HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 787-798. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 25th August, 2016, Accepted, 30th September, 2016, Published online, 1st November, 2016
DOI: 10.3987/COM-16-S(S)42

TRIPHOSGENE-MEDIATED CHLOROLACTAMIZATION AND AMINOLACTAMIZATION OF HOMOALLYLIC AMINES

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Abstract – Two types of aminocarbonylation reaction of homoallylic amines have been developed. The treatment of homoallylic amines with triphosgene in dichloromethane led to formation of the corresponding β-chlorolactams via Prins-type cyclization of a carbamoyl chloride intermediate. For the reaction in acetonitrile, β-aminolactams were obtained via sequential Prins-type cyclization and Ritter-type reactions.

INTRODUCTION

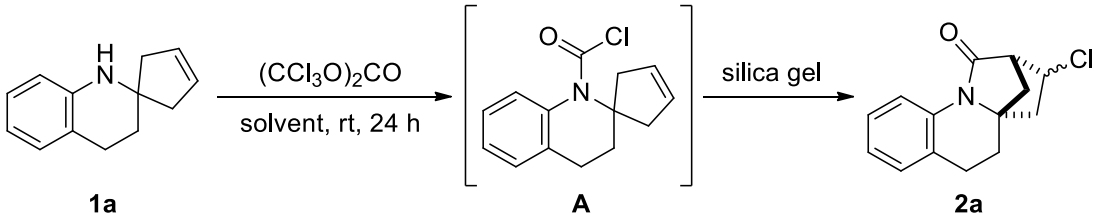
Lactams are useful heterocyclic motifs found in a wide variety of natural products[1] and bioactive compounds.[2] Among them, β-chlorolactam has gained attention because the chloro moiety can be converted into various substituents.[3] Recently, we reported a Me_2Zn-mediated chlorolactamization reaction of homoallylic amines, in which phosgene was found to be generated by Me_2Zn and chloroform.[4] In this reaction, an excess of Me_2Zn was required for efficient phosgene generation. In order to establish a more conventional chlorolactamization reaction, we focused our attention on triphosgene, which is a well-known crystalline alternative to harmful phosgene.[5] Herein, we report triphosgene-mediated chlorolactamization reactions of homoallylic amines. In addition, aminolactamization via a Ritter-type reaction of the carbocation intermediate generated by the Prins-type cyclization was also developed.

RESULTS AND DISCUSSION

We initially conducted a screening process to identify optimal conditions for the triphosgene-mediated chlorolactamization of **1a** (Table 1). When **1a** was treated with 3 equivalents of triphosgene in chloroform, a significant amount of carbamoyl chloride intermediate **A** and a small amount of desired bicyclic β-chlorolactam **2a** were detected by ^{1}H NMR and GCMS analyses of the crude product. Pleasingly,

cyclization of **A** proceeded to completion during the purification process using silica gel chromatography to form **2a** in 66% yield (entry 1). Several other solvents were screened, including benzene and dichloromethane. Dichloromethane was found to be the best solvent for this reaction (entry 3). Decreasing the amount of triphosgene to 2 equivalents reduced the chemical yield because the starting material was not completely consumed (entry 4). The stereoisomeric ratios were 2:1–3:1 in favor of the *endo* isomer.

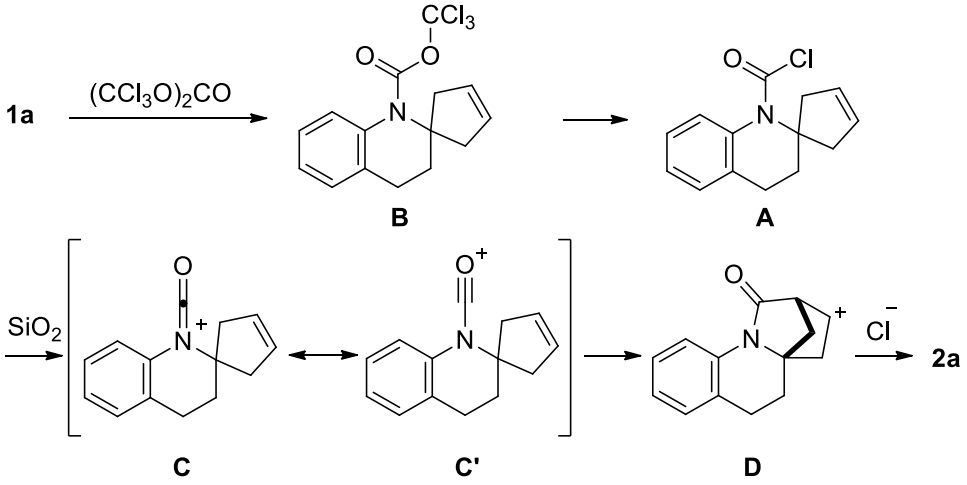
Table 1. Optimization of triphosgene-mediated chlorolactamization reaction conditions



