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Synthesis of lamellarin R, lukianol A, lamellarin O and their analogues†

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Three lamellarin alkaloids type III (lamellarin R, lukianol A and lamellarin O) were synthesized using the Barton–Zard reaction as a key step to construct the central pyrrole core. Some of their corresponding 4-benzoyl and 5-phenyl substituted pyrrole analogues were also prepared *via* an initial three-component reaction of glycine methyl ester, benzaldehyde, and chalcone to generate the pyrrolidine scaffold, and followed by DDQ oxidation and *N*-alkylation.

1 Introduction

Lamellarins are a family of pyrrole-containing alkaloids isolated from marine mollusks, ascidians, and sponges by Faulkner and co-workers since 1985.¹ Today, more than 70 different lamellarins have been identified and reported.² They can be generally classified into lamellarin alkaloids type I, II, and III, depending upon their molecular structures. These lamellarin alkaloids have been found to exhibit a variety of biological activities. For instance, lamellarin I, a representative compound in lamellarin alkaloids type I, reverses multidrug resistance by direct inhibition of P-glycoprotein-mediated drug efflux at noncytotoxic doses.³ Lamellarin D, a leading pentacyclic compound in lamellarin alkaloids type II, is a potent inhibitor of both nuclear and mitochondrial topoisomerase I.⁴ The type III lamellarin alkaloid lukianol A, exhibits significant cytotoxicity against human epidermoid carcinoma cell lines.⁵ Fig. 1 depicts the representative structures of lamellarin alkaloids type III, including ningalins A, B, lamellarins Q, O, R and lukianol A.

In light of their intriguing biological properties along with the difficulty in obtaining large quantities from natural sources, the synthesis of the lamellarins has become an attractive goal for organic chemists in the past two decades. A key feature in the synthesis of lamellarin alkaloids type III is the construction of the aryl-substituted pyrrole ring, which can be categorized into two different synthetic approaches, that is, functionalization of a simple pyrrole core and synthesis of the functionalized pyrrole moiety from the appropriate precursors. The former is represented by the works of Banwell,⁶ Iwao,⁷ Wong⁸ and

Okano's groups,⁹ whereas the latter is exemplified by Boger,¹⁰ Vazquez,¹¹ Fürstner,¹² Jia,¹³ Hwu,¹⁴ Iwao,¹⁵ and Yang's groups.¹⁶ While the total synthesis of lamellarin alkaloids type III has been documented by the aforementioned researchers, the development of more efficient and greener synthesis of these natural products along with their analogues leaves more room for improvement.

Recently, Samet and coworkers¹⁷ have reported a metal-free synthesis of ethyl-3,4-diarylpyrrole-2-carboxylate (1) *via* Barton–Zard reaction¹⁸ of nitrostilbene (2) with ethyl isocynoacetate (Scheme 1), and subsequently applied it to the synthesis of lamellarin Q. To further demonstrate the usefulness of this Barton–Zard reaction to the preparation of another lamellarin type III alkaloids, here we report the modular synthesis of lamellarin R, lukianol A and lamellarin O, utilizing the Barton–Zard reaction to construct the pyrrole core. Moreover, some of lamellarin type III alkaloid analogues were also prepared by employing a three-component reaction of glycine methyl ester, benzaldehyde and chalcone to assemble the highly substituted pyrrolidine ring.

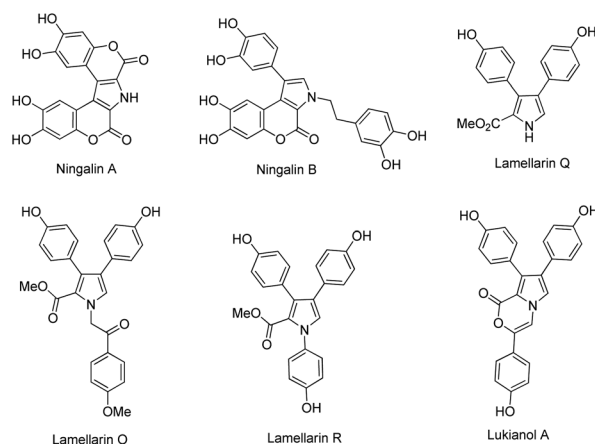


Fig. 1 Representative structures of lamellarin alkaloids type III.

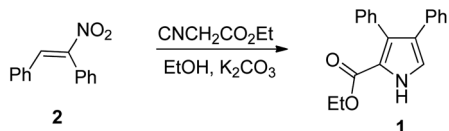
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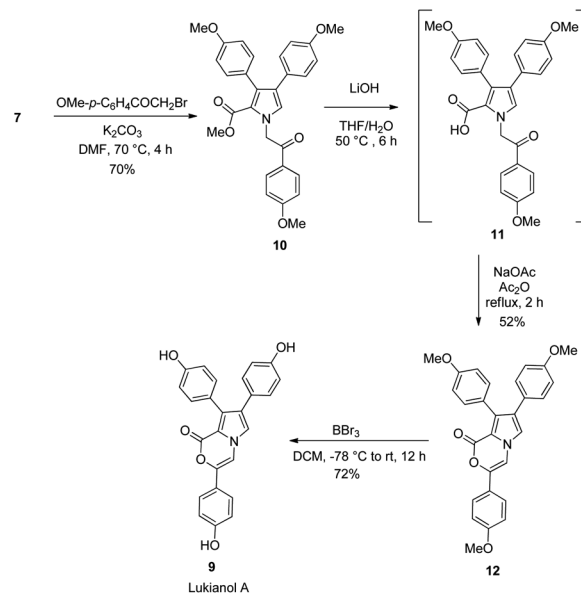
Scheme 1 Synthesis of ethyl-3,4-diarylpyrrole-2-carboxylate (1).

2 Results and discussion

Scheme 2 depicts the total synthesis of lamellarin R (3). It started with the bromination of commercially available *p*-methoxy- β -nitrostyrene (4) with Br₂ in chloroform to give the brominated compound 5. The subsequent Suzuki coupling of 5 with *p*-methoxybenzeneboronic acid under basic conditions generated the nitrostilbene 6 in 68% yield. The key Barton–Zard reaction was realized *via* reacting of nitrostilbene 6 with methyl isocyanoacetate in the presence of three equivalents of K₂CO₃ as a base in methanol to furnish the key intermediate methyl-3,4-diarylpyrrole-2-carboxylate 7 in 76% yield. The routine Buchwald–Hartwig amination¹⁹ of pyrrole 7 with *p*-iodoanisole in toluene at 110 °C for 12 h gave the corresponding *N*-substituted pyrrole 8 in 76% yield. Final exhaustive demethylation of pyrrole 8 with an excess of BBr₃ afforded the target lamellarin R in 92% yield.

