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Total Synthesis of Pseudellone C

P. Pon Sathieshkumar, Penchala Latha, Rajagopal Nagarajan*[a]

Abstract: The first chemical synthesis of a bisindole alkaloid, Pseudellone C, has been achieved in 44% overall yield. The highlighting features of the synthesis include protection free, economic, commercially available starting materials and single purification on gram scale synthesis. The key step involved in this synthesis is a formation of an amide bond between two major cores of the natural product.

Introduction

Marine organisms are rich sources of many alkaloids including bisindole alkaloids. Bisindole alkaloids have known to show potential applications in medicinal chemistry owing to their antifouling activity, antimicrobial activity, and cytotoxicity against specific cancer cell lines.[1] Pseudellone C (**1**) is a new bisindole alkaloid with a fascinating carbon framework connection. Lan group isolated this alkaloid from marine-derived fungus *Pseudallescheria ellipsoidea* in 2015 along with two other epipolythiopiperazines alkaloids.[2a] In 2016, Wang group isolated three more new alkaloids including pseudellone D from same the fungus *Pseudallescheria ellipsoidea*.[2b]

In order to study and explore biological survey of Pseudellone C (**1**), there arises a need for its synthesis because of its low abundance (i.e., 0.8 mg isolated from natural source). However, no chemical synthesis has been reported for Pseudellone C (**1**) till date. While considering the above mentioned facts, as a part of our on-going research on the total synthesis of indole alkaloids,[3] we devoted our attention towards the total synthesis of Pseudellone C (**1**). Herein we exhibit an efficient route for the total synthesis of Pseudellone C (**1**).

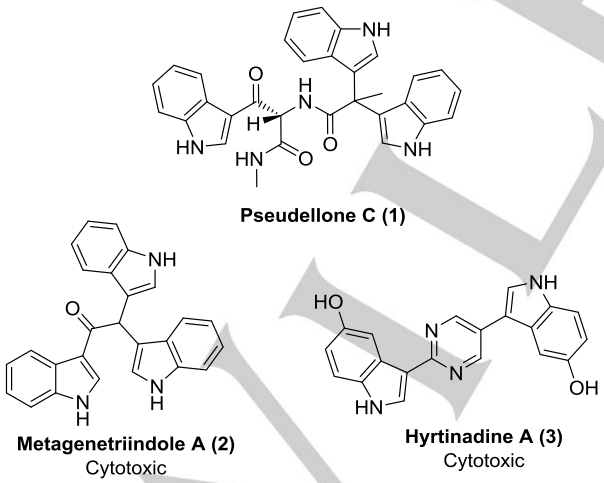

Figure 1. Related examples of marine bisindole alkaloids

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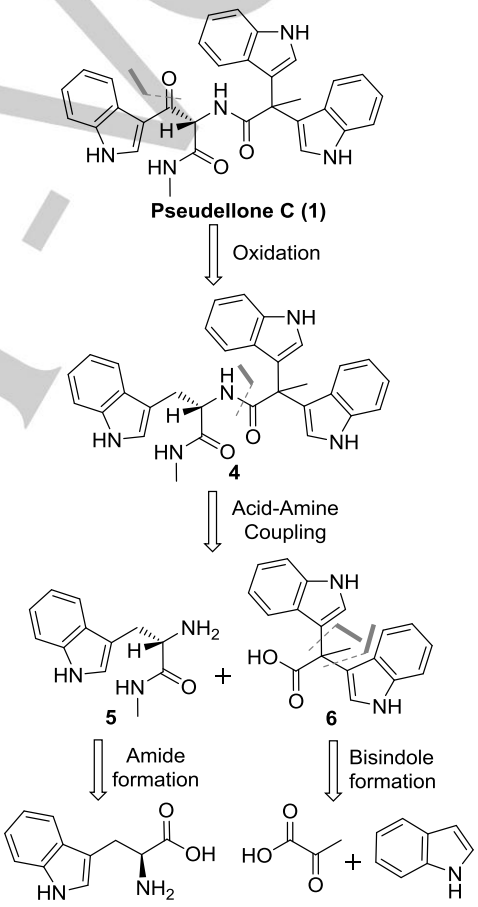
Results and Discussion

