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# Synthesis of Naturally Occurring Tropones and Tropolones

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## Abstract

Tropones and tropolones are an important class of seven-membered non-benzenoid aromatic compounds. They can be prepared directly by oxidation of seven-membered rings. They can also be derived from cyclization or cycloaddition of appropriate precursors followed by elimination or rearrangement. This review discusses the types of naturally occurring tropones and tropolones and outlines important methods developed for the synthesis of tropone and tropolone natural products.

## 1. Introduction

Tropones and tropolones refer to non-benzenoid seven-membered aromatic compounds with a carbonyl group (Scheme 1), which are also called troponoids or tropolonoids. Although the simplest tropone (R = H) is not a naturally occurring compound, it has been used as a basic building block in various cycloadditions.[1–11] The tropone moiety has only been found in several natural products. However, tropolones with a α-hydroxy or alkoxyl group (tropolone ether) are much more common in nature. Many tropolones have multiple hydroxy or alkoxyl groups in addition to the one on the α-position. The simplest tropolone (R = R′ = H) was isolated from *Pseudomonas lindbergii*. ATCC 31099 [12] and *Pseudomonas plantarii*. ATCC 43733.[13] To date, about 200 naturally occurring tropolones have been identified.[14–15] Most of the tropolones were isolated from plants and fungi. They have interesting chemical structures and biological activities such as anti-bacterial, anti-fungal, anti-tumor and anti-viral activities. Recent data showed that tropolones could be potent and selective inhibitors for enzymes with zinc-cofactor.[16–17]

The study of tropones and tropolones dates back to the 1940s, when Dewar first proposed seven-membered aromatic structures for colchicines and stipitatic acid (Scheme 2).[18–19] A few years later, the structures of thujaplicins were determined as isomers of isopropyl

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tropolones.[20–21] During the same time period, Nozoe independently assigned the correct structure for β-thujaplicin (hinokitiol).[22–23] Two reviews on the structure, biological activity and biosynthesis of tropones and tropolones were recently published.[14–15] Numerous synthetic methods have been developed for the synthesis of tropones and tropolones and some of them were discussed in early reviews published before 1991.[24–27] Three recent reviews focused on special classes of compounds, such as colchicine,[28] the five tropones derived from the *Cephalotaxus* species,[29] and α-hydroxytropolones (dihydroxytropones).[30]

Naturally occurring tropones are relatively rare. The simplest tropone is nezukone, isolated from *Thujastandishii* (Scheme 3).[31–33] Instead of hydroxy groups, some tropones have an amino or thiogroup. For example, manicoline A, isolated from *Dulaciaguianensis*, has an α-amino group.[34] Antibiotics tropodithietic acid and its valence tautomer, thiotropocin, have either thio-substituents or a carbon-sulfur double bond.[35–37] A number of related antibiotics have also been isolated.[38–39]

Diterpenoid tropones have a unique fused tetracyclic carbon skeleton (Scheme 4). Five members of them have been isolated and characterized thus far: harringtonolide, hainanolidol, for tunolide A, for tunolide B and 10-hydroxyhainanolidol. Buta's group first isolated harringtonolide in 1978, followed by Sun's group in 1979, from the seeds of *Cephalotaxus harringtonia* and the bark of the related Chinese species *Cephalotaxus hainanensis*.[40–41] Sun also reported the isolation of hainanolidol, which was proposed as the precursor for harringtonolide.[41] Harringtonolide was first found to inhibit the growth of beans and tobacco.[40] Subsequently, more interesting biological activities have been discovered, such as antiviral, antifungal and anticancer activities.[41–42] Recently, significant antitumor activity was reported with an $IC_{50}$ = 43 nM in KB cancer cells.[43] Fortunolides A and B were isolated from the stems and needles of *C. fortunei var. alpina* in 1999.[44] 11-Hydroxyhainanolidol was isolated from *C. koreana* in 2007.[45]

Pareitropone, another tropone-containing natural product, will be discussed later together with its tropolone congeners.

Benzotropolones contain a benzo-fused tropolone core (Scheme 5). The most studied member of this family is purpurogallin, a reddish crystalline substance isolated from nutgalls and oak bark, which was used as anti-oxidant in non-edible oil, fuels and lubricants.[46–47] The structure of purpurogallin was established by single crystal x-ray analysis.[48] It also inhibited the HIV-1 integrase activity through a metal chelation mechanism.[49] This compound was also used as a cardio-protector due to its antioxidant property.[50]

Theaflavins are found in black tea leaves, in which the compounds account for 2–4 wt% of the dry black tea.[51] This family of compounds also has a benzotropolone skeleton and the benzene unit is often part of a flavone moiety. Theaflavins are produced in the process of fermenting the leaves of *Camellia sinensis* from co-oxidation of selected pairs of catechins, which exist in green tea leaves. The theaflavin was first isolated from the black tea leaves in 1957.[52] Since then, extensive studies have been carried out on their chemical structures, biological activities and other properties. Numerous biological activities have been

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discovered, such as anti-oxidant, anti-pathogenic, anti-cancer, preventing heart diseases and preventing hypertension and diabetes.[53–57]

The tropoisoquinoline and tropoloisoquinoline compounds were isolated from the Menispermaceae plants *Cissampelospareira* and *Abutagrandifolia*, and proven to have cytotoxicity in selected assays.[58–63] Six members from this family of tropone/tropolone alkaloids have been characterized including grandirubrine, imerubrine, isoimerubrine, pareirubrine A, pareirubrine B and pareitropone (Scheme 6).[58,60–64] Among the family, pareitropone showed the greatest cytotoxicity in leukemia P388 cell lines ($IC_{50}$ = 0.8 ng/mL).[63]

Colchicine is the most extensively studied member of tropolones (Scheme 7). It was first isolated from the genus *Colchicum* by Pelletier and Caventou in 1820.[65] The *Colchicum* is common in Europe and North Africa, where it was used as a poison as well as a treatment of acute gout. After its isolation, colchicine was purified and named by Geiger in 1833[66] and its structure was assigned by Dewar in 1945.[19] Colchicine was found to bind to tubulin and inhibit microtubule polymerization. The FDA approved colchicine in 2009 as a mono-therapy for acute gout flares, familial Mediterranean fever and prophylaxis of gout flares. It was also used for inducing polyploidy in plant cells during cellular division. Although colchicine has significant cytotoxic activity, poor selectivity limited its clinical use for the treatment of cancer. A large number of naturally occurring colchicine congeners have been identified.[15] A small number of non-nitrogen containing colchicine derivatives, such as colchicone, have also been reported.[67]

Most tropolones are the secondary metabolites of plants and fungi and their biosynthesis has recently been reviewed.[14–15,68] The biosynthesis of many tropolones, such as thujaplicins, involves the terpene pathways. The most accepted biosynthetic pathway for colchicine and related alkaloids was proposed by Battersby.[69–74] Colchicineis derived from L-tyrosine and L-phenylalanine and its biosynthesis involves a series of CYP450-mediated oxidation and rearrangement reactions. Nay recently proposed a biosynthetic pathway for the complex norditerpene tropones based on the biosynthesis of the abietanes.[29] The seven-membered tropone was proposed to originate from intramolecular cyclopropanation of an aromatic ring followed by Cope rearrangement.

The biosynthetic pathways of benzotroponoid systems involve oxidation and coupling of polyphenols.[75–77] Nakatsuka studied the details of the biomimetic synthesis of benzotropolone **8-8** from 5-methylpyrogallol **8-1** and 4-methyl-*o*-quinone **8-2**, derived from oxidation mediated by Fetizon's reagent ($Ag_2CO_3$/celite) as shown in Scheme 8.[78] When phenol **8-1** was reacted quinone **8-2** in methylenechloride, bicyclo [3.2.1] intermediate **8-6** was formed in 68% yield as colorless crystals, which was proposed as the key intermediate in previous biosynthesis or biomimetic synthesis of benzotropolones.[79–81] Intermediate **8-6** was converted to tropolone **8-8** in nearly quantitative yield in water at room temperature after 30 min.

Using horseradish peroxidase or $Pb(OAc)_4$ as the oxidant, biomimetic syntheses crocipodin **9-4**[82] and theaflavin **9-9**[83] have been accomplished starting from the corresponding

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polyphenol precursors **9-1**, **9-2**, **9-5**, and **9-7** (Scheme 9). Previously, Sang's group prepared a series of compounds with a benzotropolone skeleton including theaflavin by the horseradish peroxidase-mediated coupling of unprotected polyphenols.[84]

Extensive research has been conducted towards chemical synthesis of tropones and tropolones. This review summarizes synthetic methods published before the end of 2013. It begins with synthetic methods that can convert simple seven-membered rings to tropones and tropolones, followed by the synthesis of tropone- and tropolone-containing natural products. The subsequent section was organized by how the 7-membered rings were formed. Although seven-membered ring syntheses have been reviewed several times, these reviews often focus on one type of method, such as the [4+3] cycloaddition,[85–87] [5+2] cycloaddition,[88–89] or other reactions.[90–91] A recent review on synthetic strategies to access seven-membered carbocycles in natural products only discussed the total synthesis of a few tropone- and tropolone-containing natural products including pareitropone, imerubrine, isoimerubrine and grandirubrine.[92]

## 2. Conversion of Simple Seven-membered Ring to Tropones and Tropolones

In earlier days, most synthetic efforts for tropones and tropolones focused on direct oxidation of substituted 7-membered rings.[24] These methods have been used for decades to access the tropone and tropolone structures.

### 2.1 Oxidation via halogenations followed by elimination

The oxidation by halogenation method was initially developed by Cook and has been most widely used in the synthesis of tropones and tropolones.[93] It started with halogenation, most commonly bromination, followed by elimination to afford halogenated tropone derivatives. The distribution of bromotropolones is highly dependent on the amount of bromine. The bromotropolones could undergo hydrogenolysis in the presence of a palladium-charcoal catalyst to give the tropolone product. Compared to bromine, the reaction with NBS could provide tropolone **10-2** directly together with other brominated tropolones. The above halogenation/elimination methods are applicable to various 7-membered ring substrates including 1,2-cycloheptanediones (e.g. **10-1**), 2-hydroxycycloheptanones (e.g. **10-3**), cycloheptanones, cycloheptenones and cycloheptadienones. When 2-hydroxycycloheptanone **10-3** was employed as substrates, the reaction afforded tropolone **10-2** as the only product in 10% yield without any other bromo-derivatives (Scheme 10).[94]

Bromination of cycloheptenone **11-1** afforded tribromotropone **11-2** only, which could undergo further hydrogenolysis to yield tropone **11-3** (Scheme 11).[24,95] Bromination of cycloheptanone **11-4** led to a mixture of brominated derivatives. The bromination/elimination method was applied to the synthesis of natural product nezukone by starting with β-isopropyl substituted cycloheptanone.[96]

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### 2.2 Oxidation of cyclohepta-1,3,5-triene

Doering and Knox reported an oxidation of cyclohepta-1,3,5-triene **12-1** to tropolone **12-2** by permanganate in 1950, albeit in a low yield (Scheme 12).[97–99] Two isomers **12-4A/B** were identified for substituted cycloheptatrienes.

A method to convert cycloheptatriene to tropone via ditropyl ether **13-2** was reported in 1960 (Scheme 13).[100] Cycloheptatriene was first oxidized by phosphorus pentachloride to tropylium cation **13-1**. In the presence of NaOH, a newly formed cyclohepta-2,4,6-trienol could be trapped by another tropylium ion to afford a ditropyl ether. Treatment of this ditropyl ether with acid led to one molecule of tropone along with one molecule of cycloheptatriene.

Tropone could also be prepared by treating tropylium ion with DMSO (Scheme 14).[101–102]

Shono's group extensively studied the electrochemical oxidation of cycloheptatrienes to tropones and tropolones (Scheme 15).[103–106] The methoxycycloheptatriene intermediate **15-1** was first formed. A series of isomerization, further electrochemical oxidation and hydrolysis led to the formation of tropone. Substituted tropones and tropolones were also prepared by this method. Cycloheptatrienes could also be oxidized directly to tropones in the presence of TEMPO catalyst under electrochemical conditions.[107]

Direct conversion of cycloheptatriene to tropone could also be achieved by oxidation using$SeO_2$ in over 100 gram scale reactions (Scheme 16).[108]

### 2.3 Oxidation by singlet oxygen via endoperoxide

Cycloheptatrienes could react with singlet oxygen to form different isomeric endoperoxides (e.g. **17-2A/B**, Scheme 17).[109–112] Some of them could be converted to tropones via Kornblum-DeLaMare rearrangement[113] followed by elimination.[114] This was applied to the synthesis of stipitatic acid isomers as discussed in later sections.[115] Tropolones could also be prepared with appropriate alkoxy substituents on the cycloheptatriene substrate.[116–117]

Oxidation of benzotropone **18-2** via endoperoxide intermediate **18-3** afforded tropolone **18-4** selectively (Scheme 18).[118] Benzotropone **18-2** was prepared by halogen-mediated oxidation of **18-1** followed by elimination. The TPP-sensitized photo-oxygenation provided the bicyclic endoperoxide intermediate **18-3**, which was reduced by thiourea in methanol to generate benzotropolone **18-4**.

### 2.4 Oxidation via dehydrogenation

Direct oxidative dehydrogenation of cycloheptanones or cycloheptenones is another obvious strategy for the preparation of tropones. However, limited examples were found in the literature using DDQ as the oxidant[119] or transition metal complex as the dehydrogenation catalyst.[120] Nicolaou showed one such example using IBX as the oxidant (Scheme 19).[121–122] Using a water-soluble ortho-iodobenzoic acid derivative AIBX, Zhang also prepared a benzotropone.[123]

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## 3. Synthesis of naturally occurring tropones and tropolones

In the following sections, we will focus on how the tropone or tropolone moiety in natural products was prepared. They can be generated from commercially available seven-membered rings or derived from various cyclization and cycloaddition reactions.

### 3.1 Conversion of commercially available seven-membered rings to tropones or tropolones

Tropolone derivatives can be prepared by Friedel-Crafts acylation of tropone iron tricarbonyl complex **20-1**, available in 85% yield by irradiation of tropone with iron pentacarbonyl in toluene (Scheme 20).[124] A mixture of tautomeric acetyltropone iron complexes (**20-2A/B**) was often obtained. Natural products β-thujaplicin and dolabrin were prepared by reacting the resulting acetyltropone iron complex with 2-diazopropane, deacetylation, oxidative decomplexation and α-functionalization.

The tropone- or tropolone moiety could be derived from naturally occurring compounds. For example, natural product dolabrin could be prepared from β-thujaplicin via a bromination and elimination sequence (Scheme 21).[125]

As another example, the tropolone moiety in colchicine was derived from naturally occurring purpurogallin in two formal syntheses of colchicine derivatives (Scheme 22).[126–127]

In Nakamura's synthesis of colchicine, the seven-membered ring was derived from an ester-substituted cycloheptanone **23-2** (Scheme 23).[128–129] Cycloheptatriene **23-5**, derived from halogenation and elimination of cycloheptene, was converted to the corresponding tropone **23-6** using the hydrolysis of ditropyl ether protocol illustrated in Scheme 13.

Shono's group reported a synthesis of β-thujaplicin from substituted cycloheptatrienes (Scheme 24).[130] The 1-methoxycycloheptatriene **24-1** and 3-methoxycycloheptatriene **24-2** starting materials were prepared from electrochemical oxidation of cycloheptatrienes followed by thermal rearrangement of the oxidation product 7-methoxycycloheptatriene **15-1** shown in Scheme 15.[103] The isopropyl group was introduced to the ring system by electro-reductive alkylation of these methoxycycloheptatrienes. A sequence of bromination followed by elimination then led to the formation of substituted tropone **24-4**, which could undergo oxidative α-amination in presence of hydrazine and hydrolysis to form the natural product target. Alternatively, the synthesis of thujaplicin could also be completed by a sequence of hydrolysis, isomerization/epoxidation, dione formation and bromination/elimination from **24-3**.

### 3.2 Formation of the seven-membered ring by cyclization

The seven-membered ring in nezukone, one of the simplest naturally occurring tropones, could be prepared by $TiCl_4$-mediated cyclization of **25-1** (Scheme 25).[131] Conversion of chloride **25-2** to ketone **25-3** through a cycloheptylstannane intermediate followed by bromination and elimination afforded the tropone moiety and completed the synthesis.

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In 1959, Van Tamelen reported a synthesis of colchicine by forming the tropolone ring via acyloin cyclization (Scheme 26).[132–133] In the presence of sodium metal in liquid ammonia, acyloin condensation provided a tetracyclic hemiketal, which was oxidized by cupric acetate in methanol to ketone **26-2**. Exposing the hemiketal to toluenesulfonic acid in refluxing benzene led to opening the epoxy bridge and then dehydration. The crude enedione was then oxidized by NBS in refluxing chloroform to yield desacetamidocolchicine derivative **26-3**, which could be converted to colchicine.

In 1965, Toromanoff reported a synthesis of desacetamidocolchicine using a strategy similar to Van Tamelen (Scheme 27).[134] The use of the cyanoesterin **27-1** rather than the corresponding diester avoids the regioselectivity issue in the cyclization step. A sequential oxygenation and oxidation with NBS led to the formation of tropolone ring.

In 1963, Woodward presented his synthesis of colchicine in the Harvey Lecture (Scheme 28).[28,135] The seven-membered tropolone ring was derived from Dieckmann condensation of **28-1**. The challenging nitrogen functionality was introduced as an isothiazole ring, which is critical for the formation of both seven-membered rings. The rest of the C=C bonds and oxygen functionality were installed via diketone intermediate **28-3**. The isothiazole ring was converted to amine by reduction with Raney nickel. No yield was available for each step of the synthesis.

Starting with limonene, Kitahara's group realized a divergent synthesis of both β- and γ-thujaplicins (Scheme 29).[136] The seven-membered ring was obtained by $TiCl_4$-mediated cyclization of a ketone enolate to dimethyl acetal in **29-1**, derived from limonene. A series of elimination and oxidation reactions then led to the formation of both tropolones regioselectively. The last step of the tropolone formation involved bromination and elimination.

In 1989, Kakisawa's group completed the synthesis of salviolone (Scheme 30),[137–138] a cytotoxic benzotropolone bisnorditerpene.[139] Although the tropolone ring was constructed quickly by a double aldol condensation reaction, the yield and regioselectivity of this key step are relatively low.

The synthesis of taxamairin B[140–141] was completed by Pan's group (Scheme 31).[142–143] The seven-membered ring in benzotropone was cyclized by an acid-mediated Friedel-Crafts acylation of **31-1**. Three double bonds in **31-3** were introduced by DDQ-mediated dehydrogenation of **31-2**. The isopropyl group was recovered by hydrogenation.

In 2007, Hanna's group applied a dienyne tandem ring-closing metathesis reaction[144–145] to the synthesis of the tricyclic core of colchicine (Scheme 32).[146] Two 7-membered rings in **32-2** were formed in this tandem reaction. After removing the TMS group and oxidation/transposition mediated by PCC, known dienone intermediate **32-3** was prepared. Following Wenkert's[147] and Nakamura's[128–129] procedures, this dienone intermediate could be converted to colchicine.

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Recently, ring-closing metathesis of dienes was also applied to the synthesis of 3,4-benzotropolones (Scheme 33).[148] One example of enyne metathesis was also realized for the synthesis of vinylbenzotropolones.

### 3.3 Formation of the seven-membered ring by ring expansion

Among all the synthetic methods for tropones and tropolones, ring expansion of readily available six-membered rings, especially cyclopropanation/ring expansion tandem reactions, was the most often used protocol. A short overview by Reisman on the applications of Buchner reaction (section 3.3.1) to natural product synthesis was recently published.[149] Maguire recently reviewed the factors that determine the distribution of norcaradiene and cycloheptatriene in various systems.[150] Qin also published a review paper on the application of cyclopropanation strategies to natural product synthesis[151] and an account about their own work on the synthesis of indole alkaloids by cyclopropanation.[152] the tropone- or tropolone-containing natural products in the following sections were not discussed in these reviews.

**3.3.1 Cyclopropanation of arenes with diazo- compounds followed by ring expansion – Buchner reaction—**Buchner first reported the cyclopropanation of arenes with carbenes derived from diazo compounds for the synthesis of norcaradiene as early as 1885.[149,153] Doering and coworkers characterized the products as a mixture of cycloheptatrienes.[97,99,154] They and others[155] also oxidized the cycloheptatriene products to tropolone derivatives. Benzotropolones were also prepared similarly.[156]

One of the early applications of Buchner reactionin natural product synthesis is Taylor's synthesis of stipitatic acid (Scheme 34).[157] The cyclopropanation of 1,2,4-trimethoxybenzene **34-1** with diazoacetic acid ester under photolytic conditions gave 7-membered cycloheptatriene product **34-3** through the ring expansion of norcaradiene intermediate **34-2**. The synthesis was completed after bromination and hydrolysis.

Transition metals, such as rhodium (II) carboxylate, catalyzed the cyclopropanation of alkenes and arenes in a much more efficient process.[158–159] In the presence of excess arenes, rhodium (II) catalyzed the decomposition of alkyl diazoacetates, which could then generate cycloheptatrienes at room temperature.

Mander's group applied the Buchner reaction to the total synthesis of hainanolidol (Scheme 35).[160] In the presence of rhodium mandelate, arene cyclopropanation occurred efficiently to afford unstable tetracyclic intermediate **35-2**, which was immediately exposed to DBU to give the cycloheptatriene product **35-3**. This triene was then converted to natural product hainanolidol after a sequence of aldol reaction, lactonization, elimination and hydrolysis/isomerization. Mander's group also tried to improve their synthesis of hainanolidol and complete the synthesis of the related bioactive congener, harringtonolide.[161–166] However, none of these further efforts led to the completion of harringtonolide.

Inspired by Mander's synthesis, Camp's group tried to prepare simplified analogues of harringtonolide.[167] However, they failed to convert the cycloheptatriene products derived from the Buchner reaction to tropones.

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Balci applied the Buchner reaction to the synthesis of stipitatic acid isomers via endoperoxide intermediate **36-3** (Scheme 36).[115] A base-mediated Kornblum-DeLaMare rearrangement[113] and cobalt *meso*-tetraphenylporphyrin-catalyzed (CoTPP) rearrangement of this endoperoxide led to isomers of stipitatic acid esters **36-4A/B**.

**3.3.2 Base promoted cyclopropanation followed by ring expansion—**In 1959, Eschenmoser finished the first total synthesis of colchicine.[168–169] In this synthesis, the tropolone ring was derived from a base promoted intramolecular cyclopropanation of **37-1** followed by ring expansion and oxidation (Scheme 37). It is also interesting to note that the benzene-fused seven-membered ring was prepared from hydrogenation of the tropolone ring in natural product purpurogallin. Although the carbon skeleton was assembled very efficiently, the installation of the rest of the functional groups proved to be difficult. For example, the positions of the oxygen functionalities (carbonyl oxygen and methoxy group) had to be readjusted and the introduction of the acetylamide group required many steps and proceeded with low yields.

In 1986, Kende reported an efficient method for the synthesis of annulated tropones and tropolones through oxidative cyclization of phenolic nitronates followed by ring expansion and elimination (Scheme 38).[170–172] Treatment of phenolic nitroalkane **38-1** with $K_3Fe(CN)_6$ in dilute KOH solution provided spirocyclicdienone **38-2** through a stepwise single electron transfer process. Formation of cyclopropane intermediate **38-3** followed by ring expansion of **38-4** afforded tropone **38-5** in good yield.

Cha's group applied this radical anion coupling strategy to the total synthesis of pareitropone (Scheme 39).[173] Exposure of the dihydroquinoline precursor **39-1** to excess amount of $K_3Fe(CN)_6$ in dilute KOH solution led to spirocyclicdienone intermediate **39-2**, which underwent cyclopropanation, ring expansion and elimination to afford the tropone-containing natural product.

**3.3.3 Simmons-Smith cyclopropanation followed by ring expansion—**In 1974, Tobinaga and his coworkers reported a synthesis of (±)-colchicine featuring a Simmons-Smith cyclopropanation followed by Jones oxidation and rearrangement to access the tropone moiety and the adjacent seven-membered ring (Scheme 40).[174] An intramolecular oxidative phenol coupling reaction provided the spirocyclic intermediate **40-2**, which was reduced to allylic alcohol for the Simmons-Smith cyclopropanation. The tricyclic carbon skeleton and the tropone moiety in **40-6** were constructed by Jones oxidation followed by an acid promoted rearrangement. The synthesis then intercepts with Eschenmosers' at this stage.[169]

The above strategy was also applied to the synthesis of monocyclic tropolones (Scheme 41).[175] A sequence of Birch reduction followed by Simmons-Smith cyclopropanation and oxidative rearrangement provided a short synthesis of various substituted tropolones from benzene derivatives.

**3.3.4 Dihalocarbene mediated cyclopropanation followed by ring expansion—**In 1968, Birch reported a synthesis of nezukone by reduction of isopropyl anisole **42-1**

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followed by cyclopropanation and silver-mediated ring expansion (Scheme 42).[176] The cyclopropanation was mediated by a dichlorocarbene species derived from chloroform.

In 1978, MacDonald prepared the tropolone moiety in γ-thujaplicin via a sequence of cyclopropanation and ring expansion (Scheme 43).[177] The diene substrate **43-2** for cyclopropanation was derived from Birch reduction of phenol derivative **43-1**. The cyclopropanation was mediated by sodium trichloroacetate through a dichlorocarbene intermediate. Epoxidation of the remaining olefin followed by an acid catalyzed rearrangement afforded α-chlorotropone intermediate **43-5**, which was converted to γ-thujaplicin under acidic conditions.

