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Intramolecular Aminolactonization for Synthesis of Furoindolin-2-One

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Abstract: Propellanes are polycyclic compounds in which tricyclic systems share one carbon–carbon single bond. Propellane frameworks that consist of larger sized rings are found in a variety of natural products. As an approach to the stereoselective synthesis of the propellane framework, one of the efficient methods is forming several rings in a single operation. Lapidilectine B (**1**) is composed of a propellane framework and was synthesized through the oxidative cyclization of trisubstituted alkenes. When the alkene with an ester moiety was treated with *N*-iodosuccinimide (NIS), iodocyclization proceeded to give the cyclic carbamate. On the other hand, when $\text{PhI}(\text{OAc})_2$ was allowed to react in the carboxyl form, a furoindolin-2-one structure corresponding to the A-B-C ring of lapidilectine B (**1**) was produced. Furthermore, when $\text{Pd}(\text{OAc})_2$ catalyst was used for cyclization under oxidative conditions, the product yield was improved.

Keywords: furoindolin-2-one; lapidilectine B; oxidative cyclization



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1. Introduction

In 1992, lapidilectine B (**1**) (Figure 1) was isolated from the leaves of *Kopsia lapidilecta* Sleesen in Malaysia [1]. Biological activity of **1** shows a reverse multidrug resistance in vincristine-resistant KB cells [2].

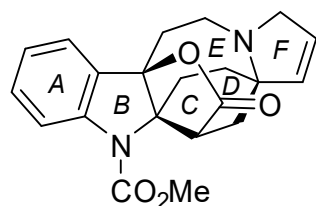


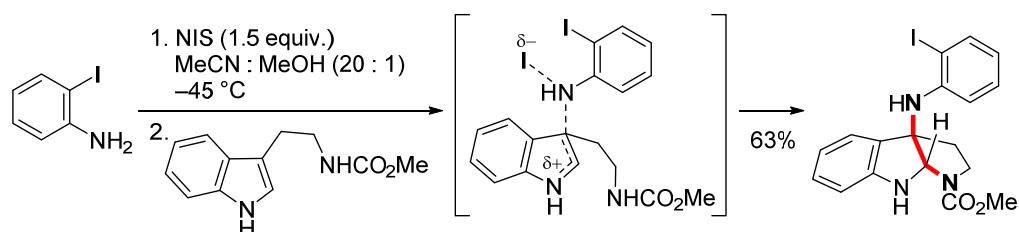
Figure 1. Lapidilectine B (**1**).

The structural feature of **1** is possessing a unique propellane structure composed of indoline, γ -lactone, and azocane. In addition, the cyclohexane ring is connected to two pyrrolidine rings via two spirocenters. The first total synthesis of **1** was achieved by Pearson in 2001, where the Smalley cyclization was used to construct the framework of the B and C rings [3,4]. The optically active form of **1** was synthesized by Nishida in 2016 via desymmetrization of the spiro center using enantioselective deprotonation with a chiral lithium amide [5]. In 2018, Ma utilized manganese (III) mediated oxidative cyclization of 2-alkylindole to form the B–C–D rings of **1** in one operation [6]. We focused on the *anti*-configuration between oxygen and nitrogen atoms in the B–C–E propellane moiety, and postulated that the simultaneous functionalization of the alkene is a key reaction for ring construction in **1**.

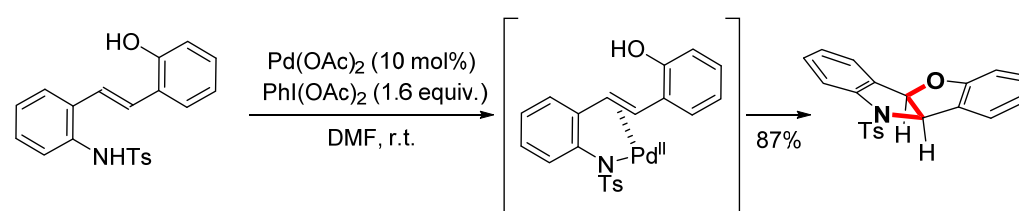
As a methodology for double functionalization with heteroatoms on C–C double bond, Baran indicated the oxidative coupling reaction of *o*-iodoaniline and tryptamine

using NIS to form the 3a substituted pyrroindoline motif in the synthesis of psychotrimine (Scheme 1A) [7,8]. The electrophilic *N*-haloaniline and the nucleophilic carbamate of the tryptamine side chain were introduced into the 2,3-positions of the indole. One of promising methods for introducing of two heteroatoms onto an alkene with a transition metal catalyst is Sharpless's asymmetric aminoxylation [9]. In 2007, Muñiz reported the palladium-catalyzed aminoalkoxylation of internal alkene bearing aniline and phenol moieties with $\text{PhI}(\text{OAc})_2$ (Scheme 1B) [10,11]. Interestingly in this method, a furoindoline skeleton is assembled by closing two rings of a disubstituted alkene at once. To construct the 5-5 bicyclo B-C ring system in lapidectine B (**1**), the *Z* trisubstituted alkene **2** was selected as the precursor for the ring closing reaction (Scheme 1C). Here, we report the efficient synthesis of furoindolin-2-one **3** by the successive cyclization of trisubstituted alkene **2** with the goal of developing a method for synthesizing the polycyclic skeleton of **1**.

