Transition Metals in Organic Synthesis, Part 82.[1] First Total Synthesis of Methyl 6-Methoxycarbazole-3-carboxylate, Glycomaurrol, the Anti-TB Active Micromeline, and the Furo[2,3-c]carbazole Alkaloid Eustifoline-D

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Dedicated to Professor Roland Mayer on the occasion of his 80th birthday

Abstract: The palladium(0)-catalyzed amination followed by palladium(II)-catalyzed oxidative cyclization of the resulting diarylamine provides a short route to a series of 6-oxygenated carbazole alkaloids: glycozoline, 3-formyl-6-methoxycarbazole, methyl 6-methoxycarbazole-3-carboxylate, glycozolinine (glycozolinol), glycomaurrol, micromeline, and eustifoline-D.

Key words: alkaloids, antibiotics, catalysis, nickel, palladium

3-Methylcarbazole has been identified as the key precursor for the biogenesis of most carbazole alkaloids found in terrestrial plants.[2,3] In the course of the biogenetic transformation this crucial intermediate is oxygenated at different positions, oxidized at the methyl group, and prenylated, which may be followed by cyclization to annulated furan and pyran rings. A systematic classification of carbazole alkaloids has been achieved based on their oxygenation pattern.[2,3] The promising pharmacological potential of carbazole alkaloids led to an intense research in this field.[1–4] We have developed diverse transition-metal-mediated and -catalyzed oxidative cyclizations to the carbazole framework.[3] For the synthesis of 2,7-dioxygenated carbazoles we used our iron-mediated route.[5] A palladium-catalyzed approach was recently applied to the total synthesis of 7-oxygenated carbazole alkaloids.[1] In this paper, we describe a palladium-catalyzed synthesis of the 6-oxygenated carbazole alkaloids glycozoline (**1**), 3-formyl-6-methoxycarbazole (**2**), methyl 6-methoxycarbazole-3-carboxylate (**3**), glycozolinine (glycozolinol; **4**), glycomaurrol (**5**), micromeline (**6**), and eustifoline-D (**7**, Figure 1). The alkaloids **3** and **5–7** are obtained by total synthesis for the first time.

Glycozoline (**1**) exhibits antibiotic and antifungal properties.[6] It was isolated first in 1966 by Chakraborty from the root bark of *Glycosmis pentaphylla* (Figure 2).[7] Later, glycozoline (**1**) was found in *Murraya koenigii*,[8] *Glycosmis arborea*,[9] *Glycosmis mauritiana*,[10] *Clausena lansium*,[11] and in the roots of the West African tree *Zanthoxylum lemairie*.[12] The corresponding alcohol, 3-methyl-6-hydroxycarbazol (**4**), has a much stronger anti-

biotic activity.[6] Compound **4** was also isolated from *Glycosmis pentaphylla*, first in 1983 by Mukherjee and named glycozolinine,[13a] and one year later by Bhattacharyya who called it glycozolinol.[13b] In 1991, 3-formyl-6-methoxycarbazole (**2**) and methyl 6-methoxycarbazole-3-carboxylate (**3**) were obtained from the roots of *Clausena lansium*.[11,14] Glycomaurrol (**5**), a 5-prenyl derivative of glycozolinine (**4**), was isolated by Reisch from the stem bark of *Glycosmis mauritiana*.[15] In an anti-tuberculosis bioassay-directed fractionation of the stem bark extract of *Micromelum hirsutum*, Franzblau isolated in 2005 3-formyl-6-methoxycarbazole (**2**) along with micromeline (**6**) as anti-TB active compounds.[16] The furo[2,3-c]carbazole alkaloid eustifoline-D (**7**) also derives from glycozolinine (**4**). Eustifoline-D (**7**) was isolated by Furukawa from the root bark of *Murraya euchrestifolia* along with its regioisomer furostifoline.[17] The extracts of the leaves and bark of this plant have been used as folk medicine in China.