Banwell applied the sequence of cyclopropanation and ring expansion to the synthesis of a number of tropone- and tropolone-containing compounds,[178–179] As shown in Scheme 44, cyclopropanation via dihalocarbene followed by ring expansion would lead to the formation of halotropone or halotropolone derivatives, which could undergo cross-coupling to form other tropone- or tropolone-containing compounds, such as β-dolabrin, β-thujaplicin, and β-thujaplicinol.[180–181] The synthesis of nezukone involved the formation of alkylidene cyclopropane from halocyclopropane followed by ring expansion.[31]

The synthesis of stipitatic acid and puberulic acidal so involved dihalocarbene-mediated cyclopropanation followed by ring expansion (Scheme 45).[182] The carboxylic acid group was introduced by quenching an alkyllithium intermediate with carbon dioxide at an early stage (from **45-1** to **45-2**) for the synthesis of stipitatic acid. A late stage Pd-catalyzed carbonylation of bromotropone **45-7** furnished the carboxylic acid group in the synthesis of puberulic acid.

In addition to tropolones, polysubstituted tropones have also been prepared from substituted cyclohexanones by this method.[183]

#### 3.3.5 Sulfur ylide mediated cyclopropanation followed by ring expansion—

Evans reported a convergent formal synthesis of (±)-colchicine utilizing a cyclopropane derivative of a quinonemonoketal (Scheme 46).[184–185] Addition of an ester enolate to the above quinonemonoketal followed by Friedel-Crafts cyclization afforded spirocyclic intermediate **46-3**, which could undergo acid-mediated rearrangement to yield two seven-membered rings in **46-4**. Oxidation by DDQ then generated the tropolone moiety in **46-5**, which could be converted to advanced colchicine precursors.

Evans also demonstrated the utility of this strategy in the total synthesis of β-dolabrin (Scheme 47).[185] The ring expansion was effected by base via electrocyclic ring opening of enolate **47-3** derived from ketone **47-2**.

In 1985, Keith prepared stipitatic acid from a quinone derivative via cyclopropanation and ring expansion (Scheme 48).[186] The reaction between the quinone substrate **48-1** and dimethylsulfonium carbomethoxymethylide **48-2** was nearly quantitative.

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In Banwell's synthesis of MY3-469 and isopygmaein, a nucleophilic cyclopropanation mediated by a sulfur ylide followed by Lewis acid promoted ring expansion afforded the tropolone core of both natural products (Scheme 49).[187]

Banwell also employed the sulfur ylide cyclopropanation/ring expansion strategy in his asymmetric synthesis of colchicine (Scheme 50).[188] Exposure of the resulting cyclopropyl ortho-quinonemonoketal **50-2** to excess of TFA promoted the rearrangement to tropolone and intercepts with previous syntheses. This asymmetric synthesis is the cumulative result of a large body of previous work.[188–192]

Later on, Banwell used the same strategy for the synthesis of tropoloisoquinoline alkaloids imerubrine and grandirubrine (Scheme 51).[188] The tetracyclic precursor **51-1** for cyclopropanation was prepared in 7 steps. Taylor-McKillop oxidation of the ortho-methoxy phenol moiety generated an ortho-quinonemonoketal intermediate, which then underwent cyclopropanation to afford **51-2**. Treatment of this cyclopropane with TFA directly yielded the natural product imerubrine. Hydrolysis followed by thermal rearrangement of the same intermediate provided grandirubrine.

In addition to sulfoxide, sulfone was also used for the cyclopropanation and ring expansion sequence for the preparation of tropones from quinonemonoketal derivatives.[193]

**3.3.6 Formation of alkylidene cyclopropanes followed by ring expansion—** Alkynyliodonium salts are useful reagents in organic synthesis because they can be easily converted to alkylidene carbenes under mild conditions. Feldman's group found that alkylidene carbenes could cyclopropanate arenes to form an alkylidene intermediate.[194] In 2002, Feldman successfully prepared tropoloisoquinoline alkaloid pareitropone by ring expansion of alkylidene cyclopropanes (Scheme 52).[195–196] Treatment of alkynylstannane **52-1** with Stang's reagent followed by base afforded alkylidiene intermediate **52-3**, which could react with the adjacent arene via a cyclopropanation and ring expansion cascade to afford cycloheptatriene **52-5**. Removal of the to syl and TIPS groups followed by oxidation provided natural product pareitropone.

**3.3.7 Ring expansion of six-membered ring via Tiffeneau-Demjanov rearrangement—**In Yoshikoshi's synthesis of β-thujaplicin, the seven-membered cycloheptanone ring was derived from Tiffeneau-Demjanov ring expansion of cyclohexanone through a cyanohydrin intermediate (Scheme 53).[197] The β-isopropyl substituted cycloheptanone **53-2A** was then oxidized to the corresponding dione by $SeO_2$. The target was completed by further bromination and elimination.

**3.3.8 Ring expansion of three-membered ring—**Recently, a synthesis of benzotropolone goupiolone A was reported featuring a ring expansion of cyclopropyl benzocyclobutene (Scheme 54).[198–199] The cyclopropyl benzocyclobutene precursor **54-1** was prepared following protocols developed previously.[198] The key ring expansion step was operated under thermal conditions to give a mixture of two diastereoisomers **54-3**. Oxidation of the benzocycloheptene with *m*CPBA followed by hydrolysis and elimination gave tropolone **54-4** as the product. Finally the methylene acetal-protecting group was removed

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and the synthesis of goupiolone A was completed. The structure of this natural product was also revised based on synthesis.

### 3.4 Formation of the seven-membered ring by [5+2] cycloaddition

The [5+2] cycloaddition has been widely used in 7-membered ring synthesis. Some of them have also been applied to the synthesis of tropones and tropolones. Based on the reactive intermediates, four types of [5+2] cycloadditions are discussed below.

**3.4.1 Perezone type [5+2] cycloaddition—**The transformation of perezone to pipitzol was first discovered by Anschutz and Leather in 1885 (Scheme 55).[200] The structure of pipitzol was later revised to a 7-membered ring with a carbonyl bridge and the mechanism of this type of [5+2] cycloaddition was studied in detail.[201–207]

Buchi's group applied this strategy to the synthesis of tropolones via a Lewis acid catalyzed [5+2] cycloaddition of quinonemonoketal and isosafrole (Scheme 56).[208] The bicyclic compound **56-3** was converted to 4-aryltropolone methyl ether **56-4** through excursion of the carbonyl bridge followed by oxidation and hydrolysis.

**3.4.2 Oxidopyrylium type [5+2] cycloaddition—**Oxidopyrylium ions can undergo cycloadditions with unsaturated C-C bonds.[209] The oxidopyrylium species can be generated by elimination of 2-acetoxypyran-5-one under basic condition[210–213] or through group transfer of β-hydroxy-γ-pyrones under thermal condition.[214] The resulting oxidopyrylium species could undergo intra- or intermolecular cycloadditions to afford oxa-bridged molecules, which then could be derivatized to tropones and tropolones.

In 2002, Baldwin and his co-workers reported a synthesis of deoxyepolone B by employing an intermolecular [5+2] cycloaddition of oxidopyrylium ion with an activated alkene (Scheme 57).[215–216] An oxidative furan ring expansion followed by acylation gave the oxidopyrylium precursor **57-2**, which underwent [5+2] cycloaddition with α-acetoxyacrylonitrile to yield seven-membered ring **57-4** with an oxygen bridge. It took over ten steps to convert this cycloaddition product to substituted tropolone **57-6** via intermediate **57-5**. Deoxyepolone B was obtained by a biomimetic hetero-Diels-Alder cycloaddition of intermediate **57-7** with humulene.

In 2005, Celanire reported their synthetic progress towards cordytropolone via an intramolecular [5+2] cycloaddition of oxidopyrylium ion with an alkyne (Scheme 58).[217] The 2,5-disubstituted furan **58-1** could be converted to 2-acetoxypyran-5-one **58-2** via oxidative rearrangement followed by acylation. A base-promoted intramolecular [5+2] cycloaddition of the resulting oxidopyrylium **58-3** with alkyne afforded intermediate **58-4** with an oxygen bridge.

In 2010, Tchabanenko's group reported a synthesis of the tropolone subunit in a model system for rubrolone aglycon (Scheme 59).[218] The intermolecular [5+2] cycloaddition of oxidopyrylium ion **59-2** with indenone occurred non-selectively to afford four isomers. All four isomers could be converted to the same tropolone **59-5** reported by Boger in 1994[219] after a series of identical manipulations including conjugate addition of thiophenol,

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Pummerer rearrangement mediated by NCS, substitution of the thiophenyl group by methoxy group, base-mediated elimination of the oxygen bridge, oxidation and $BBr_3$-mediated cleavage of methyl ether.

In 2013, Tang's group reported the first total synthesis of harringtonolide,[220] a naturally occurring tropone with significant anticancer activity. Highly substituted bicyclic decalin derivative **60-3** was converted to pentacyclic intermediate **60-5** via an intramolecular [5+2] cycloaddition of oxidopyrylium ion **60-4** and alkene (Scheme 60). After some functional group manipulations, the cycloheptadiene in **60-6** underwent a [4+2] cycloaddition with singlet oxygen. DBU-mediated Kornblum-DeLaMare rearrangement[113] and elimination under acidic conditions yielded natural product hainanolidol with the tropone moiety. Treatment of hainanolidol with lead tetraacetate following literature conditions[221] finally provided harringtonolide for the first time by total synthesis. All synthetic efforts towards harringtonolide or its related compounds from other groups[29,222–225] did not yield the tropone moiety except the previously discussed synthesis from Mander in Scheme 35.

Tang's group also reported an efficient way to convert known [5+2] cycloaddition product **61-1**[226] to tropone **61-5** in a model system of harringtonolide (Scheme 61).[220] After the introduction of allylic thioether to **61-2** by a sequence of addition of methyl Grignard reagent and $S_N1'$ displacement by thiophenol, a base-mediated anionic opening of the ether bridge occurred to yield bicyclic product **61-3**. A sequence of hetero-Diels-Alder cycloaddition of cycloheptadiene with 2-nitrosopyridine,[227] reductive cleavage of the N-O bond to an amino alcohol and double elimination in the presence of $SnCl_2$ provided the tropone product **61-5** smoothly. Unfortunately, when this method was applied to the synthesis of harringtonolide, no desired hetero-Diels-Alder cycloaddition product was observed.

Many tropolones, such as β-thujaplicinol, puberulic acid and puberulonic acid, have two or more hydroxy groups on the seven-membered ring. Murelli's group recently reported a general protocol for the synthesis of hydroxytropolones from kojic acid via [5+2] cycloaddition of oxidopyrylium followed by $BCl_3$-mediated ring-opening of the ether bridge (Scheme 62).[228] Changing the Lewis acid to triflic acid led to the formation of methoxytropolones.[229]

**3.4.3 [5+2] Cycloaddition through 3-hydroxypyridinium betaines—**Katritzky and his co-workers first developed the synthesis of tropones by cycloaddition of 3-hydroxypyridinium betaines with alkenes or alkynes.[230–233] Tamura applied this strategy to the synthesis of stipitatic acid and β-thujaplicin (Scheme 63).[234] The 1,3-dipolar [5+2] cycloaddition of 3-hydroxypyridinium betaine **63-2** with ethyl propiolate gave the *N*-bridged compound **63-3**, which underwent sequential alkylation and Hoffman elimination to afford the tropolone core in **63-5**. Further hydrolysis by acid and base provided stipitatic acid. Tropolone β-thujaplicin was prepared similarly. A copper chromite mediated decarboxylation at high temperature was required in late stage synthesis.

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### 3.5 Formation of the seven-membered ring by rhodium catalyzed [3+2] cycloaddition of carbonyl ylide

When a carbonyl ylide is constrained in a six-membered ring, a [3+2] cycloaddition can lead to the formation of seven-membered rings. In 1992, Friedrichsen reported a synthesis of benzotropolones via [3+2] cycloaddition of a carbonyl ylide with alkyne (Scheme 64).[235] In the presence of rhodium acetate, carbonyl ylide **64-2** was formed and it underwent an intramolecular [3+2] cycloaddition with the terminal alkyne to generate oxa-bridged compound **64-3**, which was easily isomerized to the corresponding benzotropolone **64-4** by treatment with Lewis acid. They also applied the same strategy to the synthesis of hetero-annulated tropolones.[236]

Baldwin's group applied the rhodium-catalyzed [3+2] cycloaddition of carbonyl ylide with alkyne to the synthesis of the tropolone core in epolone B (Scheme 65).[237] Treatment of α-diazoketone **65-1** with rhodium acetate afforded tetracyclic product **65-3** via [3+2] cycloaddition. Exposure of this product to hydrochloric acid led to the cleavage of the ether bridge and the formation of tropolone **65-4**, which underwent further transformations to yield an epolone B analogue.

Schmalz successfully applied the Rh(II)-catalyzed [3+2] cycloaddition of carbonyl ylide and alkyne to the synthesis of colchicine (Scheme 66).[238–239] Treatment of α-diazoketone **66-1** with rhodium acetate led to the formation of carbonyl ylide **66-2**, which underwent an intramolecular [3+2] cycloaddition with the terminal alkyne to generate the oxa-bridged compound **66-3**. Direct treatment of this compound with Lewis acid led to the formation of tropone **66-4**, which could undergo non-selective α-functionalization to generate two aminotropones **66-5A/B**. Reduction of the ketone in **66-3** by L-Selectride followed by TMSOTf mediated rearrangement and oxidation of the resulting diol could provide α-tropolone **66-6** selectively. The synthesis of colchicine was completed by further functionalization of this tropolone intermediate following previously established procedures.

### 3.6 Formation of the seven-membered ring by [4+3] cycloaddition

**3.6.1 Oxyallylcation [4+3] cycloaddition—**Noyori's group reported the synthesis of nezukone and β-thujaplicin in 1975 and 1978, respectively.[240–241] The synthesis of the latter is shown in Scheme 67. An iron-promoted oxyallylcation [4+3] cycloaddition between tetrabromoketone **67-1** and 2-*iso*-propyl furan **67-3** provided the seven-membered ring in **67-4** with an oxygen bridge. The resulting bicyclic ketone underwent sequential hydrogenation and an acid-promoted elimination to yield a mixture of enone and dienone (**67-5A/B**), both of which could be converted to tropone **67-6**. Treatment of the resulting tropone with hydrazine yielded the corresponding aminotropone **67-7**, which was converted to the β-thujaplicin by exposure to KOH.

The oxyallylcation species (e.g. **68-2**) could also be generated through base-promoted elimination of α-haloketones (e.g. **68-1**).[242–246] This method was applied to the synthesis of substituted tropones after dehalogenation of the cycloaddition product followed by rearrangement (Scheme 68).[247]

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Cha also applied the above method to the synthesis of tropolone thujaplicin by starting with 1,1,3-trichloroacetone and furan.[248]

The oxyallylcation can also be derived from silyl enol ether in the presence of Lewis acid (**69-1** to **69-2**, Scheme 69).[249] Cha applied this method to the synthesis of colchicine[250–251] and tropoloisoquinolines.[252] The key [4+3] cycloaddition between substituted furan **69-3** and silyl enol ether **69-1** was carried out in the presence of TMSOTf. Only one diastereomer (**69-4**) was observed with the desired regioselectivity. Cleavage of the ether bridge[253] followed by removal of the Boc group and acetylation afforded (−)-colchicine. Interestingly, in the presence of acetylamide in **69-6**, the [4+3] cycloaddition yielded an isomer with undesired regioselectivity. The difference was rationalized by hydrogen bonding between the acetylamide and the methoxy group in oxyallylcation.

The same strategy was also employed in Cha's synthesis of imerubrine (Scheme 70). The key [4+3] cycloaddition occurred under the same reaction conditions. In this case, the regioselectivity was low and a mixture of desired product **70-2B** and its isomer **70-2A** was observed in nearly a 1:1 ratio. Cleavage of the ether bridge in the desired isomer **70-2B** and elimination of water then yielded imerubrine.

**3.6.2 Rh-catalyzed [4+3] cycloaddition via tandem cyclopropanation/Cope rearrangement—**Davies' group developed a Rh-catalyzed [4+3] cycloaddition of vinylcarbenoids with 1,3-dienes for the synthesis of highly functionalized cycloheptadienes,[254–258] which could be converted to various substituted tropones and tropolones.[259–260] The cascade reaction involved cyclopropanation of the metal carbenoid derived from diazo compound **71-1** with the less hindered double bond of the diene **71-2** and Cope rearrangement. A very short synthesis of nezukone demonstrated the efficiency of this strategy (Scheme 71).[259]

Prior to Davies's work, Wenkert also prepared the seven-membered ring in nezukone using a sequence of stepwise cyclopropanation of diene with ethyl diazopyruvate **72-1**, olefination and Cope rearrangement (Scheme 72).[261] The resulting cycloheptadiene **72-3** was oxidized by air to form the hydroperoxide, which was reduced by $Me_2S$. Jones oxidation then led to the formation of keto-ester product **72-4**. A base mediated isomerization followed by in-situ protection of the ketone as anenolate and addition of MeLito the ester followed by elimination afforded nezukone.

Wenkert also applied the above method to a formal synthesis of colchicine (Scheme 73).[147] The divinylcyclopropane starting material **73-1** in this synthesis was prepared by the same strategy employed in Scheme 72.

**3.6.3 [4+3] Cycloaddition of cyclopropenone ketal with dienes—**Boger's group reported an elegant thermal cycloaddition of cyclopropenone ketals[262] with alkenes and dienes in the 1980s.[263–267] The cycloaddition with α-pyrone is particularly intriguing since it provides a way to access tropone- or tropolone-containing natural products, such as colchicine (Scheme 74).[265] It was believed that the cyclopropenone ketal **74-1** was in equilibrium with the vinylcarbene species **74-2**, which underwent [4+3] cycloaddition with

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α-pyrone **74-3** to afford intermediate **74-4** with a lactone bridge. Decarboxylation then led to the formation of cycloheptatriene or tropone products **74-5**. The synthesis of natural product colchicine was accomplished by Starting with pyrone **74-6**.

### 3.7 Formation of the seven-membered ring by other cycloadditions

**3.7.1 [2+2] Cycloaddition followed by fragmentation—**A [2+2] cycloaddition between dihaloketene **75-2** and cyclopentadiene **75-1** could generate four-five fused bicyclic compound **75-3**. Stevens and his coworkers applied this method to the synthesis of tropolone (Scheme 75).[268] In the presence of sodium acetate in acetic acid, the four-five fused bicyclic compound could undergo enolization, addition/elimination, and fragmentation to form tropolone **75-4**.[269] This method was later applied to the total synthesis of various tropolones,[269–271] such as β-thujaplicin, by starting with isopropyl substituted cyclopentadiene[272] and a synthetic intermediate for colchicine (**75-7**) as shown in Scheme 75.[273]

A synthesis of 3-substituted tropones was also reported starting with a photolytic [2+2] cycloaddition of 4-acetoxy cyclopent-2-en-1-one **76-1** and alkynes (Scheme 76).[274–276] The [2+2] photolytic cycloaddition gave a mixture of two constitutional isomers **76-2A/B**. One of them (**76-2B**) underwent an oxa-di-π-methane photo-rearrangement to afford **76-3**. When the resulting mixture was exposed to alumina, 3-substituted tropone **76-6** was formed. When R is an isopropyl group, a synthesis of nezukone was realized.[275]

Kelly applied the [2+2] cycloaddition followed by fragmentation strategy to the first synthesis of rubroloneaglycon (Scheme 77).[277] The photolytic [2+2] cycloaddition occurred regioselectively to give single adduct **77-3**. Although only one isomeric MEM ether could undergo the retroaldol fragmentation to form the tropolone product **77-4A**, the other MEM ether (**77-4B**) was recycled to diketone **77-3** after hydrolysis under acidic conditions.

**3.7.2 [4+2] Cycloaddition followed by rearrangement—**Boger reported the synthesis of tropones via a sequence of [4+3] cycloaddition of pyrone with cyclopropenone ketals followed by ring expansion and decarboxylation as discussed before. Interestingly, when the reaction was carried out at room temperature and under high pressure, a Diels-Alder [4+2] reaction occurred and the resulting adduct **78-3** was stable enough to be separated (Scheme 78).[267] Decarboxylation followed by a ring expansion yielded tropone derivative **78-5** having the R and R' groups at different positions on the ring. This method is complementary to the previous [4+3] cycloaddition for the synthesis of substituted tropones in Scheme 74. Boger's group later reported the total synthesis of grandirubrine, imerubrine and isoimerubrine by applying the [4+2] cycloaddition of cyclopropenone ketal with α-pyrone **78-6**.[278] The Diels-Alder reaction occurred at room temperature and high pressure to afford tropone products after hydrolysis. Treatment of the resulting tropone **78-8** with hydrazine followed by hydrolysis completed the synthesis of grandirubrine, which could be converted to a mixture imerubrine and isoimerubrine after methylation.

Total synthesis of rubroloneaglycon was also realized by Boger's group using a similar strategy (Scheme 79).[219,279–280] The oxygenated tropolone in **79-4** was prepared by an exo-

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selective [4 + 2] cycloaddition of diene **79-1** and cyclopropenone ketal at room temperature followed by ring expansion of norcaradiene intermediate derived from **79-3**.

Recently, Wright's group reported a synthesis of substituted tropolones involving a [4+2] cycloaddition of furans with tetrabromocyclopropene **80-1** (Scheme 80).[281] This reaction was first discovered by Tobey and West in the 1960s[282–283] and later investigated by Wright's group for the synthesis of substituted cycloheptadienes.[284–290] After the Diels-Alder cycloaddition, a sequence of rearrangement, hydrolysis in the presence of silver salts, addition of isopropyl zinc cuprate to enone and reduction by samarium diiodide yielded the tropolone natural product.

During the study of [4+2] Diels-Alder cycloaddition of o-benzoquinone **81-1** and aryl acetylene **81-2** for the synthesis of polysubstituted aromatic compounds, Nair's group accidently found that under $SnCl_4$ catalysis, the major product was tropone derivative **81-5** (Scheme 81).[291]

The o-benzoquinone underwent a Lewis acid catalyzed Diels- Alder cycloaddition with phenylacetylene to afford a bicycle [2.2.2] product. In the presence of $SnCl_4$, this intermediatere arranged to [3.2.1] bicyclic product,[292] which was converted to tropone after eliminating a carbon monoxide molecule.

## 4. Conclusion

It was a very exciting breakthrough when the structures of tropolone-containing natural products were first proposed by Dewar. Numerous synthetic efforts were reported on the synthesis and chemical reactivity of tropones and tropolones from 1950s to 1960s. During the last decades, attention was attracted to this family of compounds again because of newly isolated tropolone-containing natural products and their bioactivities. This review summarized methods developed for the synthesis of tropones and tropolones that were found in natural products based on how the seven-membered rings were constructed. It should facilitate the synthesis of tropolone-containing compounds discovered in nature or designed by medicinal chemists.

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## Biographies

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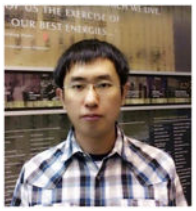

Wangze Song received his B.S. degree in Chemistry from Nankai University in 2008, where he began his undergraduate research in Professor Chi Zhang's lab. He earned his M.S. degree in Chemistry from Zhejiang University in 2011 under the supervision of Professor Yanguang Wang and Professor Ping Lv. He is currently pursuing his Ph.D. degree in Professor Weiping Tang's lab at the University of Wisconsin-Madison.

