รายงานวิจัยฉบับสมบูรณ์

โครงการ

การสังเคราะห์เสโคฟีแนนโทรอินโดลิซิดินอัลคาลอยด์ที่พบได้น้อยในธรรมชาติ
(Synthesis of rare seco-phenanthroindolizidine alkaloids; tyloindicine F and 8a-hydroxysepticine)

TRG5580007

โดย

ดร. วรรณพร ดิสดี

กรกฎาคม 2557

สัญญาเลขที่ **TRG5580007**

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ผู้วิจัย

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สังกัด

สถาบันวิจัยจุฬาภรณ์

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

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Wannaporn Disadee

บทคัดย่อ

รหัสโครงการ : TRG5580007

ชื่อโครงการ : การสังเคราะห์เสโคฟีแนนโทรอินโดลิซิดินอัลคาลอยด์ที่พบได้น้อยในธรรมชาติ

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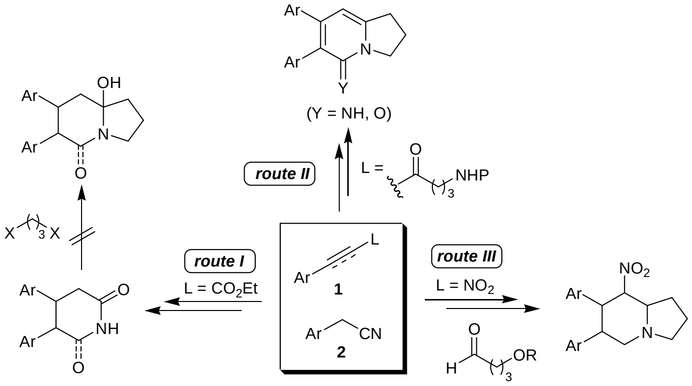

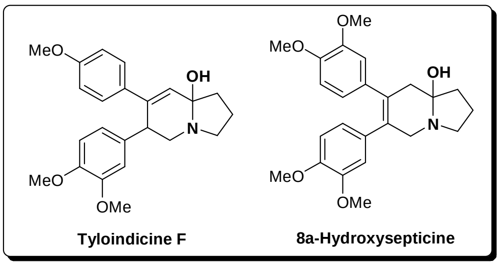

งานวิจัยนี้เป็นการสังเคราะห์สารเสโคฟีแนนโทรอินโดลิซิดินอัลคาลอยด์ซึ่งพบได้น้อยในธรรมชาติ คือ ไทโลอินดิซินเอฟและ 8a-ไฮดรอกซิเสพติซิน โดยมีวัตถุประสงค์เพื่อพัฒนาวิธีการสร้างวงเฮมิอะมินัลจากปฏิกิริยาที่ง่ายและสารตั้งต้นที่ราคาไม่แพงเพื่อเตรียมสารอนุพันธ์สำหรับประเมินค่าความเป็นพิษต่อเซลล์มะเร็งต่อไป

จากผลการทดลองเบื้องต้น การสร้างพันธะคาร์บอน-คาร์บอนโดยปฏิกิริยาไมเคิลระหว่างแอลไคน์หรือแอลคีน (**1**) กับเบนซิลไซยาไนด์ (**2**) ทำให้เกิดผลิตภัณฑ์ซึ่งใช้เป็นสารตั้งต้นที่สำคัญสำหรับการศึกษาการสร้างวงเฮมิอะมินัล ในเส้นทางที่ 1 เอไมด์ซึ่งไม่มีหมู่เร่งปฏิกิริยาไม่สามารถเกิดปฏิกิริยาบาร์เบียร์ได้ ในเส้นทางที่ 2 สามารถสังเคราะห์ไบไซคลิก-2-ไพริโดนได้โดยผ่านปฏิกิริยาการสร้างอิมีนและการสร้างวงแลคแทมภายใต้สภาวะกรดหรือเบส และในเส้นทางที่ 3 สามารถเตรียมวงอินโดลิซิดินได้ด้วยปฏิกิริยาไนโตรแมนนิชแบบวันพอต ซึ่งผลิตภัณฑ์ที่ได้จากเส้นทางที่ 2 และ 3 สามารถใช้เป็นสารสำคัญในการสังเคราะห์เสโคฟีแนนโทรอินโดลิซิดินได้

คำหลัก : ไทโลอินดิซินเอฟ, 8a-ไฮดรอกซิเสพติซิน, เฮมิอะมินัล, เสโคฟีแนนโทรอินโดลิซิดิน

Abstract

Project Code : TRG5580007

Project Title : Synthesis of rare *seco*-phenanthroindolizidine alkaloids; tyloindicine F and 8a-hydroxysepticine

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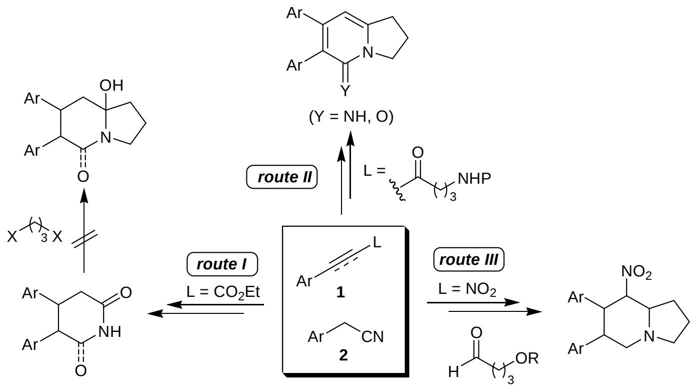
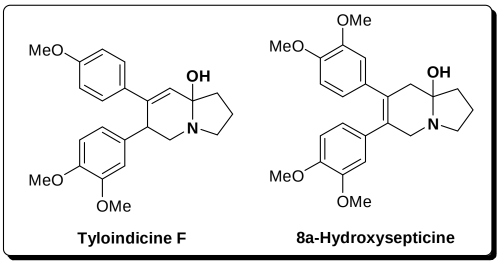
Project Period : 2 July 2012 – 1 July 2014





The main goals of our research are to establish a novel strategy of the synthesis of tyloindicine F and 8-hydroxysepticine for providing sufficient materials for their pharmacological evaluation. In the original retro-synthetic analysis (route I), the six-membered ring would be obtained via a Michael reaction/subsequent one-pot reduction/cyclization and the hemiaminal group would be prepared by a Barbier reaction. However, the alkylation step and the intramolecular Barbier reaction of unreactive amide were the main problems and difficult to accomplish. Thus, we designed a new retro-synthetic analysis on the basis of a novel methodology for the construction of indolizidine core and applied to hemiaminal formation. From the synthesis employing Michael adducts as the precursor, in route II, we have accomplished in the preparation of bicyclic 2-pyridone via the tandem double intramolecular cyclization of the imine formation and lactamization under acid or base condition. Moreover, in route III we have synthesized indolizidine core for *seco*-phenanthroindolizidines using a one-pot nitro-Mannich reaction/cyclization process. From synthetic point of views, both products from route II and III can be transformed to *seco*-phenanthroindolizidines.

Keywords : tyloindicine F, 8a-hydroxysepticine, hemiaminal, *seco*-phenanthroindolizidine

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CHAPTER I

Introduction

Isolation and Structures

The phenanthroindolizidine and phenanthroquinolizidine alkaloids are small two groups of alkaloids possessing a pentacyclic structure shown in **Figure 1-1**. These alkaloids exist principally in plants of the Asclepiadaceae, Moracea, Lauraceae, Vitaceae and Urticaceae families. Tylophorine (**1**), the representative compound of this group, was first isolated by Indian group from plant in genus *Tylophora*, a native plant of India[1] (**Figure 1-2**).

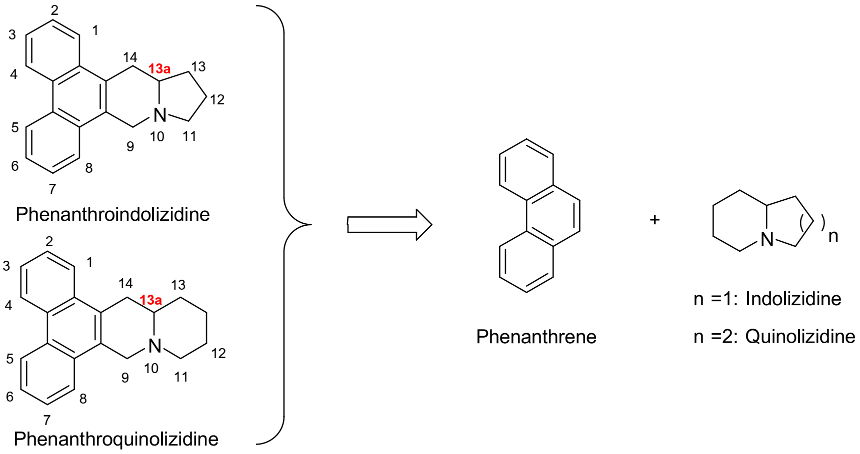


Figure 1-1 General structure feature and numbering system

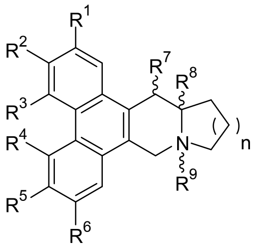
Leaves of the *Tylophora* genus have been used traditionally for centuries in the treatment of various ailments of the respiratory system such as allergies, bronchitis, dysentery, rheumatism, and asthma in India and East Asian countries.

In 1935, tyrophorine (**1**) was reported as the major alkaloid from *Tylophora indica*.[1] Its structure and stereochemistry were reported in 1960.[2] Tylophorine was initially reported as having the (*S*)-absolute stereochemistry, but a total synthesis and optical rotation measurement led to the revision to (*R*). Since their discovery, over 60 of structurally related compounds together with their *seco*- and *N*-oxides analogues have been reported and some examples are given in **Table 1-1** and **Table 1-2**.[3]

Tylophorine: R^1=R^3=OMe, R^2=X=H
Tylophorinine: R^1=R^2=H, R^3=OMe, X=OH
Tylocrebine: R^1=R^2=OMe, R^3=X=H
Antofine: R^1=OMe, R^2=R^3=X=H

Figure 1-2 *Tylophora indica* plant and the well-known phenanthroindolizidine alkaloids

Table 1-1 Examples of phenanthroindolizidine and phenanthroquinolizidine alkaloids

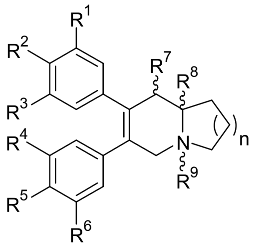


no.	name	n	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
1	tylophorine	1	OMe	OMe	H	H	OMe	OMe	H	H	-
2	6-desmethyltylophorine	1	OMe	OMe	H	H	OH	OMe	H	H	-
3	7-desmethyltylophorine	1	OMe	OMe	H	H	OMe	OH	H	H	-
4	antofine	1	OMe	OMe	H	H	OMe	H	H	H	-
5	isoantofine	1	H	OMe	H	H	OMe	OMe	H	H	-
6	6-desmethyl-antofine	1	OMe	OMe	H	H	OH	H	H	H	-
7	14-hydroxy-antofine	1	OMe	OMe	H	H	OMe	H	OH	H	-
8	antofine-*N*-oxide	1	OMe	OMe	H	H	OMe	H	H	H	O
9	14-hydroxy-antofine-*N*-oxide	1	OMe	OMe	H	H	OMe	H	OH	H	O
10	tylocrebine	1	OMe	OMe	H	OMe	OMe	H	H	H	-
11	isotylocrebine	1	H	OMe	OMe	H	OMe	OMe	H	H	-
12	14-hydroxy-isotylocrebine	1	H	OMe	OMe	H	OMe	OMe	OH	H	-
13	4-desmethyl-isotylocrebine	1	H	OMe	OH	H	OMe	OMe	H	H	
14	hypoestestatin 1	1	OMe	OMe	H	H	OMe	H	H	Me	-

Table 1-1 ***(cont.)***

no.	name	n	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
15	hypoestestatin 2	1	OMe	OMe	H	H	OMe	H	OH	Me	-
16	cryptopleurine	2	OMe	OMe	H	H	OMe	H	H	H	-
17	cryptopleuridine	2	OCH_2CH_2O		H	H	OMe	H	H	H	
18	hydroxy-cryptopleurine	2	OMe	OMe	H	H	OMe	H	OH	H	-
19	boehmeriasin A	2	H	OMe	H	H	OMe	OMe	H	H	
20	boehmeriasin B	2	H	OMe	H	H	OH	OMe	H	H	
21	ficuseptine C	1	OCH_2CH_2O		H	H	OMe	H	H	H	-
22	tylophoridine	1	H	OMe	H	H	OMe	OMe	OH	H	-
23	tylophorinidine	1	H	OMe	H	H	OH	OMe	OH	H	-
24	5-hydroxy-*O*-methyl tylophorinidine	1	H	OMe	H	OH	OMe	OMe	OH	H	-
25	tylophoridicine C	1	H	OMe	H	H	OH	OMe	OH	H	O
26	tylophoridicine F	1	H	OMe	H	H	OMe	OMe	OH	H	O

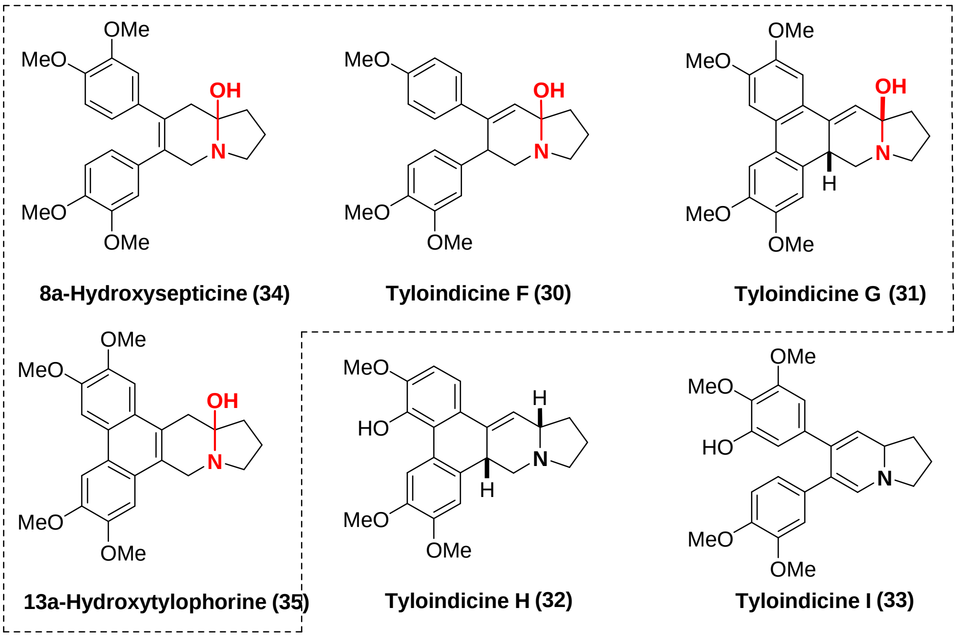
Table 1-2 Examples of *seco*-compounds of phenanthroindolizidine alkaloids



no.	name	n	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
27	*seco*-antofine	1	OMe	OMe	H	H	OMe	H	H	H	-
28	6-*O*-desmethyl-*seco*-antofine	1	OMe	OMe	H	H	OH	H	H	H	-
29	julandine	2	OMe	OMe	H	H	OMe	H	H	H	-

In 1991, Ali M. *et al*. reported the isolation of another group of phenanthroindolizidine alkaloids from *Tylophora indica* Merrill, namely tyloindicines F, G, H, and I (**Figure 1-3**).[4] This rare group contains unique features which are different from those of any previously known phenanthroindolizidines. The double bond in indolizidine ring, which is typically part of the phenanthrene core, appears at the *exo*-position (C-7 and C-8) rather than at the regular *endo*-position (C-6 and C-7, *i.e.* in tylophorine). This double bond is a common structural pattern in this newly found group of compounds. Other features include the angular tertiary hemiaminal seen in tyloindicines F and G, and an unusual diene system in tyloindicine I.

8a-Hydroxysepticine (**34**) and 13a-hydroxytylophorine (**35**) have yet to be reported for the total synthesis and cytotoxic evaluation.



8a-Hydroxysepticine (34) **Tyloindicine F (30)** **Tyloindicine G (31)**

13a-Hydroxytylophorine (35) **Tyloindicine H (32)** **Tyloindicine I (33)**

Figure 1-3 Rare phenanthroindolizidines and *seco*-derivatives containing angular hemiaminal moiety

Therapeutic Potential

These pentacyclic natural products exhibit a variety of biological effects including antitumor, anti-amoebic, anti-bacterial and anti-fungal activities. Among these biological activities, the most intriguing property is the profound cytotoxic activity against a broad range of cancer cell lines. In the early 1960's, tylocrebrine was introduced to clinical trials but failed due to CNS toxicity, manifested as disorientation and ataxia[5]. Medicinal interest in the phenanthroindolizidines was revived in the 1990's.

A number of these compounds are highly potent (10^{-8}–10^{-12} M) growth inhibitors (**Table 1-3**) in the NCI's 60 cell line assay and their mode of action appears to be different from other known anticancer compounds based on their COMPARE analysis[6]. A summary of their GI_{50} in various cancer cell lines is given in **Table 1-3**.

Table 1-3 GI_{50} values of some phenanthroindolizidines and phenanthroquinolizidines in various cancer cell lines[3b]

entry	name	cell lines[a]	GI_{50} (M)
1	(*R*)-tylophorine	KB	17×10^{-8}
2	(*S*)-tylophorine	NCI panel[b]	1.9×10^{-8}
3	tylocrebine	NCI panel[b]	3.0×10^{-8}
4	(*R*)-cryptopleurine	NCI panel[b]	1×10^{-12}
5	(*R*)-antofine	KB	1.5×10^{-8}
6	(+)-tylophorinidine	HepG2/PANC-1	1×10^{-8}
7	7-desmethyltylophorine	KB	1.5×10^{-8}
8	(*S*)-isotylocrebine	KB	4.5×10^{-8}
9	*seco*-antofine	KB	2.5×10^{-6}
10	6-*O*-desmethyl-*seco*-antofine	KB	4.0×10^{-7}
11	tyloindicine F	NCI panel[b]	1×10^{-10}
12	tyloindicine G	NCI panel[b]	1×10^{-10}
13	tyloindicine H	NCI panel[b]	4.9×10^{-10}
14	tyloindicine I	NCI panel[b]	4.4×10^{-9}
15	13(*R*)-14(*R*)-hydroxyantofine-*N*-oxide	KB	1.4×10^{-7}
16	13(*R*)-antofine-*N*-oxide	KB	1.4×10^{-7}
17	tylophoridicine C	HepG2/PANC-1	8×10^{-8}
18	tylophoridicine F	HepG2/PANC-1	7×10^{-8}

[a] *Cell Type: KB = human nasopharyngeal carcinoma (average of one or more cell lines), HepG2 = human hepatocellular carcinoma, PANC-1 = human pancreatic carcinoma.*

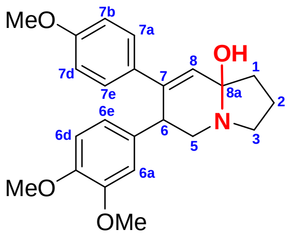
[b] *The average GI_{50} values for NCI 60-tumor cell line panels, SRB assay, search at* http://dtp.nci.nih.gov/dtpstandard/dwindex/index.jsp

Tyloindicine F demonstrated remarkable cytotoxicity against lung cancer (non-small cell and small cell) and melanoma cell lines in the nanomolar to sub-nanomolar range. Furthermore, the differential sensitivity of tyloindicine F (as revealed by COMPARE analysis) against the cell lines from different major human tumors indicated that this compound has specific anti-cancer activity and is not a general toxin. The COMPARE pattern analysis of the mean graph profile from the NCI-60 has developed into a convenient and powerful tool to correlate mechanisms of action across different anticancer agents. In this analysis, two or more compounds showing similar inhibitory profiles in the NCI-60 screen are presumed to function through the same mode of action. Tyloindicine F did not show a COMPARE pattern comparable to any known anticancer agent, thus suggesting that it acts either through a unique mechanism or a combination of several mechanisms. A new mode of action is of significant interest in anticancer drug development since cancer cells often acquire resistance against currently used chemotherapeutic agents.[7]

Background of the problem and its significance

In natural product discovery, the proposed structure of the isolated natural product can be incorrect due to errors in structure determination or through chemical reactions that occur during the isolation or characterization of the natural product. Due to the uniqueness and potential chemical instability of the structures of this group of compounds, a discussion about their structural assignment is necessary and worthwhile.

The structure of tyloindicine F was determined via chemical tests and through spectroscopic characterization[4b,8] (**Table 1-4** and **Table 1-5**).



Tyloindicine F (30)

Table 1-4 ^{1}H NMR (in TFA) data of tyloindicine F

Assignment	**δ (ppm), multiplicities**
H-7a	7.70, m
H-7b	7.10, m
H-7d	8.00, m
H-7e	7.10, m
H-6d	7.70, m
H-6e	6.96, m
H-6a	6.73, d
H-6	2.83, t
H-8	5.60, s
OMe at 6b, 6c	3.73, s
OMe at 7c	3.66, s

Table 1-5 Chemical testing data of tyloindicine F

Experiment data	**Results**	**Structural deduction**
$FeCl_3$ testing	No reaction	phenol absent
CH_2N_2 testing	No reaction	phenol absent
Ac_2O/pyridine testing	No reaction	3^o-hydroxyl
m.p.	245-247 ^{o}C	
IR	3,350 cm^{-1}	hydroxyl present
UV	No shift with NaOH addition	phenol absent
MS	M^+ 381	$C_{23}H_{27}NO_4$
MS	$[M-H_20]^+$ 363	hydroxyl present
MS	296	loss of hydroxyl-pyrrolidine

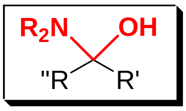
The most informative data was from NMR spectroscopy, even though no ^{13}C-NMR data were provided. Only a table of the ^{1}H-NMR peak assignments was available from the original literature. However, it was acquired on a 60 MHz Varian T-60 spectrometer using TFA as the solvent. The graphical spectrum itself, though, could not be obtained from the supporting material. It was reported that there were three methoxy group signals in the tyloindicine F ^{1}H-NMR spectrum. The substitution patterns on the southern and northern rings were undetermined and therefore assigned arbitrarily since their chemical shifts were not in accordance with other structurally related alkaloids like septicine and tylohirsuticine. Unlike the structural identification of similar phenanthroindolizidine alkaloids, no NOE experiments were carried out for tyloindicine F, and therefore the exact structure remained unsolved. Additionally, the specific optical rotation of tyloindincine F was reported as -0.5 (*c* = 0.05, acetic acid), which suggested the possibility that the compound may have been isolated as a racemic mixture.

In summary, tyloindicine F exhibited impressive anti-cancer activity and selectivity, but it has limited availability from natural sources. Hence, a total synthesis was undertaken to verify the proposed structure of tyloindicine F and to increase the supply of this natural product for biological studies.

Previous Synthesis of Tyloindicine F and Related Compounds

Natural products containing hemiaminal functional group

A hemiaminal is a functional group or type of chemical compound that has a hydroxyl group and an amine attached to the same carbon atom. Hemiaminals are intermediates in imine formation from an amine and a carbonyl compound by alkylimino-de-oxo-bisubstitution.[9]



Generic hemiaminal

Those generated from primary amines are unstable to the extent that they have never been isolated and very rarely been observed directly. In a 2007, the study of a hemiaminal substructure trapped in the cavity of a host-guest complex was carried out with a chemical half-life of 30 minutes. Because both amine and carbonyl group are isolated in a cavity, hemiaminal formation is favored due to a high forward reaction rate comparable to an intramolecular reaction and also due to restricted access of external base (another amine) to the same cavity which would favor elimination of water to the imine.[9,10]

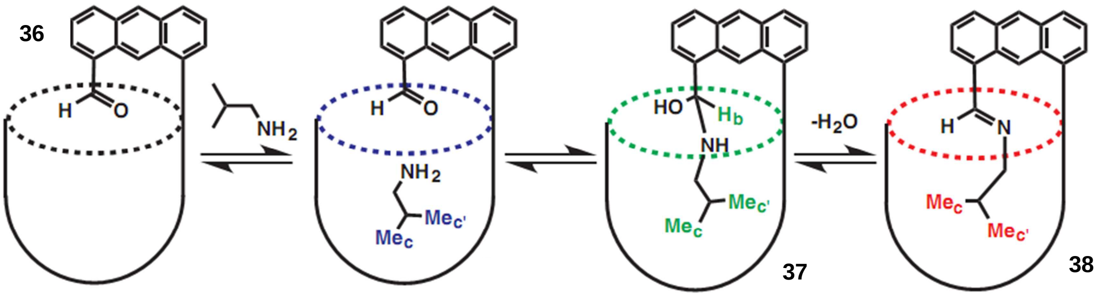
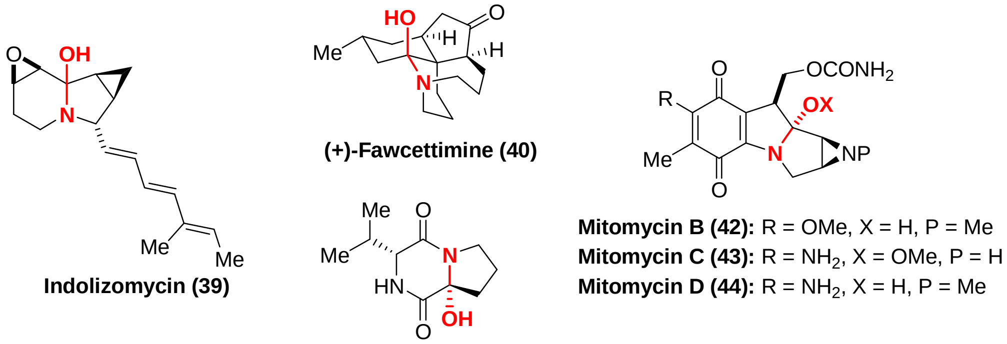


Figure 1-4 The reaction in the cavitand[2]

As for the tertiary hemiaminal at the angular position, examples of natural compounds possessing this structural feature are indolizomycin,[11] (+)-fawcettimine,[12] (+)-bacillusamide B,[13] and mitomycin B-D[14] (**Figure 1-5**) and rare phenanthroindolizidines[15-18] (**Figure 1-3**).



Indolizomycin (39)

(+)-Fawcettimine (40)

Mitomycin B (42): R = OMe, X = H, P = Me
Mitomycin C (43): R = NH_2, X = OMe, P = H
Mitomycin D (44): R = NH_2, X = H, P = Me

(+)-Bacillusamide B (41)

Figure 1-5 Examples of natural products containing angular hemiaminal

Examples of key steps for the construction of angular hemiaminal in natural compounds[11-18]

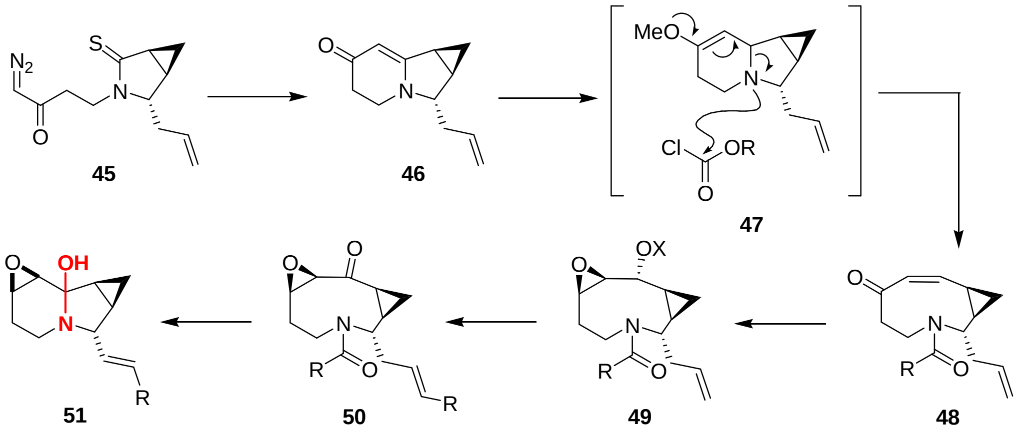
Indolizomycin (39)[11]

The first total synthesis of *dl*-indolizomycin has been achieved by Danishefsky in 1993. The key steps were:

I. aza-Robinson annulations of diazo ketone **45** to construct dihydropyridone **46**,

II. vinylogous McClusky fragmentation of **46** to provide azininone **48**,

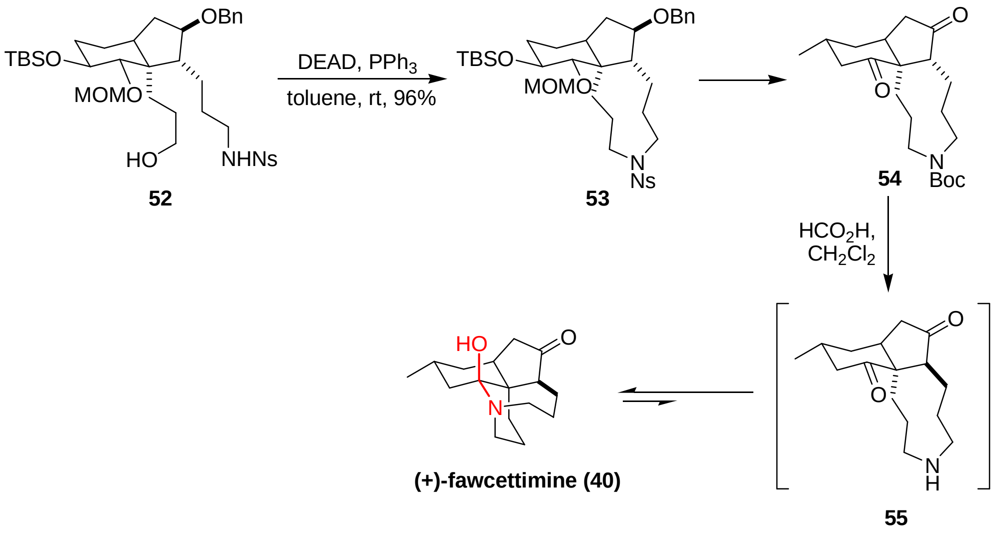
III. deprotection and in situ transannulation gave the highly unstable indolizomycin. The use of the [2-(trimethylsilyl)ethoxy]carbonyl (TEOC) protecting group was crucial for successful completion of the synthesis.



