Supplementary Material for ***B820291E***

First Total Synthesis of Antiostatin A_1 a potent carbazole-based naturally occurring antioxidant

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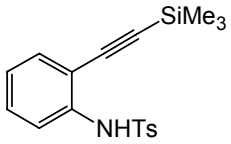
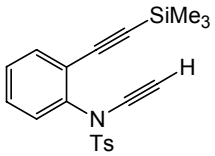
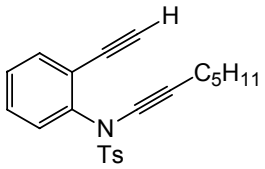


7: In a Schlenk tube under argon were introduced 2-iodoaniline (**2**) (1.9 g, 8.68 mmol), trimethylsilylacetylene (**4**) (1.6 mL, 11.3 mmol, 1.3 equiv.), $PdCl_2(PPh_3)_2$ (305 mg, 0.43 mmol, 5 mol%), CuI (165 mg, 0.87 mmol, 10 mol%), dry Et_3N (20 mL) and dry DMF (10 mL). The reaction mixture was stirred at rt overnight then worked up by concentration of solvent, addition of CH_2Cl_2 and water, extraction with CH_2Cl_2, drying ($MgSO_4$) and filtration through celite. The residue (yellow oil, 1.62 g, 99%) obtained after column chromatography (silica gel, petroleum ether/diethyl ether 9:1) was dissolved in THF (34 mL). Then pyridine (17 mL) and tosylchloride (2 g, 10.49 mmol, 1.2 equiv.) were added. The reaction mixture was stirred at rt until completion of the reaction then worked up by addition of CH_2Cl_2 and water, extraction with CH_2Cl_2, washing with brine, and drying ($MgSO_4$). Purification by column chromatography (silica gel, petroleum ether/diethyl ether 85:15) afforded pure **7** (2.75 g, 92%): white crystals; mp 81 °C (pentane/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.3 Hz, 2 H), 7.60 (d, J = 8.3 Hz, 1 H), 7.30-7.24 (m, 2 H), 7.20 (br s, 1 H), 7.19 (d, J = 8.3 Hz, 2 H), 7.00 (td, J = 7.6, 1.1 Hz, 1 H), 2.36 (s, 3 H), 0.27 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1 (C), 138.2 (C), 136.2 (C), 132.1 (CH), 130.0 (CH), 129.7 (CH), 127.4 (CH), 124.4 (CH), 119.8 (CH), 114.3 (C), 102.4 (C), 99.6 (C), 21.7 (CH_3), 0.0 (CH_3); IR (KBr, cm^{-1}) 3258, 2959, 2158, 1488, 1450, 1400, 1339, 1246, 1170, 1095, 909, 849, 753, 672, 579, 536; MS (EI, 70 eV) 343 (M^+, 100), 328 (44), 264 (24), 249 (12), 213 (4), 189 (16), 158 (35), 127 (20), 115 (7), 91 (23), 57 (17). Anal. Calcd for $C_{18}H_{21}NO_2SSi$: C, 62.94; H, 6.16; N, 4.08. Found: C, 62.70; H, 6.06; N, 3.95.

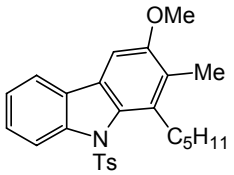


8: To a solution of **7** (715 mg, 2.08 mmol) in 100 mL of dry toluene at 0 °C was added dropwise under nitrogen a 0.5 M solution of KHMDS in toluene (5 mL, 2.5 mmol, 1.2 equiv.). After 30 min of stirring at 0 °C, a solution of alkynyliodonium salt **3** (1.18 g, 3.12 mmol, 1.5 equiv.) in dry CH_2Cl_2 (70 mL) was added dropwise. The reaction mixture was

stirred at rt overnight then worked up by concentration of solvent, addition of CH_2Cl_2 and water, extraction with CH_2Cl_2 and drying ($MgSO_4$). Purification by column chromatography (silica gel, petroleum ether/diethyl ether 9:1) afforded pure **8** (648 mg, 85%) as a pale yellow solid: mp 92–93 °C (pentane/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2 H), 7.49 (m, 1 H), 7.33-7.26 (m, 5 H), 2.82 (s, 1 H), 2.45 (s, 3 H), 0.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8 (C), 138.7 (C), 134.7 (C), 133.9 (CH), 129.6 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.5 (CH), 123.0 (C), 101.5 (C), 99.8 (C), 75.6 (C), 58.9 (CH), 21.7 (CH_3), - 0.3 (CH_3); IR (KBr, cm^{-1}) 3269, 2961, 2894, 2163, 2125, 1596, 1480, 1366, 1252, 1212, 1174, 1120, 1077, 1037, 929, 868, 762, 704; MS (EI, 70 eV) 367 (M^+, 16), 352 (12), 302 (33), 288 (17), 212 (100), 197 (12), 184 (16), 182 (21), 91 (14). Anal. Calcd for $C_{20}H_{21}NO_2SSi$: C, 65.36; H, 5.76; N, 3.81. Found: C, 65.21; H, 5.76; N, 3.86.

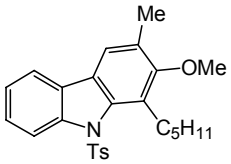


9a: To a solution of **8** (148 mg, 0.40 mmol) in 5 mL of dry THF at –78 °C was added dropwise a 0.5 M solution of LiHMDS in THF (1.2 mL, 0.6 mmol, 1.5 equiv.). The reaction mixture was gradually taken to –40 °C and kept at this temperature 1 h. Then a solution of 1-iodopentane (210 μL, 1.6 mmol, 4 equiv.) in dry THF (2 mL) was added dropwise at –40 °C. The temperature was slowly raised to –5 °C then the cold bath was replaced by an ice bath and the reaction mixture was allowed to warm up to rt overnight. The reaction mixture was worked up by addition of diethyl ether and brine, separation of the layers and extraction of the aqueous layer with diethyl ether then drying ($MgSO_4$) of the combined organic layers. The residue (117 mg) obtained after column chromatography (silica gel, petroleum ether/diethyl ether 9:1) was dissolved in wet THF (7 mL), purged by bubbling argon through it for 15 min then cooled down to 0 °C. A 1 M solution of TBAF (0.35 mL, 0.35 mmol) was added dropwise. After 15 min, the reaction mixture was worked up by addition of diethyl ether and brine, separation of the layers and extraction of the aqueous layer with diethyl ether then drying ($MgSO_4$) of the combined organic layers. Purification by column chromatography (silica gel, petroleum ether/diethyl ether 85:15) afforded **9a** (65 mg, 44% over 2 steps) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2 H), 7.52-7.50 (m, 1 H), 7.35-7.28 (m, 4 H), 7.18-7.16 (m, 1 H), 3.03 (s, 1 H), 2.46 (s, 3 H), 2.25 (t, J = 7.0 Hz, 2 H), 1.48-1.45 (m, 2 H), 1.33-1.25 (m, 4 H), 0.87 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (C), 140.5 (C), 134.2 (C), 134.1 (CH), 129.45 (CH), 129.38 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 122.3 (C), 82.7 (CH), 79.1 (C), 73.4 (C), 70.0 (C), 30.9 (CH_2), 28.5 (CH_2), 22.2 (CH_2), 21.7 (CH_3), 18.5 (CH_2), 14.0 (CH_3); IR (NaCl, cm^{-1}) 3274, 3068, 2931, 2860, 2255, 2112, 1917, 1737, 1597, 1485, 1444, 1372, 1292, 1169, 1090, 1038, 914, 850, 813, 761, 736, 704, 674, 649, 586, 542; MS (EI, 70 eV) 365 (M^+, 5), 280 (13), 210 (100), 167 (47), 128 (89), 55 (35); HRMS (ESI): found 388.1359, $C_{22}H_{23}NO_2SNa$ (MNa^+) requires 388.1342.

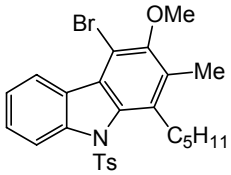


10aa: A solution of diyne **9a** (123 mg, 0.34 mmol) in dry toluene (28 mL) was purged by bubbling argon through it for 25 min. Then 1-methoxypropyne (120 mg, 1.72 mmol), and [$RhCl(PPh_3)_3$] (31 mg, 10 mol%) were added under argon. The reaction mixture was stirred at rt for 2 days then worked up by concentration of solvent and filtration through a thin pad of

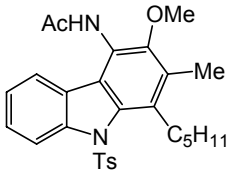
alumina to eliminate the catalyst. Column chromatography (silica gel, petroleum ether/diethyl ether 85:15) afforded **10aa**/**10ab** (121 mg, 82%, isomer ratio: 22:1).
Isomerically pure **10aa** was obtained either by column chromatography on silica gel (petroleum ether/diethyl ether 9:1) or by crystallization (pentane/$CHCl_3$) as a white solid: mp 125-126 °C (pentane/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.1 Hz, 1 H), 7.45 (d, J = 7.5 Hz, 1 H), 7.31 (dd, J = 8.1, 7.4 Hz, 1 H), 7.18 (dd, J = 7.5, 7.4 Hz, 1 H), 6.91 (s, 1 H), 6.86 (d, J = 8.5 Hz, 2 H), 6.78 (d, J = 8.5 Hz, 2 H), 3.89 (s, 3 H), 3.43-3.39 (m, 2 H), 2.35 (s, 3 H), 2.17 (s, 3 H), 1.55-1.48 (m, 2 H), 1.33-1.30 (m, 4 H), 0.86 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (C), 143.7 (C), 142.5 (C), 136.8 (C), 134.8 (C), 131.3 (C) (2 peaks), 129.6 (C), 128.2 (CH), 127.3 (CH), 126.3 (CH), 126.2 (C), 125.5 (CH), 120.4 (CH), 119.0 (CH), 98.1 (CH), 55.7 (CH_3), 32.0 (CH_2), 30.8 (CH_2), 29.3 (CH_2), 22.6 (CH_2), 21.4 (CH_3), 14.1 (CH_3), 12.9 (CH_3); IR (KBr, cm^{-1}) 3062, 2996, 2961, 2924, 2853, 1595, 1485, 1468, 1446, 1416, 1364, 1346, 1226, 1169, 1090, 771, 660, 576; MS (EI, 70 eV) 435 (M^+, 9), 350 (37), 311 (39), 280 (72), 233 (33), 224 (73), 210 (63), 209 (61), 179 (38), 156 (60), 149 (79), 128 (38), 91 (49), 57 (71), 28 (100). Anal. Calcd for $C_{26}H_{29}NO_3S$: C, 71.69; H, 6.71; N, 3.22. Found: C, 71.49; H, 6.58; N, 3.06.



