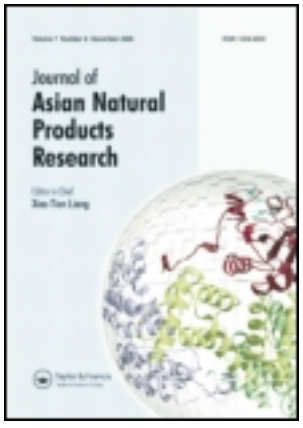

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Zhi-Yun Kang [a], Qing-Jian Zhang [a], Ruo-Yun Chen [a], Pei-Cheng Zhang [a] & De-Quan Yu [a]

[a] State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, 100050, China

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The total synthesis of hypodematine

Zhi-Yun Kang, Qing-Jian Zhang, Ruo-Yun Chen, Pei-Cheng Zhang and De-Quan Yu*

State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, China

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Hypodematine, isolated from *Hypodematium sinense* Iwatsuki as an alkaloid with a new skeleton, was synthesized via nine reaction steps, in which the synthesis of 2-aryl-1-benzazocines via Beckmann rearrangement of 5*H*-benzocyclohepten-5-one oxime mesylate in dry toluene is discussed.

Keywords: hypodematium; total synthesis; Beckmann rearrangement; Grignard reagents

1. Introduction

Hypodematine [1,2] (**1** Figure 1) was isolated from the whole plant of a fern, *Hypodematium sinense* Iwatsuki in 1991. *H. sinense* was used as a folk medicine to treat Meniere's syndrome, and the effective rate was 95.1%. Pharmacological experiments showed that it has an antifertility action, and the rate of inducing abortion in pregnant rabbits was 86.6% [1]. Hypodematine is a novel alkaloid of benzazocine with a phenyl substituent in C-2-position. There are only a limited number of natural products that incorporate the azocine ring. Although the synthetic route of the skeleton of hypodematine has been reported [3], it is difficult to synthesize the hypodematine because the azocines are very unstable. Here, we describe the synthesis of hypodematine and its analog with azocine ring (Figure 1).

2. Results and discussion

The synthetic route to hypodematine and its analogs is shown in Scheme 1. Here, we describe the synthesis and structural elucidation of these compounds.

The hydroxy group in the structure of hypodematine (**1**) makes it difficult to prepare this compound. In our early study, compound **12** was synthesized and used as the start material to prepare the hypodematine by removing the methyl, but the result showed that hypodematine (**1**) could not be prepared with this method, because the methyl was removed in the acid condition, and the structure of azocine was also destroyed in this condition. Each of the first five steps reacted intensely, and in this condition, only the methyl could be used as the protection group of hydroxy, whereas the compounds with azocine ring were very unstable, so choosing an appropriate hydroxy protect group in different stages is the key factor for preparing hypodematine (**1**). The reaction of methyl removing must be finished before the azocine is formed. Compounds **6** and **8** are likely to be the right compounds to remove the methyl. Our results showed that compound **6** is not fit to remove the methyl because of the formation of various byproducts. Compound **8** heated in dry dichloromethane (DCM) with BBr_3 gave the sole product **9A** in

*Corresponding author. Email: dqyu@imm.ac.cn

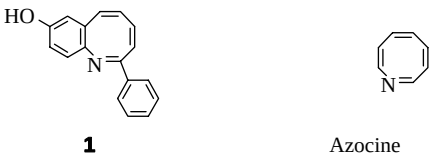
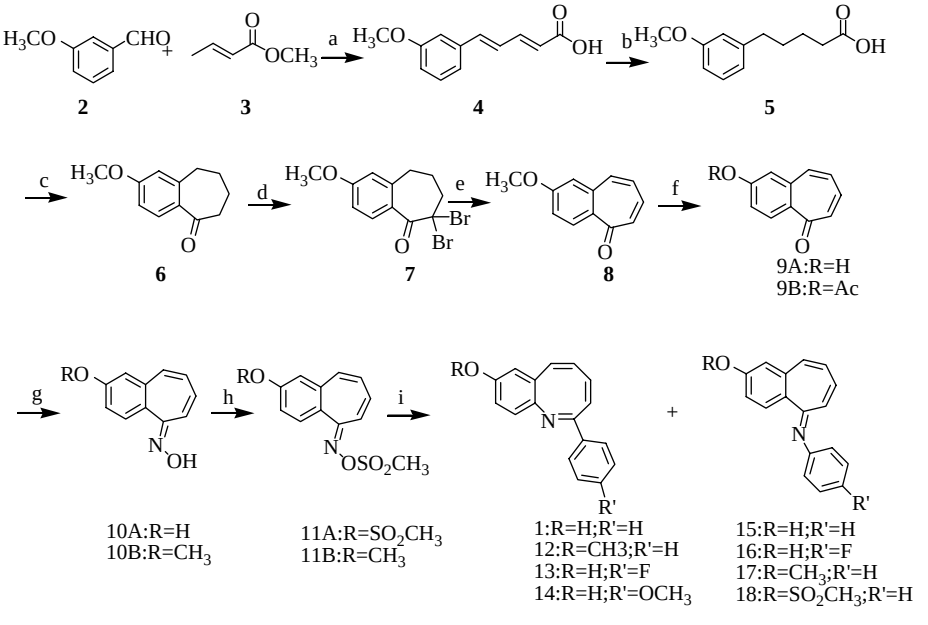
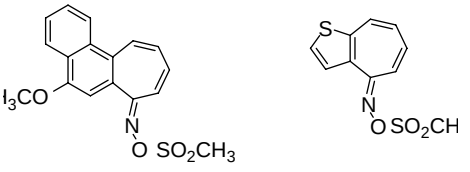


