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Dimeric Orsellinic Acid Derivatives: Valuable Intermediates for Natural Product Synthesis

Daniel Drochner,[a] Wolfgang Hüttel,[a][‡] Silke E. Bode,[a][‡] Michael Müller,*[a][‡] Ulrich Karl,[b] Martin Nieger,[c][‡‡‡] and Wolfgang Steglich*[b][‡‡‡]

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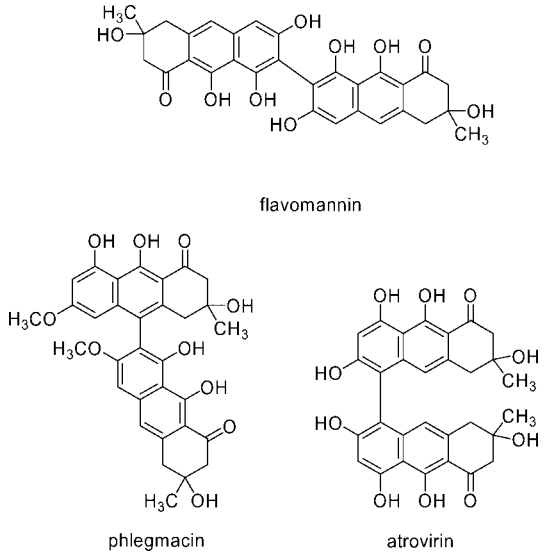
Herein we report on the synthesis of dimeric orsellinates by the Ullmann reaction as well as by biomimetic oxidative phenolic coupling. The Ullmann reaction gives the 5,5′- and 3,3′-coupled dimeric orsellinates **9** and **10** regioselectively. Oxidative phenolic coupling reaction of methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**2**) affords the regioisomeric dimeric orsellinates **11** (3,3′), **12** (5,5′) and **13** (3,5′) simultaneously, which can be separated easily by column chromatography. The atropisomers of the 5,5′- and 3,3′-coupled dimers **9** and **10** were partially resolved using chiral column chromatography. Additionally, the enantiomers of 3,3′-dimeric biaryl **11** could be obtained in pure form by derivatizing racemic **11** with chiral auxiliaries, separating the diastereomers by column chromatography and cleaving the auxiliary groups. Thereby the absolute configuration of the biaryl axis in camphanate ester (*M*)-**18** could be determined by X-ray structure analysis. The dimeric orsellinates *rac*-**10** and (*P*)-**10** were used for the synthesis of the dimeric dihydroanthracenones **21a–b** by a tandem Michael–Dieckmann reaction.

Introduction

The biaryl axis plays an important role as central structural element of diverse natural products. In fungi and plants a significant number of dimeric dihydroanthracenones (pre-anthraquinones), like flavomannin, phlegmacin, pseudophlegmacin, atrovirin or tricolorin,[1] can be found (Scheme 1). These substances differ not only in the linkage of their molecular halves (regiochemistry) but also in the configuration of the biaryl axis (stereochemistry). Although a general regio- and stereoselective approach to this class of natural products is desirable, the asymmetric synthesis of biaryls affords tedious synthesis strategies.[2]



Scheme 1. Polyketide natural products containing a dimeric dihydroanthracenone structure.

Herein, we report on the synthesis and racemic resolution of regioisomeric dimeric orsellinates and their use in natural product synthesis.

Results and Discussion

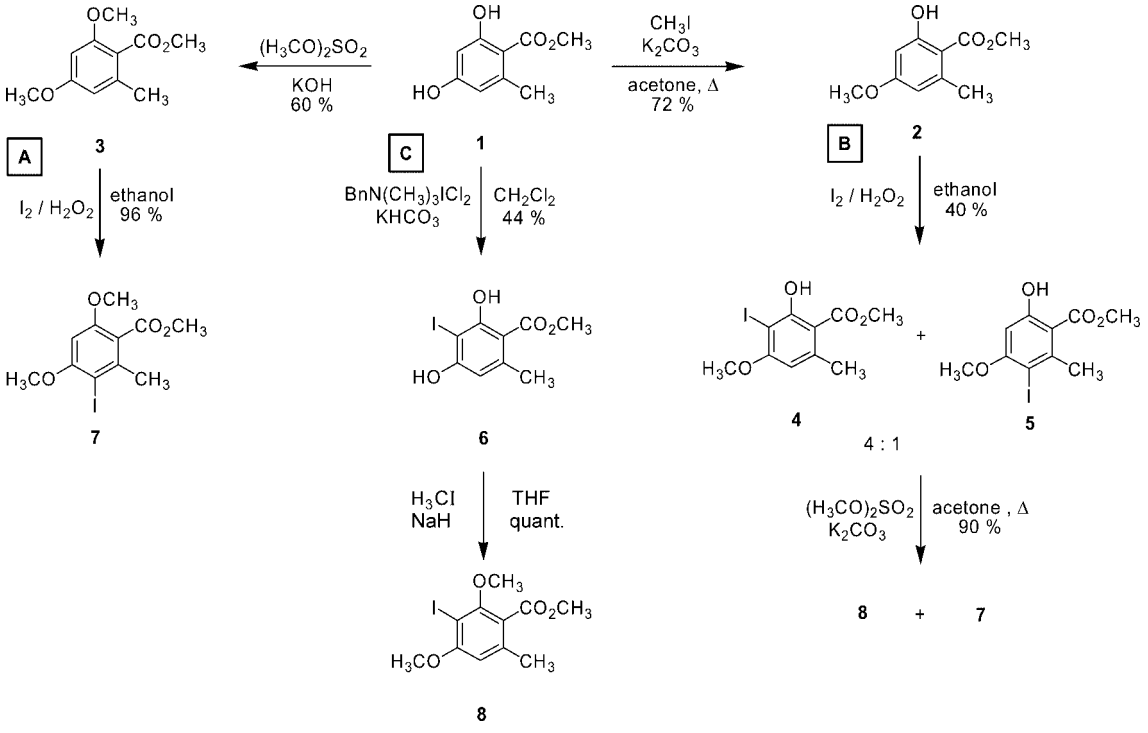
Dimeric Orsellinates via Ullmann Reaction

For the synthesis of 3,3′- and 5,5′-coupled dimeric orsellinates[3] an Ullmann reaction[4] of the corresponding iodin-

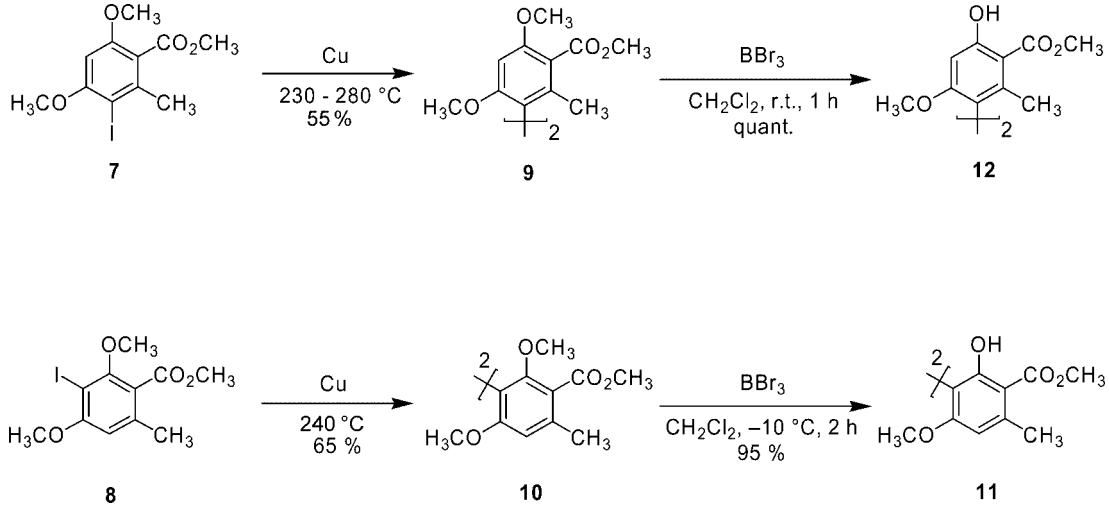
[a] Institut für Biotechnologie 2, Forschungszentrum Jülich GmbH,
52425 Jülich, Germany
[b] Kekulé-Institut für Organische Chemie und Biochemie, Rheinische Friedrich-Wilhelms-Universität,
53121 Bonn, Germany
[c] Institut für Anorganische Chemie, Rheinische Friedrich-Wilhelms-Universität,
53121 Bonn, Germany
[‡] Present address: Institut für Pharmazeutische Wissenschaften, Albert-Ludwigs-Universität Freiburg,
79104 Freiburg, Germany
Fax: +49-761-2036351
E-mail: michael.mueller@pharmazie.uni-freiburg.de
[‡‡‡] Present address: Laboratory of Inorganic Chemistry, Department of Chemistry,
00014 University of Helsinki, Finland
[‡‡‡‡] Present address: Department Chemie, Ludwig-Maximilians-Universität,
81377 München, Germany
Fax: +49-89-218077756
E-mail: wos@cup.uni-muenchen.de

ated monomeric precursors was envisaged. Since the preparation of monomeric orsellinic acid derivatives is well established, the main task was the regioselective iodination of the substrates. For this purpose we applied a strategy which uses methyl 2,4-dihydroxy-6-methylbenzoate[5] (**1**) as starting material for the synthesis of the monoiodinated regioisomeric orsellinates **7** and **8** (Scheme 2). The preparation of methyl 5-iodo-2,4-dimethoxy-6-methylbenzoate (**7**)[6] starts with the complete methylation of ester **1** using dimethyl sulfate in aqueous KOH to yield methyl 2,4-dimethoxy-6-methylbenzoate (**3**).[7] The latter was iodinated exclusively at the C-5 atom applying a method formerly used by Marsh[8] for the iodination of naphthol. Accordingly, iodine and H_2O_2 were added to a solution of compound **3** in EtOH and the product was precipitated with water affording **7** in 96% yield (Scheme 2, A).

