

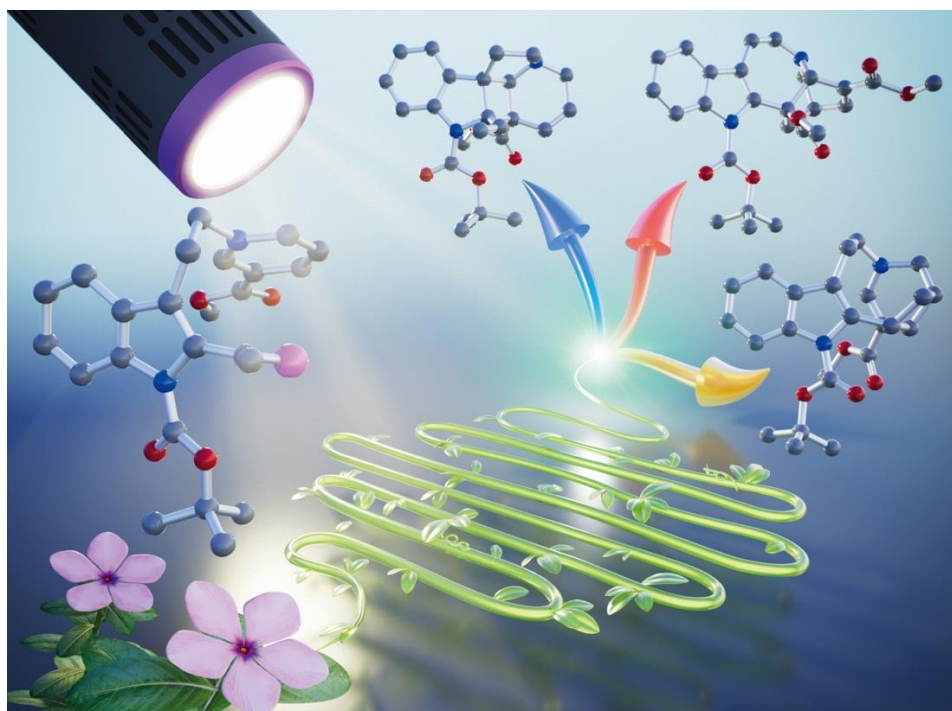
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The University of Tokyo

**Shining light on the synthesis of indole alkaloids!**  
**—Innovative photochemical flow approach**  
**for constructing complex polycyclic scaffolds—**

**Points of presentation**

- ◆ We have developed an innovative strategy in synthetic chemistry that mimics and extends the biosynthesis of naturally occurring indole alkaloids by designing appropriately stabilized multipotent intermediates. These intermediates, which resemble short-lived biosynthetic intermediates, enable a photo-mediated approach that expands the skeletal diversity in biomimetic synthesis.
- ◆ The [4+2] Diels–Alder reaction is typically conducted under thermal conditions. In contrast, our research achieved the photo-mediated flow synthesis of a biomimetic [4+2] cyclization without using photocatalysts or photosensitizers. We efficiently synthesized *iboga*-type scaffolds and applied this method to a wide range of substrates. Furthermore, by modifying the structure of the cyclization precursors, we were able to suppress the [4+2] cyclization and instead promote two distinct [2+2] cyclizations, leading to the synthesis of nitrogen-containing multicyclic alkaloidal scaffolds that are difficult to construct through natural biosynthetic pathways.
- ◆ This innovative photochemical flow synthesis has enabled the efficient and rapid construction of *iboga*-type scaffolds, which are recognized as promising lead candidates for drug discovery against cancer and opioid-related diseases. Our approach represents a significant advancement in pharmaceutical sciences, harnessing the potential of natural products for next-generation drug discovery.



