Biomimetic Synthesis of 2,5-Bis(indol-3-ylmethyl)pyrazine via Intermolecular Amino Aldehyde Cyclization

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Abstract: The biomimetic synthesis of the natural product 2,5-bis(3-indolylmethyl)pyrazine (**11**) is described. The 2,5-disubstituted pyrazine was constructed by the novel biomimetic cyclization of a tryptophan-derived amino aldehyde. The synthesis validates a recently proposed, alternative biosynthetic pathway into the construction of 2,5-disubstituted pyrazine natural products.

Key words: pyrazine, biomimetic, alkaloid, cyclization

Compounds containing the pyrazine heterocycle have widespread application in the science of food,[1] materials[2] and medicinal chemistry[3] but are not commonly observed as natural products. Although the bis-steroidal cephalostatins and ritterazines[4] are arguably the most well-known examples, the majority of pyrazine natural products are derived from amino acids. Selected examples include barrenazines A (**1**) and B (**2**),[5] botryllazines A (**3**) and B (**4**),[6] flavacol (**5**),[7] deoxymutaaspergillic acid (**6**),[7] deoxyaspergillic acid (**7**),[7] terezine A (**8**),[8] septorine (**9**),[9] actinopolymorphol C (**10**),[10] 2,5-bis(3-indolylmethyl)-pyrazine (**11**)[11] and 2,5-diisopropylpyrazine (**12**)[12] (Figure 1). Despite being small in number, the synthesis of natural pyrazines has received widespread attention. Generally speaking, construction of the pyrazine heterocycle is achieved by the condensation of a 1,2-dicarbonyl with a 1,2-diamine component,[13] metalation of a pre-constructed pyrazine[14] or the self-condensation of a non-amino acid derived 2-aminoketone.[15]

Our interest in the aforementioned natural products is focused on their biomimetic synthesis and in particular pyrazines possessing a 2,5-disubstitution pattern (i.e. **10**–**12**). Pyrazines have long been thought to originate in nature from the reduction and aromatization of diketopiperazines (Scheme 1, Path A), a postulate that is highly plausible when considering the oxygenation patterns observed in the tri- and tetrasubstituted pyrazines **5**–**9**.[16] In a fascinating recent development, labeling studies into the biosynthesis of 2,5-diisopropylpyrazine (**12**) have cast doubt into the validity of path A, instead pointing to a pathway in which the amino acid (valine) is first reduced to the amino aldehyde which then undergoes cyclization (Scheme 1, Path B).[17] It is attractive to imagine this alternative biosynthetic pathway is potentially operating for all natural 2,5-disubstituted pyrazines. Herein, we provide strong support for the biosynthesis of 2,5-disubstituted pyrazines via path B with the total synthesis of the natural product 2,5-bis(3-indolylmethyl)pyrazine (**11**) using the biomimetic cyclization of a tryptophan-derived amino aldehyde. This novel intermolecular cyclization proceeds under mild conditions, providing new insight into the biosynthesis of amino acid derived, 2,5-disubstituted pyrazines in nature.

