Synthesis of Ring Size *seco*-Analogs of the Antitumor Antibiotic CC-1065 by Two Consecutive Transition Metal-Initiated Transformations

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Novel *seco*-analogs of CC-1065 **1** were synthesized from comercially available nitroaniline by reduction, bromination, bisulfonation and bisallylation followed by reaction with *tert*-butyllithium, zirconocene and iodine. The obtained quinoline **6** was then transformed into **17** and **18**, which, upon treatment with Pd^0, led to **21** and **22**, respectively.

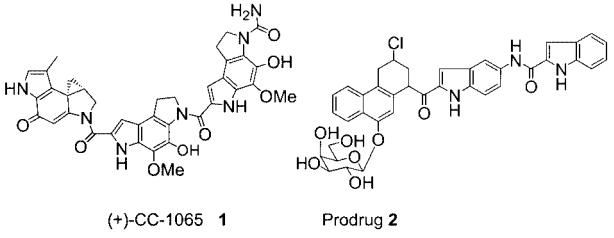
Introduction

The chemotherapy of cancer is one of the major problems in modern medicine, since the known anticancer agents usually show severe side effects which often lead to a termination of the treatment. A promising approach for more selectivity is the antibody-directed enzyme prodrug therapy (ADEPT),[1] which uses prodrugs in combination with enzyme-immunoconjugates. A requirement for this approach is a relatively low toxicity of the prodrug, whereas the corresponding drug, which is formed enzymatically from the prodrug at the cancer cells, should have a high cytotoxicity with an $ED_{50} \leq 10$ nmol.[2] Therefore appropriate derivatives of the highly cytotoxic antibiotic CC-1065 (**1**) such as the glycosidic *seco*-compound **2** are very suitable candidates for ADEPT;[3−5] however we have recently shown that the selectivity of the compounds differ strongly with their structure.[6] It is therefore important to prepare novel compounds for this approach.

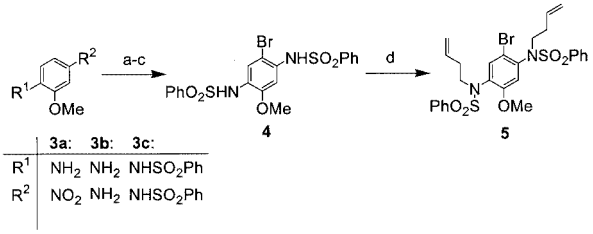
Here we describe the synthesis of two novel ring-size analogs of the pharmacophoric group of CC-1065 by employing a combination of a zirconocene-mediated[7,8] and a Pd^0-catalyzed reaction.[9] This process allowed the synthesis of compounds with a six-membered ring A and a six- as well as a seven-membered ring C.

Results and Discussion

Reduction[10] of the commercially available nitroaniline **3a**, to give **3b**, followed by formation of the bissulfonamide **3c** and bromination led to **4**, which was alkylated at the two nitrogen atoms using homoallylic iodide to afford **5** in 70% yield over four steps (Scheme 2).



Scheme 1. Synthesis of **5**: 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, 20 °C; 4-bromo-1-butene, nBu_4NI, 50 °C, 93%



Scheme 2. Zirconocene-initiated cyclization of **5**: a) $Cp_2ZrMeCl$, 2 equiv. *t*BuLi, THF; b) 2 equiv. I_2, CH_2Cl_2, **6**: 45%, **7**: 6%

Treatment of **5** with two equivalents of *tert*-butyllithium in THF at −78 °C, followed by reaction with chlorodi(cyclopentadienyl)methylzirconium {[$Cp_2ZrMeCl$], **9**}[11,12] and finally two equivalents of iodine at 20 °C led to the desired tetrahydroquinoline derivative **6** in 45% yield as the main product (Scheme 3). In addition, 7% of the monoiodo

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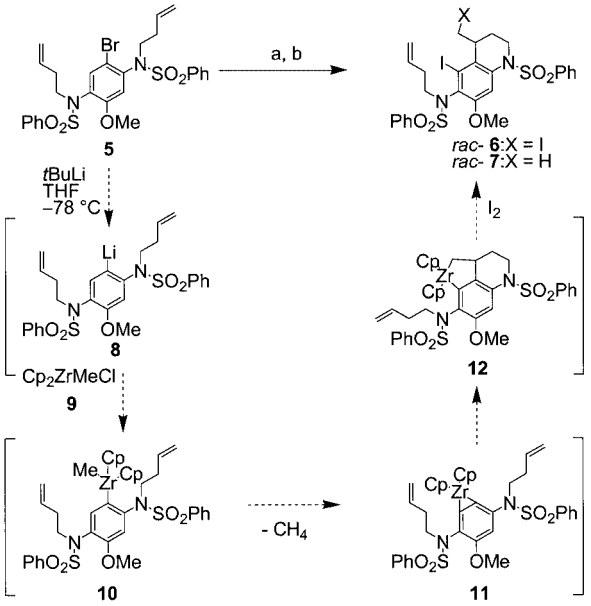
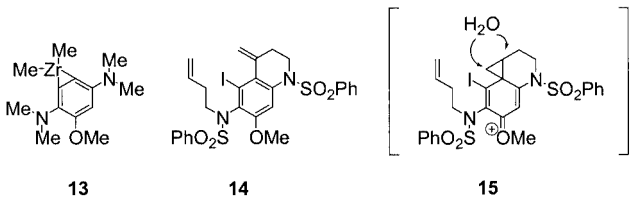


Scheme 3. Structure of model compound **13**, the possible cyclization product **14** and intermediate **15**

compound **7** was also obtained, which could not be removed by chromatography at this stage.

Mechanistically, it can be assumed that an initial halogen−metal exchange takes place to give the lithium compound **8**, which, upon reaction with [$Cp_2ZrMeCl$] (**9**), leads to the 16-electron Zr complex **10** and then, with loss of methane, to the 14-electron complex **11**. Insertion into the homoallyl moiety *meta* to the methoxy group affords the zircona-cyclopentene **12**, which, upon reaction with iodine, leads to compound **6**. The formation of **7** could be explained by reaction of **12** with one mol of iodine and one mol of water, which shows that the zirconocene−aryl bond is cleaved first. A puzzling result in the formation of **6** from the zirconacyclopropene moiety is the high regioselectivity, since only one of the two homoallylic groups in the *ortho* positions in **11** undergoes a reaction. Clearly the selectivity must be controlled by the methoxy group, though the zirconocene-mediated reaction of 3-bromo-1-methoxybenzene with acetonitrile leads to a 1:1 mixture of 2- and 3-methoxyacetophenone, as described by Buchwald.[8]

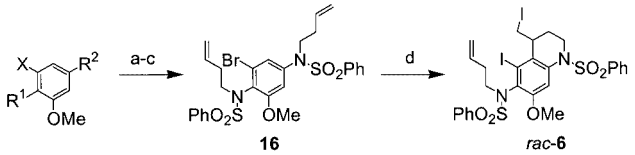
Calculations of the 5-methoxy-*N*,*N*′-tetramethyl-1,4-phenylenediamine (**13**) (Scheme 4) containing the proposed "zirconacyclopropene" moiety using PM3™ (spartan) show a strongly deformed structure of the "zirconacyclopropene" moiety.[13] The C−Zr bond in the *para*-position to the methoxy group is considerably longer (241 pm) than the C−Zr bond in the *meta*-position (220 pm). This correlates with a different electron density at the aromatic ring system: in the model compound the NBO charge at the carbon in the *para*-position to the methoxy group is −0.08 eV, whereas the value in the *meta*-position is −0.34 eV.



