

Short and Highly Efficient Synthesis of Lipid Peroxidation Inhibitor Pyrrolostatin and Some Analogues Thereof

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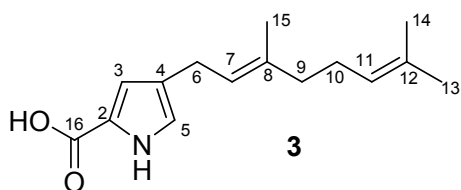
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Materials and Methods

All reagents were used as purchased from commercial suppliers. All dry solvents were purified using a solvent purification system. All reactions were performed under an atmosphere of dry nitrogen unless otherwise mentioned. Reactions were monitored by **thin layer chromatography** using silica or aluminium oxide precoated aluminium plates and stained with vanillin [vanillin (1 g), H₂SO_{4 conc} (10 mL), AcOH (20 mL) ethanol (170 mL)] or ceric ammonium molybdate [phosphomolybdic acid (25 g), Ce(SO₄)₂·2 H₂O (10 g), H₂SO_{4 conc} (60 mL), H₂O (940 mL)]. **Chromatographic purification** was performed as flash chromatography on silica gel (particle size 0.040–0.063 mm) or aluminium oxide (particle size 0.060–0.200 mm). Yields refer to chromatographically purified and spectroscopically pure compounds. **NMR spectra** were recorded on a 300 MHz (300 MHz for ¹H and 75 MHz for ¹³C acquisitions), a 400 MHz (400 MHz for ¹H and 100 MHz for ¹³C acquisitions), a 500 MHz (500 MHz for ¹H and 125 MHz for ¹³C acquisitions) and a 600 MHz (600 MHz for ¹H and 150 MHz for ¹³C acquisitions) spectrometer. Chemical shifts δ are reported in ppm with tetramethylsilane or the solvent resonance as the internal standard. Coupling constants J are given in Hertz (Hz). Multiplicities are classified as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet and combinations thereof, or m = multiplet or br = broad signal. Two-dimensional NMRs (H-COSY, HSQC, HMBC) were used for the assignment of all final compounds. **High resolution mass spectra** were obtained on an ESI-TOF mass-spectrometer. **IR spectra** were recorded on a FT-IR spectroscope by attenuated total reflection (ATR). Absorbance frequencies $\tilde{\nu}$ are reported in reciprocal centimeters (cm⁻¹). The reported **melting points** are uncorrected. For simplicity, the numbering of the carbon atoms of a given structure does not follow the IUPAC rules.



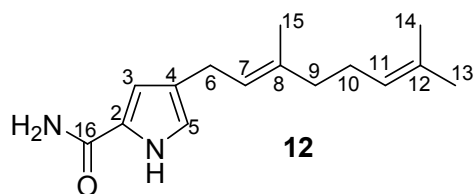
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3-Bromo-1(triisopropylsilyl)pyrrole (2.27 g, 7.52 mmol, 1.00 equiv.) in dry tetrahydrofuran (40 mL) was cooled to $-78\text{ }^{\circ}\text{C}$. *Tert*-butyllithium (1.9 M in heptane, 7.90 mL, 15.0 mmol, 2.00 equiv.) was added dropwise and the yellowish solution was stirred for 5 min. Freshly prepared *trans,trans*-geranyl bromide (1.96 g, 9.03 mmol, 1.20 equiv.) in dry tetrahydrofuran (5 mL) was added dropwise over 5 min and the mixture was stirred for 4 h with warming to $-50\text{ }^{\circ}\text{C}$. The reaction was quenched with brine (40 mL), the aqueous layer was extracted with ethyl acetate (3 x 40 mL), the combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL) and tetra-*n*-butylammonium fluoride trihydrate (2.85 g, 9.02 mmol, 1.20 equiv.) was added at rt. The reaction was stirred at rt for 30 min and the solvent was removed under reduced pressure. Flash chromatography (hexanes/ethyl acetate/ Et_3N = 85:10:5, silica) of the residue gave 3-geranyl pyrrole (1.45 g, 7.14 mmol, 95%) together with some impurities as a yellowish oil. The crude product was dissolved in dry diethyl ether (20 mL) and trichloroacetyl chloride (796 μL , 7.14 mmol, 1.00 equiv.) was added dropwise over 2 min. After stirring for 2 h at rt, the reaction mixture was quenched with brine (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was dissolved in tetrahydrofuran (10 mL), NaOH (2 M, 10 mL) was added and the residue heated at $75\text{ }^{\circ}\text{C}$ for 2 h. The residue was acidified with NaHSO_4 (1 M, 30 mL) and extracted with ethyl acetate (3 x 30 mL). Flash chromatography (hexanes/ethyl acetate/ AcOH = 85:10:5, silica) of the residue gave pyrrolostatin (**3**) along with its regioisomer as a brown residue. Precipitation from dichloromethane with hexane (1:50, 20 mL) gave pyrrolostatin (**3**) (898 mg, 48%) as a colorless amorphous powder.

