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An efficient synthesis of lamellarin alkaloids: synthesis of lamellarin G trimethyl ether

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Abstract—A general and efficient synthesis of lamellarin alkaloids is described. The synthesis involves the formation of the core pyrrolo[2,1-*a*]isoquinoline, followed by the formation of the lactone ring. © 2001 Published by Elsevier Science Ltd.

Lamellarins are a group of marine natural products which were isolated from the prosobranch mollusc *Lamellaria* sp and the ascidians.[1] The first four lamellarins were isolated by Faulkner et al. in 1985 and named lamellarins A, B, C, D. The structure of lamellarin A was determined by X-ray crystallographic analysis and the structures of the remaining compounds were derived from spectroscopic data.[2] At present 35 lamellarins have so far been isolated and identified.[2,3] Some of these lamellarins and related compounds exhibit interesting biological activities[4] including cell division inhibition, cytotoxicity and immunomodulatory activity and the recently discovered multidrug-resistant (MDR) reversal[5] and HIV-1 integrase inhibition.[6] Due to this impressive array of biological activity profiles, ever increasing elegant synthetic routes

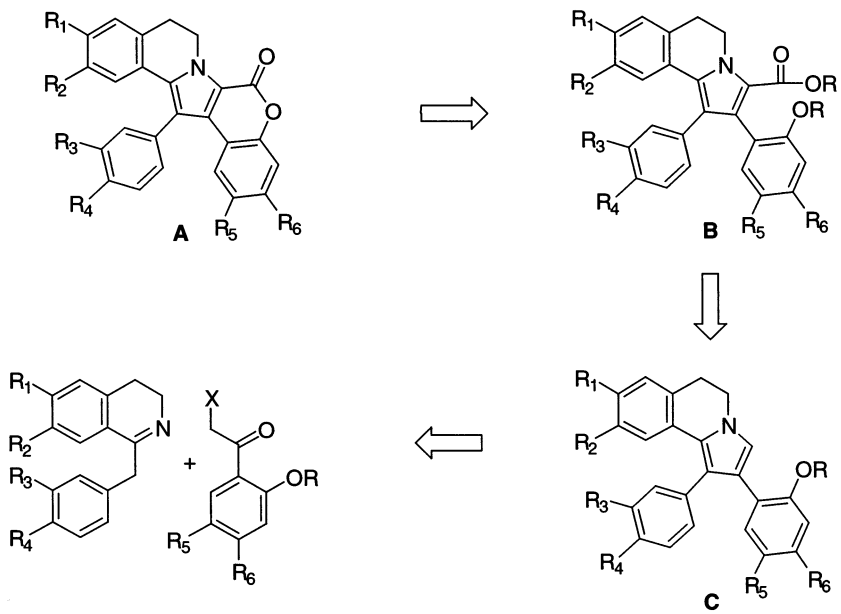

Figure 1.

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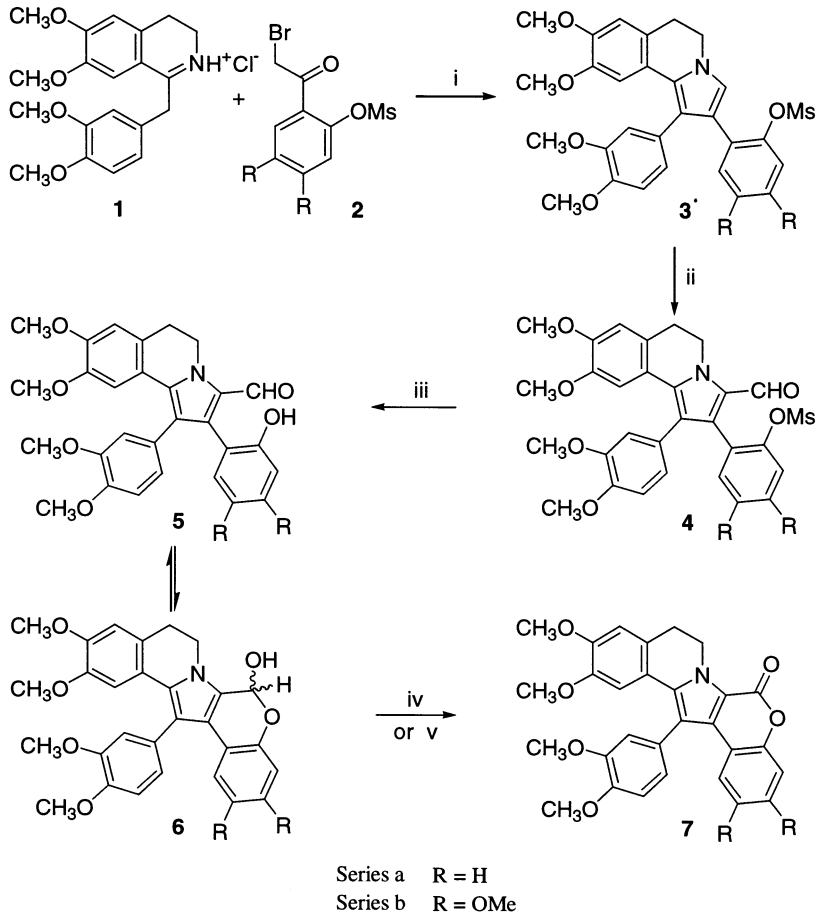
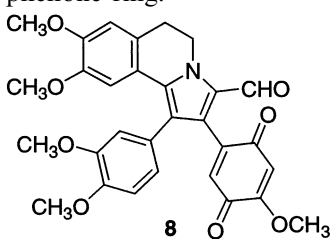


