Molecular Diversity, **xxx:** 1–11, 2004.
KLUWER/ESCOM

Full-length paper

Total asymmetric synthesis of (–)-Phenylahistine, (–)-Aurantiamine and related compounds. Part I

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Received 10 February 2004; Accepted 30 April 2004

Key words: amino acids, 2,5-diketopiperazines, Horner–Emmons reaction, natural products, ylides

Summary

A new general, short, and efficient strategy for the construction of dehydro-diketopiperazines was developed. Horner–Emmons type coupling between a phosphinyl glycine ester and a formyl heterocycle is the key coupling reaction, which proceeds in good-to-excellent yields on several sterically-hindered substrates. Moreover, racemization of the parent *L*-amino acids is avoided as a result of the mild basic conditions used. The selection of the NH protective group of the formyl heterocycle was crucial. *N*-tosylated heterocycles proved ideal for this reaction sequence. Thus, the title compounds, (–)-Phenylahistine and (–)-Aurantiamine, were prepared in high yield (four steps, 47% overall) and optical purity. Furthermore, the synthesis of unnatural derivatives including an indole analogue was successfully completed.

Abbreviations: DHP, 3,4-dihydro-2*H*-pyrane; PPTS, pyridinium *p*-toluenesulfonate; TEMPO, 2,2,6,6-tetramethyl-piperidin-1-yloxy; Im_2CO, *N*, *N*′-carbonyldiimidazole; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; HOBt, 1-hydroxybenzotriazole; EDC HCl, *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride; TFA, trifluoroacetic acid; TBAF, tetrabutylammonium fluoride; Et_3N, triethylamine; LDA, lithium diisopropylamide; TBSCl, *tert*-butyldimethylsilyl chloride; TLC, thin layer chromatography; HRMS, high resolution mass spectroscopy; FAB, fast atom bombardment; MALDI-FTMS, matrix-assisted laser desorption/ionization-fourier transform mass spectroscopy; EI, electron ionization; m.p., melting point; DMSO, dimethyl sulfoxide; THP, tetrahydropyrane; r.t., room temperature; TosCl, p-toluenesulfonyl chloride.

Introduction

Naturally occurring diketopiperazines featuring a dehydro-histidine or a dehydro-tryptophan residue (Figure 1) exhibit important biological activities, such as anti-cancer, neurotoxic, or immunosuppressive effects [1–8]. Among them, (–)-Phenylahistine and related derivatives have attracted much attention due to their strong binding affinity towards microtubules and the resulting strong growth inhibition of various tumor cell lines [9–11]. They present an outstanding potential for molecular diversity, which prompted us to seek a synthetic approach amenable to solid-phase chemistry.

The prevailing method for the chemical synthesis of diketopiperazines, first reported for the preparation of optically active Viridamine (**3**) [5], relies on direct condensation of the parent bis-*N*-acetyl-diketopiperazine with the corresponding formyl-heterocycle followed by deacetylation. However, application of this methodology for the preparation of more sterically demanding substrates, such as (–)-Phenylahistine and related compounds, resulted in less than 10% chemical yields and almost complete racemization [2, 9]. Recently, Joullie and co-workers [12] have adopted an alternative strategy for the construction of the dehydro-histidine moiety of Isoroquefortine (**6**), utilizing a Horner–Emmons type coupling of a phosphinyl-glycine ester with *N*-protected formyl-imidazole. The marginal yields of the subsequent deprotections, however, substantially reduced the overall yield of this approach. None of the reported procedures seemed to provide the versatility and efficiency required for solid-phase synthesis.

Results and discussion

To overcome these problems, two possible retrosynthetic approaches were envisioned (Figure 2): (a) the obvious disconnection of the amide bonds, suggesting the precursors *L*-amino acid **8** and enamine **9**, or (b) cleavage of the double bond and one amide bond leading to the known

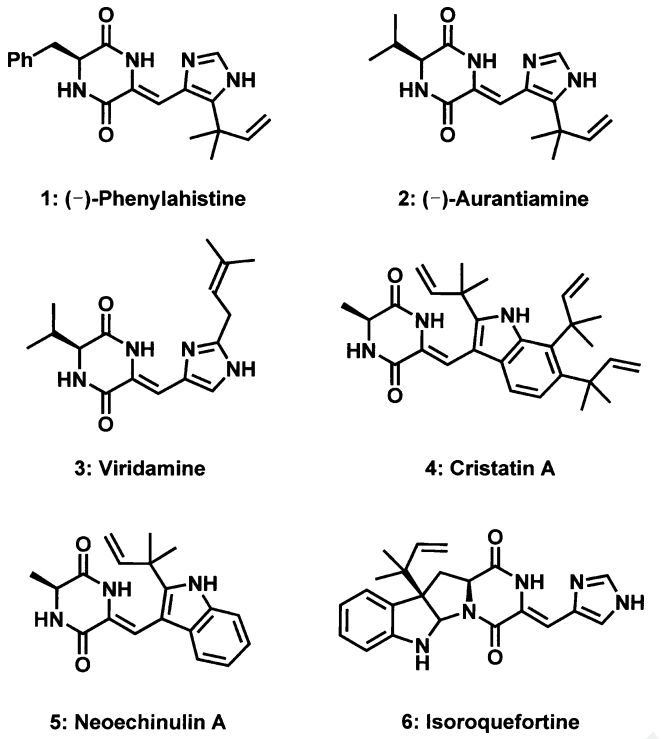

Figure 1. Naturally occurring dehydro-2,5-diketopiperazines.

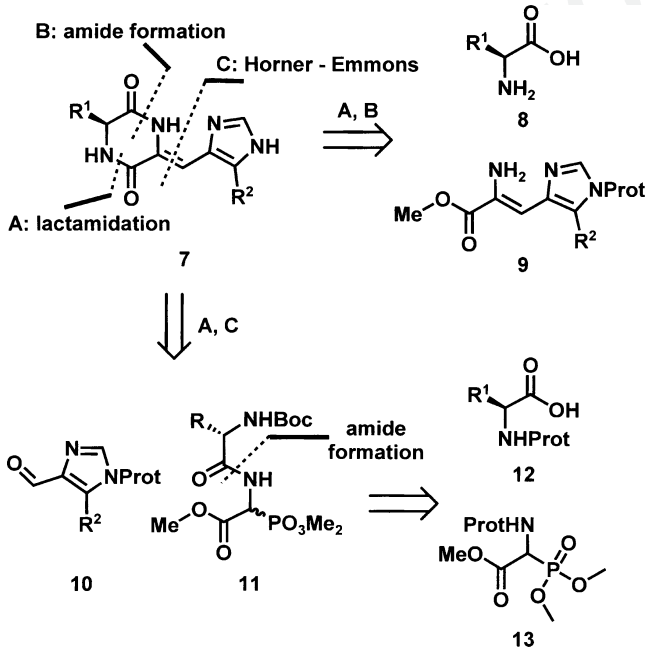

Figure 2. Retrosynthetic analysis for the preparation of dehydro-2,5-diketopiperazines (Prot = Protective group).

formyl-imidazole **10** and dipeptide **11**, which can be further reduced to the corresponding amino acid **12** and phosphinyl-glycine ester **13**. Since formation and coupling of enamines, such as **9**, are known to take place in low yields, we opted for the second approach. It was also anticipated that the above analysis should be valid for derivatives related to Cristatin

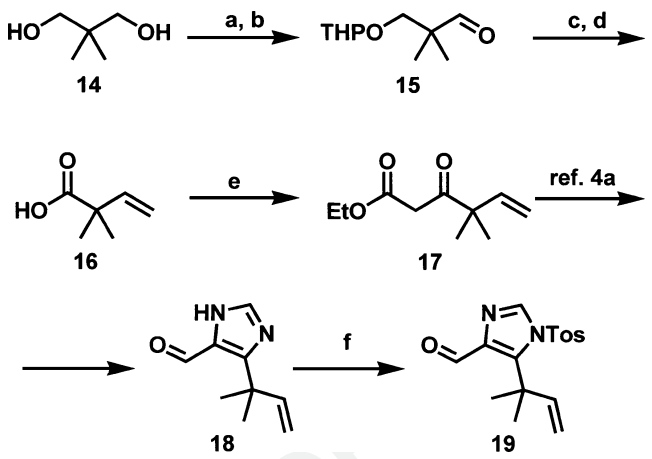

Figure 3. Preparation of the imidazole carboxaldehyde **18**. Reagents and conditions: (a) DHP, PPTS, THF, 60 °C; (b) KBr, TEMPO, NaOCl, CH_2Cl_2, H_2O, $NaHCO_3$, 0 °C, 75% (2 steps); (c) $MePPh_3$, NaH, DMSO, 65 °C to r.t.; (d) "Jones reagent", acetone, 0 °C, 80% (2 steps); (e) Im_2CO, THF, r.t., then $EtOCOCH_2CO_2H$, $Mg(OEt)_2$, THF; (f) TosCl, DBU, CH_2Cl_2, 0 °C to r.t., 80%.

