JOC The Journal of Organic Chemistry

NOTTINGHAM TRENT UNIVERSITY

Subscriber access provided by Nottingham Trent University

Article

Substitution of the Dimethylamino Group in Gramines and One-Pot Cyclization to Tetrahydro-#-carbolines Using a Triazine-Based Activating Agent

Hikaru Fujita, Riho Nishikawa, Ozora Sasamoto, Masanori Kitamura, and Munetaka Kunishima

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00039 • Publication Date (Web): 14 Jun 2019

Downloaded from http://pubs.acs.org on June 14, 2019

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

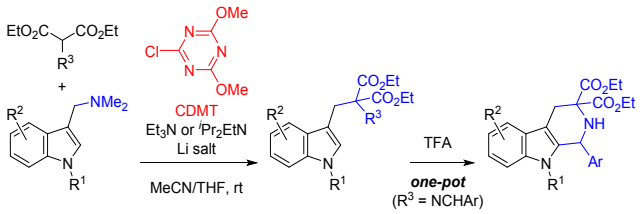
Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Substitution of the Dimethylamino Group in Gramines and One-Pot Cyclization to Tetrahydro-β-carbolines Using a Triazine-Based Activating Agent

Hikaru Fujita, Riho Nishikawa, Ozora Sasamoto, Masanori Kitamura, and Munetaka Kunishima*

Faculty of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

Table of Contents



Abstract

A new method for the substitution of 3-[(dimethylamino)methyl]indoles (gramines) with malonate-based nucleophiles was developed using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) as the activating agent for the dimethylamino group. The reaction was completed in 1.5–6 h at room temperature in the presence of a *tert*-amine base and lithium salt. CDMT afforded superior results to methyl iodide, a common activating agent for the dimethylamino group in Mannich bases, particularly in the reactions of 1-substituted gramines. The reactivity of the possible intermediates, bis(indol-3-ylmethyl)dimethylammonium salts, was examined to obtain mechanistic insights of the reaction. This substitution method with CDMT enabled the sequential transformation of gramines: substitution with (*N*-alkylidene)aminomalonates followed by the Pictet-Spengler reaction under acidic conditions afforded 1,2,3,4-tetrahydro-β-carboline derivatives in one-pot.

Introduction

The Mannich reaction introduces a C1 unit to various nucleophilic species through electrophilic aminomethylation. The (dimethylamino)methylation reaction with formaldehyde–dimethylamine[1] or Eschenmoser's salt[2] is a representative of the Mannich reaction. The resulting aminomethylated products are referred to as Mannich bases, which have established utility in organic syntheses owing to their ready accessibility and unique reactivity.[3] We have recently reported the efficient elimination of the dimethylamino group in Mannich bases derived from esters using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) as the activating agent (Figure 1a).[4] CDMT was clearly superior to methyl iodide, a classical reagent used to activate the dimethylamino group. Elimination via an *N*-triazinylammonium intermediate was completed within a short reaction time (15 min) at room temperature owing to the high leaving group ability of triazinylamine **1**. In addition, CDMT reacted with the dimethylamino group chemoselectively, even in the presence of tertiary amines such as Et_3N. This was due to a previously reported type of steric hindrance known as the *gauche* β-alkyl group effect.[5–7] Thus, due to the mild reaction conditions and high

chemoselectivity of CDMT, this methodology was applied to intermolecular substitution reactions of Mannich bases in the presence of a nucleophile. This paper describes the substitution reactions of gramine derivatives (**2**) with CDMT (Figure 1b). Gramines, the Mannich bases from indoles, are a versatile synthetic intermediate for indole derivatives.[8] Furthermore, this paper reports the one-pot substitution/cyclization of gramines for the preparation of tetrahydro-β-carbolines, an important class of indole alkaloids.[9]

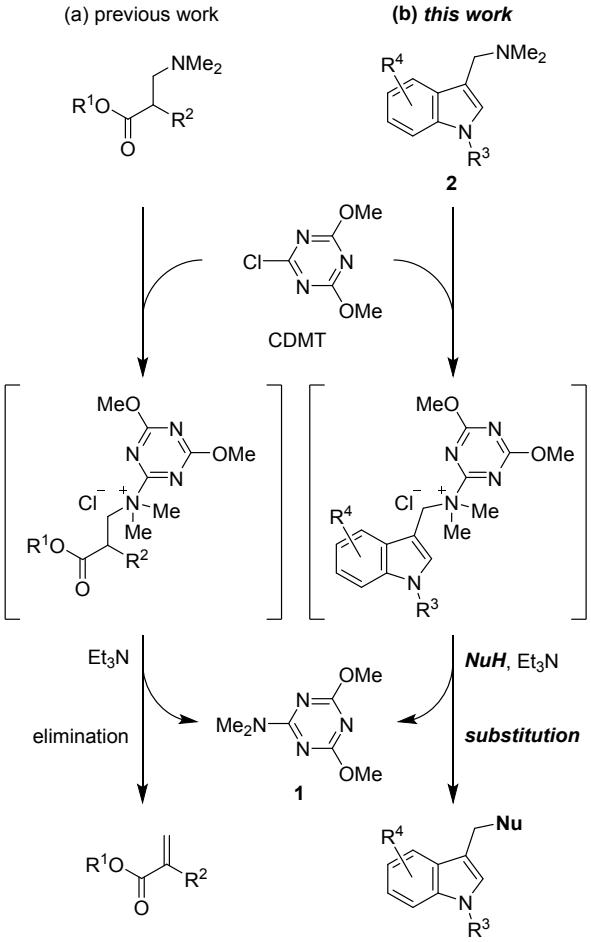


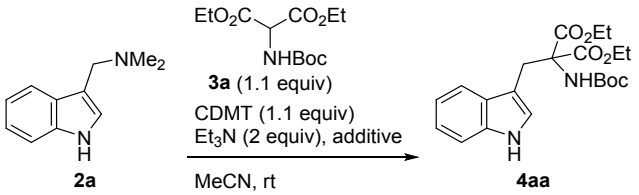
Figure 1. Activation of the dimethylamino group in Mannich bases using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT): (a) elimination to form α,β-unsaturated esters (previous work) and (b) substitution of gramines (this work).

Results and Discussion

N-protected aminomalonates are widely-used as nucleophiles toward gramines in the synthesis of tryptophan derivatives.[10–15] Thus, the reaction between unsubstituted gramine **2a** (Table 1) and *N*-Boc-aminomalonate **3a** was first studied. A traditional method for this substitution involves heating without activation of the dimethylamino group, typically by refluxing in toluene with NaOH[12,14,16–19] or in acetonitrile with tributylphosphine.[17,20–22] Since the leaving group ability of dimethylamine is poor, harsh thermal conditions are inevitable. Another traditional method relies on the alkylation of the dimethylamino group with alkylating agents such as methyl iodide,[10,13,16,23,24] ethyl iodide,[11,25] and dimethyl sulfate.[11,25–30] However, this method typically requires heating (>78 °C),[10,11,13,16,24,25] a long reaction time (overnight or >20 h),[10,16,23–25,27] and a two-step procedure[10,13,16,23,24]

or prior triisopropylsilyl-protection of the indole nitrogen atom.[31–33] In 2007, Williams and coworkers reported the use of ethyl propiolate as an activating agent for the dimethylamino group.[34] Although the substitution of gramines with this reagent took place at room temperature, moderate yields (42−65%, seven examples) were observed for the substitution with **3a**. Therefore, the development of a mild high-yielding gramine substitution method is still desirable.

Table 1. Screening of solvents and salt additives for the synthesis of **4aa** from **2a** and **3a** using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT).



entry	solvent	additive (equiv)	time (h)	yield (%)[a]
1	CH_2Cl_2	-	24	28
2	THF	-	24	8
3	EtOH	-	24	49
4	MeCN	-	24	52
5	MeCN	$LiClO_4$ (1.1)	4	100
6	MeCN	LiCl (1.1)	4	95
7	MeCN	LiBr (1.1)	4	100
8	MeCN	LiI (1.1)	4	93
9	MeCN	LiCl (0.1)	4	92 (91)[b]
10	MeCN	$LiClO_4$ (0.1)	4	80
11	MeCN	$NaClO_4$ (1.1)	24	41
12	MeCN	NaCl (1.1)	24	72
13	MeCN	$MgSO_4$ (0.1)	4	45
14	CH_2Cl_2	LiCl (0.1)	4	48
15	THF	LiCl (0.1)	4	65
16	Et_2O	LiCl (0.1)	4	trace
17	toluene	LiCl (0.1)	4	trace
18[c]	MeCN	$LiClO_4$ (1.1)	4	7
19[d]	MeCN	$LiClO_4$ (1.1)	24	10
20[e]	MeCN	$LiClO_4$ (1.1)	24	69

[a]The yield was calculated from ^{1}H NMR spectroscopic analysis using *p*-nitrotoluene as the internal standard. [b]Isolated yield. [c]The reaction was carried out without CDMT. [d]The reaction was carried out using Et_3N·HCl (1.1 equiv) instead of CDMT. [e]The reaction was carried out using methyl iodide (1.1 equiv) instead of CDMT.

When a mixture of **2a** (1 equiv) and **3a** (1.1 equiv) was treated with CDMT (1.1 equiv) in the presence of

Et_3N (2 equiv) in CH_2Cl_2, desired product **4aa** formed at room temperature after 24 h; however, only in 28% yield (Table 1, entry 1). After brief screening of the reaction solvent (entries 2–4), the yield of **4aa** improved to 52% (entry 4, in MeCN). Next, lithium cations ($LiClO_4$; 1.1 equiv) were added to the reaction mixture to promote the nucleophilic attack of the malonates.[35,36] This afforded a quantitative yield with a shorter reaction time (4 h, entry 5). The addition of lithium halides also provided high yields (LiCl, 95%, entry 6; LiBr, 100%, entry 7; and LiI, 93%, entry 8). Furthermore, a 91% yield was obtained with 0.1 equiv of LiCl (entry 9), while $LiClO_4$ (0.1 equiv) afforded the product in 80% yield (entry 10). Conversely, sodium and magnesium salts ($NaClO_4$, NaCl, and $MgSO_4$) did not afford **4aa** in high yield (41–72%, entries 11–13, respectively).[37] Trace to moderate yields were obtained with LiCl (0.1 equiv) in CH_2Cl_2, THF, Et_2O, and toluene (entries 14–17, respectively). When the substitution reaction was carried out in MeCN with $LiClO_4$ (1.1 equiv) in the absence of CDMT, **4aa** only formed in 7% yield after 4 h (entry 18). The addition of $Et_3N{\cdot}HCl$ (1.1 equiv) produced almost no effect (10% yield, entry 19). These observations indicated that CDMT plays an important role in the gramine substitution reaction. When methyl iodide (1.1 equiv) was used instead of CDMT, the yield remained at 69%, even after 24 h (entry 20), suggesting that CDMT is a better activator than methyl iodide.

The results in Table 1 reveal that LiCl acted as an effective catalyst under the conditions listed in entry 9. Thus, the reaction conditions listed in entry 9 were used in the subsequent investigations. Figure 2 illustrates the substitution reactions between various gramines and malonates. Here, MeCN/THF (8:1) was used as the solvent; for convenience, a stock solution of LiCl in THF was prepared in advance and used for a series of the experiments. Gramines comprising a chloro (4-Cl, **2b**; 5-Cl, **2c**) or alkoxy (5-BnO, **2d**; 4-MeO, **2e**; and 5-MeO, **2f**) group reacted with **3a** to afford **4ba**–**4fa**, respectively, in 90–97% yield. The reaction times for chlorogramines **2b,c** (5 h) were longer than those for alkoxygramines **2d–f** (1.5–3 h). Additionally, the substitution of 2-methylgramine (**2g**) and 2-phenylgramine (**2h**) with **3a** provided **4ga** and **4ha** in 99% and 98% yield, respectively. Compared to the reported synthesis of **4ba**–**4ha** from **2b–h**, respectively, and **3a** with ethyl propiolate,[34] this proposed method improved the yields by 27–55%. The reaction with 3-[1-(dimethylamino)ethyl]indole (**2i**) afforded the product **4ia** in 43% yield. The moderate yield of **4ia** could be due to the sensitivity of CDMT to the steric hindrance around the dimethylamino group.[5] The substitution of **2a** with *N*-Cbz-protected aminomalonate **3b**, diethyl malonate (**3c**), and diethyl methylmalonate (**3d**) was also carried out. In this case, the desired products, **4ab–ad**, respectively, were obtained in 88–95% yield. For the synthesis of **4ac**, 2.5 equivalents of **3c** was used to suppress the disubstitution side reaction.

