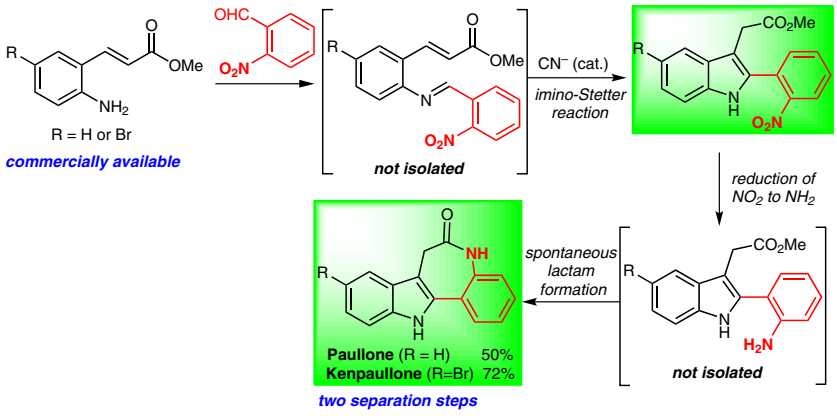
Synthesis S. E. Lee et al. Special Topic

Concise Total Syntheses of Paullone and Kenpaullone via Cyanide-Catalyzed Intramolecular Imino-Stetter Reaction

Sang Eun Lee
Seong Jong Lee
Cheol-Hong Cheon*

Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea
cheon@korea.ac.kr



Received: 01.02.2017
Accepted after revision: 22.02.2017
Published online: 14.03.2017
DOI: 10.1055/s-0036-1588749; Art ID: ss-2017-c0063-st

Abstract Highly concise total syntheses of paullone and kenpaullone were developed. Cyanide-catalyzed intramolecular imino-Stetter reaction of aldimines derived from methyl 2-aminocinnamate derivatives and 2-nitrobenzaldehyde provided 2-(2′-nitrophenyl)indole-3-acetic acid derivatives. Subsequent reduction of the nitro group with zinc under acidic conditions to an amino group followed by spontaneous lactam formation allowed for the total syntheses of paullone and kenpaullone to be completed in two steps starting from commercially available materials. The direct use of a nitro group as the precursor of an amino group present in the phenyl ring at the 2-position in the indole ring significantly streamlined the total syntheses of these target molecules.

Key words paullone, kenpaullone, total synthesis, cyanide-catalyzed imino-Stetter reaction, umpolung of aldimines

Because paullone (**1a**) and its derivatives **1b**,**c** (Figure 1) exhibit interesting biological activities such as the potent inhibition of cyclin-dependent kinase (CDK) and glycogen synthase kinase 3 (GSK 3), it is important to develop efficient synthetic routes for paullone and its derivatives.[1] The biological activities of paullone and its derivatives show a strong dependence on the substitution pattern in the indole moiety, particularly an electron-withdrawing substituent at the C-9 position of the indole ring; therefore, significant efforts have been made to develop a more facile method for preparing paullone derivatives.[2–7]

In addition to their biological activities, paullone and its derivatives have unique structural features; they contain a tetra-fused heterocyclic structure bearing a seven-membered biaryl lactam ring (C-ring) between the indole and aryl moieties.

