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Synthesis of Fluorescence-Labelled Glycosidic Prodrugs Based on the Cytotoxic Antibiotic Duocarmycin

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Dedicated to Professor Carmen Najera on the occasion of her 60th birthday

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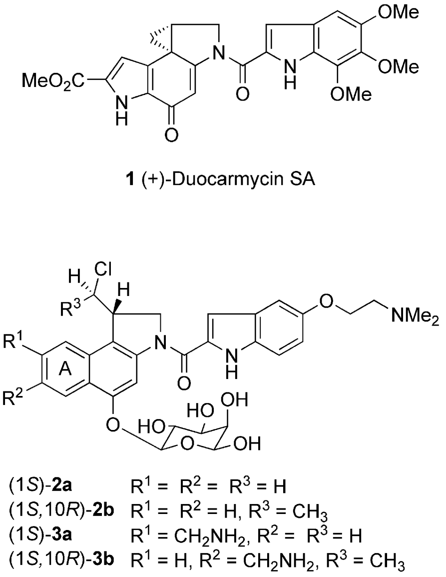
The synthesis of the glycosidic prodrugs (1*S*)-**30a**, (1*S*,10*R*)-**30b** and (1*S*,10*R*)-**32** labelled with different fluorescence dyes at different positions at the aromatic A-ring in **2** is described; the compounds are structurally based on the cytotoxic antibiotic duocarmycin SA. For binding, the amino compounds (1*S*)-**3a** and (1*S*,10*R*)-**3b** were treated with the commercially available succinimides of the dyes 5-SFX (**29**) and D10162 (**31**), respectively.

Introduction

Over the last few years we have successfully developed novel glycosidic prodrugs[1] such as **2a** and **2b** (Scheme 1), which can be used for selective treatment of cancer through antibody-directed enzyme prodrug therapy (ADEPT).[2,3]

The compounds are based on the cytotoxic antibiotic duocarmycin SA (**1**, $IC_{50} \approx 10$ pM, L1210)[4] and have as yet unsurpassed selectivity factors of $QIC_{50} = 3200$ and 4800, respectively ($QIC_{50} = IC_{50}$ of prodrug/IC_{50} of prodrug in the presence of the cleaving enzyme).[5] Here we describe the synthesis of the fluorescence-labelled derivatives (1*S*)-**30a**, (1*S*,10*R*)-**30b** and (1*S*,10*R*)-**32**, in order to determine their cellular uptakes and mode(s) of action. Fluorescence-labelled compounds can thus be used for verification of their interaction with cellular targets at the molecular level either by confocal laser scanning microscopy for cell cultures[6] or with the aid of the Explore-Optics instrument (GE) for mice.[7]

For binding to the fluorescence dyes we introduced aminomethyl groups into **2a** and **2b** at different positions in the A-ring. This should also allow us to determine the influence of the binding position on the activities of the labelled compounds. The synthesis of the corresponding substrates **3a** and **3b** started from *meta*-diiodobenzene and *para*-diiodobenzene, respectively. As dyes, flurorescein (**4**, Scheme 2) and dapoxyl (**5**) were used, through application of the commercially available activated compounds 5-SFX (**29**, Scheme 11, below) and D10162 (**31**, Scheme 13, below).



1 (+)-Duocarmycin SA

(1*S*)-**2a**	$R^1 = R^2 = R^3 = H$
(1*S*,10*R*)-**2b**	$R^1 = R^2 = H, R^3 = CH_3$
(1*S*)-**3a**	$R^1 = CH_2NH_2, R^2 = R^3 = H$
(1*S*,10*R*)-**3b**	$R^1 = H, R^2 = CH_2NH_2, R^3 = CH_3$

Scheme 1. Structures of (+)-duocarmycin SA (**1**) and the glycosidic prodrugs **2a** and **2b**, as well as the compounds **3a** and **3b**, each containing an aminomethyl group for binding with the fluorescence dye.

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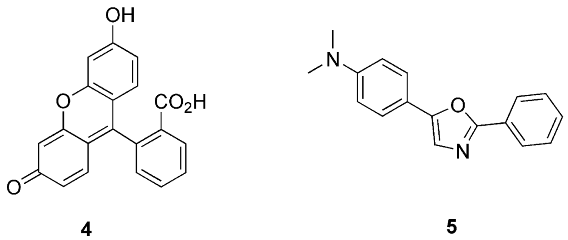
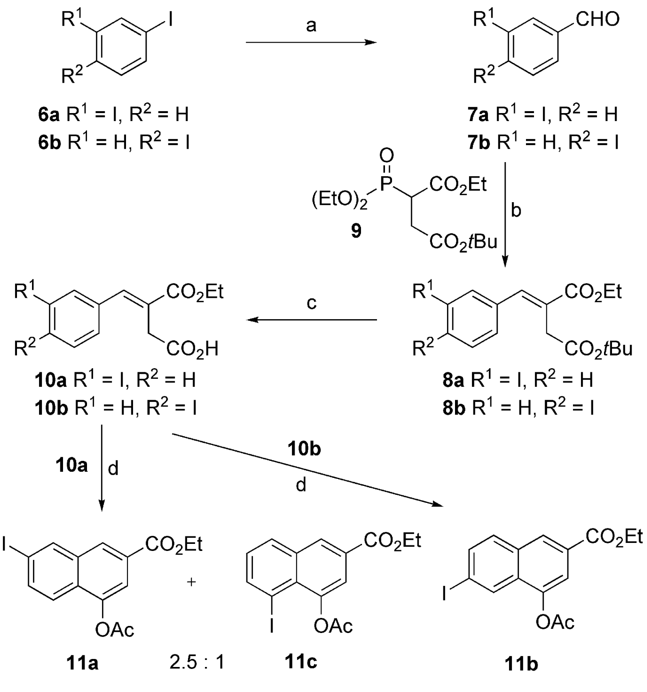
These show absorption maxima of λ_{max} = 494 nm for **4** and λ_{max} = 395 nm for **5** and emission maxima at λ_{max} = 521 nm for **4** and λ_{max} = 574 nm for **5** with high extinction coefficients.



Scheme 2. Structures of fluorescein (**4**) and dapoxyl (**5**).

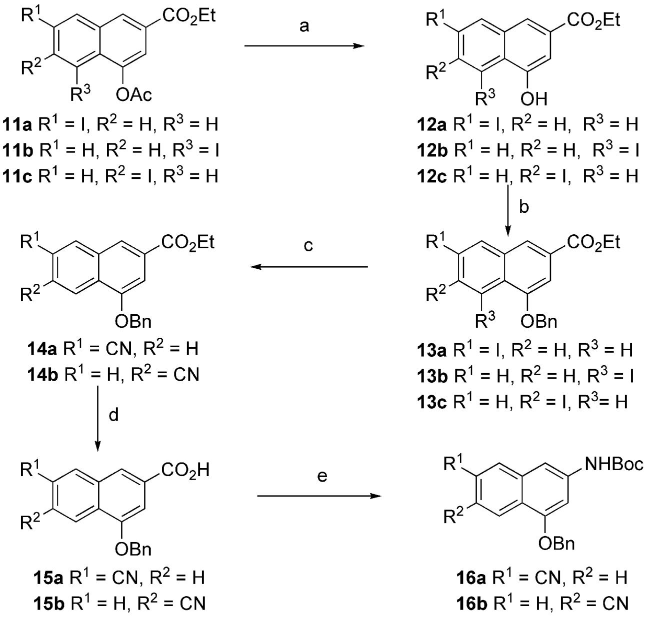
Results and Discussion

Formylation of the diiodobenzenes **6a** and **6b** (Scheme 3) by halogen/metal exchange with *n*-butyllithium at –78 °C in THF, followed by addition of DMF, led to the iodobenzaldehydes **7a** and **7b**, respectively. The aldehydes were then converted into the styrene derivatives **8a** and **8b** through Wittig–Horner reactions with the phosphonate **9** and NaH in THF. Acid-catalysed deprotection of **8a** and **8b** in TFA/H_2O yielded the carboxylic acids **10a** and **10b**, which were transformed into the naphthalene derivatives **11a** and **11b** through intramolecular Friedel–Crafts reactions by treatment with acetic anhydride and KOAc under reflux. In the case of **10a** we obtained a mixture of the desired **11a** and its regioisomer **11c** in a ratio of 2.5:1 (determined by ^1H NMR spectroscopy); at this stage it was not possible to separate the two compounds. In contrast, when starting from **10b**, compound **11b** was formed as the only product.



Scheme 3. Synthesis of the naphthalenes **11a** and **11b** starting from the diiodobenzenes **6a** and **6b**, respectively. Reagents and conditions: (a) *n*BuLi, THF, –78 °C, 20 min, then DMF, r.t., 2 h; 84–95%; (b) **9**, NaH, THF, 0 °C → r.t., 19 h; 63–72%; (c) TFA/H_2O (9:1), r.t., 6 h, 70–100%; (d) KOAc, Ac_2O, reflux, 1 h, 87–90%.

The acetates **11a/c** and **11b** were solvolysed with K_2CO_3 in ethanol to yield the phenols **12a/c** and **12b** (Scheme 4), which were protected at their phenolic hydroxy groups by treatment with BnBr and catalytic amounts of TBAI to give **13a/c** and **13b**. Exchange of the iodide for CN with CuCN under microwave conditions led to **14a/c** and **14b**.[8]

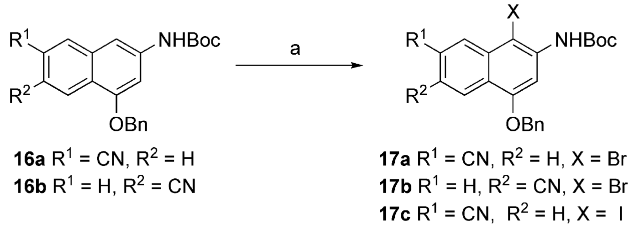


Scheme 4. Synthesis of **16a** and **16b** starting from the naphthalene derivatives **11a** and **11b**, respectively. Reagents and conditions: (a) K_2CO_3, EtOH, reflux, 4 h, 84–92%; (b) BnBr, K_2CO_3, TBAI, DMF, r.t., 15 h, 82–94%; (c) CuCN, DMF, 140 °C (microwaves), 1 h, 92–94%; (d) LiOH·H_2O, THF/MeOH/H_2O, r.t., 15 h, 87–98%; (e) DPPA, NEt_3, *t*BuOH, molecular sieves (4 Å), reflux, 20 h, 95–100%.

At this stage it was possible to recrystallise the **14a/c** mixture from *n*-pentane/EtOAc to afford pure **14a**. Hydrolysis of the ethyl carboxylates **14a** and **14b** with lithium hydroxide, followed by formation of the corresponding acyl azides and Curtius rearrangements with use of diphenylphosphoryl azide in *tert*-butyl alcohol, led to the Boc-protected aminonaphthalenes **16a** and **16b** (Scheme 4).

Bromination of **16a** and **16b** with NBS and catalytic amounts of sulfuric acid gave the compounds **17a** and **17b** (Scheme 5), whereas iodination of **16a** mediated by NIS and catalytic amounts of *p*-toluenesulfonic acid yielded compound **17c**.

For the synthesis of the aminomethyl-substituted benzoindoles **3a** and **3b** from **17** we envisaged two different approaches (Scheme 6): firstly, *N*-alkylation with the chloroallyl chlorides **18a** and **18b**, respectively, followed by radical

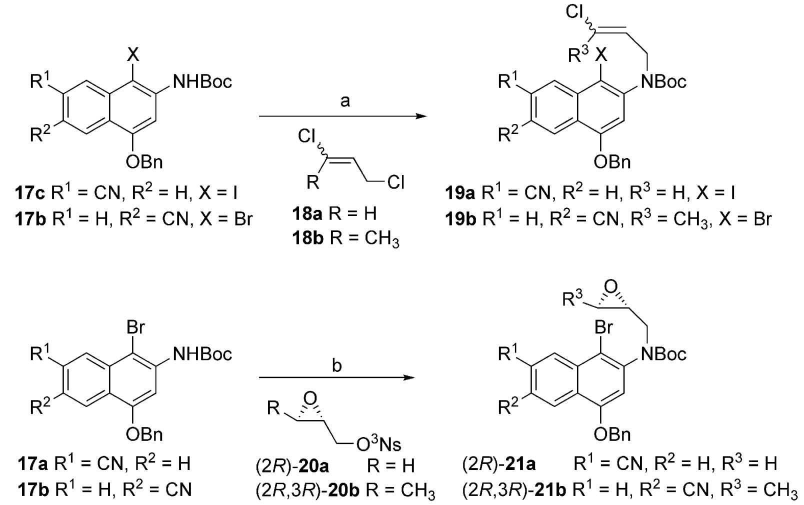


Scheme 5. Synthesis of **17a**–**17c**. Reagents and conditions: for **17a/17b**: NBS, cat. H_2SO_4, THF, –78 °C, 4 h, 81–94%; for **17c**: NIS, cat. $TsOH·H_2O$, THF, 50 °C, 1.5 h, 81%.

