AN ABSTRACT OF THE DISSERTATION OF

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Title: Tandem Intramolecular Photocycloaddition-retro-Mannich Fragmentation as a Route to Indole and Oxindole

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James D. White

Irradiation of a tryptamine linked through its side-chain nitrogen to an alkylidene malonate residue results in an intramolecular [2 + 2] cycloaddition to the indole 2,3-double bond. The resultant cyclobutane undergoes spontaneous retro-Mannich fission to produce a spiro[indoline-3,3-pyrrolenine] with relative configuration defined by the orientation of substituents in the transient cyclobutane. The novel tandem intramolecular photocycloaddition-retro-Mannich (TIPCARM) sequence leads to a spiropyrrolidine which is poised to undergo a second retro-Mannich fragmentation [TIPCA(RM)$_2$] that expels the malonate unit present in the photo substrate and generates transiently an indolenine. The indolenine undergoes rearrangement to a β-carboline which can undergo further rearrangement under oxidizing conditions to an oxindole. Three oxindole natural products, coerulescine, horsfiline and elacomine, were synthesized using this strategy.

The TIPCARM strategy was extended to an approach that would encompass the *Vinca* alkaloids vindorosine and minovine. In this case, the TIPCARM sequence was followed by an intramolecular cyclization that provided tetracyclic ketone **5.86** containing rings A, B, C and D of vindorosine. A tetracyclic intermediate was synthesized which could also provided access to the *Vinca* alkaloid minovine.

Tandem Intramolecular Photocycloaddition-
retro-Mannich Fragmentation as a Route to Indole and Oxindole

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APPROVED:

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Major Professor, representing Chemistry

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Chair of the Department of Chemistry

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Dean of the Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

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Yang Li, Author

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Chapter 1. Introduction

1.1. Introduction to Organic Photochemistry

Photochemistry, a sub-discipline of chemistry, is the study of chemical reactions that proceed with the absorption of light by atoms or molecules. Photochemistry has existed since the birth of the universe. Since ancient times, the connection between light and the quality of life has been recognized by humans as evidenced by the fact that the sun has been an object of worship by almost every civilization. However, only during the second half of the 20th century was photochemistry recognized as an independent field of science, and during the third quarter of the century (1950-1975) the first generation of photochemists established the basic "rules" and developed a detailed understanding of the subject. The latter includes the primary excited states encountered in both organic and inorganic molecules, the patterns of reactivity expected from these states, and the fundamental photochemical reaction mechanisms expected for various functional groups. The significant advances that were made during this period were driven by a number of factors including theoretical developments such as the theories of radiationless transitions and computational chemistry. In addition, remarkable progress was made in experimental techniques of photochemistry. By the late

1970s, most of the basic principles of photochemistry had been established and the field could then be characterized as a mature science.

Photochemistry, as an interdisciplinary science, is linked to many other fields such as photophysics and quantum mechanics as well as aspects of physical chemistry and organic chemistry. For modern organic chemistry, photochemistry is a highly valued experimental tool that has found use in a variety of synthetic applications and industrial processes. In the early fifties and sixties of the last century, numerous light-induced reactions were discovered, modified and applied to synthetic problems. A milestone development in the field was the discovery of the Woodward-Hoffmann rules,[1] which explained that the absorption of a photon by a reactant molecule could permit a "forbidden" reaction to occur. The Woodward-Hoffmann rules implied that a reaction may occur not just by raising a molecule above the thermal activation barrier, but also by changing the symmetry of the molecule's electronic configuration. The latter enables an otherwise inaccessible reaction pathway to occur at room temperature or below. As a result of these discoveries and developments, many useful reactions have been uncovered. The [2+2] photocycloaddition process in which two alkenes react to form a cyclobutane is one of them.

1.2. Introduction to [2+2] Photocycloaddition

Photocycloaddition was first discovered in 1908 by Ciamician when he observed that exposure of carvone **1.1** to "Italian sunlight" for one year gave carvone-camphor **1.2** (Scheme 1.1).[2] Photocycloaddition was investigated intensively in the 1950s with emphasis on the photochemical [2+2] cycloaddition of enones to alkenes. In this context, the structure originally proposed for carvone-camphor by Ciamician was confirmed by Büchi and Goldman in 1957.[3]

1.1   **1.2**
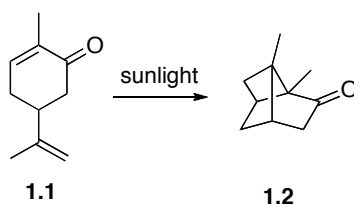
Scheme 1.1. First example of a [2+2] photocycloaddition reaction

Major advances have been achieved since the 1960's in terms of synthetic applications, experimental techniques, and mechanistic understanding of photocycloaddition.[4] In 1962, Eaton and co-workers discovered that the photocyclo-dimerization of 2-cyclopentenone yields a mixture of head-to-head (**1.4**) and head-to-tail (**1.5**) products.[5] (Scheme 1.2).

1.3   **1.4**   **1.5**
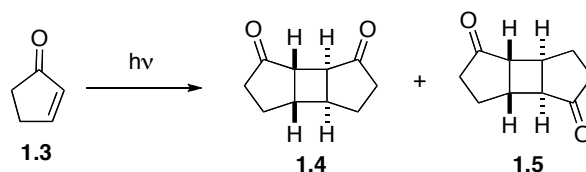
Scheme 1.2. Photocyclodimerization of 2-cyclopentenone **1.3**

In 1964, Corey and co-workers observed that the photoaddition of 2-cyclohexenone (**1.6**) to simple alkenes such as isobutylene (**1.7**) often provided both trans-fused and cis-fused cycloadducts, eg **1.8** and **1.9,** as well as head-to-head and head-to-tail products, eg **1.10** (Scheme 1.3).[6] This distribution of products suggested the intermediacy of 1,4-diradicals in these reactions.

(*E*) and (*Z*) caryophyllenes
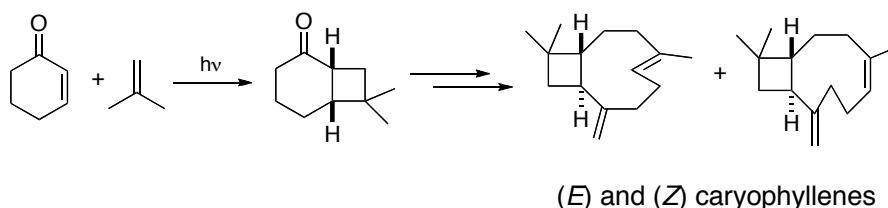
Scheme 1.3. Photoaddition of 2-cyclohexenone to isobutylene

In 1969, De Mayo reported that enone photocycloaddition to alkenes proceeds exclusively via an enone triplet excited state.[7] On the basis of earlier spectroscopic studies of steroidal enones[8] as well as energy calculations,[9] De Mayo concluded that the initial excitation of the enone is generally via a n, π* singlet state followed by intersystem crossing to either a n, π* or π, π* triplet state.[10] This conclusion has been confirmed by studies due to Schuster and co-workers using transient absorption spectroscopy[11] and time-resolved photo-acoustic calorimetry.[12] Based on the work of Corey, De Mayo and others, a general mechanism for [2+2] photocycloaddition reactions begins with photoexcitation of a conjugated system to a singlet excited state. The

excited singlet state is usually very short lived and either decays by reaction to the ground state singlet or by intersystem crossing to a triplet state. At this point, the excited triplet forms an exciplex with the ground state alkene and then generates a triplet diradical in which one σ bond has formed. Spin inversion to a singlet diradical allows formation of the second σ bond and final closure to a cyclobutane (Scheme 1.4).[13]

singlet   triplet   triplet exciplex

singlet diradical   triplet diradical
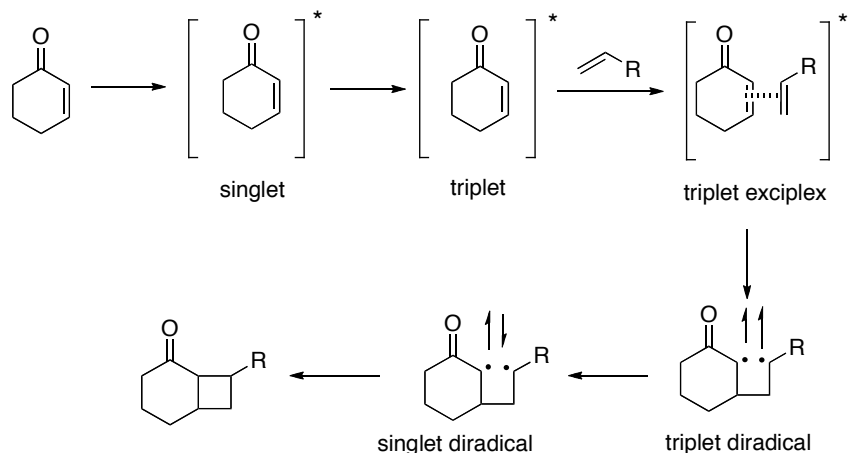
Scheme 1.4. Mechanism of [2+2] photocycloaddition of enones with alkenes

With elucidation of the mechanism of [2+2] photocycloaddition of conjugated enones, the reaction attracted intense interest, particularly in its application to the synthesis of natural products. Corey's synthesis of (*E*) and (*Z*) caryophyllenes, **1.12** and **1.13**, was among the first milestones in this area.

In 1964, Corey reported his landmark synthesis of caryophyllenes (Scheme 1.5)[6] using a strategy that is regarded as a pioneering application of [2+2] photocycloaddition to the total synthesis of natural products. Inter- as well as

intramolecular [2+2] photocycloaddition of conjugated carbonyl systems has since become part of the standard repertoire of synthetic organic chemistry for constructing cyclobutanes, and this process is now among the most widely used photochemical reactions in synthetic organic chemistry.[14] Furthermore, the 26-28 kcal/mol of strain energy present in the formed cyclobutane enables this structure to initiate ring expansions, fragmentations and other reactions that create new and interesting cyclic and acyclic structures. Two examples of this property of cyclobutanes are illustrated below.
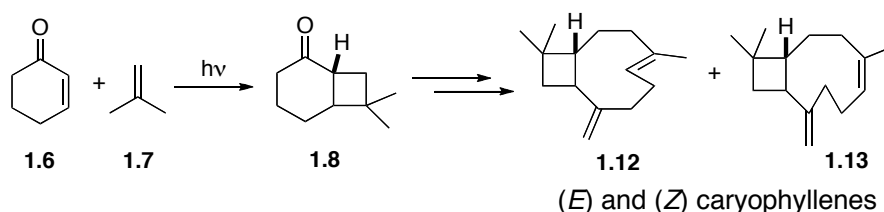
**Scheme 1.5.** Corey's application of [2+2] photocycloaddition to the synthesis of caryophyllenes

In 1986, Winkler and Hey reported the synthesis of the trans bicyclo[5.3.1]-undecane ring system **1.16**, an important structural feature of the taxane diterpenes (Scheme 1.6).[15] Irradiation of photosubstrate **1.14** produced photo-adduct **1.15**, which was directly submitted to acidic conditions to provide **1.16** via a fragmentation sequence that ruptures the cyclobutane of **1.15**.
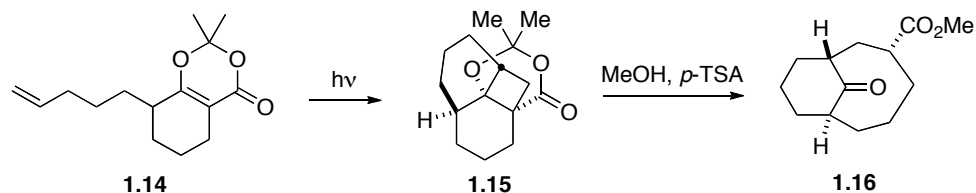
Scheme 1.6. Winkler's synthesis of a trans bicyclo[5.3.1]undecane ring system

The same strategy was applied by Winkler to a total synthesis of (±)-ingenol (**1.20**).[16] Intramolecular photocycloaddition of allylic chloride **1.17** proceeded in 60% yield to give the desired photoadduct **1.18** which underwent fragmentation with methanolic potassium carbonate to yield tricyclic ketone **1.19**. The latter provided the framework for a completed synthesis of ingenol (**1.20**) (Scheme 1.7)
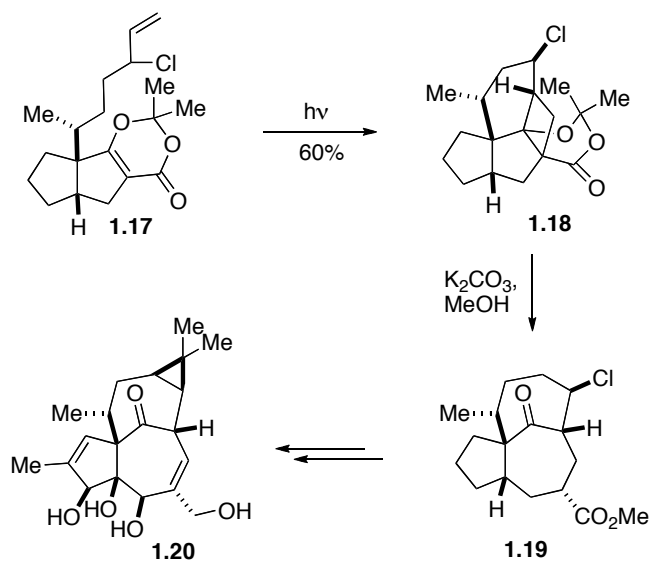
Scheme. 1.7. Winkler's synthesis of 1,9 en route to (±)-ingenol (**1.20**)

The concept of a [2 + 2] photoaddition-cycloreversion strategy for assembling carbocyclic structures was recognized as a powerful tool for medium-ring synthesis by Schaumann,[17] and in 2000 White and co-workers reported an enantiospecific synthesis of (+)-byssochlamic acid (**1.28**) using a tandem photoaddition-cycloreversion strategy.[18] White's approach to the 1,5-cyclonona-diene nucleus of **1.28** hinged on preparation of photosubstrate **1.21** which upon irradiation yielded cyclobutanes **1.22** and **1.23.** Under the reaction conditions, partial cycloreversion of **1.22** and **1.23** to **1.24** and **1.25** took place, and the fragmentation was completed when the mixture of **1.22** and **1.23** was heated in toluene. Hydrolysis of the pair of γ-lactones, oxidation of the resultant diol to tetracarboxylic acids **1.26** and **1.27,** and final treatment with hydrochloric acid to effect dehydration provided natural byssochlamic acid (+)-**1.28** and its trans isomer (+)-**1.29** (Scheme 1.8).
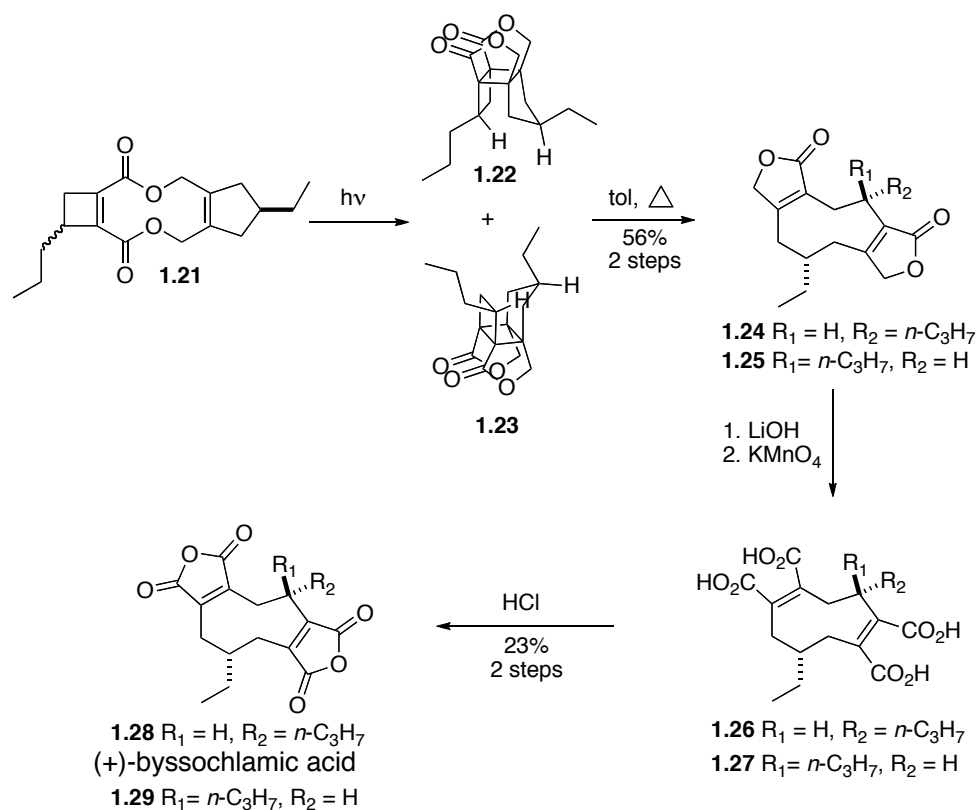
Scheme 1.8. White's enantioselective total synthesis of *cis* and *trans* byssochlamic acids (**1.28** and **1.29**)

Photocycloaddition can form not only new C-C bonds but also C-O bonds. In 1909, Paternò published the first photocycloaddition of an aromatic carbonyl compound to an alkene,[19] an experiment that was repeated by Büchi and co-workers in the mid-1950's to confirm the oxetane constitution of the photogenerated product (Scheme 1.9).[20] The photochemical cycloaddition of a carbonyl compound **1.30** to an alkene **1.31** to form an oxetane **1.32** is now known as the Paternò-Büchi reaction. This reaction can sometimes interfere with a photochemical reaction sensitized by a ketone such as benzophenone

where oxetane formation with an alkene supersedes cyclobutane synthesis.

1.30   1.31   1.32
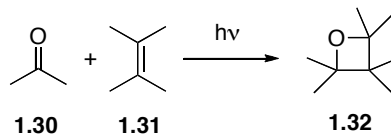
Scheme 1.9. Paternò-Büchi Reaction

In 2000, Rawal reported the application of a unique intramolecular Paternò-
Büchi reaction/fragmentation sequence to an elegant synthesis of the angular
triquinane (±)-oxosilphiperfol-6-ene (**1.35**, Scheme 1.10).[21] The photosubstrate
1.33 was irradiated with Corex-filtered light to obtain the strained cage-like
product **1.34**. Reductive cleavage of the oxetane ring with lithium
dibutylphenylide yielded an allylic alcohol, which was oxidized to the desired
α,β-unsaturated ketone **1.35** with pyridinium dichromate.

1.33   1.34   1.35
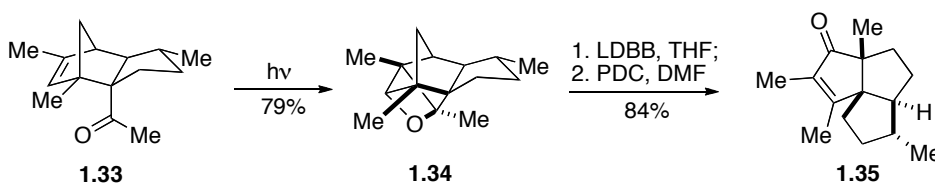
Scheme 1.10. Rawal 's synthesis of the angular triquinane (±)-oxosilphiperfol-
6-ene

1.3. Tandem Intramolecular Photocycloaddition-retro-Mannich

(TIPCARM) Fragmentation

Photochemical [2+2] cycloaddition of an α,β-unsaturated carbonyl compound to an alkene followed by fragmentation of the resultant cyclobutane is a valuable strategy for building structural complexity from simple subunits.[22] The success of the method hinges not only on release of the >25 kcal/mol of strain energy embedded in the cyclobutane but also on deployment of functional groups around the four-membered ring that steers rupture in a desired direction.[21, 23] De Mayo was the first to recognize the utility of this principle in his elegant construction of 1,5-dicarbonyl systems by irradiating an enolic β-diketone (**1.36**, X = O, Scheme 1.11) in the presence of an alkene.[24] Retro-aldol cleavage of the resultant cyclobutane **1.37** led via **1.38** to diketone **1.39**. Numerous applications of this concept to the synthesis of novel substances have evolved from De Mayo's pioneering study.[25] Vinylogous amides (enaminones, **1.36**, X = NH, Scheme 3) undergo photochemical cycloaddition to alkenes in a manner analogous to that of enolic β-diketones.[26] In this case, rupture of the cyclobutane can occur via retro-Mannich cleavage to yield a 1,5-imino ketone.
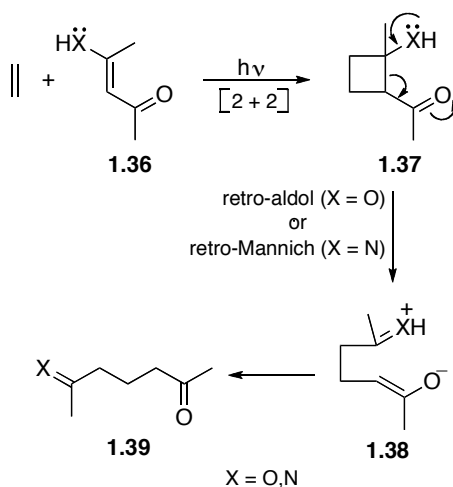
Scheme 1.11. Tandem photocycloaddition-retro-aldol/retro-Mannich fragmentation

The retro-Mannich reaction illustrated in scheme 1.12 is the reverse of a process first observed by Tollens and Von Marle in 1903 in which reaction of acetophenone with formaldehyde and ammonium chloride led to formation of a tertiary amine.[27] Later, C. Mannich recognized the generality of this reaction.[28] The condensation of an enolizable carbonyl (usually an aldehyde or ketone) with a primary or secondary amine (or ammonia) and a nonenolizable aldehyde or ketone to afford a β-amino carbonyl product is now known as the Mannich reaction (Scheme 1.12). In mechanistic terms, the initial step in a Mannich reaction is condensation of an amine **1.41** with the non-enolizable carbonyl **1.40** to form an iminium species **1.42**. This electrophile then reacts with the enolizable carbonyl compound **1.43** to produce **1.44** in a process that has formal similarity to an aldol condensation.
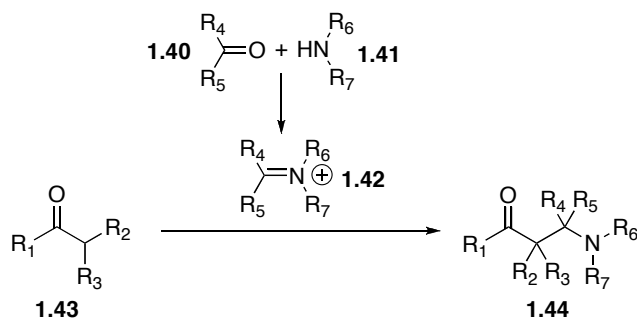
Scheme 1.12. The Mannich reaction

The intramolecular variant of the tandem photocycloaddition-retro-Mannich fragmentation (which we abbreviate as "TIPCARM") was first investigated by Schell.[29] Irradiation of vinylogous amide **1.45** in *tert*-butyl alcohol led to a single material which was recognized as amino ketone **1.48**. Thus, intramolecular [2+2] cycloaddition of **1.45** had occurred to provide cyclobutane **1.46** which spontaneously unraveled via a retro-Mannich fragmentation to provide **1.47** and then imino ketone **1.48** after proton transfer (Scheme 1.13).
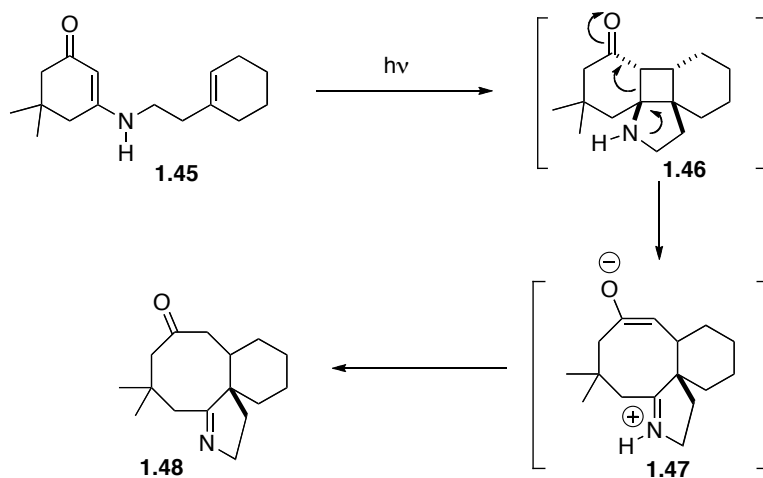
Scheme 1.13. Schell's intramolecular TIPCARM of vinylogous amide **1.45**

In 1998, Winkler reported the total synthesis of manzamine A using a TIPCARM strategy.[30] Photoaddition and retro-Mannich fragmentation of **1.49** led via cyclobutane **1.50** to **1.51** which underwent closure of the ketoiminium enolate **1.51** to aminal **1.52**. The latter was subsequently converted in several steps to manzamine A (**1.53**) (Scheme 1.14).
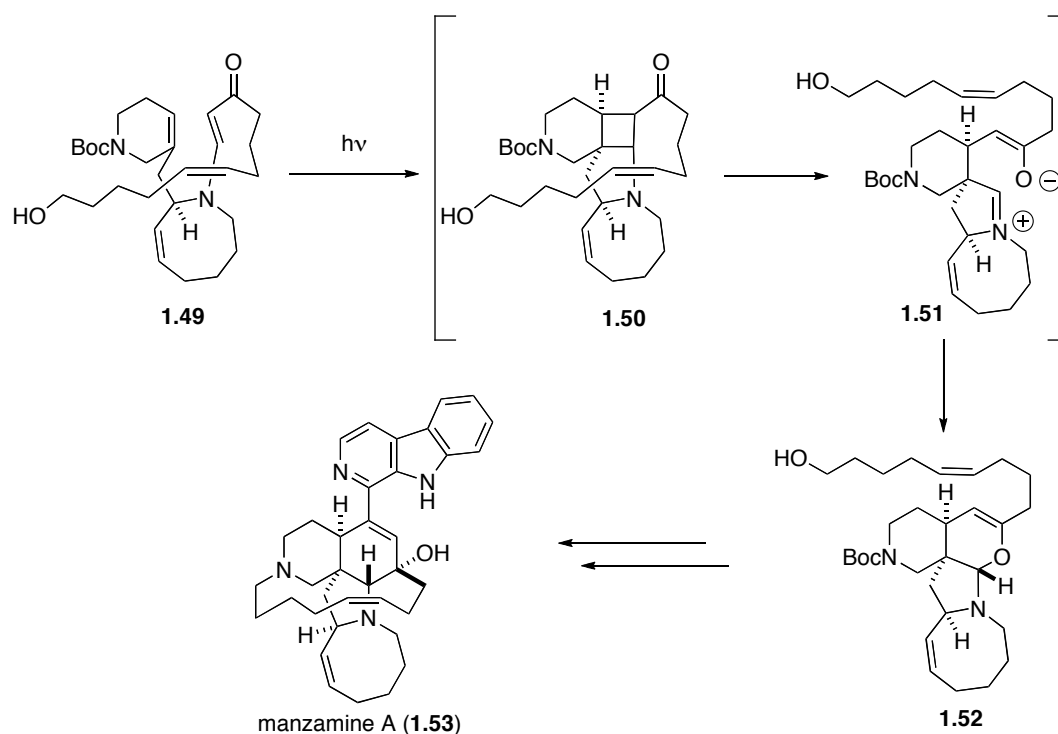
Scheme 1.15. Winkler's synthesis of **1.52** en route to manzamine A (**1.53**) employing a TIPCARM approach

Winkler's work as well as that of others illustrates the power of the TIPCARM principle as a means for constructing complex ring systems in a relatively few steps. The precedents cited above provided the inspiration that led to the genesis of the projects described in the following chapters.

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Chapter 2. Synthesis of Oxindole Alkaloids Coerulescine

and Horsfiline

2.1. Introduction to Oxindole Alkaloids

The spiro[pyrrolidine-3,3'-oxindole] ring system **2.1** is found at the core of a number of alkaloids which possess significant biological activity. The first oxindole alkaloids were discovered in the roots of *Gelsemium sempervirens* (wild yellow jasmine). Additional oxindoles were isolated from *Aspidosperma, Mitragyna, Ourouparia, Rauwolfia* and *Vinca* species.[31] Based on a structural template derived from tryptamine, most of these alkaloids are characterized by a spiro ring fusion at the 3-position of the oxindole core, with varying degrees of substitution around the pyrrolidine and oxindole rings.

2.1
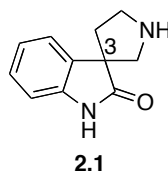
Figure 2.1. Structure of the spiro[pyrrolidine-3,3'-oxindole] ring system

The spiro architecture of **2.1** is associated with significant biological activity and renders the spiro[pyrrolidine-3,3'-oxindole] alkaloids important synthetic targets. Selected examples of alkaloids containing the spiro[pyrrolidine-3,3'-oxindole] nucleus are shown in Figure 1. Alstonisine (**2.4**), which was the first

oxindole alkaloid to be isolated, originated from *Alstonia muelleriana,*[32] and was studied by LeQuesne and Granick.[33] In 1991, the relatively unsubstituted spirooxindole (-)-horsfiline (**2.3**) was isolated from the Malaysian medicinal plant *Horsfildea superba* Warb[34] and has proven to be a popular synthetic target.[32b] The related compound coerulescine (**2.2**) from the blue canary grass *Phalaris coerulescens*[35] possesses an even simpler structure; its synthesis is often reported together with that of horsfiline. chitosenine (**2.5**), another structurally interesting oxindole natural product, exhibits short-lived inhibition of ganglionic transmission in vivo in rats and rabbits.[36] Strychnofoline (**2.6**) inhibits mitosis in a number of cell lines, including mouse melanoma B16 and Hepatom HW165.[37] The oxindoles spirotryprostatins A and B (**2.7A** and **2.7B**) which were isolated from the fermentation broth of *Aspergillus fumigatus* completely inhibit the G2/M progression of mammalian tsFT210 cells at concentrations in excess of 12.5 mg/mL[38] (Figure 2.2). A variety of strategies have been used to synthesize these and other oxindole alkaloids.[39] This chapter will review approaches employed by other research groups to two members of the oxindole family, coerulescine (**2.2**) and horsfiline (**2.3**).

R = H, Coerulescine (**2.2**)
R = OMe, Horsfiline (**2.3**)

Alstonisine (**2.4**)

Chitosenine (**2.5**)

Strychnofoline (**2.6**)

Spirotryprostatins A (**2.7 A**)

Spirotryprostatins B (**2.7 B**)
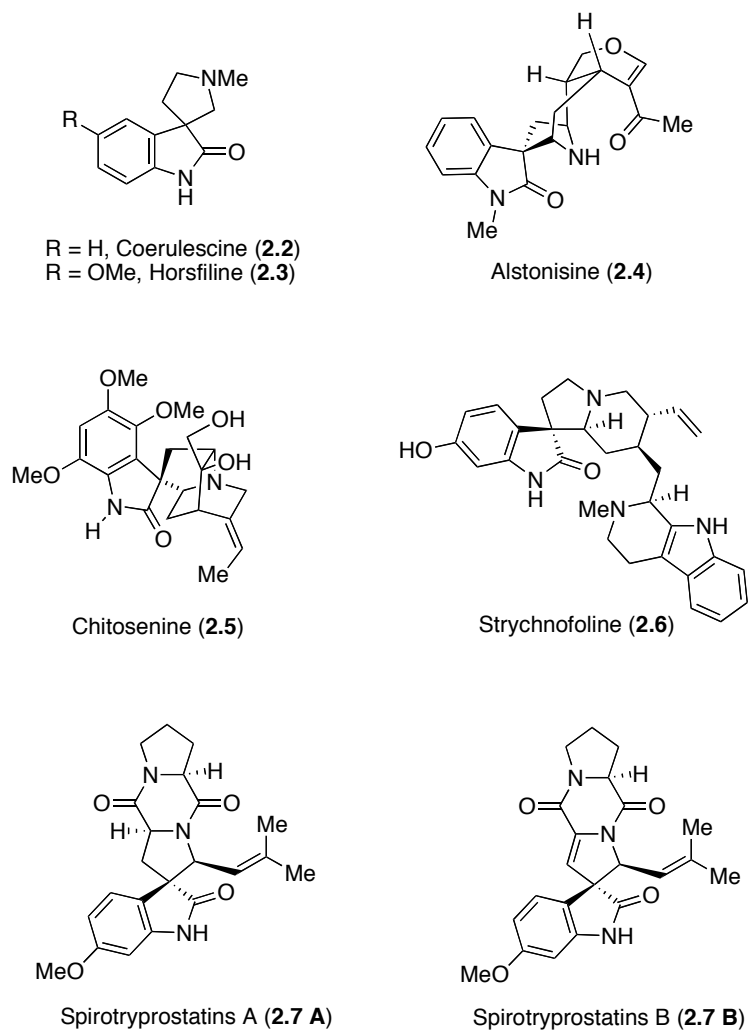
Figure 2.2. Representative spiro[pyrrolidine-3,3'-oxindole] natural products

2.2. Synthesis of Coerulescine and Horsfiline

Coerulescine (**2.2**) and horsfiline (**2.3**) represent the simplest members of the oxindole family of alkaloids and have been popular platforms for demonstrating the efficacy of new synthetic protocols. Several synthetic strategies have been developed for synthesis of the spiro[pyrrolidin-3,3'-oxindole] framework of these two alkaloids, both in racemic and enantiomeric forms. These strategies include oxidative rearrangement of a tetrahydro-β-carboline, Mannich reaction of a tryptamine-oxindole, ring expansion of spirocyclopropyl oxindoles, 1,3-dipolar cycloaddition, intramolecular radical cyclization, palladium catalyzed asymmetric allylic alkylation and palladium catalyzed coupling. Synthetic routes to horsfiline and coerulescine based on these strategies are summarized below.

2.2.1. Oxidative Rearrangement Sequences to Coerulescine and Horsfiline

A widely used approach for constructing the spirooxindole skeleton is the oxidative rearrangement of a tetrahydro-β-carboline which can be prepared from derivatives of tryptophan or tryptamine by a Pictet-Spengler reaction.[40] Treatment of a tetrahydro-β-carboline with an oxidant in combination with a hydroxide source leads to a spirooxindole (Scheme 2.1).
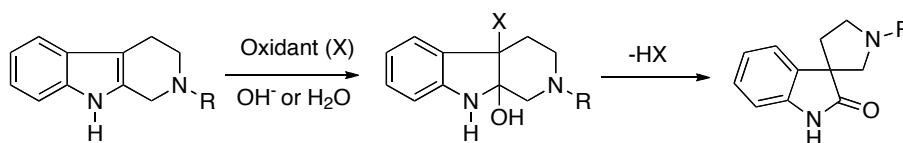
Scheme 2.1. An oxidative spiro rearrangement

A subsequent study by Taylor revealed that oxidative rearrangement of a tetrahydro-β-carboline can be achieved with tert-butyl hypochlorite followed by treatment with acetic acid.[41] In 1994, Borschberg and co-workers reported syntheses of (+)- and (-)-horsfiline (**2.3**) in which *N*-bromosuccinimide (NBS) was used as the oxidant instead of tert-butyl hypochlorite.[42] In his route to **2.3**, Borschberg observed that different substituents at the piperidine nitrogen atom of the β-carboline led to a significant preference for the formation of one oxindole diastereomer over the other in the rearrangement (Scheme 2.2). Starting from (S)-5-hydroxytryptophan (**2.8**), tetrahydro-β-carboline derivatives **2.9** and **2.10** were prepared by Pictet-Spengler cyclization and then subjected to oxidative rearrangement with *N*-bromosuccinimide. It was found that spirooxindole **2.11** was obtained in good yield from Boc derivative **2.9**, whereas stereoisomer **2.12** was the major product from *N*-methyl derivative **2.10**.
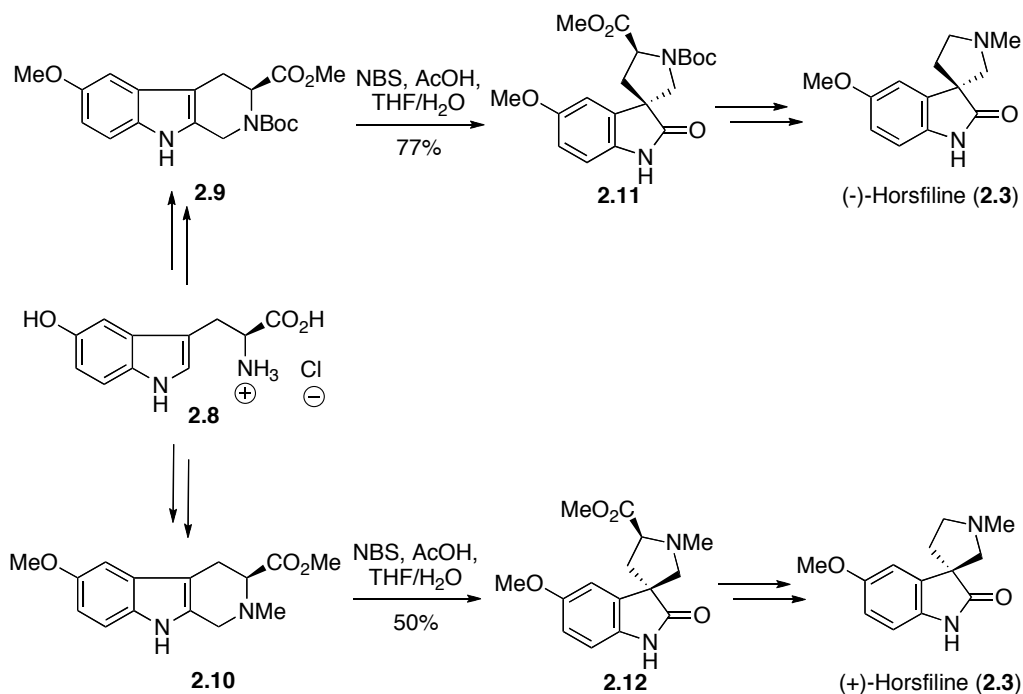
Scheme 2.2. Borschberg's synthesis of (+)- and (-)-horsfiline

The diastereoselectivity observed during oxidative rearrangement of the β-carboline precursors **2.9** and **2.10** may result from different conformations of the starting material. In the case of of **2.9**, the carbomethoxy group is axially oriented to avoid steric hindrance between the methyl ester and the tert-butyl carbonate, whereas in the protonated form **2.13** of **2.10**, the carbomethoxy group occupies an equatorial position. Maximum overlap of the relevant orbitals during the bromination step would result in either *cis* or *trans* bromoindolenines **2.15** or **2.18**, via **2.14** or **2.17**. Hydration followed by elimination of the resulting bromoindolines **2.16** and **2.19** leads to **2.11** and **2.12** (Scheme 2.3).
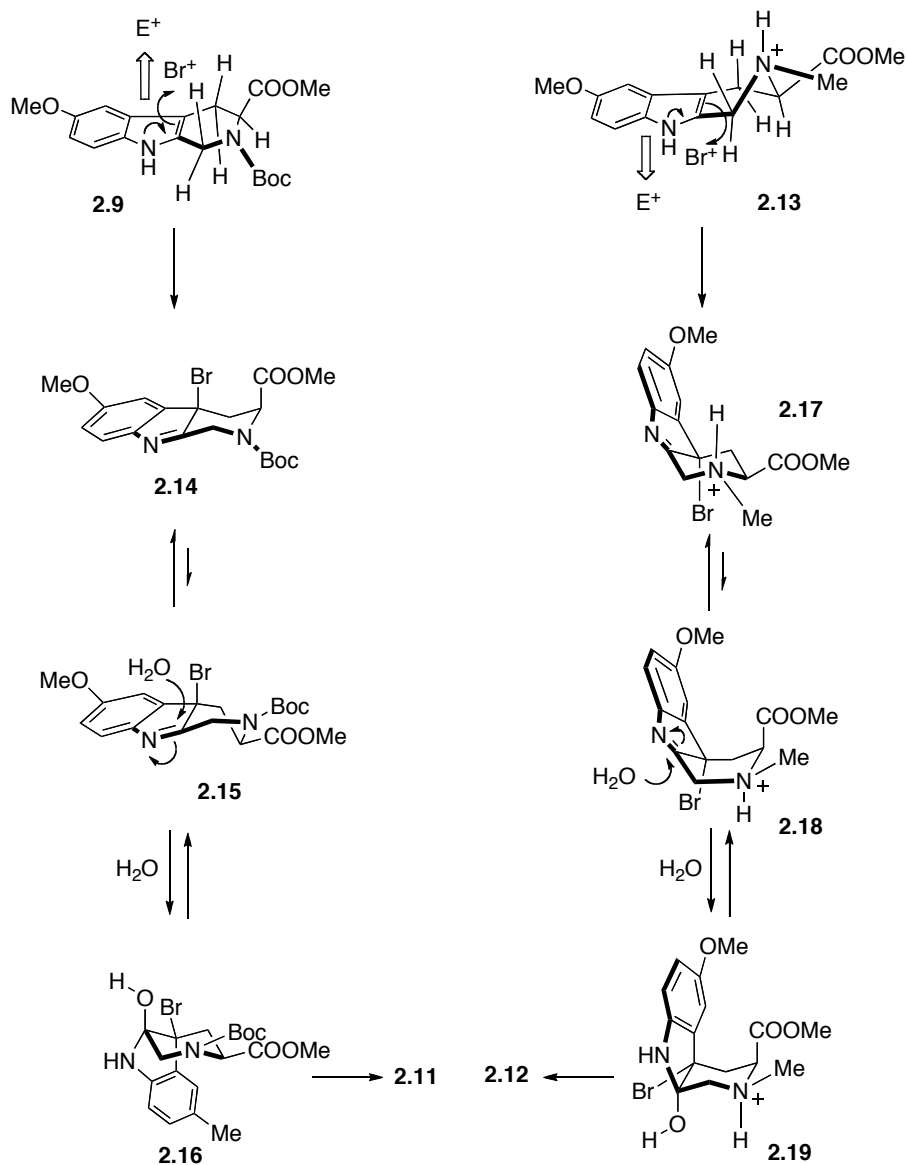
Scheme 2.3. Diastereoselectivity in the oxidative rearrangement of tetrahydro-β-carbolines **2.9** and **2.13**

