DOI: 10.1002/ejoc.200500517

Facile and Highly Diastereoselective Formation of a Novel Pentacyclic Scaffold by Direct Anodic Oxidation of 2,4-Dimethylphenol

Itamar M. Malkowsky,[a] Christina E. Rommel,[b] Katrin Wedeking,[b] Roland Fröhlich,[b] Klaus Bergander,[b] Martin Nieger,[a] Claudia Quaiser,[c] Ulrich Griesbach,[c] Hermann Pütter,[c] and Siegfried R. Waldvogel*[a,b]

Keywords: Electrochemistry / C–C coupling / Oxidation / Polycycles / Phenols / Spiro compounds

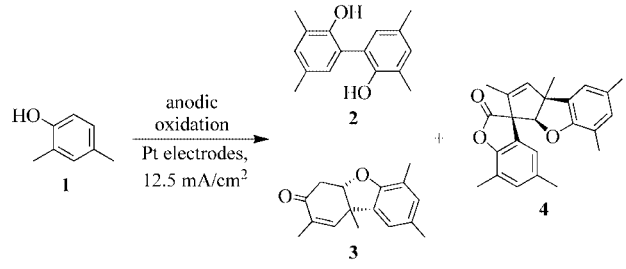
Electrochemical oxidation of 2,4-dimethylphenol directly provides pentacyclic systems being generated by an oxidative trimerization. The major pentacyclic scaffold is exclusively formed as a single diastereoisomer and is easily isolated. Three further pentacyclic compounds which occur in minor quantities were also fully characterized including their solid-state structures.

Introduction

When simple phenols are subjected to oxidative conditions, the homo coupling process to the desired biphenolic products is often accompanied by the formation of higher aggregates.[1] Phenol as well as derivatives exhibiting primary alkyl groups in 4-position mainly yield the so called Pummerer's ketone, which is formed by an *ortho*,*para*-coupling reaction followed by a conjugate cyclization. This structural feature also occurs in many natural products, e.g. (–)-galantamine[2] or lunarin,[3] both containing reduced variants of the primal Pummerer's ketone. The unreduced structure can be found in different calycopterones, which belong to a class of biflavonoids.[4] The formation of such tricyclic moieties is not observed, when instead of simple phenols the corresponding highly *tert*-butylated or more electron rich derivatives are employed as substrates. The side reaction can also be suppressed when using β-naphthols as starting material, wherein the 4-position is protected in a benzoid system.[1]

Results and Discussion

We investigated the direct anodic transformation of 2,4-dimethylphenol (**1**) to the corresponding *ortho*,*ortho*-coupled biphenol **2** (Scheme 1). Earlier reports on the oxidative treatment of **1** with metals in high oxidation states gave reasonable yields of the desired biphenol only in catalytic approaches,[5–7] whereas methods employing stoichiometric amounts of the oxidizing agent or electrochemical oxidation often lack selectivity or resulted in poor yields.[8,9] In the course of our investigations we detected besides biphenol **2** and Pummerer's ketone **3** four other distinct products, which appeared reliably. Depending on the reaction conditions these particular compounds arose in notable quantities. Since the electrolysis of **1** in acidic media promotes the formation of quinols and quinolethers,[10] a variety of neutral and basic electrolytes were studied. The nature of the electrolyte had a severe impact on the reaction outcome. Initial experiments with a neutral and inert electrolyte which is commonly used for oxidative coupling reactions,[11] gave the biphenol to some extent and Pummerer's ketone in a sluggish reaction mixture (Table 1, entry 1). When applying basic conditions **2** was no longer the major product. Mainly ketone **3** and the higher system **4** were found instead (Scheme 1).



Scheme 1. Oxidative coupling reaction of **1**.

The pentacyclic compound **4** formally represents a trimer of **1** involving three dehydrodimerization steps. The structural elucidation by nuclear resonance turned out to be

[a] Present address: Kekulé-Institut für Organische Chemie und Biochemie,
Gerhard-Domagk-Str. 1, 53121 Bonn, Germany
Fax: +49-228-73-9608
E-mail: waldvogel@uni-bonn.de
[b] Westfälische Wilhelms-Universität Münster, Organisch-Chemisches Institut,
Corrensstr. 40, 48149 Münster, Germany
[c] BASF Aktiengesellschaft,
GCI/E-M311, 67056 Ludwigshafen, Germany

Table 1. Reaction conditions for the electrochemical oxidation of **1** (general conditions: T = 20 °C, Pt electrodes, 12.5 mA/cm^2).

