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Synthesis of Spiro-lactams and Polysubstituted Pyrroles via Ceric Ammonium Nitrate-Mediated Oxidative Cyclization of *N*-Furan-2-ylmethyl-*β*-Enaminones

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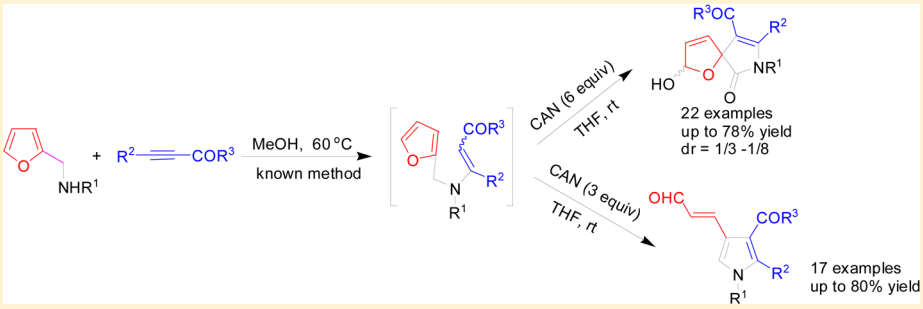
Supporting Information



ABSTRACT: Spiro-lactams and polysubstituted pyrroles were synthesized by reactions of furfurylamines with ynones followed by oxidation. Specifically, the protocol involved in situ generation of *N*-furan-2-ylmethyl-*β*-enaminones and their subsequent oxidation by ceric ammonium nitrate (6 equiv for spiro-lactam formation, 3 equiv for pyrrole formation). This useful dearomatizing oxidation, which likely proceeds via a free-radical pathway, can be expected to extend the synthetic applications of furan and pyrrole derivatives.

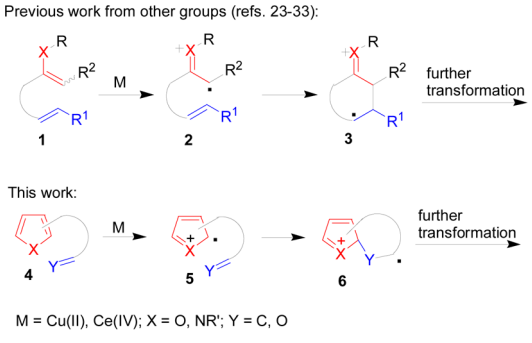
INTRODUCTION

Furans are aromatic heterocycles that act as masked functional groups such as alkenes, dienes, enol ethers, and 1,4-diketones. As such, biomass-derived furans are attractive four-carbon building blocks for the synthesis of structurally diverse molecules.[1−5] Oxidation of the electron-rich aromatic furan ring is one method of unmasking the latent functionality present within these heterocyclic molecules. For example, bromination or chlorination of furans in alcoholic solvent at low temperature efficiently produces 2,5-dialkoxy-2,5-dihydro compounds.[6−10] Furans tend to be oxidized to *α*,*β*-unsaturated-*δ*-dicarbonyl derivatives, including pyrone and pyridone, when *m*-CPBA or pyridinium chlorochromate is used as the oxidant.[11−17] Oxidation of furans with singlet molecular oxygen ($^1O_2$) provides furan endoperoxides, which can be subjected to additional transformations.[18,19] Despite the existence of these methods, development of more efficient methods for oxidative transformation of furan derivatives is of great significance for both synthetic chemistry and resource utilization chemistry.[20−22]

Oxidative cyclizations mediated by high-valent metals such as Cu(II)[23−27] and Ce(IV),[28−33] which proceed via a free-radical pathway, have received much attention in organic synthesis. Typically, enolic or enamic substrates **1** are initially oxidized by the high-valent metal to form carbon-centered radicals **2**. Radicals **2** are subsequently trapped intramolecularly by a pendant unsaturated group to form cyclized products **3**, which can be subjected to further transformations (Scheme 1). By means of this protocol, a wide range of cyclic compounds, including various natural products, can be efficiently synthesized.

Because electron-rich furans and pyrroles are essentially masked enol ethers and enamines, respectively, we envisioned that furans and pyrroles **4** could be oxidized by high-valent

Scheme 1. Oxidative Intramolecular Free-Radical Cyclizations Involving Electron-Rich Olefins and Aromatic Rings



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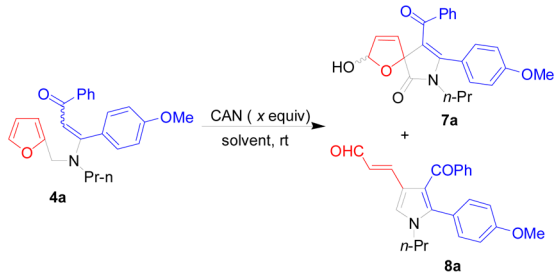
metals to form carbon-centered radicals **5**. If **5** could then be intramolecularly trapped by a suitable terminal functional group to form **6**, the result would be a novel oxidative transformation of furans and pyrroles via a free-radical pathway (Scheme 1). Recently, we reported that chlorinated pyrroles can be accessed via copper chloride−catalyzed aerobic oxidative annulation of *N*-furfuryl-*β*-enaminones, which are generated in situ from reactions of furfurylamines with ynones.[34] As an extension of our research on dearomatizing transformations of furans,[35−39] we now report the synthesis of spiro-lactams and polysubstituted pyrroles from *N*-furan-2-ylmethyl-*β*-enaminones via a dearomatizing oxidation of furan and pyrrole rings mediated by ceric ammonium nitrate (CAN).

RESULTS AND DISCUSSION

When *N*-furfuryl-*β*-enaminone **4a** was treated with 1 equiv of CAN in THF at room temperature (rt) in air, a trace of polysubstituted pyrrole **8a** was formed (Table 1, entry 1). The

Table 1. Optimization of Reactions Conditions for Oxidation of 4a by CAN[a]



entry	*x*	solvent	% yield **7a**[b] (dr[c])	% yield **8a**[b]
1	1	THF	ND	trace
2	2	THF	trace	37
3	3	THF	trace	74
4	4	THF	49 (1/2)	37
5	5	THF	50 (1/1.5)	25
6	6	THF	73 (1/3)	trace
7	7	THF	56 (1/3)	trace
8	3	AcOH	ND	35
9	3	EtOH	trace	53
10	3	THF−H_2O	trace	70
11	6	AcOH	ND	50
12	6	EtOH	ND	ND
13	6	THF−H_2O	ND	54

[a]Reaction conditions: **4a** (0.27 mmol), solvent (15 mL), in air for 1 h at rt. [b]Isolated yield; ND = not detected. [c]Ratios were determined by ^{1}H NMR spectroscopy.

possible pathway for the formation of **8a** may be similar to that of chlorinated pyrroles via Cu(II)-catalyzed oxidation of *N*-furfuryl-*β*-enaminones, previously reported by our group.[35] When the amount of CAN was increased to 2 equiv, a trace of **7a** (as a mixture of two diastereoisomers) and a 37% yield of **8a** were produced (entry 2). In the ^{1}H NMR spectrum of **7a** (Figure 1), the semiacetal protons (C1−H) of the major and minor isomers appear as broad peaks at 6.38 and 6.11 ppm, respectively. The olefinic protons at C2−H and C3−H of the major isomer appear as doublets (J = 6.0 Hz) at 6.35 and 5.95 ppm, respectively. The corresponding protons of the minor isomer appear as doublets (J = 5.7 Hz) at 6.32 and 6.13 ppm,

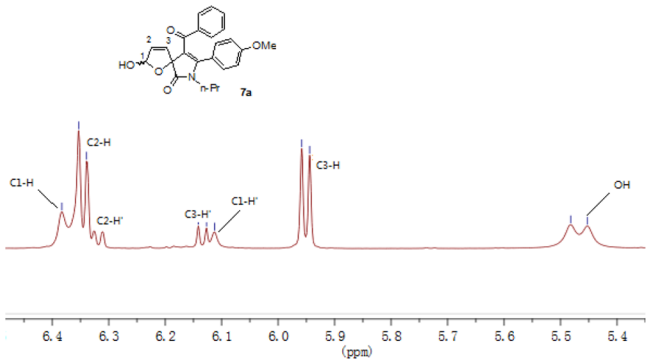


Figure 1. Partial ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7a**.

respectively. The structure of **7a** was assigned on the basis of single-crystal X-ray data for **7c** (Figure 2).