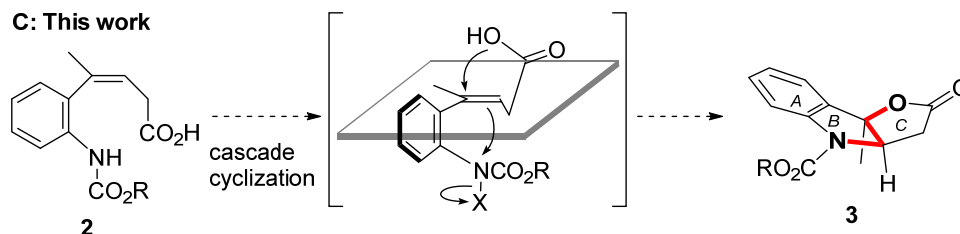
A: Baran's work



B: Muñiz's work



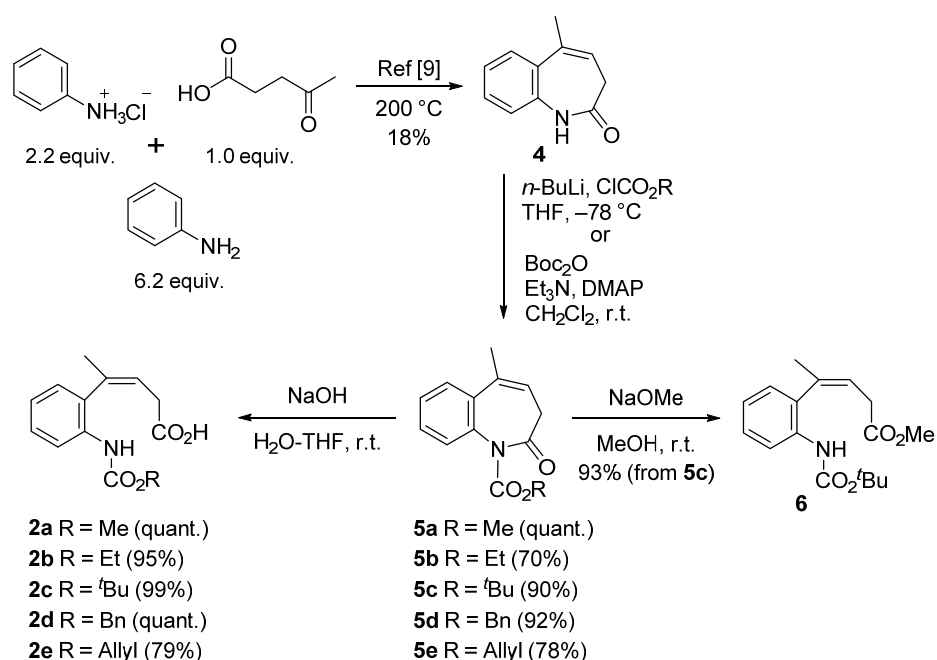
C: This work



Scheme 1. Oxidative cyclization of alkenes.

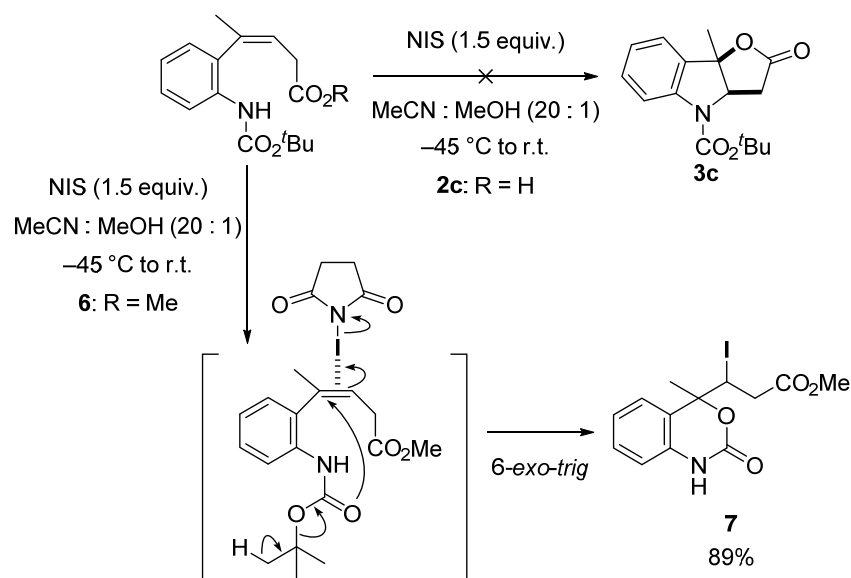
2. Results and Discussion

We synthesized trisubstituted alkenes **2** and **6** bearing an alkoxy carbonyl group on the aniline nitrogen (Scheme 2). Aniline, its hydrochloride, and 4-oxopentanoic acid were condensed under heating at $200\text{ }^\circ\text{C}$ to obtain lactam **4** according to the literature [12]. Thereafter, lactam **4** was transformed to imides **5a–e** by treating *n*-butyllithium with alkyl chloroformate or triethylamine with Boc_2O , after which imides **5** were hydrolyzed with NaOH in THF-water to prepare carboxylic acids **2a–e**. Boc form **5c** was solvolysed with sodium methoxide in MeOH to obtain methyl ester **6**.



Scheme 2. Syntheses of trisubstituted alkenes.

First, we investigated a key cyclization using compounds **2c** and **6** bearing a Boc group (Scheme 3). The treatment of carboxylic acid **2c** with NIS in a solution of MeCN and MeOH resulted in a complex mixture. On the other hand, when methyl ester **6** was treated under the same conditions as above, cyclic carbamate **7** was obtained in 89% yield as a single diastereomer. Iodocyclization triggered by the activation of the alkene with NIS, accompanied by the elimination of isobutylene from the Boc group, gave **7**.

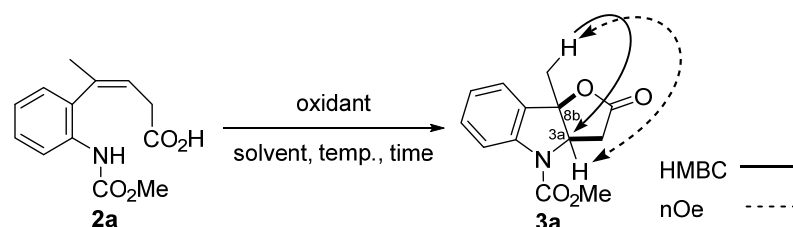


Scheme 3. Iodocyclization of alkene **6**.

Trisubstituted alkene **2a** possessing a carboxylic acid moiety was then subjected to halogenating and oxidizing agents (Table 1). The reaction yielded many products when NIS was added to **2a** (entry 1), whereas the reaction did not proceed with NCS (entry 2). When **2a** was treated with CAN in MeCN solution, the trace amount of the desired cyclized product **3a** was produced (entry 3). When the reaction was carried out with $\text{PhI}(\text{OAc})_2$ under refluxing MeCN, product **3a** was obtained in 43% yield, along with many decompo-

sition products (entry 4). Other hypervalent iodine reagents, $\text{PhI}(\text{OCOCF}_3)_2$, $\text{PhI}(\text{OH})\text{OTs}$, and PhIO were tested, product **3a** was slightly detected on TLC, however substrate **2a** was mainly decomposed (entries 5–7). The fused ring structure of product **3a** was confirmed by the correlation between the methyl proton at position 8b and the 3a carbon in the HMBC experiment, and between the methyl proton at position 8b and the 3a proton in the nOe experiment.

