

HETEROCYCLES, Vol. 96, No. 3, 2018, pp. 490 - 500. © 2018 The Japan Institute of Heterocyclic Chemistry
 Received, 9th January, 2018, Accepted, 16th February, 2018, Published online, 27th February, 2018
 DOI: 10.3987/COM-18-13866

NAZAROV CYCLIZATION OF AN INDOLYL VINYL KETONE PROMOTED BY ACETYL CHLORIDE AND SODIUM IODIDE: FORMAL SYNTHESIS OF BRUCEOLLINE E

Takumi Abe*

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan. E-mail: abe-t@hoku-iryo-u.ac.jp

Abstract – An acetyl chloride/NaI-mediated Nazarov-type cyclization of an indolyl vinyl ketone was developed to give a cyclopenta[*b*]indole in high yield. An acyl Finkelstein reaction is a key feature for this unprecedented Nazarov-type cyclization.

Plants of the genus *Brucea* have been traditionally used in China for the treatment of various parasitic disease including malaria.¹ In 1994, Ohmoto *et al.* elucidated the structures of novel cyclopenta[*b*]indole alkaloids, bruceollines D (1) and E (2), cyclopenta[*b*]indole alkaloids, isolated from the root wood of *Brucea mollis* Wall (Figure 1).² Moreover, in 2011, Yu and co-workers isolated bruceollines H–K (3–6) from *Brucea mollis*.³

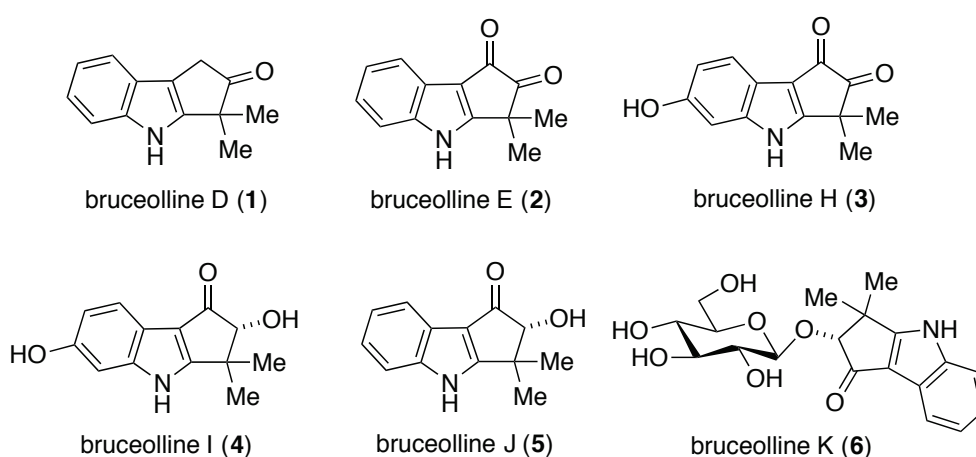
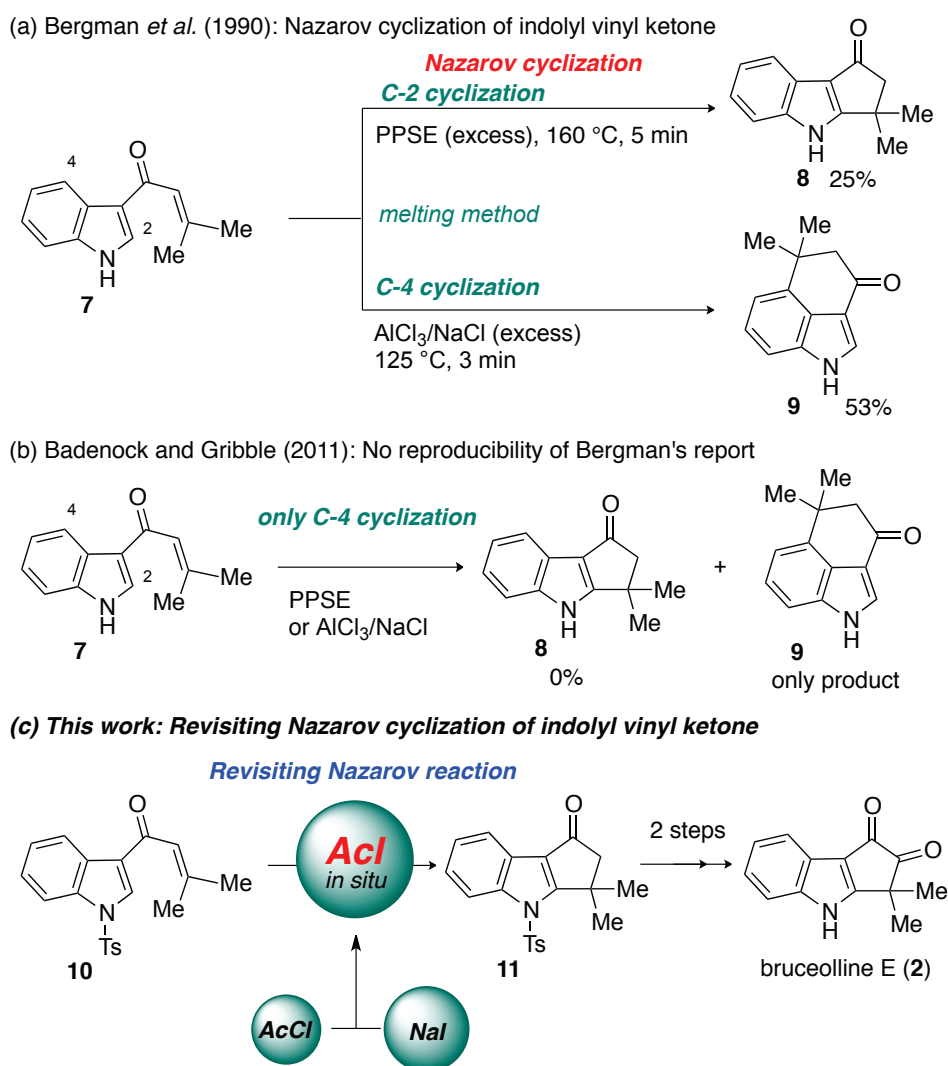


