

Full Paper

Novel Spiroannulated 3-Benzofuranones. Synthesis and Inhibition of the Human Peptidyl Prolyl *cis/trans* Isomerase Pin1

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Abstract: The novel 3H-spiro[1-benzofuran-2-cyclopentan]-3-one skeleton has been made accessible by different routes. One- and two-step protocols lead to tricyclic and tetracyclic benzofuranones **2** and **3**, respectively. A four-step synthesis to spirocompound **4** is described. The novel spirocyclic benzofuranones display modest to no inhibition of the human peptidyl prolyl *cis/trans* isomerase Pin1.

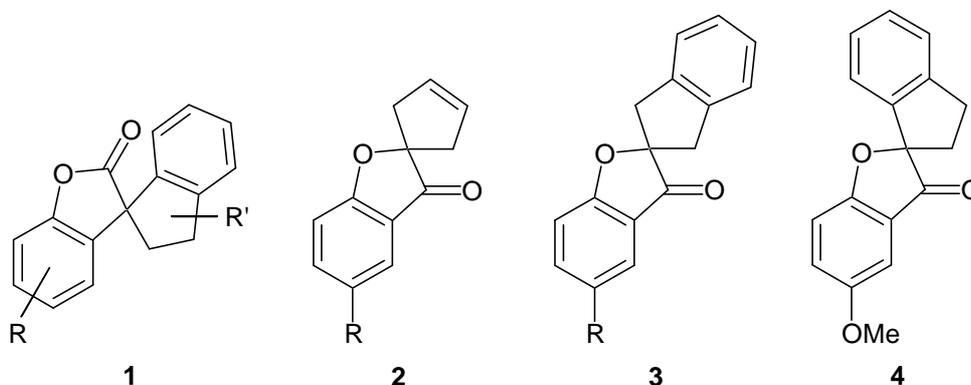
Keywords: Ketones; lithiation; cyclization; metathesis; spiroannulation

Introduction

Spirocyclic benzofuranones have attracted considerable attention with regard to their pharmaceutical activity and the various approaches directed towards their synthesis [1]. Aside from griseofulvin, known as an orally active antimycotic drug [2], synthetic and naturally occurring [3] compounds, which feature the spirobenzofuranone moiety, have been found to display *inter alia* anti-inflammatory [4] and herbicidal activity [5] or act as aromatase inhibitors [6]. We have recently shown that synthetic spirocyclic 2-benzofuranones **1**, involving a lactone skeleton, and aryl indanyl ketones

are efficient inhibitors of the human peptidyl prolyl *cis/trans* isomerase Pin1 [7]. In this article, we describe the synthesis of 3-benzofuranones **2-4**, the first representatives of the novel 3H-spiro-[1-benzofuran-2-cyclopentan]-3-one skeleton and a screening of their inhibition of Pin1.