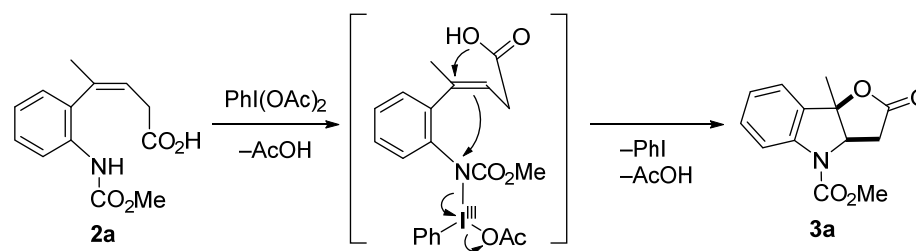
Table 1. Oxidative cyclization of alkene **2a**.



Entry	Oxidant	Equiv.	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	NIS	1.5	MeCN/MeOH (20/1)	−45	5	n.a. ¹
2	NCS	1.5	MeCN/MeOH (20/1)	−40 to r.t.	24	n.r. ²
3	CAN	1.0	MeCN	0 to r.t.	24	trace
4	$\text{PhI}(\text{OAc})_2$	1.0	MeCN	0 to reflux	24	43
5	$\text{PhI}(\text{OCOCF}_3)_2$	1.0	MeCN	0 to r.t.	24	trace
6	$\text{PhI}(\text{OH})\text{OTs}$	1.0	MeCN	0 to r.t.	24	4
7	PhIO	1.0	MeCN	0 to r.t.	24	trace

¹ Not available. ² No reaction.

A plausible reaction mechanism is shown in Scheme 4. In conjunction with the oxidative activation of the aniline nitrogen atom in **2a** by $\text{PhI}(\text{OAc})_2$, the nitrogen atom undergoes nucleophilic attack by the π -electron of the alkene, after which the carboxylic acid cyclized to give furoindolin-2-one **3a**.

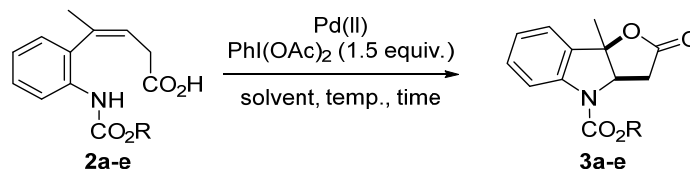


Scheme 4. Plausible reaction mechanism.

The conditions for palladium(II) mediated oxidative difunctionalization of alkenes reported by Muñiz were applied to trisubstituted alkene **2a** (Table 2). When 1 equivalent of the palladium reagent with 1.5 equivalents of $\text{PhI}(\text{OAc})_2$ treated with **2a** in DMF at room temperature, product **3a** was obtained in 19% yield with PdCl_2 , in 29% yield with $\text{Pd}(\text{OCOCF}_3)_2$, and in 58% yield with $\text{Pd}(\text{OAc})_2$ (entries 1–3). Using $\text{Pd}(\text{OAc})_2$ in MeCN, **3a** was obtained in 50% yield (entry 4). Based on the above results, a catalytic amount of $\text{Pd}(\text{OAc})_2$ was examined using DMF or MeCN. First, when 0.2 equivalent of $\text{Pd}(\text{OAc})_2$ was reacted at room temperature for 24 h, the yield of **3a** decreased to 14% in DMF and was maintained at 51% in MeCN (entries 5 and 6). When the reaction was performed under refluxing MeCN, the reaction time was shortened and the yield of **3a** increased to 78% (entry 7). Further reduction the amount of $\text{Pd}(\text{OAc})_2$ to 0.1 equivalent decreased the product yield to 47% (entry 8). With the optimum conditions in hand, the substituent effect on nitrogen

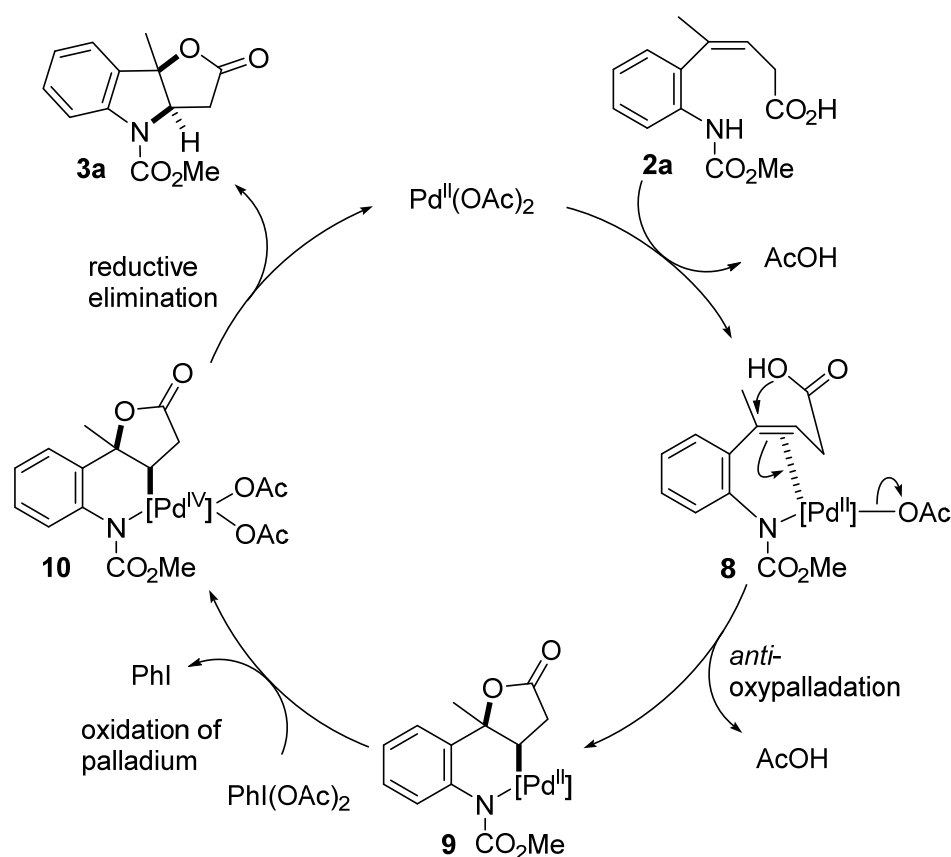
atom was examined. The ethoxycarbonyl compound **2b** gave the corresponding product **3b** in 56% yield (entry 9). Even with **2c** possessing a bulky Boc group, product **3c** was obtained in 38% yield (entry 10). Even when the Cbz and Alloc substituents attached to nitrogen, products **3d** and **3e** were obtained in 33% and 29% yields, respectively (entries 11 and 12).