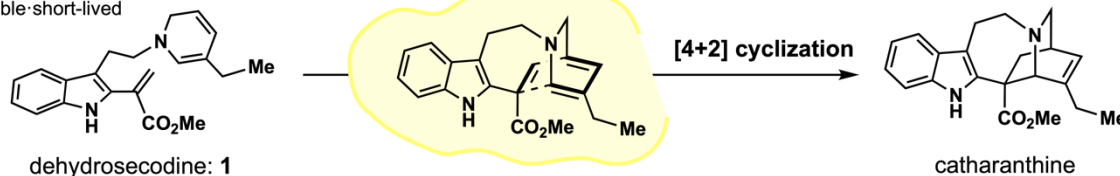
**Divergent synthesis of nitrogen-containing multicyclic scaffolds utilizing a photo-flow reaction**

## Outline of presentation

Gavin Tay (graduate student), Soushi Nishimura (graduate student at the time), and Professor Hiroki Oguri from the Graduate School of Science at the University of Tokyo pioneered a photo-flow process (Note 1) for the efficient construction of alkaloidal scaffolds (Note 2) as potential drug candidates. In this study, they designed a moderately stabilized multipotent intermediate **2** from the hypothetical biosynthetic intermediate dehydrosecodine **1** (Note 3) and developed an innovative synthetic method to construct an *iboga*-type tetracyclic scaffold **3** (Note 4) that could not be synthesized by conventional thermal activation. They established a straightforward micro-flow photochemical process without the need for additional photocatalysts or photosensitizers, demonstrating high efficiency in the rarely reported photochemical [4+2] cycloaddition reaction (Note 5) and broad substrate applicability. Furthermore, by precisely turning the electron densities and conformations of the dehydrosecodine-type intermediates, they efficiently achieved light-induced [2+2] cycloaddition reactions (Note 6), facilitating the streamlined synthesis of novel pentacyclic scaffolds **4** and **5** that are otherwise challenging to access via biosynthetic pathways.

### Biosynthesis in plants

proposed biosynthetic intermediate  
unstable·short-lived



### This study: Skeletal diversification

rational structural design  
moderate stability

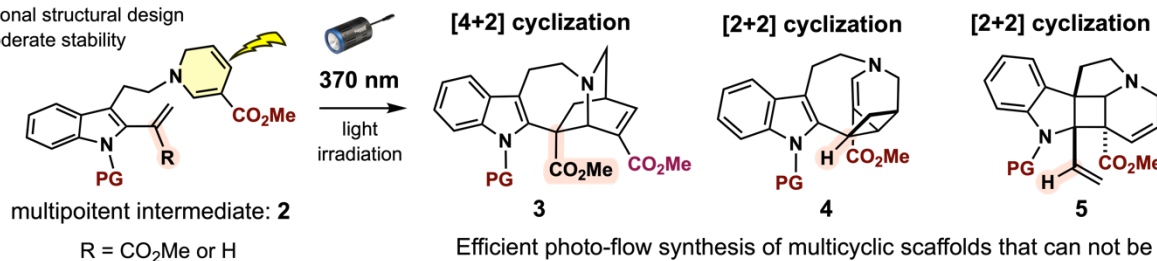


Figure 1. Photochemical flow synthesis process for constructing complex multicyclic alkaloidal scaffolds.

## Presentation details

In recent decades, photochemical reactions have made rapid advances in synthetic organic chemistry, emerging as powerful tools for accessing reaction pathways and intermediates that are otherwise difficult to achieve through conventional methods. Traditionally, the [4+2] cyclization reaction, particularly the formation of six-membered rings via the Diels–Alder (DA) reaction (Note 7), has relied primarily on thermal activation. However, recent developments in light-driven approaches have greatly expanded the reaction scope and potential, unlocking new possibilities in synthetic methodology.

