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A Metal Free Domino Process for Regioselective Synthesis of 1,2,4-Trisubstituted Pyrroles: Application towards the Formal Synthesis of Ningalin B

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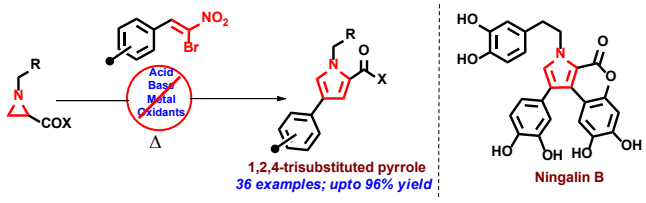


Abstract: A new one-pot transition-metal, acid/base free domino process has been developed for the regioselective synthesis of 1,2,4-trisubstituted pyrroles. The process involves 1,3-dipolar cycloaddition of unsymmetrical azomethine ylide resulting from the thermal C-C bond cleavage of unactivated aziridines with *β*-bromo-*β*-nitrostyrene, followed by a cascade of elimination and aromatization reaction sequence to preferentially furnish 1,2,4-trisubstituted pyrroles instead of the expected 1,2,3-trisubstituted pyrroles, in good to excellent yields. Further, the application of the methodology for the formal synthesis of ningalin B is delineated.

Introduction

Pyrroles are one of the most prevalent N-heterocycles which manifests in numerous molecules of natural origin[1] and human imagination for diverse applications ranging from pharmaceutics[2] to material science.[3] A few representative examples of biologically interesting and structurally fascinating pyrrole containing alkaloids and therapeutically potent molecule with a central pyrrole core are as captured in Figure 1.

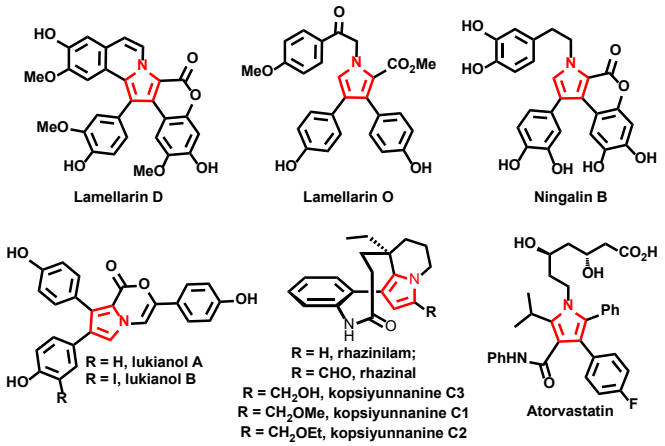
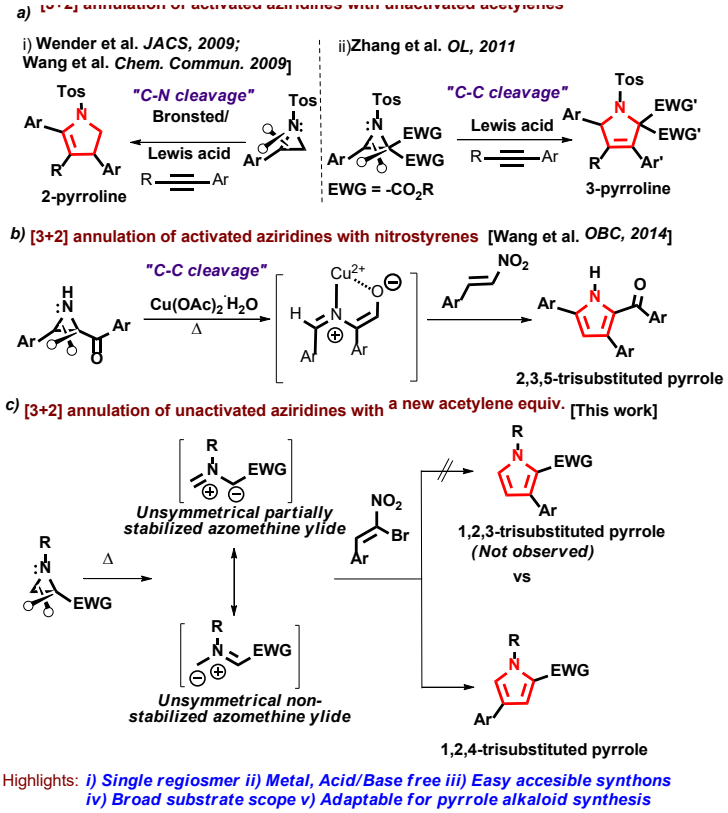


Figure 1. Representative natural products and pharmaceutically active molecule with a central pyrrole core.

Despite a plethora of classical[4] and recently developed[5] synthetic approaches towards the construction of polysubstituted pyrroles, highly regioselective synthesis of pyrroles with precise substituent location constitute a greener pasture for exploration in heterocyclic chemistry. Among the various substituted pyrroles, we comprehended that in particular, the approaches towards 1,2,3/1,2,4-trisubstituted pyrroles[6,7] are very limited despite interesting bioactivity profile of such pyrroles.[8] Therefore, in view of the scarcity of the methods towards such trisubstituted pyrroles and our ongoing interest[9] towards the synthesis of pyrrole based alkaloids we were motivated to develop a transition metal as well as acid/base free approach for the regioselective synthesis of 1,2,3/1,2,4-trisubstituted pyrroles.

Our quest for a versatile starting material culminated on aziridines in view of their inherent reactivity due to the existing ring-strain.[10] Through the seminal work of Padwa,[11] Huisgen,[12] and Katritzky[13] its well-established how the thermal C-C bond cleavage in unactivated aziridines can be exploited to harness the potential of the resultant azomethine ylides for annulation with activated dipolarophiles to access dihydropyrroles/pyrroles. However, the method suffers from the limitation of poor regioselectivity in case of unsymmetrical dipolarophiles and poor reactivity with unactivated dipolarophiles rendering them unsuitable for total synthesis endeavor.[14] Nevertheless, recently independent reports from Wender et al. as well as Wang and co-workers demonstrated the generation of 1,3-dipolar species from



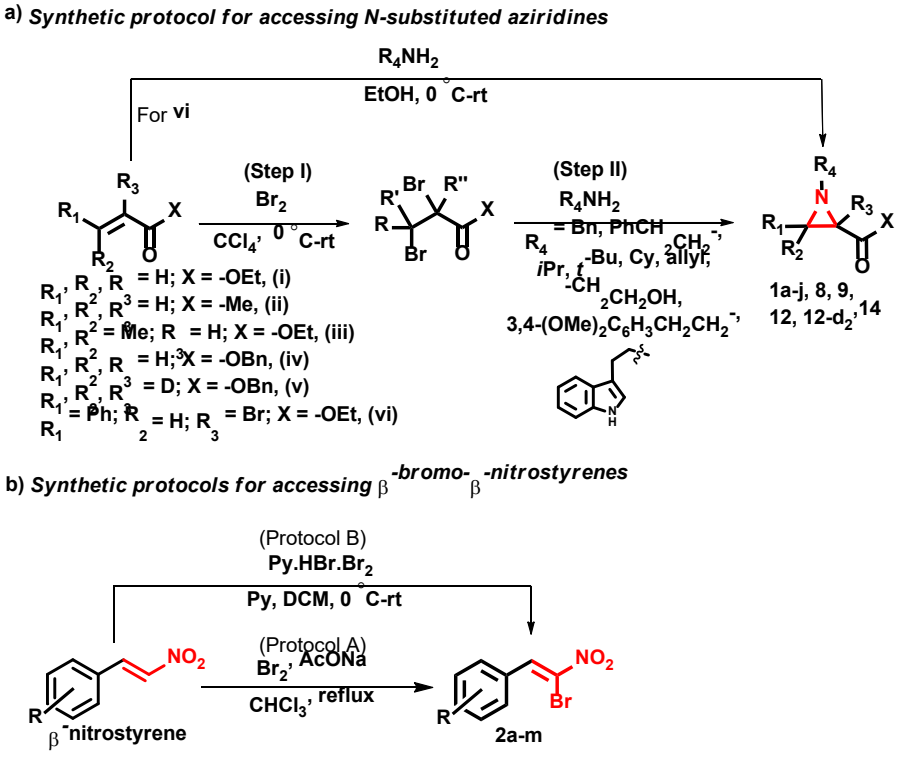
Scheme 1. Recent strategies involving [3+2] annulation of aziridines to access dihydro-pyrrole/pyrrole.

unactivated aziridine using Bronsted/Lewis acid and their subsequent annulation with unactivated, unsymmetrical dipolarophiles to access 2-pyrrolines in a regioselective manner (**Scheme 1a**).[15] Similarly, Zhang et al. demonstrated the Lewis acid mediated C-C bond cleavage of activated donor-acceptor substituted aziridine and subsequent annulation of the resultant azomethine ylide with unactivated, unsymmetrical dipolarophiles to access 3-pyrrolines in regioselective manner (**Scheme 1b**).[16] While, very recently Wang et al. demonstrated the transition metal salt assisted thermal C-C bond cleavage of activated donor-acceptor aziridine and the subsequent annulation of the resultant azomethine ylide with nitrostyrenes to access 2,3,5-substituted pyrroles (**Scheme 1c**).[17] And, to further demonstrate the versatility of aziridine we herein, disclose a transition metal as well as acid/base free one pot domino process for the regioselective synthesis of 1,4-disubstituted-2-carbonylated pyrrole involving thermal C-C bond cleavage in unactivated aziridines. Interestingly, to the best of our

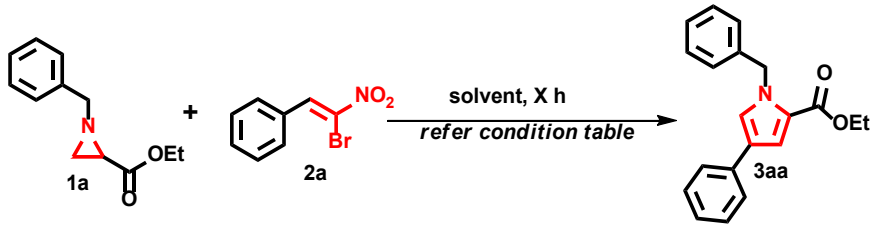
knowledge the present case is the first report on the annulation of an unactivated aziridine with unsymmetrical dipolarophile like *β*-bromo-*β*-nitrostyrene, which exclusively offers the unexpected 1,2,4-trisubstituted pyrroles instead of the expected 1,2,3-trisubstituted isomer, in a highly regioselective fashion (**Scheme 1c**). Though such anomalous trapping of the dipolarophiles in 1,3 dipolar cycloadditions is precedented for other coupling partners[18] but the excellent regioselectivity observed in the present case is something quite noteworthy.

Results and Discussion

Our foray towards the method development commenced with the preparation of aziridines and *β*-bromo-*β*-nitrostyrenes through the protocols highlighted in **Scheme 2**. With the desired aziridines and *β*-bromo-*β*-nitrostyrenes in hand, we began the reaction optimization task and for this purpose the aziridine **1a** and *β*-bromo-*β*-nitrostyrene **2a** were chosen as the coupling partners for exploring the annulation reaction. After examining the thermolysis at varied temperature, temperature of 150 °C proved to be the ideal reaction temperature while among the investigated solvents as highlighted in **Table 1**, toluene proved to be the ideal solvent for the [3+2] annulation in terms of yield by furnishing **3aa** in 96% yield . While, execution of the reaction in solvent-free condition proved to be an instant method to access **3aa** in decent yield. Further, to our delight the reaction was even feasible in 90% H_2O-EtOH mixture offering the same product **3aa** albeit in modest yield. The decomposition of the aziridines and recovery of the dipolarophile accounted for the mass balance in case of low yields.



Scheme 2: Synthetic strategy for the preparation of starting materials.



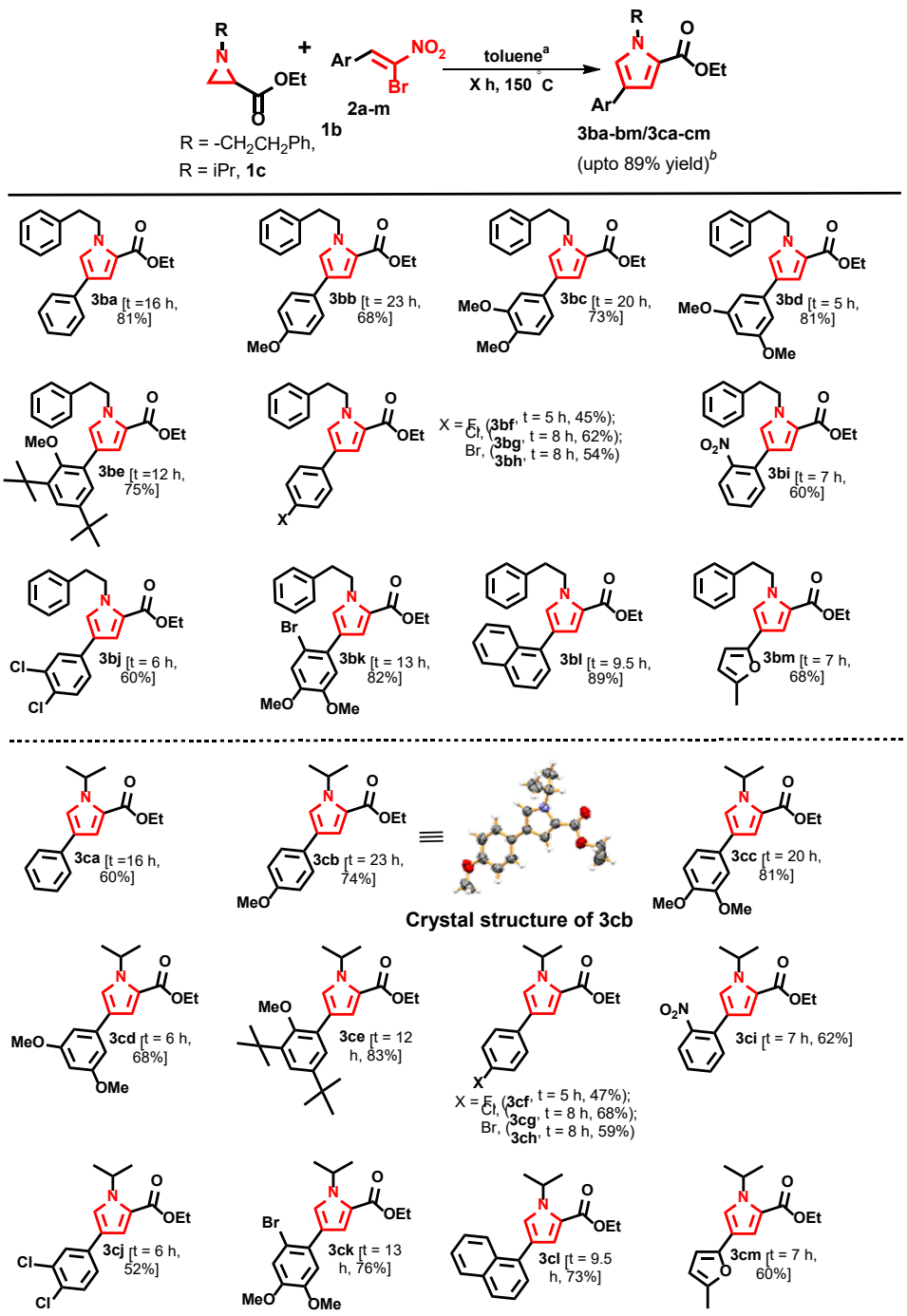
Entry	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	Benzene	150	29	69
2	Toluene	150	16	96
3	Xylene	150	2	63
4	Xylene	200	1.5	72
5	DMF	150	2.5	54
6	Dioxane	150	1.25	28
7	1,2 dichlorobenzene	150	2.5	54
8	Dichloroethane	150	16	58
9	THF	150	2.25	52
10	Dimethoxy-ethane	150	8	56
11	Ethanol	150	7	30
12	H_2O:EtOH (9:1)	150	1.25	32
13	Neat	150	0.2	51

[a] In a oven-dried sealed tube, under N_2 atmosphere, **1a** (0.22 mmol) and **2a** (0.22 mmol) were dissolved in solvent (2 ml) and placed in preheated oil bath maintained as per the indicated

temperature and upto the indicated time in the table. [b]Isolated yield after flash column chromatography.

Table 1. Reaction condition optimization for the domino process involving [3+2] annulation/subsequent elimination and aromatization sequence.

