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Application of Pauson–Khand reaction in the total synthesis of terpenes

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The Pauson–Khand reaction (PKR) is a formal [2 + 2 + 1] cycloaddition involving an alkyne, an alkene and carbon monoxide mediated by a hexacarbonyldicobaltalkyne complex to yield cyclopentenones in a single step. This versatile reaction has become a method of choice for the synthesis of cyclopentenone and its derivatives since its discovery in the early seventies. The aim of this review is to point out the applications of PKR in the total synthesis of terpenes.

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Leila Mohammadi was born in Tehran, Iran. She received her B.Sc. in 2006. Then, she received her M.Sc. degree under the supervision of Dr Sakineh Asghari on the synthesis of heterocyclic compounds at the University of Mazandaran (Babolsar). She is currently working on the Ph.D. thesis in organic chemistry under the supervision of Prof. Dr Majid M. Heravi at Alzahra University, Tehran, Iran in 2021.

1. Introduction

The Pauson–Khand reaction (PKR or PK-type reaction) is formally a chemical reaction in which a triple bond, a double bond and carbon monoxide are subjected to a [2 + 2 + 1] cycloaddition reaction to form an α,β-cyclopentenone.[1] This entails the formation of three new bonds and one or two rings in the intermolecular or intramolecular fashion, respectively (Scheme 1).[1]

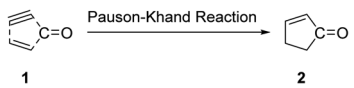
The first example of this reaction was reported in 1973.[2] In this reaction, norbornene reacted with the phenyl acetylene–hexacarbonyldicobalt complex to afford the corresponding cyclopentenone in 45% yield by using a stoichiometric amount of dicobalt octacarbonyl [$Co_2(CO)_8$] (Scheme 2).[3] This reaction was discovered by Ihsan Khand (1935–1980), who was working as a postdoctoral fellow with Peter Pauson (1925–2013),[4] at the University of Strathclyde in Glasgow.

The original PKR had several drawbacks such as only being proceeded in the presence of stoichiometric amount of dicobalt octacarbonyl ($Co_2(CO)_8$) as the only cluster, performed thermally under relatively harsh reaction conditions which resulted in desired transformations but with low efficiency. It also showed limited substrate scope covering narrow range of substrates. The use of strained olefins was necessary to obtain acceptable yields. In addition, the reactions typically afforded a mixture of regioisomers if unsymmetrical alkynes and alkenes were used. In several cases, the PKRs showed poor conversions and especially selectivities (chemo-, regio- and stereo-selectivities). Therefore, an important breakthrough was required which was obtained by Schore and co-workers,[5,6] who reported that carbon-tethered enyne precursors can be subjected to an intramolecular Pauson–Khand reaction (IPKR) in good yields with high regioselectivity. In other words, it was not necessary to use strained olefins as starting materials. In 1983, Schore and coworkers achieved and demonstrated the intramolecular PKR (IPKR).[6] A series of 5,5-disubstituted enynes **9** were subjected to PKR conditions to obtain 5,6-used bicycles **8** or **10** under PKR (thus, IPKR) conditions its good efficiency and conversions[7] (Scheme 3).[5]

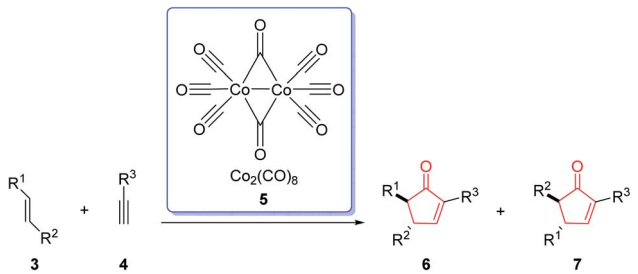
The PKR has received much attention of chemical community, especially synthetic organic chemists, as a method of choice for scientific studies because of the increase in diversity of the available starting materials. Therefore, it has rapidly improved and developed during these since its discovery.[8–15]

As an example an essential contribution to improvement of the promotion of PKR Smit and Caple in 1986.[16] They immobilized the reagents onto various solid supports. In these cases, PKRs were performed at lower temperatures and completed in shorter reaction times[16] [although other metals were found to catalyze the PKR, use of $Co_2(CO)_8$ in stoichiometric amount showed several merits. The $Co_2(CO)_8$ complex is inexpensive and commercially available, it tolerates a wide spectrum of functional groups, exhibits activity toward both terminal and internal alkynes].

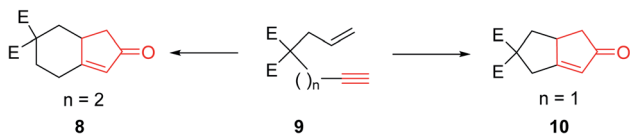
Jeong *et al.*[17] Schreiber and coworkers independently circumvented other problems such as requirement of high temperatures and CO pressures, as well as long reaction times.[18] They found that trimethylamine *N*-oxide and *N*-methylmorpholine *N*-oxide can accelerate the PKR dramatically. A wide range of cyclopentenones were obtained in good yields even at room temperature in the presence of *N*-oxides. It is presumed that *N*-oxides affect the reaction *via* oxidative liberation of the CO ligands of the metal complex facing up a coordination site. Thus, the following oxidative alkene addition becomes, the rate-determining step, accelerating the PKRs (Scheme 4). Other reagents were also found to assist PKRs to proceed smoothly



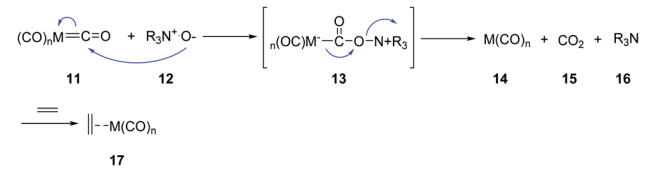
Scheme 1 Formation of three new bonds in PKR resulting in the formation of cyclopentanones.



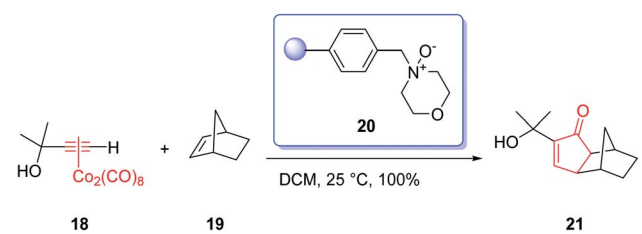
Scheme 2 The first example of Pauson–Khand reaction without regioselectivity.



Scheme 3 Regioselective intramolecular PKR.



Scheme 4 Formation of a vacant site in the cobalt cluster.



Scheme 5 A PKR performed on solid state.

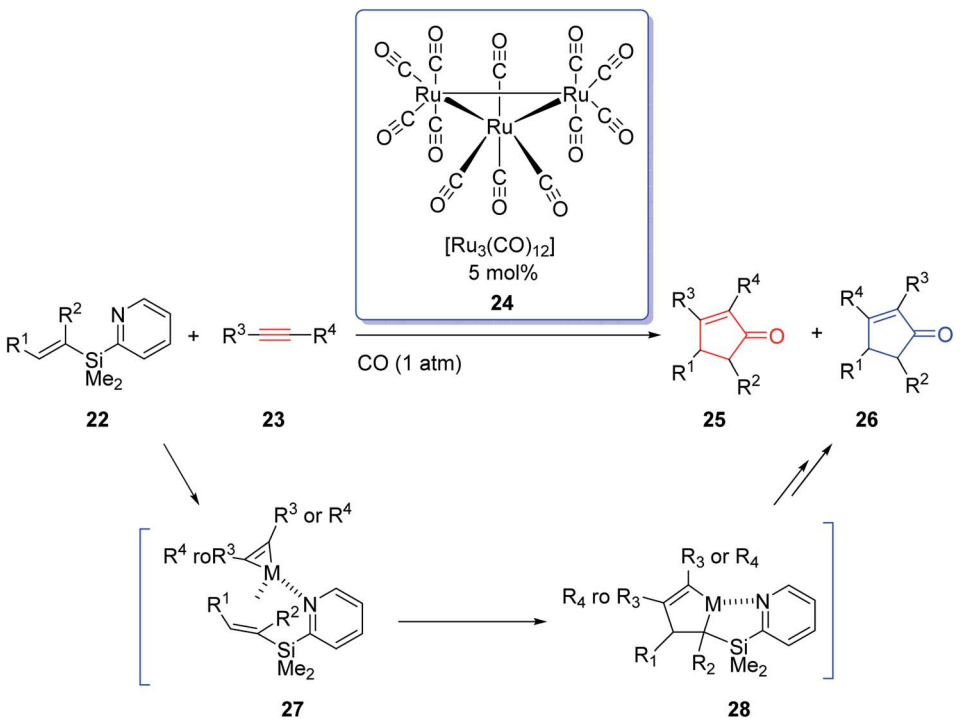
and rapidly; there include silica gel,[13,16] molecular sieves,[19,20] alkyl methyl sulfides,[21] and primary amines.[22]

The most commonly used amine *N*-oxides are trimethylamine *N*-oxide (TMANO) and *N*-methylmorpholine *N*-oxide (NMO). The latter has recently been immobilized onto a solid support which facilitates the work-up of the reaction and results in excellent yields of the products of PKRs (Scheme 5).[23]

Due to the innovation of IPKR, bicyclic frameworks which are prevalent in naturally occurring compounds can be constructed in one step *via* IPKR. Therefore, IPKR has found several applications in the total synthesis of natural products frequently used as the key step.[6,24–26] Synthetic organic chemistry has developed momentously owing to the exponential growth in transition-metal-catalyzed reactions. The effect of transition-metal-catalyzed reactions on organic synthesis could be evaluated by the wide range of molecules that have been developed from simple compounds to complex natural products. In 2002, J. Yoshida and coworkers intelligently expanded the metal-catalyzed organic transformations to PKR.[27] They used the Ru carbonyl complex $[Ru_3(CO)_{12}]$ **24** in catalytic amount (0.5 mol%) in the reaction of olefins containing an easily removable pyridisilyl group, readily obtained from alkynes under one atmosphere of CO. This metal catalyzed-PKR promotes the reaction efficiently since the pyridyl group directs it to proceed *via* the coordination of the nitrogen with the metal that provided complete regioselectivity with unsymmetrical olefins (Scheme 6).[27]

These achievements encouraged several research groups to investigate the scope and limitations of using other metals as catalyst in PKR. In this regard, various alkenes, alkynes, and carbon monoxide in the presence of different transition metals under PKR conditions were converted into the corresponding cyclopentenone derivatives.[28,29] For this purpose, various carbonyl complexes of iron (iron pentacarbonyl),[29–32] tungsten (tungsten pentacarbonyl),[32] chromium, molybdenum (molybdenum hexacarbonyl),[33] heterobimetallic cobalt/tungsten complexes,[34] and cobalt complex created *in situ* from alkyne cobalt complex and triethylsilane,[35] titanocene complexes,[34,36–38] $Co_2(CO)_8$ with high-intensity visible light system,[39] highly purified $Co_2(CO)_8$,[40] and other ruthenium complexes[35,38,41,42] were successfully used under PKR conditions.[43–46] Noticeably, the above-mentioned metal-catalyzed IPKR reactions had to be performed under medium or high pressure of carbon monoxide. In addition to ruthenium, rhodium complexes efficiently catalyze PKR which has attracted considerable attention. In 2002, Jeong and co-workers,[47] successfully used several rhodium complexes in various reactions under PKR conditions. Noticeably, some need activation with AgOTf prior to be used. After the appearance of the first IPKR in 1984,[16,48] a plethora of papers were published regarding the successful catalytic IPKR.[2,49–51]

In the nineties, several other developments in the PKR were achieved, including the introduction of an asymmetric variant (APKR). In general, bicyclic cyclopentenones as PKR products are valuable synthetic targets. The PKR is a powerful tool for the construction of such structural units. On the other hand, bicyclic cyclopentenones are prevalent scaffolds in natural products. Therefore, the asymmetric variant of PKR (APKR) is a unique and useful technique for the stereoselective construction of bicyclic cyclopentenones as a key step in the multistep total synthesis of natural products. Shibata and coworkers, reported the first example of a catalytic APKR in 2000.[29]



Scheme 6 The catalytic intermolecular Pauson–Khand reaction directed by a pyridylsilyl group.

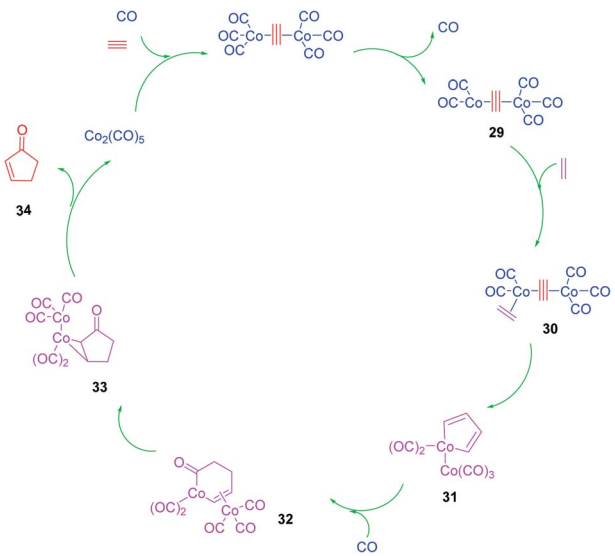
Their strategy was based on a chiral *ansa*-metallocene complex of titanium. Subsequently, other catalytic APKRs were supplemented by a plethora of promising reports, comprising chiral catalysts derived from binaphthyl phosphines and iridium, cobalt[33,52] or rhodium precatalysts.[32]

The efficiency of enantioselectivity of APKR mainly depends on the selection of correct substrates to induce asymmetry in the PKR. For this purpose, four approaches are available (a) using chiral substrate; (b) employing appropriate chiral auxiliary (c) using chiral metal complex and (d) the chiral promoter. The best results have been obtained using chiral substrates or chiral auxiliaries. Although, the use of chiral metal complex to give the best results, but it is still in the beginning stages and will be developed in a way to give excellent results expectedly in the future.

During investigation on the Rh-catalyzed PKR, two chiral catalysts were reported for APKR under an atmospheric pressure of CO. The chiral catalysts were (*S*)-BINAP/$Co_2(CO)_8$,[33,52] (*S*)-tolBINAP/$[Ir(cod)Cl]_2$ (ref. 29) and (*S*)-BINAP/$[RhCl(CO)_2]$.[2,31,32]

1.1. Mechanism of Pauson–Khand reaction

Although the Pauson–Khand reaction was discovered in 1973, a plausible mechanism for it was proposed by Magnus *et al.* in 1985 as illustrated in (Scheme 7).[53] Nowadays, this mechanism is believed to be undisputable since it has recently been confirmed by detailed negative ion electrospray collision testing.[54] Accordingly, the PKR is believed to commence with the generation of the alkyne-$Co_2(CO)_8$ complex **29**, lans of a carbonyl ligand to vacate a coordination site, olefin coordination **30**, followed by insertion, occurring at the end of the alkyne, which is less hindered to produce *in situ* the metallacycle **31**. The latter reacts promptly with inserted CO ligand to produce complex **32** followed by reductive elimination of **33** proceeds to furnish the desired target, cyclopentenone **34**. It is noteworthy that all the bond-forming steps took place on just one cobalt atom. The other cobalt atom which is present in the complex is supposed to function as an anchor which has extra electronic effects on the bond-forming metal atom *via* the present metal–metal bond[55] (Scheme 7).[53]



Scheme 7 A plausible mechanistic proposal for the Pauson–Khand reaction.

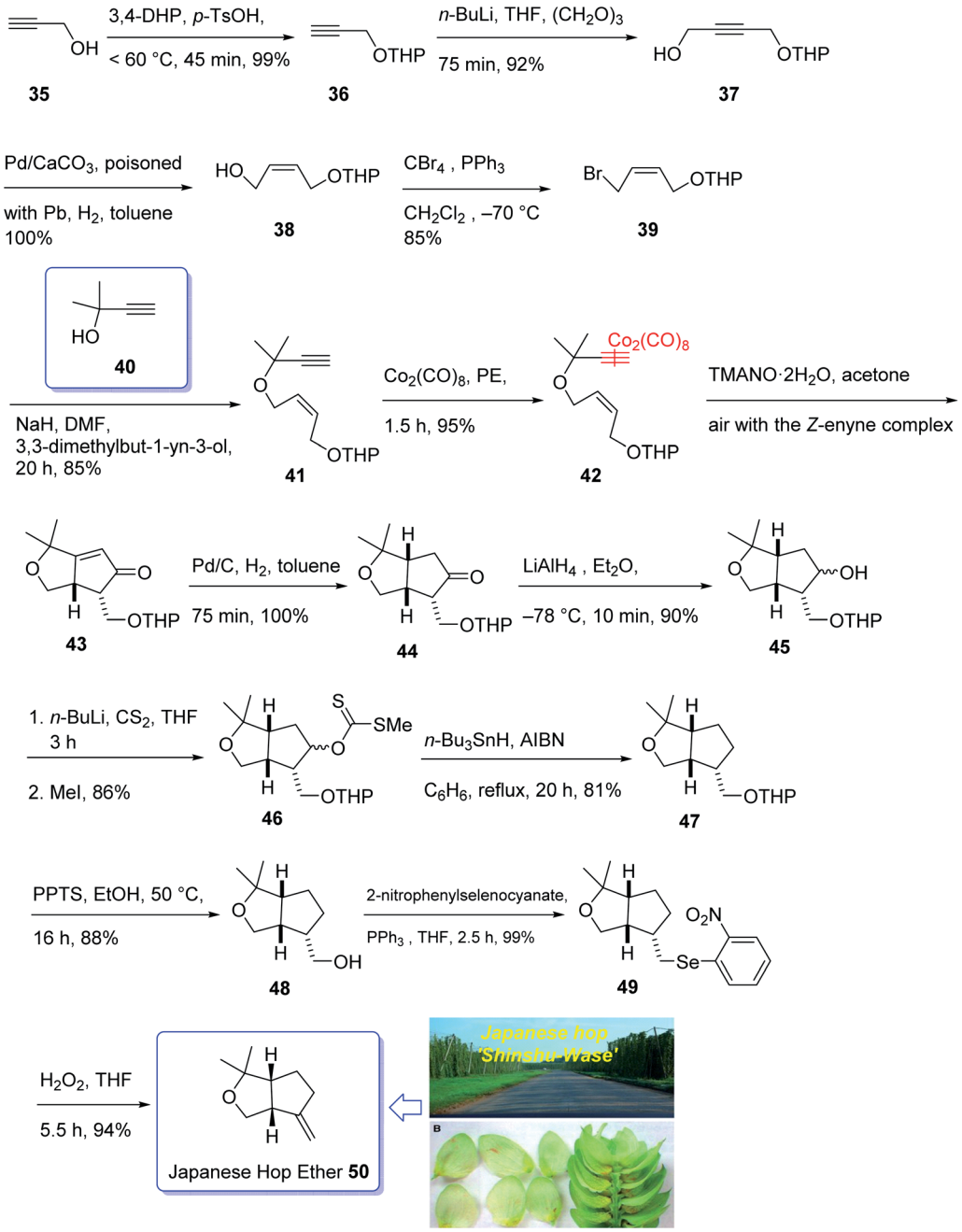
Although the prominence and importance of all kinds of PKR have been extensively covered by the previously published reviews,[56,57] its applications in total synthesis of natural products have largely been overlooked and limited to a subsection that mentions some total syntheses using PKR. These natural products are vincristine (Oncovin), Navelbine (vinorelbine), etoposide (VP-16), teniposide (VM-26), Taxol (paclitaxel) and most recently in 1996, Taxotere (docetaxel), topotecan (Hycamtin), sexestobergsterol, spatane, daphne, iridomirmecin, dendrobin, kalmanol and β-cuparenone were mentioned.[58,59]

2. Applications of Pauson–Khand reaction in the total synthesis of terpenes

2.1. Monoterpenes

In 1968, Naya and co-workers initially isolated ether **50** which is a monoterpene from the Japanese hop "Shinshu-Wase".[60] This naturally occurring compound is also present in Spalter hops.[61] Fascinatingly, it is thought to contribute to both the taste and aroma in low concentrations in a number of beers.[62–66] In 2016, Park research group produced Japanese hop extracts employing a standardized method.[67] This method facilitates the production of improved diagnostic and immunotherapeutic reagents.[67]

The first reported total synthesis of Japanese hop ether was reported by Imagawa *et al.* in 1979 which was claimed unreliable[65,68] and since that time few alternative pathways have also been claimed.[69] In 2005, Kerr *et al.* achieved and reported a concise (fourteen steps) total synthesis of monoterpene Japanese hop ether in 29% overall yield. They used an intramolecular Pauson–Khand reaction under mild *N*-oxide promoted conditions and with complete retention of alkene configuration (for both *cis*- and *trans*-alkenes) in the product cyclopentenone, as the crucial key step.[65] They started with propargyl alcohol **35** and transformed it to the corresponding THP-protected derivative **36** in almost quantitative yield. The latter upon deprotonation, using *n*-BuLi, with subsequent reaction with solid *para*-formaldehyde under ultrasound irradiation furnished the mono-protected ynediol **37** in excellent yield. The *Z*-olefin **38** was obtained in virtually quantitative yield by hydrogenation of ynediol **37** over Lindlar's catalyst and the obtained allylic alcohol was transformed to the bromide **39** in high yield upon being treated with CBr_4 and PPh_3. The bromide **39** was then reacted with the alkoxide anion of dimethylpropargyl alcohol **40** to afford allyl propargyl ether in high yield. In a key step (PKR), compound **41** underwent complexation with dicobalt of a carbonyl to afford **42** in excellent yield. Eventually, the *Z*-enyne complex **42** converted into the product **43** in high yield by use of TMANO·$2H_2O$ in acetone under air. Having compound **43** available in hand, it was deoxygenated affording **48** after several steps. The latter was then directly converted into



Scheme 8 Total synthesis of Japanese hop ether **50**.

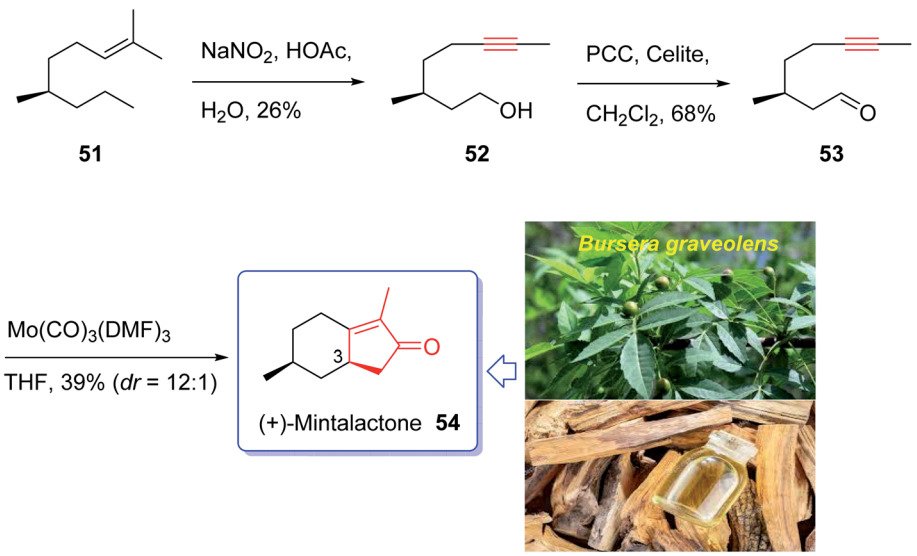
organoselenium species **49** upon reaction with *o*-nitrophenylselenyl cyanate and tri-*n*-butylphosphine in excellent yield. The latter was simply treated with H_2O_2 permitting the *in situ* generation of the selenoxide, which was subjected to elimination to furnish the desired natural product Japanese hop ether **50** in 94% yield (Scheme 8).[65]

Iwabuchi and co-workers in 1997,[70] initially isolated (+)-mintlactone **54** and (−)-isomintlactone **55** as *endo* α,β-unsaturated monoterpene-γ-lactones from the oil of the wood of *Bursera graveolens* (Palo Santo).[70] In 1968, Muraki and co-workers isolated their enantiomers, *ent*-(−)-**54** and *ent*-(+)-**55**, from *Mentha cardiaca*.[70] Also, The last two *p*-menthanolides were both isolated from *Mentha arvensis*[71] and are present as minor constituents of the commercial essential oil.[72] Interestingly, the total synthesis of the above-mentioned bicyclic monoterpene attracted much attention of synthetic organic chemists.[70,72–78] Recently, Bates *et al.*[79] achieved and reported a brief ten-step synthesis of (−)-mintlactone starting from the THP ether of propargyl alcohol *via* a highly asymmetric tin(II) chloride-catalyzed intramolecular propargylic Barbier reaction with subsequent allenol cyclocarbonylation. Furthermore, Shishido *et al.*[78] accomplished and reported a concise total synthesis of (−)-mintlactone in ten steps commencing from citronellal. In 2009, Zhai and co-workers[70] design a pathway for

total synthesis of (+)-mintlactone starting from (−)-citronellol **51**, using molybdenum-mediated intramolecular hetero-Pauson–Khand reaction as a key step. This pathway started with (−)-citronellol **51** which upon treatment with nitrous acid following Abidi's protocol gave alkynol **52** directly in three steps in 26% overall yield.[80] The latter was oxidized upon treatment with PCC in CH_2Cl_2 at ambient temperature to give ynal **53** as suitable precursor for PKR. The ynal **53** was then treated with freshly prepared organomolybdenum $Mo(CO)_3(DMF)_3$,[81] as catalyst, in THF at ambient temperature to afford the desirable natural product (+)-mintlactone (**54**, 39%) along with its inseparable diastereomer, apparently (−)-isomintlactone (**55**, 3%), in an optimized combined yield of 42%. Interestingly, in this total synthesis, during the PKR, one stereogenic center, two rings, and three covalent bonds (1 C–O and 2 C–C) are generated which proceeded in high diastereoselectivity (C-3, dr = 12 : 1). Due to more stability of a chair conformation (TS-1) in its transition state which theoretically has lower energy than a twist boat one (TS-2), thus (+)-mintlactone **54** must have emerged as a major product. In conclusion, the total synthesis of (+)-mintlactone was accomplished *via* a three-step assemblage which can be exemplified as a new concept in the art of synthetic organic chemistry as "step economy"[82] and "strategic efficiency".[83] Important aspects of this total synthesis involved HNO_2-induced formal isopropylidene "demethanation" and the $Mo(CO)_3(DMF)_3$-promoted intramolecular PKR (Scheme 9).[70]

The generic name iridoid monoterpenes is derived from the names iridomyrmecin, iridolactone, and iridodial which initially isolated from special species of *Iridomyrmexes*, ants, secreting them as defensive existing either in the glycosidic or in the non-glycosidic form,[84] these naturally occurring compounds were found the dynamic and active components of folk medicinal plants being used conventionally as medicine for long time as antiviral, antibacterial, and anti-inflammatory.[85,86] In addition, iridoids are also commercially important since can be used as sex pheromones against some agriculturally important species such as aphids.[87] Structurally, iridoids contain a confined cyclopenta[*c*]pyran framework as shown for some important members of family. Nevertheless, controlling their stereochemical complexities and the diverse oxygenation patterns, which frequently are confined in *cis*-fused bicycle, are challenging for synthetic organic chemist and render them striking targets for total synthesis. Thus, several fantastic synthetic pathways for their total synthesis have been reported.[88] Some of them are accomplished and reported by Suh and co-workers[89,90] and recently one reported by Chakraborty and co-workers.[91] In spite of the appearance of these reports among the others, a literature survey disclosed few reports on the total synthesis of diverse oxy-functionality pattern observed on the cyclopentane ring of the iridoid framework.[89,92,93] In 2019, Khan and co-workers reported an efficient and economic strategy to have access to several iridoids (**65**, **68**, **68′**, **70**, **71**, **72**, **75**, **75′**, **79**)[94] using an intramolecular Pauson–Khand reaction (IPKR) as the crucial step to access ten iridoids in a stereoselective fashion. In their strategy, bicyclic ether **61** was found to be an important intermediate, since it contains the iridoid scaffold as well as bearing a carbonyl functionality at the C6 position and tosylate at the C4 position. The manipulation of the C6 carbonyl moiety in **61** makes the construction of cyclopentane ring of the desired natural products (**65**, **68**, **68′**, **70**, **71**, **72**, **75**, **75′**, **79**) possible whereas the tosylate present at C4 can be exploited for the construction of tetrahydropyran ring, which can be extended to the δ-lactone ring or easily discarded in the framework of scholarein A **80**. In addition, total synthesis of some other natural products can be simplified by having easy access to an iridoid. For example, the total synthesis of 7-*epi*-boschnialactone **68′**.

