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Enantio- and Diastereoselective Synthesis of Duocarmycine-Based Prodrugs for a Selective Treatment of Cancer by Epoxide Opening

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Dedicated to Professor Manfred T. Reetz on the occasion of his 65th birthday

Abstract: For the enantio- und diastereoselective synthesis of the prodrug **2**, the *N-tert*-butyloxycarbonyl-protected amine **7** was alkylated with the enantiopure epoxide **14** to give the amide **10**. A regio- and facial-selective metal-mediated cyclisation by using a cuprate led to **17** with an inversion of configuration at C10. Subsequent transformation of the hydroxy group in **17** by using the Appel procedure afforded (1*S*,10*R*)-**9** with an unusual double inversion owing to neighbouring-group participation of the *N-tert*-butoxycarbonyl group. (1*S*,10*R*)-**9** is the key intermediate in the synthesis of the prodrug **2**, which has been developed for a selective treatment of cancer based on the antibody-directed enzyme prodrug therapy as an analogue of the natural antibiotic duocarmycine SA (**1**).

Keywords: Appel reactions · cuprates · epoxides · prodrugs · total synthesis

Introduction

The natural antibiotic duocarmycine SA[1](**1**) is a highly potent cytostatic compound with an IC_{50} value of about 10 pM against different cancer cell lines and thus one of the strongest anticancer agents known so far. The mode of action is a specific alkylation of 3-N of adenine in DNA, which occurs with opening of the cyclopropane moiety and establishes an aromatic state of ring B in **1**.[2] We have developed novel prodrugs such as **2** that are based on the natural antibiotic duocarmycine (**1**) and tested them for their applicability in antibody-directed enzyme prodrug therapy (ADEPT; Scheme 1).[3,4] In this approach, the toxic effector is liberated from a prodrug such as **2** by an enzymatic cleavage with a conjugate of an appropriate enzyme and a monoclonal antibody that binds to tumour-associated antigens.

Prodrug **2** is one of the best prodrugs developed so far for ADEPT: it contains a dimethylaminoethoxyindol-2-carboxylic acid (DMAI) side chain[5] for binding to the minor groove of DNA as well as improving the water solubility by formation of a salt, and has β-galactose as a protecting group. This prodrug has a rather low cytotoxicity of IC_{50} = 3600 nM, but a very high cytotoxicity in the presence of the cleaving enzyme β-galactosidase to give the *seco*-drug **3**, which then leads to the final drug **6** with an IC_{50} value of 0.75 nM. It results in a QIC_{50} value of 4800,[6a] which together with the high cytotoxicity of **3**, makes **2** into a promising candidate for a selective treatment of cancer. The excellent results in vitro have been confirmed by experiments in vivo.[7] The diastereomeric prodrug **4** cannot be used as the cytotoxicity of the corresponding *seco*-drug **5** (enantiomer of **3**) is too low.

The tricyclic skeleton **9** of the prodrug **2** was obtained by a radical cyclisation of **8**, which was easily accessible by alkylation of **7** with 1,3-dichloro-2-butene (Scheme 2). However, the cyclisation is rather unselective leading to the two possible diastereomers as racemic mixtures **9a–d** in an almost 1:1:1:1 ratio.[6b] Although the diastereomers could be separated by chromatography on silica gel and resolution of both diastereomers was possible by chromatography on a chiral support (Chiralpak IA), this synthesis does not meet the requirements for efficiency and high yields to make the

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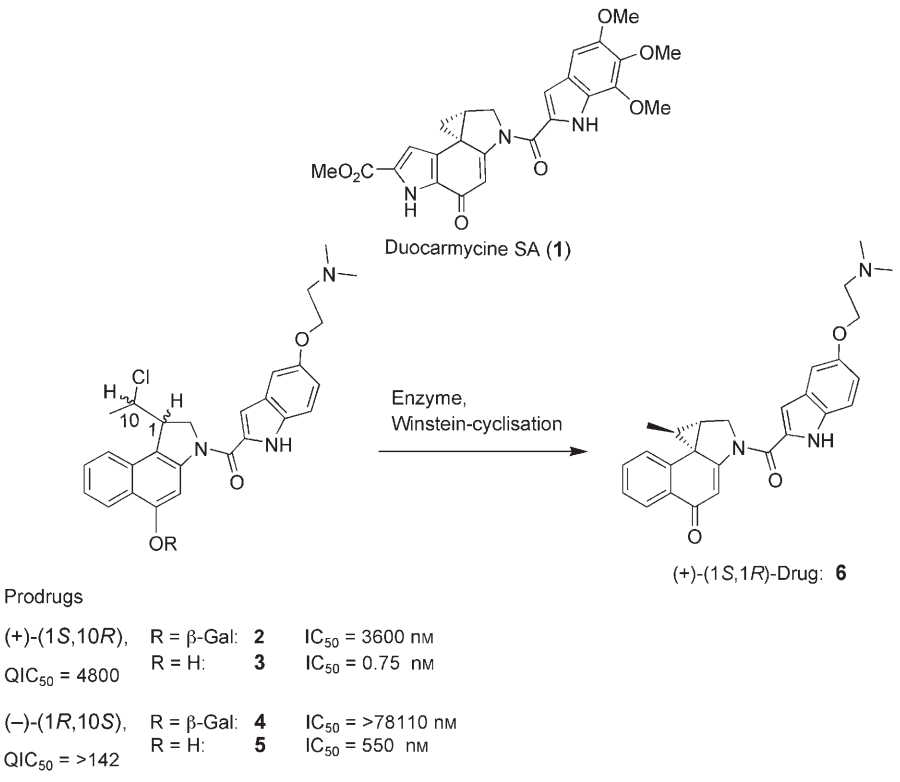
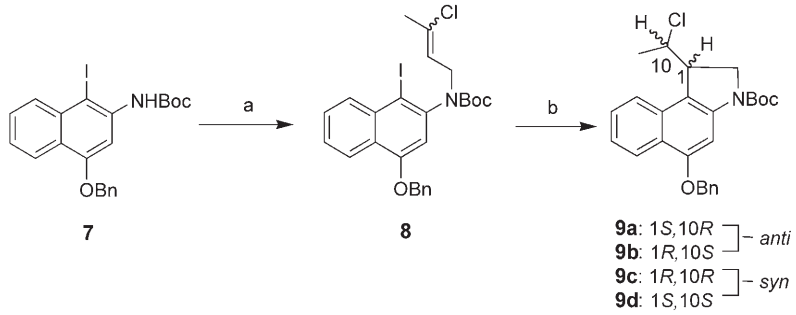


