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Synthesis of the marine alkaloids rhopaladins A, B, C and D

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Abstract—The total synthesis of all four known rhopaladins, A–D, isolated from the Okinawan marine tunicate *Rhopalaea* sp., in two synthetic steps is described, involving an imidate based cyclization with tryptophan esters as the key step to afford the appropriately substituted imidazolinone unit. A short and efficient new synthesis of indol-3-yl-carbonyl nitriles from indol-3-yl-carboxaldehydes and trimethylsilyl cyanide, followed by oxidation with DDQ is also described.

1. Introduction

Marine environments are a rich source of indole and bis-(indole) alkaloids of great structural variety. Numerous compounds belonging to these classes have been isolated from, e.g. tunicates, sponges and algae, and display a wide spectrum of biological activities.[1–4] Recently four bis-(indole) alkaloids rhopaladins A–D (**1**–**4**) (Fig. 1) were isolated from the Okinawan marine tunicate *Rhopalaea* sp. and the structures were elucidated on the basis of spectroscopic data. These bis(indole) alkaloids are the first tunicate metabolites possessing the interesting structural feature of an imidazolinone ring, and have also been demonstrated to show antibacterial activity against *Sarcina lutea* and *Corynebacterium xerosis* and inhibitory activity against cyclin dependent kinase 4 and *c-erbB*-2 kinase.[5]

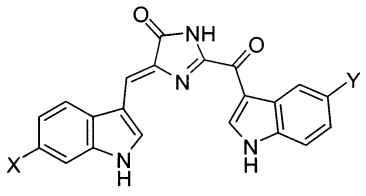
A complex total synthesis of rhopaladin D (**4**) has been reported recently by Fresneda and Molina in six steps based on the aza-Wittig reaction of the iminophosphorane derived from the α-azido-β-(3-indolyl)propenamide with indol-3-yl-glyoxylyl chloride in the presence of a polymer supported base.[6]

Compounds structurally related to the rhopaladins **1**–**4** such as the topsentins (**5**–**10**)[7–12] and nortopsentins A–D (**11**–**14**)[13,14] (Fig. 2) possessing an imidazole instead of an imidazolinone ring, have been isolated from *Topsentia genitrix* and *Spongosorites ruetzleri*, and exhibit cytotoxic, antiviral and antifungal properties.

2. Results and discussion

Here we wish to disclose the total synthesis of all four known rhopaladins A–D (**1**–**4**) in two synthetic steps. As it has been suggested that the compounds **1**–**4** may be biosynthetically derived from two molecules of tryptophan,[5] the idea was to form the central imidazolinone ring through a reaction between an amino acid ester and an imidate, a well known reaction for the construction of 4(5)-imidazolinones (Scheme 1).[15–18] The tryptophan esters **15** would provide one indole unit, with the possibility of dehydrogenation to form the *exo*-cyclic double bond at the 4-position of the imidazolinone, while the imidates **16** (obtained from an indolyl carbonyl nitrile **17**) would introduce the indolyl carbonyl group. Preparation of rhopaladins A (**1**) and B (**2**) would require the use of 6-methoxytryptophan, which would allow for a final transformation of the 6-OMe group to the desired 6-OH group by using boron tribromide[19] or a Prey demethylation[20] (i.e. heating with pyridine hydrochloride).

The most common method to synthesize indol-3-yl-carbonyl nitriles, developed by Sainsbury, involves indol-3-yl-glyoxylyl chloride and cuprous cyanide (53% yield for



1 X = OH, Y = Br
2 X = OH, Y = H
3 X = H, Y = Br
4 X = H, Y = H

Figure 1.