With 3 equiv of CAN, **8a** was obtained in 74% yield (entry 3). Increasing the amount of CAN to 4 or 5 equiv (entries 4 and 5, respectively) increased the yield of **7a** and reduced that of **8a**. Six equiv of CAN afforded the highest yield of **7a** (73%, entry 6) and the lowest yield of **8a**. The yield variations of **7a** and **8a** with the amount of CAN indicated that **7a** might be produced from **8a** or its cis-isomer by a CAN-mediated overoxidation of the pyrrole ring. The real mechanism for the transformation of **8a** into **7a** is not very clear presently and need further explorations. When we screened solvents with an OH group, as well as the use of water as a cosolvent, with 3 equiv (entries 8−10) or 6 equiv (entries 11−13) of CAN, we found that the yield of **8a** dropped, and little or no **7a** was formed.

Because polysubstituted pyrroles and spiro-lactams have been reported to have potent bioactivities[40,41] and various synthetic applications,[42−48] we proceeded to synthesize a series of these valuable heterocyclic compounds via reactions of *N*-furfuryl-*β*-enaminones with 3 or 6 equiv of CAN, respectively, in THF, as described below.[49] To our knowledge, the conventional methods for synthesis of spiro-lactam usually starts from an amide and need multiple steps to prepare the precursor for cyclization.[50−54] This access to spiro-lactams via oxidation of pyrrole ring to form the amide group accompanying with cyclization is of high efficience and novelty and has never been reported.

β-Enaminone **4a** can be prepared simply by stirring a mixture of furfurylamine **9a** and ynone **10a** in MeOH at 60 °C;[55] therefore, to simplify the reaction protocol, we investigated one-pot formation of **7a** from **9a** and **10a** (Scheme 2). Gratifyingly, we found that **7a** could be obtained in 73% yield in one pot by removal of the MeOH after the addition reaction between **9a** and **10a**, and subsequent treatment of the unpurified residue with 6 equiv of CAN in THF at rt. Using this protocol, we prepared various spiro-lactams **7** from furfurylamines **9** and ynones **10**.

As shown in Table 2, the structures of the two substrates markedly influenced the outcome of the reaction. For example, when R^2 and R^3 of **10** were aryl groups, either unsubstituted or with electron-donating or electron-withdrawing substituents, the desired spiro-lactams were obtained in moderate to good yields and with moderate diastereoselectivities (entries 1−6, 8−18, 21). Notably, when R^3 was an alkyl group (*n*-Pr) and R^2 was a phenyl group, **7g** was obtained in a good yield (entry 7). In contrast, when R^2 was an alkyl group (*n*-Pr) and R^3 was an aryl group (4-Me-Ph), a complex mixture was produced, and **7s** was

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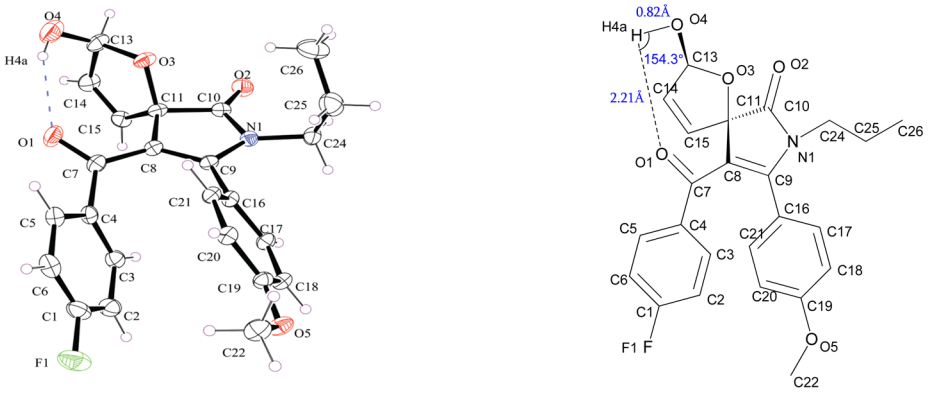


Figure 2. ORTEP diagram of **7c** with 30% ellipsoid probability (CCDC 1437106).

Scheme 2. One-Pot Protocol for the Formation of 7a

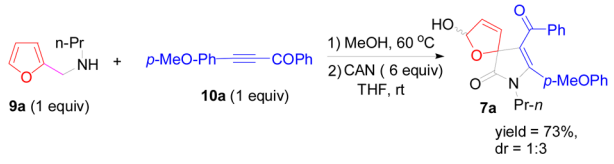
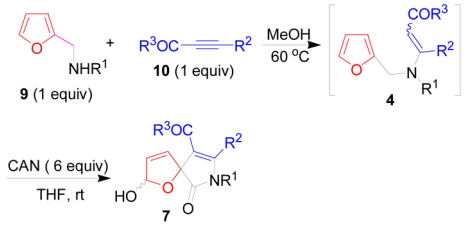


Table 2. Synthesis of Spiro-lactams[a]



entry	R^1	R^2	R^3	7 (% yield,[b] dr[c])
1	*n*-Pr	4-MeO-Ph	Ph	**7a** (73, 1/3)
2	*n*-Pr	4-MeO-Ph	2-Cl-Ph	**7b** (71, 1/8)
3	*n*-Pr	4-MeO-Ph	4-F-Ph	**7c** (63, 1/5)
4	*n*-Pr	4-Me-Ph	Ph	**7d** (70, 1/6)
5	*n*-Pr	4-Me-Ph	4-MeO-Ph	**7e** (45, 1/3)
6	*n*-Pr	4-Me-Ph	4-F-Ph	**7f** (53, 1/3)
7	*n*-Pr	Ph	*n*-Pr	**7g** (70, 1/5)
8	*n*-Pr	4-Cl-Ph	4-Me-Ph	**7h** (45, 1/4)
9	*n*-Pr	4-Cl-Ph	2-Cl-Ph	**7i** (68, 1/8)
10	*n*-Pr	4-Cl-Ph	4-F-Ph	**7j** (65, 1/3)
11	*n*-Pr	Ph	Ph	**7k** (72, 1/5)
12	*n*-Pr	Ph	4-Me-Ph	**7l** (77, 1/3)
13	*n*-Pr	Ph	4-MeO-Ph	**7m** (58, 1/3)
14	*n*-Pr	3-Br-Ph	4-Me-Ph	**7n** (60, 1/3)
15	*n*-Pr	3-Br-Ph	4-MeO-Ph	**7o** (64, 1/3)
16	*n*-Pr	4-F-Ph	4-Br-Ph	**7p** (60, 1/3)
17	*n*-Pr	4-F-Ph	4-CF_3-Ph	**7q** (78, 1/3)
18	*n*-Pr	2-Me-Ph	4-Me-Ph	**7r** (61, 1/5)
19	*n*-Pr	*n*-Pr	4-Me-Ph	**7s** (ND)
20	*n*-Pr	COOMe	COOMe	**7t** (ND)
21	Bn	Ph	Ph	**7u** (60, 1/3)
22	H	Ph	Ph	**7v** (ND)

[a]Reaction conditions: **9** (0.27 mmol), **10** (0.27 mmol), CAN (1.62 mmol), THF (15 mL), in air for 1 h at rt. [b]Isolated yield; ND = not detected. [c]The ratios in parentheses were calculated from the ratios of the areas obtained by integration of the semiacetal (CH) peaks.

not detected (entry 19). When both R^2 and R^3 were ester groups, the reaction provided not spiro-lactam **7t** (entry 20) but rather pyrrole **8m**. A substrate with a Bn group as R^1 gave desired product **7u** in 60% yield (entry 21), whereas when R^1 was H, a complex mixture was obtained (entry 22). Note that the presence of a 2-Cl group on the phenyl ring of R^3 led to higher diastereoselectivities (**7a** < **7b** > **7c**; **7h** < **7i** > **7j**). The structures of the pairs of diastereomers of **7b**–**7r** and **7u** were determined by comparison of their ^{1}H NMR spectra with the spectrum of **7a**.

