



Cite this: *RSC Adv.*, 2019, 9, 17341

Received 21st March 2019

Accepted 27th May 2019

DOI: 10.1039/c9ra02204j

rsc.li/rsc-advances

A facile approach to 2-alkoxyindolin-3-one and its application to the synthesis of *N*-benzyl matemone†

Makoto Shimizu,^a Hayao Imazato,^b Isao Mizota^b and Yusong Zhu^a

2-Alkoxy carbonylindolin-3-one is synthesized from a methoxyglycine derivative via a 1,2-aza-Brook rearrangement followed by cyclization with bis(trimethylsilyl)aluminum chloride. A short-step synthesis of *N*-benzyl matemone is successfully carried out using the present indolin-3-one synthesis.

Introduction

Heterocyclic compounds possessing an oxindole¹ skeleton have received considerable attention due to the widespread existence of naturally occurring bioactive materials containing this particular heterocycle. Among them bromine-containing and/or 2-alkoxy indolin-3-one and indole alkaloids such as matemone **3**,² cephalinone **4**,³ and bromoaplysinopisin **6** (ref. 4) show intriguing bioactivities. Regarding matemone, it was isolated from the Indian Ocean sponge *Iotrochota purpurea* and its structure was elucidated in 2000. Matemone shows mild cytotoxicity against three cancer cell lines and marginal antibacterial activity against *Staphylococcus aureus*. We have been interested in the reactivity of α -aminoesters in umpolung reactions,⁵ and a facile indolin-3-one synthesis via aza-Brook rearrangement has been developed (Scheme 1).⁶

However, difficulties have been encountered regarding the substituents at the 2-position, *i.e.*, only 2,2-disubstituted derivatives **2** could be synthesized by our previously reported procedure (compound **2**, R = Ar or CO₂R').

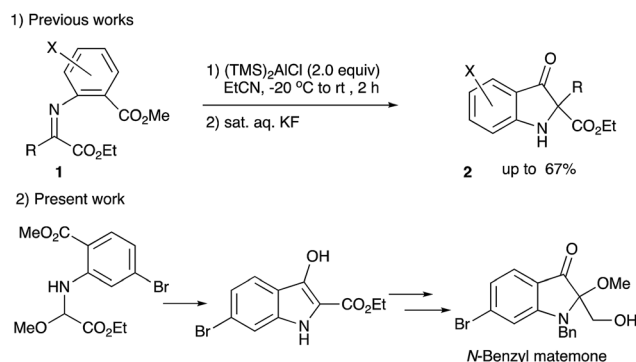
For the construction of matemone and related structures, a procedure using the aldimine of type **1** (R = H) is needed; in particular, a facile approach to 2-mono-substituted indolin-3-one, a key intermediate is needed. We have now found that methoxyglycine derivative **11** serves as a good precursor to the aldimine **10**, and 2-alkoxycarbonylindolin-3-one has been successfully synthesized using this particular imine precursor **11** (Scheme 2).

Results and discussion

For the synthesis of this particular aldimine **10**, we examined several approaches, such as direct imination of glyoxylate through dehydration and oxidation of glycine derivatives **9** (MnO₂, DDQ, NBS, *etc.*).⁷ However, none of the attempted procedures worked, and only complex mixtures were obtained (Scheme 3).

We finally found that the methoxyglycine derivative **11** could be isolated in good yield and served as a stable imine precursor.⁸ Cyclization reaction of this methoxy amino diester **11** was carried out with (TMS)₂AlCl,⁹ and the results are summarized in Table 1.

An initial examination using 2.0 equiv. of (TMS)₂AlCl in EtCN as a solvent led to the formation of the desired indolin-3-one **12** in only 15% yield (entry 1). Increasing the amount of (TMS)₂AlCl to 4.0 equiv. improved the yield to 56% (entry 2). However, the use of a large excess of the reagent decreased the yield (entry 3). Use of other solvents such as CH₂Cl₂, Et₂O, and THF was unsuccessful (entries 7, 9 and 10). Regarding the reaction temperature, the treatment of the starting



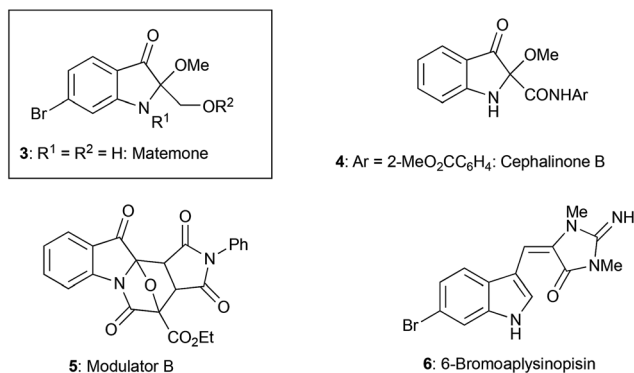
Scheme 1 A new approach to indolin-3-ones and the present *N*-benzyl matemone synthesis.

