SYNTHETIC STUDIES OF ARBOFLORINE

By
Artid Buaphan

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree
Master of Science Program in Organic Chemistry
Department of Chemistry
Graduate School, Silpakorn University
Academic Year 2013
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การศึกษาการสังเคราะห์ผลิตภัณฑ์ธรรมชาติอาโบโฟลรีน

โดย
นายอาทิตย์ บัวผัน

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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The Graduate School, Silpakorn University has approved and accredited the Thesis title of “Synthetic studies of arboflorine” submitted by Mr. Artid Buaphan as a partial fulfillment of the requirements for the degree of Master of Science in Organic Chemistry.

(Assistant Professor Panjai Tantatsanawong, Ph.D.)

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Arboflorine, a natural product isolated from the plant family *Kopsia* found in the region of Southeast Asia, India and China. In Southeast Asia, some of the traditional treatments for ailments including rheumatoid, edema and tonsillitis rely on extracts from *Kopsia* plants. Although the biological tests of arboflorine no biological activity, however many indole alkaloids isolated from the genus *Kopsia* possess interesting biological activities. Our objective of this research is to find ways to synthesize natural products and others indole alkaloid synthesis to lead by key reaction Ene-Yne metathesis reaction was to reduce the number of steps of the synthesis. Herein we report synthesis of key fragments of arboflorine via ene-yne metathesis. We have obtained a small amount of advanced intermediate via ene-yne metathesis. The obstacle of the synthesis seems to be unexpected isomerization of one of the starting material. Facing with this obstacle we turn our attention to another related indole alkaloid, hirsutine which is indoloquinolizidine alkaloid isolated from the plant family *Hirsutus* and *Uncaria* extraction used as a traditional medicine in China to treat convulsions analgesic and a sedative. Recently, hirsutine attracted the attention of the medical community for its ability to inhibit the growth of influenza A virus (subtype H3N2) with an EC$_{50}$ value of 0.40-0.57 μg/mL; thus, hirsutine is 10-20 times more potent than the clinically used drug ribavirin. Herein we report a concise synthetic method that gave the tetracyclic core of hirsutine in the form of enamide with functionality suitable for further synthetic steps toward hirsutine.
สารผลิตภัณฑ์ธรรมชาติอาโบโฟลรีนเป็นสารสกัดที่นำมาจากพืชตระกูล Kopsia พบมากในภูมิภาคเอเชียตะวันออกเฉียงใต้ในประเทศอินเดียและจีนโดยภูมิภาคเอเชียตะวันออกเฉียงใต้พบสารตระกูล Kopsia ทำให้ระดับของสารตระกูลต่างๆที่ใช้สารสกัดจากพืชตระกูล Kopsia สูงว่าระดับอื่นๆของการเจ็บป่วยโรค rheumatoid อาการบวมและต่อมท่อนซิลล์ต่อมของภูมิภาคเอเชียตะวันออกเฉียงใต้ใน indole alkaloid ตัวอื่นๆในพืชตระกูล Kopsia มีสมบัติทางกายภาพที่มีอยู่ในตัวสารประกอบ indole alkaloid สำหรับรักษาอาการเจ็บป่วยต่างๆของภูมิภาคเอเชียตะวันออกเฉียงใต้ใน indole alkaloid ที่มีพฤติกรรม eene-yne metathesis เพื่อลดขั้นตอนในการสังเคราะห์ในวิทยานิพนธ์นี้เราได้รายงานการสังเคราะห์โมเลกุลสารต่างๆในปฏิกิริยา eene-yne metathesis ที่ทำให้ได้ตัวกลางในการสังเคราะห์ขั้นสูงของอาโบโฟลรีนแต่ได้ในปริมาณน้อยเรื่องตั้งสมมุติฐานว่าเกิดจากปัญหาการเกิด isomerization ของการตัวกลางในขั้นตอนปฏิกิริยาที่พบในการสังเคราะห์อาโบโฟลรีนแต่ตัวอื่นๆใน indole alkaloid อีกชนิดหนึ่งได้แก่สารคลอคลิกซิเดิม้าหมู่ hirsutine ซึ่งเป็น indoloquinolizidine alkaloid ที่พบได้มากจากพืชตระกูล Hirsutus และ Uncaria ซึ่งใช้เป็นยาแผนโบราณในประเทศจีนในการรักษาอาการชักยาแก้ปวดและยาแก้ปวดกล้ามประสาทผลิตภัณฑ์ธรรมชาติ hirsutine มีความสามารถในการยับยั้งการติดเชื้อไวรัสไข้หวัดใหญ่ influenza A virus (subtype H3N2) โดยมี EC50 ที่เท่ากับ 0.40-0.57 μg/mL ตัวอื่น hirsutine ซึ่งมีฤทธิ์ในการหยุดไวรัส fibavirus ที่ใช้เป็นสารกำจัดในปัจจุบันต่ำ 10 เท่าก็มีประสิทธิภาพในการกั้นการสังเคราะห์ hirsutine โดยคาดหวังว่าสารประกอบชนิดนี้จะมีประโยชน์ในการเปรียบเทียบข้อมูลแผนที่คลาดเคลื่อนหลักในผลการทดลองสารประกอบ indole alkaloid ตัวอื่นๆใน indole alkaloid เพื่อนำไปสู่การสังเคราะห์โดยสมมุติแบบอย่างปฏิกิริยา N-acyliminium ion cyclization ในวิทยานิพนธ์นี้เราได้รายงานการสังเคราะห์ตัวรุ่น core ของ hirsutine ในรูปของ enamide ที่มีหมู่ฟังก์ชันเหมาะสมสำหรับการปฏิกิริยาการสังเคราะห์ให้ได้ hirsutine ในขั้นตอนต่อไป
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<td>Abbreviation</td>
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<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
<td></td>
</tr>
<tr>
<td>DIBALH</td>
<td>Diisobutyl aluminum hydride</td>
<td></td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethylamino pyridine</td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
<td></td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
<td></td>
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<tr>
<td>EDC</td>
<td>1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide hydrochloride</td>
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<td>HMBC</td>
<td>Heteronuclear multiple-bond correlation spectroscopy</td>
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<td>HMQC</td>
<td>Heteronuclear multiple quantum correlation</td>
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<td>LAH</td>
<td>Lithium aluminium hydride</td>
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<tr>
<td>NMR</td>
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<tr>
<td>NOEs</td>
<td>Nuclear Overhauser effect</td>
<td></td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
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</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
<td></td>
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<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
<td></td>
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<tr>
<td>TMSOTf</td>
<td>Trimethylsilyltrifluoromethanesulfonate</td>
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CHAPTER 1

INTRODUCTION

Prior to the enlargement of the chemical industry in the late nineteenth and early twentieth century, only substances from natural sources were offered for treating our diseases, dyeing our clothes and perfuming our bodies. Extracts of the opium poppy, for example, have been used since the seventeenth century for the relief of pain. The prized purple dye called Tyrian purple, obtained from a Middle Eastern mollusk, has been recognized since ancient times. Oils distilled from bergamot, rose and lavender have worked for centuries in making perfume.

