Efficient Synthesis of the Pharmacophore of the Highly Potent Antitumor Antibiotic CC-1065

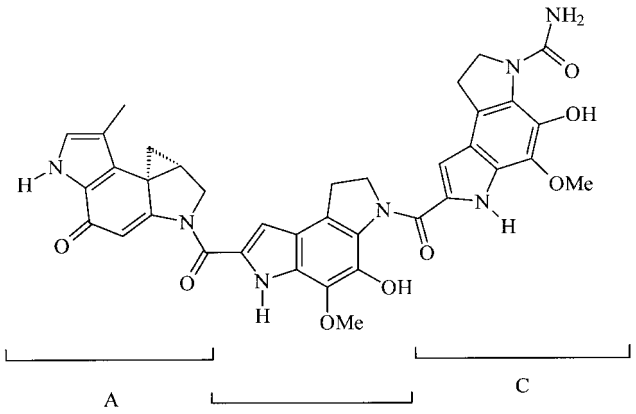
Lutz F. Tietze,* Wilm Buhr, Jan Looft, and Thomas Grote

Abstract: The pharmacophore CPI (**3**) of the potent antitumor antibiotic CC-1065 (**1**) was synthesized in a very short reaction sequence of 11 steps with an overall yield of 23 %. The key steps are two consecutive cyclizations mediated by organotransition metal complexes, which form first the pyrroline and then the pyrrole ring in **3**. Thus, halogen metal exchange of the *N*,*N*′-bisallylbromobenzene with *t*BuLi and subsequent reaction with $Cp_2ZrMeCl$ gave **11** as a single product in 60 % yield after quenching with two equivalents of iodine. Transformation of the iodomethyl group in **11** into an acetoxymethyl group, followed by Heck reaction, isomerization, and reductive cleavage, provided the pyrroloindoline system **4**, which was converted into **3**.

Keywords: antibiotics · antitumor agents · cyclizations · Heck reaction · zirconium

Introduction

The antibiotic CC-1065 (**1**), first isolated from *Streptomyces zelensis* in 1978 at the Upjohn Company, is one of the most potent antitumor agents known.[1] It consists of three pyrrolo[3,2-*e*]dihydroindole moieties, of which the A unit **2**, called CPI, is the pharmacophore. It contains an unusual spirocyclopropyl group, which is able to alkylate DNA. The B and C units are identical and have a strong influence on the binding specification[2] and the biological potency,[3] but are less toxic themselves. However, the selectivity of CC-1065 and its analogues in the differentiation between normal and malignant cells is low, and furthermore, CC-1065 itself has a delayed lethal liver toxicity. An approach to improve the selectivity of CC-1065 and its analogues is the exploitation of genetic and phenotypic differences of cancer and normal cells. Thus, recently we developed nontoxic prodrugs of CC-1065[4] that can be activated using conjugates of enzymes and antibodies[5] which bind to tumor-associated antigens.



(+)-CC-1065 **1**

Cell investigations have shown that CC-1065 alkylates DNA reversibly with a high sequence selectivity at AT-rich regions of the minor groove sites [5′d(A/GNTTA)-3′ and 5′d(AAAAA)-3′].[6] Because it is such a highly potent pharmacophore, there is a great interest in the preparation of the CPI unit. Thus, several syntheses of CPI have been published so far.[7]

Here we describe an efficient and short synthesis of the *seco*-CPI derivative **4**, which is used for the preparation of prodrugs of CC-1065,[4] and the *N*-(benzenesulfonyl)-CPI (**3**) from commercially available 2-methoxy-4-nitroaniline (**8**) based on two successive organotransition metal complex-controlled cyclizations.[8] This allows the consecutive formation of the pyrroline and the pyrrole ring of the CPI and the *seco*-CPI systems in 4 steps with 51 % yield based on **6**.

Results and Discussion

The retrosynthetic analysis of **3** (Scheme 1) first leads to **4** by breaking the spirocyclopropane moiety. The transformation

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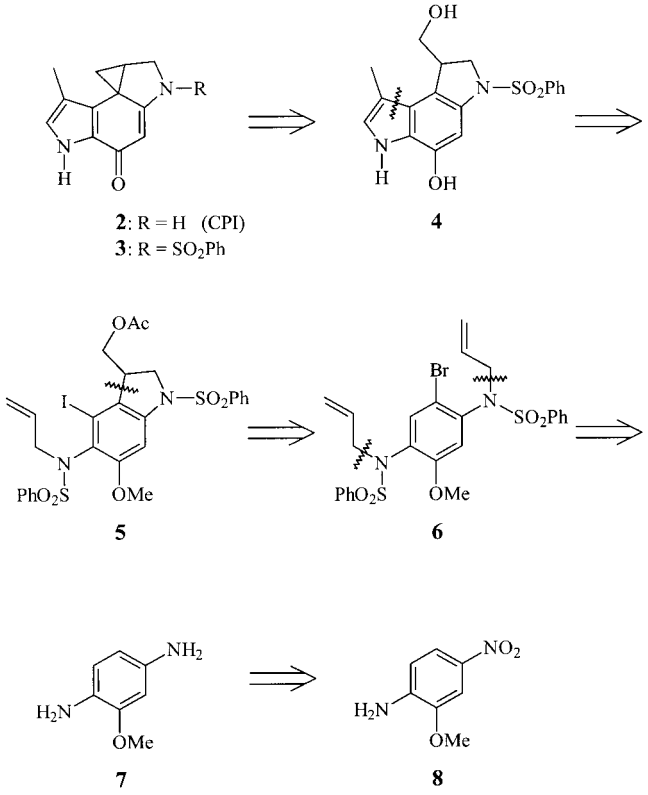
0947-6539/98/0408-1554 $ 17.50+.50/0

of **4** into **3** had already been known and can easily be performed using azodicarboxylate.[7e] Cleavage of the pyrrole ring in **4** gives compound **5**, which is clearly a good substrate for a Heck reaction.[7d, 7f, 9] Cleavage of the second heterocyclic ring would yield the benzene derivative **6** calling for a reaction which not only forms the pyrroline moiety by C–C-bond formation but also introduces a functionalized side chain and an iodo atom at the benzene ring necessary for the Heck reaction. Such a reaction can be performed using $Cp_2ZrMeCl$ and quenching with iodine.[10] The substrate **6** is easily accessible from the diamine **7** by formation of the disulfonamide, bromination, and bis-allylation, and **7** can be obtained from **8** by reduction.



2: R = H (CPI)
3: R = SO_2Ph

4

5

6

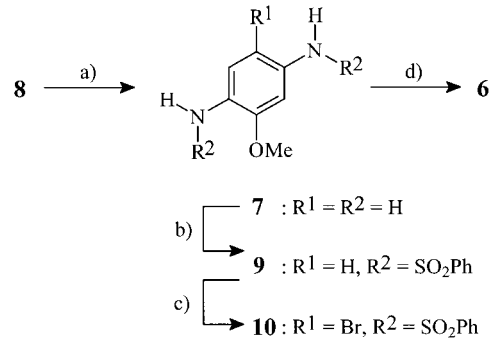
7

8

Scheme 1. Retrosynthetic analysis of CPI.

Hydrogenation of **8** in dioxane with Pt at 3 bar afforded **7**, which was not purified due to its high sensitivity to oxidation, but immediately converted with benzenesulfonyl chloride in degassed pyridine to give the stable sulfonamide **9**.[11] Subsequently, bromination of **9** with *N*-bromosuccinimide in tetrahydrofuran afforded **10** as the sole product (Scheme 2). Regioisomeric brominated compounds were not detected under these conditions. The following double allylation of **10** with allyl bromide in tetrahydrofuran in the presence of tetrabutylammonium iodide gave the bis-allylphenylenediamide **6** in an overall yield of 66% over the four steps. A great advantage of this sequence is that all compounds except **7** could be purified by a simple crystallization.

