Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: E. Park and C. Cheon, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB02691A.




ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB02691A

Journal Name

ARTICLE

# A General Strategy for the Synthesis of Indoloquinolizine Alkaloids via Cyanide-Catalyzed Imino-Stetter Reaction

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Eunjoon Park[a] and Cheol-Hong Cheon*[a]

A new strategy applicable to the synthesis of indoloquinolizine natural products has been developed. Cyanide-catalyzed intramolecular imino-Stetter reaction of aldimines, derived from 2-aminocinnamic acid derivatives and 2-pyridinecarboxaldehydes, provided indole-3-acetic acid derivatives bearing a pyridyl ring at the 2-position. Reduction of the carboxylic acid moiety to alcohol followed by activation of the resulting alcohol with $Tf_2O$ or TsCl generated indoloquinolizinium salts, which were utilized as precursors for indoloquinolizine natural products. The advantage of this protocol was successfully demonstrated in the total syntheses of arborescidine A and nauclefidine.

## Introduction

The indoloquinolizine scaffold is a common building block found in biologically important natural products and pharmaceuticals (Figure 1). Therefore, the development of novel protocols to access these building blocks has been considered the research of importance.[1]

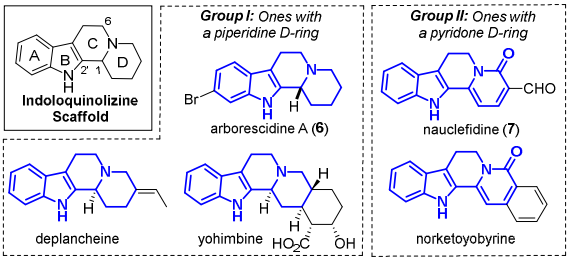
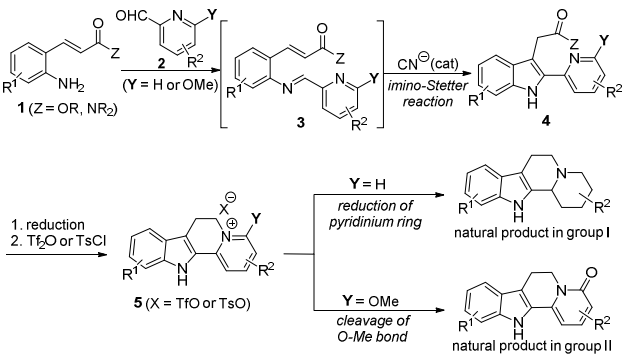



**Figure 1** Representative Examples of Indoloquinolizine Natural Products

As demonstrated in Figure 1, these natural products display considerable structural diversities. However, we noticed that these natural products could be classified into two categories based on the structure of the D-ring. For example, the first group of the natural products possess a 6-membered piperidine D-ring as a common building block (Group I), while the second group has a pyridone moiety (Group II). Considering this structural feature of these natural products, we envisioned that the 6-membered D-ring present in the indoloquinoline alkaloids could be prepared from a pyridine ring with a proper substituent(s) through selective functionalization of the pyridine ring into a 6-membered azacyclic structure.[2-4]

Herein, we disclose our new approach to access an indoloquinolizine scaffold from readily available 2-aminocinnamic acid derivatives **1** and 2-pyridinecarboxaldehydes **2** (Scheme 1). Cyanide-catalyzed imino-Stetter reaction of aldimines **3**, derived from compounds **1** and **2**, provided 2-(2-pyridyl) substituted indole-3-acetic acid derivatives **4**. Reduction of a carboxylic acid moiety to alcohol followed by the activation of the resulting alcohol with either $Tf_2O$ or TsCl led to the formation of indoloquinolizinium salt **5** via instantaneous attack of a nitrogen atom in the pyridine ring to the activated alcohol.[4] Utilizing indoloquinolizinium salts **5** as key intermediates, we completed the total syntheses of arborescidine A (**6**) and nauclefidine (**7**) as representative indoloquinolizine natural products in groups I and II, respectively.




**Scheme 1** Divergent Synthetic Route toward Indoloquinolizine Natural Products

## Results and discussions

Very recently, our group developed a highly efficient method for the synthesis of 2-substituted indole-3-acetic acid derivatives from aldimines derived from 2-aminocinnamic acid

[a] Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea.
Phone: +82-2-3290-3147; Fax: +82-2-3290-3121; E-mail: cheon@korea.ac.kr

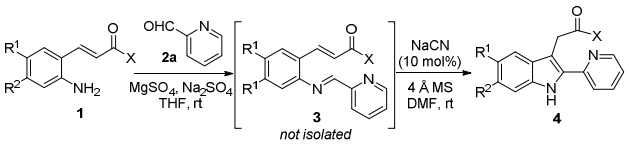
† Electronic supplementary information (ESI) available: copies of NMR spectra for all compounds. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C7OB02691A




derivatives and aldehydes via cyanide-catalyzed intramolecular imino-Stetter reaction.[5-7] We envisioned that if aldimines **3** obtained from 2-aminocinnamic acid derivatives **1** and 2-pyridinecarboxaldehydes **2** were applicable to the cyanide-catalyzed imino-Stetter reaction generating the 2-pyridyl substituted indole-3-acetic acid derivatives **4**, the indoloquinolizine scaffold could be very easily prepared from the resulting indole-3-acetic acid derivatives **4** through the subsequent 6-membered C-ring formation.

**Table 1** Substrate Scope of 2-Aminocinnamic Acid Derivatives **1**

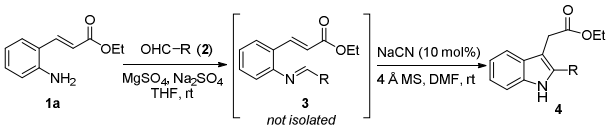



| entry | Product (**4**) | $R^1$ | $R^2$ | X | yield[a] (%) |
|---|---|---|---|---|---|
| 1[b] | **4aa** | H | H | OEt | 95 |
| 2 | **4aa** | H | H | OEt | 95 |
| 3 | **4ba** | H | H | OMe | 85 |
| 4 | **4ca** | H | H | O*i*-Pr | 83 |
| 5[c] | **4da** | H | H | O*t*-Bu | 83 |
| 6 | **4ea** | H | H | NHBn | 80 |
| 7 | **4fa** | H | H | piperidyl | 92 |
| 8 | **4ga** | Br | H | OMe | 84 |
| 9 | **4ha** | H | Br | OEt | 94 |

[a] Isolated yield. [b] Isolated aldimine **3aa** was used. [c] Reaction was carried out at 60 °C.

Based on this working hypothesis, we first explored the cyanide-catalyzed imino-Stetter reaction of aldimines **3** derived from 2-pyridinecarboxaldehyde **2a** with 2-aminocinnamic acid derivatives **1** (Table 1). When aldimine **3aa**, obtained from ethyl 2-aminocinnamate **1a** and **2a**, was subjected to the reaction conditions previously used in the imino-Stetter reaction conditions (10 mol % of cyanide in DMF),[5,6] the corresponding indole-3-acetic acid derivative **4aa** was obtained in 95% yield within 15 minutes at room temperature (entry 1). Furthermore, when aldimine **3aa**, in situ generated from **1a** and **2a**, was subjected to the above reaction conditions without its isolation, the desired indole product **4aa** was obtained in a similar yield (entry 2). Without further optimization of reaction conditions, we investigated substrate scope of 2-aminocinnamic acid derivatives **1** (entries 2-7). An ester moiety in 2-aminocinnamates was found to have a slight influence on the efficiency of this transformation. As the steric bulk of the ester moiety increased, the imino-Stetter reaction was found to proceed slowly requiring at elevated temperature and a longer reaction time for the completion of the reaction (entries 2-5). This protocol could be extended to aldimines **3** derived from 2-aminocinnamamides (entries 6 and 7). Aldimines, **3ea** and **3fa**, obtained from secondary and tertiary amides, provided the desired indole products **4ea** and **4fa** in high yields, respectively. It should be noted that the imino-Stetter reaction of aldimine **3ea** from the secondary benzylamide **1e** afforded the desired indole product **4ea** even with a catalytic amount of cyanide.[8] We further investigated the effect of a substituent on the phenyl ring in the 2-aminocinnamates. 2-Aminocinnamates bearing a bromine substituent at the either 4- or 5-position provided the desired indole products **4** in high yields regardless of the presence of the bromine substituent (entries 2 and 9, entries 3 and 8).

**Table 2** Substrate Scope of Pyridinecarboxaldehydes **2**




| entry | R (**4**) | yield[a] (%) | entry | Product (**4**) | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | (**4aa**) | 95 | 7 | (**4ag**) | 89 |
| 2 | (**4ab**) | 95 | 8 | (**4ah**) | 91 |
| 3 | (**4ac**) | 95 | 9 | (**4ai**) | 94 |
| 4 | (**4ad**) | 89 | 10 | (**4aj**) | 86 |
| 5 | (**4ae**) | 94 | 11 | (**4ak**) | 88 |
| 6 | (**4af**) | 84 | 12 | (**4al**) | 92 |

[a] Isolated yield.

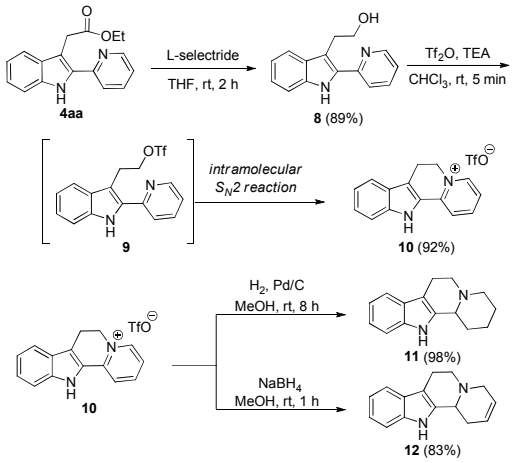
Next, we further investigated the generality of pyridinecarboxaldehydes **2** in this transformation with ethyl 2-aminocinnamate **1a** (Table 2). The position of an aldehyde group in the pyridine ring has little influence on this imino-Stetter reaction; the desired indole products **4** were obtained in excellent yields regardless of the position of the formyl group in the pyridine ring (entries 1-3). The electronic nature of 2-pyridinecarboxaldehydes was further explored (entries 1, 4-6). It was found that the electronic nature on the 2-pyridinecarboxaldehydes **2** had little influence on the efficiency of this transformation and the indole products **4** were obtained in similar yields regardless of the electronic nature of a substituent. In addition, the relative position of a substituent on the 2-pyridinecarboxaldehyde **2** was found not to affect the outcome of this transformation (entries 6-9). This

View Article Online
DOI: 10.1039/C7OB02691A



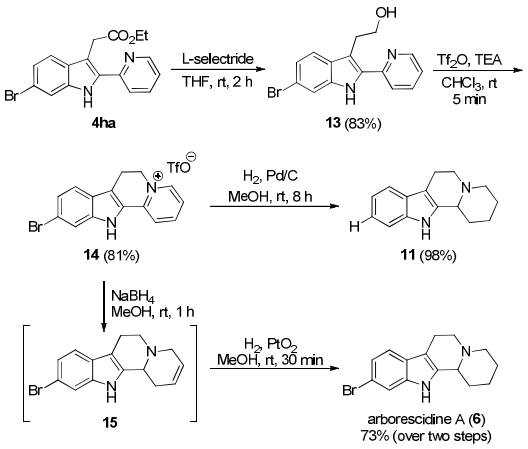

protocol could be extended to the benzofused pyridine carboxaldehydes and all the substrates afforded the desired indole products in excellent yields (entries 10-12).