A (**4**) and Neoechinulin A (**5**), substituting formyl-imidazole **10** with the corresponding indoles.

A short, scalable route was employed for the synthesis of the key-intermediate formyl-imidazole **18** (Figure 3). Diol **14** afforded the corresponding aldehyde **15**, after THP monoprotection and subsequent oxidation of the free hydroxyl group (77%, two steps) [13]. Aldehyde **15** was coupled with methylene-triphenylphosphorane, followed by "Jones reagent" – mediated one-step deprotection-oxidation to furnish acid **16** in high yield (75%, two steps). Homologation [14, 15] of **16** yielded the desired α-keto-ester **17**, which was finally transformed to the target formyl imidazole as described by Hayashi [9].

The phosphinyl ester dipeptides **23** and **24** (Figure 4), required for the synthesis of the target molecules, were prepared by coupling phosphinyl glycine derivative **20** [16] and *N*-Boc-*L*-phenylalanine or *N*-Boc-*L*-valine, in a conventional manner.

Their condensation with several *N*-Boc-formyl-imidazoles was then investigated (Table 1). Initially, methylated

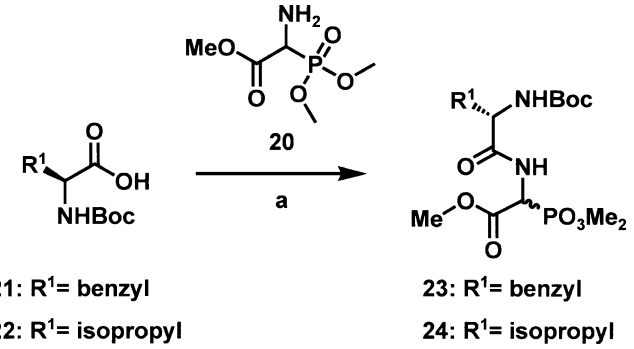

Figure 4. Preparation of the phospinyl-glycine ester. Reagents and conditions: (a) **20**, HOBt, EDC HCl, CH_2Cl_2, r.t., 80–90%.

Table 1. Horner–Emmons coupling reactions

Entry	R^1	Heterocycle	R^2	R^3	R^4	Conditions	Yield[a]
1	$PhCH_2$–	A	Me	Boc	–	LiCl/ DBU	–
2	$PhCH_2$–	A	Me	Boc	–	LiCl/ Et_3N	–
3	$PhCH_2$–	A	Me	Boc	–	DBU	traces
4	$PhCH_2$–	A	R[b]	Boc	–	LDA	–
5	$PhCH_2$–	A	R[b]	Boc	–	NaH	10%
6	$PhCH_2$–	A	R[b]	Boc	–	DBU	5–28%
7	$PhCH_2$–	A	Me	H	–	DBU	–
8	$(Me)_2CH$–	B	–	–	H	DBU	12%
9	$PhCH_2$–	A	Me	H	–	TBSCl/ DBU[c]	20–40%
10	$PhCH_2$–	A	R[b]	H	–	TBSCl/ DBU[c]	35%
11	$(Me)_2CH$–	B	–	–	TBS	DBU	33%
12	$PhCH_2$–	A	R[c]	Trityl	–	DBU	–
13	$PhCH_2$–	A	Me	Tos	–	DBU	69%
14	$(Me)_2CH$–	A	Me	Tos	–	DBU	86%
15	$PhCH_2$–	A	R[b]	Tos	–	DBU	51%[d]
16	$(Me)_2CH$–	A	R[b]	Tos	–	DBU	51%[d]
17	$(Me)_2CH$–	B	–	–	Tos	DBU	90%

[a]Yields refer to chromatographically and spectroscopically (^{1}H NMR) pure materials.
[b]Wherein R represents the group: $-CH_2C(CH_3)_2CH=CH_2$.
[c]*In situ* protection of the imidazoyl-NH carboxaldehyde.
[d]Deprotection occurred during the reaction. Yields refer to the deprotected product.

(R^2 = Me) or reverse prenylated (R^2 = -CH_2 $C(CH_3)_2$-$CH=CH_2$) heterocycles **A** were tested under various alkaline conditions. The preliminary results were rather disappointing, with DBU being the only base to furnish the desired products, albeit in low yields. Surprisingly, the bulkier aldehyde showed a better reaction profile (Table 1, entries 3 *vs.* 6). This might be attributed to the stereoelectronic influence of the bulkier substituent on the conjugation of the aldehyde. Our attention was then focussed upon the choice of the appropriate protective group [17, 18]. Several attempts employing unprotected heterocycles, *N*-trityl or *in situ* prepared *N*-silyl derivatives in the presence of DBU, resulted in only moderate improvement of the coupling yield (Table 1, entries 7–12).

Gratifyingly, tosyl groups proved to be almost ideal (Table 1, entries 13–17) and this may be attributed to the strong electron withdrawing effect of aryl sulfonyl amide. Notwithstanding the observed high chemical yields, the target compounds were also derived as single diastereomers. Proton NMR spectra revealed that both aldehydes **A** and **B** afforded the *Z*-isomer exclusively, in accordance to previous reports [19–22]. More importantly, the sensitive α-aminoacid stereochemistry was totally preserved (*vide infra*). Furthermore, since *N*-tosyl-imidazoles and *N*-tosyl-indoles are effectively deprotected under relatively mild alkaline conditions [23, 24], this protective group could, in some cases, be cleaved concurrently by prolonging the reaction time (Table 1, entries 15 and 16).

To complete the synthesis of the title compounds, the detosylated intermediate **25** (Figure 5) was treated with TFA in order to remove the Boc-protecting group and induce an *in situ* lactamidation. This intra-molecular cyclization was accelerated upon pH adjustment by means of Et_3N [25, 26]. After purification by column chromatography, (–)-Phenylahistine was obtained as white crystals in high overall yield (47% based on phosphonate **23**). The observed optical rotation of the synthetic compound was found to be slightly higher than the one reported for the isolated natural compound.[1] Similarly, the isopropyl derivative **26** furnished optically pure (–)-Aurantiamine [9, 27] in 47% overall yield, based on phosphonate **24**.

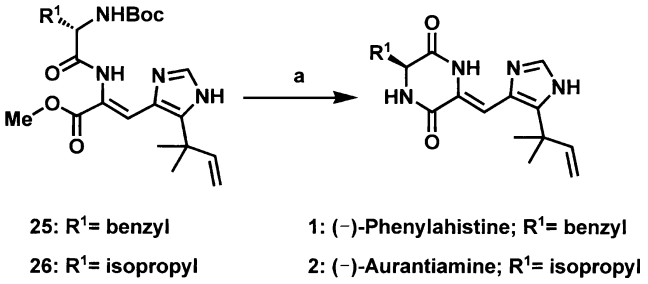

Figure 5. Synthesis of the naturally occurring dehydro-2,5-diketopi- perazine: (–)-Phenylahistine and (–)-Aurantiamine. Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C to r.t. then Et_3N, CH_2Cl_2, 0 °C to r.t., 67%.

Three unnatural derivatives were also synthesized, using this approach (Figure 6). Intermediates **27** and **28** were first detosylated employing TBAF solution in THF and sub-

[1] The specific rotation for the crystalline synthetic material was obtained to be $[\alpha]_D^{25} = -273$ (reported $[\alpha]_D^{25} = -268$). See experimental section.

