TRANSITION METAL-DIENE COMPLEXES IN ORGANIC SYNTHESIS, PART 9.[1] FIRST TOTAL SYNTHESIS OF CARBAZOMYCINAL

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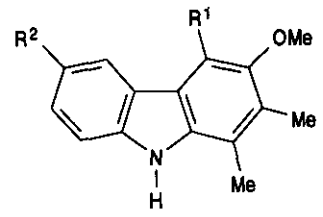
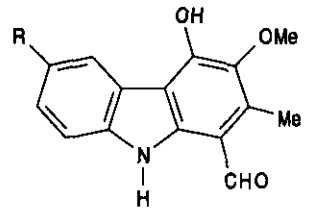
Abstract- Using consecutive iron-induced C-C and C-N bond formation the first total synthesis of carbazomycinal (carbazomycin E) was accomplished.

Carbazole alkaloids have been isolated mainly from terrestrial plants.[2] Because of the useful biological activities exhibited by many carbazole derivatives a broad range of strategies for their synthesis has been developed.[2,3] Some years ago Nakamura and co-workers described the isolation and structure elucidation of the carbazomycins A and B which are produced by microorganisms of the strain *Streptoverticillium ehimense* H 1051-MY 10.[4] The substitution pattern of these compounds was found to be quite different from the carbazole alkaloids previously known. Moreover, the carbazomycins are the first antibiotics with a carbazole framework. They inhibit the growth of phytopathogenic fungi and have antibacterial and antiyeast activities.



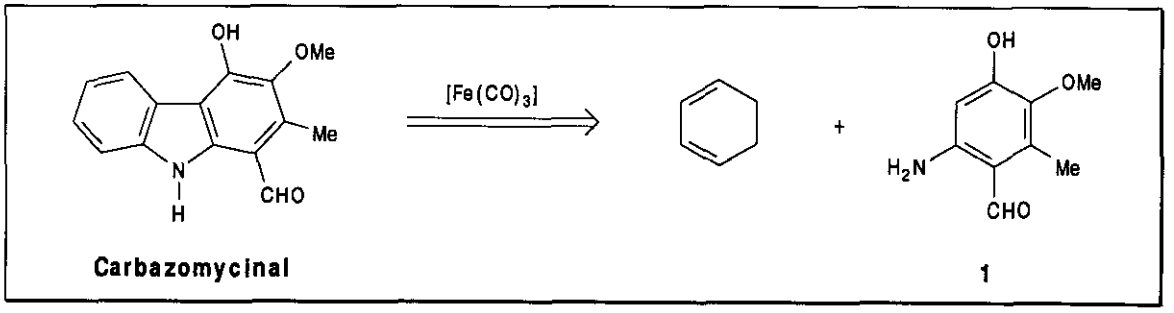
Carbazomycin A R^1=OMe, R^2=H
Carbazomycin B R^1=OH, R^2=H
Carbazomycin C R^1=OH, R^2=OMe
Carbazomycin D R^1=OMe, R^2=OMe



Carbazomycinal
(Carbazomycin E) R=H
6-Methoxycarbazomycinal
(Carbazomycin F) R=OMe