1a **A** **2a**

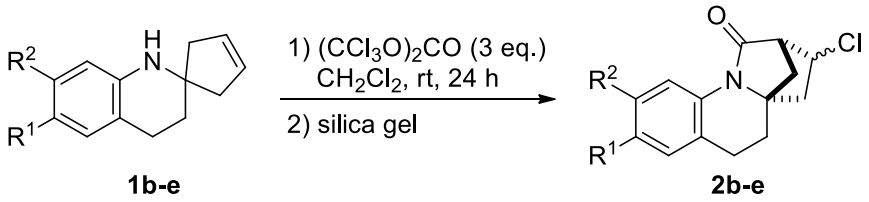
entry	$(CCl_3O)_2CO$ (eq.)	solvent	yield (%)	*endo* : *exo*
1	3	$CHCl_3$	66	3 : 1
2	3	benzene	30	3 : 1
3	3	CH_2Cl_2	75	2 : 1
4	2	CH_2Cl_2	41	3 : 1

A plausible reaction pathway is shown in Scheme 1. The reaction commenced with the acylation of **1a** with triphosgene to form carbamoyl chloride **A** via the generation of carbamic acid trichloromethyl ester **B**.[6] The SiO_2-promoted elimination of a chloride anion forms acylium ion **C** or **C'**, which would undergo an intramolecular Prins-type cyclization to generate carbocation intermediate **D**.[7,8] The subsequent introduction of chloride to **D** would provide chlorolactam **2a**.



Scheme 1. Plausible chlorolactamization reaction pathway

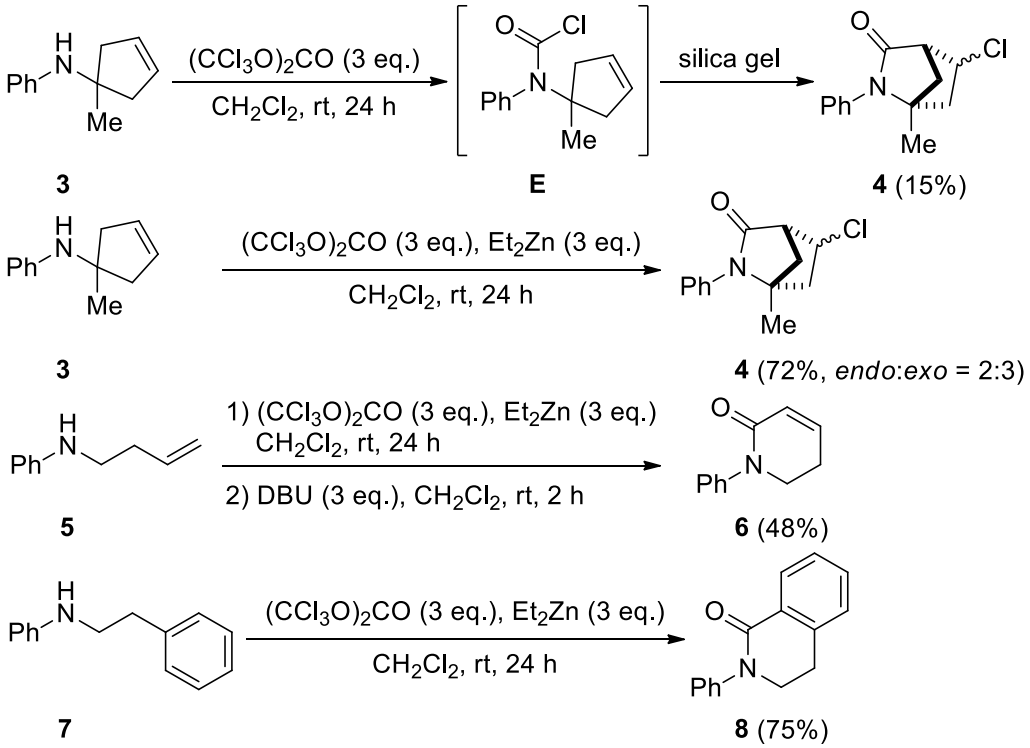
Table 2. Reactions of various cyclopentenylamines with triphosgene



1b-e **2b-e**

entry	substrate	R^1	R^2	product	yield (%)	*endo* : *exo*
1	**1b**	H	Me	**2b**	53	6 : 1
2	**1c**	OMe	H	**2c**	56	3 : 1
3	**1d**	Cl	H	**2d**	67	5 : 1
4	**1e**	Br	H	**2e**	45	10 : 1

With optimal conditions in hand, the effects of different substituents on the benzene ring were examined (Table 2). Pleasingly, spirocyclic tetrahydroquinolines with electron-donating (e.g., methyl or methoxy) and halogen groups on the benzene ring were tolerated by the reaction, giving corresponding lactams **2b–e** in moderate yields (entries 1-4).

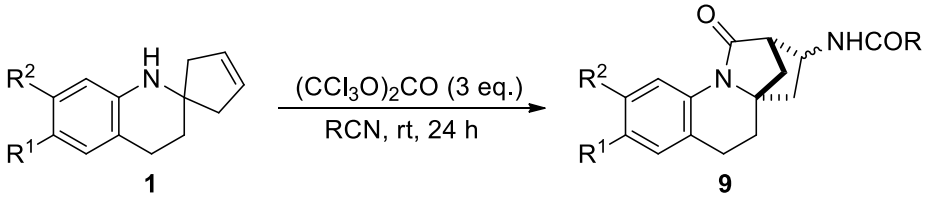


Scheme 2. Scope of the chlorolactamization reaction

To expand the substrate scope of this reaction, we next demonstrated the lactamization of several homoallylic amines (Scheme 2). Application of the optimized conditions to cyclopentenylamine **3**, which

