1. **Acetophenone carbonate.** Using the General Procedure 6, acetophenone carbonate was obtained (96%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 2.58 (s, 3H), 4.34 (q, J = 7.0 Hz, 2H), 7.21 (dd, J = 8.0, 1.0 Hz, 1H), 7.34 (dt, J = 7.4, 1.0 Hz,1H), 7.55 (dt, J = 7.4, 2.0 Hz, 1H), 7.82 (dd, J = 8.0, 2.0 Hz, 1H).

2. **3,4-Dimethoxy acetophenone carbonate.** Using the General Procedure 6, 3,4-dimethoxy acetophenone carbonate was obtained (83%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (t, J = 7.2 Hz, 3H), 2.54 (s, 3H), 3.91 (s, 6H), 4.33 (q, J = 7.2 Hz, 2H), 6.67 (s, 1H), 7.34 (s, 1H).

3. **Phenacyl bromide carbonate.** Using the General Procedure 7, phenacyl bromide carbonate was obtained (68%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 4.22 (q, J = 7.0 Hz, 2H), 4.32 (s, 2H), 6.60 (s, 1H; dibromo compound), 7.17 (dd, J = 8.0, 1.0 Hz, 1H), 7.26-7.34 (m,1H), 7.51-7.60 (m, 1H), 7.76 (dd, J = 8.0, 2.0 Hz, 1H).

4. **3,4-Dimethoxy phenacyl bromide carbonate.** Using the General Procedure 7, 3,4-dimethoxy phenacyl bromide carbonate was obtained (89%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (t, J = 7.2 Hz, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 4.38 (q, J = 7.0 Hz, 2H), 4.44 (s, 2H), 6.65 (s, 1H; dibromo compound), 6.78 (s, 1H) 7.41 (s, 1H), 7.51 (s, 1H; dibromo compound).

5. **Pyrrole carbonate.** Using the General Procedure 8 with slight modification in that the crude mixture was subjected to a carbonation condition using Et_3N, DMAP and ethylchloroformate (1.5 equivalent each), pyrrole carbonate was obtained (72%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (t, J = 7.2 Hz, 6H), 3.00 (t, J = 6.0 Hz, 2H), 3.22 (m, 4H), 3.35 (s, 3H), 3.55 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.96 (t, J = 6.0 Hz, 2H), 6.63 (s, 1H), 6.68 (s, 1H), 6.72-6.77 (m, 3H), 6.81-6.91 (m, 3H), 7.00-7.10 (m, 2H).

6. **3,4-Dimethoxy pyrrole carbonate.** Using the General Procedure 8 with slight modification in that the crude mixture was subjected to a carbonation condition using Et_3N, DMAP and ethylchloroformate (1.5 equivalent each), 3,4-dimethoxy pyrrole carbonate was obtained (60%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 6H), 3.05 (t, J = 6.0 Hz, 2H), 3.36 (br m, 4H), 3.42 (s, 3H), 3.47 (s, 3H), 3.68 (s, 3H), 3.85 (s, 6H), 3.88 (s, 3H), 4.05 (t, J = 6.0 Hz, 2H), 6.45 (s, 1H), 6.66 (s, 1H), 6.70 (s, 1H), 6.75 (s, 1H), 6.83 (s, 2H), 6.89 (m, 2H).

7. **2-Bromo pyrrole carbonate.** Using the General Procedure 9, 2-bromo pyrrole carbonate was obtained (92%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.04 (m, 6H), 2.89-3.20 (m, 2H), 3.30 (br m, 4H), 3.40 (s, 3H), 3.58 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 3.90-3.95 (m, 1H),

4.21-4.36 (m, 1H), 6.71 (s, 1H), 6.74-6.75 (m, 2H), 6.83 (s, 1H), 6.86-6.96 (m, 2H), 6.95-7.06 (m, 2H), 7.03-7.23 (m, 1H).

8. 2-Bromo 3,4-dimethoxy pyrrole carbonate. Using the General Procedure 9, 2-bromo 3,4-dimethoxy pyrrole carbonate was obtained (95%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 (m, 6H), 2.89-3.20 (m, 2H), 3.30 (br m, 4H), 3.38 (s, 3H), 3.54 (s, 3H), 3.62 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.90-3.95 (m, 1H), 4.21-4.40 (m, 1H), 6.38 (s, 1H), 6.70 (s, 1H), 6.74-6.76 (m, 2H), 6.79-6.80 (m, 2H), 6.84-6.89 (m, 1H).

9. Lamellarin skeleton. Using the General Procedure 10, the corresponding lamellarin was obtained (72%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.10 (t, J = 6.0 Hz, 2H), 3.34 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 3.97 (s, 3H), 4.78 (t, J = 6.0 Hz, 2H), 6.63 (s, 1H), 6.74 (s, 1H), 7.00-7.05 (m, 4H), 7.20-7.35 (m, 3H).

10. Lamellarin G trimethyl ether. Using the General Procedure 10, the corresponding lamellarin was obtained (67%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.12 (t, J = 7.0 Hz, 2H), 3.36 (s, 3H), 3.45 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 4.76-4.84 (m, 2H), 6.66 (s, 1H), 6.71 (s, 1H), 6.76 (s, 1H), 6.91 (s, 1H), 7.04-7.05 (m, 1H), 7.09-7.11 (m, 2H).

Output

We have successfully developed two efficient synthetic approaches for lamellarins. We have published one synthetic approach, namely the lithium-bromine exchange and submitted the other, the nitro-ester alkene for publication. The publication(s) are listed below:

1) **Ploypradith, P.**; Jinaglueng, W.; Pavaro, C.; **Ruchirawat, S.** Further developments in the synthesis of lamellarin alkaloids via direct metal-halogen exchange. *Tetrahedron Lett.* **2003**, *44*, 1363-1366.

2) **Ploypradith, P.**; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; **Ruchirawat, S.** A highly efficient synthesis of lamellarin K and L via Michael addition-ring closure reaction of benzyldihydroisoquinoline derivatives with β-ethoxycarbonyl-β-nitrostyrenyl compounds. Manuscript submitted.

