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Concise total syntheses of Marinoquinolines A–C

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ABSTRACT

The first concise total syntheses of pyrroloquinoline natural products, Marinoquinolines A–C, have been achieved in six linear steps from commercially available starting materials. The key steps were a reaction between (*p*-tolylsulfonyl)methylisocyanide (TosMIC) and α, β-unsaturated ester under basic condition to prepare the pyrrole moiety and Morgen-Walls reaction to construct quinoline ring.

The efficient syntheses of bioactive heterocyclic natural products or libraries are of major importance to academia and pharmaceutical industry due to the potential bioactivities of heterocylic molecules. Recently, Muller and co-workers isolated several pyrroloquinoline natural products, such as Marinoquinolines A–F (**1**–**6**, Fig. 1), from *Ohtaekwangia kribbensis*.[1] Among them, marinoquinoline A (**1**) has been isolated by the same group from the marine bacterium *Rapidithrix thailandica* and its structure was well characterized by X-ray crystallography.[2,3] The structural details of **2**–**6** were also elucidated by extensive 1D and 2D NMR experiments.[1] Preliminary biological screening of these compounds indicated that all of them showed multiple activities, such as antibacterial and antifungal activities, as well as moderate cytotoxicity against several cancer cell lines with IC_{50} values ranging from 0.3 to 8.0 μg/mL.[1] The unique structural features and interesting bioactive properties of these natural products promote us to initiate the total syntheses of them for further pharmacological study.

Typical synthetic route to pyrroloquinoline moiety reported in the literature relies on palladium-catalyzed annulation of halogenated aminoquinoline in one step.[4a,b] Limitations to this approach include the use of expensive transition metal catalysts and phosphine ligands, relatively harsh reaction conditions and difficulty to install functional group at 2-position of pyrroloquinoline. Therefore, developing a flexible route to 2-substituted pyrroloquinoline is still desirable.

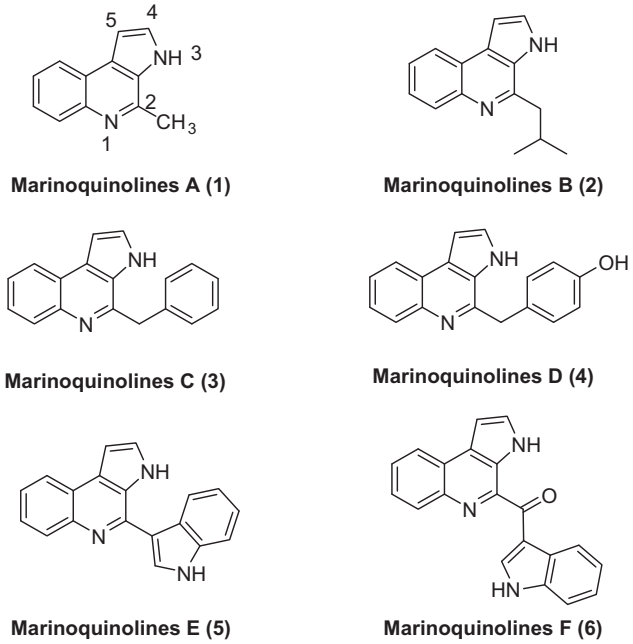

Figure 1. Structures of Marinoquinolines A–F (**1**–**6**).

We envisioned that the pyrroloquinolinone scaffold of the target compounds could be synthesized stepwise via a sequence of reactions: (i) constructing substituted pyrrole unit, (ii) building