Next, the stage was set for demonstrating the generality and broad substrate scope of the developed domino process. Towards this goal, we first explored the substrate scope with respect to *β*-bromo-*β*-nitrostyrene having diverse substitution pattern on the aryl ring. And the result of the [3+2] annulation with respect to *N*-substituted-aziridine-2-carboxylates **1b**/**c** are as captured in **Scheme 3**. Gratifyingly, in all the cases, 1,2,4-trisubstituted pyrroles were exclusively obtained in moderate to good yields. *β*-bromo-*β*-nitrostyrene with mono and polysubstituted electron donating group showed good compatibility and offered the desired pyrroles in good yields (**3bb**-**3be** /**3cb**-**3ce**). To our delight, also in case of **3cb** the crystalline nature of compound helped us in unambiguously securing the structure through X-ray crystallographic studies.[19] While, *β*-bromo-*β*-nitrostyrenes with electron withdrawing group (-F, -Cl, -Br and NO_2) proved to be comparatively more reactive furnishing the desired products (**3bf**-**3bi** /**3cf**-**3ci**) in comparatively lesser time and with yields ranging from 68-45%. Also, the annulation process was quite smooth with *β*-bromo-*β*-nitrostyrene **2j** having two –Cl atoms as well as with **2k** having both electron donating as well withdrawing group on the aryl ring affording the corresponding pyrrole **3bk**/**3ck** in good yields. Similarly, naphthalene and furan appendage on the *β*-bromo-*β*-nitrostyrene unaffected the domino process as pyrroles (**3bl**, **3bm**/**3cl**, **3cm**) were obtained in decent yields.

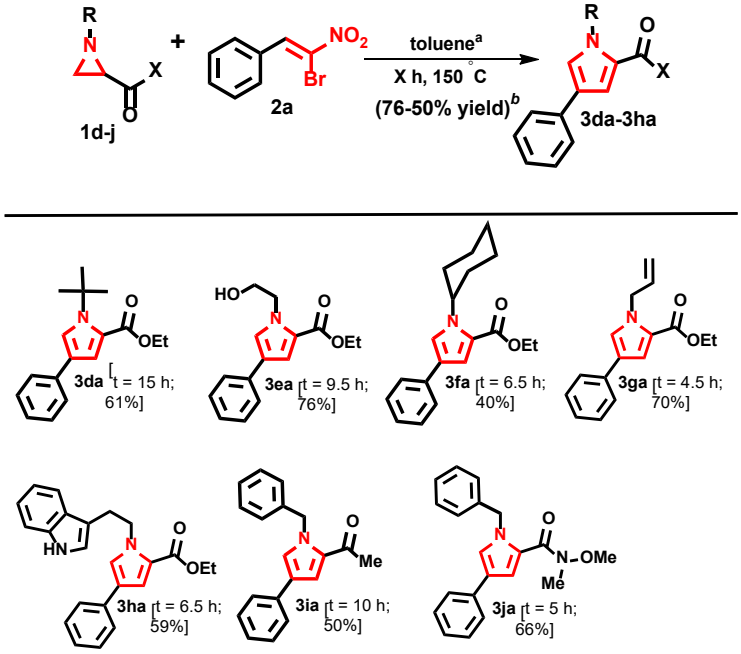


[a]Reaction condition: **1b**/**1c** (0.5 mmol) and **2a-m** (0.5 mmol) were refluxed in toluene under N_2 atmosphere in a sealed tube for specified time. [b]Isolated yield after column chromatography.

Scheme 3. Substrate scope of *β*-bromo-*β*-nitrostyrene in the domino process.

Subsequently, attention was turned towards demonstrating the generality and broad substrate scope with respect to aziridines. In this direction as depicted in **Scheme 4**, diverse *N*-substituted aziridine-2-carboxylates **1d** –**h** were subjected to the annulation protocol under the optimized reaction condition with **2a**. To our delight, in all the cases the corresponding pyrroles

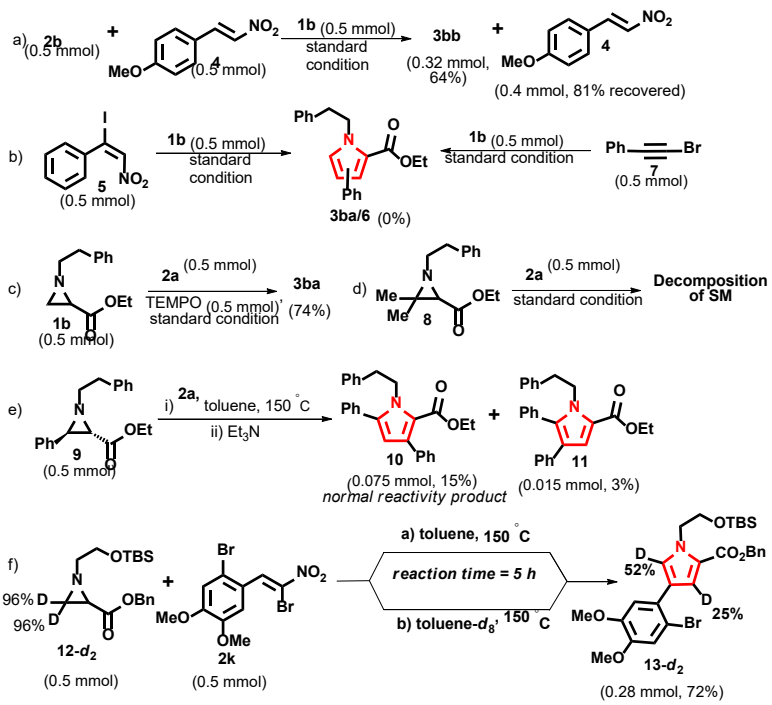
(**3da-3ha**) were obtained with excellent regioselectivity and in good yields. Also, the *N*-benzyl-2-acetyl-aziridine (**1i**) and *N*-benzyl- aziridine-2-carboxamide (**1j**) were found to be equally compatible in the domino process offering the corresponding pyrrole **3ia** and **3ja** respectively in decent yield.



[a]Reaction condition: **1d-1j** (0.5 mmol) and **2a** (0.5 mmol) were refluxed in toluene under N_2 atmosphere in a sealed tube for specified time. [b]Isolated yield after column chromatography.

Scheme 4. Substrate scope of aziridines in the domino process.

Next, in order to demonstrate the superiority and the unexpected regioselectivity offered by *β*-bromo-*β*-nitrostyrene exclusively with the presently used unactivated aziridines as well as to get some mechanistic insight for the present domino process, several experiments as highlighted in **Scheme 5** were conducted. Execution of the annulation of aziridine **1b** in presence of equimolar quantities of **2b** and nitrostyrene (**4)** under standard condition offered readily **3bb** (64% yield) along with 81% recovery of **4** (**Scheme 5a**) thereby demonstrating the superior reactivity of **2b** over **4**. While the domino process involving annulation of **1b** with **5**[20] as well as **7**[21] (**Scheme 5b**) failed to deliver **3ba/6** in either case but instead just resulted in the decomposition of aziridine which further demonstrate the versatility of *β*- bromo-*β*-

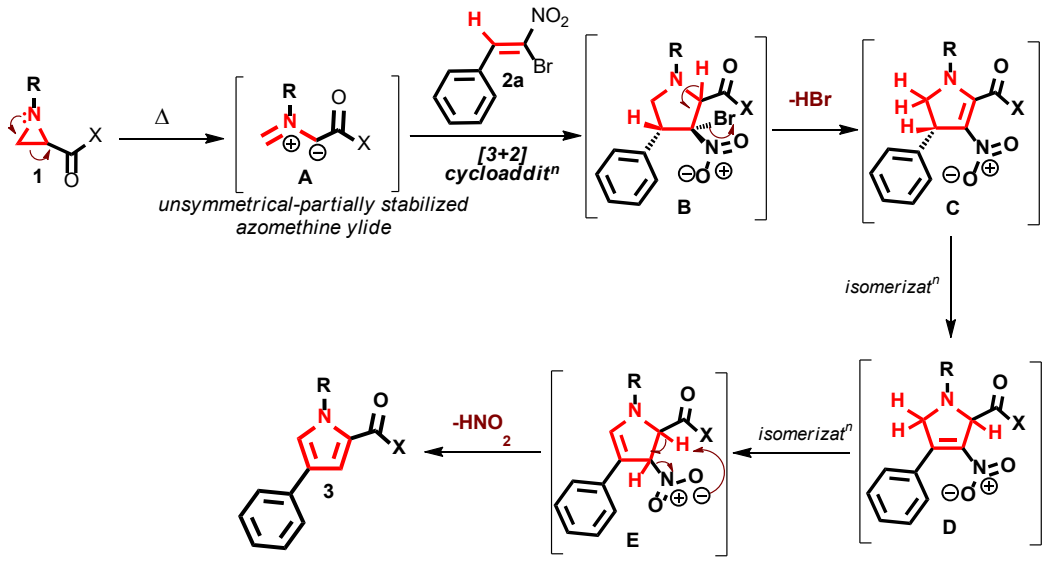


Scheme 5. Competitive, comparative and labelling experiments.

nitrostyrene in the present domino process. The formation of **3ba** in 74% yield during the annulation of **1b** with **2a** in presence of TEMPO (**Scheme 5c**) under standard condition rules out the possibility of radical mechanism for the present domino process. Next, annulation of aziridine **8** with **2a** under standard condition resulted in just decomposition of starting materials (**Scheme 5d**) thereby indicating the non-tolerance of double substitution at the C_3 position of aziridine in the present domino process. While, the annulation of donor-acceptor aziridine **9** with **2a** (**Scheme 5e**) under standard condition followed by base treatment of the resultant cycloadducts delivered the expected pyrrole **10** (15% yield) as the predominant product along with a marginal amount of **11** (3% yield). Also, C_3 labelled aziridine **12-*d*$_2$** was prepared and used for annulation with **2k** (**Scheme 5f**) in both toluene and deuterated toluene as solvent to arrive at **13-*d*$_2$** in each case with 25% and 52% of labelling at C_3 and C_5 position respectively. This indicates the C_3 position of aziridine as the source of H/D for the C_3 position of pyrrole. D/H scrambling between C_3 and C_2 position during the azomethine ylide generation from **12-*d*$_2$** could be attributed to the drop in the labelling percentage observed at C_3 and C_5 position of **13-*d*$_2$**.

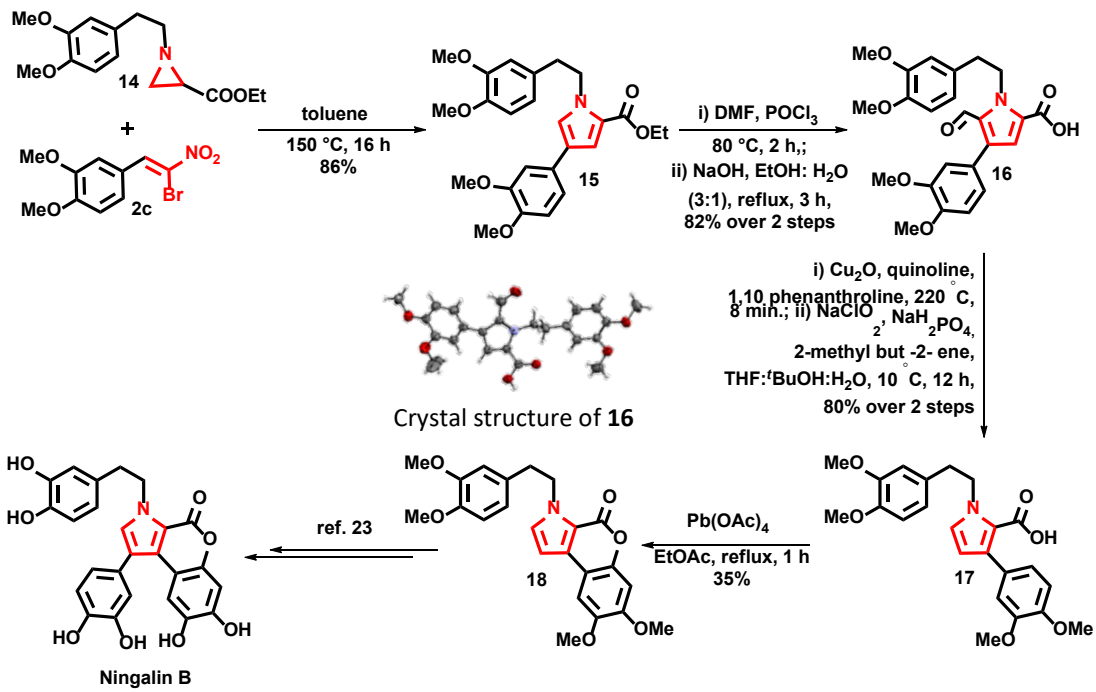
In view of the experiments described in **Scheme 5**, especially **Scheme 5d**, **5e** it is quite clear that the regioselectivity of the [3+2] annulation of N-alkyl-2-carboxyl aziridines with *β*-bromo-*β*-nitrostyrene is quite sensitive with respect to the C_3 substituents of the aziridine and is also perhaps responsible for influencing the regioselectivity in the dipolar cycloaddition. Further, keeping in mind the faster reaction rate of *β*-bromo-*β*-nitrostyrene with electron withdrawing substituents on the aryl ring compared to those having electron donating substituents, the present annulation is most likely to be associated with the Sustmann's type I class[22] of 1,3-dipolar cycloadditions with contribution of HOMO from the azomethine ylide and LUMO of the dipolarophile. While, the experimentally observed regioselectivity in case of aziridine **8** with *β*-bromo-*β*-nitrostyrene is similar to that observed by Wang and coworkers[17] (**Scheme 1c**) which can be satisfactorily accounted through FMO theory treatment. However, the anomalous regioselectivity observed with the unsymmetrical partially stabilized azomethine ylides generated in the present methodology from the C_3 nonsubstituted aziridines seems difficult to be accounted through FMO theory. Thus, as demonstrated by others[18] we look forward for a detail DFT as well as computational transition state energy investigation in quest for a convincing justification to account for the anomalous regioselectivity observed in the present domino process.

Nevertheless at this point, a plausible reaction mechanism we wish to propose for the present domino process is as delineated in **Scheme 6**. Thermal C-C bond cleavage of aziridine **1** is more likely to furnish azomethine ylide **A** which on reaction with *β*-bromo-*β*-nitrostyrene **2a** initially forms the more sterically crowded cycloadduct **B**. A spontaneous *E2* elimination of HBr in **B** results in the formation of **C** and then through two successive isomerizations **C** is anticipated to be converted into **E** via **D**. Eventually the elimination of HNO_2 in **E** is anticipated to offer the pyrrole **3**.



Scheme 6. A plausible mechanism for the present domino process.

Next, we were interested to demonstrate the efficacy of the present methodology by applying it in natural product synthesis. Among several options, marine alkaloid ningalin B[23] was chosen as the target for total synthesis. Our synthetic endeavor in this direction as highlighted in **Scheme 7**, commenced with the annulation of aziridine ester **14** with *β*-bromo-*β*-nitrostyrene **2c** under our optimized condition to access the 1,2,4-trisubstituted pyrrole ester **15** in good yield which was then subjected to Vilsmeier-Haack formylation[24] followed by saponification of the ester group to arrive at **16**. Also, the crystalline nature of **16** enabled the unambiguous structural confirmation through its X-ray crystallographic analysis.[19] Then, the intermediate **16** was elaborated to acid **17**, through a 2-step synthetic manipulation involving decarboxylation of the acid functionality in **16** and Pinnick oxidation[25] of the aldehyde functionality to acid. In context of ningalin B, the next task was to introduce the lactone fusion between the central pyrrole core and the C_3 aryl ring. After investigating various conditions, finally exposure of **17** to $Pb(OAc)_4$ afforded the desired lactone **18** in moderate yields.[26] At this stage our synthesis intercepts with that of Banwell's reported synthesis of ningalin B,[27] who has demonstrated the elaboration of **18** to ningalin B in 3 steps. Thus, in this manner our efforts culminates in the formal synthesis of ningalin B.



Scheme 7. Formal synthesis of ningalin B.