ภาคผนวก

Attached are reprint (Tetrahedron Letters) and manuscript of the papers submitted for publication.

ergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1363–1366

TETRAHEDRON LETTERS

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

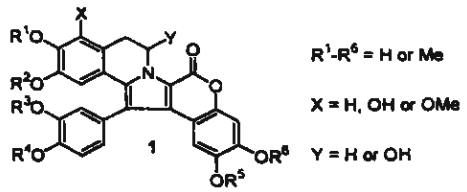
Poonsakdi Ploypradith,[a] Wiyada Jinaglueng,[b] Chitkavee Pavaro[b] and Somsak Ruchirawat[a,c,d,*]

[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*

Received 28 October 2002; revised 11 December 2002; accepted 20 December 2002

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]



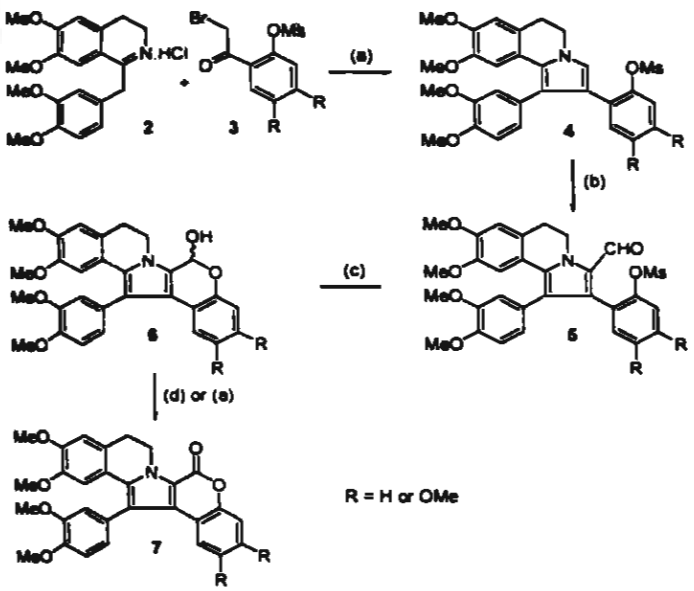
Some of the lamellarins have been found to exhibit a wide array of interesting and significant biological activities including cell division inhibition, cytotoxicity, HIV-1 integrase inhibition and immunomodulatory activity.[5,6] Lamellarin K (X = OH; R^1, R^2, R^3 and R^5 = Me; R^4 and R^6 = H; Y = 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

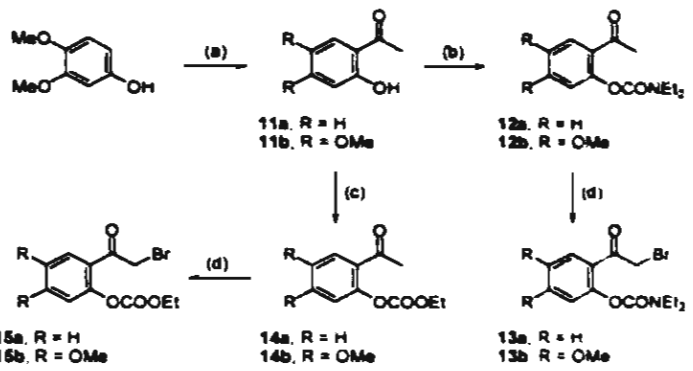
0040-4039/03/$ - see front matter
PII: S0040-4039(02)02887-3



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.

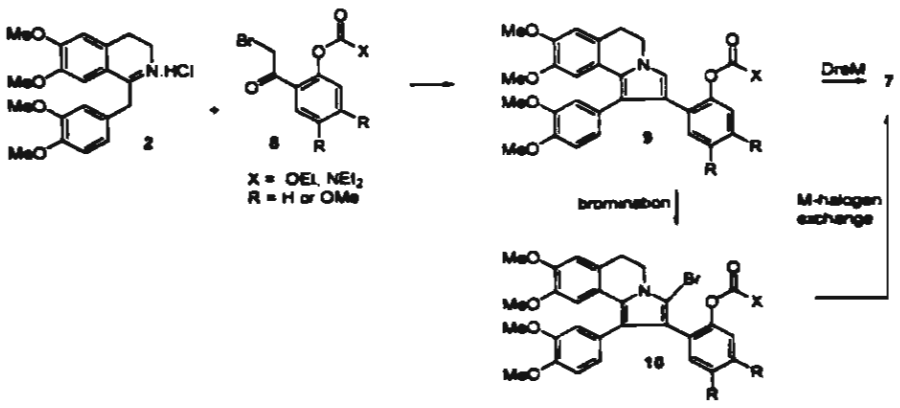
Both synthetic strategies required the benzylisoquinoline **2** and the carbonate or carbamate phenacyl bromide derivatives **8**. Our synthesis commenced with the preparation of **8** starting from commercially available 2-hydroxyacetophenone **11a** (R = H) and 2-hydroxy-4,5-dimethoxyacetophenone **11b**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



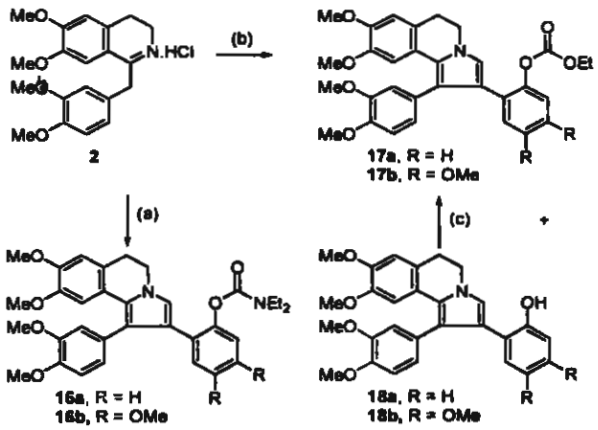
Scheme 2. Directed remote metalation (DreM) and metal–halogen exchange strategies for the synthesis of lamellarin skeleton **7**.

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.

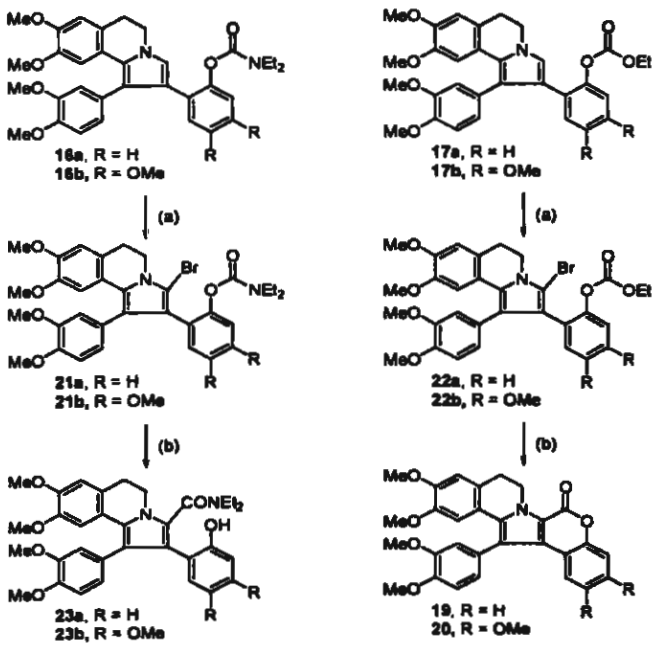
With the required carbamates **16a** and **16b** and carbonates **17a** and **17b** in our hands, we then performed a study of the DreM methodology of these compounds. After some exploratory work, we found that refluxing the carbonate **17a** with 7 equiv. of LDA in THF for 36 h gave the desired lamellarins **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.

