Synthesis S. Jana et al. Paper

Regioselective Synthesis of Dihydro-1*H*-furo[*b*]indol-1-ones and Their Carbanionic Reactivity

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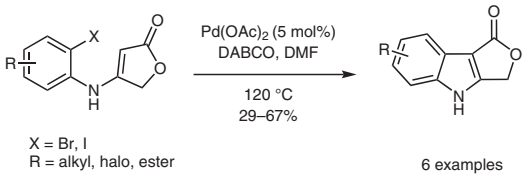

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Abstract A general synthesis of 3,4-dihydro-1*H*-furo[*b*]indol-1-ones, representing a furanone-fused pyrrole unit, has been developed. The dehydrohalogenative cyclization of 4-aminofuranones was achieved by reaction with $Pd(OAc)_2$ and DABCO in DMF. The corresponding N-protected indolones undergo alkylation at C3.

Key words γ-lactone-fused heterocycles, furoindolones, regioselectivity, carbanions

Phthalides, a class of bicyclic heterocycles featuring a γ-lactone fused with an aromatic ring, are common structural motifs of numerous natural products and synthetic materials. Many of these compounds possess useful medicinal properties. For example, butylphthalide (**1**, Figure 1) is a marketed drug used as an antiplatelet drug for ischemic cerebral apoplexy. More importantly, phthalides have been used as key intermediates for the synthesis of compounds such as phthalans, isoindolinones, carbazoles, anthraquinones, tetracenes, and lignans.[1] A wide range of natural products with broad, potent, and potentially path-pointing biological activities possess a 3-substituted phthalide core. For example, natural products like isochracinic acid, paecilocin A, and herbaric acid (**2**), which possess such a core, have antibacterial, antifungal, and antibiotic activity.[2] Therefore, the development of efficient synthetic procedures for the facile construction of phthalides and their analogues is an important activity in organic synthesis.

Quite strikingly, the chemistry of the heterocyclic analogues of phthalides has not been studied in detail. Progress in the synthesis of γ-lactones fused with a five- or six-membered-ring heterocycle has been hindered due to difficulties in constructing the γ-lactones. DeShong and Sidler's approach to the pyrrole-fused γ-lactone **3** by intramolecular azomethine ylide cycloaddition afforded **3** in only 5% yield.[3a] Thiolactone-fused furan **4** was synthesized by cyclocondensation of benzylic-type thiols at the *ortho* position of furancarboxylic acids.[3b] However, the involvement of unstable intermediates and low overall yields limit further development as a general synthetic method.

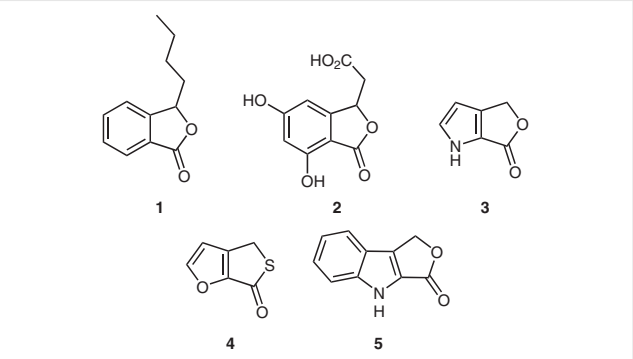
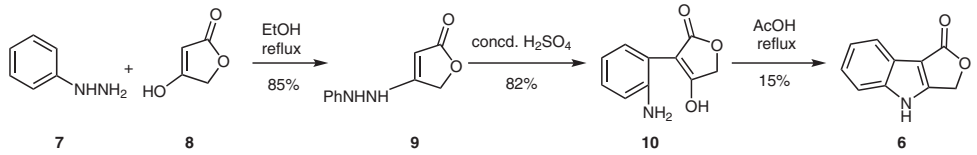


Figure 1 Some examples of important γ-lactones

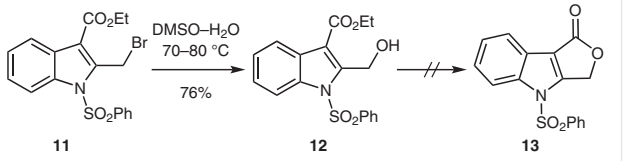
In connection with our carbazole work, where we have reported the total synthesis of several carbazole alkaloids including calothrixin B, ekeberginine, clausamine E, claulansine D, clausevatine D, and clausamine C,[4] we embarked upon the synthesis of furoindol-3-one **5**. More interestingly, we have developed a short synthesis of calothrixin B by the reaction of furoindolone **5** and bromoquinoline. On the contrary, the chemistry of the isomeric indolones, namely those based on 3,4-dihydro-1*H*-furo[3,4-*b*]indol-1-one (**6**), has not been investigated because of the problems of fusion of a furanone to a pyrrole unit.[3c] Herein, we report a facile synthesis of such furoindolones by dehydrohalogenative cyclization of 4-aminofuranones which are readily accessible from anilines.



Scheme 1 Synthesis of furoindolone **6** using the Fischer indolization of **9**

Our initial attempts were centered on the Fischer indolization of compound **9** (Scheme 1) which was prepared from tetronic acid (**8**) and phenylhydrazine (**7**) in 85% yield following a literature procedure.[5,6] On treatment of **9** with concentrated H_2SO_4 at 0 °C, a new compound **10** was formed in 82% yield.[7] Attempted ring closure of the compound **10** in acetic acid under reflux provided the desired product **6** in only 15% yield. Further improvement in the yield of furoindolone **6** could not be achieved, even though various acid catalysts were examined.

Alternatively, lactonization of the indole derivative ethyl 2-(bromomethyl)-1-(phenylsulfonyl)-1*H*-indole-3-carboxylate (**11**) was considered (Scheme 2). Heating compound **11** in DMSO–water provided compound **12**.[8] All attempts to obtain the desired furoindolone **13** failed.



