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SUPPORTING INFORMATION

RHODIUM-CATALYZED CROSSED [2+2+2] CYCLOADDITION WITH YNAMIDES: KEY-STRATEGY FOR THE CONCISE TOTAL SYNTHESIS OF 3-OXYGENATED CARBAZOLE ALKALOIDS

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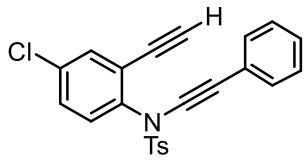
1. GENERAL INFORMATION

All reactions were performed under an atmosphere of dry nitrogen or argon. Commercially available reagents were used without further purification. Reactions were monitored by thin layer chromatography Merck silica gel 60-F254 coated 0.1 mm plates with UV detection. Flash chromatography was performed with Merck silica gel 60 (40–63 μm particle size). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300, 400 or 500 MHz Bruker Avance III spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported ppm using the TMS signal (0 ppm) and the residual peak of $CDCl_3$ (77.0 ppm) respectively as internal reference. Coupling constants *J* are reported in Hertz (Hz). Abbreviations are used as follows: s (singulet), d (doublet), t (triplet), q (quintuplet), m (multiplet), br (broad). Infrared (IR) spectra were recorded on a Perkin Elmer spectrometer. Mass spectra were obtained on a Q-TOF Micro Waters under electron spray ionisation (ESI) and a Varian MAT 311 spectrometer. Microanalyses were recorded using a Vario Micro Cube from Elementar. Melting points are uncorrected. Compounds **2c**,[1] **5**,[2] **6**[3] and **8**[4] were prepared as described in the literature.

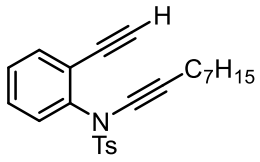
2. EXPERIMENTAL



2a

***N*-(4-Chloro-2-ethynylphenyl)-*N*-(phenylethynyl)-*p*-toluenesulfonamide (2a).**

To a solution of *N*-(4-chloro-2-ethynylphenyl)-*p*-toluenesulfonamide (**5**) (2.00 g, 6.5 mmol) in dry toluene (250 mL) at 0 °C was added dropwise a 0.5 M solution of KHMDS in toluene (15.7 mL, 7.9 mmol). After 45 min of stirring at 0 °C, alkynyl iodonium salt **6** (4.16 g, 9.2 mmol) was added in small portions. The reaction was stirred at rt overnight and then concentrated, followed by addition of CH_2Cl_2 and brine, extraction with CH_2Cl_2 and drying the organic phase with $MgSO_4$. After removal of the organic solvents the obtained product was purified by column chromatography (silica gel, 3:1 petroleum ether/Et_2O) to afford **2a** (1.59 g, 60% yield) as a yellow solid. R_f 0.66 (7:3 petroleum ether/EtOAc), mp 78 °C ($CHCl_3$/Pentane). Found: C, 67.82; H, 3.90; N, 3.47. $C_{23}H_{16}ClNO_2S$ requires C, 68.06; H, 3.97; N, 3.45%. IR (KBr) ν_{max}/cm^{-1} 3278, 2238, 1595, 1481, 1378, 1331, 1192, 1175, 1119, 1087, 1061, 906, 880, 852, 817, 762, 721, 689, 666, 611, 585, 557, 541, 532. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (3 H, s), 3.07 (1 H, s), 7.22–7.37 (9 H, m), 7.50 (1 H, d, *J* 2.5), 7.74 (2 H, d, *J* 8.4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9 (q), 70.7 (s), 77.7 (d), 82.3 (s), 84.5 (s), 122.7 (s), 123.8 (s), 128.1 (d), 128.4 (d), 128.7 (d), 129.8 (d), 130.0 (d), 130.5 (d), 131.6 (d), 133.9 (s), 134.0 (d), 135.0 (s), 138.6 (s), 145.3 (s). MS (EI, 70 eV) *m*/*z* (EI) 405 (M^+, 6%), 341 (2), 305 (3), 266 (3), 252 (33), 250 (100), 224 (2), 214 (12), 177 (3), 155 (3), 139 (5), 91 (5), 83 (22), 72 (2).

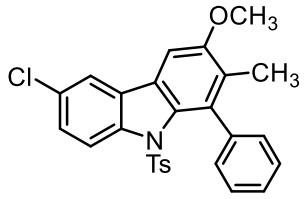


2b

***N*-(2-Ethynylphenyl)-*N*-(non-1-ynyl)-*p*-toluenesulfonamide** (**2b**). To a solution of diyne **8** (463 mg, 1.26 mmol) in dry THF (16 mL) at –78 °C under N_2 was added dropwise a 0.5 M solution of LiHMDS in THF (3.8 mL, 1.89 mmol, 1.5 equiv.). The reaction mixture was gradually taken to –40 °C and kept at this temperature for 1h. Then a solution of 1-iodoheptane (0.83 mL, 5.04 mmol, 4 equiv.) in dry THF (6.5 mL) was added dropwise at –40 °C. The temperature was slowly raised to –5 °C. Then the cooling bath was replaced by an ice bath and the reaction mixture was allowed to warm up to rt overnight. Et_2O and brine were added to the reaction mixture, the layers were separated and the aqueous layer was extracted with Et_2O. the combined organic phases were dried with $MgSO_4$. After removal of the organic solvents

the product obtained (352 mg) was purified by a column chromatography (short column: silica gel, 9:1 pentane/Et_2O). The obtained product was dissolved in wet THF (19 mL), and argon was bubbled through the solution for 15 min then cooled down to 0 °C. A 1 M solution of TBAF in THF (0.95 mL, 0.95 mmol) was added dropwise. After 20 min, the reaction mixture was worked up by addition of Et_2O and brine, separation of the layers and extraction of the aqueous layer with Et_2O, then drying the combined organic layers with $MgSO_4$. Purification by column chromatography (silica gel, 9:1 pentane/Et_2O) afforded **2b** as a yellow oil (295 mg, 59% yield). R_f 0.20 (9:1pentane/Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* 6.8 Hz), 1.25–1.37 (8 H, m), 1.42–1.51 (2 H, m), 2.25 (2 H, t, *J* 6.9 Hz), 2.45 (3 H, s), 3.03 (1 H, s), 7.16–7.19 (1 H, m), 7.28–7.33 (4 H, m), 7.49–7.52 (1 H, m), 7.71 (2 H, d, *J* 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (q) 18.5 (t), 21.6 (t), 22.6 (t), 28.7 (t), 28.76 (t), 28.82 (t), 31.8 (t), 70.1 (s), 73.5 (s), 79.2 (s), 82.7 (d), 122.4 (s), 128.58 (d), 128.64 (d), 128.9 (d), 129.3 (d), 129.4 (d), 134.1 (d), 134.4 (s), 140.5 (s), 144.5 (s). IR (NaCl) ν_{max}/cm^{-1} 3301, 3066, 2929, 2857, 2255, 1598, 1485, 1445, 1372, 1172, 1091, 929, 813, 737, 674, 586. MS (EI, 70 eV) *m*/*z* 393 (M^+, 32%), 369 (6), 322 (7), 310 (6), 271 (40), 238 (100), 213(16), 168 (47), 91 (87), 57 (83); HRMS (ESI) calcd for $C_{24}H_{27}NO_2SNa$ $[M+Na]^+$ 416.1655, found 416.1674.

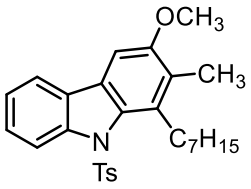
Typical procedure for the preparation of carbazoles 9a, 11, and 13.



9a

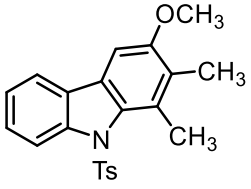
***N*-(*p*-Toluenesulfonyl)-6-chloro-3-methoxy-2-methyl-1-phenylcarbazole (9a).** Argon was bubbled through a solution of diyne **2a** (60 mg, 0.15 mmol) in dry toluene (10 mL) for 25 min. Then 1-methoxyprop-1-yne (104 mg, 1.5 mmol, 10 equiv.) and $[RhCl(PPh_3)_3]$ (6.8 mg, 5 mol%) were added. The reaction mixture was stirred at rt for 1 day, then concentrated and the remaining solvent filtrated through a plug of alumina (Alox N/III) to eliminate most of the catalyst. Thereafter, column chromatography (silica gel, 8:2 petroleum ether/Et_2O) afforded **9a** (66 mg, 93% yield) as a colorless solid. R_f 0.49 (7:3 petroleum ether/EtOAc), mp 235 °C (dec.). IR (KBr) ν_{max}/cm^{-1} 1597, 1448, 1402,1368, 1178, 1154, 1088, 1072, 1023, 883, 835, 724, 704, 688, 662, 602, 585, 546. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (3 H, s), 2.22 (3 H, s), 3.93 (3 H, s), 6.87 (2 H, d, *J* 8.3 Hz), 6.97 (2 H, d, *J* 8.3 Hz), 7.11 (1 H, s), 7.31 (1 H, dd, *J* 8.8, 2.1 Hz), 7.35–7.49 (5 H, m), 7.61 (1 H, d, *J* 2.1 Hz), 8.04 (1 H, d, *J* 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 (q), 21.6 (q), 55.9 (q), 99.7 (d), 119.2 (d), 120.9 (d), 126.7 (d), 126.8 (d), 127.2 (d), 127.4 (s), 127.9 (d), 128.2 (s), 128.9 (d), 130.7 (d), 131.0 (s), 131.4 (s), 132.8 (s), 134.1 (s), 135.1 (s), 139.2 (s), 140.4 (s),

144.0 (s), 156.9 (s). HRMS (EI, 70 eV) calcd for $C_{27}H_{22}ClNO_3S$ $[M]^+$ 475.1009, found 475.1007.



11

***N*-(*p*-Toluenesulfonyl)-1-heptyl-3-methoxy-2-methylcarbazole** (**11**). Starting from **2b** (133 mg, 0.34 mmol). Column chromatography (silica gel, 9:1 pentane/Et_2O) afforded **11** (102 mg, 65% yield, 25:1 isomer ratio). Isomerically pure **11** was obtained by column chromatography on silica gel (9:1 pentane/Et_2O) as a colorless solid. R_f = 0.30 (9:1 pentane/Et_2O), mp 114 °C (pentane/CH_2Cl_2). Found: C, 72.22; H, 7.20; N, 2.85. $C_{28}H_{33}NO_3S$ requires C, 72.54; H, 7.17; N, 3.02%.^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3 H, t, *J* 7.0 Hz), 1.25–1.34 (8 H, m), 1.49–1.54 (2 H, m), 2.19 (3 H, s), 2.36 (3 H, s), 3.41–3.44 (2 H, m), 3.90 (3 H, s), 6.79 (2 H, d, *J* 8.5 Hz), 6.87 (2 H, d, *J* 8.5 Hz), 6.92 (1 H, s), 7.22 (1 H, td, *J* = 7.5, 1.0 Hz), 7.33 (1 H, ddd, *J* 8.0, 7.5, 1.5 Hz), 7.46 (1 H, dd, *J* 7.5, 1.5 Hz), 8.11 (1 H, dd, *J* 8.0, 1.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ13.0 (q), 14.1 (q), 21.4 (q), 22.7 (t), 29.2 (t), 29.7 (t), 29.8 (t), 30.8 (t), 31.9 (t), 55.7 (q), 98.1 (d), 119.0 (d), 120.4 (d), 125.5 (d), 126.2 (s), 126.3 (d), 127.3 (d), 128.2 (d), 129.6 (s), 131.29 (s), 131.31 (s), 134.8 (s), 136.8 (s), 142.5 (s), 143.7 (s), 157.0 (s). IR (KBr) ν_{max}/cm^{-1} 2959, 2923, 2849, 1594, 1486, 1467, 1444, 1411, 1365, 1211, 1174, 1118. MS (EI, 70 eV) *m*/*z* 463 (M^+, 24%), 308 (78), 272 (3), 224 (100), 194 (14), 127 (39), 91 (9), 57 (20).