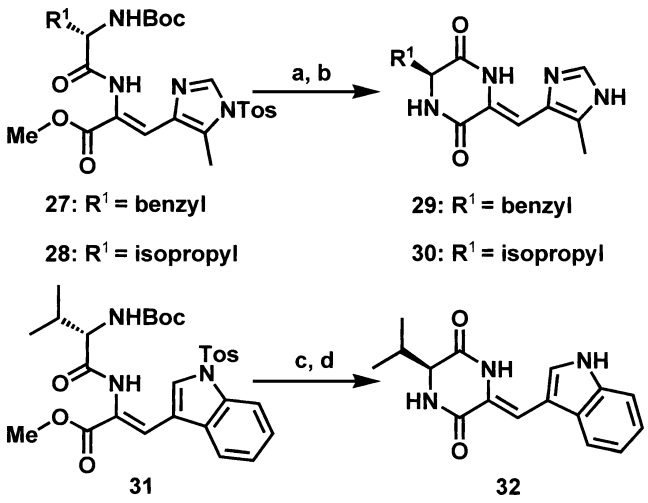

Figure 6. Synthesis of unnatural dehydro-diketopiperazines. Reagents and conditions: (a) TBAF, THF, r.t., 98%; (b) TFA, CH_2Cl_2, 0 °C to r.t. then Et_3N, CH_2Cl_2, 0 °C to r.t., 67%, two steps; (c) TBAF, THF, 55 °C, r.t., 79%; (d) TFA, CH_2Cl_2, 0 °C to r.t. then DBU, CH_2Cl_2, 0 °C to r.t., 67%, two steps.

sequently treated with TFA followed by Et_3N, to form the dehydro-diketopiperazines **29** and **30**, respectively. Finally, indole intermediate **31** was converted to dehydroindole-diketopiperazine **32** (48% overall yield based on phosphonate **24**). In this case, optimum overall yield was achieved employing a higher temperature for the detosylation step and DBU instead of Et_3N for the final cyclization. It is worth noting that an attempted cyclization prior to detosylation proved less effective.

Conclusion

We have presented a new, versatile method for the preparation of dehydro-diketopiperazines, employing a three-component-disconnection strategy. This route offers a very short and highly convergent scheme for the synthesis of the title compounds in optical pure form. Application of our method in the preparation of libraries of these very important anti-cancer lead compounds through solid-phase synthesis [28] is presented in the following article.

Experimental section

General methods

All reactions were carried out under anhydrous conditions and argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone and dichloromethane (CH_2Cl_2) distilled from CaH_2. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All reagents were purchased at highest commercial quality and used without further purification, unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F_{254}), using UV light as visualizing agent and ethanolic phosphomolybdic acid, *p*-anisaldehyde or ninhydrin solution and heat as developing agents. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker AMX-500 or AC-250 instruments. The following abbreviations were used to explain NMR signal multiplicities: br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets. IR spectra were recorded on a Nicolet Magna system 550 FT-IR instrument. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions, and matrix-assisted (MALDI-FTMS) mass spectra were recorded on a PerSeptive Biosystems Voyager IonSpect mass spectrometer. 70-eV electron ionization (EI) was recorded on Finnigan MAT MS 70 spectrometer. Melting points (m.p.) were recorded on a Gallenkamp melting point apparatus and are uncorrected.

Preparation of 2,2-dimethyl-3-(tetrahydro-pyran-2-yloxy)-propan-1-ol

A mixture of neopentyl glycol (**14**) (30 g, 0.29 moles), 2*H*,3*H*-dihydropyran (13.1 mL, 0.144 moles), and *p*-toluenesulfonic acid (496 mg, 5.76 mmoles) in THF/CH_2Cl_2 (1:2) (576 mL) was stirred at room temperature for 3 h under argon atmosphere. The solution was quenched with sodium bicarbonate and the resulting suspension was stirred for 15 min. The solid was filtered and the filtrate was concentrated under vacuum. The product was purified by flash chromatography (silica gel, Hexanes/AcOEt 9:1) to give the monoprotected alcohol as colorless oil (27.4 g, 80%).

$R_f = 0.35$ (Hexane/AcOEt 7:3); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 4.57 (m, 1H; C*H*O(THP)), 3.90–3.80 (m, 1H; CH*H*O(THP)), 3.63 (d, ^2J(H,H) = 9.3 Hz, 1H; C*H*HOTHP), 3.50–3.40 (m, 1H; C*H*HO(THP)), 3.47 (d, ^2J(H,H) = 10.7 Hz, 1H; C*H*HOH), 3.17 (d, ^2J(H,H) = 9.3 Hz, 1H; CH*H*OTHP), 2.86 (d, ^2J(H,H) = 10.7 Hz, 1H; CH*H*OH); 1.88–1.41 (m, 6H; CH_2(THP)), 0.93 (s, 6H; CH_3) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 99.4, 75.6, 62.6, 36.0, 30.5, 25.3, 21.8, 19.7 ppm; FTIR (neat): $\tilde{V}_{max}$ 3445, 2953, 1550, 1472, 1323, 1129, 1030, 900 cm^{-1}.

*Preparation of aldehyde **15***

To a solution of the THP-protected alcohol (27 g, 0.143 moles) in CH_2Cl_2 (480 mL) at 0 °C, an aqueous solution of KBr (1.7 g, 14.3 mmoles, 31 mL) was added followed by the addition of a catalytic amount of TEMPO (22.3 mg, 1.43 mmoles) as a solution in dichloromethane (143 mL). $NaHCO_3$ (15.6 g, 0.186 moles) was dissolved in water

(266 mL) and added to the mixture. NaOCl 4.8% (262.8 mL, 0.172 moles) was added drop-wise and the mixture was stirred for 45 min at 0 °C. The reaction was quenched with 2-propanol (20 mL), extracted with CH_2Cl_2 (3 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to afford aldehyde **15** as a colorless oil (25.6 g, 96%). This aldehyde was used for the next step without further purification.

$R_f = 0.45$ (Hexane/AcOEt 8:2); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 9.60 (s, 1H; C*H*O), 4.60 (m, 1H; C*H*(THP)), 3.84–3.75 (m, 1H; C*H*HO(THP)), 3.80 (d, ^2J(H,H) = 9.6 Hz, 1H; C*H*HOTHP), 3.56–3.49 (m, 1H; C*H*HO(THP)), 3.37 (d, ^3J(H,H) = 9.6 Hz, 1H; CH*H*OTHP), 1.59–1.48 (m, 6H; CH_2(THP)); 1.13 (s, 3H; CH_3); 1.10 (s, 3H; CH_3) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 205.3, 98.8, 72.3, 61.8, 46.8, 30.3, 25.3, 19.0, 18.9 ppm; FTIR (neat): $\tilde{V}_{max}$ 3010, 2947, 2873, 2715, 1730, 1123, 1034 cm^{-1}. MS (GC/MS) calculated for $C_{10}H_{18}O_3$ ([M]$^+$): m/z 186; found 186.

Preparation of 2,2-dimethyl-tetrahydropyran-but-3-enole

NaH (4.8 g, 0.2 moles) was added into a 1-L flask containing DMSO (250 mL) under argon at 0 °C. The temperature was allowed to reach 25 °C and the reaction mixture was stirred for 15 min. The solution was heated to 65 °C for 2.5 h and then cooled to 25 °C. $MePPh_3I$ (86.8 g, 0.215 moles) was added and stirring was continued for 1.5 h. Then a solution of aldehyde **15** (25 g, 0.134 moles) in DMSO (100 mL) was added by cannulation and the mixture was stirred for 30 min. The reaction was quenched with an aqueous, saturated solution of ammonium chloride (100 mL) and extracted with diethyl ether (4 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (Hexane/AcOEt 8:2) and the alkene was obtained as a colorless oil (21.5 g, 87%).

$R_f = 0.60$ (Hexane/AcOEt 8:2); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 5.84 (dd, ^3J(H,H) = 10.8, 17.5 Hz, 1H; CH=CH_2), 5.01–4.88 (m, 2H; CH = CH_2), 4.52 (t, ^3J(H,H) = 3.4 Hz, 1H; C*H*O(THP)), 3.86–3.73 (m, 1H; C*H*HOH), 3.48 (d, ^2J(H,H) = 8.9 Hz, 1H; C*H*HOTHP), 3.46–3.37 (m, 1H; C*H*HO(THP)), 3.03 (d, ^2J(H,H) = 8.9 Hz, 1H; CH*H*OTHP), 1.87–1.40 (m, 6H; CH_2(THP)); 1.01 (3H, s; CH_3); 0.99 (3H, s; CH_3) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 145.9, 111.3, 98.9, 76.2, 61.7, 37.7, 30.5, 25.5, 24.1, 24.0 ppm; FTIR (neat): $\tilde{V}_{max}$ 2950, 2883, 1725, 1140 cm^{-1}.

