Note

Total Synthesis of Lamellarin D Trimethyl Ether, Lamellarin D and Lamellarin H

Dhanaji M Lade, Amit B. Pawar, Prathama S. Mainkar, and Srivari Chandrasekhar

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 19 Apr 2017

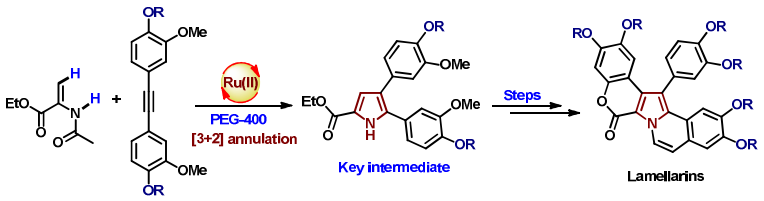
Total Synthesis of Lamellarin D Trimethyl Ether, Lamellarin D and Lamellarin H

Dhanaji M. Lade[†,‡], Amit B. Pawar[†], Prathama S. Mainkar[†] and Srivari Chandrasekhar*[†,‡]

[†]Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India

[‡]Academy of Scientific and Innovative Research (AcSIR), New Delhi, India

Email: srivaric@iict.res.in

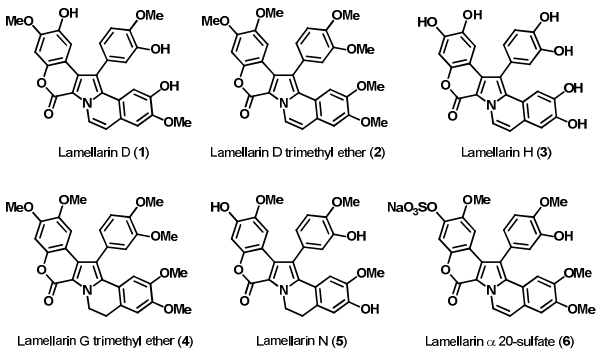


ABSTRACT: Total syntheses of three different lamellarins have been accomplished using Ru(II)-catalyzed (3+2) annulation strategy to construct central pyrrole ring. The striking features of this synthesis are use of PEG-400 as a green solvent for (3+2) annulation reaction and multiple catalytic reactions with excellent over all yield. The present route also enables the synthesis of various lamellarin analogues devoid of B ring.

The central pyrrole ring containing natural products are abundant in nature.[1] Lamellarins represent a large part of this class having marine origin. Faulkner *et al.* were the first to isolate lamellarins in 1985 from prosobranch mollusc *Lamellaria* sp.[2] Many lamellarins show profound biological effects including cytotoxicity against various cancers, inhibition of HIV-I integrase etc.[3] So far, more than 50 lamellarins have been isolated and well characterized. The most bioactive lamellarins include D, G, H, L and N (Figure 1). Of these, lamellarin D was shown to be a promising topoisomerase I inhibitor and was also found to be responsible for triggering mitochondrial permeability transition.[4] Owing to their interesting structural features and biological activities, many synthetic chemistry groups embarked on developing efficient syntheses of lamellarins. The reviews by Opatz, Alvarez and Handy; on all the

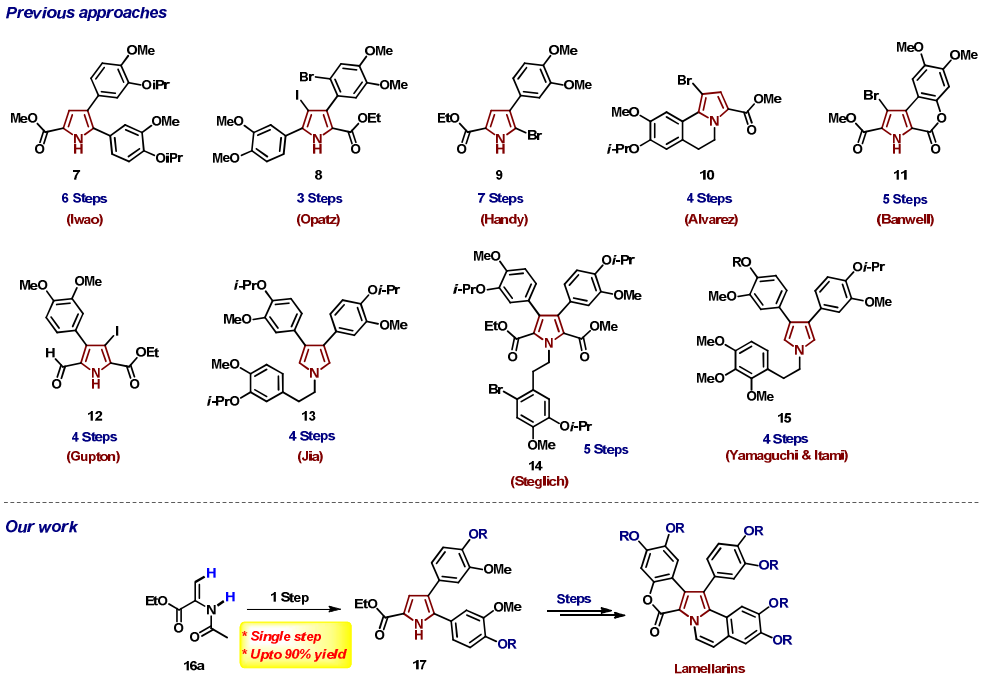
synthetic approaches reported till 2014 highlight the major developments in total synthesis of lamellarins.[5]

Figure 1. Biologically Active Lamellarins



A few more total syntheses were reported in the last couple of years engaging efficient and modular strategies.[6] The interesting biological properties exhibited by lamellarins, especially against HIV and Malaria, prompted us to explore a scalable and flexible synthesis of lamellarin D trimethyl ether, lamellarin H and lamellarin D which also could be extended to other lamellarin class of natural products and analogues with minimal synthetic operations.

Scheme 1. Synthesis of Functionalized Pyrroles for Lamellarin Synthesis



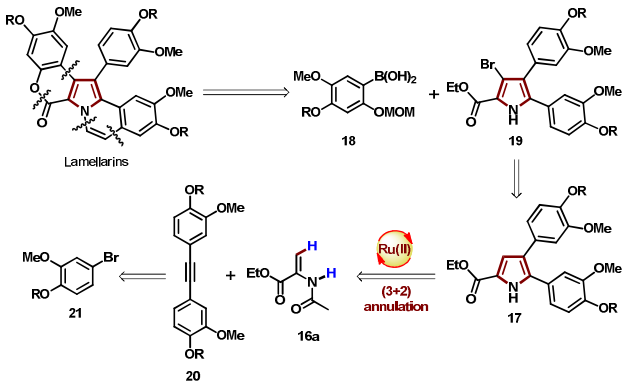
A major challenge in the synthesis of lamellarins is to synthesize the central functionalized pyrrole ring. This can be achieved *via* two different methods; first is the functionalization of simple pyrrole moiety and other is to synthesize functionalized pyrrole in one step from appropriate acyclic precursors (Scheme 1). For instance, Iwao *et. al* has synthesized functionalized pyrrole **7** starting from pyrrole in 6 steps in their synthesis of lamellarin L and N.[6a] On the other hand, Opatz and co-workers prepared iodo-pyrrole derivative **8** in 3 steps for the synthesis of lamellarin D trimethyl ether and lamellarin H starting from veratraldehyde.[6b] Handy *et al.* started their synthesis of lamellarin G trimethyl ether from pyrrole wherein the functionalized pyrrole **9** was synthesized in 6 steps.[7] Alvarez group has synthesized bromo-pyrrole derivative **10** for the synthesis of lamellarin D starting from methyl pyrrole-2-carboxylate in 4 steps.[8] Banwell and co-workers reported the synthesis of lamellarin G trimethyl ether from *N*-Boc pyrrole wherein; they have synthesized bromo-pyrrole precursor **11** in 5 steps.[9] Gupton *et al.* described formal total synthesis of lamellarin G trimethyl ether starting from substituted phenylacetic acid derivative to prepare intermediate **12** in 4 steps.[10] Jia *et al.* has synthesized tri-arylated pyrrole derivative **13** in 4 steps starting from vanillin in their synthesis of lamellarin D and H.[11] Steglich group has reported synthesis of fully functionalized pyrrole **14** in 5 steps for the synthesis of lamellarin L using *O*-isopropylisovanillin as a starting material.[12] More recently, Yamaguchi and Itami *et al.* reported synthesis lamellarin L and C starting from 2,3,4-trimethoxybenzaldehyde in which a key pyrrole intermediate **15** was synthesized in 4 steps.[6c] The major limitation of these approaches is the multistep synthesis of functionalized pyrrole required for the synthesis of lamellarins. We desired to develop a more flexible strategy which can provide advanced intermediate in a more concise manner with high yield to access diverse lamellarins along with their analogues.

