A Short and Efficient Total Synthesis of the Naturally Occurring Coumarins Siderin, Kotanin, Isokotanin A and Desertorin C

Wolfgang Hüttel,[a] Martin Nieger,[b] Michael Müller*[a]

[a] Institut für Biotechnologie 2, Forschungszentrum Jülich GmbH, 52425 Jülich
Fax +49(2461)613870; E-mail: mi.mueller@fz-juelich.de

[b] Institut für Anorganische Chemie, Rheinische Friedrich-Wilhelms-Universität, 53121 Bonn

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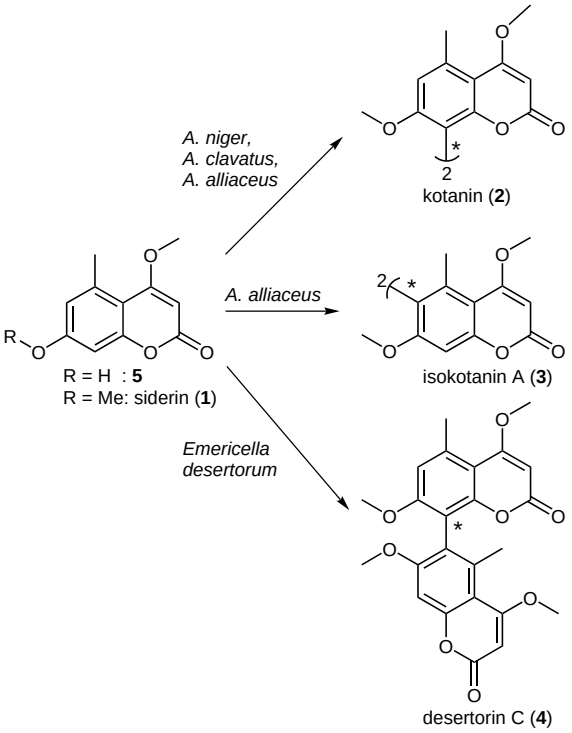
Dedicated to Professor Wolfgang Steglich on the occasion of his 70th birthday.

Abstract: Starting from methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**6**) and its regioisomeric dehydrodimers **7**–**9**, readily available by an oxidative coupling reaction of **6**, the naturally occurring coumarins siderin (**1**), kotanin (**2**), isokotanin A (**3**) and desertorin C (**4**) were synthesized in a novel and highly efficient three-step transformation. In the case of kotanin (**2**) both atropisomers were prepared from the pure atropisomers of **7**.

Key words: atropisomerism, biaryls, oxidative phenolic coupling, natural coumarins

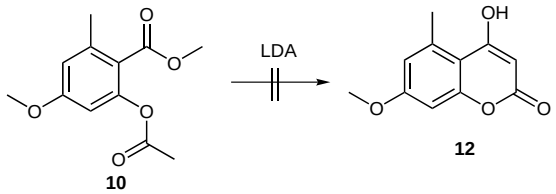
The biaryl unit is a widely distributed structure element in many natural product classes.[1] However, its chemical synthesis often requires multistep procedures especially if the synthesis has to be atropselective. The polyketide-derived[2] dehydro-metabolites discussed in this work are regioisomeric dimers of the trisubstituted coumarin siderin (**1**). They and their demethyl derivatives are produced by different *Aspergillus* species: kotanin (**2**) was isolated from *A. clavatus, A. niger* and *A. alliaceus*;[3] isokotanin A (**3**) was found in *A. alliaceus* and its teleomorph *Petromyces alliaceus*;[4] and the constitutionally unsymmetric dimer desertorin C (**4**) was obtained from *Emericella desertorum* (Scheme 1).[5] The biosynthesis of **2**–**4** is assumed to proceed through dehydrodimerization of a monomeric precursor like siderin (**1**) or its demethyl derivative **5**.

For a study on the stereo- and regioselective dimerization of these coumarins in filamentous fungi, an analytical assay had to be established. Therefore, a short and simple chemical access to both the monomeric and the oxidative coupled coumarins was required. Even though racemic and atropselective syntheses of these compounds have been reported in the literature,[6–9] these methods include multistep procedures and were not suitable for our purpose.[10] Here we describe a consistent and efficient new access to the monomeric and dimeric 4,7-dimethoxy coumarins **1**–**4** (see Scheme 4). Since the biaryl precursors **7**–**9** are available in a single step by an unselective oxidative phenol coupling[11] of readily available methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**6**), the syntheses of the three regioisomeric bicoumarins **2**–**4** could be realized efficiently.



Scheme 1 Regioisomeric bicoumarins isolated from filamentous fungi and their putative monomeric precurors in biosynthesis

For the transformation of benzoate **6** into 4-hydroxycoumarin **12**, acetic ester enolate should be added to the ester moiety followed by acidic hydrolysis and cyclization. However, neither the conversion of **6** with the lithium enolate of *tert*-butyl acetate nor treatment of acetate **10** with LDA gave the desired product (Scheme 2).[12]



Scheme 2 Attempted cyclization of **10** to 4-hydroxycoumarin **12** with LDA

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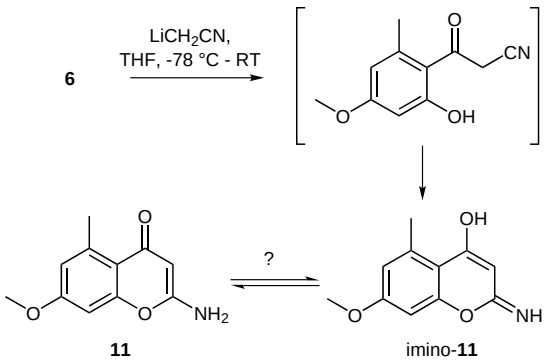
In a further attempt, we used acetonitrile as an acetic ester equivalent[13] to obtain a compound in 80% yield, which proved to be the intramolecular cyclization product **11** of the expected β-keto nitrile (Scheme 3).