Figure 1. Cyclopenta[*b*]indole alkaloids bruceollines

In view of their pharmacological importance and intriguing structures, various synthetic methods for bruceollines have been reported in the past few years by the groups of Badenock,^{4,5} and Gribble,^{4,5} Dethe,⁶ and Occhiato.⁷ Prior to the isolation of bruceollines, pioneering studies by Bergman⁸ have reported the

synthesis of cyclopenta[*b*]indoles by Nazarov cyclization of 3-(3-methylbut-2-enyl)indole (**7**); specifically, the cyclization in phosphoric acid trimethylsilyl ester affords cyclopenta[*b*]indole **8** in 25% yield, and AlCl₃/NaCl-mediated cyclization produces benzo[*cd*]indole **9** in 53% yield (Scheme 1a). However, during their studies on the one-pot tandem acylation/Nazarov cyclization, Badenock and Gribble⁴ found that these transformations were not reproducible (Scheme 1b). Hence, a straightforward access to bruceollines by Nazarov cyclization has not yet been developed,⁹ and remains highly desirable.



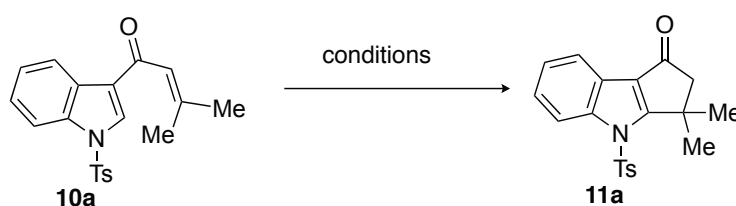
Scheme 1. Nazarov cyclizations of indolyl vinyl ketones

As part of our current interest in the synthesis of carbazole alkaloids by copper-catalyzed 6π -electrocyclization of trienes,¹⁰ we designed and developed a 4π -electrocyclization (Nazarov cyclization) approach to cyclopenta[*b*]indoles using acetyl iodide generated in situ from acetyl chloride and NaI (Scheme 1c). To the best of our knowledge, this is the first example of combining acetyl iodide-mediated Nazarov cyclization with cyclopenta[*b*]indole synthesis.

We began with our studies by revisiting previously reported conditions for the Nazarov cyclization (Table

1).¹¹ Firstly, a blank experiment confirmed that the thermal cyclization of indolyl vinyl ketone **10a** did not proceed (entry 1). Then, a variety of Lewis acids, namely, FeCl₃,^{11a} ZnCl₂,^{11b} In(OTf)₃,^{11c} Cu(OTf)₂,^{11d} (CuOTf)₂•toluene,^{11e} BF₃•OEt₂,^{11f} AlCl₃,^{11g} TFA,^{11h} and TFAA¹¹ⁱ (entries 2–10), were examined, and only TFAA provided the desired cyclopenta[*b*]indole **11a** albeit in quite low yield and accompanied by *N*-Ts indole byproduct (entry 10–12). This is in disagreement with the results of the tandem acylation/Nazarov cyclization reported by Badenock.⁴ *N*-Ts indole is presumably formed via retro-Friedel–Crafts acylation. Thus, to achieve the desired reactivity, this side reaction must be suppressed.

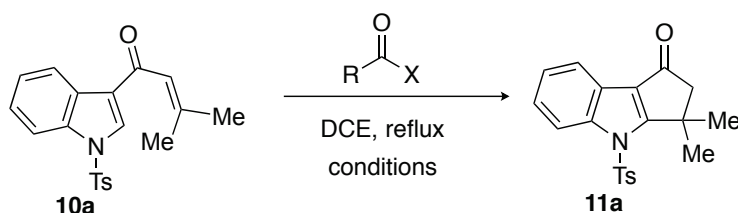
Table 1. Nazarov cyclizations of indolyl vinyl ketone 10a^a



entry	promoter	equivalents	solvent	temp °C	yield ^b
1	---	---	DCE	100	nr
2	FeCl ₃	2	DCE	100	0
3	ZnCl ₂	2	DCE	100	0
4	In(OTf) ₃	2	DCE	100	0
5	Cu(OTf) ₂	2	DCE	100	0
6	Sc(OTf) ₃	2	DCE	100	0
7	BF ₃ •OEt ₂	5	CH ₂ Cl ₂	25	0
8	AlCl ₃	5	CH ₂ Cl ₂	25	0
9	TFA	5	DCE	100	trace
10	TFAA	3	DCE	100	5 ^c
11	TFAA	5	DCE	100	7 ^c
12	TFAA	3	CCl ₄	100	trace ^c

^a **10a** (0.5 mmol) and Lewis acid (X mmol) in solvent (10 mL). ^b Isolated yields. ^c *N*-Ts indole was detected.

