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Further developments in the synthesis of lamellarin alkaloids via direct metal–halogen exchange

Poonsakdi Ploypradith,[a] Wiyada Jinaglueng,[b] Chitkavee Pavaro[b] and Somsak Ruchirawat[a,c,d,*]

[a]*Chulabhorn Research Institute, Vipavadee Rangsit Highway, Bangkok 10210, Thailand*
[b]*Department of Pharmaceutical Chemistry, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand*
[c]*Department of Chemistry, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand*
[d]*Programme on Research and Development of Synthetic Drugs, Institute of Science and Technology for Research and Development, Mahidol University, Salaya Campus, Thailand*

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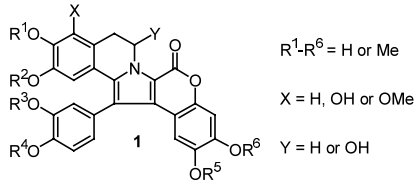
Abstract—Direct metal–halogen exchange of 2-bromopyrrole carbonate derivatives with *tert*-butyllithium followed by the intramolecular lactonization of the resulting 2-pyrrole anion onto the carbonate provided the corresponding lamellarins in moderate to good yield. The lamellarin framework could be obtained from the direct metal–halogen exchange strategy in a 26–33% overall yield over 5–6 steps.

Lamellarins **1**, whose structures contain polyoxygenated aromatics on their periphery and can be classified as 3,4-diarylpyrroloisoquinoline lactones, are a group of marine natural products isolated from the prosobranch mollusc *Lamellaria* sp. and also from the ascidians.[1,2] Including the first four lamellarins isolated by Faulkner in 1985, a total of 35 lamellarins have been isolated and identified thus far.[3,4]



Some of the lamellarins have been found to exhibit a wide array of interesting and significant biological activities including cell division inhibition, cytotoxicity, HIV-1 integrase inhibition and immunomodulatory activity.[5,6] Lamellarin K (X = OH; R^1, R^2, R^3 and R^5 = Me; R^4 and R^6 = H; Y = H) and lamellarin L (X = H; R^1, R^3, and R^6 = H; R^2, R^4 and R^5 = Me; Y = H), for example, exhibited significant cytotoxicity against P388 and A549 cultured cancer cell lines with the mean IC_{50}s of 0.7 μg/mL (0.06 μM) and 0.4 μg/mL (0.04 μM), respectively.[3] A recent study by Faulkner also showed that the presence of sulfate groups on the periphery could greatly influence the selectivity of HIV-1 integrase inhibition.[7] More importantly, lamellarins also act as non-toxic inhibitors of acquired multi-drug resistance (MDR).[8] Lamellarin I (X = OMe; R^1, R^2, R^3, R^4 and R^5 = Me; R^6 = H; Y = H) showed sensitizing effects in multidrug-resistant P388/Schabel cells to doxorubicin.[3,9]

Up to now, several studies directed towards the total synthesis of these marine natural products have been reported,[10] notably by Steglich,[11,12] Banwell,[13,14] Boger[9] and Ishibashi.[15,16] Previously, our research group reported an efficient synthesis of lamellarin derivatives, as shown in Scheme 1.[17] Synthesis of the lamellarin skeleton was achieved by first condensing the appropriately substituted benzylisoquinoline **2** with the phenacyl bromide mesylate **3**. The resulting 2*H*-3,4-disubstituted pyrrole intermediate **4** was smoothly formylated under Vilsmeier conditions. Following the removal of the mesyl group, the cyclic hemiacetal (lactol) **6** was oxidized to give the desired lamellarin skeleton **7**.

One drawback, albeit a minor one, in our previous Scheme was the use of a mesyl protecting group, which added two steps to the synthesis. It occurred to us that a better approach could be realized by using a hydroxy protecting group on the phenacyl bromide synthon that can act as a directing group for the remote deprotona-

Keywords: lamellarin alkaloid; metal–halogen exchange; DreM; natural products; pyrrole.

* Corresponding author. Tel.: 662-574-0622; fax: 662-574-2027; e-mail: somsak@tubtim.cri.or.th