did not contain a spirocyclic moiety, gave desired chlorolactam **4**, albeit in 15% yield. However, adequate generation of carbamoyl chloride **E** was detected by crude ^{1}H NMR and GCMS analyses. In order to promote cyclization, the addition of several Lewis acids, such as $FeCl_3$, BF_3•OEt_2, and Et_2Zn,[9] was examined. Et_2Zn was found to be the best additive for this reaction, giving desired lactam **4** in good yield. Acyclic homoallylic amine **5** was converted into α,β-unsaturated lactam **6** by triphosgene-mediated chlorolactamization and subsequent DBU-mediated elimination of HCl in 48% yield over two steps. Furthermore, we investigated expanding the generality of this reaction to Friedel-Crafts-type carbamoylation.[10] Indeed, phenylethylamine **7** was converted to dihydroisoquinolinone **8** in 75% yield via formation of the carbamoyl chloride intermediate and nucleophilic attack of the benzene moiety.

Table 3. Triphosgene-mediated aminolactamization reactions of various cyclopentenylamines



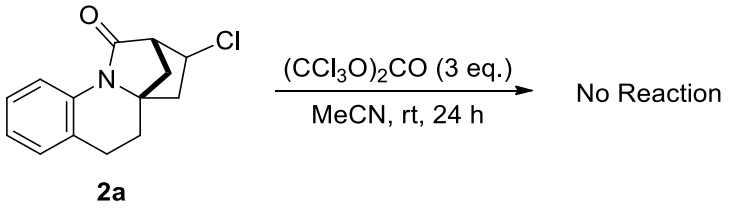
1 **9**

entry	substrate	R^1	R^2	R	product	yield (%)	*endo* : *exo*
1	**1a**	H	H	Me	**9aA**	48	1 : 7
2	**1a**	H	H	Et	**9aB**	35	1 : 4
3	**1b**	H	Me	Me	**9bA**	50	1 : 4
4	**1c**	OMe	H	Me	**9cA**	50	1 : 15
5	**1d**	Cl	H	Me	**9dA**	48	1 : 8
6	**1e**	Br	H	Me	**9eA**	48	1 : 6

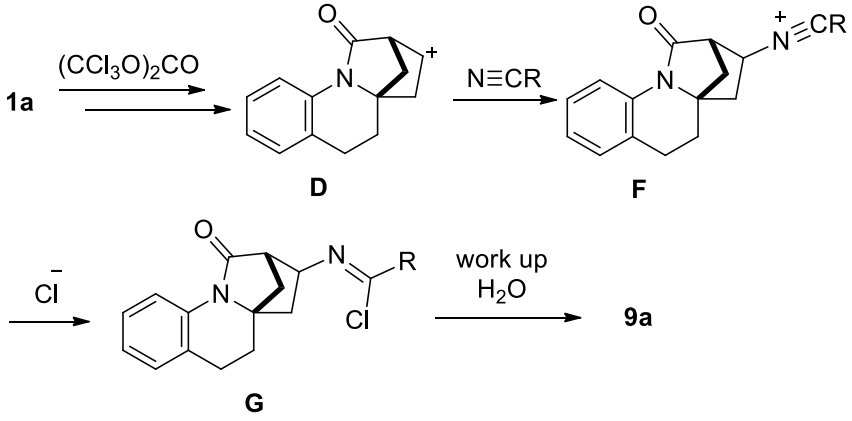
Based on the aforementioned reaction pathway, we hypothesized that carbocation intermediate **D** could be applied to a Ritter-type reaction.[11] Thus, the reaction of **1a** with triphosgene (3 equiv.) proceeded in acetonitrile, used as both solvent and nucleophile, to afford desired aminolactam **9aA** in 48% yield (Table 3, entry 1). Propionitrile was also applied to this reaction, giving desired aminolactam **9aB** (entry 2). As also found for chlorolactamization, aminolactamization was amenable to several benzene ring substituents (entries 3–6). The stereoisomeric ratios were 1:4–1:15 in favor of the *exo* isomer. It is not clear why the stereoselectivity of aminocarbonylation was reversed relative to the chloro- and aminolactamization reactions.

The reaction pathway for the formation of **9aA** by the substitution reaction of **2a** with acetonitrile was excluded, because treating **2a** with triphosgene in acetonitrile resulted in no reaction and recovery of starting material (Scheme 3). A proposed reaction mechanism is shown in Scheme 4. Carbocation

intermediate **D**, generated by the Prins-type cyclization of carbamoyl chloride, would undergo addition of a cyano group to form nitrilium ion intermediate **F**. The subsequent addition of chloride anion to **F** would give imidoylchloride **G**, which would undergo hydrolysis to produce aminolactam **9a**.



Scheme 3. Elucidation of the reaction pathway



Scheme 4. Plausible reaction pathway for aminolactamization

In conclusion, we have developed lactamization reactions of homoallylic amines. In dichloromethane, carbamoyl chloride intermediates underwent Prins-type cyclization and chlorination to afford chlorolactams. In contrast, a sequential Prins-type cyclization/Ritter-type reaction occurred in acetonitrile, affording aminolactams. These two transformations had simple methods and mild conditions, providing bridged lactams that would be difficult to prepare using conventional methods. Efforts to further expand upon, and clarify the reaction mechanism, as well as increasing the scope and demonstrate the synthetic utility of these products, are currently underway in our laboratory.