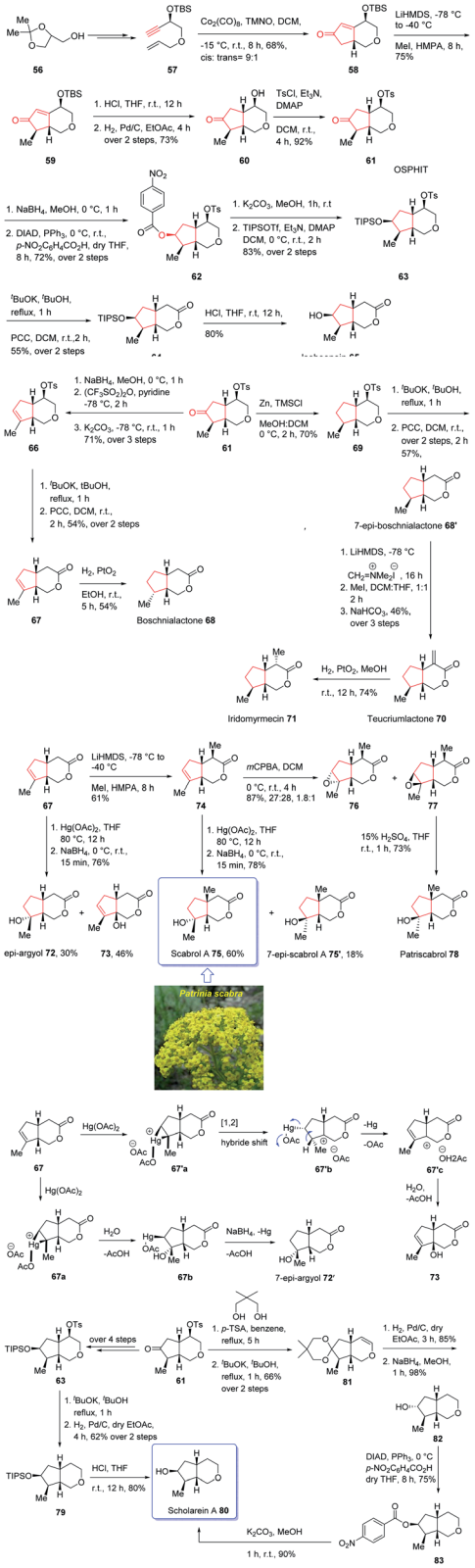
This strategy is started with the easily accessible glycerol acetonide **56**,[88,95] which in two steps was converted into the enyne **57** as an appropriate precursor of PKR. The latter in crucial step was subjected to diastereoselective conventional IPKR[88] in the presence of $Co_2(CO)_8$, TMNO to afford compound



Scheme 9 Total synthesis of (+)-mintlactone **54** and (−)-isomintlactone **55**.

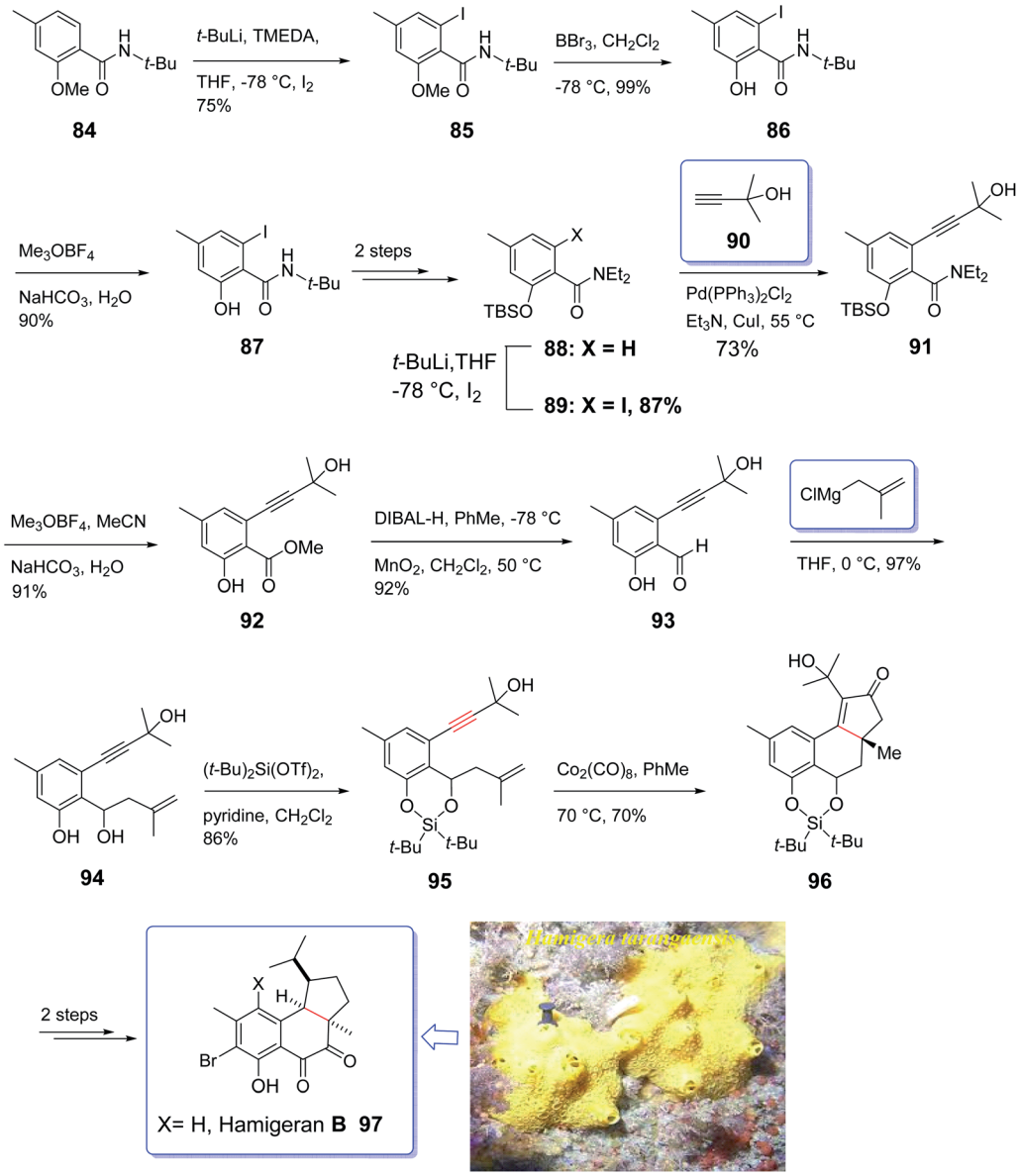
58 which was then transformed into the important intermediate **61** in three steps. This important intermediate **61**, was initially treated with Zn/TMSCl to undergo Clemensen reduction[96] to give compound **69** which after two steps involving manipulation of its C4-tosylate moiety, **69** was converted into the δ-lactone affording the C7-epimer of boschnialactone **68′** in good yield, with identical spectroscopic data to that previously reported.[97] On the other hand, intermediate **61** was converted into TIPS protected bicyclic lactone **64**. TIPS deprotection in compound **64** in the presence of 10% HCl in THF gave the desired natural product iridolactone isoboonein **65** in satisfactory yield. The spectral data of this synthetic compound **65** were found being identical to those recorded for natural isoboonein.[93] After successful synthesis of natural product **65**, the synthesis of iridoids **71**, **68** and **70** from the key intermediate **61** was contemplated. On the already prepared epimeric natural product **68′**, an exocyclic methylene group was introduced at the C4 position to obtain the other desired natural product **70** and another natural product **71** was subsequently provided through the stereoselective exocyclic double bond reduction from the *exo* face. The spectral data of the synthetic compounds **71** and **70** were compared with those already recorded and reported for the natural products,[94,98] and found being identical. Finally, noriridoid scholarein A **80** was synthesized from intermediate **61**. The latter was first converted into intermediate **63** as a TIPS ether in several steps. Then, with **63** available in hand, its C4-tosylate group in the tetrahydropyran ring was eliminated and the resultant dihydropyran was oxidized to obtain the δ-lactone, the desired natural product isoboonein **65** (Scheme 10).[94]

Hamigeran A–D are members of a family of metabolites which are isolated from the extract of sponge *Hamigera tarangaensis* by Cambie and co-workers in 2000.[99] They actually are a small class of brominated terpenes. Among members of this family, hamigeran-B **97** has exhibited remarkable biological potency as it showed 100% virus inhibitory property toward both herpes and polio viruses with negligible cytotoxicity.[100] Its tricyclic structural backbone comprising an aromatic ring, has attracted the attention of organic synthetic chemists. Therefore, several research groups have focused on its total synthesis. The first asymmetric synthesis was achieved by Nicolaou and co-workers relied on an asymmetric Diels–Alder reaction as key step,[101] Clive *et al.* employed radical cyclization for the construction of the five-membered ring conducting both a racemic and asymmetric synthesis.[102] Thereafter, Trost and co-workers applied an asymmetric allylic alkylation as the source of asymmetry in a novel synthetic strategy for total synthesis of hamigeran-B.[103] Wright *et al.* accomplished and reported the synthesis of hamigeran scaffold by employing an effective electro-oxidative coupling reaction.[104] Very recently, Lovely and co-workers completed the framework of the tricyclic structure of hamigeran using Pauson–Khand reaction. In this strategy, cyclization only occurred when the olefin-containing group was tethered to the aromatic backbone to diminish its conformational movement. To this purpose, they selected silylene protecting group. Then, effective formation of the aryl enyne from a salicylic acid derivative was achieved through *ortho*-lithiation and Sonogashira cross-coupling reaction.



Scheme 10 Total synthesis of noriridoid scholarein A **80**.

A concise strategy for the total synthesis of hamigeran B **97** commenced from the easily accessible *tert*-butyl amide **84** (ref. 105) which was provided by standard acylation of salicylic acid.



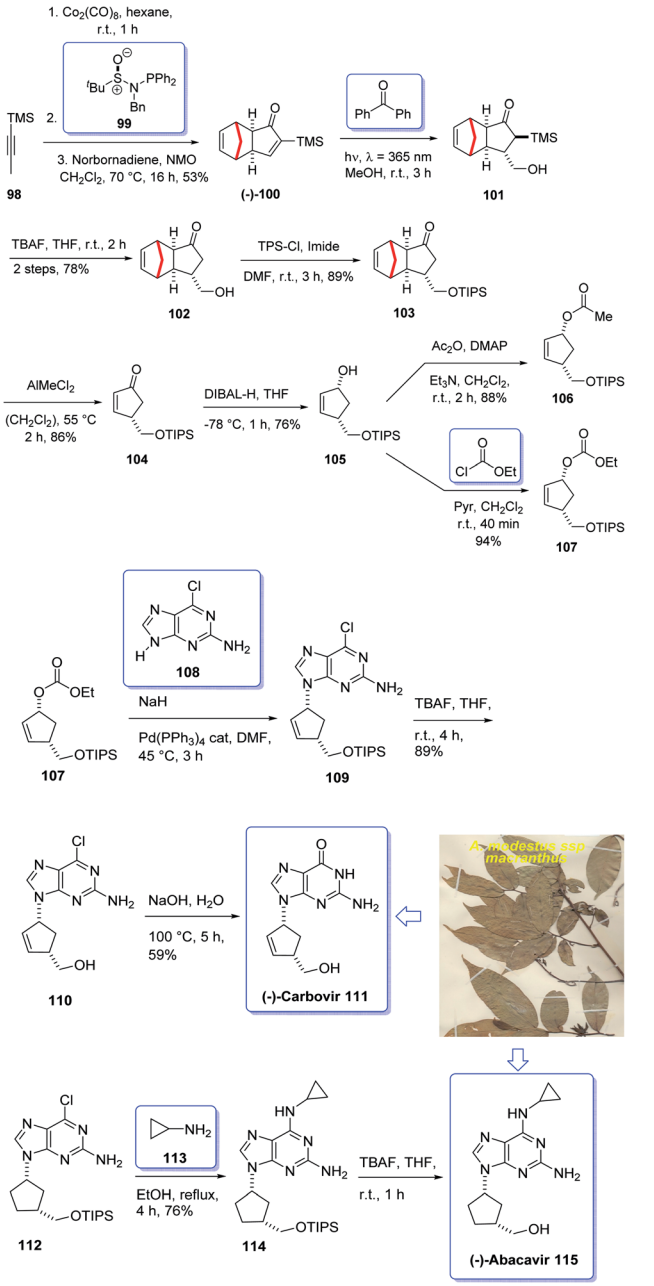
Scheme 11 Total synthesis of hamigeran B **97**.

The latter upon treatment with *n*-BuLi leading to the formation of aryl lithium which was trapped with iodine to give **85**. Upon cleavage of the methyl ether in **85** with excess BBr_3, amide **86** was obtained upon treatment with Meerwein's salt and then aqueous base. The methyl ester was provided in 89% yield *via* three sequential steps. Compound **87** was then converted into **88** in two steps. The latter was then subjected to Sonogashira cross-coupling with 2-methyl-2-butynol which upon treatment with **90**, hydrolysis of the amide employing the two-step reaction *via* the imitate gave **91**. Then, compound **91** underwent desilylation to afford **92**. Oxidation state adjustment of **92** *via* reduction using DIBAL-H gave benzyl alcohol and oxidation with MnO_2 afforded the corresponding aldehyde **93** as key intermediate. Reaction of the latter with methallylmagnesium chloride proceeded cleanly to give the diol **94**, which upon treatment with $(t\text{-Bu})_2Si(OTf)_2$ afforded the silylene derivative **95** in high yield. Pleasantly, the enyne **95** was converted into the $Co_2(CO)_8$ complex, with subsequent thermal activation at 70 °C in toluene under PKR resulted in the construction of desired tetracyclic adduct **96** in 70% yield as a sole diastereomer.[106] The desired stereochemical biases was induced by intramolecular PKR resulting in the placement of the peripheral *exo* substituents.[107] Finally, the latter was converted to the desired natural product hamigeran B **97** in two steps (Scheme 11).[104]

2.2. Terpenoids

Terpenoids represent a highly diverse group of natural products with wide applications. Terpenoids, also known as isoprenoids, are the most numerous and structurally diverse natural products found in many plants. Several studies, *in vitro*, preclinical, and clinical have confirmed that this class of compounds

displays a wide range of very important pharmacological properties. About 60% of known natural products are terpenoids. The diverse collection of terpenoid structures and functions have provoked increased interest in their commercial use resulting in some medical applications being registered as drugs on the market. Nowadays, nucleoside analogues have attracted the interest of synthetic organic chemists due to their significant biological activities and have been useful as antiviral and antitumor drugs.[108] A novel meroterpenoid named artabotramide was obtained from the petroleum ether extract of the root barks of *Artabotrys modestus* subsp. *macranthus* Verdc by Baggio in 1978.[109,110] Furthermore, the 2-azabicyclo [2.2.1]-hept-5-en-3-one (ABH) moiety present in artabotramide is of medicinal potential and one of the target pharmacophores in the synthesis of anti-retroviral carbocyclic nucleoside analogues such as (±)-carbovir **111** and abacavir **115**.[110–113] Thus, the unprecedented isolation of artabotramide from *A. modestus* ssp *macranthus* suggests the plant species to be a potential bioresource for further investigation of carbocycles that are potentially important in biomedical research. Among them, AZT (Zidovudine), antiviral toward HIV, and Acyclovir (Zovirax), antiviral toward Herpex simplex, are well-known prescribed market purchasable drugs.[114] Carbanucleosides establish a remarkable class of nucleoside analogues.[115] Aristeromycin and neplanocin are natural product carbocyclic nucleosides showing antitumor and antiviral activity as well as exhibiting better metabolic stability to phosphorylases comparing with their glycosidic relatives.[116] Carbovir **111** and abacavir (Ziagen) **115** are actually synthetic five-membered ring carbanucleosides. Since carbovir showed toxicity, it was not developed beyond the preclinical stage but abacavir was approved synthesized and launched for the treatment of HIV. Compounds **111** and **115** have been prepared by various pathways, initially *via* enzymatic resolution, kinetic resolution, as well as asymmetric synthesis stating from sugars.[117,118] Nevertheless, up to date establishment of a general strategy *via* stereoselective synthesis have been largely overlooked.[119] However, in 2005, Schmalz *et al.*[120] achieved and reported a novel strategy for the total synthesis of carbocyclic nucleosides **111** and **115** including an intramolecular Pauson–Khand reaction[121] as the key step. In this strategy, execution of kinetic resolution with the Corey's CBS reagent is required to obtain enantiopure compounds. Recently, several practical enantioselective versions of the intermolecular Pauson–Khand reaction have been reported[122] which resulted in the formation of cycloadduct in high yield and optical purity. Armed with this finding, it was envisaged compound **99** could be an appropriate starting material for the total synthesis of many carbanucleosides. Based on the above reaction, an approach for asymmetric synthesis of (−)-carbovir **111** and (−)-abacavir **115** depended on asymmetric intermolecular PK reactions were designed for the total synthesis of carbanucleosides. This approach was designed based on readily accessible cyclopentenone **100** which is provided by the reaction of trimethylsilylacetylene **98** with norbornadiene *via* asymmetric PKR and retro-Diels–Alder reaction to give (−)-**100** (Scheme 12).[122] Thus, the vital step of this synthetic strategy is the



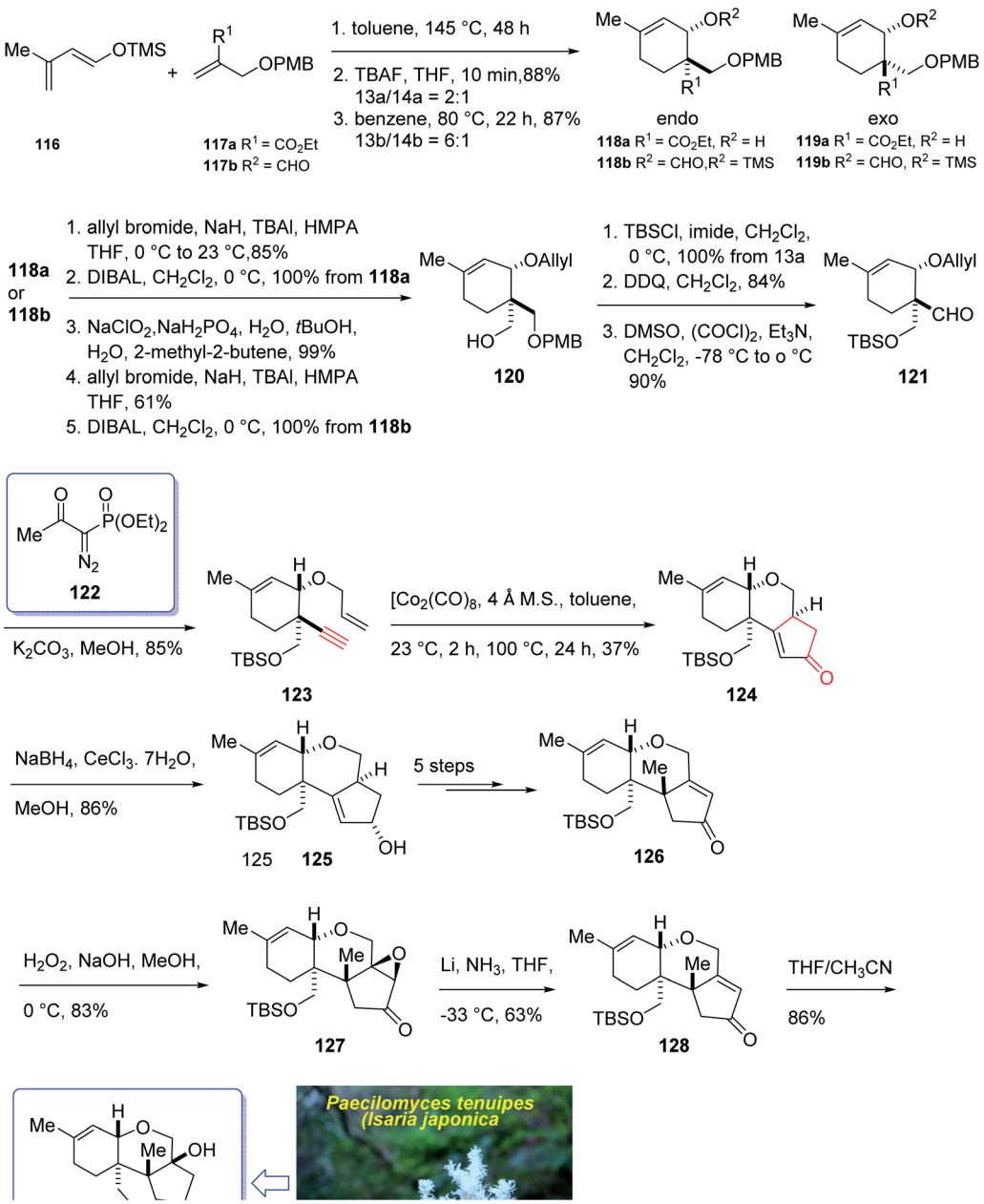
Scheme 12 Total synthesis of (−)-carbovir **111**, (−)-abacavir **115**.

stereoselective introduction of ad[1]-synthon into cyclopentenone **100** *via* intermolecular PKR.[123]

In this way, both racemic and optically active PK adduct **104** were prepared at multigram quantities with ee is of >99%. Then, compound **103** in excellent yield and with complete stereospecificity was obtained by irradiating a solution of **100** in methanol at 365 nm in the presence of benzophenone as a triplet sensitizer, following a method developed by Fraser-Reid *et al.*[124] Next, the TMS group of **103** was readily deprotected using TBA to give the required intermediate alcohol **102** in 78% yield. Thereafter, the hydroxyl group of **101** was protected as triisopropylsilyl ether under standard conditions to afford **103** in 89% yield. The protected hydroxyethyl