Figure 1. Structures of hypodematine **1** and azocine.

almost quantitative yield. We protected the hydroxy of compound **9A** with acetyl to give compound **9B**. The acetyl protective group can be removed by dibutyltin oxide, a near-neutral reagent, in methanol [4]. Both **9A** and **9B** reacted with hydroxylamine hydrochloride gave the same product **10A** in good yields. The esterification of the oxime **10A** and **10B** to the corresponding mesylates **11A** and **11B**, respectively, was best carried out with methanesulfonyl chloride and triethylamine in dry DCM. The target compound **1** and their analogs were prepared via Beckmann rearrangement of mesylates in dry toluene in which Grignard reagents were used. Both rearrangement and unrearrangement products were found in our research. As shown in Scheme 1, compounds **1** and **12**–**18** were prepared easily in dry toluene promoted by Grignard reagents under nitrogen. In our ongoing research toward Beckmann rearrangement promoted directly by Grignard reagents, another two kinds of oxime mesylates **19** and **20** (Figure 2) were prepared and used in Beckmann rearrangement. The similar method was used to prepare the intermediate (*E*)-5-methoxy-7*H*-cyclohepta[a]naphthalen-7-one oxime mesylate (**19**) and (*E*)-4*H*-cyclohepta[b] thiophen-4-one oxime mesylate (**20**) that are described in Schemes 2 and 3. Both aryl and aliphatic Grignard reagents were used in Beckmann rearrangement of mesylate **19**. We found that the reaction did not give the rearrangement compound as expected when the aliphatic Grignard reagents were used (Scheme 4). Whatever the kind of Grignard reagents reacted with



Scheme 1. Synthesis of hypodematine and its analogs. Reagents and conditions: (a) t-But-OK; (b) Al/Ni, NaOH; (c) polyphosphoric acid (PPA); (d) AcOH, Br_2; (e) LiCl, dimethylformamide (DMF) reflux; (f) BBr_3, CH_2Cl_2 reflux; (g) NH_2-OH-HCl, pyridine, C_2H_5OH; (h) Et_3N CH_3SO_2Cl; (i) R-Ph-Mg-Br, toluene, -20°C to 20°C.



19 **20**

Figure 2. Another two kinds of oxime mesylates.

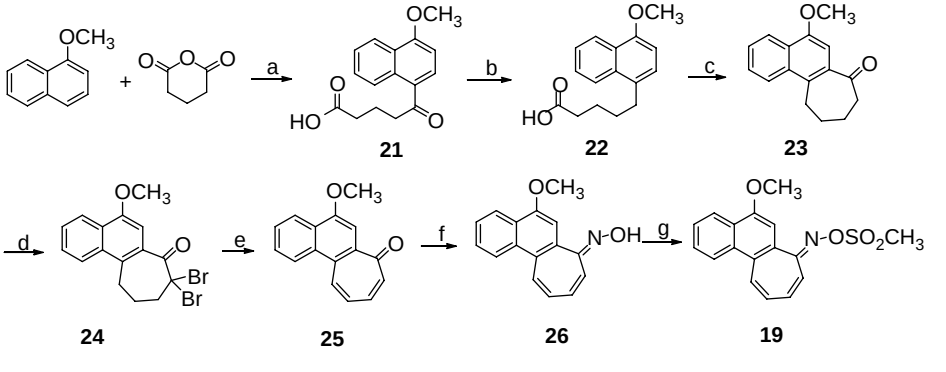
compound **20**, no rearrangement product was found (Scheme 5). In the study of the rearrangement reaction of three kinds of oxime mesylate, we found that compounds **11A** and **11B** were most efficient. When the compound **19** was studied as the substrate, rearrangement products could also be found. But the law of rearrangement was not in accord with that of compounds **11A** and **11B**. The nucleophilic ability order of Grignard reagents was IsopropylMgBr > $PhCH_2MgBr$(PhC_2H_4MgBr)> p-CH_3-OPhMgBr> PhMgBr > p-FPhMgBr. The lowest activity Grignard reagents p-FPhMgBr reacted with compound **19** to give the entire rearrangement product **33B**. Compound **25** reacted with 4-fluoroaniline gave compound **34B** in good yield. It was the lower not the higher active Girgnard reagents that were easy to produce the azocines when the compound **19** was studied. This suggests that the activity of the mesylate was the key reason for the Beckmann rearrangement. The structure of all compounds was elucidated with ^{1}H NMR, ^{13}C NMR and MS. The structure of hypodematine was determined by NMR, HR-ESI-MS, and X-ray. Unfortunately, the data of natural products isolated from *Hypodematium sinense* Iwatsuki were not in accord with that of hypodematine and turned out to be in accord with *N*-phenyl-α-naphthalene amine in structure. The hypodematine was synthesized totally.