Acknowledgements

We acknowledge the financial contribution from the Thailand Research Fund (TRF; Grant No. RTA/07/2544 for S.R. and PDF/82/2544 for P.P.) for the generous support of the research program and the award of Senior Research Scholar to S.R. We also acknowledge the facilities in the Department of Chemistry, Mahidol University provided by the Postgraduate Education and Research Program in Chemistry (PERCH).

References

1. Andersen, R. J.; Faulkner, D. J.; He, C.-H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492–5495.
2. Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771–1791.
3. Bowden, B. F. *Studies in Natural Products Chemistry (Bioactive Natural Products (Part D))* **2000**, *23*, 233–283.
4. Ham, J.; Kang, H. *Bull. Korean Chem. Soc.* **2002**, *23*, 163–166.
5. Urban, S.; Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G. *Curr. Org. Chem.* **2000**, *4*, 765–807.
6. Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901–1907.
7. Ridley, C. P.; Venkata Rami Reddy, M.; Rocha, G.; Bushman, F. D.; Faulkner, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 3285–3290.
8. Furstner, A.; Krause, H.; Thiel, O. R. *Tetrahedron* **2002**, *58*, 6373–6380.
9. Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54–62.
10. Diaz, M.; Guitian, E.; Castedo, L. *Synlett* **2001**, 1164–1166.
11. Peshko, C.; Winklhofer, C.; Steglich, W. *Chem. Eur. J.* **2000**, *6*, 1147–1152.
12. Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 155–156.
13. Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun.* **1997**, 2259–2260.
14. Banwell, M. G.; Flynn, B. L.; Hockless, D. C. R.; Longmore, R. W.; Rae, A. D. *Aust. J. Chem* **1999**, *52*, 755–765.
15. Ishibashi, F.; Miyazaki, Y.; Iwao, M. *Tetrahedron* **1997**, *53*, 5951–5962.
16. Ishibashi, F.; Tanabe, S.; Oda, T.; Iwao, M. *J. Nat Prod.* **2001**, *65*, 500–504.
17. Ruchirawat, S.; Mutarapat, T. *Tetrahedron Lett.* **2001**, *42*, 1205–1208.
18. Chauder, B. A.; Kalinin, A. V.; Taylor, N. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 1435–1438.
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.

/ Highly Efficient Synthesis of Lamellarins K and L via the Michael Addition-ling Closure Reaction of Benzyldihydroisoquinoline Derivatives with β-:thoxycarbonyl-β-nitrostyrenyl Compounds**

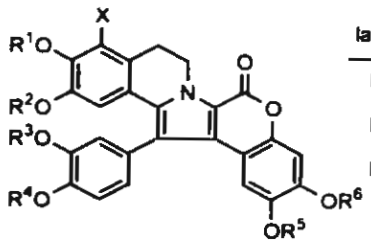
'oonsakdi Ploypradith, Chulabhorn Mahidol, Poolsak Sahakitpichan, Siriporn Wongbundit, and Somsak Ruchirawat*

Among the recently discovered marine natural products isolated from the prosobranch mollusc *Lamellaria* sp. and also from the ascidians is a group of the 3,4-diarylpyrroloisoquinoline lactone derivatives known as the lamellarins whose structures contain different patterns of polyoxygenated aromatics on their periphery (Figure 1). Since the first four alkaloids isolated by Faulkner in 1985, a total of thirty-five lamellarins have been identified thus far.[1] Several studies on their structures revealed that the aromatic ring at C-3 is orthogonal to the plane of the pyrrole ring[2a] which, in theory, could cause the lamellarins to exist as optically active atropisomers. However, isolation of these lamellarins from natural sources usually provided the compounds as inseparable (racemic) mixtures of atropisomers, suggesting a facile thermal racemization process.[2] Several attempts to separate these atropisomers into their optically active forms have been unsuccessful.[2]

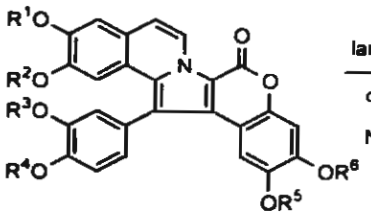
Our research group has been particularly interested in lamellarins K (**1a**) and L (**1b**) for their reported biological activities which include cytotoxicity, HIV-1 integrase inhibition and multidrug-resistant (MDR) reversal.[2, 3] A recent biological evaluation by Faulkner and his co-workers of lamellarin α (**2a**), its 20-sulfate, and 13,20-disulfate derivatives for inhibition of HIV-1 integrase

[*] Prof. Dr. S. Ruchirawat[†, ‡], Dr. P. Ploypradith, Prof. Dr. H. R. H. Princess C. Mahidol[†], Dr. P. Sahakitpichan, S. Wongbundit
Chulabhorn Research Institute, Vipavadee-Rangsit Highway, Bangkok 10210, Thailand
Fax: (662)-574-2027; e-mail: somsak@tubtim.cri.or.th
[†] Chulabhorn Research Centre, Institute of Science and Technology for Research and Development, Mahidol University, Salaya Campus, Nakhon Pathom, Thailand
[‡] Department of Chemistry, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand
[**] We acknowledge (i) the financial contribution from the Thailand Research Fund (TRF; RTA/07/2544 and Senior Research Award (S.R.) and PDF/82/2544 (P.P.)) and (ii) facilities provided by the Postgraduate Education and Research Program in Chemistry (PERCH), Department of Chemistry, Mahidol University.

showed that the presence of sulfate groups on the periphery could greatly influence selectivity in HIV-1 integrase inhibition.[4] It has also been found that lamellarins act as a non-toxic inhibitors of acquired multi-drug resistance (MDR). Lamellarin I (**1c**) showed sensitizing effects in multidrug-resistant P388/Schabel cells at concentrations as low as 0.2 μM to doxorubicin and showed full potentiation at the concentration 10 times lower than that of the prototype MDR inhibitor, verapamil.[5] Fürstner and his coworkers have recently shown that cytotoxicity and MDR reversal of lamellarins can be uncoupled.[6] The exact molecular mechanism of action of lamellarins and their related compounds is currently under extensive investigation.