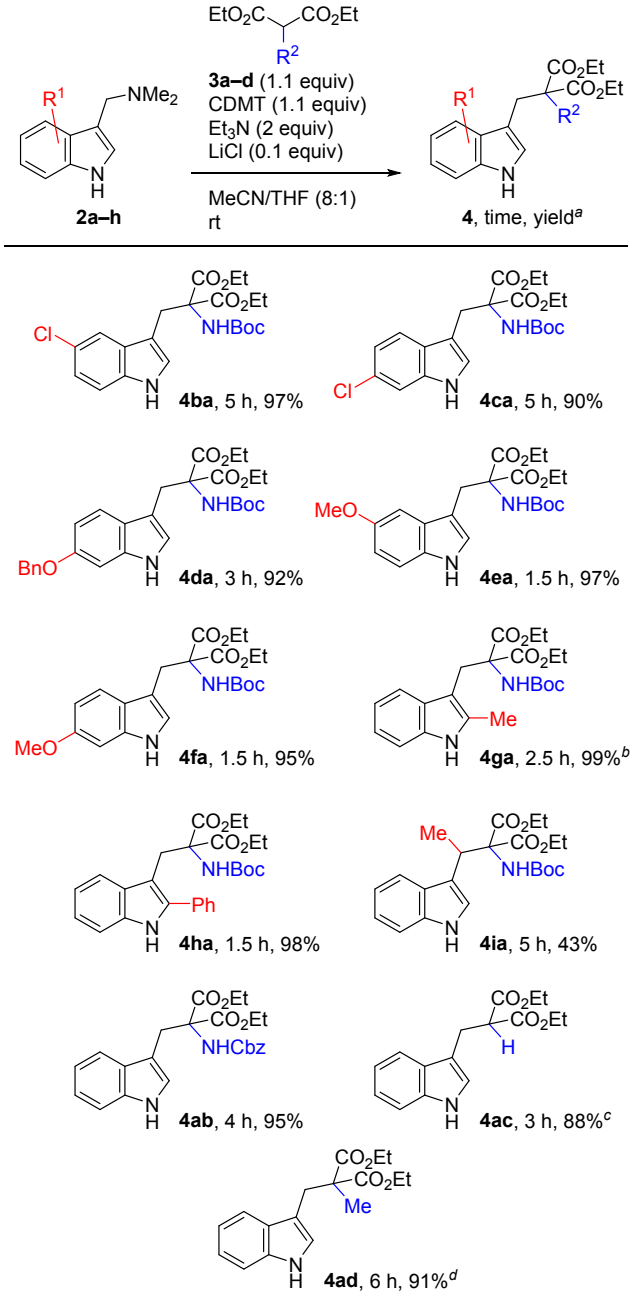
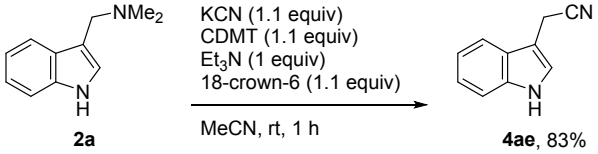


Figure 2. Substitution of the dimethylamino group with various gramines and diethyl malonates. [a]Isolated yield. [b]The reaction was carried out in MeCN with LiCl (1.1 equiv). [c]Malonate **3c** (2.5 equiv) was used. [d]The reaction was carried out in MeCN with Et_3N (3 equiv) and LiCl (1.1 equiv).

Scheme 1 illustrates the CMDT-promoted substitution of **2a** with potassium cyanide as a nucleophile. 3-(Cyanomethyl)indole (**4ae**) was obtained in 83% yield using 18-crown-6 as a solubilizing agent for the nucleophile.

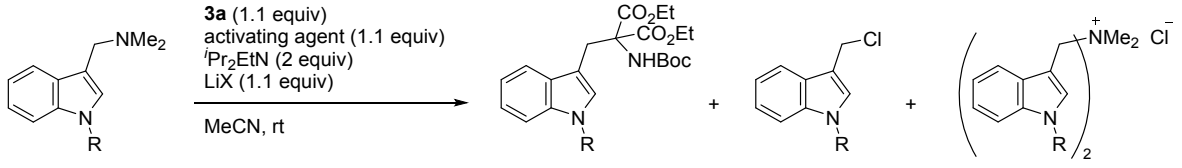


Scheme 1. Substitution reaction between gramine **2a** and potassium cyanide promoted by CDMT.

Gramines bearing a Boc or methyl group at the indole nitrogen were next examined. These substitution reactions are more challenging than those of 1-unsubstituted gramines. Studies have reported that the dimethylamino group of 1-Boc-gramines was converted into a chloro group in the first step and the resulting unstable 1-Boc-(3-chloromethyl)indole intermediate was immediately used for the next substitution step.[38,39] The substitution of 1-alkylgramines also required a multi-step procedure that included pre-activation of the dimethylamino group with methyl iodide, isolation of the resulting ammonium salt, and heating of the salt at high temperature in the presence of a malonate anion.[40–46] Thus, it is worth developing a one-step conversion of such 1-substituted gramines under mild conditions.

When CDMT was added in one portion to a mixture of 1-Boc-gramine **2j** and **3a** in MeCN in the presence of LiCl and *i*-Pr_2EtN, the substitution reaction proceeded at room temperature to afford desired product **4ja** in 39% yield (Table 2, entry 1). Careful analysis of the crude mixture suggested that 1-Boc-(3-chloromethyl)indole (**5j**) was still present (33% yield); however, it could not be isolated because of its instability.[47] As iodide salts can catalyze nucleophilic substitution reactions, LiI was employed in the reaction instead of LiCl (entry 2); however, the yield of **4ja** was unchanged. In this case, **5j** was not detected but dimeric ammonium salt **6j** (22% yield) was found in the crude mixture. This byproduct is probably formed from two molecules of **2j**. Therefore, **2j** was added dropwise over 1 h (entry 3) to maintain a low concentration of **2j** during the reaction. As a result, a 78% yield of **4ja** was achieved by suppressing the side reaction that forms **6j** (7% yield). Similar trends were observed for the substitution of 1-methylgramine (**2k**). The yield of **4ka** was 28% when CDMT was added in one portion (entry 4). On the other hand, the product was obtained in 84% yield following the dropwise addition of **2k** (entry 5). The substitution of **2j** and **2k** with methyl iodide as the activating agent was also attempted. However, the respective desired products **4ja** and **4ka** did not form after 24 h (entries 6 and 7, respectively). These results again indicated the superiority of CDMT to methyl iodide for the gramine substitution reaction.

Table 2. Substitution of gramines bearing a Boc or methyl group at the indole nitrogen.



entry	gramine **2** (addition method)	activating agent (addition method)	X	time (h)	**4** (%)[a]	**5** (%)[a]	**6** (%)[a]
1	**2j**, R = Boc	CDMT (one portion)	Cl	20	**4ja**, 39	**5j**, 33	**6j**, nd[b]
2	**2j**, R = Boc	CDMT (one portion)	I	20	**4ja**, 39	**5j**, nd[b]	**6j**, 22[c]
3	**2j**, R = Boc (dropwise over 1 h)	CDMT	I	6	**4ja**, 78[d]	**5j**, nd[b]	**6j**, 7[c]
4	**2k**, R = Me	CDMT (one portion)	I	25	**4ka**, 28	-[e]	-[e]
5	**2k**, R = Me (dropwise over 1 h)	CDMT	I	5	**4ka**, 84[d]	-[e]	-[e]

6	**2k**, R = Boc (dropwise over 1 h)	MeI	I	24	**4ka**, nd[b]	-[e]	-[e]
7	**2k**, R = Me (dropwise over 1 h)	MeI	I	24	**4ka**, nd[b]	-[e]	-[e]

[a]The yields were calculated from ^{1}H NMR spectroscopic analysis unless otherwise noted. [b]Not detected. [c]The counter anion was assumed to be a chloride ion because the reaction mixture was washed with brine after quenching. [d]Isolated yield. [e]Not determined.

The formation of **6j** (entries 2 and 3, Table 2) implied the intermediacy of the analogous dimeric ammonium salts in the reaction of 1-unsubstituted gramines such as **2a**. In fact, bis(indol-3-ylmethyl)dimethylammonium chloride (**7**) was isolated in 97% yield upon treating **2a** with CDMT (0.5 equiv) for 1 h in the absence of the nucleophile (Figure 3a). The formation of the same ammonium salt paired with iodide is known as a side reaction of the gramine methiodide preparation.[48–51] Salt **7** is active for the substitution as it reacted with **3a** smoothly to afford **4aa** in 83% yield. Thus, a plausible reaction mechanism of the substitution between **2a** and **3a** (Figure 3b) was proposed taking these facts into account: in the first step, CDMT activates the dimethylamino group in **2a** to generate triazinylammonium salt **8a**. Due to the high leaving group ability of **1**, the indole NH proton in **8a** will be easily deprotonated by Et_3N to afford 3-methyleneindolenine **9**, which is a key intermediate of the gramine substitution reactions.[8,52,53] Ammonium salt **7** is formed if **9** is captured by **2a**. Although this reaction is under equilibrium, the regeneration of **9** from **7** will be slower than its formation from **8a**. LiCl probably facilitates the deprotonation of **3a** to produce lithium complex **10**, which reacts with **9** to afford **4aa**. Triazinylammonium salt **8a** may be directly converted to **2a** and **4aa**.

Similar to **2a**, **2j** provided the corresponding dimeric ammonium chloride **6j** in 91% yield in the absence of the nucleophile (Figure 3c). However, **6j** was completely inert toward substitution by **3a**. Therefore, the reaction mechanism of the substitution of **2j** is described by the pathway presented in Figure 3d. Triazinylammonium salt **8j**, which is generated from **2j** and CDMT, releases **1** to form **5j**. On the basis of previous studies, decomposition of the triazinylammonium chloride is expected to be fast because the chloride would rapidly attack the activated benzylic position of the triazinylammonium salts in the aprotic solvents.[54,55] The electrophilicity of **5j** is not sufficient to react with **10** or **2j** under the set reaction conditions. This is supported by the presence of unreacted **5j** (entry 1, Table 3). On the other hand, once the chloro group in **5j** is replaced by an iodide group, the resulting intermediate **5j-I** can be attacked by **10** and **2j** to form **4ja** and **6j-I**, respectively. As the formation of **6j-I** is irreversible, the undesired reaction between **5j-I** and **2j** should be suppressed by the dropwise addition of **2j**. The possibility of the direct conversion of **8j** into **5j-I** and **4ja** cannot be excluded. The substitution of **2k** may occur in an analogous manner because similar results were observed for **2j** and **2k** (Table 3).