1 glycozoline R = Me
2 R = CHO
3 R = COOMe

4 glycozolinine (glycozolinol)

5 glycomaurrol R = Me
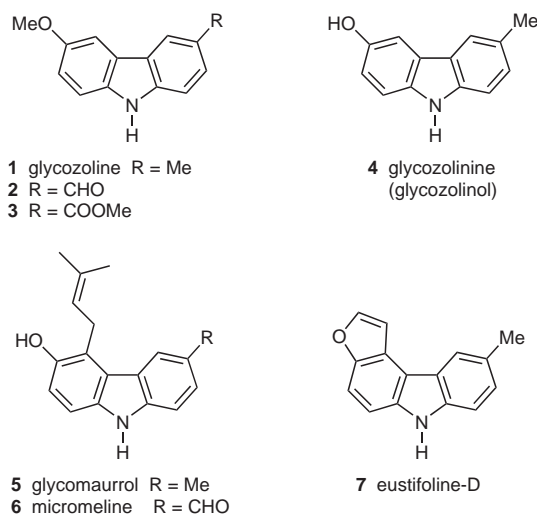**6** micromeline R = CHO

7 eustifoline-D

Figure 1 Naturally occurring 6-oxygenated carbazole alkaloids

Several total syntheses, often with low overall yields, have been reported for glycozoline (**1**),[18] 3-formyl-6-methoxycarbazole (**2**),[19] and glycozolinine (glycozolinol, **4**).[13b,20] However, the other 6-oxygenated carbazole alkaloids have not been obtained by synthesis so far. Due to their pharmacological potential the furocarbazole

Figure 2 *Glycosmis pentaphylla* (courtesy of Professor Pei-Fen Lee, National Taiwan University, Taipei, Nature Conservation Network)

alkaloids have attracted a lot of interest,[21] but the furo[2,3-c]carbazole framework of eustifoline-D (**7**) remains an unsolved problem. We envisioned a convergent common access to the 6-oxygenated carbazole alkaloids using glycozoline (**1**) as the crucial intermediate. Our synthetic strategy for construction of the carbazole nucleus is based on a palladium(0)-catalyzed Buchwald–Hartwig amination[22] of *p*-bromoanisole (**8**) and *p*-toluidine (**9**) and subsequent palladium(II)-catalyzed oxidative cyclization.[1,23]

The Pd(0)-catalyzed coupling of *p*-bromoanisole (**8**) and *p*-toluidine (**9**) afforded the diarylamine **10** (Scheme 1).[24] Oxidative cyclization of the diarylamine **10** with stoichiometric amounts of palladium(II) acetate afforded glycozoline (**1**) in only 23% yield (HOAc, 117 °C, 6 h). Cyclization using catalytic amounts of palladium(II) acetate in the presence of an excess of cupric acetate led to glycozoline (**1**) in 60% yield. We have observed previously that high concentrations of palladium(II) are harmful because they lead to decomposition of oxygenated carbazoles.[1] Support for this hypothesis in the present case derives from treatment of glycozoline (**1**) using the conditions for the stoichiometric reaction: 100 mg (0.47 mmol) **1**, 1.2 equiv Pd(OAc)$_2$, HOAc, 117 °C, 6 h. Due to decomposition only 46% of the starting material could be reisolated in this experiment.