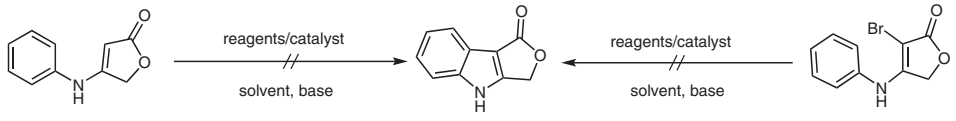
Scheme 2 Synthesis of precursors **11** and **12** for lactonization to furoindolone **13**

Next, we considered intramolecular dehydrogenative cyclization or intramolecular dehydrohalogenative cyclization for the synthesis of furoindolone **6** (Scheme 3). Several reagent systems were examined for the oxidative cyclization[9] of **14**[10] to furoindolone **6**; however, none furnished the desired cyclized product **6**.[11]

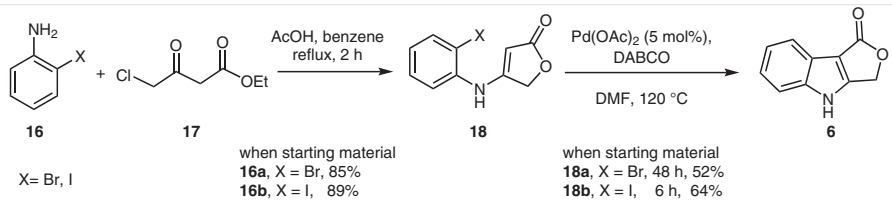
In an alternative approach, we considered the cyclization of bromo derivative **15**,[13] because intramolecular cyclization of aromatic compounds is known in the literature. Various attempts were made to cyclize intermediate **15** to furoindolone **6**.[12] None of these attempts[14] successfully gave **6**.

Following the above failures, we thought to juxtapose the halide from the lactone ring to the aromatic ring. To this end, we synthesized intermediates **18** from *o*-haloanilines **16** by reaction with **17** (Scheme 4). The precursors **18a** and **18b** were treated separately with the reagents $Pd(OAc)_2$ (5 mol%) and DABCO in DMF at 120 °C. Very interestingly, both substrates **18a** and **18b** provided the desired furoindolone **6**. The reaction was faster with the iodo derivative **18b**. Similar conditions were utilized by Chen and co-workers for the preparation of indoles; however, no lactonic compounds were synthesized. According to the Chen annulation,[15] if *o*-iodoaniline (**16a**) is reacted with tetronic acid (**8**) under the previous coupling reaction conditions, compound **6** could be synthesized in one step. But, when *o*-iodoaniline (**16a**) was treated with tetronic acid (**8**), $Pd(OAc)_2$, and DABCO in DMF at 105 °C for 3 to 36 hours, unfortunately both the starting materials were recovered. There was no indication of the formation of compound **6**.

The probable course of the cyclization reaction is related to the palladium-catalyzed aromatic substitution known as the Mizoroki–Heck reaction. As illustrated in Scheme 5,

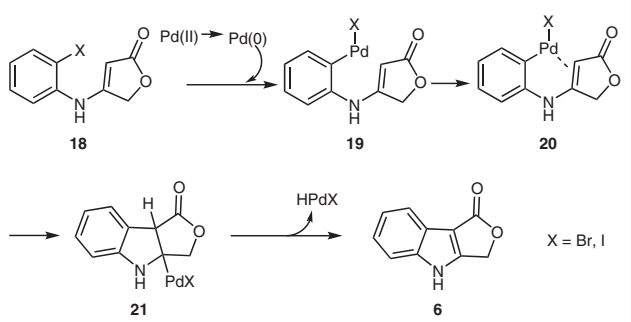


Scheme 3 Precursors (arylamino)butyrolactones **14** and **15** for attempted intramolecular dehydrogenative or dehydrohalogenative cyclization[11,12]



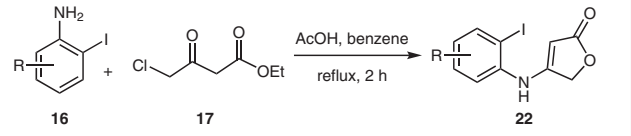
Scheme 4 Successful synthesis of furoindolone **6** by intramolecular Mizoroki–Heck-type cyclization

the reaction presumably proceeds by oxidative addition of the aryl halide **18** to an *in situ* produced palladium(0) species forming **19**, followed by insertion of the double bond in the enaminone system into the *o*-aryl–palladium bond (via **20**); then, with the loss of a palladium hydride species from **21** by β-elimination, the desired product **6** is obtained. The palladium hydride species collapses, with a base (DABCO) used to regenerate the palladium(0) catalyst.



Scheme 5 Proposed mechanism of the catalytic cyclization[16]

Considering that *o*-iodoanilines **16** are broadly available chemicals, we prepared a few *o*-iodoanilines **16** following some literature procedures.[17] To generalize the methodology, we first synthesized the precursors **22** for the coupling reaction. With the optimized conditions, the scope of the reaction for various (arylamino)butyrolactones **22** was investigated, and the results are summarized in Scheme 6. The R group in **22** can be methyl, dimethyl, chloro, bromo, or ester.