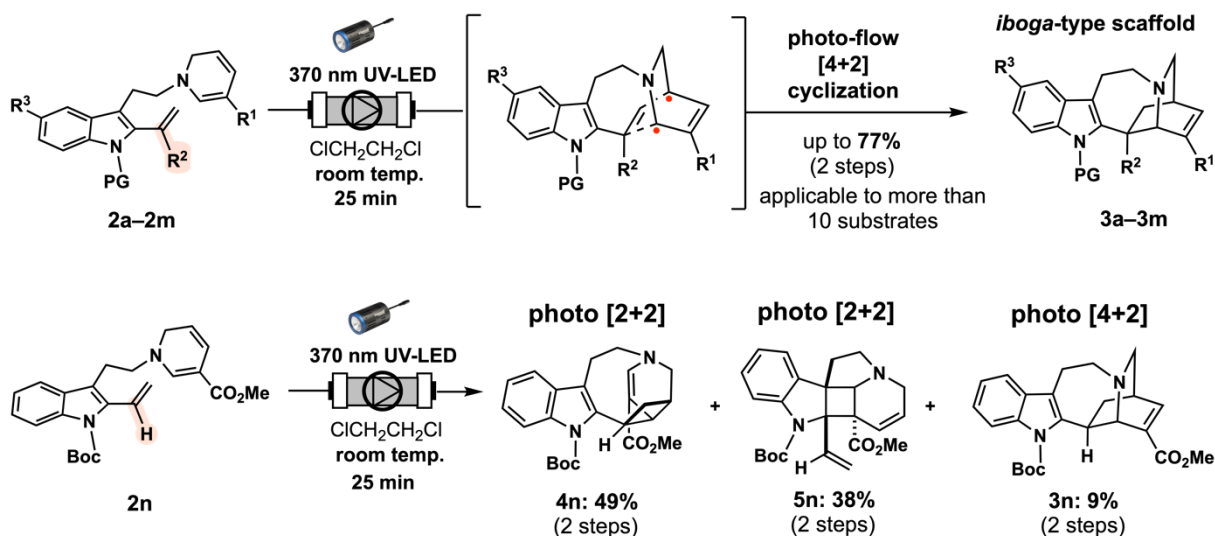


Figure 2. Skeletal diversification of alkaloid-like molecules through photochemical [4+2]/[2+2] cyclizations of multipotent intermediates.

In this study, the research team designed an appropriately stabilized multipotent intermediate **2** (Note 8) that precisely mimics the key biosynthetic intermediate dehydrosecodine **1** and generated it within a flask without using biosynthetic enzymes (Figure 1). By activating this intermediate **2** with light irradiation, they facilitated an intramolecular [4+2] cycloaddition reaction, establishing an innovative photo-flow synthesis process that efficiently constructs the *iboga*-type scaffold **3** (Figure 2). While many previously reported photo-induced DA reactions require external photosensitizers or photocatalysts, the unique feature of this approach lies in the ability to achieve the intramolecular [4+2] cyclization by directly photoactivating the substrate itself. Traditional batch methods (Note 9) suffered from low photoirradiation efficiency and often caused unwanted side reactions under prolonged light exposure, resulting in a yield of only 49% (for two steps) for the desired [4+2] cyclization product **3**. By applying a micro-flow system to this photochemical reaction, the photoirradiation efficiency was significantly improved, and the reaction time was reduced to just 25 minutes. This improvement allowed for the efficient synthesis of the *iboga*-type scaffold **3** under mild, neutral conditions without the need for external photosensitizers or photocatalysts. This photochemical approach is highly versatile, applicable to over ten different substrates, and achieved a maximum yield of 77% (for two steps).

The investigation into the reaction mechanism strongly suggests that the cyclization reaction proceeds through a series of transient biradical species (Figure 3). The dihydropyridine (DHP) ring (Note 10) of the multipotent intermediate **2** exhibits a characteristic UV absorption around 370 nm. In this study, they explored an approach to selectively activate the DHP ring using 370 nm LED light. The biradical species **Int-A1**, **Int-A2**, and **Int-A3** generated upon light irradiation are in equilibrium, with the formation of the C–C bond proceeding stepwise from **Int-A2**. This likely leads to the formation of the *iboga*-type scaffold **3** through a formal [4+2] cyclization.