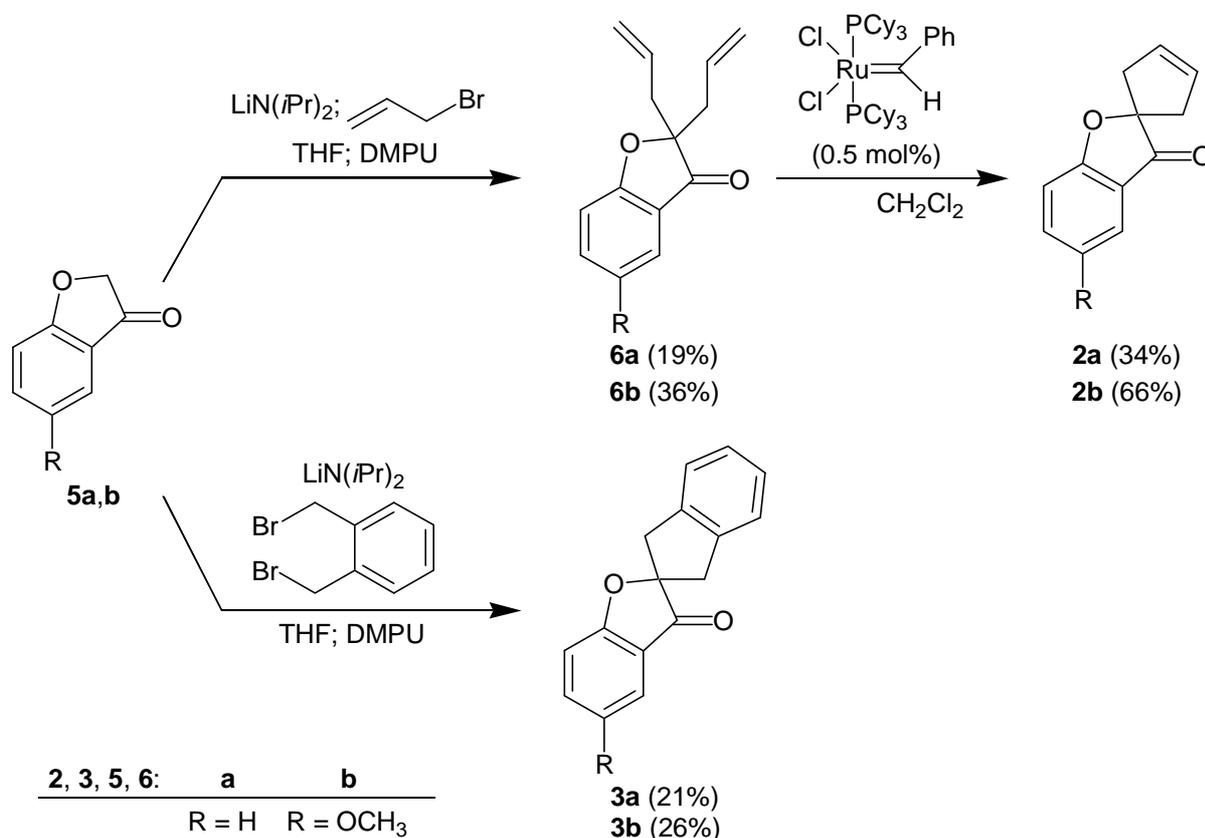
Scheme 1. Spirocyclic lactones **1** and novel spiroannulated 3-benzofuranones **2-4**.



Results and Discussion

Commercially available coumaranone **5a** and the methoxy-substituted derivative **5b** [8] served as the starting materials for the preparation of spirocyclic benzofuranones **2** and **3**, as shown in Scheme 2.