Scheme 3 Synthesis and possible tautomers of product **11**

The cyclization reaction is described in the literature to yield both 2-aminochromen-4-ones[14] like **11** and the tautomeric 2-iminochromen-4-ols (4-hydroxyiminocoumarins) like imino-**11**.[15]

However, no NMR data were given for the latter. The two-proton signal at δ = 7.18 in the ^{1}H NMR spectrum of compound **11** (DMSO-d_6) suggests the presence of an amino group as expected for an aminochromenone. Since **11** crystallized readily from an aqueous ethanol solution, the exclusive existence of this tautomer could also be proved by X-ray structure analysis (Figure 1).

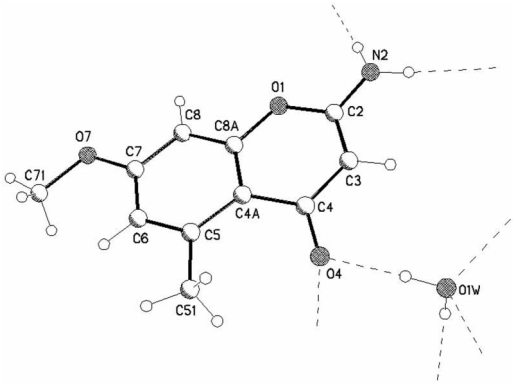
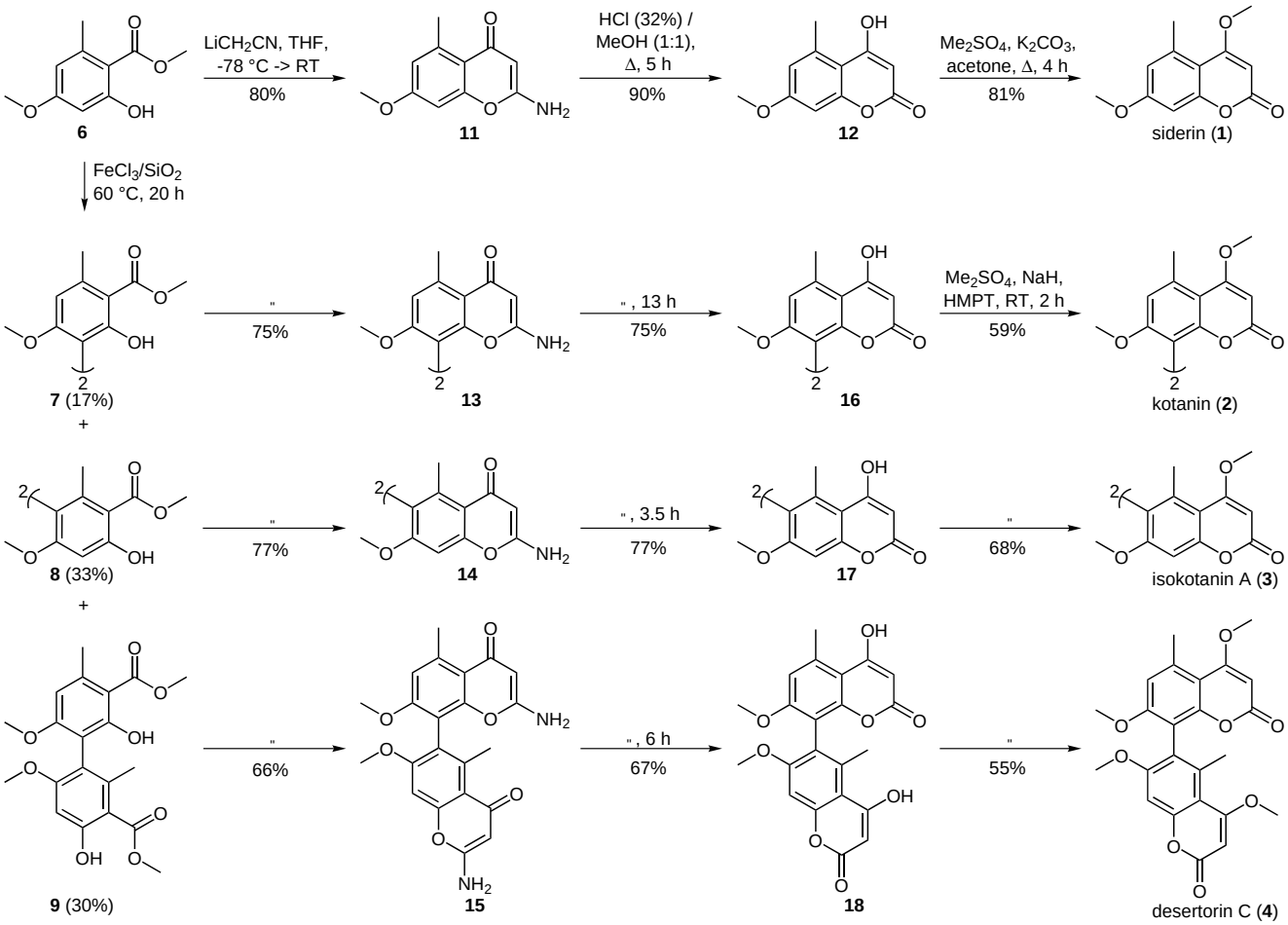


Figure 1 Molecular structure of **11**

The acidic hydrolysis of **11** was carried out by refluxing in a methanol–hydrochloric acid mixture to give the pure 4-hydroxycoumarin **12** in 90% yield. After methylation



Scheme 4 Syntheses of monomeric and dimeric coumarins starting from methyl benzoate **6**

with dimethyl sulfate under standard conditions, siderin (**1**) was obtained in 81% yield (Scheme 4).