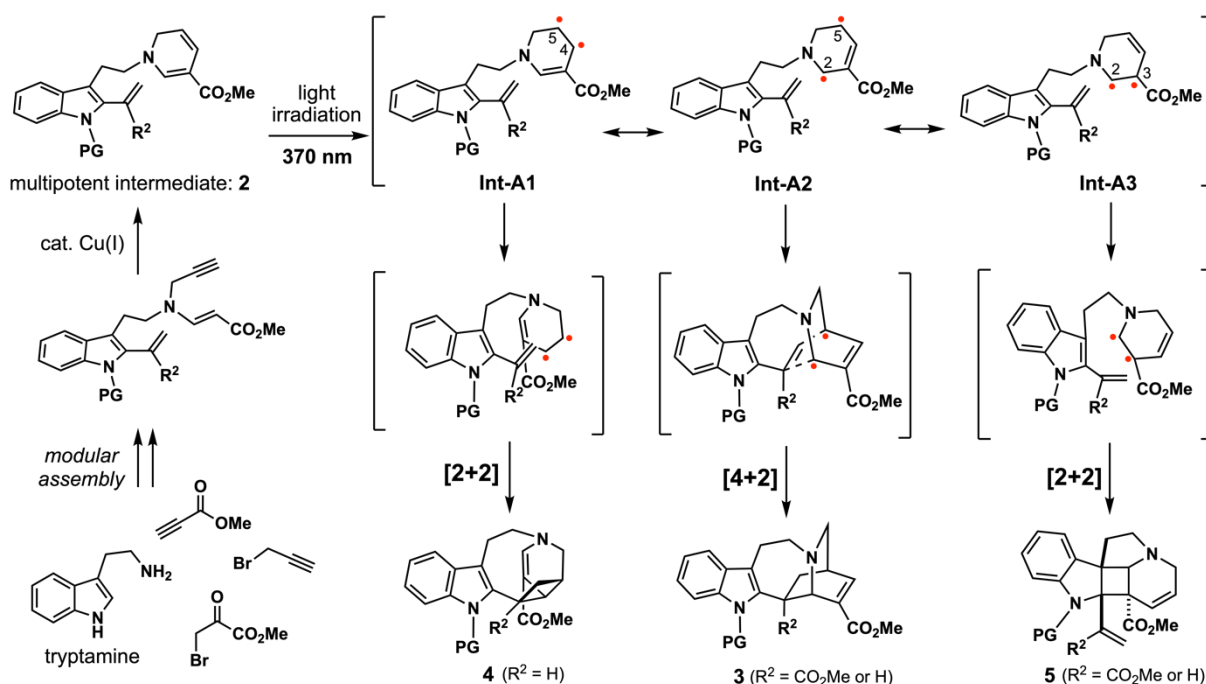


Figure 3. Proposed mechanism for the photoinduced [4+2]/[2+2] cyclization reactions through biradical intermediates.

Interestingly, when substrate **2n**, which lacks the methyl ester at the vinyl indole position (Note 11), was subjected to light irradiation, the [2+2] cyclization reaction was found to preferentially proceed over the [4+2] cyclization (Figure 2). This discovery led to the synthesis of two novel nitrogen-containing pentacyclic scaffolds, **4n** (49% yield) and **5n** (38% yield), featuring densely functionalized cyclobutane core structures and complex three-dimensional frameworks, with a high cumulative yield of 87% (for two steps). Additionally, by precisely adjusting the electronic density and steric hindrance of the cyclization precursors, it was revealed that the mode of intramolecular cyclization induced by photoexcitation drastically changes. DFT calculations (Note 12) suggest that these cyclization precursors are pre-organized in conformations suitable for [4+2] and [2+2] cyclization reactions, respectively. It is likely that under photochemical conditions at room temperature, minimal conformational changes allow the spatial arrangement between the DHP and vinyl indole moieties in each precursor to significantly influence the product distributions of **3**, **4**, and **5**. Importantly, the three scaffolds **3-5** assembled through this photochemical reaction are difficult to achieve under thermal conditions, demonstrating the effectiveness of this synthetic approach through light excitation. This research successfully realized an innovative synthetic strategy for generating three complex polycyclic alkaloidal scaffolds similar to natural products by harnessing the unique and diverse photochemical reactivity of the DHP moiety.

Previous research on the synthesis of *iboga*-type alkaloids has primarily focused on thermal approaches. In contrast, this pioneering study applied a photo-flow synthesis process, enabling the versatile formation of polycyclic frameworks of terpene indole alkaloids and their analogs. Notably, the *iboga*-type alkaloid scaffold with a unique three-dimensional structure that mimics the conformation of serotonin (Note 13) holds significant promise as a next-generation lead candidate for opioid addiction treatment. The results of this research are expected to advance the development of drug discovery research based on structurally related natural products.