A single crystal of **7c** was obtained by slow evaporation of the solvents from a saturated solution of **7c** diastereomers in 1/1 (v/v) petroleum/ethyl acetate at rt. The ORTEP diagram of **7c** is shown in Figure 2. The obtained single crystal was the *trans*-isomer, that is, the isomer with the OH group located on the opposite side of the furan ring from the amide group. Data analysis indicated the presence of an O1···H–O4 hydrogen bond in this isomer, with H–O4 and O1···H bond lengths of 0.82 and 2.21 Å, respectively, and a bond angle of 154.3°. The dihedral angle between H14 and H13 (that is, H14–C14–C13–H13) was 121.2°. The interplane angle between the two aryl groups was 20.5°. Mutarotation of the semiacetals occurred in this isomer, as indicated by the fact that its ^{1}H NMR spectrum was nearly the same as that of the mixture of diastereomers.

A library of polysubstituted pyrroles **8** was also synthesized from substrates **9** and **10** with 3 equiv of CAN as the oxidant (Table 3).[56,57] The R^1 substituent could be an alkyl group such as *n*-Pr, Et, or Bn (entries 1–13, 15, 16), but when R^1 was H or Ts, no pyrrole product was formed (entries 14 and 17). R^2 and R^3 of **10** could be unsubstituted phenyl groups or phenyl groups with electron-donating or electron-withdrawing substituents. Notably, even when either R^2 or R^3 was an alkyl group (*n*-Pr), the reaction proceeded well, affording good yields of the desired products (entries 10 and 11). However, when both R^2 and R^3 were *n*-Pr groups, **8l** was not detected (entry 12). Gratifyingly, in addition to ynones, dimethyl acetylenedicarboxylate could also be used as a substrate, affording **8m** in 60% yield (entry 13).

CONCLUSION

In summary, we have developed a simple, practical protocol for synthesis of spiro-lactams or polysubstituted pyrroles from *N*-furfuryl-*β*-enaminones mediated by ceric ammonium nitrate (6 or 3 equiv, respectively) as the oxidant. Although there have been numerous reports of CAN-mediated oxidations of enamines, to our knowledge, dearomatizing oxidation of pyrrole rings has not previously been reported. This protocol

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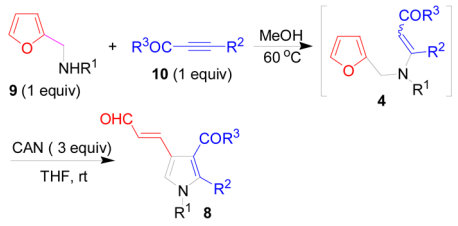
Table 3. Synthesis of Pyrroles 8[a]



entry	R^1	R^2	R^3	**8** (yield [%][b])
1	*n*-Pr	4-MeO-Ph	Ph	**8a** (74)
2	*n*-Pr	Ph	4-MeO-Ph	**8b** (46)
3	*n*-Pr	Ph	4-Me-Ph	**8c** (64)
4	*n*-Pr	2-Me-Ph	4-Me-Ph	**8d** (60)
5	*n*-Pr	Ph	Ph	**8e** (77)
6	*n*-Pr	4-F-Ph	4-Me-Ph	**8f** (76)
7	*n*-Pr	4-F-Ph	4-Br-Ph	**8g** (62)
8	*n*-Pr	4-Cl-Ph	2-Cl-Ph	**8h** (76)
9	*n*-Pr	3- Br-Ph	4-MeO-Ph	**8i** (62)
10	*n*-Pr	Ph	*n*-Pr	**8j** (62)
11	*n*-Pr	*n*-Pr	4-Me-Ph	**8k** (60)
12	*n*-Pr	*n*-Pr	*n*-Pr	**8l** (ND)
13	*n*-Pr	COOMe	COOMe	**8m** (60)
14	H	Ph	Ph	**8n** (ND)
15	Et	Ph	4-Me-Ph	**8o** (72)
16	Bn	Ph	Ph	**8p** (80)
17	Ts	Ph	Ph	**8q** (ND)

[a]Reaction conditions: **9** (0.27 mmol), **10** (0.27 mmol), CAN (0.81 mmol), THF (15 mL), in air for 1 h at rt. [b]Isolated yield; ND = not detected.

can be expected to extend the synthetic applications of furan and pyrrole derivatives.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out in air. Unless specified otherwise, all reagents and starting materials were purchased from commercial suppliers and used as received. Solvents were purified by means of standard literature procedures. FT-IR spectra were recorded with thin film samples or KBr pellets, and peaks are expressed in cm^{-1}. ^1H (400 MHz) and ^{13}C (101 MHz) NMR spectra were recorded using $CDCl_3$ as a solvent, and product ratios were determined from the ^1H NMR spectra. Chemical shifts are expressed in ppm downfield relative to tetramethylsilane. Coupling constants are reported in Hz; the following abbreviations are used for splitting patterns: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (double doublet). Analytical thin-layer chromatography was performed on silica gel with a mixture of petroleum ether and ethyl acetate as the eluent. High-resolution mass spectra were obtained with an LC/MS-IT-TOF mass spectrometer.

General Procedure for the Preparation of 7. The mixture of furfurylamine **9** (0.27 mmol), ynone **10** (0.27 mmol), and MeOH (15 mL) was stirred at 60 °C in air for about 6 h until the disappearance of the starting materials. After cooling to room temperature, the MeOH was evaporated under reduced pressure. To the mixture of the residue in THF (15 mL) was added cerium ammonium nitrate (neat, 6 equiv) in one portion at room temperature. The resulting yellow-orange solution was stirred at this temperature for 1 h. The reaction was then quenched with saturated aqueous sodium bicarbonate (10 mL). The resulting slurry was diluted with water (40 mL) and ethyl acetate (30 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3× 20 mL), and the combined organics were dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash column chromatography The crude residue was purified by flash column chromatography using petroleum ether and ethyl acetate as the eluent to give 7.

*9-Benzoyl-2-hydroxy-8-(4-methoxyphenyl)-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7a**, dr = 1/3).* White solid (79 mg, 73%); mp 148.5−149.5 °C; IR (KBr) ν 3393, 1771, 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.3 Hz, 0.5H), 7.19−6.97 (m, 6.5H), 6.70 (d, J = 8.7 Hz, 0.5H), 6.63 (d, J = 8.7 Hz, 1.5H), 6.38 (br, 0.75H), 6.35 (d, J = 6.0 Hz, 0.75H), 6.32 (d, J = 5.7 Hz, 0.25H), 6.13 (d, J = 5.7 Hz, 0.25H), 6.11 (br, 0.25H), 5.95 (d, J = 6.0 Hz, 0.75H), 5.47 (d, J = 11.9 Hz, 1H), 3.73 (s, 0.75H), 3.72 (s, 2.25H), 3.59−3.41 (m, 2H), 1.41−1.31 (m, 2H), 0.76−0.70 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7, 191.5, 177.4, 176.3, 161.2, 159.7, 139.3, 133.4, 131.0, 130.6, 128.7, 128.6, 128.3, 127.6, 127.4, 120.4, 116.0, 113.9, 106.0, 104.9, 91.8, 90.9, 55.3, 43.0, 21.7, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{23}NNaO_5$ $[M + Na]^+$ 428.1474, found 428.1468.