In addition to halogenating agents such as *N*-bromosuccinimide, metal based oxidants have also been employed for the conversion of β-carbolines to spirooxindoles. In 2000, Somi and co-workers introduced sodium tungstate for the synthesis of (±)-coerulescine (**2.2**) from **2.20**.[43] First, *N*-hydroxytetrahydro-

β-carboline **2.21** was prepared from the hexahydro-β-carboline **2.20** by oxidation with a catalytic amount of sodium tungstate and urea-hydrogen peroxide as reoxidant. Subsequent treatment of **2.21** with aqueous hydrochloric acid in methanol provided the chloroindolenine **2.22**, which underwent rearrangement to oxindole **2.23.** Final *N*-methylation of **2.23** yielded (±)-coerulescine (Scheme 2.4).
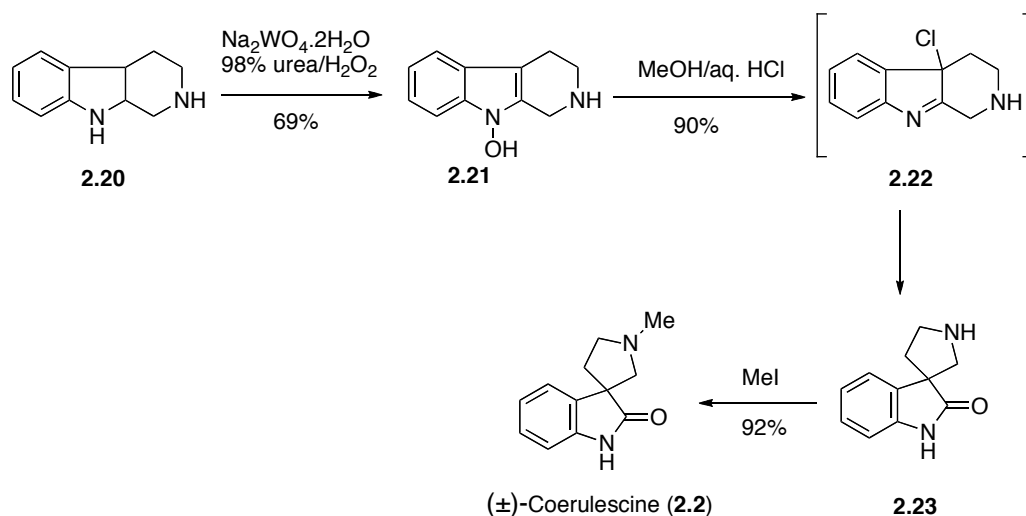
Scheme 2.4. Somi's synthesis of (±)-coerulescine

Other oxidants used to prepare spirooxindoles include lead tetraacetate[44] and osmium tetraoxide.[45]

2.2.2. Mannich Reaction Route to Horsfiline

In nature, oxindole alkaloids can occur as pairs of interconvertible isomers. Rychnophylline (**2.24**) and isorychnophylline (**2.25**) are examples of this phenomenon. This observation can be explained by an isomerization

mechanism wherein stereoisomers are equilibrated through a ring-opened form, eg **2.26**, that is accessed by a retro-Mannich reaction (Scheme 2.5).[46] The mechanism suggests that the spiro[pyrrolidine-3,3'-oxindole] core of these alkaloids could be obtained by an intramolecular forward Mannich reaction.
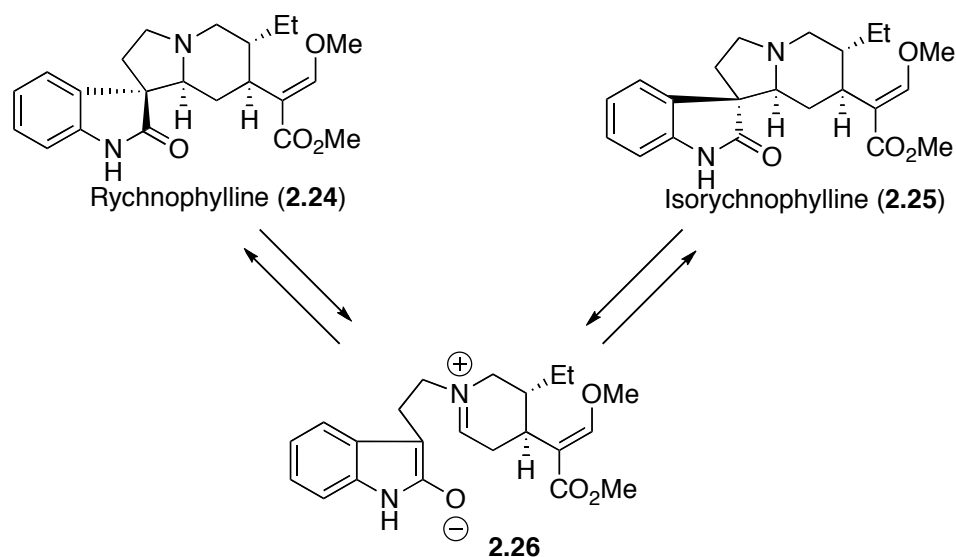
Scheme 2.5. Isomerization of rychnophylline (**2.24**) and isorychnophylline (**2.25**) through a Mannich /retro-Mannich sequence

Based on this idea, Laronze and co-workers achieved the synthesis of racemic horsfiline (**2.3**) in 1994 through an intramolecular Mannich reaction of tryptamine-oxindole **2.27** with formaldehyde (Scheme 2.6).[47]
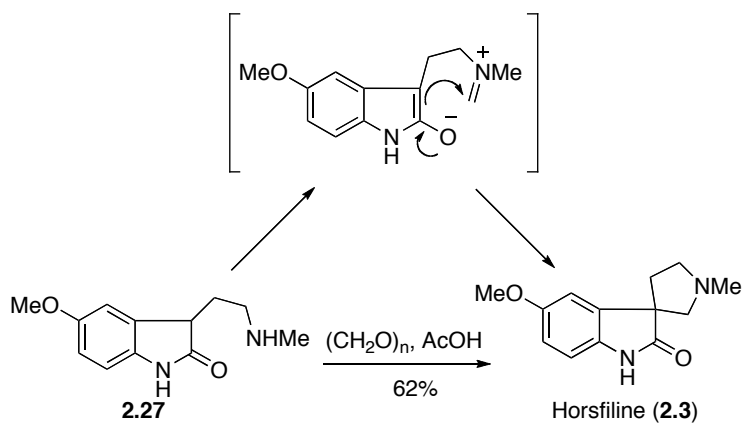
Scheme 2.6. Laronze's synthesis of (±)-horsfiline

2.2.3. Ring Expansion Route to Horsfiline

Carreira and co-workers developed a general method to access the pyrolidinylspirooxindole structure from a spirocyclopropyl oxindole.[48] The method can accommodate a variety of imine precursors to produce different spirooxindoles in good to excellent yield. The synthesis of racemic horsfiline (**2.3**) was executed using trimethyltriazinane (**2.31**) as the imine source in just five steps from **2.29** via **2.30** and **2.32**, and in 41% overall yield (Scheme 2.7).
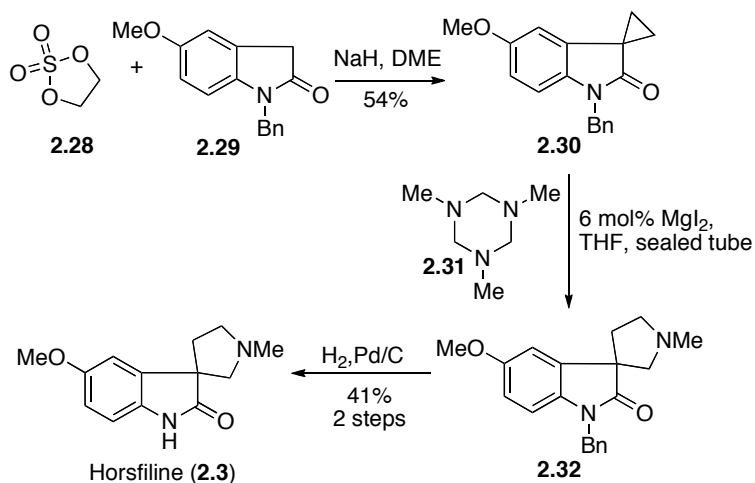
Scheme 2.7. Carreira's synthesis of (±)-horsfiline employing
a ring-expansion reaction

The magnesium iodide used in Carreira's route is believed to act as a Lewis acid, with iodide being the nucleophilic counterion to promote ring expansion. It was proposed that indole enolate **2.35** is the initial product of ring opening of **2.34** and that this is followed by enolate attack on the imine **2.33** with subsequent nucleophilic displacement of iodide from **2.37** to form the pyrrolidine ring of **2.38** (Scheme 2.8). An alternative mechanism involving direct ring opening of the cyclopropane **2.34** by the imine to form iminium ion **2.36** was considered less likely by the authors.
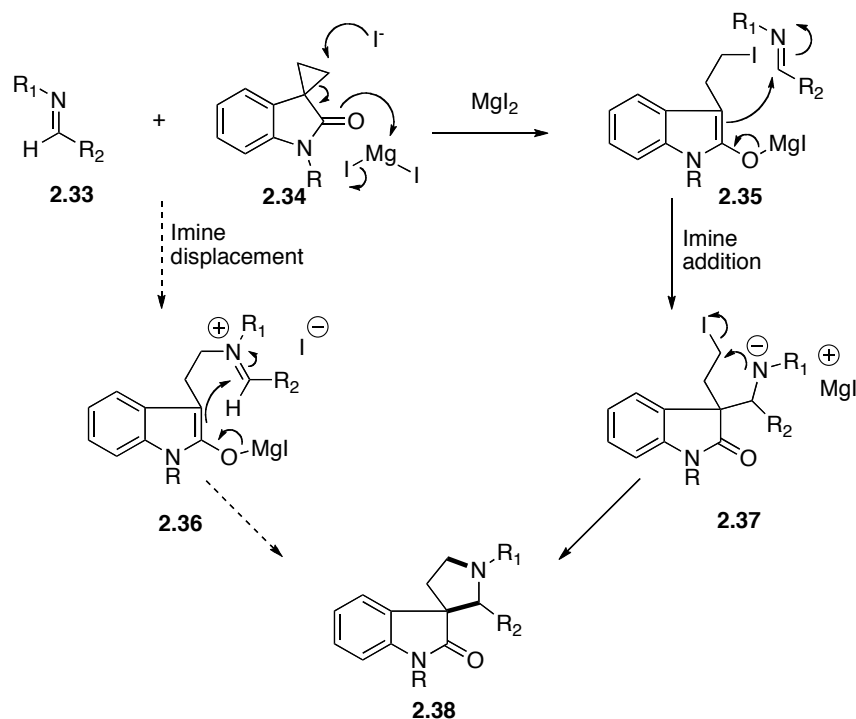
Scheme 2.8. Carreira's proposed pathway for magnesium iodide-catalyzed ring expansion of **2.34**

2.2.4. 1,3-Dipolar Cycloaddition Route to Horsfiline

Grigg was the first to use 1,3-dipolar cycloaddition to synthesize the spiro[pyrrolidine-3,3'-oxindole] skeleton,[49] and in 1996 Palmisano reported an asymmetric synthesis of (-)-horsfiline (**2.3**) using a 1,3-dipolar cycloaddition strategy. Dipolarophile **2.40** bearing a chiral auxiliary [R = (-)-menthyl] was obtained by Wittig olefination of 5-methoxyisatin (**2.39**) and its cycloaddition with the azomethine ylide **2.42**, prepared in situ from formaldehyde and sarcosine (**2.41**), yielded **2.43** (Scheme 2.9).[50]
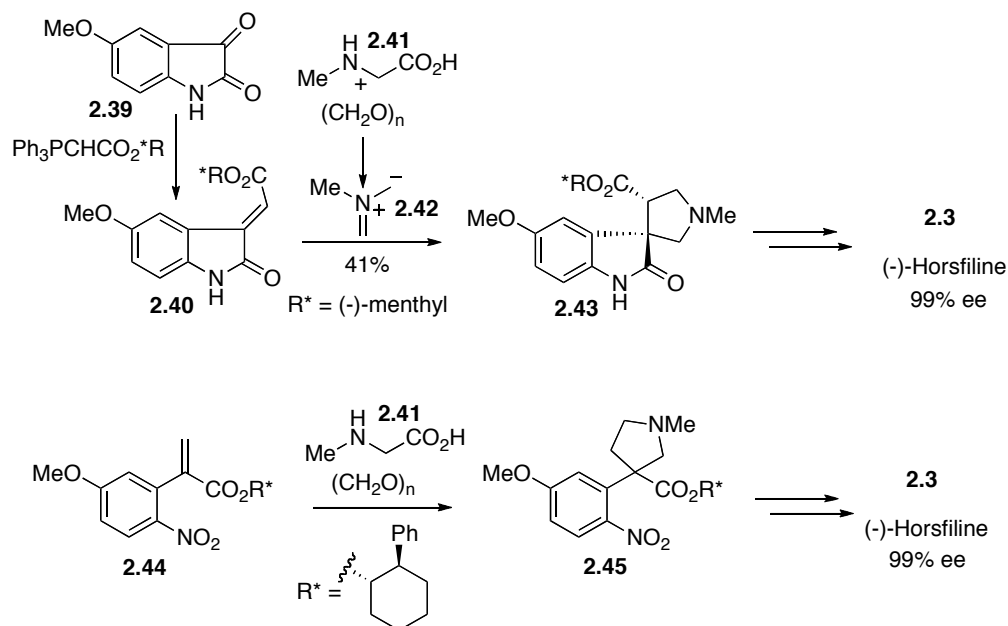
Scheme 2.9. Palmisano's synthesis of (-)-horsfiline using dipolar cycloaddition

In his subsequent work, Palmisano used a more straightforward asymmetric [2+3] cycloaddition with acrylate **2.44** to form **2.45**. Reduction of the nitro group of **2.45** and cyclization of the resulting amino ester provided (-)-horsfiline (**2.3**).[51] In 2002, Selvakumar and co-workers reported the synthesis of (±)-coerulescine (**2.2**) and (±)-horsfiline (**2.3**) using a key step similar to that in Palmisano's second-generation synthesis.[52]

2.2.5. Intramolecular Radical Cyclization Route to Horsfiline

In 1993, Jones and Wilkinson reported a new synthetic route to (±)-horsfiline (**2.3**) using radical cyclization as their key step.[53] The precursor **2.48** for radical cyclization was prepared from 2-bromo-4-methoxyaniline (**2.46**) and ethyl

ester **2.47** in a two-step sequence. Treatment of **2.48** with tributyltin hydride and azobisisobutyronitrile gave spirooxindole **2.49** in good yield. Protection of the indole nitrogen of **2.48** as its trimethylsilylethoxymethylene (SEM) derivative was found to be necessary, since a radical reaction with unprotected **2.48** led only to reduction of this aryl bromide. Other N-protecting groups on **2.48** such as trimethylsilyl resulted in 6-*endo* cyclization. (±)-Horsfiline (**2.3**) was obtained from **2.49** after deprotection followed by Eschweiler-Clarke methylation of the pyrrolidine nitrogen (Scheme 2.10).

Subsequent to Jones' publication, an intramolecular tandem radical cyclization of iodo azide **2.50** was used in a synthesis of (±)-horsfiline (**2.3**) by Murphy and co-workers.[54] Treatment of **2.50** with tris(trimethylsily)silane (TTMSS) afforded spiro[pyrrolidine-3,3'-oxindole] **2.51** which was methylated in situ and converted to (±)-horsfiline (**2.3**) after deprotection of the indole nitrogen atom. In the reaction of **2.50** with TTMSS no 6-*endo* product was observed (Scheme 2.11).
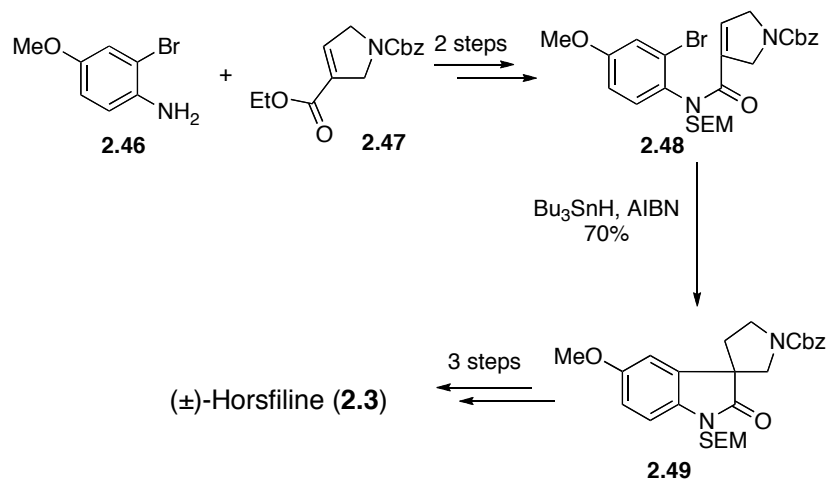
Scheme 2.10. Jones' synthesis of (±)-horsfiline (**2.3**) by radical cyclization
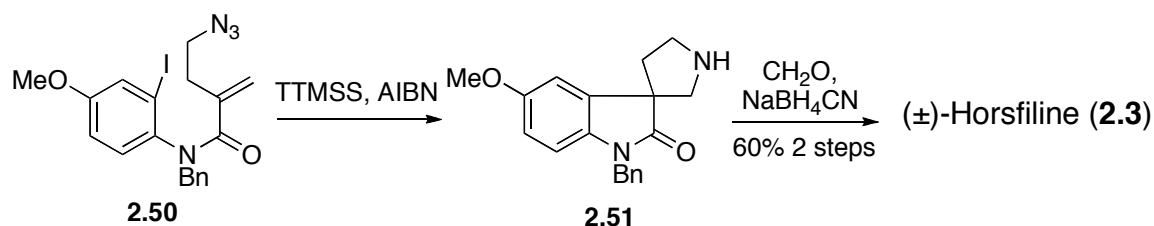
Scheme 2.11. Murphy's synthesis of (±)-horsfiline (**2.3**) using tandem radical cyclization

2.2.6. Palladium Catalyzed Asymmetric Allylic Alkylation Route to (+)-

Horsfiline

In 2006, Trost and co-workers reported an asymmetric synthesis of non-natural (+)-horsfiline using a palladium-catalyzed asymmetric allylic alkylation (AAA) as the key step. Starting from commercially available anisidine (**2.52**) and 2,4-dimethoxybenzaldehyde (**2.53**), amide **2.54** was prepared in three steps. A rhodium-catalyzed C-H insertion method developed by Padwa was

used to build the substituted indole **2.55**.[55] Treatment of **2.55** with a fluoride source generated an enolate nucleophile for asymmetric allylation with bis(ethyl)palladium(II) chloride in the presence of ligand **2.59**. This reaction gave oxindole **2.56** in near quantitative yield. Oxidative cleavage of the terminal olefin of **2.56** with osmium tetraoxide and *N*-methylmorpholine *N*-oxide (NMO) followed by lead tetraacetate resulted in aldehyde **2.57** which was converted to spirooxindole **2.58** in a two-step sequence involving imine formation and reduction with sodium borohydride. (+)-Horsfiline (**2.3**) was obtained from **2.58** by deprotection at the oxindole nitrogen followed by reduction of the lactam (Scheme 2.12).[56]
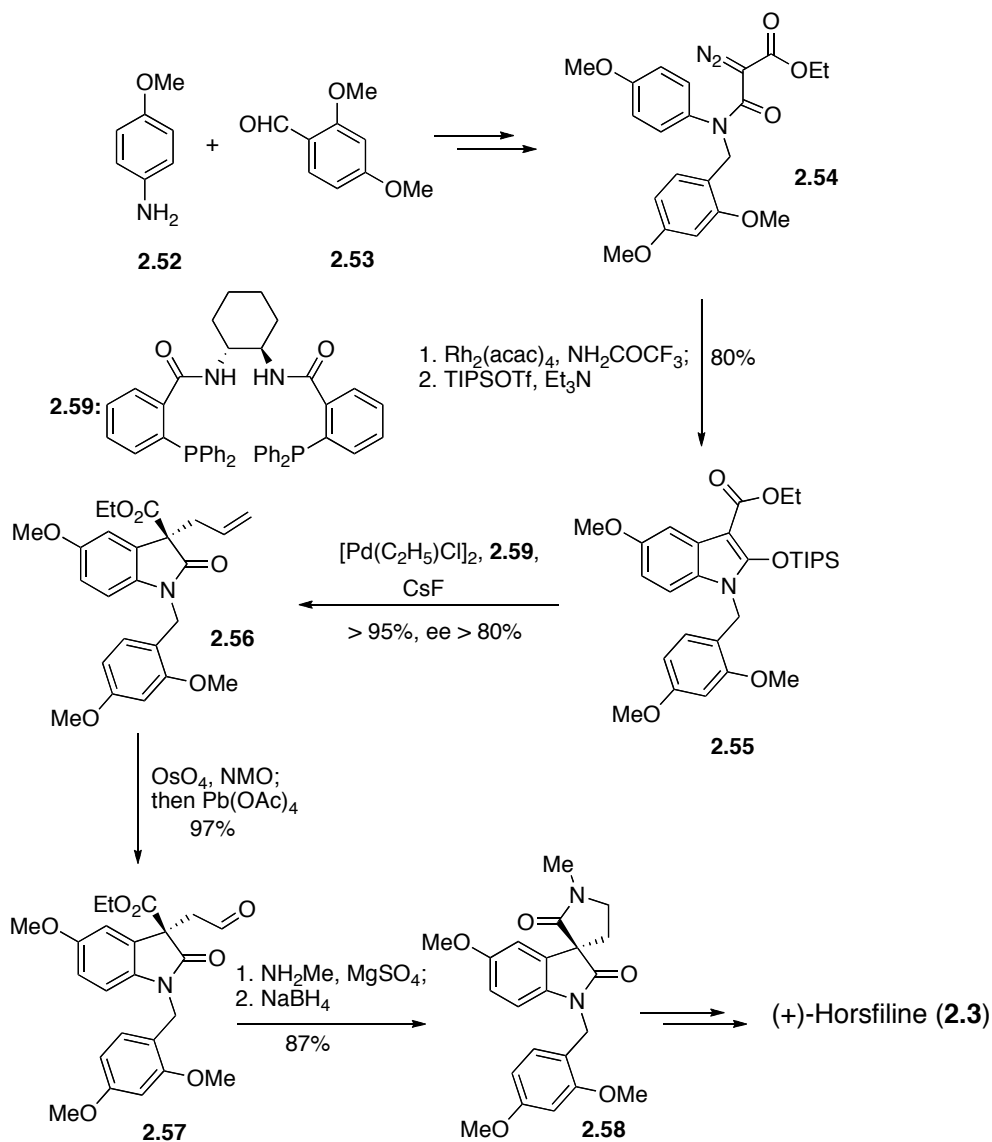
Scheme 2.12. Trost's synthesis of (+)-horsfiline using palladium catalyzed asymmetric allylic alkylation

2.2.7. Asymmetric Nitroolefination Route to (-)-Horsfiline

Fuji has shown that asymmetric nitroolefination is a powerful strategy for constructing the chiral spiro center of a spirooxindole.[57] Thus, the enolate of lactam **2.60** was reacted with enantiopure nitro enamine **2.61** to form the

quaternary carbon of **2.62** with high enantioselectivity via an addition-elimination process.[58] Functional group manipulation of **2.62** provided alcohol **2.63**, which was converted to spirooxindole **2.64** after mesylation and cyclization. (-)-Horsfiline (**2.3**) was obtained from **2.64** after debenzylation, removal of the ethyl ester and final *N*-methylation (Scheme 2.13).
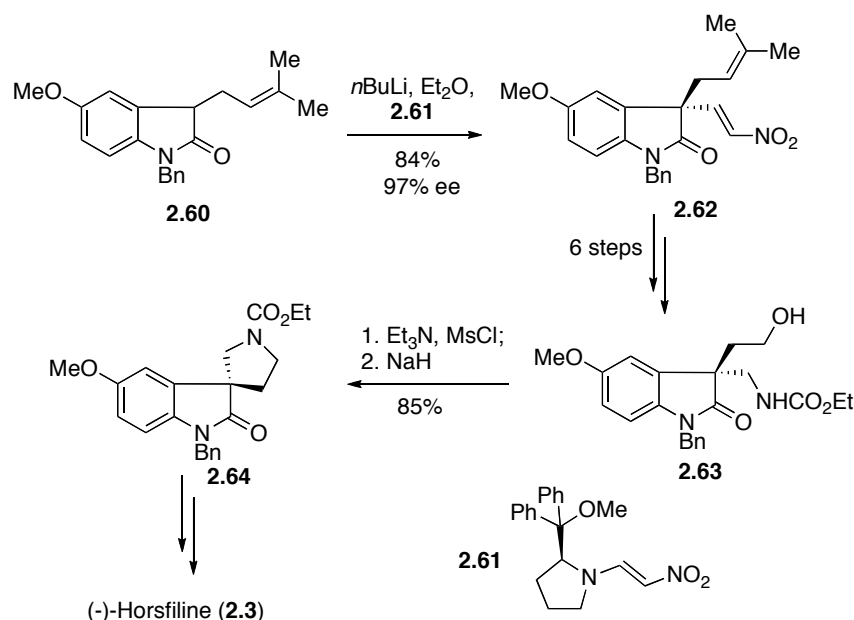
Scheme 2.13. Fuji's synthesis of (-)-horsfiline using asymmetric nitroolefination

2.2.8. Claisen Rearrangement Route to Coerulescine and Horsfiline

Claisen rearrangement of allyl vinyl ethers[59] provides access to 4-pentenals which have served as versatile intermediates for the synthesis of a number of natural products.[60] Recently, Kulkarni and co-workers reported an application of this protocol to the synthesis of (±)-coerulescine (**2.2**) and (±)-horsfiline (**2.3**) (Scheme 2.14).[61] Wittig olefination of *O*-nitrobenzaldehyde **2.65** with allyloxy-

methylenetriphenylphosphorane **2.66** furnished allyl vinyl ether **2.67** as a mixture of *E* and *Z* stereoisomers. Claisen rearrangement of **2.67** gave aldehyde **2.68** which was converted to amino ester **2.69**. The latter formed oxindole **2.70** upon refluxing in the presence of zinc in ethanol. Treatment of aldehyde **2.71** obtained from **2.70** with methylamine hydrochloride and sodium cyanoborohydride led to spirooxindole **2.72** as the precursor to (±)-coerulescine (**2.2).**
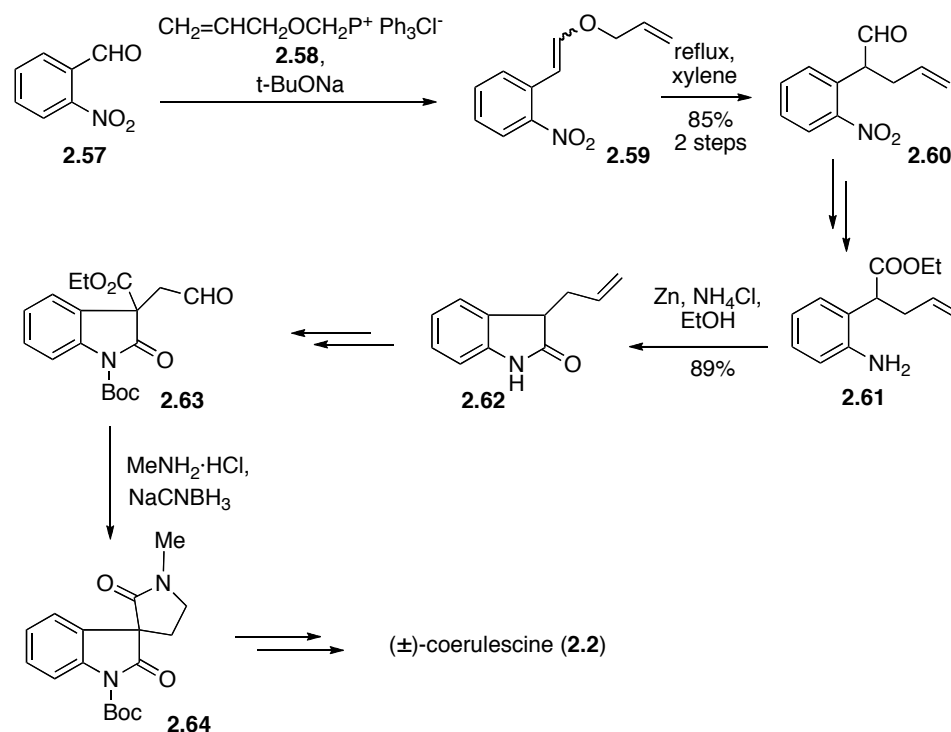
Scheme 2.14. Kulkarni's synthesis of (±)-coerulescine using a Wittig olefination-Claisen rearrangement protocol

In this chapter, eight syntheses of the oxindole alkaloids coerulescine and horsfiline have been summarized. Compared to the approaches outlined

above, our TIPCARM strategy appeared to have several advantages including fewer steps to build the spirooxindole framework, cheaper starting materials and the prospect of reactions that can be carried out on large scale. These features prompted us to explore an approach to the synthesis of oxindole alkaloids using the TIPCARM strategy, and a successful route to (±)-coerulescine (**2.2**) and (±)-horsfiline (**2.3**) will be presented in the chapter that follows.

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Chapter 3. Total Synthesis of (±)-Coerulescine and (±)-Horsfiline using a TIPCARM Strategy

It has been shown in this laboratory that the 2,3-double bond of an indole can serve as the alkene partner in intramolecular photocycloaddition with a β-amino alkylidenemalonate.[62] Subsequent retro-Mannich fragmentation of the formed cyclobutane leads to a spiro(pyrrolinoindoline) skeleton via a process abbreviated as TIPCARM (tandem intramolecular photocycloaddition-retro-Mannich) fragmentation. A second retro-Mannich fragmentation, "[TIPCA(RM)$_2$]", can be used to expel the malonate residue incorporated in the photo substrate. This second fragmentation, when followed by rearrangement of the resulting spiroindolenine to a β-carboline and then oxidation, provides access to alkaloids of the spiro[pyrrolidine-3,3'-oxindole] class (Scheme 3.1). Our TIPCA(RM)$_2$ method has now been applied to syntheses of the oxindole alkaloids (±)-coerulescine (**2.2**) and (±)-horsfiline (**2.3**).
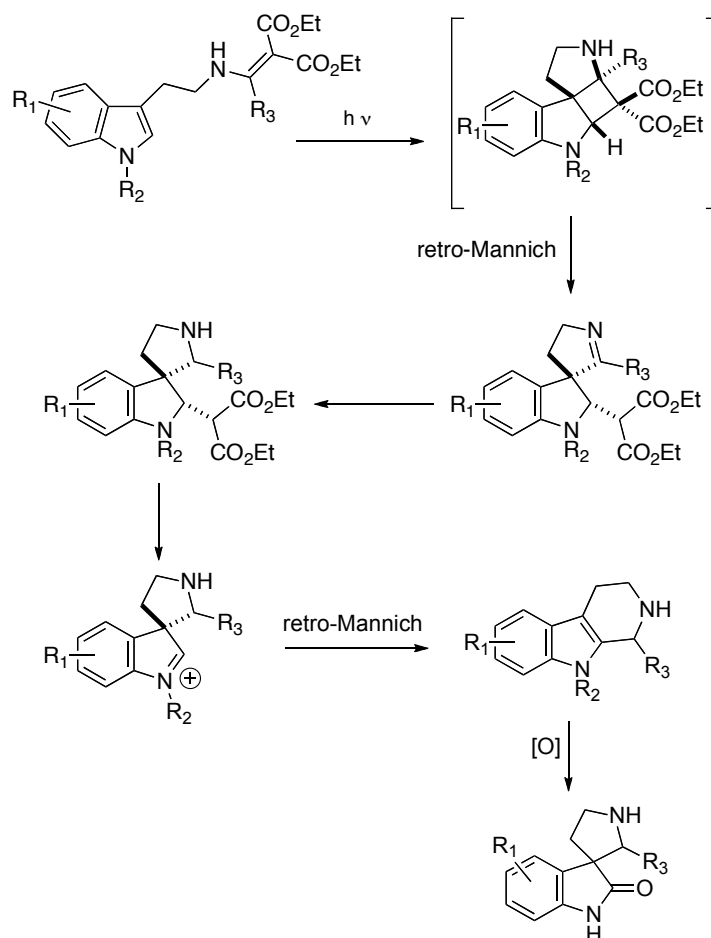
Scheme 3.1. TIPCA(RM)$_2$ route to spirooxindoles

For the synthesis of coerulescine (**2.2**), commercially available tryptamine (**3.1**) was first converted to its trifluoroacetamide **3.2** before protection of the indole nitrogen as tert-butoxycarbonyl derivative **3.3** (Scheme 3.2).[63] Removal of the trifluoroacetyl group and condensation of the liberated amine **3.4** with commercially available diethyl β-ethoxymethylidenemalonate (**3.5**)[64] afforded photo substrate **3.6**.
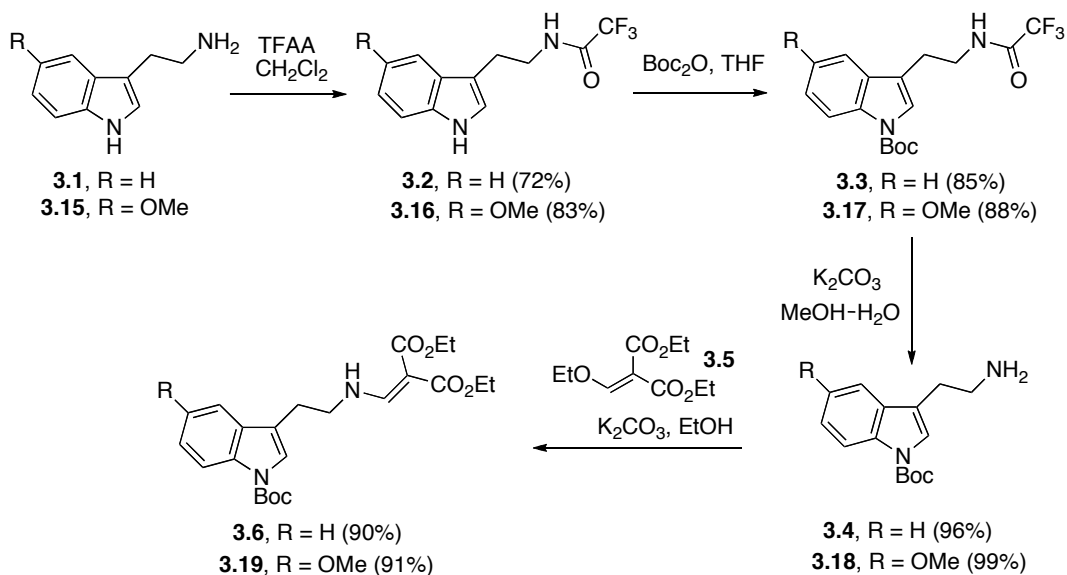
Scheme 3.2. Synthesis of photo substrates **3.6** and **3.19**

Irradiation of **3.6** in ethanol with a 450W medium-pressure mercury lamp through a Corex filter (50% transmission at 290 nm)[65] for several hours led via cycloadduct **3.7** and in situ retro-Mannich fragmentation to spiropyrrolenine **3.8** in good yield. Although formation of **3.8** was more rapid when **3.6** was irradiated through a Vycor filter (90% transmission at 280 nm), decomposition of the product complicated purification in this case. No reaction occurred when **3.6** was irradiated through Pyrex glass (20% transmission at 290 nm). These experiments established that the photocycloaddition step in our TIPCARM sequence is sensitive to the energy of the incident radiation and that there is only a narrow window through which efficient photocycloaddition can be accomplished. Treatment of **3.8** with methyl iodide gave a methiodide which

was reduced in situ with sodium borohydride to saturated spiro[pyrolidinoindoline] **3.9** (Scheme 3.3).
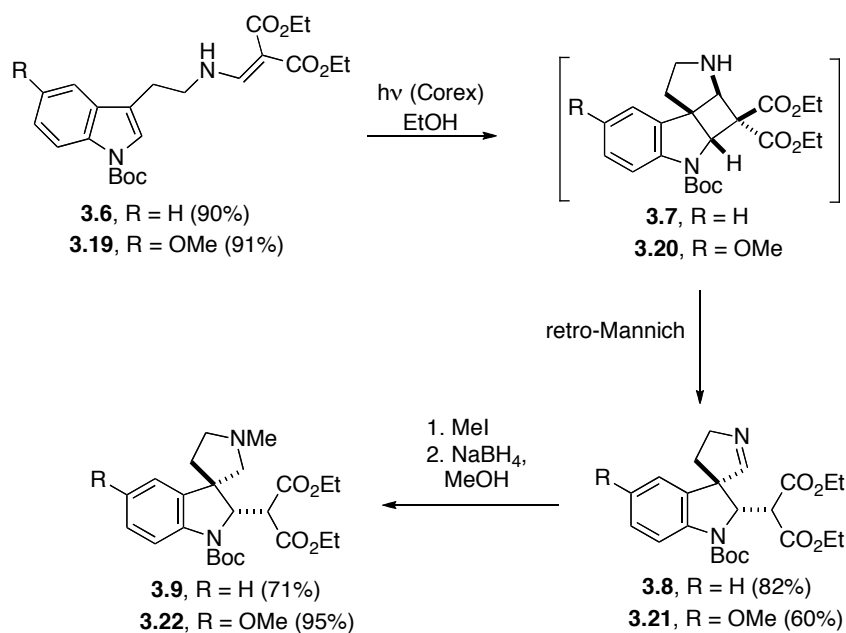
Scheme 3.3. Synthesis of spiro[pyrrolidinoindolines] **3.9** and **3.22** using a TIPCARM sequence

Removal of Boc protection from **3.9** with trifluoroacetic acid under more strenuous conditions than those used previously resulted in a second, spontaneous retro-Mannich fragmentation in which diethyl malonate was expelled to afford the known β-carboline **3.13**[66] (Scheme 3.4). *β*-Carbolines such as **3.13** are conventionally prepared by Pictet-Spengler condensation of a tryptamine with an aldehyde[67] or by Bischler-Napieralski cyclization of a tryptamide followed by reduction.[68] The route from **3.9** represents a new mode of access to the β-carboline system. Our observation that removal of the Boc

group from **3.9** was necessary in order to trigger the second retro-Mannich process argues against a fragmentation pathway to **3.13** via indole **3.14** followed by Pictet-Spengler cyclization. More likely, **3.10** leads transiently to spiroindolenine **3.11** and it is this species that rearranges spontaneously in acid to **3.13** via iminium ion **3.12**. Oxidation of **3.13** with *N*-bromosuccinimide in aqueous acetic acid following a protocol first published by Lawson and Withrop[69] and further developed by van Tamelen[70] as a general route to oxindoles gave (±)-coerulescine (**2.2**). The same oxidative rearrangement of **3.13** was recently accomplished by Danishefsky in his synthesis of (±)-(**2.2**).[71] Our overall yield of **2.2** for the nine steps from tryptamine (**3.1**) was 11%.
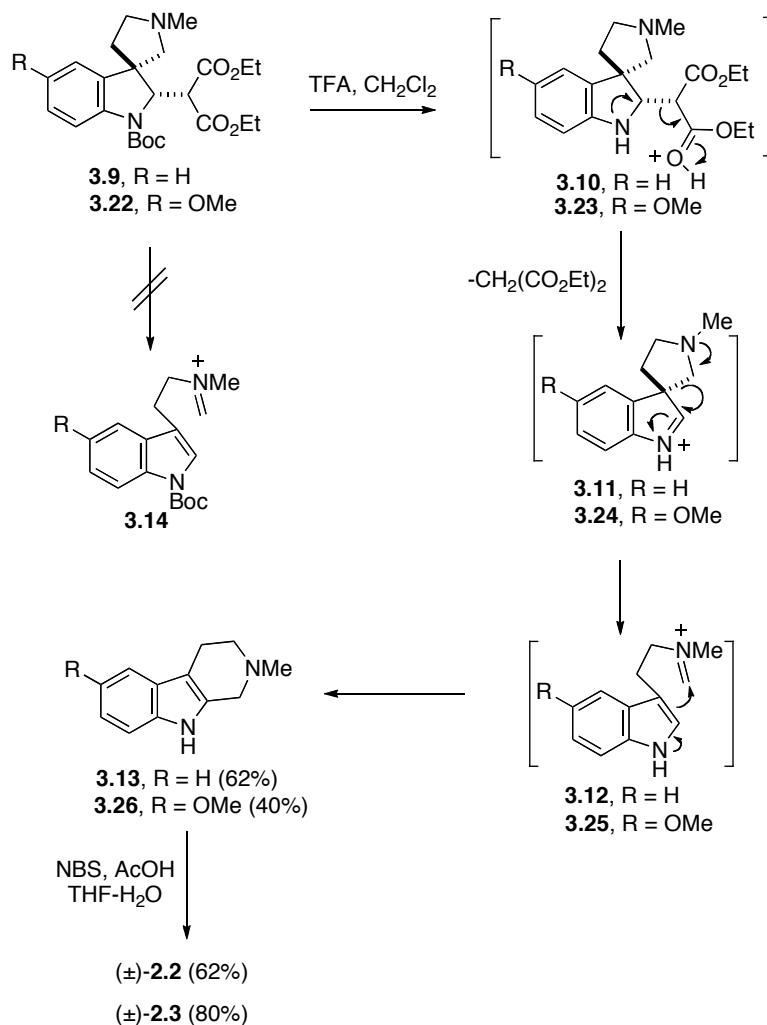
Scheme 3.4. Completion of syntheses of (±)-coerulescine (**2.2**) and (±)-horsfiline (**2.3**)

A sequence parallel to that shown in Schemes 3.2, 3.3 and 3.4 but departing from commercially available 5-methoxytryptamine (**3.15**) and proceeding via **3.19**, **3.22**, and **3.26** led to (±)-horsfiline (**2.3**) in an overall yield of 12% (Scheme 3.4). The photocycloaddition-retro-Mannich sequence from **3.19** via **3.20** to **3.21** was both slower and less efficient than the analogous conversion of **3.6** to **3.8**, probably due to partial quenching of the photo-excited

malonylidene unit of **3.19** by the methoxy substituted indole. On the other hand, the combined *N*-methylation and borohydride reduction of **3.21** resulted in more efficient preparation of **3.22** than of **3.9**. Subsequent steps from **3.22** to (±)-horsfiline (**2.3**) proceeded via **3.23, 3.24** and **3.25** to β–carboline **3.26** which was brominatively oxidized to the racemic alkaloid. The structures of (±)-**2.2** and (±)-**2.3** were confirmed by comparision of ^{1}H and ^{13}C NMR spectra with published spectra of natural coerulescine[71] and horsfiline,[43] respectively.