EXPERIMENTAL

General information: NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR), 500 MHz/125 MHz (^{1}H NMR/^{13}C NMR) or 600 MHz/150 MHz (^{1}H NMR/^{13}C NMR) using Varian Gemini-300 (300 MHz), Varian MERCURY plus 300 (300 MHz), Varian NMR system AS 500 (500 MHz) or Bruker Avance III HD (600 MHz) spectrometers. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad),

coupling constants, and integration. IR spectra were obtained on a Parkin Elmer SpectrumOne A spectrometer. Mass spectra were obtained by ESI method on a Thermo Fisher Scientific Exactive. Melting points (uncorrected) were determined on BÜCHI M-565. Flash column chromatography was performed using E. Merck Kieselgel 60 (230-240 mesh). Preparative TLC separations were carried out on precoated silica gel plates (E. Merck 60F_{254}). Unless otherwise stated, all the reagents and solvents were used as received from the manufacturer.

Starting materials: 1a-d,[4] **3**,[4] **5**,[4] and **7**[12a] were prepared according to the literature procedures. The physical and spectroscopic data of **1a-d**,[4] **3**,[4] **5**,[4] and **7**[12b] were in consistent with reported in the literature.

Reaction of 1a with triphosgene (Table 1, entry 3). Triphosgene (195.9 mg, 0.66 mmol) was added to a solution of **1a** (41.0 mg, 0.22 mmol) in CH_2Cl_2 (4.4 mL) under nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was diluted with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (*n*-Hexane : AcOEt = 5 : 1) afforded *endo*-**2a** (27.8 mg, 51%) as colorless crystals and *exo*-**2a** (13.0 mg, 24%) as a colorless oil. The physical and spectroscopic data were in consistent with reported in the literature.[4]

General procedure for chlorolactamization of 1b-e. Triphosgene (178.1 mg, 0.6 mmol) was added to a solution of **1b-e** (0.2 mmol) in CH_2Cl_2 (4.0 mL) under nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was diluted with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (*n*-Hexane : AcOEt = 5 : 1) afforded corresponding products *endo*-**2b-e** and *exo*-**2b-e** in the yields shown in Table 2. The physical and spectroscopic data of **2b-d** were in consistent with reported in the literature.[4]

6-Bromo-1,2,3,4-tetrahydro-2,2-di-(2-propen-1-yl)quinoline (S1). To a solution of 5-bromo-2,3-dihydro-1*H*-inden-1-one *O*-methyl oxime (240.9 mg, 1.0 mmol) in CH_2Cl_2 (10.0 mL) was added allyl magnesium bromide (1.0 M in Et_2O, 4.0 mL, 4.0 mmol) at room temperature, and the reaction mixture was stirred at the same temperature under nitrogen atmosphere. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash column chromatography (*n*-Hexane : AcOEt = 20 : 1) afforded **S1** (290.0 mg, 99%) as a colorless oil. IR (neat) 3397, 2927, 1486 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.12-7.08 (m, 1H), 7.08-7.02 (m, 1H), 6.36 (d, *J*=8.5 Hz, 1H), 5.93-5.78 (m, 2H), 5.20-5.07 (m, 4H), 3.85 (br s, 1H), 2.75 (t, *J*=7.0 Hz, 2H), 2.29 (dd, *J*=13.5, 7.0 Hz, 2H), 2.19 (dd, *J*=13.5, 8.0 Hz, 2H), 1.74 (t, *J*=7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.4, 133.0, 131.5, 129.3, 122.2, 118.8, 115.8, 108.1, 53.0, 42.5, 29.9, 23.3. HRMS (ESI) *m/z*: Calcd for $C_{15}H_{19}{}^{79}BrN$ ($M+H^+$) 292.0695. Found: 292.0697.

6'-Bromo-3',4'-dihydro-spiro[cyclopent-3-ene-1,2'(1'*H*)-quinoline] (1e). Grubbs second-generation catalyst (25.0 mg, 0.03 mmol) was added to a solution of **S1** (438.5 mg, 1.5 mmol) in CH_2Cl_2 (15.0 mL) under argon atmosphere, and the reaction mixture was then heated at reflux. After being stirred at the same temperature for 5 h, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (*n*-Hexane : AcOEt = 20 : 1) to afford **1e** (266.6 mg, 67%) as a colorless oil. IR (neat) 3392, 2927, 1486 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.12-7.06 (m, 1H), 7.02 (dd, *J*=8.5, 2.5 Hz, 1H), 6.30 (d, *J*=8.5 Hz, 1H), 5.71 (s, 2H), 4.08 (br s, 1H), 2.79 (t, *J*=6.5 Hz, 2H), 2.50-2.32 (m, 4H), 1.88 (t, *J*=6.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.9, 131.7, 129.4, 128.7, 122.5, 116.0, 108.3, 60.0, 46.4, 32.1, 24.7. HRMS (ESI) *m/z*: Calcd for $C_{13}H_{15}{}^{79}BrN$ ($M+H^+$) 264.0382. Found: 264.0382.

