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SYNTHESIS OF (±)-CEPHALANTHRIN A USING BAEYER-VILLIGER OXIDATION

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Abstract – Indoloquinazoline alkaloid (±)-cephalanthrin A was synthesized through the Baeyer-Villiger oxidation of the phenyl ketone derived from aldol reaction of tryptanthrin and acetophenone.

Alkaloids, characterized by an indolo[2,1-*b*]quinazoline core, exhibit a wide range of potential biological activities (Figure 1).[1] The diverse biological activities and structural intricacy elicited intense synthetic interest.[2] (+)-Cephalanthrins A (**3a**) and B (**4**) were first isolated from *Cephalantheropsis gracilis* in 2015.[3] The first enantioselective total synthesis of (+)-**3a** was achieved by the Ni-catalyzed enantioselective aldol-decarboxylation reaction of malonic acid and tryptanthrin (**1a**). The absolute configuration of (+)-**3a** was determined as (*S*) based on the asymmetric synthesis and X-ray analysis.[4]

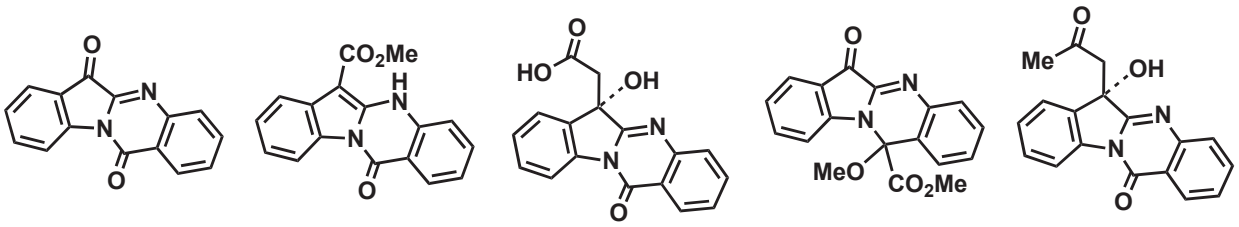
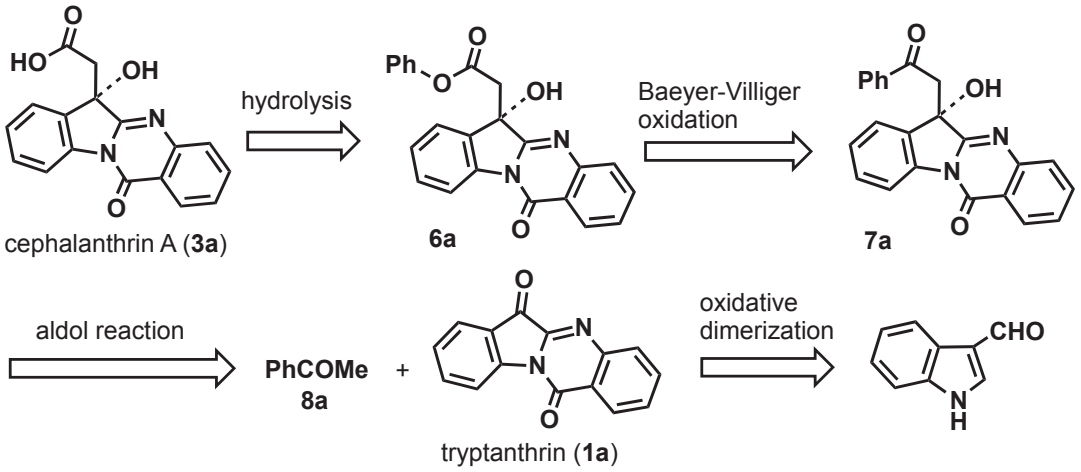


Figure 1. Indoloquinazoline alkaloids

We previously reported the one-pot synthesis of tryptanthrin (**1a**) by the oxidative dimerization of indole-3-carbaldehyde,[5a] and skatole.[5b] In this paper, we describe the synthesis of (±)-cephalanthrin A (**3a**) starting from tryptanthrin (**1a**) and acetophenone **8a** through Baeyer-Villiger oxidation of phenyl

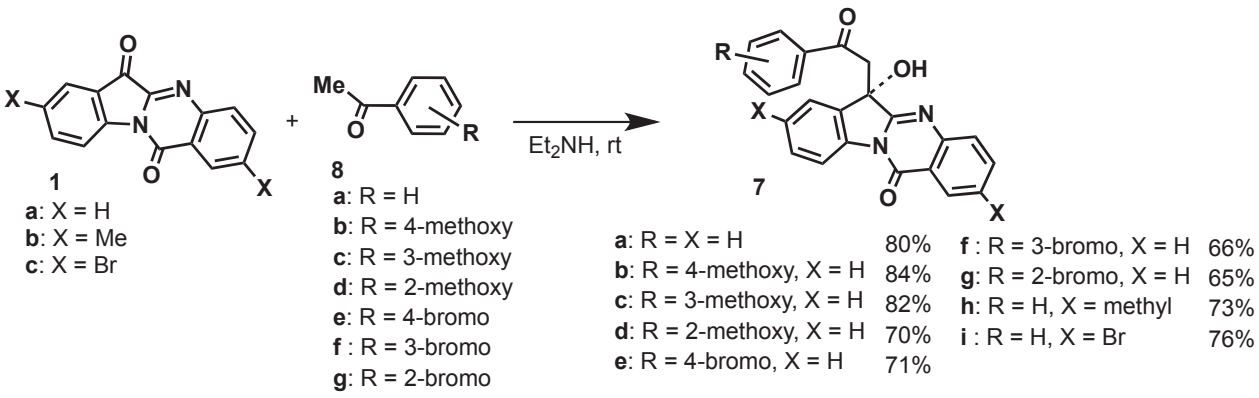
ketone **7a**.

