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TETRAHEDRON

Synthesis and Cyclisation of Didemnimide C and its Imidazol-1-yl Isomer[1]

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Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 65th birthday

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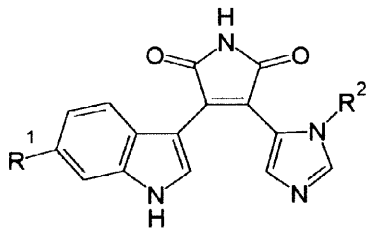
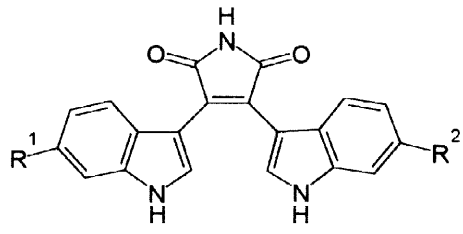
Abstract: A key step in the synthesis of the marine alkaloid didemnimide C (**1c**) is the Stille coupling between the urethane protected 3-bromo-4-(indol-3-yl)-1-methylmaleimide **3** and 5-tributylstannyl-1-methylimidazole (**4**). In this manner **1c** can be obtained in four steps in 29% overall yield. Treatment of **3** with imidazolyl magnesium bromide affords the imidazol-1-yl compound **7** which can then be converted to the cyclo derivatives **8** and **10** upon irradiation with a halogen lamp.

Recently, Vervoort et al.[2] reported the isolation of four novel alkaloids, didemnimide A-D (**1a-d**), from the Caribbean ascidian *Didemnum conchyliatum,* which function as deterrents against mangrove-specific carnivorous fishes. The didemnimides show a close structural relationship to the slime mould metabolites arcyriarubin A-C (**2a-c**).[3] We have therefore reasoned that compounds **1** might be synthesised using the same strategy as the bisindolylmaleimides **2**, i.e. by coupling of an *N*-protected bromoindolylmaleimide with a suitable heterocyclic nucleophile.[3,4]



	1a	**1b**	**1c**	**1d**
R^1	H	Br	H	Br
R^2	H	H	CH_3	CH_3



	2a	**2b**	**2c**
R^1	H	OH	OH
R^2	H	H	OH

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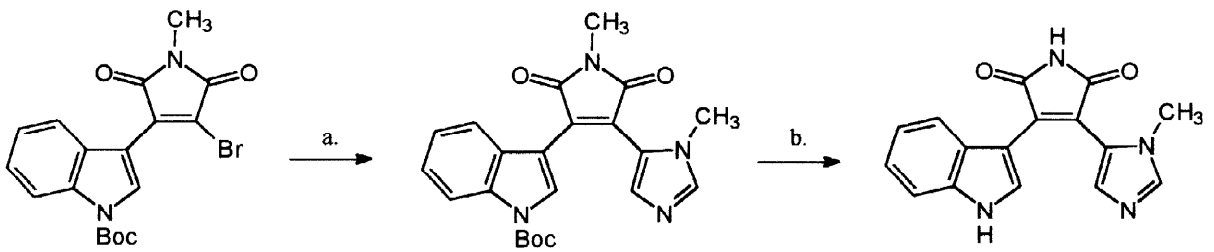
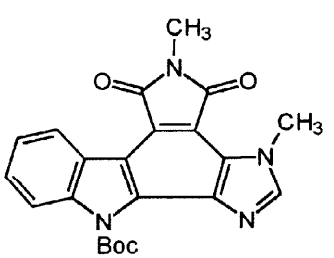
Stille coupling[5] of bromide **3**[4a] with 5-tributylstannyl-1-methyl-1*H*-imidazole (**4**)[6] afforded the 1-methylimidazol-5-yl derivative **5** in 72% yield, which was converted to didemnimide C (**1c**) without isolation of intermediates (Scheme 1). After removal of the urethane protecting group from **5**, the maleimide group was transformed into the anhydride by alkaline hydrolysis followed by treatment with acid. Heating of the crude anhydride with ammonium acetate gave didemnimide C (**1c**) in 29% overall-yield. The spectral data for synthetic **1c** are in accord with those reported for the natural product.[2]



3 **5** **1c**

Scheme 1. Reagents: (a) 3-tributylstannyl-1-methyl-1*H*-imidazole (**4**), $Pd(PPh_3)_4$, $PhCH_3$, Δ, 18 h. (b) i. 15% aq HCl, Δ, 1 h; ii. aq KOH, Δ, 2 h, then aq HCl; iii. NH_4OAc.

The tendency of didemnimide derivatives to ring-close is exemplified by the behaviour of the *N*-Boc derivative **5** which forms the pentacyclic compound **6** on irradiation in the presence of iodine[7] or even on recrystallisation from methanol. The structure of **6** was confirmed by X-ray structural analysis (Figure 1).



