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The Curtius Rearrangement: Mechanistic Insight and Recent Applications in Natural Product Syntheses

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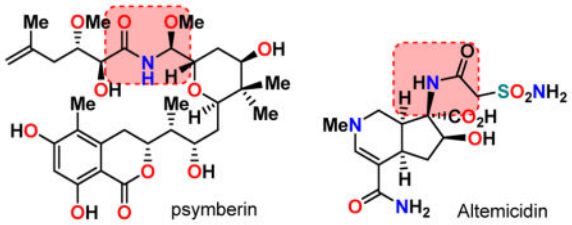
Abstract

The Curtius rearrangement is a versatile reaction in which a carboxylic acid can be converted to an isocyanate through acyl azide intermediate under mild conditions. The resulting stable isocyanate can then be readily transformed into a variety of amines and amine derivatives including urethanes and ureas. There have been wide-ranging applications of Curtius rearrangement in the synthesis of natural products and their derivatives. Also, this reaction has been extensively utilized in the synthesis and application of a variety of biomolecules. In this review, we present mechanistic studies, chemical methodologies and reagents for the synthesis of isocyanates from carboxylic acids, conversion of isocyanates to amines and amine derivatives, and their applications in the synthesis of bioactive natural products and their congeners.

Graphical Abstract



An extensive review of the Curtius reaction and its recent applications in the synthesis of bioactive natural products are reported

1. Introduction

In 1885, at Heidelberg University, Julius Wilhelm Theodor Curtius discovered that acyl azides derived from carboxylic acids undergo thermal decomposition to provide isocyanates and nitrogen.[1,2] Since then, this reaction known as Curtius rearrangement or Curtius reaction has been widely used in organic synthesis due to the usefulness of isocyanate intermediates.[3–5] Isocyanates can be readily converted to a range of functionalities including amines, urethanes and ureas by reaction with appropriate nucleophiles such as water, alcohols or

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amines, respectively (Figure 1).[6,7] These structural motifs frequently occur in natural products, pharmaceuticals and agrochemicals.[8–10]

Since amines are key precursors for the synthesis of a variety of amine derivatives, many synthetic methods have been developed for their preparation.[11,12] Amine synthesis using the Curtius rearrangement is particularly appealing since it is applicable to a wide range of carboxylic acids including aliphatic, aromatic, heterocyclic, saturated and unsaturated acids containing multiple functional groups.[6,13,14] Furthermore, many mild methods have been developed for the conversion of carboxylic acids to their acyl azides, isocyanates and amine derivatives in a one-pot fashion.[15–17] Another important feature of the Curtius rearrangement is that the reaction provides access to primary amines without contamination with secondary or tertiary amines.[18,19] Furthermore, the reaction proceeds with complete retention of stereochemistry of the migrating carbon. This stereochemical integrity has been exploited for the generation of chiral nitrogen-containing centers. For these reasons, the Curtius rearrangement is often the method of choice for the synthesis of structurally complex amines.[20–22]

Curtius rearrangement has been extensively utilized in the synthesis of bioactive natural products and in drug development. However, the full potential of this reaction has not yet been recognized.[23,24] In the present review, we will highlight the gradual development of the Curtius rearrangement, and chemical methodologies adopted for the synthesis of isocyanates, amines and amine derivatives. Furthermore, we plan to provide an overview of the applications of the Curtius rearrangement in total syntheses of natural products and their derivatives.

2. Mechanism of the Curtius Rearrangement

Over the years, the mechanism of the Curtius rearrangement has been a subject of great interest. Stieglitz in 1896, postulated that the mechanism of the Curtius rearrangement involved the loss of nitrogen from the acyl azide (**2**) and formation of an unstable acyl nitrene intermediate (**7**) where the R group migrates to the electron deficient nitrogen to give an isocyanate (**3**) (Figure 2).[25] The migration of the R group happens with complete retention of stereochemistry.[26] In 1891, Tiemann proposed a similar acyl nitrene intermediate for a related reaction, the Hofmann rearrangement.[27] However, early efforts to trap the acyl nitrene intermediate failed and it was attributed to a short lifetime for the nitrene. This argued in favor of a concerted mechanism without involving this acyl nitrene intermediate.[28–30]

Subsequent detailed mechanistic studies with a wide variety of acyl azides established that the intermediate acylnitrene can be trapped under photochemical conditions. However, the acyl nitrene could not be trapped under thermal conditions even though both thermal and photochemical decomposition of acyl azides were carried out at nearly identical reaction temperatures.[28,29] In a series of studies, Lwowski and co-workers carried out thermolysis of pivaloyl azide in hydrocarbon solvents.[29] In particular, thermolysis of pivaloyl azide in 2-methylbutane or in cyclohexene above room temperature provided quantitative yield of *tert*-butylisocyanate (Scheme 1).

There were virtually no insertion or addition products observed as the analytical method of detection would have identified 1% yield of any of these products.[29] These experiments, along with a large number of other experimental,[31] theoretical,[32,33] and computational studies,[34,35] concluded that the thermal Curtius rearrangement is a concerted reaction as shown in Scheme 2.[31,32,36]

The photochemical Curtius rearrangement, however, may take place in a concerted manner or it may involve a stepwise mechanism encompassing an acylnitrene intermediate. Lwowski and co-workers then carried out photolysis of pivaloyl azide in cyclohexane, 2-methylbutane, and cyclohexene as a solvent separately under a medium pressure mercury lamp at −15 °C to +5 °C temperature. Interestingly, these photochemical reactions furnished *tert*-butyl isocyanate **9** along with a range of products (**10–13**) arising from insertion of the nitrene into C-H bonds or its addition to the double bond.[28,29] The yield of isocyanates was around 40% for all reactions even though nitrene traps were present in these reactions. Therefore, it has been postulated that the isocyanate and the trapping products were not derived from the same intermediate. Interestingly, photolysis of benzoyl azide and their derivatives resulted in 40–50% yields of isocyanates in the presence of solvents that trap acylnitrenes or inert solvents. Based upon these results, it was suggested that carboxylnitrenes do not undergo rearrangement to isocyanates at a rate competitive to their interception by the trapping agents.[29,34,37,38]

It is generally believed that the photochemical Curtius rearrangement proceeds via two separate pathways. These include, (i) a concerted pathway leading to an isocyanate and (ii) nitrene formation which may or may not provide an isocyanate. Pritchina and co-workers showed that Ar matrix photolysis of benzoyl azide provides phenyl isocyanate by a concerted mechanism as well as through a benzoylnitrene intermediate which was revealed by IR spectroscopy.[39] Both experimental and computational work established that acylnitrenes have singlet ground states. Furthermore, calculations of the lowest singlet states of benzolynitrene and 2-naphthoylnitrene revealed that the structure of these carboxylnitrenes is an intermediate between nitrenes and oxazirenes with long N-O bonds with 1.73–1.82 Å distances. The calculated bond angle for NCO is nearly 90°. The singlet carbonylnitrene can be represented as a resonance hybrid of nitrene and oxazirene as shown in Scheme 3.[31,40]

Wentrup and Bornemann[31] showed that photolysis of benzoylazide isolated in an Ar matrix at 12 K at 308 nm provided phenyl isocyanate as the main product along with a small amount of phenyl cyanate with a characteristic C-O-C stretch of 1193 cm^{-1}. Presumably, both of these products were derived from the direct excited state of the azide or from the rapid reaction via the nitrene.

Skell and Woodworth[41] with Autrey and Schuster[38] showed that acylnitrenes react with *cis*-alkenes to form *cis*-aziridine products. This is consistent with intercepting singlet state of acylnitrene. Interestingly, Liu and co-workers[34] demonstrated that alkoxycarbonylazides upon photolysis in the presence of *cis*-alkenes resulted in both triplet and singlet acylnitrenes which provided a mixture of *cis*- and *trans*-aziridine derivatives (Scheme 4). Matrix spectroscopic experiments revealed triplet ESR spectra of alkoxycarbonylnitrenes during

low temperature photolysis. Photolysis of benzoylazides however, failed to show ESR spectra characteristics of a benzoylnitrene.[34] These spectroscopic studies suggest that acylnitrenes have singlet states. Recent theoretical studies of photochemical Curtius rearrangement on chlorodifluoroacetyl azide using the MS-CASPT2//CASSCF method along with density functional theory indicated that photo-induced Curtius rearrangement of $F_2ClC(O)N_3$ proceeds through a nitrene intermediate in a stepwise manner.[42] A series of kinetic studies on the Curtius rearrangement have been proposed over the years.[43–45]

3. General procedures for the Curtius rearrangement

Since the Curtius rearrangement is the thermal decomposition of acyl azides, extensive research has been conducted for efficient methods for the synthesis of acyl azides, and several reviews regarding their preparation have been published.[23,46] The methods for preparation mostly rely on functional group compatibilities. The two traditional routes for the preparation of acyl azides consist in i) the treatment of esters (**21**) with hydrazine to afford the corresponding hydrazides (**22**), which upon reacting with nitrous acid furnished the acyl azides (**2**) (Scheme 5A), and ii) the treatment of acid chlorides (**23**) with sodium azide (Scheme 5B). The required acid chlorides can easily be accessed from the corresponding carboxylic acids using thionyl or oxalyl chlorides.[47]

In 1942, Davis and Gardner prepared 8,9,15-trihydroxypentadecylamine from aleuritic acid using the Naegeli modification of the Curtius rearrangement (Scheme 6).[48] *N,N′-bis*-8,9,15-Trihydroxypentadecyl urea **26** was formed upon heating of azide **24** in water. However, on refluxing **24** in anhydrous ethyl alcohol, 8,9,15-trihydroxypentadecylurethane **25** was observed. When the reaction was carried out using the Naegeli modification by heating **24** in anhydrous benzene, the corresponding isocyanate **28** was formed. The isocyanate was hydrolyzed with hot aqueous alkali to obtain 8,9,15-trihydroxypentadecylamine **27**.

As mentioned earlier, one of the usual methods to prepare the acyl azides for the Curtius rearrangement is the treatment of the corresponding acid chloride with sodium azide. However, carboxylic acids may undergo decomposition or isomerization in the presence of mineral acids. In such cases, the conversion of the esters to the corresponding hydrazides, represented the only alternative.[49]

In 1936, Darapsky applied the Curtius rearrangement for preparing glycine from cyanoacetic ester.[50] Since then, this method has been widely applied for the synthesis of amino acids from α-cyanoesters.[51] As shown in Scheme 7, ester **29** was converted to the acylhydrazine derivative **30** by reaction with hydrazine. The acylhydrazine, upon reaction with nitrous acid, afforded the acyl azide **31**. Curtius rearrangement of the acyl azide in presence of ethanol furnished carbamate **32**, which upon acidic hydrolysis provided derivative **33** with the free amine and carboxylic functionalities.

Mixed carboxylic-carbonic anhydrides were popular in peptide synthesis for the preparation of amides and esters of sensitive carboxylic acids, as this avoided the ‘acid chloride route’. In 1960, Weinstock and collaborators observed that acid azides could be formed under very mild conditions upon reaction of mixed anhydrides (for example, anhydride derived from the

carboxylic acid and ethyl chloroformate) with sodium azide. The azide could be converted to the isocyanate by Curtius rearrangement and hydrolyzed to the amine, without requiring the isolation of any of the intermediates. Employing this methodology, they converted *cis*-2-phenylcyclopropanecarboxylic acid to the corresponding amine, without isomerization to the *trans* isomer, which would not be possible employing the 'acid chloride route'.[49]

In 1972, Yamada and collaborators disclosed the use of diphenylphosphoryl azide (DPPA, **35**) and proposed its application for Curtius rearrangement.[14,52] The reagent is a stable, nonexplosive liquid, bp 157 °C (0.17 mmHg), and was easily prepared by reacting diphenylphosphorochloridate (**34**) with a slight excess of sodium azide in acetone at room temperature (Scheme 8A). More recently, a procedure for large-scale synthesis of analytically pure DPPA has also been reported by Wolff and Waldvogel.[53]

Yamada and co-workers proposed that DPPA could be used for direct conversion of carboxylic acids to urethanes, through the intermediate carboxylic acid azide (Scheme 8B). The reactivity of DPPA is due to the oxophilic nature of the phosphorus center. Since this discovery, literature has often referred this procedure as the "modified Curtius rearrangement".

Yamada also used DPPA as the azido group source for racemization-free peptide synthesis.[52] When the acylamino carboxylic acid was reacted with DPPA in the presence of triethylamine and the free amino acid or peptide ester hydrochloride at 0 °C, amide bond formation was accomplished. However, when the same transformation was carried out at high temperatures, the Curtius rearrangement would take place, forming the isocyanate, and eventually resulting in formation of urea with the amino acid. In 1993, Thompson and co-workers reported a direct conversion of activated alcohols to azides using DPPA.[54]

Overman and co-workers developed a general procedure for the preparation of dienyl carbamates using the Curtius rearrangement. A representative example is shown in Scheme 9 starting from carboxylic acid **36**, through acyl azide **37**, finally providing benzyl carbamate **38**.[55,56]

Weinstock also reported a procedure for the preparation of amines from mixed carboxylic-carbonic anhydrides, similar to Overman procedure; however, they used triethylamine as the base.[57,58]

More recently, Lebel and Leogane developed a single-pot Curtius rearrangement which proceeded under very mild conditions to afford Boc-protected amines (**39**, Scheme 10).[59]

Aliphatic carboxylic acids were converted to the alkyl azides in the presence of di-*tert*-butyl dicarbonate and sodium azide. These alkyl azides undergo the Curtius rearrangement in the presence of TBAB and zinc (II) triflate spontaneously at 40 °C to furnish the corresponding isocyanate. The isocyanate is then trapped by the *tert*-butanol present in the reaction mixture, which is the slowest step of the reaction. TBAB and zinc triflate also accelerate this process, probably due to the formation of a zinc carbamoyl bromide species.

An iron(II)-catalyzed Curtius-like rearrangement of hydroxamates to isocyanates was recently reported by Li and co-workers.[60] Iron-catalyzed cleavage of the N–O bonds of functionalized heteroauxin hydroxamates (**40**) resulted in an iron-nitrenoid complex (**41**), which then decomposed to form the isocyanates (**43**) (Scheme 11).

Among a few other procedures developed for the Curtius rearrangement, trapping of the isocyanate with 2-trimethylsilylethanol, leading to trimethylsilylethyl carbamate intermediates[19] and radical azidonation of aldehydes[61,62] were also reported. A new protocol for the Curtius rearrangement was reported by Augustine and co-workers describing the conversion of carboxylic acids to carbamates in the presence of propylphosphonic acid anhydride (T3P®) and azidotrimethylsilane in a single step.[63] A one-pot domino reaction for the conversion of acrylic acid derivatives to novel photochromic oxazines was developed by Zhao and Carreira.[64] Recently, Ley and co-workers developed a modular mesofluidic flow reactor for performing Curtius rearrangement as a continuous flow process.[65]

4. Application of Curtius rearrangement in development of synthetic methodologies

Knoechel and co-workers developed a copper-catalyzed anti S_N2' allylic substitution reaction on pentafluorobenzoates of trisubstituted allylic alcohols (**44**) to generate quaternary carbon centers with high stereoselectivity (**45**).[66] These products could be converted to isocyanates (**46**) and amines (**47**) possessing a tertiary chiral center with complete retention of configuration (Scheme 12).[67]

A convenient synthesis of orthogonally protected *N*(α)-Boc_2-*N*(β)-Cbz-2,3-diaminopropionic acid (DAP, **49**) was developed by Appella. DAP is a frequently used probe for studying protein structure and function. The Curtius rearrangement was used as a key step to introduce the 3-amino group on acid derivative **48**. This strategy was much less expensive and time-consuming compared to previous reported methods (Scheme 13).[68]

Curtius rearrangement has also been applied to the synthesis of optically active cyclopropylamine derivatives. Alkaline hydrolysis of cyclopropane carboxylic acid esters or amides (eg. **50**) furnished the free acid, which subsequently underwent Curtius rearrangement to yield cyclopropylamines (eg. **51**) (Scheme 14A).[69,70] Another approach was the Sharpless oxidative degradation of the phenyl group of cyclopropane carboxylic acid ester (eg. **52**), followed by Curtius rearrangement, thus proving cyclopropylamine derivatives (eg. **53**) (Scheme 14B).[71]

Curtius rearrangement has also found application in the synthesis of species containing a metal-nitrogen double bond, through the thermolysis/photolysis of the corresponding azides, [72] in the thermolysis of silicon azides to give sila-imines, in the photolysis of germanium isologues,[73,74] and phosphinic azides,[75] and in the photolytic rearrangement of penta-coordinate phosphorus species.[76]

A highly effective chiral auxiliary was developed by Ghosh and co-workers for asymmetric alkylation and asymmetric *syn*-aldol reactions. The β-ketoester **54** was subjected to Baker's yeast reduction to provide alcohol **55**, followed by ester hydrolysis and Curtius rearrangement to furnish the cyclopentano-oxazolidinone chiral auxiliary **56** (Scheme 15).[77] Similarly, the chiral auxiliary *p*-menthane-3-carboxaldehyde was developed by Spino and collaborators using Curtius rearrangement as the key step.[78]

Taubinger and collaborators developed an interesting procedure for ring-opening of α-amino acid derived β-lactams with various *O*-, *N*- or *S*-nucleophiles. These compounds are of considerable interest on account of their possible utilization as peptidomimetics.[79] Reaction of lactam **57** with amino ester **58** in the presence of stoichiometric sodium azide afforded urea derivative **59** in good yield (Scheme 16).

A unique macrocyclization of unprotected peptide isocyanates was developed by Vinogradov and co-workers to prepare macrocyclic peptides of varying ring size, rigidity, topology and having a range of biological activities.[80] Peptides containing two glutamic acid γ-hydrazides (**60**) were converted to the acyl azides (**61**), and Curtius rearrangement of the acyl azides led to the corresponding isocyanates (**62**). The isocyanates reacted with bifunctional nucleophiles to furnish the unprotected peptide macrocycles (**63**), which were more stable than their linear analogs (Scheme 17).

The Curtius rearrangement was used to prepare spirocyclic and fused cyclic lactams (**66**) in an efficient manner. The isocyanates (**65**) formed upon the Curtius rearrangement of acids **64** underwent a cascade intramolecular nucleophilic addition through the enol carbon in the same pot (Scheme 18).[81]

5. Application of the Curtius Rearrangement in Total synthesis

5.1 Triquinacene

In 1964, Woodward and co-workers synthesized triquinacene (**70**) to gain information about the postulated phenomenon of homoaromaticity and the nature of homoallylic participation in olefin reactivity.[82] For their synthesis, they applied the Curtius rearrangement for the conversion of diacid **67** to *bis*-urethane **69**, which could be reduced to the corresponding *bis*-amine. The *bis*-amine oxide underwent Hofmann elimination to afford triquinacene (Scheme 19).

5.2 Haemanthidine

Hendrickson and co-workers utilized the Curtius rearrangement for the stereospecific insertion of the nitrogen in the total synthesis of haemanthidine (**74**).[83] For inserting the nitrogen into the molecule, it was envisioned that azide attack on the less hindered carbonyl of the anhydride **71**, followed by Curtius rearrangement would give the required product. However, azide ring opening was not successful, and the methoxide ion attacked the more hindered carbonyl, leading to the thermodynamic product. The free acid could then be converted to the acid chloride, followed by acyl azide, which was then subjected to the Curtius rearrangement to furnish the isocyanate **72**. The isocyanate was cyclized to the

lactam **73** by polyphosphoric acid, and the lactam was converted to haemanthidine in a few steps (Scheme 20).

5.3 Saxitoxin

Kishi et al. used the Curtius rearrangement for the first total synthesis of *d,l*-saxitoxin (**77**).[84] The thiourea ester **75** was converted to the thiourea urea **76**, which could be converted to saxitoxin in a few more steps (Scheme 21).