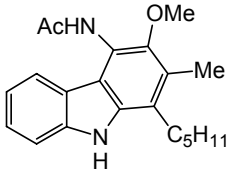
10ab: Only the NMR signals which were clearly identified are given. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.9 Hz, 1 H), 6.95 (d, J = 8.3 Hz, 2 H), 3.85 (s, 3 H), 3.37-3.33 (m, 2 H), 2.37 (s, 3 H), 2.19 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 (C), 143.9 (C), 142.2 (C), 139.7 (C), 131.9 (C), 130.2 (C), 130.0 (C), 129.7 (C), 128.4 (CH), 127.0 (CH), 126.1 (CH), 125.5 (CH), 120.0 (CH), 119.0 (CH), 60.9 (CH_3), 32.3 (CH_2), 28.8 (CH_2), 28.2 (CH_2), 22.5 (CH_2), 21.4 (CH_3), 16.8 (CH_3), 14.1 (CH_3).



11: To a solution of **10aa** (207 mg, 0.48 mmol) in dry acetonitrile (17 mL) was added NBS (93 mg, 0.52 mmol, 1.1 equiv.) and the reaction mixture was stirred at rt in the dark overnight. After concentration of solvent the residue was purified by column chromatography (silica gel, pentane/diethyl ether 8:2) to afford **11** (234 mg, 95%): white crystals; mp 121-122 °C ($CHCl_3$/pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 7.6 Hz, 1 H), 8.08 (d, J = 8.0 Hz, 1 H), 7.38 (m, 1 H), 7.26 (m, 1 H), 6.78 (m, 4 H), 3.84 (s, 3 H), 3.42-3.37 (m, 2 H), 2.48 (s, 3 H), 2.19 (s, 3 H), 1.49-1.44 (m, 2 H), 1.36-1.26 (m, 4 H), 0.86 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5 (C), 144.3 (C), 142.7 (C), 138.4 (C), 136.4 (C), 131.3 (C), 131.0 (C), 130.7 (C), 129.2 (C), 128.2 (CH), 127.2 (CH), 127.1 (CH), 125.5 (CH), 122.2 (CH), 120.2 (CH), 107.9 (CH), 60.5 (CH_3), 31.9 (CH_2), 31.1 (CH_2), 29.3 (CH_2), 22.5 (CH_2), 21.4 (CH_3), 14.0 (CH_3), 13.9 (CH_3); IR (KBr, cm^{-1}) 2952, 2925, 2856, 1595, 1463, 1371, 1341, 1306, 1214, 1174, 1115, 1087, 1006, 893, 876, 760, 665, 575, 536; MS (EI, 70 eV) 515/513 (M^+, 18), 360 (31), 358 (32), 304 (76), 302 (77), 279 (56), 224 (8), 167 (38), 149 (100), 113 (12), 84 (37), 57 (40). Anal. Calcd for $C_{26}H_{28}BrNO_3S$: C, 60.70; H, 5.49; N, 2.72. Found: C, 60.49; H, 5.39; N, 2.56.

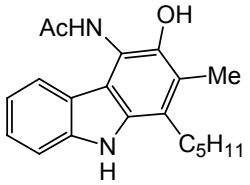


12: In a dried Schlenk tube under argon were introduced [$Pd_2(dba)_3$] (5.7 mg, 3.5 mol%), Xantphos (11 mg, 10.5 mol%), carbazole **11** (92.5 mg, 0.18 mmol, 1 equiv.), acetamide (**6**) (13 mg, 0.22 mmol, 1.2 equiv.), Cs_2CO_3 (82 mg, 0.25 mmol, 1.4 equiv.). The Schlenk tube was evacuated and backfilled with argon twice then dry dioxane (2 mL) was added through a septum. Then the septum was replaced by a screw cap and the reaction mixture was heated at 100 °C for 69 h. After cooling to rt, the reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of alumina which was washed with ethyl acetate at the end. The crude material was purified by column chromatography (silica gel, pentane/ethyl acetate 1:1 then ethyl acetate) to afford **12** (76 mg, 85%) as a white solid: mp 70-72 °C. Traces of detosylated product **13** (1.5 mg, < 3%) and unreacted bromide **11** (~ 10 mg) were also isolated. Compound **12** is a mixture of 2 rotamers (coalescence of almost all signals in toluene-d_8 at 378 K). Rotamer ratio M / m = 1:0.3 in $CDCl_3$ at 298 K, 1.1:1 in toluene-d_8 at 298 K, 1:0.4 in toluene-d_8 at 233 K; ^{1}H NMR (600 MHz, toluene-d_8, 233 K) δ 10.35 (br s, 1 H, M), 8.32 (d, J = 7.8 Hz, 1 H, M), 8.24 (d, J = 7.8 Hz, 1 H, m), 7.78 (d, J = 7.8 Hz, 1 H, M), 7.68 (br s, 1 H, m), 7.39 (d, J = 7.8 Hz, 1 H, m), 7.06 (d, J = 7.8 Hz, 2 H, m), 7.00-6.96 (m, 1 H, M+m), 6.89 (t, J = 7.2 Hz, 1 H, m), 6.80 (d, J = 8.4 Hz, 2 H, M), 6.77 (dd, J = 7.8, 7.2 Hz, 1 H, M), 6.40 (d, J = 7.8 Hz, 2 H, m), 5.91 (d, J = 7.8 Hz, 2 H, M), 4.03 (m, 2 H, M+m), 3.68 (s, 3 H, M), 3.42 (s, 3 H, m), 2.33 (s, 3 H, M), 2.26 (s, 3 H, m), 1.81 (s, 3 H, m), 1.53 (s, 3 H, m), 1.49 (m, 2 H, M+m), 1.34 (s, 3 H, M), 1.27 (m, 4 H, M+m), 1.17 (s, 3 H, M), 0.86 (t, J = 6.6 Hz, 3 H, M+m); ^{13}C NMR (150 MHz, toluene-d_8, 233 K) δ 174.7 (C, M), 168.3 (C, m), 153.7 (C, M), 152.1 (C, m), 143.9 (C, m), 143.7 (C, M), 143.0 (C, M), 142.9 (C, m), 138.2 (C, m), 137.6 (C, M), 137.1 (C, M), 137.0 (C, m), 135.2 (C, m), 131.8 (C, m), 131.2 (C, M), 130.6 (C, M), 130.3 (C, M), 130.1 (C, m), 128.8 (CH, m), 128.3 (C, M), 128.1 (CH, M), 127.5 (CH, M), 127.1 (CH, m), 127.0 (CH, m), 126.5 (2 peaks) (CH, M) and (C, m), 125.4 (CH, m), 125.2 (CH, M), 123.4 (C, M), 122.4 (CH, m), 121.2 (CH, M), 121.0 (CH, M), 119.5 (CH, m), 60.6 (CH_3, M), 60.1 (CH_3, m), 32.4 (CH_2, M+m), 31.6 (CH_2, m), 31.5 (CH_2, M), 29.7 (CH_2, M+m), 23.04 (CH_2, m), 23.02 (CH_2, M), 22.5 (CH_3, m), 20.8 (CH_3, m), 20.6 (CH_3, M), 20.3 (CH_3, M), 14.4 (CH_3, m), 14.3 (CH_3, M), 13.2 (CH_3, M), 13.0 (CH_3, m); the ^{13}C NMR signal of 1 quaternary carbon of the minor rotamer m could not be identified; IR (KBr, cm^{-1}) 2955, 2928, 2856, 1668, 1597, 1492, 1449, 1369, 1174, 1089, 1056, 1006, 754, 666, 576, 538; MS (EI, 70 eV) 492 (M^+, 57), 337 (96), 281 (100), 239 (70), 198 (9), 155 (4), 113 (34), 57 (19); HRMS (ESI): found 515.1957, $C_{28}H_{32}N_2O_4SNa$ (MNa^+) requires 515.1975.



