, H. L. McLeod, *Clin. Cancer Res.* **2001**, *7*, 3314–3324; h) P. D. Senter, C. J. Springer, *Adv. Drug Delivery Rev.* **2001**, *53*, 247–264; i) K. N. Syrigos, A. A. Epenetos, *Anticancer Res.* **1999**, *19*, 605–614; j) G. M. Dubowchik, M. A. Walker, *Pharmacol. Ther.* **1999**, *83*, 67–123; k) C. J. Springer, I. Niculescu-Duvaz, *Adv. Drug Delivery Rev.* **1997**, *26*, 151–172; l) L. N. Jungheim, T. A. Shepherd, *Chem. Rev.* **1994**, *94*, 1553–1566.
[3] A. M. Wu, P. D. Senter, *Nat. Biotechnol.* **2005**, *23*, 1137–1146.
[4] a) T. Arndt, U. Arndt, U. Reuning, H. Kessler in *Cancer Therapy: Molecular Targets in Tumor–Host Interactions* (Ed.: G. F. Weber), Horizon Bioscience, Norfolk, **2005**, 93–141; b) D. Ribatti, A. Vacca, F. Merchionne, M. Presta, *Mini-Rev. Med. Chem.* **2005**, *5*, 313–317; c) K. A. El Sayed, *Mini-Rev. Med. Chem.* **2005**, *5*, 971–993.
[5] a) S. Dziadek, D. Kowalczyk, H. Kunz, *Angew. Chem.* **2005**, *117*, 7798–7803; *Angew. Chem. Int. Ed.* **2005**, *44*, 7624–7630; b) S. Dziadek, A. Hobel, E. Schmitt, H. Kunz, *Angew. Chem.* **2005**, *117*, 7803–7808; *Angew. Chem. Int. Ed.* **2005**, *44*, 7630–7635.
[6] a) M. E. M. Noble, J. A. Endicott, L. N. Johnson, *Science* **2004**, *303*, 1800–1805; b) C. Garcia-Echeverria, D. Fabbro, *Mini-Rev. Med. Chem.* **2004**, *4*, 273–283.
[7] a) L. F. Tietze, O. Panknin, B. Krewer, F. Major, I. Schuberth, *Int. J. Mol. Sci.* **2008**, *9*, 821–837; b) L. F. Tietze, O. Panknin, F. Major, B. Krewer, *Chem. Eur. J.* **2008**, *14*, 2811–2818; c) M. Langer, F. Kratz, B. Rothen-Rutishauser, H. Wunderli-Allenspach, A. G. Beck-Sickinger, *J. Med. Chem.* **2001**, *44*, 1341–1348; d) M. Langer, A. G. Beck-Sickinger, *Curr. Med. Chem. Anti-cancer Agents* **2001**, *1*, 71–93.
[8] L. F. Tietze, T. Herzig, T. Feuerstein, I. Schuberth, *Eur. J. Org. Chem.* **2002**, 1634–1645.
[9] a) M. Ichimura, T. Ogawa, K. Takahashi, E. Kobayashi, I. Kawamoto, T. Yasuzawa, I. Takahashi, H. Nakano, *J. Antibiot.* **1990**, *43*, 1037–1038; b) M. Ichimura, T. Ogawa, S. Katsumata, K. Takahashi, I. Takahashi, H. Nakano, *J. Antibiot.* **1991**, *44*, 1045–1053; c) D. L. Boger, D. S. Johnson, *Angew. Chem.* **1996**, *108*, 1542–1580; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1438–1474.
[10] D. G. Martin, C. Biles, S. A. Gerpheide, L. J. Hanka, W. C. Krueger, J. P. McGroven, S. A. Mizsak, G. L. Neil, J. C. Stewart, J. Visser, *J. Antibiot.* **1981**, *34*, 1119–1125, and references therein.
[11] a) Y. Igarashi, K. Futamata, T. Fujita, A. Sekine, H. Senda, H. Naoki, T. Furamai, *J. Antibiot.* **2003**, *56*, 107–113; b) M. S. Tichenor, D. B Kastrinsky, D. L. Boger, *J. Am. Chem. Soc.* **2004**, *126*, 8396–8398.