Table 2. Palladium catalyzed cyclization of alkenes **2**.



Entry	2	R	Pd (Equiv.)	Solvent	Temp	Time	Yield (%)
1	2a	Me	PdCl ₂ (1.0)	DMF	r.t.	20 min	19
2	2a	Me	Pd(OCOCF ₃) ₂ (1.0)	DMF	r.t.	20 min	29
3	2a	Me	Pd(OAc) ₂ (1.0)	DMF	r.t.	20 min	58
4	2a	Me	Pd(OAc) ₂ (1.0)	MeCN	r.t.	20 min	50
5	2a	Me	Pd(OAc) ₂ (0.2)	DMF	r.t.	24 h	14
6	2a	Me	Pd(OAc) ₂ (0.2)	MeCN	r.t.	24 h	51
7	2a	Me	Pd(OAc) ₂ (0.2)	MeCN	reflux	6 h	78
8	2a	Me	Pd(OAc) ₂ (0.1)	MeCN	reflux	24 h	47
9	2b	Et	Pd(OAc) ₂ (0.2)	MeCN	reflux	6 h	56
10	2c	^t Bu	Pd(OAc) ₂ (0.2)	MeCN	reflux	6 h	38
11	2d	Bn	Pd(OAc) ₂ (0.2)	MeCN	reflux	6 h	33
12	2e	Allyl	Pd(OAc) ₂ (0.2)	MeCN	reflux	6 h	29

A reaction mechanism for the cyclization was proposed based on the report by Muñiz. [10,13–16] (Scheme 5). First, Pd(OAc)₂ reacts with the nitrogen atom of substrate **2a** and coordinates with the alkene to form intermediate **8**. Subsequently, *anti*-oxypalladation occurs on the alkene to generate the six-membered palladacycle intermediate **9**. Furthermore, palladium(II) is oxidized to palladium(IV) by PhI(OAc)₂ to form intermediate **10**, followed by the reductive elimination of palladium(IV) in **10** to produce **3a** and palladium(II) species.



Scheme 5. Plausible reaction mechanism.

3. Materials and Methods

3.1. General Information

All melting points were measured on a Yanagimoto micro melting point apparatus. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on JEOL JNM-AL 300 and 400 (300 and 400 MHz) spectrometer or JEOL JNM-ECS 400 (400 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane at δ_{H} 0.00, CDCl_3 at δ_{H} 7.26). Data are presented as follows: chemical shift (δ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. ^{13}C NMR spectra were recorded on JEOL JNM-ECA 400 (100 MHz) spectrometer. Chemical shifts are reported relative to internal standard (CDCl_3 at δ 77.00). Mass spectra were recorded on a JEOL JMS 700 instrument with a direct inlet system. Column chromatography was carried out on Kanto silica gel 60 N (40–50 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F₂₅₄ plates with visualization by ultraviolet, anisaldehyde stain solution or phosphomolybdic acid stain solution. All non-aqueous reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Reagents were purchased from TCI, nacalai tesque, Kanto chemical, FUJIFILM Wako chemicals or Sigma-Aldrich. Reagents and solvents were used without purification. Substrate 4 was synthesized by a reported method [12], and spectra data agreed with the literature values.

3.2. Preparation and Characterization of Novel Compounds

3.2.1. General Procedure for the Synthesis of Alkyl 5-Methyl-2-oxo-2,3-dihydro-1H-benzo[b]azepine-1-carboxylate (5a,b,d,e)

A solution of 4 in THF was cooled to $-78\text{ }^\circ\text{C}$, *n*-BuLi (1.6 M in *n*-hexane) was added, and the mixture was stirred for 30 min. Alkyl chloroformate was added to the mixture, and

the mixture was stirred for 20 min at same temperature. After confirming the disappearance of substrate **4** by TLC, saturated the NH_4Cl aqueous solution was added. The reaction mixture was extracted with CH_2Cl_2 . The organic layer was washed with a saturated aqueous NaCl solution, dried with anhydrous MgSO_4 , filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **5**.

Methyl 5-Methyl-2-oxo-2,3-dihydro-1*H*-benzo[*b*]azepine-1-carboxylate (**5a**)

4 (0.10 g, 0.58 mmol), THF (2.3 mL), *n*-BuLi (0.73 mL, 1.2 mmol), methyl chloroformate (90 μL , 1.2 mmol), eluent (AcOEt/*n*-hexane = 1/2), **5a** (0.14 g, quant.). Pale yellow oil. IR (KBr): 3547, 2954, 1779, 1224 cm^{-1} . $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.22 (3H, s), 2.69 (1H, brs), 3.04 (1H, brs), 3.79 (3H s), 5.90 (1H, tq, $J = 7.1, 1.4$ Hz), 7.24–7.27 (1H, m), 7.30–7.37 (2H, m), 7.47–7.49 (1H, m). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 20.8, 37.4, 54.1, 121.6, 126.5, 127.0, 127.2, 127.6, 135.5, 135.9, 136.4, 153.9, 172.5. MS (EI): m/z (%) 231 (M^+ , 13), 190 (11), 189 (100), 144 (37). HRMS (EI): m/z calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_3$ [M^+] 231.0895, found 231.0892.