Scheme 3 outlines the preparation of lukianol A (9) from intermediate 7. It began with *N*-alkylation of pyrrole 7 with 2-bromo-1-(4-methoxyphenyl)ethan-1-one under basic conditions in DMF to give the corresponding pyrrole 10 in 70% yield. The subsequent LiOH-mediated hydrolysis of methyl ester 10 generated the carboxylic acid 11 which, without isolation, was reacted with NaOAc in Ac₂O under reflux conditions for 1 h to obtain the cyclized 12 in 52% yield. The final exhaustive demethylation of pyrrole 12 with an excess of BBr₃ afforded the target lukianol A (9) in 72% yield. Thus, natural product lukianol A was successfully prepared in six steps from the commercially available *p*-methoxy- β -nitrostyrene (4) in an overall yield of 9.8%.

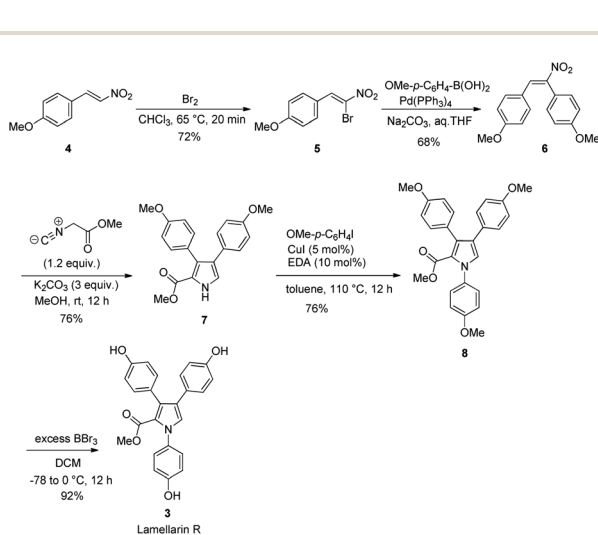
Ideally, lamellarin O can be obtained directly from pyrrole 10 if the two 4-methoxyphenyl groups substituted on pyrrole



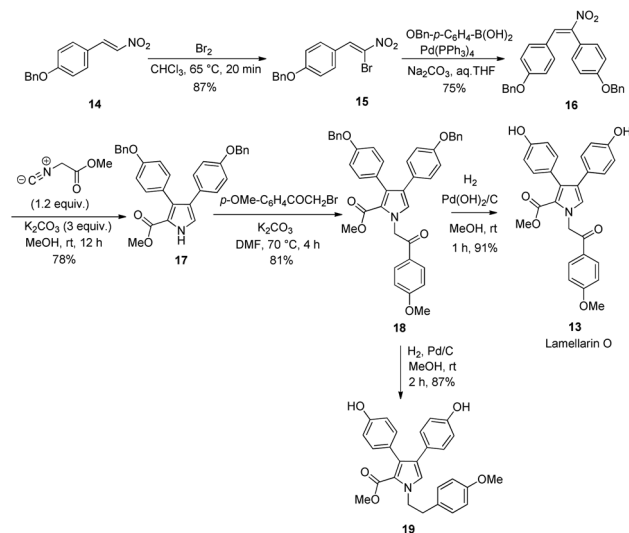
Scheme 3 Synthesis of lukianol A (9) from 7.

moiety of 10 were able to be selectively demethylated. Unfortunately, even though compound 10 was treated with different demethylation agents such as BBr₃, AlCl₃ and LiCl under various reaction conditions, all attempts failed to afford the desired lamellarin O in acceptable yield. Thus, the protection of the two hydroxyl groups on the pyrrole ring with a functional group other than OMe seems inevitable for the preparation of lamellarin O. Scheme 4 shows the synthesis of lamellarin O (13) from the OBn protected (*E*)-1-(benzyloxy)-4-(2-nitrovinyl)benzene (14). Similar to that of lamellarin R, the synthesis started with bromination of 14 with Br₂ to give the brominated 15.

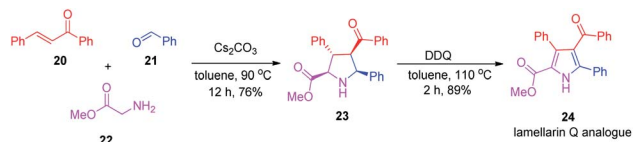
Next, the palladium-catalyzed Suzuki coupling of 15 with (*p*-(benzyloxy)phenyl)boronic acid generated the nitrostilbene 16 in 75% yield. Barton–Zard reaction between nitrostilbene 16



Scheme 2 Synthesis of lamellarin R (3).



Scheme 4 Synthesis of lamellarin O (13) and 19.



Scheme 5 Preparation of lamellarin Q analogue 24.

and methyl isocyanoacetate in methanol gave the benzyl-3,4-diarylpyrrole-2-carboxylate **17** in 78% yield. The intermediate **17** was then subjected to *N*-alkylation with 2-bromo-1-(4-methoxyphenyl)ethan-1-one under basic conditions in DMF to yield the corresponding pyrrole **18** in 81%. Final deprotection of two OBn groups on the pyrrole moiety with hydrogen in the presence of palladium hydroxide on carbon as a catalyst afforded the target lamellarin O (**13**) in an overall yield of 37.5%. It is worth mentioning that the reduced compound **19** was obtained as an exclusive product when the palladium on carbon was used as a catalyst for the debenzoylation of **18**.