5.4 Colchicine

Evans et al reported the total synthesis of (±)-colchicine (**81**), where the amine functionality was introduced via a Curtius rearrangement.[85] Treatment of carboxylic acid **78** with DPPA and triethylamine in *t*-butyl alcohol gave carbamate **79**. The Boc group was removed with simultaneous hydrolysis of the ether to provide (±)-desacetylcolchicine **80**, which was converted to (±)-colchicine (Scheme 22).

5.5 Streptonigrin

The antitumor antibiotic streptonigrin (**84**) was synthesized in an efficient manner by Kende and co-workers, where one of the amine groups was introduced by the Yamada modification of the Curtius rearrangement.[86] Similarly, in the synthesis of streptonigrone (**87**) by Boger and co-workers, the pyridine C5 amine was introduced by the Shioiri-Yamada modification of the Curtius rearrangement.[87] In this case, the intermediate isocyanate was found to be very stable. Lithium hydroxide mediated hydrolysis provided the free amine **86**. Interestingly, when the Curtius reaction was attempted without the MOM protection, the free hydroxyl attacked the acyl azide intramolecularly to form the corresponding lactone, before the rearrangement could take place. A similar strategy was also used by Ciufolini and co-workers in their total synthesis of streptonigrone (Scheme 23).[88]

5.6 Camptothecin

Vollhardt developed a method for the synthesis of 5-indolizinones by the cycloaddition of isocyanatoalkynes with alkynes through a cobalt-catalyzed reaction (Scheme 24).[89] They also applied this to the total synthesis of antitumor alkaloid camptothecin (**91**). The isocyanatoalkyne (**88**) was prepared by the Curtius rearrangement from the corresponding carboxylic acid.[89]

5.7 (−)-Huperzine A

(−)-Huperzine A (**93**) diffuses across the blood-brain barrier and is a selective, reversible inhibitor of acetylcholinesterase (AChE), used to increase the levels of cerebral acetylcholine for the treatment of symptomatic Alzheimer's disease.[90,91] (−)-Huperzine A was found to protect neuronal and glial cells against the cytotoxicity of β-amyloid plaques.[92]

Kozikowski and collaborators developed an enantioselective synthesis of (−)-huperzine A. In the last step of the synthesis, Curtius rearrangement of carboxylic acid **92** furnished (−)-huperzine A (Scheme 25).[93] (+)-Huperzine A was also synthesized following the same protocol. *In vitro* studies revealed (−)-huperzine A to be 33 times more potent than its

enantiomer. Fukuyama also introduced the amino group in (−)-huperzine A through a Curtius rearrangement.[94] However, he used DPPA for converting the carboxylic acid to the acyl azide, and trapped the isocyanate with methanol to obtain the corresponding methyl carbamate. Recently, Leman and co-workers proposed the synthesis of isotopically labelled (−)-[d_3]huperzine A through a Curtius rearrangement.[95]

5.8 (+)-Calyculin A

For the synthesis of the C_{26}–C_{32} γ-amino oxazole fragment of (+)-calyculin A (**97**), the Curtius rearrangement was utilized to introduce the nitrogen that formed the γ-amine, and ultimately led to the amide bond in (+)-calyculin A.[96] As shown, Curtius rearrangement of acid **94** efficiently installed the C_{32} amino group in protected form as in intermediate **95**. This latter was then converted into the required C_{26}–C_{32} γ-amino oxazole fragment **96** for the synthesis of (+)-calyculin A (Scheme 26).

5.9 (+)-Zampanolide

For the total synthesis of the nonnaturally occurring (+)-zampanolide (**100**), Curtius rearrangement was employed to install the *N*-acyl hemiaminal moiety.[97,98] The one-pot Curtius rearrangement protocol of Yamada using DPPA led to decomposition of the alkoxy acid. Therefore, the α-alkoxy acid **98** was converted to the acyl azide following Weinstock's procedure.[49] Curtius rearrangement of the azide formed the isocyanate, which was captured with 2-(trimethylsilyl)-ethanol to afford the α-alkoxy Teoc-carbamate **99** with complete retention of configuration (Scheme 27).

5.10 Salicylihalamide A

Brabander and collaborators synthesized salicylihalamide A (**104**) and its congeners, which are potent vacuolar (H^+)-ATPase inhibitors for possible treatment of osteoporosis and cancer.[99] The salicylihalamide class of compounds contain a highly unsaturated *N*-acyl enamine side chain. This was introduced by addition of metallo-hexadiene (**103**) to an *E*-alkenyl isocyanate. The isocyanate **102** was derived from the corresponding α,β-unsaturated carboxylic acid **101** via a Curtius rearrangement (Scheme 28).

5.11 (±)-Gelsemine

Overman and co-workers devised an aza-Cope rearrangement-Mannich cyclization sequence for construction of complex tertiary amines.[100] For synthesis of the precursors for the aza-Cope rearrangement, the Curtius rearrangement was used. Curtius rearrangement of carboxylic acid **105**, followed by trapping the isocyanate with PMB-alcohol yielded the *p*-methoxybenzyl carbamate (Moz) **106**, which was converted to aza-Cope rearrangement precursor **107** by standard synthetic manipulations. Base-promoted aza-Cope rearrangement, followed by quenching of the rearrangement product with methyl chloroformate, and cleavage of the resulting carbonate afforded carbamate **108**. Incorporation of bromine followed by reflux in TFA afforded azatricyclo[4.4.0.0]decanone **109**, an advanced intermediate for the total synthesis of (±)-gelsemine (**110**) (Scheme 29).

5.12 Methoxatin

Weinreb and co-workers described the first total synthesis of the bacterial coenzyme, methoxatin (**113**), where they used the Curtius rearrangement to introduce the nitrogen towards the beginning of the synthesis.[101] Curtius rearrangement of benzoic acid **111**, derived from 2,3-dimethoxytoluene, led to aniline **112**, which was converted to the required pyrroloquinoline quinone structure **113** through a series of steps (Scheme 30).

5.13 (+)-Sinefungin

Nucleoside antibiotic sinefungin (**118**) was synthesized by Ghosh and co-workers starting from *D*-ribose.[102] Carboxylic acid **115** was prepared using a highly diastereoselective allylation as the key step. The C-6 amine was then introduced by a Curtius rearrangement of carboxylic acid **115**, which proceeded with retention of configuration. The C-9 stereogenic center was set by a rhodium chiral bisphosphine-catalyzed asymmetric hydrogenation of an α-(acylamino)acrylate derivative. Anomeric adenosylation using Vorbruggen's protocol completed the total synthesis of (+)-sinefungin (Scheme 31).

5.14 AI-77-B

Ghosh and co-workers reported the synthesis of the gastroprotective agent AI-77-B (**122**) in a highly stereoselective manner, using an ester-derived titanium-enolate mediated *syn*-aldol reaction.[103] The β-hydroxy acid derived from **119** was converted to the β-amino acid moiety using the Curtius rearrangement at the key step. Oxazolidinone **120** was converted to acid **121** by applying Dondoni's aldehyde homologation as a key step. Acid **121** was then extended to complete the synthesis of AI-77-B (Scheme 32).

5.15 Brostallicin

Beria and collaborators proposed the synthesis of distamycin-like derivatives as novel cytotoxic DNA minor groove binders.[104] Brostallicin behaves as a DNA minor grove binder active against a broad spectrum of tumor cell lines with an excellent cytotoxicity and myelotoxicity ratio. Synthesis of brostallicin (**126**) has been achieved by these authors starting from the antibiotic distamycin A (**123**). Brostallicin behaves as a DNA minor groove binder active against a broad spectrum of tumor cell lines with an excellent cytotoxicity/ myelotoxicity ratio. A key Curtius rearrangement was carried out on the carboxylic acid **124** obtained from distamycin. The intermediate isocyanate was efficiently trapped by the neighboring carboxamide functional group, to furnish the acyl imidazolidinone **125** in 62% yield (Scheme 33). This represents a practical application of intramolecular isocyanate trapping by a carboxamide in the degradation of an oligopeptide natural product.[104]

5.16 Belactosin A

Belactosin A (**131**) and its analogs are known to be potential antitumor agents and have also shown to effect proteasome inhibition. An efficient route was developed by Armstrong and co-workers for the stereocontrolled synthesis of the unique 3-(*trans*-2-aminocyclopropyl)alanine amino acid **130** present in the enantiomer of the molecule.[105] The Wadsworth-Emmons cyclopropanation, which is the reaction of a protected glycidol with triethyl phosphonoacetate, was used to access cyclopropanecarboxylate **128**. Curtius

rearrangement was applied to convert the cyclopropane derivative **128** to aminocyclopropane **129**, which was then converted to the required amino acid in a few steps (Scheme 34).

5.17 Himandrine skeleton

The hexacyclic himandrine skeleton **135** was prepared starting from benzobicyclooctene **132**. Diels-Alder cycloaddition of **132** afforded carboxylic acid **133**, which was transformed via the Curtius rearrangement to carbamate **134**. Carbamate **134** was then converted to the himandrine skeleton, using a Birch reduction, an intramolecular nucleophilic amination and a Pd-catalyzed alkene amination as the key steps (Scheme 35).[106]

5.18 Welwitindolinones

Rawal and co-workers described a synthesis of the core bicylco[4.3.1]decane ring system of welwitindolinones (**139**).[107] *N*-methylwelwitindolinone C isothiocyanate is known to reverse multidrug resistance (MDR) in chemotherapeutic cancer treatment.[108] The authors used an intramolecular Pd-mediated enolate arylation to construct the bicyclic skeleton **137**. The bridgehead methyl ester served as the masked form of the isocyanate unit, which was introduced in the last step by the Curtius rearrangement from the corresponding carboxylic acid **138** (Scheme 36).

5.19 Diisocyanodociane

A formal total synthesis of diisocyanoadociane (**143**), a potent antimalarial diterpenoid, was reported by Mander and co-workers.[109] As shown, phenanthrenoid **140** was converted to pyrene **141** by an intramolecular Michael reaction. To maintain stereochemical control of the insertion of the isonitrile groups, they applied double Curtius rearrangement of the corresponding acyl azides to furnish the diamine **142**. The diamine was converted to diisocyanoadociane using a previously reported route (Scheme 37).

5.20 Mycalamide A

A novel $Yb(OTf)_3$-TMSCl catalytic system was developed for a cross-aldol reaction without epimerization for the synthesis of **144**. Cyclization of **144** followed by stereoselective allylation furnished trioxadecalin ring system **145**. To prepare the aminal moiety, alcohol **145** was oxidized with Jones' reagent to provide the corresponding carboxylic acid. Curtius rearrangement of the carboxylic acid stereoselectively introduced the required aminal to afford the Teoc-carbamate **146**, thus installing the nitrogen functionality for the amide in mycalamide A (**147**) (Scheme 38).[110]

5.21 Altemicidin skeleton

Altemicidin (**152**) is a monoterpene alkaloid possessing acaricidal activity. It also inhibits tumor cell growth. Kan et al reported a stereocontrolled construction of the core framework of altemicidin.[111] The bicyclo[3.3.0] scaffold **148**, obtained by an intramolecular C-H insertion reaction, was converted to the cyclic enamide-containing carboxylic acid **149** through a series of steps. To incorporate the nitrogen atom onto the quaternary carbon, the Curtius rearrangement was employed. The in situ generated isocyanate was trapped by the primary alcohol, resulting in the formation of an oxazolidinone derivative **150**, thus

generating the β-hydroxy α-disubstituted-α-amino acid framework with the required stereochemistry. Functional group interconversions and introduction of the C1 unit into the enamide led to compound **151**, which represents the altemicidin skeleton (Scheme 39).[111]

5.22 Pancratistatin

Pancratistatin (**158**), a potent and selective anticancer agent, was synthesized by Cho et al. using the cycloaddition reaction of 3,5-dibromo-2-pyrone (**153**) with the β-silyl styrene derivative **154** as the key step. The cycloadduct **155** was converted to the corresponding carboxylic acid **156**, which upon Curtius rearrangement followed by treatment with sodium methoxide afforded carbamate **157**. Further functional group manipulations, including a modified Bischler-Napieralski reaction were then performed in order to complete the total synthesis of (±)-pancratistatin (Scheme 40). The same strategy was also used for the installation of the nitrogen atoms of (±)-α-lycorane (**159**), (±)-lycorine (**160**), and (±)-1-deoxylycorine (**161**).[112,113,114]

5.23 NP25302

NP25302 (**166**), an alkaloid displaying an acylaminotetrahydropyrrolizine core, was shown to inhibit the growth of chronic myeloid leukemia cells. It was synthesized by Robertson and co-workers using a 5-*endo*-dig *N*-cyclization and a Curtius rearrangement as the key steps.[115] The novel 5-*endo*-dig cyclization was applied to pyrrolidine derivative **162** and for the first time in the synthesis of a pyrrolizidine-type system. Alkaline hydrolysis of **163** with potassium hydroxide afforded the potassium carboxylate which was nucleophilic enough in DMF to react with DPPA producing the acyl azide **164**. Interestingly, when lithium hydroxide was used for the hydrolysis, the corresponding carboxylate was unreactive, even with ethyl chloroformate. The Curtius rearrangement was applied in order to achieve the isocyanate intermediate, however attempts to trap the isocyanate with an isobutenyl organometallic led to its rapid polymerization. The isocyanate was then converted to the corresponding amine, finally acylated with **165** to provide NP25302 (Scheme 41).[115]

5.24 Dievodiamine

The first total synthesis of racemic dievodiamine (**173**) was performed in a protecting-group-free manner by Taylor and co-workers.[116] Indole **167** was converted into lactam **168** by a Curtius rearrangement as the key step. The lactam was then heated with dimethyl anthranilate **169** in the presence of phosphorus oxychloride to afford dehydroevodiamine hydrochloride (**170**, DHED·HCl), which was converted to stannane intermediate **171** using an organometallic addition as the key step. Stille coupling with derivative **172** completed the total synthesis of (±)-dievodiamine (Scheme 42).

5.25 (−)-Lyconadin C

An enantioselective total synthesis of (−)-lyconadin C (**178**) was achieved by Waters and collaborators using a one-pot, tandem Curtius rearrangement/6−-electrocyclization to construct the 2-pyridone ring system.[117] Luciduline congener **174**, prepared through a Mannich-type cycloaddition, was converted to dienyl carboxylic acid **175** in a few steps. The carboxylic acid was converted to the acyl azide, and Curtius rearrangement of the acyl azide

afforded isocyanate **176**, which was strategically used for the 6−-electrocyclization in the same pot. The conjugated dienyl isocyanate served as the perfect substrate for the electrocyclic cyclization due to system planarity and optimal orbital alignment. When the intermediate acyl azide was heated to 80 °C, tandem Curtius rearrangement and 6−-electrocyclization resulted in the pyridone ring of lyconadin C (**177**). Deprotection of the carboxybenzyl group afforded enantiopure (−)-lyconadin C (Scheme 43).

5.26 (±)-Lundurine B

Nishida and co-workers reported the total synthesis of (±)-lundurine B (**182**).[118,119] The cyclopropane-fused indoline was obtained by using the Curtius rearrangement as one of the key steps. Saponification of the lactone-ester **179** yielded the lactone-carboxylic acid, that furnished the Boc-protected amine upon Curtius rearrangement. Bromination of the aromatic ring provided bromo-derivative **180** that was submitted to a copper-mediated cyclization to afford the tetracyclic compound **181**. This latter compound was finally converted into lundurine B after a series of further steps (Scheme 44).

5.27 Axamide-1 and axisonitrile-1

For the total synthesis of axamide-1 (**187**) and axisonitrile-1 (**188**), Piers and co-workers employed the Curtius rearrangement for introducing the nitrogen atom.[120] The carboxylic acid **183** was transformed into the acyl azide **184** by standard reactions. Curtius rearrangement of the acyl azide, followed by trapping the resulting isocyanate with 2-trimethylsilylethanol, furnished the carbamate **185** with retention of configuration. Treatment of **185** with TBAF afforded the primary amine **186**, which was then formylated to provide (±)-axamide-1. Dehydration of (±)-axamide-1 furnished crystalline (±)-axisonitrile-1 (Scheme 45).

5.28 Aspeverin

Aspeverin (**192**), a prenylated indole alkaloid, was synthesized using the Curtius rearrangement as a key step.[121] The bicyclic urethane linkage functionality is distinctive of this class of natural products. To this aim ester **189** was converted into the corresponding acyl azide **190**. Following thermolysis in the presence of 2-(trimethylsilyl)ethanol yielded the desired carbamate **191**. A unique iodine(III)-mediated cyclization and a novel approach to introduce the geminal dimethyl group were then used to finalize the desired bicyclic urethane linkage (Scheme 46).

5.29 Cylindricine alkaloid

The synthesis of the cylindricine alkaloid core (**198**) reported by Dalton and collaborators envisaged a key Curtius rearrangement step.[122,123] A Negishi coupling between the organozinc intermediate **193** and iododerivative **194**, followed by hydrolysis provided the carboxylic acid, finally converted into the desired isocyanate **195** upon Curtius rearrangement. A Rh(I)·CKphos catalyzed [2+2+2] cycloaddition of the alkenyl isocyanate **195** and alkyl alkyne **196** selectively provided the vinylogous amide indolizidinone cycloadduct **197**. The cycloaddition created a quaternary stereocenter with excellent enantioselectivity. The tricyclic core of the cylindricine alkaloids (**198**) was then finalized by

reduction with DIBAL-H and subsequent cyclization in the presence of potassium *t*-butoxide with excellent regioselectivity and enantioselectivity (Scheme 47).

5.30 (−)-Cephalotaxine core

For the enantioselective synthesis of (−)-cephalotaxine (**199**), one of the most efficient strategies involved the synthetic manipulation of derivatives of the (*R*)-1-azaspiro[4.4]nonane-2,6-dione system **200** (Scheme 48).[124]

For the synthesis of cephalotaxine, spiro lactam **204** was synthesized from optically active keto diester **201**. To differentiate the two ester groups, diester **201** was converted to bicyclic lactone **202**. The Curtius rearrangement was then carried out by converting the carboxylic acid to the corresponding acyl azide using DPPA, followed by rearrangement to the benzyl carbamate **203**. This was converted to the azaspirononane derivative **204** (Scheme 49).

5.31 (−)-Esermethole

Badiola and co-workers proposed a total synthesis of (−)-esermethole (**208**) involving a Curtius rearrangement step.[125] α-Hydroxyketone **205** underwent oxidative cleavage to furnish carboxylic acid **206**. The Curtius rearrangement of carboxylic acid afforded the corresponding methyl carbamate **207**, which underwent reductive cyclization on treatment with lithium aluminum hydride to furnish (−)-esermethole in high *ee* (Scheme 50).

The following examples show the construction of natural compounds containing *N,O*-aminals/hemiaminals through a stereoselective Curtius rearrangement, with retention of the stereochemistry at the α-carbon.

5.32 (+)-Psymberin (Irciniastatin A)

The marine sponge cytotoxin (+)-psymberin (irciniastatin A, **211**) was synthesized Smith and co-workers using a late-stage Curtius rearrangement to install the sensitive *N,O*-aminal moiety.[126] Curtius rearrangement of carboxylic acid **209** followed by trapping of the resulting amine isocyanate with 2-trimethylsilylethanol provided the Teoc-protected aminal **210**, which was converted to the natural product (+)-psymberin (Scheme 51).

5.33 Pederin

The acylaminal group at C-10 is a common structural feature in pederins and mycalamide classes of natural products. However, the C-10 aminal unit is reported to be unstable under acidic, basic and neutral conditions, leading to mixtures of the corresponding amide. Roush and co-workers developed a stereoselective synthesis of the trioxodecalin nucleus of mycalamide (**213**), encompassing a stereocontrolled insertion of the C(10) amine as a carbamate through the Curtius rearrangement (Scheme 52).[127]

In 2007, Rawal installed the nitrogen atom in pederin (**216**, a potent insect toxin, with anticancer properties) by a Curtius rearrangement, which proceeded stereospecifically.[128] Saponification of the ester **214**, followed by a Curtius rearrangement protocol provided the Teoc-protected pederamine (**215**) with complete retention of stereochemistry of the aminal group. Pederamine was then converted into pederin after few additional steps (Scheme 53).