Ethyl 5-Methyl-2-oxo-2,3-dihydro-1*H*-benzo[*b*]azepine-1-carboxylate (**5b**)

4 (0.13 g, 0.74 mmol), THF (7.4 mL), *n*-BuLi (0.69 mL, 1.1 mmol), ethyl chloroformate (0.14 mL, 1.5 mmol), eluent (AcOEt/*n*-hexane = 1/2), **5b** (0.13 g, 70%). Pale yellow oil. IR (KBr): 3381, 2981, 1777, 1219 cm^{-1} . $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.25 (3H, t, $J = 7.1$ Hz), 2.21 (3H s), 2.69 (1H, brs), 3.02 (1H, brs), 4.25 (2H, brq, $J = 6.2$ Hz), 5.90 (1H, tq, $J = 7.0, 1.5$ Hz), 7.21–7.34 (3H, m), 7.46–7.49 (1H, m). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 14.4, 25.0, 34.3, 61.2, 115.2, 119.5, 121.4, 123.3, 128.0, 128.2, 134.4, 137.9, 153.9, 177.6. MS (EI): m/z (%) 245 (M^+ , 16), 204 (12), 203 (100), 173 (10), 172 (17), 158 (14), 144 (55), 143 (12), 131 (19), 130 (27). HRMS (EI): m/z calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_3$ [M^+] 245.1052, found 245.1050.

tert-Butyl 5-Methyl-2-oxo-2,3-dihydro-1*H*-benzo[*b*]azepine-1-carboxylate (**5c**)

A solution of **4** (0.31 g, 1.8 mmol) in CH_2Cl_2 (3.0 mL) was added Boc_2O (0.62 mL, 2.7 mmol), DMAP (44 mg, 0.36 mmol) and Et_3N (0.75 mL, 5.4 mmol) and stirred at rt for 24 h. After confirming the consumption of substrate **4** by TLC, saturated aqueous solution of NaHCO_3 was added to the reaction mixture. After extraction with CH_2Cl_2 , the organic layer was washed with a saturated aqueous NaCl solution, dried with anhydrous MgSO_4 , filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/2) to obtain **5c** (0.44 g, 90%) as pale yellow oil. IR (KBr): 3374, 2979, 2253, 1774, 1240 cm^{-1} . $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.44 (9H, s), 2.21 (3H, s), 2.66 (1H, brs), 2.98 (1H, brs), 5.90 (1H, tq, $J = 6.8, 1.4$ Hz), 7.22–7.31 (3H, m), 7.45–7.47 (1H, m). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 20.9, 27.6 (3C), 37.2, 83.6, 121.8, 126.4, 126.5, 126.6, 127.3, 135.1, 136.1 136.3, 151.9, 171.7. MS (EI): m/z (%) 273 (M^+ , 7), 174 (12), 173 (100), 172 (14), 158 (18), 144 (23), 131 (34), 130 (17), 57 (33). HRMS (EI): m/z calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_3$ [M^+] 273.1365, found 273.1370.

Benzyl 5-Methyl-2-oxo-2,3-dihydro-1*H*-benzo[*b*]azepine-1-carboxylate (**5d**)

4 (0.19 g, 1.1 mmol), THF (11 mL), *n*-BuLi (1.0 mL, 1.6 mmol), benzyl chloroformate (0.84 mL, 2.2 mmol), eluent (AcOEt/*n*-hexane = 1/2), **5d** (0.31 g, 92%). Pale yellow oil. IR (KBr): 3535, 2949, 1779, 1218 cm^{-1} . $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.20 (3H, s), 2.69 (1H, brs), 3.04 (1H, brs), 5.16 (1H, brs), 5.25 (1H, brs), 5.89 (1H, tq, $J = 6.9, 1.4$ Hz), 7.15 (1H, dd, $J = 8.0, 1.3$ Hz), 7.14–7.37 (7H, m), 7.46 (1H, dd, $J = 7.8, 1.6$ Hz). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 20.8, 37.4, 68.6, 121.5, 126.5, 126.9, 127.0, 127.3, 127.4, 128.0, 128.2, 128.4 (2C), 134.9, 135.5, 135.8, 136.4, 153.1, 172.4. MS (EI): m/z (%) 307 (M^+ , 14), 266 (11), 265 (59), 221 (48), 172 (24), 157 (18), 144 (15), 91 (100). HRMS (EI): m/z calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3$ [M^+] 307.1208, found 307.1206.

Allyl 5-Methyl-2-oxo-2,3-dihydro-1*H*-benzo[*b*]azepine-1-carboxylate (**5e**)

4 (0.10 g, 0.58 mmol), THF (5.8 mL), *n*-BuLi (0.54 mL, 0.87 mmol), allyl chloroformate (0.12 mL, 1.2 mmol), eluent (AcOEt/*n*-hexane = 1/2), **5e** (0.12 g, 78%). Pale yellow oil. IR (KBr): 3370, 2979, 1773, 1240 cm^{-1} . $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.21 (3H, s), 2.70 (1H,

brs), 3.03 (1H, brs), 4.67 (2H, brs), 5.18–5.29 (2H, m), 5.80–5.93 (2H, m), 7.25–7.37 (3H, m), 7.45–7.49 (1H, m). ^{13}C -NMR (100 MHz, CDCl_3): δ 25.1, 34.6, 65.9, 118.1, 119.8, 121.7, 123.6, 128.1, 128.2, 132.4, 134.3, 137.7, 153.6, 162.1, 177.8. MS (EI): m/z (%) 257 (M^+ , 16), 216 (14), 215 (100), 184 (11), 172 (19), 171 (10), 170 (21), 156 (12), 144 (35), 143 (12), 130 (19). HRMS (EI): m/z calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_3$ [M^+] 257.1052, found 257.1052.

3.2.2. General Procedure for the Synthesis of (Z)-4-{2-[(Alkoxy carbonyl)amino]phenyl}pent-3-enoic acids **2**

A solution of **5** in THF and H_2O was added NaOH and stirred at room temperature for 2 h. After confirming the consumption of substrate **5** by TLC, the reaction mixture was acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with brine, dried with anhydrous MgSO_4 , filtered. The filtrate was concentrated under reduced pressure to obtain **2**.