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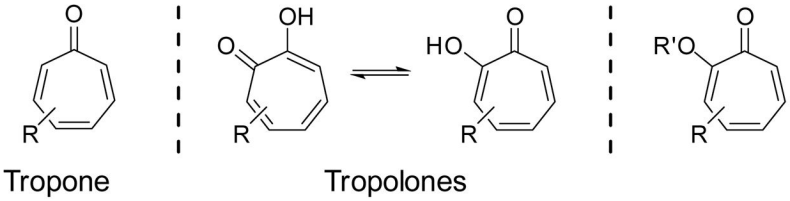


**Scheme 1.**

Tropones, tropolones and related compounds

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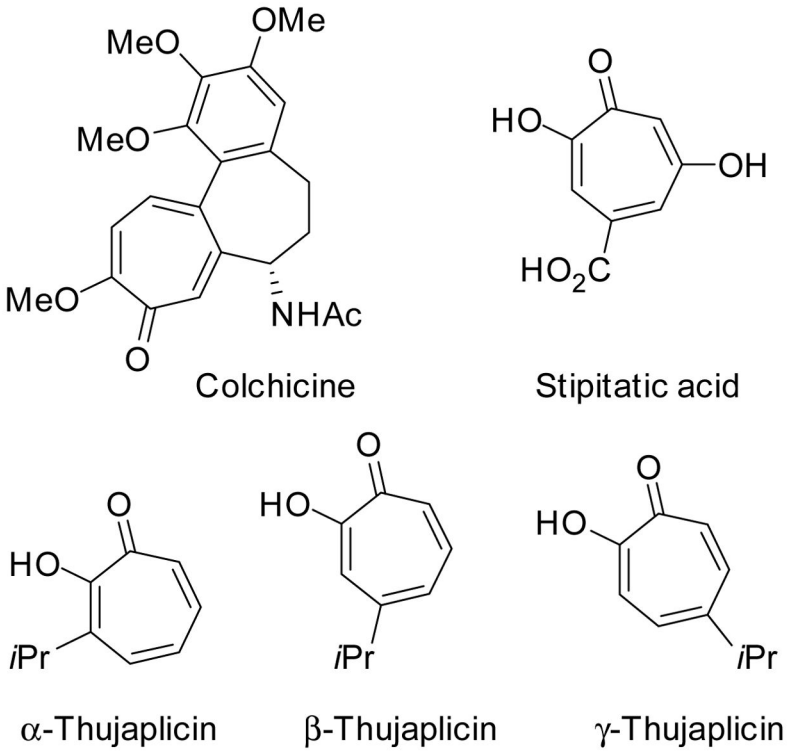


**Scheme 2.**
Tropolones discovered in early days

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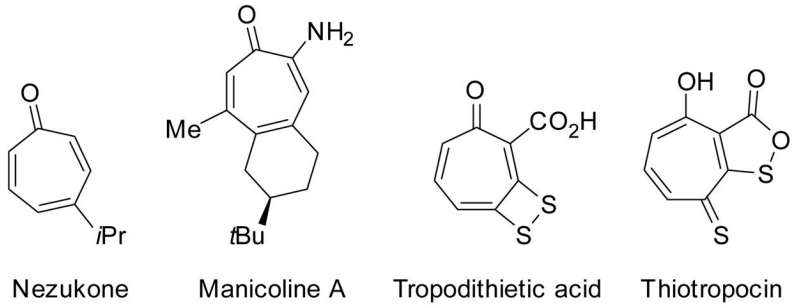


**Scheme 3.**

Examples of mono- and bicyclic naturally occurring tropones and related compounds

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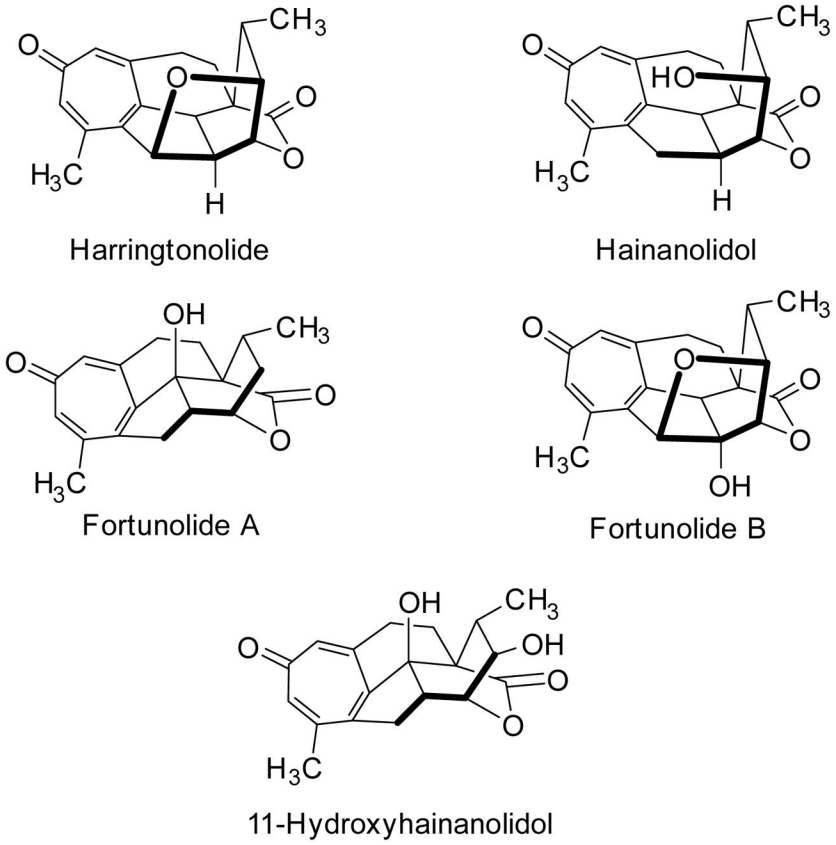


**Scheme 4.**
Norditerpene tropones

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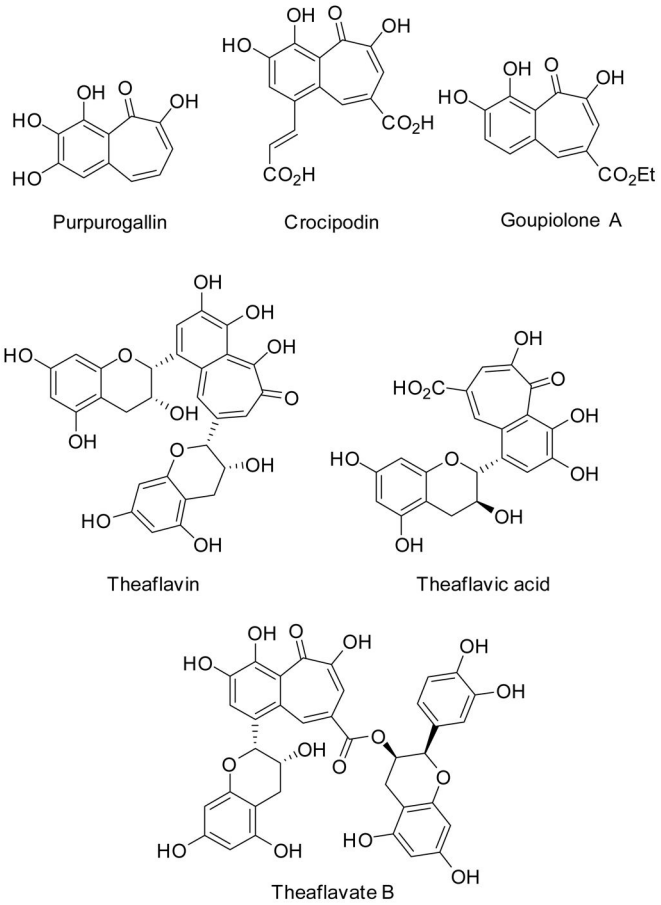


**Scheme 5.**

Examples of benzotropolones and some theaflavin derivatives

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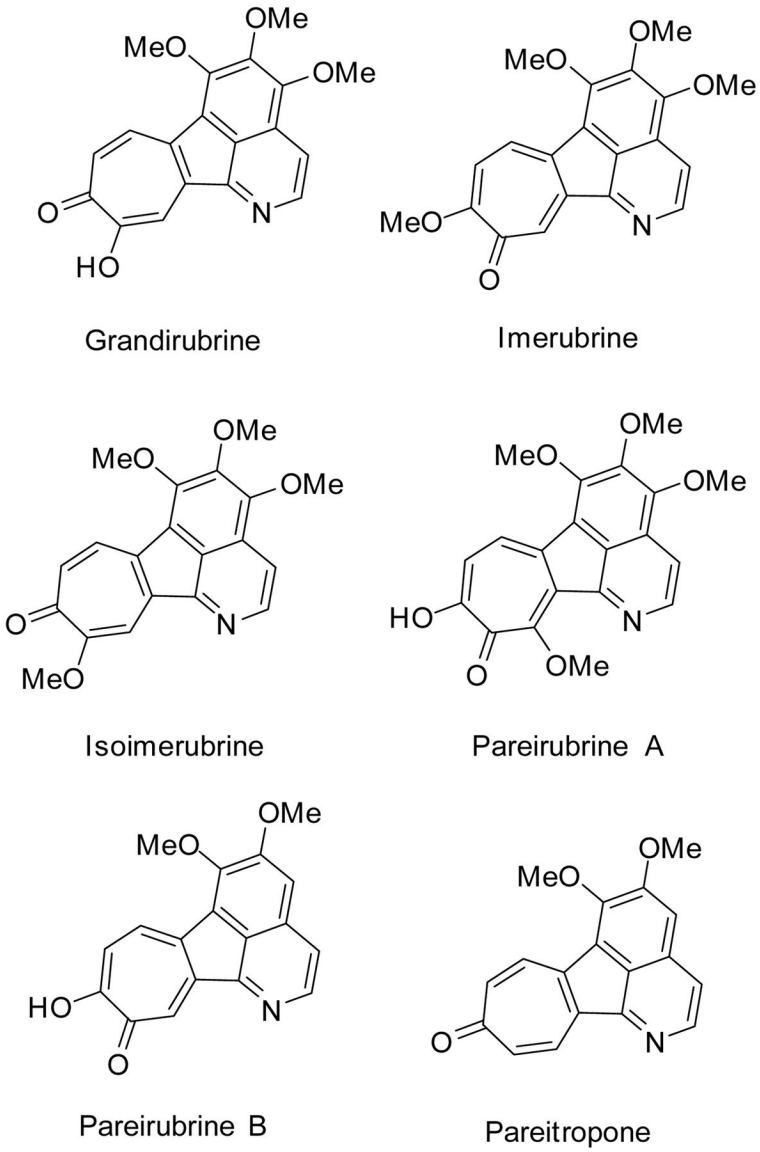


**Scheme 6.**
Tropoisoquinolines and tropoloisoquinolines

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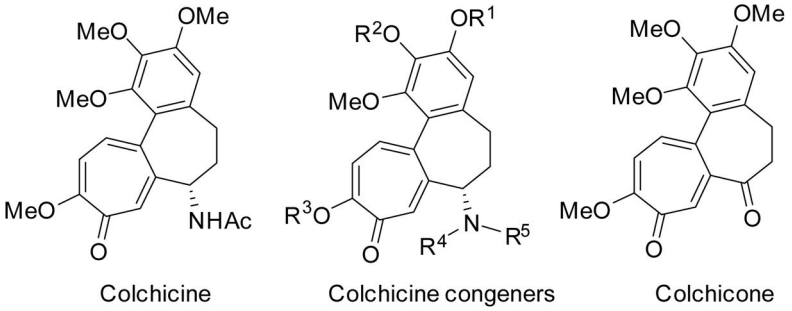


**Scheme 7.**

Colchicine and its congeners

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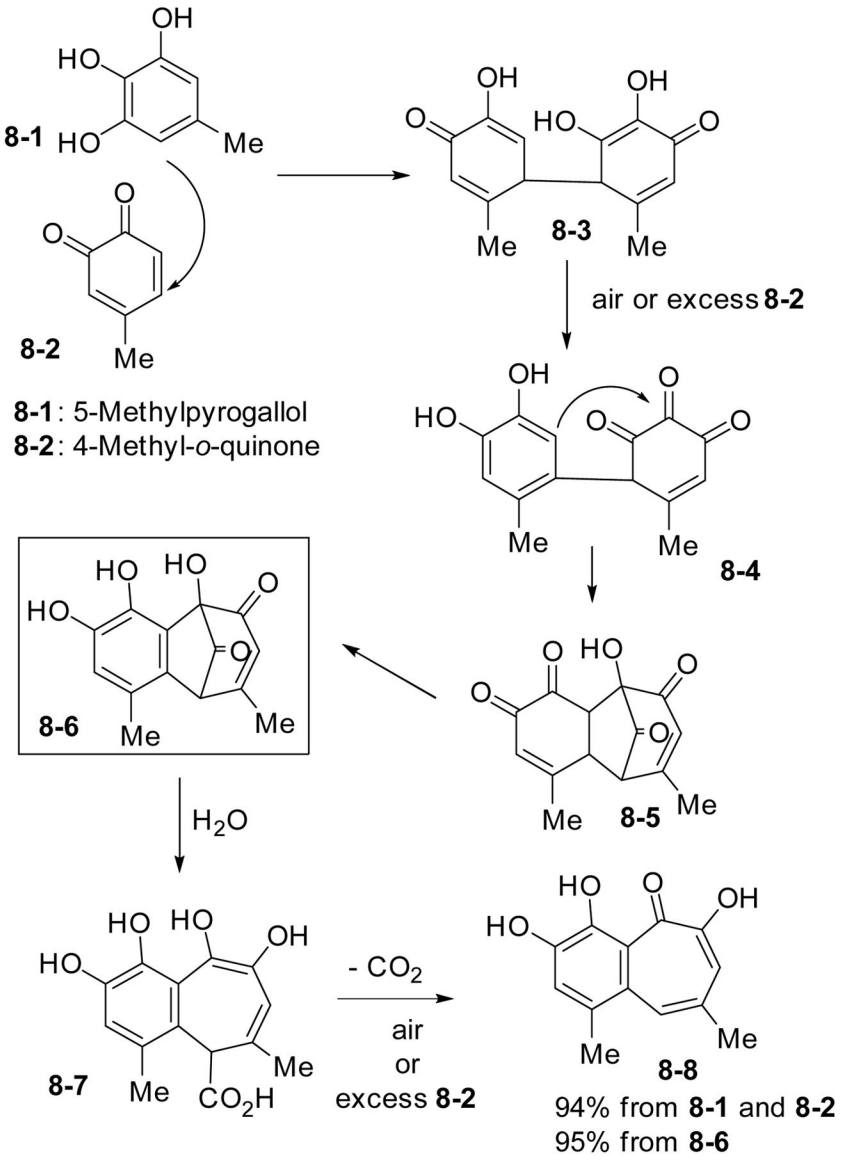


**Scheme 8.**

Biomimetic synthesis of benzotropolones

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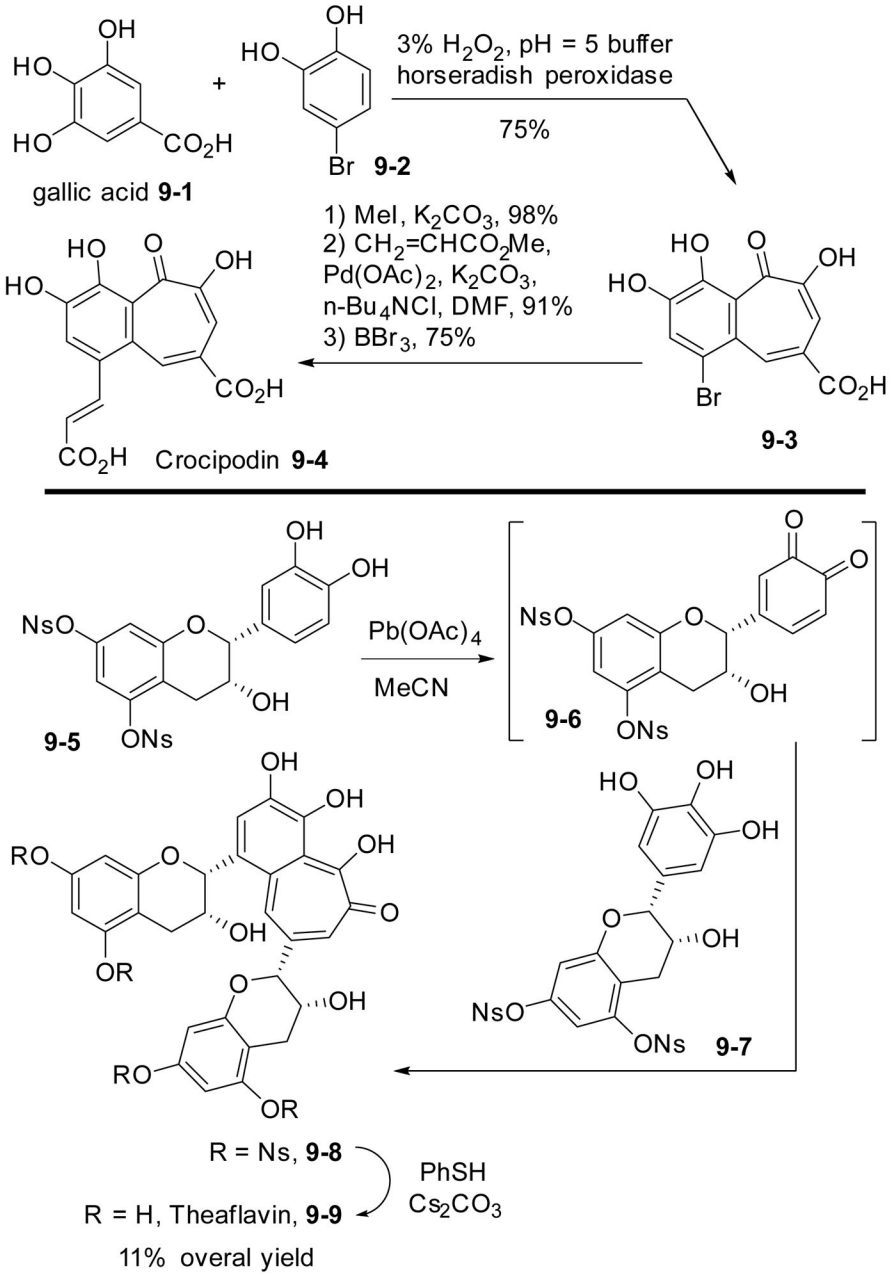


**Scheme 9.**

Biomimetic synthesis of crocipodin and theaflavin

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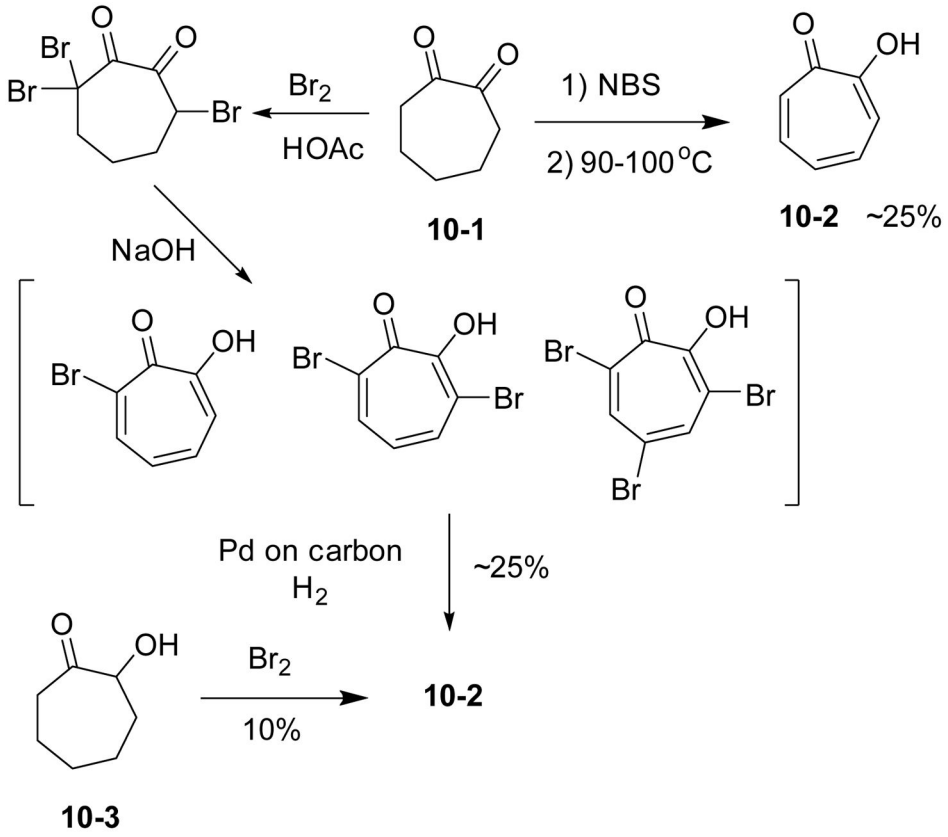


**Scheme 10.**

Oxidation of 1,2-cycloheptanedione and 2-hydroxycycloheptanone by bromine and NBS

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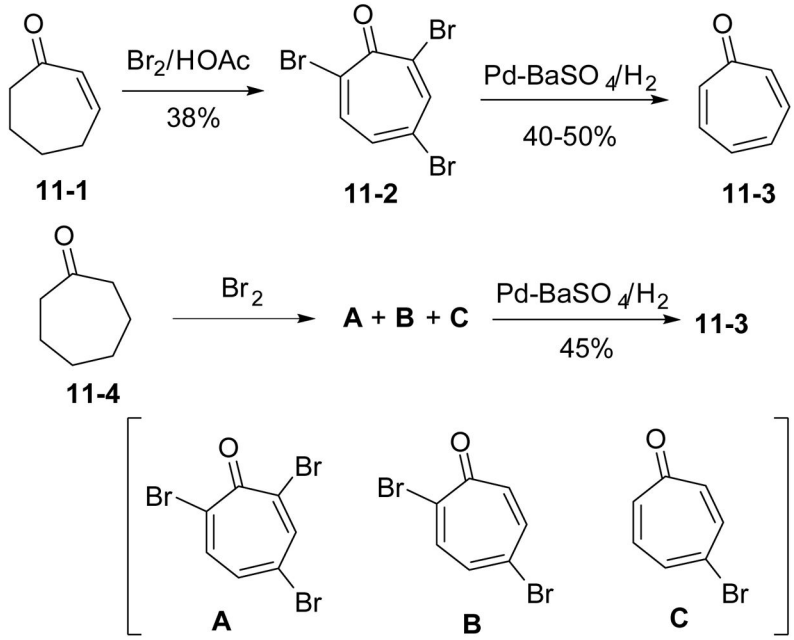


**Scheme 11.**

Oxidation of cycloheptanone to tropone by $Br_2$

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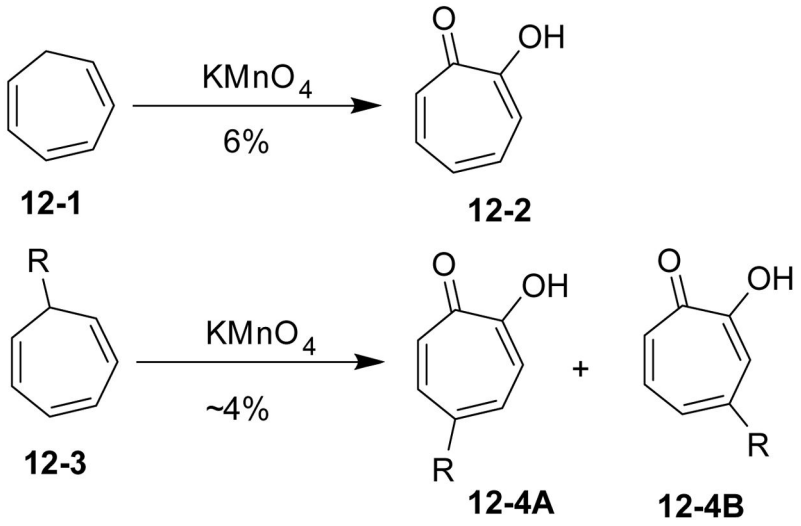


**Scheme 12.**
Oxidation of cycloheptatriene by permanganate

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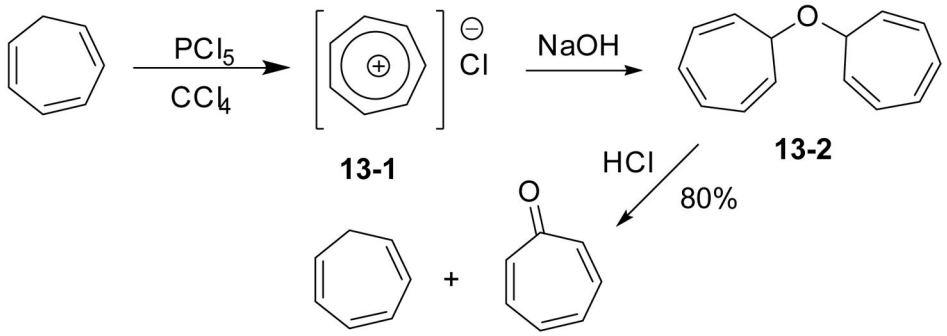


**Scheme 13.**
Synthesis of tropone via ditropyl ether

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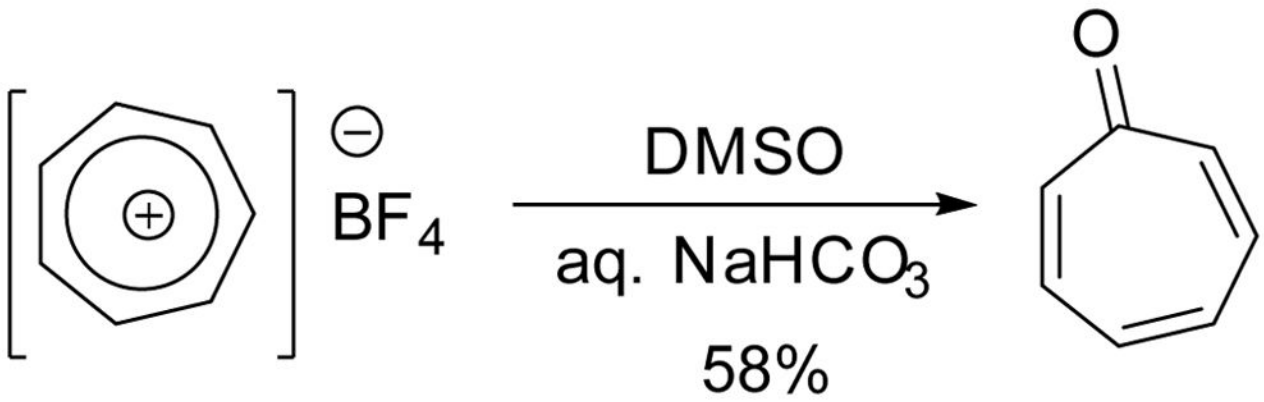


**Scheme 14.**
Synthesis of tropone from tropylium ion

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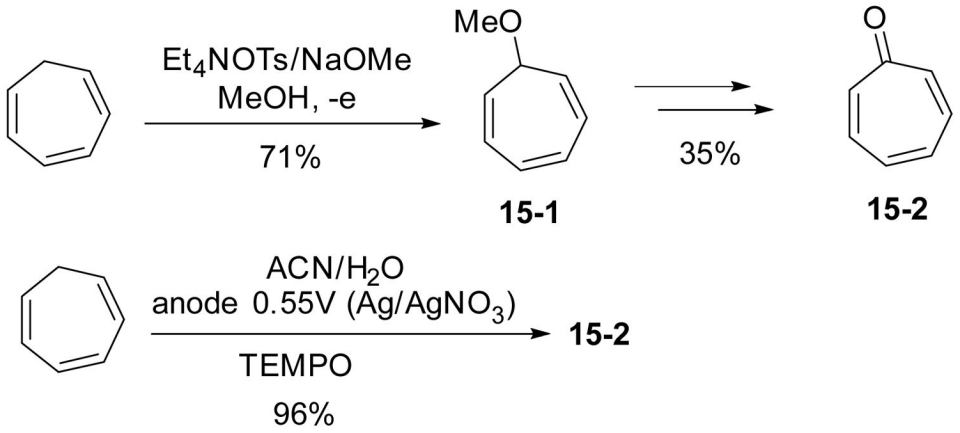


**Scheme 15.**
Synthesis of tropone by electrochemical oxidation

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**Scheme 16.**
Synthesis of tropone by $SeO_2$ oxidation