lamellarin	R^1	R^2	R^3	R^4	R^5	R^6	X
K (1a)	Me	Me	Me	H	Me	H	OH
L (1b)	H	Me	H	Me	Me	H	H
I (1c)	Me	Me	Me	Me	Me	H	OMe



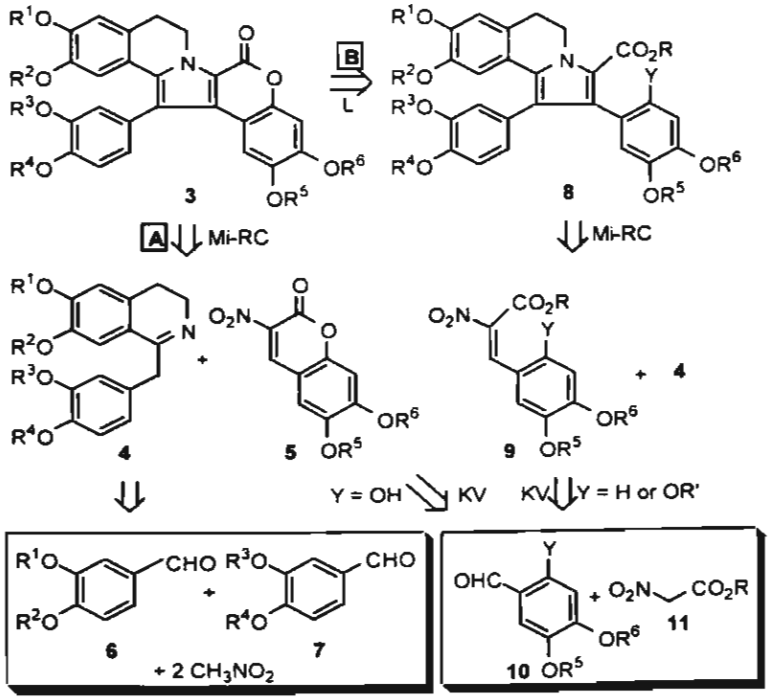
lamellarin	R^1	R^2	R^3	R^4	R^5	R^6
α (2a)	Me	Me	H	Me	Me	H
N (2b)	H	Me	H	Me	Me	H

Figure 1. Structures of lamellarins K (**1a**), L (**1b**), I (**1c**), α (**2a**) and N (**2b**).

There have been several studies[7] directed toward the total synthesis of lamellarins notably by Steglich,[8] Banwell,[9] Boger,[10] Ishibashi[11] and our research group.[12] Previously, we reported two synthetic approaches to the lamellarin skeleton, both involving the key condensation of the appropriately substituted benzyldihydroisoquinoline with the phenacyl bromide derivatives to form the pyrrole core.[12] The required lactone carbonyl group could be introduced via the Vilsmeier formylation of the 2*H*-pyrrole[12a] or alternatively via the ester group equivalent (a carbonate group) as a part of the phenacyl bromide derivative synthon.[12b] In the former, following Vilsmeier formylation and deprotection of the hydroxy group, the lactone was formed under oxidative conditions of the resulting lactol.[12a] In the latter, selective bromination at the 2*H*-position of the pyrrole and subsequent direct lithium-bromine exchange gave the anion which underwent

intramolecular lactonization with the carbonate group.[12b] It is apparent that both approaches required at least one chemical step to introduce the formyl group (or its equivalent) at the 2-position of pyrrole.

We now envisioned that the lamellarin skeleton **3** could arise from condensation of the benzyldihydroisoquinoline **4** with a Michael acceptor such as **5** or **9** which essentially would install the lactone or ester group on the 2-position as shown retrosynthetically in Scheme 1. This synthetic approach would prove highly convergent since it would form the pyrrole as well as providing the lactone directly or the ester group for subsequent lactonization in a single step. Since imines, which exist in equilibrium with their enamines, have been shown to react with β-nitrostyrene to give the corresponding pyrroles,[13] it was expected then that Michael addition of an enamine derived from benzyldihydroisoquinoline with a powerful Michael acceptor, **5** or **9**, followed by ring closure and aromatization could provide the more direct route to the lamellarin alkaloids.



Scheme 1. Retrosynthetic analysis and strategies for the synthesis of the lamellarin skeleton **3**. L = lactonization; Mi-RC = Michael addition-ring closure; KV = Knoevenagel reaction.

Modeling the Michael addition-ring closure reaction between the simple β-nitrostyrene and 3,4-dihydropapavarine hydrochloride under basic conditions resulted in complete consumption of both starting materials but gave no desired product. We then examined the use of nitro-ester alkenes in place of the simple nitroalkenes in a similar Michael addition-ring closure reaction.

Nitro-ester alkenes are more powerful Michael acceptors than the simple nitroalkenes due to the additional electron-withdrawing effect provided by the ester group, thereby allowing the nitro-ester alkenes to react under milder reaction conditions than those required for the simple nitroalkenes.

We turned our attention to the coumarin derivatives **12a** and **12b** (Figure 2) as the nitro-ester alkenes for the reaction under basic conditions (pathway A in Scheme 1). These coumarin derivatives offered a significant advantage in that their structures already contained the lactone moiety. We anticipated that if the reaction occurred with these coumarins, all of the lamellarin skeletons, especially the pyrrole and lactone, would be successfully installed in one chemical operation. Unfortunately, such reaction with these coumarins gave the desired lamellarins in only 5-6% yields.