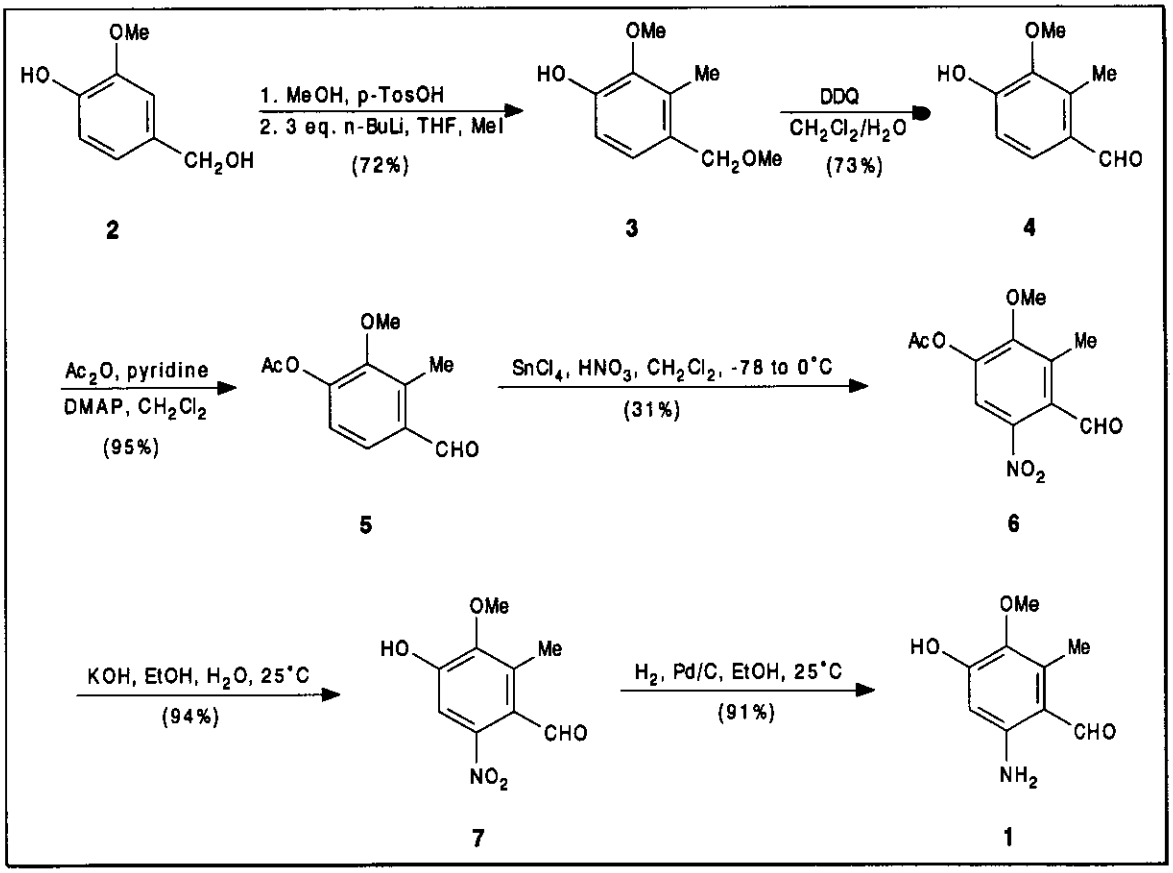
Carbazomycinal (carbazomycin E) and 6-methoxycarbazomycinal (carbazomycin F), further members of this class of alkaloids, have been isolated first by Marumo from a *Streptoverticillium* species of the strain KCC U-0166.[5] Later the same alkaloids were isolated from *Streptoverticillium ehimense* H 1051-MY 10 by Nakamura along with carbazomycins C and D.[6] The biological activities and the unusual arrangement of donor substituents induced several groups to work on total syntheses [7-9] and synthetic approaches [10,11] of the carbazomycins A and B. In this paper we describe the first total synthesis of carbazomycinal (carbazomycin E).

Tricarbonyl(η^5-cyclohexadienylium)iron salts are very useful reagents for regio- and stereoselective reactions with high potential for applications in organic synthesis.[12] Based on a procedure of consecutive iron-induced C-C and C-N bond formation we recently reported the syntheses of 4-deoxycarbazomycin B (R^1 = H, R^2 = H),[7] carbazomycin A,[7,8] carbazomycin B,[8] several 1-methoxycarbazole alkaloids,[13] as well as iron-complexed dihydrocarbazole derivatives.[7,14] This method involves electrophilic aromatic substitution of an arylamine using tricarbonyliron-complexed cations followed by oxidative cyclization to the carbazole derivative.[15] For the total synthesis of carbazomycinal by an iron-mediated carbazole construction we required the arylamine (**1**) (Scheme 1).