^aSchool of Energy Science and Engineering, Nanjing Tech University, Nanjing 211816, Jiangsu Province, China

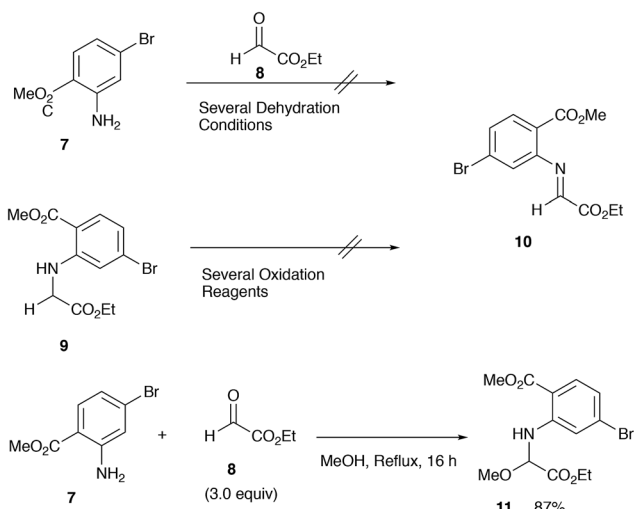
^bDepartment of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu, Mie 514-8507, Japan. E-mail: mshimizu@chem.mie-u.ac.jp

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ra02204j





Scheme 2 Bioactive compounds possessing 2-alkoxyindolin-3-one and a related structure.



Scheme 3 Attempted synthesis and a precursor **11** to the aldimine **10**.

material **11** with (TMS)₂AlCl at $-78\text{ }^{\circ}\text{C}$, followed by warming the whole mixture to room temperature recorded the best result (entry 2). The following Scheme 4 shows a possible reaction pathway.

First, the aldimine **10** is formed *in situ* by the treatment of the methoxyglycine derivative **11** with bis(trimethylsilyl) aluminum chloride. The formation of the imine **10** was detected by a direct injection EI-MS (m/z 313). This imine **10** would be attacked by the second equivalent of bis(trimethylsilyl)aluminum chloride to form the aluminum enolate **13** *via* an aza-Brook rearrangement.¹⁰ A subsequent Dieckmann cyclization followed by hydrolysis gives the indolin-3-one **12** (Scheme 5).

For the synthesis of matemone **3**, the introduction of the methoxy group at the C-2 position is needed. After several attempts using a series of oxidation reagents, we found that the oxidation of the silyl enol ether **15** with NBS in methanol gave satisfactory results.^{11,12} However, selective reduction at the ester moiety was not successful.¹³ Bis-reduction at the ketone and the ester moieties followed by oxidation at the benzylic alcohol was also failed to give only complex mixtures. We then changed the order of the functional group transformations, *i.e.*, reduction of the ester moiety, followed by the introduction of the methoxy group. This procedure worked well to give *N*-benzyl matemone **17** in high yield (Scheme 6).

This intriguing oxidation into the methoxy derivative **17** is explicable in terms of the formation of the iminium species **19**, which is attacked by methanol (Scheme 7).

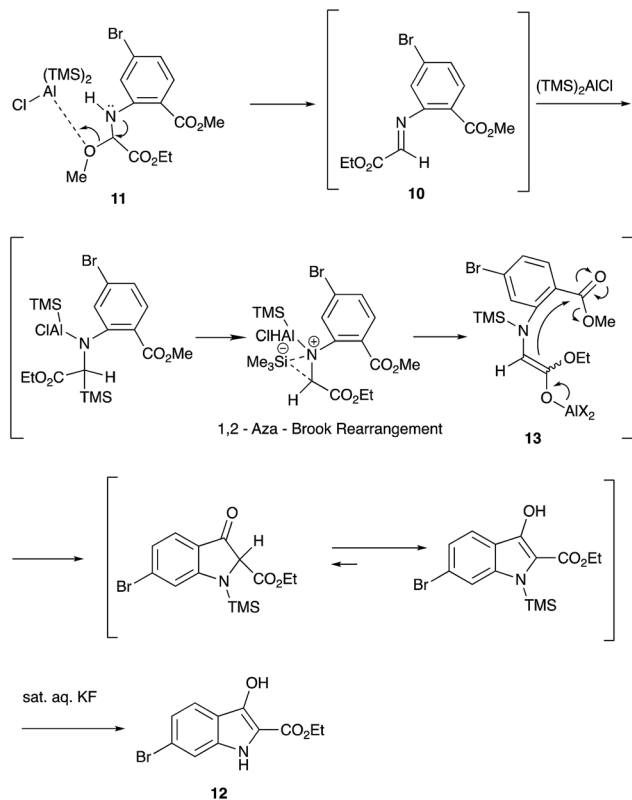
We next attempted removal of the benzyl group under a series of conditions (RSH/base, TMSI, Ca or Na/liq. NH₃, H₂/Pd or Pt, *etc.*). Although a small amount of matemone was detected by the mass spectra of the crude reaction mixtures, attempted isolation by silica gel chromatography was not