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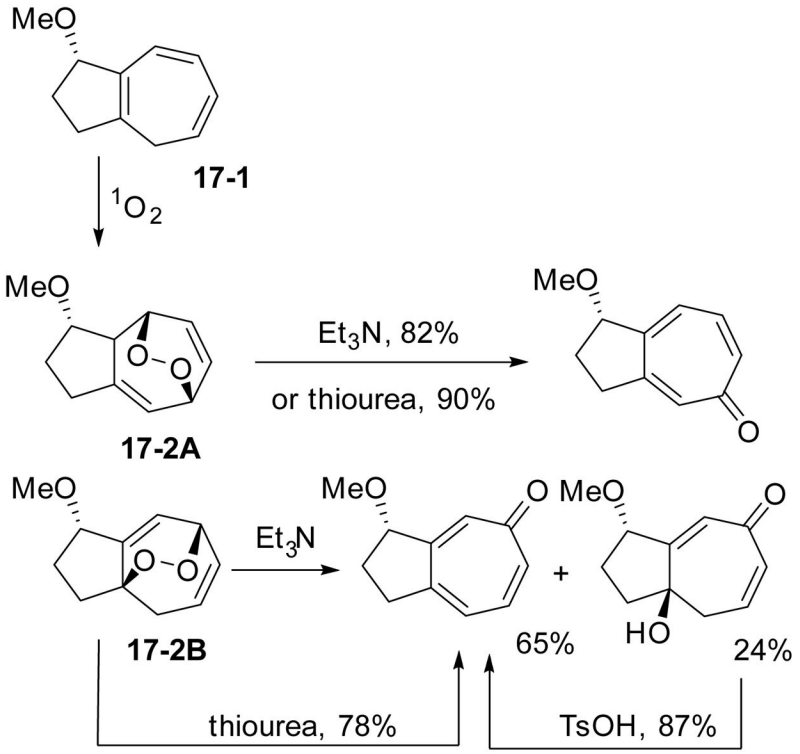


**Scheme 17.**
Synthesis of tropones from endoperoxides

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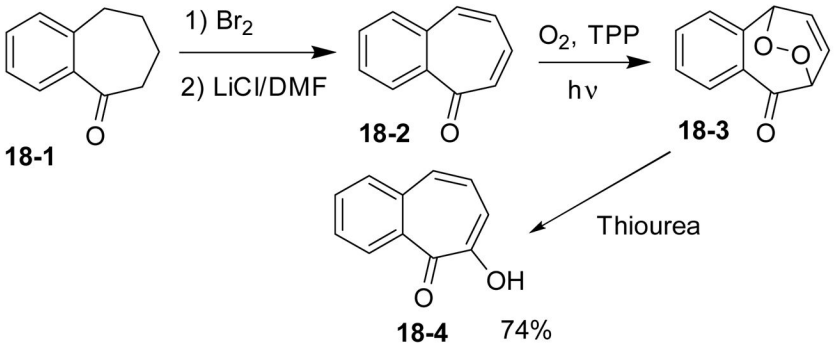


**Scheme 18.**
Oxidation of benzotropone to benzotropolone

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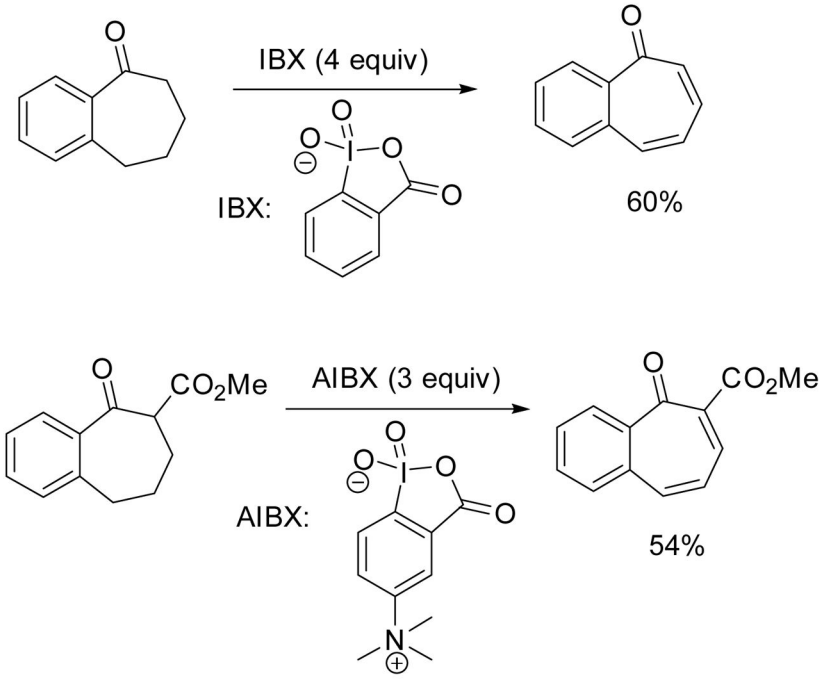


**Scheme 19.**

Dehydrogenative oxidation by hypervalent iodine reagents

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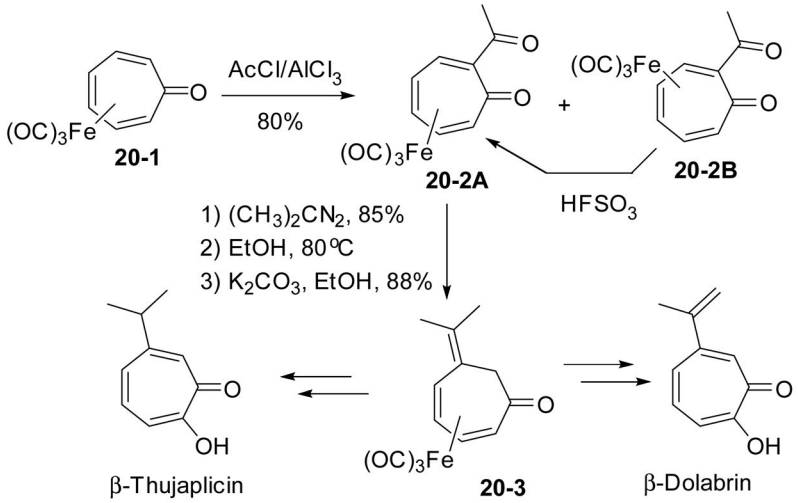


**Scheme 20.**

Synthesis of β-thujaplicin and dolabrin

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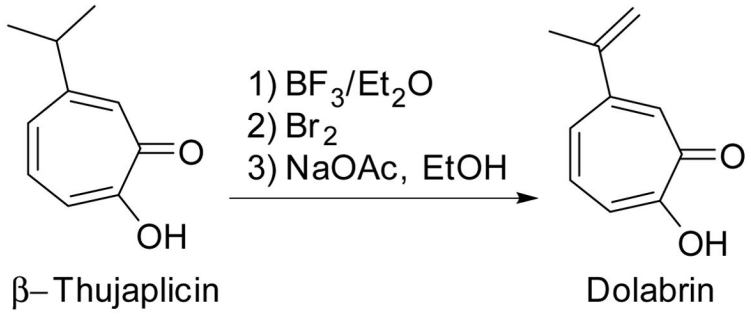


**Scheme 21.**
Synthesis of dolabrin from β-thujaplicin

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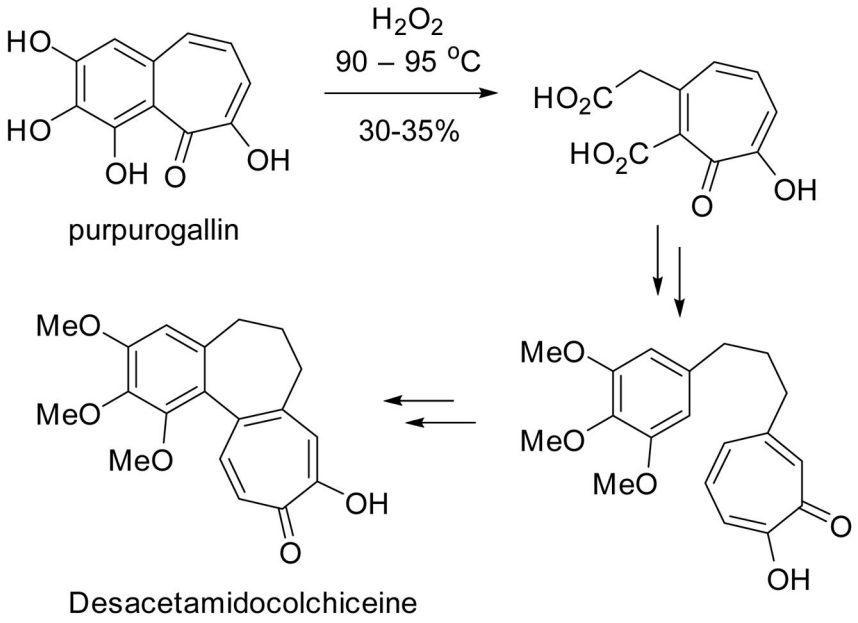


**Scheme 22.**
Formal synthesis of colchicine from purpurogallin

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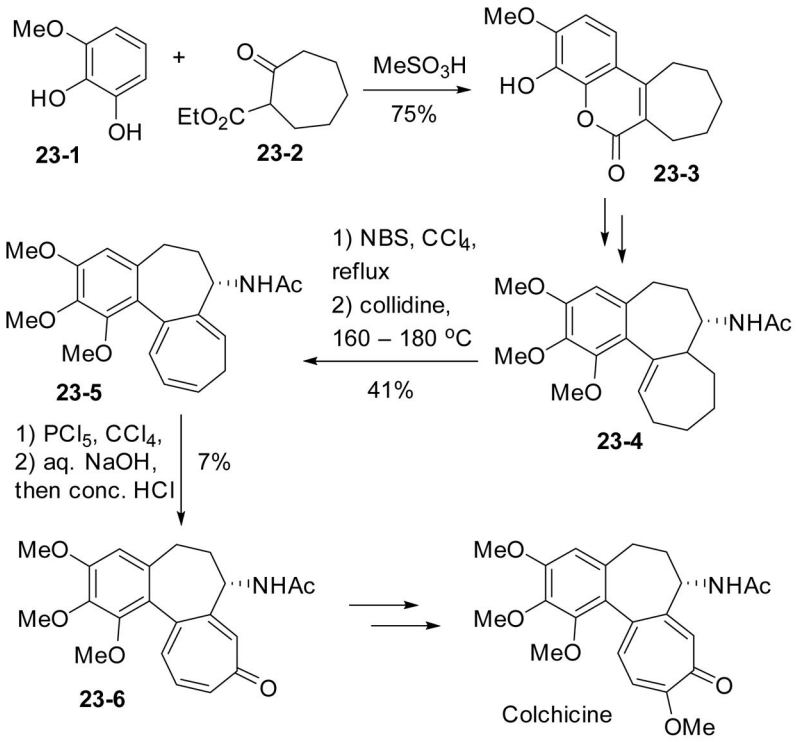


**Scheme 23.**

Synthesis of (±)-colchicine from acycloheptanone

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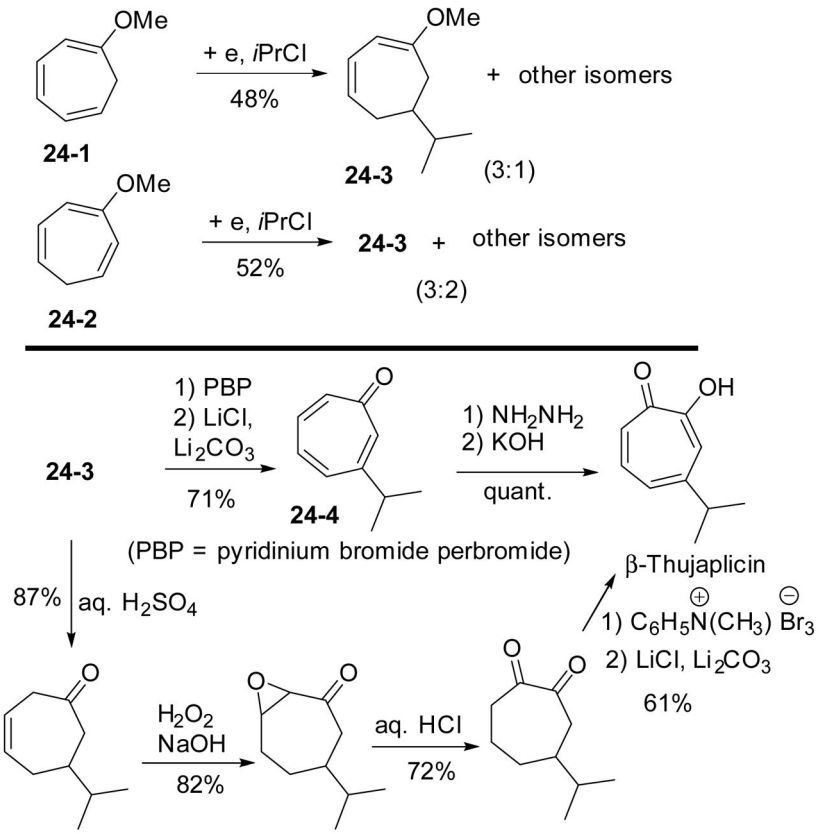


**Scheme 24.**

Synthesis of thujaplicin by electro-reductive alkylation of substituted cycloheptatrienes

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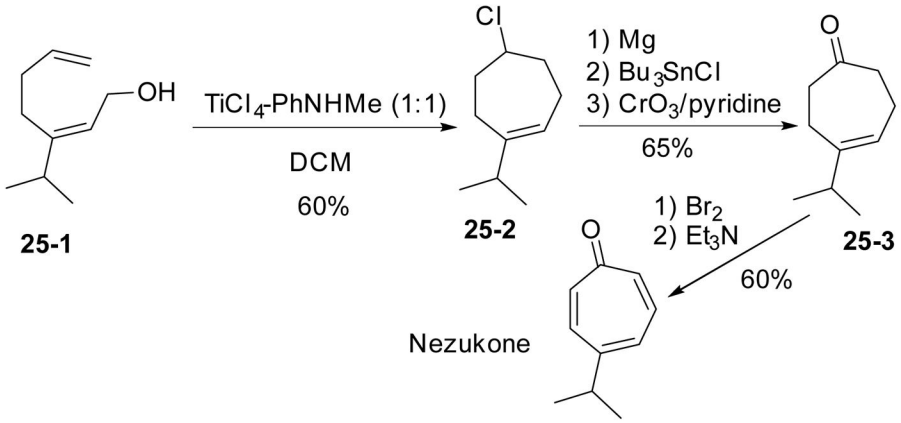


**Scheme 25.**

Synthesis of nezukone via cyclization

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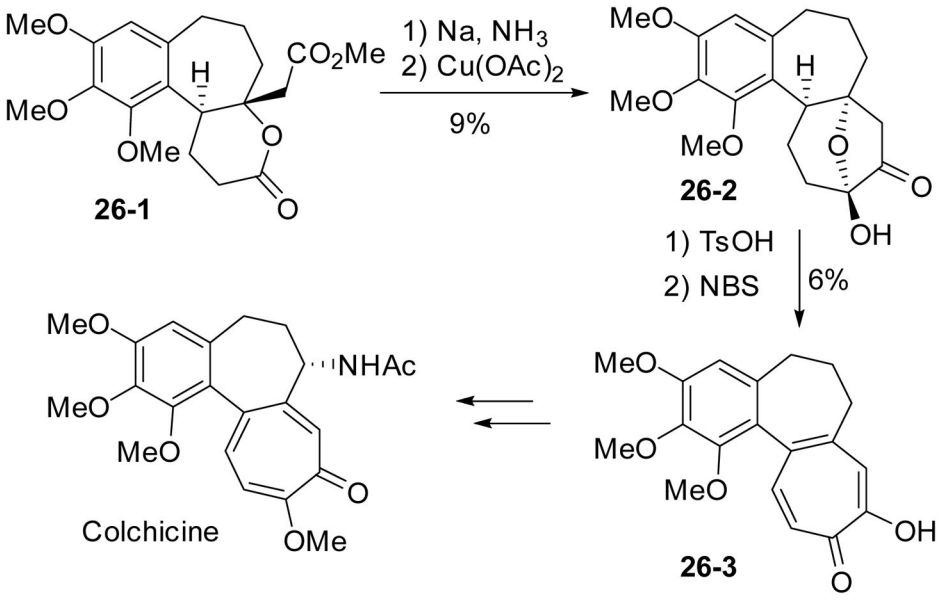


**Scheme 26.**

Synthesis of (±)-colchicine by acyloin cyclization

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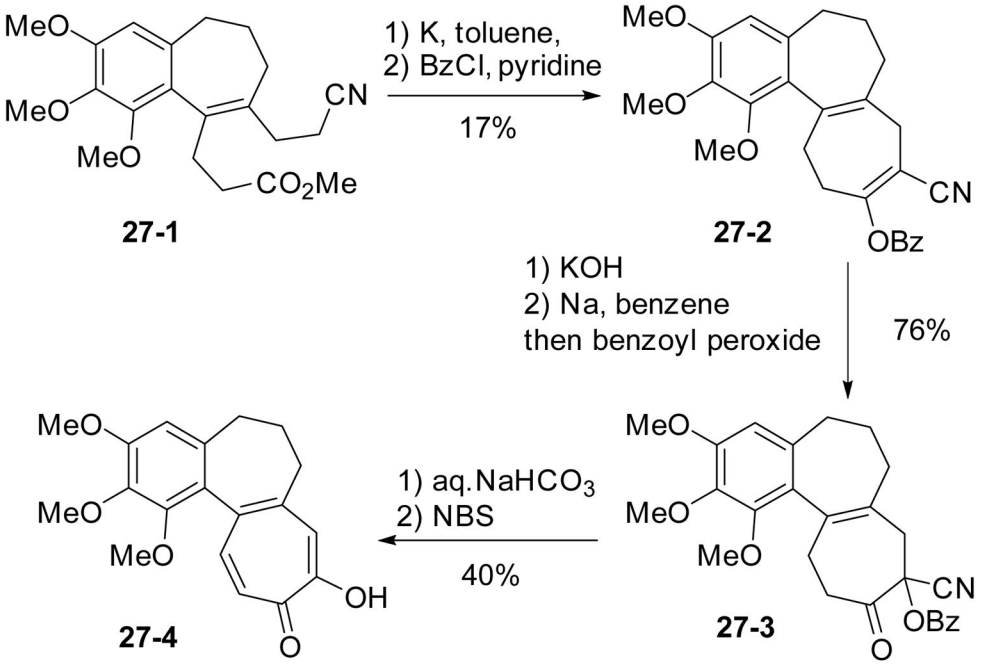


**Scheme 27.**

Formal synthesis of colchicine derivative by cyclization of a cycloheptatriene

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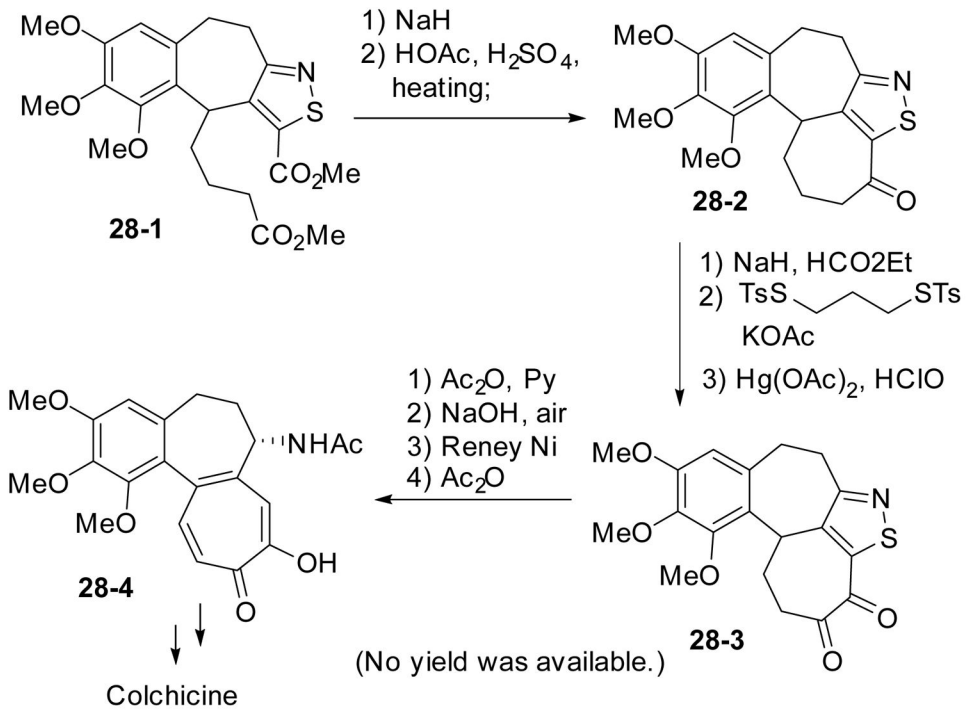
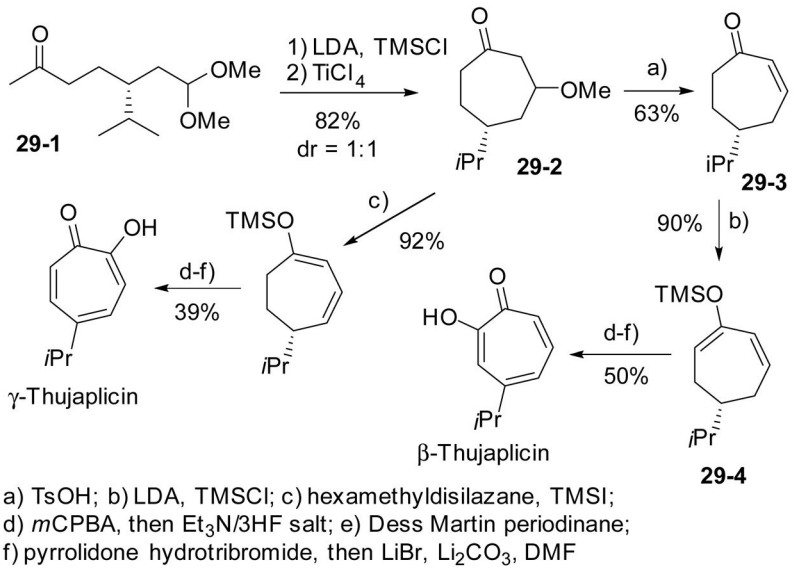



**Scheme 28.**
Woodward's synthesis of (±)-colchicine




**Scheme 29.**

Divergent regioselective synthesis of thujaplicins



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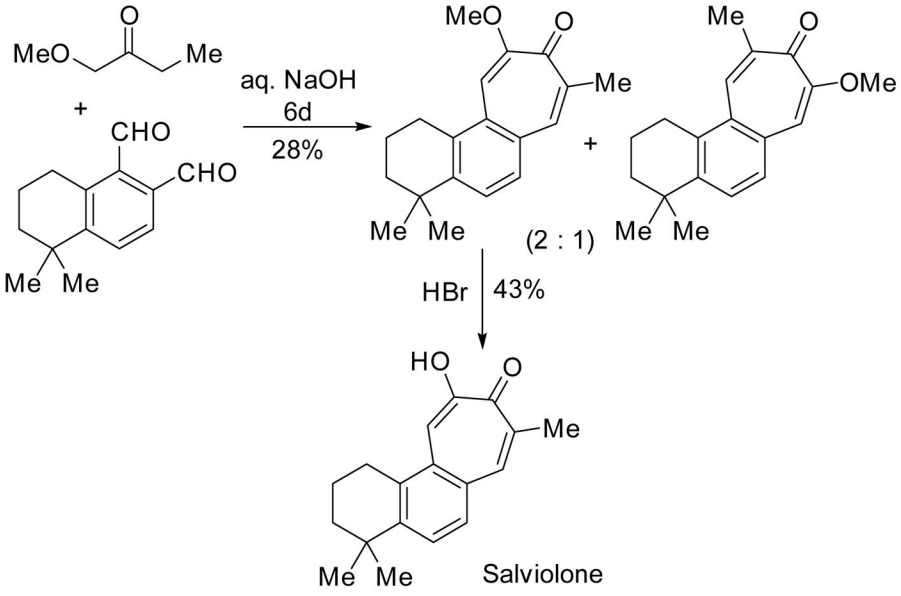


**Scheme 30.**

Synthesis of salviolone by double aldol condensation

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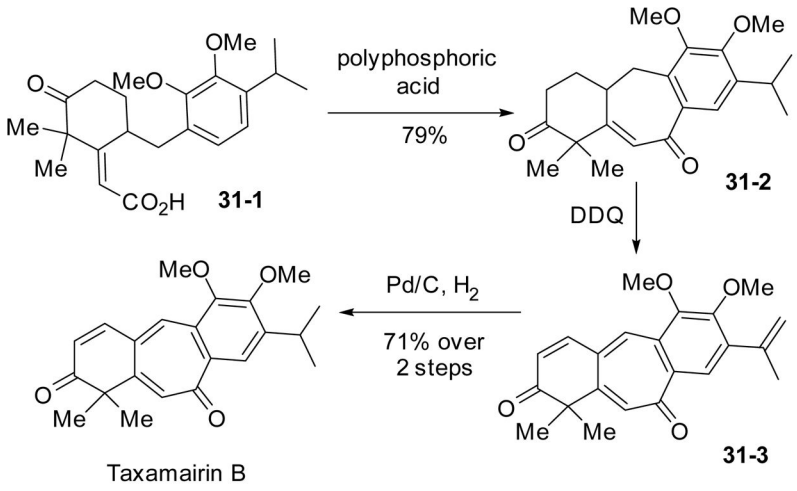