6

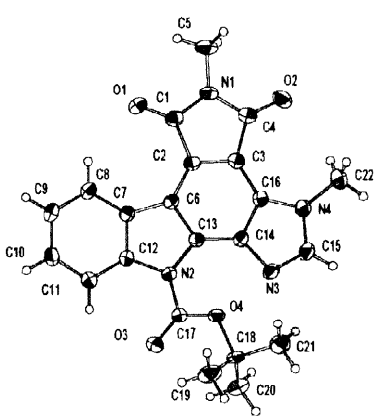
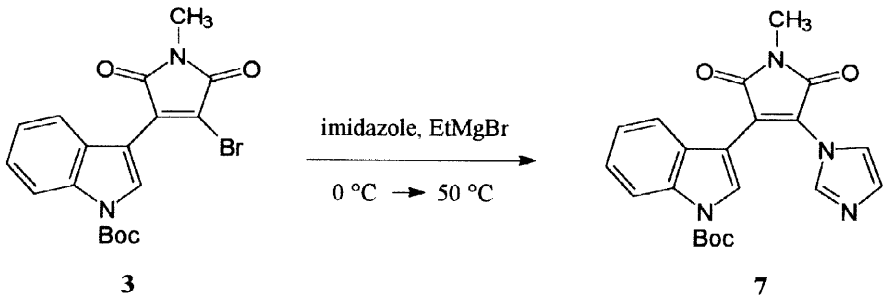


Figure 1. Molecular structure of compound **6**

Considering the ease of their formation cyclodidemnimides of type **6** may be expected to occur in nature. A precedent is the co-occurrence of arcyriarubins (**1**) and arcyriaflavins in the slime mould *Arcyria denudata*.[3]

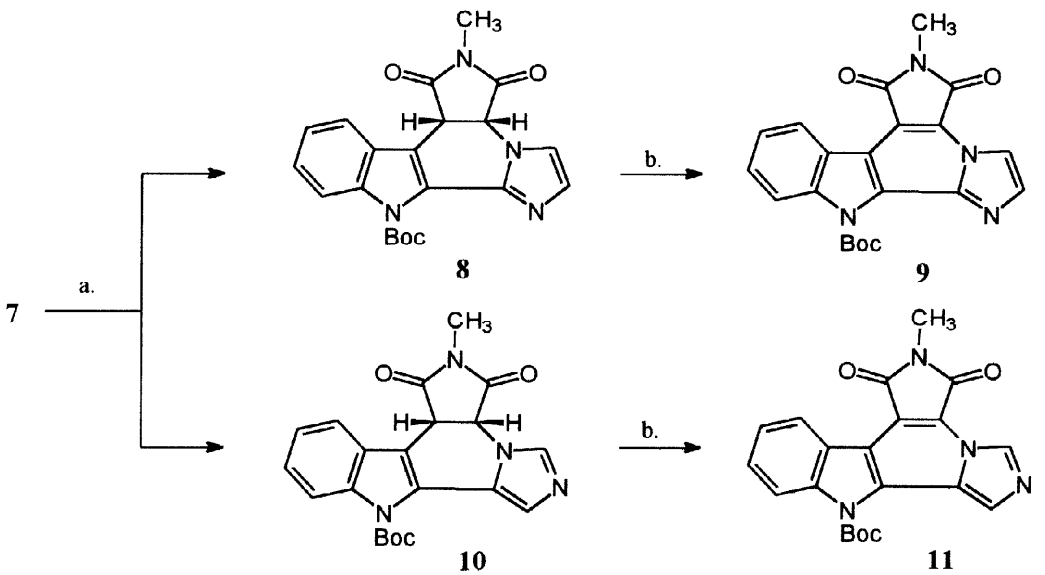
In order to study the properties of the corresponding imidazol-1-yl isomers, we synthesised compound 7 in 60% yield by treatment of bromide **3**[4a] with the bromomagnesium salt of imidazole in tetrahydrofuran (Scheme 2).



3 **7**

Scheme 2

Irradiation of maleimide 7 with a halogen lamp caused cyclisation to a 2:1 mixture of the pentacyclic compounds **8** and **10** (Scheme 3). Both isomers were easily dehydrogenated with MnO_2 to yield the aromatic compounds **9** and **11**, respectively.



Scheme 3. Reagents: (a) hν, 500 W, CH_3CN, 1.5 h. (b) MnO_2, CH_2Cl_2, 0.5 h.

The structures of compounds **9** and **10** have been confirmed by X-ray structural analyses (Figure 2). The *cis*-configuration of **8** follows from the close correspondence of the ^1H NMR signals of the bridgehead protons with those of isomer **10** ($^3J \approx 9.5$ Hz). Studies with specifically deuterated 7 to gain insight into the mechanism of this unusual ring closure are in progress.