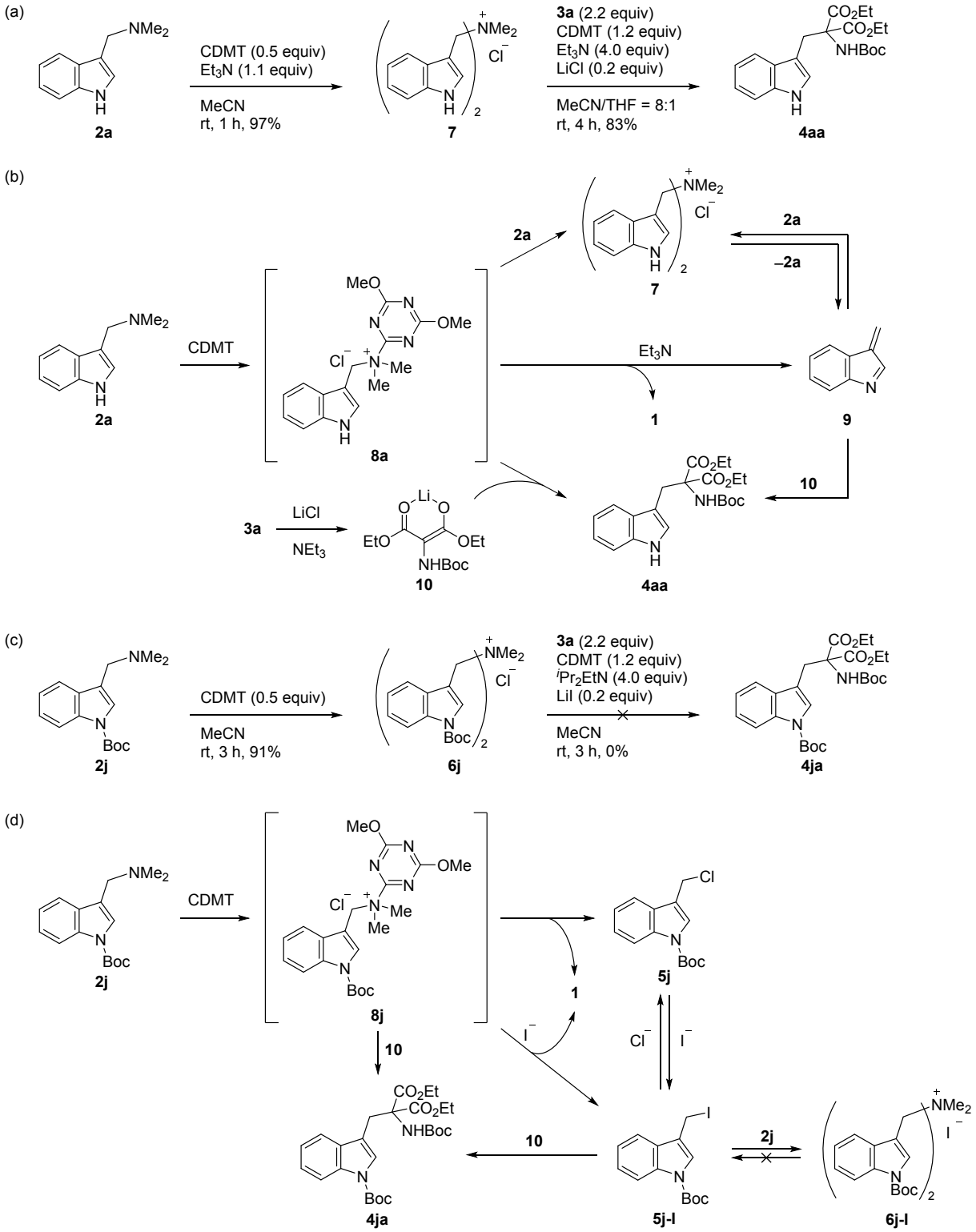
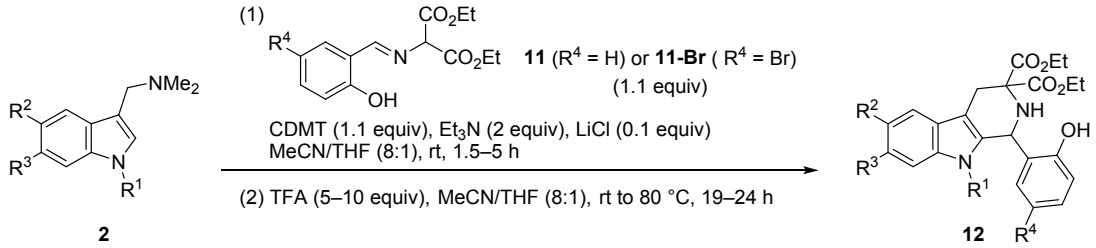


Figure 3. Mechanistic considerations: (a) isolation of **7** and its conversion into **4aa**. (b) Plausible reaction mechanism of the substitution of **2a** to **4aa** with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT). (c) Isolation of **6j** and an attempt at its conversion into **4ja**. (d) Plausible reaction mechanism of the substitution of **2j** to **4ja** with CDMT.

With the proposed substitution method for gramines in hand, 1-(2-hydroxyphenyl)-1,2,3,4-tetrahydro-β-

carboline derivatives[56–58] was next synthesized from gramines in one-pot (Table 3). To the best of our knowledge, the one-pot synthesis of tetrahydro-β-carbolines from gramines has not been reported, likely due to limitations of the traditional gramine substitution methods. *N*-[(2-Hydroxybenzylidene)amino]malonate **11**, which is readily available and easy-to-handle, was used as the nucleophile for the reaction. After treating **2a** with **11** under the standard conditions for gramine substitution with CDMT, trifluoroacetic acid (TFA, 5 equiv) was added at room temperature to induce the Pictet-Spengler reaction. This afforded tetrahydro-β-carboline **12a** in 93% yield (entry 1). Similarly, gramines with a chloro or alkoxy group at the 5 or 6 position (5-Cl, **2b**; 6-BnO, **2d**; and 5-MeO, **2e**) were converted into the corresponding tetrahydro-β-carbolines (76%, entry 2; 78%, entry 3; and 100%, entry 4, respectively). Cyclization to **12b** was carried out at 50 °C with TFA (10 equiv). Additionally, 1-methyl derivative **12k** was successfully prepared from **2k** in 48% yield, although a higher temperature (80 °C) was required for the cyclization step. The reaction between **2a** and **11-Br** bearing a 5-bromo-2-hydroxypheny group afforded the corresponding tetrahydro-β-carboline **12a-Br** in 83% yield.

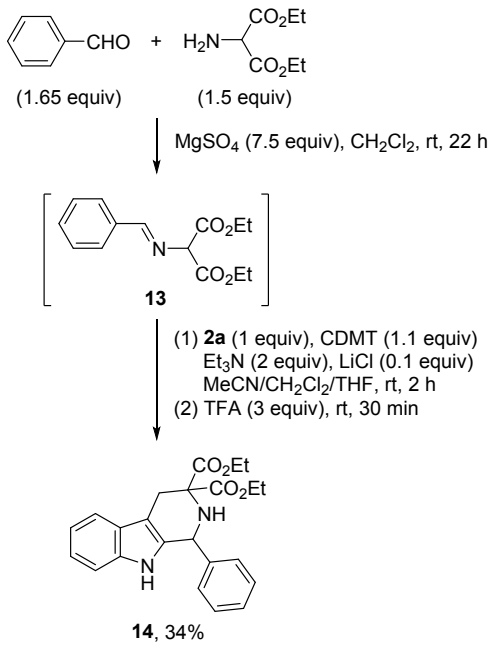
Table 3. One-pot synthesis of tetrahydro-β-carbolines **12** from gramines.



entry	**2**	R^1	R^2	R^3	R^4	the 1st step time (h)	the 2nd step time, temp.	TFA (equiv)	**12**	yield (%)[a]
1	**2a**	H	H	H	H	4	19 h, rt	5	**12a**	93
2	**2b**	H	Cl	H	H	5	19 h, 50 °C	10	**12b**	76
3	**2d**	H	H	BnO	H	3	19 h, rt	5	**12d**	78
4	**2e**	H	MeO	H	H	1.5	19 h, rt	5	**12e**	100
5[b]	**2k**	Me	H	H	H	4	24 h, 80 °C	10	**12k**	48
6	**2a**	H	H	H	Br	4	12 h, rt	5	**12a-Br**	83

[a]Isolated yield. [b]The first step was initiated by the dropwise addition of **2k** in MeCN to a reaction mixture containing $^{i}Pr_2EtN$ instead of Et_3N. The reaction solvent was MeCN.

Scheme 2 describes the one-pot synthesis of 1-phenyl-tetrahydro-β-carboline **14** from gramine **2a** and *N*-[(benzylidene)amino]malonate **13**. Unlike **11**, **13** lacking the 2-hydroxy group is typically used as a crude material due to its instability.[59–61] Therefore, **13** was prepared *in situ* via condensation of diethyl aminomalonate with benzaldehyde and used directly for the reaction. The desired product **14** was obtained in 34% yield based on **2a**. These results indicated that the 2-hydroxy group in the malonate was not necessary but desirable for this one pot synthesis.



Scheme 2. One-pot synthesis of tetrahydro-β-carboline **14** bearing a phenyl group.

Conclusion

A new method for the substitution of the dimethylamino group in gramines was developed using a unique activating agent, CDMT. Gramines bearing a substituent at the 2, 5, or 6 position were derivatized with malonate nucleophiles in the presence of Et_3N and a catalytic amount of LiCl. Compared to the traditional procedures, this proposed method is advantageous in terms of yields as well as reaction temperatures and times. In particular, a clear difference was observed in the reaction of 1-substituted gramines **2j** and **2k** with *N*-Boc-aminomalonate **3a**: the addition of CDMT afforded the coupling product in good yield whereas methyl iodide, a classical activating agent for the dimethylamino group, afforded no desired product under the same reaction conditions. Dimeric ammonium salts **7** and **6j** were isolated and evaluated to obtain mechanistic insights of the reaction. The formation of such salts is likely to compete with the desired reaction pathway, reversibly (1-unsubstituted gramines) or irreversibly (1-substituted gramines) under the employed reaction conditions. Additionally, this study demonstrated the one-pot synthesis of tetrahydro-β-carboline derivatives from gramines as an application of the gramine substitution reaction developed in this study. Thus, overall, the scope of the utility of CDMT employed for the dimethylamino group activation was extended. The sequential transformations via Mannich bases, namely, the (dimethylamino)methylation of indoles followed by the substitution of the dimethylamino group with CDMT show great potential as a useful tool for indole alkaloid syntheses.

Experimental Section

General Information. NMR spectra were recorded on a JEOL JNM-ECS400 spectrometer [^{1}H-NMR (400 MHz) and ^{13}C{^{1}H}-NMR (100 MHz)] or a JEOL JNM-ECA600 spectrometer [^{1}H-NMR (600 MHz)]. Chemical shifts for ^{1}H-NMR are reported in parts per million (δ) relative to tetramethylsilane as the internal standard. Coupling constant (J) are reported in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t =

triplet, m = multiplet. Chemical shifts for $^{13}C\{^1H\}$-NMR are reported in parts per million (δ) relative to the solvent [$CDCl_3$, δ 77.16; or $(CD_3)_2SO$, δ 39.52]. IR spectra were recorded on a Horiba FT-720 FREEXACT-II spectrophotometer and were reported in wavenumbers (cm^{-1}). Mass spectra were measured on a JMS-T100TD AccuTOF TLC (DART-MS and ESI-MS) spectrometer. Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed using glass plates precoated with 0.25 mm silica gel impregnated with a fluorescent indicator (254 nm). Preparative TLC separations were performed using glass plates precoated with 0.25 mm silica gel impregnated with a fluorescent indicator (254 nm) or Chromatorex NH TLC plates (Fuji Silysia Chemical). Flash chromatography was performed using silica gel (spherical, neutral, 40–100 mesh) or amine-functionalized silica gel (Chromatorex NH-DM2035, Fuji Silysia Chemical). Recycling preparative HPLC was performed with Japan Analytical Industry LC-928 equipped with GPC columns Jaigel-1H and 2H. All reactions sensitive to oxygen or moisture were conducted under a nitrogen atmosphere. Heating for reactions was carried out with an oil bath. Reagents were commercial grades and were used without any purification unless otherwise noted. Known compounds (**3a**,[62] **3b**,[63] **11**,[64] and **11-Br**[65]**)** were prepared according to the reported procedure.

*Diethyl 2-[(1H-indol-3-yl)methyl]-2-[(tert-butoxycarbonyl)amino]malonate (**4aa**)*.[34] CDMT (120.9 mg, 0.69 mmol, 1.1 equiv) was added to a suspension of **2a** (109.1 mg, 0.63 mmol, 1.0 equiv), **3a** (189.6 mg, 0.69 mmol, 1.1 equiv), Et_3N (174 μL, 1.25 mmol, 2.0 equiv), and LiCl (2.7 mg, 0.063 mmol, 0.1 equiv) in MeCN (2.1 mL, 0.3 M) at room temperature. After 4 h, the reaction mixture was passed through silica gel (EtOAc as an eluent). The filtrate was concentrated under reduced pressure. Column chromatography (silica gel, hexane/EtOAc = 9:1 to hexane/acetone = 9:1) afforded a white solid (229.2 mg, 91%).

General Procedure for gramine derivatives 2b–h,k (GP-1). Dimethylamine hydrochloride (1.1 equiv), Et_3N (1.1 equiv), formaldehyde aqueous solution (37%, 1.1 equiv), and acetic acid (1.5 equiv) were added to a suspension of an indole derivative (1.0 equiv) in 1,4-dioxane/H_2O (1:1, 0.3 M) at room temperature. The reaction mixture was stirred until TLC monitoring indicated complete conversion. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and then extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (amine-functionalized silica gel) to afford the desired gramine derivative.