In order to overcome this limitation, the conditions of the Nazarov cyclization reaction were optimized. A similar problem was encountered by Magnus and co-workers,¹² who reported that the use of acetyl bromide as a promoter of the Nazarov cyclization, affords cyclized products in high yields although a variety of Lewis acid could not promote the Nazarov cyclization. On the basis of this report, various acetyl halides were screened. When acetyl chloride was used, trace amounts of **11a** were detected (entry 1). Pleasingly, in the presence of acetyl bromide or iodide, **11a** was obtained in 70% and 40% yield, respectively, and no retro-Friedel–Crafts acylation product was obtained (entries 2 and 3). Changing the acyl halide to chloroacetyl chloride failed to improve the yield (entry 4), and the best result was obtained with bromoacetyl bromide (entry 5, 75% yield). These results demonstrated that the halide plays an important role in this transformation.¹³

Table 2. Screening of acid halides and salts^a

entry	acid halide	equivalents	salt	equivalents	yield ^b
1	AcCl	3	---	---	trace
2	AcBr	3	---	---	70
3	AcI	3	---	---	40
4	ClCH ₂ COCl	3	---	---	0
5	BrCH ₂ COBr	3	---	---	75
6	AcCl	3	NaBr	3	78
7 ^c	AcCl	3	NaI	3	86
8	AcCl	3	KI	3	80
9	AcCl	3	TBAI ^d	3	45
10	AcCl	2	NaI	2	81
11	AcCl	1.1	NaI	1.1	62
12	AcBr	3	NaI	3	54

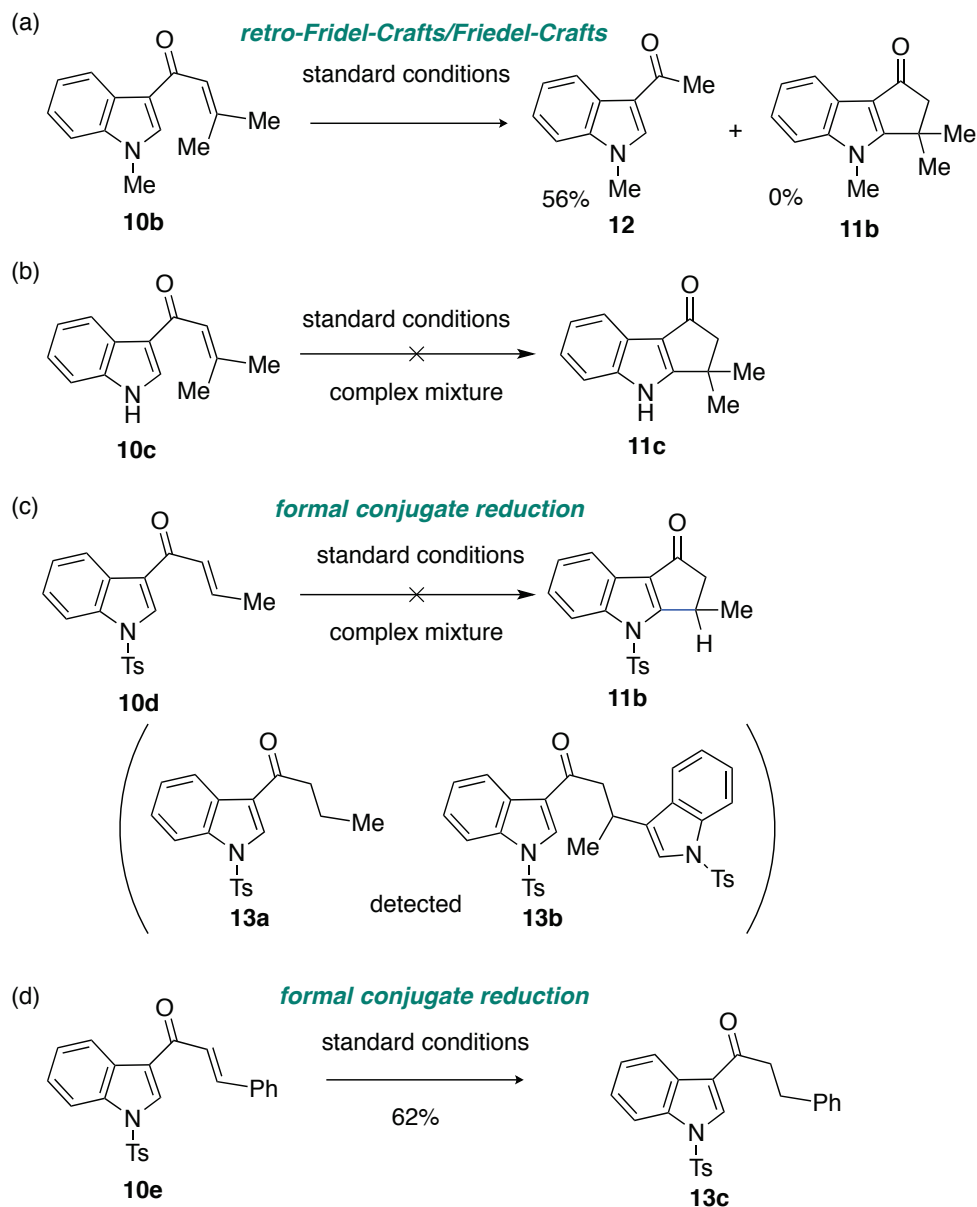
^a **10a** (0.5 mmol), acid halide (X mmol), and salt (X mmol) in DCE (10 mL). ^b Isolated yields. ^c **10a** (5 mmol), acetyl chloride (15 mmol), and NaI (15 mmol) in DCE (80 mL). ^d TBAI: Tetrabutylammonium iodide.