Entry	Electrolyte [0.1 M]	[F/mol]	Yield [%]			
			1 (recovered)	**2**	**3**	**4**
1	$TBABF_4$ in CH_2Cl_2	4.5	12	26	3	–
2	NaOH in H_2O	2.4	94	–	3	–
3	LiOH in MeOH	2.2	14	24	35	6
4	NaOH in MeOH	2.4	51	2	11	10
5	$Mg(OEt)_2$ in MeOH	1.7	5	6	27	7
6	$Ca(OMe)_2$ in MeOH	1.7	42	6	7	17
7	$Ba(OH)_2$ in MeOH	1.7	27	3	32	18
8	$Fe(ClO_4)_3$ in MeOH	1.9	62	–	7	–

challenging since only a set of singlets is obtained. The architecture of **4** could be determined by X-ray crystallography of a single crystal (Figure 1). The structure is confirmed by NMR techniques, allowing full characterization of the novel scaffold. Noteworthy, the pentacycle **4** was exclusively obtained as a single diastereoisomer. Detailed investigation of the crude reaction mixture by GC-MS techniques gave no indication of another diastereoisomer with spiro moieties. By the formation of this novel structure from simple phenol **1** three contiguous stereogenic centres were created. The strongly twisted pentacyclic framework exhibits three independent π-systems. The double bond of the central ring as well as the two aromatic moieties in the periphery have different electronic properties, which might be beneficial for subsequent chemical modifications.

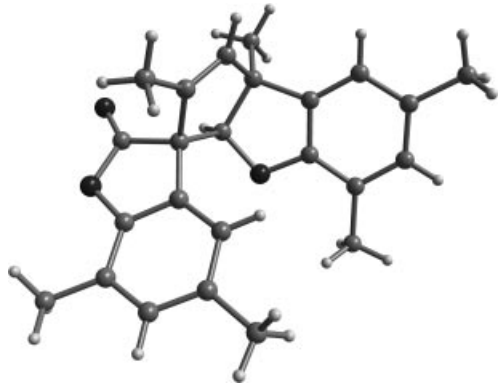
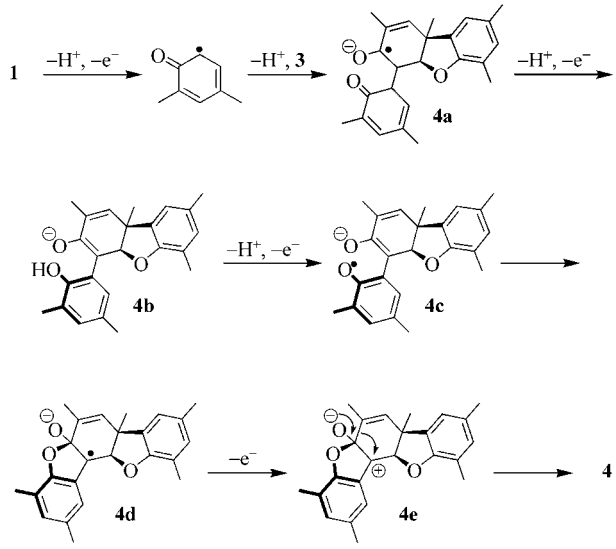


Figure 1. X-ray structure of pentacyclic spiro lactone **4**.

Electrolysis was performed using platinum electrodes in a non-divided standard electrolysis cell.[12] Anodic oxidation of **1** in alkaline aqueous electrolyte resulted in almost no conversion due to the high conductivity (Table 1, entry 2). Therefore, methanol was used as solvent and in the presence of alkali cations the pentacycle **4** appeared. The lithium containing electrolyte promoted the formation of Pummerer's ketone **3**. Switching to the doubly charged chalconide systems the performance of the electrolysis was challenging. With magnesium cations in the electrolyte almost immediately a plaque formation was observed accompanied by a sluggish reaction mixture. Similar preparative problems occurred with calcium, but the desired compound **4** was found to be the major product (Table 1, entry 6). A significant amelioration was achieved by using barium, since **4** precipitated during electrolysis (Table 1, entry 7). Therefore, it could easily be isolated and purified by sublimation. When applying large excess of current to such an electrolysis the yields of pentacyclic **4** went up to 38%, but the low current efficacy and the challenging separation from by-products made it synthetically less attractive.[13] The application of Fe^{III} as mediator for the oxidative coupling process did not result in a useful conversion since only ketone **3** was observed (Table 1, entry 8).

The formation of **4** can be explained by two pathways, on the one hand starting from dehydrodimer **2**, on the other hand through further transformation of **3**. Considering that pentacycle **4** was mainly observed in those experiments that also provided reasonable yields of Pummerer's ketone **3**, the latter is supposed to be the intermediate to **4**. Furthermore, spiro lactone **4** clearly exhibits a Pummerer's ketone unit leading to the proposed mechanism outlined in Scheme 2.



Scheme 2. Proposed mechanism for the formation of pentacyclic spiro lactone **4**.