Scheme 1. Duocarmycine SA (**1**) and the prodrugs **2**–**5**.



Scheme 2. Former synthesis of **9**: a) NaH, DMF, RT, 1 h, then (*E*/*Z*)-1,3-dichloro-2-butene, DMF, RT, 2 h, 98 %; b) TTMSS, AIBN, toluene, 80 °C, 5 h. Yields: *anti*: 44 %, *syn*: 42 %, **9a**/**9b**/**9c**/**9d** ≈ 1:1:1:1. AIBN = azoisobutyronitrile, Bn = benzyl, TTMSS = tris(trimethylsilyl)silane.

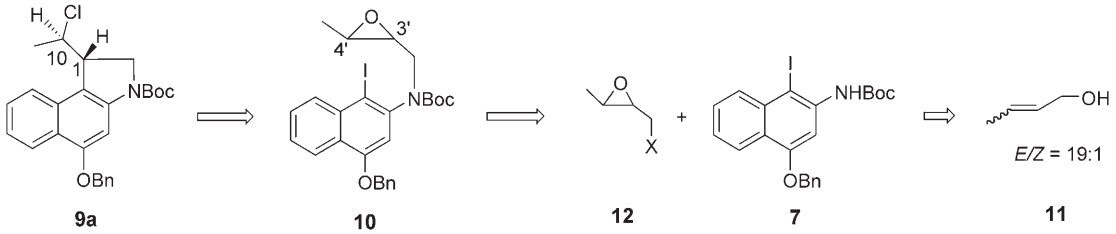
compound **2** available in the large quantities necessary for clinical trials.

Herein we describe a new synthetic approach towards (1*S*,10*R*)-**9a**, which gives direct access to the desired enantio- and diastereopure compound.

Results and Discussion

The retrosynthesis of the target molecule **9a** leads via the corresponding hydroxy compound (**9a**: OH instead of Cl) to the epoxy derivative **10**, which is accessible by N-alkylation of the naphthalene derivative **7** with the epoxide **12** (Scheme 3). The latter compound can be obtained from **11**. The epoxide **12** can exist as four stereoisomers. However, we have prepared and transformed only the enantiomeric epoxides (2*R*,3*R*)- and (2*S*,3*S*)-**12** as well as (3′*R*,4′*R*)-**10** and (3′*S*,4′*S*)-**10** as the substrate for the epoxidation **11** is available mainly as an *E* isomer. We assumed that the cyclisation reaction of **10** with opening of the epoxide would take place in an *anti* fashion with inversion of configuration at C3′. However, we did not know at that time, whether the Appel reaction[8] would occur with inversion, as usual, or with retention of configuration.

The known building block **7** was synthesised starting from the corresponding acid through a Curtius rearrangement and a Koenigstein iodination.[9] For the alkylation of **7** to give the desired amides **10**, 2,3-epoxybutanol derivatives **14** and **16a**–**e** with *R,R* and *S,S* configuration were synthesised starting from commercially available

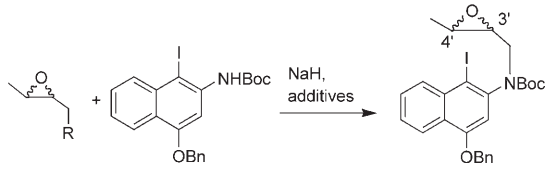


Scheme 3. Retrosynthetic analysis of **9a**.

crotylalcohol (*E*/*Z* mixture 19:1; **11**) by using the Sharpless–Katsuki procedure with L-(+)-diisopropyl tartrate and D-(−)-diethyl tartrate, respectively. The primarily formed (2*R*,3*R*)- and (2*S*,3*S*)-2,3-epoxyalcohols **13** and **15** were obtained with 71% *ee* and 74% *ee*, respectively, which corresponds with the literature.[10] A separation of the mixture of enantiomers to give the enantiopure compounds by chromatography on a chiral support on a multigram scale at this point proved to be unrealistic. The other two diastereomers (resulting from small amounts of (*Z*)-crotylalcohol) were removed by fractioned distillation.