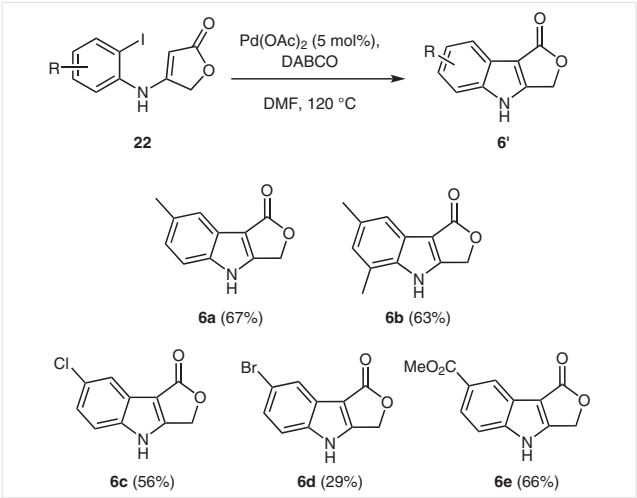


16a': R = 4-Me **16f'**: R = 4-OH **22a**: R = 4-Me (83%)
16b': R = 2,4-$(Me)_2$ **16g'**: R = 4-OMe **22b**: R = 2,4-$(Me)_2$ (86%)
16c': R = 4-Cl **16h'**: R = 4-CO_2H **22c**: R = 4-Cl (81%)
16d': R = 4-Br **16i'**: R = 4-NO_2 **22d**: R = 4-Br (79%)
16e': R = 4-CO_2Me **22e**: R = 4-CO_2Me (76%)

Scheme 6 Substrate scope of the reaction towards the intermediates **22**

(Methylphenylamino)furanone **22a** was obtained in 83% yield when 2-iodo-4-methylaniline (**16a'**) was reacted with ethyl 4-chloroacetoacetate (**17**). 2-Iodo-4,6-dimethylaniline (**16b'**) also reacted smoothly with **17** and furnished **22b** in 86% yield. Likewise, (4-chlorophenylamino)furanone **22c** was isolated in 81% yield, when 4-chloro-2-iodoaniline (**16c'**) was subjected to the reaction with **17**. 4-Bromo-2-iodoaniline (**16d'**) underwent the condensation reaction with **17** to produce (4-bromophenylamino)furanone **22d** in 79% yield. 4-Hydroxy-2-iodoaniline (**16f'**), 2-iodo-4-methoxyaniline (**16g'**), and 2-iodo-4-nitroaniline (**16i'**) were reluctant to undergo the condensation with **17**. 4-Amino-3-iodobenzoic acid (**16h'**) was not suitable for this reaction; after treating it with **17**, we recovered the starting aniline **16h'**. But, very interestingly, when the carboxylic acid group was esterified and methyl 4-amino-3-iodobenzoate (**16e'**) was used as starting material, the desired product **22e** was formed in 76% yield.

After the successful synthesis of the five precursors **22a–e** for furoindolones **6'**, we treated each precursor with $Pd(OAc)_2$ and DABCO in DMF at 120 °C, and the results are presented in Scheme 7. 7-Methyl-3,4-dihydro-1*H*-furo[3,4-*b*]indol-1-one (**6a**) was obtained in 67% yield, when **22a** was subjected to cyclization. The other precursors **22b–e** were also suitable for cyclization, giving the desired products **6b–e** in moderate to good yields. The poor yield (29%) of bromoindolone **6d** is due to debromination of product **6d** en route to **6**. When the reaction was allowed to undergo to completion, only the debrominated furoindolone **6** was obtained as the sole product in 62% yield.

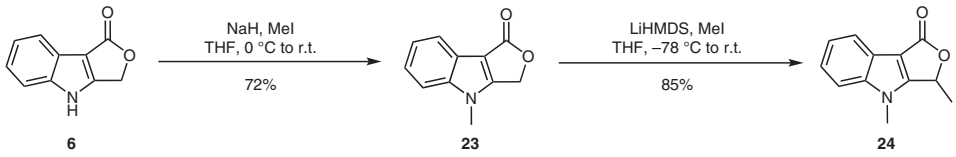


Scheme 7 Substrate scope of the reaction towards furoindolones **6'**

As a cursory experiment, compound **6** was protected as its *N*-methyl derivative and the resulting furoindolone **23** was subjected to reaction with LiHMDS followed by MeI (Scheme 8). Methylated product **24** was obtained in 85% yield, suggesting the formation of a carbanion of the protected furoindolone **23**.

The reactivity of the furo[*b*]indolones **6'** towards anionic annulations is currently being evaluated in our laboratory and the results will be reported in due course.

In conclusion, a general synthesis of 3,4-dihydro-1*H*-furoindolones in overall good yields has been developed. The key step of the methodology is an intramolecular C–X (X = Br, I) cross-coupling reaction catalyzed by $Pd(OAc)_2$. Studies are underway to explore the annulation[18] reactivity of the furoindolones **6'** with acrylates under anionic conditions.



Scheme 8 Carbanionic reactivity of furoindolone **6**

Melting points were determined in open-end capillary tubes on a melting point Sunsim apparatus and are uncorrected. Solvents were dried and distilled following standard procedures. TLC was carried out on precoated plates (silica gel 60, GF254), and the spots were visualized with UV and fluorescent lights. Column chromatography was performed on silica gel (60–120 or 230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded at 400/600 and 100/150 MHz, respectively, on Bruker Avance spectrometers. IR spectra were recorded on a Spectrum BX FT-IR instrument from Perkin Elmer using KBr pellets. A Waters XEVO-G2QTOF mass analyzer type 'TOF MS ES+' was used for recording HRMS data. The phrase 'usual workup' refers to washing of the organic phase with water (2 × 1/3 the volume of the organic phase) and brine (1 × 1/4 the volume of the organic phase), drying (anhydrous Na_2SO_4), filtration, and concentration under reduced pressure.

3,4-Dihydro-1*H*-furo[3,4-*b*]indol-1-one (6)

A solution of compound **10** (0.4 g, 2.1 mmol) in 10 mL acetic acid was heated at about 100 °C for 4.5 h. It was then neutralized with $NaHCO_3$. The obtained solid was filtered and the filtrate was extracted with EtOAc (3 × 10 mL). After usual workup of the extract, the resulting residue was mixed with the previously obtained solid and was chromatographed (hexanes/EtOAc, 3:1) to obtain **6** (55 mg, 15% yield) as a light brown solid; mp 188–190 °C.

