Synthesis of (±)-N^2-(Benzenesulfonyl)-CPI, the Protected A-Unit of the Antitumor Antibiotic CC-1065, by Two Metal-Initiated Cyclizations[1]

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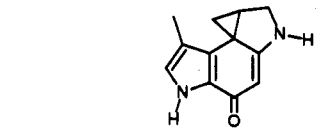
A new synthetic route to (±)-N^2-(Benzenesulfonyl)-CPI (**16**), the protected A-unit containing a cyclopropylhexadienone moiety of the highly potent antitumor antibiotic CC-1065 (**1**), from 5-(benzyloxy)-2-bromophenylamine (**3**) is described. The key steps are a zirconium- and a palladium-initiated cyclization to give the two pyrrole moieties. Reaction of **4a** with zirconocene (methyl) chloride leads after workup with I_2 to the 4-iodoindoline **7a**, which was transformed into **12** and subsequently via Heck reaction into the pyrroloindoline **15**.

Introduction

Cancer chemotherapy is badly hampered by the narrow therapeutic range of the currently available anticancer agents, and the treatment often has to be terminated because of severe side effects. In the course of our investigations[2] toward the design of tumor-selective cytotoxic drugs, we exploited phenotypic differences between malignant and normal cells. Thus, it has been shown that the pH in cancer tissue decreases to an average of 6.2 under hyperglycemic conditions, whereas the pH in the normal tissue is around 7.2 and is nearly not effected.[3] Recently, we have developed a new drug based on these differences with a phosphoramide mustard[4] as the toxic compound, which showed an increase in toxicity by the factor of 10^4 at pH 6.2 as compared to pH 7.2 according to the survival rate of different cancer cells in tissue cultures, and the compound was very successful in in vivo studies. Consequently, we have become interested in highly toxic compounds which can be detoxified by the formation of derivatives which may be cleaved at pH 6.2 with liberation of the toxin. In this paper, we describe a new synthesis of the A-unit of the antitumor antibiotic CC-1065 (**1**), which was isolated from *Streptomyces zelensis*[5] and is one of the most potent antitumor agents known. It has been shown that the A-unit **2** of CC-1065 alkylates probably reversibly and sequence-selectively the B-DNA minor groove sites [5′d(A/GNTTA)-3′and 5′d(AAAAA)-3′][6]. The dimeric pyrroloindole (B/C)-unit is responsible for the high binding specifity to the DNA. The monomers B and C are known as phosphodiesterase inhibitors (PDE-I, PDE-II).

The synthesis of CC-1065 and related analogues has been the subject of intense effort,[7] which culminated in



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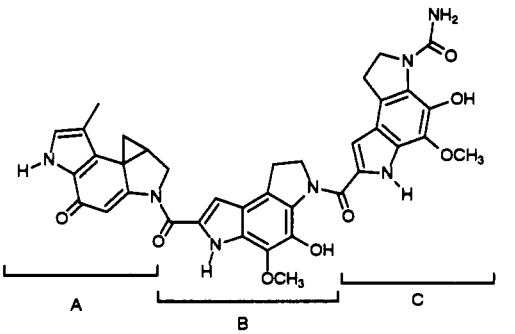

CC-1065 1

the first total synthesis of CC-1065 (**1**) by Boger et al.[8] The final step in the synthesis is the formation of the highly labile spirocyclopropylcyclohexadienone moiety in **1** by a Winstein cyclization.[9] In our synthesis of the A-unit we used two successive metal-initiated cyclizations for the formation of the pyrroline and the pyrrole ring starting from 5-(benzyloxy)-2-bromophenylamine[7f] (**3**). The first