According to established mechanistic aspects of the phenolic oxidation in basic media we propose the attack of a phenoxy radical of **1** on the enolate of ketone **3**.[11] Further oxidation and deprotonation of **4a** generate the enolate **4b**, which after transformation to the oxygen centred phenoxy radical **4c** undergoes cyclization to **4d**. The high diastereoselectivity of this step arises from the stereogenic information in the backbone of Pummerer's ketone **3**. A fourth single electron oxidation followed by a Meerwein's rearrangement affords the spiro lactone **4**. The specific role of barium or the other cations involved in this stereoselective process is still unclear, but a promoting effect on the initial adduct **4a** seems to be most likely. A large and oxophilic cationic species may serve as template for the transformation, bringing the phenoxy radical of **1** and the enolate derived from **3** together. Thus, the high diastereoselectivity in the formation of **4** could result from the coordination of the substrates. The stereochemical control by divalent cationic species (Table 1, entries 5–7) can easily be demonstrated for intermediate **4b** and its unfavoured atropisomer (Figure 2).

The chelation of a barium cation by the unfavoured conformer creates a high steric demand between the dihydrofurane and the phenol moiety, both pointing onto the same side of the molecule. On the other hand, the favoured conformer is able to chelate a barium cation with less repulsive interactions.

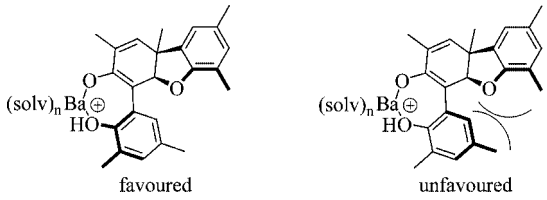


Figure 2. Possible conformations of intermediate **4b** in methanolic barium hydroxide.

The crude product of the electrolysis in methanolic barium hydroxide solution (Table 1, entry 7) contained besides **4** three additional products in smaller quantities, which also turned out to be oxidatively coupled trimers of **1** (Figure 3). More surprisingly, all were found to have a pentacyclic nature.

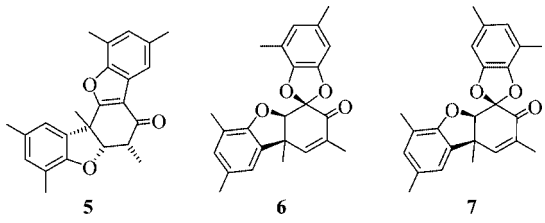


Figure 3. Oxidatively-coupled trimers of **1**.

Compound **5** was isolated in 5% yield as single diastereoisomer, **6** and **7** were obtained in about 2% yield each. Column chromatography provided **6** and **7** as a mixture, which then had to be separated by fractionated crystallization from dichloromethane/heptane. The molecular structures of **5**–**7** were elucidated by X-ray analysis of single crystals (Figure 4). The structures of the epimeric benzodioxoles **6** and **7** are unknown to literature, whereas a hydrated derivative of dibenzofuranone **5** was reported by the oxidation of *p*-cresol with ferric chloride.[14] A thorough investigation of our reaction mixture gave no indication for such an analogue to this hydrated species. From a structural point of view and in accordance to literature, compound **5** is supposed to be an oxidation product from 2,4-dimethylphenol **1** and its *ortho*,*ortho*-coupled dehydrodimer **2**.

Pentacycles **4** and **5** represent basic coupling products of the phenol **1** and a corresponding dehydrodimer by a formal four electron oxidation, therefore two new bonds were generated. However, benzodioxoles **6** and **7** contain an additional oxygen atom in the spiro benzodioxole moiety, as three new bonds were established by a formal six electron oxidation (Scheme 3). Furthermore, the introduced oxygen atom had to originate from the small amount of hydroxide ions in the electrolyte, which acted as nucleophiles during the reaction. To determine the effect of free hydroxides on

