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5,6-Dihydropyrrolo[2,1-*b*]isoquinolines as scaffolds for synthesis of lamellarin analogues

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Abstract—Efficient modular synthetic routes to open chain marine alkaloids such as lamellarins have been developed. 5,6-Dihydropyrrolo[2,1-*b*]isoquinoline scaffolds were prepared, and protocols enabling regioselective bromination followed by Suzuki cross-coupling were established for the introduction of aryl groups onto the 2- and 3-positions.

In the past decade we have witnessed a renaissance in the research of marine natural products. Several new compounds derived from natural products of the sea are now in the clinical pipeline.[1] Although, preliminary and preclinical research is usually carried out with compounds obtained directly by isolation from marine sources, late clinical phases require an efficient synthetic route. Accordingly, there is an increased need for the development of synthetic strategies for preparation of these kinds of important natural products.

Pyrrole is the core skeleton of a large number of marine alkaloids such as ningalins,[2] lukianols,[3] polycitones,[4] purpurone,[5] and lamellarins.[6] A common feature for all of these alkaloids is that the pyrrole ring contains substituted aromatic rings on positions 3 and 4. Among the more simple compounds are the tetrasubstituted pyrroles (e.g., lamellarins O and P) or the symmetrically pentasubstituted pyrroles (e.g., polycitons A and B). More complex structures contain a pyrrole ring condensed to one or two oxazinone rings as observed for lukianol A and ningalin A, respectively.

The pentacyclic lamellarins can be considered as even more complex compounds, because the pyrrole is condensed to a benzooxazinone and to a substituted dihydroisoquinoline or isoquinoline (Lamellarin D, Fig. 1). More than 30 natural lamellarins have been isolated from natural marine sources.[7] Natural as well as synthetic lamellarins should be excellent candidates for the development of new drugs due to their unique skeletal structure and their important biological activities especially as antitumor agents.[7,8]

As part of our synthetic studies concerning lamellarins,[9] we here report a concise and efficient route to scaffolds **1a** and **b**, and their roles as synthetic precursors for open chain analogues of lamellarins (Fig. 1). Scaffolds **1a**–**b** were obtained by *N*-alkylation of the pyrrole with a 2 phenylethyl *p*-toluenesulfonate derivative, followed by cyclization through a Heck reaction. Regioselective bromination of **1a**–**b** followed by Suzuki cross-coupling renders the open chain lamellarin analogues.

The initial synthetic target was the model molecule **1a** ($R^1 = R^2 = H$), which was obtained in two steps from methyl pyrrole-2-carboxylate.[10] *N*-Alkylation with the *p*-toluenesulfonate[11] **3a** in the presence of K_2CO_3 and 18-crown-6 ether in DMF at 70 °C afforded **2a** (50% yield).[12] The conditions described for *N*-alkylation of pyrrole in polycitone B[13] were unsuccessful for the methyl pyrrole-2-carboxylate.

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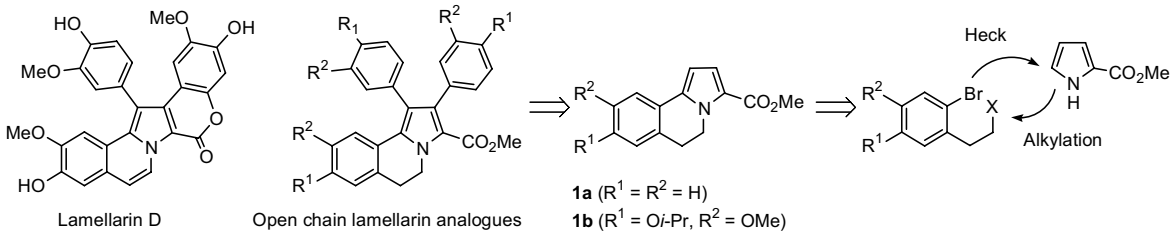


Figure 1. Structure of lamellarin D and retrosynthetic overview of the preparation of open chain lamellarin analogues.

