Pyrazine alkaloids *via* dimerization of amino acid-derived α-amino aldehydes: Biomimetic synthesis of 2,5-diisopropylpyrazine, 2,5-bis(3-indolylmethyl)pyrazine and actinopolymorphol C

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SUPPLEMENTARY INFORMATION

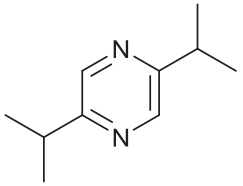
Contents

Experimental

General

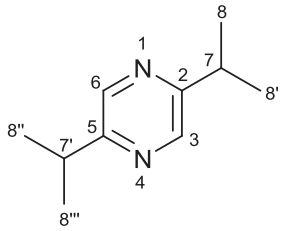
All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Infrared spectra were obtained using a Perkin Elmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Optical rotations were measured using a Perkin-Elmer 341 polarimeter at λ = 598 nm and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on either a Bruker DRX-400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei or on a Bruker Avance 300 spectrometer operating at 300 MHz and 75 MHz for ^1H and ^{13}C nuclei, respectively. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/ TMS solvent, or the residual chloroform (δ 7.26 ppm), DMSO (δ 2.50 ppm) or methanol (δ 3.31 ppm) peaks. The ^{13}C NMR values were referenced to the residual chloroform (δ 77.1 ppm), DMSO (δ 39.5 ppm) or methanol (δ 49.0 ppm) peaks. ^{13}C NMR values are reported as chemical shift δ, multiplicity and assignment. ^1H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (*J* in Hz) and assignment. Assignments are made with the aid of DEPT 135, COSY, NOESY and HSQC experiments. High resolution mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV. For all microwave-assisted reactions a single mode microwave synthesis system was used, resulting in formation of a homogeneous field pattern surrounding the sample. The reaction temperatures were measured using a surface sensor.

2,5-Diisopropylpyrazine (10)[1]



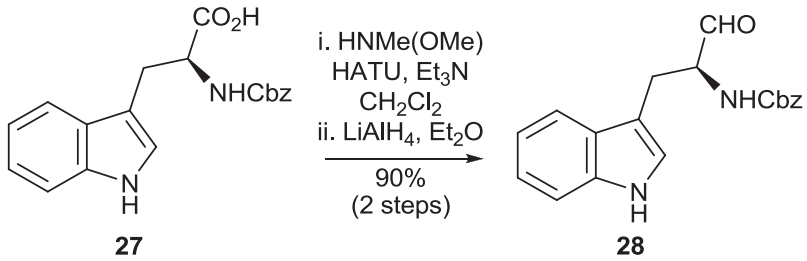
To a solution of valinal (**25c**)[2,3] (100 mg, 0.43 mmol) in acetic acid-methanol-dichloromethane (1:2:2, 5 mL) was added Pearlman's catalyst ($Pd(OH)_2$, 20% on carbon, ~15 mg) and the reaction mixture was stirred under an atmosphere of hydrogen for 1 h at room temperature. The hydrogen source was removed and the reaction mixture stirred at room temperature for a further 4 h while open to the air. The reaction mixture was filtered through Celite® and a short pad of silica using ethyl acetate-hexanes (3:1) as eluent, and the filtrate concentrated *in vacuo*. Purification by preparatory thin layer chromatography using hexanes-diethyl ether (2:1, R_f 0.4) as eluent gave the *title compound* (18 mg, 0.109 mmol, 51%) as a colourless oil; ν_{max} (neat): 2963, 2928, 2872, 1485, 1459, 1380, 1362, 1259, 1077, 1028, 801, 701 cm^{-1}; ^1H NMR and ^{13}C NMR, see Table S1 *m/z* (ESI+, %): 165 (MH^+, 100); HRMS: found $[M + H]^+$, 165.1379. $[C_{10}H_{16}N_2 + H]^+$ requires 165.1386. Spectroscopic data consistent with literature.[1]

Table S1: NMR data of synthetic and natural 2,5-diisopropylpyrazine **10**



Atom no.	Natural[1]		Synthetic	
	^{1}H (δ) (300MHz, $CDCl_3$)	^{13}C (δ) (75MHz, $CDCl_3$)	^{1}H (δ) (400MHz, $CDCl_3$)	^{13}C (δ) (100MHz, $CDCl_3$)
C2, C5		159.3		159.3
C3, C6	8.38 (2 H, s)	141.9	8.40 (2 H, s)	141.9
C7, C7'	3.07 (2 H, sept., *J* 7.9)	33.5	3.09 (2 H, sept., *J* 6.9)	33.6
C8, C8', C8'', C8'''	1.31 (12 H, d, *J* 7.9)	22.2	1.33 (12 H, d, *J* 6.8)	22.2