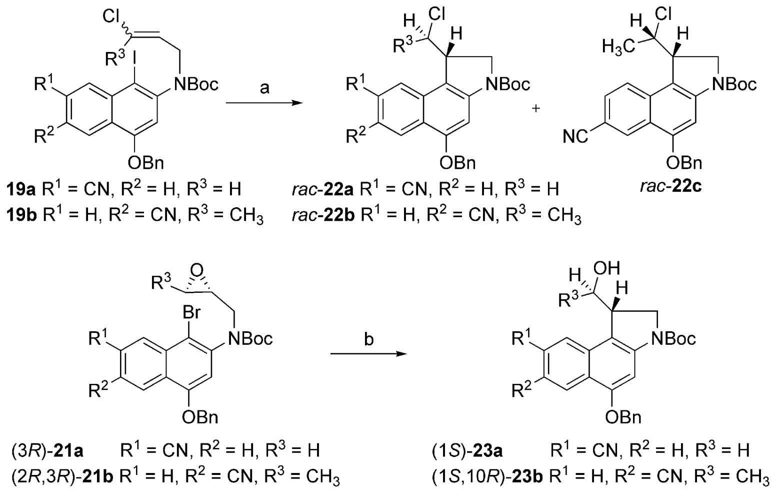
cyclisation, and secondly, *N*-alkylation with the epoxy nosylates (2*R*)-**20a** and (2*R*,3*R*)-**20b**, respectively, followed by metal-induced cyclisation. The latter approach has the advantage of leading to enantiopure – and in the case of (2*R*,3*R*)-**20b** also diastereopure – product(s).

N-Alkylation of **17c** and **17b** with the allyl halides **18a** and **18b** led to **19a** and **19b**, whereas treatment of **17a** and **17b** with the epoxy nosylates (2*R*)-**20a** and (2*R*,3*R*)-**20b** gave (2*R*)-**21a** and (2*R*,3*R*)-**21b**. Interestingly, compounds of type **21** each contain an axis of chirality along the naphthyl–N bond, so they are obtained as mixtures of diastereomers.[9]

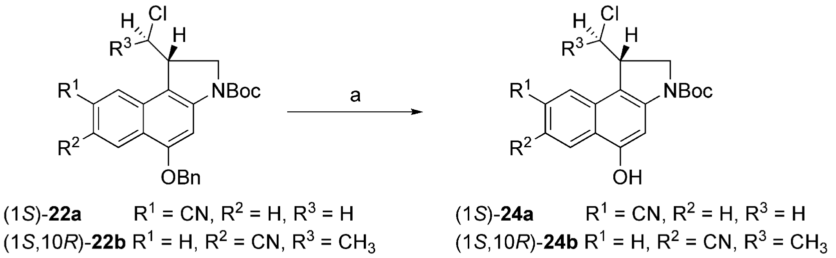
Radical cyclisation of **19a** and **19b**, mediated by tris(trimethylsilyl)silane and azobisisobutyronitrile in toluene, worked well to afford the cyclised products **22a**–**c** (Scheme 7) in 85–92% yields as racemic mixtures, and in the case of **19b** in a nearly 1:1 ratio of the two possible diastereomers **22b**/**22c**.[10] Similarly, metal-induced cyclisation of (2*R*,3*R*)-**21b** in the presence of $ZnCl_2$, MeLi and TMS-SCN led to the benzindole derivative (1*S*,10*R*)-**23b** in 53% yield, in this case as a pure enantiomer (>99% *ee*) and a pure diastereomer. In comparison, (2*R*)-**21a** gave the



Scheme 6. Synthesis of **19** and **21** from **17**. Reagents and conditions: (a) NaH, DMF, **18**, r.t., 4–14 h, 77–93%; (b) NaH, DMF, **20**, r.t., 21 h, 88–89%.



Scheme 7. Synthesis of *rac*-**22** and enantiopure **23**. Reagents and conditions: (a) TTMSS, AIBN, toluene, 80 °C, 4.5 h, 85–92%; (b) (2*R*)-**20a**: *n*BuLi (3.0 equiv.), –85 °C, 1 h, 12%; (2*R*,3*R*)-**20b**: $ZnCl_2$ (1.5 equiv.), MeLi (6.0 equiv.), TMS-SCN (1.5 equiv.), 55%.



Scheme 8. Synthesis of the phenols **24**. Reagents and conditions: (a) (1*S*)-**24a**: Pd/C, H_2, EtOAc, r.t., 5 h, 90%; (1*S*,10*R*)-**24b**: Pd/C, NH_4HCO_2, THF, 40 °C, 25 min, 86% (transfer hydrogenation).

desired product (1*S*)-**23a** in only 12% yield on treatment with *n*BuLi at –85 °C. All other attempts to initiate the cyclisation via a zincate or cuprate failed.

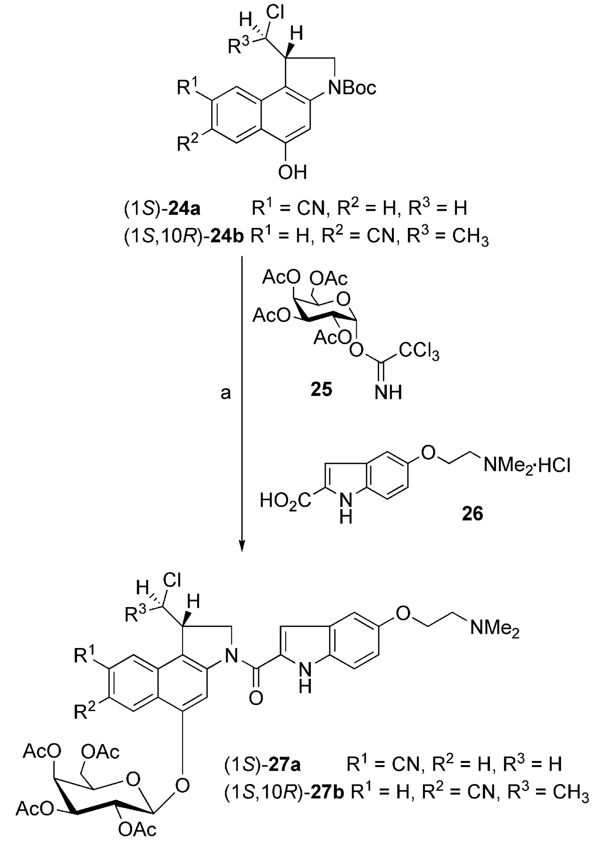
Treatment of (1*S*)-**23a** under Appel conditions afforded enantiopure (1*S*)-**22a**,[10] whereas treatment of (1*S*,10*R*)-**23b** with $SOCl_2$ in the presence of pyridine led to enantiopure (1*S*,10*R*)-**22b**. Alternatively, the enantiomeric mixture of *rac*-**22a** obtained from **19a** could be resolved by preparative HPLC on a chiral stationary support (Chiralpak IA), with *ee* values of 99.7% for (+)-(1*R*)-**22a** and 99.2% for (–)-(1*S*)-**22a**. The two diastereomers *rac*-**22b** and *rac*-**22c** obtained from **19b** were separated by column chromatography on silica gel, whereas *rac*-**22b** was resolved again by preparative HPLC on chiral support (Chiralpak IA) to obtain the desired (+)-(1*S*,10*R*)-**22b** with an *ee* value of 99.9%. Neither the diastereomer **22c** nor the enantiomer (–)-(1*R*,10*S*)-**22b** were included in further investigations, because we have shown that the corresponding *seco* drugs – without the cyano group – have much lower cytotoxicities.

Deprotection of **22a** and **22b** either with Pd/C under H_2 or with ammonium formate, respectively, gave the free phenols **24a** and **24b** in good yields (Scheme 8).

Next, the galactose moiety and the DNA binder were introduced (Scheme 9). For this purpose (1*S*)-**24a** and (1*S*,10*R*)-**24b** were glycosylated with the galactose trichloroacetimidate **25** in the presence of $BF_3{\cdot}OEt_2$ at –10 °C. Addition of an excess of $BF_3{\cdot}OEt_2$ at room temp. led to the corresponding secondary amine as a result of Boc removal. This amine was then coupled with the DNA binder DMAI **26** without isolation in the presence of EDC·HCl as the activating agent.

Nitrile reduction in (1*S*)-**27a** and (1*S*,10*R*)-**27b** in accordance with the method of Wrobel et al.[11] with $PtO_2{\cdot}H_2O$ under H_2 afforded the corresponding primary amines **28a** and **28b** (Scheme 10), and these were deprotected under basic conditions with NaOMe in MeOH to give the desired aminomethyl-substituted prodrugs (1*S*)-**3a** and (1*S*,10*R*)-**3b**.

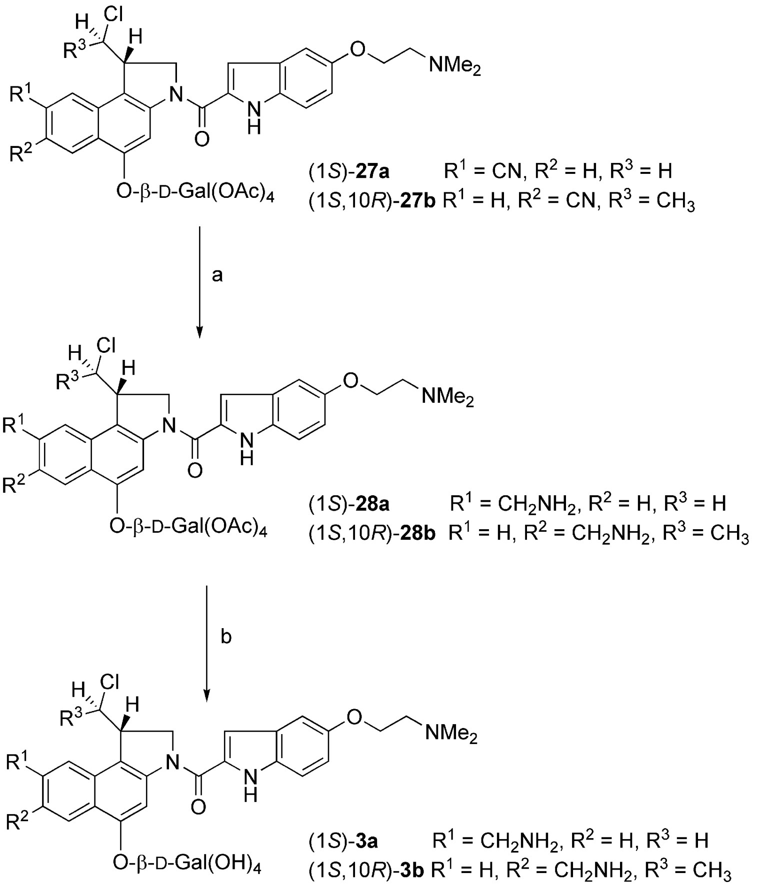
The final step in the synthesis of the fluorescence-labelled prodrugs was the coupling of (1*S*)-**3a** and (1*S*,10*R*)-**3b** with the activated commercially available dyes 5-SFX (**29**) as a derivative of fluorescein (**4**) and D10162 (**31**) as a derivative of dapoxyl (**5**). Coupling of (1*S*)-**3a** with **29** in DMF and Hünig base (Scheme 11), followed by purification by preparative HPLC (Kromasil 100 C18), gave the fluorescence-labelled prodrug (1*S*)-**30a** in 51% yield.



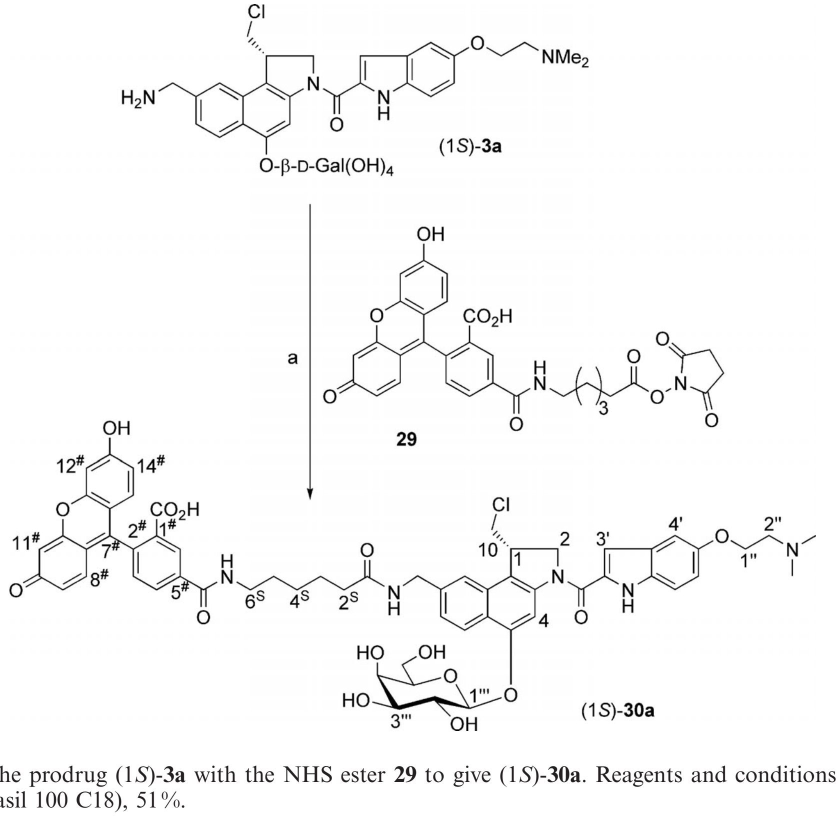
Scheme 9. Synthesis of the galactosides **27a** and **27b**. Conditions and reagents: (a) **26**, 0.5 equiv. $BF_3{\cdot}OEt_2$, CH_2Cl_2, molecular sieves (4 Å), –10 °C, 3.5 h, then 3 equiv. $BF_3{\cdot}OEt_2$, r.t., 6 h, **27**, EDC·HCl, DMF, r.t., 18 h, 52–53%.

