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## Mitsunobu reaction: assembling C–N bonds in chiral traditional Chinese medicine

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The synthesis of chiral molecules has long been a central focus and challenge in medicinal chemistry research. The Mitsunobu reaction, developed by Japanese chemist Mitsunobu in 1967, is a widely utilized bimolecular nucleophilic substitution reaction that plays a vital role in synthesizing chiral natural products. In this reaction, alcohols react with nucleophilic reagents in the presence of a phosphine ligand to form an intermediate phosphonium salt. This intermediate enables the formation of various chemical bonds. The purpose of this review is to explore the applications of the Mitsunobu chemistry in constructing pivotal carbon–nitrogen bonds in traditional Chinese medicines (TCMs). Emphasis will be placed on the preparative synthetic applications of the Mitsunobu strategy as a key step in the total synthesis of naturally occurring biologically active products.

### 1. Introduction

Chirality refers to the property of objects or molecules in three-dimensional space characterized by non-superimposable mirror images.<sup>1</sup> An object is considered chiral if it cannot perfectly align with its mirror image, like the relationship between left and right hands. In chemistry, chirality generally relates to the structural characteristics of molecules with one or more chiral centers.<sup>2</sup> In chiral molecules, the two mirror-image forms are known as enantiomers. Although their physical and chemical properties are generally similar, their behavior can vary significantly when interacting with other chiral substances, including biomolecules. As a result, chirality is critically important in various fields, with its significance particularly pronounced in drug development, synthetic chemistry, and biochemistry.<sup>3</sup> Biot identified the first scientific evidence of chirality in 1815 when he observed the optical rotation of camphor.<sup>4</sup> Pasteur found, in 1848, that two tartaric acid molecules with identical properties exhibited opposite optical rotations; the specific rotation of L-tartaric acid is  $-12.6^\circ$ , and that of D-tartaric acid is  $+12.6^\circ$ , as depicted in Fig. 1.<sup>5</sup> This groundbreaking discovery laid the foundation for stereochemistry, explicitly highlighting the concept of “chirality.”

In today's pharmaceutical landscape, more than half of the drugs on the market are chiral, with approximately 88% administered as racemic mixtures.<sup>6</sup> It's important to note that the desired biological or pharmacological effects are often associated with a specific enantiomer. In contrast, the other

enantiomer may have different effects, be inactive, or even present toxicity risks.<sup>7</sup> For example, with well-known thalidomide, the *R*-enantiomer has sedative properties, whereas the *S*-enantiomer is associated with congenital disabilities.<sup>8</sup> Therefore, separate pharmacological and toxicological evaluations are essential for each enantiomer, rather than relying solely on assessments of the racemic mixture. A thorough evaluation is needed to prevent exposure to inactive or harmful enantiomers. As a result, there has been a recent increase in the development of drugs marketed as individual enantiomers, highlighting the significance of using racemic molecules only when the enantiomers demonstrate complementary biological activities.

The Mitsunobu reaction is valuable for forming various chemical bonds, including C–O, C–N, C–S, C–C, and C–X bonds, using primary and secondary alcohols as substrates.<sup>9</sup> While primary and secondary alcohols are well-suited for this reaction, tertiary alcohols are not suitable. Typically, this reaction involves the cooperative action of triphenylphosphine and diethyl azodicarboxylate, leading to the dehydration of the alcohol hydroxyl group with acidic compounds.<sup>10</sup> When chiral alcohols are used as substrates, the resulting products usually exhibit configuration inversion, making this a valuable reaction for synthesizing chiral drugs. It is important to note that traditional Chinese medicine contains various chiral compounds, many demonstrating significant physiological

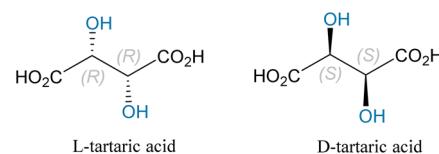


Fig. 1 Schematic structures of L-tartaric acid and D-tartaric acid.

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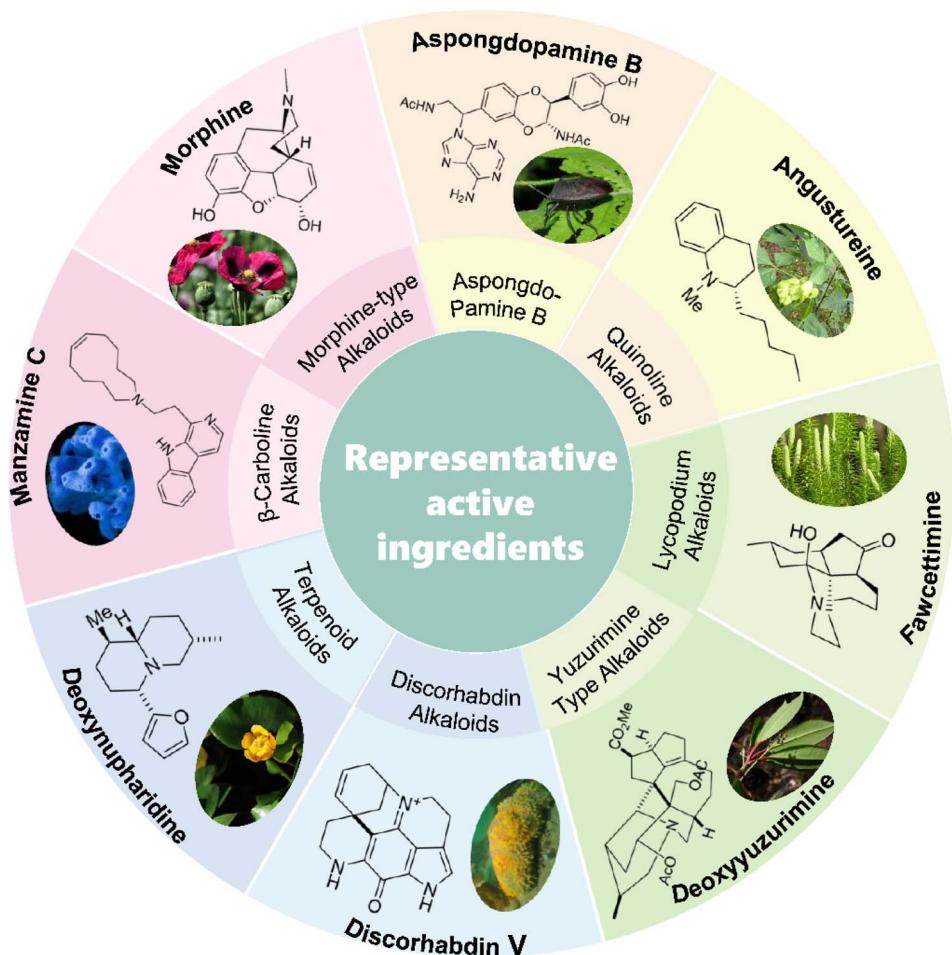


Fig. 2 Utilizing the Mitsunobu strategy in the synthesis of active alkaloids from TCMs.

activities. However, the extraction and purification of these chiral compounds can be challenging. Conventional methods often yield only small amounts of pure products, making them time-consuming and labor-intensive. Recently, there has been growing interest in utilizing appropriate chiral substrates to prepare natural chiral products efficiently through the Mitsunobu reaction. This approach not only proves effective but also enhances overall yield. In 2008, Yurovskaya *et al.* highlighted the Mitsunobu reaction's vital role in synthesizing nitrogen-containing heterocyclic compounds.<sup>11</sup> Professor Pavan Kumar reviewed its applications from 1967 to 2009, establishing a historical context.<sup>12</sup> Fletcher then examined its relevance in the 21st century,<sup>13</sup> while Panday assessed the impact of improved Mitsunobu reagents.<sup>14</sup> Additionally, Professor Mojzuch emphasized its importance in natural product synthesis,<sup>15</sup> and the Cai group explored advancements in catalytic Mitsunobu reactions.<sup>16</sup> These contributions underscore the Mitsunobu reaction's versatility and significance in modern synthetic chemistry. These comprehensive reviews have deepened our understanding of the Mitsunobu reaction from various critical angles and propelled its advancement within the chemical community. In this context, as shown in Fig. 2, we assertively summarize the applications of the classic Mitsunobu reaction

in synthesizing natural products, concentrating on constructing essential C–N bonds in compounds that typically contain chiral centers. The studies we cover span from 1978 to 2024.

## 2. Mechanism

The mechanism of the Mitsunobu reaction is controversial, as its complexity leads to debates regarding the intermediates and their roles.<sup>17</sup> The specific reaction process is elucidated below using triphenylphosphine and diethyl azodicarboxylate, as shown in Fig. 3.

The entire process can be divided into four steps: in step 1, triphenylphosphine initiates the reaction by attacking diethyl azodicarboxylate (DEAD), forming an intermediate **I** called a phosphonium salt. These intermediate **I** capture a proton from the nucleophilic  $\text{NucH}$ , creating a cation **II** in step 2. Subsequently, in step 3, the hydroxyl functional group from the substrate alcohol then targets the phosphorus center of the cation **II**, forming an oxaphosphonium ion **III**.<sup>18</sup> This step triggers the detachment of DEAD, producing hydrazine as a byproduct. Following this, an  $\text{S}_{\text{N}}2$  nucleophilic substitution reaction occurs, where the nucleophile  $\text{Nuc}^-$  attacks the alkoxy phosphonium intermediate **III**, inducing a configuration



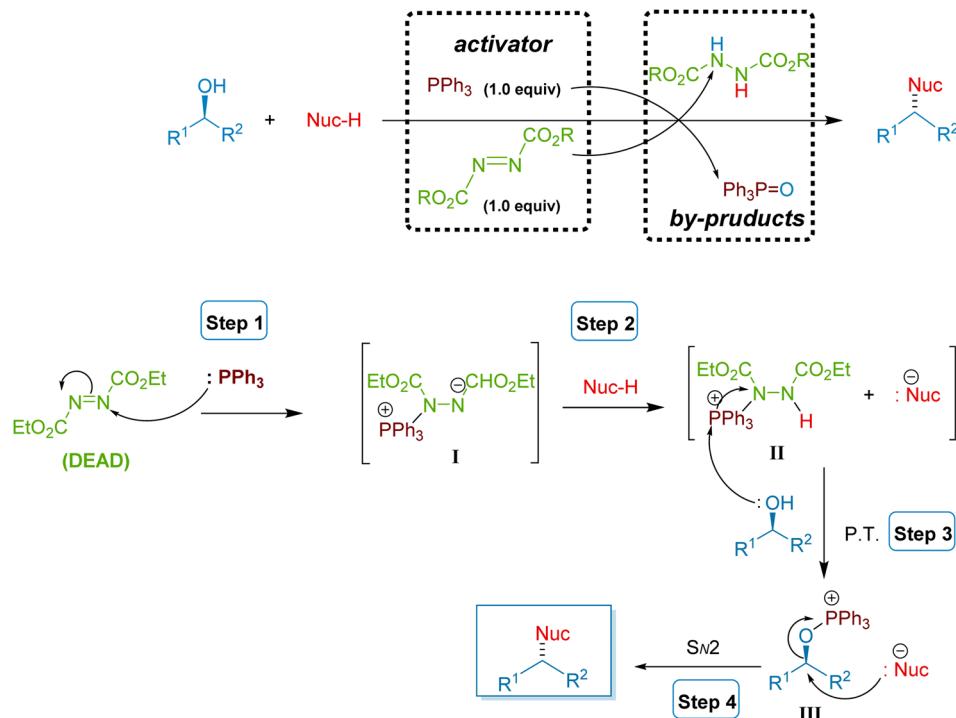


Fig. 3 The recognized mechanism of the Mitsunobu reaction.

inversion, as depicted in step 4. Ultimately, the cleavage of the carbon–oxygen bond affords products with configuration inversion alongside triphenylphosphine oxide byproducts. This reaction is fundamentally redox in nature.

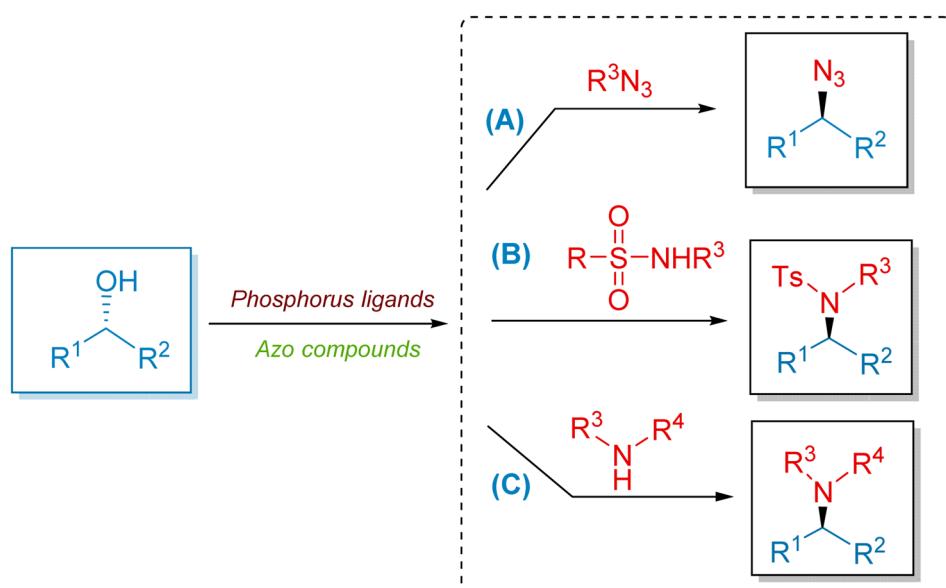
### 3. Reaction type

Herein, we summarize the applications of the classic Mitsunobu reaction in the synthesis of natural products. This

reaction involves the formation of important C–N bonds using primary or secondary alcohols with azides (Scheme 1A), sulfonamides (Scheme 1B), amines (Scheme 1C), and others.

