Total Synthesis of Phenalamide A2

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Supporting Information

Alcohol 13



To a solution of aldehyde 5 (56 mg, 138 µmol) in 1 mL toluene was added a solution of 2-[1-(1,3-diox-4-en-6-yl)-2-propenyl]-4,4,5,5,-tetramethyl-1,3,2-dioxaborolane 6 (53 mg, 210 umol) in 1 mL toluene. After 2 d at room temperature the flask was sealed and the reaction mixture was stirred at 120°C for 2 h. Upon cooling to room temperature iodine (5 mg) was added and the mixture was stirred for 10 min. CH₂Cl₂ (10 mL) was added and the mixture was washed with saturated aqueous $Na_2S_2O_3$ solution (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried (Mg₂SO₄) and concentrated. Flash chromatography (pentane/*tert*.-butyl methyl ether 1:1) provided alcohol **13** (96 μmol, 69 %) as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): $\delta = 9.45$ (dd, J = 7.7 and 2.2 Hz, 1 H), 7.15-7.27 (m, 5 H), 6.52 (m_c, 1 H), 5.98 (m_c, 2 H), 5.87 (dd, J = 6.3 and 2.2 Hz, 1 H), 5.39 (d, J = 8.5 Hz, 1 H), 5.17 (d, J = 7.3 Hz, 1 H), 3.78 (dd, J = 7.3 Hz, 1 H),6.6 and 2.6 Hz, 1 H), 2.56 (m_c, 1 H), 2.39 (m_c, 1 H), 2.24 (m_c, 2 H), 1.67 (s, 3 H), 1.64 (s, 3 H), 1.62 (s, 3 H), 1.05 (s, 9 H), 0.97 (t, J = 6.1 Hz, 3 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.16 (s, H), 0.15 (s, 3 H); ¹³C-NMR (75 MHz, CDCl₃) δ = -4.82, -4.31, 11.47, 11.77, 17.72, 18.18, 21.00, 25.83 (3 C), 31.71, 33.88, 36.81, 39.31, 41.08, 77.06, 82.88, 125.62, 128.25 (4 C), 130.38, 131.73, 132.22, 133.37, 135.34, 139.61, 142.71, 146.53, 152.21, 193.83; Analysis calc'd for C₃₂H₅₀O₃Si: C, 75.24; H, 9.87; found C, 75.22; H, 9.98.

Tetraenal 3



Methanesulfonic acid anhydride (19 mg, 112 µmol) and diisopropylethylamine (41 µL, 235 µmol) were added under complete exclusion of light) to a solution of alcohol **13** (30 mg, 60 µmol) in CH₂Cl₂ (1.2 mL). The reaction was stirred at room temperature and monitored by TLC. After all the starting material was consumed, silica gel (0.5 g) was added and the solvent was distilled off. Flash chromatography (pentane/*tert*.-butyl methyl ether 1:1) provided the tetraenal **3** (25 mg, 85 %) as a yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ = 9.60 (d, J = 8,1 Hz, 1 H), 7.12-7.35 (m, 6 H), 6.66-6.84 (m, 1 H), 6.41-6.59 (m, 2 H), 6.11-6.35 (m, 2 H), 5.58 (d, J = 9.6 Hz, 1 H), 5.15 (d, J = 9.7 Hz, 1 H), 3.75 (d, J = 7.9 Hz, 1 H), 2.76 (mc, 1 H), 2.41-2.65 (m, 2 H), 1.79 (d, J = 0.9 Hz, 3 H), 1.50-1.75 (m, 3 H), 1.61 (d, J = 1.1 Hz, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 7.0 Hz, 3 H), 0.86 (s, 9 H), 0.00 (s, 6 H); ¹³C-NMR (50 MHz, CDCl₃): δ = -4.88; -4.46; 11.40; 12.79; 17.48; 18.07; 20.72; 25.75 (3 C); 31.86; 34.04: 37.79: 39.50: 83.46: 125.23: 125.62: 128.28 (4 C): 128.52: 130.19: 133.64: 134.03:

135.21; 142.37; 142.75; 143.96; 144.52; 152.40; 193.50; HRMS calc'd for $C_{32}H_{48}O_2Si$: 492.3424; found 492,3437.