After transformation of the enantioenriched **13** and **15** into the nosylates **14** and **16a**, respectively, the two enantiomers could be obtained by fractioned crystallisation[11] in greater than 99% *ee* for **14** and greater than 95% *ee* for compounds **16** (Scheme 4). The following alkylation of **7**

Table 1. N-Alkylation of amide **7** with the epoxides **14** and **16a–e**.



14, 16a-e **7** **10**

Epoxide	Equiv	Additives[a]	*T*/*t* [°C]/[h]	Yield of **10** [%]
(2*R*,3*R*)-**14** (ONs)	1.5	–	25/1.5	99
(2*S*,3*S*)-**16a** (ONs)	1.5	–	25/1.5	99
16b (OMs)	1.5	[18]crown-6 ether (1.5), TBAI (0.1)	25/240	64
16c (Cl)	1.3	[18]crown-6 ether (1.5)	70/2	69
16d (OTf)	1.0	–	0/0.5	14
16e (ONf)	1.5	–	25/96	0

[a] TBAI = tetrabutylammonium iodide.

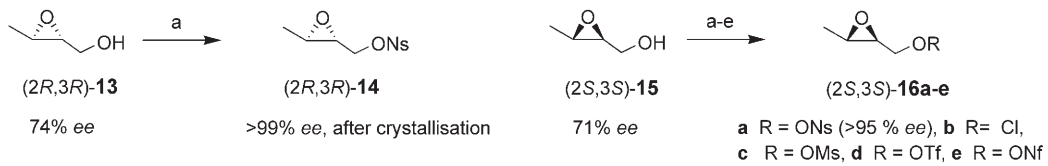
was performed by using nosylates **14** and **16a** to give **10** in 99% yield. Besides the nosylate **16a**, we have also prepared the chloride **16b**, the mesylate **16c**, the triflate **16d**[12] and the nonaflate **16e**,[13] which could not be purified and moreover gave much less satisfying results in the alkylation (Table 1).

To our surprise, all alkylation reactions yielded a mixture of two compounds in a ratio of 65:35 to 50:50, which could be separated by chromatography on silica gel.

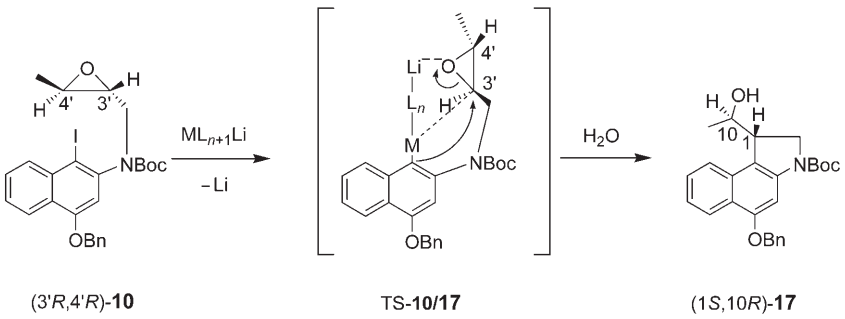
The primary assumption that regioisomers might have been formed owing to an intramolecular Payne rearrangement[14] proved to be false as the following metal-induced cyclisation of the mixture led to more than 65% yield of the desired product **17**. The existence of separable rotamers about the amide bond is less likely as these isomers are usually not stable at room temperature. Moreover, the additional existence of rotameric forms in the two separated isomers can be deduced from the NMR spectra. The two compounds, both with very similar spectroscopic data, do not convert into each other even at elevated temperatures of up to 100 °C. We assume that they are diastereomers owing to the existence of a hindered rotation about the aryl–N single bond.

To support this assumption, we have prepared compound **10** without the iodine atom at the aryl moiety. This compound, as expected, does not show any atropisomerism. The atropisomerism of **10** and related compounds will be studied in more detail in the future.[15]

For the metal-mediated cyclisation of **10** to give **17**, we had to explore several different conditions to give reasonable results. Thus, many examples for metal-catalysed cyclisation reactions with terminal epoxides and alkyl-/arylhalides through a metal-exchange reaction can be found in the literature; however, only a few cases for the reaction of non-terminal epoxides have been reported so far.[16,17a] Common reagents for the necessary halogen–metal exchange are RMgX,[17] BuLi,[18] CuI·PR_3,[19] CuBr·Me_2S,[18a] ZnX·*n*MeLi[20] and CuCN·*n*LiX.[17a,15] In the case of epoxide **10**, there are two possible reaction sites for the attack of the organometallic centre leading to the 5-*exo*-trig and/or to the 6-*endo*-trig products. However, in all the cyclisation reactions, only the *exo* product was obtained. To achieve a stereoselective reaction, we concentrated on the corresponding lithium-containing cuprates as it was known that lithium, as in the Parham cyclisation, tends to coordinate to the oxygen of the epoxide part to allow the formation of a sterically fixed transition state.[21] Thus, for the epoxide opening of (3′*R*,4′*R*)-**10**, we propose a lithium-coordinated transition state TS-**10/17** in which the attack of the metallated carbon atoms C1 to C10 occurs in an *anti* fashion to give (1*S*,10*R*)-**17** with the *S* configuration at the newly formed stereogenic centre (then C1; Scheme 5). As the second carbon (C11) of the epoxide moiety does not take part in the reaction, its original configuration should remain. It should be mentioned that the exact transition state using "cyano-Gilman cuprates", especially the location of the cyanide, has long been a subject of controversial discussions.[22] The case of the zincate with SCN ligand transition states have not been



Scheme 4. Synthesis of derivatives of 2,3-epoxybutanol. a) NsCl, Et_3N, toluene, RT, 30 min; 60% yield for **14** and 58% yield for **16a**; b) CCl_4, PPh_3, $NaHCO_3$, reflux, 2 h, 92%; c) MsCl, Et_3N, toluene, 0 °C, 1.5 h, 98%; d) *n*BuLi, −78 °C, 30 min, Tf_2O, −78 °C for 1 h followed by RT for 1 h; e) NfF, Et_3N, DMF, RT, 15 h. Ms = mesylate, Ns = nosylate, Nf = nonafluorobutanesulfonate, Tf = triflate.



