Modified Mukaiyama Reaction for the Synthesis of Quinoline Alkaloid Analogues: Total Synthesis of 3,3-Diisopentenyl-*N*-methylquinoline-2,4-dione

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Abstract: A general synthetic approach, capable of accessing a diverse range of 3,3-disubstituted quinoline-2,4-diones and 1,8-naphthyridine-2,4-diones via titanium tetrachloride catalyzed C-acylation of silyl ketene acetals is described. The suggested methodological platform is surveyed using different reaction conditions and is applied to the total syntheses of 3,3-diisopentenyl-*N*-methylquinoline-2,4-dione and 3-demethyl-*N*-methylatanine.

Key words: Lewis acids, fused-ring systems, aldol reactions, quinolines, natural products

As synthetic targets, quinolinone derivatives are highly enticing by virtue of their interesting pharmacological profile. 3,3-Disubstituted quinoline-2,4-diones and 3-alkenyl quinolin-2-ones constitute a uniquely challenging class in their own right; they are represented by beautifully structured natural products such as buchapine[1] (**1**), severibuxine[2] (**2**), 3,3-diisopentenyl-*N*-methylquinoline-2,4-dione[3] (**3**) and 3-demethyl-*N*-methylatanine[4] (**4**) (Figure 1). The alkaloid **3** was first isolated from woods of *Esenbeckia flava* Brandegee (Rutaceae)[3a] and recently from the essential oils from trunk bark, trunk wood and roots of *Esenbeckia almawillia* Kaastra.[3c]

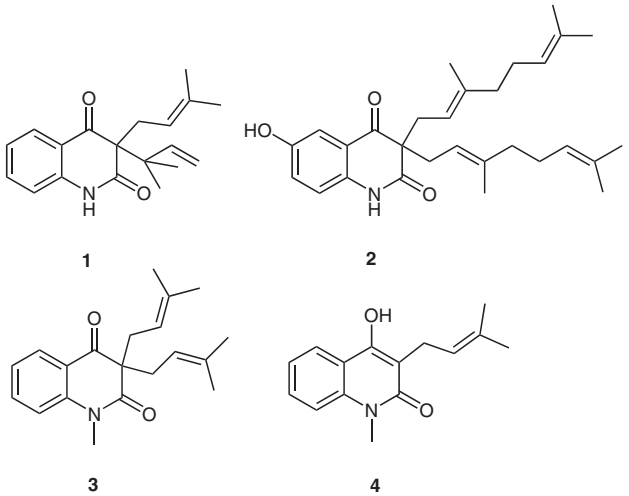

Figure 1

1,3,3-Trialkylquinoline-2,4-diones have been found to possess tranquilizing activity.[5] Moreover, some derivatives of this category have been found to have analgetic activity comparable to morphine, and considerable bacteriostatic and bacteriocidal action.[5] The 3-demethyl-*N*-methylatanine (**4**), isolated from *Almeidea guyanensis*,[4a] has been reported as a part of the natural biosynthetic sequence of edulinine[4d] and as a good precursor of furoquinolines[4d] and pyranoquinolines,[4e] which are endowed with interesting biological properties. Buchapine has been proven to be capable of protecting CEM-SS cells from the cytopathic effects of HIV-1 in vitro,[6] whilst severibuxine has shown strong cytotoxic activity against P-388.[2] Recently, 3-aryl-3-methylquinoline-2,4-diones have been proven to act as 5-HT6 receptor antagonists and may be valuably used in the treatment of central nervous system disorders.[7]

Thus, the necessity for an effective strategy for their assembly is highlighted by the significant biological profile of these molecules. To date, the prevalent synthetic route to 3,3-dialkyl or 3,3-dialkenyl quinolinones includes the two-fold alkylation or allylation of unsubstituted quinoline-2,4-dione derivatives by the use of a strong base (NaH, NaOH, K_2CO_3, LDA etc.).[6,8] The main disadvantage of this methodology is that the reaction of unsubstituted quinoline-2,4-dione with alkenyl halides in the presence of a base is often attended by the formation of mixtures of undesired C- and O-alkenylated by-products.[8]

Based on our previous experience of the chemistry of quinolinones, our group recently developed a modified Mukaiyama reaction with which we accomplished the syntheses of 1,3,3-trimethylquinoline-2,4-dione and 3,3-dimethylnaphthyridine-2,4-dione using isatoic anhydride (**5**) and pyridoxazin-4-one (**8**) respectively.[9] Thus, a reaction using Mukaiyama conditions[10] had been employed for lactones and anhydrides.