#### 3.1 Azide acts as nucleophiles

Lycopodium alkaloids (LAs) are derived from the medicinal plant *Lycopodium serratum*,<sup>19</sup> recognized for their potent inhibitory effect on acetylcholinesterase. These compounds can



Scheme 1 Synthetic route to alkaloids by Mitsunobu strategy.



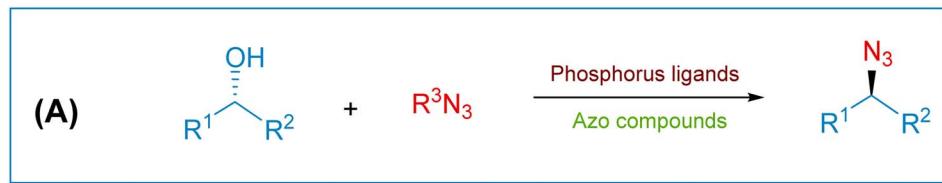


Fig. 4 Mitsunobu reaction using azide acts as nucleophiles.

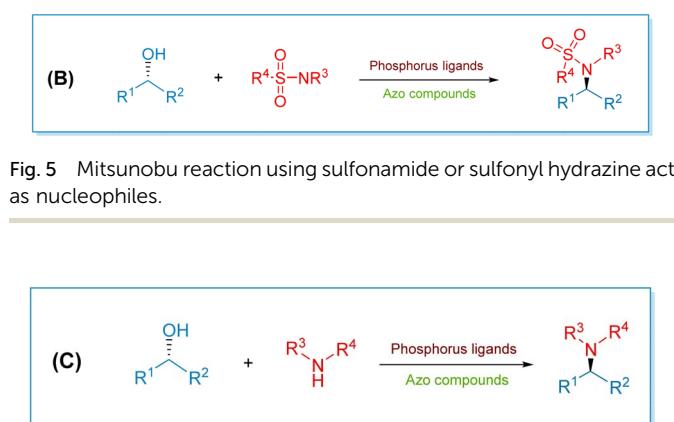


Fig. 5 Mitsunobu reaction using sulfonamide or sulfonyl hydrazine act as nucleophiles.

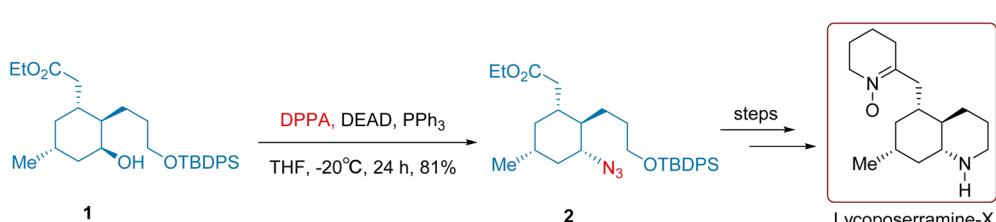
significantly enhance cognitive function and have demonstrated improvements in learning and memory.<sup>20</sup> Current research is significantly focused on applying LAs in treating Alzheimer's disease, which is expected to advance studies on synthesizing *Lycopodium* alkaloids (Fig. 4–6).<sup>21</sup>

A novel alkaloid named Lycoposerramine-X has been isolated from *Lycopodium serratum*. As depicted in Scheme 2,

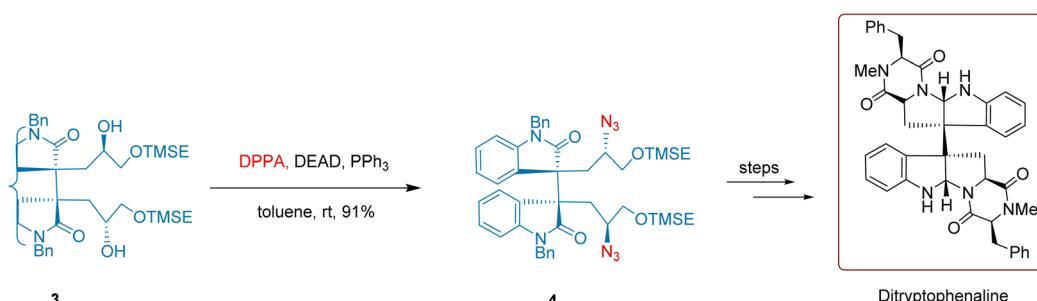
Takayama and co-workers conducted a reaction in 2009 using the chiral secondary alcohol **1** and nucleophile diphenylphosphoryl azide (DPPA) in tetrahydrofuran in the presence of Mitsunobu reagents (DEAD and  $\text{PPh}_3$ ), resulting in the formation of compound **2**. Although the yield reached 80%, the low temperature of  $-20^\circ\text{C}$  adversely affected the formation of compound **2**. Through 12 steps of reactions, the chiral piperidine derivative Lycoposerramine-X was successfully synthesized, with an overall yield of 25%.

One of the most significant challenges in treating malaria is the development of drug resistance to commonly used medications. As a result, researchers have gradually shifted their focus to natural products. Notably, certain indole alkaloids have shown high anti-malarial activity.<sup>22,23</sup> Some of these active indole alkaloids are derived from two tryptophan units, with dityryptophenaline being a prominent example.

Dityryptophenaline has been isolated from several *Aspergillus* species. In 2001, Overman and colleagues realized the chemical synthesis of dityryptophenaline. They conducted a reaction at room temperature using  $\text{C}_2$ -symmetric diol **3** and DPPA in toluene as the solvent in the presence of Mitsunobu reagents (DEAD and  $\text{PPh}_3$ ), as illustrated in Scheme 3. During this reaction, the hydroxyl groups in compound **3** were successfully

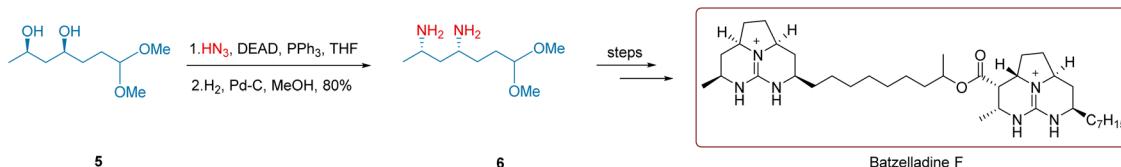


Scheme 2 Takayama's synthesis of phlegmarine-type lycopodium alkaloids.



Scheme 3 Overman's synthesis of dityryptophenaline.



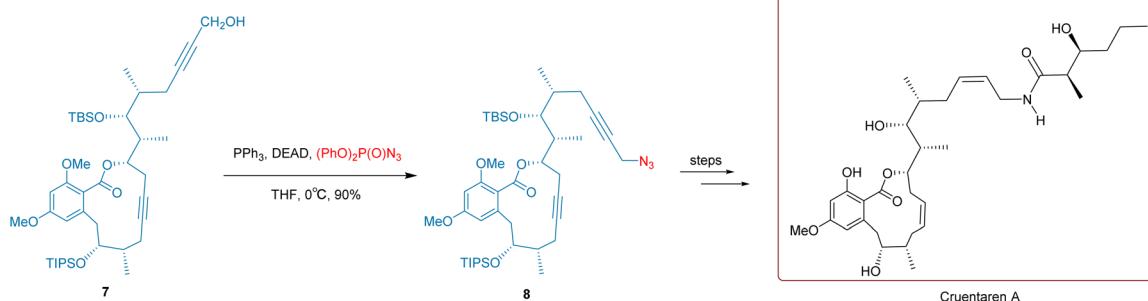


Scheme 4 Overman's synthesis of batzelladine F.

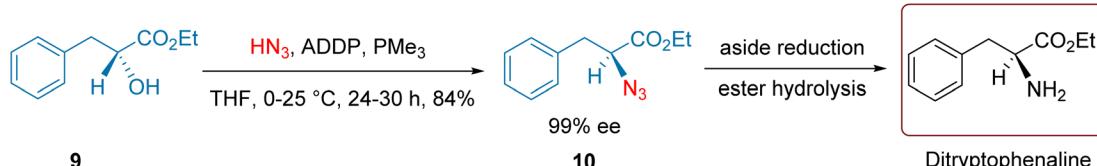
replaced with azido groups, forming compound 4 with reversed configurations in 91% yields. Further transformations, consisting of 6 steps, can then lead to synthesizing the target compound, ditryptophenaline, with an overall yield of 20%.

Batzelladine F is a marine natural product isolated from the red Jamaican sponge and plays a vital role in treating autoimmune diseases.<sup>24–26</sup> As illustrated in Scheme 4, Overman and co-workers conducted a double substitution reaction in 2005 between chiral alcohol 5 and hydrazoic acid ( $\text{HN}_3$ ) using DEAD and  $\text{PPh}_3$  as auxiliary reagents. This reaction was followed by a palladium-catalyzed carbon–carbon bond reduction, which resulted in the formation of chiral diamine 6, with a yield of 80%. This diamine 6 undergoes 8 steps, resulting in an overall yield of 21% for the final product, batzelladine F.

Cruentaren A is an antifungal benzolactone produced by the myxobacterium *Byssovorax cruenta*.<sup>27</sup> It demonstrates high cytotoxicity against cancer cell.<sup>28,29</sup> As shown in Scheme 5, Maier and co-workers 2007 conducted compound 7 in tetrahydrofuran with  $\text{PPh}_3$ , DIAD, and the azide compound  $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$ . This reaction effectively replaced the terminal hydroxyl group in the molecule with an azido group, yielding compound 8 with an impressive yield of 90%. The target compound, Cruentaren A, was ultimately synthesized with an overall yield of 34% through five subsequent steps that included reduction, acylation, and deprotection.



Scheme 5 Maier's synthesis of cruentaren A.

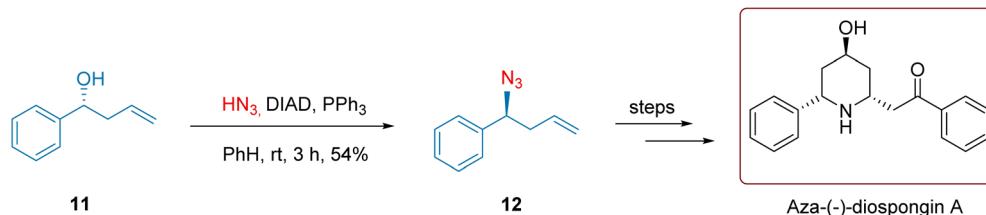


Scheme 6 McCarthy's synthesis of disubstituted amino acids.

McCarthy and his colleagues conducted a reaction, as shown in Scheme 6, using the chiral tertiary alcohol compound 9. They combined this with two equivalents of ADDP and  $\text{PMe}_3$  and two of the azide compound  $\text{HN}_3$  in tetrahydrofuran solvent for a duration exceeding 24 hours. This reaction replaced the hydroxyl group in compound 9 with an azido group, producing the chiral inverted compound 10. Namely, in compound 9, the hydroxyl functional group on the *R*-configured carbon atom effectively forms an active intermediate phosphonium salt with trimethyl phosphine. This intermediate then undergoes a well-defined  $\text{S}_{\text{N}}2$  nucleophilic substitution reaction with the azide anion, resulting in an inversion of configuration that definitively produces the *S*-configured compound 10. Subsequently, a simple reduction and hydrolysis were performed to synthesize the challenging chiral amino acid ethyl ester ditryptophenaline, with an overall yield of 56%.<sup>30</sup> In the Mitsunobu reaction, it is essential to note that when the nucleophile HA has a  $\text{p}K_{\text{a}}$  more significant than 11 or when the substrate is a tertiary alcohol, the product yield significantly diminishes. In many instances, the desired reaction may not occur at all. However, employing ADDP reagents decisively enhances the reaction's performance and can lead to successful outcomes.

Diospongins are a novel class of diaryl heptanoids isolated from the rhizomes of *Dioscorea spongiosa*.<sup>31</sup> Due to their potent anti-osteoporotic activity demonstrated in *in vitro* cell





Scheme 7 Chandrasekhar's synthesis of aza-diospongin A.

experiments and their relatively simple structure, they have garnered significant interest from synthetic chemists.<sup>32</sup>

Scheme 7 shows Chandrasekhar and co-workers 2009 synthesized aza-(-)-diospongin A. They reacted chiral benzyl alcohol **11** with the hydrazoic acid in benzene at room temperature for 3 hours, using classical Mitsunobu reagents (PPh<sub>3</sub> and DIAD). This reaction resulted in the substitution of the secondary alcohol hydroxyl group with an azido group, ultimately yielding compound **12** with a 40% overall yield, and successfully synthesized the 4-hydroxypiperidine derivative aza-(-)-diospongin A through 7 steps.