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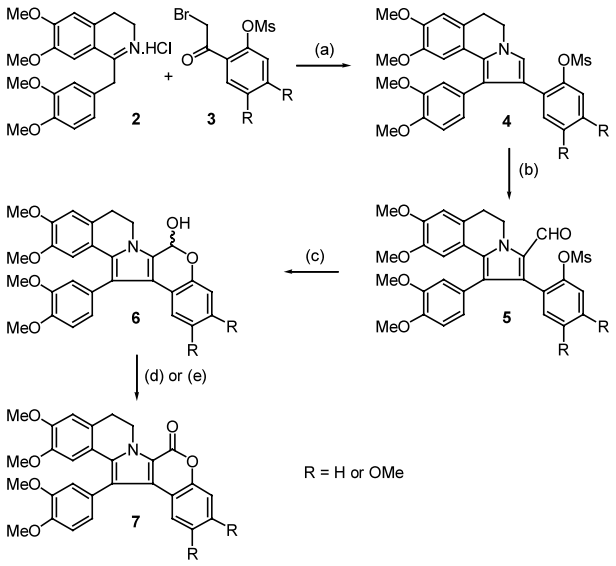
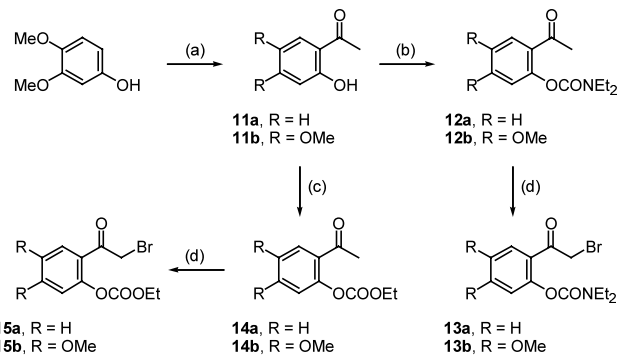


Scheme 1. *Reagents and conditions*: (a) K_2CO_3, CH_3CN, reflux, 63%; (b) DMF, $POCl_3$, rt, 80–82%; (c) KOH, EtOH, reflux, 77–81%; (d) MnO_2, CH_2Cl_2, rt, 20–54%; (e) $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, PhBr, 120°C, 12 h, 80%.

tion at the C-2 position of the pyrrole as well as being the source of the lactone group in the subsequent lactonization of the resulting anion without the need for a separate formyl group equivalent. This strategy was pioneered by Snieckus and termed DreM (for directed remote metalation).[18] The directing group is typically a carbonate or a carbamate group, as depicted in Scheme 2. Alternatively, the 2*H*-pyrrole intermediate **9** could be selectively brominated at the 2-position[8] of the pyrrole to give the corresponding bromo compound **10** which could undergo metal–halogen exchange to provide an anion similar to that from the DreM strategy after initial remote deprotonation.

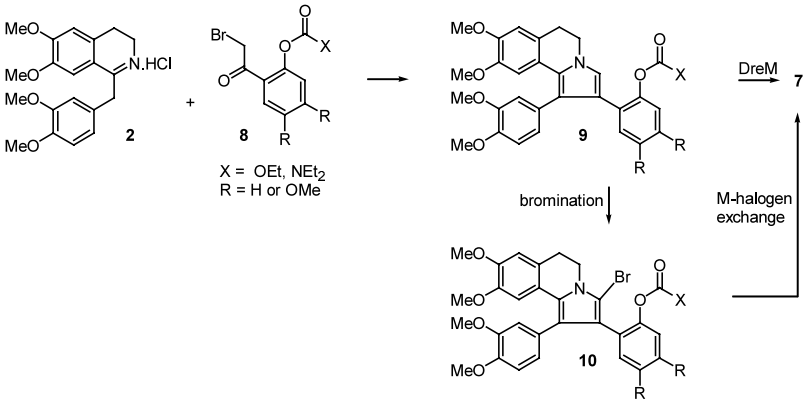
Both synthetic strategies required the benzylisoquinoline **2** and the carbonate or carbamate phenacyl bromide derivatives **8**. Our synthesis commenced with the preparation of **8** starting from commercially available 2-hydroxyacetophenone **11a** (R = H) and 2-hydroxy-4,5-dimethoxyacetophenone **11b** (R = OMe) which was



Scheme 3. *Reagents and conditions*: (a) $BF_3{\cdot}Et_2O$, Ac_2O, 80–90°C, 90%; (b) $Et_2NC(O)Cl$, DMAP (cat.), Et_3N, CH_2Cl_2, rt, 82% (**12a**) and 79% (**12b**); (c) NaH, EtOCOCl, THF, rt, 96% (**14a**) and 83% (**14b**); (d) $BnMe_3NBr_3$, CH_2Cl_2, 0°C to rt, 82% (**13a**), 70% (**13b**), 70% (**15a**) and 90% (**15b**).

synthesized in 90% yield from acetylation of 3,4-dimethoxyphenol with acetic anhydride and $BF_3{\cdot}Et_2O$, as shown in Scheme 3. Use of DMAP, Et_3N and *N*,*N*-diethylcarbamoyl chloride smoothly converted **11a** and **11b** into their corresponding carbamate derivatives **12a** and **12b** in 82 and 79% yields, respectively. However, when similar reaction conditions were used for carbonating **11a** and **11b**, the desired products **14a** and **14b** were produced in only 66 and 49% yields, respectively, since the product was often obtained as an inseparable mixture with remaining starting material. The use of a stronger base such as NaH in place of Et_3N and ethyl chloroformate yielded the desired carbonate derivatives **14a** and **14b** in 96 and 83% yields, respectively, with no starting material remaining. Subsequent bromination of **12a**, **12b**, **14a** and **14b** with $BnMe_3NBr_3$ effectively provided the desired phenacyl bromide derivatives **13a**, **13b**, **15a** and **15b** in 82, 70, 70 and 90% yields along with the dibrominated products in approximately 8% yield.