5.34 Mycalamide B

A similar strategy was undertaken by Rawal et al. for the synthesis of mycalamide B (**220**).[129] However, final coupling of the amine with pederic acid chloride was not successful. An alternative route is shown in Scheme 54. As shown, hydrogenolysis of benzyl ether **217** and saponification of the ester were followed by treatment with DPPA and triethylamine, providing the corresponding acyl azide, which underwent the Curtius rearrangement upon heating. The resulting isocyanate **218** was trapped intramolecularly by the primary alcohol to yield the required cyclic carbamate **219**. The cyclic carbamate was converted to mycalamide B (Scheme 54). The use of “chemical handcuffs” to temporarily restrict portions of the molecule thus enabled the convergent synthesis of mycalamide B.

5.35 Echinocandin C

Messik and collaborators proposed a total synthesis of echinocandin C (**223**) featuring a stereoselective Curtius rearrangement step for the synthesis of the crucial *N*-acyl hemiaminal fragment **222**. Accordingly, treatment of the crude carboxylic acid **221** with isobutyl chloroformate and subsequent reaction with aqueous sodium azide produced the corresponding acyl azide, which was heated in the presence of 2-(trimethylsilyl)ethanol to afford the Teoc-protected *N*-acyl hemiaminal **222** in very good yield (Scheme 55).[130] A number of other syntheses of echinocandin C has also been reported.[131,132]

Conclusion

Although, the Curtius rearrangement was discovered more than a century ago, this reaction remains an important strategy for the synthesis of a wide variety of nitrogen-containing functionalities in organic synthesis. One of the intriguing aspects of the Curtius rearrangement is the transformation of acyl azide intermediate to isocyanate from carboxylic acid. Even though the reaction is extensively utilized, the mechanism of this reaction remains a subject of great interest. The reaction proceeds via a concerted mechanism and the rearrangement occurs with complete retention of stereochemistry of the migrating carbon. Thus, the stereochemical integrity of this rearrangement can be exploited for the generation of chiral nitrogen containing centers. The abundance of carboxylic acids and their relatively simple conversion to acyl azides also contribute to increasing the scope of this reaction. Over the years, numerous mild methods have been developed, mostly to be compatible with the functional groups present within the molecules. This review highlights the gradual development of Curtius rearrangement, and chemical methodologies adopted for the synthesis of isocyanates, amines and amine derivatives. Amine functionalities, such as urethanes, ureas and amides are widely prevalent in naturally occurring and therapeutically relevant biomolecules, therefore the Curtius rearrangement has been strategically applied to their synthesis. The review provides an overview of the applications of the Curtius rearrangement in total synthesis of natural products and their structural derivatives. The review also provides a broad picture of the Curtius rearrangement and we hope that it will stimulate further development, particularly in the areas of asymmetric synthesis and process development.

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Abbreviations

AChE	Acetylcholinesterase
Boc	*tert*-butyloxycarbonyl
CASSCF	Complete Active State SCF
DAP	*N*(α)-Boc$_2$-*N*(β)-Cbz-2,3-diaminopropionic acid
DCM	Dichloromethane
DHED·HCl	Dehydroevodiamine hydrochloride
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DNA	Deoxyribonucleic acid
DPPA	Diphenylphosphoryl azide
ESR	Electron spin resonance
LAH	Lithium aluminum hydride
MDR	Multidrug resistance
Moz	*p*-Methoxybenzyl carbamate
MS-CASPT2	Multi-State Complete Active State Perturbation Theory 2nd Order
PMB	*p*-Methoxy benzyl
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Teoc	2-Trimethylsilylethoxycarbonyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl chloride
T3P®	Propylphosphonic acid anhydride

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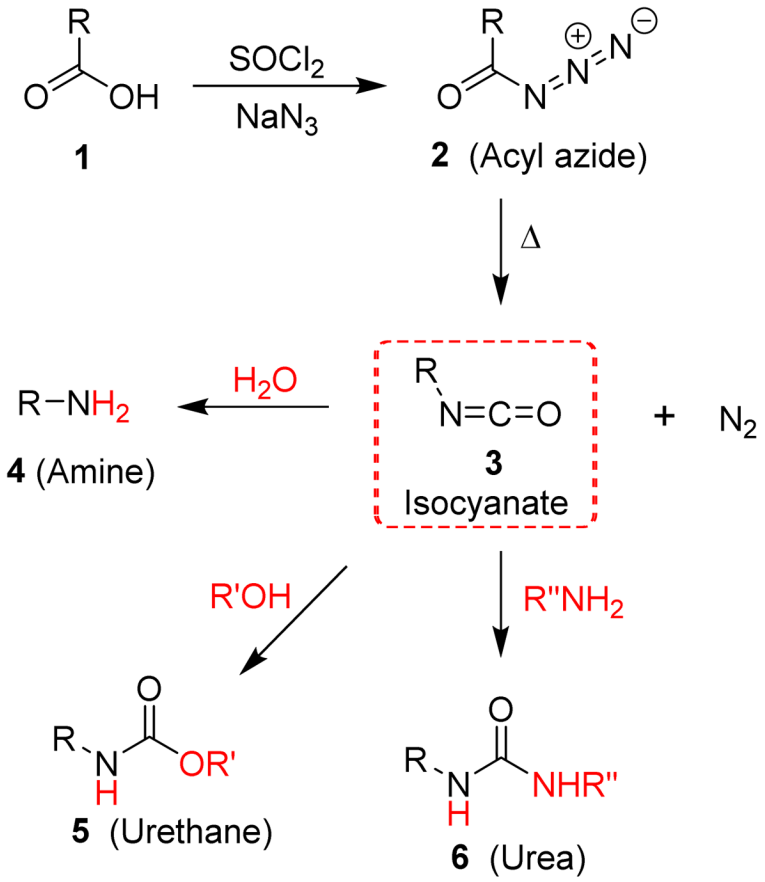


Fig. 1.
The Curtius rearrangement route to isocyanates, amines and amine derivatives.

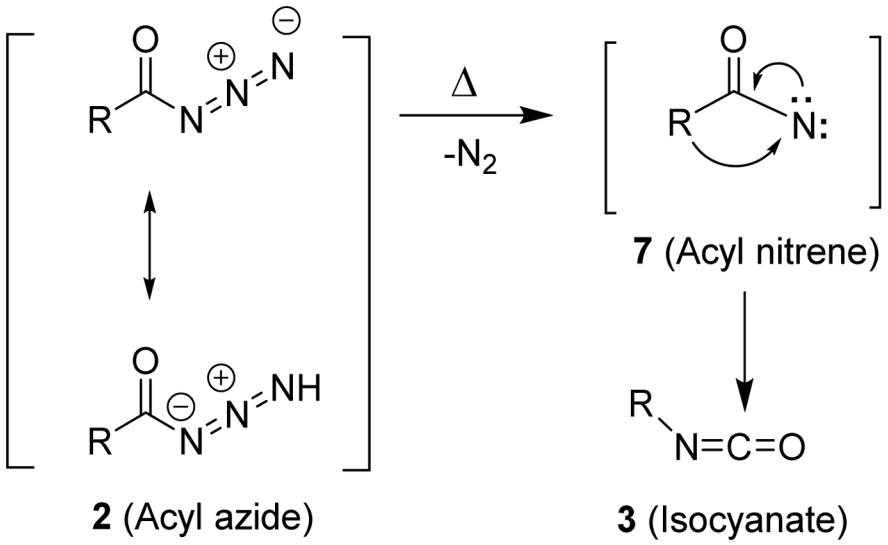
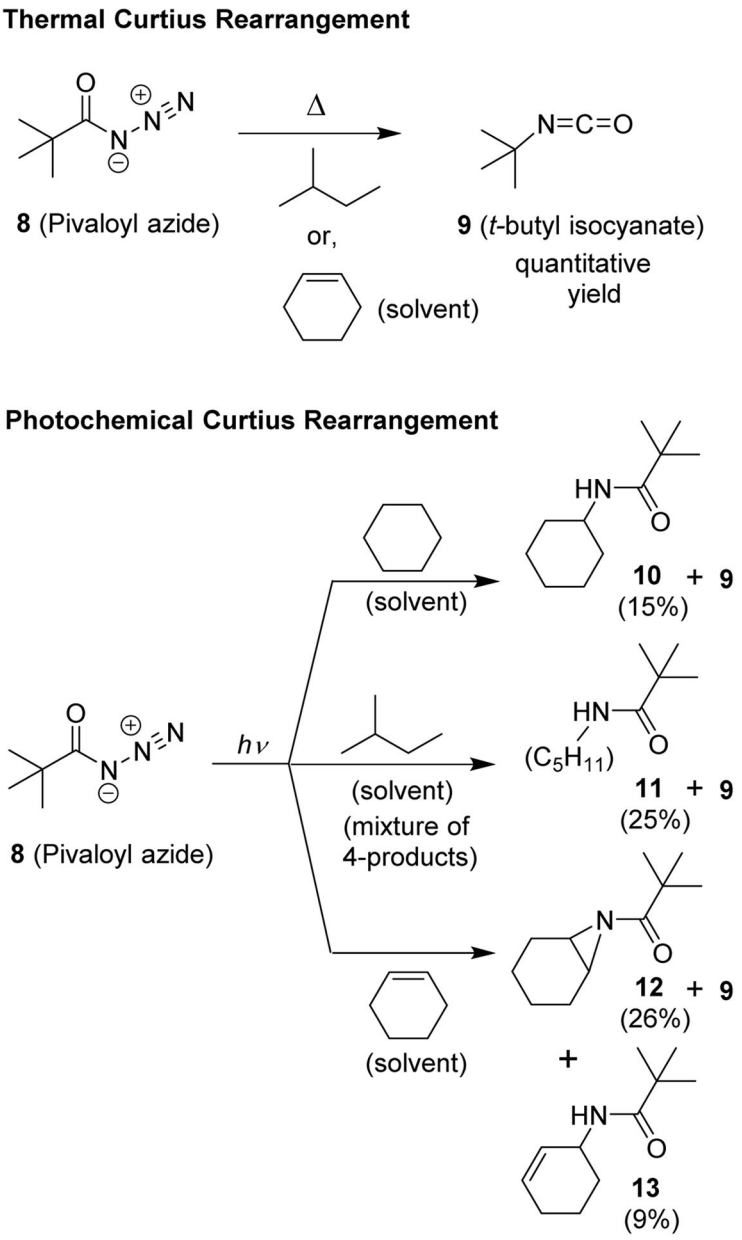
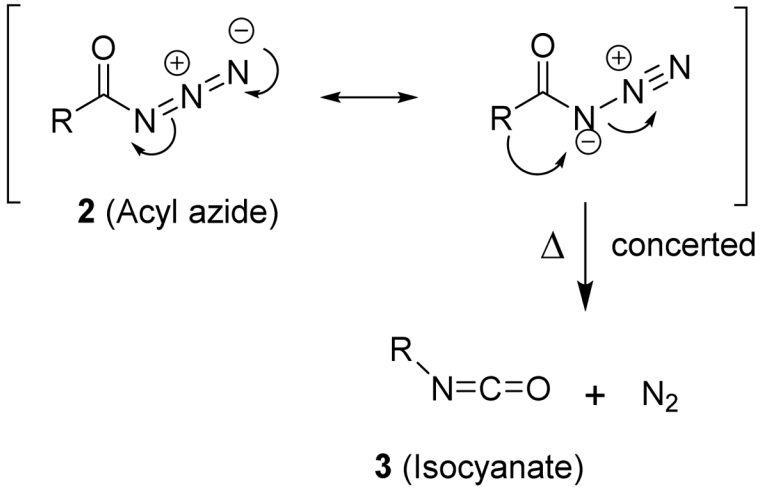


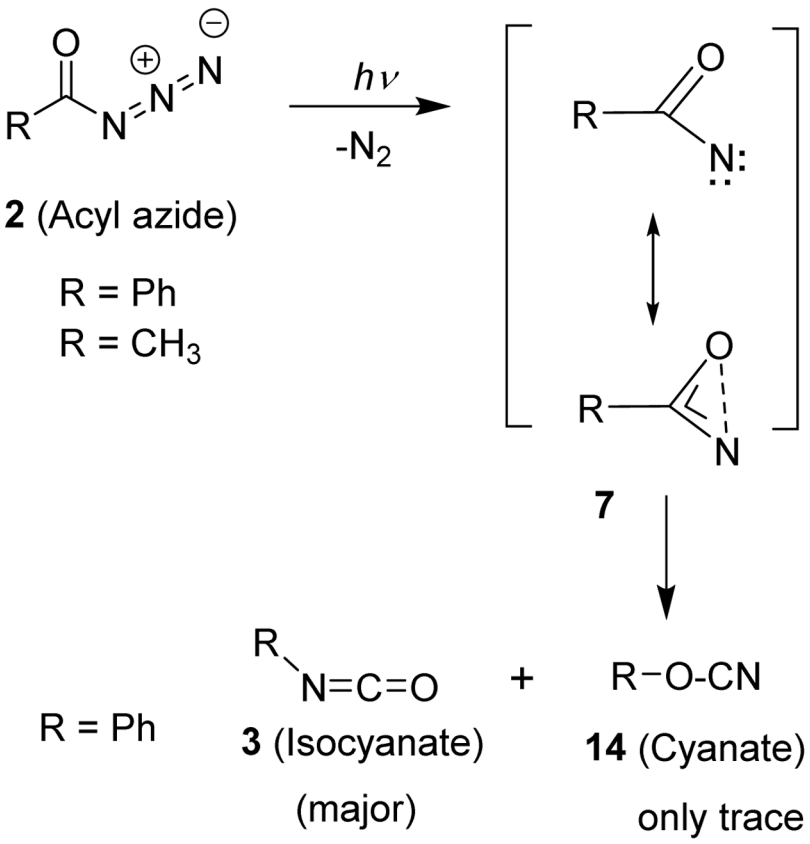
Fig. 2.
Stieglitz's mechanism via carbonylnitrene intermediate.



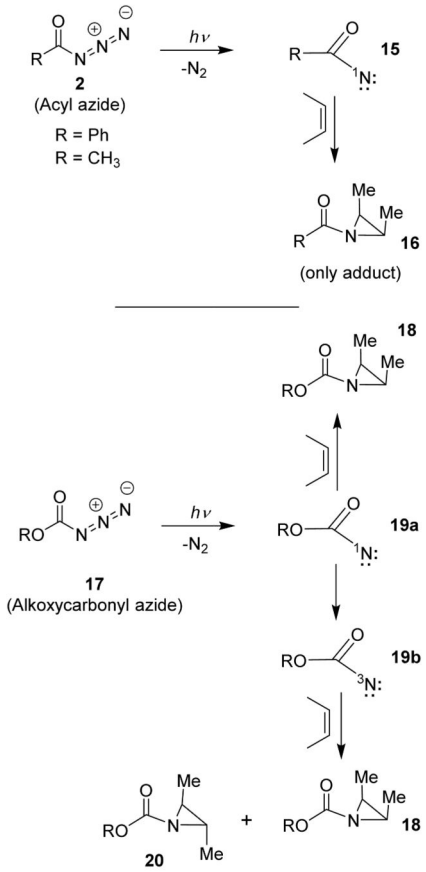
Scheme 1.
Thermal and photochemical decomposition of pivaloyl azide.



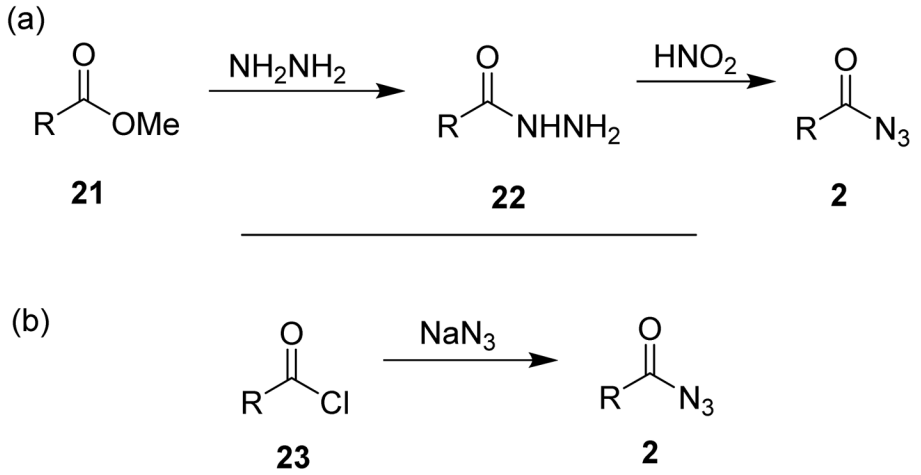
Scheme 2.
Concerted thermal Curtius rearrangement mechanism.



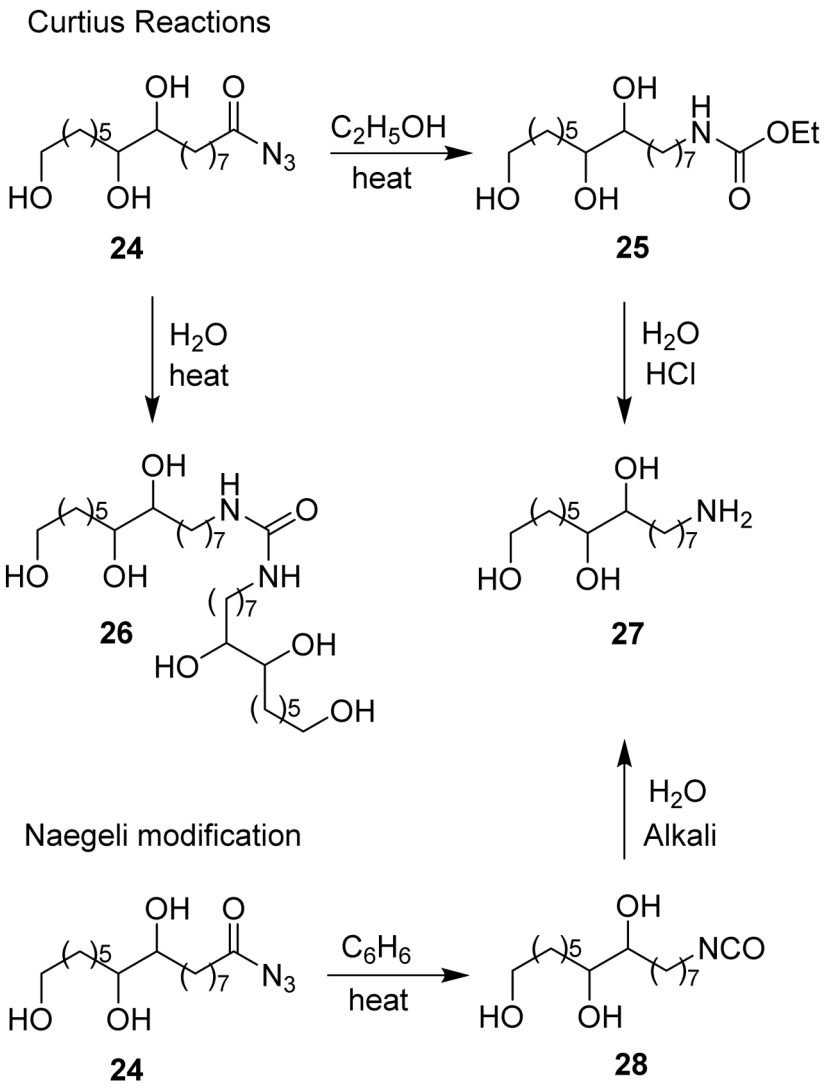
Scheme 3.
Photochemical formation of acylnitrenes.