Scheme 4. Synthesis of **16** and cyclization to give **6**: a) NBS, THF, −78−20 °C, 96%; b) hydrazine, $FeCl_3$, charcoal, methanol, reflux, 99%; c) $PhSO_2Cl$, pyridine, reflux, 80%; d) NaH, THF, 20 °C; 4-bromo-1-butene, nBu_4NI, 50 °C, 81%; d) $Cp_2ZrMeCl$, 2 equiv. *t*BuLi, THF; 2 equiv. I_2, CH_2Cl_2, **6**: 34%

However, steric interactions could also be responsible for the high chemoselectivity by causing an unfavorable orientation of the homoallylic group at the amino functionality in the *ortho*-position to the methoxy group for the insertion into the zircona species.

In order to prove that a zircona species of type **10** is an intermediate, we synthesized the bromo compound **16** with a *meta*-orientation of the bromo atom to the methoxy group, which is available in four steps from **3a** via **3d**−**f** in a total yield of 61% (Scheme 5).



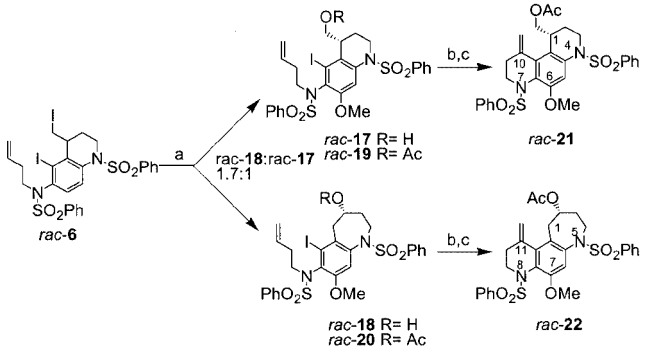
	3a	3d	3e	3f
R^1	NH_2	NH_2	NH_2	$NHSO_2Ph$
R^2	NO_2	NO_2	NH_2	$NHSO_2Ph$
X	H	Br	Br	Br

Scheme 5. Formation of tetrahydroquinoline **17** and benzazepine **18** and Pd^0-catalyzed cyclization of **19** and **20**, respectively: a) $Ag_2O{\cdot}SiO_2$, H_2O, 20 °C, 7 d, 83%, **17**:**18** ≈1:1.7; b) Ac_2O, NaOAc, 60 °C, 1 h, 96%; c) $Pd(OAC)_2$, PPh_3, Ag_2CO_3, DMF, 40 °C, 20 h, 83−85%

As expected, treatment of **16** with *tert*-butyllithium and then zirconocene **9**, and quenching the reaction with iodine, also led to compound **6** as the only isolable product.

A direct transformation of **6** into the desired pyrroloquinoline skeleton by a palladium-catalyzed transformation was not possible, since an oxidative addititon at the iodomethyl group also occurred, resulting in the formation of **14**. The iodomethyl group had therefore to be transformed into an acetoxymethyl group. A simple substitution using cesium acetate or tetrabutylammonium acetate was not suitable since an inseparable 1:1 mixture of the desired acetate **19** and the elimination product **14** was obtained (Scheme 4). Reaction of **6** with DBU afforded **14** in nearly quantitative yield. In order to avoid the elimination we used silver oxide coated on silica gel for the transformation of **6** to give the desired compound **17**. However, rather unexpectedly, the benzazepine **18** is the main product, which was formed together with the expected tetrahydroquinoline **17** in a 1.7:1 ratio in 75% overall yield. After acetylation, the

obtained two compounds **19** and **20**, respectively, could be separated by chromatography. The formation of the benzazepine derivative from **6** can be explained by assuming that a spirocyclocyclohexadiene oxenium ion of type **15** acts as an intermediate (Scheme 4). Attack of water of the silica gel at the secondary carbon of the spirocyclopropane moiety in **15** would lead to **17**, whereas an attack at the tertiary position would give **18**. Interestingly, the reaction of CC-1065, containing a spirocyclopropanecyclohexadienone moiety, with a nucleophile such as adenine takes place exclusively at the secondary carbon atom of the cyclopropane moiety. The final step in the synthesis of the new ring-size analogs of the pharmacophoric group of CC-1065 was the Pd^0-catalyzed reaction of **19** and **20** to give **21** and **22**, respectively (Scheme 6). The best results with yields of 83−85% were obtained using palladium acetate, silver carbonate as base, and triphenylphosphane as ligand at 40 °C in DMF; under these conditions an isomerization of the formed double bond did not take place.[14−17]



Scheme 6. Structure of the antitumor antibiotic CC-1065 (**1**) and prodrug **2**

The constitution of the new compounds was determined by ^1H and ^{13}C NMR spectroscopy and for **18** a crystal structure (Figure 1) was obtained.[18]

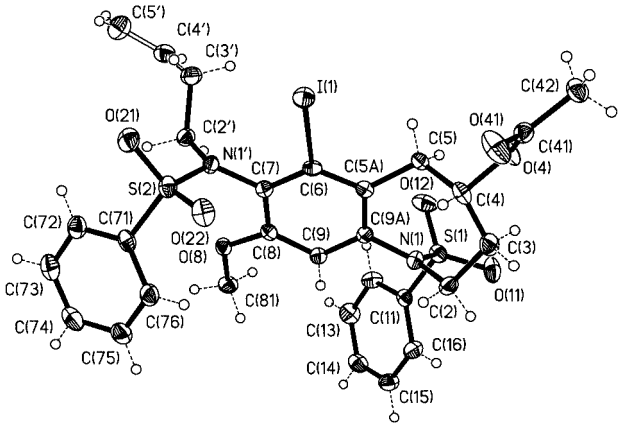


Figure 1. X-ray structure of **18**

The NMR spectra of **19** and **20** are very similar except for the signals of the CH_2OAC group in **18** and the CHOAc group in **20**. The two diastereotopic hydrogens of the CH_2OAc group resonate at δ = 3.42 ppm and δ = 3.89 ppm, whereas for the C*H*OAc group a multiplet at δ = 4.89 ppm was observed. For the two hydrogens of the methylene group of **21** and **22** two singlets at δ = 4.94 and 5.06 ppm, and at δ = 4.80 and 5.10 ppm, respectively, were found. The two hydrogens of the acetoxymethyl group in **21** resonate at δ = 3.64 ppm as a triplet with J = 10.5 Hz and at δ = 3.83 ppm as doublets of doublets with J = 10.5, 4.0 Hz, respectively. For the hydrogen of the C*H*OAc group of **22** a multiplet at δ = 4.89 ppm was observed.

Conclusion

A combination of a zirconocene-mediated and a Heck reaction allowed the synthesis of novel ring-size *seco*-analogs of the pharmacophoric group of the highly cytotoxic CC-1065. These compounds will be used for the synthesis of new prodrugs for ADEPT.

Experimental Section

General: All reactions were performed in flame-dried glassware under argon. Reagents obtained from commercial sources were used without further purification. TLC chromatography was performed on precoated aluminium silica gel SIL G/UV_{254} plates (Macherey, Nagel Co.), and silica gel 32−63 (0.032−0.064 mm) (Macherey, Nagel Co.) was used for column chromatography. (PE = petroleum ether, EA = ethyl acetate). Melting points: Mettler FP61. IR: spectra were recorded as KBr pellets or as films with a Bruker IFS 25 or Vector 22 spectrometer. NMR: Varian VXR-200 (200 MHz, ^1H), Bruker AM (300 MHz, 75 MHz, for ^1H and ^{13}C, respectively). For ^1H and ^{13}C NMR, $CDCl_3$ as solvent, TMS as internal standard. Chemical shifts are reported on the δ scale. Signals are quoted as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad). MS: Varian MAT 731. Elemental analysis: Mikroanalytisches Labor des Instituts für Organische Chemie der Universität Göttingen.