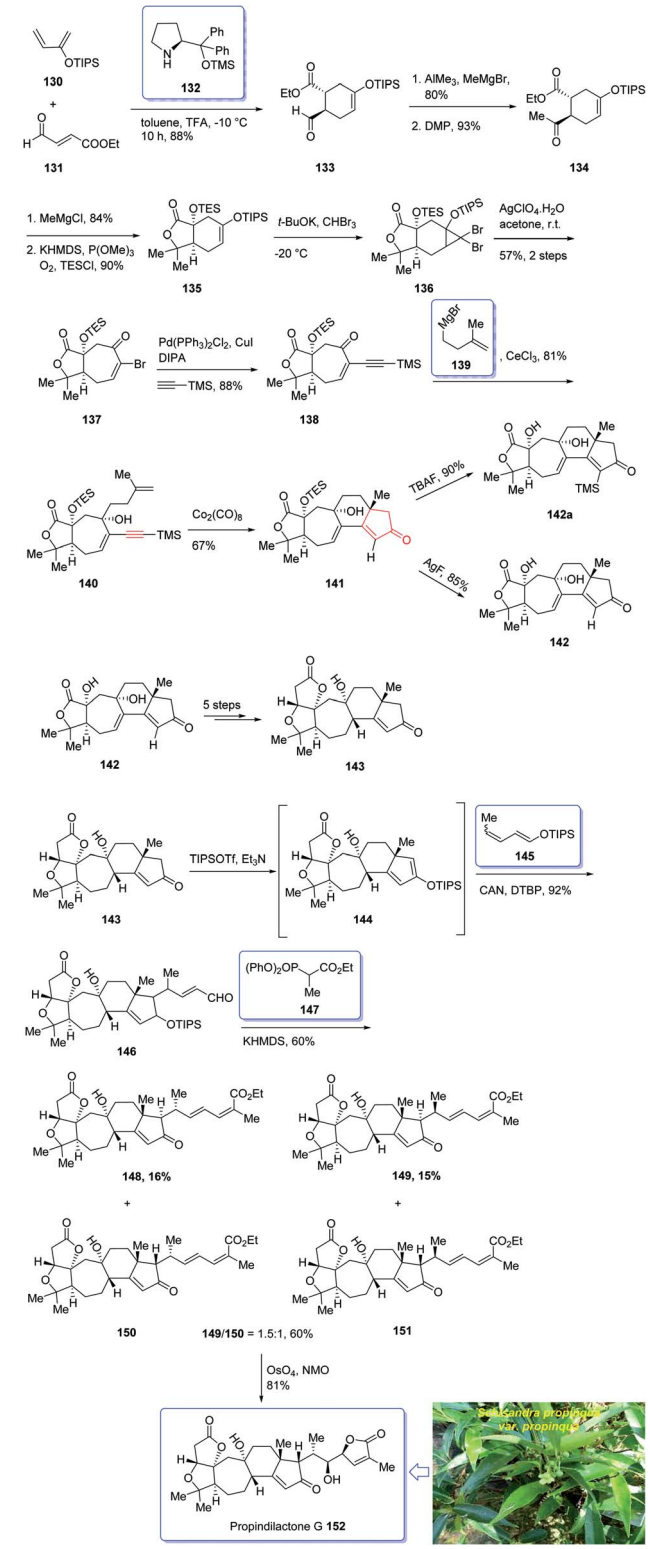
cyclopentanone **103** was then subjected to the retro-Diels–Alder conditions reported by Grieco[125] using $AlMeCl_2$ as a Lewis acid and maleic anhydride as a cyclopentadiene scavenger to afford cyclopentenone **104** in 86% yield. At this stage, the latter was reduced using DIBAL-H at low temperature to give allyl alcohol **105** in satisfactory yield. Upon allylic substitution, compound **105** was readily derivatized to the corresponding acetate **107** and carbonate **106.** Gratifyingly, reaction of carbonate **106** using sodium hydride as a base afforded the key nucleoside in 84% yield with a 4 : 1 dr of N9/N7 regioisomers. The desired regioisomer at N9 **109** was obtained in 67% yield after chromatographic purification, and ee > 99% determined by chiral HPLC. Finally, the key intermediate **110** was converted into desired natural products *i.e.* enantiomerically pure (−)-carbovir **111** and (−)-abacavir **115** using compound **110** and **114**, respectively (Scheme 12).[115]

In 2004, Oshima *et al.*[126] isolated several paecilomyces tenuipes terpenoids from extract of cultured fruiting bodies of *Paecilomyces tenuipes* (*Isaria japonica*). It was actually a common entomopathogenic fungus employed as traditional remedy and healthy foods in China.[126] Among them, compound **129** (paecilomycine A), at 10 nm, is able to promote neurite outgrowth in PC 12 cells. It was also known that paecilomycine A **129** is considerably more potent than scabronine G in increasing NGF levels. In 2007, the appearance of a fascinating skeleton for the total synthesis of paecilomycine A **129** (ref. 127) was stimulated



Scheme 13 Total synthesis of paecilomycine A **129**.

by Danishefsky and co-workers for the isolation and structure elucidation. In 1961, Martin and Hill reported an initial total synthesis of racemic **129** *via* Diels–Alder reaction to many early hindrances in their efforts[128] as well as using Pauson–Khand reaction. Initially, the Diels–Alder reaction of **116** (ref. 129) and **117a**,[130] under severely thermal conditions (at approximately 145 °C in toluene) followed by deprotection, afforded a 2 : 1 mixture of **118a** and **119a** with 88% yield. As illustrated, *O*-alkylation performed to give the corresponding allyl ether. Reduction of the ester group produced compound **120** which followed by protection as a silyl ether and deprotection of the PMB group followed by oxidation of the obtained alcohol to aldehyde afforded compound **121**. The compound **123** was afforded *via* Bestmann–Ohira reagent (dimethyl 1-diazo-2-oxopropyl phosphonate) with compound **121**. An important compound available in hand **123**, was submitted to intramolecular Pauson–Khand reaction at 100 °C (ref. 19 and 131) to afford the sole stereoisomer **124** in 37% yield. The compound **126** was transformed to desired natural product paecilomycine A **129**, involving several group functional transformation as illustrated in (Scheme 13).[127]



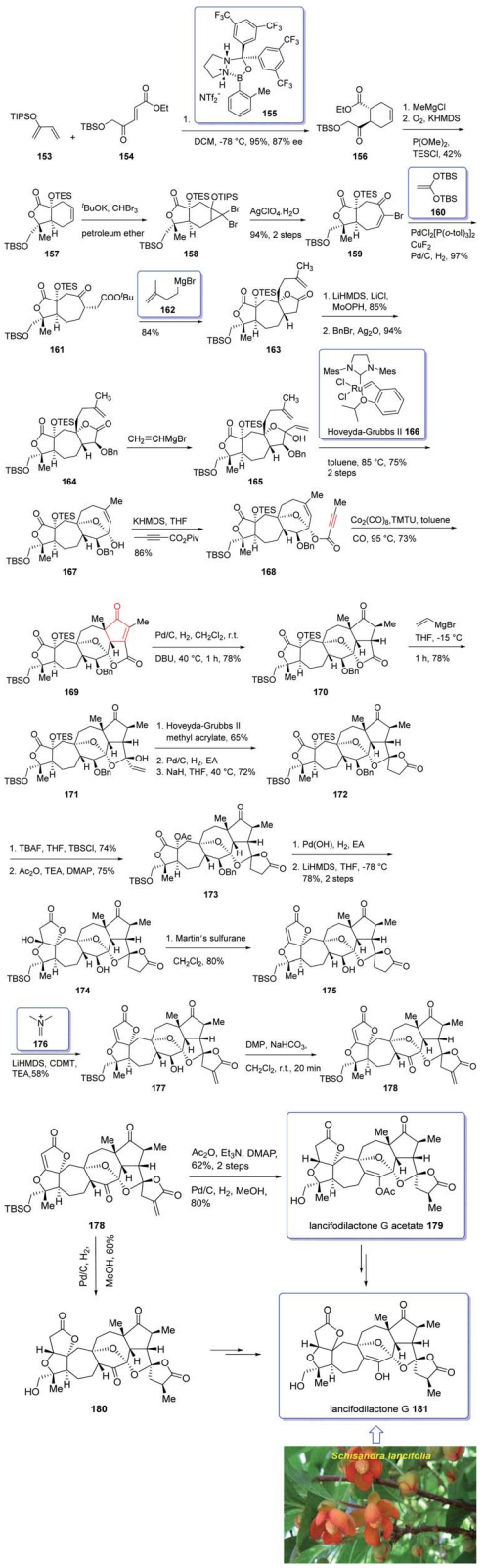
Scheme 14 Total synthesis of (+)-propindilactone G **152**.

In 2008, Sun *et al.*[132] for the first time isolated propindilactone G **152** (ref. 132) which is a member of a novel family of nor-triterpenoids[133] from different species of Schisandraceae family (*Schisandra propinqua* var. *propinqua*) from Southeast Asia.[132] It has been used as folk herb in China for liver protection and immune-regulation for a long time.[133] Structurally, propindilactone G **152** contains an exceptional 5/5/7/6/5 pentacyclic scaffold having seven chiral centers which three of them are quaternary stereogenic centers.[134] Primary biological screening of propindilactone G **152** specified that these kinds of nortriterpenoids show auspicious anti-HIV potency.[135] Their, interesting chemical structures in combination with their insufficiency in nature, which restricts their further biological screening, have prompted great interest among[136] synthetic organic chemists to design a pathway for the total synthesis of propindilactone G1.

In 2015, a brief total synthesis of (+)-propindilactone G **152** using Pauson–Khand reaction as a key step was accomplished and reported by Yang *et al.*[137]

This strategy started with an asymmetric Diels–Alder reaction of diene **130** and dienophile **131** in the presence of a chiral ligand (Jorgensen–Hayashi catalyst) **132** which afforded (−)-ester **133** in high chemical yield and in excellent ee (98%). After several steps, the latter was transformed into enyne **140** as a sole isomer. Then, the latter was subjected to PKR conditions which upon treatment with $Co_2(CO)_8$ in the presence of Celite[138] in refluxing toluene afforded cyclopentenone subunit **141** bearing an all-carbon quaternary chiral centers. After several steps, the latter was converted to a mixture of **148**, **149** and **150**/**151**. Pleasantly, compound **150** was converted into the desired natural product propindilactone G **152** upon treatment with OsO_4 as oxidant and in the presence of NMO[139] as a co-oxidant. These reactions desired the total synthesis of (+)-propindilactone G **152** in only twenty steps (Scheme 14).[166]

In 2005, Sun and his research group initially isolated lancifodilactone G **181**, as one of the most important members of the schinortriterpenoids family, from the extract of *Schisandra lancifolia*[140] which had been used as anti-hepatitis, antitumor, and anti-HIV agents as traditional medication.[133] Due to these

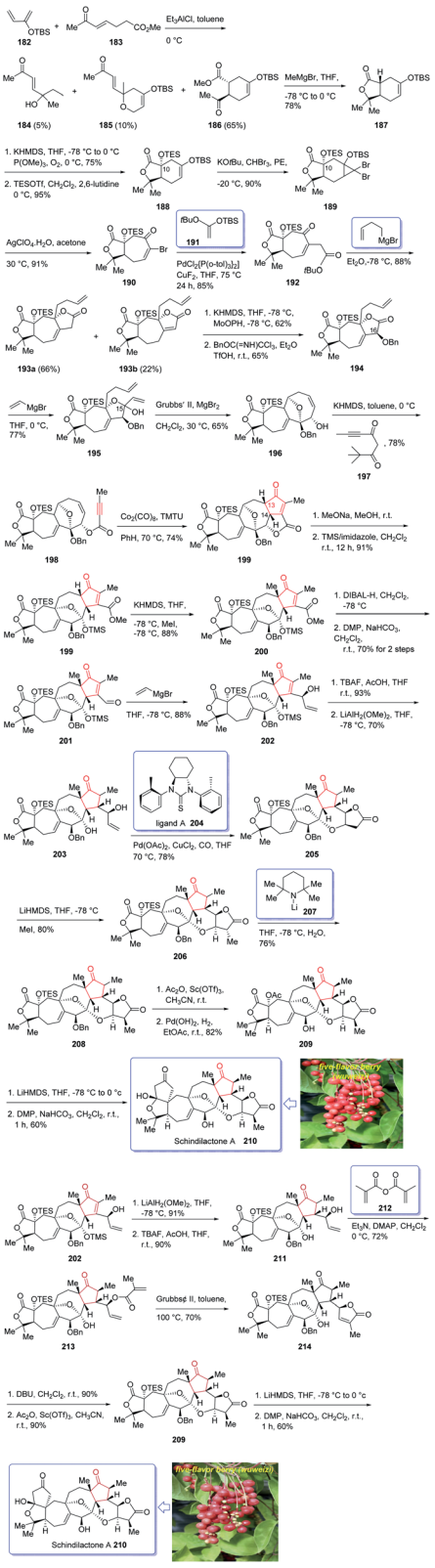


Scheme 15 Total synthesis of lancifodilactone G **181**.

biological activities and interesting chemical structure of **181**, many attempts were made to their total synthesis,[141] with the goal of fast-tracking of the assessment of its pharmacological activity. Asymmetric total synthesis of structurally fascinating and highly oxygenated lancifodilactone acetate G **7** was accomplished in twenty-eight steps from commercially available 2-(triisopropylsiloxy)-1,3-butadiene **153** reported by Yang *et al.* in 2017.[142] The total synthesis started with asymmetric intermolecular Diels–Alder reaction[143] of diene **153** with dienophile **154** catalyzed by oxazaborolidine **155** (ref. 144) to provide ketoester **156** in satisfactory chemical yield and 87% ee. After several steps, the latter was transformed into enyne **168** as an appropriate PKR precursor. The enyne **168** was then subjected a PKR upon treatment with the complex of tetramethyl thiourea (TMTU) and $Co_2(CO)_8$ under already secured optimal conditions to afford enone **169** in 73% yield as a single isomer. Next, the enone **169** was transformed after several steps into ketone **178**. The latter can be converted to lancifodilactone G acetate **179** in two steps including a Pd/C-catalyzed hydrogenation. On the other hand, ketone **178** was converted into **180** which after several steps was converted to the desired natural product lancifodilactone G **181** (Scheme 15).[142]

(±)-Schindilactone A **210** is a member of family of Schisandraceae which is valuable from both economic and medicinal points of view.[145] More than 20 species of Schisandraceae were found in China which have extensively been used as traditional medicines[146] over 2000 years in 2008 Han-Dong Sun research group isolated over 70 nortriterpenoids from Schisandraceae.[147,148] Among them, schindilactone A **210** (ref. 149 and 150) was found being conspicuous member with eminent biological potencies including inhibition of tumor growing and hepatitis, and also as anti-HIV-1.[147] In spite of its prominence, only small amounts of schindilactone A **210** can be obtained from natural sources even for its biological potencies screening, thus, its total synthesis has attracted much attention of synthetic organic chemists.

In 2012, Yang *et al.*[145] accomplished and reported the total synthesis of schindilactone A **210**. Their strategy involved (a) an Ag-mediated ring-expansion reaction to obtain vinyl bromide **180** from dibromocyclopropane **189**; (b) a Pd-catalyzed cross-coupling of vinyl bromide **190** with a copper enolate to provide ketoester **192**; (c) a RCM reaction to obtain oxabicyclononenol **196** from diene **195**; (d) construction of cyclopentenone segment in substrate **199** *via* catalyzed Pauson–Khand reaction. This total synthesis started with hetero-Diels–Alder reaction between diene **182** and dienophile **183** in toluene at 0 °C in the presence of Et_2AlCl[151] to furnish a mixture containing compound **184** (about 5% obtained from the alkylation of Et_2-AlCl to the keto group in dienophile), compounds **185** and **186** (about 10%). Then, upon the treatment of ester **186** with MeMgBr, lactone **187** was obtained in good yield. The latter was converted to enyne **198**, as an appropriate PKR precursor, after several steps involving various functional group transformations. In a key step, enyne **198** was subjected to PKR under the secured optimal PKR conditions ($Co_2(CO)_8$/TMTU in dry benzene under a CO atmosphere (balloon) at 70 °C for 4 hours) affording compound **199** in satisfactory yield. Then, the latter converted into alcohol **209** after several steps. Next, alcohol **209** was subjected to a Dieckmann-type condensation, upon treatment with LiHMDS in THF at −78 °C, followed by



Scheme 16 Total synthesis of (±)-schindilactone A **210**.

oxidation using DMP to afford the final desired natural product schindilactone A **210** in 60% overall yield over two steps (Scheme 16).[145]

2.3. Diterpenes and diterpenoids

The active component isolated from the extracts of the branch of a *Daphnopsis americana* tree in Costa Rica was so-called guanacastepene A. It is actually a diterpene having a unique carbon skeleton structure.[152] It exhibited very high potency towards faecalis (VREF) pathogens, methicillin-resistant *S. aureas* (MRSA) and vancomycin-resistant E.[152] Guanacastepene A **225** has a unique carbon skeleton and a highly functionalized upper half, thus it has attracted much attention of synthetic organic chemists worldwide, as an interesting compound for total synthesis. Due to these waves of interest, the total synthesis of **225** has been attempted and successfully achieved by several research groups.[153] Danishefsky *et al.*[154,155] accomplished and reported the first total synthesis of guanacastepene A **225**, but before long thereafter Snider *et al.* achieved and reported total synthesis of **225**.[156] Interestingly, both of these protocols started with formation of the five-membered ring with subsequent annulations of the seven- and six-membered rings. A conceptually new pathway to the highly functionalized tricyclic core of guanacastepene A **225** was designed through the use of rhodium(I)-catalyzed intramolecular allenic Pauson–Khand reaction for the construction of seven-membered rings.[157] This strategy commenced with Smith's enone **215** (ref. 158) which in enolate form was alkylated with an appropriate alkyne iodide in the presence of LDA to afford compound **218** in moderate yield.[159] Reaction of the enone **218** with lithium acetylide ethylenediamine complex *via* sequential hydrolysis of the crude product with HCl gave enone **219** in 65% yield over two steps. The hydroxyl group of the latter was protected using TBSCl to afford the corresponding silyl ether **220** in 95% yield. The carbonyl group of the latter, upon reduction following the Luche protocol provided the corresponding secondary alcohol **221** as a mixture of two diastereomers (3 : 1 ratio). Protection of the allylic alcohol gave *tert*-butyldimethylsilyl ether **222** in 88% yield over the two steps. Deprotonation of the terminal alkyne using *n*-BuLi at −78 °C, followed by the addition of paraformaldehyde afforded the corresponding propargylic alcohol **223** in satisfactory yield. The alcohol **223** upon treatment with Et_3N and MsCl produced a mesylate, which without purification was added directly to $(Me_2PhSi)_2Cu(CN)Li_2$ at −85 °C to provide the 3,3-disubstituted allene **224** in 90% yield over two steps. Having pure allenyne **224** available in hand, it was treated *via* Pauson–Khand reaction conditions (10% mol $[Rh(CO)_2Cl]_2$ in toluene at 80 °C) to give the 4-alkylidene cyclopentenone **225** as a single product in 65% yield which in fact is the tricyclic ring core system of natural product, guanacastepene A **225** (Scheme 17).[160]

Ingenol **233** is a highly oxygenated tetracyclic diterpene which in racemic form imitates the task of diacylglycerol, being the endogenous activator of protein kinase C.[161] It is actually isolated from Euphorbia family and its structure was unambiguously elucidated and reported in 1968 by Hecker *et al.*[162] This natural product **233** shows weak activity against protein kinase C.[163] Ingenol **233** which is the parent compound of several dozen of natural product ingenanes, has the same carbon scaffold but diverse peripheral functionalities.[164] Besides their fascinating "inside-outside" bridged BC ring system,[165] the ingenanes show diverse biological activities.[166] In

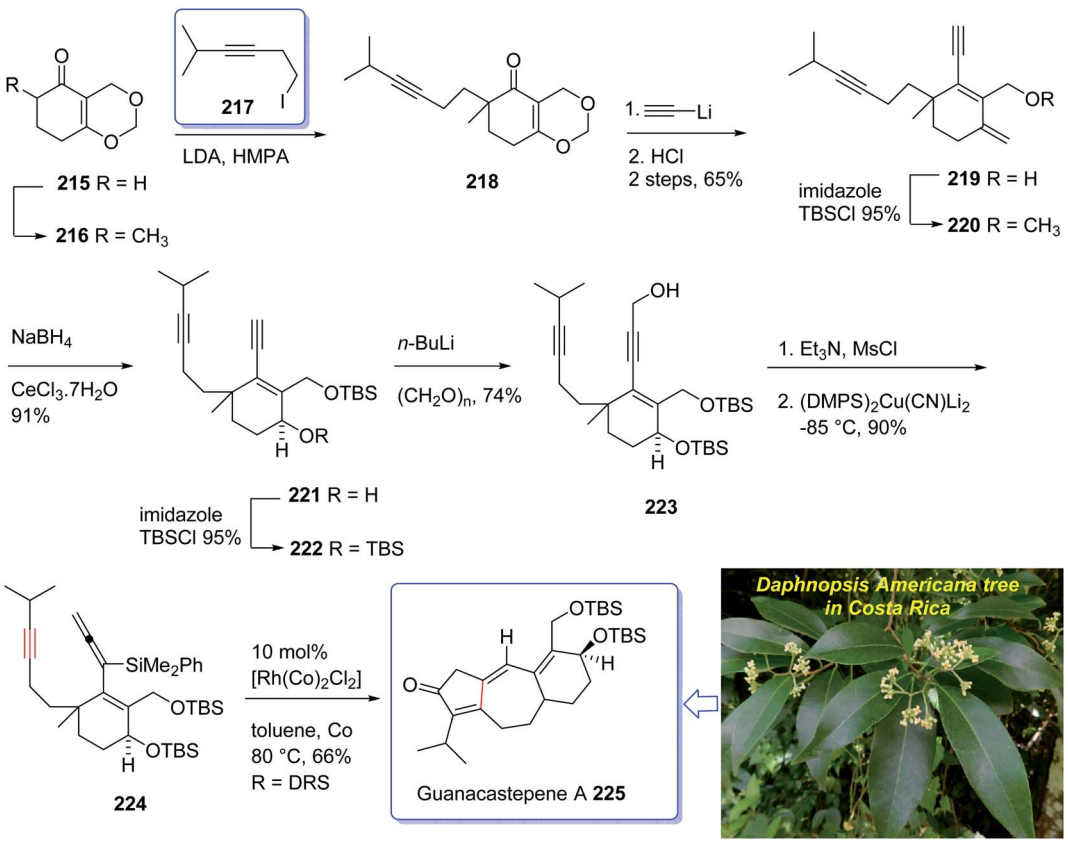
1980s, Winkler *et al.* inspired by this significant biological function and complex architecture attempted the total synthesis of **233**.[167] In 1997, the same group used the intramolecular dioxenone photocycloaddition to create its exceptional stereochemical feature.[161] In 2002, Winkler *et al.*[167] accomplished and reported the first total synthesis of racemic ingenol. The total synthesis of **233** was completed in forty-two steps in overall yield of 0.042% from commercially available.

In 2005, Winkler *et al.*[168] achieved and reported the total synthesis of racemic ingenol **233** beginning from unsaturated aldehyde 2-methyleneoct-7-enal **226** which was synthesized in a one-pot fashion involving Swern oxidation of 7-octen-1-ol followed by reaction of the intermediate aldehyde with Eschenmoser's salt.[169] Compound **226** then reacted with the conjugate base of *tert*-butyl acetate to afford compound **227**, which upon oxidation by MnO_2 gave ketoester **228**. Treatment of **228** under dioxenone-forming conditions (TFAA, TFA, Ac_2O, Me_2CO) resulted in the formation of the dioxenone photosubstrate **229** in satisfactory yield. After five steps, the desired methylene photoadduct **230** was obtained. Alkylation of the conjugate base of **230** (LDA, THF, DMPU, −78 °C) with 3-trimethylsilylpropargyl bromide followed by desilylation with TBAF (THF, 100%) the Pauson–Khand substrate **231** was provided. It is worthwhile to mention that the Pauson–Khand reaction of **231** in the presence of the Me_3N-*N*-oxide dehydrate was substantially more effective than the reaction employing anhydrous Me_3N-*N*-oxide. After several steps involving various functional group transformations, compound **232** was converted to the desired natural product ingenol **233**. In summary, the target **233** was obtained from **226** in overall yield of 0.042% (Scheme 18).[168]

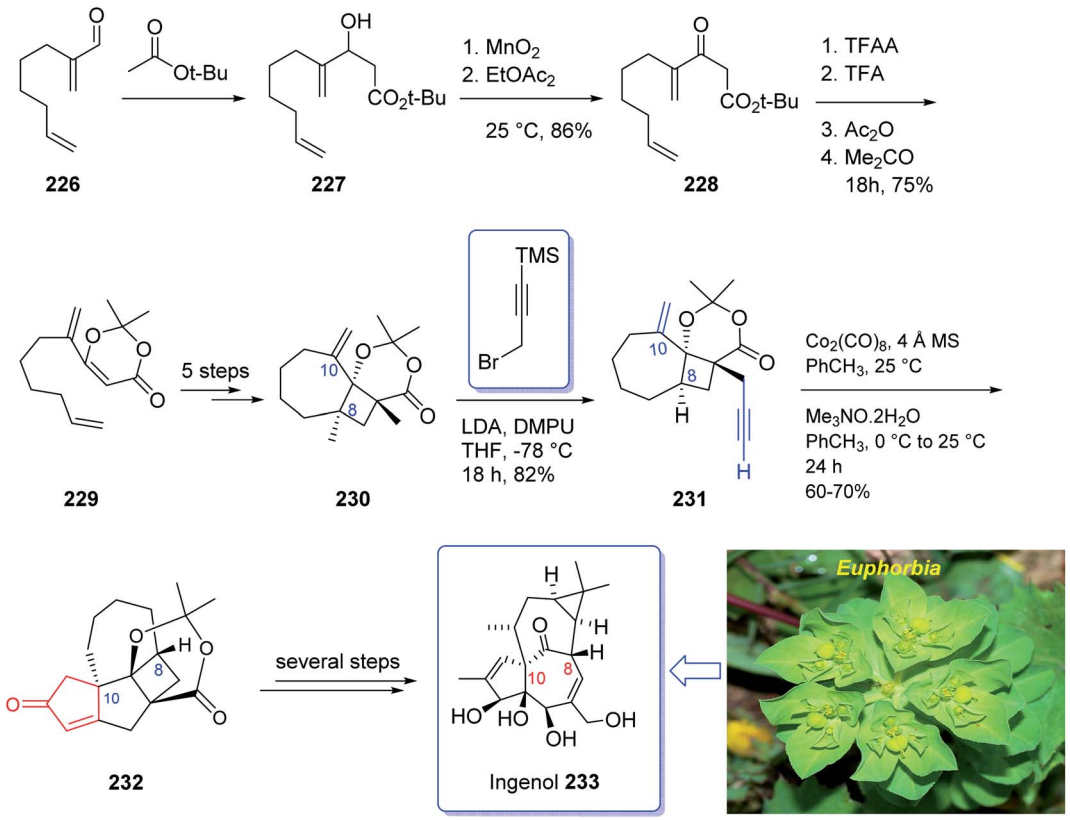
The aquariolides are actually classified as cyclic diterpenes. They were initially isolated from *Erythropodium caribaeorum*, but in 2002 aquariolide A **244** was identified from cultured specimens of this gorgonian[170] by the Andersen research group. Andersen and co-workers in 2003 achieved and reported the isolation of aquariolides A, B, and C from animals growing in the wild.[171] In fact, the distinctive feature of these naturally occurring compounds is the "aquariane" backbone, which contains two five-membered rings fused to a nine-membered ring *E. caribaeorum* was found being a source of briarane ditepenes,[172] and the aquariolides which are supposed to generate biosynthetically from a briarane precursor through a di-π-methane rearrangement followed by vinyl-cyclopropane rearrangement.[171] A brief biological screening disclosed that aquariolides B and C showed moderate *in vitro* cytotoxicity against human breast cancer MCF-7 cells.[202]

In 2006, the total synthesis of **244**, as a prelude was accomplished and reported by Burnell and co-workers involving a diastereoselective Pauson–Khand reaction and subsequent ring expansion.[173]

In this approach, the total synthesis of aquariolide A **244** is commenced from benzyl ester **234**, which was converted into ynone **235** in 85% yield *via* Yamaguchi procedure.[174] Then,



Scheme 17 Total synthesis of guanacastepene A **225**.