Many of these so-called natural products were first used lacking any knowledge of their chemical composition. As organic chemistry developed, though, chemists educated how to work out the structures of the compounds in natural products. The disease-curing properties of limes and other citrus fruits, for instance, were known for centuries but the chemical structure of vitamin C, the active ingredient, as not determined until 1933. Today there is revival of interest in folk remedies, and a large effort is being made to classify medicinally important chemical compounds found in plants.

Once a structure is known, organic chemists try to synthesize the compound in the laboratory. If the starting materials are low-cost and the synthesis process is easy enough, it may be converted into more economical to manufacture a compound than isolate it from a plant. In the case of vitamin C, a complete synthesis achieved in 1933, and it is now much inexpensive to synthesize it from glucose than to extract it from citrus or other natural sources. The well-being of modern society was unimaginable without the myriad products of industrial organic synthesis. Our quality of life was strongly dependent on the products of the pharmaceutical industry, such as antibiotics for combating disease and analgesics or anti-inflammatory drugs for relieving pain.

Alkaloids are a group of natural products that contain nitrogen atom in the molecule. Nitrogen atom may present in the forms of amine, amine oxide, amide and imide. Alkaloids have diverse and important physiological effects on humans and other animals. Alkaloids are produced by a large variety of organisms, including bacteria, fungi, plants and animals. The classification of alkaloids based on similarity of the
carbon skeleton or biogenetic precursor give 4 types of alkaloids; (1) True alkaloids, which contain nitrogen atom in a heterocycle and are originated from amino acid. (2) Protoalkaloids, which also are biosynthesized from amino acid but contain nitrogen atom that is not in a ring. (3) Polyalkamine alkaloids which are protoalkaloids that contain multiple nitrogen atoms. (4) Pseudoalkaloids which are alkaloid-like compounds that do not originate from amino acid. For example stem-bark of the Malayan *Kopsia arborea* [1] such as valpericine, arboloscine, arboricine, arboricinine, 19(S)-methoxytubotaiwine, 19(R)-methoxytubotaiwine and arboflorine (Figure 1.1) used to treat certain types of cancers. Indole alkaloid such as hirsutine (Figure 1.1) which is indoloquinolizidine alkaloid isolated from the plant family *Hirsutus* and *Uncaria*. Corynantheidine (Figure 1.1) was first isolated from the African plant *Pseudocinchona Africana*.

![Figure 1.1 Structure of valpericine, arboloscine, arboricine, arboricinine, 19(S)-methoxytubotaiwine, 19(R)-methoxytubotaiwine, arboflorine, hirsutine, and corynantheidine.](image)
Arboflorine possesses unprecedented pentacyclic ring system and structurally belongs to the monoterpenoid indole alkaloid family. It structure is shown in Figure 1.3.

Figure 1.2 Kopsia arborea

Publication of Toh-SeokKam [2] and co-workers reported the isolation and structural determination via spectroscopy of arboflorine. Arboflorine, an unusual indole alkaloid, was obtained from the Malayan plant Kopsia arborea (Figure 1.2). The structure of arboflorine was pentacyclic carbon that contained three nitrogen atoms. Arboflorine obtained as a minor alkaloid from the basic fraction derived from the ethanol (EtOH) extraction of the stem bark of Kopsia arborea following repeated chromatographic fractionation as colorless oil, 0.4 mg kg⁻¹. The UV spectrum (EtOH) showed typical indole absorptions at 224, 283, and 291 nm, whereas the infrared spectrum showed bands at 3393 and 1651 cm⁻¹. The infrared spectrum suggested the presence of NH and lactam functionalities, respectively. The electron ionization mass spectrometry (EIMS) of arboflorine showed a molecular ion at m/z 307 (base peak), the odd mass indicated the presence of a third nitrogen. The high resolution electron impact mass spectrometry (HREIMS) of arboflorine confirmed the molecular formula, C₁₉H₂₁N₃O, requiring 11 degrees of unsaturation.

Figure 1.3 Structure of arboflorine
The $^{13}$C NMR spectrum (Table 1.1) showed a total of 19 carbon resonances (one methyl, four methylenes, eight methines, and six quaternary carbons) in agreement with the molecular formula. The $^1$H NMR spectrum (Table 1.1) indicated an unsubstituted aromatic ring; two broad NH peaks at $\delta$ 9.74 and 6.11, a vinylic H, seen as a broad doublet at $\delta$ 5.92; and a methyl doublet at $\delta$ 1.37.

Table 1.1 $^1$H and $^{13}$C NMR spectral data of arboflorine

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<tr>
<td>3$\alpha$</td>
<td>45.9</td>
<td>2.90 m</td>
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<tr>
<td>3$\beta$</td>
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<td>2.82 td (11.9, 3.8)</td>
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<td>5$\alpha$</td>
<td>56.3</td>
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<td>21.6</td>
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<td>113.0</td>
<td></td>
</tr>
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<td>8</td>
<td>127.8</td>
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<td>9</td>
<td>117.6</td>
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<td>10</td>
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<td>7.09 td (7.8, 1.2)</td>
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<td>7.15 td (7.8, 1.1)</td>
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<td></td>
<td>2.61 m</td>
</tr>
<tr>
<td>15</td>
<td>120.8</td>
<td>5.92 br d (2.7)</td>
</tr>
<tr>
<td>16</td>
<td>42.0</td>
<td>4.12 br d (9.4)</td>
</tr>
<tr>
<td>17</td>
<td>171.1</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>18.1</td>
<td>1.37 d (6.4)</td>
</tr>
<tr>
<td>19</td>
<td>49.6</td>
<td>4.04 br q (6.4)</td>
</tr>
<tr>
<td>20</td>
<td>133.6</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>59.2</td>
<td>4.30 br d (9.4)</td>
</tr>
<tr>
<td>NH (indole)</td>
<td></td>
<td>9.74 br s</td>
</tr>
<tr>
<td>NH (lactam)</td>
<td></td>
<td>6.11 br s</td>
</tr>
</tbody>
</table>
A pair of AB doublets seen at $\delta$ 4.30 and 4.12 with $J = 9.4$ Hz indicated that this two carbon CHCH fragment branched from a nitrogen. This structure of arboflorine supported by the NOEs (Figure 1.4) and HMBC (Figure 1.5) spectra which also revealed the presence of $NCH_2CH_2$, $NCH_2CH_2CH=\cdot$, and CHCH$_3$ fragments, in addition to the four contiguous aromatic hydrogens.

![Figure 1.4 Selected NOEs of arboflorine](image)

![Figure 1.5 Selected HMBC of arboflorine](image)

The relative stereochemistry at the various stereogenic centers was established by NOEs experiments (NOEs; Figure 1.4). The observed NOESY between H(21) and H(19) required both of these hydrogens to be synstereochemical. A NOEs was not observed between H(16) and H(21) but was seen for H(16)/H(5$\beta$) and H(16)/H(3$\beta$). Analysis of the 1H shift values, 13C shift values, HMBC and NOEs (Table 1.1) proved Structure of arboflorine.