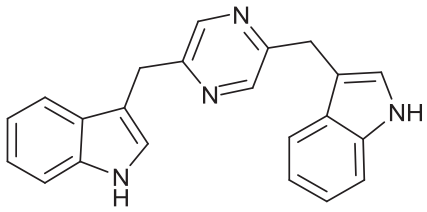
(*S*)-Benzyl 1-(indol-3-yl)-3-oxopropan-2-ylcarbamate (28)[5]



To a stirred solution of Weinreb amide[4] (derived from Cbz-tryptophan **27**) (419 mg, 1.1 mmol) in diethyl ether (60 mL) was added lithium aluminum hydride (209 mg, 5.5 mmol) at 0 °C and the reaction mixture was stirred for 2 h at this temperature. The reaction mixture was quenched with water (10 mL), filtered through Celite® and the cake washed with water (40 mL) and diethyl ether (20 mL). The filtrate was extracted with diethyl ether (3 x 30 mL) and the combined organic layers washed with hydrochloric acid (1 M, 3 x 30 mL), saturated sodium hydrogen carbonate solution (3 x 30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography using ethyl acetate-hexanes (1:1, R_f 0.5) as eluent gave the *title compound* (320 mg, 0.99 mmol, 90%) as a yellow oil. $[\alpha]_D^{21}$ +30.1 (c 1.0, CH_2Cl_2); ν_{max} (neat): 3347, 2924, 1704, 1456, 1513, 1373, 1341, 1244, 1045, 845, 744, 698 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 2.92-2.98 (1 H, m, $CH_\beta\underline{H}_\beta$) 3.21 (1 H, m, $C\underline{H}_\beta H_\beta$), 4.22-4.25(1 H, br m, CH_α), 5.03 (2 H, m, $C\underline{H}_2Ph$), 6.96 (1 H, t, *J* 6.8, Ar-H), 7.08 (1 H, m, Ar-H), 7.16 (1 H, s, Ar-H), 7.33 (6 H, m, Ar-H), 7.54 (1 H, d, *J* 8.0, Ar-H), 7.73 (1 H, d, *J* 7.6, NH), 9.59 (1 H, s, CHO), 10.86 (1 H, br s, NH); δ_C (100 MHz, d_6-DMSO) 23.7 (CH_2), 60.4 (CH), 65.5 (CH_2), 109.5 (C), 111.3 (CH), 118.1 (CH), 118.3 (CH), 120.9 (CH), 123.7 (CH), 127.6 (CH), 127.7 (2 x CH), 128.2 (CH) 128.3 (2 x CH), 136.1 (C), 136.8 (C), 156.1 (CONH), 201.2 (CHO); *m/z* (ESI+, %): 323 (MH^+, 100), 305 (65), 261 (30), 130 (10), 91 (3); HRMS: found $[M + H]^+$, 323.1383. $[C_{19}H_{18}N_2O_3 + H]^+$ requires 323.1390.

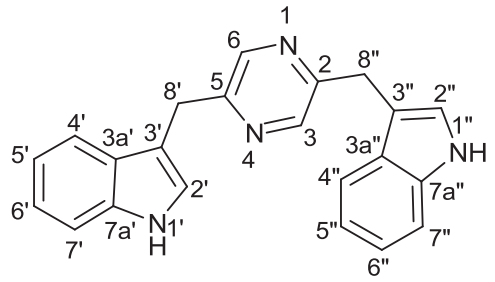
The *title compound* **28** is stable for 2 weeks at 0 °C under a blanket of argon

2,5-Bis(indol-3-ylmethyl)pyrazine (11)[6]