In recent times, transition metal catalyzed C–H functionalization has emerged as a successful tool in the area of total synthesis of natural products.[13,14] To the best of our knowledge, C–H functionalization strategy has never been utilized in the synthesis of lamellarins. In 2011, Ackermann and Wang group independently reported an elegant Ru(II)-catalyzed (3+2) annulation of enamides and alkynes for the synthesis of pyrroles.[15,16] However, utilization of this reaction for the total

synthesis of natural products is still unrevealed. Herein, we report the total synthesis of lamerllarin D trimethyl ether, D and H using Ru-catalyzed C–H functionalization strategy.

According to the retrosynthetic analysis (Scheme 2) lamellarins can be obtained from the coupling of bromopyrrole derivative **19** with appropriate boronic acid **18** followed by lactonization and Pomeranz-Fritsch type cyclization. The bromopyrrole **19** can be synthesized from key intermediate **17** which in turn could be constructed *via* Ru-catalyzed (3+2) oxidative annulation of enamide **16a** and diarylalkyne **20**. The diarylalkyne **20** can be easily synthesized from aryl bromide **21** and commercially available propiolic acid using Pd-catalyzed decarboxylative cross-coupling.[17]

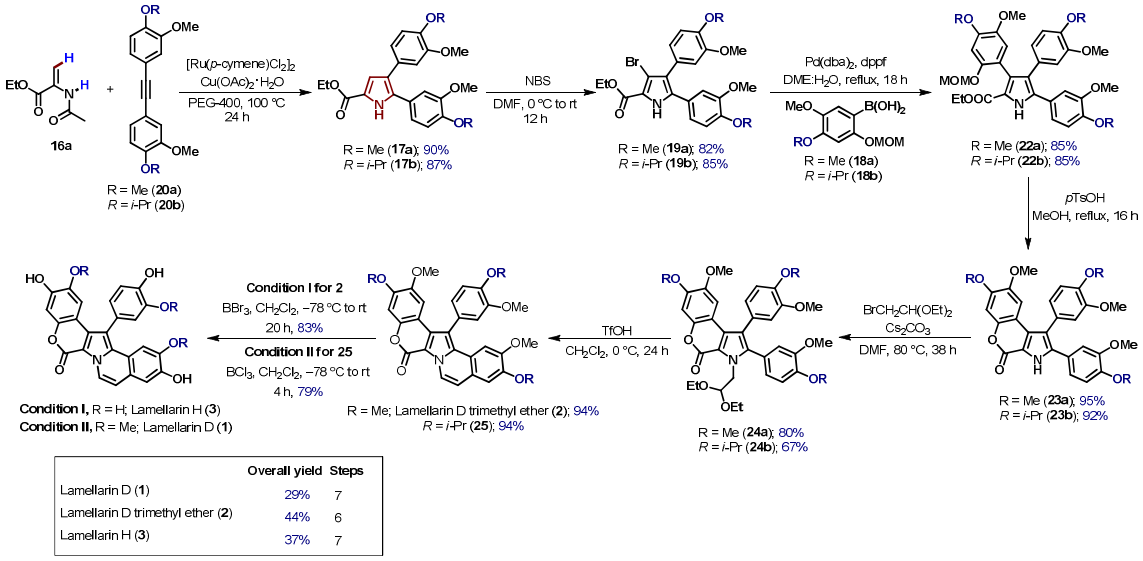
Scheme 2. Retrosynthetic Analysis



Our synthetic sequence (Scheme 3) commenced with the annulation reaction between enamide **16a** and diarylalkyne **20a** in presence of 5 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ as catalyst and $Cu(OAc)_2.H_2O$ as oxidant in PEG-400 to furnish 2,3-diaryl pyrrole-5-carboxylate **17a** in 90% yield. Recently, PEG has been used as a solvent for various Ru(II)-catalyzed C–H activation.[18] Bromination of **17a** with NBS in DMF yielded bromo-pyrrole **19a** in 82% yield. The Suzuki reaction between boronic acid **18a** and bromide **19a** with $Pd(dba)_2$ in presence of 1,1'-*bis*(diphenylphosphino) ferrocene (dppf) furnished the tetrasubstituted pyrrole **22a** in 85% yield. The one pot two step lactonization by MOM deprotection catalyzed by TsOH in MeOH furnished lactone **23a** in 95% yield. The *N*-alkylation of **23a** with bromoacetaldehyde diethyl acetal furnished **24a**; which upon Iwao's intramolecular[6a] TfOH-mediated cyclization strategy generated lamellarin D trimethyl ether (**2**) in 94% yield. The global deprotection

of methyl ethers with BBr_3 yielded lamellarin H (**3**) in 83% yield. The overall yields for lamellarin D trimethyl ether (**2**) and lamellarin H (**3**) were 44% and 37% respectively.

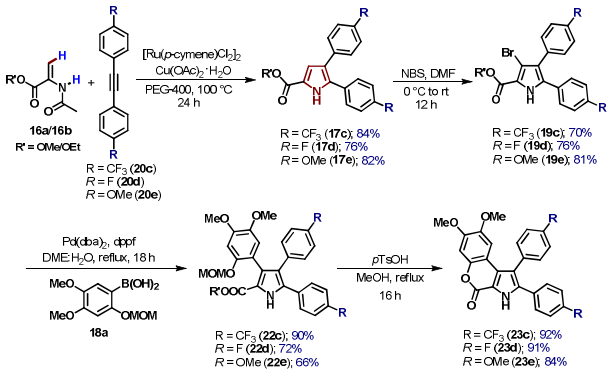
Scheme 3. Modular Total Synthesis of Lamellarin D Trimethyl Ether, Lamellarin D and Lamellarin H



	Overall yield	Steps
Lamellarin D (**1**)	29%	7
Lamellarin D trimethyl ether (**2**)	44%	6
Lamellarin H (**3**)	37%	7

After successfully synthesizing lamellarin D trimethyl ether and lamellarin H, we turned our attention towards synthesis of lamellarin D (**1**). The synthesis of lamellarin D began with Ru(II)-catalyzed (3+2) annulation of enamide **16a** with diarylalkynes **20b** to furnish pyrrole **17b**. Later on, similar synthetic sequence (bromination, Suzuki reaction, *N*-alkylation and cyclization) was followed, as described for lamellarin H synthesis, to furnish intermediate **25**. The intermediate **25** on treatment with BCl_3 furnished lamellarin D in 79% yield with 29% overall yield.

Scheme 4. Synthesis of Lamellarin Analogues



Finally, this modular synthetic strategy was applied for the synthesis of various lamellarin analogues. For this purpose, different diarylalkynes have been used in the Ru-catalyzed annulation reaction of enamide to furnished differently substituted pyrroles. Later on, similar synthetic operations were carried to furnish lactones (**23c**–**23e**) as described in Scheme 4. These lactones structurally resembles lamellarins devoid of B ring.

In conclusion, we have developed modular synthetic approach for the synthesis of various lamellarins and their analogues in an efficient and concise manner. The key steps involve Ru-catalyzed (3+2) annulation in PEG, Suzuki reaction and TfOH catalyzed cyclization. This work is amenable for synthesis of other natural products which have substituted pyrrole as the core.

EXPERIMENTAL SECTION

General Remarks

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} plates. Visualization on TLC was achieved by the use of UV light (254 nm). Column chromatography was undertaken on silica gel (100–200 mesh) using a proper eluent system. NMR spectra were recorded in chloroform-*d* and DMSO-d_6 at 300 or 400 or 500 MHz for ^{1}H NMR spectra and 75 MHz or 100 or 125 MHz for ^{13}C NMR spectra. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, dd = doublet of doublet, td = triplet of doublet, m = multiplet. Coupling constants, *J*, were reported in Hertz unit (Hz). For ^{13}C NMR chemical shifts were reported in ppm referenced to the center of a triplet at 77.0 ppm of chloroform-*d* and 40.0 ppm center for DMSO-d_6. HRMS spectra were recorded using ESI-TOF techniques. $[RuCl_2(p\text{-cymene})]_2$was purchased from sigma aldrich.