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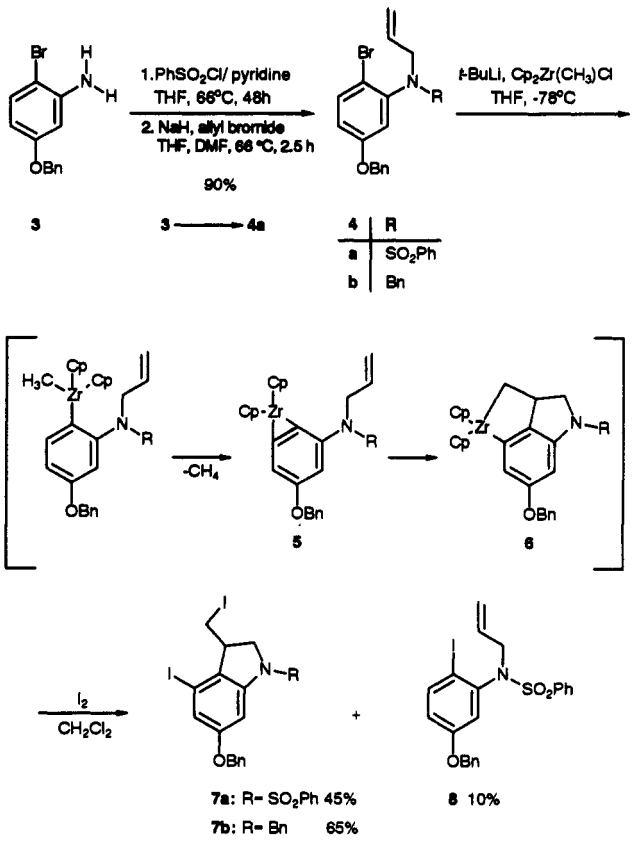
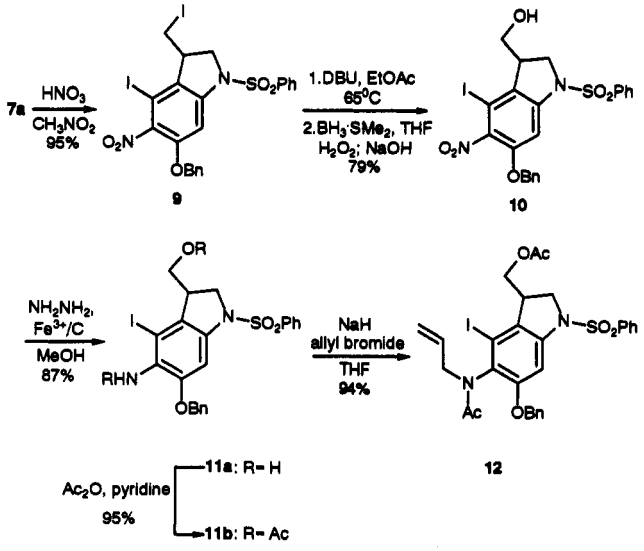
Scheme 1



Scheme 2



key step is a zirconocene (methyl) chloride mediated reaction according to Buchwald et al.[10] of **4a** to give the indoline **7a** via the zirconocene complex **5a**, and the second key step is a Heck reaction of **12** to give **13a/b**, making use of the iodine at C-4 introduced in the first cyclization.

Results and Discussion

Reaction of **3**[7f] with benzenesulfonyl chloride followed by *N*-allylation of the intermediately prepared sodium salt with allyl bromide afforded **4a** in 90% yield. For the cyclization to the indoline moiety, **4a** was treated with *t*-BuLi and zirconocene (methyl) chloride[11] to give the zirconocene complex **5a**, which rearranges to the zirconacycle **6a**. Reaction of crude **6a** with iodine afforded the 3,4-diiodoindoline **7a** in 45% yield and 10% of 2-iodophenylamine **8**, which can be reused for the zirconocene-initiated cyclization instead of 2-bromophenylamine **4a**. We also investigated the zirconocene-initiated reaction of **4b** containing a benzyl instead of a benzenesulfonyl group at the nitrogen, which led to the 3,4-diiodoindoline **7b**[12] in a better yield (65%). However, we were not able to transform **7b** into the nitro compound, required for the next steps. Using concd nitric acid, the compound was inert presumably because of protonation at the aromatic amino group. However, nitration of **7a** with concd nitric acid in nitromethane at 0 °C cleanly provided the 5-nitroindoline **9** in 95% yield. The regioisomeric 7-nitroindoline could not be detected. For the Heck reaction it was necessary to reduce the nitro group in **9** and allylate the obtained amino moiety. Since the iodomethyl group at C-3 in **9** is not stable under the reaction conditions of such a reduction, it was converted into a hydroxymethyl group as in **10** by dehydrohalogenation with DBU in ethyl acetate and hydroboration[12] with BH_3·SMe_2 followed by treatment with basic hydrogen peroxide in 79% yield. All attempts to substitute the aliphatic iodine in **7a** by acetate[7m] were unsuccessful; the only product was the corresponding 3-methylene-2,3-dihydro-1*H*-indole.[13] Reduction of the nitro group in **10** with hydrazine hydrate and Fe^{3+} in methanol[14] afforded the aminoindoline **11a** in 87% yield and using these mild conditions the iodine at the benzene ring in **10** is retained. The following acetylation of the amino and hydroxy group in **11a** with acetic anhydride/pyridine gave the bisacetylated indoline **11b** (95%), which was deprotonated and treated with allyl bromide in tetrahydrofuran to provide **12**, as the immediate precursor for the following Heck reaction in 90% yield. Treatment of **12** with $Pd(OAc)_2$, NBu_4Cl, and NaOAc in *N*,*N*-dimethylformamide according to the procedure published by Larock et al.[15] afforded a mixture of the 8-methylene-7,8-dihydro-6*H*-indole **13a** and the 8-methylindole **13b** in 64% and 30% yield, respectively. **13a** is the primary β-hydride elimination product, which under the reaction conditions should subsequently isomerize to the thermodynamically more stable product **13b** by a readdition–β-elimination process.[16] However, against our expectations the amount of **13b** did not depend on the reaction time; thus, even stirring the mixture for three days did not change the ratio of **13a** to **13b**. Also, all attempts to isomerize pure **13a** to **13b** using $Pd(OAc)_2$, NBu_4Cl, and NaOAc in *N*,*N*-dimethylformamide at temperatures of 100 °C failed, and only the unchanged 8-methylene-7,8-dihydro-6*H*-indole **13a** was recovered. We also used $Pd(PPh_3)_4$ in the Heck reaction; here, **13b** was the main product. Thus, reaction of **12** with $Pd(PPh_3)_4$