After realizing the total synthesis of lamellarin O, lamellarin R and lukianol A, we then shifted our focus to the preparation of their analogues. Scheme 5 outlines the two-step synthesis of the 4-benzoyl and 5-phenyl substituted lamellarin Q analogue **24**. It started with the Cs_2CO_3 -mediated, three-component reaction of chalcone **20**, benzaldehyde (**21**), and glycine methyl ester (**22**) in toluene at 90 °C for 12 h to give the tetra-substituted pyrrolidine **23**. The mechanism of this three-component reaction presumably involved the [3+2] cycloaddition reaction between chalcone **20** and 1,3-dipolar *N*-benzylidene glycine methyl ester generated *in situ* from benzaldehyde (**21**) and glycine methyl ester (**22**).²⁰ The subsequent DDQ oxidation of pyrrolidine **23** afforded the lamellarin Q analogue **24** in good yield. This lamellarin Q analogue **24** then serves as a common precursor for the

synthesis of lamellarin O, lamellarin R and lukianol A analogues.

Unfortunately, the Buchwald–Hartwig coupling reaction between pyrrole-2-carboxylate **24** and *p*-iodoanisole failed to give the desired lamellarin R analogue **25** (Scheme 6), presumably due to the steric hindrance induced by the nearby phenyl and ester groups adjacent to the nitrogen atom.²¹ Nevertheless, the *N*-alkylation of **24** with 2-bromo-1-(4-methoxyphenyl)ethan-1-one in the presence of K_2CO_3 in DMF did afford the lamellarin O analogue **26** in 84% yield. Saponification of the methyl ester **26** with LiOH in THF : H_2O (1 : 1) furnished the crude oxo-acid which, without isolation, was allowed to react with NaOAc in Ac_2O at 90 °C for 1 h to obtain the corresponding lukianol A analogue **27** in 58% yield.

We believe that the rapid synthesis of those potentially valuable lamellarin type III analogues may facilitate the process for the future development of novel lamellarin-derived antitumor drugs.

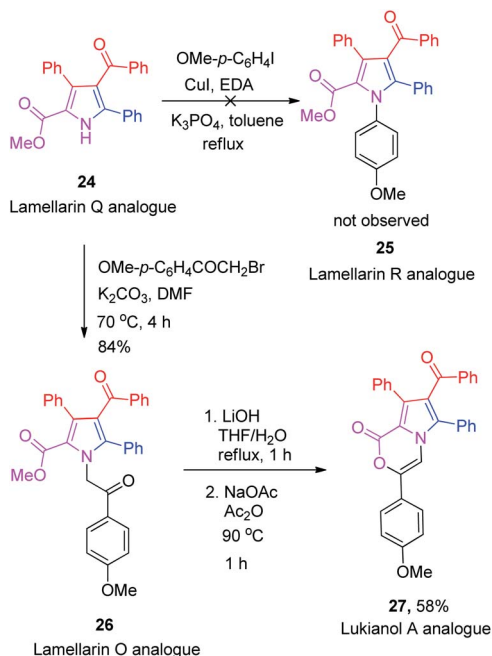
3 Conclusions

In summary, the natural products lamellarin R, lukianol A and lamellarin O were synthesized from commercially available nitrostilbenes in five, six and five steps with overall yields of 26.0, 9.8 and 37.5%, respectively. The common feature of the syntheses involved the Barton–Zard reaction to construct the pyrrole core structure. Besides, lamellarin Q, lukianol A and lamellarin O analogues bearing 4-benzoyl and 5-phenyl groups substituted on the pyrrole moiety were prepared in two to four steps from a three-component reaction of glycine methyl ester, benzaldehyde and chalcone to assemble the highly substituted pyrrolidine ring, and followed by DDQ oxidation and *N*-alkylation. The biological activities of those prepared compounds are currently under investigation.

4 Experimental

4.1 General

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and were uncorrected. Infrared (IR) spectra were recorded using 1725XFT-IR spectrophotometer. High-resolution mass spectra (HRMS) were obtained on a Thermo Fisher Scientific Finnigan MAT95XL spectrometer using a magnetic sector analyzer. Peptide mass analysis was obtained by MALDI TOF MS (Bruker), and peptide purity was confirmed by RP-HPLC (Hitachi). ^1H NMR (400 MHz) and ^{13}C NMR (100) spectra were recorded on a Bruker 400 spectrometer. Chemical shifts were reported in parts per million on the scale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. ^1H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Visualization was accomplished by using portable UV light, and an iodine chamber. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 Kieselgel 60H) by elution with the solvent



Scheme 6 Synthesis of lamellarin O and lukianol A analogues.



systems. Solvents, unless otherwise specified, were reagent grade and distilled once before use. All new compounds exhibited satisfactory spectroscopic and analytical data.

4.2 General procedure for the synthesis of 5 and 15

To a solution of β -nitrostyrene (5.58 mmol) in CHCl_3 (25 mL) was added Br_2 (5.58 mmol, 1.0 equiv.) at room temperature within 5 min. The reaction mixture was refluxed for 20 min. Upon complete consumption of the starting material, the reaction mixture was cooled to 8 °C and the solution of Et_3N (8.37 mmol, 1.5 equiv.) was added dropwise within 20 min. The mixture was maintained for 30 min and then poured into a mixture of $\text{EtOAc} : \text{H}_2\text{O}$ (1 : 1). The organic layer was washed with H_2O (200 mL), brine (2×150 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to give the title compound.

4.2.1 (Z)-1-(2-Bromo-2-nitrovinyl)-4-methoxybenzene (5). Yellow solid. $R_f = 0.5$ (10% EtOAc /hexanes). Light yellow solid, 1.04 g. Yield 72%. Mp 66–68 °C (lit. (ref. 22) 67–68 °C). ^1H NMR (CDCl_3 , 400 MHz): δ 8.66 (s, 1H), 7.95 (d, $J = 8.8$ Hz, 2H), 7.03 (d, $J = 9.2$ Hz, 2H), 3.91 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 162.8, 136.4, 133.5, 125.4, 122.4, 114.6, 55.6. IR ν_{max} (neat) 2988, 1639, 1612, 1418, 1125, 819 cm^{-1} . HRMS (EI) m/z : [M^+] calcd for $\text{C}_9\text{H}_8\text{BrNO}_3$, 256.9688; found, 256.9682.