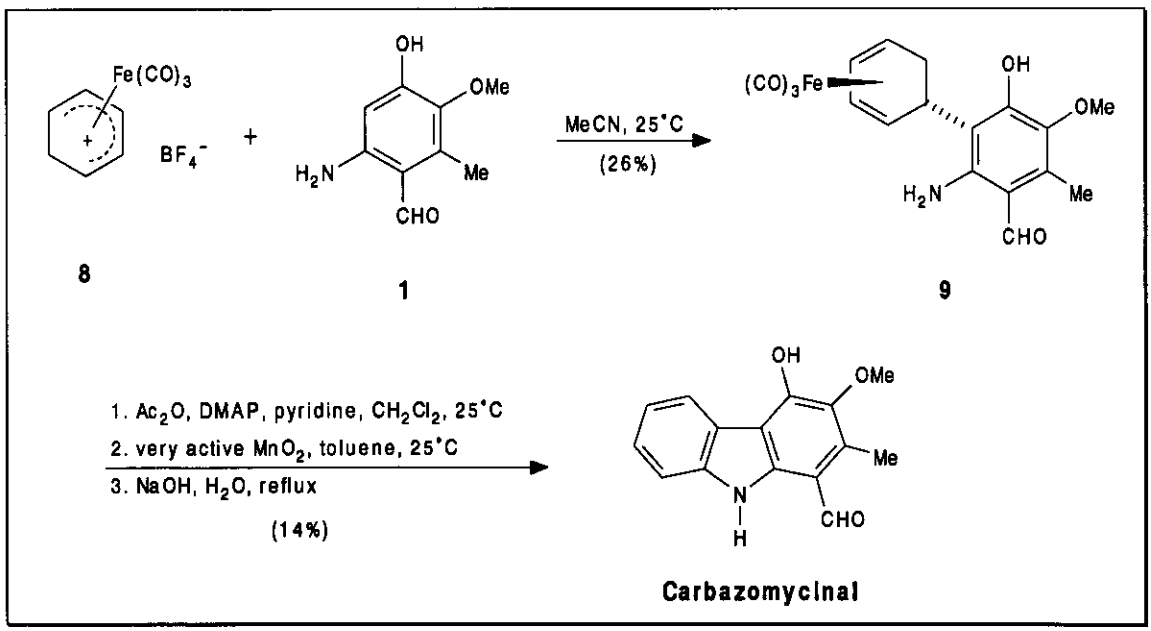


Scheme 1. Retrosynthesis of carbazomycinal

The arylamine (**1**) was conveniently prepared in 7 steps starting with vanillyl alcohol (**2**) (Scheme 2). This was transformed to the tetrasubstituted aryl derivative (**3**) via generation of the benzyl methyl ether followed by ortho-directed lithiation and subsequent methylation according to a literature procedure.[16] Direct oxidation of the benzyl methyl ether with DDQ in a mixture of methylene chloride and water (18:1)[17] afforded the aldehyde (**4**) which was converted to the *O*-acetyl derivative (**5**). The final steps to carbazomycinal resemble our total synthesis of carbazomycin B.[8] Nitration of compound (**5**) to the nitrobenzaldehyde (**6**) was achieved using the complex of tin tetrachloride and fuming nitric acid (generated in situ at room temperature under nitrogen).[18] The regiochemistry of **6** was confirmed by a long-range ^1H-^{13}C correlated 2D-nmr spectrum. Ester cleavage to the nitrophenol (**7**) with potassium hydroxide and subsequent catalytic hydrogenation provided the desired arylamine (**1**).



Scheme 2. Synthesis of the arylamine (1)



Scheme 3. Total synthesis of carbazomycinal

Electrophilic aromatic substitution of the arylamine (**1**) by the iron-complexed cation (**8**) gave the iron complex (**9**) (Scheme 3). Acetylation of complex (**9**), iron-mediated arylamine cyclization with very active manganese dioxide[19] and ester cleavage afforded carbazomycinal spectral data of which (uv, ir, ms, ^{1}H-nmr, and ^{13}C-nmr) are in full agreement with those reported for the natural product.[5]

EXPERIMENTAL

Uv spectra: Beckman 3600; ir spectra: Perkin-Elmer 1710 (FT-ir); ^{1}H-nmr spectra: Bruker WP-200 and ^{13}C-nmr spectra: Bruker AM-300, internal standard: tetramethylsilane or chloroform; mass spectra: Finnigan MAT 312, ionization potential: 70 eV; elemental analyses: Heraeus CHN-Rapid. Flash chromatography: Baker silica gel (0.03-0.06 mm) with eluents given. All reactions were carried out under dry nitrogen.