(3'*R*,4'*R*)-**10** TS-**10/17** (1*S*,10*R*)-**17**

Scheme 5. Transition state with lithium coordination.

investigated so far, but a possible ligation of SCN cannot be omitted owing to the tendency of zinc derivatives to form complexes with a tetrahedral configuration.[18b,23] In any case, a transition state of type TS-**10/17** as well as a noncoordinated *anti* attack should lead to (1*S*,10*R*)-**17** starting from (3′*R*,4′*R*)-**10**; this is indeed the case.

The best results for the cyclisation reaction (Table 2) were achieved by using the copper organyl $Li_2Cu(CN)Me_2$ and the zinc organyl $Li_2Zn(SCN)Me_3$, which led to the product (1*S*,10*R*)-**17** in 78% and 72% yield, respectively (Table 2, entries 1 and 5); in contrast, employing $Li_3Cu(CN)Me$, Li_2ZnMe_4 and $LiZnMe_3$ afforded (1*S*,10*R*)-**17** in only 34%, 13% and 24% yield, respectively (Table 2, entries 2, 4 and 6). The use of the Grignard reagent *i*PrMgCl·LiCl gave 38% of (1*S*,10*R*)-**17**, whereas employing *n*BuLi nearly exclusively afforded the dehalogenated product with only 7% of the desired product (Table 2, entries 7 and 8). This last reaction clearly shows that the use of intermetal reagents is superior for transformations with nonterminal epoxides when compared with literature-known reactions with terminal epoxides in which the use of *n*BuLi gives good yields.[13] As expected, the transformation of the other enantiomer (3′*S*,4′*S*)-**10** with $Li_2Cu(CN)Me_2$ led to the alcohol (1*R*,10*S*)-**17** in 65% yield (Table 2, entry 3).

Table 2. Cyclisation reactions of (3′*R*,4′*R*)-**10** (99% *ee*) to give (1*S*,10*R*)-**17**.

Entry	Metal organyl	Yield [%]	Selectivity[a]
1	$Li_2Cu(CN)Me_2$	78	98:2
2	$Li_3Cu(CN)Me_3$	34	–
3	$Li_2Cu(CN)Me_2$[b]	65	94:6
4	Li_2ZnMe_4	13	–
5	$Li_2Zn(SCN)Me_3$	72	98:2
6	$LiZnMe_3$	24	–
7	*i*PrMgCl·LiCl	38	97:3
8	*n*BuLi	7	–

[a] Determined by HPLC on Chiracel IA, see also Ref. [24]. [b] the reaction was performed starting with (3′*S*,4′*S*)-**10** with greater than 95% *ee*.

In all cases, the reactions proceed with little loss of stereo integrity with a selectivity[24] of 97:3 to 98:2 starting with a compound of 99% *ee* (Table 2, entries 2, 5 and 7). Thus, the formation of a carbocation as an intermediate by ring opening of the epoxide prior to the ring closure can be widely excluded.

The obtained products could be further purified by recrystallisation to give, for example, the desired enantiomer with greater than 99% *ee*. The structure of (1*S*,10*R*)-**17** was confirmed by X-ray analysis (Figure 1).[25]

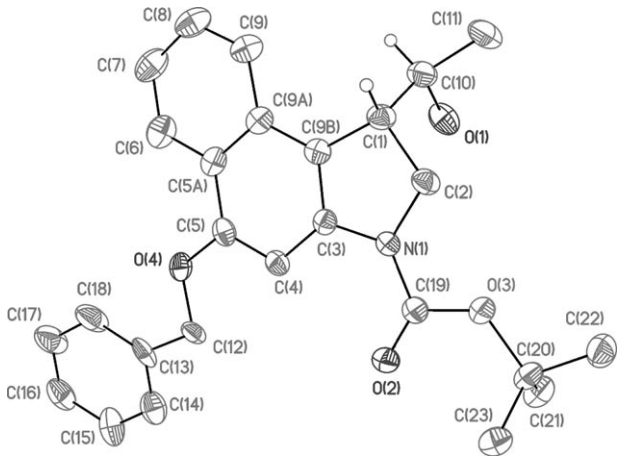
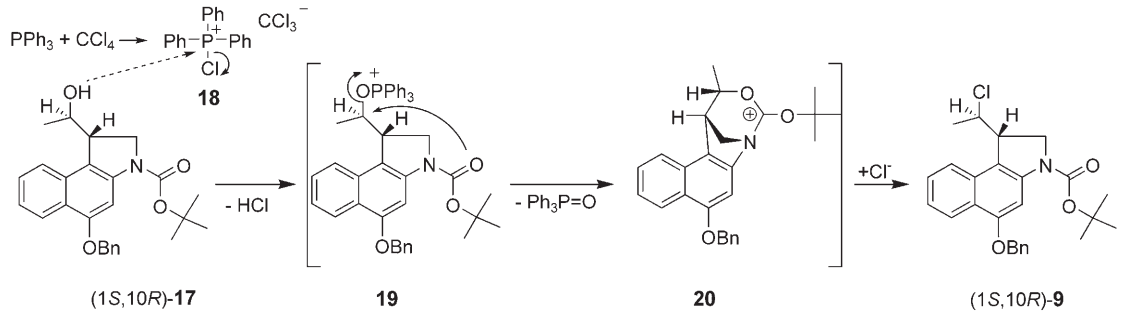


Figure 1. X-ray crystal structure of the alcohol (1*S*,10*R*)-**17**.