(2*R,3*R**,4a*R**)-8-Bromo-3-chloro-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-1-one (*endo*-2e).** A colorless oil. IR (neat) 2944, 1712, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.49 (d, *J*=8.5 Hz, 1H), 7.31 (d, *J*=8.5 Hz, 1H), 7.27 (s, 1H), 4.60 (dt, *J*=9.0, 4.0 Hz, 1H), 3.18-3.11 (m, 1H), 2.92-2.71 (m, 2H), 2.36 (dd, *J*=13.0, 9.5 Hz, 1H), 2.14-1.94 (m, 4H), 1.79 (d, *J*=9.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.1, 134.1, 131.3, 130.3, 126.7, 120.2, 115.4, 67.3, 53.7, 53.6, 43.9, 43.2, 26.8, 25.2. HRMS (ESI) *m/z*: Calcd for $C_{14}H_{14}{}^{79}Br^{35}ClNO$ ($M+H^+$) 325.9942. Found: 325.9942.

(2*R,3*S**,4a*R**)-8-Bromo-3-chloro-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-1-one (*exo*-2e).** Colorless crystals. mp 149-155 °C ($CHCl_3$-*n*-Hexane). IR ($CHCl_3$) 2931, 2853, 1710, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.35 (d, *J*=8.5 Hz, 1H), 7.34-7.25 (m, 2H), 4.36-4.29 (m, 1H), 3.09 (s, 1H), 2.92-2.72 (m, 2H), 2.60 (ddd, *J*=14.0, 7.5, 2.5 Hz, 1H), 2.35 (dd, *J*=10.0, 1.0 Hz, 1H), 2.22-2.09 (m, 2H), 2.02 (ddt, *J*=10.0, 2.5, 1.5 Hz, 1H), 1.94 (dd, *J*=14.0, 2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.6, 133.9, 131.4, 130.2, 126.8, 120.1, 115.8, 68.4, 56.0, 55.4, 45.6, 41.8, 26.5, 25.4. HRMS (ESI) *m/z*: Calcd for $C_{14}H_{14}{}^{79}Br^{35}ClNO$ ($M+H^+$) 325.9942. Found: 325.9942.

5-Chloro-1-methyl-*N*-phenyl-2-azabicyclo[2.2.1]heptan-3-one (4). Triphosgene (267.1 mg, 0.9 mmol) and Et_2Zn (1.0 M in *n*-Hexane, 0.9 mL, 0.9 mmol) were added to a solution of **3** (52.0 mg, 0.3 mmol) in CH_2Cl_2 (6.0 mL) under nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was diluted with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (*n*-Hexane : AcOEt = 1 : 1) afforded corresponding products *endo*-**4** (19.3 mg, 27%) as a white solid and *exo*-**4** (31.6 mg, 45%) as colorless crystals. The physical and spectroscopic data were in consistent with reported in the literature.[4]

5,6-Dihydro-1-phenyl-2(1*H*)-pyridinone (6). Triphosgene (267.1 mg, 0.9 mmol) and Et_2Zn (1.0 M in *n*-Hexane, 0.9 mL, 0.9 mmol) were added to a solution of **5** (44.1 mg, 0.3 mmol) in CH_2Cl_2 (30.0 mL) under nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the

reaction mixture was diluted with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (6.0 mL) was added DBU (0.13 mL, 0.9 mmol) under nitrogen atmosphere at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by preparative TLC (*n*-Hexane : AcOEt = 1 : 1) afforded **6** (24.9 mg, 48%) as colorless crystals. The physical and spectroscopic data were in consistent with reported in the literature.[4]

2-Phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (8). Triphosgene (267.1 mg, 0.9 mmol) and Et_2Zn (1.0 M in *n*-Hexane, 0.9 mL, 0.9 mmol) were added to a solution of **7** (59.2 mg, 0.3 mmol) in CH_2Cl_2 (30.0 mL) under nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was diluted with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (*n*-Hexane : AcOEt = 1 : 1) afforded corresponding products **8** (50.4 mg, 75%) as a white solid. The physical and spectroscopic data were in consistent with reported in the literature.[13]

General procedure for the aminolactamization of 1a-e. Triphosgene (178.1 mg, 0.6 mmol) was added to a solution of **1a-e** (0.2 mmol) in MeCN (4.0 mL) under nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was diluted with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (AcOEt) afforded corresponding products *endo*-**9aA-eA** and *exo*-**9aA-eA** in the yields shown in Table 3.

***N*-[(2*R**,3*R**,4a*R**)-1-Oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]acetamide (*endo*-9aA).** A colorless oil. IR (neat) 3293, 2940, 1701, 1658, 1549, 1493 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.56 (dd, *J*=8.0, 0.5 Hz, 1H), 7.26 (t, *J*=8.0 Hz, 1H), 7.18 (d, *J*=7.0 Hz, 1H), 7.04 (td, *J*=7.0, 0.5 Hz, 1H), 5.79 (br d, *J*=5.0 Hz, 1H), 4.72 (ddt, *J*=9.5, 7.5, 4.0 Hz, 1H), 3.02 (dt, *J*=4.0, 1.0 Hz, 1H), 2.91 (ddd, *J*=16.0, 12.0, 6.0 Hz, 1H), 2.83 (dt, *J*=16.0, 4.0 Hz, 1H), 2.27 (dd, *J*=13.0, 9.5 Hz, 1H), 2.15-2.05 (m, 2H), 1.96 (ddd, *J*=9.5, 3.5, 2.0 Hz, 1H), 1.93 (s, 3H), 1.80 (dd, *J*=9.5, 1.0 Hz, 1H), 1.60 (dt, *J*=13.0, 3.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 172.7, 170.3, 135.0, 129.0, 127.4, 124.9, 123.2, 118.7, 67.8, 50.6, 48.2, 43.4, 40.8, 27.2, 25.6, 23.1. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{19}N_2O_2$ ($M+H^+$) 271.1441. Found: 271.1444.