13: To a solution of carbazole **12** (45 mg, 0.09 mmol) in 4 mL of dry THF was added dropwise at rt a 1 M solution of TBAF in THF (0.46 mL, 0.46 mmol, 5 equiv.). The reaction mixture was refluxed 30 h then worked up by concentration of solvent, addition of water and extraction with CH_2Cl_2 followed by washing with brine and drying ($MgSO_4$). Purification by column chromatography (silica gel, pentane/ethyl acetate 1:1 then ethyl acetate) afforded **13** (24 mg, 77%) as a white solid: mp 225-226 °C ($CHCl_3$/pentane); the ^{1}H NMR spectrum in $CDCl_3$ at 298 K shows a mixture of 2 rotamers A/B (ratio = 1.2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.5 Hz, 1 H_A), 7.77 (d, J = 7.8 Hz, 1 H_B), 7.50-7.32 (m, 4 H_A + 4 H_B), 7.19-7.14 (m, 1 H_A + 1 H_B), 3.78 (s, 3 H_A + 3 H_B), 2.87 (t, J = 7.8 Hz, 2 H_A), 2.76 (t, J = 7.8

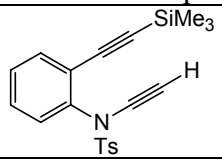
Hz, 2 H_B), 2.41 (s, 6 H_A), 2.36 (s, 3 H_B), 1.94 (s, 3 H_B), 1.63 (m, 2 H_A + 2 H_B), 1.42 (m, 4 H_A + 4 H_B), 0.92 (t, J = 6.9 Hz, 3 H_A + 3 H_B); ^{13}C NMR (75 MHz, acetone-d_6) δ 169.8 (C), 148.8 (C), 141.4 (C), 137.1 (C), 127.5 (C), 125.6 (CH), 123.9 (C), 123.6 (C), 123.3 (CH), 119.5 (C), 119.1 (CH), 111.3 (CH), 61.1 (CH_3), 32.8 (CH_2), 30.0 (CH_2), 29.2 (CH_2), 23.3 (CH_2 + CH_3), 14.3 (CH_3), 12.5 (CH_3); the ^{13}C NMR signal of 1 quaternary carbon is hidden; IR (KBr, cm^{-1}) 3294, 3047, 2931, 2857, 1655, 1507, 1456, 1400, 1294, 1143, 1108, 1060, 1011, 739; MS (EI, 70 eV) 338 (M^+, 82), 323 (6), 281 (100), 251 (3), 239 (23), 224 (16), 195 (12), 168 (2), 127 (49), 113 (6), 98 (7), 57 (28); HRMS: found 338.19850, $C_{21}H_{26}N_2O_2$ (M^+) requires 338.19943. Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.27; H, 7.68; N, 8.12.

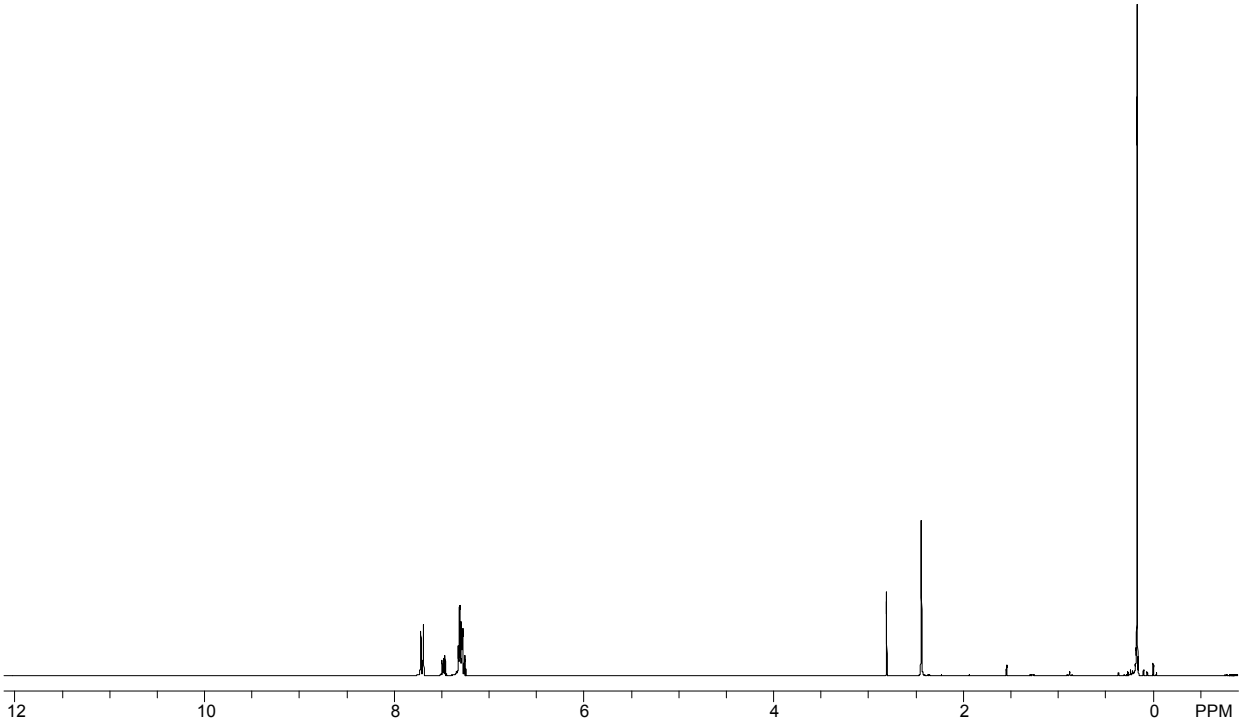


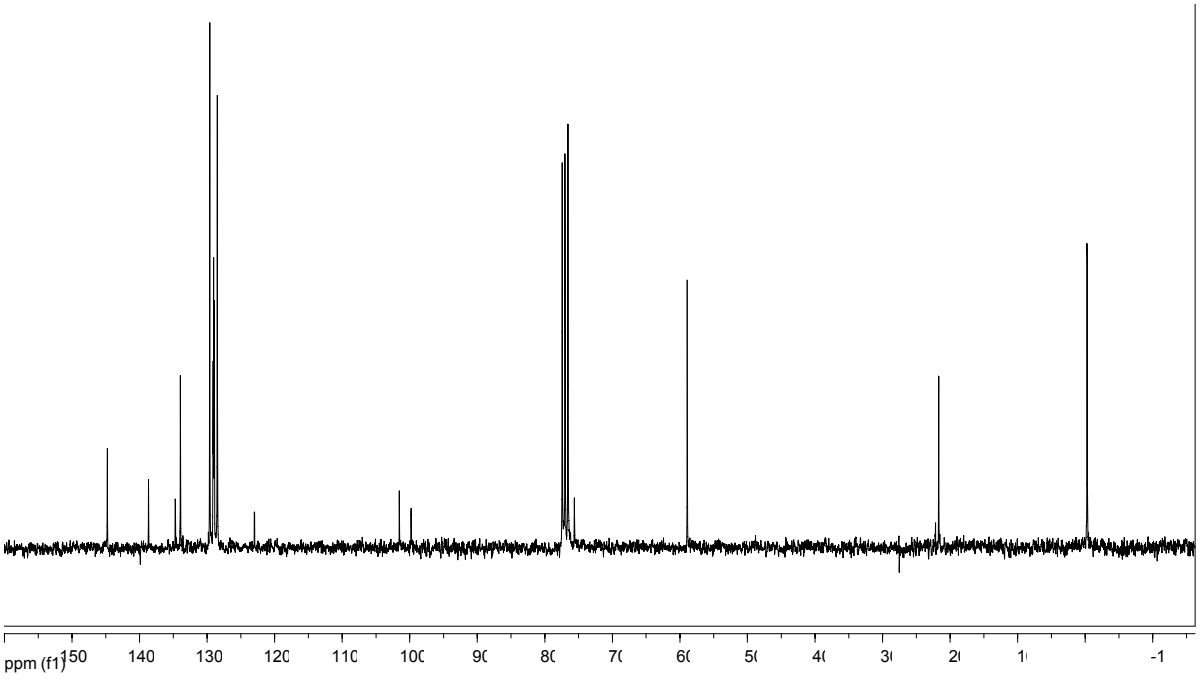
Antiostatin A_1 (1): to a solution of **13** (30 mg, 0.09 mmol) in 2 mL of dry CH_2Cl_2 was added dropwise at –78 °C a 1 M solution of BBr_3 in CH_2Cl_2 (200 μL, 0.2 mmol, 2.2 equiv.). The reaction mixture was slowly warmed up to rt then worked up by addition of water and extraction with ethyl acetate followed by washing with brine and drying ($MgSO_4$). Purification by column chromatography (short column of silica gel, pentane/ethyl acetate 1:1) afforded antiostatine A_1 (1) as a beige solid (28 mg, 94%): mp 217-218 °C (dec) (ethyl acetate/pentane) (lit. mp 180-183 °C (dec)); ^{1}H NMR (600 MHz, acetone-d_6) δ 10.20 (br s, 1 H), 9.71 (br s, 1 H), 8.11 (d, J = 7.8 Hz, 1 H), 8.01 (s, 1 H), 7.42 (d, J = 7.8 Hz, 1 H), 7.27 (dd, J = 7.8, 7.2 Hz, 1 H), 7.06 (dd, J = 7.8, 7.2 Hz, 1 H), 2.95 (m, 2 H), 2.44 (s, 3 H), 2.36 (s, 3 H), 1.63 (m, 2 H), 1.43 (m, 2 H), 1.35 (m, 2 H), 0.87 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (150 MHz, acetone-d_6) δ 171.0 (C), 143.1 (C), 140.1 (C), 133.8 (C), 124.52 (C), 124.46 (CH), 122.6 (C), 122.0 (C), 121.6 (CH), 118.0 (CH), 117.0 (C), 114.3 (C), 110.6 (CH), 31.9 (CH_2), 29.2 (CH_2), 28.2 (CH_2), 22.5 (CH_3), 22.3 (CH_2), 13.5 (CH_3), 11.8 (CH_3); IR (KBr, cm^{-1}) 3342, 2958, 2928, 2857, 1620, 1584, 1535, 1510, 1423, 1283, 1149, 1109, 1053, 892, 730, 646; MS (EI, 70 eV) 324 (M^+, 100), 281 (96), 250 (7), 225 (82), 224 (15), 195 (17), 155 (6), 127 (38), 113 (16), 99 (15), 57 (30). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.69; H, 7.34; N, 8.49.

