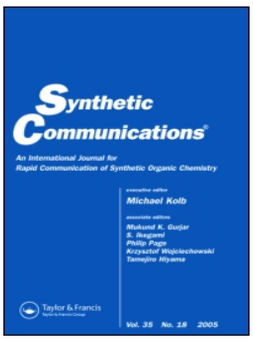

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$SbCl_3$-catalyzed solvent-free Friedel–Crafts reaction of phenols with mandelic acids to 3-aryl benzofuran-2(3*H*)-ones: Synthesis of spirocyclic 2,3-dihydrobenzofuran-2-ones

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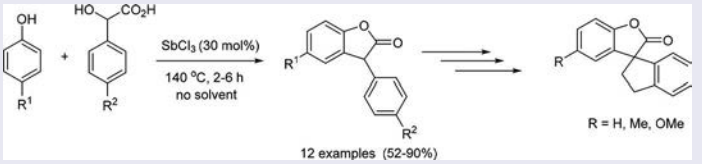
ABSTRACT

A facile, $SbCl_3$-catalyzed, one-pot, tandem Friedel–Crafts/lactonization reaction of phenols and mandelic acids has been developed under solvent-free conditions to afford 3-aryl benzofuran-2(3*H*)-ones in good to high yields (52–90%). Additionally, the utility of 3-aryl benzofuran-2(3*H*)-ones is demonstrated by using them as precursors in the synthesis of a new class of spirocyclic benzofuran-2-ones using classical synthetic methodologies.

GRAPHICAL ABSTRACT



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Introduction

3,3-Disubstituted benzofuran-2(3*H*)-ones are important building blocks in organic synthesis as they have been used in the total synthesis of a large number of biologically and pharmaceutically active natural products.[1] They display various activities including antihypoxic,[2a] antispasmodic,[2b] and neurotropic activity.[2a] Classically, synthesis of 3,3-disubstituted benzofuran-2(3*H*)-ones is achieved from 3-substituted benzofuran-2(3*H*)-ones through carbanion-induced nucleophilic attack on the α-carbon atom with a variety of electrophiles. This has been demonstrated in the synthesis of a large number of biologically active 3,3-disubstituted benzofuran-2(3*H*)-ones[3] including anticancer compounds diazonamide A,[4] hopeahainol A,[5] yuccaol A,[6] and radulifolin.[7] Also, 3-substituted benzofuran-2(3*H*)-ones, namely 5,7-di-*tert*-butyl-3-(3,4-dimethylphenyl)benzofuran-2(3*H*)-one and its analogs, are important carbon-centered radical antioxidants.[8] In spite of their importance as precursors for the synthesis of 3,3-disubstituted benzofuran-2(3*H*)-ones, direct synthesis of 3-substituted benzofuran-2(3*H*)-ones from readily available starting material in good yields is limited. Therefore, development of an efficient and flexible method for 3-substituted

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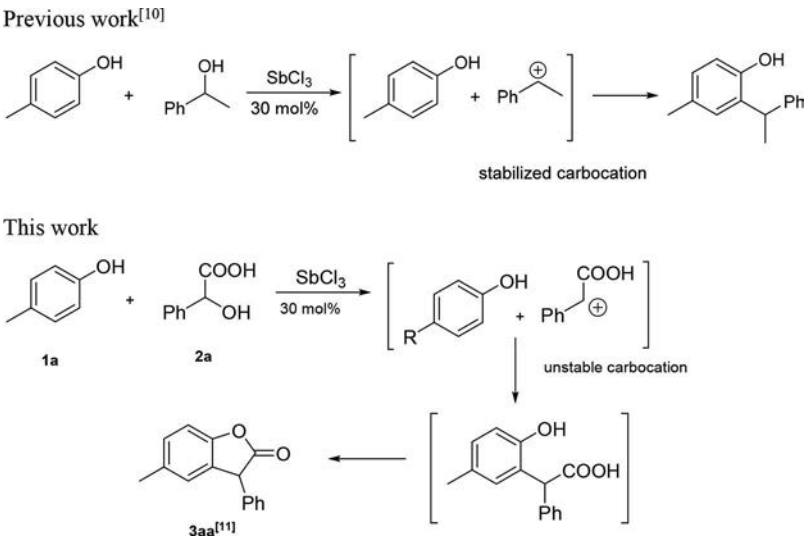
Supplemental material (full experimental details and ^1H and ^{13}C NMR spectra) can be accessed on the publisher's website.



Scheme 1. $SbCl_3$ catalyzed Friedel–Crafts alkylation of phenols with benzylic alcohols.

benzofuran-2(3*H*)-one skeletons using inexpensive starting materials/reagents remains a challenging task to synthetic organic chemists.