Encouraged by these results, we adopted this method for the syntheses of the bicoumarins **2**–**4** starting from the corresponding biaryl esters **7**–**9**. The transformation with the lithium salt of acetonitrile took place as for the monomeric compound, albeit in slightly lower yields. For the acidic hydrolysis of the resulting aminobichromenones **13**–**15**, the reaction time had to be adjusted, since the reactivity of these compounds decreases from the 6,6′-dimer **14** to the 8,8′-dimer **13**. On the other hand, decarboxylation products were observed if the reaction time was too long. Because of their low solubility even in polar solvents, the 4,4′-dihydroxybicoumarins **16**–**18** were used for the next step without further purification. Due to the low reactivity of the hydroxy group in **16**–**18**, an optimized method described in the literature was adopted for the final methylation step using dimethyl sulfate, sodium hydride, and HMPT (Scheme 4).[16] Alternatively, these highly toxic reagents can be avoided by using acid-catalyzed etherification for O-methylation.[17]

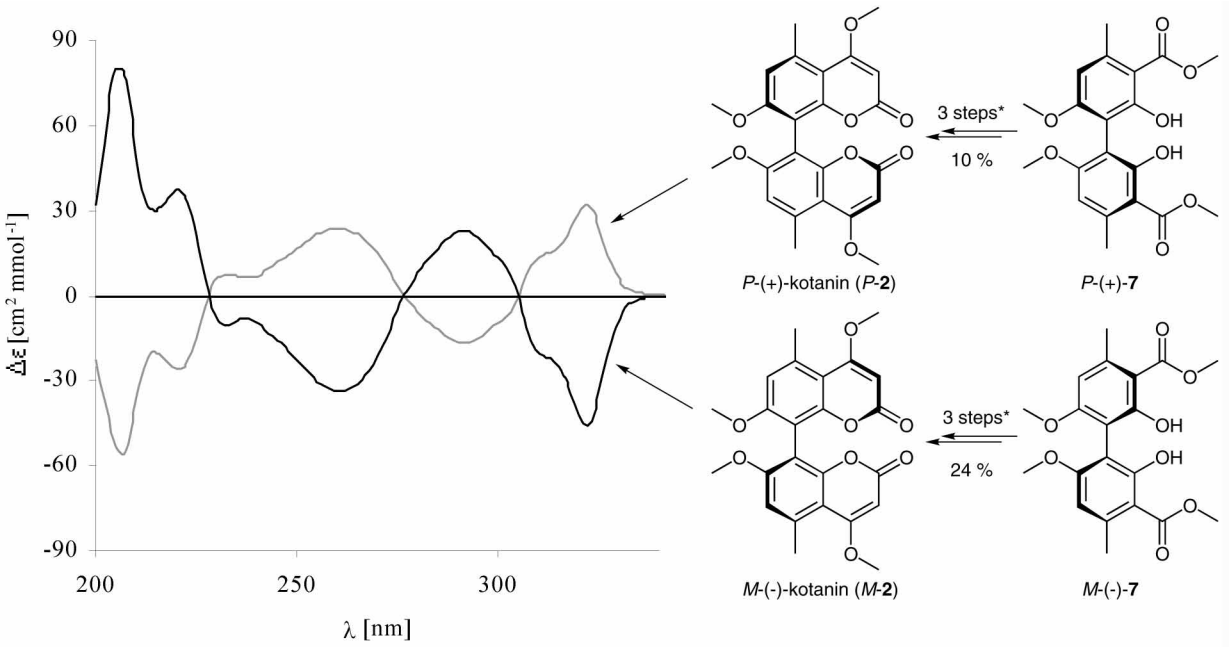
Moreover, both atropisomers of kotanin (**2**) were prepared from the pure atropisomers of dimeric ester **7**[11] in 24% and 10% yield,[18] respectively (Scheme 5). *P*-(+)-Kotanin (*P*-**2**) was obtained from *P*-(+)-**7** and *M*-(–)-kotanin (*M*-**2**) from the *M*-(–)-isomer of **7**.[19]

In summary, we have developed a new, consistent and highly efficient synthetic access to the naturally occurring coumarins siderin (**1**), kotanin (**2**), isokotanin A (**3**) and desertorin C (**4**) starting from benzoate **6** and its readily available dehydrodimers **7**–**9**. It is based on a new and straightforward synthetic approach from 2-hydroxybenzoates to 4-hydroxycoumarins. In the case of kotanin (**2**) both atropisomers were prepared in optically pure form from the corresponding isomers of biaryl ester **7**.

All reagents were used in analytical grade. Solvents were dried by standard methods, if necessary. Methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**6**)[20] and its dimers **7**, **8** and **9** were synthesized according to published procedures.[11] Flash column chromatography was carried out on silica gel 60 (Merck) (particle size 40–60 μm). NMR spectra were recorded on a Bruker AMX 300 spectrometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: δ = 7.25) and $CDCl_3$ (^{13}C: δ = 77.23) or to DMSO (^{1}H: δ = 2.50) and DMSO-d_6 (^{13}C: δ = 39.51). GC-MS were recorded on a HP 6890 Series GC System equipped with a HP 5973 Mass Selective Detector (Hewlett Packard, capillary column HP-5 MS 30 m·250 μm; T_{GC} (injector) = 250 °C, T_{MS} (ion source) = 200 °C, time program (oven): T_{0min} = 60 °C, T_{3min} = 60 °C, T_{14min} = 280 °C (heating rate = 20 °C·min^{-1}), T_{19min} = 280 °C, MS: EI, 70 eV). MS and HRMS (EI) were carried out at the Analytical Department, Chemische Institute der Universität Bonn, Germany. Optical rotations were measured on a Jasco P-1020 polarimeter. CD spectra were recorded on a Jasco J-810 Spectropolarimeter in MeCN. Circular dichroic absorptions Δε are reported in cm^2·mol^{-1}. IR spectra were recorded on a Nicolet 360 FTIR spectrometer. Melting points were measured on a Büchi B-540 heating unit.

