Total synthesis of (+)-epiquinamide

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Supporting Information

General information: Unless noted otherwise, materials were purchased from commercial suppliers and used without purification. Dichloromethane was freshly distilled from calcium hydride. THF was freshly distilled from sodium benzophenone ketyl. All air and moisture sensitive reactions were carried out under an inert atmosphere of dry argon. Column chromatography was performed using Acros silica gel (0.035–0.070 mm). TLC was performed using precoated silica gel plates (Merck 60 F₂₅₄). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Infrared spectra were recorded on an ATI Mattson Genesis FTIR spectrometer. ¹H NMR and ¹³C NMR spectra were measured on a Bruker DPX200 (200 MHz), a Bruker DMX300 (300 and 75 MHz, respectively) or a Varian 400 (400 MHz). Spectra are reported in units of ppm on the δ scale. Mass spectra were measured using a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. Melting points are uncorrected.

To stirred solution of **3a**¹ (1.50 g, 4.60 mmol) in CH₂Cl₂ (45 mL) were added allyltrimethylsilane (1.18 mL, 23 mmol) and BF₃·OEt₂ (3.68 mL, 9.20 mmol) at -30 °C. The reaction mixture was warmed to rt and stirred for 2 h, quenched with saturated aqueous NaHCO₃ (50 mL) and the aqueous phase was extracted with CH₂Cl₂ (2 × 40 mL). The combined organic phases were washed with brine (50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Flash chromatography (2:1-5:1 EtOAc:heptane) afforded product **5** as a colorless oil (1.40 g, 4.37 mmol, 95%). [α]_D²⁴ -80.9 (*c* 1.24, CH₂Cl₂). IR (film) 3451, 2950, 1735, 1696, 1412, 1296, 1208, 1010 cm⁻¹. ¹H NMR (300 MHz, CDCl₃, rotamers) δ 7.31–7.35 (m, 5H), 5.69–5.81 (m, 1H), 4.81–5.22 (m, 5H), 4.18–4.29 (m, 1H), 3.87–3.95 (m, 1H), 3.61–3.75 (m, 3H), 2.42 (bs, 1H), 2.04–2.16 (m, 3H), 1.73–1.81 (m, 1H), 1.57–1.70 (m, 2H). No clear ¹³C NMR due to rotamers. HRMS (FAB⁺): calcd for C₁₈H₂₄NO₅ (*M*+H⁺): 334.1654, found: 334.1656.

A solution of hydrogen bromide in acetic acid (33 wt%, 50 mL) was added to **5** (1.05 g, 3.27 mmol) and the resulting solution was stirred for 10 min at 0 °C. The mixture was concentrated *in vacuo*, followed by the addition of H₂O (40 mL) and toluene (40 mL). The aqueous phase was washed with toluene (2x 40 mL) and concentrated *in vacuo*, (azeotropically evaporated twice with toluene). The product was dissolved in MeOH (32 mL) and K₂CO₃ (587 mg, 4.25 mmol) was added. The mixture was diluted with H₂O (30 mL) and CH₂Cl₂ (30 mL) after 2 h and the aqueous phase was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were washed with brine (60 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Crude product **6** (547 mg, 2.75 mmol, 85%), obtained as a yellow oil, was used without further purification. ¹H NMR (200 MHz, CDCl₃) δ 5.76-5.96 (m, 1H), 5.16-5.28 (m, 2H), 3.75 (s, 3H), 3.25-3.40 (m, 2H), 2.71-2.81 (m, 1H), 2.40-2.50 (m, 1H), 2.30 (bs, 2H), 2.09-2.22 (m, 3H), 1.33-1.67 (m, 2H).