In summary, we have demonstrated the regioselective synthesis of 1,2,4-trisubstituted pyrroles via anomalous trapping of the unactivated aziridine derived azomethine ylide with *β*-bromo-*β*-nitrostyrene. The main highlights of the synthesis are i) it is metal, acid as well as base free; ii) involves cheap and readily accessible starting materials; iii) offers excellent regioselectivity; iv) broad substrate scope. Also, the efficacy of the method is demonstrated through its application for the formal synthesis of ningalin B. Further, efforts to demonstrate the applicability of the present methodology towards the synthesis of several natural and unnatural lamellarins are nearing completion in our laboratory and the outcome of that study shall be communicated soon.[28]

Experimental Section

General Method: All the reagents were purchased from commercial suppliers and used without further purification. While most of the desired solvents supplied by commercial suppliers were dried using the standard drying procedures.[29] All the moisture and air sensitive reactions were performed under a flow of nitrogen or argon atmosphere using flame-dried or oven-dried glassware with magnetic stirring. All purifications were done using column chromatography with 100-200 mesh size SiO_2-gel as the stationary phase. Distilled EtOAc and petroleum ether were typically used for column chromatography. The ^1H & $^{13}C\{^1H\}$ NMR spectra were recorded on 400 MHz Bruker spectrometer using $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) or TMS (δ = 0.0) residual solvent peaks as internal standard and DMSO-d_6 ((H: δ = 2.50 and C: δ = 39.52±0.06 ppm). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet/pentet, sept. = septet, dd = doublet of doublet, ddd= doublet of doublet of doublet, td = triplet of doublet, dq = doublet of quartet and m = multiplet. The chemical shifts are reported as δ values (ppm) and the coupling constants (*J*) values are reported in Hz. High Resolution Mass Spectra (HRMS) were obtained using electron spray ionization (ESI) technique and TOF mass analyzer. IR spectra were recorded on a Bruker FT/IR-460 Plus spectrometer. Melting points were determined on a Buchi M-560 apparatus and are uncorrected. Progress of the reactions were monitored using precoated SiO_2-gel GF254 TLC plates while spot visualizations were done under UV light and using spot developing stains like *p*-anisaldehyde, ceric ammonium molybdate, ninhydrin or $KMnO_4$.

1) General procedure for the synthesis of *N*-substituted aziridine-2-carboxy derivatives (1a-1i, 8, 9, 12, 12-d_2, 14)

Step I: Except for **vi**, to the solution of vinyl ester/ketone (10 mmol) in CCl_4 (10 mL) was added liq. Br_2 (0.77 mL,15 mmol, 1.5 equiv.) at 0 °C and the reaction was allowed to warm to rt over 12 h until complete consumption of starting material was indicated by TLC analysis. The reaction was worked up by quenching it with aq. $Na_2S_2O_8$ followed by extraction in DCM (4 x 25 mL). The combined organic phase was dried over Na_2SO_4 and then subjected to solvent removal under reduced pressure to arrive at the crude dibromo residue which was directly used in the next step.

Step II: Next, in an oven dried round-bottom flask under N_2 atmosphere, dibrominated compound derived from **i-v/vi** (2.5 mmol) was dissolved in EtOH (5 mL). After stirring the solution at 0 °C for 10 min. appropriate primary amines (7.5 mmol, 3 equiv.) dissolved in ~2 mL of ethanol were added dropwise to the flask over 10 min. The reaction was then allowed to warm to rt and continued stirring for another 6-48 h until complete consumption of starting material was indicated by the TLC analysis. Upon reaction completion, the solvent was removed under reduced pressure and the resultant residue was subjected to purification using SiO_2-gel column chromatography to arrive at the desired aziridines.

Among the synthesized aziridines, the previously reported ones are **1a**,[30] **1b**,[30] **1d**[31], **1g**[32] and **1i**[33] while **1c**, **1 e**, **1e'**, **1e'-*d*$_2$**, **1f**, **1h**, **1j**, **8, 9** and **14** are new and their spectral data are as described below:

Ethyl 1-isopropylaziridine-2-carboxylate (1c): Following general procedure 1 using dibrominated-**i**[30b] (0.65 g, 2.5 mmol) and isopropyl amine (0.44 g, 7.5 mmol), **1c** was obtained as pale yellow oil (0.35 g, 90% yield); R_f = 0.6 (30% EtOAc + pet. ether). **IR** (neat): ν_{max} 2971, 1743, 1657, 1466, 1414, 1280, 1237, 1186, 1100, 1035, 750 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 4.23 (dq, J_1 = 7.2 Hz, J_2 = 10.8 Hz, 1H), 4.14 (dq, J_1 = 7.2 Hz, J_2 = 10.8 Hz, 1H), 2.16 (dd, J_1 = 0.8 Hz, J_2 = 3.4 Hz, 1H), 2.03 (dd, J_1 = 2.8 Hz, J_2 = 6.4 Hz, 1H), 1.59 (dd, J_1 = 1.2 Hz, J_2 = 6.4 Hz, 1H), 1.54-1.48 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.17 (d, J = 3.6 Hz, 3H),

1.16 (d, J = 3.6 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 171.0, 61.4, 61.0, 37.1, 33.89, 21.9, 21.7, 14.2. HRMS (ES) m/z calcd for $C_8H_{15}NNaO_2$ $(M+Na)^+$: 180.0995; found: 180.1004.

Ethyl 1-(2-hydroxyethyl)aziridine-2-carboxylate (1e): Following general procedure 1, using dibrominated-**i**[30b] (0.65 g, 2.5 mmol) and ethanolamine (0.46 g, 7.5 mmol), **1e** was obtained as pale yellow oil (0.37 g, 95% yield); R_f = 0.5 (EtOAc). **IR** (neat): ν_{max} 2984, 1732, 1649, 1446, 1416, 1280, 1243, 1195, 1083, 1035, 748 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 4.25-4.12 (m, 2H), 3.77 (t, J = 5.2 Hz, 2H), 2.72 (br s, 1H), 2.60 (dt, J_1 = 5.1 Hz, J_2 = 12.1 Hz, 1H), 2.44-2.38 (m, 1H), 2.19 (d, J = 2.8 Hz, 1H), 2.14 (dd, J_1 = 3.2 Hz, J_2 = 6.4 Hz, 1H), 1.67 (d, J = 6.4 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H); **^{113}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 170.8, 62.2, 61.7, 61.2, 37.0, 34.2, 14.1. **HRMS** (ES) m/z calcd for $C_7H_{13}NNaO_3$ $(M+Na)^+$: 182.0788; found: 182.0800.

Benzyl 1-(2-hydroxyethyl)aziridine-2-carboxylate (1e′): Following general procedure 1, using dibrominated-**iv**[34] (0.80 g, 2.5 mmol) and ethanolamine (0.46 g, 7.5 mmol), **1e′** was obtained as colourless oil (0.47 g, 85% yield); R_f = 0.4 (EtOAc). **IR** (neat): ν_{max} 2984, 1732, 1645, 1454, 1381, 1213, 1068, 739, 698 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 5.20 (d, J = 12.4 Hz, 1H), 5.14 (d, J = 12.4 Hz, 1H), 3.76 (t, J = 5.2 Hz, 2H), 2.62 (dt, J_1 = 5.2 Hz, J_2 = 12.4 Hz, 1H), 2.42-2.37 (m, 1H), 2.22-2.19 (m, 2H), 1.69 (d, J = 6.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 170.7, 135.4, 128.6 (2C), 128.4, 128.3 (2C), 67.0, 62.2, 61.6, 36.9, 34.4. **HRMS** (ES) m/z calcd for $C_{12}H_{15}NO_3Na$ $(M+Na)^+$: 244.0944; found: 244.0940.

Benzyl 1-(2-hydroxyethyl)aziridine-2-carboxylate-3,3-d_2 (1e′-*d_2*): Following general procedure 1, using dibrominated-**v**[34,35](0.82 g, 2.5 mmol) and ethanolamine (0.46 g, 7.5 mmol), **1e′-*d_2*** was obtained as colourless oil (0.50 g, 89% yield); R_f = 0.4 (EtOAc). **IR** (neat): ν_{max} 2984, 1732, 1641, 1454, 1414, 1256, 1190, 1125, 1062, 749, 698 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 5.20 (d, J = 12.4 Hz, 1H), 5.14 (d, J = 12.4 Hz, 1H), 3.74 (br s, 2H), 2.64-2.58 (m, 1H), 2.39-2.33 (m, 1H), 2.19 (s, 1H), 1.66 (d, J = 6.4 Hz, 0.06H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 170.6, 135.3, 128.5 (2C), 128.3, 128.3 (2C), 66.9, 62.1, 61.5, 36.7. **HRMS** (ES) m/z calcd for $C_{12}H_{14}D_2NO_3$ $(M+H)^+$: 224.1250; found: 224.1250.

Ethyl 1-cyclohexylaziridine-2-carboxylate (1f): Following general procedure 1 using dibrominated-**i**[30b] (0.65 g, 2.5 mmol) and cyclohexylamine (0.74 g, 7.5 mmol), **1f** was obtained as pale yellow oil (0.45 g, 92% yield); R_f = 0.5 **(**20% EtOAc + pet. ether). **IR** (neat): ν_{max} 2930, 1744, 1450, 1413, 1370, 1282, 1235, 1184, 1089, 1027, 863, 850, 742 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 4.24-4.11 (m, 2H), 2.12 (d, J = 2.4 Hz, 1H), 2.01 (dd, J_1 = 3.2 Hz, J_2 = 6.4 Hz, 1H), 1.84-1.73 (m, 4H), 1.59-1.57 (m, 2H), 1.46-1.40 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 1.15-1.10 (m, 4H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 171.1, 69.3, 61.0, 36.4, 33.2, 32.5, 32.3, 25.9, 24.8, 24.7, 14.2. **HRMS** (ES) m/z calcd for $C_{11}H_{20}NO_2$ $(M+H)^+$: 198.1489; found: 198.1510.

Ethyl 1-(2-(1H-indol-3-yl)ethyl)aziridine-2-carboxylate (1h): Following general procedure 1, using dibrominated-**i**[30b] (0.65 g, 2.5 mmol) and tryptamine (1.2 g, 7.5 mmol), **1h** was obtained as pale yellow oil (0.63 g, 97% yield); R_f = 0.3 **(**40% EtOAc + pet. ether). **IR** (neat): ν_{max} 3054, 2986,1714, 1606, 1422, 1326, 1264, 1165, 1123, 895 cm^{-1};**^{1}H NMR** (400 MHz, $CDCl_3$):δ 8.12 (br s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.20-7.17 (m, 1H), 7.13-7.09 (m, 1H), 7.01(s, 1H), 4.24-4.10 (m, 2H), 3.16-3.03 (m, 2H), 2.72-2.61 (m, 2H), 2.17

(dd, J_1 = 0.9 Hz, J_2 = 3.0 Hz, 1H), 1.99 (dd, J_1 = 3.0 Hz, J_2 = 6.4 Hz, 1H), 1.56 (dd, J_1 = 0.9 Hz, J_2 =6.4 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 171.0, 136.2, 127.3, 121.9, 121.9, 119.2, 118.7, 113.5, 111.1, 61.4, 61.1, 37.4, 34.35, 25.4, 14.2. **HRMS** (ES) m/z calcd for $C_{15}H_{19}N_2O_2$ $(M+H)^+$: 259.1441; found: 259.1441.

Ethyl 3,3-dimethyl-1-phenethylaziridine-2-carboxylate (8): Following general procedure 1, using dibrominated-**iii**[37] (0.71 g, 2.5 mmol) and phenethylamine (0.91 g, 7.5 mmol), **8** was obtained as colourless oil (0.40 g, 65% yield); R_f = 0.3 (15% EtOAc + pet. ether). **IR** (neat): ν_{max} 1743, 1718, 1650, 1454, 1384, 1305, 1179, 1135, 1030, 750, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.20-7.16 (m, 3H), 4.20-4.11 (m, 2H), 2.93-2.83 (m, 3H), 2.61 (ddd, J_1 = 6.0 Hz, J_2 = 8.2 Hz, J_3 = 10.6 Hz 1H), 1.83 (s, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.23 (s, 3H), 1.21 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 170.2, 139.8, 128.8 (2C), 128.3 (2C), 126.1, 60.6, 54.5, 49.2, 43.9, 36.5, 21.5, 17.5, 14.2. **HRMS** (ES) m/z calcd for $C_{15}H_{22}NO_2$ $(M+H)^+$: 248.1645; found: 248.1645.

***rel*-ethyl (2S,3R)-1-phenethyl-3-phenylaziridine-2-carboxylate (9):** Following just step II of general procedure 1, using **vi**[36] (0.63 g, 2.5 mmol) and phenethylamine (0.91 g, 7.5 mmol), **9** was obtained as a colourless oil (0.40 g, 62% yield); R_f = 0.3 (10% EtOAc + pet. ether). **IR** (neat): ν_{max} 3086, 3028, 1714, 1649, 1604, 1495, 1453, 1198, 1030, 858, 740 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.2 Hz, 2H), 7.29-7.17 (m, 8H), 3.99 (dq, J_1 = 7.2 Hz, J_2 = 10.8 Hz, 1H), 3.88 (dq, J_1 = 7.2 Hz, J_2 = 10.8 Hz, 1H), 3.09-3.04 (m, 1H), 3.00-2.91 (m, 2H), 2.86 (d, J = 7.2 Hz, 1H), 2.63-2.58 (m, 1H), 2.43 (d, J = 7.2 Hz, 1H) 0.94 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 168.1, 139.2, 135.1, 128.7 (2C), 128.3 (2C), 127.8 (2C), 127.7 (2C), 127.3, 126.2, 62.2, 60.6, 47.8, 46.0, 35.8, 13.8. **HRMS** (ES) m/z calcd for $C_{19}H_{21}NO_2$ $(M+H)^+$: 296.1645; found: 296.1645.

Ethyl 1-(3,4-dimethoxyphenethyl)aziridine-2-carboxylate (14): Following general procedure 1 using dibrominated-**i**[30b] (0.65 g, 2.5 mmol) and 3,4-dimethoxyphenethylamine (1.35 g, 7.5 mmol), **1i** was obtained as pale yellow oil (0.60 g, 86% yield); R_f = 0.5 (50% EtOAc + pet. ether). **IR** (neat): ν_{max} 2937, 1739, 1516, 1465, 1417, 1262, 1237, 1189, 1157, 1028, cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.82-6.79 (m, 1H), 6.75-6.72 (m, 2H), 4.24-4.12 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.96-2.84 (m, 2H), 2.62 (ddd, J_1 = 6.2 Hz, J_2 = 8.4 Hz, J_3 = 11.5 Hz, 1H), 2.50 (ddd, J_1 = 7.0 Hz, J_2 = 8.0 Hz, J_3 = 11.5 Hz, 1H), 2.15 (dd, J_1 = 0.8 Hz, J_2 = 3.2 Hz, 1H), 1.94 (dd, J_1 = 3.2 Hz, J_2 = 6.4 Hz, 1H), 1.53 (dd, J_1 = 1.2 Hz, J_2 = 6.4 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 170.9, 148.8, 147.5, 132.1, 120.6, 112.2, 111.3, 62.6, 61.1, 55.9, 55.8, 37.6, 35.7, 34.3, 14.1. **HRMS** (ES) m/z calcd for $C_{15}H_{22}NO_4$ $(M+H)^+$: 280.1543; found: 280.1548.

1-benzyl-N-methoxy-N-methylaziridine-2-carboxamide (1j)[38]**:** In an round bottom flask, under N_2 atmosphere to an ice cold solution of **1a**[30] (1.0 g, 4.8 mmol, 1 equiv.) and *N*,*O*-dimethyl hydroxylamine hydrochloride (2.38 g, 24 mmol, 5 equiv.) in dry THF (8 mL), isopropyl magnesium chloride (2M) (9.7 mL, 19.5 mmol, 4 equiv.) was added. The reaction was allowed to warm to rt over the next 3 h. Upon complete consumption of starting material the reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (3 × 20 mL). Drying of the organic phase over Na_2SO_4 followed by removal of solvent under reduced pressure gave a crude residue which was subjected to SiO_2-gel flash column chromatography to access aziridine (**1j**) as colourless oil (0.49 g, 45% yield); R_f= 0.4 (EtOAc); **IR** (neat): ν_{max} 1645, 1485, 1454, 1396, 1339, 1180, 1153, 1017, 982, 746, 699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 7.25-7.22 (m, 1H), 3.73 (d, J = 13.2 Hz, 1H), 3.53 (s, 3H), 3.41 (d, J = 13.6 Hz, 1H), 3.18 (s, 3H), 2.66 (s, 1H), 2.32 (dd, J_1 = 1.2 Hz, J_2 = 2.8 Hz, 1H), 1.73 (dd, J_1 = 1.2 Hz, J_2 = 6.2 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 170.0, 138.1,

128.3 (2C), 128.1 (2C), 127.2, 64.3, 61.5, 34.8, 34.4, 32.5. **HRMS** (ES) m/z calcd for $C_{12}H_{16}N_2NaO_2$ $(M+Na)^+$: 243.1104; found: 243.1112.

Benzyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)aziridine-2-carboxylate (12): In an round bottom flask, under N_2 atmosphere, **1e'** (0.22 g, 1 mmol, 1 equiv.) was dissolved in DCM (2.5 mL) and cooled to 0 °C. Then, TBSCl (0.30 g, 2 mmol, 2 equiv.) and imidazole (0.14 g, 2 mmol, 2 equiv.) were added over 5 min. followed by DMAP (112.2 mg, 0.1 mmol, 0.1 equiv.) and reaction was allowed to warm to rt over 5 h. After complete consumption of starting material, water was added followed by extraction with DCM (3 × 15 mL). Drying of the organic phase over Na_2SO_4 followed by removal of solvent under reduced pressure gave a crude residue which was purified by column chromatography to access aziridine (**12**) as colourless oil (0.31 g, 93% yield); R_f= 0.2 (15% EtOAc + pet. ether); **IR** (neat): ν_{max} 2954, 2929, 1745, 1641, 1461, 1280, 1255, 1174, 1007, 941, 811, 777 cm^{-1};**^{1}H NMR** (400 MHz, $CDCl_3$):δ 7.36-7.31 (m, 5H), 5.19 (d, J = 12.4 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 3.83 (td, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 2H), 2.48 (td, J_1 = 2.4 Hz, J_2 = 5.6 Hz, 2H), 2.20 (dd, J_1 = 3.2 Hz, J_2 = 6.4 Hz, 1H), 2.16 (dd, J_1 = 0.8 Hz, J_2 = 2.8 Hz, 1H), 1.67 (dd, J_1 = 0.8 Hz, J_2 = 6.4 Hz, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 171.0, 135.6, 128.5 (2C), 128.4 (2C), 128.3, 66.8, 62.7, 62.3, 36.9, 34.1, 25.9 (3C), 18.2, -5.4, -5.5. **HRMS** (ES) m/z calcd for $C_{18}H_{30}NO_3Si$ $(M+H)^+$: 336.1989; found: 336.1988.

Benzyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)aziridine-2-carboxylate-3,3-d2 (12-*d*$_2$): Applying above described procedure for **12** on **1e'-*d*$_2$** (0.22 g, 1 mmol), aziridine (**12-*d*$_2$**) was obtained as colourless oil (0.30 g, 90% yield); R_f= 0.3 (20% EtOAc + pet. ether); **IR** (neat): ν_{max} 3036, 1728, 1643, 1461, 1256, 1172, 1110, 1006, 939, 829, 697 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 7.36-7.31 (m, 5H), 5.19 (d, J = 12.4 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 3.83 (td, J_1

= 3.2 Hz, J_2 = 5.6 Hz, 2H), 2.47 (td, J_1 = 2 Hz, J_2 = 5.6 Hz, 2H), 2.19 (s, 1H), 2.16 (d, J = 0.8 Hz, 0.02H), 1.66 (dd, J_1 = 6.4 Hz, 0.04H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.0, 135.6, 128.5 (2C), 128.4 (2C), 128.2, 66.8, 62.7, 62.2, 36.7, 25.9 (3C), 18.2, -5.4, -5.5. **HRMS** (ES) m/z calcd for $C_{18}H_{28}D_2NO_3Si$ $(M+H)^+$: 338.2115; found: 338.2126.

2) General Procedure for the preparation of *β*-bromo-*β*-nitrostyrenes (2a-m).

Protocol A: As described earlier.[39]

Protocol B: To a cold solution of *β*-nitrostyrene (2.5 mmol, 1 equiv.) in DCM at 0 °C, pyridine (0.4 mL, 5 mmol, 2 equiv.) was added followed by pyridinium tribromide (0.8 g, 2.5 mmol, 1 equiv.) in two portions. The reaction was then allowed to warm to rt over the next 3-12 h until complete consumption of starting material. Upon reaction completion, water was added followed by extraction with DCM. Drying of the organic phase over Na_2SO_4 followed by removal of solvent under reduced pressure gave a crude residue which was purified by column chromatography to access *β*-bromo-*β*-nitrostyrene.

Among the synthesized *β*-bromo-*β*-nitrostyrene, **2a-c, 2f-i** and **2l** are known[39] while **2d, 2e**, **2j**, **2k** and **2m** are new and their spectral data are as follows**:**

(*Z*)-1-(2-bromo-2-nitrovinyl)-3,5-dimethoxybenzene (2d): Following protocol B, using 3,5-dimethoxy-*β*-nitrostyrene[40] (0.52 g, 2.5 mmol), **2d** was obtained as fluorescent green solid (0.51 g, 71% yield); m.p. 113-114 °C. **IR** (neat): ν_{max} 1642, 1605, 1524, 1454, 1426, 1297, 1206, 1167, 1155, 946 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 8.55 (s, 1H), 7.01 (d, J = 2.4 Hz, 2H), 6.61 (t, J = 2 Hz, 1H), 3.84 (s, 6H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 160.8 (2C), 136.5, 131.7, 128.4, 108.8 (2C), 104.1, 55.6 (2C). **HRMS** (ES) m/z calcd for $C_{10}H_{11}BrNO_4$ $(M+H)^+$: 287.9866; found: 287.9866.

(*Z*)-1-(2-bromo-2-nitrovinyl)-3,5-di-tert-butyl-2-methoxybenzene (2e): Following protocol A,[39] using (*E*)-1,5-di-tert-butyl-2-methoxy-3-(2-nitrovinyl)benzene[41] (0.73 g, 2.5 mmol), **2e** was obtained as green solid (0.82 g, 88% yield); m.p. 120-124 °C. **IR** (neat): ν_{max} 2989, 1714, 1607, 1479, 1275, 1260, 1017, 163, 750 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.83 (d, J = 2.2 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 3.77 (s, 3H), 1.40 (s, 9H), 1.33 (s, 9H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 158.1, 145.7, 142.4, 134.6, 128.6, 128.0, 124.8, 123.9, 64.0, 35.3, 34.8, 31.4 (3C), 30.8 (3C). **HRMS** (ES) m/z calcd for $C_{17}H_{24}BrNNaO_3$ $(M+Na)^+$: 392.0832; found: 392.0832.

(*Z*)-4-(2-bromo-2-nitrovinyl)-1,2-dichlorobenzene (2j): Following protocol B, using 3,4-dichloro-β-nitrostyrene[42] (0.54 g, 2.5 mmol), **2j** was obtained as a pale yellow oil (0.70 g, 95% yield). **IR** (neat): ν_{max} 1643, 1581, 1469, 1395, 1317, 1207, 1033, 915, 883, 854 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 7.84 (d, J = 2.4 Hz, 1H), 7.57 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 6.00 (s, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 134.9, 133.5, 132.7, 132.6, 130.3, 129.9, 91.8, 56.1. **HRMS** (ES) m/z calcd for $C_8H_4BrCl_2NNaO_2$ $(M+Na)^+$: 317.8695; found: 317.8684.

(*Z*)-1-bromo-2-(2-bromo-2-nitrovinyl)-4,5-dimethoxybenzene (2k): Following protocol A,[39] using (*E*)-1-bromo-4,5-dimethoxy-2-(2-nitrovinyl)benzene (0.72 g, 2.5 mmol) **2k** was obtained as yellow solid (0.78 g, 85% yield); m.p. 133-135 °C. **IR** (neat): ν_{max}1713, 1668, 1488, 1428, 1367, 1258, 1198, 1151, 1017, 749 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 8.90 (s, 1H), 7.66 (s, 1H), 7.15 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 152.2, 148.0, 135.7, 122.4, 119.3, 115.8, 115.4, 112.2, 56.0, 56.2. HRMS (ES) m/z calcd for $C_{10}H_9Br_2NNaO_4$ $(M+Na)^+$: 387.8791; found: 387.8791.

(*Z*)-2-(2-bromo-2-nitrovinyl)-5-methylfuran (2m): Following protocol A,[39] using (*E*)-2-methyl-5-(2-nitrovinyl)furan [43] (0.38 g, 2.5 mmol), **2m** was obtained as pale yellow solid (0.52 g, 91% yield); m.p. 69-70 °C. **IR** (neat): ν_{max} 3054, 2986, 1714, 1606, 1422, 1326, 1264, 1165, 1123, 895 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 8.51 (s, 1H), 7.35 (d, J = 3.2 Hz, 1H), 6.00 (d, J = 3.2 Hz, 1H), 2.42 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 159.3, 145.2, 125.0, 122.9, 122.4, 110.7, 14.2. **HRMS** (ES) m/z calcd for $C_7H_7BrNO_3$ $(M+H)^+$: 231.9604; found: 231.9604.

3) General procedure for synthesis of 1,2,4-trisubstituted pyrroles:

In an oven-dried seal tube, under nitrogen atmosphere, β-bromo-β-nitrostyrene (0.5 mmol) was taken. After that aziridine (0.5 mmol, 1 equiv.) dissolved in toluene (2 mL) was added. The reaction was then sealed while maintaining the N_2 atmosphere and then stirred in a preheated oil bath at 150°C until complete consumption of starting materials was indicated upon reaction monitoring. After reaction completion, the solvent was removed under reduced pressure and the crude residue was subjected to purification using SiO_2-gel flash column chromatography to access 1,2,4-trisubstituted pyrrole (**3aa-3ja**, **3bb-3bm**, **3cb-3cm**, **13**, **13-d$_2$, 15**).

Ethyl 1-benzyl-4-phenyl-1H-pyrrole-2-carboxylate (3aa):[44] By following general procedure , using **1a** (102 mg, 0.5 mmol) and **2a** (114 mg, 0.5 mmol) with reaction time of 16 h, **3aa** was obtained as a yellow oil (146 mg, 96% yield); R_f = 0.6 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2927, 1700, 1605, 1453, 1397, 1268, 1210, 1094, 758, 724, 694 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8 Hz, 2H), 7.38-7.31 (m, 5H), 7.29-7.20 (m, 1H), 7.24-7.20 (m, 1H), 7.18-7.16 (m, 3H), 5.61 (s, 2H), 4.29 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.0, 138.0, 134.3, 128.7 (2C), 128.6 (2C), 127.5, 126.9

(2C), 126.1, 125.5, 125.1 (2C), 124.4, 123.1, 115.3, 60.0, 52.2, 14.3. **HRMS** (ES) m/z calcd for $C_{20}H_{20}NO_2$ $(M+H)^+$: 306.1489; found: 306.1461.

Ethyl 1-phenethyl-4-phenyl-1H-pyrrole-2-carboxylate (3ba):- By following general procedure, using **1b** (110 mg, 0.5 mmol)and **2a** (114 mg, 0.5 mmol) with reaction time of 16 h, **3ba** was obtained as a yellow oil (129 mg, 81% yield); R_f = 0.4 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2929, 1700, 1604, 1474, 1453, 1399, 1254, 1199, 758, 697 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (dd, J_1 = 1.2 Hz, J_2 = 8 Hz, 2H), 7.37-7.29 (m, 5H), 7.28-7.19 (m, 4H), 6.92 (d, J = 2 Hz, 1H), 4.56 (t, J = 7.6 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 3.11 (t, J = 7.6 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.0, 138.3, 134.5, 128.9 (2C), 128.6 (2C), 128.5 (2C), 126.5, 126.0, 125.5, 125.0 (2C), 123.8, 122.3, 115.3, 59.9, 51.0, 38.2, 14.4. **HRMS** (ES) m/z calcd for $C_{21}H_{22}NO_2$ $(M+H)^+$: 320.1651; found: 320.1645.

Ethyl 1-isopropyl-4-phenyl-1H-pyrrole-2-carboxylate (3ca):- By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2a** (114 mg, 0.5 mmol) with reaction time of 16 h, **3ca** was obtained in 16 h as a yellow oil (77 mg, 60% yield) R_f = 0.5 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2979, 1700, 1605, 1470, 1408, 1241, 1197, 1102, 1064, 758, 694 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 2H), 7.40-7.36 (m, 3H), 7.25 (d, J = 2.0 Hz 1H), 7.20 (tt, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1H), 5.49 (spt, J = 6.8 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.49 (d, J = 6.8 Hz, 6H), 1.38 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.1, 134.7, 128.7 (2C), 126.0, 125.0 (2C), 124.2, 122.6, 120.4, 115.0, 59.9, 48.6, 23.8 (2C), 14.4. **HRMS** (ES) m/z calcd for $C_{16}H_{20}NO_2$ $(M+H)^+$: 258.1494; found: 258.1489.

Ethyl 4-(4-methoxyphenyl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bb): By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2b** (129 mg, 0.5 mmol) with reaction time

of 23 h, **3bb** was obtained as a yellow oil (118.7 mg, 68% yield); R_f = 0.2 (3% EtOAc + pet. ether). **IR** (neat): ν_{max} 2932, 1696, 1566, 1511, 1249, 1197, 1094, 1032, 931, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.8 Hz, 2H), 7.32-7.28 (m, 2H), 7.26-7.22 (m, 1H), 7.21 (d, J = 2 Hz, 1H), 7.19-7.17 (m, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2 Hz, 1H), 4.54 (t, J = 7.2 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.09 (t, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.1, 158.1, 138.4, 129.0 (2C), 128.5 (2C), 127.4, 126.6, 126.3 (2C), 125.0, 123.6, 122.2, 115.1, 114.2 (2C), 60.0, 55.3, 51.1, 38.4, 14.5. **HRMS** (ES) m/z calcd for $C_{22}H_{23}NO_3$ $(M+H)^+$: 350.1756; found: 350.1751

Ethyl 1-isopropyl-4-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (3cb) : By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2b** (129 mg, 0.5 mmol) with reaction time of 23 h, **3cb** was obtained as a colourless solid (106 mg, 74% yield); R_f = 0.3 (3% EtOAc + pet. ether); m.p. 65-68 °C. **IR** (neat): ν_{max} 2979, 1697, 1564, 1510, 1469, 1407, 1246, 1197, 1102, 1064, 826, 792 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 2 Hz, 1H), 7.18 (d, J = 2 Hz, 1H), 6.09 (d, J = 8.8 Hz, 2H), 5.49 (sept, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 1.48 (d, J = 6.8 Hz, 6H), 1.38 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.2, 158.1, 127.6, 126.2 (2C), 124.0, 122.4, 119.8, 114.8, 114.1 (2C), 59.8, 55.3, 48.6, 23.8 (2C), 14.5. **HRMS** (ES) m/z calcd for $C_{17}H_{22}NO_3$ $(M+H)^+$: 288.1594; found: 288.1587.

Ethyl 4-(3,4-dimethoxyphenyl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bc): By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2c** (144 mg, 0.5 mmol) with reaction time of 20 h, **3bc** was obtained as a yellow oil (138 mg, 73% yield); R_f = 0.5 (20% EtOAc + pet. ether). **IR** (neat): ν_{max} 2933, 1698, 1564, 1514, 1456, 1249, 1196, 1093, 1026, 762, 699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.25-7.21 (m, 1H), 7.19 (d,

J = 2 Hz, 1H),7.18-7.15 (m, 2H), 6.98 (dd, J_1 = 2 Hz, J_2 = 8.2 Hz, 1H), 6.93 (d, J = 2 Hz, 1H), 6.85 (d, J = 8 Hz, 1H), 6.82 (d, J = 2 Hz, 1H), 4.54 (t, J = 7.2 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.08 (t, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.1, 149.1, 147.6, 138.4, 129.0 (2C), 128.5 (2C), 127.7, 126.6, 125.2, 123.8, 122.2, 117.4, 115.1, 111.6, 108.8, 60.0, 56.0, 55.9, 51.1, 38.3, 14.5. **HRMS** (ES) m/z calcd for $C_{23}H_{26}NO_4$ $(M+H)^+$: 380.1856; found: 380.1856.

Ethyl 4-(3,4-dimethoxyphenyl)-1-isopropyl-1H-pyrrole-2-carboxylate (3cc): By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2c** (144 mg, 0.5 mmol) with reaction time of 20 h, **3cc** was obtained as a colourless oil (128.5 mg, 81% yield); R_f = 0.6 (20% EtOAc + pet. ether). **IR** (neat): ν_{max} 2978, 1699, 1562, 1513, 1469, 1408, 1242, 1196, 1102, 1064, 1027, 762, 611 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (d, J = 2 Hz, 1H), 7.17 (d, J = 2 Hz, 1H), 7.05 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1H), 7.01 (d, J = 2 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 5.49 (sept, J = 6.4 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 1.48 (d, J = 6.4 Hz, 6H), 1.37 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.1, 149.2, 147.6, 128.0, 124.2, 122.4, 120.0, 117.4, 114.8, 111.6, 108.8, 59.9, 56.0, 55.9, 48.6, 23.8 (2C), 14.5. **HRMS** (ES) m/z calcd for $C_{18}H_{24}NO_4$ $(M+H)^+$: 318.1700; found: 318.1686.