Quinolizidine alkaloids possess a range of biological activities, including anti-cancer, antibacterial, anti-inflammatory, antiviral, and anti-arrhythmic effects.<sup>33,34</sup> These alkaloids can accumulate in various leguminous plants and have widespread applications in agriculture, pharmaceuticals, and the chemical industry.<sup>35</sup> Research has been focusing on efficient stereoselective methods to construct these organic molecules.

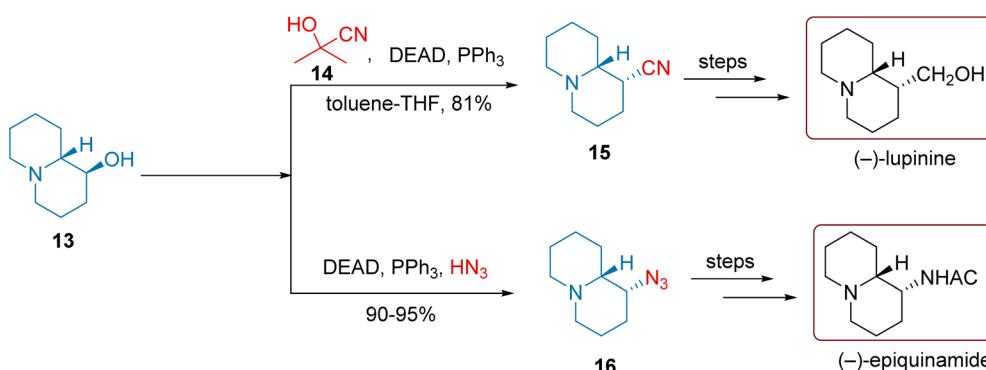
As illustrated in Scheme 8, Santos and co-workers in 2010 employed acetone cyanohydrin **14** as the cyanation reagent in a classic Mitsunobu reaction, using DEAD and PPh<sub>3</sub> as reagents. They conducted the reaction on the secondary chiral alcohol **13** in a mixed solvent of toluene and tetrahydrofuran, forming cyano compound **15** with a position at C-10 hydroxyl configuration inversion and an 81% yield. Gas chromatography analysis indicated that the reaction was completed without forming isomeric products. Similarly, using azidic acid as the nucleophilic reagent and in the presence of DEAD and PPh<sub>3</sub>, they obtained product **16** with a very high yield. Subsequent reduction and acylation, consisting of 2 steps, led to the synthesis of (-)-epiquinamide with an overall yield of 77% and the synthesis of (-)-lupinine with an overall yield of 85%, respectively.

Amaryllidaceae plants, with their unique secondary metabolites, the montanine-type alkaloids, stand out in disease treatment. These alkaloids, found exclusively in this plant family, have attracted widespread attention for their distinct anti-tumor activity. Research has revealed that Montanine Alkaloids, though present in low concentrations in plants, demonstrate significant inhibitory activity against cancer cells such as HeLa and A549.<sup>36,37</sup>

As depicted in Scheme 9, to obtain the target compound Ent brunsvigine, the authors successfully transformed the chiral enol **17** into the critical intermediate azide compound **18** with the collaborative action of DPPA, DIAD, and PPh<sub>3</sub>. After an additional **10** consecutive steps of reactions, Ent brunsvigine was obtained with an overall yield of 1.67%.

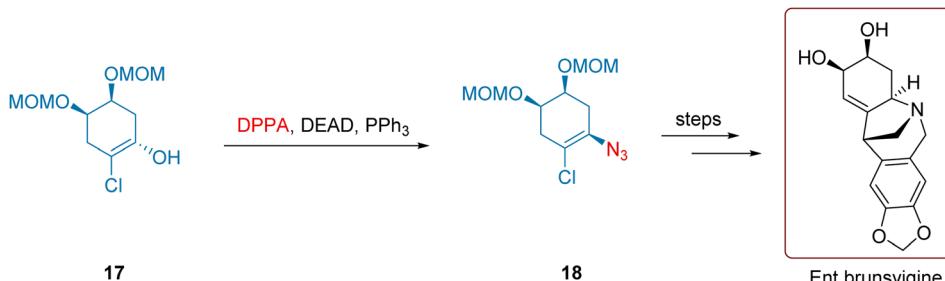
Mersicarpine is an aspidosperma alkaloid isolated from plants of the *Kopsia* genus. Its unique structural features have attracted significant attention in synthetic organic chemistry. Research has shown that it can induce apoptosis and exhibit specific inhibitory effects on protein synthesis. As a result, Mersicarpine is a novel translation inhibitor that induces apoptosis.<sup>38,39</sup>

As illustrated in Scheme 10, to obtain the target compound (-)-mersicarpine, in 2019, Wang and co-workers first performed a Mitsunobu reaction to convert the primary hydroxyl group in compound **19** into an azide-substituted compound **20**, achieving this transformation with a high yield of 98%. Notably, the reaction yield was significantly influenced by temperature, as higher temperatures led to the formation of a substantial amount of intramolecular aziridination products. After completing four consecutive reaction steps, we obtained (-)-mersicarpine with a robust overall yield of 31%.

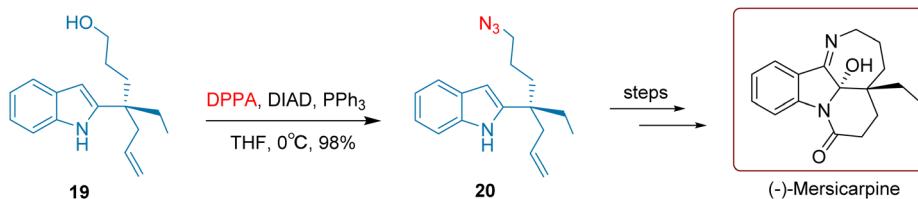


Scheme 8 Santos's synthesis of quinolizidine alkaloids.





Scheme 9 Banwell's synthesis of ent brunsigine.



Scheme 10 Wang's synthesis of mersicarpine alkaloids.

White *Candida albicans* is a common fungal infection source that often resists conventional drug treatments, leading to limited effectiveness or even treatment failure. However, animal experiments have indicated that batzelladine D could be a potential novel antifungal agent for *Candida albicans* infections.<sup>40,41</sup>

Evans group conducted a series of reactions on the 3,4-dihydropyridin-2-one derivative 21 to synthesize batzelladine D, as illustrated in Scheme 11. The process included a hydroxilylation reaction, an ester exchange reaction, and a classic Mitsunobu reaction. This sequence of reactions led to the formation of compound 22 by configuration inversion, achieving an overall yield of 95%. After completing seven consecutive reaction steps, batzelladine D was obtained with an overall yield of 24%.

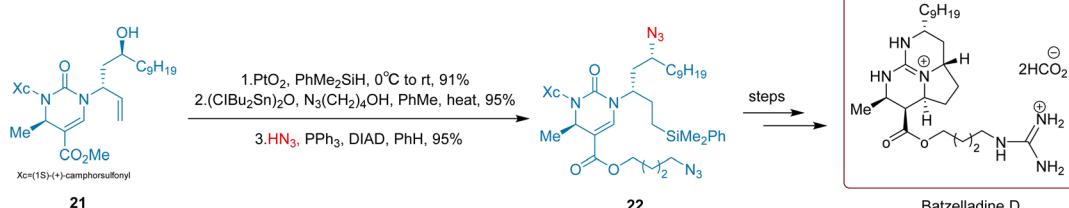
### 3.2 Sulfonamide or sulfonyl hydrazine act as nucleophiles

The bark of the *Angostura tree* in South America is widely used in Venezuelan folk medicine for treating ailments such as indigestion, dysentery, chronic diarrhea, spinal motor nerve issues, and fever.<sup>42,43</sup> Angustureine, an isoquinoline alkaloid extracted from the tree bark, is believed to be the main active component for treating the conditions above.<sup>44,45</sup>

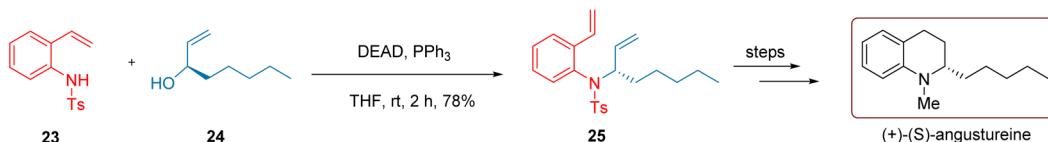
As depicted in Scheme 12, to synthesize the chiral isoquinoline angustureine, Nishida and co-workers conducted a reaction in 2004 using the secondary sulfonamide 23 and the chiral secondary alcohol 24 at room temperature with the involvement of DEAD and PPh<sub>3</sub> for 2 hours. This resulted in the intermediate diene compound 25 yielding 78%. Compound 25 underwent decomposition reactions, methylation, and hydrolysis in four steps to produce the product (+)-(S)-angustureine with an overall yield of 69%.

Deoxynupharidine is an alkaloid isolated from the rhizomes of *Nuphar species* and is a component of a larger class of terpene alkaloids. It is primarily used in treating rheumatoid arthritis and for alleviating back and leg pain and exhibits notable immunosuppressive activity.<sup>46,47</sup>

As shown in Scheme 13, obtaining deoxynupharidine, carried out by Harrity and co-workers in 2003, is a significant step in synthesizing this alkaloid. The reaction of the primary alcohol 26 in the presence of *n*-Bu<sub>3</sub>P and ADDP to form an active phosphonium intermediate, followed by the intramolecular nucleophilic attack of the sulfonamide group, led to the creation of the chiral cyclic sulfonamide compound 27 with an impressive yield of 80%. This research paves the way for further exploration and potential pharmacology and organic chemistry



Scheme 11 Evans' synthesis of tricyclic guanidine alkaloids-batzelladine D.



Scheme 12 Nishida's synthesis of quinoline alkaloids.

applications. After completing four consecutive reaction steps, deoxynupharidine was obtained with an overall yield of 35%.

Over 300 alkaloids have been isolated from the *Lycopodium* genus, with the (+)-fawcettimine alkaloids being one of the most representative classes. They are known for their neuro-protective, anti-tumor, anti-inflammatory, antimicrobial, and antiviral properties. The unique spiral ring structure present in these alkaloids may be a key factor contributing to their distinct biological activities.<sup>48–51</sup> For instance, Lycoposerramine-C is a novel alkaloid isolated from *Lycopodium serratum*, featuring a double bond at the C-6/C-7 positions of its molecule.

As illustrated in Scheme 14, Takayama *et al.* conducted a Mitsunobu reaction to develop synthesis methods for such alkaloids. They dissolved the primary alcohol 28 in tetrahydrofuran and allowed the reaction to proceed at room temperature, achieving a high yield of 91% for the macrocyclic compound 29. This transformation cleverly utilized the Mitsunobu reaction to facilitate intramolecular cyclization. Further deprotection steps ultimately led to the synthesis of Lycoposerramine-C and Phlegmariurine-A. The steps from compound 29 to Lycoposerramine-C involve five steps with an overall yield of 43.09%. In comparison, the steps from compound 29 to Phlegmariurine-A involve six steps with an overall yield of 40.93%.

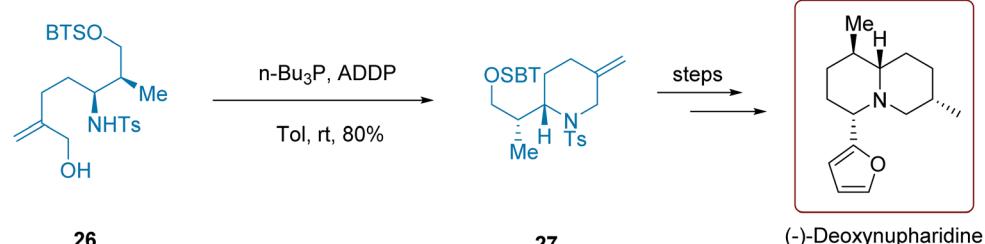
Several years later, Taniguchi and co-workers (2014) utilized a cyclization reaction to assemble the intermediate compound

31, which is crucial for obtaining (+)-fawcettimine, as shown in Scheme 15. Substrate 30 was reacted in tetrahydrofuran using DMEAD (1.5 equiv.) and PPh<sub>3</sub>. This method successfully led to the synthesis of the nine-membered ring intermediate 31. Six steps are required to go from compound 31 to the final product, with an overall yield of 38%.