*5-Chlorogramine (**2b**)*.[66] GP-1 was followed using 5-chloroindole (227.4 mg, 1.50 mmol, 1.0 equiv), dimethylamine hydrochloride (269.0 mg, 3.30 mmol, 2.2 equiv), Et_3N (459 μL, 3.30 mmol, 2.2 equiv), formaldehyde aqueous solution (253 μL, 3.30 mmol, 2.2 equiv), and acetic acid (257 μL, 4.50 mmol, 3.0 equiv) in 1,4-dioxane/H_2O (1:1, 5.0 mL). The reaction mixture was stirred for 23 h. Column chromatography (silica gel, hexane/acetone = 4:1) afforded a white solid (189.7 mg, 61%). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 134.7, 129.1, 125.4, 125.0, 122.4, 119.0, 113.4, 112.2, 54.6, 45.5.

*6-Chlorogramine (**2c**)*.[67,68] GP-1 was followed using 6-chloroindole (227.4 mg, 1.50 mmol), dimethylamine hydrochloride (134.5 mg, 1.65 mmol), Et_3N (229 μL, 1.65 mmol), formaldehyde aqueous solution (126 μL, 1.65 mmol), and acetic acid (129 μL, 2.25 mmol) in 1,4-dioxane and H_2O (1:1, 5.0 mL). The reaction mixture was stirred at 40 ℃ for 19.5 h. Column chromatography (silica gel, hexane/EtOAc = 1:1) afforded a white solid (153.8 mg, 49%). ^1H-NMR (600 MHz, $CDCl_3$): δ 8.04 (br s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 1.8 Hz, 1H), 7.12 (d, J =

2.4 Hz, 1H), 7.09 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.59 (s, 2H), 2.26 (s, 6H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ 136.7, 128.1, 126.6, 124.2, 120.42, 120.40, 113.8, 111.1, 54.6, 45.5; LRMS (ESI-TOF): *m/z* 209 ($[M + H]^+$).

*6-Benzyloxygramine (**2d**)*.[69] GP-1 was followed using 6-benzyloxyindole (334.9 mg, 1.50 mmol), dimethylamine hydrochloride (134.5 mg, 1.65 mmol), Et_3N (229 µL, 1.65 mmol), formaldehyde aqueous solution (126 µL, 1.65 mmol), and acetic acid (129 µL, 2.25 mmol) in 1,4-dioxane and H_2O (1:1, 5.0 mL). The reaction mixture was stirred at 40 ℃ for 20 h. Column chromatography (silica gel, EtOAc) and recrystallization from EtOH afforded a white solid (225.3 mg, 54%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.91 (br s, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.39 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 2.3 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 6.89 (dd, *J* = 8.5, 2.3 Hz, 1H), 5.11 (s, 2H), 3.58 (s, 2H), 2.27 (s, 6H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ 155.6, 137.6, 136.9, 128.7, 127.9, 127.6, 122.74, 122.65, 120.0, 113.2, 110.3, 96.1, 70.7, 54.7, 45.5; LRMS (ESI-TOF): *m/z* 281 ($[M + H]^+$).

*5-Methoxygramine (**2e**)*.[70] GP-1 was followed using 5-methoxyindole (220.8 mg, 1.50 mmol), dimethylamine hydrochloride (134.5 mg, 1.65 mmol), Et_3N (229 µL, 1.65 mmol), formaldehyde aqueous solution (126 µL, 1.65 mmol), and acetic acid (129 µL, 2.25 mmol) in 1,4-dioxane and H_2O (1:1, 5.0 mL). The reaction mixture was stirred for 2.5 h. Column chromatography (silica gel, hexane/acetone = 4:1) afforded a white solid (228.6 mg, 75%).

*6-Methoxygramine (**2f**)*.[14] GP-1 was followed using 6-methoxyindole (220.8 mg, 1.50 mmol), dimethylamine hydrochloride (134.5 mg, 1.65 mmol), Et_3N (229 µL, 1.65 mmol), formaldehyde aqueous solution (126 µL, 1.65 mmol), and acetic acid (129 µL, 2.25 mmol) in 1,4-dioxane and H_2O (1:1, 5.0 mL). The reaction mixture was stirred for 4 h. Column chromatography (silica gel, hexane/acetone = 4:1 to 7:3) and PTLC (amine-functionalized silica gel) afforded a white solid (231.7 mg, 76%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.92 (br s, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* =8.6, 2.1 Hz, 1H), 3.85 (s, 3H), 3.59 (s, 2H), 2.27 (s, 6H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ 156.5, 137.0, 122.5, 122.4, 120.0, 113.3, 109.6, 94.7, 55.8, 54.8, 45.5; LRMS (ESI-TOF): *m/z* 205 ($[M + H]^+$).

*2-Methylgramine (**2g**)*.[71,72] GP-1 was followed using 2-methylindole (3.9350 g, 30.0 mmol), dimethylamine hydrochloride (2.6932 g, 33.0 mmol), Et_3N (4.57 mL, 33.0 mmol), formaldehyde aqueous solution (2.53 mL, 33.0 mmol), and acetic acid (2.57 mL, 45.0 mmol) in 1,4-dioxane and H_2O (1:1, 100 mL). The reaction mixture was stirred at 40 ℃ for 3 h. Column chromatography (silica gel, hexane/EtOAc = 1:1 to EtOAc) and recrystallization from EtOAc afforded a white solid (5.6481 g, 38%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.84 (br s, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.27–7.26 (m, 1H), 7.12–7.07 (m, 2H), 3.54 (s, 2H), 2.43 (s, 3H), 2.26 (s, 6H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ 135.2, 133.7, 129.5, 120.9, 119.5, 118.5, 110.2, 108.7, 53.4, 45.5, 11.8; LRMS (ESI-TOF): *m/z* 189 ($[M + H]^+$).

*2-Phenylgramine (**2h**)*.[72] GP-1 was followed using 2-phenylindole (289.9 mg, 1.50 mmol), dimethylamine hydrochloride (134.5 mg, 1.65 mmol), Et_3N (229 µL, 1.65 mmol), formaldehyde aqueous solution (126 µL, 1.65 mmol), and acetic acid (129 µL, 2.25 mmol) in 1,4-dioxane and H_2O (1:1, 5.0 mL). The reaction mixture was stirred for 14.5 h. Column chromatography (silica gel, hexane/EtOAc = 4:1) afforded a white solid (326.7 mg, 87%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.17 (br s, 1H), 7.80–7.76 (m, 3H), 7.49 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.40–7.36 (m, 2H), 7.21 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1H), 7.15 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 3.62 (s, 2H), 2.30 (s, 6H); $^{13}C\{^{1}H\}$-NMR

(100 MHz, $CDCl_3$): δ 136.8, 135.7, 133.1, 130.2, 128.9, 128.4, 127.9, 122.4, 120.0, 119.8, 111.0, 110.8, 53.7, 45.6; LRMS (ESI-TOF): *m/z* 251 ($[M + H]^+$).

*3-[1-(Dimethylamino)ethyl]-1H-indole (**2i**).*[73] $POCl_3$ (2.0 mL, 22 mmol) followed by indole (2.0 g, 17 mmol) in *N*,*N*-dimethylacetamide (3.0 mL) was added to *N*,*N*-dimethylacetamide (7.5 mL) at 0 °C. The reaction mixture was heated to 90 °C for 1 h and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (20 mL). Sodium borohydride (2261 mg, 59.7 mmol) was added to the mixture at 0 °C. After 18.5 h, the reaction mixture was quenched by adding aqueous 1% K_2CO_3 and extracted with CH_2Cl_2/EtOAc. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure. Column chromatography (twice, amine-functionalized silica gel, hexane/EtOAc = 11:9 for the first chromatography, $CHCl_3$ for the second chromatography) afforded a pale yellow solid (266.8 mg, 8%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.27 (br s, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.20–7.05 (m, 2H), 6.94 (d, J = 2.3 Hz, 1H), 3.89 (q, J = 6.9 Hz, 1H), 2.28 (s, 6H), 1.51 (d, J= 6.9 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 136.1, 127.3, 122.3, 121.5, 119.5, 119.0, 117.0, 111.2, 56.8, 42.4, 18.9; HRMS (ESI-TOF): Calcd for $C_{12}H_{17}N_2$ $[M + H]^+$: 189.1392; Found: 189.1401.**General procedure for the substitution reactions of 1-unsubstituted gramines (GP-2).** LiCl (0.1 equiv) in THF (0.25 M), Et_3N (2.0 equiv), and CDMT (1.1 equiv) were added to a suspension of a gramine derivative (**2a**–**h**, 1.0 equiv) and a diethyl malonate derivative (**3a**–**d**, 1.1 equiv) in MeCN (0.3 M) at room temperature. The reaction mixture was stirred until TLC monitoring indicated complete conversion. The reaction mixture was diluted with EtOAc, washed with aqueous HCl (1 M) and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product.

*Diethyl 2-[(tert-butoxycarbonyl)amino]-2-[(5-chloro-1H-indol-3-yl)methyl]malonate (**4ba**).*[34] GP-2 was followed using **2b** (100.6 mg, 0.48 mmol), **3a** (146.1 mg, 0.53 mmol), LiCl in THF (194 μL, 0.048 mmol), Et_3N (134 μL, 0.97 mmol), and CDMT (93.2 mg, 0.53 mmol) in MeCN (1.6 mL). The reaction mixture was stirred for 5 h. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 9:1 to 7:3) and recycling preparative HPLC to afford a white solid (204.5 mg, 97%).

*Diethyl 2-[(tert-butoxycarbonyl)amino]-2-[(6-chloro-1H-indol-3-yl)methyl]malonate (**4ca**).*[34] GP-2 was followed using **2c** (86.0 mg, 0.41 mmol), **3a** (124.8 mg, 0.45 mmol), LiCl in THF (166 μL, 0.041 mmol), Et_3N (115 μL, 0.82 mmol), and CDMT (79.5 mg, 0.45 mmol) in MeCN (1.4 mL). The reaction mixture was stirred for 5 h. The residue was purified by column chromatography (silica gel, hexane/acetone = 4:1), preparative TLC (hexane/acetone = 4:1), and recycling preparative HPLC to afford a white solid (163.3 mg, 90%).

*Diethyl 2-{[6-(benzyloxy)-1H-indol-3-yl]methyl}-2-[(tert-butoxycarbonyl)amino]malonate (**4da**).*[34] GP-2 was followed using **2d** (128.1 mg, 0.46 mmol), **3a** (138.5 mg, 0.50 mmol), LiCl in THF (184 μL, 0.046 mmol), Et_3N (127 μL, 0.92 mmol), and CDMT (88.3 mg, 0.50 mmol) in MeCN (1.5 mL). The reaction mixture was stirred for 3 h. Column chromatography (silica gel, hexane/acetone = 9:1) afforded a white solid (213.6 mg, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.46–7.30 (m, 6H), 6.88–6.81 (m, 3H), 5.84 (s, 1H), 5.08 (s, 2H), 4.32–4.10 (m, 4H), 3.77 (s, 2H), 1.47 (s, 9H), 1.25 (t, J = 7.1 Hz, 6H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 168.1, 155.6, 154.2, 137.5, 136.5, 128.6, 127.9, 127.6, 123.0, 122.2, 119.7, 110.3, 109.4, 95.9, 80.3, 70.6, 67.6, 62.5, 28.7, 28.4, 14.1; LRMS (ESI-TOF): *m/z* 533 $[M + Na]^+$.

*Diethyl 2-[(tert-butoxycarbonyl)amino]-2-[(5-methoxy-1H-indol-3-yl)methyl]malonate (**4ea**)*.[34] GP-2 was followed using **2e** (102.5 mg, 0.50 mmol), **3a** (152.0 mg, 0.55 mmol), LiCl in THF (202 μL, 0.050 mmol), Et_3N (140 μL, 1.00 mmol), and CDMT (96.9 mg, 0.55 mmol) in MeCN (1.7 mL). The reaction mixture was stirred for 1.5 h. Column chromatography (silica gel, hexane/acetone = 9:1 to 7:3) afforded a pale pink solid (212.1 mg, 97%).