In summary, we have presented a concise approach of hypodematine. Biological evaluation of azocines is in progress.

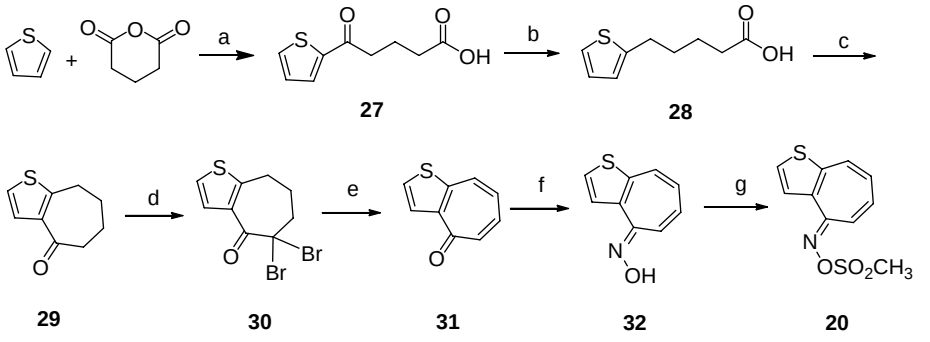
3. Experimental

3.1 General experimental procedures

Melting points were determined on an XT5B micro-melting apparatus (Beijing, China) and are uncorrected. The NMR spectra were recorded on Varian Mercury-300 spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and Varian 600 spectrometer (600 MHz for ^{1}H and 150 MHz for ^{13}C) (Varian, Palo Alto, CA, USA). EI-MS and HR-ESI-MS were obtained on AutoSpec Ultima-TOF (Micromass, Manchester, UK) and AccuTOF CS



Scheme 2. Synthesis of compound **19**. Reagents and conditions: (a) $AlCl_3$, CH_2Cl_2; (b) anhydrous NH_2NH_2, KOH; (c) PPA; (d) AcOH, Br_2; (e) LiCl, DMF, reflux; (f) NH_2-OH·HCl, pyridine, C_2H_5OH; (g) Et_3N, CH_3SO_2Cl.



Scheme 3. Synthesis of compound **20**. Reagents and conditions: (a) $AlCl_3$, CH_2Cl_2; (b) anhydrous NH_2NH_2, KOH; (c) PPA; (d) phenyltrimethylammonium tribromide (PTAT)/tetrahydrofuran (THF); (e) LiCl, DMF, reflux; (f) NH_2-OH·HCl, pyridine, C_2H_5OH; (g) Et_3N, CH_3SO_2Cl.

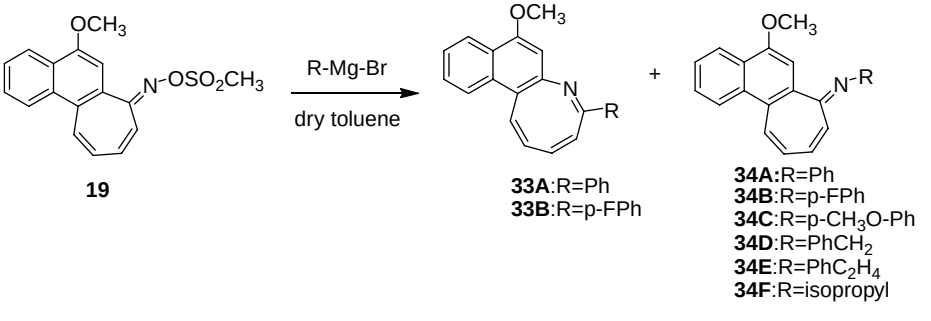
(JEOL, Tokyo, Japan) mass spectrometer, respectively.