In the same manner, coupling of (1*S*,10*R*)-**3b** with **29** (Scheme 12) afforded the fluorescence-labelled prodrug (1*S*,10*R*)-**30b** in 88% yield.

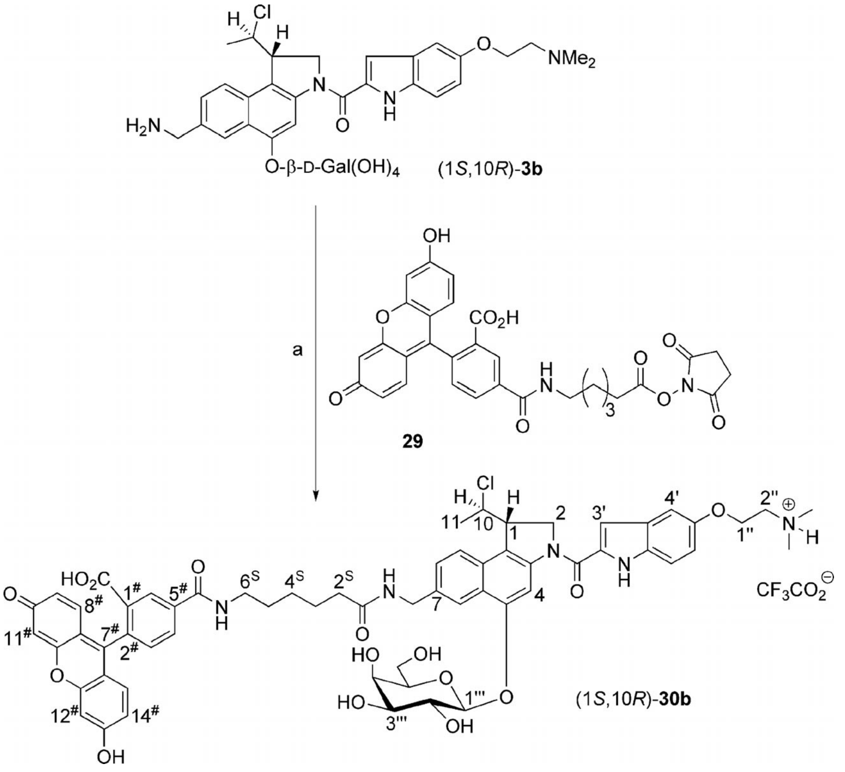
In addition, the aminomethyl-substituted prodrug (1*S*,10*R*)-**3b** was also coupled with the dapoxyl derivative **31** under the same conditions as described for **29** to give the fluorescence-labelled prodrug (1*S*,10*R*)-**32** in 89% yield (Scheme 13).



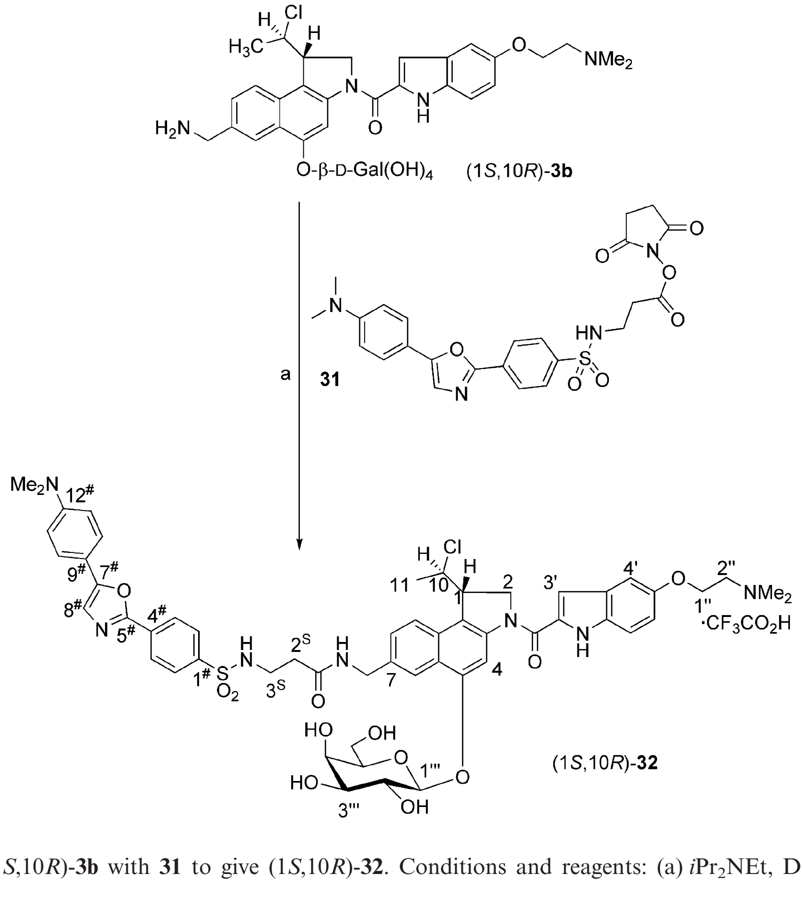
Scheme 10. Synthesis of the aminomethyl-substituted prodrugs **3**. Reactions and conditions: (a) HCl/EtOH, $PtO_2 \cdot H_2O$, H_2, r.t., 48 h, 66–81%; (b) NaOMe/MeOH, MeOH, r.t., 30 min, prep. HPLC (Kromasil 100 C18), 70–95%.



Scheme 11. Coupling of the prodrug (1*S*)-**3a** with the NHS ester **29** to give (1*S*)-**30a**. Reagents and conditions: (a) *i*Pr_2NEt, DMF, r.t., 18 h, prep. HPLC (Kromasil 100 C18), 51%.



Scheme 12. Coupling of the prodrug (1*S*,10*R*)-**3b** with the NHS ester **29** to give (1*S*,10*R*)-**30b**. Reagents and conditions: (a) *i*Pr$_2$NEt, DMF, r.t., 18 h, prep. HPLC (Kromasil 100 C18), 88 %.



Scheme 13. Coupling of (1*S*,10*R*)-**3b** with **31** to give (1*S*,10*R*)-**32**. Conditions and reagents: (a) *i*Pr$_2$NEt, DMF, r.t., 9 h, prep. HPLC, 89 %.

Conclusions

We have prepared the fluorescence-labelled prodrugs (1*S*)-**30a**, (1*S*,10*R*)-**30b** and (1*S*,10*R*)-**32** to allow investigations of their cellular uptakes and their mode(s) of action by confocal laser scanning microscopy in the case of cell cultures and with the Explore Optix (GE) instrument in the case of mice. The results will be published in due course in a more biologically orientated journal.

Experimental Section

General: All reactions were performed in flame-dried glassware under argon. Commercially available reagents were used without further purification. Thin layer chromatography (TLC) was carried out on precoated Alugram SIL G/UV254 (0.25 mm) plates from Macherey–Nagel & Co. Column chromatography (CC) was carried out on silica gel 60 from Merck with particle size 0.063–0.200 mm for normal-pressure and flash chromatography. IR spectra were determined with a Bruker Vektor 22 instrument, UV/Vis spectra with a Perkin–Elmer Lambda 2, and mass spectra with a Finnigan MAT 95 for EI HRMS and a Bruker Apex IV Fourier transform ion cyclotron resonance mass spectrometer for ESI HRMS. ^{1}H NMR spectra were recorded variously with a Varian UNITY 300 MHz, a Varian Inova 500 MHz or a Varian Inova 600 MHz instrument. ^{13}C NMR spectra were recorded at 75, 125, or 150 MHz. Spectra were taken at room temperature except when stated otherwise in deuterated solvents as indicated with use of the solvent peak as internal standard. The purities and stabilities of the target compounds were checked by HPLC-MS [ESI mass spectrometry with an ion-trap mass spectrometer LCQ (Finnigan)]. The columns used were Phenomenex Synergi Max-RP C12 (150 × 2 mm, particle size 4 µm). Chromatographic separation by HPLC was performed with use either of a Kromasil 100 C18 column (250 × 20 mm, particle size 7 µm) or of a Chiralpak IA column (250 × 20 mm, particle size 5 µm).

(*E*/*Z*)-2-Amino-4-(benzyloxy)-*N*-(*tert*-butoxycarbonyl)-*N*-(3-chloroprop-2-enyl)-7-cyano-1-iodonaphthalene (19a): NaH (399 mg, 60% dispersion in mineral oil, 10.0 mmol, 2.5 equiv.) was added at room temperature to a solution of **17c** (2.00 g, 4.00 mmol, 1.0 equiv.) in anhydrous DMF (50 mL), and the mixture was stirred for 1.5 h. Compound **18a** (986 mg, 823 µL, 8.0 mmol, 2.0 equiv.) was then added dropwise, and stirring was continued for 14 h. After addition of saturated aqueous NH_4Cl (pH = 7) the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O (3 × 100 mL) and brine (3 × 100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; PE/EtOAc, 8:1) afforded **19a** as a yellow solid (1.76 g, 3.06 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.35, 1.49–1.60 [2 × m, total 9 H, $C(CH_3)_3$], 3.69–3.83, 4.17–4.33 (2 × m, total 1 H, 1′-H_a), 4.42–4.61 (m, 1 H, 1′-H_b), 5.10–5.34 (m, 2 H, OCH_2Ph), 5.90–3.12 (m, 1 H, 2′-H), 6.74–6.92 (m, 1 H, 3-H), 7.35–7.69 (m, 5 H, 5 × Ph-H), 7.58–7.69 (m, 1 H, 6-H), 8.32–8.44 (m, 1 H, 5-H), 8.57–8.64 (m, 1 H, 8-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.12, 28.14 [$C(CH_3)_3$], 46.11, 49.19 (C-1′), 71.01, 71.10 (OCH_2Ph), 81.01, 81.07 [$C(CH_3)_3$], 94.57, 94.66 (C-1), 110.41, 110.82 (C-3), 112.19, 112.26 (C-7), 118.31, 118.35 (CN), 120.57, 121.72 (C-3′), 124.03, 124.07 (C-5), 126.7, 126.8, 127.0, 127.1, 127.2, 128.2, 128.5, 128.6, 129.5, 134.8, 134.9, 135.6, 135.7, 144.8, 145.1 (C-4a, C-8a, C-2, C-2′, 6 × Ph-C), 138.3, 138.4 (C-8), 152.9, 153.1, 155.2 (C-4, C=O) ppm. IR (KBr): $\tilde{\nu}$ = 2976, 2228, 1703, 1593, 1503, 1410, 1368, 1329, 1257, 1163 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 221.0 (4.645), 256.0 (4.509), 320.5 (3.828), 354.4 (3.638) nm. ESI-HRMS: *m*/*z* = 597.04123 [M + Na]$^+$; $C_{26}H_{24}ClIN_2O_3$ requires 597.04187.

(*E*/*Z*)-2-Amino-4-(benzyloxy)-1-bromo-*N*-(*tert*-butoxycarbonyl)-*N*-(3-chlorobut-2-enyl)-6-cyanonaphthalene (19b): NaH (863 mg, 60% dispersion in mineral oil, 21.6 mmol, 2.5 equiv.) was added at room temperature to a solution of **17b** (6.52 g, 14.4 mmol, 1.0 equiv.) in anhydrous DMF (150 mL) and the mixture was stirred for 3 h. Compound **18b** (3.59 g, 3.16 mL, 28.8 mmol, 2.0 equiv.) was then added dropwise, and stirring was continued for 4 h. After addition of saturated aqueous NH_4Cl (200 mL) and H_2O (100 mL), the mixture was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with H_2O (3 × 200 mL) and brine (3 × 200 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was washed with *n*-pentane (150 mL) and recrystallised from EtOAc. Workup of the mother liquor by column chromatography (SiO_2; PE/EtOAc, 10:1) afforded another batch of **19b** as a white solid (7.48 g, 13.8 mmol, total 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26–1.36, 1.52–1.62 [2 × m, total 9 H, $C(CH_3)_3$], 1.81–1.87, 1.99–2.10 (2 × m, total 3 H, 4′-H_3), 3.90–4.03, 4.23–4.38 (2 × m, total 1 H, 1′-H_a), 4.39–4.55 (m, 1 H, 1′-H_b), 5.13–5.37 (m, 2 H, OCH_2Ph), 5.61–5.83 (m, 1 H, 2′-H), 6.74–6.96 (m, 1 H, 3-H), 7.37–7.57 (m, 5 H, 5 × Ph-H), 7.69–7.81 (m, 1 H, 7-H), 8.33–8.41 (m, 1 H, 8-H), 8.65–8.76 (m, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.84, 26.15 (C-4′), 28.11, 28.38 [$C(CH_3)_3$], 46.19, 47.48 (C-1′), 70.83, 70.90 (OCH_2Ph), 80.94 [$C(CH_3)_3$], 108.8, 109.4, 109.6, 109.8 (C-3, C-6), 114.5, 118.8, 118.9, (C-4a, CN), 121.2, 122.5 (C-2′), 124.9 (C-1), 127.4, 127.7, 128.5, 128.7, 128.8, 128.9 (C-5, C-7, C-8, 2 × Ph-C_o, 2 × Ph-C_m, Ph-C_p), 133.3, 134.2, 135.4, 135.5, 142.1, 142.2 (C-2, C-8a, C-3′, Ph-C_i), 153.6, 154.1, 154.6 (C-4, C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3083, 2967, 2223 (CN), 1702 (C=O), 1617, 1592 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 218.0 (4.655), 256.5 (4.587), 318.0 (3.758), 335.5 (3.762), 350.5 (3.840) nm. ESI-HRMS: *m*/*z* = 541.0888 [M + H]$^+$; $C_{27}H_{26}ClIN_2O_3$ requires 541.0888.