mp: $121\text{ }^{\circ}\text{C}$; **$^1\text{H NMR}$** (400 MHz, $\text{MeOH-}d_4$): δ = 6.70 (br s, 1 H, H-5), 6.66 (br s, 1 H, H-3), 5.35–5.28 (m, 1 H, H-11), 5.15–5.07 (m, 1 H, H-7), 3.17 (d, J = 7.3 Hz, 2 H, H-6), 2.15–2.02 (m, 4 H, H-9, H-10), 1.68 (s, 3 H, H-15), 1.67 (s, 3 H, H-13), 1.60 (s, 3 H, H-14) ppm; **$^{13}\text{C NMR}$** (100 MHz, $\text{MeOH-}d_4$): δ = 164.5 (C-16), 136.1 (C-8), 132.2 (C-12), 126.2 (C-2), 125.4 (C-7), 125.0 (C-11), 123.5 (C-4), 122.3 (C-5), 116.3 (C-3), 40.8 (C-9), 27.7 (C-10), 26.3 (C-6), 25.9 (C-13), 17.8 (C-14), 16.0 (C-15) ppm; **IR** (ATR): $\tilde{\nu}$ = 3345, 2968, 2913, 2854, 2641, 1672, 1485, 1434, 1379, 1347, 1289, 1279, 1211, 1114, 965, 872, 836, 762, 698,

631, 599, 582, 563 cm⁻¹; **HRMS** (ESI-TOF) m/z : [M+H]⁺ calcd for C₁₅H₂₃NO₂ 248.1645; found: 248.1648.

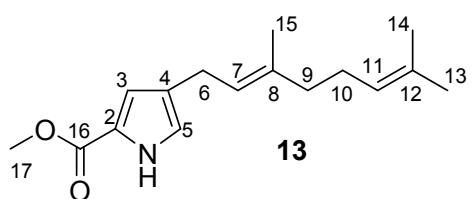
All of these data are in accord with previously published data.^{1,2}



Pyrrolostatin (**3**) (124 mg, 0.50 mmol, 1.00 equiv.) in dry dichloromethane (20 mL) was stirred at rt. *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (228 mg, 0.60 mmol, 1.20 equiv.) was added and the solution stirred for 30 min. *N,N*-diisopropylethylamine (209 μL, 1.20 mmol, 2.40 equiv.) and ammonia (7 M in methanol, 5 mL) were added and the reaction stirred for 15 h. After complete conversion of the starting material all volatiles were removed under reduced pressure. Flash chromatography (hexanes/ethyl acetate = 90:10, silica) of the residue gave product **12** (80 mg, 65%) as a white amorphous powder.

mp: 80 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 9.40 (br s, 1 H, N-H), 6.73 (br s, 1 H, H-5), 6.44 (br s, 1 H, H-3), 5.65 (br s, 2 H, NH₂), 5.37–5.28 (m, 1 H, H-11), 5.15–5.07 (m, 1 H, H-7), 3.19 (d, *J* = 7.2 Hz, 2 H, H-6), 2.14–2.00 (m, 4 H, H-9, H-10), 1.68 (br s, 6 H, H-13, H-15), 1.61 (s, 3 H, H-14) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ = 163.0 (C-16), 135.9 (C-8), 131.6 (C-12), 125.7 (C-2), 124.7 (C-7), 124.4 (C-11), 123.2 (C-4), 120.2 (C-5), 110.5 (C-3), 39.8 (C-9), 26.8 (C-10), 25.9 (C-6), 25.5 (C-13), 17.9 (C-14), 16.1 (C-15) ppm; **IR** (ATR): $\tilde{\nu}$ = 3394, 3335, 3178, 2968, 2913, 2853, 1636, 1608, 1485, 1430, 1125, 837, 821, 560 cm⁻¹;

