DOI: 10.1002/ejoc.200700583

From Central to Axial to Central Chirality: Enantioselective Construction of the *trans*-4,5,9,10-Tetrahydroxy-9,10-dihydrophenanthrene System

Georgi Stavrakov,[a] Manfred Keller,[a][‡] and Bernhard Breit*[a]

Keywords: Asymmetric synthesis / Biaryl coupling / Atropisomerism / Ullmann coupling

Enantioselective synthesis of the core *trans*-4,5,9,10-tetrahydroxy-9,10-dihydrophenanthrene parent system of the antibiotics benanimicin, pradimicin and FD 594 has been accomplished. The synthesis employs a chiral tether approach and makes use of efficient central to axial to central chirality transfer. Key to success was an "imine-directed" atropdiastereoselective Ullmann coupling under mild reaction conditions.

Introduction

The *trans*-4,5,9,10-tetrahydroxy-9,10-dihydrophenanthrene system is the core structural subunit of a wide range of biologically and medicinally interesting natural products such as the benanimicin and pradimicin antibiotics (BPAs), important due to their antifungal and anti-HIV activity,[1] as well as for the angucycline PD 116740 exhibiting anticancer activity.[2] Furthermore, the same dihydrophenanthrene system is the core structure of the cytotoxic antibiotic FD 594 which possesses moderate efficiency against several tumor cell lines as well as antibacterial activities against some Gram-positive bacteria (Figure 1).[3] Most interestingly, FD-594 features a unique solvent dependent atropisomerism, as a result of two distinct preferred conformations of the central dihydrophenanthrene system dependent on solvent polarity.[4]

Inspired by this intriguing conformational behavior, we recently identified the 9,10-dihydrophenanthrene system **1** as the minimal structural entity which is essential to mimic solvent-dependent atropisomerism (Scheme 1).[5] Such a system can be regarded as an axial-chirality switch, which has potential for application in material sciences and asymmetric catalysis.

The pronounced biological activity of these natural products as well as their molecular architecture has triggered a number of synthetic studies.[6–8] However, to the best of our knowledge to date no enantioselective synthesis of the *trans*-4,5,9,10-tetrahydroxy-9,10-dihydrophenanthrene core has been described.[9]

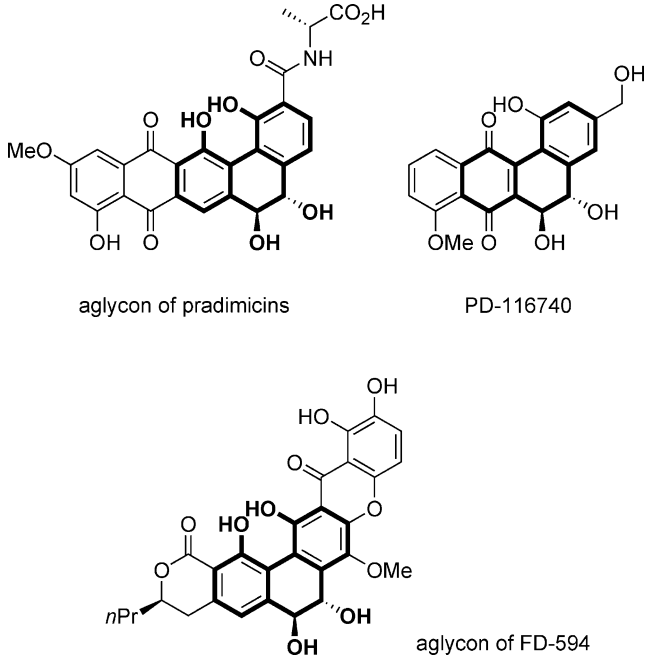
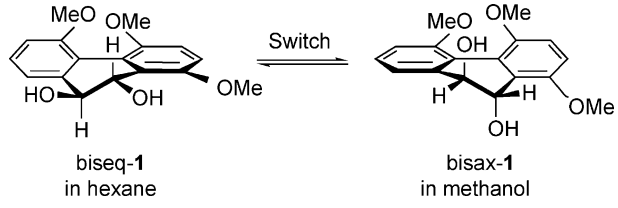


Figure 1. A selection of natural products featuring the *trans*-4,5,9,10-tetrahydroxy-9,10-dihydrophenanthrene system.



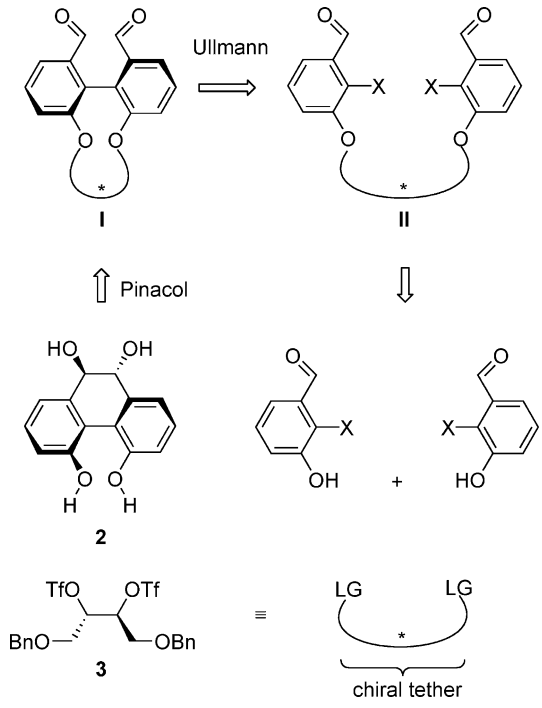
Scheme 1. Solvent-dependent atropisomerism of the 9,10-dihydrophenanthrene system **1**.[5]

Results and Discussion

We herein report on a strategy for the stereoselective construction of the central *trans*-4,5,9,10-tetrahydroxy-9,10-di-

[a] Institut für Organische Chemie und Biochemie,
Albert-Ludwigs-Universität Freiburg,
Albertstr. 21, 79104 Freiburg, Germany
Fax: +49-761-203-8715
E-mail: bernhard.breit@organik.chemie.uni-freiburg.de
[‡] X-ray crystal structure analysis.

hydrophenanthrene system **2** in enantiomerically pure form. The synthesis features a central to axial to central chirality transfer, and relies on a directed atropdiastereoselective Ullmann coupling operating under mild reaction conditions. The strategy is outlined in Scheme 2.

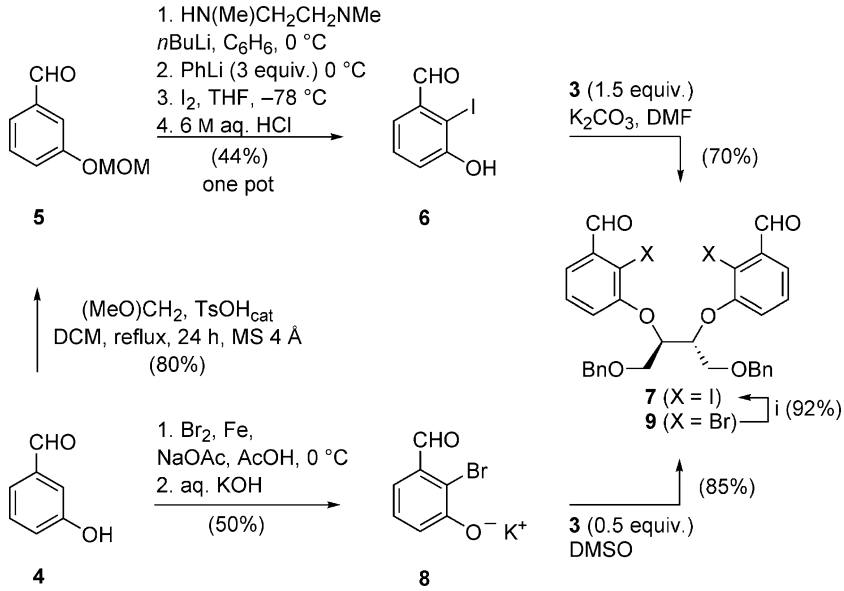


Scheme 2. Retrosynthetic analysis.