(2*R*)-2-Amino-4-(benzyloxy)-1-bromo-*N*-(*tert*-butoxycarbonyl)-7-cyano-*N*-(2,3-epoxypropyl)naphthalene [(2*R*)-21a]: NaH (173 mg, 60% dispersion in mineral oil, 4.4 mmol, 4.0 equiv.) was added to a solution of **17a** (500 mg, 1.10 mmol, 1.0 equiv.) in anhydrous DMF (5 mL), and the mixture was stirred at room temperature for 30 min. The nosylate (2*R*)-**20a** (456 mg, 1.76 mmol, 1.6 equiv.) was added, and stirring was continued for 14 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The reaction mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; PE/EtOAc, 5:1) afforded (2*R*)-**21a** as a bright yellow solid (495 mg, 972 µmol, 88%). ^{1}H NMR (300 MHz, $C_2D_2Cl_4$): δ = 1.20–1.72 [m, 9-H, $C(CH_3)_3$], 2.38–2.50 (m, 1 H, 4′-H_a) 2.67–2.81 (m, 1 H, 4′-H_b), 3.08–3.15 (m, 0.5 H, 2′-H_a), 3.15–3.28 (m, 0.5 H, 3′-H), 3.30–3.40 (m, 0.5 H, 2′-H_a), 3.51–3.73 (m, 0.5 H, 3′-H), 3.88–4.21 (m, 1 H, 2′-H_b), 5.22–5.35 (m, 2 H, OCH_2Ph), 6.93–7.13 (m, 1 H, 3-H), 7.34–7.54 (m, 5 H, 5 × Ph-H), 7.64–7.72 (m, 1 H, 6-H), 8.40–8.49 (m, 1 H, 5-H), 8.64–8.69 (m, 1 H, 8-H) ppm. IR (KBr): $\tilde{\nu}$ = 2977, 2228, 1703, 1596, 1503, 1370, 1257, 1153 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 215.5 (4.618), 256.5 (4.596), 316.0 (3.815), 352.0 (3.580) nm. ESI-HRMS: *m*/*z* = 509.10705 [M + H]$^+$; $C_{26}H_{25}BrN_2O_4$ requires 509.10759.

(+)-(2*R*,3*R*)-2-Amino-4-(benzyloxy)-1-bromo-*N*-(*tert*-butoxycarbonyl)-6-cyano-*N*-(2,3-epoxybutyl)naphthalene [(+)–(2*R*,3*R*)-21b]: NaH (397 mg, 60% dispersion in mineral oil, 16.6 mmol, 4.0 equiv.) was added to a solution of **17c** (1.88 g, 4.14 mmol, 1.0 equiv.) in anhydrous DMF (30 mL), and the mixture was stirred at 60 °C for 60 min. After the system had cooled to room temperature, the nosylate (2*R*,3*R*)-**20b** (1.70 g, 6.21 mmol, 1.5 equiv.) was added, and stirring was continued for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (100 mL). The reaction mixture was extracted with Et_2O (3× 100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; PE/EtOAc, 9:1) afforded (+)–(2*R*,3*R*)-**21b** as a white solid (1.93 g, 3.69 mmol, 89%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.41, 1.59–1.68 [2× m, total 12 H, $C(CH_3)_3$, 4′-H_3], 2.60–2.62, 2.76–2.91, 3.04–3.22, 3.27–3.36, 3.52–3.61, 3.71–4.21, 4.30–4.35 (7× m, total 4 H, 1′-H_2, 2′-H, 3′-H), 5.20–5.32 (m, 2 H, $OC\mathit{H}_2Ph$), 6.93–7.10 (m, 1 H, 3-H), 7.37–7.54 (m, 5 H, 5× Ph-H), 7.69–7.76 (m, 1 H, 7-H), 8.18–8.21, 8.33–8.38 (2× m, total 1 H, 8-H), 8.66–8.72 (m, 1 H, 5-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.2 (2 signals, C-4′), 28.0, 28.1, 28.4 (2 signals, $C(\mathit{C}H_3)_3$], 50.5, 52.1, 52.4, 53.0, 53.4, 53.6, 53.7, 54.2, 56.5, 56.8, 57.1, 57.2 (C-1′, C-2′, C-3′), 68.9, 70.9 ($O\mathit{C}H_2Ph$), 81.0, 81.1, 81.7 (2 signals, $\mathit{C}(CH_3)_3$], 109.0, 109.1, 109.3, 109.6, 109.7 (C-3, C-6), 114.0, 114.5, 114.6, 118.9, (2 signals, C-4a, CN), 125.0, 125.1, 125.9 (C-1), 127.5, 127.6, 127.8, 127.9, 128.5 (2 signals), 128.7 (2 signals), 128.8 (2 signals), 128.9 (2 signals, C-5, C-7, C-8, 2× Ph-C_o, 2× Ph-C_m, Ph-C_p), 134.1 (2 signals), 134.3, 134.4, 135.4, 135.5, 142.1, 142.2, 142.6 (C-2, C-8a, Ph-C_i), 153.5, 153.6, 153.7, 154.2 (2 signals), 154.7, 163.5 (C-4,C=O) ppm. IR (film): $\tilde{\nu}$ = 2977, 2228, 1706, 1620, 1591, 1455, 1411, 1369, 1342, 1254, 1151, 1095, 975, 910, 872, 738, 697 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 218.0 (4.630), 256.5 (4.557), 317.0 (3.812), 334.5 (3.765), 350.5 (3.814) nm. ESI-HRMS: *m*/*z* = 545.1046 $[M + Na]^+$; $C_{27}H_{27}BrN_2O_4$ requires 545.1046.

***rac*-(1*S*)-5-(Benzyloxy)-3-(*tert*-butoxycarbonyl)-1-(chloromethyl)-8-cyano-1,2-dihydro-3*H*-benz[*e*]indole (*rac*-22a):** A solution of **19a** (1.42 g, 2.47 mmol, 1.0 equiv.) in anhydrous toluene (60 mL) was flushed with argon for 10 min. Tris(trimethylsilyl)silane (836 µL, 2.72 mmol, 1.1 equiv.) and AIBN (102 mg, 618 µmol, 0.25 equiv.) were added at room temperature, and the solution was stirred at 80 °C with use of a preheated oil bath for 4.5 h. After addition of SiO_2 (3 g), the mixture was concentrated in vacuo, and the residue was purified by column chromatography (*n*-hexane/DCM, 9:1) to afford *rac*-**22a** as a white solid (940 mg, 2.10 mmol, 85%). ^1H NMR (300 MHz, $C_2D_2Cl_4$): δ = 1.64 [s, 9 H, $C(CH_3)_3$], 3.59 (dd, *J* = 9.1, 11.2 Hz, 1 H, 2-H_a), 3.89 (dd, *J* = 3.51, 11.2 Hz, 1 H, 2-H_b), 4.00 (tt, *J* = 3.2, 8.8 Hz, 1 H, 1-H), 4.21 (dd, *J* = 8.8, 11.7 Hz, 1 H, 10-H_a), 4.30 (dd, *J* = 3.2, 11.8 Hz, 1 H, 10-H_b), 5.32 (s, 2 H, $OC\mathit{H}_2Ph$), 7.36–7.57 (m, 6 H, 7-H, 5× Ph-H), 7.93 (s, 1 H, 4-H), 8.02 (dd, *J* = 0.7, 1.5 Hz, 1 H, 9-H), 8.38 (dd, *J* = 0.5, 8.7 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $C_2D_2Cl_4$): δ = 28.26 $[C(\mathit{C}H_3)_3]$, 41.01 (C-1), 46.37 (C-2), 53.15 (C-10), 70.84 ($O\mathit{C}H_2Ph$), 81.57 $[\mathit{C}(CH_3)_3]$, 99.71 (C-4), 111.1 (C-8), 114.9 (C-9b), 118.9 (CN), 123.2 (C-7), 123.6 (C-5a), 124.9 (C-6), 127.4 (C-9), 127.4 (2× Ph-C_o), 128.0 (Ph-C_p), 128.4 (2× Ph-C_m), 129.4 (C-9a), 136.1 (Ph-C_i), 143.4 (C-3a), 151.9 (C=O), 155.9 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 2977, 2230, 1693, 1593, 1455, 1409, 1374, 1336, 1257, 1146 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 210.0 (4.391), 230.0 (4.469), 268.0 (4.786), 311.5 (3.906), 322.5 (3.977), 381.0 (3.475) nm. ESI-HRMS: *m*/*z* = 471.14459 $[M + Na]^+$; $C_{26}H_{25}ClN_2O_3$ requires 471.14459.

Chromatographic Resolution of *rac*-22a: A solution of *rac*-**22a** (500 mg, 1.1 mmol) in a mixture of *n*-hexane and CH_2Cl_2 (1:1, 10 mL) was separated (injection volume: 0.15 mL) by semipreparative HPLC (Chiralpak IA; 250× 20 mm; particle size: 5 µm; *n*-hexane/CH_2Cl_2, 85:15; flow: 18 mL min^{-1}; UV detector: λ = 269 nm) to provide (+)-(1*R*)-**22a** (t_R = 12.5 min) and (–)-(1*S*)-**22a** (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, 97:3; flow: 0.8 mL min^{-1}): (+)-(1*R*)-**22a**: 99.7% *ee* (t_R = 8.4 min), $[\alpha]_D^{20}$ = +9.5 (*c* = 0.5 in $CHCl_3$); (–)-(1*S*)-**22a**: 99.2% *ee* (t_R = 6.4 min), $[\alpha]_D^{20}$ = –11.0 (*c* = 0.5 in $CHCl_3$).

***rac*-(1*S*)-5-(Benzyloxy)-3-(*tert*-butoxycarbonyl)-1-[(1*R*)-1-chloroethyl]-7-cyano-1,2-dihydro-3*H*-benz[*e*]indole (*rac*-22b) and *rac*-(1*S*)-5-(Benzyloxy)-3-(*tert*-butoxycarbonyl)-1-[(1*S*)-1-chloroethyl]-7-cyano-1,2-dihydro-3*H*-benz[*e*]indole (*rac*-22c):** A solution of **19b** (3.20 g, 5.91 mmol, 1.0 equiv.) in anhydrous toluene (150 mL) was flushed with argon for 10 min. Tris(trimethylsilyl)silane (2.00 mL, 6.48 mmol, 1.1 equiv.) and AIBN (242 mg, 1.47 mmol, 0.25 equiv.) were added at room temperature, and the solution was stirred at 80 °C with use of a preheated oil bath for 4.5 h. After the system had cooled to room temperature, the brown solid was washed with *n*-pentane. The resulting crude solid was purified by column chromatography (PE/EtOAc, 30:1 → 10:1) to afford the *syn* diastereomer *rac*-**22c** as a white solid (560 mg, 1.21 mmol, 20%), a mixture of the *syn* diastereomer *rac*-**22c** together with the dehalogenised cyclisation product as a yellow solid (380 mg) and the desired *anti* diastereomer *rac*-**22b** as a white solid (1.30 g, 2.81 mmol, 48%).

***rac*-22c:** ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.60–1.67 [m, 12 H, 11-H_3, $C(CH_3)_3$], 3.87 (m_c, 1 H, 1-H), 4.13 (dd, *J* = 11.8, 9.5 Hz, 1 H, 2-H_a), 4.37 (dd, *J* = 11.8, 2.8 Hz, 1 H, 2-H_b), 4.55 (dq, *J* = 6.8, 3.7 Hz, 1 H, 10-H), 5.33 (m_c, 2 H, $OC\mathit{H}_2Ph$), 7.37–7.57 (m, 5 H, 5× Ph-H), 7.60 (dd, *J* = 8.7, 1.6 Hz, 1 H, 8-H), 7.72 (d, *J* = 8.7 Hz, 1 H, 9-H), 7.87 (br. s, 1 H, 4-H), 8.66 (d, *J* = 1.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, $C_2D_2Cl_4$, 100 °C): δ = 23.04 (C-11), 28.24 $[C(\mathit{C}H_3)_3]$, 45.54 (C-1), 50.95 (C-2), 59.68 (C-10), 70.79 ($O\mathit{C}H_2Ph$), 81.56 $[\mathit{C}(CH_3)_3]$, 98.24 (C-4), 105.5 (C-7), 115.5 (C-9b), 119.4, 121.4 (C-5a, CN), 123.0 (C-9), 127.4, 127.6, 128.1, 128.5 (C-8, 2× Ph-C_o, 2× Ph-C_m, Ph-C_p), 129.8 (C-6), 131.7 (C-9a), 135.9 (Ph-C_i), 145.1 (C-3a), 151.7 (C=O), 156.1 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 2976, 2223 (CN), 1705 (C=O), 1622, 1577, 1478, 1456 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 214.0 (4.452), 270.5 (4.829), 353.0 (4.198) nm. ESI-HRMS: *m*/*z* = 463.1783 $[M + H]^+$; $C_{26}H_{25}ClN_2O_3$ requires 463.1783.