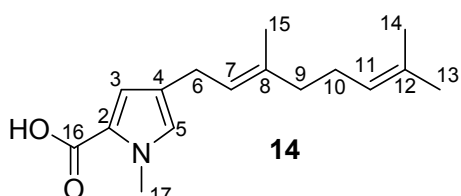
HRMS (ESI-TOF) m/z : [M+H]⁺ calcd for C₁₅H₂₃N₂O 247.1805; found: 247.1811.



Pyrrolostatin (**3**) (62 mg, 0.25 mmol, 1.00 equiv.) was dissolved in dry toluene/methanol (7:1, 8 mL) and stirred at rt. (trimethylsilyl)diazomethane (2.0 M in diethyl ether, 150 μL, 0.30 mmol, 1.20 equiv.) was added and the solution stirred for 2 h. After complete conversion of the starting material all volatiles were removed under reduced pressure. Flash chromatography (hexanes/ethyl acetate = 90:10, silica) of the residue gave product **13** (65 mg, 99%) as a colorless oil.

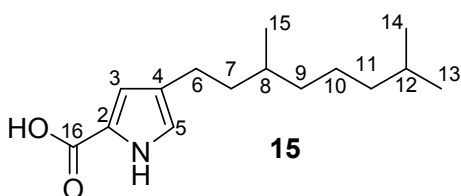
¹H NMR (600 MHz, CDCl₃): δ = 8.98 (br s, 1 H, NH), 6.79–6.68 (m, 2 H, H-3, H-5), 5.37–5.27 (m, 1 H, H-11), 5.16–5.06 (m, 1 H, H-7), 3.83 (s, 3 H, H-17), 3.19 (d, *J* = 7.2 Hz, 2 H, H-6), 2.15–2.00 (m, 4 H, H-9, H-10), 1.69 (br s, 3 H, H-13), 1.68 (br s, 3 H, H-15), 1.61 (s, 3 H, H-14) ppm; **¹³C NMR** (150 MHz, CDCl₃): δ = 161.8 (C-16), 135.9 (C-8), 131.6 (C-12), 126.0 (C-2), 124.4 (C-7), 123.1 (C-11), 122.4 (C-4), 120.8 (C-5), 115.1 (C-3), 51.5 (C-17),

39.8 (C-9), 26.7 (C-10), 25.8 (C-6), 25.5 (C-13), 17.8 (C-14), 16.1 (C-15) ppm; **IR** (ATR): $\tilde{\nu} = 3314, 2915, 2854, 1682, 1480, 1437, 1395, 1204, 1104, 998, 971, 836, 768 \text{ cm}^{-1}$; **HRMS** (ESI-TOF) m/z : $[M+H]^+$ calcd for $C_{16}H_{24}NO_2$ 262.1802; found: 262.1805.



NaH (60% dispersion in mineral oil, 48.0 mg, 1.20 mmol, 1.20 equiv.) was added to a solution of methyl ester **13** (261 mg, 1.00 mmol, 1.00 equiv.) in dry DMF (10 mL) at 0 °C and the solution was stirred for 1 h. Methyl iodide (93 μ L, 1.50 mmol, 1.50 equiv.) was added and the solution was stirred overnight. After complete conversion of the starting material diethyl ether (20 mL) and H_2O (20 mL) were added. The phases were separated and the organic phase was washed with H_2O (3 x 10 mL). The organic phase was dried over Na_2SO_4 and all volatiles were removed under reduced pressure. The crude residue was dissolved in a mixture of tetrahydrofuran/methanol/ H_2O (9 mL/6 mL/3 mL), saturated $LiOH_{aq}$ (0.5 mL) was added and the mixture stirred at rt overnight. After complete conversion the reaction mixture was acidified with $NaHSO_4$ (1 M, 5 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over Na_2SO_4 and all volatiles were removed. Flash chromatography (hexanes/ethyl acetate/AcOH = 85:10:5, silica) of the residue gave product **14** (139 mg, 0.53 mmol 53%) as a colorless oil.