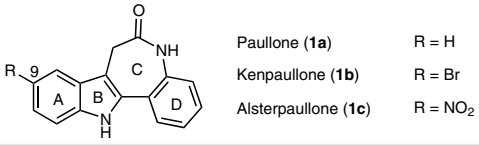
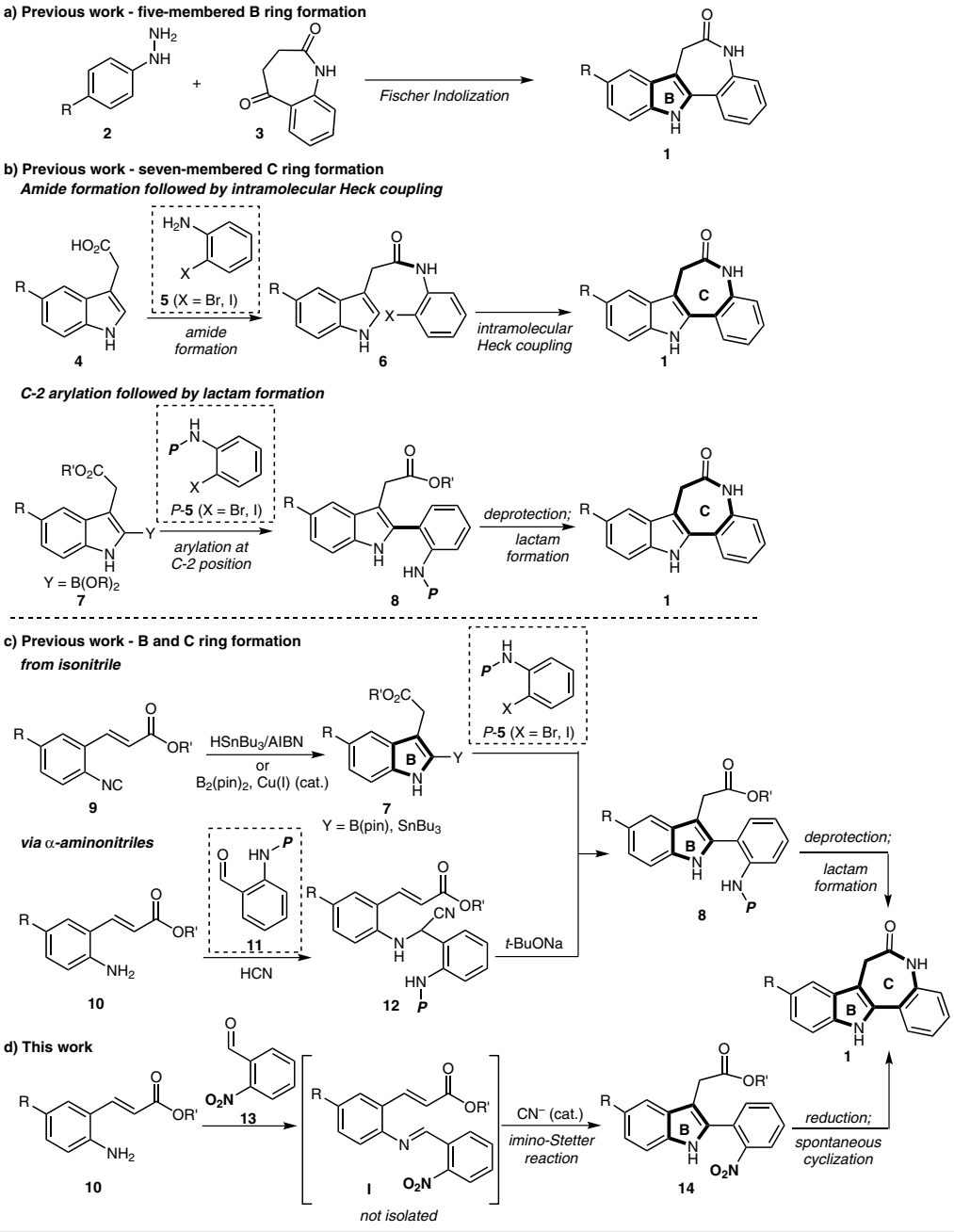


Figure 1 Structures of paullone and its derivatives

Considering their interesting biological activities and structural features, several distinct approaches have been developed for the syntheses of paullone and its derivatives.[2–7] The first strategy involves the formation of a B-ring from phenylhydrazine **2** with the seven-membered cyclic ketone **3** via Fischer indolization (Scheme 1 a).[2] Using this strategy, Kunick et al. reported several examples for the total synthesis of paullone and its derivatives. The second strategy involves the formation of a seven-membered C-ring by several disconnections (Scheme 1 b).[3–5] One approach in this strategy was the amide formation between indole-3-acetic acid **4** and 2-halogenated aniline derivatives **5**, followed by intramolecular Heck coupling at the C-2 position of the indole moiety of the resulting indole-3-acetamide derivatives **6**.[3] Alternatively, paullone and its derivatives were prepared from 2-functionalized indole-3-acetic acid derivatives **7** and N-protected 2-halogenated aniline derivatives *P*-**5** by arylation at the C-2 position in the indole ring followed by C-ring formation through amide formation of the resulting 2-arylindole-3-acetic acid derivatives **8**.[4] For example, Baudoin et al. constructed 2-functionalized indole-3-acetic acid derivatives **7** by palladium-catalyzed borylation at the 2-position of the indole ring. Subsequent Suzuki coupling reaction of the resulting 2-indoleboronic acid **7** with N-protected 2-haloaniline derivatives *P*-**5**, deprotection of the amino group, and intramolecular amide formation completed the total synthesis of paullone.



Scheme 1 Previous synthetic routes for the total synthesis of paullone and its derivatives

The third strategy involves the formation of a B-ring followed by the formation of a seven-membered C-ring (Scheme 1 c).[6,7] The research groups of Beneteau and Chatani adopted this strategy and successfully completed the total synthesis of paullone.[6] In their approaches, the radical cyclization of cinnamic acid derivatives **9** bearing an isonitrile group at the *ortho*-position with $HSnBu_3$[6a,8] or copper-catalyzed borylative cyclization of isonitrile **9**[6b] provided indole-3-acetic acid derivatives **7** bearing either tin or boron species at the 2-position of the indole ring. Subsequent arylation of indole **7** with N-protected 2-haloaniline derivatives *P*-**5** generated a 2-(N-protected 2′-aminophenyl)indole-3-acetic acid derivative **8**, which was further converted to paullone via deprotection followed by lactam formation. In 2008, Opatz et al. developed a new synthetic route to access paullone using this bond disconnection.[7] Treatment of the Strecker product **12**, obtained from 2-aminocinnamic acid derivatives **10** and N-protected 2-amino-