The diamide **6** was then transformed into the indoline **11** with a iodomethyl group at C-3 and a iodo atom at C-4 by a zirconocene-mediated cyclization followed by workup with

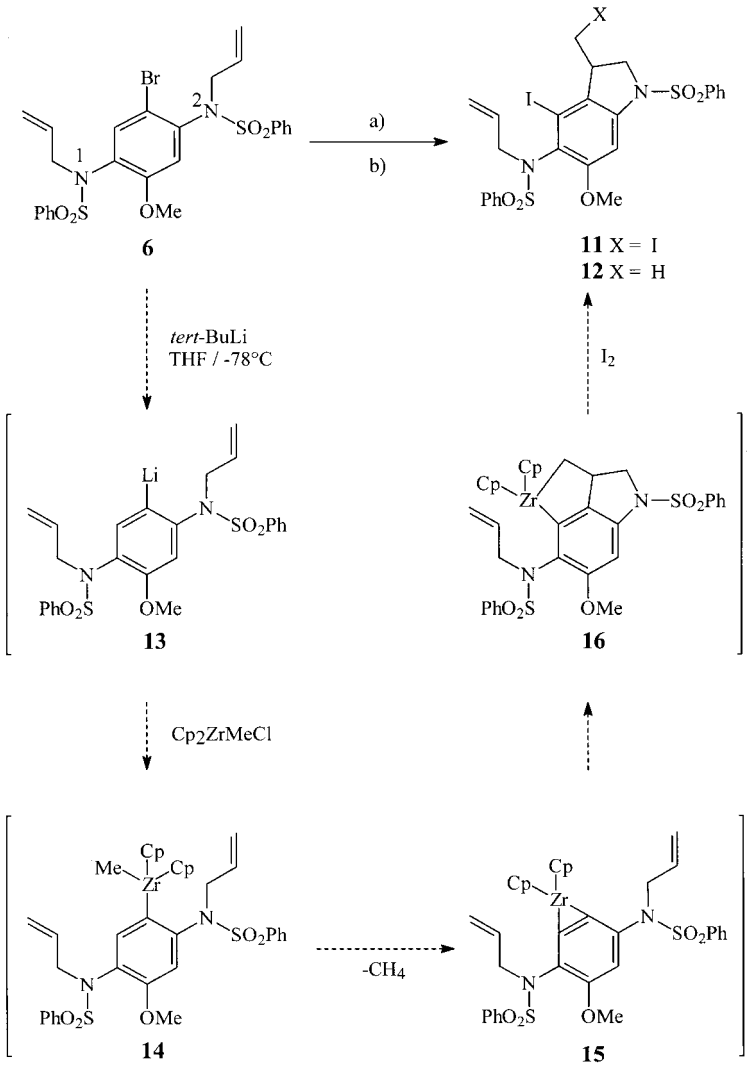


Scheme 2. Synthesis of compound **6**. Reaction conditions: a) PtO_2/H_2, dioxane, 18 h, 3 bar, quant.; b) $PhSO_2Cl$, pyridine, 3 h, 80 °C, 77%; c) NBS, THF, −78 →20 °C, 95%; d) NaH, THF, 1 h, 20 °C; allyl bromide, nBu_4NI, 5 h, 50 °C, 95%.

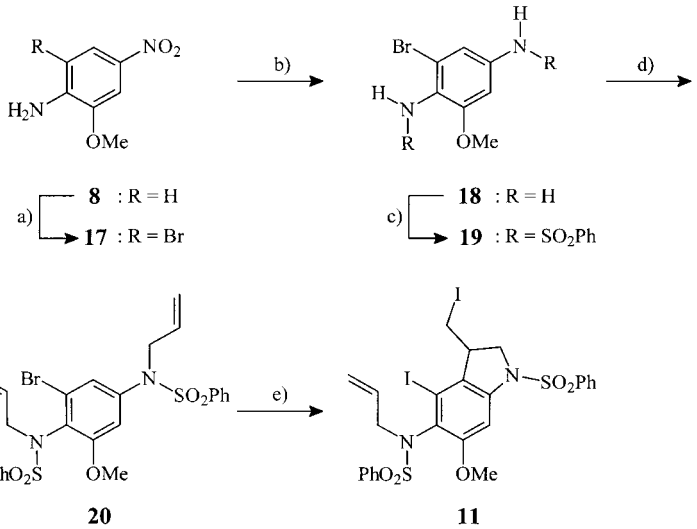
iodine.[12] Thus, addition of 2 equiv of *t*BuLi to a suspension of **6** and zirconocenemethylchloride[13] in tetrahydrofuran at −78 °C afforded at first the phenyllithium derivative **13** by halogen–metal exchange; transmetallation then led to the zirconium complex **14**, which loses methane to give (presumably) the higly unstable 16-electron zirconacyclopropene complex **15** (Scheme 3). Stabilization by a regioselective insertion into the N^2-allyl moiety yielded the zirconacyclopentene complex **16**, which reacted with two equivalents of iodine to yield the desired indoline derivative **11**. It should be pointed out that the iodine used must be anhydrous otherwise small amounts of **12** will be formed. If only one equivalent of iodine is added, followed by workup with aqueous hydrochloric acid, **12** is the final product. This clearly shows that the iodine inserts into the zirconium–aryl bond first. This observed selectivity prompted us to investigate the possibility of further differentiating between the zirconium–aryl and zirconium–alkyl bonds.[14] However, all attempts to introduce an iodine atom at the aryl moiety and a different halogen atom at the side chain in compound **16** using two different halogen-donating agents like iodine and interhalogens, *N*-halogenoimides, bromo-Meldrum's acid, or bromotrichloromethane failed.

An unexpected result in the formation of **11** was the high regioselectivity of the insertion of the zirconacarbene moiety into the allyl group at N^2. For the explanation of this selectivity and to extend the application to other substrates, the diamide **20** was prepared with a bromo substituent *meta* to the methoxy group. Diamide **20** was obtained from **8** in four steps with an overall yield of 61% (Scheme 4). Bromination of **8** with *N*-bromosuccinimide in tetrahydrofuran gave **17** in a highly regioselective manner; **17** was then reduced with hydrazine hydrate to afford **18**. Without further purification **18** was immediately converted with benzenesulfonylchloride to give the stable bis-sulfonamide **19**. Double allylation of **19** with allyl bromide in tetrahydrofuran in the presence of tetrabutylammonium iodide yielded the *N*,*N*′-bis-allylphenylenediamine **20**. Cyclization of **20** as described for **6** again furnished exclusively the indoline **11**.

Two conclusions can be drawn from this experiment: firstly, the reaction has to proceed through **15** or the corresponding benzyne complex. Secondly, the regioselectivity of the reaction is exclusively controlled by the methoxy group and not by

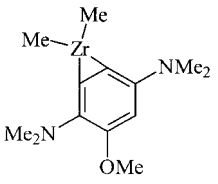


Scheme 3. Mechanism of the zirconocene-induced cyclization. Reaction conditions: a) *t*BuLi, $Cp_2ZrMeCl$, THF, 19 h, $-78 \rightarrow 20\,^{\circ}C$; b) 2 equiv I_2, CH_2Cl_2, 60 % →**11**, or I_2, HCl, CH_2Cl_2, H_2O →**12**.