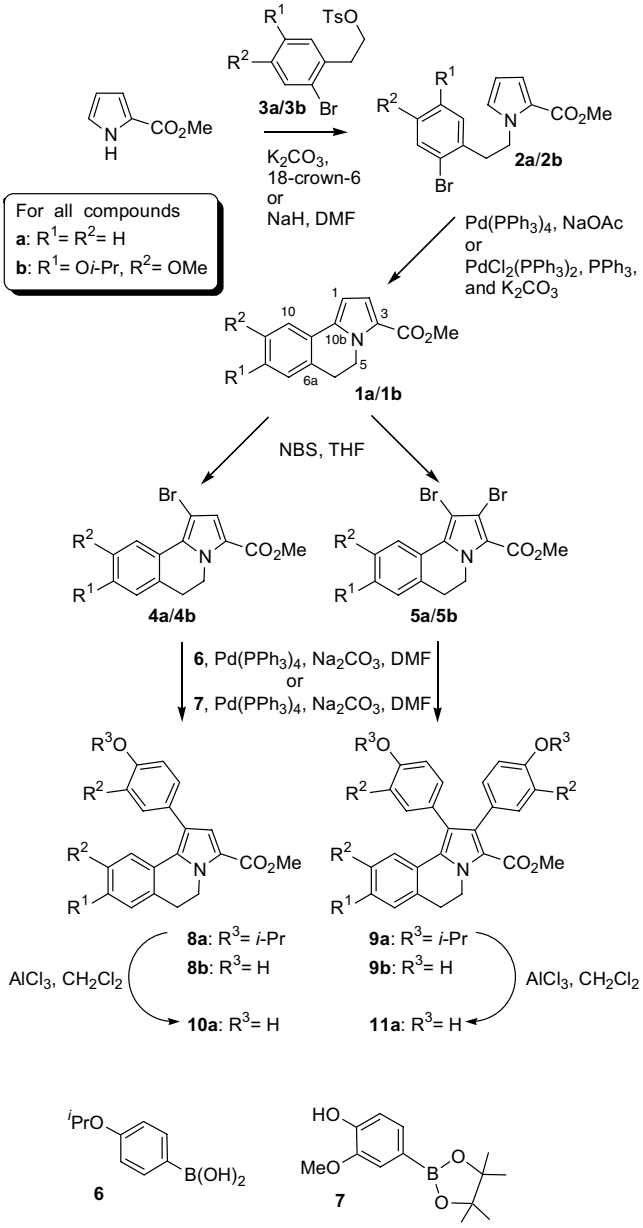
An intramolecular Heck reaction[14] of **2a** using $Pd(PPh_3)_4$ and NaOAc in DMF at 125 °C afforded the pyrroloisoquinoline **1a** in 95% yield.[15] Bromination of **1a** with NBS in dry THF occurred exclusively on the more reactive pyrrole part. By modulating the excess of NBS, the monobromoderivative **4a** or the dibromo-compound **5a** could be obtained. The methoxycarbonyl group in the 3-position of **1a** induces the regioselective bromination at position 1 giving **4a** in excellent yield (94%) when 2 equiv of NBS is used. Increase of the reaction time (from 3 to 8 h) and the amount of NBS (2.5 equiv) afforded the dibromoderivative **5a** in high yield (92%). The bromide **4a** gives access to novel derivatives of lamellarins, containing just one aryl group situated in the 1-position of the tricyclic system. Such compounds **8a**–**b** and **10** are related with the structure of natural compounds with important biological activities (e.g., variolins).[16]

The bromides **4a** and **5a** were subjected to Suzuki cross-coupling with the *p*-isopropoxyphenyl boronic acid (**6**) using $Pd(PPh_3)_4$ as catalyst in aqueous Na_2CO_3 and DMF,[17] to give the mono- and diaryl compounds **8a**[18] and **9a**,[19] respectively, in good yields.

Subsequent removal of the isopropyl protecting groups with $AlCl_3$ in CH_2Cl_2[20] afforded compounds **10a**[21] and **11a**[22] (Scheme 1).