Keywords: alkaloids; imidates; rhopaladins.
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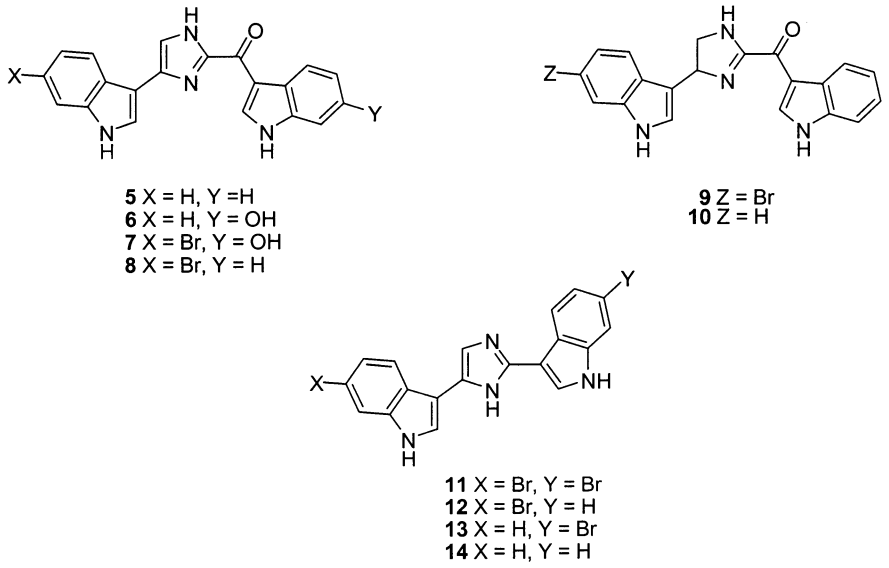
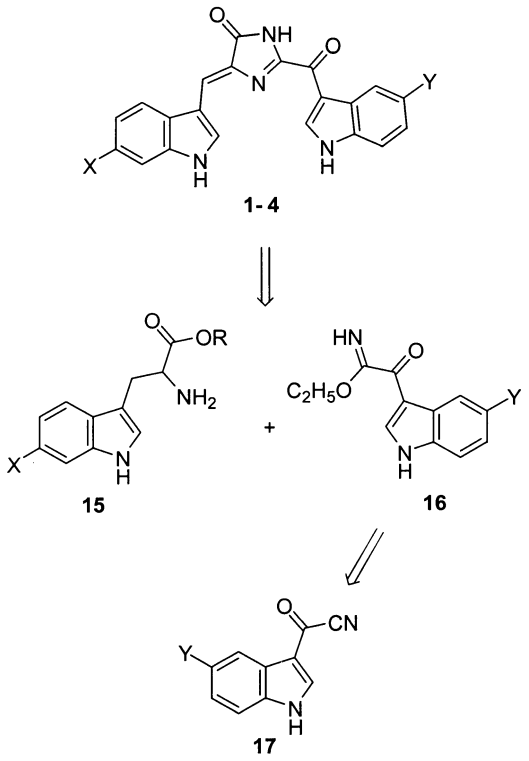
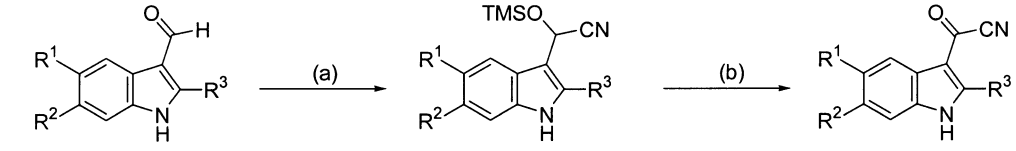


Figure 2.



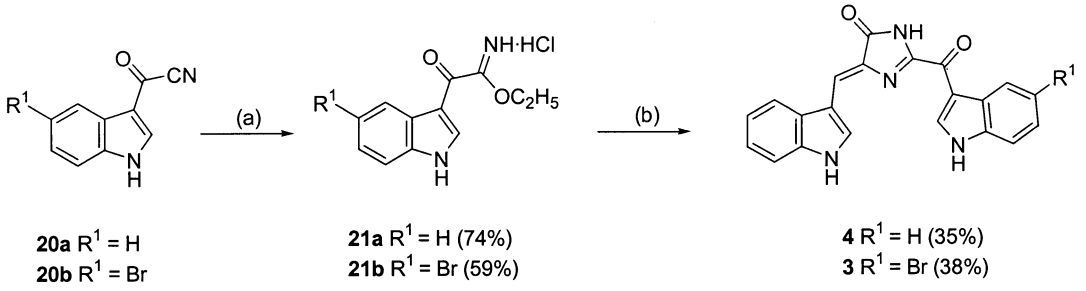
Scheme 1.

(1*H*-indol-3-yl)carbonyl nitrile).[21] We observed that the presence of a bromine in 5-position of the indole ring severely decreased the yield giving only 17–34% of the desired product, hence in order to prepare the necessary imidates, a reliable route to indol-3-yl-carbonyl nitriles had to be developed. Synthesis of acyl cyanides through O-silylated cyanohydrins and subsequent oxidation is a well described topic.[22–25] An efficient synthesis of the parent indolyl-3-carbonyl nitrile (**20a**) was thus developed via a masked cyanohydrin silylether as the intermediate followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The method was also shown to be applicable to indoles with various substituents, e.g. 5-Br, 6-OMe, 2-Ph as outlined in Scheme 2. Treatment of the 3-formylindoles **18a–d**[26–28] (prepared via the standard Vilsmeier procedure) with trimethylsilyl cyanide (TMSCN) in refluxing 1,2-dimethoxyethane (DME) or acetonitrile afforded the cyanohydrin silylethers **19a–d** in good yields. The reaction works well in both solvents with only minor differences in yields. During the development of the method it was noticed that aldehydes of high purity were essential for satisfactory results. The stability of the silylethers **19a–d** at room temperature was found to be rather low and hence these products were used immediately or stored in a refrigerator for a short period of time. Compounds **19a–d** were oxidized smoothly with DDQ in dioxane to the corresponding carbonyl nitriles **20a–d**, in good yields. The method is applicable to a number of substituted indoles, but strongly



18a R^1 = H, R^2 = H, R^3 = H	**19a** (67%)	**20a** (91%)
18b R^1 = Br, R^2 = H, R^3 = H	**19b** (88%)	**20b** (97%)
18c R^1 = H, R^2 = OCH_3, R^3 = H	**19c** (66%)	**20c** (58%)
18d R^1 = H, R^2 = H, R^3 = Ph	**19d** (91%)	**20d** (90%)

Scheme 2. *Reagents and conditions*: (a) TMSCN, DME or acetonitrile, reflux 1.5–3 h; (b) DDQ, dioxane, rt 0.5–8 h.