Scheme 4. Synthesis of compound **11** from compound **20**. Reaction conditions: a) NBS, THF, $-78 \rightarrow 20\,^{\circ}C$, 96 %; b) $N_2H_4 \cdot H_2O$, $FeCl_3$, activated carbon, EtOH, reflux, 98 %; c) $PhSO_2Cl$, pyridine, 3 h, $80\,^{\circ}C$, 81 %; d) NaH, THF, 1 h, $20\,^{\circ}C$; allyl bromide, nBu_4NI, 5 h, $50\,^{\circ}C$, 80 %; e) *t*BuLi, $Cp_2ZrMeCl$, 19 h, $-78 \rightarrow 20\,C$; 3 equiv I_2, CH_2Cl_2, 37 %.

the position of the bromine atom in the starting material. We assume that the regioselectivity is ruled by both steric hindrance and stereoelectronics. Thus, a proper orientation of the allyl moiety at N^1 is disturbed by the methoxy group in the *ortho* position; this causes an increase in activation energy of the insertion step. On the other hand, calculations for **21** carried out by means of SPARTAN[15] have provided a structure of an extended C–Zr bond *para* to the methoxy group. However, Buchwald[10] has shown that the reaction of *p*-bromomethoxybenzene with acetonitrile in the presence of $Cp_2ZrMeCl$ provides the two possible regioisomeric products as a 1:1 mixture. This result calls for a steric explanation of the regioselective formation of **11** from **6** and **20**.

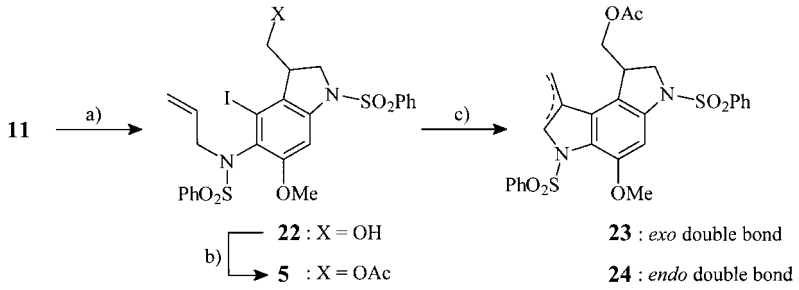


21

According to our retrosynthetic analysis the pyrrole moiety in **4** should be formed by a Heck reaction.[9] It was our hope that **11** could be used directly in this transformation since iodoarenes are more reactive than iodoalkanes; however, treatment of **11** with Pd^0 led to the formation of a methylpyrroloindole derivative. Therefore the iodomethyl group in **11** was first transformed into an acetoxymethyl group. In earlier work on the synthesis of CC-1065 analogues[8] we had shown that, by means of 1,8-diazabicyclo[5.4.0]undec-7-ene, the iodomethyl group can easily be transformed into an exocyclic double bond, which on hydroboration becomes a hydroxymethyl group. Since the yields for this two-step transformation are not very high and a hydroboration is not possible due to the second double bond in **11**, we tried to replace the iodo atom by a simple substitution with sodium acetate, cesium acetate, tetrabutylammonium acetate and several other nucleophiles. However, in all cases no substitution was observed but rather elimination followed by partial isomerization of the double bond to give the methylindole moiety. In contrast, treatment of **11** with silver oxide on silica gel in acetone and water at $20\,^{\circ}C$ for 24 h led to the hydroxymethyl compound **22**, which was acetylated with sodium acetate in acetic anhydride to give the desired product **5** (Scheme 5). Though the Heck reaction could also be performed with **22**, for the later cleavage of the aryl methyl ether with boron tribromide the hydroxymethyl group had to be protected as an acetate.

The Heck reaction of **5** gave the cyclized products **23** and **24** in a clean transformation (Scheme 5), in which the ratio of **23** and **24** could be controlled by means of different reaction conditions (Table 1). With tetrakis(triphenylphosphane)palladium as catalyst and triethylamine as base in acetonitrile for 18 hours a 17:1 mixture of **23** to **24** was formed in 90 % yield, whereas treatment of **5** with catalytic amounts of palladium acetate in the presence of silver carbonate[16] for three hours gave **23** exclusively in 90 % yield. It should be noted that the

0947-6539/98/0408-1556 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 8



Scheme 5. Synthesis of the compounds **23** and **24** by Heck reaction of **5**. Reaction conditions: a) Ag_2O, SiO_2, acetone/H_2O, 95%; b) Ac_2O, NaOAc, 99%; c) Heck reaction, 90%.

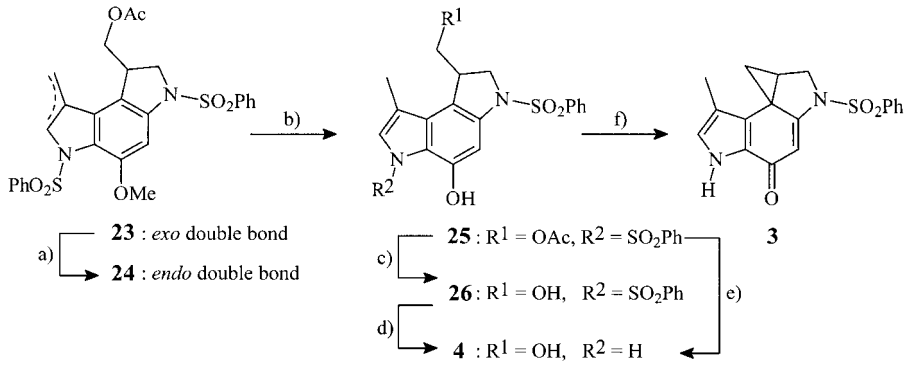
concentration of **5** also has a great influence on the product ratio. Palladium acetate at a low concentration (0.03 mol L^{-1}) of **5** provided a 1.3:1 ratio of **23** and **24** and at higher concentration (0.3 mol L^{-1}) only **23** was formed.

However, the selectivity of the Heck reaction is of little importance since **23** had to be isomerized, which was achieved with camphorsulfonic acid in dichloromethane at 20 °C to give the protected *seco*-CPI unit **24** quantitatively.

Table 1. Heck reactions of **5**.

Catalyst	Base	Solvent	Conc [mol L^{-1}]	T [°C]	t [h]	**23** [%]	**24** [%]
$Pd(PPh_3)_4$	Et_3N	CH_3CN	0.02	60–70	18	85	5
$Pd(OAc)_2$	Ag_2CO_3	DMF	0.3	20	3	90	–
$Pd(OAc)_2$	Ag_2CO_3	DMF	0.03	20	3	50	40

Subsequently the protecting groups in **24** were removed. First the methyl ether in **24** was cleaved to give the free phenol **25** by treatment with boron tribromide in dichloromethane at −10 °C for 3 h, and then the acetyl and the benzenesulfonyl group at the indole nitrogen were removed with sodium bis(2-methoxyethoxy)dihydroaluminate (Red-Al) kept at 0 °C for 3 h to provide the *N*-benzenesulfonyl-*seco*-CPI **4** in an overall yield of 83% based on **24** (Scheme 6). It is also possible to remove the acetate moiety first by solvolysis with potassium carbonate in methanol to give **26**, which is then treated with Red-Al at 20 °C for 3 h. The two-step procedure has the advantage that it avoids the formation of small amounts of the completely unprotected *seco*-CPI, which is difficult to remove from **4**. As already mentioned, the transformation of the *seco*-CPI **4** to the CPI derivative **3** is known, and was performed by Mitsunobu's method[17] with diethyl azodicarboxylate (DEAD).