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(13) 1-(Benzenesulfonyl)-6-(benzyloxy)-4-iodo-3-methylene-2,3-dihydro-1*H*-indole: ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (t, *J* = 2.90 Hz, 2 H), 4.78 (dt, *J* = 1.00, 2.90 Hz, 1 H), 5.12 (s, 2 H), 6.15 (dt, *J* = 1.00, 2.90 Hz, 1 H), 7.11 (d, *J* = 2.20 Hz, 1 H), 7.32–7.65 (m, 11 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.29, 70.17, 89.49, 101.1, 104.3, 122.5, 123.1, 127.1, 127.4, 128.2, 128.5, 128.7, 129.2, 136.1, 136.3, 136.8, 138.8, 146.9, 159.5.

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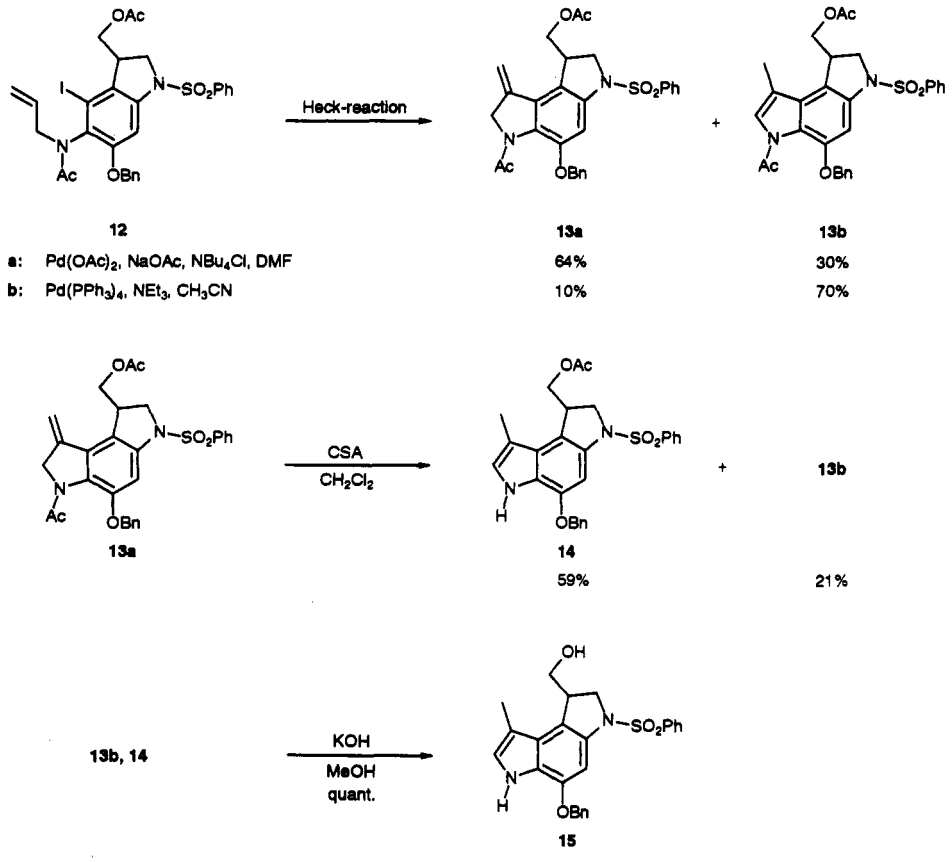
Scheme 3



and NEt_3, in CH_3CN at 78 °C for 3 days afforded a mixture of **13a** and **13b** in a ratio of 1:7 in 80% yield. However, isomerization of **13a** to give the indole moiety can easily be achieved with camphorsulfonic acid in dichloromethane, which led to a mixture of the 6-acetyl-8-methylindole **13b** (21%) and the deacetylated 8-methylindole **14** (59%). Solvolysis of the mixture of **13b** and **14** with potassium hydroxide in methanol gave 1-(hydroxymethyl)indole **15**[8] quantitively. A base-catalyzed isomerization and solvolysis of **13a** to give **15** in one step was not possible. The catalytic hydrogenolysis with Pd on carbon in ethyl acetate/ethanol of the benzyl ether in **15** and the final Ar-3′ cyclization to the spirocyclopropylcyclohexadienone **16** is described by Boger et al.[8]