To a stirred solution of **6** (574 mg, 2.88 mmol) in CH₂Cl₂ (30 mL) were added Et₃N (478 μL, 3.46 mmol) and acryloyl chloride (245 μL, 3.02 mmol) at -60 °C. After 2 h the reaction mixture was quenched with 0.5M aqueous Na₂S₂O₅ (30 mL) and warmed to rt. The organic phase was washed with 0.5M aqueous Na₂S₂O₅ (2 × 30 mL), saturated aqueous NaHCO₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄. The solution was diluted with CH₂Cl₂ (110 mL) where after argon was bubbled through, followed by the addition of Grubbs 2nd generation ruthenium catalyst (238 mg, 0.29 mmol). After stirring overnight the mixture was concentrated *in vacuo* and dissolved in MeOH (30 mL). Pd/C (31 mg, 0.29 mmol) was added and the solution was stirred under H₂ (1 atm) for 2 h. The reaction mixture was filtered over Celite and the solvent was evaporated under reduced pressure. Flash chromatography (100:0-95:5 CH₂Cl₂:MeOH) afforded product **7** as a colorless oil (380 mg, 1.81 mmol, 63%). [α]_D²⁴ -91.0 (c 0.48, CH₂Cl₂). IR (film) 3408, 2950, 2872, 1744, 1614 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 3.98-4.00 (m, 1H), 3.73 (s, 3H), 3.66-3.72 (m, 1H), 3.19-3.24 (m, 1H), 2.34-2.48 (m, 2H), 2.26-2.32 (m, 1H), 2.06-2.18 (m, 2H), 1.86-1.97 (m, 2H), 1.79 (d, *J* = 5.1 Hz, 1H), 1.67-1.77 (m, 2H), 1.45-1.54 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 171.2, 171.0, 69.6, 60.6, 56.5, 52.0, 32.4, 30.2, 26.0, 23.7, 19.0. HRMS (FAB⁺): calcd for C₁₁H₁₈NO₄ (*M*+H⁺): 228.1236, found: 228.1226.

To a solution of **7** (306 mg, 1.46 mmol) in CH₂Cl₂ (15 mL) were added Et₃N (263 μL, 1.90 mmol) and methanesulfonyl chloride (136 μL, 1.75 mmol) at 0 °C and the reaction mixture was stirred for 1 h. The reaction was quenched with saturated aqueous NaHCO₃ (10 mL), washed with brine (2 × 10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The product was dissolved in DMF (15 mL), NaN₃ (475 mg, 7.3

mmol) was added and the mixture was stirred at 100 °C for 18 h. The reaction was allowed to cool to room temperature and diluted with CH₂Cl₂ (100 mL), H₂O (30 mL) and brine (30 mL). The layers were separated and the organic phase was washed with H₂O/brine (1:1, 3 × 50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Flash chromatography (100:0-95:5 EtOAc:MeOH) afforded product **10** as a colorless oil (262 mg, 1.15 mmol, 79%). [α]_D²¹ +6.3 (*c* 0.27, CH₂Cl₂). IR (film) 2946, 2863, 2094, 1731, 1640, 1333, 1165 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 3.61-3.74 (m, 5H), 3.38-3.48 (m, 1H), 2.39-2.44 (m, 2H), 1.66-2.18 (m, 8H). ¹³C NMR (75 MHz, CDCl₃) δ 171.9, 170.4, 59.7, 58.3, 56.9, 51.8, 32.5, 26.8, 26.3, 22.1, 19.6. HRMS (FAB⁺): calcd for C₁₁H₁₇N₄O₃ (*M*+H⁺): 253.1301, found: 253.1295.

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To a solution of **10** (240 mg, 0.95 mmol) in THF was added in 4 portions over 3 h, 1M aqueous NaOH (6.7 mL). The solution was then neutralized with 1M aqueous HCl to pH = 7, concentrated *in vacuo* and acidified to pH = 2 with 1M aqueous HCl. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was dissolved in THF (9 mL) and cooled to -15 °C. Isobutyl chloroformate (123 μ L, 0.95 mmol) and *N*-methylmorpholine (104 μ L, 0.95 mmol) were added subsequently and the mixture was stirred for 5 minutes, followed by the addition of a solution of 2-mercaptopyridine-*N*-oxide (145 mg, 1.14 mmol) and Et₃N (158 μ L, 1.14 mmol) in THF (24 mL). The reaction mixture was stirred for 1 h with the exclusion of light, where after 2-methyl-2-propanethiol (321 μ L, 2.85 mmol) was added and the mixture was exposed to a sun lamp (250 W) for 3 h. The reaction was quenched with H₂O (40 mL) and extracted with CH₂Cl₂ (3 × 40 mL). The combined organic phases were washed with brine (40 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Flash chromatography (100:0-95:5 EtOAc:MeOH) afforded **11** (91 mg, 0.47 mmol, 49%) as a colorless oil. [α]_D²⁴ -17.3 (*c* 0.47, CH₂Cl₂). IR (film) 2941, 2860, 2094, 1618 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 4.77-4.83 (m, 1H), 3.64 (m, 1H), 3.42-3.47 (m, 1H), 2.31-2.47 (m, 3H), 2.14-2.20 (m, 1H), 1.91-1.78 (m, 3H), 1.73-1.77 (m, 2H), 1.57-1.64 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 169.7, 60.4, 57.9, 41.6, 32.6, 28.5, 26.5, 19.4, 18.9. HRMS (FAB⁺): calcd for C₉H₁₅N₄O (*M*+H⁺): 195.1246, found: 195.1242.