IR (KBr): 3319, 1718, 1510, 1451, 1325, 1243, 1041, 989, 958, 769, 757, 679, 658 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.09 (s, 1 H), 7.71–7.65 (m, 1 H), 7.58 (d, *J* = 8.1 Hz, 1 H), 7.29 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1 H), 7.22 (td, *J* = 7.5, 1.2 Hz, 1 H), 5.39 (s, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.3, 160.0, 142.3, 123.2, 121.6, 120.6, 118.9, 113.3, 105.3, 64.7.

HRMS (ES+): *m*/*z* calcd for $C_{10}H_8NO_2$ [M + H]$^+$: 174.0555; found: 174.0559.

4-(2-Phenylhydrazinyl)furan-2(5*H*)-one (9)

A mixture of tetronic acid (**8**) (2 g, 19.98 mmol) and phenylhydrazine (**7**) (1.96 mL, 19.98 mmol) in dried EtOH (100 mL) was heated at 70 °C for 2 h; the reaction mixture was concentrated to half-volume, and allowed to stand to give a solid. This was further crystallized (EtOH) to furnish compound **9** (3.22 g, 85% yield) as a red solid; mp 126–128 °C.

IR (KBr): 3301, 1703, 1621, 1483, 1156, 1024, 761 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.20 (br s, 1 H), 8.02 (s, 1 H), 7.19 (t, *J* = 7.8 Hz, 2 H), 6.79–6.72 (m, 3 H), 4.76 (s, 2 H), 4.53 (br s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 174.3, 170.1, 147.8, 129.0, 119.4, 112.4, 80.2, 65.4.

HRMS (ES+): *m*/*z* calcd for $C_{10}H_{11}N_2O_2$ [M + H]$^+$: 191.0821; found 191.0815.

3-(2-Aminophenyl)-4-hydroxyfuran-2(5*H*)-one (10)

To cold concd H_2SO_4 (10 mL), phenylhydrazino derivative **9** (1 g, 5.25 mmol) was added in portions and the mixture was then allowed to stand in a freezer overnight. The reaction mixture was then neutralized with saturated $NaHCO_3$ solution (17 mL). The floating solid was filtered and the filtrate was extracted with EtOAc (3 × 10 mL). After usual workup of the extract, the resulting residue was combined with the solid and was recrystallized (EtOAc/hexane) to give **10** (0.82 g, 82% yield) as a pink solid; mp 227–229 °C.

IR (KBr): 3334, 3186, 1693, 1639, 1596, 1455, 1350, 1045, 988, 775 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.99 (t, *J* = 8.3 Hz, 2 H), 6.78 (s, 1 H), 6.72 (d, *J* = 7.8 Hz, 1 H), 6.59 (t, *J* = 7.4 Hz, 1 H), 4.80 (s, 2 H), 4.67 (s, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.9, 164.0, 145.8, 130.5, 127.4, 116.4, 115.4, 91.2, 79.2, 66.3.

HRMS (ES+): *m*/*z* calcd for $C_{10}H_{10}NO_3$ [M + H]$^+$: 192.0661; found: 192.0659.

(5-Ethoxy-1-phenyl-1*H*-pyrazol-3-yl)methanol (9a′, Figure 2)

Compound **9** (0.50 g, 2.63 mmol) and PTSA·H_2O (1.1 g, 5.8 mmol) were dissolved in ethanol (20 mL) and the solution was heated under reflux until **9** was consumed, as determined by TLC. The reaction mixture was cooled to r.t., diluted with Et_2O, and neutralized with aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 × 10 mL), and combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude product by flash column chromatography (EtOAc/hexanes, 1:9) gave **9a′** (315 mg, 55% yield) as a gummy liquid.

IR (KBr): 3343, 2930, 1665, 1534, 1437, 1320, 1222, 658 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.67 (d, *J* = 8.0 Hz, 2 H), 7.45 (t, *J* = 7.8 Hz, 2 H), 7.27 (t, *J* = 7.5 Hz, 1 H), 5.84 (s, 1 H), 5.08 (br s, 1 H), 4.38 (s, 2 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 1.37 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 154.4, 153.1, 138.5, 128.9, 125.8, 121.2, 85.5, 67.9, 58.1, 14.4.

HRMS (ES+): *m*/*z* calcd for $C_{12}H_{13}N_2O$ [M + H – H_2O]$^+$: 201.1028; found: 201.1021.

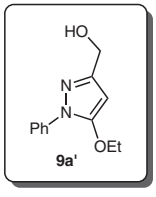


Figure 2

5-Ethoxy-1-phenyl-1*H*-pyrazole-3-carbaldehyde (9b′, Figure 3)

Compound **9a′** (20 mg, 0.092 mmol) was reacted with freshly prepared PCC (40 mg, 0.2 mmol) in dried CH_2Cl_2 (7 mL), and the reaction mixture was allowed to stir at r.t. overnight. Then, silica gel was added to the mixture and flash column chromatography (hexanes/EtOAc, 5:1) was done to afford DNP-active, yellowish solid compound **9b′** (19 mg, 95% yield); mp 178–180 °C.

IR (KBr): 2945, 2743, 1836, 1728, 1647, 1563, 1423, 1176, 773 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.89 (s, 1 H), 7.75 (d, *J* = 7.9 Hz, 2 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 6.16 (s, 1 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 1.46 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.3, 155.8, 150.4, 138.2, 129.2, 127.7, 122.8, 84.7, 68.6, 14.6.

HRMS (ES+): *m*/*z* calcd for $C_{12}H_{13}N_2O_2$ $[M + H]^+$: 217.0977; found: 217.0969.