For the synthesis of methyl 3-iodo-2,4-dimethoxy-6-methylbenzoate (**8**) compound **1** was monomethylated regioselectively at C-4 with iodomethane in presence of anhydrous K_2CO_3 delivering methyl 2-hydroxy-4-methoxy-6-methylbenzoate[9] (**2**) in 72% yield. Phenol **2** was iodinated with iodine and H_2O_2 to afford a 4:1 mixture of the two regioisomeric iodoorsellinates **4** and **5** in 40% yield.[10] The crude product was permethylated with dimethyl sulfate, and the resulting regioisomers **7** and **8** were separated by column chromatography (Scheme 2, B).[11]



Scheme 2. Synthesis of iodinated monomeric methyl orsellinates **7** and **8**.



Scheme 3. Ullmann coupling of iodinated monomeric methyl orsellinates **7** and **8**, followed by selective demethylation with BBr_3.

To avoid the problem of separating these regioisomers benzyltrimethylammonium dichloroiodate was used for the regioselective iodination of compound **1** at position 3 (Scheme 2, C).[12] The best results were achieved by converting crude **6** directly into compound **8**. No further purification of **8** was required.

For the Ullmann reaction each of the iodoorsellinic acid derivatives **7** and **8** were heated separately with activated copper powder to 230–280 °C.[13] The 5,5′- and 3,3′-coupled dimeric orsellinates, **9** and **10**, were obtained in 54 and 65% yield, respectively (Scheme 3). Finally, compounds **9** and **10** were regioselectively demethylated using boron tribromide.

Dimeric Orsellinates via Oxidative Phenolic Coupling

In addition to the Ullmann procedure a solid state oxidative phenolic coupling reaction was used to synthesize the dimeric orsellinates. Methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**2**) was oxidized with ferric chloride adsorbed on silica gel as described by Keinan and Mazur.[14] Best results were obtained by heating a mixture of orsellinate **2** with 2.8 equiv. $FeCl_3$/silica gel at 60 °C for 24 h. After flash chromatography, the 3,3′-, 5,5′- and 3,5′-coupling products, **11**, **12** and **13**, were obtained in 17, 33 and 30% yield, respectively (Scheme 4). This reaction could also be performed on a 2 g scale of **2** with a total yield of 70% dimerized products. Coinciding with our results, two published procedures describing selective[15a] and unselective coupling[15b] of analogous substrates reveal that the electronic effect of the substituent at C-6 determines the (un-)selectivity of the oxidative phenolic coupling: with a methoxy substituent at C-6, the 3,3′-dimer is the only coupling product, whereas without substituent at C-6 all possible regioisomers are formed.

Comparison of the two Coupling Methods

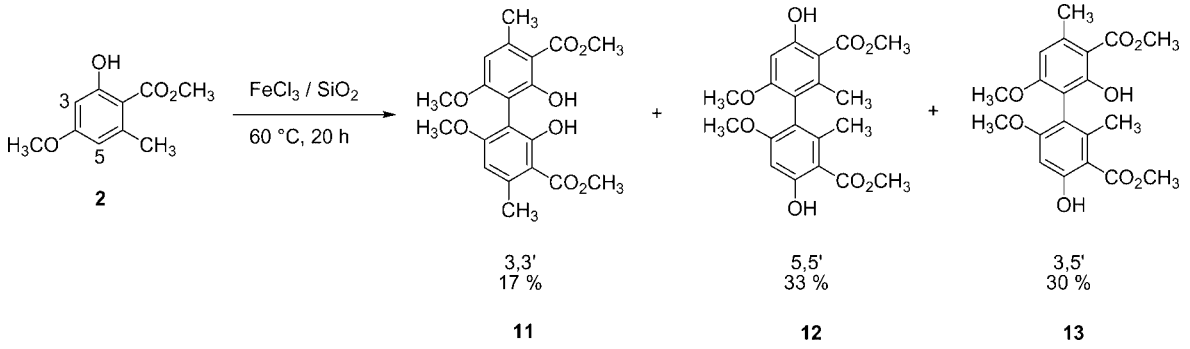
In the case of the Ullmann reaction the 3,3′- and 5,5′-coupling products **11** and **12** are formed regioselectively directed by the position of the iodo atom in the substrates. In contrast, there is no selectivity in the oxidative phenolic coupling of methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**2**). Compared to the reductive coupling, which requires five steps for the 3,3′-coupled dimeric orsellinate **11** and four steps for the 5,5′-coupled dimeric orsellinate **12** starting from **1**, the oxidative coupling proceeds in only two steps. Another advantage of this approach is the facile availability of the unsymmetrically 3,5′-coupled product, which requires a multistep approach when regioselective coupling methods are used. The oxidative phenolic coupling, however, appears to be limited to methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**2**) as substrate. Neither **1** nor **3** gave any detectable dimerization product under various conditions. Since the Ullmann reaction is incompatible with hydroxy groups or sterically demanding substituents this route is limited to the *O*-methylated iodoorsellinates **7** and **8** as substrates. Moreover, the unsymmetrical 3,5′-dimer **13** or its tetramethoxy derivative are hardly accessible by using this strategy.[16]

Resolution of Atropisomers

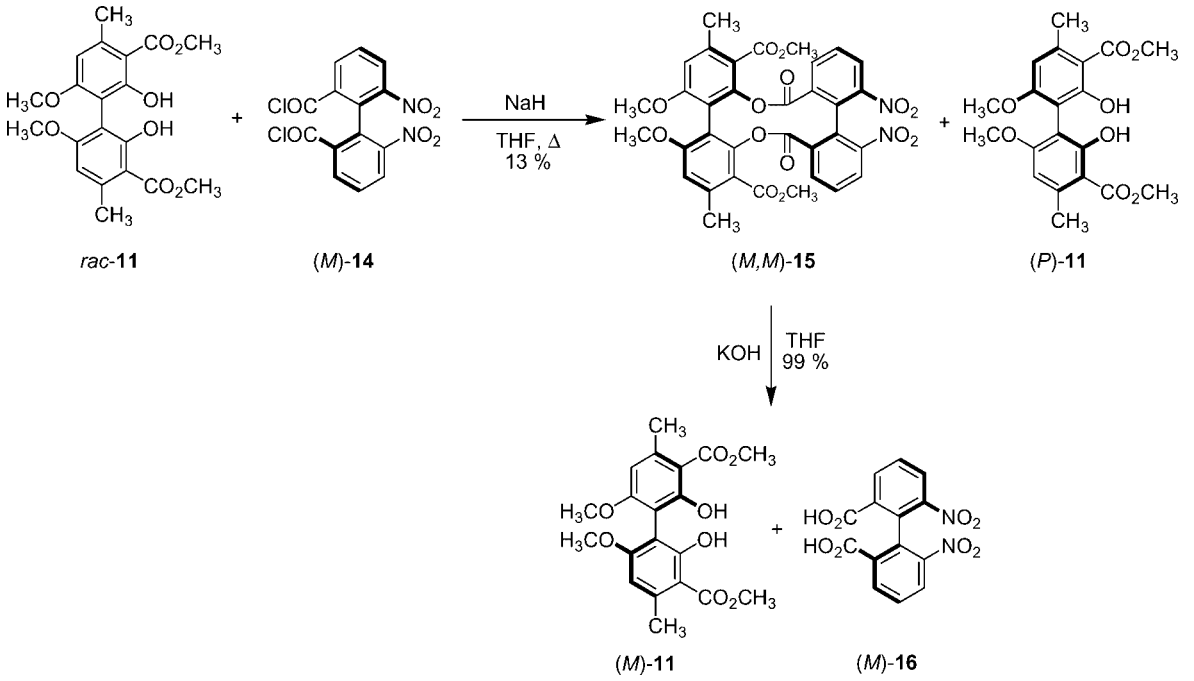
The resolution of the racemic dimeric orsellinates **9** and **10** was performed by column chromatography with triacetylcellulose as stationary phase and EtOH as eluent. However, due to the large tailing of the eluting compounds the enantiomeric excess, which was determined by ^{1}H NMR with $Pr(hfc)_3$ as shift reagent, was below 15%.