2-Methoxy-1,4-phenylenediamine (3b): A solution of 2-amino-5-nitroanisole (**3a**, 22.1 g, 0.130 mmol) in 1,4-dioxane (170 mL) was treated with $PtO_2{\cdot}H_2O$ (0.20 g, 0.80 mmol). The mixture was placed under hydrogen (3 bar) and stirred for 16 h. After removal of the catalyst by filtration through celite the solution was evaporated to dryness. The diamine **3b** was obtained as a pink solid and was used in the next step without further purification. R_f = 0.68 (PE/EA, 1:1); m.p. 101 °C. ^1H NMR (200 MHz, [D_6]DMSO): δ = 3.24 (br s, 4 H, NH_2), 3.80 (s, 3 H, OCH_3), 6.19 (dd, J = 2.2, 8.1 Hz, 1 H, 5-H), 6.27 (d, J = 2.2 Hz, 1 H, 3-H), 6.57 (d, J = 8.1 Hz, 1 H, 6-H) ppm. $C_7H_{10}N_2O$ (138.16).

2-Methoxy-N^1,N^4-bis(phenylsulfonyl)-1,4-phenylenediamine (3c): Benzenesulfonyl chloride (34 mL, 0.26 mol) was added dropwise over 5 min to a solution of **3b** in 300 mL of degassed pyridine and the reaction mixture was heated at 80 °C for 3 h. After removal of 150 mL of the solvent, the solution was poured slowly into a 5% HCl solution (500 mL). The formed solid was washed with water and crystallized twice from ethyl acetate (250 mL) adding charcoal to give **3c** (44.2 g, 0.11 mol, 79%) as colorless crystals. R_f = 0.12 (EA/PE, 1:1); m.p. 208 °C. IR (KBr): $\tilde{\nu}$ = 3236 cm^{-1} (N−H), 3098

(Ar−H), 1610 (C=C_{Ar}), 1342 (S=O), 1166 (C−O−C). UV (CH_3CN): λ_{max} (lg ε) = 207.0 nm (4.596), 242.0 (4.037). ^{1}H NMR (200 MHz, [D_6]DMSO): δ = 3.29 (s, 3 H, OCH_3), 6.54 (d, *J* = 2.5 Hz, 1 H, 3-H), 6.58 (d, *J* = 9.0 Hz, 1 H, 6-H), 7.04 (dd, *J* = 2.5, 9.0 Hz, 1 H, 5-H), 7.40−7.66 (m, 6 H, Ph−H), 7.67−7.76 (m, 4 H, Ph−H), 9.70 (br. s, 2 H, N−H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 55.1 (OCH_3), 104.0 (C-3), 112.0 (C-5), 121.2 (C-1), 126.5 (C-Ph), 126.6 (C-Ph), 126.8 (C-6), 128.5 (C-Ph), 129.1 (C-Ph), 132.3 (C-Ph), 132.8 (C-Ph), 136.6 (C-4), 139.3 (C-Ph), 140.4 (C-Ph), 153.2 (C-2) ppm. MS (70 eV): *m*/*z* (%) = 418 (13) [M^+], 277 (100) [$M^+ - SO_2Ph$], 141 (27) [SO_2Ph^+], 77 (91) [$C_6H_5^+$], 43 (48) [$C_2H_3O^+$]. $C_{19}H_{18}N_2O_5S_2$ (418.48): calcd. C 54.53, H 4.34; found C 54.66, H 4.41.

2-Bromo-5-methoxy-*N*^{1},*N*^{4}-bis(phenylsulfonyl)-1,4-phenylenediamine (4): NBS (10.6 g, 59.7 mmol) was added to a solution of **3c** (25.0 g, 59.7 mmol) in 500 mL of THF at −78 °C and the solution was stirred at −78 °C for 30 min. The reaction mixture was concentrated in vacuo and the residue was washed with water. Crystallization from glacial acetic acid (500 mL) yielded **7** (28.17 g, 56.64 mmol, 95%) as colorless crystals. R_f = 0.27 (PE/EA, 3:1); m.p.224 °C, IR (KBr): $\tilde{\nu}$ = 3248 cm^{-1} (N−H), 3068 (Ar−H), 1602 (C=C), 1344 (S=O), 1160 (S=O), 1042 (C−O−C). UV (CH_3CN): λ_{max} (lg ε) = 241 nm (4.425), 299.9 (4.579). ^{1}H NMR (200 MHz, [D_6]DMSO): δ = 3.31 (s, 3 H, O−CH_3), 6.59 (s, 1 H, 6-H), 7.30 (s, 1 H, 3-H), 7.48−7.70 (m, 10 H, Ph−H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 55.5 (OCH_3), 109.9 (C-2), 111.1 (C-6), 124.9 (C-4), 126.5 (C-Ph), 126.7 (C-Ph), 128.2 (C-3), 128.8 (C-Ph), 129.0 (C-Ph), 132.7 (C-Ph), 132.8 (C-1), 140.4 (C-Ph), 151.6 (C-5) ppm. MS (70 eV): *m*/*z* (%) = 497 (26) [M^+], 356 (100) [$M^+ - SO_2Ph$], 141 (38) [SO_2Ph^+], 77 (72) [$C_6H_5^+$]. $C_{19}H_{17}BrN_2O_5S_2$ (497.38): calcd. C 45.88, H 3.45; found C 46.08, H 3.48.

2-Bromo-*N*^{1},*N*^{4}-bis(3-butenyl)-5-methoxy-*N*^{1},*N*^{4}-bis(phenylsulfonyl)-1,4-phenylenediamine (5): A solution of **4** (5.00 g, 10.1 mmol) and NaH (603 mg, 25.1 mmol) in THF (100 mL) was refluxed for 5 min. After cooling, 4-bromo-1-butene (3.39 g, 2.57 mL, 25.1 mmol) and *n*Bu_4NI (5.00 g, 13.5 mmol) were added to the reaction mixture and the solution was refluxed for 24 h. Water (20 mL) was added and the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate (50 mL), the organic layer was washed three times with water (20 mL) as well as brine and dried with Na_2SO_4. Removal of the solvent in vacuo and crystallization from ethanol gave **5** (5.66 g, 9.35 mmol, 93%) as colorless crystals. R_f = 0.12 (PE/EA, 4:1); m.p.149 °C. IR (KBr): $\tilde{\nu}$ = 3072 cm^{-1} (Ar−H), 2944 (C−H), 1696 (C=C_{chain}), 1592 (C=C_{core}), 1348 (S=O), 1164 (S=O). UV (CH_3CN): λ_{max} (lg ε) = 272.5 nm (3.523), 298.5 (3.656). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 2 H, 2′-H_a, 2′-H_b), 2.32 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 2 H, 2′′-H_a, 2′′-H_b), 3.26 (s, 3 H, OCH_3), 3.54−3.82 (m, 4 H, 1′-H_a, 1′-H_b, 1′′-H_a, 1′′-H_b), 4.99−5.20 (m, 4 H, 2 × CH=CH_2), 5.64−5.82 (m, 2 H, 2 × C*H*=CH_2), 6.71 (s, 1 H, 6-H), 7.44−7.64 (m, 7 H, 3-H, Ph−H), 7.65−7.70 (m, 2 H, Ph−H), 7.72−7.78 (m, 2 H, Ph−H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.4 (C-2′′), 33.5 (C-2′), 49.3 (C-1′′), 50.1 (C-1′), 55.4 (OCH_3), 114.3 (C-2), 116.7 (C-6), 117.2, 117.4 (2 × CH=*C*H_2), 127.5, 127.7, 128.5, 128.5 (C-2, C-3, C-5, C-6, 2 × SO_2Ph), 127.4 (C-4), 132.5, 133.0 (C-4, 2 × SO_2Ph), 134.6, 134.6 (2 × *C*H=CH_2), 137.7 (C-3), 138.4 (C-1), 139.6. 136.9 (C-1, 2 × SO_2Ph), 155.8 (C-5) ppm. MS (70 eV): *m*/*z* (%) = 606 (14) [M^+], 565 (100) [$M - C_3H_5^+$]. $C_{27}H_{29}BrN_2O_5S_2$ (605.57): calcd. C 53.55, H 4.83; found C 53.85, H 4.79.