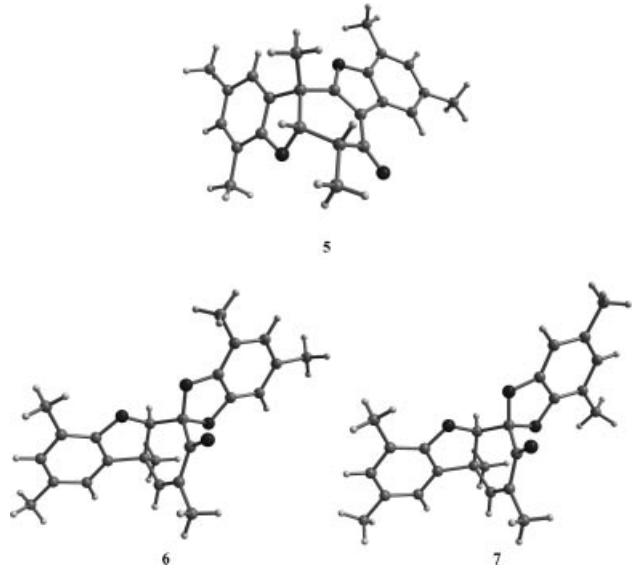
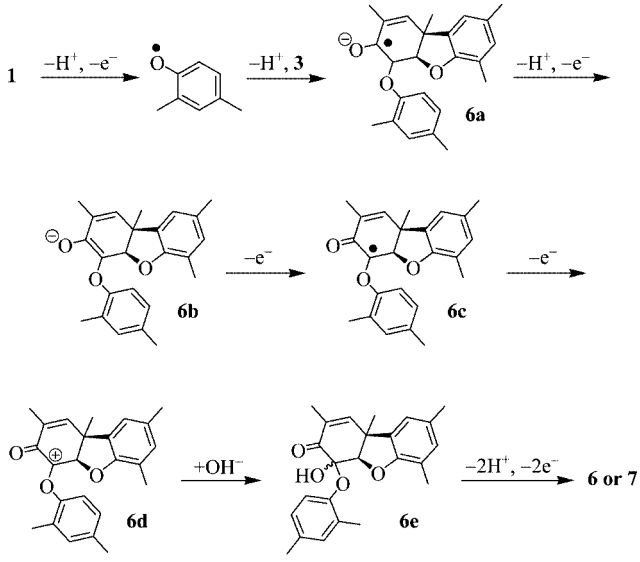


Figure 4. X-ray structure of pentacycles **5**, **6**, and **7**.

the formation of **6** and **7**, we compared the electrolysis in Methanol/NaOH and MeOH/NaOMe. As a result of these experiments, no benzodioxoles **6** or **7** were observed under hydroxide free conditions, whereas these epimers were obtained in 1% yield each using the hydroxide containing electrolyte.



Scheme 3. Proposed mechanism for the formation of benzodioxoles **5** and **6**.

In contrast to the process leading to pentacycle **4**, benzodioxoles **6** and **7** have to derive from the attack of an oxygen centred phenoxy radical on the enolate of **3** leading to intermediate **6a** (Scheme 3). Single electron oxidation and deprotonation provide enolate **6b**, which is transformed by two electron oxidation to cationic **6d**. The nucleophilic attack of a hydroxide anion seems to occur with no diastereoselectivity, despite an adjacent stereogenic centre. Epimers **6e** undergo oxidative cyclization affording benzodioxoles **6** or **7**, respectively.

Conclusions

By simple anodic oxidation employing basic media 2,4-dimethylphenol gives a facile access to novel pentacyclic structures. Besides a major pentacyclic scaffold **4** three minor pentacyclic components were isolated and fully characterized. Since the novel structure **4** is easily prepared and obtained diastereomerically pure, it might serve as addressable scaffold for further chemical modifications. The construction of the pentacyclic architecture most likely involves Pummerer's ketone **3** as a synthetic intermediate. Based on the proposed mechanism the direct synthesis of mixed pentacyclic aggregates of different phenols will be reported in due course.

Experimental Section

General Remarks: All reagents were used in analytical grades. Solvents were desiccated if necessary by standard methods. Column chromatography was performed on silica gel (particle size 63–200 μm, Merck, Darmstadt, Germany) using mixtures of cyclohexane with ethyl acetate as eluents. TLC was done on silica gel 60 F_{254} on glass (Merck, Darmstadt, Germany). Melting points were determined on a Melting Point Apparatus SMP3 (Stuart Scientific, Watford Herts, UK) and were uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrometer Paragon 500. Microanalysis was performed using a Vario EL III (Elementar-Analysensysteme, Hanau, Germany). NMR spectra were recorded on a Bruker ARX 300, AMX 300, or AMX 400 (Analytische Messtechnik, Karlsruhe, Germany) or on a Varian Unity plus 600 MHz (Varian Associated, Palo Alto, CA, USA) using TMS as internal standard or $CDCl_3$ with δ = 7.26 ppm for ^{1}H NMR, and δ = 77.0 ppm for ^{13}C NMR spectroscopy. The NMR spectroscopic data are given in ppm. Mass spectra were obtained on a MAT8200 (Finnigan, Bremen, Germany) employing EI, or on a MS50 (Kratos, Manchester, England) or MAT95XL (Finnigan, Bremen, Germany) employing EI and HRMS.