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Chapter 4. Synthesis of Elacomine and 6-Deoxyelacomine using a TIPCARM Strategy

4.1. Introduction to Elacomine

Elacomine (**4.1**) was originally isolated from the shrub *Elaeaguns Commutata* by Slywka in 1969.[72] The relative stereochemistry of the hemiterpene spirooxindole alkaloid was unambiguously determined by X-ray analysis of a racemic natural sample (Figure 4.1). Elacomine (**4.1**) was found to isomerize to isoelacomine (**4.2**) under weakly basic conditions;[73] it was also confirmed by careful isolation studies that **4.1** and **4.2** occur naturally in racemic form. The first enantioselective total synthesis of **4.1** was achieved by Borschberg and co-workers in 1994 through oxidative rearrangement of a β-carboline.[73] In 2004, Horne and co-workers reported the total synthesis of **4.1** and **4.2** based on a stereoselective intramolecular iminium ion spirocyclization method.[74] Recently, Takemoto's group published a formal synthesis of elacomine (**4.1**) and isoelacomine (**4.2**) using a palladium-catalyzed Heck cyclization along with a bismuth-catalyzed hydroamination reaction.[75] These three accounts are thus far the only reported efforts directed towards synthesis of the elacomine-isoelacomine alkaloid family.
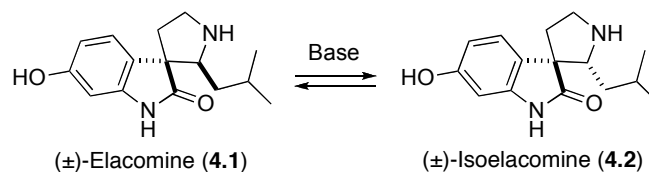
Figure 4.1. Structure of elacomine (**4.1**) and isoelacomine (**4.2**)

4.2. Previous Syntheses of Elacomine and Isoelacomine

Three syntheses of elacomine and isoelacomine have been published to date. Two of these routes, those of Borschberg and Horne, begin from a tryptamine derivative and employ 3-methylbutanal in a Pictet-Spengler cyclization which proceeds to a spirooxindole, either directly (Horne) or indirectly via a tetrahydro- β-carboline (Borschberg). A third route to elacomine and isoelacomine due to Takemoto creates the oxindole nucleus via a novel palladium mediated Heck reaction of an aniline derivative which is then transformed into a spirooxindole through a bismuth(III) mediated cyclization. These three routes are summarized below.

4.2.1. Borschberg's Synthesis of (+)-Elacomine and (-)-Isoelacomine

In 1994, Borschberg and co-workers reported the first total synthesis of (+)-elacomine and (-)-isoelacomine.[73] Their synthesis commenced from the 6-hydroxy-L-tryptophan derivative (+)-**4.4** which was prepared according to the method of Taniguchi and Hino[76] from (-)-**4.3** and transformed into the 6-(2-nitrobenzyloxy) tryptamine derivative **4.5**. Pictet-Spengler condensation of **4.5** with isovaleraldehyde furnished a 1:3 mixture of the *cis*- and *trans*-β-carbolines (-)-**4.6** and (+)-**4.7**. The ester of the major product **4.7** was removed and the β-carboline nitrogen atom was protected as its carbobenzyloxy (Cbz) derivative. The resulting carboline **4.8** was oxidized with *N*-bromosuccinimide to furnish a 2:3 mixture of a pair of protected spirooxindole isomers which were separated by chromatography. The two protecting groups of each isomer were removed by hydrogenolysis to give (+)-elacomine (**4.1**) and (-)-isoelacomine (**4.2**) (Scheme 4.1). The ee value of **4.1.** is 76%, and the erosion observed can be explained by an isomerization mechanism wherein stereoisomers are equilibrated through a ring-opened, that is accessed by a retro-Mannich reaction.
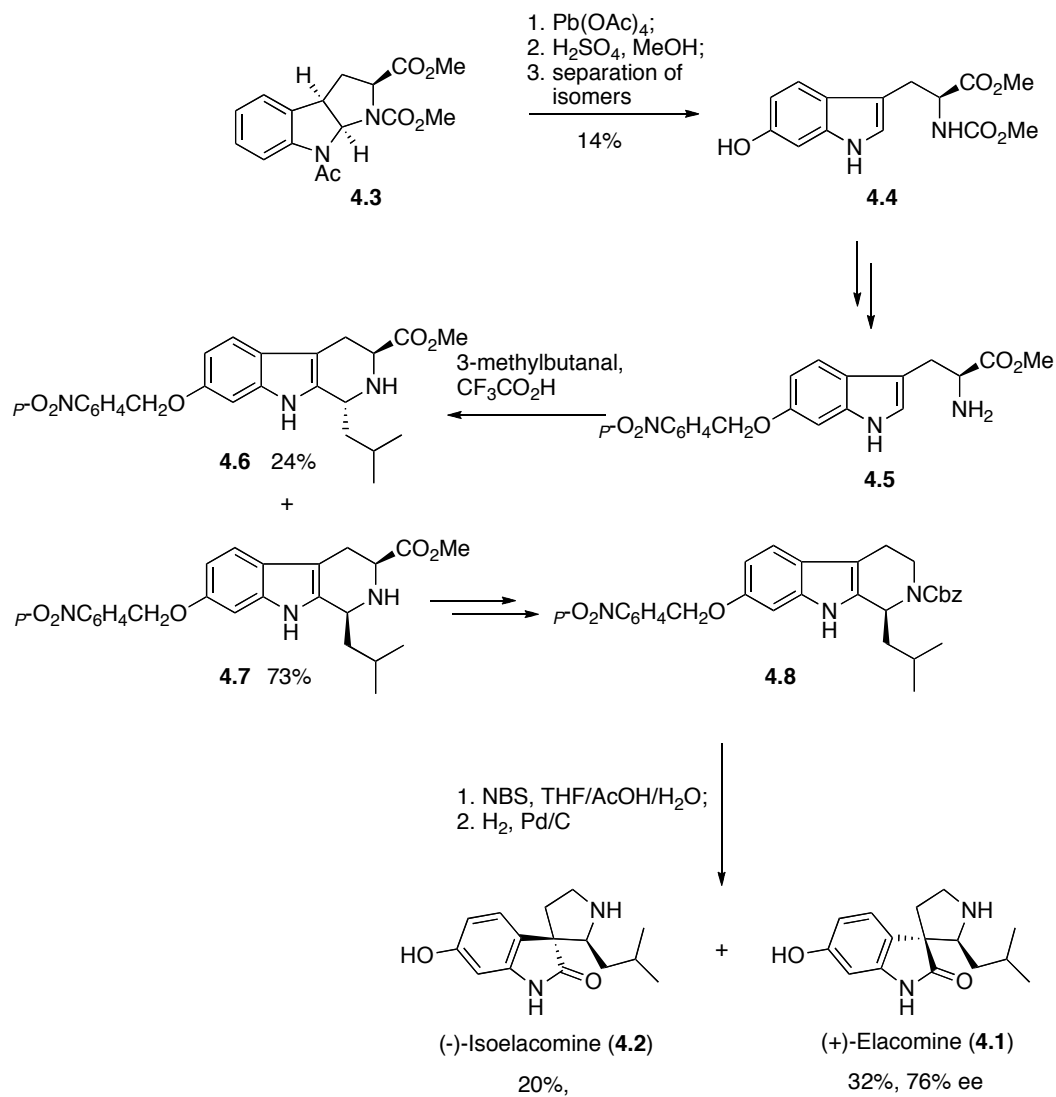
Scheme 4.1. Borschberg's synthesis of (+)-elacomine and (-)-isoelacomine

4.2.2. Horne's Synthesis of (±)-Elacomine and (±)-Isoelacomine Using Intramolecular Iminium Ion Spirocyclization

Horne reported the synthesis of elacomine and isoelacomine starting from tryptamine (**3.1**) and using an intramolecular iminium ion spirocyclization.[74] First, 2,6-dibromotryptamine (**4.9**) was prepared from **3.1** with two equivalents of *N*-bromosuccinimide (Scheme 4.2). Condensation of **4.9** with isovaleraldehyde followed by treatment with trifluoroacetic acid produced spirooxindole **4.10** as the major diastereoisomer (>97:3).

Horne's explanation for the stereoselectivity favoring **4.10** in this step involves minimization of a steric interaction depicted in transition state **4.13** between the isobutyl group and the bromine atom at C2 of the indole moiety. Consequently, **4.10** is formed via transition state **4.12**, as shown in Scheme 4.3. Under the acidic reaction conditions, protonation of the pyrrolidine nitrogen of **4.10** prevents a retro-Mannich process that could lead to isomerization of the isobutyl substituent, but attempts to purify **4.10** by flash chromatography using methanol as eluent did result in its isomerization to **4.11**. The presence of the 6-bromo substituent in **4.10** and **4.11** accelerated isomerization resulting from this retro-Mannich process. Deprotection of the pyrrolidine nitrogen atom followed by copper-catalyzed methoxylation[77] of aryl bromides **4.10** and **4.11** and methylation afforded (±)-elacomine (**4.2**) and (±)-isoelacomine (**4.2**).
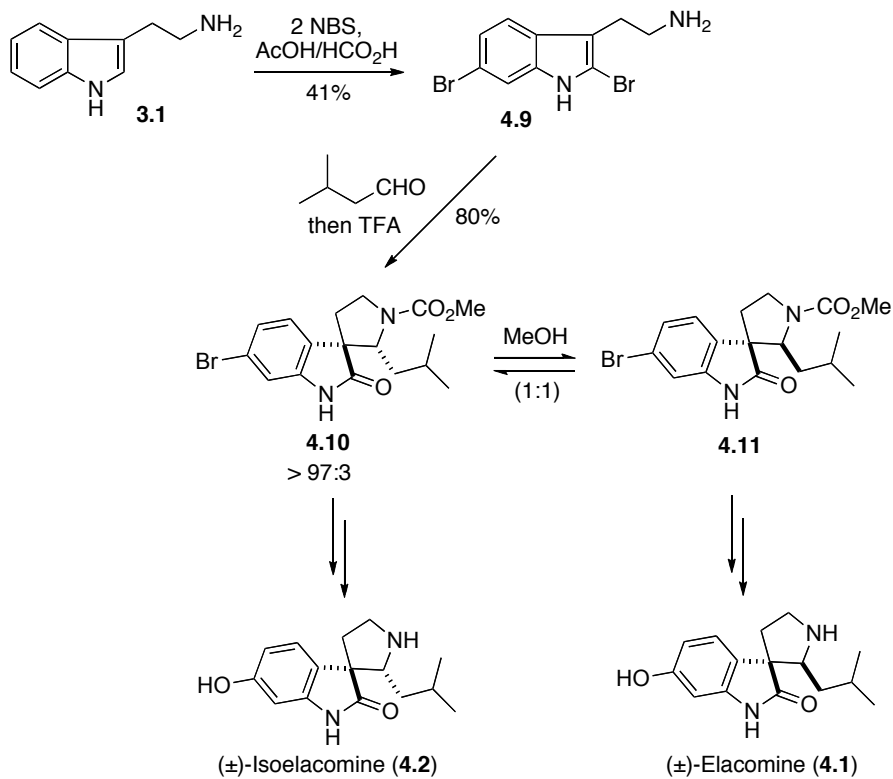
Scheme 4.2. Horne's synthesis of elacomine and isoelacomine using intramolecular iminium ion spirocyclization
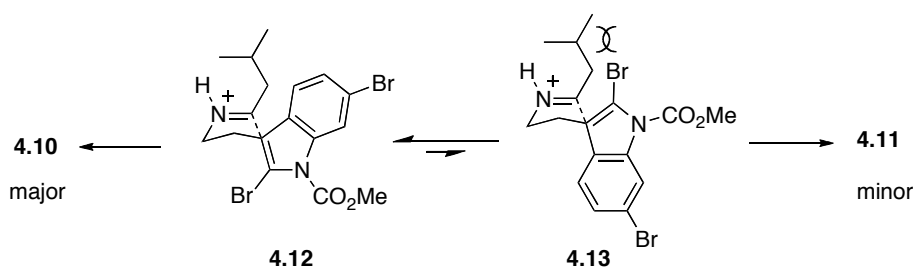
Scheme 4.3. Horne's stereochemical rationale for formation of **4.10** as the major product from **4.9**

4.2.3. Takemoto's Domino Palladium-catalyzed Heck Cyclization and Bismuth-catalyzed Hydroamination Route to (±)-Elacomine and (±)-Isoelacomine

Recently, Takemoto reported the application of a domino palladium-catalyzed Heck cyclization together with a bismuth-catalyzed hydroamination sequence to a synthesis of elacomine (**4.1**) and isoelacomine (**4.2**).[75] The *E*-diene-containing carbamoyl chloride substrate for this process **4.16** was prepared from iodoaniline derivative **4.14** and commercially available 5,6-dihydro-2*H*-pyran-2-one (**4.15**) in 12 steps and 25% overall yield. Treatment of **4.16** with palladium acetate and cesium carbonate did not provide the predicted product **4.18**; instead, oxindole **4.17** was obtained in 86% yield (Scheme 4.4).
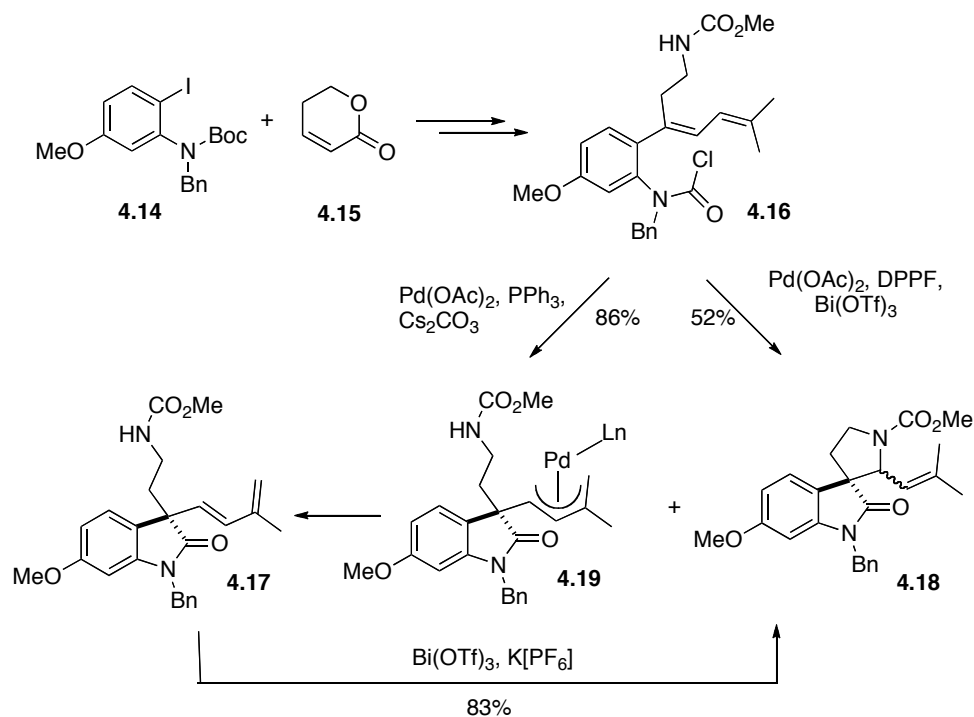
Scheme 4.4. Takemoto's domino palladium-catalyzed spirooxindole synthesis

Apparently, **4.17** was produced by rapid β-elimination of the intermediate π-allyl palladium complex **4.19** formed from **4.16**, thus preventing nucleophilic addition of the exocyclic nitrogen atom to give the desired spirooxindole **4.18**. Based on this result, Takemoto examined various additives and ligands in the reaction of **4.16** with palladium acetate and found that 1,1'-bis(diphenylphosphino)ferrocene (DPPF) with bismuth tris(trifluoromethane-sulfonate) gave **4.18** as a mixture of two diastereomers.

To clarify the effect of additives on the palladium-catalyzed cyclization of **4.16**, intramolecular hydroamination of diene **4.17** with various Lewis acid catalysts was investigated. It was found that **4.17** could be converted into **4.18** by Lewis

acid-catalyzed hydroamination, indicating that the formation of **4.18** from **4.16** may be a two-step process involving Heck cyclization and β-elimination followed by hydroamination. Subsequently, spirooxindole **4.18** was synthesized from **4.16** via **4.17** in better yield and with higher diastereoselectivity using stepwise Heck cyclization and bismuth tris(trifluoromethanesulfonate)-catalyzed hydroamination. The spirooxindole **4.18** was converted to racemic elacomine (**4.1**) and isoelacomine (**4.2**) by hydrogenolysis and deprotection via **4.20** and **4.21** (Scheme 4.5).
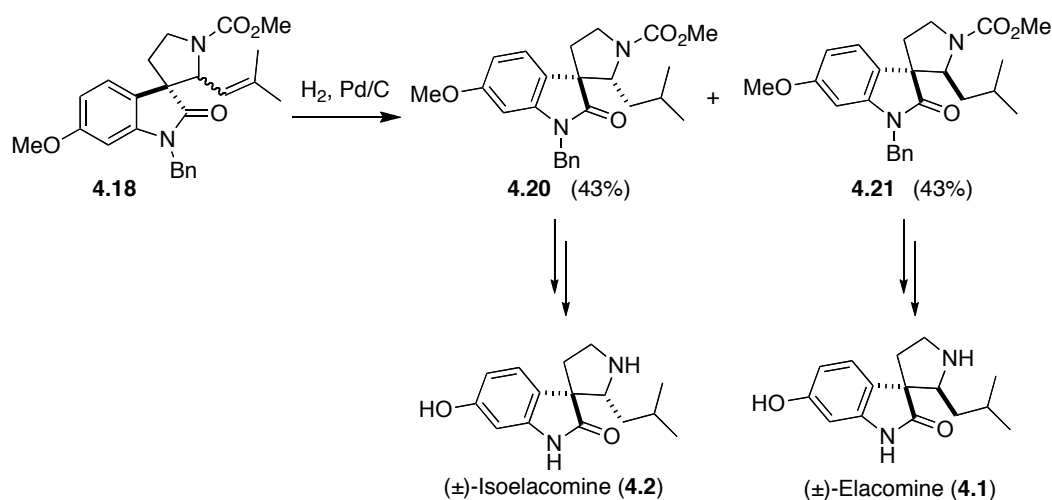
Scheme 4.5. Takemoto's synthesis of elacomine (**4.1**) and isoelacomine (**4.2**) from spirooxindole **4.18**

4.3. Total Synthesis of (±)-Elacomine and (±)-6-Deoxyelacomine Using a TIPCA(RM)$_2$ Strategy

The isobutyl substituent located at C4' in elacomine presented our TIPCA(RM)$_2$ strategy with two new challenges. Since we wished to bring the isobutyl appendage into our synthetic sequence at an early stage, the first goal involved incorporation of that substituent into the aminomalonylidene portion of our photo substrate. A second issue concerned the new stereocenter at C4' and specifically whether it would be oriented correctly with respect to the adjacent spiro carbon at C3. Some precedent for both of these operations existed in the research described in chapter 3, but it was unclear whether the more sterically demanding isobutyl group would impose a constraint on the photocycloaddition step of TIPCARM which would now generate a more highly congested cyclobutane intermediate. Our solution to the first of these tasks was straightforward and required only acylation of diethyl malonate with isovaleryl chloride (**4.22**) followed by O-methylation of **4.23**[78] to provide **4.24** (Scheme 4.6).
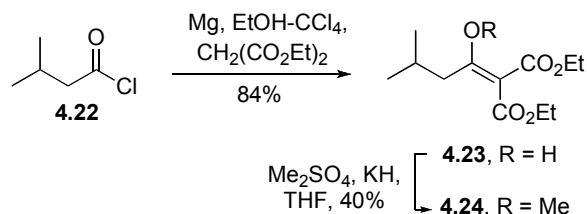
Scheme 4.6. Preparation of malonate derivative **4.24**

We chose initially to test our approach to elacomine (**4.1**) in the context of 6-deoxyelacomine (**4.33**) for the reason that we could now depart directly from *N*-Boc tryptamine (**3.4**). Although **4.33** has not been found in Nature, we foresaw that our route would pass through the known alkaloid **4.29**, a substance previously obtained by Borschberg in the course of his synthesis of (±)-elacomine. Correlation would therefore provide assurance that our TIPCA(RM)$_2$ strategy was applicable to elacomine itself.

First, *N*-Boc tryptamine **3.4** was condensed under basic conditions with **4.24** to furnish photo substrate **4.25** in excellent yield (Scheme 4.7). Irradiation of **4.25** under conditions used previously for photolysis of **3.6** and **3.19** led directly to spiropyrrolenine **4.26** which was immediately subjected to reduction with sodium cyanoborohydride. Our expectation based on steric grounds was that hydride ion would be delivered to imine **4.26** with high selectivity from the face opposite the C2 branched indoline substituent, and our prediction was confirmed with the isolation of **4.27** as a single stereoisomer in high yield.
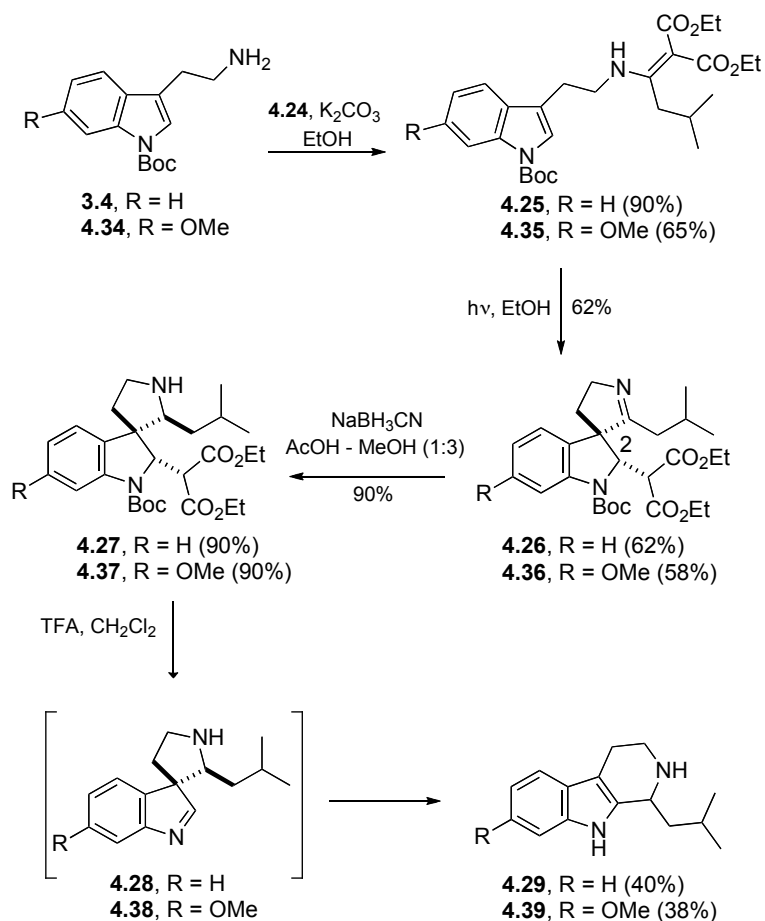
Scheme 4.7. Synthesis of β-carbolines **4.29** and **4.39** via TIPCA(RM)$_2$

Exposure of spiropyrrolidine **4.27** to trifluoroacetic acid removed Boc

protection from *N*1 of the indoline and led spontaneously to retro-Mannich

expulsion of the malonate residue. This sequence produced transiently

spiroindolenine **4.28** and then by further rearrangement β-carboline **4.29.** The

spectral properties of **4.29** matched those reported by Borschberg[73] for this

substance, and data for the hydrochloride of **4.29** agreed with those published

by Slywka and Locock for the corresponding salt of the β-carboline alkaloid

isolated from *E. Commutata*.[72] The presence of a secondary amine in **4.29**

prevented its direct conversion to an oxindole, as was executed successfully with **3.13** and **3.26**, and therefore **4.29** was protected as its carbobenzyloxy derivative **4.30** (Scheme 4.8). Treatment of **4.30** with *N*-bromosuccinimide in an aqueous medium containing tetrahydrofuran and acetic acid gave stereoisomers **4.31** and **4.32**, and after separation by chromatography, hydrogenolysis of **4.31** gave (±)-6-deoxyelacomine (**4.33**). The ^{1}H and ^{13}C NMR spectra of (±)-6-deoxyelacomine (**4.33**) were identical to NMR spectra of the corresponding material as published by Horne.[74]
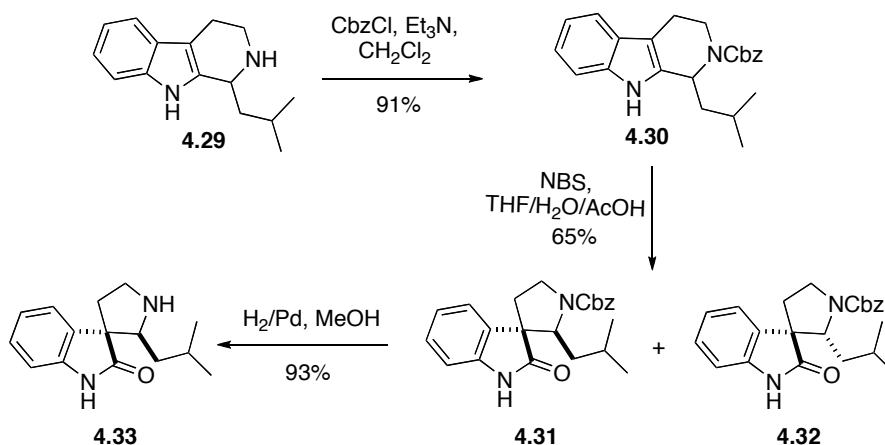
Scheme 4.8. Synthesis of (±)-6-deoxyelacomine (**4.33**)

For the synthesis of (±)-elacomine (**4.1**), we chose *N*-protected 6-methoxytryptamine **4.34** (Scheme 4.7) as our starting material with the expectation that judicious timing of the methyl ether cleavage would need to be made at some stage in the sequence. Tryptamine derivative **4.34** was prepared by a known route from indole (**4.40**)[79] by first converting indole to its

N-pivaloyl derivative **4.41**. Regioselective chloroacetylation of **4.41** followed by Baeyer-Villiger oxidation of α-chloro ketone **4.42** produced the α-chloroacetate **4.43** which was cleaved with thiolate to provide 6-hydroxyindole (**4.44**). The latter was converted 6-methoxyindole **4.45** which was acylated with oxalyl chloride to yield **4.46**. Treatment of **4.46** with ammonia followed by hydride reduction of the derived α-keto amide afforded 6-methoxytryptamine **4.47**. The latter was converted to **4.34** using an identical procedure to that employed for synthesis of **3.4** from **3.1** (Scheme 4.9).
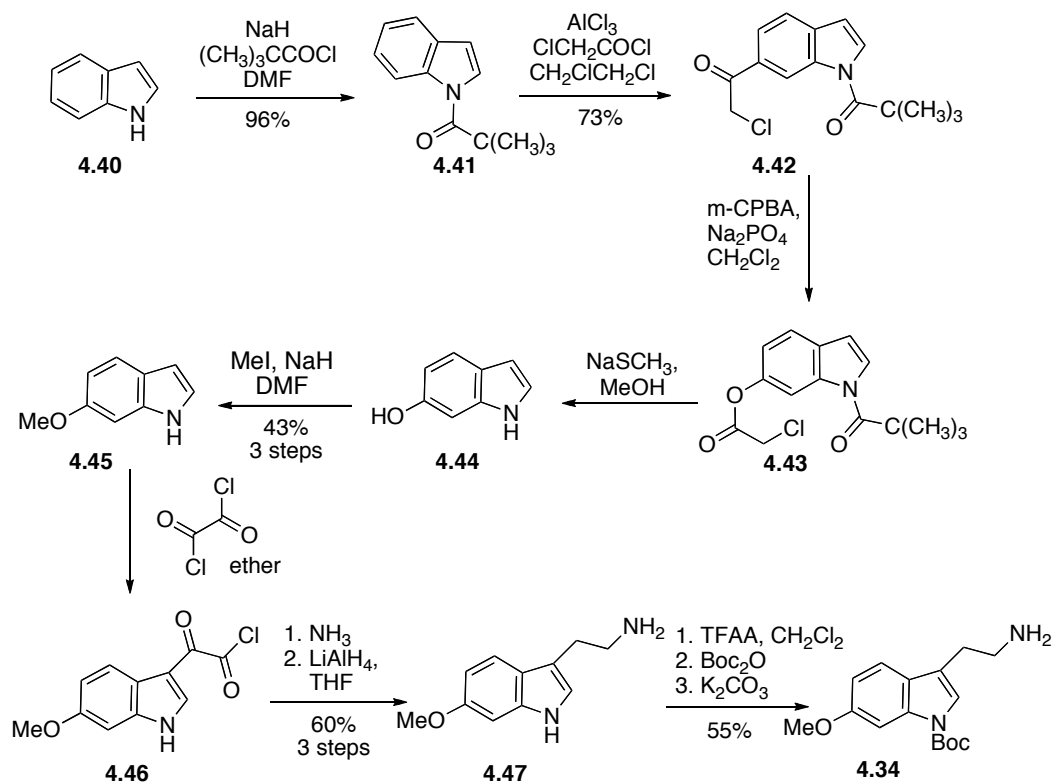
Scheme 4.9. Synthesis of 6-methoxytryptamine derivative **4.34**

Tryptamine derivative **4.34** was condensed with **4.24** to furnish photo substrate **4.35** which was irradiated through Corex to give **4.36** in 58% yield.

Subsequent reduction of **4.36** to **4.37** with sodium cyanoborohydride followed by retro-Mannich fission via **4.38** yielded β-carboline **4.39** in a process that closely paralleled the sequence from **3.4** to **4.29**. However, in attempting to advance **4.39** towards elacomine (**4.1**), it became clear that unmasking the hydroxyl group of the alkaloid as the final step was likely to be problematic. Consequently, we chose **4.39** as a more opportune vehicle for accomplishing this transformation, and when **4.39** was reacted with boron tribromide at low temperature it gave the hydroxy β-carboline **4.48** in good yield. Protection of both the amine and hydroxyl substituent of **4.48** as bis-carbobenzyloxy derivative **4.49** followed by brominative oxidation and rearrangement produced oxindole **4.50**. Final hydrogenolysis then yielded (±)-elacomine (**4.1**) (Scheme 4.10). The ^{1}H and ^{13}C NMR spectra (±)-elacomine (**4.1**) were identical to corresponding spectra of the racemic alkaloid published by Horne.[74] The synthesis of **4.1** was accomplished in eight steps from tryptamine **4.34** and in an overall yield of 7%.
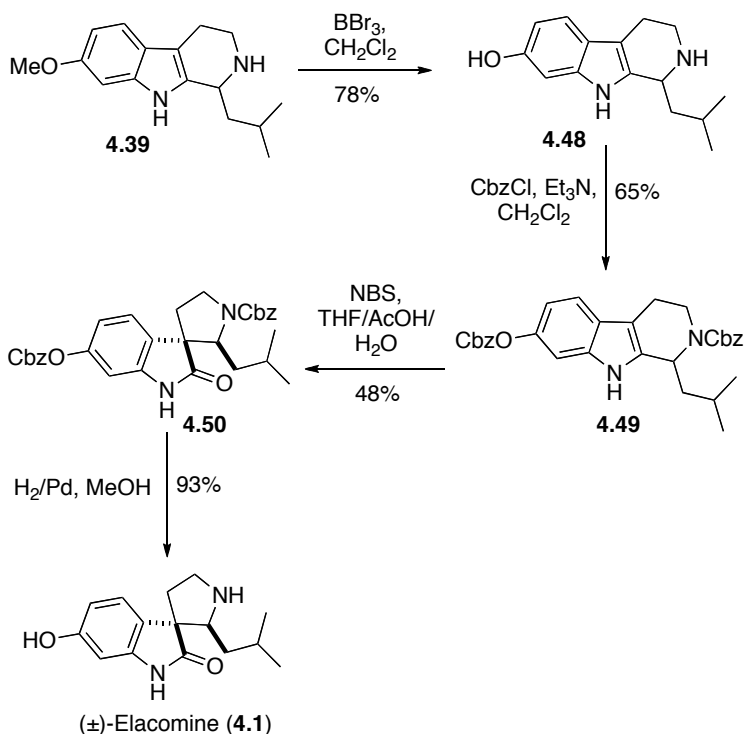
Scheme 4.10. Synthesis of (±)-elacomine (**4.1**)

In the foregoing research, we have shown that an intramolecular photocycloaddition-retro-Mannich sequence applied to various tryptamine systems provides a new entry to spiro[pyrrolidino-3,3'-indolines] and to corresponding oxindole alkaloids found in Nature. Although a malonyl unit present in the photo substrate is subsequently expelled in a second retro-Mannich fragmentation after spiro[pyrrolinoindoline] formation, retention of the malonyl function would afford opportunities for accessing more complex alkaloid skeletons, including those of the *Vinca* family. This extension of our TIPCARM methodology is exemplified in the chapter that follows.

4.4. References

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Chapter 5. Studies Towards the Synthesis of *Vinca* Alkaloids

5.1. Introduction to *Vinca* Alkaloids Vindoline, Vindorosine

and Minovine

Vinca alkaloids vinblastine (**5.1**) and vincristine (**5.2**) are the most widely recognized members of a class of bisindole alkaloids as a result of their clinical use as antitumor drugs (Figure 5.1).[80] Originally isolated in trace quantities from *Cantharanthus roseus* (L.) G. Don,[81] their biological activities were among the first to be shown to arise from inhibition of microtubule formation and mitosis. Today vinblastine (**5.1**) and vincristine (**5.2**) are still regarded as among the most successful drugs for the treatment of cancer.[82] Vindoline (**5.3**), a major alkaloid of *Cantharanthus roseus*, constitutes the more complex half of vinblastine and serves as both a biosynthetic and synthetic precursor to the natural product.[83] Vindorosine (**5.4**),[84] also isolated from *Catharanthus roseus* (L.), is identical in structure to vindoline with the exception that it lacks the C16 methoxy substituent. Minovine (**5.5**),[85] a naturally occurring *Aspidosperma* alkaloid isolated from *Vinca minor L.*, has the same pentacyclic skeleton as vindoline and vindorosine. Due to their unique structures and bioactivities, vindoline (**5.3**), vindorosine (**5.4**) and minovine (**5.5**) (Figure 5.1) have attracted much attention among synthetic chemists. To date, more than 20 groups have reported racemic and/or

enantioselective total syntheses of these *Vinca* alkaloids.[86, 87, 88] The following section will focus on the approaches employed for the synthesis of vindoline (**5.3**).
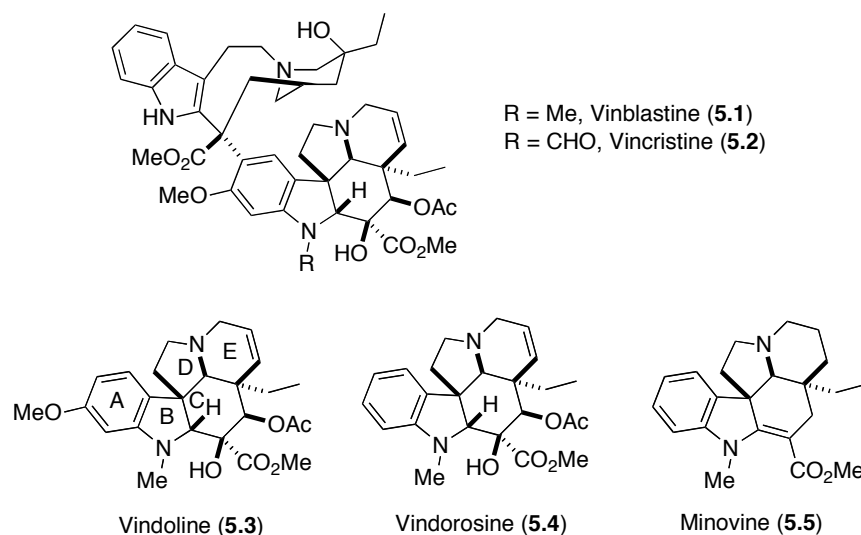
Figure 5.1. Structures of vinblastine, vincristine, vindoline, vindorosine and minovine

5.2. Previous Syntheses of Vindoline

5.2.1. Büchi's Synthesis of Vindoline

In 1971, Büchi and co-workers reported the first total synthesis of (±)-vindoline (**5.3**).[86a] The key feature of this synthesis was an acid catalyzed cyclization to form tetracylic ring system **5.8**, which was further elaborated to (±)-vindoline (**5.3**). Cyclization of tryptamine derivative **5.6** with boron trifluoride etherate gave in high yield the stereochemically homogeneous cis, cis indoline **5.8** via

an intramolecular Mannich reaction. Deprotection of **5.8** and *O*-methylation led

to **5.9**. Condensation of secondary amine **5.9** with acrolein in methanol

containing sodium methoxide, followed by dehydration of the aldol product with

methanesulfonyl chloride in pyridine, gave the unsaturated ketone **5.10** which

was converted to (±)-vindoline (**5.3**) through standard functional group

manipulations (Scheme 5.1).
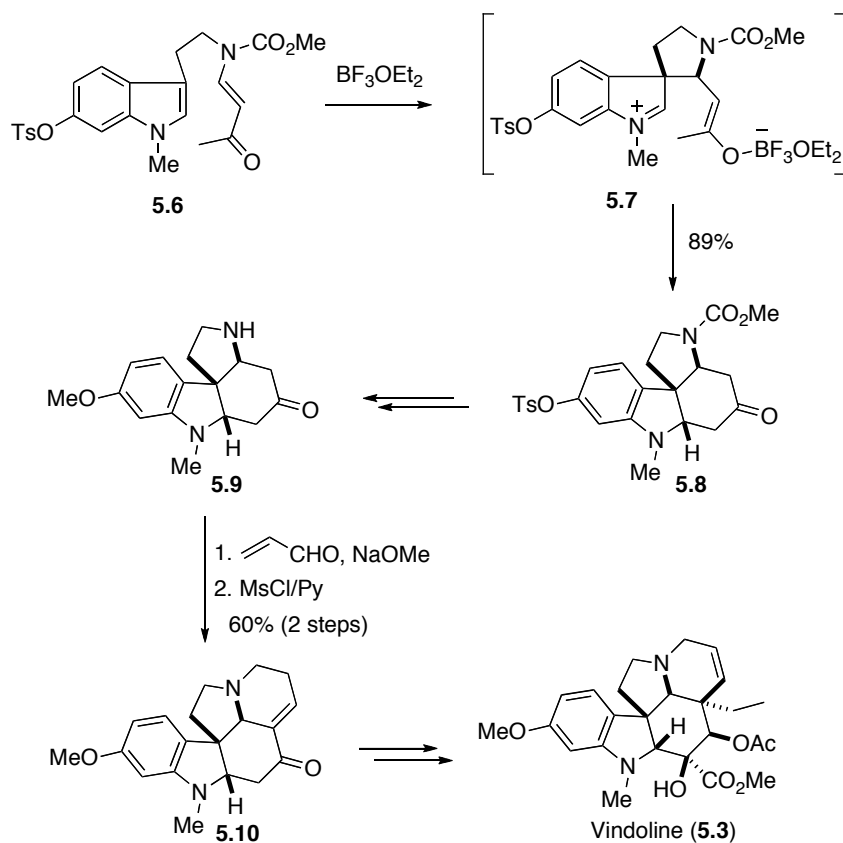
Scheme 5.1. Büchi's synthesis of (±)-vindoline

Subsequent to Büchi's publication, several syntheses of the tetracyclic ketone

5.8 or its close relatives were reported.[86 d, e] These routes to ketone **5.8** via a

Mannich reaction are now regarded as "Büchi-type syntheses".