The final step towards the desired compound (1*S*,10*R*)-**9** was the replacement of the hydroxy group in (1*S*,10*R*)-**17** by a chloride group by using an Appel reaction. Usually, the Appel reaction proceeds with inversion of configuration. However, in the transformation of (1*S*,10*R*)-**17**, we observed a retention of configuration. The best results were obtained by using a mixture of CH_3CN/CCl_4 (3:1) as the solvent and 2.2 equivalents of triphenylphosphine to give the desired (1*S*,10*R*)-**9** in 87% yield and 99.8% *ee*. We assume that this stereochemical outcome is caused by a double inversion under neighbouring-group participation of the *N-tert*-butyloxycarbonyl (Boc) protecting group (Scheme 6). From carbohydrate chemistry, many examples of neighbouring-group participation are known with unhindered acyl derivatives.[26] However, the involvement of a sterically highly demanding Boc group is astounding. As part of the mechanism for the Appel reaction of (1*S*,10*R*)-**17**, we can assume that primarily the phosphane **19** is formed by nucleophilic attack of the phosphonium salt **18**. This is followed by an attack of the carbonyl oxygen of the Boc protecting group with inversion of the configuration and displacement of triphenylphosphine oxide to give **20**. The subsequent nucleophilic attack at C10 with chloride takes place with a second inversion of the configuration in a S_N2 fashion to give the desired compound (1*S*,10*R*)-**9**.



Scheme 6. Proposed neighbouring-group effect in the Appel reaction of (1*S*,10*R*)-**17** to give (1*S*,10*R*)-**9**.

We also performed the reaction in pure CCl_4; under these conditions a 1:1 mixture of *syn*- and *anti*-**9** was obtained. This validates the above described mechanism as the reaction proceeds via the polar intermediate **20** and should have a lower energy of activation in a polar solvent. In all cases, an undesired β elimination took place to some extent as a consequence of the instability of the intermediate carboxonium ion **20**. An increase in β elimination took place in the order of decreasing polarity of the solvent used in the transformation (CH_3CN-CCl_4 < CCl_4-CH_2Cl_2 < CCl_4).

Conclusion

We developed a method of enantioselective access to (1*S*,10*R*)-**9**, which is the key intermediate in the synthesis of the highly potent prodrug **2** used in ADEPT. After alkylation of amide **7** with the enantiopure epoxy-nosylate **14** to give **10**, a copper organyl mediated cyclisation was found to best lead to **17**. Astoundingly, **10** was obtained as a mixture of atropisomers owing to a hindered rotation about the aryl–N single bond. In the last step, the Appel reaction for the transformation of the hydroxy group into the desired chloride (1*S*,10*R*)-**9** proceeded with retention of configuration owing to neighbouring-group participation of the Boc protecting group. This is a rare example for an Appel reaction with induced double inversion with very high selectivity. In conclusion, the sequence allows the synthesis of the enantiopure *anti*-methyl-*seco*-CBI (cyclopropabenzindole) unit (1*S*,10*R*)-**9** on a gram scale with an overall yield of 67% in three steps from the known amide **7**.

Experimental Section

General: All reactions were performed in flame-dried glassware under an atmosphere of argon. Solvents were dried and purified according to the method defined by Perrin and Armarego. Commercial reagents were used without further purification. Crotylalcohol (*E*/*Z* 19:1) was purchased at Fluka. TLC was carried out on precoated Alugram SIL G/UV254 (0.25 mm) plates from Macherey-Nagel & Co. Column chromatography was carried out on silica gel 60 from Merck with a particle size of 0.063–0.200 mm for normal pressure and 0.020–0.063 mm for flash chromatography (pentane was used as the solvent). Melting points were recorded on a Mettler FP61 and are uncorrected. IR spectra were determined on a Bruker Vektor 22, UV/Vis spectra were recorded on a Perkin-Elmer Lambda 2 and mass spectra were recorded on a Varian MAT 311 A, Varian MAT 731 for EI-HRMS and a Bioapex fourier transformation ion cyclotron resonance mass spectrometer for ESI-HRMS.

^{1}H NMR spectra were recorded either on a Varian VXR-200 MHz or Varian UNITY-300 MHz. ^{13}C NMR spectra were recorded at 50 or 75 MHz. Spectra were recorded at room temperature (except when otherwise stated) and in deuterated solvents as indicated with the solvent peak as the internal standard.

Selected experimental data, including representatives of each of the synthetic methods, are given below. Full experimental data for all other reactions are given in the Supporting Information.

Synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-2,3-epoxy-1-nitrobenzenesulfonyloxybutane (14) and (16a):[11] Nosylchloride (3.54 g, 16.0 mmol, 1.05 equiv) was added portionwise to a stirred solution of (2*R*,3*R*)-**13**[10] (71% *ee*) or (2*S*,3*S*)-**15** (74% *ee*; 1.34 g, 15.2 mmol, 1.0 equiv) and triethylamine (2.54 mL, 1.84 g, 18.2 mmol, 1.2 equiv) in toluene (30 mL) at 0°C. Stirring was continued for 30 min at 25°C and then the orange-coloured solution was filtered over Celite and washed with toluene (50 mL). The solvent was evaporated and the crude material was placed on a short silica gel column and eluted with diethyl ether (250 mL). After removal of 50% of the solvent, the white precipitated solid (racemate) was filtered off and the mother liquor evaporated to dryness. Repeated crystallisation (approximately two times) from diethyl ether (100 mL) afforded the nosylates **14a** (1.66 g, 40%) and **16a** (1.50 g, 36%), respectively, as yellow crystals with stable optimal rotation values; mp 65–65.5°C; $[\alpha]_D^{25}$ ($CHCl_3$, c = 0.8, 99.8% *ee*) = +39.6°; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, J = 5.3 Hz, 3H; 4-H_3), 2.87–2.99 (m, 2H; 2-H, 3-H), 4.04 (dd, J = 11.5, 6.4 Hz, 1H; 1-H_a), 4.42 (dd, J = 11.5, 3.1 Hz, 1H; 1-H_b), 8.10–8.17 (m, 2H; 2× Ph-H), 8.39–8.45 ppm (m, 2H; 2× Ph-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.88 (C4), 52.60, 55.34 (C2, C3), 71.38 (C1), 124.5, 129.3 (Ph-C_o, Ph-C_m), 141.5, 150.8 ppm (Ph-C_i, Ph-C_p); IR (KBr) $\tilde{\nu}$: 3112, 1524, 1365, 1196, 1097 cm^{-1}; UV λ_{max} (log ε): 251 nm (0.55); MS (DCI): m/z (%): 291 (100%) $[M+NH_4]^+$; HRMS (ESI): m/z: calcd for $C_{11}H_{15}N_2O_6S$ $[M+NH_4]^+$: 291.06459; found: 291.06453;

Synthesis of (2*S*,3*S*)-2,3-epoxy-1-methanesulfonyloxybutane (16b): A solution of mesylchloride (650 mg, 5.70 mmol, 1.0 equiv) in toluene (2 mL) was added dropwise to a stirred solution of (2*S*,3*S*)-**15**[10] (74% *ee*; 500 mg, 5.67 mmol, 1.0 equiv) and triethylamine (0.92 mL, 0.67 g, 6.67 mmol, 1.2 equiv) in toluene (10 mL) at 0°C within 10 min. After stirring at 0°C for 1 h, the solution was filtered over Celite and the solvent removed under slightly reduced pressure to yield the analytically pure product **16b** (920 mg, 98%) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, J = 5.0 Hz, 3H; 4-H_3), 2.91–3.04 (m, 2H; 2-H, 3-H), 3.05 (s, 3H; S-CH_3), 4.08 (dd, J = 12.0, 6.1 Hz, 1H; 1-H_a), 4.45 ppm (dd, J = 12.0, 2.8 Hz, 1H; 1-H_b); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.00 (C4), 37.81 (S-CH_3), 52.56, 55.70 (C2, C3), 69.79 ppm (C1); MS (DCI): m/z (%): 184 (100%) $[M+NH_4]^+$; HRMS (ESI): m/z: calcd for $C_5H_{14}NO_4S$ $[M+NH_4]^+$: 184.06375; found: 184.06381;

Synthesis of (2*S*,3*S*)-1-chloro-2,3-epoxybutane (16c): A mixture of CCl_4 (7 mL), PPh_3 (1.78 g, 6.80 mmol, 1.2 equiv), $NaHCO_3$ (100 mg,

1.19 mmol, 0.2 equiv) and (2*S*,3*S*)-**15**[10] (74% *ee*) (500 mg, 5.67 mmol, 1.0 equiv) was refluxed for 2 h. Filtration over a short silica gel column, washing with diethyl ether (50 mL) and removal of the solvent under slightly reduced pressure afforded the target compound **16c** (560 mg, 92%) as a colourless liquid. $[\alpha]_D^{20}$ (C_6H_6, $c=1.0$, 74% *ee*) $=-36.5°$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.36$ (d, $J=5.1$ Hz, 3H; 4-H_3), 2.93–3.01 (m, 2H; 2-H, 3-H), 3.53–3.58 ppm (m, 2H, 1-$H_{a,b}$), ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=17.1$ (C4), 44.6 (C1), 55.0, 58.0 ppm (C2, C3); IR (film) $\tilde{\nu}$: 3444, 2971, 1439, 1380, 1265 cm^{-1}.