Scheme 1-1 Total synthesis of indolizomycin reported by Danishefsky *et al*.

(+)-Fawcettimine (40)[12]

The total synthesis of (+)-fawcettimine, one of the representative compounds of many *Lycopodium* alkaloids, was completed in a highly stereoselective manner by Mukai group. The crucial steps involve: (I) the efficient construction of the azonane framework **53** by the intramolecular Mitsunobu reaction of **52**, (II) removal of the Boc group and isomerization at the C_4-position to afford **55**, and (III) the carbinol-amine formation to the desired product **40**.



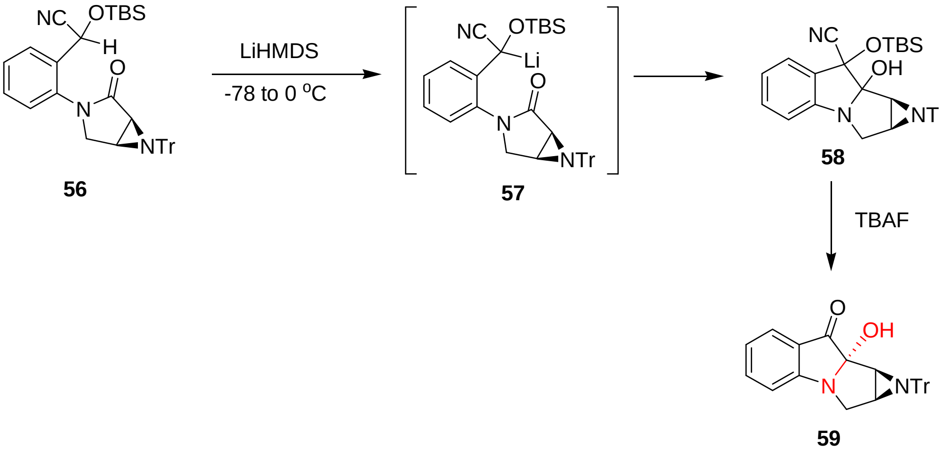
Scheme 1-2 Total synthesis of (+)-fawcettimine reported by Mukai *et al*.

(+)-Bacillusamide B (41)[13]

A new diketopiperazine derivative, bacillusamides B, has been isolated from the EtOAc extract of the sea urchin-derived *Bacillus* sp. This structure was elucidated by extensive spectroscopic methods. Furthermore, the absolute configurations of the amino acid residues were determined using Marfey's method. It displayed weak antifungal activity against Aspergillus niger. Nowaday, the total synthesis of bacillusamides B has yet been reported.

Mitomycin analogues (42-44)[14]

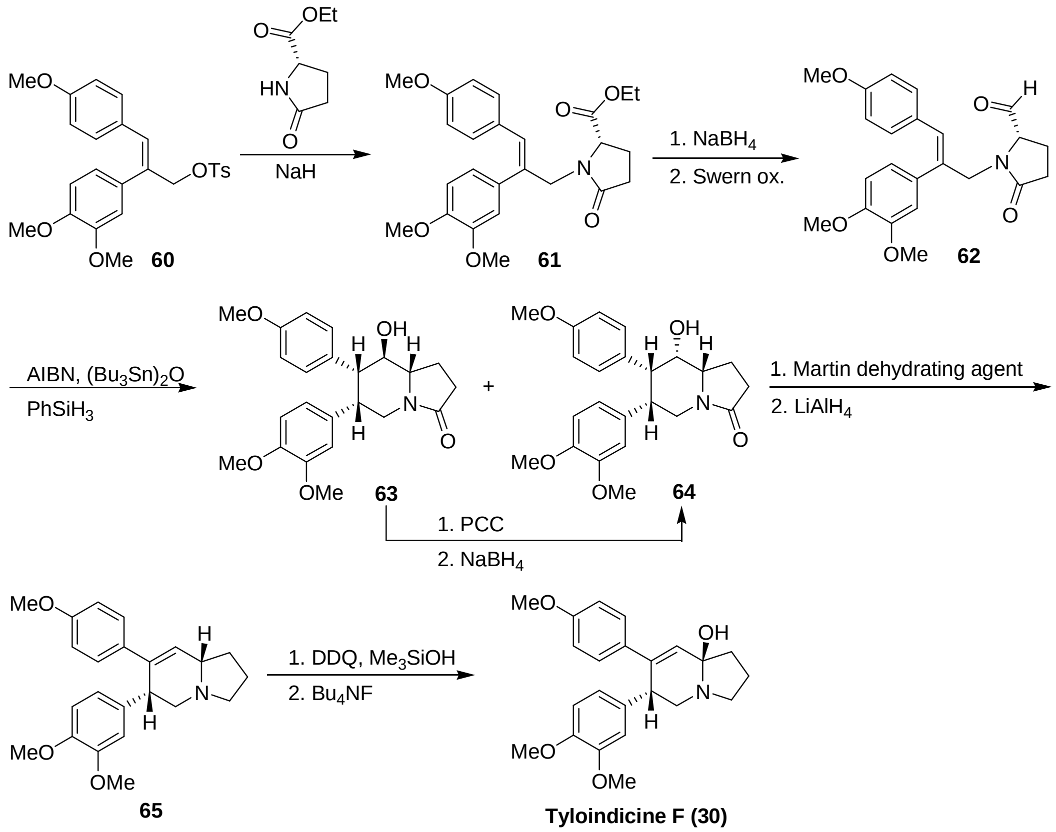
Mitosane-ketol analogues was accessed by internal acyl anion equivalent-lactam cyclization of adduct **57** and subsequent deprotection of TBS-group to furnish the desired compound **59**.



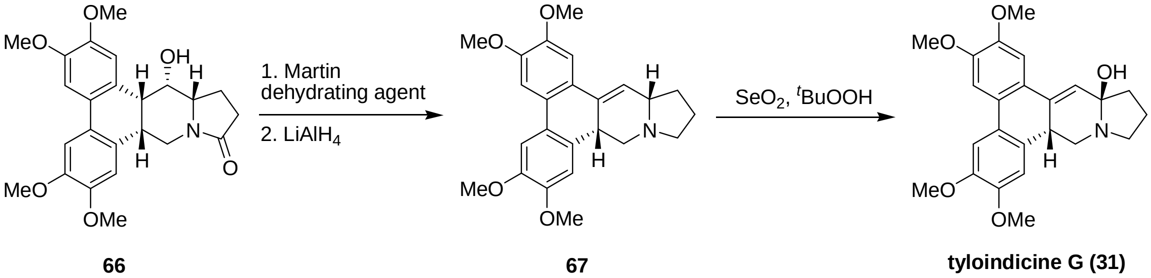
Scheme 1-3 Model strategy for mitosane-ketol reported by Vedejs *et al*.

Tyloindicines F-G (30 and 31)[15,16]

In 2003, Baker *et al*. published a patent claiming the synthesis of tyloindicines F-I.[15] However, the synthetic procedures in this patent were vague and little supporting data was presented. The same group subsequently published several journal articles describing the synthesis and evaluation of novel cytotoxic tylophorine analogues, but they did not report the syntheses of tyloindicines F-I.[16] From the patent, tyloindicine F was synthesized according to **Scheme 1-4**. Displacement of the tosylate **60** with ethyl (+)-(*S*)-2-pyrrolidine-5-carboxylate sodium salt gave benzyl amine derivative **61**. Reduction of the ester function, followed by Swern oxidation, gave the aldehyde **62**. This aldehyde was reductively cyclized to give the isomeric mixtures of saturated alcohols **63/64**. The more stable isomer **64** could be obtained by the sequence of PCC oxidation and $NaBH_4$ reduction. Martin sulfurane dehydration of alcohol adduct afforded the unsaturated intermediate, which was reduced with $LiAlH_4$ to *seco*-phenanthroindolizidine **65**. To the end, a process was developed that shows allylic selectivity over the allylic-benzylic protons and generates iminium ion by DDQ oxidative. Addition of Me_3SiOH and deprotection of silyl group gave tyloindicine F (**30**). The methodology developed for tyloindicine F was likewise applied to tyloindicine G (**31**) (**Scheme 1-5**).



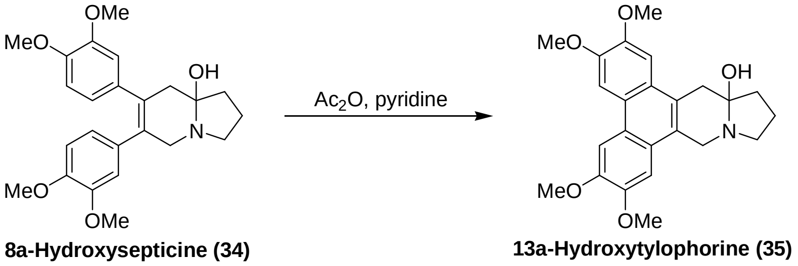
Scheme 1-4 Total synthesis of tyloindicine F published in US patent by Baker *et al*.



Scheme 1-5 Total synthesis of tyloindicine G published in US patent by Baker *et al*.

8a-Hydroxysepticine (34)/13a-Hydroxytylophorine (35)[17,18]

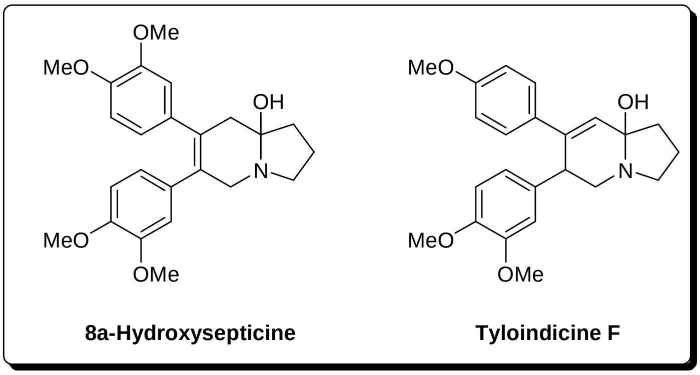
8a-Hydroxysepticine (**34**) was isolated from *Tylophora hirsute*.[17] It has not been reported for the synthesis and cytotoxic evaluation. On acetylation with acetic anhydride in the presence of pyridine, *seco*-compound **34** was converted into 13a-hydroxytylophorine (**35**).[18]



Scheme 1-6 Conversion of 8a-hydroxysepticine to 13a-hydroxytylophorine

CHAPTER II

Methodology



8a-Hydroxysepticine **Tyloindicine F**

Objectives

Tyloindicine F and 8a-hydroxysepticine isolated principally from the *Tylophora* genus are rare *seco*-phenanthroindolizidine alkaloids possessing an angular tertiary hemiaminal moiety at C_8 position of indolizidine ring. Tyloindicine F demonstrated the profound cytotoxic activity against the NCI-60 human cancer cell lines in sub-nanomolar range. However, 8a-hydroxysepticine has yet to be reported for its preparation and evaluation for cytotoxic activity.

Therefore, the main goals of our efforts are

1. To develop a practical synthetic method for the construction of the hemi-aminal moiety,
2. To verify their proposed structures,
3. To provide sufficient material for their pharmacological evaluation, comparing toxicity with our tylophora series.

Synthetic Plan

In the original retro-synthetic analysis, the introduction of the unstable hemiaminal moiety is to be carried out as the last step of the reaction sequence. We plan to construct the [6,5]-bicyclic system in a stepwise fashion. The six-membered ring would be obtained via a Michael reaction and subsequent one-pot reduction/cyclization to afford the desired lactam. The hemiaminal group and the five-membered ring would be prepared by either a Barbier reaction or a free radical reaction. All reactions involved in our approach are classical organic chemistry transformations with plentiful examples.

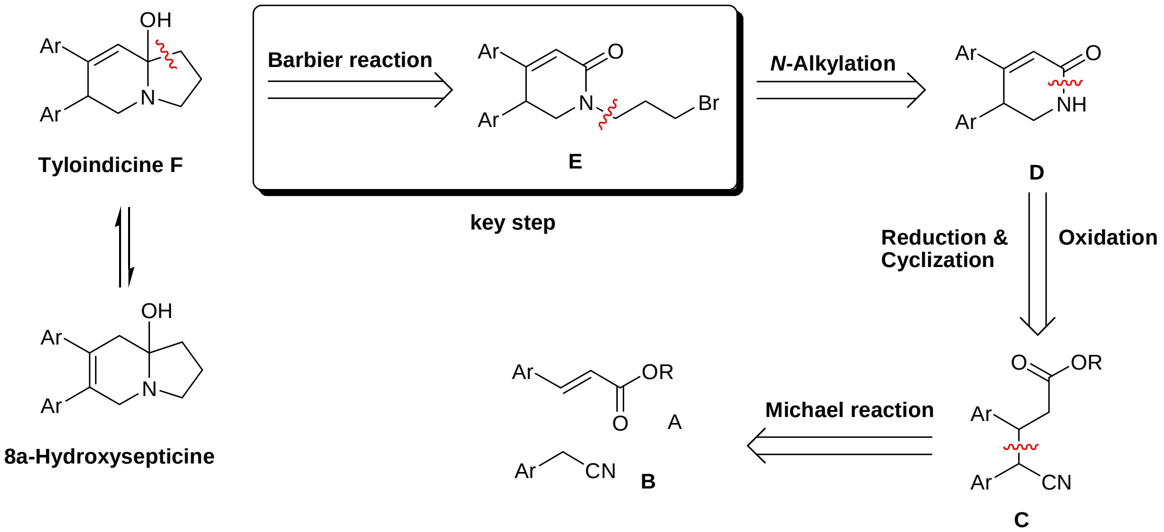
Retro-synthetic route I: Original Proposed Synthetic Route

This project will be planned to design the construction of hemiaminal skeleton of seco-phenanthroindolizidines found in tyloindicene F and 8a-hydroxysepticine and evaluate their cytotoxic activity.

Retro-synthetic analysis: Key steps in the synthesis of the tyloindicine F and 8a-hydroxysepticine will be :

1. The Michael reaction between cinnamate **A** and benzyl cyanide **B**,
2. A one-pot cyanide reduction and cyclization to lactam,
3. The intramolecular Barbier reaction of lactam and alkyl halide.

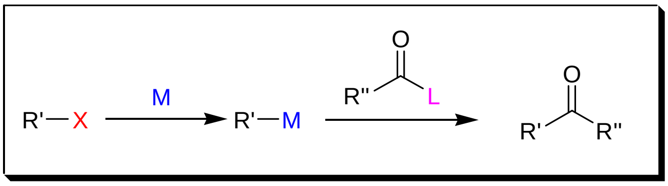
In the original proposed synthetic analysis, the introduction of the unstable hemiaminal moiety is to be carried out as the last step of the reaction sequence. We will plan to construct the [6,5]-bicyclic system in a stepwise fashion. The six-membered ring can be obtained via a Michael reaction and subsequent one-pot reduction/ cyclization to afford the desired lactam. The hemiaminal group and the five-membered ring would be prepared by either a Barbier reaction or a free radical reaction. All reactions involved in our approach are classical organic chemistry transformations with plentiful examples.



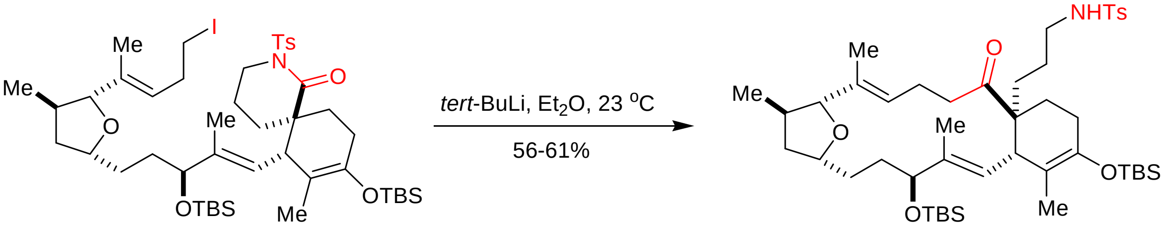
Scheme 2-1 Original retro-synthetic analysis

About a key step: Barbier reaction

The Barbier reaction is an organic reaction between an alkyl halide and a carbonyl group as an electrophilic substrate in the presence of metal such as In, Sn, Zn, Mg, Bi, and Cd or its salts.



The proposed formation of hemiaminal through nucleophilic opening of lactam by sp^3 carbanion is rare. One example employed a Barbier-type macrocyclization in the synthesis of gymnodimine using organo-lithium as nucleophile and *N*-tosyl lactam as electrophile.[19]

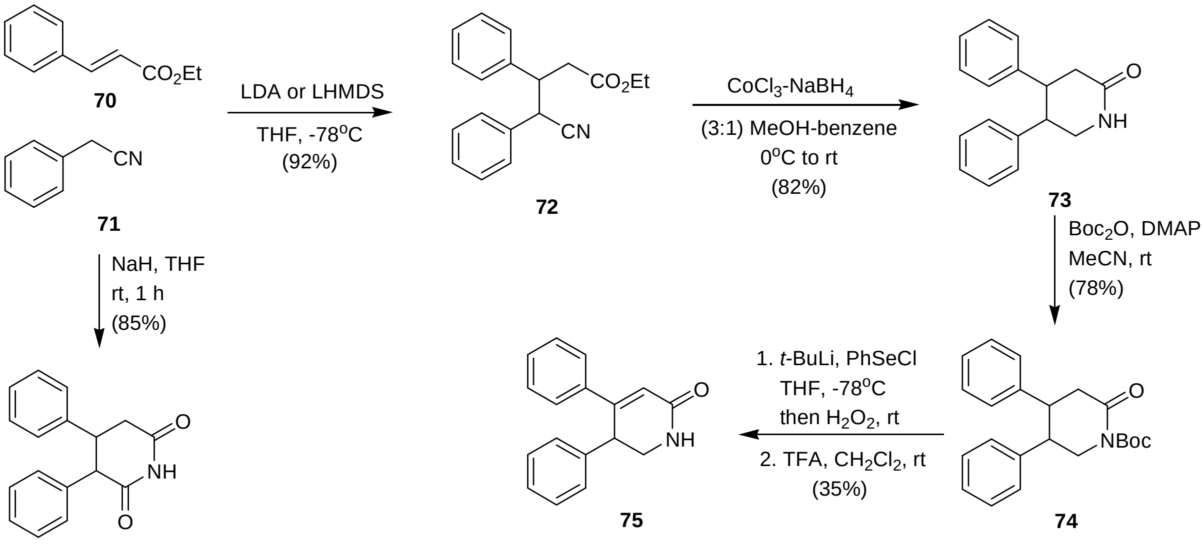


68 **69**

Scheme 2-2 Example of a Barbier-type macrocyclization, a key step for the synthesis of marine toxin gymnodimine

Experimental details

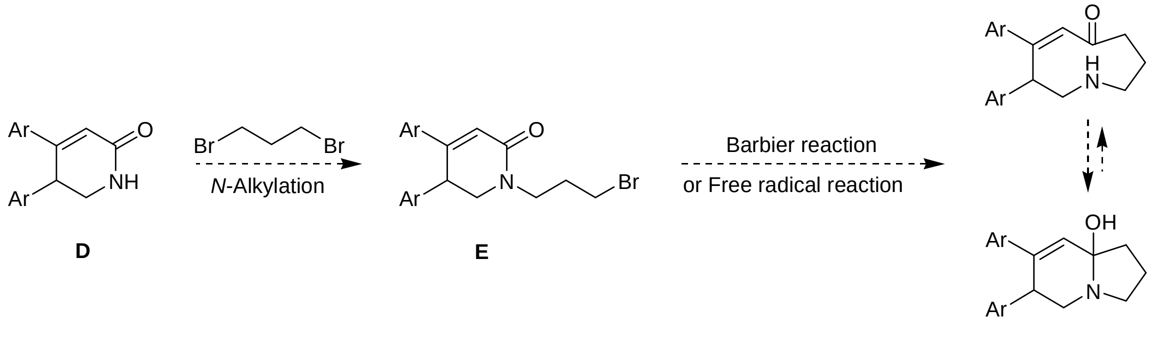
I. Preparation of 4,5-diaryl piperidine-2-one (D)



Scheme 2-3 Preparation of 4,5-diaryl piperidine-2-one (**75**)

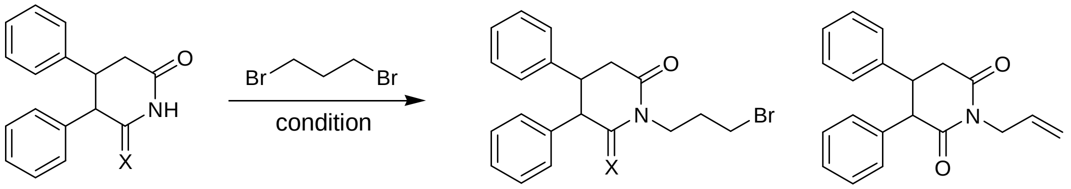
The construction of lactam **D** was started from the Michael reaction between an easily accessible ethyl cinnamate **70** and benzyl cyanide **71** in the presence of base such as LDA or LHMDS in THF at low temperature to obtain Michael adduct **72** in excellent yield. When the reaction was treated with NaH in DMF, the diimide **76** was formed in good yield. For the next step, we investigated the one-pot lactam formation via the reduction of cyanide group and subsequent lactamization to lactam **73**. The cyanide group of the obtained adduct **72** will be converted into amine by using $NaBH_4/CoCl_2$ in benzene-MeOH. The cyclized product was further oxidized into lactam **D** using the oxidation of phenyl selenide and selenoxide elimination process. Deprotection of compound **74** with *tert*-BuLi followed by an addition of phenylselenyl chloride gave phenylselenide adduct. Oxidative elimination of selenoxide using hydrogen peroxide afforded the α,β-unsaturated lactam. The Boc functionality was removed in acid condition which gave lactam **75** in low yield.

II. Construction of hemiaminal group of tyloindicine F: Trial for Barbier reaction



Tyloindicine F

This step will be planned mainly to optimize condition for the hemiaminal ring formation using the intramolecular Barbier reaction. With the six-membered framework in hand, regioselective *N*-monoalkylation of lactam **73** with dibromopropane was performed using NaH in DMF. Thus, the preparation of compound **77** should be carefully carried out under controlled conditions to avoid the formation of dialkylated product. However, the desired compound **77** could not be prepared from compound **73**. We employed the more reactive diimide **76** and obtained compound **78** in low yield (**78**=32% yield; **79**= ~3% yield). Our several attempts to optimize the conditions were unsuccessful.



73: X = H, H
76: X = O

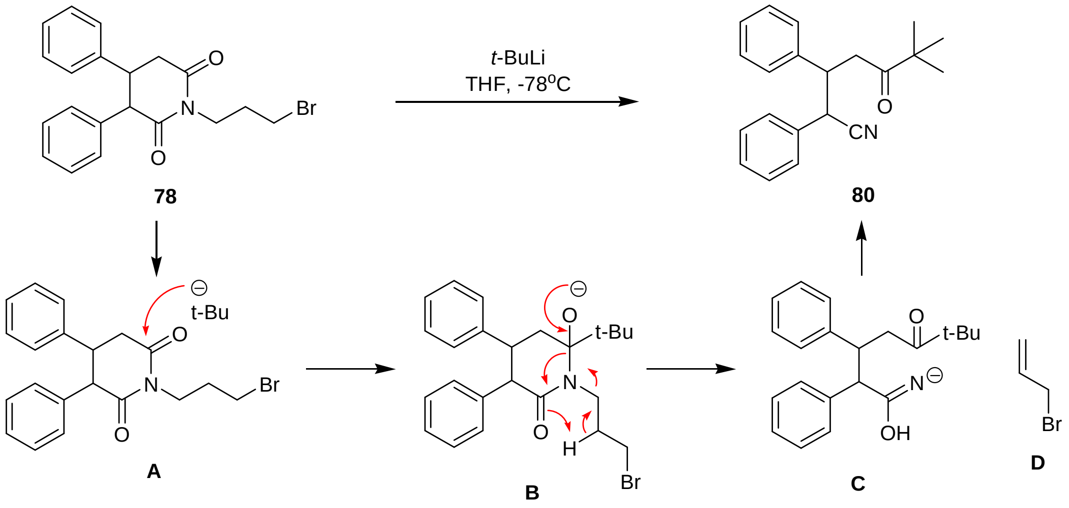
77: X = H, H
78: X = O

79

Scheme 2-4 Trial for Barbier reaction

Thus, we intended to examine systematically on the organo-lithium mediated intramolecular Barbier reaction of diimide **78** with alkyl bromide. We hope that the obtained ketone adduct would be automatically cyclized into the desired hemiaminal product.

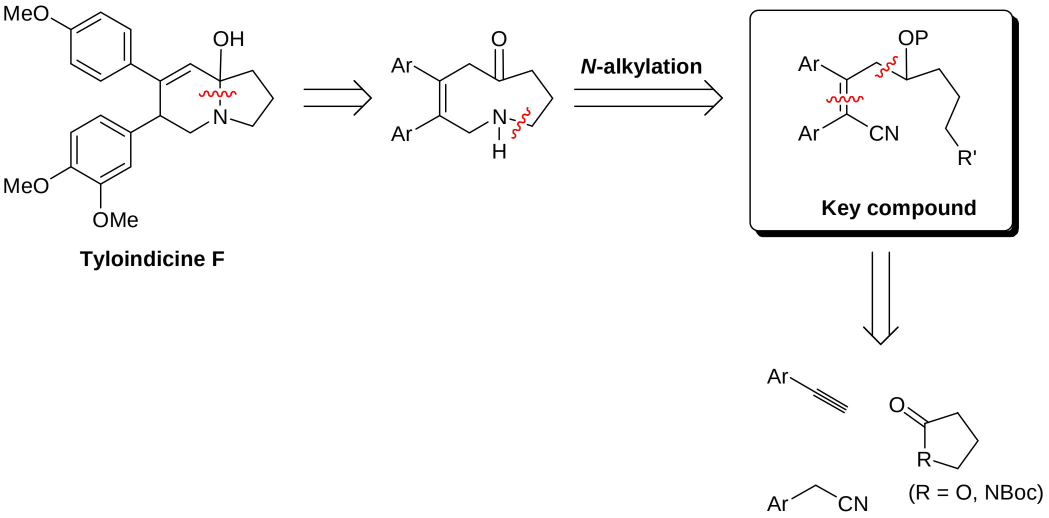
According to a model reaction for the key step "Barbier reaction", we obtained a compound **80**, generated from the addition of ^{t}BuLi to the more active carbonyl group (intermediate **B**), following by rearrangement to the nitrile product **80**.



Scheme 2-5 A proposed mechanism for ketone **80**

Retro-synthetic route II

Although the original retro-synthesis (route I) presented a concise and formal pathway to Tyloindicine F, Barbier reaction was difficult to pass through. We will plan to design a new route by the coupling between amine and nitrile as a key step for macrocyclization.



Scheme 2-6 Retro-synthetic route-II

About a key step: Monoalkylation of primary amines using nitriles as an alkylating Reagent

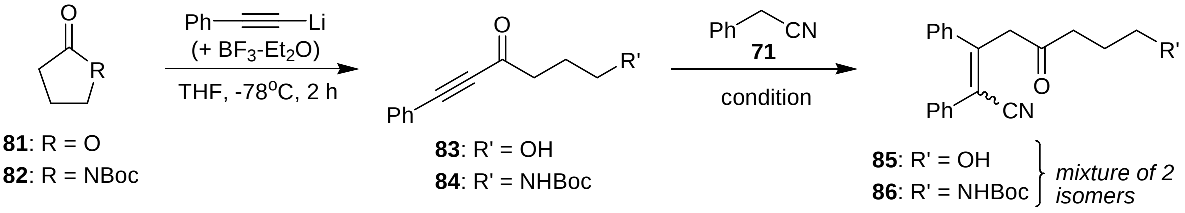
$$\text{Ar-NH}_2 \xrightarrow[\text{RCN, MeOH, rt}]{\text{10\% Pd/C, H}_2\text{,}} \text{Ar-NHCH}_2\text{R}$$

$$\text{Alkyl-NH}_2 \xrightarrow[\text{RCN, MeOH, rt}]{\text{5\% Rh/C, H}_2\text{,}} \text{Alkyl-NHCH}_2\text{R}$$

A selective and catalytic mono-*N*-alkylation method of both aromatic and aliphatic amines using nitriles as an alkylating agent with Pd/C or Rh/C as a catalyst has been reported.[20] However, using this method, the desired double bond will be hydrogenated. We will try this route as a model reaction.