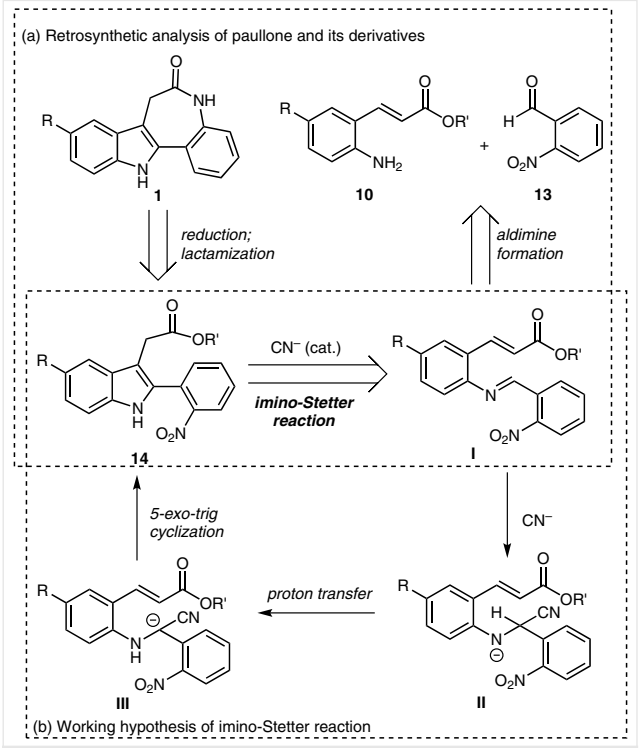
benzaldehyde **11**, with a stoichiometric amount of a strong base provided similar indole-3-acetic acid derivatives **8**. Subsequent deprotection of the amino group and intramolecular amide formation provided the paullone product.

Despite these successful results in the previous total syntheses of paullone and its derivatives, most of the previous syntheses required relatively lengthy synthetic sequences with respect to the size and complexity of these target molecules. This is probably because most of the previous approaches directly utilized *ortho*-functionalized aniline derivatives, either **5** or **11**, as the precursor of the amino group present in the seven-membered C-ring, requiring lengthy synthetic sequences in not only the preparation of parent 2-functionalized anilines[9] but also the protection/deprotection of the amino group in the required aniline derivatives. Thus, it is highly desired to develop a more efficient synthetic route for paullone and its derivatives utilizing readily available starting materials for the preparation of a sufficient amount of the sample for further biological evaluation.

Herein, we report highly concise total syntheses of paullone (**1a**) and kenpaullone (**1b**) from commercially available 2-aminocinnamic acid derivatives **10** and 2-nitrobenzaldehyde (**13**). Cyanide-catalyzed imino-Stetter reaction of the aldimines **I** derived from 2-aminocinnamic acid derivatives **10** and 2-nitrobenzaldehyde (**13**) provided 2-(2′-nitrophenyl)indole-3-acetic acid derivatives **14**. Subsequent reduction of the nitro group in the phenyl group at the 2-position to an amino group under acidic conditions provided 2-(2-aminophenyl)indole-3-acetates, which underwent spontaneous lactam formation under the same conditions to afford paullone and kenpaullone in only two separation steps from commercially available starting materials (Scheme 1 d).

Although most of the previous approaches utilized N-protected 2-functionalized aniline derivatives, either **5** or **11**,[3–7] we envisioned that if a nitro group were used as the precursor of the amino group present in the phenyl moiety at the 2-position in the indole ring, the synthetic sequence for paullone and its derivatives would be significantly streamlined because 1) 2-nitrobenzaldehyde (**13**) is commercially available and 2) the direct use of a nitro group as the precursor of the amino group would eliminate the protection/deprotection of the amino group.

Based on this idea, the retrosynthetic analysis of paullone and its derivatives is described in Scheme 2. Paullone and its derivatives could be prepared from 2-(2′-nitrophenyl)indole-3-acetates **14** through the reduction of the nitro group to an amino group, followed by lactam formation. Indole-3-acetic acid derivatives **14** could be prepared from aldimines **I** derived from 2-aminocinnamates **10** and 2-nitrobenzaldehyde (**13**), which would be the key for the success in our approach.



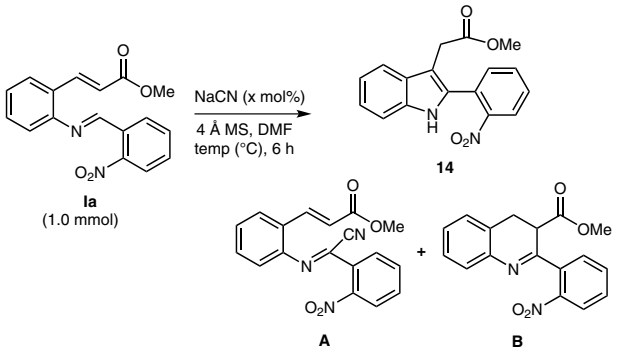
Scheme 2 (a) Retrosynthetic analysis for the synthesis of paullone and its derivatives, and (b) working hypothesis of imino-Stetter reaction