Ethyl 4-(3,5-dimethoxyphenyl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bd): By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2d** (144 mg, 0.5 mmol) with reaction time of 20 h, **3bc** was obtained as a yellow oil (153.5 mg, 81% yield); R_f= 0.4 (10% EtOAc + pet. ether). **IR** (neat): ν_{max} 1694, 1642, 1565, 1514, 1249, 1195, 1093, 1026, 699, 673, 663 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.25-7.20 (m, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.16-7.14 (m, 2H), 6.86 (d, J = 2.0 Hz, 1H), 6.58 (d, J = 2.4 Hz, 2H), 6.33 (t, J = 2.0 Hz, 1H), 4.53 (t, J = 7.6 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.81 (s, 6H), 3.08 (t, J = 7.6 Hz,

2H), 1.40 (t, J =7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 161.0 (2C), 161.0, 138.3, 136.5, 129.0 (2C), 128.6 (2C), 126.6, 125.8, 123.8, 122.3, 115.5, 103.3 (2C), 98.2, 60.1, 55.4, 51.1, 38.3, 14.5. **HRMS** (ES) m/z calcd for $C_{23}H_{26}NO_4$ $(M+H)^+$: 380.1856; found: 380.1855.

Ethyl 4-(3,5-dimethoxyphenyl)-1-isopropyl-1H-pyrrole-2-carboxylate (3cd): By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2d** (144 mg, 0.5 mmol) with reaction time of 20 h, **3cd** was obtained as a pale yellow oil (108 mg, 68% yield); R_f = 0.6 (10% EtOAc + pet. ether). **IR** (neat): ν_{max} 2979, 1701, 1596, 1486, 1461, 1403, 1230, 1204, 1174, 1155, 1103, 1065 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, J = 2 Hz, 1H), 7.21 (d, J = 2 Hz, 1H), 6.67 (d, J = 2.0 Hz, 2H), 6.34 (t, J = 2 Hz, 1H), 5.49 (sept, J = 6.8 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.83 (s, 6H), 1.48 (d, J = 6.8 Hz, 6H), 1.38 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.1 (2C), 161.0, 136.8, 124.2, 122.5, 120.7, 115.2 , 103.3 (2C), 98.2, 59.9, 55.4 (2C), 48.7, 23.8 (2C), 14.5. **HRMS** (ES) m/z calcd for $C_{18}H_{24}NO_4$ $(M+H)^+$: 318.1700; found: 318.1692.

Ethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1-phenethyl-1H-pyrrole-2-carboxylate (3be):- By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2e** (185 mg, 0.5 mmol) with reaction time of 12 h, **3be** was obtained as a colourless oil (172 mg, 75% yield); R_f = 0.5 (3% EtOAc + pet. ether). **IR** (neat): ν_{max} 2959, 1701, 1479, 1382, 1361, 1290, 1251, 1231, 1194, 1095, 1008, 699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 3H), 7.24-7.17 (m, 4H), 7.14 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 2 Hz, 1H), 4.58 (t, J = 7.2 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 3.39 (s, 3H), 3.12 (t, J = 7.2 Hz, 2H), 1.43 (s, 9H), 1.41 (t, J = 7.2 Hz, 3H), 1.33 (s, 9H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.3, 154.9, 145.4, 142.0, 138.5, 129.0 (2C), 128.5 (2C), 128.2, 127.7, 126.6, 125.2, 122.4, 121.4 (2C), 117.8, 60.1, 59.9, 51.0, 38.3, 35.3,

34.5, 31.6 (3C), 31.1 (3C), 14.6. **HRMS** (ES) m/z calcd for $C_{30}H_{40}NO_3$ $(M+H)^+$: 462.3008; found: 462.3003.

Ethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1-isopropyl-1H-pyrrole-2-carboxylate (3ce) : By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2e** (185 mg, 0.5 mmol) with reaction time of 12 h, **3ce** was obtained as a colourless oil (165.6 mg, 83% yield); R_f = 0.7 (3% EtOAc + pet. ether). **IR** (neat): ν_{max} 2961, 1702, 1469, 1394, 1361, 1281, 1226, 1200, 1101, 1064, 1008, 758 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.20 (s, 1H), 5.54 (sept, J = 6.4 Hz,1H), 4.33 (q, J = 7.2 Hz, 2H), 3.47 (s, 3H), 1.49 (d, J = 6.4 Hz, 6H), 1.44 (s, 9H), 1.40 (t, J = 7.2 Hz, 3H), 1.34 (s, 9H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.3, 154.8, 145.5, 142.0, 128.0, 125.2, 123.6, 122.4, 121.8, 121.5, 117.2, 59.9, 59.8, 48.5, 35.3, 34.5, 31.6 (3C), 31.1 (3C), 24.0 (2C), 14.5. **HRMS** (ES) m/z calcd for $C_{25}H_{38}NO_3$ $(M+H)^+$: 400.2846; found: 400.2832.

Ethyl 4-(4-fluorophenyl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bf): By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2f** (123 mg, 0.5 mmol) with reaction time of 5 h, **3bf** was obtained as a colorless solid (76 mg, 45% yield); R_f = 0.5 (5% EtOAc + pet. ether); m.p. 68-70 °C. **IR** (neat): ν_{max} 2981, 1695, 1566, 1510, 1475, 1424, 1397, 1255, 1227, 1197, 1094, 824 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39-7.36 (m, 2H), 7.32-7.28 (m, 2H), 7.26-7.22 (m, 1H), 7.21 (d, J = 2 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.03 (t, J = 8.8 Hz, 2H), 6.83 (d, J = 2 Hz, 1H), 4.54 (t, J = 7.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.09 (t, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.4 (d, J = 243 Hz, 1C), 161.0, 138.2, 130.6 (d, J = 3 Hz, 1C) , 128.9 (2C), 128.5 (2C), 126.5 (d, J = 3 Hz, 2C), 126.4, 125.2, 122.9, 122.4, 115.4 (d, J = 21 Hz, 2C), 115.1, 60.0, 51.0, 38.2, 14.4. **HRMS** (ES) m/z calcd for $C_{21}H_{21}FNO_2$ $(M+H)^+$: 338.1556; found: 338.1551.

Ethyl 4-(4-fluorophenyl)-1-isopropyl-1H-pyrrole-2-carboxylate (3cf):- By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2f** (123 mg, 0.5 mmol) with reaction time of 5 h, **3cf** was obtained as a yellow oil (64.6 mg, 47% yield); R_f = 0.3 (3% EtOAc + pet. ether). **IR** (neat): ν_{max} 2981, 1699, 1564, 1508, 1473, 1407, 1242, 1196, 1103, 1065, 827, 755 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48-7.44 (m, 2H), 7.25 (d, J = 2 Hz, 1H), 7.18 (d, J = 2 Hz, 1H), 7.06-7.01 (m, 2H), 5.41 (sept, J = 6.8, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.48 (d J = 6.8 Hz, 6H), 1.38 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.4 (d, J = 242 Hz, 1C), 161.0, 130.9 (d, J = 3 Hz, 1C), 126.5 (d, J = 7 Hz, 2C), 123.3, 122.6, 120.1, 115.5 (d, J = 21 Hz, 2C), 114.9, 59.9, 48.6, 23.8 (2C), 14.4. **HRMS** (ES) m/z calcd for $C_{16}H_{18}FNO_2$ $(M+H)^+$: 276.1394; found: 276.1399.

Ethyl 4-(4-chlorophenyl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bg):- By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2g** (130 mg, 0.5 mmol) with reaction time of 8 h, **3bg** was obtained as white solid (109.5 mg, 62% yield); R_f = 0.4 (5% EtOAc + pet. ether); m.p. 103-104 °C. **IR** (neat): ν_{max} 2981, 1698, 1646, 1495, 1474, 1453, 1254, 1197, 1091, 752, 699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.30-7.27 (m, 4H), 7.25-7.23 (m, 1H), 7.21 (d, J = 2 Hz, 1H), 7.16-7.14 (m, 2H), 6.85 (d, J = 2 Hz, 1H), 4.54 (t, J = 7.2 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.08 (t, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.0, 138.3, 133.1, 131.6, 129.0 (2C), 128.8 (2C), 128.6 (2C), 126.6, 126.3 (2C), 125.5, 122.6, 122.6, 115.2, 60.1, 51.2, 38.3, 14.5. **HRMS** (ES) m/z calcd for $C_{21}H_{21}ClNO_2$ $(M+H)^+$: 354.1261; found: 354.1255.

Ethyl 4-(4-chlorophenyl)-1-isopropyl-1H-pyrrole-2-carboxylate (3cg):- By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2g** (130 mg, 0.5 mmol) with reaction time

of 8 h, **3cg** was obtained as yellow oil (99 mg, 68% yield); R_f = 0.5 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2980, 1700, 1494, 1406, 1242, 1197, 1103, 1064, 823, 792 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 2 Hz, 1H), 7.20 (d, J = 2 Hz, 1H), 5.49 (sept, J = 6.8 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.48 (d, J = 6.8 Hz, 6H), 1.38 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.0, 133.3, 131.5, 128.8 (2C), 126.2 (2C), 123.1, 122.8, 120.3, 114.9, 60.0, 48.7, 23.8 (2C), 14.4. **HRMS** (ES) m/z calcd for $C_{16}H_{19}ClNO_2$ $(M+H)^+$: 292.1099; found: 292.1087.

Ethyl 4-(4-bromophenyl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bh):- By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2h** (154 mg, 0.5 mmol) with reaction time of 8 h, **3bh** was obtained as a fluorescent green solid (107.2 mg, 54% yield); R_f = 0.4 (3% EtOAc + pet. ether); m.p. 115-116 °C. **IR** (neat): ν_{max} 1699, 1558, 1493, 1473, 1419, 1255, 1198, 1095, 1008, 929 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2H), 7.30-7.20 (m, 4H), 7.20-7.22 (m, 1H), 7.21 (d, J = 2.8 Hz, 1H), 7.16-7.14 (m, 2H), 6.86 (d, J = 2 Hz, 1H), 4.54 (t, J = 7.2 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.08 (t, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.0, 138.2, 133.5, 131.8 (2C), 129.0 (2C), 128.6 (2C), 126.65, 126.62 (2C), 125.5, 122.6, 122.6, 119.6, 115.2, 60.1, 51.2, 38.3, 14.5. **HRMS** (ES) m/z calcd for $C_{21}H_{21}BrNO_2$ $(M+H)^+$: 398.0756; found: 398.0747.

Ethyl 4-(4-bromophenyl)-1-isopropyl-1H-pyrrole-2-carboxylate (3ch):- By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2h** (154 mg, 0.5 mmol) with reaction time of 8 h, **3ch** was obtained as a yellow oil (98.8 mg, 59% yield); R_f = 0.5 (3% EtOAc + pet. ether). **IR** (neat): ν_{max} 1700, 1470, 1406, 1310, 1241, 1195, 1103, 1064, 1008, 930, 791 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 2 Hz, 1H), 7.20 (d, J = 2 Hz, 1H), 5.49 (sept, J = 6.4 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.48 (d

J = 6.4 Hz, 6H), 1.38 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.0, 133.7, 131.7 (2C), 126.6 (2C), 123.0, 122.8, 120.3, 119.5, 114.9, 60.0, 48.8, 23.8 (2C), 14.5. **HRMS** (ES) m/z calcd for $C_{16}H_{19}BrNO_2$ $(M+H)^+$: 336.0594; found: 336.0579.

Ethyl 4-(2-nitrophenyl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bi): By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2i** (137 mg, 0.5 mmol) with reaction time of 7 h, **3bi** was obtained as a yellow oil (109.2 mg, 60% yield); R_f = 0.4 (10% EtOAc + pet. ether). **IR** (neat): ν_{max} 3028, 1702, 1609, 1526, 1401, 1364, 1253, 1199, 1098, 748, 701 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (dd, J_1 = 0.8 Hz, J_2 = 7.8 Hz, 1H), 7.49 (td, J_1 = 1.2 Hz, J_2 = 7.4 Hz, 1H), 7.37-7.21 (m, 5H), 7.13 (d, *J* = 7.2 Hz, 2H), 7.05 (d, *J* = 2 Hz, 1H), 6.74 (d, *J* = 2.0 Hz, 1H), 4.53 (t, *J* = 7.2 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.37 (t, *J* =7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 160.9, 149.0, 138.1, 131.8, 131.1, 129.0 (2C), 128.8, 128.6 (2C), 127.3, 127.0, 126.6, 123.6, 122.5, 118.1, 117.5, 60.2, 51.2, 38.2, 14.5. **HRMS** (ES) m/z calcd for $C_{21}H_{21}N_2O_4$ $(M+H)^+$: 365.1501; found: 365.1494.

Ethyl 1-isopropyl-4-(2-nitrophenyl)-1H-pyrrole-2-carboxylate (3ci): By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2i** (137 mg, 0.5 mmol) with reaction time of 7 h, **3ci** was obtained as a yellow oil (93.6 mg, 62% yield); R_f = 0.5 (10% EtOAc + pet. ether). **IR** (neat): ν_{max} 1703, 1527, 1407, 1369, 1239, 1197, 1105, 1064, 495 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (dd, J_1 = 0.8 Hz, J_2 = 8.0 Hz, 1H), 7.53-7.47 (m, 2H), 7.34 (ddd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, J_2 = 8.0 Hz 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 5.47 (sept, *J* = 6.8 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.46 (d *J* = 6.8 Hz, 6H), 1.35 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 160.9, 149.0, 131.8, 131.0, 129.0, 126.9, 123.6, 122.6, 122.4, 118.4, 117.2, 60.0, 49.0, 23.8 (2C), 14.4. **HRMS** (ES) m/z calcd for $C_{16}H_{19}N_2O_4$ $(M+H)^+$: 303.1339; found: 303.1325.

Ethyl 4-(3,4-dichlorophenyl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bj): By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2j** (149 mg, 0.5 mmol) with reaction time of 6 h, **3bj** was obtained as a yellow oil (116 mg, 60% yield); R_f = 0.6 (10% EtOAc + pet. ether). **IR** (neat): ν_{max} 1702, 1598, 1487, 1472, 1453, 1416, 1396, 1275, 1256, 1199, 1096, 1027, 793 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, J = 2 Hz, 1H), 7.36 (d, J = 7.2 Hz, 1H), 7.32-7.21 (m, 4H), 7.20 (d, J = 2 Hz, 1H), 7.15 (d, J = 7.2 Hz, 2H), 6.89 (d J = 2 Hz, 1H), 4.54 (t, J = 7.2 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.08 (t, J = 7.2 Hz, 2H), 1.41 (t, J =7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 160.9, 138.2, 134.8, 132.7, 130.6, 129.5, 128.9 (2C), 128.6 (2C), 126.73, 126.71, 125.7, 124.3, 122.8, 121.5, 115.2, 60.2, 51.2, 38.2, 14.5. **HRMS** (ES) m/z calcd for $C_{21}H_{20}Cl_2NO_2$ $(M+H)^+$: 388.0871; found: 388.0867.

Ethyl 4-(3,4-dichlorophenyl)-1-isopropyl-1H-pyrrole-2-carboxylate (3cj): By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2j** (149 mg, 0.5 mmol) with reaction time of 6 h, **3cj** was obtained as a yellow color oil (85 mg, 52% yield); R_f = 0.7 (10% EtOAc + pet. ether). **IR** (neat): ν_{max} 1702, 1639, 1599, 1467, 1407, 1241, 1196, 1133, 1104, 1065, 818, 791, 755 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.32 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 5.49 (sept, J = 6.8 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.48 (d, J = 6.8 Hz, 6H), 1.38 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 160.9, 135.0, 132.7, 130.6, 129.4, 126.7, 124.2, 123.1, 121.9, 120.5, 114.9, 60.1, 48.8, 23.8 (2C), 14.4. **HRMS** (ES) m/z calcd for $C_{16}H_{18}Cl_2NO_2$ $(M+H)^+$: 326.0709; found: 326.0694.

Ethyl 4-(2-bromo-4,5-dimethoxyphenyl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bk): By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2k** (184 mg, 0.5 mmol) with

reaction time of 13 h, **3bk** was obtained as a brown oil (187.4 mg, 82% yield); R_f = 0.6 **(**20% EtOAc + pet. ether). **IR** (neat): ν_{max} 2934, 1697, 1557, 1505, 1454, 1344, 1245, 1212, 1095, 1031, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.23-7.14 (m, 4H), 7.06 (s, 1H), 6.89 (d, J = 2 Hz, 1H), 6.75 (s, 1H), 4.56 (t, J = 7.6 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.10 (t, J = 7.6 Hz, 2H), 1.40 (t, J =7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.1, 148.3, 148.1, 138.4, 129.0 (2C), 128.5 (2C), 128.4, 128.0, 126.5, 122.4, 121.2, 118.3, 116.1, 113.3, 112.2, 60.0, 56.2, 56.1, 51.1, 38.2, 14.5. **HRMS** (ES) m/z calcd for $C_{23}H_{25}BrNO_4$ $(M+H)^+$: 458.0967; found: 458.0965.