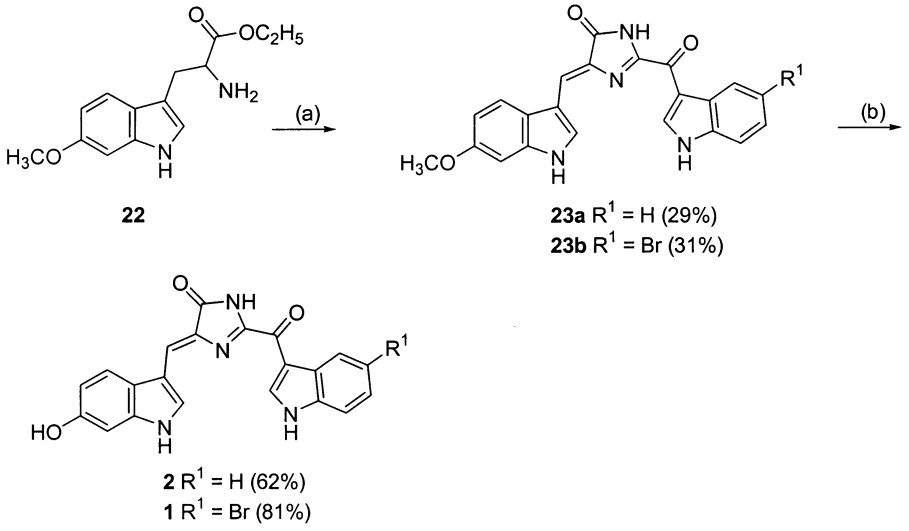
Scheme 3. *Reagents and conditions*: (a) HCl (g), EtOH, Et_2O, 0°C, 8 h; (b) TrpOMe·HCl, Et_3N, dioxane, ~60°C, 3 days.

electron-withdrawing substituents (e.g. 4-NO_2) or *N*-protecting groups (e.g. SO_2Ph) on the cyanohydrin silylether prevent the DDQ-oxidation. In conclusion, this methodology to prepare indol-3-yl-carbonyl nitriles is a good complement to the already existing one, with advantages of good overall yields, shorter reaction times, and tolerance towards a variety of substituents.

Imidates are often prepared in a Pinner reaction where a nitrile and an alcohol are reacted under anhydrous conditions in the presence of hydrogen chloride.[15–18] To the best of our knowledge no heterocyclic acyl imidates have been previously reported, and only few cyclic acyl imidates are known.[29,30] In our application of the Pinner protocol, carbonyl nitriles **20a**, **b** underwent transformation in respectable yields into the imidates **21a**, **b** when exposed to gaseous hydrogen chloride and ethanol in dry ether (Scheme 3). The imidates **21a**, **b** were found to be rather labile and moisture sensitive when isolated, but can be stored under dry conditions in a refrigerator for a short period of time. Reliable NMR data for the imidates **21a**, **b** could not be obtained since a rapid hydrolysis of the imine functionality into a carbonyl takes place in the presence of even minute amounts of moisture in, e.g. DMSO-d_6, thus producing the corresponding dicarbonyl compounds.[31] Nevertheless, FAB- and electrospray-MS data, as well as the IR spectra strongly support the assigned structures **21a**, **b**. The coupling of the imidates **21a**, **b** with tryptophan methyl ester hydrochloride (TrpOMe·HCl) in dioxane in presence of triethylamine resulted in the formation of rhopaladins C (**3**) and D (**4**) in moderate yields (38 and 35%, respectively). The reaction may as well be performed at reflux, run for various periods of time (1–4.5 days) or be performed in acetonitrile without notable differences in yield.

Interestingly, the outcome of this reaction is the result of a coupling followed by a cyclization and a final spontaneous dehydrogenation. The reaction specifically produces the (*Z*)-isomers of the rhopaladins, which appears to be the most stable arrangement. The presence of the (*E*)-isomers could not be detected. The (*Z*)-orientation of the *exo*-cyclic double bond was elucidated using difference-NOE experiments, as irradiation of the 2-hydrogen resonance of the carbonyl bridged indole unit produced enhancement of the signals corresponding to the 2- and 4-protons of the second indole, thus also establishing the presence of rotamers as indicated previously.[5]

The precursors of rhopaladins A and B (**23a**, **b**) were prepared from 6-methoxytryptophan ethyl ester[32] (6-MeOTrpOEt) (**22**) using the same imidate based cyclization as described above. The geometry of the double bond was also in these cases shown as (*Z*) on the basis of NOE-experiments. The final O-demethylation was accomplished by treatment of **23a** or **23b** with BBr_3 in dichloromethane to afford rhopaladins A (**1**) and B (**2**) in yields of 81 and 62%, respectively, after purification by column chromatography (Scheme 4).