Very recently, our group developed a new method to access 2-substituted indole-3-acetic acid derivatives from aldimines obtained from 2-aminocinnamic acid derivatives and aromatic/α,β-unsaturated aldehydes via cyanide-catalyzed imino-Stetter reaction.[10,11] Based on this protocol, we hypothesized that the key intermediates **14** in our approach for the total synthesis of paullone and its derivatives could be prepared using a similar protocol from aldimines **I** derived from 2-aminocinnamic acid derivatives **10** and 2-nitrobenzaldehyde (**13**) in the presence of cyanide. The cyanide adducts **II** of aldimines **I** could undergo proton transfer from the α-carbon atom to the nitrogen atom, generating umpolung **III** of aldimines. Imino-Stetter reaction of the resulting carbanionic intermediates **III** would afford indole-3-acetic acid derivatives **14** bearing an *o*-nitrophenyl group at the C-2 position (Scheme 2 b).

With this idea in mind, we first started the total synthesis of paullone (**1a**) by optimizing the imino-Stetter reaction of aldimine **Ia** derived from methyl 2-aminocinnamate (**10a**) and 2-nitrobenzaldehyde (**13**) (Table 1). When aldimine **Ia** was subjected to the reaction conditions[10] previously used for imino-Stetter reaction with a catalytic amount of cyanide, rather disappointingly, the desired indole product **14** was obtained in a very low yield only, and a considerable amount of aldimine **Ia** remained unreacted (Table 1, entry 1). To increase the yield of indole product **14**, the same transformation was performed with 30 mol% of

cyanide. Although the yield of **14** increased, rather unexpectedly, a few by-products, iminonitrile **A** and dihydroquinoline **B**, were obtained in low yields (entry 2).

Table 1 Optimization of Imino-Stetter Reaction of **Ia**

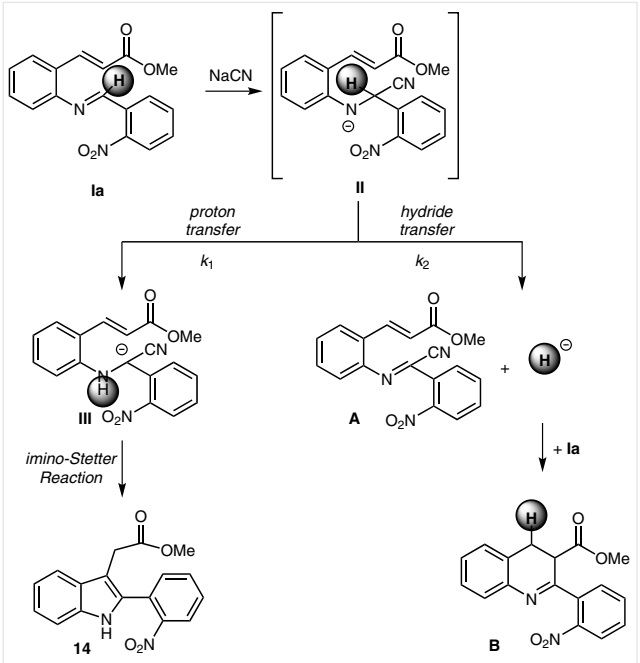


Entry	NaCN (x mol%)	Temp (°C)	Yield (%) of **14** (ratio **A**/**B**)[a,b]
1	10	60	trace (N.D.)
2	30	60	12 (10:9)
3	100	60	32 (29:26)
4	100	r.t.	53 (26:16)
5	50	r.t.	51 (21:13)
6	20	r.t.	N.D.
7	10	r.t.	N.D.
8[c]	50	r.t.	50 (N.D.)
9[d]	50	r.t.	52 (N.D.)

[a] The values in parentheses indicate the yields of by-products **A** and **B**.
[b] N.D.: Not determined.
[c] Reaction was performed using **10** and **13** without the isolation of aldimine **Ia**.
[d] Reaction conducted in 10 mmol scale.

With these results in hand, we sought to rationalize the formation of indole **14** along with other by-products (Scheme 3). Cyanide adduct **II**, generated by the addition of cyanide to aldimine **Ia**, could undergo two possible reaction pathways.[12] As expected, cyanide adduct **II** underwent proton transfer from the α-carbon atom to the nitrogen atom providing carbanionic intermediate **III**. Subsequent intramolecular imino-Stetter reaction to the adjacent α,β-unsaturated ester moiety furnished the expected indole product **14**. On the other hand, the hydride transfer in cyanide adduct **II** could provide iminonitrile **A**.[13] The resulting hydride undergoes Michael addition to the α,β-unsaturated ester moiety in aldimine **Ia**, and subsequent addition of the resulting enolate to aldimine moiety leads to dihydroquinoline **B**.