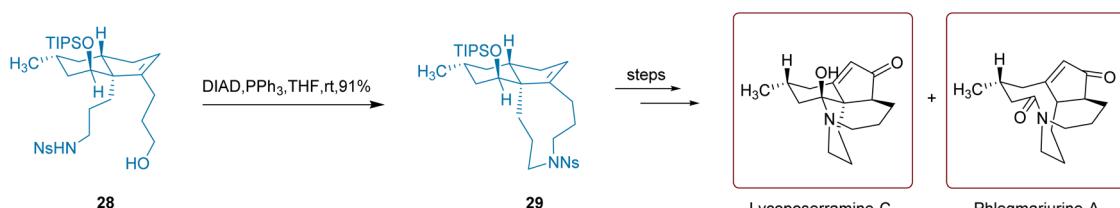
Serinolamide A and columbamide D are bioactive marine natural products. In recent years, the former was isolated from the cyanobacteria *Lyngbya majuscula* in Papua New Guinea.<sup>52,53</sup>

As illustrated in Scheme 16, Muthukrishnan and co-workers 2019 utilized a chiral glycerol derivative 32, protected at the C1 and C3 positions, and methyl naphthylsulfonamide 33 in tetrahydrofuran as the solvent. In the presence of PPh<sub>3</sub> and DIAD, the reaction was conducted for 6 hours, transforming 32 to 34 with a high yield of 95%. The S<sub>N</sub>2 reaction ensured that the absolute configuration of the intermediate 34 was the *S*-configuration. Further transformations successfully synthesized Serinolamide A and Columbamide D. There are three steps from compound 34 to Serinolamide A, resulting in an overall yield of 71%. Additionally, there are three steps from compound 34 to Columbamide D, achieving an overall yield of 68%.

Epidithiodiketopiperazine natural products (ETPs) are significant fungal metabolites known for their unique structures and potent biological activities.<sup>54,55</sup> These characteristics have drawn considerable interest from synthetic chemists and

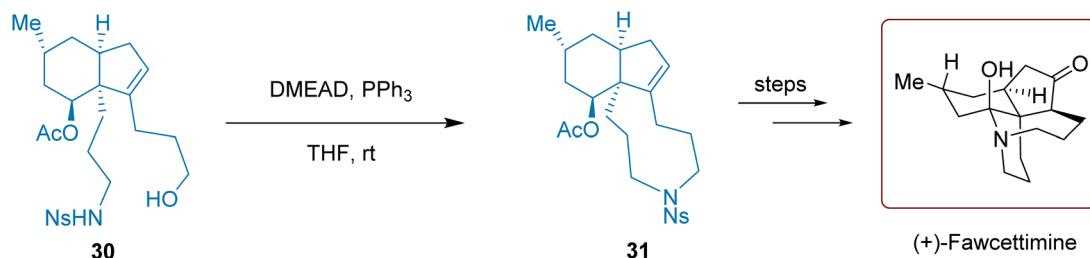


Scheme 13 Harrity's synthesis of nuphar alkaloids.

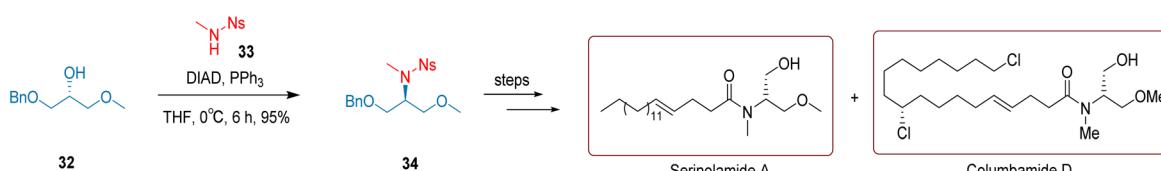


Scheme 14 Takayama's synthesis of fawcettimine-type lycopodium alkaloids.





Scheme 15 Taniguchi's synthesis of lycopodium alkaloids.



Scheme 16 Muthukrishnan's synthesis of serinolamide A and columbamide D.

pharmacologists. Despite decades of research, only a limited number of total syntheses of ETPs have been accomplished, which has hindered their further profiling and applications. Scabrosins, a distinct subgroup of ETPs (a–e), were first isolated in 1978.<sup>56</sup> After, their structures were revised based on 2D NMR and X-ray structural analysis.

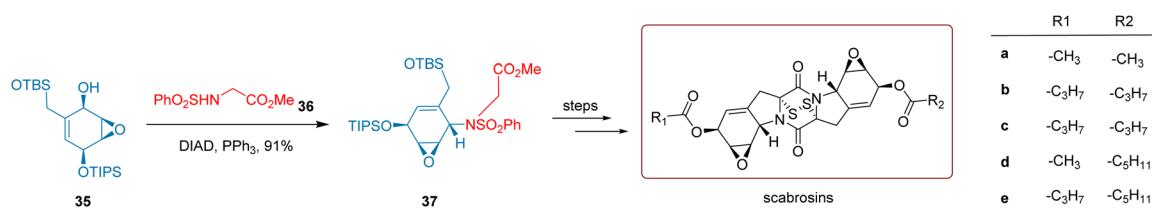
As illustrated in Scheme 17, He and co-workers 2019 successfully constructed a polar inverted chiral C–N bond through a Mitsunobu reaction involving the *ortho*-hydroxy epoxide 35 in the presence of  $\text{PPh}_3$  and DIAD, reacting with sulfonamide 36. This reaction formed a critical intermediate 37 with a high yield of 91%. Through further synthetic transformations, the target compounds, scabrosins, were ultimately synthesized over six reaction steps, achieving an overall yield of approximately 31.18%.

Lycopoclavamine-A is a structurally unique *Lycopodium* alkaloid with inhibitory effects on acetylcholinesterase,

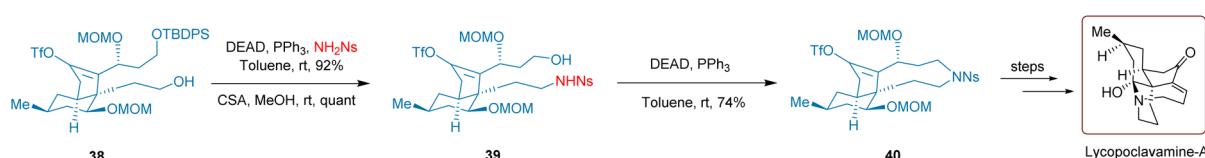
showing significant potential and promise for treating Alzheimer's disease (AD).<sup>57,58</sup>

To achieve the synthesis of Lycopoclavamine-A, Takayama and co-workers employed a two-step Mitsunobu reaction in 2019. As illustrated in Scheme 18, the authors first performed the initial Mitsunobu reaction, converting the primary alcohol 38 into compound 39 with a high yield of 92%, using three equivalents of  $\text{NsNH}_2$ . Subsequently, in the presence of DEAD and  $\text{PPh}_3$ , compound 39 underwent an intramolecular Mitsunobu reaction, yielding the nine-membered ring product 40 with a yield of 74%. After six consecutive reaction steps, including removing the sulfonyl group, an intramolecular nucleophilic substitution was conducted, ultimately synthesizing the target compound Lycopoclavamine-A with an overall yield of 78%.

Morphine is classified as an essential medicine by the World Health Organization and is an effective opioid analgesic.<sup>59,60</sup>

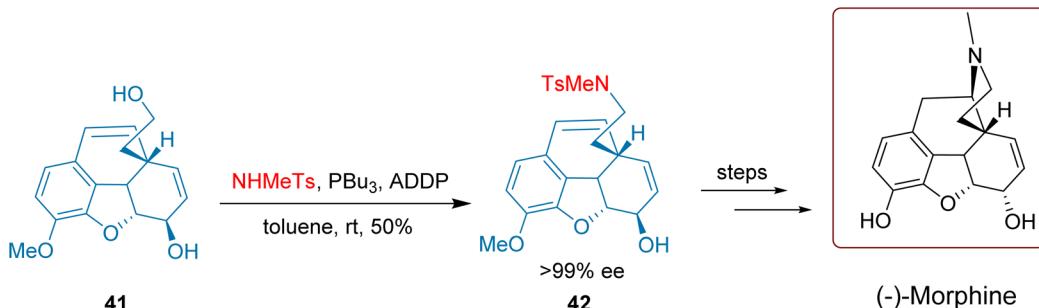


Scheme 17 He's synthesis of scabrosins



Scheme 18 Takayama's synthesis of lycopodium alkaloid.





Scheme 19 Tu's synthesis of morphine-type alkaloids.

Due to its synthetically challenging chiral molecular structure and significant clinical application value, the synthesis of morphine-type alkaloids has attracted considerable attention.

To synthesize (−)-morphine, Tu *et al.*, 2019 utilized the differing reactivity of the alcohol hydroxyl groups in the substrates. They synthesized the critical intermediate **42** through a highly regioselective intermolecular Mitsunobu reaction between the fused ring compound **41** and methyl phenylacetamide, yielding the intermediate with a 50% yield. The results are illustrated in Scheme 19. It takes three steps from compound **42** to the final product, with an overall yield of 51%.

Ar-macrocarpene is a naturally occurring irregular aromatic sesquiterpene with a 3,3,4'-trimethyl-1,1'-(bi-cyclohexyl) skeleton found in the leaves of *Cupressus macrocarpa*.<sup>61–63</sup>

In 2019, Bisai and co-workers reacted to synthesize (+)-ar-macrocarpene, using tetrahydrofuran as the solvent. They conducted the chiral enol **43** at low temperatures with  $\text{PPh}_3$ , DIAD, and 2-nitrophenyl hydrazone **44**, successfully constructing a C–N bond in compound **45**. The results of this reaction are illustrated in Scheme 20. The transformation of compound **45** into the final product is achieved in three straightforward steps, yielding an impressive overall result of 64%.

Daphniphyllum alkaloids are nitrogen-containing polycyclic natural products isolated from *Daphniphyllum macropodum*.<sup>64,65</sup> Due to their complex chemical structures and specific anti-cancer and anti-HIV properties, these alkaloids have attracted widespread attention in the synthetic community.<sup>66</sup>

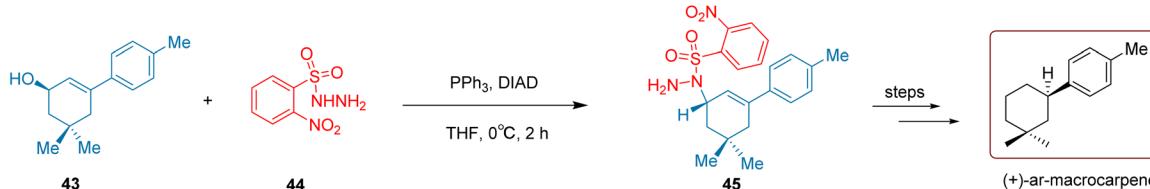
Sakakura and co-workers 2019 designed a reaction using Mitsunobu reagents (DIAD and  $\text{PPh}_3$ ) to synthesize the target daphniphyllum Alkaloid in toluene at room temperature. They replaced the chiral secondary alcohol in compound **46** with a naphthyl sulfonamide, achieving intramolecular cyclization

and obtaining the pyrrole derivative **47**. This synthetic route involves simple operations and applies to synthesizing other daphniphyllum Alkaloids, as illustrated in Scheme 21. Transforming compound **47** into the final product requires four steps, achieving an overall yield of 37%.

Communesin A and B are two complex alkaloids isolated from algal-derived *Penicillium fungus*. They exhibit cytotoxicity against lymphocytes and leukemia cells.<sup>67,68</sup> Movassaghi and co-workers 2019 first synthesized a pivotal intermediate to obtain these compounds. They utilized an amino-protected naphthyl sulfonamide reagent to successfully convert the hydroxyl group in compound **48** into an amino group in compound **49**, laying a solid foundation for the further synthesis of the target compounds. The results of this transformation are illustrated in Scheme 22. Reaching Communesin A from compound **49** requires six steps and achieves an overall yield of 38%. In contrast, it takes seven steps to reach Communesin B from compound **49**, resulting in a total yield of 35%.