(4*RS*)-6-[3-Butenyl(phenylsulfonyl)amino]-5-iodo-4-iodomethyl-7-methoxy-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (6) and (4*RS*)-6-[3-Butenyl(phenylsulfonyl)amino]-5-iodo-7-methoxy-4-methyl-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (7): 1. A solution of *tert*-butyllithium (1.70 M in hexane) was added dropwise over 5 min to a solution of **5** (4.00 g, 6.61 mmol) and [Cp_2ZrCH_3Cl] (1.90 g, 7.30 mmol) in freshly distilled and degassed THF (50 mL) at −78 °C. The solution was stirred at −78 °C for 1 h, then warmed up to 20 °C within 10 min and stirred at 40 °C for 5 h. After removal of the solvent in vacuo, the residue was dissolved in dry, degassed CH_2Cl_2 and cooled to 0 °C. A solution of freshly sublimed iodine (3.50 g, 13.9 mmol) in CH_2Cl_2 (10 mL) was added over 15 min and then the reaction mixture was stirred at 20 °C for 14 h. The solvent was removed in vacuo and the residue was diluted with ethyl acetate (100 mL). Na_2SO_3 (5.00 g, 39.7 mmol) was then added to remove the excess iodine and the resulting suspension stirred for 1 h. After filtration of the solid, the filtrate was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. Chromatography (PE/EA, 5:1) gave the diiodo- and monoiodo compounds **6** (2.31 g, 2.97 mmol) and **7** (277 mg, 0.42 mmol) as an inseparable mixture (7:1) in an overall yield of 51% as a colorless amorphous solid.

2. Compound **13** (1.00 g, 1.65 mmol) was transformed as described previously to 436 mg (0.56 mmol, 34%) of **6**. R_f = 0.20 (PE/EA, 4:1); m.p.70 °C. UV (CH_3CN): λ_{max} (lg ε) = 232.0 nm (4.510), 303.5 (3.687). IR (KBr): $\tilde{\nu}$ = 3064 cm^{-1} (Ar−H), 2936 (C−H), 1682 (C=C_{chain}), 1586 (C=C_{core}), 1348 (S=O), 1164 (S=O).

6: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65−1.80 (m, 2 H, 3-H_a, 3-H_b), 1.95−2.13 (m, 1 H, 2′-H_a), 2.17 (dq, *J* = 4.5, 14.0 Hz, 1 H, 4-H), 2.29−2.45 (m, 1 H, 2′-H_b), 3.03 (dd, *J* = 4.5, 10.0 Hz, 1 H, 1′′-H_a), 3.13−3.25 (m, 1 H, 1′′-H_b), 3.21 (s, 3 H, OCH_3), 3.37 (ddd, *J* = 5.3, 11.0, 13.5 Hz, 1 H, 1′-H_a), 3.42 (ddd, *J* = 4.5, 13.0, 13.0 Hz, 1 H, 2-H_a), 3.75 (ddd, *J* = 5.3, 11.0, 22.0 Hz, 1 H, 1′-H_b), 3.85 (ddd, *J* = 3.8, 8.0, 13.0 Hz, 1 H, 2-H_b), 4.87−4.99 (m, 2 H, CH=CH_2), 5.59 (m_c, 1 H, C*H*=CH_2), 7.39−7.56 (m, 9 H, Ph−H, 8-H), 7.65−7.73 (m, 2 H, Ph−H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 6.8 (C-1′′), 25.9 (C-3), 32.9 (C-2′), 42.7 (C-1′), 44.3 (C-4), 49.5 (C-2), 55.1 (OCH_3), 107.7 (C-8), 114.9 (C-5), 116.7 (CH=*C*H_2), 127.0, 127.9, 128.4 129.3 (C-2, C-3, C-5, C-6, 2 × SO_2Ph), 127.2 (C-6), 127.5 (C-4a), 132.3, 134.9 (C-4, 2 × SO_2Ph), 133.6 (*C*H=CH_2), 137.6, 137.7 (C-1, 2 × SO_2Ph), 140.9 (C-8a), 155.7 (C-7) ppm. MS (70 ev): *m*/*z* (%) = 778 (10) [M^+], 637 (100) [$M - SO_2Ph^+$], 596 (8) [$M - SO_2PH - C_3H_5^+$]. HRMS calcd. for $C_{27}H_{28}I_2N_2O_5S_2$ 777.9529; found 777.9529.

7: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.16−1.28 (m, 1 H, 3-H_a), 1.60−1.76 (m, 1 H, 3-H_b), 2.40 (q, *J* = 6.0 Hz, 2′-H_a, 2′-H_b), 2.50 (m_c, 4-H), 3.30 (s, 3 H, OCH_3), 3.52−3.94 (m, 4 H, 1′-H_a, 1′-H_b, 2-H_a, 2-H_b), 4.96−5.03 (m, 2 H, CH=CH_2), 5.66−5.96 (m, 1 H, C*H*=CH_2), 7.04 (s, 1 H, 8-H), 7.40−7.70 (m, 8 H, Ph−H), 7.72−7.98 (m, 2 H, Ph−H) ppm.

2-Bromo-6-methoxy-4-nitroaniline (3d): NBS (22.2 g, 125 mmol) was added to a solution of 2-amino-5-nitroanisole (**3a**, 20.0 g, 119 mmol) in THF (500 mL) at −78 °C and the reaction mixture was stirred at −78 °C for 30 min and then at 20 °C for 2 h. The solution was concentrated in vacuo and the residue was washed with water. Crystallization of the crude product from glacial acetic acid (100 mL) yielded **3d** (28.2 g, 114 mmol, 96%) as red crystals. R_f = 0.38 (PE/EA, 2:1, VS: yellow); m.p.104 °C. UV (CH_3CN): λ_{max} (lg ε) = 194.5 nm (3.942), 262.0 (3.421), 375.0 (3.710). IR (KBr): $\tilde{\nu}$ = 3502 cm^{-1} (N−H), 3394 (N−H), 1602 (Ar), 1502 (NO_2), 1320 (NO_2), 1284, 1234 (C−O−C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.98 (s, 3 H, O−CH_3), 4.95 (br. s, 2 H, NH_2), 7.63 (d, *J* = 2.5 Hz, 1 H, 5-H), 8.10 (d, *J* = 2.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 56.3 (O−CH_3), 103.2 (C-6),

104.5 (C-5), 121.7 (C-3), 135.8 (C-4), 143.0 (C-1), 145.0 (C-2) ppm. 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) [$C_4H_3^+$]. $C_7H_7BrN_2O_3$ (247.04): calcd. C 34.03, H 2.86; found C 33.98, H 2.89.

2-Bromo-6-methoxy-1,4-phenylenediamine (3e): Hydrazine hydrate (80%, 12.5 mL, 201 mmol) was added to a mixture of **3d** (10.0 g, 40.5 mmol), charcoal (4.60 g, 383 mmol) and $FeCl_3 \cdot H_2O$ (4.33 g, 1.60 mmol) in methanol and the solution was heated to reflux for seven days. The reaction mixture was then diluted with ethyl acetate (150 mL) and the solid filtered off. The organic layer was washed four times with water (100 mL) and brine (100 mL) and dried with Na_2SO_4. Removal of the solvent yielded **3e** as a crimson solid which was used in the next step without further purification due to its sensitivity to oxygen.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.45 (br. s, 4 H, NH_2), 3.80 (s, 3 H, O−CH_3), 6.19 (d, *J* = 2.3 Hz, 1 H, 5-H), 6.46 (d, *J* = 2.3 Hz, 1 H, 3-H) ppm.