1,2-bis(3,4-Dimethoxyphenyl)ethyne **(20a).**[19] The diarylalkyne was prepared by using Lee *et al.* protocol[16] by modifying reaction condition: In a round bottam flask under nitrogen atmosphere were

placed propiolic acid (700 mg, 1.0 mol, 1 equiv), bromoveratrol **21a** (434 mg, 2.0 mol, 2 equiv), $PdCl_2(PPh_3)_2$ (171 mg, 5 mol%, 0.05 equiv), dppb (426 mg, 10 mol %, 0.1 equiv), DBU (3.05 gm, 2.0 mol, 2 equiv) and DMSO (30 mL).The resulting reaction mixture was heated at 110 ^{0}C for 24 h, after completion of the reaction it was diluted with saturated NH_4Cl solution (250 mL) and extracted with ethyl acetate (50 mL × 3), washed with brine, dried on Na_2SO_4. The solvent was removed under vacuo, crude mixture was purified by column chromatography on silica gel to furnish **20a** as white solid (2.4 gm, 80%). mp 155–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 8.3, 1.9 Hz, 2H), 7.04 (d, *J* = 1.8 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 3.90 (s, 6H), 3.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 148.6, 124.6, 115.6, 114.1, 111.0, 87.9, 55.8.

Ethyl 4,5-bis(3,4-dimethoxyphenyl)-1H-pyrrole-2-carboxylate **(17a).** In a sealed tube a mixture of ethyl 2-acedamidoacrylate **16a** (471 mg, 3.00 mmol), 1,2-bis(3,4-dimethoxyphenyl)ethyne **20a** (982 mg, 3.30 mmol), $[RuCl_2(p\text{-cymene})]_2$ (91.0 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (598 mg, 3.00 mmol) in PEG-400 (5 mL) was stirred at 100 °C for 24 h. After completion ot the reaction (TLC), the reaction mixture was cooled to room temperature, then reaction mixture was diluted with sat. aq.NH_3 (30%, 50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc : 2:1) to yield **17a** as white solid (940 mg, 90%). mp 127–129 °C; IR (neat) *v* (cm^{-1}) = 3306, 2939, 2836, 1678, 1566, 1521, 1470, 1314, 1243, 1213, 1134, 1026, 811, 759; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.98 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.92–6.78 (m, 5H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 148.9, 148.8,148.6, 147.6, 132.8, 128.2, 124.6, 123.3, 121.8, 120.7, 120.2, 116.3, 111.9, 111.3, 111.23,111.20, 60.4, 55.9, 55.8, 55.7, 14.5; HRMS (ESI) m/z calcd. for $C_{23}H_{25}NNaO_6[M+Na]^+$: 434.1580, found: 434.1559.

Ethyl 3-bromo-4,5-bis(3,4-dimethoxyphenyl)-1H-pyrrole-2-carboxylate **(19a).** Under nitrogen atmosphere, NBS (178 mg, 1 mmol) was added portionwise to a solution of **17a** (411 mg, 1 mmol) in DMF (20 mL) at 0 °C. After stirring reaction mixture at 0 °C for 1 h, then it was warmed to room

temperature and stir for another 12 h. Then it was diluted with water and extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel (hexane/ethyl acetate = 2:1) to give **19a** as a colourless solid (405 mg, 82%); mp 174–176 °C; IR (neat) ν (cm^{-1}) = 3289, 2937, 2837, 1669, 1521, 1472, 1246, 1141, 1029, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 6.90–6.86 (m, 2H), 6.86–6.82 (m, 2H), 6.80 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.78 (s, 3H), 3.61 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 149.0, 148.7, 148.6, 148.2, 133.1, 126.1, 124.3, 123.6, 123.2, 119.6, 119.3, 114.0, 111.1, 111.0, 110.8, 106.0, 60.9, 55.84, 55.81, 55.6, 14.4; HRMS (ESI) m/z calcd. for $C_{23}H_{24}BrNNaO_6$ $[M+Na]^+$: 512.0679, found: 512.0705.

Ethyl 3-(4,5-dimethoxy-2-(methoxymethoxy)phenyl)-4,5-bis(3,4-dimethoxyphenyl)-1H-pyrrole-2-carboxylate **(22a).** Under nitrogen atmosphere, a mixture of **19a** (98 mg, 0.2 mmol), **18a** (72 mg, 0.3 mmol), $Pd(dba)_2$ (11.5 mg, 10 mol %), dppf (11.1 mg, 10 mol %), Na_2CO_3 (140 mg, 1.26 mmol), DME (5.0 mL), and degassed water (1.0 mL) was refluxed for 18 h. After cooling to room temperature, the solvent was evaporated, and the crude residue was extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel (n-hexane/ethyl aceate=1:1) to give **22a** as a pale-yellow solid (88 mg, 85%). mp 80–82 °C; IR (neat) ν (cm^{-1}) = 3310, 2944, 2839, 1676, 1517, 1446, 1248, 1024, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 6.97 (dd, J = 8.3, 1.8 Hz, 1H), 6.85–6.81 (m, 2H), 6.78 (s, 1H), 6.68–6.64 (m, 2H), 6.61–6.58 (m, 2H), 4.79 (d, J = 6.8 Hz, 1H), 4.56 (d, J = 6.8 Hz, 1H), 4.25–4.12 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.71 (s, 3H), 3.64 (s, 3H), 3.52 (s, 3H), 3.27 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 149.9, 148.8, 148.7, 148.2, 147.3, 143.5, 132.2, 127.6, 127.4, 124.5, 123.6, 122.5, 119.9, 119.2, 116.8, 115.3, 113.5, 111.2, 111.1, 110.7, 101.6, 96.5, 60.0, 56.2, 55.9, 55.8, 55.7, 55.6, 55.55, 55.52, 14.2; HRMS (ESI) m/z calcd. for $C_{33}H_{38}NO_{10}[M+H]^+$: 608.2490, found: 608.2486.

1,2-bis(3,4-Dimethoxyphenyl)-7,8-dimethoxychromeno[3,4-b]pyrrol-4(3H)-one **(23a).** Under nitrogen atmosphere, a solution of **22a** (270 mg, 0.21 mmol) and *p*-TsOH·H_2O (8 mg, 10 mol %) in MeOH (10

mL) was refluxed for 16 h. After cooling to room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel (n-hexane/ethyl acetate = 1:1) to give **23a** as a pale-yellow solid (219 mg, 95%). mp 170–172 °C; IR (neat) ν (cm^{-1}) = 3281, 2927, 2846, 1694, 1523, 1464, 1258, 1144, 1023, 859, 806; ^1H NMR (400 MHz, DMSO-d_6) δ 12.75 (s, 1H), 7.21 (d, J = 1.9 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.07–7.00 (m, 3H), 6.95–6.86 (m, 2H), 6.57 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.63 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.9, 149.8, 149.2, 149.1, 149.0, 148.7, 146.2, 145.6, 139.3, 128.2, 127.6, 123.8, 123.6, 120.9, 117.2, 115.0, 114.9, 112.9, 111.9, 110.2, 104.9, 101.5, 56.3, 56.2, 55.9, 55.6, 55.4; HRMS (ESI) m/z calcd. for $C_{29}H_{28}NO_8$ $[M+H]^+$: 518.1809, found: 518.1797.

3-(2,2-Diethoxyethyl)-1,2-bis(3,4-dimethoxyphenyl)-7,8-dimethoxychromeno[3,4b]pyrrol 4(3H)-one **(24a).** Under nitrogen atmosphere, a solution of **23a** (102 mg, 0.197 mmol), 2-bromo- 1,1-diethoxyethane (178 μL, 1.18 mmol), and Cs_2CO_3 (385.69 mg, 1.18 mmol) in DMF (20 mL) was stirred for 38 h at 110 °C. After cooling to room temperature, the mixture was diluted with water, extracted with ethyl acetate. The combined organic layer dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography over silica gel (n-hexane/ethyl acetate = 2:1) to give **24a** as a yellowish gummy solid (100 mg, 80%). IR (neat) ν (cm^{-1}) = 2936, 2844, 1706, 1527, 1457, 1260, 1143, 1037, 821, 759; ^1H NMR (300 MHz, $CDCl_3$) δ 6.99–6.88 (m, 4H), 6.87 – 6.76 (m, 4H), 5.02 (t, J = 5.6 Hz, 1H), 4.50 (brs, 2H), 3.91 (s, 3H), 3.88 (s, 6H), 3.73 (s, 3H), 3.72 (s, 3H), 3.71–3.64 (m, 2H), 3.51 (s, 3H), 3.49–3.36 (m, 2H), 1.14 (t, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 149.1, 149.0, 148.7, 148.4, 148.2, 146.3, 145.5, 144.3, 127.7, 127.0, 124.1, 123.6, 122.3, 118.4, 114.6, 114.3, 111.0, 110.7, 110.2, 104.9, 102.6, 100.5, 64.1, 56.1, 55.9, 55.82, 55.76, 55.7, 48.8, 15.3. HRMS (ESI) m/z calcd. for $C_{35}H_{39}NNaO_{10}$ $[M+Na]^+$: 656.2466, found: 656.2471.