Summary

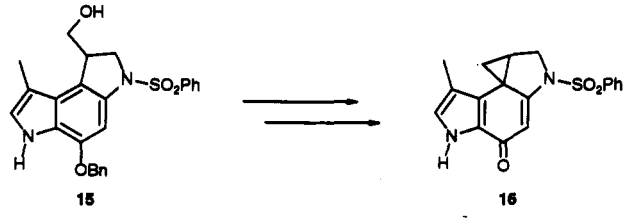
(±)-N^2-(Benzenesulfonyl)-CPI (**16**), the protected A-unit of CC-1065, was synthesized in 13 steps from **3** with an overall yield of 8%. The two pyrrole moieties in **16** were obtained by a zirconocene and a Pd(0)-initiated cyclization. It should be stressed that in the first cyclization a iodinated benzene moiety **7a** is obtained with the iodine at the correct position as needed for the following Heck reaction. Also, the nitrogen at C-5 was introduced completely regioselectively. Thus, the described synthesis represents an excellent entry to the racemic CPI unit. However, also the enantiopure CPI unit may be synthesized by this route, since Boger et al.[8] have shown that **15** can be resolved after cleavage of the *N*-benzenesulfonyl group and formation of a BOC amide.

Experimental Section

Instrumentation. Multiplicities of ^{13}C NMR peaks were determined with APT pulse sequence. Mass spectra were measured at 70 eV. IR spectra were recorded as KBr pellets or as films. Melting points are corrected.

Materials. All solvents were dried and distilled prior to use. All reactions were performed in flame-dried flasks under a positive pressure of nitrogen and monitored by TLC (Machery, Nagel & Co. Sil G/UV_{254}). Flash chromatography was carried out on SiO_2 (Silica Woelm 32-63 active, Fa. Woelm Pharma, Eschwege).

Scheme 4



***N*-Allyl-*N*-(benzenesulfonyl)-5-(benzyloxy)-2-bromophenylamine (4a).** A solution of 5-(benzyloxy)-2-bromophenylamine (**3**)[7f] (4.17 g 10.0 mmol) in anhydrous DMF (50 mL) was treated with NaH (250 mg, 10.0 mmol) and stirred for 30 min at 23 °C (evolution of hydrogen); allyl bromide was added, and the reaction mixture was warmed at 90 °C for 2 h. The mixture was treated with saturated aqueous NaCl (50 mL), diluted with Et_2O (120 mL), and separated. The Et_2O layer was washed with H_2O (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. Crystalization from EtOH afforded **4a** (4.36 g, 95%) as a white solid: mp 92 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 4.19 (m, 2 H), 4.97 (m, 4 H), 5.77 (dtt, J = 16.9, 10.2, 6.4 Hz, 1 H), 6.69 (d, J = 2.9 Hz, 1 H), 6.83 (dd, J = 8.9, 2.9 Hz, 1 H), 7.30–7.62, 7.75–7.83 (m, 11 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.89, 70.30, 116.1, 117.1, 118.9, 119.5, 127.5, 127.8, 128.2, 128.7, 128.9, 132.3, 132.8, 133.9, 136.1, 138.0, 139.6, 157.9); MS (70 eV) 459 (20, M^+), 91 (100, $C_7H_7^+$); IR (KBr) 3090, 2864, 1598, 1571, 1478, 1237 cm^{-1}. Anal. Calcd. for $C_{22}H_{20}BrNO_3S$: C, 58.65; H, 4.40. Found: C, 58.36; H, 4.70.

(3*RS*)-1-(Benzenesulfonyl)-6-(benzyloxy)-4-iodo-3-(iodomethyl)-2,3-dihydro-1*H*-indole (7a). A flame-dried Schlenk flask was charged with a stir bar, THF (50 mL), zirconocene

(methyl) chloride (2.39 g, 8.8 mmol), and **4a** (4.04 g, 8.8 mmol). The solution was cooled to −78 °C, and *tert*-butyllithium in hexane (17.6 mmol) was added. Stirring was continued at −78 °C for 15 min, after which time the solution was allowed to warm to 23 °C and stirred for an additional 2 h. The THF was then removed in vacuo, and the residue was dissolved in CH_2Cl_2 (50 mL). To this solution was added a suspension of I_2 (5.20 g, 20.5 mmol) in CH_2Cl_2 (50 mL), and stirring was continued at 0 °C for 4 h. The CH_2Cl_2 was removed in vacuo and the residue dissolved in Et_2O (100 mL). The organic layer was washed with saturated aqueous Na_2SO_3 (3 × 100 mL) and H_2O (3 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (200 g SiO_2, EtOAc/petroleum ether (1:10)) yielded **7a** (2.3 g, 45%) as a yellow solid: mp 49 °C (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (m, 1 H), 3.33 (m, 2 H, 2-H), 3.87 (m, 1 H), 4.09 (dd, J = 11.5, 1.9 Hz, 1 H), 5.10 (s, 2 H), 7.05 (d, J = 2.9 Hz, 1 H), 7.30–7.82 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.75, 46.39, 55.68, 70.39, 92.39, 102.3, 120.6, 127.2, 127.6, 128.2, 128.7, 128.8, 136.2, 136.5, 142.3, 160.0; MS (70 eV) 631 (18, M^+), 504 (22, $M^+ - I$), 91 (100, $C_7H_7^+$); IR (KBr) 3440, 2934, 1598, 1448, 1168, 1026 cm^{-1}. Anal. Calcd for $C_{22}H_{19}I_2NO_3S$: C, 41.86; H, 3.03. Found: C, 41.99; H, 3.32.