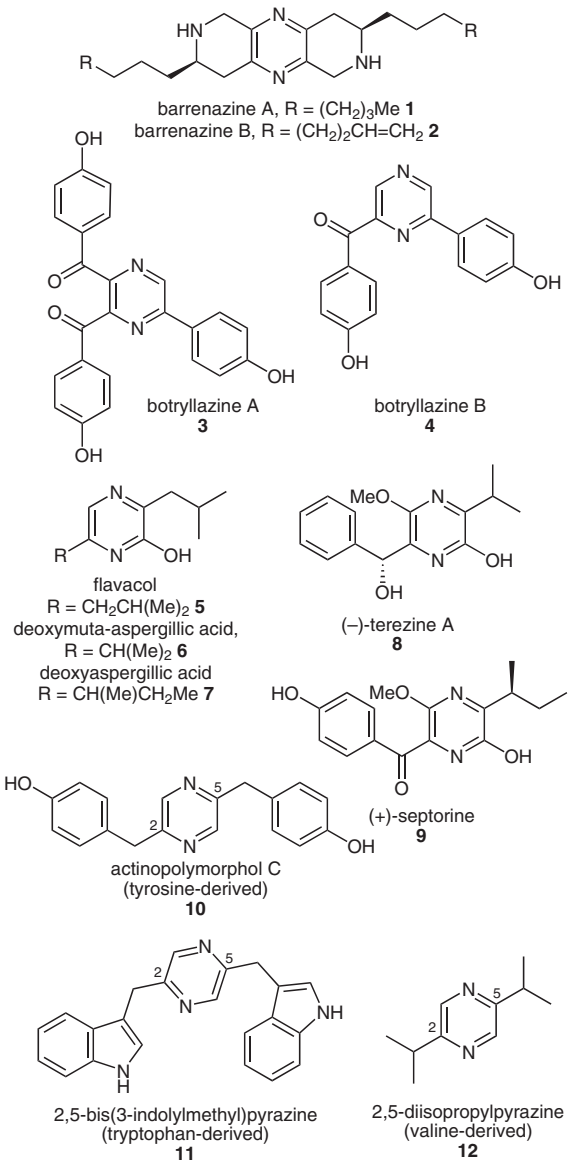

Figure 1 Selected amino acid derived pyrazines

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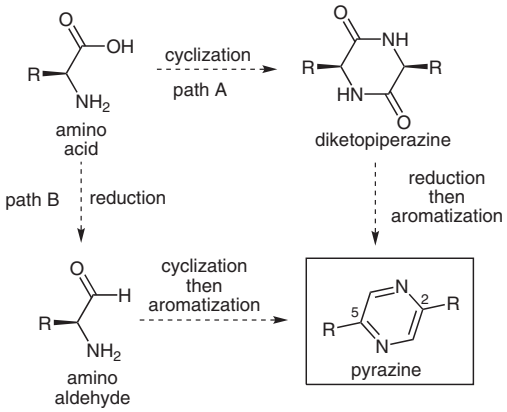
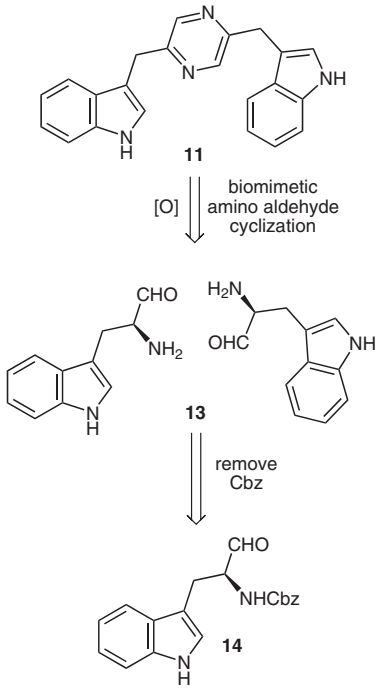


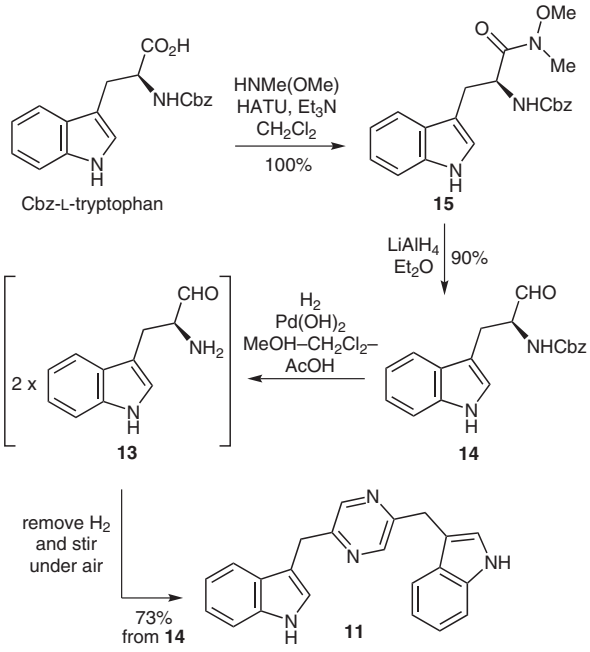
Scheme 1 Proposed biosyntheses of 2,5-disubstituted pyrazines