**Scheme 31.**

Synthesis of taxamairin B by Friedel-Crafts acylation

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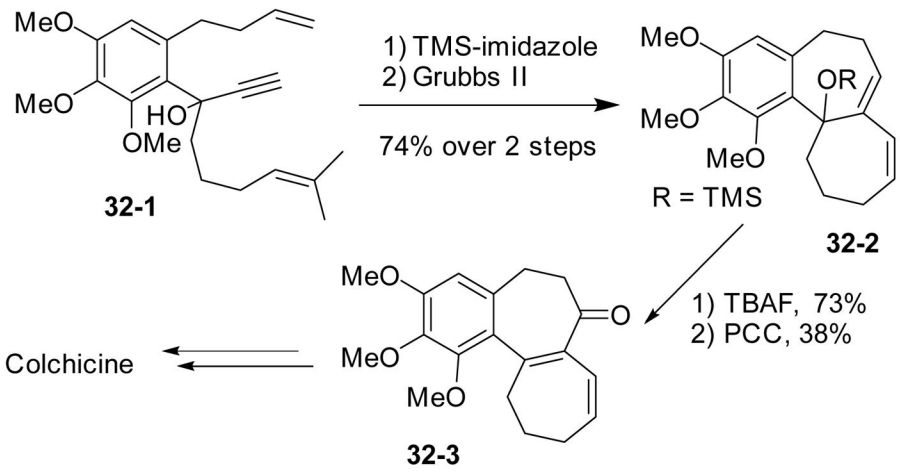


**Scheme 32.**

Formal synthesis of colchicine by dienyne metathesis

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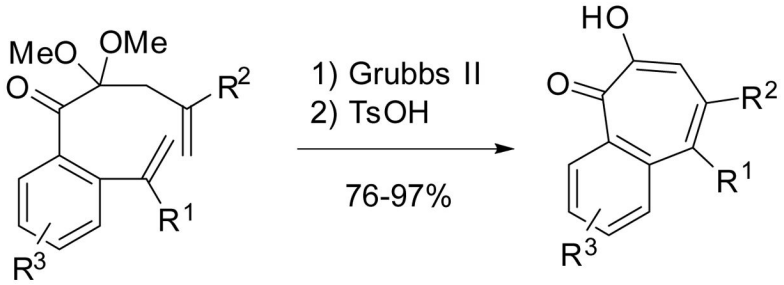


**Scheme 33.**

Synthesis of 3,4-benzotropolones by ring-closing metathesis

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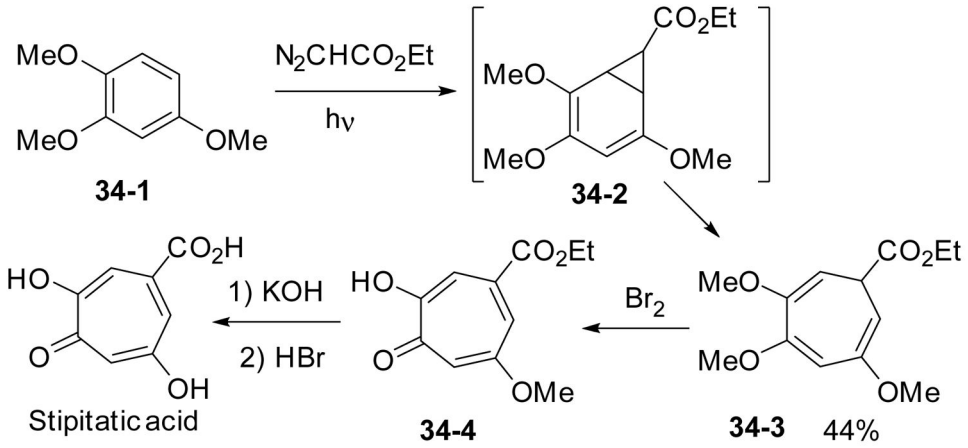


**Scheme 34.**

Synthesis of stipitatic acid using Buchner reaction

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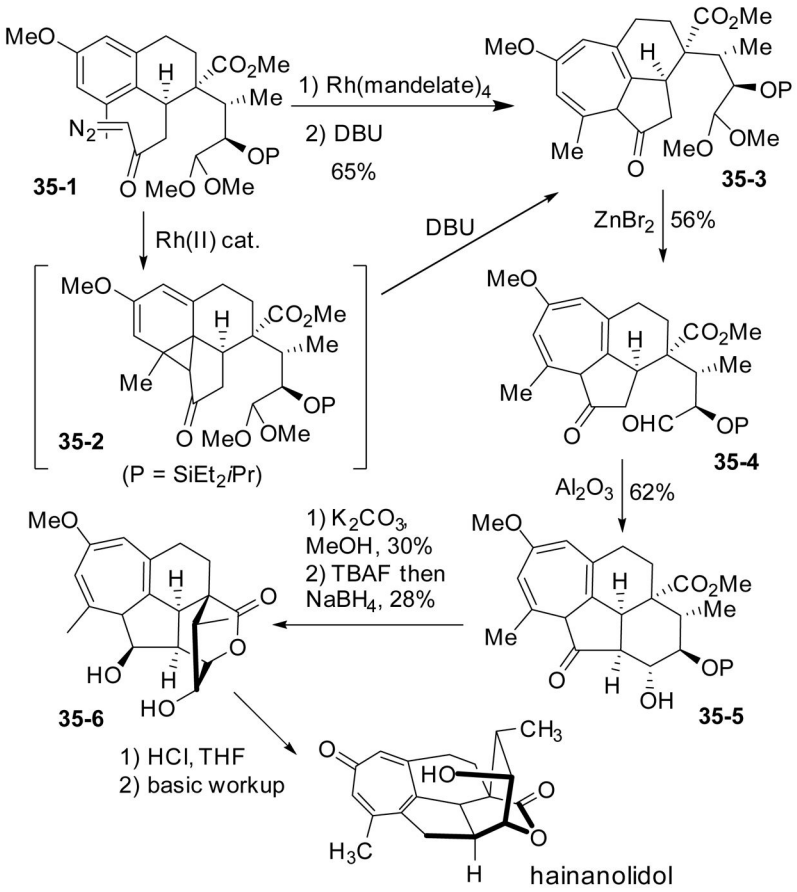


**Scheme 35.**

Mander's synthesis of (±)-hainanolidol

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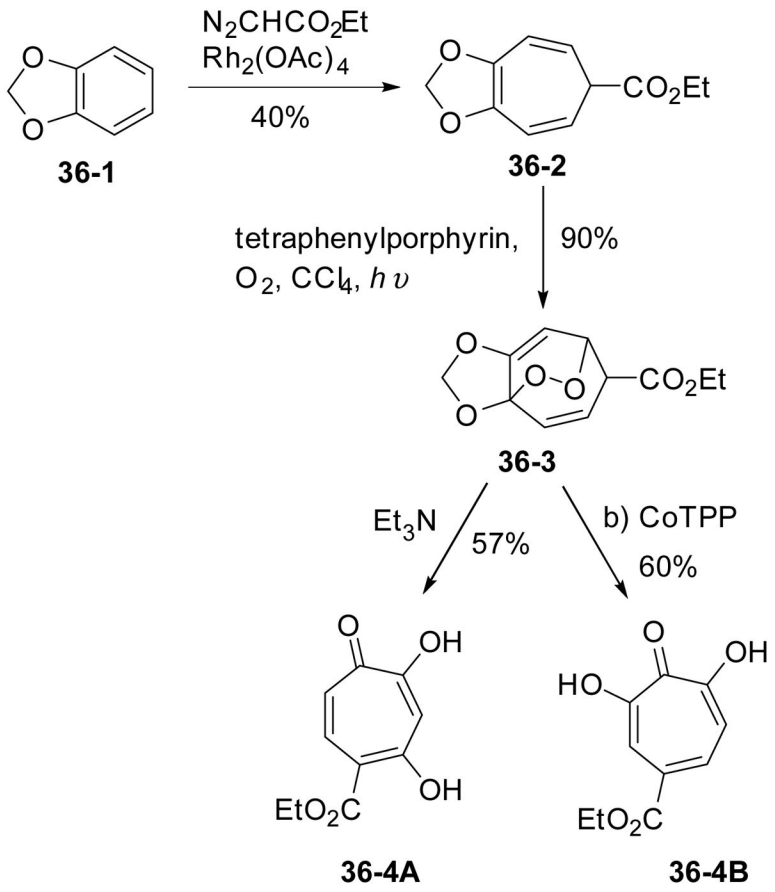


**Scheme 36.**

Balci's synthesis of isomers of stipitatic acid esters

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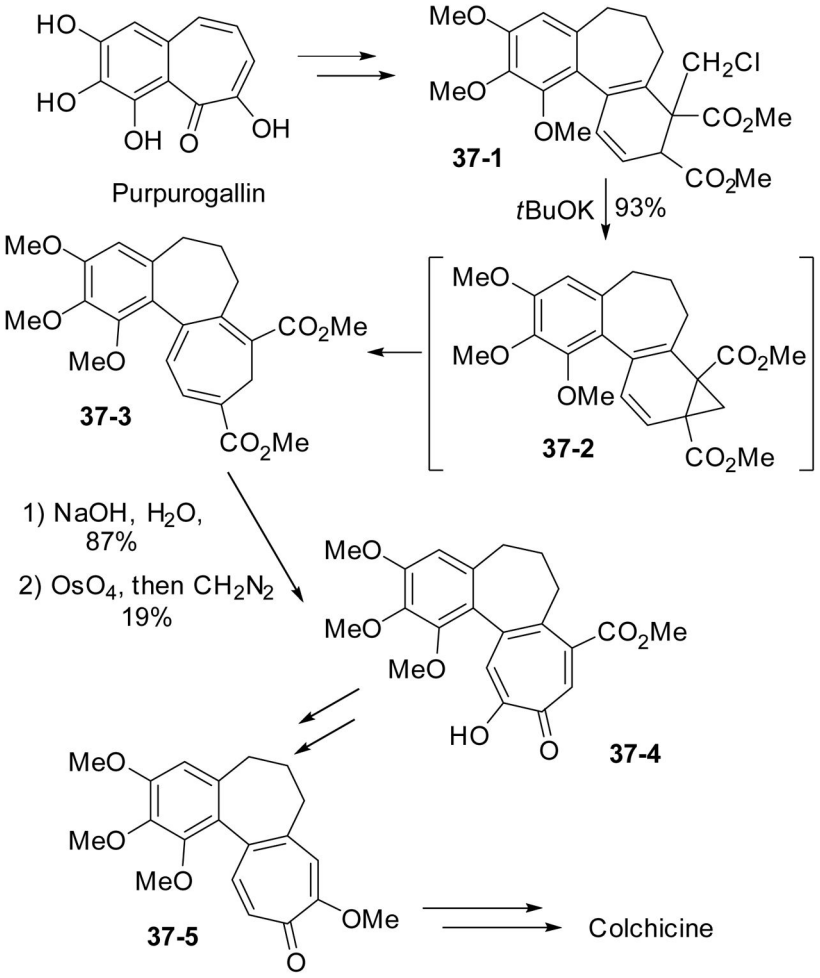


**Scheme 37.**

Eschenmoser's synthesis of (±)-colchicine

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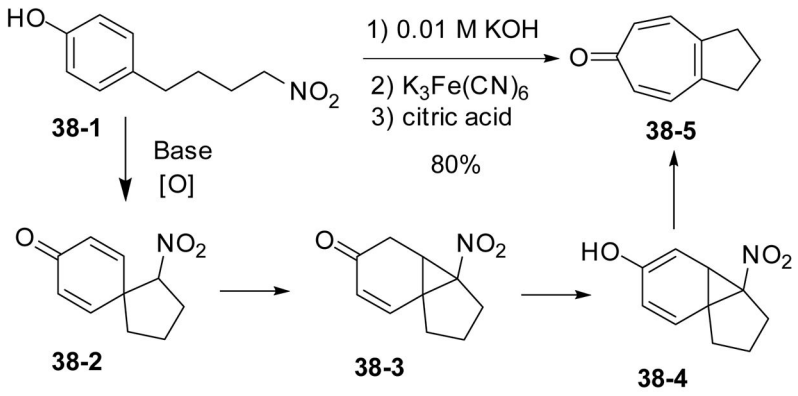


**Scheme 38.**

Intramolecular radical cyclization of phenolic nitronates developed by Kende

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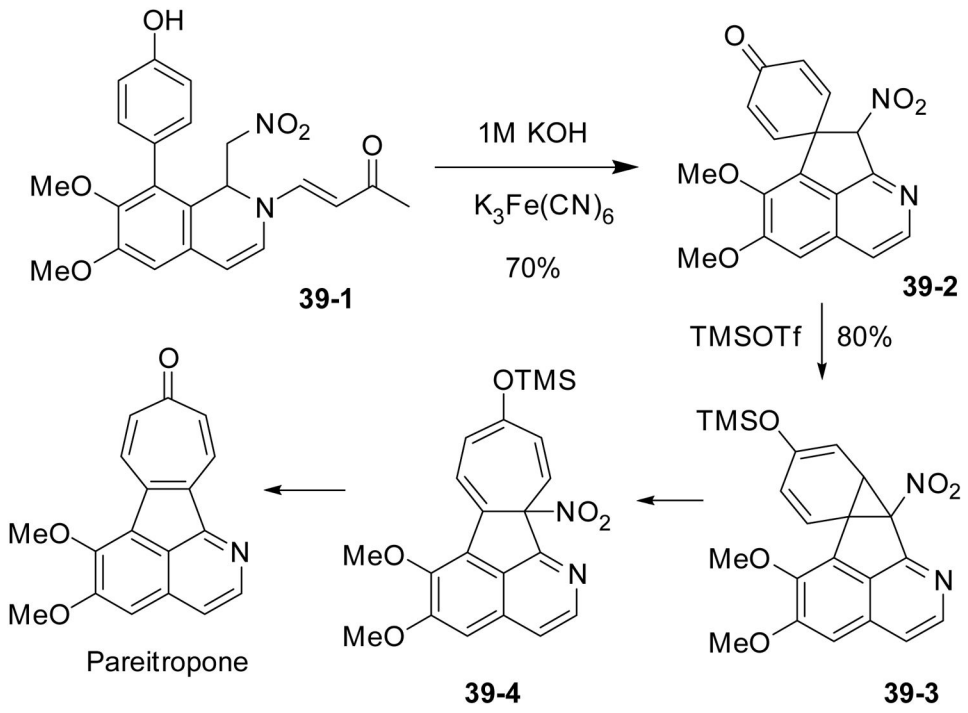


**Scheme 39.**
Cha's synthesis of pareitropone

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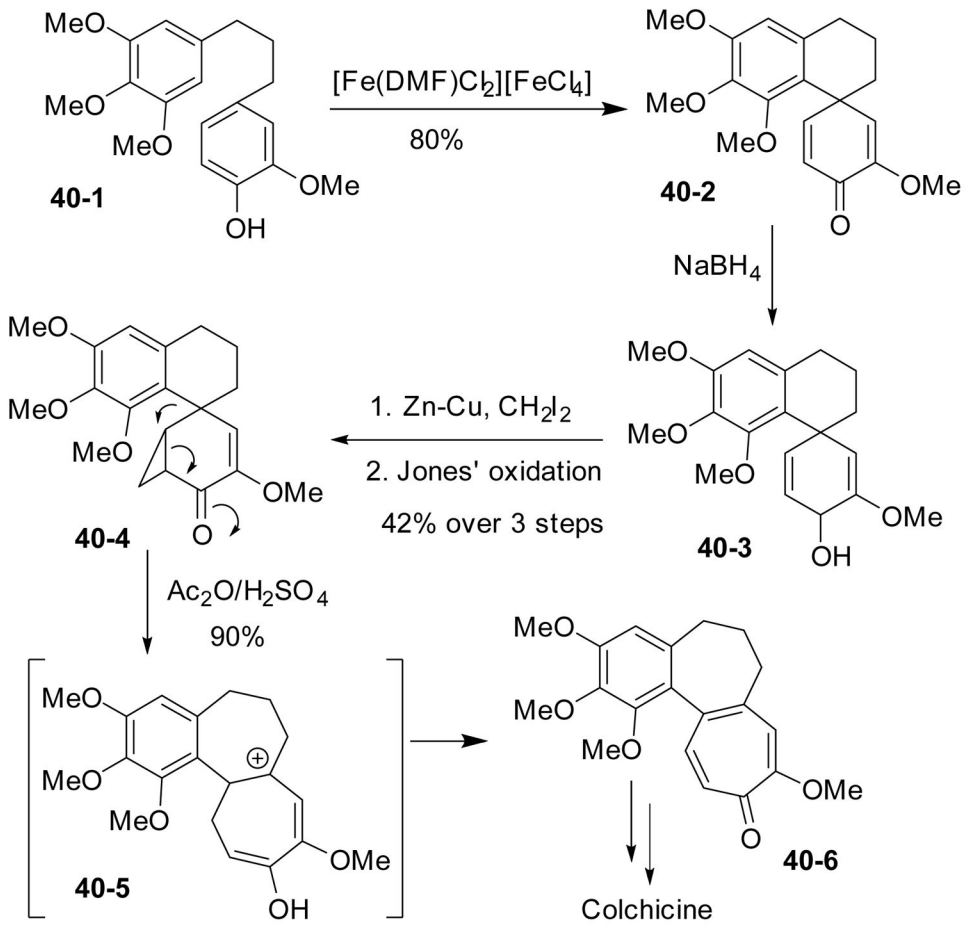


**Scheme 40.**

Tobinaga's formal synthesis of (±)-colchicine

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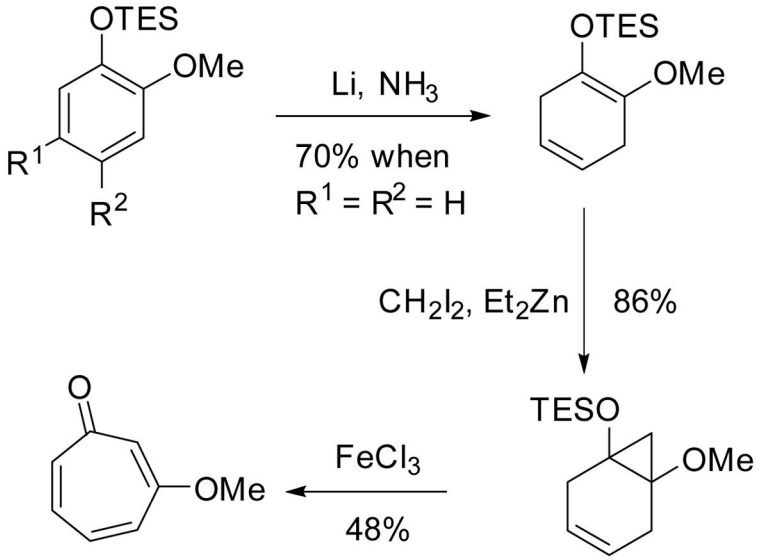


**Scheme 41.**

Synthesis of monocyclic tropolones via Simmons-Smith cyclopropanation and ring expansion

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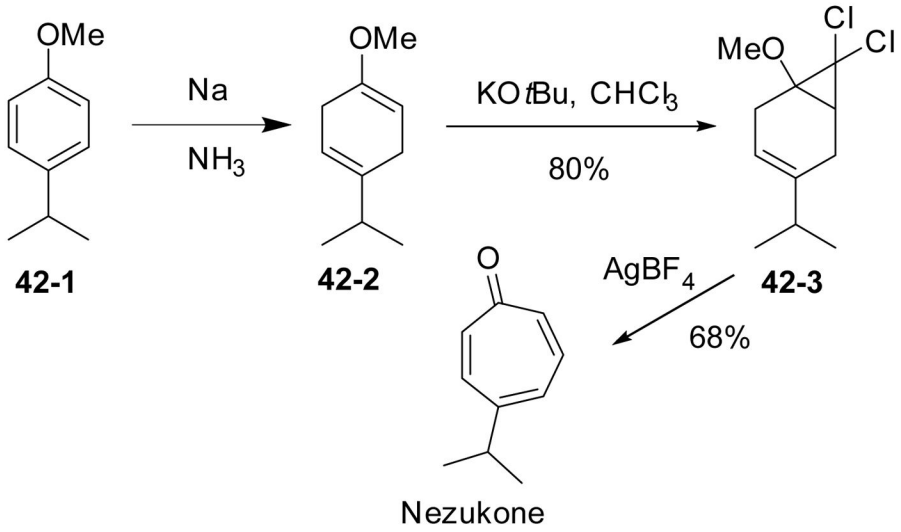


**Scheme 42.**
Synthesis of nezukone via dihalocarbene

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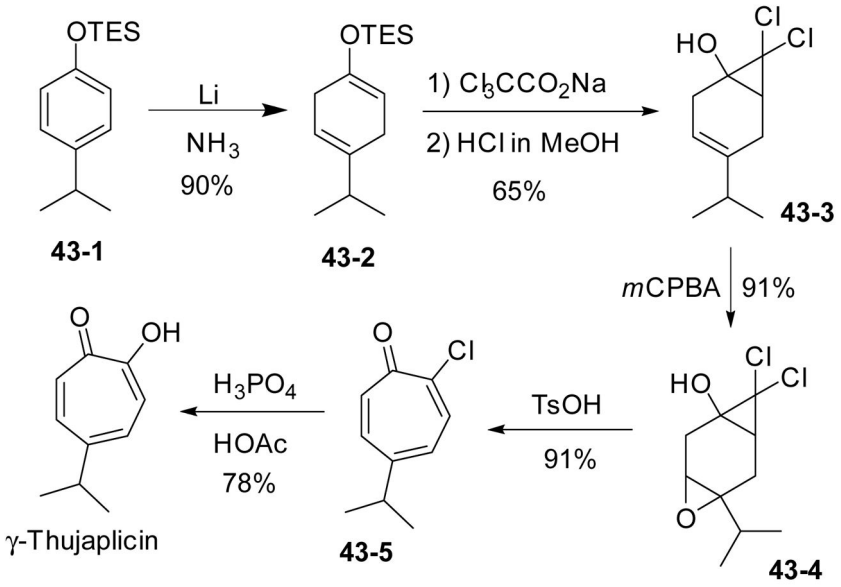


**Scheme 43.**

Synthesis of γ-thujaplicin via dihalocarbene

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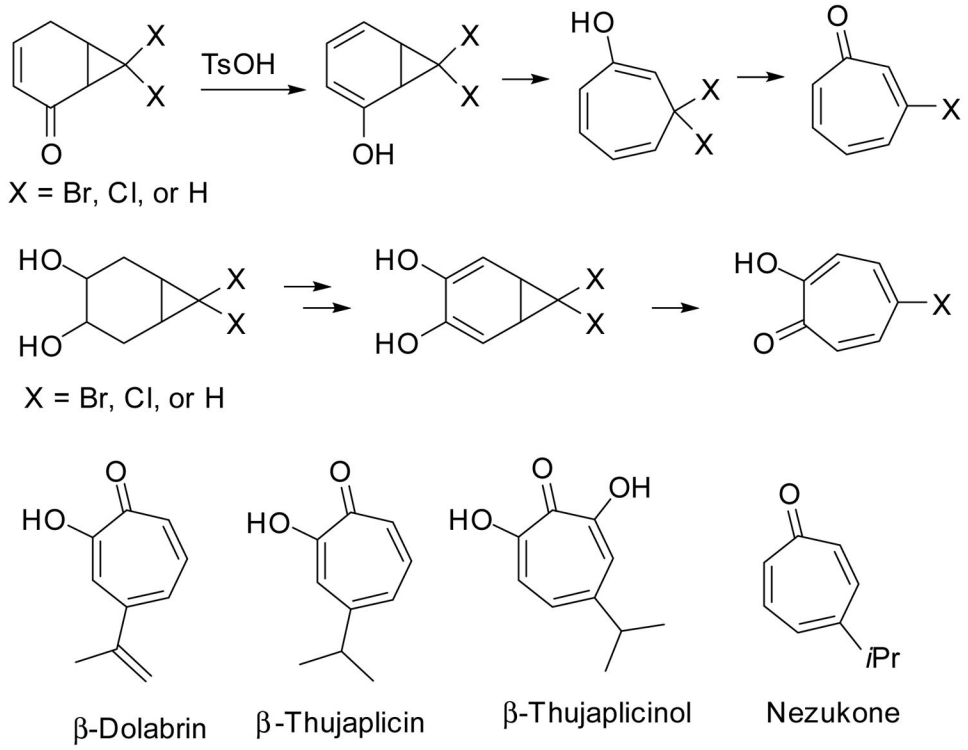


**Scheme 44.**

Halotropones and halotropolones derived from cyclopropanation and ring expansion

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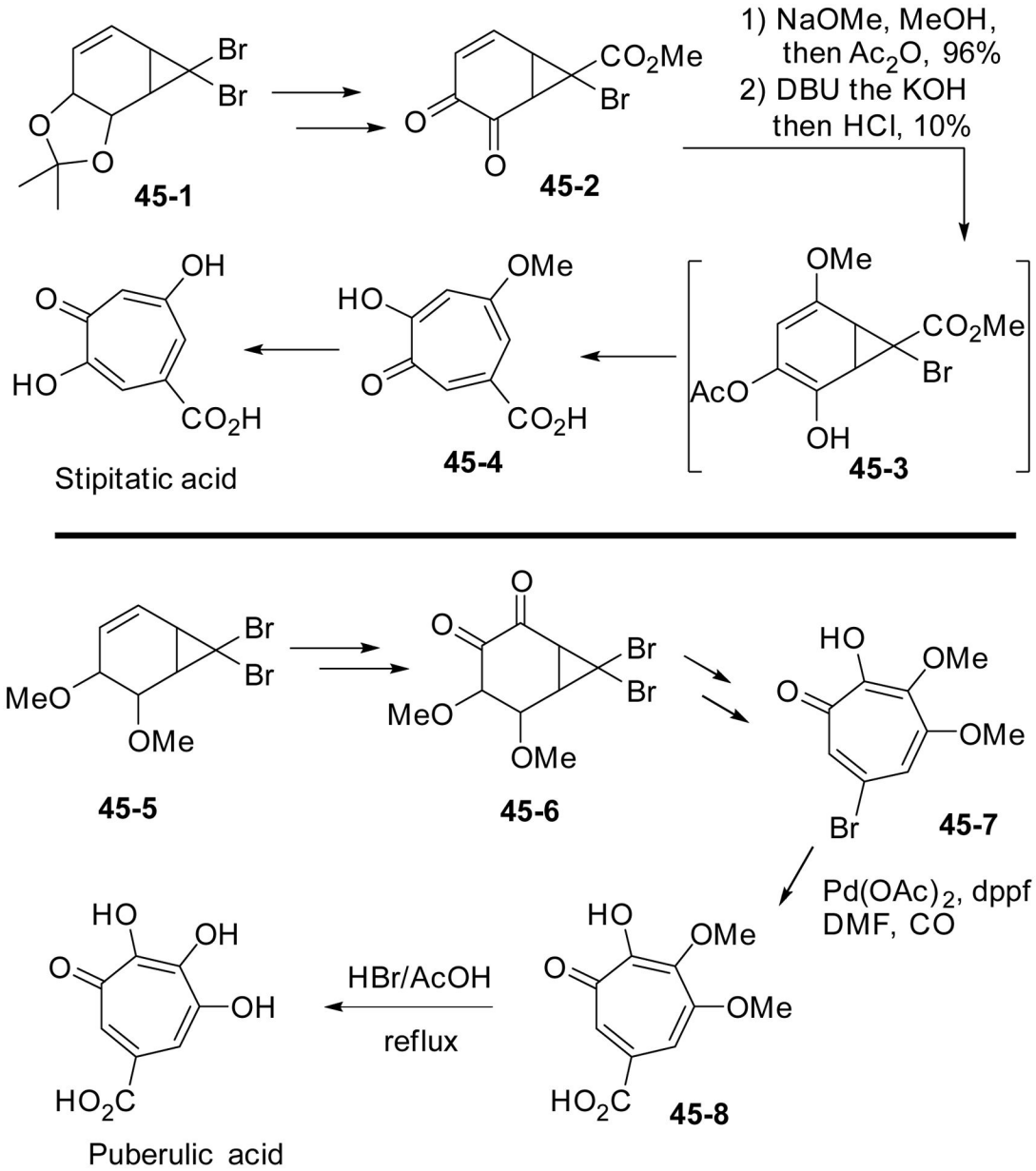