Baeyer-Villiger oxidation is a valuable process by which ketones are converted into esters or lactones.[6] In 2013, Baeyer-Villiger oxidation of phaitanthrin A (**5**) with *m*-CPBA in CH_2Cl_2 was reported. Because the Me group is a poor migrator, the methyl ketone in **5** was converted to acetate ester though migration of the methylene unit.[7] Therefore, we were interested in whether phenyl migration would be dominant during the oxidation of ketone **7a**, leading to ester **6a**. Tryptanthrin (**1a**) can be obtained on the gram scale from indole-3-carbaldehyde,[5a] and ketone **7a** can be obtained by aldol reaction of **1a** with acetophenone **8a**. Hydrolysis of **6a** could produce (±)-cephalanthrin A (**3a**) (Scheme 1).



Scheme 1

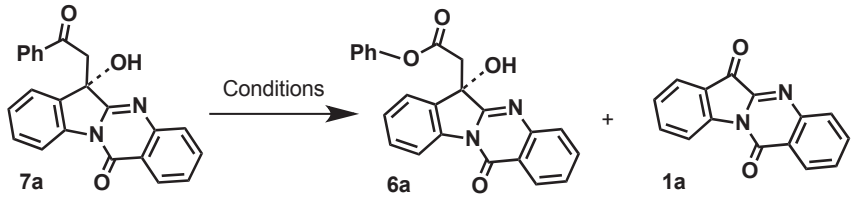
Aldol reaction of **1** and acetophenone **8** (4 equiv) was performed in diethylamine at room temperature for 16 h, smoothly affording **7** (Scheme 2).



Scheme 2

Baeyer-Villiger oxidation of ketone **7a** was investigated (Table 1). Initially, **7a** was treated with *m*-CPBA, but no reaction occurred (Entry 1). Treating **7a** with urea hydrogen peroxide (UHP) produced **1a** in 10% yield without **6a** (Entry 2). Because Baeyer-Villiger oxidation is assisted by an acid or base,[6,8] the reaction was examined in the presence of $NaHCO_3$, although only **1a** was obtained in 20% yield (Entry 3). In addition, the oxidation was examined in the presence of a catalytic amount of acid. Although treating **7a** with concentrated H_2SO_4 in CH_2Cl_2 afforded trace amounts of **6a** and **1a** (Entry 4), replacing CH_2Cl_2 with MeCN increased the yield to 58% (Entry 5). Moreover, the reaction in DMF produced **6a** in 72% yield (Entry 6). TFA and AcOH were less effective than concentrated H_2SO_4 (Entries 7 and 8). In addition, UHP was used for the oxidation instead of *m*-CPBA. The oxidation in DMF produced trace amounts of **6a** (Entry 9). The reaction was greatly accelerated in MeCN, affording **6a** in 80% yield (Entry 10). Only trace amounts of **1a** were produced with AcOH (Entry 11), and **6a** was obtained in 53% yield in the presence of TFA (Entry 12).