Scheme 6. Synthesis of compound **3** (CPI–SO_2Ph). Reaction conditions: a) CSA, CH_2Cl_2, 2 h, 20 °C, 99%; b) BBr_3, CH_2Cl_2, 93%; c) K_2CO_3, MeOH, 99%; d) Red-Al, toluene, 90%; e) Red-Al, toluene, 90%; f) DEAD, PPh_3, THF, 49%.

Conclusion

The synthesis of the pharmacologically active CPI unit **3** described here was carried out in 11 steps with an overall yield of 23% starting from commercially available 2-methoxy-4-nitroaniline **8**. It is the shortest synthesis so far of CPI.

Experimental Section

General aspects: All reactions were performed in oven-dried glassware under an atmosphere of argon unless otherwise stated. Melting points were determined on a Mettler FP61 and are uncorrected. IR spectra were recorded on a Bruker IFS25 FT-IR, and ^{1}H NMR and ^{13}C NMR spectra with a Bruker AM-300 and a Varian VXR-200. Chemical shifts were reported on the δ scale relative to $CDCl_3$ as internal standard. Mass spectra were measured at 70 eV with a Varian MAT311A and the high-resolution mass spectra with a Varian MAT731. TLC chromatography was performed on precoated silica gel SIL G/UV_{254} plates (Machery Nagel). All products were isolated by column chromatography on silica gel 32–63 (0.063–0.200 mm) (Machery Nagel) and silica gel 60 (0.040–0.063 mm) (Merck). The chiral compounds were obtained as racemic mixtures. The microanalyses were carried out by the Mikroanalytisches Labor of the Institute of Organic Chemistry of the University of Göttingen.

***N,N′*-Dibenzenesulfonyl-2-methoxy-1,4-phenylenediamine** (**9**): A solution of 5-nitro-2-aminoanisole (**8**, 22.1 g, 0.13 mmol) in dioxane (170 mL) was hydrogenated with PtO_2 (0.20 g, 0.80 mmol) for 16 h at 3 atm of H_2. The mixture was filtered under argon and the solution evaporated in vacuo to obtain the diamine **7** as a pink solid, which was immediately used for the preparation of **9**. Benzenesulfonyl chloride (34.0 mL, 0.26 mol) was added slowly to a solution of **7** in dry degassed pyridine (300 mL) and the solution stirred for 3 h at 80 °C. After concentration in vacuo to give a volume of about 200 mL, ice-cold aqueous hydrochloric acid (500 mL, 5% HCl) was added, the resulting black oil separated and crystallized from glacial acetic acid to yield **9** (42.0 g, 0.10 mol, 77%) as colorless crystals. M.p. 207.6 °C; IR (KBr): $\tilde{\nu}$ = 3236, 3098, 1610, 1342, 1166 cm^{-1}; ^{1}H NMR (200 MHz, [D_6]DMSO): δ = 3.29 (s, 3H, O–CH_3), 6.54–6.60 (m, 2H, 3-H, 5-H), 7.20 (d, J = 9.0 Hz, 1H, 6-H), 7.40–7.66 (m, 6H, Ph–H), 7.67–7.76 (m, 4H, Ph–H), 9.20 (s, 1H, N–H), 10.14 (s, 1H, N–H); ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 55.13 (O–CH_3), 104.0 (C-3), 112.0 (C-5), 121.3 (C-1), 126.5 (C-2″, C-6″), 126.7 (C-2′, C-6′), 126.9 (C-6), 128.5 (C-3″, C-5″), 129.1 (C-3′, C-5′), 132.3 (C-4″), 132.8 (C-4′), 136.6 (C-4), 139.3 (C-1″), 140.4 (C-1′), 153.2 (C-2); MS (70 eV): m/z (%) = 418 (13) [M^+], 277 (100) [M – SO_2Ph^+], 141 (27) [SO_2Ph^+], 77 (91) [$C_6H_5^+$], 43 (48) [$C_2H_3O^+$]; $C_{19}H_{18}N_2O_5S_2$ (418.5): calcd C 54.53, H 4.33; found C 54.60, H 4.33.

***N,N′*-Dibenzenesulfonyl-5-bromo-2-methoxy-1,4-phenylenediamine** (**10**): *N*-bromosuccinimide (1.27 g, 7.17 mmol) was slowly added with stirring to a solution of **9** (3.00 g, 7.17 mmol) in THF (200 mL) at −78 °C. Stirring was continued for 3 h, and the mixture was allowed to warm to 20 °C. The solvent was evaporated in vacuo, the residue washed with water and recrystallized from acetic acid to give **10** (3.50 g, 7.03 mmol, 95%) as colorless crystals. M.p. 224.4 °C; IR (KBr): $\tilde{\nu}$ = 3248,

3068, 1602, 1344, 1160, 1042 cm^{-1}; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.31 (s, 3H, O–CH$_3$), 6.59 (s, 1H, 3-H), 7.30 (s, 1H, 6-H), 7.48–7.70 (m, 10H, Ph–H); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 55.56 (O–CH$_3$), 109.9 (C-5), 111.2 (C-3), 125.0 (C-1), 126.5 (C-2″, C-6″), 126.8 (C-2′, C-6′), 128.3 (C-4), 128.8 (C-3″, C-5″), 129.1 (C-3′, C-5′), 132.7 (C-4″, C-4′), 132.8 (C-6), 140.4 (C-1′, C-1″), 151.6 (C-2); MS (70 eV): *m*/*z* (%) = 497 (26) [*M*$^+$], 356 (100) [*M* – SO$_2$Ph$^+$], 141 (38) [SO$_2$Ph$^+$], 77 (72) [C$_6$H$_5^+$]; $C_{19}H_{17}N_2O_5S_2Br$ (497.3): calcd C 45.88, H 3.44; found C 45.94, H 3.48.

***N,N′*-Diallyl-*N,N′*-dibenzenesulfonyl-5-bromo-2-methoxy-1,4-phenylenediamine (6)**: A solution of **10** (2.00 g, 4.02 mmol) in THF (50 mL) was added at 20 °C with stirring to a suspension of NaH (203 mg, 8.44 mmol) in THF (10 mL), and after stirring for 1 h at 50 °C allylbromide (0.70 mL, 8.04 mmol) and *n*Bu$_4$NI (20 mg) were added at 20 °C. The mixture was stirred under reflux for 5 h, then treated with saturated aqueous NH$_4$Cl (10 mL) and concentrated in vacuo. The residue was dissolved in CH$_2$Cl$_2$ (50 mL), washed with brine, dried over MgSO$_4$, and concentrated in vacuo. Recrystallization from EtOH yielded **6** (2.20 g, 3.82 mmol, 95%) as colorless crystals. M.p. 139.5 °C; IR (KBr): $\tilde{\nu}$ = 3070 (Ar–H), 1642 (C=C), 1354 (S=O), 1168 (C–O–C), 1036 cm^{-1} (Ar–Br); ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.08 (s, 3H, O–CH$_3$), 4.12 (br d, *J* = 6.0 Hz, 4H, 2 × CH$_2$) 4.96–5.16 (m, 4H, 2 × CH=C*H*$_2$), 5.58–5.83 (m, 2H, 2 × C*H*=CH$_2$), 6.30 (s, 1H, 3-H), 7.42 (s, 1H, 6-H), 7.52–7.78 (m, 10H, Ph–H); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 51.82, 53.52 (2 × CH$_2$), 55.19 (O–CH$_3$), 114.5 (C-3), 114.8 (C-5), 118.2, 119.6 (2 × CH=*C*H$_2$), 126.9 (C-2″, C-6″), 127.1 (C-1), 127.5 (C-2′, C-6′), 128.8 (C-3″, C-5″), 129.2 (C-3′, C-5′), 132.0 (*C*H=CH$_2$), 132.8 (C-4″), 133.0 (*C*H=CH$_2$), 133.3 (C-4′), 136.0 (C-3), 138.0 (C-1″), 138.2 (C-1′), 138.9 (C-4), 155.4 (C-2); MS (70 eV): *m*/*z* (%) = 578 (15) [*M*$^+$], 437 (100) [*M* – SO$_2$Ph$^+$], 141 (48) [SO$_2$Ph$^+$], 77 (18) [C$_6$H$_5^+$]; $C_{25}H_{25}N_2O_5S_2Br$ (578.3): calcd C 51.99, H 4.36; found C 52.14, H 4.46.