In order to achieve a stereocontrolled biaryl axis formation we chose a chiral tether strategy.[10] Among the chiral tethers employed for this purpose the 1,4-di-*O*-benzyl-D-threitol tether derived from L-tartrate introduced by Lipshutz for oxidative cuprate coupling was selected.[11] In a subsequent Ullmann cross coupling reaction of dialdehyde **II** we hoped for efficient central to axial chirality transfer. A diastereoselective pinacol coupling of biaryl dialdehyde **I** with efficient axial to central chirality transfer would furnish after tether removal the target dihydro-phenanthrene system **2**. Efficient axial to central chirality transfer in the course of the pinacol coupling of related system has been reported by Suzuki et al.[12]

The synthesis commenced from 3-hydroxybenzaldehyde (**4**). After protection of the phenolic hydroxy group as a MOM ether directed *ortho*-metallation with phenyllithium was achieved after in situ protection of the aldehyde with lithio *N*′,*N*,*N*-trimethylethylene aminoamide.[13] Trapping of the intermediate 2-lithio aryl species with iodine followed by an acidic workup, to liberate the aldehyde function, furnished the desired 2-iodo-3-hydroxybenzaldehyde (**6**). The threitol tether was introduced via nucleophilic displacement with bistriflate **3**. Unfortunately, an unusually large excess of bistriflate **3** was required in order to achieve complete consumption of phenolic starting material **6**. A closer inspection of side products revealed that bistriflate **3** decomposed under the reaction conditions to give the corresponding alkyne as a consequence of a twofold β-elimination of triflic acid. As the origin of undesired elimination we identified the base, potassium carbonate, which was required to generate in situ the phenolate nucleophile. Finally, the problem could be solved when preformed phenolate salts were employed (vide infra) (Scheme 3).

As a more reliable route for large-scale preparations proved the direct bromination of **4** with bromine and iron powder in an acetate buffer.[14] The resulting 2-bromine-substituted phenol was quantitatively transformed into its potassium salt upon treatment with potassium hydroxide. Reaction with stoichiometric amounts of bistriflate **3** pro-



Scheme 3. Synthesis of Ullmann coupling precursor **7**. i a) $CyNH_2$, $MgSO_4$, DCM; b) *n*BuLi, THF, –78 °C, then I_2 and warm to room temp. (92% two steps).

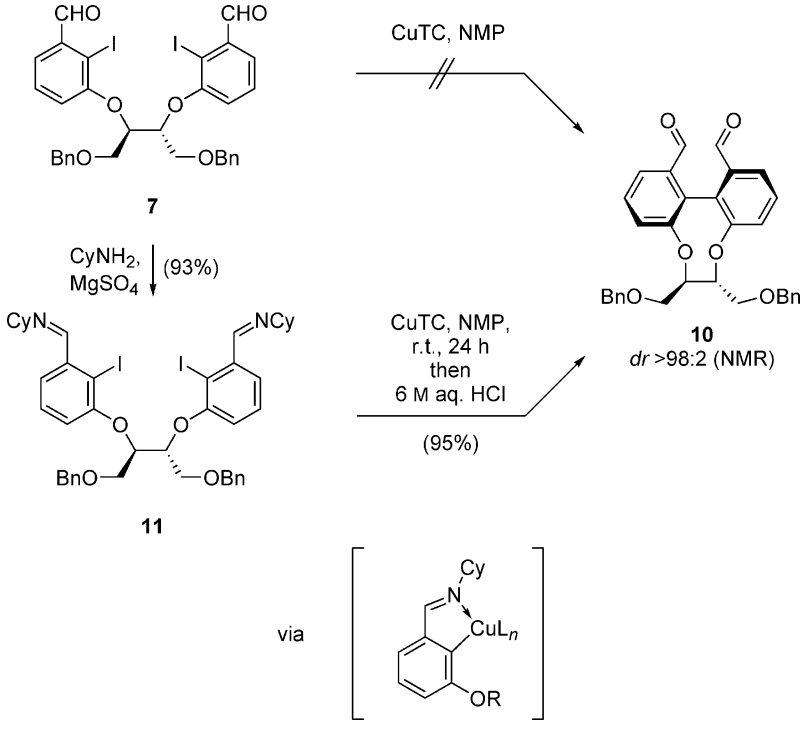
ceeded smoothly in DMSO and furnished the tethered dibromide **9** in good yield. Bromine–iodine exchange was achieved in excellent yield employing a one-pot three-step procedure. First the dialdehyde was protected as the bisimine upon condensation with cyclohexylamine. Bromine–lithium exchange proceeded quantitatively in THF at –78 °C followed by a quench with iodine. Acidic workup liberated the iodinated bisaldehyde **7** in overall excellent yield (92%).

In order to achieve maximum levels of stereocontrol in the course of the Ullmann coupling step we chose the CuTC reagent introduced by Liebeskind et al.[15] This reagent allows to perform ambient-temperature Ullmann coupling reactions of aryl iodides. However, the reaction is restricted to aryl substrates equipped with a directing group in *ortho*-position relative to iodide. As effective directing groups had been identified previously, carboxylic esters, amides, carbamates, methylene hydroxy and methylene amine functions etc.[15] To the best of our knowledge successful examples of CuTC Ullmann coupling reactions employing substrates equipped with an aldehyde function in the *ortho*-position were unknown. As such, subjection of bisaldehyde **7** to the Liebeskind conditions did not show any reaction at all, even not at longer reaction times and higher temperatures. Starting material was reisolated quantitatively. Thus, if precoordination of the CuTC reagent is prerequisite for a successful coupling reaction, an aldehyde is not an effective directing group. As a consequence, we transformed the dialdehyde into the corresponding bisimine **11** which should be a significantly stronger donor towards a copper(I) center and which could act as a removable directing group for aldehyde substrates. Interestingly, subjection of bisimine **11** to the same Liebeskind conditions (CuTC, NMP, room temp.) led to a smooth coupling reaction which proceeded almost quantitatively. After acidic workup the biaryldialdehyde **10** was obtained in excellent yield (95%) and diastereoselectivity (>98:2, NMR). Hence, this is the first example of a highly atropdiasteroselective Ullmann coupling with an excellent central to axial chirality transfer operating under mild reaction conditions (Scheme 4).