Table 1. Baeyer-Villiger oxidation of ketone **7a**

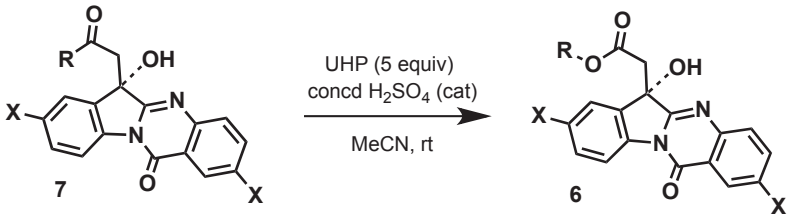


Entry	Conditions	Yield (%)[a]	
		6a	**1a**
1	*m*-CPBA (5 equiv), CH_2Cl_2, rt, 72 h	---[b]	---
2	UHP (5 equiv), CH_2Cl_2, rt, 16 h	---[c]	10
3	*m*-CPBA (5 equiv), $NaHCO_3$ (5 equiv), CH_2Cl_2, rt, 72 h	---[d]	20
4	*m*-CPBA (5 equiv), concd H_2SO_4 (cat), CH_2Cl_2, rt, 16 h	6	5
5	*m*-CPBA (5 equiv), concd H_2SO_4 (cat), MeCN, rt, 16 h	58	---
6	*m*-CPBA (5 equiv), concd H_2SO_4 (cat), DMF, rt, 16 h	72	---
7	*m*-CPBA (5 equiv), TFA (cat), DMF, rt, 16 h	68	---
8	*m*-CPBA (5 equiv), AcOH (cat), DMF, rt, 16 h	34	---
9	UHP (5 equiv), concd H_2SO_4 (cat), DMF, rt, 16 h	5	---
10	UHP (5 equiv), concd H_2SO_4 (cat), MeCN, rt, 16 h	80	---
11	UHP (5 equiv), AcOH (cat), MeCN, rt, 16 h	---	10
12	UHP (5 equiv), TFA (cat), MeCN, rt, 16 h	53	---

[a]Isolated yield. [b]Recovery of **7a** in 75%. [c]Recovery of **7a** in 50%. [d]Recovery of **7a** in 40%.

In addition, the oxidation of aryl ketones **7b**–**7i** was examined under the optimized conditions (UHP, concentrated H_2SO_4, MeCN). Initially, methoxyphenyl ketones **7b**–**7d** were oxidized. The reaction of **7b** and **7c** reached completion within 16 h to produce **6b** and **6c** in 75% and 79% yields, respectively (Table 2, Entries 1 and 2), and **6d** was obtained in 45% yield from **7d**, although the reaction took 24 h (Entry 3). Moreover, bromophenyl ketones **7e**–**7g** were oxidized under the same conditions to give **6e**–**6g** but in decreased yields (40% to 60%) (Entries 4–6) and required a long reaction time (96 h). The reactions of **7h** and **7i**, which had a Me or Br substituent on the quinazoline system, respectively, produced **6h** in 70% yield and **6i** in 65% yield (Entries 7 and 8).

Table 2. Baeyer-Villiger oxidation of ketones **7b**–**7i**

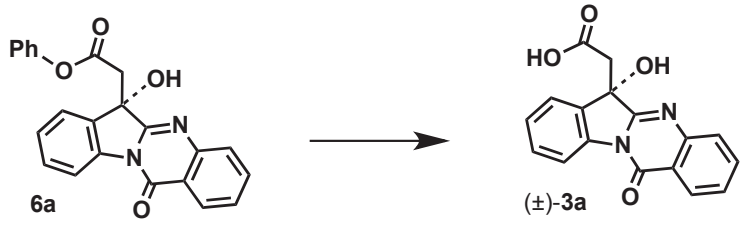


Entry	7	X	Reaction time	Yield (%)[a]
1	**7b** (R = 4-methoxyphenyl)	H	16 h	75 (**6b**)
2	**7c** (R = 3-methoxyphenyl)	H	16 h	79 (**6c**)
3	**7d** (R = 2-methoxyphenyl)	H	24 h	45 (**6d**)
4	**7e** (R = 4-bromophenyl)	H	96 h	52 (**6e**)
5	**7f** (R = 3-bromophenyl)	H	96 h	60 (**6f**)
6	**7g** (R = 2-bromophenyl)	H	96 h	40 (**6g**)
7	**7h** (R = phenyl)	Me	96 h	70 (**6h**)
8	**7i** (R = phenyl)	Br	96 h	65 (**6i**)

[a]Isolated yield.

Finally, **6a** was subjected to hydrolytic cleavage. Ester **6a** was not appreciably hydrolyzed by 10% aq. KOH in 1,4-dioxane, and (±)-cephalanthrin A (**3a**) was obtained in 25% yield by treating **6a** with 10% aq. NaOH. Hydrolysis of **6a** with Cs_2CO_3 in THF/MeOH produced (±)-**3a** in 60% yield, whereas hydrolysis of **6a** with LiOH in THF/H_2O afforded (±)-**3a** in 87% yield (Scheme 3). The NMR data of (±)-**3a** were good agreement with those reported in the literature.[3]

In conclusion, (±)-cephalanthrin A (**3a**) was synthesized starting from tryptanthrin (**1a**) and acetophenone (**8a**) through Baeyer-Villiger oxidation of ketone **7a**.



10% aq. KOH, 1,4-dioxane, rt, 16 h	---
10% aq. NaOH, 1,4-dioxane, rt, 16 h	25%
Cs_2CO_3 (3 equiv), THF/H_2O, rt, 16 h	60%
LiOH (3 equiv), THF/H_2O, rt, 3 h	87%

Scheme 3

EXPERIMENTAL

Melting points were recorded with a Yamato MP21 and were uncorrected. High-resolution MS spectra were recorded with a JEOL JMS-T100LP mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer. The NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer, and chemical shifts are expressed in ppm (δ).

General procedure for aldol reaction between 1a and 8: Acetophenone **8** (40 mmol) was added to a solution of tryptanthrin (**1**) (10 mmol) in diethylamine (80 mL), and the mixture was stirred at room temperature for 16 h. The mixture was added to 10% HCl aqueous solution (100 mL). The mixture was extracted with AcOEt (500 mL), and the extract was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (1:2) to give **7**.