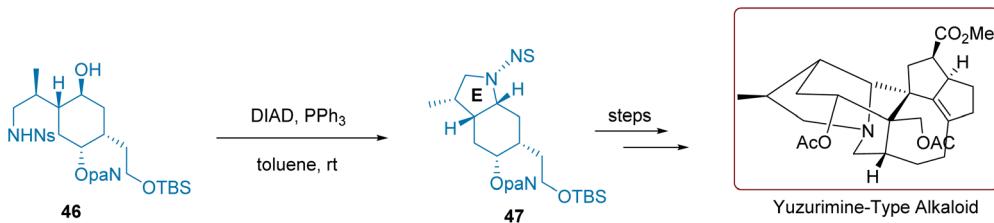
Research has shown that Leuconodines D and E exhibit moderate cytotoxicity against KB cells and possess specific antimalarial activity against *Plasmodium falciparum*, generating significant interest among synthetic chemists.<sup>69–71</sup>

In 2019, Han group utilized 2-nitrophenylsulfonamide acetate **50** as a nucleophilic reagent in a mixed solvent of tetrahydrofuran and toluene. They performed a Mitsunobu reaction at room temperature for 10 hours with 1.5 equivalents of DEAD and  $\text{PPh}_3$  and 1.5 equivalents of primary alcohol **51**, forming the indole derivative **52**. Following this, a palladium–carbon-catalyzed hydrogenation reaction yielded Leuconodine E with an 88% yield. After oxidizing Leuconodine E, they successfully synthesized Leuconodine D with a yield of 66%. The results of these transformations are illustrated in Scheme 23. The synthesis of Leuconodine D from compound **52** requires

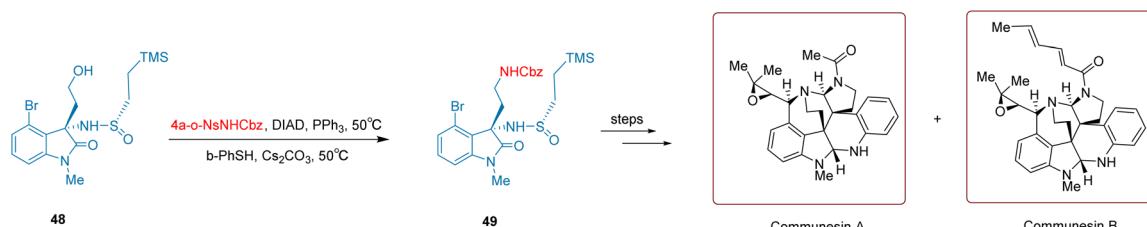


Scheme 20 Bisai's synthesis of (+)-ar-macrocarpene.





Scheme 21 Sakakura's synthesis of daphniphyllum alkaloids.



Scheme 22 Movassaghi's synthesis of communesin alkaloids.

12 steps, achieving an overall yield of 9.2%. In comparison, synthesizing Leuconodine E from compound 52 involves only 10 steps, resulting in a significantly higher overall yield of 17%.

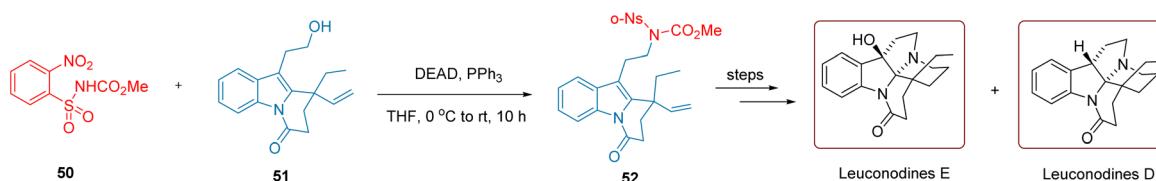
Calyciphylline B-type alkaloids are a subclass of calyciphylline alkaloids that belong to the more prominent family of *Daphniphyllum* alkaloids. Deoxycalyciphylline B is extracted from the stems of *D. subverticillatum*.<sup>72,73</sup> These alkaloids exhibit various biological activities, including antioxidant and anti-cancer properties, and can promote nerve growth factors.<sup>74,75</sup>

Recently, Raghavan and co-workers attempted to synthesize a key intermediate using Mitsunobu reagents to obtain deoxycalyciphylline B. In the presence of DIAD and  $\text{PPh}_3$ , they reacted in tetrahydrofuran as the solvent at room temperature for 24

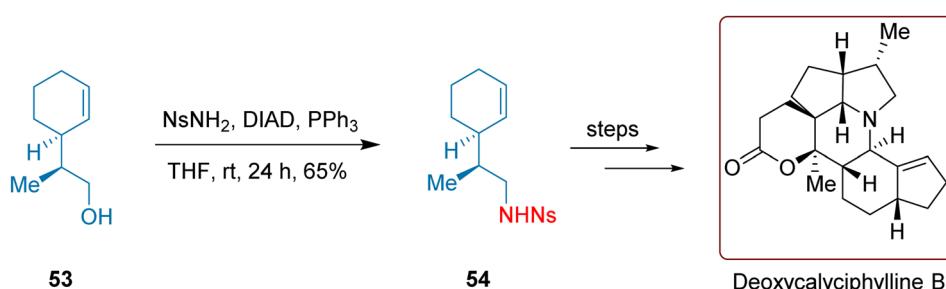
hours, successfully converting from compound 53 to compound 54 with a yield of 65%. The results of this transformation are illustrated in Scheme 24.

Aspidosperma alkaloids are characterized by their polycyclic structures, and common compounds such as deoxoaopidine and kopsifoline D belong to this class.<sup>76</sup> Deoxoaopidine is primarily isolated from *Tabernaemontana armeniaca*, and its presence has also been discovered in *Hazunta modesta*. On the other hand, kopsifoline D was initially isolated from leaf extracts of the Malayan *Kopsia* species.<sup>77,78</sup>

Peng and co-workers conducted extensive experiments in 2019 to synthesize deoxoaopidine and kopsifoline D. As illustrated in Scheme 25, in a tetrahydrofuran solvent, the primary

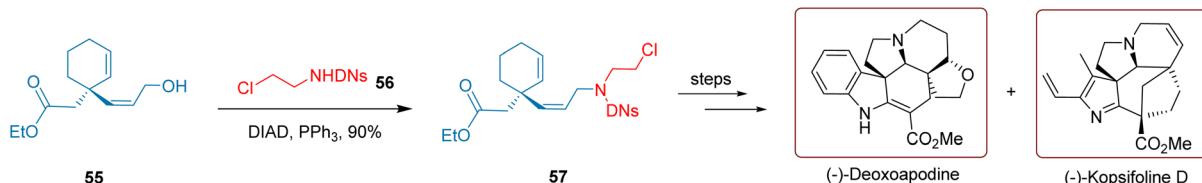


Scheme 23 Han's synthesis of leuconodines D and E.

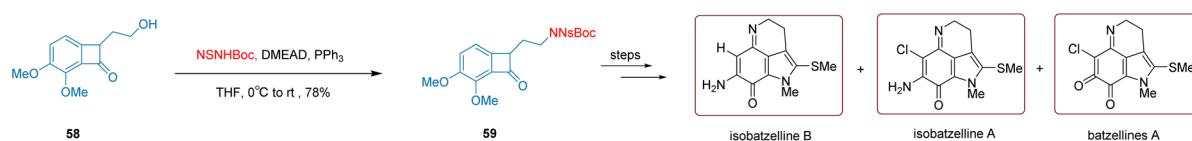


Scheme 24 Raghavan's synthesis of deoxycalyciphylline B.





Scheme 25 Peng's synthesis of aspidosperma and kopsia alkaloids.



Scheme 26 Tokuyama's synthesis of marine alkaloids.

alcohol **55** underwent a continuous reaction for 12 hours with Mitsunobu reagents (DIAD,  $\text{PPh}_3$ ) and sulfonyl amide **56**, ultimately converting to compound **57** with a high yield of 90%. The successful preparation of **57** laid a solid foundation for synthesizing deoxoapodine and kopsifoline D target compounds. The conversion from compound **57** to deoxoapodine requires precisely seven steps, yielding an overall return of 5.59%. In contrast, the process from compound **57** to kopsifoline D also involves seven steps, but produces a lower overall yield of 3.43%.

Batzellines and isobatzellines are marine alkaloids that possess a pyrrole framework. Batzellines exhibit selective cytotoxicity towards specific pancreatic cancer cell lines. At the same time, isobatzellines show inhibitory effects on pancreatic cancer cells and have low toxicity towards normal cells, making them candidates for chemotherapy.<sup>79,80</sup>

Tokuyama and co-workers designed a new synthetic route to prepare these molecules in 2020 to synthesize the key intermediate **59**. As shown in Scheme 26, they reacted the primary alcohol substrate **58** with  $\text{NsNHBOC}$  in the presence of DMEAD and  $\text{PPh}_3$  in a tetrahydrofuran solvent, successfully converting the hydroxyl functional group with a yield of 78%, completing the synthesis of intermediate **59**. The pathway from compound **59** to isobatzelline B requires ten steps, just as it does to reach isobatzelline A. However, it only takes nine steps to convert to Batzellines A. The overall yield for these reactions ranges from 20% to 30%.

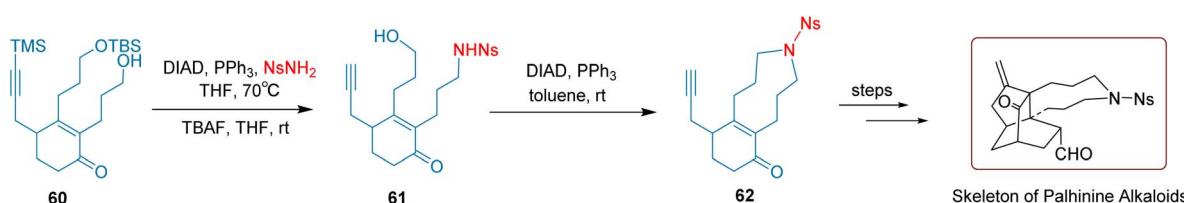
Palhinine A is primarily isolated from the whole plant of *Palhinhaea cernua* L. (Lycopodiaceae) and belongs to the class of

Lycopodium alkaloids. It exhibits acetylcholinesterase (AChE) inhibitory effects, which can improve cognitive impairments and alleviate symptoms of Parkinson's disease.<sup>81-83</sup>

To chemically synthesize Palhinine A, He and co-workers designed a two-step Mitsunobu reaction in 2020 to synthesize the critical intermediate **62**. In this process, the selective protection of the two side chains of the primary alcohol substrate **60** underwent sequential intramolecular Mitsunobu reactions, silicon deprotection, and another intramolecular Mitsunobu reaction, successfully converting **60-62**. The results of this transformation are illustrated in Scheme 27. To reach the final product from compound **62**, two steps are needed, yielding 28%.

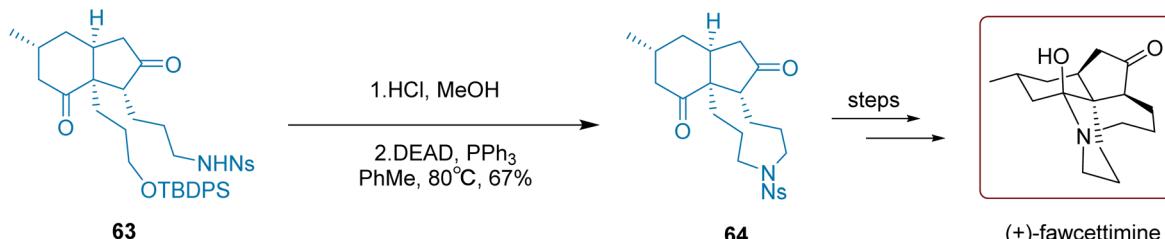
Over 400 Lycopodium alkaloids have been isolated and identified from the Lycopodiaceae family, with five novel Lycopodium alkaloids discovered in the whole plant of *Huperzia serrata*. Many of these alkaloids have been found to exhibit pharmacological activities such as acetylcholinesterase inhibition, neuroprotection, anti-tumor, and anti-inflammatory effects.<sup>84,85</sup> These alkaloids' unique chemical structures and diverse pharmacological properties continue to captivate plant chemistry and synthesis experts.

Introducing a sulfonyl amide group into the molecule and subsequently introducing a nitrogen atom through deprotection is a critical strategy in synthetic chemistry. As illustrated in Scheme 28, Qiu and co-workers successfully synthesized compound **64** using this approach in 2020. Specifically, under acidic conditions, the silicon-protecting group of compound **63** was cleaved to generate a primary alcohol. Subsequent



Scheme 27 He's synthesis of the skeleton of palhinine alkaloids.





Scheme 28 Qiu's synthesis of lycopodium alkaloids.

intramolecular cyclization was achieved by treating Mitsunobu reagents (DEAD and  $\text{PPh}_3$ ). Notably, this step required high-temperature conditions at 80 °C and converted **63** to **64** with a moderate yield of 67%. Subsequent multi-step reactions ultimately led to the completion of the synthesis of (+)-fawcettimine. The process requires just one step to convert compound **64** into the final product, achieving a yield of 81%.

Asperipin-2a is a bicyclic hexapeptide isolated from *Aspergillus flavus*,<sup>86,87</sup> featuring eight chiral centers within its molecular structure. The chemical synthesis of such compounds poses significant challenges. As illustrated in Scheme 29, Hutton *et al.* utilized chiral secondary alcohol **65** and a tyrosine derivative **66** to perform a Mitsunobu reaction, forming the polar inverted compound **67**. Subsequent deprotection and sulfonylation gave compound **68**. Under the influence of Mitsunobu reagents (DIAD and  $\text{PPh}_3$ ), compound **68** underwent an intramolecular *ortho*-Mitsunobu reaction, forming aziridine **69** with a yield of 90%. This total synthesis of aspirin-2a involved two Mitsunobu reactions, highlighting the widespread applicability of the Mitsunobu reaction in the synthesis of natural products. The process from compound **69** to the final product consists of ten steps, achieving an overall yield of 6.47%.