***N*-Allyl-*N*-(benzenesulfonyl)-5-(benzyloxy)-2-iodophenylamine (8)** (405 mg, 10%) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 4.15 (m, 2 H), 4.95 (m, 4 H), 5.76 (dtt, J = 16.9, 10.2, 6.4 Hz, 1 H), 6.52 (d, J = 2.9 Hz, 1 H), 6.74 (dd, J = 8.9, 2.9 Hz, 1 H), 7.30–7.62, 7.75–7.83 (m, 11 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.50, 70.08, 91.32, 117.1, 117.8, 119.7, 127.3, 127.5, 128.0, 128.6, 128.9, 131.9, 132.9, 136.4, 139.2, 140.1, 158.8; MS (70 eV) 505 (20, M^+), 378 (30, $M^+ - I$), 91 (100, $C_7H_7^+$); IR (KBr) 3090, 3034, 2864, 1598, 1478, cm^{-1}; EIHRMS m/e 505.0081 $C_{22}H_{20}INO_3S$ requires 505.0081).

(3*RS*)-1-(Benzenesulfonyl)-6-(benzyloxy)-4-iodo-3-(iodomethyl)-5-nitro-2,3-dihydro-1*H*-indole (9). Nitric acid (90%, 0.45 mL, 6.9 mmol) was slowly added to a solution of **7a** (2.11 g, 3.36 mmol) in 120 mL of nitromethane at 0 °C. After being stirred for 1 h at 0 °C and 2 h at rt, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with saturated aqueous sodium bicarbonate (2 × 100 mL) and saturated NaCl (2 × 100 mL). After drying ($MgSO_4$), the organic layer was concentrated in vacuo. Crystalization from EtOAc/hexane afforded **9** (2.2 g, 95%) as yellow crystals (EtOAc/petroleum ether (1:7)): mp 171 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.83 (dd, J = 11.0, 8.5 Hz, 1 H), 3.35 (dd, J = 11.0, 2.8 Hz, 1 H), 3.45 (m, 1 H), 3.84 (dd, J = 11.0, 2.8 Hz, 1 H), 3.98 (dd, J = 11.0, 8.5 Hz, 1 H), 5.40 (s, 2 H), 7.34 (s, 1 H), 7.35–7.78 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.27, 44.44, 55.48, 70.80, 87.58, 100.1, 126.4, 127.1, 127.2, 127.9, 128.6, 129.7, 129.4, 134.3, 135.5, 141.9, 142.6, 150.8; MS (70 eV) 676 (15, M^+), 549 (6, $M^+ - I$), 91 (100, $C_7H_7^+$); IR (KBr) 3444, 2952, 1596, 1446, 1362 cm^{-1}. Anal. Calcd for $C_{22}H_{18}I_2N_2O_5S$: C, 39.07; H, 2.68. Found: C, 39.02; H, 2.66.

(3*RS*)-1-(Benzenesulfonyl)-6-(benzyloxy)-3-(hydroxymethyl)-4-iodo-5-nitro-2,3-dihydro-1*H*-indole (10). A stirred solution of **9** (1.50 g, 2.22 mmol) in EtOAc (40 mL) was charged with DBU (383 μL, 2.66 mmol) and heated for 30 min at 60 °C, after which time it was concentrated in vacuo. The residue was dissolved in THF (40 mL), cooled to 0 °C, and treated with borane methyl sulfide (440 μL, 4.40 mmol). The reaction mixture was allowed to warm to rt and stirred for 3 h. After being cooled to 0 °C, it was treated sequentially with H_2O (2.20 mL), 2 N aqueous NaOH (2.20 mL), and 30% aqueous hydrogen peroxide (1.40 mL). The reaction mixture was warmed for 30 min to 45 °C and then stirred for 16 h at 22 °C. The solution was diluted with saturated NaCl (50 mL), extracted with EtOAc (100 mL), and washed with H_2O (2 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to column chromatography (100 g SiO_2, EtOAc/petroleum ether (1:1)) to yield **10** (993 mg, 79%) as a white solid: mp 170 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.87 (ddt, J = 10.2, 8.7, 5.3 Hz, 1 H), 3.12 (m, 1 H), 3.49 (ddt, J = 10.2, 7.0, 5.3 Hz, 1 H), 3.83 (dd, J = 10.2, 8.7 Hz, 1 H), 4.14 (dd, J = 10.2, 2.0 Hz, 1 H), 5.02 (t, J = 5.3 Hz, 1 H), 5.17 (s, 2 H), 7.13 (s, 1 H), 7.18–7.65 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 45.50, 52.59, 60.82, 70.60, 87.14, 99.72, 127.0, 128.2, 128.7, 129.6, 134.1, 135.5, 135.6, 141.6, 142.8, 149.8; MS (70 eV) 566 (9, M^+), 535 (19, $M^+ - CH_2OH$), 91 (100, $C_7H_7^+$); IR (KBr) 3538, 3034, 1598, 1362, 1168 cm^{-1}. Anal. Calcd for $C_{22}H_{19}IN_2O_6S$: C, 46.65; H, 3.38. Found: C, 46.78; H, 3.59.