These results strongly indicate that the cyanide adduct **II** had the two pathways (proton transfer and hydride transfer),[12] and the two pathways probably compete with each other. To increase the rate of proton transfer over hydride

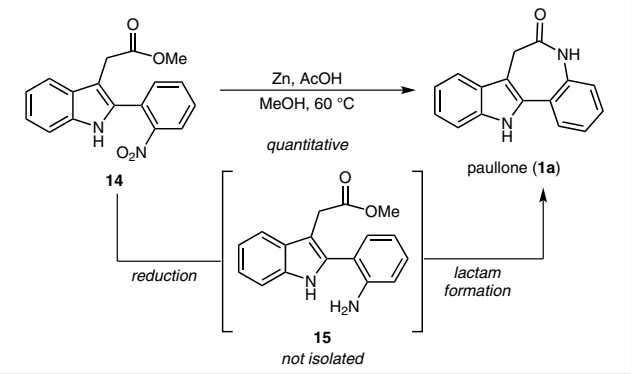


Scheme 3 A rationale for the formation of indole **14** and by-products **A** and **B** from cyanide adduct **II**

transfer, that is, $k_1 > k_2$, this reaction was carried out with a stoichiometric amount of cyanide expecting that the rate of hydride transfer (k_2) will decrease by decreasing the concentration of hydride acceptor, namely free aldimine **Ia**, leading to the improvement of the yield of the desired indole product **14**. When the reaction was performed with a stoichiometric amount of cyanide, to our delight, the yield of the desired indole product **14** increased to 32%, even though we could not prevent the formation of by-products (Table 1, entry 3). When the reaction was performed at room temperature, the yield of indole product **14** was further improved to 52% (entry 4). Furthermore, the amount of cyanide was reduced to 50 mol% without any loss of its efficiency (entry 5). However, when the reaction was performed with less than 50 mol% of cyanide, the yield of the desired product **14** decreased, and a large amount of aldimine **Ia** remained unreacted in the reaction mixture (entries 6 and 7). In addition, the reaction could be performed using a one-pot protocol starting from methyl 2-aminocinnamate (**10**) and 2-nitrobenzaldehyde (**13**) without the isolation of aldimine intermediate **Ia**, and the desired product **14** was obtained in a similar yield (entry 8). Furthermore, the same transformation could be carried out in a 10 mmol scale without any loss of its efficiency (entry 9).

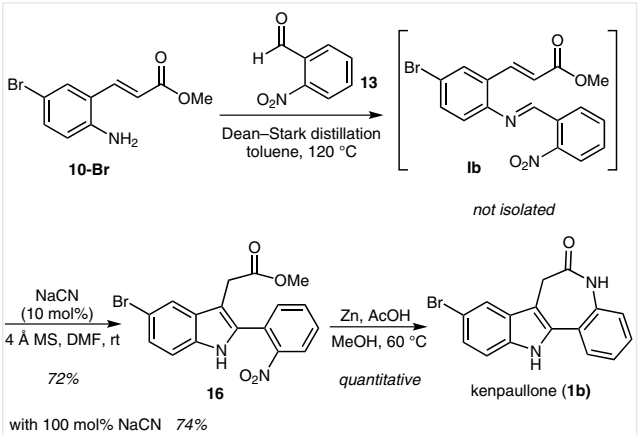
With this indole compound **14** in hand, the total synthesis of paullone (**1a**) was completed (Scheme 4). Reduction of the nitro group with zinc metal in acetic acid to an amino group provided the corresponding amino compound **15**.[14] This spontaneously underwent lactam formation under the same conditions affording paullone (**1a**) in quanti-

tative yield (Scheme 4). Overall, we completed the total synthesis of paullone (**1a**) in 52% overall yield in two steps starting from commercially available materials.



Scheme 4 End game in the total synthesis of paullone (**1a**)

With this successful result in hand, we further attempted to extend this strategy to the total synthesis of kenpaullone (**1b**) (Scheme 5). In this case, methyl 2-amino-5-bromocinnamate (**10-Br**) was used instead of methyl 2-aminocinnamate (**10**). When aldimine **Ib**, in situ derived from methyl 2-amino-5-bromocinnamate (**10-Br**) and 2-nitrobenzaldehyde (**13**), was subjected to the optimized conditions for the synthesis of paullone, rather surprisingly, the desired indole product **16** was obtained in 74% yield without any formation of by-products such as the corresponding iminonitrile and dihydroquinoline. Furthermore, the amount of cyanide could be decreased to 10 mol% without any loss of the efficiency in this transformation. Subsequent treatment of indole **16** with zinc in acidic conditions provided the desired kenpaullone (**1b**) in quantitative yield via the reduction of the nitro group to an amino group followed by spontaneous lactam formation. Although at this moment, we do not clearly understand the role of the bromine substituent at the 5-position in aldimines during the



Scheme 5 Total synthesis of kenpaullone (**1b**)

cyanide-catalyzed imino-Stetter,[15] we were able to complete the total synthesis of kenpaullone (**1b**) in only two steps from commercially available starting materials.