[12] D. L. Boger, T. Ishizaki, R. J. Wysocki, Jr., S. A. Munk, *J. Am. Chem. Soc.* **1989**, *111*, 6461–6463.
[13] For an extensive coverage of CBI-related literature, see: W. Jin, J. D. Trzupek, T. J. Rayl, M. A. Broward, G. A. Vielhauer, S. J. Weir, I. Hwang,

D. L. Boger, *J. Am. Chem. Soc.* **2007**, *129*, 15391–15397 and references therein.
[14] a) 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; b) L. F. Tietze, M. Lieb, T. Herzig, F. Haunert, I. Schuberth, *Bioorg. Med. Chem.* **2001**, *9*, 1929–1939.
[15] a) L. F. Tietze, T. Herzig, unpublished results; b) T. Herzig, *Dissertation*, Cuvillier, Göttingen **2000** (ISBN: 978-3898-7307-23).
[16] J. B. J. Milbank, M. Tercel, G. J. Atwell, W. R. Wilson, A. Hogg, W. A. Denny, *J. Med. Chem.* **1999**, *42*, 649–658.
[17] L. F. Tietze, F. Major, *Eur. J. Org. Chem.* **2006**, 2314–2321.
[18] a) L. F. Tietze, F. Major, I. Schuberth, *Angew. Chem.* **2006**, *118*, 6724–6727; *Angew. Chem. Int. Ed.* **2006**, *45*, 6574–6577; b) L. F. Tietze, B. Krewer, H. Frauendorf, F. Major, I. Schuberth, *Angew. Chem.* **2006**, *118*, 6720–6724; *Angew. Chem. Int. Ed.* **2006**, *45*, 6570–6574; c) L. F. Tietze, F. Major, I. Schuberth, D. A. Spiegl, B. Krewer, K. Maksimenka, G. Bringmann, J. Magull, *Chem. Eur. J.* **2007**, *13*, 4396–4409.
[19] D. L. Boger, J. A. McKie, *J. Org. Chem.* **1995**, *60*, 1271–1275.
[20] D. L. Boger, C. W. Boyce, R. M. Garbaccio, M. Searcey, *Tetrahedron Lett.* **1998**, *39*, 2227–2230.
[21] D. L. Boger, W. Yun, *J. Am. Chem. Soc.* **1994**, *116*, 7996–8006.
[22] a) R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213–236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212–235; b) W. Dullenkopf, J. C. Castro-Palomino, L. Manzoni, R. R. Schmidt, *Carbohydr. Res.* **1996**, *296*, 135–147.
[23] G. Zemplén, E. Pacsu, *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 1613–1614.
[24] a) D. B. Kastrinsky, D. L. Boger, *J. Org. Chem.* **2004**, *69*, 2284–2289; b) L. Ling, Y. Xie, J. W. Lown, *Heterocycl. Commun.* **1997**, *3*, 405–408.
[25] a) D. L. Boger, J. A. McKie, C. W. Boyce, *Synlett* **1997**, 515–517; b) F. Mohamadi, M. M. Spees, G. S. Staten, P. Marder, J. K. Kipka, D. A. Johnson, D. L. Boger, H. Zarrinmayeh, *J. Med. Chem.* **1994**, *37*, 232–239.
[26] a) P. A. Aristoff, P. D. Johnson, *J. Org. Chem.* **1992**, *57*, 6234–6239; b) P. A. Aristoff, P. D. Johnson, D. Sun, L. H. Hurley, *J. Med. Chem.* **1993**, *36*, 1956–1963.
[27] L. F. Tietze, H. J. Schuster, S. M. Hampel, S. Rühl, R. Pfoh, *Chem. Eur. J.* **2008**, *14*, 895–901.
[28] a) J. M. Klunder, T. Onami, K. B. Sharpless, *J. Org. Chem.* **1989**, *54*, 1295–1304; b) R. M. Hanson, *Chem. Rev.* **1991**, *91*, 437–475.
[29] M. S. Tichenor, J. D. Trzupek, D. B. Kastrinsky, F. Shiga, I. Hwang, D. L. Boger, *J. Am. Chem. Soc.* **2006**, *128*, 15683–15696.

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