*9-(2-Chlorobenzoyl)-2-hydroxy-8-(4-methoxyphenyl)-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7b**, dr = 1/8).* White solid (84 mg, 71%); mp 140.3−142 °C; IR (KBr) ν 3349, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12−6.94 (m, 5H), 6.93−6.85 (m, 1H), 6.72−6.52 (m, 2H), 6.39 (br, 0.89H), 6.36 (d, J = 5.2 Hz, 0.89H), 6.28 (d, J = 5.7 Hz, 0.11H), 6.15 (br, 0.11H), 6.06 (d, J = 5.7 Hz, 0.11H), 5.98 (d, J = 5.2 Hz, 0.89H), 5.54 (d, J = 12.4 Hz, 1H), 3.75 (s, 0.33H), 3.72 (s, 2.67H), 3.43−3.23 (m, 2H), 1.38−1.27 (m, 2H), 0.73−0.67 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6, 176.1, 162.1, 160.9, 139.5, 133.4, 130.1, 129.3, 129.0, 128.3, 126.4, 119.3, 116.7, 113.6, 106.1, 105.0, 90.0, 55.3, 42.9, 21.8, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{22}ClNNaO_5$ $[M + Na]^+$ 462.1084, found 462.1079.

*9-(4-Fluorobenzoyl)-2-hydroxy-8-(4-methoxyphenyl)-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7c**, dr = 1/5).* White solid (72 mg, 63%); mp 164.1−164.5 °C; IR (KBr) ν 3350, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.43 (m, 0.33H), 7.24−7.17 (m, 1.67H), 7.10−7.02 (m, 2H), 6.76−6.64 (m, 4H), 6.36 (br, 0.83H), 6.34−6.30 (m, 1H), 6.12 (d, J = 5.8 Hz, 0.17H), 6.10 (br, 0.17H), 5.94 (d, J = 5.7 Hz, 0.83H), 5.34 (d, J = 12.0 Hz, 1H), 3.74 (s, 3H), 3.58−3.41 (m, 2H), 1.44−1.29 (m, 2H), 0.76−0.67 (m, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1, 189.8, 177.1, 176.2, 163.8 (d, J_{C-F} = 250.0 Hz), 161.4, 159.6, 135.5 (d, J_{C-F} = 3.0 Hz), 131.3 (d, J_{C-F} = 9.0 Hz), 130.8, 128.5, 120.3, 115.9, 114.5 (d, J_{C-F} = 21.0 Hz), 114.0, 106.0, 104.8, 91.9, 90.9, 55.4, 43.0, 21.8, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{22}FNNaO_5$ $[M + Na]^+$ 446.1380, found 446.1374.

*9-Benzoyl-2-hydroxy-7-propyl-8-(p-tolyl)-1-oxa-7-azaspiro[4.4]-nona-3,8-dien-6-one (**7d**, dr = 1/6).* White solid (74 mg, 70%); mp 144.1−144.5 °C; IR (KBr) ν 3398, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.6 Hz, 0.3H), 7.17−6.88 (m, 8.7H), 6.37−6.27 (m, 1.86H), 6.13 (d, J = 5.7 Hz, 0.14H), 6.09 (br, 0.14H), 5.96 (d, J = 5.7 Hz, 0.86H), 5.43 (d, J = 10.3 Hz, 1H), 3.56−3.38 (m, 2H), 2.23 (s, 0.43H), 2.21 (s, 2.57H), 1.40−1.28 (m, 2H), 0.75−0.66 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7, 177.3, 176.2, 160.0, 140.9, 133.4, 130.4, 129.2, 129.1, 128.9, 128.6, 128.2, 127.5, 127.4, 125.4, 116.2, 106.0, 104.7, 91.8, 90.9, 42.9, 21.8, 21.2, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{23}NNaO_4$ $[M + Na]^+$ 412.1525, found 412.1519.

*2-Hydroxy-9-(4-methoxybenzoyl)-7-propyl-8-(p-tolyl)-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7e**, dr = 1/3).* White solid (51 mg, 45%); mp 141−141.4 °C; IR (KBr) ν 3329, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.7 Hz, 0.5H), 7.19 (d, J = 8.7 Hz, 1.5H), 7.09−6.94 (m, 4H), 6.61 (d, J = 8.7 Hz, 0.5H), 6.46 (d, J = 8.7 Hz, 1.5H), 6.36 (br, 0.75H), 6.32 (d, J = 6.0 Hz, 0.75H), 6.29 (d, J = 5.8 Hz, 0.25H), 6.15 (d, J = 5.8 Hz, 0.25H), 6.05 (br, 0.25H), 5.93 (d, J = 6.0 Hz, 0.75H), 5.35 (d, J = 11.6 Hz, 1H), 3.74 (s, 0.75H), 3.69 (s, 2.25H), 3.58−3.39 (m, 2H), 2.27 (s, 0.75H), 2.25 (s, 2.25H), 1.41−1.27 (m, 2H), 0.75−0.68 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 189.9, 177.3, 176.2, 162.6, 161.9, 158.3, 140.7, 140.5, 133.4, 131.5, 130.7, 129.3, 129.2, 129.0, 128.9, 128.6, 125.8, 125.7, 116.4, 113.0, 112.7, 105.9, 104.6, 91.2, 92.1, 55.3, 42.9, 21.8, 21.3, 10.9; HRMS (ESI) m/z calcd for $C_{25}H_{25}NNaO_5$ $[M + Na]^+$ 442.1630, found 442.1625.

*9-(4-Fluorobenzoyl)-2-hydroxy-7-propyl-8-(p-tolyl)-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7f**, dr = 1/3).* Syrup (58 mg, 53%); IR (film) ν 3389, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

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7.53−7.35 (m, 0.5H), 7.19−7.17 (m, 1.5H), 7.07−6.95 (m, 4H), 6.75 (t, J = 8.3 Hz, 0.5H), 6.64 (t, J = 8.3 Hz, 1.5H), 6.37−6.30 (m, 1.75H), 6.12 (d, J = 5.7 Hz, 0.25H), 6.10 (br, 0.25H), 5.94 (d, J = 5.8 Hz, 0.75H), 5.31 (d, J = 12.1 Hz, 1H), 3.59−3.34 (m, 2H), 2.27 (s, 3H), 1.39−1.29 (m, 2H), 0.75−0.66 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 189.8, 176.1, 177.3, 163.9 (d, J_{C-F} = 250.0 Hz), 159.8, 141.3, 135.5 (d, J_{C-F} = 3.0 Hz), 133.5, 130.6 (d, J_{C-F} = 8.0 Hz), 129.3, 129.1, 128.5, 125.4, 116.2, 114.4 (d, J_{C-F} = 22.0 Hz), 106.0, 104.8, 90.9, 91.9, 43.0, 21.8, 21.3, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{22}FNNaO_4$ $[M + Na]^+$ 430.1431, found 430.1425.

*9-Butyryl-2-hydroxy-8-phenyl-7-propyl-1-oxa-7-azaspiro[4.4]-nona-3,8-dien-6-one (**7g**, dr = 1/5).* Syrup (64 mg, 70%); IR (film) ν 3388, 1744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.52 (m, 3H), 7.49−7.34 (m, 2H), 6.41−6.17 (m, 2H), 6.02 (d, J = 5.8 Hz, 0.16H), 5.85 (d, J = 5.7 Hz, 0.84H), 5.51 (d, J = 12.2 Hz, 1H), 3.29−3.15 (m, 2H), 1.89−1.70 (m, 2H), 1.44−1.25 (m, 4H), 0.72 (t, J = 7.4 Hz, 3H), 0.58 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3, 194.3, 177.0, 175.6, 158.2, 156.6, 132.8, 131.1, 130.9, 129.8, 129.4, 129.0, 128.8, 128.3, 117.6, 116.9, 106.1, 104.8, 91.2, 90.2, 43.1, 42.8, 22.1, 17.8, 13.5, 11.0; HRMS (ESI) m/z calcd for $C_{20}H_{23}NNaO_4$ $[M + Na]^+$ 364.1525, found 364.1519.