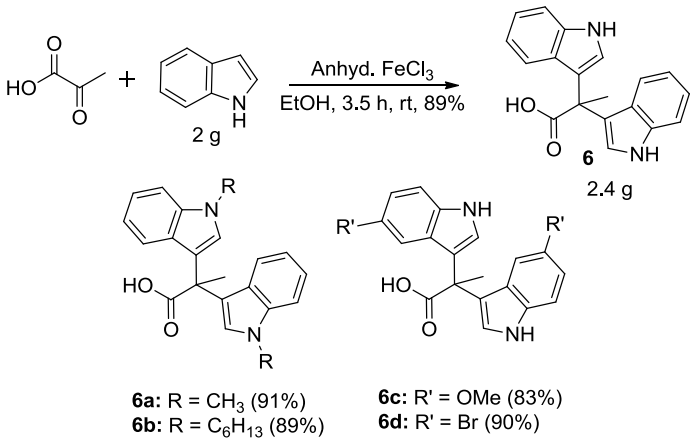
The retrosynthetic approach followed is depicted in **Scheme 1**. As can be seen from the retrosynthetic scheme, Pseudellone C (**1**) could be obtained from **4** by the oxidation of methylenic carbon on the tryptophan moiety of **4**. Compound **4** could, in turn be obtained by the formation of the amide connection between the two fragments **5** and **6**. The compound **5** could be derived from tryptophan and compound **6**, itself a natural product, could be generated from pyruvic acid and indole.



Scheme 1. Retrosynthetic appraoch for Pseudellone C (**1**)

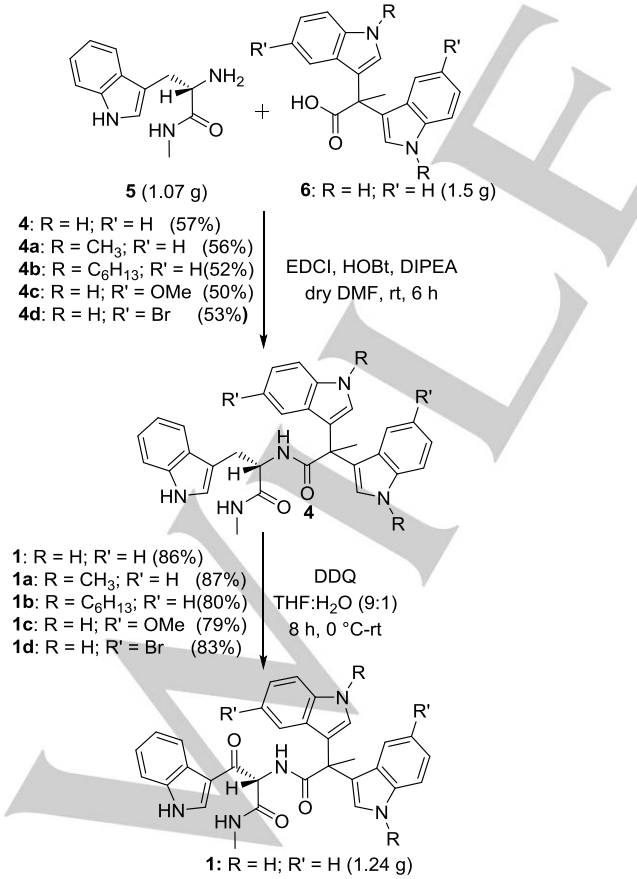
The synthesis of Pseudellone C (**1**) commenced with the preparation of 2, 2-disubstituted propanoic acid **6**. Garbe and co-workers have reported the isolation as well as the synthesis of **6**.[4] However, they have used excess of pyruvic acid in their synthesis. Moreover, attempting to synthesis its analogues using the same method leads to poor yields (<25%). Chakrabarty and co-workers have also reported the synthesis of **6** from pyruvic acid and indole.[5] Though their method requires montmorillonite K10 clay and the yield was 67%. As these reported procedures have above mentioned limitations such as the use of excess pyruvic acid and low yields, a new method has been devised to overcome these problems. The Lewis acid catalyzed synthesis

of **6** was investigated using different Lewis acid (such as $CeCl_3$, anhydrous $FeCl_3$, $Sc(OTf)_3$ and $Cu(OTf)_2$) catalysed bisindole formation in different solvent systems (acetonitrile, ethanol, DMSO and THF). The condition involving anhydrous $FeCl_3$ (20 mol%)/ ethanol/ rt was screened and gave good yields of **6** (89%) and its analogues (**6a-6d**, 83-91%) in 3.5 h. The amine **5** was prepared from commercially available tryptophan in two steps by adopting the procedure provided in the literature.[7] The yield was 84% without involving any column purifications.