*Diethyl 2-[(tert-butoxycarbonyl)amino]-2-[(6-methoxy-1H-indol-3-yl)methyl)]malonate (**4fa**)*.[34] GP-2 was followed using **2f** (96.4 mg, 0.47 mmol), **3a** (143.0 mg, 0.52 mmol), LiCl in THF (190 μL, 0.047 mmol), Et_3N (131 μL, 0.94 mmol), and CDMT (91.1 mg, 0.52 mmol) in MeCN (1.6 mL). The reaction mixture was stirred for 1.5 h. The residue was purified by column chromatography (silica gel, hexane/acetone = 4:1 to hexane/EtOAc = 7:3) to afforded a pale pink solid (194.3 mg, 95%).

*Diethyl 2-[(tert-butoxycarbonyl)amino]-2-[(2-methyl-1H-indol-3-yl)methyl]malonate (**4ga**)*.[34] GP-2 was followed using **2g** (108.8 mg, 0.58 mmol), **3a** (174.9 mg, 0.64 mmol), LiCl (26.9 mg, 0.64 mmol, 1.1equiv), Et_3N (161 μL, 1.16 mmol), and CDMT (111.5 mg, 0.64 mmol) in MeCN (1.9 mL). The reaction mixture was stirred for 2.5 h. Column chromatography (silica gel, hexane/acetone = 9:1 to 7:3) afforded a white solid (238.7 mg, 99%).

*Diethyl 2-[(tert-butoxycarbonyl)amino]-2-[(2-phenyl-1H-indol-3-yl)methyl]malonate (**4ha**)*.[34] GP-2 was followed using **2h** (107.4 mg, 0.43 mmol), **3a** (130.0 mg, 0.47 mmol), LiCl in THF (174 μL, 0.043 mmol), Et_3N (119 μL, 0.86 mmol), and CDMT (82.9 mg, 0.47 mmol) in MeCN (1.4 mL). The reaction mixture was stirred for 1.5 h. Column chromatography (silica gel, hexane/acetone = 9:1) afford a pale pink solid (201.3 mg, 98%).

Diethyl 2-[1-(1*H*-indol-3-yl)ethyl]-2-[(*tert*-butoxycarbonyl)amino]malonate (4ia). GP-2 was followed using **2i** (30 mg, 0.16 mmol), **3a** (48 mg, 0.18 mmol), LiCl in THF (64 μL, 0.016 mmol), Et_3N (44.5 μL, 0.32 mmol), and CDMT (31 mg, 0.18 mmol) in MeCN (0.54 mL). The reaction mixture was stirred for 5 h. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 4:1) to afforded a white solid (28 mg, 42%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.17 (br s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.19–7.03 (m, 3H), 5.89 (br s, 1H), 4.29–4.15 (m, 3H), 4.03–3.90 (m, 1H), 3.71–3.65 (m, 1H), 1.55 (d, J = 6.9 Hz , 3H), 1.44 (s, 9H), 1.26 (t, J = 7.3 Hz, 3H), 1.06 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 168.3, 167.5, 154.6, 135.6, 126.8, 122.5, 121.8, 119.4, 119.2, 115.9, 111.1, 79.9, 69.4, 62.3, 61.8, 36.6, 28.2, 18.1, 14.0, 13.6; HRMS (ESI-TOF): Calcd for $C_{22}H_{31}N_2O_6$ $[M + H]^+$: 419.21821; Found: 419.21668.

Diethyl 2-[(1*H*-indol-3-yl)methyl]-2-{[(benzyloxy)carbonyl]amino}malonate (4ab). GP-2 was followed using **2a** (183.8 mg, 1.06 mmol), **3b** (359.0 mg, 1.16 mmol), LiCl in THF (428 μL, 0.11 mmol), Et_3N (293 μL, 2.11 mmol), and CDMT (203.8 mg, 1.16 mmol) in MeCN (3.5 mL). The reaction mixture was stirred for 4 h. Column chromatography (silica gel, hexane/EtOAc = 9:1 to 7:3) afforded a pale red oil (441.1 mg, 95%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.33–7.25 (m, 6H), 7.10 (dd, J = 7.1, 7.1 Hz, 1H), 6.97 (dd, J = 7.6, 7.6 Hz, 1H), 6.80 (d, J = 2.3 Hz, 1H), 6.12 (s, 1H), 5.13 (s, 2H), 4.23–4.08 (m, 4H), 3.84 (s, 2H), 1.17 (t, J = 7.1 Hz, 6H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 167.8, 154.6, 136.2, 135.9, 128.5, 128.3, 128.2, 128.0, 123.6, 121.8, 119.3, 118.5, 111.3, 108.4, 67.7, 66.9, 62.6, 28.5, 13.8; IR ($CHCl_3$): 3479, 3417, 3087, 3060, 3039, 3022, 3012, 2987, 2954, 2943, 2908, 1739, 1720, 1603, 1496, 1458, 1302, 1261, 1190, 1036, 812, 731; HRMS (ESI-TOF): Calcd for $C_{24}H_{26}N_2NaO_6$ $[M + Na]^+$: 461.1689; Found: 461.1674; Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.49; H, 5.75; N, 6.40.

*Diethyl 2-[(1H-indol-3-yl)methyl]malonate (**4ac**)*.[66] GP-2 was followed using **2a** (174.3 mg, 1.00 mmol), **3c** (380

μL, 2.50 mmol, 2.5 equiv), LiCl in THF (404 μL, 0.10 mmol), Et_3N (278 μL, 2.00 mmol), and CDMT (193.1 mg, 1.10 mmol) in MeCN (3.3 mL). The reaction mixture was stirred for 3 h. Column chromatography (silica gel, hexane/acetone = 9:1 to 7:3) afforded a white solid (253.7 mg, 88%). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 169.5, 136.2, 127.1, 122.7, 122.0, 119.4, 118.6, 111.9, 111.3, 61.5, 53.1, 24.6, 14.0.

*Diethyl 2-[(1H-indol-3-yl)methyl]-2-methylmalonate (**4ad**).*[21] GP-2 was followed using **2a** (174.3 mg, 1.00 mmol), **3d** (188 μL, 1.10 mmol), LiCl (46.6 mg, 1.10 mmol), Et_3N (417 μL, 3.00 mmol, 3.0 equiv), and CDMT (193.1 mg, 1.10 mmol) in MeCN (3.3 mL). The reaction mixture was stirred for 6 h. Column chromatography (silica gel, hexane/acetone = 9:1) afforded a pale yellow oil (274.7 mg, 91%). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 172.6, 135.9, 128.4, 123.6, 121.7, 119.3, 118.9, 111.2, 110.1, 61.4, 55.4, 30.7, 20.3, 14.0; LRMS (ESI-TOF): *m/z* 326 $[M + Na]^+$.

*3-(Cyanomethyl)-1H-indole (**4ae**).*[74] CDMT (56 mg, 0.32 mmol) was added to a suspension of **2a** (50 mg, 0.29 mmol), Et_3N (40 μL, 0.29 mmol), potassium cyanide (21 mg, 0.32 mmol), and 18-crown-6 (85 mg, 0.32 mmol) in MeCN (960 μL) at room temperature. After 1 h, the reaction mixture was diluted with EtOAc. The mixture was washed with H_2O and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure. Column chromatography (amine-functionalized silica gel, hexane/EtOAc = 7:3) afforded a pale yellow solid (37.6 mg, 83%).

*1-(tert-Butoxycarbonyl)gramine (**2j**).*[75] Di-*tert*-butyl dicarbonate (2.6190 g, 12.0 mmol, 1.2 equiv) was added to a suspension of NaH (480.0 mg, 12.0 mmol, 1.2 equiv), *N,N*-dimethyl-4-aminopyridine (122.2 mg, 1.0 mmol, 0.1 equiv), and **2a** (1.7425 g, 10.0 mmol, 1.0 equiv) in THF (33 mL, 0.3 M) at 0 ℃. After 3 h, the reaction mixture was quenched with aqueous 1 M NaOH and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. Twice column chromatography (amine-functionalized silica gel, hexane/EtOAc = 7:3; silica gel, EtOAc to $CHCl_3$/MeOH = 7:3) afforded a white solid (2.1661 g, 79%).

*1-Methylgramine (**2k**).*[76] GP-2 was followed using 1-methylindole (1.25 mL, 10.0 mmol), dimethylamine hydrochloride (896.9 mg, 11.0 mmol), Et_3N (1.53 mL, 11.0 mmol), formaldehyde aqueous solution (0.84 mL, 11.0 mmol), and acetic acid (0.86 mL, 15.0 mmol) in 1,4-dioxane and H_2O (1:1, 34 mL). The reaction mixture was stirred at room temperature for 4 h. Column chromatography (silica gel, hexane/acetone = 9:1 to 7:3) afforded a brawn oil (884.3 mg, 47%). LRMS (ESI): *m/z* 189 $([M + H]^+)$.

Diethyl 2-{[1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]methyl}-2-[(*tert*-butoxycarbonyl)amino]malonate (4ja). Compound **2j** (39.5 mg, 0.14 mmol, 1.0 equiv) in MeCN (1.0 mL) was added dropwise over 1 h to a mixture of **3a** (43.7 mg, 0.16 mmol, 1.1 equiv), LiI (21.3 mg, 0.16 mmol, 1.1 equiv), CDMT (27.9 mg, 0.16 mmol, 1.1 equiv), and $^iPr_2EtN$ (50 μL, 0.29 mmol, 2.0 equiv) in MeCN (0.4 mL) at room temperature. After 5 h, the reaction mixture was diluted with EtOAc, washed with aqueous HCl (1 M) and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 9:1) and recycling preparative HPLC to afford a colorless oil (56.4 mg, 78%). ^1H-NMR (400 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.31–7.26 (m, 2H), 7.18 (dd, J = 7.6, 7.6 Hz, 1H), 5.87 (s, 1H), 4.34–4.15 (m, 4H), 3.76 (s, 2H), 1.65 (s, 9H), 1.48 (s, 9H), 1.28 (t, J = 7.1 Hz, 6H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 167.8, 154.2, 149.7, 135.2, 131.3, 124.7, 124.5, 122.5, 119.265, 119.255, 115.3, 114.4, 83.7, 80.4, 67.2, 62.8, 28.4, 28.3, 28.18, 28.17, 14.19, 14.16; IR ($CHCl_3$): 3421, 3033, 2985, 2966, 2935, 2904, 2877, 1757, 1738, 1718, 1489, 1454, 1389, 1369, 1304, 1261, 1190, 1161, 1057, 1036, 768, 685; HRMS (ESI-TOF): Calcd for $C_{26}H_{36}N_2NaO_8$ $[M + Na]^+$:

527.2369; Found: 527.2371.

Diethyl 2-[(*tert*-butoxycarbonyl)amino]-2-[(1-methyl-1*H*-indol-3-yl)methyl]malonate (4ka). Compound **2k** (29.0 mg, 0.154 mmol, 1.0 equiv) in MeCN (1.0 mL) was added dropwise over 1 h to a mixture of **3a** (46.7 mg, 0.17 mmol, 1.1 equiv), LiI (22.8 mg, 0.17 mmol, 1.1 equiv), CDMT (29.8 mg, 0.17 mmol, 1.1 equiv), and $^{i}Pr_2EtN$ (54 μL, 0.31 mmol, 2.0 equiv) in MeCN (0.5 mL) at room temperature. After 4 h, the reaction mixture was diluted with EtOAc, washed with aqueous HCl (1 M) and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1) to afford a white solid (54.1 mg, 84%). Mp: 95.5–97 ℃. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.21–7.15 (m, 1H), 7.08–7.02) m, 1H), 6.75 (s, 1H), 5.83 (s, 1H), 4.23–4.12 (m, 4H), 3.80 (s, 2H), 3.72 (s, 3H), 1.49 (s, 9H), 1.26 (t, J = 7.1 Hz, 6H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 168.1, 154.1, 136.7, 128.8, 128.0, 121.6, 119.2, 119.0, 109.2, 107.8, 80.2, 67.5, 62.5, 32.8, 28.6, 28.4, 14.1; IR (KBr): 3431, 2981, 2939, 1765, 1718, 1477, 1367, 1313, 1298, 1250, 1201, 1171, 1090, 741; HRMS (ESI-TOF): Calcd for $C_{22}H_{30}N_2NaO_6$ $[M + Na]^+$: 441.2002; Found: 441.1972; Anal. Calcd for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.91; H, 7.11; N, 6.70.