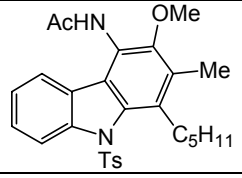
^{1}H and ^{13}C NMR data are in agreement with the literature (C.-J. Mo, K. Shin-Ya, K. Furihata, K. Furihata, A. Shimazu, Y. Hayakawa, H. Seto *J. Antibiotics* 1990, *43*, 1337) but the assignment of the ^{13}C NMR signals of the aromatic methyl group and of the methyl group of the pentyl chain are inverted.

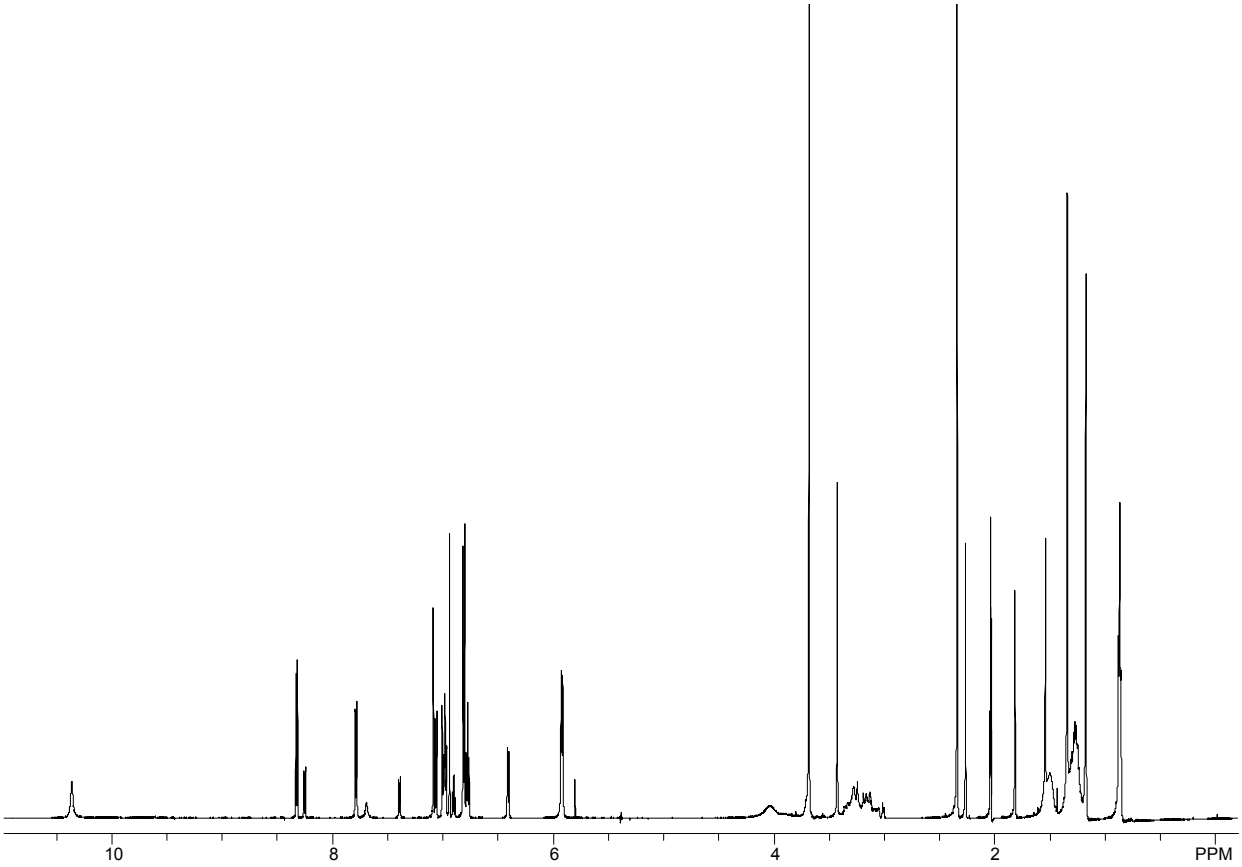
Selected ^{1}H, and ^{13}C NMR spectra:

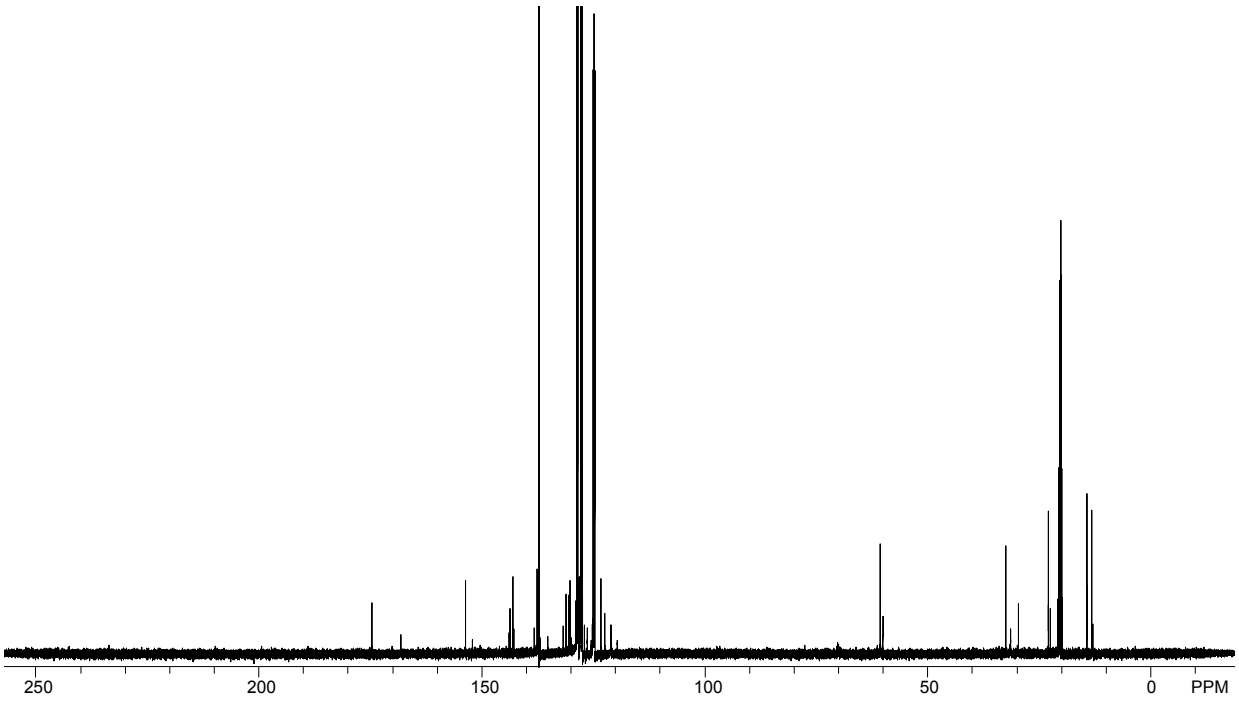
	**11** ^{1}H NMR (400 MHz, $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$)