With these results in hand, we further attempted to develop a synthetic protocol to construct indoloquinolizine scaffold from the resulting indole products **4** (Scheme 2). The reduction of an ester group in indole **4aa** with L-selectride provided the corresponding alcohol **8** in 89% yield. Treatment of the resulting alcohol **8** with triflic anhydride ($Tf_2O$) afforded the activated alcohol **9**, which underwent spontaneous cyclization to provide indoloquinolizinium salt **10** in 92% yield.[4,9] The pyridinium ring in compound **10** could be selectively reduced into a piperidine ring under different conditions. When **10** was subjected to hydrogenation in the presence of palladium, the pyridinium ring could be completely reduced to the piperidine ring yielding 10-desbromoarborescidine A (**11**) in a quantitative yield.[10] Furthermore, the pyridinium ring was partially reduced by the reaction of **10** with $NaBH_4$ leading to dihydroindoloquinolizine **12** in 83% yield.[11]




**Scheme 2** Preparation of Indoloquinolizine Scaffold

As demonstrated in Scheme 2, we successfully developed a protocol to access an indoloquinolizine core structure, and thus we attempted to apply this protocol to the total synthesis of arborescidine A (**6**), a representative indoloquinolizine natural product in group I, using indole-3-acetate **4ha** bearing a bromide group at the 6-position of indole (entry 8, Table 1) as a starting material (Scheme 3).[12] Indole-3-acetate **4ha** was converted into the corresponding alcohol in 83% yield by the reaction with L-selectride. Subsequent treatment of the resulting alcohol with $Tf_2O$ provided indoloquinolizinium salt **13** in 81% yield. Attempt to reduce the pyridinium ring into a piperidine ring with hydrogen in the presence of palladium, unfortunately, failed to provide arborescidine A (**6**). Instead, under these conditions, 10-desbromoarborescidine A (**11**) was obtained in a quantitative yield via the simultaneous reduction of pyridinium ring and bromide. However, we were fortunately able to reduce the pyridinium ring without any concomitant debromination reaction via the partial reduction of the pyridinium ring with $NaBH_4$ followed by hydrogenation of the remaining double bond with platinum catalyst rather than palladium generated arborescidine A (**6**).[13] Overall, we completed the total synthesis of arborescidine A (**6**) in 46% yield from known starting materials in five steps (the previous total synthesis of arborescidine A was completed in 50% overall yield in 5 steps, see ref 12b).




**Scheme 3** Total Synthesis of Arborescidine A (**6**)

With a successful application of our protocol to the total synthesis of arborescidine A (**6**) belonging to group I of the indoloquinolizine natural products, we further attempted to synthesize nauclefidine (**7**), an representative indoloquinolizine natural product in group II demonstrating the advantage of our protocol (Scheme 4).[14] Nauclefidine (**7**) could be prepared by C3-formylation on the pyridone ring in compound **17**, which could be prepared through the C-ring formation from indole-3-acetate **4ae** (entry 5, Table 2).

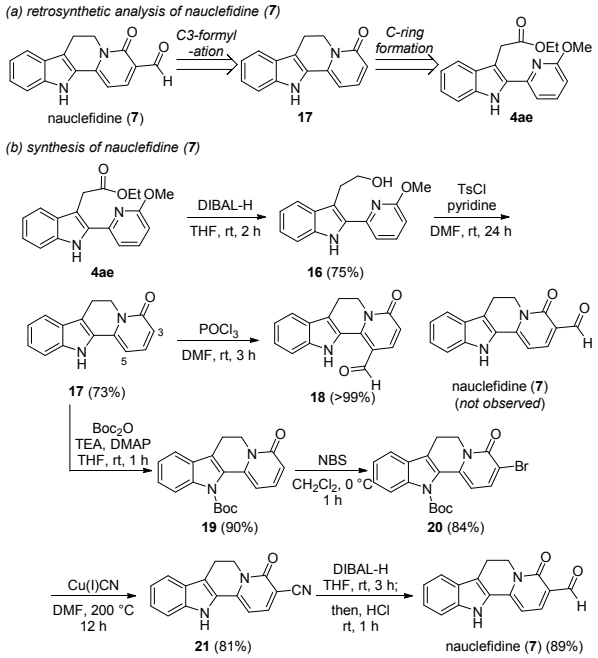
With this synthetic plan in mind, we first commenced with this research by the preparation of compound **17**. Reaction of indole **4ae** with DIBAL-H generated alcohol **16** in 75% yield. Subsequent treatment of the resulting alcohol **16** with TsCl instead of $Tf_2O$ provided compound **17** in 73% yield via spontaneous cyclization leading to indoloquinolizinium chloride followed by the cleavage of methyl ether in the indoloquinolizinium salt with the resulting chloride anion.[15]

With compound **17** in hand, we focused on the introduction of a formyl group at the 3-position of the pyridone ring to complete the total synthesis of nauclefidine (**7**). When compound **17** was subjected to the Vilsmeier-Haack reaction with $POCl_3$ in DMF, unfortunately, the desired nauclefidine (**7**) was not obtained. Instead, the regioisomer **18** bearing a formyl group at the *C*-5 position was obtained in a quantitative yield.[16] Since this result strongly suggested that the most nucleophilic carbon on the pyridone ring in compound **17** might be the C-5 rather than C-3 position,[17] we concentrated on developing a method to introduce a formyl group at the C-3 position on the pyridone ring. It was hypothesized that the installation of a bulky protecting group on the nitrogen atom in the indole ring would diminish the reactivity at the C-5 position toward electrophilic substitution reaction leading to the incorporation of an electrophile at the C-3 position.

View Article Online
DOI: 10.1039/C7OB02691A




Based on this hypothesis, an indolic NH group in compound **17** was protected with a bulky Boc group generating N-Boc protected indole **19** in 90% yield. Unfortunately, the Vilsmeier-Haack reaction was carried out on the Boc-protected compound **19**, indicating that the reaction did not proceed at all. When compound **19** was treated with NBS, to our delight, bromination took place at the C-3 position to afford compound **20** in 84% yield. Our first attempt to directly convert the bromide group in **20** into a formyl group via lithium-bromide exchange and subsequent trapping of the resulting organolithium species with DMF turned out to fail. Under these conditions, no formation of the desired product was observed and a rather complex mixture was obtained. Thus, we developed a two-step sequence to convert the bromide group to a formyl group. The bromine group in **20** was converted into a nitrile group by the reaction of compound **20** with CuCN.[18] Furthermore, during this transformation, the Boc group was also removed to provide the cyanated compound **21** in 81% yield. Subsequent treatment of compound **21** with DIBAL yielded the desired nauclefidine (**7**) in 89% yield. Overall, we were able to finish the total synthesis of nauclefidine (**7**) in 28% overall yields in 7 steps (the previous total synthesis of arborescidine A was completed in 67% overall yield in 4 steps, see ref 14b).




**Scheme 4** Total Synthesis of Nauclefidine (**7**)

## Conclusions

In conclusion, we developed a general synthetic strategy to access indoloquinolizine scaffold from readily available 2-aminocinnamic acid derivatives and 2-pyridinecarboxaldehydes. Cyanide-catalyzed imino-Stetter reaction of aldimines derived from 2-aminocinnamic acid derivatives and 2-pyridinecarboxaldehydes provided indole-3-acetic acid derivatives bearing (2'-pyridyl) moiety at the 2-position. Subsequent conversion of carboxylic acid moiety to an alcohol followed by the activation of the alcohol with either $Tf_2O$ or TsCl afforded indoloquinolizinium salts. Subsequent functionalization of the pyridinium ring in the indoloquinolizinium intermediates allowed us to complete the total synthesis of arborescidine A (**6**) and nauclefidine (**7**), two different types of indoloquinolizine natural products. Further applications of this protocol to the total synthesis of other natural products are currently underway in our laboratory and will be reported in due course.

## Experimental section

**General.**

All reactions were carried out in an oven-dried glassware under an argon atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using precoated 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. Pyridinecarboxaldehyde derivatives (**2**) and other commercial grade reagents and solvents were purchased from chemical suppliers and used without further purification. (*E*)-2-Aminocinnamic acid derivatives (**1**) were prepared by the reported procedures.[6a] $^1$H NMR and $^{13}$C NMR spectra were recorded on 500 MHz and 125 MHz spectrometers, respectively. Residual NMR solvents (either $CDCl_3$ ($\delta_H$: 7.26 ppm, $\delta_C$: 77.16 ppm) or DMSO-$d_6$ ($\delta_H$: 2.50 ppm, $\delta_C$: 39.52 ppm) were used as internal standards for $^1$H NMR and $^{13}$C NMR spectra, respectively. The proton spectra are reported as follows δ (multiplicity, coupling constant *J*, number of protons, position of proton). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br s (broad). High resolution mass spectra (HRMS) were recorded on quadrupole time-of-flight mass spectrometer (QTOF-MS) using electrospray ionization (ESI) as an ionization method.

**Synthesis of 2-Pyridyl Substituted Indole-3-Acetic Acid Derivatives (4) (Tables 1 and 2).**

To a solution of (*E*)-2-aminocinnamic acid derivative **1** (0.30 mmol) in anhydrous THF (3.0 mL) were added aldehyde **2** (0.30 mmol), $Na_2SO_4$ (100 mg) and $MgSO_4$ (100 mg) at room temperature. The mixture was stirred at room temperature and monitored by $^1$H NMR analysis of the crude mixture. After the complete conversion of amine **1** and aldehyde **2** into aldimine **3,** the reaction mixture was filtered to remove $MgSO_4$ and $Na_2SO_4$. The filtrate was concentrated in vacuo to furnish the crude product of aldimine **3**, which was used in the next step without further purification. To a solution of the crude mixture in anhydrous DMF (3.0 mL) were added NaCN (1.5 mg;

View Article Online
DOI: 10.1039/C7OB02691A




0.030 mmol) and 4 Å molecular sieves (100 mg) at room temperature. After the complete consumption of aldimine **3**, the reaction mixture was filtered to remove molecular sieves and the filtrate was concentrated in vacuo. The residue was purified by column chromatography to afford indole **4**.