Although Friedel–Crafts (F-C) reaction of phenols with mandelic acids is the most convenient approach to the synthesis of 3-aryl benzofuran-2(3*H*)-ones, only a few reports are available so far on this transformation, possibly due to the formation of destabilized benzylic carbocation attached to carboxylic acid function[3f] (Scheme 1). So far F-C alkylation of phenols/aryl alkyl ethers with mandelic acid has been accomplished in poor to moderate yields using strong acid catalysts ($HClO_4$, H_2SO_4, and $MeSO_3H$).[9] However, to the best of our knowledge, no systematic study on this reaction using mild Lewis acids has been reported to date. Herein, we report an efficient one-pot synthesis of 3-aryl benzofuran-2(3*H*)-ones from $SbCl_3$-catalyzed F-C alkylation/lactonization of phenols with mandelic acids and their utility in the synthesis of spirocyclic benzofuran-2-one derivatives.

Results and discussion

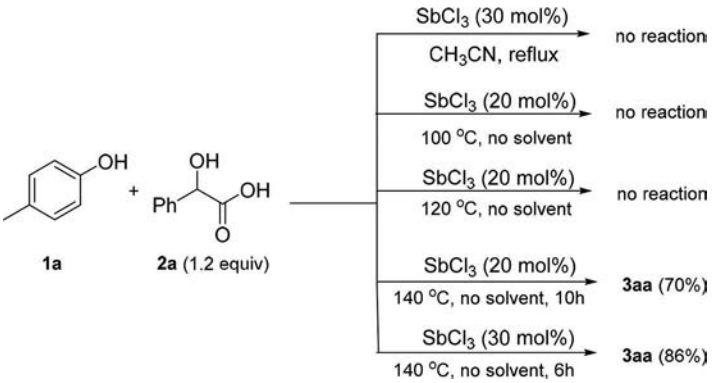
In recent years F-C alkylation of electron-rich aromatic/heteroaromatic compounds with alcohols using Brønsted acids/Lewis acids as catalyst has emerged as an important environmentally friendly protocol as water is the only by-product formed.[10a] Earlier, we have developed an efficient protocol for F-C alkylation of phenols/alkyl aryl ethers with benzylic alcohols using $SbCl_3$ as catalyst.[10b] To explore its catalytic potential further, we wanted to evaluate its efficacy in the F-C reaction of phenols with less stabilized benzylic cation such as carbocation derived from mandelic acid. Mechanistically, F-C alkylation of 4-substituted phenol with mandelic acid is expected to form the intermediate 2-(2-hydroxyaryl)-2-phenylacetic acid, which in turn is likely to undergo in situ lactonization to form 3-phenyl 2,3-dihydrobenzofuran-2-one skeleton (Scheme 1).

At the outset, a model reaction of 4-methylphenol (**1a**) with mandelic acid (**2a**) was chosen for optimization of reaction conditions. Thus, reaction of **1a** (5 mmol) with **2a**

(6 mmol) in acetonitrile (2 mL/mmol) using a catalytic amount of $SbCl_3$ (0.5 mmol, 10 mol%) was carried out both at ambient temperature (25 °C) as well as under refluxing conditions (90 °C). Disappointingly, in both the cases, no reaction occurred to get 5-methyl-3-phenyl benzofuran-2(3*H*)-ones (**3aa**). Also, increase in catalyst loading up to 30 mol% could not initiate the reaction for the formation of **3aa** (Scheme 2).