In 2006, publication of Richmond Sarpong [3] and co-workers reported progress toward the synthesis of arboflorine. The success of the synthetic route rested on the use of a borylative C-H functionalization reaction, Suzuki cross-coupling and transannular dehydrogenative C-N bond forming reaction. In the retrosynthetic
analysis of arboflorine (Scheme 1.1), they were drawn to the implementation of strategy. They envisioned that the natural product would arise from pentacycle 2, whereby, in the forward direction, a formal hydrogenation and double bond transposition. Pentacycle 2 was expected to be formed from macrocycle 3 using a formally dehydrogenative, transannular, carbon-nitrogen (C-N) bond construction as the key reaction. Macrocycle 3 would be formed from the components of tryptamine (4), ethyl acrylate (5) and bromomethoxypicoline 6.

![Diagram of retrosynthetic analysis of arboflorine](image)

Scheme 1.1 Richmond’s retrosynthetic analysis of arboflorine

In the synthetic studies, preparation of pentacyclic skeleton of indole alkaloid arbflorine showed Scheme 1.2. First, Heck cross-coupling of bromomethoxypicoline (6) with ethyl acrylate (5) gave adduct 7 in 93% yield. A two-stage reduction of 7 by hydrogenation of the enoate double bond and lithium aluminum hydride reduction of the ester group gave alcohol 8. Protection of the primary hydroxyl group gave MOM ether 9. Next, borylative C-H functionalization of ether 9 produced boronic ester 10. Suzuki cross-coupling between 2-bromotryptamine derivative 4a with boronic ester 10 gave Suzuki coupling product 11. Deprotection of the primary hydroxyl by removal of
the MOM group and macrocyclization under Mitsunobu conditions gave macrocycle 12. Protection of the indole nitrogen of macrocycle 12 with a Di-tert-butyl dicarbonate and selective cleavage of the nosyl group provided amine 3. Intramolecular reaction of amine 3 followed by reduction to give pyridine 17. Last, methylation and nonspecific decomposition of pyridine 17 gave tetracycle 20 respectively. In synthetic plan has not as yet culminated in a total synthesis of arboflorine, primarily because of difficulties associated with the late-stage reduction of the pyridine and pyridone moieties.
Scheme 1.2 Richmond’s synthesis of indole alkaloid arboflorine

In this thesis we also discuss synthetic studies of another indole alkaloid natural product hirsutine (21) which is indoloquinolizidine alkaloid isolated from the plant family Hirsutus and Uncaria. Hirsutine demonstrated to exert central depressive and vasodilatory effects as protective effects against neuronal death in cultured rat
cerebellar granule cells. In addition, hirsutine displayed antihypertensive, negative chronotropic, and antiarrhythmic activity. Hirsutine attracted the attention of the medical community for its ability to inhibit the growth of influenza A virus (subtype H3N2) with an EC\textsubscript{50} value of 0.40-0.57 µg/mL; thus, hirsutine is 10-20 times more potent than the clinically used drug ribavirin.

In 2012, publication of Qhyun Kwon [4] and co-workers reported progress toward the synthesis of hirsutine. The success of the synthetic route rested on the use of phosphine-catalyzed [4+2] annulation, Michael addition and selective reduction. In the retro-synthetic analysis of hirsutine (21) (Scheme 1.3), they were drawn to the implementation of strategy. They envisioned that the natural product would arise from tetracycle 22 by selective reduction and enol methylation. Tetracycle 22 was expected to be formed from tetracycle 23 using selective reduction and methylenation. Tricycle 25 was expected to be formed from tetracycle 23 using conjugate addition and C ring formation. Tricycle 25 would be formed from the components of ethyl α-
methylallenoate (26) and indolylimine 27 by phosphine-catalyzed [4+2] annulation as the key reaction.

Scheme 1.4 Ohyun’s synthesis of hirsutine

Ohyun’s synthesis of hirsutine is shown in Scheme 1.4. First, Boc protection of indole 2-carboxaldehyde (28) gave N-Boc-protected aldehyde 29 in 98% yield. Next, reaction of N-Boc-protected aldehyde 29 with o-nitrobenzenesulfonamide (NsNH₂) in the presence of Et₃N and catalytic TiCl₄ gave N-(o-nosy)limine 30. The phosphine-catalyzed annulation of imine 30 with ethyl α-methylallenoate (26) produced
compound 31 in 73% yield from the aldehyde 29 over two steps. Deprotection of compound 31 produced compound 32 using SiO₂ in reflux toluene, in 90% yield. Acylation at the C3 position of indole moiety in 32 with oxalyl chloride, followed by reduction of the resulting keto acid chloride with borane, furnished the requisite tryptophol 33. The nosyl group of 33 removed in the presence of PhSH and K₂CO₃ in MeCN at 50 °C produced tetracycle 35. Formation of the C-ring through intramolecular N-alkylation proceeded under the influence of I₂ and PPh₃ to give the tetracycle 35. Michael addition of tetracycle 35 with dimethyl malonate anion provided the trimester 36 in 89% yield. Selective reduction of trimester 36 followed by Wittig olefination, obtained the alkene 38 in 41% yield over two steps from the trimester 36. Next, hydrogenation of alkene 38 produced compound 39 in 99% yield. Selective reduction of compound 39 followed by methylation, obtained the hirsutine 21 in 31% yield over two steps from the compound 39.
CHAPTER 2
Synthetic studies of arboflorine by ene-yne metathesis

In this chapter we describe synthetic studies of arboflorine (Figure 1.3). We designed two key reactions of olefin metathesis for synthesis arboflorine as ene-yne metathesis and ene-yne-ene metathesis. Ene-yne-ene metathesis is a tandem or cascade process, in which multiple transformations occur in one operation, which is a desirable practice in organic synthesis.

Olefin metathesis

Olefin metathesis is an organic reaction that entails the reorganization of fragments of alkenes (olefins) by the scission and renewal of carbon-carbon double bonds. Catalysts for this reaction have evolved rapidly for the past few decades. Because of the relative ease of olefin metathesis, it often creates less undesired by-products and hazardous wastes than other organic reactions. For their explanation of the reaction mechanism and their discovery of a variety of highly efficient and selective catalysts, Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock were collectively awarded the 2005 Nobel Prize in Chemistry. The reaction is catalyzed by metal complexes. Grubbs’ catalysts are ruthenium (II) carbenoid complexes. Grubbs’ catalysts are often customized with a chelating isopropoxystyrene ligand to form the related Hoveyda–Grubbs catalyst.

![Figure 2.1 Structure of first generation Grubbs’ catalysts (a), second generation Grubbs’ catalysts (b) and Hoveyda-Grubbs’ catalyst (c)](image)

(a)                             (b)                                         (c)
Reaction mechanism

The [2+2] cycloaddition of two alkenes is formally symmetry forbidden and thus has high activation energy. Interaction with the d-orbitals on the metal catalyst lowers the activation energy enough that the reaction can continue rapidly at middle temperatures. The mechanism involves the [2+2] cycloaddition of an alkene double bond to a transition metal alkylidene to form a metallacyclobutane intermediate. The metallacyclobutane produced cyclorevert to provide either the original species or a new alkene and alkylidene of ene-yne metathesis (scheme 2.1).
Retrosynthetic analysis of arboflorine by ene-yne metathesis

The retrosynthetic analysis of arboflorine (1) is summarized in scheme 2.2. The key step for construction of arboflorine involves tandem indole cyclization and ene-yne metathesis. We envision that the natural product would arise from tricyclic 42 via a tandem indole cyclization at a late stage. Tricyclic 42 is expected to be formed from diene 43 and acrylamide (44) using substitution and ring closing metathesis. Diene 43 would be formed from the readily available components of enamide 45, alkyne 46 by ene-yne metathesis as the key reaction.