Lamellarin D trimethyl ether **(2)**[6d] Under nitrogen atmosphere, 1 drop of TfOH was added to a solution of **24a** (40 mg, 63.1 μmol) in DCM (4.0 mL) at 0 °C. After 24 h of stirring at 0 °C, Na_2CO_3 (5.0 mg) and Na_2SO_4 (5.0 mg) were added to the mixture. The suspension was allowed to warm to

room temperature and then passed through a pad of celite. The filtrate was evaporated, and the residue was purified by column chromatography over silica gel (n-hexane/ethyl acetate = 1:3) to give lamellarin D trimethyl ether **(2)** as a colourless solid (32 mg, 94%). mp 277 – 278 °C; IR (neat) *v* (cm^{-1}) = 3011, 2939, 2837, 1698, 1616, 1459, 1419, 1265, 1162, 1038, 940, 855, 753; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (d, *J* = 7.3 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.18 (s, 1H), 7.17 (d, *J* = 2.6 Hz, 1H),7.16 (d, *J* = 6 Hz, 1H), 7.08 (s, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.89 (s, 1H), 6.74 (s, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.49 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 150.1, 149.9, 149.5, 149.2, 149.1, 146.7, 145.5, 134.3, 129.3, 128.2, 124.8, 124.1, 123.3, 119.1, 114.5, 112.3, 112.0, 110.9, 109.8, 107.8, 107.4, 105.3, 105.0, 100.5, 56.3, 56.2, 56.0, 55.9, 55.5, 55.2; HRMS (ESI) m/z calcd. for $C_{31}H_{28}NO_8$ $[M+H]^+$: 542.1809, found: 542.1815. The spectral data are in accordance with the literature values (See the Supporting Information for detail comparison of ^{1}H and ^{13}C NMR).

Lamellarin H **(3).**[6d] To a stirred solution of **2** (15 mg, 0.027 mmol, 1.00 equiv) in dry DCM (5 mL) under nitrogen, BBr_3 (1.7 mL, 0.277 mmol, 1 M in DCM, 10 equiv) was added dropwise at −78 °C and was stirred at same temperature for another 15 min followed by removal of the cooling bath. The dark-red solution was stirred for an additional 20 h at room temperature and then quenched by addition of MeOH (4 mL). The solvent was removed and the residue suspended in water (30 mL) followed by extraction with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was concentrated in vacuo. The residue was purified by column chromatogarphy on silica gel to furnish lamellarin H **(3)** as a brownish amorphous solid (10 mg, 83%). mp > 300 °C; IR (neat) *v* (cm^{-1}) = 3394, 2256, 2129, 1658, 1048, 1023, 994, 824, 761; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (br s, 1H), 9.75 (br s, 1H), 9.40 (br s, 1H), 9.19 (br s, 2H), 8.99 (d, *J* = 7.3 Hz, 1H), 8.90 (br s, 1H),7.14 (d, *J* = 8.4 Hz, 1H), 7.14 (s, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.95 (s, 1H), 6.80 (s, 1H), 6.79 (d, *J* = 1.8 Hz, 1H), 6.71 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.56 (s, 1H).^{13}C NMR (125 MHz, DMSO-d_6) δ 155.0, 148.1, 147.3, 147.0, 146.7, 146.0, 145.7, 142.6, 134.4, 129.3, 125.9, 124.2, 121.9, 121.6, 118.6, 118.0, 117.5, 113.0, 111.9, 111.7, 110.1, 110.0, 109.2, 106.8, 103.8; HRMS (ESI) m/z calcd. for $C_{25}H_{15}NNaO_8$ $[M+Na]^+$: 480.0690, found: 480.0684. The spectral

data are in accordance with the literature values (See the Supporting Information for detail comparison of ^{1}H and ^{13}C NMR).

1,2-Bis(4-isopropoxy-3-methoxyphenyl)ethyne **(20b).** According to the described procedure for **20a**, the same procedure followed for **20b**; In a round bottam flask under nitrogen atmosphere placed propiolic acid (700 mg, 1.0 mol, 1 equiv), 4-bromo-1-isopropoxy-2-methoxybenzene **(21b)** (462 mg, 2.0 mol, 2 equiv), $PdCl_2(PPh_3)_2$ (171mg, 5 mol%, 0.05 equiv), dppb (426 mg, 10 mol %, 0.1 equiv), DBU (3.044 gm, 2.0 mol, 2 equiv) and DMSO (30 mL).The resulting reaction mixture was heated at 110^0 C for 24 h, after completion of the reaction it was diluted with saturated NH_4Cl solution (250 mL) and extracted with ethyl acetate (50 ml × 3), washed with brine, dried on Na_2SO_4. The solvent was removed under vacuo, crude reaction mixture was purified by using column chromatography on silica gel to furnish **20b** as a white solid (1.7 gm, 50%); mp 163– 165 °C; IR (neat) ν (cm^{-1}) = 2981, 2928, 2356, 1669, 1523, 1460, 1335, 1233, 1140, 1105, 1037, 952, 855, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, J = 8.3, 1.8 Hz, 2H), 7.03 (d, J = 1.7 Hz, 2H), 6.85 (s, 1H), 6.83 (s, 1H), 4.62–4.51 (m, 2H), 3.87 (s, 6H), 1.38 (d, J = 6.1 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.6, 124.5, 115.8, 115.0, 114.9, 88.0, 71.3, 55.9, 22.0; HRMS (ESI) m/z calcd. for $C_{22}H_{27}O_4$ $[M+H]^+$: 355.1909, found: 355.1909.

Ethyl 4,5-bis(4-isopropoxy-3-methoxyphenyl)-1H-pyrrole-2-carboxylate **(17b).** According to the procedure described for the preparation of **17a**, the same procedure followed for **17b** using ethyl 2-acetamidoacrylate **16a** (400 mg, 2.54 mmol), 1,2-bis(4-isopropoxy-3-methoxyphenyl)ethyne **20b** (951 mg, 2.79 mmol), $[RuCl_2(p\text{-cymene})]_2$ (78 mg, 5.0 mol %) and $Cu(OAc)_2 \bullet H_2O$ (508 mg, 2.54 mmol) in PEG-400 (5 mL) to furnish **17b** as a gummy solid (960 mg, 87%); IR (neat) ν (cm^{-1}) = 3302, 2977, 2933, 1680, 1516, 1472, 1239, 1114, 1031, 951, 855, 816, 766; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.03 (d, J = 2.6 Hz, 1H), 6.96 (dd, J = 8.2, 2.0 Hz, 1H), 6.89–6.82 (m, 5H), 4.58–4.45 (m, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.69 (s, 3H), 3.65 (s, 3H), 1.40 – 1.34 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 150.1, 147.2, 145.8, 133.0, 128.8, 124.9, 123.4, 121.7, 120.7, 120.1, 116.4, 116.0, 115.5, 112.6, 112.0, 71.5, 71.39, 60.4, 55.8, 22.1, 22.0, 14.5; HRMS (ESI) m/z calcd. for $C_{27}H_{33}NNaO_6$ $[M+Na]^+$: 490.2206, found: 490.2187.