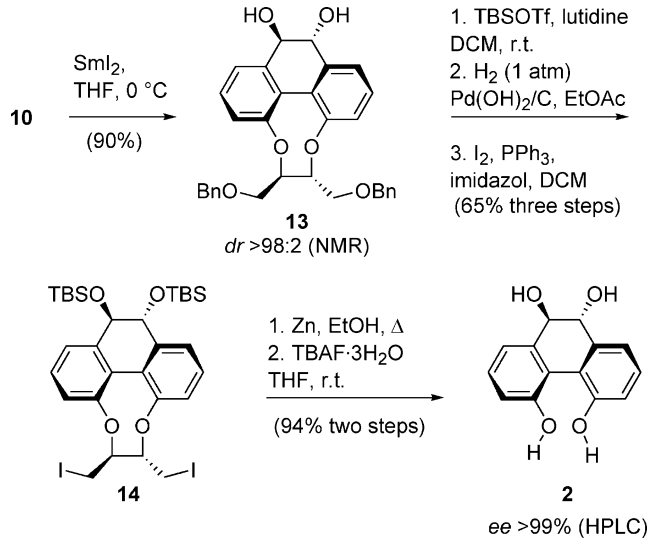
In order to build the C9,10 glycol-bridge bisaldehyde **10** was subjected to the conditions of a SmI_2-mediated pinacol coupling reaction.[12] In accord with literature precedence, this reaction occurred highly chemo- and diastereoselectively with an excellent axial to central chirality transfer to give the *trans*-diastereomer **13** (>98:2, NMR). Removal of the threitol tether required TBS protection of the vicinal diol function. The benzyl ethers were cleaved with Pearlman's catalyst and the resulting primary alcohol functions transferred into iodide **14**. Zn-initiated reductive elimination followed by silyl ether cleavage liberated the desired tetrol **2** in overall good yield and enantiomerically pure form (> 99% *ee*, HPLC) (Scheme 5).

In order to establish the relative and absolute configuration of the *trans*-4,5,9,10-tetrahydroxy-9,10-dihydrophenanthrene core, X-ray crystal structure analyses of diol **13** and diiodide **14** were performed (Figures 2 and 3, respectively).[16]

According to both X-ray structures, the oxygen substituents at the glycol bridge occupy a pseudo-equatorial position and have the *R*,*R* configuration. The biaryl axis displays *P*-configuration. Optical rotation of the parent tetrol system **2** in chloroform is similar to that in methanol (see



Scheme 4. Directed diastereoselective Ullmann coupling of diimine **11** and proposed intermediate.



Scheme 5. Completion of the synthesis of **2**: Diastereoselective pinacol-coupling and chiral tether removal.

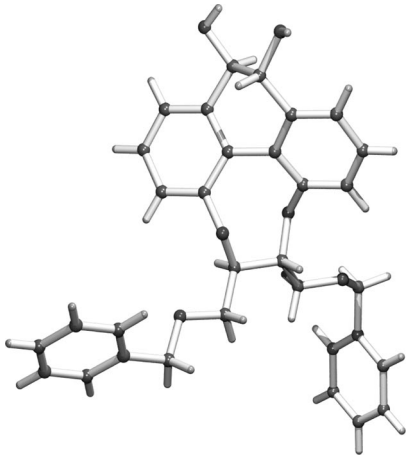


Figure 2. X-ray plot of the structure of diol **13** in the solid state.[5]

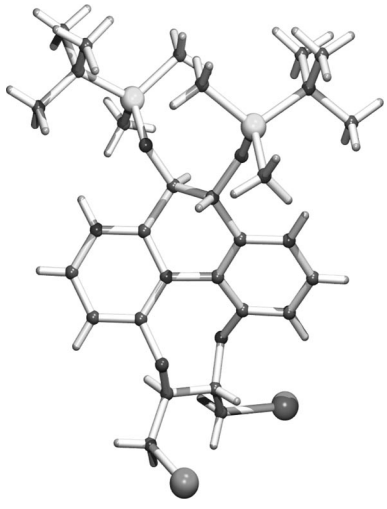


Figure 3. X-ray plot of the structure of diiodide **14** in the solid state.

Exp. Sect.). Hence, system **2** does not display solvent-dependent atropisomerism. This is in accord with our previous studies which identified the additional methoxy substituent at C1 in **1** as an essential structural element for this unique conformational behavior.[5]

Conclusions

Enantioselective synthesis of the core *trans*-4,5,9,10-tetrahydroxy-9,10-dihydrophenanthrene parent system of the antibiotics benanimicin, pradimicin and FD 594 has been achieved. The synthesis employs a chiral tether approach and makes use of efficient central to axial to central chirality transfer. Key to success was an imine-directed atropdiastereoselective Ullmann coupling under mild reaction conditions. The synthesis is intrinsically flexible and should allow the preparation of unsymmetrical und higher substituted 9,10-dihydrophenanthrene systems. This strategy may become key to future total syntheses of this important class of natural products and analogues.

Experimental Section

General Remarks: All manipulations of oxygen- and moisture-sensitive materials were carried out in dried glassware under argon atmosphere. Air- and moisture-sensitive liquids and solutions were transferred via syringe. All reagents were obtained commercially unless otherwise noted. Copper(I) thiophenecarboxylate (CuTC) was synthesized according to a literature procedure.[15] All solvents were dried and distilled by standard procedures. Organic solutions were concentrated under reduced pressure by rotary evaporation. Chromatographic purification of products was accomplished using flash column chromatography on Macherey–Nagel silica gel 60 (230–400 mesh). Nuclear magnetic resonance spectra were acquired on a Varian Mercury spectrometer (300 MHz and 75 MHz for ^{1}H and ^{13}C respectively), on a Bruker AC 250 (250 MHz), Bruker DRX 300 (300 MHz and 75 MHz for ^{1}H and ^{13}C, respectively), Bruker AMX 400 (400 MHz and 100 MHz for ^{1}H and ^{13}C, respectively), Bruker DRX 500 (500 MHz and 125 MHz for ^{1}H and ^{13}C, respectively) and are referenced according to residual protio solvent signals. Data for ^{1}H NMR are recorded as follows: chemical shift (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, m_c = centrosymmetric multiplet, br. = broad, dd = doubled doublet; dt = doubled triplet, dm = doubled multiplet, p = pseudo), coupling constant J (Hz), integration. Data for ^{13}C-NMR are reported in terms of chemical shift (δ in ppm), multiplicity (if not a singlet), coupling constant J (Hz). High-resolution mass spectra were obtained on a Finnigan MAT 8200 instrument. Elementary analysis was performed on an elementar vario (Fa. Elementar Analysysteme GmbH). Analytical HPLC was performed on a Dionex P580 (pump) with an UVD 170S detector. CD measurements were done on a Fa. Jasco spectropolarimeter J-810. The petroleum ether used had a boiling range of 40–60 °C.

(2*S*,3*S*)-1,4-Bis(benzyloxy)butane-2,3-diylbis(trifluoromethanesulfonate) (3): To a solution of (2*S*,3*S*)-1,4-bis(benzyloxy)-2,3-butanediol[17] (8.66 g, 28.7 mmol) and pyridine (13.6 g, 14 mL, 172 mmol)in dichloromethane (250 mL) at –40 °C was added dropwise Tf_2O (24.26 g, 14.5 mL, 86 mmol). The mixture was allowed to reach room temperature overnight, quenched with satd. aq. $KHSO_4$ (150 mL), and extracted with diethyl ether (3 times,

200 mL). The combined organic layers were washed with water, dried ($MgSO_4$), concentrated, and filtered through a pad of silica gel (EtOAc). Concentration afforded 16.25 g (28.7 mmol, quant.) of the desired bis(triflate) **3** as a brown oil. $[\alpha]_D^{24}$ = +15.4 (*c* = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.75 (d, *J* = 12.0 Hz, 4 H), 4.48 (d, *J* = 12.0 Hz, 4 H), 5.26 (m, 2 H), 7.23–7.42 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.1 (2 C), 74.0 (2 C), 83.5 (2 C), 118.4 (q, *J* = 319.70 Hz, 2 C), (128.2, 128.5, 128.7, 136.3, 12 C) ppm.