Scheme 2.3 Synthesis of N-Boc-3-butenoyltryptamine (50)
Synthesis of \( N\)-Boc-3-butenoyltryptamine (50)

Our synthetic studies commenced with the preparation of \( N\)-Boc-3-butenoyltryptamine (50) (scheme 2.3). First, amide bond formation of tryptamine (47) with but-3-enoic acid (48) gave 3-butenoyltryptamine (49) in 46% yield. Next, protection of the indole nitrogens of 49 with Boc groups provided \( N\)-Boc-3-butenoyltryptamine (50) in 100% yield.

Scheme 2.4 Synthesis of 4-(trimethylsilyl)but-3-yn-2-ol (53)

Synthesis of 4-(trimethylsilyl)but-3-yn-2-ol (53)

Synthesis of 4-(trimethylsilyl)but-3-yn-2-ol (53) by nucleophilic addition of (trimethylsilyl)ethynyllithium generated from reaction of ethynyltrimethylsilane (51) and normal butyllithium to acetaldehyde (52) gave adduct (53) in 100% yield (scheme 2.4).

Scheme 2.5 Ene-yne metathesis of \( N\)-Boc-3-butenoyltryptamine (50) and 4-(trimethylsilyl)but-3-yn-2-ol (53)
Ene-yne metathesis of \(N\text{-}Boc\text{-}3\text{-}butoxytryptamine\) and \(4\text{-}(\text{trimethylsilyl})\text{but}-3\text{-}yn\text{-}2\text{-}ol\)

Ene-yne metathesis of \(N\text{-}Boc\text{-}3\text{-}butoxytryptamine\) (50) and \(4\text{-}(\text{trimethylsilyl})\text{but}-3\text{-}yn\text{-}2\text{-}ol\) (53) gave a large quantity of isomerized product enamide 55 and small amount of diene intermediate 54, along with dimerized product 56 reacting from homo coupling of 50 by treatment with first generation Grubb's catalyst (scheme 2.5).

\[\text{Scheme 2.6 Synthesis of arboflorine (1) by ene-yne metathesis}\]

Synthesis of arboflorine (1) by ene-yne metathesis

We envision that coupling of diene intermediate 54 with \textit{tert}-butyl acryloylcarbamate (57) followed by ring closing metathesis would provide the full carbon skeleton 58 of arboflorine (1). Indole cyclization of tricycle 58 then should provide arboflorine (1) in the final step (Scheme 2.6).
**Synthetic studies of arboflorine by ene-yne-ene metathesis**

Retrosynthetic analysis of arboflorine by ene-yne-ene metathesis

![Diagram of retrosynthetic analysis of arboflorine](image1)

Scheme 2.7 Retrosynthetic analysis of arboflorine

The retrosynthetic analysis for target arboflorine is showed in scheme 2.7. The key step for construction of arboflorine involve ene-yne-ene metathesis. We envision that the natural product would arise from tricyclic 59 via cyclization at a late stage. We envisioned cyclic dienamide intermediate 59 of arboflorine to be derived from ene-yne-ene metathesis of N-butenyltryptamine 60 and yne-enamide 61. Yne-enamide 61 is expected to be formed from alkyne 62 using amide bond formation. Alkyne 62 is expected to be formed from aldehyde 63 using Bestmann-Ohira reaction. Aldehyde 63 would be formed from acid 64.

**Synthesis of N-Butenyltryptamine**

![Diagram of synthesis of N-Butenyltryptamine](image2)

Scheme 2.8 Synthesis of N-Butenyltryptamine (66)

Tryptamine underwent alkylation with 1-Bromo-3-butene 65 to give N-butenyltryptamine 66 and N,N-dibutenyltryptamine as a by-product (scheme 2.8).
Synthesis of yne-enamide

Yne-enamide 73 partner of the key transformation could be synthesized in 6 steps (scheme 2.9). Boc-L-alanine 67 underwent esterification to give ester 68 which was subsequently reduced to alcohol 69 with lithium aluminum hydride. Swern oxidation of alcohol 69 gave aldehyde 70 which was subsequently treated with Bestmann-Ohira reagent to give alkyne 71. Amide bond formation of alkyne 71 gave yne-enamide 73 using DCC, DMAP and acrylic acid.
Synthesis of arboflorine (1) by ene-yne-ene metathesis

With the two fragments in hand, the major task is to investigate the key transformation ene-yne-ene metathesis. The result of the investigation which is being carried out in our laboratory as well as the completion of alboflorine synthesis will be reported in due course. We envision that coupling of yne-enamide 73 with N-butenyltriptamine 66 provide tricycle 74 by ene-yne metathesis as the key reaction. Indole cyclization of tricycle 74 then should provide arboflorine (1) in the final step (Scheme 2.10).

With the difficulty we faced in synthetic studies of arboflorine, we turn our attention to synthetic studies of another indole alkaloid, hirsutine. This alkaloid has the core structure of indoloquinolizidinone ring system which is in common with arboricine and arboricinine which are found in the same plant as arboflorine and maybe related biosynthetically.
**Synthetic studies of hirsutine**

Intramolecular cyclization of $N$-acyliminium ions

Iminium ions are important, reaction species in organic synthesis for construction of carbon-carbon and carbon-heteroatom bonds. There has been considerable interest in the development of cyclizations that proceed via $N$-acyliminium species, in contrast to cyclizations involving iminium cations, such as the Mannich reaction and the Pictet-Spengler reaction. Both reactions have been employed in organic chemistry for nearly 100 years. The $N$-acyl iminium carbon is more electron-deficient due to the electron attracting properties of carbonyl group on nitrogen, which causes $N$-acyliminium ions to be more reactive as electrophile than simple $N$-acyliminium ions. This versatile electrophile is very useful in the $\alpha$-amidoalkylation with various nucleophiles (scheme 2.11), as expresses in reaction.

$N$-Acyliminium ions can be generated as discrete salts, paired with non-nucleophilic anions, although this is a relatively rare undertaking restricted to physicochemical studies. In synthetic transformations, the reactive species are almost exclusively produced in situ during the course of desired reaction by variety of useful techniques, such as reaction of amide with aldehyde or ketone, addition of nucleophile to imide, and acylation of $N$-substituted imine.
Retrosynthetic analysis of hirsutine

Scheme 2.12 Retrosynthetic Analysis of hirsutine (21)

Scheme 2.12 outlines our retrosynthetic analysis of hirsutine. Hirsutine (21) is expected to be formed from malonate 75 using selective reduction and addition. Malonate 75 could be introduced through substitution of alkene in tetracycle 76. Alkene in tetracycle expected to be formed from tetracycle 77 using Cope elimination. We envision that the tetracycle 77 would arise from hydroxylactam 78 via intramolecular cyclization of N-acyliminium ion as key reaction. Hydroxylactam 78 would be formed from the amide 79 by reduction.
Synthetic studies of hirsutine (21)