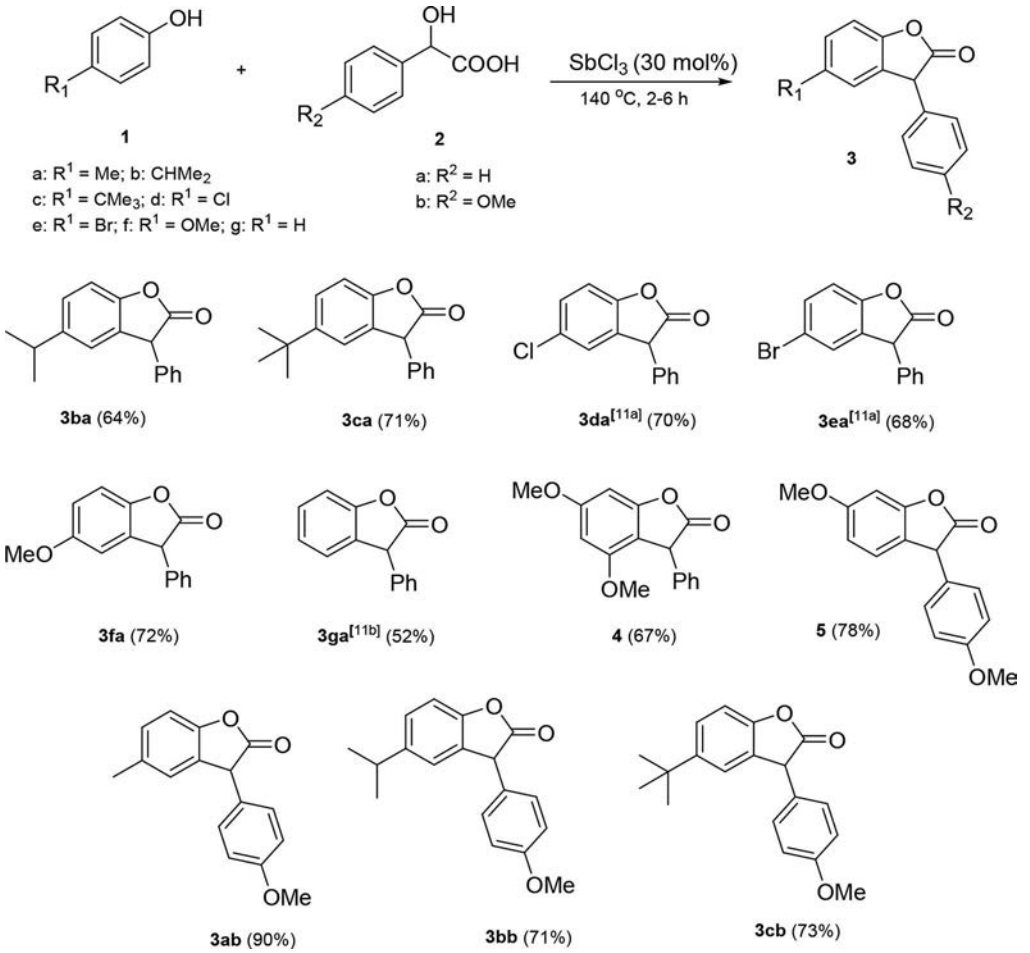
During the course of our previous work on microwave-assisted $SbCl_3$-catalyzed F-C reaction of phenols with benzylic alcohols,[10] it was noticed that the reaction rate is drastically reduced on dilution with solvent. Keeping this in view as well as the requirement of green synthesis for environmental concern, we planned to carry out the reaction under solvent-free conditions. Initially, reaction of **1a** (5 mmol) and **2a** (6 mmol) with $SbCl_3$ (1.0 mmol, 20 mol%) was carried out at 100 °C without any solvent when no reaction was observed. Increase in reaction temperature to 120 °C also could not initiate the reaction. To our surprise, when the reaction temperature was increased to 140 °C, a smooth reaction took place to afford **3aa** in good yield (70%) in 10 h. Moreover, increase in catalyst loading to 30 mol% helped in increasing the reaction rate, leading to completion of the reaction in 6 h to afford **3aa**[11] as sole product in 86% yield (Scheme 2). However, during the entire course of the reaction we could not detect the formation of the intermediate, 2-(2-hydroxy-5-methylphenyl)-2-phenylacetic acid (Scheme 1). The compound **3aa** was fully characterized by ^{1}H NMR, ^{13}C NMR, and DEPT (Distortionless Enhancement by Polarization Transfer in NMR) and compared with the reported values. Further increase in catalyst loading (50 mol%) did not reduce the reaction time significantly and therefore use of 30 mol% of catalyst without using any solvent was considered as optimized reaction conditions and used for subsequent studies.

To see the generality of the solvent-free F-C reaction, alkylation of a various substituted phenol derivatives (**1b–e**) with both **2a** and 4-methoxymandelic acid (**2b**) was explored. As revealed in Table 1, reaction of *p*-substituted phenols with both electron-donating as well as electron-withdrawing substituents reacted smoothly with **2a/2b** to afford the corresponding 3-aryl benzofuran-2(3*H*)-ones in good to high yields. Reaction of phenol (**1g**) with mandelic acid, however, afforded the expected 3-phenyl benzofuran-2(3*H*)-one **3ga,** albeit in moderate yield (52%), possibly due to alkylation at the electron-rich *para*-position as a side reaction. Similarly, reaction of 3,5-dimethoxyphenol and 3-methoxyphenol with **2a** and **2b** respectively yielded corresponding benzofuranones **4** and **5** respectively in good



Scheme 2. Condition optimization.