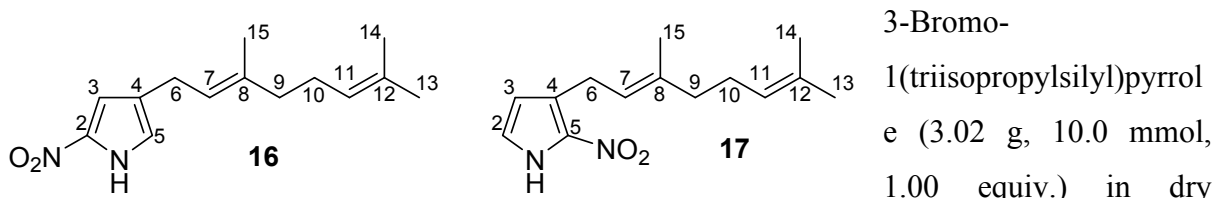
1H NMR (500 MHz, $CDCl_3$): $\delta = 6.89$ (br s, 1 H, H-5), 6.61 (br s, 1 H, H-3), 5.34–5.27 (m, 1 H, H-11), 5.14–5.07 (m, 1 H, H-7), 3.86 (s, 3 H, H-17), 3.14 (d, $J = 7.2$ Hz, 2 H, H-6), 2.14–2.00 (m, 4 H, H-9, H-10), 1.69 (s, 3 H, H-13), 1.67 (s, 3 H, H-15), 1.61 (s, 3 H, H-14) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$): $\delta = 165.6$ (C-16), 135.9 (C-8), 131.6 (C-12), 129.0 (C-3), 124.4 (C-7), 123.7 (C-2), 123.1 (C-11), 121.2 (C-4), 119.3 (C-5), 39.8 (C-9), 37.0 (C-17), 26.8 (C-10), 25.9 (C-13), 25.3 (C-6), 17.9 (C-14), 16.2 (C-15) ppm; **IR** (ATR): $\tilde{\nu} = 2965, 2914, 2853, 1657, 1448, 1270, 1137, 1104, 1056, 832, 727, 613, 561 \text{ cm}^{-1}$; **HRMS** (ESI-TOF) m/z : $[M+H]^+$ calcd for $C_{16}H_{24}NO_2$ 262.1802; found: 262.1804.



Pd/C (10%, 42 mg, 0.025 mmol, 0.1 equiv.) was added to a stirred solution of pyrrolostatin (**3**) (62 mg, 0.25 mmol, 1.00 equiv.) in methanol at rt. The solution was stirred under a hydrogen atmosphere (1 bar) for

3 h. The reaction mixture was filtered over Na₂SO₄ and all volatiles were removed. The pure product **15** (65 mg, 99%) was isolated as a colorless amorphous solid.

mp: 132 °C; **¹H NMR** (500 MHz, CDCl₃): δ = 8.98 (br s, 1 H, N-H), 6.89 (s, 1 H, H-5), 6.80 (s, 1 H, H-3), 2.60–2.38 (m, 2 H, H-6), 1.67–1.08 (m, 10 H, H-7 to H-12), 0.91 (s, 3 H, H-13/H-14/H-15), 0.87 (s, 3 H, H-13/H-14/H-15), 0.86 (s, 3 H, H-13/H-14/H-15) ppm; **¹³C NMR** (125 MHz, CDCl₃): δ = 165.4 (C-16), 127.7 (C-4), 122.0 (C-2), 121.4 (C-5), 117.0 (C-3), 39.5, 38.4, 37.3, 32.5, 28.1, 24.9, 24.3, 22.9, 22.8, 19.7 (C-6 to C-15) ppm; **IR** (ATR): $\tilde{\nu}$ = 3365, 3075, 2954, 2922, 1681, 1488, 1439, 1343, 1279, 1207, 1129, 1113, 965, 883, 835, 818, 764, 681, 632, 610, 574 cm⁻¹; **HRMS** (ESI-TOF) m/z : [M+H]⁺ calcd for C₁₅H₂₆NO₂ 252.1958; found: 252.1962.