Chromatographic Resolution of *rac*-22b: A solution of *rac*-**22b** (1.0 g, 2.2 mmol) in a mixture of *n*-heptane/CH_2Cl_2 (1:1, 25 mL) was separated (injection volume: 1.0 mL) by semipreparative HPLC (Chiralpak IA; 250× 20 mm; particle size: 5 µm; *n*-heptane/CH_2Cl_2, 80:20; flow: 18 mL min^{-1}; UV detector: λ = 250 nm) to provide (+)-(1*S*,10*R*)-**22b** (t_R = 8.2 min) and (–)-(1*R*,10*S*)-**22b** (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}): (+)-(1*S*,10*R*)-**22b**: 99.9% *ee* (t_R = 37.6 min), $[\alpha]_D^{20}$ = +24.6 (*c* = 0.5 in $CHCl_3$); (–)-(1*R*,10*S*)-**22b**: 98.7% *ee* (t_R = 33.9 min), $[\alpha]_D^{20}$ = –24.4 (*c* = 0.5 in $CHCl_3$).

(1*S*)-5-(Benzyloxy)-3-(*tert*-butoxycarbonyl)-8-cyano-1-(hydroxymethyl)-1,2-dihydro-3*H*-benz[*e*]indole [(1*S*)-23a]: A solution of *n*-butyllithium in *n*-hexane (2.5 M, 245 µL, 612 µmol, 3.0 equiv.) was added slowly at –90 °C to a stirred solution of (2*R*)-**21a** (104.0 mg, 20.4 mmol, 1.0 equiv.) in anhydrous THF (10 mL), and stirring was continued at –78 °C for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL), and the mixture was extracted with EtOAc (2× 100 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude solid by column chromatography (SiO_2; PE/EtOAc, 4:1) afforded (1*S*)-**23a** as a bright brown solid (10.1 mg, 2.35 mmol, 12%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.58 [s, 9 H, $C(CH_3)_3$], 3.66–4.26 (m, 5 H, 1-H, 2-H, 10-H), 5.23 (s, 2 H, $OC\mathit{H}_2Ph$), 7.31–7.55 (m, 6 H, 7-H, 5× Ph-H), 7.94–8.05 (m, 1 H, 4-H), 8.05–8.08 (m, 1 H, 9-H), 8.26–8.35 (m, 1 H, 6-

H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.38 [$C(CH_3)_3$], 41.13 (C-1), 52.48 (C-2), 64.79 (C-10), 70.54 (OCH_2Ph), 81.60 [$C(CH_3)_3$], 99.10 (C-4), 110.6 (C-8), 115.0 (C-9b), 119.4 (CN), 123.2 (C-7), 123.5 (C-5a), 124.8 (C-6), 127.4 (C-9), 127.7 (2× Ph-C_o), 128.2 (Ph-C_p), 128.6 (2× Ph-C_m), 129.7 (C-9a), 136.2 (Ph-C_i), 143.7 (C-3a), 152.5 (C=O), 155.4 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 2974, 2227, 1701, 1623, 1291, 1455, 1369, 1257, 1143, 1092, 1031 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 209.0 (4.393), 229.0 (4.435), 267.5 (4.683), 313.0 (3.848), 323.5 (3.878), 375.0 (3.405) nm. ESI-HRMS: *m*/*z* = 431.19653 $[M + H]^+$; $C_{26}H_{26}N_2O_4$ requires 431.19653.

(+)-(1*S*)-5-(Benzyloxy)-3-(*tert*-butoxycarbonyl)-7-cyano-1-[(1*R*)-1-hydroxyethyl]-1,2-dihydro-3*H*-benz[*e*]indole [(+)-(1*S*,10*R*)-23b]: Freshly fused $ZnCl_2$ (544 mg, 3.99 mmol, 1.5 equiv.) was suspended in anhydrous THF (50 mL), and the mixture was cooled to 0 °C. A solution of methyllithium in Et_2O (1.6 M, 9.98 mL, 16.0 mmol, 6.0 equiv.) was slowly added to the stirred mixture, and stirring was continued at 0 °C for 30 min. The mixture was cooled to –78 °C, and TMS-NCS (563 µL, 524 mg, 3.99 mmol, 1.5 equiv.) was added dropwise. The mixture was warmed to 0 °C and stirred for 30 min. After the mixture had again been cooled to –78 °C, a solution of (+)-(2′*R*,3′*R*)-**21b** (1.39 g, 2.66 mmol, 1.0 equiv.) in anhydrous THF (25 mL) was added dropwise, and the resulting mixture was stirred at –78 °C for 30 min. After warming to 0 °C, the mixture was stirred for 1 h, and, after warming to room temperature, it was stirred for 2.5 h. Saturated aqueous NH_4Cl (200 mL) was slowly added, and the mixture was extracted with CH_2Cl_2 (4× 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; PE/EtOAc, 5:2) afforded (+)-(1*S*,10*R*)-**23b** as a white solid (840 mg, 1.89 mmol, 71%, 98.8% *ee*). ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.27 (d, *J* = 6.4 Hz, 3 H, 10-CH_3), 1.63 [br. s, 9 H, $C(CH_3)_3$], 3.71 (dt, *J* = 9.9, 3.1 Hz, 1 H, 1-H), 4.09 (dd, *J* = 11.6, 9.9 Hz, 1 H, 2-H_a), 4.26 (dd, *J* = 11.6, 3.4 Hz, 1 H, 2-H_b), 4.33 (m_c, 1 H, 10-H), 5.32 (s, 2 H, OCH_2Ph), 7.38–7.54 (m, 5 H, 5× Ph-H), 7.58 (dd, *J* = 8.8, 1.7 Hz, 1 H, 8-H), 7.83 (d, *J* = 8.8 Hz, 1 H, 9-H), 7.89 (br. s, 1 H, 4-H), 8.64 (d, *J* = 1.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR (150 MHz, $C_2D_2Cl_4$, 100 °C): δ = 20.2 (C-11), 28.3 [$C(CH_3)_3$], 45.0 (C-1), 49.9 (C-2), 68.7 (C-10), 70.8 (OCH_2Ph), 81.4 [$C(CH_3)_3$], 98.3 (C-4), 105.5 (C-7), 115.7 (C-9b), 119.5, 121.4 (C-5a, CN), 123.7 (C-9), 127.4 (2 signals), 128.1, 128.5 (C-8, 5× Ph-CH), 129.7 (C-6), 132.0 (C-9a), 136.0 (Ph-C_i), 145.2 (C-3a), 151.8 (C=O), 155.9 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 2973, 2222, 1702, 1620, 1577, 1479, 1455, 1413, 1373, 1325, 1255, 1144, 909, 822, 736, 696 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 215.0 (4.462), 271.5 (4.835), 355.5 (4.211) nm. ESI-HRMS: *m*/*z* = 445.2121 $[M + H]^+$; $C_{27}H_{28}N_2O_4$ requires 445.2122.

(+)-(1*S*)-5-(Benzyloxy)-3-(*tert*-butoxycarbonyl)-1-[(1*R*)-1-chloroethyl]-7-cyano-1,2-dihydro-3*H*-benz[*e*]indole [(+)-(1*S*,10*R*)-22b]: $SOCl_2$ (206 µL, 337 mg, 2.83 mmol, 10.0 equiv.) and pyridine (572 µL, 560 mg, 7.09 mmol, 25.0 equiv.) were added at 0 °C to a solution of (+)-(1*S*,10*R*)-**23b** (126 mg, 283 µmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (6 mL). The reaction mixture was stirred at room temperature for 4 h. After concentration, the crude product was purified by column chromatography (PE/EtOAc, 5:1) to afford (+)-(1*S*,10*R*)-**22b** as a white solid (57.8 mg, 164 µmol, 58%, 99.0% *ee*).

(–)-(1*S*)-3-(*tert*-Butoxycarbonyl)-1-(chloromethyl)-8-cyano-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole [(–)-(1*S*)-24a]: Pd/C (10%, 140 mg, 129 µmol, 0.1 equiv. based on Pd) was added to a solution of (–)-(1*S*)-**22a** (250 mg, 557 µmol, 1.0 equiv.) in anhydrous EtOAc (17 mL). The mixture was flushed with argon and H_2, and the mixture was stirred at room temperature under H_2 for 5 h. The reaction mixture was filtered through Celite, the filter cake was washed with EtOAc (800 mL), and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; PE/EtOAc, 5:1) afforded (–)-(1*S*)-**24a** as a yellow solid (179 mg, 499 µmol, 90%). ^1H NMR (300 MHz, $[D_6]DMSO$): δ = 1.54 [s, 9 H, $C(CH_3)_3$], 3.77–4.31 (m, 5 H, 1-H, 2-H_2, 10-H_2), 7.50 (dd, *J* = 1.5, 8.7 Hz, 1 H, 7-H), 7.72 (br. s, 1 H, 4-H), 8.18 (d, *J* = 8.7 Hz, 1 H, 6-H), 8.41 (dd, *J* = 0.5, 1.5 Hz, 1 H, 9-H), 10.88 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $[D_6]DMSO$): δ = 27.98 [$C(CH_3)_3$], 47.86 (C-1), 52.50 (C-2), 61.92 (C-10), 80.8 [$C(CH_3)_3$], 101.0 (C-4), 109.7 (C-8), 114.1 (C-9b), 119.2 (CN), 122.0 (C-5a), 122.5 (C-7), 124.5 (C-6), 128.8 (C-9), 129.2 (C-9a), 143.2 (C-3a), 151.5 (C=O), 154.6 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 3350, 2230, 1676, 1626, 1595, 1513, 1422, 1369, 1223, 1144 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 210.5 (4.221), 229.5 (4.369), 269.0 (4.787), 312.5 (3.826), 323.5 (3.861), 381.0 (3.428) nm. ESI-HRMS: *m*/*z* = 381.09764 $[M + Na]^+$; $C_{19}H_{19}ClN_2O_3$ requires 381.09764.

Chromatographic Resolution of (–)-(1*S*)-24a: A solution of (–)-(1*S*)-**24a** (250 mg, 697 µmol) in a mixture of *n*-hexane/*i*PrOH (1:1, 10 mL) was separated consecutively (injection volume: 0.5 mL) by semipreparative HPLC (Chiralpak IA; 250 × 20 mm; particle size: 5 µm; *n*-hexane/*i*PrOH, 98:2; flow: 18 mL min^{-1}; UV detector: λ = 250 nm) to provide (–)-(1*S*)-**24a** (t_R = 19.4 min), $[\alpha]_D^{20}$ = –20.0 (*c* = 0.5 in $CHCl_3$).

(+)-(1*S*)-3-(*tert*-Butoxycarbonyl)-1-[(1*R*)-1-chloroethyl]-7-cyano-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole [(+)-(1*S*,10*R*)-24b]: A solution of (+)-(1*S*,10*R*)-**22b** (130 mg, 281 µmol, 1.0 equiv.) in anhydrous THF (9 mL) was warmed to 40 °C and Pd/C (10%, 30 mg, 28 µmol, 0.1 equiv. based on Pd) was added. A solution of NH_4CHO_2 in H_2O (25%, 0.30 mL) was added dropwise, and the mixture was stirred at 40 °C for 25 min. The mixture was filtered through Celite, the filter cake was washed with acetone (300 mL), and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; PE/EtOAc, 10:1→5:1→3:1) afforded (+)-(1*S*,10*R*)-**24b** as a white solid (92 mg, 247 µmol, 88%). $[\alpha]_D^{20}$ = +22.8 (*c* = 0.5 in $CHCl_3$). ^1H NMR (300 MHz, $[D_6]DMSO$): δ = 1.54 [s, 9 H, $C(CH_3)_3$], 1.58 (d, *J* = 6.8 Hz, 3 H, 11-H_3), 3.98–4.16 (m, 3 H, 1-H, 2-H_2), 4.71 (m_c, 1 H, 10-H), 7.65 (m_c, 2 H, 4-H, 8-H), 7.93 (d, *J* = 8.8 Hz, 1 H, 9-H), 8.46 (d, *J* = 1.2 Hz, 1 H, 6-H), 10.89 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $[D_6]DMSO$): δ = 22.92 (C-11), 27.96 [$C(CH_3)_3$], 44.07 (C-1), 49.46 (C-2), 61.24 (C-10), 80.93 [$C(CH_3)_3$], 99.61 (C-4), 103.8 (C-7), 114.7 (C-9b), 119.6, 119.9 (C-5a, CN), 123.9 (C-9), 127.2 (C-8), 129.5 (C-6), 131.3 (C-9a), 144.7 (C-3a), 151.3 (C=O), 155.1 (C-5) ppm. UV (CH_3CN): λ_{max} (lg ε) = 214.5 (4.347), 271.5 (4.820), 355.5 (4.148) nm. IR (KBr): $\tilde{\nu}$ = 3361 (C=O), 2978, 2221 (CN), 1687 (C=O), 1623, 1577 cm^{-1}. ESI-HRMS: *m*/*z* = 373.1314 $[M + H]^+$; $C_{20}H_{21}ClN_2O_3$ requires 373.1314.