Alternatively, the atropisomers of the 3,3′-coupled racemic dimeric orsellinate **11** were resolved by formation of diastereomeric dilactones.[17] For this purpose, the sodium dianion of the racemic biaryl **11** was treated with (*M*)-6,6′-dinitro-2,2′-diphenoyl dichloride[18] [(*M*)-**14**] to give dilactone (*M*,*M*)-**15** in 13% isolated yield, in addition to unreacted starting material (*P*)-**11**. Vice versa the reaction of the racemic biaryl **11** with (*P*)-**14** gave the dilactone (*P*,*P*)-**15** and unreacted dimeric orsellinate (*M*)-**11**. The enantioenrichment of the reisolated starting materials was not determined. After purification by preparative TLC, the lactones **15** were saponified with KOH to yield the atropisomeric dimeric orsellinates (*P*)-**11** and (*M*)-**11**, respectively, and 6,6′-dinitro-2,2′-diphenic acid (**16**) in quantitative yield (Scheme 5).

The optically active compounds **10** and **11** were correlated by regioselective demethylation of **10** with boron tribromide.[19] Demethylation of dimeric orsellinate (+)-**10** afforded compound (*M*)-**11**; and the reaction with (–)-**10** gave



Scheme 4. Unselective oxidative phenolic coupling of **2**.

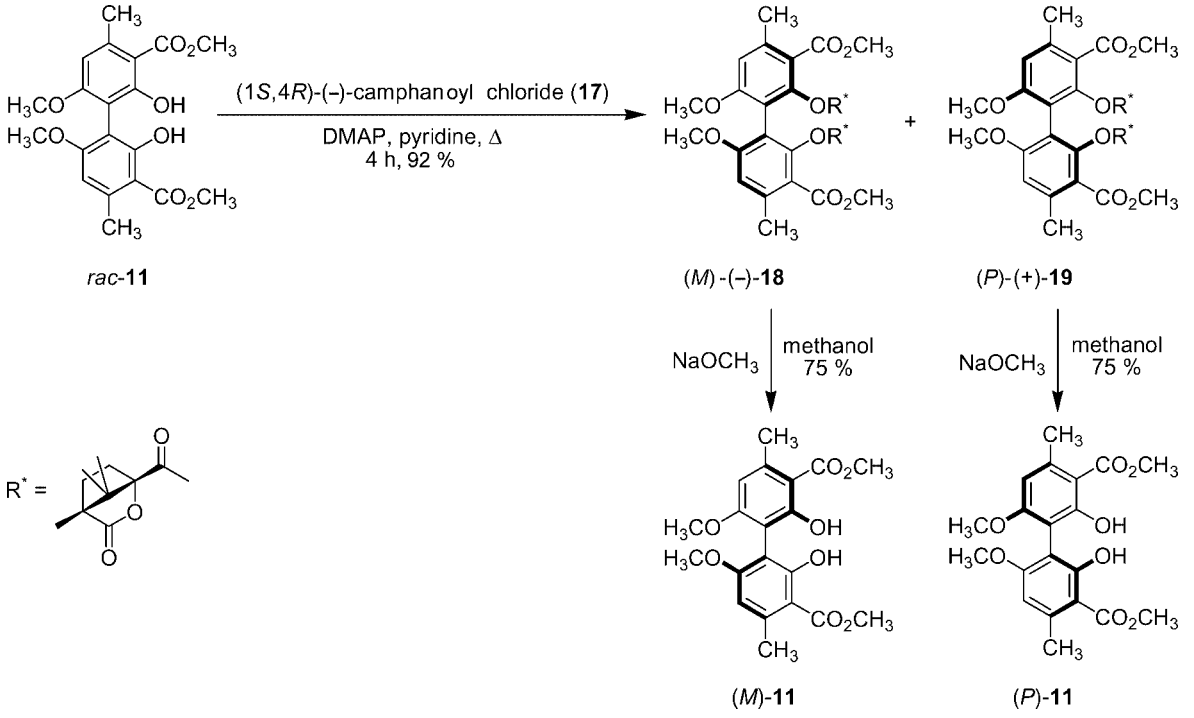


Scheme 5. Racemic resolution of dimeric orsellinate **11** by formation of diastereomeric dilactones.

(*P*)-**11**. This proved the (*M*)-configuration for (+)-**10** and the (*P*)-configuration for (–)-**10**, respectively.

The dinitrodiphenic acid method provides an effective racemic resolution of the dimeric orsellinate **11**. Due to the low yield, however, this procedure is not practicable on a preparative scale.

Therefore, an alternative route for the racemic resolution was applied. The racemic 3,3′-coupled dimeric orsellinate **11** was treated with (1*S*,4*R*)-(–)-camphanoyl chloride (**17**) to yield a mixture of diastereomeric camphanate esters **18** and **19** (Scheme 6).[15a] On separation by flash chromatography with a silica gel column the ester (–)-**18** (47%) was



Scheme 6. Racemic resolution of dimeric orsellinate **11** by chromatographic separation of diastereomeric camphanate esters **18** and **19**.

first eluted followed by (+)-**19** (45%). The diastereomers can be distinguished by their chemical shifts in the ^{1}H NMR spectra. As no signal of the other diastereomer was observed in the spectra of isolated (–)-**18** or (+)-**19**, the diastereomeric excess was estimated as at least 95%.

Recrystallization of the ester (–)-**18** from *n*-hexane/EtOAc provided crystals suitable for X-ray diffraction.[20,21] The absolute configuration of the biphenyl moiety of the ester (–)-**18** was determined as (*M*) by using the known absolute configuration of the camphanate ester auxiliary as internal reference (Figure 1).

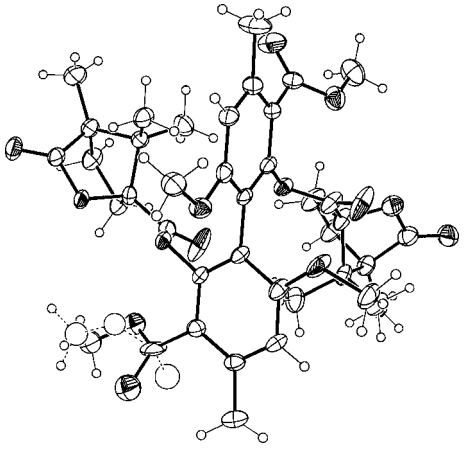


Figure 1. Molecular structure of (*M*)-(–)-**18** (non-hydrogen atoms shown at 50% probability level).

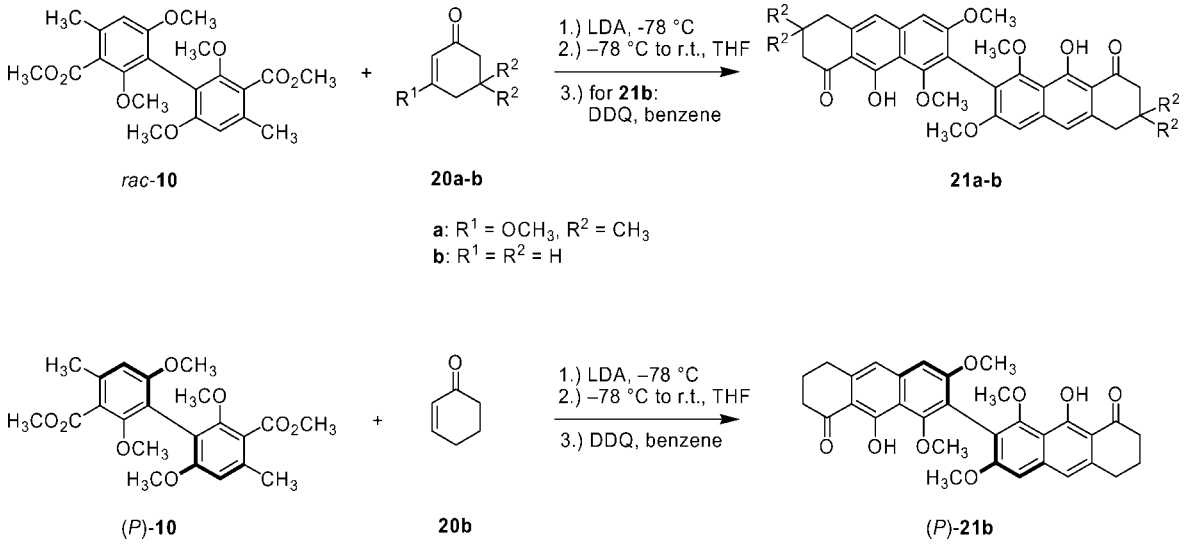
Cleavage of the camphanic acid moiety was performed with sodium methoxide to give the atropisomeric 3,3′-coupled biaryls (*M*)-**11**, and (*P*)-**11**, in 75% yield each (Scheme 6). This outcome corresponds with the absolute configurations determined by the dinitrodiphenic acid method (see above). The camphanic acid method allows an efficient approach to both atropisomers of **11** in good yields.