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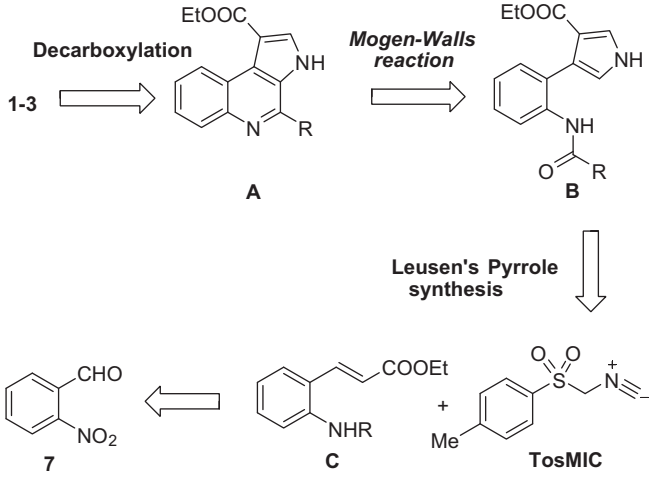
quinoline ring through condensation. In the past few decades, lots of efforts have been made developing practical methods for the synthesis of pyrrole unit bearing appropriate functionality. Among them, van Leusen pyrrole synthesis through a reaction of TosMIC with a Michael acceptor, such as α, β-unsaturated ester, represents one of the most convenient methods to access to 3, 4-disubstituted pyrroles.[5a] This procedure has been extensively applied to the synthesis of various pyrroles, in which the substituent at 3-position comes from the Michael acceptor.[5a–e] In 2002, Smith et al. demonstrated a modified route to 3-aryl and 3, 4-diarylsubstituted pyrroles in one step from TosMIC and readily accessible arylsubstituted alkenes in moderate to good yields.[6] Considering the feasibility of constructing pyrrole unit using the above methods, we herein wish to describe the first and concise total syntheses of **1**–**3** using TosMIC methodology.

Our retrosynthetic analysis of **1–3** is outlined in Scheme 1. **1**–**3** could be prepared via a decarboxylation of **A**. We envisioned that the quinoline scaffold of **1–3** could be constructed by Morgen-Walls reaction from amide **B**. The pyrrole moiety of **B** would be acquired by Leusen's methodology between α, β-unsaturated ester **C** and commercially available reagent TosMIC. Finally, **C** could be readily derived from commercially available aldehyde **7**.

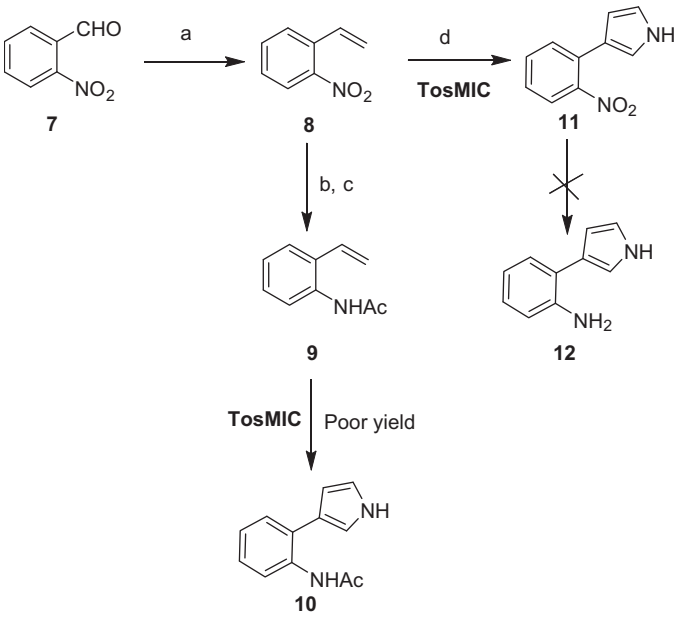
As the carboxyl group of **A** must be removed at late stage to accomplish the total syntheses of the desired products, we first tried Smith's single-step method to prepare the key intermediate of **1** as shown in Scheme 2. Thus, Wittig coupling of aldehyde 7 with CH_3PPh_3I and DBU in THF, reduction by Fe powder in mixed solvents at 85 °C and acetylation with CH_3COCl smoothly gave the phenylethylene **9**. When we tested the pyrrole synthesis under several conditions, however, we found that **9** could not efficiently convert into pyrrole **10** under smith's condition (no reaction or in very poor yield). This result could be explained by the fact that electron-rich arylethylene exhibits poor reactivity, while electron-deficient arylethylene generally afforded pyrrole product in high yield.[6] Indeed, we found the condensation between 2-nitrophenylethylene **8** and TosMIC in anhydrous DMSO using *t*-BuOK as a base could furnish pyrrole **11** in about 80% yield. However, the subsequent reduction of nitro group of **11** under various standard conditions, such as Fe/NH_4Cl, Fe/HOAc, H_2/Pd-C, and $SnCl_2 \cdot H_2O$, failed to give the desired product **12**.