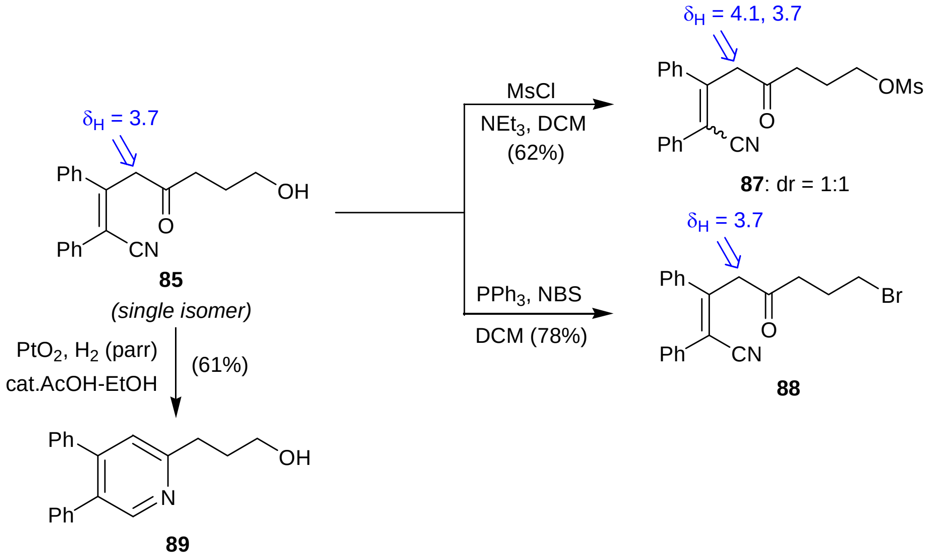
Experimental details

The Michael substrates were prepared by the addition of γ-butylolactone (**81**) or *N*-Boc lactam (**82**) with alkynyl trifluoroborate salts, readily generated in situ by the addition of $BF_3{\cdot}OEt_2$ to alkynyllithium, to afford α-alkynones (**83** and **84**).[21] The Michael reaction between alkynones **83** or **84** and benzyl cyanide **71** in the presence of base such as LDA or LHMDS in THF at low temperature gave 1,2-addition product. When the reaction was treated with NaH in DMF, the complex mixture was observed. The Michael adducts **85** and **86** was obtained in high yields with diastereomeric mixture when the reaction was operated in the presence of KO^{t}Bu in NMP.



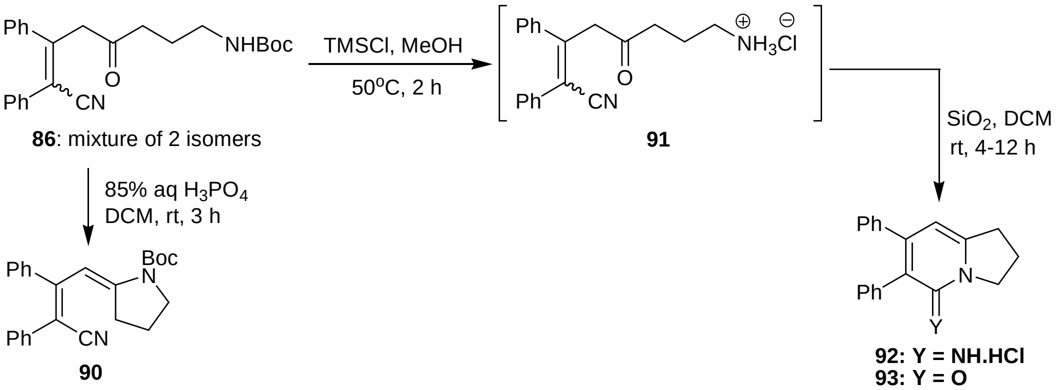
Scheme 2-7 Preparation of Michael adducts **85** and **86**

Initially, we examined the conversion of hydroxy group in compound **85** to mesyl group under basic condition resulted in the isomerzation of methylene moiety, however, in neutral condition the single product **88** was observed. Under high pressure hydrogenation of compound **85** catalyzed with PtO_2 in acidic EtOH resulted in the formation of pyridine **89**.



Scheme 2-8 Trial for mesylation and bromination of alcohol **85**

Trial of removing Boc group in compound **86** by treatment with phosphoric acid in DCM afforded pyrrolidine **90**. Using the *in situ* generated HCl from TMSCl in MeOH resulted in the formation of imine **92** after stirring in the SiO_2-DCM mixture. The structure of bicyclic imine **92** was determined by means of the chemical hydrolysis to pyridone **93**, using alkoxide solution (KOH/aq.EtOH) under refluxing for a long time, 1D/2D-NMR spectroscopy and X-ray crystallographic analysis.

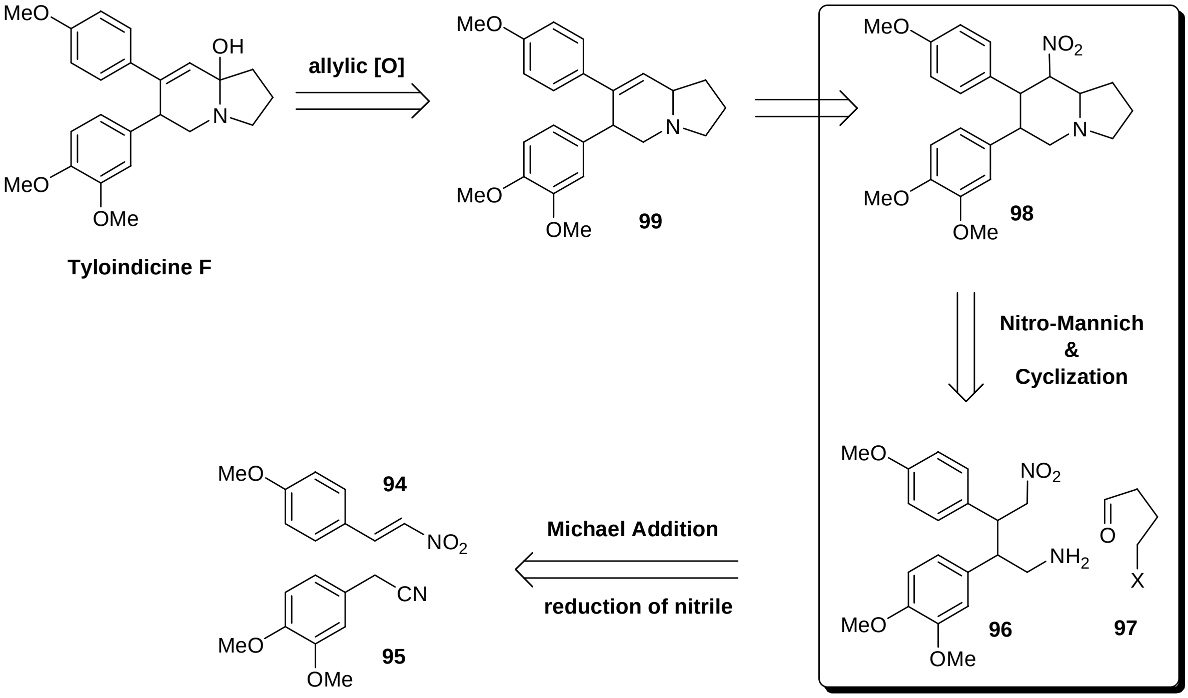


Scheme 2-9 Trial for deprotection of *N*-Boc **86**

These results became a main problem for continuing in route II. Although we could not prepare the target compound using this route, some results could be further considerable to publish in journal. Because this route presents a novel method, simple and high yielding process for the preparation of compound **92**, we plan to prepare a series of bicyclic amidines for further SAR studies.

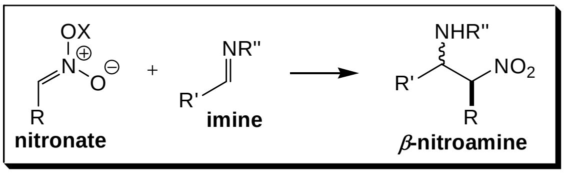
Retro-synthetic route III

In this retro-synthetic route (route III), we wish to explore the one-pot nitro-Mannich/cyclization cascade for the construction of indolizidine ring from an unactivated imine generated from compounds **96** and **97**.

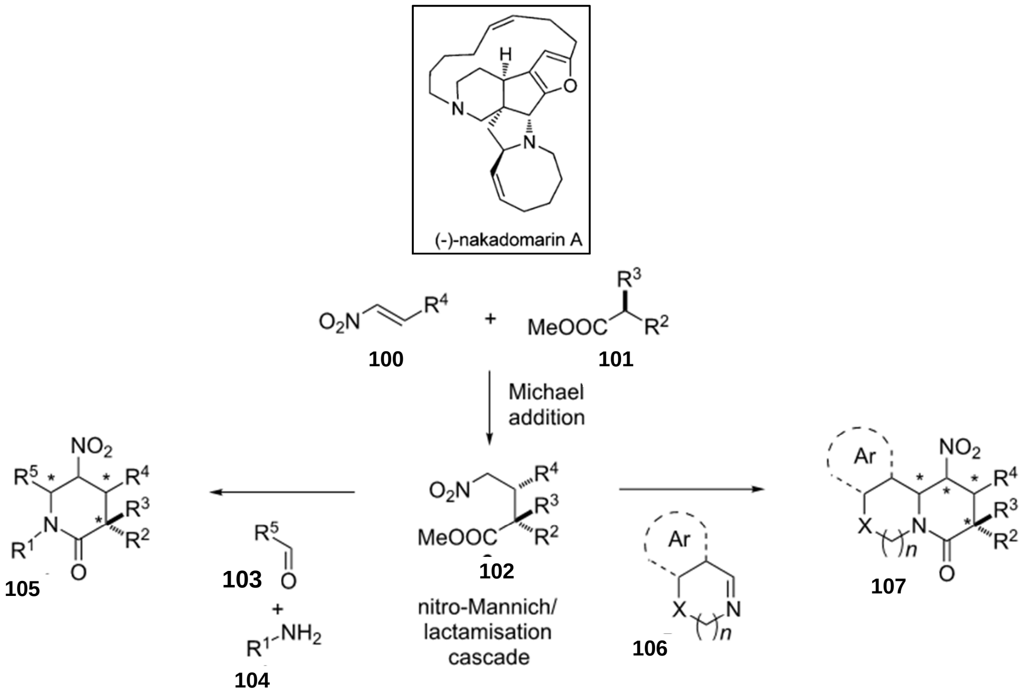


Scheme 2-10 Revised synthetic analysis route-III

About a key step: nitro-Mannich (aza-Henry) Reaction



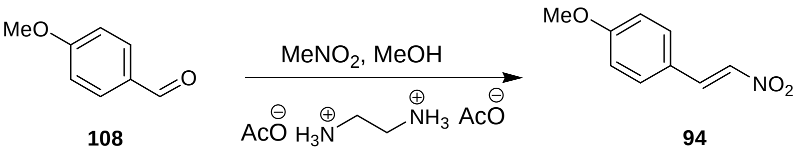
The nitro-Mannich (or aza-Henry) reaction is the reaction between a nitronate nucleophile and an imine electrophile. The efficiency of the nitro-Mannich reaction and the versatility of the β-nitroamine products have resulted in application to the synthesis of a number of natural products and pharmaceuticals.[22] More recently, Dixon *et al*. utilized the nitro-Mannich/lactamization chemistry in the total syntheses of (–)-nakadomarin A.[23]



Scheme 2-11 Example of nitro-Mannich/lactamization cascades by Prof. Darren J. Dixon

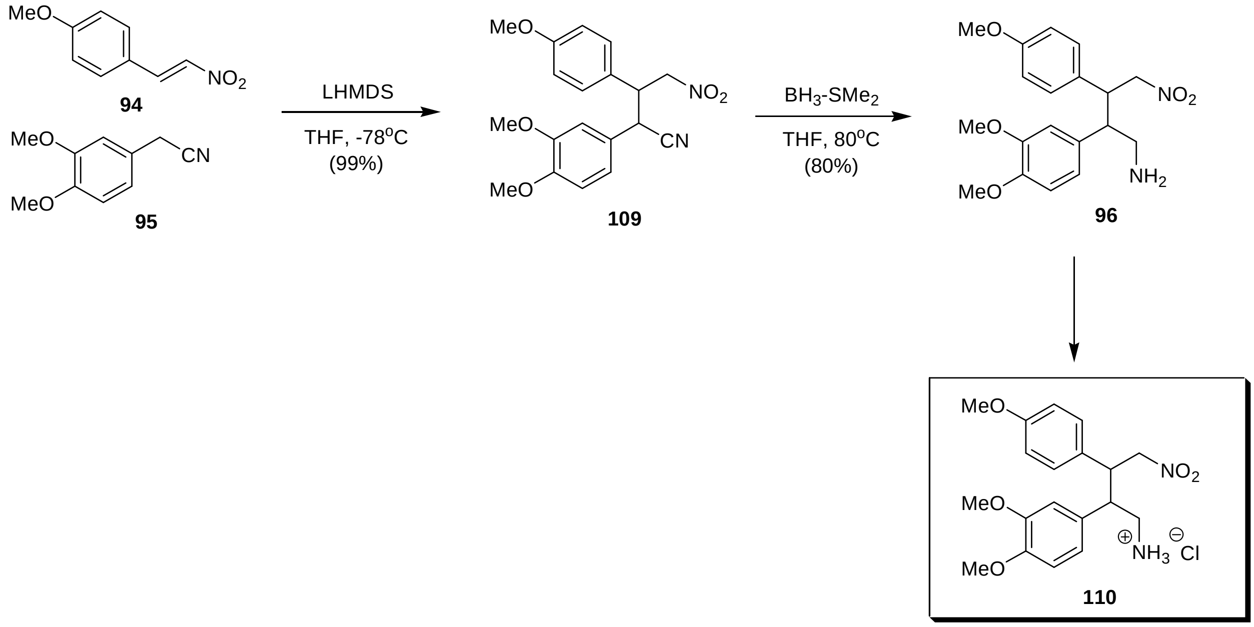
Experimental details

We prepared nitroalkene using a Henry reaction[24] by the condensation of nitromethane with aryl aldehyde **108** in the presence of catalytic amount of ethylene diammonium diacetate to produce β-nitrostyrene **94** in excellent yield.



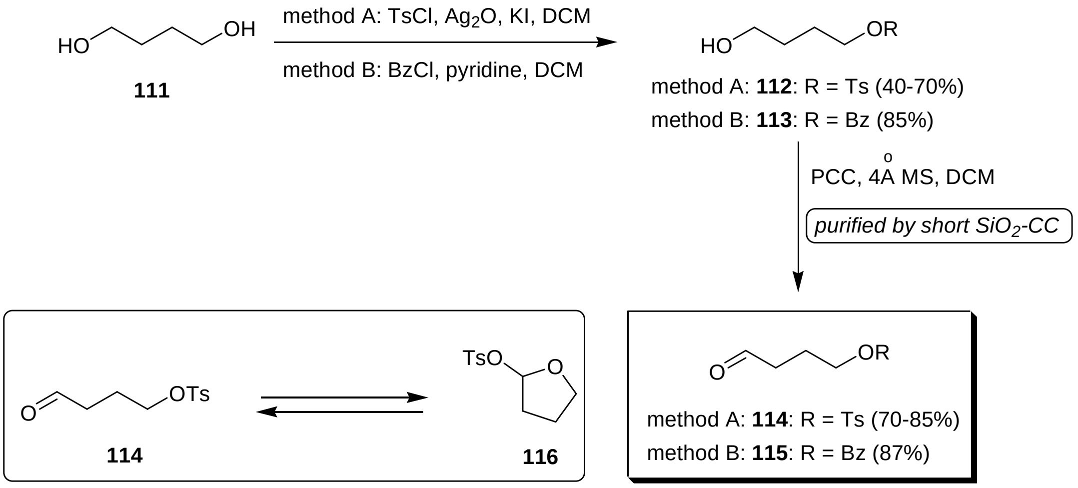
Scheme 2-12 Preparation of nitro-styrene **94**

The conjugate addition of benzyl cyanide **95** to nitroalkene **94** using LHMDS as base at -78°C provided β-nitroalkane **109** in excellent yield (99% yield) but low level of dias-stereocontrol (dr~1:1). While the diastereomers of compound **109** were hardly separated by chromatography, one diastereomers could be easily separated by mean of recrystallization in AcOEt. Without any optimization in this step, we played an attention on the next step. Treatment of nitrile **109** with boran dimethyl sulfide complex (BMS, DMSB) afforded the desired primary amine product **96**. The crude amine was purified through the formation of its chloride salt **110**.



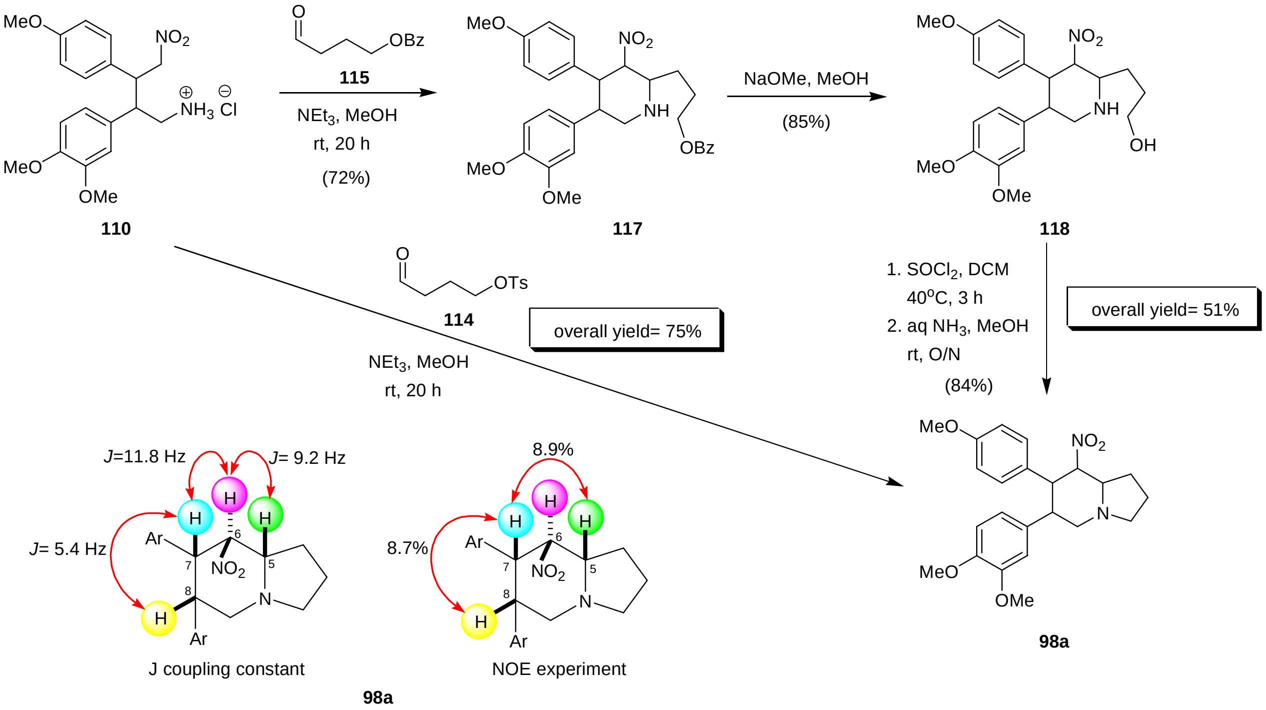
Scheme 2-13 Preparation of nito-amine **96** and its chloride-salt **110**

Monotosylation of 1,4-butane diol **111** was prepared by treatment with a stoichiometric amount of *p*-toluenesulfonyl chloride in the presence of silver(I) oxide and catalytic amount of potassium iodide led selectively to the desired product **112** in good yield (method A).[25] Monobenzoylation of **113** was also prepared in good yield using method B. Further oxidation of primary alcohol with PCC in DCM in the presence of 4Å molecular sieve resulted in the corresponding aldehyde **114** and **115** with good conversion yield. However, especially aldehyde **114** is unstable and easily tautomerize to cyclic enol ether **116**. After purification using flash silica chromatography, this aldehyde has been stored at -20°C and the purity was confirmed before applying to the reaction.



Scheme 2-14 Preparation of 4C-aldehyde **114/115**

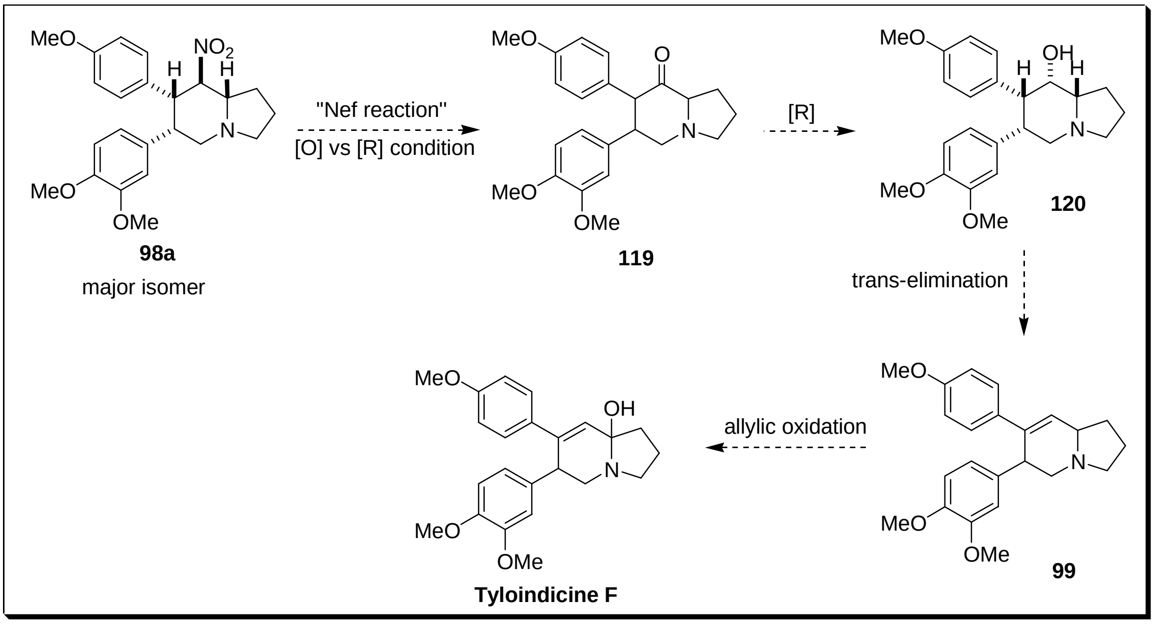
At the outset for a key step one-pot nitro-Mannich/cyclization, the mixture of chloride-salt **110** and aldehyde **114** in MeOH was treated with NEt_3 at room temperature for 20 h to afford the desired nitro-indolizidine **98** as a major product in 75% yield. In order to optimize the condition, solvents such as MeOH, DCM, THF, MeCN, organic and inorganic bases such as NEt_3, imidazole, DMAP, quinine, NaOMe, K_3PO_4, Cs_2CO_3 and K_2CO_3 were applied to the reaction. A step-wised reaction, including imine formation, aza-Henry reaction, and *N*-alkylation also performed to compare a chemical yield and diastereochemical outcome.



Scheme 2-15 Step-wised and one-pot process for nitro-Mannich reaction

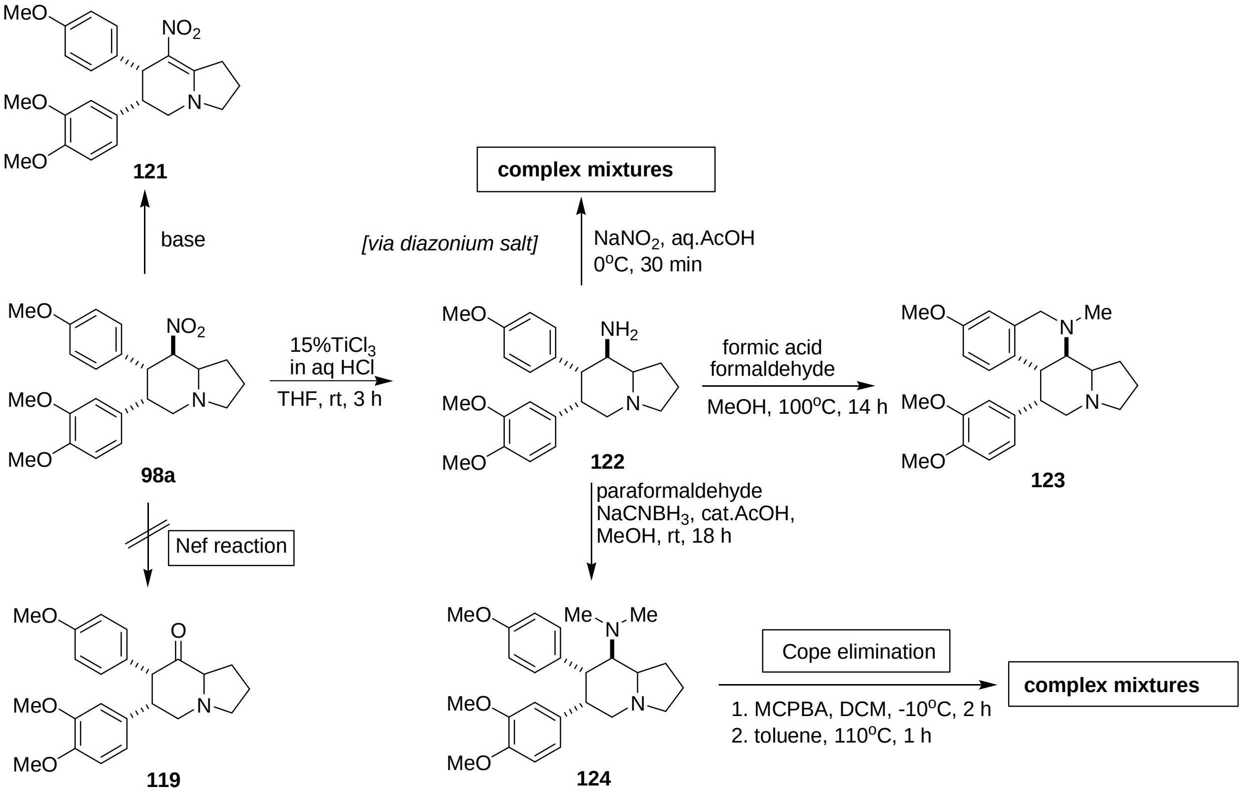
After some experimentation, we found that NEt_3 and K_2CO_3 in methanol gave the desired product in good chemical yield with high diastereomeric ratio, up to 78% yield. The stereochemical outcome of all isomers were analyzed from crude reaction using C_{18}-reversed phase HPLC and the configuration of each isomers was determined using 1D- and 2D-NMR spectroscopy, including NOE experiments.

For the synthesis of tyloindicine F, we are concentrating on the synthetic transformations using the following **Scheme 2-16**.



Scheme 2-16 Transformation of nitro-Mannich compound to tyloindicine F

We have attempted to directly transform nitro group to ketone (**119**) group by mean of reductive or oxidative Nef reaction, but only nitro-alkane **98a** or nitro-alkene **121** was observed.[26] Stepwise conversion of nitro-alkane **98a** to ketone **120** via diazonium salt of 1°-amine **122** or Cope elimination of dimethyl-amine **124** was not successful.[27]



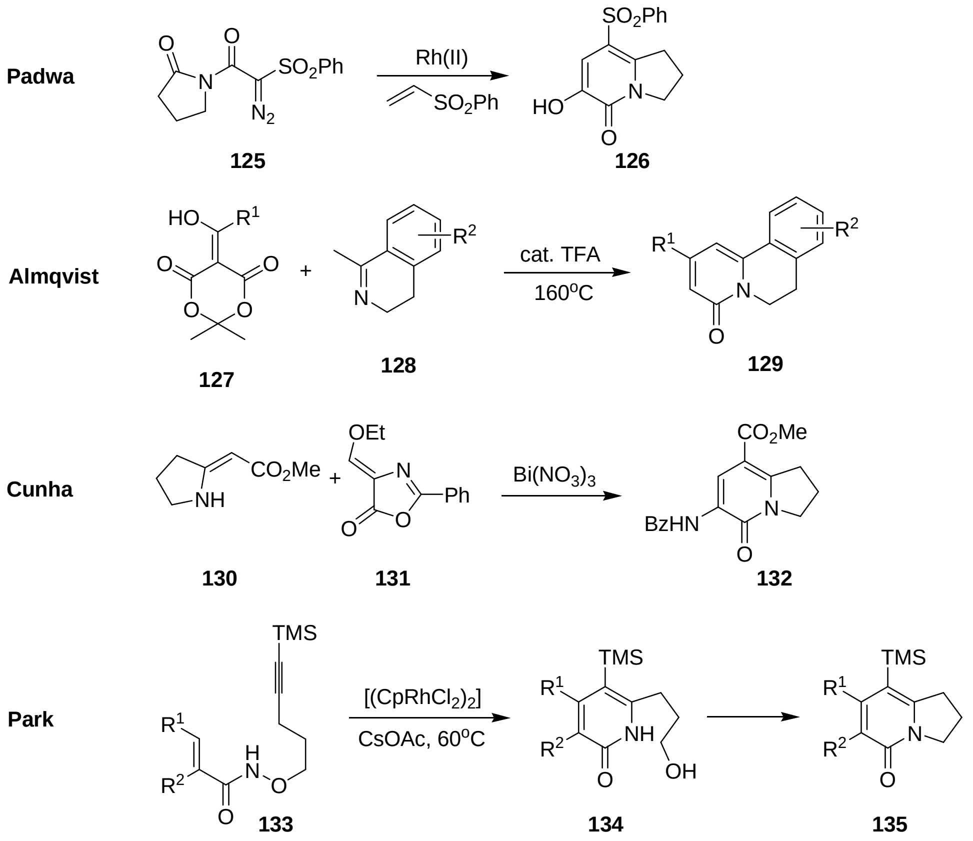
Scheme 2-17 trial for conversion of nitro-alkane **98a** to ketone **119**

A Novel Approach to Bicyclic 2-Pyridones and Application to the Synthesis of seco-Phenanthroindolizidine/quinolizidine Alkaloids

During synthetic studies of this compound, from retro-synthetic route II, we found a novel methodology for construction of bicyclic amidines and bicyclic 2-pyridones from inexpensive commercially available starting materials. According to preliminary results, we would like to apply this synthetic route by transformation Michael adducts to bicyclic 2-pyridones which are versatile intermediates for further transformation to many key compounds such as aza-cyclic compound, quinolizidine and indolizidine alkaloids.