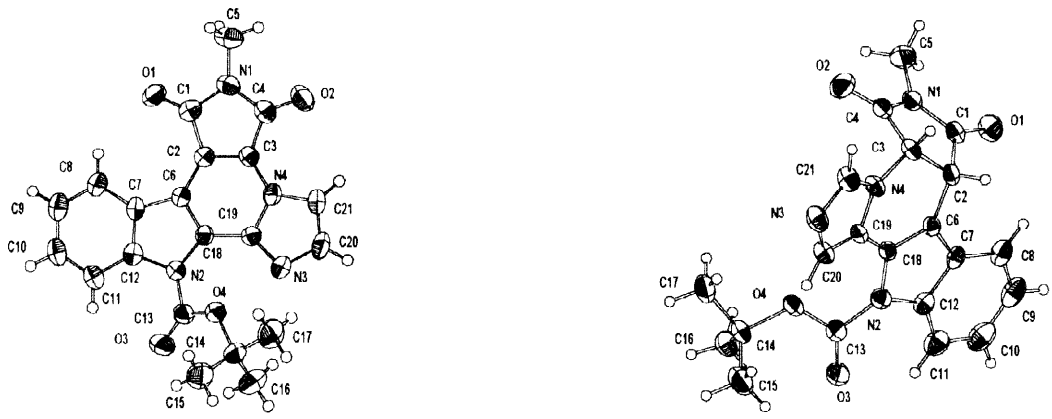


Figure 2. Molecular structures of compounds **9** and **10**

EXPERIMENTAL

General. All solvents were distilled before use. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl under argon prior to use. *n*-Butyllithium was purchased from Acros. The reactions were monitored by TLC and/or ^{1}H NMR prior to work-up. Solvents were evaporated from the reaction mixtures at $\leq$ 40 °C with a rotavapor. TLC was run on silica plates 60 F_{254} (Merck) and visualised with UV fluorescence (254 and 366 nm). Flash chromatography was performed on SiO_2 60, 0.063 - 0.200 mm (Merck). For the irradiation experiments a halogen lamp (Osram®, Halolinc 500 W, 230 V) was used. M.ps. were determined on a micro hot stage apparatus (Reichert Thermovar) and are uncorrected. IR spectra were recorded on a Bruker IFS 45 FT-IR, UV spectra on a Hewlett Packard 8452 diode array spectrometer. ^{1}H and ^{13}C NMR spectra were measured on Bruker AMX 300, AMX 600 and Varian VXR 400 S instruments. Chemical shifts are given as δ values from internal TMS. The mass spectra were recorded on Finnigan MAT 90 and MAT 95 Q instruments. The X-ray diffraction analyses were carried out on a Enraf-Nonius CAD4 diffractometer at room temperature [293(2) K] using Mo K_α (λ = 0.71073 A) radiation. For the solution of the structures SHELXS-86[8] and for the refinement SHELXL-93[9] were used.

***tert*-Butyl 3-[1-Methyl-4-(3-methyl-3*H*-imidazol-4-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-indole-1-carboxylate (5).** A solution of 5-tributylstannyl-1-methyl-1*H*-imidazole[6] (**4**) (3.00 g, 8 mmol), bromo(indolyl)maleimide **3**[4a] (1.65 g, 4 mmol) and tetrakis(triphenylphosphine)palladium(0) (96 mg, 0.08 mmol) in toluene (100 ml) was heated at 110 °C for 20 h. After evaporation of the solvent the product was purified by repeated flash chromatography on silica gel ($CHCl_3$/CH_3OH = 10:1 and EtOAc/PE = 7:1). Dark-orange solid (1.19 g, 72%), m.p. 82-84 °C; UV/VIS (CH_3OH): λ_{max} (ε) = 204 (31870), 286 (10690

), 408 nm (6745). - IR (KBr): $\tilde{\nu}$ = 3435 (s, br.), 2929 (w), 1739 (m), 1704 (s), 1636 (w), 1551 (w), 1507 (w), 1452 (m), 1437 (m), 1370 (m), 1308 (w), 1298 (w), 1259 (w), 1234 (w), 1154 (s), 1118 (m), 1067 (w), 1019 (w), 982 (w), 923 (w), 839 (w), 749 (m), 721 (m), 696 (m), 666 (w), 542 cm^{-1} (s). - ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.69 (s, 9H) 3.18 (s, 3H), 3.21 (s, 3H), 6.55 (d, *J* = 7.6 Hz, 1H), 6.99 ('td', *J* = 7.6 and 1.0 Hz, 1H), 7.28 ('td', *J* = 7.8 and 1.0 Hz, 1H), 7.41 (d, *J* = 0.9 Hz, 1H), 7.48 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.32 (s, 1H). - ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.42 (NCH_3), 28.05 (Boc CH_3), 32.87 (NCH_3), 85.04 (Boc C), 109.65 (C), 115.32 (CH), 120.12 (CH), 122.55 (C), 123.29 (C), 123.69 (CH), 125.24 (CH), 127.10 (C), 130.04 (C), 130.25 (CH), 134.58 (CH), 135.30 (C), 140.91 (CH), 148.80 (Boc C=O),