(Z)-4-{2-[(Methoxycarbonyl)amino]phenyl}pent-3-enoic Acid (**2a**)

5a (0.11 g, 0.49 mmol), THF (4.9 mL), H_2O (4.9 mL), NaOH (58 mg, 2.5 mmol), **2a** (0.15 g, quant.). Yellow oil. IR (KBr): 3311, 2959, 1710, 1523, 1219 cm^{-1} . ^1H -NMR (500 MHz, CDCl_3): δ 2.00 (3H, s), 2.85 (2H, d, $J = 7.3$ Hz), 3.73 (3H, s), 5.78 (1H, td, $J = 7.3, 1.2$ Hz), 6.98–7.00 (2H, m), 7.06 (1H, t, $J = 7.3$ Hz), 7.28 (1H, t, $J = 8.8$ Hz), 8.02 (1H, brs). ^{13}C -NMR (125 MHz, CDCl_3): δ 25.0, 34.2, 52.2, 119.6, 121.4, 123.5, 128.0, 128.3, 130.1, 134.4, 138.1, 154.2, 177.2. MS (FAB): m/z (%) 250 ($\text{M}+\text{H}^+$, 64), 204 (11). HRMS (FAB): m/z calcd for $\text{C}_{13}\text{H}_{16}\text{NO}_4$ [$\text{M}+\text{H}^+$] 250.1079, found 250.1078.

(Z)-4-{2-[(Ethoxycarbonyl)amino]phenyl}pent-3-enoic Acid (**2b**)

5b (0.23 g, 0.92 mmol), THF (9.2 mL), H_2O (9.2 mL), NaOH (0.18 g, 4.6 mmol), **2b** (0.23 g, 95%). Pale yellow oil. IR (KBr): 3396, 2979, 1731, 1215 cm^{-1} . ^1H -NMR (500 MHz, CDCl_3): δ 1.27 (3H, t, $J = 7.3$ Hz), 1.99 (3H, s), 2.83 (2H, d, $J = 6.4$ Hz), 4.18 (2H, q, $J = 7.0$ Hz), 5.77 (1H, brs), 6.98–7.06 (2H, m), 7.27 (1H, t, $J = 7.0$ Hz), 8.02 (1H, brs). ^{13}C -NMR (125 MHz, CDCl_3): δ 14.4, 25.1, 34.5, 61.3, 119.6, 121.6, 123.4, 128.1, 128.2, 130.2, 134.4, 137.8, 154.0, 177.8. MS (EI): m/z (%) 263 (M^+ , 15), 204 (22), 203 (100), 144 (69), 132 (11), 131 (21), 130 (31). HRMS (EI): m/z calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4$ [M^+] 263.1158, found 263.1154.

(Z)-4-{2-[(*tert*-Butoxycarbonyl)amino]phenyl}pent-3-enoic Acid (**2c**)

5c (0.27 g, 0.97 mmol), THF (9.7 mL), H_2O (9.7 mL), NaOH (0.20 g, 4.9 mmol), **2c** (0.28 g, 99%). Yellow solids. mp: 126–128 $^\circ\text{C}$, IR (KBr): 3410, 2977, 1730, 1164 cm^{-1} . ^1H -NMR (300 MHz, CDCl_3): δ 1.49 (9H, s), 2.01 (3H, s), 2.86 (2H, d, $J = 6.2$ Hz), 5.79 (1H, td, $J = 7.3, 1.4$ Hz), 6.71 (1H, s), 6.96–7.05 (2H, m), 7.23–7.29 (1H, m), 8.01 (1H, d, $J = 8.0$ Hz). ^{13}C -NMR (100 MHz, CDCl_3): δ 25.0, 28.2 (3C), 34.3, 80.5, 119.6, 121.3, 123.0, 128.0, 128.2, 129.8, 134.8, 138.0, 153.0, 177.4. MS (FAB): m/z (%) 292 ($\text{M}+\text{H}^+$, 42), 236 (68), 192 (45), 146 (23). HRMS (FAB): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4$ [$\text{M}+\text{H}^+$] 292.1549, found 292.1544.

(Z)-4-{2-[(Benzyloxycarbonyl)amino]phenyl}pent-3-enoic Acid (**2d**)

5d (0.12 g, 0.37 mmol), THF (3.7 mL), H_2O (3.7 mL), NaOH (74 mg, 1.9 mmol), **2d** (0.13 g, quant.). Pale yellow oil. IR (KBr): 3401, 2965, 1736, 1216 cm^{-1} . ^1H -NMR (500 MHz, CDCl_3): δ 1.98 (3H, s), 2.81 (2H, d, $J = 7.0$ Hz), 5.16 (2H, brd, $J = 9.5$ Hz), 5.74 (1H, qt, $J = 1.5, 8.0$ Hz), 6.98 (1H, d, $J = 7.0$ Hz), 7.05 (1H, t, $J = 7.3$ Hz), 7.25–7.39 (6H, m), 8.06 (1H, brs). ^{13}C -NMR (125 MHz, CDCl_3): δ 25.1, 34.3, 66.9, 119.7, 121.4, 123.5, 127.0, 128.1, 128.2, 128.3 (2C), 128.5 (2C), 130.1, 134.3, 136.1, 137.9, 153.5, 177.6. MS (EI): m/z (%) 325 (M^+ , 10), 265 (12), 190 (40), 175 (10), 144 (54), 130 (14), 91 (100). HRMS (EI): m/z calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4$ [M^+] 325.1314, found 325.1312.

(Z)-4-{2-[(Allyloxycarbonyl)amino]phenyl}pent-3-enoic Acid (**2e**)

5e (0.18 g, 0.65 mmol), THF (6.5 mL), H_2O (6.5 mL), NaOH (0.13 g, 3.3 mmol), **2e** (0.14 g, 79%). Pale yellow oil. IR (KBr): 3393, 2940, 1732, 1213 cm^{-1} . ^1H -NMR (500 MHz,

CDCl₃): δ 1.98 (3H, s), 2.82 (2H, brs), 4.63 (2H, d, $J = 4.5$ Hz), 5.21 (1H, d, $J = 10.5$ Hz), 5.32 (1H, d, $J = 17.0$ Hz), 5.76 (1H, brs), 5.89–5.98 (1H, m), 6.96–7.08 (2H, m), 7.25–7.28 (1H, m), 8.01 (1H, brs). ¹³C-NMR (125 MHz, CDCl₃): δ 25.1, 34.7, 65.9, 118.1, 119.7, 121.8, 123.6, 128.1, 128.2, 130.4, 132.5, 134.3, 137.6, 153.6, 177.8. MS (EI): m/z (%) 275 (M⁺, 21), 216 (27), 215 (100), 190 (21), 172 (15), 170 (11), 145 (11), 144 (86), 131 (21), 130 (40). HRMS (EI): m/z calcd for C₁₅H₁₇NO₄ [M⁺] 275.1158, found 275.1159.