Ethyl 3-bromo-4,5-bis(4-isopropoxy-3-methoxyphenyl)-1H-pyrrole-2-carboxylate **(19b).** According to the procedure described for the preparation of **19a**, the same procedure followed for **19b**; using **17b** (460 mg, 0.985 mmol), NBS (175 mg, 0.985 mmol) DMF (10 mL) to give **19b** as light yellow solid (460 mg, 85%). mp 128–130 °C; IR (neat) ν (cm^{-1}) = 3284, 2977, 2933, 1670, 1554, 1517, 1472, 1382, 1243, 1037, 1139, 1108, 1037, 951, 860, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 6.90–6.85 (m, 2H), 6.84–6.77 (m, 3H), 6.69 (d, J = 2.0 Hz, 1H), 4.59–4.46 (m, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.55 (s, 3H), 1.42–1.34 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 149.9, 147.3, 146.5, 133.3, 126.4, 124.4, 123.7, 123.1, 119.3, 119.2, 115.3, 115.1, 114.7, 111.5, 105.9, 71.2, 60.8, 55.9, 55.6, 22.1, 22.0, 14.4; HRMS (ESI) m/z calcd. for $C_{27}H_{32}BrNNaO_6$ $[M+Na]^+$: 568.1305, found: 568.1322.

Ethyl 4,5-bis(4-isopropoxy-3-methoxyphenyl)-3-(4-isopropoxy-5-methoxy-2 (methoxymethoxy)phenyl) -1H-pyrrole-2-carboxylate **(22b).** According to the procedure described for the preparation of **22a**, the same procedure followed for **22b**; using **19b** (120 mg, 0.219 mmol), **18b** (89 mg, 0.318 mmol), $Pd(dba)_2$ (13 mg, 10 mol %), dppf (13 mg, 10 mol %), Na_2CO_3 (163 mg, 1.53 mmol), DME (5.0 mL), and degassed water (1.0 mL) to furnish **22b** as a white solid (130 mg, 85%); mp 98–100 °C; IR (neat) ν (cm^{-1}) = 3296, 2976, 2932, 1667, 1510, 1464, 1381, 1312, 1245, 1146, 1112, 1029, 862, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 6.97 – 6.93 (m, 1H), 6.87–6.78 (m, 3H), 6.69 – 6.63 (m, 2H), 6.59–6.54 (m, 2H), 4.79 (d, J = 6.8 Hz, 1H), 4.57–4.38 (m, 4H), 4.24–4.11 (m, 2H), 3.65 (s, 3H), 3.58 (s, 3H), 3.47 (s, 3H), 3.24 (s, 3H), 1.40–1.33 (m, 12H), 1.30 (d, J = 6.1 Hz, 6H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 149.9, 149.8, 149.7, 146.97, 146.95,145.3, 145.1, 132.2, 128.0, 127.6, 124.8, 123.6, 122.5, 119.6, 119.2, 117.6, 116.1, 115.6, 115.2, 114.2, 111.9, 105.9, 96.4, 71.6, 71.3, 60.0, 56.4, 55.6, 55.5, 55.4, 22.04, 22.00, 14.2; HRMS (ESI) m/z calcd. for $C_{39}H_{49}NNaO_{10}$ [M+Na]+: 714.3249, found: 714.3231.

7-Isopropoxy-1,2-bis(4-isopropoxy-3-methoxyphenyl)-8-methoxychromeno[3,4-b]pyrrol-4(3H)-one **(23b)**. According to the procedure described for the preparation of **23a**, the same procedure followed for **23b**; using **22b** (130 mg, 0.205 mmol) and p-TsOH·H_2O (4 mg, 10 mol%) in MeOH (10 mL) to furnish **23b** as a white solid (132 mg, 92%); mp 145– 147 °C; IR (neat) ν (cm^{-1}) = 3283, 2976, 2935,

1691, 1521, 1464, 1440, 1383, 1262, 1281, 1146, 1110, 1033, 1009, 940, 858, 829, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ10.02 (s, 1H), 7.05 – 6.93 (m, 6H), 6.86 – 6.78 (m, 2H), 4.62 – 4.51 (m, 3H), 3.78 (s, 3H), 3.65 (s, 3H), 3.47 (s, 3H), 1.40 (d, *J* = 6.1 Hz, 12H), 1.37 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 150.9, 150.0, 147.6, 147.3, 146.8, 146.7, 146.2, 138.9, 129.0, 127.8, 123.5, 123.4, 119.7, 117.2, 116.5, 115.0, 114.9, 114.7, 111.2, 110.5, 105.0, 103.8, 71.7, 71.5, 71.2, 56.1, 55.6, 55.5, 22.0, 21.8; HRMS (ESI) m/z calcd. for$C_{35}H_{40}NO_8$ $[M+H]^+$: 602.2676, found: 602.2673.

3-(2,2-Diethoxyethyl)-7-isopropoxy-1,2-bis(4-isopropoxy-3-methoxyphenyl)-8-methoxychromeno[3,4-b]pyrrol-4(3H)-one **(24b).** According to the procedure described for the preparation of **24a**, the same procedure followed for **24b**; using **23b** (100 mg, 0.144 mmol), 2-bromo- 1,1-diethoxyethane (130 µL, 0.868 mmol), and Cs_2CO_3 (283 mg, 0.868 mmol) in DMF (10 mL) to furnish **24b** as gummy solid (70 mg, 67%); IR (neat) *v* (cm^{-1}) = 3776, 3712, 3590, 2920, 2354, 1676, 1592, 1482, 1435, 1291, 1221, 1031, 924, 770; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.91 (m, 3H), 6.90 – 6.79 (m, 4H), 6.72 (d, *J* = 1.7 Hz, 1H), 5.00 (t, *J* = 5.6 Hz, 1H), 4.60 – 4.47 (m, 5H), 3.76 – 3.67 (m, 2H), 3.66 (s, 3H), 3.65 (s, 3H), 3.47 (s, 3H), 3.47 – 3.36 (m, 2H), 1.40 (d, *J* = 6.1 Hz, 6H), 1.38 – 1.33 (m, 12H), 1.16 – 1.08 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 150.2, 149.5, 147.4, 147.2, 146.5, 146.3, 146.2, 144.4, 127.8, 127.6, 123.9, 123.5, 122.4, 118.5, 115.9, 115.2, 115.0, 114.6, 114.5, 110.3, 105.3, 103.5, 102.6, 71.5, 71.1, 64.1, 55.8, 55.6, 48.8, 22.0, 21.8, 15.4; HRMS (ESI) m/z calcd. for $C_{41}H_{51}NNaO_{10}$ $[M+Na]^+$: 740.3405, found: 740.3420.

3,11-Diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-6H-chromeno[4',3':4,5] pyrrolo[2,1-a]isoquinolin-6-one **(25).**[11] According to the procedure described for the preparation of **2**, the same procedure followed for **25**; using **24b** (35 mg, 48.8 µmol) and TfOH to furnish **25** as a white solid (28.3 mg, 94%); mp 189–190 °C; IR (neat) *v* (cm^{-1}) = 3777, 3502, 2979, 2933, 2355, 1707, 1601, 1475, 1429, 1384, 1268, 1172, 1113, 1035, 944, 860, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 7.3 Hz, 1H), 7.19 (s, 1H), 7.17 (d, *J* = 1.0 Hz, 2H), 7.15 – 7.12 (m, 1H), 7.10 (s, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.97 (s, 1H), 6.76 (s, 1H), 4.73 – 4.53 (m, 3H), 3.84 (s, 3H), 3.45 (s, 3H), 3.44 (s, 3H), 1.43 (d, *J* = 6.1 Hz, 12H), 1.40 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 151.4,

150.2, 148.5, 147.9, 147.2, 146.6, 146.5, 134.4, 129.4, 128.8, 124.7, 123.9, 123.2, 119.0, 116.9, 115.0, 112.3, 111.0, 110.5, 110.0, 107.8, 105.7, 105.5, 103.5, 71.8, 71.5, 71.2, 56.2, 55.4, 55.1, 21.9, 21.8; HRMS (ESI) m/z calcd. for $C_{37}H_{40}NO_8$ $[M+H]^+$: 626.2754, found: 626.2750.

Lamellarin D **(1).**[11] Following the procedure by Iwao *et al.*[6a]; under an argon atmosphere, a DCM solution of BCl_3 (1.0 M, 200 µL, 0.192 mmol) was added dropwise to a solution of **25** (15 mg, 24.1 µmol) in DCM (5.0 mL) at −78 °C, and the mixture was allowed to warm to room temperature. After 4h of stirring at room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$, and the crude reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel (ethyl acetate) to give lamellarin D **(1)** as a white solid (9.5 mg, 79%); mp > 300 °C; IR (neat) ν (cm^{-1}) = 3409, 2254, 2128, 1658, 997, 824, 762; ^{1}H NMR (400 MHz, DMSO –d_6) δ 9.93 (s, 1H), 9.82 (s, 1H), 9.33 (s, 1H), 9.01 (d, J = 7.4 Hz, 1H), 7.24 – 7.15 (m, 3H), 7.14 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.87 (s, 1H), 6.72 (s, 1H), 3.77 (s, 3H), 3.38 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO –d_6) δ 154.8, 149.2, 149.0, 148.8, 148.3, 147.3, 146.8, 145.0, 134.6, 129.5, 125.9, 125.2, 124.3, 122.5, 118.0, 116.9, 115.4, 112.9, 112.0, 111.3, 108.8, 106.9, 106.2, 105.8, 104.2, 56.4, 55.5, 55.0; HRMS (ESI) m/z calcd. for $C_{28}H_{22}NO_8$ $[M+H]^+$: 500.1345, found: 500.1346. The spectral data are in accordance with the literature values (See the Supporting Information for detail comparison of ^{1}H and ^{13}C NMR).