3-(Methoxymethoxy)benzaldehyde (5): A dried 1 L flask was loaded under an atmosphere of argon with 3-hydroxybenzaldehyde (30.5 g, 0.25 mol), dichloromethane (500 mL), dimethoxymethane (110 mL, 1.25 mol), and *p*-toluenesulfonic acid monohydrate (0.3 g). The mixture was heated to reflux overnight under an atmosphere of Ar using a Soxhlet apparatus containing activated (24 h, 180 °C, vacuum) molecular sieves (4 Å, 150 g). The reaction was cooled to room temperature, quenched with triethylamine (1 mL) to neutralize the acid catalyst, diluted with additional 300 mL of CH_2Cl_2, washed with 10% aq. NaOH (2 times, 200 mL) and water, dried ($MgSO_4$), filtered through a pad of silica gel, and concentrated to give 33.32 g (0.2 mol, 80%) of **5** as a brown oil; b.p. 90–100 °C/0.5 Torr. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.35 (s, 3 H), 5.13 (s, 2 H), 7.16–7.22 (m, 1 H), 7.31–7.46 (m, 3 H), 9.85 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1, 94.4, 116.0, 122.8, 123.8, 130.1, 137.9, 157.8, 191.9 ppm. analytical data corrrespond to those reported previously.[18]

3-Hydroxy-2-iodobenzaldehyde (6): A dried 1 L, three-necked flask equipped with a dropping funnel and an argon inlet was loaded under an atmosphere of Ar with *N*′,*N*,*N*-trimethylethylenediamine (6.8 g, 66 mmol, 1.1 equiv.) and benzene (170 mL). The solution was cooled to 0 °C and to it was added dropwise a 1.44 M solution of *n*BuLi in hexane (46 mL, 66 mmol, 1.1 equiv.). The mixture was stirred at room temp. for 15 min, and then again cooled to 0 °C. To the mixture was added dropwise 3-(methoxymethoxy)benzaldehyde **5** (8.2 g, 60 mmol, 1 equiv.). Stirring for another 15 min at room temp., was followed by cooling to 0 °C, and a dropwise addition of a 1.6 M solution of PhLi in dibutyl ether (103 mL, 180 mmol, 3 equiv.). The reaction was stirred at room temp. for 12 h, then diluted with 170 mL of dry THF and cooled to –78 °C. To it was added dropwise a solution of I_2 (76.5 g, 301 mmol, 5 equiv.) in dry THF (150 mL) until the red colour of iodine persisted. The mixture was warmed to room temp., and poured into cold (0 °C), 1 M aq. HCl (500 mL). Stirring for 12 h allowed hydrolysis of the MOM protecting group. The reaction was then extracted with diethyl ether (3 times, 200 mL). The combined organic layers were washed with satd. aq. $Na_2S_2O_3$ (2 times, 250 mL), and extracted with 10% aq. NaOH (3 times, 50 mL). The combined water phases were acidified with 6 M aq. HCl, and extracted with CH_2Cl_2 (3 times, 100 mL). The dichloromethane layers were dried ($MgSO_4$) and concentrated. Filtration through a pad of silica gel (EtOAc) and crystallisation (Et_2O/petroleum ether, 1:1) afforded 3.73 g (15.1 mmol, 44%) of 3-hydroxy-2-iodobenzaldehyde as yellow crystals; m.p. 160 °C (EtOH). ^1H NMR (250 MHz, $CDCl_3$): δ = 5.67 (br. s, 1 H), 6.98 (pdd, *J* = 1.8, 7.9 Hz, 1 H), 7.23 (pt, *J* = 7.9 Hz, 1 H) 7.28 (pdd, *J* = 1.8, 7.8 Hz, 1 H), 9.78 (s, 1 H) ppm. Analytical data corrrespond to those reported previously.[19]

3,3′-{[(2*R*,3*R*)-1,4-Bis(benzyloxy)butane-2,3-diyl]bis(oxy)}bis(2-iodobenzaldehyde) (7): A dried 100 mL flask was loaded under an atmosphere of Ar with phenol **6** (2.11 g, 8.5 mmol), DMF (40 mL) and K_2CO_3 (10 g). The reaction mixture was stirred at room temperature for 15 min followed by the addition of bis-triflate **3** (7.17 g, 12.75 mmol) in three portions within 2 h. The mixture was stirred at room temperature for further 12 h, diluted with diethyl ether (100 mL), filtered, and washed with water (50 mL), 10% aq. NaOH (2 times, 25 mL), and water (50 mL). The combined organic layers were dried ($MgSO_4$), concentrated, purified via flash-column chromatography (silica gel, CH_2Cl_2; R_f = 0.28, petroleum ether/EtOAc, 4:1) and crystallized (1 mL, petroleum ether/EtOAc, 3:1) to give 2.27 g (2.98 mmol, 70%) of the di-iodide **7** as colourless crystals. Acidification and extraction (EtOAc) of the combined water layers allowed reisolation of the not reacted phenol (0.59 g, 2.38 mmol, 28%); m.p. 123 °C (petroleum ether/EtOAc). $[\alpha]_D^{24}$ = –2.0 (*c* = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.75 (pdd, *J* = 5.2, 10.3 Hz, 2 H), 3.90 (pdd, *J* = 5.2, 10.3 Hz, 2 H), 4.4 (AB, *J* = 11.9 Hz, 4 H), 4.86 (m_c, 2 H), 7.07–7.33 (m, 14 H), 7.45 (pdd, *J* = 1.8, 7.6 Hz, 2 H), 10.08 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.1 (2 C), 73.8 (2 C), 78.9 (2 C), 95.5 (2 C), 119.4 (2 C), 123.2 (2 C), (127.9, 128.0, 128.5, 10 C), 129.5 (2 C), 137.0 (2 C), 137.5 (2 C), 157.6 (2 C), 196.5 (2 C) ppm. $C_{32}H_{28}I_2O_6$ (762.37): calcd. C 50.41, H 3.70; found C 50.12, H 3.81.