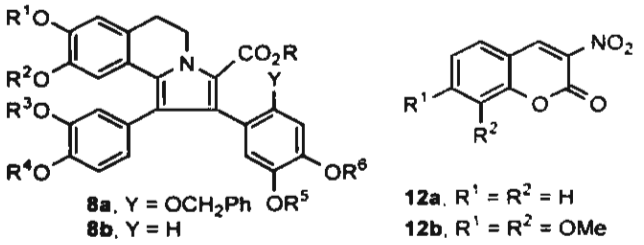
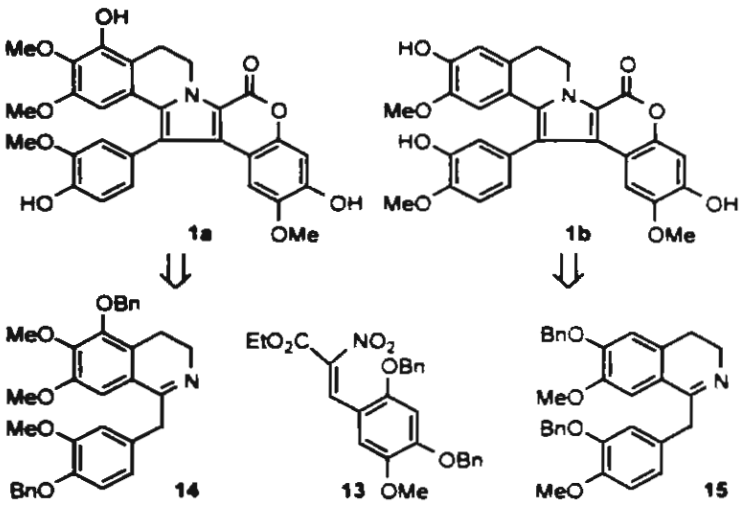


Figure 2. Structures of pyrrole esters **8a** and **8b** and nitrocoumarins **12a** and **12b**.

The poor yield resulting from the reaction using nitrocoumarins **12a** and **12b** prompted us to examine the use of acyclic nitro-ester alkenes like **9** (pathway B in Scheme 1). Despite adding one step of lactonization into the synthesis, this alternative synthetic route would probably allow for a more effective preparation of the lamellarin framework. Our required intermediate would then assume the structures of either compound **8a** or **8b** as shown in Figure 2.

From the structure of compound **8a** (Y = OCH_2Ph), it was apparent that the desired lactone moiety could be formed by unmasking the benzyloxy-protected phenol via hydrogenolysis and its subsequent base-mediated lactonization. Retrosynthetic analysis, as shown in Scheme 2, revealed that our target lamellarins K and L would require the same nitro-ester alkene **13** which could be prepared in 56% overall yield over 3 steps via the Knoevenagel condensation of aldehyde **16**[14] with ethyl nitroacetate as shown in Scheme 3. As an alternative to Scheme 3, aldehyde **16** could be prepared from selective bisdemethylation of 2,4,5-trimethoxybenzaldehyde using $AlCl_3$[15] followed

benzylation in 79% overall yield. Synthesis of the substituted benzyldihydroisoquinolines **14** and **15** are well known in the literature[16-24] and both compounds were synthesized in seven steps via Bischler-Napieralski reactions of the appropriate arylethylamines and homoveratric acids readily prepared from three common starting materials **17-19** (Scheme 3).

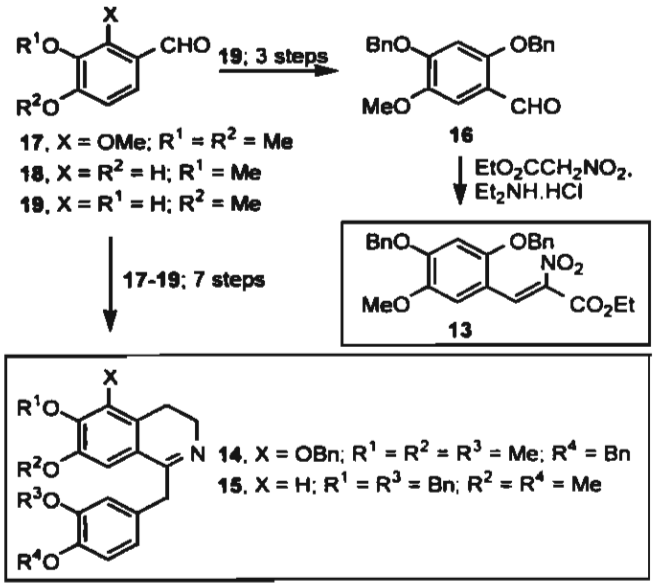


Scheme 2. Retrosynthetic analysis for the synthesis of lamellarins K (**1a**) and L (**1b**) Bn = benzyl group (CH_2Ph).

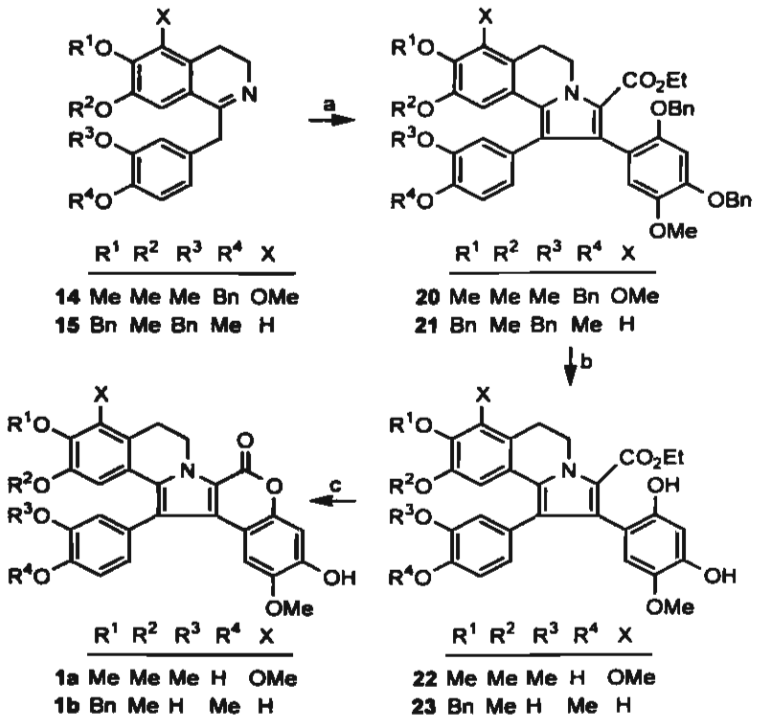
The key step of Michael addition-ring closure reaction of the imines **14** and **15** with the nitro-ester alkene **13** in the presence of $NaHCO_3$ in refluxing anhydrous acetonitrile proceeded smoothly to give the desired pyrroles **20** and **21**, both in 70% yield as shown in Scheme 4. The syntheses were completed by subjecting pyrroles **20** and **21** to hydrogenolysis to give compounds **22** and **23** quantitatively followed by base-mediated lactonization using sodium hydride in dry THF to produce lamellarin K (**1a**) in 93% and lamellarin L (**1b**) in 87% yields over two steps.