*8-(4-Chlorophenyl)-2-hydroxy-9-(4-methylbenzoyl)-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7h**, dr = 1/4).* White solid (51 mg, 45%); mp 170.1−170.2 °C; IR (KBr) ν 3411, 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 7.8 Hz, 0.5H), 7.13 (d, J = 7.8 Hz, 0.7H), 7.05 (d, J = 7.8 Hz, 2H), 6.97 (d, J = 7.8 Hz, 2.8H), 6.85 (d, J = 7.6 Hz, 0.4H), 6.73 (d, J = 7.6 Hz, 1.6H), 6.27 (s, 0.8H), 6.26 (d, J = 5.7 Hz, 0.8H), 6.22 (d, J = 5.7 Hz, 0.2H), 6.04 (d, J = 5.7 Hz, 0.2H), 5.99 (br, 0.2H), 5.86 (d, J = 5.7 Hz, 0.8H), 5.28 (br, 1H), 3.50−3.24 (m, 2H), 2.19 (s, 0.6H), 2.15 (s, 2.4H), 1.30−1.22 (m, 2H), 0.70−0.59 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 190.9, 176.0, 157.6, 141.8, 136.8, 136.3, 133.7, 130.6, 130.2, 128.6, 128.5, 128.4, 128.3, 128.2, 127.1, 117.0, 106.1, 104.8, 90.9, 43.0, 21.9, 21.3, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{22}ClNNaO_4$ $[M + Na]^+$ 446.1135, found 446.1130.

*9-(2-Chlorobenzoyl)-8-(4-chlorophenyl)-2-hydroxy-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7i**, dr = 1/8).* White solid (81 mg, 68%); mp 157−158 °C; IR (KBr) ν 3410, 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11−6.80 (m, 8H), 6.30−6.28 (m, 1.78H), 6.20 (d, J = 5.7 Hz, 0.11H), 6.05 (br, 0.11H), 5.97 (d, J = 5.7 Hz, 0.11H), 5.90 (d, J = 5.6 Hz, 0.89H), 5.36 (d, J = 12.4 Hz, 1H), 3.31−3.11 (m, 2H), 1.31−1.21 (m, 2H), 0.63 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.2, 175.8, 160.4, 139.3, 136.7, 133.7, 133.2, 130.3, 130.1, 129.3, 128.8, 128.5, 128.4, 128.1, 126.5, 126.2, 125.8, 117.3, 106.3, 105.1, 90.5, 89.9, 43.0, 22.0, 10.9; HRMS (ESI) m/z calcd for $C_{23}H_{19}Cl_2NNaO_4$ $[M + Na]^+$ 466.0589, found 466.0583.

*8-(4-Chlorophenyl)-9-(4-fluorobenzoyl)-2-hydroxy-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7j**, dr = 1/3).* Yellow oil (75 mg, 65%); IR (film) ν 3427, 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−6.89 (m, 8H), 6.35−6.30 (m, 1.75H), 6.15−6.04 (m, 0.5H), 5.94 (d, J = 5.2 Hz, 0.75H), 5.22 (s, 1H), 3.50−3.24 (m, 2H), 1.32−1.22 (m, 2H), 0.77−0.66 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1, 189.9, 177.0, 175.9, 163.8 (d, J_{C-F} = 250.0 Hz), 158.7, 138.0, 137.3, 133.7, 133.0, 131.5 (d, J_{C-F} = 8.0 Hz), 130.8, 129.7, 128.3, 125.6, 124.4 (d, J_{C-F} = 4.0 Hz), 116.7, 116.0 (d, J_{C-F} = 22.0 Hz), 106.1, 104.9, 91.6, 90.7, 43.0, 21.8, 10.9; HRMS (ESI) m/z calcd for $C_{23}H_{19}ClFNNaO_4$ $[M + Na]^+$ 450.0884, found 450.0879.

*9-Benzoyl-2-hydroxy-8-phenyl-7-propyl-1-oxa-7-azaspiro[4.4]-nona-3,8-dien-6-one (**7k**, dr = 1/5).* Yellow oil (73 mg, 72%); IR (film) ν 3379, 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 7.2 Hz, 0.34H), 7.14−6.84 (m, 9.66H), 6.34−6.18 (m, 1.83H), 6.08 (d, J = 5.7 Hz, 0.17H), 6.02 (br, 0.17H), 5.90 (d, J = 5.6 Hz, 0.83H), 5.32 (br, 1H), 3.48−3.29 (m, 2H), 1.32−1.20 (m, 2H), 0.67−0.57 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7, 192.2, 177.2, 176.1, 159.6, 139.2, 138.6, 133.5, 130.7, 130.5, 129.3, 128.5, 128.3, 128.2, 127.6, 127.4, 117.3, 116.4, 106.1, 104.7, 91.9, 90.9, 43.0, 21.8, 10.9; HRMS (ESI) m/z calcd for $C_{23}H_{21}NNaO_4$ $[M + Na]^+$ 398.1368, found 398.1363.

*2-Hydroxy-9-(4-methylbenzoyl)-8-phenyl-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7l**, dr = 1/3).* White solid (81 mg, 77%); mp 133−134 °C; IR (KBr) ν 3416, 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 7.5 Hz, 0.5H), 7.24−7.05 (m, 6.5H), 6.87 (d, J = 7.7 Hz, 0.5H), 6.73 (d, J = 7.7 Hz, 1.5H), 6.35 (br, 0.75H), 6.34−6.28 (m, 1H), 6.15 (d, J = 5.8 Hz, 0.25H), 6.08 (br, 0.25H), 5.96 (d, J = 5.7 Hz, 0.75H), 5.40 (br, 1H), 3.57−3.37 (m, 2H), 2.21 (s, 0.75H), 2.15 (s, 2.25H), 1.40−1.26(m, 2H), 0.75−0.66 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 191.0, 177.4, 176.2, 158.9, 142.3, 141.3, 136.4, 135.6, 133.5, 132.6, 130.1, 129.3, 128.9, 128.5, 128.3, 128.1, 117.6, 116.5, 106.0 104.6, 92.0, 91.0, 42.9, 21.8, 21.3, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{23}NNaO_4$ $[M + Na]^+$ 412.1525, found 412.1519.

*2-Hydroxy-9-(4-methoxybenzoyl)-8-phenyl-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7m**, dr = 1/3).* White solid (63 mg, 58%); mp 128.2−128.3 °C; IR (KBr) ν 3396, 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.6 Hz, 0.5H), 7.22−7.07 (m, 6.5H), 6.51 (d, J = 8.6 Hz, 0.5H), 6.38 (d, J = 8.6 Hz, 1.5H), 6.27 (br, 0.75H), 6.25−6.18 (m, 1H), 6.09 (d, J = 5.6 Hz, 0.25H), 5.99 (br, 0.25H), 5.88 (d, J = 5.7 Hz, 0.75H), 5.27 (br, 1H), 3.65 (s, 0.75H), 3.60 (s, 2.25H), 3.51−3.31 (m, 2H), 1.30−1.20 (m, 2H), 0.68−0.58 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5, 190.1, 177.3, 176.2, 162.7, 161.9, 157.9, 133.5, 132.5, 131.4, 130.7, 130.4, 130.2, 129.4, 128.9, 128.6, 128.4, 117.7, 116.6, 113.0, 112.8, 105.9, 104.6, 92.2, 91.2, 55.3, 42.9, 21.8, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{23}NNaO_5$ $[M + Na]^+$ 428.1474, found 428.1468.