Amide 14



To a solution of diisopropylethylamine (24 μ L, 168 μ mol) in THF (2 mL) cooled to 0°C was added n-butyllithium (114 µL, 1.48 M in hexane, 169 µmol). After 15 min at this temperature [1-(2-tert.-butyldimethylsilyloxy-1-methyl-ethylcarbamoyl)-ethyl]-phosphonic acic diethylester 4 (44 mg, 112 µmol) in THF (1 mL) was added dropwise. After another 15 min a solution of the tetraenal 3 (25 mg, 51 μ mol) in THF (0.5 mL) was added. The reaction mixture was stirred at 0°C for 30 min under complete exclusion of light. Silica gel (0.5 g) was added and the solvent was distilled off. Flash chromatography (pentane/tert.-butyl methyl ether 1:1) provided amide 14 (28 mg, 76 %) as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): $\delta =$ 7.25 (m_c, 2 H), 7.14 (m_c, 3 H), 6.98 (dd, J = 10.7 and 1.5 Hz, 1 H), 6.29-6.50 (m, 4 H), 6.18 (dd, J = 15.1 and 9.9 Hz, 1 H), 6.03 (d, J = 7.7 Hz, 1 H), 5.38 (d, J = 9.2 Hz, 1 H), 5.07 (d, J = 9.4 Hz, 1 H), 4.08-4.21 (m, 1 H), 3.67 (d, J = 7.7 Hz, 1 H), 3.64 (dd, J = 10.0 and 4.1 Hz, 1 H), 3.56 (dd, J = 9.9 and 2.9 Hz, 1 H), 2.37-2.73 (m, 4 H), 1.94 (d, J = 0.7 Hz, 3 H), 1.76 (d, J = 1.1 Hz, 3 H), 1.54 (d, J = 1.4 Hz, 3 H), 1.46-1.66 (m, 2 H), 1.18 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.71 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H), -0.07 (s, 3 H), -0.07 (s, 3H), the signal of the amide-proton wasn't resolved; ¹³C-NMR (50 MHz, CDCl₃): $\delta = -5.48$ (2 C), -4.94, -4.58, 11.40. 12.86, 12.92, 17.51, 17.59, 18.00, 18.07, 20.75, 25.76 (3 C), 25.85 (3 C), 31.85, 34.06, 37.63, 39.54, 46.45, 65.93, 83.57, 126.41, 126.89, 127.57, 129.08 (2 C), 129.11 (2 C), 131.94, 133.76, 134.47, 134.60, 134.77, 136.19, 137.45, 139.32, 140.38, 141.05, 143.62, 168.85.

Some peaks could be assigned to the C-6/C-7 – Z –isomer: $\delta = 6.74$ (d, J = 15.0 Hz, 0.1 H), 6.60 (dd, J = 15.0, and 11.0 Hz, 0.1 H).

Phenalamide A₂ 1b



To a solution of amide 14 (10 mg, 14 μ mol) in acetonitrile (0.5 mL) was added hydrofluoric acid (0.1 mL) at 0°C. The reaction mixture was stirred under complete exclusion of light and monitored by TLC. After 3 h saturated aqueous NaHCO₃ (2 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic phases were dried (MgSO₄) and the solvent was distilled off. The crude product was purified by chromatography on reversed-phase silica gel (methanol/water 9:1) to give 6 mg (86 %) of Phenalamide A₂ **1b**. ¹H-NMR (500 MHz, CD₃OD): δ = 7.22 (t, J = 7.5 Hz, 2 H), 7.12 (m, 3 H), 6.92 (d, J = 8.9 Hz, 1 H), 6.51-6.59 (m, 2 H), 6.36-6.43 (m, 3 H), 6.25-6.30 (m, 1 H), 5.53 (d, J = 9.6 Hz, 1 H), 5.20 (d, J = 9.2 Hz, 1 H), 4.01-4.06 (m, 1 H), 3.76 (d, J = 7.6 Hz, 1 H), 3.51 (ddd, J = 16.8, 11.3, and 5.6 Hz, 2 H), 2.72-2.79 (m, 1 H), 2.60 (ddd, J = 14.3, 8.9, and 4.6 Hz, 1 H), 2.48-2.54 (m, 1 H), 2.39-2.45 (m, 1 H), 1.97 (s, 3 H), 1.82 (s, 3 H), 1.62-1.69 (m, 1 H), 1.60 (s, 3 H), 1.47-1.55 (m, 1 H), 1.25 (d, J = 6.8 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H) the signals of the NH and the OH protons waren't

34.97, 38.03, 40.82, 66.14, 83.56, 126.65, 127.72, 128.13, 129.29 (2 C), 129.33 (2 C), 130.72, 132.78, 135.14, 135.24, 135.32, 136.32, 137.76, 139.42, 139.91, 141.00, 143.94, 171.82, one signal was obscured by the solvent peak. HRMS calc'd for $C_{32}H_{45}NO_3$: 491,3399, found: 491,3410.