Ethyl 4-(2-bromo-4,5-dimethoxyphenyl)-1-isopropyl-1H-pyrrole-2-carboxylate (3ck): By following general procedure, using **1c** (79 mg, 0.5 mmol)and **2k** (184 mg, 0.5 mmol) with reaction time of 13 h, **3ck** was obtained as a colourless oil (150 mg, 76% yield) R_f = 0.7 (20% EtOAc + pet. ether). **IR** (neat): ν_{max} 2978, 1699, 1505, 1469, 1416, 1232, 1211, 1103, 1063, 1031, 782 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, J = 2 Hz, 1H), 7.12 (d, J = 2 Hz, 1H), 7.08 (s, 1H), 6.88 (s, 1H), 5.49 (sept, J = 6.8 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 1.48 (d, J = 6.8 Hz, 6H), 1.36 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.1, 148.4, 148.0, 128.3, 123.4, 122.8, 121.4, 117.9, 116.1, 113.3, 112.1, 59.9, 56.2, 56.1, 48.7, 23.8 (2C), 14.5. **HRMS** (ES) m/z calcd for $C_{18}H_{23}BrNO_4$ $(M+H)^+$: 396.0805; found: 396.0794.

Ethyl 4-(naphthalen-1-yl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bl): By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2l** (139 mg, 0.5 mmol) with reaction time of 9.5 h, **3bl** was obtained as a yellow oil (164.5 mg, 89% yield); R_f= 0.5 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2979, 1699, 1475, 1453, 1380, 1274, 1174, 1092, 797, 777, 699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8 Hz, 1H), 7.79 (d, J = 8 Hz,

1H), 7.53-7.44 (m, 3H), 7.40 (d, J = 7.2 Hz, 1H), 7.36-7.26 (m, 4H), 7.19 (d, J = 7.2 Hz, 2H), 6.76 (s, 1H), 4.64 (t, J = 6.8 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 3.19 (t, J = 6.8 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.3, 138.5, 133.9, 133.3, 131.7, 129.1 (2C), 128.64 (2C), 128.60, 128.3, 127.0, 126.61, 126.59, 125.94, 125.92, 125.7, 125.5, 122.2, 121.6, 119.2, 60.1, 51.2, 38.2, 14.6. **HRMS** (ES) m/z calcd for $C_{25}H_{24}NO_2$ $(M+H)^+$: 370.1807; found: 370.1803.

Ethyl 1-isopropyl-4-(naphthalen-1-yl)-1H-pyrrole-2-carboxylate (3cl): By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2l** (139 mg, 0.5 mmol) with reaction time of 9.5 h, **3cl** was obtained as a yellow oil (112 mg, 73% yield); R_f = 0.5 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2979, 1700, 1473, 1417, 1378, 1260, 1238, 1209, 1100, 1063, 790, 776 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27-8.24 (m, 1H), 7.90-7.88 (m, 1H), 7.80-7.78 (m, 1H), 7.52-7.46 (m, 4H), 7.27 (d, J = 2Hz, 1H), 7.25 (d, J = 2 Hz, 1H), 5.59 (sept, J = 6.8 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 1.54 (d, J = 6.8 Hz, 6H), 1.39 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 161.3, 134.0, 133.6, 131.8, 128.4, 127.0, 126.6, 126.0, 125.9, 125.7, 125.5, 123.2, 122.9, 122.0, 118.8, 59.9, 48.7, 23.9 (2C), 14.5. **HRMS** (ES) m/z calcd for $C_{20}H_{22}NO_2$ $(M+H)^+$: 308.1645; found: 308.1648.

Ethyl 4-(5-methylfuran-2-yl)-1-phenethyl-1H-pyrrole-2-carboxylate (3bm): By following general procedure, using **1b** (110 mg, 0.5 mmol) and **2m** (116 mg, 0.5 mmol) with reaction time of 7 h, **3bm** was obtained as a yellow oil (110 mg, 68% yield); R_f = 0.4 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2980, 1701, 1474, 1453, 1397, 1254, 1210, 1186, 1097, 1077, 778, 699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 7.25-7.15 (m, 2H), 7.12 (d, J = 2 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.16 (d, J = 3.2 Hz, 1H), 5.97 (dd, J_1 = 1.2 Hz, J_2 = 3 Hz, 1H), 4.51 (t, J = 7.2 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 3.07 (t, J = 7.2 Hz, 2H), 2.32 (s, 3H), 1.38 (t,

J =7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.0, 150.0, 148.4, 138.3, 128.9 (2C), 128.56 (2C), 126.59, 124.3, 122.1, 115.7, 114.0, 107.0, 103.5, 60.0, 51.0, 38.4, 14.5, 13.6. **HRMS** (ES) m/z calcd for $C_{20}H_{22}NO_3$ $(M+H)^+$: 324.1600; found: 324.1593.

Ethyl 1-isopropyl-4-(5-methylfuran-2-yl)-1H-pyrrole-2-carboxylate (3cm): By following general procedure, using **1c** (79 mg, 0.5 mmol) and **2m** (116 mg, 0.5 mmol) with reaction time of 7 h, **3cm** was obtained as a yellow oil (79 mg, 60% yield); R_f = 0.5 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2980, 1703, 1471, 1399, 1306, 1240, 1207, 1194, 1176, 1102, 1064, 778 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 2 Hz, 1H), 7.09 (d, *J* = 2 Hz, 1H), 6.18 (d, *J* = 3.2 Hz, 1H), 5.96 (dd, J_1 = 0.8 Hz, J_2 = 3.2 Hz, 1H), 5.47 (sept, *J* = 6.8 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.32 (d, *J* = 0.8 Hz, 3H), 1.46 (d, *J* = 6.8 Hz, 6H), 1.36 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 161.1, 149.9, 148.6, 122.2, 119.5, 115.9, 113.8, 107.0, 103.4, 59.9, 48.6, 23.8 (2C), 14.4, 13.6. **HRMS** (ES) m/z calcd for $C_{15}H_{19}NO_3$ $(M+H)^+$: 262.1438; found: 262.1427.

Ethyl 1-(tert-butyl)-4-phenyl-1H-pyrrole-2-carboxylate (3da):- By following general procedure, using **1d** (86 mg, 0.5 mmol) and **2a** (114 mg, 0.5 mmol) with reaction time of 15 h, **3da** was obtained as a yellow oil (83 mg, 61% yield); R_f = 0.4 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2978, 1708, 1605, 1449, 1369, 1257, 1192, 1146, 1061, 758, 695 cm^{-1};**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (dd, J_1 = 1.0 Hz, J_2 = 8.0 Hz, 2H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.20 (tt, J_1 = 1.0 Hz, J_2 = 7.6 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.77 (s, 9H), 1.39 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.2, 134.7, 129.8, 128.7 (2C), 127.6, 125.9, 125.0(2C), 123.0, 119.0, 60.1, 58.6, 30.3 (3C), 14.5. **HRMS** (ES) m/z calcd for $C_{17}H_{22}NO_2$ $(M+H)^+$: 272.1645; found: 272.1646.

Ethyl 1-(2-hydroxyethyl)-4-phenyl-1H-pyrrole-2-carboxylate (3ea):- By following general procedure, using **1e** (80 mg, 0.5 mmol) and **2a** (114 mg, 0.5 mmol) with reaction time of 9.5 h, **3ea** was obtained as a colourless oil (98.5 mg, 76% yield); R_f = 0.4 (30% EtOAc + pet. ether). **IR** (neat): ν_{max} 2979, 1697, 1605, 1474, 1443, 1398, 1271, 1205, 1100, 758 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.27 (d, J = 2.0 Hz, 1H), 7.21 (tt, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 2H), 4.48 (t, J = 5.2 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 3.93 (t, J = 5.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.7, 134.3, 128.8 (2C), 126.4, 126.2, 125.1 (2C), 124.3, 122.7, 115.6, 63.0, 60.3, 51.4, 14.4. **HRMS** (ES) m/z calcd for $C_{15}H_{18}NO_3$ $(M+H)^+$: 260.1281; found: 260.1286.

Ethyl 1-cyclohexyl-4-phenyl-1H-pyrrole-2-carboxylate (3fa):- By following general procedure, using **1f** (99 mg, 0.5 mmol) and **2a** (114 mg, 0.5 mmol) with reaction time of 6.5 h, **3fa** was obtained as a colourless oil (59.5 mg, 40% yield); R_f = 0.7 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2932, 1701, 1605, 1469, 1451, 1407, 1254, 1230, 1192, 1093, 758 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (dd, J_1 = 1.2 Hz, J_2 = 8.2 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.33 ((d, J = 2 Hz, 1H), 7.26 (d, J = 2 Hz, 1H), 7.20 (tt, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H), 5.06 (tt, J_1 = 3.6 Hz, J_2 = 11.2 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 2.16 (d, J = 12 Hz, 2H), 1.91 (d, J = 13.2 Hz, 2H), 1.77 (d, J = 13.2 Hz, 1H), 1.66-1.49 (m, 4H), 1.39 (t, J = 7.2 Hz, 3H), 1.30-1.23 (m, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.2, 134.8, 128.7 (2C), 126.0, 125.0 (2C), 124.0, 122.5, 121.0, 115.0, 59.9, 56.5, 34.7 (2C), 25.9 (2C), 25.7, 14.5. **HRMS** (ES) m/z calcd for $C_{19}H_{24}NO_2$ $(M+H)^+$: 298.1802; found: 298.1806.

Ethyl 1-allyl-4-phenyl-1H-pyrrole-2-carboxylate (3ga):- By following general procedure, using **1g** (78 mg, 0.5 mmol) and **2a** (114 mg, 0.5 mmol) with reaction time of 4.5 h, **3ga** was obtained as brown oil (89.3 mg, 70% yield); R_f= 0.5 (5% EtOAc + pet. ether). **IR** (neat): ν_{max}

1698, 1644, 1471, 1270, 1211, 1098, 930, 905, 837, 758 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (dd, J_1 = 1.2 Hz, J_2 = 8.2 Hz, 2H), 7.35 (t, J = 8.0 Hz, 2H), 7.27 (d, J = 2.0 Hz, 1H), 7.20 (tt, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H), 7.15 (d, J = 2.0 Hz, 1H), 6.05 (ddt, J_1 = 5.2 Hz, J_2 = 10.0 Hz, J_3 = 17.2 Hz 1H), 5.18 (dq, J_1 = 1.6 Hz, J_2 = 10.0 Hz, 1H), 5.06 (dq, J_1 = 1.6 Hz, J_2 = 17 Hz, 1H), 4.99 (dq, J_1 = 1.6 Hz, J_2 = 5.2 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.1, 134.5 (2C), 128.7 (2C), 126.1, 125.1 (2C), 125.0, 124.3, 122.8, 116.9, 115.1, 60.0, 51.2, 14.4. **HRMS** (ES) m/z calcd for $C_{16}H_{17}NNaO_2$ $(M+Na)^+$: 278.1151; found: 278.1151.

Ethyl 1-(2-(1H-indol-3-yl)ethyl)-4-phenyl-1H-pyrrole-2-carboxylate (3ha):- By following general procedure, using **1h** (129 mg, 0.5 mmol) and **2a** (114 mg, 0.5 mmol) with reaction time of 6.5 h, **3ha** was obtained as a colourless oil (105.6 mg, 59% yield); R_f = 0.4 (20% EtOAc + pet. ether). **IR** (neat): ν_{max} 2980, 1697, 1605, 1456, 1419, 1264, 1201, 1095, 759, 742, 695 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8 Hz, 2H), 7.39-7.35 (m, 4H), 7.28-7.19 (m, 3H), 6.93 (d, J = 2 Hz, 1H), 6.82 (d, J = 2 Hz, 1H), 4.64 (t, J = 7.2 Hz, 2H), 4.39 (q, J = 7.2 Hz, 2H), 3.29 (t, J = 7.2 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.1, 136.1, 134.5, 128.6 (2C), 127.1, 125.9, 125.7, 125.0 (2C), 123.5, 122.4, 122.3, 121.9, 119.4, 118.6, 115.2, 112.1, 111.1, 60.1, 50.0, 27.7, 14.4. **HRMS** (ES) m/z calcd for $C_{23}H_{23}N_2O_2$ $(M+H)^+$: 359.1760; found: 359.1754.

1-(1-benzyl-4-phenyl-1H-pyrrol-2-yl)ethan-1-one (3ia):- By following general procedure, using **1i** (88 mg, 0.5 mmol) and **2a** (114 mg, 0.5 mmol) with reaction time of 10 h, **3ia** was obtained as a yellow oil (69 mg, 50% yield); R_f = 0.2 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 2924, 1650, 1605, 1563, 1395, 1355, 1268, 1211, 758, 730, 696 cm^{-1};**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (dd, J_1 = 1.2 Hz, J_2 = 8.2 Hz, 2H), 7.38- 7.29 (m, 5H), 7.27 (d, J = 2 Hz, 1H),

7.26-7.22 (m, 1H), 7.20 (d, J = 2 Hz, 1H), 7.21-7.16 (m, 2H), 5.62 (s, 2H), 2.48 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.6, 138.0, 134.1, 131.0, 128.8 (2C), 128.7 (2C), 127.6, 127.2 (2C), 127.1, 126.4, 125.1 (2C), 124.5, 117.2, 52.8, 27.4. **HRMS** (ES) m/z calcd for $C_{19}H_{18}NO$ $(M+H)^+$: 276.1383; found: 276.1382.

1-benzyl-N-methoxy-N-methyl-4-phenyl-1H-pyrrole-2-carboxamide (3ja):-By following general procedure, using **1j** (110 mg, 0.5 mmol) and **2a** (114 mg, 0.5 mmol) with reaction time of 5 h, **3ja** was obtained as a yellow oil (105.6 mg, 66% yield); R_f = 0.5 (30% EtOAc + pet. ether). **IR** (neat): ν_{max} 2360, 1627, 1562, 1497, 1455, 1391, 1355, 1208, 1065, 1029, 978, 931, 696 cm^{-1};**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (dd, J_1 = 1.2 Hz, J_2 = 8 Hz, 2H), 7.37-7.33(m, 2H), 7.37-7.33(m, 2H), 7.32-7.28(m, 2H), 7.25-7.20(m, 3H), 7.18-7.13(m, 3H), 5.56(s, 2H), 3.57(s, 3H), 3.28(s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 162.1, 138.6, 134.7, 128.7 (2C), 128.5 (2C), 127.4, 127.0 (2C), 125.9, 125.0 (2C), 124.1, 124.1, 123.8, 113.9, 61.0, 52.4, 33.7. **HRMS** (ES) m/z calcd for $C_{20}H_{21}N_2O_2$ $(M+H)^+$: 321.1598; found: 321.1615.

Ethyl 1-phenethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate (10): In an oven-dried seal tube, under nitrogen atmosphere, β-bromo-β-nitrostyrene **2a** (114 mg, 0.5 mmol) was taken. After that aziridine **9** (147.5 mg, 0.5 mmol, 1 equiv.) dissolved in toluene (2 mL) was added. The reaction was then sealed while maintaining the N_2 atmosphere and then stirred in a preheated oil bath at 150°C for 8 h until complete consumption of starting materials was indicated upon reaction monitoring. After reaction completion, the solvent was removed under reduced pressure and the crude residue was subjected to purification using SiO_2-gel flash column chromatography to access **10** & **11**. Yield for **10** = 29.6 mg, 15% yield) R_f = 0.6 (5% EtOAc + pet. ether). Data for **10**: **IR** (neat): ν_{max} 3508, 3455, 1690, 1644, 1454, 1403, 1374, 1245, 1182, 1094, 756, 698 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 7.44-7.25 (m, 12H), 7.19 (d, J = 6.4 Hz, 2H), 6.95 (d, J = 6 Hz, 1H), 6.18 (s, 1H), 4.56 (t, J = 7.6 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H) 2.92

(t, J = 7.6 Hz, 2H), 1.07 (t, J = 7.2 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 162.0, 140.2, 138.3, 137.0, 134.0, 132.3, 129.6 (2C), 129.5 (2C), 128.8 (2C), 128.38 (2C), 128.36 (2C), 128.2, 127.4 (2C), 126.5, 126.4, 118.9, 111.9, 59.9, 47.6, 38.1, 13.8. **HRMS** (ES) m/z calcd for $C_{27}H_{26}NO_2$ $(M+H)^+$: 396.1958; found: 396.1961.