Scheme 4. *Reagents and conditions*: (a) **21a** or **21b**, Et_3N, dioxane, ~60°C, 2.5 days; (b) BBr_3, CH_2Cl_2, −78°C to rt, 4.5 days.

A rather large excess of BBr_3 (~30 equiv.) and long reaction times (4.5 days) were needed to ensure deprotection as the precursors **23a**, **b** have limited solubility in CH_2Cl_2. The spectroscopic data for all rhopaladins were in excellent agreement to those reported for the natural products. However, we found that all rhopaladins were insufficiently soluble in MeOH-d_4 (dark red crystals quickly separated from the solution), thus all NMR data were recorded in DMSO-d_6. In the publication describing the isolation of the rhopaladins A–D,[5] MeOH-d_4 was used as the NMR solvent for **2**–**4** and DMSO-d_6 for **1**.

In conclusion we have devised a two step synthesis of the marine alkaloids rhopaladins A–D (**1**–**4**), starting from indol-3-yl-carbonyl nitriles **20a**, **b** in overall yields of 13–26%. Furthermore, the central imidate based cyclization may be considered as a possible tool for creating other imidazolinone or imidazole containing indole alkaloids.

3. Experimental

3.1. General

NMR spectra were recorded at 300 MHz for ^1H and 75 MHz for ^{13}C, respectively. Coupling constants are given in Hz. The IR spectra were acquired using a FT-IR instrument. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. High-resolution mass spectroscopic (HRMS) analyses were performed by E. Nilsson, University of Lund, Sweden, or Sveriges Lantbruksuniversitet (SLU), Uppsala, Sweden. Melting points were determined on a capillary melting point apparatus or a Kofler hot stage and are uncorrected. Chromatography was performed on Merck Silica Gel 60. All reagents were purchased from Aldrich or Lancaster and were used as received. All solvents were purified by distillation or were of analytical grade. Diethyl ether was stored over sodium wire. The indolyltrimethylsiloxyacetonitriles **19a**–**d** are unstable at room temperature and should preferably be used within 24 h.

3.1.1. (1*H*-Indol-3-yl)-(trimethylsiloxy)acetonitrile (19a). To a solution of 1*H*-indol-3-yl-carboxaldehyde (**18a**) (1.16 g, 8.0 mmol) in acetonitrile (10 mL) was added TMSCN (1.39 mL, 10.4 mmol). The mixture was heated at reflux for 2 h and thereafter allowed to cool. The solvent was evaporated, and the brown residue was subjected to column chromatography (hexane/ethyl acetate 80:20) to afford **19a** (1.30 g, 67%) as a yellow oil. IR ($CHCl_3$) 3474, 3013, 2961, 1554, 1456, 1254, 1085, 1047, 868 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.31 (s, 1H), 7.68 (d, J=7.7 Hz, 1H), 7.52 (d, J=1.8 Hz, 1H) 7.45 (d, J=8.0 Hz, 1H), 7.19–7.06 (m, 2H), 6.16 (s, 1H), 0.12 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 136.5 (s), 125.0 (d), 124.7 (s), 121.9 (d), 120.1 (s), 119.5 (d), 118.6 (d), 112.0 (d), 110.6 (s), 57.0 (d), −0.2 (q); MS (ESI) m/z 243 $(M-H)^-$.

3.1.2. (5-Bromo-1*H*-indol-3-yl)-(trimethylsiloxy)acetonitrile (19b). The procedure above was used with 5-bromo-1*H*-indol-3-yl-carboxaldehyde (**18b**)[26] (1.62 g, 7.2 mmol) and TMSCN (1.06 mL, 7.9 mmol) in DME (10 mL) to give **19b** (2.05 g, 88 %) as a yellow oil. Reaction time 1.5 h. IR ($CHCl_3$) 3471, 2961, 1551, 1457, 1257, 1091, 868 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.53 (s, 1H), 7.80 (d, J=1.9 Hz, 1H), 7.59 (s, 1H), 7.43 (d, J=8.7 Hz, 1H), 7.30 (dd, J=8.7, 1.9 Hz, 1H), 6.19 (s, 1H), 0.13 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 135.2 (s), 126.5 (d) 126.4 (s), 124.5 (d), 120.7 (d), 119.9 (s), 114.1 (d), 112.1(s), 110.4 (s), 56.8 (d), −0.3 (q); MS (ESI) m/z 321 and 323 $(M-H)^-$.