In the following, glycozoline (**1**) was exploited as relay compound en route to the other 6-oxygenated carbazole alkaloids (Scheme 1). Oxidation of **1** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave 3-formyl-6-methoxycarbazole (**2**). Further oxidation of **2** using manganese dioxide in the presence of potassium cyanide in methanol[25] afforded methyl 6-methoxycarbazole-3-carboxylate (**3**). Cleavage of the ether with boron tribromide transforms glycozoline (**1**) into glycozolinine (glycozolinol, **4**). Electrophilic bromination of **4** led to the bromocarbazole **11**. Prenylation using the π-prenylnickel–bromide complex, prepared in situ from prenyl bromide and bis(1,5-cyclooctadiene)nickel(0),[26] provided glycomaurrol (**5**).[27] The spectroscopic data (UV, IR, ^{1}H NMR,
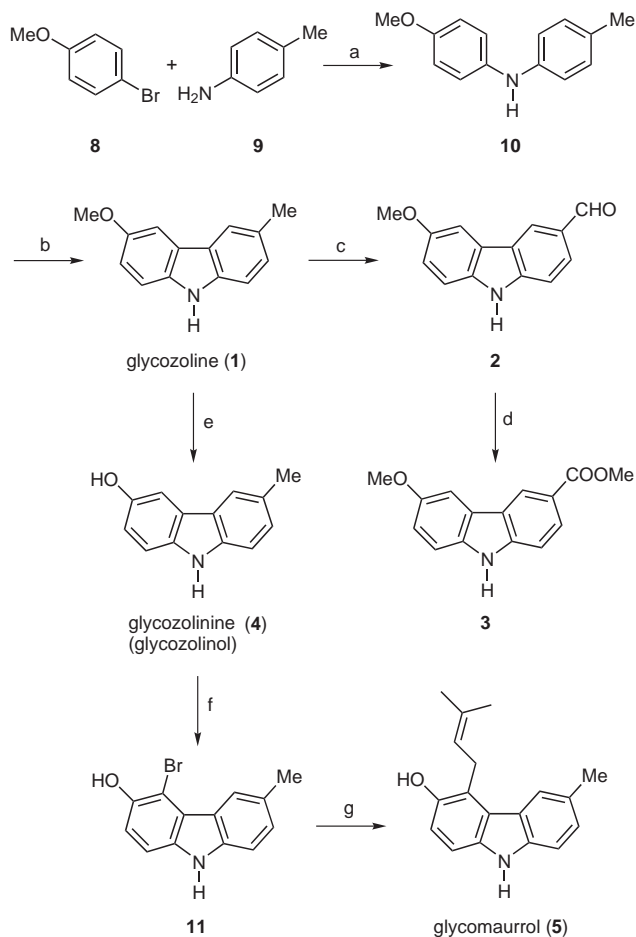
Scheme 1 Synthesis of the carbazole alkaloids **1**-**5**. *Reagents and conditions*: a) 7 mol% Pd(OAc)$_2$, 8 mol% *rac*-BINAP, 1.4 equiv Cs$_2$CO$_3$, toluene, 110 °C, 6 d (97%); b) 10 mol% Pd(OAc)$_2$, 2.5 equiv Cu(OAc)$_2$, HOAc, 117 °C, 24 h (60%); c) 4.2 equiv DDQ, MeOH–H$_2$O (16:1), r.t., 85 min (76%); d) 26 equiv MnO$_2$, 5 equiv KCN, MeOH, r.t., 17 h (97%); e) 2 equiv BBr$_3$, CH$_2$Cl$_2$, –78 °C to r.t., 4 h (97%); f) 1.1 equiv NBS, CH$_2$Cl$_2$, r.t., 6 h (45%); g) 9 equiv prenyl bromide, 14 equiv Ni(COD)$_2$, DMF, r.t., 6 d (glove box; 25%).
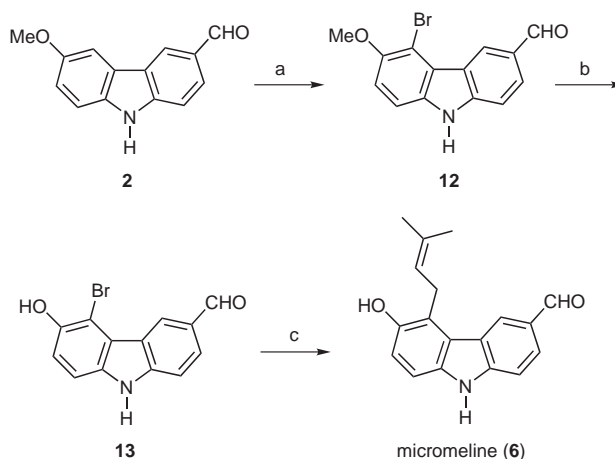
Scheme 2 Synthesis of micromeline (**6**). *Reagents and conditions*: a) 1.1 equiv NBS, cat. HBr, MeCN, r.t., 3 h (82%); b) 3.4 equiv BBr$_3$, CH$_2$Cl$_2$, –78 °C to –20 °C, 3 d (50%); c) 10 equiv prenyl bromide, 15 equiv Ni(COD)$_2$, DMF, r.t., 6 d (glove box; 52%).