3.2 General procedures for compounds 1 and 12–18

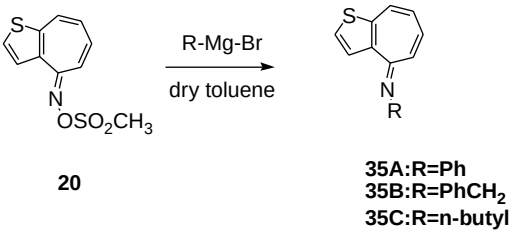
PhMgBr (0.5 ml of a 3 M ethereal solution, 1.5 mmol) was added to a solution of benzotropone oxime mesylate **4** (279 mg, 1 mmol) in dry toluene (5 ml) at −20°C. The resulting solution was stirred at −20°C for 30 min and at 0°C for 1 h. The reaction was carried out under an argon atmosphere all the time. Ether enriched with water was used to quench the reaction, and the aqueous layer was separated and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (elution with ethyl acetate/petroleum ether 1:9). Compound **12** was obtained as a yellow solid in 90% yield. Compounds **1** and **13**–**18** were synthesized by the same procedure. Compounds **1**, **13**, and **14** are yellow solid in 48.6%, 33%, and 87% yield, respectively. Compounds **15** and **16** are orange-red solid in 17% and 23% yield, respectively. Compounds **17** and **18** are orange solid in a little amount.

3.2.1 Compound 1

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 8.08 (s, 1H), 7.91 (d, $J = 6.6$ Hz, 2H), 7.45 (m, 1H), 7.43 (m, 2H), 6.78 (br s,



Scheme 4. The rearrangement reaction of compound **19**.



Scheme 5. The rearrangement reaction of compound **20**.

2H), 6.50 (m, 1H), 6.48 (d, $J = 2.1$ Hz, 1H), 6.30 (ddd, $J = 0.9$, 3.6, 11.7 Hz, 1H), 6.14 (dd, $J = 3.6$, 11.7 Hz, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 167.2, 154.5, 144.7, 139.2, 135.6, 133.4, 132.1, 131.3 (2C), 129.1 (2C), 129.0, 128.5 (2C), 124.2, 116.1, 115.8. HR-ESI-MS: *m/z* 248.1061 $[M + H]^+$ (calcd for $C_{17}H_{14}NO$, 248.1075).

3.2.2 *Compound* ***12***

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 7.92 (dd, $J = 7.5$, 1.2 Hz, 2H), 7.40–7.50 (m, 3H), 6.88 (m, 2H), 6.56 (d, $J = 6.3$ Hz, 2H), 6.49 (d, $J = 11.4$ Hz, 1H), 6.29 (dd, $J = 11.4$, 3.0 Hz, 1H), 6.16 (dd, $J = 11.4$, 3.0 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 167.4, 156.9, 145.6, 139.0, 135.6, 133.3, 132.2, 131.3, 131.2, 129.2 (2C), 128.4 (2C), 124.1, 115.0, 114.1, 55.6. EI-MS: *m/z*: 262.2 $[M + H]^+$.

3.2.3 *Compound* ***13***

^{1}H NMR (600 MHz, CD_3COCD_3) δ (ppm): 8.16 (s, 1H), 7.96 (dd, $J = 5.4$, 9.0 Hz, 2H), 7.19 (t, $J = 9.0$ Hz, 2H), 6.79 (dd, $J = 2.4$, 8.4 Hz, 1H), 6.76 (d, $J = 8.4$ Hz, 1H),6.47 (m, 1H), 6.31 (dd, $J = 12$, 3.6 Hz, 1H), 6.14 (dd, $J = 12$, 3.6 Hz, 1H). ^{13}C NMR (150 MHz, CD_3COCD_3) δ (ppm): 166.0, 164.3, 154.5, 144.4, 135.9, 135.6 (3C), 133.4, 132.1, 130.9, 130.8 (2C), 129.0, 124.2, 116.1, 115.9. HR-ESI-MS: *m/z* 266.0967 $[M + H]^+$ (calcd for $C_{17}H_{13}NOF$, 266.0981).

3.2.4 *Compound* ***14***

^{1}H NMR (600 MHz, CD_3COCD_3) δ (ppm): 8.07 (s, 1H), 7.86 (d, $J = 9.3$ Hz, 2H), 6.96 (d, $J = 9.3$ Hz, 2H), 6.77 (dt, $J = 14.4$, 5.5 Hz, 2H), 6.48 (m, 2H), 6.45 (s, 1H), 6.28 (dd, $J = 11.4$, 3.3 Hz, 1H), 6.13 (dd, $J = 11.4$, 3.3 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (150 MHz, CD_3COCD_3) δ (ppm): 166.4, 162.6, 154.2, 144.9, 135.2, 133.4, 132.0, 131.8, 131.4, 130.0 (2C), 129.1, 124.2, 116.0, 115.7, 114.3(2C), 55.7.HR-ESI-MS: *m/z* 278.1179 $[M + H]^+$ (calcd for $C_{18}H_{16}NO_2$, 278.1181).