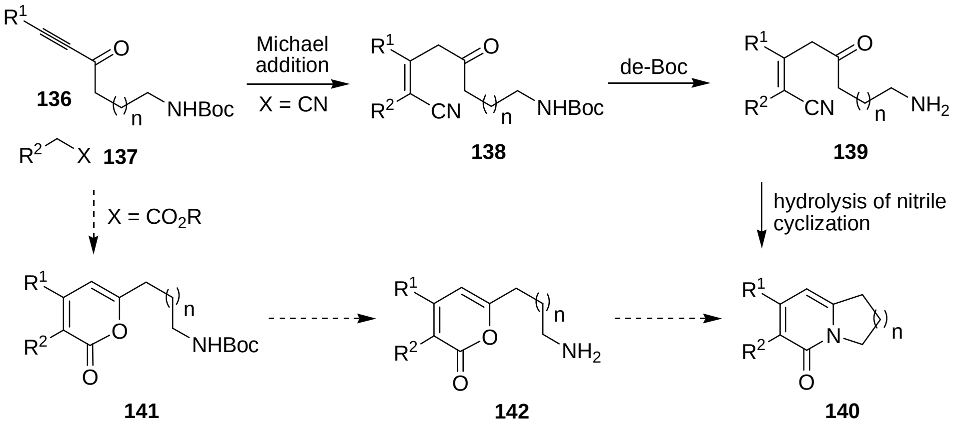
In recent decades, the relevant natural and synthetic molecules with 2-pyridone as central structural scaffold have attracted remarkable attention, due to their extensive applications in many fields such as pharmaceutical[28] and material sciences[29]. For examples, substituted 2-pyridones[30] and multi-fused-ring 2-pyridones[31] have been evaluated as potential therapeutic agents. Since 2-pyridone ring can act as a versatile synthon for transformation to the aza-cyclic analogs, thus, several valuable compounds have emerged in chemistry's world.[32] From these points, this core skeleton has inspired both synthetic and medicinal chemists to develop the novel synthetic methods.[33]

Considering the ever growing in chemistry of anticancer during the past several decades, phenanthroindolizidine and phenanthroquinolizidine alkaloids have been extensively investigated as targets compounds due to their revision in medicinal testing by NCI-group.[34] Thus, a number of novel synthetic methods have been emerged over the past several years.[35] Among them, bicyclic 2-pyridones have been also used as key intermediates for conversion to the aza-bicyclic systems. In previous synthesis (**Scheme 3-1**), an elegant synthetic method was from Padwa's group involving the rhodium-catalyzed 1,3-dipolar cycloaddition of diazo compounds **125** and dipolarophiles.[36] This method has proven to be enormously effective in providing advanced intermediates in the synthesis of numerous natural products. Gilbertson *et al*. further applied this method in the preparation of 2-pyridone library for further Principle Component Analysis (PCA) studies.[37] In the Almqvist approach, the acyl-ketene-imine cyclocondensation was employed for the synthesis of multi-fused ring 2-pyridones applied to sempervilam.[38] The other approach involving the aza-[3+3] cycloaddition of heterocyclic enaminones **130** and oxazolones **131** for the synthesis of bicyclic 2-pyridones **129** and aza-bicyclic compounds was reported by Cunha's group.[39] Recently, Park et al. demonstrated an elegant procedure for 2-pyridones preparation by employing rhodium(III) catalyzed intramolecular annulation of compound **133** through C-H activation.[40]



Scheme 3-1 Examples of Previously reported methods for bicyclic 2-pyridones formation

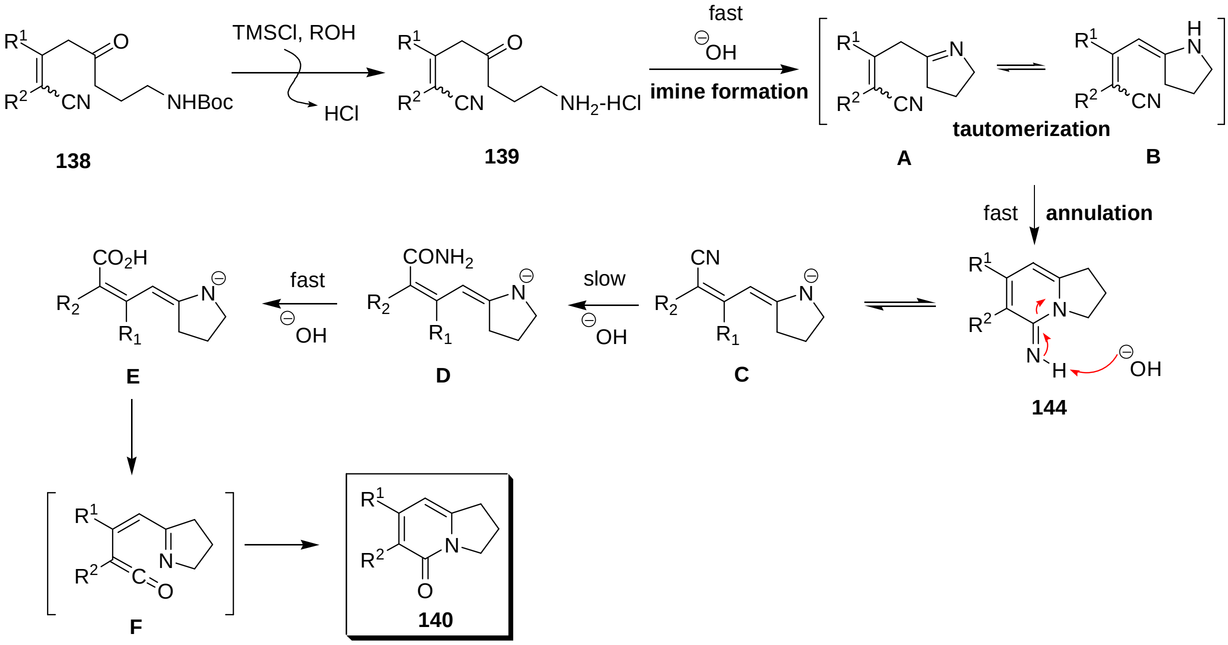
Although in almost examples reported previously, the potential approaches came from the transition metal-catalyzed reaction, we need to develop other approaches for the easy access to both [6,5]- and [6,6]-ring pyridones systems. The exploration of functional groups within this core was performed for further apply to natural product synthesis.



Scheme 3-2 The typical process for the preparation of bicyclic 2-pyridones

The typical process we envisaged is shown in **Scheme 3-2**, involving the transformations of the Michael adducts **138** generated from internal alkynones **136** and acetonitriles **137** (X = CN) to bicyclic 2-pyridones via the tandem double intramolecular cyclization of the imine formation, nitrile oxidation and lactamization under acid or base condition.

Proposed mechanism



Scheme 3-3 The proposed reaction mechanism

We believe that, our one-pot process would occur as follow: (I) Boc group in Michael adduct **139** is de-protected with in situ generated HCl from TMSCl and alcohol; (II) Upon basification with hydroxide base, condensation between amine and carbonyl generated cyclic imine **A**. This compound tautomerized to enamine **B** and interacted with nitrile group to the compound **144**, which is called amidine; (III) Then, in strong base this amidine is unstable. It is deprotonated and isomerized to a more stable isomer, nitrile **C**; (IV) Then, nitrile was hydrolyzed to amide **D**, carboxylic acid **E** and condensed with pyrrolidine ring, via a ketene intermediate **F**, to furnish a target compound **140**.

From another perspective, in **Scheme 3-2**, the Michael addition between active methylenes **137** (RCH_2X: R = ary; X = CO_2R) and internal alkynones acceptor to pyrone derivatives have also been reported.[41] Furthermore, pyrone can be converted to pyridone via intramolecular lactamization. This idea was preliminary examined by applying the reported conditions to our internal alkyne having enolizable carbonyl and amine groups (**136al**, R^1 = Ph, n = 1) and phenyl acetate (**137**: R =

Ph, X = CO_2Me). However, no reaction or other products, from **136al**, were observed. On the other hand, the reaction with phenyl acetonitrile (**137a**: R = Ph, X = CN) gave a good chemical conversion to **138aal** (R^1, R^2 = Ph, n =1) in up to 91% isolated yield.

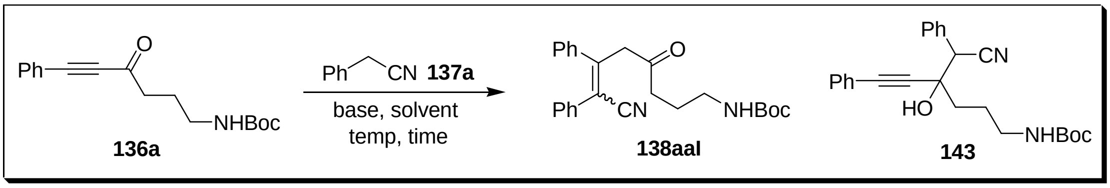


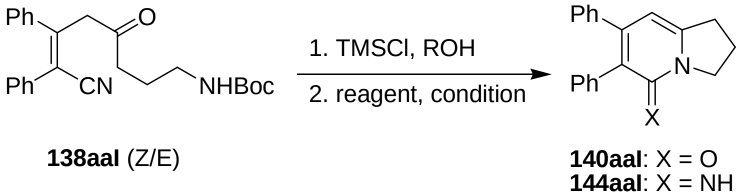
Table 3-1 Screenning of bases, solvents, and reaction conditions

entry	base	solvent	temp (^{o}C)	time (h)	conversion (**136a** : **138aal**)	isomer ratio of **138aal**	yield of **138aal** (%)
1	LHMDS	THF	-78	1	compound **143**	-	**143** : 89
2	NaH	DMF	rt	2	4:96	10 : 13	89
3	K_2CO_3	MeCN	rt	2	100:0	-	-
4	NaOMe	MeCN	rt	2	100:0	-	-
5	LiO^{t}Bu	MeCN	rt	2	100:0	-	-
6	NaO^{t}Bu	MeCN	rt	2	81:19	10 : 13	-
7	KO^{t}Bu	MeCN	rt	2	51:49	10 : 15	-
8	KO^{t}Bu	THF	rt	2	29:71	7 : 5	63
9	KO^{t}Bu	DME	rt	2	23:77	6 : 5	69
10	KO^{t}Bu	DMF	rt	2	0:100	10 : 13	91
11	KO^{t}Bu	NMP	rt	2	18:82	5 : 6	75
12	KO^{t}Bu	1,4-dioxane	rt	2	23:77	10 : 15	66
13	LiO^{t}Bu	DMF	rt	2	20:80	10 : 13	75
14	NaO^{t}Bu	DMF	rt	2	29:71	5 : 7	65
15	DBU	DMF	rt	2	65:35	1 : 1	-

From the outset, we envisioned a protocol in which the Boc-protecting group would be removed to liberate a free amine that would react with the tethered ketone moiety generating pyrrolidine ring. We supposed that both isomers of the Michael adducts would be isomerized under acid or base conditions and gave the identical cyclization results.

The initial investigation of the two fold cyclization was operated based on the reaction of **138aal**. Regardless of the *E* or *Z* geometry, removal of the Boc group was readily accomplished **139aal** (R^1, R^2 = Ph, n = 1) using the in situ generated HCl from trimethylsilyl chloride (TMSCl) in ethanol.[42] Treatment a solution of **139aal** with 50% aqueous KOH in ethanol in a conventional round-bottomed flask at 100^{o}C for a day, surprisingly, no the desired product **140aal** was observed.[43] Only a Pinner amidine **144aal** was detected (**Table 3-1**, **entry 1**). We also examined the use of microwave irradiation (MW) for this reaction at 150°C for 1 h, but a low conversion was obtained (**Table 3-1**, **entry 2**). To our knowledge, the thermal direct amide formation between carboxylic acids and amines, via pyrolysis of ammonium acetate, typically occurs at high temperature.[44] Accordingly, in order to optimize reaction temperature, our one-pot process was operated in a pressure tube. Upon treatment with 50% aqueous KOH in ethanol and prolonged heating the mixture at 150°C for 12 h, compound **139aal** was converted into the desired target **140aal** in 45% isolated yield (**Table 3-1**, **entry 3**). A variety of conditions were then examined to effect the conversion of **144aal** to **140aal**. The reaction became two phases, when it was initially heated. Therefore, the ability of phase transfer catalyst (PTC) was investigated at 100°C and 160°C (**Table 3-1**, **entries 4** and **5**). However, only the reaction at higher temperature gave a better conversion; comparison with **entry 3**, in the absence of PTC. From the results, we concluded that temperature has a high impact on chemical conversion. To further improve this method, high boiling point ethylene glycol (bp. 197°C), instead of ethanol, and concentrations of KOH were investigated (**Table 3-1**, **entries 6-10**) and it was found that the best result was obtained using conditions in the presence of 30-50% aqueous KOH at 190-210°C (**Table 3-1**, **entries 8-11**). However, the reaction in decrease amount of organic solvent provided the product in low yield, due to incomplete conversion (**Table 3-1**, **entry 12**). Hydrolysis under acid conditions (**Table 3-1**, **entries 13** and **14**) resulted in more complex product mixtures, and 5aal could be separated in trace amount.

Table 3-1 Optimized reaction conditions for **140aal**



entry	reagent[a]	condition[b]	ratio of **144aal**/**140aal**[c]	yield (%) of **140aal**[d]
1	A	100°C, 24 h	100 : 0	-
2	B	150°C, 1 h	95 : 5	-
3	A	150°C, 12 h	19 : 81	45
4	A[e]	100°C, 12 h	71 : 29	24
5	A[e]	160°C, 12 h	6 : 94	50
6	C	190°C, 2 h	14 : 86	27
7	D	190°C, 2 h	6 : 94	70
8	E	190°C, 2 h	3 : 97	81
9	F	190°C, 2 h	2 : 98	78
10	G	190°C, 2 h	0 : 100	76
11	G	210°C, 1 h	0 : 100	77
12	G[f]	210°C, 2 h	22 : 78	65
13	H	140°C, 6 h	CM[g]	4
14	I	110°C, 12 h	CM[g]	5

[a] A: 50% aq. KOH in EtOH; B: solid KOH (50 equiv) in EtOH; C: 20% aq. KOH in EtOH; 10% aq. KOH in ethylene glycol; D: 20% aq.KOH in ethylene glycol; E: 30% aq. KOH in ethylene glycol; F: 40% aq. KOH in ethylene glycol; G: 50% aq. KOH in ethylene glycol; H: TMSCl in EtOH; I: 98% H_2SO_4 in EtOH.

[b] Entry 1, the reaction was operated in a round-bottom flask. Entry 2, the reaction was operated in a microwave apparatus. Entry 3-14, the reaction was operated in a pressure tube.

[c] The ratio was determined by ^{1}H-NMR spectroscopic analysis of the unpurified reaction mixture.

[d] Isolated yields based on combined yield from crystallization and column chromatography.

[e] Tetrabutyl ammonium iodide (TBAI, 0.5 equiv.) was added.

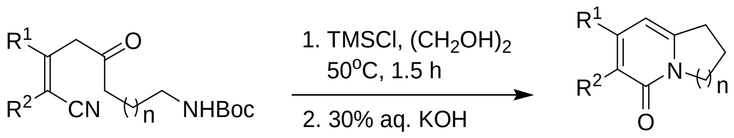
[f] Solvent ratio of ethylene glycol : H_2O was 1 : 5.

[g] CM is complex mixture.

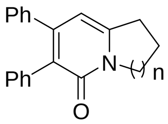
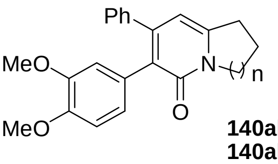
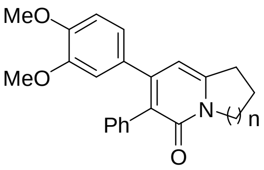
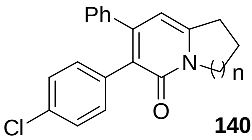
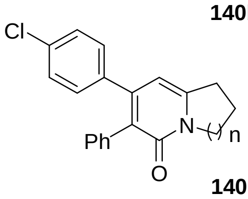
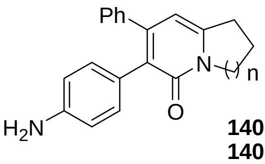
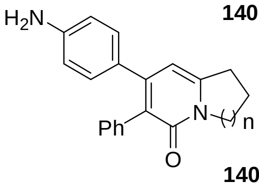
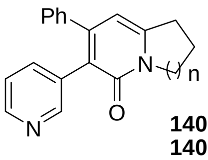
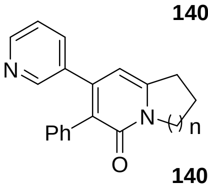
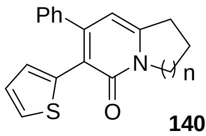
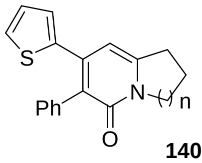
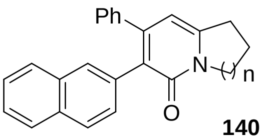
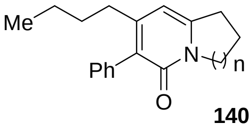
Having established a simple method for the synthesis of bicyclic 2-pyridones, we proceeded to investigate the substrates scope around R^1 and R^2 and ring sizes (n = 1 and 2) (**Tables 3-2**), using the Michael adducts generated from various alkynones **136** and acetonitriles **137**. In general, most of the substrates proceeded to afford the desired bicyclic pyridones in moderate to good yields (59-85% yields) under standard optimized reaction conditions. The two-fold cyclization for [6,6]-ring system proceeded smoothly in good chemical yields (**Table 3-2**, n = 2). In the case of aryl substituted Michael adducts, the yields were high when unsubstituted and weakly activating aromatic rings were presented (**Table 3-2**, **140aaI/II**, **140abI/II**, **140acI/II**, **140agI/II**, **140baI/II**, and **140caI/II**). Exceptionally, in the case of aromatic ring having base sensitive functional groups such as nitro in **138d** series (**138**: R^1 or R^2 = *p*-NO_2Ph, n = 1, 2), the obtained products were amino instead of nitro group in low yield (30%). This trans formation was previously reported using a similar condition (glucose, aqueous KOH, heat).[45] Our methodology involving the direct amide formation required relatively harsh conditions that preclude the presences of base sensitive functional groups such as nitro and iodo compounds. Nevertheless, amino group can be interconverted to various functional groups, such as nitro, halo, and hydroxyl groups. Consequently, the Michael adducts having amino group **138h** series (**138**: R^1 or R^2 = *p*-NHBocPh, n =1, 2) were explored under the optimized condition and resulted in **140d** series in 59-65% yields (**Table 3-2**, **140adI/II** and **140daI/II**). In the same manner with aromatic compounds, the substrate scope was expanded to heterocycle and alkyl Michael adducts which underwent the double cyclization in moderate to good yields (**Table 3-2**, **140aeI/II**, **140eaI/II**, **140afI/II**, **140faI/II**, and **140gaI/II**).

From a practical point of view, it would be ideal if a mild condition could be applied. Thus, further investigation was emphasized on the employment of more active methylenes **137i** (**137**: R^2 = CO_2Et, X = CN) and **137j** (**137**: R^2, X = CO_2Et) (**Scheme 3-4**). During purification using silica chromatography, Michael adducts **138aiI** and **138ajI** were unstable and the corresponding pyrones were observed.[46] Thus, without purifications, the mixtures were examined for the double cyclization using silica gel in dichloromethane at room temperature for 3 h to afford the target pyridones **140aiI** and **140ajI** in 45-53% yields from **136aI**. To highlight our methodology, the above process was applied to the pyridone **(140iiI)**, a relevant structure of peptidomimetics[47], ACE inhibiors[36a,48], and Alzheimer's amyloid formation inhibitors.[49]

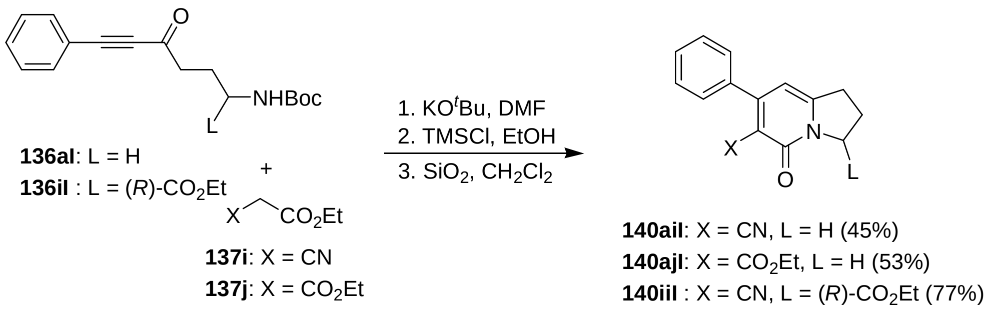
Table 3-2 Scope for [6,5]- and [6,6]-pyridones formation



138 **140**

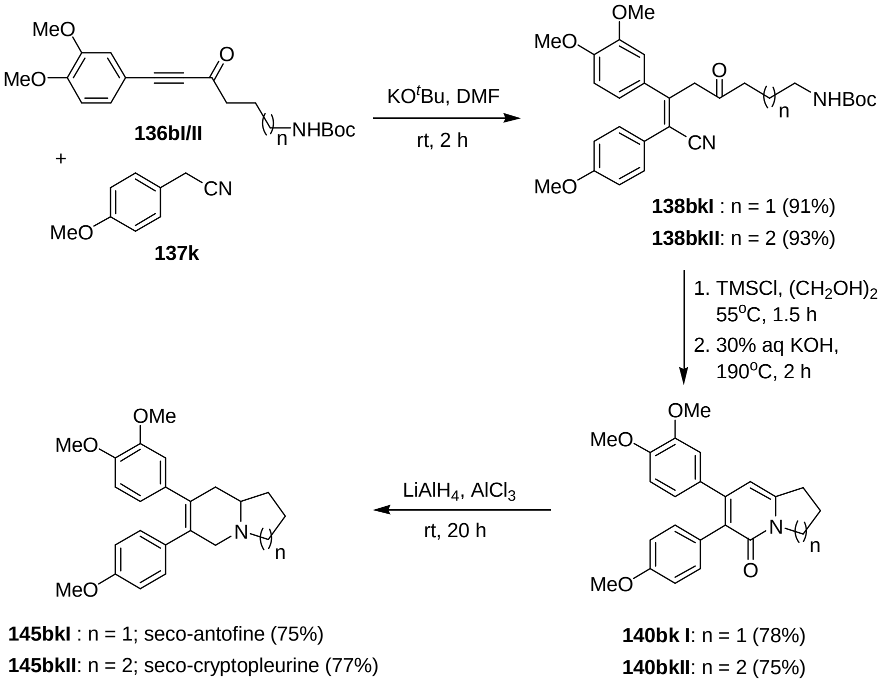
Product: yield %[a]	Product: yield %[a]
 **140aal** : n = 1 (81%) **140aall**: n = 2 (80%)	
 **140abl** : n = 1 (65%) **140abll**: n = 2 (68%)	 **140bal** : n = 1 (78%) **140ball**: n = 2 (75%)
 **140acl** : n = 1 (78%) **140acll**: n = 2 (76%)	 **140cal** : n = 1 (73%) **140call**: n = 2 (75%)
 **140adl** : n = 1 (61%) **140adll**: n = 2 (59%)	 **140dal** : n = 1 (65%) **140dall**: n = 2 (60%)
 **140ael** : n = 1 (65%) **140aell**: n = 2 (62%)	 **140eal** : n = 1 (68%) **140eall**: n = 2 (65%)
 **140afl** : n = 1 (78%) **140afll**: n = 2 (79%)	 **140fal** : n = 1 (80%) **140fall**: n = 2 (78%)
 **140agl** : n = 1 (85%) **140agll**: n = 2 (81%)	 **140gal** : n = 1 (66%) **140gall**: n = 2 (65%)

[a] Isolated yields based on crystallization and chromatography.



Scheme 3-4. [6,5]-Pyridones Formation using SiO_2 in CH_2Cl_2

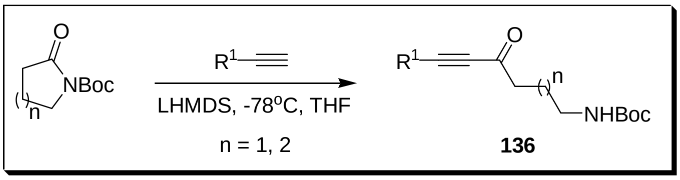
Previously, Padwa[36] and Park[40] have demonstrated that their synthesized 2-pyridones could be converted to phenanthroindolizidine alkaloids. Each of synthetic routes employed a different strategy and required multistep reaction sequences. Thus, we demonstrated that our methodology was also efficient for the preparation bicyclic pyridones **140bkl** and **140bkll** required for the synthesis of *seco*-antofine (**145bkl**) and julandine (**145bkll**), respectively. Michael adducts **138bkl** and **138bkll** were prepared from the corresponding internal alkynone **136bl** or **136bll** and acetonitrile **137k** in good yields, and were converted to the desired compounds via pyridone reduction using the reported conditions (**Scheme 3-5**).[36,40]



Scheme 3-5 Synthesis of *seco*-antofine **145bkl** and julandine **145bkll**

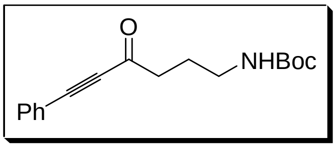
Experimental Part

1. General procedure for the preparation of alkynones 136



Lithium hexamethyldisilazane (LHMDS, 1 M in THF, 1.5 equiv) was added dropwise to a solution of alkynes (1.2 equiv) in THF (5 mL) at -78°C and further stirred for 45 min. Then, the solution of lactam (3 mmol, 1.0 equiv) in THF (10 mL) was added dropwise and the mixture was stirred for an additional 4 h. The reaction was quenched with saturated NH_4Cl solution, gradually warmed up to room temperature and extracted with EtOAc. The combined organic part was washed with water, dried over Na_2SO_4, and the solvent was concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of EtOAc as eluent to afford compounds **136**.

tert-Butyl 4-oxo-6-phenylhex-5-ynylcarbamate (136al)



81% yield, white solid, m.p. 69.5–70.5°C

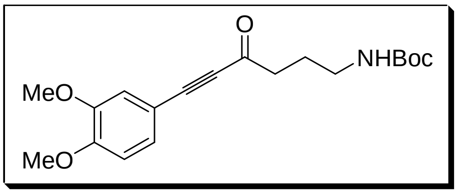
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.35 (m, 5H), 4.64 (br s, 1H), 3.20 (br q, J = 6.5 Hz, 2H), 2.74 (t, J =7.2 Hz, 2H), 1.92 (pent, J = 7.0 Hz, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.12, 155.93, 132.96, 130.67, 128.54, 119.75, 90.96, 87.62, 79.15, 42.64, 39.71, 28.29, 24.33

IR (UATR) ν_{max} 3361, 2976, 2201, 1669, 1513, 1365, 1249, 1166, 1052, 758, 689 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{17}H_{21}N_1Na_1O_3$ (M+Na)$^+$ 310.1414, found 310.1416.

tert-Butyl 6-(3,4-dimethoxyphenyl)-4-oxohex-5-ynylcarbamate (136bl)



75% yield, white solid, m.p. 80.1–80.5°C

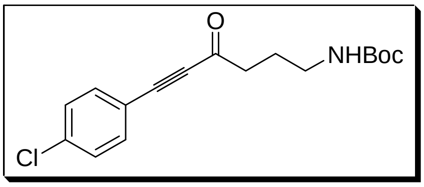
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.06 (d, *J* = 1.3 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 4.65 (br s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.20 (br q, *J* = 6.4 Hz, 2H), 2.73 (t, *J* =7.2 Hz, 2H), 1.92 (pent, *J* = 7.0 Hz, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.79, 155.73, 151.30, 148.43, 127.14, 115.03, 111.23, 110.76, 91.83, 87.04, 78.67, 55.59, 55.57, 42.23, 39.46, 28.02, 24.13

IR (UATR) ν_{max} 3391, 2974, 2186, 1709, 1663, 1596, 1513, 1249, 1170, 1023, 855, 810, 763 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{19}H_{25}N_1Na_1O_5$ $(M+Na)^{+}$ 370.1625, found 370.1623.

*tert*-Butyl 6-(4-chlorophenyl)-4-oxohex-5-ynylcarbamate (136cl)



79% yield, white solid, m.p. 104.3–105°C

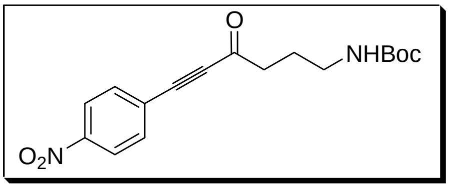
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 4.75 (br s, 1H), 3.19 (br q, *J* = 6.5 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 1.91 (pent, *J* = 7.0 Hz, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.85, 155.91, 137.05, 134.13, 129.00, 118.24, 89.41, 88.28, 79.17, 42.60, 39.70, 28.29, 24.30

IR (UATR) ν_{max} 3316, 2977, 2202, 1684, 1669, 1533, 1365, 1289, 1167, 1088, 822, 758 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{17}H_{20}Cl_1N_1Na_1O_3$ $(M+Na)^{+}$ 344.1024, found 344.1022.

*tert*-Butyl 6-(4-nitrophenyl)-4-oxohex-5-ynylcarbamate (136dl)



73% yield, yellow solid, m.p. 120.1–121.0°C

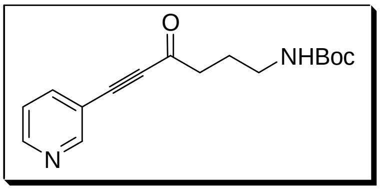
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.9 Hz, 2H), 7.73 (d, *J* = 8.9 Hz, 2H), 4.62 (br s, 1H), 3.20 (br q, *J* = 6.5 Hz, 2H), 2.77 (t, *J* =7.2 Hz, 2H), 1.93 (pent, *J* = 7.0 Hz, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.48, 155.94, 148.37, 133.56, 126.45, 123.65, 90.41, 86.94, 79.21, 42.65, 39.60, 28.27, 24.17

IR (UATR) ν_{max} 3306, 2973, 2207, 1681, 1674, 1521, 1348, 1286, 1172, 1036, 857, 750, 685 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{17}H_{20}N_2Na_1O_5$ $(M+Na)^{+}$ 355.1264, found 355.1264.