^{13}C NMR, and MS) of the 6-oxygenated carbazole alkaloids **1**–**5** are in full agreement with those reported for the corresponding natural products.[7–15]

For the synthesis of the *Micromelum hirsutum* metabolite micromeline, 3-formyl-6-methoxycarbazole (**2**) was used as starting material (Scheme 2). Reaction with *N*-bromosuccinimide afforded the bromocarbazole **12**. The regiochemistry of this intermediate was proven by an X-ray crystal structure determination (Figure 3).[28] Cleavage of the methyl ether to **13** followed by nickel-mediated prenylation[26] provided micromeline (**6**).[29] The spectroscopic data of our synthetic micromeline are in full agreement with those reported for the natural product. The identity was additionally confirmed by comparison of the ^{1}H NMR spectrum of our synthetic compound with the original ^{1}H NMR spectrum of the natural product, kindly provided by Professor S. G. Franzblau and Professor G. F. Pauli.
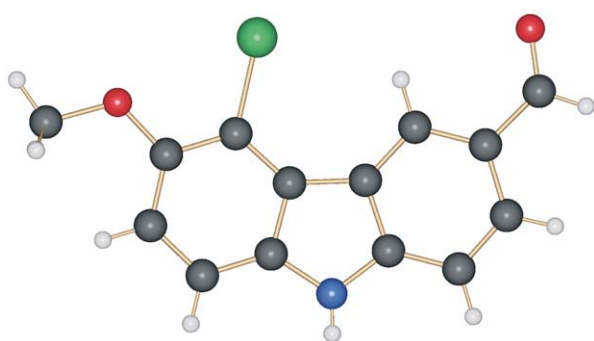

Figure 3   Molecular structure of the bromocarbazole **12** in the crystal

Eustifoline-D (**7**) displaying an unprecedented furo[2,3-*c*]carbazole framework could also be prepared starting from glycozolinine (**4**, Scheme 3). A Williamson ether synthesis with 2-bromo-1,1-diethoxyethane afforded compound **14**. Subsequent cyclization using catalytic amounts of amberlyst 15 in chlorobenzene at reflux[30,31] provided eustifoline-D (**7**) along with isoeustifoline-D (**15**) in a ratio of 4.3:1.[32] The spectroscopic data of eustifoline-D (**7**) are in full agreement with those of the natural product. Although, natural eustifoline-D (**7**) was described as an oil, we obtained this compound as colorless crystals (mp 156 °C). Thus, eustifoline-D (**7**) has been obtained in five steps and 20% overall yield based on *p*-bromoanisole (**8**).

In conclusion, we have developed a straightforward access to biologically active 6-oxygenated carbazole alkaloids using a sequence of palladium(0)-catalyzed amination and palladium(II)-catalyzed oxidative cyclization. Methyl 6-methoxycarbazole-3-carboxylate (**3**), glycomaurrol (**5**), the anti-TB active micromeline (**6**), and the furo[2,3-*c*]carbazole eustifoline-D (**7**) have been obtained by synthesis for the first time. The pharmacological activities and the structure–activity relationships for these compounds as well as their structural analogues are under
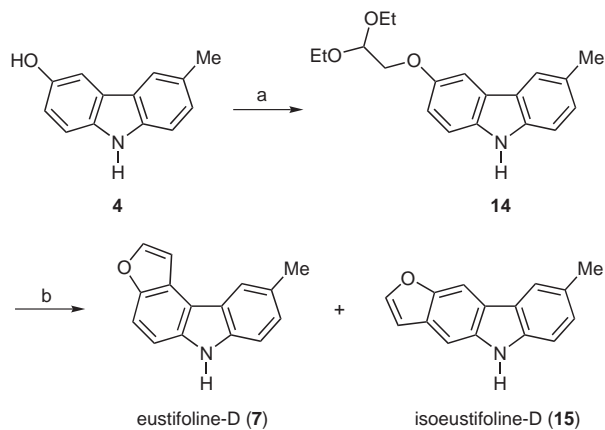
Scheme 3   Synthesis of eustifoline-D (**7**). *Reagents and conditions*: a) K$_2$CO$_3$, 1.1 equiv 2-bromo-1,1-diethoxyethane, DMF, 152 °C, 38 h (75%); b) amberlyst 15, PhCl, 120 °C, 1 h (48% of **7** and 11% of **15**).

active investigation in the frame of our program[33,34] and will be reported in due course.