The natural product 2,5-bis(3-indolylmethyl)pyrazine (**11**) was isolated in 2002 from the bacterial strain *Cytophaga* sp. AM13.1 obtained from the North sea. As alluded to previously, the pyrazine ring present in **11** is potentially constructed biosynthetically by the intermolecular cyclization of an amino aldehyde (Scheme 1, path B) and is not derived from the corresponding diketopiperazine.[18] We set out to test this hypothesis and instigated a biomimetic synthesis of **11** based on this recently proposed alternative biosynthetic pathway[17] and the retrosynthesis of **11** is shown in Scheme 2. In the key biomimetic step, the pyrazine core of **11** was to be obtained from the intermolecular cyclization of the amino aldehyde **13**. Due to the stability issues often associated with α-amino aldehydes, we sought to unmask **13** by the hydrogenolysis[19] of the Cbz-derivative **14**.



Scheme 2 Retrosynthesis of 2,5-bis(3-indolylmethyl)pyrazine (**11**)

Thus, a scalable synthesis of the key biomimetic cyclization precursor **14** was sought. Commercially available Cbz-L-tryptophan underwent straightforward HATU-mediated amide coupling with *N*,*O*-dimethylhydroxylamine hydrochloride furnishing the known Weinreb amide **15**.[20] Treatment of **15** with lithium aluminum hydride delivered aldehyde **14**,[21,22] the masked amino aldehyde substrate for the proposed biomimetic cyclization, in excellent overall yield (Scheme 3).

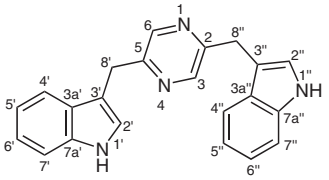


Scheme 3 Biomimetic synthesis of 2,5-bis(3-indolylmethyl)pyrazine (**11**)

With multigram quantities of **14** to hand, we were keen to attempt the key biomimetic cyclization. Upon subjecting **14** to an atmosphere of hydrogen over $Pd(OH)_2$ (Pearlman's catalyst), TLC analysis of the reaction mixture indicated the formation of a polar product, assumed to be the amino aldehyde **13**. At this point the hydrogen gas was immediately removed (to avoid the hydrogenation of any imine intermediates) and the reaction mixture was stirred at room temperature under air. Upon purification, the sole product isolated was gratifyingly confirmed as **11**, as determined by the excellent agreement between the spectroscopic data of our synthetic material[23,24] and those of the natural product[11] (Scheme 3, Table 1).

In conclusion, we have achieved a biomimetic synthesis of the natural product 2,5-bis(3-indolylmethyl)pyrazine (**11**). The 2,5-disubstituted pyrazine was constructed in a single pot by a novel biomimetic cyclization of a tryptophan-derived amino aldehyde. The synthesis validates a recently proposed alternative biosynthetic pathway into the construction of 2,5-disubstituted pyrazines in nature. Synthetic studies towards the biomimetic synthesis of further 2,5-disubstituted pyrazines is in progress and will be reported in due course.

Table 1 NMR Data of Synthetic and Natural 2,5-Bis(3-indolylmethyl)pyrazine (**11**)



Atom no.	Natural 2,5-bis(3-indolylmethyl)pyrazine[11]		Synthetic 2,5-bis(3-indolylmethyl)pyrazine[23,24]	
	^{1}H NMR (δ) (300 MHz, $CDCl_3$)	^{13}C NMR (δ) (75 MHz, DMSO-d_6)	^{1}H NMR (δ) (400 MHz, $CDCl_3$)	^{13}C NMR (δ) (100 MHz, DMSO-d_6)
C2, C5		153.7		153.7
C3, C6	8.43 (s, 2 H)	142.9	8.44 (s, 2 H)	142.9
N1′, N1″	8.05 (br s, 2 H)		8.03 (br s, 2 H)	
C2′, C2″	7.05 (d, *J* = 0.8 Hz, 2 H)	123.4	7.06 (d, *J* = 0.8 Hz, 2 H)	123.4
C3′, C3″		111.6		111.5
C3a′, C3a″		126.8		126.8
C4′, C4′	7.35 (dd, *J* = 8.3, 1.1 Hz, 2 H)	121.0	7.35 (d, *J* = 8.4 Hz, 2 H)	120.9
C5′, C5″	7.07 (dt, *J* = 7.2 1.1 Hz, 2 H)	118.4[a]	7.08 (dt, *J* = 7.0, 1.1 Hz, 2 H)	118.4[a]
C6′, C6″	7.18 (dt, *J* = 7.2, 1.2 Hz, 2 H)	118.4[a]	7.18 (dt, *J* = 8.4, 1.2 Hz, 2 H)	118.4[a]
C7′, C7″	7.53 (dd, *J* = 7.9, 1.1 Hz, 2 H)	111.4	7.53 (dd, *J* = 8.0, 0.8 Hz, 2 H)	111.3
C7a′, C7a″		136.2		136.2
C8′, C8″	4.26 (s, 4 H)	30.8	4.26 (s, 4 H)	30.8