2-Amino-7-methoxy-5-methyl-4*H*-chromen-4-one (11)

Under argon, *n*-BuLi (2.5 M in hexane, 8.16 mL, 20.4 mmol) was added dropwise to a solution of anhyd MeCN (1.13 mL, 20.39 mmol) in anhyd THF (50 mL) at –78 °C. After stirring for 45 min at –78 °C, a solution of methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**6**; 1.00 g, 5.10 mmol) in THF (20 mL) was added over a 10 min period. After stirring for 30 min at –78 °C, the reaction mixture was allowed to warm to r.t. and was stirred for a further 60 min. The reddish suspension was hydrolyzed with aq NH_4Cl solution (120 mL) and diluted with EtOAc (120 mL). The aqueous layer was separated and extracted with EtOAc (3 × 70 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed at reduced pressure. The crude product was purified by flash column



Scheme 5 Syntheses of *P*- and *M*-kotanin (**2**) and CD spectra (acetonitrile) (*For reaction conditions, see Scheme 4)

chromatography (EtOAc–propan-2-ol, 10:1) and recrystallization (EtOAc) to give product **11** as colorless needles (833 mg, 80%); R_f 0.29; mp 225–226 °C.

IR (KBr): 3347, 3117, 1655, 1616 cm^{-1}.

^1H NMR: (DMSO-d_6): δ = 2.68 (s, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 5.04 (s, 1 H, CH), 6.62 ('s', 2 H, ArH), 7.18 (s, 2 H, NH_2).

^{13}C NMR: (DMSO-d_6): δ = 22.4 (CH_3), 55.5 (OCH_3), 85.8 (CH), 98.5 (CH), 114.56 (C_q), 114.65 (CH), 140.7, 156.3, 160.7, 163.4, 177.5 (C_q).

MS (EI): *m*/*z* (%) = 205 (M^+, 100), 164 ($M^+ - C_3H_2N$, 10).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{11}NO_3$: 205.0739; found: 205.0741.

X-ray Structure Analysis[21]

$C_{11}H_{13}NO_4$: colorless crystals, crystal dimension 0.15 × 0.30 × 0.40 mm^3; M = 223.22; monoclinic, space group $P2_1/c$ (No. 14), a = 10.6943(3), b = 8.1814(3), c = 12.9573(5) Å, β = 114.006(2)°, V = 1035.63(7) $Å^3$, Z = 4, $\mu(Mo_{K\alpha})$ = 0.110 mm^{-1}, T = 123(2) K, $F(000)$ = 472. 4804 reflections up to $2\theta_{max}$ = 50° were measured on a Nonius KappaCCD diffractometer with $Mo_{K\alpha}$ radiation, 1824 of which were independent and used for all calculations. The structure was solved by direct methods and refined to F^2 anisotropically, the H atoms were refined with a riding model [H(O, N) free]. The final quality coefficient $wR2(F^2)$ for all data was 0.0884, with a conventional $R(F)$ = 0.0354 for 158 parameters and 4 restraints.

4-Hydroxy-7-methoxy-5-methyl-2*H*-chromen-2-one (12)

2-Amino-7-methoxy-5-methyl-4*H*-chromen-4-one (**11**; 500 mg, 2.44 mmol) was dissolved in a mixture of MeOH (25 mL) and HCl (32%, 25 mL) and refluxed for 5 h. From the resulting suspension, the MeOH was evaporated at reduced pressure and H_2O was added (50 mL). The colorless precipitate was filtered off, washed with dil. HCl (1%, 30 mL) and air dried at 60 °C to yield the crude product as a colorless solid (455 mg, 90%), pure enough to be applied for the next step. For further purification, the crude product was recrystallized from MeOH as colorless needles (68%); mp 289 °C (dec.).

^1H NMR: (DMSO-d_6): δ = 2.60 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 5.39 (s, 1 H, CH), 6,69 (d, 1 H, ^4J = 2.6 Hz, ArH), 6.74 (d, 1 H, ^4J = 2.6 Hz, ArH), 12.20 (s, 1 H, OH).

^{13}C NMR: (DMSO-d_6): δ = 22.8 (CH_3), 55.7 (OCH_3), 88.7 (CH), 98.7 (CH), 107.6 (C_q), 114.8 (CH), 138.6, 157.0, 161.7, 161.8, 168.9 (C_q).

MS (EI): *m*/*z* (%) = 206 (M^+, 97), 178 ($M^+ - CO$, 6), 164 ($M^+ - C_2H_2O$, 100), 136 ($M^+ - C_3H_2O_2$, 24).

4,7-Dimethoxy-5-methyl-2*H*-chromen-2-one (Siderin, 1)

4-Hydroxy-7-methoxy-5-methyl-2*H*-chromen-2-one (**12**; 250 mg, 1.21 mmol), K_2CO_3 (610 mg, 4.41 mmol) and dimethyl sulfate (0.32 mL, 3.41 mmol) were suspended in acetone (50 mL) and refluxed for 4 h. The mixture was then diluted with H_2O and extracted with $CHCl_3$ (4 × 75 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. After purification by flash column chromatography ($CHCl_3$–EtOAc, 10:1) product **1** was obtained as colorless needles (216 mg, 81%); R_f 0.45; mp 191 °C.