(1*S*)-1-(Chloromethyl)-8-cyano-3-({5-[2-(dimethylamino)ethoxy]indol-2-yl}carbonyl)-1,2-dihydro-3*H*-benz[*e*]indol-5-yl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside [(+)-(1*S*)-27a]: A mixture of the phenol (–)-(1*S*)-**24a** (283 mg, 663 µmol, 1.00 equiv.) in dry CH_2Cl_2 (20 mL) and freshly activated molecular sieves (4 Å, 2.00 g) was stirred at room temperature for 30 min. After addition of the trichloroacetimidate **25** (427 mg, 870 µmol, 1.3 equiv.) and cooling to –10 °C, the promoter $BF_3\cdot OEt_2$ (50 µL) in dry CH_2Cl_2 (4 mL) was added dropwise, and the mixture was stirred for 3.5 h. Additional $BF_3\cdot OEt_2$ (250 µL) in CH_2Cl_2 (4 mL) was then added, and the mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was transferred by cannula into a new flask for separation of the molecular sieves, which were washed with CH_2Cl_2 (30 mL). The obtained organic solution was concentrated in vacuo, and the residue was dissolved in DMF (38 mL) and cooled to 0 °C. EDC·HCl (450 mg, 2.36 mmol, 3.5 equiv.) and DMAI·HCl (**26**, 336 mg, 1.35 mmol, 2.0 equiv.) were added, and the reaction mixture was stirred at room temperature for 18 h. After dilution with EtOAc (70 mL), H_2O (70 mL) and saturated aqueous $NaHCO_3$ (70 mL) were added, and the aqueous phase was extracted with EtOAc (4× 150 mL). The combined organic layers were washed with brine (4× 200 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; CH_2Cl_2/MeOH, 6:1) afforded (+)-(1*S*)-**27a** as a white solid (340 mg, 416 µmol, 53%). $[\alpha]_D^{20}$ = +6.0 (*c* = 0.3 in $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 2.01 [s, 6 H, 2× C(O)CH_3], 2.03 [s, 3 H, C(O)CH_3], 2.16 [s, 3 H, C(O)CH_3], 2.37 (s, 6 H, NMe_2), 2.79 (t, *J* = 5.7 Hz, 2 H, 2′′-H_2), 3.55 (dd, *J* = 11.5, 10.0 Hz, 1 H, 10-H_a), 3.78–3.85 (m, 1 H, 1-H), 3.90 (dd, *J* = 11.5, 3.2 Hz, 1 H, 10-H_b), 4.05–4.23 (m, 5 H, 1′′-H_2, 5′′′-H, 6′′′-H_2), 4.69–4.75 (m, 1 H, 2-H_a), 4.84 (dd, *J* = 10.6, 2.0 Hz, 1 H, 2-H_b), 4.99 (dd, *J* = 10.5, 3.2 Hz, 1 H, 3′′′-H), 5.27 (d, *J* = 7.9 Hz, 1 H, 1′′′-H), 5.38 (d, *J* = 3.3 Hz, 1 H, 4′′′-H), 5.63 (dd, *J* = 10.5, 7.9 Hz, 1 H, 2′′′-H), 7.03–7.06 (m, 2 H, 3′-H, 6′-H), 7.14 (d, *J* = 2.2 Hz, 1 H, 4′-H), 7.37 (d, *J* = 8.9 Hz, 1 H, 7′-H), 7.53 (dd, *J* = 8.7, 1.5 Hz, 1 H, 7-H), 8.08 (d, *J* = 0.8 Hz, 1 H, 9-H), 8.21 (d, *J* = 8.7 Hz, 1 H, 6-H), 8.51 (s, 1 H, 4-H), 10.05 (s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.63, 20.69, 20.72, 20.84 [4× C(O)*C*H_3], 45.84 (NMe_2), 45.96 (C-10), 54.99 (C-2), 58.35 (C-2′′), 61.16 (C-6′′′), 66.33 (C-1′′), 66.78 (C-4′′′), 68.43 (C-2′′′), 70.51 (C-3′′′), 71.20 (C-1), 99.02 (C-1′′′), 103.52 (C-4′), 103.9 (C-4), 106.4 (C-6′*), 111.6 (C-5a), 112.7 (C-7′), 117.8 (C-3′*), 118.6 (C-8), 118.8, 124.4 (C-5a, C-9b), 124.8 (C-6), 125.0 (C-7), 128.0 (C-9), 128.2, 128.7, 130.0, 131.5 (CN, C-2′, C-3a′, C-7a′), 143.7 (C-3a), 153.3 (C-5), 153.9 (C-5′), 160.8 (C=O), 169.5, 169.7, 170.0, 170.3 [4× *C*(O)CH_3] ppm. IR (KBr): $\tilde{\nu}$ = 3406 (NH), 2942, 2229 (CN), 1754 (C=O), 1626, 1521, 1457, 1396, 1226 cm^{-1}. UV (CH_3CN): λ_{max} (lg*ε*) = 212.5 (4.712), 261.5 (4.431), 302.0 (4.546), 399.0 (4.519) nm. ESI-HRMS: *m*/*z* = 819.2651 $[M + H]^+$; $C_{41}H_{43}ClN_4O_{12}$ requires 819.2639.

(+)-(1*S*)-1-[(1*R*)-1-Chloroethyl]-7-cyano-3-({5-[2-(dimethylamino)ethoxy]indol-2-yl}carbonyl)-1,2-dihydro-3*H*-benz[*e*]indol-5-yl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside [(+)-(1*S*,10*R*)-27b]: A mixture of the phenol (+)-(1*S*,10*R*)-**24b** (218 mg, 585 µmol, 1.00 equiv.) in dry CH_2Cl_2 (29 mL) and freshly activated molecular sieves (4 Å, 1.50 g) was stirred at room temperature for 30 min. After addition of the trichloroacetimidate **25** (317 mg, 643 µmol, 1.1 equiv.) and cooling to –10 °C, the promoter BF_3·OEt_2 (37 µL, 292 µmol, 0.5 equiv.) in dry CH_2Cl_2 (2.9 mL) was added dropwise, and the mixture was stirred for 3.5 h. Additional BF_3·OEt_2 (222 µL, 1.75 mmol, 3.0 equiv.) in CH_2Cl_2 (2.8 mL) was then added, and the mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was transferred by cannula into a new flask for separation of the molecular sieves, which were washed with CH_2Cl_2 (2× 20 mL). The obtained organic solution was concentrated in vacuo, and the residue was dissolved in DMF (29 mL) and cooled to 0 °C. EDC·HCl (336 mg, 1.75 mmol, 3.0 equiv.) and DMAI·HCl (**26**, 250 mg, 878 µmol, 1.5 equiv.) were added, and the reaction mixture was stirred at room temperature for 18 h. After dilution with EtOAc (50 mL), H_2O (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added, and the aqueous phase was extracted with EtOAc (4× 100 mL). The combined organic layers were washed with brine (4× 200 mL) and dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; CH_2Cl_2/MeOH, 10:1) afforded (+)-(1*S*,10*R*)-**27b** as a white solid (254 mg, 305 µmol, 52%). $[\alpha]_D^{20}$ = +6.7 (*c* = 0.3 in $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 1.63 (d, *J* = 6.7 Hz, 3 H, 11-H_3), 2.00 [s, 3 H, C(O)CH_3], 2.02 [s, 3 H, C(O)CH_3], 2.06 [s, 3 H, C(O)CH_3], 2.19 [s, 3 H, C(O)CH_3], 2.39 (s, 6 H, NMe_2), 2.81 (t, *J* = 5.6 Hz, 2 H, 2′′-H_2), 4.02–4.07 (m, 2 H, 1-H, 5′′′-H), 4.11–4.23 (m, 4 H, 1′′-H_2, 6′′′-H_2), 4.52 (m_c, 1 H, 10-H), 4.63 (m_c, 1 H, 2-H_a), 4.86 (dd, *J* = 10.6, 2.1 Hz, 1 H, 2-H_b), 5.10 (dd, *J* = 10.5, 3.5 Hz, 1 H, 3′′′-H), 5.30 (d, *J* = 8.0 Hz, 1 H, 1′′′-H), 5.44 (m_c, 1 H, 4′′′-H), 5.66 (dd, *J* = 10.5, 8.0 Hz, 1 H, 2′′′-H), 7.01–7.06 (m, 2 H, 3′-H, 6′-H), 7.13 (d, *J* = 2.3 Hz, 1 H, 4′-H), 7.36 (d, *J* = 8.9 Hz, 1 H, 7′-H), 7.62 (dd, *J* = 8.7, 1.5 Hz, 1 H, 8-H), 7.75 (d, *J* = 8.7 Hz, 1 H, 9-H), 8.43 (br. s, 1 H, 4-H), 8.51 (d, *J* = 1.5 Hz, 1 H, 6-H), 9.62 (br. s, 1 H, NH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.6 (3 signals), 20.7 [4× C(O)*C*H_3], 23.69 (C-11), 45.74 (NMe_2), 47.15 (C-1), 53.06 (C-2), 58.25 (C-2′′), 59.32 (C-10), 61.09 (C-6′′′), 66.26 (C-1′′), 66.74 (C-4′′′), 68.46 (C-2′′′), 70.58 (C-3′′′), 71.19 (C-5′′′), 99.44 (C-1′′′), 103.3, 103.5 (C-4, C-4′), 106.3 (C-3′), 107.4 (C-7), 112.8 (C-7′), 117.7 (C-6′), 119.2, 119.4, 122.6 (C-5a, C-9b, CN), 123.6 (C-9), 128.1, 128.2 (C-8, C-3a′), 129.8, 130.1, 131.1, 131.6 (C-6, C-9a, C-2′, C-7a′), 145.3 (C-3a), 153.7, 153.9 (C-5, C-5′), 160.7 (C=O), 169.4, 170.0, 170.2, 170.5 [4× *C*(O)CH_3] ppm. IR (KBr): $\tilde{\nu}$ = 3406 (NH), 2940, 2226 (CN), 1752 (C=O), 1624, 1521, 1457 cm^{-1}. UV (CH_3CN): λ_{max} (lg*ε*) = 218.0 (4.656), 266.5 (4.415), 309.0 (4.487), 359.0 (4.540) nm. ESI-HRMS: *m*/*z* = 833.2795 $[M + H]^+$; $C_{42}H_{45}ClN_4O_{12}$ requires 833.2796.

(+)-(1*S*)-8-(Aminomethyl)-1-(chloromethyl)-3-({5-[2-(dimethylamino)ethoxy]indol-2-yl}carbonyl)-1,2-dihydro-3*H*-benz[*e*]indol-5-yl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside [(+)-(1*S*)-28a]: A solution of (+)-(1*S*)-**27a** (50 mg, 61 µmol, 1.0 equiv.) in anhydrous EtOH (3 mL) was flushed with argon, and a solution of HCl in EtOH (1.25 M, 98 µL, 122 µmol, 2.0 equiv.), H_2O (0.15 mL) and PtO_2·H_2O (3.0 mg, 12.2 µmol, 0.2 equiv.) were added. The mixture was stirred at room temperature under H_2 for 48 h and then filtered through Celite, with washing with MeOH (200 mL), and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; CH_2Cl_2/MeOH, 5:1) afforded (+)-(1*S*)-**28a** as a white solid (33 mg, 40 µmol, 66%). $[\alpha]_D^{20}$ = +2.0 (*c* = 0.3 in DMSO). ^1H NMR (600 MHz, $[D_6]$DMSO): δ = 1.98 [s, 3 H, C(O)CH_3], 2.01 [s, 3 H, C(O)CH_3], 2.04 [s, 3 H, C(O)CH_3], 2.18 [s, 3 H, C(O)CH_3], 2.24 (s, 6 H, NMe_2), 2.65 (t, *J* = 5.8 Hz, 2 H, 2′′-H_2), 3.89–3.97 (m, 3 H, C*H*$_2$$NH_2$, 10-$H_a$), 4.07 (t, *J* = 5.9 Hz, 2 H, 1′′-H_2), 4.14 (m, 3 H, 6′′′-H_2, 10-H_b), 4.26 (m, 1 H, 1-H), 4.49 (m, 1 H, 5′′′-H), 4.57–4.62 (m, 1 H, 2-H_a), 4.83 (m, 1 H, 2-H_b), 5.38–5.46 (m, 3 H, 2′′′-H, 3′′′-H, 4′′′-H), 5.56 (m, 1 H, 1′′′-H), 6.92 (dd, *J* = 8.9, 2.3 Hz, 1 H, 6′-H), 7.10 (s, 1 H, 3′-H), 7.17 (d, *J* = 2.1 Hz, 1 H, 4′-H), 7.41 (d, *J* = 8.9 Hz, 1 H, 7′-H), 7.44 (d, *J* = 8.7 Hz, 1 H, 7-H), 7.86 (s, 1 H, 9-H), 7.90 (d, *J* = 8.7 Hz, 1 H, 6-H), 8.18 (s, 1 H, 4-H), 11.55 (s, 1 H, NH) ppm. ^{13}C NMR (125 MHz): δ = 20.29, 20.34, 20.50 [4× C(O)*C*H_3], 40.09 (C-1), 41.14 (C-10), 45.51 (*C*$H_2$$NH_2$), 47.42 ($NMe_2$), 55.01 (C-2), 57.76 (C-2′′), 60.94 (C-1′′), 66.22 (C-6′′′), 67.03, 68.49, 69.66, 70.29 (C-2′′′, C-3′′′, C-4′′′, C-5′′′), 98.90 (C-1′′′), 101.6 (C-4), 103.1 (C-4′), 105.2 (C-3′), 113.1 (C-7′), 115.7 (C-6′), 118.8, 121.2, 127.3, 129.5, 130.7, 131.5 (C-5a, C-9a, C-9b, C-8, C-2′, C-3a′, C-7a′), 121.6 (C-6), 124.5 (C-7), 141.8 (C-3a), 152.6, 152.8 (C-5, C-5′), 160.1 (C=O), 169.2, 169.3, 169.7, 169.8 [4× *C*(O)CH_3] ppm. IR (KBr): $\tilde{\nu}$ = 3421 (NH), 1749 (C=O), 1628, 1519, 1404 cm^{-1}. UV (CH_3CN): λ_{max} (lg*ε*) = 206.0 (4.461), 300.0 (4.312), 336.0 (4.249) nm. ESI-HRMS: *m*/*z* = 823.2941 $[M + H]^+$; $C_{41}H_{47}ClN_4O_{12}$ requires 823.2952.