Encouraged by this result, we carried out reactions with a series of silyl ketene acetals using different reaction conditions. The present work optimizes and explores the versatility of a novel method for the synthesis of 3,3-functionalized quinolinone derivatives using new silylating reagents under mild conditions. Scheme 1 shows this synthetic approach is capable of accessing a wide range of 3,3-disubstituted quinoline-2,4-diones and 1,8-naphthyridine-2,4-diones under acidic conditions. The reaction of *N*-methylisatoic anhydride (**5**) with an excess of silyl

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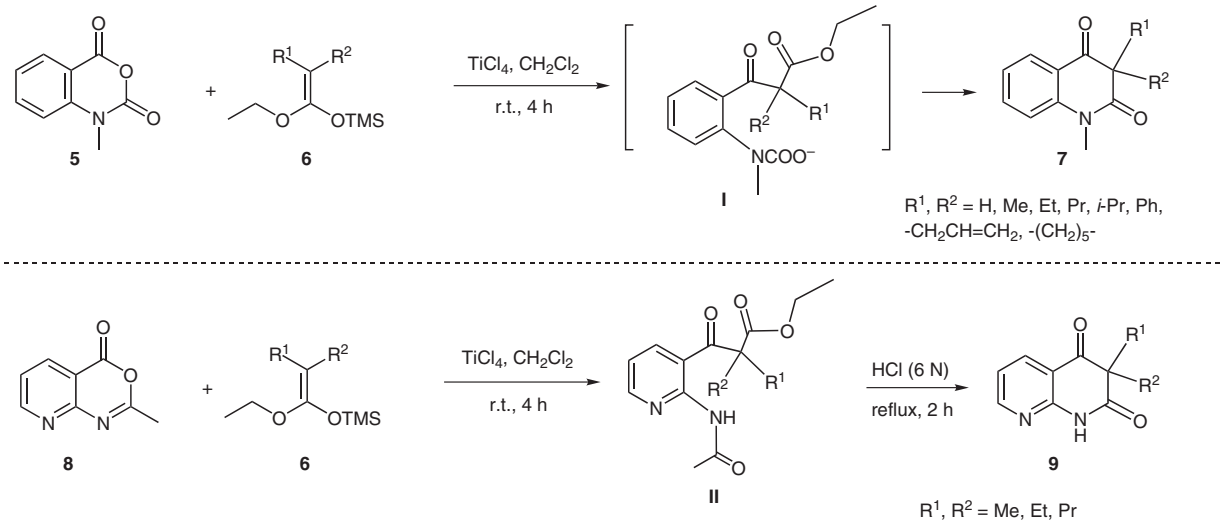


Scheme 1 Construction of 3,3-disubstituted quinoline-2,4-diones and 1,8-naphthyridine-2,4-diones

ketene acetals gave the 3,3-disubstituted 1-methylquinoline-2,4-dione **7** directly, whilst the reaction of 2-methylpyridoxazin-4-one (**8**) with the same silyl acetals yielded a mixture of the corresponding C-acylation product (II) and the target 3,3-dialkyl-1,8-naphthyridine-2,4-dione **9**. However, under acidic conditions (6 N HCl) the above mixture provided the desired 3,3-dialkyl-1,8-naphthyridine-2,4-dione through cyclization of the C-acylated compound. In addition, the reaction of the anhydride **5** with 1-ethoxy-1-trimethylsiloxypropene (**6i**) provided the 1,3-dimethyl-4-hydroxyquinolin-2-one (**10a**). The corresponding procedure with 1-ethoxy-2-phenylvinyloxytrimethylsilane (**6j**) gave a mixture of the C-acylation product and the 4-hydroxy-1-methyl-3-phenylquinolin-2-one (**10b**); acidic treatment (6 N HCl, reflux 2 h) of this mixture gave the final product **10b**.