We also examined an alternative direct lactonization of compound **8b** (Y = H; Figure 2) by oxidative lactonization of the corresponding acid **24a** using $Pb(OAc)_4$ in refluxing ethanol, a condition previously employed in the synthesis of lamellarin G trimethyl ether.[9b] This process would essentially simplify the structure of the required nitro-ester alkene as well as reducing one step in the synthesis (hydrogenolysis). Pyrrole ester **24b** was prepared by a similar Michael addition-ring closure reaction between appropriate starting materials. Unfortunately, various attempts to hydrolyze the ester by standard conditions such as KOH in refluxing ethanol to the corresponding acid only gave the decarboxylated 2*H*-pyrrole product **24c** virtually quantitatively

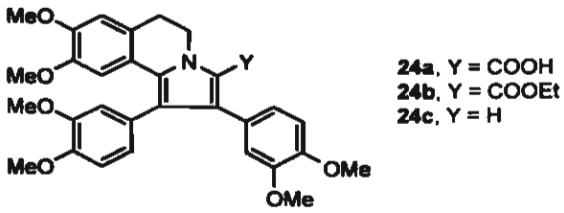
Figure 3). When the crude mixture containing the presumed acid was used in the $Pb(OAc)_4$ oxidative condition, the decarboxylated compound **24c** was the only isolable product.



Scheme 3. Synthesis of nitro-ester alkene **13** and benzyldihydroisoquinoline derivatives **14** and **15**.



Scheme 4. Synthesis of lamellarins K (**1a**), and L (**1b**). a) $NaHCO_3$, **13**, CH_3CN, reflux, 70% (**20**), 70% (**21**); b) H_2, Pd/C, EtOAc; c) NaH, THF, 93% (**1a**, over two steps), 87% (**1b**, over two steps).



24a, Y = COOH
24b, Y = COOEt
24c, Y = H

Figure 3. Structures of the acid **24a**, the pyrrole ester **24b** and the decarboxylated product **24c**.

In summary, lamellarins K and L were successfully synthesized in three steps from benzyldihydroisoquinolines **14** and **15** with nitro-ester alkene **13** in 65% and 61% overall yields, respectively. The key step was the Michael addition-ring closure reaction which proceeded in 70% yield for both lamellarins. The basic building blocks for the lamellarins are only the simple and easily prepared substituted benzaldehyde derivatives. Each lamellarin could be analyzed to consist of three such building blocks, two in the benzyldihydroisoquinoline derivative and the other in the nitro-ester alkene. In addition, our convergent synthetic approach offers a significant improvement over others reported thus far in that it allows for an easy incorporation of all aryl groups on the lamellarin skeleton without the need for complex protecting group strategies. The benzyl group was chosen as the only necessary hydroxy-protecting group since all of the benzyl groups could be removed in the same step by simple palladium-catalyzed hydrogenolysis. The syntheses of other lamellarins employing this similar approach will be reported in due course.

References

[1] a) R. J. Andersen, D. J. Faulkner, C.-H. He, G. D. Van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1985**, *107*, 5492; b) B. F. Bowden, *Studies in Natural Products Chemistry (Bioactive Natural Products (Part D))* **2000**, *23*, 233; c) S. Urban, S. J. H. Hickford, J. W. Blunt, M. H. G. Munro, *Curr. Org. Chem.* **2000**, *4*, 765.

[2] a) J. Ham, H. Kang, *Bull. Korean. Chem. Soc.* **2002**, *23*, 163; b) S. Urban, R. J. Capon, *Aust. J. Chem.* **1996**, *49*, 711.

[3] M. V. R. Reddy, M. R. Rao, D. Rhodes, M. S. T. Hansen, K. Rubins, F. D. Bushman, Y. Venkateswarlu, D. J. Faulkner, *J. Med. Chem* **1999**, *42*, 1901.

[4] C. P. Ridley, M. Venkata Rami Reddy, G. Rocha, F. D. Bushman, D. J. Faulkner, *Bioorg. Med. Chem.* **2002**, *10*, 3285.

[5] A. R. Quesada, M. D. G. Gravalos, J. L. F. Puentes, *Brit. J. Cancer* **1996**, *74*, 677.

[6] A. Fürstner, H. Krause, O. R. Thiel, *Tetrahedron* **2002**, *58*, 6373.

[] a) M. Diaz, E. Guitian, L. Castedo, *Synlett* **2001**, *7*, 1164; b) O. Barun, S. Chakrabarti, I. H., H. Junjappa, *J. Org. Chem.* **2001**, *66*, 4457; c) S. Kim, S. Son, H. Kang, *Bull. Korean Chem. Soc.* **2001**, *22*, 1403.

8] a) C. Peshko, C. Winklhofer, W. Steglich, *Chem. Eur. J.* **2000**, *6*, 1147; b) A. Heim, A. Terpin, W. Steglich, *Angew. Chem. Int. Ed.* **1997**, *36*, 155.

[9] a) M. G. Banwell, B. Flynn, D. Hockless, *Chem Commun.* **1997,** 2259; b) M. G. Banwell, B. L. Flynn, E. Hamel, D. C. R. Hockless, *Chem. Commun.* **1997**, 207; c) M. G. Banwell, B. L. Flynn, D. C. R. Hockless, R. W. Longmore, A. D. Rae, *Aust. J. Chem.* **1999**, *52*, 755.

[10] D. L. Boger, C. W. Boyce, M. A. Labroli, C. A. Sehon, Q. Jin, *J. Am. Chem. Soc.* **1999**, *121*, 54.

[11] a) F. Ishibashi, Y. Miyazaki, M. Iwao, *Tetrahedron* **1997**, *53*, 5951; b) F. Ishibashi, S. Tanabe, O. Tatsuya, M. Iwao, *J. Nat. Prod.* **2002**, *65*, 500; c) M. Iwao, T. Takeuchi, N. Fujikawa, T. Fukuda, F. Ishibashi, *Tetrahedron Lett.* **2003**, *44*, 4443.

[12] a) S. Ruchirawat, T. Mutarapat, *Tetrahedron Lett.* **2001**, *42*, 1205; b) P. Ploypradith, W. Jinaglueng, C. Pavaro, S. Ruchirawat, *Tetrahedron Lett.* **2003**, *44*, 1363.

[13] a) S. Lim, I. Jabin, G. Revial, *Tetrahedron Lett.* **1999**, *40*, 4177; b) G. Revial, S. Lim, B. Viossat, P. Lemoine, A. Tomas, A. F. Duprat, M. Pfau, *J. Org. Chem.* **2000**, *65*, 4593.

[14] M. Tsukayama, A. Oda, Y. Kawamura, M. Nishiuchi, K. Yamashita, *Tetrahedron Lett.* **2001**, *42*, 6163.