4.2.2 (Z)-1-(Benzyloxy)-4-(2-bromo-2-nitrovinyl)benzene (15). Yellow solid. $R_f = 0.5$ (10% EtOAc /hexanes). 1.63 g. Yield 87%. Mp 166–168 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 8.66 (s, 1H), 7.95 (d, $J = 8.8$ Hz, 2H), 7.48–7.39 (m, 5H), 7.10 (d, $J = 8.8$ Hz, 2H), 5.18 (s, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 161.9, 136.3, 136.0, 133.5, 128.8, 128.4, 127.5, 125.6, 122.7, 115.4, 70.3. IR ν_{max} (neat) 3011, 1644, 1612, 1572, 1414, 965, 879 cm^{-1} . HRMS (EI) m/z : [M^+] calcd for $\text{C}_{15}\text{H}_{12}\text{BrNO}_3$, 333.0001; found, 333.0005.

4.3 General procedure for the synthesis of 6 and 16

To a stirred solution of 5 or 15 (1.94 mmol, 1.0 equiv.) and (4-methoxyphenyl)boronic acid (2.91 mmol, 1.5 equiv.) in THF (10 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (0.01 equiv.) and Na_2CO_3 (4.85 mmol, 2.5 equiv. in 5 mL of H_2O) at room temperature. The resulting light yellow solution was stirred at room temperature for 30 min and then heated to reflux in an oil bath for 6 h. After cooled down to room temperature, the mixture was filtered through Celite with the aid of ethyl acetate and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (5% EtOAc in hexanes) to give the title compound.

4.3.1 (E)-4,4'-(1-Nitroethene-1,2-diyl)bis(methoxybenzene) (6). Yellow solid. $R_f = 0.5$ (5% EtOAc /hexanes). 378 mg. Yield 68%. Mp 140–142 °C (lit. (ref. 23) 140–141 °C). ^1H NMR (CDCl_3 , 400 MHz): δ 8.21 (s, 1H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.04 (d, $J = 8.8$ Hz, 2H), 6.78 (d, $J = 8.8$ Hz, 2H), 3.91 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 161.7, 160.7, 147.5, 134.7, 133.2, 132.1, 123.9, 123.0, 114.8, 114.3, 55.37, 55.36. IR ν_{max} (neat) 2944, 2839, 1642, 1588, 1508, 1425, 848, 744 cm^{-1} . HRMS (EI) m/z : [M^+] calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_4$, 285.1001; found, 285.1006.

4.3.2 (E/Z)-4,4'-(1-Nitroethene-1,2-diyl)bis((benzyloxy)benzene) (16). Yellow solid. $R_f = 0.5$ (5% EtOAc /hexanes).

638 mg. Yield 75%. Mp 240–242 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 8.21 (s, 1H), 7.51–7.39 (m, 10H), 7.28 (d, $J = 8.8$ Hz, 2H), 7.12 (d, $J = 8.8$ Hz, 2H), 7.11 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.16 (s, 2H), 5.07 (s, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 160.9, 159.9, 147.5, 136.5, 136.2, 134.7, 133.2, 132.1, 129.8, 128.7, 128.3, 127.7, 127.5, 124.1, 123.3, 115.7, 115.4, 115.2, 70.2, 70.1. IR ν_{max} (neat) 2944, 2839, 1642, 1588, 1508, 1425, 848, 744 cm^{-1} . HRMS (EI) m/z : [M^+] calcd for $\text{C}_{28}\text{H}_{23}\text{NO}_4$, 437.1627; found, 437.1625.

4.4 General procedure for the synthesis of 7 and 17

To a stirred solution of 6 or 16 (1.75 mmol, 1.0 equiv.) and K_2CO_3 (5.26 mmol, 3.0 equiv.) in MeOH (10 mL) was added methyl isocyanoacetate (2.10 mmol, 1.2 equiv.) at room temperature. The yellow solution was stirred at that temperature for 12 h. The reaction mixture was diluted with water (30 mL), neutralized with HCl and extracted with ethyl acetate (3×5 mL). The solvent was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (10% EtOAc in hexanes) to give the title compound.

4.4.1 Methyl-3,4-bis(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (7). Brown solid. $R_f = 0.5$ (50% EtOAc /hexanes). 460 mg. Yield 76%. Mp 176–178 °C (lit. (ref. 15) 176–177 °C). ^1H NMR (CDCl_3 , 400 MHz): δ 9.20 (s, 1H), 7.21 (d, $J = 8.8$ Hz, 2H), 7.045 (d, $J = 8.8$ Hz, 2H), 7.051 (s, 1H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 161.7, 158.5, 158.0, 131.9, 129.5, 129.1, 127.1, 126.5, 120.2, 119.3, 113.7, 113.1, 55.18, 55.16, 51.3. IR ν_{max} (neat) 3424, 3277, 3042, 2949, 1705, 1466, 1299, 1244 cm^{-1} . HRMS (EI) m/z : [M^+] calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_4$, 337.1314; found, 337.1319.

4.4.2 Methyl-3,4-bis(4-(benzyloxy)phenyl)-1H-pyrrole-2-carboxylate (17). Brown solid. $R_f = 0.5$ (50% EtOAc /hexanes). 670 mg. Yield 78%. Mp 166–168 °C (lit. (ref. 19c) 166–168 °C). ^1H NMR (CDCl_3 , 400 MHz): δ 9.22 (s, 1H), 7.50–7.35 (m, 10H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.06 (d, $J = 8.4$ Hz, 2H), 7.05 (s, 1H), 6.96 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.10 (s, 2H), 5.04 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 161.5, 157.9, 157.3, 137.13, 137.08, 131.9, 129.5, 129.0, 128.6, 127.9, 127.7, 127.5, 127.3, 126.7, 126.5, 120.1, 119.4, 114.6, 114.0, 70.0, 51.3. IR ν_{max} (neat) 3310, 2999, 2948, 2836, 1715, 1646, 1254, 975 cm^{-1} . HRMS (EI) m/z : [M^+] calcd for $\text{C}_{32}\text{H}_{27}\text{NO}_4$, 489.1940; found, 489.1936.

4.5 Procedure for the synthesis of 8

To a suspension of 1-iodo-4-methoxybenzene (0.29 mmol, 1.1 equiv.) and powdered molecular sieves 4 Å in toluene (5.0 mL) was successively added 7 (0.27 mmol, 1.0 equiv.), ethylene diamine (0.026 mmol, 0.1 equiv.) and CuI (0.013 mmol, 0.05 equiv.) under N_2 at room temperature. The resulting mixture was then heated at 120 °C in an oil bath for 12 h. After cooled down to room temperature, the mixture was passed through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to give the title compound.