Table 1 Preparation of indolin-2-one **12**

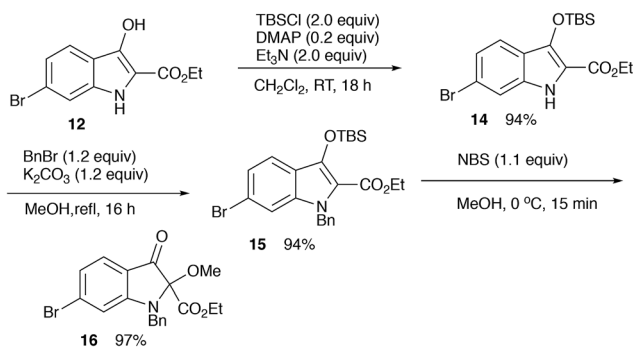
Entry	Temperature	(TMS) ₂ AlCl (equiv.)	Solvent	Yield of 12 ^a (%)
1	$-78\text{ }^{\circ}\text{C}$ to rt	2.0	EtCN	15
2	$-78\text{ }^{\circ}\text{C}$ to rt	4.0	EtCN	56
3	$-78\text{ }^{\circ}\text{C}$ to rt	6.0	EtCN	38
4	$-40\text{ }^{\circ}\text{C}$ to rt	4.0	EtCN	37
5	-78 to $0\text{ }^{\circ}\text{C}$	4.0	EtCN	36
6	-78 to $50\text{ }^{\circ}\text{C}$	4.0	EtCN	46
7	$-78\text{ }^{\circ}\text{C}$ to rt	4.0	CH ₂ Cl ₂	6
8	$-78\text{ }^{\circ}\text{C}$ to rt	4.0	EtCN/CH ₂ Cl ₂ (1 : 1)	50
9	$-78\text{ }^{\circ}\text{C}$ to rt	4.0	Et ₂ O	26
10	$-78\text{ }^{\circ}\text{C}$ to rt	4.0	THF	38

^a Isolated yield.



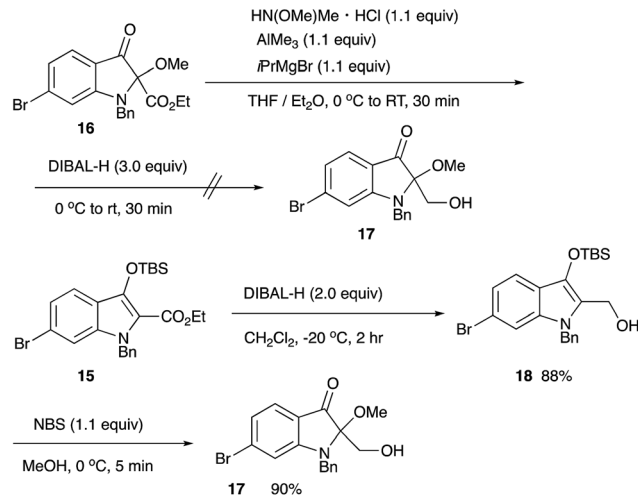


Scheme 4 A proposed reaction mechanism of the indolin-3-one **12** synthesis.

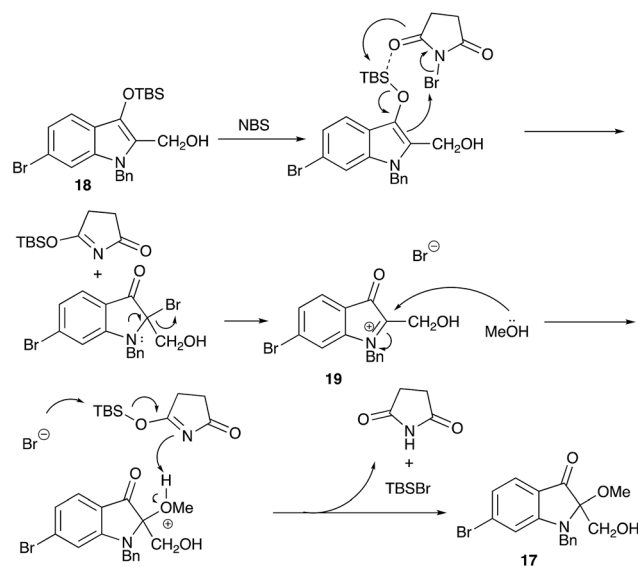


Scheme 5 Introduction of 2-methoxy group.

successful. We also attempted the isolation as an acetate form by treatment of the whole reaction mixtures with an excess AcCl /base. However, the acetate was not isolated in sufficient quantity. Studies indicated that unprotected matemone was unstable due to a solvent-induced polymerization process.² Therefore, matemone was immediately converted to the stable acetate derivative **3** ($\text{R}^2 = \text{Ac}$), and detailed spectroscopic analyses were carried out with the acetate derivative. We found that *N*-protected matemone **18** was also reasonably stable and would be subject to further functional group interconversions.¹⁴



Scheme 6 Synthesis of *N*-benzyl matemone.