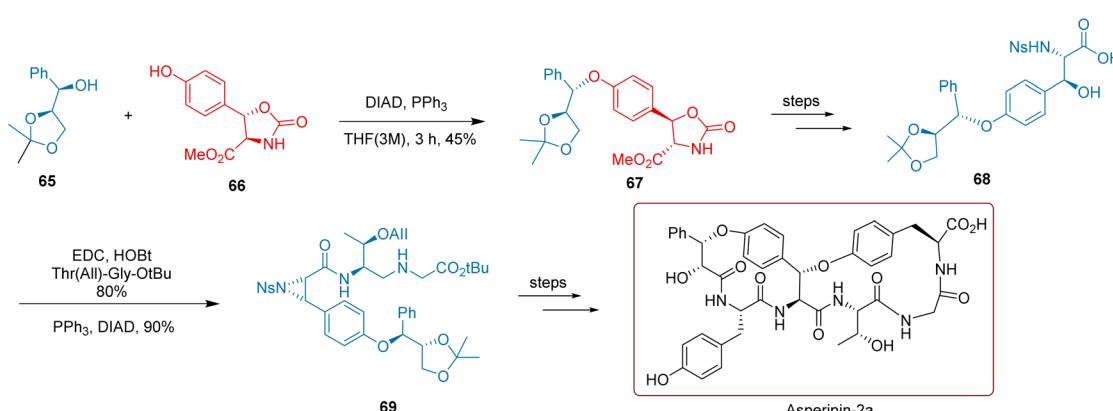
The discorhabdin alkaloid family is isolated from *marine sponges* and exhibits various bioactivities, including antibacterial,<sup>88,89</sup> antiviral, and antitumor effects<sup>90</sup> and potential therapeutic effects on neurodegenerative diseases.<sup>91</sup> Due to their wide-ranging pharmacological activities and unique structures, the chemical synthesis of discorhabdin alkaloids has garnered significant interest in the synthetic community.<sup>92</sup>

As illustrated in Scheme 30, Tokuyama and co-workers synthesized compound **72** in 2021 by reacting a dihydroindole derivative with a chiral secondary alcohol **71** using Mitsunobu reagents (DIAD and  $\text{PPh}_3$ ). They removed the silyl-protecting groups, giving **73**, and Ns-protecting groups, generating **74**, to synthesize the intramolecular cyclic product discorhabdin V. There are seven steps required to transform compound **74** into the final product, resulting in an overall yield of 14%.

Diterpenoid alkaloids are primarily isolated from the plant *Aconitum septentrionale* and are effective in treating pain and rheumatoid arthritis and exerting specific effects in antiarrhythmic therapy.<sup>93-95</sup>

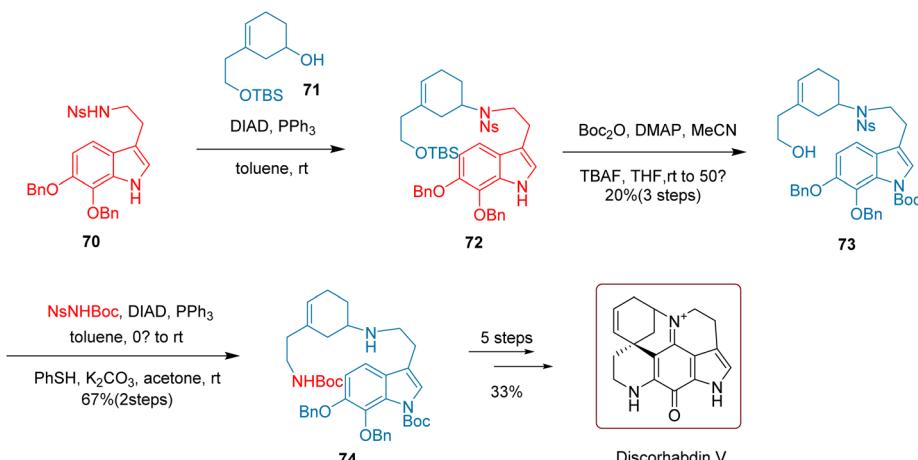
In 2024, Liu and colleagues employed the classical sulfonyl-amine nucleophilic reagent in conjunction with alcohol substrates under Mitsunobu conditions to achieve the chemical synthesis of these alkaloids. As illustrated in Scheme 31, using toluene as the solvent, the naphthyl sulfonyl amide in compound **75** reacted with the intramolecular primary alcohol group in the presence of DIAD and  $\text{PPh}_3$ , resulting in the construction of compound **76** with a yield of 80%. This compound is a crucial synthetic intermediate in the chemical synthesis of diterpenoid alkaloids. The conversion of compound **76** to the final product involves five essential steps, yielding an overall result of 22%.

Manzamines are a class of bioactive compounds extracted from marine organisms. Sakai *et al.* first discovered them in 1986 in a marine sponge.<sup>96</sup> These compounds exhibit various pharmacological effects, including anticancer and anti-



Scheme 29 Hutton's synthesis of bicyclic hexapeptide.





Scheme 30 Tokuyama's synthesis of discorhabdin alkaloids.

inflammatory properties and significant effects on diseases such as hyperlipidemia and atherosclerosis.<sup>97</sup>

To synthesize manzamine C, as shown in Scheme 32, Cheng and colleagues 2024 utilized compound 77 in a Mitsunobu reaction involving DIAD and PPh<sub>3</sub> to cyclize the molecule intramolecularly. Following purification by column chromatography, compound 78 was obtained with a yield of 53%. After removing the naphthyl sulfonyl group, intermediate 78 underwent nucleophilic substitution with an indole derivative to yield the desired manzamine C. There are two steps required to convert compound 78 into the final product, resulting in an overall yield of 70%.

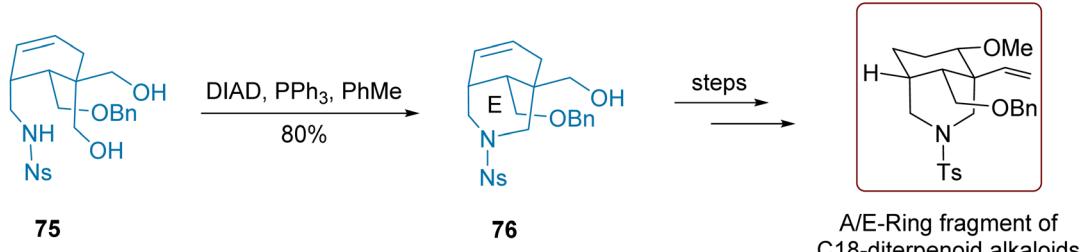
### 3.3 Fatty amines, aromatic amines, amides, nucleosides act as nucleophiles

Aspongopus chinensis (Pentatomidae) is primarily found in southern China. Aspongopamine B is a compound isolated

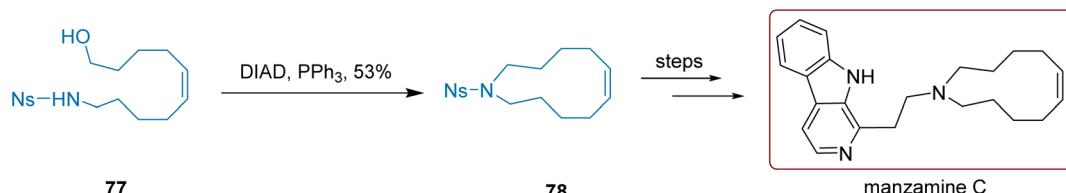
from the insect *Aspongopus chinensis*.<sup>98,99</sup> As a TCM, it has been widely used to treat diseases such as cancer, severe stomach pain, and indigestion.

Compound 81 is a critical intermediate in the design and synthesis route of aspongopamine B. As illustrated in Scheme 33, Cheng and co-workers 2020 reacted the secondary alcohol substrate 79 with a purine derivative 80 in the presence of PPh<sub>3</sub> and DIAD, using tetrahydrofuran as the reaction solvent, at room temperature for 30 minutes. This reaction successfully transformed compound 79 into 81 with a yield of 70%. It takes six steps to go from compound 81 to the final product, with an overall yield of 23.32%.

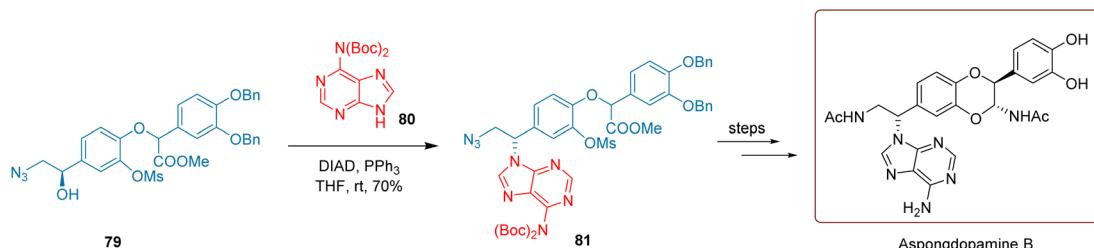
In 2000, Kashman and co-workers successfully isolated and extracted polycitone A from marine ascidians, which exhibits potent antiviral effects.<sup>100,101</sup> The main challenge in the chemical synthesis of polycitone A lies in connecting the *para*-hydroxyphenylethyl group to the pyrrole nitrogen atom within the molecule.



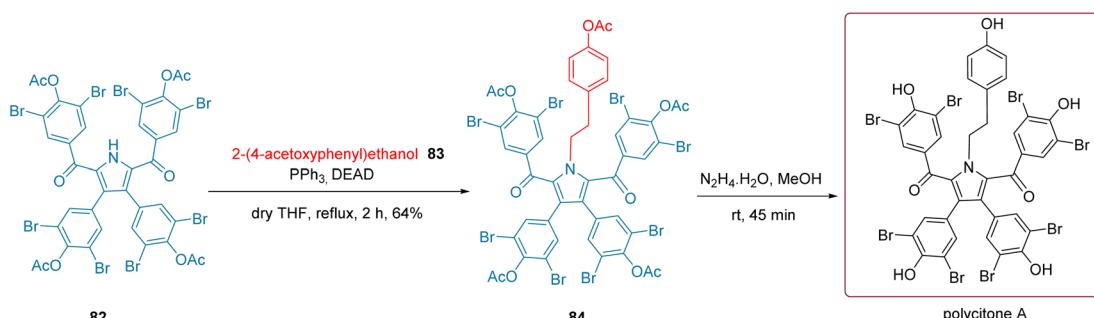
Scheme 31 Liu's synthesis of A/E-ring fragment of C18-diterpenoid alkaloids.



Scheme 32 Cheng's synthesis of manzamine C.



Scheme 33 Cheng's synthesis of aspong dopamine B.



Scheme 34 Steglich's synthesis of marine pyrrole alkaloids.

After, Steglich and co-workers ingeniously designed a one-step Mitsunobu reaction. They treated the pyrrole derivative **82** with 2-(4-acetoxyphenyl)ethanol **83**, PPh<sub>3</sub> (4 equiv.), and DEAD (4 equiv.), refluxed in tetrahydrofuran for 2 hours, purified by column chromatography, and finally obtained **84** with a yield of 64%. By removing the acetyl group using hydrazine hydrate, polycitone A was obtained with an 88% yield, as depicted in Scheme 34. The transformation from compound **84** to the final product occurs in a single step and delivers an impressive overall yield of 88%.

Lentiginosine possesses a *trans*-1,2-dihydroxyindolizidine skeleton and has been shown to induce apoptosis in tumor cells.<sup>102</sup> Mechanistic studies suggest that this effect may be attributed to its ability to inhibit glycosidases, making it a promising candidate for new anticancer drugs.<sup>103</sup>

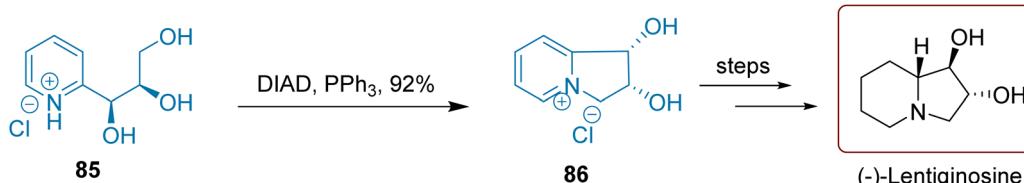
Bischoff and co-workers in 2007 employed a pyridine derivative **85** containing glycerol to synthesize such molecules. They first successfully constructed the C–N bond through an intramolecular Mitsunobu reaction, achieving the cyclized product **86** with a yield of 92%. Subsequently, they synthesized (–)-lentiginosine through reduction and polar inversion

methods. The results are illustrated in Scheme 35. To reach the final product from compound **86**, two steps are needed, resulting in an overall yield of 90.25%.