Methyl (Z)-4-[2-[(*tert*-Butoxycarbonyl)amino]phenyl]pent-3-enoate (6)

A solution of **5c** (0.27 g, 1.0 mmol) in MeOH (10 mL) was added NaOMe (54 mg, 5.0 mmol) and stirred at rt for 1.5 h. After confirming the consumption of substrate **5c** by TLC, the reaction mixture was acidified with 10% HCl and extracted with AcOEt, the organic layer was washed with brine, dried with anhydrous MgSO₄, filtered, and the filtrate was concentrated under reduced pressure to obtain **6** (0.28 g, 93%). Colorless oil. IR (KBr): 3399, 2978, 1731, 1516, 1160 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃): δ 1.51 (9H, s), 2.01 (3H, s), 2.82 (2H, d, $J = 7.5$ Hz), 3.65 (3H, s), 5.81 (1H, t, $J = 7.5$ Hz), 6.72 (1H, brs), 6.96–7.04 (2H, m), 7.25 (1H, t, $J = 8.0$ Hz), 8.03 (1H, d, $J = 8.0$ Hz). ¹³C-NMR (125 MHz, CDCl₃): δ 25.0, 28.3 (3C), 34.4, 51.9, 80.3, 119.5, 121.9, 123.0, 128.0, 128.1, 129.9, 134.8, 137.5, 153.0, 172.2. MS (FAB): m/z (%) 306 (M+H⁺, 45), 250 (69), 206 (100), 146 (29), 131 (27). HRMS (FAB): m/z calcd for C₁₇H₂₄NO₄ [M+H⁺] 306.1705, found 306.1712.

3.2.3. Methyl 3-Iodo-3-(4-methyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-4-yl)propanoate (7)

To a solution of **6** (30 mg, 0.10 mmol) in a mixture of MeCN/MeOH (1.2 mL, 20/1) was added a solution of NIS (3.4 mg, 0.15 mmol) in MeCN (0.30 mL) at -45 °C. The reaction mixture was stirred and allowed to room temperature for 5 h. After confirming the consumption of substrate **6** by TLC, the reaction was quenched with aqueous solution of Na₂S₂O₃. After extraction with AcOEt, the organic layer was washed with brine, dried with anhydrous MgSO₄, filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/2) to obtain **7** (33 mg, 89%) as a pale yellow oil. IR (KBr): 3619, 3019, 1730, 1046 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ 1.87 (3H, s), 3.11 (1H, dd, $J = 16.5, 10.2$ Hz), 3.20 (1H, dd, $J = 16.6, 3.9$ Hz), 3.70 (3H, s), 4.79 (1H, dd, $J = 10.2, 3.6$ Hz), 6.91 (1H d, $J = 7.8$ Hz), 7.08 (1H, t, $J = 7.8$ Hz), 7.17 (1H, d, $J = 7.3$ Hz), 7.30 (1H, t, $J = 7.8$ Hz), 9.21 (1H, s). ¹³C-NMR (100 MHz, CDCl₃): δ 24.5, 33.8, 40.9, 52.3, 85.5, 115.1, 122.2, 123.6, 124.4, 129.9, 133.9, 151.0, 170.7. MS (EI): m/z (%) 375 (M⁺, 13), 162 (100), 144 (27), 130 (12). HRMS (EI): m/z calcd for C₁₃H₁₄NO₄I [M⁺] 374.9968, found 374.9960.

3.2.4. General Procedure for the Oxidative Cyclization of 2

To a solution of **2** in MeCN was added Pd(OAc)₂ and PhI(OAc)₂. The reaction mixture was stirred under reflux for 6 h. After confirming the consumption of substrate **2** by TLC, the reaction was quenched with aqueous solution of Na₂S₂O₃. After extraction with AcOEt, the organic layer was washed with brine, dried with anhydrous MgSO₄, filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain **3**.

Methyl (3aR*,8bR*)-8b-Methyl-2-oxo-2,3,3a,8b-tetrahydro-4H-furo[3,2-*b*]indole-4-carboxylate (3a)

2a (78 mg, 0.31 mmol), MeCN (3.1 mL), Pd(OAc)₂ (14 mg, 60 μ mol), PhI(OAc)₂ (0.15 g, 0.47 mmol), eluent (AcOEt/*n*-hexane = 1/2), **3a** (59 mg, 78%). Yellow solid. mp: 160–162 °C. IR (KBr): 3021, 1776, 1716 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ 1.82 (3H, s), 2.96 (1H, d, $J = 19.5$ Hz), 3.23 (1H, dd, $J = 19.5, 8.2$ Hz), 3.89 (3H s), 4.60 (1H, d, $J = 6.3$ Hz), 7.11 (1H, t, $J = 7.3$ Hz), 7.36 (1H, d, $J = 7.8$ Hz), 7.40 (1H, d, $J = 7.8$ Hz), 7.91 (1H, brs). ¹³C-NMR (100 MHz, CDCl₃): δ 24.4, 36.3, 53.1, 64.6, 89.4, 115.2, 123.7, 124.1, 129.8, 131.1, 141.8, 152.6, 174.1. MS (EI): m/z (%) 247 (M⁺, 83), 202 (60), 188 (100), 158 (35), 146 (17), 144 (83), 143 (21). HRMS (EI): m/z calcd for C₁₃H₁₃NO₄ [M⁺] 247.0845, found 247.0847.