Syntheses of Dimeric Dihydroanthracenones

The retrosynthetic analysis of dimeric dihydroanthracenones reveals that they might be synthesized either by a biomimetic dimerisation of their monomeric precursors[22] or by a tandem Michael–Dieckmann reaction of dimeric orsellinates with the corresponding Michael acceptors.[23] Monomeric dihydroanthracenones can be iodinated or brominated selectively, however, the dimerization of the resulting halogenides by the classical Ullmann reaction or palladium-catalyzed Stille coupling fails.

The 3,3′-dimeric orsellinates *rac*-**10** and (*P*)-**10** were used for the syntheses of several flavomannin analogues by tandem-Michael–Dieckmann condensation.[23] This reaction includes Michael addition of a benzyl anion derived from the dimeric orsellinate **10**, to a Michael acceptor, here the cyclohexenone derivative **20**, followed by an intramolecular Dieckmann condensation, which establishes the desired ring system.

The dimeric orsellinate **10** was deprotonated to the corresponding benzyl dianion at –78 °C with an excess of lithium diisopropylamide (Scheme 7). The nucleophile attacks the cyclohexenone **20** exclusively through an 1,4-addition to form an intermediate enolate, which then reacts with the ester group to provide, after warming to room temperature, the anellated product. Two types of cyclohexenones were used. Type A containing a β-methoxy moiety is able to eliminate spontaneously MeOH after the tandem Michael–Dieckmann reaction to provide directly the aromatic system. Type B cyclohexenones lack this β-methoxy moiety. After the tandem Michael–Dieckmann reaction, a dehydrogenation reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is required in this case. Three different flavomannin analogues were synthesized. Using 5,5-dimethyl-3-methoxycyclohex-2-en-1-one[24] (**20a**) the substituted flavomannin analogue **21a** was prepared in a single-step with 27% isolated yield. The two step conversion with cyclohex-2-en-1-one (**20b**) to compound **21b** was performed also with



Scheme 7. Synthesis of dimeric dihydroanthracenones.

enantioenriched (*P*)-**10**, which afforded (*P*)-**21b** (Scheme 7). The circular dichroism (CD) of this compound reveals a typical split CD curve with a positive Cotton effect at 280 nm first and a second negative Cotton effect at 260 nm. Through exciton coupling methodology this allows the determination of the absolute configuration at the chiral biaryl axis in natural occurring flavomannins.[25]

Conclusions

Two different strategies for the preparation of enantiomerically pure dimeric orsellinates were elaborated. Both start from easily available methyl 2,4-dihydroxy-6-methylbenzoate (**1**), but differ in the dimerisation method. The Ullmann reaction requires a substrate which is iodinated at the desired coupling position and lacks free hydroxy groups. Unlike that, the oxidative phenolic coupling reaction requires a hydroxy function at C-2, but shows no regioselectivity regarding the coupling position.

The atropisomers of the dimeric orsellinates were resolved by column chromatography with triacetylcellulose as stationary phase, by the dinitrodiphenic acid method and by separation of the diastereomeric camphanate esters, whereupon the latter method is more practicable due to higher yields.

The value of dimeric orsellinates in natural product syntheses is emphasized by the synthesis of the flavomannin analogues **21a**–**b** using a tandem Michael–Dieckmann reaction with cyclohexenone derivatives **20a**–**b**.

Moreover, (*M*)- and (*P*)-**11** were applied in the synthesis of both atropisomers of vioxanthin[26] and dimeric coumarins of the kotanin type.[27] In the latter case all possible regioisomeric dimeric coumarins were synthesized starting from **11** (3,3′), **12** (5,5′) and **13** (3,5′), thus pinpointing the high potential of unselective phenol coupling in biomimetic natural product synthesis.

Experimental Section

General Remarks: All reagents were used in analytical grade. Solvents were desiccated by standard methods if necessary. Methyl 2,4-dihydroxy-6-methylbenzoate (**1**),[5] methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**2**),[10] methyl 2,4-dimethoxy-6-methylbenzoate (**3**),[7] (*M*)- and (*P*)-6,6′-dinitro-2,2′-diphenoyl dichloride, (*M*)-(**14**) and (*P*)-(**14**),[16] and 3-methoxy-5,5-dimethylcyclohex-2-en-1-one[17] (**20a**) were synthesised according to published procedures. New compounds are marked with an asterisk. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel 60F_{254} (Merck). Detection was performed under UV light (λ = 254 nm). Preparative column chromatography was carried out on silica gel 60 (Merck) (particle size 40–63 μm) or Sephadex LH-20 (Pharmacia). NMR spectra were recorded on a AMX 300 (Bruker Physik AG, Germany) or a Varian VXR 400 S (Varian GmbH, Germany). Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H, δ = 7.26 ppm) and $CDCl_3$ (^{13}C, δ = 77.0 ppm) as internal standard. GC-MS spectra were determined on a HP 6890 series GC-system fitted with a HP 5973 mass selective detector [Hewlett–Packard; column HP-5MS, 30 m × 250 μm; T_{GC}(injector) = 250 °C, T_{MS}(ion source) = 200 °C, time program (oven): $T_{0\,min}$ = 60 °C, $T_{3\,min}$ = 60 °C, $T_{14\,min}$ = 280 °C (heating rate 20 °C min^{-1}), $T_{19\,min}$ = 280 °C]. HRMS (EI) was performed on an A.E.I. MS 50, MS (FAB) with a Finnigan MAT 95 Q in a *m*-nitrobenzyl alcohol matrix and elemental analysis with a Vario EL (Heraeus) at the Institut für Anorganische Chemie, Rheinische Friedrich-Wilhelms-Universität, Bonn. Optical rotations were measured with a polarimeter 241 (Perkin–Elmer) and with a polarimeter P-1020 (Jasco). UV/Vis spectra were recorded with a Zeiss spectral photometer DMR 10 (Carl Zeiss Jena GmbH, Germany). Absorption coefficients ε are reported relative to the highest peak. CD spectra were recorded with a CNRS Roussel-Jouan Dichrographe III (Jobin Yvon) and on a Jasco J-720 spectral polarimeter. Molar circular-dichroic absorptions $\Delta\varepsilon$ are reported in cm^2 × mmol^{-1}. Melting points were measured with a Büchi B-540 heating unit.

Methyl 2,4-Dimethoxy-6-methylbenzoate (3): Methyl 2,4-dihydroxy-6-methylbenzoate (**1**) (1.00 g, 5.50 mmol) and dimethyl sulfate (2.1 mL, 22.2 mmol) were added to a solution of sodium methoxide (0.89 g, 16.5 mmol) in dry MeOH (15 mL). After stirring for 5 h at 65 °C, the solvent was evaporated under reduced pressure and water (100 mL) was added. The mixture was acidified to pH 1.5–2.0 with 2 M HCl and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by column chromatography (isohexane/EtOAc, 4:1) to give **3** (740 mg, 64%, R_f = 0.24) as a colourless solid, m.p. 41.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.30 (s, 2 H, H_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9 (CH_3), 52.0 (OCH_3), 55.3 (OCH_3), 55.9 (OCH_3), 96.2 (CH_{ar}), 106.7 (CH_{ar}), 116.4 (C_q), 138.3 (C_q), 158.2 (C_q), 161.4 (C_q), 168.7 (C_q) ppm. MS (EI): *m*/*z* (%) = 210 (89) [M$^+$], 179 (100) [$C_{10}H_{11}O_4^+$]. GC-MS: R_t = 10.78 min, *m*/*z* (%) = 210 (44) [M$^+$], 179 (100) [$C_{10}H_{11}O_4^+$].

Methyl 2-Hydroxy-3-iodo-4-methoxy-6-methylbenzoate (4)* and Methyl 2-Hydroxy-5-iodo-4-methoxy-6-methylbenzoate (5)*

Unselective Iodination: A solution of iodine (6.48 g, 25.51 mmol) in EtOH (50 mL) and 30% H_2O_2 (1000 mL) were added to a solution of methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**2**) (5.00 g, 25.51 mmol) in EtOH (150 mL) subsequently. The solid was completely precipitated by addition of water (1000 mL) and then separated by filtration. The title compounds **4** and **5** were obtained as a 4:1 mixture of colourless solids (3.29 g, 40%).

4: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.64 (s, 1 H, OH), 6.30 (s, 1 H, ar-H), 3.97 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 2.56 (s, 3 H, CH_3) ppm. GC-MS: R_t = 12.60 min, *m*/*z* (%) = 322 (38) [M$^+$], 290 (100) [$C_9H_7IO_3^+$], 247 (13) [$C_7H_4IO_2^+$], 163 (13) [$C_9H_7O_3^+$].

5: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.53 (s, 1 H, OH), 6.37 (s, 1 H, ar-H), 3.96 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 2.78 (s, 3 H, CH_3) ppm. GC-MS: **5**, R_t = 12.97 min, *m*/*z* (%) = 322 (32) [M$^+$], 290 (100) [$C_9H_7IO_3^+$], 247 (11) [$C_7H_4IO_2^+$], 163 (12) [$C_9H_7O_3^+$].