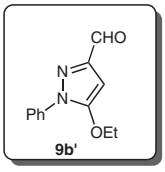


Figure 3

***N*-(2-(4-Hydroxy-2-oxo-2,5-dihydrofuran-3-yl)phenyl)acetamide (10a′, Figure 4)**

Compound **10** (50 mg, 0.26 mmol) was treated with Et_3N (0.2 mL) and acetyl chloride (0.2 mL, 2.6 mmol) with a pinch of DMAP in 12 mL dried acetone. The reaction mixture was allowed to stir at 0 °C to r.t. for 5–6 h. After reaction completion, acetone was evaporated, and the remainder was extracted with water and EtOAc. The organic layer was further washed with water and dried over Na_2SO_4, and the solvent was evaporated. The crude residue was chromatographed (hexanes/EtOAc, 6:1) to furnish **10a′** (55.7 mg, 92% yield) as a white solid; mp 170–172 °C.

IR (KBr): 3431, 3286, 1665, 1593, 1434, 1323, 1145, 725 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.87 (br s, 1 H), 7.89 (d, *J* = 8.1 Hz, 1 H), 7.27–7.18 (m, 2 H), 7.10 (t, *J* = 7.5 Hz, 1 H), 7.05 (br s, 1 H), 4.71 (s, 2 H), 2.00 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 174.1, 168.1, 165.3, 136.4, 130.5, 126.9, 123.8, 123.1, 90.4, 66.7, 24.0.

HRMS (ES+): *m*/*z* calcd for $C_{12}H_{11}NO_4$ $[M + H]^+$: 233.0688; found: 233.0693.

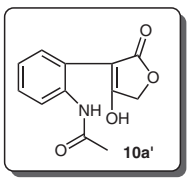


Figure 4

3-(2-(Dimethylamino)phenyl)-4-hydroxyfuran-2(5*H*)-one (10b′, Figure 5)

Compound **10** (100 mg, 0.52 mmol) in 7 mL acetone, excess K_2CO_3, and excess MeI were charged in a 25-mL round-bottom flask. Then, the reaction mixture was stirred at r.t. overnight. When the reaction was completed (checked by TLC), water was added to the reaction mixture and acetone was evaporated in vacuo. Next, the mixture was extracted with EtOAc, and the organic layers were washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexanes, 5:1) to afford **10b′** (102.5 mg, 90% yield) as a white solid; mp 163–165 °C.

IR (KBr): 3303, 2936, 1696, 1628, 1593, 1457, 1350, 1201, 1058, 990, 776 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.25 (d, *J* = 5.6 Hz, 1 H), 7.08 (dd, *J* = 7.8, 6.0 Hz, 2 H), 6.17 (s, 1 H), 4.70 (s, 2 H), 2.69 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.6, 162.0, 149.4, 131.1, 127.8, 125.1, 122.7, 117.8, 95.9, 66.2, 43.1.

HRMS (ES+): *m*/*z* calcd for $C_{12}H_{14}NO_3$ $[M + H]^+$: 220.0974; found: 220.0967.

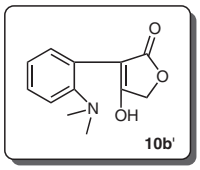


Figure 5

Ethyl 2-(Hydroxymethyl)-1-(phenylsulfonyl)-1*H*-indole-3-carboxylate (12)

A mixture of compound **11** (1 g, 2 mmol), DMSO (25 mL), and water (5 mL) was heated at 70–80 °C with stirring for 10–12 h. Then, it was cooled, poured into water (250 mL), and extracted with Et_2O (4 × 25 mL), and the combined extract was subjected to the usual workup. The resulting solid was crystallized (CH_2Cl_2/petroleum ether) to give **12** (0.65 g, 76% yield) as a white solid; mp 99–101 °C.

IR (KBr): 3496, 1692, 1381, 1209, 1178, 1093, 994 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.21–8.17 (m, 1 H), 8.05 (m, 1 H), 7.97–7.92 (m, 2 H), 7.58–7.24 (m, 5 H), 5.38 (d, *J* = 6.0 Hz, 2 H), 4.44 (ABq, *J* = 7.2 Hz, 2 H), 3.7 (br s, 1 H), 1.44 (t, *J* = 7.2 Hz, 3 H).

Ethyl 2-Formyl-1-(phenylsulfonyl)-1*H*-indole-3-carboxylate (12a′, Figure 6)

To a stirred solution of compound **12** (0.5 g, 1.45 mmol) in dried CH_2Cl_2 (50 mL), PCC (1.24 g, 5.79 mmol) was added. After overnight stirring, the reaction mixture was filtered. The filtrate was concentrated and dissolved in Et_2O (50 mL). The ether layer was washed repeatedly with water (5 × 10 mL) and, after usual workup, gave a solid which was chromatographed (hexanes/EtOAc, 5:1) to give **12a′** (0.31 g, 60% yield) as an off-white solid; mp 79–81 °C.

IR (KBr): 2977, 2889, 1713, 1679, 1533, 1368, 1230, 1177, 1085 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.57 (s, 1 H), 8.17–8.04 (m, 4 H), 7.63–7.38 (m, 5 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.8, 163.2, 139.2, 138.0, 136.5, 134.7, 129.5, 128.1, 127.7, 126.4, 125.3, 123.3, 118.3, 114.7, 61.8, 14.3.

HRMS (ES+): *m*/*z* calcd for $C_{18}H_{16}NO_5S$ $[M + H]^+$: 358.0749; found: 358.0741.