The synthesis of hirsutine (scheme 2.13) began with amide formation of tryptamine (47) and benzylated glutamic acid 80 to give amide using DDC and DMAP in 54% yield. This amide converted to imide 81 by treatment with LAH. DIBALH reduction of the imide carbonyl 81 was completely regioselective at the less hindered carbonyl group when toluene was used as solvent and the temperature was controlled at -78°C to give hydroxylactam 78 in 85% yield as a single product. N-acyliminium ion cyclization of hydroxylactam 78 treatment with TMSOTf in dichloromethane produced dibenzylaminoidoloquinolizidinone 77 as key reaction. In this regard, dibenzylaminoidoloquinolizidinone 77 converted to tetracycle 82 using an N-
protection in 100% yield. Cope elimination upon treatment of tetracycle 82 with m-CPBA in dichloromethane to give enamide in 59% yield. We envision that addition of diester in compound 76 by Michael addition to give malonate 75. The remaining steps toward hirsutine would involve alkylation, lactam reduction, partial reduction of malonate and methyl enol ether formation.
CHAPTER 3
General conclusion

In synthetic studies of arboflorine (Ene-yne metathesis)

We have reported a synthetic sequence to an advanced intermediate of arboflorine. Our synthetic sequence feature ene-yne metathesis as the key reaction. Our synthetic plan has not culminated in a total synthesis of arboflorine, primarily because of difficulties associated with ene-yne metathesis of N-Boc-3-butenoyltryptamine (50) and 4-(trimethylsilyl)but-3-yn-2-ol (53). Isomerization of N-Boc-3-butenoyltryptamine (50) seems to be the main obstacle of our approach. We do not know the mechanism of this isomerization. However it could be in the same vain as transition metal-mediated isomerization of alkene (Pt, Pd). Once the isomerized product 55 is formed it does not undergo ene-yne metathesis. To verify this hypothesis we are currently conducting ene-yne metathesis of homolog of compound 50 which is not capable of isomerization into the corresponding α,β-unsaturated enamide. The results will be reported in due course. In synthetic studies of arboflorine (Ene-yne-ene metathesis), we have synthesized the N-butenyltryptamine and yne-enamide however the yields of these key fragments are not high and needed to be optimized. The next task will be to investigate the key transformation Ene-Yne-Ene metathesis. With the difficulties we faced in synthetic studies of arboflorine, we turned our attention to another indole alkaloid, hirsutine. We have reported a synthetic sequence to tetracycle of hirsutine. Our synthetic sequence feature N-acyliminium ion cyclization as the key reaction.
CHAPTER 4
Experimental procedures

General methods

All commercially available reagents were used without purification. Moisture and air-sensitive compounds were used under an argon atmosphere with oven-dried glasswares. Nuclear magnetic resonance (NMR) spectra were obtained in CDCl$_3$ on a 300 MHz Bruker spectrometer. Chemical shifts are $\delta$ (ppm) with tetramethylsilane as an internal standard. Coupling constants are reported in hertz (Hz). Thin layer chromatography (TLC) was performed on Fluka aluminum backed silica gel plates with 0.2 mm thickness. Ultraviolet (UV) active compounds were visualized with UV a light at 254 nm and vanillin stain. Column chromatography was performed using silica gel 60, 230-400 mesh.
SYNTHESIS OF ARBOFLORINE BY ENE-YNE METATHESIS

4-(trimethylsilyl)but-3-yn-2-ol (53)

Ethyltrimethylsilane (0.10 mL, 0.723 mmol) was dissolved in dry THF (15 mL) under an argon atmosphere at -78°C. To this solution was added 1.6M n-buthyllithium (0.451 mL, 0.723 mmol) and the mixture was stirred for 30 minutes. The mixture was added acetaldehyde (0.407 mL, 7.23 mmol) and stirred for additional 2 hours. The reaction was quenched with saturated ammonium chloride (20 mL). The resulting mixture was extracted with ethyl acetate (4 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to give 4-(trimethylsilyl)but-3-yn-2-ol as a yellow oil (0.1020 g, 100%).

\[
\text{H NMR (300 MHz, CDCl}_3\text{) } \delta 4.50 (q, J = 6.7 \text{ Hz, 1H}), 1.45 (d, J = 6.7 \text{ Hz, 3H}), 0.20 (s, 9H).
\]

But-3-enoic acid (48)

Dry tetrahydrofuran (10 mL) was purged carbondioxide for 5 minutes at -78°C. To this solution was added allyl magnesium bromide (10.0 mL, 1.0M in THF, 10.0 mmol) at -78°C. The mixture was stirred vigorously for 5 minutes. The reaction was quenched with drop-wise 1M hydrochloric acid solution (10.0 mL). The mixture was extracted with ethyl acetate (5 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give but-3-enoic acid as a yellow oil (0.60 g, 70%).

\[
\text{H NMR (300 MHz, CDCl}_3\text{) } \delta 7.29 (s, 1H); 5.95 (m, 1H); 5.20 (d, 2H); 3.15 (d, 2H).
\]
3-Butenoyltryptamine (49)

To a solution of acid 48 (0.2740 g, 3.186 mmol) in dry CH₂Cl₂ (10 mL) under an argon atmosphere at room temperature were added DMAP (0.0260 g, 0.2128 mmol), tryptamine (0.1700 g, 1.061 mmol) and DCC (0.6560 g, 3.179 mmol). The mixture was stirred vigorously. Upon completion as monitored by TLC (1 day), saturated sodium bicarbonate solution (20 mL) was added, and the mixture was extracted with CH₂Cl₂ (4 x 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give crude brown oil. This oil was further purified by column chromatography (silica gel, 1:1 hexane/ethyl acetate) to give 3-butenoyltryptamine as a light brown oil (0.1114 g, 46%).

\[ \delta \text{H NMR (300 MHz, CDCl}_3\text{)} \]
\[ \delta 7.60 (d, J = 7\text{Hz, 1H}), 7.40 (d, J = 7\text{Hz, 1H}), 7.15 (m, 2H), 7.00 (s, 1H), 5.90 (m, 1H), 5.20 (s, 1H), 5.10 (s, 1H), 3.60 (m, 2H), 3.00 (m, 4H); \]

\[ \delta \text{C NMR (75 MHz, CDCl}_3\text{)} \]
\[ \delta 171.0, 166.4, 136.5, 127.3, 125.1, 122.3, 119.7, 119.2, 118.6, 112.5, 111.4, 41.6, 40.0, 25.6. \]

N-Boc-3-Butenoyltryptamine (50)

Amide 49 (0.0695 g, 0.30 mmol) was dissolved in dry CH₂Cl₂ (15 mL) under an argon atmosphere at room temperature. To this solution was added di-tert-butyldicarbonate (0.6646 g, 3.045 mmol), DMAP (0.0073 g, 0.060 mmol) and triethylamine (0.4180 mL, 3.0 mmol). Upon completion as monitored by TLC (1 hour), the reaction was quenched with water (20 mL). The resulting mixture was extracted with CH₂Cl₂ (4 x 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give a yellow oil. This oil was
further purified by column chromatography (silica gel, 10:1 hexane/ethyl acetate) to give N-Boc-3-butenoyltryptamine as a yellowish oil (0.1300 g, 100%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 7$ Hz, 1H), 7.65 (d, $J = 7$ Hz, 1H), 7.40 (s, 1H), 7.30 (m, 2H), 6.05 (m, 1H), 5.20 (m, 2H), 4.00 (t, $J = 6.5$ Hz, 2H), 3.70 (d, $J = 6.5$ Hz, 2H), 2.90 (t, $J = 7$ Hz, 2H), 1.70 (s, 9H), 1.40 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.1, 152.9, 149.7, 135.4, 131.5, 130.5, 124.3, 123.2, 122.5, 119.1, 118.0, 117.6, 115.2, 83.4, 83.2, 44.6, 43.1, 28.2, 28.2, 28.2, 27.8, 27.8, 27.8, 24.2.