Table 1. Scope of the reaction.



yields. Importantly, the rate of the reactions with **2b** as electrophile was faster, as exemplified by the completion of the reactions within 2–2.5 h as compared to that with **2a** (4–6 h).

Spirocyclic benzofuran-2-one units are privileged structural skeletons found in many natural and pharmaceutically important compounds with a broad range of biological activities[12] (Fig. 1). For example, spirocyclic indeno-benzofuran-2-one **9c** was used as specific inhibitor for (PO_3H_2)Ser/(PO_3H_2)Thr-Pro-specific peptidyl-prolyl- *cis/trans*-isomerases.[13] Also, both abiesinol E (**10**) and rosmadial (**11**) have displayed promising cytotoxic activity against human cancer cell lines.[14] Although few methods are reported on the synthesis of spirocyclic benzofuran-2-ones,[15] more efficient strategies for the synthesis of those are still in high demand. Because of their intriguing biological profile, the possibility of developing an efficient route to the synthesis of spirocyclic benzofuranone using 3-aryl benzofuran-2-(3*H*)-ones as synthon appeared interesting to us.

From a retrosynthetic perspective, we felt that synthesis of spirocyclic benzofuran-2-ones (**9**) could be accomplished through alkylation of 3-aryl benzofuran-2(3*H*)-ones at 3-position at the first step. Accordingly, **3aa** was alkylated at 3-position with *tert*-butyl

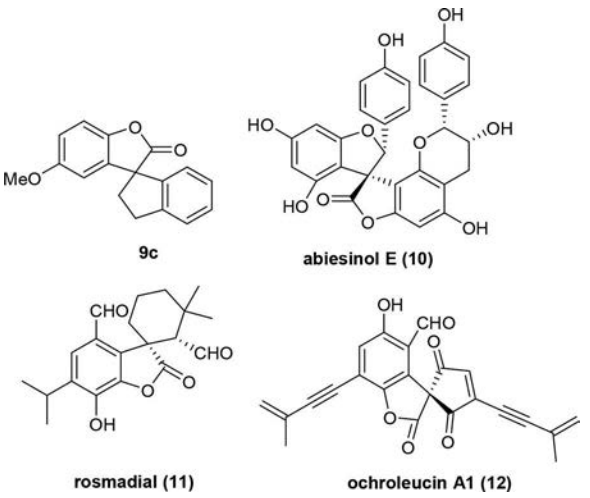
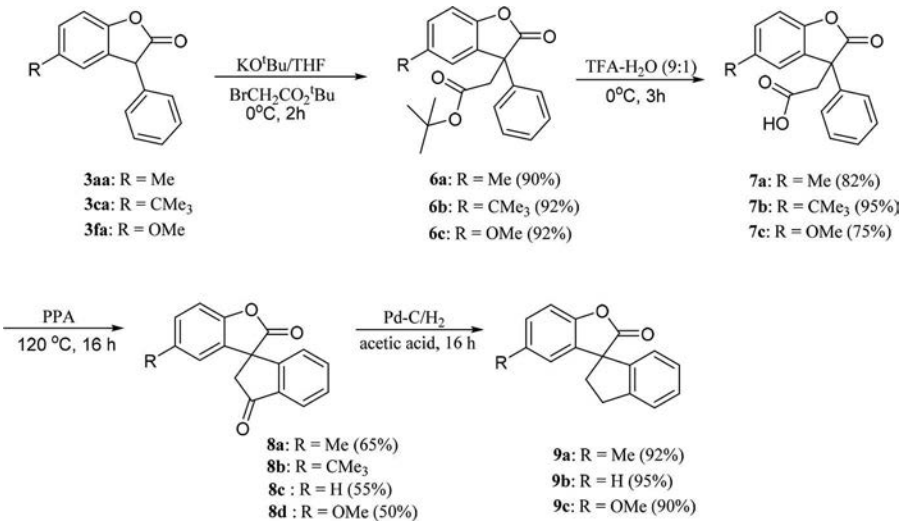


Figure 1. Representative biologically active spiro-cyclic benzofuran-2-ones.

bromoacetate[3m] to afford corresponding lactone ester **6a** in 90% yield, which was subsequently hydrolyzed with trifluoroacetic acid[16] to get 5-methyl dihydrobenzofuran-2-one-3-acetic acid (**7a**) in high yield (82%). Intramolecular cyclo-dehydration of **7a** with polyphosphoric acid[17] (PPA) at 120 °C led to smooth conversion to spiro-cyclic benzofurandione **8a** (65%). Finally, catalytic hydrogenation of **8a** with Pd-C/H_2 in acetic acid as solvent led to reductive deoxygenation of ketone to methylene unit,[18] affording **9a** as the only product in excellent yield (Scheme 3). In a similar way benzofuran-2-one **3ca** was converted to corresponding carboxy benzofuran-2-one **7b** in good yield. However, treatment of **7b** with PPA under identical reaction conditions as that of **7a** led to