3.2.5 *Compound* ***15***

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 9.75(s, 1H), 8.18 (d, $J = 8.7$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 2H), 7.14 (dd, $J = 2.7$, 9.0 Hz, 1H), 6.90 (m, 1H), 6.88 (m, 2H), 6.80 (d, $J = 7.8$ Hz, 2H), 6.40 (m, 3H). ^{13}C NMR(75 MHz, CD_3COCD_3) δ (ppm): 163.3, 159.8, 152.2, 138.1, 137.2(2C), 132.6, 132.0, 129.9 (2C), 129.1, 127.5, 123.8, 120.6(2C), 119.0, 117.2. HR-ESI-MS: *m/z* 248.1077 $[M + H]^+$ (calcd for $C_{17}H_{14}NO$,248.1075).

3.2.6 *Compound* ***16***

Orange solid, ^{1}H NMR (600 MHz, CD_3COCD_3) δ (ppm): 8.94 (s, 1H), 8.16 (d, $J = 9.0$ Hz, 1H), 7.10 (dd, $J = 4.8$, 9.0 Hz, 2H), 7.08 (m, 1H), 6.99 (dd,

$J = 2.4$, 10.8 Hz, 1H), 6.96 (d, $J = 3.0$ Hz, 1H), 6.83 (dd, $J = 4.8$, 9.0 Hz, 2H), 6.47 (ddd, $J = 2.4$, 7.2, 10.2 Hz, 1H), 6.43 (ddd, $J = 2.4$, 7.2, 10.8 Hz, 1H), 6.37 (dd, $J = 2.4$, 10.2 Hz, 1H). ^{13}C NMR (150 MHz, CD_3COCD_3) δ (ppm): 164.0, 160.8, 159.8, 159.3, 148.4, 138.1, 132.5, 132.1, 131.4, 128.9, 127.6, 122.2, 122.1, 119.1, 117.2, 116.5, 116.4. HR-ESI-MS: *m/z* 266.0987 $[M + H]^+$(calcd for $C_{17}H_{13}NOF$, 266.0981).

3.2.7 Compound **17**

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 8.24 (d, $J = 9.0$ Hz, 1H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.16 (dd, $J = 2.7$, 9.0 Hz, 1H), 7.05 (m, 3H), 6.80(d, $J = 7.8$ Hz, 2H), 6.38–6.45 (m, 3H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 163.1, 160.6, 150.7, 136.9, 136.8, 132.3, 131.9, 130.8, 129.5 (2C), 128.9, 127.2, 123.6, 120.2 (2C), 117.9, 115.0, 55.3. HR-ESI-MS: *m/z* 262.1242 $[M + H]^+$ (calcd for $C_{17}H_{16}NO$,262.1232).

3.2.8 Compound **18**

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.28 (d, $J = 8.5$ Hz, 1H), 7.46 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.37 (d, $J = 2.0$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.11(t, $J = 8.0$ Hz, 1H), 6.96 (d, $J = 11.5$ Hz, 1H),6.89 (dd, $J = 8.0$, 1.0 Hz, 2H),6.48 (m,1H), 6.41 (d, $J = 4.0$ Hz, 2H), 3.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 162.9, 150.0, 149.9, 137.4, 137.1, 134.9, 132.0, 129.5, 129.2 (2C), 128.9, 128.1, 124.0, 123.4, 123.3, 120.0 (2C), 37.6.

3.3 General procedures for compounds 11A, 11B, 19, and 20

To a solution of **26** (125 mg, 0.01 mol) in 100 ml dry DCM, Et_3N of 6 ml was added. The reaction was cooled to 0°C, and 0.8 ml methylsufonyl chloride was added and stirred for 10 min. The reaction was diluted with DCM, and the organic phase was washed with brine and dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The residue was washed with methanol. Compound **19** was obtained as a yellow powder in 87% yield. Compounds **11A**, **11B**, and **20** were synthesized by the same procedure.

3.3.1 Compound **19**

^{1}H NMR (300 MHz, DMSO) δ (ppm): 8.50 (d, $J = 7.8$ Hz, 1H), 8.29 (dd, $J = 7.8$, 1.8 Hz, 1H), 8.08 (d, $J = 12.0$ Hz, 1H), 7.73 (m, 2H), 7.25 (s, 1H), 6.84 (m, 2H), 6.74 (m, 1H), 4.09(s, 3H), 3.44 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ (ppm): 162.1, 156.6, 132.4, 131.7, 130.4, 129.8, 128.3, 127.3, 126.3, 125.7, 125.6, 125.0, 122.0, 120.6, 103.3, 55.9, 36.7; ESI-MS: *m/z* 330 $[M + H]^+$.