***N*-[(2*R**,3*S**,4a*R**)-1-Oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]acetamide (*exo*-9aA).** A colorless foam. IR (neat) 3289, 2944, 1686, 1654, 1546, 1493 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.46 (dd, *J*=8.0, 0.5 Hz, 1H), 7.19 (t, *J*=8.0 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 6.98 (td, *J*=8.0, 1.0 Hz, 1H), 6.32 (d, *J*=6.0 Hz, 1H), 4.33-4.28 (m, 1H), 2.92-2.85 (m, 1H), 2.91 (s, 1H), 2.77 (dt, *J*=16.0, 4.0 Hz, 1H), 2.50 (ddd, *J*=13.0, 8.0, 2.5 Hz, 1H), 2.17 (td, *J*=13.0, 5.0 Hz, 1H), 2.12 (ddd, *J*=13.0, 5.5, 3.5

Hz, 1H), 2.00 (s, 3H), 2.03-1.94 (m, 2H), 1.51 (dd, *J*=13.0, 3.5, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 173.3, 170.1, 135.3, 128.9, 127.3, 125.0, 123.1, 118.6, 67.8, 52.2, 49.1, 42.2, 41.9, 27.0, 25.6, 23.3. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{19}N_2O_2$ ($M+H^+$) 271.1441. Found: 271.1441.

***N*-[(2*R**,3*R**,4a*R**)-9-Methyl-1-oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]acetamide (*endo*-9bA).** Colorless crystals. Decomp. 165 °C ($CHCl_3$-*n*-Hexane). IR ($CHCl_3$) 1682, 1602, 1508 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.36 (s, 1H), 7.02 (d, *J*=7.5 Hz, 1H), 6.81 (dd, *J*=7.5, 1.0 Hz, 1H), 5.85-5.70 (m, 1H), 4.67 (ddt, *J*=9.5, 7.5, 4.0 Hz, 1H), 3.00-2.94 (m, 1H), 2.90-2.70 (m, 2H), 2.34 (s, 3H), 2.23 (dd, *J*=13.0, 9.5 Hz, 1H), 2.12-2.02 (m, 2H), 1.99-1.86 (m, 1H), 1.90 (s, 3H), 1.76 (dd, *J*=9.5, 1.0 Hz, 1H), 1.56 (dt, *J*=13.0, 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.5, 170.1, 137.1, 134.7, 128.7, 123.9, 121.9, 119.0, 67.8, 50.7, 48.3, 43.4, 40.8, 27.4, 25.3, 23.2, 21.5. HRMS (ESI) *m/z*: Calcd for $C_{17}H_{21}N_2O_2$ ($M+H^+$) 285.1598. Found: 285.1599.

***N*-[(2*R**,3*S**,4a*R**)-9-Methyl-1-oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]acetamide (*exo*-9bA).** A colorless foam. IR (neat) 3293, 2940, 1686, 1546, 1508 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 7.05 (d, *J*=6.5 Hz, 1H), 7.01 (d, *J*=8.0 Hz, 1H), 6.80 (d, *J*=8.0 Hz, 1H), 4.33-4.23 (m, 1H), 2.91 (s, 1H), 2.82 (dd, *J*=16.0, 8.5 Hz, 1H), 2.71 (dt, *J*=16.0, 4.0 Hz, 1H), 2.56 (br s, 1H), 2.43 (ddd, *J*=13.0, 8.0, 2.5 Hz, 1H), 2.30 (s, 3H), 2.18-1.88 (m, 3H), 2.01 (s, 3H), 1.56 (dd, *J*=13.0, 3.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.4, 170.2, 136.9, 134.9, 128.6, 123.8, 122.0, 118.8, 67.9, 52.3, 49.1, 41.8, 41.5, 27.2, 25.2, 23.2, 21.5. HRMS (ESI) *m/z*: Calcd for $C_{17}H_{21}N_2O_2$ ($M+H^+$) 285.1598. Found: 285.1597.

***N*-[(2*R**,3*R**,4a*R**)-8-Methoxy-1-oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]acetamide (*endo*-9cA).** Colorless crystals. Decomp. 202 °C ($CHCl_3$-*n*-Hexane). IR ($CHCl_3$) 3422, 3009, 1678, 1499 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.47 (d, *J*=9.0 Hz, 1H), 6.80 (dd, *J*=9.0, 3.0 Hz, 1H), 6.70 (d, *J*=3.0 Hz, 1H), 5.77 (br d, *J*=7.5 Hz, 1H), 4.69 (ddt, *J*=9.5, 7.5, 4.0 Hz, 1H), 3.79 (s, 3H), 3.00-2.96 (m, 1H), 2.95-2.70 (m, 2H), 2.30 (s, 1H), 2.24 (dd, *J*=130, 9.5 Hz, 1H), 2.12-2.04 (m, 2H), 1.91 (s, 3H), 1.76 (dd, *J*=10.0, 1.5 Hz, 1H), 1.60-1.48 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.8, 175.0, 160.0, 133.2, 131.2, 124.5, 118.8, 117.2, 67.7, 55.4, 50.5, 48.4, 43.4, 40.6, 27.2, 25.8, 23.1. HRMS (ESI) *m/z*: Calcd for $C_{17}H_{21}N_2O_3$ ($M+H^+$) 301.1547. Found: 301.1548.