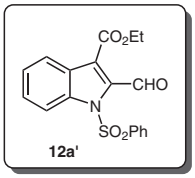


Figure 6

Synthesis of the Cyclization Precursors; General Procedure

An *o*-haloaniline **16** (11 mmol) and glacial acetic acid (2 mmol) were added to a solution of ethyl 4-chloroacetoacetate (**17**) (1.65 g, 10 mmol) in dried benzene (40 mL), and the resulting mixture was heated under reflux for 2 h. After cooling, the solid precipitate was collected, washed with benzene, and triturated with ethanol to give the 4-((2-halophenyl)amino)furan-2(5*H*)-one. In cases where a solid deposition of product was not obtained, benzene was evaporated in vacuo and the reaction mixture was extracted with EtOAc and water. The water layer was washed several times with EtOAc. Then, the combined organic extracts were concentrated and purified by flash column chromatography (EtOAc/hexane) to obtain the solid product.

4-((2-Bromophenyl)amino)furan-2(5*H*)-one (18a)

Yield: 2.15 g (85%); yellow solid (hexanes/EtOAc, 8:1); mp: 171–173 °C.

IR (KBr): 3140, 2983, 1738, 1591, 1561, 1507, 1402, 1260, 1140, 1047, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.57 (m, 1 H), 7.41–7.33 (m, 2 H), 7.07–7.02 (m, 1 H), 6.75 (s, 1 H), 5.36 (s, 1 H), 4.89 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.8, 163.4, 137.4, 133.5, 128.7, 126.3, 121.9, 116.0, 86.5, 68.7.

HRMS (ES+): *m*/*z* calcd for $C_{10}H_9BrNO_2$ $[M + H]^+$: 253.9817; found 253.9811.

4-((2-Iodophenyl)amino)furan-2(5*H*)-one (18b)

Yield: 2.55 g (89%); white solid (hexanes/EtOAc, 5:1); mp: 175–177 °C.

IR (KBr): 3246, 1718, 1615, 1576, 1541, 1437, 1310, 1156, 1049, 895, 769 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 1 H), 7.45–7.31 (m, 2 H), 7.02 (br s, 1 H), 6.99–6.77 (m, 1 H), 5.16 (s, 1 H), 4.89 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.5, 163.5, 140.0, 139.9, 129.7, 127.1, 122.1, 92.5, 86.6, 68.5.

HRMS (ES+): *m*/*z* calcd for $C_{10}H_9INO_2$ $[M + H]^+$: 301.9678; found: 301.9669.

4-((2-Iodo-4-methylphenyl)amino)furan-2(5*H*)-one (22a)

Yield: 2.6 g (83%); brown solid (hexanes/EtOAc, 5:1); mp 183–185 °C.

IR (KBr): 3246, 1710, 1610, 1594, 1444, 1308, 1163, 1046, 897, 786, 657 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 1.7 Hz, 1 H), 7.20–7.11 (m, 2 H), 6.57 (s, 1 H), 5.07 (s, 1 H), 4.79 (s, 2 H), 2.25 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.4, 163.4, 140.1, 137.5, 130.5, 121.8, 100.1, 92.6, 86.5, 68.3, 20.5.

HRMS (ES+): *m*/*z* calcd for $C_{11}H_{11}INO_2$ $[M + H]^+$: 315.9834; found: 315.9826.

4-((2-Iodo-4,6-dimethylphenyl)amino)furan-2(5*H*)-one (22b)

Yield: 2.8 g (86%); brown solid (hexanes/EtOAc, 5:1); mp 179–181 °C.

IR (KBr): 3227, 3044, 2919, 1706, 1615, 1589, 1558, 1539, 1469, 1303, 1124, 1042, 896, 784, 700, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.53 (s, 1 H), 7.24 (s, 1 H), 7.03 (s, 1 H), 4.81 (s, 2 H), 4.40 (s, 1 H), 2.28 (s, 3 H), 2.24 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.3, 167.2, 140.1, 137.9, 136.9, 136.1, 132.3, 99.3, 84.6, 68.0, 20.6, 19.1.

HRMS (ES+): *m*/*z* calcd for $C_{12}H_{13}INO_2$ $[M + H]^+$: 329.9991; found: 329.9989.

4-((4-Chloro-2-iodophenyl)amino)furan-2(5*H*)-one (22c)

Yield: 2.7 g (81%); yellow solid (hexanes/EtOAc, 4:1); mp 175–177 °C.

IR (KBr): 3059, 1700, 1608, 1589, 1495, 1329, 1161, 1044, 825, 784, 707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 2.3 Hz, 1 H), 7.32 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.24–7.16 (m, 1 H), 6.42 (br s, 1 H), 5.17 (s, 1 H), 4.80 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.7, 162.1, 139.1, 138.6, 131.2, 130.0, 121.7, 92.0, 87.8, 68.3.

HRMS (ES+): *m*/*z* calcd for $C_{10}H_8ClINO_2$ $[M + H]^+$: 335.9288; found: 335.9280.

4-((4-Bromo-2-iodophenyl)amino)furan-2(5*H*)-one (22d)

Yield: 3.0 g (79%); yellow solid (hexanes/EtOAc, 5:1); mp 140–142 °C.

IR (KBr): 3238, 3122, 2933, 1717, 1655, 1616, 1586, 1459, 1372, 1228, 1167, 1043, 1031, 829, 786, 710, 667 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.18 (br s, 1 H), 8.11 (s, 1 H), 7.61–7.60 (m, 1 H), 7.35 (d, *J* = 8.4 Hz, 1 H), 4.84 (s, 2 H), 4.81 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 174.8, 165.9, 141.5, 141.2, 132.8, 126.4, 118.9, 96.4, 84.1, 68.2.

HRMS (ES+): *m*/*z* calcd for $C_{10}H_8BrINO_2$ $[M + H]^+$: 379.8783; found: 379.8775.

Methyl 3-Iodo-4-((5-oxo-2,5-dihydrofuran-3-yl)amino)benzoate (22e)

Yield: 2.7 g (76%); reddish solid (hexanes/EtOAc, 10:1); mp 187–189 °C.