A suggested reaction mechanism for the formation of these compounds, which is consistent with the mechanism proposed by Mukaiyama for the silicon enolate mediated crossed aldol reactions, was included in our preliminary communication.[9]

The effect of solvent, temperature and Lewis acid on the product yield was examined using the reaction of anhydride **5** with 1-methoxy-2-methyl-1-trimethylsiloxypropene (**6a**) in the presence of four different Lewis acids under various reaction conditions. The results, summarized in Table 1, indicate that titanium tetrachloride (2 equiv) in dichloromethane at room temperature, in a mixture of anhydride **5** (1 equiv) and the silyl ketene acetal **6a** (2 equiv) gave optimal yields of the desired product **7a**.

We then focused on the synthesis of silyl ketene acetals in order to further investigate the methodology described above. Silyl ketene acetals were prepared from the corresponding carboxylic esters via a modification[11] of the Ainsworth methodology.[12]

A series of 3,3-disubstituted quinoline-2,4-diones, with straight, branched or unsaturated carbon chains, as well as phenyl or spirocyclohexane substituents were obtained in

Table 1 Effect of Solvent, Temperature and the Lewis Acid on the Yield of **7a**

Lewis acid (LA)	Solvent	Temp (°C)	Time (h)	Ratio **5**/**6a**/LA	Yield of **7a** (%)
BCl_3 (1 M in CH_2Cl_2)	CH_2Cl_2	r.t.	4	1:1:1	55
$BF_3{\cdot}OEt_2$	CH_2Cl_2	r.t.	4	1:1:1	48
$SnCl_4$ (1 M in CH_2Cl_2)	CH_2Cl_2	r.t.	4	1:1:1	trace
$TiCl_4$ (neat)	toluene	r.t.	4	1:1:1	63
$TiCl_4$ (neat)	Et_2O	r.t.	4	1:1:1	40
$TiCl_4$ (neat)	THF	r.t.	4	1:1:1	trace
$TiCl_4$ (1 M in CH_2Cl_2)	CH_2Cl_2	–78	4	1:1:1	38
$TiCl_4$ (1 M in CH_2Cl_2)	CH_2Cl_2	0	4	1:1:1	60
$TiCl_4$ (1 M in CH_2Cl_2)	CH_2Cl_2	r.t.	4	1:1:1	69
$TiCl_4$ (1 M in CH_2Cl_2)	CH_2Cl_2	r.t.	4	1:2:2	86

good yields (Table 2), indicating the versatility of this method for the preparation of 3,3-disubstituted quinolin-2,4-diones (**7a**–**h**) and naphthyridine-2,4-diones (**9a**–**c**). Moreover, the proposed methodology is efficient for the construction of 3-alkyl or 3-phenyl-4-hydroxyquinolin-2-ones (compounds **10a** and **10b** respectively, Table 2) although the reaction yields were lower (43 and 46%) than the yields observed in the synthesis of 3,3-disubstituted derivatives.

Table 2 Reaction of Silyl Ketene Acetals with **5** and **8**

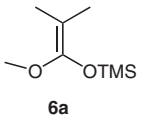
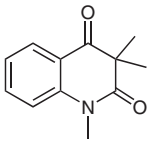
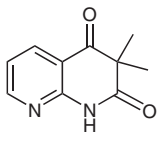
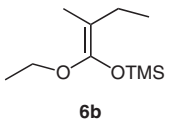
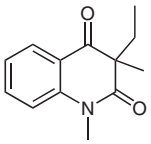
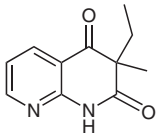
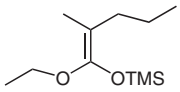
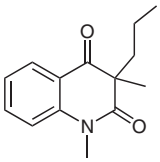
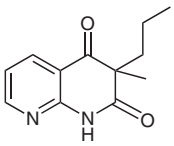
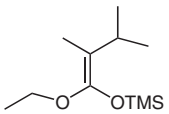
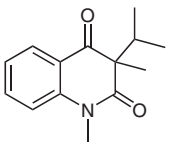
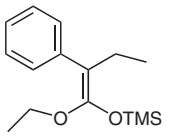
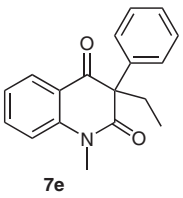
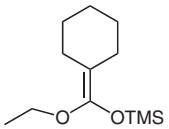
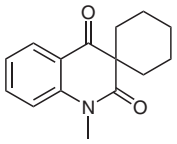
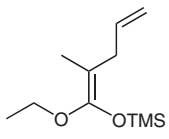
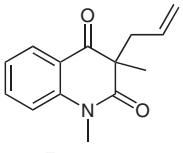
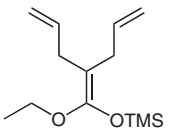
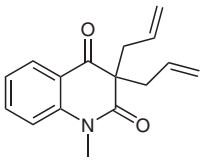
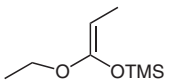
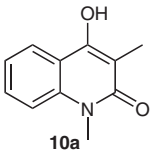
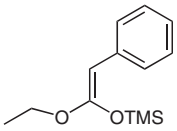
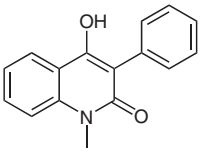
Silyl ketene acetal	Product		Yield (%)
 **6a**	 **7a**	 **9a**	86, 71
 **6b**	 **7b**	 **9b**	64, 55
 **6c**	 **7c**	 **9c**	79, 88
 **6d**	 **7d**		68
 **6e**	 **7e**		60
 **6f**	 **7f**		63
 **6g**	 **7g**		76