Hence, the Nazarov cyclization of **10a** was achieved by a modified Magnus method. However, this reaction was not amenable to gram-scale operations due to difficult handling and its instability to water and air. We envisioned that the combination of acetyl chloride and a metal halide¹⁴ could be an alternative easy-to-handle promoter; notably, an acyl Finkelstein reaction has not yet been reported.¹⁴

Thus, the effects of metal halides on the reaction of **10a** was investigated. Remarkably, the yield was improved by addition of metal halides to the reaction with acetyl chloride (entries 6–12). In particular, the combination of acetyl chloride and NaI, which produced AcI and NaCl in situ, showed the highest reactivity (entry 7). It should be highlighted that this acyl Finkelstein reaction was applicable to the gram-scale synthesis of cyclopenta[*b*]indole **11a** in 86% yield. Among halides, TBAI resulted in the dropped yield (entry 9). This may be a reason that the acetyl chloride/TBAI system affords AcI and tetrabutylammonium chloride in situ, which is more soluble in DCE than NaCl, and the acyl Finkelstein reaction is slow.

Next, various indolyl vinyl ketones were subjected to the optimized reaction conditions to explore the scope and limitations of this transformation (Scheme 2). The reaction of **10b** bearing a methyl group on the indole nitrogen failed to produce the desired product **11b**, and only 3-acetylidole **12** was obtained in 56% yield (Scheme 2a), presumably by retro-Friedel–Crafts/Friedel–Crafts acylation. On the other hand, the reaction of unprotected substrate was unsuccessful (Scheme 2b). Moreover, disubstituted alkene **10d**

gave the unexpected product **13a** by formal conjugate reduction and 1,4-adduct **13b** (Scheme 2c). Substrate **10e** also gave the corresponding conjugate reduction product **13c** in 62% yield (Scheme 2d). In 2016, Martin and co-workers reported that alkyl bromides act as mild hydride sources in the presence of Ni catalyst.¹⁵