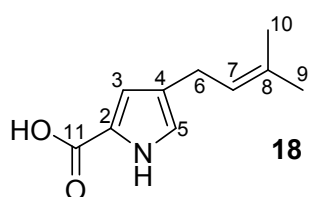


tetrahydrofuran (50 mL) was cooled to -78 °C. *Tert*-butyllithium (1.9 M in heptane, 10.5 mL, 20.0 mmol, 2.00 equiv.) was added dropwise and the yellowish solution was stirred for 5 min. Freshly distilled *trans,trans*-geranyl bromide (2.61 g, 12.0 mmol, 1.20 equiv.) in dry tetrahydrofuran (5 mL) was added dropwise over 5 min and the mixture was stirred for 4 h with warming to -50 °C. The reaction was quenched with brine (50 mL), the aqueous layer was extracted with ethyl acetate (3 x 50 mL), the combined organic layers were dried over Na₂SO₄ and the solvents were removed under reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL) and tetra-*n*-butylammonium fluoride trihydrate (3.79 g, 12.0 mmol, 1.20 equiv.) was added at rt. The reaction was stirred for 30 min at rt and the solvent was removed under reduced pressure. Flash chromatography (hexanes/ethyl acetate/Et₃N = 85:10:5, silica) of the residue gave the sensitive 3-geranylated pyrrole. Immediately after the purification of geranylpyrrole it was dissolved in nitroethane (30 mL) and cooled to 0 °C. In a separate flask HNO₃ (>90%, 417 μL, 10.0 mmol, 1.00 equiv.) was added to cooled acetic anhydride (5 mL) and stirred for 5 min. The nitronium acetate solution was added dropwise to the nitroethane solution of geranylpyrrole at 0 °C and stirred for 1 h. After complete conversion toluene (100 mL) was added and all volatiles were removed under reduced pressure. Flash chromatography (hexanes/ethyl acetate = 95:5, silica) of the raw product gave 2-nitro-4-geranylpyrrole (**16**)

(247 mg, 1.00 mmol, 10 %) and 2-nitro-3-geranylpyrrole (**17**) (294 mg, 1.18 mmol, 12 %) as yellowish oils.

Analytical data for 2-nitro-4-geranyl pyrrole (**16**): $^1\text{H NMR}$ (300 MHz, CDCl_3): δ = 9.30 (br s, 1 H, N-H), 6.98–6.93 (m, 1 H, H-5), 6.78–6.71 (m, 1 H, H-3), 5.34–5.23 (m, 1 H, H-11), 5.14–5.04 (m, 1 H, H-7), 3.18 (d, J = 7.2 Hz, 2 H, H-6), 2.18–2.00 (m, 4 H, H-9 to H-10), 1.69 (s, 3 H, H-15), 1.67 (s, 3 H, H-13), 1.61 (s, 3 H, H-14) ppm; $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ = 164.5 (C-16), 137.1 (C-8), 131.6 (C-12), 127.1 (C-2), 124.1 (C-7), 122.3 (C-4), 121.5 (C-11), 121.0 (C-5), 110.8 (C-3), 39.6 (C-9), 26.5 (C-10), 25.7 (C-6), 25.3 (C-13), 17.7 (C-14), 16.0 (C-15) ppm; 3 IR (ATR): $\tilde{\nu}$ = 3314, 2915, 2854, 1682, 1480, 1437, 1395, 1204, 1104, 998, 971, 836, 768 cm^{-1} ; HRMS (ESI-TOF) $\frac{m}{z}$: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_2$ 249.1598; found: 249.1597.