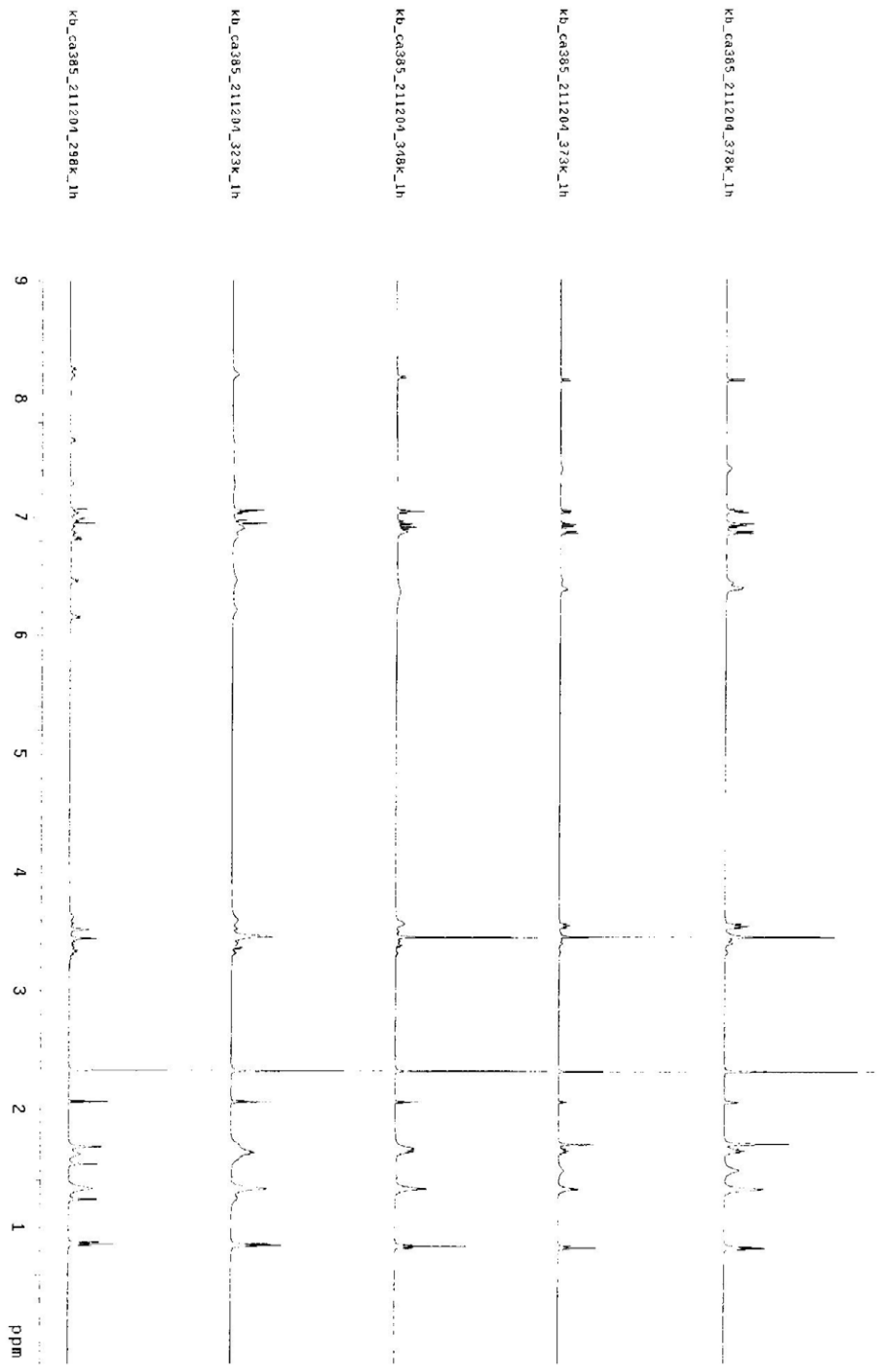


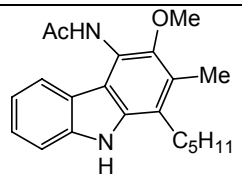
	**12**: ^{1}H NMR (600 MHz, toluene-d_8, 233 K) ^{13}C NMR (150 MHz, toluene-d_8, 233 K)

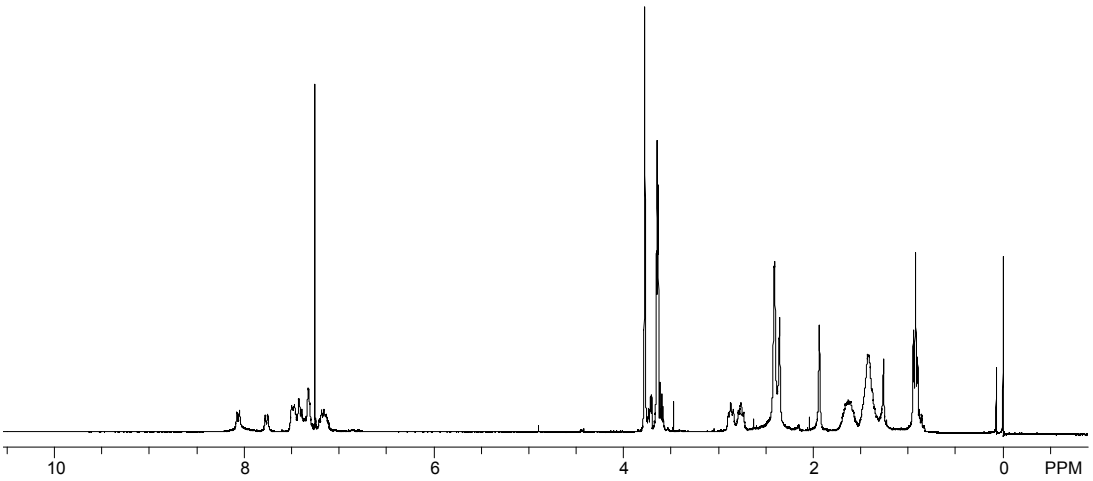


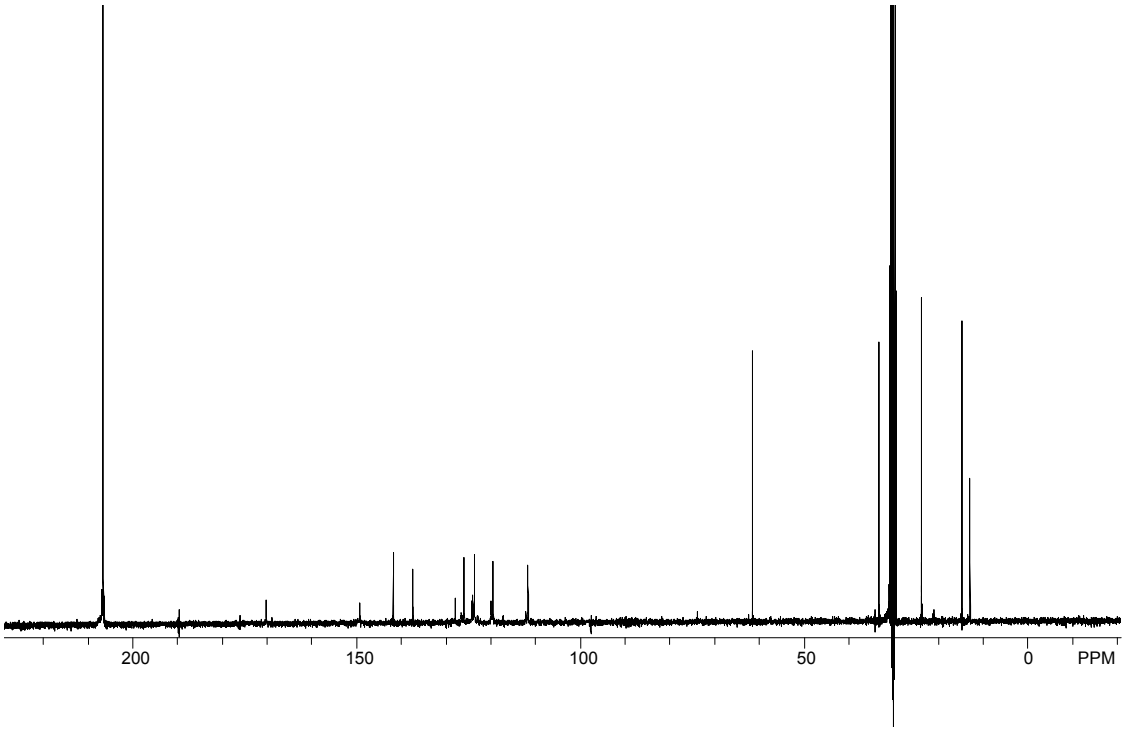


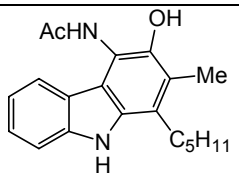
Temperature depending ^{1}H NMR studies with **12** (500 MHz, toluene-d_8)