170.16 (C=O), 170.29 (C=O). - EI MS (150 °C): *m/z* (%) = 406 (5) $[M]^+$, 350 (8) [M - isoprene]$^+$, 308 (12), 307 (23) [M + H - Boc]$^+$, 306 (100) [M - Boc]$^+$, 305 (40), 304 (16), 290 (11), 265 (16), 221 (11), 220 (11), 179 (8), 57 (28). - HRMS: calcd for $C_{22}H_{22}N_4O_4$: 406.1653; found: 406.1647.

***tert*-Butyl 3,5-Dimethyl-4,6-dioxo-3,4,5,6-tetrahydro-imidazo[4,5-a]pyrrolo[3,4-c]carbazole-11-carboxylate (6).** A solution of **5** (200 mg, 0.49 mmol) and a catalytical amount of iodine in CH_3CN (20 ml) was irradiated with a halogen lamp (500 W) for 3 h with cooling. After evaporation, the residue was chromatographed on silica gel (flash, CH_2Cl_2/Aceton = 9:1) to give the title compound **6** (45 mg, 23%) and starting material **5** (135 mg, 68%). **6**: M.p. > 300 °C, yellow crystals with green fluorescence. - UV/VIS ($CHCl_3$): λ_{max} (ε) = 245 (30810), 258 (31020), 288 (26980), 390 nm (7395). - IR (KBr): $\tilde{\nu}$ = 3438 (s, br.), 3091 (w), 2979 (w), 2933 (w), 1757 (m), 1731 (s), 1708 (s), 1628 (w), 1592 (w), 1508 (w), 1476 (m), 1435 (m), 1412 (w), 1380 (s), 1361 (s), 1331 (m), 1318 (s), 1304 (s), 1282 (w), 1258 (w), 1222 (m), 1182 (w), 1156 (s), 1118 (w), 1086 (m), 1019 (w), 1006 (w), 982 (w), 892 (w), 854 (w), 846 (w), 826 (w), 804 (w), 769 (w), 758 (w), 743 (m), 695 (w), 626 (w), 604 (w), 474 (w), 447 cm^{-1} (w). - ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.77 (s, 9H), 3.24 (s, 3H), 4.34 (s, 3H), 7.45 ('t', *J* = 7.2 Hz, 1H), 7.56 ('t', *J* = 8.4 Hz, 1H), 7.99 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 9.22 (d, *J* =7.2 Hz, 1H). - ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.94 (NCH_3), 28.03 (Boc CH_3), 36.62 (NCH_3), 85.14 (Boc C), 112.69 (C), 114.11 (CH), 117.73 (C), 122.23 (C), 123.36 (C), 123.50 (CH), 125.09 (CH), 127.75 (CH), 130.43 (C), 134.02 (C), 136.60 (C), 139.81 (C), 146.29 (CH), 149.88 (Boc C=O), 167.73 (C=O), 168.98 (C=O). - EI MS (150 °C): *m/z* (%) = 404 (2) $[M]^+$, 306 (2), 305 (15), 304 (100) [M - Boc]$^+$, 303 (9), 259 (5), 247 (2), 245 (2), 219 (6), 152 (3), 57 (2), 56 (2). - HRMS: calcd for $C_{22}H_{20}N_4O_4$: 404.1485; found: 404.1499.

Crystal data and structure refinement for **6**. Empirical formula $C_{22}H_{20}N_4O_4$; formula weight 404.42; temperature 293(2) K; wavelength 0.71073 Å; crystal system monoclinic; space group *P*21/*n*; unit cell dimensions *a* = 8.5762(12) Å; *b* = 10.2361(12) Å; *c* = 21.794(4) Å; β = 91.731(13)°; *V* = 1912.3(5) Å^3; *Z* = 4; ρ_{calcd} = 1.405 Mg/m^3; μ = 0.099 mm^{-1}; *F*(000) 848; crystal size .40 x .40 x .20 mm; θ-range for data collection 2.53 to 23.98°; index ranges -9 ≤ h ≤ 9, 0 ≤ k ≤ 11, -24 ≤ l ≤ 0; reflections collected 3083; independent reflections 2999 [*R*(int) = 0.0206]; absorption correction: semi-empirical from φ-scans; max. and min. transmission 0.9954 and 0.9740; refinement method: full-matrix least-squares on F^2; data / restraints / parameters 2999 / 0 / 277; goodness-of-fit on F^2 1.140; final *R* indices [I>2σ(I)] *R*1 = 0.0470, *wR*2 = 0.1046; *R* indices (all data) *R*1 = 0.0714, *wR*2 = 0.1175; extinction coefficient 0.0045(8); largest diff. peak and hole 0.174 and -0.177 e Å^{-3}.[10]