4-Hydroxy-3-methoxy-2-methylbenzaldehyde (4)

DDQ (10.2 g, 44.9 mmol) is added to a solution of the hydroxybenzyl ether (**3**) (7.78 g, 42.8 mmol) in methylene chloride (180 ml) / H_2O (10 ml). After stirring for 4 h at room temperature the solution is filtrated through a short path of magnesium sulfate and the solvent is evaporated. Flash chromatography (ethyl acetate/light petroleum 1:4) at silica gel gives **4** (5.18 g, 73%), colorless crystals; mp 101-103°C (from ethyl acetate/light petroleum); ir (KBr) ν 3256, 1671, 1592, 1493, 1460, 1439, 1411, 1313, 1214, 1176, 1095, 987, 784, 665 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 3.81 (s, 3H), 2.62 (s, 3H); ^{13}C-nmr and APT (75 MHz, $CDCl_3$) δ 191.7 (CHO), 154.3 (C), 145.9 (C), 134.4 (C), 131.1 (CH), 128.3 (C), 113.3 (CH), 61.1 (CH_3), 11.8 (CH_3); ms (20°C) *m/z* (%) 166 (M^+, 100), 165 (40), 151 (62), 150 (8), 148 (9), 137 (22), 135 (16), 123 (64). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H 6.07. Found: C, 65.11; H 6.00.

4-Acetoxy-3-methoxy-2-methylbenzaldehyde (5)

Dry pyridine (1.1 ml, 1.06 g, 13.4 mmol), acetic anhydride (1.1 ml, 1.17 g, 11.5 mmol) and 4-dimethylamino-pyridine (117 mg, 0.96 mmol) are added to a solution of the hydroxybenzaldehyde (**4**) (1.59 g, 9.55 mmol) in dry methylene chloride (60 ml). The solution is stirred for 2 h at room temperature and the solvent is evaporated. Flash chromatography (ethyl acetate/light petroleum 1:4) at silica gel affords **5** (1.89 g, 95%), yellow crystals; ir (KBr) ν 1765, 1694, 1591, 1479, 1460, 1402, 1379, 1267, 1237, 1196, 1153, 1093, 1029 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 3.78 (s, 3H), 2.61 (s, 3H), 2.36 (s, 3H); ^{13}C-nmr and APT (75 MHz, $CDCl_3$) δ 191.5 (CHO), 168.4 (CO), 150.8 (C), 148.3 (C), 135.8 (C), 133.3 (C), 128.2 (CH), 121.1 (CH), 60.9 (CH_3), 20.8 (CH_3), 11.4 (CH_3); ms (20°C) *m/z* (%) 208 (M^+, 21), 198 (3), 166 (100), 151 (68), 148 (12), 137 (31). HRms calcd for $C_{11}H_{12}O_4$: 208.0736, found: 208.0735.

4-Acetoxy-3-methoxy-2-methyl-6-nitrobenzaldehyde (6)

A solution of tin tetrachloride (1.14 ml, 9.74 mmol) and fuming HNO_3 (0.41 ml) in dry methylene chloride (6 ml) is added to a solution of the benzaldehyde (**5**) (923 mg, 4.44 mmol) in dry methylene chloride (15 ml) at -78°C. The reaction mixture is stirred for 16 h at 0°C. After addition of 2 N HCl (20 ml) the aqueous layer is extracted with methylene chloride. The combined organic layers are extracted with saturated sodium bicarbonate solution and dried with magnesium sulfate. Removal of the solvent in vacuo and flash chromatography (ethyl acetate/light petroleum 1:4) of the residue at silica gel provides **6** (344 mg, 31%), yellow crystals; mp 102-103°C (from ethyl acetate/light petroleum); ir (KBr) ν 2964, 1771, 1698, 1515, 1478, 1396, 1342, 1277, 1246, 1197 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.85 (s, 1H), 3.89 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H); ^{13}C-nmr and DEPT (75 MHz, $CDCl_3$) δ 189.8 (CHO), 168.0 (CO), 155.9 (C), 144.2 (C), 143.1 (C), 133.4 (C), 132.7 (C), 118.4 (CH), 61.2 (CH_3), 20.7 (CH_3), 12.9 (CH_3); ms (50°C) *m/z* (%) 253 (M^+, 3), 211 (100), 193 (26), 181 (23), 178 (14), 167 (38), 166 (71), 165 (32), 149 (58), 138 (43). HRms calcd for $C_{11}H_{11}NO_6$: 253.0586, found: 253.0586.