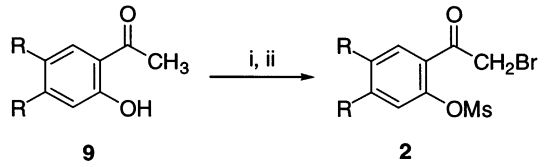
Scheme 1. *Reagents and conditions*: (i) K_2CO_3, CH_3CN, reflux (**3a**, 63%; **3b**, 63%); (ii) DMF, $POCl_3$, rt (**4a**, 80%; **4b**, 82%); (iii) KOH, EtOH, reflux (**5a**, 77%; **5b**, 81%); (iv) MnO_2, CH_2Cl_2, rt (**7a**, 54%; **7b**, 20% and **8**, 37%); (v) $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, PhBr, 120°C, 12 h (**7a**, 80%; **7b**, 80%).

have been developed for the synthesis of lamellarins[7] and related 3,4-diaryl pyrrole derivatives,[8] notably by Steglich and Banwell. The core skeleton of these lamellarins **A** can be viewed as the fusion of the pyrrolo[2,1-*a*]isoquinoline with the lactone unit. Our retrosynthetic analysis as shown in Fig. 1 involves the lactonization of the appropriate pyrrolo[2,1-*a*]isoquinoline derivative **B**. Pyrrolo[2,1-*a*]isoquinoline **C** can be synthesized from the reaction of 3,4-dihydroisoquinoline with a phenacyl bromide derivative.

In practice, the condensation of 3,4-dihydropapaverine hydrochloride **1** with *o*-mesyloxyphenacyl bromide **2a**[9] in the presence of potassium carbonate in acetonitrile gave the expected mesyloxy pyrrolo[2,1-*a*]isoquinoline analogue **3a** in 63% yield. The reaction presumably involves the intramolecular reaction of the derived enamine from the isoquinolinium salt and the ketone as found in the Knorr pyrrole synthesis.[10] The introduction of the formyl group on the pyrrole ring was accomplished by the Vilsmeier reaction.[11] The reaction was carried out using dimethylformamide in phosphorus oxychloride as a formylating agent at room temperature. The expected product **4a** was obtained in 85% yield after purification by preparative thin layer chromatography. The mesyl protecting group in the derived aldehyde intermediate was easily removed by heating with potassium hydroxide in ethanol. The phenol **5a** was produced in 77% yield after purification by preparative thin layer chromatography. We found that manganese dioxide in dichloromethane could be used to oxidize the phenolic aldehyde **5a** to the corresponding lamellarin derivative **7a** in 54% yield, presumably via the hemiacetal intermediate **6a**.

The above approach has also been applied to the synthesis of lamellarin G trimethyl ether as shown in series b of Scheme 1. The first three steps used in the synthesis proceeded well as planned. The condensation of 3,4-dihydroisoquinoline **1** with the phenacyl bromide derivative **2b**[9] gave the corresponding pyrrolo[2,1-*a*]isoquinoline **3b** in 63% yield. The introduction of the formyl group and the removal of mesyloxy protecting group could be accomplished in 82 and 81% yield, respectively. However, the oxidation of compound **5b** with manganese dioxide gave lamellarin G trimethyl ether **7b** in disappointing yield (20%). The byproduct was found to be the quinone derivative **8** formed by the preferred oxidation of the electron rich phenolic ring.





9 2

Series a R = H
Series b R = OMe

Scheme 2. *Reagents and conditions*: Series a. (i) $MeSO_2Cl$, Et_3N, CH_2Cl_2 (97%); (ii) $BnN^+Me_3Br_3^-$, CH_2Cl_2 (**2a**, 81%): Series b. (i) $MeSO_2Cl$, Et_3N, CH_2Cl_2 (97%); (ii) $BnN^+Me_3Br_3^-$, CH_2Cl_2 (**2b**, 83%).