Table 2 Reaction of Silyl Ketene Acetals with **5** and **8** (continued)

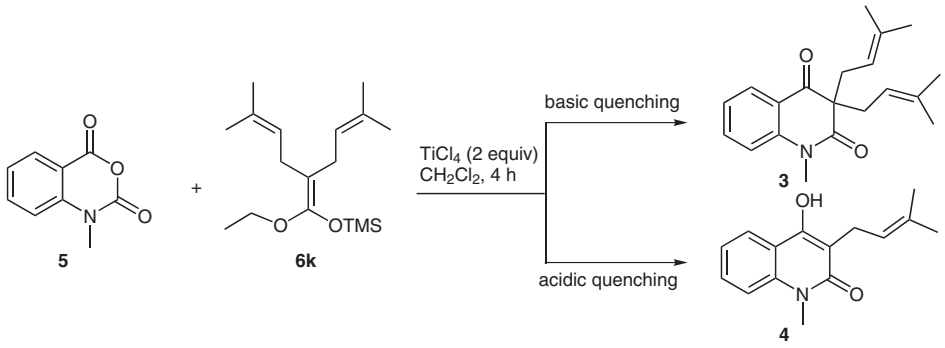
Silyl ketene acetal	Product		Yield (%)
 **6h**	 **7h**		71
 **6i**	 **10a**		43
 **6j**	 **10b**		46

We set the synthesis of the natural product 3,3-diisopentenyl-*N*-methylquinoline-2,4-dione[3] (**3**) as a further goal. The reaction of *N*-methylisatoic anhydride (**5**) with the silyl ketene acetal **6k** (Scheme 2) afforded, under the typical reaction conditions and work up, the natural product 3-demethyl-*N*-methylatanine (**4**) instead of the expected 3,3-disubstituted compound. This result led us to believe that although the reaction did yield the desired 3,3-diprenyl compound, this was unstable under the work-up conditions. We surmised that quenching the reaction mixture with water under acidic conditions may bring about partial deallylation of the product. Upon quenching the reaction with triethylamine and pouring the neutralized reaction mixture into a saturated solution of sodium bicarbonate, we obtained the 3,3-diisopentenyl-*N*-methylquinoline-2,4-dione (**3**) as the exclusive product (Scheme 2).

In summary, we have demonstrated a facile synthetic procedure for the preparation of 3,3- and 3-functionalized quinolinone and naphthyridinone derivatives in good yields. The titanium chloride promoted C-acylation of silyl ketene acetals with *N*-methylisatoic anhydride (**5**) or 2-methyl pyridoxazin-4-one (**8**) thus provides a useful, versatile synthetic tool. The variety of silyl acetals available makes this approach valuable for the synthesis of complex natural or designed molecules of biological interest.

All reactions were carried out under an argon atmosphere with anhydrous solvents under anhydrous conditions, unless otherwise noted. Commercially available THF, CH_2Cl_2 and diisopropyl amine were dried prior to use by distillation from sodium, phosphorus pentoxide and NaH, respectively. Petroleum ether (PE), where used, had a boiling range of 40–60 °C.