4-Hydroxy-3-methoxy-2-methyl-6-nitrobenzaldehyde (7)

The acetoxybenzaldehyde derivative (**6**) (601 mg, 2.38 mmol) is dissolved in a mixture of 10% aqueous KOH (4.8 ml) and ethanol (12 ml) and stirred for 16 h at room temperature. After dilution with H_2O and washing of the alkaline solution with methylene chloride the aqueous layer is acidified at 0°C with conc. HCl and extracted several times with diethyl ether. The combined ether layers are dried with magnesium sulfate and the solvent is evaporated. Flash chromatography (ethyl acetate/ light petroleum 1:3) at silica gel affords **7** (469 mg, 94%), light yellow crystals; mp 114°C (from ethyl acetate/light petroleum); ir (KBr) ν 3305, 1682, 1606, 1520, 1481, 1425, 1397, 1348, 1321, 1257, 1201, 1159, 1099, 982, 715 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 10.18 (s, 1H), 7.55 (s, 1H), 6.39 (br s, 1H), 3.86 (s, 3H), 2.44 (s, 3H); ^{13}C-nmr (75 MHz, $CDCl_3$) δ 189.3 (CHO), 151.5 (C), 150.0 (C), 146.8 (C), 133.1 (C), 125.5 (C), 109.9 (CH), 61.4 (CH_3), 13.1 (CH_3); ms (60°C) *m/z* (%) 211 (M^+, 36), 193 (25), 180 (35), 166 (100), 164 (51), 138 (62), 136 (39). HRms calcd for $C_9H_9NO_5$: 211.0481, found: 211.0481. Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.54; H, 4.44; N 6.66.

6-Amino-4-hydroxy-3-methoxy-2-methylbenzaldehyde (1)

The nitro derivative (**7**) (1.45 g, 6.87 mmol) is dissolved in ethanol (100 ml), 10% palladium on activated carbon (148 mg) is added and the reaction mixture is stirred under hydrogen atmosphere (1.2 bar) at room temperature. After completion of the reaction the catalyst is removed by filtration and the solvent is evaporated. Flash chromatography (ethyl acetate/light petroleum 1:2) of the residue at silica gel provides the arylamine (**1**) (1.13 g, 91%), yellow crystals; mp 122-124°C (from ethyl acetate/light petroleum); ir (KBr) ν 3445, 3333, 1636, 1590,

1544, 1483, 1441, 1328, 1244, 1191 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 10.12 (s, 1H), 6.41 (br s, 3H), 6.05 (s, 1H), 3.72 (s, 3H), 2.48 (s, 3H); ^{13}C-nmr and APT (75 MHz, $CDCl_3$) δ 190.4 (CHO), 156.4 (C), 150.8 (C), 137.2 (C), 134.7 (C), 110.5 (C), 99.3 (CH), 61.4 (CH_3), 10.8 (CH_3); ms (50°C) *m/z* (%) 181 (M^+, 47), 166 (68), 152 (6), 138 (100), 111 (42). HRms calcd for $C_9H_{11}NO_3$: 181.0739, found: 181.0734.

Tricarbonyl{2-[η^4-cyclohexa-2,4-dienyl]-6-formyl-3-hydroxy-4-methoxy-5-methylbenzeneamine}iron (9)