Ethyl 1-phenethyl-4,5-diphenyl-1H-pyrrole-2-carboxylate (11): Yield = 5.9 mg, 3% yield); R_f = 0.4 (5% EtOAc + pet. ether). **IR** (neat): ν_{max} 3675, 3027, 1692, 1603, 1548, 1454, 1403, 1374, 1246, 1182, 1094, 1027, 157, 698 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.36 (m, 1H), 7.34-7.25 (m, 6H), 7.22-7.20 (m, 3H), 7.16-7.07 (m, 3H), 7.00-6.94 (m, 2H), 6.81 (s, 1H), 4.58 (t, J = 7.6 Hz, 2H), 4.06 (q, J = 7.2 Hz, 2H) 3.14 (t, J = 7.6 Hz, 2H), 0.93 (t, J = 7.2 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.7, 138.4, 136.2, 134.5, 131.4, 130.6 (2C), 129.6, 129.0 (2C), 128.8, 128.5 (2C), 128.0 (2C), 127.4 (2C), 126.6, 126.4, 126.2, 125.7, 124.0, 119.6, 59.7, 51.5, 38.4, 13.6. **HRMS** (ES) m/z calcd for $C_{27}H_{26}NO_2$ $(M+H)^+$: 396.1958; found: 396.1960.

Benzyl 4-(2-bromo-4,5-dimethoxyphenyl)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1H-pyrrole-2-carboxylate (13): By following general procedure, using **12** (168 mg, 0.5 mmol) and **2k** (184 mg, 0.5 mmol)with reaction time of 5 h in both toluene as well as toluene-d_8, **13** was obtained as yellow color oil (215.5 mg, 75% yield); R_f = 0.6 (20% EtOAc + pet. ether). **IR** (neat): ν_{max} 2953, 2929, 2855, 1731, 1702, 1505, 1462, 1437, 1415, 1387, 1248, 1214, 1098, 1031, 836 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.40-7.30 (m, 3H), 7.24 (d, J = 2 Hz, 1H), 7.21 (d, J = 2 Hz, 1H), 7.08 (s, 1H), 6.84 (s, 1H), 5.30 (s, 2H), 4.71(t, J = 4.8 Hz, 2H), 3.92 (t, J = 4.8 Hz, 2H) 3.88 (s, 3H), 3.86 (s, 3H), 0.83 (s, 9H), -0.06 (s, 6H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.0, 148.3, 148.1, 136.4, 129.9, 128.5 (2C), 128.0, 127.98, 127.95 (2C), 122.5, 120.7, 118.8, 116.1, 113.2, 112.2, 65.5, 63.0, 56.2, 56.0, 51.7, 25.8 (3C),

18.2, -5.6 (2C). **HRMS** (ES) m/z calcd for $C_{28}H_{37}BrNO_5Si$ $(M+H)^+$: 574.1619; found: 574.1619.

Benzyl 4-(2-bromo-4,5-dimethoxyphenyl)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1H-pyrrole-2-carboxylate-3,5-d2 (13-*d*$_2$): By following general procedure, using **12-*d*$_2$** (169 mg, 0.5 mmol) and **2k** (184 mg, 0.5 mmol) with reaction time of 5 h in both toluene as well as toluene-d_8, **13-*d*$_2$** was obtained as yellow colour oil (207.5 mg, 72% yield); R_f = 0.6 (20% EtOAc + pet. ether). **IR** (neat): ν_{max} 2953, 2929, 2855, 1731, 1702, 1505, 1462, 1437, 1415, 1387, 1248, 1214, 1098, 1031, 836 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.40-7.31 (m, 3H), 7.23 (d, J = 1.6 Hz, 0.45 H), 7.21 (d, J = 1.2 Hz, 0.68 H), 7.08 (s, 1H), 6.84 (s, 1H), 5.29 (s, 2H), 4.46 (t, J = 5.2 Hz, 2H), 3.91 (t, J = 5.2 Hz, 2H) 3.88 (s, 3H), 3.86 (s, 3H), 0.83 (s, 9H), -0.07 (s, 6H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 160.9, 148.3, 148.0, 136.4, 129.8, 128.5 (2C), 128.0, 127.9 (3C), 122.5, 120.7, 118.8, 116.1, 113.2, 112.2, 65.5, 63.0, 56.2, 56.0, 51.7, 25.8 (3C), 18.2, -5.7 (2C). **HRMS** (ES) m/z calcd for $C_{28}H_{35}D_2BrNO_5Si$ $(M+H)^+$: 576.1744; found: 576.1744.

Gram Scale Synthesis of Ethyl 1-(3,4-dimethoxyphenethyl)-4-(3,4-dimethoxyphenyl)-1H-pyrrole-2-carboxylate (15): By following general procedure, using **14** [ethyl 1-(3,4-dimethoxyphenethyl)aziridine-2-carboxylate] (1.6 g, 5.7 mmol, 1 equiv.) and **2c** [(*Z*)-4-(2-bromo-2-nitrovinyl)-1,2-dimethoxybenzene] (1.3 g, 5.7 mmol, 1 equiv.) with a reaction time of 16 h, **15** was obtained after flash column chromatography as pale yellow oil (2.16 g, 86% yield); R_f = 0.7 (20% EtOAc + pet. ether). **IR** (neat): ν_{max} 2935, 2835, 1697, 1589, 1564, 1515, 1465, 1419, 1250, 1195, 1092, 1027, 801, 762 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (d, J = 2 Hz, 1H), 6.97 (dd, J_1 = 2 Hz, J_2 = 8.6 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 6.71 (dd, J_1 = 1.6 Hz, J_2 = 8 Hz, 1H),

6.55 (d, J = 3.2 Hz, 1H), 4.52 (t, J = 7.2 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 3.02 (t, J = 7.2 Hz, 2H), 1.40 (t, J =7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 161.1, 149.1, 148.8, 147.7, 147.6, 131.0, 127.7, 125.4, 123.8, 122.2, 120.9, 117.4, 115.1, 112.1, 111.6, 111.2, 108.7, 60.0, 55.97, 55.87, 55.86, 55.75, 51.2, 37.8, 14.5. **HRMS** (ES) m/z calcd for $C_{25}H_{30}NO_6$ $(M+H)^+$: 440.2068; found: 440.2088.

1-(3,4-dimethoxyphenethyl)-4-(3,4-dimethoxyphenyl)-5-formyl-1H-pyrrole-2-carboxylic acid (16): In a 25 mL RB flask, 0.62 g of dry DMF (8.55 mmol, 5 equiv.) was taken and cooled at 0 °C. Then 0.795 mL of $POCl_3$ (8.55 mmol, 5 equiv.) was added dropwise at the same temperature. After 15 min, to the resulting yellow solution, compound **15** (0.75 g, 1.71 mmol, 1 equiv.) dissolved in dry DMF (1.5 mL) was added and the reaction was allowed to warm to rt. The reaction was then heated at 80 °C for 2 h until completion of the reaction was indicated by TLC analysis. The reaction mixture was worked up by quenching it with aq. $NaHCO_3$ followed by extraction with EtOAc (3 × 20 mL). The organic layer was then dried over Na_2SO_4 and then concentrated in vacuum to arrive at a crude residue which was purified by SiO_2-gel column chromatography to access the Vilsmeir-Haack formylated pyrrole ester (0.72 g, 90% yield); R_f = 0.4 (20% EtOAc + pet. ether). **IR** (neat): ν_{max} 2925, 1714, 1657, 1513, 1463, 1419, 1260, 1245, 1155, 1094, 1026 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 6.93-6.89 (m, 4H), 6.85 – 6.75 (m, 3H), 5.03 (t, J = 7.6 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 2.99 (t, J = 7.6 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 182.1, 160.6, 149.1, 149.0, 148.8, 147.7, 138.0, 130.8, 130.1, 128.3, 125.7, 122.3, 121.2, 116.8, 112.7, 112.4, 111.2, 111.2, 61.0, 56.0, 55.99, 55.89, 55.80, 48.3, 37.5, 14.3.

To a solution of the formylated product (0.6 g, 1.29 mmol, 1 equiv.) obtained from above step, in ethanol : water (3:1, 12 mL), crushed NaOH pellets (0.26 g, 6.45 mmol, 5 equiv.)

were added at rt and the reaction was then allowed to reflux for 3 h, until completion of the saponification process was indicated by TLC analysis. The reaction was worked up by removing the volatiles under reduced pressure and then neutralization of the resultant residue by 1N HCl. The aqueous phase was subjected to extraction with EtOAc (4 × 20 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude residue which was subjected to SiO_2-gel column chromatography to access pure formylated pyrrole-2-carboxylic acid **16** as a yellow solid (0.51 g, 91% yield); R_f = 0.2 (50% EtOAc + pet. ether); m.p. 166-168 °C. **IR** (neat): ν_{max} 2924, 1654, 1513, 1462, 1420, 1259, 1140, 1025, 764 cm^{-1} ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.12 (s, 1H), 6.94 (s, 2H), 6.91 (s, 1H), 6.84 – 6.79 (m, 3H), 5.05 (t, J = 7.6, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.03 (t, J = 7.6, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 182.4, 165.0, 149.2, 149.0, 148.8, 147.7, 137.9, 131.0, 130.6, 126.8, 125.3, 122.3, 121.1, 118.6, 112.6, 112.2, 111.24, 111.21, 56.04, 56.03, 55.9, 55.8, 48.5, 37.6. **HRMS** (ES) m/z calcd for $C_{24}H_{26}NO_7$ $(M+H)^+$: 440.1704; found: 440.1683.

1-(3,4-dimethoxyphenethyl)-3-(3,4-dimethoxyphenyl)-1H-pyrrole-2-carboxylic acid (17):

In an oven-dried sealed tube compound **16** (0.45 g, 1.03 mmol, 1 equiv.) was added along with 1 mL of quinoline, followed by copper (I) oxide (0.08 mg, 1.03 mmol, 1 equiv.) and 1,10-phenanthroline (0.19 g, 1.03 mmol, 1 equiv.). The reaction vessel was then sealed and subjected to heating at 220 °C for 5-7 min until complete decarboxylation was indicated by TLC analysis. Upon reaction completion the volatiles were removed under vacuum and the crude residue was subjected to SiO_2-gel column chromatography to access the decarboxylated pyrrole aldehyde (0.37 g, 92% yield); R_f = 0.4 (30% EtOAc + pet. ether). **IR** (neat): ν_{max} 2853, 1649, 1543, 1514, 1463, 1427, 1356, 1251, 1139, 1027 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 6.97 (dd, J_1 = 8.2, J_2 = 1.8 Hz, 1H), 6.93 (d, J = 2.1 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.78 (d, J =

8.2 Hz, 1H), 6.71 (dd, J_1 = 8.1, J_2 = 1.4 Hz, 1H), 6.64 (d, J = 2.3 Hz, 1H), 6.57 (d, J = 1.6 Hz, 1H), 6.17 (d, J = 2.5 Hz, 1H), 4.52 (t, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.00 (t, J = 7.1 Hz, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 180.4, 148.90, 148.88, 148.83, 147.7, 140.6, 130.8, 130.7, 126.8, 126.5, 122.1, 120.9, 112.7, 112.1, 111.2, 111.2, 109.4, 55.9 (2C), 55.8, 51.7, 37.5.

As per the reported procedure,[26] to a solution of decarboxylated pyrrole aldehyde (0.35 g, 0.88 mmol, 1 equiv.) in THF (2 mL) and *t*-BuOH (2 mL) was added 2-methylbut-2-ene (0.4 mL) at 10 °C. Subsequently, a solution of $NaClO_2$ (0.24 g, 3.08 mmol, 3 equiv.) and NaH_2PO_4 (0.32 g, 3.08 mmol, 3 equiv.) in 1.5 mL water was added to the solution and the mixture was stirred for next 12 h at same temperature. On indication of completion of reaction by TLC analysis, the reaction was quenched with saturated aqueous NH_4Cl and then extracted with EtOAc (3 × 20 mL). The combined organic extracts were then washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to arrive at a crude residue which was purified by SiO_2-gel column chromatography to access acid **17** (0.317 g, 87% yield); R_f = 0.2 (30% EtOAc + pet. ether). **IR** (neat): ν_{max} 2853, 1654, 1515, 1463, 1261, 1236, 1141, 1026, 808 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.03-6.99 (m, 2H), 6.88 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.67 (dd, J_1 = 8.1, J_2 = 1.6 Hz, 1H), 6.62 (d, J = 2.5 Hz, 1H), 6.50 (d, J = 1.6 Hz, 1H), 6.10 (d, J = 2.5 Hz, 1H), 4.49 (t, J = 7.0 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.74 (s, 3H), 3.01 (t, J = 7.0 Hz, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 165.9, 148.8, 148.2, 148.0, 147.7, 136.5, 130.9, 129.6, 129.1, 121.8, 120.8, 116.3, 113.4, 112.0, 111.2, 110.8, 110.6, 55.8 (3C), 55.6, 52.4, 27.7. **HRMS** (ES) m/z calcd for $C_{23}H_{26}NO_6$ $(M+H)^+$: 412.1755; found: 412.1736.

3-(3,4-dimethoxyphenethyl)-7,8-dimethoxychromeno[3,4-b]pyrrol-4(3H)-one (18): [27] To a solution of acid **17** (0.315 g, 0.77 mmol, 1 equiv.) in dry EtOAc (15 mL) was added $Pb(OAc)_4$

(0.34 g, 0.77 mmol, 1 equiv.) and the resulting mixture was stirred at rt for 1 h until complete consumption of starting material was indicated by TLC analysis. The reaction was worked up by diluted it with EtOAc (5 mL) and then filtering it through a short celite bed. Removal of volatiles under reduced pressure afforded a crude residue which was purified by SiO_2-gel column chromatography to access the lactone **18** (0.11 g, 35% yield) with spectral data similar to that reported by others.[27] R_f = 0.7 (30% EtOAc + pet. ether); m.p. 159-160 °C. **IR** (neat): ν_{max} 3418, 1643, 1517, 1451, 1426, 1261, 1235, 1191, 1154, 1027, 1003 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12 (s, 1H), 6.96 (s, 1H), 6.85 (d, J = 2.7 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.66 (dd, J_1 = 8.1, J_2 = 1.9 Hz, 1H), 6.60 (d, J = 1.9 Hz, 1H), 6.45 (d, J = 2.7 Hz, 1H), 4.64 (t, J = 7.0 Hz, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.10 (t, J = 7.0 Hz, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 155.3, 149.3, 148.8, 147.7, 146.2, 146.0, 132.8, 131.1, 130.4, 120.8, 114.8, 111.9, 111.1, 110.2, 104.0, 100.6, 100.4, 56.3, 56.1, 55.8, 55.7, 50.9, 37.7.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H & ^{13}C NMR spectral data of the synthesized compounds. CIF files and X-ray Crystallographic data. The Supporting Information is available free of charge on the ACS publications website.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

DEDICATION

This work is dedicated to Prof. Goverdhan Mehta (Univ. of Hyderabad, India) on the occassion of his 76th birthday.

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REFERENCES

1) (a) Sundburg, R. J. In Comprehensive Heterocyclic Chemistry II Vol. 2 (Eds.: Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.), Pergamon Press: Oxford, **1996**, pp. 119-206. (b) Fürstner, A. Chemistry and biology of roseophilin and the prodigiosin alkaloids: a survey of the last 2500 years. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582-3603. (c) Fan, H.; Peng, J. M.; Hamann, T.; Hu, J.-F. Lamellarins and Related Pyrrole-Derived Alkaloids from Marine Organisms. *Chem. Rev.* **2008**, *108*, 264-287 and references cited therein.

2) (a) Domagala, A.; Jarosz, T.; Lapkowski, M. Living on pyrrolic foundations – Advances in natural and artificial bioactive pyrrole derivatives. *Eur. J. Med. Chem.* **2015**, *100*, 176-187. (b) Gholap, S. S. Pyrrole: An emerging scaffold for construction of valuable

therapeutic agents. *Eur. J. Med. Chem.* **2016**, *110*, 13-31. (c) de Laszlo, S. E.; Hacker, C.; Li, B.; Kim, D.; MacCoss, M.; Mantlo, N.; Pivnichny, J. V.; Colwell, L.; Koch, G. E.; Cascieri, M. A.; Hagmann, W. K. Potent, orally absorbed glucagon receptor antagonists. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 641-646. (d) La Regina, G.; Silvestri, R.; Artico, M.; Lavecchia, A.; Novellino, E.; Befani, O.; Turini, P.; Agostinelli, E. New Pyrrole Inhibitors of Monoamine Oxidase: Synthesis, Biological Evaluation, and Structural Determinants of MAO-A and MAO-B Selectivity. *J. Med. Chem.* **2007**, *50*, 922-931.

