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PAPER

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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The dimerization of amino acid-derived α-amino aldehydes provides a short, biomimetic synthesis of several 2,5-disubstituted pyrazine natural products. The α-amino aldehyde intermediates were generated *in situ* by the hydrogenolysis of their Cbz-derivatives. It was found that a judicious choice of reaction solvent facilitated hydrogenolysis, dimerization and oxidation to the natural product in a one-pot operation. This methodology demonstrates the viability of a recently proposed, alternative biosynthetic route to 2,5-disubstituted pyrazines in nature. Furthermore, this work describes a novel, concise approach to pyrazines from α-amino aldehydes derived from readily available, cheap amino acids.

Introduction

Compounds containing the pyrazine heterocycle play a huge role in everyday life, with widespread application in materials science[1] and medicinal chemistry.[2] The pyrazine motif is also observed in a large number of compounds that are responsible for the unique flavor and aroma of several foodstuffs and wines.[3]

Despite the abundance of this heterocyclic motif alluded to in the above, natural products possessing a pyrazine motif are relatively rare. The most eminent examples are arguably the anti-tumour, bis-steroidal cephalostatins and ritterazines.[4] However, the majority of natural pyrazines are derived from amino-acids; barrenazines A (**1**) and B (**2**),[5] botryllazines A (**3**) and B (**4**),[6] flavacol (**5**),[7] aspergillic acids (**6**) and (**7**),[7] terezine A (**8**),[8] septorine (**9**),[9] 2,5-diisopropylpyrazine (**10**),[10] 2,5-bis(3-indolylmethyl)pyrazine (**11**)[11] and actinopolymorphol C (**12**)[12] are selected examples (Fig. 1).

Our interest in the aforementioned pyrazine natural products is focused on their biomimetic synthesis,[13–16] an area that has not been studied in great detail. During the biomimetic syntheses of flavacol (**5**), aspergillic (**6**) and deoxyaspergillic acids (**7**), Okada and co-workers showed that upon deprotection of several dipeptidyl aldehydes **13a–c**, the resulting intermediates **14a–c** underwent spontaneous intramolecular cyclization affording the natural products in poor yield (Scheme 1).[17] Bischoff and co-workers have reported the biomimetic synthesis of the core (**15**) of barrenazine A.[18] The pyrazine was constructed by unmasking of the oxime **17** and spontaneous dimerization of the resultant α-aminoketone **16** (Scheme 1). These aforementioned biomimetic approaches focus on the synthesis of tri- and tetrasubstituted pyrazines and neither offer insight into the biogenesis of disubstituted pyrazines such as **10–12**. Herein, we report the full details of our endeavours towards the biomimetic syntheses of the natural products **10–12**,[19] demonstrating the viability of a recently proposed biosynthetic route to this fascinating class of natural products.

In 2010, Schulz and co-workers set out to investigate the biosynthesis of 2,5-diisopropylpyrazine **10** (and its 2,6-regioisomer) by employing feeding experiments in the myxobacteria *Nannocystis exedens* and *Chondromyces crocatus*.[20] Using a previously reported hypothesis[21] as a guide, it was assumed the biosynthetic route commences with the dimerization of L-valine **18** to diketopiperazine **19**, which undergoes reduction (*via* tautomer **20**) to hemiaminal **21** that upon loss of two molecules of water and aromatization gives the pyrazine **10** (Scheme 2). This proposed biogenesis was initially considered highly plausible, especially considering the oxygenation pattern present in the natural products **5–9**. Furthermore, in what can be classed as biomimetic approaches, several syntheses of natural pyrazines proceed *via* the corresponding diketopiperazine, demonstrating that this transformation is indeed a viable one.[22,23]

Upon feeding labelled valine [$^2H_8$]-**18** to *Chondromyces crocatus*, Schulz and co-workers detected 2% incorporation into [$^2H_{14}$]-**10** and 22% incorporation into [$^2H_7$]-**10**, confirming the host organism incorporated the labelled amino acid into the natural product (Study A, Scheme 3). Next, feeding experiments with the labelled diketopiperazine [$^2H_{16}$]-**19** were carried out (Study B, Scheme 3). Surprisingly, a virtually identical incorporation pattern into [$^2H_{14}$]-**10** and [$^2H_7$]-**10** was observed when