NMR data were obtained using a Varian Gemini 2000 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C). Chemical shifts are quoted in ppm, and coupling constants (*J*) are given in Hz. Melting points were recorded using a Galenkamp HFB-595 melting point appara-



Scheme 2 Total syntheses of 3,3-diisopentenyl-*N*-methylquinoline-2,4-dione (**3**) and 3-demethyl-*N*-methylatanine (**4**)

tus and are uncorrected. High-resolution mass spectra (HRMS) were recorded in the Liverpool University Mass spectra core facility on a VG 7070E instrument and were obtained by chemical ionozation (CI) with ammonia. Column chromatography was performed using Fluka Silica gel 60 (70–230 mesh ASTM). *N*-Methylisatoic anhydride (**5**) is commercially available. 2-Methylpyridoxazinone (**8**) was prepared according to the literature.[13]

Preparation of Silyl Ketene Acetals 6a–k; General Procedure

Silyl ketene acetals were prepared from the corresponding carboxylic esters according to the literature.[11] The esters were either commercially available or prepared according to the literature.[14] The syntheses of the α,α-diallyl ester for the preparation of silyl ketene acetal **6h** and the α,α-dimethylallyl ester for the preparation of the silyl ketene acetal **6k** are reported in the literature.[15,16]

An equimolar amount of *n*-BuLi (2.5 M in hexane, 11 mmol, 4.4 mL) was added dropwise to a stirred solution of anhydrous (*i*-Pr)$_2$NH (11 mmol, 1.11 g, 1.56 mL) in THF (10 mL) at 0 °C under argon. Stirring was continued for 15 min under the same conditions then the flask was cooled to –78 °C. The corresponding ester (11 mmol) was added dropwise and the mixture was stirred for an additional 30 min at –78 °C. TMSCl (12 mmol, 1.30 g, 1.51 mL) was added dropwise and the mixture was stirred for 3 h under the same conditions. MeI (40 mmol, 5.68 g, 2.49 mL) and then PE (30 mL) were added and the mixture was kept at 4 °C overnight. The precipitated LiCl and quaternary salt were removed by filtration and the filtrate was concentrated in vacuo to afford the desired silyl ketene acetal as a liquid, which was used directly without further purification.

1-Methoxy-2-methyl-1-trimethylsiloxypropene (**6a**) is commercially available. The silyl ketene acetals **6b**,[17] **6d**,[18] **6e**,[19] **6f**,[12,19] **6g**,[17] **6i**[18] and **6j**[20] were prepared according to the general procedure and their analytical data were in accordance with literature values.

1-Ethoxy-2-methyl-1-trimethylsiloxypentene (6c)

Mixture of *E*/*Z* isomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.18 (s, 9 H), 0.86 (t, *J* = 8 Hz, 3 H), 1.21 (t, *J* = 9 Hz, 3 H), 1.35 (m, 2 H), 1.48, 1.53 (2 × s, 3 H), 1.85–2.01 (m, 2 H), 3.69–3.80 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.14, 13.9, 14.0, 14.1, 14.5, 15.0, 19.9, 21.1, 21.4, 32.5, 32.9, 64.5, 64.6, 96.0, 96.1, 148.5, 148.6.

(2-Allyl-1-ethoxypenta-1,4-dienyloxy)trimethylsilane (6h)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.21 (s, 9 H), 1.22 (t, *J* = 7 Hz, 3 H), 2.67–2.76 (m, 4 H), 3.79 (q, *J* = 7 Hz, 2 H), 4.95–5.01 (m, 4 H), 5.6–5.8 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.2, 14.9, 32.6, 32.9, 65.0, 96.3, 114.6, 114.9, 137.1, 137.7, 150.0.

[1-Ethoxy-5-methyl-2-(3-methylbut-2-enyl)hexa-1,4-dienyloxy]trimethylsilane (6k)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.18 (s, 9 H), 1.20 (t, *J* = 6.9 Hz, 3 H), 1.58, 1.65 (2 × s, 12 H), 2.61 (2 × d, *J* = 6.9 Hz, 4 H), 3.77 (t, *J* = 6.9 Hz, 2 H), 5.00 (t, *J* = 1.4 Hz, 2 H).