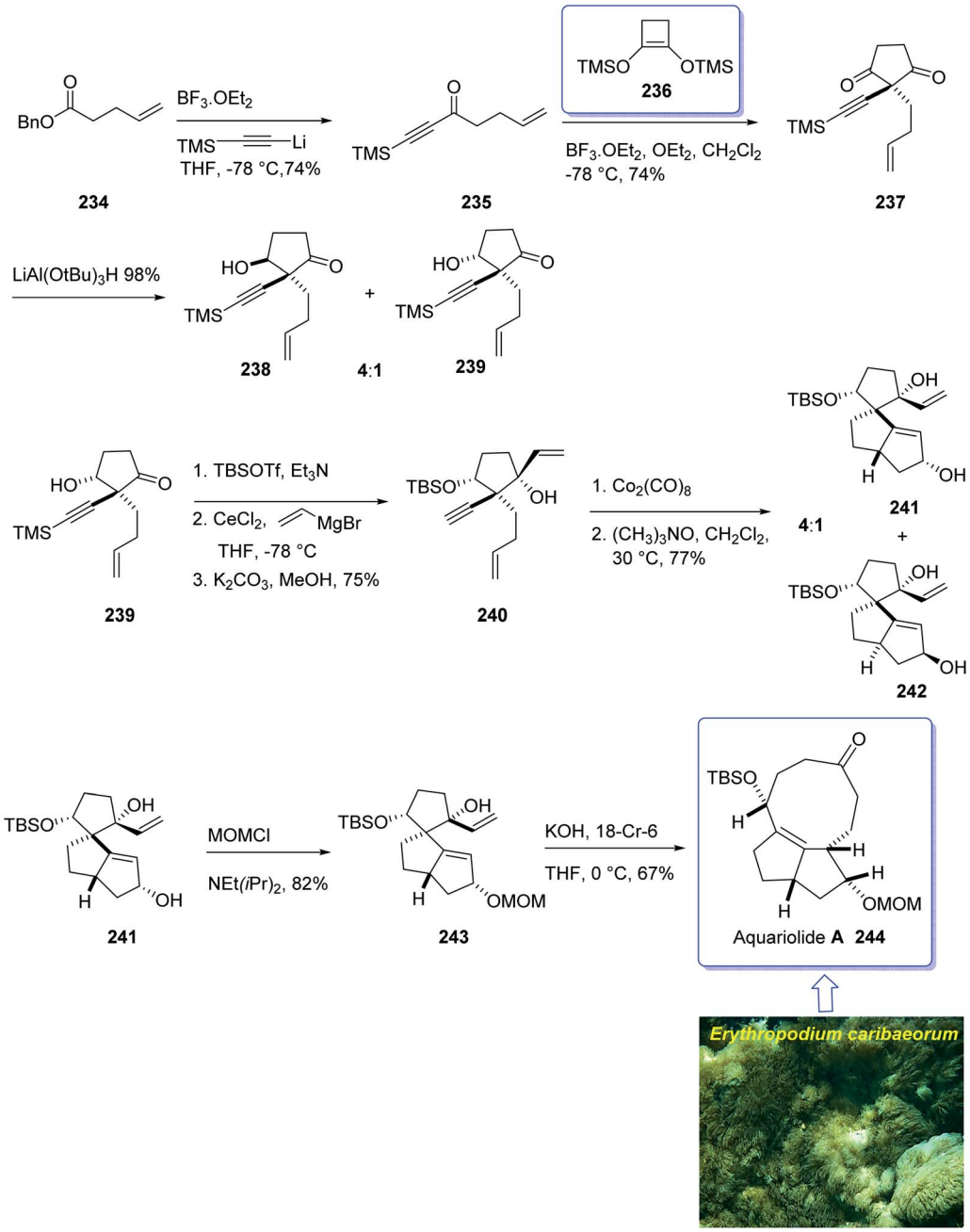
Scheme 18 Total synthesis of ingenol **233**.

ketone **235** was subjected into geminal acylation upon reaction with **236** in the presence of $BF_3 \cdot OEt_2$ to provide diketone **237**. Protection of the latter hence provided the extra advantage of further directing addition of a vinyl Grignard reagent *via* blocking the alkenyl face of the cyclopentanone. Thus, the mono reduction of diketone **237** using lithium tri(*tert*-butoxy)-aluminohydride afforded diastereomeric alcohols (**238** and **239**) in a ratio of 4 : 1. Keto-alcohol **239**, the other product from the reduction of **237**, was reacted with triethylsilane in TFA, and then protected by TBSCl and reacted with vinylmagnesium bromide in the presence of anhydrous $CeCl_3$,[175] followed by basic methanolysis of the TMS group to give compound 7 as the sole product. It was obtained upon treatment of the latter with $Co_2(CO)_8$ and trimethylamine *N*-oxide, under the Pauson–Khand reaction conditions (in dichloromethane at 30 °C) as a 4 : 1 ratio of inseparable diastereomers **241** and **242** (in a ratio of about 4 : 1 determined by NMR).

Protection of the major alcohol **241** as a MOM ether afforded **243**. As expected, subjecting **243** to appropriately basic conditions smoothly provided ketone **244**. The latter *via* viable routes to the ring system of the aquariolide diterpenes have been accomplished in two steps *via* generation of **241** and **243** in which the latter was transformed to desired natural product aquariolide A **244** in 67% overall yield (Scheme 19).[173]

Cyanthiwigins[176] **257** contain a cyclohepta[*e*]indene core and structurally belongs to the diverse cyathane class of diterpene.[177] They were isolated from the extract of the marine sponges *Epipolasis reiswigi* and *Mermekioderma styx*. Biologically, cyanthiwigins were found being cytotoxic towards A549 lung cancer cells and primary tumor cells.[178] Cyanthiwigins have 5-6-7 tricarbocyclic core with carbons in different oxidation states. An efficient total synthesis of cyanthiwigins **257** was achieved and reported by Phillips *et al.* in 2005.[179] Then, the Stoltz research group developed and reported a brief strategy involving double asymmetric catalyzed alkylation and an RCM reaction as the key steps in the total synthesis of cyanthiwigins B, F, and G.[180] In 2013, Gao *et al.* accomplished a brief synthetic strategy for the total synthesis of cyanthiwigins A, C, G, and H[181] comprising a common intermolecular [4 + 2] cycloaddition and RCM reaction as vital steps.

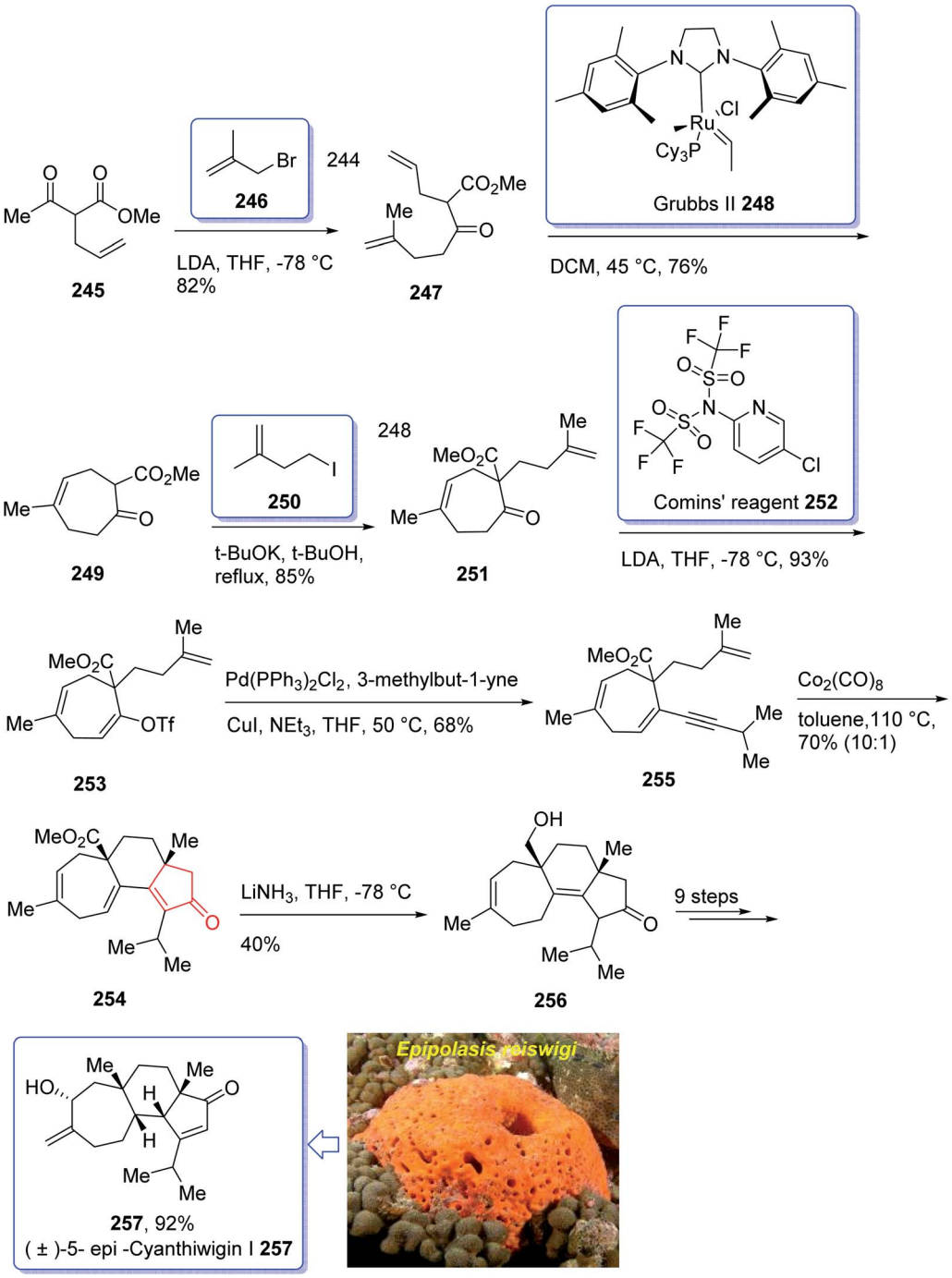
In 2018, Yang *et al.* developed a strategy for the total synthesis of 5-*epi*-cyanthiwigin I **257** using Pauson–Khand reaction (PKR) as a vital step. The total synthesis of **257** began with **245** which was reacted with allyl bromide **246** in the presence of LDA to afford diene **247** in high yield.[182] The latter was further treated with Grubbs II catalyst **248** (ref. 183) to provide ketoester **249**, which upon alkylation with 4-iodo-2-methylbut-1-ene **250** in the presence of KOBu-*t* in *tert*-BuOH afforded ketone **251** in high yield. The key intermediate **254** was obtained by converting the ketone group of the latter upon treatment with LDA to the corresponding enolate, which was subsequently reacted with Comins' reagent **252** to provide the respective vinyl triflate **253** in excellent yield. The latter was reacted with 3-methylbut-1-yne under Sonogashira coupling



Scheme 19 Total synthesis of aquariolide A **244**.

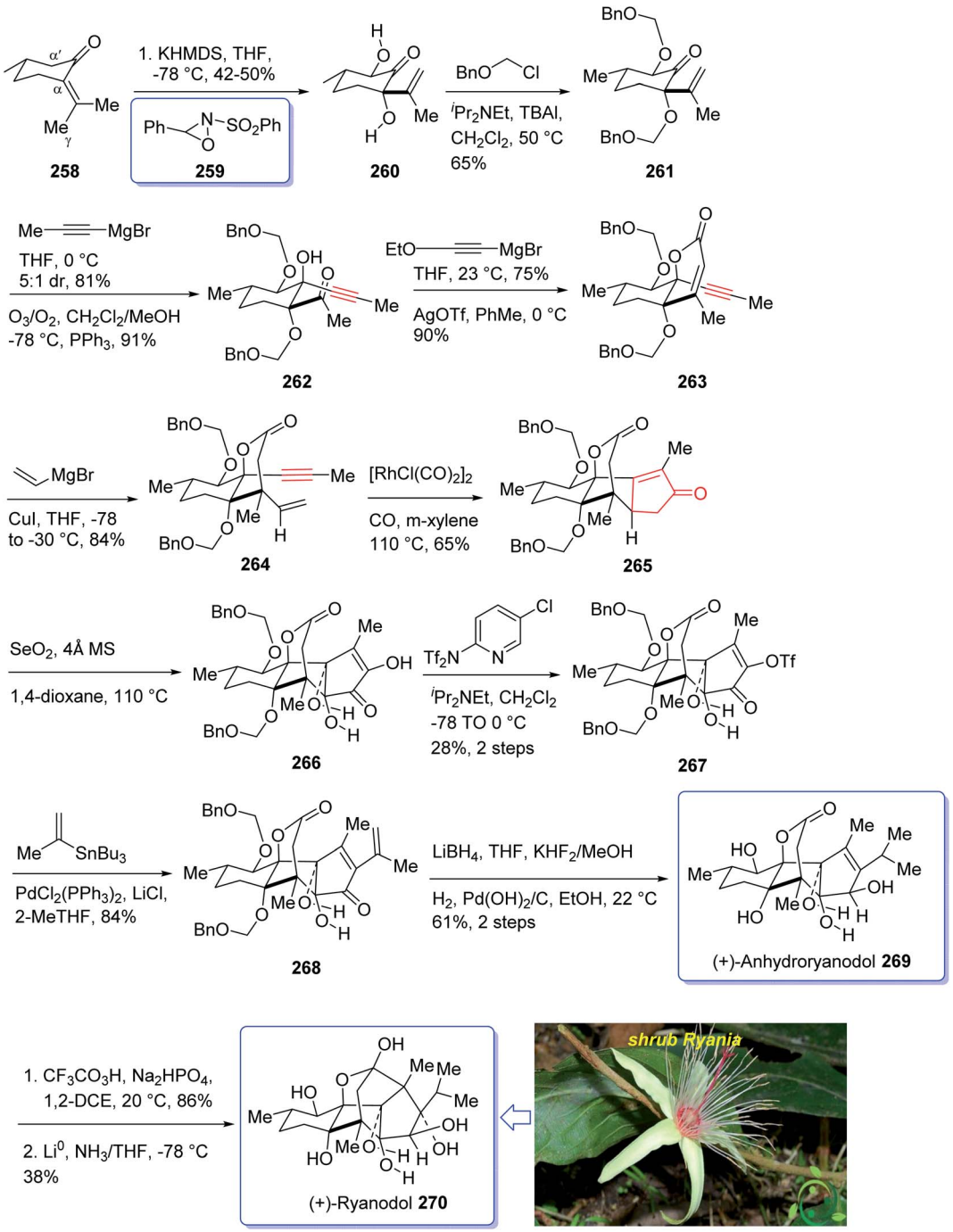
reaction conditions with enyne **254** in good yield. Next, enyne **254** was treated with $Co_2(CO)_8$ (1.2 equiv.) in refluxing toluene under PKR conditions for the construction of the indene core **255** of cyanthiwigins in good yield. Upon treatment of **255** with Li/NH_3 in THF at −78 °C, compound **256** was obtained in 40% yield which after nine steps was transformed to the desired C5-*epi*-cyanthiwigin I **257** in 92% yield. The developed chemistry enables the total synthesis of 5-*epi*-cyanthiwigin I **257** in seventeen steps and can be used for the total synthesis of other cyanthiwigins (Scheme 20).[177]

Naturally occurring compound, ryanodine[184,185] and its hydrolysis product ryanodol **270**,[185,186] are among the most highly oxidized diterpenoids reported so far. Ryanodol **270** was isolated from the extracted tropical shrub *Ryania* speciose Vahl reported by Pepper and Carruth in 1945,[187] and then by other research groups.[188] It showed insecticidal properties[184] and is an important family of ion channels that regulate intracellular Ca^{2+} release and play a key role in signal transduction.[189] In 2016, Chuang *et al.*[190] achieved and reported a brief total synthesis of (+)-ryanodol in fifteen steps stating from the commercially available terpene (*S*)-pulegone **258**. In this strategy, the utilization of a Pauson–Khand reaction rapidly construct the carbon skeleton along with a SeO_2-catalyzed oxidation to assemble three oxygen atoms *via* a single step. In this approach, reaction



Scheme 20 Total synthesis of (±)-5-*epi*-cyanthiwigin **257**.

of (*S*)-pulegone **258** with KHMDS at −78 °C followed by dropwise addition of **259** gave α,α′-diol **260** which was isolated as a single diastereomer in 42% yield. Treatment of diol **260** with excess benzyl chloromethyl ether resulted in the protection of both alcohols as benzyloxymethyl ethers to afford **261**. At this point, the D-ring was created by an effective four-step sequence. Initially, propynylmagnesium bromide was added to **261** at 0 °C which proceeded in 5 : 1 dr to give the equatorially disposed alkyne in 81% yield. The latter upon ozonolysis was cleaved to give methyl ketone **262**. Then, the ketone was effectively transformed to α,β-unsaturated lactone **263** *via* 1,2-addition of ethoxyethynylmagnesium bromide with subsequent sequential Ag-catalyzed cyclization and elimination reactions.[191] Having lactone **263** available in hand, 1,4-addition of magnesium divinyl cuprate gave the respective enyne **264** as a sole diastereomer in satisfactory yield. In a crucial step, compound **264** was treated with 1 mol% $[RhCl(CO)_2]_2$ (ref. 30) under an atmosphere of carbon monoxide (PKR) gave the desired intermediate **265** as a sole diastereomer and in high chemical yield. This intermediate was transformed after four steps to afford

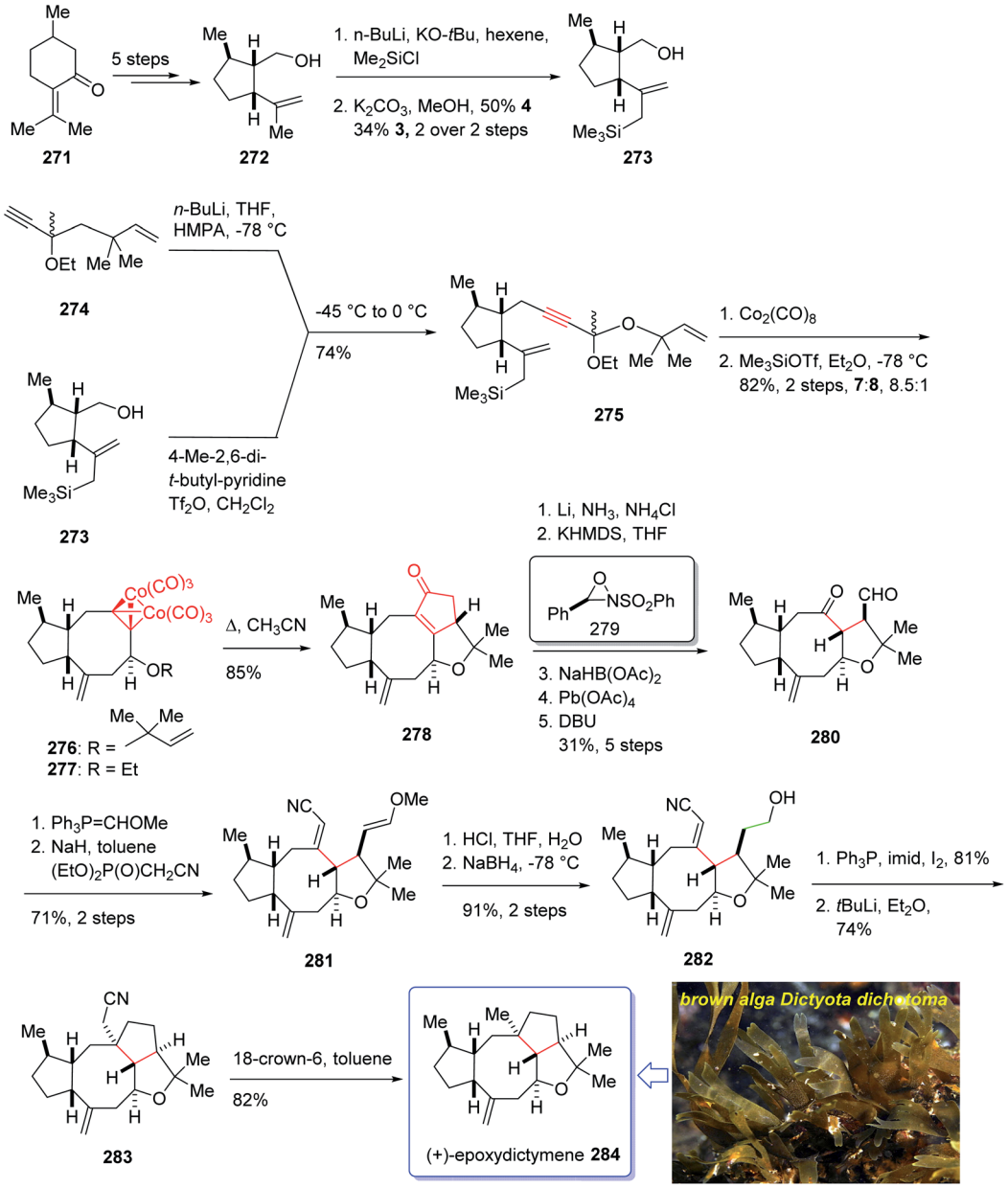


Scheme 21 Total synthesis of (+)-ryanodol **270**.

(+)-anhydroryanodol **269** in 61% yield. The latter was then treated with trifluoroperacetic acid to give epianhydroryanodol epoxide which is subjected to reductive cyclization to give the desired natural product (+)-ryanodol **270** in 0.42% overall yield over fifteen steps starting from commercially available (*S*)-pulegone **258** (Scheme 21).[190]

Epoxydictymene **284** is a diterpene naturally occurring compound which is present in the brown alga *Dictyota dichotoma* isolated.[192] In the early 1980s, Matsumoto *et al.*[193] isolated cyclononane and hydroazulene diterpenoids and in 1983 Ishida *et al.*[194] elucidated its structure as epoxydictymene **284**. It contains a 5-8-5-5 (ref. 195) tetracyclic scaffold containing a strained *trans*-3-oxabicyclo [3.3.0] octane (*trans*-5-5).[196]

The total synthesis of **284** was achieved and reported by Schreiber and co-workers in 1994 (ref. 197) by employing Pauson–Khand reaction as a key step. The total synthesis started from commercially available (+)-puelgone **271** which after several steps was converted into compound **272**. The latter was transformed in two steps involving protection of hydroxyl group by TMSCl in the presence of *n*-BuLi to afford compound **273**.