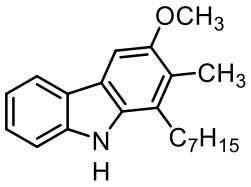


13

***N*-(*p*-Toluenesulfonyl)-3-methoxy-1,2-dimethylcarbazole (13).** Starting from **2c** (687 mg, 2.22 mmol) to give compound **13** (749 mg, 89% yield, 21:1 isomer ratio). Isomerically pure **13** was obtained by crystallization (pentane/CH_2Cl_2) as a colorless solid. R_f 0.45 (8:2 pentane/EtOAc), mp 184 °C. Found: C, 69.31; H, 5.51; N, 3.51. $C_{22}H_{21}NO_3S$ requires C, 69.63; H, 5.58; N, 3.69%. IR (KBr) ν_{max}/cm^{-1} 2995, 2962, 2931, 1595, 1454, 1407, 1362, 1173, 1097, 967, 874, 763, 571. RMN ^{1}H (400 MHz; $CDCl_3$) δ2.17 (3 H, s), 2.31 (3 H, s), 2.71 (3 H, s), 3.89 (3 H, s), 6.79 (2 H, d, *J* 8.2 Hz), 6.90 (2 H, d, *J* 8.2 Hz), 6.96 (1 H, s), 7.22 (1 H, m), 7.32 (1 H, m), 7.48 (1 H, d, *J* 7.6 Hz), 8.11 (1 H, d, *J* 8.0 Hz). ^{13}C NMR (150 MHz; $CDCl_3$) δ 12.6 (q), 19.1 (q), 21.4 (q), 55.8 (q), 98.2 (d), 119.1 (d), 120.0 (d), 125.4 (d), 126.3 (d), 126.6

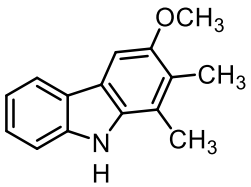
(s), 127.1 (d), 128.3 (d), 129.2 (s), 130.9 (s), 131.4 (s), 131.5 (s), 135.1 (s), 142.1 (s), 143.7 (s), 156.3 (s). MS (EI, 70 eV) *m/z* 379 (M^+, 16%), 272 (1), 224 (100), 181 (26), 155 (4), 127 (18), 91 (5), 57 (11).

General procedure for the *N*-detosylation with TBAF and the preparation of products 12, 14, 1b, 1c, and 1d.



12

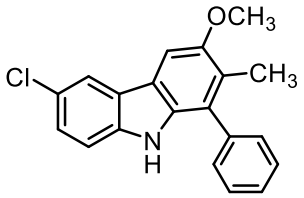
1-Heptyl-3-methoxy-2-methyl-9*H*-carbazole (**12**). To a solution of **11** (100 mg, 0.22 mmol) in dry THF (15 mL) was added dropwise a 1 M solution of TBAF in THF (1.1 mL, 1.1 mmol, 5 equiv.) at rt. The solution was heated to reflux for 21 h then worked up by concentration of the solvent, addition of H_2O and extraction with CH_2Cl_2 followed by washing with brine and drying the combined organic phases with $MgSO_4$. Product purification by column chromatography (silica gel, 19:1 pentane/Et_2O) afforded **12** (56 mg, 84% yield) as a colorless solid. R_f 0.31 (19:1 pentane/Et_2O), mp 102 °C (CH_2Cl_2/pentane). Found: C, 81.15; H, 8.77; N, 4.54. $C_{21}H_{27}NO$ requires C, 81.51; H, 8.79; N, 4.53%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* 6.9 Hz) 1.27−1.48 (8 H, m), 1.59−1.69 (2 H, m), 2.34 (3 H, s), 2.83−2.88 (2 H, m), 3.93 (3 H, s), 7.14−7.21 (1 H, m), 7.31−7.41 (3 H, m), 7.74 (1 H, br s), 7.97 (1 H, d, *J* 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0 (q), 14.1 (q), 22.6 (t), 28.7 (t), 29.3 (t), 29.5 (t), 30.0 (t), 31.8 (t), 56.2 (q), 99.0 (d), 110.6 (d), 118.9 (d), 119.8 (d), 120.4 (s), 123.8 (s), 124.1 (s), 124.2 (s), 124.9 (d), 133.7 (s), 139.6 (s), 152.8 (s). IR (KBr) ν_{max}/cm^{-1} 3423, 2922, 2854, 1583, 1493, 1451, 1425, 1307, 1256, 1206, 1146, 1113, 1098, 830, 769, 744. MS (EI, 70 eV) *m/z* 309 (M^+, 100%), 294 (17), 251 (2), 225 (13), 224 (52), 180 (16), 167 (5), 127 (7), 113 (5), 98 (3), 55 (9).



14

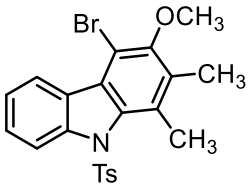
4-Deoxycarbazomycin B (14). Starting from **13** (100 mg, 0.26 mmol). Column chromatography (silica gel, 9:1 pentane/EtOAc) afforded **14** (58 mg, 98% yield) as a colorless solid. R_f 0.51 (8:2 pentane/EtOAc), mp 130–131 °C (pentane/CH_2Cl_2), lit. 129–130 °C,[5] 129–131 °C,[6] 120–121 °C[7]). Found: C, 79.91; H, 6.70; N, 6.14. $C_{15}H_{15}NO$ requires C, 79.97; H, 6.71; N, 6.22%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (3 H,

s), 2.42 (3 H, s), 3.93 (3 H, s), 7.18 (1 H, ddd *J* 7.8, 6.8, 1.4 Hz), 7.73 (1 H, br s), 7.32–7.40 (3 H, m), 7.98 (1 H, d, *J* 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2 (q), 13.8 (q), 56.3 (q), 99.0 (d), 110.7 (d), 118.9 (d), 119.0 (s), 119.8 (d), 120.1 (s), 124.1 (s), 124.2 (s), 124.9 (d), 134.1 (s), 139.6 (s), 152.5 (s). MS (EI) *m/z* 225 (M^+, 38%), 210 (40), 69 (19), 57 (51), 42 (100).



1b : 6-chlorohyellazole

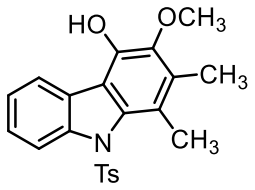
6-Chlorohyellazole (1b). Following the general procedure for the *N*-detosylation reaction with TBAF and starting from **9a** (78 mg, 0.16 mmol) 6-chlorohyellazole (**1b**) was obtained after column chromatography (silica gel, 9:1 petroleum ether/Et_2O) as a colorless solid (18 mg, 97% yield). R_f 0.55 (7:3 petroleum ether/EtOAc), mp 165 °C (pentane/$CHCl_3$), lit.[8] 163−164 °C. ^{1}H NMR (400 MHz, aceton-D_6) δ 2.13 (3 H, s), 3.98 (3 H, s), 7.26 (1 H, dd, *J* 8.7, 2.1 Hz), 7.38−7.47 (5 H, m), 7.51−7.55 (1 H, m), 7.75 (1 H, s), 8.12 (1 H, d, *J* 2.1 Hz), 9.68 (1 H, br s).^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9 (q), 55.3 (q), 99.2 (d), 110.7 (d), 118.6 (s), 118.8 (d), 123.4 (s), 123.9 (s), 124.0 (s), 124.2 (d), 124.9 (s), 126.9 (d), 128.2 (d), 129.0 (d), 133.0 (s), 136.4 (s), 136.9 (s), 152.1 (s). MS (EI, 70 eV) *m/z* 321 (M^+, 70%), 306 (11), 288 (3), 281 (16), 271 (31), 254 (5), 247 (10), 246 (76), 241 (8), 223 (9), 217 (3), 199 (23), 191 (5), 183 (2), 167 (1), 149 (18), 141 (6), 112 (4), 97 (11), 85 (10).



15

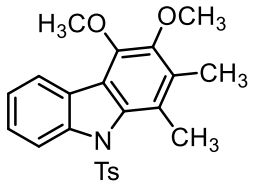
***N*-(*p*-Toluenesulfonyl)-4-bromo-3-methoxy-1,2-dimethylcarbazole (15).** To a solution of **13** (200 mg, 0.53 mmol) in dry CH_3CN (30 mL) was added NBS (103 mg, 0.58 mmol) and the reaction mixture was stirred at 40 °C in the dark overnight. After solvent concentration the product was purified by column chromatography (silica gel, 9:1 petroleum ether/EtOAc) to afford **15** (226 mg, 93% yield) as a colorless solid. R_f 0.47 (8:2 pentane/EtOAc), mp 182-183 °C. Found: C, 57.70; H, 4.45; N, 3.02; S, 7.10. $C_{22}H_{20}BrNO_3S$ requires C, 57.65; H, 4.40; N, 3.06; S, 7.00%. IR (KBr) ν_{max}/cm^{-1} 2999, 2967, 2935, 2846, 1596, 1467, 1366, 1175, 1088, 1074, 761, 570. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (3 H, s), 2.43 (3 H, s), 2.68 (3 H, s), 3.84 (3 H, s), 6.80–6.85 (4 H, m), 7.27 (1 H, m), 7.39 (1 H, m), 8.10 (1 H, d, *J* 8.0 Hz), 8.32

(1 H, dd, *J* 7.8, 0.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (q), 19.4 (q), 21.4 (q), 60.6 (q), 108.0 (s), 119.7 (d), 122.2 (d), 125.3 (d), 127.08 (d), 127.10 (d), 128.4 (d), 128.7 (s), 130.6 (s), 131.1 (s), 131.2 (s), 131.7 (s), 138.7 (s), 142.4 (s), 144.3 (s), 153.8 (s). MS (EI, 70 eV) *m*/*z* 459/457 (M^+, 14%), 304 (92), 302 (100), 261 (11), 259 (10), 213 (8), 180 (29), 127 (47), 113 (10), 57 (26). HRMS (ESI) calcd for $C_{22}H_{20}BrNO_3SNa$ $[MNa]^+$ 482.0221, found 482.0210.



16

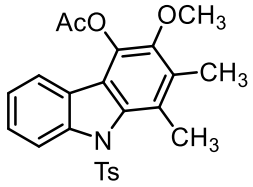
***N*-(*p*-Toluenesulfonyl)-4-hydroxy-3-methoxy-1,2-dimethylcarbazole (16).** To a solution of **15** (120 mg, 0.26 mmol) in dry THF (5 mL) at –78 °C was added dropwise a 1.5 M solution of *t*-BuLi in pentane (0.2 mL, 0.3 mmol). After 15 min trimethylborate (70 μL, 0.63 mmol) was added and the reaction mixture was allowed to warm up to 0 °C within 2 h. A mixture of H_2O_2 (35%, 0.8 mL) and NaOH (2 M, 0.8 mL) was added and the mixture was stirred for 5 min. The reaction was then acidified with 10% HCl, diluted with H_2O (20 mL), and extracted with Et_2O (3 x 15 mL). The organic layer was washed with H_2O and brine, dried with $MgSO_4$ and concentrated. The product was purified by column chromatography (silica gel, 9:1 to 8:2 petroleum ether/EtOAc) to give, along with **13** (15 mg, 15% yield), **16** (83 mg, 80% yield) as a colorless solid. R_f 0.24 (8:2 pentane/EtOAc), mp 173–175 °C. Found: C, 66.71; H, 5.27; N, 3.58; S, 7.91. $C_{22}H_{21}NO_4S$ requires C, 66.82; H, 5.35; N, 3.54; S, 8.11%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (3 H, s), 2.37 (3 H, s), 2.62 (3 H, s), 3.81 (3 H, s), 5.84 (1 H, s), 6.81 (2 H, d, *J* 8.4 Hz), 6.93 (2 H, d, *J* 8.4 Hz), 7.23 (1 H, ddd, *J* 7.6, 7.4, 1.2 Hz), 7.31 (1 H, ddd, *J* 8.0, 7.4, 1.6 Hz), 7.80 (1 H, dd, *J* 7.6, 1.6 Hz), 8.07 (1 H, dd, *J* 8.0, 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4 (q), 18.5 (q), 21.4 (q), 61.2 (q), 116.7 (s), 119.4 (d), 122.2 (d), 122.5 (s), 125.7 (d), 125.8 (d), 127.1 (d), 128.4 (d), 129.6 (s), 130.0 (s), 131.8 (s), 137.8 (s), 141.4 (s), 141.5 (s), 143.5 (s), 143.9 (s). MS (EI, 70 eV) *m*/*z* 395 (M^+, 5%), 241 (40), 83 (100).



17

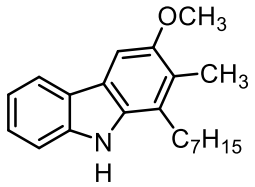
***N*-(*p*-Toluenesulfonyl)-3,4-dimethoxy-1,2-dimethylcarbazole (17).** To a solution of **16** (96 mg, 0.24 mmol) in acetone (4 mL) was added MeI (0.5 mL) and K_2CO_3 (500 mg) and the suspension was heated

under reflux for 3 h. The reaction mixture was diluted with Et_2O (30 mL), filtered and evaporated to dryness. The residue was purified by column chromatography (silica gel, 8:2 petroleum ether/EtOAc) to afford **17** (99 mg, 99% yield) as a colorless solid. R_f 0.44 (8:2 pentane/EtOAc), mp 132–133 °C (CH_2Cl_2/pentane). Found: C, 67.41; H, 5.27; N, 3.17; S, 7.81. $C_{23}H_{23}NO_4S$ requires C, 67.46; H, 5.66; N, 3.42; S, 7.83%. IR (ATR) ν_{max}/cm^{-1} 2988, 2960, 2939, 2840, 1595, 1487, 1446, 1385, 1358, 1173, 1074, 1005, 982, 768. ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.17 (3 H, s), 2.35 (3 H, s), 2.65 (3 H, s), 3.81 (3 H, s), 3.87 (3 H, s), 6.78 (2 H, d, *J* 8.0 Hz), 6.86 (2 H, d, *J* 8.4 Hz), 7.23 (1 H, ddd, *J* 7.6, 7.4, 1.0 Hz), 7.32 (1 H, ddd, *J* 8.2, 7.4, 1.4 Hz), 7.75 (1 H, dd, *J* 7.6, 1.4 Hz), 8.07 (1 H, dd, *J* 8.2, 1.0 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ 13.1 (q), 18.8 (q), 21.4 (q), 60.3 (q), 60.7 (q), 119.8 (d), 122.0 (d), 122.7 (s), 125.9 (d), 126.2 (d), 126.8 (s), 127.1 (d), 128.2 (d), 129.6 (s), 131.3 (s), 131.7 (s), 137.5 (s), 141.7 (s), 143.9 (s), 145.3 (s), 149.4 (s). MS (EI) *m*/*z* 409 (M^+, 100%), 254 (67), 114 (35), 91 (95).