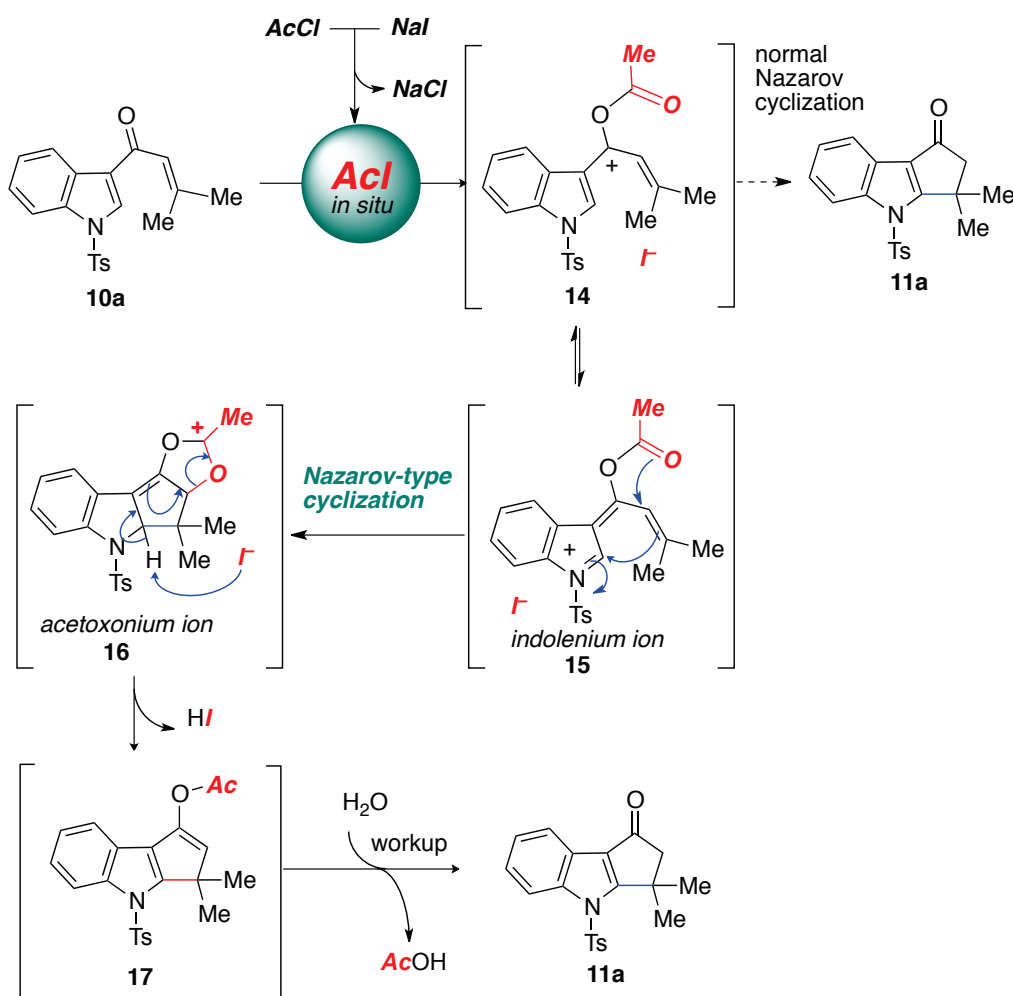


Scheme 2. Limitations of the Nazarov cyclization

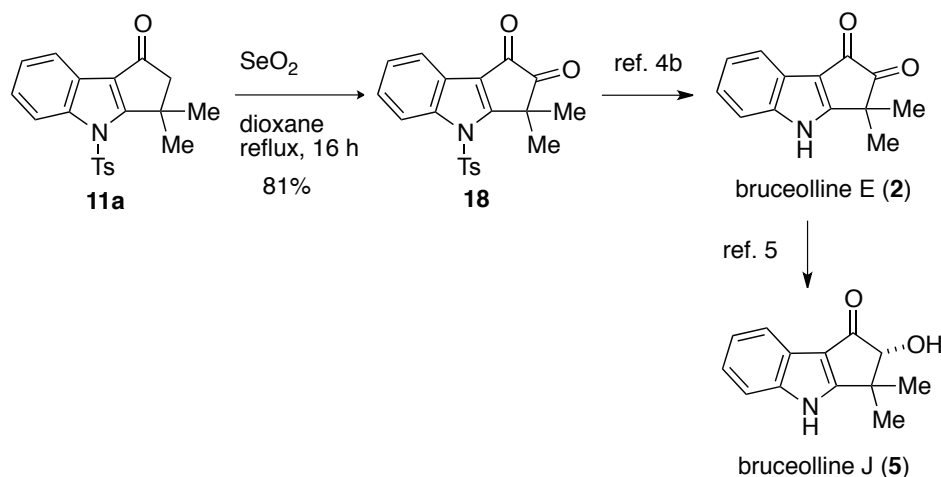
We therefore assume that, in our system, DCE exchanged its chlorine atoms with iodine, and then acted as a hydride source. To the best of our knowledge, conjugate reductions using acetyl iodide in DCE have not been reported so far. In preliminary experiments, chalcone was not amenable to conjugate reduction under our standard conditions. Thus, it is reasonable to assume that this transformation proceeds via intermediate **11b**, which undergoes a reductive ring-opening reaction with the hydride from

dichloroethane.¹⁶ The mechanistic details are still unclear and under investigation. These results indicate that this cyclization relies on a delicate balance between electron density of the substrate and olefin substitution pattern.

On the basis of the experimental results and previous reports, plausible reaction pathways are proposed in Scheme 3.¹² Acetylation of **10a** by the in situ formed acetyl iodide affords carbocation **14**, which then undergoes Nazarov cyclization to provide **11a**. In another pathway, the Nazarov-type cyclization proceeds through a stepwise mechanism. Carbocation **14** gives indolenium ion **15**, which cyclizes to form acetoxonium ion **16**. Subsequent release of HI gives acetate **17** and final aqueous workup provides the product **11a** by release of AcOH. The use of acetyl iodide was suspected to be crucial for the reaction: its higher reactivity compared to acetyl chloride and bromide results in a higher rate of the key acetylation step, promoting the formation of initial intermediate **14**. This could also explain why the in situ formed acetyl iodide was the most effective promoter of this Nazarov cyclization, in strikingly contrast with the classical Nazarov cyclization typically promoted by a Lewis acid.



Scheme 3. Plausible reaction pathway



Scheme 4. Formal synthesis of bruceolline E (2)

The prepared cyclopenta[*b*]indole **11a** was used to complete the formal synthesis of bruceolline E (**2**). SeO₂-mediated oxidation of **11a** afforded **18** in 81% yield. Since **18** was transformed into bruceolline E (**2**) by hydrolysis of Ts group, this completed the formal synthesis of bruceolline E (**2**).

In conclusion, we have developed an unprecedented Nazarov-type cyclization mediated by acetyl iodide formed in situ by salt metathesis between acetyl chloride and NaI to afford a cyclopenta[*b*]indole, which served as an intermediate for the synthesis of bruceolline E. The protocol using the acyl Finkelstein reaction is highly tunable for its reactivity. Further studies on extending the use of this transformation to the synthesis of cyclopenta[*b*]indole alkaloids are underway in our laboratory.

EXPERIMENTAL

Melting points were recorded with a Yamato MP21 and are uncorrected. High-resolution MS spectra were recorded with a JEOL JMS-T100LP mass spectrometers. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer. The NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference. Column chromatography and Flash column chromatography were performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd.).

General procedure for the synthesis of ketones 10a, 10b, 10c, 10d, and 10e:

TFAA (20 mmol) was added to a mixture of indoles (4 mmol) and α,β -unsaturated carboxylic acids (10 mmol) in DCE (50 mL) at room temperature and reflux for 16 h. The mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography with hexane/AcOEt (5/1) to give **10**.

3-Methyl-1-(1-tosyl-1H-indol-3-yl)but-2-en-1-one (10a).