3-Bromo-5-nitro-2-aminoanisole (17): *N*-bromosuccinimide (22.2 g, 125 mmol) was slowly added to a solution of 5-nitro-2-aminoanisole **8** (20.0 g, 119 mmol) in THF (150 mL) at –78 °C and the mixture stirred for 3 h at the same temperature. Stirring was continued at 20 °C for 20 h. Evaporation of the solvent in vacuo and washing of the residue with water gave **17** (28.2 g, 114 mmol, 96%) after recrystallization (ethanol, 100 mL) as red crystals. M.p. 104.2 °C; IR (KBr): $\tilde{\nu}$ = 3502 (N–H), 3394 (N–H), 1602 (Ar), 1502 (NO$_2$), 1320 (NO$_2$), 1284, 1234 cm^{-1} (C–O–C); ^{1}H NMR (200 MHz, CDCl$_3$): δ = 3.98 (s, 3H, O–CH$_3$), 4.95 (br s, 2H, NH$_2$), 7.63 (d, *J* = 2.5 Hz, 1H, 6-H), 8.10 (d, *J* = 2.5 Hz, 1H, 4-H); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 56.29 (O–CH$_3$), 103.2 (C–3), 104.5 (C-6), 121.7 (C-4), 135.8 (C-2), 143.0 (C-5), 145.0 (C-1); MS (70 eV): *m*/*z* (%) = 264 (100) [*M*$^+$], 226 (34) [*M* – NH$_2^+$], 216 (34), 200 (19) [*M* – NO$_2^+$], 93 (37), 78 (80) [Br$^+$], 51 (24) [C$_4$H$_3^+$]; $C_7H_7BrN_2O_3$ (247.0): calcd: C 34.03, H 2.86; found C 33.98, H 2.89.

***N,N′*-Dibenzenesulfonyl-6-bromo-2-methoxy-1,4-phenylenediamine (19)**: Hydrazine hydrate (80%, 12.5 mL, 201 mmol) was added to a mixture of **17** (10.0 g, 40.5 mmol), activated carbon (4.60 g, 383 mmol), and $FeCl_3 \cdot H_2O$ (4.33 g, 1.60 mmol) in methanol (150 mL) over a period of 7 days under reflux with stirring. Then ethyl acetate (200 mL) was added and the solids were filtered off. The organic layer was washed with H$_2$O (4 × 100 mL) and brine (50 mL) and dried over Na$_2$SO$_4$. Evaporation of the solvent gave crude 1,4-diamine **18** (8.61 g, 39.7 mmol, 98%) as a purple solid. Owing to its sensitivity, the product was used without further purification for the preparation of **19**. Benzenesulfonyl chloride (14.0 g, 79.4 mmol) was added to a solution of **18** (8.61 g, 39.7 mmol) in dry degassed pyridine (300 mL) and the mixture stirred for 3 h at 80 °C. After concentration to a volume of about 100 mL, ice-cold aqueous hydrochloric acid (500 mL, 5% HCl) was added, the resulting black oil separated and crystallized from glacial acetic acid to give **19** (16.0 g, 32,2 mmol, 81%) as colorless crystals. M.p. 208.5 °C (decomposition); IR (KBr): $\tilde{\nu}$ = 3252 (N–H), 1596 (Ar), 1384 (S=O), 1322 (C–N), 1166 (C–O–C), 1044 cm^{-1} (Ar–Br); ^{1}H NMR (200 MHz, CDCl$_3$): 3.41 (s, 3H, O–CH$_3$), 6.13 (br s, 1H, N–H), 6.53 (br s, 1H, N–H), 6.66 (d, *J* = 2.5 Hz, 1H, 3-H), 6.77 (d, *J* = 2.5 Hz, 1H, 5-H), 7.40–7.66 (m, 8H, Ph–H), 7.70–7.83 (m, 2H, Ph–H); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 55.07 (O–CH$_3$), 102.0 (C-3), 114.4 (C-5), 119.6 (C-6), 126.1 (C-1), 126.4 (C-2″, C-6″), 126.7 (C-2′, C-6′), 128.4 (C-3″, C-5″), 129.4 (C-3′, C-5′), 132.0 (C-4″), 133.3 (C-4′), 138.7 (C-4), 139.0 (C-1″), 142.2 (C-1′), 157.3 (C-2); MS (70 eV): *m*/*z* (%) = 496 (8.0) [*M*$^+$], 355 (100) [*M* – SO$_2$Ph$^+$], 215 (25) [*M* – 2 × SO$_2$Ph$^+$], 141 (21) [SO$_2$Ph$^+$], 77 (33) [C$_6$H$_5^+$]; $C_{19}H_{17}N_2O_5S_2Br$ (497.3): calcd C 45.88, H 3.44; found C 46.19, H 3.62.

***N,N′*-Diallyl-*N,N′*-dibenzenesulfonyl-6-bromo-2-methoxy-1,4-phenylenediamine (20)**: As in the preparation of **6**, compound **20** was synthesized by the reaction of **19** (1.50 g, 3.02 mmol), NaH (152 mg, 6.33 mmol), allylbromide (0.53 mL, 6.03 mmol), and *n*Bu$_4$NI (20 mg) in THF (30 mL). Recrystallization from ethanol gave **19** (1.40 g, 2.42 mmol, 80%) as colorless crystals. M.p. 104.2 °C; IR (KBr): $\tilde{\nu}$ = 3086 (Ar–H), 1644 (C=C), 1448 (C–H), 1350 (S=O), 1168 (C–O–C), 1046 cm^{-1} (Ar–Br); ^{1}H NMR (200 MHz, CDCl$_3$): δ = 3.27 (s, 3H, O–CH$_3$), 3.83–4.30 (m, 4H, 2 × CH$_2$), 4.82–5.14 (m, 4H, 2 × CH=C*H*$_2$), 5.57–5.89 (m, 2H, 2 × C*H*=CH$_2$), 6.57 (d, *J* = 2.4 Hz, 1H, 3-H), 6.62 (d, *J* = 2.4 Hz, 1H, 5-H), 7.36–7.62 (m, 8H, Ph–H), 7.69–7.78 (m, 2H, Ph–H); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 52.71, 53.39 (2 × CH$_2$), 55.42 (O–CH$_3$), 112.1 (C–3), 118.2, 119.4 (2 × CH=*C*H$_2$), 123.7 (C-5), 126.2 (C-6), 127.6 (C-2″, C-6″), 127.7 (C-2′, C-6′), 128.1 (C-1), 128.5 (C-3″, C-5″), 128.9 (C-3′, C-5′), 132.2, 132.4 (2 × *C*H=CH$_2$), 132.7 (C-4″), 133.1 (C-4′), 137.5 (C-1″), 140.7 (C-1′, C-4), 158.1 (C-2); MS (70 eV): *m*/*z* (%) = 437 (12) [*M*$^+$], 437 (100) [*M* – SO$_2$Ph$^+$], 295 (6.3) [*M* – 2 × SO$_2$Ph$^+$], 77 (6) [C$_6$H$_5^+$]; $C_{25}H_{25}N_2O_5S_2Br$ (578.3): calcd C 51.99 H 4.36; found C 52.26 H 4.20.