Scheme 4.
Photolysis of alkoxycarbonyl azide.

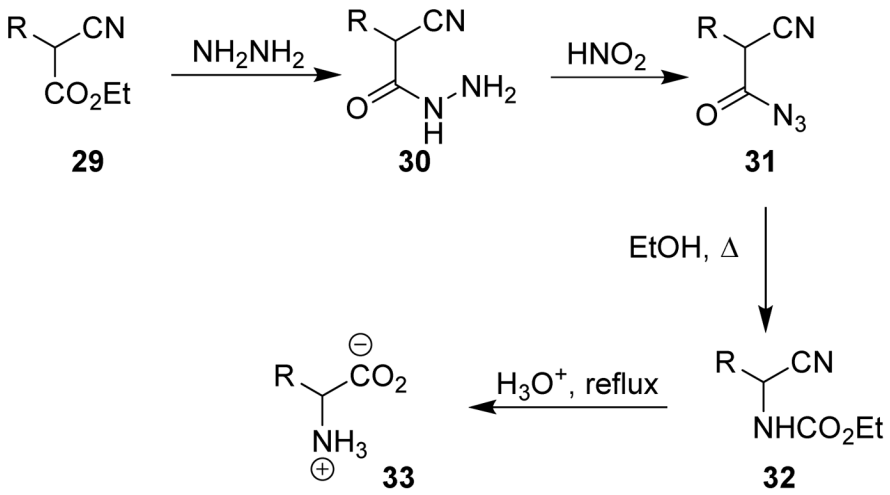


Scheme 5.
Preparation of acyl azides.

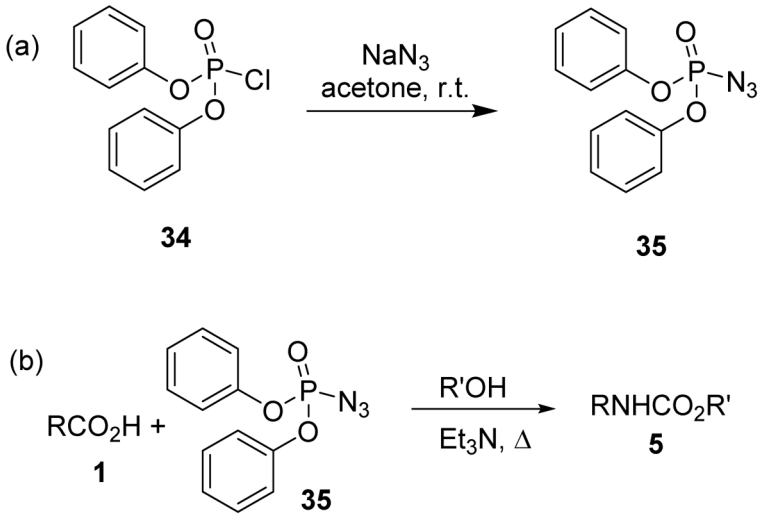


Scheme 6.

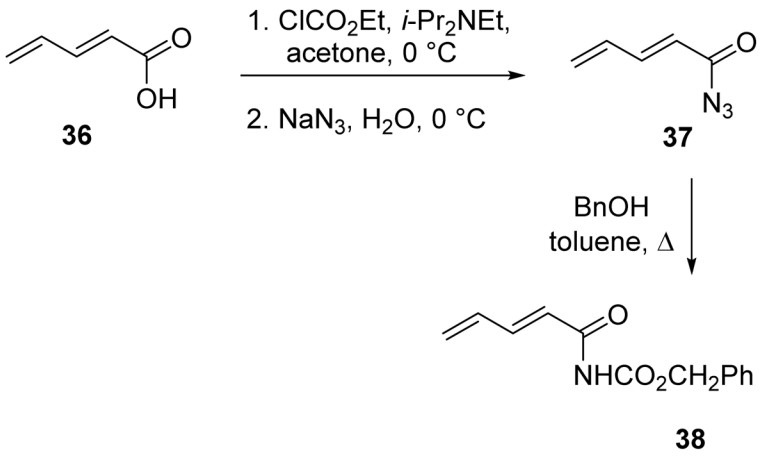
Preparation of 8,9,15-trihydroxypentadecylamine using the Naegeli modification.



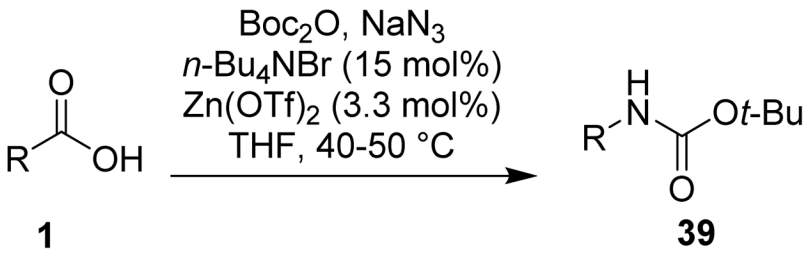
Scheme 7.
Synthesis of amino acid derivatives from α-cyanoacetic esters.



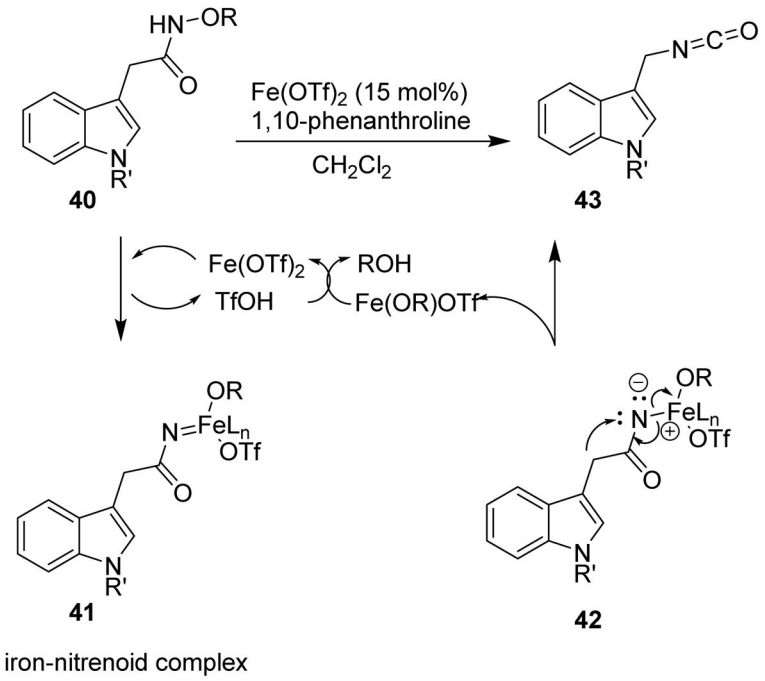
Scheme 8.
Synthesis of DPPA and modified Curtius rearrangement.



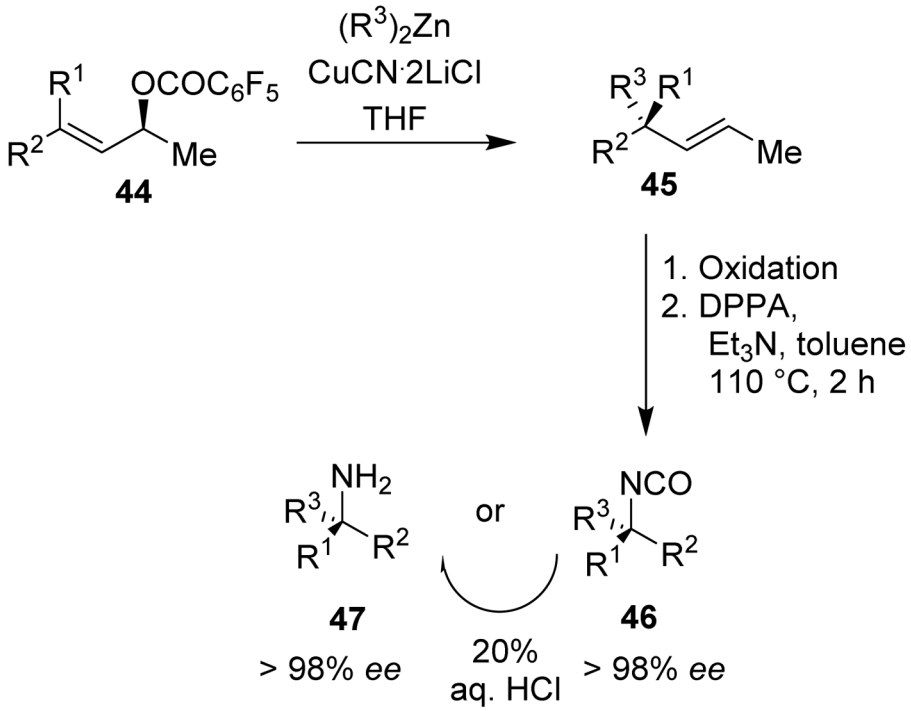
Scheme 9.
Overman procedure for the Curtius rearrangement.



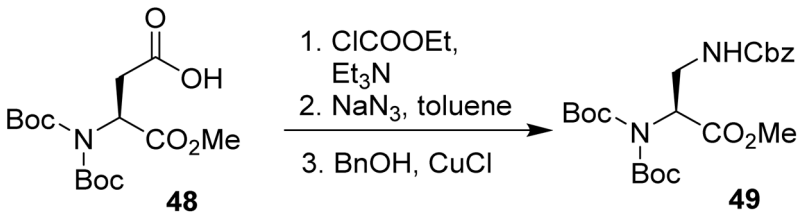
Scheme 10.
General procedure developed by Lebel.



Scheme 11.
Protocol for the Curtius rearrangement by Li and co-workers.

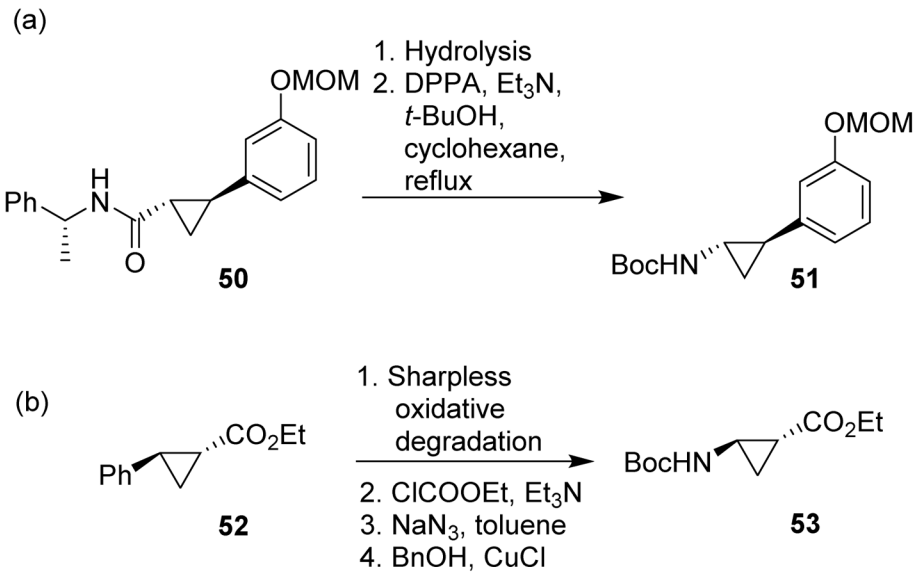


Scheme 12.
Knoechel protocol for quaternary carbon centers.

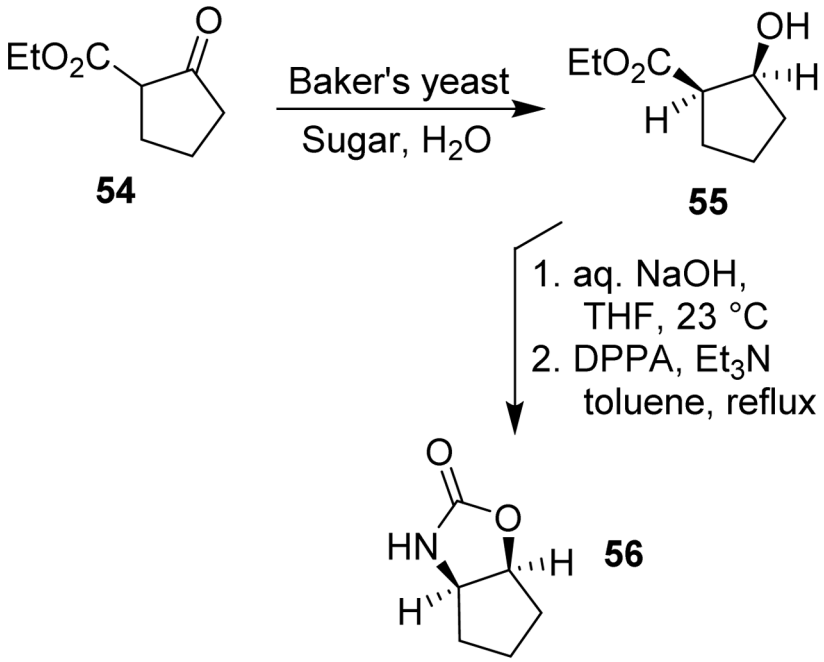


Scheme 13.

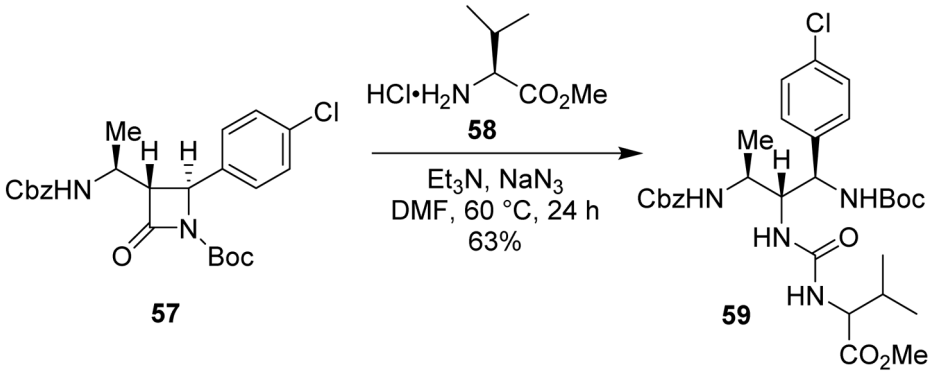
Synthesis of orthogonally protected diaminopropionic acid.



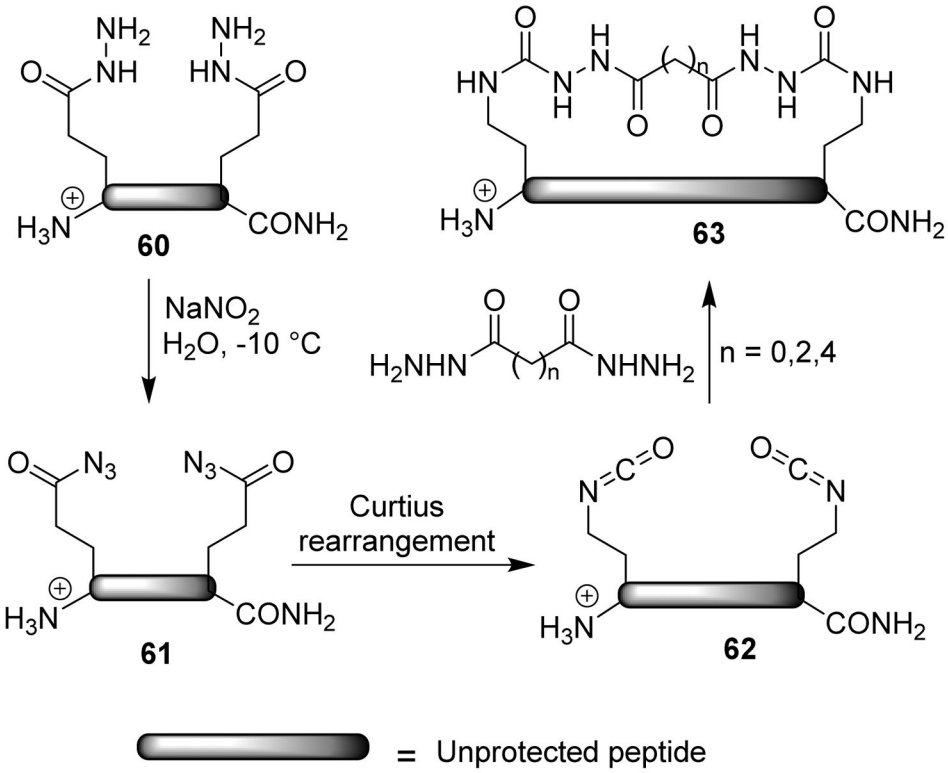
Scheme 14.
Synthesis of optically active cyclopropylamines.



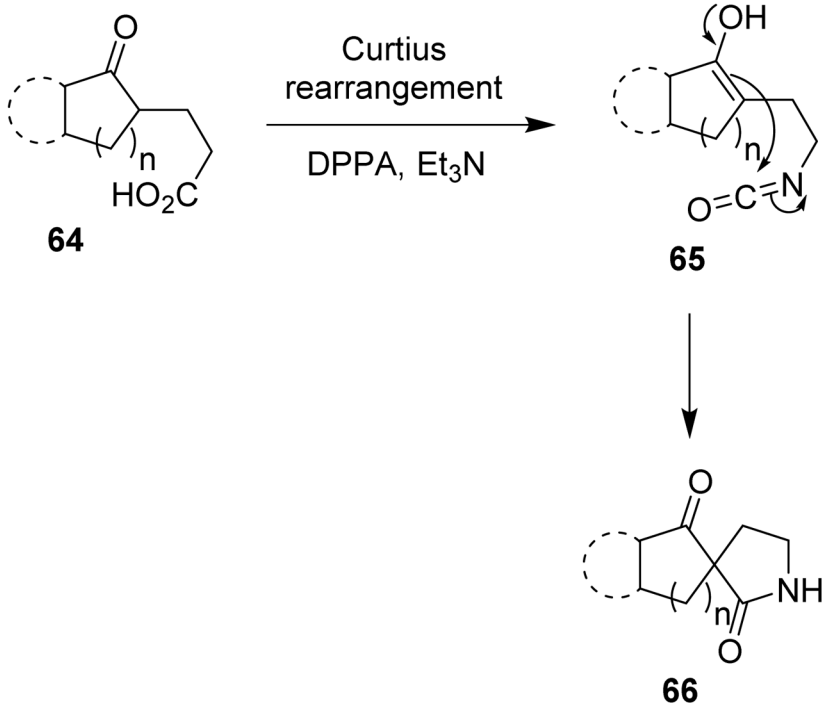
Scheme 15.
Synthesis of a cyclopentano-oxazolidinone.



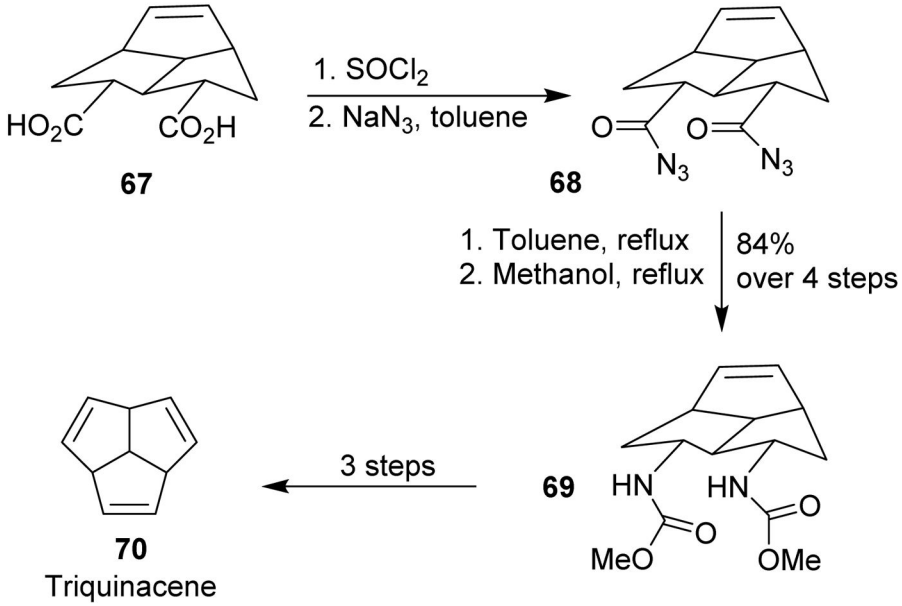
Scheme 16.
Synthesis of peptidomimetic derivatives.