We then applied Leusen's methodology to the syntheses of our targets. Leusen has demonstrated that the reaction between TosMIC and α, β-unsaturated ester could provide various pyrroles in high yields with very good functional group tolerance. As depicted in Scheme 3, Knoevenagel condensation of aldehyde **7** furnished α, β-unsaturated acid, which was then converted into ester **13** under EtBr/K_2CO_3 or EtOH/H_2SO_4 in good yields. Very interestingly, reduction of **13** by Fe powder in mixed solvents, could generated free amine, which was followed by acetylation with RCOCl (**14a**–**14c**) to furnish the desired α, β-unsaturated esters **15a–15c**. As expected, condensation of **15a**–**15c** with TosMIC proceeded smoothly to afford pyrroles **16a–16c** under Leusen's condition in 48–76% yields.

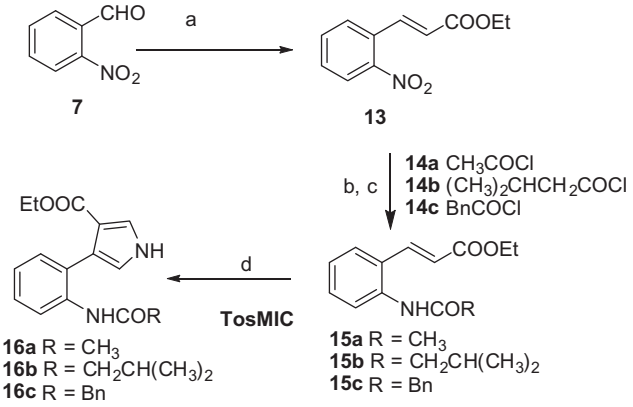
After we achieved the key intermediates **16a**–**16c**, we next applied Morgen-Walls reaction[7] to constructing the quinoline unit. As shown in Table 1, treatment of **16a** with $SOCl_2$ or P_2O_5 gave the desired product **17a** in very low yield (Table 1, entries 1, 2), while the use of PPA or Tf_2O failed to produce **17a** (entries 3, 4). Very gratifyingly, treatment of **16a-16c** with TFAA or refresh distilled $POCl_3$ in anhydrous toluene or CH_3CN smoothly afforded



Scheme 1. Retrosynthetic analysis of Marinoquinolines A–C (**1**–**3**).

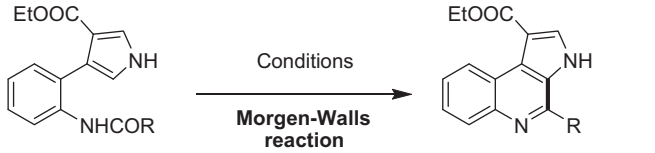


Scheme 2. Initial synthesis of pyrrole moiety of **1**. Reagents and conditions: (a) CH_3PPh_3I, DBU, reflux, 2 h, (45%); (b) Fe/NH_4Cl, EtOH/THF/H_2O = 6/2/1, 85 °C, 1 h; (c) CH_3COCl, Et_3N, CH_2Cl_2, rt 4 h (65%, two steps); (d) TosMIC, *t*-BuOK, anhydrous DMSO, rt, 1 h (80%).



Scheme 3. Total **s**ynthesis of **1**–**3**. Reagents and conditions: (a) (i) $CH_2(COOH)_2$, piperidine, pyridine, 85 °C, 12 h; (ii) EtBr, K_2CO_3/DMF, rt, overnight (86% over two steps) or EtOH conc. H_2SO_4, reflux, overnight (68% over two steps); (b) Fe/NH_4Cl, EtOH/THF/H_2O = 6/2/1, 85 °C, 1 h; (c) **14a**–**14c**, Et_3N, CH_2Cl_2, rt, 4 h (82% for **15a**, 73% for **15b**, 75% for **15c**, two steps); (d) TosMIC, *t*-BuOK, anhydrous DMSO, rt, 1 h (76% for **16a**, 68% for **16b**, 45% for **16c**).