Bis[(1*H*-indol-3-yl)methyl]dimethylammonium chloride (**7**). CDMT (175.5 mg, 1.00 mmol, 1.0 equiv) was added to a suspension of **2a** (348.5 mg, 2.00 mmol, 2.0 equiv) and Et_3N (305.8 μL, 2.20 mmol, 2.2 equiv) in MeCN (6.7 mL, 0.3 M) at room temperature. After 1 h, the reaction mixture was filtered. The filtrate was washed with CH_2Cl_2 and concentrated under reduced pressure to afford a white solid (331.0 mg, 97%). Mp: 174.5–176.5 ℃. ^{1}H-NMR [400 MHz, $(CD_3)_2SO$]: δ 11.75 (s, 2H), 7.88 (d, J = 7.8 Hz, 2H), 7.73 (d, J = 2.3 Hz, 2H), 7.49 (d, J = 7.8 Hz, 2H), 7.21–7.13 (m, 4H), 4.81 (s, 4H), 2.86 (s, 6H); ^{13}C{^{1}H}-NMR [100 MHz, $(CD_3)_2SO$]: δ 136.1, 130.4, 127.9, 121.8, 120.1, 118.6, 112.2, 101.6, 58.9, 47.2; IR (KBr): 3118, 3099, 3033, 2854, 1475, 1460, 1431, 1344, 1250, 818, 748; HRMS (ESI-TOF): Calcd for $C_{20}H_{22}N_3$ $[M - Cl]^+$: 304.1814; Found: 304.1785.

Bis{[1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]methyl}dimethylammonium chloride (6j). CDMT (52.7 mg, 0.30 mmol, 1.0 equiv) was added to a suspension of **2j** (164.6 mg, 0.60 mmol, 2.0 equiv) in MeCN (2.0 mL, 0.3 M) at room temperature. After 3 h, the reaction mixture was concentrated under reduced pressure. Silica gel column chromatography afforded a white solid (147.2 mg, 91%). Mp: 154–156 ℃. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.18 (br s, 2H), 8.08 (d, J = 7.8 Hz, 2H), 7.91 (br s, 2H), 7.31–7.28 (m, 4H), 5.55 (br s, 4H), 3.23 (br s, 6H), 1.67 (s, 18H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 149.0, 135.2, 130.8, 129.9, 125.4, 124.1, 120.5, 115.3, 107.6, 85.1, 59.5, 48.7, 28.3; IR (KBr): 3005, 2978, 2931, 1738, 1560, 1475, 1456, 1373, 1358, 1275, 1259, 1236, 1155, 1088, 835, 768, 750; HRMS (ESI-TOF): Calcd for $C_{30}H_{38}N_3O_4$ $[M - Cl]^+$: 504.2862; Found: 504.2857.

General Procedure for the synthesis of 1,2,3,4-tetrahydro-β-carboline derivatives (GP-3). LiCl (0.1 equiv) in THF (0.25 M), Et_3N (2.0 equiv), and CDMT (1.1 equiv) were added to a suspension of a gramine derivative (**2a**, **2b**, **2d**, or **2e**; 1.0 equiv) and **11** or **11-Br** (1.1 equiv) in MeCN (0.3 M) at room temperature. After 1.5–5 h, TFA (5–10 equiv) was added to the reaction mixture. The reaction mixture was stirred for 19 h at room temperature or 50 °C. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified to afford the desired product.

Diethyl 1-(2-hydroxyphenyl)-1,2,4,9-tetrahydro-3*H*-pyrido[3,4-*b*]indole-3,3-dicarboxylate (12a). GP-3 was

followed using **2a** (69.7 mg, 0.40 mmol), **11** (122.9 mg, 0.44 mmol), LiCl in THF (160 μL, 0.040 mmol), Et_3N (111 μL, 0.80 mmol), and CDMT (77.2 mg, 0.44 mmol) in MeCN (1.3 mL) for the first step (4 h) followed by TFA (153 μL, 2.00 mmol) for the second step (room temperature). Column chromatography (silica gel, hexane/acetone = 9:1) afforded a white solid (152.0 mg, 93%). Mp: 70.5–72.5 ℃. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.53–7.50 (m, 2H), 7.22–7.18 (m, 2H), 7.11–7.05 (m, 3H), 6.87 (dd, J = 6.9, 6.9 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 5.53 (s, 1H), 4.30–4.06 (m, 4H), 3.85–3.81 (m, 2H), 3.32 (dd, J = 15.8, 2.5 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 169.2, 168.6, 157.4, 136.6, 131.0, 130.1, 128.7, 126.9, 123.5, 122.2, 119.68, 119.67, 118.4, 117.9, 111.1, 105.9, 66.8, 62.8, 62.5, 55.6, 26.8, 14.08, 14.05; IR (KBr): 3443, 3305, 2983, 1736, 1491, 1454, 1315, 1248, 1198, 752; HRMS (ESI-TOF): Calcd for $C_{23}H_{24}N_2NaO_5$ [M + Na]$^+$: 431.1583; Found: 431.1570; Anal. Calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.56; H, 5.82; N, 6.83.

Diethyl 6-chloro-1-(2-hydroxyphenyl)-1,2,4,9-tetrahydro-3*H*-pyrido[3,4-*b*]indole-3,3-dicarboxylate (12b). GP-3 was followed using **2b** (41.7 mg, 0.20 mmol), **11** (61.4 mg, 0.22 mmol), LiCl in THF (80 μL, 0.020 mmol), Et_3N (56 μL, 0.40 mmol), and CDMT (38.6 mg, 0.22 mmol) in MeCN (0.7 mL) for the first step (5 h) followed by TFA (153 μL, 2.00 mmol) for the second step (50 °C). The residue was purified by column chromatography (silica gel, hexane/acetone = 9:1 to 7:3) and recycling preparative HPLC to afford a white solid (67.5 mg, 76%). Mp: 79.5–81.5 ℃. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.29–7.25 (m, 2H), 7.09–7.04 (m, 2H), 6.94 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.51 (s, 1H), 4.37–4.10 (m, 4H), 3.82–3.75 (m, 2H), 3.27 (dd, J = 16.0, 2.8 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 169.1, 168.4, 157.5, 134.9, 132.6, 130.4, 128.7, 128.1, 125.6, 123.2, 122.6, 119.9, 118.2, 112.1, 106.0, 66.8, 63.0, 62.7, 55.6, 26.6, 14.18, 14.17; IR (KBr): 3410, 3311, 2935, 2900, 2862, 1736, 1718, 1491, 1471, 1444, 1278, 1196, 1043, 1003, 858, 752; HRMS (ESI-TOF): Calcd for $C_{23}H_{23}ClN_2NaO_5$ [M + Na]$^+$: 465.1193; Found: 465.1171; Anal. Calcd for $C_{23}H_{23}ClN_2O_5$: C, 62.37; H, 5.23; N, 6.33. Found: C, 62.18; H, 5.18; N, 6.20.

Diethyl 7-(benzyloxy)-1-(2-hydroxyphenyl)-1,2,4,9-tetrahydro-3*H*-pyrido[3,4-*b*]indole-3,3-dicarboxylate (12d). GP-3 was followed using **2d** (52.1 mg, 0.19 mmol), **11** (57.2 mg, 0.21 mmol), LiCl in THF (76 μL, 0.019 mmol), Et_3N (52 μL, 0.37 mmol), and CDMT (36.0 mg, 0.21 mmol) in MeCN (0.6 mL) for the first step (3 h) followed by TFA (71 μL, 0.93 mmol) for the second step (room temperature). The residue was purified by column chromatography (silica gel, hexane/acetone = 9:1 to 7:3) and recycling preparative HPLC to afford a white solid (74.8 mg, 78%). Mp: 195–196 ℃. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.42–7.22 (m, 9H), 6.92 (dd, J = 7.3, 7.3 Hz, 1H), 6.85–6.82 (m, 2H), 6.73 (d, J = 1.8 Hz, 1H), 5.50 (s, 1H), 5.04 (s, 2H), 4.36–4.09 (m, 4H), 3.80–3.77 (m, 2H), 3.28 (dd, J = 16.0, 2.3 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 169.3, 168.6, 157.6, 155.8, 137.5, 137.3, 130.2, 129.9, 128.68, 128.65, 127.9, 127.5, 123.6, 121.7, 119.7, 119.1, 118.1, 110.3, 106.0, 96.5, 70.7, 66.9, 62.9, 62.6, 55.7, 26.8, 14.19, 14.16; IR (KBr): 3419, 3305, 2983, 2906, 2868, 1732, 1701, 1541, 1508, 1493, 1473, 1458, 1271, 1205, 1155, 754; HRMS (ESI-TOF): Calcd for $C_{30}H_{30}N_2NaO_6$ [M + Na]$^+$: 537.2002; Found: 537.1979; Anal. Calcd for $C_{30}H_{30}N_2O_6$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.77; H, 5.80; N, 5.46.

Diethyl 1-(2-hydroxyphenyl)-6-methoxy-1,2,4,9-tetrahydro-3*H*-pyrido[3,4-*b*]indole-3,3-dicarboxylate (12e). GP-3 was followed using **2e** (40.9 mg, 0.20 mmol), **11** (61.4 mg, 0.22 mmol), LiCl in THF (80 μL, 0.020 mmol), Et_3N (56 μL, 0.40 mmol), and CDMT (38.6 mg, 0.22 mmol) in MeCN (0.7 mL) for the first step (1.5 h) followed by

TFA (77 μL, 1.00 mmol) for the second step (room temperature). Column chromatography (silica gel, hexane/acetone = 4:1) afforded a white solid (87.5 mg, quant.). Mp: 68–70 ℃. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.97 (br, 1H), 7.31 (s, 1H), 7.26–7.22 (m, 2H), 7.04 (d, J = 9.2 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.91 (dd, J = 7.5, 7.5 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.75 (dd, J = 9.2, 2.3 Hz, 1H), 5.52 (s, 1H), 4.34–4.09 (m, 4H), 3.83–3.78 (m, 5H), 3.30 (dd, J = 15.8, 2.0 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 169.3, 168.6, 157.5, 154.2, 131.8, 131.7, 130.2, 128.7, 127.4, 123.5, 119.7, 118.0, 112.2, 111.8, 105.9, 100.6, 66.9, 62.9, 62.6, 56.0, 55.7, 26.8, 14.2, 14.1; IR (KBr): 3392, 3315, 2981, 2935, 2902, 2831, 1738, 1591, 1489, 1458, 1292, 1254, 1215, 756; HRMS (ESI-TOF): Calcd for $C_{24}H_{26}N_2NaO_6$ $[M + Na]^+$: 461.1689; Found: 461.1665.

Diethyl 1-(2-hydroxyphenyl)-9-methyl-1,2,4,9-tetrahydro-3*H*-pyrido[3,4-*b*]indole-3,3-dicarboxylate (12k). ^{i}Pr$_2$EtN (71 μL, 0.41 mmol, 2.0 equiv) and LiCl in THF (81 μL, 0.020 mmol, 0.1 equiv) were added to a suspension of **11** (62.6 mg, 0.22 mmol, 1.1 equiv) and CDMT (39.3 mg, 0.22 mmol, 1.1equiv) in MeCN (0.6 mL) at room temperature. Compound **2k** (38.3 mg, 0.20 mmol, 1.0 equiv) in MeCN (1.4 mL) was added dropwise to the mixture over 2 h. After 2 h, TFA (156 μL, 2.03 mmol, 10 equiv) was added. The reaction mixture was heated to 80 °C for 24 h, and then cooled to room temperature. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 9:1 to 7:3) and recycling preparative HPLC to afford a pale yellow solid (39.3 mg, 46%). Mp: 169–171 ℃. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.97 (br s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.26–7.10 (m, 5H), 6.90–6.83 (m, 2H), 5.65 (s, 1H), 4.26–4.05 (m, 4H), 3.71 (dd, J = 15.8, 1.6 Hz, 1H), 3.43 (dd, J = 15.8, 2.4 Hz, 1H), 3.27 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 169.6, 168.6, 157.4, 138.0, 131.7, 130.6, 130.2, 126.2, 124.3, 122.0, 119.6, 119.3, 118.5, 117.9, 109.0, 106.3, 66.3, 62.7, 62.4, 55.0, 30.9, 27.5, 14.12, 14.09; IR (KBr): 3315, 2981, 2945, 1745, 1473, 1458, 1277, 1246, 1203, 1053, 752; HRMS (ESI-TOF): Calcd for $C_{24}H_{26}N_2NaO_5$ $[M + Na]^+$: 445.1739; Found: 445.1755; Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.02; H, 6.17; N, 6.62.