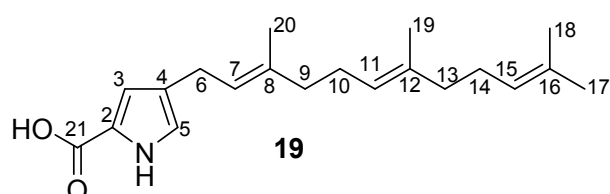
Analytical data for 2-nitro-3-geranyl pyrrole (**17**): $^1\text{H NMR}$ (300 MHz, CDCl_3): δ = 9.45 (br s, 1 H, N-H), 6.86 (t, J = 3.0 Hz, 1 H, H-2), 6.23–6.16 (m, 1 H, H-3), 5.39–5.29 (m, 1 H, H-11), 5.15–5.05 (m, 1 H, H-7), 3.60 (d, J = 7.3 Hz, 2 H, H-6), 2.17–2.00 (m, 4 H, H-9, H-10), 1.69 (s, 6 H, H-13, H-15), 1.60 (s, 3 H, H-14) ppm; $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ = 137.8 (C-8), 131.7 (C-12), 129.6 (C-2), 124.3 (C-4), 122.1 (C-11), 120.4 (C-7), 112.5 (C-3), 39.8 (C-9), 26.7 (C-10), 25.9 (2 C, C-6 and C-13), 17.8 (C-14), 16.3 (C-15) ppm; 3 IR (ATR): $\tilde{\nu}$ = 3325, 2917, 2859, 1685, 1483, 1429, 1200, 1115, 993, 968 cm^{-1} ; HRMS (ESI-TOF) $\frac{m}{z}$: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_2$ 249.1598; found: 249.1595.



Compound **18** was synthesized according to the procedure described for the synthesis of pyrrolostatin (**3**) from 3-bromo-1-(triisopropylsilyl)pyrrole (3.66 g, 12.1 mmol, 1.00 equiv.) and 3,3-dimethylallyl bromide (1.67 mL, 14.5 mmol, 1.20 equiv.). Flash chromatography (hexanes/ethyl acetate/AcOH = 85:10:5, silica) gave the product along with its regioisomer as an off-white solid. Precipitation from dichloromethane with hexane (1:50, 20 mL) gave compound **18** (915 mg, 5.11 mmol, 42%) as a colorless amorphous powder.

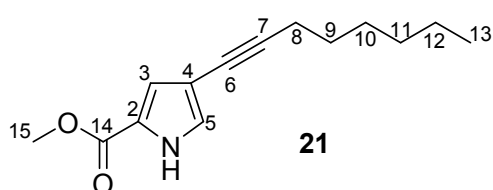
mp: 180 °C (decomposition); $^1\text{H NMR}$ (600 MHz, $\text{DMSO}-d_6$): δ = 12.05 (br s, 1 H, COOH), 11.38 (br s, 1 H, NH), 6.69 (s, 1 H, H-5), 6.51 (s, 1 H, H-3), 5.30–5.22 (m, 1 H, H-7), 3.08 (d, J = 4.2 Hz, 2 H, H-6), 1.68 (s, 3 H, H-9/H-10), 1.63 (s, 3 H, H-9/H-10) ppm; $^{13}\text{C NMR}$ (150 MHz, $\text{DMSO}-d_6$): δ = 161.8 (C-11), 130.6 (C-8), 123.9 (C-2), 123.8 (C-7),

122.5 (C-5), 120.9 (C-4), 114.3 (C-3), 25.4 (C-6), 25.0 (C-9/C-10), 17.5 (C-9/C-10) ppm; **IR** (ATR): $\tilde{\nu} = 3356, 2968, 2920, 1683, 1485, 1438, 1350, 1235, 1115, 967, 857, 816, 763, 689, 612 \text{ cm}^{-1}$; **HRMS** (ESI-TOF) m/z : $[M+H]^+$ calcd for $C_{10}H_{14}NO_2$ 180.1019; found: 180.1018.



3-Farnesylpyrrol⁴ (6.00 g, 22.1 mmol, 1.00 equiv.) was dissolved in diethyl ether (50 mL) at rt and trichloroacetyl chloride (2.59 mL, 23.2 mmol, 1.05 equiv.) was added dropwise. After 2 h reaction time all volatiles were removed and the residue was chromatographically purified (hexanes/ethyl acetate = 90:10, silica). The sensible product was dissolved in tetrahydrofuran (10 mL), NaOH (2 M, 60 mL) was added and the mixture was heated at 75 °C for 2 h. The solution was acidified with NaHSO₄ (1 M, 150 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried over Na₂SO₄, all volatiles were removed and the residue was purified by column chromatography (hexanes/ethyl acetate/AcOH = 90:5:5, silica). The regioisomerically pure product **19** (3.13 g, 9.94 mmol, 45 %) was isolated as a colorless amorphous powder after precipitation from dichloromethane with hexane (1:50, 40 mL).