*Preparation of acid **16***

A solution of the above 2,2-dimethyl-tetrahydropyran-but-3-enole (21.5 g, 0.117 moles) in acetone (700 mL) at 0 °C was treated with "Jones Reagent". After completion of the reaction (TLC monitoring), 2-propanol (60 mL) was added. The reaction mixture was filtered through a celite pad and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (300 mL), washed with saturated $NaHCO_3$ (100 mL), H_2O (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, Hexane/AcOEt 9:1) to afford acid **16** as a colorless liquid (11.0 g, 80%).

$R_f = 0.45$ (Hexane/AcOEt 8:2); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 11.73 (br s, 1H; COOH), 6.04 (dd, ^3J(H,H) = 10.4, 17.1 Hz, 1H; C*H* = CH_2), 5.13 (dd, ^3J(H,H) = 1.0, 17.1 Hz, 1H; CH = C*H*H), 5.05 (dd, ^3J(H,H) = 1.0, 10.4 Hz, 1H; CH = CH*H*), 1.27 (6H, s; CH_3) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 182.3, 14.9, 113.4, 44.7, 29.7, 24.3, 24.0 ppm; FTIR (neat): $\tilde{V}_{max}$ 3250, 2950, 2883, 1700, 1640 cm^{-1}.

*Preparation of ester **17***

To a solution of acid **16** (8.6 g, 0.075 moles) in dry THF (128 mL) under argon, CDI (14.6 g, 0.09 moles) was added and the mixture was stirred at 25 °C for 2 h. Magnesium ethyl malonate (prepared from monoethyl malonate (40.63 g, 0.3075 moles) and magnesium ethoxide (17.166 g, 0.15 moles) [14, 15]) was added by cannulation and the mixture stirred for another 20 h at 25 °C. The solvent was evaporated under vacuum and the residue was dissolved in ethyl acetate (150 mL), washed with aq. saturated NH_4Cl (80 mL), H_2O (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, Hexane/AcOEt 9:1) to afford acid **17** as a yellow oil (11.6 g, 84%).

$R_f = 0.36$ (Hexane/AcOEt 9:1); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 5.86 (dd, ^3J(H,H) = 10.4, 17.1 Hz, 1H; C*H* = CH_2), 5.22 (dd, ^3J(H,H) = 1.0, 10.4 Hz, 1H; CH = C*H*H), 5.17 (dd, ^3J(H,H) = 1.0, 17.1 Hz, 1H; CH = CH*H*), 4.12 (q, ^3J(H,H) = 7.2 Hz, 2H; OCH_2CH$_3$), 3.51 (s, 2H; COCH_2CO), 1.29 (t, ^3J(H,H) = 7.2 Hz, 3H; OCH$_2$CH_3), 1.27 (s, 6H; CH_3) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 205.2, 167.4, 141.3, 115.2, 61.3, 51.4, 44.3, 23.2, 14.2 ppm; FTIR (neat): $\tilde{V}_{max}$ 3010, 2985, 1790, 1735, 1635 cm^{-1}.

*Preparation of aldehyde **19***

To a solution of aldehyde **18** (5 mg, 0.30 mmoles) in dry CH_2Cl_2 (0.4 mL) under argon at 0 °C, DBU (0.13 ml, 0.91 mmoles) and TosCl (143 mg, 0.75 mmoles) were added. After stirring at 25 °C for 16 h, the reaction mixture was quenched with 1N HCl (5mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, Hexane/AcOEt 8:2) to afford tosylate **19** as a light yellow solid (90 mg, 95 %).

$R_f = 0.55$ (Hexane/AcOEt 7:3); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 10.00 (s, 1H; C*H*O), 8.37 (s, 1H;

CH_{Imid}), 7.97 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_{ar}), 7.36 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_{ar}), 6.12 (dd, ^3J(H,H) = 10.4, 17.5 Hz, 1H; CH = CH_2), 5.10 (d, ^3J(H,H) = 17.5 Hz, 1H; CH = CHH), 5.07 (d, ^3J(H,H) = 10.4 Hz, 1H; CH = CHH), 2.49 (s, 3H; Me_{Tos}), 1.48 (s, 6H; *Me*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 178.5, 146.2, 145.7, 141.2, 133.9, 129.7, 129.0, 128.6, 128.2, 112.3, 28.2, 21.7, 9.1 ppm; FTIR (KBr): $\tilde{V}_{\text{max}}$ 3138, 3099, 3063, 2960, 2933, 2873, 1681, 1674, 1599, 1459, 1375, 1348, 1185, 1107, 676 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{16}H_{18}N_2O_3S$ ($[M+H]^+$): m/z 319.1111; found 319.1111.

Preparation of N-p-toluenesulfonylo-5-methyl-imidazole-4-carboxaldehyde

To a solution of 5-methyl-imidazole-4-carboxaldehyde (984 mg, 8.94 mmoles) in dry CH_2Cl_2 (4.5 mL) under argon at 0 °C, DBU (3.4 mL, 22.3 mmoles) and TosCl (3.4 g, 17.8 mmoles) were added. After stirring at 25 °C for 4 h, the reaction mixture was quenched with 1N HCl (10 mL) and extracted with $CHCl_3$ (2 × 20 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 99:1 to 98:2) to afford the *N-p*-toluenesulfonyl-5-methyl-imidazole-4-carboxaldehyde as a light yellow solid (2 g, 85%).

R_f = 0.50 ($CHCl_3$/MeOH 9:1); m.p. 136–139 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 9.87 (s, 1H; CHO), 8.09 (s, 1H; CH_{imid}), 7.77 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_{ar}), 7.35 (d, ^3J(H,H) = 8.2 Hz, 2H; CH_{ar}), 2.55 (s, 3H; Me_{Tos}), 2.40 (s, 3H; *Me*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 187.4, 147.2, 138.5, 137.2, 134.5, 133.8, 130.7, 129.3, 21.8, 9.9 ppm; FTIR (KBr): $\tilde{V}_{\text{max}}$ 3608, 3521, 3450, 3368, 3134, 3088, 3058, 2961, 2931, 2824, 2768, 1688, 1593, 1571, 1490, 1380, 1340, 1200, 1180, 1095, 1052, 790, 710, 670 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{12}H_{12}N_2O_3S$ ($[M+H]^+$): m/z 265.0641; found 265.0637.

Preparation of N-p-toluenesulfonylo-indole-3-carboxaldehyde

To a solution of indole-3-carboxaldehyde (1.16 g, 8 mmoles) in dry Et_3N (20.1 mL), TosCl (2.3 mg, 12 mmoles) was added. The mixture was refluxed for 1.5 h. The reaction mixture was quenched with 1N HCl (5 mL) and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with saturated $NaHCO_3$ (15 mL), brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, Hexane/AcOEt 8:2) to afford the expected tosylated product as a light yellow solid (2.02 g, 85%).

R_f = 0.40 (Hexane/AcOEt 5:5); m.p. 147–149 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 10.08 (s, 1H; CHO), 8.25 (s, 1H; C = CHN(Tos)$_{\text{indole}}$), 8.23 (d, ^3J(H,H) = 7.8 Hz, 1H;CH_{indole}), 7.95 (d, ^3J(H,H) = 7.8 Hz, 1H; CH_{indole}), 7.83 (d, ^3J(H,H) = 8.2 Hz, 2H; CH_{ar}), 7.43–7.27 (m, 2H; CH_{ar}), 7.23 (d, ^3J(H,H) = 8.2 Hz, 2H; CH_{ar}), 2.29 (s, 3H; *Me*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 185.5, 146.2, 136.4, 135.2, 134.2, 130.3, 129.6, 127.2, 126.3, 125.0, 122.6, 122.3, 113.3, 21.6 ppm; FTIR (KBr): $\tilde{V}_{\text{max}}$ 3136, 3087, 3062, 2849, 1669, 1594, 1540, 1450, 1403, 1381, 1290, 1242, 1176, 1130, 1100, 1083, 975, 784, 763, 714, 663 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{16}H_{13}NO_3S$ ($[M+H]^+$): m/z 300.0689; found 300.0684.