Ethyl 4,5-bis(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carboxylate **(17c)**.[20] According to the procedure described for the preparation of **17a**, the same procedure followed for **17c**; using ethyl 2-acedamidoacrylate **16a** (220 mg, 1.39 mmol), 1,2-*bis*(4-(trifluoromethyl)phenyl)ethyne **20c** (527 mg, 1.67 mmol), $[RuCl_2(p\text{-cymene})]_2$ (42.85 mg, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (280 mg, 1.39 mmol) in PEG-400 (5 mL) to yield **17c** as a white solid (400 mg, 84%); mp 206–208 °C; IR (neat) ν (cm^{-1}) = 3296, 3025, 2354, 1690, 1462, 1223, 1011, 834, 755, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 2.6 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 138.7, 135.0, 132.1, 130.2 (d, $J_{C\text{-}F}$ = 44 Hz), 128.6, 128.4, 125.8 (d, $J_{C\text{-}F}$ = 5 Hz),

125.8 (d, $J_{C\text{-}F}$ = 5 Hz),123.7 (d, $J_{C\text{-}F}$ = 7 Hz),122.3 (d, $J_{C\text{-}F}$ = 32 Hz), 116.7, 60.9, 14.3; HRMS (ESI) m/z calcd. for $C_{21}H_{14}F_6NNaO_2$ $[M+Na]^+$: 449.0821, found: 449.0828.

Ethyl 3-bromo-4,5-bis(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carboxylate **(19c).** According to the procedure described for the preparation of **19a**, the same procedure followed for **19c**; using **17c** (300 mg, 0.702 mmol) and NBS (138 mg, 0.775 mmol) DMF (8 mL) to give **19c** as a white solid (250 mg, 70%); mp 190–192 °C; IR (neat) ν (cm^{-1}) = 3261, 2987, 1667, 1472, 1323, 1265, 1169, 1122, 1064, 1017, 846, 765; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.63 (d, J = 7.9 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 136.7, 134.0, 132.2, 131.0, 130.3 (q, $J_{C\text{-}F}$ = 32.5 Hz), 129.7 (q, $J_{C\text{-}F}$ = 32.5 Hz), 128.0, 125.8 (d, $J_{C\text{-}F}$ = 2.5 Hz), 125.4 (d, $J_{C\text{-}F}$ = 3.5 Hz), 125.0(d, $J_{C\text{-}F}$ = 43.75 Hz),124.6, 122.9 (d, $J_{C\text{-}F}$= 43.75 Hz), 121.3, 105.6, 61.4, 14.3; HRMS (ESI) m/z calcd. for $C_{21}H_{15}BrF_6NO_2$ $[M+H]^+$: 506.0190, found: 506.0188.

Ethyl 3-(4,5-dimethoxy-2-(methoxymethoxy)phenyl)-4,5-bis(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carboxylate **(22c).** According to the procedure described for the preparation of **22a**, the same procedure followed for **22c**; using **19c** (190 mg, 0.375 mmol), **12a** (136 mg, 0.561 mmol), $Pd(dba)_2$ (21 mg, 10 mol %), dppf (20 mg, 10 mol %), Na_2CO_3 (278 mg, 2.62 mmol), DME (5.0 mL), and degassed water (1.0 mL) to give **22c** as a white solid (210 mg, 90%); mp 188–190 °C; IR (neat) ν (cm^{-1}) = 3282, 2942, 1670, 1617, 1444, 1323, 1214, 1163, 1122, 1066, 1016, 848, 758; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.45 – 7.37 (m, 4H), 7.12 (d, J = 8.0 Hz, 2H), 6.77 (s, 1H), 6.61 (s, 1H), 4.80 (d, J = 6.9 Hz, 1H), 4.57 (d, J = 6.9 Hz, 1H), 4.22 – 4.05 (m, 2H), 3.87 (s, 3H), 3.69 (s, 3H), 3.19 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 149.7, 149.3, 143.5, 138.3, 134.9, 131.2, 130.2,129.8 (q, $J_{C\text{-}F}$ = 32.5 Hz), 128.5 (q, $J_{C\text{-}F}$ = 32.5 Hz), 128.1, 127.7, 125.7 (d, $J_{C\text{-}F}$ = 3.75 Hz), 125.0 (d, $J_{C\text{-}F}$ = 3.75 Hz), 124.1, 122.2 (d, $J_{C\text{-}F}$ = 21 Hz), 121.0, 115.3, 115.2, 101.1, 96.1, 60.5, 56.3, 55.9, 55.5, 14.1; HRMS (ESI) m/z calcd. for $C_{31}H_{28}F_6NO_6$ $[M+H]^+$: 624.1815, found: 624.1809.

7,8-Dimethoxy-1,2-bis(4-(trifluoromethyl)phenyl)chromeno[3,4-b]pyrrol-4(3H)-one **(23c).** According to the procedure described for the preparation of **23a**, the same procedure followed for **23c**; using **22c** (170 mg, 0.272 mmol) and *p*-TsOH·H_2O (4.7 mg, 10 mol %) in MeOH (10 mL) to yield **23c** as white solid (134 mg, 92%); mp 311– 313 °C; IR (neat) ν (cm^{-1}) = 3275, 2926, 2356, 1693, 1329, 1133, 1072, 1022, 847, 771; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.30 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 7.9 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.10 (m,1H), 6.36 (m, 1H), 3.81 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.8, 149.4, 146.2, 145.7, 139.2, 137.7, 134.6, 132.7, 129.6, 129.1 (q, $J_{C\text{-}F}$ = 43.5 Hz), 128.7 (q, $J_{C\text{-}F}$ = 43.5 Hz), 127.5, 126.4 (d, $J_{C\text{-}F}$ = 1.25 Hz), 125.9 (d, $J_{C\text{-}F}$ = 2.5 Hz), 125.6, 123.5 (d, $J_{C\text{-}F}$ = 25 Hz), 117.5, 116.7, 109.4, 104.2, 101.7, 56.4, 55.0; HRMS (ESI) m/z calcd. for $C_{27}H_{17}F_6NNaO_4$ $[M+Na]^+$: 556.0954, found: 556.0965.

Methyl 4,5-bis(4-fluorophenyl)-1H-pyrrole-2-carboxylate **(17d)**. According to the procedure described for the preparation of **17a**, the same procedure followed for **17d**; using methyl 2-acetamidoacrylate **16b** (180 mg, 1.25 mmol), 1,2-*bis*(4-fluorophenyl)ethyne **20c** (270 mg, 1.26 mmol), $[RuCl_2(p\text{-cymene})]_2$ (38 mg, 5.0 mol %) and $Cu(OAc)_2$•H_2O (251 mg, 1.25 mmol) in PEG-400 (4 mL) to obtain **17d** as white solid (260 mg, 76%); mp 164–166 °C; IR (neat) ν (cm^{-1}) = 3299, 2362, 1689, 1521, 1456, 1287, 1228, 1160, 1010, 837, 769; ^{1}H NMR (400 MHz, $CDCl_3$) δ9.51 (s, 1H), 7.38 – 7.30 (m, 2H), 7.25 – 7.18 (m, 2H), 7.11 – 6.87 (m, 5H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ δ 162.5 (d, $J_{C\text{-}F}$ = 247 Hz), 161.70, 161.69 (d, $J_{C\text{-}F}$ = 244 Hz), 132.4, 131.2 (d, $J_{C\text{-}F}$ = 3 Hz), 130.0 (d, $J_{C\text{-}F}$ = 8 Hz), 129.8 (d, $J_{C\text{-}F}$ = 8 Hz),127.9 (d, $J_{C\text{-}F}$ = 3 Hz), 123.1, 122.1, 116.7, 115.7 (d, $J_{C\text{-}F}$ = 22 Hz), 115.4 (d, $J_{C\text{-}F}$ = 21 Hz), 51.7; HRMS (ESI) m/z calcd. for $C_{18}H_{14}F_2NO_2[M+H]^+$: 314.0987, found: 314.0983.