Synthesis of 3,3-Disubstituted Quinoline-2,4-diones 7a–h and Natural Products 3 and 4; General Procedure

To a solution of *N*-methylisatoic anhydride (**5**; 70 mg, 0.40 mmol) in anhydrous CH_2Cl_2 (10 mL), silyl ketene acetal (2 equiv) and $TiCl_4$ (1 M in CH_2Cl_2; 0.80 mmol, 2 equiv) were added dropwise under argon. Stirring was continued for 4 h then the mixture was quenched by addition of H_2O (10 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were evaporated in vacuo. Et_2O (10 mL) was added to the residue and the precipitated *N*-methylisatoic anhydride was removed by filtration. The filtrate was evaporated in vacuo and the residue was purified by column chromatography to afford the desired product.

1,3,3-Trimethylquinoline-2,4-dione (7a)[9,21]

Purified by flash chromatography (PE–EtOAc, 7:3). Yield: 70 mg (86%); light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 6 H), 3.45 (s, 3 H), 7.14–7.20 (m, 2 H), 7.61 (app t, 1 H), 7.99 (dd, *J* = 1.4, 7.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0, 30.0, 53.2, 114.8, 120.0, 123.1, 128.3, 135.9, 143.2, 174.4, 197.8.

1,3-Dimethyl-3-ethylquinoline-2,4-dione (7b)[8e]

Purified by flash chromatography (PE–EtOAc, 7:3). Yield: 56 mg (64%); thick yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 8 Hz, 3 H), 1.41 (s, 3 H), 1.93 (m, 2 H), 3.43 (s, 3 H), 7.10–7.15 (m, 2 H), 7.58 (app t, 1 H), 7.95 (dd, *J* = 2, 7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.5, 21.9, 29.7, 32.7, 57.9, 114.7, 120.5, 123.0, 127.9, 135.9, 143.3, 173.8, 197.5.

1,3-Dimethyl-3-propylquinoline-2,4-dione (7c)

Purified by flash chromatography (PE–EtOAc, 8.5:1.5). Yield: 74 mg (79%); light-yellow solid; mp 84–86 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7 Hz, 3 H), 1.10–1.25 (m, 2 H), 1.47 (s, 3 H), 1.88–1.96 (m, 2 H), 3.47 (s, 3 H), 7.18 (app t, 2 H), 7.62 (app t, 1 H), 8.00 (dd, *J* = 2, 7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 18.5, 22.9, 29.8, 42.1, 57.5, 114.8, 120.5, 123.1, 128.2, 136.1, 143.4, 174.0, 197.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}NO_2$: 232.13375; found: 232.13341.

1,3-Dimethyl-3-isopropylquinoline-2,4-dione (7d)
Purified by flash chromatography (PE–EtOAc, 8:2). Yield: 63 mg (68%); yellow solid; mp 72–74 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 7 Hz, 3 H), 0.91 (d, *J* = 7 Hz, 3 H), 1.4 (s, 3 H), 2.19 (m, 1 H), 3.45 (s, 3 H), 7.11–7.17 (m, 2 H), 7.59 (app t, 1 H), 7.93 (dd, *J* = 2, 8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9, 17.9, 29.9, 37.6, 61.3, 114.6, 121.6, 123.1, 127.8, 135.7, 143.3, 173.7, 179.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}NO_2$: 232.13375; found: 232.13362.

3-Ethyl-1-methyl-3-phenylquinoline-2,4-dione (7e)[5,22]
Purified by flash chromatography ($CHCl_3$–MeOH, 10:0.1). Yield: 67 mg (60%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7 Hz, 3 H), 2.40–2.58 (m, 2 H), 3.56 (s, 3 H), 7.10–7.27 (m, 7 H), 7.55 (app t, 1 H), 7.99 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7, 23.9, 30.2, 67.4, 114.9, 121.5, 123.2, 126.6, 127.8, 128.2, 128.9, 136.0, 138.9, 142.9, 171.5, 195.2.