[15] J. Demyttenaere, K. Van Syngel, A. P. Markusse, S. Vervisch, S. Debenedetti, N. De Kimpe, *Tetrahedron* **2002**, *58*, 2163.

[16] A. Bhattacharjya, R. Mukhopadhyay, S. C. Pakrashi, *Synthesis* **1985**, 886.

[17] T. Nakanishi, M. Suzuki, *Org. Lett.* **1999**, *1*, 985.

[18] a) L. Pouysegu, A.-V. Avellan, S. Quideau, *J. Org. Chem.* **2002**, *67*, 3425; b) Y.-C. Wang, P. E. Georghiou, *Synthesis* **2002**, 2187.

9] A. Bermejo, I. Andreu, F. Suvire, S. Leonce, D. H. Caignard, P. Renard, A. Pierre, R. D. Enriz, D. Cortes, N. Cabedo, *J. Med. Chem.* **2002**, *61*, 709.

20] L. F. Tietze, T. Eicher in *Reactions and Synthesis in the Organic Chemistry Laboratory*, University Science Books, Mill Valley **1989**, pp. 177-178.

[21] C.-M. Chen, Y.-F. Fu, T.-H. Yang, *J. Nat. Prod.* **1995**, *58*, 1767.

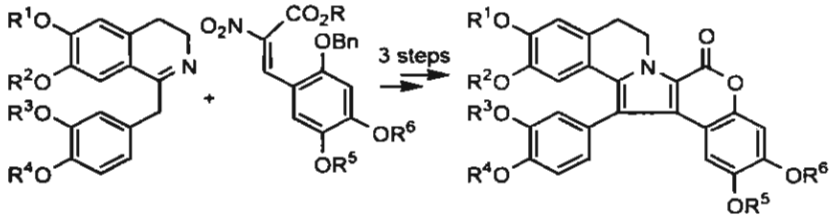
[22] J. Z. Ginos, F. C. Brown, *J. Med. Chem.* **1978**, *21*, 155.

[23] C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 234.

[24] T. Kametani, K. Takahashi, K. Fukumoto, *J. Chem. Soc.* **1971**, 3617.

able of Contents

lamellarins, a new class of potential non-toxic inhibitors against HIV-1 integrase and multidrug-esistance (MDR) in cancer cell lines, could be synthesized in three chemical steps and in 60% overall yields from two simple starting materials (see picture). The key step in our convergent synthetic approach involved the novel Michael addition-ring closure (Mi-RC) reaction, giving the pyrrole core and the required ester group for subsequent lactonization in the same step.



Keywords: marine alkaloids, cyclization, Michael addition, nitroalkenes, total synthesis

upporting Information

Experimental Section

13: A round-bottomed flask equipped with a Dean-Stark apparatus was charged with aldehyde **16** (3.60 g, 10.3 mmole), $Et_2NH.HCl$ (1.25 g, 15.5 mmole), ethyl nitroacetate (1.38 mL, 12.4 mmole) and toluene (120 mL) at rt. The mixture was refluxed under argon for 48 h. Toluene was removed and water and CH_2Cl_2 were added. Two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which was recrystallized from MeOH to furnish the desired product **13** as a yellow-orange solid (3.28 g, 67%): m.p. 104-105 °C; IR (KBr): ν_{max} = 2938, 1754, 1714, 1608, 1573, 1522, 1268, 1225 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.99 (s, 1H), 7.27-7.36 (m, 10 H), 6.83 (s, 1H), 6.50 (s, 1H), 5.12 (s, 2H), 5.00 (s, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.9, 153.8, 152.9, 144.2, 137.9, 136.0, 135.8, 128.70 (2 carbons), 128.66, 128.2, 127.4, 127.1 (2 carbons), 110.5, 110.3, 100.4, 71.6, 70.9, 62.5, 56.2, 14.0; MS (EI): *m/z* (%): 464 (7) [M^++1], 463 (40) [M^+], 326 (28), 236 (29), 181 (36), 91 (100); HR-MS (FAB): calcd for $C_{26}H_{26}NO_7$ (M + H): 464.1709, found: 464.1699; Anal. calcd for $C_{26}H_{25}NO_7$: C 67.38, H 5.44, N 3.02, found: C 67.51, H 5.62, N 2.98.

20: To a mixture of benzyldihydroisoquinoline **14** (0.77 g, 1.47 mmole) and $NaHCO_3$ (0.12 g, 1.47 mmole) in acetonitrile (15 mL) was added nitro-ester alkene **13** (0.45 g, 0.98 mmole). The resulting mixture was refluxed for 15 h. After being allowed to cool to rt, water and EtOAc were added. The two layers were separated and the aqueous phase was extracted with EtOAc (3 x). The combined organic layers were washed once with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude which was further purified by column chromatography on silica (20% EtOAc/hexanes) to furnish the desired product as a sticky gum (0.64 g, 70%): IR (KBr): ν_{max} = 2934, 1685, 1508, 1457, 1417, 1216, 1206 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.07-7.44 (m, 20H), 6.56-6.76 (m, 4H), 6.53 (s, 1H), 6.43 (s, 1H), 5.13 (s, 2H),

.08 (s, 2H), 5.03 (s, 2H), 4.73 (s, 2H), 4.40 (br s, 2H), 3.99 (br q, J = 7.1 Hz, 2H), 3.87 (s, 3H), .63 (s, 3H), 3.54 (s, 3H), 3.22 (s, 3H), 2.91 (br s, 2H), 0.83 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 151.5, 150.6, 149.1, 148.8, 147.1, 146.5, 143.5, 141.2, 137.8, 137.3, 137.2, 137.1, 130.3, 128.8, 128.6, 128.5, 128.47, 128.2, 127.79, 127.77, 127.4, 127.2, 127.0, 126.7, 123.1, 122.4, 119.9, 119.4, 118.6, 116.1, 114.5, 113.5, 105.2, 103.0, 75.4, 71.4, 71.2, 70.7, 61.0, 59.6, 56.5, 55.8, 55.2, 42.5, 29.7, 22.6, 13.7; MS (EI): *m/z* (%): 938 (4) [$M + H^+$], 573 (92), 91 (100), 42 (90); HR-MS (FAB): calcd for $C_{59}H_{56}NO_{10}$ (M + H): 938.3904, found: 938.3905.