**Ethyl 2-(2-(pyridin-2-yl)-1*H*-indol-3-yl)acetate (4aa)**

A bright yellow solid (80 mg, 0.29 mmol, 95%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.59 (br s, 1H, indole N*H*), 8.68 - 8.63 (m, 1H, pyridine 6-H), 8.02 (d, *J* = 7.9 Hz, 1H, pyridine 3-H), 7.79 (td, *J* = 7.8, 1.8 Hz, 1H, pyridine 4-H), 7.72 (dd, *J* = 7.9, 0.6 Hz, 1H, indole 4-H), 7.39 (d, *J* = 8.1 Hz, 1H, indole 7-H), 7.25 - 7.20 (m, 2H, indole 6-H, pyridine 5-H), 7.16 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H, indole 5-H), 4.18 (q, *J* = 7.1 Hz, 2H, -$CH_2CO_2CH_2CH_3$), 4.06 (s, 2H, -$CH_2CO_2CH_2CH_3$), 1.24 (t, *J* = 7.1 Hz, 3H, -$CH_2CO_2CH_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 171.8, 150.4, 149.6, 137.0, 135.5, 134.0, 129.7, 123.6, 122.2, 121.7, 120.0, 119.6, 111.4, 107.1, 61.1, 31.7, 14.4; HRMS (ESI) calcd for $C_{17}H_{16}N_2O_2Li$ 287.1372, found 287.1369.

**Methyl 2-(2-(pyridin-2-yl)-1*H*-indol-3-yl)acetate (4ba)**

A brown solid (68 mg, 0.26 mmol, 85%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.62 (br s, 1H, indole N*H*), 8.67-8.63 (m, 1H, pyridine 6-H), 7.98 (d, *J* = 8.1 Hz, 1H, pyridine 3-H), 7.79 (td, *J* =7.8, 1.8 Hz, 1H, pyridine 4-H), 7.71 (d, *J* = 7.9 Hz, 1H, indole 4-H), 7.39 (d, *J* = 8.1 Hz, 1H, indole 7-H), 7.27-7.20 (m, 2H, indole 6-H, pyridine 5-H), 7.16 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H, indole 5-H), 4.08 (s, 2H, -$CH_2CO_2CH_3$), 3.72 (s, 3H, -$CH_2CO_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 172.3, 150.3, 149.7, 137.1, 135.5, 134.0, 129.7, 123.7, 122.2, 121.6, 120.1, 119.6, 111.4, 106.9, 52.3, 31.5; HRMS (ESI) calcd for $C_{16}H_{14}N_2O_2Li$ 273.1215, found 273.1210.

**Isopropyl 2-(2-(pyridin-2-yl)-1*H*-indol-3-yl)acetate (4ca)**

A bright yellow solid (73 mg, 0.25 mmol, 83%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.46 (br s, 1H, indole N*H*), 8.67 - 8.63 (m, 1H, pyridine 6-H), 8.03 (dt, *J* =8.1, 0.9 Hz, 1H, pyridine 3-H), 7.78 (td, *J* =7.8, 1.8 Hz, 1H, pyridine 4-H), 7.72 (dd, *J* = 7.9, 0.8 Hz, 1H, indole 4-H), 7.40 (d, *J* = 8.2 Hz, 1H, indole 7-H), 7.25 - 7.20 (m, 2H, indole 6-H, pyridine 5-H), 7.15 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H, indole 5-H), 5.03 (td, *J* = 12.5, 6.3 Hz, 1H, -$CH_2CO_2CH(CH_3)_2$), 4.02 (s, 2H, -$CH_2CO_2CH(CH_3)_2$), 1.22 (d, *J* = 6.3 Hz, 6H, -$CH_2CO_2CH(CH_3)_2$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 171.4, 150.4, 149.6, 136.9, 135.5, 134.0, 129.8, 123.6, 122.2, 121.7, 120.0, 119.7, 111.3, 107.3, 68.6, 32.0, 22.0; HRMS (ESI) calcd for $C_{18}H_{18}N_2O_2Li$ 301.1528, found 301.1526.

**tert-Butyl 2-(2-(pyridin-2-yl)-1*H*-indol-3-yl)acetate (4da)**

An orange solid (77 mg, 0.25 mmol, 83%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.58 (br s, 1H, indole N*H*), 8.66 - 8.62 (m, 1H, pyridine 6-H), 8.08 (d, *J* = 7.9 Hz, 1H, pyridine 3-H), 7.79 (td, *J* = 7.8, 1.8 Hz, 1H, pyridine 4-H), 7.73 (dd, *J* = 7.9, 0.6 Hz, 1H, indole 4-H), 7.39 (d, *J* = 8.2 Hz, 1H, indole 7-H), 7.26 - 7.20 (m, 2H, indole 6-H, pyridine 5-H), 7.15 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H, indole 5-H), 3.96 (s, 2H, -$CH_2CO_2C(CH_3)_3$), 1.43 (s, 9H, -$CH_2CO_2C(CH_3)_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 171.1, 150.5, 149.6, 136.9, 135.5, 133.9, 129.8, 123.5, 122.1, 121.8, 119.9, 119.8, 111.3, 107.7, 81.3, 33.0, 28.2; HRMS (ESI) calcd for $C_{19}H_{20}N_2O_2Na$ 331.1422, found 331.1419.

***N*-Benzyl-2-(2-(pyridin-2-yl)-1*H*-indol-3-yl)acetamide (4ea)**

An orange solid (82 mg, 0.24 mmol, 80%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.42 (br s, 1H, indole N*H*), 8.59 - 8.54 (m, 1H, pyridine 6-H), 7.77 - 7.72 (m, 1H, pyridine 4-H), 7.70 (dd, *J* = 7.9, 0.6 Hz, 1H, indole 4-H), 7.68 - 7.64 (m, 1H, pyridine 3-H), 7.42 (d, *J* = 8.1 Hz, 1H, indole 7-H), 7.30 - 7.26 (m, 1H, indole 6-H), 7.22 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H, pyridine 5-H), 7.20 - 7.15 (m, 4H, indole 5-H, -$CONHCH_2C_6H_3(H_2)$), 7.05 (dd, *J* = 6.9, 2.6 Hz, 2H, -$CONHCH_2C_6H_2(H_3)$), 6.86 (br s, 1H, -$CONHCH_2C_6H_5$), 4.38 (d, *J* = 6.0 Hz, 2H, -$CONHCH_2C_6H_5$), 4.09 (s, 2H, -$CH_2$CONH-); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 171.3, 150.1, 149.6, 138.4, 137.3, 135.7, 133.9, 129.5, 128.6, 127.4, 127.3, 124.2, 122.4, 121.2, 120.6, 119.3, 111.5, 108.2, 43.5, 33.7; HRMS (ESI) calcd for $C_{22}H_{19}N_3OLi$ 348.1688, found 348.1683.

**2-(2-(pyridin-2-yl)-1*H*-indol-3-yl)-acetic acid piperidyl amide (4fa)**

An orange solid (88 mg, 0.27 mmol, 92%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.70 (br s, 1H, indole N*H*), 8.63 - 8.58 (m, 1H, pyridine 6-H), 7.78 - 7.75 (m, 1H, pyridine 3-H), 7.73 - 7.68 (m, 1H, pyridine 4-H), 7.66 (dd, *J* = 7.9, 0.5 Hz, 1H, indole 4-H), 7.32 (d, *J* = 8.1 Hz, 1H, indole 7-H), 7.20 - 7.14 (m, 2H, indole 6-H, pyridine 5-H), 7.09 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H, indole 5-H), 4.18 (s, 2H, -C*H2*CO(piperidine)), 3.59 - 3.54 (m, 2H, piperidine), 3.44 - 3.36 (m, 2H, piperidine), 1.56 - 1.49 (m, 2H, piperidine), 1.49 - 1.40 (m, 2H, piperidine), 1.31 - 1.23 (m, 2H, piperidine); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 169.4, 150.8, 149.5, 136.8, 135.8, 133.4, 129.4, 123.4, 121.9, 121.7, 119.8, 119.6, 111.4, 108.6, 47.2, 43.3, 31.8, 26.2, 25.8, 24.6; HRMS (ESI) calcd for $C_{20}H_{21}N_3ONa$ 342.1582, found 342.1581.

**Methyl 2-(5-bromo-2-(pyridin-2-yl)-1*H*-indol-3-yl)acetate (4ga)**

A yellow solid (87 mg, 0.25 mmol, 84%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.52 (br s, 1H, indole N*H*), 8.65 (d, *J* = 4.6 Hz, 1H, pyridine 6-H), 7.95 (d, *J* = 7.9 Hz, 1H, pyridine 3-H), 7.83 - 7.78 (m, 2H, indole 4-H, pyridine 4-H), 7.34 - 7.31 (m, 1H, indole 6-H), 7.28 (s, 1H, indole 7-H), 7.26 - 7.22 (m, 1H, pyridine 5-H), 4.01 (s, 2H, -$CH_2CO_2CH_3$), 3.73 (s, 3H, -$CH_2CO_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 172.1, 149.8, 149.6, 137.2, 135.2, 134.2, 131.3, 126.4, 122.6, 122.0, 121.7, 113.3, 112.9, 106.4, 52.4, 31.3; HRMS (ESI) calcd for $C_{16}H_{13}BrN_2O_2Na$ 367.0058, found 367.0055.

**Ethyl 2-(6-bromo-2-(pyridin-2-yl)-1*H*-indol-3-yl)acetate (4ha)**

A yellow solid (101 mg, 0.28 mmol, 94%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ = 9.58 (br s, 1H, indole N*H*), 8.64 (dt, *J* = 4.0, 0.7 Hz, 1H, pyridine 6-H), 7.98 (d, *J* = 7.9 Hz, 1H, pyridine 3-H), 7.79 (td, *J* = 7.8, 1.8 Hz, 1H, pyridine 4-H), 7.56 (d, *J* = 8.5 Hz, 1H, indole 4-H), 7.52 (d, *J* = 1.1 Hz, 1H, indole 7-H), 7.25 - 7.21 (m, 2H, indole 5-H, pyridine 5-H), 4.17 (q, *J* = 7.1 Hz, 2H, -$CH_2CO_2CH_2CH_3$), 4.03 - 4.00 (m, 2H, -$CH_2CO_2CH_2CH_3$), 1.26 - 1.22 (m, 3H, -$CH_2CO_2CH_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 171.6, 149.9, 149.7, 137.1, 136.2, 134.6, 128.6, 123.4, 122.5, 121.7, 120.9, 117.2, 114.2, 107.2, 61.3, 31.6, 14.4; HRMS (ESI) calcd for $C_{17}H_{15}BrN_2O_2Na$ 381.0215, found 381.0210.