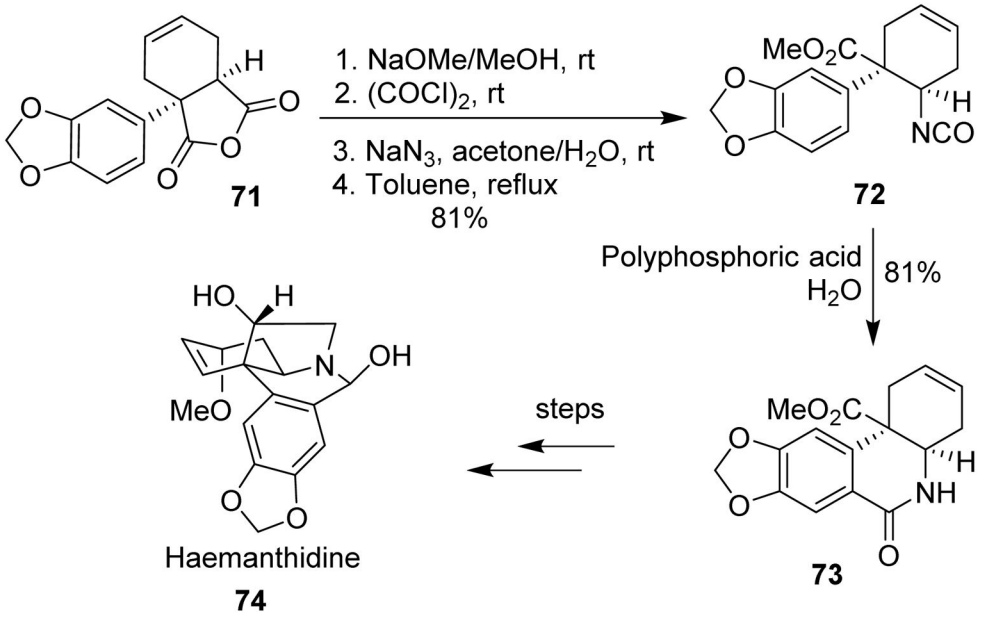
Scheme 17.
Synthesis of macrocylic derivatives.



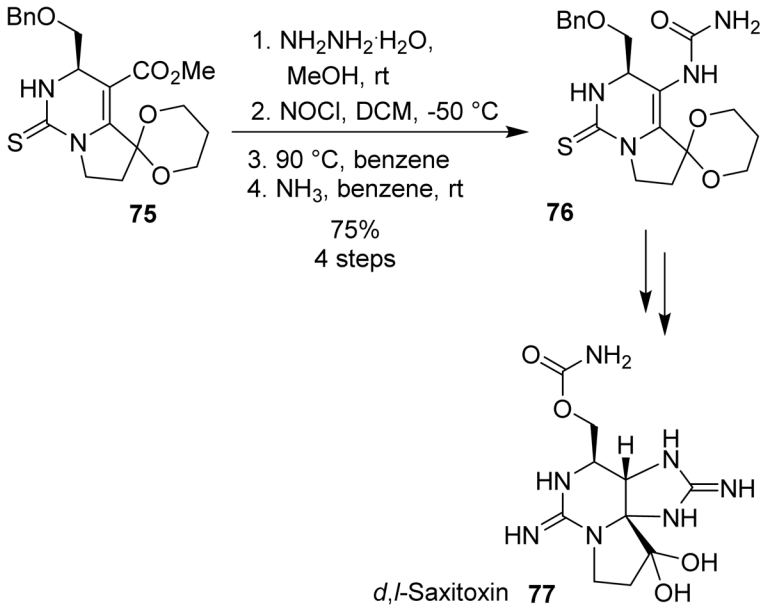
Scheme 18.
Synthesis of spirocyclic lactam derivatives.



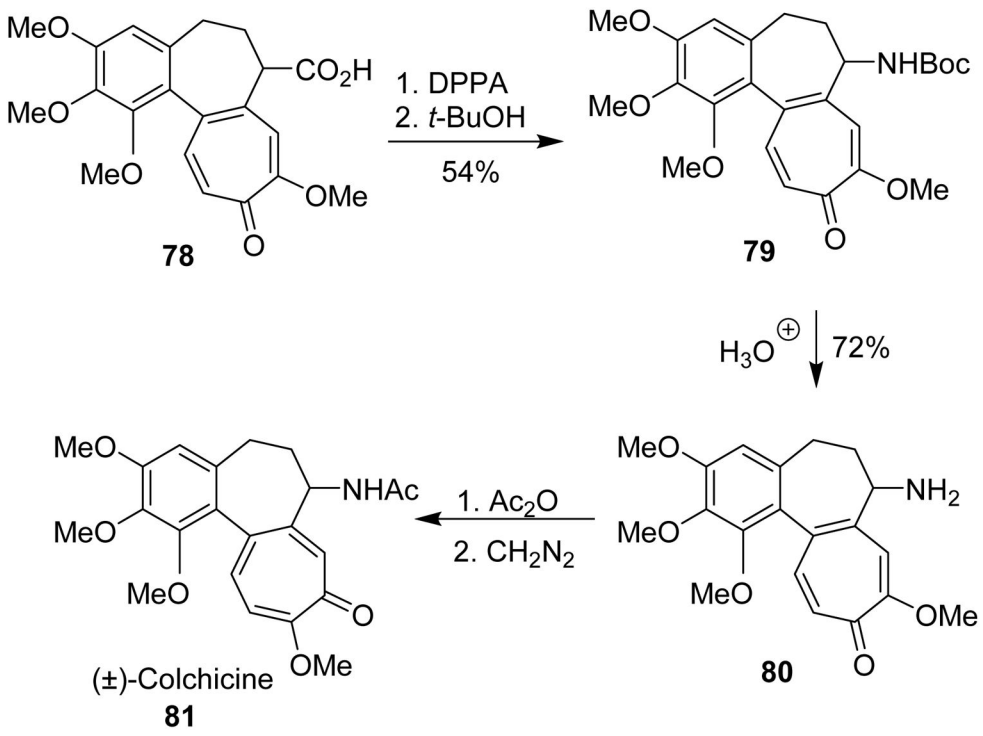
Scheme 19.
Synthesis of triquinacene.



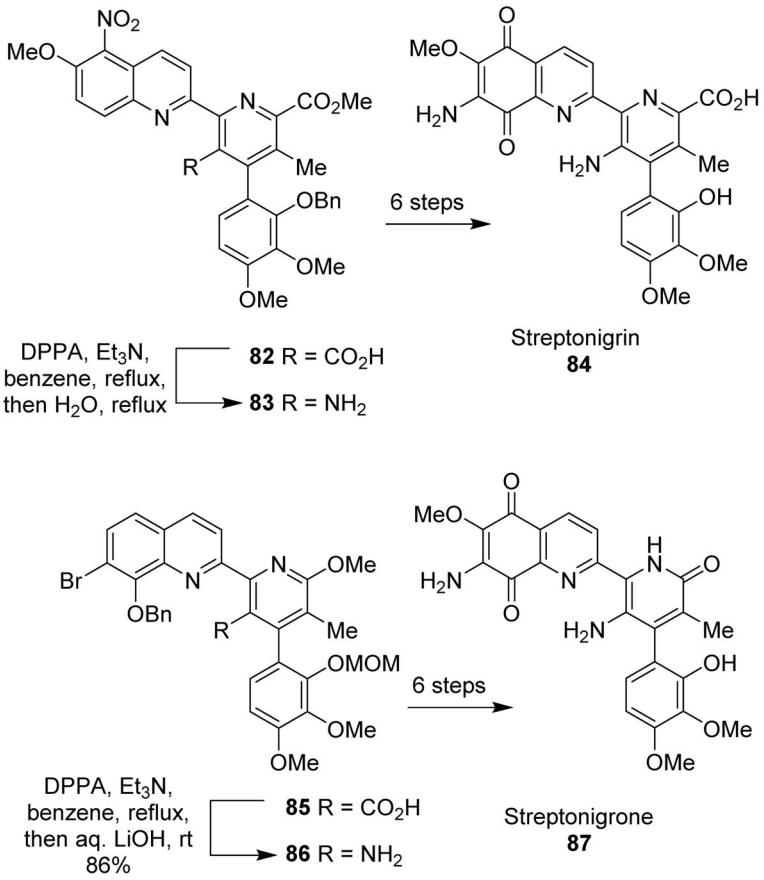
Scheme 20.
Synthesis of haemanthidine.



Scheme 21.
Synthesis of saxitoxin.

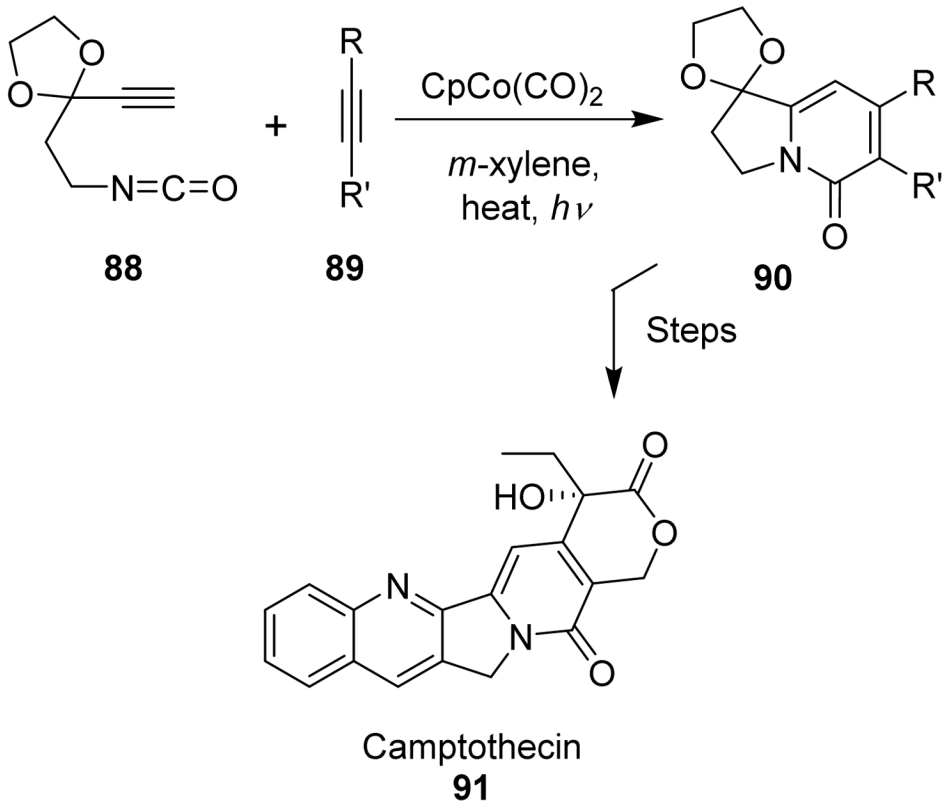


Scheme 22.
Synthesis of colchicine.

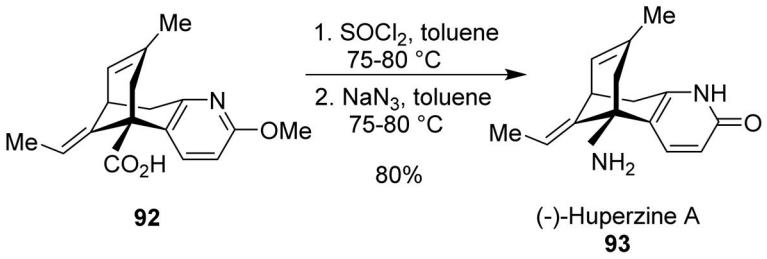


Scheme 23.

Synthesis of streptonigrin and streptonigrone.

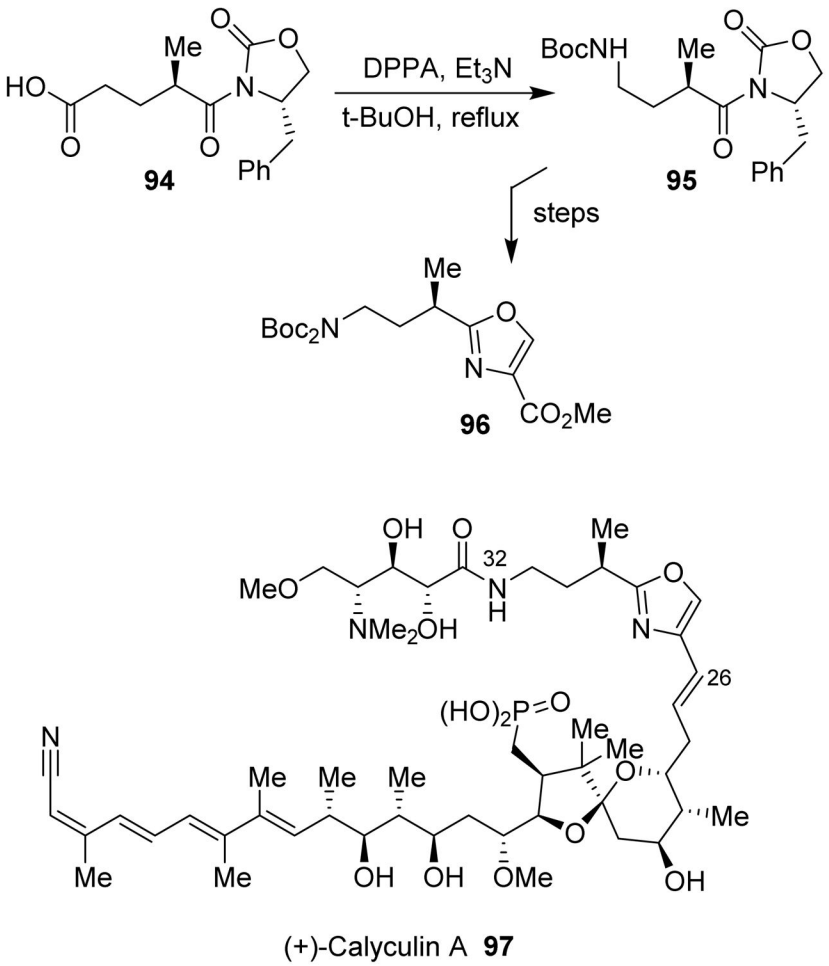


Scheme 24.
Synthesis of camptothecin.

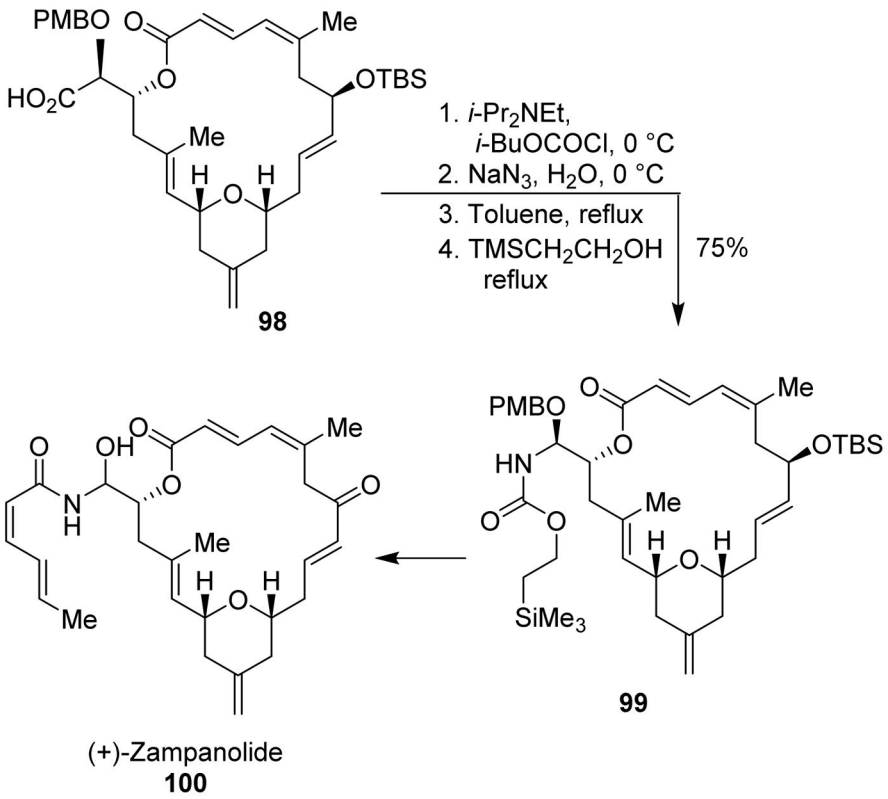


92 (-)-Huperzine A 93

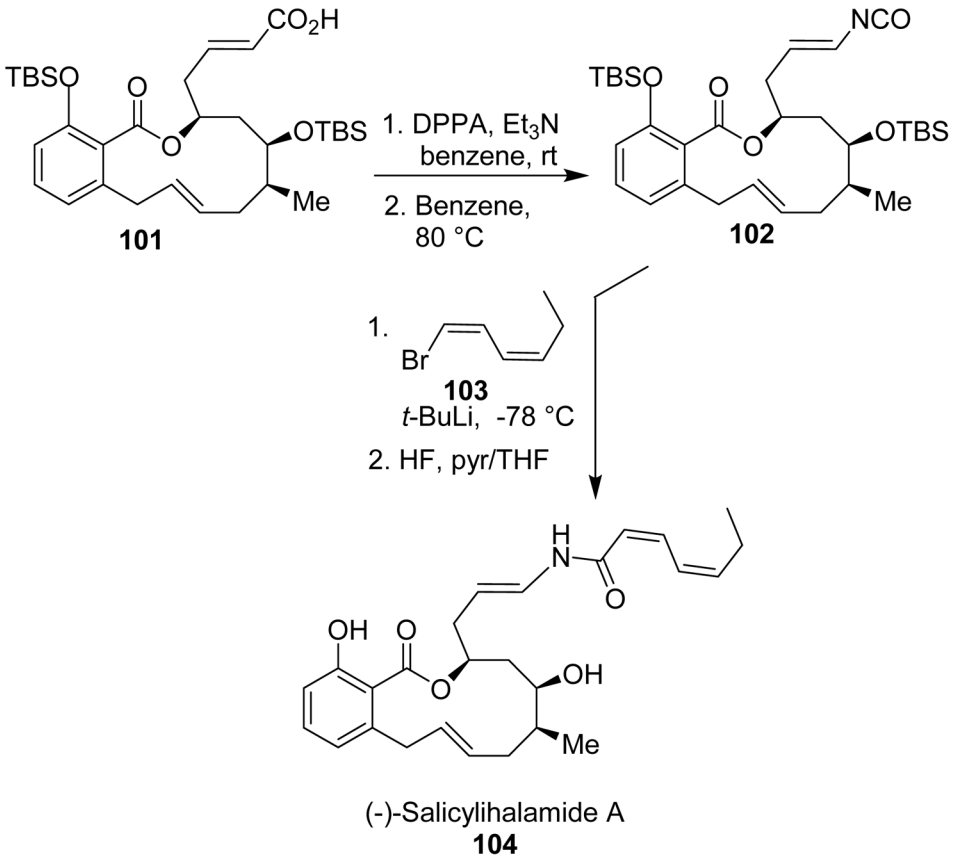
Scheme 25.
Synthesis of huperzine A.