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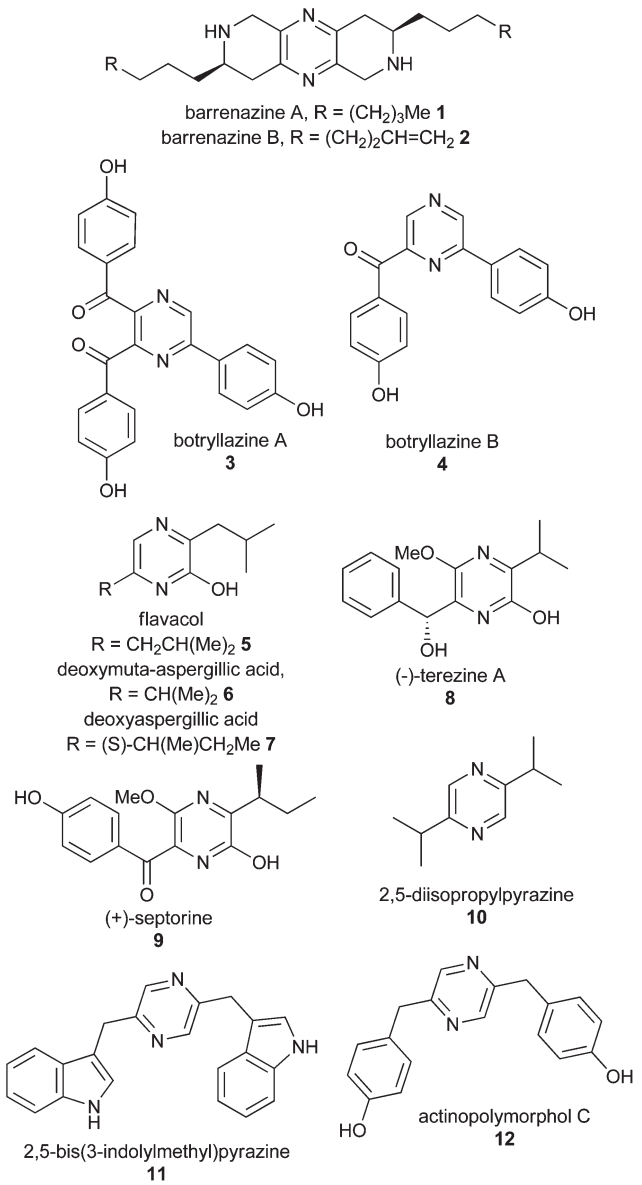


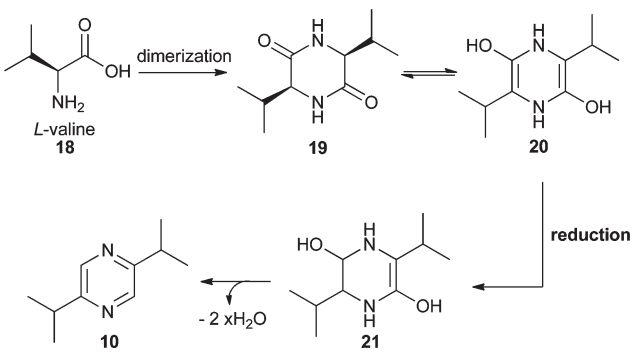
Fig. 1 Amino acid-derived pyrazines.

feeding with diketopiperazine [$^2H_{16}$]-**19** as with the amino acid [$^2H_8$]-**18**. Furthermore, upon feeding with diketopiperazine [$^2H_{12}$]-**19**, no [$^2H_{12}$]-**10** was observed (Study C, Scheme 3). These labelling results infer that the biosynthetic pathway outlined in Scheme 2 is not operating and the host organism does not produce 2,5-diisopropylpyrazine **10** from diketopiperazine **19**. Interestingly, it appears that the diketopiperazine **19** is merely a source of valine **18**, which is then converted to the natural product 2,5-diisopropylpyrazine **10** by a different biosynthetic pathway to that outlined in Scheme 2.