In 1978, Oishi and co-workers reported a formal synthesis of (±)-vindoline

(**5.3**).[86c] The key feature was stereoselective ring closure of ketone **5.15** to

obtain tetracyclic enone **5.16** (Scheme 5.2). A Mannich reaction of oxindole

5.12 and aldehyde **5.13** provided spirooxindole **5.14** which was treated with

triethyloxonium tetrafluoroborate and then with sodium hydride to furnish

tetracycle **5.16**. The latter was converted to Büchi's tetracyclic ketone **5.9** via

N-methylation, conjugate reduction and deprotection.
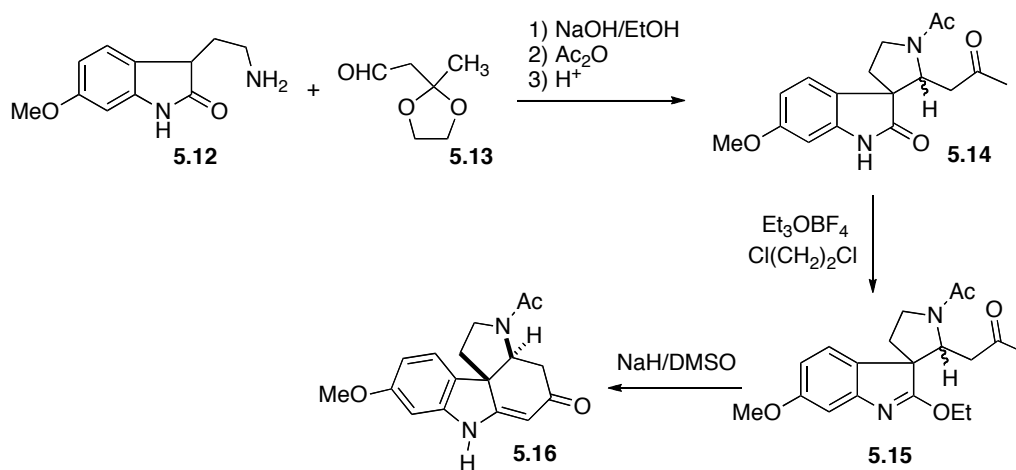
Scheme 5.2. Oishi's synthesis of (±)-vindoline (**5.3**)

5.2.2. Syntheses of Vindoline Based on Indoloquinolizidine Derivatives

After the elegant total synthesis of vindoline (**5.3**) by Büchi, several improvements directed towards "Büchi-type synthesis" appeared in the literature. For example, in 1985 Langlois and co-workers reported a total synthesis of (±)-vindoline (**5.3**) which passed through enone **5.23**.[89] The strategy employed for construction of vindoline was centered around the preparation of [2,3-α]indoloquinolizidine derivative **5.22** which led directly to pentacyclic ketone **5.23** via acid-catalyzed rearrangement.[90] Starting from 6-methoxy-*N*-methyltryptamine (**5.17**), a classical route to 9-methyldihydro-β-carboline was used to prepare **5.18**.[89] An imino Diels-Alder reaction[91] between **5.18** and diene **5.19** furnished indoloquinolizidines **5.20** and **5.21** which were alkylated with ethyl iodide. This was followed by treatment with dimsyllithium to provide keto sulfoxide **5.22**. The latter, in the presence of *p*-toluenesulfonic acid, afforded pentacyclic enone **5.23** after a Pummerer reaction[92] and intramolecular nucleophilic attack on the indole nucleus. Finally, **5.23** was converted to vindoline (**5.3**) using conventional chemistry (Scheme 5.3).

MeO ... N ... NH$_2$ ... Me
5.17

MeO ... N ... N ... Me
5.18

5.19 CO$_2$Me
chlorobenzene
88%

MeO ... H ... N ... Me MeO$_2$C
5.20

+

MeO ... H ... N ... Me MeO$_2$C
5.21

1. LDA/THF/HMPA, EtI
2. MeS(O)CH$_2$Li, THF
64%

MeO ... H ... N ... Me ... Me(O)S ... O ... Et
5.22

TsOH,
THF/H$_2$O
70%

MeO ... N ... Me ... SMe ... O ... Et
5.23
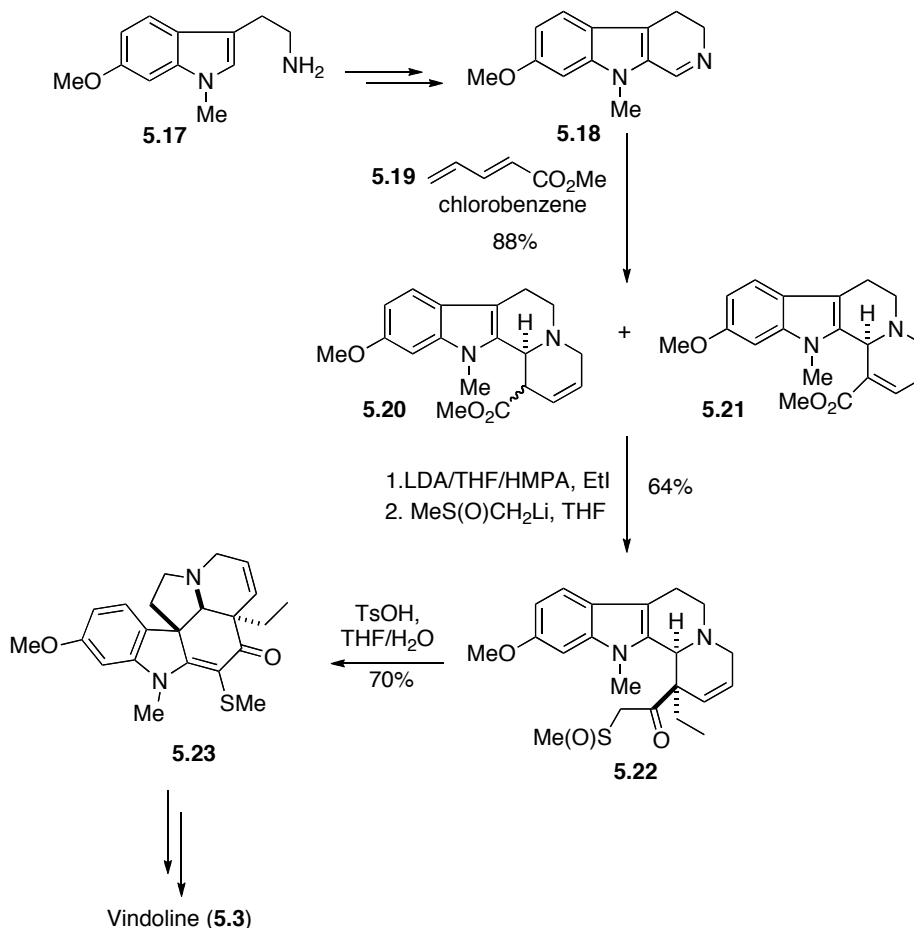
Vindoline (**5.3**)

Scheme 5.3. Langlois' synthesis of (±)-vindoline

The first asymmetric synthesis of (-)-vindoline (**5.3**) was reported by Feldman and Rapoport in 1987 and involved indoloquinolizidine derivative **5.28**.[93] The route proceeded from L-aspartic acid **5.24** to tetrahydropyridine **5.25**, which was coupled with 6-methoxytryptophyl bromide **5.26** to afford **5.27**. The latter was converted to indoloquinolidizine **5.28** using an iminium ion cyclization. Elaboration of **5.28** to **5.30** following Langlois' protocol led to racemic pentacyclic ketone **5.30** due to an intervening reversible Mannich reaction.[94] To avoid this loss of stereospecificity, a modified approach was employed for

conversion of **5.28** to **5.29** via a three-step sequence that commenced with acetylation of the indole nitrogen and continued with Dieckmann condensation and basic opening of the resultant ε-lactam.
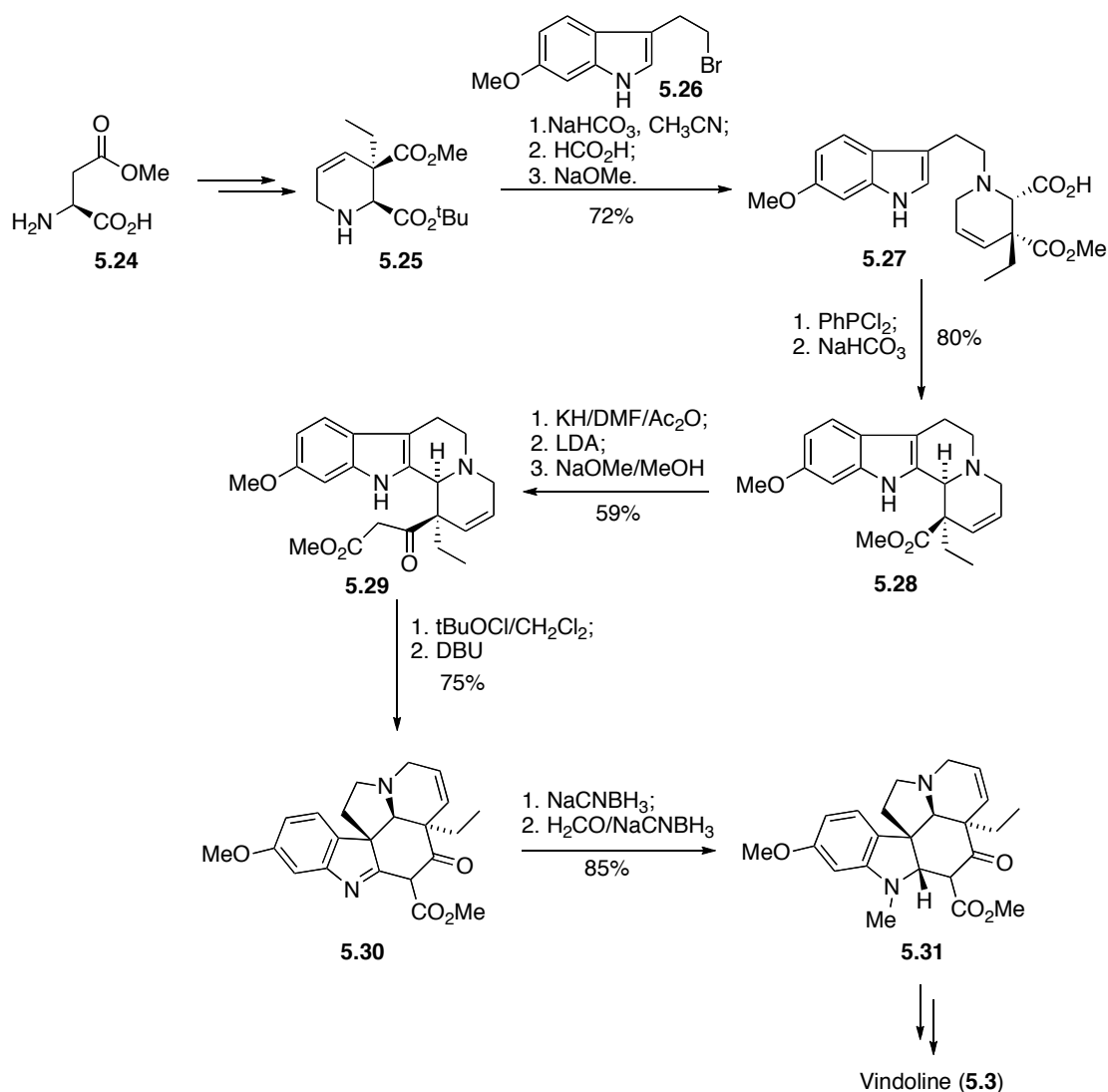
Scheme 5.4. Rapoport's asymmetric synthesis of vindoline

The cyclization of **5.29** to pentacyclic keto ester **5.30** was accomplished with *t*-butyl hypochlorite followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); subsequent treatment of indolenine **5.30** with sodium cyanoborohydride

followed by *N*-methylation and reduction generated pentacyclic ketone **5.31**. The latter was converted to (-)-vindoline (**5.3**) using a procedure similar to that employed by Büchi.[86a]

5.2.3. Intramolecular [4+2]/[3+2] Cycloaddition Cascade Route to

Vindoline

In 2006, a very concise total synthesis of (-)-vindoline (**5.3**) was reported by Boger and co-workers using a unique tandem intramolecular [4+2]/[3+2] cycloaddition cascade of a 1,3,4-oxadiazole. This brilliantly crafted synthesis introduced the C, D and E rings and four C-C bonds characteristic of the pentacyclic nucleus, set all six stereocenters, and introduced essentially all the functionality found in the natural product in a single step.[95]
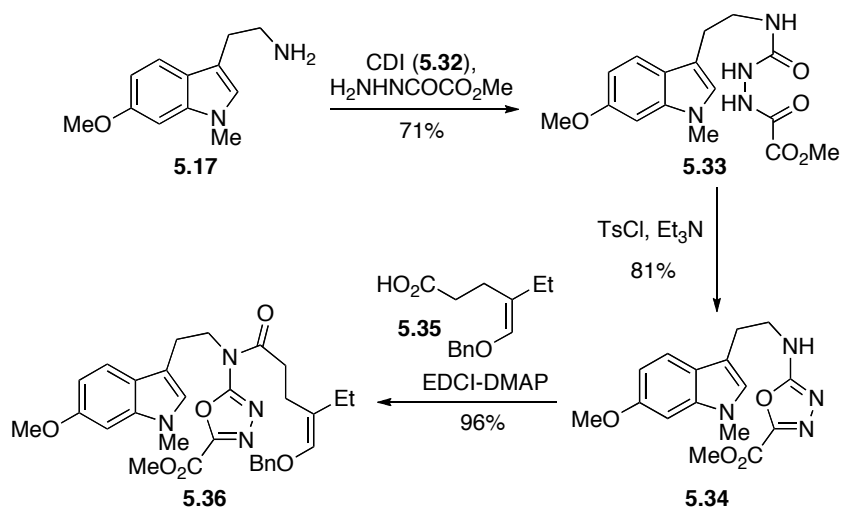
Scheme 5.5. Boger's preparation of cycloaddition substrate **5.36**

Preparation of the precursor oxadiazole **5.36** for the tandem intramolecular [4+2]/[3+2] cycloaddition is shown in Scheme 5.5. Treatment of 6-methoxy-*N*-methyltryptamine (**5.17**) with carbonyldiimidazole (CDI, **5.32**) followed by methyl oxalylhydrazide furnished **5.33.** Closure of **5.33** to 1,3,4-oxadiazole **5.34** and subsequent *N*-acylation with carboxylic acid **5.35** provided the key cycloaddition substrate (*Z*)-**5.36** bearing a tethered 6-methoxyindole dipolarophile and a stereochemically defined electron-rich dienophile.
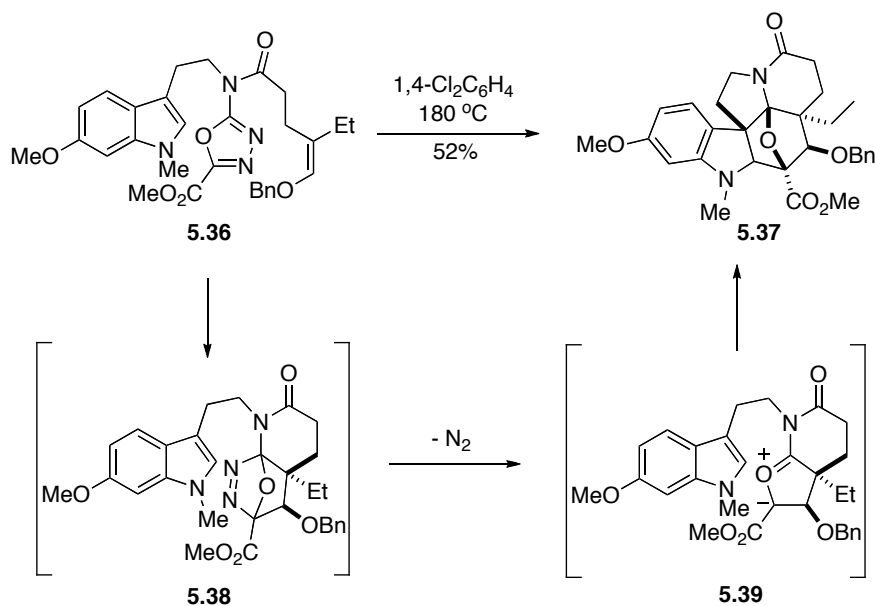
Scheme 5.6. Boger's tandem [4+2]/[3+2] cycloaddition cascade

Oxodiazole **5.36** underwent the key [4+2]/[3+2] cycloaddition cascade in refluxing dichlorobenzene to give the pentacyclic product **5.37** in moderate yield. The sequence is initiated by intramolecular [4+2] cycloaddition of the 1,3,4-oxadiazole with the tethered dienophile containing an electron-rich enol ether whose reactivity and regioselectivity are matched with the electron-

deficient oxadiazole in this inverse electron demand Diels-Alder reaction. Loss of nitrogen from **5.38** generated a carbonyl ylide **5.39** which underwent subsequent intramolecular 1,3-dipolar cycloaddition with the tethered indole (Scheme 5.6).[96] Enantiomers of **5.37** were separated by resolution using chiral HPLC. The relative configuration of **5.37** is controlled by a combination of the dienophile geometry and endo orientation in the [3+2] cycloaddition step. The latter is dictated by the dipolarphile tether which sterically directs the indole to the face opposite the newly formed fused lactam (Figure 5.2).[97]
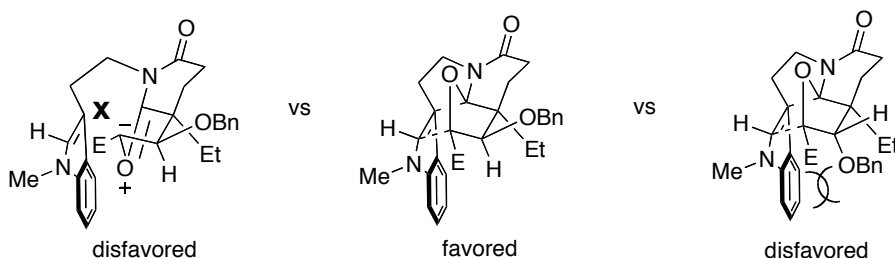
Figure 5.2. The stereochemistry of tandem [4+2]/[3+2] cycloaddition of **5.36**

To conclude the vindoline synthesis, **5.37** was treated with lithium diisopropylamide and bis(trimethylsilyl)peroxide (TMSOOTMS); a quench with trimethylsilyl trifluoromethanesulfonate (TIPSOTf) resulted in silyl ether **5.40**. The extraneous carbonyl group in **5.40** was removed using Lawesson's reagent to generate thiolactam **5.41** and then reduction with Raney nickel. This procedure also served to cleave the benzyl ether of **5.41** to provide **5.42**. Acetylation of the resulting secondary alcohol followed by reductive cleavage of the oxide bridge upon catalytic hydrogenation gave **5.43**. Silyl ether

cleavage, secondary alcohol activation, and subsequent regioselective elimination from **5.43** furnished (-)-vindoline (**5.3**) (Scheme 5.7).
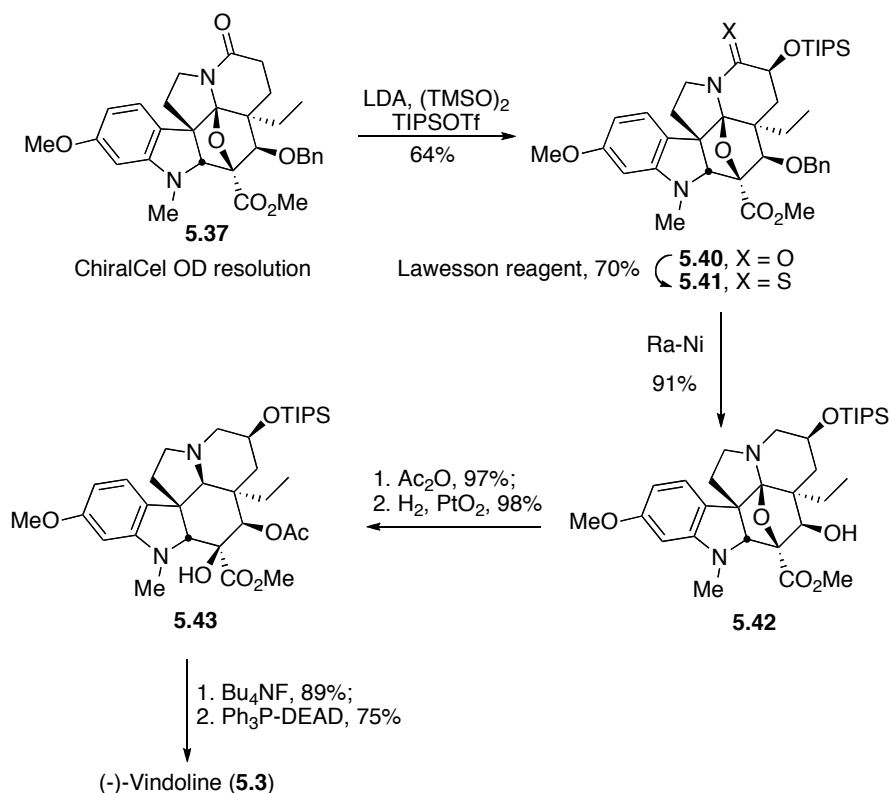
Scheme 5.7. Boger's synthesis of (-)-vindoline (**5.3**)

In 2000, Boger reported an asymmetric synthesis of vindoline based on his intramolecular [4+2]/[3+2] cycloaddition cascade sequence. [98] A chiral substituent on the tether linking the dienophile and oxadiazole of **5.44** was used to control facial selectivity in the initiating inverse electron demand Diels-Alder reaction and to set absolute configuration at the six stereocenters in the cycloadduct. Refluxing **5.44** in dichlorobenzene afforded cycloadduct **5.45**

which was converted to aldehyde **5.47** via diol **5.46**. This approach required that the tether linking the dienophile to the oxadiazole is short so that the intramolecular Diels-Alder reaction of **5.44** could be directed by the chiral substituent in the side chain. In this case, the cycloaddition cascade afforded the fused 5-membered ring structure **5.45**. A subsequent ring expansion was therefore needed to establish the unsaturated 6-membered E ring found in the natural product (Scheme 5.8).
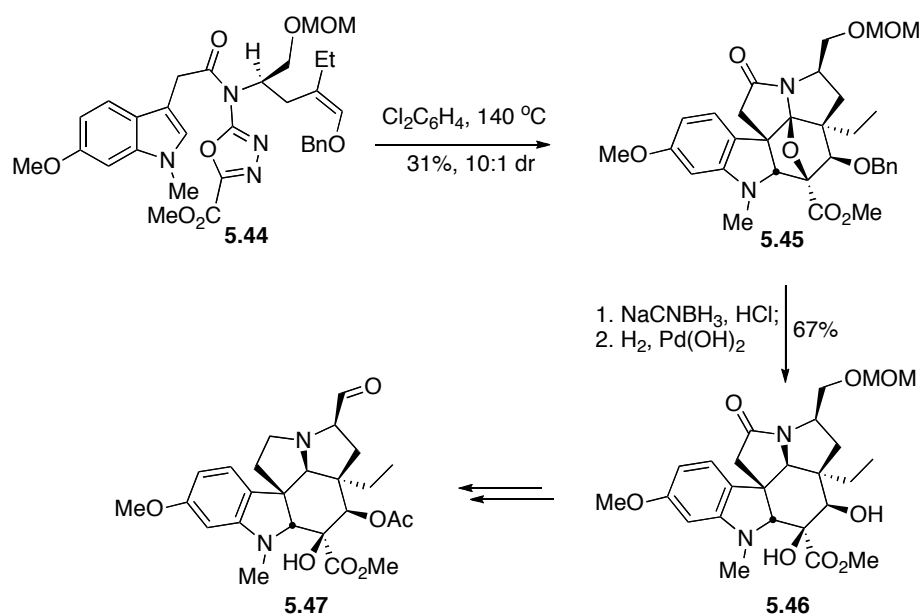
Scheme 5.8. Boger's asymmetric tandem [4+2]/[3+2] cycloaddition cascade

Exposure of **5.47** to silica gel in the presence of triethylamine afforded a *N,O*-ketal which was tosylated to furnish hexacycle **5.48**. Treatment of **5.48** with mild base accomplished the desired ring-expansion to yield ketone **5.49** which was converted to (-)-vindoline via reduction and elimination (Scheme 5.9).
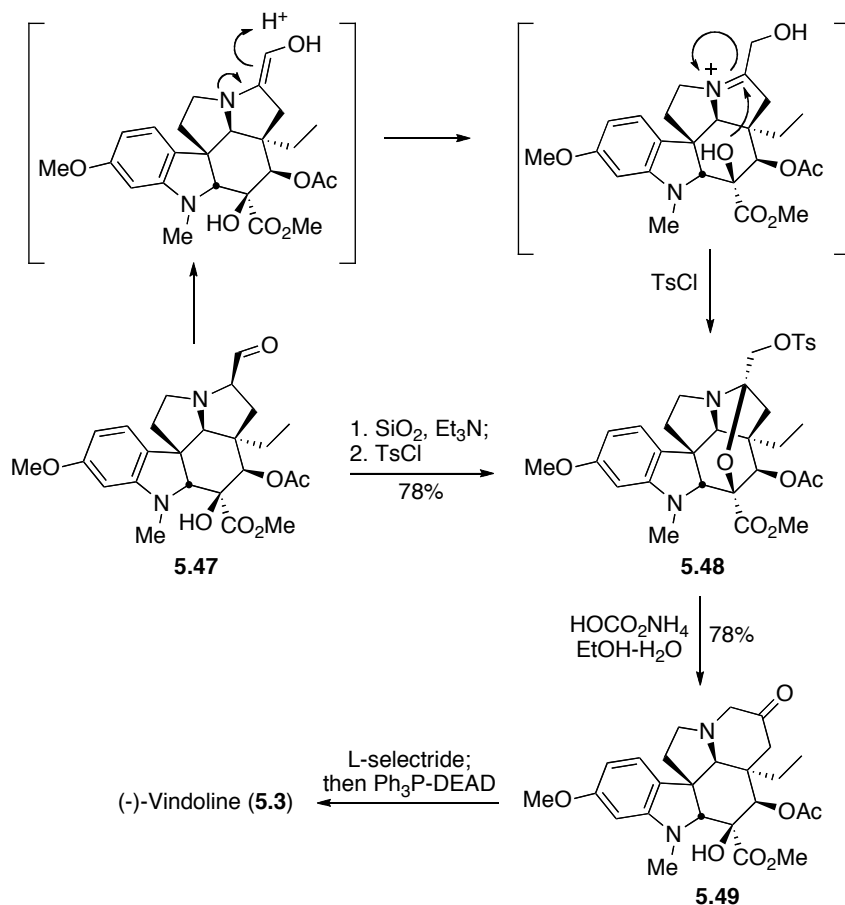
Scheme 5.9. Boger's competion of (-)-vindoline via ring-expansion

The foregoing descriptions of synthetic routes to vindoline, along with the many other published syntheses of members of the *Vinca* alkaloid family, affirm the importance of this subset of natural products. It is also clear that these alkaloids have provided a challenging platform for testing new synthetic strategies addressed at creating the stereochemically complex polycyclic framework present in this class of compounds. The section that follows describes our approach to this problem based upon our TIPCARM concept.

5.3. Studies Towards the Total Synthesis of the *Vinca* Alkaloid

Vindorosine Using a TIPCARM Strategy

Our successful research described in chapters 3 and 4 persuaded us to explore our TIPCARM concept in the context of a synthesis of vindorosine (**5.4**). A retrosynthetic analysis for vindorosine is outlined in Scheme 5.10, although the same strategy could be applicable to vindoline (**5.3**) and minovine (**5.5**) due to the similarity of their structures. We envisioned acquiring **5.4** from keto ester **5.50** which would be prepared from **5.54** using our TIPCARM approach. Thus, intramolecular photochemical [2+2]-cycloaddition of **5.54** followed by fragmentation of the resultant cyclobutane **5.53** would provide zwitterion **5.52** which could equilibrate with **5.51**. A transannular Mannich reaction of iminium ion **5.51** with the embedded enolate would in principle generate pentacyclic ketone **5.50** assuming enolate attack occurs at the *si* face of the iminium double bond.
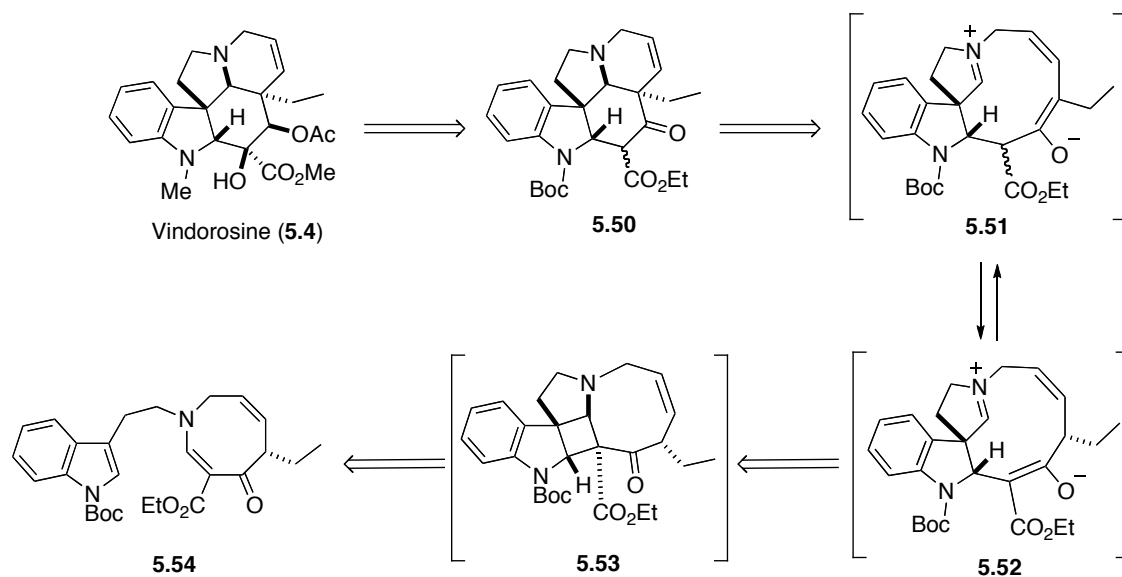
Scheme 5.10. Retrosynthetic analysis of vindorosine (**5.4**)

Photo substrate **5.54** would be prepared from the *N*-protected bromoethyl indole **5.55** and enone **5.56**, the latter being generated from triene **5.57** via ring-closing metathesis.[99] Triene **5.57** results from condensation of allylamine with enoate **5.58,** and **5.58** is derived from keto ester **5.59**[100] via pentenyl bromide **5.60** and ethyl cyanoacetate **5.61** using a known procedure (Scheme 5.11).[101]
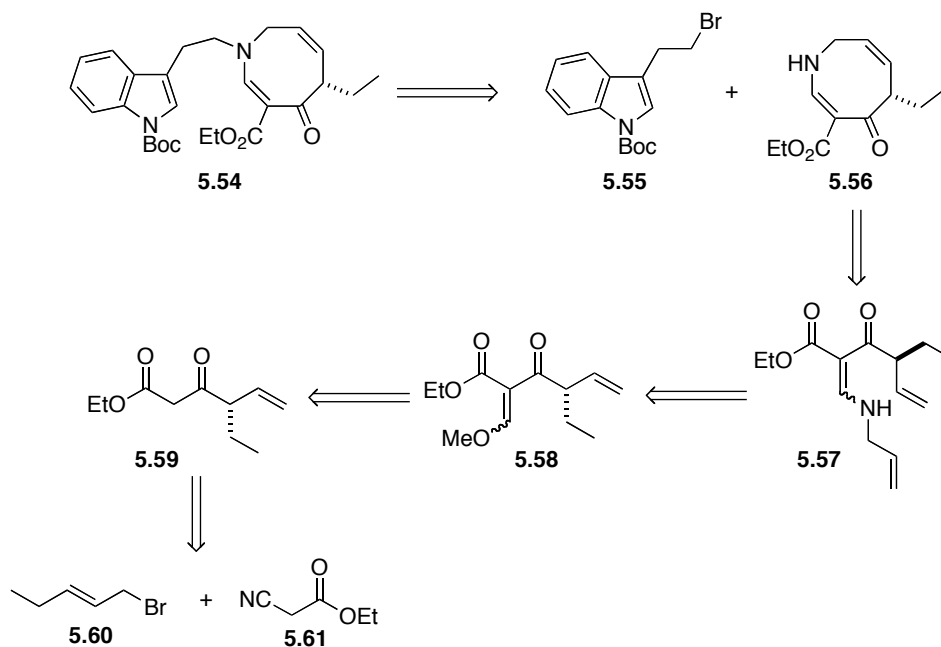
Scheme 5.11. Retrosynthetic analysis of vindorosine (**5.4**)

Starting from inexpensive trans-2-pentenal (**5.62**), (*E*)-pent-2-en-1-ol (**5.63**) was prepared by reduction with lithium aluminum hydride (Scheme 5.12) and was converted to bromide **5.64** by treatment with triphenylphosphine and bromine in tetrahydrofuran. Reaction of ethyl cyanoacetate **5.61** with **5.60** in the presence of aluminum chloride and zinc powder gave ethyl 4-ethyl-3-oxohex-5-enoate (**5.59**), which was treated with trimethyl orthoformate in acetic anhydride to provide ethyl 4-ethyl-2-(methoxymethylene)-3-oxohex-5-enoate (**5.58**) as a mixture of (*E*) and (*Z*) isomers. Condensation of **5.58** with allylamine (**5.64**) gave (*E*)-ethyl 2-((allylamino)methylene)-4-ethyl-3-oxohex-5-enoate (**5.57**), our putative substrate for ring-closing metathesis, as a 10:1 mixture of diastereoisomers.
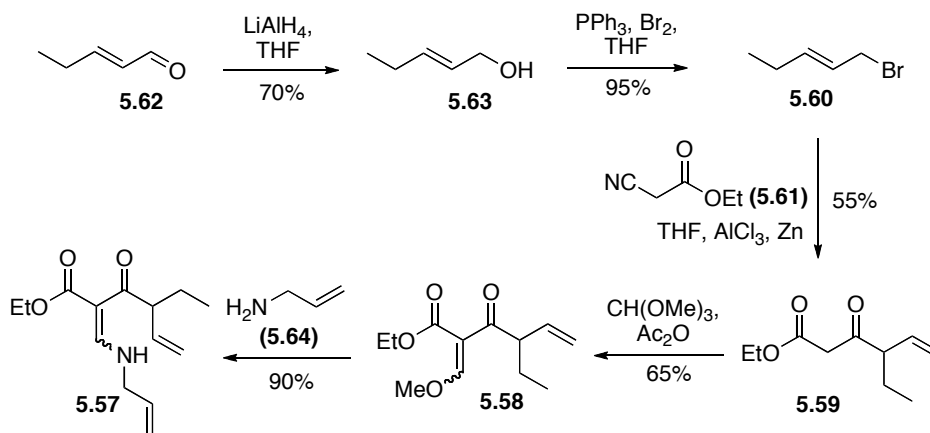
Scheme 5.12. Preparation of triene **5.57**

Unfortunately, treatment of **5.57** with Grubbs' second generation metathesis catalyst **5.69** failed to provide any trace of **5.56**. It was believed that this failure could be due to the presence of a free amine in **5.57**, but protection of the secondary amine with *tert*-butyldimethylsilyl chloride and subsequent treatment of **5.65** with Grubbs' catalyst **5.69** again resulted in recovery of the starting material (Scheme 5.13). Analysis indicated that the high strain energy presented in the eight-membered cyclodiene led to the failure of ring-closing metathesis, and prevented from furnishing either *cis, cis* or *trans, trans* **5.56**. This disappointing outcome caused us to revise our plan for preparing our TIPCARM precursor.
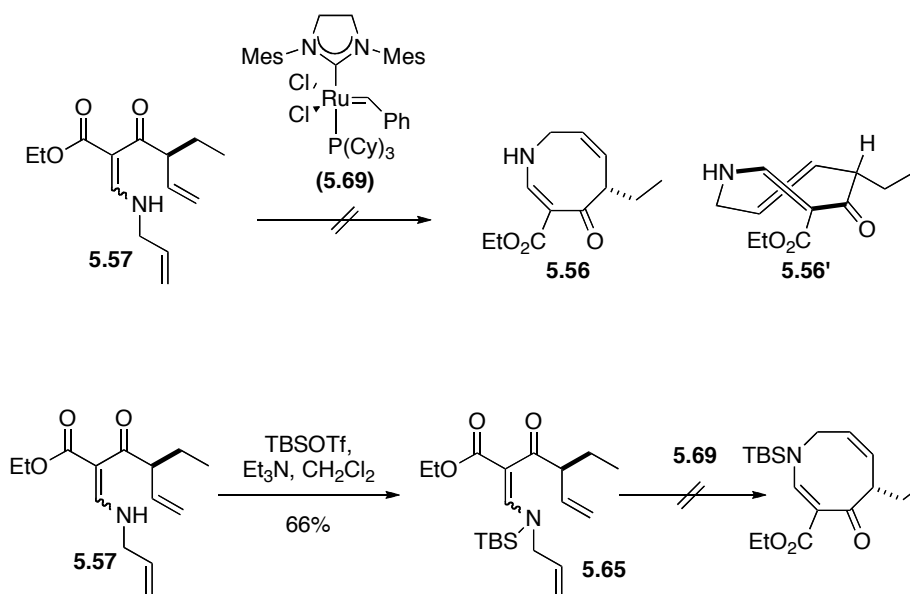
Scheme 5.13. Attempted ring-closing metathesis of trienes **5.57** and **5.65**