In conclusion, we have developed highly concise total syntheses of paullone (**1a**) and kenpaullone (**1b**) starting from commercially available materials. Cyanide-catalyzed imino-Stetter reactions of aldimines derived from 2-aminocinnamate derivatives and 2-nitrobenzaldehyde provided the corresponding indole-3-acetic acid derivatives **14** and **16** bearing a 2′-nitrophenyl moiety at the 2-position of the indole ring. Subsequent reduction of the nitro group to an amino group with zinc under acidic conditions and spontaneous lactam formation of the resulting amino group allowed us to complete the total syntheses of paullone and kenpaullone. The direct use of a nitro group as the precursor of the amino group in the lactam ring present in paullone and kenpaullone significantly streamlined the total syntheses of paullone and kenpaullone leading to the completion of these target molecules in only two steps starting from commercially available materials. Further application of imino-Stetter reaction to the total synthesis of other indole alkaloids and the elucidation of role of bromine substituent on imino-Stetter reaction are currently underway.

All the reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise noted. Except as otherwise indicated, all the reactions were magnetically stirred and monitored by analytical TLC using pre-coated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm). Flash column chromatography was performed using silica gel 60 (230–400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Methyl 2-aminocinnamate (**10**) and its 5-bromo analogue **10-Br** were purchased from Aldrich. Other commercial grade reagents and solvents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded using 500 and 125 MHz spectrometers, respectively. TMS (δ = 0.0) and a residual NMR solvent, either $CDCl_3$ (δ_H: 7.26, δ_C: 77.16) or DMSO (δ_H: 2.50, δ_C: 39.52), were used as internal standards for ^{1}H NMR and ^{13}C NMR spectra, respectively. The ^{1}H NMR spectra are reported as follows: δ (position of proton, multiplicity, coupling constant *J*, and number of protons). Standard abbreviations for indicating multiplicities are used. High-resolution mass spectra (HRMS) were recorded on quadrupole time-of-flight mass spectrometer (QTOF-MS) using electrospray ionization (ESI).

Synthesis of Paullone (1a)

Methyl 2-[2-(2-Nitrophenyl)-1*H*-indol-3-yl]acetate (14)

A solution of methyl 2-aminocinnamate (**10**; 1.8 g, 10 mmol) and 2-nitrobenzaldehyde (**13**; 1.5 g, 10 mmol) in toluene (100 mL) was stirred at 120 °C for overnight using a Dean–Stark apparatus, and the reaction was monitored by ^{1}H NMR analysis. After completion of the aldimine formation, the reaction mixture was concentrated under reduced pressure. Then, the crude mixture was dissolved in DMF (50 mL), and NaCN (0.24 g, 5 mmol) and 4Å MS (1.5 g) were added to the reaction mixture. The mixture was stirred at r.t. and the reaction

progress was monitored by TLC. After complete consumption of aldimine **Ia**, the mixture was filtered to remove 4Å MS and the filtrate was concentrated under reduced pressure. Chromatography (EtOAc/hexane, 1:5 v/v, 1:3 v/v, and then 1:2 v/v) furnished **14** as a yellow liquid in 52% (1.6 g, 5.2 mmol mg) yield along with other by-products **A** and **B** (Table 1).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.29 (br, 1 H), 7.99 (d, *J* = 8.1 Hz, 1 H), 7.69 (m, 2 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.6 (m, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.25 (m, 1 H), 7.18 (m, 1 H), 3.63 (s, 5 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.2, 149.9, 136.1, 133.8, 132.8, 130.9, 129.9, 127.9, 126.7, 124.6, 123.3, 120.4, 119.4, 111.3, 108.4, 52.2, 30.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{14}N_2O_4Na$: 333.0846; found: 333.0846.

Compound A

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.18 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.89 (m, 3 H), 7.80 (m, 1 H), 7.73 (d, *J* = 7.2 Hz, 1 H), 7.53 (m, 1 H), 7.41 (m, 1 H), 7.28 (m, 1 H), 6.46 (d, *J* = 16 Hz, 1 H), 3.81 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 167.2, 147.9, 147.2, 139.9, 138.3, 134.3, 132.7, 131.4, 131.3, 129.9, 128.7, 127.9, 127.6, 125.4, 120.2, 119.1, 110.5, 52.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{13}N_3O_4Na$: 358.0798; found: 358.0799.

Compound B

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.90 (m, 2 H), 7.56 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.32 (m, 1 H), 7.25 (m, 1 H), 7.18 (dtd, *J* = 8.6, 7.7, 0.8, 2 H), 5.7 (t, *J* = 6.3 Hz, 1 H), 3.77 (s, 3 H), 3.12 (dd, *J* = 16.3, 6.1 Hz, 1 H), 2.89 (dd, *J* = 16.5, 6.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.8, 160.1, 146.8, 135.1, 133.0, 132.9, 129.8, 125.3, 123.6, 122.0, 120.4, 113.2, 110.9, 59.8, 52.5, 40.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{14}N_2O_3Na$: 317.0897; found: 317.0905.