Anodic Oxidation of 2,4-Dimethylphenol: 2,4-Dimethylphenol (6.1 g, 50 mmol) was dissolved in 0.1 M barium hydroxide octahydrate in methanol (25 mL) and transferred into a non-divided standard electrolysis cell[12] equipped with two platinum sheets as anode and cathode, respectively. At 20 °C a galvanostatic electrolysis with a current density of 12.5 mA/cm² was performed. During the electrolysis vigorous stirring is necessary and the formation of a light brown precipitate can be observed. After ca. 8300 C (1.7 F/mol) were applied the mixture was filtered and the precipitate was washed with methanol (10 mL), dried in vacuo and purified by sublimation (105 °C, 4.3×10^{-3} mbar) yielding analytically pure **4**. The filtrate was diluted with water (100 mL) and extracted with *tert*-butyl methyl ether (TBME, 3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (cyclohexane/ethyl acetate, 98:2) yielded **2**, **3**, **5** and the mixture of **6** and **7**, which was separated by crystallization (dichloromethane/heptane).

3,3′,5,5′-Tetramethyl-2,2′-biphenol (2): 195 mg, 0.8 mmol, 3%. Colourless solid, m.p. 135 °C (cyclohexane, ref.[15] m.p. 134–135 °C). IR (KBr): $\tilde{\nu}$ = 3518, 2918, 1466, 1212, 1185, 1113, 859, 784 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 12 H, CH_3), 5.04 (s, 2 H, OH), 6.85 (s, 2 H, 4-H), 6.98 (s, 2 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1 (3-CH_3), 20.4 (5-CH_3), 122.2 (C-1), 125.2 (C-3), 128.5 (C-6), 130.0 (C-5), 132.0 (C-4), 149.2 (C-2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 242 (100) [M]$^{+\cdot}$, 227 (29), 209 (11), 199 (18), 173 (5), 115 (3), 91 (5), 77 (3) ppm. $C_{16}H_{18}O_2$ (242.13): calcd. C 79.31, H 7.49; found C 79.21, H 7.35.

(4a*RS*,9b*RS*)-4a,9b-Dihydro-2,6,8,9b-tetramethyl-4*H*-dibenzofuran-3-one (3): 1.94 g, 8 mmol, 32%. Colourless solid, m.p. 138 °C (ethanol, ref.[8] m.p. 137 °C). IR (KBr): $\tilde{\nu}$ = 2966, 2986, 1679, 1475, 1369, 1210, 990, 868 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (s, 3 H, 9b-CH_3), 1.71 (s, 3 H, 2-CH_3), 2.14 (s, 3 H, 8-CH_3), 2.28 (s, 3 H, 6-CH_3), 2.77 (dd, ^2J = 17.6, ^3J = 3.9 Hz, 1 H, 4-H^A), 3.06 (dd, ^2J = 17.6, ^3J = 3.9 Hz, 1 H, 4-H^B), 4.61 (dd, ^3J = 3.9, ^3J = 3.9 Hz, 1 H, 4a-H), 6.21 (s, 1 H, 1-H), 6.80 (s, 1 H, 7-H), 6.82 (s, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (6-CH_3), 15.7 (2-CH_3), 20.5 (9b-CH_3), 21.7 (8-CH_3), 37.8 (C-4), 45.2 (C-9b), 86.6 (C-4a), 120.0 (C-9a), 120.1 (C-6), 130.6 (C-9), 130.8 (C-7), 131.9 (C-8), 132.3 (C-2), 145.4 (C-1), 155.3 (C-5a), 195.0 (C-3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 242 (100) [M]$^{+\cdot}$, 227 (96), 199 (49) ppm. $C_{16}H_{18}O_2$ (242.13): calcd. C 79.31, H 7.49; found C 79.15, H 7.52.

(1*SR*,3a*SR*,8a*RS*)-3a,8a-dihydro-2,3a,5,7,5′,7′-hexamethylspiro-[cyclopenta[*b*]benzo[*d*]furan-1,3′(3′*H*)-benzofuran]-2′-one (4): 1.07 g, 3 mmol, 18%. Colourless solid, m.p. 133 °C (methanol). IR (KBr): $\tilde{\nu}$ = 2972, 2921, 1794, 1628, 1481, 1227, 1191, 1120, 1087, 858 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.36 (s, 3 H, 2-CH_3), 1.67 (s, 3 H, 3a-CH_3), 2.03 (s, 3 H, 7-CH_3), 2.19 (s, 3 H, 5′-CH_3), 2.29 (s, 3 H, 7′-CH_3), 2.30 (s, 3 H, 5-CH_3), 5.02 (s, 1 H, 8a-H), 5.80 (s, 1 H, 3-H), 6.37 (s, 1 H, 4′-H), 6.79 (s, 1 H, 6′-H), 6.83 (s, 1 H, 4-H), 6.93 (s, 1 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.3 (2-CH_3), 14.9 (7-CH_3), 15.0 (7′-CH_3), 20.8 (5-CH_3), 20.9 (5′-CH_3), 24.6 (3a-CH_3), 60.2 (C-3a), 68.3 (C-1), 95.5 (C-8a), 119.6 (C-7), 120.1 (C-7′), 120.5 (C-4), 124.8 (C-4′), 130.2 (C-6), 130.6 (C-5), 131.3 (C-6′), 132.7 (C-3b), 133.1 (C-5′), 136.7 (C-3), 136.8 (C-2), 150.2 (C-7a′), 154.7 (C-7a), 178.2 (C-2′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 360 (100) [M]$^{+\cdot}$, 345 (54), 317 (69) ppm. $C_{24}H_{24}O_3$ (360.17): calcd. C 79.97, H 6.71; found C 79.78, H 6.71.