Ethyl (3aR*,8bR*)-8b-Methyl-2-oxo-2,3,3a,8b-tetrahydro-4H-furo[3,2-b]indole-4-carboxylate (**3b**)

2b (0.23 g, 0.87 mmol), Pd(OAc)₂ (40 mg, 0.18 mmol), PhI(OAc)₂ (0.42 g, 1.3 mmol), MeCN (8.7 mL), eluent (AcOEt/*n*-hexane = 1/2), **3b** (0.10 g, 56%). Yellow solid. mp: 116–118 °C. IR (KBr): 3532, 2980, 1778, 1713, 1225 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ 1.38 (3H, brs), 1.83 (3H, s), 2.98 (1H, d, *J* = 19.0 Hz), 3.23 (1H, dd, *J* = 19.2, 8.2 Hz), 4.35 (2H, brq, *J* = 6.6 Hz), 4.60 (1H, dd, *J* = 8.2, 2.0 Hz), 7.10 (1H, t, *J* = 7.3 Hz), 7.36 (1H, d, *J* = 7.7 Hz), 7.41 (1H, d, *J* = 8.2 Hz), 7.93 (1H, brs). ¹³C-NMR (100 MHz, CDCl₃): δ 14.5, 24.4, 36.5, 62.2, 64.6, 89.4, 115.2, 123.6, 124.1, 130.0, 131.1, 141.7, 152.2, 174.3. MS (EI): *m/z* (%) 261 (M⁺, 71), 188 (42), 146 (23), 144 (100), 130 (30). HRMS (EI): *m/z* calcd for C₁₄H₁₅NO₄ [M⁺] 261.1001, found 261.0999.

tert-Butyl (3aR*,8bR*)-8b-Methyl-2-oxo-2,3,3a,8b-tetrahydro-4H-furo[3,2-b]indole-4-carboxylate (**3c**)

2c (0.16 g, 0.55 mmol), Pd(OAc)₂ (25 mg, 0.11 mmol), PhI(OAc)₂ (0.27 g, 0.83 mmol), MeCN (5.5 mL), eluent (AcOEt/*n*-hexane = 1/2), **3c** (60 mg, 38%). Yellow solid. mp: 172–174 °C. IR (KBr): 3534, 2976, 1778, 1711, 1381, 1166 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃): δ 1.58 (9H, s), 1.82 (3H, s), 2.99 (1H, brs), 3.20 (1H, dd, *J* = 19.5, 8.0 Hz), 4.54 (1H, brs), 7.08 (1H, t, *J* = 7.5 Hz), 7.35 (1H, t, *J* = 8.0 Hz), 7.39 (1H, d, *J* = 7.5 Hz), 7.92 (1H, brs). ¹³C-NMR (100 MHz, CDCl₃): δ 24.4, 28.3 (3C), 36.7, 64.6, 82.1, 89.5, 115.1, 123.3, 124.1, 129.6, 131.0, 142.3, 152.1, 174.5. MS (EI): *m/z* (%) 289 (M⁺, 27), 233 (100), 189 (41), 188 (23), 144 (58), 57 (68). HRMS (EI): *m/z* calcd for C₁₆H₁₉NO₄ [M⁺] 289.1314, found 289.1311.

Benzyl (3aR*,8bR*)-8b-Methyl-2-oxo-2,3,3a,8b-tetrahydro-4H-furo[3,2-b]indole-4-carboxylate (**3d**)

2d (0.28 g, 0.85 mmol), Pd(OAc)₂ (38 mg, 0.17 mmol), PhI(OAc)₂ (0.41 g, 1.3 mmol), MeCN (8.5 mL), eluent (AcOEt/*n*-hexane = 1/2), **3d** (90 mg, 33%). Yellow solid. mp: 140–142 °C. IR (KBr): 3532, 2974, 1777, 1719, 1402, 1226 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃): δ 1.81 (3H, s), 2.93 (1H, brs), 3.17 (1H, brs), 4.60 (1H, brs), 5.27 (1H, brs), 5.31 (1H, brs), 7.10 (1H, brs), 7.37–7.41 (7H, m), 7.96 (1H, brs). ¹³C-NMR (100 MHz, CDCl₃): δ 24.5, 36.6, 64.6, 67.9, 89.6, 115.3, 123.8, 124.1, 128.3 (2C), 128.6, 128.8 (2C), 129.8, 131.1, 135.4, 141.7, 151.8, 174.1. MS (EI): *m/z* (%) 323 (M⁺, 30), 279 (16), 144 (18), 91 (100). HRMS (EI): *m/z* calcd for C₁₉H₁₇NO₄ [M⁺] 323.1158, found 323.1155.

Allyl (3aR*,8bR*)-8b-Methyl-2-oxo-2,3,3a,8b-tetrahydro-4H-furo[3,2-b]indole-4-carboxylate (**3e**)

2e (0.14 g, 0.52 mmol), Pd(OAc)₂ (22 mg, 0.10 mmol), PhI(OAc)₂ (0.25 g, 0.78 mmol), MeCN (5.2 mL), eluent (AcOEt/*n*-hexane = 1/2), **3e** (41 mg, 29%). Yellow solid. mp: 70–72 °C. IR (KBr): 3533, 2933, 1778, 1720, 1397, 1226 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): δ 1.83 (3H, s), 2.98 (1H, d, *J* = 18.0 Hz), 3.24 (1H, dd, *J* = 18.0, 8.1 Hz), 4.62 (1H dd, *J* = 8.1, 2.7 Hz), 4.77 (2H, brs), 5.32 (1H, d, *J* = 10.5 Hz), 5.39 (1H, d, *J* = 17.1 Hz), 5.95–6.05 (1H, m), 7.11 (1H, t, *J* = 7.5 Hz), 7.28–7.43 (2H, m), 7.90 (1H, brs). ¹³C-NMR (125 MHz, CDCl₃, major): δ 24.5, 36.6, 64.6, 66.7, 89.5, 115.3, 119.1, 123.8, 124.1, 129.8, 131.2, 131.8, 141.9, 151.7, 174.2. MS (EI): *m/z* (%) 273 (M⁺, 100), 188 (22), 146 (56), 144 (85), 41 (20). HRMS (EI): *m/z* calcd for C₁₅H₁₅NO₄ [M⁺] 273.1001, found 273.1000.

4. Conclusions

We investigated the construction of the furoindolin-2-one structure corresponding to the A to C ring system of lapidilectine B (**1**). The furoindolin-2-one structure was constructed directly by double functionalization of the internal alkene with carboxyl and carbamoyl groups under oxidative conditions using PhI(OAc)₂. Furthermore, we succeeded in obtaining the desired product in higher yield with a palladium(II) catalyst under oxidative conditions. We are currently synthesizing more advanced substrates for the synthesis of lapidilectine B (**1**).

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