***N*,*N*′-{[(2*R*,3*R*)-1,4-Bis(benzyloxy)butane-2,3-diyl]bis[oxy(2-iodo-3,1-phenylene)-(*E*)-methylidene]}dicyclohexanamine (11):** A 250 mL flask was loaded with bis-aldehyde **7** (2.29 g, 3 mmol), dichloromethane (75 mL), $MgSO_4$ (30 g), and cyclohexylamine (0.89 g, 1 mL, 9 mmol). The slurry was stirred at room temp. for 2 h, filtered, concentrated, and crystallized (petroleum ether/Et_2O, 2:1) to give 2.58 g (2.79 mmol, 93%) of the desired bis-imine **11** as colourless crystals; m.p. 113 °C (Et_2O). $[\alpha]_D^{25}$ = –3.8 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.1–1.8 (m, 20 H), 3.24 (m_c, 2 H), 3.75 (pdd, *J* = 5.1, 10.2 Hz, 2 H), 3.93 (pdd, *J* = 5.1, 10.2 Hz, 2 H), 4.4 (AB, *J* = 11.8 Hz, 4 H), 4.79 (m_c, 2 H), 6.95 (pdd, *J* = 1.3, 8.2 Hz, 2 H) 7.05–7.25 (m, 12 H), 7.50 (pdd, *J* = 1.3, 7.6 Hz, 2 H), 8.45 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = (24.8, 25.8, 34.4, 10 C), 68.3 (2 C), 69.6 (2 C) 73.7 (2 C), 78.5 (2 C), 94.5 (2 C), 115.5 (2 C), 122.2 (2 C), (127.8, 127.9, 128.5, 10 C), 129.1 (2 C), 137.8 (2 C), 139.5 (2 C), 157.2 (2 C), 162.7 (2 C) ppm. $C_{44}H_{50}I_2N_2O_4$ (924.69): calcd. C 57.15, H 5.45, N 3.03; found C 57.06, H 5.62, N 2.88.

2-Bromo-3-hydroxybenzaldehyde: A 250 mL flask was loaded with 3-hydroxybenzaldehyde (16.1 g, 132 mmol, 1 equiv.), iron powder (0.56 g, 10 mmol), anhydrous sodium acetate (21.3 g, 260 mmol, 1.97 equiv.) and glacial acetic acid (120 mL). The suspension was warmed until a clear solution was obtained, and then allowed slowly to cool to room temp. To the mixture was added dropwise, over 15 min, a solution of bromine (24.0 g, 150 mmol, 1.14 equiv.) in glacial acetic acid (25 mL). The reaction temperature was not allowed to rise above room temperature. One hour after the completion of the addition, the reaction mixture was poured into ice-water (800 mL), and extracted with CH_2Cl_2 (3 times, 200 mL). The combined organic extracts were dried ($MgSO_4$) and filtered through a pad of silica gel (CH_2Cl_2). Concentration and crystallization from CH_2Cl_2 (20 mL) afforded 10.6 g (52.8 mmol, 40%) 2-bromo-3-hydroxybenzaldehyde. Flash-column chromatography (silica, CH_2Cl_2; R_f = 0.28, petroleum ether/EtOAc, 2:1) of the mother liquor afforded another 2.7 g (13.43 mmol, 10%) of the desired product; m.p. 145 °C (CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.80 (s, 1 H), 7.26 (pdd, *J* = 1.7, 7.9 Hz, 1 H), 7.36 (pt, *J* = 7.9 Hz, 1 H), 7.45 (pdd, *J* = 1.7, 7.5 Hz, 1 H), 10.03 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.5, 121.8, 122.9, 129.0, 134.0, 153.1, 191.2 ppm. $C_7H_5BrO_2$ (201.02): calcd. C 41.82, H 2.51; found C 41.44, H 2.58.

Potassium 2-Bromo-3-formylphenolate (8): 2-Bromo-3-hydroxybenzaldehyde (2.02 g, 10.05 mmol) was suspended in water (40 mL). To the stirred suspension was added dropwise a solution

of KOH (0.56 g, 10.1 mmol) in water. The reaction was stirred for additional 5 min and the water evaporated under reduced pressure. The residue was dried for 12 h in a desiccator (vacuum, P_2O_5) to give phenolate **8** (2.4 g, quant.) as a yellow solid. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.49 (pdd, J = 1.7, 7.3 Hz, 1 H), 6.59 (pdd, J = 1.7, 8.2 Hz, 1 H), 6.87 (pt, J = 7.7 Hz, 1 H), 10.22 (s, 1 H) ppm. ^{13}C NMR (100.62 MHz, [D$_6$]DMSO): δ = 108.2, 119.5, 125.4, 127.4, 134.2, 166.8, 194.4 ppm.

3,3′-{[(2*R*,3*R*)-1,4-Bis(benzyloxy)butane-2,3-diyl]bis(oxy)}bis(2-bromobenzaldehyde) (9): A 100 mL flask was loaded with phenolate **8** (2.06 g, 8.61 mmol) and DMSO (10 mL). To the clear solution was added dropwise the bis-triflate **3** (2.44 g, 4.3 mmol) in three portions within 0.5 h. The mixture was stirred for 2 h, quenched with water (50 mL) and extracted with diethyl ether (3 times 50 mL). The combined ether extracts were washed with 5% aq. KOH (2 times 50 mL) and water (2 times 50 mL), dried ($MgSO_4$), concentrated, and crystallized (Et_2O/petroleum ether, 1:2) to give bis-aldehyde **9** (2.44 g, 3.66 mmol, 85%) as colourless crystals (R_f = 0.65, petroleum ether/EtOAc, 2:1). Acidification (6 M aq. HCl, pH < 6) and extraction (EtOAc) of the combined water layers allowed reisolation of the unreacted phenol (0.22 g, 1.1 mmol, 13%); m.p. 100 °C (petroleum ether/Et_2O). $[\alpha]_D^{25}$ = –11.5 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (pdd, J = 4.8, 10.4 Hz, 2 H), 3.89 (pdd, J = 4.4, 10.4 Hz, 2 H), 4.42 (AB, J = 11.9 Hz, 4 H), 4.80 (m$_c$, 2 H), 7.08–7.33 (m, 14 H), 7.46 (pdd, J = 2.2, 4.7 Hz, 2 H), 10.34 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.2 (2 C), 73.8 (2 C), 79.3 (2 C), 118.7 (2 C), 121.0 (2 C), 122.6 (2 C), 127.9 (6 C), 128.4 (2 C), (128.5, 135.1, 6 C), 137.6 (2 C), 155.7 (2 C), 192.2 (2 C) ppm. $C_{32}H_{28}Br_2O_6$ (668.37): calcd. C 57.50, H 4.22; found C 57.64, H 4.35.

***N*,*N*′-{[(2*R*,3*R*)-1,4-Bis(benzyloxy)butane-2,3-diyl]bis[oxy(2-bromo-3,1-phenylene)-(*E*)-methylidene]}dicyclohexanamine (12):** A 250 mL flask was loaded with bis-aldehyde **9** (5.01 g, 7.5 mmol), dichloromethane (150 mL), $MgSO_4$ (75 g), and cyclohexylamine (2.23 g, 2.56 mL, 22.5 mmol). The slurry was stirred at room temperature for 2 h, filtered, concentrated and crystallized (petroleum ether/Et_2O, 2:1) to give 6.04 g (7.275 mmol, 97%) of the desired bis-imine **12** as colourless crystals; m.p. 95 °C (petroleum ether/Et_2O). $[\alpha]_D^{25}$ = –15.4 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.1–1.8 (m, 20 H), 3.2 (m$_c$, 2 H), 3.75 (pdd, J = 5.0, 10.3 Hz, 2 H), 3.9 (pdd, J = 5.0, 10.3 Hz, 2 H), 4.41 (AB, J = 12.1 Hz, 4 H), 4.75 (m$_c$, 2 H), 7.05 (pdd, J = 1.6, 8.1 Hz, 2 H) 7.08–7.2 (m, 12 H), 7.55 (pdd, J = 1.6, 7.6 Hz, 2 H), 8.63 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = (24.8, 25.7, 34.4, 10 C), 68.3 (2 C), 69.9 (2 C) 73.7 (2 C), 79.0 (2 C), 116.6 (2 C), 117.2 (2 C), 121.9 (2 C), (127.8, 127.8, 6 C), 128.0 (2 C), (128.4, 136.8, 6 C), 137.9 (2 C), 155.2 (2 C), 158.2 (2 C) ppm. $C_{44}H_{50}Br_2O_4$ (830.69): calcd. C 63.62, H 6.07; found C 63.14, H 6.21.