3.1.3. (6-Methoxy-1*H*-indol-3-yl)-(trimethylsiloxy)acetonitrile (19c). The procedure above was used with 6-methoxy-1*H*-indol-3-yl-carboxaldehyde (**18c**)[27] (350 mg, 2.0 mmol) and TMSCN (0.35 mL, 2.6 mmol) in acetonitrile (10 mL) to give **19c** (364 mg, 66%) as a yellow oil. Reaction time 2 h. IR ($CHCl_3$) 3474, 3013, 2960, 2838, 1555, 1458, 1258, 1084, 852 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.09 (s, 1H), 7.53 (d, J=8.7 Hz, 1H), 7.37 (d, J=2.5 Hz, 1H), 6.92 (d, J=2.2 Hz, 1H), 6.77 (dd, J=8.7, 2.2 Hz, 1H), 6.11 (s, 1H), 3.79 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 156.0 (s), 137.3 (s), 123.6 (d), 120.1 (s), 119.2 (d), 119.0 (s), 110.6 (s), 109.8 (d), 94.9 (d), 57.1 (d), 55.2 (q), −0.2 (q); MS (ESI) m/z 273 $(M-H)^-$.

3.1.4. (2-Phenyl-1*H*-indol-3-yl)-(trimethylsiloxy)acetonitrile (19d). The procedure above was used with 2-phenyl-1*H*-indol-3-yl-carboxaldehyde (**18d**)[28] (442 mg, 2.0 mmol) and TMSCN (0.35 mL, 2.6 mmol) in acetonitrile (10 mL) to give **19d** (585 mg, 91%) as a yellow oil. Reaction time 3 h. IR ($CHCl_3$) 3460, 2959, 1454, 1255, 1078, 870 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.75 (s, 1H), 7.82 (d, J=7.6 Hz, 1H) 7.67–7.44 (m, 6H), 7.22–7.15 (m, 2H), 6.05 (s, 1H), 0.01 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 137.3 (s) 135.8 (s), 131.0 (s), 128.9 (d), 128.7 (d), 128.7 (d), 126.2 (s), 122.3 (d), 119.9 (d), 119.7 (s), 118.9 (d), 111.7 (d), 106.8 (s), 56.4 (d), −0.4 (q); MS (ESI) m/z 319 $(M-H)^-$.

3.1.5. (1*H*-Indol-3-yl)carbonyl nitrile (20a). A solution of DDQ (2.05 g, 9.0 mmol) in dioxane (60 mL) was added dropwise to compound **19a** (2.0 g, 8.2 mmol) dissolved in dioxane (10 mL) at room temperature. The mixture was stirred for 2 h and the solid formed was thereafter filtered off. The filtrate was evaporated, leaving a dark brown residue which was purified by column chromatography (CH_2Cl_2) to afford **20a** (1.27 g, 91%) as an off-white solid: mp 224–226°C [lit.[20] ~190°C (dec.)]; IR (KBr) 3230, 1622, 1514, 1435, 1234, 919, 744 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.89 (s, 1H), 8.63 (d, J=3.4 Hz, 1H), 8.06–8.03 (m, 1H), 7.60–7.57 (m, 1H), 7.37–7.30 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 158.5 (s), 141.3 (d), 137.5 (s), 124.9 (d), 124.1(s), 123.8 (d), 121.0 (d), 116.2 (s), 114.3 (s), 113.3 (d); MS (ESI) m/z 171 $(M+H)^+$.

3.1.6. (5-Bromo-1*H*-indol-3-yl)carbonyl nitrile (20b). The procedure above was used with compound **19b** (1.83 g, 5.7 mmol) and DDQ (1.42 g, 6.2 mmol). Purification by column chromatography hexane/ethyl acetate (60:40) afforded **20b** (1.37 g, 97%) as a yellow solid: mp 265–266°C; IR (KBr) 3248, 3112, 2200 (w), 1612 (s), 1519, 1436, 1225, 802 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.04 (s, 1H), 8.68 (s, 1H), 8.14 (d, J=1.9 Hz, 1H), 7.58 (d, J=8.6 Hz, 1H), 7.53 (dd, J=8.6, 1.9 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 158.7 (s), 142.0 (d), 136.3 (s), 127.6 (d), 125.9 (s), 123.0 (d), 116.4 (s), 115.5 (s), 115.4 (d), 114.1 (s); MS (ESI) m/z 247 and 249 $(M-H)^-$; Anal. calcd for

$C_{10}H_5BrN_2O$: C, 48.22; H, 2.02; N, 11.25. Found: C, 48.29; H, 1.98; N, 11.19.