2-Bromo-6-methoxy-*N*^{1},*N*^{4}-bis(phenylsulfonyl)-1,4-phenylenediamine (3f): Benzenesulfonyl chloride (14.0 g, 79.4 mmol) was added dropwise to a solution of **3e** (8.61 g, 39.7 mmol) in dry, degassed pyridine (300 mL) and the solution was refluxed for 3 h. The reaction mixture was reduced in vacuo to 100 mL and the resulting black oil was poured into an ice cooled HCl solution (500 mL, 5% HCl). Removal of the solid and crystallization from glacial acetic acid gave **3f** as colorless crystals (16.0 g, 32.2 mmol, 81%). R_f = 0.08 (PE/EA, 2:1); m.p. 208.5 °C (dec.). UV (CH_3CN): λ_{max} (lg ε) = 213.0 nm (3.928), 292.5 (2.961), 272.0 (3.038). IR (KBr): $\tilde{\nu}$ = 3252 cm^{-1} (N−H), 1596 (Ar), 1384 (S=O), 1322 (C−N), 1166 (C−O−C), 1044 (Ar−Br). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.41 (s, 3 H, OCH_3), 6.13 (br. s, 1 H, N−H), 6.53 (br. s, 1 H, N−H), 6.66 (d, *J* = 2.5 Hz, 1 H, 5-H). 6.77 (d, *J* = 2.5 Hz, 1 H, 3-H), 7.40−7.66 (m, 8 H, Ph−H), 7.70−7.83 (m, 2 H, Ph−H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 55.1 (OCH_3), 102.0 (C-5), 114.4 (C-3), 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) ppm. MS (70 eV): *m/z* (%) = 496 (8.0) [M^+], 355 (100) [M − SO_2Ph^+], 215 (25) [M − 2 × SO_2Ph^+], 141 (21) [SO_2Ph^+], 77 (33) [$C_6H_5^+$]. $C_{19}H_{17}BrN_2O_5S_2$ (497.38): calcd. C 45.88, H 3.44; found C 46.19, H 3.62.

2-Bromo-*N*^{1},*N*^{4}-bis(3-butenyl)-6-methoxy-*N*^{1},*N*^{4}-bis(phenylsulfonyl)-1,4-phenylenediamine (16): A solution of **3f** (2.00 g, 4.02 mmol) and NaH (193 mg, 8.04 mmol) in THF (100 mL) was refluxed for 5 min. After cooling, 4-bromo-1-butene (0.41 mL, 4.02 mmol) and *n*Bu_4NI (20 mg) were added and the reaction mixture was heated under reflux for 24 h. Water (20 mL) was then added and the organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate (50 mL), the organic layer washed three times with water (20 mL) as well as brine and dried over Na_2SO_4. Removal of the solvent in vacuo and crystallization of the residue from ethanol gave **16** (1.97 g, 3.26 mmol, 81%) as colorless crystals. R_f = 0.20 (PE/EA, 2:1); m.p. 130.5 °C. UV (CH_3CN): λ_{max} (lg ε) = 293.5 nm (2.870), 272.0 (2.890). IR (KBr): $\tilde{\nu}$ = 3084 cm^{-1} (Ar−H), 1642 (C=C), 1447 (C−H), 1351 (S=O), 1167 (S=O), 1042 (C−O−C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.07−2.51 (m, 4 H, 2 × CH_2), 3.3.34 (s, 3 H, OCH_3), 3.36−3.84 (m, 4 H, 2 × CH_2), 4.95−5.15 (m, 4 H, 2 × CH=CH_2), 5.72 (m_c, 2 H, 2 × CH=CH_2), 6.81 (s, 2 H, 3-H, 5-H), 7.45−7.70 (m, 8 H, Ph−H), 7.77−7.86 (m, 2 H, Ph−H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.8, 33.2 (2 × CH_2), 49.5, 49.9 (2 × CH_2), 55.5 (OCH_3), 113.0 (C-5), 116.7, 117.5 (2 × CH=CH_2), 124.0 (C-3), 126.8 (C-6), 127.6, 127.8 (C-2′, C-6′, C-2′′, C-6′′), 128.3 (C-1), 128.5, 129.0 (C-3′, C-5′, C-3′′, C-5′′), 132.4 (C-4′), 133.1 (C-4′′), 134.1 (*C*H=CH_2), 134.7 (*C*H=CH_2), 137.6 (C-4), 140.7 (C-1′, C-1′′), 158.2 (C-2) ppm. MS (70 eV): *m/z* (%) = 606 (15) [M^+], 565 (69) [M − $C_3H_5^+$], 465 (100) [M − SO_2Ph^+], 281 (75), 240 (83). $C_{27}H_{29}BrN_2O_5S_2$ (605.56): calcd. C 53.85, H 4.79; found C 53.55, H 4.83.

6-[3-Butenyl(phenylsulfonyl)amino]-5-iodo-7-methoxy-4-methylene-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (14): 1,8-Diazabicyclo[5.4.0]undec-7-ene (58.6 mg, 57 μL, 0.385 mmol) was added to a solution of **6** (300 mg, 0.385 mmol) in toluene (7.5 mL) and the reaction mixture was stirred at 60 °C for 1.5 h. Removal of the solvent in vacuo and chromatographic purification of the crude product (2 × 30 g SiO_2, PE/EA, 2:1; 4:1) gave **14** as colorless amorphous solid (228 mg, 0.35 mmol, 90%). R_f = 0.5 (PE/EA, 1:1). UV (CH_3CN): λ_{max} (lg ε) = 220.0 nm (3.722), 302.5 (2.877). IR (KBr): $\tilde{\nu}$ = 3061 cm^{-1} (Ar−H), 2963 (C−H), 1734, 1639 (C=C_{chain}), 1587, 1445, 1355 (S=O), 1250, 1168 (S=O), 1090 (C−O−C), 1018, 923, 725, 694, 594. ^{1}H NMR (300 MHz, C_6D_6): δ = 1.94 (t, *J* = 7.4 Hz, 2 H, 3-H_2), 2.40 (m_c, 1 H, 2′-H_a), 2.67 (m_c, 1 H, 2′-H_b), 2.86 (s, 3 H, OCH_3), 3.40−3.51 (m, 2 H, 2-H_2), 3.58 (ddd, *J* = 5.5, 11.0, 13.5 Hz, 1 H, 1′-H_a), 3.98 (ddd, *J* = 5.4, 12.0, 13.5 Hz, 1 H, 1′-H_b), 4.42 (s, 1 H, C^4=CH_2), 4.83−4.94 (m, 2 H, HC=CH_2), 4.91 (s, 1 H, C^4=CH_2), 5.55 (m_c, 1 H, *H*C=CH_2), 6.70−7.98 (m, 6 H, Ph−H), 7.40 (s, 1 H, 8-H), 7.41−7.48 (m, 2 H, Ph−H), 7.76−7.80 (m, 2 H, Ph−H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9 (C-2′), 34.3 (C-3), 46.4 (C-1′), 49.7 (C-2), 55.2 (OCH_3), 108.1 (C-5), 110.6 (C-8), 116.6 (C^4=*C*H_2), 117.5 (C-4′), 127.2, 127.8 (C-2, C-6, SO_2Ph), 128.4, 128.8 (C-3, C-5, SO_2Ph), 129.7 (C-4a), 132.2 (C-4, SO_2Ph), 132.3 (C-6), 133.0 (C-4, SO_2Ph), 134.9 (C-3′), 137.8 (C-8a), 138.6, 138.9 (C-1, SO_2Ph), 140.9 (C-4), 156.1 (C-7) ppm. MS (70 eV): *m/z* (%) = 650 (4) [M^+], 527 (10) [M^+ − I], 509 (25) [M^+ − SO_2Ph], 385 (59) [M^+ − 2 × SO_2Ph], 203 (75), 162 (100), 147 (27) [SO_2Ph^+], 77 (81) [$C_6H_5^+$]. HRMS calcd. for $C_{27}H_{27}IN_2O_5S_2$: 650.0406; found 650.0406. $C_{27}H_{27}IN_2O_5S_2$ 650.54): calcd. C 49.85, H 4.18; found C 50.11, H 4.11.