[a] The peaks corresponding to the chemical shift of the carbons at C5′, C5″, C6″ and C6″ overlap in ^{13}C NMR spectrum of both the natural and synthetic samples.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(22) (*S*)-Benzyl 1-(indol-3-yl)-3-oxopropan-2-ylcarbamate (**14**):[21] To a stirred solution of Weinreb amide **15** (416 mg, 1.1 mmol) in Et_2O (60 mL) was added $LiAlH_4$ (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 H_2O (10 mL), filtered through Celite® and the cake was washed with H_2O (40 mL) and then with Et_2O (20 mL). The filtrate was extracted with Et_2O (3 × 30 mL) and the combined organic layers were washed with HCl acid (1 M, 3 × 30 mL), sat. $NaHCO_3$ solution (3 × 30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography using EtOAc–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). IR (neat): 3347, 2924, 1704, 1456, 1513, 1373, 1341, 1244, 1045, 845, 744, 698 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.91 (m, 1 H, $CH_\beta H_\beta CH_\alpha$), 3.21 (m, 1 H, $CH_\beta H_\beta CH_\alpha$), 4.25 (s, 1 H, CH_α), 5.03 (m, 2 H, CH_2Ph), 6.96 (t, *J* = 6.8 Hz, 1 H, ArH), 7.08 (m, 1 H, ArH), 7.16 (s, 1 H, ArH), 7.33 (m, 6 H, ArH), 7.54 (d, *J* = 8.0 Hz, 1 H, ArH), 7.73 (d, *J* = 7.6 Hz, 1 H, NH), 9.59 (s, 1 H, CHO), 10.86 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 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 × CH), 128.2 (CH), 128.3 (2 × CH), 136.1 (C), 136.8 (C), 156.1 (CONH), 201.2 (CHO). MS: *m*/*z* (ESI+, %) = 323 (30) $[M + H]^+$, 305 (65), 261 (30), 130 (10), 91 (3). HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{18}N_2O_3$ + H: 323.1380; found: 323.1383.

(23) 2,5-Bis(indol-3-ylmethyl)pyrazine (**11**):[11,24] To a solution of aldehyde **14** (85 mg, 0.26 mmol) in MeOH–CH_2Cl_2–AcOH (2:2:1, 5 mL) was added Pearlman's catalyst [$Pd(OH)_2$, 20% on carbon, ca.10 mg] and the reaction mixture was stirred under an atmosphere of hydrogen for 2 h. The hydrogen balloon was removed and the reaction mixture was stirred for a further 15 h while open to the air, filtered through Celite® and the filtrate was concentrated in vacuo. Purification by flash chromatography using EtOAc–hexanes (1:1, R_f 0.46) as eluent gave the title compound (32 mg, 0.095 mmol, 73%) as a colorless oil. IR (neat): 3223, 2955, 2912, 2850, 1659, 1493, 1458, 1375, 1343, 1259, 1095, 1044, 970, 922, 797, 732, 589 cm^{-1}. For ^1H NMR and ^{13}C NMR data see, Table 1. MS: *m*/*z* (ESI+, %) = 339 (100) $[M + H]^+$, 282 (20), 242 (15), 157 (2). HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{18}N_4$ + H: 339.1604; found: 339.1593.

(24) See Supplementary Information for ^1H NMR and ^{13}C NMR spectra of synthetic **11**.