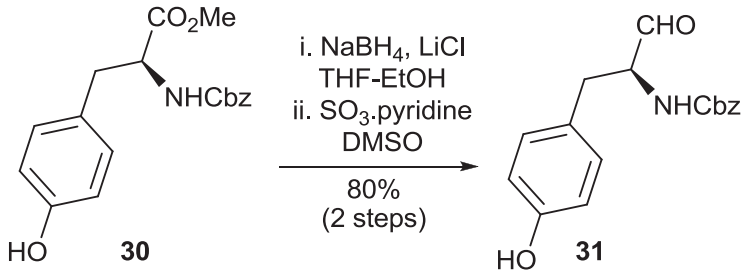
To solution of tryptophal (**28**) (85 mg, 0.26 mmol) in a mixture of acetic acid-methanol-dichloromethane (1:2:2, 5 mL) was added Pearlman's catalyst ($Pd(OH)_2$, 20% on carbon, ~10 mg) and the reaction mixture was stirred under an atmosphere of hydrogen for 2 h at room temperature. The hydrogen source was removed and the reaction mixture stirred at room temperature for a further 15 h while open to the air, filtered through Celite® and the filtrate concentrated *in vacuo*. Purification by flash chromatography using ethyl acetate-hexanes (1:1, R_f 0.46) as eluent gave the *title compound* (32 mg, 0.095 mmol, 73%) as a colorless oil; ν_{max} (neat): 3223, 2955, 2912, 2850, 1659, 1493, 1458, 1375, 1343, 1259, 1095, 1044, 970, 922, 797, 732, 589 cm^{-1}; ^1H NMR and ^{13}C NMR, see Table S2; *m/z* (ESI+, %): 323 (30) $[M+H]^+$, 305 (65), 261 (30), 130 (10), 91 (3); HRMS: found $[M + H]^+$, 339.1593. $[C_{22}H_{18}N_4 + H]^+$ requires 339.1604. Spectroscopic data consistent with literature.[6]

Table S2: NMR data of synthetic and natural 2,5-bis(3-indolylmethyl)pyrazine **11**



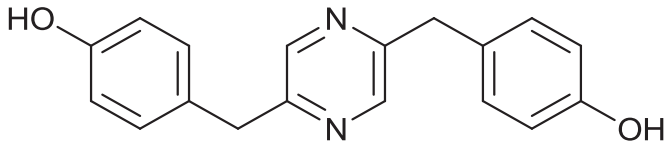
Atom no.	Natural[6]		Synthetic	
	^{1}H (δ) (300MHz,$CDCl_3$)	^{13}C (δ) (75MHz, d_6-DMSO)	^{1}H (δ) (400MHz, $CDCl_3$)	^{13}C (δ) (100MHz, d_6-DMSO)
C2, C5		153.7		153.7
C3, C6	8.43 (2 H, s)	142.9	8.43 (2 H, s)	142.9
N1', N1''	8.05 (2 H, br s)		8.02 (2 H, br s)	
C2', C2''	7.05 (2 H, d, *J* 0.8)	123.4	7.05 (2 H, d, *J* 0.8)	123.4
C3', C3''		111.6		111.5
C3a', C3a		126.8		126.8
C4', C4'	7.35 (2 H, dd, *J* 8.3 and 1.1)	121.0	7.35 (2 H, d, *J* 8.4)	120.9
C5', C5''	7.07 (2 H, dt, *J* 7.2 and 1.1)	118.4	7.07 (2 H, dt, *J* 7.0 and 1.1)	118.4
C6', C6''	7.18 (2 H, dt, *J* 7.2 and 1.2)	118.4	7.18 (2 H, dt, *J* 8.4 and 1.2)	118.4
C7', C7''	7.53 (2 H, dd, *J* 7.9 and 1.1)	111.4	7.54 (2 H, dd, *J* 8.0 and 0.8)	111.3
C7a', C7a''		136.2		136.2
C8', C8''	4.26 (4 H, s)	30.8	4.26 (4 H, s)	30.8

(*S*)-Benzyl (1-(4-hydroxyphenyl)-3-oxopropan-2-yl)carbamate (31)[7]