In our revised plan, the TIPCARM sequence would precede ring-closing

metathesis en route to the tetracyclic skeleton of vindorosine (**5.4**). For

example, irradiation of **5.67** would afford tetracyclic keto ester **5.66** which

would be used to fabricate pentacycle **5.50** via ring-closing metathesis

(Scheme 5.14). In addition to **5.67**, two other photochemical precursors, **5.70**

and **5.71,** were prepared using conditions similar to those employed

previously. Thus, bromide **5.55** was reacted with allylamine (**5.64**) to give **5.68**

which underwent condensation with **5.58** to yield **5.67.** Alternatively,

tryptamine **3.4** was condensed directly with **5.58** to afford **5.70** or with **5.59** to

provide **5.71**. However, irradiation of these three substrates produced none of

the desired TIPCARM product and resulted in either decomposed material or

return of starting compound (Scheme 5.15).
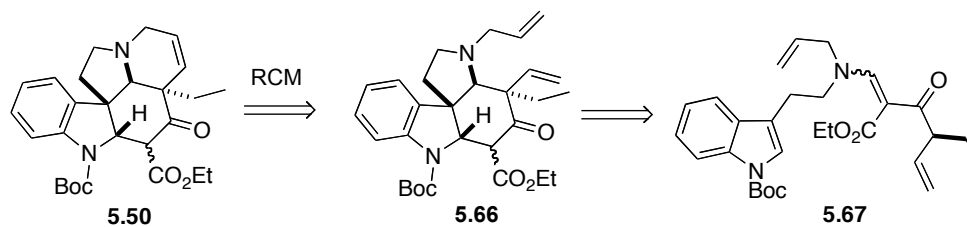
Scheme 5.14. Revised plan for synthesis of the pentacyclic skeleton **5.50**
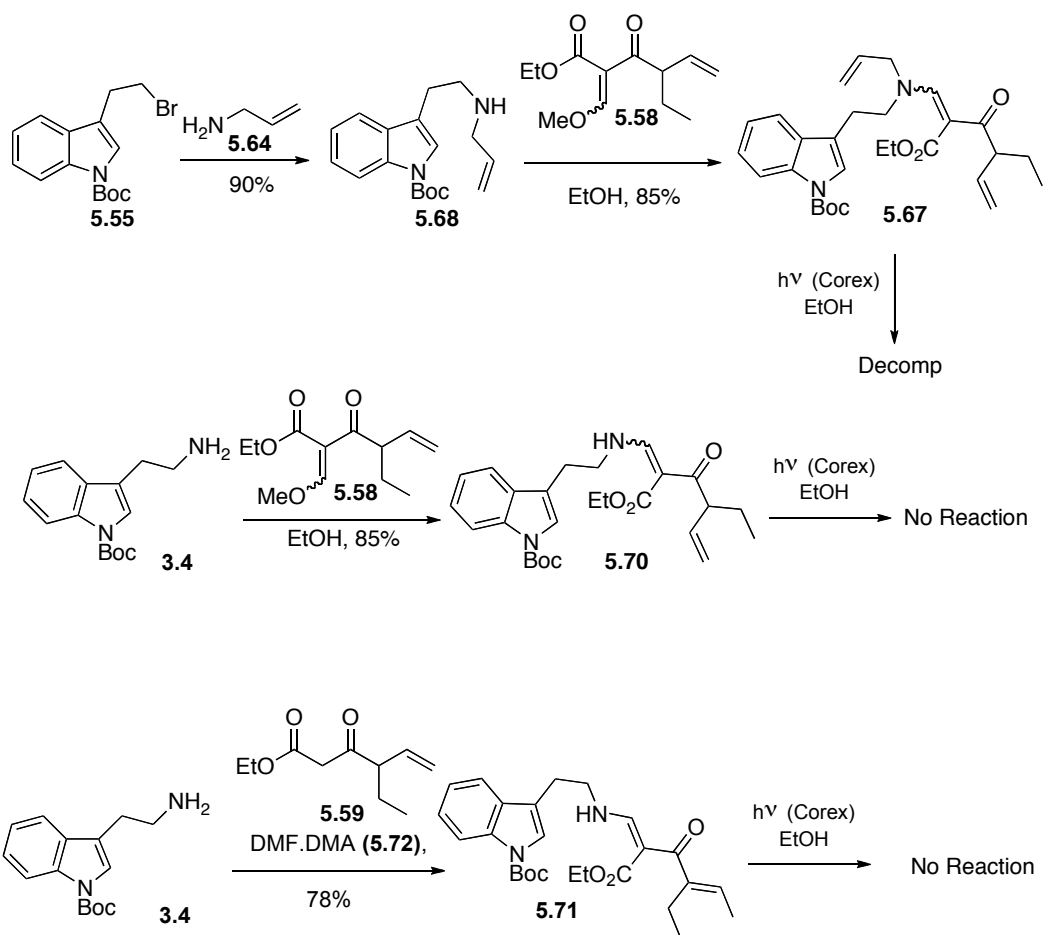
Scheme 5.15. Attempted TIPCARM of **5.67**, **5.70** and **5.71**

An alternative TIPCARM candidate for acquiring our desired spiro indoline that

seemed more promising was keto ester **5.75** lacking both the N-allyl

substituent and side-chain unsaturation**.** This photo substrate was prepared by condensation of commercially available ethyl butyrylacetate (**5.73**) with *N,N*-dimethylformamide dimethyl acetal (**5.72**) in the presence of *p*-toluenesulfonic acid to give **5.74** which was then condensed with protected tryptamine **3.4** to furnish **5.75**. Irradiation of **5.75** in ethanol for 48 hours afforded TIPCARM product **5.76** in good yield as a pair of stereoisomers at the β–keto ester carbon (Scheme 5.16). Iminium methiodide **5.77** was obtained from **5.76** by exposure to methyl iodide, and treatment of **5.77** with sodium hydride and lithium diisopropylamide resulted in its clean cyclization to **5.78** as a mixture of isomers (5:2).
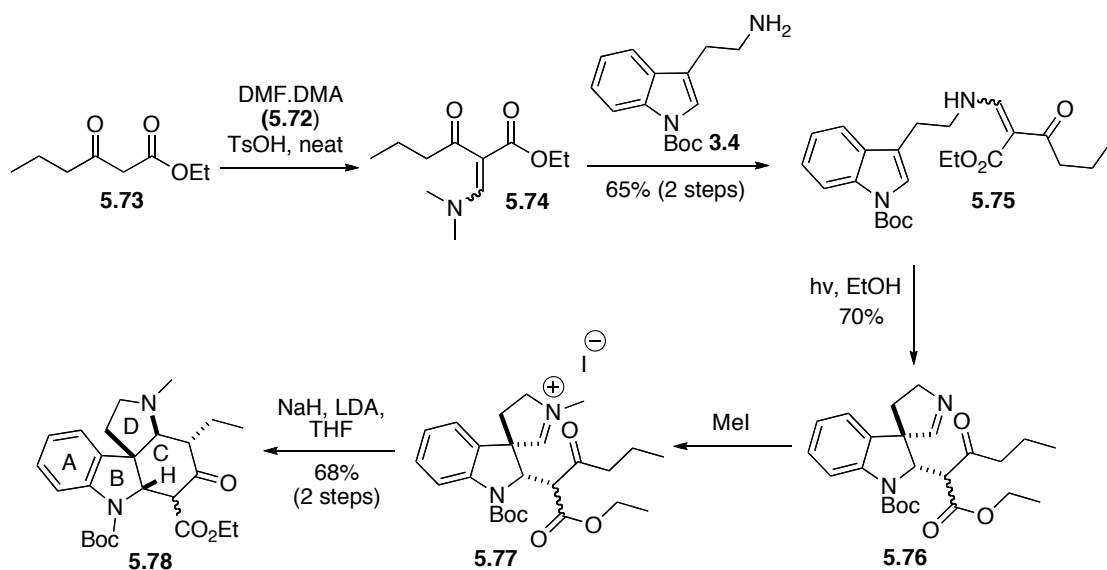
Scheme 5.16. Synthesis of tetracyclic keto ester **5.78**
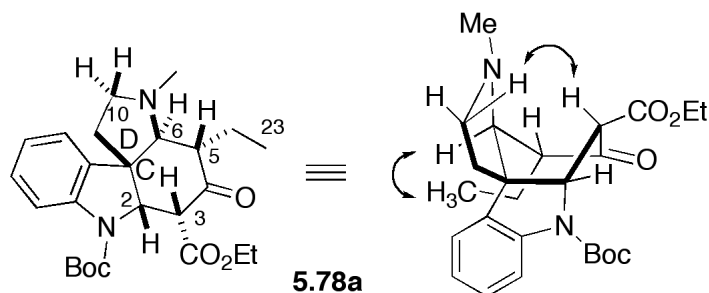
Figure 5.3. The structure of **5.78a**

The structure of the major isomer **5.78a** is shown in Figure 5.3. The configuration of **5.78a** was established by careful 1D and 2D ^{1}H NMR studies. The ^{1}H NMR spectrum of **5.78a** shows a singlet for H-2 at δ 5.02 ppm, which suggests that H-2 and H-3 (δ 3.28 ppm) are *cis* with an angle between these two protons of near 90°. This assignment was further confirmed by a strong NOESY correlation between H-3 and H10$_b$ which therefore requires that ring C adopts a boat conformation and places H-3 on the endo face of the C/D ring system. The H-5 proton appears as a doublet of triplets (J = 8.4 and 1.1 Hz) at δ 2.43 ppm. The small coupling constant of the doublet indicates that H-6 (δ 2.31 ppm) and H-5 are nearly orthogonal on ring C, ie *trans*. A strong NOESY correlation between H-6 and methyl protons H-23 (δ 0.9 ppm) proves that the ethyl group and H-6 are *cis* so that H-5 can be assigned *trans* to H-6 (and therefore *cis* to H-3). The H-3 (δ 3.68 ppm) at minor isomer appears doublet (J = 7.9 Hz), which suggests an axial-axial coupling with H-2. This assignment indicates a chair conformation of C ring, which is also proved by the fact that there is no NOESY correlation between H10$_b$ and the protons belong to the

ethyl ester.

This sequence to **5.78** confirmed that our plan for building rings A, B, C and D of vindorosine in stereoselective fashion was not only viable but was likely to be efficient. For vindorosine, however, it would be necessary to replace methyl iodide in the reaction with **5.76** by a more highly functionalized alkylating agent in order to set the stage for fabricating ring E of the alkaloids.

For advancement of our TIPCARM route towards vindorosine, pyrroline **5.76** was alkylated with iodide **5.79**. This provided iminium iodide **5.80** but cyclization of the dienolate of **5.80**, prepared with sodium hydride and lithium diisopropylamide in tetrahydrofuran, furnished tetracyclic ketone **5.81** in only low yield. Subsequent cleavage of the silyl ether of **5.81** with tetrabutylammonium fluoride followed by oxidation of the resultant alcohol **5.82** afforded aldehyde **5.83** (Scheme 5.17). However, aldehyde **5.83** was unstable, perhaps due to a retro-Mannich fragmentation that removed the propanal side chain, and **5.83** could not be converted to **5.84** by the intramolecular aldol reaction we had envisioned.
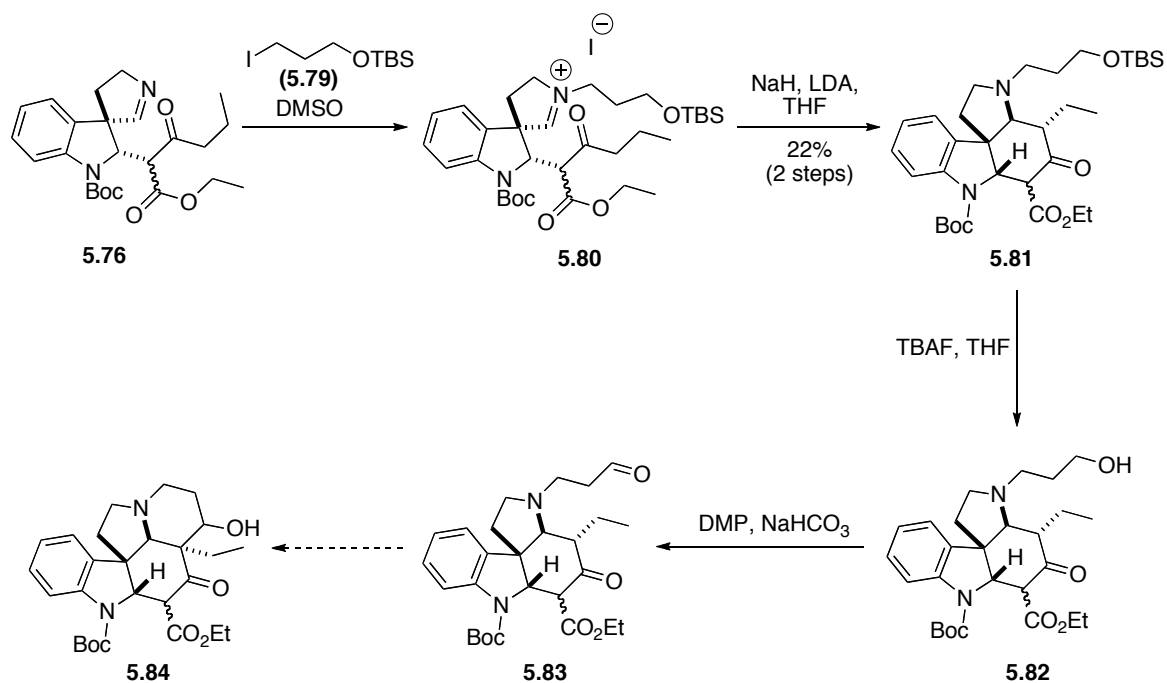
Scheme 5.17. Synthesis of tetracyclic keto ester **5.81** and its conversion to aldehyde **5.83**

The low yield of the two-step conversion of **5.76** to tetracycle **5.81** together with the instability associated with aldehyde **5.83** prompted us to devise an alternative plan for constructing ring E of vindorosine that aimed for a regioisomer of alcohol **5.84**. This involved alkylation of **5.76** with allyl iodide (**5.77**) to furnish iminiun iodide **5.85**, cyclization of which with sodium hydride and lithium diisopropylamide led to tetracyclic ketone **5.86** (as a mixture of stereoisomers) in good yield. Unfortunately, attempts to effect epoxidation of the terminal alkene of **5.86** with reagents such as *meta*-chloroperoxybenzoic acid led to decomposition of starting material with no apparent formation of **5.87** due to retro-Mannich fragmentation which can open C or D ring.

Epoxidation with *tert*-butyl hydroperoxide under neutral or basic condition would form amine oxide, which led to rearrangement of the tertiary amine and decomposition.
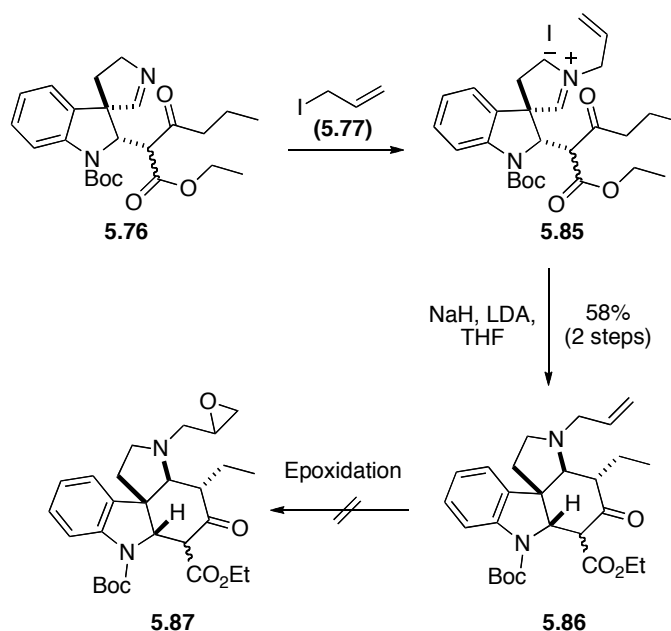
Scheme 5.18. Synthesis of tetracyclic ketone **5.86**

A new route to **5.87** would be available if the *N*-allyl residue of **5.86** were replaced by a glycidyl substituent and in fact the first step in this sequence has been accomplished with the conversion of **5.86** to tetracycle **5.88** using tetrakistriphenylphosphinepalladium (Scheme 5.19).[102] Secondary amine **5.88** can now be used as the focal intermediate for installation of a glycidyl unit at the pyrrolidine nitrogen atom unit with bromide **5.87**. Cyclization of **5.87** via its dienolate followed by dehydration and subsequent functional group manipulations would furnish vindorosine (**5.4**). Similarly, alkylation of **5.88** with iodo bromide **5.90** would lead to tetracyclic bromide **5.91** which could be used

as an entry to minovine (**5.5**) containing a saturated E ring (Scheme 5.19)**.**
Vindoline (**5.3**) could be synthesized by a route analogous to that employed to
reach **5.4** by starting from 6-methoxytryptamine. These endgame strategies
remain to be reduced to practice.
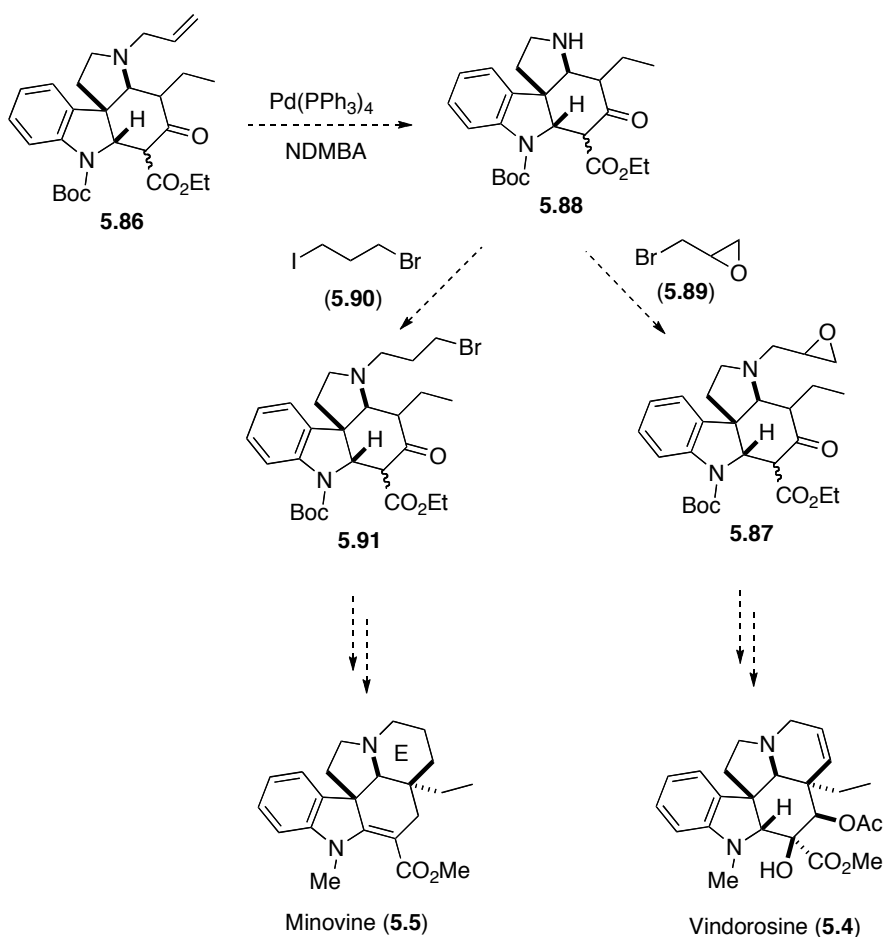
Scheme 5.19. Alternative route to vindorosine (**5.4**) and minovine (**5.5**)

An alternative plan is inspired by Büchi's synthesis. Condensation of **5.88** with
acrolein in methanol containing sodium methoxide would lead to alcohol **5.92**,
which could be dehydrated to furnish tetrahydropyridine **5.93**. Subsequent
functional group manipulations would provide vindorosine (**5.4**).
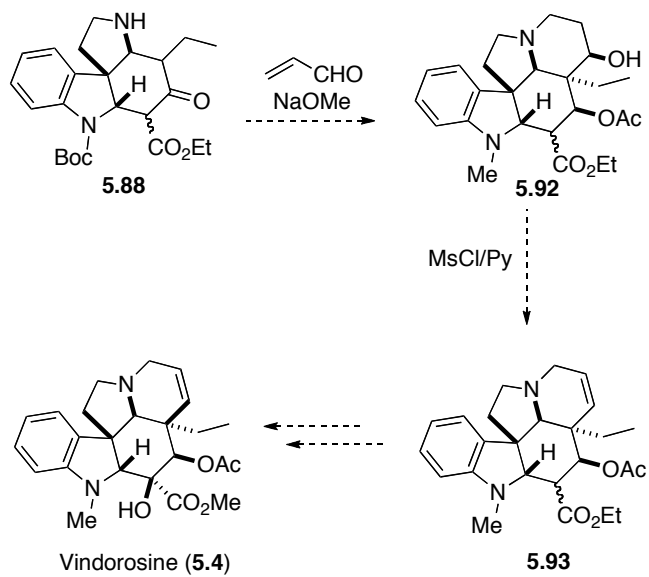
Scheme 5.20. Alternative plan to vindorosine (**5.4**)

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Chapter 6. Conclusion

The study described in this dissertation presents a novel tandem intramolecular photocycloaddition-retro-Mannich (TIPCARM) sequence as a route to indole and oxindole alkaloids. Irradiation of a tryptamine linked through its side-chain nitrogen to an alkylidene malonate residue results in an intramolecular [2 + 2] cycloaddition to the indole 2,3-double bond. The resultant cyclobutane undergoes spontaneous retro-Mannich fission to produce a spiro[indoline-3,3-pyrrolenine] with relative configuration defined by the orientation of substituents in the transient cyclobutane. The TIPCARM sequence leads to a spiropyrrolidine which is poised to undergo a second retro-Mannich fragmentation [TIPCA(RM)$_2$] that expels the malonate unit present in the photo substrate and generates transiently an indolenine. The indolenine undergoes rearrangement to a β-carboline which can undergo further rearrangement under oxidizing conditions to an oxindole. Three oxindole natural products, coerulescine, horsfiline and elacomine, were synthesized using this strategy.

The TIPCARM strategy was extended to an approach that would encompass the *Vinca* alkaloids vindorosine and minovine. In this case, the TIPCARM sequence was followed by an intramolecular cyclization that provided

tetracyclic ketone **5.86** containing rings A, B, C and D of vindorosine. A tetracyclic intermediate was synthesized which could also provided access to the *Vinca* alkaloid minovine.

Experimental Section

General. Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1}. ^1H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent.

Routine monitoring of reactions was performed using silica gel on aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on 230- 400 mesh silica gel.

Air and/or moisture sensitive reactions were performed under inert atmosphere conditions. Reactions requiring rigorously anhydrous conditions were performed under a blanket of argon in glassware dried in an oven at 150 °C or by flame and then cooled under argon. Dry THF and dichloromethane were obtained from a commercial solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without further purification.
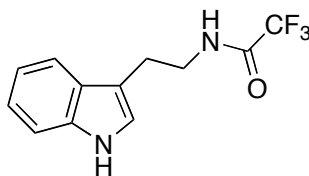
3.2

N-(2-(1H-Indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (3.2). To a solution of tryptamine (**3.1**, 1.00 g, 6.24 mmol) in CH_2Cl_2 (56 mL) containing pyridine (5.6 mL) at 0 °C under argon was added dropwise trifluoroacetic anhydride (920 μL, 6.60 mmol). After 5 min, the cold bath was removed and the mixture was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2 and the solution was washed with satd aq NaHCO$_3$, aq NH$_4$Cl, and H$_2$O. The combined extracts were dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes: EtOAc 3:1) afforded **3.2** as a colorless oil (944 mg, 72%): IR (neat) 3406, 1701, 1560, 1173, 749 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.10 (t, J = 6.7 Hz, 2H), 3.73 (dd, J = 6.5, 6.4 Hz, 2H), 7.08 (d, J = 2.3 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 8.12 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 24.7, 40.1, 111.4, 111.8, 118.5, 119.8, 122.2, 122.6, 127.0, 136.5; HRMS calcd for $C_{12}H_{11}N_2F_3O$ m/z 256.0824, found 256.0820.

3.3
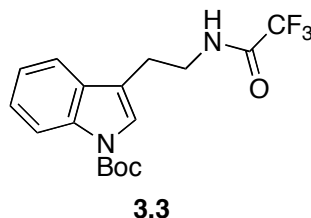
***tert*-Butyl   3-(2-(2,2,2-Trifluoroacetamido)ethyl)-1*H*-indole-1-carboxylate**

(3.3). To a solution of **3.2** (1.00 g, 3.90 mmol) in THF (39.0 mL) was added

Boc₂O (916 mg, 4.68 mmol) followed by DMAP (24.0 mg, 5 mol%).   The

solution was warmed to 40 °C for 1h, then was diluted with CH_2Cl_2 and

washed with H_2O. The solution was dried (Na_2SO_4) and filtered, and the filtrate

was concentrated in vacuo. Purification of the residue by chromatography on

silica gel (hexanes: EtOAc 10:1) gave **3.3** as a colorless oil **(**1.25 g, 85%): IR

(neat) 3314, 2982, 1723, 1566, 1462, 1380, 1168, 1086, 754 cm^{-1}; ¹H NMR

(400 MHz, CDCl₃) δ 1.70 (s, 9H), 3.05 (t, *J* = 6.7 Hz, 2H), 3.61 (dd, *J* = 6.5, 6.4

Hz, 2H), 6.60 (bs, 1H), 7.22 (t, *J* = 7.8 Hz 1H), 7.34 (t, *J* = 8.0 Hz 1H), 7.42 (s,

1H), 7.52 (d, *J* = 7.8 Hz 1H), 8.15 (d, *J* = 7.8 Hz 1H); ¹³C NMR (100 MHz,

CDCl₃) δ 24.5, 28.2, 39.6, 83.2, 115.5, 116.5, 118.6, 122.7, 123.4, 124.8,

128.5, 129.3, 135.1, 149.0; HRMS calcd for $C_{17}H_{19}N_2F_3O_3$ *m/z* 356.1348,

found 356.1360.

3.6
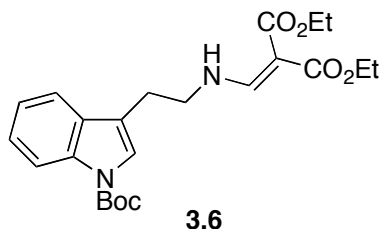
Diethyl 2-((2-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)ethylamino)methylene)-malonate (3.6). To a solution of **3.3** (700 mg, 1.85 mmol) in MeOH-H_2O (18.5 mL, 70:30) was added K_2CO_3 (900 mg) in one portion. The mixture was stirred for 48 h, then was poured into H_2O and extracted with CH_2Cl_2 (3 x 50 mL). The extract was dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo to afford crude **3.4** as a pale yellow oil (880 mg, 96%). This material was used without further purification in the next reaction.

To a solution of **3.4** obtained above (880 mg, 3.02 mmol) and diethyl ethoxymethylene malonate (345 μL, 3.44 mmol) in EtOH (3 mL) was added K_2CO_3 (520 mg, 3.94 mmol) and the mixture was stirred at room temp for 5 h. The resulting yellow solution, which contained a small amount of white solid, was poured into H_2O (50 mL) and was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo to afford crude **3.6** as a yellow oil. The crude product was purified by chromatography on silica gel (hexanes: EtOAc 4:1) to give pure **3.6** as a pale yellow solid (1.37 g, 90%): mp 58-63 $^{\circ}$C; IR (KBr) 3276, 3192, 3112, 3057, 2979, 2935, 2901, 1734, 1653, 1616, 1456, 1375, 1258,

1217, 1154, 1088, 1033, 802, 747 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.23 (t, J = 6.7 Hz, 3H), 1.31 (t, J =6.7 Hz, 3H), 1.66 (s, 9H), 2.98 (t, J = 6.8 Hz, 2H), 3.63 (q, J = 5.9 Hz, 2H), 4.13 (q, J = 6.9 Hz, 2H), 4.21 (q, J = 6.9 Hz, 2H), 7.24 (m, 1H), 7.33 (m, 1H), 7.41 (s, 1H), 7.47 (m, 1H), 7.90 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 7.9 Hz, 1H), 9.27 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.3, 14.4, 26.8, 28.1, 49.3, 59.6, 59.8, 83.5, 89.8, 113.2, 116.1, 124.3, 130.6, 135.5, 149.5, 156.0, 165.9, 169.2; HRMS calcd for C$_{23}$H$_{31}$N$_2$O$_6$ m/z 431.2182, found 431.2163.

3.8
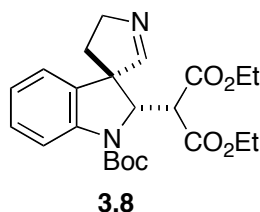
Diethyl   2-(1-(*tert*-Butoxycarbonyl)-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-2-yl)malonate (3.8). A degassed solution of **3.6** (200 mg, 0.47 mmol) in EtOH (100 mL) was irradiated with a 450W medium-pressure mercury lamp through a Corex filter for 12 h. The solution was concentrated in vacuo and the resulting yellow oil was purified by chromatography on silica gel (hexanes : EtOAc 1:1) to afford **3.8** as a pale yellow oil (164 mg, 82%): IR (neat) 2978, 2936, 2863, 1733, 1700, 1481, 1381, 1305, 1283, 1253, 1165, 1033, 754 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.03 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 1.57 (s, 9H), 1.99 (ddd, J = 12.8, 6.8, 6.8 Hz, 1H), 2.30 (ddd, J = 12.8, 6.8, 6.8

Hz, 1H), 3.85 (m, 2H), 3.99 (t, J = 6.4 Hz, 2H), 4.15 (m, 2H), 4.22 (d, J = 6.4 Hz, 2H), 4.96 (bs, 1H), 6.80 (dt, J = 7.6, 1.2 Hz, 1H), 6.95 (dt, J = 7.6, 1.2 Hz, 1H), 7.18 (dt, J = 7.8, 1.2 Hz, 1H), 7.79 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.6, 13.8, 28.4, 42.1, 52.6, 59.9, 60.0, 61.6, 64.1, 67.8, 115.5, 122.6, 123.5, 128.6, 134.7, 140.2, 166.5, 166.9, 167.0; HRMS calcd for C$_{23}$H$_{30}$N$_2$O$_6$ *m/z* 430.2104, found 430.2115.
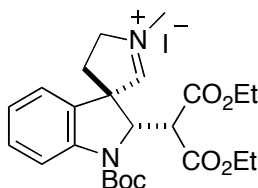
1-(*tert*-Butoxycarbonyl)-2-(1,3-diethoxy-1,3-dioxopropan-2-yl)-1'-methyl-4',5'-dihydrospiro[indoline-3,3'-pyrrol]-1'-ium Iodide. A mixture of methyl iodide (1.10 mL, 2.00 mmol) and **3.8** (380 mg, 0.88 mmol) was stirred for 48 h. The resulting yellow solution was concentrated in vacuo and the residual solid was dried under high vacuum to afford the title compound as a pale yellow solid (475 mg, 94%): IR (KBr) 3444, 2979, 2935, 1716, 1483, 1382, 1287, 1256, 1162, 1032, 758 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.96 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.61 (s, 9H), 2.75 (m, 2H), 3.52 (m, 1H), 3.87 (m, 1H), 4.14 (s, 2H), 4.22 (m, 2H), 4.39 (m, 2H), 4.95 (bs, 1H), 4.97 (ddd, J = 13.6, 7.2, 7.2 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.40 (bs, 1H), 7.85 (bs, 1H), 9.09 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.5, 13.9,

27.2, 28.3, 39.8, 44.1, 60.3, 62.4, 63.0, 67.6, 83.6, 115.2, 124.8, 126.1, 129.2, 130.4, 139.5, 151.4, 167.5, 168.3, 178.4. This material was used without further purification in the next reaction.

3.9
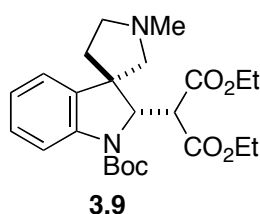
Diethyl 2-(1-(*tert*-Butoxycarbonyl)-1'-methylspiro[indoline-3,3'-pyrrolidine]-2-yl)malonate (3.9). To a solution of the iodide obtained above (500 mg, 0.873 mmol) in MeOH (10 mL) was added NaBH$_4$ (50.0 mg, 1.32 mmol) in one portion. The solution was stirred for 3 h, after which aq NH$_4$Cl was added. The mixture was concentrated by removing solvent in vacuo and the residue was extracted with EtOAc (3 x 5 mL). The combined extracts were dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH$_2$Cl$_2$: MeOH 20:1) gave **3.9** as a colorless oil (268 mg, 71%): IR (neat) 3048, 2978, 2938, 2838, 2780, 1733, 1708, 1602, 1481, 1387, 1280, 1254, 1168, 1039, 868, 753 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.08 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H), 1.55 (s, 9H), 1.85 (ddd, J = 12.8, 8.0, 8.0 Hz, 1H), 2.18 (ddd, J = 12.8, 8.0, 4.0, 1H), 2.56 (s, 3H), 2.70 – 3.10 (m, 3H), 3.31 (m, 1H), 3.75 – 4.00 (m,

3H), 4.11 (m, 2H), 4.99 (d, J = 4.8 Hz, 1H), 7.00 (t, J = 7.6, 1H), 7.15 (t, J = 7.6

Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.49 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ

13.6, 13.9, 28.4, 28.4, 43.7, 54.6, 60.1, 60.6, 61.8, 69.4, 115.2, 123.6, 127.9,

167.6; HRMS calcd for $C_{24}H_{34}N_2O_6$ *m/z* 446.2417, found 446.2493.

3.13
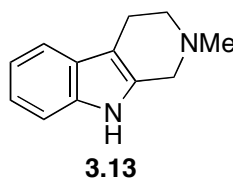
2-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (3.13). To a solution of

3.9 (200 mg, 0.45 mmol) in CH$_2$Cl$_2$ was added TFA (1.60 mL) and the solution

was stirred for 24 h. Satd aq Na$_2$CO$_3$ was added and the mixture was

extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined extracts were dried

(Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. Purification

of the residue by chromatography on silica gel (CH$_2$Cl$_2$: MeOH 50:1) gave **3.13**

as a colorless oil (53.4 mg, 62%): IR (neat) 3411, 2927, 2851, 1674, 1457, 738

cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.51 (s, 3H), 2.85 (m, 4H), 3.58 (s, 2H),

7.13 (m, 2H), 7.30 (m, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.95(bs, 1H); ^{13}C NMR

(100 MHz, CDCl$_3$) δ31.9, 45.2, 52.0, 52.9, 107.7, 110.9, 118.0, 119.3, 121.4,

127.1, 131.2, 136.2; HRMS calcd for $C_{12}H_{14}N_2$ *m/z* 186.1157, found

186.1159.

2.2
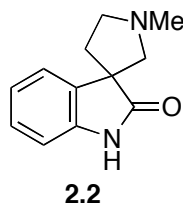
(±)-**Coerulescine (2.2).** To a solution of **3.13** (33 mg, 0.18 mmol) in THF-H_2O-AcOH (1 mL, 1:1:1.5) was added NBS (18 mg, 0.09 mmol). The mixture was stirred for 15 min at room temperature, after which satd aq $NaHCO_3$ was added and the mixture was extracted with EtOAc-Et_3N (6:1, 3 x 5 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH_2Cl_2: MeOH 50:1) afforded **2.2** as a colorless oil (21 mg, 62%): IR (neat) 3225, 1712, 1626, 1470, 1190, 1108, 758 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.13 (m, 1H), 2.45(m, 1H), 2.51 (s, 3H), 2.80 (m, 2H), 2.91 (m, 1H), 3.08 (m, 1H), 6.91 (d, J = 7.6 Hz, 1H), 7.08 (dt, J = 7.6, 1.1 Hz, 1H), 7.23 (dt, J = 7.6, 1.2 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 8.29 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 38.0, 41.9, 53.7, 56.8, 66.4, 109.4, 122.9, 123.4, 127.8, 136.3, 140.0, 182.7; HRMS calcd for $C_{12}H_{14}N_2O$ *m/z* 202.1106, found 202.1108.

3.16
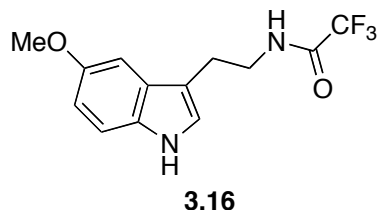
2,2,2-Trifluoro-*N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)acetamide (3.16). To a solution of 5-methoxytryptamine (**3.15**, 100 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) containing pyridine (1 mL) at 0°C under argon was added dropwise trifluoroacetic anhydride (78 μL, 0.55 mmol). After 5 min, the cold bath was removed and the mixture was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2 and the solution was washed with satd aq $NaHCO_3$, aq NH_4Cl, and H_2O. The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes: EtOAc 3:1) yielded **3.16** as a colorless oil (125 mg, 83%): IR (neat) 3335, 1701, 1489, 1216, 1173, 792 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.04 (t, *J* = 6.7, 2H), 3.71 (dd, *J* = 6.3, 6.3 Hz, 2H), 3.91 (s, 3H), 6.39 (bs, 1H), 6.91 (dd, *J* = 8.8, 2.6 Hz 1H), 7.05 (dd, *J* = 8.3, 2.1 Hz, 2H), 7.29 (d, *J* = 8.5 Hz 1H), 8.02 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 24.7, 40.0, 55.9, 100.1, 111.5, 112.2, 112.8, 123.0, 154.3; HRMS calcd for $C_{13}H_{14}N_2F_3O_2$ *m/z* 287.1007, found 287.1011.

3.17
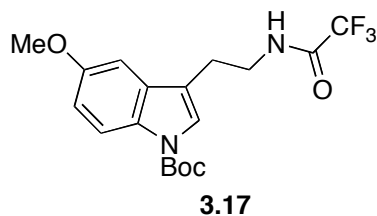
***tert*-Butyl 5-Methoxy-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1*H*-indole-1-carboxylate (3.17).** To a solution of **3.16** (120 mg, 0.42 mmol) in THF (5 mL) was added Boc_2O (98 mg, 0.50 mmol) followed by DMAP (2.5 mg, 5 mol%). The solution was stirred at 40 °C for 1h, then was diluted with CH_2Cl_2 and washed with H_2O. The solution was dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (hexanes: EtOAc 10:1) afforded **3.17** as a colorless oil **(**150 mg, 88%): IR (neat) 2941, 1723, 1481, 1388, 1126, 1081, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 9H), 2.97 (t, J = 6.7 Hz, 2H), 3.71 (dd, J = 6.6, 6.6 Hz, 2H), 3.94 (s, 3H), 6.39 (bs, 1H), 6.98 (dd, J = 8.2, 2.4 Hz 2H), 7.29 (s, 1H), 8.02 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 28.2, 39.6, 55.8, 101.3, 113.4, 116.3, 124.0, 156.0; HRMS calcd for $C_{18}H_{21}N_2F_3O_4$ *m/z* 386.1453, found 386.1470.

3.18
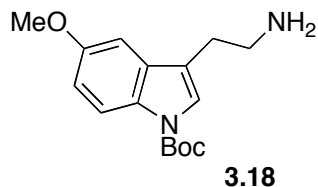
***tert*-Butyl 3-(2-Aminoethyl)-5-methoxy-1*H*-indole-1-carboxylate (3.18).** To a solution of **3.17** (130 mg, 0.318 mmol) in MeOH-H_2O (70:30, 5 mL) was added K_2CO_3 (250 mg) in one portion. The mixture was stirred at room temperature for 48 h and was poured into H_2O. The mixture was extracted with CH_2Cl_2 and the extract was dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to afford virtually pure **3.18** as a pale yellow oil (99 mg, 99%): IR (neat) 2921, 1723, 1478, 1385, 1265, 1009, 792 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.65 (s, 9H), 3.18 (bs, 2H), 3.25 (bs, 2H), 3.84 (s, 3H), 6.90 (dd, *J* = 7.8, 3.0 Hz, 1H), 7.06 (s, 1H), 7.52 (s, 1H), 7.95 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 28.2, 29.7, 39.6, 55.9, 101.3, 113.4, 116.3, 156.0; HRMS calcd for $C_{16}H_{23}N_2O_3$ *m/z*+1 291.1709, found 291.1701.