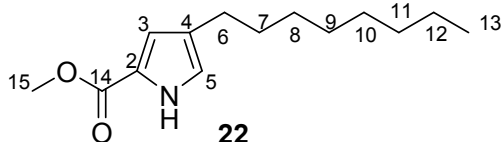
mp: 101-102 °C; **¹H NMR** (600 MHz, CDCl₃): $\delta = 9.04$ (br s, 1 H, N-H), 6.88 (br s, 1 H, H-3), 6.78 (br s, 1 H, H-5), 5.33 (t, $J = 7.2$ Hz, 1 H, H-7), 5.14–5.09 (m, 2 H, H-11/H-15), 3.20 (t, $J = 7.2$ Hz, 2 H, H-6), 2.14–1.98 (m, 8 H, H-9, H-10, H-13, H-14), 1.69 (s, 3 H, H-20), 1.68 (s, 3 H, H-17), 1.604 (s, 3 H, H-19), 1.598 (s, 3 H, H-18) ppm; **¹³C NMR** (150 MHz, CDCl₃): $\delta = 165.8$ (C-21), 136.1 (C-8), 135.3 (C-12), 131.5 (C-16), 126.6 (C-4), 124.5 (C-11/C-15), 124.3 (C-11/C-15), 123.0 (C-7), 122.1 (C-5), 121.6 (C-2), 117.1 (C-3), 39.9 (C-9/C-13), 39.8 (C-9/C-13), 26.9 (C-10/C-14), 26.7 (C-10/C-14), 25.8 (C-17), 25.5 (C-6), 17.8 (C-18), 16.2 (2 C, C-19/C-20) ppm; **IR** (ATR): $\tilde{\nu} = 3347, 2967, 2913, 2854, 1678, 1487, 1442, 1381, 1348, 1289, 1237, 1115, 966, 887, 873, 837, 772, 762, 699, 631 \text{ cm}^{-1}$; **HRMS** (ESI-TOF) m/z : $[M+H]^+$ calcd for $C_{20}H_{30}NO_2$ 316.2271; found: 316.2275.



Iodide **20** (251 mg, 1.00 mmol, 1.00 equiv.) was dissolved in dry and degassed dimethylformamide (5 mL). Successively, 1-octin (295 μ L, 2.00 mmol,

2.00 equiv.), triethylamine (557 μ L, 4.00 mmol, 4.00 equiv.), copper(I) iodide (10 mg, 0.05 mmol, 0.05 equiv.) and Pd(PPh₃)₄ (58 mg, 0.05 mmol, 0.05 equiv.) were added and the reaction mixture was stirred at 50 °C for 24 h. Then the reaction mixture was diluted with diethyl ether (50 mL) and extracted with H₂O (3 x 10 mL). The organic phase was dried over Na₂SO₄, all volatiles were removed under reduced pressure and the residue was purified by flash chromatography (hexanes/ethyl acetate = 90:10, silica) to yield product **21** (191 mg, 0.82 mmol, 82%) as a colorless oil.

¹H NMR (600 MHz, CDCl₃): δ = 9.10 (br s, 1 H, N-H), 7.04–7.03 (m, 1 H, H-5), 6.90–6.89 (m, 1 H, H-3), 3.84 (s, 3 H, H-15), 2.36 (t, J = 7.2 Hz, 2 H, H-8), 1.59–1.55 (m, 2 H, H-10/H-11), 1.45–1.40 (m, 2 H, H-10/H-11), 1.36–1.27 (m, 4 H, H-9, H-12), 0.90 (t, J = 6.9, 3 H, H-13) ppm; **¹³C NMR** (150 MHz, CDCl₃): δ = 161.3 (C-14), 125.8 (C-5), 122.4 (C-2), 118.1 (C-3), 107.7 (C-4), 89.3 (C-7), 73.9 (C-6), 51.8 (C-15), 31.5 (C-12), 29.0, 28.8 (C-10 to C-11), 22.7 (C-9), 19.6 (C-8), 14.2 (C-13) ppm; **IR** (ATR): $\tilde{\nu}$ = 3279, 2955, 2932, 2854, 1679, 1487, 1444, 1383, 1267, 1212, 1124, 979, 914, 846, 774, 742, 720, 635, 609 cm⁻¹; **HRMS** (ESI-TOF) $\frac{m}{z}$: [M+H]⁺ calcd for C₁₄H₂₀NO₂ 234.1489; found: 234.1489.