6-Hydroxy-6-(2-oxo-2-phenylethyl)indolo[2,1-*b*]quinazolin-12(6*H*)-one (7a): A colorless solid. Mp 224-225 °C. IR ($CHCl_3$): 3447, 3013, 2976, 1681, 1670 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.12 (d, J = 18.3 Hz, 1H), 4.51 (d, J = 18.3 Hz, 1H), 6.56 (br s, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.42-7.48 (m, 3H), 7.57-7.61 (m, 2H), 7.65 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.81-7.84 (m, 3H), 8.30 (dd, J = 1.2, 8.1 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 48.3, 75.6, 116.5, 121.9, 124.3, 127.0, 127.1, 127.9, 128.0, 128.5, 129.3, 130.2, 134.3, 134.7, 135.3, 136.1, 139.9, 147.7, 159.5, 162.0, 197.3. HRMS (ESI) *m/z*: Calcd for $C_{23}H_{16}N_2NaO_3$ [(M + Na)$^+$] 391.1059. Found 391.1062.

6-Hydroxy-6-[2-(4-methoxyphenyl)-2-oxoethyl]indolo[2,1-*b*]quinazolin-12(6*H*)-one (7b): A colorless solid. Mp 213-214 °C. IR ($CHCl_3$): 3447, 3012, 2976, 1680, 1672, 1647, 1602 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.77 (s, 3H), 4.05 (dd, J = 2.3, 18.4 Hz, 1H), 4.44 (d, J = 18.4 Hz, 1H), 6.53 (br s, 1H), 6.94 (d, J = 8.6 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 8.1 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.6 Hz, 2H), 7.83 (t, J = 8.0 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 47.9, 56.1, 75.7, 114.4, 116.5, 121.9, 124.2, 126.9, 127.8, 127.9, 129.1, 130.1, 130.9, 134.8, 135.3, 140.0, 147.7, 159.5, 162.2, 164.0, 195.5. HRMS (ESI) *m/z*: Calcd for $C_{24}H_{18}N_2NaO_4$ [(M + Na)$^+$] 421.1164. Found 421.1161.

6-Hydroxy-6-[2-(3-methoxyphenyl)-2-oxoethyl]indolo[2,1-*b*]quinazolin-12(6*H*)-one (7c): A colorless solid. Mp 170-172 °C. IR ($CHCl_3$): 3385, 3365, 3014, 2976, 1683, 1647, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.71 (s, 3H), 4.11 (d, J = 18.9 Hz, 1H), 4.51 (d, J = 18.9 Hz, 1H), 6.55 (br s, 1H), 7.14 (dd, J = 2.9, 8.0 Hz, 1H), 7.26 (s, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.83 (t, J = 8.6 Hz, 1H), 8.31 (d, J = 8.1 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 48.4, 55.8, 75.6, 112.4, 116.5, 120.8, 121.2, 121.9, 124.3, 126.9, 127.1, 127.9, 128.0, 130.2, 130.5, 134.7, 135.3, 137.4, 140.0, 147.6, 159.5, 159.9, 162.0, 197.1. HRMS (ESI) *m/z*: Calcd for $C_{24}H_{18}N_2NaO_4$ [$(M + Na)^+$] 421.1164. Found 421.1168.

6-Hydroxy-6-[2-(2-methoxyphenyl)-2-oxoethyl]indolo[2,1-*b*]quinazolin-12(6*H*)-one (7d): A colorless solid. Mp 206-208 °C. IR ($CHCl_3$): 3447, 3010, 2976, 1684, 1647, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.94 (s, 3H), 4.11 (dd, J = 18.9 Hz, 1H), 4.26 (d, J = 18.4 Hz, 1H), 6.50 (br s, 1H), 6.84 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 1.7, 8.0 Hz, 1H), 7.28 (dt, J = 1.2, 7.5 Hz, 1H), 7.44-7.49 (m, 2H), 7.57-7.60 (m, 2H), 7.71 (d, J = 7.5 Hz, 1H), 7.84 (dt, J = 1.8, 8.6 Hz, 1H), 8.29 (dd, J = 1.2, 8.0 Hz, 1H), 8.41 (d, J = 8.1 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 53.6, 56.5, 75.5, 113.1, 116.5, 120.9, 121.9, 124.2, 126.4, 126.9, 127.8, 128.0, 130.0, 130.1, 134.6, 135.2, 135.3, 139.9, 147.7, 159.4, 159.5, 162.1, 197.7. HRMS (ESI) *m/z*: Calcd for $C_{24}H_{18}N_2NaO_4$ [$(M + Na)^+$] 421.1164. Found 421.1162.