(4*RS*)-6-[3-Butenyl(phenylsulfonyl)amino]-4-hydroxymethyl-5-iodo-7-methoxy-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (17) and (4*RS*)-7-[3-Butenyl(phenylsulfonyl)amino]-4-hydroxymethyl-6-iodo-8-methoxy-1-phenylsulfonyl-2,3,4,5-tetrahydrobenzazepine (18): A suspension of silver oxide (1.04 g, 4.49 mmol) and silica gel (3.56 g) in acetone (15 mL) was evaporated in vacuo until dryness, the residue was dissolved in a mixture of acetone (15 mL), **14** (1.74 g, 2.24 mmol), and water (0.15 mL, 8.33 mmol), and stirred at 20 °C for 7 d. Removal of the solvent in vacuo and flash chromatography of the resulting solid yielded 1.24 g (83%) of a mixture (1:1.7) of tetrahydroquinoline **17** and tetrahydrobenzazepine **18** which could be separated by column chromatography (EA). However, a separation after acetylation to give **19** and **20** is more appropriate (PE/EA, 2:1).

(4*RS*)-7-[3-Butenyl(phenylsulfonyl)amino]-4-hydroxymethyl-6-iodo-8-methoxy-1-phenylsulfonyl-2,3,4,5-tetrahydrobenzazepine (18): R_f = 0.083 (EA). UV (CH_3CN): λ_{max} (lg ε) = 219.0 nm (4.536), 303.0 (3.706). IR (KBr): $\tilde{\nu}$ = 3448 cm^{-1} (OH), 3066 (Ar−H), 2964 (C−H), 1638 (C=C_{chain}), 1586 (C=C_{Ar}), 1348 (S=O), 1164 (S=O), 1090 (C−O−C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.68−2.00 (m, 2 H, 3-H_2), 2.10−2.33 (m, 1 H, 2′-H_a), 2.35−2.59 (m, 1 H, 2′-H_b), 2.80−3.08 (m, 2 H, 5-H_2), 3.22 (s, 3 H, OCH_3), 3.42 (ddd, *J* = 5.6, 11.2, 13.5 Hz, 1 H, 1′-H_a), 3.52−3.80 (m, 1 H, 2-H_a), 3.77 (ddd, *J* = 5.6, 11.0, 13.5 Hz, 1 H, 1′-H_b), 3.81−4.02 (m, 2 H, 2-H_b, 4-H), 4.95−5.09 (m, 2 H, CH=CH_2), 5.68 (m_c, 1 H, CH=

CH_2), 6.82 (s, 1 H, 9-H), 7.42−7.68 (m, 6 H, Ph−H), 7.75−7.81 (m, 4 H, Ph−H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.7 (C-5), 33.1 (C-2′), 35.4 (C-3), 46.1 (C-2), 49.9 (C-1), 55.1 (OCH_3), 65.8 (C-4), 113.0 (C-9), 116.8 (CH=CH_2), 127.1, 127.9 (C-2, C-5, 2 × SO_2Ph), 128.5, 129.3 (C-1, C-6, 2 × SO_2Ph), 130.5 (C-5a), 132.3 (C-4, SO_2Ph), 132.7 (C-7), 133.1 (C-4, SO_2Ph), 134.9 (*C*H=CH_2), 139.9 (C-9a), 140.8, 141.0 (C-1, 2 × SO_2Ph), 155.6 (C-8) ppm. MS (70 ev): *m*/*z* (%) = 668 (11) [M^+], 527 (100) [M^+ − SO_2Ph], 486 (10) [M^+ − C_3H_5−SO_2Ph], 77 (44) [$C_6H_5^+$], 69 (74) [$C_4H_5O^+$]. HRMS calcd. for $C_{27}H_{29}IN_2O_6S_2$: 668.0511; found 668.0511. $C_{27}H_{29}IN_2O_6S_2$ (668.57): calcd. C 48.51, H 4.37; found C 48.36, H 4.37.

(4*RS*)-6-[3-Butenyl(phenylsulfonyl)amino]-4-hydroxymethyl-5-iodo-7-methoxy-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (17): R_f = 0.125 (EA). UV (CH_3CN): λ_{max} (lg ε) = 217.0 nm (4.614), 292.0 (3.782), 300.0 (3.776). IR (KBr): $\tilde{\nu}$ = 3438 cm^{-1} (OH), 3068 (Ar−H), 2926 (C−H), 1640 (C=C_{chain}), 1586 (C=C_{Ar}), 1346 (S=O), 1162 (S=O), 1088 (C−O−C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62−1.77 (m, 1 H, 3-H_a), 2.07−2.27 (m, 2 H, 3-H_b, 2′-H_a), 2.37−2.52 (m, 1 H, 2′-H_b), 2.72 (m_c, 1 H, 4-H), 3.18 (m_c, 1 H, 1′′-H_a), 3.28 (s, 3 H, OCH_3), 3.43 (ddd, *J* = 5.5, 10.5, 13.0 Hz, 1 H, 1′-H_a), 3.55 (m_c, 1 H, 1′′-H_b), 3.67 (dt, *J* = 4.5, 12.0 Hz, 1 H, 2-H_a), 3.81 (ddd, *J* = 5.5, 11.0, 13.0 Hz, 1′-H_b), 3.97 (ddd, *J* = 4.0, 6.0, 12.0 Hz, 1 H, 2-H_b), 4.93−5.04 (m, 2 H, CH=CH_2), 5.66 (m_c, 1 H, C*H*=CH_2), 7.42−7.66 (m, 9 H, Ph−H, 8-H), 7.74−7.81 (m, 2 H, Ph−H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.9 (C-2′), 33.0 (C-3), 43.4 (C-1′), 44.6 (C-4), 49.7 (C-2), 55.0 (OCH_3), 62.7 (4-CH_2), 107.4 (C-8), 115.3 (C-5), 116.7 (C=*C*H_2), 125.7 (C-4a), 127.1 (C-2, C-6, SO_2Ph), 127.3 (C-6), 127.9 (C-2, C-6, SO_2Ph), 128.5, 129.2 (C-3, C-5, 2 × SO_2Ph), 132.3, 133.5 (C-4, 2 × SO_2Ph), 135.0 (*C*H=CH_2), 138.3, 138.4 (C-1, 2 × SO_2Ph), 141.0 (C-8a), 155.3 (C-7) ppm. MS (70 ev): *m*/*z* (%) = 668 (24) [M^+], 627 (98) [M^+ − C_3H_5], 527 (100) [M^+ − SO_2Ph], 486 (10) [M^+ − C_3H_5 − SO_2Ph], 347 (32) [M^+ − 2 × SO_2Ph − C_3H_5], 77 (23) [$C_6H_5^+$]. HRMS calcd. for $C_{27}H_{29}IN_2O_6S_2$ 668.0511; found 668.0511. $C_{27}H_{29}IN_2O_6S_2$ (668.56): calcd. C 48.51, H 4.37; found C 48.60, H 4.42.