Table 1
The screening of Morgen-Walls reaction [a]



16a R = CH_3
16b R = $CH_2CH(CH_3)_2$
16c R = Bn

17a R = CH_3
17b R = $CH_2CH(CH_3)_2$
17c R = Bn

Entry	Substrate	Condition	Yield [b]
1	**16a**	$SOCl_2$,CH_3CN, reflux, 12 h	**17a**, 5%
2	**16a**	P_2O_5, CH_3CN, reflux, 12 h	**17a**, 34%
3	**16a**	Tf_2O, DMAP, CH_2Cl_2, rt12 h	**17a**, N.R
4	**16a**	PPA, CH_3CN, reflux, 12 h	**17a**, N.R
5	**16a**	TFAA, CH_3CN, reflux, 12 h	**17a**, 84%
6	**16a**	$POCl_3$, Toluene, reflux, 12 h	**17a**, 80%
7	**16a**	$POCl_3$, CH_3CN, reflux, 12 h	**17a**, 92%
8	**16b**	$POCl_3$, CH_3CN, reflux, 12 h	**17b**, 85%
9	**16c**	$POCl_3$, CH_3CN, reflux, 12 h	**17c**, 90%

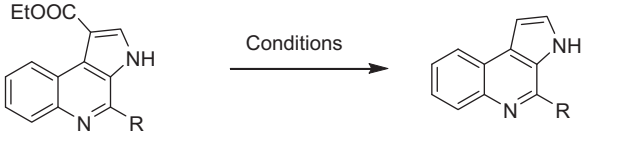
[a] All reactions were performed in 0.5 mmol scale in anhydrous solvents.
[b] Isolated yield after flash column chromatography.

pyrroloquinolines **17a** in excellent yields (entries 5–7). Similarly, treatment of **16b** and **16c** with $POCl_3$ in anhydrous CH_3CN could afford the corresponding products **17b** and **17c** in 85% and 90% yields, respectively (entries 8, 9).[8–10]

Finally, we examined the decarboxylation of **17a–17c** to synthesize **1–3** and the results are summarized in Table 2. We first used **17a** as a substrate to probe an optimal reaction condition. We found that treatment of **17a** under several typical conditions such as Ag_2CO_3/HOAc,[11] NaOH/EtOH, or NaOH/$(CH_2OH)_2$[12] at high temperature only gives **1** in very poor yields (table 2, entries 1–3). The decarboxylation of **17a** could proceed smoothly to afford **1** in about 65% yield with concentrated HCl for 12 h (entry 4).[13] The carboxylate groups of **17b** and **17c** could also be removed under the same condition to afford **2–3** (entries 5, 6). The structures of **1–3** were confirmed by ^{1}H NMR, ^{13}C NMR, IR, and HRMS (ESI).[14–16] The spectroscopic data of **1–3** were identical to those of authentic samples reported in the literature.[1]

In summary, the first concise total syntheses of Marinoquinolines A–C (**1**–**3**) in short linear steps were successfully achieved using readily available starting materials. The synthetic route is highlighted by the construction of the pyrrole moiety via a reaction between TosMIC and α, β-unsaturated ester under basic condition and the efficient construction of quinoline ring through Morgen-Walls reaction. In particular, our synthetic route could enable the installation of various functional groups at 2-position of pyrroloquinoline, which facilitates the syntheses of other related natural products and structural modification for further pharmacological study.

Table 2
Optimization of decarboxylation of **17a–17c**[a]



17a R = CH_3
17b R = $CH_2CH(CH_3)_2$
17c R = Bn

1 R = CH_3
2 R = $CH_2CH(CH_3)_2$
3 R = Bn

Entry	Substrate	Condition	Yield [b]
1	**17a**	NaOH, EtOH, then 10% Ag_2CO_3, 5% HOAc, DMSO, 120 °C	**1**, NR
2	**17a**	NaOH, EtOH, reflux, 12 h	**1**, Trace
3	**17a**	NaOH, $(CH_2OH)_2$, 120–160 °C	**1**, 10%
4	**17a**	Conc. HCl, reflux, 12 h	**1**, 65%
5[c]	**17b**	Conc. HCl, reflux, 12 h	**2**, 72%
6[c]	**17c**	Conc. HCl, reflux, 12 h	**3**, 57%

[a] The reactions were performed in 0.43 mmol scale.
[b] Isolated yield after flash column chromatography.
[c] The reactions were performed in 0.25 mmol scale.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.124.