6-Hydroxy-6-[2-(4-bromophenyl)-2-oxoethyl]indolo[2,1-*b*]quinazolin-12(6*H*)-one (7e): A colorless solid. Mp 201-202 °C. IR ($CHCl_3$): 3447, 3016, 2976, 1728, 1684 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.09 (d, J = 18.3 Hz, 1H), 4.49 (d, J = 18.4 Hz, 1H), 6.57 (br s, 1H), 7.29 (dt, J = 1.2, 6.9 Hz, 1H), 7.47 (dt, J = 1.2, 8.0 Hz, 1H), 7.59 (dt, J = 1.2, 8.6 Hz, 1H), 7.63-7.66 (m, 3H), 7.70 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 6.9 Hz, 2H), 7.83 (dt, J = 1.2, 7.5 Hz, 1H), 8.30 (dd, J = 1.2, 8.1 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ: 48.2, 75.6, 116.5, 121.9, 124.3, 127.0, 127.1, 127.9, 128.0, 128.5, 130.3, 130.6, 132.3, 134.5, 135.1, 135.3, 139.9, 147.6, 159.5, 161.9, 196.6. HRMS (ESI) *m/z*: Calcd for $C_{23}H_{15}BrN_2NaO_3$ [$(M + Na)^+$] 469.0164, 471.0143. Found 469.0159, 471.0148.

6-Hydroxy-6-[2-(3-bromophenyl)-2-oxoethyl]indolo[2,1-*b*]quinazolin-12(6*H*)-one (7f): A colorless solid. Mp 203-204 °C. IR ($CHCl_3$): 3458, 3014, 2976, 1684, 1651, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.11 (d, J = 18.3 Hz, 1H), 4.54 (d, J = 18.3 Hz, 1H), 6.57 (br s, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.47 (dt, J = 1.1, 8.0 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1H), 7.82-7.85 (m, 2H), 8.30 (d, J = 6.9 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 48.3, 75.6, 116.5, 121.9, 122.7, 124.4, 127.0, 127.1, 127.6, 127.9, 128.0, 130.3, 131.2, 131.5, 134.5, 135.3, 136.9, 138.0, 139.9, 147.6, 159.5, 161.9, 196.4. HRMS (ESI) *m/z*: Calcd for $C_{23}H_{15}BrN_2NaO_3$ [$(M + Na)^+$] 469.0164, 471.0143. Found 469.0163, 471.0156.

6-Hydroxy-6-[2-(2-bromophenyl)-2-oxoethyl]indolo[2,1-*b*]quinazolin-12(6*H*)-one (7g): A colorless solid. Mp 198-199 °C. IR ($CHCl_3$): 3447, 3419, 3014, 2976, 1683, 1649 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.05 (d, J = 17.8 Hz, 1H), 4.27 (d, J = 17.8 Hz, 1H), 6.62 (br s, 1H), 7.32-7.35 (m, 2H), 7.38 (dt, J = 1.2,

7.5 Hz, 1H), 7.49 (dt, *J* = 1.2, 8.0 Hz, 2H), 7.56 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.60 (dt, *J* = 1.2, 7.4 Hz, 1H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.86 (dt, *J* = 1.8, 7.9 Hz, 1H), 8.29 (dd, *J* = 1.2, 8.1 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 51.5, 75.5, 116.6, 118.5, 121.9, 124.7, 126.9, 127.1, 127.9, 128.1, 128.3, 129.8, 130.4, 133.1, 133.9, 134.2, 135.4, 139.7, 139.8, 147.6, 159.4, 161.4, 200.1. HRMS (ESI) *m/z*: Calcd for $C_{23}H_{15}BrN_2NaO_3$ [(M + Na)$^+$] 469.0164, 471.0143. Found 469.0158, 471.0151.

6-Hydroxy-2,8-dimethyl-6-(2-oxo-2-phenylethyl)indolo[2,1-*b*]quinazolin-12(6*H*)-one (7h): A colorless solid. Mp 214-216 °C. IR ($CHCl_3$): 3447, 3014, 2976, 1716, 1680, 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.29 (s, 3H), 2.46 (s, 3H), 4.10 (d, *J* = 18.3 Hz, 1H), 4.45 (d, *J* = 18.3 Hz, 1H), 6.49 (br s, 1H), 7.25 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.56-7.59 (m, 2H), 7.62 (dd, *J* = 1.2, 8.6 Hz, 1H), 7.82 (d, *J* = 6.9 Hz, 2H), 8.08 (s, 1H), 8.29 (d, *J* = 8.6 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 21.3, 21.4, 48.3, 75.5, 116.3, 121.7, 124.7, 126.3, 127.8, 128.5, 129.3, 130.4, 134.2, 134.7, 136.1, 136.3, 136.4, 137.5, 137.8, 145.7, 161.3, 197.2. HRMS (ESI) *m/z*: Calcd for $C_{25}H_{20}N_2NaO_3$ [(M + Na)$^+$] 419.1372. Found 419.1375.