(6*RS*,6a*SR*,11b*SR*)-6a,11b-Dihydro-1,3,6,8,10,11b-hexamethyl-6*H*-benzofuro[2,3-*c*]dibenzofuran-5-one (5): 290 mg, 0.8 mmol, 5%. Colourless solid, m.p. 226 °C (dichloromethane). IR (KBr): $\tilde{\nu}$ = 2923, 1687, 1481, 1214, 1120, 939, 852 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (d, ^3J = 7.0 Hz, 3 H, 6-CH_3), 1.88 (s, 3 H, 11b-CH_3), 2.09 (s, 3 H, 8-CH_3), 2.31 (s, 3 H, 10-CH_3), 2.38 (s, 3 H, 3-CH_3), 2.43 (s, 3 H, 1-CH_3), 3.03 (qd, ^3J = 7.0, ^3J = 3.2 Hz, 1 H, 6-H), 4.76 (d, ^3J = 3.2 Hz, 1 H, 6a-H), 6.78 (s, 1 H, 9-H), 6.88 (s, 1 H, 2-H), 7.15 (s, 1 H, 11-H), 7.66 (s, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.9 (6-CH_3), 14.7 (8-CH_3), 14.8 (1-CH_3), 20.6 (11b-CH_3), 20.9 (10-CH_3), 21.2 (3-CH_3), 42.0 (C-6), 46.3 (C-11b), 92.4 (C-6a), 114.0 (C-4b), 119.1 (C-4), 120.2 (C-8), 120.8 (C-1), 121.7 (C-11), 123.1 (C-4a), 127.3 (C-2), 130.0 (C-11a), 130.7 (C-10), 131.2 (C-9), 134.1 (C-3), 152.8 (C-12a), 154.8 (C-7a), 167.3 (C-11c), 193.1 (CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 360 (26) [M]$^{+\cdot}$, 345 (21), 302 (22), 256 (100), 241 (56), 213 (29). HRMS: calcd. 360.1725; found 360.1723.

(4′*RS*,4a′*RS*,9b′*SR*)-4a′,9b′-Dihydro-4,6-dimethylspiro[benzo[1,3]-dioxol-2,4′-dibenzofuran]-3′-one (6): 112 mg, 0.3 mmol, 2%. Colourless solid, m.p. 201 °C (dichloromethane). IR (KBr): $\tilde{\nu}$ = 2924, 1701, 1496, 1281, 1193, 1027, 978 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (s, 3 H, 9b′-CH_3), 1.81 (d, ^3J = 1.3 Hz, 3 H, 2′-CH_3), 2.17 (s, 3 H, 4-CH_3), 2.23 (s, 3 H, 6′-CH_3), 2.29 (s, 3 H, 6-CH_3), 2.30 (s, 3 H, 8′-CH_3), 4.68 (d, ^3J = 1.8 Hz, 1 H, 4a′-H), 6.34–6.35 (m, 1 H, 1′-H), 6.48 (s, 1 H, 5-H), 6.51 (s, 1 H, 7-H), 6.82 (s, 1 H, 9′-H), 6.84 (s, 1 H, 7′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (4-CH_3), 14.9 (6′-CH_3), 16.1 (2′-CH_3), 20.8 (8′-CH_3), 21.1 (6-CH_3), 23.2 (9b′-CH_3), 48.1 (C-9b′), 87.6 (C-4a′),

106.9 (C-7), 107.3 (C-4′), 119.1 (C-4), 119.7 (C-9′), 120.8 (C-6′), 124.4 (C-5), 130.2 (C-2′), 131.2 (C-8′), 131.4 (C-9a′), 131.4 (C-7′), 131.7 (C-6), 143.8 (C-3a), 145.6 (C-7a), 145.7 (C-1′), 154.4 (C-5a), 187.4 (CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 376 (100) $[M]^{+\cdot}$, 361 (15), 333 (25), 239 (18), 216 (23), 188 (93). HRMS: calcd. 376.1675; found 376.1674.