Scheme 2. Synthesis of **6** and its analogues

Once the required amine **5** and acid **6** were synthesized, the next stage was the synthesis of **4** by the acid amine coupling reaction. Initially, *N,N'*-carbonylimidazole (CDI) mediated coupling was attempted for the synthesis of **4** but the coupling was unsuccessful.



Scheme 3. Synthesis of Pseudellone C (**1**) and its analogues

Then, acid-amine coupling with different reagents, additive[8-11] viz. *N,N'*-dicyclohexylcarbodiimide (DCC), *N,N'*-diisopropyl carbodiimide, (DIC), 1-ethyl-3-(3-dimethylamino propyl) carbodiimide, and bases (triethylamine, *N,N*-diisopropyl ethylamine, 4-dimetylaminopyridine, 1-hydroxybenzotriazole) in various solvent systems (DCM, THF, DMF) were screened. The results of the coupling experiments revealed that coupling with EDCI/HOBt[12], *N,N*-diisopropylethylamine as a base in DMF solvent was the best condition for this acid-amine coupling which provided 57% yield of coupled product **4.** This optimized condition was further used to synthesize analogues of **4**, (**4a-d**). Then, remaining step to complete the total synthesis is oxidation of the methylenic carbon on the tryptophane core of amide **4**. The oxidation of **4** underwent chemoselectively at the methylenic carbon with DDQ in THF-water (9:1) solvent system[13, 14] and the clean reaction furnished Pseudellone C (**1**) in good yield (86%). The spectroscopic data of synthesized Pseudellone C was in good agreement with isolated compound.[2a] Following the same condition, its analogues (**1a-d**) were synthesized from **4a-d**. Once accomplished the total synthesis, we were interested in gram scale synthesis to explore its industrial application. The gram scale synthesis was performed and Pseudellone C was obtained in 1.24 g (44% overall yield) by a single column chromatographic separation.

Conclusions

In summary, we have successfully achieved the first total synthesis of Pseudellone C (**1**) in 44% overall yield from cheap, commercially available and easily accessible starting materials without using any protecting group. Gram scale synthesis of **1** was also demonstrated with a single column chromatographic separation. We have shown that the strategy is also efficient to synthesize its analogues.

Experimental Section

General information: Acetone-d_6, DMSO-d_6 and $CDCl_3$ were used as the solvent to record ^1H and ^{13}C spectra and 400 MHz or 500 MHz Bruker NMR analyzers were used to record NMR. Chemical shift values were assigned with either with relative to NMR solvent residual peaks or with respect to TMS peak and the splitting patterns were presented as: s: singlet, d:doublet, br d: broad doublet, t: triplet, td: triplet of doublet, m: multiplet. HRMS were obtained from TOF and quadrupole mass analyzer types. Melting points were recorded in open tube and uncorrected. All the chemicals purchased were used as such. IR measurements were recorded in FT-IR using KBr pellet or neat methods. Specific rotations were measured in AUTOPOL IV polarimeter. Purifications of compounds were performed in 100-200 mesh silica column chromatography.

Synthesis of **6**: To a solution of indole (117 mg, 1 mmol) in ethanol (2 mL), pyruvic acid (44 mg, 0.5 mmol, 0.5 eq) was added in drops. After 3 minutes of stirring, anhydrous $FeCl_3$ (33 mg, 0.2 mmol, 20 mol%) was added pinch by pinch over a minute. The reaction mixture was allowed to stir for 3.5 h at room temperature. After completion of the reaction, the reaction mixture was quenched with water (5 mL). Then, 3 mL of 2 N NaOH was added, stirred for a minute and extracted with chloroform (20 mL × 2) to remove nonpolar impurities. Then, the aqueous layer was neutralized with 20% HCl and extracted with ethyl acetate (20 mL × 2). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated under vacuum to obtain red color floppy solid. The product (**6**) was isolated using flash column (ethyl acetate:chloroform (3:7)) in 89% (135 mg) of yield. The same synthesis was carried out on gram scale with same mole ratios of indole (2 g, 17.1