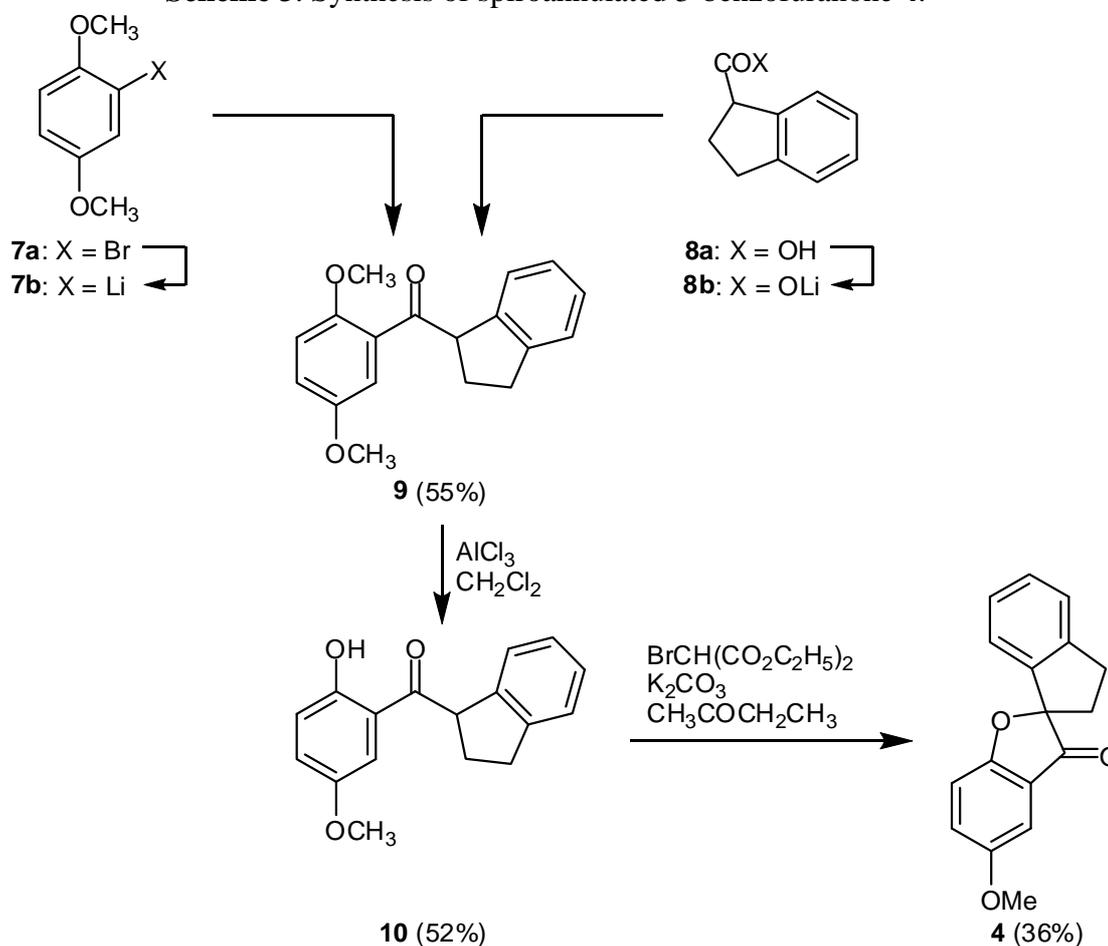
Scheme 2. Synthesis of spiroannulated 3-benzofuranones **2** and **3**.



Thus, deprotonation of the ketones **5a,b** with lithium diisopropylamide and subsequent treatment with allyl bromide led to the dienes **6a,b**. Although the protocol aimed at a double allylation, neither the base nor the electrophile were used in a 2:1 molar ratio with respect to the ketone because these conditions led mainly to the formation of aldol products and other side reactions that obviously consumed the electrophile. Although the allylic alkylation protocol was not thoroughly optimized, it was observed that the additive 1,3-dimethyltetrahydro-2(1*H*)pyrimidone (DMPU) was crucial, because, in its absence, the reaction failed completely. Ring closing metathesis [9] permitted conversion of the dienes **6a,b** into the spirocyclic ketones **2a,b**. A one-step procedure led to the formation of spirocycles **3a,b** when the coumaranones **5a,b** were treated with two equivalents of lithium diisopropylamide and α,α' -dibromoxylene. Again, the yields were moderate due to various side reactions, wherein condensation and subsequent reduction-oxidation processes seem to take place prior to the desired reaction with the electrophile. Again, the protocol was not optimized.

Benzofuranone **4**, isomeric to **3b** and featuring an angular arrangement of the spirocyclic indane moiety was synthesized in a three-step protocol, outlined in Scheme 3. Thus, 2-bromo-1,4-dimethoxybenzene (**7a**) was submitted to a bromine/lithium exchange to give lithioarene **7b** and subsequently allowed to react with the lithium salt **8b** generated from indanecarboxylic acid (**8a**). The ketone **9** thus obtained was selectively deprotected by treatment with aluminum chloride cleaving the methoxy group *ortho* to the carbonyl group.

Scheme 3. Synthesis of spiroannulated 3-benzofuranone **4**.