Scheme 7 A proposed pathway for the introduction of a methoxy group.

Conclusions

We have found that the methoxyglycine derivative **11** is a good precursor to the aldimine **10** derived from glyoxylate, and the subsequent treatment of this particular methoxyglycine **11** with bis(trimethylsilyl)aluminum chloride provides 2-alkoxycarbonylindolin-3-ones. Further oxidation of the silyl enol ether prepared from the 2-alkoxycarbonylindolin-3-one undergoes a facile oxidation reaction with NBS in methanol to give the 2-methoxy derivatives in high yields. This procedure has proved to be effective for the synthesis of *N*-benzyl matemone as a reasonably stable derivative. Although we have not examined the bioactivity of the *N*-benzyl matemone **17** yet, we will submit it and other derivatives to bioassay in due course.



Experimental

General aspects

Infrared spectra were determined on a JASCO FT/IR-460 plus spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded with a JEOL ECX-400P, or a JEOL A-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL MS-700D spectrometer. Propionitrile (EtCN) and acetonitrile (MeCN) were distilled from phosphorus pentoxide and then from calcium hydride and stored over Molecular Sieves 4 Å. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride and stored over Molecular Sieves 4 Å. Toluene was dried over calcium chloride, distilled, and stored over Molecular Sieves 4 Å. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from benzophenone ketyl immediately before use or purified by Glass Contour Organic Solvent Purification System of Nikko Hansen & Co., Ltd. MeOH was heated at reflux over magnesium for 5 h, distilled, and stored over Molecular Sieves 3 Å. Purification of products was performed by column chromatography on silica gel (Kanto Silica Gel 60N) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254 or Wako Gel B-5F).

Methyl 4-bromo-2-[(2-ethoxy-1-methoxy-2-oxoethyl)amino]-benzoate (11)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and an argon balloon were placed methyl 2-amino-4-bromobenzoate (460.0 mg, 2.00 mmol) prepared according to the reported procedures,¹⁵ ethyl glyoxylate (1.23 mL, 6.00 mmol, 50% in toluene), and methanol (10.0 mL), respectively. The mixture was stirred at reflux for 16 h. After cooling to room temperature, the mixture was concentrated *in vacuo* to give a crude oil, which was purified by silica gel chromatography (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **11** (604.6 mg, 87%) as white crystals.

Yield 87% (604.6 mg); white crystals; mp 86–88 °C; R_f = 0.50 (*n*hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 1.36 (t, J = 7.3 Hz, 3H), 3.30 (s, 3H), 3.89 (s, 3H), 4.34 (q, J = 7.3 Hz, 2H), 5.26 (d, J = 6.4, 1H), 6.88–6.91 (m, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 8.98 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 51.6, 51.9, 62.2, 81.4, 110.9, 116.1, 120.7, 129.5, 132.7, 148.6, 167.9, 168.0; IR (neat) 3329, 2952, 1743, 1693, 1571, 1505, 1240, 1095, 1064, 769 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{13}\text{H}_{16}\text{BrNO}_5$ (M^+)⁺ 345.0212 found 345.0196.

General procedure: synthesis of ethyl 6-bromo-3-hydroxy-1H-indole-2-carboxylate (12) (Table 1)

Under an argon atmosphere, a solution of methyl 4-bromo-2-[(2-ethoxy-1-methoxy-2-oxoethyl)amino]-benzoate **11** (100.0 mg, 0.29 mmol) in EtCN (30.0 mL) was placed at –78 °C and to it was added a propionitrile solution (10 mL) of $(\text{TMS})_2\text{AlCl}$, which was prepared by mixing aluminum chloride (52.0 mg, 0.39 mmol) and $(\text{TMS})_3\text{Al}\cdot\text{Et}_2\text{O}$ (0.62 mL, 0.77 mmol, 1.25 M in Et_2O) at room temperature in another flask. After the mixture was stirred for 2 hours at room temperature, to it was added saturated aqueous potassium fluoride followed by a saturated aqueous

Rochelle's salt to quench the reaction. The whole mixture was extracted with ethyl acetate (10 mL \times 3). The combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo* to give a crude product. Purification by silica gel column chromatography (*n*hexane : ethyl acetate = 4 : 1 as an eluent) gave ethyl 6-bromo-3-hydroxy-1H-indole-2-carboxylate **12** (44.8 mg, 56%) as yellow crystals.