4.5.1 Methyl-1,3,4-tris(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (8). White solid. $R_f = 0.5$ (20% EtOAc /hexanes).



98 mg. Yield 76%. Mp 42–44 °C (lit. (ref. 17c) 42–44 °C). ^1H NMR (CDCl_3 , 400 MHz): δ 7.34 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.04 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.50 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 161.7, 158.9, 158.5, 158.0, 134.1, 131.8, 131.0, 129.4, 127.3, 127.1, 126.8, 126.5, 125.0, 121.3, 113.9, 113.7, 113.1, 55.5, 55.2, 50.9. IR ν_{max} (neat) 2948, 1708, 1644, 1514, 1256, 845 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{27}\text{H}_{25}\text{NO}_5$, 443.1733; found, 443.1729.

4.6 Procedure for the synthesis of lamellarin R (3)

To a stirred solution of **8** (0.23 mmol, 1.0 equiv.) in DCM (30 mL) was added BBr_3 (3.0 equiv. in 30 mL of DCM) at -78°C under N_2 atmosphere. The mixture was allowed to stir at 0°C in an ice bath for 12 h. After diluted with MeOH (5 mL), the solvent was removed under reduced pressure. The residue was dissolved in H_2O and extracted with EtOAc (2×30 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to give the title compound.

4.6.1 Methyl-1,3,4-tris(4-hydroxyphenyl)-1H-pyrrole-2-carboxylate (3). White solid. R_f = 0.5 (30% EtOAc/hexanes). 85 mg. Yield 92%. Mp 142–144 °C. ^1H NMR (acetone- d_6 , 400 MHz): δ 8.76 (s, 1H), 8.42 (s, 1H), 8.33 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.13 (s, 1H), 7.08 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 3.42 (s, 3H). ^{13}C NMR (acetone- d_6 , 100 MHz): δ 161.2, 156.8, 156.3, 155.8, 133.1, 131.8, 130.3, 129.3, 126.6, 126.2, 125.9, 125.7, 124.9, 121.5, 115.2, 114.9, 114.4, 50.0. IR ν_{max} (neat) 3364, 1694, 1624, 1442, 1133, 846 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{24}\text{H}_{19}\text{NO}_5$, 401.1263; found, 401.1269.

4.7 Procedure for the synthesis of lukianol A (9)

To a stirred solution of **12** (0.22 mmol, 1.0 equiv.) in DCM (30 mL) at -78°C was added BBr_3 (3.0 equiv. in 30 mL of DCM) over a period of 20 min. The solution was stirred at -78°C for 1 h and then at room temperature for 12 h. The solution was diluted with Et_2O (25 mL) and EtOAc (5 mL) and washed aqueous NaHCO_3 (5 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to give the title compound.

4.7.1 3,7,8-Tris(4-hydroxyphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (9). White solid. R_f = 0.5 (60% EtOAc/hexanes). 65 mg. Yield 72%. Mp 262–264 °C (lit. (ref. 10a) 264–266 °C). ^1H NMR (acetone- d_6 , 400 MHz): δ 9.89 (s, 1H), 9.47 (s, 1H), 9.43 (s, 1H), 8.08 (s, 1H), 7.60 (s, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.8 Hz, 2H). ^{13}C NMR (acetone- d_6 , 100 MHz): δ 158.9, 157.1, 156.8, 154.1, 141.3, 132.2, 129.9, 129.2, 127.8, 126.0, 124.4, 123.6, 121.7, 120.4, 116.3, 115.7, 115.1, 112.4, 103.5. IR ν_{max} (neat) 3412, 1696, 1618, 1422, 1268, 9983 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{25}\text{H}_{17}\text{NO}_5$, 411.1107; found, 411.1121.

4.8 General procedure for the synthesis of 10, 18 and 26

A mixture of **7**, **17** or **24** (0.74 mmol, 1.0 equiv.), anhydrous potassium carbonate (4.44 mmol, 6.0 equiv.) and 2-bromo-1-(4-methoxyphenyl)ethan-1-one (1.11 mmol, 1.5 equiv.) in DMF (10 mL) was heated at 70°C in oil bath for 4 h. After cooled to room temperature, the solvent was evaporated, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to give the title compound.

4.8.1 Methyl-3,4-bis(4-methoxyphenyl)-1-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (10). Yellow solid. R_f = 0.5 (50% EtOAc/hexanes). 250 mg. Yield 70%. Mp 68–70 °C (lit. (ref. 11) 68–72 °C). ^1H NMR (CDCl_3 , 400 MHz): δ 8.05 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.03–7.01 (m, 4H), 6.95 (s, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 5.76 (s, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 3.77 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 191.9, 164.0, 162.3, 158.3, 157.9, 131.9, 131.1, 130.3, 129.4, 128.2, 127.9, 127.2, 127.0, 124.7, 119.8, 114.1, 113.5, 112.9, 55.63, 55.55, 55.1, 50.8. IR ν_{max} (neat) 3008, 2938, 2844, 2041, 1722, 1688, 1568, 1172 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{29}\text{H}_{27}\text{NO}_6$, 485.1838; found, 485.1844.

4.8.2 Methyl-3,4-bis(4-(benzyloxy)phenyl)-1-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (18). Yellow solid. R_f = 0.5 (50% EtOAc/hexanes). 382 mg. Yield 81%. Mp 120–122 °C (lit.¹¹ 120–122 °C). ^1H NMR (CDCl_3 , 400 MHz): δ 8.06 (d, J = 8.8 Hz, 2H), 7.51–7.35 (m, 10H), 7.22 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.97–6.95 (m, 3H), 6.84 (d, J = 8.4 Hz, 2H), 5.74 (s, 2H), 5.10 (s, 2H), 5.02 (s, 2H), 3.91 (s, 3H), 3.50 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 191.8, 164.0, 162.3, 157.6, 157.2, 137.2, 137.1, 131.9, 131.1, 130.4, 129.4, 128.6, 128.2, 127.9, 127.7, 127.5, 127.3, 127.2, 124.6, 119.8, 114.5, 114.1, 113.9, 70.0, 55.6, 55.5, 50.8. IR ν_{max} (neat) 3028, 2931, 1716, 1678, 1608, 1544, 1248, 1072 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{41}\text{H}_{35}\text{NO}_6$, 637.2464; found, 637.2457.