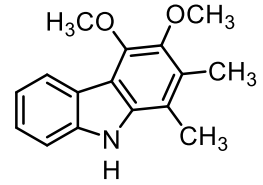
18

***N*-(*p*-Toluenesulfonyl)-4-acetyloxy-3-methoxy-1,2-dimethylcarbazole (18).** To a solution of **16** (83 mg, 0.21 mmol) in dry CH_2Cl_2 (5 mL) was added dry pyridine (25 μL, 0.3 mmol), DMAP (3 mg, 10 mol%), and Ac_2O (30 μL, 0.32 mmol). The reaction mixture was stirred overnight at rt. After evaporation to dryness, the residue was purified by column chromatography (silica gel, 7:3 petroleum ether/EtOAc) to afford **18** (91 mg, 98% yield) as a colorless solid. R_f 0.42 (7:3 pentane/EtOAc), mp 154–155 °C (CH_2Cl_2/pentane). Found: C, 65.82; H, 5.43; N, 3.12; S, 7.31. $C_{24}H_{23}NO_5S$ requires C, 65.89; H, 5.30; N, 3.20; S, 7.33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (3 H, s), 2.38 (3 H, s), 2.39 (3 H, s), 2.68 (3 H, s), 3.79 (3 H, s), 6.82 (2 H, d, *J* 8.2 Hz), 6.88 (2 H, d, *J* 8.4 Hz), 7.20 (1 H, td, *J* 7.6, 1.0 Hz), 7.33 (1 H, ddd, *J* 8.2, 7.4, 1.3 Hz), 7.43 (1 H, ddd, *J* 7.6, 1.3, 0.6 Hz), 8.08 (1 H, ddd, *J* 8.2, 1.0, 0.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3 (q), 19.1 (q), 20.5 (q), 21.3 (q), 61.0 (q), 119.8 (d), 121.1 (d), 122.4 (s), 125.8 (d), 126.7 (d), 126.9 (d), 128.4 (d), 128.6 (s), 129.3 (s), 131.3 (s), 131.7 (s), 135.8 (s), 137.6 (s), 142.0 (s), 144.2 (s), 148.5 (s); 168.0 (s). MS (EI) *m*/*z* 437 (M^+, 11%), 282 (62), 240 (100).



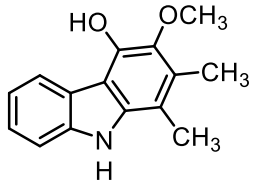
carazostatin (**1f**)

Carazostatin (1f). To a solution of **12** (55 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was added at −78 °C a 1 M solution of BBr_3 in CH_2Cl_2 (370 µL, 0.37 mmol, 2.1 equiv.). The reaction was warmed up to rt and then H_2O was added followed by extraction with EtOAc and by washing with brine and drying the combined organic phases with $MgSO_4$. Product purification by column chromatography (silica gel, 9:1 pentane/EtOAc) afforded carazostatin (**1f**) as a colorless solid (42 mg, 80% yield). R_f 0.16 (9:1 pentane/EtOAc), mp 155−156 °C (pentane/CH_2Cl_2), lit. 149−152 °C,[9] 162−163 °C,[10] 159−160 °C,[11] 153−155 °C[12]). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* 6.8 Hz), 1.26−1.47 (8 H, m), 1.59−1.67 (2 H, m), 2.35 (3 H, s), 2.83−2.87 (2 H, m), 4.57 (1 H, br s), 7.15 (1 H, t, *J* 7 Hz), 7.29 (1 H, s), 7.32−7.40 (2 H, m), 7.73 (1 H, br s), 7.89 (1 H, d, *J* 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0 (q), 14.1 (q), 22.7 (t), 28.8 (t), 29.3 (t), 29.5 (t), 30.0 (t), 31.9 (t), 103.0 (d), 110.6 (d), 118.9 (d), 120.0 (d), 120.8 (s), 121.4 (s), 123.7 (s), 124.1 (s), 125.2 (d), 134.0 (s), 139.8 (s), 148.1 (s). IR (KBr) ν_{max}/cm^{-1} 3485, 3416, 2959, 2924, 2855, 1590, 1496, 1463, 1439, 1381, 1315, 1259, 1231, 1219, 1145, 1063, 846, 770, 743. MS (EI, 70 eV) *m/z* 295 (M^+, 100%), 272 (2), 231 (3), 210 (69), 180 (6), 167 (9), 127 (28), 113 (4), 98 (4), 57 (17). HRMS (ESI) calcd for $C_{20}H_{25}NONa$ $[MNa]^+$ 318.1828, found 318.1831.



carbazomycin A (**1c**)

Carbazomycin A. Following the general procedure for the *N*-detosylation reaction and starting from **17** (41 mg, 0.10 mmol) carbazomycin A (**1c**) was obtained after column chromatography (silica gel, 8:2 pentane/EtOAc) as a pale-yellow solid (25 mg, 96% yield). R_f 0.45 (8:2 pentane/EtOAc), mp 138 °C (pentane/CH_2Cl_2), lit. 51−52.5 °C,[5] 143−146 °C[7]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (3 H, s), 2.38 (3 H, s), 3.89 (3 H, s), 4.10 (3 H, s), 7.19−7.23 (1 H, m), 7.33−7.40 (2 H, m), 7.82 (1 H, br s), 8.23 (1 H, d, *J* 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6 (q), 13.6 (q), 60.5 (q), 61.1 (q), 110.2 (d), 113.5 (s), 114.4 (s), 119.4 (d), 122.5 (d), 122.8 (s), 125.0 (d), 128.8 (s), 136.4 (s), 139.4 (s), 144.4 (s), 146.0 (s). MS (EI) *m/z* 255 (M^+, 67%), 240 (100), 197 (46). HRMS (ESI) calcd for $C_{16}H_{18}NO_2$ $[MH]^+$ 256.1338, found 256.1349.



carbazomycin B (**1d**)

Carbazomycin B. Following the general procedure for the *N*-detosylation reaction with TBAF and starting from **18** (71 mg, 0.16 mmol) carbazomycin B (**1d**) was obtained after column chromatography (silica gel, 85:15 pentane/EtOAc) as a colorless solid (11 mg, 28% yield, 2 steps). R_f 0.46 (7:3 pentane/EtOAc). Lit. 158.5−160 °C,[5] 162−164 °C,[7] 148 °C[13].^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3 H, s), 2.39 (3 H, s), 3.82 (3 H, s), 6.06 (1 H, s), 7.19-7.23 (1 H, m), 7.33−7.39 (2 H, m), 7.77 (1 H, br s), 8.24 (1 H, d, *J* 7.6 Hz). MS (EI) *m/z* 241 (M^+, 100%). HRMS (ESI) calcd for $C_{15}H_{16}NO_2$ $[MH]^+$ 242.1181, found 242.1189.

3. ^{1}H AND ^{13}C NMR SPECTRA

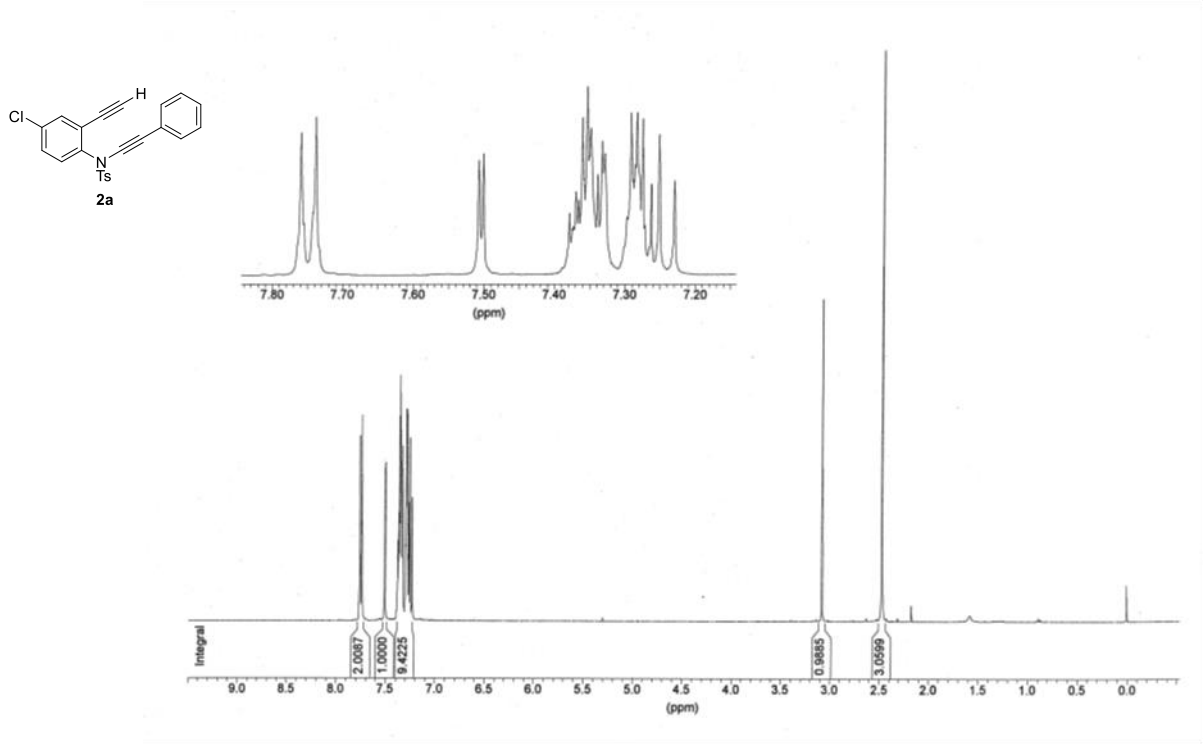


Figure S1 ^{1}H NMR (400 MHz, $CDCl_3$) of yne-ynamide **2a**.

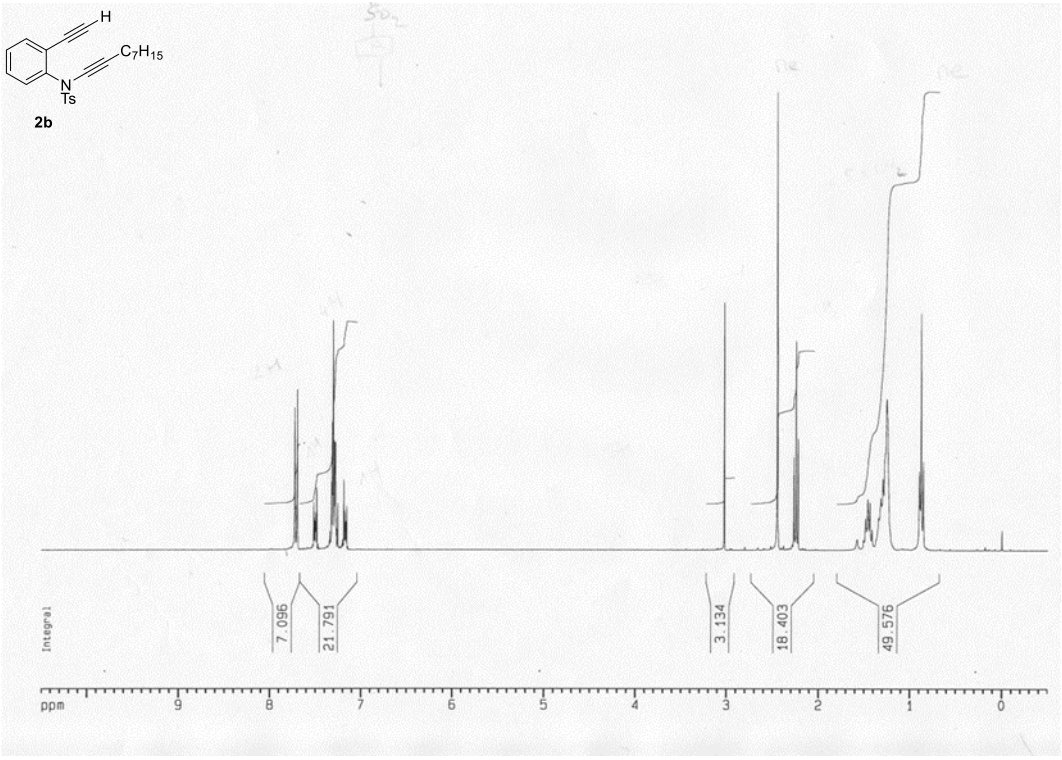


Figure S2 ^{1}H NMR (300 MHz, $CDCl_3$) of yne-ynamide **2b**.