(+)-(1*S*)-7-(Aminomethyl)-1-[(1*R*)-1-chloroethyl]-3-({5-[2-(dimethylamino)ethoxy]indol-2-yl}carbonyl)-1,2-dihydro-3*H*-benz[*e*]indol-5-yl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside [(+)-(1*S*,10*R*)-28b]: A solution of (+)-(1*S*,10*R*)-**27b** (50 mg, 60 µmol, 1.0 equiv.) in anhydrous EtOH (3 mL) was flushed with argon, and a solution of HCl in EtOH (1.25 M, 96 µL, 120 µmol, 2.0 equiv.), H_2O (0.15 mL) and PtO_2·H_2O (3.0 mg, 12.0 µmol, 0.2 equiv.) were added. The mixture was stirred at room temperature under H_2 for 48 h and was then filtered through Celite, with washing with MeOH (100 mL), and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; CH_2Cl_2/MeOH, 5:1) afforded (+)-(1*S*,10*R*)-**28b** as a white solid (41 mg, 49 µmol, 82%). $[\alpha]_D^{20}$ = +4.4 (c = 0.25 in DMSO). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 1.64 (d, J = 6.3 Hz, 3 H, 11-H$_3$), 1.98, 1.99, 2.06, 2.18 [4× s, 12 H, 4× C(O)CH$_3$], 2.25 (m$_c$, 6 H, NMe$_2$), 2.67 (m$_c$, 2 H, 2′′-H$_2$), 3.93–4.19 (m, 6 H, 1′′-H$_2$, 6′′′-H$_2$, C*H*$_2$NH$_2$), 4.27 (m$_c$, 1 H, 1-H), 4.45–4.53 (m, 1 H, 5′′′-H), 4.58–4.65 (m, 1 H, 2-H$_a$), 4.73–4.84 (m, 2 H, 2-H$_b$, 10-H), 5.35–5.48 (m, 3 H, 2′′′-H, 3′′′-H, 4′′′-H), 5.59 (d, J = 7.5 Hz, 1 H, 1′′′-H), 6.92 (m$_c$, 1 H, 6′-H), 7.14–7.20 (m, 2 H, 3′-H, 4′-H), 7.40–7.44 (m, 1 H, 7′-H), 7.72–7.79 (m, 1 H, 6-H), 7.93 (br. s, 1 H, 9-H*), 8.03 (d, J = 8.6 Hz, 1 H, 8-H*), 8.24 (br. s, 1 H, 4-H), 11.57 (m$_c$, 1 H, NH) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 20.30 (3 signals), 20.60 [4× C(O)*C*H$_3$], 23.29 (C-11), 44.29 (*C*H$_2$NH$_2$), 45.45 (NMe$_2$), 45.92 (C-1), 52.07 (C-2), 57.74 (C-2′′), 61.03, 61.25 (C-10, C-6′′′), 66.24 (C-1′′), 67.14, 68.66, 69.89 (C-2′′′, C-3′′′, C-4′′′), 70.43 (C-5′′′), 99.16 (C-1′′′), 102.8 (C-4), 103.3 (C-4′), 105.6 (C-3′), 113.2 (C-7′), 115.9 (C-6′), 120.2, 121.4, 122.4, 123.5 (C-7, C-8, C-9, C-9b*), 127.5, 127.9, 128.8, 130.7, 131.8, 134.5 (C-6, C-5a*, C-9a, C-2′, C-3a′, C-7a′), 141.9 (C-3a), 152.6, 153.0 (C-5, C-5′), 160.2 (C=O), 169.4, 169.6, 169.9, 170.0 [4× *C*(O)CH$_3$] ppm. IR (KBr): ṽ = 3417 (NH), 1750 (C=O), 1624, 1520, 1471, 1409 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 202.5 (4.555), 249.0 (4.248), 298.0 (4.343), 337.5 (4.331) nm. ESI-HRMS: m/z = 837.3108 [M + H]$^+$; $C_{42}H_{49}ClN_4O_{12}$ requires 837.3109.

(1*S*)-8-(Aminomethyl)-1-(chloromethyl)-3-({5-[2-(dimethylamino)-ethoxy]indol-2-yl}carbonyl)-1,2-dihydro-3*H*-benz[*e*]indol-5-yl β-D-Galactopyranoside [(1*S*)-3a]: A solution of NaOMe in MeOH (5.4 M, 8.5 µL, 46 µmol, 2.0 equiv.) was added at 0 °C to a solution of (+)-(1*S*)-**28a** (19 mg, 23 µmol, 1.0 equiv.) in MeOH (3 mL). The mixture was allowed to warm to room temperature and stirred for 30 min. MeOH (1 mL), H_2O (1 mL) and Amberlite IR-120 were then added (pH = 7). The mixture was filtered, the filter cake was washed with MeOH (25 mL), and the filtrate was concentrated in vacuo. The residue was dissolved in H_2O + 0.1% CF_3CO_2H/CH_3CN (4:1) (4 mL) and purified by prep. HPLC to afford **3a** as a white solid (12.7 mg, 19.4 µmol, 84%). ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 2.90 (s, 6 H, NMe$_2$), 3.44–4.21 (m, 7 H, 1′′-H, 2′′′-H, 3′′′-H, 4′′′-H, 5′′′-H, 6′′′-H), 4.20–4.31 (m, 3 H, C*H*$_2$NH$_2$, 1-H), 4.31–4.40 (m, 2 H, 2′′-H$_2$), 4.57–4.66 (m, 2 H, 10-H$_2$), 4.82–4.93 (m, 3 H, 2-H$_2$, 1′′′-H), 7.01 (dd, J = 8.9, 2.4 Hz, 1 H, 6′-H), 7.14 (d, J = 1.6 Hz, 1 H, 3′-H), 7.26 (d, J = 2.3 Hz, 1 H, 4′-H), 7.45 (d, J = 8.9 Hz, 1 H, 7′-H), 7.49 (dd, J = 8.8, 1.3 Hz, 1 H, 7-H), 8.01 (s, 1 H, 9-H), 8.37 (d, J = 8.7 Hz, 1 H, 6-H), 8.42 (s, 1 H, 4-H), 11.74 (s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 41.29 (C-1), 42.30 (*C*H$_2$NH$_2$), 42.80 (NMe$_2$), 47.27 (C-10), 54.89 (C-2), 55.55 (C-1′′), 59.45 (C-6′′′), 62.72 (C-2′′), 67.40, 70.38, 73.02, 75.05 (C-2′′′, C-3′′′, C-4′′′, C-5′′′), 102.1 (C-1′′′), 103.9 (C-4′), 105.2 (C-3′), 113.2 (C-7′), 115.6 (C-6′), 117.8 (C-4*), 122.3 (C-9b), 122.5 (C-9), 123.7 (C-6), 124.1 (C-7), 127.2, 129.1, 131.0, 131.9, 133.1 (C-5a, C-9a, C-2′, C-3a′, C-7a′, C-8), 142.5 (C-3a), 151.9, 153.6 (C-5, C-5′), 160.1 (C=O) ppm. ESI-HRMS: m/z = 655.2526 [M + H]$^+$; $C_{33}H_{39}ClN_4O_8$ requires 655.2529.

(–)-(1*S*)-7-(Aminomethyl)-1-[(1*R*)-1-chloroethyl]-3-({5-[2-(dimethylamino)ethoxy]indol-2-yl}carbonyl)-1,2-dihydro-3*H*-benz[*e*]indol-5-yl β-D-Galactopyranoside Bis(trifluoroacetate) [(–)-(1*S*,10*R*)-3b]: A solution of NaOMe in MeOH (5.4 M, 44 µL, 239 µmol, 2.0 equiv.) was added at 0 °C to a solution of (+)-(1*S*,10*R*)-**28b** (100 mg, 119 µmol, 1.0 equiv.) in MeOH (12 mL). The reaction mixture was allowed to warm to room temperature and stirred for 30 min. MeOH (4 mL), H_2O (4 mL) and Amberlite IR-120 were added (pH = 7). The reaction mixture was filtered, the filter cake was washed with MeOH (120 mL), and the filtrate was concentrated in vacuo. The residue was dissolved in H_2O + 0.1% CF_3CO_2H/CH_3CN (4:1) (12 mL) and purified by prep. HPLC to afford (–)-(1*S*,10*R*)-**3b** as a white solid (75 mg, 84 µmol, 70%). $[\alpha]_D^{20}$ = –9.0 (c = 0.3 in DMSO). ^{1}H NMR (600 MHz, [D$_6$]DMSO, 100 °C): δ = 1.65 (d, J = 6.5 Hz, 3 H, 11-H$_3$), 2.90 (s, 6 H, NMe$_2$), 3.48–3.55, 3.56–3.64 (2× m, 5 H, 2′′-H$_2$, 3′′′-H, 5′′′-H, 6′′′-Ha), 3.67–3.73 (m, 1 H, 6′′′-H$_b$), 3.82–3.89 (m, 2 H, 2′′′-H, 4′′′-H), 4.18–4.29 (m, 3 H, 1-H, C*H*$_2$NH$_3^+$), 4.36 (m$_c$, 2 H, 1′′-H$_2$), 4.62–4.67 (m, 1 H, 2-H$_a$), 4.74 (m$_c$, 1 H, 2-H$_b$), 4.82 (m$_c$, 1 H, 10-H), 4.97 (d, J = 7.6 Hz, 1 H, 1′′′-H), 7.02 (m$_c$, 1 H, 6′-H), 7.15 (d, J = 1.8 Hz, 1 H, 3′-H), 7.28 (br. s, 1 H, 4′-H), 7.47 (d, J = 8.9 Hz, 1 H, 7′-H), 7.64 (d, J = 8.8 Hz, 1 H, 8-H), 8.03 (d, J = 8.6 Hz, 1 H, 9-H), 8.24 (br. s, 1 H, 4-H), 8.41 (br. s, 1 H, 6-H), 11.52 (s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 23.28 (C-11), 42.65 (*C*H$_2$NH$_3^+$), 42.84 (NMe$_2$), 45.89 (C-1), 52.03 (C-2), 55.60 (C-2′′), 59.60 (C-6′′′), 61.27 (C-10), 62.81 (C-1′′), 67.48, 70.56 (C-2′′′, C-4′′′), 73.01, 75.20 (C-3′′′, C-5′′′), 101.9 (C-4), 102.2 (C-1′′′), 104.1 (C-4′), 105.5 (C-3′), 113.3 (C-7′), 115.7 (C-6′), 118.8, 122.5 (C-7, C-9b), 123.6 (C-9), 123.8 (C-6), 127.4, 127.7, 129.1, 129.2, 131.1, 132.1 (C-5a, C-8, C-9a, C-2′, C-3a′, C-7a′), 142.6 (C-3a), 152.0, 153.7 (C-5, C-5′), 158.1 [q, $^2J_{C,F}$ = 32 Hz, CF$_3$*C*(O)], 160.1 (C=O) ppm. IR (KBr): ṽ = 3406 (NH), 1679, 1624, 1521, 1472, 1412 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 207.5 (4.416), 250.5 (4.158), 299.0 (4.247), 337.5 nm (4.230). ESI-HRMS: m/z = 669.2686 [M – 2× CF_3CO_2 – H]$^+$; $C_{38}H_{43}ClF_6N_4O_{12}$ requires 669.2685.