Paullone [7,12-Dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one, 1a]

To a solution of **14** (0.31 g, 1 mmol) in MeOH (10 mL) were added Zn (0.32 g, 5 mmol) and AcOH (0.57 mL, 10 mmol) and the reaction mixture was stirred at 60 °C overnight. After complete consumption of **14**, the mixture was cooled to r.t. Then, the mixture was filtered to remove the remaining Zn and the filtrate was concentrated in vacuo. The mixture was partitioned between aq NH_4Cl and EtOAc. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was further purified by fresh column chromatography on silica to furnish paullone (**1a**) as a pale yellow solid in quantitative yield (0.24 g, 0.99 mmol); mp >250 °C. Spectroscopic data were in good agreement with those reported in the literature.[2–7]

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 11.60 (br, 1 H), 10.11 (s, 1 H), 7.75 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H) 7.37 (d, *J* = 6.9 Hz, 1 H), 7.27 (m, 2 H), 7.18 (m, 1 H), 7.08 (m, 1 H), 3.50 (s, 2 H).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 171.6, 137.4, 135.4, 132.5, 128.0, 126.9, 126.6, 123.7, 122.9, 122.3, 122.1, 119.1, 118.0, 111.5, 107.6, 31.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{12}N_2ONa$: 271.0842; found: 271.0843.

Synthesis of Kenpaullone (1b)

Methyl 2-[5-Bromo-2-(2-nitrophenyl)-1*H*-indol-3-yl]acetate (16)

Same protocol for the synthesis of **14** was followed, except **10-Br** was used instead of **10**. Compound **16** was obtained as a yellow solid in 72% yield (0.56 g, 1.4 mmol); mp 151–152 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.30 (br, 1 H), 8.02 (d, *J* = 8.1 Hz, 1 H), 7.77 (s, 1 H), 7.70 (m, 2 H), 7.63 (m, 1 H), 7.33 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.24 (d, *J* = 8.5 Hz, 1 H), 3.65 (s, 3 H), 3.57 (s, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.8, 149.8, 134.7, 133.8, 133.0, 132.2, 130.2, 129.6, 126.2, 126.2, 124.7, 122.1, 113.7, 112.8, 108.0, 52.3, 30.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{13}BrN_2O_4Na$: 410.9951; found: 410.9952.

Kenpaullone [9-Bromo-7.12-dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one, 1b]

Same protocol for the synthesis of paullone (**1a**) was followed, except **16** was used instead of **14**. Kenpaullone (**1b**) was obtained as a pale yellow solid in quantitative yield (0.46 g, 1.4 mmol); mp >250 °C. Spectroscopic data were in good agreement with those reported in the literature.[3d]

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 11.83 (br, 1 H), 10.16 (s, 1 H), 7.92 (d, *J* = 1.7 Hz, 1 H), 7.74 (d, *J* = 6.7 Hz, 1 H), 7.39 (m, 2 H), 7.27 (m, 3 H), 3.53 (s, 2 H).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 171.6, 136.1, 135.7, 134.1, 128.5, 128.4, 127.1, 124.6, 123.8, 122.4, 122.4, 120.5, 113.5, 111.8, 107.2, 31.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{11}BrN_2ONa$: 348.9947; found: 348.9949.

Acknowledgment

This work was supported by the National Research Foundation of Korea (NRF) grants funded by the Korean Government (NRF-20100020209 and NRF-2015R1D1A1A01057200). C.-H.C. is also thankful for financial support from an NRF grant funded by the Korean Government (NRF-2014-011165, Center for New Directions in Organic Synthesis).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588749.

References

(1) (a) Zaharevitz, D. W.; Gussio, R.; Leost, M.; Senderowicz, A. M.; Lahusen, T.; Kunick, C.; Meijer, L.; Sausville, E. A. *Cancer Res.* **1999**, *59*, 2566. (b) Leost, M.; Schultz, C.; Link, A.; Wu, Y.-Z.; Biernat, J.; Mandelkow, E.-V.; Bibb, J. A.; Snyder, G. L.; Greengard, P.; Zaharevitz, D. W.; Gussio, R.; Senderowicz, A. M.; Suasville, E. A.; Kunick, C.; Meijer, L. *Eur. J. Biochem.* **2000**, *267*, 5983. (c) Pies, T.; Schaper, K.-J.; Leost, M.; Zaharevitz, D. W.; Gussio, R.; Meijer, L.; Kunick, C. *Arch. Pharm. (Weinheim)* **2004**, *337*, 486. (d) Tolle, N.; Kunick, C. *Curr. Top. Med. Chem.* **2011**, *11*, 1320.

(2) (a) Schultz, C.; Link, A.; Leost, M.; Zaharevitz, D. W.; Gussio, R.; Sausville, E. A.; Meijer, L.; Kunick, C. *J. Med. Chem.* **1999**, *42*, 2909. (b) Kunick, C.; Schultz, C.; Lemcke, T.; Zaharevitz, D. W.; Gussio, R.; Jalluri, R. K.; Sausville, E. A.; Leost, M.; Meijer, L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 567. (c) Wieking, K.; Knockaert, M.; Leost, M.; Zaharevitz, D. W.; Meijer, L.; Kunick, C. *Arch. Pharm. (Weinheim)* **2002**, *335*, 311. (d) Kunick, C.; Lauenroth, K.; Leost, M.; Meijer, L.; Lemcke, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 413. (e) Stukenbrock, H.; Mussmann, R.; Geese, M.; Ferandin, Y.; Lozach, O.; Lemcke, T.; Kegel, S.; Lomow, A.; Burk, U.; Dohrmann, C.; Meijer, L.; Austen, M.; Kunick, C. *J. Med. Chem.* **2008**, *51*, 2196.