3.1.7. (6-Methoxy-1*H*-indol-3-yl)carbonyl nitrile (20c). The procedure above was used with compound **19c** (164 mg, 0.60 mmol) and DDQ (150 mg, 0.66 mmol). Reaction time 0.5 h. Trituration of the crude product with hexane/ethyl acetate (60:40) afforded **20c** (70 mg, 58%) as a yellow solid. An analytical sample was obtained by recrystallization from 2-propanol: mp 236–237°C; IR (KBr) 3212, 1614, 1523, 1446, 1431, 1382, 1232, 1162, 1093, 824 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.69 (br s, 1H), 8.51 (s, 1H), 7.91 (d, J=8.7 Hz, 1H), 7.06 (d, J=2.3 Hz, 1H), 6.98 (dd, J=8.7, 2.3 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 158.2 (s), 157.7 (s), 140.9 (d), 138.8 (s), 121.6 (d), 117.9 (s), 116.4 (s), 114.4 (s), 113.2 (d), 96.5 (d), 55.4 (q); MS (ESI) m/z 199 $(M-H)^-$; Anal. calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.78; H, 3.99; N, 13.84.

3.1.8. (2-Phenyl-1*H*-indol-3-yl)carbonyl nitrile (20d). The procedure above was used with compound **19d** (920 mg, 2.87 mmol) and DDQ (724 mg, 3.19 mmol). Reaction time 8 h. Trituration of the crude product with hexane/ethyl acetate (60:40) afforded **20d** (640 mg, 90%) as a yellow solid. An analytical sample was obtained by recrystallization from 2-propanol: mp 261–262°C; IR (KBr) 3222, 1583, 1453, 1428, 1366, 1242, 1197, 949, 746 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.03 (br s, 1H), 8.19–8.16 (m, 1H), 7.81–7.78 (m, 2H), 7.63–7.53 (m, 4H), 7.39–7.36 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 159.5 (s), 151.5 (s), 135.8 (s), 130.8 (d), 130.7 (d), 129.1 (s), 128.3 (d), 126.2 (s), 124.8 (d), 123.8 (d), 128.8 (d), 114.5 (s), 112.7 (d), 112.1 (s); MS (ESI) m/z 245 $(M-H)^-$; Anal. calcd for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09; N, 11.38. Found: C, 77.96; H, 4.03; N, 11.32.

3.1.9. (1*H*-Indol-3-yl-carbonyl)ethyl imidate hydrochloride (21a). Compound **20a** (289 mg, 1.70 mmol) was dissolved in dry ether (150 mL) and ethanol (0.11 mL, 1.87 mmol) was added. A continuous flow of gaseous hydrogen chloride was introduced into the solution at 0°C over approximately 6 h. The resulting mixture was stored at −20°C overnight and the precipitate was thereafter collected by filtration, washed with dry ether and dried to give **21a** (318 mg, 74%) as a yellow solid. This material was used directly in the next step: mp 225–227°C (dec.); IR (KBr) 3155, 1628, 1507, 1437, 1236, 1159, 848, 751, 638 cm^{-1}; MS (ESI) m/z 215 $(M-H)^-$; HRMS (FAB+) m/z calcd for $C_{12}H_{13}N_2O_2$ $(M+H)^+$ 217.0977, found 217.0982.

3.1.10. (5-Bromo-1*H*-indol-3-yl-carbonyl)ethyl imidate hydrochloride (21b). The procedure above was used with compound **20b** (249 mg, 1.00 mmol) and ethanol (0.06 mL, 1.10 mmol) to give **21** (197 mg, 59%) as a yellow solid. This material was used directly in the next step: mp 229.5–231°C (dec.); IR (KBr) 3226 (b), 1613, 1519, 1451, 1225, 886, 802 cm^{-1}; MS (ESI) m/z 293 and 295 $(M-H)^-$; HRMS (FAB+) m/z calcd for $C_{12}H_{12}N_2O_2{}^{79}Br$ $(M+H)^+$ 295.0082, found 295.0083.

3.1.11. 2-(1*H*-Indole-carbonyl)-5-[1-(6-methoxy-1*H*-indol-3-yl)-meth-(*Z*)-ylidene]-3,5-dihydro-imidazol-4-one (23a). To a stirred suspension of **21a** (96 mg, 0.38 mmol) and triethylamine (0.10 mL, 0.76 mmol) in dioxane (2 mL) was added 6-MeOTrpOEt (**22**) (100 mg, 0.38 mmol) dissolved in 1,4-dioxane (8 mL). The mixture was kept at 60°C for 2.5 days, a dark red color appeared with time. After cooling, the solvent was evaporated and the residue subjected to column chromatography using ethyl acetate as eluent to yield compound **23a** (42 mg, 29%) as a red solid. An analytically pure sample was obtained by crystallization from MeOH, which afforded **23a** as dark red crystals: mp 302.5–304.5°C; IR (KBr) 3231, 1673, 1613, 1593, 1513, 1490, 1441, 1411, 1362, 1228, 1156, 1119, 975 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.32 (br s, 1H), 12.11 (br s, 1H), 11.72 (br s, 1H), 9.02 (s, 1H), 8.49 (br, 1H), 8.34–8.31 (m, 2H), 7.60–7.56 (m, 2H), 7.32–7.25 (m, 2H), 7.03 (d, J=2.3 Hz, 1H), 6.91 (dd, J=8.8, 2.3 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 177.1 (s), 169.6 (s), 156.8 (s), 153.9 (s), 138.2 (s), 137.1 (s), 136.3 (d), 135.4 (d), 134.7 (s), 127.1 (d), 126.3 (s), 123.5 (d), 122.5 (d), 121.8 (d), 121.4, (d), 120.1 (s), 113.4 (s), 112.6 (s), 112.6 (d), 111.2 (d), 95.5 (d), 55.3 (q); MS (ESI) m/z 383 $(M-H)^-$; HRMS (FAB+) m/z calcd for $C_{22}H_{17}N_4O_3$ $(M+H)^+$ 385.1301, found 385.1300.