Some peaks could be assigned to the C-6/C-7 – Z –isomer Phenalamide A₁ **1a**: $\delta = 7.08$ (dd, J = 15.0, and 11.1 Hz, 0.2 H), 7.00 (d, J = 12.2 Hz, 0.2 H), 6.74 (dd, J = 15.5, and 10.0 Hz, 0.2 H), 6.15 (m, 0.4 H).

O-tert-butyldimethylsilyl-alaninol 7

A solution of *tert*-butyldimethylchlorsilane (9.04 g, 60 mmol) in Hexane (10 mL) was added by a syringe pump to a cooled (0°C) solution of alaninol (3.76 g, 50 mmol) and imidazole (4.08 g, 60 mmol) in CH₂Cl₂ (30 mL). After 18 h at room temperature saturated aqueous NaHCO₃ (75 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (4 x 30 mL). The combined organic phases were dried (MgSO₄) and the solvent was distilled off. Destillation of the residue provided *O-tert*-butyldimethylsilyl-alaninol **7** (8.71 g, 92 %) as a colorless liquid. Bp: 67°C (11 mbar); ¹H-NMR (500 MHz, CDCl₃): δ = 0.01 (s, 6 H), 0.85 (s, 9 H), 0.96 (d, J = 6.5 Hz, 3 H), 2.91 (quind, J = 6.7 and 4.3 Hz, 1 H), 3.22 (dd, J = 9.7 and 7.4 Hz, 1 H), 3.46 (dd, J = 9.6 and 4.2 Hz, 1 H); ¹³C-NMR (50 MHz, CDCl₃): δ = -5.03, -5.00, 18.15, 19.58, 26.26 (3 C), 48.90, 70.11; HRMS calc'd for C₉H₂₃NOSi: 189,1549, found: 189,1536.

Phosphonate **4**

Carbonyldiimidazole (4.20 g, 20 mmol) was added in small portions at 0°C to a solution of 2diethylphosphonopropionic acid (4.20 g, 20 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at 0°C for 30 min, washed with water (10 mL), dried (MgSO₄) and concentrated. The crude imidazolide (4.50 g, 17.1 mmol) was dissolved in CH₂Cl₂ (34 mL) and O-tertbutyldimethylsilyl-alaninol (3,25 g, 17,1 mmol) in CH₂Cl₂ (17 mL) was added dropwise at 0°C. After 30 min at 0°C the reaction mixture was quenched with saturated aqueous NH₄Cl solution (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried (MgSO₄) and the solvent was distilled off. Flash chromatography (tert.-butyl methyl ether) provided phosphonate 4 (5.26 g, 81 %) as a colorless oil. ¹H-NMR (200 MHz, CDCl₃): $\delta = 6.63$ (broad t, J = 9.1 Hz, 1 H), 4.06 (mc, 5 H), 3.49 (d, J = 4.0 Hz, 2 H), 2.75 (dqd, J = 22.5, 7.3, and 3.3 Hz, 1 H), 1.34 (ddd, J = 17.8, 7.3, and 2.5 Hz, 3 H), 1.26 (td, J = 7.2 and 2.0 Hz, 6 H), 1.09 (d, J = 6.5 Hz, 3 H), 0.83 (s, 9 H), 0.01 (s, 6 H); ¹³C-NMR (50 MHz, CDCl₃): $\delta = -5.16$ (2 C), 11.68 (d, J_{CP} = 6.2 Hz), 12.23 (d, $J_{CP} = 6.2$ Hz), 16.70 (d, J = 5.8 Hz), 17.43 (d, J = 4.5 Hz), 18.59 (s), 26.16 (s, 3 C), 38.70 (d), 41.31 (d), 47.27 (s), 62.88 (t, J = 6.8 Hz), 66.18 (d), 167.60 (d, J = 1.8 Hz); Calc'd for C₁₆H₃₆NO₅PSi: C, 50,37; H, 9,51; N, 3,67; found: C, 50,34; H, 9,30; N, 3,86.

E tip 2P



Olefinic part of the spectrum of amide 14.



Olefinic part of the spectrum of a 4 : 1 mixture of phenalamide A_2 1b and phenalamide A_1 1a.