(3*RS*)-5-Amino-1-(benzenesulfonyl)-6-(benzyloxy)-4-iodo-3-(hydroxymethyl)-2,3-dihydro-1*H*-indole (11a). Dropwise addition of hydrazine hydrate (1.02 mL) to **10** (750 mg, 1.32 mmol), $FeCl_3$-$6H_2O$ (1.02 mg), and activated carbon (130 mg) in 4 mL of MeOH was carried out at 65 °C for 1 h. After 10 h of reflux the cooled reaction mixture was filtered, and the solid obtained was extracted with hot MeOH (10 mL). Removal of the MeOH gave an oil, which was chromatographed (50 g SiO_2, EtOAc/petroleum ether (1:1)) to give **11a** (660 mg, 87%) as white crystals: mp 155 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (m, 1 H), 2.94 (m, 1 H), 3.50 (m, 1 H), 3.65 (dd, J = 10.2, 8.7 Hz, 1 H), 4.05 (dd, J = 10.0, 2.0 Hz, 1 H), 4.58 (s, 2 H), 4.83 (t, J = 5.3 Hz, 1 H), 5.23 (s, 2 H), 7.12 (s, 1 H), 7.32–7.65 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.91, 51.99, 61.14, 69.85, 81.81, 100.4, 127.3, 127.1, 127.2, 127.8, 128.5, 129.2, 131.1, 135.0, 135.5, 136.8, 143.9; MS (70 eV) 536 (30, M^+), 395 (100, M^+ – benzenesulfonyl), 91 (95, $C_7H_7^+$); IR (KBr) 3520, 2878, 1584, 1348, 1164 cm^{-1}. Anal. Calcd for $C_{22}H_{21}IN_2O_4S$: C, 49.26; H, 3.95. Found: C, 49.42; H, 3.92.

(3*RS*)-3-(Acetoxymethyl)-5-(acetylamino)-1-(benzenesulfonyl)-6-(benzyloxy)-4-iodo-2,3-dihydro-1*H*-indole (11b). A mixture of **11a** (449 mg, 0.84 mmol), sodium acetate (83 mg, 0.84 mmol), and acetic anhydride (4 mL) was warmed at 60 °C for 90 min, cooled to rt, treated with saturated aqueous sodium bicarbonate (20 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (25 g SiO_2, EtOAc/petroleum ether (1:1)) afforded **11b** (491 mg, 95%) as a white solid: mp 87 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 3 H), 2.20 (s, 3 H), 3.32 (m, 1 H), 3.42 (m, 1 H), 3.71 (m, 1 H), 4.10 (dd, J = 10.0, 2.0 Hz, 1 H), 4.30 (m, 1 H), 5.22 (m, 2 H), 6.77 (m, 1 H), 7.25 (s, 1 H), 7.32–7.62 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.44, 22.65, 42.65, 52.38, 63.12, 69.65, 99.68, 101.4, 125.3, 126.0, 126.7, 126.9, 127.6, 128.4, 129.5, 135.5, 135.7, 140.5, 154.4, 168.3, 170.0; MS (70 eV) 620 (50, M^+), 427 (97, M^+ – benzyl – $2CH_3CO$), 91 (100, $C_7H_7^+$); IR (KBr) 3382, 1740, 1498, 1360, 1168 cm^{-1}. Anal. Calcd for $C_{26}H_{25}IN_2O_6S$: C, 50.33; H, 4.06. Found: C, 50.47; H, 4.13.