The conversion of *ortho*-hydroxy aryl ketones to 3-benzofuranones [10] was applied in the final step to the spiroannulated compound **4**. Thus, phenolic ketone **10** was treated with ethyl bromomalonate in the presence of potassium carbonate and butanone, leading to 3-benzofuranone **4** in 36% yield. As a mechanistic explanation of this transformation, it is assumed that ethyl bromomalonate acts as an electrophilic brominating agent [10, 11] that brings about the introduction of the α -bromo substituent into the ketone **10**. Under the basic conditions, a final intramolecular nucleophilic substitution leads to a ring closure. It deserves to be mentioned that this protocol has neither been applied to the generation of quaternary carbon centers nor to the preparation of spirocyclic compounds. Although the yield is moderate and the product is accompanied by unidentified phenolic compounds, the latter can be easily separated by column chromatography. Thus, the protocol provides a ready access to the hitherto unknown spiroannulated system **4**.

The inhibition of human Pin1 by the spiroannulated 3-benzofuranones **2-4** was determined in a protease-free PPlase assay with Suc-Ala-Glu-Pro-Phe-4-nitroanilide as substrate [12]. As shown in Table 1, the spirocompounds **2b**, **3b**, and **4** (entries 2, 4, and 5) caused modest inhibition whereas two related compounds (**2a** and **3a**) were completely inactive (entries 1 and 3). It seems that the 6-methoxy substituent in the benzofuranone fragment has a positive effect on the inhibition.

Table 1. Inhibition of benzofuranones **2-4**.

Entry	Benzofuranones	K_i [μ M]
1	2a	a)
2	2b	65
3	3a	a)
4	3b	100
5	4	77

a) noninhibitory

Conclusions

Benzofuranones **2-4** featuring a novel spirocyclic skeleton have been synthesized in one- to three-step procedures. They were tested as inhibitors of a peptidyl prolyl *cis/trans* isomerase. This study shows, however, that the activity of the spiroannulated 3-benzofuranone derivatives **2-4** is distinctly lower than that obtained with the lactone-type spirocompounds **1** on the one hand [7a] and aryl indanyl ketones [7b, 13] on the other hand.

Experimental

General

Melting points (uncorrected) were determined with a Büchi melting points apparatus. IR spectra: Bruker Vector 22. Mass spectra: Varian MAT 311 A. NMR spectra: Bruker DRX 500 operating at 500 MHz (^1H) and 125 MHz (^{13}C), respectively; all spectra were recorded in CDCl_3 . TLC: silica gel 60 F 254 (Merck). Column chromatography: Machery-Nagel Kieselgel 60 and Merck Kieselgel 60, mesh

size 0.04-0.063. Elemental analyses were carried out with a Perkin Elmer CHN Analysator 263 at the Institute of Pharmaceutical Chemistry, University of Düsseldorf. 2-Coumaranone (**5a**), allyl bromide and 1,3-dimethyltetrahydro-2(1*H*)pyrimidone (DMPU) were purchased from Sigma-Aldrich Chemie GmbH and purified by distillation. Diisopropylamine (purity >99.5 %) was also purchased from Sigma-Aldrich. α,α' -Dibromo-*o*-xylene (purity 96 %) was obtained from the same supplier. It was refluxed over calcium hydride and distilled under nitrogen. General remarks concerning the handling of moisture and air-sensitive compounds are given in ref. [14].

General procedure for the double allylation of benzofuranones 5 (G. P. 1):

A 250-mL Schlenk-flask was equipped with a magnetic stirrer, a thermocouple and a septum and was connected to a combined argon/vacuum line. The air in the flask was replaced by argon. Diisopropylamine (1.49 g, 2.07 mL, 14.7 mmol) and dry THF (52 mL) were injected, and the mixture was stirred at -78°C . A solution of *n*-butyllithium (9.75 mL, 15.6 mmol) in hexane was added at such a rate that the temperature did not exceed -70°C . Stirring was continued at 0°C for 30 min.