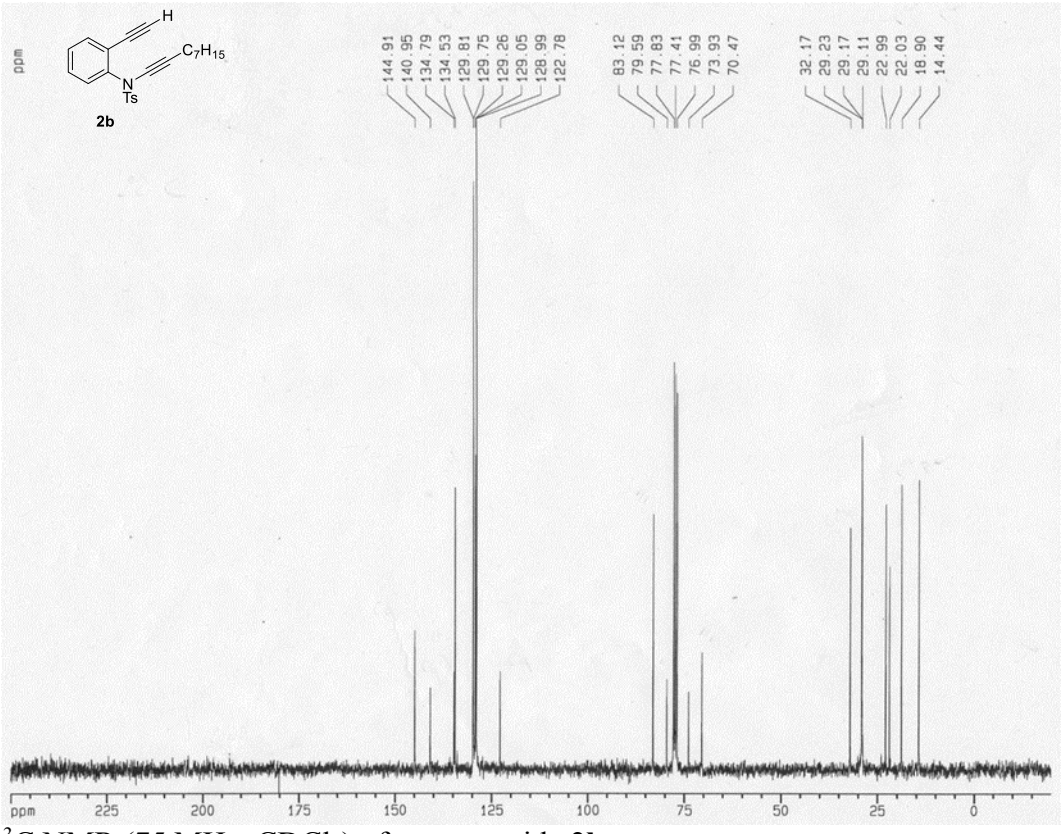


Figure S3 ^{13}C NMR (75 MHz, $CDCl_3$) of yne-ynamide **2b**.

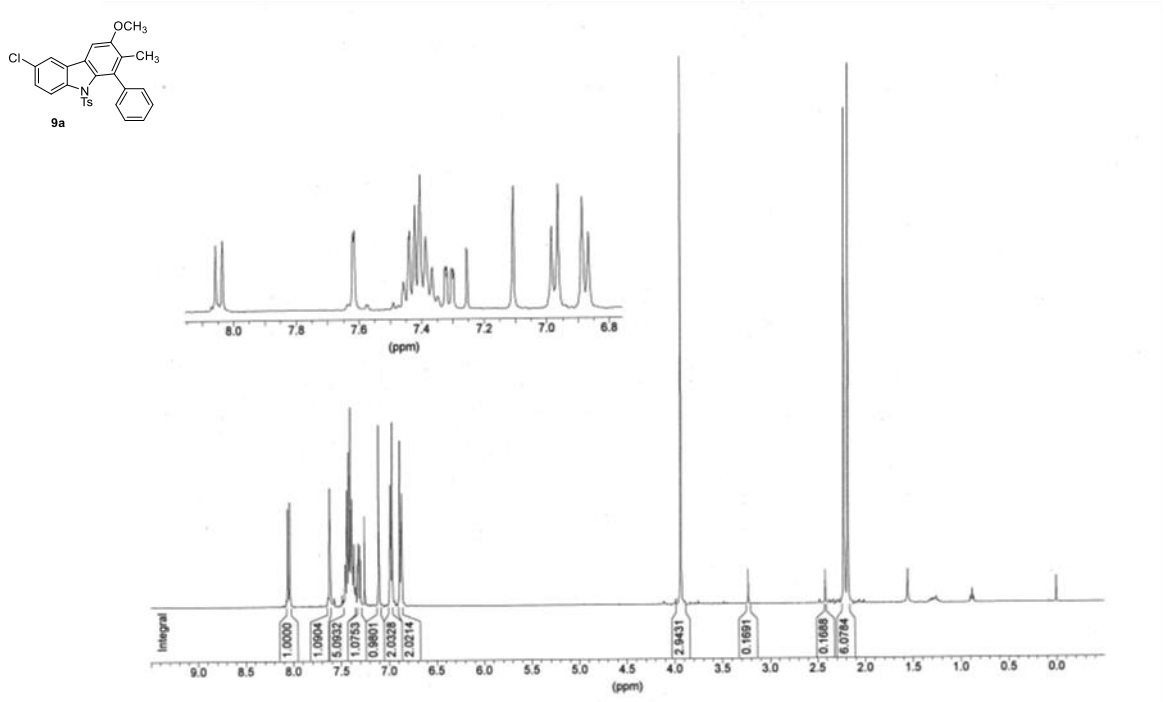


Figure S4 ^{1}**H NMR** (400 MHz, $CDCl_3$) of yne-ynamide **9a**.

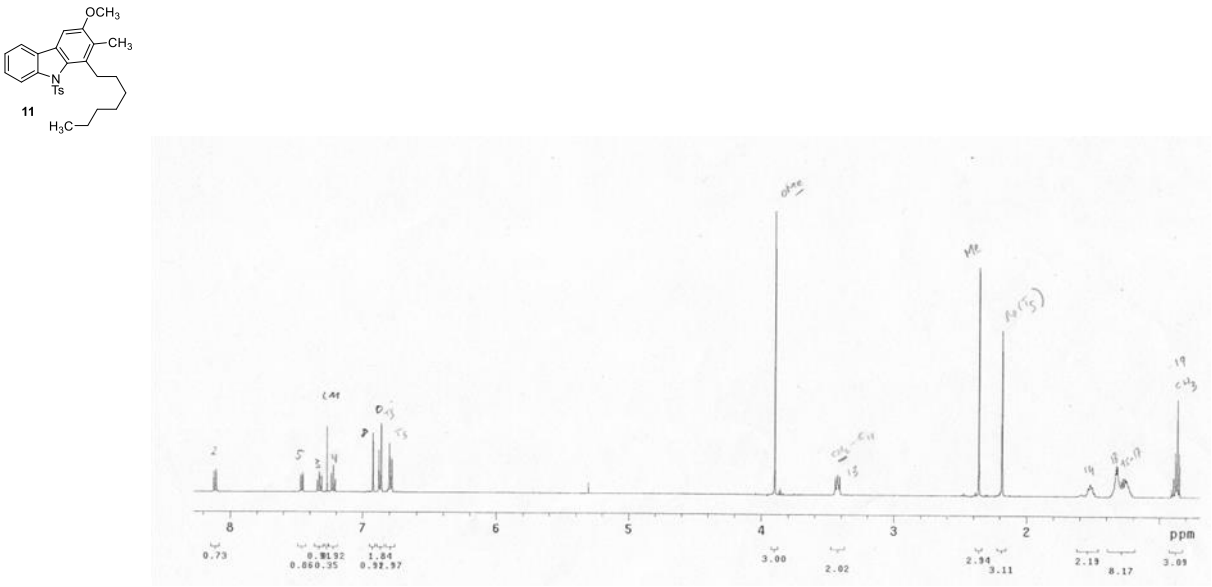


Figure S5 ^{1}H NMR (500 MHz, $CDCl_3$) of carbazole **11**.

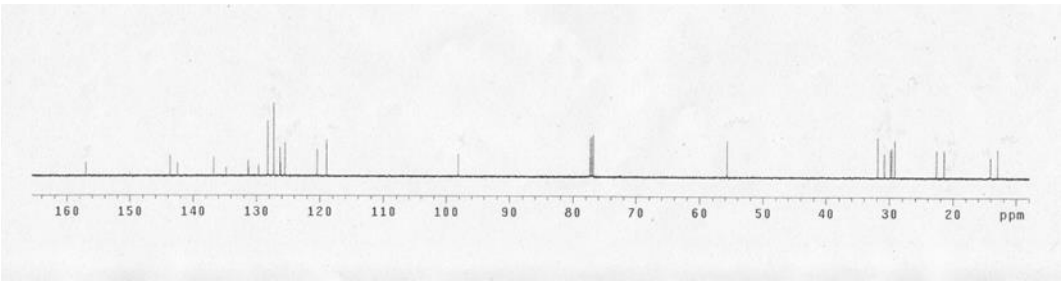


Figure S6 ^{13}C NMR (125 MHz, $CDCl_3$) of carbazole **11**.

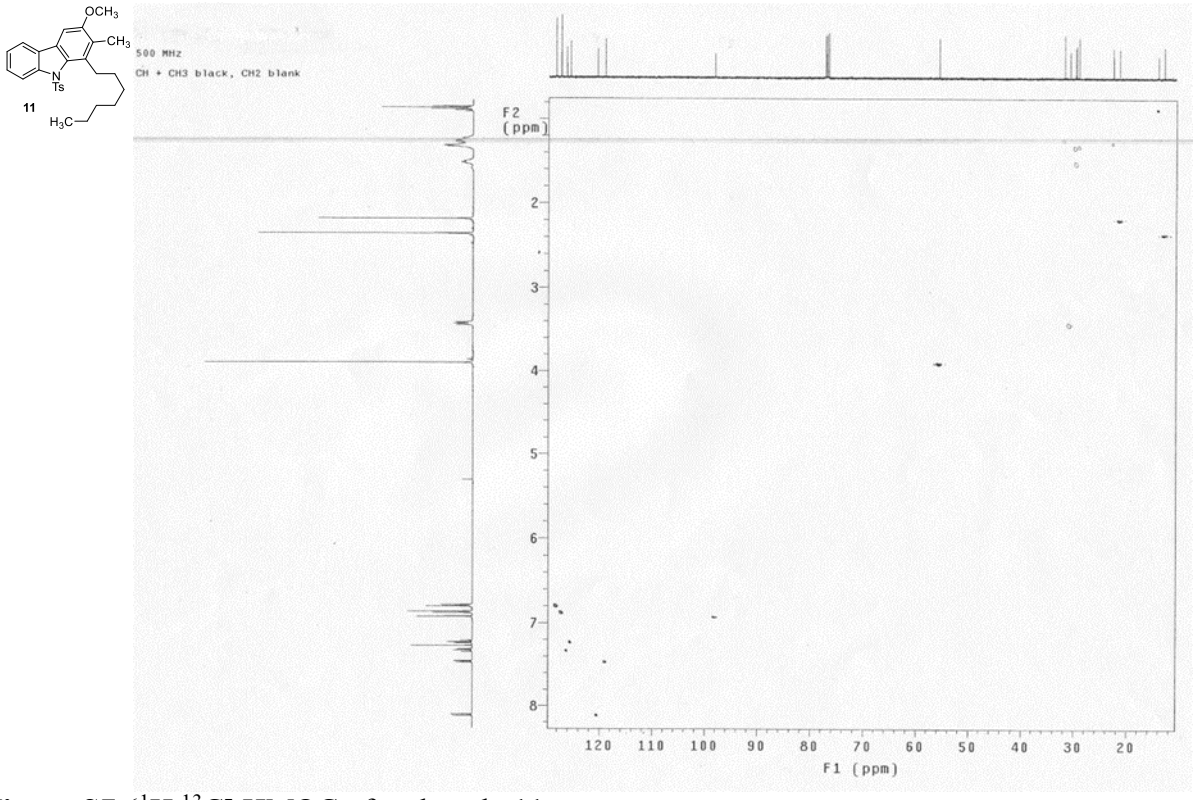


Figure S7 {^{1}H,^{13}C] HMQC of carbazole **11**.