*8-(3-Bromophenyl)-2-hydroxy-9-(4-methylbenzoyl)-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7n**, dr = 1/5).* Yellow oil (76 mg, 60%); IR (film) ν 3367, 1744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.26 (m, 2H), 7.20 (s, 0.66H), 7.11−7.02 (m, 3.34H), 6.93 (d, J = 7.9 Hz, 0.34H), 6.81 (d, J = 7.9 Hz, 1.66H), 6.37 (br, 0.83H), 6.34 (d, J = 5.2 Hz, 0.83H), 6.30 (d, J = 5.8 Hz, 0.17H), 6.12 (d, J = 5.8 Hz, 0.17H), 6.07 (br, 0.17H), 5.94 (d, J = 5.2 Hz, 0.83H), 5.32 (d, J = 12.3 Hz, 1H), 3.55−3.33 (m, 2H), 2.25 (s, 0.5H), 2.20 (s, 2.5H), 1.39−1.27 (m, 2H), 0.77−0.69 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 190.9, 176.9, 175.9, 157.1, 142.5, 141.5, 136.4, 135.8, 133.7, 133.0, 132.5, 130.5, 129.8, 128.3, 128.2, 128.1, 127.5, 127.3, 122.4, 118.5, 117.3, 106.1, 104.8, 91.7, 90.8, 43.0, 21.9, 21.3, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{22}BrNNaO_4$ $[M + Na]^+$ 490.0630, found 490.0624.

*8-(3-Bromophenyl)-2-hydroxy-9-(4-methoxybenzoyl)-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7o**, dr = 1/3).* Yellow oil (83 mg, 64%); IR (film) ν 3462, 1744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.5 Hz, 0.5H), 7.44−7.31 (m, 1.5H), 7.28 (s, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.16−7.03 (m, 2H), 6.65 (d, J = 8.5 Hz, 0.5H), 6.53 (d, J = 8.5 Hz, 1.5H), 6.42−6.21 (m, 1.75H), 6.13 (d, J = 5.6 Hz, 0.25H), 6.06 (br, 0.25H), 5.94 (d, J = 5.6 Hz, 0.75H), 5.24 (br, 1H), 3.76 (s, 0.75H), 3.73 (s, 2.25H), 3.57−3.36 (m, 2H), 1.43−1.30 (m, 2H), 0.79−0.68 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 189.8, 177.0, 175.9, 162.9, 162.0, 156.1, 133.7, 133.3, 132.5, 131.3, 130.6, 130.4, 130.1, 129.9, 128.4, 127.7, 127.4, 122.6, 122.5, 117.4, 113.1, 113.0, 106.0, 104.1, 92.0, 91.0, 55.4, 43.0, 21.9, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{22}BrNNaO_5$ $[M + Na]^+$ 506.0579, found 506.0574.

*9-(4-Bromobenzoyl)-8-(4-fluorophenyl)-2-hydroxy-7-propyl-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7p**, dr = 1/3).* White solid (76 mg, 60%); mp 150−151 °C; IR (KBr) ν 3464, 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.42 (m, 0.5H), 7.29−7.07 (m, 5.5H), 6.82 (t, J = 8.4 Hz, 0.5H), 6.71 (t, J = 8.4 Hz, 1.5H), 6.35−6.33 (m, 1.5H), 6.30 (d, J = 5.8 Hz, 0.25H), 6.11 (d, J = 5.8 Hz, 0.25H), 6.07 (br, 0.25H), 5.95 (d, J = 5.7 Hz, 0.75H), 5.19 (s, 1H), 3.58−3.35 (m, 2H), 1.40−1.28 (m, 2H), 0.77−0.67 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 189.6, 177.0, 175.9, 164.2 (d, J_{C-F} = 250.0 Hz), 157.9, 137.1, 135.3 (d, J_{C-F} = 3.0 Hz), 132.2, (d, J_{C-F} = 9.0 Hz), 130.7, 130.6, 128.9, 128.3, 126.9, 116.8, 114.7 (d, J_{C-F} = 22.0 Hz), 106.1, 104.8, 91.8, 90.9, 43.0, 21.8, 10.9; HRMS (ESI) m/z calcd for $C_{23}H_{19}BrFNNaO_4$ $[M + Na]^+$ 494.0379, found 494.0374.

*8-(4-Fluorophenyl)-2-hydroxy-7-propyl-9-(4-(trifluoromethyl)-benzoyl)-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7q**, dr = 1/3).* White solid (97 mg, 78%); mp 146.5−147 °C; IR (KBr) ν 3417, 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.7 Hz, 0.5H), 7.35 (d, J = 8.3 Hz, 0.5H), 7.26 (d, J = 8.3 Hz, 1.5H), 7.21 (d, J = 7.7 Hz,

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1.5H), 7.18−7.11 (m, 0.5H), 7.10−7.05 (m, 1.5H), 6.91 (t, J = 7.8 Hz, 0.5H), 6.84 (t, J = 7.8 Hz,1.5H), 6.40−6.31 (m, 1.75H), 6.12 (br, 0.25H), 6.09 (d, J = 5.6 Hz, 0.25H), 5.96 (d, J = 5.5 Hz, 0.75H), 5.23 (d, J = 12.1 Hz, 1H), 3.53−3.32 (m, 2H), 1.40−1.30 (m, 2H), 0.75−0.69 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 189.9, 176.9, 175.8, 163.7 (d, J_{C-F} = 250.0 Hz), 159.8, 142.5, 142.0, 133.8, 132.0 (q, J_{C-F} = 32.0 Hz), 131.4 (d, J_{C-F} = 9.0 Hz), 130.5, 128.6, 128.2, 124.5 (q, J_{C-F} = 3.7 Hz), 123.4 (q, J_{C-F} = 270.8 Hz), 116.8, 116.0 (d, J_{C-F} = 22.0 Hz), 106.2, 104.9, 91.4, 90.5, 43.1, 21.8, 10.9; HRMS (ESI) m/z calcd for $C_{24}H_{19}F_4NNaO_4$ $[M + Na]^+$ 484.1148, found 484.1142.

*2-Hydroxy-9-(4-methylbenzoyl)-7-propyl-8-(o-tolyl)-1-oxa-7-azaspiro[4.4]nona-3,8-dien-6-one (**7r**, dr = 1/5).* Yellow oil (66 mg, 61%); IR (film) ν 3412, 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04−6.66 (m, 8H), 6.38 (br, 0.83H), 6.35 (d, J = 5.6 Hz, 0.83H), 6.27 (d, J = 5.9 Hz, 0.17H), 6.08 (br, 0.17H), 6.06 (d, J = 5.9 Hz, 0.17H), 5.96 (d, J = 5.6 Hz, 0.83H), 5.55 (d, J = 11.3 Hz, 1H), 3.4 0−3.22 (m, 2H), 2.23 (s, 0.5H), 2.23 (s, 0.5H), 2.20 (s, 2.5H), 2.18 (s, 2.5H), 1.36−1.25 (m, 2H), 0.73−0.66 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 192.6, 177.3, 176.1, 161.3, 140.4, 140.0, 134.4, 133.4, 130.0, 128.8, 128.7, 128.5, 128.2, 127.4, 124.9, 124.8, 118.0, 117.5, 106.1, 104.7, 91.1, 90.3, 42.9, 21.8, 21.2, 19.3, 10.9; HRMS (ESI) m/z calcd for $C_{25}H_{25}NNaO_4$ $[M + Na]^+$ 426.1681, found 426.1676.