**Scheme 45.**

Banwell's synthesis of stipitatic acid and puberulic acid

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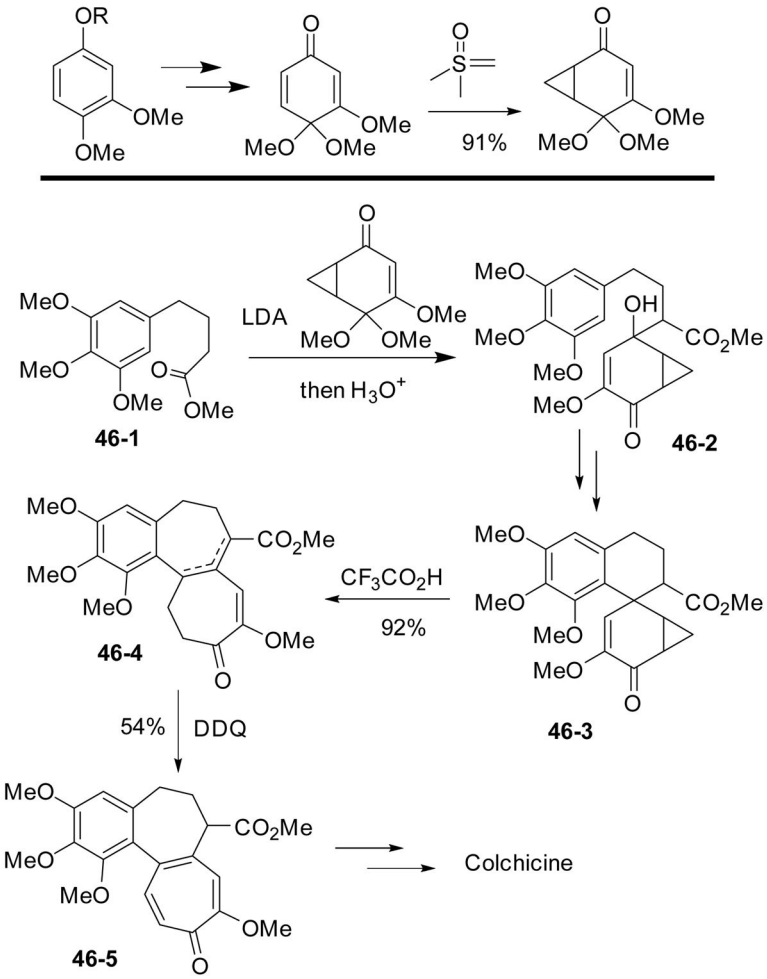


**Scheme 46.**

Evans' formal synthesis of (±)-colchicine

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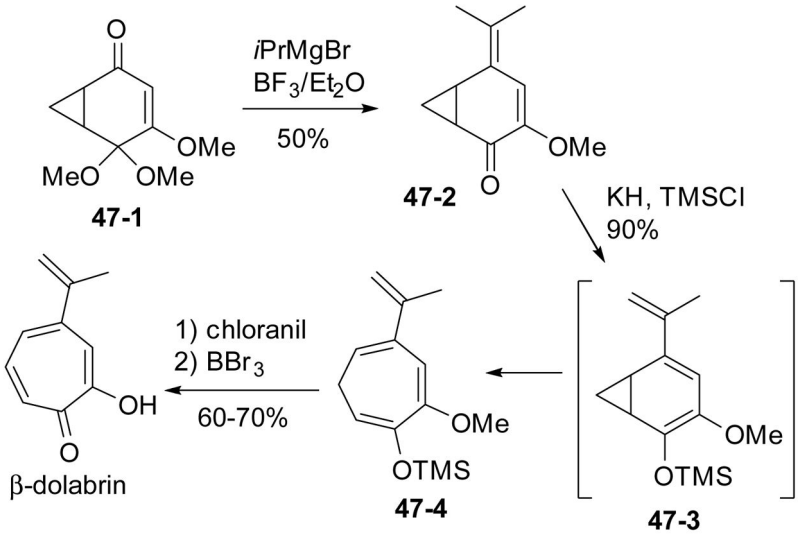


**Scheme 47.**

Evans' total synthesis of β-dolabrin

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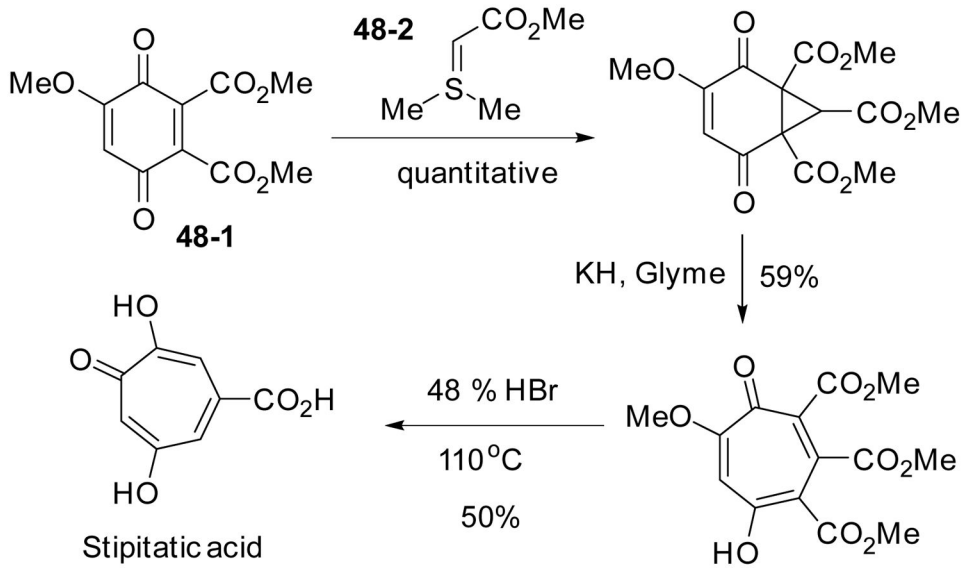


**Scheme 48.**
Synthesis of stipitatic acid via cyclopropylquinone

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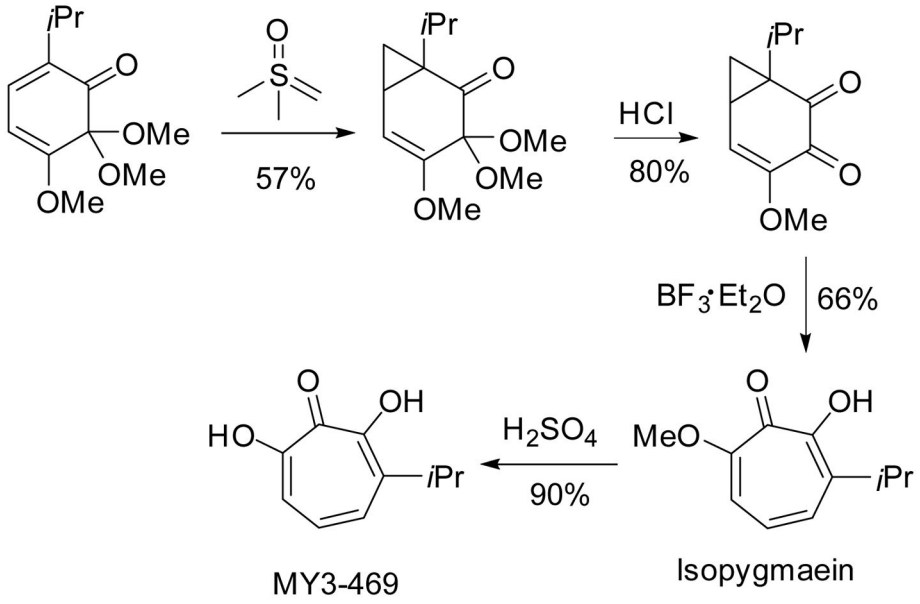


**Scheme 49.**

Banwell's synthesis of MY3-469 and isopygmaein by sulfur ylide-mediated cyclopropanation

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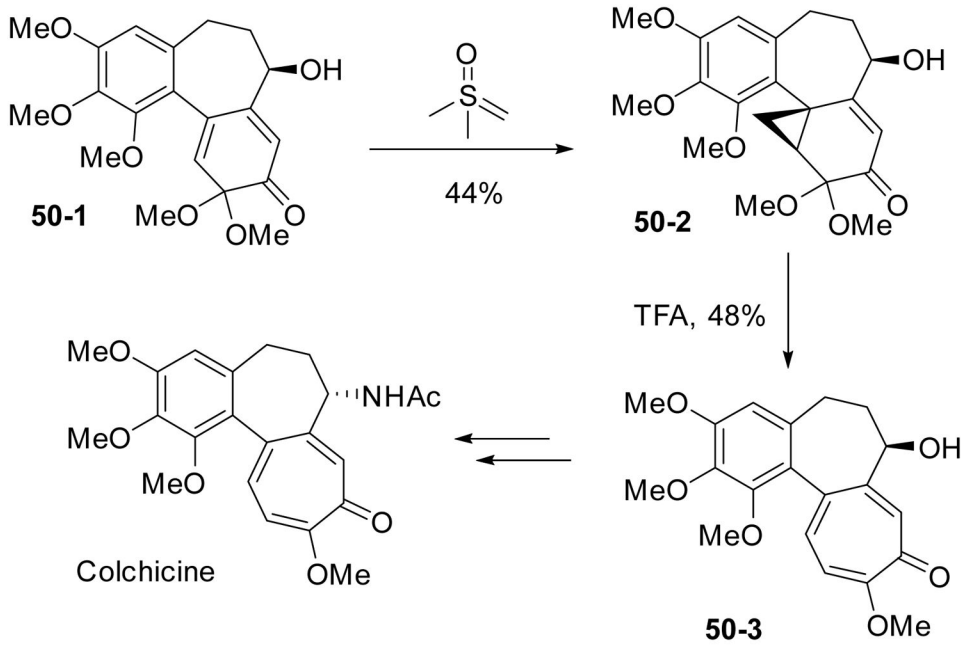


**Scheme 50.**

Banwell's synthesis of (−)-colchicine by sulfur ylide-mediated cyclopropanation

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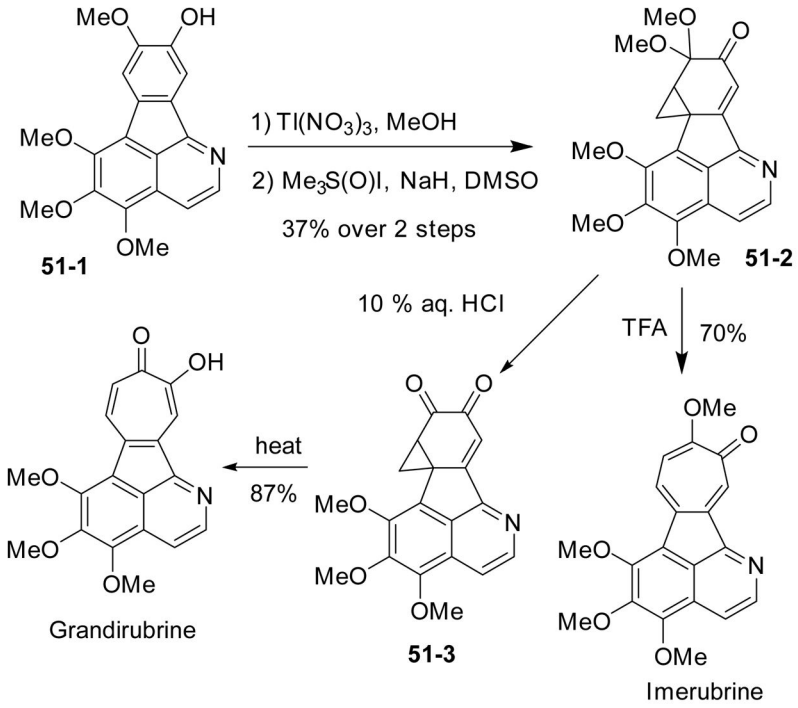


**Scheme 51.**

Banwell's synthesis of imerubrine and grandirubrine

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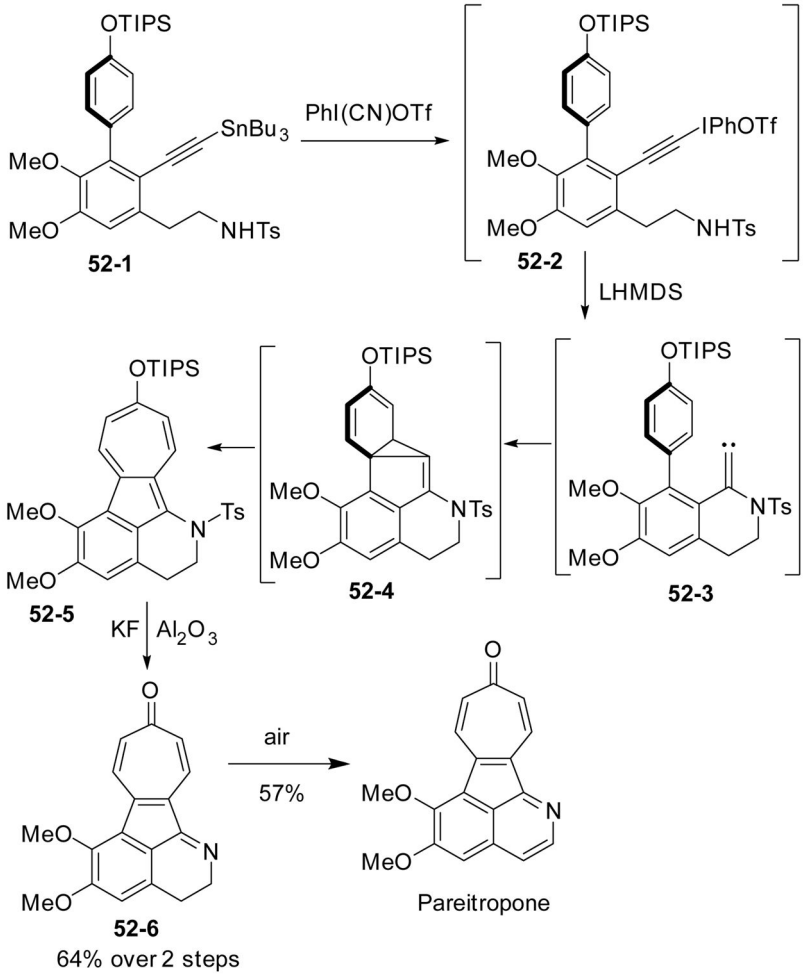


**Scheme 52.**

Feldman's synthesis of pareitropone via ring expansion of alkylidene cyclopropane

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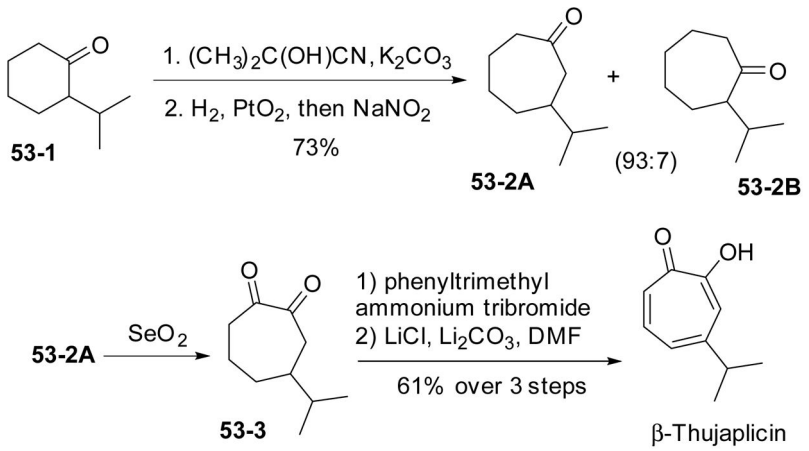


**Scheme 53.**

Ring expansion followed by oxidation of cycloheptanone to tropone

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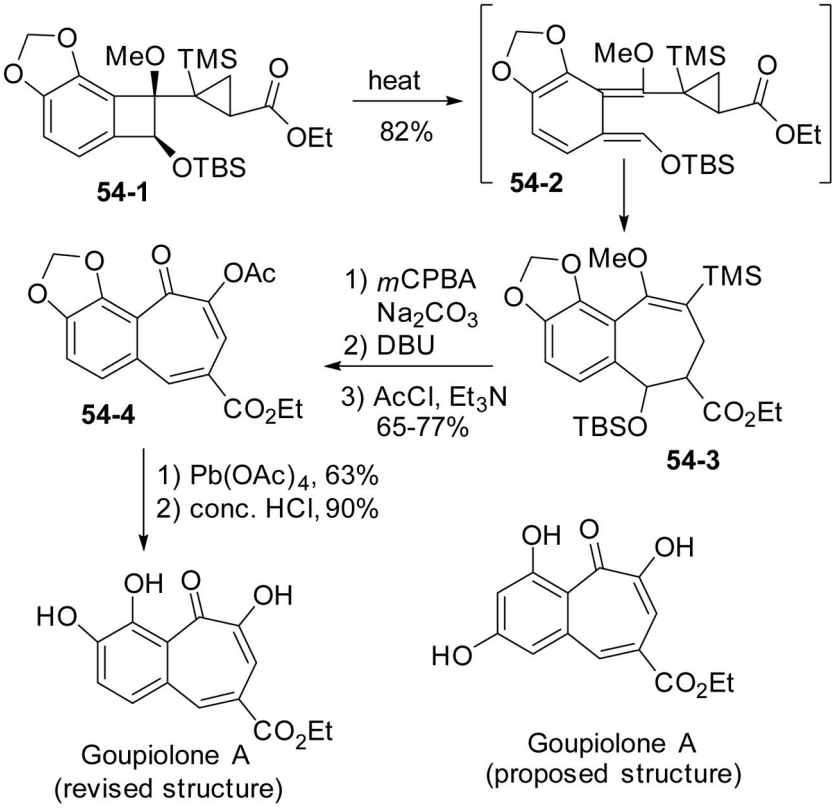


**Scheme 54.**

Synthesis of goupiolone A via ring expansion of cyclopropyl-benzocyclobutenes and structural revision

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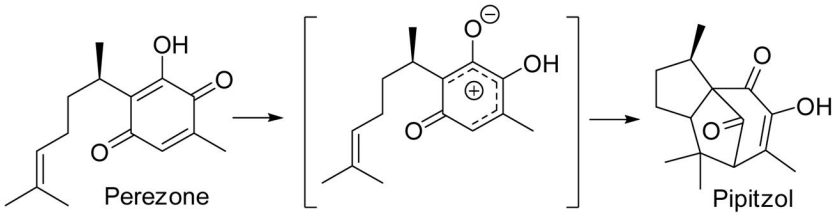


**Scheme 55.**
Transformation of perezone to pipitzol

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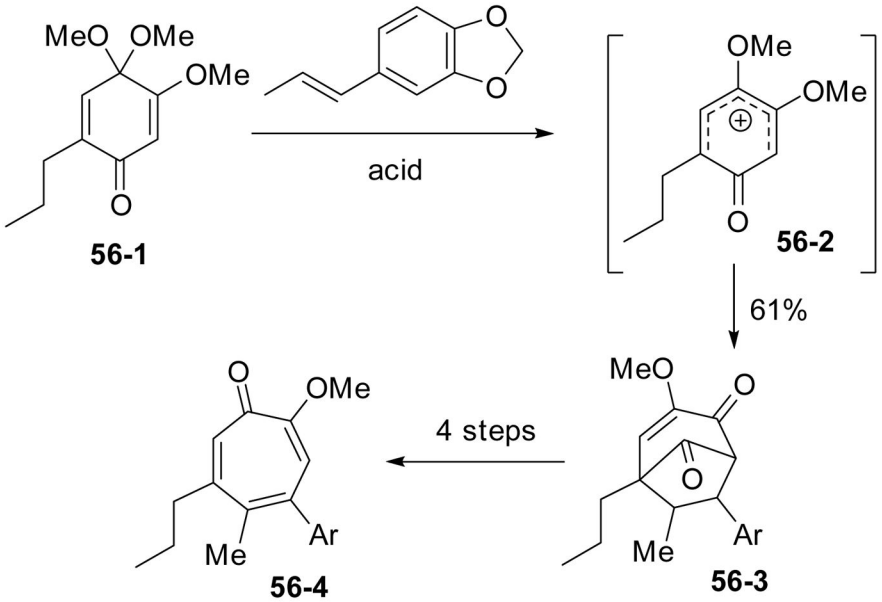


**Scheme 56.**

Synthesis of substituted tropolones via perezone type [5+2] cycloaddition

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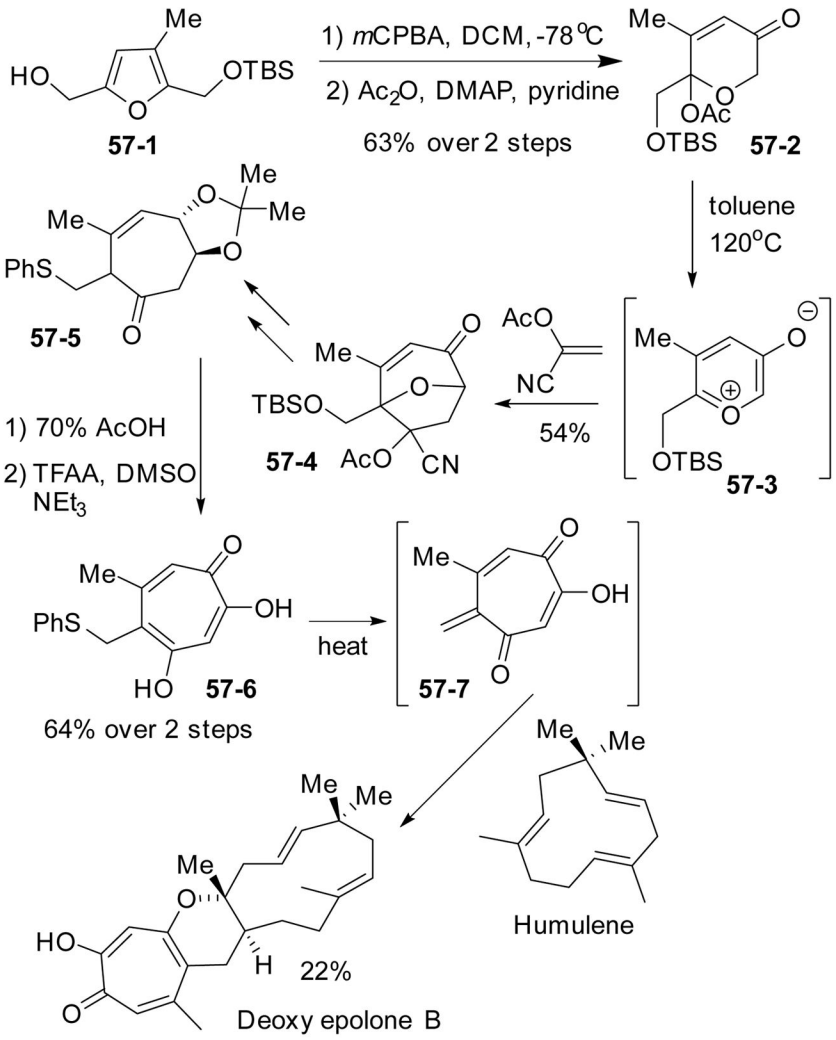


**Scheme 57.**

Biomimetic synthesis of (±)-deoxyepolone B

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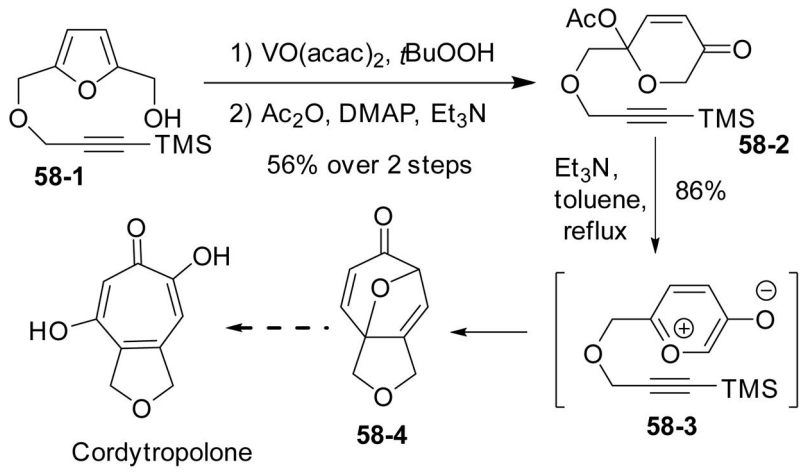