![Diagram of compound 54]

Ene-yne metathesis of indole-alkene 50 and alkyne 53

To a solution of indole-alkene 50 (34 mg, 0.08 mmol) and alkyne 53 (90 mg, 0.64 mmol) in CH$_2$Cl$_2$ (3 mL) was added Grubbs’ $1^{\text{st}}$ gen. catalyst (1.5 mg, 1.8 $\mu$mol) and the mixture was heated to reflux and stirred for 24 h. Filtration through short silica column and concentration under vacuum gave a crude mixture as a brown oil which was purified by flash column chromatography (silica gel, 20:1 hexane/ethyl acetate) to give diene 54 (2.7 mg, 6%), isomerized enamide 55 (20 mg, 58%), and bisindole 56 (3.3 mg, 10%) as clear oils; diene 54 $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 7$ Hz, 1H), 7.65 (d, $J = 7$ Hz, 1H), 7.40 (s, 1H), 7.30 (m, 2H), 6.10-5.70 (m, 1H), 5.20-4.85 (m, 3H), 3.85 (t, $J = 6.5$ Hz, 2H), 3.65 (t, $J = 6.5$ Hz, 2H), 2.98-2.79 (m, 3H), 1.70 (s, 9H), 1.60-1.55 (m, 3H), 1.45 (s, 9H), 0.07 (s, 9H).
(E)-tert-butyl 3-(2-(N-(tert-butoxycarbonyl)but-2-enamido)ethyl)-1H-indole-1-carboxylate (55)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.10 (d, 1H), 7.65 (d, 1H), 7.40 (s, 1H), 7.30 (m, 2H), 7.00 (m, 1H), 6.80 (d, 1H), 4.00 (t, 2H), 2.90 (t, 2H), 1.95 (d, 3H), 1.70 (s, 9H), 1.40 (s, 9H).

(E)-di-tert-butyl 3,3’-((2,2,15,15-tetramethyl-4,6,11,13-tetraoxo-3,14-dioxa-5,12-diazahexadec-8-ene-5,12-diyl)bis(ethane-2,1-diyl))bis(1H-indole-1-carboxylate) (56)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.10 (d, 2H), 7.65 (d, 2H), 7.40 (s, 2H), 7.30 (m, 4H), 5.80 (s, 2H), 3.95 (t, 4H), 3.70 (d, 4H), 2.90 (t, 4H), 1.70 (s, 18H), 1.40 (s, 18H).
SYNTHESIS OF ARBOFLORINE BY ENE-YNE-ENE METATHESIS

(R)-methyl 2-((tert-butoxycarbonyl)amino)propanoate (68)

Boc-L-alanine (1.0 g, 5.29 mmol) was dissolved in methanol (5 mL). To this solution were added concentration sulfuric acid (0.2 mL, 3.68 mmol). The mixture was stirred vigorously for 1 day. The combined organic layers were concentrated under reduced pressure to give (R)-methyl 2-((tert-butoxycarbonyl)amino)propanoate as a colorless oil (1.06 g, 98%).

\[
1H \text{ NMR (300 MHz, CDCl}_3\text{) } \delta 5.30 \text{ (s, 1H), 4.30 \text{ (s, 1H), 3.75 \text{ (s, 3H), 1.50 \text{ (s, 12H);}}}
\]
\[
13C \text{ NMR (75 MHz, CDCl}_3\text{) } \delta 175.5, 173.7, 155.1, 79.5, 52.0, 49.0, 30.8, 28.8, 28.1.
\]

(R)-tert-butyl (1-hydroxypropan-2-yl)carbamate (69)

(R)-methyl 2-((tert-butoxycarbonyl)amino)propanoate (1.00 g, 4.88 mmol) was dissolved in dry THF (20 mL) under an argon atmosphere at 0 °C. To this solution was added LAH (0.28 g, 7.31 mmol). The mixture was stirred vigorously at 0 °C for 1 hour. The reaction was quenched with drop-wise saturated sodium bicarbonate solution (20 mL). The mixture was extracted with ethyl acetate (6 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (R)-tert-butyl (1-hydroxypropan-2-yl)carbamate as a colorless oil (0.415 g, 49%).

\[
1H \text{ NMR (300 MHz, CDCl}_3\text{) } \delta 3.75 \text{ (m, 1H); 3.55 \text{ (d, 2H); 1.45 \text{ (s, 9H); 1.15 \text{ (d, 3H);}}}
\]
\[
13C \text{ NMR (75 MHz, CDCl}_3\text{) } \delta 156.3, 79.6, 66.6, 48.4, 28.4, 28.3, 28.1, 18.5.
\]
(R)-tert-butyl (1-oxopropan-2-yl)carbamate (70)

Oxalyl chloride (0.984 mL, 11.6 mmol) was dissolved in dry dichloromethane (20 mL) under an argon atmosphere at -78 °C. To this solution was added drop-wise DMSO (1.65 mL, 23.3 mmol) under an argon atmosphere at -78 °C for 30 minutes. The mixture was added (R)-tert-butyl (1-hydroxypropan-2-yl)carbamate (67.8 mg, 3.88 mmol) under an argon atmosphere at -78 °C for 1 hour. To this solution was added dry triethylamine (4.86 mL, 34.9 mmol) at -78 °C to 0 °C. The mixture was extracted with ethyl acetate (6 x 20 mL) and water (5 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (R)-tert-butyl (1-oxopropan-2-yl)carbamate as a colorless oil (0.394 g, 59%).

\[ ^1H \text{ NMR (300 MHz, CDCl}_3\] \( \delta \) 9.72 (s, 1H); 4.20 (m, 1H); 1.50 (s, 9H); 1.15 (d, 3H);

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3\] \( \delta \) 200.1, 155.3, 80.5, 55.5, 28.4, 28.3, 27.3, 14.7.

Dimethyl (1-diazo-2-oxopropyl)phosphonate (83)

Dimethyl (2-oxopropyl)phosphonate (0.416 mL, 3.00 mmol) was dissolved in dry acetonitrile (5 mL) under an argon atmosphere at 0 °C. To this solution was added anhydrous potassium carbonate (0.86 g, 6.6 mmol) and tosylazide (1 mL, 6.6 mmol) under an argon atmosphere. The mixture was stirred vigorously at room temperature for 75 minutes. The resulting mixture was concentrated under reduced pressure to give crude product. The crude product was purified by flash chromatography (silica gel, 1:1 hexane/ethyl acetate) to provide dimethyl (1-diazo-2-oxopropyl)phosphonate (67.5 mg, 12%) as a colorless oil.
(R)-tert-butyl but-3-yn-2-ylcarbamate (71)

(R)-tert-butyl (1-oxopropan-2-yl)carbamate (45.3 mg, 0.268 mmol) was dissolved in anhydrous methanol (5 mL) under an argon atmosphere at room temperature. To this solution was added anhydrous potassium carbonate (57.9 mg, 0.419 mmol) and dimethyl (2-oxopropyl)phosphonate (0.10 g, 0.524 mmol) under an argon atmosphere. The mixture was stirred vigorously at room temperature for 24 hours. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (R)-tert-butyl but-3-yn-2-ylcarbamate as a colorless oil (0.152 g).