IR (KBr): 3238, 3122, 2933, 1717, 1655, 1616, 1586, 1459, 1372, 1356, 1303, 1285, 1177, 1043, 1031, 786, 667 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 2.4 Hz, 1 H), 8.08 (dd, *J* = 1.8, 8.4 Hz, 1 H), 7.40–7.38 (m, 1 H), 6.75 (br s, 1 H), 5.51 (s, 1 H), 4.94 (s, 2 H), 3.95 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.2, 164.8, 160.4, 143.2, 141.2, 131.2, 127.4, 118.2, 89.7, 68.4, 52.5.

HRMS (ES+): *m*/*z* calcd for $C_{12}H_{11}INO_4$ $[M + H]^+$: 359.9733; found: 359.9721.

Cyclization; General Procedure

A mixture of a 4-((2-iodophenyl)amino)furan-2(5*H*)-one **22** (10 mmol), DABCO (3.36 g, 30 mmol, 3 equiv), and $Pd(OAc)_2$ (112 mg, 0.5 mmol, 5 mol%) in dried DMF (30 mL) was degassed via vacuum/nitrogen purges and heated to 105 °C. The mixture was heated at 120 °C for 6 h (for the bromo derivative **18a**, 36 h) or until the reaction was complete (usually, less than 8 h). The reaction mixture was cooled to r.t. and partitioned between EtOAc (150 mL) and water (50 mL). The

organic layer was separated, washed with brine (5 × 20 mL), and concentrated under reduced pressure to dryness. The residue was chromatographed to give the furoindol-1-one **6′** in moderate to good yield.

7-Methyl-3,4-dihydro-1*H*-furo[3,4-*b*]indol-1-one (6a)

Yield: 1.25 g (67%); brown solid (hexanes/EtOAc, 5:1); mp 195–197 °C.

IR (KBr): 3447, 3186, 2924, 2851, 1713, 1456, 1046 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.96 (br s, 1 H), 7.64–7.32 (m, 2 H), 7.10 (dd, *J* = 8.3, 1.9 Hz, 1 H), 5.36 (s, 2 H), 2.40 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.5, 159.9, 140.6, 130.7, 124.6, 120.9, 118.9, 113.0, 104.9, 64.7, 21.1.

HRMS (ES+): *m*/*z* calcd for $C_{11}H_{10}NO_2$ $[M + H]^+$: 188.0712; found: 188.0718.

5,7-Dimethyl-3,4-dihydro-1*H*-furo[3,4-*b*]indol-1-one (6b)

Yield: 1.27 g (63%); brown solid (hexanes/EtOAc, 5:1); mp 184–186 °C.

IR (KBr): 3278, 1763, 1726, 1597, 1518, 1420, 1317, 1206, 1026, 979, 828, 675 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.05 (s, 1 H), 7.29 (s, 1 H), 6.91 (s, 1 H), 5.37 (s, 2 H), 2.46 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.5, 159.6, 140.0, 130.7, 125.4, 122.0, 120.6, 116.4, 105.1, 64.5, 21.0, 16.6.

HRMS (ES+): *m*/*z* calcd for $C_{12}H_{12}NO_2$ $[M + H]^+$: 202.0868; found: 202.0859.

7-Chloro-3,4-dihydro-1*H*-furo[3,4-*b*]indol-1-one (6c)

Yield: 1.16 g (56%); brown solid (hexanes/EtOAc, 5:1); mp 191–193 °C.

IR (KBr): 3332, 1723, 1653, 1547, 1514, 1426, 1357, 1236, 1136, 945, 856, 654 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.25 (br s, 1 H), 7.65 (s, 1 H), 7.61 (dd, *J* = 8.7, 2.8 Hz, 1 H), 7.48–7.17 (m, 1 H), 5.40 (s, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 167.6, 161.9, 141.2, 127.1, 124.1, 121.9, 118.9, 115.4, 105.4, 65.6.

HRMS (ES+): *m*/*z* calcd for $C_{10}H_7ClNO_2$ $[M + H]^+$ 208.0165; found: 208.0172.

7-Bromo-3,4-dihydro-1*H*-furo[3,4-*b*]indol-1-one (6d)

In this case, there was a mixture of compound **6d** and its dehalogenated derivative **6**, from the ^1H NMR spectrum in a ratio **6d**/**6** of 1:2. From the starting material **22d** (3.8 g, 10 mmol), 1.73 g product was obtained, with the mixture of compounds **6d**/**6** in a 1:2 ratio. Thus, we calculated the yield of **6d** as 29%. Compound **6d** isolated (0.73 g, 29% yield) was obtained as a brown solid (hexanes/EtOAc, 5:1).

^1H NMR (400 MHz, DMSO-d_6): δ (**6** and **6d**) = 12.26 (br s, 0.54 H), 12.10 (br s, 1 H), 7.78 (s, 0.54 H), 7.68–7.13 (m, 6.50 H), 5.40 (s, 1.40 H), 5.38 (s, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ (**6** and **6d**) = 166.4, 165.9, 161.1, 160.1, 142.3, 141.1, 126.0, 123.3, 122.3, 121.7, 121.2, 120.7, 119.0, 115.4, 114.3, 113.4, 105.3, 105.0, 65.0, 64.8.

Methyl 1-Oxo-3,4-dihydro-1*H*-furo[3,4-*b*]indole-7-carboxylate (6e)

Yield: 1.52 g (66%); brown solid (hexanes/EtOAc, 5:1); mp 190–192 °C.