(4*RS*)-4-Acetoxymethyl-6-[3-butenyl(phenylsulfonyl)amino]-5-iodo-7-methoxy-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (19): A solution of **17** (495 mg, 0.740 mmol) and sodium acetate (74.5 mg, 0.908 mmol) in acetic anhydride (5 mL) was stirred at 60 °C for 1 h. The reaction mixture was diluted with toluene (80 mL) and the solvents were removed in vacuo. The residue was dissolved with ethyl acetate (50 mL), and the organic layer was washed twice with water (10 mL) and brine, dried with Na_2SO_4 and the solvents were removed in vacuo. Purification by column chromatography (50 g SiO_2, PE/EA, 2:1) furnished **19** (506 mg, 0.712 mmol, 96%) as a colorless solid. R_f = 0.30 (PE/EA, 2:1). UV (CH_3CN): λ_{max} (lg ε) = 219.5 nm (3.740), 302.0 (2.884), 295.0 (2.861). IR (KBr): $\tilde{\nu}$ = 3900 cm^{-1}, 3444, 2856 (C−H), 1736 (C=O), 1352 (S=O), 1248, 1168 (S=O), 1090 (C−O−C), 592. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.66−1.84 (m, 1 H, 3-H_a), 1.90−2.25 (m, 2 H, 3-H_b, 2′-H_a), 2.04 (s, 3 H, CH_3COO), 2.30−2.55 (m, 1 H, 2′-H_b), 3.19 (m_c, 1 H, 4-H), 3.28 (s, 3 H, OCH_3), 3.33−3.50 (m, 2 H, 1′-H_a, 1′′-H_a), 3.65 (dt, *J* = 4.7, 13.0 Hz, 1 H, 2-H_a), 3.72−3.89 (m, 2 H, 1′′-H_b, 1′-H_b), 3.96 (ddd, *J* = 3.0, 6.0, 13.0 Hz, 1 H, 2-H_b), 4.92−5.09 (m, 2 H, CH=CH_2), 5.66 (m_c, 1 H, C*H*=CH_2), 7.42−7.68 (m, 9 H, Ph−H, 8-H), 7.73−7.83 (m, 2 H, Ph−H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.8 (*C*H_3COO), 23.3 (C-2′), 32.9 (C-3), 41.4 (C-4), 43.1 (C-1), 49.6 (C-2), 54.9 (OCH_3), 62.9 (C-1′), 107.3 (C-8), 115.1 (C-5), 116.7 (CH=*C*H_2), 124.8 (C-4a), 127.0 (C-2, C-5, SO_2Ph), 127.2 (C-6), 127.8 (C-2, C-5, SO_2Ph), 128.4, 129.2 (C-1, C-6, 2 × SO_2Ph), 132.2 (*C*H=CH_2), 133.6, 134.8 (C-4, 2 × SO_2Ph), 137.9, 138.5 (C-1, 2 × SO_2Ph), 140.9 (C-8a), 155.5 (C-7), 170.5 (C=O) ppm. MS (70 ev): *m*/*z* (%) = 710 (11), [M^+], 569 (100) [M^+ − SO_2Ph], 528 (8) [M^+ − SO_2Ph − CH_3CO], 429 (13), 327 (18). HRMS calcd. for $C_{29}H_{31}IN_2O_7S_2$ 710.0617; found 710.0617 (MS). $C_{29}H_{31}IN_2O_7S_2$ (710.59): calcd. C 49.02, H 4.40; found C 49.15, H 4.33.

(4*RS*)-4-Acetoxymethyl-7-[3-butenyl(phenylsulfonyl)amino]-6-iodo-8-methoxy-1-phenylsulfonyl-2,3,4,5-tetrahydrobenzazepine (20): A solution of **18** (558 mg, 0.84 mmol) and sodium acetate (83.5 mg, 1.02 mmol) in acetic anhydride (6 mL) was stirred at 60 °C for 1 h. The reaction mixture was diluted with toluene (100 mL) and the solvents were removed in vacuo. The residue was dissolved in ethyl acetate (50 mL), and the organic layer was washed twice with water (10 mL) and brine, dried with Na_2SO_4 and the solvent was removed in vacuo. Purification by column chromatography (50 g SiO_2, PE/EA, 2:1) furnished **20** (572 mg, 0.805 mmol, 96%) as a colorless solid. R_f = 0.23 (PE/EA, 2:1). UV (CH_3CN): λ_{max} (lg ε) = 218.5 nm (3.729), 301.0 (2.788). IR (KBr): $\tilde{\nu}$ = 3068 cm^{-1} (Ar−H), 2940 (C−H), 1738 (C=O), 1586 (C=C), 1444, 1348 (S=O), 1244, 1164 (C−O−C). ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.75−1.85 (m, 1 H, 3-H_a), 1.92 (s, 3 H, CH_3COO), 1.92−2.05 (m, 1 H, 3-H_b), 2.11−2.28 (m, 1 H, 2′-H_a), 2.29−2.45 (m, 1 H, 2′-H_b), 2.94 (dd, *J* = 3.0, 14.5 Hz, 1 H, 5-H_a), 3.11 (dd, *J* = 8.0, 14.5 Hz, 1 H, 5-H_b), 3.28 (s, 3 H, OCH_3), 3.48 (ddd, *J* = 5.7, 10.0, 14.5 Hz, 1 H, 1′-H_a), 3.67−3.80 (m, 3 H, 1′-H_b, 2-H_2), 4.91−5.00 (m, 3 H, 4-H, CH=CH_2), 5.66 (m_c, 1 H, C*H*=CH_2), 6.77 (s, 1 H, 9-H), 7.43−7.63 (m, 6 H, SO_2Ph), 7.74−7.80 (m, 4 H, SO_2Ph) ppm. ^{13}C NMR (75 MHz, $C_2D_2Cl_4$, 100 °C): δ = 20.7 (*C*H_3COO), 32.0 (C-5), 32.4 (C-2′), 42.1 (C-3), 45.7 (C-2), 49.7 (C-1′), 54.9 (OCH_3), 67.2 (C-4), 112.8 (C-9), 114.3 (C-6), 116.2 (C-4′), 126.8, 127.7, 128.1. 129.0 (C-2, C-3, C-5, C-6, 2 × SO_2Ph), 130.9 (C-5a), 131.97 (C-4, SO_2Ph), 132.4 (C-7), 132.8 (C-4, SO_2Ph), 134.8 (C-3′), 139.2 (C-9a), 140.6, 141.1 (C-1, 2 × SO_2Ph), 156.0 (C-8), 169.3 (C=O) ppm. MS (70 eV): *m*/*z* (%) = 710 (18) [M^+], 669 (100) [M^+ − CH_3CO], 569 (100) [M^+ − SO_2Ph], 528 (30) [M^+ − SO_2Ph − CH_3CO], 327 (61). HRMS calcd. for $C_{29}H_{31}IN_2O_7S_2$ 710.0617; found 710.0617. $C_{29}H_{31}IN_2O_7S_2$ (710.59): calcd. C 49.02, H 4.40; found C 48.93, H 4.21.