Scheme 3. Elaboration of 3-aryl benzofuran-2(3*H*)-ones to the syntheses of spirocyclic benzofuran-2-ones.

cyclo-dehydration with concomitant de-*tert*-butylation to afford spirocyclic benzofuran-dione **8c** as the only product instead of expected product **8b**. As in the case of **9a, 8c** was smoothly converted to **9b** under catalytic hydrogenation conditions. Also, compound **3fa** was converted to **9c** following a similar procedure adopted for **9a**. Incidentally, this is the first report on synthesis of spirocyclic benzofuran-2-ones from 3-aryl benzofuran-2(3*H*)-ones.

Conclusion

In summary we have developed an easy and efficient $SbCl_3$-catalyzed synthesis of 3-aryl benzofuran-2(3*H*)-ones in good to high yields from inexpensive and readily available starting materials such as mandelic acid and substituted phenols under solvent-free conditions. The synthetic utility of these molecules has been demonstrated by the synthesis of a new class of potential bio-active spirocyclic benzofuran-2-ones through alkylation of 3-aryl benzofuran-2(3*H*)-ones at 3-position with *tert*-butyl bromoacetate as a key step. To the best of our knowledge, this is the first report on synthesis of spirocyclic benzofuran-2-ones from 3-aryl benzofuran-2(3*H*)-ones.

Experimental

General procedure for $SbCl_3$-catalyzed Friedel–Crafts reaction/lactonization of phenols with mandelic acids to 3-aryl benzofuran-2-ones

In a flame-dried, three-necked, round-bottom flask, a mixture of phenol/substituted phenol (**1**) (5 mmol), mandelic acid/4-methoxymandelic acid (**2**) (6 mmol), and $SbCl_3$ (1.5 mmol) was taken and the mixture was heated at 50 °C with stirring under a nitrogen atmosphere when the mixture turned into a viscous oil. In the case of high-melting phenols, a little amount of acetonitrile (~0.2 mL/mmol) was used to make a paste. The viscous oil/paste heated at 140 °C under stirring. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction (4–6 h for mandelic acid and 2–2.5 h for 4-methoxymandelic acid), the mixture was cooled to ambient temperature and quenched with cold 10% aqueous $NaHCO_3$ solution. The reaction mixture was diluted with ethyl acetate passed through a Celite bed to remove antimony salts. The filtrate was extracted with ethyl acetate (3 × 40 mL) and the combined organic layer was washed with water and brine and dried (Na_2SO_4). Removal of solvent afforded a thick mass, which was purified by silica-gel column chromatography to afford pure 3-aryl benzofuran-2(3*H*)-ones.

5-Methyl-3-phenyl-benzofuran-2(3H)-one[11] (3aa)

Yield: 965 mg (86%); colorless solid; mp 78–79 °C; IR ($CHCl_3$): 2899, 1790, 1620, 1597, 1292 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.05 (m, 8H), 4.90 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.29, 151.70, 135.27, 134.05, 129.62, 128.97, 128.16, 128.01, 126.92, 125.61, 110.27, 49.74, 20.93. Anal. calcd. for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.37; H, 5.37.

Typical procedure for the synthesis of tert*-butyl 2-(2,3-dihydro-5-methyl-2-oxo-3-phenylbenzofuran-3-yl)acetate (6a)*

To an ice-cooled solution of potassium *tert*-butoxide (1.50 g, 13.37 mmol) in dry tetrahydrofuran (THF, 30 mL) under argon, a solution of **3aa** (2.0 g, 8.92 mmol) in THF (20 mL) was added. The reaction mixture was stirred at 0 °C for 2 h and then a solution of *tert*-butyl bromoacetate (2.60 g, 13.37 mmol) in THF (20 mL) was added to the reaction mixture dropwise. Stirring was continued at 0 °C. After completion of the reaction (cf. TLC, 2 h), the reaction mixture was quenched with ice-cooled water (20 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with H_2O and brine and then dried (Na_2SO_4). Removal of solvent in vacuo followed by column chromatography (silica gel, using petroleum ether–ethyl acetate as eluent) afforded pure **6a.** Yield: 2.720 g (90%); colorless solid; mp 100–101 °C; IR ($CHCl_3$): 3022, 2981, 1803, 1729, 1486 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.33 (m, 5H), 7.17 (d, J = 8.5 Hz, 1H), 7.12 (s, 1H), 7.08 (d, J = 7.5 Hz, 1H), 3.62 (d, J = 15.5 Hz, 1H), 3.08 (d, J = 16.0 Hz, 1H), 2.38 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.46, 167.84, 151.65, 138.11, 133.85, 129.71, 129.15, 128.86, 128.04, 126.39, 125.15, 110.46, 82.02, 52.72, 44.25, 27.29, 21.07. HRMS (ESI): Calcd for $C_{21}H_{22}NaO_4$ $(M + Na)^+$: 361.1410; found: 361.1412.