Scaffold **1b** was synthesized in order to target open chain compounds with a substitution pattern resembling lamellarin D, which is a highly potent cytotoxic agent in numerous multi drug resistant (MDR) cell lines.[8] Preparation of **1b** was achieved from methyl pyrrole-2-carboxylate by *N*-alkylation to give **2b** followed by intramolecular Heck cyclization as also described above for **1a**. The *N*-alkylation using 2-(2-bromo-5-isopropoxy-4-methoxyphenyl)ethyl *p*-toluenesulfonate (**3b**)[23] was performed in dry DMF with NaH as base (77% yield). The presence of two alkoxy groups in the phenyl ring of **3b** presumably causes lower acidity of the benzylic protons as compared to **3a**, thus decreasing the competitive elimination process in favor of the *N*-alkylation.

The 2-(2-bromo-5-isopropoxy-4-methoxyphenyl)ethanol needed for the preparation of **3b** was obtained from the previously described 2-bromo-5-isopropoxy-4-methoxybenzaldehyde.[24] This aldehyde was converted into the substituted styrene by Wittig reaction,[25] and subsequent addition of borane–dimethylsulfide and H_2O_2[26] afforded the corresponding 2-phenethylalcohol.



Scheme 1. Synthetic sequences.

Scaffold **1b** was obtained in excellent yield (81%) from **2b** using $Pd(PPh_3)_2Cl_2$ and Ph_3P as catalyst in dry DMF with K_2CO_3 added as base. The two-step assembly of this dihydroisoquinoline moiety (62% yield) is relatively similar to that of an intermediate of lamellarin G trimethylether very recently published.[27] However,

the latter mentioned required Suzuki cross-coupling, tosylation, and finally intramolecular alkylation, which proceded less efficiently with an overall yield of 33%.

Mono- and dibromination of **1b** to give **4b** and **5b**, respectively, proceeded in good yields as described for **4a/5a** above. The subsequent Suzuki cross-coupling reactions with the commercially available 3-hydroxy-4-methoxyphenyl boronic ester (**7**) furnished the mono- and diaryl lamellarin D-type open chain compounds **8b**[28](78%) and **9b**[29] (80%), respectively.

Preliminary testing of **8b**, **9b**, **10a**, and **11a** in various tumor cell lines showed cytotoxic effects in the low micromolar area, **9b** being the most potent of the four.

In summary, efficient preparation of scaffolds suitable for the synthesis of open chain lamellarin analogues has been established. A key aspect of these reactions is the regioselective bromination of the pyrrole scaffold, which can be modulated to give mono- and dibromo derivatives, this in turn affords the mono- and the diaryl lamellarin derivatives. The methodologies presented herein constitute a concise route to open chain lamellarin-type compounds with attractive biological activities. The positive pharmacological results encourage the preparation of libraries based on these open structures for SAR studies. This work is in progress and will be communicated in due course.

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15. **1a** was totally characterized with the aid of NOE and HMBC experiments. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, J = 7.4 Hz, 1H, H10); 7.24 (m, 3H, H7, H8, H9); 7.01 (d, J = 4.2 Hz, 1H, H2); 6.53 (d, J = 4.2 Hz, 1H, H1); 4.63 (t, J = 6.6 Hz, 2H, H5); 3.83 (s, 3H, OMe); 3.07 (t, J = 6.6 Hz, 2H, H6). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0 (s, CO); 136.4 (s, C3); 131.9 (s, C10b); 128.6 (s, C10a); 128.6 (d, C10); 128.1 (d, C8); 127.7 (d, C9); 123.9 (d, C7); 122.0 (s, C6a); 118.6 (d, C2); 104.7 (d, C1); 51.3 (q, OMe); 42.4 (t, C5); 29.1 (t, C6).
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17. General procedure: To a solution of **4** (1 equiv) in dry DMF (25 mL) was added 4-isopropoxy phenyl boronic acid **6** (1.5 equiv), $Pd(PPh_3)_4$ (25%), and 2 M aqueous Na_2CO_3 (1.63 mL). The reaction mixture was stirred at 125 °C for 24 h. After this time the solvent was evaporated and the residue was dissolved in CH_2Cl_2. The organic solution was washed with brine and water, dried and concentrated to give a crude material which was purified by column chromatography on silica gel.
18. The position of the introduced aryl group as well as the regioselectivity in the formation of monobromoderivative