Methyl 5-Iodo-2,4-dimethoxy-6-methylbenzoate (7) and Methyl 3-Iodo-2,4-dimethoxy-6-methylbenzoate (8)*: Anhydrous K_2CO_3 (9.00 g, 65.22 mmol) and dimethyl sulfate (4.13 mL, 43.48 mmol) were added to a solution of methyl 2-hydroxy-3-iodo-4-methoxy-6-methylbenzoate (**4**) and methyl 2-hydroxy-4-methoxy-5-iodo-6-methylbenzoate (**5**) (7.00 g, 21.74 mmol) in acetone (500 mL). After stirring for 24 h at 56 °C, the solvent was evaporated under reduced pressure and water (700 mL) was added. The mixture was extracted with EtOAc (3 × 500 mL), the combined organic layers were dried

($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by column chromatography (isohexane/EtOAc = 4:1) to give **7** (2.43 g, 30%, R_f = 0.16) and **8** (4.87 g, 60%, R_f = 0.31) as colourless solids.

7: M.p. 133 °C. IR (KBr): $\tilde{\nu}$ = 1720, 1585, 1323, 1262, 1205, 1072, 940, 807 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.31 (s, 1 H, ar-H), 3.90 (s, 6 H, OCH_3), 3.84 (s, 3 H, OCH_3), 2.40 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.29 (C=O), 159.45 (C_q), 157.74 (C_q), 139.98 (C_q), 117.41 (C_q), 92.76 (CH), 82.84 (C_q), 56.44 (OCH_3), 55.95 (OCH_3), 52.31 (OCH_3), 25.95 (CH_3) ppm. GC-MS: R_t = 12.76 min, *m/z* (%) = 336 (100) [M^+], 305 (70) [$C_{10}H_{10}IO_3^+$]. $C_{11}H_{13}IO_4$ (336.12): calcd. C 39.31, H 3.90; found C 39.58, H 3.77.

8: M.p. 72 °C. IR (KBr): $\tilde{\nu}$ = 1715, 1210, 1085 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.44 (s, 1 H, ar-H), 3.89 (s, 3 H, OCH_3), 3.85 (s, 1 H, OCH_3), 3.82 (s, 3 H, OCH_3), 2.29 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 167.51 (C=O), 159.81 (C_q), 158.34 (C_q), 138.45 (C_q), 121.67 (C_q), 108.41 (CH), 80.23 (C_q), 62.14 (OCH_3), 56.45 (OCH_3), 52.14 (OCH_3), 19.73 (CH_3) ppm. GC-MS: R_t = 12.35 min, *m/z* (%) = 336 (85) [M^+], 305 (100) [$C_{10}H_{10}IO_3^+$], 290 (28) [$C_9H_7IO_3^+$]. $C_{11}H_{13}IO_4$ (336.12): calcd. C 39.31, H 3.90; found C 39.62, H 4.07.

Methyl 2,4-Dihydroxy-3-iodo-6-methylbenzoate (6)*

Selective Iodination: Benzyltrimethylammonium dichloroiodate (191 mg, 0.55 mmol) and $KHCO_3$ (330 mg, 3.30 mmol) were added to a solution of methyl 2,4-dihydroxy-6-methylbenzoate (**1**) (100 mg, 0.55 mmol) in CH_2Cl_2 (10 mL). After stirring the mixture for 24 h, a $NaHCO_3$ solution (20 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (toluene/acetone, 60:1; R_f = 0.23) to give **6** (75 mg, 44%) as a colourless solid, m.p. 143 °C. IR (KBr): $\tilde{\nu}$ = 3406, 1630, 1408, 1316, 1267, 798 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 12.77 (s, 1 H, OH), 6.45 (s, 1 H, ar-H), 5.82 (s, 1 H, OH), 3.93 (s, 3 H, OCH_3), 2.47 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.76 (C=O), 163.35 (C_q), 159.45 (C_q), 143.90 (C_q), 110.26 (CH), 105.61 (C_q), 74.12 (CH), 52.36 (OCH_3), 24.10 (CH_3) ppm. GC-MS: R_t = 12.03 min, *m/z* (%) = 308 (33) [M^+], 276 (100) [$C_8H_5IO_3^+$], 248 (9) [$C_7H_5IO_2^+$], 149 (16) [$C_8H_5O_3^+$]. $C_9H_9IO_4$ (308.07): calcd. C 35.09, H 2.94; found C 35.38, H 2.88; HRMS: calcd. for $C_9H_9IO_4$ 307.9546; found 307.9541.

Methyl 5-Iodo-2,4-dimethoxy-6-methylbenzoate (7)

Selective Iodination: A solution of iodine (6.05 g, 20.81 mmol) in EtOH (50 mL) and 30% H_2O_2 (1000 mL) was added subsequently to a solution of methyl 2,4-dimethoxy-6-methylbenzoate (**3**) (5.00 g, 23.81 mmol) in EtOH (150 mL). The solid was completely precipitated by addition of water (1000 mL) and then separated by filtration. The residue was recrystallized (cyclohexane/EtOAc) to give **7** (7.68 g, 96%) as a colourless solid. All spectral characteristics were identical with those of compound **7**, obtained by unselective iodination and methylation (see above).

Methyl 3-Iodo-2,4-dimethoxy-6-methylbenzoate (8)*: An excess of methyl iodide was added to a solution of methyl 2,4-dihydroxy-3-iodo-6-methylbenzoate (**6**) (300 mg, 1.47 mmol) and NaH in dry THF. Compound **8** was obtained in quantitative yield. All spectral characteristics were identical with those of compound **8** obtained by unselective iodination and methylation (see above).

Dimethyl 4,4′,6,6′-Tetramethoxy-2,2′-dimethyl-3,3′-biphenyldicarboxylate (9): An intimate mixture of the iodo compound **7** (5.00 g, 14.88 mmol) and activated copper bronze (5 g) was heated under nitrogen at 280 °C for 1 h. The cooled mixture was exhaustively extracted with boiling EtOAc, the extracts were filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (isohexane/EtOAc, 2:1; R_f = 0.24) to give **9** (1.71 g, 55%) as a colourless solid, m.p. 209 °C. IR (KBr): $\tilde{\nu}$ = 1720, 1587, 1315, 1205, 1095, 1080 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.38 (s, 2 H, 2 × ar-H), 3.86 (s, 6 H, 2 × OCH_3), 3.84 (s, 6 H, 2 × OCH_3), 3.66 (s, 6 H, 2 × OCH_3), 1.82 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.10 (2 × C=O), 158.84 (2 × C_q), 156.97 (2 × C_q), 136.83 (2 × C_q), 117.9 (2 × C_q), 116.63 (2 × C_q), 93.00 (2 × CH), 55.80 (2 × OCH_3), 55.65 (2 × OCH_3), 51.94 (2 × OCH_3), 16.69 (2 × CH_3) ppm. MS: *m/z* (%) = 418 (100) [M^+], 387 (59) [$C_{21}H_{23}O_7^+$], 355 (13) [$C_{20}H_{19}O_6^+$]. $C_{22}H_{26}O_8$ (418.16): calcd. C 63.15, H 6.26; found C 63.51, H 6.33; HRMS: calcd. for $C_{22}H_{26}O_8$ 418.1628; found 418.1623.

Dimethyl 2,2′,6,6′-Tetramethoxy-4,4′-dimethyl-3,3′-biphenyldicarboxylate (10)*: An intimate mixture of the iodo compound **8** (5.00 g, 14.88 mmol) and activated copper bronze (5 g) was heated under nitrogen at 240 °C for 2 h. The cooled mixture was exhaustively extracted with boiling EtOAc, the extracts were filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (isohexane/EtOAc, 7:2; R_f = 0.24) to give **10** (2.03 g, 65%) as a colourless solid, m.p. 185 °C. IR (KBr): $\tilde{\nu}$ = 1720, 1595, 1295, 1207, 1190, 1165, 1105 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.53 (s, 2 H, 2 × ar-H), 3.84 (s, 6 H, 2 × OCH_3), 3.68 (s, 6 H, 2 × OCH_3), 3.41 (s, 6 H, 2 × OCH_3), 2.34 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.70 (2 × C=O), 159.09 (2 × C_q), 157.02 (2 × C_q), 137.67 (2 × C_q), 121.02 (2 × C_q), 114.42 (2 × C_q), 108.24 (2 × CH), 61.45 (2 × OCH_3), 55.81 (2 × OCH_3), 51.89 (2 × OCH_3), 20.15 (2 × CH_3) ppm. MS: *m/z* (%) = 418 (81) [M^+], 386 (100) [$C_{21}H_{22}O_7^+$], 355 (24) [$C_{20}H_{19}O_6^+$]. $C_{22}H_{26}O_8$ (418.16): calcd. C 63.15, H 6.26; found C 63.31, H 6.20. HRMS: calcd. for $C_{22}H_{26}O_8$ 418.1628; found 418.1619.

Alternative Synthesis of 10: To a solution of **11** (79 mg, 0.2 mmol) in 30 mL acetone were added anhydrous K_2CO_3 (112 mg, 0.8 mmol) and methyl iodide (38 μL, 0.6 mmol). After reflux for 24 h, the reaction mixture was concentrated in vacuo, the residue distributed between water and EtOAc, and the aqueous phase extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 2:1; R_f = 0.20) to give **10** (79 mg, 94%) as a colourless solid.