After some experimentation, we found that the above conversion could be conveniently carried out by oxidation with bromobenzene, palladium acetate and triphenylphosphine using DMF as the solvent and potassium carbonate as the base in the reaction.[12] The product **7b** was formed in 80% yield. The physical and spectroscopic data of the product **7b** are in good agreement with that reported for lamellarin G trimethyl ether.[7] Tetrakis(triphenylphosphine)palladium(0) could be used in place of palladium acetate and the reaction proceeded in the same yield. The oxidation of unsubstituted analogue **5a** with the above system also gave the required lactone **7a** in 80% yield.

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14. Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Fujisaki, S. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 1159–1160. All compounds have been fully characterized. Spectroscopic data of some selected compounds. 2-(3″,4″-Dimethoxy-2″-mesyloxyphenyl)-1-(3′,4′-dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline **(3b)** mp (MeOH): 186–187°C; FTIR ($CHCl_3$): ν_{max} 3027, 2938, 2839, 1539, 1465, 1365, 1259, 1205 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.86 (s, 3H, OSO_2CH_3), 3.08 (t, 2H, $J=6.5$ Hz, CH_2CH_2N), 4.13 (t, 2H, $J=6.5$ Hz, CH_2CH_2N), 3.41, 3.48, 3.72, 3.88, 3.89, 3.90 (6s, 18H, C-9, C-21, C-8, C-13, C-20 and C-14, 6×OCH_3), 6.53 (s, 1H, C-10Ar*H*), 6.72 (s, 1H, C-7Ar*H*), 6.74 (s, 1H, C-19Ar*H*), 6.82 (dd, 1H, $J=8.0$ and 1.6 Hz, C-16Ar*H*), 6.84 (d, 1H, $J=8.0$ Hz, C-15Ar*H*), 6.87 (d, 1H, $J=1.6$ Hz, C-12Ar*H*), 6.89

(s, 1H, C-22Ar*H*), 6.99 (s, 1H, C-3Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9, 147.8, 147.4, 147.2, 147.1, 147.0, 139.9, 128.8, 125.9, 124.0, 123.0, 121.8, 121.0, 120.0, 119.2, 117.8, 114.1, 113.7, 112.3, 111.1, 107.4, 106.9, 56.1, 56.0, 55.9 (2×C), 55.6, 55.2, 44.8, 38.0, 29.4. MS: 595 (M^+, 44.78), 516 (100.0), 499 (11.61), 485 (29.25), 470 (10.22), 442 (6.65), 426 (5.39), 410 (5.53), 243 (28.77). Anal. calcd for $C_{31}H_{33}NO_9S$: C, 62.49; H, 5.59; N, 2.35. Found: C, 62.46; H, 5.71; N, 2.07. 3-Formyl-2-(3″,4″-dimethoxy-2″-mesyloxyphenyl)-1-(3′,4′-dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (**4b**) mp (MeOH): 192–193°C; FTIR ($CHCl_3$): ν_{max} 3026, 2939, 2839, 1643, 1531, 1483, 1465, 1426, 1263 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89 (s, 3H, OSO_2CH_3), 3.00–3.20 (m, 2H, CH_2CH_2N), 4.51 (m, 1H, CH_2CHHN), 4.95 (m, 1H, CH_2CHHN), 3.35, 3.60, 3.68, 3.85, 3.89, 3.90 (6s, 18H, C-9, C-21, C-8, C-20, C-13 and C-14, 6×OCH_3), 6.57 (s, 1H, C-10Ar*H*), 6.76 (s, 2H, C-19, C-22Ar*H*), 6.82 (m, 3H, C-12, C-15, C-16Ar*H*), 6.87 (s, 1H, C-7Ar*H*), 9.45 (s, 1H, C-23C*H*O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 149.0 (2×C), 148.9, 148.0, 147.3, 147.2, 140.2, 133.8, 132.4, 126.8, 126.7, 125.7, 122.9, 122.3, 119.6, 118.0, 114.7, 114.0, 111.0, 110.7, 109.1, 106.5, 56.1, 55.9 (3×C), 55.8, 55.2, 42.3, 38.4, 28.7. MS: 623 (M^+, 20.55), 528 (100.0), 516 (18.48), 485 (9.73), 470 (6.23), 454 (3.81), 440 (3.73), 410 (3.57), 272 (35.41), 264 (61.22), 243 (38.99). Anal. calcd for $C_{32}H_{33}NO_{10}S$: C, 61.61; H, 5.34; N, 2.25. Found: C, 61.56; H, 5.28; N, 2.01.