1.05 g, 74%. Colorless viscous oil. IR (CHCl₃): 1654, 1613 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.98 (s, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 6.66 (s, 1H), 7.17 (d, *J* = 7.4 Hz, 2H), 7.28-7.35 (m, 2H), 7.80 (d, *J* = 8.6 Hz, 2H),

7.93 (d, $J = 7.5$ Hz, 1H), 8.26 (s, 1H), 8.42 (d, $J = 7.5$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3) δ : 21.2, 21.6, 28.0, 113.2, 121.7, 123.2, 123.4, 124.7, 125.7, 127.2, 128.4, 130.3, 131.0, 134.6, 135.0, 145.9, 156.2, 186.7. HR-ESI-MS m/z : Calcd for $\text{C}_{20}\text{H}_{20}\text{NSO}_3$ [(M+H) $^+$]: 354.1164. Found 354.1167.

3-Methyl-1-(1-methyl-1H-indol-3-yl)but-2-en-1-one (10b).

557 mg, 65%. Colorless oil. IR (CHCl_3): 1647, 1609 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.98 (s, 3H), 2.23 (s, 3H), 3.83 (s, 3H), 6.58 (t, $J = 1.2$ Hz, 1H), 7.29-7.34 (m, 3H), 7.72 (s, 1H), 8.43-8.45 (m 1H). $^{13}\text{C-NMR}$ (CDCl_3) δ : 20.9, 27.8, 33.6, 109.7, 118.3, 122.6, 122.7, 122.8, 123.4, 126.8, 135.3, 137.6, 152.6, 187.5. HR-ESI-MS m/z : Calcd for $\text{C}_{14}\text{H}_{15}\text{NNaO}$ [(M+Na) $^+$]: 236.1051. Found 236.1051.

1-(1H-Indol-3-yl)-3-methylbut-2-en-1-one (10c).

556 mg, 70%. Colorless viscous oil. IR (CHCl_3): 3462, 1649, 1607 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 1.92 (s, 3H), 2.15 (s, 3H), 6.79 (s, 1H), 7.12-7.17 (m, 2H), 7.41 (d, $J = 7.5$ Hz, 1H), 8.25 (d, $J = 8.0$ Hz, 1H), 8.30 (d, $J = 3.5$ Hz, 1H), 11.86 (br s, 1H). $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$) δ : 20.9, 27.8, 112.5, 118.8, 122.0, 122.2, 122.9, 123.3, 126.4, 133.5, 137.2, 151.6, 186.7. HR-ESI-MS m/z : Calcd for $\text{C}_{13}\text{H}_{13}\text{NNaO}$ [(M+Na) $^+$]: 222.0895. Found 222.0893.

(E)-1-(1-Tosyl-1H-indol-3-yl)but-2-en-1-one (10d).

899 mg, 66%. Colorless oil. IR (CHCl_3): 1667, 1608 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.01 (dd, $J = 2.6, 6.9$ Hz, 3H), 2.35 (s, 3H), 6.79 (d, $J = 14.9$ Hz, 1H), 7.09 (dd, $J = 7.5, 15.5$ Hz, 1H), 7.26 (d, $J = 8.1$ Hz, 2H), 7.32-7.38 (m, 2H), 7.82 (d, $J = 8.1$ Hz, 2H), 7.92 (d, $J = 8.1$ Hz, 1H), 8.23 (s, 1H), 8.37 (d, $J = 7.5$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3) δ : 18.5, 21.7, 113.1, 121.8, 123.4, 124.9, 125.9, 127.2, 128.2, 128.3, 130.3, 131.6, 134.6, 135.1, 143.3, 146.0, 185.4. HR-ESI-MS m/z : Calcd for $\text{C}_{19}\text{H}_{17}\text{NNaSO}_3$ [(M+Na) $^+$]: 362.0827. Found 362.0822.

(E)-3-Phenyl-1-(1-tosyl-1H-indol-3-yl)prop-2-en-1-one (10e).

1.27 g, 79%. Colorless viscous oil. IR (CHCl_3): 1659, 1599 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.34 (s, 3H), 7.24-7.26 (m, 2H), 7.35-7.40 (m, 2H), 7.41-7.45 (m, 4H), 7.67-7.69 (m, 2H), 7.84 (d, $J = 6.3$ Hz, 1H), 7.85 (d, $J = 8.6$ Hz, 2H), 7.96 (dd, $J = 1.2, 8.1$ Hz, 1H), 8.41 (s, 1H), 8.45 (dd, $J = 1.7, 6.9$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3) δ : 21.7, 113.2, 122.4, 122.9, 123.5, 125.0, 126.0, 127.3, 128.2, 128.6, 129.1, 130.4, 130.6, 131.8, 134.6, 134.8, 135.1, 143.3, 146.1, 185.1. HR-ESI-MS m/z : Calcd for $\text{C}_{24}\text{H}_{20}\text{NSO}_3$ [(M+H) $^+$]: 402.1164. Found 402.1179.

3,3-Dimethyl-4-tosyl-3,4-dihydrocyclopenta[*b*]indol-1(2H)-one (11a).

NaI (2.25 g, 15 mmol) and AcCl (1.18 g, 15 mmol) was successively added to a solution of **10a** (1.77 g, 5 mmol) in DCE (80 mL) at room temperature and reflux for 16 h. The mixture was concentrated in vacuo, and the residue was diluted with H_2O (60 mL). The mixture was extracted with AcOEt (3 x 100 mL), washed with brine, and dried over MgSO_4 . The solvent was removed, and the residue was purified by

silica gel column chromatography and purified by silica gel column chromatography with hexane/AcOEt (5/1) to give **11a** (1.52 g, 86%) as yellow solids.