(+)-1

To a solution of **11** (80 mg, 0.41 mmol) in THF was added LiAlH₄ (6.2 mL of a 1M soln. in THF, 6.2 mmol) and the reaction was stirred overnight at 60 °C. The reaction was carefully quenched by addition of H₂O (305 mg, 1.3 mg/mg LiAlH₄), aqueous NaOH (15% in H₂O, 305 mg, 1.3 mg/mg LiAlH₄) and again H₂O (763 mg, 3.25 mg/mg LiAlH₄). The resulting suspension was stirred vigorously for 10 min, filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in dioxane (4 mL) and treated with 1M aqueous NaOH (4.1 mL, 4.1 mmol) and acetic anhydride (194 μ L, 2.06 mmol). After stirring for 2 h, the reaction mixture was diluted with saturated aqueous NaHCO₃ (5 mL) and CH₂Cl₂ (10 mL). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*, yielding (+)-epiquinamide **1** (68 mg, 0.35 mmol, 84%) as a white solid. Mp 124 °C. [α]_D²⁰ +28 (*c* 0.23, CHCl₃). IR (film) 2933, 1652, 1539, 1444, 1456, 765 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 6.15 (bs, 1H), 3.90-3.94 (m, 1H), 2.73-2.80 (m, 2H), 2.00 (s, 3H),

1.84-1.96 (m, 4H), 1.73-1.70 (m, 2H), 1.38-1.58 (m, 5H), 1.23-1.36 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.5, 64.3, 56.8, 56.7, 48.1, 29.6, 29.1, 25.6, 24.0, 23.4, 20.6. HRMS (FAB $^+$): calcd for $\text{C}_{11}\text{H}_{21}\text{N}_2\text{O}$ ($M+\text{H}^+$): 197.1654, found: 197.1656.

^1H NMR spectrum (300 MHz, CDCl_3) of (+)-epiquinamide **1**:

To compare the spectral of (+)-**1** with the literature data,² the corresponding HCl salt was prepared according to the following procedure.

(+)-**1** was dissolved in a saturated solution of HCl in EtOAc, and after 5 minutes the mixture was concentrated *in vacuo*, yielding the HCl salt of (+)-equinamide as a white solid. Mp 218 °C. $[\alpha]_D^{20}$ -15 (c = 0.26, MeOH).

The ^1H NMR spectrum in d_6 -acetone corresponded completely to the literature data. The ^1H NMR spectrum in CD_3OD (also stated in the literature) differed slightly, due to the apparant omission of 1 proton in the literature data. ^1H NMR (400 MHz, CD_3OD) δ 4.14 (bs, 1H), 3.29-3.35 (m, 2H), 3.21-3.24 (m, 1H),

2.86-2.93 (m, 2H), 2.02-2.08 (m, 1H), 1.96 (s, 3H), 1.67-1.78 (m, 7H), 1.60-1.64 (m, 1H) 1.48-1.57 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 174.3, 67.4, 57.8, 56.7, 49.2, 29.9, 29.1, 25.2, 24.0, 23.7, 20.37.

Reaction sequence according to Scheme 3.

L-allysine ethylene acetal (**4**) (5.0 g, 26 mmol) was suspended in dioxane (12.5 mL) and cooled to 0 °C. A solution of NaOH (3.71 g, 91 mmol) in H_2O (37.5 mL) was added, followed by NaHCO_3 (3.33 g, 26 mmol) and *trans*-cinnamoyl chloride (6.50 g, 39 mmol, added in five portions over 5 h). After stirring overnight the solvent was removed under reduced pressure, and a solution of 2.5% aqueous NaHCO_3 (125 mL) was added. The aqueous solution was extracted with Et_2O (3×50 mL), acidified by dropwise addition of 6M aqueous HCl to pH = 3 and the product was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was then dissolved in DMF (25 mL), and K_2CO_3 (5.39 g, 39 mmol) was added portionwise at 0 °C. The resulting suspension was stirred vigorously at 0 °C for 10 min. Subsequently, MeI (3.43 mL, 57 mmol) was added dropwise and stirring was continued for 2 h at rt. The reaction mixture was quenched by addition of H_2O (50 mL), and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with 0.5M aqueous $\text{Na}_2\text{S}_2\text{O}_5$ (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give product **8** as a white solid (8.366 g, 25 mmol, 97%). Mp 97 °C. $[\alpha]_{\text{D}}^{21} +23.0$ (c 0.29, CH_2Cl_2). IR (film) 3269, 2950, 2878, 1655, 1740, 1620, 1537, 1206, 1141 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.57 (d, J = 15.6 Hz, 1H), 7.41-7.43 (m, 2H), 7.28-7.30 (m, 3H), 6.56 (d, J = 7.8 Hz, 1H), 6.44 (d, J = 15.6 Hz, 1H), 4.71-4.81 (m, 2H), 3.86-3.90 (m, 2H), 3.78-3.85 (m, 2H), 3.73 (s, 3H), 1.89-1.94 (m, 1H), 1.75-1.80 (m, 1H), 1.65-1.69 (m, 2H), 1.45-1.55 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 172.3, 164.9, 141.0, 134.1, 129.2, 128.2, 127.3, 119.6, 103.6, 64.5, 52.2, 52.0, 33.1, 32.1, 19.7. HRMS (FAB^+): calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_5$ ($M+\text{H}^+$): 334.1654, found: 334.1656.