When benzylisoquinoline **2** was reacted with the carbamate derivatives **13a** and **13b** in the presence of $NaHCO_3$ in refluxing acetonitrile,[17] the corresponding pyrrole carbamates **16a** and **16b** were obtained in 91 and 81% yields, respectively (Scheme 4). The carbonate



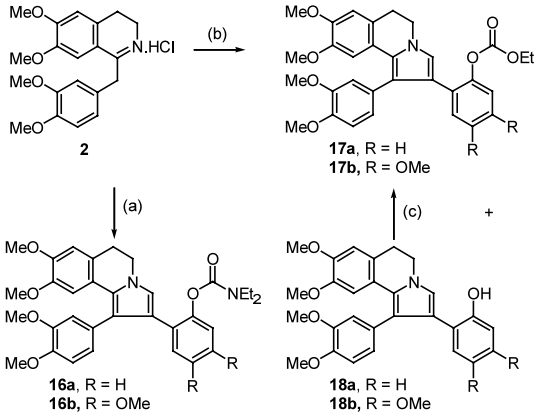
Scheme 2. Directed remote metalation (DreM) and metal–halogen exchange strategies for the synthesis of lamellarin skeleton **7**.

derivatives **15a** and **15b** were also coupled with **2** under similar conditions to give the pyrrole carbonates **17a** and **17b** in 72 and 60% overall yields after subjecting the inseparable mixture of the desired carbonate product and the pyrrole phenols **18a** and **18b** (the decarbonated products) obtained from the coupling reaction to the carbonation conditions with DMAP, Et_3N and ethyl chloroformate.

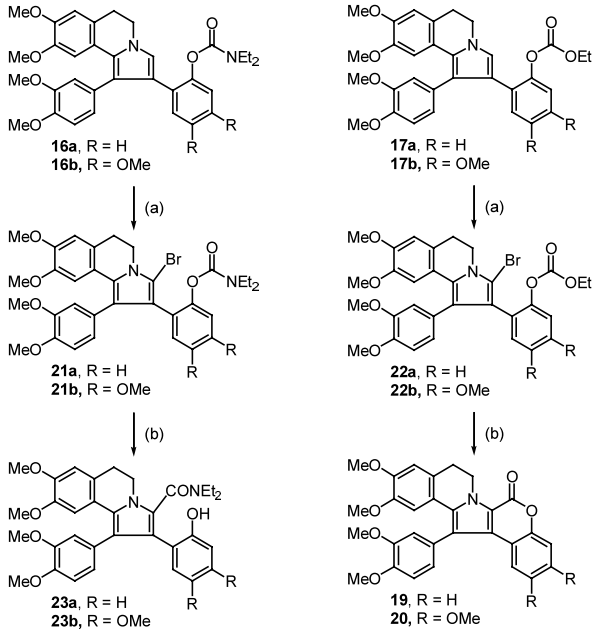
With the required carbamates **16a** and **16b** and carbonates **17a** and **17b** in our hands, we then performed a study of the DreM methodology of these compounds. After some exploratory work, we found that refluxing the carbonate **17a** with 7 equiv. of LDA in THF for 36 h gave the desired lamellarins **19** but in only 35% yield. In addition to the low yields, in our hands, the DreM/cyclization reactions were not highly reproducible and partial deprotonation of the starting material was frequently encountered. These problems together with the seemingly required prolonged reaction time have prompted us to consider another approach. The alternative approach ideally would feature a more effective means of generating the C-2 pyrrole anion as well as of facilitating the cyclization of the resulting anion onto the carbonate or carbamate at lower temperature and with a shorter reaction time.