1.52 g, 86%. Yellow solids. Mp 125-127 °C (EtOH). IR (CHCl₃): 1694, 1670 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.76 (s, 6H), 2.37 (s, 3H), 2.93 (s, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.29-7.34 (m, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.88-7.89 (m, 1H), 7.93-7.96 (m, 1H). ¹³C-NMR (CDCl₃) δ: 21.7, 27.9, 40.4, 59.8, 114.9, 121.2, 121.8, 124.9, 125.5, 125.9, 126.9, 130.2, 135.6, 141.1, 145.8, 172.4, 195.9. HR-ESI-MS *m/z*: Calcd for C₂₀H₂₀NSO₃ [(M+H)⁺]: 354.1164. Found 354.1159.

1-(1-Methyl-1*H*-indol-3-yl)ethan-1-one (12).

NaI (450 mg, 3 mmol) and AcCl (236 mg, 3 mmol) was successively added to a solution of **10b** (213 mg, 1 mmol) in DCE (30 mL) at room temperature and reflux for 16 h. The mixture was concentrated in vacuo, and the residue was diluted with H₂O (30 mL). The mixture was extracted with AcOEt (3 x 50 mL), washed with brine, and dried over MgSO₄. The solvent was removed, and the residue was purified by silica gel column chromatography and purified by silica gel column chromatography with hexane/AcOEt (5/1) to give **12** (97 mg, 56%) as yellow oil.

97 mg, 56%. Yellow oil. IR (CHCl₃): 1684, 1670 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.57 (s, 3H), 3.86 (s, 3H), 7.32-7.35 (m, 3H), 7.77 (s, 1H), 8.33-8.35 (m, 1H). ¹³C-NMR (CDCl₃) δ: 27.1, 33.8, 109.9, 116.7, 122.7, 123.1, 123.7, 126.2, 136.9, 137.7, 194.7. HR-ESI-MS *m/z*: Calcd for C₁₁H₁₂NO [(M+H)⁺]: 174.0919. Found 174.0923.

3-Phenyl-1-(1-tosyl-1*H*-indol-3-yl)propan-1-one (13c).

NaI (450 mg, 3 mmol) and AcCl (236 mg, 3 mmol) was successively added to a solution of **10e** (402 mg, 1 mmol) in DCE (30 mL) at room temperature and reflux for 16 h. The mixture was concentrated in vacuo, and the residue was diluted with H₂O (30 mL). The mixture was extracted with AcOEt (3 x 50 mL), washed with brine, and dried over MgSO₄. The solvent was removed, and the residue was purified by silica gel column chromatography and purified by silica gel column chromatography with hexane/AcOEt (5/1) to give **13b** (250 mg, 62%) as colorless oil.

250 mg, 62%. Colorless oil. IR (CHCl₃): 1668, 1599 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.36 (s, 3H), 3.09 (t, *J* = 8.0 Hz, 2H), 3.23 (t, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.25-7.27 (m, 4H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.32-7.38 (m, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.16 (s, 1H), 8.33 (d, *J* = 6.9 Hz, 1H). ¹³C-NMR (CDCl₃) δ: 21.7, 30.3, 41.9, 113.2, 121.2, 123.2, 124.9, 125.8, 126.3, 127.2, 127.7, 128.5, 128.7, 130.3, 131.8, 134.6, 135.0, 141.2, 146.0, 195.2. HR-ESI-MS *m/z*: Calcd for C₂₄H₂₂NSO₃ [(M+H)⁺]: 404.1320. Found 404.1335.

3,3-Dimethyl-4-tosyl-3,4-dihydrocyclopenta[*b*]indole-1,2-dione (18).

SeO₂ (555 mg, 5 mmol) was added to a solution of **11a** (353 mg, 1 mmol) in 1,4-dioxane (10 mL) at room temperature and reflux for 16 h. The mixture was concentrated in vacuo, and the residue was purified by

silica gel column chromatography with hexane/AcOEt (5/1) to give **18** (298 mg, 81%) as yellow solids. 298 mg, 81%. Yellow solids. Mp 160-162 °C (EtOH). IR (CHCl₃): 1660, 1600 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.76 (s, 6H), 2.40 (s, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.45 (td, *J* = 1.8, 7.5 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.98 (d, *J* = 8.6 Hz, 1H), 8.02 (dd, *J* = 1.2, 7.5 Hz, 1H). ¹³C-NMR (CDCl₃) δ: 21.8, 23.4, 46.5, 114.8, 121.9, 122.3, 125.9, 127.2, 127.3, 127.6, 130.5, 134.6, 138.6, 146.8, 170.2, 177.8, 204.2. HR-ESI-MS *m/z*: Calcd for C₂₀H₁₈NSO₄ [(M+H)⁺]: 368.0957. Found 368.0942.

ACKNOWLEDGEMENTS

This work was financially supported by JSPS (KAKENHI Grant Number 16K18849 for T.A.) as a Grant-in-Aid for Young Scientists (B).