3.19
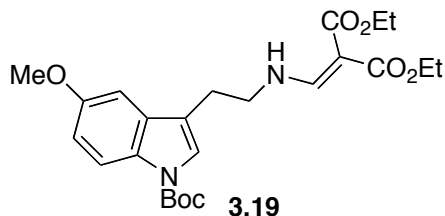
Diethyl 2-((2-(1-(t*ert*-Butoxycarbonyl)-5-methoxy-1*H*-indol-3-yl)ethylamino) methylene)malonate (3.19). To a solution of **3.18** (100 mg, 0.32 mmol) and **3.5** (37 μL, 0.35 mmol) in EtOH (3 mL) was added K_2CO_3 (55

mg, 0.40 mmol). The mixture was stirred at room temperature for 5 h and the resulting yellow solution was poured into H_2O (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried with Na_2SO_4 and filtered. The filtrate was concentrated under vacuum to afford a yellow oil which was purified by chromatography on silica gel (hexanes: EtOAc 4:1) to give **3.19** as a pale yellow oil (134 mg, 91%): IR (neat) 2970, 1728, 1658, 1609, 1472, 1385, 1265, 1157, 1075, 803 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.28 (m, 6H), 1.66 (s, 9H), 2.97 (t, J = 6.8 Hz, 2H), 3.64 (dd, J = 6.8, 6.8 Hz, 2H), 3.86 (s, 3H), 4.15 (q, J = 7.3 Hz, 2H), 4.22(q, J = 7.3 Hz, 2H), 6.93 (m, 2H), 7.39 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 8.04 (m, 1H), 9.26 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.3, 14.4, 26.8, 28.2, 49.4, 55.7, 59.6, 59.8, 83.5, 89.8, 101.4, 113.2, 116.0, 116.2, 124.2, 130.7, 149.3, 155.9, 159.8, 166.0, 169.2; HRMS calcd for $C_{24}H_{32}N_2O_7$ m/z 460.2210, found 460.2216.

3.21
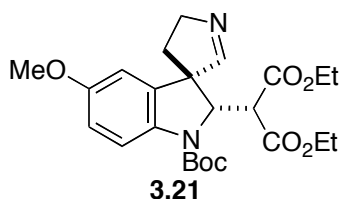
Diethyl 2-(1-(*tert*-Butoxycarbonyl)-5-methoxy-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-2-yl)malonate (3.21). A degassed solution of **3.19** (100 mg, 0.21 mmol) in EtOH (100 mL) was irradiated with a 450W medium-pressure mercury lamp through a Corex filter for 12 h. The solution was concentrated in

vacuo and the resulting yellow oil was purified by chromatography on silica gel (hexanes : EtOAc 1:1) to give **3.21** as a pale yellow oil (60 mg, 60%): IR (neat) 2970, 1734, 1494, 1385, 1282, 1162, 1037 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.10 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.59 (s, 9H), 2.05 (m, 1H), 2.32 (m, 1H), 3.75 (3H, s), 3.94 (m, 2H), 4.02 (dt, J = 6.9, 2.2 Hz, 2H), 4.20 (m, 4H), 4.99 (bs, 1H), 6.40 (d, J = 2.6 Hz, 1H), 6.75 (dd, J = 8.8, 2.5 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.7, 13.9, 28.4, 42.0, 55.7, 60.1, 61.6, 61.9, 68.0, 108.4, 113.5, 116.1, 156.3, 166.5, 166.9; HRMS calcd for C$_{24}$H$_{32}$N$_2$O$_7$ m/z 460.2210, found 460.2213.
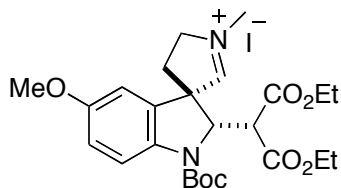
1-(*tert*-Butoxycarbonyl)-2-(1,3-diethoxy-1,3-dioxopropan-2-yl)-5-methoxy-1'-methyl-4',5'dihydrospiro[indoline-3,3'-pyrrol]-1'-ium Iodide. A mixture of methyl iodide (370 mg, 2.60 mmol) and **3.21** (60 mg, 0.130 mmol) was stirred for 48h. The resulting pale yellow solution was concentrated in vacuo and the residue was dried under high vacuum to afford crude title compound. The crude product was used for the next step without purification.

3.22
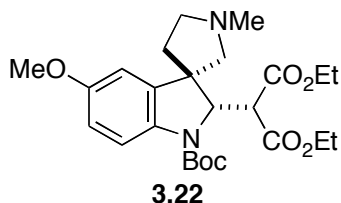
Diethyl 2-(1-(*tert*-Butoxycarbonyl)-5-methoxy-1'-methylspiro[indoline-3,3'-pyrrolidine]-2-yl)malonate (3.22). To a solution of the crude iodide obtained above in MeOH (1 mL) was added NaBH$_4$ (7.4 mg, 0.20 mmol) in one portion. The solution was stirred for 3h, after which satd aq NH$_4$Cl was added. The solvent was evaporated, the residue was extracted with EtOAc (3 x 10 mL) and the combined extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (CH$_2$Cl$_2$: MeOH 20 : 1) to give **3.22** as a colorless oil **(**57 mg, 95% from **3.21**): IR (neat) 2976, 2832, 1734, 1707, 1494, 1391, 1255, 1162, 1037, 868 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.10 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.59 (s, 9H), 1.97 (bs, 2H), 2.22 (bs, 1H), 2.46 (bs, 3H), 2.90 (m, 3H), 3.20 (bs, 1H), 3.80 (s, 3H), 3.94 (m, 3H), 4.16 (m, 2H), 5.00 (bs, 1H), 6.71 (dd, *J* = 9, 3 Hz, 1H), 6.97 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 3.7, 13.9, 28.4, 54.7, 55.8, 61.5, 61.6, 69.6, 115.9, 127.9, 167.2; HRMS calcd for C$_{25}$H$_{36}$N$_2$O$_7$ *m/z* 476.2522, found 476.2525.
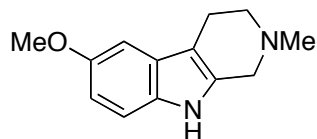
3.26

6-Methoxy-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (3.26). To a

solution of **3.22** (150 mg, 0.33 mmol) in CH_2Cl_2 was added TFA (200 μL) and

the solution was stirred for 24h. Aq Na_2CO_3 was added and the mixture was

extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried

(Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification

of the residue by chromatography on silica gel (CH_2Cl_2: MeOH 50:1) afforded

3.26 as a colorless oil (28 mg, 40%): IR (neat) 3462, 2943, 2829, 1483, 1456,

1216, 1151, 835, 786 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.52 (s, 3H), 2.84 (s,

4H), 3.58 (s, 2H), 3.87 (s, 3H), 6.80 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.95 (d, *J* = 2.4

Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.94(bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ

29.7, 45.5, 52.3, 53.0, 55.3, 100.4, 107.8, 111.0, 111.4, 113.8, 127.6, 131.2,

154.0; HRMS calcd for $C_{13}H_{16}N_2O$ *m/z* 216.1263, found 216.1269.

2.3
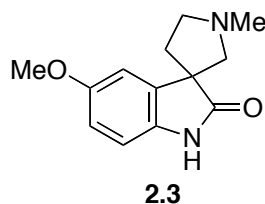
(±)-Horsfiline (2.3). To a solution of **3.26** (16.0 mg, 0.073 mmol) in THF-H_2O-AcOH (1 mL, 1:1:1.5) was added NBS (14 mg, 0.078 mmol) and the mixture was stirred for 15 min at room temperature. Aq $NaHCO_3$ was added and the solution was extracted with a mixture of EtOAc and Et_3N (6:1, 3 x 5 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH_2Cl_2: MeOH 50:1) afforded **2.3** as a colorless oil (13.5 mg, 80%): IR (neat) 3232, 2943, 2834, 1707, 1483, 1304, 1200, 808 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.10 (m, 1H), 2.42 (m, 1H), 2.47 (s, 3H), 2.75 (m, 1H), 2.87 (d, J = 1.6 Hz, 1H), 2.91 (m, 1H), 3.03 (m, 1H), 3.82 (s, 3H), 6.74 (dd, J = 8.4, 2.3 Hz, 1H), 6.77 (m, 1H), 7.05 (d, J = 2.5 Hz, 1H), 7.59 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 29.7, 38.2, 41.8, 54.1, 55.9, 56.7, 66.5, 109.6, 110.4, 112.4, 133.1, 137.7, 156.2; HRMS calcd for $C_{13}H_{16}N_2O_2$ *m/z* 232.1212, found 232.1219.

4.23
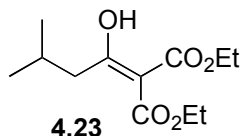
Diethyl 2-(3-Methylbutanoyl)malonate (4.23). In a round-bottom flask was placed Mg (1.25 g, 51.3 mmol), absolute EtOH (1.25 mL), and CCl_4 (0.05 mL). A small portion of a solution of diethyl malonate (7.8 mL, 50 mmol) in EtOH (4 mL) was added and the mixture was gently warmed until H_2 evolution began. The remaining solution of diethyl malonate in EtOH was added at such a rate that the exothermic reaction proceeded vigorously but under control. When the reaction moderated, the flask was cooled in ice-water and Et_2O (30 mL) was added. The mixture was heated again on a water bath until no further H_2 was evolved. The mixture was cooled to room temperature and a solution of isovaleryl chloride (**4.22**, 6.5 mL, 51.5 mmol) in Et_2O (20 mL) was added slowly. The mixture was refluxed for 15 min, cooled to room temperature, and dilute acetic acid (10% in water w/v) was added slowly until the pH was approximately 7. The mixture was extracted with Et_2O (3 x 100 mL) and the extracts were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo and the residual oil was purified by chromatography on silica gel (hexanes: EtOAc 20:1) to yield **4.23** as a colorless liquid (10.3 g, 84%): IR (neat) 2964, 1738, 1645, 1599, 1241, 1085, 1046 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.95 (dd, J = 6.7 Hz, 3.4Hz, 6H), 1.31 (m, 6H), 2.15 (m, 1H), 2.33 (d, J = 6.8 Hz, 1H), 2.50 (d, J = 6.8 Hz, 1H), 4.26 (m, 4H); ^{13}C NMR (100

MHz, CDCl$_3$) δ 13.9, 18.0, 22.3, 23.9, 48.4, 62.1, 67.2, 168.2, 201.9; HRMS calcd for C$_{12}$H$_{20}$O$_5$ *m/z* 244.1311, found 244.1315.

4.24
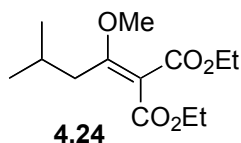
Diethyl 2-(1-Methoxy-3-methylbutylidene)malonate (4.24). To a solution of **4.23** (1.00 g, 4.11 mmol) in THF (20 mL) at 0 ^{o}C was added KH (329 mg, 8.2 mmol) slowly. The mixture was warmed to room temperature and was stirred for 30 min. Dimethyl sulfate (0.77 mL, 8.2 mmol) was added dropwise and the mixture was stirred for 24h at room temperature. Aq NH$_4$Cl was added, the mixture was extracted with Et$_2$O (3 x 30 mL), and the extracts were washed with brine, dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (hexanes: EtOAc 10:1) to give **4.24** as a colorless oil **(**410 mg, 40%): IR (neat) 2961, 1735, 1710, 1614, 1213, 1093 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.03 (d, *J* = 6.6 Hz, 6H), 1.29 (m, 6H), 1.98 (m, 1H), 2.77 (d, *J* = 7.4 Hz, 2H), 3.78 (s, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.1, 22.3, 27.7, 35.6, 56.2, 60.4, 61.0, 109.5, 165.0, 173.2; HRMS calcd for C$_{13}$H$_{22}$O$_5$ *m/z* 258.1467, found 258.1470.
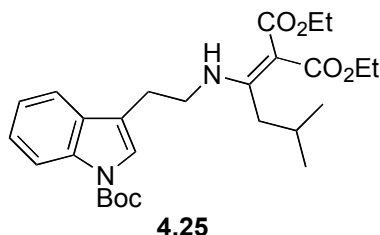
4.25

Diethyl 2-(1-(2-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)ethylamino)-3-methylbutylidene)malonate (4.25). To a solution of **3.4** (1.00 g, 3.90 mmol) and **4.24 (**1.00 g, 3.55 mmol) in EtOH (4.0 mL) was added K_2CO_3 (638 mg, 4.62 mmol). The reaction vessel was sealed and the mixture was stirred at room temperature for 48 h. The resulting yellow solution which contained a white precipitate was poured into H_2O (50 mL) and was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo to afford crude **4.25** as a yellow oil. The crude product was purified by chromatography on silica gel (hexanes: EtOAc 4:1) to give **4.25** (1.37 g, 65%): IR (neat) 3276, 3192, 3112, 3057, 2979, 2935, 2901, 1734, 1653, 1616, 1456, 1375, 1258, 1217, 1154, 1088, 1033, 802, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 0.94 (m, 6H), 1.29 (m, 6H), 1.69 (s, 9H), 1.84 (m, 1H), 2.42 (d, J = 7.4 Hz, 2H), 2.98 (t, J = 7.3 Hz, 2H), 3.60 (q, J = 5.9 Hz, 2H), 4.21 (m, 4H), 7.24 (m, 1H), 7.41 (s, 1H), 7.47 (m, 1H), 8.14 (d, J = 7.7 Hz, 1H), 9.85 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.3, 26.7, 28.1, 49.3, 59.5, 59.7, 83.6, 89.7, 115.4, 116.1, 118.4, 122.5, 123.6, 124.6, 129.8, 135.5, 149.5, 159.8, 165.9, 169.2; HRMS calcd for $C_{27}H_{38}N_2O_6$ *m/z* 487.2781, found 487.2788.

4.26
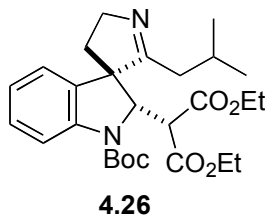
Diethyl 2-((2S,3S)-1-(*tert*-Butoxycarbonyl)-2'-isobutyl-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-2-yl)malonate (4.26). A degassed solution of **4.25** (400 mg, 0.82 mmol) in EtOH (100 mL) was irradiated with a Hanovia 450W medium-pressure mercury lamp through a Corex filter for 12 h. The solution was concentrated in vacuo, and the resulting yellow oil was purified by chromatography on silica gel (hexanes : EtOAc 5:1) to afford **4.26** as a pale yellow oil (248 mg, 62%): IR (neat) 2980, 1727, 1700, 1478, 1376, 1305, 1162, 750 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.98 (d, J = 6.4 Hz, 6H), 1.25 (tt, J = 7.4, 7.1 Hz, 6H), 1.55 (s, 9H), 1.87 (m, 2H), 2.05 (m, 2H), 2.23 (m, 1H), 2.41 (m, 1H), 3.60 (d, J = 9.3 Hz, 1H), 3.85 (m, 1H), 4.11 (m, 4H), 5.18 (d, J = 9.0 Hz, 1H), 6.98 (dt, J = 7.4, 0.8 Hz, 1H), 7.18 (dt, J = 7.4, 1.0 Hz, 1H), 7.28 (m, 1H), 7.56 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.8, 13.9, 21.0, 22.7, 23.3, 28.2, 40.9, 44.4, 53.2, 57.6, 60.4, 61.7, 65.3, 66.2, 82.1, 116.5, 123.5, 123.9, 128.3, 134.9, 141.9, 152.3, 166.5, 166.9, 175.5; HRMS calcd for C$_{27}$H$_{38}$N$_2$O$_6$ *m/z* 486.2730, found 486.2722.
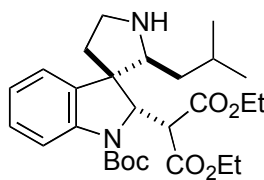
4.27

Diethyl 2-((2S,2'S,3R)-1-(*tert*-Butoxycarbonyl)-2'-isobutylspiro[indoline-3,3'-pyrrolidine]-2-yl)malonate (4.27). To a solution of **4.26** (300 mg, 0.62 mmol) in a mixture of MeOH and AcOH (3:1, 12 mL) was added NaBH$_3$CN (85.0 mg, 1.35 mmol) in one portion. The mixture was stirred at room temperature for 1 h, after which satd aq NaHCO$_3$ was added slowly. The mixture was concentrated by removing volatiles in vacuo, and the residual oil was extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (hexanes : EtOAc 1:1 and 10% Et$_3$N) gave **4.27** as a colorless oil (271 mg, 90%): IR (neat) 2956, 1731, 1700, 1490, 1377, 1163, 1049, 753 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.87 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H),1.21 (m, 6H), 1.24 (m, 1H), 1.55 (s, 9H), 1.75 (m, 2H), 1.89 (m, 2H), 2.25 (dt, *J* = 12.5, 7.3, 1H), 3.06 (m, 2 H), 3.29 (d, J = 9.8, 1H), 3.9 (d, *J* = 7.0 Hz, 1H), 4.11 (m, 4 H), 5.10 (d, *J* = 7.0 Hz, 1H), 7.00 (t, *J* = 7.7, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.59 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.9, 21.1, 24.2, 26.4, 28.3, 42.3, 43.6, 44.4, 52.5, 57.7, 58.9, 61.6, 67.4, 81.7, 116.2, 122.7, 125.2, 127.4, 136.1, 141.6, 152.2, 167,1, 168.1; HRMS calcd for C$_{27}$H$_{41}$N$_2$O$_6$ *m/z*+1 489.2965, found 489.2936.

4.29
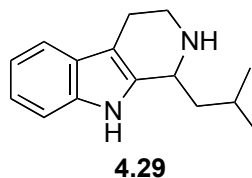
1-Isobutyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4.29). To a solution of **4.27** (150 mg, 0.31 mmol) in CH_2Cl_2 (1 mL) was added TFA (200 μL) and the solution was stirred for 24 h. Aq Na_2CO_3 was added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH_2Cl_2: MeOH 50 : 1) afforded **4.29** as a colorless oil (45 mg, 40%): IR (neat) 3462, 2943, 2929, 1483, 1456 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.02 (d, *J* = 6.6 Hz, 3H), 1.05, (d, *J* = 6.6 Hz, 3H), 1.63 (m, 3H), 2.00 (m, 1H), 2.75 (m, 2H), 3.04 (ddd, *J* = 13.3, 7.5, 5.8 Hz, 1H), 3.36 (dt, *J* = 12.8, 4.8 Hz, 1H), 4.12 (ddt, *J* = 8.3, 6.2, 1.8 Hz, 1H), 7.11 (ddd, *J* = 7.3, 6.9, 1.2 Hz, 1H), 7.16 (ddd, *J* = 7.3, 6.9, 1.2 Hz, 1H), 7.33 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.50 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.79 (bs, s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.7, 22.8, 23.9, 24.6, 42.5, 44.5, 50.5, 108.8, 110.7, 118.0, 119.4, 121.5, 127.6, 135.6, 136.8; HRMS calcd for $C_{15}H_{20}N_2$ *m/z* 228.1627, found 228.1623.

4.30
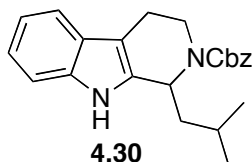
Benzyl 1-Isobutyl-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate

(4.30). To a solution of **4.29** (60 mg, 0.26 mmol) and Et$_3$N (0.1 mL) in CH$_2$Cl$_2$

(3 mL) at -10 °C was added benzyl chloroformate (0.06 mL, 0.37 mmol). The

mixture was stirred for 75 min at room temperature and was poured into H$_2$O.

The mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL), and the combined extracts

were washed with aq NaHCO$_3$ and brine, dried (Na$_2$SO$_4$) and filtered. The

filtrate was concentrated in vacuo and the residual oil was purified by

chromatography on silica gel (hexanes : EtOAc 5:1) to afford **4.30** as a

colorless oil (86 mg, 91%): IR (neat) 3324, 2954, 1671, 1423, 1441, 1222,

1086 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$)

showed severe line broadening with doubling of certain signals due to the

presence of rotational conformers; HRMS calcd for C$_{23}$H$_{26}$N$_2$O$_2$ *m/z* 363.2073,

found 363.2069.
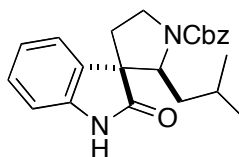
4.31

(2'*S*,3*R*)-Benzyl 2'-Isobutyl-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (4.31). To a solution of **4.30** (47.0 mg, 0.13 mmol) in THF/AcOH/H$_2$O (3 mL, 1:1:1) was added NBS (25 mg). After stirring vigorously in the dark for 2 h at room temp, the mixture was poured slowly into aq. NaHCO$_3$ and was extracted with a mixture of EtOAc and Et$_3$N (6:1, 3 x 5 mL). The combined extracts were dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes : EtOAc 2:1) gave **4.31** as a colorless oil (28 mg, 57%) and **4.32** as a colorless oil(15 mg, 30%). Data for **4.31**: IR (neat) 3420, 2945, 1715, 1613, 1462, 1445, 1407, 1352, 1328, 1109 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 0.72 (m, 3 H), 0.78 (m, 3 H), 1.31 (m, 1H), 1.71 (m, 2H), 2.06 (m, 1H), 2.31 (m, 1H), 3.78 (m, 2H), 4.00 (m, 1H), 5.02 (m, 2H), 6.90 (m, 1H), 6.98 (m, 1H), 7.21 (m, 2H), 7.30 (m, 5H), 9.20 (bs, d, 1H); ^{13}C NMR (100 MHz, DMSO) δ 22.3, 22.9, 25.2, 34.7, 39.9, 44.6, 55.8, 63.7, 67.1, 109.6, 122.5, 123.1, 128.0, 128.3, 134.2, 136.9, 140.0, 155.0, 178.7; HRMS calcd for C$_{23}$H$_{27}$N$_2$O$_3$ *m/z+*1 379.2022, found 379.2031.
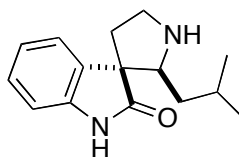
4.33

6-Deoxyelacomine (4.33). To a solution of **4.31**(40.0 mg, 0.11 mmol) in MeOH (4 mL) was added 10 % Pd/C (4 mg). The mixture was stirred vigorously under an atmosphere of H_2 at 1 bar for 3 h and then filtered through Celite. The filtrate was evaporated and the residue was chromatographed on silica gel (EtOAc : MeOH 5:1) to afford **4.33** as a colorless oil (24 mg, 93%): IR (neat) 3420, 2957, 1705, 1620, 1471, 1346, 920 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.75 (d, J = 6.6 Hz, 3 H), 0.78 (d, J = 6.6 Hz, 3 H), 0.95 (ddd, J = 12.2, 8.8, 3.7 Hz, 1 H), 1.47 (ddd, J = 14.0, 9.0, 5.0 Hz, 1H), 1.63 (m, 1 H), 2.31 (ddd, J = 13.4, 8.8, 6.8 Hz, 1 H), 2.34 (ddd, J = 13.4, 8.8, 6.8 Hz, 1H), 3.37 (ddd, J = 12.0, 9.6, 5.7 Hz, 1H), 3.45 (dd, J = 10.2, 3.6 Hz, 1H), 3.54 (m, 1H), 6.96 (dd, J = 7.8, 1.0 Hz, 1H), 7.07 (td, J = 8.0, 1.0 Hz, 1 H), 7.24 (m, 2 H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.8, 23.5, 25.8, 37.7, 38.0, 46.2, 58.1, 68.8, 109.6, 122.5, 122.8, 128.0, 131.2, 140.9, 181.4; HRMS calcd for C$_{15}$H$_{20}$N$_2$O m/z 244.1576, found 244.1585.
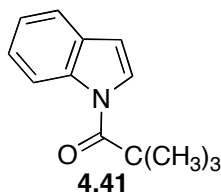
1-Pivaloylindole (4.41). To a suspension of NaH (8.84g, 0.22 mol, 60%) in DMF (200 mL) was added indole (20.0g, 0.17 mol) at 0 ^{o}C and the mixture was stirred for 15 min. To the mixture at 0 °C was added pivaloyl chloride (23 mL, 0.19 mol). After stirring for 15 min, the mixture was poured into ice-cold H_2O (500 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo and the residual solid was recrystallized from hexanes to yield **4.41** as white prisms (32 g, 95%): mp 67-69 ^{o}C; IR (neat) 3180, 2980, 1690, 1535, 1320, 1241, 1085, 1046 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.56 (s, 9H), 6.65 (d, J = 3.8 Hz, 1H), 7.30 (ddd, J = 1.2, 7.8, 7.8 Hz, 1H), 7.38 (ddd, J = 1.5, 7.8, 8.2 Hz, 1H), 7.58 (dd, J = 1.5, 7.8 Hz, 1H), 7.72 (d, J = 3.5 Hz, 1H), 8.56 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 28.7, 41.3, 108.3, 117.4, 120.5, 123.6, 125.1, 125.6, 129.4, 136.8, 177.1; HRMS calcd for C$_{13}$H$_{15}$NO m/z 201.1154, found 201.1164.
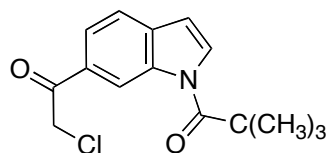
4.42

6-Chloroacetyl-1-pivaloylindole (4.42). To a suspension of AlCl$_3$ (8.9 g, 67 mmol) in 1,2-dichloroethane (60 mL) at 0 °C was added chloroacetyl chloride (5.9 mL, 70 mmol). The mixture was stirred for 20 min and then warmed to room temperature. To this solution was added **4.41** (3.0 g, 1.5 mmol) and the mixture was stirred for 15 min. The mixture was poured into ice-cold H$_2$O (100 mL) and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined extracts were washed with aq. NaHCO$_3$, brine, dried (Na$_2$SO$_4$), and filtered. The filtrate was concentrated in vacuo and the residual solid was recrystallized from MeOH to yield **4.42** as white needles (3.0 g, 73%): mp 107-109 °C; IR (neat) 3100, 2980, 1690, 1525, 1320, 1241, 1085, 1046 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.56 (s, 9H), 4.86 (s, 2H), 6.65 (d, J = 3.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.97 (m, 2H), 9.16 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 28.6, 41.4, 46.3 108.2, 118.4, 120.9, 123.7, 129.4, 131.2, 133.8, 136.3, 177.3, 191.1; HRMS calcd for C15H16ClNO$_2$ *m/z* 277.0870, found 277.0856.

4.45
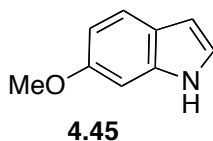
6-Methoxyindole (4.45). To a suspension of anhydrous Na$_2$HPO$_4$ (5.0 g) and **4.42** (2.3 g, 8.5 mmol) in CH$_2$Cl$_2$ (25.0 mL) at room temperature was added *m*-CPBA (2.2 g, 10.2 mmol, 80%) and the mixture was stirred for 1 h. The mixture was poured into ice-cold H$_2$O (100 mL) and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined extracts were washed with aq. NaHCO$_3$, brine, dried (Na$_2$SO$_4$), and filtered. The filtrate was concentrated in vacuo to provide the crude solid **4.43** which was used for the next step without purification.

To a solution of **4.43** obtained above (1.20 g, 4.10 mmol) in MeOH (36 mL) was added aq NaSMe (3.7 mL) at room temperature. After 10 min, the mixture was poured into EtOAc (50 mL), neutralized with aq 1N HCl, and extracted with EtOAc (3 x 50 mL). The extracts were washed with brine, dried (Na$_2$SO$_4$) and evaporated to dryness to give crude **4.44**.

NaH (60 mg, 1.5 mmol, 60%) was added to a solution of crude **4.44** (200 mg, 1.5 mmol) obtained above and MeI (0.10 mL, 1.6 mmol) in DMF (0.8 mL) at -20 $^{\circ}$C under Ar. The mixture was stirred for 10 min, then poured into ice-cold H$_2$O (30 mL) and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined extracts were washed with brine, dried (Na$_2$SO$_4$), and filtered. The filtrate was concentrated in vacuo and the residual solid was purified by chromatography on silica gel (hexanes: EtOAc 10:1) to yield **4.45** as white plates (650 mg, 43%

for 3 steps); IR (neat) 3200, 1625, 1500, 1466, 1250, 1217, 1095, 1032 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.78 (s, 3H), 6.49 (ddd, J = 0.9, 2.2 3.8 Hz, 1H), 6.83 (dd, J = 2.2 8.4 Hz, 1H), 6.86 (d, J = 2.5 Hz, 1H), 7.00 (dd, J = 2.5, 3.3 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.99 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 55.8, 92.9, 100.9, 108.3, 121.5, 122.8, 127.8, 137.6, 156.3; HRMS calcd for C$_9$H$_9$NO m/z 147.0684, found 147.0699.
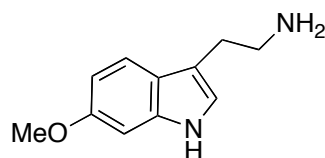
4.47

6-Methoxytryptamine (4.47). To a solution of **4.45** (300 mg, 2 mmol) in Et$_2$O (20 mL) was added oxalyl dichloride (260 mg, 2 mmol). The resultant red suspension was filtered and the collected red solid was added to NH$_3$H$_2$O (2 mL) under stirring to afford a green suspension which was filtered to afford a green solid. To a solution of the green solid in THF (20 mL) at 0 ^{o}C was added LiAlH$_4$ (158 mg, 4 mmol), and the mixture was stirred for 2 h at room temperature. Ice-cold H$_2$O (20 mL) was added to the reaction which was extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined extracts were washed with brine, dried (Na$_2$SO$_4$), and filtered. The filtrate was concentrated in vacuo and the residual solid was recrystallized from MeOH to yield **4.47** as a gray plat (230 mg, 60%); IR (neat) 3409, 3200, 3054, 2919, 1661, 1572, 1456, 1339,

1229, 742 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.46 (bs, 2H), 2.90 (t, J = 6.7 Hz, 2H), 3.05 (t, J = 6.7 Hz, 2H), 3.88 (s, 3H), 6.82 (dt, J = 2.6 8.8 Hz, 1H), 6.89 (d, J = 2.2 Hz, 1H), 6.96 (d, J = 2.5 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.91 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 29.6, 42.4, 55.7, 94.7, 109.3, 113.9, 119.5, 120.7, 122.0, 137.2, 156.6; HRMS calcd for C$_{11}$H$_{14}$N$_2$O m/z 190.1106, found 190.1110.

4.35
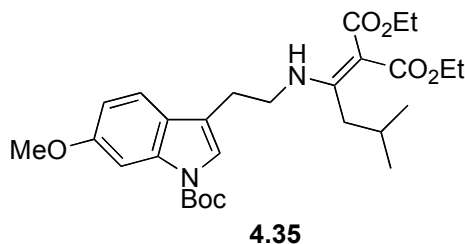
Diethyl 2-(1-(2-(1-(*tert*-Butoxycarbonyl)-6-methoxy-1*H*-indol-3-yl)ethylamino) -3-methylbutylidene)malonate (4.35). To a solution of **4.34** (160 mg, 0.62 mmol) and **4.24** (160 mg, 0.51 mmol) in EtOH (1.0 mL) was added K$_2$CO$_3$ (92 mg, 0.70 mmol). The reaction vessel was sealed and the mixture was stirred at room temperature for 48h. The resulting yellow solution which contained residual K$_2$CO$_3$ was poured into H$_2$O (50 mL) and was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined extracts were dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo to afford crude **4.35** as a yellow oil. The crude product was purified by chromatography on silica gel (hexanes: EtOAc 4:1) to give pure **4.35** (1.37 g, 65%) as a pale

yellow oil: IR (neat) 2977, 1730, 1648, 1597, 1488, 1444, 1383, 1256, 1159, 1110, 1040 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.94 (m, 6 H), 1.23 (m, 6 H), 1.68 (s, 9H), 1.86 (m, 1 H), 2.44 (d, J = 7.4 Hz, 2 H), 2.95 (t, J = 7.0 Hz, 2H), 3.58 (tt, J = 5.8, 6.9 Hz, 2H), 3.89 (s, 9H), 4.21 (m, 5 H), 6.90 (m, 1H), 7.28 (m, 1H), 7.36 (m, 2H), 7.76 (s, 1H), 9.85 (bs, s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.2, 14.4, 22.4, 26.3, 27.6, 28.2, 37.1, 43.3, 55.6, 59.3, 60.4, 92.7, 116.7, 118.9, 122.1, 158.0, 166.4, 168.0, 169.2; HRMS calcd for C$_{28}$H$_{40}$N$_2$O$_7$ m/z 516.2836, found 516.2851.

4.36
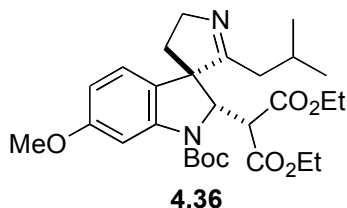
Diethyl   2-((2S,3S)-1-(*tert*-Butoxycarbonyl)-2'-isobutyl-6-methoxy-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-2-yl)malonate   (4.36). A degassed solution of **4.35** (200 mg, 0.41 mmol) in EtOH (100 mL) was irradiated with a Hanovia 450W medium pressure mercury lamp through a Corex filter for 12 h. The solution was concentrated in vacuo and the resulting yellow oil was purified by chromatography on silica gel (hexanes : EtOAc 5:1) to afford **4.36** as a pale yellow oil (116 mg, 58%): IR (neat) 2957, 1733, 1706, 1616, 1597, 1500, 1453, 1369, 1306, 1256, 1226, 1161, 1035, 860, 733 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.98 (dd, J = 6.5, 1.8 Hz, 6 H), 1.26 (dd, J = 7.1, 6.8 z,

6H), 1.55 (s, 9H), 1.87 (m, 1 H), 2.38 (m, 2H), 3.02 (m, 2H), 3.58 (d, J = 9.2 Hz, 2H), 3.82 (s, 3 H), 4.15 (m, 4H), 6.83 (d, J = 8.4 Hz, 1H), 7.22 (s, 1 H), 7.35 (m, 1H), 7.76 (s, 1H), 9.85 (s, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.8, 13.9, 22.7, 23.3, 26.3, 28.2, 40.9, 44.3, 53.2, 55.5, 57.5, 61.7, 65.6, 66.0, 82.1, 102.6, 109.6, 124.3, 126.8, 143.2, 152.2, 160.2, 166.5, 166.9, 175.8; HRMS calcd for C$_{28}$H$_{40}$N$_2$O$_7$ m/z 516.2836, found 516.2841.
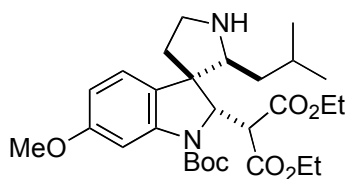
4.37

Diethyl 2-((2S,2'S,3R)-1-($tert$-Butoxycarbonyl)-2'-isobutyl-6-methoxyspiro-[indoline-3,3'-pyrrolidine]-2-yl)malonate (4.37). To a solution of **4.36** (170 mg, 0.33 mmol) in MeOH and AcOH (3:1, 4 mL) was added NaBH$_3$CN (45 mg, 0.66 mmol) in one portion. The mixture was stirred at room temperature for 1 h, after which satd aq NaHCO$_3$ was added slowly. The mixture was concentrated by removing volatiles in vacuo and the residue was extracted with EtOAc (3 x 10 mL). The combined extracts were dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (hexanes : EtOAc 1:1 and 10% Et$_3$N) gave **4.37** as a colorless oil **(**155 mg, 90%): IR (neat) 2956, 1707, 1498, 1369, 1163, 1036, 733 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (dd, J = 21.5, 6.1 Hz, 6H),

1.24 (tt, J = 7.9, 7.2 Hz, 6H), 1.56 (s, 9H), 1.72 (m, 2H), 1.91 (m, 2H), 2.23 (m, 1H), 3.03 (m, 2H), 3.26 (dd, J = 10.8, 1.6 Hz, 1H), 3.80 (t, 1H), 3.81 (s, 3H), 4.15 (m, 4H), 5.10 (d, J = 7.0 Hz, 1H), 6.54 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.25 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.9, 21.0, 24.2, 26.3, 28.3, 42.5, 43.5, 44.2, 52.5, 55.4, 58.7, 61.6, 67.9, 81.7, 102.4, 108.2, 120.5, 124.3, 125.5, 127.9, 144.1, 153.1 159.4, 167.1, 168.1; HRMS calcd for C$_{28}$H$_{42}$N$_2$O$_7$ m/z 518.2992, found 518.2982.

4.39
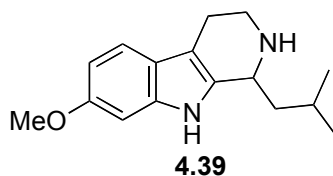
1-Isobutyl-7-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (4.39). To a solution of **4.37** (80 mg, 0.31 mmol) in CH$_2$Cl$_2$ (1 mL) was added TFA (100 μL) and the solution was stirred for 24 h. Aq Na$_2$CO$_3$ was added and the mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined extracts were dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH$_2$Cl$_2$: MeOH 50 : 1) gave **4.39** as a colorless solid (24 mg, 38%): mp 146 – 149 ^{o}C; IR (neat) 3462, 2954, 1699, 1628, 1465, 1155 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.00 (d, J = 6.5 Hz, 3H), 1.05, (d, J = 6.5 Hz, 3H), 1.61 (m, 1 H), 1.66 (m, 1H), 1.94 (m, 1H), 2.71 (m, 2H), 3.04 (ddd, J = 12.7, 8.0, 5.5 Hz, 1H), 3.36 (dt, J = 12.7,

4.7Hz, 1H), 3.85 (s, 3H), 4.11 (ddt, J = 8.7, 5.5, 2.1 Hz, 1H), 6.75 (dd, J = 8.6,

2.2Hz, 1H), 6.84 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.61 (bs, 1H);

^{13}C NMR (100 MHz, CDCl$_3$) δ 21.8, 22.7, 23.9, 24.6, 42.4, 44.5, 50.5, 55.8,

95.0, 108.6, 108.7, 118.5, 122.1, 134.8, 136.6, 156.1; HRMS calcd for

C$_{16}$H$_{22}$N$_2$O m/z 258.1732, found 258.1732.

4.48
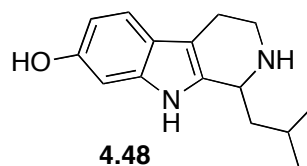
7-Hydroxy-1-isobutyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (4.48). To

a solution of **4.39** (170 mg) in CH$_2$Cl$_2$ (3 mL) was added dropwise BBr$_3$ (1.7

mL, 1M in CH$_2$Cl$_2$) at room temperature under Ar. The solution was stirred for

12h, MeOH was added, and the mixture was poured into H$_2$O (10 mL). The

mixture was extracted with CH$_2$Cl$_2$ and Et$_3$N (3 x 20 mL, 2 mL) and the

combined extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was

concentrated in vacuo, and the residue was purified by chromatography on

silica gel (CH$_2$Cl$_2$: MeOH 50 : 1) to provide **4.48** as an unstable solid (125

mg, 78%): IR (neat) 3462, 2954, 1629, 1456, 1152, 1124 cm^{-1}; ^{1}H NMR (400

MHz, CDCl$_3$) δ 1.01 (d, J = 10.8 Hz, 3H), 1.02, (d, J = 10.8 Hz, 3H), 1.62 (m, 2

H), 1.97 (m, 1H), 2.71 (m, 2H), 3.04 (m, 2 H), 3.36 (dt, J = 12.7, 4.7 Hz, 2H),

4.07 (m, 1 H), 6.67 (dd, J = 8.4, 2.1 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1H), 7.31

(OH, 1H), 7.52 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.8, 22.7, 23.9, 24.6, 42.4, 44.3, 50.5, 97.0, 108.5, 109.3, 118.5, 121.8, 135.1, 136.6, 152.3; HRMS calcd for C$_{15}$H$_{20}$N$_2$O *m/z* 244.1576, found 244.1571.