*Preparation of phosphonate **23***

To a solution of methyl-2-(benzyloxycarbonylamino)-2-(dimethoxyphosphinyl)-acetate (1 g, 3.02 mmoles) in methanol (55 mL), a catalytic amount of 10% of palladium activated on carbon (100 mg) was added and the mixture was stirred for 4 h under hydrogen atmosphere. The reaction mixture was filtered through a celite pad and the solvent was removed under reduced pressure. The crude mixture of amine **20** was then dissolved in CH_2Cl_2 (40 mL) and *N*-Boc protected *L*-phenylalanine (**21**) (1.04 g, 3.92 mmoles) was added. The mixture was cooled to 0 °C, and HOBT (530.3 mg 3.92 mmoles) and EDC HCl (752.5 mg, 3.92 mmoles) were added successively. The reaction mixture was stirred for 3 h at 25 °C, and then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (40 mL), washed with saturated $NaHCO_3$ (30 mL), H_2O (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 99:1) to afford phosphonate **23** as a light yellow foam (1.073 g, 80%).

R_f = 0.29 ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25} = -11.02$ (c = 2.9 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 7.38–7.15 (m, 5H; *Ph*), 5.26–5.10 (dd, ^2J(H,P) = 21.9 Hz, ^3J(H,H) = 8.93 Hz, 1H; CHPO), 5.04–4.86 (m, 2H; NH), 4.54–4.36 (m, 2H; CHCH$_2$Ph), 3.87–3.68 (m, 6H; PO*Me*), 3.79 (s, 3H; O*Me*), 3.23–2.94 (m, 2H; CH_2Ph), 1.39 (s, 9H; *Boc*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 171.6, 171.5, 166.8, 166.7, 166.6, 155.3, 136.5, 132.1, 131.9, 129.3, 128.5, 128.3, 126.8, 79.9, 64.2, 55.4, 54.2 (d, ^2J(COP) = 7.7 Hz), 54.01 (d, ^2J(COP) = 6.8 Hz), 53.2, 50.1 (d, ^1J(CP) = 150.89 Hz), 38.2, 28.2 ppm; FTIR (neat): $\tilde{V}_{\text{max}}$ 3275, 3030, 3009, 2966, 2930, 2859, 1757, 1714, 1676, 1530, 1500, 1456, 1435, 1368, 1258, 1176, 1031 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{19}H_{29}N_2O_8P$ ($[M+Na]^+$): m/z 467.1554; found 467.1559.

*Preparation of phosphonate **24***

To a solution of methyl-2-(benzyloxycarbonylamino)-2-(dimethoxyphosphinyl)-acetate (297 mg, 0.89 mmoles) in methanol (10 mL), a catalytic amount of 10% of palladium activated on carbon (30 mg) was added and the mixture was stirred for 4 h under hydrogen atmosphere. The

reaction mixture was filtered through a celite pad and the solvent was removed under reduced pressure. The crude mixture of amine **20** was subsequently dissolved in CH_2Cl_2 (10 mL) under argon and *N*-Boc protected *L*-valine (**22**, 253.23 mg, 1.17 mmoles) was added. The mixture was cooled to 0 °C, and HOBT (181.5 mg, 1.34 mmoles) and EDC HCl (257.5 mg, 1.34 mmoles) were added successively. The reaction mixture was stirred for 3 h at 25 °C, and then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (30 mL), washed with saturated $NaHCO_3$ (20 mL), H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, and the solvent was concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 99:1) to afford phosphonate **24** as a white solid (310 mg, 87%).

$R_f = 0.13$ ($CHCl_3$/MeOH 95:5); m.p. 93–95 °C; $[\alpha]_D^{25} = -10$ (c = 2.37 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 7.69–7.44 (m, 1H; N*H*CO), 5.36–5.21 (m, 1H; C*H*PO), 5.17 (d, ^3J(H,H) = 8.9 Hz, 1H; N*H*Boc), 4.23–4.01 (m, 1H; C*H*CHMe$_2$), 3.82–3.69 (m, 6H; PO(*Me*)$_2$), 3.76 (s, 3H; O*Me*), 2.19–1.99 (m, 1H; C*H*Me$_2$), 1.37 (s, 9H; *Boc*), 0.92 (d, ^3J(H,H) = 6.69 Hz, 3H; CH*Me*), 0.85 (d, ^3J(H,H) = 6.69 Hz, 3H; C*H*Me) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 171.8, 166.8, 155.6, 128.2, 79.6, 59.5 (d, ^2J(COP) = 9.3 Hz), 54.2 (d, ^2J(COP) = 6.8 Hz), 53.1 (d, ^2J(COP) = 5.1 Hz), 49.9 (d, ^1J(CP) = 149.2 Hz), 31.1, 28.2, 19.1, 17.4 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3262, 2966, 2863, 1748, 1670, 1530, 1460, 1376, 1253, 1176, 1045 cm^{-1}, HRMS (MALDI-FTMS) calculated for $C_{15}H_{29}N_2O_8P$ ($[M + Na]^+$): m/z 419.1554; found 419.1558.

*Preparation of N-tosyl alkene **27***

To a mixture of *N*-*p*-toluenesulfonyl-5-methyl-imidazole-4-carboxaldehyde (16 mg, 0.061 mmoles) and phosphonate **23** (37.6 mg, 0.085 mmoles) in dry CH_2Cl_2 (0.3 mL) under argon at 0 °C, DBU (18.1 μl, 0.121 mmoles) was added. After stirring at 25 °C for 1.5 h, the reaction mixture was quenched with saturated NH_4Cl (3 mL) and extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, Hexane/AcOEt 7:3 to 5:5) to afford alkene **27** as a light yellow oil (24.4 mg, 69%).

$R_f = 0.41$ (Hexane/AcOEt 5:5); $[\alpha]_D^{25} = -16.4$ (c = 0.44 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 10.42 (br s, 1H; N*H*CO), 8.03 (s, 1H; CH_{imid}), 7.77 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_{Tos}), 7.38 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_{Tos}), 7.31–7.04 (m, 5H; *Ph*), 6.33 (s, 1H; C=C*H*-Imid), 5.11 (br s, 1H; N*H*Boc), 4.69–4.50 (m, 1H; C*H*CH$_2$Ph), 3.83 (s, 3H; O*Me*), 3.25–3.01 (m, 2H; CH_2Ph), 2.47 (s, 3H; *Me*$_{Tos}$), 2.31 (s, 3H; *Me*$_{Imid}$), 1.46 (s, 9H; *Boc*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 187.6, 169.8, 165.5, 155.2, 146.8, 136.3, 134.3, 130.6, 129.6, 128.3, 127.6, 127.2, 126.8, 110.0, 79.8, 55.6, 52.4, 38.7, 29.7, 28.3, 21.8, 9.3 ppm; FTIR (neat): $\tilde{V}_{max}$ 3457, 3036, 2960,. 2929, 2861, 1729, 1693, 1657, 1483, 1384, 1308 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{29}H_{34}N_4O_7S$ ($[M + H]^+$): m/z 583.2221; found 583.2249.

*Preparation of NH-alkene of **27***

To a solution of *N*-Tosyl imidazole derivative **27** (20 mg, 0.034 mmoles) in THF (0.2 mL) at 0 °C, TBAF (1M in THF, 70 μL) was added. The ice-bath was removed and the reaction was stirred for 20 min at 25 °C. The reaction mixture was quenched with saturated ammonium chloride (2 mL) and extracted with $CHCl_3$ (2 × 15 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 97:3) to afford the deprotected alkene as a white solid (14.3 mg, 98%).

$R_f = 0.54$ ($CHCl_3$/MeOH 9:1); m.p. 120–124 °C; $[\alpha]_D^{25} = +8.5$ (c = 0.24 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 11.18 (br s, 1H; CON*H*C=), 10.54 (br s, 1H; NH_{Imid}), 7.54 (br s, 1H; CH_{Imid}), 7.46–7.14 (m, 5H; *Ph*), 6.57 (s, 1H; C=C*H*-Imid), 5.30–5.05 (m, 1H; N*H*Boc), 4.72–4.16 (m, 1H; C*H*CHMe$_2$), 3.81 (s, 3H; OMe), 3.31 (dd, ^3J(H,H) = 5.1 Hz, ^2J(H,H) = 13.8 Hz, 1H; C*H*HPh), 3.19–2.98 (m, 1H; CH*H*Ph), 2.29 (s, 3H; *Me*), 1.39 (s, 9H; *Boc*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 165.6 138.6, 136.0, 133.8, 130.9, 129.1, 128.8, 128.3, 127.3, 124.4, 112.9, 81.8, 57.4, 55.7, 52.3, 36.7, 29.7, 28.3 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3365, 2975, 2934, 1682, 1503, 1444, 1371 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{22}H_{28}N_4O_5$ ($[M + H]^+$): m/z 429.2132; found 429.2126.