(3) (a) Joucla, L.; Putey, A.; Joseph, B. *Tetrahedron Lett.* **2005**, *46*, 8177. (b) Avila-Zarraga, J. G.; Lujan-Montelongo, A.; Covarrubias-Zuniga, A.; Romero-Ortega, M. *Tetrahedron Lett.* **2006**, *47*, 7987. (c) Joucla, L.; Popowyca, F.; Lozach, O.; Meijer, L.; Joseph, B. *Helv. Chim. Acta* **2007**, *90*, 753. (d) For another approach through this disconnection via photocyclization of indole-3-acetamide derivatives, see: Li, Z.; Lu, N.; Wang, L.; Zhang, W. *Eur. J. Org. Chem.* **2012**, 1019.

(4) Baudoin, O.; Cesario, M.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **2002**, *67*, 1199.

(5) Although it was not shown in Scheme 1, another strategy via the seven-membered C-ring formation through free radical cyclization of *N*-[2-(1*H*-indol-2-yl)phenyl]-*N*-benzyl-2-iodoacetamides has been reported, see: Bremner, J. B.; Sengpracha, W. *Tetrahedron* **2005**, *61*, 5489.

(6) (a) Henry, N.; Blu, J.; Beneteau, V.; Merour, J.-Y. *Synthesis* **2006**, 3895. (b) Tobisu, M.; Fujihara, H.; Koh, K.; Chatani, N. *J. Org. Chem.* **2010**, *75*, 4841.

(7) Ferenc, D.; Opatz, T. *Synthesis* **2008**, 3941.

(8) For the original study on the indolization from isonitrile **9**, see: Peng, G.; Chen, X.; Fukuyama, T. *J. Am. Chem. Soc.* **1994**, *116*, 3127.

(9) N-Protected 2-aminobenzaldehyde **11** was generally prepared from *o*-nitrobenzaldehyde in 4 steps. For recent examples, see: (a) Storz, M. P.; Maurer, C. K.; Zimmer, C.; Wagner, N.; Brengel, C.; de Jong, J. C.; Lucas, S.; Musken, M.; Haussler, S.; Steinbach, A.; Hartmann, R. W. *J. Am. Chem. Soc.* **2012**, *134*, 16143. (b) Raven, W.; Selig, P. *Org. Lett.* **2014**, *16*, 5192.

(10) (a) Lee, S. J.; Seo, H.-A.; Cheon, C.-H. *Adv. Synth. Catal.* **2016**, *358*, 1566. (b) Seo, H.-A.; Cheon, C.-H. *J. Org. Chem.* **2016**, *81*, 7917.

(11) For the application of this approach toward skeleton-divergent total syntheses of rutaecarpine and luotonin A, see: Kwon, S. H.; Seo, H.-A.; Cheon, C.-H. *Org. Lett.* **2016**, *18*, 5280.

(12) For similar competing pathways from cyanide adducts **II** of aldimines, see: Seo, H.-A.; Cho, Y.-H.; Lee, Y.-S.; Cheon, C.-H. *J. Org. Chem.* **2015**, *80*, 11993.

(13) For previous examples of the formation of iminonitriles from the cyanide adducts **II** of aldimines without any additives, see: Jursic, B. S.; Douelle, F.; Bowdy, K.; Stevens, E. D. *Tetrahedron Lett.* **2002**, *43*, 5361.

(14) For previous examples of the reduction of nitro group with zinc metal, see: (a) Ferenc, D.; Opatz, T. *Org. Lett.* **2006**, *8*, 4473. (b) Kratz, F.; Warnecke, A. *J. Org. Chem.* **2008**, *73*, 1546. (c) Higuchi, K.; Sato, Y.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Org Lett.* **2009**, *11*, 197. (d) Cid, M. B.; Duce, S.; Morales, S.; Rodrigo, E.; Ruano, J. L. G. *Org. Lett.* **2010**, *12*, 3586. (e) Xu, Z.; Hu, W.; Liu, Q.; Zhang, L.; Jia, Y. *J. Org. Chem.* **2010**, *75*, 7626.

(15) For previous examples of the difference in reactivity depending on Br substituents, see: (a) Cho, C.-G.; Kim, Y.-W.; Lim, Y.-K.; Park, J.-S.; Lee, H.; Koo, S. *J. Org. Chem.* **2002**, *67*, 290. (b) Gao, L.; Hwang, G.-S.; Ryu, D. H. *J. Am. Chem. Soc.* **2011**, *133*, 20708. (c) Shim, S. Y.; Kim, J. Y.; Nam, M.; Hwang, G.-S.; Ryu, D. H. *Org Lett.* **2016**, *18*, 160.