Methyl 3-bromo-4,5-bis(4-fluorophenyl)-1H-pyrrole-2-carboxylate **(19d)**. According to the procedure described for the preparation of **19a**, the same procedure followed for **19d**; using **17d** (250 mg, 0.798 mmol) and NBS (157 mg, 0.882 mmol) DMF (8 mL) to give **19d** as a white solid solid (240 mg, 76%); mp 190–192 °C; IR (neat) ν (cm^{-1}) = 3299, 2956, 2361, 1674, 1522, 1464, 1220, 1160, 1043, 839, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.25 – 7.13 (m, 4H), 7.10 – 6.90 (m, 4H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, $J_{C\text{-}F}$ = 248 Hz), 162.2 (d, $J_{C\text{-}F}$ = 245 Hz), 132.7,

132.3 (d, $J_{C\text{-}F}$ = 8 Hz), 129.5 (d, $J_{C\text{-}F}$ = 8 Hz), 129.0 (d, $J_{C\text{-}F}$ = 3 Hz), 126.8 (d, $J_{C\text{-}F}$ = 3 Hz), 124.0, 119.9, 115.8 (d, $J_{C\text{-}F}$ = 22 Hz), 115.4 (d, $J_{C\text{-}F}$ = 21 Hz), 105.9, 51.9; HRMS (ESI) m/z calcd. for $C_{18}H_{12}BrF_2NO_2Na$ $[M+Na]^+$: 413.9912, found: 413.9916.

Methyl 3-(4,5-dimethoxy-2-(methoxymethoxy)phenyl)-4,5-bis(4-fluorophenyl)-1H-pyrrole-2-carboxy late **(22d)**. According to the procedure described for the preparation of **22a**, the same procedure followed for **22d**; using **13d** (196 mg, 0.500 mmol), **18a** (182 mg, 0.752 mmol), $Pd(dba)_2$ (29 mg, 10 mol %), dppf (28 mg, 10 mol %), Na_2CO_3 (371 mg, 3.5 mmol), DME (5.0 mL), and degassed water to furnish **22d** as a white solid (185 mg, 72%); mp 109–111°C; IR (neat) ν (cm^{-1}) = 3298, 2948, 2359, 1680, 1513, 1451, 1218, 1157, 1010, 841, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.29 – 7.25 (m, 2H), 7.03 – 6.89 (m, 4H), 6.88 – 6.76 (m, 3H), 6.59 (s, 1H), 4.79 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 6.9 Hz, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.68 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (d, $J_{C\text{-}F}$ = 247 Hz), 161.7, 161.5 (d, $J_{C\text{-}F}$ = 244 Hz), 149.8, 148.9, 143.4, 131.7, 131.6 (d, $J_{C\text{-}F}$ = 8 Hz), 130.5 (d, $J_{C\text{-}F}$ = 3 Hz), 129.6 (d, $J_{C\text{-}F}$ = 8 Hz), 127.7 (d, $J_{C\text{-}F}$ = 3 Hz), 127.6, 123.5, 119.4, 115.7 (d, $J_{C\text{-}F}$ = 21 Hz), 115.2, 115.0 (d, $J_{C\text{-}F}$ = 21Hz), 101.3, 96.4, 56.2, 55.8, 55.6, 51.4; HRMS (ESI) calcd. for $C_{28}H_{25}F_2NNaO_6$ $[M+Na]^+$: 532.1542, found: 532.155.

1,2-Bis(4-fluorophenyl)-7,8-dimethoxychromeno[3,4-b]pyrrol-4(3H)-one **(23d).** According to the procedure described for the preparation of **23a**, the same procedure followed for **23d**; using **22d** (110 mg, 0.216 mmol) and *p*-TsOH·H_2O (4 mg, 10 mol%) in MeOH (10 mL) to yield **23d** as gummy solid (85 mg, 91%); IR (neat) ν (cm^{-1}) = 3200, 2842, 1687, 1513, 1284, 1218, 1080, 1020, 840, 760; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 7.49 – 7.40 (m, 4H), 7.38 – 7.30 (m, 2H), 7.23 – 7.15 (m, 2H), 7.07 (s, 1H), 6.52 (s, 1H), 3.80 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4 (d, $J_{C\text{-}F}$ = 245 Hz), 162.3 (d, $J_{C\text{-}F}$ = 243 Hz), 154.8, 149.2, 146.2, 145.7, 138.7, 133.7 (d, $J_{C\text{-}F}$ = 8 Hz), 131.0 (d, $J_{C\text{-}F}$ = 8 Hz), 127.6, 127.4 (d, $J_{C\text{-}F}$ = 3 Hz), 116.8, 116.4 (d, $J_{C\text{-}F}$ = 21 Hz), 115.9 (d, $J_{C\text{-}F}$ = 21 Hz), 115.7, 109.9, 104.5, 101.6, 56.3, 55.4; HRMS (ESI) calcd. for $C_{25}H_{17}F_2NNaO_4$ $[M+Na]^+$: 456.1018, found: 456.102.

Ethyl 4,5-bis(4-methoxyphenyl)-1H-pyrrole-2-carboxylate **(17e).** According to the procedure described for the preparation of **17a**, the same procedure followed for **17e**; using ethyl 2-acetamidoacrylate **16a** (300 mg, 1.90 mmol), 1,2-bis(4-methoxyphenyl)ethyne **20e** (500 mg, 2.10 mmol), $[RuCl_2(p\text{-cymene})]_2$ (58 mg, 5.0 mol %) and $Cu(OAc)_2 \bullet H_2O$ (381 mg, 1.90 mmol) in PEG-400 (4 mL) to give **17e** as a white solid (550 mg, 82%); mp 162–163 °C; IR (neat) ν (cm^{-1}) = 3295, 2990, 2837, 1679, 1612, 1522, 1464, 1239, 1184, 1131, 1028, 833, 762; ^{1}H NMR (400 MHz, $CDCl_3$)δ 9.40 (s, 1H), 7.33 – 7.27 (m, 2H), 7.24 – 7.19 (m, 2H), 7.03 – 6.97 (m, 1H), 6.87 – 6.79 (m, 4H), 4.29 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 1.34 (t, J = 7.1 Hz,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 159.3, 158.1, 132.9, 129.5, 129.2, 128.0, 124.6, 123.1, 121.8, 116.5, 114.1, 113.8, 60.4, 55.21, 55.16, 14.5; HRMS (ESI) calcd. for $C_{21}H_{21}NNaO_4$ $[M+Na]^+$: 374.1363, found: 374.1371.

Ethyl 3-bromo-4,5-bis(4-methoxyphenyl)-1H-pyrrole-2-carboxylate **(19e).** According to the procedure described for the preparation of **19a**, the same procedure followed for **19e**; using **17e** (140 mg, 0.398 mmol) and NBS (78 mg, 0.438 mmol) in DMF (6 mL) to give **19e** as a brown solid (100 mg, 81%); mp 172– 174 °C; IR (neat) ν (cm^{-1}) = 3284, 2991, 2353, 1672, 1614, 1566, 1524, 1467, 1411, 1254, 1186, 1100, 1036, 835, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.21 – 7.13 (m, 4H), 6.93 – 6.85 (m, 2H), 6.83 – 6.76 (m, 2H), 4.35 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 159.4, 158.7, 133.2, 131.8, 128.8, 125.7, 124.0, 123.5, 119.3, 114.1, 113.7, 106.1, 60.8, 55.2, 55.1, 14.4; HRMS (ESI) m/z calcd. for $C_{21}H_{20}BrNNaO_4$ $[M+Na]^+$: 452.0468, found: 452.0469.