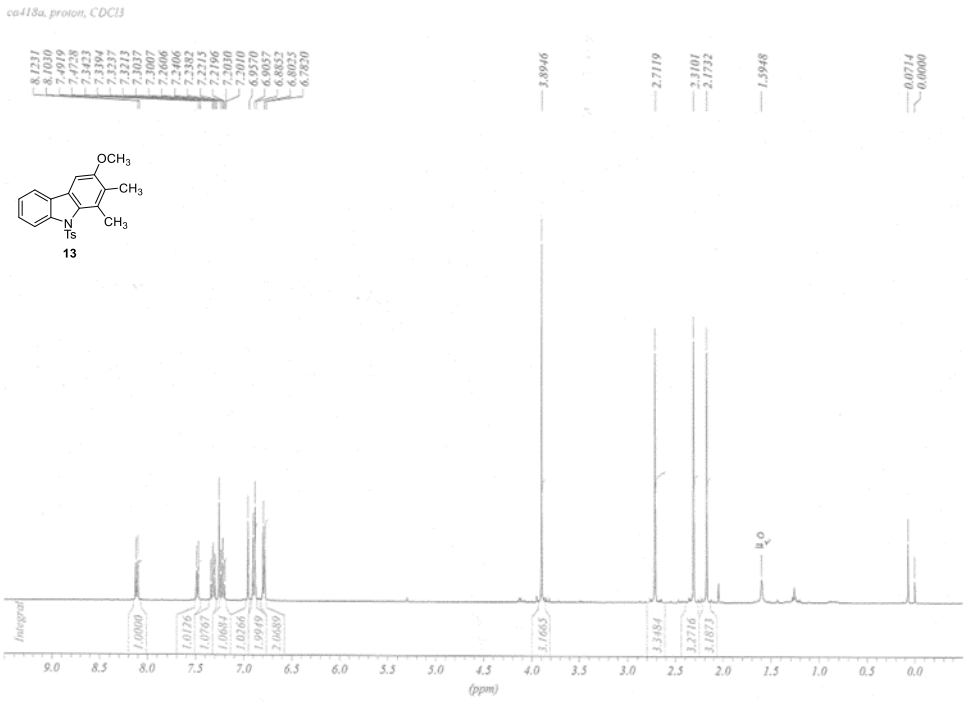


Figure S8 ^{1}H NMR (400 MHz, $CDCl_3$) of carbazole **13**.

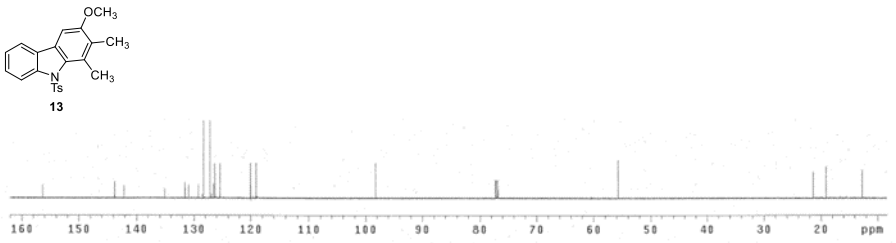


Figure S9 ^{13}C NMR (125 MHz, $CDCl_3$) of carbazole **13**.

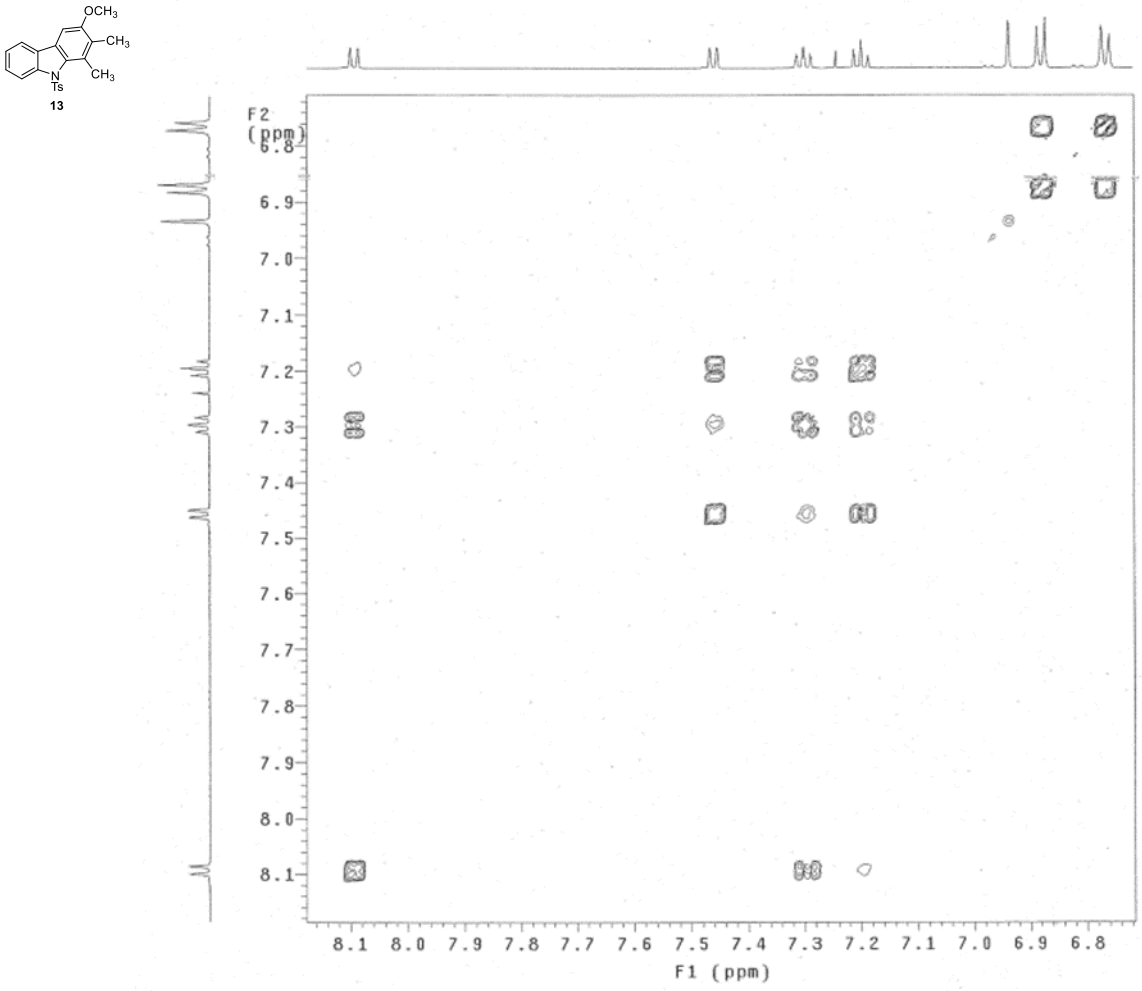


Figure S10 {^{1}H,^{1}H} COSY of carbazole **13**.

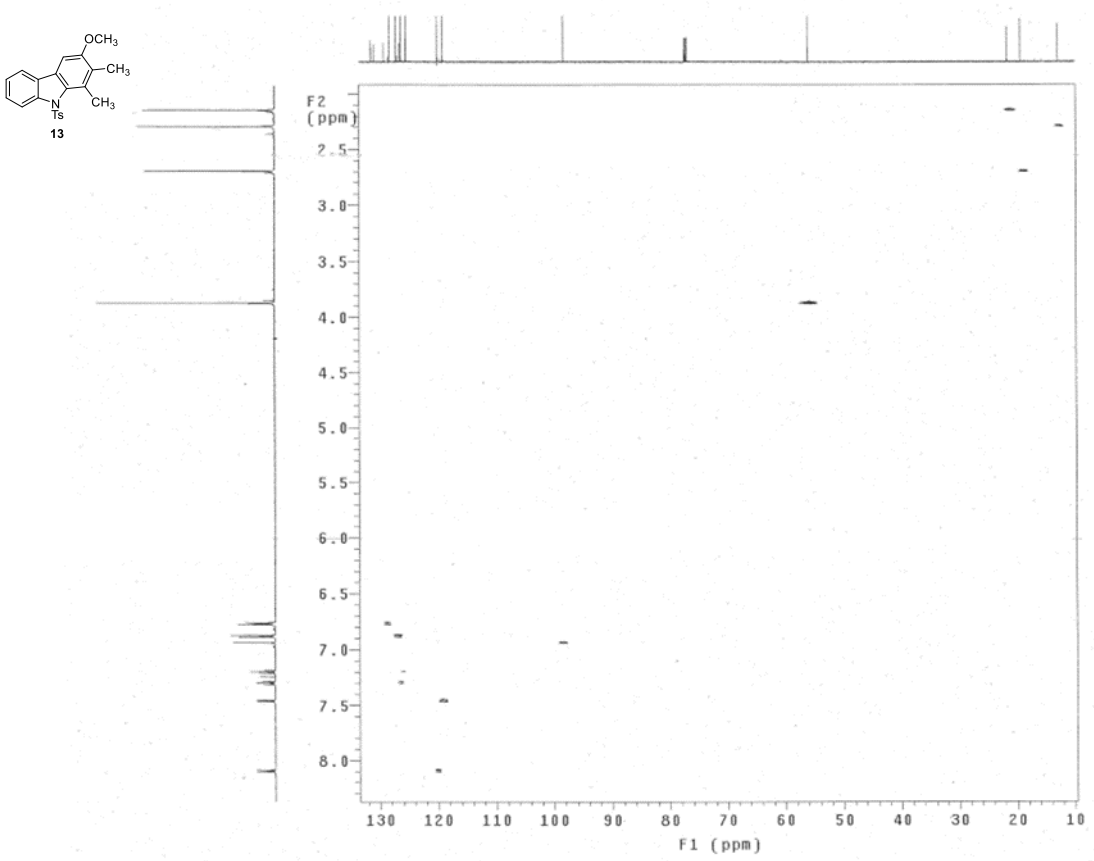


Figure S11 {^{13}C,^{1}H} COSY of carbazole **13**.

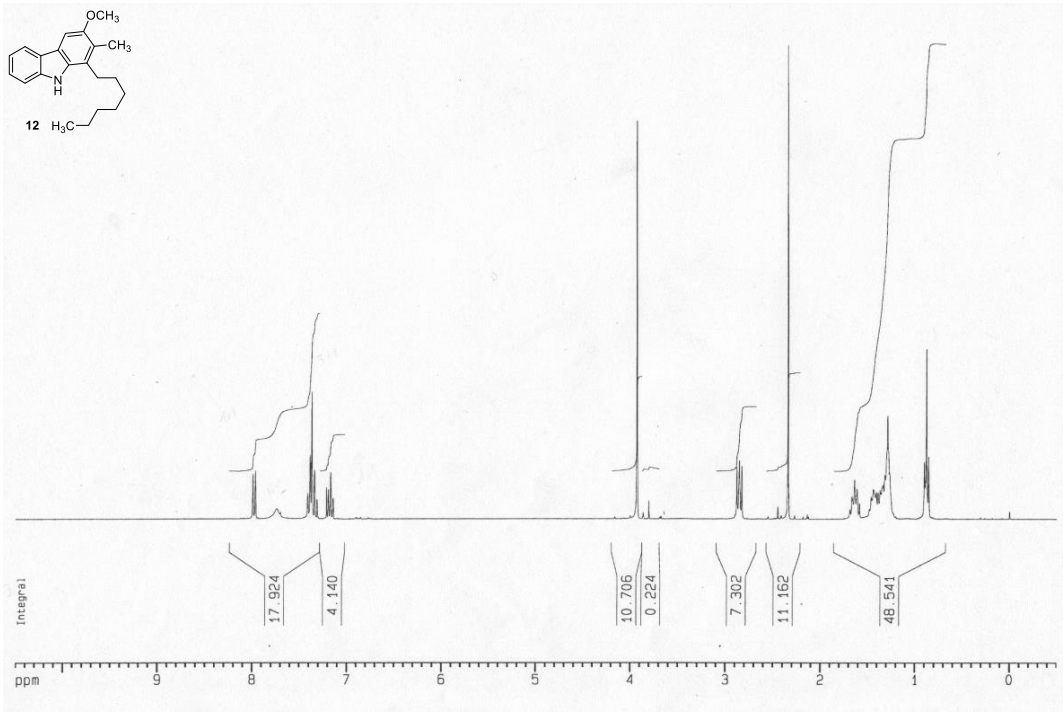


Figure S12 ^{1}H NMR (300 MHz, $CDCl_3$) of carbazole **12**.

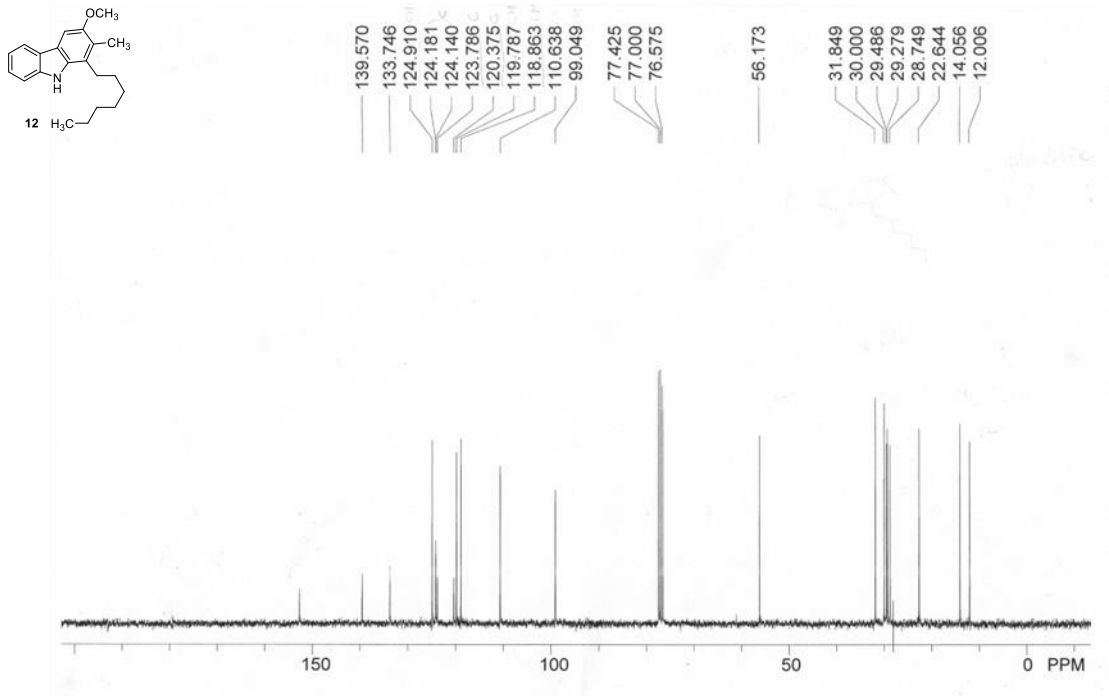


Figure S13 ^{13}C NMR (75 MHz, $CDCl_3$) of carbazole **12**.