(3-*RS*)-5-(Allylbenzenesulfonylamino)-1-benzenesulfonyl-6-methoxy-4-iodo-3-iodomethyl-2,3-dihydro-1*H*-indole (11):

*a) Starting from compound **6***: A solution of *tert*-butyllithium in hexane (0.41 mL, 0.70 mmol, 1.7 M) was slowly added to a solution of **6** (200 mg, 0.34 mmol) and Cp$_2$ZrMeCl (106 mg, 0.35 mmol) in dry degassed THF (10 mL) at –78 °C under stirring, and stirring was continued for 1 h at –78 °C and then for 18 h at 20 °C. The solvent was evaporated in vacuo and the residue dissolved in CH$_2$Cl$_2$ (20 mL). To this solution a suspension of sublimed iodine (178 mg, 0.72 mmol) in CH$_2$Cl$_2$ (20 mL) was added slowly at 0 °C and the mixture stirred for 1 h at 0 °C and for 36 h at 20 °C. The mixture was filtered through Celite, the filtrate washed with saturated aqueous Na$_2$SO$_3$ solution and brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate = 3:1) to afford **11** (153 mg, 0.20 mmol, 60%) as a brown amorphous solid. Recrystallization from ethyl acetate afforded **11** as colorless crystals.

*b) Starting from compound **20***: According to the above described procedure, reaction of **20** (200 mg, 0.34 mmol), Cp$_2$ZrMeCl (106 mg, 0.35 mmol) and a solution of *tert*-butyllithium in hexane (0.41 mL, 0.70 mmol, 1.7 M) and followed by quenching with iodine (267 mg, 1.08 mmol) gave **11** (94.3 mg, 0.13 mmol, 37%) as colorless crystals.

M.p. 206.9 °C (decomposition); IR (KBr): $\tilde{\nu}$ = 3070 (Ar–H), 1590 (C=C), 1354 (S=O), 1166 (C–O–C), 1072 cm^{-1} (Ar–I); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.34 (dd, *J* = 10.0, 9.0 Hz, 1H, 3-CH$_a$), 3.32 (s, 3H, O–CH$_3$), 3.34–3.46 (m, 2H, 3-H, 3-CH$_b$), 3.85–4.00 (m, 2H, 2-H$_a$, 1′-H$_a$), 4.10 (d, *J* = 12.0 Hz, 1H, 2-H$_b$), 4.49 (dd, *J* = 13.5, 6.0 Hz, 1H, 1′-H$_b$), 4.93 (d, *J* = 6.0 Hz, 1H, *trans*-CH=C*H*$_2$), 4.98 (s, 1H, *cis*-CH=C*H*$_2$), 5.83–5.97 (mc, 1H, -C*H*=CH$_2$), 7.14 (s, 1H, 7-H), 7.48–7.69 (m, 6H, Ph-H), 7.72–7.79 (m, 2H, Ph–H), 7.82 (d, *J* = 8.0 Hz, 2H, Ph–H); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 7.643 (CH$_2$–I), 47.54 (C-3), 53.08 (N–CH$_2$), 55.34 (O-CH$_3$), 55.37 (C-2), 98.63 (C-7), 105.6 (C-4), 119.1 (CH=*C*H$_2$), 125.6 (C-5), 127.2 (C-2″, C-6″), 127.8 (C-2′, C-6′), 128.5 (C-3″, C-5″), 129.4 (C-3′, C-5′), 129.6 (C-3a), 132.3 (C-4″), 132.8 (*C*H=CH$_2$), 134.0 (C-4′), 136.7 (C-7a), 140.9 (C-1′), 142.1 (C-1″), 157.9 (C-6); MS (70 eV): *m*/*z* (%) = 750 (12) [*M*$^+$], 623 (5) [*M* – I$^+$], 609 (100) [*M* – SO$_2$Ph$^+$], 483 (13) [*M* – SO$_2$Ph – I$^+$], 77 (12) [C$_6$H$_5^+$]; $C_{25}H_{24}N_2O_5S_2I_2$ (750.0): calcd C 40.02, H 3.22; found C 39.65, H 3.46.

(3-*RS*)-5-(Allylbenzenesulfonylamino)-1-benzenesulfonyl-6-methoxy-4-iodo-3-hydroxymethyl-2,3-dihydro-1*H*-indole (22): A suspension of compound **11** (20.0 mg, 0.03 mmol) and Ag$_2$O (6.30 mg, 0.03 mmol) on silica gel in acetone and water (100:1) was stirred for 48 h at 20 °C. The solvent was removed in vacuo and the residue dissolved in dichloromethane, washed with water and brine, dried over MgSO$_4$, and concentrated in vacuo. Chromatography (petroleum ether/ethyl acetate = 2:1) afforded **22** (18.2 mg, 28.5 μmol, 95%) as a colorless amorphous solid. IR (KBr): $\tilde{\nu}$ = 3480, 3090, 2926, 1594, 1352, 1166 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.50 (t, *J* = 5.4 Hz, 1H, OH), 3.04–3.16 (m, 1H, 3-CH$_a$), 3.18–3.27 (m, 1H, 3-CH$_b$), 3.29 (s, 3H, O–CH$_3$), 3.77–3.85 (m, 2H, 2-H$_a$, 3-H), 3.96 (dd, *J* = 14.4, 8.4 Hz, 1H, 2′-H$_a$), 4.27 (dd, *J* = 10.5, 1.5 Hz, 1H, 2-H$_b$), 4.37 (dd, *J* = 14.4, 8.4 Hz, 1H, 2′-H$_b$), 4.96 (dd, *J* = 13.5, 1.8 Hz, 2H, CH=C*H*$_2$), 5.84–5.99 (m, 1H, C*H*=CH$_2$), 7.13 (s, 1H, 7-H), 7.47–7.69 (m, 6H, Ph–H), 7.70–7.77 (m, 2H, Ph–H), 7.81–7.86 (m, 2H, Ph–H); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 46.98 (C-3), 52.77 (N–CH$_2$), 53.22 (C-2), 55.26 (O–CH$_3$),

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62.48 (O–CH_2), 98.08 (C-7), 105.4 (C-4), 118.9 (CH=CH_2), 125.0 (C-5), 127.3 (C-2″, C-6″), 127.8 (C-2′, C-6′), 127.9 (C-3a), 128.5 (C-3″, C-5″), 129.3 (C-3′, C-5′), 132.3 (C-4″), 133.0 (*C*H=CH_2), 133.8 (C-4′), 136.8 (C-7a), 141.0 (C-1′), 142.8 (C-1″), 157.6 (C-6); MS (70 eV): *m/z* (%) = 640 (8) [M^+], 499 (100) [$M - SO_2Ph^+$], 144 (8) [SO_2Ph^+], 77 (75) [$C_6H_5^+$]; $C_{25}H_{25}N_2O_6S_2I$ (640.5): calcd C 46.88, H 3.93; found C 47.02, H 3.96.