Synthesis of the Fluorescein-Labelled Compound (1*S*)-30a: A solution of **3a** (11.9 mg, 18.2 µmol, 1.3 equiv.) and *i*Pr$_2$NEt (11 µL, 14.5 µg, 66 µmol, 4.5 equiv.) in anhydrous DMF (150 µL) was added to a solution of **29** (8.90 mg, 15.2 µmol, 1.0 equiv.) in anhydrous DMF (150 µL), and the mixture was stirred at room temperature for 18 h; then H_2O + 0.1% CF_3CO_2H (3.0 mL) and CH_3CN (2.5 mL) were added, and the compound was purified by prep. HPLC to afford (1*S*)-**30a** as a yellow solid (7.8 mg, 6.9 µmol, 46%). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 1.08–1.70 (m, 6 H, 3^S-H$_2$, 4^S-H$_2$, 5^S-H$_2$), 2.20 (m, 2 H, 2^S-H), 2.87 (s, 6 H, NMe$_2$), 3.18–4.26 (m, 13 H, 2′′′-H, 3′′′-H, 4′′′-H, 5′′′-H, 6′′′-H$_2$, 10-H$_2$, 1-H, 6^S-H$_2$, 1′′-H$_2$), 4.37 (m, 2 H, 2′′-H), 4.47 (m, 2 H, Ar-C*H*$_2$), 4.59 (m, 1 H, 2-H$_a$), 4.85 (m, 1 H, 2-H$_b$), 4.90 (m, 1 H, 1′′′-H), 6.53–6.60 (m, 4 H, Ar-H), 6.69 (d, J = 2.1 Hz, 1-H, Ar-H), 7.01 (dd, J = 8.9, 2.4 Hz, 1 H, 6′-H), 7.18 (m, 1 H, 3′-H), 7.27 (d, J = 2.1 Hz, 1 H, 4′-H), 7.30–7.38 (m, 2 H, 7′-H, Ar-H), 7.45 (d, J = 8.9 Hz, 1 H, 7-H), 7.72 (m, 1 H, Ar-H), 8.24 (m, 1 H, Ar-H), 8.30 (d, J = 8.8 Hz, 1 H, 6-H), 8.41 (t, J = 6.0 Hz, 1 H, Ar-H), 8.45 (d, J = 9.6 Hz, 1 H, Ar-H), 8.79 (t, J = 5.4 Hz, 1 H, Ar-H), 9.75, 10.05 (s, 2 H, OH, CO$_2$ H), 11.70 (s, 1 H, indole-NH) ppm. ESI-HRMS: m/z = 1126.3832 [M + H]$^+$; $C_{60}H_{60}ClN_5O_{15}$ requires 1126.3847.

Chromatographic Resolution of (1*S*)-30a: Compound (1*S*)-**30a** was separated consecutively (injection volume: 2.0 mL) by semipreparative HPLC [Kromasil 100 C18; 250 × 20 mm; particle size: 7 µm; gradient: H_2O (0.1% CF_3CO_2H)/CH_3CN, 83:17 for 60 min, then H_2O (0.1% CF_3CO_2H)/CH_3CN, 50:50 for 10 min, then H_2O (0.1% CF_3CO_2H)/CH_3CN, 83:17 for 10 min; flow: 12 mL min^{-1}; UV detector: λ = 250 nm] to provide (1*S*)-**30a** (t_R = 33.1 min).

Synthesis of the Fluorescein-Labelled Compound (1*S*,10*R*)-30b: A solution of (–)-(1*S*,10*R*)-**3b** (11.95 mg, 13.3 µmol, 1.0 equiv.) and *i*Pr$_2$NEt (11 µL, 14.5 µg, 66 µmol, 5.0 equiv.) in anhydrous DMF (150 µL) was added to a solution of **29** (8.28 mg, 14.1 µmol, 1.0 equiv.) in anhydrous DMF (150 µL), and the mixture was stirred at room temperature for 19 h; then H_2O + 0.1% CF_3CO_2H (3.0 mL) and CH_3CN (2.7 mL) were added, and the compound was purified by prep. HPLC to afford (1*S*,10*R*)-**30b** as a yellow solid (14.7 mg, 11.7 µmol, 88%). ^{1}H NMR (600 MHz, [D$_6$]DMSO, 80 °C): δ = 1.37–1.45 (m, 2 H, 4^{S}-H$_2$), 1.57–1.69 (m, 7 H, 11-H$_3$, 3^{S}-H$_2$, 5^{S}-H$_2$), 2.22 (m$_c$, 2 H, 2^{S}-H$_2$), 2.92 (s, 6 H, NMe$_2$), 3.34 (m$_c$, 2 H, 6^{S}-H$_2$), 3.47–3.63 (m, 5 H, 2′′-H$_2$, 3′′′-H, 5′′′-H, 6′′′-H$_a$), 3.67–3.72 (m, 1 H, 6′′′-H$_b$), 3.81–3.87 (m, 2 H, 2′′′-H, 4′′′-H), 4.22 (m$_c$, 1 H, 1-H), 4.36 (m$_c$, 2 H, 1′′-H$_2$), 4.45 (m$_c$, 2 H, ArC*H*$_2$), 4.63 (m$_c$, 1 H, 2-H$_a$), 4.71 (m$_c$, 1 H, 2-H$_b$), 4.81 (m$_c$, 1 H, 10-H), 4.93 (d, *J* = 7.5 Hz, 1 H, 1′′′-H), 6.56 (m$_c$, 4 H, 4× Ar-H), 6.70 (br. s, 2 H, 2× Ar-H), 7.02 (m$_c$, 1 H, 6′-H), 7.13 (d, *J* = 1.5 Hz, 1 H, 3′-H), 7.25–7.35, 7.44–7.51 (2× m, 4 H, 8-H, 4′-H, 7′-H, Ar-H), 7.91 (d, *J* = 8.7 Hz, 1 H, 9-H), 8.07–8.27 (m, 4 H, 4-H, 2× Ar-H, NH), 8.44 (br. s, 1 H, 6-H), 8.58 (br. s, 1 H, NH), 9.89, 9.59 (2× br. s, 2 H, OH, CO$_2$ H), 11.51 (br. s, 1 H, indole-NH) ppm. ESI-HRMS: *m*/*z* = 1140.4004 [M – 2× CF$_3$CO$_2$]$^+$; $C_{63}H_{63}ClF_3N_5O_{17}$ requires 1140.4004.

Chromatographic Purification of (1*S*,10*R*)-30b: Semipreparative HPLC [Kromasil 100 C18; 250 × 20 mm; particle size: 7 µm; gradient: H$_2$O (0.1% CF$_3$CO$_2$H)/CH$_3$CN, 83:17 for 60 min, then H$_2$O (0.1% CF$_3$CO$_2$H)/CH$_3$CN, 50:50 for 10 min, then H$_2$O (0.1% CF$_3$CO$_2$H)/CH$_3$CN, 83:17 for 10 min; flow: 12 mL min^{-1}; UV detector: λ = 250 nm; injection volume: 2.0 mL]. (1*S*)-**30a** (t_R = 36.6 min).

Synthesis of the Dapoxyl-Labelled Compound (–)-(1*S*,10*R*)-32: A solution of (–)-(1*S*,10*R*)-**3b** (25.0 mg, 27.9 µmol, 1.0 equiv.) and *i*Pr$_2$NEt (23 µL, 30.3 µg, 139 µmol, 5.8 equiv.) in anhydrous DMF (150 µL) was added to a solution of **31** (12.3 mg, 24.0 µmol, 1.0 equiv.) in anhydrous DMF (200 µL), and the mixture was stirred at room temperature for 9 h. H$_2$O (+ 0.1% CF$_3$CO$_2$H) (3.0 mL) and CH$_3$CN (2.5 mL) were added, and the compound was purified by prep. HPLC to afford (–)-(1*S*,10*R*)-**32** as a yellow solid (27.8 mg, 21.5 µmol, 89%). ^{1}H NMR (600 MHz, [D$_6$]DMSO, 80 °C): δ = 1.63 (d, *J* = 6.6 Hz, 3 H, 11-H$_3$), 2.40 (t, *J* = 7.4 Hz, 2 H, 2^{S}-H$_2$), 2.93 (s, 6 H, 2′′-NMe$_2$), 2.98 (s, 6 H, 12$^{\#}$-NMe$_2$), 3.14 (t, *J* = 7.4 Hz, 2 H, 3^{S}-H$_2$), 3.48 (dd, *J* = 9.6, 3.2 Hz, 1 H, 3′′′-H), 3.52–3.57 (m, 3 H, 5′′′-H, 2′′-H$_2$), 3.60 (dd, *J* = 10.6, 5.5 Hz, 1 H, 6′′′-H$_a$), 3.69 (dd, *J* = 10.6, 7.2 Hz, 1 H, 6′′′-H$_b$), 3.81–3.86 (m, 2 H, 2′′′-H, 4′′′-H), 4.20 (dt, *J* = 9.4, 2.6 Hz, 1 H, 1-H), 4.36 (t, *J* = 5.0 Hz, 2 H, 1′′-H$_2$), 4.42 (m$_c$, 2 H, 12-H$_2$), 4.62 (dd, *J* = 11.0, 2.6 Hz, 1 H, 2-H$_a$), 4.70 (dd, *J* = 11.0, 9.4 Hz, 1 H, 2-H$_b$), 4.79 (dq, *J* = 6.6, 3.0 Hz, 1 H, 10-H), 4.92 (d, *J* = 7.8 Hz, 1 H, 1′′′-H), 6.83 (d, *J* = 9.0 Hz, 2 H, 2× Ar-H), 7.01 (dd, *J* = 9.0, 2.2 Hz, 1 H, 6′-H), 7.12 (d, *J* = 2.0 Hz, 1 H, 3′-H), 7.28 (d, *J* = 2.2 Hz, 1 H, 4′-H), 7.45–7.48 (m, 2 H, 7′-H, 8-H), 7.54–7.56 (m, 2 H, 3^{S}-NH, 8$^{\#}$-H), 7.65 (d, *J* = 9.0 Hz, 2 H, 2× Ar-H), 7.89 (d, *J* = 8.5 Hz, 1 H, 9-H), 7.96 (d, *J* = 8.4 Hz, 2 H, 2× Ar-H), 8.18 (s, 1 H, 12-NH), 8.20–8.23 (m, 4 H, 4-H, 6-H, 2× Ar-H), 9.64 (br. s, 1 H, NH$^+$), 11.5 (s, 1 H, 1′-NH) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 23.4 (C-11), 35.5 (C-2^{S}), 38.7 (C-3^{S}), 40.1 (12$^{\#}$-NMe$_2$), 42.5 (C-12), 42.9 (2′′-NMe$_2$), 46.0 (C-1), 52.0 (C-2), 55.7 (C-2′′), 59.5 (C-6′′′), 61.4 (C-10), 62.7 (C-1′′), 67.5 (C-4′′′), 70.5 (C-2′′′), 73.1 (C-3′′′), 75.2 (C-5′′′), 101.8 (C-9b), 102.1 (C-1′′′), 104.0 (C-4′), 105.4 (C-3′), 112.1 (2× Ar-C), 113.3 (C-7′), 114.6 (*C*F$_3$CO$_2$), 115.6 (C-6′), 118.9 (C-5a), 121.4 (C-8$^{\#}$), 121.7 (C-4, C-6), 122.7 (C-7), 123.3 (C-9), 125.5 (2× Ar-C), 126.1 (2× Ar-C), 127.4 (C-8), 127.4 (2× Ar-C), 128.5 (C-4$^{\#}$), 130.2 (C-9$^{\#}$), 131.2 (C-9a), 132.0 (C-3a′), 134.7 (C-7a′), 141.1 (C-2′, C-1$^{\#}$), 141.6 (C-3a), 150.1 (C-7$^{\#}$), 152.0 (C-12$^{\#}$), 152.7 (C-5′), 153.4 (C-5), 157.5 (C-5$^{\#}$, 1′-C=O), 160.0 (CF$_3$*C*O$_2$), 169.6 (2^{S}-C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3406, 2924, 2819, 1675, 1616, 1510, 1407, 1161, 800 cm^{-1}. UV (MeOH): λ_{max} (lg ε) = 202.5 (4.821), 252.0 (4.514), 289.0 (4.546), 299.5 (4.582), 349.0 nm (4.627). ESI-HRMS: *m*/*z* = 1066.3778 [M – 2× CF$_3$CO$_2$]$^+$; $C_{56}H_{61}ClF_3N_7O_{14}S$ requires 1066.3782.

Chromatographic Purification of (–)-(1*S*,10*R*)-32: Semipreparative HPLC [Kromasil 100 C18; 250 × 20 mm; particle size: 7 µm; gradient: H$_2$O (0.1% CF$_3$CO$_2$H)/CH$_3$CN, 83:17 for 60 min, then H$_2$O (0.1% CF$_3$CO$_2$H)/CH$_3$CN, 50:50 for 10 min, then H$_2$O (0.1% CF$_3$CO$_2$H)/CH$_3$CN, 83:17 for 10 min; flow: 12 mL min^{-1}; UV detector: λ = 250 nm; injection volume: 2.0 mL]. (1*S*,10*R*)-**32** (t_R = 38.5 min). $[\alpha]_D^{20}$ = –14.0 (*c* = 0.15, MeOH).

Supporting Information (see footnote on the first page of this article): Experimental Section for the synthesis of molecules **7a**–**17c**.

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