REFERENCES AND NOTES

1. Z. Guo, S. Vangapandu, R. W. Sindelar, L. A. Walker, and R. D. Sindelar, *Curr. Med. Chem.*, 2005, **12**, 173.
2. Y. Ouyang, K. Koike, and T. Ohmoto, *Phytochemistry*, 1994, **37**, 575.
3. H. Chen, J. Bai, Z.-F. Fang, S.-S. Yu, S.-G. Ma, S. Xu, Y. Li, J. Qu, J.-H. Ren, L. Li, Y.-K. Si, and X.-G. Chen, *J. Nat. Prod.*, 2011, **74**, 2438.
4. (a) J. A. Jordan, G. W. Gribble, and J. C. Badenock, *Tetrahedron Lett.*, 2011, **52**, 6772; (b) E. Li, C. Li, J. Wang, J. Wang, L. Dong, X. Guo, C. Song, and J. Chang, *Tetrahedron*, 2014, **70**, 874.
5. J. M. Lopchuk, I. L. Green, J. C. Badenock, and G. W. Gribble, *Org. Lett.*, 2013, **15**, 4485.
6. D. H. Dethe and V. Kumar B, *Org. Chem. Front.*, 2015, **2**, 548.
7. (a) D. Scarpi, M. Petrović, B. Fiser, E. Gómez-Bengoa, and E. G. Occhiato, *Org. Lett.*, 2016, **18**, 3922; (b) D. Scarpi, C. Faggi, and E. G. Occhiato, *J. Nat. Prod.*, 2017, **80**, 2384.
8. J. Bergman, L. Venemalm, and L. Gogoll, *Tetrahedron*, 1990, **46**, 6067.
9. Recent reviews on the Nazarov reactions, see: (a) N. Jana and T. G. Driver, *Org. Biomol. Chem.*, 2015, **13**, 9720; (b) N. S. Sheikh, *Org. Biomol. Chem.*, 2015, **13**, 10774; (c) M. A. Tius, *Chem. Soc. Rev.*, 2014, **43**, 2979; (d) M. J. Di Grandi, *Org. Biomol. Chem.*, 2014, **12**, 5331; (e) W. T. Spencer III, T. Vaidya, and A. J. Frontier, *Eur. J. Org. Chem.*, 2013, **2013**, 3621.
10. (a) T. Itoh, T. Abe, T. Choshi, T. Nishiyama, R. Yanada, and M. Ishikura, *Eur. J. Org. Chem.*, 2016, **2016**, 2290; (b) T. Abe, T. Ikeda, T. Choshi, S. Hibino, N. Hatae, E. Toyota, R. Yanada, and M. Ishikura, *Eur. J. Org. Chem.*, 2012, **2012**, 5018; (c) T. Abe, T. Ikeda, R. Yanada, and M. Ishikura, *Org. Lett.*, 2011, **13**, 3356.
11. For selected examples, see: (a) K. Yaji and M. Shindo, *Tetrahedron*, 2010, **66**, 9808; (b) G.-P. Wang, M.-Q. Chen, S.-F. Zhu, and Q.-L. Zhou, *Chem. Sci.*, 2017, **8**, 7197; (c) D. V. Patil, L. H. Phun, and S.

- France, *Org. Lett.*, 2010, **12**, 5684; (d) W. He, X. Sun, and A. J. Frontier, *J. Am. Chem. Soc.*, 2003, **125**, 14278; (e) J. A. Malona, J. M. Colbourne, and A. J. Frontier, *Org. Lett.*, 2006, **8**, 5661; (f) P. Chiu and S. Li, *Org. Lett.*, 2004, **6**, 613; (g) G. Liang, S. N. Gradl, and D. Trauner, *Org. Lett.*, 2003, **5**, 4931; (h) Y.-K. Wu and F. G. West, *J. Org. Chem.*, 2010, **75**, 5410; (i) C. Song, D. W. Knight, and M. A. Whatton, *Org. Lett.*, 2006, **8**, 163; For a review on the catalytic Nazarov cyclization, see: (j) T. Vaidya, R. Eisenberg, and A. J. Frontier, *ChemCatChem*, 2011, **3**, 1531; For a review on the asymmetric Nazarov cyclization, see: (k) N. Shimada, C. Stewart, and M. A. Tius, *Tetrahedron*, 2011, **67**, 5851.
12. For an example of the Nazarov-type cyclization promoted by acetyl bromide, see: P. Magnus, W. A. Freund, E. J. Moorhead, and T. Rainey, *J. Am. Chem. Soc.*, 2012, **134**, 6140.
13. J. M. Briody and D. P. N. Satchell, *J. Chem. Soc.*, 1964, 3724.
14. (a) H. Finkelstein, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 1528; (b) A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 14844; (c) S. G. Newman, J. K. Howell, N. Nicolaus, and M. Lautens, *J. Am. Chem. Soc.*, 2011, **133**, 14916; (d) A. A. Cant, R. Bhalla, S. L. Pimlott, and A. Sutherland, *Chem. Commun.*, 2012, **48**, 3993; (e) J. Serra, C. J. Whiteoak, F. Acuña-Parés, M. Font, J. M. Luis, J. Lloret-Fillol, and X. Ribas, *J. Am. Chem. Soc.*, 2015, **137**, 13389; (f) A. Nitelet and G. Evano, *Org. Lett.*, 2016, **18**, 1904; (g) D. A. Petrone, I. Franzoni, J. Ye, J. F. Rodríguez, A. I. Poblador-Bahamonde, and M. Lautens, *J. Am. Chem. Soc.*, 2017, **139**, 3546.
15. (a) X. Wang, M. Nakajima, E. Serrano, and R. Martin, *J. Am. Chem. Soc.*, 2016, **138**, 15531; (b) F. Chen, K. Chen, Y. Zhang, Y. He, Y.-M. Wang, and S. Zhu, *J. Am. Chem. Soc.*, 2017, **139**, 13929.