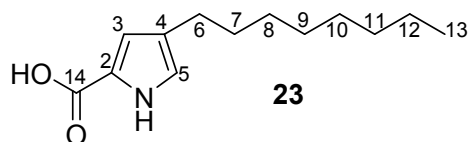


Pd/C (10%, 43 mg, 0.026 mmol, 0.1 equiv.) was added to a stirred solution of alkyne **21** (63 mg, 0.26 mmol, 1.00 equiv.) in methanol (10 mL) at rt.

The solution was stirred under a hydrogen atmosphere (1 bar) for 3 h. The reaction mixture was filtered over Na₂SO₄ and all volatiles were removed. Flash chromatography (hexanes/ethyl acetate = 90:10, silica) of the residue gave product **22** (61 mg, 99%) as a colorless amorphous solid.

mp: 56 °C; **¹H NMR** (500 MHz, CDCl₃): δ = 8.90 (br s, 1 H, N-H), 6.77–6.71 (m, 2 H, H-3, H-5), 3.83 (s, 3 H, H-15), 2.45 (t, J = 7.6 Hz, 2 H, H-6), 1.59–1.51 (m, 2 H, H-7), 1.36–1.22 (m, 10 H, H-8 to H-12), 0.88 (t, J = 7.0 Hz, 3 H, H-13) ppm; **¹³C NMR** (125 MHz, CDCl₃): δ = 161.7 (C-14), 127.0 (C-4), 122.3 (C-2), 120.7 (C-5), 115.1 (C-3), 51.5 (C-15), 32.0, 31.1, 29.6, 29.39, 29.37, 26.8 (C-6 to C-11), 22.8 (C-12), 14.3 (C-13) ppm; **IR** (ATR): $\tilde{\nu}$ = 3290, 2954, 2918, 2850, 1688, 1441, 1393, 1214, 1131, 1110, 993, 971, 769, 603 cm⁻¹;

HRMS (ESI-TOF) $\frac{m}{z}$: [M+H]⁺ calcd for C₁₄H₂₄NO₂ 238.1802; found: 238.1809.



23

Methyl ester **22** (795 mg, 3.35 mmol, 1.00 equiv.) was dissolved in a mixture of tetrahydrofuran/methanol/H₂O (9 mL/6 mL/3 mL) and KOH (940 mg, 16.8 mmol, 5.00 equiv.) was added. The resulting mixture was stirred for 20 h at rt. After complete conversion the reaction mixture was acidified with NaHSO₄ (1 M, 20 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic phases were dried over Na₂SO₄ and all volatiles were removed. Flash chromatography (hexanes/ethyl acetate/AcOH = 88:10:2 in hexanes, silica) of the residue gave product **23** (572 mg, 76%) as a colorless amorphous powder.

mp: 153 °C; **¹H NMR** (400 MHz, DMSO-*d*₆): δ = 12.02 (br s, 1 H, OH), 11.35 (br s, 1 H, NH), 6.72 (m, 1 H, H-5), 6.54 (m, 1 H, H-3), 2.36 (t, *J* = 7.5 Hz, 2 H, H-6), 1.54–1.42 (m, 2 H, H-7), 1.36–1.15 (m, 10 H, H-8 to H-12), 0.85 (t, *J* = 6.8 Hz, 3 H, H-13) ppm; **¹³C NMR** (100 MHz, DMSO-*d*₆): δ = 161.8 (C-14), 124.7 (C-4), 122.3 (C-2), 121.0 (C-5), 114.3 (C-3), 31.3, 30.6, 28.8, 28.7 (2 C), 26.2 (C-6 to C-11), 22.1 (C-12), 13.9 (C-13) ppm; **IR** (ATR): $\tilde{\nu}$ = 3366, 2952, 2918, 2849, 1665, 1574, 1486, 1435, 1341, 1277, 1216, 1129, 1114, 961, 883, 837, 817, 764, 593 cm⁻¹; **HRMS** (ESI-TOF) $\frac{m}{z}$: [M+H]⁺ calcd for C₁₃H₂₂NO₂ 224.1645; found: 224.1647.

Literature:

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