<u>*tert*-Butyl 4-oxo-6-(pyridin-3-yl)hex-5-ynylcarbamate (136el)</u>



71% yield, brown solid, m.p. 79.3–80.0°C

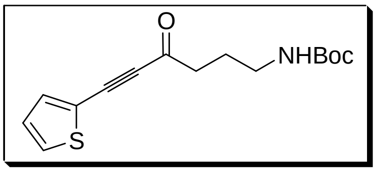
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, J = 1.4 Hz, 1H), 8.66 (dd, J = 4.9, 1.5 Hz, 1H), 7.86 (dt, J = 7.9, 1.9 Hz, 1H), 7.34 (ddd, J = 7.9, 4.9, 0.7 Hz, 1H), 4.71 (br s, 1H), 3.20 (br q, J = 6.5 Hz, 2H), 2.76 (t, J =7.2 Hz, 2H), 1.92 (pent, J = 7.0 Hz, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.65, 155.95, 153.24, 150.71, 139.82, 123.20, 117.21, 90.11, 86.79, 79.28, 42.66, 39.69, 28.33, 24.27

IR (UATR) ν_{max} 3347, 2976, 2206, 1694, 1674, 1516, 1366, 1250, 1167, 808, 703 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{16}H_{20}N_2Na_1O_3$ (M+Na)$^+$ 311.1366, found 311.1375.

<u>*tert*-Butyl 4-oxo-6-(thiophen-2-yl)hex-5-ynylcarbamate (136fl)</u>



76% yield, white solid, m.p. 77.1–77.4°C

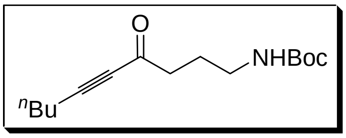
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, J = 3.0, 1.0 Hz, 1H), 7.34 (dd, J = 5.0, 3.0 Hz, 1H), 7.22 (dd, J = 5.0, 1.0 Hz, 1H), 4.66 (br s, 1H), 3.19 (br q, J = 6.5 Hz, 2H), 2.72 (t, J =7.2 Hz, 2H), 1.91 (pent, J = 7.0 Hz, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.99, 155.87, 133.81, 130.09, 126.11, 119.00, 87.85, 86.27, 79.06, 42.47, 39.68, 28.27, 24.31

IR (UATR) ν_{max} 3372, 2977, 2195, 1699, 1667, 1516, 1365, 1250, 1169, 787 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{15}H_{19}N_1Na_1O_3S_1$ (M+Na)$^+$ 316.0978, found 316.0989.

<u>*tert*-Butyl 4-oxodec-5-ynylcarbamate (136gl)</u>



71% yield, colorless oil

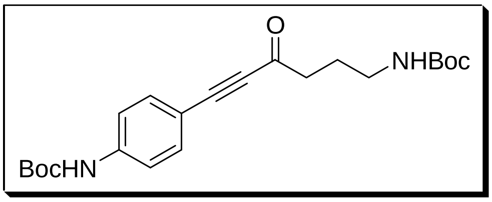
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (br s, 1H), 3.14 (br q, *J* = 6.2 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 1.83 (pent, *J* = 7.0 Hz, 2H), 1.55 (sext, *J* = 7.2 Hz, 2H), 1.50–1.36 (m, 2H), 1.44 (s, 9H), 0.93 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.28, 155.82, 94.55, 80.55, 78.87, 42.53, 39.54, 29.46, 28.16, 24.14, 21.72, 18.39, 13.26

IR (UATR) ν_{max} 3368, 2934, 2211, 1702, 1677, 1509, 1367, 1250, 1166 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{15}H_{25}N_1Na_1O_3$ $(M+Na)^+$ 290.1727, found 290.1719.

<u>*tert*-Butyl 4-oxo-6-{4-(*N*-*tert*-butoxycarbonyl)aminophenyl}hex-5-ynylcarbamate (136hl)</u>



74% yield, white solid, m.p. 139.3–140.0°C

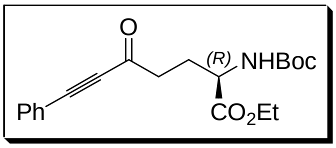
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 6.61 (br s, 1H), 4.61 (br s, 1H), 3.19 (br q, *J* = 6.7 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 1.91 (pent, *J* = 7.0 Hz, 2H), 1.53 (s, 9H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.16, 155.98, 152.28, 141.22, 134.18, 117.94, 113.11, 92.10, 87.57, 80.93, 79.11, 42.47, 39.68, 28.26, 28.12, 24.34,

IR (UATR) ν_{max} 3336, 2978, 2194, 1692, 1520, 1587, 1233, 1155, 1050, 840, 774 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{22}H_{30}N_2Na_1O_5$ $(M+Na)^+$ 425.2047, found 425.2060.

<u>(*R*)-Ethyl 2-(*tert*-butoxycarbonyl)-5-oxo-7-phenylhept-6-ynoate (136il)</u>



81% yield, yellow solid, m.p. 45.0–46.0°C, $[\alpha]_D^{28}$ +10.8 (*c* 1.1, MeOH)

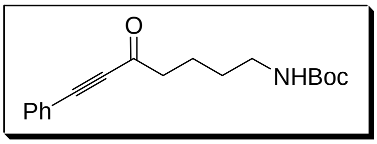
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.55 (m, 2H), 7.50–7.35 (m, 3H), 5.19 (d, *J* = 7.7 H, 1H), 4.34 (br s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.91–2.70 (m, 2H), 2.35–2.22 (m, 1H), 2.14–1.98 (m, 1H), 1.45 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.14, 172.04, 155.32, 132.99, 130.74, 128.56, 119.70, 91.24, 87.48, 79.93, 61.52, 52.78, 41.34, 28.20, 26.70, 14.07

IR(UATR) ν_{max} 3365, 2979, 2202, 1742, 1713, 1671, 1490, 1368, 1252, 1160, 1027, 759, 690 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{20}H_{25}N_1Na_1O_5$ (M+Na)$^+$ 382.1625, found 382.1636.

tert-Butyl 5-oxo-7-phenylhept-6-ynylcarbamate (136aII)



78% yield, white solid, m.p. 57.0–57.9°C

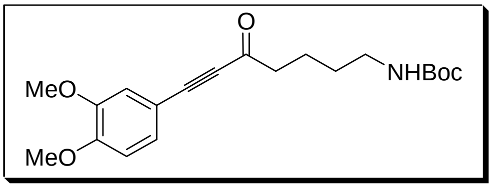
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.60–7.32 (m, 5H), 4.78 (br s, 1H), 3.15 (br q, *J* = 6.4 Hz, 2H), 2.70 (t, *J* =7.2 Hz, 2H), 1.82–1.70 (m, 2H), 1.62–1.50 (m, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 187.38, 155.85, 132.84, 130.55, 128.45, 119.69, 90.62, 87.56, 78.82, 44.76, 39.94, 29.16, 28.22, 20.97

IR (UATR) ν_{max} 3362, 2933, 2202, 1694, 1669, 1510, 1366, 1248, 1169, 1066, 758, 690 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{18}H_{23}N_1Na_1O_3$ (M+Na)$^+$ 324.1570, found 324.1586.

tert-Butyl 7-(3,4-dimethoxyphenyl)-5-oxohept-6-ynylcarbamate (136bII)



72% yield, white solid, m.p. 70.3–71.0°C

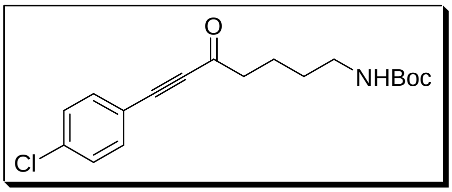
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.21 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.05 (d, *J* = 1.7 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.03 (br s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.16 (br q, *J* = 6.3 Hz, 2H), 2.70 (t, *J* =7.2 Hz, 2H), 1.83–1.70 (m, 2H), 1.63–1.52 (m, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 187.51, 155.95, 151.63, 148.81, 127.45, 115.40, 111.68, 111.04, 91.97, 87.42, 79.11, 55.98, 55.95, 44.77, 40.13, 29.35, 28.37, 21.18

IR (UATR) ν_{max} 3393, 2936, 2186, 1702, 1665, 1514, 1250, 1170, 1023, 856, 763 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{20}H_{27}N_1Na_1O_5$ (M+Na)$^+$ 384.1781, found 384.1796.

tert-Butyl 7-(4-chlorophenyl)-5-oxohept-6-ynylcarbamate (136cII)



71% yield, white solid, m.p. 81.1–82.0°C

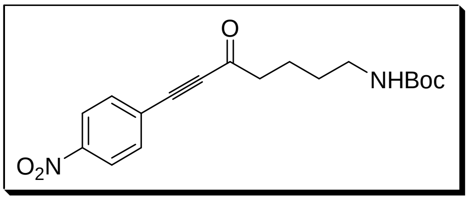
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 4.85 (br s, 1H), 3.16 (br q, J = 6.4 Hz, 2H), 2.70 (t, J =7.2 Hz, 2H), 1.82–1.70 (m, 2H), 1.62–1.50 (m, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.85, 155.68, 136.59, 133.81, 128.65, 117.95, 88.76, 88.01, 78.42, 44.49, 39.66, 28.92, 28.00, 20.68,

IR (UATR) ν_{max} 3362, 2933, 2202, 1694, 1670, 1489, 1366, 1248, 1167, 1090, 829, 765 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{18}H_{22}Cl_1N_1Na_1O_3$ (M+Na)$^+$ 358.1180, found 358.1186.

<u>*tert*-Butyl 7-(4-nitrophenyl)-5-oxohept-6-ynylcarbamate (136dII)</u>



69% yield, white solid, m.p. 105.3–106.0°C

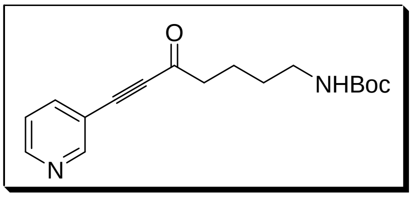
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 8.9 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H), 4.68 (br s, 1H), 3.17 (br q, J = 6.5 Hz, 2H), 2.75 (t, J =7.2 Hz, 2H), 1.84–1.71 (m, 2H), 1.63–1.51 (m, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.80, 155.92, 148.39, 133.56, 126.51, 123.67, 90.51, 86.76, 79.08, 44.87, 39.97, 29.26, 28.30, 20.81

IR (UATR) ν_{max} 3364, 2936, 2208, 1694, 1677, 1595, 1522, 1345, 1250, 1168, 858, 750, 687 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{18}H_{22}N_2Na_1O_5$ (M+Na)$^+$ 369.1421, found 369.1420.

<u>*tert*-Butyl 7-(pyridin-3-yl)-5-oxohept-6-ynylcarbamate (136eII)</u>



74% yield, yellow solid, m.p. 69.3–70.0°C

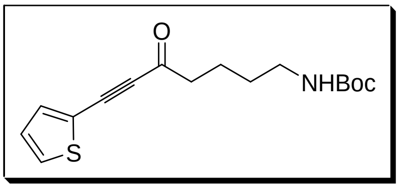
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (dd, J = 1.9, 0.8 Hz, 1H), 8.67 (dd, J = 4.9, 1.7 Hz, 1H), 7.86 (dt, J = 7.9, 1.9 Hz, 1H), 7.34 (ddd, J = 7.9, 4.9, 0.8 Hz, 1H), 4.58 (br s, 1H), 3.16 (br q, J = 6.5 Hz, 2H), 2.73 (t, J =7.2 Hz, 2H), 1.83–1.71 (m, 2H), 1.62–1.51 (m, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.67, 155.75, 152.75, 150.28, 139.52, 122.96, 116.89, 89.82, 86.17, 78.51, 44.54, 39.66, 28.92, 28.01, 20.62

IR (UATR) ν_{max} 3348, 2933, 2206, 1702, 1674, 1516, 1366, 1249, 1169, 808, 704 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{17}H_{22}N_2Na_1O_3$ (M+Na)$^+$ 325.1523, found 325.1537.

tert-Butyl 7-(thiophen-2-yl)-5-oxohept-6-ynylcarbamate (136fII)



71% yield, white solid, m.p. 65.4–65.7°C

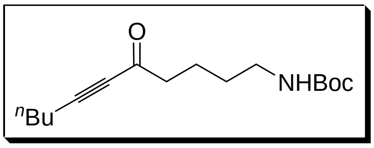
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.34 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.22 (dd, *J* = 5.0, 1.1 Hz, 1H), 4.58 (br s, 1H), 3.15 (br q, *J* = 6.5 Hz, 2H), 2.69 (t, *J* =7.2 Hz, 2H), 1.81–1.70 (m, 2H), 1.61–1.49 (m, 2H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.41, 155.88, 133.78, 130.12, 126.11, 119.05, 87.89, 86.10, 78.96, 44.69, 40.02, 29.24, 28.29, 21.04

IR (UATR) ν_{max} 3363, 2933, 2190, 1698, 1667, 1510, 1365, 1249, 1169, 1063, 787 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{16}H_{21}N_1Na_1O_3S_1$ (M+Na)$^+$ 330.1134, found 330.1137.

tert-Butyl 5-oxoundec-6-ynylcarbamate (136gII)



72% yield, colorless oil

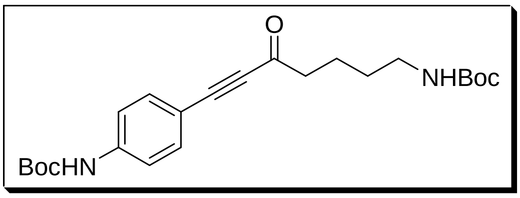
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (br s, 1H), 3.12 (br q, *J* = 6.2 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.37 (t, *J* = 6.8 Hz, 2H), 1.75–1.35 (m, 8H), 1.44 (s, 9H), 0.93 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.61, 155.79, 94.26, 80.56, 78.70, 44.71, 39.87, 29.45, 29.06, 28.15, 21.68, 20.87, 18.34, 13.22

IR (UATR) ν_{max} 3361, 2934, 2212, 1694, 1673, 1515, 1366, 1249, 1166 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{16}H_{27}N_1Na_1O_3$ (M+Na)$^+$ 304.1883, found 304.1895.

***tert*-Butyl 7-{4-(*N-tert*-butoxycarbonyl)aminophenyl}-5-oxohept-6-ynylcarbamate (136hll)**



75% yield, white solid, m.p. 120.7–121.4°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 6.75 (br s, 1H), 4.59 (br s, 1H), 3.15 (br q, *J* = 6.4 Hz, 2H), 2.68 (t, *J* = 7.2 Hz, 2H), 1.82–1.69 (m, 2H), 1.61–1.49 (m, 2H), 1.52 (s, 9H), 1.44 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.46, 155.92, 152.30, 141.32, 133.97, 117.86, 112.82, 91.92, 87.45, 80.56, 78.75, 44.54, 39.85, 29.03, 28.14, 27.97, 20.95

IR (UATR) ν_{max} 3334, 2977, 2192, 1689,1586, 1518, 1231, 1152, 1050, 839, 773 cm^{-1}

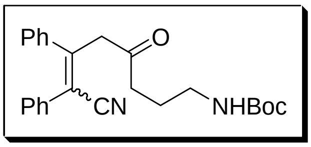
HRMS (ESI$^+$) calcd for $C_{23}H_{32}N_2Na_1O_5$ (M+Na)$^+$ 439.2203, found 439.2186.

2. General procedure for Michael reaction

*2.1 Screening of bases, solvents, and reaction conditions for Michael reaction between alkynone **136al** and benzyl cyanide **137a***

A solution of alkynone **136al** (0.35 mmol) in solvent (1.0 mL) were added to a mixture of benzyl cyanide **137a** (1.1 equiv.) and base (1.1 equiv.) in solvent (1.0 mL) at room temperature. The reaction was stirred at room temperature for 1-2 h. Then, the mixture was cooled down under ice-bath and neutralized with 1 N HCl. The products were extracted with EtOAc. The combined organic layers were washed with water, successively, dried over Na_2SO_4, and the solvent was concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel using hexanes and increasing proportion of EtOAc as eluent to afford compound **138aal**.

***tert*-Butyl 7-cyano-4-oxo-6,7-diphenylhept-6-enylcarbamate (138aal)**



81% yield, yellow oil

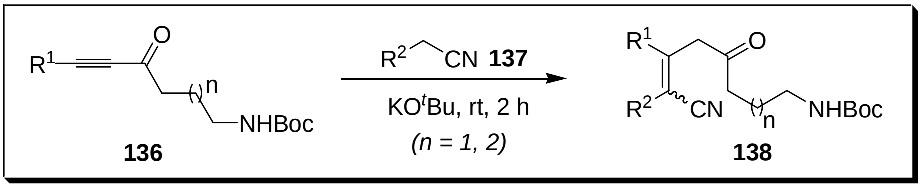
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 45:55) 7.52–7.36 (m, 10H), 7.23–7.02 (m, 10H), 4.79 (br s, 1H), 4.67 (br s, 1H), 4.03 (s, 2H), 3.67 (s, 2H), 3.06 (br q, *J* = 6.4 Hz, 2H), 2.94 (br q, *J* = 6.4 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.26 (t, *J* = 7.1 Hz, 2H), 1.74 (pent, *J* = 7.0 Hz, 2H), 1.58 (pent, *J* = 7.0 Hz, 2H), 1.42 (s, 9H), 1.40 (s, 9H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 45:55) 205.41, 204.40, 155.89, 155.83, 152.59, 151.21, 138.79, 137.71, 133.82, 132.93, 129.67, 129.27, 129.19, 129.02, 128.86, 128.61, 128.52, 128.36, 128.35, 128.24, 128.16, 128.09, 127.59, 118.50, 118.42, 115.33, 115.11, 78.87, 51.99, 48.38, 40.14, 39.91, 39.38, 39.30, 28.17, 28.15, 23.71, 23.59

IR (UATR) ν_{max} 3384, 2976, 2214, 1708, 1510, 1366, 1249, 1167, 763, 698 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{25}H_{28}N_2Na_1O_3$ (M+Na)$^+$ 427.1992, found 427.1978.

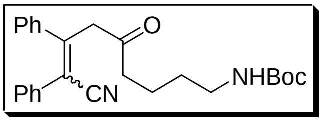
*2.2 General procedure for Michael reaction with various alkynones **136** and nitriles **137***



A solution of alkyne carbamate **136** (0.35 mmol) in DMF (1 mL) were added to a mixture of nitrile **137** (1.1 equiv) and KO^{t}Bu (1.1 equiv) in DMF (1 mL) at room temperature. The reaction was stirred at room temperature for 2 h. Then, the mixture was cooled down under ice-bath and neutralized with 1 N HCl. The products were extracted with EtOAc. The combined organic layers were washed with water, successively, dried over Na_2SO_4, and the solvent was concentrate under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of EtOAc as eluent to afford compound **138**.

Note: (a) For the synthesis of compounds **138adI**, **138adII**, **138daI**, and **138daII**, K_2CO_3 was used as base instead of KO^{t}Bu and the reaction was stirred for 4 h. (b) For the synthesis of compounds **3aiI**, **3ajI**, **3iiI**, the reaction was stirred for 30 min and after purification, the mixtures was used in the next step without purifications.

***tert*-Butyl 8-cyano-7,8-diphenyl-5-oxooct-7-enylcarbamate (138aaII)**



89% yield, yellow oil

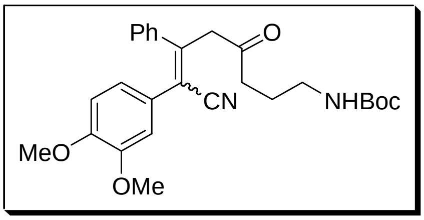
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 45:55) 7.52–7.36 (m, 11H), 7.23–7.02 (m, 9H), 4.71 (br s, 1H), 4.64 (br s, 1H), 4.02 (s, 2H), 3.66 (s, 2H), 3.06 (br q, *J* = 6.3 Hz, 2H), 2.97 (br q, *J* = 6.3 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.26 (t, *J* = 7.1 Hz, 2H), 1.65–1.52 (m, 2H), 1.52–1.32 (m, 4H), 1.42 (s, 18H), 1.32–1.20 (m, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 45:55) 205.71, 204.65, 155.82, 152.67, 151.25, 138.87, 137.77, 133.88, 132.96, 129.27, 129.22, 129.05, 128.85, 128.61, 128.54, 128.38, 128.37, 128.26, 128.23, 128.18, 127.60, 118.50, 118.42, 115.40, 115.15, 78.86, 52.06, 48.44, 42.51, 42.32, 39.82, 39.66, 29.04, 28.96, 28.20, 20.39, 20.25

IR (UATR) ν_{max} 3382, 2934, 2215, 1710, 1512, 1366, 1249, 1169, 764, 699 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{26}H_{30}N_2Na_1O_3$ (M+Na)$^+$ 441.2149, found 441.2154.

***tert*-Butyl 7-(3,4-dimethoxyphenyl)-7-cyano-4-oxo-6-phenylhept-6-enylcarbamate (138abl)**



75% yield, yellow oil

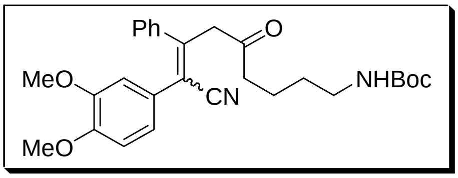
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 48:52) 7.51–7.39 (m, 5H), 7.29–7.22 (m, 3H), 7.10 (dd, *J* = 8.7, 2.0 Hz, 2H), 7.00–6.95 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.47 (d, *J* = 2.0 Hz, 1H), 4.62 (br s, 1H), 4.50 (br s, 1H), 4.02 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.72 (s, 2H), 3.48 (s, 3H), 3.09 (br q, *J* = 6.4 Hz, 2H), 2.98 (br q, *J* = 6.4 Hz, 2H), 2.58 (t, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.1 Hz, 2H), 1.77 (pent, *J* = 7.0 Hz, 2H), 1.61 (pent, *J* = 7.0 Hz, 2H), 1.43 (s, 9H), 1.41 (s, 9H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 48:52) 205.83, 204.69, 155.97, 155.89, 151.78, 149.69, 149.50, 149.08, 148.22, 138.99, 138.47, 129.41, 128.73, 128.68, 128.59, 128.29, 127.75, 126.43, 125.34, 122.26, 121.23, 118.64, 115.40, 115.34, 112.32, 111.60, 111.21, 110.62, 79.17, 55.94, 55.89, 55.71, 55.36, 52.26, 48.76, 40.52, 40.07, 39.58, 39.52, 28.31, 28.28, 23.89, 23.83

IR (UATR) ν_{max} 3391, 2975, 2213, 1709, 1600, 1515, 1366, 1262, 1171, 1025, 765, 701 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{27}H_{32}N_2Na_1O_5$ (M+Na)$^+$ 487.2203, found 487.2196.

***tert*-Butyl 8-cyano-8-(3,4-dimethoxyphenyl)-5-oxo-7-phenyloct-7-enylcarbamate (138abII)**



74% yield, yellow oil

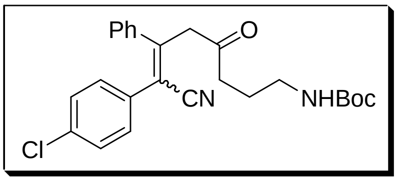
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 48:52) 7.50–7.39 (m, 5H), 7.27–7.23 (m, 3H), 7.13–7.07 (m, 2H), 7.00–6.95 (m, 2H), 6.90 (d, J = 8.4 Hz, 1H), 6.87 (dd, J = 8.4, 2.1 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.48 (d, J = 2.1 Hz, 1H), 4.58 (br s, 1H), 4.53 (br s, 1H), 4.01 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.70 (s, 2H), 3.48 (s, 3H), 3.08 (br q, J = 6.4 Hz, 2H), 2.99 (br q, J = 6.4 Hz, 2H), 2.55 (t, J = 7.1 Hz, 2H), 2.30 (t, J = 7.1 Hz, 2H), 1.68–1.55 (m, 2H), 1.51–1.24 (m, 6H), 1.43 (s, 9H), 1.42 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 48:52) 206.08, 204.89, 155.88, 151.92, 149.73, 149.54, 149.11, 148.26, 139.07, 138.52, 129.37, 128.71, 128.68, 128.57, 128.27, 127.74, 126.50, 125.38, 122.27, 121.24, 118.62, 115.44, 115.32, 112.38, 111.69, 111.25, 110.67, 79.02, 55.96, 55.91, 55.72, 55.38, 52.31, 48.78, 42.87, 42.45, 39.99, 39.86, 29.21, 28.33, 28.32, 20.55, 20.42

IR (UATR) ν_{max} 3391, 2935, 2212, 1706, 1599, 1513, 1365, 1247, 1169, 1024, 861, 765, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{28}H_{34}N_2Na_1O_5$ (M+Na)$^+$ 501.2360, found 501.2347

***tert*-Butyl 7-(4-chlorophenyl)-7-cyano-4-oxo-6-phenylhept-6-enylcarbamate (138acI)**



87% yield, yellow oil

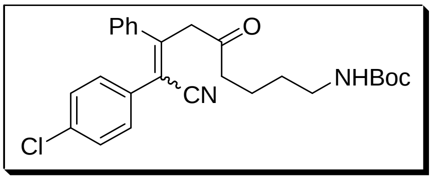
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 50:50) 7.50–7.33 (m, 9H), 7.26–7.18 (m, 3H), 7.14 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.6 Hz, 2H), 7.07–7.02 (m, 2H), 4.76 (br s, 1H), 4.65 (br s, 1H), 4.03 (s, 2H), 3.67 (s, 2H), 3.08 (br q, J = 6.2 Hz, 2H), 2.97 (br q, J = 6.2 Hz, 2H), 2.56 (t, J = 7.1 Hz, 2H), 2.30 (t, J = 7.1 Hz, 2H), 1.75 (pent, J = 7.0 Hz, 2H), 1.60 (pent, J = 7.0 Hz, 2H), 1.42 (s, 19H), 1.41 (s, 19H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 50:50) 205.28, 204.24, 155.94, 155.89, 153.17, 151.99, 138.60, 137.50, 135.19, 134.27, 132.25, 131.48, 130.56, 129.88, 129.49, 129.15, 128.88, 128.63, 128.58, 128.47, 128.15, 127.57, 118.15, 118.11, 114.26, 114.17, 78.98, 52.05, 48.41, 40.27, 40.03, 39.40, 39.27, 28.20, 28.18, 23.78, 23.69

IR (UATR) ν_{max} 3378, 2977, 2214, 1707, 1512, 1366, 1250, 1168, 1093, 833, 767, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{25}H_{27}Cl_1N_2Na_1O_3$ (M+Na)$^+$ 461.1602, found 461.1595.

***tert*-Butyl 8-cyano-8-(4-chlorophenyl)-5-oxo-7-phenyloct-7-enylcarbamate (138acII)**



81% yield, yellow oil

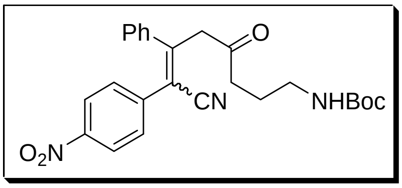
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 48:52) 7.49–7.33 (m, 9H), 7.27–7.20 (m, 3H), 7.15 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 7.06–7.01 (m, 2H), 4.65 (br s, 1H), 4.59 (br s, 1H), 4.02 (s, 2H), 3.65 (s, 2H), 3.07 (br q, *J* = 6.4 Hz, 2H), 2.99 (br q, *J* = 6.4 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.29 (t, *J* = 7.1 Hz, 2H), 1.66–1.55 (m, 2H), 1.52–1.37 (m, 2H), 1.43 (s, 9H), 1.42 (s, 9H), 1.35–1.24 (m, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 48:52) 205.54, 204.44, 155.86, 155.83, 153.24, 152.03, 138.68, 137.59, 135.27, 134.33, 132.35, 131.54, 130.61, 129.91, 129.51, 129.16, 128.90, 128.67, 128.62, 128.51, 128.16, 127.59, 118.16, 118.10, 114.37, 114.23, 78.96, 52.14, 48.48, 42.74, 42.45, 39.87, 39.70, 29.13, 29.08, 28.26, 20.46, 20.27

IR (UATR) ν_{max} 3382, 2976, 2213, 1710, 1507, 1366, 1249, 1169, 1093, 834, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{26}H_{29}Cl_1N_2Na_1O_3$ (M+Na)$^+$ 475.1759, found 475.1754.

***tert*-Butyl 7-cyano-7-(4-nitrophenyl)-4-oxo-6-phenylhept-6-enylcarbamate (138adI)**



70% yield, yellow oil

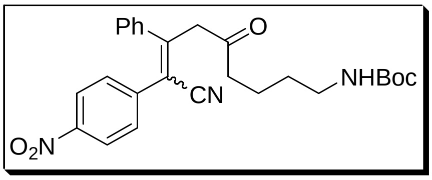
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 60:40) 8.29 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.53–7.42 (m, 5H), 7.35–7.22 (m, 5H), 7.05 (dd, *J* = 8.0, 1.6 Hz, 2H), 4.74 (br s, 1H), 4.63 (br s, 1H), 4.10 (s, 2H), 3.72 (s, 2H), 3.10 (br q, *J* = 6.4 Hz, 2H), 3.00 (br q, *J* = 6.3 Hz, 2H), 2.51 (t, *J* = 7.1 Hz, 2H), 2.35 (t, *J* = 7.0 Hz, 2H), 1.78 (pent, *J* = 7.0 Hz, 2H), 1.62 (pent, *J* = 6.8 Hz, 2H), 1.43 (s, 9H), 1.39 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 60:40) 204.93, 203.82, 155.94, 154.94, 147.94, 147.08, 140.11, 139.66, 138.29, 137.08, 130.30, 129.86, 129.78, 129.43, 128.81, 128.76, 128.11, 127.53, 124.11, 123.41, 117.58, 117.54, 113.53, 79.01, 52.19, 48.46, 40.34, 40.18, 39.39, 39.12, 28.21, 28.14, 23.86, 23.82

IR (UATR) ν_{max} 3363, 2977, 2213, 1705, 1636, 1518, 1344, 1246, 1166, 1044, 854, 768, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{25}H_{27}N_3Na_1O_5$ (M+Na)$^+$ 472.1843, found 472.1842.