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \delta 3.60 (m, 1H); 2.05 (s, 1H); 1.50 (s, 9H); 1.15 (d, 3H);

\[ ^13C \text{NMR (75 MHz, CDCl}_3 \] \delta 153.7, 83.5, 80.2, 69.1, 44.1, 27.3, 27.3, 27.2, 21.4.

(S)-but-3-yn-2-amine (72)

To a solution of (R)-tert-butyl but-3-yn-2-ylcarbamate (0.050 g, 0.296 mmol) in THF (4 mL) at room temperature were added 1N hydrochloric acid (2 mL). The mixture was stirred vigorously. Upon completion monitored by TLC (3 hours), saturated sodium bicarbonate solution (10 mL) was added drop-wise, and the mixture was extracted with ethyl acetate (5 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude (0.069 g).

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \delta 4.10 (m, 1H); 2.00 (s, 1H); 1.50 (d, 3H).
(S)-N-(but-3-yn-2-yl)acrylamide (73)

To a solution of (S)-but-3-yn-2-amine (0.045 g, 0.656 mmol) in dry dichloromethane (3 mL) under an argon atmosphere at room temperature were added DDC (0.203 g, 0.985 mmol) and acrylic acid (0.090 mL, 1.31 mmol). The mixture was stirred vigorously. Upon completion monitored by TLC (1 day), saturated sodium bicarbonate solution (5 mL) was added drop-wise, and the mixture was extracted with dichloromethane (5 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude (0.243 g).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.55 (dd, 1H); 6.40 (dd, 1H); 5.85 (m, 1H); 4.50 (m, 1H); 2.00 (s, 1H); 1.30 (m, 3H).
SYNTHESIS OF HIRSUTINE

(S)-4-((benzyloxy)carbonyl)-2-(dibenzylamino)butanoic acid (80)

L-glutamic acid (5 g, 0.03 mol) was dissolved in 100 mL of 1:1 methanol/water. To this solution were added benzyl chloride (15.64 mL, 0.13 mol), potassium carbonate (10.56 g, 0.07 mol), and sodium hydroxide (3.06 g, 0.07 mol). The reaction was heated to reflux overnight. 1M hydrochloric acid (50 mL) were added and then the mixture was extracted with dichloromethane (6 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude material as a yellow oil. The crude product was purified by flash chromatography (silica gel, 10:1 hexane/ethyl acetate) to provide the product as a yellow oil (4.43 g, 32%).

\[ \delta = 7.45-7.12 \text{ (m, 15H); } 5.20 \text{ (AB system, } J = 12.2 \text{ Hz, } J = 37.4 \text{ Hz, 2H); } 3.90 \text{ (d, } J = 13.6 \text{ Hz, 2H); } 3.48 \text{ (d, } J = 13.6 \text{ Hz, 2H); } 3.38 \text{ (t, } J = 6.9 \text{ Hz, 1H); } 2.37 \text{ (m, 2H); } 2.09 \text{ (m, 2H); } 13C \text{ NMR (75 MHz, CDCl}_3\text{) } \delta = 178.9, 172.1, 139.0, 138.9, 135.9, 129.7, 129.2, 129.0, 128.9, 128.6, 128.5, 128.4, 128.3, 127.6, 127.4, 127.1, 127.0, 126.6, 66.3, 59.8, 54.4, 31.9, 30.4, 23.9, 22.6, 21.0.\]

(S)-benzyl 4-(2-(1H-indol-3-yl)ethylcarbamoyl)-4-(dibenzylamino)butanoate (79)

To a solution of 1-benzyl-N,N-dibenzyl-L-glutamate (0.50 g, 1.21 mmol) in dry dichloromethane (20 mL) under an argon atmosphere at room temperature were added DMAP (8.70 mg, 0.080 mmol), tryptamine (64.5 mg, 0.40 mmol) and DCC (0.249 g, 1.21 mmol). The mixture was stirred vigorously. Upon completion monitored by TLC (2 days), saturated sodium bicarbonate solution (30 mL) was added drop-wise, and the
mixture was extracted with dichloromethane (5 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude yellow oil. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/ethyl acetate) to provide the product as a light yellow oil (0.1725 g, 76%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.60 (d, 1H); 7.50-7.10 (m, 18H); 6.90 (s, 1H); 5.27 (d, $J = 12.2$ Hz, 1H); 5.17 (d, $J = 12.2$ Hz, 1H); 3.84 (d, 2H); 3.53 (d, 2H); 3.41-3.28 (m, 2H); 2.91-2.83 (m, 2H); 2.30-2.15 (m, 1H); 1.90-1.75 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.2, 172.2, 139.4, 139.3, 136.4, 135.9, 128.9, 128.9, 128.5, 128.4, 128.2, 127.3, 127.0, 122.0, 119.3, 118.6, 112.8, 111.3, 66.1, 60.3, 54.6, 54.5, 51.1, 49.1, 39.8, 39.7, 33.9, 33.1, 25.6, 25.4, 25.3, 25.2, 24.9, 24.6.

(S)-1-(2-(1H-indol-3-yl)ethyl)-3-(dibenzylamino)piperidine-2,6-dione (81)

To a solution of amido-ester 79 (98.3 mg, 0.175 mmol) was dissolved in dry THF (5 mL) under an argon atmosphere at 0 °C. To this solution was added LAH (0.01 g, 0.26 mmol). The mixture was stirred vigorously at 0 °C. Upon completion monitored by TLC (2 hours). The reaction was quenched with drop-wise saturated sodium bicarbonate solution (5 mL). Water (5 mL) was added and the mixture was extracted with ethyl acetate (6 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude yellow oil. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/ethyl acetate) to provide the product as a light yellow oil (0.0424 g, 54%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.10 (s, 1H); 7.80 (d, 1H); 7.48-7.19 (m, 11H); 7.14 (m, 1H); 7.10 (m, 1H); 7.02 (d, 1H); 4.13 (m, 1H); 3.99 (m, 1H); 3.84 (d, 2H); 3.54 (d, 2H); 3.39 (m, 1H); 3.11-2.91 (m, 2H); 2.73 (m, 1H); 2.35 (m, 1H); 2.10 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.2, 171.8, 139.7, 139.4, 136.1, 128.8, 128.5, 128.3,
127.7, 127.5, 127.1, 122.2, 122.0, 119.4, 119.0, 114.4, 112.8, 111.0, 66.1, 60.6, 59.2, 54.8, 54.6, 48.1, 40.5, 33.5, 33.0, 32.2, 29.6.