Ethyl 3-(4,5-dimethoxy-2-(methoxymethoxy)phenyl)-4,5-bis(4-methoxyphenyl)-1H-pyrrole-2-carboxylate **(22e)**. According to the procedure described for the preparation of **22a**, the same procedure followed for **22e**; using **19e** (100 mg, 0.232 mmol), **18a** (85 mg, 0.351 mmol), $Pd(dba)_2$ (14 mg, 10 mol %), dppf (13 mg, 10 mol %), Na_2CO_3 (171.5 mg, 1.62 mmol), DME (5.0 mL), and degassed water (1.0 mL) to furnish **22e** isolated as a brown solid (76 mg, 66%); mp 162–164°C; IR (neat) ν (cm^{-1}) = 3296, 2945, 2839, 2348, 1672, 1612, 1517, 1443, 1287, 1249, 1179, 1081, 1025, 838, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.26–7.21 (m, 2H), 6.94–6.89 (m, 2H), 6.85–6.80 (m, 2H), 6.78 (s, 1H), 6.70–6.65 (m, 2H), 6.63 (s, 1H), 4.78 (d, J = 6.9 Hz, 1H), 4.53 (d, J = 6.9 Hz, 1H),

4.27–4.09 (m, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.69 (s, 3H), 3.28 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 159.1, 157.9, 149.8, 148.6, 143.4, 132.2, 131.2, 128.9, 127.6, 127.2, 124.4, 123.5, 119.1, 116.7, 115.3, 114.0, 113.4, 101.5, 96.6, 60.0, 56.1, 55.8, 55.6, 55.2, 55.0, 14.3; HRMS (ESI) m/z calcd. for $C_{31}H_{34}NO_8$ $[M+H]^+$: 548.2279, found: 548.2267.

7,8-Dimethoxy-1,2-bis(4-methoxyphenyl)chromeno[3,4-b]pyrrol-4(3H)-one **(23e)**. According to the procedure described for the preparation of **23a**, the same procedure followed for **23e**; using **16e** (40 mg, 0.0731 mmol) and *p*-TsOH·H_2O (2 mg, 10 mol%) in MeOH (10 mL) to furnish **23e** as white solid (25 mg, 84%); mp 242–244 °C; IR (neat) ν (cm^{-1}) = 3254, 2929, 1692, 1611, 1523, 1453, 1251, 1138, 1149, 1026, 839, 757; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (s, 1H), 7.39 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 7.7 Hz, 2H), 7.10–7.00 (m, 3H), 6.88 (d, J = 8.7 Hz, 2H), 6.54 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.6, 159.3, 154.8, 149.1, 146.2, 145.6, 139.5, 132.7, 130.0, 128.0, 127.0, 123.6, 116.9, 115.1, 114.9, 114.3, 110.2, 104.7, 101.5, 56.3, 55.7, 55.6, 55.4; HRMS (ESI) m/z calcd. for $C_{27}H_{23}NNaO_6$ $[M+Na]^+$: 480.1418, found: 480.1398.

ASSOCIATED CONTENT

Supporting Information

characterization of new compounds (^{1}H, ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: srivaric@iict.res.in

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

D.M.L thanks Council of Scientific and Industrial Research (CSIR), New Delhi for senior research fellowship. A.B.P thanks DST, New Delhi for the INSPIRE Faculty Award (CH-157, GAP 0520). The

authors thank CSIR-New Delhi for financial support as part of XII five-year programme project under ORIGIN (CSC-108). S.C thank DST for J. C. Bose fellowship (SB/S2/JCB-002/2015).

REFERENCES

(1) (a) Fan, H., Peng, J., Hamann, M. T.; Hu, J. *Chem. Rev*. **2008**, *108*, 264. (b) Estevez, V., Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev*., **2014**, *43*, 4633.

(2) Andersen, R. J.; Faulkner, D. J.; He, C.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc*. **1985**, *107*, 5492.

(3) (a) Kluza, J.; Gallego, M.-A.; Loyens, A.; Beauvillain, J.-C.; Sousa-Faro, J. -M. F.; Cuevas, C.; Marchetti, P.; Bailly, C. *Cancer Res.* **2006**, *66*, 3177. (b) Bailly, C. Curr. Med. Chem.: *Anti-Cancer Agents* **2004**, *4*, 363.

(4) (a) Marco, E.; Laine W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem*. **1999**, *42*, 1901. (b) Bailly, C. *Mar. Drugs* **2015**, *13*, 1105. (c) Pla, D.; Sischka, A.; Albericio, F.; Alvarez, M.; Fernandez-Busquets, X.; Anselmetti, D. *Small*, **2009**, *5*, 1269–1272. (d) Ballot, C.; Kluza, J.; Lancel, S.; Martoriati, A.; Hassoun, S. M.; Mortier, L.; Vienne, J.-C.; Briand, G.; Formstecher, P.; Bailly, C.; Neviere, R.; Marchetti, P. *Apoptosis* **2010**, 15, 769.

(5) (a) Imbri, D.; Tauber, J.; Opatz, T. *Mar. Drugs* **2014**, *12*, 6142. (b) Pla, D.; Albericio, F.; Alvarez, M. *Anti-Cancer Agents Med. Chem.*, **2008**, *15*, 746. (c) Pla, D.; Albericio, F.; Alvarez, M. *Med. Chem. Commun*., **2011**, *2*, 689. (d) Handy, S. T.; Zhang, Y. *Org. Prep. Proced. Int*. **2005**, *37*, 411.

(6) (a) Komatsubara, M.; Umeki, T.; Fukuda, T.; Iwao, M. *J. Org. Chem.* **2014**, *79*, 529. (b) Dialer, C.; Imbri, D.; Hansen, S. P.; Opatz, T. *J. Org. Chem*. **2015**, *80*, 11605. (c) Ueda, K.; Amaike, K.; Maceiczyk, R. M.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc*. **2014**, *136*, 13226. (d) Manjappa, K. B.; Syu, J.; Yang, D. *Org. Lett*., **2016**, *18*, 332.

(7) Handy, S. T.; Zhang, Y. N.; Bregman, H. *J. Org. Chem*. **2004**, *69*, 2362.

(8) Pla, D.; Marchal, A.; Olsen, C. A.; Albericio, F.; Alvarez, M. *J. Org. Chem.* **2005**, *70*, 8231.

(9) Hasse, K.; Willis, A. C.; Banwell, M. G. *Eur. J. Org. Chem*. **2011**, 88.

(10) Gupton, J. T.; Giglio, B. C.; Eaton, J. E.; Rieck, E. A.; Smith, K. L.; Keough, M. J.; Barelli, P. J.; Firich, L. T.; Hempel, J. E.; Smith, T. M. *Tetrahedron* **2009**, *65*, 4283.

(11) Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. *Org. Lett*. **2011**, *13*, 312.

(12) Peschko, C.; Winklhofer, C.; Steglich, W. *Chem. Eur. J*. **2000**, *6*, 1147.

(13) For selected recent reviews on C–H functionalization in natural product synthesis, see: (a) Mcmurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev*. **2011**, *40*, 1885. (b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev*. **2011**, *40*, 1976. (c) Chen, D. Y.-K.; Youn, S. W. *Chem. – Eur. J*. **2012**, *18*, 9452. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed*. **2012**, *51*, 8960.

(14) For selected recent reports natural product syntheses using C–H activation strategy, see: (a) Tao, P; Chen, Z; Jia, Y. *Chem. Commun.,* **2016**, *52*, 11300. (b) Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.*, **2012**, *134*, 13573. (c) Cherney, E. C.; Lopchuk, J. M.; Green, J. C.; Baran, P. S. *J. Am. Chem. Soc*. **2014**, *136*, 12592. (d) Zhao, L.; Tsukano, C.; Kwon, E.; Takemoto, Y.; Hirama, M. *Angew. Chem., Int. Ed*. **2013**, *52*, 1722. (e) Wang, H., Li, G.; Engle, K. M.; Yu, J. -Q.; Davies, H. M. L. *J. Am. Chem. Soc*. **2013**, *135*, 6774. (f) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc*. **2016**, *138*, 3926.

(15) (a) Wang L.; Ackermann, L. *Org. Lett*. **2013**, *15*,176. (b) Li, B.; Wang, N.; Liang, Y.; Xu S.; Wang, B. *Org. Lett*. **2013**,*15*, 136.

(16) For other Ru(II)-catalyzed C–H/N–H activation for alkyne annulations, see: (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379. (b) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281.

(17) Park, K.; Bae, G.; Moon, J.; Choe, J.; Ho Song, K.; Lee, S. *J. Org. Chem*. **2010**, *75*, 6244.

(18) (a) Yedage, S. L.; Bhanage, B. M. *Green Chem.* **2016**, *18*, 5635. (b) Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922.

(19) Trosien, S.; Waldvoge, S. R. *Org. Lett.*, **2012**, *14* , 2976.

(20) Lade, D. M.; Pawar, A. B. *Org. Chem. Front*., **2016**, *3*, 836.