***N*-[(2*R**,3*S**,4a*R**)-8-Methoxy-1-oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]acetamide (*exo*-9cA).** A white powder. mp 91-95 °C ($CHCl_3$-*n*-Hexane). IR ($CHCl_3$) 3444, 3004, 1693, 1501 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.39 (d, *J*=9.0 Hz, 1H), 6.76 (dd, *J*=9.0, 3.0 Hz, 1H), 6.67 (d, *J*=2.5 Hz, 1H), 5.81 (br s, 1H), 4.34-4.26 (m, 1H), 3.77 (s, 3H), 2.89 (s, 1H), 2.94-2.82 (m, 1H), 2.74 (dt, *J*=16.5, 4.0 Hz, 1H), 2.50 (dd, *J*=13.0, 8.5 Hz, 1H), 2.23-2.04 (m, 2H), 2.00 (s, 3H), 1.95 (s, 2H), 1.46 (dd, *J*=13.0, 3.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.8, 170.2, 155.1, 128.8, 126.6, 119.7,

114.1, 112.4, 67.7, 55.4, 52.1, 49.2, 41.9, 41.8, 27.0, 25.8, 23.2. HRMS (ESI) *m/z*: Calcd for $C_{17}H_{21}N_2O_3$ ($M+H^+$) 301.1547. Found: 301.1548.

***N*-[(2*R**,3*R**,4a*R**)-8-Chloro-1-oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]acetamide (*endo*-9dA).** Colorless crystals. Decomp. 160 °C ($CHCl_3$-*n*-Hexane). IR ($CHCl_3$) 3294, 1704, 1658, 1555, 1486 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.46 (d, *J*=9.0 Hz, 1H), 7.20-7.07 (m, 2H), 5.90-5.75 (m, 1H), 4.67 (ddt, *J*=9.5, 7.5, 4.0 Hz, 1H), 3.04-2.96 (m, 1H), 2.94-2.72 (m, 2H), 2.24 (dd, *J*=13.0, 9.5 Hz, 1H), 2.16-1.84 (m, 3H), 1.91 (s, 3H), 1.79 (d, *J*=10.0 Hz, 1H), 1.54 (dt, *J*=13.0, 3.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.5, 170.1, 133.4, 128.6, 127.9, 127.2, 126.5, 119.7, 67.7, 50.5, 48.3, 43.3, 40.6, 26.9, 25.5, 23.2. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{17}{}^{35}ClN_2O_2Na$ ($M+Na^+$) 327.0871. Found: 327.0865.

***N*-[(2*R**,3*S**,4a*R**)-8-Chloro-1-oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]acetamide (*exo*-9dA).** A white powder. mp 118-220 °C ($CHCl_3$-*n*-Hexane). IR ($CHCl_3$) 3288, 2946, 1704, 1655, 1554, 1486 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.41 (d, *J*=8.5 Hz, 1H), 7.16-7.08 (m, 2H), 5.89-5.78 (m, 1H), 4.35-4.24 (m, 1H), 2.90 (s, 1H), 2.84 (dd, *J*=10.5, 6.5 Hz, 1H), 2.75 (dt, *J*=16.5, 4.0 Hz, 1H) 2.54-2.44 (m, 1H), 2.23-2.08 (m, 2H), 2.00 (s, 3H), 1.97 (s, 1H), 1.74 (s, 1H), 1.46 (dd, *J*=13.0, 3.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.7, 169.6, 133.7, 128.4, 127.8, 127.2, 126.4, 119.7, 67.7, 52.0, 49.1, 42.5, 41.9, 26.8, 25.5, 23.4. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{17}{}^{35}ClN_2O_2Na$ ($M+Na^+$) 327.0871. Found: 327.0863.

***N*-[(2*R**,3*R**,4a*R**)-8-Bromo-1-oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]acetamide (*endo*-9eA).** Colorless crystals. Decomp. 170 °C ($CHCl_3$-*n*-Hexane). IR ($CHCl_3$) 3288, 2938, 1704, 1656, 1555, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.40 (d, *J*=8.5 Hz, 1H), 7.33-7.24 (m, 2H), 5.84-5.66 (m, 1H), 4.67 (ddt, *J*=9.5, 7.5, 4.0 Hz, 1H), 3.00 (dt, *J*=4.0, 1.5 Hz, 1H), 2.93-2.68 (m, 2H), 2.24 (dd, *J*=13.0, 9.5 Hz, 1H), 2.16-1.98 (m, 2H), 1.97-1.84 (m, 1H), 1.91 (s, 3H), 1.78 (d, *J*=10.0 Hz, 1H), 1.54 (dt, *J*=13.0, 3.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.6, 170.1, 133.9, 131.5, 130.2, 126.9, 120.1, 115.7, 67.7, 50.6, 48.3, 43.3, 40.7, 26.9, 25.4, 23.2. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{18}{}^{79}BrN_2O_2$ ($M+H^+$) 349.0546. Found: 349.0542.