6-Hydroxy-2,8-dibromo-6-(2-oxo-2-phenylethyl)indolo[2,1-*b*]quinazolin-12(6*H*)-one (7i): A colorless solid. Mp 258-260 °C (decomp.). IR ($CHCl_3$): 3447, 3017, 2976, 1716, 1688 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.13 (d, *J* = 18.4 Hz, 1H), 4.63 (d, *J* = 18.9 Hz, 1H), 6.70 (br s, 1H), 7.45 (t, *J* = 8.1 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.69 (dd, *J* = 1.7, 8.6 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.94 (d, *J* = 1.7 Hz, 1H), 7.99 (dd, *J* = 2.3, 8.6 Hz, 1H), 8.33 (d, *J* = 8.6 Hz, 1H), 8.38 (d, *J* = 2.3 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 48.2, 75.6, 118.4, 119.7, 120.7, 123.4, 127.6, 128.6, 129.2, 129.3, 130.4, 133.1, 134.4, 135.9, 137.3, 138.4, 138.9, 146.6, 158.2, 162.1, 197.5. HRMS (ESI) *m/z*: Calcd for $C_{23}H_{14}Br_2N_2NaO_3$ [(M + Na)$^+$] 546.9269, 548.9248, 550.9228. Found 546.9262, 548.9246, 550.9241.

General procedure for Baeyer-Villiger oxidation: UHP (941 mg, 10 mmol) was added to a solution of ketone **7** (2 mmol) in MeCN (30 mL), followed by the addition of concentrated H_2SO_4 (10 μL) at 0 °C. The mixture was stirred at room temperature. After specific time, the resulting mixture was added to saturated $NaHCO_3$ solution, extracted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (1:2) to give ester **6**.

Phenyl 2-(6-hydroxy-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (6a): A colorless solid. Mp 197-198 °C. IR ($CHCl_3$): 3393, 1703, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.52 (d, *J* = 16.0 Hz, 1H), 3.69 (d, *J* = 16.1 Hz, 1H), 4.96 (br s, 1H), 6.78 (d, *J* = 8.1 Hz, 2H), 7.11-7.24 (m, 5H), 7.46 (td, *J* = 1.7, 7.0 Hz, 1H), 7.62 (d, *J* = 6.9 Hz, 1H), 7.71-7.77 (m, 2H), 8.16 (d, *J* = 7.5 Hz, 1H), 8.26 (d, *J* = 8.1 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ: 43.3, 75.5, 116.9, 121.3, 121.7, 123.7, 126.2, 127.1, 127.2, 127.6, 127.8, 129.5, 130.8, 131.3, 134.6, 139.0, 147.2, 149.9, 159.4, 159.8, 168.3. HRMS (ESI) *m/z*: Calcd for $C_{23}H_{16}N_2NaO_4$ [(M + Na)$^+$] 407.1008. Found 407.1005.

4-Methoxyphenyl 2-(6-hydroxy-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (6b): A

colorless solid. Mp 169-170 °C. IR ($CHCl_3$): 3446, 1749, 1681, 1649, 1604 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.60 (s, 3H), 3.61 (d, *J* = 15.5 Hz, 1H), 3.66 (d, *J* = 15.5 Hz, 1H), 6.48 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 9.2 Hz, 2H), 6.77 (br s, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.88 (t, *J* = 7.5 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 43.8, 55.9, 75.5, 114.9, 116.6, 121.8, 122.4, 124.9, 127.0, 127.3, 128.2, 130.8, 133.4, 135.5, 139.6, 143.5, 147.5, 157.4, 159.3, 161.1, 168.4. HRMS (ESI) *m/z*: Calcd for $C_{24}H_{18}N_2NaO_5$ [$(M + Na)^+$] 437.1113. Found 437.1116.

3-Methoxyphenyl 2-(6-hydroxy-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (6c): A colorless solid. Mp 145-146 °C. IR ($CHCl_3$): 3361, 3336, 1759, 1683, 1666, 1649, 1606 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.56 (s, 3H), 3.62 (d, *J* = 15.5 Hz, 1H), 3.67 (d, *J* = 15.5 Hz, 1H), 6.06 (t, *J* = 2.3 Hz, 1H), 6.15 (dd, *J* = 1.7, 8.0 Hz, 1H), 6.66 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.81 (br s, 1H), 7.10 (t, *J* = 8.6 Hz, 1H), 7.43 (td, *J* = 1.2, 6.9 Hz, 1H), 7.55 (td, *J* = 1.2, 8.1 Hz, 1H), 7.60 (td, *J* = 1.2, 7.5 Hz, 1H), 7.79 (d, *J* = 6.9 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.88 (td, *J* = 1.1, 7.5 Hz, 1H), 8.26 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 43.9, 55.8, 75.5, 107.4, 112.3, 113.8, 116.6, 121.8, 125.1, 127.0, 127.4, 128.1, 128.2, 130.5, 130.9, 133.3, 135.5, 139.5, 147.5, 151.1, 159.3, 160.5, 160.9, 167.9. HRMS (ESI) *m/z*: Calcd for $C_{24}H_{18}N_2NaO_5$ [$(M + Na)^+$] 437.1113. Found 437.1112.