<u>*tert*-Butyl 8-cyano-8-(4-nitrophenyl)-5-oxo-7-phenyloct-7-enylcarbamate (138adII)</u>



68% yield, yellow oil

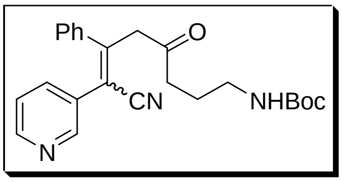
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 65:35) 8.30 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.53–7.42 (m, 5H), 7.35–7.22 (m, 5H), 7.05 (dd, *J* = 7.6, 1.6 Hz, 2H), 4.72 (br s, 1H), 4.66 (br s, 1H), 4.10 (s, 2H), 3.70 (s, 2H), 3.09 (br q, *J* = 6.3 Hz, 2H), 3.00 (br q, *J* = 6.4 Hz, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.35 (t, *J* = 7.1 Hz, 2H), 1.70–1.58 (m, 2H), 1.53–1.38 (m, 4H), 1.43 (s, 9H), 1.42 (s, 9H), 1.38–1.27 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 65:35) 205.29, 204.07, 155.81, 154.96, 147.92, 147.02, 140.14, 139.62, 138.21, 137.05, 130.27, 129.84, 129.72, 129.38, 128.78, 128.73, 128.04, 127.48, 124.05, 123.38, 117.50, 113.52, 113.39, 78.83, 52.19, 48.39, 42.87, 42.53, 39.76, 39.56, 29.04, 28.98, 28.19, 28.17, 20.38, 20.11

IR (UATR) ν_{max} 3361, 2934, 2354, 1709, 1597, 1520, 1346, 1249, 1168, 855, 769, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{26}H_{29}N_3Na_1O_5$ (M+Na)$^+$ 486.1999, found 486.1994.

<u>*tert*-Butyl 7-cyano-7-(pyridin-3-yl)-4-oxo-6-phenylhept-6-enylcarbamate (138aeI)</u>



73% yield, yellow oil

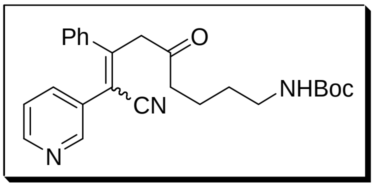
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 60:40) 8.67 (d, *J* = 2.0 Hz, 1H), 8.65 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.42 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.34 (d, *J* = 1.7 Hz, 1H), 7.79 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.52–7.42 (m, 6H), 7.39 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.28–7.19 (m, 3H), 7.15 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.08–7.01 (m, 2H), 4.82 (br s, 1H), 4.74 (br s, 1H), 4.08 (s, 2H), 3.69 (s, 2H), 3.09 (br q, *J* = 6.4 Hz, 2H), 2.97 (br q, *J* = 6.4 Hz, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.32 (t, *J* = 7.0 Hz, 2H), 1.77 (pent, *J* = 7.0 Hz, 2H), 1.61 (pent, *J* = 6.8 Hz, 2H), 1.43 (s, 9H), 1.40 (s, 9H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 60:40) 204.93, 203.95, 155.94, 154.57, 153.77, 151.12, 149.92, 149.05, 149.03, 138.41, 137.13, 136.45, 136.20, 130.10, 129.71, 129.38, 129.16, 128.73, 128.72, 128.14, 127.53, 123.65, 122.96, 117.84, 117.75, 112.19, 112.05, 78.97, 52.05, 48.40, 40.35, 40.13, 39.41, 39.22, 28.22, 28.19, 23.83, 23.73

IR (UATR) ν_{max} 3336, 2977, 2156, 1702, 1626, 1525, 1366, 1248, 1168, 767, 702 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{24}H_{27}N_3Na_1O_3$ (M+Na)$^+$ 428.1945, found 428.1945.

tert-Butyl 8-cyano-8-(pyridin-3-yl)-5-oxo-7-phenyloct-7-enylcarbamate (138aeII)



79% yield, yellow oil

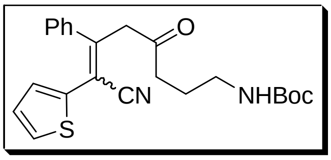
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 55:45) 8.67 (d, *J* = 1.7 Hz, 1H), 8.65 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.43 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.34 (d, *J* = 1.7 Hz, 1H), 7.79 (dt, *J* = 8.0, 1.8 Hz, 1H), 7.52–7.42 (m, 6H), 7.39 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.30–7.19 (m, 3H), 7.15 (ddd, *J* = 8.0, 4.9, 0.6 Hz, 1H), 7.07–7.01 (m, 2H), 4.66 (br s, 2H), 4.07 (s, 2H), 3.67 (s, 2H), 3.08 (br q, *J* = 6.4 Hz, 2H), 2.99 (br q, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.68–1.56 (m, 2H), 1.51–1.37 (m , 4H), 1.43 (s, 9H), 1.42 (s, 9H), 1.36–1.25 (m, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 55:45) 205.26, 204.23, 155.92, 154.66, 153.86, 150.18, 149.95, 149.05, 138.48, 137.20, 136.54, 136.29, 130.21, 129.76, 129.45, 129.21, 128.80, 128.78, 128.16, 127.57, 123.69, 123.03, 117.86, 117.78, 112.30, 112.05, 78.98, 52.15, 48.48, 42.83, 42.56, 39.87, 39.71, 29.15, 29.06, 28.29, 20.47, 20.34,

IR (UATR) ν_{max} 3341, 2933, 2212, 1704, 1634, 1516, 1365, 1249, 1168, 767, 701 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{25}H_{29}N_3Na_1O_3$ (M+Na)$^+$ 442.2101, found 442.2097

***tert*-Butyl 7-cyano-7-(thiophen-2-yl)-4-oxo-6-phenylhept-6-enylcarbamate (138afI)**



70% yield, yellow oil

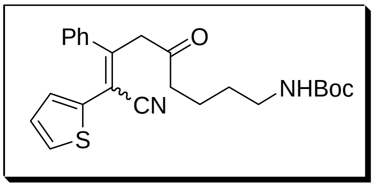
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 55:45) 7.49–7.36 (m, 9H), 7.29 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.23–7.18 (m, 3H), 7.11 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.08 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.63 (br s, 1H), 4.56 (br s, 1H), 3.97 (s, 2H), 3.93 (s, 2H), 3.08 (br q, *J* = 6.6 Hz, 2H), 3.03 (br q, *J* = 6.6 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.43 (t, *J* = 7.1 Hz, 2H), 1.75 (pent, *J* = 7.0 Hz, 2H), 1.68 (pent, *J* = 7.0 Hz, 2H), 1.42 (s, 18H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 55:45) 204.56, 204.18, 155.82, 151.92, 148.21, 139.22, 137.71, 135.22, 134.87, 129.71, 129.42, 129.34, 129.14, 129.06, 128.52, 128.00, 127.75, 127.60, 127.33, 126.05, 117.67, 117.09, 110.70, 109.03, 78.84, 52.58, 49.37, 40.04, 39.98, 39.39, 28.16, 23.70, 23.64

IR (UATR) ν_{max} 3385, 2976, 2219, 1706, 1513, 1366, 1249, 1168, 765, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{23}H_{26}N_2Na_1O_3S_1$ (M+Na)$^+$ 433.1556, found 433.1551.

***tert*-Butyl 8-cyano-8-(thiophen-2-yl)-5-oxo-7-phenyloct-7-enylcarbamate (138afII)**



75% yield, yellow oil

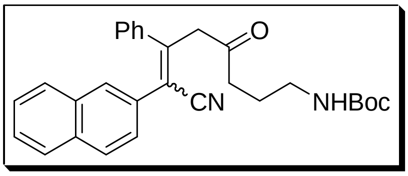
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 60:40) 7.47–7.37 (m, H), 7.29 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.24–7.18 (m, 4H), 7.12 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.08 (dd, *J* = 4.7, 3.7 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.53 (br s, 2H), 3.96 (s, 2H), 3.91 (s, 2H), 3.13–2.99 (m, 4H), 2.57 (t, *J* = 7.1 Hz, 2H), 2.42 (t, *J* = 7.1 Hz, 2H), 1.67–1.32 (m, 8H), 1.43 (s, 18H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 60:40) 204.80, 204.41, 155.82, 152.08, 148.27, 139.32, 137.83, 135.31, 134.95, 129.77, 129.46, 129.38, 129.18, 129.11, 128.59, 128.03, 127.82, 127.64, 127.63, 127.35, 126.10, 117.69, 117.13, 110.82, 109.13, 78.86, 52.69, 49.44, 42.45, 42.41, 39.85, 39.78, 29.11, 28.24, 20.45, 20.30

IR (UATR) ν_{max} 3378, 2933, 2218, 1706, 1509, 1365, 1247, 1167, 851, 766, 699 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{24}H_{28}N_2Na_1O_3S_1$ $(M+Na)^+$ 447.1713, found 447.1726

tert-Butyl 7-cyano-7-(naphthalen-2-yl)-4-oxo-6-phenylhept-6-enylcarbamate (138agI)



99% yield, yellow oil

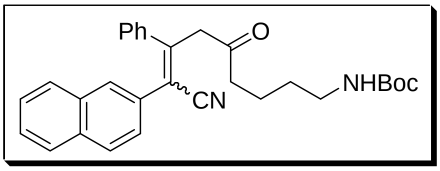
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 50:50) 7.92–7.79 (m, 5H), 7.73–7.67 (m, 2H), 7.40–7.57 (m, 11H), 7.23–7.14 (m, 3H), 7.11 (d, *J* = 1.6 Hz, 1H), 7.09 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.04 (dd, *J* = 8.6, 1.8 Hz, 1H), 4.68 (br s, 1H), 4.52 (br s, 1H), 4.08 (s, 2H), 3.72 (s, 2H), 3.10 (br q, *J* = 6.4 Hz, 2H), 2.94 (br q, *J* = 6.4 Hz, 2H), 2.60 (t, *J* = 7.1 Hz, 2H), 2.26 (t, *J* = 7.1 Hz, 2H), 1.77 (pent, *J* = 7.0 Hz, 2H), 1.58 (pent, *J* = 7.0 Hz, 2H), 1.43 (s, 9H), 1.39 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 50:50) 205.54, 204.51, 155.98, 155.86, 152.84, 151.31, 138.89, 137.84, 133.07, 132.92, 132.78, 132.61, 131.26, 130.50, 129.44, 129.10, 128.83, 128.67, 128.53, 128.44, 128.12, 128.10, 128.04, 127.72, 127.64, 127.42, 127.03, 126.79, 126.38, 126.35, 125.56, 118.72, 118.53, 115.40, 115.30, 79.02, 52.19, 48.59, 40.27, 40.03, 39.49, 39.40, 28.26, 28.21, 23.83, 23.73

IR (UATR) ν_{max} 3386, 2976, 2212, 1707, 1506, 1366, 1249, 1166, 861, 820, 750, 699 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{29}H_{30}N_2Na_1O_3$ $(M+Na)^+$ 477.2149, found 477.2150.

tert-Butyl 8-cyano-8-(naphthalen-2-yl)-5-oxo-7-phenyloct-7-enylcarbamate (138agII)



95% yield, yellow oil

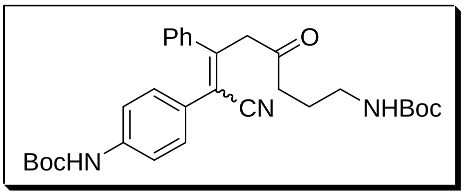
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 50:50) 7.90–7.77 (m, 5H), 7.70–7.64 (m, 2H), 7.55–7.37 (m, 11H), 7.21–7.12 (m, 3H), 7.10–7.05 (m, 2H), 7.03 (dd, *J* = 8.6, 1.8 Hz, 1H), 4.68 (br s, 1H), 4.54 (br s, 1H), 4.06 (s, 2H), 3.69 (s, 2H), 3.07 (br q, *J* = 6.4 Hz, 2H), 2.92 (br q, *J* = 6.4 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.22 (t, *J* = 7.1 Hz, 2H), 1.68–1.54 (m, 2H), 1.49–1.33 (m , 4H), 1.43 (s, 9H), 1.41 (s, 9H), 1.28–1.17 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 50:50) 205.71, 204.63, 155.85, 155.77, 152.91, 151.32, 138.94, 137.83, 133.02, 132.88, 132.73, 132.55, 131.28, 130.49, 129.33, 129.04, 128.76, 128.73, 128.59, 128.46, 128.36, 128.04, 128.01, 127.98, 127.66, 127.64, 127.60, 127.37, 126.98, 126.74, 126.33, 126.29, 125.52, 118.64, 118.46, 115.37, 115.19, 78.81, 52.17, 48.58, 42.55, 42.36, 39.85, 39.66, 29.09, 28.99, 28.23, 28.21, 20.43, 20.32

IR (UATR) ν_{max} 3384, 2932, 2208, 1709, 1505, 1365, 1248, 1169, 751, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{30}H_{32}N_2Na_1O_3$ (M+Na)$^+$ 491.2305, found 491.2304

<u>*tert*-Butyl 7-cyano-7-{4-(*N*-*tert*-butoxycarbonyl)aminophenyl}-4-oxo-6-phenylhept-6-enyl carbamate (138ahl)</u>



81% yield, yellow oil

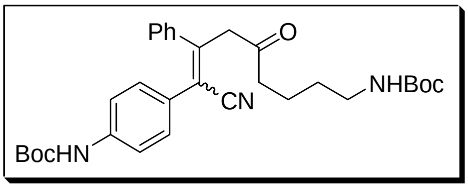
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 43:57) 7.50–7.38 (m, 7H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.24–7.16 (m, 5H), 7.09–7.04 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.84 (br s, 1H), 6.66 (br s, 1H), 4.63 (br s, 1H), 4.55 (br s), 4.01 (s, 2H), 3.68 (s, 2H), 3.08 (br q, *J* = 6.4 Hz, 2H), 2.96 (br q, *J* =6.6 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.76 (pent, *J* = 6.9 Hz, 2H), 1.60 (pent, *J* =7.0 Hz, 2H), 1.52 (s, 9H), 1.48 (s, 9H), 1.43 (s, 9H), 1.41 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 43:57) 205.61, 204.68, 155.99, 155.93, 152.53, 152.36, 152.11, 150.09, 139.36, 139.04, 138.60, 138.05, 130.11, 129.39, 129.31, 128.72, 128.70, 128.62, 128.33, 128.30, 127.74, 127.31, 118.67, 118.60, 117.83, 115.11, 115.02, 80.87, 80.74, 79.15, 52.24, 48.61, 40.37, 40.05, 39.55, 28.33, 28.32, 28.24, 28.21, 23.88, 23.81

IR (UATR) ν_{max} 3335, 2978, 2213, 1701, 1522, 1234, 1156, 1054, 841, 772, 699 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{30}H_{37}N_3Na_1O_5$ (M+Na)$^+$ 542.2625, found 542.2606.

***tert*-Butyl 8-{4-(*N*-*tert*-butoxycarbonyl)aminophenyl}-8-cyano-5-oxo-7-phenyloct-7-enyl carbamate (138ahII)**



85% yield, yellow oil

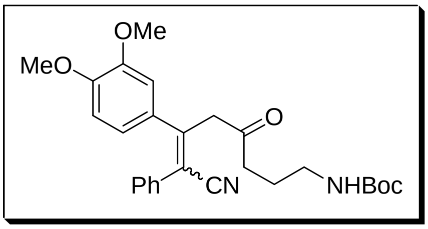
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 50:50) 7.50–7.37 (m, 7H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.24–7.16 (m, 5H), 7.08–7.02 (m, 4H), 6.89 (br s, 1H), 6.65 (br s, 1H), 4.59 (br s, 2H), 4.00 (s, 2H), 3.67 (s, 2H), 3.07 (br q, *J* = 6.4 Hz, 2H), 2.99 (br q, *J* =6.4 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.66–1.25 (m, 8H), 1.52 (s, 9H), 1.48 (s, 9H), 1.43 (s, 18H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 50:50) 205.94, 204.90, 155.94, 152.57, 152.36, 152.22, 150.13, 139.39, 139.12, 138.58, 138.09, 130.12, 129.35, 129.29, 128.69, 128.62, 128.33, 127.74, 127.34, 118.66, 118.60, 117.82, 115.14, 115.01, 80.87, 80.75, 79.08, 52.29, 48.64, 42.71, 42.44, 39.98, 39.91, 29.20, 28.35, 28.25, 28.21, 20.53

IR (UATR) ν_{max} 3344, 2977, 2213, 1709, 1521, 1235, 1158, 1054, 841, 771, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{31}H_{39}N_3Na_1O_5$ (M+Na)$^+$ 556.2782, found 556.2768.

***tert*-Butyl 7-cyano-6-(3,4-dimethoxyphenyl)-4-oxo-7-phenylhept-6-enylcarbamate (138baI)**



89% yield, yellow oil

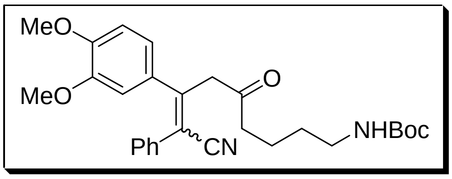
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 50:50) 7.47–7.33 (m, 5H), 7.25–7.14 (m, 5H), 7.12 (d, *J* = 1.7 Hz, 1H), 7.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.73 (s, 2H), 6.48 (s, 1H), 4.77 (br s, 1H), 4.66 (br s, 1H), 4.05 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 3.68 (s, 2H), 3.49 (s, 3H), 3.09 (br q, *J* = 6.4 Hz, 2H), 2.97 (br q, *J* = 6.4 Hz, 2H), 2.60 (t, *J* = 7.1 Hz, 2H), 2.29 (t, *J* = 7.1 Hz, 2H), 1.76 (pent, *J* = 7.0 Hz, 2H), 1.61 (pent, *J* = 7.0 Hz, 2H), 1.43 (s, 9H), 1.41 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 50:50) 205.70, 204.79, 155.95, 155.87, 152.17, 150.87, 150.00, 149.47, 148.69, 148.28, 134.25, 133.62, 131.09, 129.76, 129.27, 128.98, 128.93, 128.50, 128.41, 128.22, 121.21, 120.56, 118.95, 118.88, 114.07, 113.99, 112.30, 111.16, 110.91, 110.71, 79.05, 55.96, 55.75, 55.62, 55.41, 51.77, 48.35, 40.12, 39.86, 39.45, 28.23, 28.21, 23.88, 23.79

IR (UATR) ν_{max} 3379, 2932, 2211, 1699, 1513, 1366, 1249, 1168, 766, 701 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{27}H_{32}N_2Na_1O_5$ $(M+Na)^+$ 487.2203, found 487.2186

tert-Butyl 8-cyano-7-(3,4-dimethoxyphenyl)-5-oxo-8-phenyloct-7-enylcarbamate (138ball)



82% yield, yellow oil

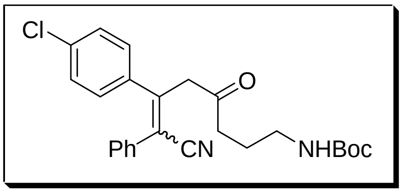
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 48:52) 7.45–7.35 (m, 5H), 7.24–7.15 (m, 5H), 7.11 (d, J = 2.1 Hz, 1H), 7.06 (dd, J = 8.3, 2.1 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.70 (dd, J = 8.4, 1.8 Hz, 1H), 6.46 (d, J = 1.8 Hz, 1H), 4.65 (br s, 1H), 4.58 (br s, 1H), 4.04, 3.94 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.66 (s, 2H), 3.49 (s, 3H), 3.08 (br q, J = 6.4 Hz, 2H), 3.00 (br q, J = 6.4 Hz, 2H), 2.57 (t, J = 7.1 Hz, 2H), 2.28 (t, J = 7.1 Hz, 2H), 1.68–1.57 (m, 2H), 1.52–1.24 (m, 6H), 1.43 (s, 9H), 1.42 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 48:52) 205.91, 204.96, 155.87, 155.83, 152.22, 150.86, 150.02, 149.49, 148.72, 148.32, 134.28, 133.64, 131.18, 129.81, 129.28, 128.99, 128.91, 128.51, 128.41, 128.22, 121.14, 120.53, 118.93, 118.85, 114.16, 114.07, 112.35, 111.23, 110.96, 110.75, 78.96, 55.98, 55.77, 55.64, 55.44, 51.83, 48.38, 42.53, 42.30, 39.91, 39.76, 29.18, 29.11, 28.25, 20.46, 20.32

IR (UATR) ν_{max} 3362, 2932, 2213, 1699, 1493, 1367, 1250, 1168, 1093, 1014, 834, 765, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{28}H_{34}N_2Na_1O_5$ $(M+Na)^+$ 501.2360, found 501.2344.

tert-Butyl 7-cyano-6-(4-chlorophenyl)-4-oxo-7-phenylhept-6-enylcarbamate (138cal)



90% yield, yellow oil

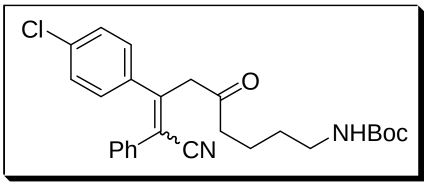
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 45:55) 7.48–7.32 (m, 9H), 7.24–7.10 (m, 7H), 7.00 (d, *J* = 8.5 Hz, 2H), 4.77 (br s, 1H), 4.66 (br s, 1H), 4.02 (s, 2H), 3.66 (s, 2H), 3.09 (br q, *J* = 6.4 Hz, 2H), 2.98 (br q, *J* = 6.4 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.75 (pent, *J* = 7.0 Hz, 2H), 1.60 (pent, *J* = 7.0 Hz, 2H), 1.42 (s, 9H), 1.40 (s, 9H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 45:55) 205.27, 204.33, 155.93, 155.85, 151.41, 149.93, 137.33, 136.23, 135.27, 134.61, 133.54, 132.68, 129.79, 129.21, 129.19, 129.12, 128.95, 128.82, 128.65, 128.52, 128.39, 128.29, 118.26, 118.18, 115.90, 115.69, 78.97, 51.73, 48.31, 40.06, 39.94, 39.32, 28.19, 28.17, 23.81, 23.71

IR (UATR) ν_{max} 3365, 2977, 2215, 1704, 1492, 1366, 1249, 1165, 1093, 833, 765, 699 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{25}H_{27}Cl_1N_2Na_1O_3$ (M+Na)$^{+}$ 461.1602, found 461.1591.

***tert*-Butyl 7-(4-chlorophenyl)-8-cyano-5-oxo-8-phenyloct-7-enylcarbamate (138caII)**



93% yield, yellow oil

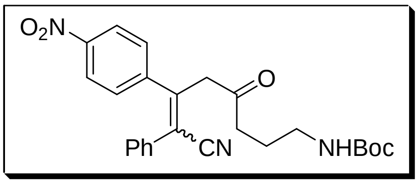
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 47:53) 7.47–7.33 (m, 9H), 7.22–7.10 (m, 7H), 7.00 (d, *J* = 8.6 Hz, 2H), 4.76 (br s, 1H), 4.69 (br s, 1H), 4.01 (s, 2H), 3.65 (s, 2H), 3.10 (br q, *J* = 6.3 Hz, 2H), 3.00 (br q, *J* = 6.3 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.28 (t, *J* = 7.0 Hz, 2H), 1.67–1.53 (m, 2H), 1.43 (s, 9H), 1.42 (s, 9H), 1.50–1.25 (m, 6H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 47:53) 205.55, 204.55, 155.78, 151.46, 149.92, 137.34, 136.20, 135.18, 134.54, 133.51, 132.63, 129.71, 129.18, 129.14, 129.07, 128.88, 128.76, 128.60, 128.48, 128.34, 128.23, 118.21, 118.14, 115.88, 115.62, 78.79, 51.71, 48.29, 42.39, 42.32, 39.74, 39.58, 29.02, 28.96, 28.16, 20.34, 20.20

IR (UATR) ν_{max} 3363, 2932, 2213, 1703, 1510, 1493, 1366, 1249, 1167, 1093, 833, 764, 700 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{26}H_{29}Cl_1N_2Na_1O_3$ (M+Na)$^{+}$ 475.1759, found 475.1747.

tert-Butyl 7-cyano-6-(4-nitrophenyl)-4-oxo-7-phenylhept-6-enylcarbamate (138daI)



68% yield, yellow oil

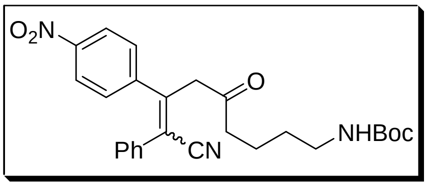
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 46:54) 8.27 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.48–7.34 (m, 5H), 7.28 (d, J = 8.7 Hz, 2H), 7.27–7.08 (m, 5H), 4.80 (br s, 1H), 4.69 (br s, 1H), 4.10 (s, 2H), 3.76 (s, 2H), 3.11 (br q, J = 6.4 Hz, 2H), 3.00 (br q, J = 6.4 Hz, 2H), 2.62 (t, J = 7.1 Hz, 2H), 2.33 (t, J = 7.1 Hz, 2H), 1.78 (pent, J = 7.0 Hz, 2H), 1.63 (pent, J = 7.0 Hz, 2H), 1.42 (s, 9H), 1.40 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 46:54) 205.10, 204.18, 155.98, 155.90, 150.52, 148.94, 147.83, 147.21, 145.54, 144.68, 132.89, 132.10, 129.57, 129.18, 129.06, 129.01, 128.57, 128.20, 123.75, 123.50, 117.68, 117.59, 117.20, 78.99, 51.34, 48.24, 39.92, 39.85, 39.23, 28.16, 28.14, 23.87, 23.78

IR (UATR) ν_{max} 3363, 2977, 2215, 1701, 1597, 1521, 1346, 1249, 1167, 857, 763, 700 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{25}H_{27}N_3Na_1O_5$ (M+Na)$^{+}$ 472.1843, found 472.1835.

tert-Butyl 8-cyano-7-(4-nitrophenyl)-5-oxo-8-phenyloct-7-enylcarbamate (138daII)



67% yield, yellow oil

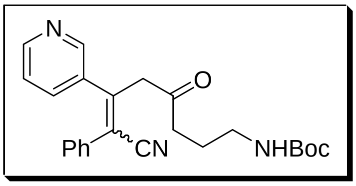
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 48:52) 8.28 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), 7.42–7.48 (m, 3H), 7.34–7.39 (m, 2H), 7.17–7.30 (m, 5H), 7.14 (dd, J = 7.8, 1.7 Hz, 2H), 4.68 (br s, 1H), 4.62 (br s, 1H), 4.07 (s, 2H), 3.72 (s, 2H), 3.09 (br q, J = 6.4 Hz, 2H), 3.01 (br q, J = 6.4 Hz, 2H), 2.60 (t, J = 7.1 Hz, 2H), 2.33 (t, J = 7.1 Hz, 2H), 1.71–1.58 (m, 2H), 1.56–1.32 (m, 6H), 1.43 (s, 9H), 1.42 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 48:52) 205.36, 204.43, 155.87, 150.52, 148.92, 147.95, 147.32, 145.60, 144.77, 132.97, 132.13, 129.64, 129.54, 129.23, 129.10, 129.07, 129.01, 128.62, 128.25, 126.44, 123.84, 123.59, 117.78, 117.68, 117.57, 117.35, 79.00, 51.46, 48.36, 42.49, 42.37, 39.80, 39.64, 29.16, 29.11, 28.24, 28.23, 20.44, 20.29

IR (UATR) ν_{max} 3362, 2933, 2213, 1701, 1598, 1521, 1347, 1249, 1168, 857, 763, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{26}H_{29}N_3Na_1O_5$ (M+Na)$^+$ 486.1999, found 486.1980.

***tert*-Butyl 7-cyano-6-(pyridin-3-yl)-4-oxo-7-phenylhept-6-enylcarbamate (138eaI)**



75% yield, yellow oil

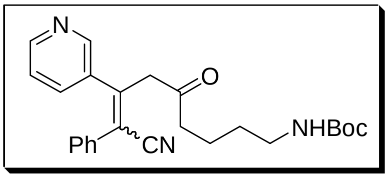
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 45:55) 8.71 (d, *J* = 1.9 Hz, 1H), 8.64 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.45 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.30 (d, *J* = 1.7 Hz, 1H), 7.90 (ddd, *J* = 8.0, 2.2, 1.7 Hz, 1H), 7.46–7.34 (m, 7H), 7.23–7.10 (m, 6H), 4.81 (br s, 1H), 4.71 (br s, 1H), 4.07 (s, 2H), 3.72 (s, 2H), 3.11 (br q, *J* = 6.4 Hz, 2H), 2.99 (br q, *J* = 6.4 Hz, 2H), 2.62 (t, *J* = 7.1 Hz, 2H), 2.33 (t, *J* = 7.1 Hz, 2H), 1.78 (pent, *J* = 7.0 Hz, 2H), 1.63 (pent, *J* = 7.0 Hz, 2H), 1.43 (s, 9H), 1.41 (s, 9H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 45:55) 205.16, 204.30, 156.05, 155.97, 150.08, 149.32, 149.28, 148.81, 148.01, 147.85, 136.20, 135.90, 135.18, 134.13, 133.24, 132.35, 129.49, 129.36, 129.08, 128.86, 128.61, 128.32, 123.43, 123.17, 117.94, 117.83, 117.30, 117.21, 79.14, 51.49, 48.35, 40.07, 39.38, 28.26, 28.24, 23.93, 23.84

IR (UATR) ν_{max} 3332, 2976, 2156, 1701, 1634, 1522, 1367, 1250, 1168, 701 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{24}H_{27}N_3Na_1O_3$ (M+Na)$^+$ 428.1945, found 428.1950.