4.49
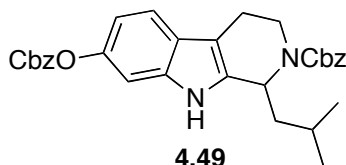
Benzyl 7-(Benzyloxycarbonyloxy)-1-isobutyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (4.49). To a solution of **4.48** (180 mg, 0.74 mmol) and Et$_3$N (0.5 mL) in CH$_2$Cl$_2$ (25 mL) at –10°C was added benzyl chloroformate (1.5 mL, 2.4 mmol). The mixture was stirred for 75 min at room temperature and was poured into H$_2$O. The mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined extracts were washed with aq NaHCO$_3$ and brine, dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexanes : EtOAc 5:1) to give **4.49** as a colorless oil (260 mg, 65%): IR (neat) 3351, 2954, 1695, 1456, 1423, 1227, 1095 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, severe line broadening and doubling of certain signals), δ 0.92 (d, *J* = 6.0 Hz, 2 H), 0.99 (d, *J* = 6.0 Hz, 2H), 1.1 (d, *J* = 6.0 Hz, 2H), 1.52 (m, 2H), 1.77 (m, 2H), 2.73 (m, 2H), 3.19 (m, 1H), 4.44 (d, *J* = 7.9 Hz, 1H), 5.28 (m, 5H), 6.91 (m, 1H), 7.10 (m, 1H), 7.46 (m, 10H), 7.80 (m, 1H); ^{13}C NMR (100 MHz, DMSO, severe

line broadening and doubling of certain signals), δ 20.9, 21.5, 22.4, 23.4, 24.9, 25.1, 37.9, 38.2, 43.9, 44.3, 49.8, 49.9, 67.3, 67.6, 70.3, 103.6, 108.0, 108.6, 113.0, 118.3, 118.5, 125.1, 127.8, 128.0, 128.2, 128.7, 134.9, 135.5, 135.9, 146.8, 154.6, 155.9; HRMS calcd for $C_{31}H_{32}N_2O_5$ m/z 512.2311, found 512.2322.
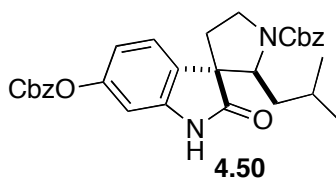
(2'S,3R)-Benzyl 6-(Benzyloxycarbonyloxy)-2'-isobutyl-2-oxospiro-[indolin-3,3'-pyrrolidine]-1'-carboxylate (4.50). To a solution of **4.49** (150 mg,) in THF/AcOH/H$_2$O (18 mL, 1:1:1) was added NBS (58 mg, 0.33 mmol). After being stirred vigorously in the dark for 2h at room temperature, the mixture was poured slowly into aq. NaHCO$_3$ and was extracted with a mixture of EtOAc and Et$_3$N (6:1, 3 x 15 mL). The combined extracts were dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes : EtOAc 2:1) afforded **4.50** as a colorless oil (78 mg, 48%): IR (neat) 3247, 2957, 1712, 1458, 1412, 1230, 1110 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 0.75 (m, 6H), 0.71 (m, 1H), 1.30 (bs, 2H), 1.68 (m, 2H), 2.08 (m, 1H), 2.27 (m, 1H), 3.78 (m, 2H), 3.98 (m, 1H), 5.30 (m, 4H), 6.77 (m, 1H), 7.03 (m, 1H), 7.30 (m, 10H); ^{13}C NMR (100

MHz, DMSO) δ 22.1, 22.9, 24.7, 24.8, 25.2, 35.2, 40.9, 45.4, 61.4, 67.1, 70.6, 71.0, 104.0, 114.5, 125.8, 127.0, 128.0, 128.4, 128.5, 128.6, 128.7, 128.9, 134.6, 141.8, 151.3, 153.5, 155.7, 180.8; HRMS (FAB) calcd for $C_{31}H_{32}N_2O_6$ *m/z+ Na* 551.2158, found 551.2139.

4.1
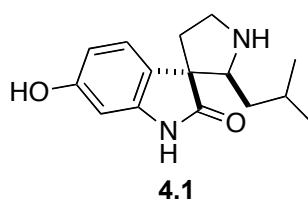
(±)-Elacomine (4.1). To a solution of **4.50** (70 mg, 0.13 mmol) in MeOH (20 mL) was added 10% Pd/C (7 mg) and the suspension was stirred vigorously under an atmosphere of H_2 at 1 bar for 3 h. The suspension was filtered through Celite, the filtrate was concentrated and the residue was chromatographed on silica gel (EtOAc : MeOH 5:1) to afford **4.1** as a colorless solid (24 mg, 93%): mp 173 - 177 °C (decomp); IR (neat) 3264, 2957, 1699, 1632, 1468, 1346, 1156, 1113 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.75 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.95 (ddd, *J* = 13.8, 9.0, 4.3 Hz, 1H), 1.36 (ddd, *J* = 13.8, 9.5, 5.4 Hz, 1H), 1.51 (m, 1H), 2.21 (ddd, *J* = 13.3, 9.4, 6.1 Hz, 1H), 2.25 (ddd, *J* = 13.3, 8.8, 5.5 Hz, 1H), 3.14 (ddd, *J* = 11.8, 9.4, 6.0 Hz, 1H), 3.21 (dd, *J* = 9.2, 4.3 Hz, 1H), 3.37 (ddd, *J* = 12.0, 8.4, 6.2, 1H), 6.40 (d, *J* = 2.1 Hz, 1H), 6.47 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.05 (d, *J* = 8.3, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.9, 22.3, 25.2, 37.0, 38.3, 45.1, 57.4,

67.0, 97.8, 108.7, 121.5, 122.7, 142.8, 157.7, 182.9; HRMS calcd for $C_{15}H_{20}N_2O_2$ *m/z* 260.1525, found 260.1531.

5.59
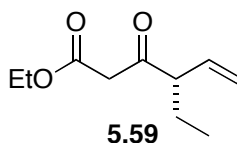
4-Ethyl-3-Oxohex-5-enoate (5.59). To a suspension of Zn powder (19.0 g, 291 mmol) in anhydrous THF at 0 ^{o}C was added **5.61** (7.8 mL, 73.1 mmol) and **5.60** (13.0 g, 87.0 mmol). AlCl$_3$ (3.9 g, 29.2 mmol) was added slowly to the mixture, which was warmed to room temperature and stirred for 1h. After the reaction was complete, aq HCl (2 M, 50 mL) was added and the mixture was stirred for 5 min. The mixture was filtered through a short silica gel column to remove remaining solids and the filtrate was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with NaHCO$_3$ and brine, and dried (Na$_2$SO$_4$). The solvent was removed in vacuo and the residual oil was purified by chromatography (hexanes:EtOAc 10 : 1) to give **5.59** as a yellow oil (4.0 g, 55%): IR (neat) 3425, 2968, 2877, 1746, 1634, 1463, 1410, 1314, 1233, 1155, 1031 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.87 (t, J = 7.8 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.52 (m, 1H), 1.82 (m, 1H), 3.13 (q, J = 6.8 Hz, 1H), 3.48 (d, *J* = 7.5 Hz, 2H), 4.17 (q, *J* = 6.2 Hz, 2H), 5.22 (m, 2H), 5.64 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 11.4, 14.1, 23.5, 25.1, 47.8, 59.3, 61.3, 88.9, 119.2, 135.3, 167.2, 203.2; HRMS calcd for $C_{10}H_{16}O_3$ *m/z* 184.1100, found 184.1100
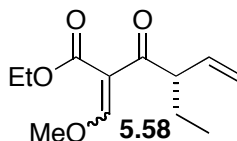
Ethyl 4-Ethyl-2-(methoxymethylene)-3-oxohex-5-enoate (5.58). A mixture

of **5.59** (1.00 g, 5.4 mmol), Ac$_2$O (1.0 mL, 11.0 mmol) and HC(OMe)$_3$ (0.6 mL,

5.4 mmol) was heated to 110 $^{\circ}$C in a sealed tube. After 4h, the mixture was

cooled to room temperature and poured into H$_2$O (20 mL). The mixture was

extracted with EtOAc (3 x 10 mL) and the combined extracts were washed

with aq NaHCO$_3$ and brine and dried (Na$_2$SO$_4$). The solvent was removed in

vacuo to give **5.58** as a yellow oil (0.69 g, 65%) which was used for the next

step without purification.
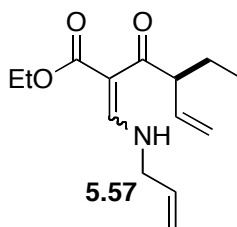
Ethyl 2-((Allylamino)methylene)-4-ethyl-3-oxohex-5-enoate (5.57). A

mixture of **5.58** (200 mg, 0.88 mmol) and **5.64** (660 µL, 8.8 mmol) was stirred

at room temperature for 2 h. The excess **5.64** was removed in vacuo and the

residue was purified by chromatography (hexanes : EtOAc 3:1) to provide **5.57**

as yellow oil (200 mg, 90%): IR (neat) 2964, 2932, 1697, 1628, 1578, 1412,

1227, 1110, 1056 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (t, J = 7.5 Hz, 3H),

1.34 (t, J = 6.9 Hz, 3H), 1.54 (m, 1H), 1.82 (m, 1H), 3.75 (s, 1H), 3.97 (t, J =

5.8 Hz, 2H), 4.23 (tt, J = 7.1, 7.2 Hz, 2H), 4.31 (m, 1H), 5.11 (m, 2H), 5.26 (m,

1H), 5.29 (d, J = 6.3 Hz, 1H), 5.91 (m, 2H), 8.03 (d, J = 13.0 Hz, 1H); ^{13}C NMR

(100 MHz, CDCl$_3$) δ 11.8, 14.5, 25.5, 52.0, 54.1, 59.6, 100.1, 115.9, 118.2,

132.8, 138.6, 160.6, 166.9, 202.7; HRMS calcd for C$_{14}$H$_{21}$NO$_3$ m/z 251.1521,

found 251.1524.

5.68
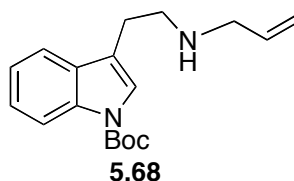
***tert*-Butyl 3-(2-(Allylamino)ethyl)-1*H*-indole-1-carboxylate (5.68)**. To a

solution of **5.55** (1.0 g, 4.5 mmol) in THF (10 mL) was added **5.64** (1.1 g, 5.4

mmol) and the solution was heated at 40 °C for 1 h. The mixture was poured

into H$_2$O (100 mL) and was extracted with EtOAc (3 x 40 mL). The combined

extracts were washed with brine and dried (Na$_2$SO$_4$) and the solvent was

removed in vacuo. The residual oil was purified by chromatography (hexanes :

EtOAc 50:1) to give **5.68** as a white solid (1.3 g, 90%): mp 186–189 °C; IR

(film) 3425, 2968, 2877, 1746, 1634, 1463, 1410, 1314, 1233, 1155, 1031 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.67 (s, 9H), 3.28 (m, 2H), 3.42 (dd, J = 7.5,

8.9 Hz, 2H), 3.73 (t, J = 6.2 Hz, 2H), 5.4 (d, J = 10.8, 1H), 5.53 (m, 2H), 6.11

(m, 1H), 7.24 (t, J = 8.2 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.51 (s, 1H), 7.65 (d,

J = 8.2 Hz, 1H), 8.11 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 28.2,

44.2, 46.1 49.7, 83.9, 115.0, 115.4, 118.9, 122.4, 123.9, 124.8, 127.2, 128.8,

129.5, 135.5; HRMS calcd for $C_{18}H_{25}N_2O_2$ m/z 301.1916, found 301.1917.
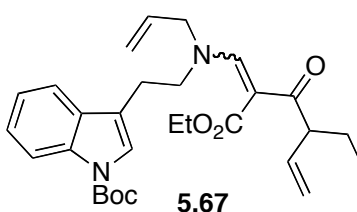
5.67

***tert*-Butyl** **2-(2-(Allyl(2-(ethoxycarbonyl)-4-ethyl-3-oxohexa-1,5-**

dienyl)amino) ethyl)-1*H*-indole-1-carboxylate (5.67). To a solution of **5.58**

(20 mg, 0.09 mmol) in EtOH (1 mL) at room temperature was added Hunig's

Base (8.6 mg, 0.07 mmol) and **5.68** (20 mg, 0.07 mmol). The mixture was

stirred for 2 h, and the solvent was removed in vacuo. The residue was

purified by chromatography (hexanes : EtOAc 10:1) to give **5.59** as a yellow oil

(20 mg, 85%): IR (neat) 2976, 2933, 1732, 1630, 1454, 1374, 1256, 1158,

1087; ^{1}H (CDCl$_3$): δ 0.89 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 6.8 Hz, 3H), 1.53 (m,

1H), 1.68 (s, 9H), 1.86 (m, 1H), 2.95 (t, J = 7.7 Hz, 2H), 3.59 (m, 2H), 3.74 (m,

1H), 3.85 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 5.07 (dt, J = 7.1, 11.0 Hz, 2H),

5.24 (d, J = 11.0 Hz, 2H), 5.80 (m, 1H), 7.26 (t, J = 7.1 Hz, 1H), 7.34 (t, J =

7.7, 1H), 7.41 (s, 1H), 7.49 (d, J = 7.7, 1H), 7.59 (m, 1H), 8.15 (d J = 7.4 Hz,

1H); ^{13}C (CDCl$_3$): δ 9.1, 11.8, 14.3, 24.6, 25.2, 28.7, 51.8, 58.4, 60.4, 83.7,

115.5, 116.0, 118.5, 122.6, 123.7, 124.7, 129.8, 138.6, 148.9, 175.8; MS:

[M+H] calcd for $C_{29}H_{38}N_2O_5$, 494.2781; found 494.2804.
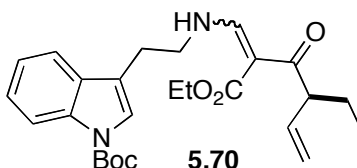
5.70

***tert*-Butyl 2-(2-(Allyl(2-(ethoxycarbonyl)-4-ethyl-3-oxohexa-1,5-dienyl)amino) ethyl)-1*H*-indole-1-carboxylate (5.70)**. To a solution of **5.58**

(20 mg, 0.09 mmol) in EtOH (1 mL) at room temperature was added Hunig's

Base (9.1 mg, 0.07 mmol) and **3.4** (18 mg, 0.07 mmol). The mixture was

stirred for 2 h and the solvent was removed in vacuo. The residue was purified

by chromatography (hexanes : EtOAc 5:1) to give **5.70** as an oil (24 mg,

85%): IR (neat) 2976, 1731, 1624, 1454, 1379, 1256, 1159, 1092; ^{1}H (CDCl$_3$):

δ 0.93 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 2H), 1.51 (m, 1H), 1.69 (s, 9H),

1.82 (m, 1H), 3.02 (t, *J* = 7.7 Hz, 2H), 3.65 (d, *J* = 6.6, 2H), 4.16 (m, 1H), 4.30

(m, 1H), 5.11 (dd, *J* = 9.2, 13.2 Hz, 2H), 5.90 (m, 1H), 7.28 (m, 1H), 7.36 (t, *J*

= 7.7, 1H), 7.42 (s, 1H), 7.49 (d, *J* = 7.7, 1H), 7.90 (d, *J* = 13.2 Hz, 1H), 8.20

(m, 1H), 8.24 (bs, 1H), 11.23 (bs, 1H); ^{13}C (CDCl$_3$): δ 9.1, 11.9, 14.4, 25.5,

26.7, 28.2, 49.8, 54.0, 59.5, 83.7, 99.7, 115.5, 116.0, 118.5, 122.6, 123.7,

124.7, 129.8, 138.6, 148.9, 160.7, 168.6, 202.7; MS: [M+H] calcd for

$C_{26}H_{35}N_2O_5$, 455.2567; found 455.2577.

5.71
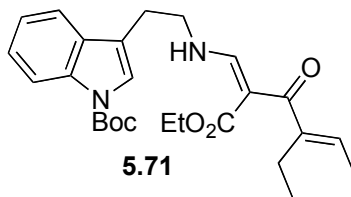
tert-Butyl 3-(2-((-2-(Ethoxycarbonyl)-4-ethyl-3-oxohexa-1,4-dien-1-yl) amino) ethyl)-1H-indole-1-carboxylate (5.71). To a mixture of **5.72** (70 µL, 0.5 mmol) and *p*-TsOH (10 mg, 0.05 mmol) was added **5.59** (100 mg, 0.5 mmol) and the mixture was stirred for 20 min. To the mixture was added **3.4** (220 mg, 0.5 mmol) in one portion and the mixture stirred for 6 h. The mixture was poured into H_2O (10 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by flash chromatography (hexanes : EtOAc 10:1) to give **5.71** as a yellow oil (177 mg, 78%): IR (neat) 2976, 1731, 1624, 1454, 1379, 1256, 1159, 1092; ^{1}H (CDCl$_3$): δ 0.99 (t, J = 7.6, 3H), 1.22 (t, J = 6.4 Hz, 3H), 1.68 (s, 9H), 1.72 (m, 2H), 2.36 (m, 2H), 3.01 (tt, J = 6.4, 6.8 Hz, 2H), 3.65 (t, J = 7.6 Hz, 2H), 4.12 (m, 2H), 5.64 (m, 1H), 5.73 (m, 1H), 7.25 (m, 2H), 7.33 (t, J = 7.6 Hz, 1H), 7.43 (s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 13.2 Hz, 1H), 8.11 (s, 1H), 8.97 (m, 1H), 10.39 (m, 1H); ^{13}C (CDCl$_3$): δ 13.2, 14.3, 21.0, 26.8, 28.3, 49.5, 59.5, 83.7, 100.2, 100.5, 115.5, 116.2, 116.3, 118.5, 122.6, 123.6, 124.6, 125.5, 129.9,

130.0, 145.5, 145.8, 149.6, 158.6, 159.3, 168.1, 169.4, 196.4, 199.2; MS: [M+H] calcd for $C_{26}H_{35}N_2O_5$, 455.2546; found 455.2537.
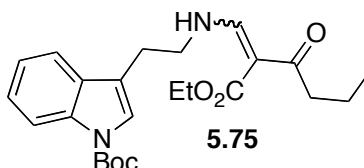
tert-Butyl 3-(2-((2-(Ethoxycarbonyl)-3-oxohex-1-en-1-yl)amino)ethyl)-1H-indole-1- carboxylate (5.75). To a mixture of **5.73** (0.5 mL, 4.0 mmol) and **5.72** (600 mg, 3.8 mmol) was added p-TsOH (50 mg, 0.26 mmol) and the mixture was stirred for 20 min. To the mixture was added **3.4** (1.0 g, 3.8 mmol) in one portion. The mixture was stirred for 3 h and was poured into H_2O (10 mL). The mixture was extracted with EtOAc (3 x 50 mL) and the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by flash chromatography (hexanes : EtOAc 10:1) to give **5.75** as a colorless oil (1.1 g, 65%): IR (neat) 2976, 1732, 1694, 1634, 1453, 1379, 1255, 1158, 1092, 768, 746 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.22 (t, J = 6.8 Hz, 3H), 1.64 (m, 2H), 1.68 (s, 9H), 2.87 (t, J = 7.3 Hz, 2H), 3.02 (t, J = 7.0 Hz, 2H), 3.65 (tt, J = 6.9 Hz, 6.9), 4.15 (tt, J = 6.9, 6.1 Hz, 2H), 7.27 (m, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.42 (s, 1H), 7.49 (d, J = 7.4 Hz, 1H), 8.16 (d, J = 13.0 Hz, 1H), 11.17 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.1, 14.5, 18.5, 26.7, 28.2, 44.0, 49.7,

59.4, 83.3, 99.9, 115.5, 116.1, 118.5, 122.5, 123.7, 124.7, 129.5, 135.0, 149.8, 160.1, 165.5, 202.1; HRMS (CI) calcd for $C_{24}H_{32}N_2O_5$ $m/z+1$ 429.2311, found 429.2561.

5.76
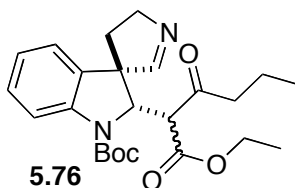
(2S,3S)-tert-Butyl 2-((R)-1-Ethoxy-1,3-dioxohexan-2-yl)-4',5'-dihydrospiro [indoline-3,3'-pyrrole]-1-carboxylate (5.76). A degassed solution of **5.75** (500 mg, 1.2 mmol) in EtOH (100 mL) was irradiated with a Hanovia 450 W medium pressure mercury lamp through a Corex filter for 40 h. The solution was concentrated in vacuo, and the resulting yellow oil was purified by chromatography on silica gel (hexanes : EtOAc 5:1) to afford **5.76** as a pale yellow oil (355 mg, 70%): IR (neat) 2972, 2932, 1709, 1481, 1382, 1251, 1166, 1055, 752, 733 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.83 (t, J = 7.9 Hz, 1H), 0.98 (t, J = 7.9 Hz, 2H), 1.11 (t, J = 7.1 Hz, 1H), 1.21 (t, J = 7.1 Hz, 2H), 1.51 (m, 2H), 1.60 (s, 9H), 2.00 (m, 1H), 2.06 (d, J = 4.6 Hz, 1H), 2.36 (m, 2H), 2.60 (m, 1H), 3.90 (m, 1H), 4.00 (m, 2H), 4.11 (m, 2H), 5.05 (t, J = 7.0 Hz, 1H), 6.84 (t, J = 9.6 Hz, 1H), 6.90 (m, 1H), 7.23 (tt, J = 6.9, 6.9 Hz, 1H), 7.64 (d, J = 11.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.4, 13.8, 14.1, 16.8, 25.9, 28.3, 41.6,

46.3, 59.5, 60.2, 61.8, 67.7, 82.3, 115.9, 122.8, 123.6, 128.7, 166.1, 166.8, 167.5; HRMS calcd for $C_{24}H_{32}N_2O_5$ *m/z* 428.2311, found 428.2322.
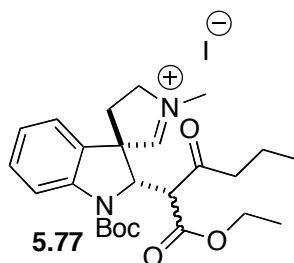
(2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-2-((*R*)-1-ethoxy-1,3-dioxohexan-2-yl)-1'-me-thyl-4',5'-dihydrospiro[indoline-3,3'-pyrrol]-1'-ium Iodide (5.77). Methyl iodide (2.2 mL, 4.0 mmol) was added to **5.76** (430 mg, 1.0 mmol), the reaction vessel was sealed and the contents were stirred for 4h. The pale yellow solution was concentrated in vacuo and the resulting solid was dried under high vacuum to afford **5.77** as a yellow solid (510 mg, 90%). This material was used for the next step without purification.
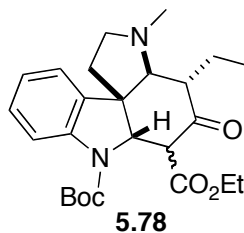
(3a*R*,6*R*,6a*S*,11b*R*)-7-*tert*-Butyl 6-Ethyl 4-Ethyl-3-methyl-5-oxo-3,3a,4,5,6,6a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6,7(2*H*)-dicarboxylate (5.78). To a suspension of NaH (2.1 mg, 0.06 mmol) in THF at 0 °C was added

5.77 (30 mg, 0.04 mmol) under Ar. After 20 min, LDA (0.06 mL, 1M in THF) was added to the suspension and the mixture was stirred for 4 h. Aq. NH$_4$Cl was added and the mixture was extracted with EtOAc (3 x 5 mL). The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes : EtOAc 4:1) afforded **5.78** as a colorless oil (23 mg, 75%): IR (neat) 2970, 1709, 1614, 1479, 1367, 1251, 1165, 1101, 1049 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.86 (t, J = 7.7 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.50 (s, 9H), 1.66 (m, 2H), 1.89 (m, 1H), 2.09 (m, 1H), 2.29 (m, 2H), 2.37 (s, 3H), 2.43 (t, J = 7.7 Hz, 1H), 2.53 (m, 1H), 3.15 (dd, J = 9.2, 9.2 Hz, 1H), 3.3 (dd, J = 7.9, 7.9 Hz, 1H), 3.72 (d, J = 2.5 Hz, 1H), 4.24 (m, 2H), 5.00 (d, J = 2.6 Hz, 1H), 7.00 (dd, J = 7.4, 10.0 Hz, 1H), 7.15 (d, J = 7.1 Hz, 1H), 7.21 (m, 1H), 7.74 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.9, 14.3, 20.9, 28.4, 31.5, 34.9, 36.2, 51.2, 51.5, 59.9, 61.6, 81.3, 97.2, 100.4, 115.3, 122.6, 123.2, 128.2, 136.1, 142.0, 152.6, 166.4, 168.7; HRMS (CI) calcd for C$_{25}$H$_{34}$N$_2$O$_5$ *m/z+1* 443.2546, found 443.2557.

5.80
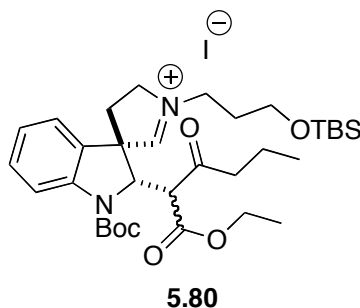
(2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-1'-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-2-((*R*)-1-ethoxy-1,3-dioxohexan-2-yl)-4',5'-dihydrospiro[indoline-3,3'-pyrrol]-1'-ium Iodide (5.80). To a solution of **5.76** (78 mg, 0.18 mmol) in DMSO (2 mL) at room temperature was added **5.79** (550 mg, 1.8 mmol), the reaction vessel was sealed, and the mixtue was stirred for 4 h. The solution was diluted with CH₂Cl₂ (15 mL), washed with brine (6 x 5 mL) and dried (Na₂SO₄). The solvent was removed in vacuo to give **5.80** as a yellow oil (54 mg, 50%). The material was used for the next step without purification.

5.81
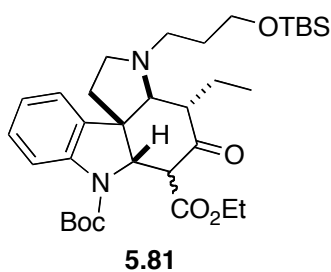
7-*tert*-Butyl   6-Ethyl   3-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-4-ethyl-5-oxo-3,3a,4,5,6,6a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6,7(2*H*)-dicarboxylate (5.81). To a suspension of NaH (2.1 mg, 0.06 mmol) in THF at 0 °C was added **5.80** (30 mg, 0.04 mmol) under Ar. After 20 min, LDA (0.06

mL, 1M in THF) was added to the suspension and the mixture was stirred for 4 h. Aq. NH$_4$Cl was added to the mixture which was extracted with EtOAc (3 x 5 mL). The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes : EtOAc 5:1) afforded **5.81** as a colorless oil (12 mg, 40%): IR (neat) 2930, 2856, 1711, 1479, 1367, 1252, 1185, 1097, 836 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.09 (d, J = 7.5 Hz, 6H), 0.88 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.53 (s, 9H), 1.65 (m, 2H), 1.98 (m, 1H), 2.60 (m, 1H), 2.80 (m, 4H), 3.24 (m, 1H), 3.60 (tt, J = 4.1, 6.3 Hz, 2H), 3.85 (m, 1H), 4.08 (t, J = 7.2 Hz, 2H), 5.11 (d, J = 10.9 Hz, 1H), 7.00 (t J = 7.2 Hz, 1H), 7.20 (m, 2H), 7.62 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ -5.3, 13.9, 14.3, 18.3, 21.0, 25.9, 28.3, 28.5, 30.3, 31.1, 34.9, 45.3, 49.1, 50.6, 59.9, 61.0, 61.5, 81.3, 94.6, 99.2, 115.2, 122.4, 123.4, 128.2, 136.2, 141.8, 152.6, 166.2, 168.9; HRMS (CI) calcd for C$_{33}$H$_{52}$N$_2$O$_6$Si $m/z+1$ 601.3673, found 601.3701.

5.85
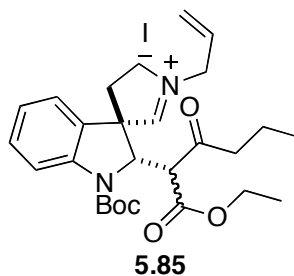
(2S,3S)-1'-Allyl-1-(*tert*-Butoxycarbonyl)-2-(1-ethoxy-1,3-dioxohexan-2-yl)-4',5'-dihydrospiro[indoline-3,3'-pyrrol]-1'-ium iodide (5.85). 5.77 (678 mg, 4.0 mmol) was added to **5.76** (430 mg, 1.0 mmol) and the reaction vessel was sealed and left to stir for 4h. The pale yellow solution was concentrated to remove excess **5.77** in vacuo and the resulting solid was dried under high vacuo to afford **5.85** as yellow solid (540 mg, 90%). **5.85** was used for the next step without purification.

5.86
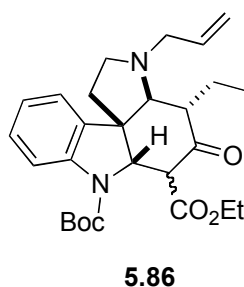
(3aS,4S,6aS,11a1R)-7-*tert*-Butyl 6-Ethyl 3-Allyl-4-ethyl-5-oxo-3,3a,4,5,6,6a-hexahydro-1H-pyrrolo[2,3-d]carbazole-6,7(2H)-dicarboxylate (5.86). To a suspension of NaH (2.1 mg, 0.06 mmol) in THF at 0 °C was added **5.85** (24 mg, 0.04 mmol) under Ar. After 20 min, LDA (0.06 mL, 1M in THF) was added to the suspension and the mixture was stirred for 4 h. Aq. NH_4Cl was added to

the mixture which was extracted with EtOAc (3 x 5 mL). The combined extracts were washed was brine, dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes : EtOAc 5:1) afforded **5.86** as a colorless oil (19 mg, 75%): IR (neat) 2975, 2931, 1711, 1479, 1367, 1251, 1103, 1063, 836 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.85 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.44 (s, 9H), 1.63 (m, 2H), 2.25 (m, 1H), 2.54 (m, 1H), 2.76 (m, 1H), 2.89 (m, 1H), 3.18 (tt, J = 4.9, 5.4 Hz, 1H), 3.36 (dd, J = 5.9, 13.0 Hz, 1H), 3.48 (dd, J = 6.4, 13.0 Hz, 1H), 4.25 (m, 2H), 4.99 (s, 1H), 5.16 (d, J = 9.9 Hz, 1H), 5.22 (d, J = 17.0 Hz, 1H), 5.86 (m, 1H), 7.00 (t, J = 7.2 Hz, 1H), 7.20 (m, 2H), 7.62 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.9, 14.3, 21.0, 28.2, 30.7, 34.9, 48.8, 50.9, 52.0, 59.9, 61.5, 81.3, 94.8, 99.8, 106.8, 115.2, 117.1, 122.4, 123.4, 128.2, 136.1, 141.9, 152.6, 166.1, 168.8; HRMS (CI) calcd for C$_{28}$H$_{37}$N$_2$O$_5$ *m/z+1* 469.2678, found 469.2682.

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APPENDICES

8.120
7.635
7.633
7.615
7.614
7.440
7.420
7.290
7.285
7.272
7.269
7.252
7.249
7.206
7.203
7.186
7.168
7.166
7.088
7.082
6.369

3.2

3.753
3.736
3.721
3.704

3.108
3.091
3.074

1.630

0.86
1.00
0.98
1.59
1.01
1.00
0.90
2.11
2.11

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 ppm

136.48

126.94

122.58
122.22
119.83
118.48

111.80
111.42

77.35
77.03
76.71

3.2

40.06

24.74

3.3

8.255

7.338
7.254
7.235
7.218

4.144
4.126

3.623
3.612

3.3

124.79
123.41
122.73

118.62
116.45
115.46

77.36
77.05
76.73

39.60

28.19

24.47

3.6

169.23
166.00
159.84
155.92

130.71

124.25

116.19
116.00
113.17

89.84

83.52
77.50
77.08
76.65

59.80
59.56

49.37

28.18
26.81

14.40
14.34

3.6

CO2Et
CO2Et
N
H
N
Boc

3.8

7.835
7.827
7.280
7.220
7.218
7.215
7.007
6.982
6.978
6.957
6.953
6.852
6.850
6.847
6.845
6.827
6.825
6.822
6.820

4.263
4.192
4.168
4.144
4.022
4.014
3.921
3.905
3.897
3.882

2.050

1.604
1.288
1.285
1.265
1.261
1.241
1.237
1.093
1.069
1.045

3.8

Peaks:
- 167.04
- 166.85
- 166.51
- 134.75
- 128.57
- 123.48
- 122.56
- 115.45
- 82.30
- 77.45
- 77.23
- 77.03
- 76.61
- 75.50
- 67.76
- 64.11
- 61.90
- 61.63
- 60.01
- 52.55
- 42.17
- 36.66
- 29.69
- 28.35
- 24.70
- 23.43
- 13.86
- 13.68

3.9

7.408
7.286
7.285
7.204
7.201
7.184
7.165
7.162
7.034
7.032
7.016
7.014
6.997
6.995

4.987
4.975
4.213
4.204
4.195
4.186
4.177
4.168
4.159
4.150
4.141
4.132
3.962
3.936
3.918

3.017
2.871
2.781

2.550

2.268

1.601
1.296
1.282
1.274
1.264
1.246
1.071
1.053
1.035

1.09
0.89
0.91

0.82

2.00
1.85
1.03

0.98

2.64

2.40

0.95

0.86

8.44

3.24

2.58

3.9

3.13

7.509
7.507
7.484
7.479
7.314
7.311
7.308
7.290
7.284
7.281
7.178
7.173
7.155
7.150
7.131
7.125
7.106
7.101
7.082
7.078

5.319

3.575
2.885
2.873
2.868
2.861
2.855
2.853
2.839
2.825
2.812
2.808
2.510

1.745

136.19
131.23
127.08
121.42
119.34
117.97
110.91
107.69

77.37
77.05
76.73

52.91
51.99

45.24

32.03
31.96
29.74

22.73
21.22

3.13

8.5

0.83

8.0

7.5

0.89
0.95
0.94
0.98

7.0

6.5

6.0

5.5

5.0

4.5

4.0

3.5

1.00
1.52
2.20

3.0

2.95
1.08

2.5

1.30

2.0

1.5

1.0

0.5

ppm

7.424
7.401
7.281
7.238
7.234
7.213
7.208
7.187
7.183
7.087
7.084
7.062
7.059
7.037
7.034
6.904
6.879

Coerulescine (**2.2**)

3.048
3.044
3.032
3.028
3.019
3.003
2.891
2.888
2.839
2.814
2.810
2.784
2.759
2.477
2.457
2.447
2.431
2.414
2.405
2.389
2.163
2.138
2.120
2.113
2.095
2.071
2.063
1.276
1.272

0.088

Coerulescine (2.2)

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

182.74

139.98
136.27

127.75
123.38
122.89

109.41

77.36
77.24
77.04
76.72

66.40

56.77
53.66

41.86
38.01

29.64

8.018
7.324
7.302
7.297
7.296
7.295
7.294
7.293
7.292
7.291
7.290
7.289
7.286
7.283
7.282
7.281
7.280
7.279
7.062
7.056
7.041
7.035
6.938
6.932
6.916
6.910
6.395

3.937
3.919
3.909
3.892
3.874
3.858
3.852
3.821
3.818
3.740
3.724
3.708
3.692
3.069
3.053
3.036

1.665

1.280

3.16

0.78
0.97
2.02
1.00
0.80
3.36
2.13
2.00
1.66

154.33

122.92

112.86
112.19
111.52

100.15

77.23

55.91

40.05

24.74

160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

3.16

7.290
7.283
7.281
7.280
7.279
7.278
7.277

4.069
3.937
3.877
3.852
3.846
3.821
3.738
3.688

2.971

3.17

MeO

N
Boc

H
N

O

CF₃

0.76
0.84
1.92
0.79
3.00
1.99
1.93
8.64

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

156.03

124.02

116.26
113.45

101.30

55.76

39.55

28.21
24.53

3.17

MeO

N
Boc

O

N
H

CF₃

150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

7.521
7.332
7.286
7.062
6.993
6.925
6.920
6.902
6.897

MeO

3.18
Boc
Crude

NH₂

3.892
3.835

3.325
3.179

1.646

0.90
0.95
1.30
1.33
3.18
1.83
2.00
9.44

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

157.91

149.82

154.33
121.77
119.42
118.30

111.72

99.51

83.30
77.38
77.27
77.06
76.74

55.64

41.58

29.28
28.23

MeO

N
Boc
3.18
Crude

NH₂

9.259

8.038
8.011
7.946
7.899

7.394
7.279
6.963
6.955
6.934
6.925
6.914
6.906

4.258
4.234
4.210
4.186
4.162
4.138
4.114
3.862
3.645
3.623

2.986
2.963

1.658
1.346
1.322
1.299
1.272
1.248
1.225

0.91
0.80
1.10
0.90
2.01
4.16
3.07
2.10
2.00
9.47
3.27
3.22

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

MeO

N
Boc **3.19**

H
N

CO₂Et
CO₂Et

169.23
166.00
159.84
155.92
130.71
124.25
116.19
116.00
113.17
101.37
89.84
83.52
77.50
77.08
76.65
59.80
59.56
55.72
49.37
28.18
26.81
14.40
14.34

MeO

Boc

N

3.19

H
N

CO₂Et
CO₂Et

7.831

7.285

6.763
6.756
6.741
6.734
6.400
6.393

4.991

4.244
4.174
4.166
4.148
4.021
3.952
3.934
3.745

2.333
2.317
2.059
2.056
2.027

1.595
1.284
1.266
1.248
1.120
1.102
1.084

Peak labels:
166.87
166.46
156.30
116.10
113.54
108.39
77.37
77.05
76.73
67.98
61.89
61.64
60.10
55.66
41.99
28.38
13.87
13.75

3.21

MeO

N
Boc

CO2Et
CO2Et

N

7.289
7.283
7.281
6.973
6.725
6.718
6.703
6.696

5.000
4.192
4.183
4.179
4.175
4.161
4.157
4.143
4.139
4.135
4.126
4.000
3.979
3.888
3.802
3.152

2.868
2.717

2.461

2.223

1.973

1.586
1.282
1.264
1.246
1.119

7.935

7.285
7.197
7.175
6.954
6.948
6.818
6.812
6.796
6.790

MeO

3.26

N
H

NMe

3.875

3.579

2.838

2.517

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

0.81

0.99

0.92

0.99

3.00

1.90

3.81

2.96

- 154.00

- 132.51
- 131.16
- 129.23
- 128.78
- 127.61

- 113.76
- 111.39
- 110.99
- 107.83

- 100.40

- 77.35
- 77.23
- 77.03
- 76.71
- 72.66

- 55.94
- 55.29
- 52.98
- 52.32

- 45.54

- 29.72

- 21.42

MeO

3.26

N
H

NMe

Horsfiline (**2.3**)

Horsfiline (2.3)

4.5 0.49 6.51 4.0 3.5 3.0 2.5 1.06 2.00 1.89 2.0 1.5 9.81 1.0 9.69 ppm

4.438
4.299
4.275
4.263
4.252
4.240
4.228

2.515
2.493
2.352
2.350
2.329
2.326

4.23

CO_2Et OH CO_2Et

1.314
1.310
1.297

0.967
0.952
0.945
0.930

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

201.89

168.62

77.44
77.02
76.59

67.22

62.06

48.41

23.91
22.35
18.05
13.91

4.23

OH
CO₂Et
CO₂Et

4.261
4.259
4.237
4.235
4.214
4.213
4.191
4.189
4.167
4.165
4.143
4.141

3.777
3.775

2.784
2.760

2.005
1.982
1.959

1.596
1.569
1.342
1.340
1.318
1.316
1.310
1.306
1.304
1.294
1.292
1.290
1.282
1.268
1.266
1.244
1.242
1.034
1.033

4.56
2.99
1.98
1.11
7.16
6.21

4.0   3.5   3.0   2.5   2.0   1.5   1.0   ppm

4.24

OMe

CO2Et

CO2Et

173.21
165.00

109.47

61.00
60.35
56.21

35.57
27.66
22.26
14.13
14.10

4.24

OMe

CO₂Et

CO₂Et

9.867

8.175
8.148
7.513
7.487
7.472
7.343
7.319
7.288
7.283
7.279
7.275
7.262
7.238

4.224
4.201
4.177
4.164
4.141

3.605
3.585

2.998

2.454
2.430

2.057

1.687

1.285
1.276

0.901

4.25

0.87

0.87

1.89
2.36

4.74

2.00

1.93

1.94

2.35
8.85

20.45

19.31

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

172.61

149.66

135.59
130.36
124.51
123.14
122.53
118.93
117.76
115.31

83.55
77.54
77.12
76.69

46.08

38.99

28.20
26.09
25.26
22.46

4.25

(Structure: indole with N-Boc substituent, bearing a 2-(ethyl chain) connecting to NH, attached to C=C(CO$_2$Et)$_2$ with an isobutyl group)

N
Boc

H
N

CO$_2$Et
CO$_2$Et

4.26

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

175.48
166.89
166.49
152.34
141.93
134.91
128.34
123.93
123.54
116.47

82.11
77.35
77.03
76.72
66.18
65.32
61.75
60.38
57.63
53.19
44.43
40.92
28.22
26.29
23.28
22.66
21.04
14.19
13.86
13.81