In a 50 mL Schlenk-flask, benzofuranone **5** (12.3 mmol) was dissolved in dry THF (20 mL) under argon. This solution was added through a cannula to the mixture of lithium diisopropylamide, prepared as described above, at -78°C . Stirring was continued at the same temperature for 2 h. Freshly distilled allyl bromide (1.73 g, 1.24 mL, 14.3 mmol) and 1,3-dimethyltetrahydro-2(1*H*)pyrimidone (DMPU) (1.89 g, 1.78 mL, 14.7 mmol) were injected. The mixture was allowed to warm up to room temperature overnight and stirred for 48 h at this temperature. The solution was washed with a saturated aqueous solution (50 mL) of NH_4Cl . The aqueous solution was extracted with chloroform (3 times 50 mL). The organic layers were combined and dried with Na_2SO_4 . The solvent was removed in a rotary evaporator and the oily residue was purified by column chromatography on silica gel. According to this procedure the following products were obtained:

2,2-Bis(prop-2-en-1-yl)-2,3-dihydro-1-benzofuran-3-one (6a): Prepared from **5a**; $R_f = 0.57$ (*n*-hexane/ethyl acetate, 10 : 1); yield (relative to **5a**): 19%; $^1\text{H-NMR}$: δ 2.53-2.63 (m, 4H, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.02 (dd, $J = 10.1$ Hz, $J = 1.6$ Hz, 2H, $\text{CH}_2\text{CH}=\text{CHH}$), 5.13 (dd, $J = 17.3$ Hz, $J = 1.6$ Hz, 2H, $\text{CH}_2\text{CH}=\text{CHH}$), 5.59-5.67 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 7.03-7.26 (m, 2H, aromatic H), 7.58-7.60 (m, 2H, aromatic H); $^{13}\text{C-NMR}$: δ 39.9, 91.3, 113.2, 119.8, 121.4, 121.7, 124.2, 130.5, 138.1, 171.8, 203.2; IR (thin film, cm^{-1}): 3050, 2955, 1710, 1490, 1435, 1340, 1275, 1245, 1215, 1140, 1030, 825, 755; MS (70 eV): m/z (%): 214 (28, $[\text{M}]^+$), 199 (6), 185 (6), 172 (100), 147 (12), 145 (40), 128 (56), 115 (32), 91, (28), 76 (27), 65 (36), 55 (42); HRMS: (EI) calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_2$: 214.0994, found 214.0993.

5-Methoxy-2,2-bis(prop-2-en-1-yl)-2,3l-dihydro-1-benzofuran-3-one (6b): Prepared from **5b**; $R_f = 0.57$ (ethyl acetate); yield (relative to **5b**): 36%; $^1\text{H-NMR}$: δ 2.52-2.61 (m, 4H, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.79 (s, 3H, OCH_3), 5.02 (dd, $J = 8.5$ Hz, $J = 1.0$ Hz, 2H, $\text{CH}_2\text{CH}=\text{CHH}$), 5.12 (dd, $J = 17.0$ Hz, $J = 1.0$ Hz, 2H, $\text{CH}_2\text{CH}=\text{CHH}$), 5.58-5.63 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 7.00-7.10 (m, 2H, 4H, and 7-H), 7.24 (dd, $J = 9.1$ Hz, $J = 2.8$ Hz, 1H, 6-H); $^{13}\text{C-NMR}$: δ 40.0, 55.8, 92.0, 103.8, 114.1, 119.7, 121.2, 128.3, 130.6, 154.8, 167.2, 203.5; IR (thin film, cm^{-1}): 3060, 2910, 1710, 1490, 1435, 1340, 1275, 1245, 1215, 1140,

1030, 825, 775; MS (70 eV): m/z (%): 244 (100, $[M]^+$), 217 (13), 203 (88), 175 (21), 150 (32), 124 (12), 123 (19), 91 (15), 79 (18), 55 (27).

General procedure for the preparation of spiroannulated benzofuranones 2 by ring-closing metathesis (G. P. 2):

A mixture of benzylidene-bis-(tricyclohexylphosphino)-dichlororuthenium ("Grubbs catalyst I") (0.016 g, 0.02 mmol) in dry dichloromethane (50 mL) was stirred under argon in a 100-mL flask equipped with a magnetic stirrer, a septum and a connection to the combined argon/vacuum line. At room temperature, diallyl compound **6** (4.0 mmol), dissolved in 6 mL of dry dichloromethane, was added and the mixture was stirred at room temperature for 19 h. The solvent was removed in a rotary evaporator and the residue was purified by column chromatography. According to this procedure the following products were obtained:

3H-Spiro[1-benzofuran-2,1'-cyclopentan]-3'-en-3-one (2a): Prepared from **6a**; colorless oil; $R_f = 0.43$ (chloroform); yield: 34%; $^1\text{H-NMR}$: δ 2.69 (d, $J = 17.0$ Hz, 2H, 2'-H and 5'-H), 2.95 (d, $J = 17.0$ Hz, 2H, 2'-H and 5'-H), 5.81 (s, 2H, 3'-H and 4'-H), 7.07-7.10 (m, 2H, aromatic H), 7.60-7.64 (m, 2H, aromatic H); $^{13}\text{C-NMR}$: δ 44.1, 95.4, 113.4, 120.6, 212.8, 124.5, 127.8, 138.1, 171.4, 203.8; IR (thin film, cm^{-1}): 3060, 2920, 2850, 1710, 1615, 1460, 1325, 1270, 1205, 1135, 1035, 945, 920, 845, 760, 680; MS (70 eV): m/z (%): 186 (100, $[M]^+$), 171 (46), 157 (12), 121 (96), 92 (36). Anal. calcd. for $\text{C}_{12}\text{O}_2\text{H}_{10}$: C, 77.40; H, 5.41. Found C, 77.71; H, 5.41.

5-Methoxy-3H-spiro[1-benzofuran-2,1'-cyclopentan]-3'-en-3-one (2b): Prepared from **6b**; colorless oil; $R_f = 0.71$ (chloroform); yield: 66%; $^1\text{H-NMR}$: δ 2.68 (d, $J = 16.8$ Hz, 2H, 2'-H and 5'-H), 2.94 (d, $J = 16.8$ Hz, 2H, 2'-H and 5'-H), 3.80 (s, 3H, OCH_3), 5.80 (s, 2H, 3'-H and 4'-H), 7.10 (d, $J = 9.1$ Hz, 1H, 7-H), 7.08 (d, $J = 2.8$ Hz, 1H, 4-H), 7.26 (dd, $J = 9.1$ Hz, $J = 2.8$ Hz, 1H, 6-H); $^{13}\text{C-NMR}$: δ 44.1, 55.9, 96.1, 104.1, 114.3, 120.3, 127.8, 128.2, 195.0, 166.9, 204.0; IR (thin film, cm^{-1}): 3070, 2940, 2835, 1705, 1600, 1490, 1440, 1275, 1235, 1205, 1130, 1030, 875, 825, 755; MS (70 eV): m/z (%): 216 (61, $[M]^+$), 204 (10), 151 (100), 150 (57).

General procedure for the preparation of spiroannulated benzofuranones 3 (G. P. 3):

According to G. P. 1, benzofuranones **5** were deprotonated with lithium diisopropylamide. Then, the solution was treated with 1 equivalent (relative to **5**) of α,α' -dibromo-*o*-xylene, dissolved in THF, and 1 equivalent of DMPU. The mixture was warmed up to room temperature. After work up according to G. P. 1, the residue was purified by column chromatography. According to this procedure the following compounds were obtained:

1',3'-Dihydro-3H-spiro[benzofuran-2,2'-indene]-3-one (3a): Prepared from **5a**; colorless oil; $R_f = 0.43$ (*n*-hexane/ethyl acetate, 10:1); yield: 21%; $^1\text{H-NMR}$: δ 3.18 (d, $J = 17.0$ Hz, 2H, 1'-H and 3'-H), 3.55 (d, $J = 17.0$ Hz, 2H, 1'-H and 3'-H), 7.05-7.73 (m, 8H, aromatic H); $^{13}\text{C-NMR}$: δ 44.0, 97.2, 114.0, 121.0, 122.2, 125.0, 127.8, 138.7, 140.0, 171.8, 202.7; IR (thin film, cm^{-1}): 2940, 1710, 1615,

1460, 1330, 1285, 1195, 1020, 915, 685; MS (70 eV): m/z (%): 236 (88, $[M]^+$), 219 (11), 121 (100), 115 (41). Anal. calcd. for $C_{17}H_{12}O_2$: C, 81.34; H, 5.12. Found C, 81.04; H, 5.15.