(3*RS*)-3-(Acetoxymethyl)-5-(acetylallylamino)-1-(benzenesulfonyl)-6-(benzyloxy)-4-iodo-2,3-dihydro-1*H*-indole (12). A solution of **11b** (481 mg, 0.78 mmol) in dry THF (4 mL) was treated with NaH (30 mg, 1.16 mmol) and stirred at rt under nitrogen for 15 min. Allyl bromide (80.5 mL, 0.93 mmol) was added to the reaction mixture, and stirring was continued for 1 h. The solution was quenched with H_2O (4 mL) and extracted with EtOAc (3 × 5 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the resulting residue was chromatographed (25 g SiO_2, EtOAc/petroleum ether (1:1)) to give **12** (485 mg, 94%) as a white solid: mp 56 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (2 s, 3 H), 2.05 (s, 3 H), 3.35 (m, 1 H), 3.50 (m, 1 H), 3.78 (m, 1 H), 3.92 (m, 1 H), 4.11 (dd, J = 10.0, 2.0 Hz, 1 H), 4.22 (m, 1 H), 4.49 (m, 1 H), 4.98 (m, 2 H), 5.20 (q, J = 12.3 Hz, 2 H), 5.90 (m, 1 H), 7.28 (s, 1 H), 7.35–7.62 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.30, 21.71, 42.66, 49.80, 52.58, 63.12, 70.09, 99.39, 102.1, 117.7, 117.8, 126.7, 127.1, 127.9, 128.5, 128.6, 133.3, 134.0, 135.7, 141.7, 155.0, 169.5, 169.8. MS (70 eV) 660 (60, M^+), 533 (40, $M^+ - I$), 91 (100, $C_7H_7^+$); IR (KBr) 3442, 1742, 1454, 1360, 1170 cm^{-1}. Anal. Calcd for $C_{29}H_{29}IN_2O_6S$: C, 52.73; H, 4.47. Found: C, 52.90; H,4.53.

Heck Reaction. (A) A mixture of **12** (260 mg, 0.39 mmol), NaOAc (66 mg, 0.78 mmol), $N(Bu)_4Cl$ (116 mg, 0.39 mmol), and $Pd(OAc)_2$ (2.1 mg, 0.08 mmol) in dry DMF (0.7 mL) was stirred and heated at 70 °C for 30 min under an atmosphere of dry nitrogen. The cooled reaction mixture was then filtered, diluted with H_2O (5 mL), and extracted with EtOAc (3 × 5 mL). The organic layer was dried ($MgSO_4$) and evaporated to leave a solid. Flash chromatography (20 g SiO_2, EtOAc/petroleum ether (1:1)) provided **13a** (134 mg, 64%) and **13b** (62 mg, 30%) as white solids: **13a** mp 131 °C (EtOAc/petroleum ether), **13b** mp 111 °C (EtOAc/petroleum ether).

(B) A mixture of **12** (200 mg, 0.30 mmol), triethylamine (1.50 mL, 1.50 mmol), and $Pd[P(Ph)_3]_4$ (17.33 mg, 0.015 mmol) in dry degassed CH_3CN was stirred and heated for 70 h to 65 °C under an atmosphere of dry nitrogen. The cooled reaction mixture was then filtered, diluted with H_2O (5 mL), and extracted with EtOAc

(3 × 5 mL). The organic layer was dried ($MgSO_4$), evaporated in vacuo, and chromatographed (20 g SiO_2, EtOAc/petroleum ether (1:1)) to give **13a** (12 mg, 10%) and **13b** (112 mg, 70%).

(1*RS*)-6-Acetyl-3-(benzenesulfonyl)-5-(benzyloxy)-1-(acetoxymethyl)-8-methylene-1,2,7,8-tetrahydro-6*H*-pyrrolo[3,2-*e*]indole (13a): ^1H NMR (500 MHz, $CDCl_3$) δ 2.03 (s, 3 H) 2.10 (s, 3 H), 3.04 (t, J = 10.8 Hz, 1 H), 3.61 (m, 1 H), 3.74 (ddd, J = 11.0, 8.0, 1.0 Hz, 1 H), 4.15 (dd, J = 11.0, 1.0 Hz, 1 H), 4.21 (ddd, J = 11.0, 8.0, 1.0 Hz, 1 H), 4.65, 4.72 (2 × dt, J = 15.2, 2.9 Hz, 2 H), 5.24 (dd, J = 15.0, 12.1 Hz, 2 H), 5.23 (t, J = 2.9 Hz, 1 H), 5.48 (t, J = 2.9 Hz, 1 H), 7.23 (s, 1 H), 7.28-7.60 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.90, 23.94, 38.04, 53.54, 56.50, 63.23, 71.15, 102.1, 107.0, 117.2, 127.2, 127.6, 128.3, 128.8, 129.2, 130.2, 131.1, 133.5, 136.1, 136.2, 140.7, 148.7, 170.7, 170.8; MS (70 eV) 532 (100, M^+), 399 (60, $M^+ - Ac - C_7H_7$); IR (KBr) 3064, 1740, 1448, 1360, 1168 cm^{-1}. Anal. Calcd for $C_{29}H_{28}N_2O_6S$: C, 65.40, H, 5.30. Found: C, 65.44; H, 5.47.