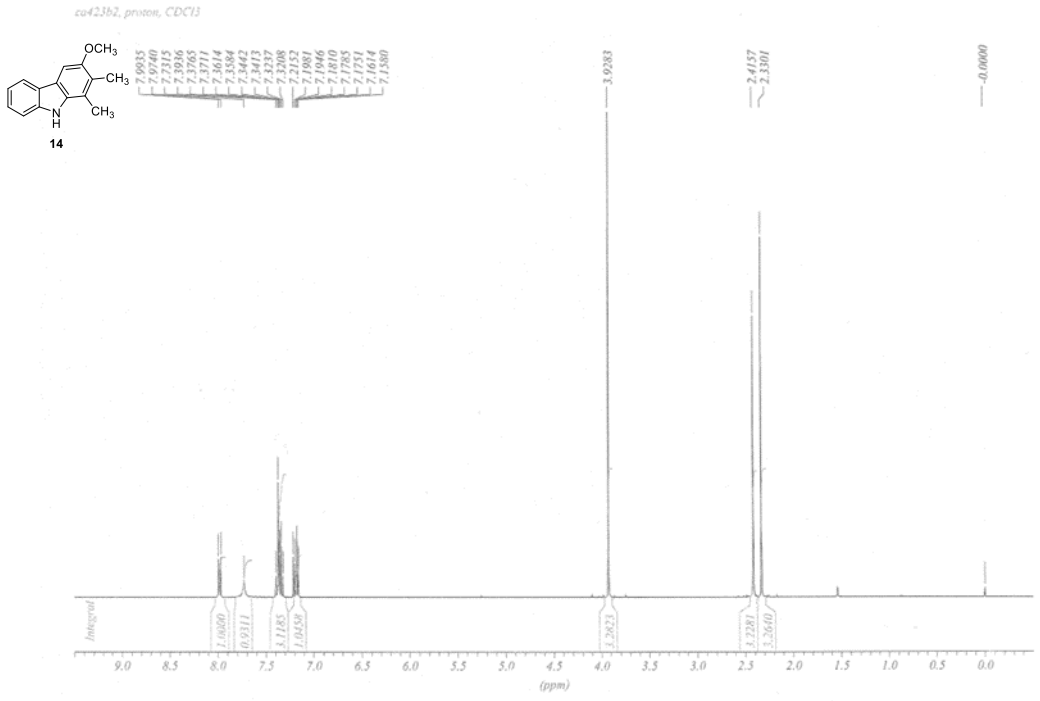


Figure S14 ^{1}H NMR (400 MHz, CDCl) of **4-deoxycarbazomycin B** (**14**).

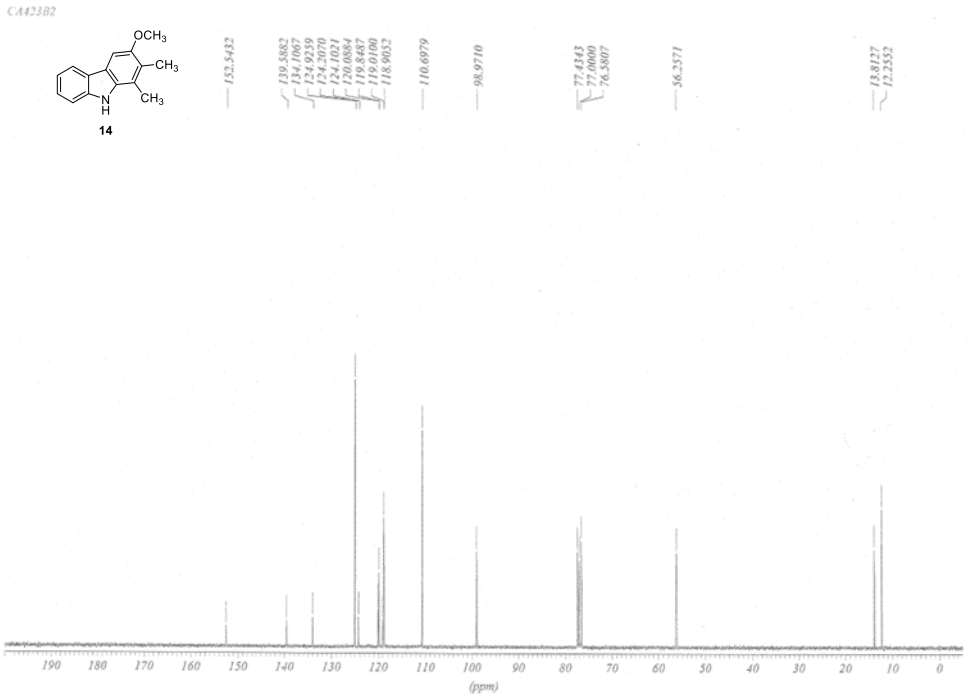


Figure S15 ^{13}C NMR (100 MHz, $CDCl_3$) **4-deoxycarbazomycin B** (**14**).

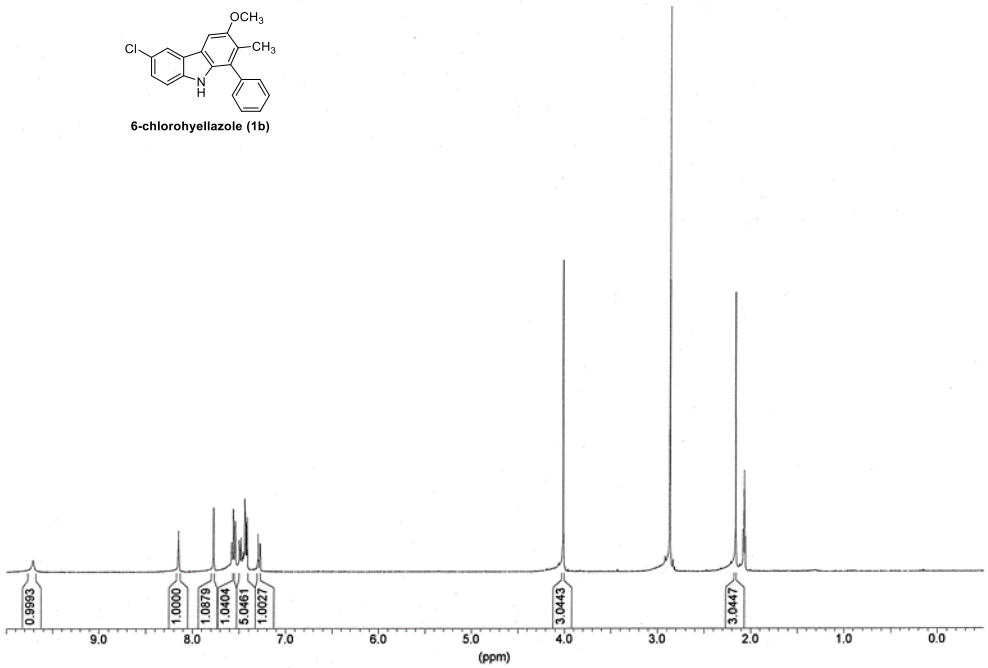


Figure S16 ^{1}H NMR (400 MHz, acetone-d_6) of **6-chlorhyellazole** (**1b**).

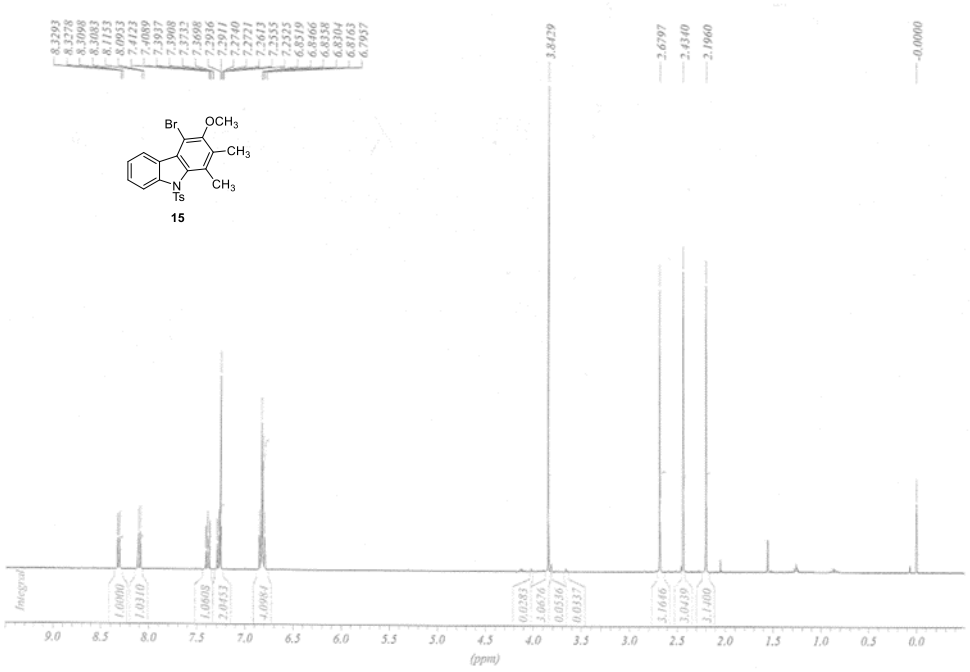


Figure S17 ^{1}H NMR (400 MHz, $CDCl_3$) of carbazole **15**.

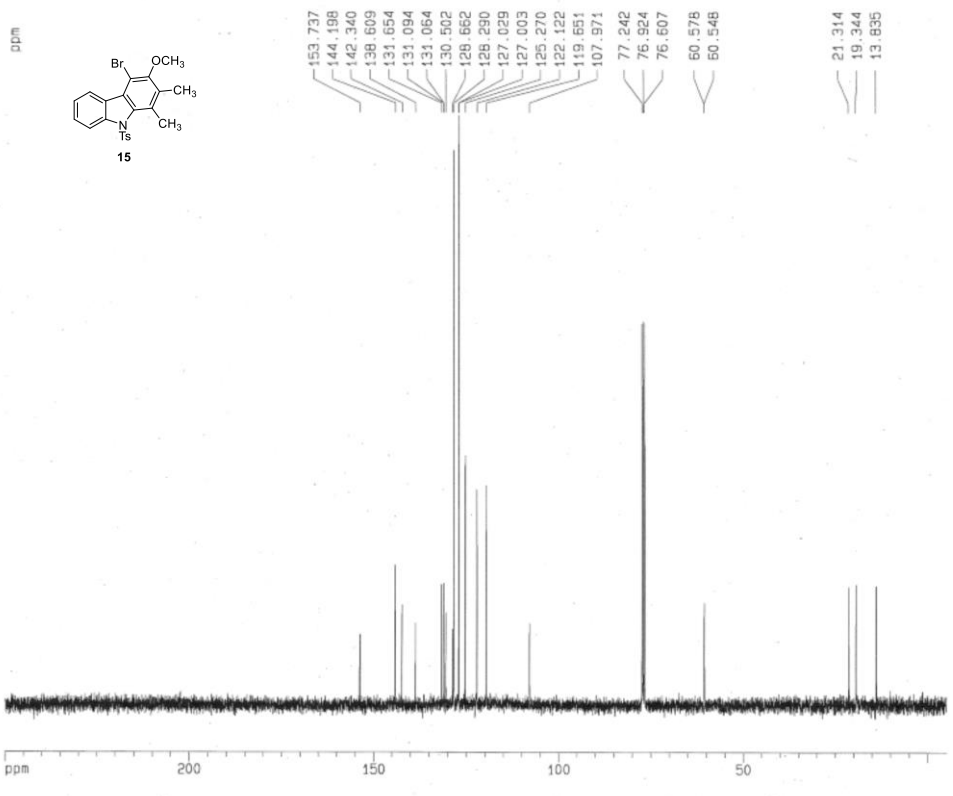


Figure S18 ^{13}C NMR (100 MHz, $CDCl_3$) of carbazole **15**.