5-Methoxy-1',3'-dihydro-3H-spiro[1-benzofuran-2,2'-indene]-3-one (3b): Prepared from **5b**; colorless oil; $R_f = 0.73$ (*n*-hexane/ethyl acetate, 2:1); yield: 26%; 1H -NMR: δ 3.18 (d, $J = 16.7$ Hz, 2H, 1'-H and 3'-H), 3.55 (d, $J = 16.7$ Hz, 2H, 1'-H and 3'-H), 3.82 (s, 3H, OCH₃), 7.00 (d, $J = 9.1$ Hz, 1H, 7-H), 7.11 (d, $J = 2.8$ Hz, 1H, 4-H), 7.24-7.28 (m, 5H, remaining aromatic H); ^{13}C -NMR: δ 43.7, 56.0, 97.5, 104.2, 114.5, 120.5, 124.6, 127.3, 128.4, 139.7, 155.0, 166.8, 202.5; IR (thin film, cm^{-1}): 2940, 1700, 1490, 1350, 1280, 1230, 1195, 1125, 1025, 840, 740; MS (70 eV): m/z (%): 266 (19, $[M]^+$), 207 (22), 205 (96), 183 (59), 140 (54), 105 (100), 103 (31), 78 (37), 58 (31).

(2,3-Dihydro-1H-inden-1-yl) (2,5-dimethoxyphenyl)methanone (9):

Under nitrogen, a solution of **7a** (6.015 g, 27.27 mmol) in dry diethyl ether (60 mL) was stirred at $-78^\circ C$ in a two-necked flask, equipped with a magnetic stirrer, a septum and a connection to the nitrogen/vacuum line. A solution of *n*-butyllithium (19.8 mL, 31.6 mmol) was added slowly by syringe, and stirring was continued at the same temperature for 30 min. In a second flask, 1-indanecarboxylic acid (**8a**, 2.25 g, 14.0 mmol) was dissolved in dry diethyl ether (30 mL), and treated at $-78^\circ C$ under stirring with a solution of *n*-butyllithium (8.6 mL, 13.8 mmol). Stirring was continued at $20^\circ C$ for 30 min. The solution of the first flask was added through a cannula, and the mixture was allowed to reach room temperature overnight. Water (20 mL) was added, followed by 2 N hydrochloric acid (3 mL) and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried with magnesium sulfate, the solvent was removed in a rotary evaporator and the residue was purified by column chromatography to give colorless, oily **9** (1.68 g, 55%); $R_f = 0.36$ (chloroform); 1H -NMR: δ 2.32-2.52 (m, 2H, CH₂), 2.88-2.99 (m, 2H, CH₂), 3.76 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 5.12 (dd, $J = 8.5$ Hz, $J = 5.8$ Hz, 1H, COCH), 6.95 (d, $J = 8.9$ Hz, 1H, 3-H), 7.04 (dd, $J = 8.9$ Hz, $J = 3.2$ Hz, 1H, 4-H), 7.09 (d, $J = 3.2$ Hz, 1H, 6-H), 7.05-7.26 (m, 4H, indenyl aromatic H); ^{13}C -NMR: δ 29.5, 32.5, 56.9, 57.2, 58.6, 113.6, 115.1, 119.7, 125.1, 125.6, 126.6, 127.6, 129.6, 142.6, 145.1, 153.0, 154.0, 203.9; IR (thin film, cm^{-1}): 2940, 1675, 1495, 1465, 1410, 1280, 1225, 815, 755; MS (70 eV): m/z (%): 282 (4, $[M]^+$), 165 (100), 150 (6), 122 (7), 115 (10), 92 (6), 77 (10).