Typical procedure for the synthesis of 2-(2,3-dihydro-5-methyl-2-oxo-3-phenylbenzofuran-3-yl)acetic acid (7a)

To an ice-cooled solution of **6a** (2.5 g 7.39 mmol) in dichloromethane was added 10 mL aqueous solution of TFA (TFA/H_2O = 9:1) and the mixture was stirred at 0 °C. After completion of reaction (cf. TLC, 3 h) a saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture to neutralize acid. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts were washed with H_2O and brine, and dried (Na_2SO_4). Removal of solvent in vacuo followed by column chromatography (silica gel, using $CHCl_3$/MeOH as eluent) afforded pure **7a.** Yield: 82%; colorless solid; mp 169–170 °C; IR ($CHCl_3$): 3400, 2926, 1796, 1743, 1487 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.46 (bs, 1H), 7.22–7.50 (m, 8H), 3.82 (d, J = 17.2 Hz, 1H), 3.47 (d, J = 17.2 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.56, 174.88, 151.60, 137.48, 133.99, 129.99, 128.96, 128.80, 128.21, 126.35, 124.75, 110.65, 52.08, 42.11, 21.16. HRMS (ESI): calcd. for $C_{17}H_{14}NaO_4$ $(M + Na)^+$: 305.0784; found: 305.0796.

*Typical procedure for the synthesis of 5-methyl-2*H*-spiro[benzofuran-3,1′-indene]-2,3′(2′*H*)-dione (8a)*

A mixture of **7a** (1.0 g, 3.54 mmol) and polyphosphoric acid (10 mL) was heated overnight (16 h) at 120 °C under argon when the reaction completed. The reaction mixture was cooled in ice; water (100 mL) was added slowly and then extracted with $CHCl_3$. The organic layer was washed with water (2 × 50 mL) and brine and then dried (Na_2SO_4). Removal of solvent in vacuo followed by column chromatography (silica gel, using petroleum ether–ethyl acetate as eluent) afforded pure **8a**. Yield: 65%; colorless solid; mp 106–107 °C; IR ($CHCl_3$): 3020, 1804, 1722, 1487 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$):

δ = 7.87 (d, J = 8.0 Hz, 1H), 7.58–7.61 (m, 1H), 7.52 (t, J = 7.0 Hz, 1H), 7.13–7.19 (m, 2H), 7.07 (d, J = 7.0 Hz, 1H), 6.80 (s, 1H), 3.33 (d, J = 18.5 Hz, 1H), 2.99 (d, J = 18.5 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.90, 177.48, 153.25, 151.15, 135.96, 135.15, 130.32, 130.24, 129.71, 124.89, 124.30, 123.88, 110.77, 52.61, 48.24, 21.02. HRMS (ESI): calcd. for $C_{17}H_{13}O_3$ $(M + H)^+$: 265.0859; found: 265.0860.

Typical procedure for the synthesis of 5-methyl-2′,3′-dihydro-2H-spiro [benzofuran-3,1′-inden]-2-one (9a)

To a solution of **8a** (0.265 g, 1.0 mmol) in glacial acetic (10 mL) under a hydrogen atmosphere, 10% Pd-C (0.050 g) was added, and the mixture was stirred overnight (16 h) at ambient temperature. The reaction mixture was passed through a small pad of silica and the pad was washed with ethyl acetate. Solvent was removed in vacuo and the residue was purified by preparative TLC to afford pure **9a**. Yield: 92%; thick oil; IR ($CHCl_3$): 3020, 1801, 1486 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38 (d, J = 7.0 Hz, 1H), 7.27–7.30 (m, 1H), 7.13–7.16 (m, 2H), 7.08 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.78 (d, J = 7.5 Hz, 1H), 3.43–3.50 (m, 1H), 3.19–3.25 (m, 1H), 2.76–2.81 (m, 1H), 2.46–2.52 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.96, 151.14, 144.59, 143.08, 134.38, 132.17, 129.46, 128.55, 127.20, 125.12, 124.18, 123.67, 110.24, 58.53, 39.04, 31.43, 21.08. HRMS (ESI): calcd. for $C_{17}H_{14}NaO_2$ $(M + Na)^+$: 273.0886; found: 273.0881.