Compound **8** (1.67 g, 5.0 mmol) was dissolved in TFA (25 mL) and the mixture was stirred for 10 min. The reaction mixture was quenched with saturated aqueous NaHCO_3 (250 mL) and extracted with EtOAc (3×100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Product **9** (1.36 g) was obtained as a yellow oil which was used without further purification. ^1H NMR (300 MHz, CDCl_3 , rotamers) δ 7.71 (d, J = 15.3 Hz, 1H), 7.50-7.52 (m, 2H), 7.31-7.37 (m, 3H), 6.93 (d, J = 15.3 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 5.31-5.33 and 5.11-5.13 ($2 \times$ m, 1H), 4.99-5.03 and 4.89-4.91 ($2 \times$ m, 1H), 3.73-3.74 (m, 3H), 2.34-2.44 (m, 1H), 1.91-2.07 (m, 3H).

A solution of **9** (1.36 g) in MeOH (10 mL) was added to a suspension of Oxone (4.04 g, 6.57 mmol) and NaHCO₃ (637 mg, 7.57 mmol) in MeOH (10 mL). The mixture was stirred overnight, after which solids were removed by filtration. The filtrate was diluted with CH₂Cl₂ (30 mL) and saturated aqueous NaHCO₃ (30 mL). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Product **3b** (1.18 g) was obtained as yellow oil which was used without further purification. ¹H NMR (300 MHz, CDCl₃, rotamers) δ 7.64-7.74 (m, 1H), 7.45-7.47 (m, 2H), 7.30-7.32 (m, 3H), 6.89-7.02 (m, 1H), 5.69-5.71 and 5.37-5.39 (2 × m, 1H), 5.11-5.12 and 4.58-4.60 (2 × m, 1H), 3.95-3.96 (m, 1H), 3.69-3.72 (m, 3H), 3.26-3.31 (m, 3H), 1.98-2.17 (m, 3H), 1.61-1.65 (m, 1H).

A solution of **3b** (1.18 g) in CH₂Cl₂ (40 mL) was cooled to -30 °C. Allyltrimethylsilane (2.6 mL, 18 mmol) and BF₃·OEt (0.95 mL, 7.5 mmol) were added subsequently and the mixture was allowed to warm to rt. The reaction mixture was quenched with saturated aqueous NaHCO₃ (40 mL) after stirring for 2 h. The layers were separated and the organic phase was washed with H₂O (25 mL) and brine (25 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Product **2b** (1.18 g) was obtained as a yellow oil which was used without further purification. ¹H NMR (300 MHz, CDCl₃, rotamers) δ 7.70-7.78 (m, 1H), 7.48-7.51 (m, 2H), 7.36-7.38 (m, 3H), 6.90-6.95 (m, 1H), 5.78-5.95 (m, 1H), 5.55-5.58 and 4.76-4.86 (2x m, 1H), 5.03-5.25 (m, 2H), 3.98-4.02 (m, 1H), 3.72-3.76 (m, 3H), 2.40-2.44 (m, 1H), 2.11-2.32 (m, 2H), 1.90-2.01 (m, 1H), 1.77-1.67 (m, 3H).

Compound **2b** (1.18 g) was dissolved in toluene (180 mL) and the solution was degassed by bubbling through with argon for 10 min. Then, Grubbs 2nd generation ruthenium catalyst (154 mg, 0.36 mmol) was added. The reaction mixture was stirred overnight and concentrated *in vacuo*. The residue was dissolved in MeOH (36 mL), Pd/C (38 mg, 0.36 mmol) was added and the mixture was stirred under an atmosphere of H₂ for 2 h. Next, the mixture was filtered over Celite and the solvent was evaporated under reduced pressure. Flash chromatography (100:0-95:5 EtOAc:MeOH) afforded product **7** as a colorless oil (250 mg, 1.10 mmol, 22% over 5 steps).

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² Fitch, R. W.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345.