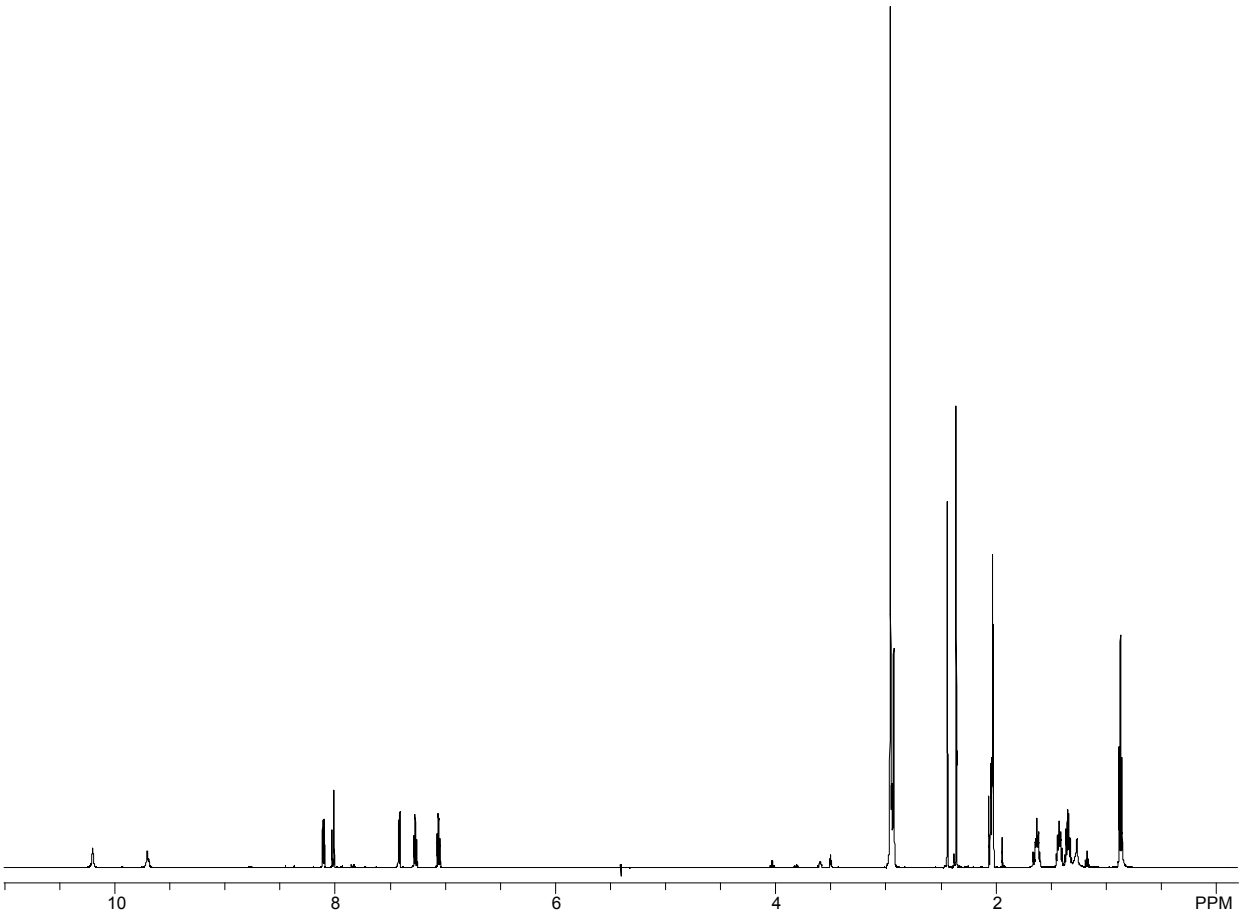


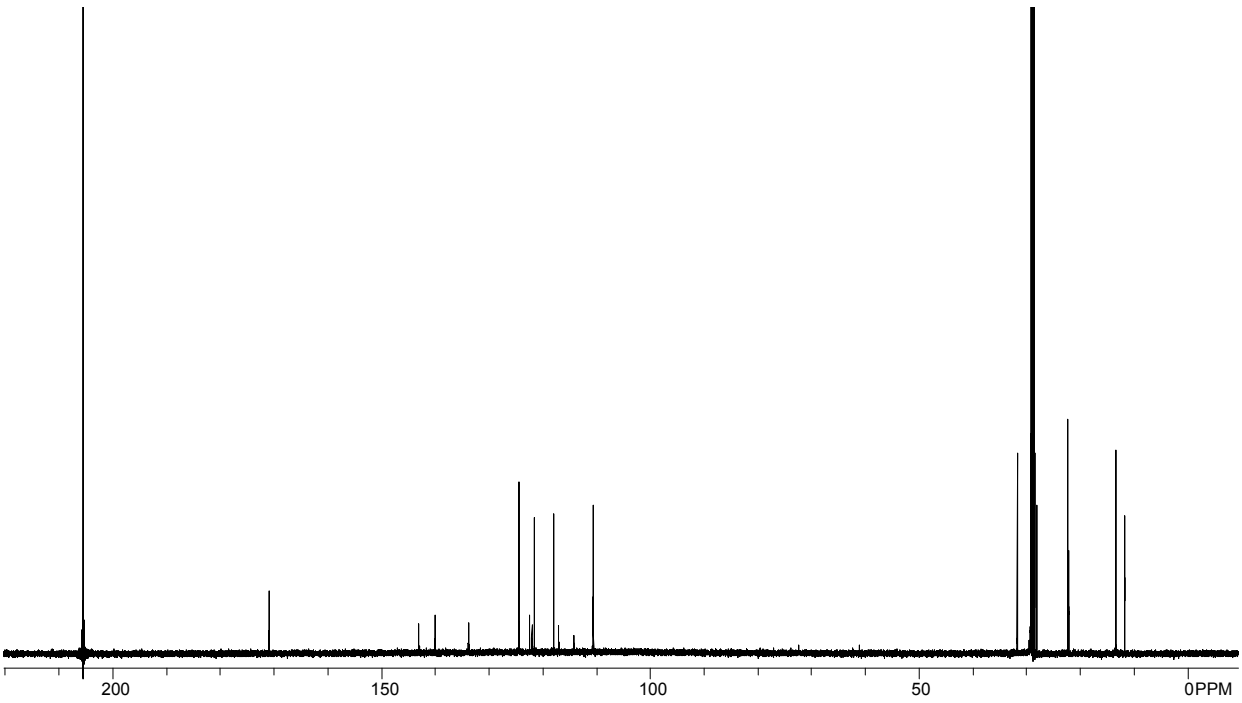
	**13**: ^{1}H NMR (300 MHz, $CDCl_3$) ^{13}C NMR (75 MHz, acetone-d_6)





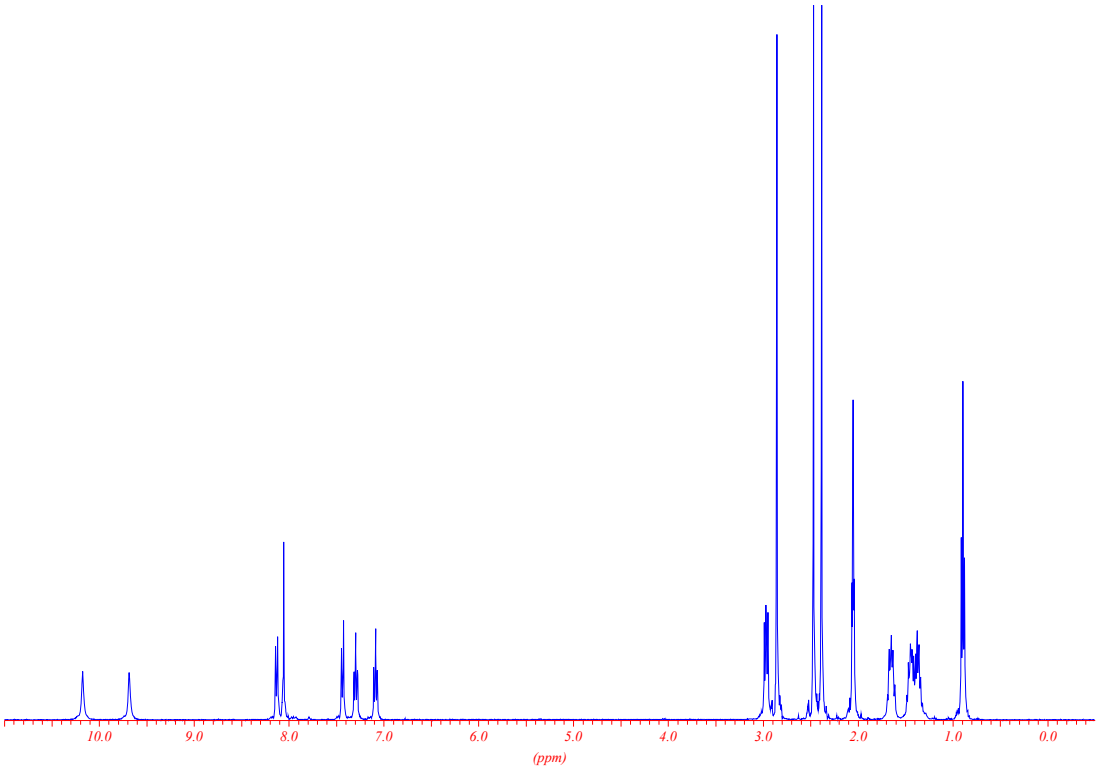
	Antiostatin A_1 (**1**) ^{1}H NMR (600 MHz, acetone-d_6) ^{13}C NMR (150 MHz, acetone-d_6):



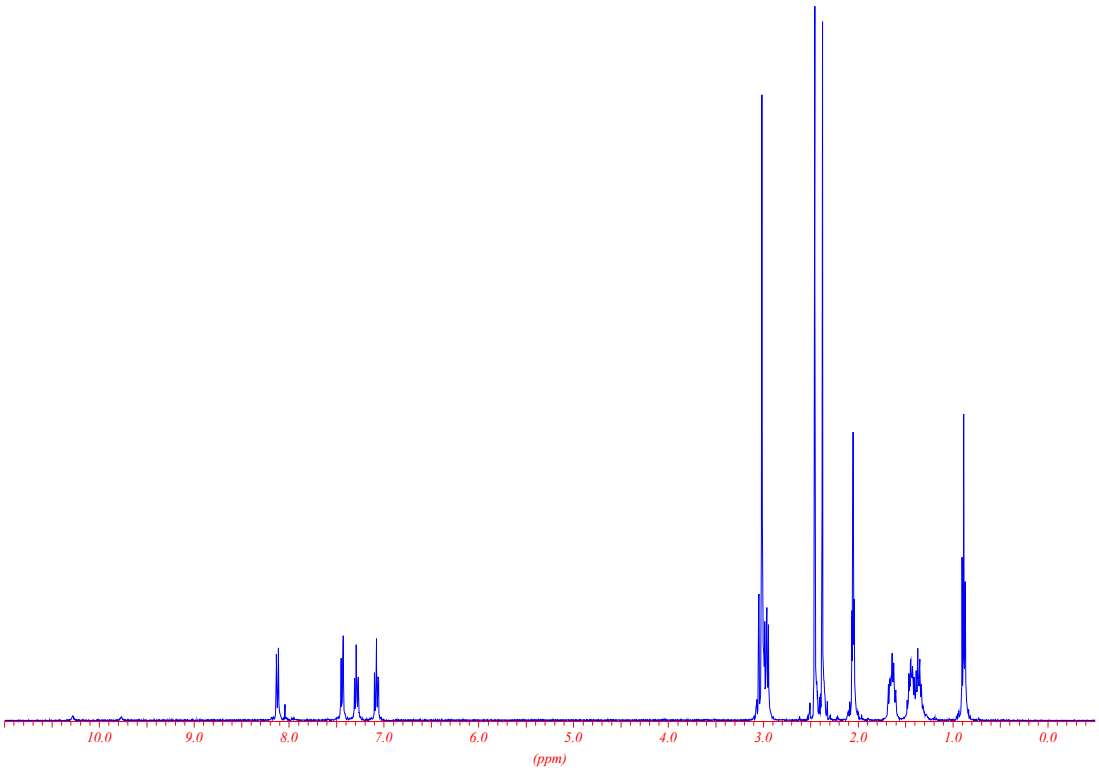


H/D-exchange experiment:

^{1}H NMR Antiostatin A_1, acetone-d_6, 400 MHz



^{1}H NMR Antiostatin A_1, acetone-d_6 + 1 drop D_2O, 400 MHz



X-ray crystallographic structure of synthetic antiostatin A_1 (**1**)

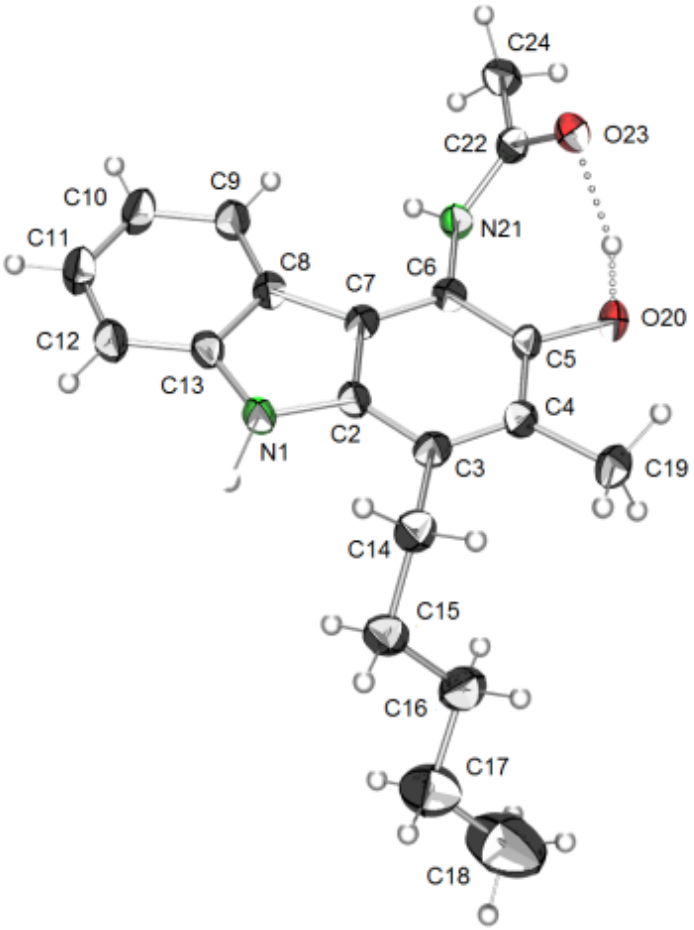


Table 1. Bond lengths [A] and angles [deg] for **1**.

N(1)-C(2)	1.383(3)
N(1)-C(13)	1.387(3)
C(2)-C(3)	1.402(3)
C(2)-C(7)	1.406(3)
C(3)-C(4)	1.396(3)
C(3)-C(14)	1.513(3)
C(4)-C(5)	1.414(3)
C(4)-C(19)	1.519(3)
C(5)-O(20)	1.384(3)
C(5)-C(6)	1.390(3)
C(6)-C(7)	1.397(3)
C(6)-N(21)	1.427(3)
C(7)-C(8)	1.447(3)
C(8)-C(13)	1.409(3)
C(8)-C(9)	1.410(3)
C(9)-C(10)	1.390(3)
C(10)-C(11)	1.393(4)
C(11)-C(12)	1.376(3)
C(12)-C(13)	1.392(3)
C(14)-C(15)	1.529(3)
C(15)-C(16)	1.498(4)
C(16)-C(17)	1.521(4)

C(17)-C(18)	1.512(3)
N(21)-C(22)	1.348(3)
C(22)-O(23)	1.245(3)
C(22)-C(24)	1.499(3)

C(2)-N(1)-C(13)	108.99(19)
N(1)-C(2)-C(3)	127.4(2)
N(1)-C(2)-C(7)	108.9(2)
C(3)-C(2)-C(7)	123.6(2)
C(4)-C(3)-C(2)	116.8(2)
C(4)-C(3)-C(14)	124.9(2)
C(2)-C(3)-C(14)	118.3(2)
C(3)-C(4)-C(5)	120.2(2)
C(3)-C(4)-C(19)	122.2(2)
C(5)-C(4)-C(19)	117.6(2)
O(20)-C(5)-C(6)	120.9(2)
O(20)-C(5)-C(4)	117.0(2)
C(6)-C(5)-C(4)	122.0(2)
C(5)-C(6)-C(7)	118.7(2)
C(5)-C(6)-N(21)	122.2(2)
C(7)-C(6)-N(21)	119.1(2)
C(6)-C(7)-C(2)	118.6(2)
C(6)-C(7)-C(8)	134.7(2)
C(2)-C(7)-C(8)	106.7(2)
C(13)-C(8)-C(9)	118.2(2)
C(13)-C(8)-C(7)	106.6(2)
C(9)-C(8)-C(7)	135.1(2)
C(10)-C(9)-C(8)	118.9(2)
C(9)-C(10)-C(11)	120.9(2)
C(12)-C(11)-C(10)	121.7(2)
C(11)-C(12)-C(13)	117.5(2)
N(1)-C(13)-C(12)	128.5(2)
N(1)-C(13)-C(8)	108.7(2)
C(12)-C(13)-C(8)	122.8(2)
C(3)-C(14)-C(15)	115.0(2)
C(16)-C(15)-C(14)	115.4(2)
C(15)-C(16)-C(17)	112.2(2)
C(18)-C(17)-C(16)	113.1(3)
C(22)-N(21)-C(6)	126.0(2)
O(23)-C(22)-N(21)	121.8(2)
O(23)-C(22)-C(24)	121.2(2)
N(21)-C(22)-C(24)	116.9(2)

Table 2. Torsion angles [deg] for **1**.

C(13)-N(1)-C(2)-C(3)	178.3(2)
C(13)-N(1)-C(2)-C(7)	0.5(3)
N(1)-C(2)-C(3)-C(4)	-180.0(2)
C(7)-C(2)-C(3)-C(4)	-2.5(3)
N(1)-C(2)-C(3)-C(14)	-2.0(3)
C(7)-C(2)-C(3)-C(14)	175.5(2)
C(2)-C(3)-C(4)-C(5)	1.0(3)
C(14)-C(3)-C(4)-C(5)	-176.9(2)
C(2)-C(3)-C(4)-C(19)	179.5(2)
C(14)-C(3)-C(4)-C(19)	1.6(4)
C(3)-C(4)-C(5)-O(20)	-177.7(2)
C(19)-C(4)-C(5)-O(20)	3.7(3)
C(3)-C(4)-C(5)-C(6)	0.8(3)
C(19)-C(4)-C(5)-C(6)	-177.8(2)
O(20)-C(5)-C(6)-C(7)	177.3(2)
C(4)-C(5)-C(6)-C(7)	-1.1(3)
O(20)-C(5)-C(6)-N(21)	-1.3(3)
C(4)-C(5)-C(6)-N(21)	-179.7(2)
C(5)-C(6)-C(7)-C(2)	-0.3(3)
N(21)-C(6)-C(7)-C(2)	178.3(2)
C(5)-C(6)-C(7)-C(8)	179.5(2)
N(21)-C(6)-C(7)-C(8)	-1.9(4)
N(1)-C(2)-C(7)-C(6)	-179.9(2)
C(3)-C(2)-C(7)-C(6)	2.2(3)
N(1)-C(2)-C(7)-C(8)	0.2(3)
C(3)-C(2)-C(7)-C(8)	-177.7(2)
C(6)-C(7)-C(8)-C(13)	179.3(3)
C(2)-C(7)-C(8)-C(13)	-0.9(3)
C(6)-C(7)-C(8)-C(9)	-0.1(5)
C(2)-C(7)-C(8)-C(9)	179.7(3)
C(13)-C(8)-C(9)-C(10)	-0.6(4)
C(7)-C(8)-C(9)-C(10)	178.7(3)
C(8)-C(9)-C(10)-C(11)	-0.3(4)
C(9)-C(10)-C(11)-C(12)	1.1(4)
C(10)-C(11)-C(12)-C(13)	-0.8(4)
C(2)-N(1)-C(13)-C(12)	178.7(2)
C(2)-N(1)-C(13)-C(8)	-1.1(3)
C(11)-C(12)-C(13)-N(1)	-180.0(2)
C(11)-C(12)-C(13)-C(8)	-0.1(4)
C(9)-C(8)-C(13)-N(1)	-179.3(2)
C(7)-C(8)-C(13)-N(1)	1.2(3)
C(9)-C(8)-C(13)-C(12)	0.9(4)
C(7)-C(8)-C(13)-C(12)	-178.6(2)
C(4)-C(3)-C(14)-C(15)	-100.9(3)
C(2)-C(3)-C(14)-C(15)	81.3(3)
C(3)-C(14)-C(15)-C(16)	69.0(3)
C(14)-C(15)-C(16)-C(17)	176.5(2)
C(15)-C(16)-C(17)-C(18)	-176.5(3)
C(5)-C(6)-N(21)-C(22)	-49.2(3)

C(7)-C(6)-N(21)-C(22)	132.2(2)
C(6)-N(21)-C(22)-O(23)	5.9(4)
C(6)-N(21)-C(22)-C(24)	-175.2(2)