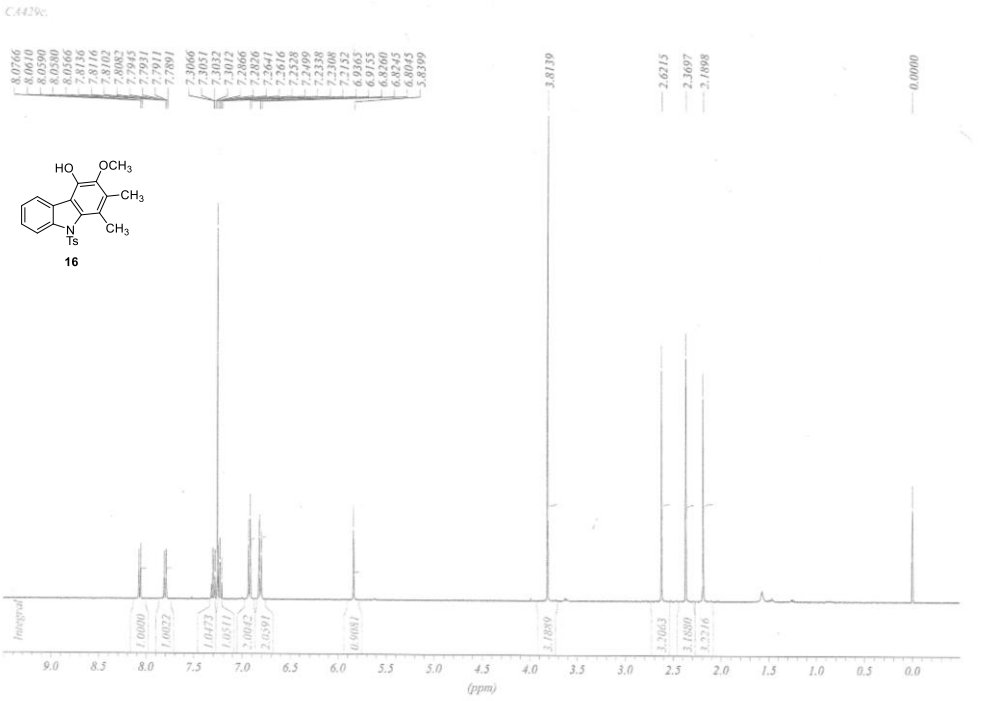


Figure S19 ^{1}H NMR (400 MHz, $CDCl_3$) of carbazole **16**.

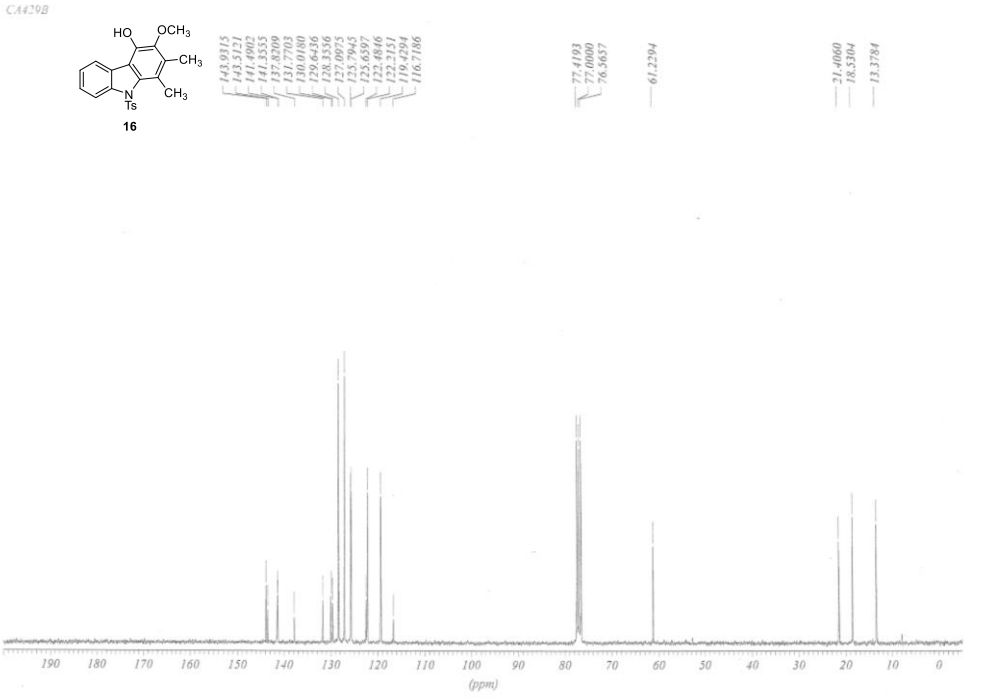


Figure S20 ^{13}C NMR (75 MHz, $CDCl_3$) of carbazole **16**.

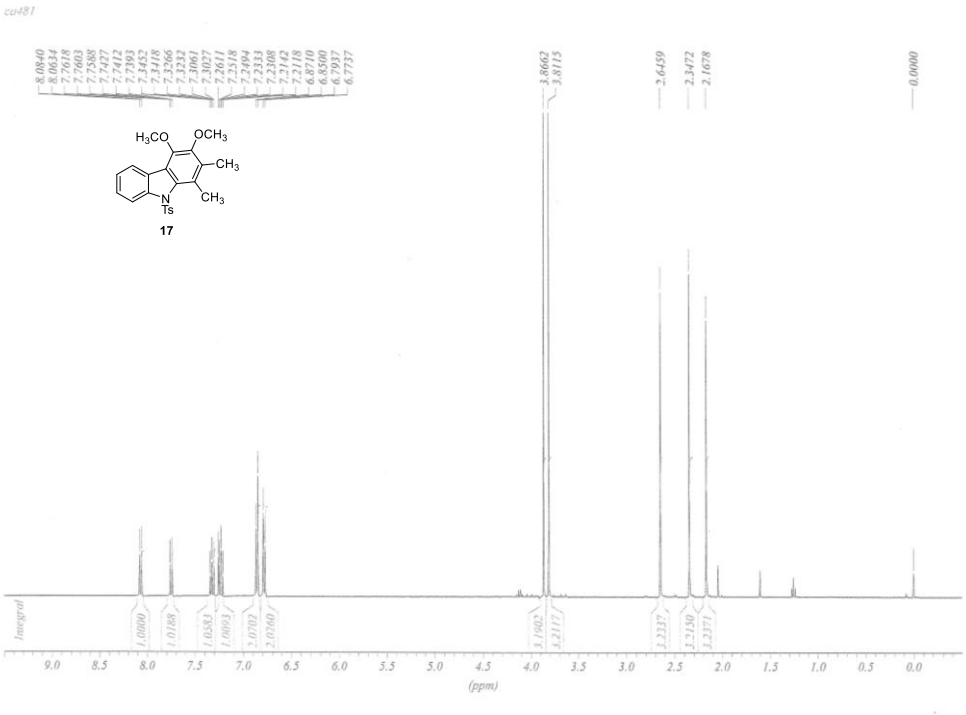


Figure S21 ^{1}H NMR (400 MHz, $CDCl_3$) of carbazole **17**.

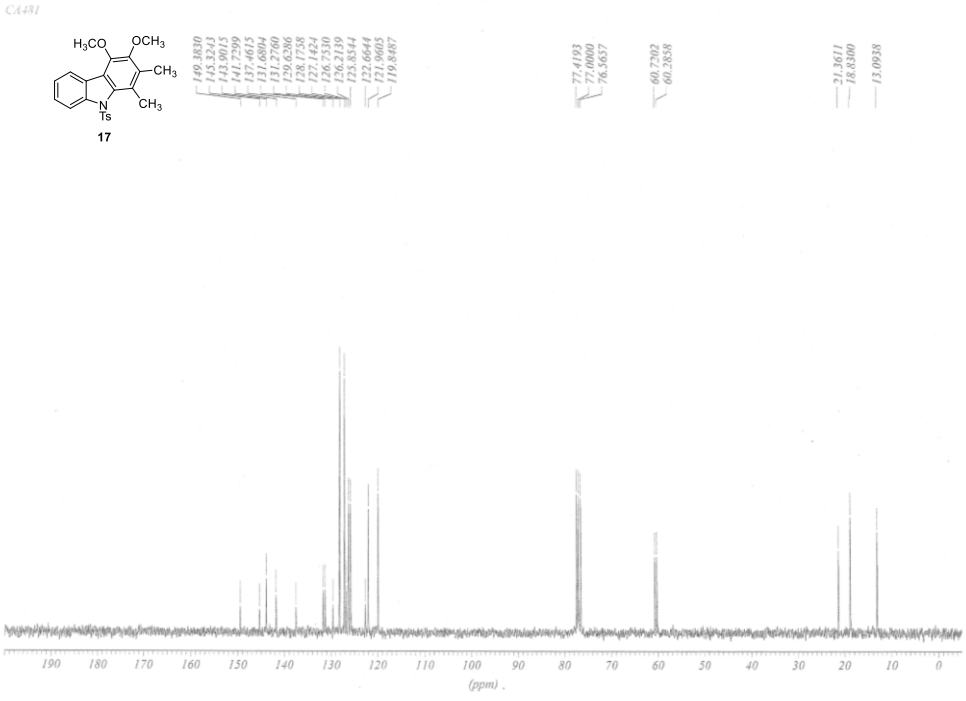


Figure S22 ^{13}C NMR (75 MHz, $CDCl_3$) of carbazole **17**.

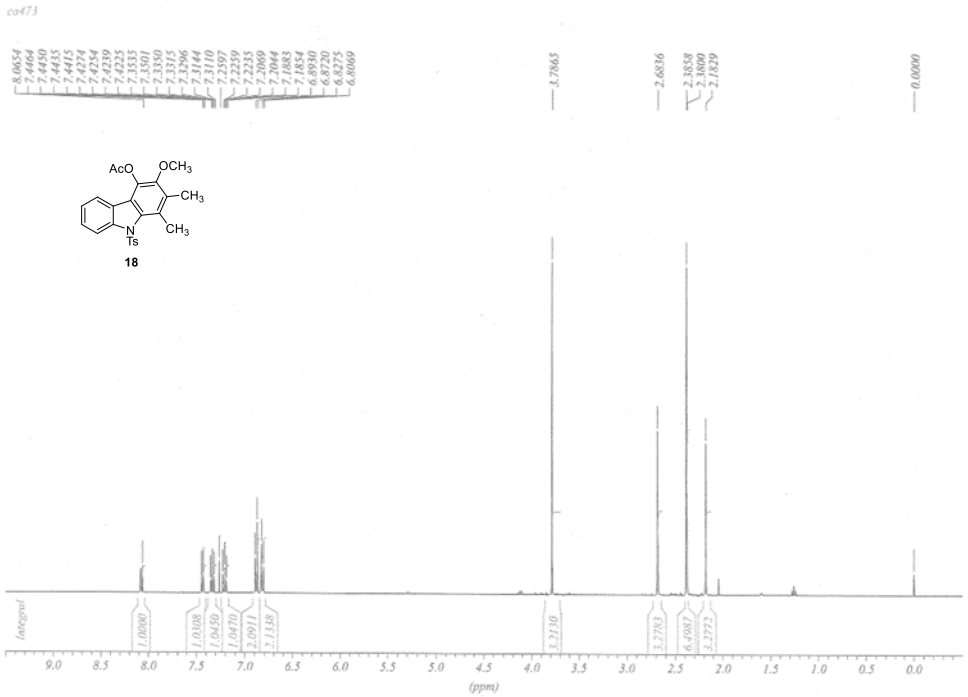


Figure S23 ^{1}H NMR (400 MHz, $CDCl_3$) of carbazole **18**.

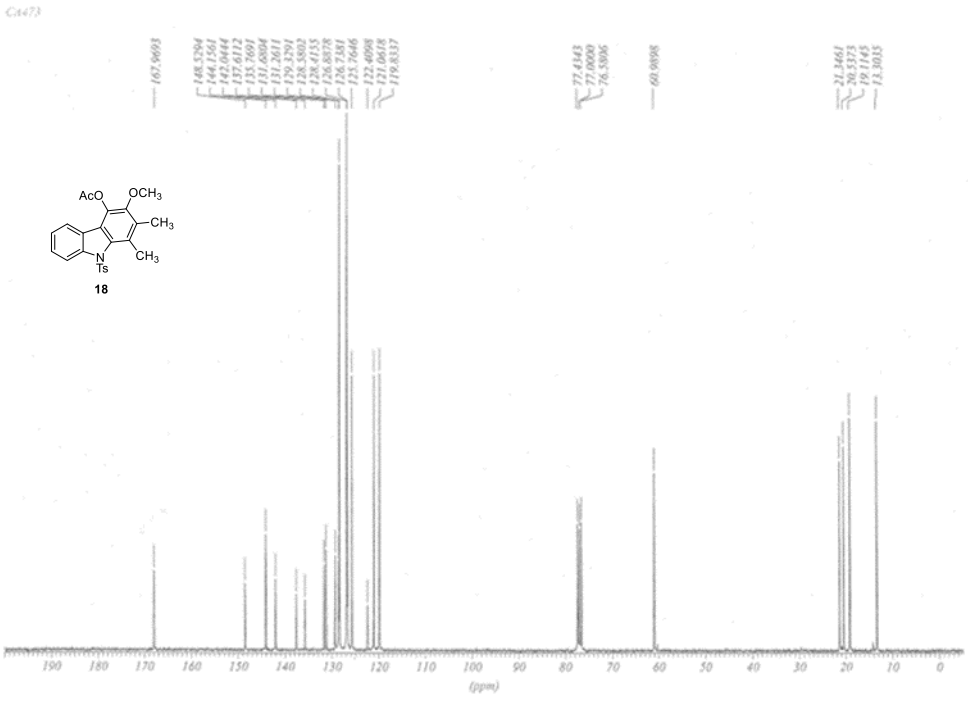


Figure S24 ^{13}C NMR (75 MHz, $CDCl_3$) of carbazole **18**.