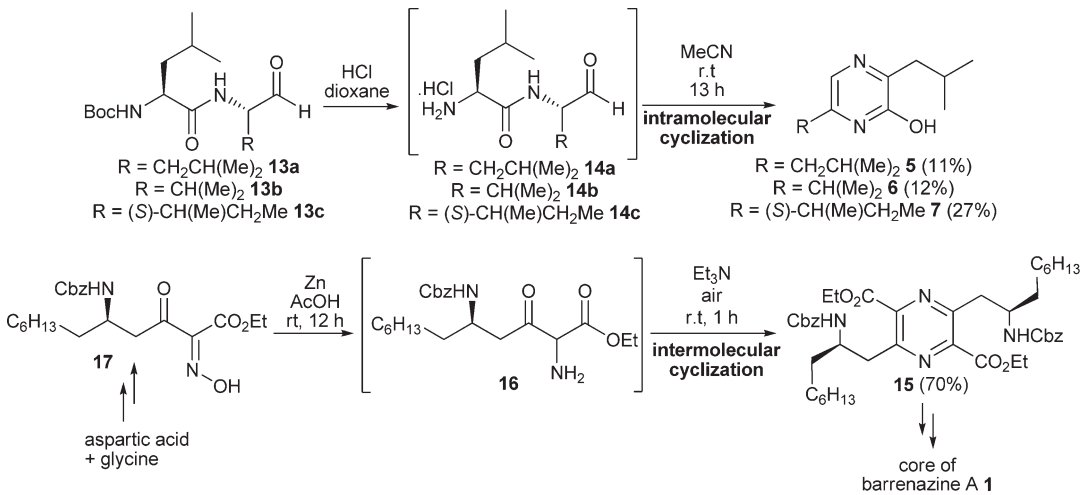
In a new biosynthetic pathway that is supported by the aforementioned labelling studies, Schulz and co-workers proposed that valine **18** is reduced to the α-amino aldehyde **23** which undergoes dimerization *via* two condensation reactions to form the dihydropyrazine **24**. Finally, oxidation (either enzymatically or non-enzymatically) delivers the pyrazine **10** (Scheme 4). The occurrence of dihydropyrazine intermediates in the biosynthesis of pyrazines is supported by the recent identification of 3,6-dihydro-2,5-dimethylpyrazine along with 2,5-dimethylpyrazine in emissions of the fruit fly *Anastrepha serpentine*.[24]

Results and discussion

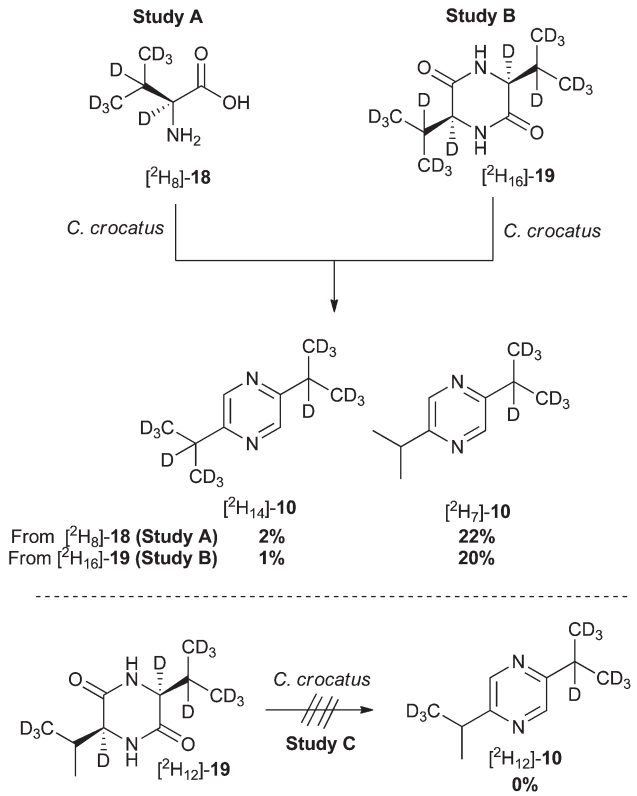
Intrigued by the Schulz proposal for the alternative biosynthesis of 2,5-diisopropylpyrazine **10** (and presumably the related



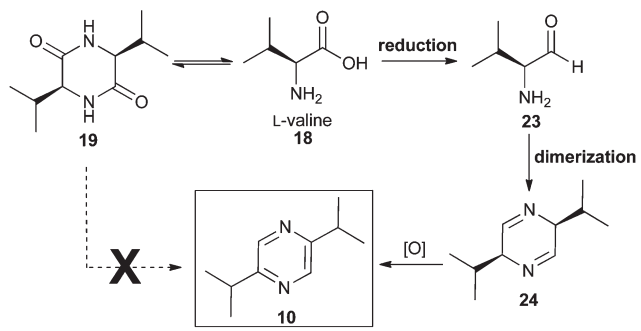
Scheme 2 Initially postulated biosynthesis of 2,5-diisopropylpyrazine **10.**