***N*,*N*′-{[(2*R*,3*R*)-1,4-Bis(benzyloxy)butane-2,3-diyl]bis[oxy(2-iodo-3,1-phenylene)-(*E*)-methylidene]}dicyclohexanamine (11) from the Corresponding Dibromide 12:** To a dried 250 mL flask was added under an atmosphere of argon dibromide **12** (3.32 g, 4 mmol) and dry THF (750 mL). The clear solution was cooled to –78 °C. A 1.6 M solution of *n*-butyllithium in hexane (7.5 mL, 12 mmol, 3 equiv.) was added slowly via syringe at such a rate as to maintain the temperature below –70 °C. The mixture was stirred for 30 min at –78 °C. A solution of 5.08 g (20 mmol, 5 equiv.) I_2 in 10 mL dry THF was added via a dropping funnel until the red colour of iodine persisted. During the addition the temperature was not allowed to rise above –70 °C. The mixture was warmed to room temperature, poured into water and extracted with CH_2Cl_2 (3 times, 200 mL). The combined organic extracts were washed with satd. aq. $Na_2S_2O_3$, dried ($MgSO_4$), filtered, concentrated, and crystallized from Et_2O/petroleum ether (1:2) to give 3.51 g (3.8 mmol, 95%) of the di-iodide **11** as colourless crystals. For analytical and spectroscopic data of **11** see above.

(6*R*,7*R*)-6,7-Bis[(benzyloxy)methyl]-6,7-dihydrodibenzo[*e*,*g*][1,4]-dioxocine-1,12-dicarbaldehyde (10): A dried 100 mL flask was loaded under an atmosphere of Ar with di-iodide **11** (3.01 g, 3.25 mmol, 1 equiv.) and NMP (15 mL). To the vigorously stirred clear solution was added CuTC (1.85 g, 9.75 mmol, 3 equiv.) in one portion. After stirring at room temp. for 24 h, the reaction mixture was diluted with 30 mL EtOAc, and the resulting slurry was filtered through a pad of silica gel, using EtOAc as eluent. The filtrate was concentrated, the residue dissolved in dichloromethane (20 mL), and stirred for 0.5 h with 6 N aq. HCl (60 mL). The mixture was extracted with Et_2O (3 times, 50 mL). The combined organic extracts were washed with water (3 times, 100 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, petroleum ether/EtOAc, 4:1; R_f = 0.68, petroleum ether/EtOAc, 1:1) to give 1.57 g (3.1 mmol, 95%) of the biphenyl **10** as a colourless solid in 95% yield; m.p. 88 °C (petroleum ether/EtOAc). $[\alpha]_D^{25}$ = +104.0 (c = 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.53 (pdt, J = 3.0, 10.7 Hz, 2 H), 3.67 (pdt, J = 3.0, 10.7 Hz, 2 H), 4.13 (pt, J = 2.1 Hz, 2 H), 4.49 (AB, J = 12.2 Hz, 4 H), 7.17–7.33 (m, 10 H), 7.43–7.56 (m, 4 H), 7.76 (pdd, J = 1.83, 7.32 Hz, 2 H), 9.67 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.2 (2 C), 73.9 (2 C), 85.7 (2 C), 124.8 (2 C), 127.9 (3 C), 128.0 (3 C), 128.4 (2 C), 128.6 (4 C), 129.1 (2 C), 130.8 (2 C), 136.6 (2 C), 137.7 (2 C), 159.6 (2 C), 190.8 (2 C) ppm.

(5*R*,6*R*,11*R*,12*R*)-5,6-Bis[(benzyloxy)methyl]-5,6,11,12-tetrahydrophenanthro[4,5-*efg*][1,4]dioxocine-11,12-diol (13): A dried flask was loaded under an atmosphere of argon with bis-aldehyde **10** (0.51 g, 1 mmol, 1 equiv.) and THF (10 mL). A separate dried flask was loaded under argon with a 0.1 M solution of SmI_2 (30 mL, 3 mmol, 3 equiv.). Both flasks were cooled to 0 °C, and the bis-aldehyde was added dropwise via a syringe to the SmI_2 solution. The reaction was monitored by TLC until the bis-aldehyde was consumed (ca. 15 min), quenched with NH_4Cl and extracted with diethyl ether (3 times, 50 mL). The organic phase was washed with NH_4Cl (50 mL), $NaHCO_3$ (50 mL), and brine (50 mL). Drying ($MgSO_4$), concentration, and crystallization (MeOH) afforded 0.46 g (0.9 mmol, 90%) of the desired *trans*-diol **13** (R_f = 0.36, petroleum ether/EtOAc, 1:1) as colourless crystals; m.p. 121 °C (MeOH). $[\alpha]_D^{25}$ = –32.0 (c = 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.6 (br. s, 2 H), 3.58 (pdt, J = 2.0, 10.0 Hz, 2 H), 3.75 (br. d, J = 10.0 Hz, 2 H), 4.15 (pt, J = 2.0 Hz, 2 H), 4.45 (br. s, 2 H), 4.55 (AB, J = 12.1 Hz, 4 H), 7.1–7.4 (m, 16 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.4 (2 C), 73.8 (2 C), 74.2 (2 C), 83.0 (2 C), 119.3 (2 C), 122.1 (2 C), 123.9 (2 C), (127.9, 128.5, 128.6, 10 C), 129.5 (2 C), 138.0 (2 C), 138.2 (2 C), 156.3 (2 C) ppm. $C_{32}H_{30}O_6 \times 0.5\,CH_3OH$ (526.60): calcd. C 74.13, H 6.12; found C 74.21, H 6.03.

{(5*R*,6*R*,11*R*,12*R*)-5,6-Bis[(benzyloxy)methyl]-5,6,11,12-tetrahydrophenanthro[4,5-*efg*][1,4]dioxocine-11,12-diyl}bis(oxy)bis[*tert*-butyl(dimethyl)silane]: A dried 25 mL flask was loaded under an atmosphere of argon with the diol **13** (0.51 g, 1 mmol) and CH_2Cl_2 (5 mL). To the solution was added 2,6-lutidine (0.43 g, 0.46 mL, 4 mmol) followed by TBDMS-OTf (0.33 g, 0.29 mL, 1.24 mmol). The mixture was stirred at room temperature for 0.5 h, diluted with CH_2Cl_2 (15 mL), and washed with water (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Filtration through a pad of silica gel (CH_2Cl_2) and concentration afforded the desired ether (0.72 g, 0.97 mmol, 97%) as colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.01 (s, 6 H), 0.1 (s, 6 H), 0.97 (s,

18 H), 3.57 (pdm, J = 10.6 Hz, 2 H), 3.75 (br. d, J = 10.6 Hz), 4.16 (m_c, 2 H), 4.39 (s, 2 H), 4.51 (AB, J = 12.3 Hz, 4 H), 7.10 (pdd, J = 1.0, 7.9 Hz, 2 H), 7.18–7.24 (m, 14 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6 (2 C), –3.5 (2 C), 18.2, 18.7, 25.8 (6 C), 70.5 (2 C), 73.8 (2 C), 74.8 (2 C), 83.1 (2 C), 114.9 (2 C), (120.2, 121.7, 124.3, 127.9, 128.5, 128.9, 138.1, 141.1, 156.0, 22 C) ppm.