A solution of the iron complex salt (**8**) (41 mg, 0.13 mmol) in degassed acetonitrile (3 ml) is added to a solution of the arylamine (**1**) (53 mg, 0.29 mmol) in degassed acetonitrile (3 ml). The reaction mixture is stirred for 3 days at room temperature. Evaporation of the solvent and flash chromatography (ethyl acetate/light petroleum 1:3) of the residue at silica gel gives the iron complex (**9**) (14 mg, 26%), light yellow crystals; mp decomposition above 110°C; ir ($CHCl_3$) ν 3498, 3300, 2049, 1978, 1640, 1614, 1561, 1455, 1266 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 10.11 (s, 1H), 6.88 (br s, 2H), 6.51 (s, 1H), 5.52 (m, 2H), 4.02 (m, 1H), 3.69 (s, 3H), 3.27 (m, 1H), 2.99 (ddd, J = 4.7, 3.1, 1.5 Hz, 1H), 2.44 (s, 3H), 2.10 (ddd, J = 15.5, 11.4, 4.1 Hz, 1H), 1.87 (m, 1H); ms (100°C) *m/z* (%) 399 (M^+, 10), 371 (40), 343 (49), 314 (99), 312 (100), 299 (66), 297 (47), 295 (57), 282 (53), 259 (34), 237 (40). HRms calcd for $C_{18}H_{17}NO_6Fe$: 399.0405, found: 399.0405.

Carbazomycinal

Dry pyridine (62 µl, 60.6 mg, 0.77 mmol), acetic anhydride (62 µl, 67.1 mg, 0.66 mmol) and a few crystals of 4-dimethylamino-pyridine are added to a solution of the iron complex (**9**) (220 mg, 0.55 mmol) in dry methylene chloride (15 ml). The solution is stirred for 2 h at room temperature and the solvent is evaporated. Flash chromatography (ethyl acetate/light petroleum 1:3) of the residue at silica gel affords the acetyl derivative of complex (**9**) (189 mg, 78%), which is used for oxidative cyclization without further characterization.

Very active manganese dioxide (945 mg) is added to a solution of the acetyl derivative of **9** (189 mg, 0.43 mmol) in dry toluene (25 ml). The resulting mixture is stirred at room temperature. After 7 h further 567 mg and after 24 h further 378 mg of very active manganese dioxide are added. The entire reaction time is 31 h, after which the oxidizing reagent is removed by filtration over a short path of Celite. Removal of the solvent in vacuo and flash chromatography (ethyl acetate/light petroleum 1:4) of the residue at silica gel gives a mixture of *O*-acetyl-carbazomycinal and of the corresponding tricarbonyl(η^4-4a,9a-dihydro-9*H*-carbazol)iron complex (50 mg) which is resubmitted to oxidation. The solution of this mixture in dry methylene chloride (10 ml) is treated with very active manganese dioxide (100 mg) and the reaction mixture is stirred for 2 h at room temperature. Filtration over a short path of Celite, removal of the solvent and flash chromatography (ethyl acetate/light petroleum 1:4) affords *O*-acetylcarbazomycinal (32 mg, 25%), which is submitted to ester cleavage without further characterization.

Degassed 10% aqueous NaOH (8 ml) is added to *O*-acetylcarbazomycinal (32 mg, 0.108 mmol) and the mixture is heated for 1 h and 45 min. The solution is cooled down, treated with 6 N HCl (4 ml), and extracted with diethyl ether. The combined organic layers are dried with magnesium sulfate and the solvent is evaporated. Flash chromatography (ethyl acetate/light petroleum 1:4) of the residue at silica gel provides carbazomycinal (20 mg, 73%, 14% based on iron complex **9**), yellow crystals; mp 215-217°C (from ethyl acetate/light petroleum, lit.[5]: mp 224°C); uv (MeOH) λ_{max} 215, 228, 263, 296, 320, 372 nm; ir (KBr) ν 3362, 2927, 2863, 1650, 1584, 1568, 1485, 1450, 1435, 1343, 1291, 1224, 1168, 1140, 1005, 745 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 10.62 (br s, 1H), 10.40 (s, 1H), 8.23 (d, J = 7.6 Hz, 1H), 7.20-7.55 (m, 3H), 7.01 (br s, 1H), 3.87 (s, 3H), 2.76 (s, 3H); DEPT (75 MHz, $CDCl_3$) δ 190.0 (CHO), 125.7 (CH), 122.6 (CH), 120.6 (CH), 111.0 (CH), 62.0 (CH_3), 11.2 (CH_3); ms (100°C) *m/z* (%) = 255 (M^+, 58), 240 (100), 212 (26), 184 (7), 183 (5), 182 (6), 156 (10), 155 (9). HRms calcd for $C_{15}H_{13}NO_3$: 255.0895, found: 255.0894.

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