Scheme 1 Biomimetic synthesis of tri- and tetrasubstituted pyrazines.[17,18]

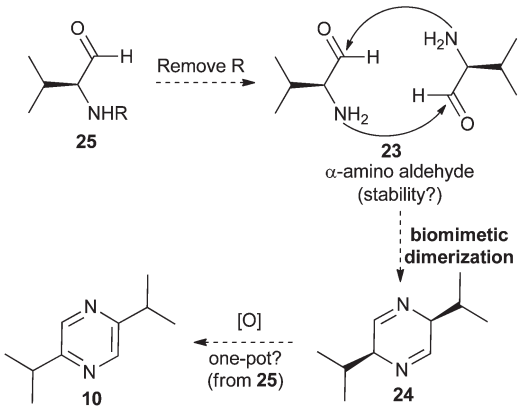


Scheme 3 Results from feeding experiments by Schulz and co-workers.[20]

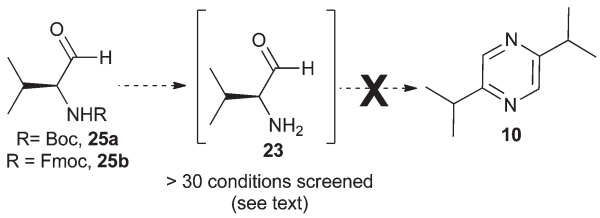


Scheme 4 Alternative biosynthesis of 2,5-diisopropylpyrazine **10.**

pyrazines **11** and **12**), we initiated a programme designed to test the hypothesis. Initial focus was aimed toward the same natural product (**10**) used in the labeling studies (Scheme 5). The biomimetic synthesis commences with valinal **25**, whereby the amino group will be masked with a suitable protecting group (R). In the key biomimetic step, upon the removal of R the resulting α-amino aldehyde **23** will undergo spontaneous dimerization forming the dihydropyrazine **24**, which should readily oxidize to the natural product **10**.[25] Importantly, the reaction conditions employed to remove R must be compatible with the dimerization of α-amino aldehyde **23**, an ambitious task as α-amino aldehydes are notoriously unstable synthetic intermediates.[26] Furthermore, it is highly desirable that the entire process (**25** → **10**) be conducted in one-pot. Not only would this synthesis serve to validate an alternative biosynthetic pathway, it also involves a



Scheme 5 Proposed biomimetic synthesis of 2,5-diisopropylpyrazine **10.**



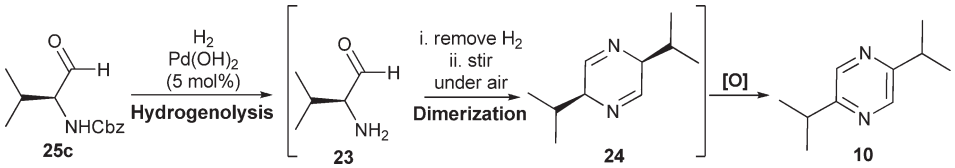
Scheme 6 Failed biomimetic dimerization of Boc- and Fmoc-protected valinals **25a** and **25b.**

concise, novel synthetic approach to pyrazines from α-amino aldehydes derived from readily available, cheap amino acids.

In order to gauge the viability of this approach, the first task was to achieve a scalable synthesis of a suitably protected valinal derivative in order to attempt the biomimetic proposal. Initial consideration was aimed at the use of *tert*-butyloxycarbonyl (Boc) and the fluorenylmethyloxycarbonyl (Fmoc) protecting groups. In preparation for the proposed biomimetic dimerization, Boc-L-valinal **25a** and Fmoc-L-valinal **25b** were synthesized according to the literature procedures (Scheme 6).[27,28]

In an attempt to effect the desired biomimetic transformation, **25a** and **25b** were subjected to a plethora of Boc- and Fmoc-cleavage conditions, all without success. None of the α-amino aldehyde **23** or 2,5-diisopropylpyrazine **10** were ever detected (Scheme 6). This universal failure was attributed to the unmasked valinal **23** rapidly degrading under the acidic (Boc-cleavage) and basic (Fmoc-cleavage) reaction conditions.