3.1.12. 2-(5-Bromo-1*H*-indole-carbonyl)-5-[1-(6-methoxy-1*H*-indol-3-yl)-meth-(*Z*)-ylidene]-3,5-dihydro-imidazol-4-one (23b). The procedure above was used with compound **21b** (218 mg, 0.66 mmol), triethylamine (0.18 mL, 1.32 mmol) and 6-MeOTrpOEt (**22**) (173 mg, 0.66 mmol) to give **23b** (94 mg, 31%) as a red solid. An analytically pure sample was obtained by crystallization from MeOH, which afforded **23b** as dark red crystals: mp 323.5–325.5°C; IR (KBr) 3393, 3336, 3114, 1680, 1615, 1572, 1495, 1412, 1348, 1238, 1160, 979, 844 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.27 (br, 2H), 11.76 (br s, 1H), 9.04 (s, 1H), 8.45 (br, 1H), 8.45 (d, J=1.9 Hz, 1H), 8.33 (s, 1H), 7.61 (s, 1H), 7.59 (d, J=8.6 Hz, 1H), 7.46 (dd, J=8.6, 1.9 Hz, 1H), 7.03 (d, J=2.2 Hz, 1H), 6.90 (dd, J=8.8, 2.2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 177.1 (s), 169.5 (s), 156.8 (s), 153.5 (s), 138.2 (s), 138.1 (d), 135.7 (d), 135.1 (s), 134.6 (s), 128.1 (s), 127.4 (d), 126.0 (d), 123.5 (d), 121.8 (d), 120.1 (s), 115.3 (s), 114.7 (d), 112.8 (s), 112.6 (s), 111.2 (d), 95.5 (d), 55.9 (q); MS (ESI) m/z 461 and 463 $(M-H)^-$; HRMS (FAB+) m/z calcd for $C_{22}H_{16}N_4O_3{}^{79}Br$ $(M+H)^+$ 463.0406, found 463.0423.

3.1.13. Rhopaladin A (1). To a suspension of compound **23b** (10.0 mg, 0.021 mmol) in dichloromethane (10 mL) at −78°C under nitrogen atmosphere was added BBr_3 in dichloromethane (1 M, 0.65 mL, 0.65 mmol). The mixture was allowed to reach room temperature over 4.5 days, saturated aqueous $NaHCO_3$ (15 mL) was thereafter added, followed by extraction with ethyl acetate (25 mL) containing a small amount of MeOH (~1%). The aqueous layer was extracted once more with ethyl acetate (25 mL) and the combined organic phases were washed with brine (40 mL), dried over Na_2SO_4 and finally evaporated. The dark red residue was subjected to gradient column chromatography starting with ethyl acetate/hexane (70:30) with increasing amounts of ethyl acetate to yield rhopaladin A (**1**) (8.0 mg, 81%) as a red solid. An analytically pure sample was obtained by crystallization from MeOH, which afforded **1** as dark red crystals. The spectral data of this material were identical with those reported previously:[5]

mp 299.0–300.5°C; IR (KBr) 3356, 3218, 1683, 1623, 1494, 1445, 1416, 1351, 1264, 1140, 976, 886 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.10 (br, 2H), 11.74 (br s, 1H), 9.32 (br s, 1H), 9.03 (s, 1H), 8.44 (d, J=1.9 Hz, 1H), 8.33 (br, 1H), 8.27 (s, 1H), 7.58 (d, J=8.6 Hz, 1H), 7.57 (s, 1H), 7.42 (dd, J=8.6, 1.9 Hz, 1H), 6.88 (d, J=2.1 Hz, 1H), 6.75 (dd, J=8.6, 2.1 Hz, 1H); MS (ESI) m/z 447 and 449 $(M-H)^-$; HRMS (FAB+) m/z calcd for $C_{21}H_{14}N_4O_3{}^{79}Br$ $(M+H)^+$ 449.0249, found 449.0235.