Diethyl 1-(5-bromo-2-hydroxyphenyl)-1,2,4,9-tetrahydro-3*H*-pyrido[3,4-*b*]indole-3,3-dicarboxylate (12a-Br). GP-3 was followed using **2a** (36 mg, 0.21 mmol), **11-Br** (81 mg, 0.23 mmol), LiCl in THF (82 μL, 0.021 mmol), Et_3N (57 μL, 0.41 mmol), and CDMT (40 mg, 0.23 mmol) in MeCN (680 μL) for the first step (4 h) followed by TFA (78.5 μL, 1.03 mmol) for the second step (room temperature, 12 h). Column chromatography (silica gel, hexane/acetone = 4:1) afforded a pale yellow solid (82.8 mg, 83%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 10.05 (br, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.46 (br s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.33 (dd, J = 8.6 Hz, 2.4 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 7.18–7.08 (m, 2H), 6.70 (d, J = 8.6 Hz, 1H), 5.49 (s, 1H), 4.39–4.27 (m, 2H), 4.26–4.19 (m, 1H), 4.15–4.08 (m, 1H), 3.89–3.75 (m, 2H), 3.31 (dd, J = 15.8, 2.7 Hz, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ 169.0, 168.3, 156.6, 136.6, 132.8, 131.0, 130.0, 126.8, 125.4, 122.5, 119.8, 119.7, 118.5, 111.2, 111.1, 106.3, 66.7, 62.8, 62.5, 55.1, 26.6, 14.02, 13.97; HRMS (ESI-TOF): Calcd for $C_{23}H_{24}BrN_2O_5$ $[M + H]^+$: 487.0869; Found : 487.0892.

Diethyl 1-phenyl-1,2,4,9-tetrahydro-3*H*-pyrido[3,4-*b*]indole-3,3-dicarboxylate (14). Benzaldehyde (240 μL, 2.36 mmol) was added to a suspension of $MgSO_4$ (1,29 mg, 10.7 mmol) and diethyl aminomalonate (334 μL, 2.15 mmol) in CH_2Cl_2 (5.5 mL) at room temperature. After 22 h, MeCN (5.5 mL), LiCl in THF (572 μL, 0.143 mmol), **2a** (250 mg, 1.43 mmol), Et_3N (400 μl, 2.86 mmol), and CDMT (276 mg, 1.57 mmol) were added to the reaction

mixture at room temperature. After 2 h, TFA (330 µl, 4.29 mmol) was added to the reaction mixture at room temperature. After 30 min, the reaction mixture was filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ and braine, dried (Na_2SO_4), and filtered. This filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (twice, silica gel with hexane/EtOAc = 4:1 for the first chromatography, amine-functionalized silica gel with hexane/EtOAc = 4:1 for the second chromatography) to afford a white solid (192 mg, 34%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.58–7.52 (m, 1H), 7.46 (br s, 1H), 7.39–7.27 (m, 5H), 7.14–7.05 (m, 3H), 5.44 (s, 1H), 4.30–4.14 (m, 3H), 4.12–4.03 (m, 1H), 3.74 (dd, J = 15.1, 1.4 Hz, 1H), 3.33 (dd, J = 15.1, 2.4 Hz 1H), 3.16 (br s, 1H), 1.28 (t, J = 7.3 Hz, 3H), 1.16 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ 170.4, 141.4, 136.3, 133.5, 128.7, 128.6, 128.3, 127.0, 121.7, 119.3, 118.2, 110.8, 106.7, 67.2, 62.2, 61.8, 55.4, 27.1, 14.0, 13.9; HRMS (ESI-TOF): Calcd for $C_{23}H_{25}N_2O_4$ $[M + H]^+$: 393.1814; Found : 393.1801.

Associated Content

Supporting Information. This material is available free of charge on the ACS Publications website. Spectroscopic data (PDF).

Author Information

Corresponding Author

*kunisima@p.kanazawa-u.ac.jp

Notes

The authors declare no competing financial interest.

Acknowledgment

This work was partially supported by the JSPS Grants-in-Aid for Scientific Research program (KAKENHI, grant number 17H03970).

References

(1) Larsen, S. D. Formaldehyde-Dimethylamine. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd: Chichester, UK, 2001; pp 1–3.

(2) Kleinman, E. F. Dimethyl(methylene)ammonium Iodide. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd: Chichester, UK, 2001; pp 1–4.

(3) Tramontini, M.; Angiolini, L. Further Advances in the Chemistry of Mannich Bases. *Tetrahedron* **1990**, *46*, 1791–1837.

(4) Yamada, K.; Masaki, K.; Hagimoto, Y.; Kamiya, S.; Kunishima, M. A New Method Using 2-Chloro-4,6-dimethoxy-1,3,5-triazine for Facile Elimination of Dimethylamino Group in Eschenmoser's Methylenation for Synthesis of α,β-Unsaturated Esters. *Tetrahedron Lett.* **2013**, *54*, 1758–1760.

(5) Kunishima, M.; Ujigawa, T.; Nagaoka, Y.; Kawachi, C.; Hioki, K.; Shiro, M. Study on 1,3,5-Triazine Chemistry in Dehydrocondensation: Gauche Effect on the Generation of Active Triazinylammonium Species. *Chem. Eur. J.* **2012**, *18*, 15856–15867.

(6) Kitamura, M.; Yamamura, S.; Kobayashi, H.; Yamamoto, M.; Tada, K.; Hioki, K.; Yamada, K.; Kunishima, M. Synthesis of Pyrrolidinium Salts Using a Triazine-Based Reagent under Mild Conditions. *Chem. Lett.* **2014**, *43*, 1593–1595.

(7) Kitamura, M.; Yamamura, S.; Yamada, K.; Kunishima, M. Alcohol- and Amine-Tolerant Synthesis of Six-Membered Cyclic Quaternary Ammonium Salts by Using a Triazine-Based Reagent. *Asian J. Org. Chem.* **2016**, *5*, 1508–1517.

(8) Semenov, B. B.; Granik, V. G. Chemistry of *N*-(1*H*-Indol-3-ylmethyl)-*N*,*N*-dimethylamine (Gramine): A Review. *Pharm. Chem. J.* **2004**, *38*, 287–310.

(9) Cox, E. D.; Cook, J. M. The Pictet-Spengler Condensation: A New Direction for an Old Reaction. *Chem. Rev.* **1995**, *95*, 1797–1842.

(10) Snyder, H. R.; Smith, C. W. A Convenient Synthesis of DL-Tryptophan. *J. Am. Chem. Soc.* **1944**, *66*, 350–351.

(11) Albertson, N. F.; Archer, S.; Suter, C. M. The Synthesis of Tryptophan from Gramine. *J. Am. Chem. Soc.* **1945**, *67*, 36–37.

(12) Howe, E. E.; Zambito, A. J.; Snyder, H. R.; Tishler, M. The Application of a New Alkylation Reaction to the Synthesis of Tryptophan. *J. Am. Chem. Soc.* **1945**, *67*, 38–39.

(13) Uhle, F. C.; Harris, L. S. The Synthesis of α-Methylamino Acids. *J. Am. Chem. Soc.* **1956**, *78*, 381–384.

(14) Bergmann, E. D.; Hoffmann, E. 6 -Fluoro-, 6-Methoxy-, and 7-Methoxy-tryptophan. *J. Chem. Soc.* **1962**, *46*, 2827–2829.

(15) Hoffmann, E.; Ikan, R.; Galun, A. B. The Synthesis of 5-Fluoro- and 7-Methyl-indole and -tryptophane. *J. Heterocycl. Chem.* **1965**, *2*, 298–299.

(16) Houghton, E.; Saxton, J. E. Studies in the Echinulin Series. Part II. Synthesis of (±)-Alanyltryptophan Anhydride and L-Alanyl-2-(1,1-dimethylallyl)tryptophan Anhydride. *J. Chem. Soc. C* **1969**, 1003–1012.

(17) Kozikowski, A. P.; Okita, M.; Kobayashi, M.; Floss, H. G. Probing Ergot Alkaloid Biosynthesis: Synthesis and Feeding of a Proposed Intermediate along the Biosynthetic Pathway. A New Amidomalonate for Tryptophan Elaboration. *J. Org. Chem.* **1988**, *53*, 863–869.

(18) Teng, X.; Degterev, A.; Jagtap, P.; Xing, X.; Choi, S.; Denu, R.; Yuan, J.; Cuny, G. D. Structure–Activity Relationship Study of Novel Necroptosis Inhibitors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5039–5044.

(19) Dong, X.; Zhang, Z.; Wen, R.; Shen, J.; Shen, X.; Jiang, H. Structure-Based de Novo Design, Synthesis, and Biological Evaluation of the Indole-Based PPARγ Ligands (I). *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5913–5916.

(20) Somei, M.; Karasawa, Y.; Kaneko, C. Synthesis of 4-Alkylindoles from 2-Methyl-5-nitroisoquinolinium Iodide. *Chem. Lett.* **1980**, *9*, 813–816.

(21) Somei, M.; Karasawa, Y.; Kaneko, C. Selective Monoalkylation of Carbon Nucleophiles with Gramine. *Heterocycles* **1981**, *16*, 941–949.

(22) Boyles, D. A.; Nichols, D. E. Formal Synthesis of Clavicipitic Acid Based on a Biosynthetic Proposal. *J. Org. Chem.* **1988**, *53*, 5128–5130.

(23) Filler, R.; Woods, S. M.; White, W. L. Polyfluoroaralkyl Amines. Further Studies on the Reactivity of 4,5,6,7-

Tetrafluoroindole. *Can. J. Chem.* **1989**, *67*, 1837–1841.

(24) Barry, S. M.; Kers, J. A.; Johnson, E. G.; Song, L.; Aston, P. R.; Patel, B.; Krasnoff, S. B.; Crane, B. R.; Gibson, D. M.; Loria, R.; et al. Cytochrome P450–Catalyzed L-Tryptophan Nitration in Thaxtomin Phytotoxin Biosynthesis. *Nat. Chem. Biol.* **2012**, *8*, 814–816.

(25) Ritchie, R.; Saxton, J. E. Studies on Indolic Mould Metabolites. Total Synthesis of l-Prolyl-2-methyltryptophan Anhydride and Deoxybrevianamide E. *Tetrahedron* **1981**, *37*, 4295–4303.

(26) Endo, Y.; Shudo, K.; Itai, A.; Hasegawa, M.; Sakai, S. Synthesis and Stereochemistry of Indolactam-V, an Active Fragment of Teleocidins. Structural Requirements for Tumor-Promoting Activity. *Tetrahedron* **1986**, *42*, 5905–5924.

(27) Settimj, G.; Del Giudice, M. R.; Ferretti, R.; Gatta, F. β-Carbolines as Agonistic or Antagonistic Benzodiazepine Receptor Ligands. 1. Synthesis of Some 5-, 6- and 7-Amino Derivatives of 3-Methoxycarbonyl-β-carboline (β-CCM) and of 3-Ethoxycarbonyl-β-carboline (β-CCE). *J. Heterocycl. Chem.* **1988**, *25*, 1391–1397.

(28) Hagen, T. J.; Narayanan, K.; Names, J.; Cook, J. M. DDQ Oxidations in the Indole Area. Synthesis of 4-Alkoxy-β-carbolines Including the Natural Products Crenatine and 1-Methoxycanthin-6-one. *J. Org. Chem.* **1989**, *54*, 2170–2178.

(29) Ley, S. V.; Priour, A. Total Synthesis of the Cyclic Peptide Argyrin B. *Eur. J. Org. Chem.* **2002**, 3995–4004.

(30) King, R. R.; Calhoun, L. A. Synthesis and NMR Characteristics of *N*-Acetyl-4-nitro, *N*-Acetyl-5-nitro, *N*-Acetyl-6-nitro and N-Acetyl-7-nitrotryptophan Methyl Esters. *Magn. Reson. Chem.* **2009**, *47*, 273–276.

(31) Iwao, M.; Motoi, O. Methodology for the Efficient Synthesis of 3,4-Differentially Substituted Indoles. Fluoride Ion-Induced Elimination-Addition Reaction of 1-Triisopropylsilylgramine Methiodides. *Tetrahedron Lett.* **1995**, *36*, 5929–5932.

(32) Iwao, M.; Ishibashi, F. A Concise Total Synthesis of (±)-*cis*-and (±)-*trans*-Clavicipitic Acids by Combinational Use of Directed Lithiation and Flouride Ion-Induced Elimination-Addition Reaction of 1-(Triisopropylsilyl)gramine Derivatives. *Tetrahedron* **1997**, *53*, 51–58.