3) (a) Higgins, S. J. Conjugated polymers incorporating pendant functional groups—synthesis and characterisation. *Chem. Soc. Rev.* **1997**, *26*, 247-257. (b) Novak, P.; Müller, K.; Santhanam, S. V.; Hass, O. Electrochemically Active Polymers for Rechargeable Batteries. *Chem. Rev.* **1997**, *97*, 207-281. c) Gabriel, S.; Cecius, M.; Fleury-Frenette, K.; Cossement, D.; Hecq, M.; Ruth, N.; Jerome, R.; Jerome, C. Synthesis of Adherent Hydrophilic Polypyrrole Coatings onto (Semi)conducting Surfaces. *Chem. Mater.* **2007**, *19*, 2364-2371. (d) Li, C.-S.; Tsai, Y.-H.; Lee, W.-C.; Kuo, W.-J. Synthesis and Photophysical Properties of Pyrrole/Polycyclic Aromatic Units Hybrid Fluorophores. *J. Org. Chem.* **2010**, *75*, 4004-4013.

4) (a) Paal, C. Synthese von Thiophen- und Pyrrolderivaten. *Ber. Dtsch. Chem. Ges*. **1885**, *18*, 367-371. (b) Knorr, L. Synthese von Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1884**, 17, 1635-1642. (c) Piloty, O. Synthesis of Pyrrole Derivatives: Pyrroles from Succinylosuccinic Ester, Pyrroles from Azines. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 489-498. (d) Robinson, G. M.; Robinson, R. New synthesis of tetraphenylpyrrole. *J. Chem. Soc.*, *Trans.* **1918**, *113*, 639-645. (e) Hantzsch, A. Neue Bildungsweise yon Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474−1476.

5) For recent selected examples see: (a) Chiu. H.-C.; Tonks, I. A. Trimethylsilyl-Protected Alkynes as Selective Cross-Coupling Partners in Titanium-Catalyzed [2+2+1] Pyrrole

Synthesis. *Angew. Chem. Int. Ed.* **2018**, 57, 6090–94. (b) Liu, Y.; Hu, H.; Wang, X.; Zhi, S.; Kan, Y.; Wan, C. Synthesis of Pyrrole via a Silver-Catalyzed 1,3-Dipolar Cycloaddition/Oxidative Dehydrogenative Aromatization Tandem Reaction. *J. Org. Chem.*, **2017**, *82*, 4194-4202 and ref. cited therein. (c) Mishra, P. K.; Verma, S.; Kumar, M.; Verma, A. K. Base-Mediated Direct Transformation of *N*-Propargylamines into 2,3,5-Trisubstituted 1*H*-Pyrroles. *Org. Lett.*, **2018**, *20*, 7182–7185 and ref. cited therein.

6) For 1,2,3-trisubstituted pyrroles synthesis see: (a) Wing, H. C.; Albert, W. M. L.; Ka, M. L.; Tin, Y. L. Unsaturated sulfoxides in organic synthesis: a new general pyrrole synthesis. *J. Chem. Soc.*, Perkin Trans. 1 **1994**, 2355-2356. (b) Yuri, N. R.; Michael, T. H. L.; Roland, B. The facile synthesis of 1,2,3-trisubstituted pyrroles from the reaction of chlorocarbenes with 1-azabuta-1,3-dienes. *Chem. Commun.* **1999**, *5*, 447-448. (c) Xu, P.; Huang, K.; Liu, Z.; Zhou, M.; Zeng, W. An efficient and convenient synthesis of 1,2,3-trisubstituted pyrroles via iodocyclization from ethyl acetoacetate. *Tetrahedron Lett.* **2013**, *54*, 2929-2933. (d) Xu, P.; Huang, K.; Cao, D.; Zeng, W. A Green and Efficient One-pot Synthesis of 1,2,3-Trisubstituted Pyrroles via Iodine-catalyzed Tandem Reaction. *Lett. Org. Chem.* **2015**, *12*, 290-298.

7) For 1,2,4-trisubstituted pyrroles synthesis see: (a) Banwell, M. G.; Flynn, B. L.; Hockless, D. C. R.; Longmore, R. W.; Rae, A. D. Assessment of Double-Barrelled Heck Cyclizations as a Means for Construction of the 14-Phenyl-8,9-dihydro- 6H-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin- 6-one Core Associated with Certain Members of the Lamellarin Class of Marine Natural Product. *Aust. J. Chem.,* **1999**, *52*, 755. (b) Chen, W.-L.; Li, J.; Zhu, Y.-H.; Ye, L.-T.; Hu, W.; Mo, W.-M. AgOTf-catalyzed cyclization of enynals or enynones with amines: an efficient synthesis of 1,2,4-trisubstituted pyrroles and 2,3,5-trisubstituted furans. *Arkivoc*, **2011**, 381-392. (c) Demir, A. S.; Igdir, A. C.; Gunay, B. Amination/annulation of chlorobutenones with chiral amine

compounds: synthesis of 1,2,4-trisubstituted pyrroles.*Tetrahedron: Asymmetry*, **2005**, *16*, 3170-3175. (d) Li, E.; Cheng, X.; Wang, C.; Sun, X.; Li, Y. Copper-catalyzed synthesis of 1,2,4-trisubstituted pyrroles via cascade reactions of aryloxy-enynes with amines *RSC Adv.* **2013**, *3*, 22872–22876.

8) Mai, A.; Massa, S.; Cerbara, I.; Valente, S.; Ragno, R.; Bottoni, P.; Scatena, R.; Loidl, P.; Brosch, G.3-(4-Aroyl-1-methyl-1*H*-2-pyrrolyl)-*N*-hydroxy-2-propenamides as a New Class of Synthetic Histone Deacetylase Inhibitors. 2. Effect of Pyrrole-C_2 and/or -C_4 Substitutions on Biological Activity. *J. Med. Chem.* **2004**, *47*, 1098-1109.

9) Khan, T.; Kumar, V.; Das, O. An Improved Synthesis of Natural Product Inspired Chromenopyrrolizines and Chromenoindolizines Scaffolds: Rapid Access to the Diverse Pyrrolizine Analogs of Aza-Medicarpin and Tetracyclic Isolamellarin Core through a General Base and Metal Free Strategy. *Bull. Chem. Soc. Jpn.* **2016**, *89*, 1331-1340.

10) (a) Singh, G. S; Sudheesh, S.; Keroletsweb, N. Recent applications of aziridine ring expansion reactions in heterocyclic synthesis. *Arkivoc,* **2018**, part i, 50-113; b) Feng, J.-J.; Zhang, J. Synthesis of Unsaturated N-Heterocycles by Cycloadditions of Aziridines and Alkynes. *ACS Catal.* **2016**, *6*, 6651−6661.

11) Padwa, A.; Hamilton, L. Reactions of aziridines with dimethylacetylene dicarboxylate. *Tetrahedron Lett.* **1965**, *6*, 4363−4367.

12) (a) Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H. 1,3-Cycloadditionen von azomethin-yliden aus aziridin-carbonestern. *Tetrahedron Lett.* **1966**, *7*, 397−404. (b) Huisgen, R.; Scheer, W.; Huber, H.Stereospecific Conversion of *cis-trans* Isomeric Aziridines to Open-Chain Azomethine Ylides. *J. Am. Chem. Soc.* **1967**, *89*, 1753-1755.

13) Katritzky, A. R.; Yao, J.; Bao, W.; Qi, M.; Steel, P. J. 2-Benzotriazolylaziridines and Their Reactions with Diethyl Acetylenedicarboxylate. *J. Org. Chem.* **1999**, *64*, 346−350.

14) Padwa, A.; Chen, Y.-Y., Dent, W.; Nimmesgern, H. Synthetic application of cyanoaminosilanes as azomethine ylide equivalents. *J. Org. Chem.* **1985**, *50*, 4006-4014.

15) (a) Wender, P. A.; Strand, D. Cyclocarboamination of Alkynes with Aziridines: Synthesis of 2,3-Dihydropyrroles by a Catalyzed Formal [3 + 2] Cycloaddition. *J. Am. Chem. Soc.* **2009**, *131*, 7528−7529. (b) Fan, J.; Gao, L.; Wang, Z. Facile construction of highly functionalized 2-pyrrolines *via* $FeCl_3$-catalyzed reaction of aziridines with arylalkynes. *Chem. Commun.* **2009**, 5021-23.

16) Li, L.; Zhang, J. Lewis Acid-catalyzed [3 + 2] Cyclo-addition of Alkynes with *N*-Tosyl-aziridines via Carbon–Carbon Bond Cleavage: Synthesis of Highly Substituted 3-Pyrrolines. *Org. Lett*., **2011**, *13*, 5940-43.

17) Wang, S.; Zhu, X.; Chai, Z.; Wang, S. Synthesis of polysubstituted pyrroles *via* [3 + 2]-annulation of aziridines and β-nitroalkenes under aerobic conditions. *Org. Biomol. Chem.* **2014**, *12*, 1351-1356.

18) (a) Lopchuk, J. M.; Hughes, R. P., Gribble, G. W. What Controls Regiochemistry in 1,3-Dipolar Cycloadditions of Münchnones with Nitrostyrenes? *Org. Lett.*, **2013**, *15*, 5218-5221. (b) Avalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. Münchnone−Alkene Cycloadditions: Deviations from the FMO Theory. Theoretical Studies in the Search of the Transition State. *J. Org. Chem.* **1996,** *61,* 7291-7297. (c) Coppola, B. P.; Noe, M. C.; Schhwartz, D. J.; Abdont, R. L. II; Trost, B. M. Intermolecular 1,3-dipolar cycloadditions of müchnones with acetylenic dipolarophiles: Sorting out the regioselectivity. *Tetrahedron*, **1994**, *50*, 93-116.

19) CCDC 1902854 and 1912026 contain the crystallographic information for the crystal **3cb** and **16** respectively. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre by emailing at deposit@ccdc.cam.ac.uk or by contacting The

Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

20) Hlekhlai, S.; Samakkanad, N.; Sawangphon, T.; Pohmakotr, M.; Reutrakul, V.; Soorukram, D.; Jaipetch, T.; Kuhakarn, C. Oxone®/KI-Mediated Nitration of Alkenes and Alkynes: Synthesis of Nitro- and β-Iodonitro-Substituted Alkenes. *Eur. J. Org. Chem.* **2014**, 7433-7442.

21) (a) Ratovelomanana, V.; Rollin, Y.; Gebehenne, C.; Gosmini, C.; Perichon, J. DBU/DMSO promoted dehydrobromination of 1,1-dibromoolefins. A general synthesis of 1-bromoaromatic alkynes under mild conditions. *Tetrahedron Lett.* **1994**, *35*, 4777-4780. (b) Okutani, M.; Mori, Y. Conversion of Bromoalkenes into Alkynes by Wet Tetra-*n*-butylammonium Fluoride. *J. Org. Chem.* **2009**, *74*, 442-444.

22) Sustmann, R. Orbital energy control of cycloaddition reactivity. *Pure Appl. Chem.* **1974**, *40*, 569–593.

23) Kang, H.; Fenical, W. Ningalins A−D: Novel Aromatic Alkaloids from a Western Australian Ascidian of the Genus Didemnum. *J. Org. Chem.* **1997**, *62*, 3254-3262.

24) Vilsmeier, A.; Haack, A. Action of phosphorus halides on alkylformanilides. A new method for the preparation of secondary and tertiary p-alkylaminonobenzaldehydes. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 119-122.

25) Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. Total Synthesis of Lamellarins D, H, and R and Ningalin B. *Org. Lett*., **2011**, *13*, 312-315.

26) (a) Heim, A.; Terpin, A.; Steglich, W. Biomimetic Synthesis of Lamellarin G. Trimethyl Ether. *Angew. Chem., Int. Ed.* **1997**, *36*, 155–156. (b) Peschko, C.; Winklhofer, C.; Steglich, W. Biomimetic Total Synthesis of Lamellarin L by Coupling of Two Different Arylpyruvic Acid Units. *Chem. Eur. J.* **2000**, *6*, 1147–1152.

27) Hasse, K.; Willis, A. C.; Barnwell, M. G. A Total Synthesis of the Marine Alkaloid Ningalin B from (*S*)-Proline. *Aust. J. Chem.* **2009**, *62*, 683–691.

28) A manuscript describing the total synthesis of some natural and unnatural lamellarins is under the consideration of the Editor for publication in *The Journal of Organic Chemistry*.

29) Armarego, D. L. F.; Perrin, D. D. *Purification of Laboratory chemicals*, IV Ed., **1996**, pp. 110-349.

30) a) Luisi, R.; Capriati, V.; Di Cunto, P.; Florio, S.; Mansueto, R. Regio- and Stereoselective Lithiation of Terminal Oxazolinylaziridines: The Aziridine *N*-Substituent and the Oxazolinyl Group Effect. *Org. Lett.* **2007**, *9*, 3295-3298; b) Sharma, S. D.; Kanwar, S.; Rajpoot, S. Aziridines as templates: A general strategy for the stereospecific synthesis of 2-azetidinones. *J. Heterocycl. Chem.,* **2006**, *43*, 11-19.

31) Baret, P.; Buffet, H.; Pierre, J. L. New synthesis of the aziridine ring. Application of the Simmons-Smith reaction to an iminoester. *Bull. Soc. Chim. Fr.*, **1972**, *2*, 825.

32) Barros, M. T.; Maycock, C. D.; Ventura, M. R. A synthesis of aziridines from α-iodoenones. *Tetrahedron Lett.* **2002**, *43*, 4329–31.

33) Mahoney, J. M.; Smith, C. R.; Johnston, J. N. Brønsted Acid-Promoted Olefin Aziridination and Formal *anti*-Aminohydroxylation. *J. Am. Chem. Soc.* **2005**, *127*, 1354-1355.

34) Bickley, J. F.; Gilchrist, T. L.; Mendonça, R. Hydroxylation of 1-azabicyclo[4.1.0]hept-3-enes formed by Diels– Alder reactions of benzyl 2H-azirine-3-carboxylate. *Arkivoc*, **2002**, (vi), 192-204.

35) Keller, P.; Thomsen III, D. L.; Li, M.-H. Facile and Inexpensive Synthesis of α,β,β'-Deuterated Liquid Crystalline and Classical Acrylate Monomers. *Macromolecules*, **2002**, *35*, 581-584.

36) Marsura, A.; Duc, C. L. A New Method for the Synthesis of 2,6-Disubstituted 4(3*H*)-Pyrimidinones from Benzamidine. *Synthesis*, **1982**, *7*, 595.

37) Korhonen, I. O. O.; Pitkanen, M.; Korvola, J. N. J. Addition of chlorine, bromine and bromine chloride to some α,β-unsaturated methyl esters. *Tetrahedron* **1982**, *38*, 2837-2841.

38) Kim, J. H. Lee, S. B.; Lee, W. K.; Yoon, D.-H.; Ha, H.-J. Synthesis of 1,2,5- and 1,2,3,5-substituted pyrroles from substituted aziridines via Ag(I)-catalyzed intramolecular cyclization. *Tetrahedron*, **2011**, *67*, 3553-3558.

39) a) Ganesh, M.; Namboothiri, I. N. N. Stereospecific approach to α, β-disubstituted nitroalkenes via coupling of α-bromonitroalkenes with boronic acids and terminal acetylenes. *Tetrahedron* **2007**, *63*, 11973-11983; b) Yu, S.; Zhao, S.; Chen, H.; Xu, X.; Yaun, W.; Zhang, M. X. Construction of Novel Kojic Acid Fused Furans by Domino Reactions of a Kojic Acid Derivative with (*Z*)-Bromonitroalkenes. *ChemistrySelect,* **2018**, *3,* 4827-4830.

40) Qian, W.; Lu, W.; Sun, H.; Li, Z.; Zhu, L.; Zhao, R.; Zhang, L.; Zhou, S.; Zhou, Y.; Jiang, H.; Zhen, X.; Liu, H. Design, synthesis, and pharmacological evaluation of novel tetrahydroprotoberberine derivatives: selective inhibitors of dopamine D_1 receptor. *Bioorg. Med. Chem.* **2012**, *20*, 4862–4871.

41) Dong, X.-W.; Liu, T.; Hu, Y.-Z.; Liu, X.-Y.; Che, C.-M. Urea post modified in a metal–organic framework as a catalytically active hydrogen-bond-donating heterogeneous catalyst. *Chem. Commun*. **2013**, *49*, 7681-7683.

42) Andrey, O.; Alexakis, A.; Bernardinelli, G. Asymmetric Michael Addition of α-Hydroxyketones to Nitroolefins Catalyzed by Chiral Diamine. *Org. Lett.* **2003**, *5*, 2559-2561.

43) Sorokina, M. V.; Pankova, A. S.; Kuznetso, M. A. Oxidative Aminoaziridination of 2-Vinylfuran Derivatives as an Approach to Hexa-2,5-diene-1,4-dione Monohydrazones. *Asian J. Org. Chem.* **2016**, *5*, 389–398.

44) Handy, S. T.; Bregman, H.; Lewis, J.; Zhang, X.; Zhang, Y. An unusual dehalogenation in the Suzuki coupling of 4-bromopyrrole-2-carboxylates. *Tetrahedron Lett.* **2003**, *44*, 427–430.