View Article Online
DOI: 10.1039/C7OB02691A




**Ethyl 2-(2-(pyridin-3-yl)-1*H*-indol-3-yl)acetate (4ab)**

A yellow solid (80 mg, 0.29 mmol, 95%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 8.91 (d, *J* = 1.8 Hz, 1H, pyridine 2-H), 8.64 (dd, *J* = 4.8, 1.6 Hz, 1H, pyridine 6-H), 8.29 (br s, 1H, indole N*H*), 8.06 (dt, *J* = 7.9, 1.9 Hz, 1H, pyridine 4-H), 7.71 (d, *J* = 7.6 Hz, 1H, indole 4-H), 7.45 - 7.40 (m, 2H, indole 7-H, pyridine 5-H), 7.28 - 7.24 (m, 1H, indole 6-H), 7.21 - 7.17 (m, 1H, indole 5-H), 4.18 (q, *J* = 7.2 Hz, 2H, -$CH_2CO_2CH_2CH_3$), 3.81 (s, 2H, -$CH_2CO_2CH_2CH_3$), 1.29 – 1.24 (m, 3H, -$CH_2CO_2CH_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 172.0, 149.2, 149.1, 136.3, 135.8, 132.8, 129.0, 128.7, 123.9, 123.3, 120.5, 119.7, 111.2, 107.5, 61.2, 31.2, 14.4; HRMS (ESI) calcd for $C_{17}H_{16}N_2O_2$ 348.1688, found 348.1683.

**Ethyl 2-(2-(pyridin-4-yl)-1*H*-indol-3-yl)acetate (4ac)**

A yellow solid (80 mg, 0.29 mmol, 95%). Spectroscopic data were in good agreement with the literature.[7] $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 8.70 (d, *J* = 6.0 Hz, 2H, pyridine 2-H, 6-H), 8.53 (br s, 1H, indole N*H*), 7.72 (d, *J* = 8.1 Hz, 1H, indole 4-H), 7.63 - 7.60 (m, 2H, pyridine 3-H, 5-H), 7.40 (d, *J* = 8.1 Hz, 1H, indole 7-H), 7.30 - 7.26 (m, 1H, indole 6-H), 7.21 - 7.17 (m, 1H, indole 5-H), 4.20 (q, *J* = 7.2 Hz, 2H, -$CH_2CO_2CH_2CH_3$), 3.88 (s, 2H, -$CH_2CO_2CH_2CH_3$), 1.27 (t, *J* = 7.1 Hz, 3H, -$CH_2CO_2CH_2CH_3$).

**Ethyl 2-(2-(6-bromopyridin-2-yl)-1*H*-indol-3-yl)acetate (4ad)**

A white solid (96 mg, 0.27 mmol, 89%). $^1$H NMR (500 MHz, DMSO-$d_6$, ppm) δ 11.65 (s, 1H, indole N*H*), 7.92 (d, *J* = 7.6 Hz, 1H, pyridine 3-H), 7.86 (t, *J* = 7.8 Hz, 1H, pyridine 4-H), 7.62 (d, *J* = 7.9 Hz, 1H, indole 4-H), 7.52 (d, *J* = 7.6 Hz, 1H, pyridine 5-H), 7.45 (d, *J* = 8.1 Hz, 1H, indole 7-H), 7.20 (t, *J* = 7.2 Hz, 1H, indole 6-H), 7.09 - 7.02 (m, 1H, indole 5-H), 4.16 (s, 2H, -$CH_2CO_2CH_2CH_3$), 4.07 (q, *J* = 7.2 Hz, 2H, -$CH_2CO_2CH_2CH_3$), 1.17 (t, *J* = 7.1 Hz, 3H, -$CH_2CO_2CH_2CH_3$); $^{13}$C NMR (125 MHz, DMSO-$d_6$, ppm) δ 171.3, 152.2, 140.8, 140.2, 136.2, 131.6, 128.9, 125.6, 123.3, 119.4, 119.4, 119.2, 111.7, 109.4, 60.0, 30.5, 14.1; HRMS (ESI) calcd for $C_{17}H_{15}BrN_2ONa$ 381.0215, found 381.0215.

**Ethyl 2-(2-(6-methoxypyridin-2-yl)-1*H*-indol-3-yl)acetate (4ae)**

A white solid (87 mg, 0.28 mmol, 94%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.18 (br s, 1H, indole N*H*), 7.70 (d, *J* = 7.9 Hz, 1H, indole 4-H), 7.67 (dd, *J* = 8.2, 7.6 Hz, 1H, pyridine 4-H), 7.51 (d, *J* = 7.5 Hz, 1H, pyridine 3-H), 7.42 (d, *J* = 8.2 Hz, 1H, indole 7-H), 7.27 - 7.23 (m, 1H, indole 6-H), 7.18 - 7.14 (m, 1H, indole 5-H), 6.71 - 6.67 (m, 1H, pyridine 5-H), 4.16 (q, *J* = 7.2 Hz, 2H, -$CH_2CO_2CH_2CH_3$), 4.09 (s, 2H, -$CH_2CO_2CH_2CH_3$), 4.05 (s, 3H, -$OCH_3$), 1.23 (t, *J* = 7.1 Hz, 3H, -$CH_2CO_2CH_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 171.9, 163.8, 147.9, 139.5, 135.3, 133.9, 129.8, 123.5, 120.1, 119.6, 114.3, 111.2, 109.6, 107.3, 61.1, 53.6, 31.7, 14.4; HRMS (ESI) calcd for $C_{18}H_{18}N_2O_3Li$ 317.1477, found 317.1477.

**Ethyl 2-(2-(6-methylpyridin-2-yl)-1*H*-indol-3-yl)acetate (4af)**

A yellow solid (74 mg, 0.25 mmol, 84%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.49 (br s, 1H, indole N*H*), 7.80 (d, *J* = 7.8 Hz, 1H, indole 4-H), 7.71 (d, *J* = 7.8 Hz, 1H, pyridine 3-H), 7.67 (t, *J* = 7.7 Hz, 1H, pyridine 4-H), 7.40 (d, *J* = 8.2 Hz, 1H, indole 7-H), 7.24 (td, *J* = 7.6, 1.0 Hz, 1H, indole 6-H), 7.17 - 7.13 (m, 1H, indole 5-H), 7.08 (d, *J* = 7.5 Hz, 1H, pyridine 5-H), 4.17 (q, *J* = 7.1 Hz, 2H, -$CH_2CO_2CH_2CH_3$), 4.05 (s, 2H, -$CH_2CO_2CH_2CH_3$), 2.61 (s, 3H, -$CH_3$), 1.24 (t, *J* = 7.2 Hz, 3H, -$CH_2CO_2CH_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 171.9, 158.4, 149.6, 137.2, 135.4, 134.2, 129.8, 123.4, 121.8, 119.9, 119.6, 118.7, 111.3, 106.8, 61.1, 31.7, 24.8, 14.4; HRMS (ESI) calcd for $C_{18}H_{18}N_2O_2Li$ 301.1528, found 301.1519.

**Ethyl 2-(2-(5-methylpyridin-2-yl)-1*H*-indol-3-yl)acetate (4ag)**

A yellow solid (79 mg, 0.27 mmol, 89%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.52 (d, *J* = 13.7 Hz, 1H, indole N*H*), 8.47 (s, 1H, pyridine 6-H), 7.91 (d, *J* = 8.1 Hz, 1H, pyridine 3-H), 7.71 (d, *J* = 7.9 Hz, 1H, indole 4-H), 7.60 (dd, *J* = 8.1, 1.7 Hz, 1H, pyridine 4-H), 7.38 (dd, *J* = 8.1, 0.8 Hz, 1H, indole 7-H), 7.25 - 7.21 (m, 1H, indole 6-H), 7.17 - 7.12 (m, 1H, indole 5-H), 4.17 (q, *J* = 7.1 Hz, 2H, -$CH_2CO_2CH_2CH_3$), 4.03 (s, 2H, -$CH_2CO_2CH_2CH_3$), 2.38 (s, 3H, -$CH_3$), 1.24 (t, *J* = 7.1 Hz, 3H, -$CH_2CO_2CH_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 171.9, 150.0, 147.8, 137.5, 135.4, 134.2, 131.9, 129.8, 123.4, 121.2, 119.9, 119.5, 111.3, 106.4, 61.1, 31.7, 18.4, 14.4; HRMS (ESI) calcd for $C_{18}H_{18}N_2O_2Na$ 317.1266, found 317.1261.

**Ethyl 2-(2-(4-methylpyridin-2-yl)-1*H*-indol-3-yl)acetate (4ah)**

A yellow solid (80 mg, 0.27 mmol, 91%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.92 (br s, 1H, indole N*H*), 8.50 (d, *J* = 4.9 Hz, 1H, pyridine 6-H), 7.88 - 7.84 (m, 1H, pyridine 3-H), 7.73 (d, *J* = 7.9 Hz, 1H, indole 4-H), 7.35 (dd, *J* = 8.1, 0.8 Hz, 1H, indole 7-H), 7.22 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H, indole 6-H), 7.17 - 7.13 (m, 1H, indole 5-H), 7.06 - 7.03 (m, 1H, pyridine 5-H), 4.20 (q, *J* = 7.1 Hz, 2H, -$CH_2CO_2CH_2CH_3$), 4.07 (s, 2H, -$CH_2CO_2CH_2CH_3$), 2.45 (s, 3H, -$CH_3$), 1.27 (t, *J* = 7.1 Hz, 3H, -$CH_2CO_2CH_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 171.9, 150.3, 149.3, 148.1, 135.6, 134.2, 129.7, 123.4, 123.3, 122.7, 119.9, 119.6, 111.4, 106.8, 61.1, 31.8, 21.5, 14.4; HRMS (ESI) calcd for $C_{18}H_{18}N_2O_2Li$ 301.1528, found 301.1524.

**Ethyl 2-(2-(3-methylpyridin-2-yl)-1*H*-indol-3-yl)acetate (4ai)**

A yellow solid (82 mg, 0.28 mmol, 94%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 8.95 (br s, 1H, indole N*H*), 8.38 (d, *J* = 4.1 Hz, 1H, pyridine 6-H), 7.64 (d, *J* = 7.8 Hz, 1H, indole 4-H or pyridine 4-H), 7.61 (dd, *J* = 7.8, 0.8 Hz, 1H, indole 4-H or pyridine 4-H), 7.32 (d, *J* = 8.1 Hz, 1H, indole 7-H), 7.21 - 7.12 (m, 3H, indole 5-H, 6-H, pyridine 5-H), 4.06 (q, *J* = 7.1 Hz, 2H, -$CH_2CO_2CH_2CH_3$), 3.75 (s, 2H, -$CH_2CO_2CH_2CH_3$), 2.35 (s, 3H, -$CH_3$), 1.16 (t, *J* = 7.1 Hz, 3H, -$CH_2CO_2CH_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 171.9, 150.6, 146.6, 139.0, 136.1, 133.8, 133.3, 128.2, 123.0, 122.7, 119.8, 119.4, 111.4, 107.9, 60.7, 31.2, 19.1, 14.2; HRMS (ESI) calcd for $C_{18}H_{18}N_2O_2Li$ 301.1528, found 301.1523.