*Preparation of alkene **25***

To a mixture of *N*-*p*-toluenesulfonyl-5-(1,1-dimethyl-2-propenyl)-imidazole-4-carboxaldehyde (**19**, 46 mg, 0.145 mmoles) and phosphonate **23** (96.3 mg, 0.217 mmoles) in dry CH_2Cl_2(0.5 mL) under argon at 0 °C, DBU (43.2 μL, 0.289 mmoles) was added. After stirring at room temperature for 16 h, the reaction mixture was quenched with saturated NH_4Cl (5 mL) and extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, Hexane/AcOEt 7:3 to 5:5) to afford alkene **25** as a yellow oil (36.2 mg, 51.7%).

$R_f = 0.25$ (Hexane/AcOEt 6:4); $[\alpha]_D^{25} = +13.42$ (c = 2.23 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 11.24 (br s, 1H; CON*H*C=), 10.11 (br s, 1H; NH_{Imid}), 7.56 (br s, 1H; CH_{Imid}), 7.42–7.19 (m, 5H; *Ph*), 6.80 (s, 1H; C=C*H*-Imid), 6.28–5.85 (m, 1H; C*H*=CH$_2$), 5.30 (br s, 1H; N*H*Boc), 5.24–5.01 (m, 2H; CH=CH_2), 4.72–4.32 (m, 1H; C*H*CH$_2$Ph), 3.79 (s, 3H; O*Me*), 3.42–2.93 (m, 2H; CH_2Ph), 1.48 (s, 6H; *Me*), 1.41 (s, 9H; *Boc*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 170.5, 165.7,155.9,

145.7, 136.2, 130.9, 129.4, 128.8, 128.6, 127.6, 126.9, 112.2, 80.6, 56.4, 52.3, 38.3, 30.3, 28.2 ppm; FTIR (neat): $\tilde{V}_{max}$ 3310, 3011, 2962, 2933, 2870, 1734, 1696, 1501, 1472, 1373 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{26}H_{34}N_4O_5$ ($[M+H]^+$): m/z 483.2602; found 483.2590.

*Preparation of N-tosyl alkene **28***

To a mixture of *N*-*p*-toluenesulfonyl-5-methyl-imidazole-4-carboxaldehyde (23.1 mg, 0.087 mmoles) and phosphonate **24** (48.5 mg, 0.122 mmoles) in dry CH_2Cl_2 (0.44 mL) under argon at 0 °C, DBU (26.1 μL, 0.175 mmoles) was added. After stirring at 25 °C for 1.5 h, the reaction mixture was quenched with saturated NH_4Cl (4 mL) and extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, Hexane/AcOEt 7:3 to 5:5) to afford alkene **28** as a white foam (40.3 mg, 86.2%).

$R_f = 0.41$ (Hexane/AcOEt 6:4); $[\alpha]_D^{25} = +8.2$ (c = 0.6 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 10.41 (s, 1H; CON*H*C=), 8.12 (s, 1H; C*H*$_{Imid}$), 7.76 (d, ^3J(H,H) = 8.7 Hz, 2H; C*H*$_{Tos}$), 7.38 (d, ^3J(H,H) = 8.7 Hz, 2H; C*H*$_{Tos}$), 6.31 (s, 1H; C=C*H*-Imid), 5.21 (d, ^3J(H,H) = 9.2 Hz, 1H; N*H*Boc), 4.33–4.18 (m, 1H; C*H*CHMe$_2$), 3.78 (s, 3H; O*Me*), 2.44 (s, 3H; *Me*$_{Tos}$), 2.28 (s, 3H; *Me*$_{Imid}$), 2.30–2.17 (m, 1H; C*H*Me$_2$), 1.44 (s, 9H; *Boc*), 1.02 (d, ^3J(H,H) = 6.4 Hz, 3H; CH*Me*), 0.94 (d, ^3J(H,H) = 6.9 Hz, 3H; CH*Me*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 170.3, 165.4, 164.3, 155.7, 146.8, 136.5, 134.2, 130.6, 128.5, 128.3, 127.6, 127.3, 109.7, 79.6, 59.3, 52.3, 31.8, 28.4, 21.8, 19.1, 17.3, 9.4 ppm; FTIR (neat): $\tilde{V}_{max}$ 3416, 3008, 2962, 2926, 1683, 1647, 1486, 1381 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{25}H_{34}N_4O_7S$ ($[M+H]^+$): m/z 535.2221; found 535.2226.

*Preparation of NH-alkene of **28***

To a solution of alkene **28** (20 mg, 0.037 mmoles) in THF(0.21 mL) at 0 °C, TBAF (1M in THF, 75 μL) was added. The ice-bath was removed and the reaction was stirred for 20 min at room temperature. The reaction mixture was quenched with saturated NH_4Cl (2 mL) and extracted with $CHCl_3$ (2 × 15 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 98:2) to afford the expected alkene as a colorless oil (14.3 mg, 99%).

$R_f = 0.50$ ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25} = +100$ (c = 0.24 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 11.27 (br s, 1H; CON*H*C=), 10.70 (br s, 1H; N*H*$_{Imid}$), 7.71 (s, 1H; C*H*$_{Imid}$), 6.54 (s, 1H; C=C*H*-Imid), 5.13 (br s, 1H; N*H*Boc), 4.14–3.98 (m, 1H; C*H*CHMe$_2$), 3.79 (s, 3H, O*Me*), 2.45–2.12 (m, 4H; *Me*, C*H*Me$_2$), 1.44 (s, 9H; *Boc*), 1.18–0.94 (m, 6H; CH*Me*$_2$) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 167.7, 165.6, 138.6, 133.9, 130.9, 128.8, 112.9, 80.1, 52.2, 28.4, 19.3 ppm; FTIR (neat): $\tilde{V}_{max}$ 3284, 2960, 2928, 2879, 2862, 1728, 1683, 1507, 1474, 1376 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{18}H_{28}N_4O_5$ ($[M+H]^+$): m/z 381.2132; found 381.2137.

*Preparation of alkene **26***

To a mixture of *N*-*p*-toluenesulfonyl-5-(1,1-dimethyl-2- propenyl)-imidazole-4-carboxaldehyde (19.2 mg, 0.060 mmoles) and phosphonate **24** (33 mg, 0.084 mmoles) in dry CH_2Cl_2 (0.2 mL) under argon at 0 °C, DBU (18 μL, 0.120 mmoles) was added. After stirring at 25 °C for 24 h, the reaction mixture was quenched with saturated NH_4Cl (4 mL) and extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 98:2) to afford alkene **26** as a colorless oil (13.4 mg, 51.1%).

$R_f = 0.46$ ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25} = +57.9$ (c = 0.1 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 11.17 (br s, 1H; CON*H*C=), 10.45 (br s, 1H; N*H*$_{Imid}$), 7.79 (br s, 1H; C*H*$_{Imid}$), 6.83 (s, 1H; C=C*H*-Imid), 6.26–5.86 (m, 1H; C*H*=CH$_2$), 5.44 (br d, ^3J(H,H) = 10.1 Hz, 1H; N*H*Boc), 5.24–5.03 (m, 2H; CH=C*H*$_2$), 4.34–4.15 (m, 1H; C*H*CHMe$_2$), 3.79 (s, 3H; O*Me*), 2.35–2.14 (m, 1H; C*H*Me$_2$), 1.46 (s, 6H; C*Me*$_2$), 1.44 (s, 9H; *Boc*), 1.17–0.86 (m, 6H; CH*Me*$_2$) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 169.9, 165.7, 156.1, 144.8, 137.2, 133.2, 128.6, 125.6, 113.9, 112.8, 79.8, 62.2, 59.7, 52.2, 32.6, 29.6, 28.3, 28.0, 19.1, 17.3 ppm; FTIR (neat): $\tilde{V}_{max}$ 3424, 3010, 2972, 2930, 2863, 1670, 1651, 1499, 1370 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{22}H_{34}N_4O_5$ ($[M+H]^+$): m/z 435.2602; found 435.2604.