4.8.3 Methyl-4-benzoyl-1-(2-(4-methoxyphenyl)-2-oxoethyl)-3,5-diphenyl-1H-pyrrole-2-carboxylate (26). Yellow solid. R_f = 0.5 (10% EtOAc/hexanes). 330 mg. Yield 84%. Mp 152–154 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 7.99 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.32 (d, J = 7.2 Hz, 4H), 7.25–7.10 (m, 9H), 6.98 (d, J = 8.8 Hz, 2H), 5.64 (s, 2H), 3.88 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 193.5, 192.1, 164.1, 162.2, 141.4, 138.5, 134.5, 133.6, 132.1, 130.5, 130.4, 130.3, 129.8, 129.6, 129.1, 128.4, 127.8, 127.6, 127.1, 126.8, 124.1, 119.5, 114.1, 55.6, 53.0, 51.0. IR ν_{max} (neat) 3022, 2913, 2837, 1729, 1689, 1665, 1629, 1519, 915 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{34}\text{H}_{27}\text{NO}_5$, 529.1889; found, 529.1891.

4.9 General procedure for the synthesis of 12 and 27

To a stirred solution of **10** or **26** (0.41 mmol, 1.0 equiv.) and LiOH (0.82 mmol, 2.0 equiv.) in 1 : 1 THF– H_2O (10 mL) was heated to 50°C in oil bath for 6 h. After cooled down to room temperature, the solution was concentrated *in vacuo*, the residue was diluted with 10% aqueous KOH (15 mL) and extracted with EtOAc (20 mL). The aqueous phase was acidified with 1 N HCl (pH = 1), extracted with CH_2Cl_2 , dried with Na_2SO_4 and concentrated under reduced pressure. The remaining residue was suspended in Ac_2O (20 mL) and was added NaOAc



(0.82 mmol, 2.0 equiv.). The resulting mixture was refluxed in oil bath for 1 h. The excess Ac_2O was removed by co-evaporation with toluene *in vacuo*. The crude product was taken up in Et_2O (50 mL) and washed with aqueous NaHCO_3 . The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to give the title compound.

4.9.1 3,7,8-Tris(4-methoxyphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (12). Brown solid. $R_f = 0.5$ (40% EtOAc/hexanes). 97 mg. Yield 52%. Mp 206–208 °C (lit. (ref. 12) 206–208 °C). ^1H NMR (CDCl_3 , 400 MHz): δ 7.69 (d, $J = 8.8$ Hz, 2H), 7.36 (s, 1H), 7.31 (d, $J = 8.8$ Hz, 2H), 7.24 (s, 1H), 7.11 (d, $J = 8.8$ Hz, 2H), 6.99 (d, $J = 8.8$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 160.5, 159.0, 158.6, 154.4, 142.0, 132.1, 129.8, 129.2, 128.2, 125.9, 124.7, 123.1, 119.0, 114.7, 114.3, 113.9, 113.4, 113.0, 102.7, 55.4, 55.22, 55.16. IR ν_{max} (neat) 3112, 3038, 2948, 1745, 1614, 1422, 1188 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{28}\text{H}_{23}\text{NO}_5$, 453.1576; found, 453.1582.

4.9.2 7-Benzoyl-3-(4-methoxyphenyl)-6,8-diphenyl-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (27). Brown solid. $R_f = 0.5$ (20% EtOAc/hexanes). 119 mg. Yield 58%. Mp 224–226 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 7.62–7.59 (m, 4H), 7.45–7.41 (m, 7H), 7.33 (s, 1H), 7.31 (t, $J = 7.2$ Hz, 1H), 7.22–7.19 (m, 3H), 7.16 (t, $J = 7.6$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 3.84 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 192.8, 160.8, 154.3, 143.1, 137.6, 133.9, 132.8, 131.4, 130.5, 130.3, 129.7, 129.0, 128.1, 128.0, 127.9, 127.7, 126.3, 126.2, 122.8, 114.3, 111.9, 100.2, 55.4. IR ν_{max} (neat) 3222, 3016, 2955, 1733, 1688, 1635, 1624, 1522, 976 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{33}\text{H}_{23}\text{NO}_4$, 497.1627; found, 497.1623.

4.10 Procedure for the synthesis of lamellarin O (13)

A mixture of **18** (0.078 mmol, 1.0 equiv.) and $\text{Pd}(\text{OH})_2/\text{C}$ (10 mol%) in MeOH was stirred under H_2 atmosphere at room temperature for 1 h. After that, the mixture was filtered through Celite and the solvent was evaporated under reduced pressure. The resulting crude residue was then purified by flash column chromatography (80% EtOAc in hexanes) to afford the desired product **13** as a colorless solid.

4.10.1 Methyl-3,4-bis(4-hydroxyphenyl)-1-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (13). White solid. $R_f = 0.5$ (50% EtOAc/hexanes). 32.5 mg. Yield 91%. Mp 258–260 °C (lit. (ref. 11) 258–260 °C). ^1H NMR (acetone- d_6 , 400 MHz): δ 8.35 (s, 1H), 8.27 (s, 1H), 8.09 (d, $J = 8.8$ Hz, 2H), 7.20 (s, 1H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.04 (d, $J = 8.8$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 6.79 (d, $J = 8.4$ Hz, 2H), 6.67 (d, $J = 8.4$ Hz, 2H), 5.91 (s, 2H), 3.93 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (acetone- d_6 , 100 MHz): δ 191.8, 164.0, 161.9, 156.1, 155.6, 131.8, 130.6, 130.1, 129.2, 128.3, 127.4, 127.1, 126.2, 124.2, 119.8, 114.9, 114.3, 114.0, 55.5, 55.1, 49.8. IR ν_{max} (neat) 3379, 3148, 3019, 2928, 2835, 1752, 1668, 1156 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{27}\text{H}_{23}\text{NO}_6$, 457.1525; found, 457.1529.

4.11 Procedure for the synthesis of 19

A mixture of **18** (0.078 mmol, 1.0 equiv.) and Pd/C (10 mol%) in MeOH was stirred under H_2 atmosphere at room temperature

for 1 h. After that, the mixture was filtered through Celite and the solvent was evaporated under reduced pressure. The resulting crude residue was purified by flash column chromatography (60% EtOAc in hexanes) to afford the desired product **19** as a colorless solid.