**Ethyl 2-(2-(quinolin-2-yl)-1*H*-indol-3-yl)acetate (4aj)**

A brown solid (85 mg, 0.26 mmol, 86%). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.72 (br s, 1H, indole N*H*), 8.23 (d, *J* = 8.5 Hz, 1H, quinoline 4-H), 8.14 (d, *J* = 8.7 Hz, 1H, quinoline 3-H), 8.10 (d, *J* = 8.4 Hz, 1H, quinoline 8-H), 7.84 - 7.81 (m, 1H, quinoline 5-H), 7.77 - 7.71 (m, 2H, indole 4-H, quinoline 7-H), 7.53 (ddd, *J* =

View Article Online
DOI: 10.1039/C7OB02691A




8.0, 6.9, 1.1 Hz, 1H, quinoline 6-H), 7.44 (d, *J* = 8.1 Hz, 1H, indole 7-H), 7.29 - 7.26 (m, 1H, indole 6-H), 7.17 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H, indole 5-H), 4.22 - 4.16 (m, 4H, -C*H*$_2$CO$_2$C*H*$_2$CH$_3$), 1.25 (t, *J* = 7.1 Hz, 3H, -CH$_2$CO$_2$CH$_2$C*H*$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$, ppm) δ 171.8, 150.4, 148.2, 136.9, 135.8, 134.2, 130.1, 129.9, 129.2, 127.8, 127.3, 126.5, 124.0, 120.1, 119.8, 119.8, 111.5, 108.4, 61.2, 31.8, 14.4; HRMS (ESI) calcd for $C_{21}H_{18}N_2O_2Na$ 353.1266, found 337.1266.

**Ethyl 2-(2-(isoquinolin-3-yl)-1*H*-indol-3-yl)acetate (4ak)**

A brown solid (87 mg, 0.26 mmol, 88%). $^1$H NMR (500 MHz, CDCl$_3$, ppm) δ 9.64 (br s, 1H, indole N*H*), 9.28 (s, 1H, isoquinoline 1-H), 8.39 (s, 1H, isoquinoline 4-H), 7.98 (d, *J* = 8.2 Hz, 1H, isoquinoline 8-H), 7.92 (d, *J* = 8.2 Hz, 1H, isoquinoline 5-H), 7.75 (d, *J* = 7.9 Hz, 1H, indole 4-H), 7.74 - 7.70 (m, 1H, isoquinoline 6-H), 7.62 - 7.58 (m, 1H, isoquinoline 7-H), 7.43 (d, *J* = 7.9 Hz, 1H, indole 7-H), 7.26 - 7.23 (m, 1H, indole 6-H), 7.19 - 7.15 (m, 1H, indole 5-H), 4.22 (q, *J* = 7.2 Hz, 2H, -CH$_2$CO$_2$C*H*$_2$CH$_3$), 4.14 (s, 2H, -C*H*$_2$CO$_2$CH$_2$CH$_3$), 1.27 (t, *J* = 7.2 Hz, 3H, -CH$_2$CO$_2$CH$_2$C*H*$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$, ppm) δ 172.0, 152.4, 144.1, 136.7, 135.5, 134.5, 131.0, 129.9, 127.8, 127.8, 127.4, 127.4, 123.3, 120.0, 119.5, 118.0, 111.3, 106.4, 61.1, 31.9, 14.4; HRMS (ESI) calcd for $C_{21}H_{18}N_2O_2Li$ 337.1528, found 337.1523.

**Ethyl 2-(2-(isoquinolin-1-yl)-1*H*-indol-3-yl)acetate (4al)**

A brown solid (91 mg, 0.28 mmol, 92%). $^1$H NMR (500 MHz, CDCl$_3$, ppm) δ 9.25 (br s, 1H, indole N*H*), 8.56 (d, *J* = 5.6 Hz, 1H, isoquinoline 3-H), 8.23 (d, *J* = 8.5 Hz, 1H, isoquinoline 8-H), 7.88 (d, *J* = 8.2 Hz, 1H, isoquinoline 5-H), 7.73 - 7.66 (m, 2H, indole 4-H, isoquinoline 7-H), 7.64 (d, *J* = 5.6 Hz, 1H, isoquinoline 4-H), 7.56 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H, isoquinoline 6-H), 7.36 (d, *J* = 7.9 Hz, 1H, indole 7-H), 7.24 (td, *J* = 7.6, 1.1 Hz, 1H, indole 6-H), 7.20 - 7.16 (m, 1H, indole 5-H), 4.07 (q, *J* = 7.2 Hz, 2H, -CH$_2$CO$_2$C*H*$_2$CH$_3$), 3.78 (s, 2H, -C*H*$_2$CO$_2$CH$_2$CH$_3$), 1.13 (t, *J* = 7.1 Hz, 3H, -CH$_2$CO$_2$CH$_2$C*H*$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$, ppm) δ 171.8, 152.6, 142.4, 136.9, 136.4, 133.2, 130.6, 128.6, 127.8, 127.6, 127.4, 127.1, 123.3, 120.6, 120.1, 119.7, 111.5, 109.3, 60.8, 31.7, 14.3; HRMS (ESI) calcd for $C_{21}H_{18}N_2O_2Na$ 353.1266, found 337.1266.

**Synthesis of Indoloquinolizine Scaffold and Its Derivatives**

**2-(2-(Pyridin-2-yl)-1*H*-indol-3-yl)ethan-1-ol (8)**

To a solution of the indole **4aa** (84 mg, 0.30 mmol) in anhydrous THF (3.0 mL) was slowly added L-selectride solution (0.90 mL, 1.0 M THF solution) at room temperature. The mixture was stirred and monitored by TLC at room temperature. After the complete consumption of indole **4aa**, the reaction mixture was quenched with water and stirred vigorously for 15 min. The crude mixture was extracted with ethyl acetate. The organic layers were combined, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:2) to afford alcohol **8** as a white solid (64 mg, 0.27 mmol, 89%). Spectroscopic data were in good agreement with the literature.[4]

$^1$H NMR (500 MHz, CDCl$_3$, ppm) δ 9.01 (br s, 1H, indole N*H*), 8.63 - 8.60 (m, 1H, pyridine 6-H), 7.82 - 7.76 (m, 2H, pyridine 3-H, 4-H), 7.64 (dd, *J* = 7.9, 0.8 Hz, 1H, indole 4-H), 7.41 - 7.38 (m, 1H, indole 7-H), 7.25 - 7.21 (m, 2H, indole 6-H, pyridine 5-H), 7.14 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H, indole 5-H), 4.08 - 4.03 (m, 2H, -CH$_2$C*H*$_2$OH), 3.77 (br s, 1H, -CH$_2$CH$_2$O*H*), 3.36 (t, *J* = 6.2 Hz, 2H, -C*H*$_2$CH$_2$OH).

**7,12-Dihydro-6*H*-indolo[2,3-*a*]quinolizin-5-ium trifluoromethanesulfonate (10)**

To a solution of alcohol **8** (71 mg, 0.30 mmol) and triethylamine (63 µL, 0.45 mmol) in dry CHCl$_3$ (3.0 mL) at 0 °C was slowly added trifluoromethanesulfonic anhydride (61 µL, 0.36 mmol). After stirring for 5 min, the resulting yellow precipitate was collected by filtration and washed with CHCl$_3$. The yellow solid was identified as compound **10** (100 mg, 0.28 mmol, 92%). Spectroscopic data were in good agreement with the literature.[4]

$^1$H NMR (500 MHz, DMSO-d$_6$, ppm) δ 12.31 (br s, 1H, indole N*H*), 8.93 (d, *J* = 6.1 Hz, 1H, pyridinium 6-H), 8.55 (t, *J* = 7.7 Hz, 1H, pyridinium 4-H), 8.21 (d, *J* = 8.1 Hz, 1H, pyridinium 3-H), 7.81 (t, *J* = 6.7 Hz, 1H, pyridinium 5-H), 7.74 (d, *J* = 8.1 Hz, 1H, indole 4-H or 7-H), 7.55 (d, *J* = 8.2 Hz, 1H, indole 4-H or 7-H), 7.38 (t, *J* = 7.6 Hz, 1H, indole 6-H), 7.21 - 7.15 (m, 1H, indole 5-H), 4.90 (t, *J* = 7.2 Hz, 2H, -CH$_2$C*H*$_2$N$^+$-), 3.39 (t, *J* = 7.2 Hz, 2H, -C*H*$_2$CH$_2$N$^+$-).

**10-Desbromoarborescidine A (11)**

The pyridinium salt **10** (110 mg, 0.30 mmol) was dissolved in MeOH (3.0 mL) and Pd/C powder was added to the reaction mixture. The above mixture was stirred at room temperature under a hydrogen atmosphere, and monitored by TLC. After complete consumption of the starting material **10**, the reaction mixture was filtered through celite, and washed with dichloromethane. Then, the filtrate was concentrated, and the crude product was purified by flash column chromatography (100% ethyl acetate) on silica to provide the desired product **11** as a white solid (66 mg, 0.29 mmol, 98%). Spectroscopic data were in good agreement with the literature.[10a]

$^1$H NMR (500 MHz, CDCl$_3$, ppm) δ 7.90 (br s, 1H, indole N*H*), 7.46 (d, *J* = 7.8 Hz, 1H, indole 4-H), 7.33 (d, *J* = 7.9 Hz, 1H, indole 7-H), 7.13 (td, J = 7.5, 1.1 Hz, 1H, indole 6-H), 7.11 - 7.06 (m, 1H, indole 5-H), 3.33 (d, *J* = 7.3 Hz, 1H, piperidine 2-H), 3.13 (dd, *J* = 10.6, 5.9 Hz, 1H, piperidine 6-H), 3.09 - 2.99 (m, 2H, C=CC*H*(H)C*H*(H)N), 2.78 - 2.64 (m, 2H, C=CC*H*(H)C*H*(H)N), 2.49 - 2.40 (m, 1H, piperidine 6-H), 2.09 (dd, *J* = 12.7, 2.7 Hz, 1H, piperidine 3-H), 1.83 (d, *J* = 9.9 Hz, 1H, piperidine 4-H), 1.80 - 1.69 (m, 2H, piperidine 5-H$_2$), 1.59 (q, *J* = 11.7 Hz, 1H, piperidine 3-H), 1.53 - 1.41 (m, 1H, piperidine 4-H); $^{13}$C NMR (125 MHz, CDCl$_3$, ppm) δ 136.1, 135.2, 127.6, 121.4, 119.5, 118.2, 110.8, 108.3, 60.4, 55.9, 53.7, 30.1, 25.9, 24.4, 21.7; HRMS (ESI) calcd for $C_{15}H_{19}N_2$ 227.1548, found 227.1543.