Racemic Resolution: The atropisomers (+)-**10** and (–)-**10** could be separated by column chromatography on triacetylcellulose: Crystalline triacetylcellulose was heated under reflux in EtOH for 30 min, then filtered, slurried in EtOH, degassed by sonification and, under slight pressure, filled in a column. Racemic **10** was dissolved in EtOH and eluted under slight pressure. Both enantiomers were eluted in overlapping broad bands. First the dextrorotatory (+)-**10** was eluted, then (–)-**10**.[19]

The enantiomeric excess was determined by ^1H NMR with shift reagent [Pr(hfc)$_3$] in $CDCl_3$. Optically active samples obtained by racemic resolution showed *ee* values in the range from 7–13%.

(+)-10: $[\alpha]_{578}$ = +0.6 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{546}$ = +1.4 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{436}$ = +2.8 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{365}$ = +6.1 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1).

(–)-10: $[\alpha]_{578}$ = –0.6 (*c* = 0.9, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{546}$ = –1.3 (*c* = 0.9, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{436}$ = –5.7 (*c* = 0.9, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{365}$ = –10.8 (*c* = 0.9, dioxane/CH_2Cl_2, 1:1).

(*M*)-Dimethyl 2,2′,6,6′-Tetramethoxy-4,4′-dimethyl-3,3′-biphenyldicarboxylate [(*M*)-10]*: The synthesis of (*M*)-(+)-**10** was performed analogously to the synthesis of *rac*-**10** starting with a solution of (*M*)-**11** (120 mg, 0.3 mmol) in 50 mL acetone, anhydrous K_2CO_3 (171 mg, 1.2 mmol) and methyl iodide (58 μL, 0.9 mmol). After purification by column chromatography on silica gel (isohexane/EtOAc, 2:1; R_f = 0.20), (*M*)-**10** was obtained as a colourless solid (112 mg, 86%), m.p. 113.1 °C. $[\alpha]_D^{26}$ = –6.30 (*c* = 1.4, $CHCl_3$), $[\alpha]_D^{20}$ = +14.58 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{578}^{20}$ = +15.42 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{546}^{20}$ = +17.50 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{436}^{20}$ = +32.50 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{365}^{20}$ = +62.08 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1); CD (acetonitrile): λ = ($\Delta\varepsilon$) [nm] = 197 (+20.6), 214 (–26.9), 240 (+8.7), 263 (+0.3), 274 (+0.8). All other spectral characteristics were identical with those of racemic **10**.

(*P*)-Dimethyl 2,2′,6,6′-Tetramethoxy-4,4′-dimethyl-3,3′-biphenyldicarboxylate [(*P*)-10]*: The synthesis of (*P*)-(–)-**10** was performed analogously to that of *rac*-**10** starting with a solution of (*P*)-**11** (120 mg, 0.3 mmol) in 50 mL acetone, K_2CO_3 (171 mg, 1.2 mmol) and methyl iodide (58 μL, 0.9 mmol). After purification by column chromatography on silica gel (isohexane/EtOAc, 2:1; R_f = 0.20), (*P*)-**10** was obtained as a colourless solid (112 mg, 86%), m.p. 131.0 °C. $[\alpha]_D^{26}$ = +4.56 (*c* = 1.6, $CHCl_3$), $[\alpha]_D^{22}$ = +7.48 (*c* = 0.2, $CHCl_3$), $[\alpha]_D^{24}$ = –13.81 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{578}^{20}$ = –14.29 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{546}^{20}$ = –16.90 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{436}^{20}$ = –32.38 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1), $[\alpha]_{365}^{20}$ = –63.81 (*c* = 0.2, dioxane/CH_2Cl_2, 1:1); CD (acetonitrile): λ = ($\Delta\varepsilon$) [nm] = 197 (–20.6), 214 (–26.9), 240 (+8.8), 263 (+0.3), 274 (+0.8). All other spectral characteristics were identical with those of compound *rac*-**10**.

Dimethyl 2,2′-Dihydroxy-6,6′-dimethoxy-4,4′-dimethyl-3,3′-biphenyldicarboxylate (11), Dimethyl 4,4′-Dihydroxy-6,6′-dimethoxy-2,2′-dimethyl-3,3′-biphenyldicarboxylate (12) and Dimethyl 2,4′-Dihydroxy-6,6′-dimethoxy-2′,4-dimethyl-3,3′-biphenyldicarboxylate (13). Oxidative Phenolic Coupling: The silica gel-bound $FeCl_3$ was prepared as follows. Silica gel (7.24 g) was added to a solution of $FeCl_3 \cdot 6H_2O$ (3.52 g, 13.02 mmol) in Et_2O (190 mL) and MeOH (10 mL). The solvents were evaporated and the yellow solid was dried in vacuo at 70 °C (0.4 mbar) for 8 h. The silica gel bound $FeCl_3$ was obtained as a yellow-green solid. The oxidative coupling reaction was carried out by adding this reagent (1.40 g) to a solution of methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**2**) (146 mg, 0.74 mmol) in CH_2Cl_2 (30 mL). After efficient mixing, the solvent was removed under reduced pressure to give a dark solid, which was heated at 60 °C for 24 h. MeOH (50 mL) was added and the mixture filtered through Celite. The solvent was removed in vacuo and the dark residue purified by column chromatography (isohexane/EtOAc, 5:1, 4:1, 3:1, 2:1) to yield the biphenyldiols **11** (22 mg, 17%), **12** (42 mg, 33%) and **13** (38 mg, 30%) as colourless solids. From fractions containing **11** and **13** the symmetric compound **11** crystallized quantitatively while the unsymmetric compound **13** remained in solution. After separation by centrifugation, analytically pure (NMR) **11** and **13** were obtained.

Alternatively, for the oxidative coupling in larger scale, orsellinate **2** (4.73 g, 24.1 mmol) and silica gel bound $FeCl_3$ (47.00 g) were suspended in 20 mL CH_2Cl_2, and the solvent was removed at 40 °C under reduced pressure within 60 min. The cycle of suspending and drying was repeated four times until formation of by-products was detected by TLC. The dark residue was filtered through a short silica gel column (chloroform/2-propanol, 40:1), and the eluate was concentrated in vacuo. The residue was dissolved in boiling EtOAc (200 mL) and the solution mixed with cyclohexane (800 mL). After 16 h incubation at room temperature, the 3,3′-coupling product **11** crystallized (24% isolated yield). The mother liquor was concentrated and, after flash column chromatography on silica gel (isohexane/EtOAc, 3:1, 1:1), the 5,5′- and 3,5′-coupling products **12** and **13** were obtained in 16 and 31% isolated yield, respectively.

11: R_f = 0.22 (isohexane/EtOAc, 2:1), m.p. 246 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.81 (s, 2 H, 2 × OH), 6.41 (s, 2 H, 2 × ar-H), 3.91 (s, 6 H, 2 × OCH_3), 3.77 (s, 6 H, 2 × OCH_3), 2.59 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 172.37 (2 × C=O), 161.90 (2 × C_q), 161.50 (2 × C_q), 143.10 (2 × C_q), 107.84 (2 × C_q), 106.69 (2 × CH), 105.97 (2 × C_q), 55.82 (2 × OCH_3), 51.85 (2 × OCH_3), 24.96 (2 × CH_3) ppm. MS: *m*/*z* (%) = 390 (67) [M^+], 358 (70) [$C_{19}H_{18}O_7^+$], 327 (65) [$C_{18}H_{15}O_6^+$], 295 (100) [$C_{17}H_{11}O_5^+$]. HRMS: calcd. for $C_{20}H_{22}O_8$ 390.1315; found 390.1311.

12: R_f = 0.33 (isohexane/EtOAc, 2:1), m.p. 183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.77 (s, 2 H, 2 × OH), 6.41 (s, 2 H, 2 × ar-H), 3.91 (s, 6 H, 2 × OCH_3), 3.67 (s, 6 H, 2 × OCH_3), 2.10 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 172.49 (2 × C=O), 164.47 (2 × C_q), 162.25 (2 × C_q), 141.41 (2 × C_q), 119.15 (2 × C_q), 105.55 (2 × C_q), 97.29 (2 × CH), 55.69 (2 × OCH_3), 51.83 (2 × OCH_3), 19.36 (2 × CH_3) ppm. MS: *m*/*z* (%) = 390 (47) [M^+], 358 (31) [$C_{19}H_{18}O_7^+$], 327 (100) [$C_{18}H_{15}O_6^+$], 295 (100) [$C_{17}H_{11}O_5^+$]. HRMS: calcd. for $C_{20}H_{22}O_8$ 390.1315; found 390.1314.