^1H NMR: ($CDCl_3$): δ = 2.56 (s, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 5.48 (s, 1 H, CH), 6.55 (d, 1 H, ^4J = 2.6 Hz, ArH), 6.60 (d, 1 H, ^4J = 2.6 Hz, ArH).

^{13}C NMR: ($CDCl_3$): δ = 23.6 (CH_3), 55.7 (OCH_3), 56.1 (OCH_3), 87.6 (CH), 98.8 (CH), 108.0 (C_q), 115.7 (CH), 138.6, 156.8, 162.0, 163.3, 169.9 (C_q).

MS (EI): *m*/*z* (%) = 220 (M^+, 100), 205 ($M^+ - CH_3$, 3), 192 ($M^+ - CO$, 43), 177 ($M^+ - CO, CH_3$, 28).

2,2′-Diaminobichromenones 13–15; General Procedure

Under argon, *n*-BuLi was added dropwise to a solution of anhyd MeCN in anhyd THF at –78 °C. After stirring for 45 min at –78 °C, the appropriate biaryl orsellinate **7**–**9**, dissolved (suspended in the case of **7**) in THF, was added during 10 min. After stirring for 30 min at –78 °C, the reaction mixture was allowed to warm to r.t. and stirred for a further 60 min. The reddish suspension was hydrolyzed with aq NH_4Cl solution and diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc (3 ×). The organic layers were combined and dried ($MgSO_4$). After removal of the solvent, the crude product was purified by flash column chromatography (EtOAc–propan-2-ol, 3:1) to yield the product as a yellowish solid. The product can be recrystallized (MeOH–EtOAc) to obtain colorless needles.

(*rac*)-2,2′-Diamino-7,7′-dimethoxy-5,5′-dimethyl-4*H*,4′*H*-8,8′-bichromene-4,4′-dione (13)

Compound **13** was obtained from (*rac*)-dimethyl 2,2′-dihydroxy-6,6′-dimethoxy-4,4′-dimethyl-1,1′-biphenyl-3,3′-dicarboxylate (**7**; 100 mg, 0.26 mmol), MeCN (84 mg, 2.05 mmol) and *n*-BuLi (2.5 M in hexane, 0.82 mL, 2.05 mmol) in THF (15 mL) according to the general procedure; yield: 79 mg (75%); R_f 0.41; mp 335 °C (dec.).

IR (KBr): 3475, 1648, 1619, 1581 cm^{-1}.

^1H NMR: (DMSO-d_6): δ = 2.80 (s, 6 H, 2 × CH_3), 3.74 (s, 6 H, 2 × OCH_3), 4.98 (s, 2 H, 2 × CH), 6.88 (s, 2 H, 2 × ArH), 6.89 (s, 4 H, 2 × NH_2).

^{13}C NMR: (DMSO-d_6): δ = 22.9 (2 × CH_3), 55.9 (2 × OCH_3), 85.4 (2 × CH), 107.0 (2 × C_q), 111.3 (2 × CH), 114.8, 140.1, 153.4, 158.3, 163.3, 177.7 (12 × C_q).

MS (EI): *m*/*z* (%) = 408 (M^+, 100), 393 ($M^+ - CH_3$, 58), 377 ($M^+ - OCH_3$, 19).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{20}N_2O_6$: 408.1321; found: 408.1330.

(*rac*)-2,2′-Diamino-7,7′-dimethoxy-5,5′-dimethyl-4*H*,4′*H*-6,6′-bichromene-4,4′-dione (14)

Compound **14** was obtained from (*rac*)-dimethyl 4,4′-dihydroxy-6,6′-dimethoxy-2,2′-dimethyl-1,1′-biphenyl-3,3′-dicarboxylate (**8**; 500 mg, 1.28 mmol), MeCN (468 mg, 11.4 mmol) and *n*-BuLi (1.6 M in hexane, 7.13 mL, 11.4 mmol) in THF (60 mL) according to the general procedure; yield (after recrystallization): 403 mg (77%); R_f 0.36; mp 262 °C (dec.).

IR (KBr): 3386, 3152, 1654, 1602, 1547 cm^{-1}.

^1H NMR: (DMSO-d_6): δ = 2.30 (s, 6 H, 2 × CH_3), 3.69 (s, 6 H, 2 × OCH_3), 5.07 (s, 2 H, 2 × CH), 6.79 (s, 2 H, 2 × ArH), 7.17 (s, 4 H, 2 × NH_2).

^{13}C NMR: (DMSO-d_6): δ = 17.4 (2 × CH_3), 55.9 (2 × OCH_3), 86.1 (2 × CH), 97.0 (2 × CH), 114.4, 123.0, 138.9, 155.8, 158.9, 163.1, 177.8 (14 × C_q).

MS (EI): *m*/*z* (%) = 408 (M^+, 30), 393 ($M^+ - CH_3$, 100), 377 ($M^+ - OCH_3$, 26).

(*rac*)-2,2′-Diamino-7,7′-dimethoxy-5,5′-dimethyl-4*H*,4′*H*-6,8′-bichromene-4,4′-dione (15)

Compound **15** was obtained from (*rac*)-dimethyl 2,4′-dihydroxy-6,6′-dimethoxy-2′,4-dimethyl-1,1′-biphenyl-3,3′-dicarboxylate (**9**; 500 mg, 1.28 mmol), MeCN (468 mg, 11.4 mmol) and *n*-BuLi (1.6 M in hexane, 7.13 mL, 11.4 mmol) in THF (60 mL) according to the general procedure; yield (after recrystallization): 347 mg (66%); R_f 0.38; mp 264 °C (dec.).