With the failure of the masked valinal substrates **25a** and **25b** in the biomimetic dimerization, attention turned to the carboxybenzyl (Cbz) protecting group. This strategy was initially avoided as it was envisaged the reductive conditions commonly employed to effect Cbz-cleavage would not be compatible with the imine moieties in dihydropyrazine **24**, nor the subsequent oxidation to pyrazine **10**. Regardless, we pressed forward with the synthesis of Cbz-valinal **25c**[29,30] and attempted the key biomimetic dimerization (Scheme 7, Table 1). It was anticipated that the intermolecular condensation would proceed best under acidic conditions, so the hydrogenolysis was initially trialled in acetic acid with the hope of effecting Cbz-cleavage and concomitant dimerization. However, this strategy failed (entry 1) and only degradation was observed. Changing the solvent to ethyl



Scheme 7 Hydrogenolysis–dimerization–oxidation.

Table 1 Optimization of the hydrogenolysis–dimerization–oxidation

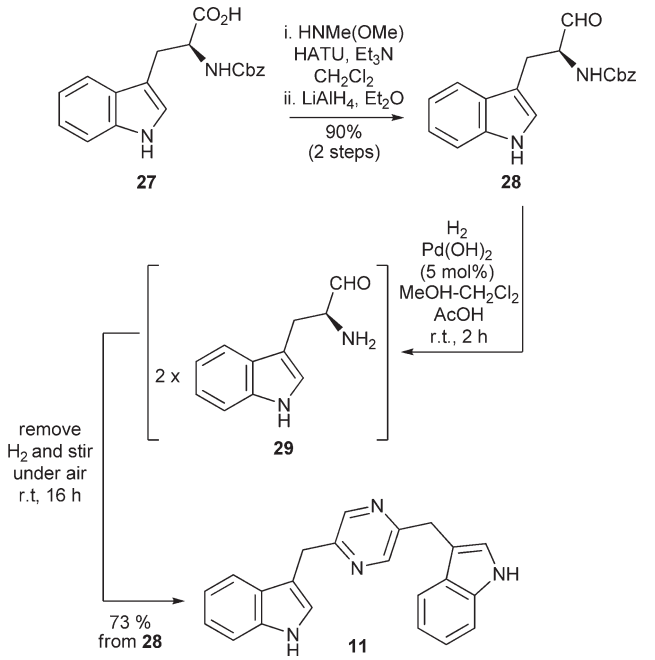
	Hydrogenolysis[a,b,c,d]			Dimerization			
Entry	Solvent	Time	Catalyst filtered	Temp.	Time (h)	Notes	Yield **10** (%)
1	AcOH	30 min	Yes and No	r.t – 40 °C	16	—	—
2	EtOAc	12 h	Yes and No	r.t-Reflux	16	—	—
3	EtOAc	12 h	Yes	r.t	16	[e]	—
4	THF	15 h	Yes	r.t	12	—	2%
5	THF	2 h	No	r.t	12	—	8%
6	THF	2 h	No	r.t	12	[e]	8%
7	THF	2 h	No	r.t	12	[f]	—
8	THF	2 h	No	r.t	1	—	20%
9	Dioxane	3 h	No	r.t	3	—	1%
10	EtOH	2.5 h	No	r.t	16	—	—
11	MeOH	3 h	No	r.t	16	—	2%
12	CH_2Cl_2	3 h	No	r.t	16	—	—
13	**CH_2Cl_2–MeOH–AcOH (2 : 2 : 1)**	**1 h**	**No**	**r.t**	**4**	—	**51%**

[a] Valinal **25c** (100 mg, 0.43 mmol) was subjected to the hydrogenolysis conditions. Upon formation of α-amino aldehyde **23** (polar product detected by TLC), the hydrogen was immediately removed (to avoid the reduction of any imine intermediates) and the dimerization conditions were employed. [b] Palladium on carbon (Pd/C) failed to effect hydrogenolysis. All examples in Table 1 use 20% palladium hydroxide on carbon (Pearlman's catalyst). [c] All hydrogenolyses were conducted at room temperature. [d] Aqueous workup after the hydrogenolysis caused instant degradation of valinal **23**. [e] Molecular sieves (4 Å) were added after hydrogenolysis was complete. [f] Triethylamine (3 equiv) added after hydrogenolysis.