Acknowledgment

References and Notes

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(27) Pure glycomaurrol (**5**) was obtained by preparative HPLC on a Vydac C8 50 mm column (gradient elution with 50 mL/min MeCN–H_2O, 30–60% MeCN in 30 min). Glycomaurrol (**5**): colorless crystals; mp 141 °C. UV (MeOH): λ_{max} = 257, 269, 292 (sh), 301, 350, 362 (sh) nm. IR (ATR): ν = 3409, 3214, 2917, 1589, 1512, 1499, 1476, 1442, 1390, 1349, 1309, 1282, 1267, 1225, 1166, 1148, 1100, 1069, 1030, 954, 871, 850, 797, 739, 694, 648 cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.72 (d, J = 1.2 Hz, 3 H), 1.98 (s, 3 H), 2.51 (s, 3 H), 4.01 (d, J = 6.5 Hz, 2 H), 5.37 (t, J = 6.5 Hz, 1 H), 7.03 (d, J = 8.5 Hz, 1 H), 7.19 (d, J = 8.5 Hz, 1 H), 7.20 (m, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 7.70 (s, 1 H), 7.95 (s, 1 H), 9.94 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 18.34 (CH$_3$), 21.67 (CH$_3$), 25.83 (CH$_3$), 26.24 (CH$_2$), 109.21 (CH), 111.09 (CH), 115.52 (CH), 122.15 (C), 122.97 (C), 123.29 (CH), 124.05 (CH), 124.34 (C), 126.87 (CH), 127.59 (C), 131.86 (C), 136.06 (C), 140.13 (C), 148.19 (C). MS (100 °C): m/z (%) = 265 (100) [M$^+$], 210 (71), 209 (87), 181 (14), 180 (19), 167 (9). HRMS: m/z calcd for $C_{18}H_{19}NO$ [M$^+$]: 265.1467; found: 265.1454.

(28) Crystal data for the bromocarbazole **12**: $C_{14}H_{10}BrNO_2$, M = 304.14, monoclinic, space group: $P2_1/c$, a = 19.570(4), b = 8.296(2), c = 7.360(2) Å, β = 94.77(3)°, V = 1190.8(5) Å^3, Z = 4, D_c = 1.696 g cm^{-3}, μ = 3.444 mm^{-1}, T = 198(2) K, λ = 0.71073 Å, θ range: 3.13–30.00°, 29544 reflections collected, 3454 independent (R_{int} = 0.0629), 168 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; final R indices [I > 2σ(I)]: R_1 = 0.0405, wR_2 = 0.0761; maximal residual electron density: 0.598 e Å^{-3}. CCDC-628163 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(29) Pure micromeline (**6**) was obtained by preparative HPLC on a Vydac C8 50 mm column (gradient elution with 50 mL/min MeCN–H_2O, 30–60% MeCN in 30 min). Micromeline (**6**): colorless crystals; mp 205–206 °C. UV (MeOH): λ_{max} = 231, 252, 276 (sh), 278, 281, 295 (sh), 300, 340 nm. IR (ATR): ν = 3156, 2963, 2911, 2854, 2740, 1663, 1649, 1629, 1603, 1566, 1522, 1464, 1446, 1371, 1310, 1291, 1271, 1228, 1202, 1181, 1164, 1120, 1063, 1028, 958, 899, 883, 851, 811, 792, 717, 663 cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.72 (d, J = 1.1 Hz, 3 H), 2.03 (s, 3 H), 4.07 (d, J = 6.4 Hz, 2 H), 5.36 (t, J = 6.4 Hz, 1 H), 7.15 (d, J = 8.5 Hz, 1 H), 7.33 (d, J = 8.5 Hz, 1 H), 7.63 (d, J = 8.5 Hz, 1 H), 7.95 (dd, J = 8.5, 1.4 Hz, 1 H), 8.03 (br s, 1 H), 8.69 (s, 1 H), 10.09 (s, 1 H), 10.70 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 18.43 (CH$_3$), 25.80 (CH$_3$), 26.19 (CH$_2$), 110.07 (CH), 111.79 (CH), 116.63 (CH), 122.76 (C), 123.26 (C and CH), 124.05 (C), 126.63 (CH), 127.40 (CH), 129.39 (C), 132.83 (C), 136.07 (C), 145.38 (C), 149.40 (C), 191.85 (CHO). MS (150 °C): m/z (%) = 279 (93) [M$^+$], 224 (81), 223 (100), 208 (7), 195 (13), 194 (10), 183 (11), 167 (11). HRMS: m/z calcd for $C_{18}H_{17}NO_2$ [M$^+$]: 279.1259; found: 279.1262. Anal. Calcd (%) for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.50; H, 6.22; N, 5.03.