Table 3. Hydrogen bonds for **1** [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(20)#1	1.07	1.90	2.961(2)	168.6
O(20)-H(20)...O(23)	1.03	1.64	2.641(2)	161.0
N(21)-H(21)...O(23)#2	0.92	2.23	3.072(3)	151.9

Symmetry transformations used to generate equivalent atoms:
#1 x-1/2,-y+1/2,z+1/2 #2 x-1,y,z

Kristalldaten für **1** (C. Alayrac, D. Schollmeyer, B. Witulski)

Summenformel	$C_{20}H_{24}O_2N_2$
M_r	324.4 $gmol^{-1}$
Absorption	$\mu = 0.08$ mm^{-1}
Kristallgröße	0.05 x 0.160 x 0.25 mm^3 farblose Nadel
Raumgruppe	P $2_1/n$ (monoklin)
Gitterkonstanten	a = 4.9084(2)Å
(berechnet aus	b = 24.3209(12)Å ß = 92.651(1)°
2220 Reflexen mit	c = 14.3390(8)Å
2.1° < Θ < 23.6°)	V = 1711.7(2)$Å^3$ z = 4 F(000) = 696
Temperatur	-80°C
Dichte	$d_{rön}$ = 1.259 gcm^{-3}

Datensammlung

Diffraktometer	SMART CCD
Strahlung	Mo-K_α Graphitmonochromator
Scan – Typ	ω,φ−scans
Scan – Breite	0.5°
Meßbereich	2° ≤ θ <56°
	-6 ≤ h≤ 6 -31 ≤ k ≤ 31 -18 ≤ l ≤ 18
Reflexzahl:	
gemessen	18097
unabhängige	4085 (R_σ = 0.1027)
beobachtete	2250 (|F|/σ (F) > 4.0)

Datenkorrektur, Strukturlösung und -verfeinerung

Korrekturen	Lorentz- und Polarisationskorrektur.
Lösung	Programm: SIR-97 (Direkte Methoden)
Verfeinerung	Programm: SHELXL-97 (Vollmatrixverfahren). 220 verfeinerte Parameter, gewichtete Verfeinerung: $w=1/[\sigma^2(F_o^2) + (0.05*P)^2]$ wobei $P=(Max(F_o^2,0)+2*F_o^2)/3$. Wasserstoffatome geometrisch eingefügt (NH lokalisisert) und reitend verfeinert, Nichtwasserstoffatome anisotrop verfeinert.
Diskrepanzfaktor	wR2 = 0.1120 (R1=0.0477 für beobachtete Reflexe, 0.1064 für alle Reflexe)
Fitgüte	S = 0.86
maximale Änderung der Parameter	0.001 * e.s.d
maximale Peakhöhe in diff. Fouriersynthese	0.26, -0.25 $eÅ^{-3}$
Bemerkung	Kristall ist verzwillingt.

Endkoordinaten und äquivalente Auslenkungsparameter (Å^2)
$U_{äq} = (1/3)*\sum\sum_{ij} \mathbf{a}_i^* a_j^* \mathbf{a}_i \mathbf{a}_j$

Atom	X	Y	Z	$U_{äq}$
N1	0.6915(4)	0.28081(8)	0.2910(1)	0.0276(6)
C2	0.8282(5)	0.28043(9)	0.2067(2)	0.0253(7)
C3	1.0300(5)	0.24341(9)	0.1776(2)	0.0271(8)
C4	1.1385(5)	0.25155(9)	0.0888(2)	0.0269(8)
C5	1.0475(5)	0.29594(9)	0.0332(2)	0.0239(7)
C6	0.8525(5)	0.33301(9)	0.0644(2)	0.0236(7)
C7	0.7402(5)	0.32545(9)	0.1530(2)	0.0242(7)
C8	0.5403(5)	0.35452(9)	0.2083(2)	0.0257(7)
C9	0.3794(5)	0.4019(1)	0.1956(2)	0.0319(8)
C10	0.1999(6)	0.4175(1)	0.2658(2)	0.0387(9)
C11	0.1773(6)	0.3868(1)	0.3474(2)	0.0394(9)
C12	0.3335(5)	0.3407(1)	0.3627(2)	0.0330(8)
C13	0.5138(5)	0.3252(1)	0.2926(2)	0.0267(7)
C14	1.1208(5)	0.19917(9)	0.2450(2)	0.0334(8)
C15	0.9351(5)	0.1488(1)	0.2498(2)	0.0378(9)
C16	0.9335(6)	0.1132(1)	0.1645(2)	0.0460(10)
C17	0.7579(7)	0.0622(1)	0.1769(2)	0.064(1)
C18	0.767(1)	0.0239(2)	0.0938(3)	0.125(2)
C19	1.3598(5)	0.2148(1)	0.0490(2)	0.0320(8)
O20	1.1567(3)	0.30033(6)	-0.0555(1)	0.0316(5)
N21	0.7595(4)	0.37770(7)	0.0083(1)	0.0255(6)
C22	0.9181(5)	0.41383(9)	-0.0378(2)	0.0274(8)
O23	1.1701(3)	0.40856(6)	-0.0414(1)	0.0318(6)
C24	0.7766(5)	0.46041(9)	-0.0863(2)	0.0343(9)

anisotrope Auslenkungsparameter

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N1	0.031(1)	0.028(1)	0.024(1)	0.0016(10)	0.005(1)	0.0048(9)
C2	0.026(1)	0.027(1)	0.023(1)	-0.003(1)	0.002(1)	-0.001(1)
C3	0.025(1)	0.025(1)	0.031(1)	-0.001(1)	-0.003(1)	-0.002(1)
C4	0.022(1)	0.027(1)	0.032(1)	-0.001(1)	0.001(1)	-0.004(1)
C5	0.025(1)	0.026(1)	0.021(1)	-0.002(1)	0.003(1)	-0.004(1)
C6	0.025(1)	0.024(1)	0.022(1)	-0.003(1)	-0.003(1)	0.001(1)
C7	0.024(1)	0.025(1)	0.024(1)	-0.001(1)	-0.003(1)	-0.002(1)
C8	0.024(1)	0.030(1)	0.024(1)	-0.002(1)	-0.001(1)	-0.002(1)
C9	0.034(1)	0.033(1)	0.029(1)	0.004(1)	0.003(1)	0.002(1)
C10	0.043(2)	0.039(2)	0.034(2)	0.013(1)	0.007(1)	-0.003(1)
C11	0.038(2)	0.044(2)	0.036(2)	0.005(1)	0.011(1)	-0.007(1)
C12	0.035(1)	0.038(1)	0.025(1)	-0.002(1)	0.005(1)	0.000(1)
C13	0.024(1)	0.030(1)	0.026(1)	-0.004(1)	0.002(1)	-0.001(1)
C14	0.032(1)	0.032(1)	0.036(1)	0.004(1)	-0.002(1)	0.003(1)
C15	0.032(1)	0.032(1)	0.049(2)	0.006(1)	0.000(1)	0.010(1)
C16	0.041(2)	0.035(2)	0.062(2)	0.002(1)	0.002(2)	-0.003(1)
C17	0.066(2)	0.055(2)	0.070(2)	-0.014(2)	-0.009(2)	-0.002(2)
C18	0.208(6)	0.092(3)	0.075(3)	-0.069(4)	0.007(3)	-0.013(2)
C19	0.027(1)	0.034(1)	0.035(1)	0.004(1)	0.000(1)	-0.004(1)
O20	0.0376(10)	0.0322(9)	0.0251(9)	0.0005(8)	0.0100(9)	-0.0031(8)
N21	0.026(1)	0.025(1)	0.025(1)	0.0028(9)	0.0011(10)	0.0036(9)
C22	0.032(1)	0.029(1)	0.022(1)	-0.003(1)	0.001(1)	-0.004(1)
O23	0.0248(10)	0.0336(10)	0.037(1)	-0.0035(8)	0.0033(9)	-0.0003(8)
C24	0.034(2)	0.030(1)	0.038(2)	-0.001(1)	0.000(1)	0.005(1)

Endkoordinaten und isotrope Auslenkungsparameter der Wasserstoffatome(Å²)

Atom	X	Y	Z	U_{iso}
H1	0.68708	0.24759	0.34019	0.0331
H9	0.39323	0.42294	0.13997	0.0383
H10	0.09126	0.44946	0.25797	0.046
H11	0.05075	0.39798	0.39379	0.047
H12	0.31879	0.32018	0.41884	0.0395
H14A	1.13361	0.21547	0.30816	0.0401
H14B	1.30582	0.18693	0.22709	0.0401
H15A	0.99158	0.12605	0.30371	0.045
H15B	0.74659	0.16143	0.26165	0.045
H16A	1.12251	0.10182	0.15005	0.055
H16B	0.86419	0.13476	0.11095	0.055
H17A	0.82013	0.04200	0.23292	0.077
H17B	0.56700	0.07368	0.18757	0.077
H18A	0.65601	0.03918	0.04319	0.187
H18B	0.69515	-0.01214	0.11174	0.187
H18C	0.95577	0.01994	0.07267	0.187
H19A	1.43923	0.19255	0.09918	0.048
H19B	1.50207	0.23753	0.02064	0.048
H19C	1.28098	0.19048	0.00160	0.048
H20	1.19157	0.34213	-0.06046	0.0475
H21	0.59125	0.39419	0.01178	0.0306
H24A	0.83384	0.49534	-0.05847	0.052
H24B	0.57902	0.45621	-0.07961	0.052
H24C	0.82446	0.46011	-0.15267	0.052