IR (KBr): 3386, 3152, 1655, 1604, 1546 cm^{-1}.

^1H NMR: (DMSO-d_6): δ = 2.38 (s, 3 H, CH_3), 2.79 (s, 3 H, CH_3), 3.70 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.96 (s, 1 H, CH), 5.06 (s,

1 H, CH), 6.79 (s, 1 H, ArH), 6.84 (s, 1 H, ArH), 6.86 (s, 2 H, NH_2), 7.14 (s, 2 H, NH_2).

^{13}C NMR: (DMSO-d_6): δ = 17.8 (CH_3), 22.8 (CH_3), 55.85 (OCH_3), 55.88 (OCH_3), 85.4 (CH), 86.0 (CH), 97.0 (CH), 110.5 (C_q), 111.0 (CH), 114.5, 114.8, 119.3, 139.4, 140.0, 153.1, 156.0, 157.9, 159.3, 163.0, 163.3, 177.64, 177.72 (C_q).

MS (EI): *m*/*z* (%) = 408 (M^+, 100), 393 ($M^+ - CH_3$, 21), 377 ($M^+ - OCH_3$, 70).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{20}N_2O_6$: 408.1321; found: 408.1330.

Acidic Hydrolysis of the 2,2′-Diaminobichromenones 13–15; General Procedure

The aminochromenone was dissolved in a mixture of MeOH and 32% HCl (1:1) and refluxed for several hours. From the resulting suspension, the MeOH was evaporated at reduced pressure and H_2O was added. The colorless precipitate was filtered off, washed with dil. HCl (1%) and air dried at 60 °C to yield a crude product as a colorless solid which is pure enough to be used in the next step.

(*rac*)-4,4′-Dihydroxy-7,7′-dimethoxy-5,5′-dimethyl-2*H*,2′*H*-8,8′-bichromene-2,2′-dione (16)

(*rac*)-2,2′-Diamino-7,7′-dimethoxy-5,5′-dimethyl-4*H*,4′*H*-8,8′-bichromene-4,4′-dione (**13**; 69 mg, 0.16 mmol) was refluxed for 13 h in the hydrolytic mixture (20 mL) according to the general procedure; yield: 45 mg (67%); mp >350 °C.

^{1}H NMR: (DMSO-d_6): δ = 2.75 (s, 6 H, 2 × CH_3), 3.75 (s, 6 H, 2 × OCH_3), 5.38 (s, 2 H, 2 × CH), 6.97 (s, 2 H, 2 × ArH), 12.27 (s, 2 H, 2 × OH).

^{13}C NMR: (DMSO-d_6): δ = 23.2 (2 × CH_3), 56.1 (2 × OCH_3), 88.6 (2 × CH), 106.4, 107.9 (4 × C_q), 111.2 (2 × CH), 138.6, 153.7, 159.3, 161.6, 169.1 (10 × C_q).

MS (EI): *m*/*z* (%) = 410 (M^+, 100), 369 (98), 327 (93), 295 (83), 269 (75).

(*rac*)-4,4′-Dihydroxy-7,7′-dimethoxy-5,5′-dimethyl-2*H*,2′*H*-6,6′-bichromene-2,2′-dione (17)

(*rac*)-2,2′-Diamino-7,7′-dimethoxy-5,5′-dimethyl-4*H*,4′*H*-6,6′-bichromene-4,4′-dione (**14**; 100 mg, 0.24 mmol) was refluxed for 3.5 h in the hydrolytic mixture (10 mL) according to the general procedure; yield: 73 mg (73%); mp 206–208 °C.

^{1}H NMR: (DMSO-d_6): δ = 2.22 (s, 6 H, 2 × CH_3), 3.70 (s, 6 H, 2 × OCH_3), 5.47 (s, 2 H, 2 × CH), 6.94 (s, 2 H, 2 × ArH), 12.30 (s, 2 H, 2 × OH).

^{13}C NMR: (DMSO-d_6): δ = 18.2 (2 × CH_3), 56.2 (2 × OCH_3), 89.1, 97.6 (4 × CH), 107.6, 122.7, 136.8, 156.6, 159.9, 161.7, 169.2 (14 × C_q).

(*rac*)-4,4′-Dihydroxy-7,7′-dimethoxy-5,5′-dimethyl-2*H*,2′*H*-6,8′-bichromene-2,2′-dione (18)

(*rac*)-2,2′-Diamino-7,7′-dimethoxy-5,5′-dimethyl-4*H*,4′*H*-6,8′-bichromene-4,4′-dione (**15**; 320 mg, 0.78 mmol) was refluxed for 6 h in the hydrolytic mixture (32 mL) according to the general procedure; yield: 215 mg (67%); mp >350 °C.

^{1}H NMR: (DMSO-d_6): δ = 2.26 (s, 3 H, CH_3), 2.74 (s, 3 H, CH_3), 3.68 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 5.40 (s, 1 H, CH), 5.48 (s, 1 H, CH), 6.94 (s, 1 H, ArH), 6.97 (s, 1 H, ArH), 12.30 (br s, 2 H, 2 × OH).

^{13}C NMR: (DMSO-d_6): δ = 18.2 (CH_3), 23.3 (CH_3), 56.07 (OCH_3), 56.14 (OCH_3), 88.7 (CH), 89.1 (CH), 97.6 (CH), 107.6, 108.0, 110.3 (C_q), 111.1 (CH), 119.2, 137.1, 138.5, 153,5, 156.7, 159.0, 160.1, 161.66, 161.71 (C_q), 169.2 (2 × C_q).

MS (EI): *m*/*z* (%) = 410 (M^+, 100), 382 (45), 368 (90), 351 (94), 295 (69).