***tert*-Butyl 8-cyano-5-oxo-8-phenyl-7-(pyridin-3-yl)oct-7-enylcarbamate (138eaII)**



79% yield, yellow oil

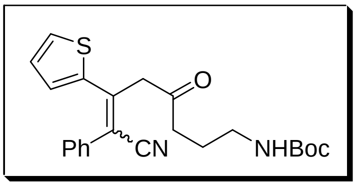
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 47:53) 8.71 (d, *J* = 1.8 Hz, 1H), 8.62 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.44 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.29 (d, *J* = 1.7 Hz, 1H), 7.88 (dt, *J* = 8.0, 1.8 Hz, 1H), 7.46–7.33 (m, 7H), 7.22–7.14 (m, 6H), 4.91 (br s, 1H), 4.85 (br s, 1H), 4.06 (s, 2H), 3.70 (s, 2H), 3.09 (br q, J = 6.4 Hz, 2H), 3.00 (br q, J =6.3 Hz, 2H), 2.58 (t, J = 7.10 Hz, 2H), 2.31 (t, J = 7.1 Hz, 2H), 1.68–1.28 (m, 8H), 1.43 (s, 9H), 1.42 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 47:53) 205.37, 204.41, 155.82, 155.78, 149.92, 149.28, 149.19, 148.66, 147.93, 147.80, 135.95, 135.62, 135.07, 133.96, 133.12, 132.24, 129.35, 129.19, 128.91, 128.69, 128.45, 128.15, 123.24, 123.00, 117.78, 117.71, 117.11, 116.95, 78.73, 51.36, 48.21, 42.36, 42.31, 39.69, 39.54, 29.00, 28.94, 28.13, 20.35, 20.21

IR (UATR) ν_{max} 3357, 2930, 2155, 1702, 1627, 1522, 1366, 1245, 1168, 1045, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{25}H_{29}N_3Na_1O_3$ (M+Na)$^+$ 442,2101, found 442.2096.

tert-Butyl 7-cyano-6-(thiophen-2-yl)-4-oxo-7-phenylhept-6-enylcarbamate (138fal)



92% yield, yellow oil

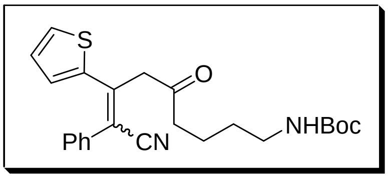
^{1}H NMR (300 MHz, $CDCl_3$) δ (isomeric ratio 44:56) 7.71 (d, J = 1.4 Hz, 1H), 7.46–7.16 (m, 13H), 7.07 (dd, J = 5.0, 3.0 Hz, 1H), 6.56 (d, J = 5.0 Hz, 1H), 4.86 (br s, 1H), 4.77 (br s, 1H), 4.03 (s, 2H), 3.65 (s, 2H), 3.08 (br q, J = 6.3 Hz, 2H), 2.98 (br q, J = 6.3 Hz, 2H), 2.60 (t, J = 7.1 Hz, 2H), 2.31 (t, J = 7.1 Hz, 2H), 1.76 (pent, J = 6.9 Hz, 2H), 1.62 (pent, J = 6.9 Hz, 2H) 1.43 (s, 9H), 1.41 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (isomeric ratio 44:56) 205.55, 204.71, 155.88, 155.81, 145.98, 145.25, 138.75, 137.90, 134.03, 133.44, 128.98, 128.92, 128.84, 128.59, 128.47, 128.36, 127.46, 126.83, 126.73, 126.31, 126.16, 125.52, 119.00, 118.65, 113.92, 112.59, 78.81, 51.55, 48.05, 39.69, 39.48, 39.25, 28.12, 23.72, 23.63

IR(UATR) ν_{max} 3378, 2976, 2211, 1708, 1687, 1595, 1515, 1366, 1249, 1167, 1046, 765, 698 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{23}H_{26}N_2Na_1O_3S_1$ (M+Na)$^+$ 433.1556, found 433.1572.

tert-Butyl 8-cyano-5-oxo-8-phenyl-7-(thiophen-2-yl)oct-7-enylcarbamate (138fall)



97% yield, yellow oil

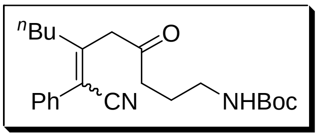
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 46:54) 7.69 (dd, J = 2.9, 1.4 Hz, 1H), 7.43–7.33 (m, 7H), 7.31–7.22 (m, 5H), 7.13 (dd, J = 2.9, 1.4 Hz, 1H), 7.10 (dd, J = 5.0, 2.9 Hz, 1H), 6.58 (dd, J = 5.0, 1.4 Hz, 1H), 4.65 (br s, 1H), 4.60 (br s, 1H), 4.02 (s, 2H), 3.64 (s, 2H), 3.08 (br q, J = 6.3 Hz, 2H), 3.01 (br q, J = 6.3 Hz, 2H), 2.59 (t, J = 7.1 Hz, 2H), 2.32 (t, J = 7.1 Hz, 2H), 1.69–1.57 (m, 2H), 1.55–1.30 (m, 6H), 1.43 (s, 18H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 46:54) 205.82, 204.97, 155.80, 146.06, 145.30, 138.83, 137.96, 134.11, 133.49, 129.05, 129.00, 128.88, 128.65, 128.52, 128.44, 127.50, 126.76, 126.68, 126.25, 126.22, 125.63, 119.01, 118.68, 114.17, 112.85, 78.83, 51.70, 48.15, 42.21, 41.99, 39.81, 39.66, 29.02, 28.21, 20.40, 20.28

IR (UATR) ν_{max} 3393, 2928, 2206, 1708, 1513, 1366, 1244, 1167, 1045, 768, 700 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{24}H_{28}N_2Na_1O_3S_1$ (M+Na)$^{+}$ 447.1713, found 447.1709.

***tert*-Butyl 7-cyano-6-butyl-4-oxo-7-phenylhept-6-enylcarbamate (138gal)**



94% yield, yellow oil

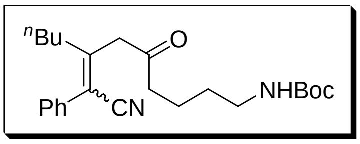
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 23:77) 7.43–7.19 (m, 10H), 4.94 (br s, 1H), 4.85 (br s, 1H), 3.71 (s, 2H), 3.33 (s, 2H), 3.15 (br q, J = 6.4 Hz, 2H), 3.05 (br q, J = 6.3 Hz, 2H), 2.64 (t, J = 7.1 Hz, 2H), 2.58 (dd, J = 8.0, 7.5 Hz, 2H), 2.35 (t, J = 7.1 Hz, 2H), 2.24 (dd, J = 8.0, 7.5 Hz, 2H), 1.82 (pent, J = 6.9 Hz, 2H), 1.68 (pent, J = 6.9 Hz, 2H), 1.59–1.13 (m, 4H), 1.44 (s, 9H), 1.42 (s, 9H), 0.92 (t, J = 7.1 Hz, 3H), 0.79 (t, J = 7.2 Hz, 3H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 23:77) 205.57, 204.73, 155.86, 155.16, 133.50, 133.08, 128.64, 128.55, 128.48, 128.38, 128.31, 118.21, 117.76, 114.23, 113.82, 78.76, 48.39, 45.49, 39.76, 39.73, 39.25, 36.32, 32.55, 29.62, 29.33, 28.09, 28.08, 23.78, 23.72, 22.22, 22.16, 13.56, 13.33

IR (UATR) ν_{max} 3390, 2966, 2202, 1680, 1615, 1509, 1413, 1364, 1252, 1165, 1096, 708 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{23}H_{33}N_2O_3$ (M+H)$^{+}$ 385.2486, found 385.2499.

tert-Butyl 8-cyano-5-oxo-8-phenyl-7-butyloct-7-enylcarbamate (138gall)



83% yield, yellow oil

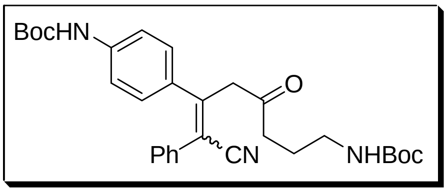
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 27:73) 7.42–7.29 (m, 5H), 7.25–7.20 (m, 5H), 4.62 (br s, 1H), 4.56 (br s, 1H), 3.69 (s, 2H), 3.31 (s, 2H), 3.14 (br q, J = 6.4 Hz, 2H), 3.07 (br q, J = 6.4 Hz, 2H), 2.63 (t, J = 7.0 Hz, 2H), 2.58 (dd, J = 8.0, 7.0 Hz, 2H), 2.33 (t, J = 7.1 Hz, 2H), 2.24 (dd, J = 8.0, 7.0 Hz, 2H), 1.73–1.13 (m, 8H), 1.44 (s, 18H), 0.92 (t, J = 7.1 Hz, 3H), 0.79 (t, J = 7.2 Hz, 3H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 27:73) 205.84, 204.98, 155.81, 155.78, 155.08, 154.96, 133.56, 133.13, 128.66, 128.59, 128.52, 128.41, 128.36, 118.22, 117.78, 114.31, 113.90, 78.74, 48.47, 45.55, 42.26, 39.79, 39.65, 36.38, 32.56, 29.64, 29.38, 29.07, 28.14, 22.26, 22.20, 20.43, 20.34, 13.58, 13.36

IR (UATR) ν_{max} 3374, 2933, 2131, 1709, 1511, 1366, 1249, 1169, 766, 701 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{24}H_{34}N_2Na_1O_3$ (M+Na)$^+$ 421.2462, found 421.2465.

tert-Butyl 7-cyano-6-{4-(N-tert-butoxycarbonyl)aminophenyl}-4-oxo-7-phenylhept-6-enylcarbamate (138hal)



91% yield, white foam

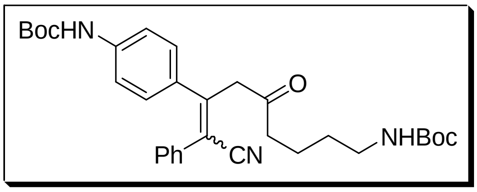
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 54:46) 7.45 (s, 4H), 7.43–7.35 (m, 5H), 7.22 (d, J = 8.7 Hz, 2H), 7.22–7.14 (m, 5H), 6.98 (d, J = 8.7 Hz, 2H), 6.77 (br s, 1H), 6.64 (br s, 1H), 4.64 (br s, 1H), 4.53 (br s, 1H), 4.02 (s, 2H), , 3.66 (s, 2H), 3.08 (br q, J = 6.5 Hz, 2H), 2.97 (br q, J = 6.5 Hz, 2H), 2.57 (t, J = 7.1 Hz, 2H), 2.28 (t, J = 7.1 Hz, 2H), 1.75 (pent, J = 7.0 Hz, 2H), 1.60 (pent, J = 7.0 Hz, 2H), 1.52 (s, 9H), 1.49 (s, 9H), 1.43 (s, 9H), 1.41 (s, 9H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 54:46) 205.62, 204.73, 155.95, 155.89, 152.48, 152.37, 152.16, 150.72, 139.81, 139.18, 134.13, 133.26, 132.83, 131.63, 129.36, 129.27, 128.98, 128.90, 128.55, 128.46, 128.34, 128.24, 118.83, 118.80, 118.16, 117.89, 114.42, 114.16, 80.58, 79.01, 51.91, 48.27, 40.18, 39.89, 39.46, 28.24, 28.23, 28.14, 28.10, 23.79, 23.69

IR (UATR) ν_{max} 3344, 2977, 2209, 1705, 1589, 1520, 1234, 1155, 1052, 840, 765, 699 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{30}H_{37}N_3Na_1O_5$ (M+Na)$^+$ 542.2625, found 542.2641.

tert-Butyl 7-{4-(N-tert-butoxycarbonyl)aminophenyl}-8-cyano-5-oxo-8-phenyl-oct-7-enylcarbamate (138haII)



92% yield, white foam

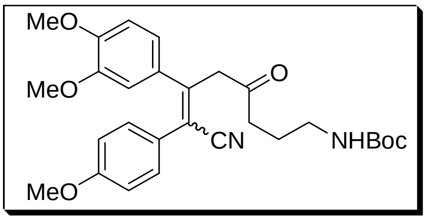
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 57:43) 7.43 (s, 4H), 7.43–7.35 (m, 5H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.22–7.14 (m, 5H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.78 (br s, 1H), 6.65 (br s, 1H), 4.60 (br s, 1H), 4.55 (br s, 1H), 4.01 (s, 2H), , 3.65 (s, 2H), 3.07 (br q, *J* = 6.4 Hz, 2H), 3.00 (br q, *J* = 6.4 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.67–1.24 (m, 8H), 1.52 (s, 9H), 1.49 (s, 9H), 1.43 (s, 18H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 57:43) 205.88, 204.92, 155.89, 155.86, 152.51, 152.39, 152.23, 150.74, 139.79, 139.17, 134.13, 133.25, 132.85, 131.61, 129.30, 129.25, 128.95, 128.85, 128.50, 128.43, 128.30, 128.21, 118.80, 118.78, 118.18, 117.90, 114.40, 114.11, 80.52, 78.85, 51.92, 48.27, 42.53, 42.26, 39.88, 39.74, 29.07, 29.01, 28.23, 28.12, 28.08, 20.41, 20.28

IR (UATR) ν_{max} 3343, 2977, 2212, 1708, 1590, 1520, 1234, 1155, 1052, 840, 765, 699 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{31}H_{39}N_3Na_1O_5$ (M+Na)$^+$ 556.2782, found 556.2807.

tert-Butyl 7-cyano-6-(3,4-dimethoxyphenyl)-7-(4-methoxyphenyl)-4-oxohept-6-enylcarbamate (138bkI)



91% yield, yellow oil

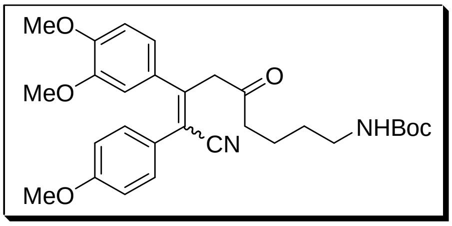
^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 50:50) 7.32 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.06 (dd, *J* = 8.4, 2.1 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.77–6.68 (m, 4H), 6.53 (d, *J* = 1.8 Hz, 1H), 4.64 (br s, 1H), 4.54 (br s, 1H), 4.02 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.844 (s, 3H), 3.837 (s, 3H), 3.76 (s, 3H), 3.69 (s, 2H), 3.57 (s, 3H), 3.10 (br q, *J* = 6.5 Hz, 2H), 3.00 (br q, *J* = 6.5 Hz, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.32 (t, *J* = 7.1 Hz, 2H), 1.77 (pent, *J* = 7.0 Hz, 2H), 1.63 (pent, *J* = 7.0 Hz, 2H), 1.43 (s, 9H), 1.41 (s, 9H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 50:50) 205.91, 205.02, 160.04, 159.42, 155.98, 155.91, 151.29, 149.99, 149.39, 149.31, 148.77, 148.49, 131.33, 130.66, 130.20, 129.93, 126.54, 125.81, 121.23, 120.59, 119.18, 119.07, 114.33, 113.93, 113.83, 112.15, 111.26, 110.99, 110.85, 79.12, 56.04, 55.82, 55.70, 55.59, 55.28, 55.18, 51.97, 48.50, 40.25, 39.90, 39.57, 28.31, 28.28, 23.96, 23.90

IR (UATR) ν_{max} 3393, 2936, 2155, 1709, 1606, 1513, 1252, 1174, 1026, 836, 767 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{28}H_{34}N_2Na_1O_6$ (M+Na)$^+$ 517.2309, found 517.2305

***tert*-Butyl 8-cyano-7-(3,4-dimethoxyphenyl)-8-(4-methoxyphenyl)-5-oxooct-7-enylcarbamate (138bkII)**



92% yield, yellow oil

^{1}H NMR (300 MHz, CDCl$_3$) δ (isomeric ratio 46:54) 7.29 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 3H), 7.02 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 3H), 6.86 (s, 1H), 6.75–6.64 (m, 3H), 6.50 (d, *J* = 1.8 Hz, 1H), 4.66 (br s, 1H), 4.60 (br s, 1H), 4.02 (s, 2H), 3.98 (s, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 3.65(s, 2H), 3.53 (s, 3H), 3.05 (br q, *J* = 6.4 Hz, 2H), 2.98 (br q, *J* = 6.4 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.64–1.53 (m, 2H), 1.52–1.22 (m, 6H), 1.40 (s, 18H)

^{13}C NMR (75 MHz, CDCl$_3$) δ (isomeric ratio 46:54) 206.09, 205.13, 159.95, 159.32, 155.83, 151.35, 149.88, 149.30, 149.27, 148.66, 148.40, 131.33, 130.55, 130.13, 129.81, 126.46, 125.74, 121.10, 120.48, 119.09, 118.95, 114.22, 113.85, 113.80, 113.74, 112.12, 111.24, 110.93, 110.80, 78.92, 55.94, 55.72, 55.61, 55.49, 55.18, 55.07, 51.89, 48.40, 42.54, 42.22, 39.89, 39.75, 29.12, 28.22, 20.44, 20.30

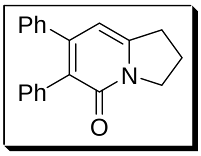
IR (UATR) ν_{max} 3390, 2936, 2208, 1709, 1606, 1513, 1251, 1174, 1025, 836, 767 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{29}H_{36}N_2Na_1O_6$ (M+Na)$^+$ 531.2466, found 531.2474

3. General procedure for the synthesis of bicyclic 2-pyridones 140

In a pressure tube, a solution of compound **138** (0.2 mmol) in ethylene glycol (3 mL) was added trimethylsilyl chloride (5 equiv.) at room temperature and heated at 55°C for 2 h. Then, the reaction was cooled down to room temperature, 50% aq. KOH solution (3 mL) was added dropwise and the mixture was heated at 190°C for 2 h. The reaction was cooled down under ice-bath, diluted with water and extracted with EtOAc. The combined organic part was washed successively with water, dried over Na_2SO_4, and the solvent was concentrate under reduced pressure. The obtained solid was purified by the combined techniques of crystallization from EtOAc and column chromatography on silica gel using hexanes and EtOAc as eluent to give the desired pyridones **140**.

6,7-Diphenyl-2,3-dihydroindolizin-5(*1H*)-one (140aal)



81% yield, white solid, m.p. 213.3–213.7°C

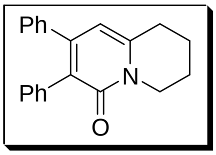
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.05 (m, 10H), 6.24 (s, 1H), 4.23 (t, *J* = 7.2 Hz, 2H), 3.15 (t, *J* = 7.8 Hz, 2H), 2.25 (tt, *J* = 7.8, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.32, 150.62, 148.32, 139.85, 135.65, 131.18, 128.86, 127.81, 127.43, 127.35, 126.60, 126.48, 103.71, 49.07, 31.76, 21.34

IR (UATR) ν_{max} 2924, 1643, 1582, 1528, 1440, 1234, 1071, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{20}H_{18}N_1O_1$ (M+H)$^+$ 288.1383, found 288.1376.

2,3-Diphenyl-6,7,8,9-tetrahydroquinolizin-4-one (140aall)



80% yield, white solid, m.p. 188.6–189.3°C

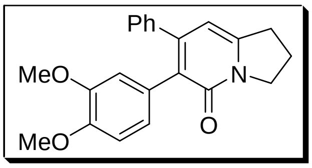
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.22–7.05 (m, 10H), 6.13 (s, 1H), 4.07 (t, *J* = 6.3 Hz, 2H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.01 (tt, *J* = 6.6, 6.3 Hz, 2H), 1.85 (tt, *J* = 6.6, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 162.77, 149.01, 145.57, 139.56, 136.14, 131.19, 128.90, 127.87, 127.51, 127.42, 126.50, 125.89, 107.46, 42.26, 28.91, 22.43, 18.81

IR (UATR) ν_{max} 2954, 1634, 1584, 1536, 1444, 1250, 1019, 767, 698 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{21}H_{20}N_1O_1$ $(M+H)^+$ 302.1539, found 302.1530.

6-(3,4-Dimethoxyphenyl)-7-phenyl-2,3-dihydroindolizin-5(*1H*)-one (140abI)



65% yield, white solid, m.p. 145.1–146.0°C

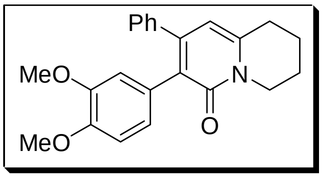
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20–7.07 (m, 5H), 6.78 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 1.9 Hz, 1H), 6.24 (s, 1H), 4.23 (t, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.60 (s, 3H), 3.14 (t, *J* = 7.6 Hz, 2H), 2.24 (tt, *J* = 7.6, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 161.42, 150.44, 148.00, 147.85, 147.57, 140.16, 128.73, 127.97, 127.92, 127.28, 126.13, 123.89, 114.75, 110.39, 103.77, 55.60, 55.49, 49.10, 31.73, 21.38

IR (UATR) ν_{max} 2935, 1638, 1579, 1526, 1464, 1249, 1026, 727 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{22}H_{22}N_1O_3$ $(M+H)^+$ 348.1594, found 348.1607.

3-(3,4-Dimethoxyphenyl)-2-phenyl-6,7,8,9-tetrahydroquinolizin-4-one (140abII)



68% yield, white solid, m.p. 158.2–158.9°C

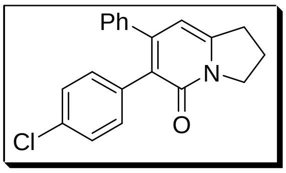
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.22–7.06 (m, 5H), 6.79 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 1.9 Hz, 1H), 6.12 (s, 1H), 4.08 (t, *J* = 6.3 Hz, 2H), 3.82 (s, 3H), 3.60 (s, 3H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.02 (tt, *J* = 6.6, 6.3 Hz, 2H), 1.85 (tt, *J* = 6.6, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 162.84, 148.85, 147.95, 147.62, 145.30, 139.91, 128.78, 128.54, 127.98, 127.35, 125.44, 123.90, 114.81, 110.50, 107.44, 55.70, 55.57, 42.27, 28.89, 22.45, 18.83

IR (UATR) ν_{max} 2948, 1635, 1575, 1535, 1443, 1260, 1139, 1027, 764, 701 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{23}H_{23}N_1Na_1O_3$ $(M+Na)^+$ 384.1570, found 384.1567.

6-(4-Chorophenyl)-7-phenyl-2,3-dihydroindolizin-5(*1H*)-one (140acI)



78% yield, white solid, m.p. 231.0–231.9°C

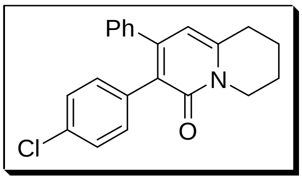
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.05 (m, 9H), 6.24 (s, 1H), 4.22 (t, *J* = 7.2 Hz, 2H), 3.15 (t, *J* = 7.6 Hz, 2H), 2.25 (tt, *J* = 7.6, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.14, 150.90, 148.74, 139.60, 134.22, 132.64, 132.38, 128.86, 128.09, 127.75, 127.64, 125.32, 103.77, 49.15, 31.86, 21.39

IR (UATR) ν_{max} 3053, 2927, 1640, 1582, 1525, 1088, 845, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{20}H_{17}Cl_1N_1O_1$ (M+H)$^+$ 322.0993, found 322.0989.

3-(4-Chorophenyl)-2-phenyl-6,7,8,9-tetrahydroquinolizin-4-one (140acII)



76% yield, white solid, m.p. 218.1–219.2°C

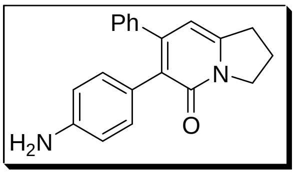
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.06 (m, 9H), 6.12 (s, 1H), 4.06 (t, *J* = 6.3 Hz, 2H), 2.85 (t, *J* = 6.5 Hz, 2H), 2.02 (tt, *J* = 6.5, 6.3 Hz, 2H), 1.86 (tt, *J* = 6.5, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.58, 149.29, 146.01, 139.28, 134.66, 132.63, 132.36, 128.87, 128.11, 127.78, 127.68, 124.54, 107.54, 42.35, 28.96, 22.42, 18.78

IR (UATR) ν_{max} 2949, 1634, 1574, 1534, 1253, 1090, 835, 767, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{21}H_{18}Cl_1N_1Na_1O_1$ (M+Na)$^+$ 358.0969, found 358.0960.

6-(4-Aminophenyl)-7-phenyl-2,3-dihydroindolizin-5(*1H*)-one (140adI)/(140ahI)



59% yield, brown solid, m.p. 275.0–276.2°C;

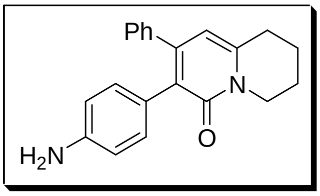
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.08 (m, 5H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.20 (s, 1H), 4.21 (t, *J* = 7.3 Hz, 2H), 3.53 (br s, 2H), 3.12 (t, *J* = 7.7 Hz, 2H), 2.23 (tt, *J* = 7.7, 7.3 Hz, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 161.74, 149.86, 147.49, 144.89, 140.42, 132.19, 128.96, 127.89, 127.17, 126.68, 125.72, 114.48, 103.73, 49.06, 31.76, 21.46

IR (UATR) ν_{max} 3402, 3339, 3240, 2958, 1642, 1588, 1533, 1237, 770, 698 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{20}H_{18}N_2Na_1O_1$ (M+Na)$^+$ 325.1311, found 325.1317.

3-(4-Aminophenyl)-2-phenyl-6,7,8,9-tetrahydroquinolizin-4-one (140adII)/(140ahII)



59% yield, brown solid, m.p. 260.0–261.7°C;

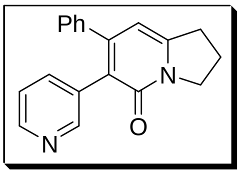
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.23–7.08 (m, 5H), 6.93 (d, J = 8.2 Hz, 1H), 6.51 (d, J = 8.2 Hz, 1H), 6.09 (s, 1H), 4.06 (t, J = 6.3 Hz, 2H), 3.49 (br s, 2H), 2.83 (t, J = 6.5 Hz, 2H), 2.00 (tt, J = 6.5, 6.3 Hz, 2H), 1.84 (tt, J = 6.5, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 163.15, 148.37, 144.82, 144.77, 140.05, 132.16, 128.96, 127.91, 127.22, 126.24, 125.90, 114.52, 107.55, 42.27, 28.89, 22.50, 18.88

IR (UATR) ν_{max} 3342, 3225, 2926, 1634, 1571, 1542, 1252, 1179, 835, 766, 699 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{21}H_{20}N_2Na_1O_1$ (M+Na)$^+$ 339.1468, found 339.1478.

7-Phenyl-6-(pyridin-3-yl)-2,3-dihydroindolizin-5(*1H*)-one (140aeI)



65% yield, yellow solid, m.p. 199.4–200.1°C

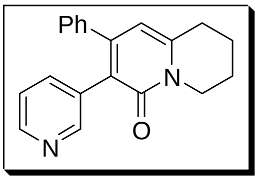
^{1}H NMR (300 MHz, CDCl$_3$) δ 8.36 (dd, J = 4.8, 1.6 Hz, 1H), 8.26 (dd, J = 2.0, 0.6 Hz, 1H), 7.59 (dt, J = 7.9, 1.8 Hz, 1H), 7.25–7.18 (m, 3H), 7.15 (dd, J = 7.9, 4.9 Hz, 1H), 7.09–7.03 (m, 2H), 6.28 (s, 1H), 4.24 (t, J = 7.2 Hz, 2H), 3.18 (t, J = 8.0 Hz, 2H), 2.28 (tt, J = 7.6, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 161.16, 151.87, 151.76, 149.38, 147.46, 139.21, 138.71, 131.82, 128.95, 128.27, 127.95, 123.01, 122.47, 103.92, 49.23, 31.95, 21.420

IR (UATR) ν_{max} 2929, 1637, 1592, 1373, 1239, 1023, 768 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{19}H_{17}N_2O_1$ (M+H)$^+$ 289.1335, found 289.1334.

2-phenyl-3-(pyridin-3-yl)-6,7,8,9-tetrahydroquinolizin-4-one (140aeII)



62% yield, yellow solid, m.p. 179.1–180.0°C

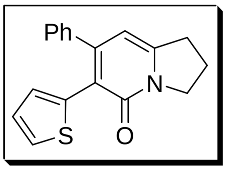
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (dd, J = 4.9, 1.6 Hz, 1H), 8.27 (dd, J = 2.0, 0.6 Hz, 1H), 7.60 (dt, J = 7.9, 2.0 Hz, 1H), 7.24–7.18 (m, 3H), 7.13 (dd, J = 7.9, 4.9 Hz, 1H), 7.11–7.03 (m, 2H), 6.16 (s, 1H), 4.08 (t, J = 6.3 Hz, 2H), 2.88 (t, J = 6.6 Hz, 2H), 2.04 (tt, J = 6.6, 6.3 Hz, 2H), 1.87 (tt, J = 6.6, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.56, 151.83, 150.11, 147.39, 146.64, 138.86, 138.70, 132.21, 128.92(2C), 128.24(2C), 127.94, 122.46, 122.12, 107.67, 42.40, 28.98, 22.36, 18.71

IR (UATR) ν_{max} 2929, 1633, 1576, 1538, 1256, 1123, 798, 701 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{20}H_{19}N_2O_1$ $(M+H)^+$ 303.1492, found 303.1506.