Yield 56% (44.8 mg); mp 167–169 °C; yellow crystals; R_f = 0.32 (*n*hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 1.41 (t, J = 6.9 Hz, 3H), 4.39 (q, J = 6.9 Hz, 2H), 7.04–7.06 (m, 1H), 7.48–7.49 (m, 1H), 7.58–7.60 (m, 1H), 8.79 (s, 1H), 10.70 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.2, 58.7, 108.1, 113.6, 115.5, 118.0, 119.9, 120.3, 134.2, 142.8, 160.9; IR (neat) 3341, 1672, 1608, 1583, 1308, 1240, 1141, 1104, 1018, 770 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{10}\text{BrNO}_3$ (M^+)⁺ 282.9844 found 282.9842.

Ethyl 6-bromo-3-[(*tert*-butyldimethylsilyloxy)-1H-indole-2-carboxylate (14)

In a 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and an argon balloon was placed ethyl 6-bromo-3-hydroxy-1H-indole-2-carboxylate (125.4 mg, 0.44 mmol), DMAP (0.09 mmol, 10.8 mg), triethylamine (0.12 mL, 0.88 mmol) and CH_2Cl_2 (10 mL), and to it was added a solution of TBDMSCl (0.88 mmol, 132.6 mg) in CH_2Cl_2 (4 mL). After the mixture was stirred for 16 h at room temperature, it was concentrated *in vacuo* to give a crude oil, which was purified by silica gel column chromatography (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **14** (165.0 mg, 94%) as white crystals.

Yield 94% (165.0 mg); white crystals; mp 135–136 °C; R_f = 0.54 (*n*hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 0.21 (s, 6H), 1.09 (s, 9H), 1.43 (t, J = 6.9, 3H), 4.44 (q, J = 7.3, 2H), 7.19–7.17 (m, 1H), 7.47–7.49 (m, 2H), 8.65 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ –4.2, 14.7, 18.3, 25.7, 60.7, 114.4, 114.7, 120.0, 120.6, 121.5, 123.0, 133.8, 139.7, 161.7; IR (neat) 3313, 2952, 1675, 1568, 1472, 1316, 1240, 1145, 851, 783 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{24}\text{BrNO}_3\text{Si}$ (M^+)⁺ 397.0709 found 397.0707.

Ethyl 1-benzyl-6-bromo-3-[(*tert*-butyldimethylsilyloxy)-1H-indole-2-carboxylate (15)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and an argon balloon was placed ethyl 6-bromo-3-[(*tert*-butyldimethylsilyloxy)-1H-indole-2-carboxylate (37.0 mg, 0.09 mmol), K_2CO_3 (15.2 mg, 0.11 mmol), benzyl bromide (0.01 mL) and MeCN (15 mL), and to it was added a solution of TBDMSCl (132.6 mg, 0.88 mmol) in MeCN (15 mL, 0.11 mmol). After the mixture was stirred for 16 h at reflux, it was filtered through a plug of cotton and concentrated *in vacuo* to give a crude oil, which was purified on silica gel TLC (*n*hexane : ethyl acetate = 5 : 1) to give the title compound **15** (165.0 mg, 94%) as a colourless oil.

Yield 94% (41.1 mg); colourless oil; R_f = 0.68 (*n*hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 0.18 (s, 6H), 1.08 (s, 9H), 1.28 (t, J = 7.1, 3H), 4.31 (q, J = 7.3, 2H), 5.65 (s, 2H), 6.95–6.97 (m, 2H), 7.16–7.25 (m, 4H), 7.43–7.44 (m, 1H), 7.49–7.51 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ –4.2, 14.5, 18.4, 25.8,



48.1, 60.3, 133.3, 116.0, 119.5, 120.1, 121.7, 123.1, 126.0, 127.1, 128.6, 137.4, 138.1, 141.1, 161.6; IR (neat) 2930, 2857, 1698, 1532, 1437, 1329, 1257, 1119, 830, 781 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{24}\text{H}_{30}\text{BrNO}_3\text{Si}$ (M^+) 487.1178 found 487.1163.

Ethyl 1-benzyl-6-bromo-2-methoxy-3-oxindoline-2-carboxylate (16)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and an argon balloon was placed NBS (59.1 mg, 0.33 mmol) and MeOH (6.0 mL), and to it was added a solution of ethyl 1-benzyl-6-bromo-3-[[*tert*-butyldimethylsilyl]oxy]-1*H*-indole-2-carboxylate (59.1 mg, 0.30 mmol) in MeOH (4 mL) at 0 °C. After the mixture was stirred for 15 min at 0 °C, to it was added saturated aqueous K_2CO_3 to quench the reaction. The whole mixture was extracted with ethyl acetate (50 mL \times 3). The combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo* to give a crude product, which was purified by silica gel column chromatography (*n*hexane : ethyl acetate = 4 : 1) to give the title compound **16** (117.6 mg, 97%) as a yellow oil.