3.1.14. Rhopaladin B (2). The procedure above was used with compound **23a** (5.0 mg, 0.013 mmol) and BBr_3 in dichloromethane (1 M, 0.16 mL, 0.16 mmol) to give rhopaladin B (**2**) (3.0 mg, 62%) after gradient column chromatography starting with ethyl acetate/hexane (70:30) with increasing amounts of ethyl acetate. An analytically pure sample was obtained by crystallization from MeOH, which afforded **2** as dark red crystals: mp 239.5–241.5°C; IR (KBr) 3251, 2426, 2292, 1676, 1622, 1593, 1509, 1499, 1326, 1227, 921 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.36 (br s, 1H), 11.95 (br s, 1H), 11.69 (br s, 1H), 9.31 (br s, 1H), 9.01 (s, 1H), 8.36 (br, 1H), 8.34–8.31 (m, 1H), 8.26 (s, 1H), 7.59–7.55 (m, 2H), 7.33–7.26 (m, 2H), 6.88 (d, J=2.1 Hz, 1H) 6.72 (dd, J=8.6, 2.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 177.1 (s), 169.6 (s), 154.6 (s), 153.5 (s), 138.5 (s), 137.1 (d), 136.3 (s), 135.1 (d), 134.3 (s), 127.2 (d), 126.3 (s), 123.4 (d), 122.5 (d), 121.7 (d), 121.4 (d), 119.1 (s), 113.4 (s), 112.7 (s), 112.5 (d), 111.6 (d), 97.6 (d); MS (ESI) m/z 369 $(M-H)^-$; HRMS (FAB+) m/z calcd for $C_{21}H_{15}N_4O_3$ $(M+H)^+$ 371.1144, found 371.1148.

3.1.15. Rhopaladin C (3). To a solution of **21b** (100 mg, 0.30 mmol) and triethylamine (0.08 mL, 0.60 mmol) in dioxane (8 mL) was added Trp–OMeHCl (77 mg, 0.30 mmol). The mixture was kept at 60°C for 3 days, during that period a dark red color appeared. After cooling, the solvent was evaporated and the residue subjected to column chromatography using ethyl acetate as eluent to yield rhopaladin C (**3**) (50 mg, 38%) as a red solid. An analytically pure sample was obtained by crystallization from MeOH, which afforded **3** as dark red crystals: mp 332.5–333.5°C; IR (KBr) 3266, 3101, 2933, 1666, 1589, 1490, 1420, 1235, 1132, 975, 840, 747 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.39 (br s, 1H), 12.39 (br s, 1H), 11.79 (br s, 1H), 9.07 (s, 1H), 8.49 (s, 1H), 8.49–8.45 (br s, 1H), 8.47 (d, J=1.9 Hz, 1H), 7.86 (s, 1H), 7.59–7.53 (m, 2H), 7.46 (dd, J=8.6, 1.9 Hz, 1H), 7.31–7.21 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 177.1 (s), 169.5 (s), 153.9 (s), 138.3 (d), 137.0 (s), 135.7 (d), 135.1 (s), 134.9 (s), 128.1 (s), 126.9 (d), 126.5 (s), 126.1 (d), 123.5 (d), 123.2 (d), 121.5 (d), 120.4 (d), 115.3 (s), 114.7 (d), 112.8 (s), 112.5 (d), 112.1 (s); MS (ESI) m/z 431 and 433 $(M-H)^-$; HRMS (FAB+) m/z calcd for $C_{21}H_{14}N_4O_2{}^{79}Br$ $(M+H)^+$ 433.0300, found 433.0292.

3.1.16. Rhopaladin D (4). The procedure above was used with **21a** (105 mg, 0.42 mmol), triethylamine (0.12 mL, 0.83 mmol) and Trp–OMeHCl (107 mg, 0.42 mmol) to give rhopaladin D (**4**) (52 mg, 35%) after column chromatography using ethyl acetate as eluent. An analytically pure sample was obtained by crystallization from MeOH, which afforded **4** as dark red crystals: mp 315.5–317.5°C (lit.[6] 287–290°C); IR (KBr) 3436, 3284, 2934, 1162, 1612, 1594, 1581, 1490, 1426, 1359, 1232, 1131, 981, 835, 741 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.31 (br, 2H), 11.74 (br s, 1H), 9.05 (s, 1H), 8.48 (br, 2H), 8.35–8.32 (m, 1H), 7.66 (s, 1H), 7.61–7.53 (m, 2H), 7.32–7.22 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 177.2 (s), 169.6 (s), 154.3 (s), 137.3 (s), 137.0 (d), 136.4 (s), 135.6 (d), 134.9 (s), 126.6 (s), 126.5 (s), 126.3 (d), 123.5 (d), 123.2 (d), 122.6 (d), 121.5 (d), 121.4 (d), 120.5 (d), 113.4 (s), 112.6 (d), 112.6 (d), 112.1 (s); MS (ESI) m/z 353 $(M-H)^-$; HRMS (EI) m/z calcd for $C_{21}H_{14}N_4O_2$ (M^+) 354.1117, found 354.1120.

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