Synthesis of (3′*R*,4′*R*)- and (3′*S*,4′*S*)-2-amino-4-benzyloxy-*N*-(3,4-epoxybutyl)-1-iodo-*N*-(*tert*-butoxycarbonyl)-naphthalene (3′*R*,4′*R*)-10) and (3′*S*,4′*S*)-10): Coupling with the nosylates **14/16a**. A NaH (168 mg 60% suspension, 4.28 mmol, 4.0 equiv) was added to a stirred solution of the carbamate **7** (500 mg, 1.05 mmol, 1.0 equiv) in DMF (5 mL) at 25°C and stirring was continued for 30 min. After addition of the nosylate **14** or **16a** (431 mg, 1.58 mmol, 1.5 equiv), the solution was stirred at 25°C for 1.5 h. The reaction was quenched by the addition of a saturated $NaHCO_3$ solution (100 mL) and the mixture was then extracted with CH_2Cl_2 (3× 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over Na_2SO_4. Column chromatography on silica (pentane/ethyl acetate 10:1) yielded the title compound as a yellow solid (562 mg of (3′*R*,4′*R*)-**10** and (3′*S*,4′*S*)-**10**, respectively (99%)). ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100°C, both atropisomers, differing signals assigned with *): $\delta=$ 1.20, 1.22 (2×d, 3H, $J=5.1$ Hz; 12-H, 5′-H*), 1.33–1.44 (m, 9H; C-$(CH_3)_3$), 2.65 (dq, $J=5.1$, 2.2 Hz, 0.5H; 4′-H*), 2.78 (dq, $J=5.1$, 2.2 Hz, 0.5H; 4′-H), 2.81 (dt, $J=5.3$, 2.2 Hz, 0.5H; 3′-H), 3.16 (ddd$_c$, $J=6.5$, 4.8, 2.2 Hz, 0.5H; 3′-H*), 3.30 (dd, $J=14.6$, 6.4 Hz, 0.5H; 2′-H_a*), 3.41 (dd, $J=$ 14.6, 5.3 Hz, 0.5H; 2′-H_a), 3.90 (dd, $J=14.6$, 4.7 Hz, 0.5H; 2′-H_b*), 4.11 (dd, $J=14.6$, 5.0 Hz, 0.5H; 2′-H_b), 5.26, 5.24 (2×s, 2H; OCH_2Ph), 6.83, 6.90 (2×s, 1H; 3-H), 7.27–7.60 (m, 7H; 6-H, 7-H, 5×Ph-H), 8.18, 8.18 ppm (2×m$_c$, 2H; 5-H, 8-H); ^{13}C NMR (300 MHz, $C_2D_2Cl_4$, 90°C, both atropisomers, differing signals are assigned with *): $\delta=16.96$ (C5′), 28.1, 28.2 (C(CH_3)$_3$), 50.91 (C2′*), 52.42 (C2′), 53.56 (C4′*), 53.73 (C4′), 56.46 (C3′*), 56.84 (C3′), 70.59*, 70.61(OCH_2Ph), 80.46 (*C*(CH_3)$_3$), 94.66 (C1), 107.8, 108.0* (C3), 122.4 (C5), 125.5 (C4a), 126.0, 126.1*, 127.1, 127.2* (C6, C7), 127.9, 128.2, 128.3, 128.4, 128.5 (5×Ph-CH), 132.5 (C8), 135.2*, 135.3 (C8a), 136.3*, 136.4 (Ph-C$_i$), 143.1, 143.7* (C2), 153.4, 153.69* (C=O), 155.5 ppm (C-4); IR (KBr): $\tilde{\nu}=$2986, 1691, 1592, 1379, 1334, 1150, 762 cm^{-1}; UV/Vis (MeCN): λ_{max} (log ε) $=216$ (1.14), 244 (0.65), 305 nm (0.21); HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{29}INO_4$ $[M+H]^+$: 546.11334; found: 546.11358; *m*/*z*: calcd for $C_{26}H_{28}INO_4Na$ $[M+Na]^+$: 568.09530; found: 568.09552.

Synthesis of (1*S*,10*R*)-5-benzyloxy-3-(*tert*-butoxycarbonyl-1-(10-hydroxyethyl)-1,2-dihydro-3*H*-benz[*e*]indole ((1*S*,10*R*)-17)): Cyclisation reaction using $Li_2Cu(CN)Me_2$. MeLi (1.8 mL of a 1.6 M solution in Et_2O, 2.92 mmol, 3.0 equiv) was added dropwise to a stirred suspension of CuCN (131 mg, 1.46 mmol, 1.5 equiv) in THF (5 mL) at −78°C and stirring was continued for 30 min at −40°C. After cooling again to −78°C, a solution of (3′*R*,4′*R*)-**10** (530 mg, 0.972 mmol, 1.0 equiv) in THF (5 mL) was added dropwise and stirring was continued for 1 h at −78°C. The mixture was then allowed to warm to 25°C (30 min) and stirring was continued for and additional 45 min. Afterwards, the solvent was removed under high vacuum. The residue was dissolved in ice water (200 mL), the mixture extracted with CH_2Cl_2 (3×100 mL), the combined organic extracts washed with brine (100 mL), dried over Na_2SO_4 and the solvent finally evaporated. Purification by column chromatography on silica gel (pentane/ethyl acetate 5:1) yielded (1*S*,10*R*)-**17** as a colourless foam (317 mg, 78%); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=1.30$ (d, $J=6.5$ Hz, 3H; 11-H_3), 1.60 (s, 9H; C(CH_3)$_3$), 3.72 (m$_c$, 1H; 1-H), 4.03 (m$_c$, 1H; 2-H_a), 4.27 (m$_c$, 1H; 2-H_b), 4.43 (m$_c$, 1H; 10-H), 5.29 (s, 2H; OCH_2Ph), 7.30–7.60 (m, 7H; 7-H, 8-H, 5×Ph-H), 7.71 (d, $J=8.3$ Hz; 9-H), 7.93 (br s, 1H; 4-H), 8.31 ppm (d, $J=8.6$ Hz, 1H; 6-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=20.22$ (11-CH_3), 28.51 (C(CH_3)$_3$), 45.57 (C1), 49.13 (C2), 68.33 (C10), 70.38 (OCH_2Ph), 80.80 (*C*(CH_3)$_3$), 96.31 (C4), 114.6 (C9b), 122.4 (C5a), 122.5, 122.9, 123.5 (C6, C7, C9), 127.2 (C8), 127.6, 127.9, 128.5 (5×Ph-CH), 130.5 (C9a), 136.9 (Ph-C$_i$), 142.3 (C3a), 152.5 (C=O), 155.7 (C5); IR (KBr): $\tilde{\nu}=$3442, 2925, 2854, 1698, 1626, 1583, 1458 cm^{-1}; UV/Vis (MeCN): λ_{max} (log ε) $=208$ (0.48), 256 (0.75), 304 (0.14), 315 nm (0.15); MS (ESI): *m*/*z* (%): 442 (100) $[M+Na]^+$; HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{29}NO_4Na$ $[M+Na]^+$: 442.19861; found: 442.19888.