**Scheme 58.**
Synthetic effort towards cordytropolone

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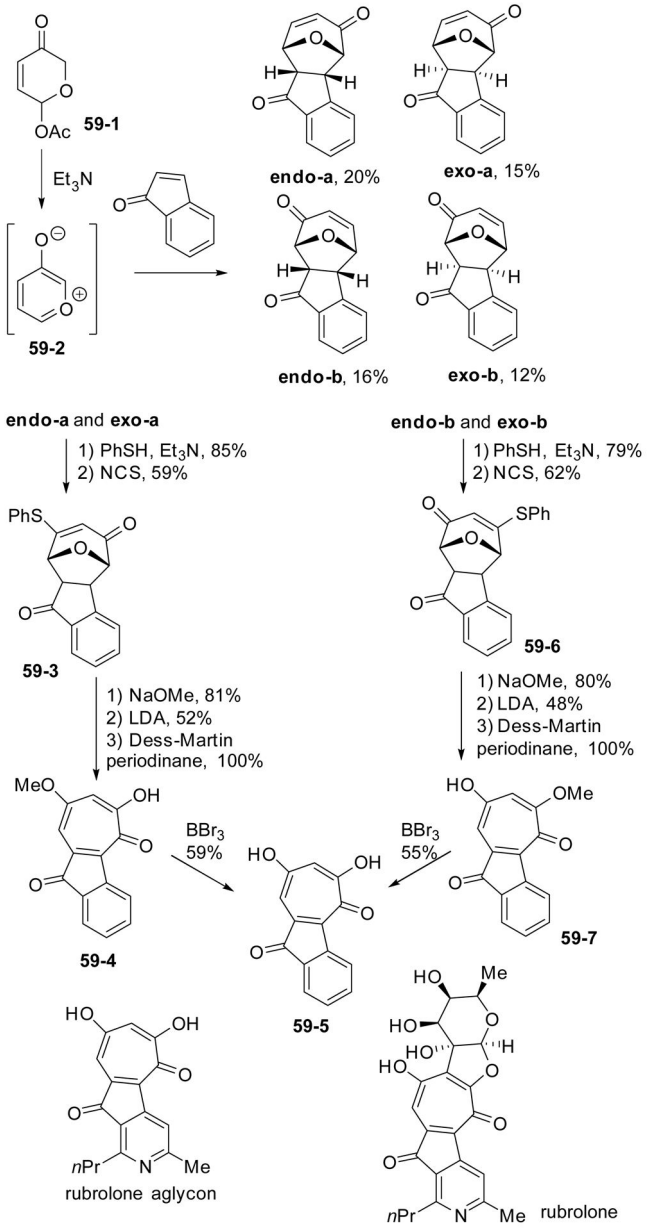


**Scheme 59.**

Synthesis of tropolone subunit in a model compound for rubroloneaglycon via cycloaddition of oxidopyrylium ion

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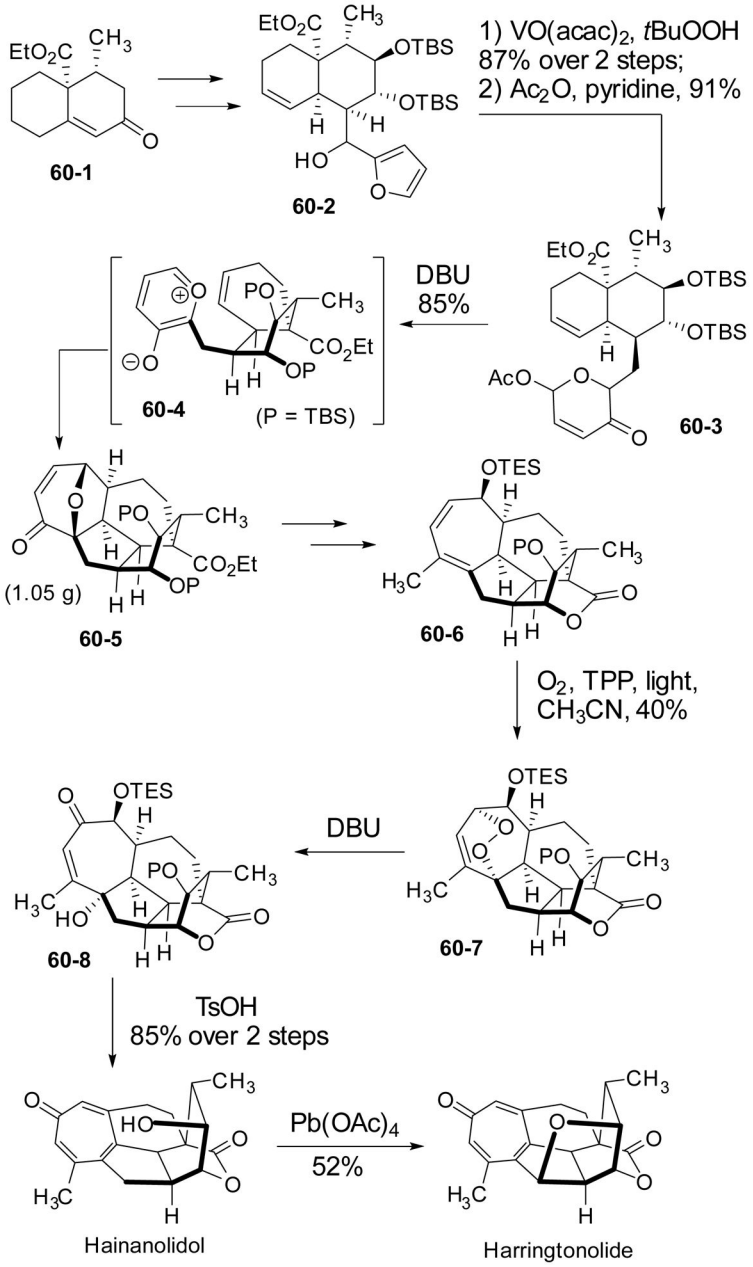


**Scheme 60.**

Total synthesis of (±)-harringtonolide

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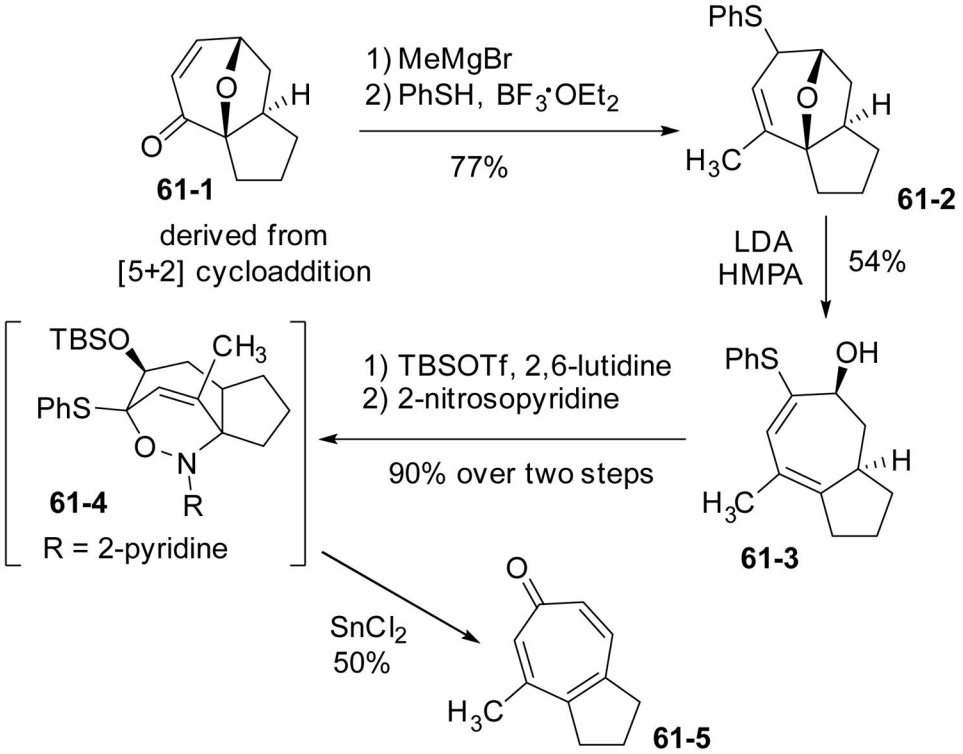


**Scheme 61.**

Synthesis of tropone from [5+2] cycloaddition product in a model system for (±)-harringtonolide

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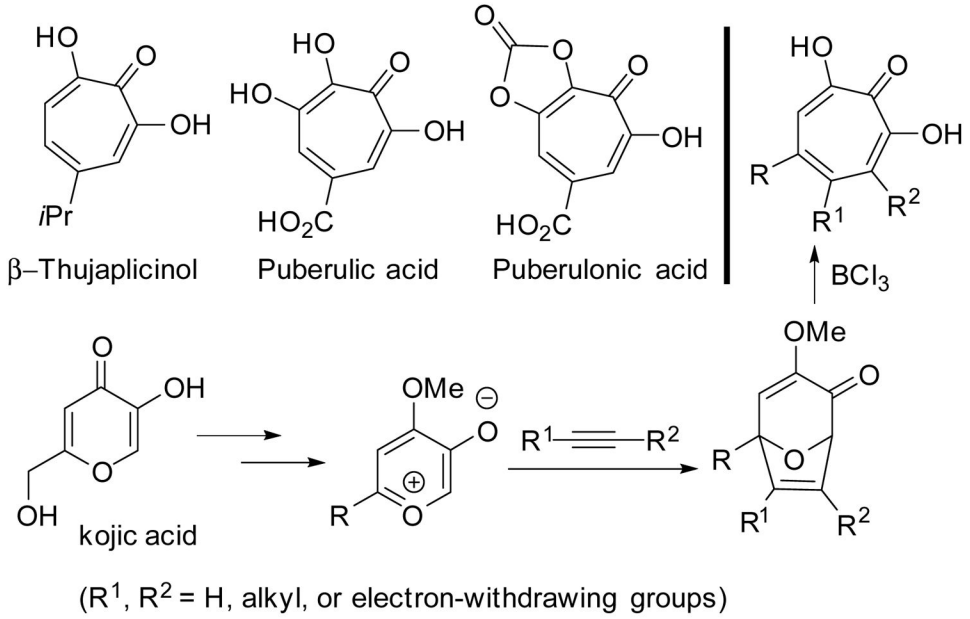


**Scheme 62.**
Synthesis of hydroxytropolones

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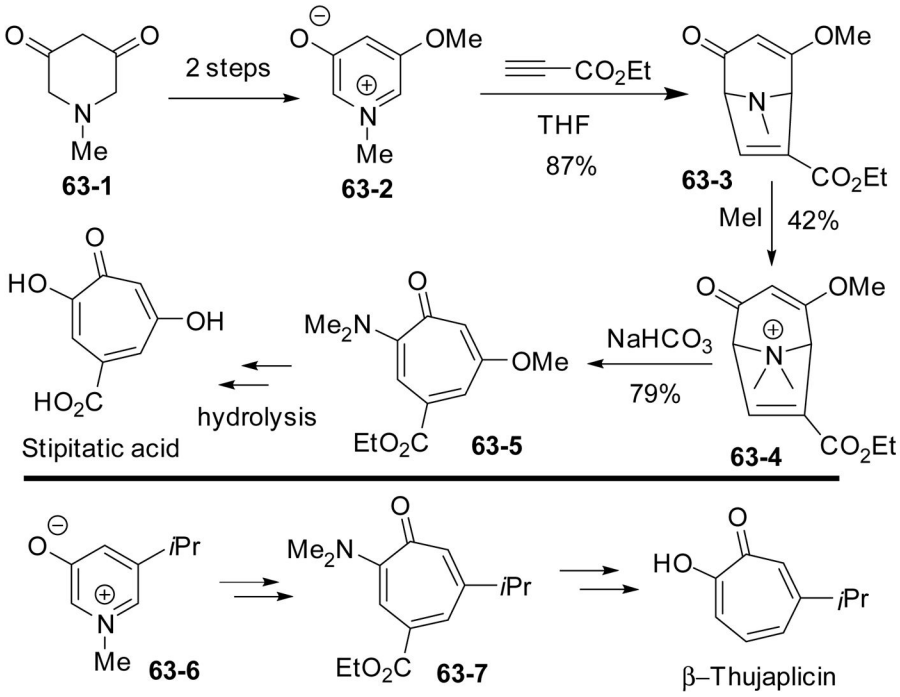


**Scheme 63.**

Synthesis of stipitatic acid and β-thujaplicin via 1,3-dipolar cycloaddition

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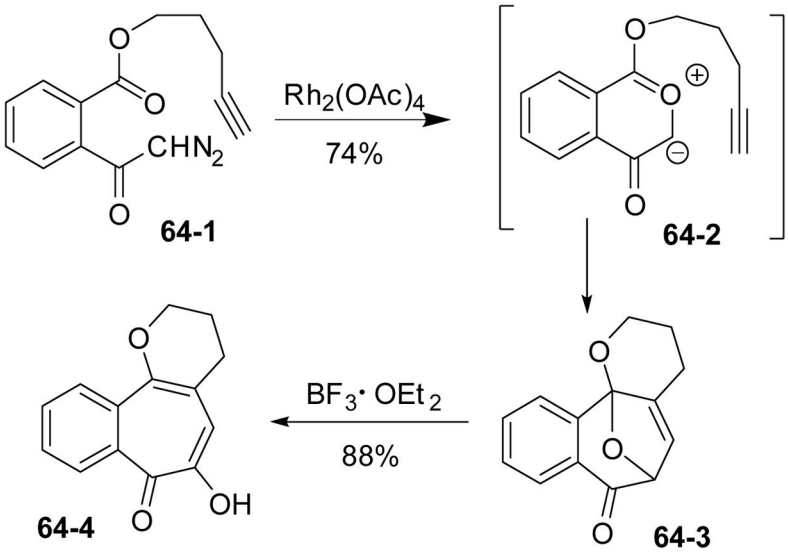


**Scheme 64.**

Synthesis of benzotropolones through Rh (II) catalyzed [3+2] cycloaddition

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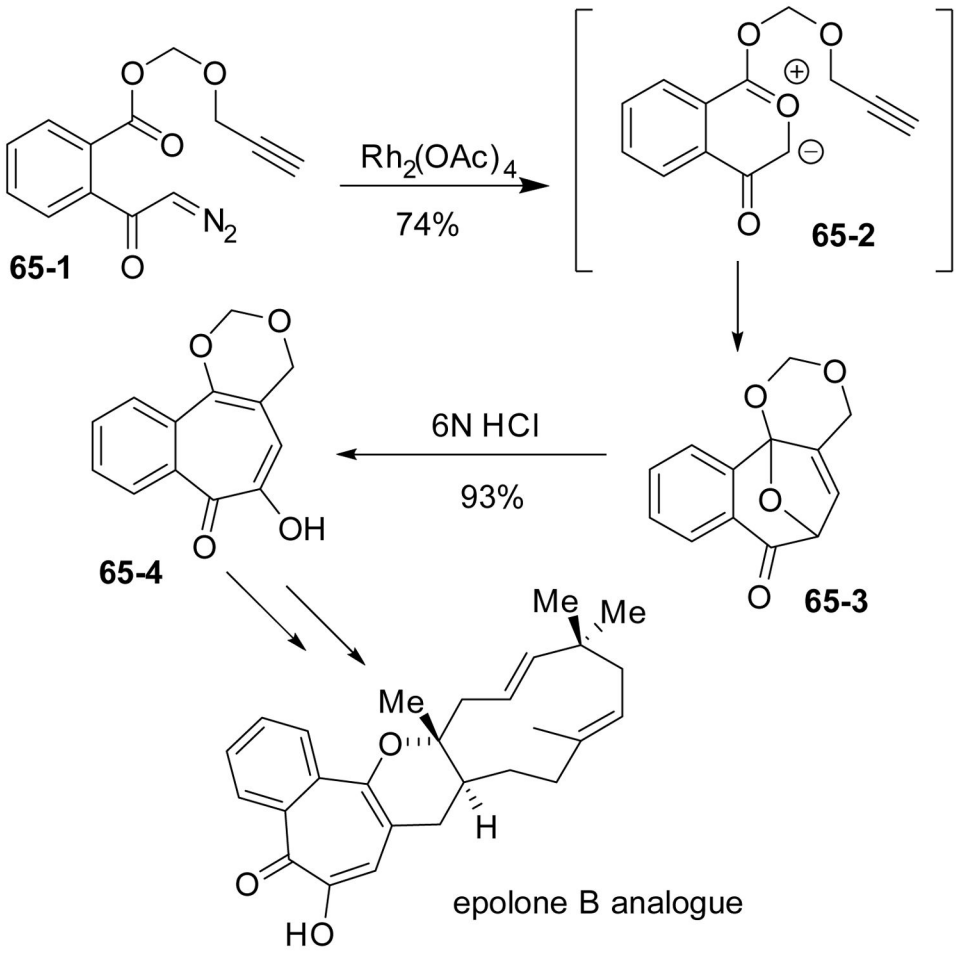


**Scheme 65.**

Biomimetic synthesis of (±)-epolone B analogue

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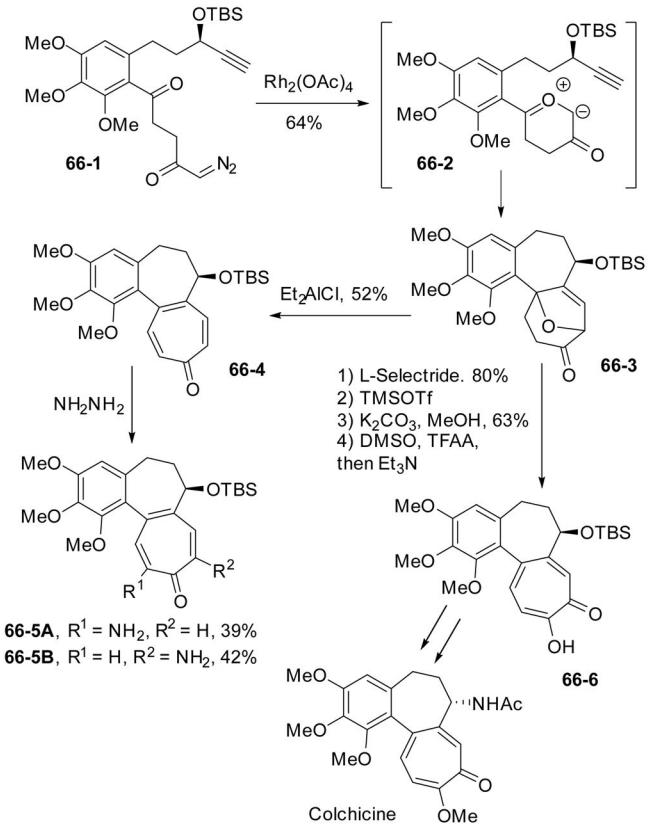


**Scheme 66.**

Schmalz's synthesis of (−)-colchicines via Rh-catalyzed carbonyl ylide cycloaddition

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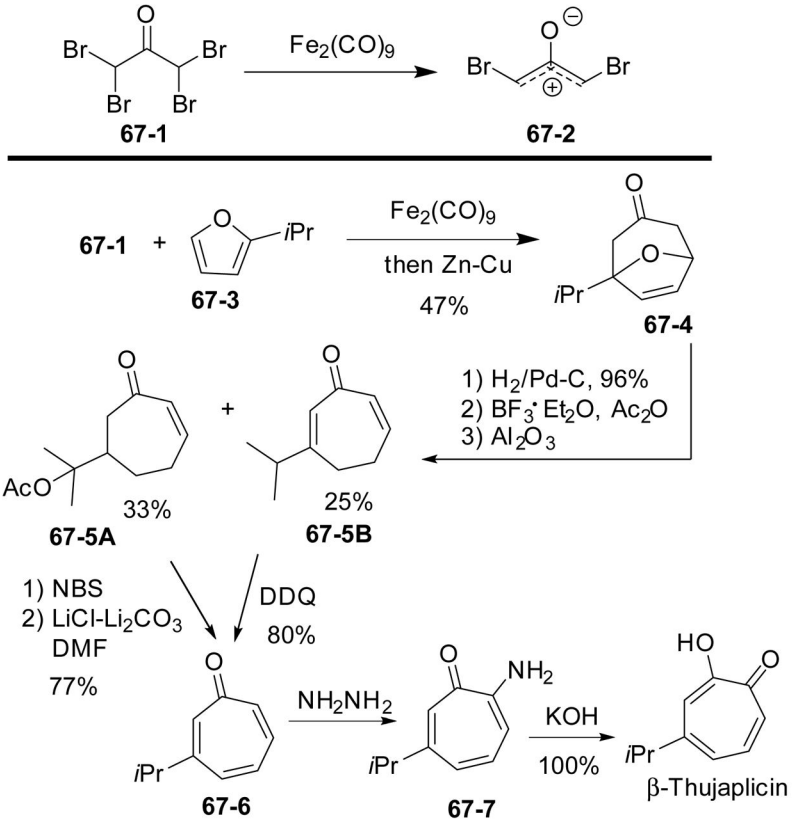
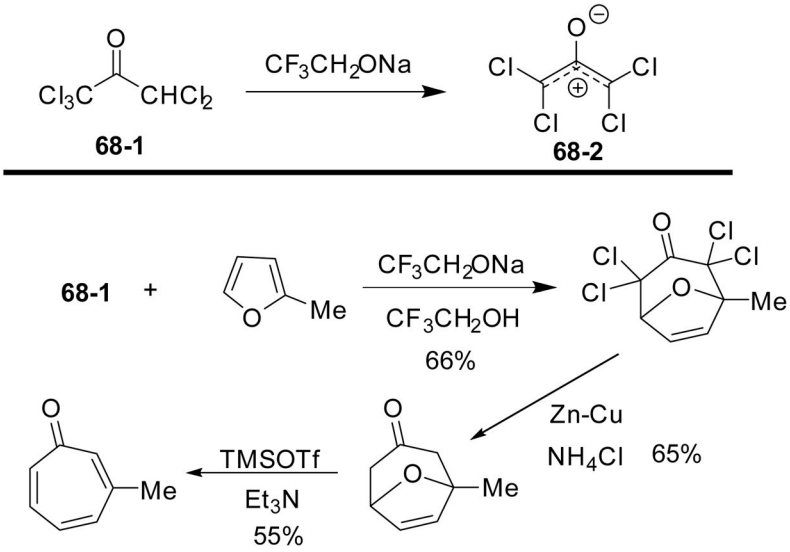



**Scheme 67.**

Noyori's synthesis of β-thujaplicin via oxyallylcation [4+3] cyclization




**Scheme 68.**

Preparation of 3-methyl tropone via oxyallylcation [4+3] cycloaddition



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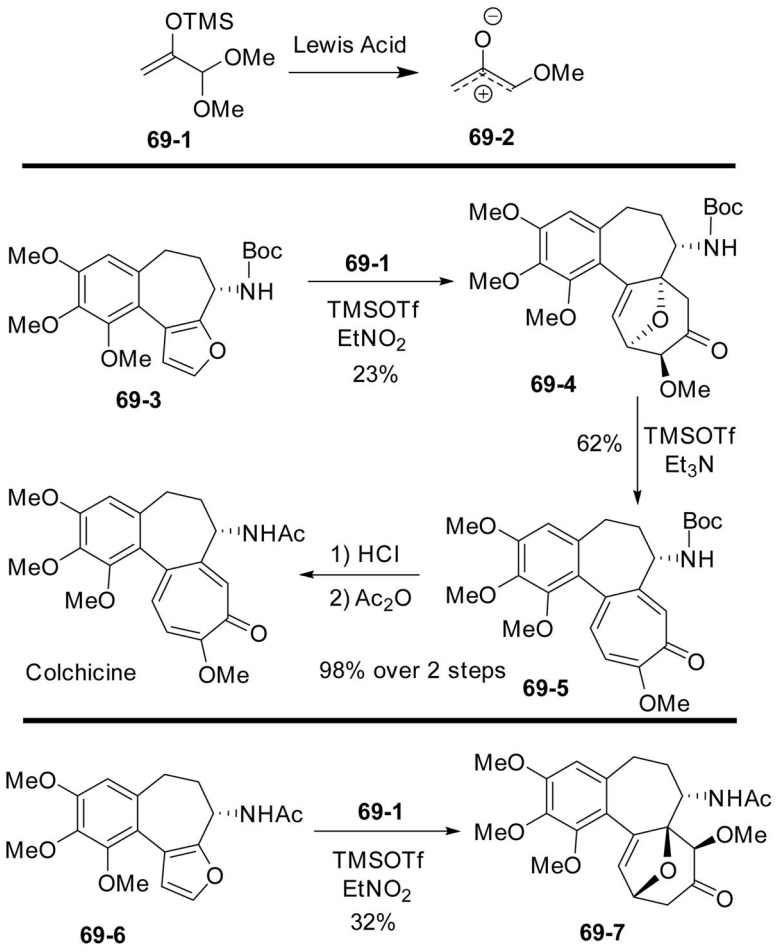