1-Methyl-3-spirocyclohexanequinoline-2,4-dione (7f)
Purified by flash chromatography (PE–EtOAc, 94:6). Yield: 62 mg (63%); off-white solid; mp 73–75 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45–1.49 (m, 2 H), 1.66–1.73 (m, 4 H), 1.91–1.97 (m, 4 H), 3.41 (s, 3 H), 7.07–7.14 (m, 2 H), 7.55 (app t, 1 H), 7.87 (dd, *J* = 2, 8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 25.2, 30.1, 31.6, 57.4, 114.4, 121.1, 123.0, 127.9, 135.2, 142.8, 174.0, 198.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}NO_2$: 244.13375; found: 244.13294.

3-Allyl-1,3-dimethylquinoline-2,4-dione (7g)
Purified by flash chromatography (PE–EtOAc, 9:1). Yield: 70 mg (76%); light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 3 H), 2.63–2.67 (m, 2 H), 3.43 (s, 3 H), 4.91–5.01 (m, 2 H), 5.50–5.59 (m, 1 H), 7.15 (app t, 2 H), 7.60 (app t, 1 H), 7.97 (dd, *J* = 2, 8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 29.8, 43.3, 57.3, 114.8, 119.1, 120.4, 123.1, 128.1, 132.4, 136.1, 143.3, 173.3, 197.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}NO_2$: 230.11810; found: 230.11777.

3,3-Diallyl-1-methylquinoline-2,4-dione (7h)[7d]
Purified by flash chromatography (PE–EtOAc, 9:1). Yield: 73 mg (71%); light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71–2.75 (m, 4 H), 3.45 (s, 3 H), 4.89 (d, *J* = 10.0 Hz, 2 H), 5.04 (d, *J* = 17.0 Hz, 2 H), 5.48–5.57 (m, 2 H), 7.11–7.18 (m, 2 H), 7.61 (dt, *J* = 1.4, 8 Hz, 1 H), 8.00 (dd, *J* = 8, 1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6, 43.0, 61.7, 114.9, 119.2, 121.0, 123.1, 127.9, 132.2, 136.3, 143.4, 172.3, 196.6.

3-Demethyl-*N*-methylatanine (4)[4]
Purified by flash chromatography (PE–EtOAc, 8:2). Yield: 54 mg (55%); light-yellow solid; mp 160–161 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 and 1.87 (2 × s, 6 H), 3.54 (d, *J* = 7.5 Hz, 2 H), 3.72 (s, 3 H), 5.42 (t, *J* = 7.5 Hz, 1 H), 7.23 (app t, 1 H), 7.32 (d, *J* = 8.4 Hz, 1 H), 7.55 (app t, 1 H), 7.93 (dd, *J* = 2, 8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 24.2, 26.0, 29.9, 109.1, 113.9, 116.3, 121.3, 121.8, 123.2, 130.6, 137.6, 138.8, 157.5, 163.6.

3,3-Diisopentenyl-*N*-methylquinoline-2,4-dione (3)[3]
Obtained using the general procedure described above, but worked up as follows: The reaction mixture was neutralized with Et_3N and poured into sat. $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were evaporated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 9:1, 1% Et_3N) to afford **3**. Yield: 77 mg (62%); light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 6 H), 1.56 (s, 6 H), 2.70 (m, 4 H), 3.46 (s, 3 H), 4.82 (t, *J* = 7 Hz, 2 H), 7.11 (app t, 2 H), 7.59 (app t, 1 H), 7.98 (dd, *J* = 1.7, 7.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 25.9, 29.7, 37.8, 62.2, 114.7, 118.2, 121.4, 122.8, 127.6, 135.7, 136.0, 143.6, 173.1, 197.6.

Synthesis of 3,3-Disubstituted 1,8-Naphthyridine-2,4-diones 9a–c; General Procedure
To a solution of 2-methylpyridoxazin-4-one (**8**; 70 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (10 mL), silyl ketene acetal (0.86 mmol, 2 equiv) and $TiCl_4$ (1 M in CH_2Cl_2; 0.86 mmol, 0.86 mL, 2 equiv) were added dropwise under argon. Stirring was continued for 4 h then the mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were evaporated in vacuo to give a mixture of the C-acylation product and the naphthyridine-2,4-dione derivative. HCl (6 N, 5 mL) was added to the crude mixture, which was refluxed for 2 h and then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were evaporated in vacuo and purified by column chromatography to afford the desired product.