7-Phenyl-6-(thiophen-2-yl)-2,3-dihydroindolizin-5(*1H*)-one (140afI)



78% yield, white solid, m.p. 172.2–172.9°C

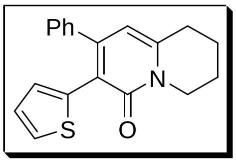
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.18 (m, 6H), 6.78 (dd, J = 5.1, 3.7 Hz, 1H), 6.65 (dd, J = 3.7, 1.1 Hz, 1H), 6.20 (s, 1H), 4.26 (t, J = 7.2 Hz, 2H), 3.15 (t, J = 7.6 Hz, 2H), 2.26 (tt, J = 7.6, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.62, 150.71, 147.89, 140.57, 136.38, 129.03, 128.36, 128.35, 127.81, 125.99, 125.54, 119.62, 104.31, 49.31, 31.80, 21.38

IR (UATR) ν_{max} 2925, 1637, 1588, 1228, 768, 698 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{18}H_{16}N_1O_1S_1$ $(M+H)^+$ 294.0947, found 294.0950

2-Phenyl-3-(thiophen-2-yl)-6,7,8,9-tetrahydroquinolizin-4-one (140afII)



79% yield, white solid, m.p. 165.4–166.1°C

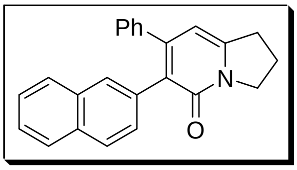
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.18 (m, 6H), 6.76 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.61 (dd, *J* = 3.7, 1.1 Hz, 1H), 6.07 (s, 1H), 4.09 (t, *J* = 6.3 Hz, 2H), 2.83 (t, *J* = 6.6 Hz, 2H), 2.00 (tt, *J* = 6.6, 6.3 Hz, 2H), 1.83 (tt, *J* = 6.6, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.96, 149.02, 145.15, 140.22, 136.71, 128.85, 128.30, 128.28, 127.76, 125.85, 125.41, 118.68, 108.12, 42.53, 28.77, 22.36, 18.69

IR (UATR) ν_{max} 2947, 1630, 1580, 1574, 1442, 1244, 844, 763, 699 cm^{-1}

HRMS (ESI^+) calcd for $C_{19}H_{18}N_1O_1S_1$ $(M+H)^+$ 308.1104, found 308.1115.

6-(Naphthalen-2-yl)-7-phenyl-2,3-dihydroindolizin-5(*1H*)-one (140agI)



85% yield, white solid, m.p. 175.4–176.1°C

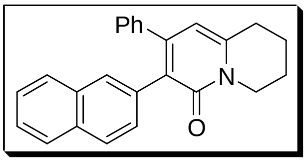
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.62 (m, 3H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.41–7.31 (m, 2H), 7.19 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.15–7.06 (m, 5H), 6.28 (s, 1H), 4.25 (t, *J* = 7.2 Hz, 2H), 3.17 (t, *J* = 7.6 Hz, 2H), 2.26 (tt, *J* = 7.6, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.49, 150.91, 148.49, 139.85, 133.25, 133.12, 132.23, 130.49, 129.34, 128.93, 128.02, 127.98, 127.47, 127.37, 126.77, 126.39, 125.49, 125.29, 103.88, 49.15, 31.85, 21.41

IR (UATR) ν_{max} 3053, 1637, 1577, 1525, 1437, 1221, 830, 744 cm^{-1}

HRMS (ESI^+) calcd for $C_{24}H_{20}N_1O_1$ $(M+H)^+$ 338.1539, found 338.1547.

3-(Naphthalen-2-yl)-2-phenyl-6,7,8,9-tetrahydroquinolizin-4-one (140agII)



81% yield, white solid, m.p. 157.2–157.9°C

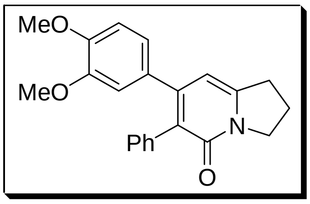
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.62 (m, 3H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.41–7.31 (m, 2H), 7.24 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.15–7.08 (m, 5H), 6.16 (s, 1H), 4.09 (t, *J* = 6.3 Hz, 2H), 2.86 (t, *J* = 6.6 Hz, 2H), 2.02 (tt, *J* = 6.6, 6.3 Hz, 2H), 1.85 (tt, *J* = 6.6, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.89, 149.30, 145.74, 139.52, 133.72, 133.17, 132.25, 130.38, 129.38, 128.91, 128.03, 127.98, 127.47, 127.37, 126.78, 125.60, 125.44, 125.25, 107.60, 42.27, 28.93, 22.44, 18.81

IR (UATR) ν_{max} 3054, 2948, 1635, 1574, 1538, 1442, 1264, 819, 734, 699 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{25}H_{22}N_1O_1$ (M+H)$^+$ 352.1696, found 352.1683.

7-(3,4-Dimethoxyphenyl)-6-phenyl-2,3-dihydroindolizin-5(*1H*)-one (140baI)



78% yield, white solid, m.p. 127.0–127.9°C

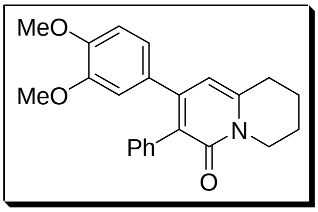
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.09 (m, 5H), 6.81 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 6.28 (s, 1H), 4.22 (t, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 3.47 (s, 3H), 3.16 (t, *J* = 7.6 Hz, 2H), 2.25 (tt, *J* = 7.6, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.35, 150.00, 148.35, 148.28, 147.88, 136.19, 132.07, 131.06, 127.68, 126.44, 126.13, 121.17, 112.96, 110.43, 103.47, 55.63, 55.40, 48.99, 31.75, 21.36

IR (UATR) ν_{max} 2935, 1639, 1590, 1514, 1257, 1137, 1024, 807, 746, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{22}H_{21}N_1Na_1O_3$ (M+Na)$^+$ 370.1414, found 370.1404.

2-(3,4-Dimethoxyphenyl)-3-phenyl-6,7,8,9-tetrahydroquinolizin-4-one (140baII)



75% yield, white solid, m.p. 122.0–122.7°C

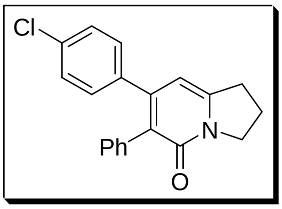
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.10 (m, 5H), 6.81 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.44 (d, *J* = 1.9 Hz, 1H), 6.16 (s, 1H), 4.05 (t, *J* = 6.3 Hz, 2H), 3.82 (s, 3H), 3.46 (s, 3H), 2.84 (t, *J* = 6.6 Hz, 2H), 1.99 (tt, *J* = 6.6, 6.3 Hz, 2H), 1.83 (tt, *J* = 6.6, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.64, 148.32, 148.27, 147.83, 145.45, 136.57, 131.65, 130.95, 127.60, 126.30, 125.24, 121.07, 112.89, 110.40, 107.10, 55.56, 55.33, 42.03, 28.76, 22.27, 18.67

IR (UATR) ν_{max} 2924, 1632, 1577, 1514, 1457, 1261, 1135, 1026, 791, 702 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{23}H_{24}N_1O_3$ (M+H)$^+$ 362.1751, found 362.1745.

7-(4-Chorophenyl)-6-phenyl-2,3-dihydroindolizin-5(*1H*)-one (140caI)



73% yield, white solid, m.p. 255.0–256.0°C

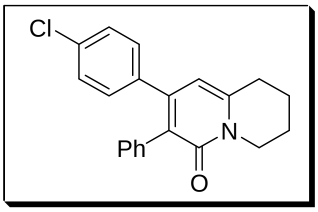
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.09 (m, 7H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.19 (s, 1H), 4.20 (t, *J* = 7.2 Hz, 2H), 3.13 (t, *J* = 7.6 Hz, 2H), 2.23 (tt, *J* = 7.6, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.20, 149.22, 148.61, 138.32, 135.37, 133.41, 131.12, 130.25, 128.11, 127.66, 127.72, 103.25, 49.11, 31.81, 21.36

IR (UATR) ν_{max} 2927, 1640, 1577, 1492, 1239, 1090, 830, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{20}H_{17}Cl_1N_1O_1$ (M+H)$^+$ 322.0993, found 322.1001.

2-(4-Chorophenyl)-3-phenyl-6,7,8,9-tetrahydroquinolizin-4-one (140caII)



75% yield, white solid, m.p. 212.6–213.5°C

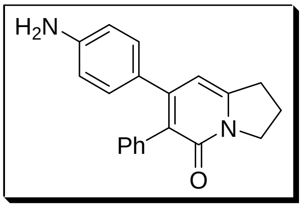
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.09 (m, 7H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.07 (s, 1H), 4.06 (t, *J* = 6.3 Hz, 2H), 2.84 (t, *J* = 6.6 Hz, 2H), 2.01 (tt, *J* = 6.6, 6.3 Hz, 2H), 1.85 (tt, *J* = 6.6, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.63, 147.64, 145.87, 137.99, 135.82, 133.46, 131.09, 130.25, 128.13, 127.68, 126.69, 125.96, 106.98, 42.27, 28.90, 22.37, 18.75

IR (UATR) ν_{max} 2925, 1631, 1568, 1537, 1491, 1248, 1085, 827, 697 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{21}H_{19}Cl_1N_1O_1$ (M+H)$^+$ 336.1150, found 336.1146.

7-(4-Aminophenyl)-6-phenyl-2,3-dihydroindolizin-5(*1H*)-one (140daI)/(140haI)



65% yield, yellow solid, m.p. 233.4–234.4°C

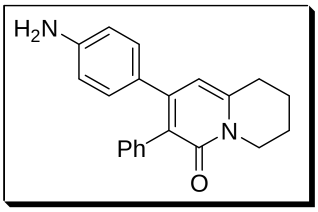
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.11 (m, 5H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.47 (d, *J* = 8.4 Hz, 2H), 6.24 (s, 1H), 4.20 (t, *J* = 7.2 Hz, 2H), 3.71 (br s, 2H), 3.13 (t, *J* = 7.6 Hz, 2H), 2.24 (tt, *J* = 7.6, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.53, 150.59, 148.00, 145.88, 136.33, 131.31, 130.25, 129.74, 127.58, 126.34, 125.85, 114.37, 103.82, 49.01, 31.79, 21.44

IR (UATR) ν_{max} 3411, 3340, 3233, 2927, 1634, 1609, 1570, 1521, 1307, 823, 700 cm^{-1}

HRMS (ESI^+) calcd for $C_{20}H_{18}N_2Na_1O_1$ $(M+Na)^+$ 325.1311, found 325.1322.

2-(4-Aminophenyl)-3-phenyl-6,7,8,9-tetrahydroquinolizin-4-one (140dall)/(140hall)



60% yield, yellow solid, m.p. 224.6–225.6°C

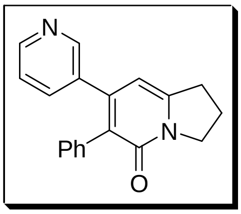
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.11 (m, 5H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.47 (d, *J* = 8.6 Hz, 2H), 6.12 (s, 1H), 4.05 (t, *J* = 6.3 Hz, 2H), 3.67 (br s, 2H), 2.84 (t, *J* = 6.6 Hz, 2H), 2.00 (tt, *J* = 6.6, 6.3 Hz, 2H), 1.84 (tt, *J* = 6.6, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.89, 148.89, 145.91, 145.20, 136.77, 131.25, 130.21, 129.33, 127.57, 126.27, 125.08, 114.35, 107.55, 42.14, 28.91, 22.48, 18.88

IR (UATR) ν_{max} 3337, 3225, 2926, 1636, 1607, 1571, 1524, 1374, 1283, 1182, 820, 735, 699 cm^{-1}

HRMS (ESI^+) calcd for $C_{21}H_{21}N_2O_1$ $(M+H)^+$ 317.1648, found 317.1651.

6-Phenyl-7-(pyridin-3-yl)- 2,3-dihydroindolizin-5(*1H*)-one (140eal)



68% yield, yellow solid, m.p. 220.5–221.5°C

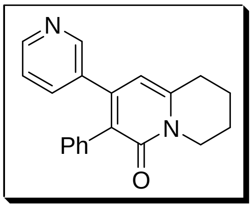
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.40 (d, *J* = 2.0 1H), 7.31 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.23–7.10 (m, 5H), 7.08 (dd, *J* = 7.9, 4.9 Hz, 1H), 6.22 (s, 1H), 4.24 (t, *J* = 7.3 Hz, 2H), 3.18 (t, *J* = 7.6 Hz, 2H), 2.27 (tt, *J* = 7.6, 7.3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.13, 149.41, 149.04, 148.55, 146.92, 136.30, 135.68, 134.92, 131.21, 127.81, 127.53, 127.02, 122.64, 102.96, 49.21, 31.90, 21.38

IR (UATR) ν_{max} 3030, 1638, 1578, 1527, 1439, 1371, 1231, 1023, 791, 705 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{19}H_{17}N_2O_1$ $(M+H)^+$ 289.1335, found 289.1346

3-Phenyl-2-(pyridin-3-yl)-6,7,8,9-tetrahydroquinolizin-4-one (140eaII)



65% yield, yellow solid, m.p. 178.4–179.4°C

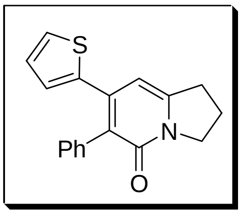
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.43 (br d, *J* = 1.7 Hz, 1H), 7.33 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.26–7.11 (m, 5H), 7.10 (ddd, *J* = 8.0, 4.9, 0.7 Hz, 1H), 6.13 (s, 1H), 4.10 (t, *J* = 6.3 Hz, 2H), 2.90 (t, *J* = 6.6 Hz, 2H), 2.05 (tt, *J* = 6.6, 6.3 Hz, 2H), 1.89 (tt, *J* = 6.6, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.52, 149.41, 148.56, 146.31, 145.35, 136.28, 135.35, 135.32, 131.14, 127.80, 126.94, 126.61, 122.62, 106.65, 42.34, 28.93, 22.33, 18.68

IR (UATR) ν_{max} 2949, 1634, 1584, 1535, 1258, 1015, 767, 702 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{20}H_{18}N_2Na_1O_1$ $(M+Na)^+$ 325.1311, found 325.1321.

6-Phenyl-7-(thiophen-2-yl)-2,3-dihydroindolizin-5(*1H*)-one (140faI)



80% yield, white solid, m.p. 222.0–223.0°C

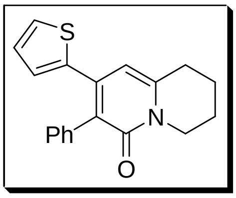
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.15 (m, 5H), 7.08 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.02 (dd, *J* = 3.0, 1.2 Hz, 1H), 6.65 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.31 (s, 1H), 4.20 (t, *J* = 7.2 Hz, 2H), 3.14 (t, *J* = 7.6 Hz, 2H), 2.24 (tt, *J* = 7.6, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.44, 148.36, 144.76, 140.13, 136.21, 130.82, 128.27, 127.85, 126.90, 126.39, 124.81, 124.73, 103.03, 49.03, 31.80, 21.42

IR (UATR) ν_{max} 2925, 1644, 1606, 1238, 1082, 781, 701 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{18}H_{16}N_1O_1S_1$ $(M+H)^+$ 294.0947, found 294.0953.

3-Phenyl-2-(thiophen-2-yl)-6,7,8,9-tetrahydroquinolizin-4-one (140faII)



78% yield, white solid, m.p. 189.8–190.5°C

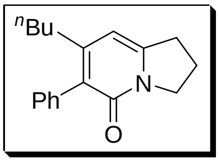
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H), 7.08 (dd, J = 5.0, 3.0 Hz, 1H), 7.03 (dd, J = 3.0, 1.3 Hz, 1H), 6.67 (dd, J = 5.0, 1.3 Hz, 1H), 6.20 (s, 1H), 4.05 (t, J = 6.3 Hz, 2H), 2.85 (t, J = 6.5 Hz, 2H), 2.01 (tt, J = 6.5, 6.3 Hz, 2H), 1.85 (tt, J = 6.5, 6.3 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.87, 145.58, 143.17, 139.76, 136.65, 130.75, 128.23, 127.90, 126.87, 125.57, 124.87, 124.74, 106.77, 42.19, 28.91, 22.42, 18.83

IR (UATR) ν_{max} 2947, 1634, 1584, 1543, 1254, 1021, 846, 783, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{19}H_{18}N_1O_1S_1$ (M+H)$^+$ 308.1104, found 308.1097.

7-(*n*-Butyl)-6-phenyl-2,3-dihydroindolizin-5(*1H*)-one (140gaI)



66% yield, white solid, m.p. 121.0–122.7°C

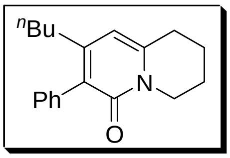
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.18 (m, 5H), 6.11 (s, 1H), 4.12 (t, J = 7.2 Hz, 2H), 3.06 (t, J = 7.7 Hz, 2H), 2.30 (dd, J = 8.0, 7.6 Hz, 2H), 2.16 (tt, J = 7.7, 7.2 Hz, 2H), 1.49–1.36 (m, 2H), 1.19 (sext, J = 7.3 Hz, 2H), 0.77 (t, J = 7.3 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.29, 152.15, 147.80, 136.18, 130.13, 127.88, 127.58, 126.75, 102.69, 48.71, 32.97, 32.03, 31.48, 22.26, 21.27, 13.58

IR (UATR) ν_{max} 2957, 1645, 1575, 1441, 1268, 1088, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{18}H_{22}N_1O_1$ (M+H)$^+$ 268.1696, found 268.1702.

2-(*n*-Butyl)-3-phenyl-6,7,8,9-tetrahydroquinolizin-4-one (140gaII)



65% yield, white solid, m.p. 104.3–105.0°C

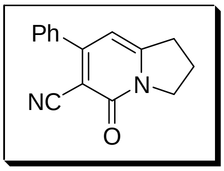
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.43–7.34 (m, 2H), 7.33–7.27 (m, 1H), 7.24–7.18 (m, 2H), 5.97 (s, 1H), 3.99 (t, *J* = 6.3 Hz, 2H), 2.79 (t, *J* = 6.6 Hz, 2H), 2.27 (dd, *J* = 8.0, 7.7 Hz, 2H), 1.96 (pent, *J* = 6.6 Hz, 2H), 1.82 (pent, *J* = 6.6 Hz, 2H), 1.48–1.36 (m, 2H), 1.20 (sext, *J* = 7.3 Hz, 2H), 0.78 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 162.63, 150.63, 144.94, 136.57, 130.10, 127.93, 127.09, 126.73, 106.63, 41.86, 32.65, 31.96, 28.67, 22.35, 22.31, 18.77, 13.63

IR (UATR) ν_{max} 2955, 2869, 1638, 1550, 1443, 1260, 1099, 700 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{19}H_{24}N_1O_1$ (M+H)$^{+}$ 282.1852, found 282.1857.

6-Cyano-7-phenyl-2,3-dihydroindolizin-5(*1H*)-one (140ail)



45% yield, white solid, m.p. 220.0–221.6°C

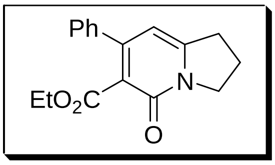
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67–7.42 (m, 5H), 6.29 (s, 1H), 4.20 (t, *J* = 7.3 Hz, 2H), 3.21 (t, *J* = 7.7 Hz, 2H), 2.27 (tt, *J* = 7.6, 7.4 Hz, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 160.13, 159.86, 155.65, 136.01, 130.19, 128.68, 127.88, 116.10, 102.95, 98.70, 49.48, 32.57, 20.76

IR (UATR) ν_{max} 3051, 2217, 1666, 1594, 1523, 1204, 764, 699 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{15}H_{13}N_2O_1$ (M+H)$^{+}$ 237.1022, found 237.1025.

Ethyl 5-oxo-7-phenyl-1,2,3,5-tetrahydroindolizine-6-carboxylate (140ajl)



53% yield, white solid, m.p. 150.3–151.0°C

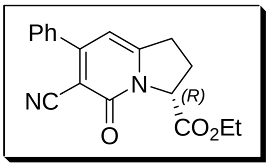
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 (s, 5H), 6.17 (s, 1H), 4.19 (t, *J* = 7.3 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 2.23 (tt, *J* = 7.6, 7.4 Hz, 2H), 1.02 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 166.59, 158.90, 152.08, 151.14, 138.27, 128.72, 128.37, 127.37, 120.86, 102.55, 61.01, 48.89, 31.95, 21.16, 13.68

IR (UATR) ν_{max} 2981, 1726, 1643, 1596, 1530, 1379, 1259, 1169, 1104, 767, 702 cm^{-1}

HRMS (ESI^{+}) calcd for $C_{17}H_{17}N_1Na_1O_3$ (M+Na)$^{+}$ 306.1101, found 306.1112.

(*R*)-Ethyl 6-cyano-5-oxo-7-phenyl-2,3-tetrahydroindolizine-3-carboxylate (140iil)



77% yield, brown solid, m.p. 155.0–157.0°C, $[\alpha]_D^{28}$ +247.2 (*c* 1.1, MeOH)

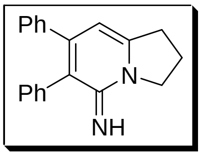
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.44 (m, 5H), 6.31 (s, 1H), 5.18 (dd, *J* = 9.6, 3.0 Hz, 1H), 4.36–4.21 (m, 2H), 3.36–3.15 (m, 2H), 2.68–2.53 (m, 1H), 2.41–2.30 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.20, 161.03, 159.32, 155.28, 135.90, 130.42, 128.77, 127.95, 115.66, 103.10, 99.40, 62.18, 62.06, 31.29, 25.76, 13.97

IR (UATR) ν_{max} 2983, 2219, 1742, 1651, 1599, 1518, 1448, 1377, 1196, 1019, 766, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{18}H_{16}N_2Na_1O_3$ (M+Na)$^+$ 331.1053, found 331.1062.

6,7-Diphenyl-2,3-dihydroindolizin-5(*1H*)-imine (144aal)



Yellow solid, m.p. 201.7–203.5°C;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.00 (m, 10H), 5.86 (s, 1H), 4.12 (t, *J* = 7.2 Hz, 2H), 3.04 (t, *J* = 7.7 Hz, 2H), 2.24 (tt, *J* = 7.7, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.59, 148.14, 145.67, 140.24, 136.41, 130.97, 128.65, 128.59, 127.68, 127.15, 127.01, 125.11, 100.02, 49.76, 31.33, 21.34

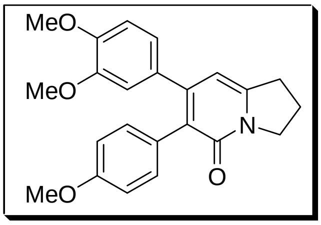
IR (UATR) ν_{max} 3327, 1636, 1557, 1516, 1239, 1014, 768, 700 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{20}H_{19}N_2$ (M+H)$^+$ 287.1543, found 287.1557.

4. Synthesis of (±)-seco-antofine 140bkl and (±)-julandine 140bkll

Employing the general procedure for the synthesis of bicyclic 2-pyridines afforded **140bkl/ll**.

7-(3,4-Dimethoxyhenyl)-6-(4-methoxyphenyl)-2,3-dihydroindolizin-5(*1H*)-one (140bkl)



78% yield, white solid, m.p. 146.0–146.4°C

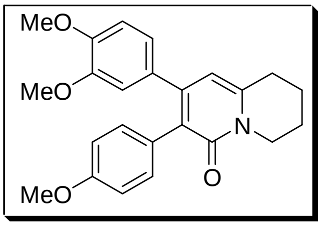
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.08 (d, *J* = 8.7 Hz, 2H), 6.82–6.72 (m, 4H), 6.49 (d, *J* = 1.6 Hz, 1H), 6.26 (s, 1H), 4.21 (t, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 3.53 (s, 3H), 3.13 (t, *J* = 7.6 Hz, 2H), 2.24 (tt, *J* = 7.6, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 161.49, 158.09, 149.64, 148.23, 147.92, 147.85, 132.35, 132.12, 128.36, 125.71, 121.18, 113.19, 112.84, 110.45, 103.38, 55.60, 55.42, 55.02, 48.91, 31.67, 21.34

IR (UATR) ν_{max} 2927, 1639, 1574, 1511, 1464, 1241, 1025, 807, 732 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{23}H_{24}N_1O_4$ (M+H)$^+$ 378.16998, found 378.1700.

2-(3,4-Dimethoxyhenyl)-3-(4-methoxyphenyl)-6,7,8,9-tetrahydroquinolizin-4-one (140bkII)



75% yield, white solid, m.p. 144.2–144.9°C

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.08 (d, *J* = 8.7, 1.8 Hz, 2H), 6.83–6.72 (m, 4H), 6.49 (d, *J* = 1.8 Hz, 1H), 6.14 (s, 1H), 4.06 (t, *J* = 6.3 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 3.53 (s, 3H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.01 (tt, *J* = 6.6, 6.3 Hz, 2H), 1.85 (tt, *J* = 6.6, 6.3 Hz, 2H)

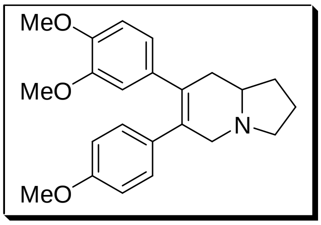
^{13}C NMR (75 MHz, CDCl$_3$) δ 163.01, 158.16, 148.34, 148.18, 148.00, 145.16, 132.16, 132.04, 128.85, 125.06, 121.21, 113.30, 112.88, 110.51, 107.25, 55.69, 55.50, 55.13, 42.17, 28.88, 22.42, 18.82

IR (UATR) ν_{max} 2949, 1634, 1574, 1509, 1464, 1242, 1139, 1024, 833, 761 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{24}H_{25}N_1Na_1O_4$ (M+Na)$^+$ 414.1676, found 414.1672.

General procedure for reduction of 2-pyridone: A solution of 2-pyridone **140bkI** or **140bKII** (2.0 mmol) in THF (14 mL) was added slowly to a suspension of $LiAlCl_4$ (13 equiv.) and $AlCl_3$ (10 equiv.) in THF (14 mL) at 0 °C. The reaction was allowed to further stir at room temperature for 20 h. The yellow suspension was quenched with EtOH (1 mL) at 0 °C to destroy the excess reagent and poured onto ice-crashed water. The mixture was basified to pH 12 and extracted with AcOEt. The combined organic layers were washed with water, dried over Na_2SO_4, and the solvent was concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using AcOEt and an increasing proportion of MeOH as eluent to afford compound **145bkI** or **145bkII**.

(±)-*seco*-Antofine (145bkI)



75% yield, yellow foam

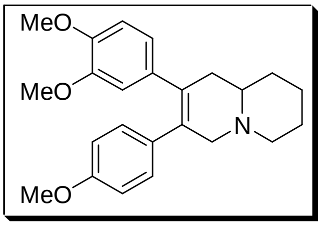
^{1}H NMR (300 MHz, CDCl$_3$) δ 6.98 (d, J = 8.8 Hz, 2H), 6.72–6.65 (m, 4H), 6.47 (d, J = 0.9 Hz, 1H), 3.88 (d, J = 16.0 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.54 (s, 3H), 3.32 (td, J = 8.6, 2.1 Hz, 1H), 3.11 (dd, J = 16.0, 3.8 Hz, 1H), 2.73 (dd, J = 12.9, 2.1 Hz, 1H), 2.53–2.37 (m, 2H), 2.35–2.24 (m, 1H), 2.18–2.04 (m, 1H), 2.00–1.80 (m, 2H), 1.66–1.51 (m 1H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 157.95, 147.82, 147.13, 134.78, 133.25, 132.51, 132.24, 130.13, 120.60, 113.33, 112.99, 110.38, 60.34, 57.40, 55.60, 55.41, 55.04, 53.95, 37.97, 30.57, 21.38

IR (UATR) ν_{max} 2925, 1607, 1510, 1464, 1246, 1169, 1028, 832, 763 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{23}H_{28}N_1O_3$ (M+H)$^+$ 366.2064, found 366.2068.

(±)-Julandine (145bkII)



77% yield, yellow foam

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.98 (d, J = 8.8 Hz, 2H), 6.72–6.65 (m, 4H), 6.46 (s, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.63 (d, J = 16.8 Hz, 1H), 3.53 (s, 3H), 3.16–3.01 (m, 2H), 2.60–2.29 (m, 4H), 2.18–2.07 (m, 1H), 1.90–1.69 (m, 4H), 1.43–1.32 (m, 2H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 157.99, 147.87, 147.18, 134.44, 133.18, 131.38, 131.25, 130.14, 120.51, 113.38, 112.98, 110.43, 60.32, 57.89, 55.67, 55.52, 55.45, 55.12, 39.48, 33.26, 25.84, 24.32

IR (UATR) ν_{max} 2933, 1606, 1509, 1463, 1245, 1169, 1026, 833, 763 cm^{-1}

HRMS (ESI$^+$) calcd for $C_{24}H_{30}N_1O_3$ (M+H)$^+$ 380.2220, found 380.2233.

CONCLUSION

During synthetic studies of this compound, from retro-synthetic route II, we found a novel methodology for construction of bicyclic 2-pyridones from inexpensive commercially available starting materials. Thus, a one-pot methodology for the bicyclic 2-pyridones formation has been developed. Further utilization of our methodology has been successfully applied for the preparation of the representative prototype compounds of *seco*-phenanthroindolizidines and *seco*-phenanthroquinolizidines. This protocol would serve as a versatile approach for the rapid assembly of [6,5]- and [6,6]-bicyclic 2-pyridones. Although some aspects of this procedure may possibly be improved upon in the future, we believe that the present strategy has provided the easy access to a variety of tylophora alkaloids for further medicinal studies.

For the synthesis of tyloindicine F using retrosynthetic route III, we employed a one-pot nitro-Mannich reaction and alkylation as a key step for the construction of indolizidine ring. Although we could not prepare the target compound using our various synthetic routes, some results could be further considerable to publish in journal. For the total synthesis of tyloindicine F, other reaction conditions for transformation of nitroalkane to the desired product are being under operated.

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OUTPUT

ผลงานที่ได้รับระหว่างที่รับทุนจาก สกว. มีจำนวน 1 เรื่อง ซึ่งอยู่ระหว่างรอการพิจารณาตัดสิน

Journal Publication:

1. Disadee, W.; Ruchirawat, S. A One-pot, Metal-free Approach to Bicyclic 2-Pyridones. *Submitted*.