Didemnimide C (1c). Maleimide **5** (160 mg, 0.4 mmol) was dissolved in 15% aq HCl (10 ml) and stirred for 1 h at ambient temperature. The solution was poured on KOH pellets (5.00 g) and refluxed for 2 h. After neutralisation with concentrated HCl, ammonium acetate (30 g) was added and the solvent evaporated. Heating of the remaining solid for 15 min at 150 °C yielded an orange melt. After extraction with EtOAc and evaporation of the solvent the residue was washed with methanol to yield **1c** (46 mg, 40%) as dark red solid, m.p. >300 °C; UV/VIS (DMSO): λ_{max} (ε) = 274 (9110), 353 (3690), 441 nm (8990). - IR (KBr): $\tilde{\nu}$ = 3431 (s), 3170 (m), 3055 (m), 2924 (m), 2853 (w), 2737 (w), 1766 (m), 1702 (s), 1630 (m), 1580 (w), 1539 (s), 1499 (w), 1483 (w), 1462 (w), 1446 (m), 1345 (m), 1312 (w), 1279 (w), 1258 (w), 1236 (m), 1221 (m), 1165 (w), 1146 (w), 1117 (m), 1091 (w), 1014 (w), 937 (w), 913 (w), 840 (w), 824 (w), 748 (m), 687 (w), 666 (m), 642 (w), 628 (w), 569 (w), 499 (m), 424 cm^{-1} (w). - ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.16 (s, 3H), 6.39 (d, *J* = 8.1 Hz, 1H), 6.79 ('t', *J* = 8.1 Hz, 1H), 7.08 (s, 1H), 7.10 ('t', *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.71 (s, 1H), 8.08 (s, 1H), 11.13 (s, 1H), 12.02 (s, 1H). - ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 32.05 (NCH_3), 104.99 (C), 112.25 (CH), 118.55 (C), 119.64 (CH), 120.63 (CH), 122.41 (CH), 122.76 (C), 124.75 (C), 131.59 (CH), 131.96 (CH), 133.84 (C), 136.37 (C), 140.05 (CH), 171.77 (C=O), 171.96 (C=O). - EI MS (150 °C): *m/z* (%) = 293 (19), 292 (100) $[M]^+$, 291 (55), 276 (6), 251 (27), 248 (7), 221 (9), 220 (11), 58 (7), 43 (13). - HRMS: calcd for $C_{16}H_{12}N_4O_2$: 292.0960; found: 292.0956.

***tert*-Butyl 3-(4-Imidazol-1-yl-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indole-1-carboxylate (7).** To a stirred solution of imidazole (1.02 g, 15.0 mmol) in dry THF (50 ml) EtMgBr (5.35 ml, 15.0 mmol, 2.8M solution in THF) was added dropwise at 0 °C. After warming the solution to 20 °C a solution of bromo(indolyl)maleimide **3**[4a] (2.25 g, 5.6 mmol) in dry THF (100 ml) was added. The mixture was heated for 15 h at 50 °C and after addition of aqueous NaOH (20 ml) extracted with EtOAc (3 × 30 ml). The organic layers were washed with water and brine. After drying over $MgSO_4$ the solvent was evaporated. Repeated chromatography of the residue on silica gel (Et_2O/hexane = 1:1 and $CHCl_3$/MeOH = 10:1) yielded **7** as a light yellow solid (1.31 g, 60%), m.p. 78-80 °C. - UV/VIS (CH_3OH): λ_{max} (ε) = 203 (30455), 251 (17485), 285 (7580), 394 nm (5570). IR (KBr): $\tilde{\nu}$ = 3464 (w, br.), 3165 (w), 3117 (w), 2983 (w), 2934 (w), 1774 (w), 1741 (s), 1714 (s), 1654 (w), 1578 (w), 1522 (m), 1478 (m), 1454 (s), 1385 (m), 1372 (m), 1356 (m), 1334 (w), 1309 (m), 1281 (m), 1260 (m), 1232 (s), 1188 (w), 1152 (s), 1112 (w), 1104 (w), 1071 (m), 1022 (w), 1005 (w), 984 (w), 900 (w), 855 (w), 838 (w), 818 (w), 766 (m), 748 (m), 664 (w), 652 (w), 627 (w), 614 (w), 592 (w), 540 (w), 474 (w), 452 (w), 434 cm^{-1} (w). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.71 (s, 9H), 3.19 (s, 3H), 6.51 (d, *J* = 8.1 Hz, 1H), 7.05 ('td', *J* = 7.6 and 0.8 Hz, 1H), 7.08 (s, 1H), 7.23 (s, 1H), 7.33 ('td', *J* = 7.8 and 1.1 Hz, 1H), 7.97 (s, 1H), 8.19 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H). - ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.38 (CH_3), 28.02 (Boc CH_3), 85.14 (Boc C), 106.63 (C), 115.49 (CH), 118.92 (CH), 120.02 (CH), 120.09 (C), 123.64 (CH), 125.45 (CH), 126.37 (C), 128.43 (C), 130.06 (CH), 130.09 (CH), 135.33 (C), 137.51 (CH), 148.72 (Boc C=O), 166.52 (C=O), 168.77 (C=O). - EI MS (150 °C): *m/z* (%) = 392 (7) $[M]^+$, 336 (6) [M- isoprene]$^+$, 293 (18), 292 (100) [M + H - Boc]$^+$, 291 (33) [M - Boc]$^+$, 264 (6), 207 (11), 57 (33). - HRMS: calcd for $C_{21}H_{20}N_4O_4$: 392.1488; found: 392.1486. - $C_{21}H_{20}N_4O_4$ × 0.5 HOAc (422.44): calcd C 62.55; H 5.25; N 13.2; found C 62.82; H 5.28; N 13.24.