(S)-1-(2-(1H-indol-3-yl)ethyl)-3-(dibenzylamino)-6-hydroxypiperidin-2-one (78)

To this solution of imide 81 (72 mg, 0.16 mmol) was dissolved in dry toluene (4 mL) under an argon atmosphere at -78 °C. To this solution was added DIBALH (1.60 mL, 1.0M in toluene, 1.60 mmol). The reaction was allowed to warm to -20 °C and stirred vigorously. This procedure was repeated twice with 1.6 mL and 1.6 mL of DIBALH (1.0M in toluene), respectively. Upon completion monitored by TLC (45 minutes), the reaction was quenched with drop-wise saturated potassium sodium tartrate solution (5 mL). The mixture was stirred at room temperature for 45 minutes. The mixture was extracted with ethyl acetate (6 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude yellow oil (61.56 mg, 85%).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.30 (brs, 1H); 7.70 (d, 1H); 7.50-7.13 (m, 12H); 7.13-7.03 (m, 1H); 7.00 (s, 1H); 4.67 (t, 1H); 4.00 (d, 2H); 3.94-3.70 (m, 3H); 3.64 (d, 2H); 3.38-3.22 (m, 1H); 3.17-3.02 (m, 2H); 2.20-2.00 (m, 2H); 2.00-1.71 (m, 2H).

(3S,12bR)-3-(dibenzylamino)-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one (77a)

Hydroxylactam 78 (141.80 mg, 0.31 mmol) was dissolved in dry dichloromethane (20 mL) under an argon atmosphere at 0 °C. To this solution was
added TMSOTf (0.10 mL, 0.63 mmol) via syringe. The mixture was stirred at 0 °C for 3 hours. The reaction was quenched with drop-wise saturated sodium bicarbonate solution (20 mL). The mixture was extracted with dichloromethane (5 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude yellow oil. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/ethyl acetate) to give 2 diastereomers of the indoloquinolizidinone product 77a and 77b (99.70 mg, 2.3:1, 74% combined yield).

1H NMR (300 MHz, CDCl3) δ 7.80 (s, 1H); 7.50 (d, 1H); 7.42 (m, 13H); 5.03 (dd, J = 12.0 Hz, J = 3.2 Hz, 1H); 4.75 (s, 1H); 4.04 (d, J = 13.9 Hz, 2H); 3.65 (d, J = 13.9 Hz, 2H); 3.41 (dd, J = 10.1 Hz, J = 6.8 Hz, 1H); 3.07-2.82 (m, 2H); 2.73 (d, J = 12.0 Hz, 1H); 2.30-2.10 (m, 2H); 2.00-1.77 (m, 1H).

![Image of 77b](image)

(3S,12bS)-3-(dibenzylamino)-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one (77b)

1H NMR (300 MHz, CDCl3) δ 7.80 (s, 1H); 7.45 (d, 1H); 7.40-7.02 (m, 13H); 5.22 (m, J = 16.0 Hz, J = 8.0 Hz 1H); 4.70 (d, J = 8.0 Hz, 1H); 4.15 (d, J = 14.0 Hz, 2H); 3.80 (d, J = 14.0 Hz, 2H); 3.39 (dd, J = 11.6 Hz, J = 6.3 Hz, 1H); 2.94-2.70 (m, 3H); 2.40 (m, J = 13.2 Hz, J = 3.5 Hz, 1H); 2.20-2.02 (m, 1H); 2.06-1.91 (m, 1H); 1.80-1.60 (m, 1H).
N-Boc-dibenzylaminoindoloquinolizidinone (82)

Tetracyclic indoloquinolizidinone 77a (45.0 mg, 0.103 mmol) was dissolved in dry dichloromethane (3 mL) under an argon atmosphere at 0 °C. To this solution was added di-tert-butyldicarbonate (112 mg in 1 mL CH₂Cl₂, 0.515 mmol), triethyl amine (72 μL, 0.515 mmol) and DMAP (1.3 mg, 0.0103 mmol). The mixture was stirred vigorously at room temperature for 6 hours. Water (3 mL) and dichloromethane (3mL) were added and the mixture was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by flash chromatography (silica gel, 10:1 hexane/ethyl acetate) to provide N-Boc-dibenzylaminoindoloquinolizidinone (55.0 mg, 100%).

1H NMR (300 MHz, CDCl₃) δ 8.03 (d, J = 8.0 Hz, 1H); 7.50-7.10 (m, 13H); 5.20 (d, J = 11.7 Hz, 1H); 5.08 (d, J = 10.5 Hz, 1H); 4.10 (m, J = 13.9 Hz, 2H); 3.83 (d, J = 13.8 Hz, 2H); 3.39 (dd, J = 11.3 Hz, J = 7.6 Hz, 1H); 2.90-2.69 (m, 3H); 2.59 (d, J = 13.2 Hz, 1H); 2.15-1.90 (m, 3H); 1.65 (s, 9H); 13C NMR (75 MHz, CDCl₃) δ 170.9, 150.2, 140.8, 136.8, 135.2, 128.7, 128.5, 128.2, 127.2, 126.8, 124.6, 123.0, 118.3, 115.5, 84.3, 58.7, 56.2, 55.4, 38.7, 29.7, 28.2, 26.4, 21.6.

(S)-tert-Butyl 1,6,7,12b-tetrahydro-4-oxoindolo[2,3-a]quinoline-12(4H)-carboxylate (76)

N-Boc-dibenzylaminoindoloquinolizidinone 82 (48.0 mg, 0.0901 mmol) was dissolved in dry dichloromethane (5 mL) under an argon atmosphere at 0 °C. To this solution was added meta-Chloroperoxybenzoic acid (33.3 mg, 0.135 mmol) at 0 °C.
The mixture was stirred vigorously at room temperature for 30 minutes. The reaction was quenched with drop-wise saturated sodium bicarbonate solution (5 mL). The mixture was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/ethyl acetate) to provide tetracyclic enamide (18.0 mg, 59%) as a colorless oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 7.5$ Hz, 1H); 7.50 (dd, $J = 7.5$ Hz, $J = 1.6$ Hz, 1H); 7.46-7.23 (m, 2H); 6.72 (ddd, $J = 9.1$ Hz, $J = 6.7$ Hz, $J = 2.0$ Hz, 1H); 6.13 (dd, $J = 9.7$ Hz, $J = 2.9$ Hz, 1H); 5.28 (d, $J = 11.7$ Hz, 1H); 5.05 (dd, $J = 12.7$ Hz, $J = 3.4$ Hz, 1H); 3.06 (ddd, $J = 17.1$ Hz, $J = 6.5$ Hz, $J = 3.5$ Hz, 1H); 2.96-2.71 (m, 2H); 2.28-2.12 (m, 1H); 1.70 (s, 9H); 1.90-1.40 (buried m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 164.9, 150.1, 139.1, 136.6, 134.1, 128.6, 125.5, 124.7, 123.1, 118.4, 118.0, 115.8, 84.5, 53.3, 37.6, 31.7, 28.2, 21.6.
REFERENCES


Appendix
### 1H NMR and 13C NMR spectra of compounds

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Compound 81 $^1$H NMR spectrum.........................................................69

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Compound 76 $^1$H NMR spectrum.............................................76

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\(^1\)H NMR spectrum of compound 48
$^1$H NMR spectrum of compound 49
$^{13}$C NMR spectrum of compound 49
$^1$H NMR spectrum of compound 50
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# Biography

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**Education**

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