The oriodin alkaloids are primarily isolated from marine sponges belonging to the orders *Agelasida*, *Axinellida*, and *Halicordida*.<sup>104,105</sup> They have demonstrated anti-inflammatory effects in a zebrafish inflammation model.<sup>106</sup> Due to their complex structures and broad biological activities, these alkaloids continue to attract synthetic chemists' attention.<sup>107,108</sup>

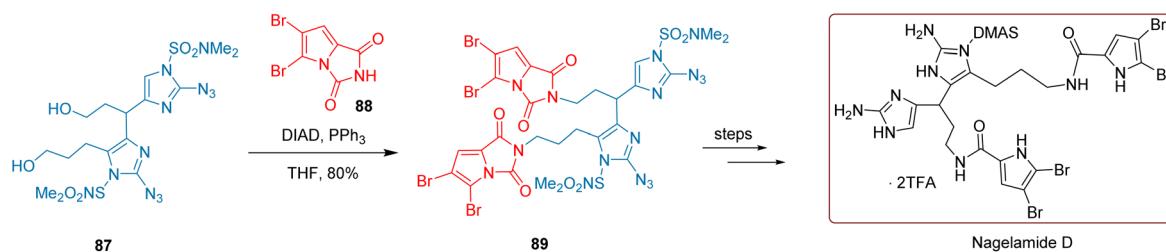
As illustrated in Scheme 36, Lovely and co-workers conducted a Mitsunobu reaction in 2009 using tetrahydrofuran as the solvent. In this reaction, a dimethylamine **88** was successfully coupled with an imidazole substrate **87** containing primary alcohol facilitated by PPh<sub>3</sub> and DIAD, forming compound **89** with an 80% yield. Further transformations of this compound led to the target molecule nagelamide D. It takes three definitive steps to convert compound **89** into the final product, achieving an overall yield of 22.70%.

Tetrodotoxin (TTX) is the main toxic component responsible for pufferfish poisoning and is one of the most famous marine natural products.<sup>109</sup> In toxic marine organisms, tetrodotoxin is



Scheme 35 Bischoff's synthesis of lentiginosine.





Scheme 36 Lovely's synthesis of nagelamide D.

believed to be produced by marine bacteria and accumulates through the food chain.<sup>110,111</sup> Cep-212 and Cep-210 are crucial intermediates in the biosynthesis of tetrodotoxin.

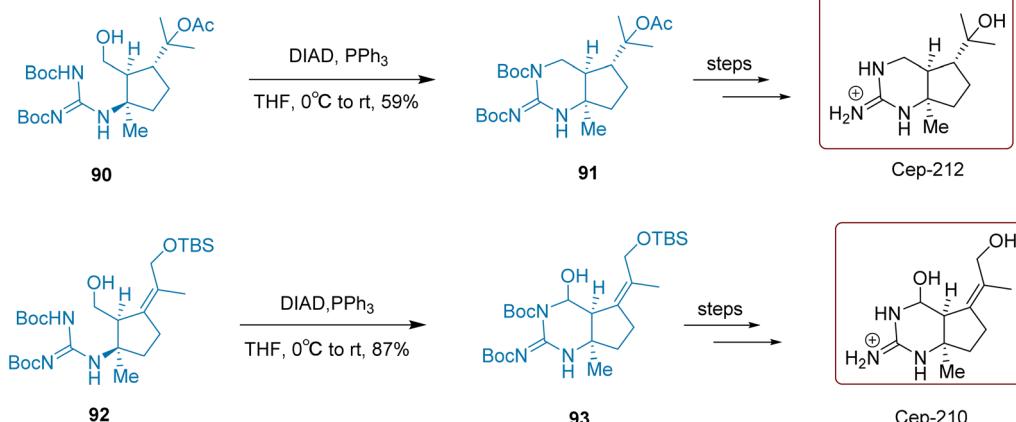
To synthesize these two intermediates, Nishikawa and co-workers 2018 utilized Boc-protected urea derivatives **90** and **92** in separate intramolecular cyclization steps under the influence of Mitsunobu reagents (DIAD and  $\text{PPh}_3$ ) in tetrahydrofuran as the solvent. They obtained compounds **91** and **93** with 59% and 87% yields, respectively. Subsequent deprotection strategies led to the target molecules Cep-212 and Cep-210. The results are depicted in Scheme 37. The conversion of compound **91** to the product Cep-212 occurs in six definitive steps, resulting in an overall yield of 60.15%.

Caprazamycins are a class of nucleoside antibiotics produced by *Streptomyces* sp.<sup>112,113</sup> Research has shown they can potentially treat tuberculosis.<sup>114</sup> The construction of a seven-membered ring is thermodynamically less stable than that of

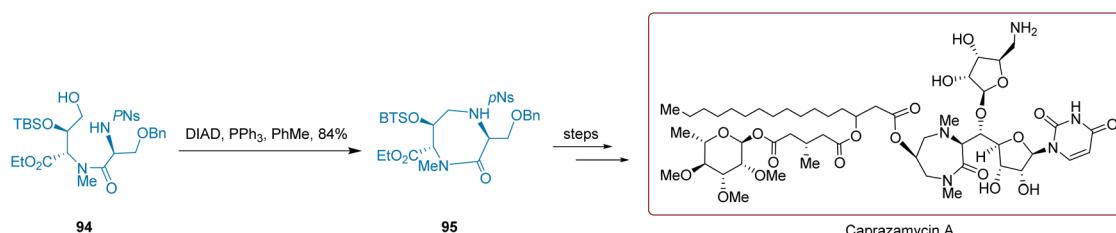
a six-membered ring, making synthesizing such molecules require unique strategies.

To chemically synthesize caprazamycin A and related molecules, Takemoto and co-workers 2019 employed Mitsunobu reagents (DIAD (1.5 equiv.) and  $\text{PPh}_3$ ) to facilitate the intramolecular formation of a C–N bond in compound **94**. This reaction successfully yielded compound **95** with an 84% yield. This step provided an essential intermediate for the further synthesis of the target molecule caprazamycin A. The results are illustrated in Scheme 38. The conversion of compound **95** to the final product demands eight precise steps, achieving an overall yield of 36.46%.

Morphine and its analogs, derived from opium poppy latex, are the oldest and most extensively studied alkaloids known to date.<sup>115,116</sup> Due to their potent neurological and immunological activities, opioid analgesics such as morphine and fentanyl are widely used in the field of medicine. They are used as powerful

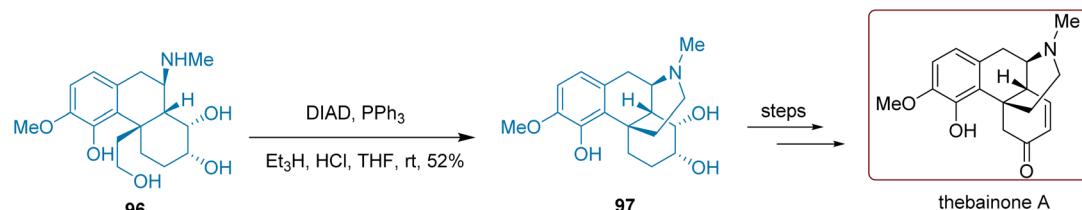


Scheme 37 Nishikawa's synthesis of cep-212 and cep-210.

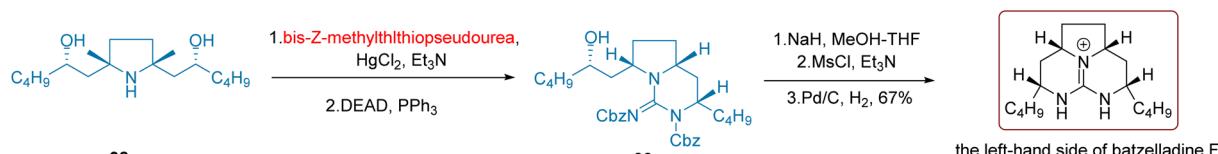


Scheme 38 Takemoto's synthesis of liponucleoside antibiotics.





Scheme 39 Dong's synthesis of thebainone A.



Scheme 40 Nagasawa's synthesis of phlegmarine-type lycopodium alkaloids - the left-hand side of batzelladine F.

pain relievers in the treatment of cancer pain in the third stage. Given the extensive applications of these molecules, a series of novel morphine-like derivatives have been synthesized.

As shown in Scheme 39, Dong and co-workers 2021 utilized a pre-synthesized polyhydroxy substrate **96** to undergo a classic Mitsunobu reaction at room temperature, converting to compound **97** with a yield of 52%. This reaction established a new carbon–nitrogen bond, facilitating intramolecular cyclization and providing important synthetic intermediates for the subsequent transformation and synthesis of thebainone A. The conversion of compound **97** to the final product involves six decisive steps, achieving an overall yield of 9.02%.

Multiple structurally unique alkaloids have been discovered in sponges, exhibiting promising anti-tumor activity.<sup>117</sup> As demonstrated in Scheme 40, Nagasawa *et al.* employed a one-pot synthesis approach in 2001 to construct guanidine **99** from tetrahydropyran **98**. Initially, the chiral secondary alcohol substrate **98** reacted with bis-Z-methylthiopseudourea under the influence of  $HgCl_2$  and triethylamine, generating an intermediate that underwent a reaction with DEAD, facilitating the creation of a new C–N bond through a Mitsunobu reaction. Finally, by selectively deprotecting the secondary alcohol hydroxyl group in **99** and deprotecting the guanidine to remove Cbz, the left-hand portion of batzelladine F was obtained with a yield of 67%.

### 3.4 Other nucleophiles

Batzelladine A, a type of polyguanidine marine natural product derived from the Caribbean sponge *Batzella* sp., displays

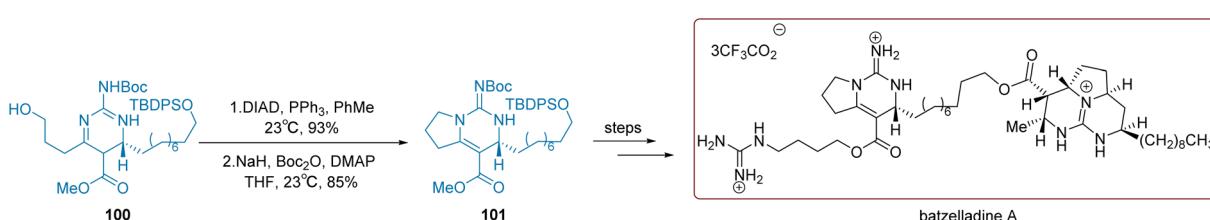
inhibitory properties against the binding of human CD4 and HIV gp120.<sup>118,119</sup>

To synthesize batzelladine A, researchers activated the pre-synthesized primary alcohol derivative **100** in toluene at room temperature using DIAD and  $PPh_3$ , successfully facilitating an intramolecular cyclization reaction. The deprotected Boc group was then re-protected, yielding compound **101**. This step provided an essential intermediate for synthesizing batzelladine A, as illustrated in Scheme 41. There are eight steps to transform compound **101** into the final product, yielding an overall return of 12.00%.

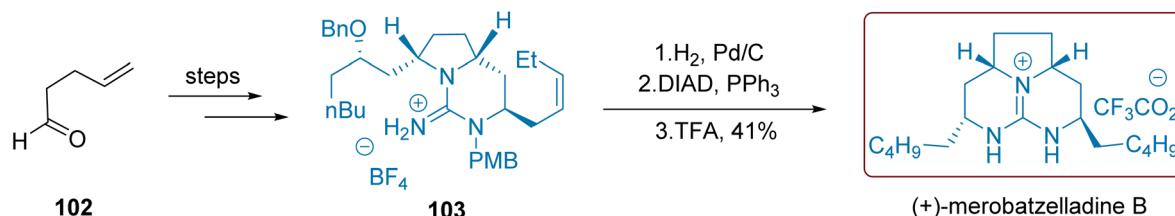
While numerous secondary metabolites with cytotoxic properties have been identified in marine invertebrates, compounds with antibacterial activity are less common. Merobatzelladine B was isolated by researchers from an extract of the sponge *Monanchora* sp., demonstrating antimicrobial effects against *Vibrio anguillarum*.<sup>120,121</sup>

As depicted in Scheme 42, Wolfe group synthesized (+)-merobatzelladine B in 2012, starting from 4-pentenal **102** and proceeding through 12 steps to yield compound **103**. Subsequently, compound **103** underwent a palladium-catalyzed carbon–hydrogen reduction reaction, deprotection, and intramolecular cyclization using Mitsunobu reagents (DIAD and  $PPh_3$ ). After trifluoroacetic acid hydrolysis, (+)-merobatzelladine B was obtained. To reach the final product from compound **103**, three steps are required, resulting in an overall yield of 41%.

Kopsifolines are alkaloids extracted and isolated from the leaves of Malayan *Kopsia* species, containing several chiral centers within their molecular structure.<sup>122,123</sup>



Scheme 41 Abdullah's synthesis of tricyclic guanidine alkaloids - batzelladine A.



Scheme 42 Wolfe's synthesis of merobatzzelladine B.

As illustrated in Scheme 43, in 2021, Movassaghi and colleagues obtained (−)-kopsifoline E from the primary alcohol derivative **104** with a yield of 78% using tetrahydrofuran as the solvent and with the assistance of DIAD and  $\text{PPh}_3$ . Furthermore, (−)-kopsifoline E can be further transformed into (−)-kopsifoline A. The Mitsunobu reaction, a classic synthetic method, is widely employed in synthesizing such alkaloids. It takes one step from kopsifoline E to kopsifoline A, with an overall yield of 73%.