(4′*SR*,4a′*RS*,9b′*SR*)-4a′,9b′-Dihydro-4,6-dimethylspiro[benzo[1,3]-dioxol-2,4′-dibenzofuran]-3′-one (7): 111 mg, 0.3 mmol, 2%. Colourless solid, m.p. 192 °C (dichloromethane). IR (KBr): $\tilde{\nu}$ = 2925, 1701, 1495, 1203, 1029, 978 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.72 (s, 3 H, 9b′-CH_3), 1.82 (d, ^3J = 1.3 Hz, 3 H, 2′-CH_3), 2.16 (s, 3 H, 4-CH_3), 2.18 (s, 3 H, 6′-CH_3), 2.25 (s, 3 H, 6-CH_3), 2.30 (s, 3 H, 8′-CH_3), 4.68 (d, ^3J = 1.9 Hz, 1 H, 4a′-H), 6.32–6.33 (m, 1 H, 1′-H), 6.47 (s, 1 H, 5-H), 6.68 (s, 1 H, 7-H), 6.83 (s, 1 H, 9′-H), 6.84 (s, 1 H, 7′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (4-CH_3), 15.0 (6′-CH_3), 16.0 (2′-CH_3), 20.8 (8′-CH_3), 21.2 (6-CH_3), 22.9 (9b′-CH_3), 48.1 (C-9b′), 87.3 (C-4a′), 107.3 (C-4′), 107.7 (C-7), 118.4 (C-4), 119.8 (C-9′), 120.9 (C-6′), 123.8 (C-5), 130.1 (C-2′), 131.4 (C-8′), 131.5 (C-7′), 131.6 (C-9a′), 132.0 (C-6), 142.3 (C-3a), 145.8 (C-1′), 147.0 (C-7a), 154.3 (C-5a), 187.3 (CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 376 (100) $[M]^{+\cdot}$, 361 (15), 333 (26), 239 (17), 216 (23), 188 (95). HRMS: calcd. 376.1675; found 376.1676.

X-ray Crystal Structure Analysis for 4: Formula $C_{24}H_{24}O_3$, M = 360.43, colourless crystal 0.50 × 0.35 × 0.20 mm, a = 7.592(1), b = 18.091(3), c = 14.396(2) Å, β = 100.99(2)°, V = 1941.0(5) $Å^3$, $\rho_{calcd.}$ = 1.233 g cm^{-3}, μ = 6.36 cm^{-1}, empirical absorption correction (0.742 ≤ T ≤ 0.883), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, T = 223 K, ω/2θ scans, 8125 reflections collected (±h, ±k, –l), [(sinθ)/λ] = 0.62 $Å^{-1}$, 3974 independent (R_{int} = 0.040) and 3510 observed reflections [$I \geq 2\ \sigma(I)$], 251 refined parameters, R = 0.043, wR_2 = 0.123, max. residual electron density 0.30 (–0.20) e·$Å^{-3}$, hydrogens calculated and refined as riding atoms.

X-ray Crystal Structure Analysis for 5: Formula $C_{24}H_{24}O_3$, M = 360.43, colourless crystal 0.60 × 0.50 × 0.03 mm, a = 8.495(1), b = 10.633(1), c = 20.955(4) Å, β = 93.61(1)°, V = 1889.1(5) $Å^3$, $\rho_{calcd.}$ = 1.267 g cm^{-3}, μ = 6.53 cm^{-1}, empirical absorption correction (0.695 ≤ T ≤ 0.981), Z = 4, monoclinic, space group $P2_1/n$ (No. 14), λ = 1.54178 Å, T = 223 K, ω/2θ scans, 4117 reflections collected (+h, –k, ±l), [(sinθ)/λ] = 0.62 $Å^{-1}$, 3849 independent (R_{int} = 0.042) and 2743 observed reflections [$I \geq 2\ \sigma(I)$], 250 refined parameters, R = 0.052, wR_2 = 0.152, max. residual electron density 0.24 (–0.23) e·$Å^{-3}$, hydrogens calculated and refined as riding atoms.

Data sets were collected with an Enraf Nonius CAD4 diffractometer. Programs used: data collection EXPRESS (Nonius B.V., 1994), data reduction MolEN (K. Fair, Enraf–Nonius B.V., **1990**), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Cryst*. **1990**, *A46*, 467–473), structure refinement SHELXL-97 (G. M. Sheldrick, University of Göttingen, **1997**), graphics DIAMOND 3.0d (Crystal Impact GbR, Bonn, Germany).

CCDC-276238 (for **4**) and -276239 (for **5**) contain the supplementary crystallographic data for this paper. These 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: +44-1223-336-033, E-mail: deposit@ccdc.cam.ac.uk].