(1*RS*)-1-Acetoxymethyl-6-methoxy-10-methylene-4,7-bis(phenylsulfonyl)-1,2,3,4,7,8,9,10-octahydropyridino[3,2-*f*]quinoline (21): A mixture of palladium acetate (6.70 mg, 29.8 μmol) and triphenylphosphane (15.4 mg, 58.7 μmol) in degassed DMF (5 mL) was stirred at 20 °C for 5 min. Silver carbonate (78.5 mg, 285 μmol) and a solution of **19** (100 mg, 140 μmol) in DMF (1 mL) were added and the reaction mixture was heated at 60 °C for 20 h. The mixture was diluted with ethyl acetate, filtered through a short column with layers of SiO_2/Celite/charcoal/Celite/SiO_2, washed twice with water and brine, dried with Na_2SO_4 and the solvent was removed in vacuo and the residue purified by column chromatography (15 g SiO_2, PE/EA, 3:1) to yield **21** (70.0 mg, 120 μmol, 85%) as colorless amorphous solid. R_f = 0.44 (PE/EA, 2:1). UV (CH_3CN): λ_{max} (lg ε) = 220.0 nm (3.687). IR (KBr): $\tilde{\nu}$ = 3446 cm^{-1}, 3420, 1738 (C=O), 1588 (C=C_{Ar}), 1476, 1446, 1352 (S=O), 1232, 1164 (S=O), 1090 (C−O−C), 1036, 752 598, 580. ^1H NMR (300 MHz, C_6D_6, 50 °C): δ = 1.23−1.38 (m, 2 H, 2-H_2), 1.56 (s, 3 H, CH_3COO), 2.20−2.32 (m, 1 H, 9-H_a), 2.37−2.51 (m, 1 H, 9-H_b), 3.06−3.20 (m, 1 H, 8-H_a), 3.27−3.36 (m, 1 H, 1-H), 3.43 (t, *J* = 10.5 Hz, 1 H, −CH_a−O), 3.50 (s, 3 H, OCH_3), 3.58−3.73 (m, 2 H, 3-H_2), 3.66 (dd, *J* = 10.5, 4.0 Hz, 1 H, −CH_b−O), 3.81 (dd, *J* = 13.2, 4.5, 4.5 Hz, 1 H, 8-H_b), 4.68 (s, 1 H, C=CH_2), 4.76 (s, 1 H, C=CH_2), 6.88−7.04 (m, 7 H, Ph−H, 5-H), 7.61−7.67 (m, 2 H,

Ph−H), 7.68−7.76 (m, 2 H, Ph−H) ppm. ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 120 °C): δ = 1.69−1.83 (m, 1 H, 2-H_a), 1.92−2.03 (m, 1 H, 2-H_b),1.97 (s, 3 H, CH_3COO), 2.68 (ddd, *J* = 3.5, 7.0, 14.0 Hz, 1 H, 9-H_a), 2.82 (dt, *J* = 7.0, 14.0 Hz, 1 H, 9-H_b), 3.51 (ddd, *J* = 5.5, 9.0, 16.0 Hz, 1 H, 8-H_a), 3.54−3.60 (m, 1 H, 1-H), 3.64 (t, *J* = 10.5 Hz, 1 H, 1-CH_a−), 3.78 (s, 3 H, OCH_3), 3.83 (dd, *J* = 4.0, 10.5 Hz, 1 H, 1-CH_b−), 3.85−3.98 (m, 3 H, 3-H, 8-H_b), 4.94 (s, 1 H, C=CH_2), 5.06 (s, 1 H, C=CH_2), 7.41 (s, 1 H, 5-H), 7.42−7.65 (m, 6 H, Ph−H), 7.70−7.79 (m, 2 H, Ph−H), 7.80−7.89 (m, 2 H, Ph−H) ppm. ^{13}C NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 20.3 (*C*H_3COO), 24.1 (C-2), 31.4 (C-1), 36.1 (C-9), 43.1 (C-3), 45.4 (C-8), 55.7 (OCH_3), 65.1 (C-1′), 108.1 (C-5), 116.2 (C=*C*H_2), 118.2 (C-10b), 124.8 (C-6a), 126.9, 127.3 (C-3, C-5, 2 × SO_2Ph), 128.2, 128.9 (C-2, C-6, 2 × SO_2Ph), 132.0, 132.8 (C-4, 2 × SO_2Ph), 136.9 (C-10a), 137.3 (C-4a), 138.2, 139.5 (C-1, 2 × SO_2Ph), 141.24 (C-6), 153.8 (C-10), 169.9 (C=O) ppm. MS (70 eV): *m*/*z* (%) = 582 (6) [M^+], 441 (100) [M^+ − SO_2Ph], 301 (15) [M^+ −2 × SO_2Ph], 91 (11) [$C_7H_7^+$], 77 (8) [$C_6H_6^+$]. HRMS calcd. for $C_{29}H_{30}N_2O_7S_2$ 582.1494; found 582.1494. $C_{29}H_{30}N_2O_7S_2$ (582.68): calcd. C 59.78, H 5.19; found C 60.06, H 5.28.

(2*RS*)-2-Acetoxy-7-methoxy-11-methylene-5,8-bis(phenylsulfonyl)-1,2,3,4,8,9,10,11-octahydroazepino[3,2-*f*]quinoline (22): A solution of palladium acetate (6.70 mg, 29.8 μmol) and triphenylphosphane (15.4 mg, 58.7 μmol) in degassed DMF (5 mL) was stirred at 20 °C for 5 min. Silver carbonate (78.5 mg, 285 μmol) and a solution of **20** (100 mg, 140 μmol) in DMF (1 mL) were added and the reaction mixture was heated at 60 °C for 20 h. The mixture was diluted with ethyl acetate, filtered through a short column with layers of SiO_2/Celite/charcoal/Celite/SiO_2, washed twice with water and brine, dried with Na_2SO_4 and the solvent was removed in vacuo and the residue purified by column chromatography (15 g SiO_2, PE/EA, 3:1) to yield **22** (68.5 mg, 118 μmol, 84%) as a colorless amorphous solid. R_f = 0.32 (PE/EA, 2:1); m.p. 70 °C. UV (CH_3CN): λ_{max} (lg ε) = 225.5 nm (2.729), 300.0 (1.791). IR (KBr): $\tilde{\nu}$ = 3434 cm^{-1}, 2934 (C−H), 1736 (C=O), 1446, 1342 (S=O), 1244, 1224, 1162 (S=O), 1092 (C−O−C), 692, 578 ppm. ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 120 °C): δ = 1.98 (s, 3 H, CH_3COO), 2.01−2.13 (m, 2 H, 3-H_2), 2.62−2.80 (m, 2 H, 10-H_2), 2.91 (d, *J* = 6.0 Hz, 2 H, 1-H_2), 3.53−3.70 (m, 2 H, 4-H_a, 9-H_a), 3.64 (s, 3 H, OCH_3), 3.82 (ddd, *J* = 5.0, 9.0, 14.0 Hz, 1 H, 4-H_b), 4.01 (ddd, *J* = 4.5, 6.5, 14.0 Hz, 1 H, 9-H_b), 4.84−4.94 (m, 1 H, 2-H), 4.88 (s, 1 H, C=CH_2), 5.10 (s, 1 H, C=CH_2), 6.77 (s, 1 H, 6-H), 7.42−7.67 (m, 6 H, Ph−H), 7.83−7.93 (m, 4 H, Ph−H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2 (*C*H_3COO), 33.2−33.8 (C-1), 34.4 (C-3), 35.3 (C-10), 45.2 (C-4), 46.9 (C-9), 55.6 (OCH_3), 69.2−69.9 (C-2), 111.6 (C-6), 118.2 (C=*C*H_2), 124.4 (C-11b), 127.0 (C-7a), 127.1, 127.7 (C-2, C-6, 2 × SO_2Ph), 128.6, 129.1 (C-3, C-5, 2 × SO_2Ph), 132.5, 132.9 (C-4, 2 × SO_2Ph), 136.6 (C-11a), 139.5 (C-5a), 140.4, 141.0 (C-1, 2 × SO_2Ph), 141.4 (C-7), 153.6 (C-11), 170.0 (C=O) ppm. MS (70 eV): *m*/*z* (%) = 582 (7) [M^+], 441 (100) [M^+ − SO_2Ph], 381 (3) [M^+ − SO_2Ph − CH_3COO], 301 (12) [M^+ − 2 × SO_2Ph], 241 (12) [M^+ − 2 × SO_2Ph − CH_3COO], 77 (10) [$C_6H_5^+$]. HRMS calcd. for $C_{29}H_{30}N_2O_7S_2$: 582.1494, found 582.1494.

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