(3-*RS*)-5-(Allylbenzenesulfonylamino)-1-benzenesulfonyl-6-methoxy-4-iodo-3-acetoxymethyl-2,3-dihydro-1*H*-indole (**5**): A mixture of **22** (200 mg, 0.31 mmol) and NaOAc (31.0 mg, 0.38 mmol) in acetic anhydride (2 mL) was stirred for 1 h at 60 °C. The suspension was diluted with dichloromethane (10 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/ethyl acetate = 2:1) provided **5** (211 mg, 0.31 mmol, 99 %) as a colorless solid. IR (KBr): $\tilde{\nu}$ = 3068, 2942, 1742, 1594, 1354), 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.05 (s, 3H, OAc), 3.32 (s, 3H, OCH_3), 3.34–3.47 (m, 2H, 3-CH_a, 3-H), 3.80 (dd, *J* = 10.5, 7.8 Hz, 1H, 3-CH_b), 3.97 (dd, *J* = 13.5, 8.0 Hz, 1H, 2-H_a), 4.11 (d, *J* = 10.5 Hz, 1H, 2′-H_a), 4.24–4.40 (m, 2H, 2′-H_b, 2-H_b), 4.94 (d, *J* = 8.0 Hz, 1H, CH=CH*H*), 4.98 (s, 1H, CH=C*H*H), 5.81–5.96 (m, 1H, C*H*=CH_2), 7.14 (s, 1H, 7-H), 7.46–7.70 (m, 6H, Ph–H), 7.74 (d, *J* = 7.5 Hz, 2H, Ph–H), 7.82 (d, *J* = 7.5 Hz, Ph–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.79 (CH_3), 43.83 (C-3), 53.00 (C-2), 53.15 (N–CH_2), 55.30 (O–CH_3), 63.62 (O–CH_2), 98.11 (C-7), 105.6 (C-4), 119.1 (CH=CH_2), 125.3 (C-5), 127.0 (C-3a), 127.2 (C-2″, C-6″), 127.9 (C-2′, C-6′), 128.5 (C-3″, C-5″), 129.4 (C-3′, C-5′), 132.3 (C-4″), 132.7 (*C*H=CH_2), 134.0 (C-4′), 136.7 (C-7a), 141.0 (C-1′), 142.8 (C-1″), 157.9 (C-6), 170.5 (C=O); MS (70 eV): *m/z* (%) = 682 (7) [M^+], 541 (100) [$M - SO_2Ph^+$], 400 (2) [$M - 2 \times SO_2Ph^+$]; $C_{27}H_{27}N_2O_7S_2I$ (682.6): calcd C 47.51, H 3.99; found C 47.97, H 4.11.

(1-*RS*)-6-Benzenesulfonyl-3-benzenesulfonyl-1-acetoxymethyl-8-methylidene-1,2,7,8-tetrahydro-6*H*-pyrrolo[3,2-*e*]indole (**23**): A mixture of **5** (100 mg, 0.15 mmol), Ag_2CO_3 (81.6 mg, 0.29 mmol), $Pd(OAc)_2$ (7.00 mg, 0.03 mmol), PPh_3 (16.0 mg, 0.06 mmol), and DMF (2 mL) was stirred at 20 °C for 3 h. After dilution with Et_2O, the reaction mixture was filtered, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to give **23** (79.0 mg, 0.14 mmol, 90 %) as an amorphous solid. IR (KBr): $\tilde{\nu}$ = 3066, 2928, 1738, 1608, 1358, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3H, OAc), 2.85 (t, *J* = 10.1 Hz, 1H, 1-H), 3.40–3.66 (m, 1H, 1-CH_b), 3.70–3.80 (m, 1H, 1-CH_a), 3.76 (s, 3H, OCH_3), 3.96 (dd, *J* = 11.2, 3.6 Hz, 1H, 2-H_a), 4.12 (d, *J* = 11.2 Hz, 1H, 2-H_b), 4.69 (s, 2H, 7-H_a, 7-H_b), 5.04 (s, 1H, 8-CH*H*), 5.28 (s, 1H, 8-C*H*H), 7.28–7.36 (m, 2H, Ph–H), 7.38 (s, 1H, 4-H), 7.45–7.57 (m, 3H, Ph–H), 7.58–7.67 (m, 3H, Ph–H), 7.80 (d, *J* = 6.7 Hz, 2H, Ph–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.83 (CH_3), 37.81 (C-1), 53.59 (C-2), 56.25 (O–CH_3), 57.47 (C-7), 63.41 (O–CH_2), 101.4 (C-4), 107.2 (8-CH_2), 116.6 (C-1a), 127.3, 127.4 (C-2″, C-6″, C-2′, C-6′), 128.5, 129.3 (C-3″, C-5″, C-3′, C-5′), 130.6 (C-5a), 131.3 (C-8), 132.7, 133.7 (C-4″, C-4′), 136.5 (C-3a), 139.0 (C-1′), 140.8 (C-8a), 141.4 (C-1″), 151.7 (C-5), 170.7 (C=O); MS (70 eV): *m/z* (%) = 554 (30) [M^+], 413 (100) [$M - SO_2Ph^+$], 353 (7) [$M - SO_2Ph - C_2H_4O_2^+$], 212 (40) [$M - 2 \times SO_2Ph - C_2H_4O_2^+$], 77 (27) [$C_6H_5^+$]; $C_{27}H_{26}N_2O_7S_2$ (554.6): calcd C 58.47, H 4.72; found C 58.55, H 4.86.

(1-*RS*)-6-Benzenesulfonyl-3-benzenesulfonyl-5-methoxy-1-acetoxymethyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole (**24**): A solution of **23** (33.0 mg, 0.06 mmol) and camphorsulfonic acid (27.0 mg, 0.12 mmol) in dichloromethane (5 mL) was stirred for 2 h at 20 °C. The mixture was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (petroleum ether/ethyl acetate = 2:1) afforded **24** (33.3 mg, 0.06 mmol, 99 %) as an amorphous solid. IR (KBr): $\tilde{\nu}$ = 3066, 2956, 1740, 1604, 1358, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3H, OAc), 2.32 (s, 3H, 8-CH_3), 2.94 (t, *J* = 10.5 Hz, 1H, 1-H), 3.68 (s, 3H, OCH_3), 3.61–3.71 (m, 1H, 1-CH_a), 3.78 (dd, *J* = 10.5, 8.0 Hz, 1H, 1-CH_b), 4.10–4.18 (m, 2H, 2-H_a, 2-H_b), 7.21 (s, 1H, 7-H), 7.27 (s, 1H, 4-H), 7.40–7.62 (m, 6H, Ph–H), 7.76 (d, *J* = 7.5 Hz, 2H, Ph–H), 7.72 (d, *J* = 7.5 Hz, 2H, Ph–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.08 (8-CH_3), 20.82 (OAc), 38.45 (C-1), 53.67 (C-2), 55.62 (O–CH_3), 65.75 (O–CH_2), 95.83 (C-4), 113.4 (C-8), 114.9 (C-8a), 122.5 (C-1a), 126.9, 127.2 (C-2″, C-6″, C-2′, C-6′), 127.7 (C-7), 128.8, 129.1 (C-3″, C-5″, C-3′, C-5′), 130.6 (C-5a), 133.1, 133.4 (C-4″, C-4′), 136.4 (C-3a), 139.0, 140.4 (C-1″, C-1′), 148.0 (C-5), 170.5 (C=O); MS (70 eV): *m/z* (%) = 554 (85) [M^+], 481 (32) [$M - C_3H_5O_2^+$], 413 (70) [$M - SO_2Ph^+$], 353 (100) [$M - SO_2Ph - C_2H_4O_2^+$], 212 (82) [$M - 2 \times SO_2Ph - C_2H_4O_2^+$], 77 (88) [$C_6H_5^+$]; $C_{27}H_{26}N_2O_7S_2$ (554.6): calcd C 58.47, H 4.72; found C 58.55, H 4.86.