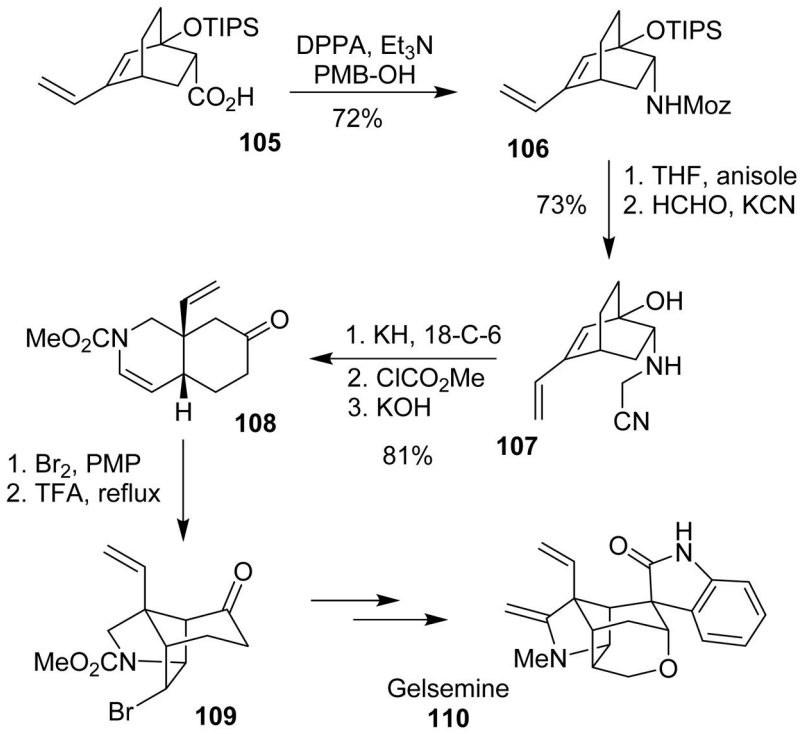
Scheme 26.
Synthesis of calyculin A.



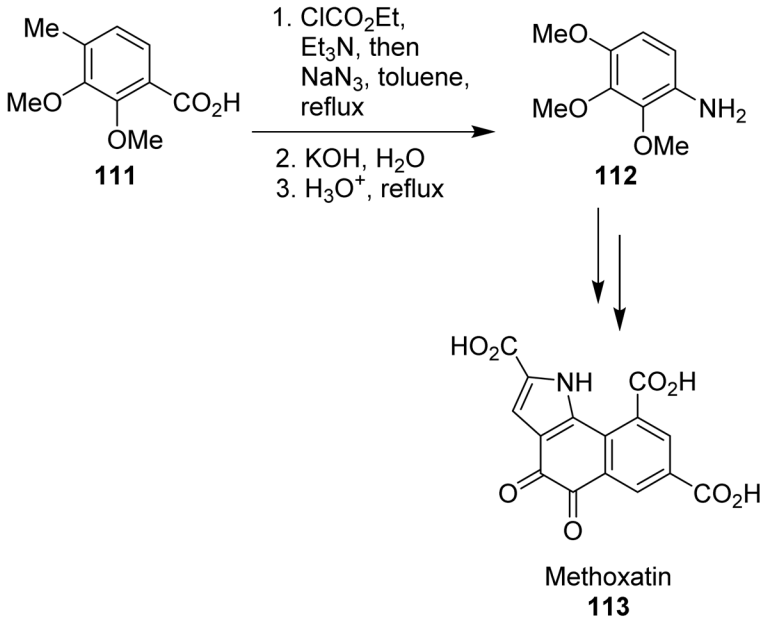
Scheme 27.
Synthesis of zampanolide.



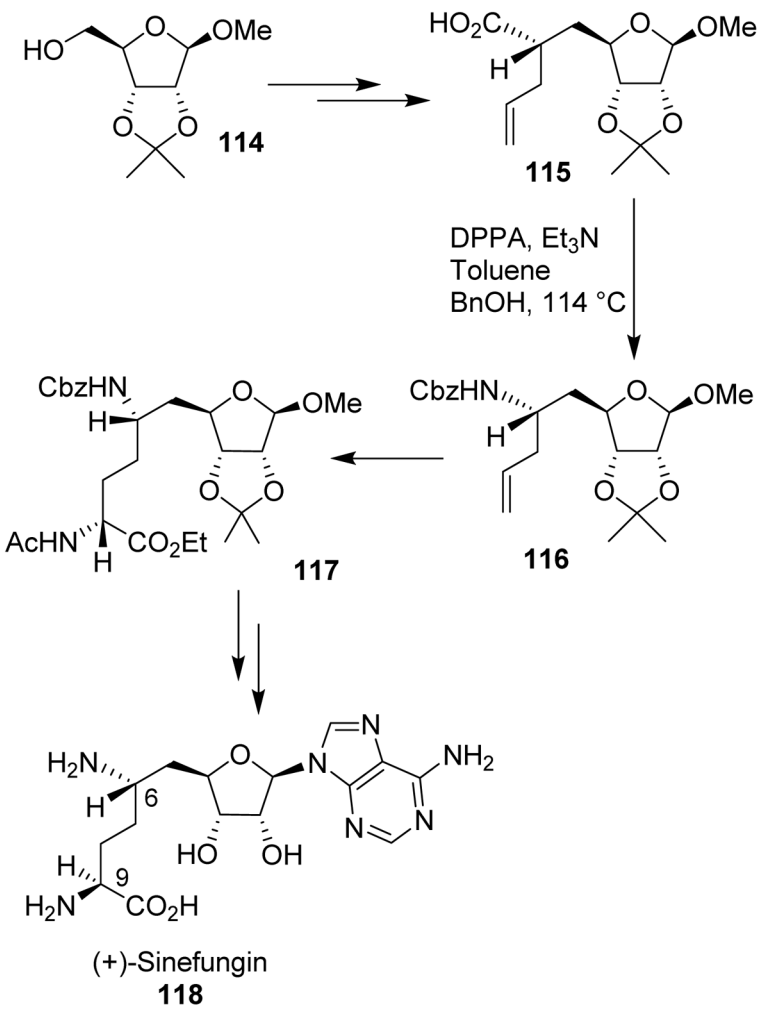
Scheme 28.
Synthesis of salicylihalamide.



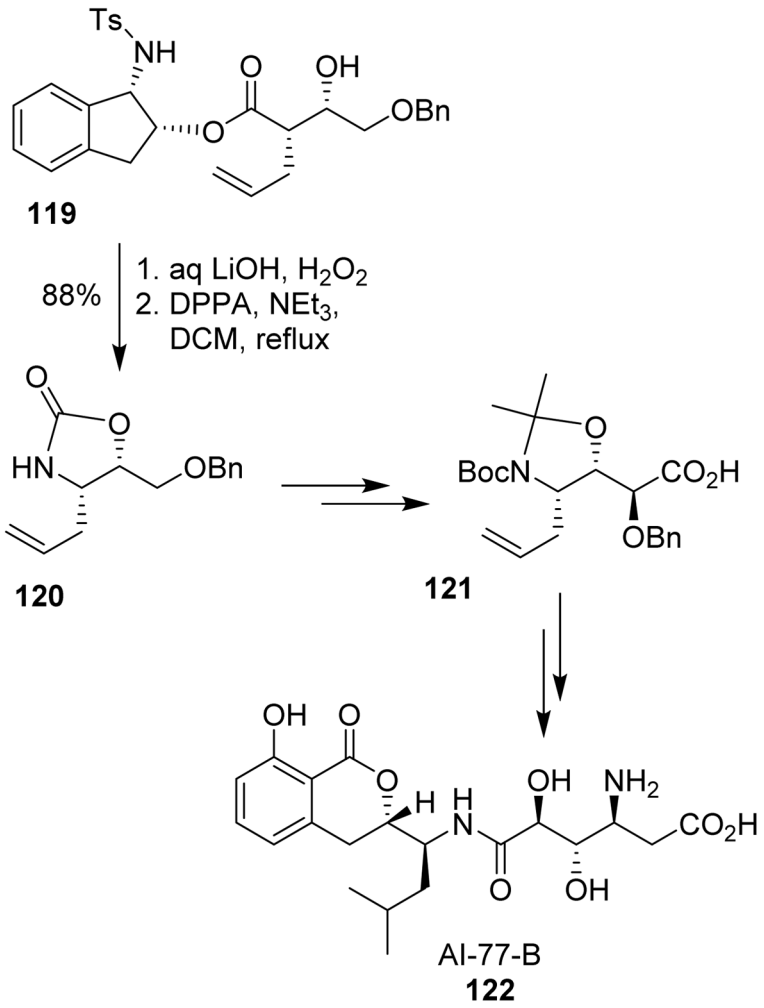
Scheme 29.
Synthesis of gelsemine.



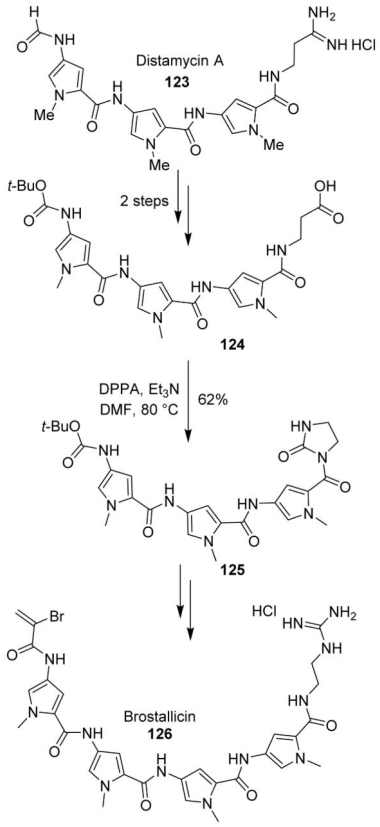
Scheme 30.
Synthesis of methoxatin.



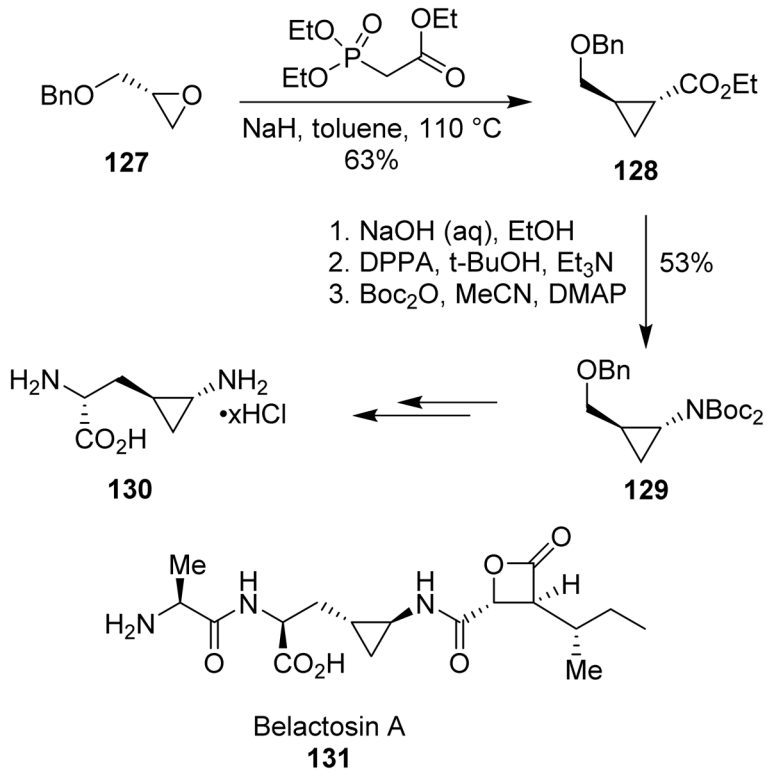
Scheme 31.
Synthesis of sinefungin.



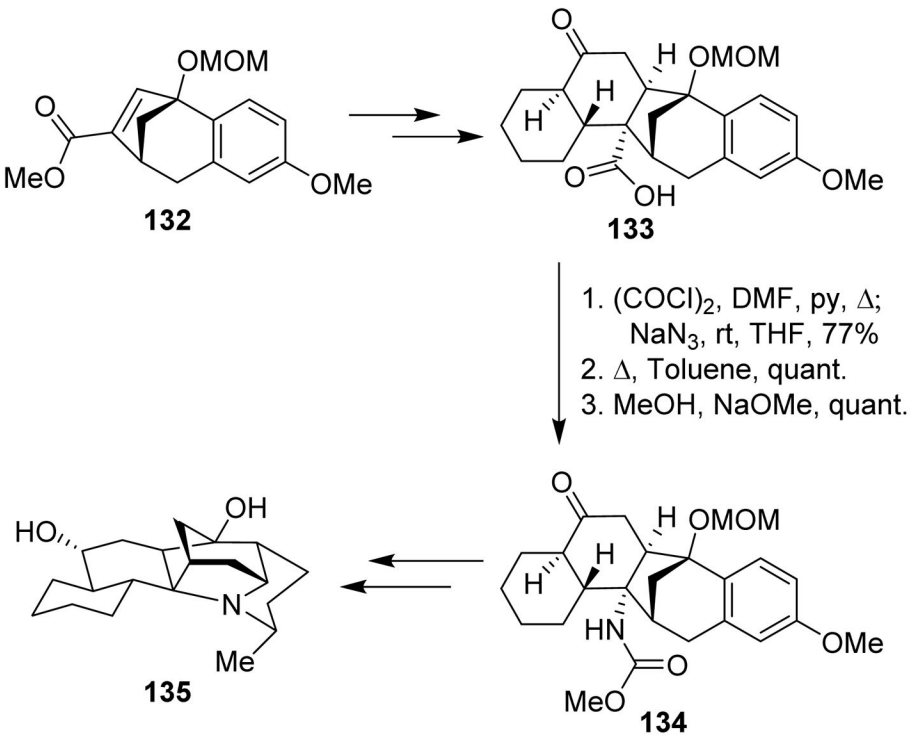
Scheme 32.
Synthesis of AI-77-B.



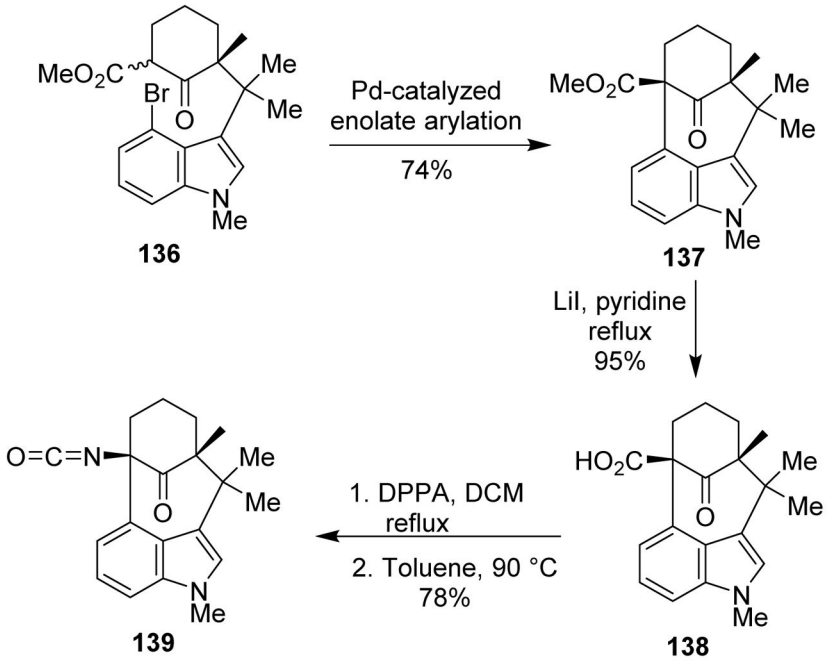
Scheme 33.
Synthesis of brostallicin.



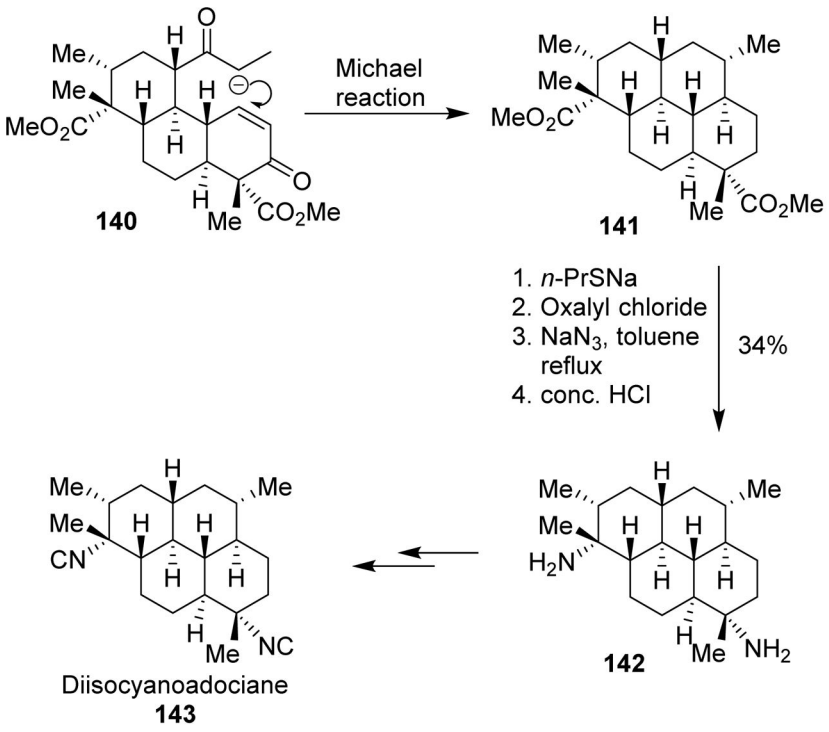
Scheme 34.
Synthesis of belactosin A.



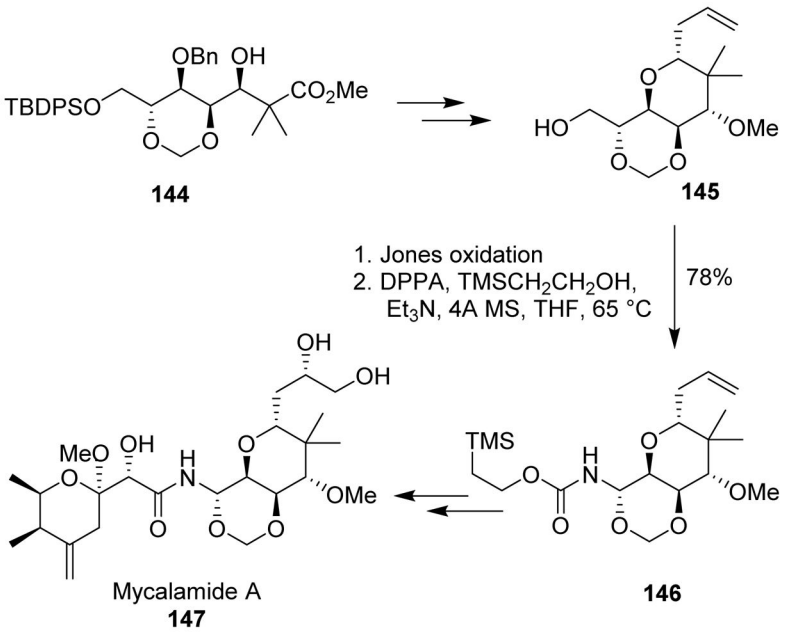
Scheme 35.
Synthesis of the himandrine skeleton.