3.3.2 Compound **11A**

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.94 (d, $J = 6.6$ Hz, 1H), 7.55 (m, 2H), 7.05 (d, $J = 11.7$ Hz, 1H), 6.89 (d, $J = 11.7$ Hz, 1H), 6.60 (dd, $J = 11.4$, 7.2 Hz, 1H), 6.46 (dd, $J = 11.4$, 7.2 Hz, 1H), 3.51 (s, 3H), 3.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.0, 151.6, 138.4, 135.1, 132.6, 131.6, 128.5, 124.7, 124.5, 122.1, 37.7, 36.8; ESI-MS: *m/z* 344.02 $[M + H]^+$, 248.04 $[M-CH_3SO_3]^+$, 709.02 $[2M + Na]^+$.

3.3.3 Compound **11B**

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.92 (d, $J = 9.0$ Hz, 1H), 7.10 (dd, $J = 9.0$, 2.1 Hz, 1H), 6.95 (m, 3H), 6.58 (dd, $J = 11.7$, 6.9 Hz, 1H), 6.47 (dd, $J = 11.7$, 4.5 Hz, 1H), 3.89 (s, 3H), 3.21 (s, 3H).

3.3.4 Compound **20**

m.p. 136–137°C. ^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 7.90 (d, $J = 5.7$ Hz, 1H), 7.74 (d, $J = 5.7$ Hz, 1H), 7.30 (d, $J = 11.4$ Hz, 1H), 7.16 (d, $J = 12.6$ Hz, 1H), 6.91 (dd, $J = 12.6$, 8.1 Hz, 1H), 6.56 (dd, $J = 11.8$, 8.1 Hz, 1H). ^{13}C NMR

(75 MHz, CD_3COCD_3) δ (ppm): 158.3, 135.5, 132.2, 130.0, 128.5, 125.3, 121.2, 36.5.

3.4 General procedures for compounds 33A, 33B, 34A, 34B, 34C, 34D, 34E, and 34F

Compounds **33A**, **33B**, **34A**, **34B**, **34C**, **34D**, **34E**, and **34F** were synthesized by the same procedure as compound **12**. Compounds **33A**, **33B**, **34A**, **34B**, and **34C** were isolated by HPLC in lower yield less than 10%. Compounds **34D**, **34E**, and **34F** were prepared in quantitative yields.

*3.4.1 Compound **33A***

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 8.17 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.99 (dd, $J = 1.2$, 0.6 Hz, 2H), 7.76 (d, $J = 6.0$ Hz, 1H), 7.52 (m, 1H), 7.49 (m, 3H), 7.41 (dt, $J = 8.4$, 0.6 Hz, 1H), 6.90 (d, $J = 11.4$ Hz, 1H), 6.60 (s, 1H), 6.57 (d, $J = 11.4$ Hz, 1H), 6.40 (dd, $J = 11.4$, 3.6 Hz, 1H), 6.36 (dd, $J = 11.4$, 3.6 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 167.4, 156.4, 151.4, 138.9, 136.8, 134.3, 132.6, 131.6, 131.2, 129.3 (3C), 128.8 (2C), 127.8, 124.8, 124.7, 123.9, 122.9, 113.2, 101.6, 56.1. HR-MS-ESI: *m/z* 312.1388 $[M + H]^+$ (calcd for $C_{22}H_{18}NO$, 312.1388).

*3.4.2 Compound **33B***

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 8.17 (d, $J = 7.5$ Hz, 1H), 8.04 (dd, $J = 5.4$, 2.1 Hz, 2H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.50 (dt, $J = 8.4$, 1.5 Hz, 1H), 7.41 (dt, $J = 7.5$, 1.5, Hz, 1H), 7.24 (dd, $J = 5.4$, 2.1 Hz, 2H), 6.90 (d, $J = 7.8$ Hz, 1H), 6.60 (s, 1H), 6.56 (d, $J = 11.1$ Hz, 1H), 6.39 (dd, $J = 15.0$, 3.6 Hz, 1H), 6.35 (dd, $J = 7.8$, 3.6 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 166.9, 156.2, 151.0, 137.0, 135.5, 135.3, 135.1, 134.1, 132.5, 130.7, 131.6, 130.1, 130.0, 127.6, 124.6, 124.5, 122.7, 116.1, 115.7, 113.1, 101.3, 55.9. HR-MS-ESI: *m/z* 330.1290 $[M + H]^+$ (calcd for $C_{22}H_{17}FNO$, 330.1294).