((5*R*,6*R*,11*R*,12*R*)-11,12-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5,6,11,12-tetrahydrophenanthro[4,5-*efg*][1,4]dioxocine-5,6-diyl)dimethanol: A 25 mL flask was loaded with the benzyl ether (0.7 g, 0.95 mmol), EtOAc (6 mL), and $Pd(OH)_2$ (10% on carbon, 0.1 g) followed by vacuum – hydrogen exchange (6 times). The mixture was stirred for 2 h, filtered through a pad of $MgSO_4$ (EtOAc) and concentrated to give 0.42 g (0.75 mmol, 79%) of the diol (R_f = 0.28, petroleum ether/EtOAc, 1:2) as a colourless volatile oil which can be crystallized from Et_2O/petroleum ether (1:2) to give a colourless solid; m.p. 137 °C (Et_2O/PE). $[\alpha]_D^{22}$ = –143.6 (c = 0.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.32 (s, 6 H), 1.19 (s, 18 H), 2.72 (br. s, 2 H), 3.88 (pd, J = 10.0 Hz, 2 H), 4.06 (pd, J = 10.0 Hz, 2 H), 4.24 (br. s, 2 H), 4.62 (s, 2 H), 7.27 (pd, J = 7.8 Hz, 2 H), 7.47 (pt, J = 7.7 Hz, 2 H), 7.57 (pd, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6 (2 C), –3.5 (2 C), 18.7 (2 C), 26.6 (6 C), 62.8 (2 C), 74.6 (2 C), 83.8 (2 C), 120.6 (2 C), 121.4 (2 C), 124.1 (2 C), 129.2 (2 C), 141.3 (2 C), 155.4 (2 C) ppm. $C_{30}H_{46}O_6Si_2$ (558.85): calcd. C 64.48, H 8.30; found C 64.70, H 8.24.

{[(5*S*,6*S*,11*R*,12*R*)-5,6-Bis(iodomethyl)-5,6,11,12-tetrahydrophenanthro[4,5-*efg*][1,4]dioxocine-11,12-diyl]bis(oxy)}bis[*tert*-butyl(dimethyl)silane] (14): A dried 25 mL flask was loaded with triphenylphosphane (0.184 g, 0.7 mmol), imidazole (0.143 g, 2.1 mmol) and CH_2Cl_2 (3 mL). The clear solution was cooled to 0 °C, and to it was added I_2 (0.178 g, 0.7 mmol). The mixture was stirred for 10 min at room temperature with formation of a yellow precipitate. The iodine compound was stabilized by addition of 2-methyl-2-butene (0.37 mL). To the mixture was added a solution of the diol (0.185 g, 0.33 mmol, 1 equiv.) in CH_2Cl_2 (3 mL). After stirring at room temp. for 1 h, the reaction was quenched with water (20 mL), and extracted with Et_2O (2 times 50 mL). The organic phase was washed with satd. aq. $Na_2S_2O_3$ (20 mL), diluted H_2O_2 (10 mL), water (20 mL), dried ($MgSO_4$), concentrated, and filtered through a pad of silica gel (CH_2Cl_2; R_f = 0.88, petroleum ether/EtOAc, 4:1). Concentration and crystallization (MeOH) afforded the desired bis-iodide **14** (0.216 g, 28 mmol, 84%) as colourless crystals; m.p. 151 °C (MeOH). $[\alpha]_D^{26}$ = –66.2 (c = 0.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.18 (s, 6 H), 1.05 (s, 18 H), 3.27 (pdm, J = 10.0 Hz, 2 H), 3.53 (pd, J = 9.9 Hz, 2 H), 3.97–4.10 (m, 2 H), 4.47 (s, 2 H), 7.37 (pt, J = 7.8 Hz, 2 H), 7.46 (pd, J = 6.8 Hz, 2 H), 7.52 (pdd, J = 1.0, 7.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6 (2 C), –3.6 (2 C), 25.8, 26.1, 26.6 (6 C), 72.2 (2 C), 74.6, 85.4 (2 C), 120.9 (2 C), 121.4 (2 C), 124.1 (2 C), 129.1 (2 C), 141.3 (2 C), 155.1 (2 C) ppm.

(9*R*,10*R*)-9,10-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-9,10-dihydrophenanthrene-4,5-diol: A dried 50 mL flask was loaded under an atmosphere of argon with bis-iodide **14** (0.19 g, 0.24 mmol), EtOH (20 mL), and Zn powder (0.65 g, 10 mmol). The suspension was refluxed for 2 h, cooled to room temp., diluted with Et_2O (20 mL), and filtered. The filtrate was washed with satd. aq. $Na_2S_2O_4$, dried ($MgSO_4$), filtered and concentrated. Flash-column chromatography (silica gel, petroleum ether/EtOAc, 4:1, R_f = 0.68) furnished the desired bis-phenol (0.1 g, 0.23 mmol, 96%) as a yellow oil. $[\alpha]_D^{26}$ = –109.1 (c = 1, $CHCl_3$). $[\alpha]_D^{26}$ = –154.5 (c = 1, MeOH). ^{1}H NMR (500 MHz, [D$_8$]toluene, 360 K): δ = –0.16 (s, 6 H), 0.06 (s, 6 H), 0.76 (s, 9 H), 4.68 (s, 2 H), 6.12 (br. s, 2 H), 6.63 (pd, J = 9.3 Hz, 2 H), 6.98 (m_c, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 (br. s, 4 C), 25.6 (br. s, 4 C), 26.5 (br. s, 2 C) 74.2 (br. s, 2 C), 117.3 (2 C), 118.7 (2 C), 120.1 (2 C), 123.7 (2 C), 128.3 (2 C), 128.8 (2 C) ppm.

(9*R*,10*R*)-4,5,9,10-Tetrahydroxy-9,10-dihydrophenanthrene (2): A 25 mL flask was loaded with (9*R*,10*R*)-9,10-bis[*tert*-butyl(dimethyl)silyl]oxy-9,10-dihydrophenanthrene-4,5-diol (0.14g, 0.3 mmol. 1 equiv.), THF (5 mL), and TBAF·3H$_2$O (1 g, 3 mmol, 10 equiv.). The mixture was stirred at room temp. for 24 h, then quenched with MeOH (3 mL), and concd. HCl (5 drops). Concentration and flash-column chromatography (silica gel, EtOAc + 1% MeOH, R_f = 0.28, petroleum ether/EtOAc, 1:2) afforded the tetraol **2** (0.07 g, 0.29 mmol, 95%) as a colourless solid; m.p. 87 °C (CH_2Cl_2). $[\alpha]_D^{24}$ = +106.7 (c = 0.15, MeOH). $[\alpha]_D^{24}$ = +120.5 (c = 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_4$]MeOH): δ = 4.39 (s, 2 H), 6.95–7.03 (m, 2 H), 7.26–7.31 (m, 4 H) ppm. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (s, 2 H), 7.00 (pt, J = 4.8 Hz, 2 H), 7.34 (pd, J = 4.8 Hz, 4 H) ppm. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 2.8 (br. s, 2 H), 4.21 (s, 2 H), 6.86 (pdd, J = 1.4, 8.0 Hz, 2 H), 7.13 (pt, J = 7.5 Hz, 2 H), 7.28 (pdd, J = 1.2, 8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, [D$_4$]MeOH): δ = 74.7 (2 C), 116.8 (2 C), 119.5 (2 C), 121.6 (2 C), 129.0 (2 C), 140.8 (2 C), 156.7 (2 C) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 74.0 (2 C), 117.5 (2 C), 117.9 (2 C), 119.5 (2 C), 129.3 (2 C), 141.8 (2 C), 153.1 (2 C) ppm. HRMS ($C_{14}H_{12}O_4$): calcd. 244.0735 found 244.0742. Enantiomeric excess of **2** was determined after derivatization to the corresponding dimethyl ether **2a**.