We then considered a more direct way to generate the C-2 pyrrole anion via metal–halogen exchange, this would require the corresponding C-2 halo pyrrole. As shown in Scheme 5, the C-2 position of the pyrroloisoquinolines **16a**, **16b**, **17a** and **17b** could be selectively brominated with *N*-bromosuccinimide (NBS) to give the corresponding bromo pyrroles **21a**, **21b**, **22a**[19] and **22b** in excellent yields (>95%). Subsequent lithium–halogen exchange of carbamates **21a** and **21b** using *tert*-BuLi gave only the corresponding 2-(*N*,*N*-diethyl)amido-pyrroles **23a** and **23b** in virtually quantitative yield. Various attempts to affect the ring closure of these amido-pyrroles failed.[18] Lithium–halogen exchange of carbonates **22a** and **22b** with *tert*-BuLi,[20] on the other hand, proceeded smoothly to give the desired lamellarins **19**[17] and **20**[17] in 72 and 67% yields, respectively. From the isolation of **23a** and **23b** as the product, it appears that cyclization of the C-2 pyrrole anion may proceed via the intermediacy of the corresponding 2-amido and 2-alkoxycarbonyl pyrroles.[18]

In conclusion, two approaches towards the total synthesis of the lamellarin skeleton have been developed. Both DreM and metal–halogen exchange strategies share a similar C-2 pyrrole anion intermediate which, upon cyclization onto a carbonate or carbamate, gives the desired lamellarin framework. Results from both DreM and metal–halogen exchange are summarized in Table 1. From Table 1, the synthesis of lamellarin **20**, with two methoxy groups on the periphery, is less efficient than that of lamellarin **19**. These two strategies are relatively short (only 4–6 steps) and more efficient than our previously reported one which provided lamellarin **19** only in 25% overall yield in six steps and lamellarin **20** in 15% overall yield in seven steps. Between the two strategies, the direct metal–halogen exchange provided lamellarins more efficiently. The two best overall yields for the synthesis of **19** and **20** from DreM and metal–halogen exchange strategies are 33% in five steps and 26% in six steps, respectively.



Scheme 4. *Reagents and conditions*: (a) $NaHCO_3$, CH_3CN, reflux, **13a**, 91% (**16a**), or **13b**, 81% (**16b**); (b) $NaHCO_3$, CH_3CN, reflux, **15a** or **15b**; (c) DMAP, Et_3N, CH_2Cl_2, ClC(O)OEt, 72% (**17a**), 60% (**17b**).



Scheme 5. *Reagents and conditions*: (a) NBS, CH_2Cl_2, rt, 99% (**21a**), 99% (**21b**), 99% (**22a**), 95% (**22b**); (b) *tert*-BuLi, THF, −78°C to rt, 99% (**23a**), 98% (**23b**), 72% (**19**), 67% (**20**).

Table 1. Summary of total syntheses of lamellarins **19** and **20**

Lamellarins	DreM	Metal–halogen exchange	
	Carbonate yield (%)	Carbonate yield (%)	Carbamate yield (%)
19	17	33[b]	–[d]
20	–[a]	26[c]	–[d]

[a] The reaction was not performed.
[b] The overall yield of five steps.
[c] The overall yield of six steps.
[d] The reaction gave only the amido-pyrrole intermediate.

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19. **22a**: Mp 88–89°C; IR (KBr): ν_{max} 2937, 1759, 1495, 1466, 1248, 1135, 1029 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, 3H, $J=7.2$ Hz, OCH_2CH_3), 3.00–3.11 (m, 2H, NCH_2CH_2Ar), 3.40, 3.60, 3.83, 3.87 (4s, 12H, OCH_3), 4.09–4.26 (m, 4H, OCH_2CH_3 and NCH_2CH_2Ar), 6.71–6.78 (m, 4H, Ar*H*), 6.83–6.89 (m, 1H, Ar*H*), 7.08–7.11 (m, 2H, Ar*H*), 7.14–7.18 (m, 1H, Ar*H*), 7.22–7.27 (m, 1H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.02, 29.02, 43.33, 55.22, 55.65, 55.76, 55.83, 64.25, 102.9, 107.5, 110.9, 111.0, 114.2, 119.5, 121.1, 121.7, 121.8, 122.7, 123.9, 125.4, 126.6, 127.2, 127.8, 127.9, 132.9, 147.2, 147.4, 147.6, 148.6, 149.2, 152.9; LRMS (EI) *m*/*z* (rel. intensity) 609 (M^++2, 37), 607 (M^+, 43), 529 (100), 483 (23), 481 (23); HRMS (FAB) ($C_{31}H_{30}BrNO_7$+H) calcd 608.1284, found 608.1282.
20. A typical procedure is as follows: To a mixture of **22a** (0.30 g, 0.49 mmol) in THF (10 mL) at −78°C was added *tert*-butyllithium (0.73 mL, 1.23 mmol, $c=1.7$ M in pentane). The mixture turned dark red immediately. The mixture was allowed to stir at −78°C and slowly warmed up to room temperature at which the mixture was stirred for 16 h. The reaction was then quenched with water (5 mL) and diluted with EtOAc (5 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (2×10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which was further purified by column chromatography on silica (50% EtOAc/hexanes) to give the desired lamellarin **19** as a solid (0.17 g, 0.35 mmol, 72%). Spectroscopic data of **19** were identical to those of the compound synthesized by a different approach previously reported in Ref. 17.