2-(2,3-Dihydro-1H-inden-1-ylcarbonyl)-4-methoxyphenol (10):

In a 250-mL flask equipped with a drying tube, **9** (1.68 g, 7.64 mmol) was dissolved in dichloromethane and cooled to $0^\circ C$. Aluminum chloride (5 g, 37.5 mmol) were added, and stirring was continued at $0^\circ C$ for 1 h and at room temperature for another 70 min. Water (20 mL) and 2 N hydrochloric acid (20 mL) were added carefully. The organic layer was separated and the aqueous phase was extracted three times with chloroform. The combined organic layers were dried with magnesium sulfate, the solvent was removed under reduced pressure, and the residue was purified by column chromatography to give crystalline, yellow **10** (1.06, 52%); $R_f = 0.59$ (chloroform); mp. $105-106^\circ C$; 1H -NMR: δ 2.41-2.56 (m, 2H CH₂), 2.98-3.24 (m, 2H, CH₂), 3.82 (s, 3H, OCH₃), 5.03 (t, $J =$

7.7 Hz, 1H, COCH), 6.98 (d, $J = 9.1$ Hz, 1H, 6-H), 7.17 (dd, $J = 9.1$ Hz, $J = 3.0$ Hz, 1H, 5-H), 7.39 (d, $J = 3.0$ Hz, 1H, 3-H), 7.10-7.33 (m, 4H, indenyl aromatic H), 12.0 (s, 1H, OH); $^{13}\text{C-NMR}$: δ 30.0, 32.0, 52.2, 56.0, 113.4, 118.6, 119.6, 124.3, 124.9, 125.0, 126.5, 127.7, 141.0, 144.7, 151.8, 157.8, 206.3; IR (thin film, cm^{-1}): 3060, 3006, 2939, 2846, 1644, 1615, 1481, 1418, 1353, 1242, 1212, 1165, 1039, 829, 788, 753; MS (70 eV): m/z (%): 268 (21, $[\text{M}]^+$), 151 (100), 117 (12), 115 (13), 95 (5). Anal. calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_3$: C, 76.10; H, 6.01. Found C, 75.82; H, 5.98.

5-Methoxy-2',3'-dihydro-3H-spiro[1-benzofuran-2,1'-indene]-3-one (4):

Under nitrogen, a mixture of **10** (57.6 mg, 0.215 mmol), diethyl bromomalonate (77 mg, 0.322 mmol), anhydrous potassium carbonate (89 mg, 0.645 mmol) and dry butanone were refluxed for 9 h. The mixture was filtered and the residue was washed with butanone. The combined filtrates were evacuated and the residue was submitted to a column chromatography. The yellowish crude product was recrystallized from ethanol to give **4** in 36% yield (20.5 mg); $R_f = 0.41$ (chloroform); mp 129°C ; $^1\text{H-NMR}$: δ 2.45 (ddd, $J = 13.8$ Hz, $J = 4.7$ Hz, $J = 8.5$ Hz, 1H, CHH), 2.67 (ddd, 1H, $J = 13.8$ Hz, $J = 6.5$ Hz, $J = 8.5$ Hz, 1H, CHH), 3.15-3.33 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 6.89 (d, $J = 7.7$ Hz, 1H), 6.96 (d, 1H, $J = 9.0$ Hz), 7.04 (d, $J = 2.8$ Hz, 1H), 7.09 (pseudo-*t*, $J = 6.8$ Hz, 1H), 7.20 (m, 1H), and 7.27 (m, 1H) (aromatic H); $^{13}\text{C-NMR}$: δ 30.6, 35.9, 55.9, 98.9, 104.3, 114.3, 120.2, 123.2, 125.2, 127.2, 128.3, 129.8, 140.1, 145.6, 155.0, 167.4, 202.8; IR (thin film, cm^{-1}): 3070, 2921, 2851, 1708, 1604, 1551, 1481, 1430, 1341, 1263, 1206, 1158, 1095, 1026, 998, 938, 915, 836, 801, 755, 652; MS (70 eV): m/z (%): 266 (56, $[\text{M}]^+$), 151 (100), 123 (11), 115 (24), 32 (68); HRMS: (EI) cald. for $\text{C}_{17}\text{H}_{14}\text{O}_3$: 266.0943, found 266.0940.

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Sample Availability: Samples of the compounds **6a**, **9**, **10**, **4** are available from authors.