**Scheme 69.**

Cha's synthesis of (−)-colchicine via oxyallylcation [4+3] cycloaddition

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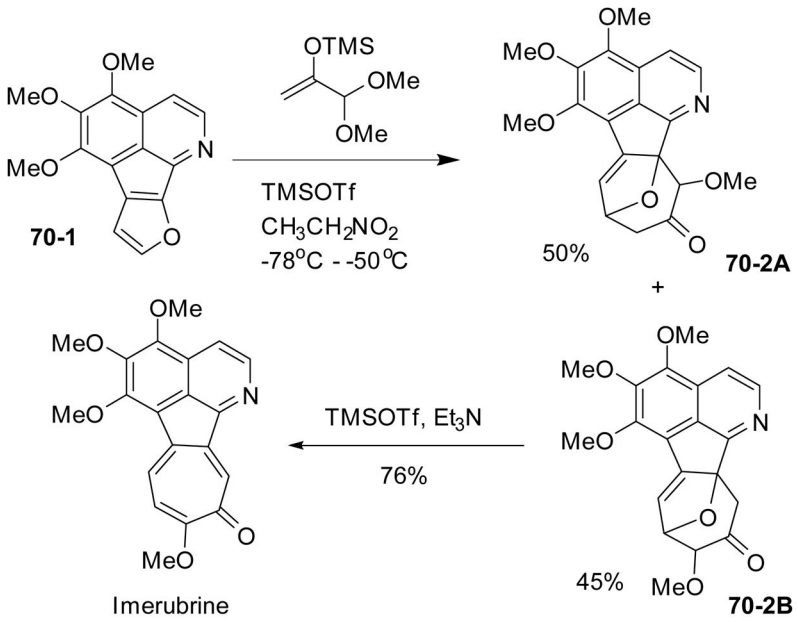


**Scheme 70.**

Synthesis of imerubrine via oxyallylcation [4+3] cycloaddition

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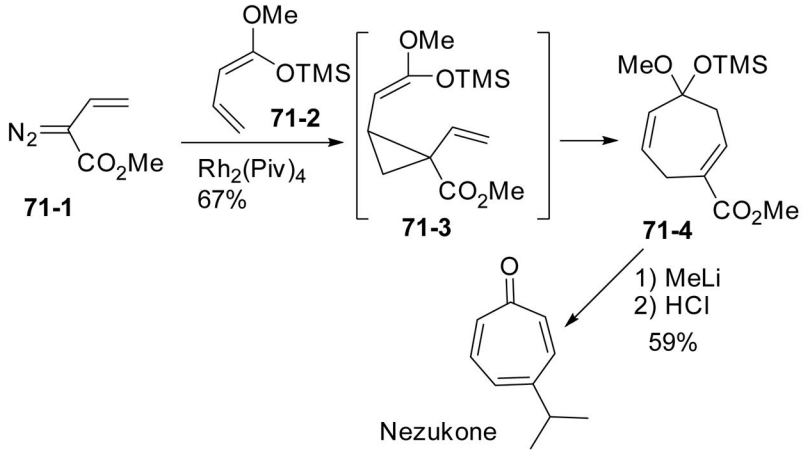


**Scheme 71.**
Davies's synthesis of nezukone

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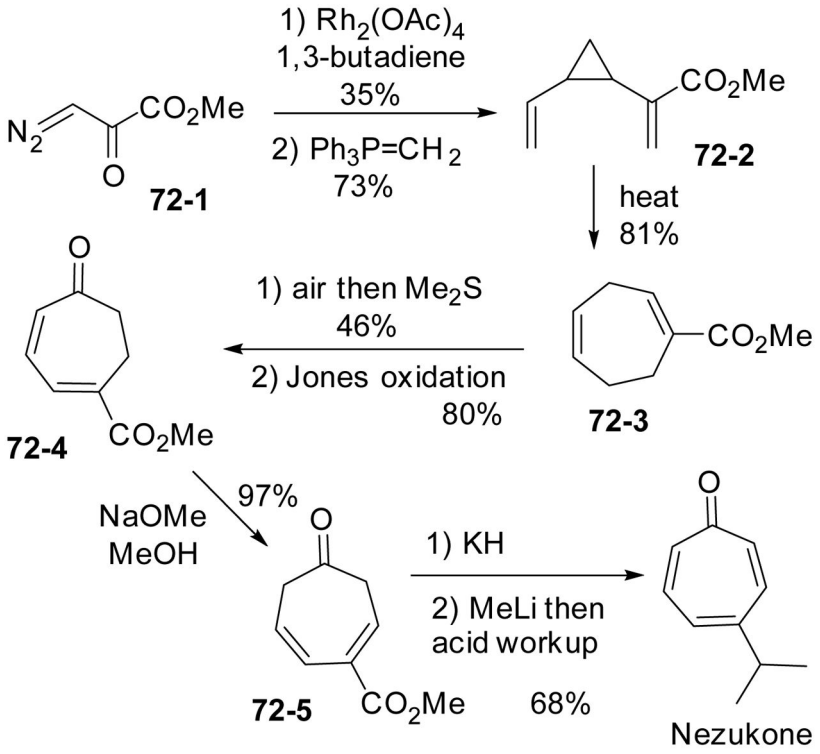


**Scheme 72.**

Wenkert's synthesis of nezukone via cyclopropanation and Cope rearrangement

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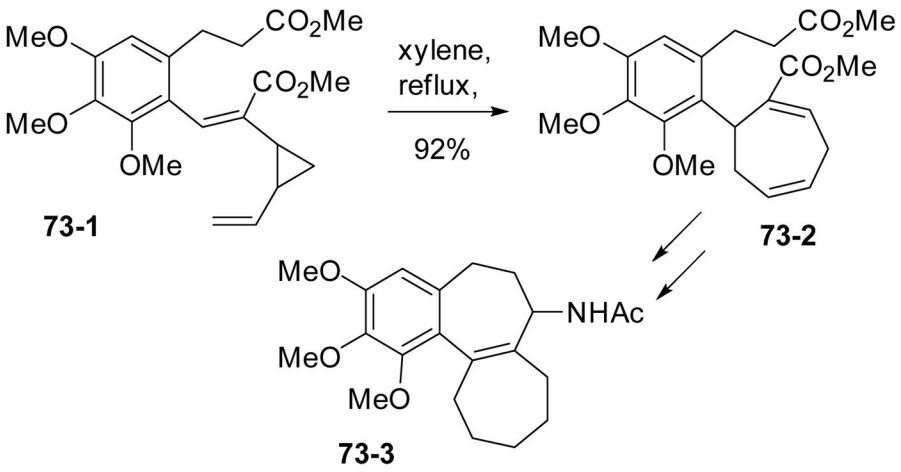


**Scheme 73.**

Wenkert's formal synthesis of (±)-colchicine via cyclopropanation and Cope rearrangement

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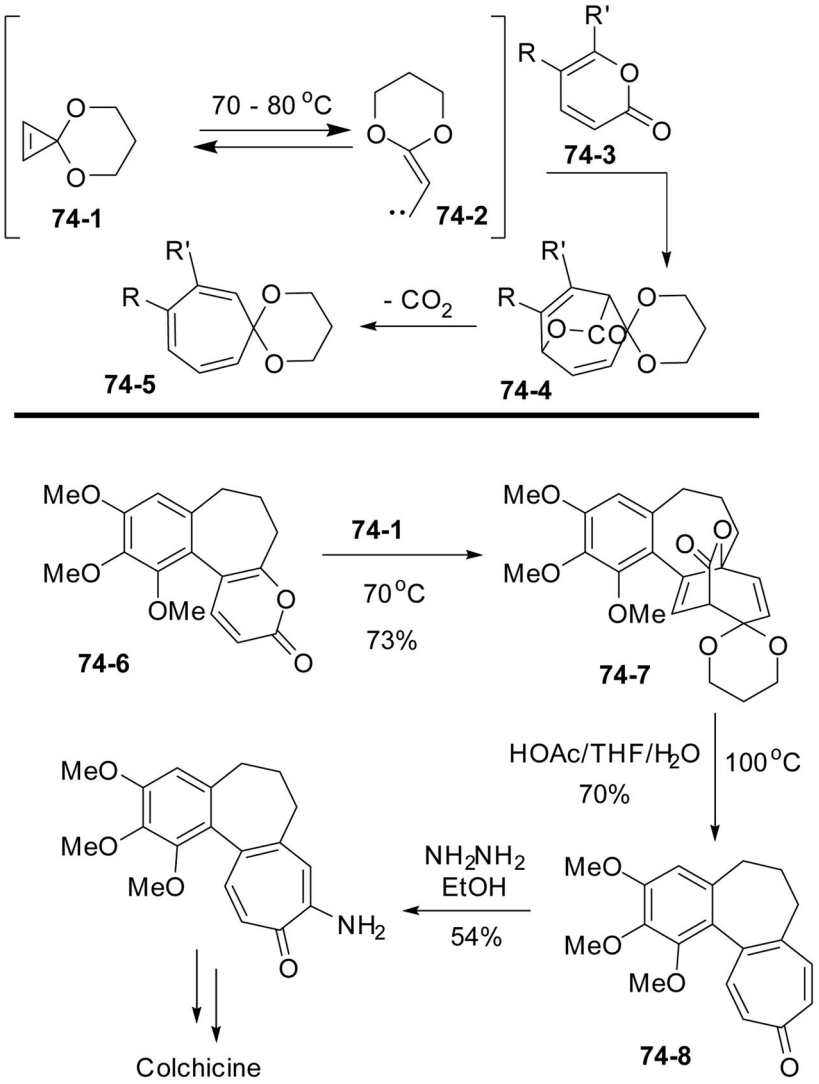


**Scheme 74.**

Boger's formal synthesis of (±)-colchicines via cycloaddition of cyclopropenone ketal with α-pyrone

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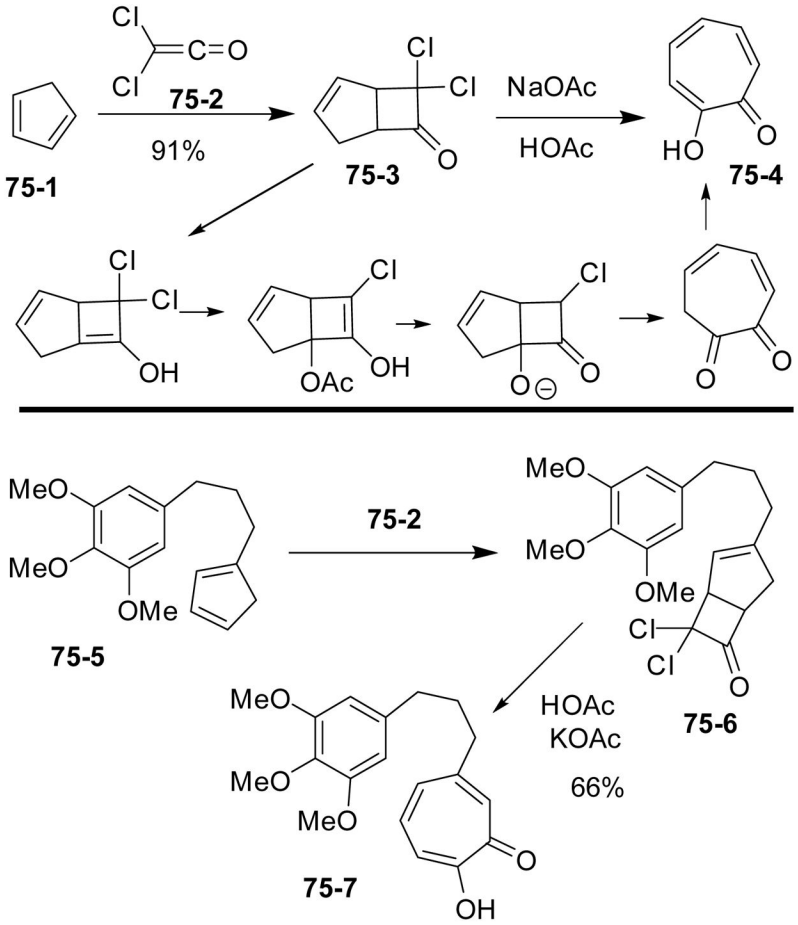


**Scheme 75.**

Synthesis of tropolone via [2+2] cycloaddition of cyclopentadiene with dihaloketene and its application in a formal synthesis of colchicine

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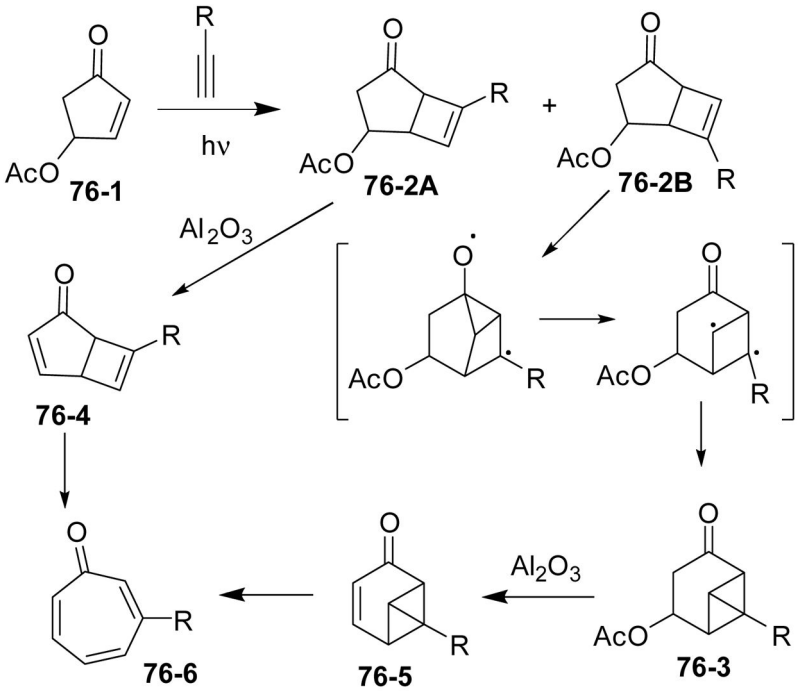


**Scheme 76.**

Synthesis of 3-substituted tropone (e.g. nezukone) under photolytic conditions

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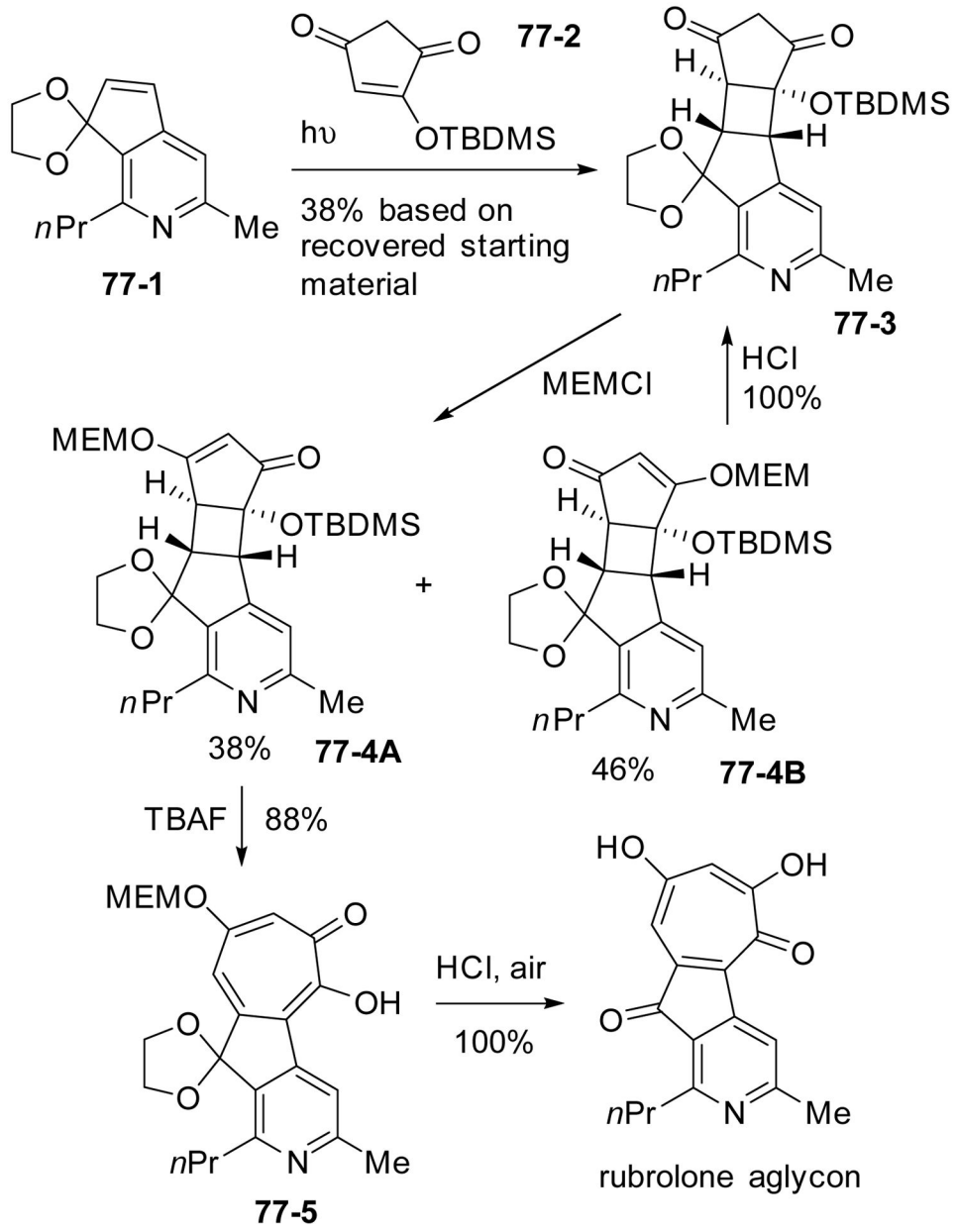


**Scheme 77.**

Synthesis of rubroloneaglycon via [2+2] cycloaddition and fragmentation

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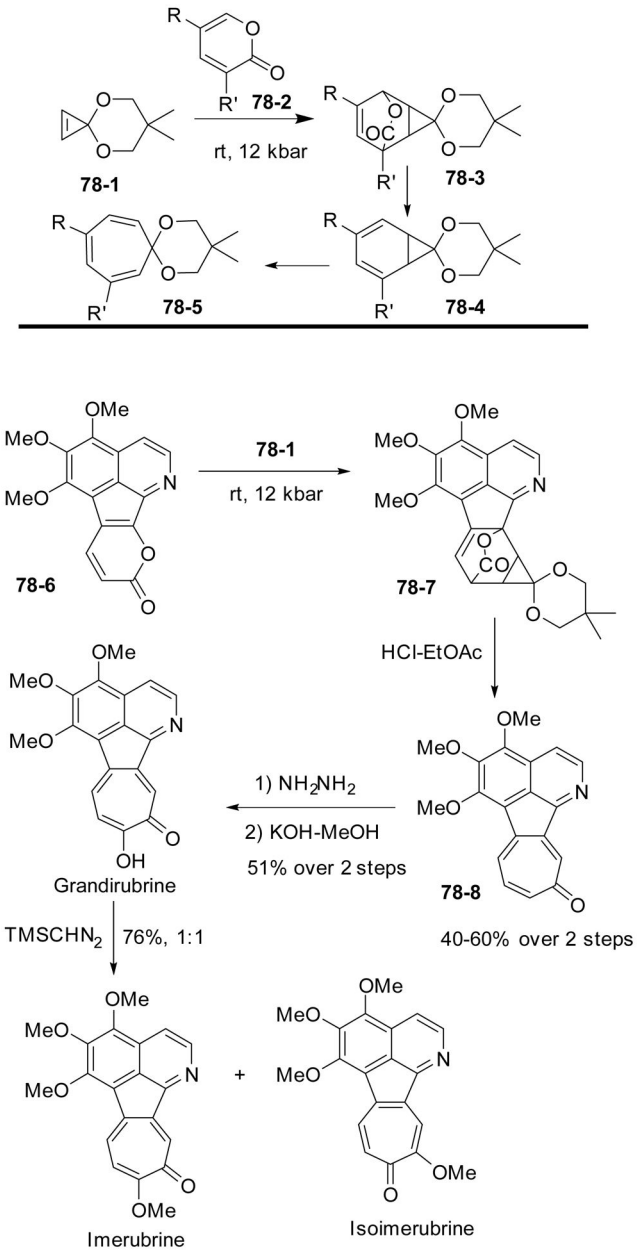


**Scheme 78.**

Synthesis of grandirubrine and imerubrine via cycloaddition of cyclopropenone ketal and α-pyrone

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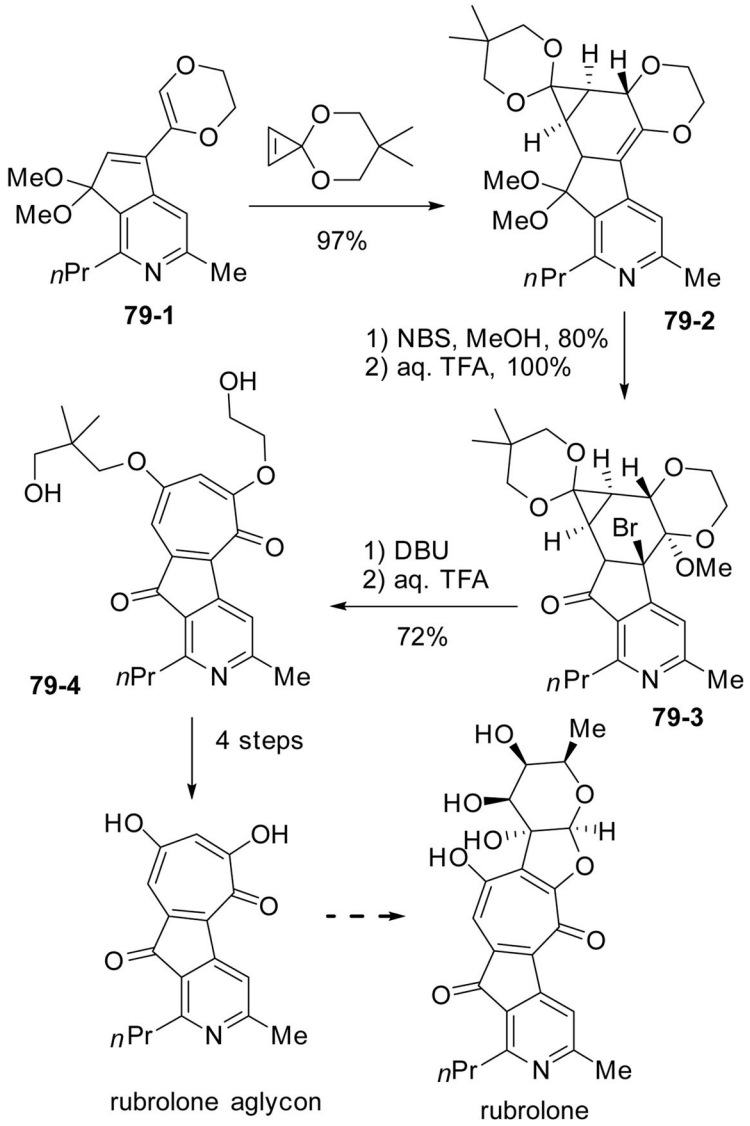


**Scheme 79.**

Synthesis of rubroloneaglycon via cycloaddition of cyclopropenone ketal and ring expansion

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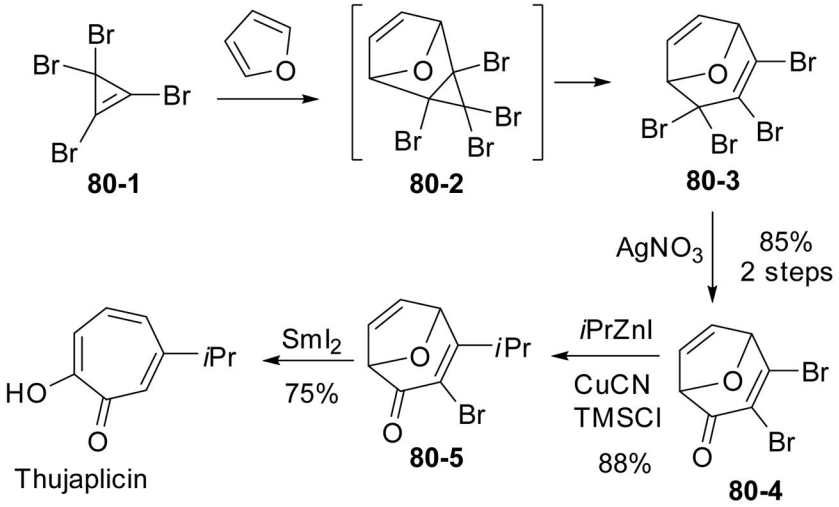


**Scheme 80.**

Synthesis of tropolones from cycloaddition of furan with TBCP and its application to the synthesis of thujaplicin

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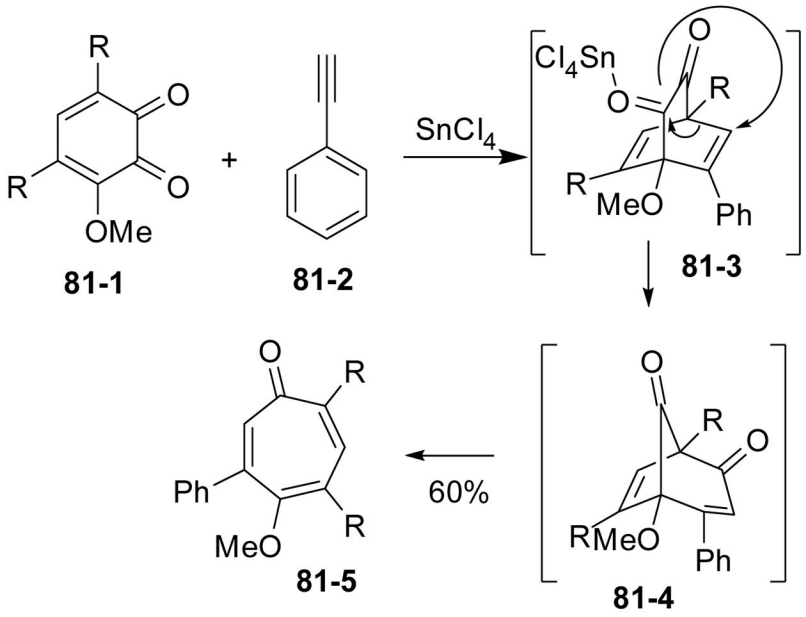


**Scheme 81.**

Synthesis of tropones via [4+2] cycloaddition followed by rearrangement