*3.4.3 Compound **34A***

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 8.50 (d, $J = 8.4$ Hz, 1H), 8.35 (dd, $J = 7.2$, 1.2 Hz, 1H), 8.03 (d, $J = 7.8$ Hz, 1H), 7.76 (s, 1H), 7.71 (dt, $J = 7.2$, 1.8 Hz, 1H), 7.65 (dt, $J = 7.2$, 1.2 Hz, 1H), 7.37 (dt, $J = 7.8$, 1.2 Hz, 2H), 7.09 (dt, $J = 0.6$, 1.8 Hz, 1H), 6.90 (dd, $J = 7.8$, 1.2 Hz, 2H), 6.70 (ddd, $J = 1.2$, 6.0, 7.8 Hz, 1H), 6.59 (dd, $J = 10.8$, 6.0 Hz, 1H), 6.36 (d, $J = 10.8$ Hz, 1H), 4.15 (s, 3H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 165.3, 157.8, 151.9, 140.6, 133.5, 132.0, 130.9, 130.1 (2C), 129.0, 128.7, 127.5, 127.3, 126.1 (2C), 125.8, 124.5, 123.1, 120.9 (2C), 105.2, 56.3. HR-ESI-MS: *m/z* 312.1387 $[M + H]^+$ (calcd for $C_{22}H_{18}NO$, 312.1388).

*3.4.4 Compound **34B***

^{1}H NMR (600 MHz, CD_3COCD_3) δ (ppm): 6.38 (d, $J = 11.7$ Hz, 1H), 6.62 (dd, $J = 11.7$, 6.6 Hz, 1H), 6.70 (ddd, $J = 6.6$, 3.6, 1.2, Hz, 1H), 8.02 (d, $J = 11.4$ Hz, 1H), 8.35 (dd, $J = 9.3$, 1.5 Hz, 1H), 7.70 (m, 1H), 7.64 (m, 1H), 8.47 (d, $J = 5.7$ Hz, 1H), 7.73 (s, 1H), 6.94 (m, 2H), 7.14 (t, $J = 8.0$, 7.0 Hz, 2H), 4.14 (s, 3H). ^{13}C NMR (150 MHz, CD_3COCD_3) δ (ppm): 165.2, 161.3 (F-C), 158.2 (F-C), 157.1, 156.2, 147.2, 139.7, 132.7, 131.4, 130.2, 128.0, 127.9, 126.8, 126.6, 126.5, 125.4, 125.0, 122.4, 121.9, 121.8, 116.0, 115.7, 104.4, 55.5. HR-MS-ESI: *m/z* 330.1290 $[M + H]^+$ (calcd for $C_{22}H_{17}FNO$, 330.1303).

*3.4.5 Compound **34C***

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 8.46 (d, $J = 8.4$ Hz, 1H), 8.34 (dd, $J = 8.4$, 1.5 Hz, 1H), 8.00 (d, $J = 12.0$ Hz, 1H), 7.73 (s, 1H), 7.68 (dd,

$J = 8.4$, 1.5 Hz, 1H), 7.66 (dd, $J = 8.4$, 1.5 Hz, 1H), 6.95 (dd, $J = 6.3$, 3.0 Hz, 2H), 6.90 (dd, $J = 6.3$, 3.0 Hz, 2H), 6.68 (dd, $J = 12.0$, 6.6 Hz, 1H), 6.59 (dd, $J = 12.0$, 6.6 Hz, 1H), 6.41 (d, $J = 12.0$ Hz, 1H), 4.18 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 164.8, 157.5, 157.4, 144.2, 140.6, 133.2, 131.4, 130.6, 129.2, 128.4, 127.2, 127.1, 127.0, 125.7, 125.6, 122.9, 122.4 (2C), 115.0 (2C), 105.0, 56.0, 55.6. HR-MS-ESI: *m/z* 342.1501 $[M + H]^+$ (calcd for $C_{23}H_{20}NO_2$, 342.1494).

3.4.6 Compound **34D**

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 8.42 (d, $J = 11.7$ Hz, 1H), 8.32 (d, $J = 8.1$ Hz, 1H), 7.95 (d, $J = 12.9$ Hz, 1H), 7.67 (dt, $J = 8.1$, 1.2 Hz, 1H), 7.60 (dt, $J = 11.7$, 0.9 Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 7.33 (t, $J = 6.9$ Hz, 2H), 7.44 (s, 1H), 7.22 (t, $J = 7.5$ Hz, 1H), 6.66 (m, 3H), 4.81 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 164.9, 156.4, 140.8, 140.3, 132.0, 129.7, 129.5, 128.1 (2C), 127.3, 127.5 (2C), 126.2 (2C), 125.9, 125.8, 125.7, 124.5, 123.5, 122.0, 104.2, 55.1, 53.8. HR-MS-ESI: *m/z* 326.1550 $[M + H]^+$ (calcd for $C_{23}H_{20}NO$, 326.1545).