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References

[1] For recent references on benzofuran-2-ones, see (a) Wang, H.; Dong, B.; Wang, Y.; Li, J.; Shi, Y. *Org. Lett.* **2014**, *16*, 186; (b) Li, Y.; Lampkins, A. J.; Baker, M. B.; Sumpter, B. G.; Huang, J.; Abboud, K. A.; Castellano, R. K. *Org. Lett.* **2009**, *11*, 4314; (c) Panisheva, E. K.; Alekseeva, L. M.; Evstratova, M. I.; Kiselev, S. S.; Granik, V. G. *Pharm. Chem. J.* **2007**, *41*, 549; (d) Kwon, Y.-J.; Sohn, M.-J.; Zheng, C.-J.; Kim, W.-G. *Org. Lett.* **2007**, *9*, 2449; (e) Adediran, S. A.; Cabaret, D.; Drouillat, B.; Pratt, R. F.; Wakselman, M. *Bioorg. Med. Chem.* **2001**, *9*, 1175; (f) Su, B.-N.; Takaishi, Y.; Tori, M.; Takaoka, S.; Honda, G.; Itoh, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O. *Org. Lett.* **2000**, *2*, 493; (g) Close, A.; Haefliger, W.; Hauser, D.; Gubler, H. U.; Dewald, B.; Baggiolini, M. *J. Med. Chem.* **1981**, *24*, 1465.

[2] (a) Lavielle, G.; Lepagnol, J. US Pat. 4 859 700, **1989**; *Chem. Abstr.* **1989**, *110*, 75296; (b) Weston, A. W.; Brownell, W. B. *J. Am. Chem. Soc.* **1952**, *74*, 653.

[3] For recent references on 3,3-disubstituted benzofuran-2-ones, see (a) Ohmatsu, K.; Ito, M.; Kunieda, T.; Ooi, T. *J. Am. Chem. Soc.* **2013**, *135*, 590; (b) Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 1236; (c) Li, X.; Zhang, Y.-Y.; Xue, X.-S.; Jin, J.-L.; Tan, B.-X.; Liu, C.; Dong, N.; Cheng, J.-P. *Eur. J. Org. Chem.* **2012**, 1774; (d) Wang, D.; Yang, Y.-L.; Jiang, J.-J.; Shi, M. *Org. Biomol. Chem.* **2012**, *10*, 7158; (e) Li, X.; Xue, X.-S.; Liu, C.; Wang, B.; Tan, B.-X.; Jin, J.-L.; Zhang, Y.-Y.; Dong, N.; Cheng, J.-P. *Org. Biomol. Chem.* **2012**, *10*, 413; (f) Chen, L.; Zhou, F.; Shi, T.-D.; Zhou, J. *J. Org. Chem.* **2012**, *77*, 4354; (g) Zhu, C.-L.; Zhang, F.-G.; Meng, W.; Nie, J.; Cahard, D.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5869; (h) Pesciaioli, F.; Tian, X.; Bencivenni, G.; Bartoli, G.; Melchiorre, P. *Synlett* **2010**, 1704; (i) Li, X.; Xi, Z.; Luo, S.; Cheng, J.-P. *Adv. Synth. Catal.* **2010**, *352*, 1097; (j) Wada, S.-I.; Hitomi, T.; Tanaka, R. *Helv. Chim. Acta*

2009, *92*, 1610; (k) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921; (l) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **2001**, *57*, 791; (m) Fuerst, D. E.; Stolz, B. M.; Wood, J. L. *Org. Lett.* **2000**, *2*, 3521; (n) Onan, K. D.; Kelley, C. J.; Patarapanich, C.; Leary, J. D.; Aladesanmi, A. J. *J. Chem. Soc., Chem. Commun.* **1985**, 121.

[4] Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303.

[5] Nicolaou, K. C.; Kang, Q.; Wu, T. R.; Lim, C. S.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 7540.

[6] Piacente, S.; Montoro, P.; Oleszek, W.; Pizza, C. *J. Nat. Prod.* **2004**, *67*, 882.

[7] Ramírez, M. L. G.; Trejo, A.; Navarro, V.; Bye, R.; Linares, E.; Delgado, G. *J. Nat. Prod.* **2001**, *64*, 432.