The Mitsunobu reaction is an essential tool for constructing C–N bonds and synthesizing C–O and C–S bonds. This capability provides critical strategic support that drives the advancement and success of natural product chemistry.

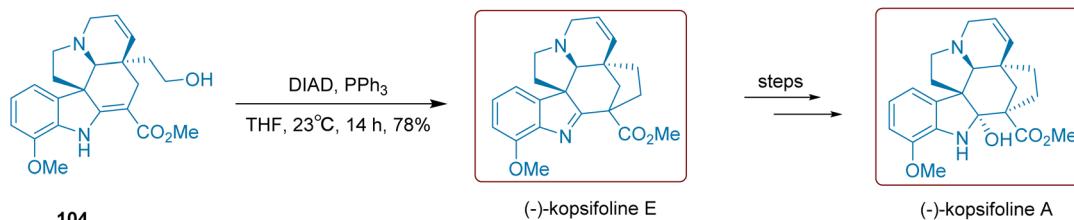
For example, the analogs of bactobolin A are crucial synthetic intermediates, which Sathyamoorthi *et al.* utilized to study and develop various analogs of bactobolin A. These analogs exhibit potential antimicrobial activity and serve as valuable tool compounds for in-depth investigations into the structure and function of bacterial ribosomes, as well as their role in antimicrobial mechanisms. With further structural optimization and bioactivity research, these analogs hold significant promise for the development of novel antibiotics.

As illustrated in Scheme 44, compound **1** undergoes a reaction with 3,5-dinitrobenzoic acid in the presence of  $\text{PPh}_3$  and

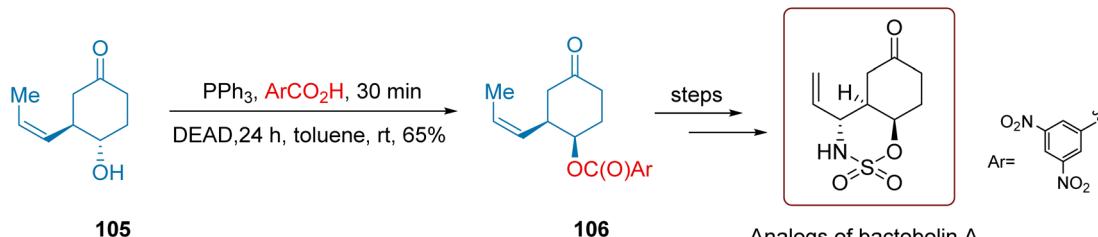
DEAD during a Mitsunobu reaction. This process converts the C6 hydroxyl group of compound **105** into a 3,5-dinitrobenzoate, yielding compound **106** with a 65% yield. Subsequently, through ester hydrolysis and aza-Wacker cyclization, three additional steps were completed to synthesize more analogs of bactobolin A, resulting in a total yield of 14.09%. This demonstrates the diversity and complexity involved in synthesizing intricate organic molecules.<sup>124</sup>

Xanthohumol is a powerful natural compound extracted from hops, renowned for its significant pharmacological activities, including potent antioxidant, anti-inflammatory, and anticancer effects.<sup>125,126</sup> Given the compound's diverse biological activities, there is a compelling need for research into its synthesis to support *in vivo* efficacy and toxicity studies.

Erhardt *et al.* adeptly conducted a Mitsunobu reaction, successfully reacting the hydroxyl group of compound **107** with 3-methyl-2-buten-1-ol (**108**), achieving an impressive 80% yield of compound **109**, as illustrated in Scheme 45. Following this, they efficiently carried out four subsequent steps, which included Claisen rearrangement, methylation, and deprotection of the MOM group, ultimately synthesizing the target compound, Xanthohumol, with a satisfactory total yield of 22.67%.

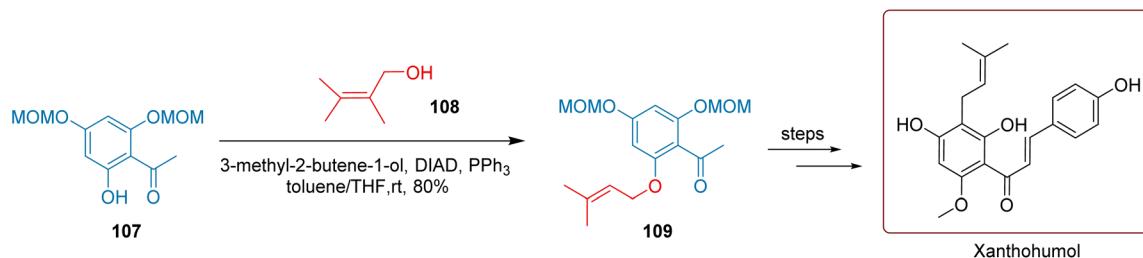


Scheme 43 Movassaghi's synthesis of kopsifoline A.

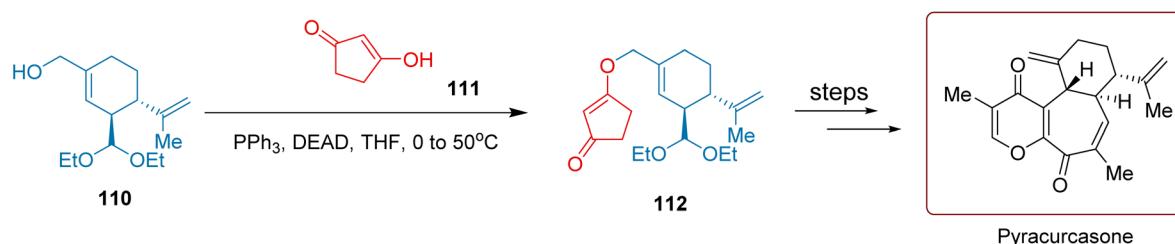


Scheme 44 Sathyamoorthi's synthesis of analogs of bactobolin A.





Scheme 45 Erhardt's synthesis of xanthohumol.



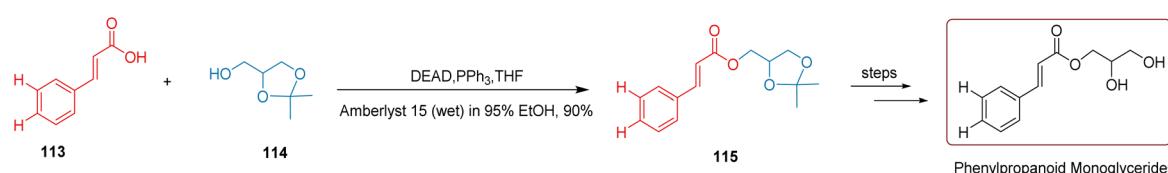
Scheme 46 Dai's synthesis of pyracurcasone.

Pyracurcasone exhibits powerful inhibitory effects on cancer cells by effectively targeting the BRAT1 protein. This inhibition significantly reduces cancer cell migration, proliferation, and the ability to repair DNA damage, thereby enhancing the sensitivity of cancer cells to DNA-damaging drugs.<sup>127,128</sup> These compelling results establish pyracurcasone as a promising candidate with substantial potential for anticancer applications and a key player in developing new anticancer therapeutics.

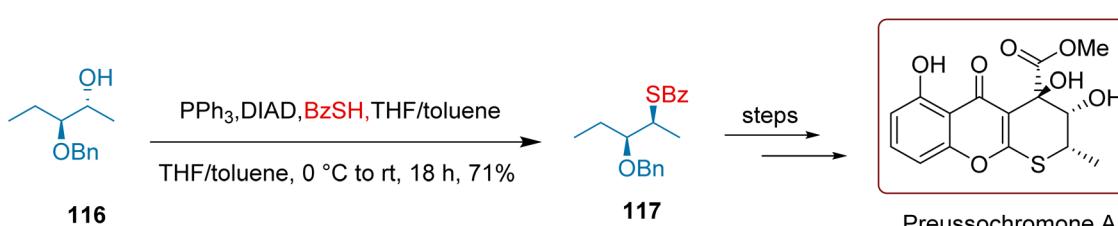
Dai *et al.* successfully transformed compounds 110 and 111 into compound 112 using a Mitsunobu reaction that involved  $\text{PPh}_3$  and DEAD. They then synthesized Pyracurcasone through a meticulously executed series of seven steps, including Claisen rearrangement, addition,  $\alpha$ -iodination, and  $\alpha$ -methylation, resulting in an impressive total yield of 1.16%, as demonstrated in Scheme 46.

Phenylpropanoid monoglycerides display a range of pharmacological activities, such as antioxidant properties and anti-proliferative effects against tumor cells.<sup>129,130</sup> As illustrated in Scheme 47, Ubukata *et al.* successfully synthesized compound 115 with a yield of 90% using a Mitsunobu reaction. They subsequently produced the final product, phenylpropanoid monoglycerides, with an impressive yield of 95% in a single step.

Preussochromone A is a remarkable natural product isolated from fungi, distinguished by its unique tricyclic structure and notable cytotoxic activity. Its effectiveness against HeLa cells and another cell line clearly indicates substantial pharmacological potential, making further investigation into its applications in drug development essential.<sup>131,132</sup>



Scheme 47 Ubukata's synthesis of Phenylpropanoid Monoglycerides.



Scheme 48 Koert's synthesis of Preussochromone A.

In a well-executed series of experiments, as illustrated in Scheme 48, Koert *et al.* converted compound **116** to compound **117**, achieving an impressive yield of 71% through a Mitsunobu reaction employing DIAD and  $\text{PPh}_3$ . They then synthesized Preussochromone A over 11 meticulously planned steps, including both addition and cyclization, ultimately securing an overall yield of 2.64%.

In summary, nitrogen-containing compounds are essential in medicinal chemistry because they are critical in drug design and synthesis. Nitrogen atoms impart unique chemical properties and biological activities to these compounds, making them integral components of many pharmaceuticals. Consequently, various synthetic methodologies aim to incorporate nitrogen atoms into these molecular structures,<sup>133–136</sup> with the Mitsunobu reaction being a noteworthy synthetic method that plays a crucial role in constructing C–N bond connections in nitrogen-containing compounds.

## 4. Conclusion

The Mitsunobu reaction is essential for introducing nitrogen-containing groups into chiral molecular frameworks, making it a powerful tool for designing specific chiral centers during the reaction process. This capability allows researchers to efficiently synthesize a variety of nitrogen-containing compounds with chiral centers, including amino alcohols, amino phenols, and amino acid derivatives. These compounds are critical in chiral drug design and discovery, firmly establishing the Mitsunobu reaction as a key method for constructing C–N bond connections, which supports groundbreaking advancements in medicinal chemistry—particularly in the total synthesis of natural products and the development of novel pharmaceuticals.

Moreover, the Mitsunobu reaction presents several compelling advantages, including smooth inversion of configuration, short reaction times, mild conditions, and straightforward separation and purification techniques. Researchers have effectively utilized a diverse array of pronucleophiles, such as azides, sulfonamides, amines, and imides, to construct valuable chiral natural products, facilitating the formation of desired C–N bonds. However, it is crucial to acknowledge some limitations inherent in this method. For instance, the Mitsunobu reaction often struggles to achieve the desired yields in large-scale syntheses. Additionally, the reliance on stoichiometric amounts of oxidation and reducing reagents can be costly and cumbersome to manage during standard work-ups, which raises important concerns about the reaction's atom economy.

Significant progress has been made to overcome these challenges, with the development of a catalytic Mitsunobu reaction being hailed as the "Holy Grail" of Mitsunobu chemistry. Electroreduction is emerging as a promising pathway for realizing the catalytic cycle of organophosphorus compounds under greener and milder reaction conditions, effectively substituting chemical energy with electrical energy. These challenges point to both the obstacles that need to be addressed and the abundant opportunities for future advancements within the field. Ultimately, the Mitsunobu reaction's vital

contributions to constructing C–N bonds, combined with its inherent advantages, unequivocally enhance its significance in medicinal chemistry and pharmaceutical innovation.

This review provides valuable insights into the Mitsunobu reaction and its applications. It offers an overview of the reaction's role in synthesizing nitrogen-containing heterocyclic compounds, referencing the work of Yurovskaya *et al.* (2008) and placing it in historical context with Professor Pavan Kumar's review from 1967 to 2009. Additionally, contemporary relevance is discussed, along with the improved Mitsunobu reagents identified by Panday and the importance of the reaction in natural product synthesis, as noted by Professor Mojzych. Advancements in catalytic Mitsunobu reactions presented by the Cai group are also highlighted. By synthesizing these contributions, the review demonstrates the versatility and significance of the Mitsunobu reaction in synthetic chemistry, particularly in constructing C–N bonds in chiral compounds. Covering studies from 1978 to 2024, this review is a valuable resource for researchers aiming to utilize the Mitsunobu reaction, offering insights into its history, current applications, and future directions.

## Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Author contributions

Xue Zhou: literature collection, formal analysis, writing-original draft; Liang Xu: literature collection, formal analysis; Zhanhui Ma: formal analysis; Jin Cui: formal analysis; Bin Wang: project administration, writing – reviewing, editing.

## Conflicts of interest

There are no conflicts to declare.

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