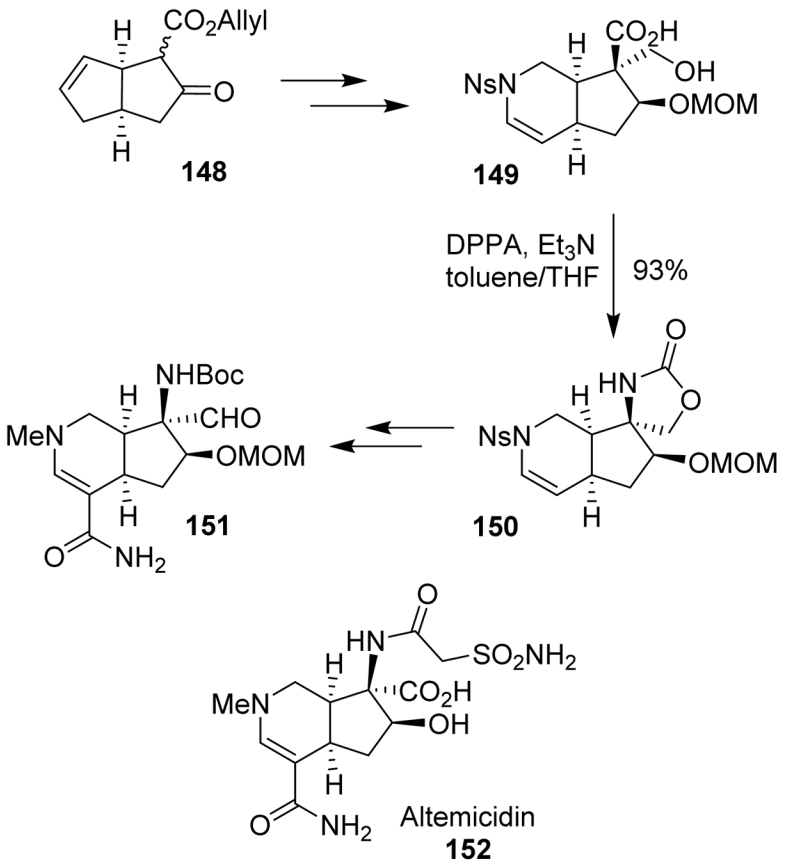
Scheme 36.
Synthesis of welwitindolinones.



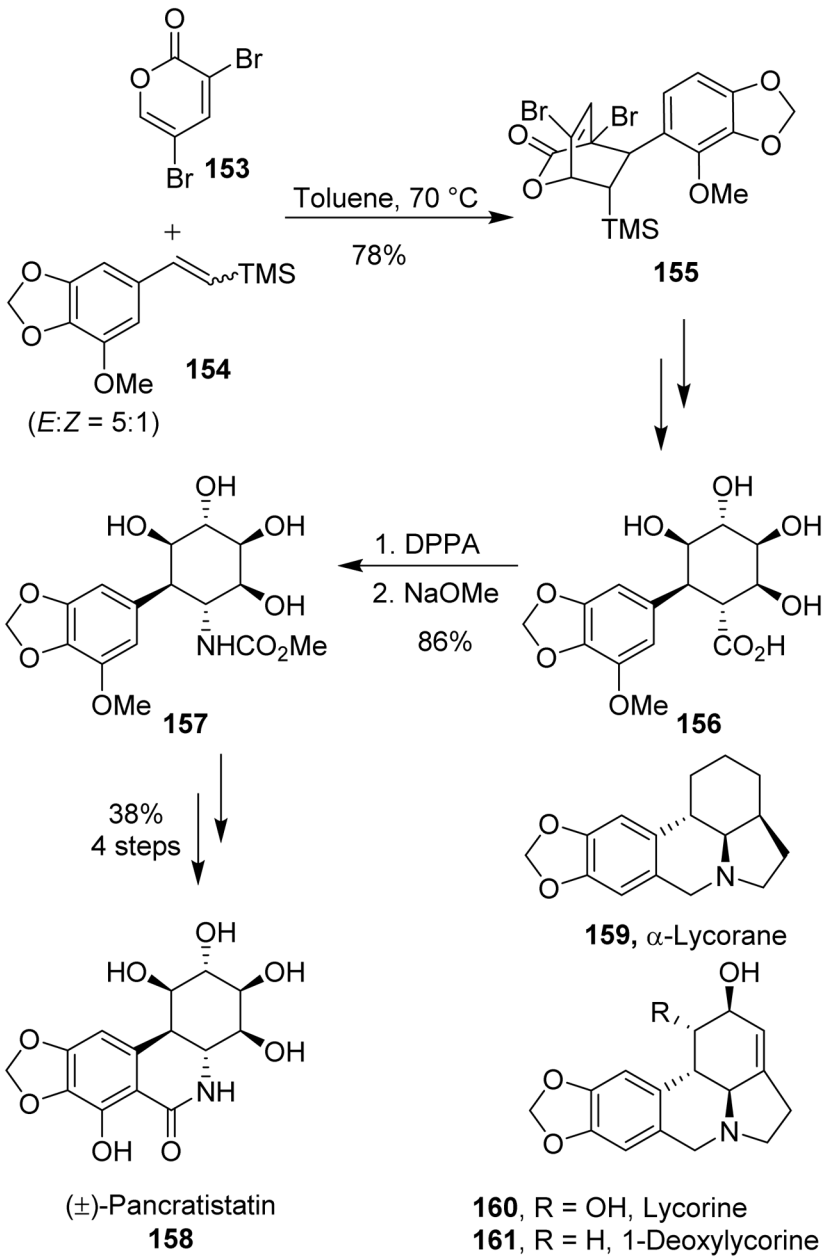
Scheme 37.
Synthesis of diisocyanoadociane.



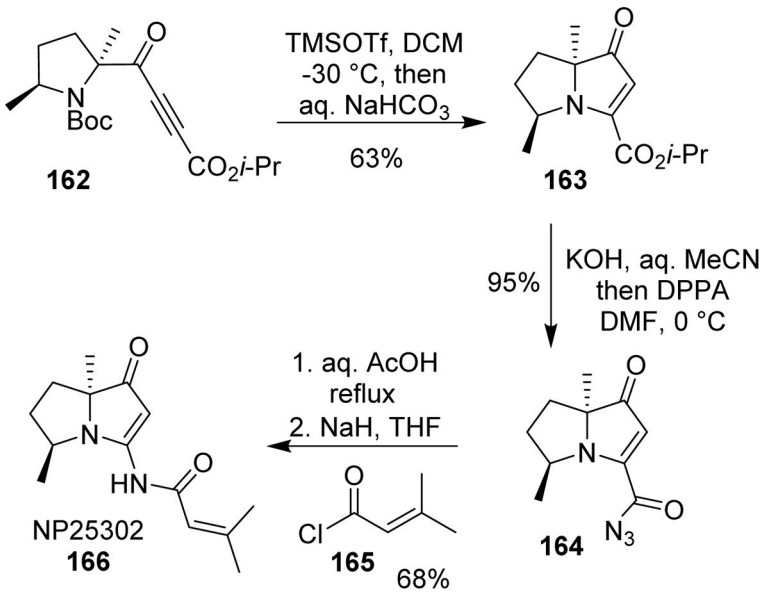
Scheme 38.
Synthesis of mycalamide A.



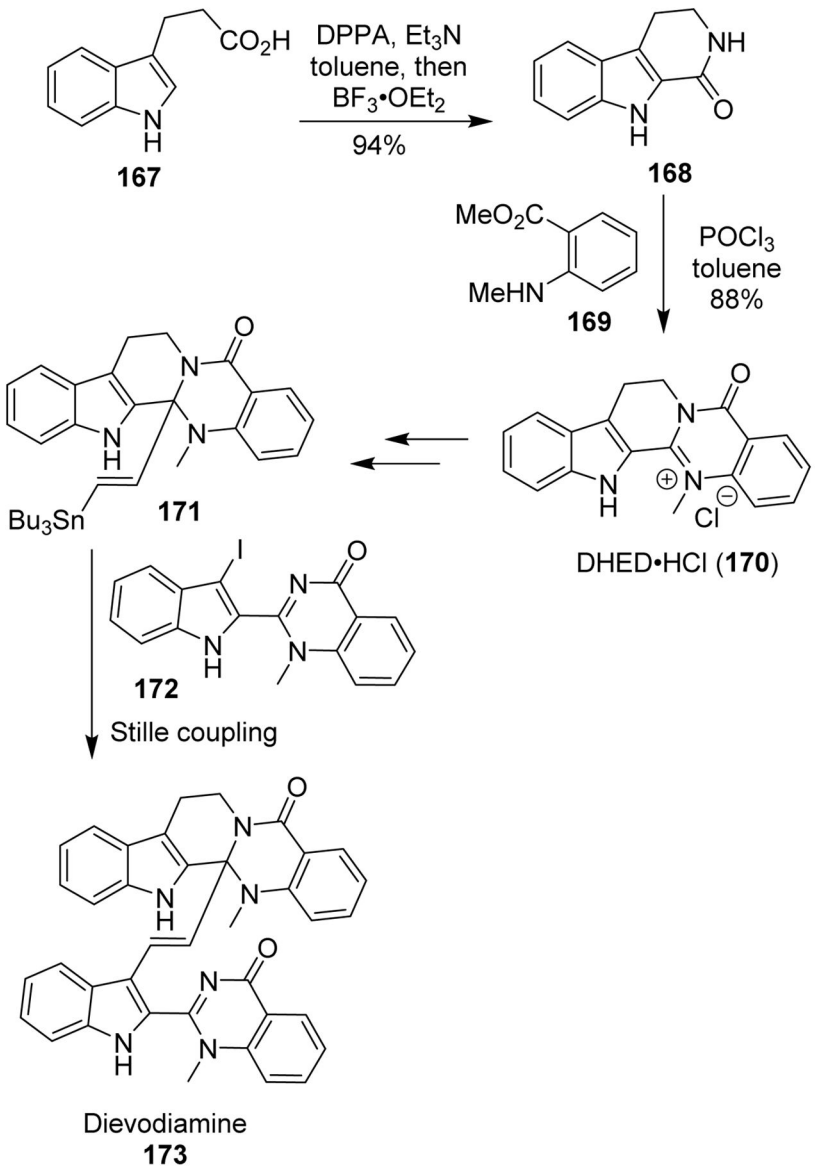
Scheme 39.
Synthesis of altemicidin core.



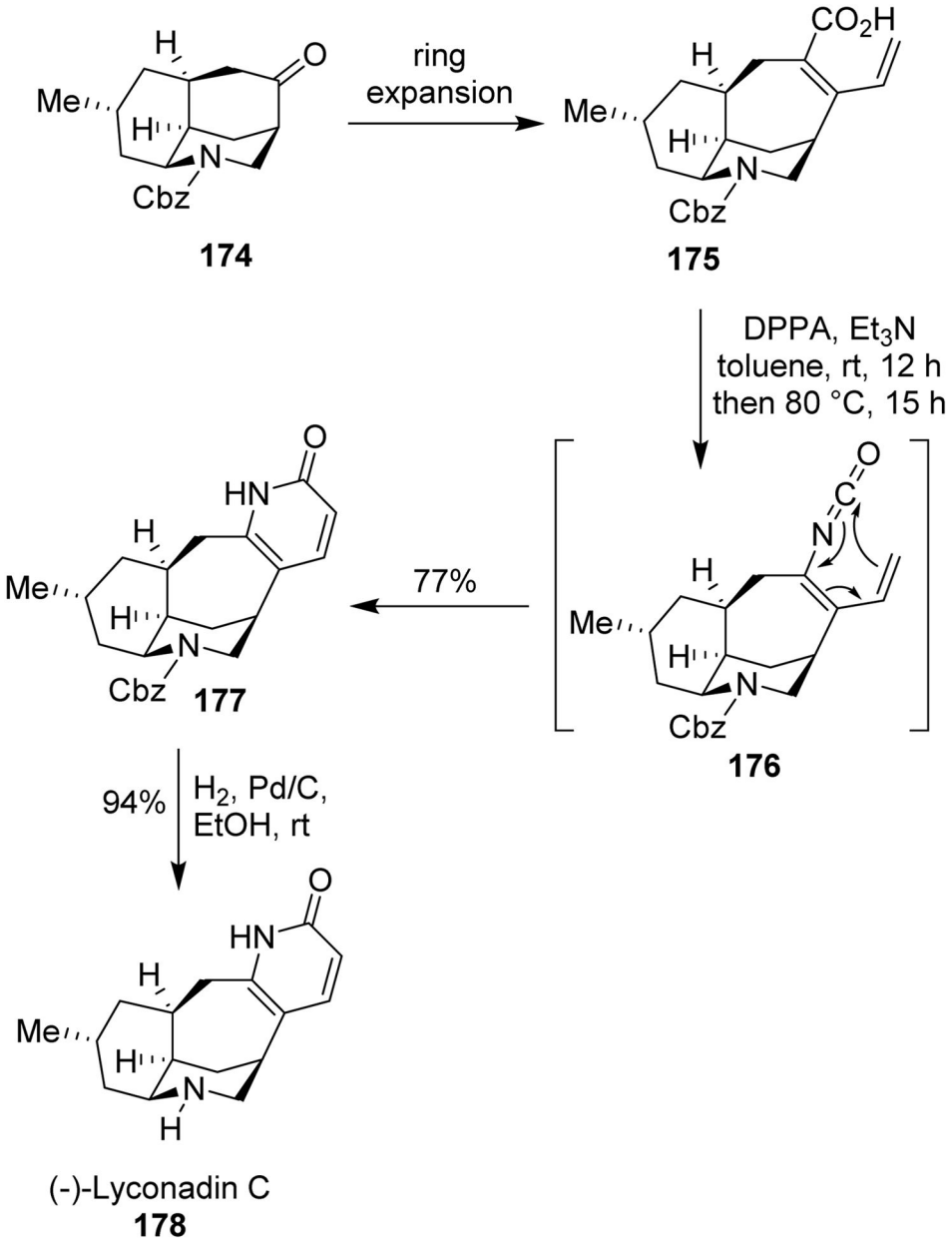
Scheme 40.
Synthesis of pancratistatin.



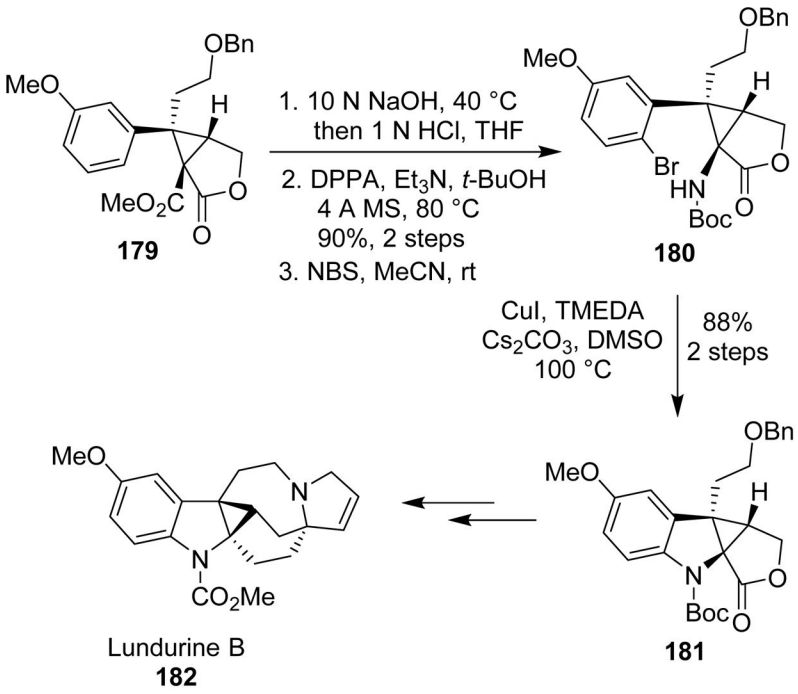
Scheme 41.
Synthesis of NP25032.



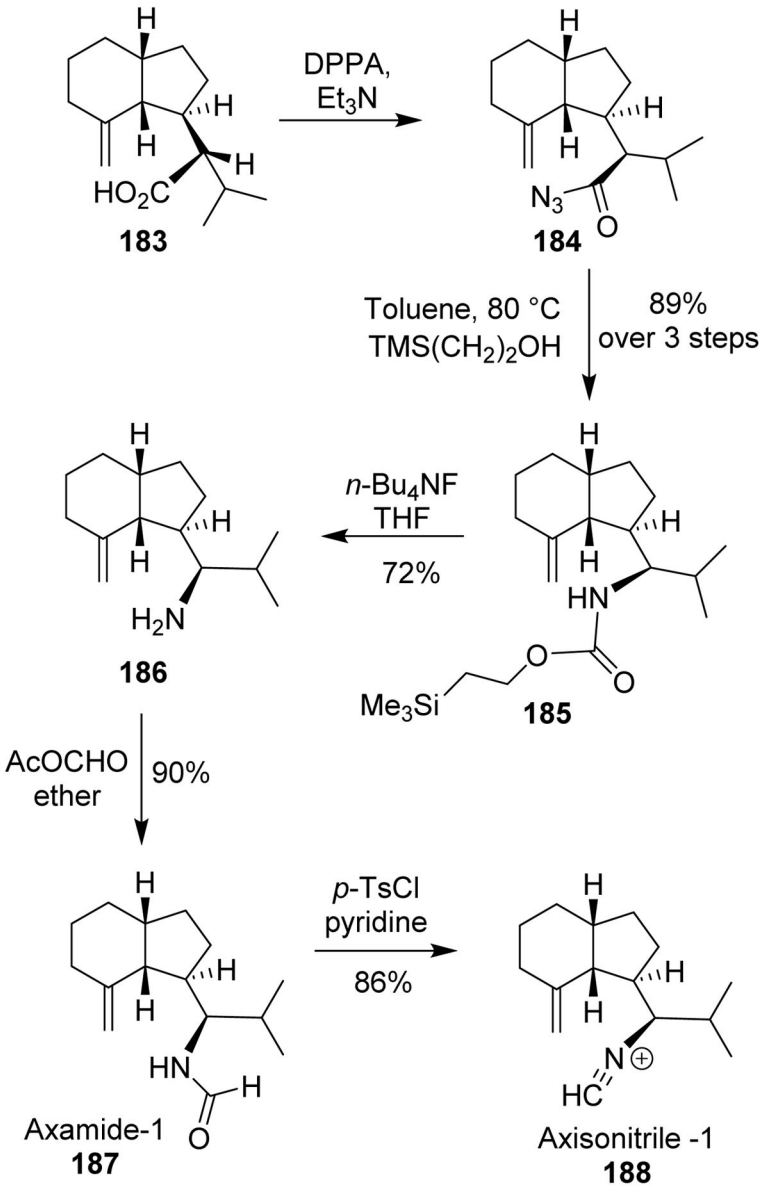
Scheme 42.
Synthesis of dievodiamine.