Yield 97% (117.6 mg); yellow oil; R_f = 0.42 (*n*hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 1.09–1.13 (m, 3H), 3.27 (s, 3H), 3.96–4.10 (m, 2H), 4.47–4.60 (m, 2H), 6.90–7.05 (m, 2H), 7.29–7.37 (m, 5H), 7.44–7.48 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 46.6, 52.1, 32.5, 112.7, 118.0, 122.7, 126.0, 127.1, 127.7, 128.8, 134.2, 135.9, 161.4, 165.1, 193.5; IR (neat) 2930, 1721, 1605, 1465, 1311, 1260, 1148, 1098, 906, 699 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{16}\text{BrNO}_3$ (M^+) 403.0419 found 403.0414.

1-Benzyl-6-bromo-3-[[*tert*-butyldimethylsilyl]oxy]-1*H*-indol-2-yl] methanol (18)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and an argon balloon was placed a solution of ethyl 1-benzyl-6-bromo-3-[[*tert*-butyldimethylsilyl]oxy]-1*H*-indole-2-carboxylate (23.0 mg, 0.05 mmol) in CH_2Cl_2 (5.0 mL), and to it was added dropwise DIBAL-H (0.09 mL, 0.09 mmol, 10% in *n*-hexane) at –20 °C. After the mixture was stirred for 30 min at 0 °C, to it was added saturated aqueous Rochelle's salt to quench the reaction. The whole mixture was filtered through a Celite pad, and was extracted with CH_2Cl_2 (10 mL \times 3). The combined organic phases were dried over Na_2SO_4 , and concentrated *in vacuo* to give a crude product, which was purified on silica gel TLC (*n*hexane : ethyl acetate = 4 : 1) to give the title compound **18** (19.6 mg, 88%) as a yellow green oil.

Yield 88% (19.6 mg); yellow green oil; R_f = 0.31 (*n*hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 0.18 (s, 6H), 1.08 (s, 9H), 4.65 (d, J = 5.5 Hz, 2H), 5.38 (s, 2H), 6.92–6.94 (m, 2H), 7.14–7.42 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ –4.4, 18.2, 25.8, 46.8, 53.5, 112.4, 116.4, 119.8, 120.1, 122.2, 125.0, 125.7, 127.4, 128.8, 132.6, 135.3, 137.8; IR (neat) 3413, 2931, 2858, 1584, 1468, 1364, 1253, 1189, 1008, 829, 781 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{22}\text{H}_{28}\text{BrNO}_2\text{Si}$ (M^+) 445.1073 found 445.1073.

1-Benzyl-6-bromo-2-(hydroxymethyl)-2-methoxyindolin-3-one (17)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and an argon balloon was placed NBS (89.4 mg, 0.50 mmol) and MeOH (25.0 mL), and

to it was added a solution of 1-benzyl-6-bromo-3-[[*tert*-butyldimethylsilyl]oxy]-1*H*-indol-2-yl]methanol (203.8 mg, 0.46 mmol) in MeOH (4 mL) at 0 °C. After the mixture was stirred for 5 min at 0 °C, to it was added saturated aqueous K_2CO_3 to quench the reaction. The whole mixture was extracted with ethyl acetate (50 mL \times 3). The combined organic phases were dried over Na_2SO_4 , and concentrated *in vacuo* to give a crude product, which was purified on silica gel TLC (*n*hexane : ethyl acetate = 3 : 1) to give the title compound **17** (150.4 mg, 90%) as a yellow green oil.

Yield 90% (150.4 mg); R_f = 0.19 (*n*hexane : ethyl acetate = 4 : 1); ^1H NMR (400 MHz, CDCl_3) δ 3.12 (s, 3H), 3.65 (d, J = 0.0 Hz, 1H), 3.85–3.91 (m, 1H), 4.59 (s, 2H), 6.90–6.96 (m, 2H), 7.36–7.40 (m, 5H), 7.42–7.44 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 45.2, 52.0, 63.9, 112.0, 114.5, 121.9, 122.7, 125.5, 126.7, 127.8, 129.4, 149.8, 213.3; IR (neat) 3462, 2929, 1716, 1606, 1472, 1312, 1092, 1053, 937, 755 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{16}\text{BrNO}_3$ (M^+) 361.0314 found 361.0297.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research (B) and on Innovative Areas “Organic Synthesis Based on Reaction Integration. Development of New Methods and Creation of New Substances” from JSPS and MEXT.