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(32) A separation of the two isomers **7** and **15** was achieved by preparative HPLC on a Vydac C8 30 mm column (gradient elution with 40 mL/min MeCN–H_2O, 30–46% MeCN in 32 min). Eustifoline-D (**7**): colorless crystals; mp 156 °C. UV (MeOH): λ_{max} = 253, 260 (sh), 268, 298, 310, 339, 354 nm.

IR (ATR): ν = 3406, 2919, 2856, 1615, 1575, 1484, 1443, 1432, 1409, 1360, 1300, 1275, 1242, 1229, 1209, 1139, 1074, 1051, 946, 886, 875, 800, 789, 780, 750, 731, 690, 659 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.59 (s, 3 H), 7.26 (dd, J = 8.3, 1.2 Hz, 1 H), 7.31 (d, J = 8.8 Hz, 1 H), 7.33 (dd, J = 2.0, 0.4 Hz, 1 H), 7.36 (d, J = 8.3 Hz, 1 H), 7.58 (d, J = 8.8 Hz, 1 H), 7.81 (d, J = 2.0 Hz, 1 H), 7.98 (s, 1 H), 8.03 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, CDCl$_3$): δ = 21.51 (CH$_3$), 105.40 (CH), 107.38 (CH), 109.43 (CH), 110.43 (CH), 114.80 (C), 120.42 (C), 120.93 (CH), 123.23 (C), 126.54 (CH), 128.71 (C), 135.92 (C), 137.65 (C), 145.14 (CH), 150.27 (C). MS (20 °C): m/z (%) = 221 (100) [M$^+$], 220 (53), 192 (7), 191 (8). HRMS: m/z calcd for C$_{15}$H$_{11}$NO [M$^+$]: 221.0841; found: 221.0853. Anal. Calcd (%) for C$_{15}$H$_{11}$NO: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.23; H, 5.07; N, 6.24.

Isoeustifoline-D (**15**): colorless crystals; mp 154 °C. UV (MeOH): λ$_{max}$ = 247, 255, 264, 272 (sh), 304, 311 (sh), 316, 349, 365 nm. IR (ATR): ν = 3403, 2918, 2854, 1617, 1533, 1504, 1483, 1446, 1342, 1326, 1307, 1292, 1262, 1220, 1175, 1154, 1125, 1097, 1030, 978, 879, 840, 799, 790, 756, 731, 697, 619 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.54 (s, 3 H), 6.83 (d, J = 2.1 Hz, 1 H), 7.24 (d, J = 8.2 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 1 H), 7.47 (s, 1 H), 7.68 (d, J = 2.1 Hz, 1 H), 7.81 (br s, 1 H), 7.89 (s, 1 H), 8.10 (s, 1 H). ^{13}C NMR and DEPT (125 MHz, CDCl$_3$): δ = 21.39 (CH$_3$), 100.56 (CH), 101.66 (CH), 106.53 (CH), 110.05 (CH), 120.17 (CH), 121.93 (C), 123.65 (C), 126.73 (C), 127.23 (CH), 128.34 (C), 137.38 (C), 139.00 (C), 145.65 (CH), 150.38 (C). MS (20 °C): m/z (%) = 221 (100) [M$^+$], 220 (53), 192 (7), 191 (6). HRMS: m/z calcd for C$_{15}$H$_{11}$NO [M$^+$]: 221.0841; found: 221.0851. Anal. Calcd (%) for C$_{15}$H$_{11}$NO: C, 81.43; H, 5.01; N, 6.33. Found: C, 80.59; H, 5.06; N, 6.15.

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