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## Paper information

Journal: Chemical Science

Title: Direct photochemical intramolecular [4+2] cycloadditions of dehydrosecodine-type substrates for the synthesis of the *iboga*-type scaffold and divergent [2+2] cycloadditions employing micro-flow systems

Authors: Gavin Tay, Soushi Nishimura, Hiroki Oguri\* (\*Corresponding authors)

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## Terminology definitions

(Note 1) Photo-flow process

The photo-flow process involves passing the reaction solution through a microchannel within a small tubular reactor while simultaneously conducting the photoreaction. This method achieves high photoirradiation efficiency and allows photochemical reactions, which typically occur near the solution surface, to proceed efficiently.

(Note 2) Indole alkaloidal scaffolds

Indole alkaloids are a group of naturally occurring organic compounds characterized by the presence of an indole ring in the structure. The indole consists of a six-membered benzene ring fused with a five-membered pyrrole ring containing a nitrogen atom. The term "indole alkaloidal scaffolds" specially refers to compounds that possess this molecular component as part of their core structure.

(Note 3) Dehydrosecodine

Dehydrosecodine is an unstable and short-lived hypothetical intermediate that is biosynthesized through a multistep enzymatic transformation of tryptophan. During the biosynthetic process, it is stabilized by enzymes and serves as a common intermediate from which various indole alkaloids are derived.

(Note 4) *iboga*-type scaffold

The *iboga*-type scaffold refers to an indole alkaloid skeleton that possesses three structural components: isoquinuclidine, tetrahydroazepine, and indole. In the biosynthetic process, a series of natural products with the *iboga*-type scaffold are assembled through enzyme-catalyzed intramolecular cyclization reactions of dehydrosecodine.

(Note 5) Photochemical [4+2] cycloaddition reaction

A photochemical [4+2] cycloaddition reaction is a type of cyclization that occurs between two  $\pi$ -conjugated systems consisting of four and two atoms, respectively, specifically activated by light. This reaction results in the formation of a new six-membered ring.

(Note 6) Photochemical [2+2] cycloaddition reaction

A photochemical [2+2] cycloaddition reaction is a type of cyclization that occurs between two  $\pi$ -conjugated systems, each consisting of two atoms, specifically under light. This reaction results in the formation of a new four-membered ring.

(Note 7) Diels–Alder (DA) reaction

The Diels–Alder (DA) reaction is a cycloaddition reaction between a conjugated diene (a system with two double bonds) and a dienophile (an olefin), resulting in the formation of a six-membered ring structure. It is a representative type of [4+2] cycloaddition widely used to construct six-membered rings.

(Note 8) Multipotent intermediate

A multipotent intermediate is a molecule designed with multiple reactive sites within its structure. Due to its various modes of cyclizations, it can be directed to form several different polycyclic compounds with distinct molecular skeletons.

(Note 9) Batch methods

A batch process is a traditional synthetic method where chemical reactions take place in a reaction vessel, such as a flask. When the reaction is complete, the products are extracted and used for the next reaction. This method is in contrast to flow reactions, where products are continuously extracted and directly fed into subsequent reactions.

(Note 10) Dihydropyridine ring

A dihydropyridine ring is a nitrogen-containing six-membered ring with conjugated double bonds (diene) within the ring.

(Note 11) Vinyl indole

Vinyl indole refers to a moiety in which a vinyl (ethenyl group) is conjugated with the indole ring and attached at the C2 position of the indole.

(Note 12) Density Functional Theory (DFT) calculation

Density Functional Theory (DFT) is a computational method used to calculate physical properties of compounds from their electron density. It is widely used in organic chemistry to predict reaction pathways and perform other analyses.

(Note 13) Serotonin

Serotonin is a molecule with an indole substructure and a hydroxyl group at the C5 position of the indole in tryptamine. It is a neurotransmitter in the brain, and imbalances of this substance are closely associated with mental disorders.

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