**1,4,6,7,12,12*b*-Hexahydroindolo[2,3-*a*]quinolizine (12)**

To a solution of pyridinium salt **10** (110 mg, 0.30 mmol) in MeOH (3.0 mL) was added NaBH$_4$ (34 mg, 0.90 mmol) in two portions. After stirring for 3 h at room temperature, the

View Article Online
DOI: 10.1039/C7OB02691A




reaction mixture was quenched with water and diluted with ethyl acetate. The crude mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate only) to afford **12** as a white solid (56 mg, 0.25 mmol, 83%). Spectroscopic data were in good agreement with the literature.[19]

$^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 7.72 (br s, 1H, indole N*H*), 7.50 (d, *J* = 7.6 Hz, 1H, indole 4-H), 7.31 (d, *J* = 7.9 Hz, 1H, indole 7-H), 7.16 (td, *J* = 7.5, 1.2 Hz, 1H, indole 6-H), 7.13 - 7.09 (m, 1H, indole 5-H), 5.88 - 5.77 (m, 2H, -C*H*=C*H*-), 3.61 - 3.53 (m, 1H, piperidine 2-H), 3.51 - 3.44 (m, 1H, piperidine 6-H), 3.19 (dd, *J* = 11.3, 4.7 Hz, 1H, C=CCH$_2$C*H*(H)N), 3.15 - 3.08 (m, 1H, piperidine 6-H), 3.08 - 2.99 (m, 1H, C=CC*H*(H)CH$_2$N), 2.80 - 2.73 (m, 1H, C=CC*H*(H)CH$_2$N), 2.66 (td, *J* = 11.4, 4.0 Hz, 1H, C=CCH$_2$C*H*(H)N), 2.53 - 2.45 (m, 1H, piperidine 3-H), 2.38 - 2.29 (m, 1H, piperidine 3-H); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 136.3, 134.8, 127.3, 126.2, 124.2, 121.6, 119.6, 118.3, 110.9, 108.7, 55.6, 54.6, 52.4, 31.5, 21.6; HRMS (ESI) calcd for $C_{15}H_{17}N_2$ 225.1392, found 225.1386.

**Total Synthesis of Arborescidine A (6)**

**2-(6-bromo-2-(pyridin-2-yl)-1*H*-indol-3-yl)ethan-1-ol (13)**

To a solution of indole **4ha** (110 mg, 0.30 mmol) in anhydrous THF (3.0 mL) was slowly added L-selectride solution (0.90 mL 1.0 M THF solution) at room temperature. The mixture was stirred and monitored by TLC. After the complete conversion of indole **4ha** into alcohol **13**, the reaction mixture was quenched with water and stirred vigorously for 15 min. The crude mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:2) to afford alcohol **13** as a white solid (79 mg, 0.25 mmol, 83%).

$^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 9.37 (br s, 1H, indole N*H*), 8.43 - 8.35 (m, 1H, pyridine 6-H), 7.69 (td, *J* = 1.8, 7.7 Hz, 1H, pyridine 4-H), 7.59 (d, *J* = 7.9 Hz, 1H, pyridine 3-H), 7.37 (d, *J* = 8.5 Hz, 1H, indole 4-H), 7.27 (d, *J* = 1.5 Hz, 1H, indole 7-H), 7.18 (dd, *J* = 8.4, 1.7 Hz, 1H, indole 5-H), 7.12 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H, pyridine 5-H), 4.98 (br s, 1H, -CH$_2$CH$_2$O*H*), 4.08 (t, *J* = 6.0 Hz, 2H, -CH$_2$C*H*$_2$OH), 3.24 (t, *J* = 6.0 Hz, 2H, -C*H*$_2$CH$_2$OH); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 150.2, 148.9, 137.2, 137.0, 134.3, 127.9, 123.1, 122.2, 121.6, 120.2, 117.2, 114.5, 113.0, 63.4, 27.3; HRMS (ESI) calcd for $C_{15}H_{13}BrN_2ONa$ 339.0109, found 339.0109.

**10-bromo-7,12-dihydro-6*H*-indolo[2,3-*a*]quinolizin-5-ium trifluoromethanesulfonate (14)**

To a solution of alcohol **13** (95 mg, 0.30 mmol) and triethylamine (63 µL, 0.45 mmol) in dry $CHCl_3$ (3.0 mL) at 0 °C was slowly added trifluoromethanesulfonic anhydride (61 µL, 0.36 mmol). After stirring for 5 min the resulting yellow precipitate was collected by filtration and washed with $CHCl_3$. The yellow solid was identified as compound **14** (110 mg, 0.24 mmol, 81%).

$^1$H NMR (500 MHz, DMSO-$d_6$, ppm) δ 12.47 (s, 1H, indole N*H*), 8.95 (d, *J* = 6.1 Hz, 1H, pyridinium 6-H), 8.62 - 8.52 (m, 1H, pyridinium 4-H), 8.27 - 8.17 (m, 1H, pyridinium 3-H), 7.84 (ddd, *J* = 7.6, 6.3, 1.4 Hz, 1H, pyridinium 5-H), 7.75 (d, *J* = 1.5 Hz, 1H, indole 7-H), 7.71 (d, *J* = 8.5 Hz, 1H, indole 4-H), 7.32 (dd, *J* = 8.5, 1.7 Hz, 1H, indole 5-H), 4.90 (t, *J* = 7.3 Hz, 2H, -CH$_2$C*H*$_2$N$^+$-), 3.40 (t, *J* = 7.3 Hz, 2H, -C*H*$_2$CH$_2$N$^+$-); $^{13}$C NMR (125 MHz, DMSO-$d_6$, ppm) δ 145.7, 145.6, 142.6, 139.9, 126.0, 124.0, 123.8, 123.7, 122.5, 121.0, 119.2, 117.7, 115.2, 55.7, 18.7; HRMS (ESI) calcd for $C_{15}H_{12}BrN_2^+$ 299.0178, found 229.0178.

**10-bromo-1,4,6,7,12,12*b*-hexahydroindolo[2,3-*a*]quinolizine (15)**

To a solution of pyridinium salt **14** (130 mg, 0.30 mmol) in MeOH (3.0 mL) was added $NaBH_4$ (34 mg, 0.90 mmol) in two portions. After stirring for 3 h the reaction mixture was quenched with water and diluted with ethyl acetate. The crude mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (100% ethyl acetate) to afford compound **15** as a white solid (74 mg, 0.25 mmol, 81%).

$^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 7.70 (br s, 1H, indole N*H*), 7.46 (d, *J* = 1.7 Hz, 1H, indole 7-H), 7.34 (d, *J* = 8.4 Hz, 1H, indole 4-H), 7.20 (dd, *J* = 8.3, 1.6 Hz, 1H, indole 5-H), 5.87 - 5.79 (m, 2H, -C*H*=C*H*-), 3.57 - 3.52 (m, 1H, piperidine 2-H), 3.49 - 3.44 (m, 1H, piperidine 6-H), 3.17 (dd, *J* = 11.3, 4.6 Hz, 1H, C=CCH$_2$C*H*(H)N), 3.14 - 3.08 (m, 1H, piperidine 6-H), 3.04 - 2.95 (m, 1H, C=CC*H*(H)CH$_2$N), 2.74 - 2.69 (m, 1H, C=CC*H*(H)CH$_2$N), 2.64 (td, *J* = 11.4, 4.1 Hz, 1H, C=CCH$_2$C*H*(H)N), 2.52 - 2.45 (m, 1H, piperidine 3-H), 2.37 - 2.28 (m, 1H, piperidine 3-H); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 137.2, 135.5, 126.3, 126.2, 124.0, 122.9, 119.5, 115.0, 113.9, 108.9, 55.5, 54.5, 52.3, 31.3, 21.4; HRMS (ESI) calcd for $C_{15}H_{16}BrN_2$ 303.0497, found 303.0494.

**Arborescidine A (6)**

The compound **15** (91 mg, 0.30 mmol) was dissolved in MeOH (3.0 mL) and $PtO_2$ (3.4 mg, 0.015 mmol) was added to the reaction mixture. The above mixture was stirred at room temperature under a hydrogen atmosphere, and monitored by $^1$H NMR analysis of the crude mixture. After 30 minutes, the reaction mixture was filtered through celite, and washed with dichloromethane. Then, the filtrate was concentrated, and the crude product was purified by flash column chromatography (100% ethyl acetate) on silica to provide arborescidine A (**6**) as a white solid (83 mg, 0.27 mmol, 91%). Spectroscopic data were in good agreement with the literature.[12a]

$^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 7.72 (br s, 1H, indole N*H*), 7.44 (d, *J* = 1.7 Hz, 1Hm, indole 7-H), 7.31 (d, *J* = 8.4 Hz, 1H, indole 4-H), 7.17 (dd, *J* = 8.4, 1.7 Hz, 1H, indole 5-H), 3.21 (d, *J* = 10.1 Hz, 1H, piperidine 2-H), 3.11 - 2.94 (m, 3H, piperidine 6-H, C=CC*H*(H)C*H*(H)N), 2.71 - 2.58 (m, 2H, C=CC*H*(H)C*H*(H)N), 2.39 (td, *J* = 4.1, 11.1 Hz, 1H, piperidine 6-H), 2.05 (dd, *J* = 12.4, 2.8 Hz, 1H, piperidine 3-H), 1.91 (d, *J* = 13.0 Hz, 1H, piperidine 4-H), 1.82 - 1.72 (m, 2H, piperidine 5-H$_2$), 1.64 - 1.54 (m, 1H, piperidine 3-H), 1.49 (d, *J* = 12.7 Hz, 1H, piperidine 4-H); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 136.9, 135.9, 126.5, 122.7,

View Article Online
DOI: 10.1039/C7OB02691A




119.4, 114.7, 113.8, 108.4, 60.2, 55.8, 53.5, 30.0, 25.8, 24.4, 21.6; HRMS (ESI) calcd for $C_{15}H_{18}BrN_2$ 305.0653, found 305.0649.

**Total Synthesis of Nauclefidine (7)**

**2-(2-(6-Methoxypyridin-2-yl)-1*H*-indol-3-yl)ethan-1-ol (16)**

To a solution of the indole **4ea** (84 mg, 0.30 mmol) in anhydrous THF (3.0 mL) was slowly added DIBAL-H solution (0.90 mL, 1.0 M THF solution) at room temperature. The mixture was stirred and monitored by TLC. After the complete conversion of indole **4ea** into alcohol **16**, the reaction mixture was quenched with water and stirred for 10 min. The crude mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:2) to afford alcohol **16** as a white solid (64 mg, 0.27 mmol, 89%).