(1*RS*)-6-Acetyl-3-(benzenesulfonyl)-5-(benzyloxy)-1-(acetoxymethyl)-8-methyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole (13b): ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3 H) 2.28 (s, 3 H), 2.58 (s, 3 H), 3.00 (t, J = 11.0 Hz, 1 H), 3.68 (m, 1 H), 3.75 (ddd, J = 11.0, 8.0, 1.0 Hz, 1 H), 4.18 (dd, J = 11.0, 1.0 Hz, 1 H), 4.20 (ddd, J = 11.0, 8.0, 1.0 Hz, 1 H), 5.34 (q, J = 12.2 Hz, 2 H), 7.28 (s, 1 H), 7.32–7.70 (m, 11 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.09, 20.83, 25.78, 38.43, 53.70, 65.79, 70.91, 97.14, 113.4, 115.6, 122.7, 127.0, 127.1, 127.7, 128.1, 128.7, 129.0, 130.7, 133.2, 136.2, 136.5, 139.0, 147.6, 168.7, 170.5; MS (70 eV) 532 (40, M^+); IR (KBr) 3030, 1608, 1360, 1168 cm^{-1}. Anal. Calcd for $C_{29}H_{28}N_2O_6S$: C, 65.40; H, 5.30. Found: C, 65.44; H, 5.47.

(1*RS*)-3-(Benzenesulfonyl)-5-(benzyloxy)-1-(acetoxymethyl)-8-methyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole (14). A solution of **13a** (125 mg, 0.24 mmol) in dry CH_2Cl_2 (3 mL) was treated with camphorsulfonic acid (55 mg, 0.24 mmol) and was stirred under nitrogen for 21 h at room temperarure. The mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography (20 g SiO_2, EtOAc/petroleum ether (1:2)) provided **14** (68 mg, 59%) as white solid, mp 92 °C (EtOAc), and **13b** (26 mg, 21%); ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3 H), 2.33 (s, 3 H), 2.80 (t, J = 11.0 Hz, 1 H), 3.65 (m, 1 H), 3.83 (dd, J = 11.0, 8.0 Hz, 1 H), 4.19 (dd, J = 11.0, 8.0 Hz, 2 H), 5.33 (s, 2 H), 6.92 (s, 1 H), 7.32–7.62 (m, 11 H), 8.20 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.09, 20.87, 38.91, 53.67, 66.38, 70.23, 93.99, 111.0, 112.9, 123.1, 124.7, 125.1, 127.2, 127.7, 128.1, 128.7, 128.8, 135.2, 136.5, 136.8, 145.2, 170.5; MS (70 eV) 490 (50, M^+), 91 (100, $C_7H_7^+$); IR (KBr) 3380, 1584, 1446, 1310, 1166 cm^{-1}. Anal. Calcd for $C_{27}H_{26}N_2O_5S$: C, 66.94; H, 5.39. Found: C, 66.94; H, 5.29.

(1*RS*)-3-(Benzenesulfonyl)-5-(benzyloxy)-1-(hydroxymethyl)-8-methyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole (15). Compounds **13b** (26 mg, 0.05 mmol) and **14** (68 mg, 0.14 mmol) were dissolved in a mixture of MeOH (0.6 mL), acetone (0.2 mL), and H_2O (0.2 mL). The solution was treated with KOH (92 mg, 0.03 mmol) and stirred for 18 h at rt. The mixture was diluted with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (3 × 1 mL). The dried ($MgSO_4$) organic layer was concentrated in vacuo, and the residue was purified by crystallization from EtOAc to afford **15** (85 mg, quantitative) as white needles: mp 187–188 °C (lit.[8] mp 184–185 °C); ^1H NMR (500 MHz, acetone-d_6) δ 2.23 (s, 3 H), 2.55 (m, 1 H), 3.52 (m, 1 H), 3.58 (m, 1 H), 3.78 (ddd, J = 11.2, 8.0, 1.0 Hz, 1 H), 4.06 (t, J = 8.0 Hz, 1 H), 4.26 (dd, J = 11.2, 1.0 Hz, 1 H), 5.18 (s, 2 H), 7.01 (s, 1 H), 7.25 (s, 1 H), 7.35–7.64 (m, 10 H), 10.19 (s, 1 H); ^{13}C NMR (50 MHz, acetone-d_6) δ 11.32, 43.49, 54.58, 65.93, 70.44, 94.27, 110.8, 115.4, 124.8, 126.0, 128.3, 128.4, 128.6, 129.3, 129.8, 135.3, 137.6, 138.5, 145.8; MS (70 eV) 448 (15, M^+), 307 (45, M^+ – benzenesulfonyl), 91 (100, $C_7H_7^+$); IR (KBr) 3528, 2940, 1628, 1568, 1444, 1164 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_4S$: C, 64.30; H, 4.96. Found: C, 64.54, H, 5.04.

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