*9-Benzoyl-7-benzyl-2-hydroxy-8-phenyl-1-oxa-7-azaspiro[4.4]-nona-3,8-dien-6-one (**7u**, dr = 1/3).* Yellow oil (68 mg, 60%); IR (film) ν 3349, 1746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 0.5H), 7.12−6.72 (m, 14.5H), 6.32 (d, J = 11.8 Hz, 0.75H), 6.28 (d, J = 5.8 Hz, 0.75H), 6.25 (d, J = 5.9 Hz, 0.25H), 6.09 (d, J = 5.9 Hz, 0.25H), 6.06 (br, 0.25H), 5.93 (dd, J = 5.8 Hz, 0.75H), 5.29 (d, J = 12.3 Hz, 1H), 4.70−4.48 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 191.2, 177.3, 176.3, 159.3, 139.1, 138.4, 135.8, 133.7, 130.8, 130.4, 129.5, 129.2, 128.6, 128.4, 128.2, 128.1, 127.7, 127.4, 127.2, 117.7, 116.7, 106.2, 105.0, 92.0, 91.0, 45.0; HRMS (ESI) m/z calcd for $C_{27}H_{21}NNaO_4$ $[M + Na]^+$ 446.1368, found 446.1363.

General Procedure for the Preparation of 8. The mixture of furfurylamine **9** (0.27 mmol), ynone **10** (0.27 mmol), and MeOH (15 mL) was stirred at 60 °C in air for about 6 h until the disappearance of the starting materials. After cooling to room temperature, the MeOH was evaporated under reduced pressure. To the mixture of the residue in THF was added cerium ammonium nitrate (neat, 3 equiv) in one portion at room temperature. The resulting yellow-orange solution was stirred at this temperature for 1 h. The reaction was then quenched with saturated aqueous sodium bicarbonate (10 mL). The resulting slurry was diluted with water (40 mL) and ethyl acetate (30 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3× 20 mL), and the combined organics were dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash column chromatography using petroleum ether and ethyl acetate as the eluent to give **8**.

*(E)-3-(4-Benzoyl-5-(4-methoxyphenyl)-1-propyl-1H-pyrrol-3-yl)-acrylaldehyde (**8a**).* Yellow oil (75 mg, 74%); IR (film) ν 1736, 1621 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 15.9 Hz, 1H), 7.55 (d, J = 7.5 Hz, 2H), 7.31−7.25 (m, 2H), 7.14 (t, J = 7.7 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 6.70 (d, J = 8.6 Hz, 2H), 6.45 (dd, J = 15.9, 8.0 Hz, 1H), 3.83 (t, J = 7.3 Hz, 2H), 3.71 (s, 3H), 1.65 (dd, J = 14.7, 7.4 Hz, 2H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 193.6, 159.6, 146.7, 139.2, 138.9, 131.9, 129.5, 127.7, 126.4, 122.9, 122.4, 121.9, 120.3, 113.7, 55.2, 49.2, 24.2, 11.0; HRMS (ESI) m/z calcd for $C_{24}H_{24}NO_3$ $[M + H]^+$ 374.1756, found 374.1751.

*(E)-3-(4-(4-Methoxybenzoyl)-5-phenyl-1-propyl-1H-pyrrol-3-yl)-acrylaldehyde (**8b**).* Yellow oil (46 mg, 46%); IR (film) ν 1736, 1671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 9.3 Hz, 3H), 7.30−7.36 (m, 3H), 7.27 (s, 1H), 7.15−7.06 (m, 2H), 6.69 (d, J = 7.9 Hz, 2H), 6.42 (dd, J = 15.9, 7.9 Hz, 1H), 3.85 (t, J = 7.1 Hz, 2H), 3.78 (s, 3H), 1.70−1.61 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 191.8, 163.0, 146.1, 136.3, 133.4, 132.4, 131.9, 131.5, 129.8, 129.2, 126.6, 123.3, 123.0, 122.2, 120.2, 113.2, 55.4, 49.4, 24.3, 11.0; HRMS (ESI) m/z calcd for $C_{24}H_{24}NO_3$ $[M + H]^+$ 374.1756, found 374.1751.

*(E)-3-(4-(4-Methylbenzoyl)-5-phenyl-1-propyl-1H-pyrrol-3-yl)-acrylaldehyde (**8c**).* Yellow oil (62 mg, 64%); IR (film) ν 1734, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 15.9 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.28 (s, 1H), 7.18 (t, J = 6.5 Hz, 5H), 6.95 (d, J = 8.0 Hz, 2H), 6.43 (dd, J = 15.9, 8.0 Hz, 1H), 3.87−3.83 (m, 2H), 2.25 (s, 3H), 1.69−1.62(m, 2H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 193.2, 167.0, 146.7, 142.8, 138.7, 136.1, 130.6, 129.8, 128.5, 128.4, 128.2, 126.3, 123.1, 122.4, 120.2, 49.3, 24.2, 21.5, 11.0; HRMS (ESI) m/z calcd for $C_{24}H_{24}NO_2$ $[M + H]^+$ 358.1807, found 358.1802.

*(E)-3-(4-(4-Methylbenzoyl)-1-propyl-5-(o-tolyl)-1H-pyrrol-3-yl)-acrylaldehyde (**8d**).* Yellow oil (60 mg, 60%); IR (film) ν 1735, 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 16.0 Hz, 1H), 7.25 (s, 1H), 7.10−6.97 (m, 2H), 6.94−6.81 (m, 6H), 6.51 (dd, J = 16.0, 7.8 Hz, 1H), 3.70 (t, J = 6.8 Hz, 2H), 2.27 (s, 3H), 2.23 (s, 3H), 1.65−1.56 (m, 2H), 0.78 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 194.5, 147.2, 141.1, 140.3, 138.3, 136.1, 130.3, 130.2, 129.6, 129.0, 128.5, 127.0, 126.7, 124.8, 122.9, 122.5, 120.5, 49.1, 24.2, 21.1, 19.8, 11.0; HRMS (ESI) m/z calcd for $C_{25}H_{25}NNaO_2$ $[M + Na]^+$ 394.1783, found 394.1777.

*(E)-3-(4-Benzoyl-5-phenyl-1-propyl-1H-pyrrol-3-yl)acrylaldehyde (**8e**).* Yellow oil (71 mg, 77%); IR (film) ν 1731, 1667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 16.0 Hz, 1H), 7.54 (d, J = 7.4 Hz, 2H), 7.32−7.24 (m, 2H), 7.19−7.07 (m, 7H), 6.47 (dd, J = 16.0, 8.0 Hz, 1H), 3.85 (t, J = 7.3 Hz, 2H), 1.69−1.60 (m, 2H), 0.80 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 193.5, 146.6, 139.2, 138.8, 132.0, 130.6, 130.3, 129.5, 128.5, 128.2, 127.7, 126.5, 123.1, 122.1, 120.4, 49.3, 24.2, 11.0; HRMS (ESI) m/z calcd for $C_{23}H_{22}NO_2$ $[M + H]^+$ 344.1651, found 344.1645.

*(E)-3-(5-(4-Fluorophenyl)-4-(4-methylbenzoyl)-1-propyl-1H-pyrrol-3-yl)acrylaldehyde (**8f**).* Yellow oil (78 mg, 76%); IR (film) ν 1731,1664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 15.9 Hz, 1H), 7.48 (d, J = 7.7 Hz, 2H), 7.29 (s, 1H), 7.20−7.10 (m, 2H), 6.98 (d, J = 7.7 Hz, 2H), 6.90 (t, J = 8.2 Hz, 2H), 6.42 (dd, J = 15.9, 7.9 Hz, 1H), 3.82 (t, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.71−1.58 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 193.0, 163.8, 161.4, 146.4, 143.1, 137.4, 136.1, 132.5, 132.4, 129.8, 128.6, 126.4, 123.1, 122.6, 120.1, 115.5, 115.3, 49.2, 24.2, 21.5, 11.0; HRMS (ESI) m/z calcd for $C_{24}H_{23}FNO_2$ $[M + H]^+$ 376.1713, found 376.1707.