X-ray Crystal Structure Analysis for 6: Formula $C_{24}H_{24}O_4$, M = 376.43, colourless crystal 0.30 × 0.15 × 0.10 mm, a = 8.3123(2), b = 14.8628(3), c = 15.9555(3) Å, V = 1971.21(7) $Å^3$, $\rho_{calcd.}$ = 1.268 g cm^{-3}, μ = 0.085 mm^{-1}, Z = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), λ = 0.71073 Å, T = 123 K, 20034 reflections collected ($2\Theta_{max.}$ = 55°, Nonius KappaCCD diffractometer), 4470 independent (R_{int} = 0.048) and 3204 observed reflections [$I \geq 2\ \sigma(I)$], 258 refined parameters, R = 0.0375 [for $I \geq 2\ \sigma(I)$], wR_2 = 0.0863 (all data), max./min. residual electron density 0.166/–0.157 e·$Å^{-3}$, hydrogens calculated and refined as riding atoms. The absolute configuration could not be determined reliably by refinement of Flack's x-parameter [x = –0.4(9)].

X-ray Crystal Structure Analysis for 7: Formula $C_{24}H_{24}O_4$, M = 376.43, yellow crystal 0.50 × 0.45 × 0.40 mm, a = 16.5148(2), b = 14.1036(1), c = 16.8916(2) Å, V = 3934.36(7) $Å^3$, $\rho_{calcd.}$ = 1.271 g cm^{-3}, μ = 0.086 mm^{-1}, Z = 8, orthorhombic, space group $Pbca$ (No. 61), λ = 0.71073 Å, T = 123 K, 59552 reflections collected ($2\Theta_{max.}$ = 55°, Nonius KappaCCD diffractometer), 4498 independent (R_{int} = 0.041) and 3734 observed reflections [$I \geq 2\ \sigma(I)$], 258 refined parameters, R = 0.0456 [for $I \geq 2\ \sigma(I)$], wR_2 = 0.1330 (all data), max./min. residual electron density 0.369/–0.256 e·$Å^{-3}$, hydrogens calculated and refined as riding atoms.

CCDC-276674 (for **6**) and -276675 (for **7**) 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.

Acknowledgments

Financial support by the BASF AG and the International Graduate College "Template-Directed Chemical Synthesis" (DFG) is highly appreciated.

[1] G. Lessene, K. S. Feldman, in: *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, chapter 14.
[2] For reviews see: O. Hoshino, in: *The Alkaloids*, vol. 51 (Ed.: G. A. Cordell), Academic Press, New York, **1998**, 323–424; S. F. Martin, in: *The Alkaloids*, vol. 30 (Ed.: A. Brossi), Academic Press, New York, **1987**, 251–376.
[3] R. B. Herbert, *Nat. Prod. Rep.* **2001**, *18*, 50–65.
[4] M. E. Wall, M. C. Wani, F. Fullas, J. B. Oswald, D. M. Brown, T. Santisuk, V. Reutrakul, A. T. McPhail, N. R. Farnsworth, *J. Med. Chem.* **1994**, *37*, 1465–1470.
[5] W. Qiu, U. S. Patent No. US 6077979, **2000**, p. 3.
[6] A. G. M. Barrett, T. Itoh, E. M. Wallace, *Tetrahedron Lett.* **1993**, *34*, 2233–2234.
[7] D.-R. Hwang, C.-P. Chen, B.-J. Uang, *Chem. Commun.* **1999**, 1207–1208.
[8] For oxidizing agents see: C. G. Haynes, A. H. Turner, W. A. Waters, *J. Chem. Soc.* **1956**, 2823–2829.
[9] For anodic oxidation see: L. L. Miller, R. F. Stewart, *J. Org. Chem.* **1978**, *43*, 1580–1586.
[10] A. Nilsson, A. Ronlan, V. D. Parker, *J. Chem. Soc., Perkin Trans. 1* **1973**, 2337–2345.
[11] J. Grimshaw, *Electrochemical Reactions and Mechanisms in Organic Chemistry*, Elsevier, Amsterdam, **2000**, chapter 6.
[12] H. J. Schäfer, in: *Radicals in Organic Synthesis*, vol.1 (Ed.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, chapter 2.6, p. 257.
[13] Neither by column chromatography or crystallization, nor by fractionated sublimation a higher purity than 94% could be achieved from this crude **4**. Yield was consistently determined by GC and ^1H NMR spectroscopy.
[14] C.-L. Chen, W. J. Connors, W. M. Shinker, *J. Org. Chem.* **1969**, *34*, 2966–2971.
[15] G. Sartori, R. Maggi, F. Bigi, A. Arienti, G. Casnati, *Tetrahedron* **1992**, *48*, 9483–9494.

Received: July 11, 2005
Published Online: October 25, 2005