4.26

7.606
7.587
7.314
7.295
7.287
7.194
6.985

5.107
5.090

4.232
4.214
4.147
4.129
4.123
4.105
4.096
4.080
4.062
3.806
3.788
3.305
3.277
3.073
3.064
3.056
3.047
3.041
3.029

2.261
2.244
1.928
1.911
1.893
1.879
1.754
1.745
1.717

1.238
1.207
0.974
0.957
0.886
0.869

4.27

Boc   CO₂Et

N

CO₂Et

NH

0.95
1.21
1.13
1.10

1.00

4.32
1.09

1.01
2.10

1.07

2.15
2.26
9.77
1.89
6.46
3.19
3.35

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

168.14
167.06

152.23

141.61

136.12

127.39
125.21
122.74

116.15

81.67
77.37
77.06
76.74

67.39

61.64
61.58
58.90
57.72

52.53

44.41
43.58
42.35

28.34
28.26
26.41
24.24
21.06

13.87

4.27

4.29

7.811
7.500
7.280
7.144
7.139

4.138
4.132
4.113

3.398
3.356
3.077
3.071
3.052
2.781
2.774
2.768
2.763

2.010
1.988

1.645

1.070
1.048
1.041
1.019

0.84 0.97 0.98 2.01 1.01 1.01 1.07 1.87 1.17 1.25 2.19 6.58

136.75
135.57

127.62

121.46
119.37
118.02

110.64
108.83

50.50

44.46
42.48

24.62
23.86
22.76
21.74

4.29

140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 ppm

65C

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

155.67

136.52
135.83
128.81
128.29
127.01
121.28
118.93
118.00
111.50
106.87

67.00

50.45
43.74
38.29
31.00
25.13
23.81
22.49

4.30

N
H

NCbz

65 C

10.344
7.384
7.373
7.347
7.338
7.326
7.318
7.209
7.206
7.190
7.187
7.171
7.168
7.058
7.039
6.942
6.925
6.923
6.906
6.904
6.864
6.845
5.705
5.175
5.143
5.121
5.113
5.082
3.986
3.969
3.952
3.821
3.815
3.808
3.800
3.793
3.788
3.773
3.728
3.710
3.703
3.124
2.514
2.509
2.505
2.500
2.495
2.295
2.291
2.279
2.264
2.260
2.244
2.092
2.073
2.070
2.058
2.054
2.042
2.038
1.716
1.700
1.258
1.241
1.224
0.995
0.707
0.691
0.665
0.649

4.31

0.76

4.73
0.88
0.87
0.84
0.90

1.97

0.91
1.90

1.00
0.87

1.89

1.03

5.98

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

65 C

177.92

154.64

141.36
137.49
133.93
131.30
128.79
128.49
128.27
128.19
128.01
122.65
122.33
109.92

66.64
63.73
55.76
55.22
45.07
40.96
40.75
40.54
40.34
40.13
39.92
39.71
34.91
25.02
23.39
22.38

0.52

4.31

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

4.33

7.286
7.261
7.252
7.249
7.245
7.242
7.234
7.230
7.225
7.104
7.102
7.085
6.972
6.953
6.951

3.537
3.529
3.521
3.516
3.500
3.451
3.442
3.426
3.417
3.396
3.381
3.373
3.358
2.374
2.340
2.090
2.064
1.658
1.653
1.648
1.635
1.508
1.496
1.483
1.473
1.461
1.449
1.436
0.957

0.68
2.12
1.08
1.02
1.56
1.02
1.11
1.07
2.00
0.43
1.05
1.11
1.25
6.48

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

181.64
180.95

141.55
140.71
131.15
129.98
128.38
128.24
122.86
122.68
122.49
110.35

77.41
77.09
76.78

67.28
65.72

57.74
57.73

45.36
39.04
37.89
37.60
36.65

25.67
25.57
23.42
23.03
22.17
21.70

4.33

8.564
8.552

7.773
7.768
7.599
7.588
7.384
7.303
7.302
7.290
6.658
6.652

1.00

1.02
1.00
1.03
1.22

1.00

9.35

1.559

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm

4.41

O=C(CH₃)₃

BRUKER

177.11

136.79

129.41
125.67
125.12
123.56
120.49
117.35

108.25

41.26

28.73

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

4.41

O

C(CH₃)₃

BRUKER

9.165

7.973
7.971
7.965
7.960
7.675
7.664
7.289

6.716
6.711

4.860

1.571

1.00
1.97
1.00
0.99
2.01
9.15

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 ppm

4.42

4.42

191.12
177.26
136.23
133.85
131.17
129.32
123.74
120.95
118.44
108.17
46.35
41.44
28.64

7.590
7.578

7.008
7.003
6.864
6.861

6.502
6.498

3.772

1.00
1.17
2.11
1.00
2.81

8.0   7.5   7.0   6.5   6.0   5.5   5.0   4.5   4.0   ppm

4.45

MeO

N
H

7.908
7.511
7.499
7.290
6.962
6.960
6.959
6.894
6.891
6.830
6.827
6.818
6.814

3.878

3.047
2.902

1.468

0.45
0.50
0.49
0.47
0.51

1.54

0.96
1.04

2.00

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 ppm

4.47

MeO

N
H

NH₂

BRUKER

4.47

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

156.60
137.19
121.99
120.70
119.51
113.92
109.29
94.72
55.73
42.40
29.61

NAME   1y120114-4
EXPNO   2
PROCNO   1
Date_   20120114
Time   16.28
INSTRUM   spect
PROBHD   5 mm PABBO BB-
PULPROG   zgpg30
TD   65536
SOLVENT   CDCl3
NS   480
DS   4
SWH   41666.668 Hz
FIDRES   0.635783 Hz
AQ   0.7864820 sec
RG   203
DW   12.000 usec
DE   6.50 usec
TE   298.5 K
D1   2.00000000 sec
D11   0.03000000 sec
TD0   1

======= CHANNEL f1 =======
NUC1   13C
P1   9.30 usec
PL1   2.00 dB
PL1W   67.83342743 W
SFO1   176.0697436 MHz

======= CHANNEL f2 =======
CPDPRG2   waltz16
NUC2   1H
PCPD2   80.00 usec
PL2   -3.00 dB
PL12   12.30 dB
PL13   12.30 dB
PL2W   32.08600616 W
PL12W   0.94692516 W
PL13W   0.94692516 W
SFO2   700.1499406 MHz
SI   32768
SF   176.0521380 MHz
WDW   EM
SSB   0
LB   3.00 Hz
GB   0
PC   1.40

8.0 0.87
7.5 1.05
7.0 0.97 0.95 1.01
6.5 0.85
4.0 2.95
3.5 1.98
3.0 1.89
ppm

7.957

7.484
7.455

6.966
6.958
6.908
6.901
6.862
6.855
6.834
6.826

6.349
6.332

3.876
3.734
3.713
3.692
3.670

3.061
3.039
3.017

156.92
137.30
120.91
119.09
109.89
94.82
77.22
55.71
40.02
24.79

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

219

0.86

0.98
0.85

0.96

0.85

2.98

2.00

1.96

8.90

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

158.19
157.44
157.07

122.01
119.09
117.22
116.39
112.11

99.57

83.69
77.35
77.03
76.72

55.65

39.58

28.19
24.53

MeO

N
Boc

N
H
O
CF₃

7.757
7.418
7.390
7.315
7.281
6.906
6.898
6.878
6.870

3.890
3.847

3.061
3.038
3.017
2.834
2.814
2.811
2.789

1.680

4.34

MeO

N
Boc

NH₂

0.90
0.96
0.9
0.99

3.02

2.04
2.00

9.01

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

MeO

4.34

N
Boc

NH₂

157.91
149.82
124.33
121.77
119.42
118.30
111.72
99.51
83.30
77.38
77.27
77.06
76.74
55.64
41.58
29.28
28.23

4.35

MeO

N
Boc

H
N

CO₂Et
CO₂Et

9.845

7.760
7.368
7.340
7.282
7.279
6.920
6.917
6.912
6.909
6.891
6.888
6.883
6.880

4.285
4.261
4.246
4.223
4.199
4.191
4.184
4.175
4.171
4.167
4.160
4.136
4.113
3.897
3.894
3.781
3.777
3.608
3.584
3.564
3.540
2.977
2.952
2.928
2.785
2.761
2.449
2.424
1.683
1.593
1.272
0.950
0.928

0.57
0.51
1.18
0.69
0.66
3.19
1.99
1.33
1.25
1.24
6.06
5.99
5.17

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

4.35

169.36
169.20
166.38
158.01
122.12
118.96
116.71
92.68
83.44
77.22
60.99
60.39
59.34
55.64
43.28
37.08
28.31
28.19
28.08
27.65
26.26
22.39
22.25
14.37
14.18

ppm
200 180 160 140 120 100 80 60 40 20 0

4.36

MeO

N
Boc

CO2Et

CO2Et

N

175.84

166.89
166.52
160.19

152.23

143.15

126.75
124.30

109.65

102.59

82.14
77.35
77.04
76.72

66.01
65.58
61.73
57.49
55.45
53.16

44.34
40.89

28.22
26.32
23.28
22.69

14.02
13.85
13.83

4.37

7.285
7.191
7.170

6.555
6.548
6.534
6.527

5.099
5.082

4.165
4.147
4.093

3.807

3.275
3.269
3.247
3.242
3.033

2.226
2.210

1.877
1.846
1.721
1.686
1.565

1.246
1.226
0.973
0.957
0.885
0.869

0.67
0.86
1.00
0.78
3.48
4.06
0.80
1.67
0.85
2.55
1.96
8.10
0.66
6.11
6.22

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

4.37

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

168.14
167.09
159.40
127.96
125.55
102.39
81.74
77.35
77.03
76.72
67.96
61.64
61.59
58.72
55.39
52.50
44.22
43.45
42.47
28.38
28.26
26.34
24.24
21.03
13.89
13.87

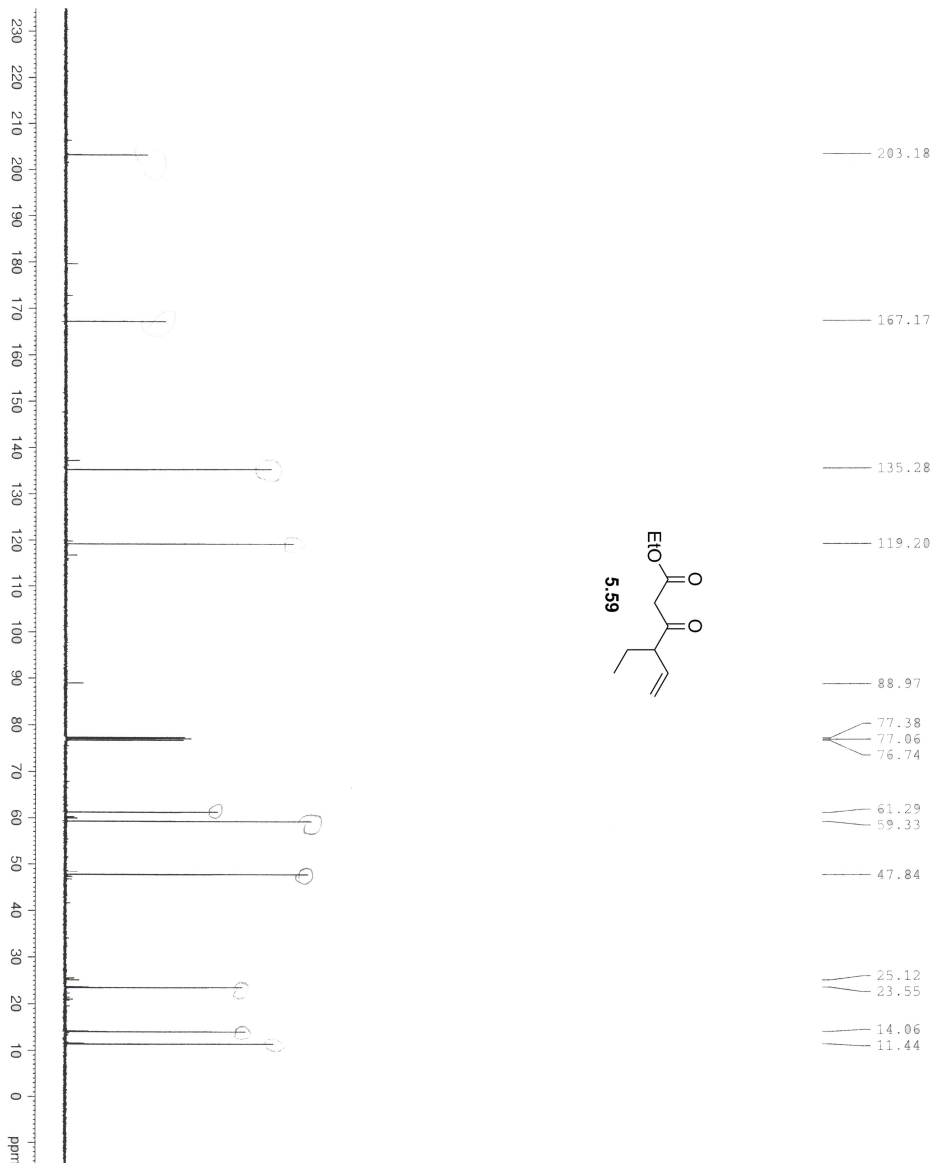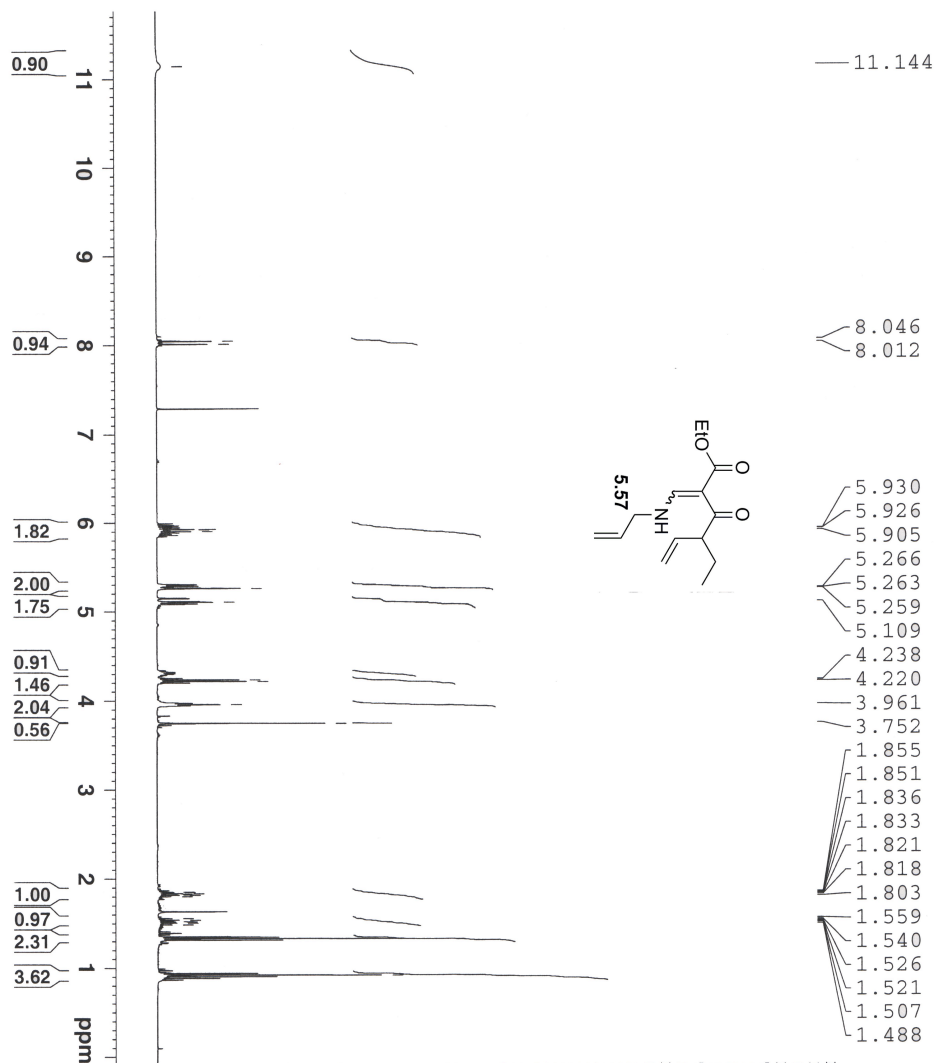Current Data Parameters
NAME   1y-2009-07-22
EXPNO   4
PROCNO   1
DU   /m
USER   yangli

F2 - Acquisition Parameters
Date_   20090722
Time   14.40
INSTRUM   DPX400
PROBHD   5 mm BBO BB-1H
PULPROG   zgpg30
TD   65536
SOLVENT
NS   3968
DS   4
SWH   25125.629 Hz
FIDRES   0.383387 Hz
AQ   1.3042164 sec
RG   16384
DW   19.900 us
DE   6.00 us
TE   299.2 K
D1   0.15000001 sec
d11   0.03000000 sec
DELTA   0.05000000 sec
TD0   1

======== CHANNEL f1 ========
NUC1   13C
P1   7.80 us
PL1   -3.00 dB
SFO1   100.5785700 MHz

======== CHANNEL f2 ========
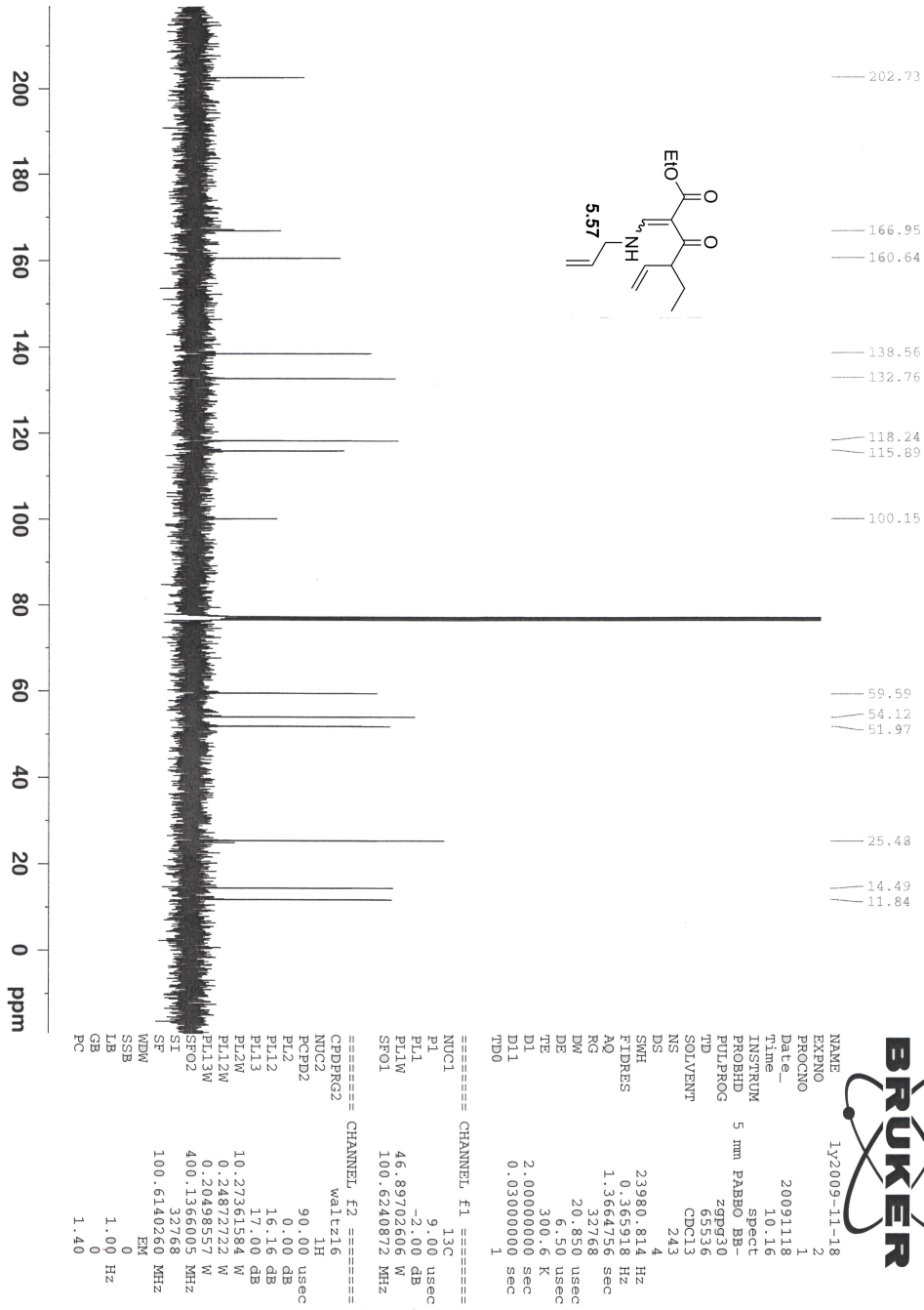CPDPRG2   waltz16
NUC2   1H
PCPD2   135.00 us
PL2   17.40 dB
PL12   17.40 dB
PL13   17.40 dB
SFO2   399.9516000 MHz

F2 - Processing parameters
SI   32768
SF   100.5675080 MHz
WDW   no
SSB   0
LB   0.00 Hz
GB   0
PC   1.40

0.87
0.95

2.01

7.630
7.627
7.379
7.351

6.859
6.853
6.800
6.793
6.772
6.764

MeO

4.39

N
H

NH

1.02
3.00

4.122
4.102
4.095
4.076
3.856

1.08

1.05

1.99

3.334
3.055
3.030
2.735
2.733
2.726
2.719
2.713
2.708

1.13

2.067
1.994
1.972

5.69

1.645

6.29

1.056
1.034
1.031
1.009

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
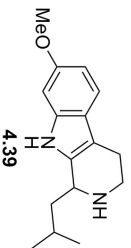
156.13
122.11
118.50
108.67
108.59
95.04
77.21
55.81
50.47
44.49
42.41
24.63
23.82
22.72
21.80

7.522
7.312
6.736
6.731
6.692
6.686
6.671
6.665

4.121
4.116
4.109
4.104
4.098
4.093
4.087
3.353
3.341
3.051
2.724
2.705
1.987
1.982
1.965
1.650
1.638
1.633
1.628
1.621
1.615
1.611
1.599
1.056
1.040
1.030
1.014

0.93
0.44

2.03

1.09

2.00

1.56

4.04

1.22

1.98

2.79
6.15

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

4.48

152.31

136.59
135.13

121.76
118.47

109.33
108.52

97.05

77.23

50.45
45.84
44.27
42.32

24.62
23.84
22.65
21.76

4.48

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0   ppm

155.89
154.56

146.81

135.89
135.54
134.94
128.70
128.22
128.04
127.82
125.11

118.54
118.33

113.07

108.64
108.07

103.62

70.28
67.62
67.27

49.94
49.85

44.28
43.89

38.19
37.89

25.13
24.90
23.38
22.42
21.48
20.92

4.49

7.442
7.427
7.381
7.371
7.080
7.061
6.777
6.772
6.753
5.321
5.281
5.140
5.112
3.989
3.973
3.956
3.806
3.786
3.771
3.741
3.721
3.594
2.269
2.094
2.079
1.680
1.263
0.714
0.697
0.678
0.662

10.74
0.78
1.35
1.97
2.00
0.77
1.61
1.24
0.79
2.03
4.19
0.90
6.40

ppm

CbzO

H
N
4.50

O
NCbz

235

(±)-Elacomine (4.1)

(±)-Elacomine (4.1)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

— 182.92

— 157.66

— 142.82

— 122.71
— 121.48

— 108.66

— 97.76

— 66.98

— 57.41

— 48.09
— 47.88
— 47.66
— 45.09
— 38.26
— 37.03

— 25.20
— 22.32
— 20.89

Current Data Parameters
NAME   1y-2008-09-28-1
EXPNO   4
PROCNO   1
DU   /m
USER   yangli

F2 - Acquisition Parameters
Date_   20090928
Time   22.18
INSTRUM   DPX400
PROBHD   5 mm BBO BB-1H
PULPROG   zgpg30
TD   65536
SOLVENT   CDCl3
NS   9557
DS   4
SWH   23980.814 Hz
FIDRES   0.365918 Hz
AQ   1.3664756 sec
RG   9195.2
DW   20.850 us
DE   6.00 us
TE   299.2 K
D1   2.00000000 sec
d11   0.03000000 sec
DELTA   1.89999998 sec
TD0   1

======== CHANNEL f1 ========
NUC1   13C
P1   8.30 us
PL1   -3.00 dB
SFO1   100.6504921 MHz

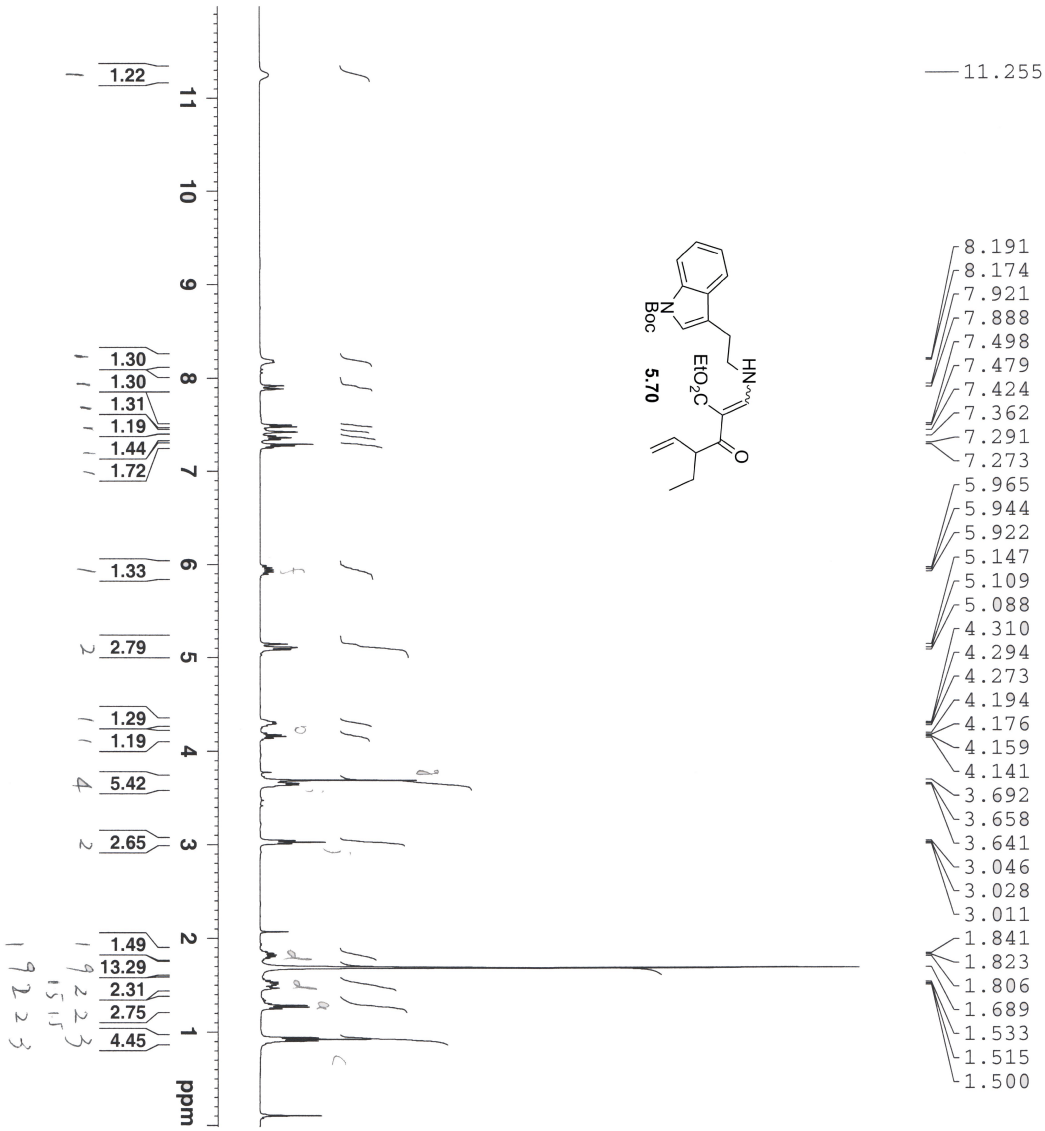======== CHANNEL f2 ========
CPDPRG2   waltz16
NUC2   1H
PCPD2   90.00 us
PL2   -3.00 dB
PL12   15.00 dB
PL13   15.00 dB
SFO2   400.2416010 MHz

F2 - Processing parameters
SI   32768
SF   100.6404280 MHz
WDW   no
SSB   0
LB   0.00 Hz
GB   0
PC   1.40

5.59

5.701
5.676
5.646
5.641
5.611
5.242
5.236
5.210
5.178

4.210
4.186
4.162
4.139

3.542
3.490
3.471
3.419
3.141
3.118

2.032
1.803
1.781
1.532
1.510
1.261
0.876

0.94   2.00   2.27   1.85   0.88   1.47   1.21   3.49   3.33

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

203.18
167.17
135.28
119.20
88.97
77.38
77.06
76.74
61.29
59.33
47.84
25.12
23.55
14.06
11.44

5.59

EtO

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

11.144

8.046
8.012

EtO

5.57

NH

5.930
5.926
5.905
5.266
5.263
5.259
5.109
4.238
4.220
3.961
3.752
1.855
1.851
1.836
1.833
1.821
1.818
1.803
1.559
1.540
1.526
1.521
1.507
1.488

0.90

0.94

1.82

2.00
1.75

0.91
1.46
2.04
0.56

1.00
0.97
2.31

3.62

11 10 9 8 7 6 5 4 3 2 1 ppm

BRUKER

5.57

202.73

166.95
160.64

138.56
132.76

118.24
115.89

100.15

59.59
54.12
51.97

25.48

14.49
11.84

200 180 160 140 120 100 80 60 40 20 0 ppm

8.123
8.103
7.659
7.640
7.512
7.320
7.281
7.235
6.160
6.143
6.125
6.118
6.099
6.083
6.056
5.573
5.543
5.531
5.505
5.480
5.423
5.397
3.737
3.425
3.402
3.307
3.283
1.670

5.68

1.34
1.00
0.94
0.93
0.96
1.58
2.46
0.73
3.20
1.82
1.79
8.23

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 ppm

130 120 110 100 90 80 70 60 50 40 30 ppm

135.47
129.55
128.77
127.19
124.84
124.78
123.90
122.82
122.42
118.91
115.39
115.02

83.93

77.36
77.04
76.73
75.12

49.72
46.11
42.24

28.22
22.03

5.68

7.595
7.515
7.495
7.439
7.421
7.370
7.352
7.331
7.271
7.255
7.253

5.828
5.816
5.811
5.801
5.797
5.790
5.785
5.780
5.776
5.274
5.271
5.099

4.239
4.221

3.863
3.837
3.749
3.605
3.585

2.970

1.851
1.541
1.532
1.522
1.317

0.903
0.901

5.67

0.98
0.97
1.03
0.91
1.03
1.36

2.00

2.05
1.99

1.47
2.19
1.80
2.95

2.01

1.45
9.60
1.66
2.87

3.39

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

5.67

175.83
169.17
169.14
169.07
168.74
162.88
154.07
149.56
139.40
136.88
136.35
135.52
132.10
130.07
124.62
123.51
122.60
120.45
119.37
119.58
117.52
116.59
115.42
83.59
78.43
77.25
77.21
77.03
76.71
75.19
75.02
74.94
74.76
72.85
72.36
62.31
60.41
58.43
56.11
55.12
52.02
51.80
50.67
50.40
50.35
26.25
25.23
24.68
24.05
20.50
19.75
18.60
18.14
15.28
14.32
14.04
11.84

200   180   160   140   120   100   80   60   40   20   0   ppm

— 11.255

8.191
8.174
7.921
7.888
7.498
7.479
7.424
7.362
7.291
7.273
5.965
5.944
5.922
5.147
5.109
5.088
4.310
4.294
4.273
4.194
4.176
4.159
4.141
3.692
3.658
3.641
3.046
3.028
3.011
1.841
1.823
1.806
1.689
1.533
1.515
1.500

13C

202.
197.39

168.62
166.88
160.68
157.89
148.99
148.93
138.55
129.82
124.68
123.72
122.65
118.48
116.08
115.93
115.49
101.82
99.69
83.72
77.33
77.22
77.02
76.70
74.82
74.67
59.51
54.04
49.76
29.70
28.19
26.68
25.51
14.44
11.89
9.10

5.70

200 180 160 140 120 100 80 60 40 20 ppm

10.386

8.972

7.839
7.805
7.502
7.483
7.438
7.348
7.328
7.261
7.242

5.838
5.821
5.661
5.644
5.627

4.156
4.138
4.114
4.096
3.663
3.647
3.631
3.025
3.007
2.384
2.364
2.343
1.722
1.683
1.606
1.215

5.71

0.48
0.24
0.86
0.55
0.32
1.96
1.00
2.33
0.72
2.01
2.07
2.00
1.92
2.87
9.57
1.98
3.64
3.13

10 9 8 7 6 5 4 3 2 1 ppm

199.17
196.43
169.43
168.12
159.32
158.56
149.57
145.77
145.54
130.03
129.87
125.53
124.64
123.63
123.56
122.62
122.60
118.57
118.51
116.35
116.17
115.48
100.50
100.21
83.69
77.22
59.54
59.30
49.57
49.48
28.38
28.20
26.86
26.78
21.13
20.61
14.34
14.31
13.53
13.27

5.71

200   180   160   140   120   100   80   60   40   20   ppm

11.158

8.154
8.141
8.105
7.878
7.844
7.496
7.476
7.418
7.368
7.350
7.332
7.329
7.281
7.262
7.245
7.243

4.176
4.158
4.140
4.122
3.656
3.639
3.036
3.018
3.001
2.884
2.865
2.846
1.685
1.272
1.254
1.236
0.990
0.972
0.953

5.75

0.82

0.97
0.88
0.99
1.00
1.12
1.38

1.84

2.00

2.02
1.89

12.13

2.95

3.02

5.75

5.76

7.652
7.622
7.281
7.257
7.240
7.222
7.204
7.024
7.006
6.989
6.971
6.868
6.844
6.825

5.067
5.046
5.030
4.142
4.125
4.107
4.092
4.074
4.042
4.026
4.020
4.008
3.991
3.964
3.946
3.896
3.878
2.677
2.635
2.580
2.562
2.544
2.537
2.518
2.501
2.410
2.357
2.339
2.068
2.057
2.039
2.023
2.012
2.007
1.994
1.562
1.529
1.510
1.499
1.227
1.112
0.926
0.908
0.889
0.831

1.04
0.76
1.44
1.17
1.14

1.00

1.93
2.74
0.97

0.57
0.55
2.28

2.08

10.10
3.86
2.41
1.83
2.10
1.46

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

206.53

172.77

152.20

141.61
139.38

128.57
127.82
123.05
123.00
122.78
115.94
115.76

95.82

81.11
80.30
71.74
69.48
63.56
61.29
60.48
56.85
53.41
52.80
45.85
45.55
40.84
40.55
39.60
39.24
29.71
28.33
24.66
21.81
14.87
14.22
14.11
12.67
12.40
1.03

200 180 160 140 120 100 80 60 40 20 0 ppm

5.78

Boc

N

H

N

CO₂Et

O

BRUKER

7.051

5.171
5.145
4.242
4.098
4.082
3.723
3.712
3.708
3.697
3.693
3.677
3.655
3.638
3.632
3.402
2.412
2.392
2.309
2.290
2.265
2.038
2.005
1.838
1.819
1.625
1.613
1.591
1.484
1.272
1.202
0.884
0.089
0.084

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

0.40
2.31
1.26
0.70

0.45

0.90
1.24
2.96
0.83
0.98
1.00

0.65
0.97
1.02
0.77
1.71
3.48
10.54
1.70
2.52
10.10
2.80

6.67

5.81

Current Data Parameters
NAME   1y-2011-01-30
EXPNO   2
PROCNO   1

F2 - Acquisition Parameters
Date_   20110130
Time   16.32
INSTRUM   DPX400
PROBHD   5 mm BBO BB-1H
PULPROG   zg30
TD   32768
SOLVENT   CDCl3
NS   32
DS   2
SWH   6410.256 H
FIDRES   0.195625 H
AQ   2.5559540 s
RG   322.5
DW   78.000 u
DE   6.00 u
TE   298.2 K
D1   2.00000000 s
TD0   1

======== CHANNEL f1 ========
NUC1   1H
P1   13.50 u
PL1   -3.00 d
SFO1   400.2478017 M

F2 - Processing parameters
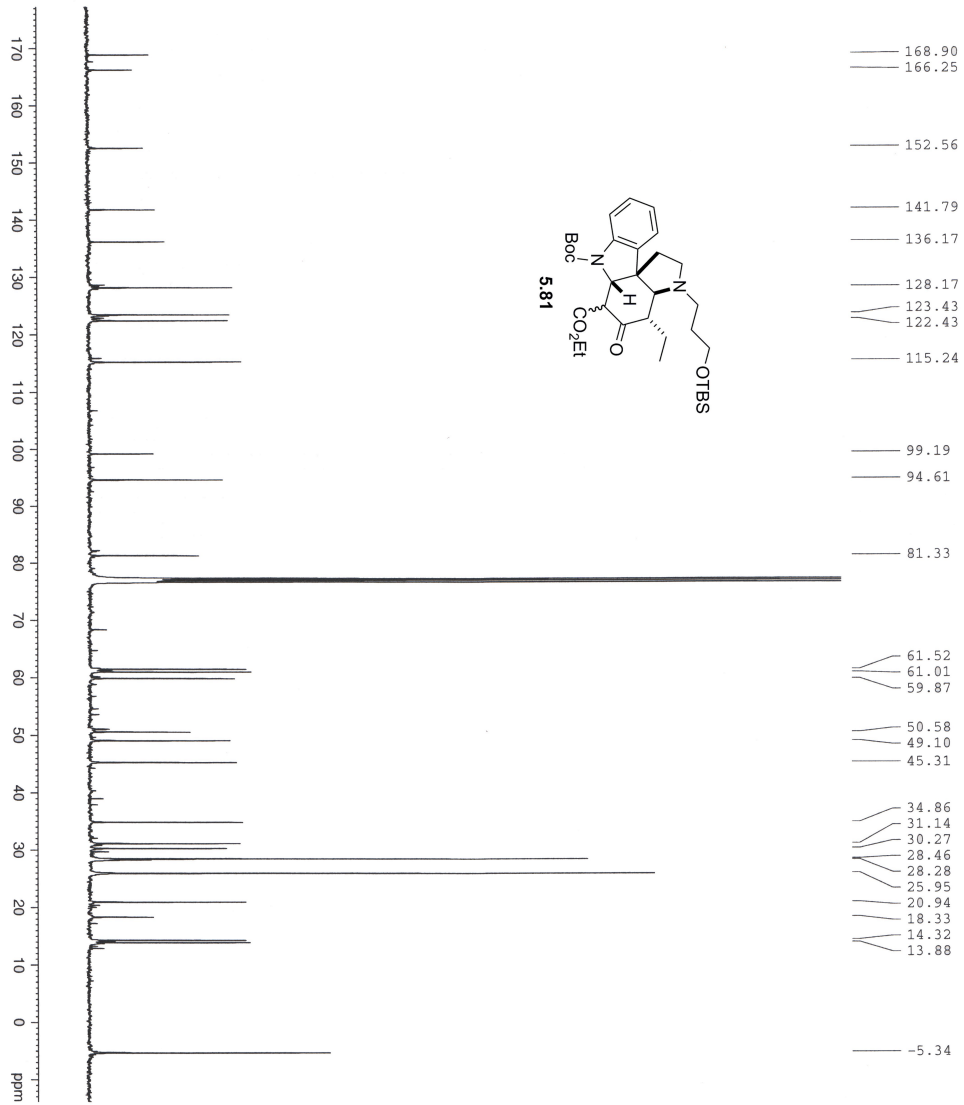SI   32768
SF   400.2450000 M
WDW   EM
SSB   0
LB   0.30 H
GB   0
PC   1.00

5.81

5.86

5.86

168.78
166.14
152.56
141.87
136.10
135.21
128.51
128.20
123.40
123.27
122.48
117.14
116.99
115.26
106.78
99.80
94.81
82.06
81.34
61.55
59.89
52.01
50.86
48.84
34.87
30.69
28.18
20.88
14.31
13.87