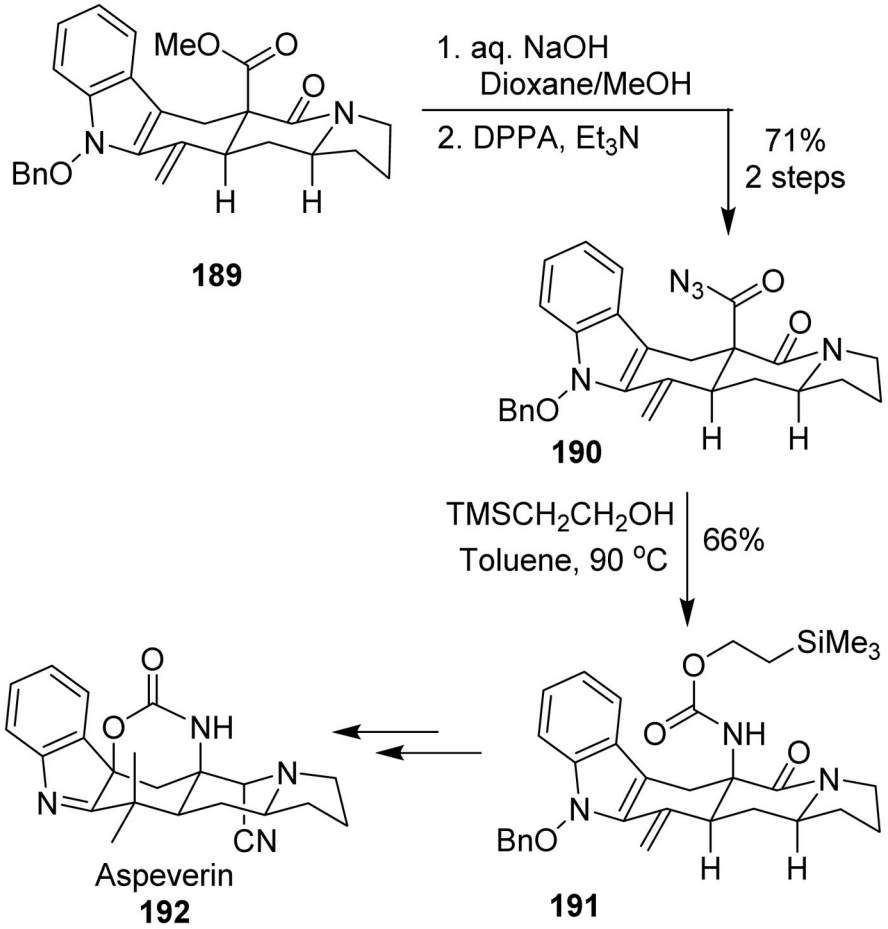
Scheme 43.
Synthesis of lyconadin C.



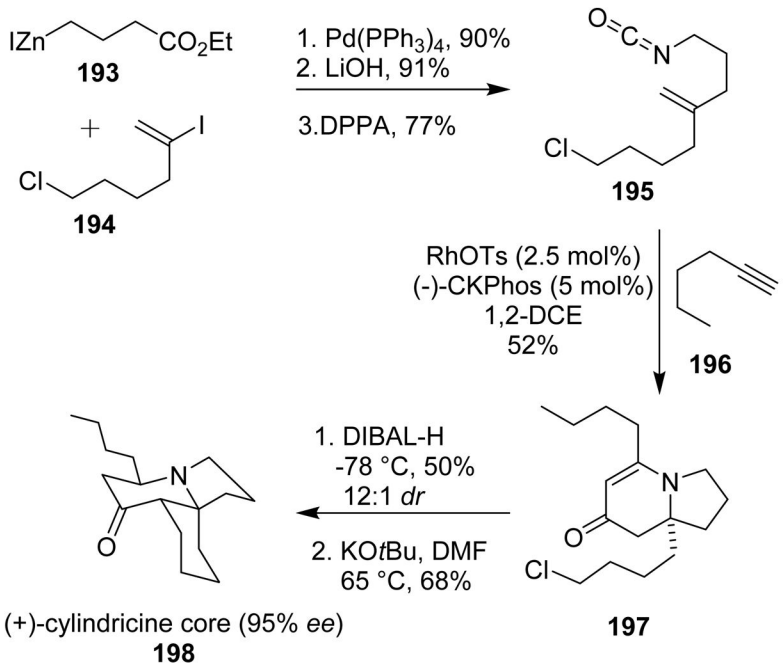
Scheme 44.
Synthesis of lundurine B.



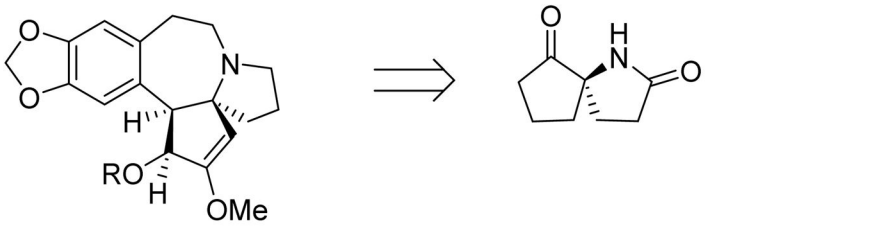
Scheme 45.
Synthesis of axisonitrile and axamide.



Scheme 46.
Synthesis of aspeverin.



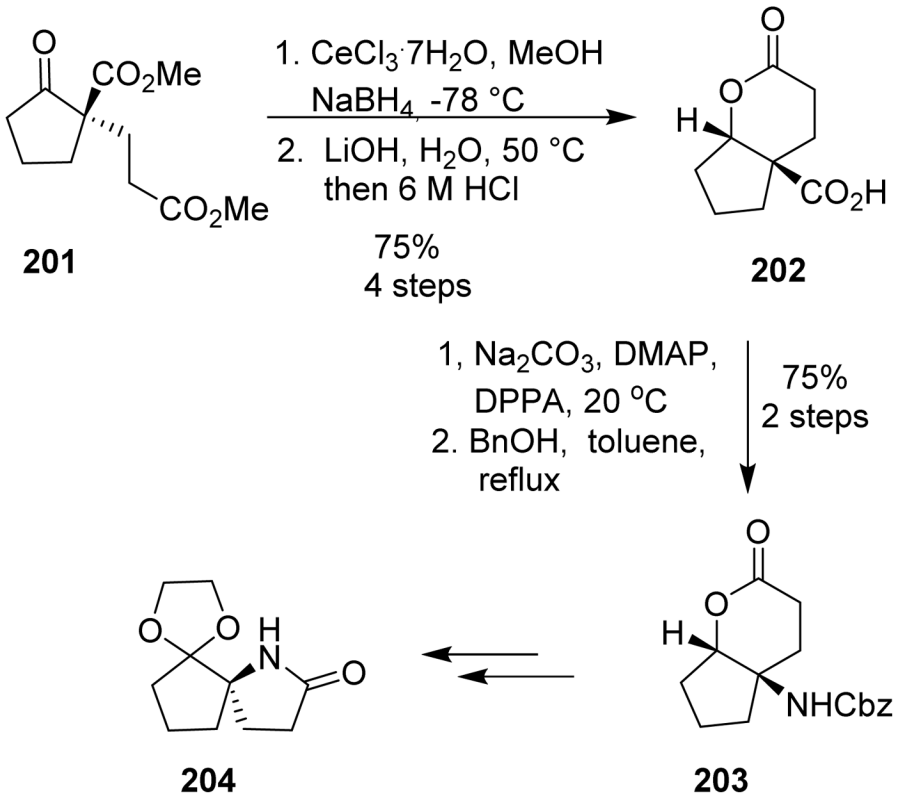
Scheme 47.
Synthesis of cyclindricine core.



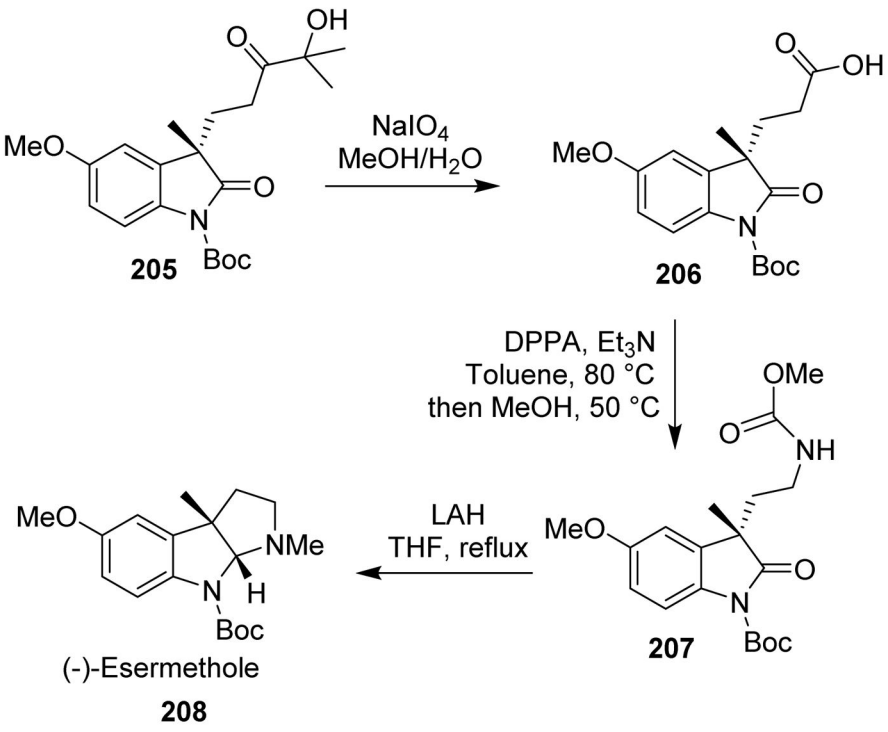
Cephalotaxine
199

(*R*)-1-azaspiro[4.4]nonane-2,6-dione
200

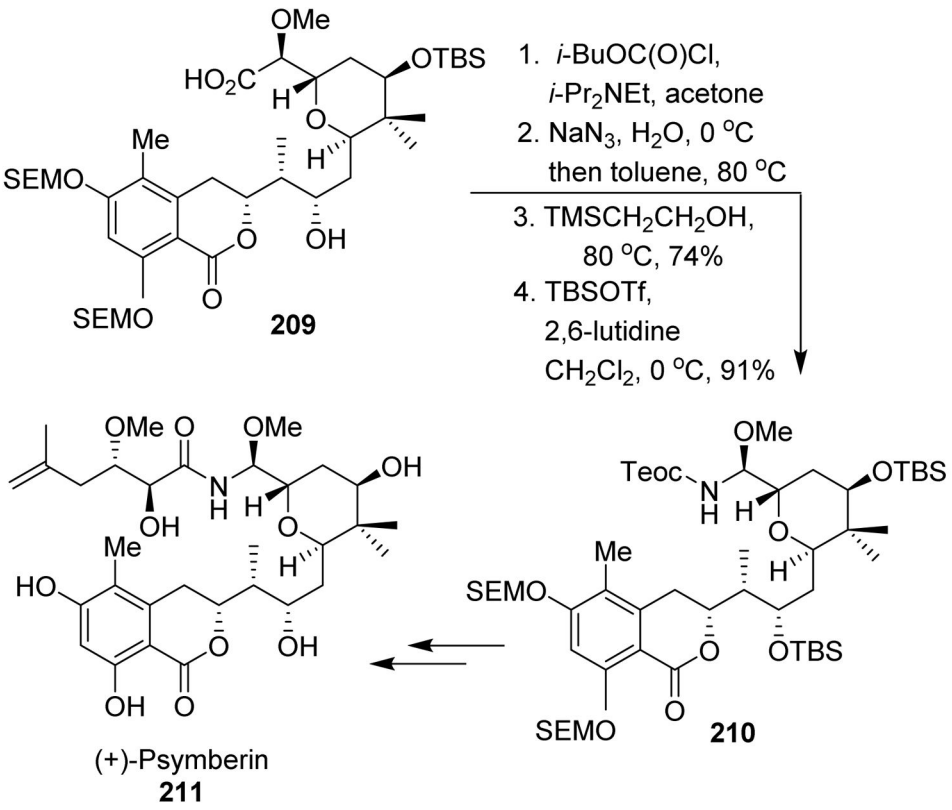
Scheme 48.
Retrosynthetic approach to cephalotaxine.



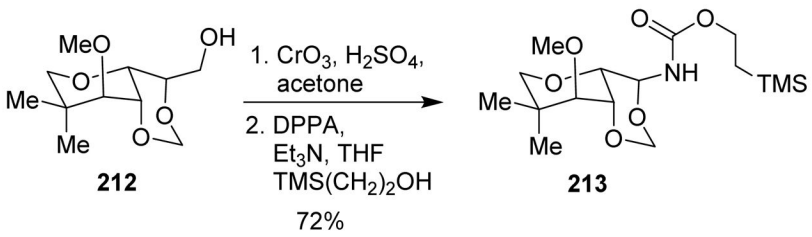
Scheme 49.
Synthesis of azaspiro[4.4]nonane-2,6-dione **204**.



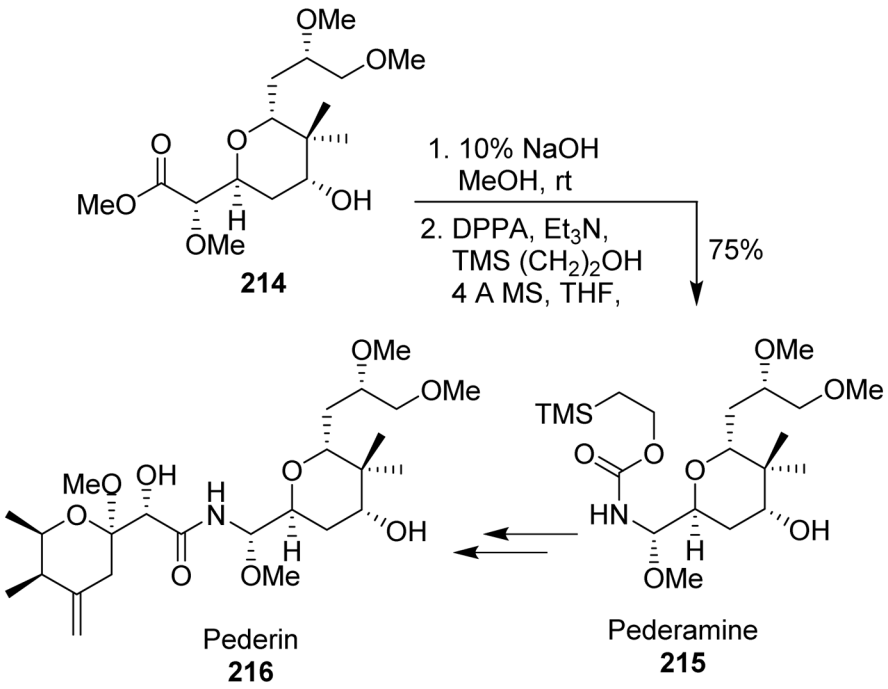
Scheme 50.
Synthesis of (−)-esermethole.



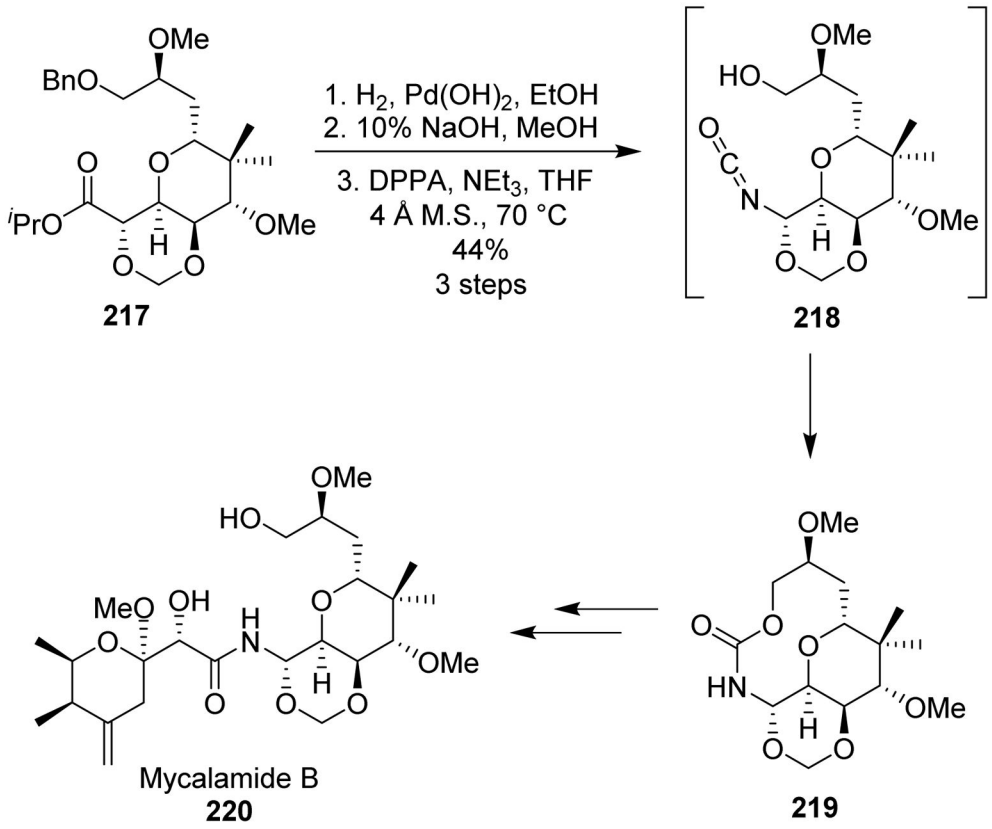
Scheme 51.
Synthesis of psymberin.



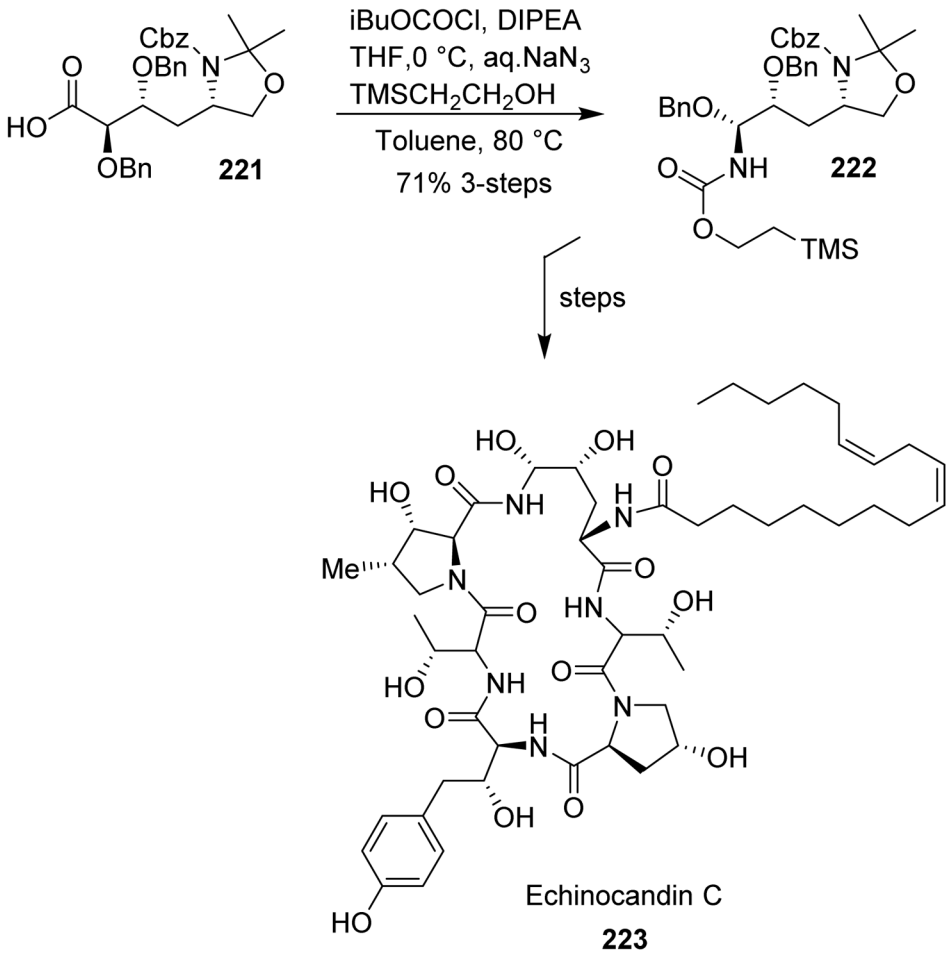
Scheme 52.
Synthesis of the mycalamide nucleus.



Scheme 53.
Synthesis of pederin.



Scheme 54.
Synthesis of mycalamide B.



Scheme 55.
Synthesis of echinocandin C.