(9*R*,10*R*)-4,5-Dimethoxy-9,10-dihydrophenanthrene-9,10-diol (2a): A 10 mL flask was loaded with tetraol **2** (0.018 g, 0.074 mmol), acetone (3 mL), K_2CO_3 (0.2 g), and MeI (0.1 g, 0.05 mL, 0.74 mmol). The reaction mixture was heated to reflux for 6 h, filtered, and concentrated. Purification via flash-column chromatography (silica, PE/EE, 1:1, R_f = 0.65) afforded 0.01 g (0.036 mmol, 48%) of the diol **2a** as a yellow solid; m.p. 103 °C (PE/EE). $[\alpha]_D^{32}$ = +109.7 (c = 0.3, MeOH). $[\alpha]_D^{32}$ = +160.0 (c = 0.3, $CHCl_3$); $ee > 99\%$ {determined by chiral HPLC analysis using a Chiralpak-OD-H column, 250 mm × 4.6 mm, *n*-heptane/2-propanol (95:5), 1 mL/min, 35 °C, 270 nm, t_R [(*P*)-enantiomer] = 30.7 min, t_R [(*M*)-enantiomer] = 47.3 min}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (br. s, 2 H), 3.90 (s, 6 H), 4.46 (s, 2 H), 6.99 (pd, J = 8.2 Hz, 2 H), 7.25 (pd, J = 7.1 Hz, 2 H), 7.3 (pt, J = 7.8 Hz, 2 H) ppm. ^{1}H NMR (300 MHz, [D$_4$]MeOH): δ = 3.84 (s, 6 H), 4.87 (s, 2 H), 6.99 (d, J = 9.2 Hz, 2 H), 7.25–7.33 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1 (2 C), 74.6 (2 C), (111.7, 115.6, 119.4, 129.1, 129.3, 10 C), 156.5 (2 C) ppm. ^{13}C NMR (100 MHz, [D$_4$]MeOH): δ = 56.4 (2 C), 74.8 (2 C), (112.4, 141.5 116.9, 120.7, 129.4, 10 C), 157.7 (2 C) ppm. HRMS($C_{16}H_{16}O_4$): calcd. 272.10486 found 272.10480.

Acknowledgments

This work was supported by the Fonds der Chemischen Industrie, and the Alfried Krupp Award for young university teachers of the Krupp foundation (to BB). We thank Jürgen Leonhardt for technical and Gerd Fehrenbach for analytical assistance.

[1] a) T. Takeuchi, T. Hara, H. Naganawa, M. Okada, M. Hamada, H. Umezaw, S. Gomi, M. Sezaki, S. Kondo, *J. Antibiot.* **1988**, *41*, 807; b) T. Oki, M. Konishi, K. Tomatsu, K. Tomita, K. Saitoh, M. Tsunakawa, M. Nishio, T. Miyaki, H. Kawaguchi, *J. Antibiot.* **1988**, *41*, 1701; c) J. Rohr, R. Thiericke, *Nat. Prod. Rep.* **1992**, *9*, 103.

[2] J. H. Wilton, D. C. Cheney, G. C. Hokanson, C. J. French, H. Cunheng, J. Clardy, *J. Org. Chem.* **1985**, *50*, 3936.
[3] K. Kondo, T. Eguchi, K. Kakinuma, K. Mizoue, Y. Qiao, *J. Antibiot.* **1998**, *51*, 288.
[4] T. Eguchi, K. Kondo, K. Kakinuma, H. Uekusa, Y. Ohashi, K. Mizoue, Y.-F. Qiao, *J. Org. Chem.* **1999**, *64*, 5371.
[5] S. Reichert, B. Breit, *Org. Lett.* **2007**, *9*, 899.
[6] a) M. Kitamura, K. Ohmori, T. Kawase, K. Suzuki, *Angew. Chem.* **1999**, *111*, 1308; *Angew. Chem. Int. Ed.* **1999**, *38*, 1226; b) H. Kato, K. Ohmori, K. Suzuki, *Tetrahedron Lett.* **2000**, *41*, 6827; c) K. Ohmori, K. Mori, Y. Ishikawa, H. Tsuruta, S. Kuwahara, N. Harada, K. Suzuki, *Angew. Chem.* **2004**, *116*, 3229; *Angew. Chem. Int. Ed.* **2004**, *43*, 3167.
[7] a) F. M. Hauser, W. A. Dorsch, D. Mal, *Org. Lett.* **2002**, *4*, 2237; b) F. M. Hauser, H. Liao, Y. Sun, *Org. Lett.* **2002**, *4*, 2241.
[8] a) T. R. Kelly, Q. Li, V. Bhushan, *Tetrahedron Lett.* **1990**, *31*, 161; b) S. Hirosawa, T. Nishizuka, S. Kondo, D. Ikeda, *Chem. Lett.* **1997**, 305.
[9] Known synthesis of BPAs and the angucycline PD 116740 and TAN 1084 are either racemic or include a resolution step.
[10] For reviews on stereoselective biaryl axis formation see: a) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384; b) T. W. Wallace, *Org. Biomol. Chem.* **2006**, *4*, 3197.
[11] a) B. H. Lipshutz, F. Kayser, Z. P. Liu, *Angew. Chem.* **1994**, *106*, 1962; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1842; b) B. H. Lipshutz, P. Müller, D. Leinweber, *Tetrahedron Lett.* **1999**, *40*, 3677.
[12] K. Ohmori, M. Kitamura, K. Suzuki, *Angew. Chem.* **1999**, *111*, 1304; *Angew. Chem. Int. Ed.* **1999**, *38*, 1226.
[13] D. L. Comins, J. D. Brown, *J. Org. Chem.* **1989**, *54*, 3730.
[14] J. E. Toth, P. R. Hamann, P. L. Fuchs, *J. Org. Chem.* **1988**, *53*, 4694.
[15] S. Zhang, D. Zhang, L. S. Liebeskind, *J. Org. Chem.* **1997**, *62*, 2312.
[16] CCDC-651219 (for **13**), -651220 (for **14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[17] R. Kataky, P. E. Nicholson, D. Parker, *J. Chem. Soc. Perkin Trans. 2* **1990**, 321.
[18] P. Leblanc, G. Gerber, *Can. J. Chem.* **1984**, *62*, 1767.
[19] J. M. Lensinger, R. C. Ronald, *Synth. Commun.* **1979**, *9*, 341.

Received: June 25, 2007
Published Online: October 4, 2007