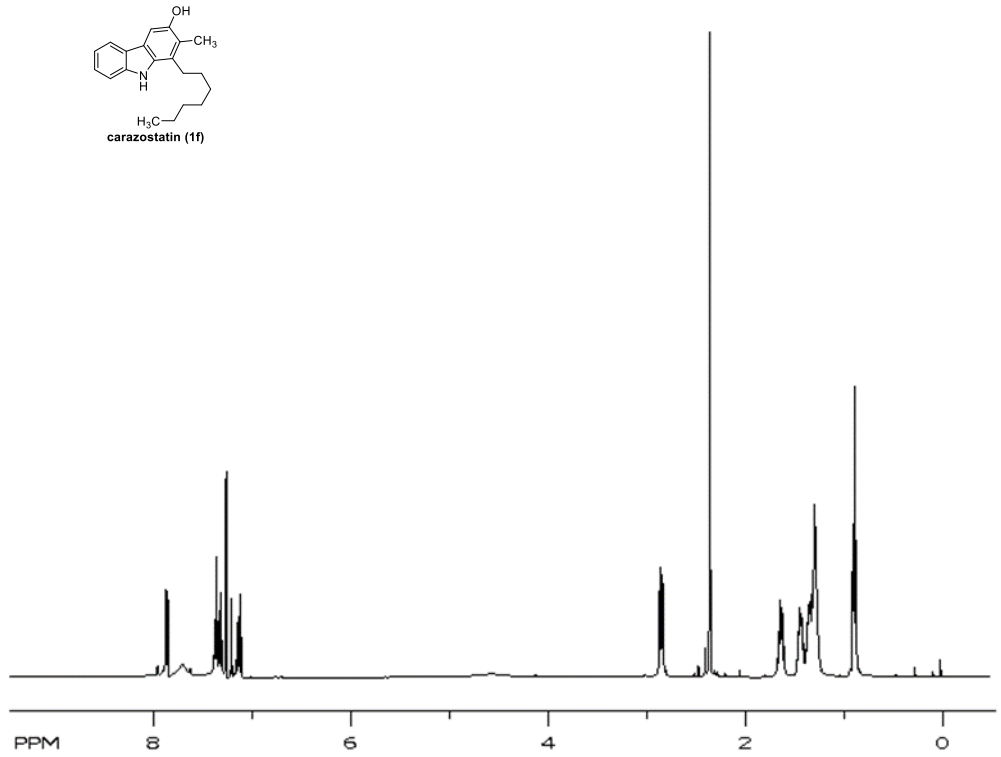


Figure S25 ^{1}H NMR (400 MHz, $CDCl_3$) of synthetic **carazostatin** (**1f**).

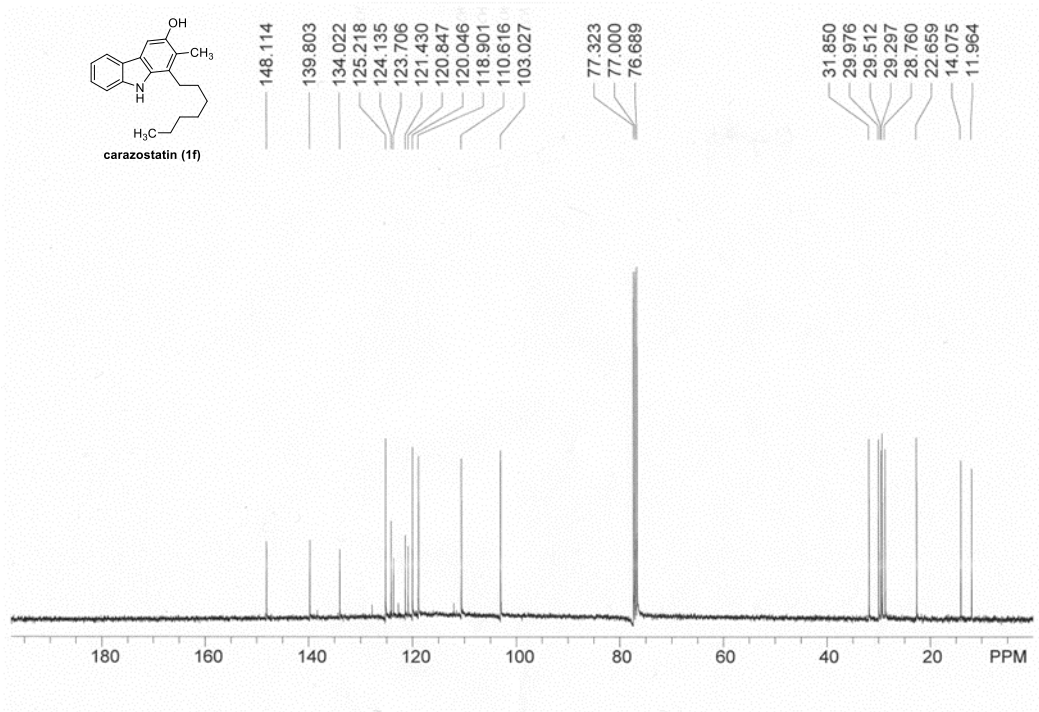


Figure S26 ^{13}C NMR (100 MHz, $CDCl_3$) of synthetic **carazostatin** (**1f**).

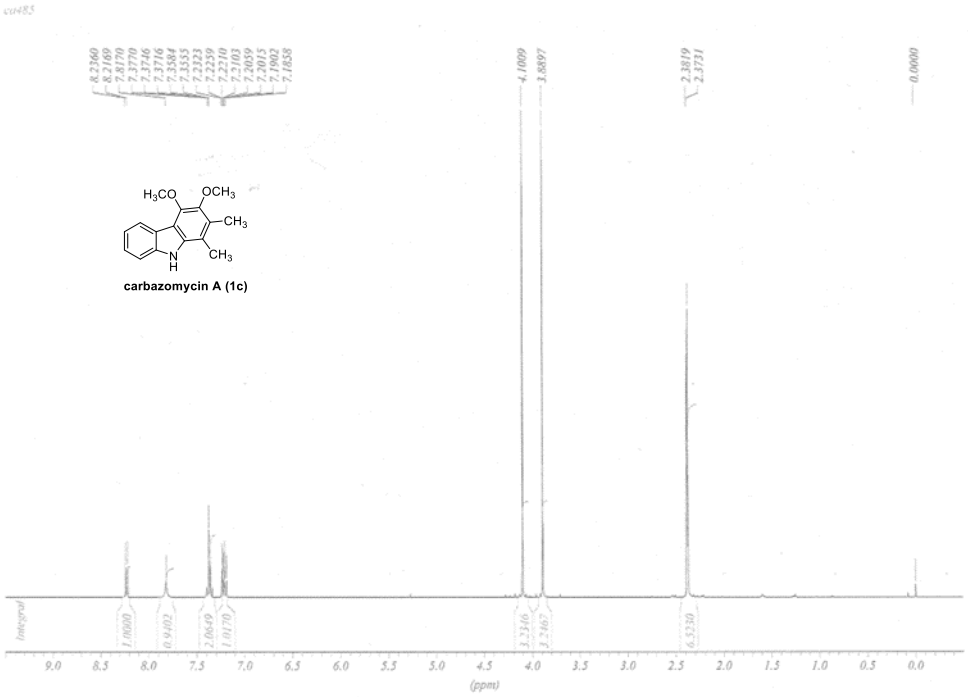


Figure S27 ^{1}H NMR (400 MHz, $CDCl_3$) of **carbazomycin A** (**1c**).

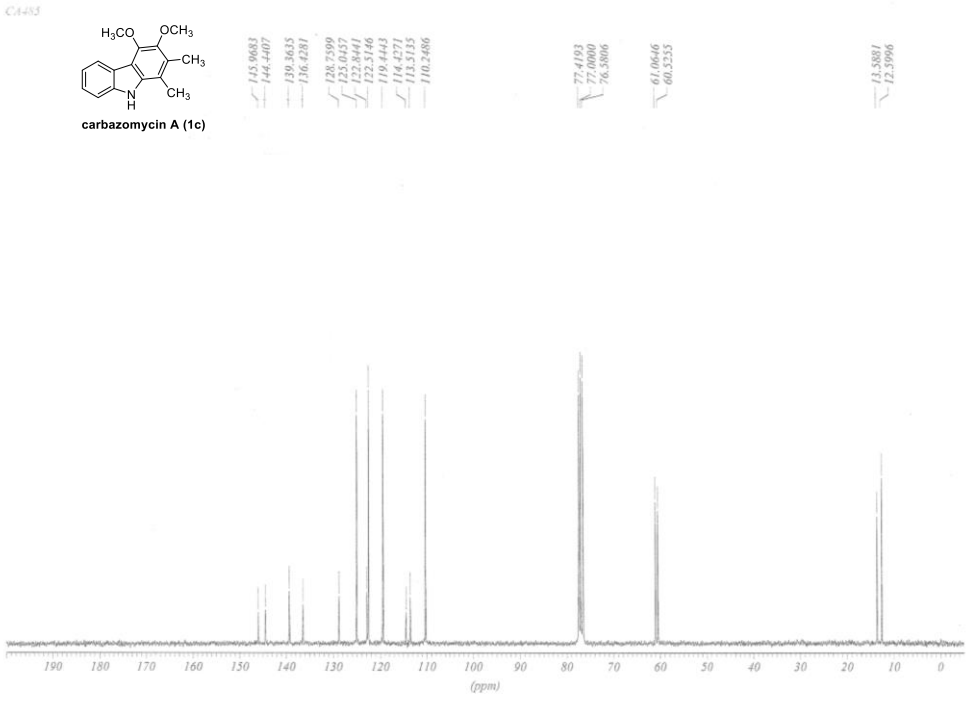


Figure S28 ^{13}C NMR (100 MHz, $CDCl_3$) of **carbazomycin A** (**1c**).

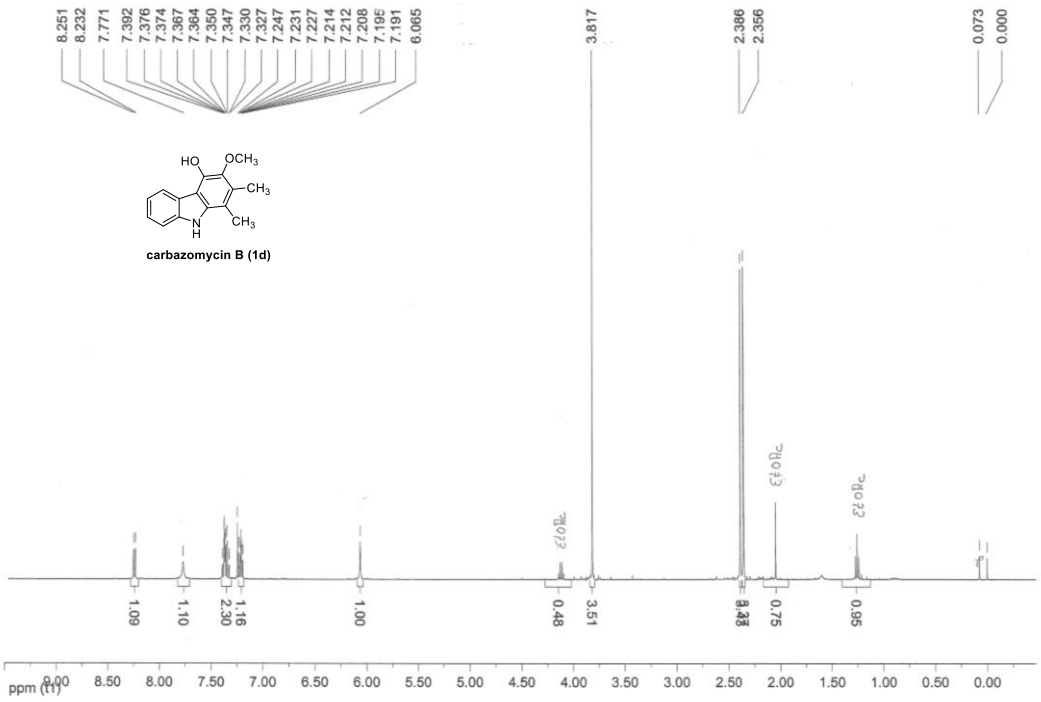


Figure S29 ^{1}H NMR (400 MHz, $CDCl_3$) of **carbazomycin B** (**1d**).

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