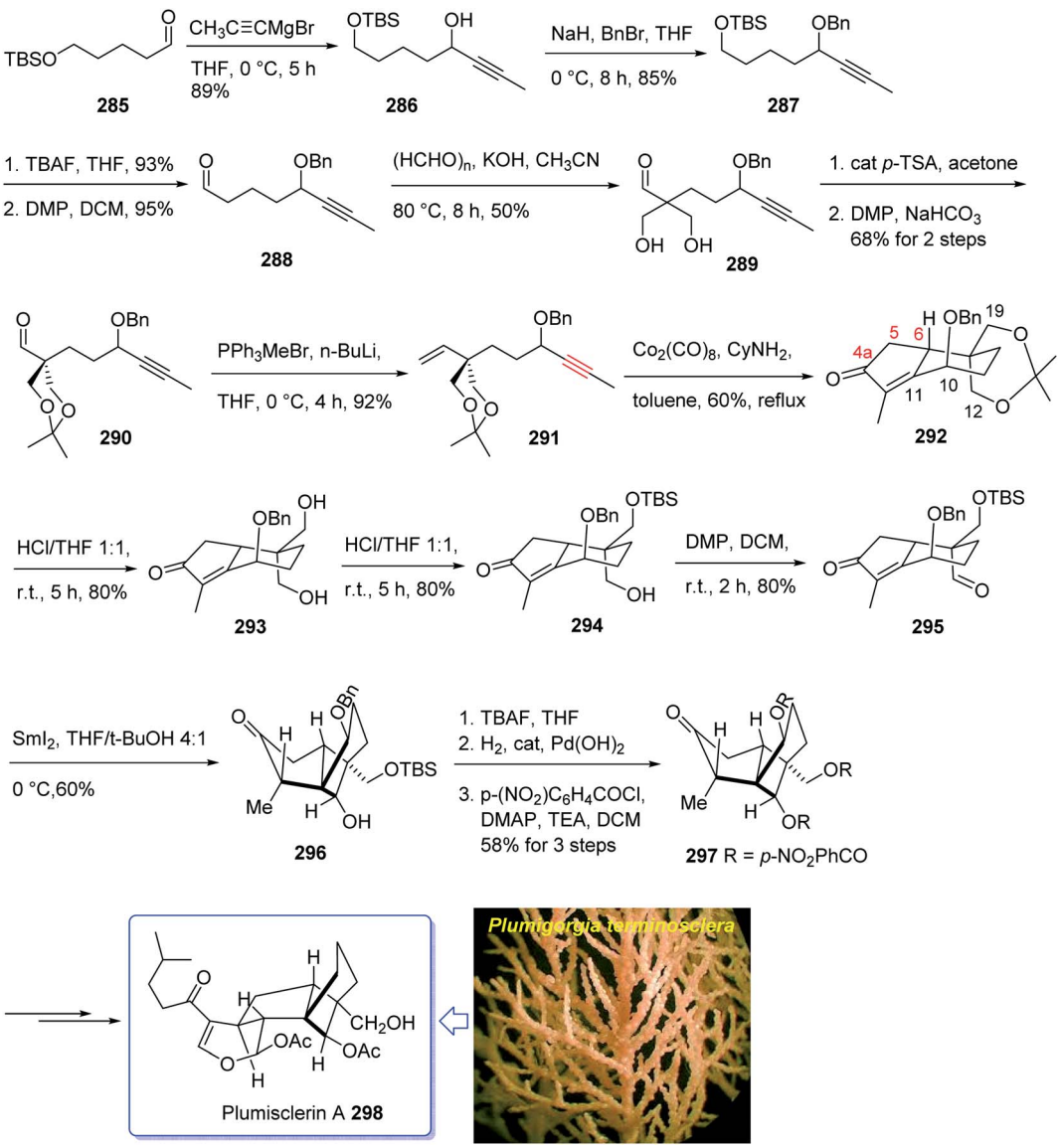
Scheme 22 Total synthesis of epoxydictymene **284**.

Reaction of lithium anion of **274** and alcohol **273** through displacement of a triflate ester under carefully controlled conditions, furnished alkyne **275** as suitable PKR precursor in high yield. In a crucial stage, the latter was treated with $Co_2(CO)_8$ under PKR conditions to afford the desired organometallic cluster, which was then subjected to catalyzed Lewis acid cyclization[197] (Me_3SiOTf, Et_2O, −78 °C, 15 min) to furnish ethers **276** and **277** in 82% overall yield as an 8.5 : 1 mixture of diastereomerically pure compounds. After several steps, ether **276** was converted into nitrile **283** containing the complete framework and configurations of the target natural product. Reductive decyanation[198] of nitrile **283** gave the desired natural product (+)-epoxydictymene **284** (Scheme 22).[192]

Plumisclerin A **298**, an exceptional marine diterpenoid, was initially isolated by Reyes research group in 2010 from the samples of *Plumigorgia terminosclera* collected at Mayotte Island.[199] Structurally, plumisclerin A **298** has a complicated and compact ring system bearing a fully-substituted cyclobutane (C ring), a bridged cyclohexane (D ring), a polysubstituted cyclopentane (B ring), as well as a fused dihydropyran ring (A ring). Its distinctive rigid tricyclo [4,3,1,$0^{1,5}$] decane framework probably is the first reported of such a plumisclerane framework in the field of naturally occurring compounds. Dihydropyran ring (A ring) in plumisclerin A **298**, is *trans*-fused to the cyclopentane ring (B ring), while, most terpenoids have a *cis*-fused dihydropyran ring.[200] It also bears seven chiral centers involving two all-carbon quaternary chiral

centers compactly spread in the molecule. Plumisclerin A **298** exhibits modest cytotoxicities towards numerous common tumor cells such as lung, colon cancer and breast cancers.[199] The interesting structure and its valuable biological activity, make plumisclerin A **298** as an important target for synthetic organic chemists. An effective strategy for the synthesis of the tricyclo [4,3,1,$0^{1,5}$] decane core (B/C/D rings) of plumisclerin A **295** was designed and successfully accomplished by Yao and co-workers in 2015.[201] In this strategy, the Pauson–Khand reaction and a SmI_2-catalyzed radical 1,4-conjugate addition play vital roles in the construction of fully functionalized 5,6-fused rings and the very strained cyclobutanol moiety with exact relative stereochemistries, respectively.

This attempt started with alcohol **286** which in turn is provided from the addition of propynyl magnesium to the known aldehyde **285**.[202] Alcohol **286** is converted after several steps to enyne **291** as a suitable precursor of PKR *via* various functional group transformations as well as protecting–deprotecting processes. Having enyne **291** available in hands, it was investigated in a PKR[5,7] explaining various combinations to find an optimal reaction conditions. Eventually, enyne **291** was converted to the desired compound **292** in modest yield when PKR was catalyzed by $Co_2(CO)_8$ in the presence of cyclohexylamine ($CyNH_2$). Worthy to mention that, the C10-OBn of enyne **291** in PKR, played a vital role to control the newly generated chiral center at C6 position, when the requisite cyclopentenone ring was constructed. Then, compound **292** was converted to compound **295** in three steps in which the latter upon treatment with SmI_2 in THF and *t*-BuOH (4 : 1, v/v) as mixed solvents at 0 °C afforded the anticipated bridged-compound **296** in good yield. After three steps, the latter was unambiguously transformed into the respective tri-*p*-nitro-benzoate **297** (confirmed by single crystal X-ray analysis). The latter was then transformed to the desired plumisclerin A **298** after several steps. In

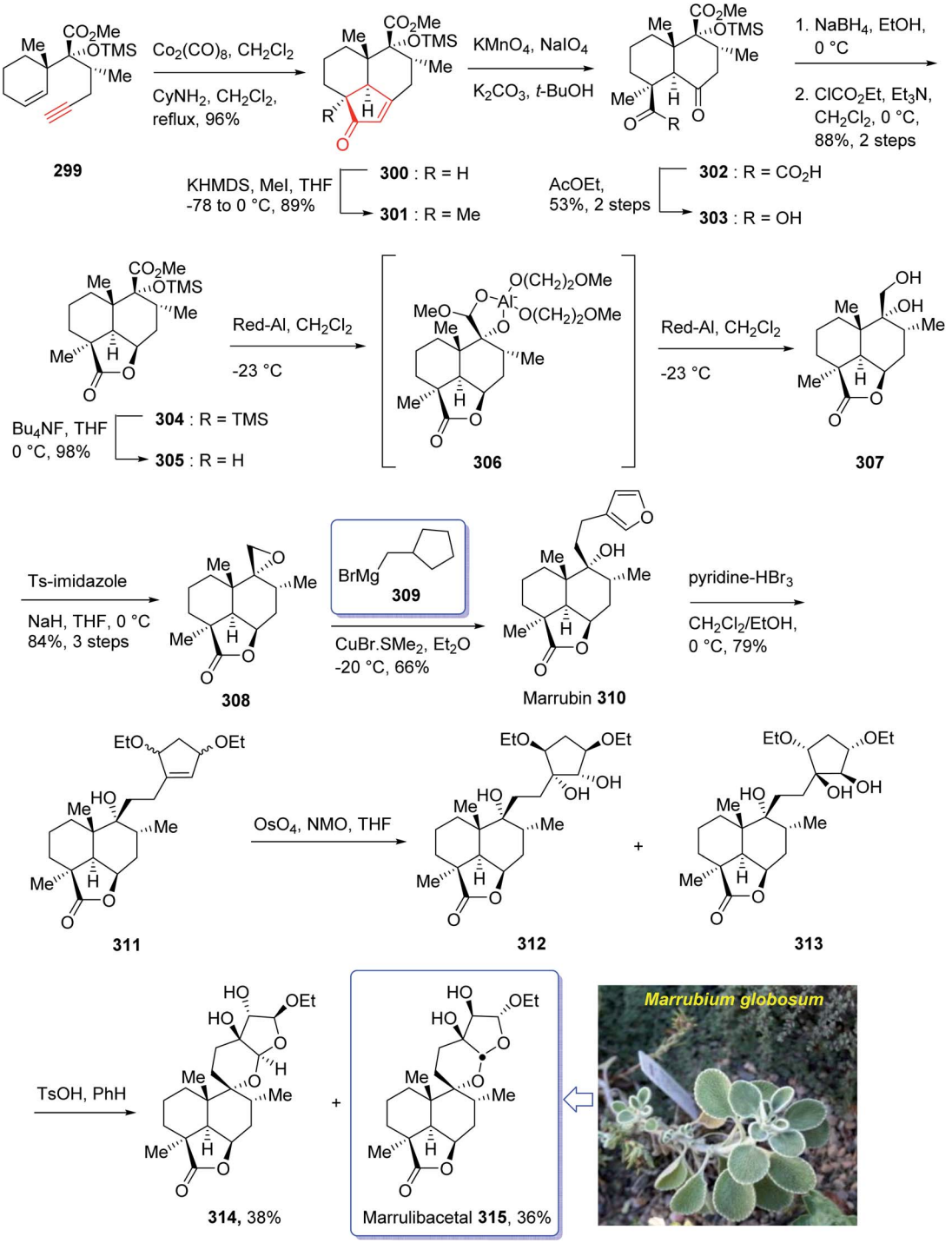


Scheme 23 Total synthesis of plumisclerin A **298**.

conclusion, an efficient asymmetric synthesis of the tricyclo [4,3,1,$0^{1,5}$] decane core of cytotoxic marine diterpenoid plumisclerin A **298** was successfully achieved in several steps from the easily accessible ω-hydroxypentanal **285** (Scheme 23).[201]

Marrulibacetal **315**, a diterpenoid, was initially isolated from the aerial parts of *Marrubium globosum* ssp. *libanoticum* by Borrelli *et al.* in 2009.[203] The same group reported the structural elucidation of marrulibacetal **315** in the same year.[203,204] *Marrubium globosum* ssp. *libanoticum* have been used for a long time as medicinal plant which are used as hypoglycemic, febrifuge, antispasmodic, and anti-inflammatory drugs in Northern Lebanon.[203]

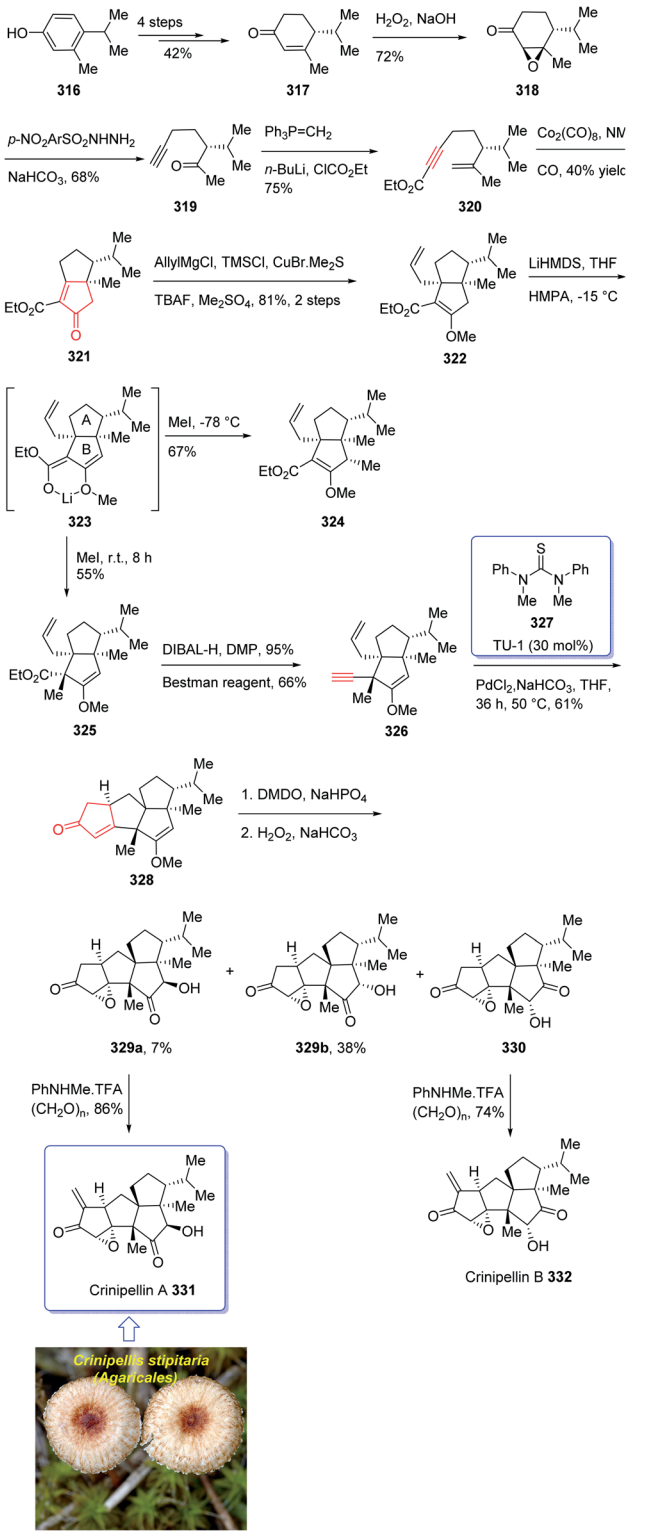
In 2016, Nakamura *et al.*[205] achieved and reported a stereoselective total synthesis of (+)-marrubiin commencing from a chiral scaffold *via* the $CyNH_2$-catalyzed Pauson–Khand reaction followed by oxidative cleavage of the resultant



Scheme 24 Total synthesis of marrulibacetal **315**.

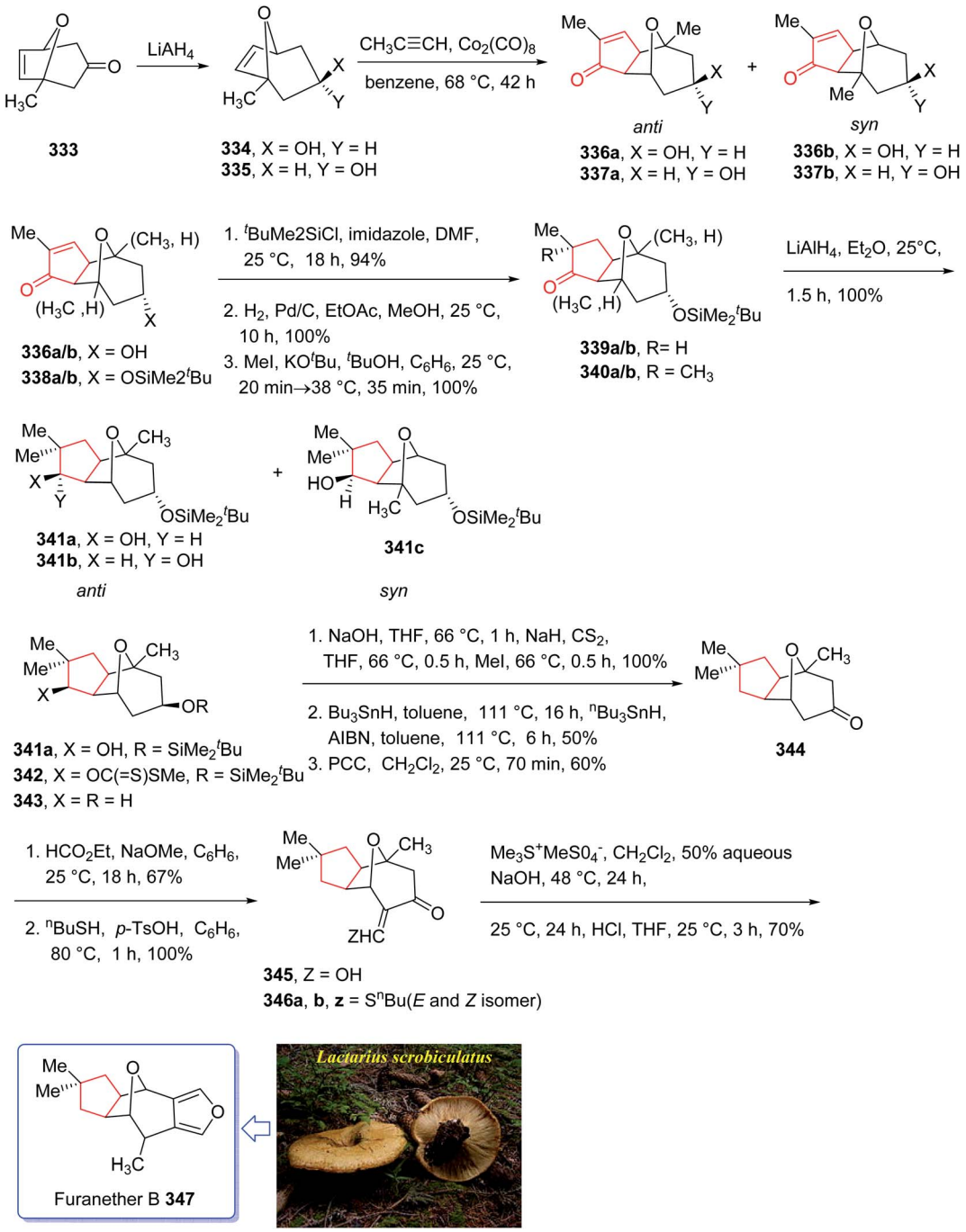
cyclopentenone ring. This strategy started from enyne **299** (ref. 206) which was subjected to PKR using $Co_2(CO)_8$ in CH_2Cl_2 at ambient temperature with subsequent addition of cyclohexylamine, followed by dilution with dichloromethane, and refluxing the mixture to afford tricyclic enone **300**. The latter was transformed to a 1 : 1 diastereomeric mixture of *cis*-diols **312** and **313** after several steps, including various functional group transformations. Ultimately, internal transacetalization of *cis*-diols **312** and **313** in the presence of TsOH in benzene gave the desired natural product, (−)-marrulibacetal **315**, along with its isomer (Scheme 24).[205,207]

Crinipellin A **331** is classified as diterpenoid.[208] It was isolated and reported in 1979 by Steglich *et al.* from the fungus *Crinipellis stipitaria* (Agaricales).[208,209] It has an interesting chemical structure bearing α-methylene ketone moiety and an exceptional tetraquinane core, containing eight chiral centers, in which three of them are adjoining all-carbon quaternary carbons. From biological points of view, **331** and **332** were found to exhibit antibiotic potencies.[208,209] The total synthesis of racemic **332** was accomplished in twenty-two steps *via* Barbier annulation by Piers and co-workers and reported in 1993.[210] In 2014, Lee and co-workers achieved and reported the first asymmetric total synthesis of **331** through a tandem [3 + 2] cycloaddition reaction for the construction of its tetraquinane scaffold containing three successive quaternary chiral centers.[136,211,212] In 2018, Yang and co-workers[213] accomplished and reported the asymmetric total syntheses of (−)-crinipellin A **331** and (−)-crinipellin B **332** in eighteen steps from the commercialized phenol **316**, respectively. These total syntheses featured a developed thiourea/Pd-catalyzed intramolecular Pauson–Khand reaction for the asymmetric construction of the tetraquinane scaffold present in crinipellins. As a matter of fact, the vital step was PKR which provided compound **321** containing two *cis*-configured vicinal chiral centers.[214] The required enyne ester **320**, as a required precursor of PKR, which was provided *via* the Trost methodology[215] from already known compound (R)-4-isopropyl-3-methylcyclohex-2-en-1-one **317**. The latter in turn was synthesized in four steps from market purchasable 4-isopropyl-3-methylphenol **316**.[216] Having compound **318** in hand, it was subjected to an asymmetric Weitz–Scheffer-type epoxidation,[217] to give ketone **319** which was condensed with p-$NO_2ArSO_2NHNH_2$ followed by treatment with $NaHCO_3$ to undergo Eschenmoser fragmentation[218] to give the acetylene ketone **319** in 68% yield. The latter first underneath a Wittig reaction, and the resultant enyne, upon sequential direct treatment with BuLi and ethyl chloroformate afforded enyne **320** as a suitable precursor for PKR. This one-pot transformation is essential to ensure a high yield because the intermediate enyne is volatile. After considerable experimentation, it was found by a crucial step, enyne **320** was treated with a stoichiometric quantity of $Co_2(CO)_8$ at ambient temperature for a while and then the resultant enyne/Co complex was gradually heated to 76 °C in the presence of 4-methylmorpholine *N*-oxide (NMO) for relatively long time (36 h), to obtain **322** in modest yield but excellent ee (98% ee) after crystallizations. This obtained ketoester **322** was reacted with an organocopper reagent (provided from treatment of allylmagnesium chloride and $CuBr{\cdot}Me_2S$[219] at −78 °C) proceeded *via* highly diastereoselective conjugate addition reaction, to give the anticipated enolate which was reacted with Me_2SO_4 in the presence of Cs_2CO_3 and tetrabutylammonium fluoride (TBAF)[220] to afford methyl vinyl ether **322** as a sole isomer in satisfactory yield. On



Scheme 25 Total synthesis of crinipellin A **331**, crinipellin B **332**.

the other hand, compound **323** was converted to another key intermediate **325**, in two steps involving regio- and stereoselective assemblage of quaternary chiral center. This vital intermediate ester **325** was reduced with DIBAL-H, with subsequent oxidation of the resultant using the Dess–Martin reagent followed by reaction with the Bestmann reagent[221] to afford enyne **326** as a suitable PKR precursor in good yield. Enyne **326** was then subjected to Pd-catalyzed PKR for the successful construction of tetraquinane **328**. It is worthwhile mentioning that use of TU-1 ligand **327** (ref. 222) improved the diastereoselectivity of this PKR affectedly. Treatment of **328** with dimethyldioxirane (DMDO) in a Na_2HPO_4 solution[223] and H_2O_2/$NaHCO_3$ in sequence afforded the epoxides **329a** and **329b** after several steps in 7% and 38% yields, respectively. Then, compound **329a** was subjected to modified Eschenmoser methylenation upon treatment with *N*-methylanilinium trifluoroacetate and paraformaldehyde in THF at 70 °C to afford the desired natural product crinipellin A **331** in 86% yield.[209] Having **329b** in hands, it was converted to the thermodynamically stable compound **330** *via* isomerization[224] of its α-hydroxy



Scheme 26 Total synthesis of furanether B **347**.

ketone motif. This isomerization of **329b** to **330** was successfully accomplished by treatment of **329b** with various acidic and basic reagents. Compound **330** was then treated with *N*-methylanilinium trifluoroacetic acid (TFA) and paraformaldehyde in THF at 70 °C to afford the other natural product, crinipellin B **332** in 74% yield (Scheme 25).[213]

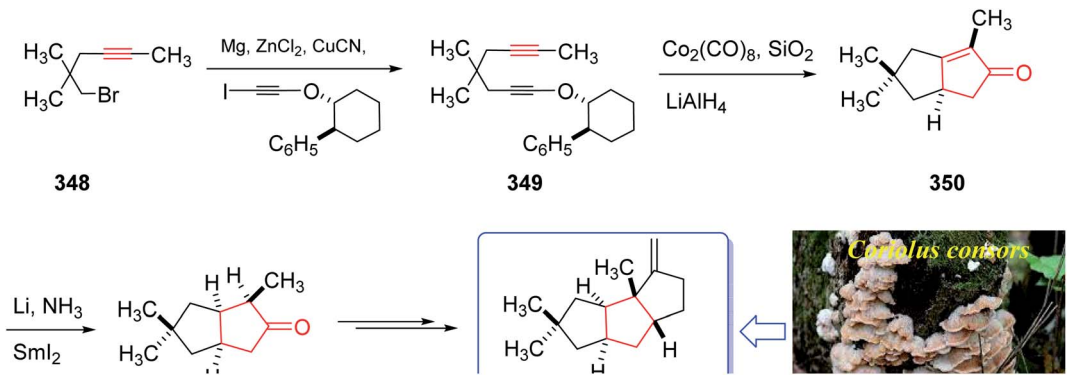
2.4. Sesquiterpenes

Furanether B **347**, a member of the lactarane class of sesquiterpenes, was initially isolated by Vita-Finsi and co-workers in 1980.[225] The total synthesis of furanether B **347** was achieved and reported by Schore in co-workers in 1989 (ref. 226) using PKR as a key step. This strategy started with ketone l-methyl-8-oxabicyclo [3.2.l] oct-6-en-3-one **333**, provided *via* a reported method by Noyori *et al.* from 2-methylfuran and tetra-bromoacetone.[227] Ketone **333**, upon reduction by lithium aluminum hydride as reducing agent gave *exo* : *endo* isomeric alcohols **334** and **335** in 2 : 1 ratio and in 94% yield. Stereoisomeric alcohols **334** and **335** were reacted with propyne under PKR conditions ($Co_2(CO)_8$, benzene, heat) to afford a mixture of four isomeric tricyclic ketones (**336a**, **336b** and **337a**, **337b**). Pauson–Khand cycloaddition by reduction of **333** with lithium aluminum hydride. Pauson–Khand cycloaddition of propyne and the mixture of stereoisomeric alcohols **334** and **335** gave 75% yield of a mixture of four isomeric tricyclic ketones (**336a**, **336b** and **337a**, **337b**). Among them, **336a** was converted to ketone **344** after several steps. The latter was then formylated regiospecifically to afford compound **333** in good chemical yield.[228] In solution, **345** contains 75–80% intramolecular hydrogen-bonded (*Z*)-β-hydroxyenone, the remainder being the *E*-isomer and traces of ketoaldehyde. Compound **345** was subjected to Ireland's procedure for the synthesis of the thiomethylene derivative to give **346a** and **346b** in almost quantitative yield.[229] This mixture with treated with trimethylsulfonium methylsulfate in a two-phase system to give an epoxide that upon rearrangement on standing at ambient temperature for 24 h (ref. 230) followed by aromatization in the presence of HCl in THF gave the desired natural product, furanether B **347** in moderate yield.[231] Spectral data obtained for synthetic **334** were in agreement with those obtained from the isolated natural product (Scheme 26).[226]