13: R_f = 0.24 (isohexane/EtOAc, 2:1), m.p. 190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.79 (s, 1 H, OH), 11.74 (s, 1 H, OH), 6.44 (s, 1 H, ar-H), 6.38 (s, 1 H, ar-H), 3.92 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 2.60 (s, 3 H, CH_3), 2.22 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 172.53 (C=O), 172.41 (C=O), 164.74 (C_q), 162.34 (C_q), 161.90 (C_q), 161.35 (C_q), 142.80 (C_q), 141.64 (C_q), 115.71 (C_q), 111.16 (C_q), 106.45 (CH), 105.87 (C_q), 105.65 (C_q), 97.50 (CH), 55.81 (OCH_3), 55.69 (OCH_3), 51.91 (OCH_3), 51.78 (OCH_3), 24.94 (CH_3), 19.67 (CH_3) ppm. MS: *m*/*z* (%) = 390 (53) [M^+], 358 (66) [$C_{19}H_{18}O_7^+$], 326 (100) [$C_{18}H_{14}O_6^+$]. HRMS: calcd. for $C_{20}H_{22}O_8$ 390.1315; found 390.1323.

Resolution of the Atropisomers via the DNPS Method

(*M*,*M*)-Dimethyl 4,5-Dimethoxy-2,7-dimethyl-14,15-dinitro-10,19-dioxo-10,19-dihydro-9,20-dioxa-tetrabenzo[*a*,*c*,*g*,*i*]cyclododecene-1,8-dicarboxylate [(*M*,*M*)-15]*: Dimethyl 2,2′-dihydroxy-6,6′-dimethoxy-4,4′-dimethyl-3,3′-biphenyldicarboxylate (**11**) (75 mg, 0.19 mmol) was added to a suspension of sodium hydride (30 mg, 0.76 mmol) in dry THF (80 mL). After stirring for 30 min at 67 °C, this solution and a solution of (*M*)-(+)-6,6′-dinitro-2,2′-diphenoyl dichloride [(*M*)-(+)-**14**] (71 mg, 0.19 mmol) in dry THF (80 mL) were transferred simultaneously within 1 h to boiling THF.[28] After stirring for 3 h at 67 °C, the reaction mixture was acidified with 2 N HCl. The aqueous phase was extracted with EtOAc (3 × 150 mL), the organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by preparative TLC (isohexane/EtOAc, 2:3; R_f = 0.26) to give (*M*,*M*)-**15** (17 mg, 13%) as a colourless solid, m.p. 149 °C. IR (KBr): $\tilde{\nu}$ = 1750, 1715, 1530, 1260, 1100 cm^{-1}. $[\alpha]_D^{25}$ = –21.8 (*c* = 0.06, dioxane/CH_2Cl_2, 1:1); CD (dioxane): λ = ($\Delta\varepsilon$) [nm] = 239 (+1.0), 262 (–0.8); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (dd, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1 H, 2 × ar-H), 8.06 (dd, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1 H, 2 × ar-H), 7.58 (t, ^3J = 7.8 Hz, 1 H, 2 × ar-H), 6.63 (s, 1 H, 2 × ar-H), 3.69 (s, 3 H, 4 × OCH_3), 2.46 (s, 3 H, 2 × CH_3) ppm. MS: *m*/*z* (%) = 686 (100) [M^+], 654 (34) [$C_{33}H_{22}N_2O_{13}^+$]. HRMS: calcd. for $C_{34}H_{26}N_2O_{14}$ 686.1384; found 686.1377.

(*P*,*P*)-Dimethyl 4,5-Dimethoxy-2,7-dimethyl-14,15-dinitro-10,19-dioxo-10,19-dihydro-9,20-dioxa-tetrabenzo[*a*,*c*,*g*,*i*]cyclododecene-1,8-

dicarboxylate [(*P*,*P*)-15]*: According to the foregoing procedure starting from 2,2′-dihydroxy-6,6′-dimethoxy-4,4′-dimethyl-3,3′-biphenyldicarboxylate (**11**) (75 mg, 0.19 mmol) and (*P*)-(–)-6,6′-dinitro-2,2′-diphenoyl dichloride [(*P*)-(–)-**14**] (71 mg, 0.19 mmol) the title compound was obtained as a colourless solid. $[\alpha]_D^{20}$ = +51.2 (*c* = 0.3, $CHCl_3$). All other spectral characteristics were identical with those of compound (*M*,*M*)-**15**.

Resolution of the Atropisomers via the Camphanate Method

Dimethyl 2,2′-Bis(camphanyloxy)-4,4′-dimethoxy-6,6′-dimethyl-3,3′-biphenyldicarboxylates [(*M*)-(–)-18 and (*P*)-(+)-19]*: 4-(Dimethylamino)pyridine (100 mg, 0.81 mmol) was added to a solution of dimethyl 2,2′-dihydroxy-6,6′-dimethoxy-4,4′-dimethyl-3,3′-biphenyldicarboxylate *rac*-(**11**) (964 mg, 2.474 mmol) and (1*S*,4*R*)-(–)-camphanoyl chloride (**17**) (4.42 g, 19.76 mmol) in dry pyridine (60 mL). After refluxing for 4 h, CH_2Cl_2 (500 mL) was added and the reaction mixture washed with 2 N HCl (2 × 250 mL), saturated aqueous $NaHCO_3$ (100 mL), and water (100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (isohexane/EtOAc, 1:1) to yield the camphanate esters (–)-**18** (871 mg, 47%), and (+)-**19** (834 mg, 45%) as colourless solids.

(*M*)-(–)-18: R_f = 0.38 (isohexane/EtOAc, 1:1), m.p. 209 °C. $[\alpha]_D^{24}$ = –26.1 (*c* = 1.0, $CHCl_3$); CD (acetonitrile): λ = ($\Delta\varepsilon$) [nm] = 211 (–55.92), 243 (+13.9), 261 (–5.6), 280 (+1.9). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.67 (s, 2 H, 2 × ar-H), 3.77 (s, 6 H, 2 × OCH_3), 3.76 (s, 6 H, 2 × OCH_3), 2.41 (s, 6 H, 2 × CH_3), 2.19 (ddd, *J* = 13.6 Hz, *J* = 10.9 Hz, *J* = 4.5 Hz, 2 H, 2 × CH), 1.97 (ddd, *J* = 13.6 Hz, *J* = 9.3 Hz, *J* = 4.5 Hz, 2 H, 2 × CH), 1.81 (ddd, *J* = 13.6 Hz, *J* = 10.9 Hz, *J* = 4.5 Hz, 2 H, 2 × CH), 1.60 (ddd, *J* = 13.6 Hz, *J* = 9.3 Hz, *J* = 4.5 Hz, 2 H, 2 × CH), 0.99 (s, 6 H, 2 × CH_3), 0.81 (s, 6 H, 2 × CH_3), 0.47 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 178.22 (2 × C=O), 166.34 (2 × C=O), 164.75 (2 × C=O), 159.63 (2 × C_q), 147.70 (2 × C_q), 140.65 (2 × C_q), 118.43 (2 × C_q), 113.40 (2 × C_q), 111.29 (2 × CH), 90.81 (2 × C_q), 56.26 (2 × OCH_3), 54.83 (2 × C_q), 54.05 (2 × C_q), 52.12 (2 × OCH_3), 31.00 (2 × CH_2), 28.80 (2 × CH_2), 21.51 (2 × CH_3), 16.00 (2 × CH_3), 15.10 (2 × CH_3), 9.57 (2 × CH_3) ppm. MS: *m*/*z* (%) = 750 (7) [M^+], 718 (100) [$C_{39}H_{42}O_{13}^+$], 341 (14) [$C_{18}H_{13}O_7^+$]. HRMS: calcd. for $C_{40}H_{46}O_{14}$ 750.2888; found 750.2940.

(*P*)-(+)-19: R_f = 0.31 (isohexane/EtOAc, 1:1), m.p. 223 °C. $[\alpha]_D^{25}$ = +19.4 (*c* = 1.0, $CHCl_3$); CD (acetonitrile): λ = ($\Delta\varepsilon$) [nm] = 211 (+71.23), 243 (–21.5), 261 (+4.7), 280 (–0.34); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.70 (s, 2 H, 2 × ar-H), 3.80 (s, 6 H, 2 × OCH_3), 3.74 (s, 6 H, 2 × OCH_3), 2.44 (s, 6 H, 2 × CH_3), 2.15 (ddd, *J* = 13.6 Hz, *J* = 10.9 Hz, *J* = 4.5 Hz, 2 H, 2 × CH), 1.80 (ddd, *J* = 13.6 Hz, *J* = 9.3 Hz, *J* = 4.5 Hz, 2 H, 2 × CH), 1.50 (m, 4 H, 2 × CH_2), 1.03 (s, 6 H, 2 × CH_3), 0.88 (s, 6 H, 2 × CH_3), 0.82 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 178.21 (2 × C=O), 166.50 (2 × C=O), 164.56 (2 × C=O), 159.43 (2 × C_q), 147.33 (2 × C_q), 139.99 (2 × C_q), 119.18 (2 × C_q), 113.33 (2 × C_q), 111.20 (2 × CH), 90.99 (2 × C_q), 56.22 (2 × OCH_3), 54.90 (2 × C_q), 54.10 (2 × C_q), 52.19 (2 × OCH_3), 30.41 (2 × CH_2), 28.80 (2 × CH_2), 21.33 (2 × CH_3), 16.04 (2 × CH_3), 15.94 (2 × CH_3), 9.59 (2 × CH_3) ppm. MS: *m*/*z* (%) = 750 (5) [M^+], 718 (100) [$C_{39}H_{42}O_{13}^+$], 341 (19) [$C_{18}H_{13}O_7^+$]. HRMS: calcd. for $C_{40}H_{46}O_{14}$ 750.2888; found 750.2871.