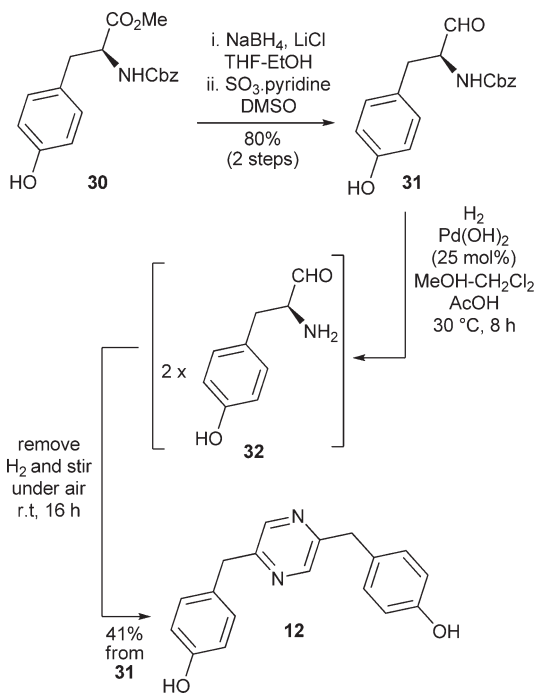
acetate also gave no positive results (entries 2–3). However, upon switching the solvent to THF, trace amounts of the natural product **10** were observed (entry 4). Encouraged by this result, we set out to examine the effect the other reactants had on the process. Interestingly, leaving the hydrogenolysis catalyst present in the reaction mixture during the dimerization–oxidation increased the yield (entry 5), but the addition of molecular sieves to the dimerization–oxidation appeared to have no effect (entry 6). Following a literature procedure that describes the positive effect base can have on intermolecular aminoketone cyclizations,[18a] triethylamine was added at the dimerization–oxidation stage. However, this had a detrimental effect, causing degradation of the reaction mixture (entry 7). At this stage, it was discovered that reducing the length of the dimerization–oxidation reaction time increased the yield, suggesting the natural product **10** was not entirely stable under the reaction conditions (entry 8). Changing the solvent to dioxane (entry 9), ethanol (entry 10), methanol (entry 11) or dichloromethane (entry 12) had a negative effect on the reaction. After significant literature searching, employing the solvent mixture of dichloromethane–methanol–acetic acid (2 : 2 : 1)[31] gave a pleasing 51% yield of the natural product 2,5-diisopropylpyrazine[10a,32] (entry 13). The biomimetic synthesis of **10** reported herein is significantly more efficient than previous syntheses.[10b,c]

Having successfully established that the dimerization of an α-amino aldehyde is a viable basis for the formation of the natural product 2,5-diisopropylpyrazine **10**, we set out to extend this new methodology toward the biomimetic synthesis of other 2,5-disubstituted pyrazines. Attention turned to the natural product 2,5-bis(3-indolylmethyl)pyrazine **11**, isolated in 2002 from the bacterial strain *Cytophaga* sp. AM13.1 obtained from the North sea.[11] Accordingly, a biomimetic synthesis of 2,5-bis(3-indolylmethyl)pyrazine was initiated. Commercially available Cbz-L-tryptophan **27** underwent straightforward Weinreb amide[33] formation followed by reduction, delivering tryptophal **28**,[32,34] the masked α-amino aldehyde substrate for the proposed biomimetic dimerization, in excellent overall yield (Scheme 8). Upon subjecting **28** to the optimized hydrogenolysis conditions employed during the synthesis of 2,5-diisopropylpyrazine **10**, the hydrogenolysis was complete (as indicated by the formation of the highly polar **29** by TLC) within 2 h. At this stage the hydrogen gas was immediately removed and the reaction mixture stirred under air for 16 h (Scheme 8). Gratifyingly, the natural product **11** was obtained in excellent yield and all the spectroscopic data was in full agreement with the natural product.[32]

In order to demonstrate the versatility of this methodology further, we were keen to attempt this biomimetic dimerization toward the synthesis of a third natural product. Actinopolymorphol C **12** was isolated in 2010 from the recently identified bacterium *Actinopolymorpha rutilus* (YIM45725) found in a forest soil sample collected from Yunnan province, China.[12] In a different synthetic route to that employed during the synthesis of the natural products **10** and **11**, the known tyrosine derivative **30**[35] was reduced ($NaBH_4$–LiCl) then oxidized under Parikh–Doering conditions, furnishing tyrosinal **31** in excellent yield.[35] Complete hydrogenolysis of **31** required 8 h at 30 °C, at which point the hydrogen gas was removed and the reaction mixture stirred under air for 16 h. Gratifyingly, the natural product