21: Using a procedure similar to that of **20**, compound **21** was obtained as a sticky gum (70%): IR (KBr): ν_{max} = 2933, 1685, 1498, 1381, 1254, 1212, 1174 1206 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06-7.46 (m, 20H), 6.76 (s, 1H), 6.74 (s, 1H), 6.65 (s, 1H), 6.57 (s, 1H), 6.44 (s, 1H), 5.14 (s, 1H), 5.01 (s, 2H), 4.77 (s, 2H), 4.72 (s, 2H), 4.59 (br s, 2H), 3.99 (br q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.64 (s, 3H), 3.31 (s, 3H), 2.99 (br s, 2H), 0.82 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 150.6, 148.2, 147.9, 147.8, 147.1, 143.5, 137.9, 137.1, 137.01, 136.95, 130.9, 128.6, 128.5, 128.4, 128.2, 127.9, 127.7, 127.4, 127.3, 127.2, 126.8, 125.6, 123.7, 121.7, 121.5, 119.1, 118.8, 116.5, 116.1, 113.1, 111.5, 109.1, 103.1, 71.7, 71.2, 71.0, 70.8, 59.6, 56.5, 56.0, 55.2, 42.8, 29.6, 13.7; MS (EI): *m/z* (%): 908 (6) [$M + H^+$], 615 (100), 573 (84), 84 (38); HR- MS (FAB): calcd for $C_{58}H_{54}NO_9$ (M + H): 908.3799, found: 908.3791.

22: A solution of pyrrole **20** (1.15 g, 1.22 mmole) in EtOAc (115 mL) was placed in a high pressure Parr apparatus at rt. To this solution was added palladium on activated charcoal (*ca.* 100 mg). The resulting mixture was hydrogenated (75 psi) until all starting material was consumed (normally 15 hours) as indicated by tlc. The mixture was then filtered through a plug of Celite® and concentrated under reduced pressure to give a sticky solid (0.70 g, quantitative) which was used in the next step without further purification: IR (KBr): ν_{max} = 3420 (br), 2939, 1683, 1422, 1247 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55-6.83 (m, 3H), 6.54 (s, 1H), 6.40 (s, 1H), 6.32 (s, 1H), 5.98 (br s, 1H), 5.57 (br s, 2H), 5.47 (br s, 2H), 5.00 (m, 1H), 4.20 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.64 (s, 3H), 3.55 (s, 3H), 3.35 (s, 3H), 3.04-3.16 (br m, 2H), 1.08 (t, J = 7.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 150.2, 148.7, 146.3, 145.9, 145.7, 144.4, 140.1, 134.7, 131.6, 126.8, 123.8, 123.6, 123.5, 119.6, 114.2, 114.0, 113.3, 112.4, 102.5, 101.8, 61.0, 60.4, 56.4, 55.9, 55.2, 42.7, 21.7, 13.8 MS (EI): *m/z* (%): 577 (4) [*M*$^+$], 91 (100); HR-MS (FAB): calcd for $C_{31}H_{32}NO_{10}$ (M + H): 578.2026, found: 578.2023.

23: Using a procedure similar to that of **22**, compound **23** was obtained as a sticky solid (quantitative) which was used in the next step without further purification: IR (KBr): ν_{max} = 3410 (br), 2935, 1675, 1546, 1481, 1413, 1327, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (m, 2H), 6.71 (s, 1H), 6.62 (s, 1H), 6.62 (m, 1H), 6.52 (s, 1H), 6.40 (s, 1H), 5.65 (br s, 1H), 5.58 (br s, 1H), 5.57 (br s, 1H), 5.38 (br s, 1H), 4.87 (m, 1H), 4.32 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.60 (s, 3H), 3.38 (s, 3H), 2.90-3.10 (br m, 2H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 148.6, 145.6, 145.5, 145.3, 145.0, 144.9, 140.0, 132.3, 128.3, 126.8, 122.6, 122.2, 120.0, 119.0, 117.0, 114.3, 113.7, 110.6, 108.5, 60.3, 56.5, 55.9, 55.3, 42.9, 28.7, 13.8; MS (EI): *m/z* (%): 547 (4) [*M*$^+$], 91 (100); HR-MS (FAB): calcd for $C_{30}H_{30}NO_9$ (M − H): 548.1921, found: 548.1918.

1a: To a solution of pyrrole **22** (0.63 g, 1.09 mmole) in THF (70 mL) at 0 °C was added NaH (80% in paraffin, 0.20 g, 6.67 mmole). The resulting mixture turned red and was allowed to stir at that temperature for 15 minutes. The reaction was then slowly warmed up to rt and stirred at rt for 2 h. Water and EtOAc were added and the resulting biphasic mixture was allowed to stir at rt overnight. Two layers were separated and the aqueous was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude lamellarin. Recrystallization from MeOH gave the desired lamellarin K as a white solid (0.54 g, 93%): m.p. >250 °C; IR (KBr): ν_{max} = 3404 (br), 2936, 1712, 1544, 1510, 1457, 1265, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 1.8 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.79 (s, 1H), 6.55 (s, 1H), 6.33 (s, 1H), 4.73 (m, 1H), 4.55 (m, 1H), 4.08 (br s, 3 H), 3.78 (s, 3H), 3.75 (s, 3H), 3.39 (s, 3H), 3.28 (s, 3H), 3.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 150.7, 148.0, 146.7, 146.1, 146.0, 145.9, 144.4, 136.1, 135.9, 128.7,

126.8, 123.9, 123.1, 115.7, 115.6, 113.84, 113.75, 113.3, 109.8, 104.5, 103.5, 101.5, 60.7, 56.0, 55.3, 54.9, 42.0, 21.4; MS (EI): *m/z* (%): 532 (38) [*M*$^+$+1], 531 (100) [*M*$^+$], 516 (52), 484 (23). These spectroscopic data are identical to those reported previously.[9b]

1b: Using the procedure similar to that of **1a**, compound **1b** was obtained as a white solid (87%): m.p. >250 °C; IR (KBr): ν_{max} = 3629 (br), 3473 (br), 3266 (br), 2957, 1672, 1589, 1485, 1421, 1278 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.98 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.89 (s, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 4.64-4.80 (m, 2H), 3.96 (s, 3H), 3.52 (s, 3 H), 3.41 (s, 3H), 3.05 (apparent t, *J* = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 146.8, 146.6, 146.1, 145.9, 145.8, 145.4, 143.9, 136.4, 128.5, 127.3, 122.8, 119.3, 117.6, 114.4, 113.2, 111.7, 109.9, 108.8, 104.5, 103.4, 56.2, 55.4, 55.1, 42.3, 28.3; MS (EI): *m/z* (%): 501 (1) [*M*$^+$], 251 (51), 42 (100). These spectroscopic data are identical to those reported previously.[9b]