$^1$H NMR (500 MHz, DMSO-$d_6$, ppm) δ 11.26 (s, 1H, indole N*H*), 7.80 (t, *J* = 7.9 Hz, 1H, pyridine 4-H), 7.60 (d, *J* = 7.9 Hz, 1H, indole 4-H), 7.48 (d, *J* = 7.5 Hz, 1H, pyridine 3-H), 7.41 (d, *J* = 8.2 Hz, 1H, indole 7-H), 7.14 (td, *J* = 7.6, 0.9 Hz, 1H, indole 6-H), 7.05 - 7.00 (m, 1H, indole 5-H), 6.72 (d, *J* = 8.1 Hz, 1H, pyridine 5-H), 4.69 (t, *J* = 5.3 Hz, 1H, -$CH_2CH_2OH$), 3.99 (s, 3H, -$OCH_3$), 3.71 - 3.64 (m, 2H, -$CH_2CH_2$OH), 3.34 - 3.31 (m, 2H, -$CH_2CH_2$OH); $^{13}$C NMR (125 MHz, DMSO-$d_6$, ppm) δ 163.1, 149.2, 139.7, 136.0, 132.3, 129.3, 122.6, 119.0, 118.9, 113.4, 112.3, 111.4, 108.4, 61.7, 53.3, 28.8; HRMS (ESI) calcd for $C_{16}H_{16}N_2O_2Na$ 291.1109, found 291.1107.

**7,12-Dihydroindolo[2,3-*a*]quinolizin-4(6*H*)-one (17)**

To a solution of alcohol **16** (80 mg, 0.30 mmol) and p-toluenesulfonyl chloride (120 mg, 0.63 mmol) in anhydrous DMF (3.0 mL) was added pyridine (27 µL, 0.33 mmol). The mixture was stirred and monitored by TLC. After complete conversion of starting alcohol **16**, the reaction mixture was extracted with ethyl acetate and water. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. Recrystallization of the crude product in a mixture of dichloromethane and hexanes provided the desired compound **17** as a yellow solid (52 mg, 0.22 mmol, 73%).

$^1$H NMR (500 MHz, DMSO-$d_6$, ppm) δ 11.65 (s, 1H, indole N*H*), 7.60 (d, *J* = 7.9 Hz, 1H, indole 4-H), 7.48 (dd, *J* = 9.0, 7.0 Hz, 1H, pyridone 4-H), 7.42 (d, *J* = 8.2 Hz, 1H, indole 7-H), 7.22 (d, *J* = 1.2 Hz, 1H, indole 6-H), 7.10 - 7.04 (m, 1H, indole 5-H), 6.65 (d, *J* = 7.0 Hz, 1H, pyridone 5-H), 6.33 (d, *J* = 9.0 Hz, 1H, pyridone 3-H), 4.28 (t, *J* = 6.9 Hz, 2H, -$CH_2CH_2$N-), 3.05 (t, *J* = 6.9 Hz, 2H, -$CH_2CH_2$N-); $^{13}$C NMR (125 MHz, DMSO-$d_6$, ppm) δ 161.4, 138.8, 138.1, 138.0, 127.6, 125.3, 123.9, 119.6, 119.4, 117.4, 113.2, 111.8, 99.7, 30.7, 19.0; HRMS (ESI) calcd for $C_{15}H_{12}N_2ONa$ 259.0847, found 259.0844.

**4-Oxo-4,6,7,12-tetrahydroindolo[2,3-*a*]quinolizine-1-carbaldehyde (18)**

To a solution of pyridone **17** (24 mg, 0.10 mmol, indole N*H*) in anhydrous DMF (1.0 mL) was added phosphoryl chloride (9.3 µL, 0.10 mmol) at room temperature. The reaction mixture was stirred at 60 °C and monitored by TLC. After complete conversion of pyridone **17**, the reaction mixture was quenched with water and extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (ether:hexanes = 10:1) to afford compound **18** as a yellow solid (26 mg, 0.10 mmol, 100%). Spectroscopic data were in good agreement with the literature.[14b]

$^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 12.70 (br s, 1H, indole N*H*), 9.61 (s, 1H, -C*H*O), 7.72 (d, *J* = 9.5 Hz, 1H, pyridone 4-H), 7.64 (d, *J* = 8.1 Hz, 1H, indole 4-H), 7.54 (d, *J* = 8.4 Hz, 1H, indole 7-H), 7.39 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H, indole 6-H), 7.18 (td, *J* = 7.5, 0.8 Hz, 1H, indole 5-H), 6.57 (d, *J* = 9.6 Hz, 1H, pyridone 3-H), 4.64 - 4.56 (m, 2H, -$CH_2CH_2$N-), 3.19 - 3.12 (m, 2H, -$CH_2CH_2$N-).

**tert-Butyl 4-oxo-6,7-dihydroindolo[2,3-*a*]quinolizine-12(4*H*)-carboxylate (19)**

To a solution of pyridone **17** (71 mg, 0.30 mmol), $Boc_2O$ (72 mg, 0.33 mmol) and DMAP (9.2 mg, 0.075 mmol) in anhydrous THF (3.0 mL) was added TEA (46 µL, 0.33 mmol) at room temperature. The reaction mixture was stirred at room temperature and monitored by TLC. After the complete conversion of pyridone **17**, the reaction mixture was quenched with water and extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (100% ethyl acetate) to afford compound **19** as a yellow solid (90 mg, 0.27 mmol, 90%).

$^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 8.08 (d, *J* = 8.5 Hz, 1H, indole 4-H), 7.54 (d, *J* = 7.8 Hz, 1H, indole 7-H), 7.42 (td, *J* = 7.9, 1.2 Hz, 1H, indole 6-H), 7.35 (dd, *J* = 9.0, 7.3 Hz, 1H, pyridone 4-H), 7.33 - 7.28 (m, 1H, indole 5-H), 6.54 (dd, *J* = 9.1, 1.1 Hz, 1H, pyridone 3-H), 6.36 - 6.32 (m, 1H, pyridone 5-H), 4.49 (t, *J* = 6.5 Hz, 2H, -$CH_2CH_2$N-), 2.96 (t, *J* = 6.5 Hz, 2H, -$CH_2CH_2$N-), 1.66 - 1.60 (m, 9H, -$NCO_2C(CH_3)_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 162.2, 150.1, 140.0, 137.9, 137.3, 129.8, 127.1, 126.9, 125.9, 123.7, 119.6, 118.4, 115.6, 104.9, 84.9, 39.0, 28.1, 20.5; HRMS (ESI) calcd for $C_{20}H_{20}N_2O_3Na$ 359.1372, found 359.1367.

**tert-Butyl 3-bromo-4-oxo-6,7-dihydroindolo[2,3-*a*]quinolizine-12(4*H*)-carboxylate (20)**

To a mixture of pyridone **19** (100 mg, 0.30 mmol) and NBS (53 mg, 0.30 mmol) was added anhydrous dichloromethane (3.0 mL) at 0 °C. The reaction mixture stirred and monitored by TLC at the same temperature. After complete conversion of pyridone **19**, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$, and extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:3 to 1:1) to afford compound **20** as a yellow solid (105 mg, 0.25 mmol, 84%).

$^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 8.08 (d, *J* = 8.4 Hz, 1H, indole 4-H), 7.76 (d, *J* = 7.9 Hz, 1H, pyridone 4-H), 7.55 (d, *J* = 7.6 Hz, 1H, indole 7-H), 7.44 (ddd, *J* = 8.4, 7.3, 1.1 Hz, 1H, indole 6-H), 7.34 - 7.29 (m, 1H, indole 5-H), 6.26 (d, *J* = 7.9 Hz, 1H, pyridone

View Article Online
DOI: 10.1039/C7OB02691A




5-H), 4.55 (t, *J* = 6.5 Hz, 2H, -$CH_2CH_2$N-), 2.96 (t, *J* = 6.5 Hz, 2H, -$CH_2CH_2$N-), 1.66 - 1.62 (m, 9H, -$NCO_2C(CH_3)_3$); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 158.6, 150.0, 140.1, 140.0, 137.0, 129.5, 127.5, 126.9, 126.2, 123.9, 119.8, 115.8, 113.8, 104.9, 85.2, 40.8, 28.2, 20.6; HRMS (ESI) calcd for $C_{20}H_{19}BrN_2O_3Na$ 437.0477, found 437.0474.

**4-Oxo-4,6,7,12-tetrahydroindolo[2,3-*a*]quinolizine-3-carbonitrile (21)**

A solution of pyridone **20** (120 mg, 0.30 mmol) and Cu(I)CN (54 mg, 0.60 mmol) in anhydrous DMF (3.0 mL) was refluxed at 200 °C and the reaction mixture was monitored by TLC (the product has sky blue emission under 365 nm irradiation). After complete conversion of pyridone **20**, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ and stirred for additional 1 h. The mixture was extracted with dichloromethane and the combined organic layers were washed a few times with saturated aqueous $NH_4Cl$, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:1 to 2:1) to afford compound **21** as a yellow solid (63 mg, 0.24 mmol, 81%).

$^1$H NMR (500 MHz, DMSO-$d_6$, ppm) δ 11.91 (br s, 1H, indole N*H*), 8.15 (d, *J* = 7.6 Hz, 1H, pyridone 4-H), 7.66 (d, *J* = 8.1 Hz, 1H, indole 4-H), 7.46 (d, *J* = 8.4 Hz, 1H, indole 7-H), 7.30 (td, *J* = 7.6, 0.9 Hz, 1H, indole 6-H), 7.12 (t, *J* = 7.5 Hz, 1H, indole 5-H), 6.78 (d, *J* = 7.8 Hz, 1H, pyridone 5-H), 4.35 (t, *J* = 7.2 Hz, 2H, -$CH_2CH_2$N-), 3.13 (t, *J* = 7.2 Hz, 2H, -$CH_2CH_2$N-); $^{13}$C NMR (125 MHz, DMSO-$d_6$, ppm) δ 159.6, 146.6, 143.0, 139.1, 126.5, 125.4, 124.8, 120.2, 117.2, 116.9, 112.2, 99.9, 98.9, 40.7, 18.7; HRMS (ESI) calcd for $C_{16}H_{11}N_3ONa$ 284.0800, found 284.0796.