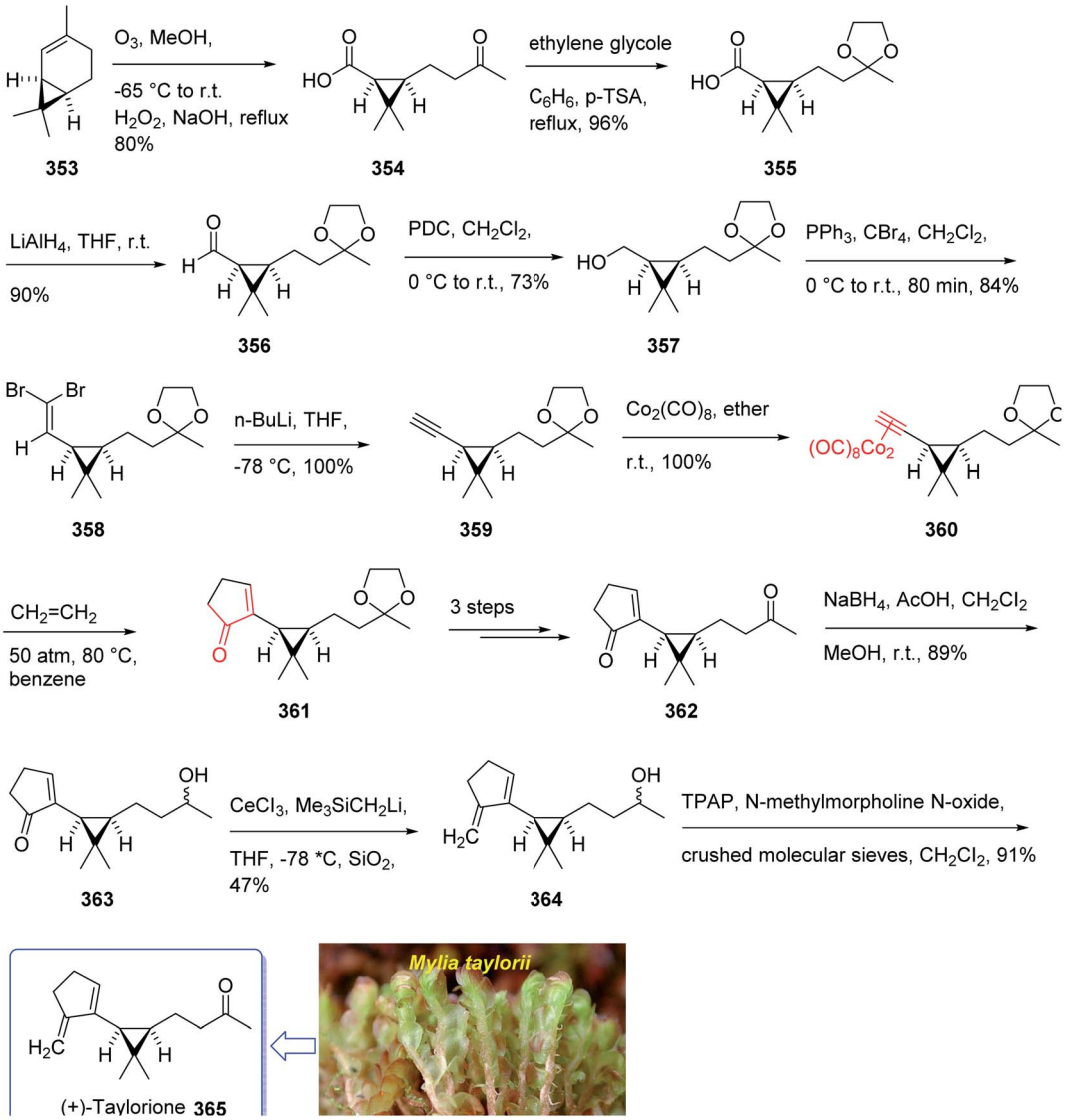
The mold metabolite, hirsutene **352**, is parent member of an important class of linear triquinane sesquiterpene. It was initially isolated from the hydrocarbon extracts of fermented mycelium of *Coriolus consors* by Nozoe and co-workers in 1976.[232] Hirsutene **352** did not show any significant biological potency whereas its derivative, diketocoriolin B, exhibited a prominent cytotoxic,[233] antibiotic and antitumor potencies.[234] Therefore, its total synthesis attracted much attention of synthetic organic chemists.[234] Hirsutene **352** was fully characterized by analysis of combined data, obtained from various spectroscopic techniques, commonly used for the structural elucidation of organic compounds.[232] In 1990, Pericas and co-workers[235] achieved and reported an efficient total synthesis of hirsutene **352** using intramolecular Pauson–Khand reaction.[232] Homochiral diyne **352** was easily synthesized from coupling of **348** *via* a Cu-mediate coupling reaction[236] involving the zinc reagent. In this strategy, enyne **349** as an appropriate PKR precursor was converted initially to the respective *E*-enol ether by treatment of the latter with $LiAlH_4$ in THF and the subjection of the resultant to PKR conditions ($Co_2(CO)_8$, SiO_2, purification, 85%) as key bicyclization under mild reaction conditions[5,237] to afforded enone 350 diastereoselectively. The latter upon either Birch reduction or less effectively, catalytic hydrogenation[238] gave **351** in racemic form. This bicyclic ketone **351**, was transformed to the desired natural product hirsutene **352** in several steps following the previously reported procedure (Scheme 27).[235]

(+)-Taylorione **365** is the pure enantiomer of the principal sesquiterpene isolated from extract of the common leafy liverwort *Mylia taylorii*[239] found on the northern hemisphere. The structure of (+)-taylorione **365** was elucidated and its absolute configuration was determined by combination of its spectral data analysis and degradation investigation.[240]

The total synthesis (+)-taylorione **365** was accomplished and reported by Kerr *et al.* in 1996 (ref. 241) using the Pauson–Khand annulation reaction as the key step. It began from already prepared (+)-2-carene **353** (ref. 241 and 242) which upon ozonolysis and subsequent oxidation with basified hydrogen peroxide, gave the keto acid **354** in 80% yield. The latter was converted to the ketal **351** upon the reaction with ethylene glycol in the presence of *p*-TSA in refluxing benzene. Since compound **355** found to be unstable to storage, it was instantly reduced to the corresponding alcohol **356** by treatment with $LiAlH_4$ in THF



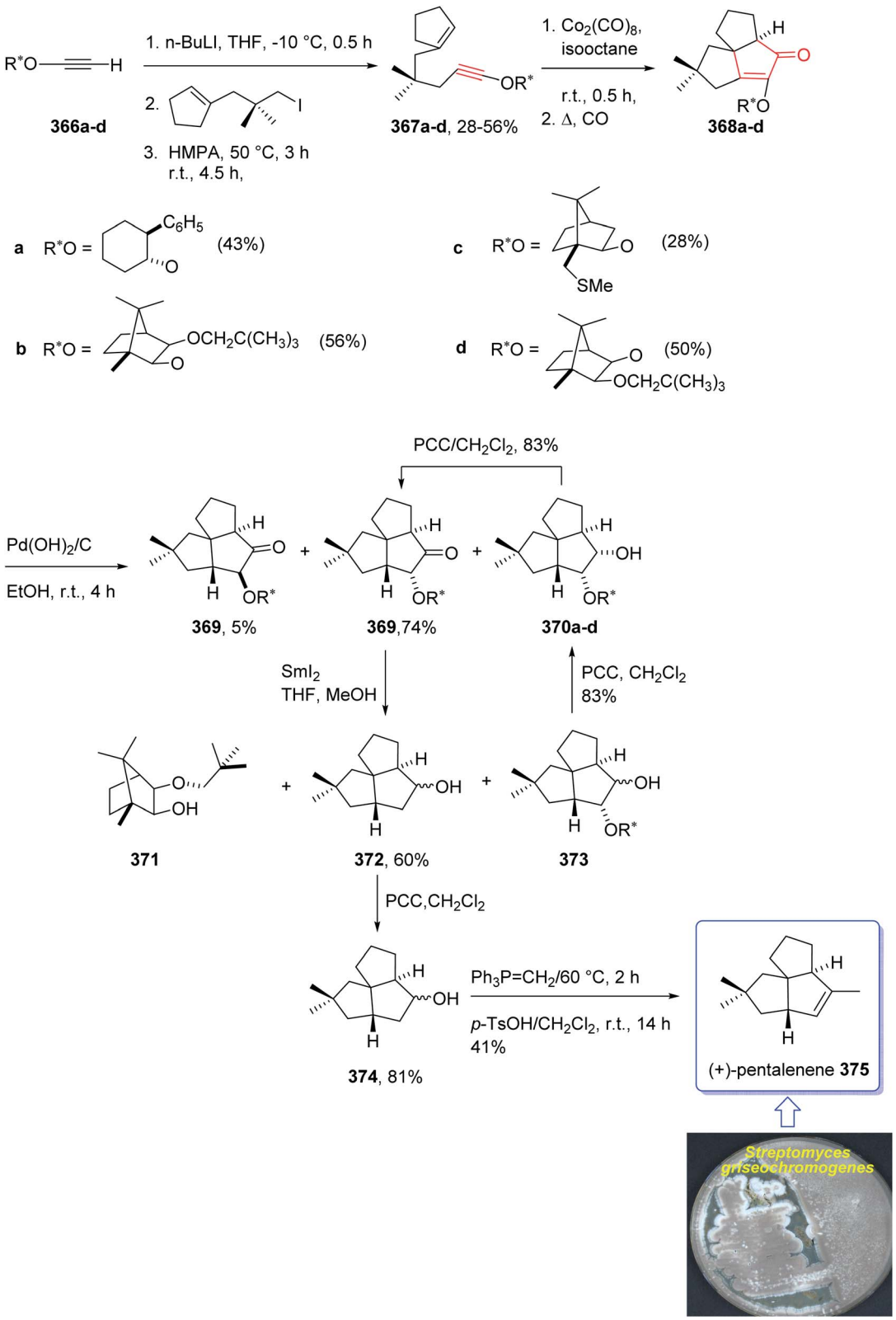
Scheme 27 Total synthesis of hirsutene **352**.



Scheme 28 Total synthesis of (+)-taylorione **365**.

followed by oxidation with PDC to the corresponding aldehyde **357** in 73% yield. Having aldehyde **353** in hand, the synthesis of the essential alkyne complex **360** was contemplated. The latter was treated with CBr_4 in CH_2Cl_2 to obtain the desired dibromo olefin **358** in 84% yield in pure form after column chromatography. The dihalo alkene **358** was transformed to the pure terminal alkyne **359** rapidly upon treatment with *n*-BuLi followed by aqueous work up. Then, alkyne **359** was reacted with octacarbonyldicobalt at ambient temperature to afford the dicobalt complex **360** in almost quantitative yield. The alkyne complex **360** was then underwent PK annulation reaction (C_2H_4, 50 atmospheres, 80 °C, benzene) to afford the desired cyclopentenone **361** in 38%. Pleasantly, upon treatment of cyclopentenone **361** with PPh_3 and CCl_4 in CH_2CI_2 at 0 °C to ambient temperature, the required diketone **362** was provided in an excellent yield. Having **362** available in hands, the remaining steps in the synthesis proceeded with no complication. The latter was subjected to selective carbonyl reduction under Ward conditions[243] ($NaBH_4$ in CH_2C1_2/AcOH/MeOH) to provide the hydroxy ketones **363**. After conversion of the latter to the diene **364** in moderate yield, to obtain optimum oxidation, it was reacted with Griffith–Ley tetrapropylammonium perruthenate (TPAP) agent to obtain the desired natural product **365** in 91% yield. In conclusion, the total synthesis of enantiopure (+)-taylorione **365** was accomplished starting from readily accessible chiral pool reagent (+)-2-carene **353**, in a brief manner (in twelve steps) in a good overall yield of 12% (Scheme 28).[241]

(+)-Pentalenene **375** (1*R*,3a*S*,5a*S*,8a*R*)-1,2,3,3a,5a,6,7,8-octahydro-1,4,7,7-tetramethyl cyclopenta[*c*]pentalene, was initially isolated by Seto and co-workers in 1980 (ref. 244) from the extract of *Streptomyces griseochromogenes*. Its structure elucidation revealed it has angularly fused triquinanes.[245,246] This tricyclic sesquiterpene **375** is involved in the biosynthesis of neopentalenolactone antibiotic.



Scheme 29 Total synthesis of (+)-pentalenene **375**.

Its total synthesis has been benchmark of various strategies involving the regio- and stereo-selective assembly of cyclopentanoid systems.[246,276]

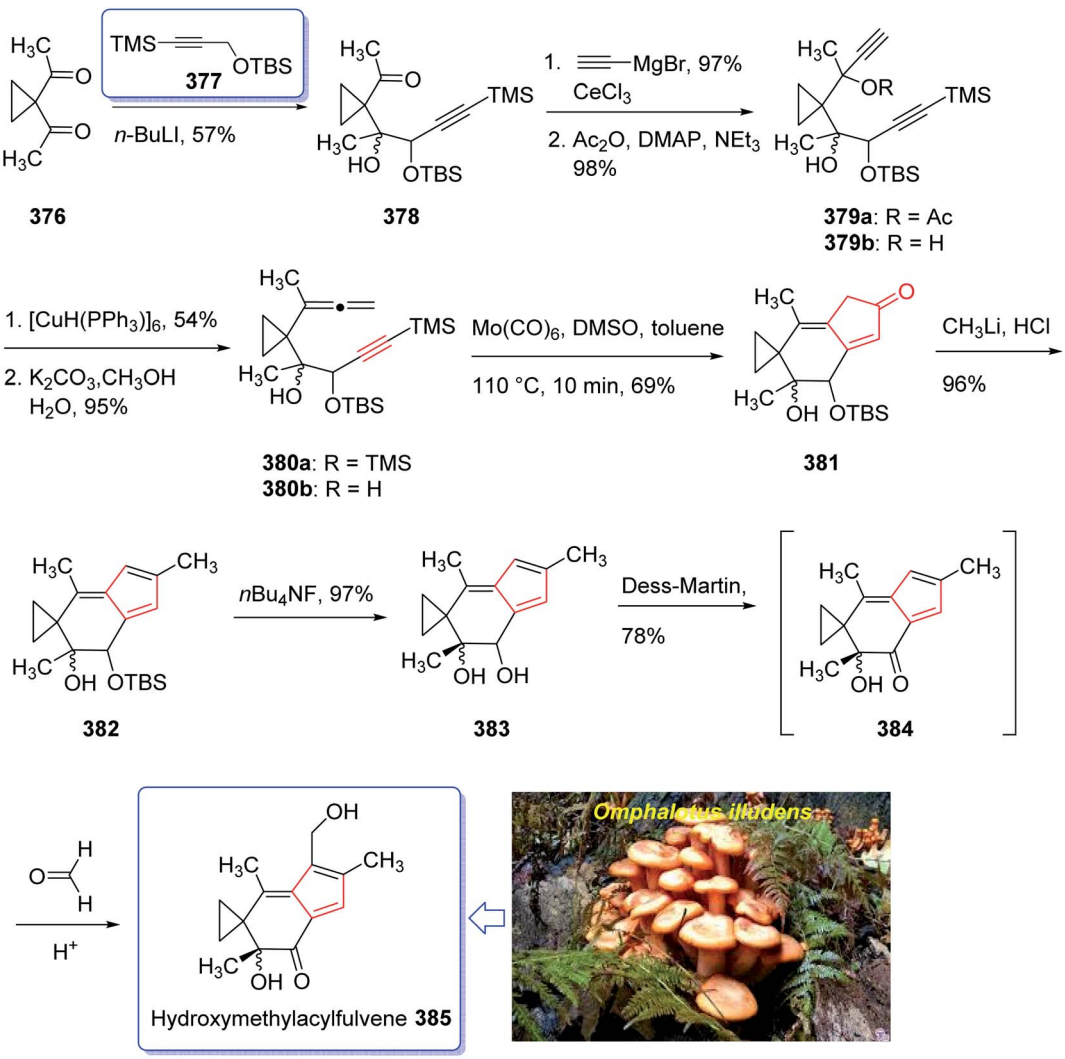
In 1997, Moyano and co-workers achieved and reported an effective total synthesis of **375** using Pauson–Khand reaction as key step.[247] Accordingly, the total synthesis started from lithium

acetylide derived from (±)-(*trans*-2-phenylcyclohexyloxy)ethyne **366a**, created in dry tetrahydrofuran as solvent to furnish in enyne **367a** in moderate yield. The latter was subjected to a diastereoselective intramolecular Pauson–Khand reaction, following the procedure, already reported by Schore *et al.* who have synthesized the triquinane system of racemic **375** (ref. 245) in this way, the enyne **367** underwent a diastereoselective cyclization to provide the key intermediate **368**. Noticeably, it became evident that for such diastereoselective Pauson–Khand reaction, the best choice of chiral auxiliary is 3-(neopentyloxy) isoborneol. After several steps involving various functional group transformations, compound **368** converted to ketone **374** as illustrated in (Scheme 29). The configuration of **374** was determined from absolute configuration of **368c**, **369**, **370**, and **372** thus, had been established, unambiguously.

In the final step of this total synthesis, ketone **374** was transformed into the desired natural product, (+)-pentalenene **375**, *via* Wittig olefination and acid-promoted isomerization of the exocyclic double bond (Scheme 29).[248]

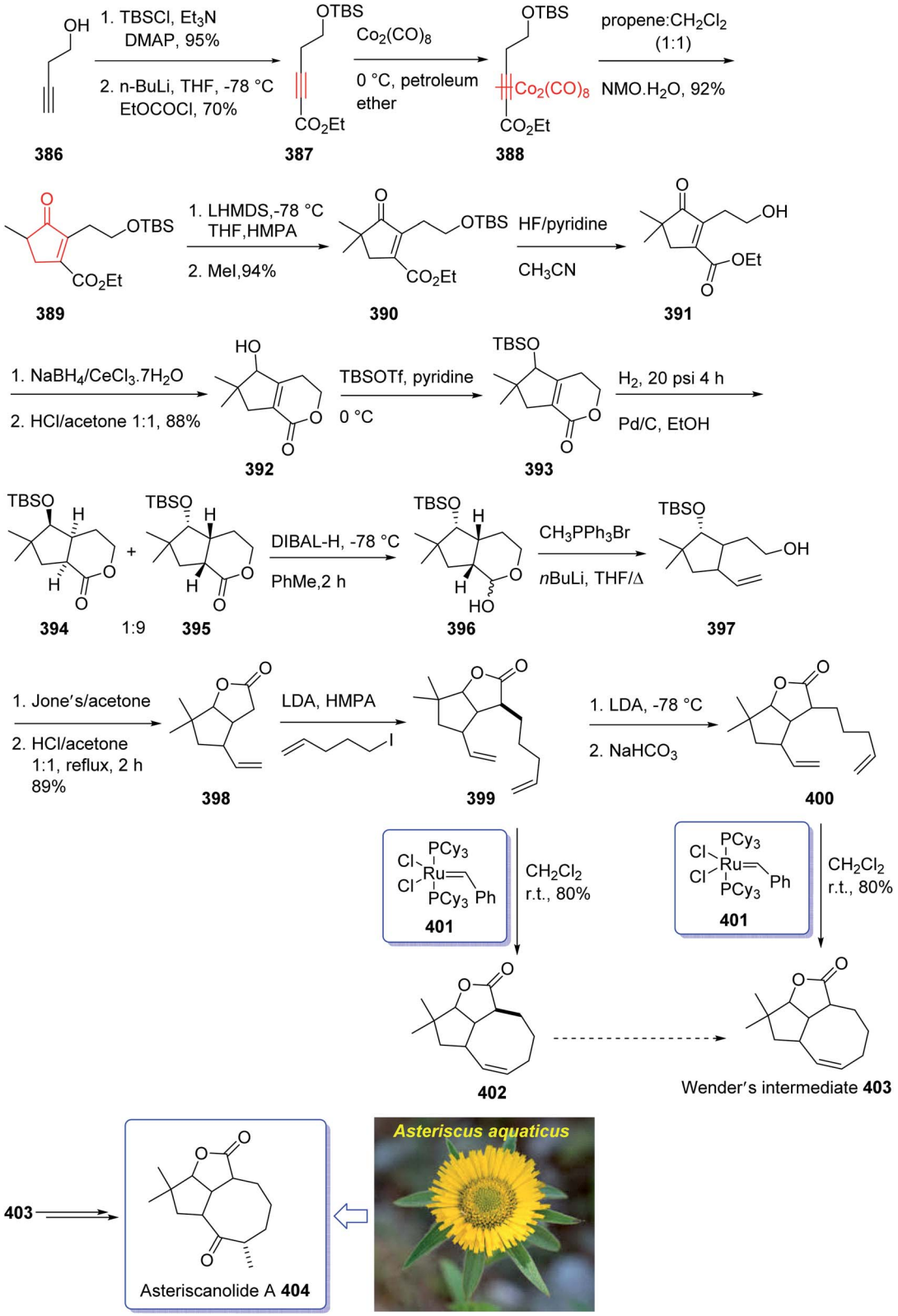
Sesquiterpene, illudin S, exhibited high antitumor activity.[249] Later, illudin analogues were synthesized showing highly improved effectiveness in comparison with the parent compounds.[250] One of such analogues is hydroxymethylacylfulvene **381** (HMAF, also called MGI 114). Since it was found to be active against breast, lung, and colon tumors, it has attracted much attention of synthetic organic chemists while showing intensely abridged toxicity. In addition, HMAF[251] as also found to be potent towards the MDR phenotype.[252]

The hydroxymethylacylfulvene **385** can be provided semi-synthetically from the naturally occurring sesquiterpene illudin S. Illudin S is generated in cultures of *Omphalotus illudens* (Jack o'-lantern mushroom). Upon treatment of illudin S with formaldehyde in 1 N H_2SO_4 solution, HMAF can be obtained through a reverse Prins reaction to give the intermediate acylfulvene **384** which next can be subjected to an ene reaction with formaldehyde.[253] The first total synthesis of HMAF was achieved and reported by McMorris *et al.* in 1997 (ref. 254) comprising a Padwa kind carbonyl ylide 1,3-dipolar cycloaddition[255] to achieve the illudin scaffold.