Chromatographic resolution of *rac*-(1*S*,10*R*)-17: A solution of *rac*-(1*S*,10*R*)-**17** (500 mg, 1.19 mmol) in a 3:2 mixture of *n*-heptane and CH_2Cl_2 (10 mL) was separated (injection volume: 0.2 mL) by semipreparative HPLC (Chiralpak IA, 250×20 mm, particle size: 5 μm, *n*-heptane/CH_2Cl_2 78:22, flow: 18 mL min^{-1}; UV-detector: $\lambda=250$ nm, *Jasco*-module) to provide (−)-(1*R*,10*S*)-**17** ($t_R=13.7$ min) and (+)-(1*S*,10*R*)-**17** ($t_R=17.9$ min). The optical purity was determined by analytical HPLC (Chiralpak IA, 250×4.6 mm, particle size: 10 μm, *n*-hexane/*i*PrOH 7:3, flow: 0.8 mL min^{-1}; UV detector: $\lambda=250$ nm, *Kontron*-module): (−)-(1*R*,10*S*)-**17**: 91.4% *ee* ($t_R=5.2$ min); $[\alpha]_D^{20}=-20.5°$($CHCl_3$, c=0.8); (+)-(1*S*,10*R*)-**17**: 98.9% *ee* ($t_R=5.9$ min); $[\alpha]_D^{20}=+22.5°$($CHCl_3$, c=0.5).

(1*S*,10*R*)-5-benzyloxy-3-(*tert*-butoxycarbonyl-1-(10-chloroethyl)-1,2-dihydro-3*H*-benz[*e*]indole ((1*S*,10*R*)-9)):[6b] PPh_3 (1.38 g, 5.24 mmol, 2.2 equiv) was added to a stirred solution of (1*S*,10*R*)-**17** (1.00 g, 2.38 mmol, 1.0 equiv) in CCl_4 (10 mL) and CH_3CN (30 mL) at −18°C. After 30 min, the mixture was allowed to warm to 0°C and stirring was continued for another 3 h. The reaction was quenched by the addition of silica gel (5 g) and evaporation of the solvent. Column chromatography on silica gel (pentane/ethyl acetate 10:1) yielded a colourless solid (905 mg, 87%). The optical purity was determined as described in the literature;[6b] $[\alpha]_D^{20}=+28.0°$ ($CHCl_3$, $c=0.8$, 99.8% *ee*);[6b] $[\alpha]_D^{20}=+28.0°$ ($CHCl_3$, c 0.8, 99.9% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.48$–1.56 (m, 12H; C(CH_3)$_3$, 11-H_3), 3.78 (m$_c$, 1H; 1-H), 4.00 (m$_c$, 1H; 2-H_a), 4.26 (m$_c$, 1H; 2-H_b), 4.53 (m$_c$, 1H; 10-H), 5.19 (s, 2H; OCH_2Ph), 7.09–7.63 (m, 8H; 7-H, 8-H, 9-H, 5×Ph-H), 7.78 (br s, 1H; 4-H), 8.23 ppm (d, $J=$ 8.2 Hz, 1H; 6-H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=23.74$ (C11), 28.50 (C(*C*H_3)$_3$), 46.09 (C1), 50.88 (*C*2), 60.20 (C10), 70.22 (OCH_2), 80.79 (*C*-$(CH_3)_3$), 96.24 (C4), 115.0 (C9b), 122.0 (C5a), 122.4, 122.8, 123.6 (C6, C7, C9), 127.6, 127.9, 128.5 (5×Ph-CH), 127.2 (C8), 130.4 (C9a), 136.9 (Ph-C$_i$), 142.1 (C3a), 152.4 (C=O), 155.8 ppm (C5); *m*/*z* found [ESI]: 460 (100%, $[M+Na]^+$). $C_{26}H_{28}NO_3Na$ requires 460.166.

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[25] CCDC-652396 contains the supplementary crystallographic data for this paper. The structure can be found in the ESI and was solved by direct methods by using SHELXS-97[27] and was refined against F^2 on all data by full-matrix least squares with SHELXL-97.[28] These data can also be obtained free of charge from The Cambridge Crystallographic Data Centre via ;www.ccddc.cam.ac.uk/data_request/cif.

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