O-Methylation of the 4,4′-Dihydroxybicoumarins 16–18; General Procedure

To a stirred solution of 4,4′-dihydroxybicoumarin in anhyd hexamethylphosphoric acid triamide (HMPT) under argon was added NaH. After the evolution of gas had ceased dimethyl sulfate was added and stirring was continued for 2 h. The reaction mixture was diluted with EtOAc (15 mL), washed with 2 M HCl (2 × 15 mL) and brine (15 mL). The brine washing was extracted with $CHCl_3$ (10 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash column chromatography ($CHCl_3$–EtOAc, 3:1) to yield the product as a colorless solid.

4,4′,7,7′-Tetramethoxy-5,5′-dimethyl-2*H*,2′*H*-8,8′-bichromene-2,2′-dione (Kotanin) (2)

Racemic Kotanin (2)

Racemic kotanin (**2**) was obtained from (*rac*)-**16** (55 mg, 0.13 mmol), NaH (60% in oil, 14 mg, 0.33 mmol), dimethyl sulfate (51 mg, 0.40 mmol) and HMPT (0.8 mL) according to the general procedure; yield: 35 mg (59%); R_f 0.31; mp 360 °C (dec.).

^{1}H NMR: ($CDCl_3$): δ = 2.70 (s, 6 H, 2 × CH_3), 3.79 (s, 6 H, 2 × OCH_3), 3.92 (s, 6 H, 2 × OCH_3), 5.50 (s, 2 H, 2 × CH), 6.71 (s, 2 H, 2 × ArH).

^{13}C NMR: ($CDCl_3$): δ = 24.3 (2 × CH_3), 56.1 (2 × OCH_3), 56.3 (2 × OCH_3), 87.9 (2 × CH), 107.6, 108.6 (4 × C_q), 111.6 (2 × CH), 138.7, 153.7, 159.7, 163.3, 170.1 (10 × C_q).

MS (EI): *m*/*z* (%) = 438 (M^+, 57), 421 ($C_{24}H_{21}O_7^+$, 15), 407 ($C_{23}H_{19}O_7^+$, 100).

Atropisomerically pure *P*-(+)- and *M*-(–)-kotanin (*P*-**2**, *M*-**2**) were obtained from the corresponding isomerically pure biarylic esters *P*-(+)-**7** and M-(–)-**7** in 10% and 24% overall yield, respectively, as described for the racemic compound.

P-(+)-Kotanin (*P*-2)

Mp >320 °C; $[\alpha]_D^{25}$ +27.6 (*c* = 0.4, $CHCl_3$) {Lit.[7b] $[\alpha]_D^{20}$ +38.4 (*c* = 0.44, $CHCl_3$); Lit.[3] $[\alpha]_D^{23}$ +40.0 (*c* = 1.65, $CHCl_3$)}.

CD: λ (Δε) = 206 (–55), 215 (–20), 220 (–26), 232 (+7), 238 (+6), 260 (+24), 291 (–17), 322 nm (+32).

MS and NMR spectra identical to those of racemic **2**.

M-(–)-Kotanin (*M*-2)

Mp >320 °C; $[\alpha]_D^{25}$ –37.2 (*c* = 0.3, $CHCl_3$).

CD: λ (Δε) = 206 (+79), 215 (+30), 220 (+37), 232 (–10), 238 (–8), 260 (–34), 291 (+23), 322 nm (–46).

MS and NMR spectra identical to those of racemic **2**.

(*rac*)-4,4′,7,7′-Tetramethoxy-5,5′-dimethyl-2*H*,2′*H*-6,6′-bichromene-2,2′-dione (Isokotanin A, 3)

Racemic isokotanin A (**3**) was obtained from (*rac*)- **17** (55 mg, 0.13 mmol), NaH (60% in oil, 14 mg, 0.34 mmol), dimethyl sulfate (51 mg, 0.40 mmol) and HMPT (0.8 mL) according to the general procedure; yield: 35 mg (68%); R_f 0.37; mp 321 °C (dec.).

^{1}H NMR ($CDCl_3$): δ = 2.22 (s, 6 H, 2 × CH_3), 3.71 (s, 6 H, 2 × OCH_3), 3.93 (s, 6 H, 2 × OCH_3), 5.58 (s, 2 H, 2 × CH), 6.77 (s, 2 H, 2 × ArH).

^{13}C NMR: ($CDCl_3$): δ = 18.9 (2 × CH_3), 56.2 (4 × OCH_3), 88.1 (2 × CH), 97.6 (2 × CH), 108.3, 123.6, 137.4, 156.5, 160.3, 163.3, 170.3 (14 × C_q).

MS (EI): *m*/*z* (%) = 438 (M^+, 100), 410 ($C_{23}H_{22}O_7^+$, 8).

(*rac*)-4,4′,7,7′-Tetramethoxy-5,5′-dimethyl-2*H*,2′*H*-6,8′-bichromene-2,2′-dione (Desertorin C, 4)

a) According to the General Procedure: Racemic desertorin C (**4**) was obtained from (*rac*)-**18** (150 mg, 0.37 mmol), NaH (60% in oil,

30 mg, 0.73 mmol), dimethyl sulfate (111 mg, 0.88 mmol) and HMPT (2 mL) according to the general procedure; yield: 88 mg (55%); R_f 0.34.

*b) From 6,8′-Aminobichromenone **15***: (*rac*)-**15** (30 mg, 0.07 mmol) was dissolved in MeOH (2 mL) and HCl (37%, 1 mL) and refluxed for 4.5 h. The mixture was diluted with MeOH (2 mL) and dimethyl carbonate (2.7 mL, 32.0 mmol), and acetyl chloride (0.38 mL, 5.4 mmol) was added dropwise. After refluxing for a further 24 h, the reaction mixture was poured into H_2O (30 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography ($CHCl_3$–MeOH–formic acid, 30:2:1) to yield desertorin C (**4**) as a colorless solid (11 mg, 34%); R_f 0.57; mp 332 °C (dec.).