3,3-Dimethyl-1,8-naphthyridine-2,4-dione (9a)[9]
Purified by flash chromatography ($CHCl_3$–MeOH, 99:1). Yield: 59 mg (71%); light-yellow solid; mp 202–205 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (s, 6 H), 7.17 (dd, *J* = 5, 8 Hz, 1 H), 8.27 (dd, *J* = 2, 8 Hz, 1 H), 8.69 (dd, *J* = 2, 5 Hz, 1 H), 11.06 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 53.4, 114.0, 119.5, 137.7, 153.8, 154.6, 175.3, 197.1.

3-Ethyl-3-methyl-1,8-naphthyridine-2,4-dione (9b)
Purified by flash chromatography (PE–EtOAc, 8:2). Yield: 49 mg (55%); white solid; mp 159–161 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7 Hz, 3 H), 1.50 (s, 3 H), 2.04 (m, 2 H), 7.16 (dd, *J* = 5, 8 Hz, 1 H), 8.26 (dd, *J* = 2, 8 Hz, 1 H), 8.63 (dd, *J* = 2, 5 Hz, 1 H), 9.66 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.6, 22.2, 32.5, 58.3, 114.6, 119.6, 137.2, 153.7, 154.8, 176.4, 197.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}N_2O_2$: 205.09770; found: 205.09739.

3-Methyl-3-propyl-1,8-naphthyridine-2,4-dione (9c)
Purified by flash chromatography (PE–EtOAc, 7:3). Yield: 83 mg (88%); white solid; mp 142–144 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7 Hz, 3 H), 1.12–1.28 (m, 2 H), 1.49 (s, 3 H), 1.94–2.00 (m, 2 H), 7.15 (dd, *J* = 5, 8 Hz, 1 H), 8.26 (dd, *J* = 2, 8 Hz, 1 H), 8.72 (dd, *J* = 2, 5 Hz, 1 H), 11.39 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 18.6, 22.9, 41.5, 57.6, 114.5, 119.5, 137.4, 154.1, 154.5, 174.9, 197.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}N_2O_2$: 219.11335; found: 219.11394.

1,3-Dimethyl-4-hydroxyquinolin-2-one (10a)[23]

To a solution of *N*-methylisatoic anhydride (**5**; 0.40 mmol, 70 mg) in anhydrous CH_2Cl_2 (10 mL), silyl ketene acetal (**6i**; 0.80 mmol, 2 equiv) and $TiCl_4$ (1 M in CH_2Cl_2; 0.80 mmol, 2 equiv) were added dropwise under argon. Stirring was continued for 5 h then the mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were evaporated in vacuo and the residue was recrystallized (CH_2Cl_2–Et_2O) to afforded **10a**. Yield: 32 mg (43%); white solid; mp 217–219 °C (Lit.[23] 216–218 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.05 (s, 3 H), 3.59 (s, 3 H), 7.24 (app t, 1 H), 7.46 (d, *J* = 8 Hz, 1 H), 7.56 (app t, 1 H), 7.96 (dd, *J* = 2, 8 Hz, 1 H), 10.8 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.2, 29.2, 106.4, 114.2, 116.2, 121.2, 122.8, 130.1, 138.1, 156.0, 163.0.

4-Hydroxy-1-methyl-3-phenylquinolin-2-one (10b)[23]

To a solution of *N*-methylisatoic anhydride (**5**; 0.40 mmol, 70 mg) in anhydrous CH_2Cl_2 (10 mL), silyl ketene acetal (**6j**; 0.80 mmol, 2 equiv) and $TiCl_4$ (1 M in CH_2Cl_2; 0.80 mmol, 2 equiv) were added dropwise under argon. Stirring was continued for 5 h then the mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were evaporated in vacuo and HCl (6 N, 5 mL) was added to the residue. The mixture was refluxed for 2 h then extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were evaporated in vacuo to afford **10b**. Yield: 46 mg (46%); off-white solid; mp 220–222 °C (Lit.[23] 222–224 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 3 H), 6.20 (br s, 1 H), 7.24–7.30 (m, 1 H), 7.37–7.53 (m, 6 H), 7.59–7.65 (m, 1 H), 8.06 (dd, *J* = 2, 8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 112.0, 114.0, 115.5, 121.9, 124.2, 128.7, 129.6, 130.7, 131.4, 131.6, 139.5, 155.7, 162.5.

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