Notes and references

- (a) T. Kawasaki, A. Ogawa, Y. Takashima and M. Sakamoto, *Tetrahedron Lett.*, 2003, **44**, 1591; (b) P. N. Wyrembak and A. D. Hamilton, *J. Am. Chem. Soc.*, 2009, **131**, 4566; (c) K. Okuma, N. Matsunaga, N. Nagahora, K. Shioji and Y. Yokomori, *Chem. Commun.*, 2010, 5822; (d) Y. Sun and R. Fan, *Chem. Commun.*, 2010, 6834; (e) W. Sun, L. Hong and R. Wang, *Chem.-Eur. J.*, 2011, **17**, 6030; (f) A. Wetzel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7354.
- (a) I. Carletti, B. Banaigs and P. Amade, *J. Nat. Prod.*, 2000, **63**, 981; (b) S.-S. Wen, Z.-F. Zhou, J.-A. Xiao, J. Li, H. Xiang and H. Yang, *New J. Chem.*, 2017, **41**, 11503; (c) For a review see, G. W. Gribble in *Progress in Heterocyclic Chemistry*, ed by G. W. Gribble and J. A. Joule, Pergamon, Kidlington, vol. 15, 2003, pp. 58–74.
- (a) P. S. Baran and E. J. Corey, *J. Am. Chem. Soc.*, 2002, **124**, 7904; (b) P.-L. Wu, Y.-L. Hsu and C.-W. Jao, *J. Nat. Prod.*, 2006, **69**, 1467; (c) L. A. Adams, M. W. N. Valente and R. M. Williams, *Tetrahedron*, 2006, **62**, 5195; (d) D. D. O'Rell, F. G. H. Lee and V. Boekelheide, *J. Am. Chem. Soc.*, 1972, **94**, 3205; (e) S. Tsukamoto, H. Umaoka, K. Yoshikawa, T. Ikeda and H. Hirota, *J. Nat. Prod.*, 2010, **73**, 1438; (f) A. Karadeolian and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2010, **49**, 1133; (g) A. Karadeolian and M. A. Kerr, *J. Org. Chem.*, 2010, **75**, 6830.