**Nauclefidine (7)**

To a solution of the nitrile **21** (78 mg, 0.30 mmol) in anhydrous THF (3.0 mL) was slowly added DIBAL-H solution (0.99 mL 1.0 M THF solution) at room temperature. The mixture was stirred and monitored by TLC (yellow spot at 365 nm). After the complete consumption of nitrile **21**, the reaction mixture was quenched with 3.0 mL of 1.0 N HCl and stirred vigorously for 1 h. The crude mixture was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:1 to 2:1) to afford nauclefidine (**7**) as a white solid (71 mg, 0.27 mmol, 89%). Spectroscopic data were in good agreement with the literature.[14]

$^1$H NMR (500 MHz, DMSO-$d_6$, ppm) δ 11.97 (s, 1H, indole N*H*), 10.14 (s, 1H, -C*H*O), 8.05 (d, *J* = 7.6 Hz, 1H, pyridone 4-H), 7.68 (d, *J* = 7.9 Hz, 1H, indole 4-H), 7.47 (d, *J* = 8.2 Hz, 1H, indole 7-H), 7.32 (t, *J* = 7.6 Hz, 1H, indole 6-H), 7.13 (t, 7.4 Hz, 1H, indole 5-H), 6.86 (d, *J* = 7.6 Hz, 1H, pyridone 5-H), 4.40 (t, *J* = 7.2 Hz, 2H, -$CH_2CH_2$N-), 3.16 (t, *J* = 7.2 Hz, 2H, -$CH_2CH_2$N-); $^{13}$C NMR (125 MHz, DMSO-$d_6$, ppm) δ 188.7, 161.7, 144.5, 140.3, 139.2, 126.9, 125.5, 124.9, 120.7, 120.2, 117.5, 112.3, 100.2, 18.8; HRMS (ESI) calcd for $C_{16}H_{12}N_2O_2Na$ 287.0796, found 287.0791.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by National Research Foundation of Korea (NRF) grants funded by the Korean Government (NRF-2015R1D1A1A01057200, NRF-2017M2A8A4018045, and NRF-20100020209). C.-H.C. thanks the financial support from an NRF grant funded by the Korean Government (NRF-2014-011165, Center for New Directions in Organic Synthesis).

## Notes and references

1 For a review on indoloquinolizine natural products, see: M. Pérez, M. Espadinha and M. M. M. Santos, *Curr Pharm Des.*, 2015, **21**, 5518.

2 Conventionally, these tetrafused heterocyclic scaffolds were constructed from pyridinium ions, generated from tryptophols and pyridines, through intramolecular cyclization at the C1-C2' disconnection leading to the C-ring formation. For recent examples, see: (a) S.-G. Wang, Z.-L. Xia, R.-Q. Xu, X.-J. Liu, C. Zheng and S. L. You, *Angew. Chem. Int. Ed.*, 2017, **56**, 7440; (b) M. Vendrell, A. Soriano, V. Casad, J. L. Diaz, R. Lavilla, E. I. Canela, C. Lluis, R. Franco, F. Albericio and M. Royo, *ChemMedChem*, 2009, **4**, 1514; (c) N. Kogure, A. Someya, A. Urano, M. Kitajima and H. Takayama, *J. Nat. Med.*, 2007, **61**, 208; (d) T. Putkonen, A. Tolvanen and R. Jokela, *Tetrahedron Lett.*, 2001, **42**, 6593; (e) T. Putkonen, A. Tolvanen, R. Jokela, S. Caccamesec and N. Parrinello *Tetrahedron*, 2003, **59**, 8589; (f) J.-C. Fernandez, N. Valls, J. Bosch and J. Bonjoch, *J. Chem. Soc., Chem. Commun.*, 1995, 2317; (g) E. Wenkert, M. Guo, M. J. Pestchanker, Y.-J. Shi and Y. D. Vankar, *J. Org. Chem.*, 1989, 54, 1166; (h) D. Spitzner, K. Arnold, J. J. Stezowski, T. Hildenbrand and S. Henkel, *Chem. Ber.*, 1989, **122**, 2027; (i) E. Wenkert, E. C. Angell, J. Drexler, P. D. R. Moeller, J. St. Pyrek, Y.-J. Shi, M. Sultana and Y. D. Vankar, *J. Org. Chem.*, 1986, **51**, 2995.

3 Alternatively, the indoloquinolizine scaffold was prepared by the Bischler-Napieralski reaction of either a 6-membered lactam or imide generated from tryptamine with a suitable carboxylic acid derivative. For the recent examples, see: (a) B. J. English and R. M. Williams, *J. Org. Chem.*, 2010, **75**, 7869; (b) J. Szawkało, S. J. Czarnocki, A. Zawadzka, K. Wojtasiewicz, A. Leniewski, J. K. Maurin, Z. Czarnockia and J. Drabowicz, *Tetrahedron: Asymmetry*, 2007, **18**, 406; (c) A. Deiters, M. Pettersson and S. F. Martin, *J. Org. Chem.*, 2006, **71**, 6547; (d) M. Ohba, T. Ohashi and T. Fujii, *Heterocycles*, 1991, **32**, 319.

4 Recently, the Bannister group developed a novel protocol to access these scaffolds via successive palladium-catalyzed Sonogashira coupling reactions of 2-bromopyridines and *ω*-alkynol followed by Larock indolization of the resulting Sonogashira coupled products with ortho-bromoaniline derivatives leading to 2-(indol-3-yl)ethanol derivatives bearing 2-pyridyl ring at the 2-position on the indole ring. Subsequent C-ring formation from the alcohol provided pyridinium salts as a precursor of indoloquinolizines, see: X. Pan and T. D. Bannister, *Org. Lett.* 2014, **16**, 6124.

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

6 (a) S. Lee, K.-H. Kim and C.-H. Cheon, *Org. Lett.*, 2017, **19**, 2785; (b) S. E. Lee, S. J. Lee and C.-H. Cheon, *Synthesis*, 2017,



View Article Online
DOI: 10.1039/C7OB02691A


**49**, 4247; (c) S. H. Kwon, H.-A. Seo and C.-H. Cheon, *Org. Lett.*, 2016, **18**, 5280.

7 Prior to our reports, a similar protocol for the synthesis of 2-arylindole-3-acetic acid derivatives from 2-aminocinnamic acid derivatives **1** and aldehydes was reported. However, the previous report, the umpolung of the aldmines was generated by the deprotonation of Strecker products, obtained from compounds **1** and aldehydes with a stoichiometric amount of a strong base. See: T. Opatz and D. Ferenc, *Org. Lett.*, 2006, **8**, 4473.

8 In our previous studies, imino-Stetter reactions of aldimines bearing an acidic proton, such as ones derived from secondary amides of 2-aminocinnamic acid generally required a stoichiometric amount of cyanide, rather than a catalytic amount of cyanide. For details, see refs 5 and 6c.

9 For the previous examples to prepare the C-ring through the N-C6 disconnection, see: (a) A. Fürstner, A. Ernst, H. Krause and A. Ptock, *Tetrahedron*, 1996, **52**, 7329; (b) G. W. Gribble, T. C. Barden and D. A. Johnson, *Tetrahedron*, 1988, **44**, 3195; (c) G. W. Gribble and D. A. Johnson, *Tetrahedron Lett.*, 1987, **28**, 5259; (d) ref 4.

10 For selective examples of the total synthesis of 10-desbromoarborescidine A (**11**), see: (a) B.-Y. Lim, B.-E. Jung and C.-G. Cho, *Org. Lett.*, 2014, **16**, 4492; (b) I. Dion, J.-F. Vincent-Rocan, L. Zhang, P. H. Cebrowski, M.-E. Lebrun, J. Y. Pfeiffer, A.-C. Bédard and A. M. Beauchemin, *J. Org. Chem.*, 2013, **78**, 12735; (c) P. Mondal and N. P. Argade, *J. Org. Chem.*, 2013, **78**, 6802; (d) S. Mangalaraj and C. R. Ramanathan, *RSC Adv.*, 2012, **2**, 12665; (e) F. D. King, *J. Heterocyclic Chem.*, 2007, **44**, 1459; (f) Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer and A. Davis, *Org. Lett.*, 2005, **7**, 1047; (g) S. M. Allin, C. I. Thomas, J. E. Allard, K. Doyle and M. R. J. Elsegood, *Eur. J. Org. Chem.*, 2005, 4179; (h) S. M. Allin, C. I. Thomas, J. E. Allard, K. Doyle and M. R. J. Elsegood, *Tetrahedron Lett.*, 2004, **45**, 7103.

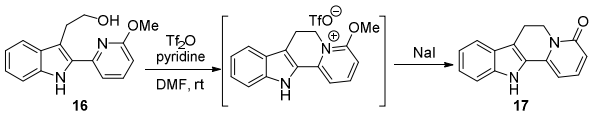
11 For reduction of pyridinium ring in indoloquinilizium salts with $NaBH_4$, see: (a) R. K. Manna, P. Jaisankar and V. S. Giri, *J. Chem. Res. (S)*, 1999, 350; (b) H. Takayama, M. Maeda, S. Ohbayashi, M. Kitajima, S.-I. Sakai and N. Aimi, *Tetrahedron Lett.*, 1995, **36**, 9337; (c) A. R. Stoit and U. K. Pandit, *Heterocycles*, 1987, **25**, 7; (d) R. Oehl, G. Lanzer and P. Rosenmund, *Chem. Ber.*, 1976, **109**, 705.

12 For the isolation of arborescidine A (**6**), see: (a) M. Chbani, M. Pais, *J. Nat. Prod.*, 1993, **56**, 99. For the previous total synthesis, see: (b) L. S. Santos, R. A. Pilli and V. H. Rawal, *J. Org. Chem.*, 2004, **69**, 1283; (c) B. E. A. Burm, M. M. Meijler, J. Korver, M. J. Wanner and G.-J. Koomen, *Tetrahedron*, 1998, **54**, 6135.

13 Other attempts to convert double bond into a single bond was unsuccessful. Hydroboration or hydrosilylation followed by protodeboronation or protodesilylation provided no desired product.

14 For the isolation of nauclefidine (**7**), see: (a) L. Mao, L. Xin, Y. Dequan, *Planta Medica*, 1984, **50**, 459. For the previous total synthesis, see: (b) R. K. Manna, P. Jaisankar and V. S. Giri, *Synth. Commun.*, 1998, **28**, 9; (c) H. Takayama, R. Yamamoto, M. Kurihara, M. Kitajima, N. L. Mao and S.-I. Sakai, *Tetrahedron Lett.*, 1994, **35**, 8813; (d) for synthetic studies for this natural product: G. A. Kraus and J. H. Malpert, *Synlett*, 1997, 107.

15 Alternatively, compound **17** could be prepared by the reaction with $Tf_2O$ followed by the treatment of NaI. Reaction of **16** with $Tf_2O$ furnished indoloquinolizinium triflate, which was treated with NaI leading to **17** via the cleavage of O-Me bond with NaI.




16 For the previous synthesis of compound **18** rather than the C-3 isomer. See ref. 14b.

17 (a) U. Dutta, A. Deb, D. W. Lupton and D. Maiti, *Chem. Commun.*, 2015, **51**, 17744. (b) V. Cañibano, J. F. Rodríguez, M. Santos, M. A. Sanz-Tejedor, M. C. Carreño, G. González and J. L. García-Ruano, *Synthesis*, 2001, **14**, 2175.

18 For a review on the cyanation of arylhalides, see: P. Anbarasan, T. Schareina and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 5049.

19 M. Lounasmaa and R. Jokela, *Tetrahedron*, 1989, **45**, 3975.