4.11.1 Methyl-3,4-bis(4-hydroxyphenyl)-1-(4-methoxyphenethyl)-1H-pyrrole-2-carboxylate (19). White solid. $R_f = 0.5$ (40% EtOAc/hexanes). 30.2 mg. Yield 87%. Mp 174–176 °C. ^1H NMR (acetone- d_6 , 400 MHz): δ 8.32 (s, 1H), 8.24 (s, 1H), 7.17 (d, $J = 8.4$ Hz, 2H), 7.03 (s, 1H), 7.00 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 4H), 6.78 (d, $J = 8.4$ Hz, 2H), 6.65 (d, $J = 8.8$ Hz, 2H), 4.54 (t, $J = 7.2$ Hz, 2H), 3.78 (s, 3H), 3.56 (s, 3H), 3.05 (t, $J = 7.2$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (acetone- d_6 , 100 MHz): δ 161.9, 158.5, 156.0, 155.6, 131.7, 130.7, 130.6, 129.9, 129.2, 127.3, 126.3, 126.2, 123.9, 119.1, 114.8, 114.2, 113.8, 54.6, 51.1, 49.9, 37.3. IR ν_{max} (neat) 3382, 3154, 3021, 2932, 2831, 1741, 1614, 1544, 1216 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{27}\text{H}_{25}\text{NO}_5$, 443.1733; found, 443.1729.

4.12 Procedure for the synthesis of 23

A mixture of chalcone **20** (0.48 mmol, 1.0 equiv.), amine **22** (1.2 equiv.) and aldehyde **21** (1.2 equiv.) in toluene was stirred at 90 °C in an oil bath for 12 h. After cooled to room temperature, the reaction was quenched with water (30 mL). The mixture was extracted with ethyl acetate (3×10 mL) and concentrated under reduced pressure to give the crude product **23** which was further purified by flash column chromatography (10% EtOAc in hexanes) to give the title compound.

4.12.1 Methyl-4-benzoyl-3,5-diphenylpyrrolidine-2-carboxylate (23). $R_f = 0.5$ (20% EtOAc/hexanes). 141 mg. Yield 76%. ^1H NMR (CDCl_3 , 400 MHz): δ 7.57–7.55 (m, 2H), 7.42–7.40 (m, 2H), 7.36 (t, $J = 7.6$ Hz, 2H), 7.28–7.25 (m, 4H), 7.15–7.09 (m, 5H), 5.02 (d, $J = 8.4$ Hz, 1H), 4.54 (t, $J = 7.6$ Hz, 1H), 4.22–4.13 (m, 2H), 3.77 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz): δ 198.7, 173.4, 140.8, 139.0, 137.5, 132.8, 128.8, 128.2, 128.13, 128.06, 127.7, 127.6, 127.4, 127.1, 67.7, 66.7, 60.6, 52.8, 52.3. IR ν_{max} (neat) 3029, 2988, 1721, 1675, 1600, 1344, 1160, 1098, 784 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_3$, 385.1678; found, 385.1672.

4.13 Procedure for the synthesis of 24

A mixture of **23** (0.52 mmol, 1.0 equiv.) and DDQ (3.0 equiv.) in toluene was refluxed in an oil bath for 2 h. After cooled down to room temperature, the resulting mixture was filtered through Celite and the solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (30% EtOAc in hexanes) to afford the desired product **24** as a colorless solid.

4.13.1 Methyl-4-benzoyl-3,5-diphenyl-1H-pyrrole-2-carboxylate (24). White solid. $R_f = 0.5$ (10% EtOAc/hexanes). 177 mg. Yield 89%. Mp 88–90 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 9.41 (s, 1H), 7.68–7.66 (m, 2H), 7.48–7.46 (m, 2H), 7.33–7.30 (m, 6H), 7.23–7.16 (m, 5H), 3.78 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 194.0, 161.8, 138.2, 137.02, 137.00, 133.2, 133.0, 132.6, 130.5, 130.3, 129.8, 128.7, 128.1, 127.9, 127.4, 127.3, 123.3, 118.7, 51.7. IR ν_{max} (neat) 3308, 2831, 1741, 1681, 1621, 1444, 854 cm^{-1} . HRMS (EI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{25}\text{H}_{19}\text{NO}_3$, 381.1365; found, 381.1362.



Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 R. J. Andersen, D. J. Faulkner, C. H. He, G. D. V. Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1985, **107**, 5492.
- 2 (a) N. Lindquist, W. Fenical, G. D. V. Duyne and J. Clardy, *J. Org. Chem.*, 1988, **53**, 4570; (b) A. R. Carroll, B. F. Bowden and J. C. Coll, *Aust. J. Chem.*, 1993, **46**, 489; (c) S. Urban, M. S. Butler and R. J. Capon, *Aust. J. Chem.*, 1994, **47**, 1919; (d) S. Urban, L. Hobbs, J. N. A. Hooper and R. J. Capon, *Aust. J. Chem.*, 1995, **48**, 1491; (e) S. Urban and R. J. Capon, *Aust. J. Chem.*, 1996, **49**, 711; (f) M. V. R. Reddy, D. J. Faulkner, Y. Venkateswarlu and M. R. Rao, *Tetrahedron*, 1997, **53**, 3457; (g) C. L. Cantrell, A. Groweiss, K. R. Gustafson and M. R. Boyd, *Nat. Prod. Lett.*, 1999, **14**, 39; (h) R. A. Davis, A. R. Carroll, G. K. Pierens and R. J. Quinn, *J. Nat. Prod.*, 1999, **62**, 419; (i) M. V. R. Reddy, M. R. Rao, D. Rhodes, M. S. T. Hansen, K. Rubins, F. D. Bushman, Y. Venkateswarlu and D. J. Faulkner, *J. Med. Chem.*, 1999, **42**, 1901; (j) J. Ham and H. Kang, *Bull. Korean Chem. Soc.*, 2002, **23**, 163; (k) P. Krishnaiah, V. L. N. Reddy, G. Venkataramana, K. Ravinder, M. Srinivasulu, T. V. Raju, K. Ravikumar, D. Chandrasekar, S. Ramakrishna and Y. Venkateswarlu, *J. Nat. Prod.*, 2004, **67**, 1168; (l) S. M. Reddy, M. Srinivasulu, N. Satyanarayana, A. K. Kondapi and Y. Venkateswarlu, *Tetrahedron*, 2005, **61**, 9242; (m) F. Plisson, X. C. Huang, H. Zhang, Z. Khalil and R. J. Capon, *Chem.-Asian J.*, 2012, **7**, 1616.
- 3 A. R. Quesada, M. D. G. Grávalos and J. L. F. Puentes, *Br. J. Cancer*, 1996, **74**, 677.
- 4 (a) M. Facompré, C. Tardy, C. Bal-Mahieu, P. Colson, C. Perez, I. Manzanares, C. Cuevas and C. Bailly, *Cancer Res.*, 2003, **63**, 7392; (b) E. Marco, W. Laine, C. Tardy, A. Lansiaux, M. Iwao, F. Ishibashi, C. Bailly and F. Gago, *J. Med. Chem.*, 2005, **48**, 3796.
- 5 (a) J. Kluza, M. A. Gallego, A. Loyens, J. C. Beauvillain, J. M. F. Sousa-Faro, C. Cuevas, P. Marchetti and C. Bailly, *Cancer Res.*, 2006, **66**, 3177; (b) C. Ballot, J. Kluza, S. Lancel, A. Martoriati, S. M. Hassoun, L. Mortier, J. C. Vienne, G. Briand, P. Formstecher, C. Bailly, R. Nevière and P. Marchetti, *Apoptosis*, 2010, **15**, 769.
- 6 K. Hasse, A. C. Willis and M. G. Banwell, *Eur. J. Org. Chem.*, 2011, 88.
- 7 (a) M. Iwao, T. Takeuchi, N. Fujikawa, T. Fukuda and F. Ishibashi, *Tetrahedron Lett.*, 2003, **44**, 4443; (b) N. Fujikawa, T. Ohta, T. Yamaguchi, T. Fukuda, F. Ishibashi and M. Iwao, *Tetrahedron*, 2006, **62**, 594; (c) M. Komatsubara, T. Umeki, T. Fukuda and M. Iwao, *J. Org. Chem.*, 2014, **79**, 529; (d) T. Fukuda, E. I. Sudo, K. Shimokawa and M. Iwao, *Tetrahedron*, 2008, **64**, 328.
- 8 J. H. Liu, Q. C. Yang, T. C. W. Mak and H. N. C. Wong, *J. Org. Chem.*, 2000, **65**, 3587.
- 9 D. Morikawa, K. Morii, Y. Yasuda, A. Mori and K. Okano, *J. Org. Chem.*, 2020, **85**, 8603.
- 10 (a) D. L. Boger, C. W. Boyce, M. A. Labroli, C. A. Schon and Q. Jin, *J. Am. Chem. Soc.*, 1999, **121**, 54; (b) D. L. Boger, D. R. Soenen, C. W. Boyce, M. P. Hedrick and Q. Jin, *J. Org. Chem.*, 2000, **65**, 2479.
- 11 A. Ramirez-Rodriguez, J. M. Mendez, C. C. Jimenez, F. Leon and A. Vazquez, *Synthesis*, 2012, **44**, 3321.
- 12 A. Fuerstner, H. Weintritt and A. Hupperts, *J. Org. Chem.*, 1995, **60**, 6637.
- 13 Q. Li, J. Jiang, A. Fan, Y. Cui and Y. Jia, *Org. Lett.*, 2011, **13**, 312.
- 14 J. R. Hwu, A. Roy, A. Panja, W. C. Huang, Y. C. Hu, K. T. Tan, C. C. Lin, K. C. Hwang, M. H. Hsu and S. C. Tsay, *J. Org. Chem.*, 2020, **85**, 9835.
- 15 K. Takamura, H. Matsuo, A. Tanaka, J. Tanaka, T. Fukuda, F. Ishibashi and M. Iwao, *Tetrahedron*, 2013, **69**, 2782.
- 16 (a) K. B. Manjappa, J. R. Syu and D. Y. Yang, *Org. Lett.*, 2016, **18**, 332; (b) K. B. Manjappa, J. M. Lin and D. Y. Yang, *J. Org. Chem.*, 2017, **82**, 7648; (c) S. Vyasamudri and D. Y. Yang, *J. Org. Chem.*, 2019, **84**, 3662.
- 17 E. A. Silyanova, A. V. Samet, L. K. Salamandra, V. N. Khrustalev and V. V. Semenov, *Eur. J. Org. Chem.*, 2020, 2093.
- 18 (a) D. H. R. Barton and S. Z. A. Zard, *J. Chem. Soc., Chem. Commun.*, 1985, 1098; (b) D. H. R. Barton, J. Kervagoret and S. Z. A. Zard, *Tetrahedron*, 1990, **46**, 7587; (c) G. W. Gribble, *Names Reactions in Heterocyclic Chemistry*, 2005, p. 70; (d) N. Ono, *Heterocycles*, 2008, **75**, 243; (e) S. C. Zheng, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2019, **58**, 9215.
- 19 (a) A. S. Guram, R. A. Rennels and S. L. A. Buchwald, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1348; (b) J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, 1995, **36**, 3609; (c) H. Zavala-Gómez, A. Ramírez-Rodríguez and A. Vázquez, *J. Chem. Res.*, 2017, **41**, 677; (d) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400.
- 20 (a) S. K. Ray, R. G. Biswas, A. Suneja, M. M. Sadhu and V. K. Singh, *J. Org. Chem.*, 2018, **83**, 2293; (b) Z. Zhu, H. S. Chandak and D. Seidel, *Org. Lett.*, 2018, **20**, 4090; (c) L. Zhu, X. Ren, Z. Liao, J. Pan, C. Jiang and T. Wang, *Org. Lett.*, 2019, **21**, 8667.
- 21 J. C. Antilla, J. M. Baskin, T. E. Barder and S. L. Buchwald, *J. Org. Chem.*, 2004, **69**, 5578.
- 22 L. V. Romashov, Y. A. Khomutova, V. M. Danilenko, S. L. Ioffe and A. V. Lesiv, *Synthesis*, 2010, 407.
- 23 J. G. Greger, S. J. P. Yoon-Miller, N. R. Bechtold, S. A. Flewelling, J. P. MacDonald, C. R. Downer, E. A. Cohen and E. T. Pelkey, *J. Org. Chem.*, 2011, **76**, 8203.