2-Methoxyphenyl 2-(6-hydroxy-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (6d): A colorless solid. Mp 170-172 °C. IR ($CHCl_3$): 3462, 3446, 1681, 1668, 1656 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.35 (s, 3H), 3.65 (d, *J* = 16.6 Hz, 1H), 3.69 (d, *J* = 15.5 Hz, 1H), 6.60 (dd, *J* = 1.7, 8.0 Hz, 1H), 6.72-6.75 (m, 2H), 6.88 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.06 (dt, *J* = 1.7, 8.3 Hz, 1H), 7.42 (dt, *J* = 1.1. 8.0 Hz, 1H), 7.52 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.59 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.78 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.87 (dt, *J* = 1.2, 8.0 Hz, 1H), 8.26 (dd, *J* = 1.2, 8.1 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 43.2, 55.9, 75.3, 113.3, 116.5, 120.9, 121.9, 122.6, 124.9, 126.9, 127.2, 127.5, 128.1, 130.7, 133.5, 135.4, 139.1, 139.7, 147.6, 150.9, 159.3, 161.0, 167.5. HRMS (ESI) *m/z*: Calcd for $C_{24}H_{18}N_2NaO_5$ [$(M + Na)^+$] 437.1113. Found 437.1115.

4-Bromophenyl 2-(6-hydroxy-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (6e): A colorless solid. Mp 223-224 °C. IR ($CHCl_3$): 3462, 3446, 1749, 1684 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.67 (s, 2H), 6.61 (d, *J* = 8.6 Hz, 2H), 6.79 (br s, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.88 (t, *J* = 6.9 Hz, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 8.39 (d, *J* = 8.1 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 43.7, 75.4, 116.6, 118.8, 121.9, 124.1, 125.0, 127.0, 127.3, 128.1, 128.2, 130.9, 132.9, 133.3, 135.5, 139.5, 147.5, 149.4, 159.3, 160.9, 168.0. HRMS (ESI) *m/z*: Calcd for $C_{23}H_{15}BrN_2NaO_4$ [$(M + Na)^+$] 485.0113, 487.0092. Found 485.0109, 487.0085.

3-Bromophenyl 2-(6-hydroxy-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (6f): A colorless solid. Mp 184-185 °C. IR ($CHCl_3$): 3447, 1749, 1684 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.64 (d, *J* = 16.1 Hz, 1H), 3.68 (d, *J* = 16.1 Hz, 1H), 6.65 (dd, *J* = 1.8, 7.5 Hz, 1H), 6.81 (br s, 1H), 6.84 (t, *J* = 2.3 Hz,

1H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 8.1 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 2H), 7.88 (t, *J* = 7.5 Hz, 1H), 8.26 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 43.7, 75.4, 116.6, 121.1, 121.8, 121.9, 124.9, 125.1, 127.0, 127.4, 128.1, 128.2, 129.6, 130.9, 131.8, 133.3, 135.5, 139.5, 147.5, 150.8, 159.3, 160.9, 168.0. HRMS (ESI) *m/z*: Calcd for $C_{23}H_{15}BrN_2NaO_4$ [(M + Na)$^+$] 485.0113, 487.0092. Found 485.0110, 487.0092.

2-Bromophenyl 2-(6-hydroxy-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (6g): A colorless solid. Mp 213-215 °C. IR ($CHCl_3$): 3523, 3446, 1762, 1683 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.74 (d, *J* = 16.6 Hz, 1H), 3.79 (d, *J* = 16.6 Hz, 1H), 6.81 (br s, 1H), 6.85 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.08 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.25 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.40 (dt, *J* = 1.1, 7.5 Hz, 1H), 7.49 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.51 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.59 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.87 (dt, *J* = 1.2, 6.9 Hz, 1H), 8.25 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 43.2, 75.2, 115.7, 116.6, 121.9, 124.2, 125.1, 127.0, 127.3, 128.1, 128.2, 128.6, 129.6, 130.8, 133.3, 133.5, 135.4, 139.7, 147.5, 147.7, 159.3, 160.8, 167.5. HRMS (ESI) *m/z*: Calcd for $C_{23}H_{15}BrN_2NaO_4$ [(M + Na)$^+$] 485.0113, 487.0092. Found 485.0111, 487.0085.

Phenyl 2-(6-hydroxy-2,8-dimethyl-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (6h): A colorless solid. Mp 218-220 °C. IR ($CHCl_3$): 3446, 1749, 1680, 1647 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.38 (s, 3H), 2.45 (s, 3H), 3.59 (d, *J* = 15.5 Hz, 1H), 3.66 (d, *J* = 15.5 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 2H), 6.72 (br s, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.59 (s, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 8.03 (s, 1H), 8.26 (d, *J* = 8.1 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 21.3, 21.4, 43.8, 75.3, 116.3, 121.6, 125.3, 126.3, 126.5, 127.9, 129.9, 131.0, 133.5, 136.5, 136.8, 137.4, 137.9, 145.5, 150.2, 159.1, 160.3, 168.1. HRMS (ESI) *m/z*: Calcd for $C_{25}H_{20}N_2NaO_4$ [(M + Na)$^+$] 435.1321. Found 435.1325.