IR (KBr): 3338, 1753, 1715, 1634, 1548, 1527, 1508, 1472, 1347, 1236, 1056, 959, 826, 665 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 12.44 (br s, 1 H), 8.29 (s, 1 H), 7.91 (dd, *J* = 1.8, 9.0 Hz, 1 H), 7.69 (d, *J* = 9.0 Hz, 1 H), 5.43 (s, 2 H), 3.87 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 167.1, 166.5, 162.4, 145.5, 124.7, 123.6, 121.1, 120.7, 114.0, 106.7, 65.6, 52.5.

HRMS (ES+): *m*/*z* calcd for $C_{12}H_{10}NO_4$ $[M + H]^+$: 232.0610; found: 232.0602.

4-Methyl-3,4-dihydro-1*H*-furo[3,4-*b*]indol-1-one (23)

To a stirred solution of compound **6** (173 mg, 1.0 mmol) in dried THF (10 mL), NaH (24 mg, 1.0 mmol) was added at 0 °C. After 30 min, MeI (0.30 mL, 5.0 mmol) was added. Then, the reaction mixture was stirred for another 6–10 h at r.t. After reaction completion (checked by TLC), saturated ammonium chloride solution was added and THF was evaporated under reduced pressure. The mixture was extracted with EtOAc, and the extracts were washed with brine (3 × 1/3 vol), dried (Na_2SO_4), and concentrated to provide the crude product. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc, 3:1) to obtain **23** (135 mg, 72% yield) as a semi-solid.

IR (KBr): 3342, 1734, 1534, 1444, 1325, 1223, 1047, 967, 929, 752, 745, 638, 627 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.8 Hz, 1 H), 7.37–7.30 (m, 3 H), 5.15 (s, 2 H), 3.76 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.5, 159.6, 143.1, 123.7, 122.4, 121.4, 120.4, 110.4, 105.9, 63.4, 31.6.

HRMS (ES+): *m*/*z* calcd for $C_{11}H_{10}NO_2$ $[M + H]^+$: 188.0712; found: 188.0710.

3,4-Dimethyl-3,4-dihydro-1*H*-furo[3,4-*b*]indol-1-one (24)

To a stirred solution of compound **23** (34 mg, 0.18 mmol) in dried THF (5 mL), 1 M LiHMDS in hexanes (0.3 mL, 1.6 mmol) was added at –78 °C. After 30 min, excess MeI (0.19 mL, 3.0 mmol) was added. Then, the reaction mixture was stirred for another 6–10 h at r.t. After reaction completion (checked by TLC), saturated ammonium chloride solution was added and THF was evaporated under reduced pressure. The mixture was extracted with EtOAc, and the extracts were washed with brine (3 × 1/3 vol), dried (Na_2SO_4), and concentrated to provide the crude product. The crude solid product was purified by column chromatography on silica gel (EtOAc/hexanes, 2:1) to obtain **24** (31 mg, 85% yield) as a brown solid; mp 163–165 °C.

IR (KBr): 2925, 1743, 1618, 1550, 1451, 1398, 1081, 963, 913 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.8 Hz, 1 H), 7.40–7.32 (m, 3 H), 5.54 (q, *J* = 6.6 Hz, 1 H), 3.82 (s, 3 H), 1.75 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.8, 162.6, 143.1, 123.7, 122.5, 121.3, 120.7, 110.3, 106.2, 71.7, 31.3, 19.3.

HRMS (ES+): *m*/*z* calcd for $C_{12}H_{12}NO_2$ $[M + H]^+$: 202.0868; found: 202.0862.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610439.

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(6) The reaction of **7** with **8** was carried out with the aim of increasing the yield of Fischer indole product **6**, but interestingly pyrazole **9a′** was also obtained. For further structure confirmation, pyrazole **9a′** was oxidized to aldehyde **9b′**. Pyrazole **9a′** was obtained in 55% yield when furanone **9** was treated with PTSA in refluxing ethanol (see experimental section).

(7) The structure of compound **10** was further confirmed by synthesis of the *N*-acetyl-protected compound **10a′** and the *N*,*N*-dimethyl derivative **10b′** (see experimental section).

(8) The structure of compound **12** was further confirmed by oxidation of its primary alcohol to give aldehyde derivative **12a′** (see experimental section).

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(11) Several reagents were examined for the oxidative cyclization of **14**; however, the desired cyclized product, furoindolone **6**, was not furnished: either starting material (SM) was recovered or an intractable reaction mixture (IRM) was obtained. We tried the following combinations: $Cu(OAc)_2·H_2O/Pd(OAc)_2$, K_2CO_3, DMF, 80 °C (SM recovered); $PdCl_2(PPh_3)_2$, TEA, DMF, 110 °C (SM recovered); I_2, K_2CO_3, DMF, 100 °C (SM recovered); $Ag_2O/Pd(OAc)_2$, KOAc, DMF, 140 °C (IRM); $PPh_3/Pd_2(dba)_3/Cu(OAc)_2·H_2O$, TEA, DMF, 140 °C (IRM); I_2, K_2CO_3, DMF, 100–140 °C (IRM).

(12) We tried the dehydrohalogenative cyclization of **15** with the following combinations: $Cu(OAc)_2$, Cs_2CO_3, DMF, 125 °C; TBAB/$Pd(OAc)_2$, K_2CO_3, DMF, 100 °C; CuI, Cs_2CO_3, DMF, 125 °C; $PdCl_2(PPh_3)_2$, Cs_2CO_3, 1,4-dioxane, 100 °C; $Pd(PPh_3)_4$, TEA, DMF, 140 °C; $PPh_3/Pd_2(dba)_3$, K_3PO_4, toluene, 120 °C; AcOH/$Pd(OAc)_2$, 140 °C; LiCl/$Pd(PPh_3)_4$, Na_2CO_3, MeCN, 140 °C; LiCl, $PPh_3/Pd(OAc)_2$, K_2CO_3, DMF, 140 °C; $PdCl_2(PPh_3)_2$, TEA, DMF, 110 °C.

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