mmol, 1 eq), pyruvic acid (0.75 g, 8.54 mmol, 0.5 eq) and anhydrous $FeCl_3$ (0.553 g, 1.71 mmol, 20 mol%). After the workup as above and evaporation produced 2.4 g of **6** (almost single in TLC and used directly without further purification for the synthesis of **1** on the gram scale). Red solid; m.p. = 90 °C; R_f = 0.36 (100% ethyl acetate); IR (KBr): ν_{max} (cm^{-1}) 3456, 3043, 2981, 2840,1678; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H), 10.87 (d, *J* = 1.8 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H) 7.31 (d, *J* = 8.1 Hz, 2H), 7.04-6.98 (m, 4H), 6.82 (t, *J* = 7.8 Hz, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.7, 137.2, 126.4, 123.5, 121.2, 121.0, 118.6, 118.4, 111.9, 45.9, 26.5; HRMS (ESI) calcd for $C_{19}H_{16}N_2O_2Na$ $[M+Na]^+$ 327.1104, found: 327.1104.

Synthesis of **4**: To a solution of amine **5** (66 mg, 0.3 mmol, 1 eq) in dry DMF, HOBt (45 mg, 0.33 mmol, 1.1 eq) was added followed by bisindolyl propanoic acid **6** (92 mg, 0.3 mmol, 1 eq), EDCI (66 mg, 0.43 mmol, 1.4) and diisopropyl ethyl amine (98 mg or 0.13 mL, 0.76 mmol, 2.5 eq). The reaction mixture was stirred for 6 h at room temperature. After completion of the reaction, the reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with 5% HCl (10 mL × 2) followed by saturated sodium bicarbonate solution (15 mL). Then, the organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to obtain dark brown solid which was further purified by column chromatography (ethyl acetate-chloroform (1:1)) to afford 86 mg (57%) of **4**. The analogues of **4** were synthesized using the same procedure and mole ratio. Off white solid; m.p. = 178 °C; R_f = 0.32 (80% ethyl acetate in chloroform); $[\alpha]_D^{30}$ = -10 (*c* = 0.2); IR (KBr): ν_{max} (cm^{-1}) 3428, 3381, 3245, 2958, 1669, 1541; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.90 (br d, *J* = 1.8, 1H), 10.85 (br d, *J* = 1.75 Hz, 1H), 10.65 (br s, 1H), 7.56 (q, *J* = 4.6 Hz 1H), 7.36 -7.33 (m, 3H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.10 (t, *J* = 8.2 Hz, 2H), 7.1 (d, *J* = 2.45 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 7.00 (q, *J* = 5.7 Hz, 2H), 6.91 (t, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 2.45 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.72 (dt, *J* = 7.7 , 2.9 Hz, 2H), 6.5 (d, *J* = 2.1 Hz, 1H), 4.5 (q, *J* = 7.4 Hz, 1H), 2.88 (d, *J* = 6.5 Hz, 2H), 2.40 (d, *J* = 4.5 Hz, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.5, 171.1, 136.7, 136.66, 135.9, 127.0, 125.5, 125.4, 123.6, 123.4, 123.1, 120.6, 120.5, 120.4, 120.3, 120.1, 118.1, 118.08, 118.0, 117.98, 117.89, 117.86, 111.4, 111.3, 111.0, 109.1, 53.2, 46.2, 27.9, 25.5, 25.2; HRMS (ESI): calcd for $C_{31}H_{29}N_5O_2Na$ $[M+Na]^+$ 526.2213, found: 526.2208.