***tert*-Butyl 6-Methyl-5,7-dioxo-(4a*r*,7a*c*)-5,6,7,7a-tetrahydro-4a*H*-imidazo[1′,2′:1,2]pyrrolo[3′,4′:5,6]pyrido-[3,4-*b*]-indole-12-carboxylate (8) and *tert*-Butyl 2-Methyl-1,3-dioxo-(3a*r*,12c*c*)-2,3,3a,12c-tetrahydro-1*H*-imidazo-[1′,5′:1,2]pyrrolo[3′,4′:5,6]pyrido[3,4-*b*]indole-8-carboxylate (10).** A solution of maleimide **7** (1.05 g, 2.7 mmol) in acetonitrile (50ml) was irradiated with a halogen lamp (500 W) for 1.5 h. After evaporation of the solvent the products were separated by column chromatography on silica gel. Compound **8** (630 mg, 60%) was eluted with CH_2Cl_2/acetone = 15:1, isomer **10** (305 mg, 29%) with CH_2Cl_2/acetone = 3:1.

8: M.p. 162-163 °C (after darkening >135 °C); UV/VIS ($CHCl_3$): λ_{max} (ε) = 254 (4770), 329 nm (19045). - IR (KBr): $\tilde{\nu}$ = 3436 (s, br.), 2981 (w), 2933 (w), 1791 (w), 1712 (s), 1630 (w), 1522 (w), 1477 (w), 1439 (s), 1384 (w), 1356 (s), 1314 (m), 1286 (s), 1260 (w), 1154 (s), 1093 (w), 1066 (w), 958 (w), 924 (w), 866 (w), 844 (w), 833 (w), 806 (w), 766 (m), 749 (m), 712 (w), 526 (w), 443 cm^{-1} (w). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.67 (s, 9H), 3.09 (s, 3H), 4.76 (d, *J* = 9.9 Hz, 1H), 5.39 (d, *J* = 9.9 Hz, 1H), 7.23 (s, 1H), 7.28 (s, 1H), 7.30 ('t', *J* = 7.8 Hz, 1H), 7.36 ('t', *J* = 7.7 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H). - ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 26.19 (NCH_3), 28.27 (Boc CH_3), 40.72 (CH), 55.56 (CH), 85.65 (Boc C), 110.55 (C), 114.85 (CH), 120.27 (CH), 121.45 (CH), 123.84 (CH), 125.86 (C), 126.40 (CH), 126.84 (C), 130.52 (CH), 136.68 (C), 138.29 (C), 149.78 (Boc C=O), 172.84 (C=O), 173.64 (C=O). - EI MS (150 °C): *m/z* (%) = 392 (11) $[M]^+$, 293 (19), 292 (100), 276 (6), 251 (5), 208 (6), 207 (40), 206 (8). - HRMS: calcd for $C_{21}H_{20}N_4O_4$: 392.1485; found: 392.1500. - $C_{21}H_{20}N_4O_4$ × 0.33 H_2O (398.42): calcd C 63.31; H 5.23; N 14.06; found C 63.55; H 5.18; N 14.11.