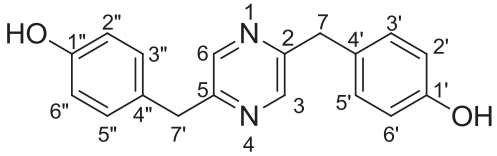
A solution of alcohol[7] (derived from reduction of Cbz-tyrosine **30**) (200 mg, 0.66 mmol) in dimethyl sulfoxide (5 mL) and dichloromethane (2.5 mL), was cooled to 0 ºC. *N,N*-diisopropylethylamine (0.4 mL, 1.98 mmol) and sulfur trioxide·pyridine complex (315 mg, 1.98 mmol) in dimethyl sulfoxide (2 mL) were added. The mixture was stirred for 1 h at room temperature and the reaction mixture diluted with ethyl acetate. The resulting solution was washed with hydrochloric acid (1M, 3 x 30 mL), saturated sodium hydrogen carbonate solution (3 x 30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the *title compound* (158 mg, 0.53 mmol, 80%) as a colorless oil; ν_{max} (neat): 3327, 3032, 2938, 1691, 1614, 1596, 1513, 1445, 1374, 1343, 1226, 1174, 1104, 1042, 1027, 913, 826, 773, 738, 697, 606; δ_H (400 MHz, d_6-DMSO) 2.50-2.52 (1 H, m, $CH_\beta C\underline{H}_\beta$), 3.04 (1 H, dd, *J* 14.0, 4.0, $C\underline{H}_\beta CH_\beta$), 4.09-4.15 (1 H, br m, CH_α), 5.03 (2 H, s, CH_2Ph), 6.67 (2 H, d, *J* 8.0, Ar-H), 7.02 (2 H, d, *J* 8.0, Ar-H), 7.32-7.36 (5 H, m, Ar-H), 7.70 (1 H, d, *J* 7.7, NH), 9.21 (1 H, br s, OH), 9.56 (1 H, s, CHO); δ_C (100 MHz, d_6-DMSO) 32.6 (CH_2), 61.4 (CH), 65.4 (CH_2), 115.0 (2 x CH), 127.5 (2 x CH), 127.7 (2 x CH), 128.3 (CH), 130.0 (2 x CH), 136.9 (C), 155.8 (C), 156.1 (C), 170.3 (C=O), 201.0 (CHO); *m/z* (ESI+, %): 322 (MNa^+, 10), 270 (9), 197 (7) 91 (3); HRMS: found $[M + Na]^+$, 322.1033. $[C_{17}H_{17}NO_4 + Na]^+$ requires 322.1050.

Actinopolymorphol C (12)[8]



To a solution of tyrosinal (**31**) (50 mg, 0.17 mmol) in acetic acid-methanol-dichloromethane (1:2:2, 5 mL) was added Pearlman's catalyst ($Pd(OH)_2$, 20% on carbon, ~30 mg) and the reaction mixture was stirred under an atmosphere of hydrogen for 8 h at 30 °C. The hydrogen source was removed and the reaction mixture stirred at room temperature for 16 h while open to the air, filtered through Celite® and the filtrate concentrated *in vacuo*. Purification by preparatory thin layer chromatography using ethyl acetate-hexanes (1:1, R_f 0.4) as eluent gave the *title compound* (10 mg, 0.03 mmol, 41%) as a colorless oil; ν_{max} (neat): 3316, 2971, 2960, 2889, 1378, 1089, 1048, 953, 881, 818, 614 cm^{-1}; ^1H NMR and ^{13}C NMR, see Table S3; *m/z* (ESI+, %): 293 (MH^+, 100), 282 (5), 276 (2), 253 (10), 191 (13), 155 (20); HRMS: found $[M + H]^+$, 293.1282. $[C_{18}H_{16}N_2O_2 + H]^+$ requires 293.1285. Spectroscopic data consistent with literature.[8]

Table S3: NMR data of synthetic and natural actinopolymorphol C **(12)**



Atom no.	Natural[8]		Synthetic	
	^{1}H (δ) (500 MHz, d_6-DMSO)	^{13}C (δ) (125 MHz, d_6-DMSO)	^{1}H (δ) (400MHz, d_6-DMSO)	^{13}C (δ) (100 MHz, d_6-DMSO)
C1′, C1″		156.5		156.3
C2, C5		154.7		154.5
C3, C6	8.44 (2 H, s)	143.9	8.44 (2 H, s)	143.8
C2′, C2″	6.67 (2 H, d, *J* 9.0)	130.5	6.67 (2 H, d, *J* 8.6)	130.3
C3′, C3″	7.06 (2 H, d, *J* 9.0)	116.0	7.06 (2 H, d, *J* 8.5)	116.0
C4′, C4″		129.8		129.7
C5′, C5″	7.06 (2 H, d, *J* 9.0)	116.0	7.06 (2 H, d, *J* 8.5)	116.0
C6′, C6″	6.67 (2 H, d, *J* 9.0)	130.5	6.67 (2 H, d, *J* 8.6)	130.3
C7, C7′	3.96 (4 H, s)	40.2	3.92 (4 H, s)	40.2
OH	Not observed		9.22 (2 H, br s)	

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5. Tryptophal **28** has been employed as an intermediate in alkaloid syntheses, but has not been previously characterized due reportedly poor stability. See: (a) H. Dyke, P. G. Steel and E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1,* 1989, 525. (b) R. Herranz, S. Vinuesa, C. Pérez, M. T. García-López, M. L. De Ceballos and J. del Rio, *J. Chem. Soc., Perkin Trans. 1,* 1991, 2749.

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