[8] (a) Ingold, K. U.; Pratt, D. A. *Chem. Rev.* **2014**, *114*, 9022, and references cited therein; (b) Filippino, V.; Frenette, M.; Scaino, J. C. *Org. Lett.* **2009**, *11*, 3634; (c) Frenette, M.; MacLean, P. D.; Barclay, L. R. C.; Scaino, J. C. *J. Am. Chem. Soc.* **2006**, *128*, 16432.

[9] (a) Chen, L.; Zhou, J. *Chem. Asian J.* **2012**, *7*, 2510; (b) Imato, K.; Nishihara, M.; Kanahara, T.; Amamoto, Y.; Takahara, A.; Otsuka, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1138; (c) Padwa, A.; Dehm, D.; Oine, T.; Lee, G. A. *J. Am. Chem. Soc.* **1975**, *97*, 1837.

[10] (a) Chen, L.; Yin, X.-P.; Wang, C.-H.; Zhou, J. *Org. Biomol. Chem.* **2014**, *12*, 6033; (b) Shukla, P.; Choudhary, M. K.; Nayak, S. K. *Synlett* **2011**, 1585.

[11] (a) Zhu, X.-Q.; Zhou, J.; Wang, C.-H.; Li, X.-T.; Shajling *J. Phys. Chem. B* **2011**, *115*, 3588; (b) Li, X.; Hu, S.; Xi, Z.; Zhang, L.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2010**, *75*, 8697.

[12] For recent references on bio-active spirocyclic benzofuran-2-ones, see (a) Pertino, M. W.; Theoduloz, C.; Rodríguez, J. A.; Lazo, V.; Yanez, Y.; Hirschmann, G-S. *J. Nat. Prod.* **2010**, *73*, 639; (b) Peŕez-Fons, L.; Garzoń, M. T.; Micol, V. *J. Agric. Food Chem.* **2010**, *58*, 161; (c) Nicolaou, K. C.; Wu, T. R.; Kang, Q.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3440; (d) Ge, H. M.; Zhu, C. H.; Shi, D. H.; Zhang, L. D.; Xie, D. Q.; Yang, J.; Ng, S. W.; Tan, R. X. *Chem. Eur. J.* **2008**, *14*, 376; (e) Sontag, B.; Ruth, M.; Spiteller, P.; Arnold, N.; Steglich, W.; Reichert, M.; Bringmann, G. *Eur. J. Org. Chem.* **2006**, 1023; (f) Yang, L.; Qin, L.-H.; Bligh, S. W. A.; Bashall, A.; Zhang, C.-F.; Zhang, M.; Wang, Z.-T.; Xu, L.-S. *Bioorg. Med. Chem.* **2006**, *14*, 3496.

[13] Hernandez Alvarez, B.; Fischer, G.; Braun, M.; Hessamian-Alinejad, A.; Fliri, H. WO Patent 2003093258, 2003.

[14] (a) Wada, S.-I.; Hitomi, T.; Tokuda, H.; Tanaka, R. *Chem. Biodiversity* **2010**, *7*, 2303; (b) Guerrero, I. C.; Andres, L. S.; Leon, L. G.; Machin, R. P.; Padron, J. M.; Luis, J. G.; Delgadillo, J. *J. Nat. Prod.* **2006**, *69*, 1803.

[15] Recent references on spirocyclic benzofuranone synthesis: (a) Li, X.; Lin, M.-H.; Han, Y.; Wang, F.; Cheng, J.-P. *Org. Lett.* **2014**, *16*, 114; (b) Albertshofer, K.; Tan, B.; Barbas, C. F. , III. *Org. Lett.* **2013**, *15*, 2958; (c) Li, X.; Yang, C.; Jin, J.-L.; Xue, X.-S.; Cheng, J.-P. *Chem.-Asian J.* **2013**, *8*, 997; (d) Qi, L.-W.; Wang, L.-L.; Peng, L.; Jia, L.-N.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Tetrahedron* **2013**, *69*, 9303; (e) Li, X.; Wang, F.; Dong, N.; Cheng, J.-P. *Org. Biomol. Chem.* **2013**, *11*, 1451; (f) Cassani, C.; Tian, X.; Escudero-Adan, E. C.; Melchiorre, P. *Chem. Commun.* **2011**, *47*, 233.

[16] Davies, S. G.; Foster, E. M.; McIntosh, C. R.; Roberts, P. M.; Rosser, T. E.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2011**, *22*, 1035.

[17] Li, Y.; Plesescu, M.; Prakash, S. R. *Tetrahedron Lett.* **2011**, *52*, 1807.

[18] Kundu, K.; Tyagi, M.; Patro, B. S.; Chattopadhyay, S.; Nayak, S. K. *Org. Commun.* **2014**, *7*, 85.