10: M.p. 218-219 °C (after darkening >185 °C); UV/VIS ($CHCl_3$): λ_{max} (ε) = 255 (5160), 324 (20890), 339 nm (14650). - IR (KBr): $\tilde{\nu}$ = 3437 (s, br.), 2981 (w), 2933 (w), 1791 (w), 1713 (s), 1633 (w), 1442 (s), 1372 (m), 1357 (s), 1328 (m), 1300 (m), 1230 (w), 1150 (s), 1119 (m), 1071 (w), 929 (w), 845 (w), 766 (w), 747 (w), 652 (w), 527 cm^{-1} (w). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.73 (s, 9H), 3.05 (s, 3H), 4.75 (d, *J* = 9.6 Hz, 1H), 5.41 (d, *J* = 9.6 Hz, 1H), 7.35-7.30 (m, 2H), 7.80 (s, br., 1H), 7.95 (s, br., 1H), 8.02-7.99 (m, 1H), 8.09-8.06 (m, 1H). - ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.75 (NCH_3), 28.13 (Boc CH_3), 39.88 (CH), 53.09 (CH), 85.52 (Boc C), 105.92 (CH), 115.25 (CH), 120.55 (C), 120.72 (CH), 123.50 (CH), 125.27 (CH), 126.02 (C), 127.18 (CH), 129.74 (C), 136.46 (C), 138.10 (C), 149.68 (Boc C=O), 172.35 (C=O), 173.06 (C=O). - EI MS (150 °C): *m/z* (%) = 392 (15) $[M]^+$, 337 (15), 336 (74) [M - isoprene]$^+$,

293 (19), 292 (100) [M - Boc]$^+$, 290 (15), 251 (8), 207 (46), 206 (12). - HRMS: calcd for $C_{21}H_{20}N_4O_4$: 392.1485; found: 392.1484.. - $C_{21}H_{20}N_4O_4 \times 0.33\ H_2O$ (398.42): calcd C 63.31; H 5.23; N 14.06; found C 62.35; H 5.25; N 13.81.

Crystal data and structure refinement for **10**. Empirical formula $C_{21}H_{20}N_4O_4$; formula weight 392.41; temperature 293(2) K; wavelength 0.71073 Å; crystal system monoclinic; space group $P2_1/c$; unit cell dimensions a = 17.241(3) Å; b = 12.108(2) Å; c = 19.456(5) Å; β = 103.31(2)°; V = 3952.5(13) Å^3; Z = 8; ρ_{calcd} = 1.319 Mg/m^3; μ = 0.094 mm^{-1}; F(000) 1648; crystal size .53 × .20 × .20 mm; θ-range for data collection 2.15 to 22.58°; index ranges $0 \le h \le 20$, $0 \le k \le 14$, $-23 \le l \le 20$; reflections collected 5417; independent reflections 5210 [R(int) = 0.0181]; absorption correction: semi-empirical from ϕ-scans; max. and min. transmission 0.9998 and 0.8789; refinement method: full-matrix least-squares on F^2; data / restraints / parameters 5210 / 0 / 531; goodness-of-fit on F^2 1.119; final R indices [I>2σ(I)] $R1$ = 0.0529, $wR2$ = 0.1152; R indices (all data) $R1$ = 0.0869, $wR2$ = 0.1349; largest diff. peak and hole 0.225 and -0.191 e Å^{-3}.[10]

***tert*-Butyl 6-Methyl-5,7-dioxo-6,7-dihydro-5*H*-imidazo[1′,2′:1,2]pyrrolo[3′,4′:5,6]pyrido[3,4-*b*]indole-12-carboxylate (9).** To a solution of compound **8** (200 mg, 0.5 mmol) in dichloromethane (25 ml) MnO_2 (250 mg, 2.9 mmol) was added. The solution was stirred for 30 min at room temperature and filtered over Celite®. Evaporation of the filtrate yielded **9** as a yellow solid (195 mg, 100%), m.p. >300 °C; UV/VIS (DMSO): λ_{max} (qual.) = 313, 441 nm. - IR (KBr): $\tilde{\nu}$ = 3436 (s, br.), 2981 (w), 1770 (w), 1736 (m), 1715 (s), 1647 (w), 1542 (w), 1478 (w), 1457 (w), 1418 (w), 1383 (m), 1344 (w), 1323 (m), 1309 (m), 1290 (m), 1254 (w), 1200 (w), 1122 (w), 1108 (w), 1067 (w), 1040 (w), 996 (w), 882 (w), 844 (w), 808 (w), 767 (w), 751 (m), 734 (m), 687 (w), 674 (w), 469 (w), cm^{-1} 446 (w). - ^{1}H NMR (TFA, 600 MHz): δ = 3.46 (s, 3H), 7.54 ('t', J = 7.0 Hz, 1H), 7.80-7.76 (m, 3H), 8.19 (d, J = 1.6 Hz, 1H), 8.76 (d, J = 8.0 Hz, 1H), 8.84 (d, J = 1.6 Hz, 1H); Boc group is cleaved by the solvent! - ^{13}C NMR (TFA, 75 MHz): δ = 25.67 (NCH_3), 114.88 (CH), 116.55 (CH), 119.90 (C), 121.83 (C), 122.77 (C), 122.98 (C), 125.96 (CH), 126.22 (CH), 126.34 (C), 126.62 (CH), 133.15 (CH), 133.59 (C), 143.42 (C), 166.19 (C=O), 168.75 (C=O); Boc group is cleaved by the solvent! - EI MS (150 °C): m/z (%) = 390 (1) [M]$^+$, 291 (18), 290 (100) [M - Boc]$^+$, 233 (5), 231 (9), 207 (5), 205 (8). - HRMS: calcd for $C_{21}H_{18}N_4O_4$: 390.1328; found: 390.1358.