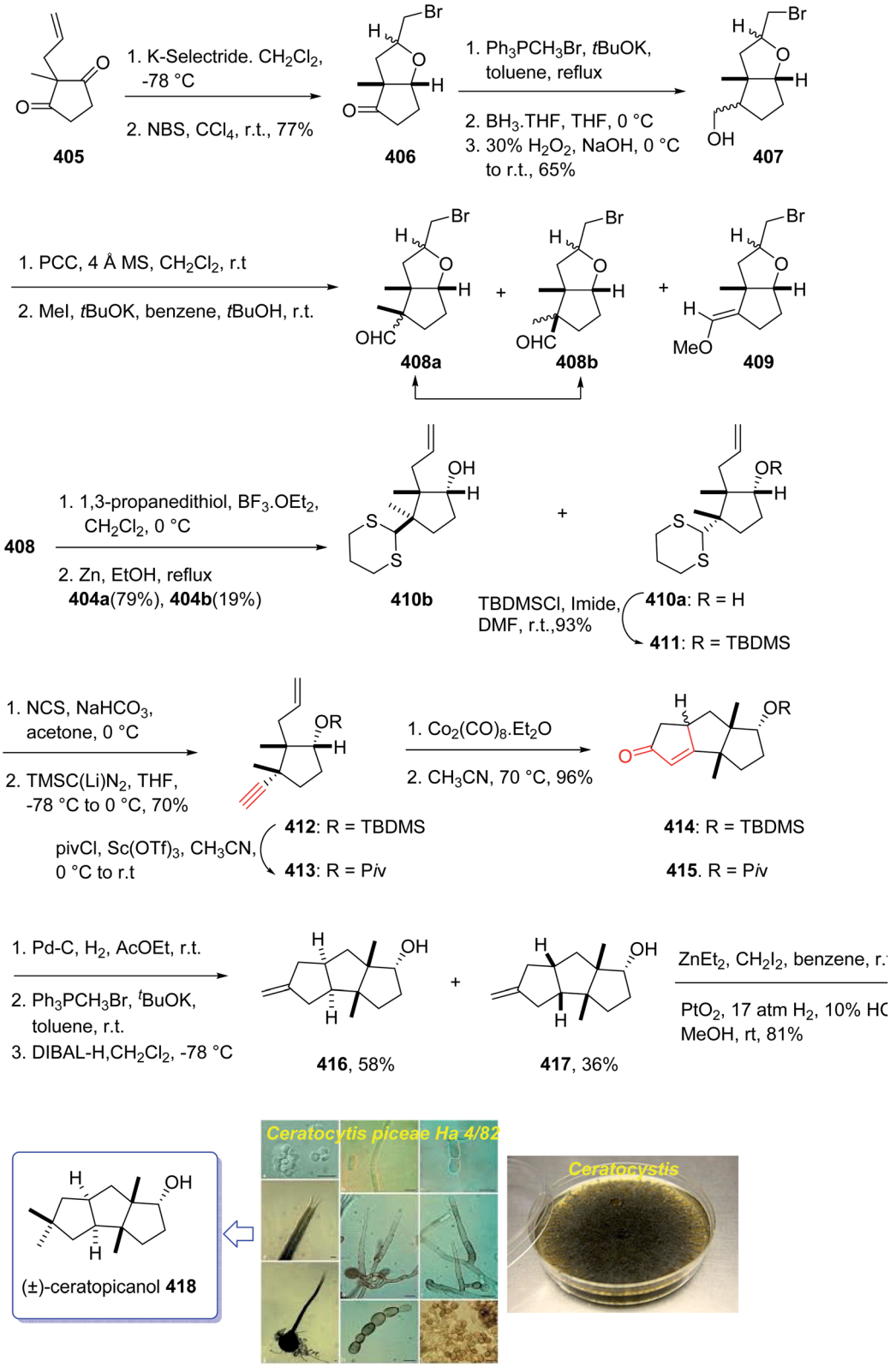
Scheme 30 Total synthesis of hydroxymethylacylfulvene (HMAF) **385**.

A brief synthetic approach involving eleven steps of HMAF was accomplished and reported by Brummond and co-workers in 1999,[256] including an intramolecular [2 + 2 + 1] Pauson–Khand reaction. In this strategy, the easily accessible 1,1-diacetylcyclopropane **376**,[256] reacted with the lithio derivative of the *tert*-butyl-dimethylsilyl ether of 3-trimethylsilylpropyn-1-ol **377** to give the expected ketone **378** as a 1.3 : 1 mixture of diastereomers in good yield. After several steps, the latter was



Scheme 31 Total synthesis of asteriscanolide **404**.

transformed into alkynyl allene **380b** which was subjected to fast cycloaddition under the conventional PKR conditions [$Mo(CO)_6$, DMSO, toluene, 110 °C][257,258] to afford the 4-alkylidene cyclopentenone **381** as single product in good yield. The latter was transformed into the secondary alcohol **383** after several steps which was oxidized using Dess–Martin oxidative



Scheme 32 Total synthesis of (+)-ceratopicanol **418**.

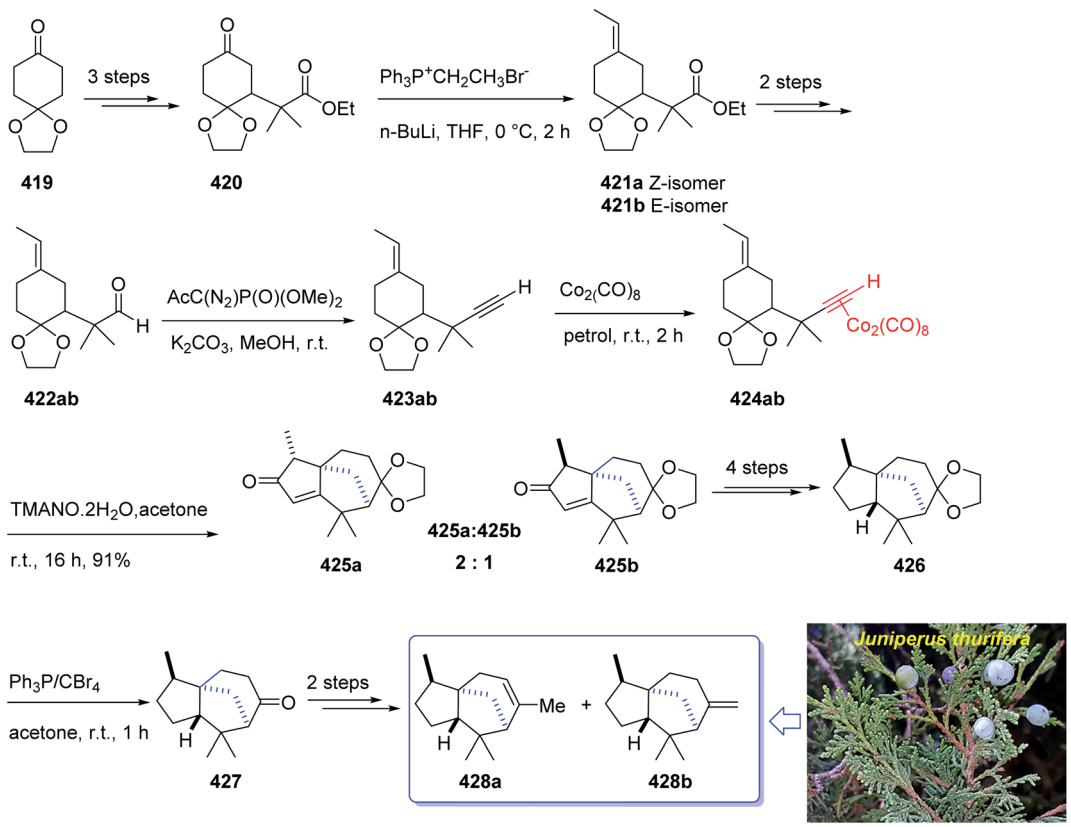
reagent to the corresponding ketone, acylfulvene **384**, in good yield. The latter was then reacted with formaldehyde in the presence of H_2SO_4 in acetone/water to give HMAF **385** in good yield (Scheme 30).[256]

Recently, asteriscanolide **404** which is a cyclooctane sesquiterpene lactone has attracted much attention of organic synthetic chemists. It was initially isolated in 1985 by the Feliciano research group from the hexane extract of *Asteriscus aquaticus*.[259] Several successful attempts have been reported. Wender and co-workers,[260] the Paquette group[261] and very recently the Snapper research group[262] have reported the total synthesis of asteriscanolide **404**.

In 2001, Krafft *et al.* reported an intermolecular Pauson–Khand cycloaddition and a ring-closing metathesis as vital steps.[263] This strategy incorporates the cyclooctane chiral center prior to ring construction. Remarkably, the ring-closing metathesis creates a new eight-membered ring with an "in–out" intrabridgehead relationship which come across the principles as mentioned above.

The total synthesis started from the protected 3-butyn-1-ol **386** as the corresponding *tert*-butyldimethylsilyl (TBS) ether which was converted into the corresponding alkynoate **387** *via* treatment with *n*-BuLi in THF at −78 °C to create the lithio alkyne and then added to ethyl chloroformate in THF at −78 °C. Treatment of **387** with dicobalt octacarbonyl in petroleum ether gave the desired precursor for PKR, hexacarbonyl-dicobalt complexed alkyne **388**. The latter was then reacted with propene in methylene chloride followed by incremental addition of *N*-methyl-morpholine-*N*-oxide monohydrate under PKR conditions. This afforded the highly functionalized cyclopentenone **389** which comprises different functional groups suitably placed for further employing of the side chains. After several steps, the latter was converted into trisubstituted cyclooctene **403**. The latter was a key intermediate for the successful total synthesis of desired natural product, asteriscanolide A **404**, after several steps (Scheme 31).[263]

Optically active (+)-ceratopicanol **418**, as a novel triquinane sesquiterpene was initially isolated from the extract of fungus *Ceratocystis piceae* Ha 4/82 (ref. 264) by Hanssen and co-workers in 1998.[264] Its structure was elucidated and its relative stereochemistry was determined as (1*R**,2*S**,6*S**,8*S**,9*R**)-1,4,4,8-tetramethyltricyclo[6.3.0.$0^{2,6}$]-undecan-9-ol.[264] The absolute configuration of (+)-ceratopicanol **418** was determined unambiguously when the total synthesis of its unnatural (−)-stereoisomer was completed and its X-ray analysis was compared to the (+)-natural product **418**.[265] Ceratopicanol **418** has a fascinating and exceptional structural characteristic containing five stereogenic centers among which are two adjoining bridgehead quaternary carbon centers. Due to these exceptional features, ceratopicanol **419** was selected as a target to be synthesized by several research groups.[265,266] In 2002, Mukai *et al.*[267] studied the stereoselective reduction of the 1,3-dicarbonyl **405** resulting in the formation of a compound containing hydroxyl and allyl moieties with *cis*-relationship. They found out when compound



Scheme 33 Total synthesis of α-cedrene **428a** and β-cedrene **428b**.

405 is treated with *K*-selectride, the highest stereoselectivity was obtained. To remove the undesired *trans*-hydroxy compound, a mixture obtained from reduction step was subsequently treated with *N*-bromosuccinimide (NBS) in CCl_4 to provide a mixture containing two stereoisomers of the 2-oxabicyclo [3.3.0]octa-6-one derivative **406**, because of the presence of C_3 stereogenic center, in satisfactory overall yield. After the next steps including different functional group transformations such as treatment of **408** with 1,3-propanedithiol in the presence of $BF_3 \cdot OEt_2$ which provided separable **410a** (75%) and **410b** (19%), conversion of secondary hydroxyl group of **410a** to **411** in 93% yield, followed by treatment with lithiotrimethylsilyldiazomethane, the alkyne derivative **412** was obtained as key intermediate. In accordance with the classical Pauson–Khand reaction procedure, compound **412** was treated with $[Co_2(CO)_8]$ in Et_2O to give the corresponding alkyne–cobalt complex. This complex upon heating at 70 °C in CH_3CN[268] gave compound **414** in high yield. Then, to a pivaloyl group was introduced on the secondary hydroxyl group of **412** to produce **413**. After treatment with $Co_2(CO)_8$, the latter was transformed to the corresponding cobalt-complex **415**. Elimination of the pivaloyl group resulted in the isolation of the desired compound **416** together with **415**. Finally, compound **416** in pure form, treated with diethyl zinc and diiodomethane in benzene under the Simmons–Smith reaction to obtain the cyclopropane derivative which upon hydrogenation in the presence of PtO_2 under pressure gave the desired natural product (±)-ceratopicanol **418** in 81% yield (Scheme 32).[267]

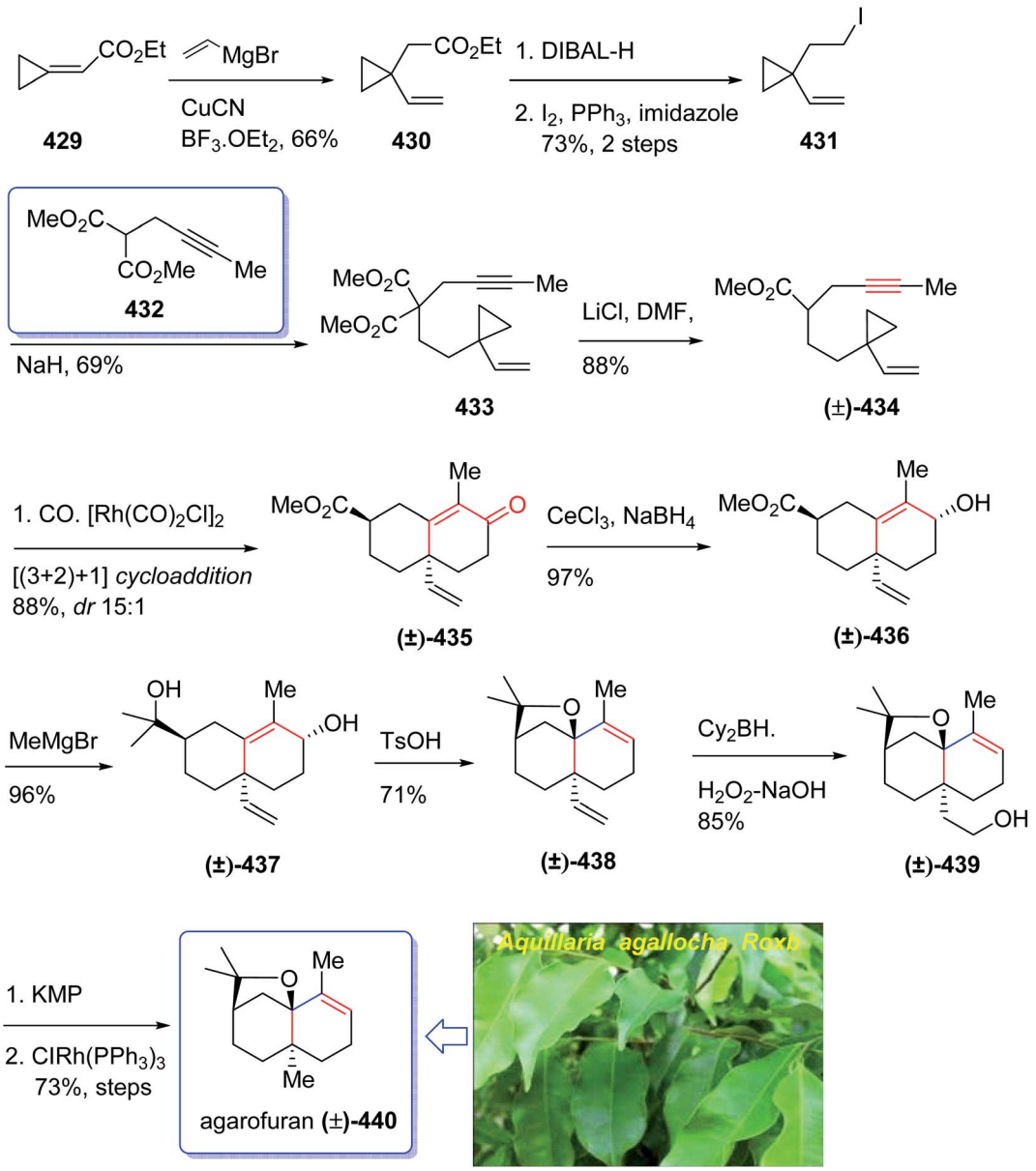
The tricyclic sesquiterpenes α-cedrene **428a** and β-cedrene **428b** were initially isolated by Barrero *et al.*,[269] in 1996 from *Juniperus cedrus* and *Juniperus thurifera*.[269–271] With these natural products, α-cedrene **428a** and β-cedrene **428b**, a range of accurately relative oxygenated terpenoid analogues were also isolated from the same source. Due to their fascinating [5.3.1.$0^{1,5}$] tricyclic structure, the cedrene family and their relative naturally occurring compounds have attracted much attention of synthetic organic chemists over the years since initial characterization of α-cedrene **428a** and β-cedrene **428b** in 1953 by Stork research group.[272]

In 2006, Kerr and co-workers[273] developed a pathway involving an intramolecular Pauson–Khand reaction in which the cedrene carbon scaffold was effectively installed from a simple monocyclic precursor directly.

A small number of further synthetic manipulations provided a concise formal total synthesis of α- and β-cedrene. The cyclisation precursor was readily prepared with a stereoselective ketone alkenylation selectively providing the olefin required for efficient access to the natural target. Using a simple monocyclic precursor led to the direct and highly effective formation of the interesting tricyclic [5.3.1.$0^{1,5}$] carbon scaffold of α-cedrene **428a** (and β-cedrene **428b**). It is noteworthy that in the crucial key Pauson–Khand annulation step, the olefinic precursors reacted with retention of configuration to afford the expected cyclopentenone epimer for synthesis of the desired natural products in excess. For further magnifying the effectiveness of this total synthetic design, the remaining and undesired cyclopentenone was also transformed into the vital isomer by a simple base-prompted epimerization course. In sequence, the desired cyclopentenone intermediate was further expanded to cedrone **427**, therefore, establishing a formal total synthesis of α- and β-cedrene. Ultimately, it is worthwhile to notice that compound **425a** underneath a reaction sequence comparable to those conducted on **425b** resulting in the synthesis of *epi*-cedrone.

As a matter of fact, this synthetic pathway is commenced with the introduction of α,β-unsaturation into the market purchasable cyclohexanedione monoethylene acetal **419**. After three steps, compound **419** was converted into **420** *via* Saegusa oxidation. The latter was then subjected to standard Wittig reaction at 0 °C employing the ethyltriphenylphosphonium bromide salt and *n*-BuLi to give olefins **425a**/**425b** in 92% yield as a 2 : 1 mixture of geometric isomers. The compound **421a**/**421b** was transformed into aldehydes **422ab** in 97% yield by oxidation after two steps.[274] For the transformation of aldehydes **422ab** into alkynes,[221,275] the Ohira–Bestmann technique (with the reagent dimethyl acetyldiazomethyl-phosphonate) was applied. In this case, this mild strategy gave alkynes **423a**/**423b** in 81% yield. In sequence, these were habitually complexed with octacarbonyldicobalt to provide the stable cyclisation precursors **424a**/**424b** in a virtually quantitative yield. At this vital step and with the essential complexes in hand, the Pauson–Khand annulation for the installation of the required tricyclic carbon α-cedrene scaffold was examined. Delightfully, intramolecular Pauson–Khand cyclisation of **424a**/**424b** proceeded smoothly to afford the enones **425a**/**425b** in high yield as a mixture of stereoisomers in the ratio of 2 : 1. This indicated that relative stereochemistry present in the initial olefins **421a**/**421b** had been carried *via* the cyclisation of precursors **424a**/**424b**. Using an efficient and selective approach to **425b**, an essential deoxygenated product **426** was provided after four steps. Upon treatment of **426** with Ph_3P/CBr_4, desired cedrone **428** was obtained in 99% yield.[276] Then, the latter in two steps was converted to desired natural product α- and β-cedrene, **428a** and **428b** (Scheme 33).[273]

(±)-α-Agarofuran **440** is a racemic furanoid sesquiterpene natural product. In 1962, Bhattacharyya *et al.*,[277] isolated α- and β-agarofuran from extract of agarwood C (*Aquilaria agallocha Roxb*).[278] Its structure was elucidated by chemical degradation and spectroscopic data analysis, chemical examination of fungus infected agarwood C (*Aquilaria agallocha Roxb*).[279,280] An approach to the total synthesis of α-agarofuran including Pauson–Khand reaction as a key step was presented by Yu *et al.* in 2010.[281] This strategy started from cyclopropylidene ester **429**,[282] which in two steps using conventional organic reactions, was converted to vinyl cyclopropane iodide **431**. Next, the latter was coupled with propargyl diester **446** to afford the *gem*-diester-tethered 1-yne-VCP **433**. Then, the latter was subjected to Krapcho decarboxylation[283] to provide monoester-substituted 1-yne-VCP **434**. This compound can act as a suitable precursor for homo-Pauson–Khand cycloaddition reaction under already secured optimal reaction conditions to give bicyclic cyclohexenone **435** in 86% isolated yield with a good diastereoselectivity. Compound **438** having the tetrahydrofuran framework of agaroguran,[284] was synthesized from **435** after



Scheme 34 Total synthesis of (±)-α-agarofuran **440**.

several steps. Ultimately, the vinyl unit was converted respectively to its corresponding alcohol and then angular methyl group by a sequential hydroboration–oxidation–decarbonylation to afford the desired natural product as a racemat (±)-α-agarofuran **440** (Scheme 34).[280,281]

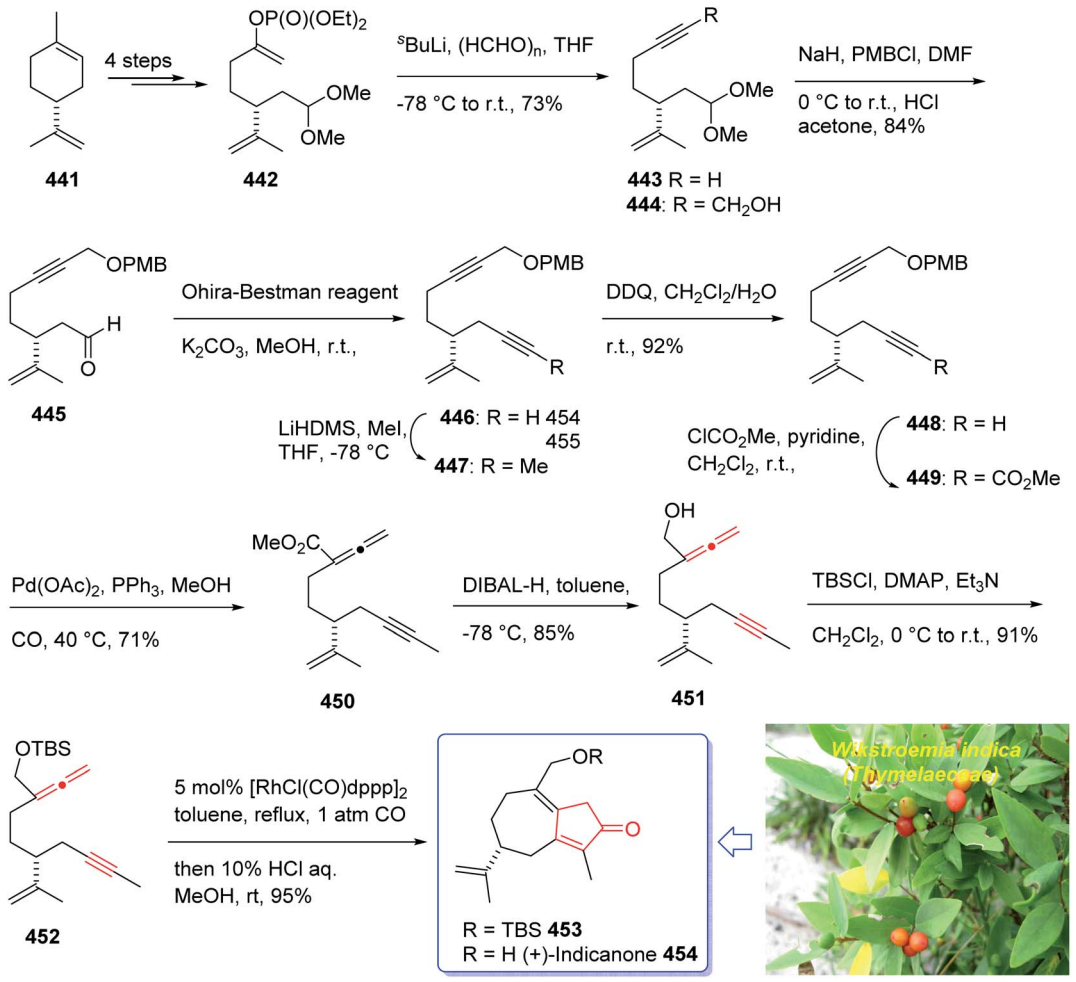
Kitanaka[285] and co-workers in 2005 for the first time isolated a new guaiane-type sesquiterpene, (+)-indicanone **454**, from the extract root of *Wikstroemia indica* (Thymelaeceae), collected from the southeast China. Notably, in this isolation, two already known and reported biflavonoids (*i.e.* sikokianin B and sikokianin C) were also obtained. Wikstroemia indica has been used to treat pneumonia, rheumatism, and bronchitis as folk medicine in China for long time. In 2012, the total synthesis of (+)-indicanone **454** was reported by Mukai and co-workers[286] through the Rh(I)-catalyzed Pauson–Khand reaction of the allenyne derivative which was derived from (+)-limonene.