(1-*RS*)-6-Benzenesulfonyl-3-benzenesulfonyl-5-hydroxy-1-acetoxymethyl-8-methyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole (**25**): Boron tribromide (1.00 mL, 1.00 mmol, 1M in dichloromethane) was added dropwise with stirring to a solution of **24** (100 mg, 0.18 mmol) in dichloromethane (2 mL) at −10 °C, and stirring was continued for 4 h. The reaction mixture was diluted with water (5 mL) and dichloromethane (15 mL), the organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/ethyl acetate = 2:1) provided **25** (90.0 mg, 0.17 mmol, 93 %) as an amorphous solid. IR (KBr): $\tilde{\nu}$ = 3342, 3070, 2960, 1738, 1614, 1360, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3H, OAc), 2.21 (s, 3H, 8-CH_3), 3.10 (dd, *J* = 10.0, 9.0 Hz, 1H, 1-CH_a), 3.52–3.78 (m, 2H, 1-H, 1-CH_b), 4.06 (dd, *J* = 11.5, 3.5 Hz, 1H, 2-H_a) 4.16 (d, *J* = 11.5 Hz, 2-H_b), 7.15 (s, 1H, 7-H), 7.37 (s, 1H, 4-H), 7.38–7.63 (m, 6H, Ph–H), 7.76 (d, *J* = 8.0 Hz, 2H, Ph–H), 7.85 (d, *J* = 8.0 Hz, 2H, Ph–H), 8.85 (s, 1H, Ph–OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.23 (8-CH_3), 20.75 (OAc), 38.17 (C-1), 53.67 (C-2), 65.48 (O–CH_2), 101.3 (C-4), 112.8 (C-8), 120.3 (C-8a), 120.5 (C-1a), 126.9, 127.3 (C-2″, C-6″, C-2′, C-6′), 127.0 (C-7), 129.1, 129.5 (C-3″, C-5″, C-3′, C-5′), 131.6 (C-5a), 133.4, 134.2 (C-4″, C-4′), 136.4 (C-3a), 136.6, 140.5 (C-1″, C-1′), 145.8 (C-5), 170.6 (C=O); MS (70 eV): *m/z* (%) = 540 (62) [M^+], 467 (50) [$M - C_3H_5O_2^+$], 339 (100) [$M - SO_2Ph - C_2H_4O_2^+$], 198 (42) [$M - 2 \times SO_2Ph - C_2H_4O_2^+$]; $C_{26}H_{24}N_2O_7S_2$ (540.6): calcd C 57.77, H 4.47; found C 57.83, H 4.46.

(1-*RS*)-6-Benzenesulfonyl-3-benzenesulfonyl-5-hydroxy-1-hydroxymethyl-8-methyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole (**26**): A suspension of **25** (25.0 mg, 0.05 mmol) and potassium carbonate (19.0 mg, 0.13 mmol) in methanol (2 mL) was stirred for 2 h at room temperature. The solvent was evaporated in vacuo and the residue purified by column chromatography (petroleum ether/ethyl acetate = 1:1) to yield **26** (24.9 mg, 0.05 mmol, quant.) as an amorphous colorless solid. IR (KBr): $\tilde{\nu}$ = 3354, 3066, 2926, 1612, 1356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.52 (br s, 1H, CH_2–O*H*), 2.19 (d, *J* = 2.2 Hz, 1H, 8-CH_3), 2.89–3.08 (m, 1H, 1-H), 3.39–3.55 (m, 2H, CH_2–OH), 3.73 (dd, *J* = 11.2, 8.9 Hz, 1H, 2-H_a), 4.20 (d, *J* = 11.2 Hz, 1H, 2-H_b), 7.16 (d, *J* = 2.2 Hz, 1H, 7-H), 7.39 (s, 1H, 4-H), 7.40–7.62 (m, 6H, Ph–H), 7.76 (dd, *J* = 6.7, 1.8 Hz, 2H, Ph–H), 7.87 (dd, *J* = 6.7, 1.8 Hz, 2H, Ph–H), 8.84 (s, 1H, Ph–OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.51 (8-CH_3), 41.24 (C-1), 53.71 (C-2), 65.19 (O–CH_2), 101.3 (C-4), 114.0 (C-8), 120.3 (C-8a), 120.5 (C-1a), 127.0, 127.4 (C-2″, C-6″, C-2′, C-6′), 129.0 (C-7), 129.1, 129.5 (C-3″, C-5″, C-3′, C-5′), 131.9 (C-5a), 133.3, 134.1 (C-4″, C-4′), 136.7 (C-3a), 136.6, 140.6 (C-1″, C-1′), 145.5 (C-5); MS (70 eV): *m/z* (%) = 498 (17) [M^+], 467 (37) [$M - CH_3O^+$], 327 (29) [$M - SO_2Ph - CH_3O^+$], 218 (100) [$M - 2 \times SO_2Ph - CH_3O^+$]; $C_{24}H_{22}N_2O_6S_2$ (498.6): calcd 498.0919; found 498.0919 (MS).

(1-*RS*)-3-Benzenesulfonyl-5-hydroxy-1-hydroxymethyl-8-methyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole (**4**):

*a) Starting from compound **26***: Sodium bis(2-methoxyethoxy)dihydroaluminate (Red-Al) (0.05 mL, 0.20 mmol, 70 % in toluene) was added dropwise at 20 °C to a stirred solution of **26** (11.0 mg, 0.02 mmol) in toluene (3 mL). After 3 h the reaction mixture was diluted with phosphate buffer (5 mL, pH 7.0) and ethyl acetate (10 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (petroleum ether/ethyl acetate = 1:1) of the residue provided **4** (6.50 mg, 18.1 μmol, 91 %) as a colorless solid.

*b) Starting from compound **25***: Similarly, **25** (11.0 mg, 0.02 mmol) was treated with Red-Al (0.05 mL, 0.20 mmol, 70 % in toluene) in toluene (3 mL) at 20 °C for 18 h to give **4** (6.49 mg, 18.0 μm) in 90 % yield.

IR (KBr): $\tilde{\nu}$ = 3340, 3060, 2926, 1614, 1348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (br s, 1H, CH_2–O*H*), 2.29 (s, 3H, 8-CH_3), 2.81 (t, *J* = 9.0 Hz, 1H, 1-H), 3.53–3.65 (m, 2H, 1-CH_2), 3.85 (dd, *J* = 12.0, 9.0 Hz, 1H, 2-H_a), 4.21 (d, *J* = 9.0 Hz, 1H, 2-H_b), 5.66 (br s, 1H, Ph–OH), 6.93 (s, 1H, 7-H), 7.23 (s, 1H, 4-H), 7.37–7.45 (m, 2H, Ph–H), 7.49–7.55 (m, 1H, Ph–H), 7.83 (d, *J* = 7.5 Hz, 2H, Ph–H), 8.15 (br s, 1H, N–H); MS (70 eV): *m/z* (%) = 358 (85) [M^+], 327 (100) [$M - CH_2OH^+$], 217 (92) [$M - SO_2Ph^+$], 187 (86) [$M - SO_2Ph - CH_3O^+$], 142 (14) [SO_2Ph^+]; $C_{18}H_{18}O_4NS$ (358.5): calcd 358.09837; found 358.09837 (MS).

Acknowledgments: Generous financial support by the Deutsche Forschungsgemeinschaft (SFB 416) and the Fonds der Chemischen Industrie is gratefully appreciated.

Received: January 27, 1998 [F978]

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