- 4 P. H. B. França, D. P. Barbosa, D. L. da Silva, Ê. A. N. Ribeiro, A. E. G. Santana, B. V. O. Santos, J. M. Barbosa-Filho, J. S. S. Quintans, R. S. S. Barreto, L. J. Quintans-Júnior and J. X. de Araújo-Júnior, *BioMed Res. Int.*, 2014, 1.
- 5 For *N*-alkylation to α -imino esters in our laboratory, see, (a) M. Shimizu and Y. Niwa, *Tetrahedron Lett.*, 2001, **42**, 2829; (b) Y. Niwa, K. Takayama and M. Shimizu, *Tetrahedron Lett.*, 2001, **42**, 5473; (c) Y. Niwa, K. Takayama and M. Shimizu, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1819; (d) Y. Niwa and M. Shimizu, *J. Am. Chem. Soc.*, 2003, **125**, 3720; (e) M. Shimizu, H. Itou and M. Miura, *J. Am. Chem. Soc.*, 2005, **127**, 3296; (f) M. Shimizu, *Pure Appl. Chem.*, 2006, **78**, 1867; (g) M. Shimizu, I. Hachiya and I. Mizota, *Chem. Commun.*, 2009, 874; (h) I. Mizota, K. Tanaka and M. Shimizu, *Tetrahedron Lett.*, 2012, **53**, 1847; (i) T. Nishi, I. Mizota and M. Shimizu, *Pure Appl. Chem.*, 2012, **84**, 2609; (j) S. Hata, T. Maeda and M. Shimizu, *Bull. Chem. Soc. Jpn.*, 2012, **85**, 1203; (k) M. Shimizu, D. Kurita and I. Mizota, *Asian J. Org. Chem.*, 2013, **2**, 208; (l) T. Sano, I. Mizota and M. Shimizu, *Chem. Lett.*, 2013, **42**, 995; (m) I. Mizota, Y. Matsuda, S. Kamimura, H. Tanaka and M. Shimizu, *Org. Lett.*, 2013, **15**, 4206; (n) H. Tanaka, I. Mizota and M. Shimizu, *Org. Lett.*, 2014, **16**, 2276; (o) K. Koyama, I. Mizota and M. Shimizu, *Pure Appl. Chem.*, 2014, **86**, 755; (p) M. Shimizu, M. Tateishi and I. Mizota, *Chem. Lett.*, 2014, **43**, 1752; (q) I. Mizota, T. Maeda and M. Shimizu, *Tetrahedron*, 2015, **71**, 5793; (r) I. Mizota and M. Shimizu, *Chem. Rec.*, 2016, **16**, 688; (s) T. Tanaka, I. Mizota, K. Umezū, A. Ito and M. Shimizu, *Heterocycles*, 2017, **95**, 830; (t) M. Kawanishi, I. Mizota, K. Aratake, H. Tanaka, K. Nakahama and M. Shimizu, *Bull. Chem. Soc. Jpn.*, 2017, **90**, 395; (u) I. Mizota, Y. Nakajima, A. Higashino and M. Shimizu, *Arabian J. Sci. Eng.*, 2017, **42**, 4249; (v) I. Mizota, C. Ueda, Y. Tesong, Y. Tsujimoto and M. Shimizu, *Org. Lett.*, 2018, **20**, 2291; (w) K. Nakahama, M. Suzuki, M. Ozako, I. Mizota and M. Shimizu, *Asian J. Org. Chem.*, 2018, **7**, 910.
- 6 M. Shimizu, Y. Takao, H. Katsurayama and I. Mizota, *Asian J. Org. Chem.*, 2013, **2**, 130.
- 7 (a) L. Blackburn and R. J. K. Taylor, *Org. Lett.*, 2001, **3**, 1637; (b) T. Mukaiyama, A. Kawana, Y. Fukuda and J. Matsuo, *Chem. Lett.*, 2001, 390; (c) K. C. Nicolaou, C. J. N. Mathison and T. Montagnon, *Angew. Chem.*, 2003, **115**, 4211; (d) M. S. Kwon, S. Kim, S. Park, W. Bosco, R. K. Chidrala and J. Park, *J. Org. Chem.*, 2009, **74**, 2877; (e) E. Zhang, H. Tian, S. Xu, X. Yu and Q. Xu, *Org. Lett.*, 2013, **15**, 2704; (f) R. Kumar, E. H. Gleißner, E. G. V. Tiu and Y. Yamakoshi, *Org. Lett.*, 2016, **18**, 184.
- 8 For the formation of hemiaminal ethers, see, (a) G. Li, F. R. Fronczek and J. C. Antilla, *J. Am. Chem. Soc.*, 2008, **130**, 12216; (b) K. Xu, Z. Wang, J. Zhang, L. Yu and J. Tan, *Org. Lett.*, 2015, **17**, 4476; (c) A. Beltran, E. Alvarez, M. M. Diaz-Requejo and P. J. Perez, *Adv. Synth. Catal.*, 2015, **357**, 2821; (d) M. Li, B. Luo, Q. Liu, Y. Hu, A. Ganesan, P. Huang and S. Wen, *Org. Lett.*, 2014, **16**, 10; (e) H. Yu and J. Shen, *Org. Lett.*, 2014, **16**, 3204; (f) For a related work, see, T. Kano, T. Yurino, D. Asakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 5532.
- 9 (a) M. A. Avery, W. K. M. Chong and C. Jennings-White, *J. Am. Chem. Soc.*, 1992, **114**, 974; (b) L. Ręsch, G. Altnau and W. H. Otto, *Angew. Chem., Int. Ed.*, 1981, **20**, 581.
- 10 (a) A. G. Brook and J. M. Duff, *J. Am. Chem. Soc.*, 1974, **96**, 4692; (b) T. Honda and M. Mori, *J. Org. Chem.*, 1996, **61**, 1196; (c) M. Suginome, T. Fukuda and Y. Ito, *J. Organomet. Chem.*, 2002, **643**, 508.
- 11 For the bromination of silyl enol ethers, see, (a) R. H. Reuss and A. Hassner, *J. Org. Chem.*, 1974, **39**, 1785; (b) L. Blanco, P. Amice and J. M. Conia, *Synthesis*, 1976, 194; (c) G. F. Hambly and T. H. Chan, *Tetrahedron Lett.*, 1986, 27, 2563.
- 12 For the oxidative formation of iminium salts from amino ketene silyl acetals, see, S. Hata, H. Koyama and M. Shimizu, *J. Org. Chem.*, 2011, **76**, 9670.
- 13 (a) J. L. Luche and A. L. Gemal, *J. Am. Chem. Soc.*, 1979, **101**, 5848; (b) M. T. Reetz, B. Wenderoth and R. Peter, *J. Chem. Soc., Chem. Commun.*, 1983, 406; (c) K. Maruoka, S. Saito, A. B. Concepcion and H. Yamamoto, *J. Am. Chem. Soc.*, 1993, **115**, 1183; (d) G. Bastug, S. Dierick, F. Lebreux and I. E. Mark, *Org. Lett.*, 2012, **14**, 1306; (e) H. Fujioka, K. Yahata, O. Kubo, Y. Sawama, T. Hamada and T. Maegawa, *Angew. Chem., Int. Ed.*, 2011, **50**, 12232; (f) F. J. Barrios, B. C. Springer and D. A. Colby, *Org. Lett.*, 2013, **15**, 3082.
- 14 Although we attempted to synthesize *N,O*-bis-TBS derivative of the compound **12** or its TIPS counterpart as a trialkylsilyl-protected derivative, upon treatment with an excess TBS-Cl, only the mono-*O*-TBS derivative **14** was isolated after work-up, whereas an excess TIPS-Cl treatment led to the recovery of the starting material **12**.
- 15 (a) P. Imming, I. Imhof and M. Zentgraf, *Synth. Commun.*, 2001, **31**, 3721; (b) B. D. Allison, V. K. Phuong, L. C. McAtee, M. Rosen, M. Morton, C. Prendergast, T. Barrett, G. Lagaud, J. Freedman, L. Li, X. Wu, H. Venkatesan, M. Pippel, C. Woods, M. C. Rizzolio, M. Hack, K. Hoey, X. Deng, C. King, N. P. Shankley and M. H. Rabinowitz, *J. Med. Chem.*, 2006, **49**, 6371.