3a was confirmed with NOE experiments. Irradiation on the H2 (δ 6.96 ppm) enhances the intensity of the methyl singlet at 3.83 ppm. **8a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (m, 3H, H10, H2′, H6′); 7.22 (m, 1H, H8); 7.12 (td, J = 7.4 and 1.2 Hz, 1H, H9); 7.00 (td, J = 7.8 and 1.2 Hz, 1H, H7); 6.96 (s, 1H, H2); 6.88 (d, J = 8.5 Hz, 2H, H3′, H5′); 4.61 (t, J = 6.6 Hz, 2H, H5); 4.57 (m, 1H, OCH); 3.83 (s, 3H, OMe); 3.10 (t, J = 6.6 Hz, 2H, H6); 1.37 (d, J = 5.8 Hz, 6H, Me).

19. Compound **9a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, J = 7.4 Hz, 1H, H10); 7.12 (td, J = 7.4 and 1.2 Hz, 1H, H8); 7.01 (td, J = 7.4, 1.2 Hz, H9); 6.96 (d, J = 8.9 Hz, 4H, H2′, H2″, H6′, H6″); 6.94 (td, J = 7.4 and 1.2 Hz, H7); 6.72 (d, J = 8.9 Hz, 4H, H3′, H3″, H5′, H5″); 4.61 (t, J = 6.6 Hz, 2H, H5); 4.50 (q, J = 6.0 Hz, 2H, OCH); 3.59 (s, 3H, OMe); 3.10 (t, J = 6.6 Hz, 2H, H6); 1.31 (d, J = 6.0 Hz, 6H, Me); 1.30 (d, J = 6.0 Hz, 6H, Me).
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22. Compound **11a**: ^{1}H NMR (Acetone-d_6, 400 MHz) δ 8.31 (s, 1H, OH); 8. 15 (s, 1H, OH); 7.28 (d, J = 7.4 and 1.2 Hz, 1H, H10); 7.13 (td, J = 7.4 and 1.2 Hz, 1H, H8); 6.97 (td, J = 7.4 and 1.2 Hz, 1H, H9); 6.91 (m, 5H, H2′, H2″, H6′, H6″, H7); 6.70 (dd, J = 8.6 Hz, 2H, H3′, H5′); 6.65 (d, J = 8.6 Hz, 2H, H3″, H5″); 4.57 (t, J = 6.6 Hz, 2H, H5); 3.54 (s, 3H, OMe); 3.11 (t, J = 6.6 Hz, 2H, H6).
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28. Compound **8b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (s, 1H, H10); 6.96 (dd, J = 8.0 and 2.0 Hz, 1H, H6′); 6.94 (d, J = 2.0 Hz, 1H, H2′); 6.92 (d, J = 8.0 Hz, 1H, H5′); 6.89 (s, 1H, H7); 6.74 (s, 1H, H2); 5.62 (br s, 1H, OH); 4.60 (t, J = 6.4 Hz, 2H, H5); 4.53 (heptet, J = 6.0 Hz, 1H, OCH); 3.84 (s, 6H, 2 × OMe); 3.42 (s, 3H, OMe); 2.99 (t, J = 6.4 Hz, 2H, H6); 1.37 (d, J = 6.0 Hz, 6H, 2×Me).
29. Compound **9b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ6.82 (d, J = 8.0 Hz, 1H, H5′); 6.78 (d, J = 8.0 Hz, 1H, H5″); 6.75 (dd, J = 8.0 and 1.6 Hz, 1H, H6′); 6.73 (s, 1H, H10); 6.69 (dd, J = 8.0 and 1.6 Hz, 1H, H6″); 6.68 (s, 1H, H7); 6.57 (d, J = 1.6 Hz, 1H, H2″); 6.56 (d, J = 1.6 Hz, 1H, H2′); 5.58 (s, 1H, OH); 5.54 (s, 1H, OH); 4.61 (t, J = 6.2 Hz, 2H, H5); 4.53 (heptet, J = 6.4 Hz, 1H, OCH); 3.65 (s, 3H, OMe); 3.62 (s, 6H, 2×OMe); 3.33 (s, 3H, OMe); 3.03 (t, J = 6.2 Hz, 1H, H6); 1.36 (d, J = 6.4 Hz, 6H, 2×Me).