*(E)-3-(4-(4-Bromobenzoyl)-5-(4-fluorophenyl)-1-propyl-1H-pyrrol-3-yl)acrylaldehyde (**8g**).* Yellow oil (73 mg, 62%); IR (film) ν 1734, 1666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, J = 7.9 Hz, 1H), 7.65−7.43 (m, 3H), 7.22 (s, 1H), 7.13 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 7.8 Hz, 2H), 6.78 (t, J = 8.4 Hz, 2H), 6.36 (dd, J = 15.9, 7.9 Hz, 1H), 3.75 (t, J = 7.2 Hz, 2H), 1.64−1.52 (m, 2H), 0.74 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 191.6, 166.4, 163.9, 145.9, 137.4, 135.0, 135.9, 134.9, 132.1, 132.0, 131.8, 128.7, 128.6, 123.4, 122.2, 120.4, 115.2, 114.9, 49.4, 24.2, 11.0; HRMS (ESI) m/z calcd for $C_{23}H_{19}BrFNNaO_2$ $[M + Na]^+$ 462.0481, found 462.0475.

*(E)-3-(4-(2-Chlorobenzoyl)-5-(4-chlorophenyl)-1-propyl-1H-pyrrol-3-yl)acrylaldehyde (**8h**).* Yellow oil (84 mg, 76%); IR (film) ν 1726, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 16.0 Hz, 1H), 7.28 (s, 1H), 7.13−6.95 (m, 8H), 6.56 (dd, J = 16.0, 8.0 Hz, 1H), 3.65 (t, J = 7.2 Hz, 2H), 1.65−1.55 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4, 191.3, 146.9, 140.4, 140.1, 135.0, 131.8, 130.9, 130.4, 129.5, 129.2, 128.1, 127.4, 126.2, 122.8, 121.8, 121.0, 49.2, 24.1, 10.9; HRMS (ESI) m/z calcd for $C_{23}H_{20}Cl_2NO_2$ $[M + H]^+$ 412.0871, found 412.0866.

*(E)-3-(5-(3-Bromophenyl)-4-(4-methoxybenzoyl)-1-propyl-1H-pyrrol-3-yl)acrylaldehyde (**8i**).* Yellow oil (52 mg, 62%); IR (film) ν 1734, 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, J = 7.9 Hz, 1H), 7.65−7.54 (m, 3H), 7.37−7.27 (m, 3H), 7.14−7.05 (s, 2H), 6.69 (d, J = 8.7 Hz, 2H), 6.42 (dd, J = 15.9, 7.9 Hz, 1H), 3.85 (t, J = 7.2 Hz, 2H), 3.77 (s, 3H), 1.71−1.60 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 191.8, 163.0, 146.2, 136.4, 133.4, 132.4, 131.9, 131.5, 129.8, 129.2, 126.5, 123.3, 123.0, 122.2, 120.2, 113.2, 55.4, 49.4, 24.2, 11.0; HRMS (ESI) m/z calcd for $C_{24}H_{22}BrNNaO_3$ $[M + Na]^+$ 474.0681, found 474.0675.

*(E)-3-(4-Butyryl-5-phenyl-1-propyl-1H-pyrrol-3-yl)acrylaldehyde (**8j**).* Yellow oil (52 mg, 62%); IR (film) ν 1731, 1669 cm^{-1}; ^{1}H NMR

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(400 MHz, $CDCl_3$) δ 9.63 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 16.0 Hz, 1H), 7.52 (s, 3H), 7.35 (s, 2H), 7.21 (s, 1H), 6.50 (dd, J = 16.0, 7.8 Hz, 1H), 3.65 (t, J = 6.8 Hz, 2H), 2.04 (t, J = 6.6 Hz, 2H), 1.67−1.58 (m, 2H), 1.48−1.39 (m, 2H), 0.80 (t, J = 6.8 Hz, 3H), 0.65 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3, 194.6, 148.1, 139.3, 131.6, 130.7, 129.6, 128.9, 126.8, 122.6, 122.0, 120.2, 49.2, 43.9, 24.2, 18.0, 13.6, 11.0; HRMS (ESI) m/z calcd for $C_{20}H_{24}NO_2$ $[M + H]^+$ 310.1807, found 310.1802.

*(E)-3-(4-(4-Methylbenzoyl)-2-oxo-1,5-dipropyl-2,3-dihydro-1H-pyrrol-3-yl)acrylaldehyde (**8k**).* Yellow oil (52 mg, 60%); IR (film) ν 1725, 1640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, J = 7.4 Hz, 1H), 7.69 (d, J = 7.8 Hz, 2H), 7.28−7.26 (m, 3H), 6.71 (d, J = 12.0 Hz, 1H), 6.09−5.98 (m, 1H), 3.58−3.44 (m, 1H), 3.27−3.12 (m, 1H), 2.43 (s, 3H), 2.15−1.95 (m, 2H), 1.86−1.64 (m, 2H), 1.33−1.16 (m, 2H), 0.98 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 191.1, 166.8, 146.5, 135.3, 133.3, 129.9, 129.8, 92.7, 41.4, 37.9, 22.1, 21.9, 17.4, 13.8, 11.7; HRMS (ESI) m/z calcd for $C_{21}H_{26}NO_2$ $[M + H]^+$ 324.1964, found: 324.1958.

*(E)-Dimethyl 4-(3-oxoprop-1-en-1-yl)-1-propyl-1H-pyrrole-2,3-dicarboxylate (**8m**).* Yellow oil (45 mg, 60%); IR (film) ν 1707, 1662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 16.0 Hz, 1H), 7.19 (s, 1H), 6.43 (dd, J = 16.0, 7.8 Hz, 1H), 4.17 (t, J = 7.2 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 1.85−1.75 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 165.1, 160.9, 144.1, 127.4, 126.4, 124.7, 120.7, 118.6, 52.2, 51.3, 24.5, 10.9; HRMS (ESI) m/z calcd for $C_{14}H_{17}NO_5$ $[M + Na]^+$ 302.1004, found 302.0999.

*(E)-3-(4-Benzoyl-1-ethyl-5-phenyl-1H-pyrrol-3-yl)-propenal (**8o**).* Yellow oil (62 mg, 72%); IR (film) ν 1734, 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 15.9 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.29 (s, 1H), 7.17−7.14 (m, 5H), 6.93 (d, J = 7.9 Hz, 2H), 6.43 (dd, J = 15.9, 8.0 Hz, 1H), 3.91 (q, J = 7.2 Hz, 2H), 2.23 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 193.0, 146.5, 142.6, 138.3, 136.0, 130.4, 130.2, 129.7, 128.4, 128.3, 128.1, 126.2, 122.3, 120.2, 42.5, 21.4, 16.3; HRMS (ESI) m/z calcd for HRMS (ESI) m/z calcd for $C_{23}H_{22}NO_2$ $[M + H]^+$ 344.1651, found 344.1645.

*(E)-3-(4-Benzoyl-1-benzyl-5-phenyl-1H-pyrrol-3-yl)acrylaldehyde (**8p**).* Yellow oil (84 mg, 80%); IR (film) ν 1731, 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 16.0 Hz, 1H), 7.50−7.45 (m, 2H), 7.23−7.16 (m, 5H), 7.05−6.98 (m, 7H), 6.92−6.88 (m, 2H), 6.33 (dd, J = 16.0, 8.0 Hz, 1H), 4.96 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 193.5, 146.3, 139.6, 138.7, 136.3, 132.1, 130.7, 130.0, 129.6, 129.0, 128.6, 128.2, 127.8, 127.0, 126.9, 123.7, 122.2, 120.9, 51.3; HRMS (ESI) m/z calcd for $C_{27}H_{22}NO_2$ $[M + H]^+$ 392.1651, found 392.1645.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02919.

Crystal data for **7c**. (CIF)

X-ray data for **7c**, HSQC of **7a**, **7b**, **7e** and **7r**, copies of ^{1}H and ^{13}C NMR spectra of all the new compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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