(33) Meseguer, B.; Alonso-Díaz, D.; Griebenow, N.; Herget, T.; Waldmann, H. Solid-Phase Synthesis and Biological Evaluation of a Teleocidin Library-Discovery of a Selective PKC*δ* down Regulator. *Chemistry* **2000**, *6*, 3943–3957.

(34) Jones, D. T.; Artman, G. D.; Williams, R. M. Coupling of Activated Esters to Gramines in the Presence of Ethyl Propiolate under Mild Conditions. *Tetrahedron Lett.* **2007**, *48*, 1291–1294.

(35) Saidi, M. R.; Azizi, N.; Akbari, E.; Ebrahimi, F. $LiCO_4/Et_3N$: Highly Efficient and Active Catalyst for Selective Michael Addition of Active Methylene Compounds under Solvent-Free Condition. *J. Mol. Catal. A Chem.* **2008**, *292*, 44–48.

(36) Marques, M. V.; Sá, M. M. Lithium Chloride-Mediated Stereoselective Synthesis of Cyclopropanecarboxamides from *γ*,*δ*-Epoxy Malonates through a Domino Cyclopropanation/Lactonization/Aminolysis Process. *J. Org. Chem.* **2014**, *79*, 4650–4658.

(37) The crucial role of the lithium cation was also observed in the simple alkylation of malonates. Yoo, S.-E.; Yi, K. Y. A Mild Condition for C-Alkylation of β-Ketoester. *Bull. Korean Chem. Soc.* **1989**, *10*, 112.

(38) Shinohara, H.; Fukuda, T.; Iwao, M. A Formal Synthesis of Optically Active Clavicipitic Acids, Unusual Azepinoindole-Type Ergot Alkaloids. *Tetrahedron* **1999**, *55*, 10989–11000.

(39) Okada, M.; Sato, I.; Cho, S. J.; Suzuki, Y.; Ojika, M.; Dubnau, D.; Sakagami, Y. Towards Structural Determination of the ComX Pheromone: Synthetic Studies on Peptides Containing Geranyltryptophan. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 2374–2387.

(40) Snyder, H. R.; Smith, C. W.; Stewart, J. M. Carbon-Alkylation with Quaternary Ammonium Salts. A New Approach to the Synthesis of Compounds Containing the β-Indolemethylene Group. *J. Am. Chem. Soc.* **1944**, *66*, 200–204.

(41) Snyder, H. R.; Eliel, E. L. An Alkylation with the Methiodide of 1-Methyl-3-dimethylaminomethylindole (1-Methylgramine). *J. Am. Chem. Soc.* **1948**, *70*, 1703–1705.

(42) Snyder, H. R.; Eliel, E. L. Carbon Alkylations with 1-Methylgramine and Its Methiodide. *J. Am. Chem. Soc.* **1949**, *71*, 663–669.

(43) Cook, J. W.; Loudon, J. D.; McCloskey, P. The Chemistry of the Mitragyna Genus. Part II. Synthesis of 7-Methoxy-2-methyl- and 7-Methoxy-1:2-dimethyl-β-carboline. *J. Chem. Soc.* **1951**, 1203–1207.

(44) Cook, J. W.; Gailey, R. M.; Loudon, J. D. Some Methyl Derivatives of β-Carboline. *J. Chem. Soc.* **1954**, 568–569.

(45) Domschke, G.; Müller, G. Über Substituierte 5-Hydroxy-Indole. III. [1-Benzyl-2-methyl-5-methoxy]-tryptamin Und -tryptophan. *J. für Prakt. Chemie* **1963**, *21*, 85–91.

(46) Miranda, S.; López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. Convenient Synthesis of Highly Functionalized, 3,4-Disubstituted Indole Building Blocks. *Open Org. Chem. J.* **2007**, *1*, 1–12.

(47) The observed ^{1}H-NMR signals from **5i** in the crude mixture were compatible with data reported in the literature. Chen, X.; Fan, H.; Zhang, S.; Yu, C.; Wang, W. Facile Installation of 2-Reverse Prenyl Functionality into Indoles by a Tandem *N*-Alkylation-Aza-Cope Rearrangement Reaction and Its Application in Synthesis. *Chem. Eur. J.* **2016**, *22*, 716–723.

(48) Geissman, T. A.; Armen, A. The Reaction of Gramine with Methyl Iodide. The Preparation and Properties of Gramine Methiodide. *J. Am. Chem. Soc.* **1952**, *74*, 3916–3919.

(49) Gray, A. P. The Alkylation of Gramine and of Indole-*N*-methyl-gramine. *J. Am. Chem. Soc.* **1953**, *75*, 1252–1253.

(50) Lown, J. W.; Weir, G. L. Studies Related to Antitumor Antibiotics. Part XIII. Reactivity of 2- and 3-Indolylcarbinyl Compounds as Models for Mitosane Action. *Can. J. Chem.* **1978**, *56*, 249–257.

(51) Melhado, L. L. Reaction of Methyl Iodide with Gramine and with Nitro-Substituted Gramines. *J. Org. Chem.* **1981**, *46*, 1920–1923.

(52) Palmieri, A.; Petrini, M.; Shaikh, R. R. Synthesis of 3-Substituted Indoles via Reactive Alkylideneindolenine Intermediates. *Org. Biomol. Chem.* **2010**, *8*, 1259–1270.

(53) Wang, L.; Chen, Y.; Xiao, J. Alkylideneindoleninium Ions and Alkylideneindolenines: Key Intermediates for the Asymmetric Synthesis of 3-Indolyl Derivatives. *Asian J. Org. Chem.* **2014**, *3*, 1036–1052.

(54) Kunishima, M.; Kawachi, C.; Morita, J.; Terao, K.; Iwasaki, F.; Tani, S.; Terao, K. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Chloride: An Efficient Condensing Agent Leading to the Formation of

Amides and Esters. *Tetrahedron* **1999**, *55*, 13159–13170.

(55) Yamada, K.; Tsukada, Y.; Karuo, Y.; Kitamura, M.; Kunishima, M. Development of a New Benzylating Reagent Spontaneously Releasing Benzyl Cation Equivalents at Room Temperature. *Chem. Eur. J.* **2014**, *20*, 12274–12278.

(56) Johnson, S. L.; Chen, L.-H.; Pellecchia, M. A High-Throughput Screening Approach to Anthrax Lethal Factor Inhibition. *Bioorg. Chem.* **2007**, *35*, 306–312.

(57) Verma, R. P.; Hansch, C. Combating the Threat of Anthrax: A Quantitative Structure-Activity Relationship Approach. *Mol. Pharm.* **2008**, *5*, 745–759.

(58) Bi, W.; Bi, Y.; Xue, P.; Zhang, Y.; Gao, X.; Wang, Z.; Li, M.; Baudy-Floc'H, M.; Ngerebara, N.; Michael Gibson, K.; et al. A New Class of β-Carboline Alkaloid-Peptide Conjugates with Therapeutic Efficacy in Acute Limb Ischemia/Reperfusion Injury. *Eur. J. Med. Chem.* **2011**, *46*, 1453–1462.

(59) Reboredo, S.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; de Cózar, A.; Cossío, F. P. An Amine-Catalyzed Enantioselective [3+2] Cycloaddition of Azomethine Ylides and α,β-Unsaturated Aldehydes: Applications and Mechanistic Implications. *Chem. Eur. J.* **2012**, *18*, 7179–7188.

(60) Ugarriza, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. Organocatalytic Enantioselective [3+2] Cycloaddition of Azomethine Ylides and Acrolein. *Asymmetric Catal.* **2015**, *2*, 26–36.

(61) Wu, Y.; Qiao, G.; Liu, H.; Zhang, L.; Sun, Z.; Xiao, Y.; Guo, H. Brønsted Acid-Promoted [3 + 3] Cycloaddition of Azomethine Ylides with Quinone Monoimine: A Practical Method towards Dihydrobenzoxazine Derivatives. *RSC Adv.* **2015**, *5*, 84290–84294.

(62) Okubo, T.; Yoshikawa, R.; Chaki, S.; Okuyama, S.; Nakazato, A. Design, Synthesis, and Structure–Activity Relationships of Novel Tetracyclic Compounds as Peripheral Benzodiazepine Receptor Ligands. *Bioorg. Med. Chem.* **2004**, *12*, 3569–3580.

(63) Hroch, L.; Hrušková, M.; Schmitz, J.; Schnakenburg, G.; Gütschow, M. 3,5,5-Trisubstituted Hydantoins from Activated (Benzyloxycarbonyl-amino)malonic Acids. *Synthesis* **2012**, *44*, 1907–1914.

(64) Tian, L.; Xu, G.-Q.; Li, Y.-H.; Liang, Y.-M.; Xu, P.-F. An Efficient Strategy for the Synthesis of Polysubstituted Chromeno[4,3-*b*]pyrrolidine Derivatives. *Chem. Commun.* **2014**, *50*, 2428–2430.

(65) Huang, Z.; Bao, Y.; Zhang, Y.; Yang, F.; Lu, T.; Zhou, Q. Hydroxy-Assisted Regio- and Stereoselective Synthesis of Functionalized 4-Methylenepyrrolidine Derivatives via Phosphine-Catalyzed [3 + 2] Cycloaddition of Allenoates with *o*-Hydroxyaryl Azomethine Ylides. *J. Org. Chem.* **2017**, *82*, 12726–12734.

(66) Bandini, M.; Eichholzer, A. Enantioselective Gold-Catalyzed Allylic Alkylation of Indoles with Alcohols: An Efficient Route to Functionalized Tetrahydrocarbazoles. *Angew. Chem., Int. Ed.* **2009**, *48*, 9533–9537.

(67) Hall, A.; Billinton, A.; Brown, S. H.; Chowdhury, A.; Giblin, G. M. P.; Goldsmith, P.; Hurst, D. N.; Naylor, A.; Patel, S.; Scoccitti, T.; Theobald, P. J. Discovery of a Novel Indole Series of EP1 Receptor Antagonists by Scaffold Hopping. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2684–2690.

(68) Luo, Y.-H.; Yang, L.-J.; Han, G.; Liu, Q.-L.; Wang, W.; Ling, Y.; Sun, B.-W. Influences of Halogen Atoms on Indole-3-acetonitrile (IAN): Crystal Structure and Hirshfeld Surfaces Analysis. *J. Mol. Struct.* **2014**, *1076*, 679–686.

(69) Gaddum, J. H.; Hameed, K. A.; Hathway, D. E.; Stephens, F. F. Quantitative Studies of Antagonists for 5-

Hydroxytryptamine. *Q. J. Exp. Physiol. Cogn. Med. Sci.* **1955**, *40*, 49–74.

(70) Morales-Ríos, M. S.; Joseph-Nathan, P. NMR Studies of Indoles and Their *N*-Carboalkoxy Derivatives. *Magn. Reson. Chem.* **1987**, *25*, 911–918.

(71) Bennett, R.; Maggiolo, A.; Shah, T. Displacement of the Indolyl Sulfide Linkage in the Synthesis of 3-Substituted Indoles. *J. Heterocycl. Chem.* **1981**, *18*, 391–394.

(72) Pretka, J. E.; Lindwall, H. G. Application of Reformatsky and Grignard Reagents to 1,2-Disubstituted Indoxyls. *J. Org. Chem.* **1954**, *19*, 1080–1088.

(73) Le Goffic, F.; Gouyette, A.; Ahond, A. Une Nouvelle Synthese de l'ellipticine et Ses Analogues Structuraux. *Tetrahedron* **1973**, *29*, 3357–3362.

(74) Bencivenni, G.; Lanza, T.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. Iminyl Radicals from α-Azido o -Iodoanilides via 1,5-H Transfer Reactions of Aryl Radicals: New Transformation of α-Azido Acids to Decarboxylated Nitriles. *J. Org. Chem.* **2008**, *73*, 4721–4724.

(75) Lucchetti, N.; Tkacheva, A.; Fantasia, S.; Muñiz, K. Radical C−H-Amination of Heteroarenes Using Dual Initiation by Visible Light and Iodine. *Adv. Synth. Catal.* **2018**, *360*, 3889–3893.

(76) Hogan, M.; Gleeson, B.; Tacke, M. Synthesis and Preliminary Cytotoxicity Studies of Achiral Indolyl-Substituted Titanocenes. *Organometallics* **2010**, *29*, 1032–1040.