Phenyl 2-(2,8-dibromo-6-hydroxy-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (6i): A colorless solid. Mp 222-224 °C. IR ($CHCl_3$): 3446, 1738, 1684 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.54 (d, *J* = 16.6 Hz, 1H), 3.71 (d, *J* = 16.6 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.22-7.28 (m, 4H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 7.86 (dd, *J* = 2.3, 8.6 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 8.19 (d, *J* = 1.7 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ: 43.1, 75.3, 118.2, 120.9, 121.2, 122.0, 122.8, 126.4, 127.1, 129.5, 129.6, 133.5, 133.9, 137.6, 138.2, 145.9, 149.8, 158.4, 159.2, 168.1. HRMS (ESI) *m/z*: Calcd for $C_{23}H_{14}Br_2N_2NaO_4$ [(M + Na)$^+$] 562.9218, 564.9198, 566.9177. Found 562.9225, 564.9203, 566.9173.

Synthesis of (±)-cephalanthrin A (3a): LiOH•H_2O (420 mg, 10 mmol) was added to a solution of phenyl ester **7a** (1.47 g, 4 mmol) in THF (80 mL) and H_2O (20 mL) and the mixture was stirred at room temperature. After 3 h, the resulting mixture was added to 10% HCl aq. solution, extracted with AcOEt (300 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (1:1) to give (±)-**3a** (1.08 g, 87%). A

pale purple amorphous powder. Mp 218-220 °C (lit.[1] Mp 212-214 °C). IR ($CHCl_3$): 3444, 1710, 1683, 1605 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 3.46 (d, J = 16.6 Hz, 1H), 3.57 (d, J = 16.6 Hz, 1H), 5.56 (br s, 1H), 7.37 (dt, J = 1.1, 7.4 Hz, 1H), 7.57 (dt, J = 1.2, 8.0 Hz, 1H), 7.59 (dt, J = 1.2, 7.5 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.85 (dt, J = 1.7, 8.6 Hz, 1H), 8.33 (dd, J = 1.7, 8.0 Hz, 1H), 8.48 (d, J = 8.0 Hz, 1H), 10.91 (br s, 1H). ^{13}C-NMR (acetone-d_6) δ: 42.7, 75.2, 116.5, 122.2, 123.9, 126.5, 126.6, 127.3, 127.8, 130.1, 133.3, 134.5, 140.1, 147.7, 159.2, 161.1, 169.9. HRMS (ESI) *m/z*: Calcd for $C_{17}H_{12}N_2NaO_4$ [$(M + Na)^+$] 331.0695. Found 331.0699.

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REFERENCES

1. a) B. Krivogorsky, A. C. Nelson, K. A. Douglas, and P. Grundt, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1032; b) J.-M. Hwang, T. Oh, T. Kaneko, A. M. Upton, S. G. Franzblau, Z. Ma, S.-N. Cho, and P. Kim, *J. Nat. Prod.*, 2013, **76**, 354; c) K. Seya, A. Yamaya, S. Kamachi, M. Murakami, H. Kitahara, J. Kawakami, K. Okumura, M. Murakami, S. Motomura, and K.-I. Furukawa, *J. Nat. Prod.*, 2014, **77**, 1413.
2. a) A. M. Tucker and P. Grundt, *ARKIVOC*, 2012, **i**, 546; b) Y. Jahng, *Arch. Pharm. Res.*, 2013, **36**, 517; c) U. A. Kshirsagar, *Org. Biomol. Chem.*, 2015, **13**, 9336.
3. C.-F. Chang, Y.-L. Hsu, C.-Y. Lee, C.-H. Wu, Y.-C. Wu, and T.-H. Chuang, *Int. J. Mol. Sci.*, 2015, **16**, 3980.
4. H. Gao, Z. Luo, P. Ge, J. He, F. Zhou, P. Zheng, and J. Jiang, *Org. Lett*., 2015, **17**, 5962.
5. a) T. Abe, T. Itoh, T. Choshi, S. Hibino, and M. Ishikura, *Tetrahedron Lett.*, 2014, **55**, 5268; b) T. Itoh, T. Abe, S. Nakamura, and M. Ishikura, *Heterocycles*, 2015, **91**, 1423.
6. a) G. R. Krow, 'Organic Reactions: The Baeyer-Villiger Oxidation of Ketones and Aldehydes,' Vol. 43, ed. by L. A. Paquette, John Wiley & Sons, Inc., New York, 1993, pp. 251-798; b) G.-J. ten Brink, I. W. C. E. Arends, and R. A. Sheldon, *Chem. Rev.*, 2004, **104**, 4105.
7. G. Kang, Z. Luo, C. Liu, H. Gao, Q. Wu, H. Wu, and J. Jiang, *Org. Lett.*, 2013, **15**, 4738.
8. R. D. Bach, *J. Org. Chem.*, 2012, **77**, 6801.