3.4.7 Compound **34E**

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 8.40 (d, $J = 12.3$ Hz, 1H), 8.30 (d, $J = 8.1$ Hz, 1H), 7.89 (d, $J = 12.3$ Hz, 1H), 7.66 (dt, $J = 8.1$, 1.5 Hz, 1H), 7.57 (t, $J = 12.3$ Hz, 1H), 7.36 (d, $J = 7.2$ Hz, 2H), 7.29 (t, $J = 6.6$ Hz, 3H), 7.18 (m, 1H), 6.58 (m, 2H), 6.48 (m, 1H), 4.07 (s, 3H), 3.82 (t, $J = 6.9$ Hz, 2H), 3.06 (t, $J = 6.9$ Hz, 2H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 165.3, 127.1, 130.0, 126.7, 130.2, 124.3, 132.9, 125.4, 128.3, 126.8, 122.9, 124.3, 157.2, 105.4, 141.2, 141.7, 129.9 (2C), 128.9(2C), 126.7, 38.0, 52.8, 56.0. HR-MS-ESI: *m/z* 340.1691 $[M + H]^+$ (calcd for $C_{24}H_{22}NO$, 340.1701).

3.4.8 Compound **34F**

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 8.37 (d, $J = 8.4$ Hz, 1H), 8.30 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.88 (d, $J = 12.6$ Hz, 1H), 7.65 (dt, $J = 8.4$, 1.5 Hz, 1H), 7.57 (dt, $J = 7.2$, 1.2 Hz, 1H), 7.27 (s, 1H), 6.60 (m, 3H), 4.11 (m, 1H), 4.06 (s, 3H), 1.17 (d, $J = 3.3$ Hz, 6H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 162.3, 157.2, 141.2, 132.9 (2C), 130.2, 130.1, 128.2, 126.8 (2C), 126.6, 125.4, 124.1, 122.9, 105.3, 56.0, 50.1, 23.8 (2C). HR-MS-ESI: *m/z* 278.1539 $[M + H]^+$ (calcd for $C_{19}H_{20}NO$, 278.1545).

3.5 General procedures for compounds 35A, 35B, and 35C

To a solution of **20** (50 mg, 0.19 mmol) in 10 ml dry toluene, PhMgBr (0.1 ml of 2.8 M ethereal solution) at -20°C was added. The resulting solution was stirred at -20°C for 30 min. The reaction was carried out under an argon atmosphere all the time. Brine was used to quench the reaction, and the aqueous layer was separated and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (elution with petroleum ether). Compound **35A** was obtained as a red solid in quantitative yield. Compounds **35B** and **35C** were synthesized by the same procedure.

3.5.1 Compound **35A**

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 7.92 (d, $J = 5.4$ Hz, 1H), 7.78 (d, $J = 5.4$ Hz, 1H), 7.74 (t, $J = 5.1$ Hz, 2H), 7.18 (d, $J = 11.1$ Hz, 1H), 7.04 (t, $J = 7.5$ Hz, 1H), 6.79 (d, $J = 5.1$ Hz, 2H), 6.58 (m, 2H), 6.04–6.44 (m, 1H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 158.5, 152.1, 144.0, 143.2, 132.9, 131.2, 130.6, 130.2 (2C), 129.6, 128.4, 125.5, 123.5, 120.4 (2C).

*3.5.2 Compound **35B***

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 8.14 (d, $J = 5.4$ Hz, 1H), 7.80 (d, $J = 5.4$ Hz, 1H), 7.49 (d, $J = 7.2$ Hz, 2H), 7.30 (q, $J = 7.2$, 2.7 Hz, 3H), 7.22 (t, $J = 7.2$ Hz, 1H), 7.00 (d, $J = 12.3$ Hz, 1H), 6.86 (dd, $J = 12.6$, 8.1 Hz, 1H), 6.55 (dd, $J = 10.8$, 7.5 Hz, 1H), 4.73 (s, 2H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 159.3, 143.4, 142.7, 141.1, 133.9, 131.1, 131.0, 130.2 (2C), 128.8 (2C), 128.3, 127.0, 126.0, 125.3, 52.8; ESI-MS: *m/z* 252.1179 $[M + H]^+$.

*3.5.3 Compound **35C***

^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 7.70 (d, $J = 5.1$ Hz, 1H), 7.60 (d, $J = 5.1$ Hz, 1H), 7.02 (d, $J = 12.6$ Hz, 1H), 6.74 (d, $J = 12.6$ Hz, 1H), 6.56 (dd, $J = 12.6$, 7.8 Hz, 1H), 6.32 (dd, $J = 12.6$, 7.8 Hz, 1H), 3.38 (t, $J = 6.6$ Hz, 2H), 1.71 (m, 2H), 1.63 (m, 2H), 0.96 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 158.4, 145.0, 140.4, 131.2 (2C), 129.5, 128.9, 126.6, 124.8, 50.3, 34.2, 21.4, 14.3; ESI-MS: *m/z* 218.1420 $[M + H]^+$.

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