*Preparation of N-tosyl-indole **31***

To a mixture of *N*-*p*-toluenesulfonyl-indole-3-carbox aldehyde (100 mg, 0.334 mmoles) and phosphonate **24** (172.1 mg, 0.434 mmoles) in dry CH_2Cl_2 (1.1 mL) under argon at 0 °C, DBU (0.1 mL, 0.668 mmoles) was added. After stirring at 25 °C for 45 min, the reaction mixture was quenched with saturated NH_4Cl (5 mL) and extracted with $CHCl_3$ (2 × 20 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 101:1) to afford alkene **31** as a light yellow solid (175 mg, 90%).

$R_f = 0.40$ ($CHCl_3$/MeOH 9:1); m.p. 137–140 °C; $[\alpha]_D^{25} = +1.2$ (c = 0.36 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 7.96 (br s, 1H; CON*H*C=), 7.95–7.56 (m, 4H; C*H*$_{ar}$), 7.35 (s, 1H; C=C*H*-Indole), 7.34–7.19 (m, 4H; C*H*$_{ar}$), 5.06 (d, ^3J(H,H) = 7.8 Hz, 1H; N*H*Boc), 4.14 (dd, ^3J(H,H) = 5.9, 8.6 Hz, 1H; C*H*CHMe$_2$), 3.85 (s, 3H;O*Me*), 2.34 (s, 3H, *Me*$_{Tos}$), 2.33–2.29 (m, 1H; C*H*Me$_2$),

1.49 (s, 9H; *Boc*), 1.08 (d, ^3J(H,H) = 6.7 Hz, 3H; CH*Me*Me), 1.02 (d, ^3J(H,H) = 7.1 Hz, 3H; CHMe*Me*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 170.3, 129.9, 128.1, 127.1, 125.3, 123.7, 122.9, 119.3, 113.6, 80.7, 60.5, 52.6, 30.3, 29.7, 28.3, 21.6, 19.5, 17.7 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3337, 3010, 2967, 1722, 1685, 1509, 1388; HRMS (MALDI-FTMS) calculated for $C_{29}H_{35}N_3O_7S$ ($[M + Na]^+$): m/z 592.2088; found 592.2111.

Preparation of NH-indole

To a solution of *N*-tosyl-indole derivative **31** (31.3 mg, 0.055 mmoles) in THF (0.55 mL) 25 °C, TBAF (1M in THF, 0.26 mL) was added. The reaction was heated at 55 °C and stirred for 24 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL) and extracted with $CHCl_3$ (2 × 15 mL). The organic layer was washed with citric acid (10%, 5mL), H_2O (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 150:0.1) to afford the expected alkene as a yellow foam (18 mg, 79%).

R_f = 0.65 ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25}$ = +10.2 (c = 0.14 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 9.06 (br s, 1H; NH_{Indole}), 8.04 (br s, 1H; CON*H*C=), 7.79 (br s, 1H; C=C*H*-NH_{Indole}), 7.54 (d, ^3J(H,H) = 7.8 Hz, 1H; CH_{Indole}), 7.36 (s, 1H; C=C*H*-Indole), 7.30 (d, ^3J(H,H) = 7.8 Hz, 1H; CH_{Indole}), 7.14 (t, ^3J(H,H) = 7.1 Hz, 1H; CH_{Indole}), 7.05 (t, ^3J(H,H) = 7.4 Hz, 1H; CH_{Indole}), 5.24 (d, ^3J(H,H) = 9.3 Hz, 1H; N*H*Boc), 4.76–4.63 (m, 1H; C*H*CH(Me)$_2$), 3.86 (s, 3H; O*Me*), 2.51–2.32 (m, 1H; C*H*(Me)$_2$), 1.30 (s, 9H; *Boc*), 1.12 (d, ^3J(H,H) = 7.1 Hz, 3H; *Me*), 1.08 (d, ^3J(H,H) = 6.7 Hz, 3H; *Me*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 130.9, 128.8, 127.7, 127.6, 127.3, 122.8, 120.8, 118.9, 118.1, 111.5, 80.4, 59.7, 58.9, 52.2, 31.4, 30.9, 29.7, 28.2, 24.1, 19.8, 19.5, 17.1, 14.1, 13.7 ppm; FTIR (neat): $\tilde{V}_{max}$ 3285, 3062, 2968, 2929, 2863, 1714, 1667, 1633, 1521, 1466, 1432, 1372 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{22}H_{29}N_3O_5$ ($[M + Na]^+$): m/z 438.1999; found 438.1994.

*Preparation of dehydro-2,5-diketopiperazine **29***

To a solution of detosylated **27** (13.5 mg, 0.031 mmoles) in dry CH_2Cl_2 (2.1 mL) under argon at 0 °C, trifluoroacetic acid (0.52 mL) was added. The ice-bath was removed and the reaction was stirred for 3.5 h at room temperature. The solvent and the excess of TFA were removed under reduced pressure and the residue was redissolved using dry CH_2Cl_2 (2.52 mL) under argon. Triethylamine (20% in CH_2Cl_2) was then added at 25 °C. After completion of the reaction (4 h), an aqueous saturated NH_4Cl solution (5 mL) was added and the mixture was extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 98:2) to afford 2,5-diketopiperazine **29** as a white solid (7.5 mg, 80.3% 2 steps).

R_f = 0.28 ($CHCl_3$/MeOH 9:1); m.p. 283–284 °C; $[\alpha]_D^{25}$ = −168.1 (c = 0.21 in DMSO); ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ 11.48 (br s, 1H; CON*H*C=), 8.32 (br s, 1H; NH_{Imid}), 7.74 (s, 1H; CH_{Imid}), 7.24–7.14 (m, 5H; *Ph*), 6.21 (s, 1H; C=C*H*-Imid), 4.49–4.45 (m, 1H; C*H*CH$_2$Ph), 3.33 (br s, 1H; CHN*H*CO), 3.20 (dd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 4.2 Hz, 1H; C*H*HPh), 2.94 (dd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 4.8 Hz, 1H; CH*H*Ph), 2.19 (s, 3H; *Me*) ppm; ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, 25 °C): δ 164.2, 158.9, 135.6, 134.6, 132.5, 130.1, 130.0, 128.0, 127.8, 127.5, 126.6, 123.4, 101.6, 55.9, 38.7, 9.1 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3397, 3180, 2961, 2931, 2880, 2859, 1736, 1680, 1446, 1287 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{16}H_{16}N_4O_2$ ($[M + Na]^+$): m/z 319.1165; found 319.1163.

Preparation of (–)-phenylahistine, 1

To a solution of alkene **25** (28.6 mg, 0.051 mmoles) in dry CH_2Cl_2(3.4 mL) under argon at 0 °C, trifluoroacetic acid (0.85 mL) was added. The ice-bath was removed and the reaction was stirred for 2 h at 25 °C. The excess of TFA and the solvent were removed under reduced pressure and the residue was redissolved using dry CH_2Cl_2(4.1 mL) under argon. Triethylamine (20% in CH_2Cl_2, 1 mL) was then added at 25 °C. After completion of the reaction (2h), an aqueous saturated ammonium chloride solution (10 mL) was added and the mixture was extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 99:1) to afford the natural product (–)-Phenylahistine **1**, ($[\alpha]_D^{25}$ = – 180.5) as a white solid (16.1 mg, 90% 2 steps). One recrystallization from benzene afforded almost quantitatively white crystals of the natural product, $[\alpha]_D^{25}$ = −273, (reported $[\alpha]_D^{25}$ = −268).