^{1}H NMR: ($CDCl_3$): δ = 2.26 (s, 3 H, CH_3), 2.71 (s, 3 H, CH_3), 3.68 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 5.50 (s, 1 H, CH), 5.53 (s, 1 H, CH), 6.70 (s, 1 H, ArH), 6.74 (s, 1 H, ArH).

^{13}C NMR: ($CDCl_3$): δ = 19.4 (CH_3), 24.3 (CH_3), 56.09 (OCH_3), 56.15 (OCH_3), 56.17 (OCH_3), 56.21 (OCH_3), 87.9 (CH), 88.0 (CH), 97.7 (CH), 108.3, 108.6 (C_q), 111.3 (CH), 111.5, 119.5, 137.8, 138.4, 153,5, 156.7, 159.4, 160.5, 163.1, 163.4, 169.9, 170.4 (C_q).

MS (EI): *m*/*z* (%) = 438 (M^+, 100), 407 ($C_{23}H_{19}O_7$, 23).

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References

(1) Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O.; Tasler, S. *Prog. Chem. Org. Nat. Prod.* **2001**, *82*, 1.
(2) Stothers, J. B.; Stoessl, A. *Can. J. Chem.* **1988**, *66*, 2816.
(3) (a) Büchi, G.; Luk, K. C.; Kobbe, B.; Townsend, J. M. *J. Org. Chem.* **1977**, *42*, 244. (b) See also Refs.[2,4b,7a]
(4) (a) Laakso, J. A.; Narske, E. D.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1994**, *57*, 128. (b) Nozawa, K.; Nakajima, S.; Kawai, K.-I.; Udagawa, S. I.; Miyaji, M. *Phytochemistry* **1994**, *35*, 1049.
(5) Nozawa, K.; Seyea, H.; Nakajima, S.; Udagawa, S. I.; Kawai, K. I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1735.
(6) Siderin(**1**): (a) Venturella, P.; Bellino, A.; Piozzi, F. *Tetrahedron Lett.* **1974**, *15*, 979. (b) Chexal, K. K.; Fouweather, C.; Holker, J. S. E. *J. Chem. Soc., Perkin Trans. 1* **1974**, 554. (c) Ahluwalia, V. K.; Kumar, D. *Indian J. Chem., Sect. B* **1976**, *14*, 589.
(7) Kotanin(**2**) (a) *Racemic*: Büchi, G.; Klaubert, D. H.; Shank, R. C.; Weinreb, S. M.; Wogan, G. N. *J. Org. Chem.* **1971**, *36*, 1143. (b) *Stereoselective*: Lin, G.-Q.; Zhong, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1369.
(8) Isokotanin A(**3**) (a) *Racemic*: Lin, G.-Q.; Zhong, M. *Acta Chim. Sin.* **1997**, *55*, 97; *Chem. Abstr.* **1997**, *126*, 211942. (b) *Stereoselective*: Lin, G.-Q.; Zhong, M. *Tetrahedron Lett.* **1996**, *37*, 3015. (c) *Stereoselective*: Bringmann, G.; Hinrichs, J.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E.-M. *Eur. J. Org. Chem.* **2002**, 1096.
(9) Desertorin C(**4**) (a) *Racemic*: Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2425. (b) *Stereoselective:* Kyasnoor, R. V.; Sargent, M. V. *Chem. Commun.* **1998**, 2713. (c) *Steroselective*: Baker, R. W.; Kyasnoor, R. V.; Sargent, M. V.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **2000**, *53*, 487.
(10) The total syntheses of the three biaryl coumarins **2**–**4** require ca. 25 steps according to the literature.
(11) (a) Drochner, D.; Hüttel, W.; Nieger, M.; Müller, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 931; *Angew. Chem.* **2003**, *115*, 961. (b) Drochner, D.; Karl, U.; Nieger, M., Müller, M.; Steglich, W., manuscript in preparation.
(12) Similar reactions are reported in the literature. However, yields are low and reaction conditions cannot be applied to substrate **6**., e.g.: Connor, D. T.; Sorenson, R. J. *J. Heterocycl. Chem.* **1981**, *18*, 587.
(13) Long, R. S. *J. Am. Chem. Soc.* **1947**, *69*, 990.
(14) Basiski, W. *Polish J. Chem.* **1995**, *69*, 376; *Chem. Abstr.* **1995**, *123*, 32908.
(15) Szabó, V.; Borda, J.; Theisz, E. *Acta Chim. Acad. Sci. Hung.* **1980**, *103*, 271; *Chem. Abstr.* **1981**, *94*, 103116.
(16) (a) Suzuki, E.; Katsuragawa, B.; Inoue, S. *Synthesis* **1978**, 144. (b) See also Refs.[7b,8].
(17) This was demonstrated for the 6,8′-bisaminochromenone **15**, which was converted to desertorin C (**4**) in a single step. Hence, the hydrolytic mixture was dehydrated chemically with dimethyl carbonate after no starting material could be detected (TLC). Acetyl chloride was added to generate additional HCl. The yield (34%) is comparable to the overall yield of the two-step procedure (36%).
(18) The low yield in the case of *M*-(–)-**2** is mainly due to a nonoptimized reaction time for acidic hydrolysis.
(19) The isomers of kotanin(**2**) were erroneously mismatched in a previous publication.[11a]
(20) (a) Chiarello, J.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 41. (b) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans.Trans.1* **1981**, 855.
(21) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-215646. Copies of the data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: int. code+44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].