Synthesis of **Pseudellone C** (**1**): To a solution of amide **4** (52 mg, 0.1 mmol, 1 eq) in 10 mL of THF-water (9:1) mixture, DDQ (57 mg, 0.25 mmol, 2.5 eq) was added in three portions at 0 °C and then stirred in room temperature for 8 h. After completion of the reaction, the solvent was evaporated then ethyl acetate (30 mL) was added, and the organic layer was washed with saturated sodium bicarbonate solution (20 mL × 3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to obtain brown solid which on purification by column chromatography (ethyl acetate-chloroform (3:2)) provided 45 mg (86%) of Pseudellone C (**1**). Off white solid; m.p. = 220 °C; R_f = 0.28 (80% ethyl acetate in chloroform); $[\alpha]_D^{30}$ = -14 (*c* = 0.25) **IR** (KBr): ν_{max} (cm^{-1}) 3455, 3422, 3289, 1658, 1612, 1519; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.24 (s, 1H), 10.33 (s, 1H), 10.28, (s, 1H), 8.56 (d, *J* = 2.9 Hz, 1H), 8.23 (dt, *J* = 7.3, 0.6 Hz, 1H), 7.73 (d, *J* = 6.0 Hz, 1H), 7.57-7.55 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.49-7.47 (m, 2H), 7.36 (d, *J* = 2.5 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.28 (td, *J* = 7.6, 0.9 Hz, 1H), 7.24 (td *J* = 7.3, 0.7 Hz, 1H), 7.15 (td, *J* = 8.36, 1.1 Hz, 1H), 7.10 (td, *J* = 8.10, 0.8 Hz, 1H), 7.00 (td, *J* = 8.1, 0.9 Hz, 1H), 6.90 (td, *J* = 7.9, 0.9 Hz, 1H), 6.64 (d, *J* = 4.4 Hz, 1H), 5.83 (d, *J* = 6.1 Hz, 1H), 2.53 (d, *J* = 4.8 Hz, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.1, 175.9, 168.3, 138.6, 138.5, 137.8, 137.0, 127.1, 127.06, 127.0, 125.2, 124.7, 124.3, 123.2, 122.7, 122.3, 122.2, 121.7, 121.5, 119.73, 119.72, 119.66, 119.62, 115.2, 113.1, 112.9, 112.7, 62.5, 48.2, 26.4, 26.36; HRMS (ESI): calcd for $C_{31}H_{27}N_5O_3Na$ $[M+Na]^+$ 540.2006, found: 540.2013.

Gram scale Synthesis of **Pseudellone C** (**1**): To a solution of amine **5** (1.07 g, 4.93 mmol, 1 eq) in dry DMF, HOBt (0.732 g, 5.42 mmol, 1.1 eq) was added followed by bisindolyl propanoic acid **6** (1.5 g, 4.93 mmol, 1 eq), EDCI (1.07 g, 6.9 mmol, 1.4 eq) and diisopropyl ethyl amine (1.59 g or 2.2 mL, 12.32 mmol, 2.5 eq). The reaction mixture was stirred for 6 h at room temperature and quenched with water (25 mL) then extracted with ethyl acetate (50 mL × 3). The combined organic layer was washed with 5% HCl (20 mL × 2) and saturated sodium bicarbonate solution (30 mL × 2). Then, the organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to obtain dark brown solid. The brown solid was dissolved in 300 mL of THF-water (9:1) mixture, DDQ (2.8 g, 12.34 mmol, 2.5 eq) was added in portions over 2 minutes at 0 °C and then stirred in room temperature for 8 h. After completion of the reaction, same workup procedure and separation of the product was followed as in the synthesis of **1** to obtain 1.24 g (44%) of **Pseudellone C** (**1**).

Acknowledgements

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Keywords: Bisindole alkaloid • Pseudellone C • Total synthesis

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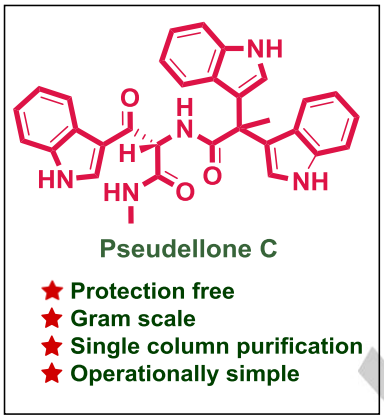
Protection free total synthesis of Pseudellone C was achieved for the first time on gram scale with overall yield of 44% from economic and commercially available starting materials.



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Page No. – Page No.

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