R_f = 0.39 ($CHCl_3$/MeOH 9:1); m.p. 228–229 °C; $[\alpha]_D^{25}$ = −273 (c = 0.1 in MeOH); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 12.00 (br s, 1H; CON*H*C=), 9.14 (br s, 1H; NH_{Imid}), 7.55 (s, 1H; CH_{Imid}), 7.42–7.19 (m, 5H, *Ph*), 6.88 (s, 1H; C=C*H*-Imid), 6.02 (dd, ^3J(H,H) = 17.5, 10.8 Hz, 1H; C*H*=CH$_2$), 5.76 (br s, 1H; CHN*H*CO), 5.20 (d, ^3J(H,H) = 10.8 Hz, 1H; CH=C*H*H), 5.15 (d, ^3J(H,H) = 17.5 Hz, 1H; CH=CH*H*), 4.34 (ddd, ^3J(H,H) = 10.1, 3.4, 2.3 Hz, 1H; C*H*CH$_2$Ph), 3.50 (dd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 3.4 Hz, 1H; C*H*HPh), 2.95 (dd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 10.1 Hz, 1H; CH*H*Ph), 1.50 (s, 6H; *Me*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 164.7, 159.9, 144.6, 136.6, 135.5, 132.4, 132.2, 129.5, 129.1, 127.5, 123.8, 113.5, 105.4, 57.2, 41.3, 37.6, 27.9 ppm; FTIR (KBr): $\tilde{V}_{max}$ 3434, 2961, 2928, 1651, 1452, 1391, 1277 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{20}H_{22}N_4O_2$ ($[M + H]^+$): m/z 351.1815; found 351.1825.

*Preparation of dehydro-2,5-diketopiperazine **30***

To a solution of detosylated **28** (11.4 mg, 0.030 mmoles) in dry CH_2Cl_2 (1.6 mL) under argon at 0 °C, trifluoroacetic acid (0.4 mL) was added. The ice-bath was removed and the reaction was stirred for 4.5 h at 25 °C. The excess of TFA and the solvent were removed under reduced pressure and the residue was redissolved using dry CH_2Cl_2 (2 mL) under argon. Triethylamine (20% in CH_2Cl_2, 0.52 mL) was then added at 0 °C. After completion of the reaction (24 h), an aqueous saturated NH_4Cl solution (5 mL) was added and the mixture was extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 98:2) to afford 2,5-diketopiperazine **30** asa colorless foam (5.9 mg, 80% 2 steps).

$R_f = 0.40$ ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25} = -77$ (c = 0.18 in MeOH); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 11.77 (br s, 1H; CON*H*C=), 9.18 (br s, 1H; NH_{Imid}), 7.58 (s, 1H; CH_{Imid}), 6.69 (s, 1H; C=C*H*-Imid), 5.88 (br s, 1H; CON*H*CH), 4.07 (t, ^3J(H,H) = 2.8 Hz, 1H; C*H*CH(Me)$_2$), 2.55–2.42 (m, 1H; C*H*(Me)$_2$), 2.37 (s, 3H; *Me*$_{\text{Imid}}$), 1.06 (d, ^3J(H,H) = 6.9 Hz, 3H; CH*Me*), 0.96 (d, ^3J(H,H) = 6.9 Hz, 3H; C*H*Me) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 164.9, 133.5, 130.9, 128.8, 109.5, 103.9, 61.3, 33.0, 18.6, 15.8, 9.5 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3433, 2958, 2926, 2863, 1732, 1682, 1664, 1636, 1462, 1280 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{12}H_{16}N_4O_2$ ([M + H]$^+$): *m*/*z*249.1346; found 249.1343.

Preparation of (–)-aurantiamine, 2

To a solution of alkene **26** (9 mg, 0.021 mmoles) in dry CH_2Cl_2 (0.83 mL) under argon at 0 °C, trifluoroacetic acid (0.21 mL) was added. The ice-bath was removed and the reaction was stirred for 1.5 h at 25 °C. The excess of TFA and the solvent were removed under reduced pressure and the residue was redissolved using dry CH_2Cl_2 (1.7 mL) under argon. Triethylamine (20% in CH_2Cl_2, 0.41 mL) was then added at 0 °C. The ice-bath was removed and the reaction was allowed to stir for 12 h at 25 °C. After completion of the reaction, an aqueous, saturated NH_4Cl solution (5 mL) was added and the mixture was extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 99:1) to afford the natural product (–)-Aurantiamine **2** as a white solid (5.8 mg, 92% 2 steps).

$R_f = 0.39$ ($CHCl_3$/MeOH 9:1); m.p. 236–237 °C; $[\alpha]_D^{25} = -95$ (c = 0.1 in MeOH); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 12.05 (br s, 1H; CON*H*C=), 9.37 (br s, 1H; NH_{Imid}), 7.55 (s, 1H; CH_{Imid}), 6.94 (s, 1H; C=C*H*-Imid), 6.19 (br s, 1H; CHN*H*CO), 6.04 (dd, ^3J(H,H) = 10.6, 17.7Hz, 1H; C*H*=CH$_2$), 5.19 (d, ^3J(H,H) = 10.5 Hz, 1H; CH=C*H*H), 5.16 (d, ^3J(H,H) = 17.4 Hz, 1H; CH=CH*H*), 4.06 (t, ^3J(H,H) = 2.3 Hz, 1H; C*H*CHMe$_2$), 2.57–2.38 (m, 1H; C*H*Me$_2$), 1.51 (s, 6H; C(*Me*)$_2$), 1.06 (d, ^3J(H,H) = 6.9 Hz, 3H; CH*Me*), 0.96 (d, ^3J(H,H) = 6.9 Hz, 3H; CH*Me*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 165.1, 160.7, 144.7, 136.7, 132.5, 132.3, 123.7, 113.3, 105.2, 61.2, 37.6, 32.9, 27.9, 18.7, 15.7 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3405, 2958, 2921, 2866, 1738, 1674, 1641, 1443 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{16}H_{17}N_3O_2$ ([M + H]$^+$): *m*/*z* 303.1815; found 303.1813.

*Preparation of dehydro-indole-2,5-diketopiperazine **32***

To a solution of the detosylated indole derivative **31** (10.4 mg, 0.025 mmoles) in dry CH_2Cl_2 (0.67 mL) under argon at 0 °C, trifluoroacetic acid (0.17 mL) was added. The ice-bath was removed and the reaction was stirred for 2 h at 25 °C. The excess of TFA and the solvent were removed under reduced pressure and the residue was redissolved using dry CH_2Cl_2 (0.5 mL) under argon. DBU (19 μL) was then added at 0 °C. The ice-bath was removed and the reaction was allowed to stir for 24 h at 25 °C. After completion of the reaction, an aqueous saturated NH_4Cl solution (5 mL) was added and the mixture was extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The mixture was subjected to flash chromatography (silica gel, $CHCl_3$/MeOH 99:1) to afford 2,5-diketopiperazine **32** as a light yellow foam (4.8 mg, 67.3% 2 steps).

$R_f = 0.42$ ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25} = -4.7$ (c = 0.38 in DMSO); ^{1}H NMR (250 MHz, DMSO-*d*6, 25 °C): δ 11.62 (br s, 1H; NH_{Indole}), 9.48 (br s, 1H; CON*H*C=), 8.30 (br s, 1H; CON*H*CH), 7.91 (d, ^3J(H,H) = 2.1 Hz, 1H; C=C*H*NH$_{\text{Indole}}$), 7.63 (d, ^3J(H,H) = 7.0 Hz, 1H; CH_{Indole}), 7.42 (d, ^3J(H,H) = 7.4 Hz, 1H; CH_{Indole}), 7.22–7.04 (m, 2H; CH_{Indole}), 6.98 (s, 1H; C=C*H*-Indole), 3.77 (t, ^3J(H,H) = 3.3 Hz, 1H; C*H*CH(Me)$_2$), 2.57–2.47 (m, 1H; C*H*(Me)$_2$), 0.95 (d, ^3J(H,H) = 7.0 Hz, 3H; *Me*), 0.88 (d, ^3J(H,H) = 7.0 Hz, 3H; *Me*) ppm; ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, 25 °C): δ 166.2, 161.1, 135.6, 126.9, 126.3, 122.5, 122.0, 119.8, 118.0, 111.8, 107.9, 107.3, 60.7, 33.3, 18.3, 17.1 ppm; FTIR (KBr): $\tilde{V}_{\max}$ 3415, 2965, 2932, 2851, 1742, 1676, 1657, 1463, 1434, 1387 cm^{-1}; HRMS (MALDI-FTMS) calculated for $C_{16}H_{17}N_3O_2$ ([M]$^+$): *m*/*z* 283.1321; found 283.1319.

Acknowledgement

The authors would like to thank Dr. A.T. Strongilos for his assistance in the synthesis of reverse prenylated formylimidazole 18.

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