***N*-[(2*R**,3*S**,4a*R**)-8-Bromo-1-oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]acetamide (*exo*-9eA).** Colorless crystals. Decomp. 190 °C ($CHCl_3$-*n*-Hexane). IR ($CHCl_3$) 3288, 2947, 1706, 1550, 1485 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.34 (d, *J*=9.5 Hz, 1H), 7.30-7.22 (m, 2H), 6.61 (br d, *J*=6.5 Hz, 1H), 4.34-4.23 (m, 1H), 2.90 (s, 1H), 2.92-2.79 (m, 1H), 2.74 (dt, *J*=16.5, 4.0 Hz, 1H), 2.44 (ddd, *J*=13.0, 8.5, 2.0 Hz, 1H), 2.20-2.08 (m, 2H), 2.05 (d, *J*=10.0 Hz, 1H), 1.99 (s, 3H), 1.94 (d, *J*=10.0 Hz, 1H), 1.53 (dd, *J*=13.0, 3.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.1, 169.9, 134.1, 131.4, 130.0, 126.9, 119.9, 115.4, 67.7, 52.2, 49.0, 41.84, 41.78, 26.7, 25.4, 23.3. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{18}{}^{79}BrN_2O_2$ ($M+H^+$) 349.0546. Found: 349.0540.

***N*-(1-Oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl)propanamide (9aB).** Triphosgene (356.1 mg, 1.2 mmol) was added to a solution of **1a** (74.0 mg, 0.4 mmol) in EtCN (8.0 mL) under nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was diluted with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (AcOEt) afforded corresponding products *endo*-**9aB** (8.3 mg, 7%) as colorless crystals and *exo*-**9aB** (31.4 mg, 28%) as a colorless oil.

***N*-[(2*R**,3*R**,4a*R**)-1-Oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]propanamide (*endo*-9aB).** Decomp. 174 °C ($CHCl_3$-*n*-Hexane). IR ($CHCl_3$) 3302, 2940, 1686, 1650, 1542, 1493 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.53 (dd, *J*=8.5, 1.0 Hz, 1H), 7.23 (t, *J*=8.5 Hz, 1H), 7.15 (d, *J*=7.5 Hz, 1H), 7.01 (td, *J*=7.5, 1.0 Hz, 1H), 5.73 (br d, *J*=5.5 Hz, 1H), 4.70 (ddt, *J*=9.0, 7.5, 4.0 Hz, 1H), 2.99 (dt, *J*=4.0, 1.5 Hz, 1H), 2.89 (ddd, *J*=16.0, 11.5, 6.0 Hz, 1H), 2.80 (dt, *J*=16.0, 4.0 Hz, 1H), 2.25 (dd, *J*=13.0, 9.5 Hz, 1H), 2.18-2.05 (m, 4H), 1.94 (ddd, *J*=9.5, 3.5, 1.5 Hz, 1H), 1.79 (dd, *J*=10.0, 1.5 Hz, 1H), 1.56 (dt, *J*=13.0, 3.5 Hz, 1H), 1.09 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 174.0, 172.8, 135.0, 129.0, 127.4, 125.0, 123.2, 118.7, 67.8, 50.7, 48.1, 43.4, 40.9, 29.4, 27.2, 25.6, 9.6. HRMS (ESI) *m/z*: Calcd for $C_{17}H_{21}N_2O_2$ ($M+H^+$) 285.1598. Found: 285.1593.

***N*-[(2*R**,3*S**,4a*R**)-1-Oxo-2,3,4,4a,5,6-hexahydro-2,4a-methano-1*H*-benzo[*c*]quinolizin-3-yl]propanamide (*exo*-9aB).** IR (neat) 3293, 2940, 1684, 1647, 1542, 1493 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.47 (dd, *J*=8.5, 0.5 Hz, 1H), 7.19 (t, *J*=8.0 Hz, 1H), 7.12 (d, *J*=7.5 Hz, 1H), 6.98 (td, *J*=7.5, 1.0 Hz, 1H), 5.86 (br d, *J*=5.5 Hz, 1H), 4.34-4.28 (m, 1H), 2.892 (s, 1H), 2.888 (ddd, *J*=16.0, 12.0, 5.0 Hz, 1H), 2.78 (dt, *J*=16.0, 4.0 Hz, 1H), 2.53 (ddd, *J*=13.0, 7.5, 2.0 Hz, 1H), 2.21 (q, *J*=7.5 Hz, 2H), 2.21-2.08 (m, 2H), 2.02-1.94 (m, 2H), 1.47 (dd, *J*=13.0, 3.5 Hz, 1H), 1.15 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.6, 173.1, 135.3, 128.8, 127.4, 124.9, 123.0, 118.6, 67.8, 52.2, 49.0, 42.6, 42.0, 29.6, 27.1, 25.6, 9.8. HRMS (ESI) *m/z*: Calcd for $C_{17}H_{21}N_2O_2$ ($M+H^+$) 285.1598. Found: 285.1597.

ACKNOWLEDGEMENTS

This work was supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT), the MEXT-supported Program for the Strategic Research Foundation at Private Universities, and the Uehara Memorial Foundation.

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