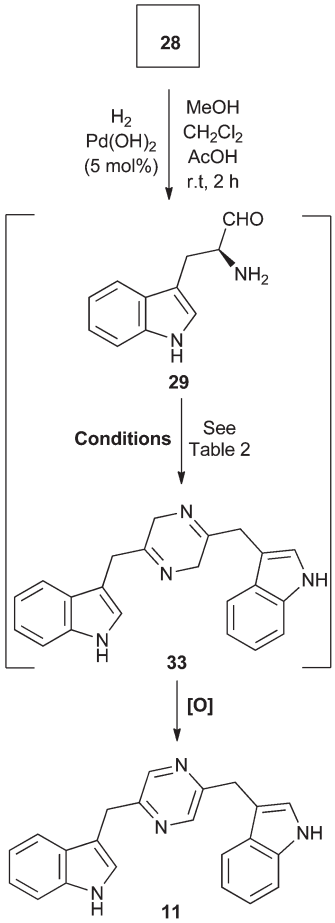
Scheme 8 Biomimetic synthesis of 2,5-bis(3-indolylmethyl)pyrazine **11**.



Scheme 9 Biomimetic synthesis of actinopolymorphol C **12.**

actinopolymorphol C **12** was isolated in good overall yield (Scheme 9). All the spectroscopic data of the synthetic material was in full agreement with the natural product.[32]

Having completed the biomimetic synthesis of **10**, **11** and **12**, clearly demonstrating the viability of a recently proposed, alternative biosynthetic route to 2,5-disubstituted pyrazines in nature, it was decided to further study the key biomimetic dimerization–oxidation step.



Scheme 10 Dimerization–oxidation.

The conversion of Cbz-tryptophal **28** into 2,5-bis(3-indolylmethyl)pyrazine **10** was chosen, primarily as it was the cleanest and easiest to monitor of all the biomimetic syntheses described herein. Thus, four different reaction vessels containing tryptophal **28** were simultaneously subjected to the same hydrogenolysis conditions (Scheme 10, Table 2). Upon completion of the hydrogenolysis (2 h, polar product by TLC), the four reactions were each subjected to dimerization–oxidation conditions and their effect on the subsequent yield of the product was monitored. Entry 1 shows the standard conditions, resulting in a similar yield to that reported in the original synthesis (Scheme 8). Interestingly, if the hydrogenolysis catalyst is removed from the reaction mixture during the dimerization–oxidation event, the yield of the natural product drops significantly (entry 2). Similarly, running the dimerization–oxidation under an inert atmosphere in the presence of the catalyst also results in a

Table 2 Conditions for dimerization–oxidation

Entry	Conditions[a]	Yield **11** (%)
1	Remove H_2, stir under air	69
2	Remove H_2 and $Pd(OH)_2$, stir under air	33
3	Remove H_2, stir under N_2	20
4	Maintain H_2	0

[a] All reactions were conducted simultaneously on 50 mg scale.

relatively poor yield of the product (entry 3). From these observations it is clear that the oxidation step is facilitated by the synergistic combination of air and palladium hydroxide (entries 2 and 3). Running the entire reaction sequence under an atmosphere of hydrogen led to no detectable product (entry 4).

Conclusions

In conclusion, we have investigated the proposed biomimetic dimerization of amino acid-derived α-amino aldehydes into natural 2,5-disubstituted pyrazines. Whilst Boc- and Fmoc-valinals **25a** and **25b** were not viable substrates for this biomimetic transformation, Cbz-valinal **25c** underwent hydrogenolysis, dimerization and oxidation to the natural product 2,5-diisopropylpyrazine **10** in a one-pot operation. This route was successfully extended to the biomimetic synthesis of 2,5-bis(3-indolylmethyl)pyrazine **11** and actinopolymorphol C **12**. The biomimetic synthesis of the three natural products **10**, **11** and **12** clearly demonstrates the viability of this recently proposed, alternative biosynthetic route to 2,5-disubstituted pyrazines in nature.[36] It is envisaged the methodology reported herein will provide a useful alternative to existing pyrazine syntheses.

Experimental

Full experimental details are included in the ESI.†

Acknowledgements

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