Crystal data and structure refinement for **9**. Empirical formula $C_{21}H_{18}N_4O_4$; formula weight 390.39; temperature 293(2) K; wavelength 0.71073 Å; crystal system monoclinic; Space group $P2_1/c$; unit cell dimensions a = 6.9195(13) Å; b = 11.651(5) Å; c = 23.036(7) Å; β = 93.78(3)°; V = 1853.1(10) Å^3; Z=4; ρ_{calcd} = 1.399 Mg/m^3; μ = 0.100 mm^{-1}; F(000) 816; crystal size .53 x .40 x .10 mm; θ-range for data collection 2.49 to 24.98°; index ranges $-8 \le h \le 0$, $0 \le k \le 13$, $-27 \le l \le 27$; reflections collected 3540; independent reflections 3251 [R(int) = 0.0439]; absorption correction: semi-empirical from ϕ-scans; max. and min. transmission 0.9972 and 0.9722; refinement method: full-matrix least-squares on F^2; data / restraints / parameters 3251 / 0 / 266; goodness-of-fit on F^2 1.140; final R indices [I>2σ(I)] $R1$ = 0.0774, $wR2$ = 0.1631; R indices (all data) $R1$ = 0.1389, $wR2$ = 0.1955; largest diff. peak and hole 0.264 and -0.286 e Å^{-3}.[10]

***tert*-Butyl 2-Methyl-1,3-dioxo-2,3-dihydro-1*H*-imidazo[1′,5′:1,2]pyrrolo[3′,4′:5,6]pyrido[3,4-*b*]indole-8-carboxylate (11).** To a solution of compound **10** (200 mg, 0.5 mmol) in dichloromethane (25 ml) MnO_2 (250 mg, 2.9 mmol) was added. The mixture is stirred for 30 min at room temperature and filtered over Celite®. Evaporation of the filtrate yielded **11** as a purple solid (195 mg, 100%), m.p. >300 °C; UV/VIS (DMSO): λ_{max} (qual.) = 308, 327, 495 nm. - IR (KBr): $\tilde{\nu}$ = 3437 (s, br.), 2982 (w), 1770 (w), 1750 (m), 1717 (s), 1636 (m), 1528 (w), 1445 (w), 1417 (w), 1398 (w), 1379 (m), 1322 (w), 1302 (w), 1302 (m), 1290 (m), 1256 (w), 1231 (w), 1153 (m), 1134 (w), 997 (w), 916 (w), 850 (w), 806 (w), 763 (w), 736 (m), 650 (w), 474 (w), 444 cm^{-1} (w). - ^{1}H NMR ([D$_6$]DMSO + 0.05ml TFA, 300 MHz): δ = 1.73 (s, 9H), 3.12 (s, 3H), 7.42 ('t,' J = 7.8 Hz, 1H), 7.53 ('t', J = 7.2 Hz, 1H), 8.04 (d, J = 8.7 Hz, 1H), 8.55 (s, 1H), 8.69 (d, J = 8.1 Hz, 1H), 9.97 (s, 1H). - ^{13}C NMR (TFA, 75 MHz): δ = 25.51 (NCH_3), 112.51 (CH), 114.07 (C), 114.41 (CH), 119.18 (C), 122.59 (C), 125.51 (2 × CH), 126.08 (CH), 126.59 (C), 127.13 (C), 130.74 (CH), 132.87 (C), 141.55 (C), 166.81 (C=O), 169.04 (C=O); Boc group is cleaved by the solvent! - EI MS (150 °C): m/z (%) = 390 (1) [M]$^+$, 334 (7) [M -

isoprene]$^{+}$, 292 (14), 291 (19), 290 (100) [M - Boc]$^{+}$, 289 (6), 207 (11), 206 (6), 205 (9), 178 (6), 151 (5), 88 (8), 86 (48), 84 (73), 56 (5), 51 (11), 49 (32), 47 (5). - HRMS: calcd for $C_{21}H_{18}N_4O_4$: 390.1328; found: 390.1333.

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