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8. Compound **17a**: White solid; mp. 196–198 °C; IR (KBr) 3474, 2922, 1716, 1443, 1369, 1292, 1195, 1150, 1103, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63–9.66 (m, 1H), 8.16 (s, 1H), 8.09–8.13 (m, 1H), 7.60–7.63 (m, 2H), 4.44 (q, J = 7.1 Hz, 2H), 1.44 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.67, 145.78, 143.54, 133.53, 129.80, 127.85, 127.13, 127.08, 126.50, 125.79, 123.11, 111.90, 60.42, 20.50, 14.49; HRMS (ESI) m/z calcd for $C_{15}H_{15}N_2O_2$: 254.1055; Found: 254.1068.
9. Compound **17b**: White solid; mp. 180–182 °C; IR (KBr) 3504, 3085, 2929, 1712, 1686, 1587, 1357, 1154, 1135 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (br, 1H), 9.64–9.67 (m, 1H), 8.05–8.14 (m, 1H), 7.57–7.65 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 2.99 (d, J = 6.9 Hz, 2H), 2.10–2.19 (m, 1H), 1.44 (d, J = 7.1 Hz, 3H), 0.67 (d, J = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.88, 149.53, 143.33, 134.15, 130.00, 127.67, 127.19, 127.14, 125.80, 123.16, 111.71, 60.44, 43.13, 22.23, 14.52; HRMS (ESI) m/z calcd for $C_{15}H_{15}N_2O_2$: 297.1525; Found: 297.1538.
10. Compound **17c**: White solid; mp 175–176 °C; IR (KBr) 3448, 2920, 1707, 1589, 1480, 1175, 1105, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61–9.64 (m, 1H), 8.16–8.19 (m, 1H), 7.29 (s, 1H), 7.62–7.67 (m, 2H), 7.15–7.19 (m, 2H), 6.79–6.82 (m, 2H), 4.52 (s, 2H), 4.40 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 1.40 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 165.55, 150.04, 144.86, 140.112, 135.86, 130.63, 130.36, 130.14, 129.89, 127.83, 127.69, 127.58, 127.01, 126.52, 123.90, 111.37, 61.18, 40.81, 15.77; HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_2$: 330.1368; Found: 330.1385.
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14. *Marinoquinoline A* (**1**): White solid; mp. 238–240 °C; IR (KBr) 3457, 3081, 2922, 1587, 1533, 1480, 1198, 1137, 751 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 11.12 (br s, 1H), 8.19–8.24 (m, 1H), 7.98–8.02 (m, 1H), 7.57 (d, J = 2.8 Hz, 1H), 7.29 (s, 1H), 7.46–7.56 (m, 2H), 7.15–7.19 (m, 2H), 7.11 (d, J = 2.8 Hz, 1H), 2.83 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 146.97, 143.88, 129.94, 128.46, 127.17, 126.14, 125.72, 124.28, 123.79, 102.05, 21.32; HRMS (ESI) m/z calcd for $C_{12}H_{11}N_2$: 182.0844; Found: 182.0849.
15. *Marinoquinoline B* (**2**): White solid; mp 196–198 °C; IR (KBr) 3463, 2956, 2926, 1588, 1482, 1362, 752 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 11.16 (br s, 1H),

8.23–8.26 (m, 1H), 8.03–8.06 (m, 1H), 7.48–7.58 (m, 3H), 7.14–7.15 (m, 1H), 3.08 (d, J = 7.2 Hz, 1H), 2.83 (s, 3H), 2.42–2.52 (m, 1H),1.04 (d, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 150.01, 143.70, 130.00, 129.83, 128.60, 126.96, 125.97, 125.57, 124.04, 123.63, 101.86, 44.00, 28.93, 22.96; HRMS (ESI) m/z calcd for $C_{15}H_{17}N_2$: 224.1324; Found: 224.1313.

16. *Marinoquinoline C* (**3**): White solid; mp 187–188 °C; IR (KBr) 3445, 3086, 2914, 1588, 1480, 1363, 1125, 724 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 11.04 (br s, 1H), 8.23–8.26 (m, 1H), 8.05–8.08 (m, 1H), 7.49–7.57 (m, 3H), 7.43 (d, J = 7.5 Hz, 2H), 7.25 (t, J = 7.1 Hz, 2H), 7.13–7.18 (m, 2H), 4.57 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 148.95, 143.82, 139.96, 130.25, 129.76, 129.36, 129.18, 127.48, 127.09, 126.26, 125.99, 124.29, 123.77, 41.62; HRMS (ESI) m/z calcd for $C_{18}H_{15}N_2$: 258.1157; Found: 258.1170.