(*M*)-Dimethyl 2,2′-Dihydroxy-6,6′-dimethoxy-4,4′-dimethyl-3,3′-biphenyldicarboxylate [(*M*)-11]

Dinitrodiphenic Acid Method: A catalytic amount of KOH was added to a solution of (*M*,*M*)-**15** (17 mg, 0.02 mmol) in dry THF (5 mL). After stirring for 2 h at room temperature, the solvent was evaporated in vacuo and 2 N HCl (5 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by preparative TLC (isohexane/EtOAc, 2:1; R_f = 0.22) to give (*M*)-**11** (7 mg, 90%) as a colourless solid, m.p. 229 °C. All other spectral characteristics were identical with those of compound *rac*-**11**.

Camphanate Ester Method: A solution of camphanate ester (*M*)-**18** (28 mg, 0.04 mmol) and sodium methoxide (20 mg, 0.36 mmol) in dry MeOH (5 mL) was refluxed until no more starting material was detectable by TLC (1 h). The reaction mixture was quenched with 1 N H_2SO_4 (2 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 15 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (isohexane/EtOAc, 2:1; R_f = 0.22) to give (*M*)-**11** (11 mg, 75%) as a colourless solid, m.p. 228 °C. $[\alpha]_D^{20}$ = –53.3 (*c* = 0.15, $CHCl_3$); CD (trifluoroethanol): λ = ($\Delta\varepsilon$) [nm] = 205 (+96.6), 224 (–56.1), 260 (+37.9), 278 (–17.1), 311 (–5.0). All other spectral characteristics were identical with those of compound *rac*-**11**.

(*P*)-Dimethyl 2,2′-Dihydroxy-6,6′-dimethoxy-4,4′-dimethyl-3,3′-biphenyldicarboxylate [(*P*)-11]

Dinitrodiphenic Acid Method: According to the foregoing procedure starting from (*P*,*P*)-**15** (17 mg, 0.02 mmol) the title compound was prepared in 90% yield (7 mg) as a colourless solid, m.p. 229 °C. $[\alpha]_D^{20}$ = +27.0 (*c* = 0.2, $CHCl_3$). All other spectral characteristics were identical with those of compound *rac*-**11**.

Camphanate Ester Method: According to the foregoing procedure starting from camphanate ester (*P*)-**18** (28 mg, 0.04 mmol) the title compound was prepared in 75% yield (11 mg) as a colourless solid, m.p. 223 °C. $[\alpha]_D^{20}$ = +36.4 (*c* = 0.11, $CHCl_3$); CD (trifluoroethanol): λ = ($\Delta\varepsilon$) [nm] = 206 (–51.0), 223 (+35.3), 260 (–18.5), 279 (+12.6), 312 (+6.3). All other spectral characteristics were identical with those of compound *rac*-**11**.

Syntheses of Dimeric Dihydroanthracenones

General Procedure for the Tandem Michael–Dieckmann Reaction: A solution of dimethyl 2,2′,6,6′-tetramethoxy-4,4′-dimethyl-3,3′-biphenyldicarboxylate (**10**) (105 mg, 0.25 mmol) in dry THF (5 mL) was added at –78 °C to a solution of lithium diisopropylamide in dry THF (30 mL), prepared from diisopropylamine (0.35 mL, 2.5 mmol) and a 2.5 M solution of *n*-butyllithium (0.8 mL, 2.0 mmol). The red solution was stirred for 10 min at –78 °C, then warmed to –40 °C for 5 min and cooled again to –78 °C. Then a solution of the cyclohexenone **20** (2.0 mmol) in dry THF (5 mL) was added. The reaction mixture was stirred for 15 min at –78 °C, before it was hydrolyzed with dry EtOH (1 mL) and warmed to room temperature. After addition of AcOH (1 mL) and saturated aqueous NH_4Cl (200 mL), the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

(±)-3,3′,4,4′-Tetrahydro-9,9′-dihydroxy-6,6′,8,8′-tetramethoxy-3,3,3′,3′-tetramethyl-7,7′-bianthracene-1,1′(2*H*,2′*H*)-dione (*rac*-21a)*: The title compound was prepared according to the general procedure starting from dimeric orsellinate *rac*-**10** (105 mg, 0.25 mmol) and 5,5-dimethyl-3-methoxycyclohex-2-en-1-one (**20a**) (308 mg, 2.0 mmol). The crude product was purified by column chromatography on Sephadex LH-20 (acetone/MeOH, 4:1) to give *rac*-**21a** (40 mg, 26%) as a yellow solid, m.p. 255 °C. UV (MeOH):

$\lambda = (\varepsilon)$ [nm] = 220 (0.34), 279 (0.90), 315 (0.20), 332 (0.18), 392 (0.26). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.01 (s, 2 H, 2×OH), 6.96 (s, 2 H, 2×ar-H), 6.87 (s, 2 H, 2×ar-H), 3.80 (s, 6 H, 2×OCH_3), 3.70 (s, 6 H, 2×OCH_3), 2.84 (s, 4 H, 2×CH_2), 2.57 (s, 4 H, 2×CH_2), 1.12 (s, 6 H, 2×CH_3), 1.10 (s, 6 H, 2×CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 203.89 (2×C=O), 164.77 (2×C_q), 160.51 (2×C_q), 158.43 (2×C_q), 141.30 (2×C_q), 138.05 (2×C_q), 117.90 (2×C_q), 116.70 (2×CH), 113.51 (2×C_q), 109.95 (2×C_q), 101.90 (2×CH), 61.96 (2×OCH_3), 55.73 (2×OCH_3), 52.15 (2×CH_2), 43.94 (2×CH_2), 32.95 (2×C_q), 28.22 (2×CH_3), 28.01 (2×CH_3) ppm. MS (FAB): *m/z* (%) = 599 (100) [MH^+], 598 (67) [M^+], 584 (10) [$C_{35}H_{36}O_8^+$], 583 (21) [$C_{35}H_{35}O_8^+$], 567 (7) [$C_{35}H_{35}O_7^+$], 553 (10) [$C_{34}H_{33}O_7^+$], 552 (10) [$C_{34}H_{32}O_7^+$], 391 (3) [$C_{20}H_{23}O_8^+$], 307 (13) [$C_{16}H_{19}O_6^+$], 289 (9) [$C_{16}H_{17}O_5^+$]. $C_{36}H_{38}O_8$ (598.69): calcd. C 72.22 H 6.40; found C 71.74 H 6.45.

(±)-3,3′,4,4′-Tetrahydro-9,9′-dihydroxy-6,6′,8,8′-tetramethoxy-7,7′-bianthracene-1,1′(2*H*,2′*H*)-dione (*rac*-21b)*: The title compound was prepared according to the general procedure starting from dimeric orsellinate *rac*-**10** (105 mg, 0.25 mmol) and cyclohex-2-en-1-one (**20b**) (192 mg, 2.0 mmol). The crude product was directly dehydrogenated by refluxing with DDQ in dry benzene for 6 h. After column chromatography on silica gel (isohexane/EtOAc, 4:1), *rac*-**21b** was obtained as a yellow solid. IR (KBr): $\tilde{\nu}$ = 2930, 1610, 1560, 1450, 1370, 1210, 1165, 1110, 1095, 710 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 15.07 (s, 2 H, 2×OH), 6.97 (s, 2 H, 2×ar-H), 6.84 (s, 2 H, 2×ar-H), 3.76 (s, 6 H, 2×OCH_3), 3.65 (s, 6 H, 2×OCH_3), 2.97 (s, 4 H, 2×CH_2), 2.72 (s, 4 H, 2×CH_2), 2.07 (s, 4 H, 2×CH_2) ppm. MS: *m/z* (%) = 542 (8) [M^+], 527 (4) [$C_{31}H_{27}O_8^+$], 494 (9) [$C_{30}H_{22}O_7^+$], 480 (100) [$C_{30}H_{14}O_6^+$], 449 (24) [$C_{29}H_{11}O_5^+$], 433 (10) [$C_{29}H_{11}O_4^+$], 417 (25) [$C_{29}H_{11}O_3^+$]. HRMS: calcd. for $C_{32}H_{30}O_8$ 542.1940; found 542.1942.

The two-step reaction with cyclohex-2-en-1-one (**20b**) to compound **21b** was also performed with enantioenriched (*P*)-**10**, which afforded (*P*)-**21b***. The CD of this sample is in accordance with the known configuration of the starting material. Comparison of the CD of model compound (*P*)-**21b** with that of natural occurring flavomannins enabled us to determine the configuration at the chiral biaryl axis in the natural products.

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