In this strategy, the total synthesis of (+)-indicanone **441** commenced with vinyl phosphate **442**,[287] prepared from commercially available (+)-limonene after four steps. Compound **442** after several steps involving different common functional group transformations as well as protection–deprotection of some functional groups was converted to the allenyl alcohol of **451** which upon protection by a silyl group gave compound **452** as an appropriate precursor for PKR. The latter was subjected to PKR, upon treatment with 5 mol% [RhCl(CO)dppp]$_2$ in toluene under reflux conditions and carbon monoxide (1 atm) supplied compound **453** in moderate yield. The latter was then desilylated using aqueous HCl gave the desired natural product (+)-indicanone **454**. This strategy to the first

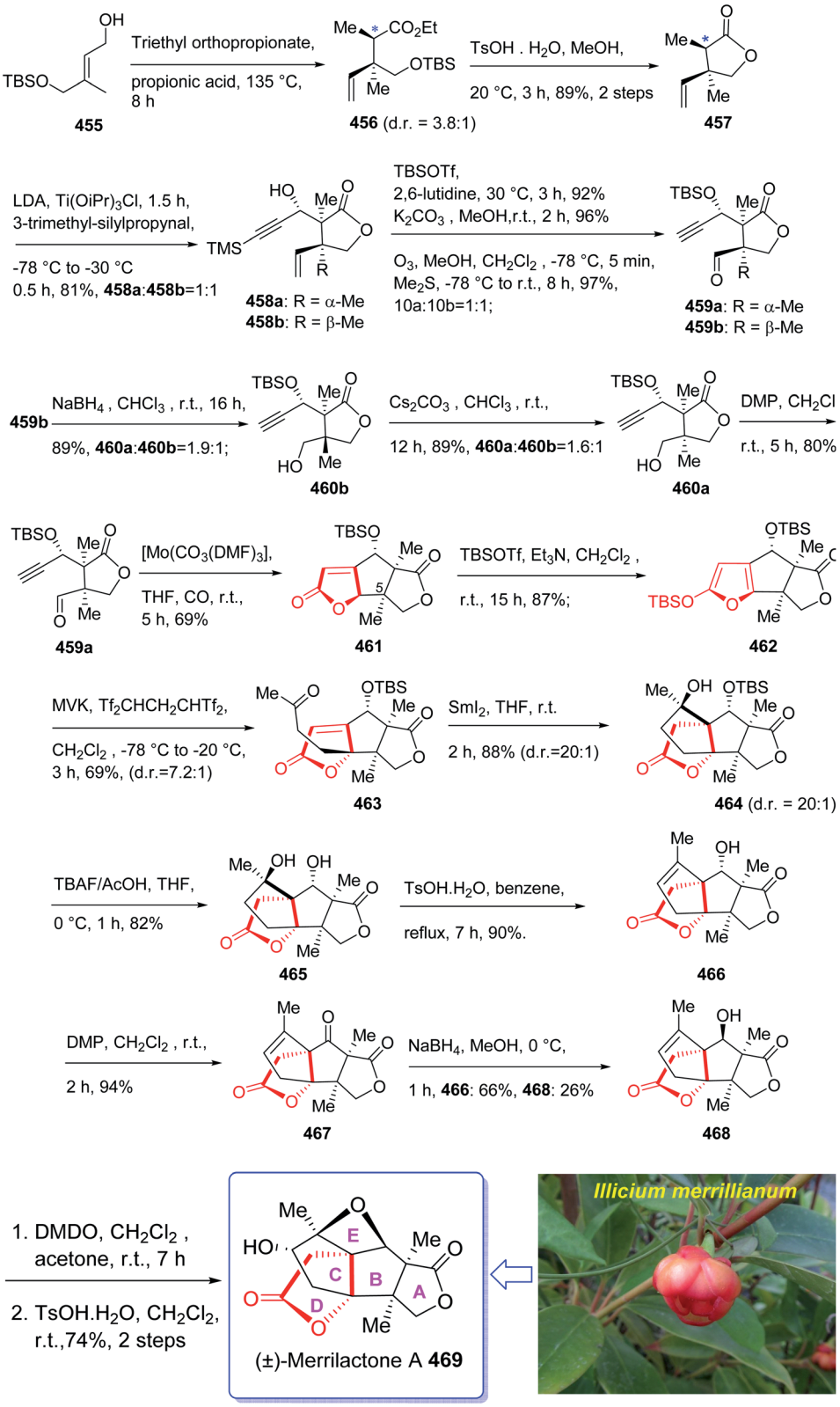
total synthesis of (+)-indicanone **454** was completed in ten steps starting from easily accessible known phosphate **442** in 29% overall yield. In addition, this total synthesis confirmed the complete structure and absolute stereochemistry of (+)-indicanone **454**, unambiguously (Scheme 35).[288]

In 2000, Fukuyama and his research group isolated merrilactone A **469**, a complex cage-shaped pentacyclic sesquiterpene, from extract of *Illicium merrillianum*.[289] Its structure was fully characterized showing it has an oxetane moiety, two γ-lactone functionalities, and a highly substituted cyclopentane ring at its core. In addition, merrilactone A **469** contains seven adjoining stereogenic centers, involving five quaternary ones. From the biological point of view, merrilactone A **469** is a non-peptidal neurotrophic factor which stimulated neurite development in the values of fetal rat cortical neurons.[289] Total synthesis of merrilactone A **469** has received much attention of organic synthetic chemists due to its exceptional and interesting structure as well as the reported activity against neurodegenerative diseases.[290] Among them, Inoue and Hirama,[291–293] Mehta,[294] Frontier,[295] Greaney[296] and almost twenty years ago Danishefsky[290,297] research groups have reported the total syntheses of merrilactone A **469**. Other synthetic approaches have also been renowned for the total synthesis of related natural products to merrilactone A **469**.[298–301] Significantly, in 2012 Zhai and co-workers[302] achieved and reported a new and proficient strategy to the total synthesis of (±)-**469** involving the Pauson–Khand reaction (PKR)[58] and hetero-Pauson–Khand reaction (h-PKR) in 2012.[303,304] An effective total synthesis of (±)-merrilactone A was developed by recognition of an efficient installation of (+)-mintlactone through an intramolecular ynal h-PKR.[70] It was commenced from the already reported alcohol **455**,[305] which upon treatment with triethyl orthopropionate and propionic acid provided the Johnson–Claisen rearrangement[306,307] product **456** (dr = 3.8 : 1) that upon desilylation and lactonization produced compound **457** (dr = 2.9 : 1), 89% over two steps from **455** mediated by $TsOH\cdot H_2O$. Treatment of compound **457** with LDA, $Ti(OiPr)_3Cl$, and then 3-trimethylsilylpropynal resulted in 1 : 1 mixture of inseparable aldols **458a** and **458b** in 81% combined yield alongside with two other inseparable isomers in 9% overall yield.[308]

Alcohols **458a** and **458b** were transformed smoothly into the two separable ynals **459a** and **459b** (1 : 1). Upon sequential hydroxyl protection, alkyne desilylation,[256] and selective ozonolysis.[309] Conversion of **459b** into **459a** was achieved *via*



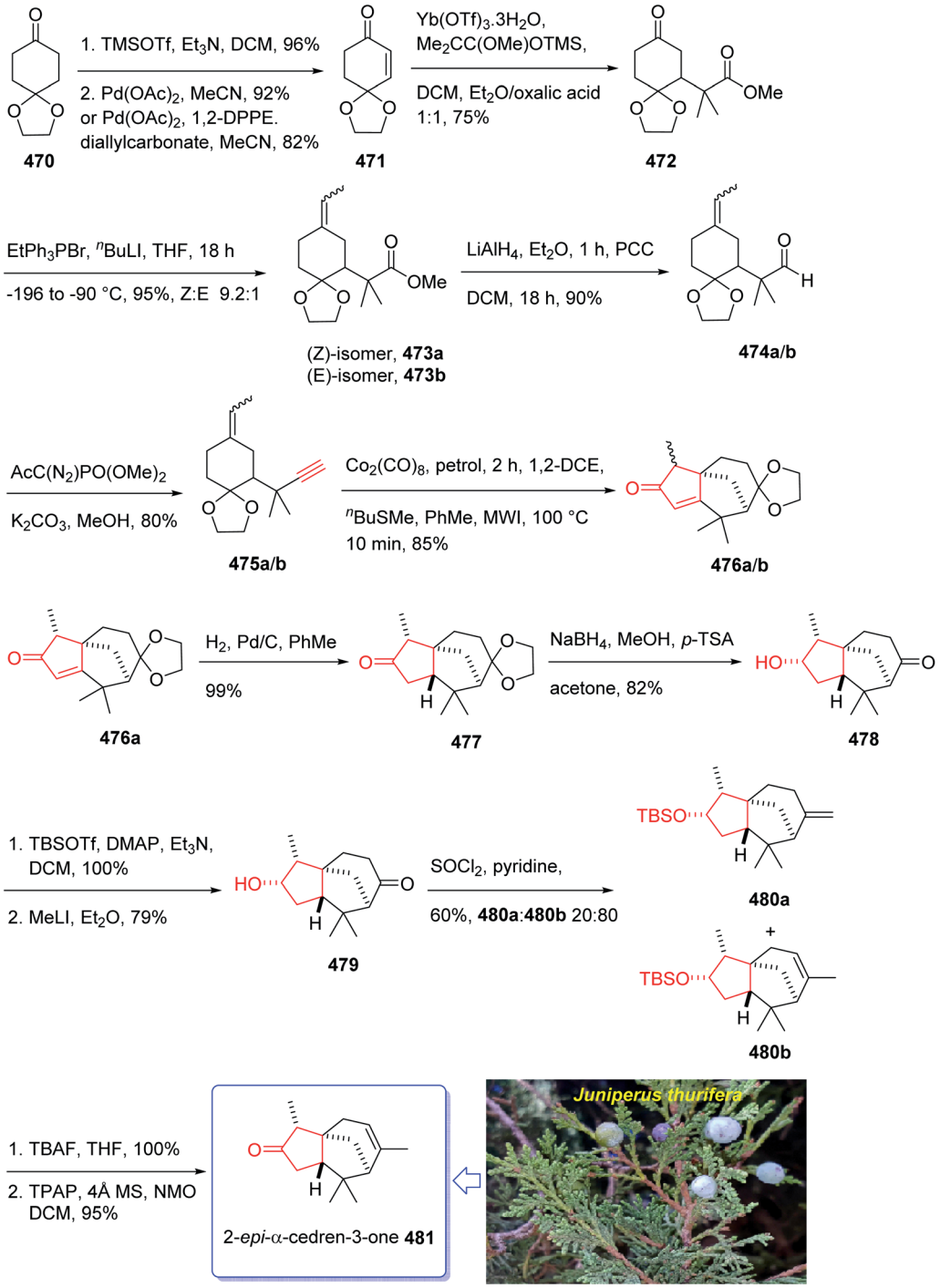
Scheme 35 Total synthesis of (+)-indicanone **454**.



Scheme 36 Total synthesis of merrilactone A **469**.

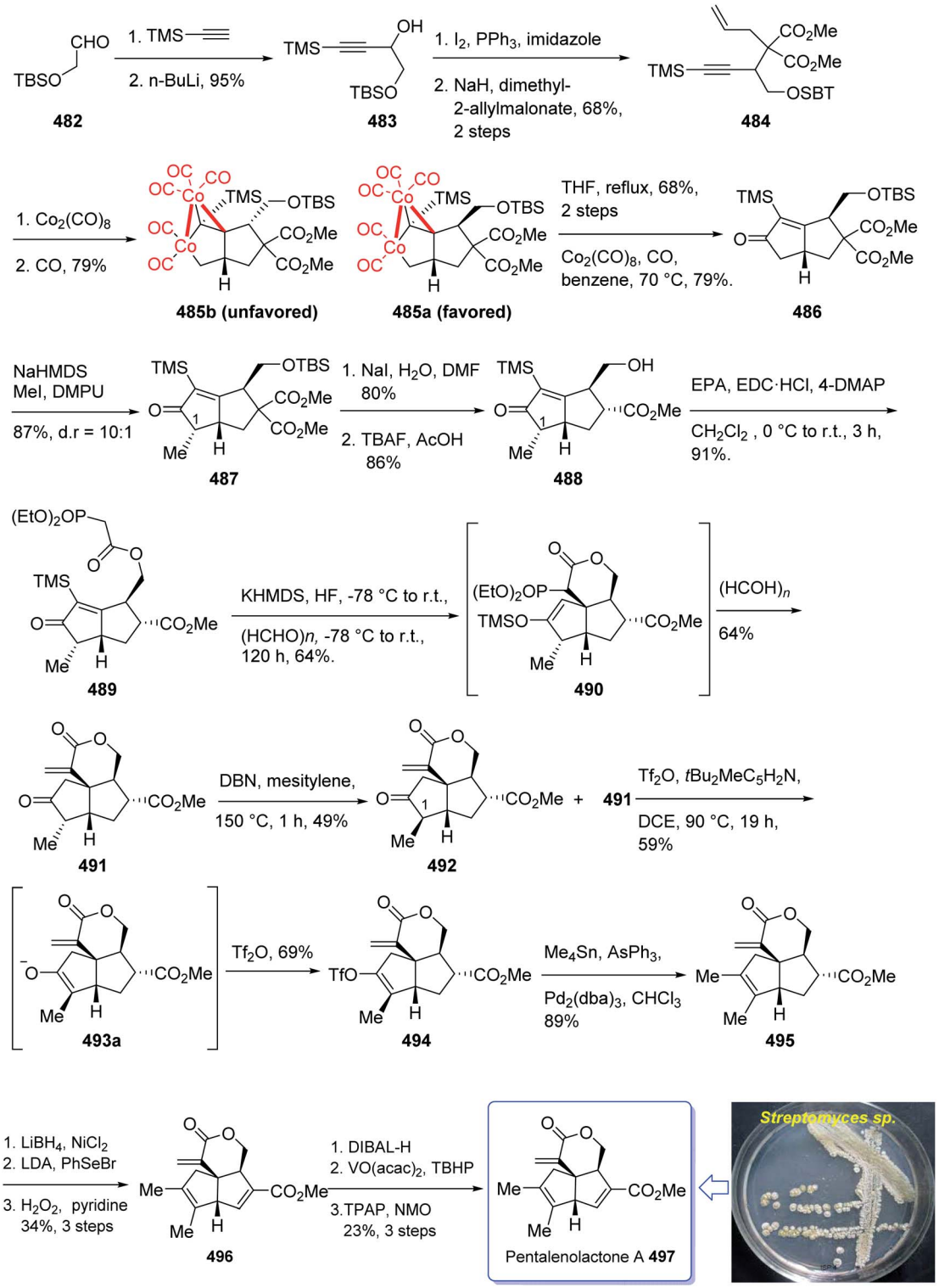
reduction of **459b** using $NaBH_4$ and intramolecular trans-esterification. Pleasantly, **460a** was provided from **460b** by initial transformation into a mixture of **460a** and **460b** (1.6 : 1) in the presence of Cs_2CO_3 *via* intramolecular trans-esterification. Having ynal **461a** available in hand, the vital h-PKR was performed to obtain the **B** and **D** rings of the target

468. The latter was treated with $Mo(CO)_3(DMF)_3$ (ref. 70 and 304) in THF at room temperature and under argon atmosphere provided tricycle **461** in 69% yield. Worthy to mention that **459a** was not used up totally by replacing argon with carbon monoxide (CO). Pleasingly, when **459a** was exposed to $[Mo(CO)_3(DMF)_3]$ in THF at room temperature firstly under argon atmosphere for a while and then under CO atmosphere (balloon), compound **461** was obtained (69%). Then, α,β-unsaturated lactone **461** was transformed into silyloxyfuran **462**,[310] upon treatment with MVK mediated by $Tf_2CHCH_2CHTf_2$ (ref. 311) under the Taguchi's strategy[311,312] to give ketone **3** (61%) alongside with *epi*-3 (8%) *via* a vinylogous Mukaiyama/Michael addition reaction. Expectedly, the C ring could be constructed *via* a reductive carbonyl-alkene coupling reaction.[313,314] Compound **463** was expectedly cyclized to furnish the desired tetracycle **464** (88%) as basically a simple diastereoisomer (dr = 20 : 1) upon treatment with SmI_2 in THF. Reaction of the latter with $TsOH\cdot H_2O$ in refluxing benzene with



Scheme 37 Total synthesis of 2-*epi*-α-cedren-3-one **481**.

concurrent dehydration and desilylation resulted in the formation of the trisubstituted alkene **465** in 91% yield. On contrary, treatment of **464** with TBAF and AcOH instead of desilylation,[294] gave diol **465** in 82% yield. Compound **465** upon dehydration in the presence of $TsOH \cdot H_2O$ in refluxing benzene gave compound **466**.[295] Precisely, compound **466** by oxidation with DMP gave ketone **467** (94%) which after reduction with $NaBH_4$ furnished an easily separable mixture of **468** (26%) and **466** (66%). This procedure was repeated many times to collect adequate quantities of alcohol **468**. Ultimately, the latter was converted into the desired natural product, merrilactone, following a recognized procedure involving a stereoselective

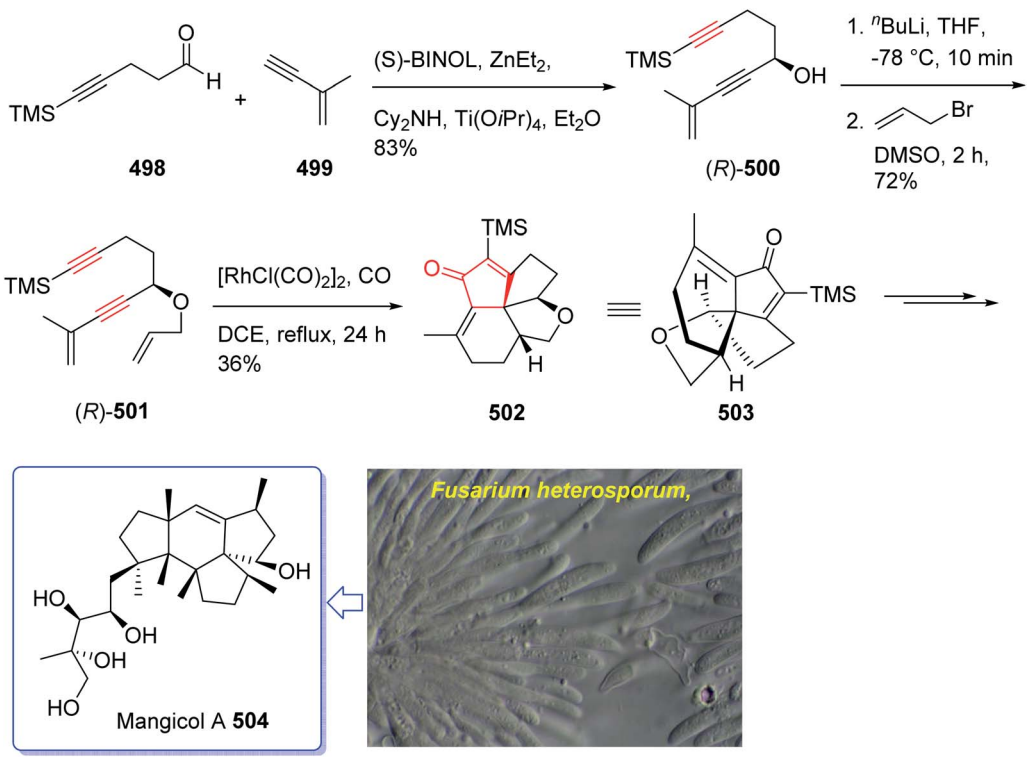


Scheme 38 Total synthesis of pentalenolactone A **497**.

epoxidation and epoxide ring opening/oxetane generation (by homo-Payne rearrangement).[291,315] The spectroscopic data of synthesized (±)-merrilactone A **469** was identical to those which already have reported for the natural product in the chemical literature.[289,290,294,295] An efficient total synthesis of (±)-merrilactone A **469** has been reported in fifteen reaction steps for the shortest sequence from 7 which is a known compound (Scheme 36).[302,305]

A sesquiterpene, 2-*epi*-α-cedren-3-one **481** is a natural compound, isolated from the essential oil of *Juniperus thurifera* in 2000 by Barrero and co-workers.[269] Several efforts have been made to achieve its total synthesis due to its interesting molecular structure. A synthetic strategy was reported by Kerr and co-workers in 2018.[316] involving a highly (*Z*)-selective Wittig olefination reaction. This reaction was performed at very low temperature which was essential to obtain of the same configuration within the desired natural product **481** and catalyzed intramolecular Pauson–Khand cyclisation reaction being conducted under MWI for the construction of the required tricyclic core of compound **481**. This synthetic pathway started with market purchasable cyclohexanedione monoethylene acetal **470** which was converted to α,β-unsaturated ketone **471** *via* Pd-catalyzed Saegusa oxidation reaction.[317] The latter was then converted into ketoester **472** *via* a conjugate addition of the silyl ketene acetal of methyl isobutyrate, mediated by ytterbium(III) triflate trihydrate.[318] Conversion of the latter to obtain the required alkene moiety is needed for (*Z*)-selective olefination reaction to attain the relative stereochemistry, more unambiguously being aligned with the methyl group *syn* to the methylene bridge in 2-*epi*-α-cedren-3-one, **481**. Wittig olefination reaction was performed at ambient temperature to give olefins **473a** and **473b** in excellent yield. At this point, compounds **473a** and **473b** were found to be practically inseparable. Therefore, aldehydes **474a**/**b** were provided *via* a two-step sequential reduction/oxidation. This mixture **474a**/**b** was treated with the Ohira–Bestmann reagent[221,319] (dimethyl acetyldiazomethylphosphonate) to obtain the alkyne **475a**/**b** as suitable PKR precursors. Having enynes **475a**/**b** available in hand, the effectiveness of the PKR, for the construction of tricyclic skeleton as core should have been optimized. To the purpose, addition of *n*-butyl methyl sulfide, as a promoter of PKR initially recognized by Sugihara and Yamaguchi,[320] along with employing sub-stoichiometric quantities of $Co_2(CO)_8$ were successfully examined to obtain cyclopentenone **476a**/**b**. It is worthwhile mentioning, as proved and reported earlier,[273] the ratio of inseparable stereoisomers obtained *via* the Wittig olefination relates always directly to the ratio of cyclopentenone **476a**/**b** provided in all PKRs reported previously. The mixture of **476a**/**b** was converted into **480a** and **480b** after several steps. This mixture **480a**/**480b** was separated and **480b** was subjected to sequential deprotection and oxidation afforded the desired natural product **481** in 95% overall yield over two final steps. In conclusion, the total synthesis of 2-*epi*-α-cedren-3-one has been accomplished in seventeen steps using PKR as a vital step (Scheme 37).[316]

Pentalenolactone A **497** is a conspicuous member of naturally occurring antibiotics, generated by prokaryotic organisms.[321–324] which was initially isolated and characterized as an

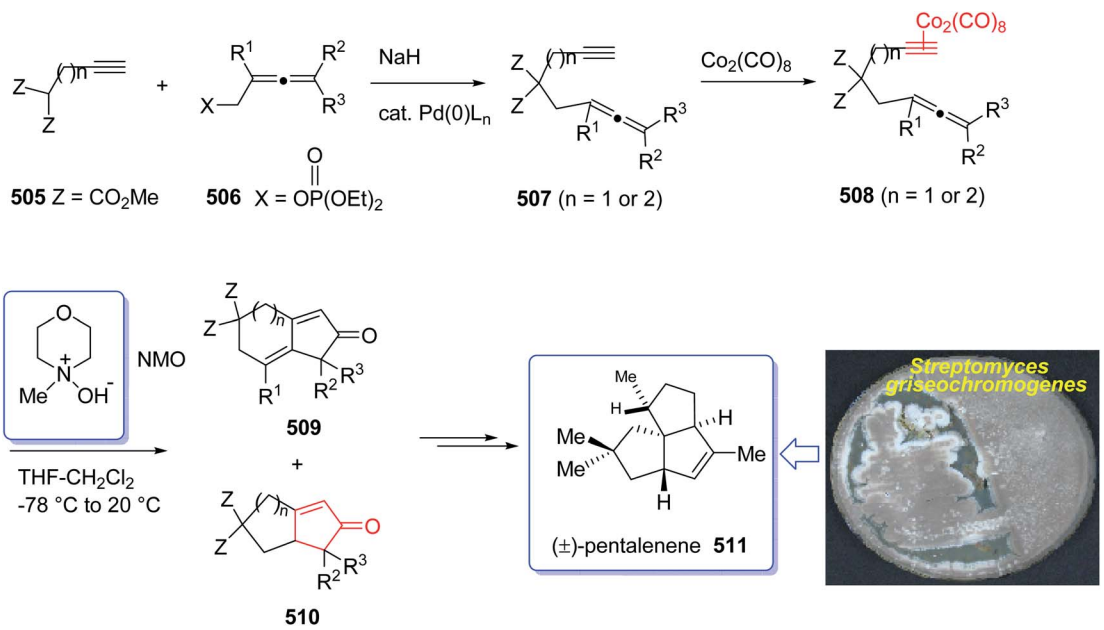


Scheme 39 Total synthesis of mangicol A **504**.

acidic lipophilic antibiotic. The sesquiterpene antibiotic pentalenolactone **497**, isolated from a variety of *Streptomyces species*, is a rare example of a cyclic terpenoid produced by a prokaryotic organism. Following the original isolation in 1957 by Koe and co-workers, McBride and co-workers,[324,325] the structure and absolute configuration were eventually assigned in 1970 by combination of spectroscopic and X-ray crystallographic methods.[326,327] The structure of pentalenolactone A **497** was determined by NMR analysis of its methyl ester derivative. The analysis showed that the structure consists of a highly compact carbon framework with a rare, angularly fused tricyclic pentanoid lactone having various oxidation states in each of the rings. It has a tricyclic core showing cytotoxic activity.[328,329] Such compounds also show a broad spectrum of potencies towards bacteria, fungi, viruses, and tumors. Its stimulating properties and substantial chemical activity prompted Danishefsky *et al.* to develop a fascinating total synthesis of **497** in 1978.[330–332]

In 2012, Li and co-workers[332] reported a protocol[333,334] for the asymmetric total synthesis of methyl ester of pentalenolactone A **497** based on an intramolecular Pauson–Khand reaction. It began with aldehyde **493** which upon treatment with lithium ethynylate at −78 °C afforded propargyl alcohol **483** in 95% yield. The newly formed hydroxyl group in **483** was transformed into the respective iodo compound upon treatment with I_2/imidazole mediated by Ph_3P and the resulting iodo species was next reacted with sodium dimethyl 2-allylmalonate to furnish the enyne **484** in 68% yield in two steps as an ideal precursor for the PKR. The latter was then converted to cyclopetenone **486** *via* PKR. The exclusive construction of **486** was most probably to minimize the steric interaction between the TMS and CH_2OTBS (TBS = *tert*-butyldimethylsilyl) moieties in complex **485a**[53,247] relative to complex **485b**, which consequently resulted in the formation of the desired annulated product **486** as the sole product. Having the latter available in hand, product **496** in an overall yield of 34% was converted to the desired natural product methyl ester of pentalenolactone A **497** after several steps following the already reported procedure by Danishefsky and co-workers in 1978 (Scheme 38).[332,335]

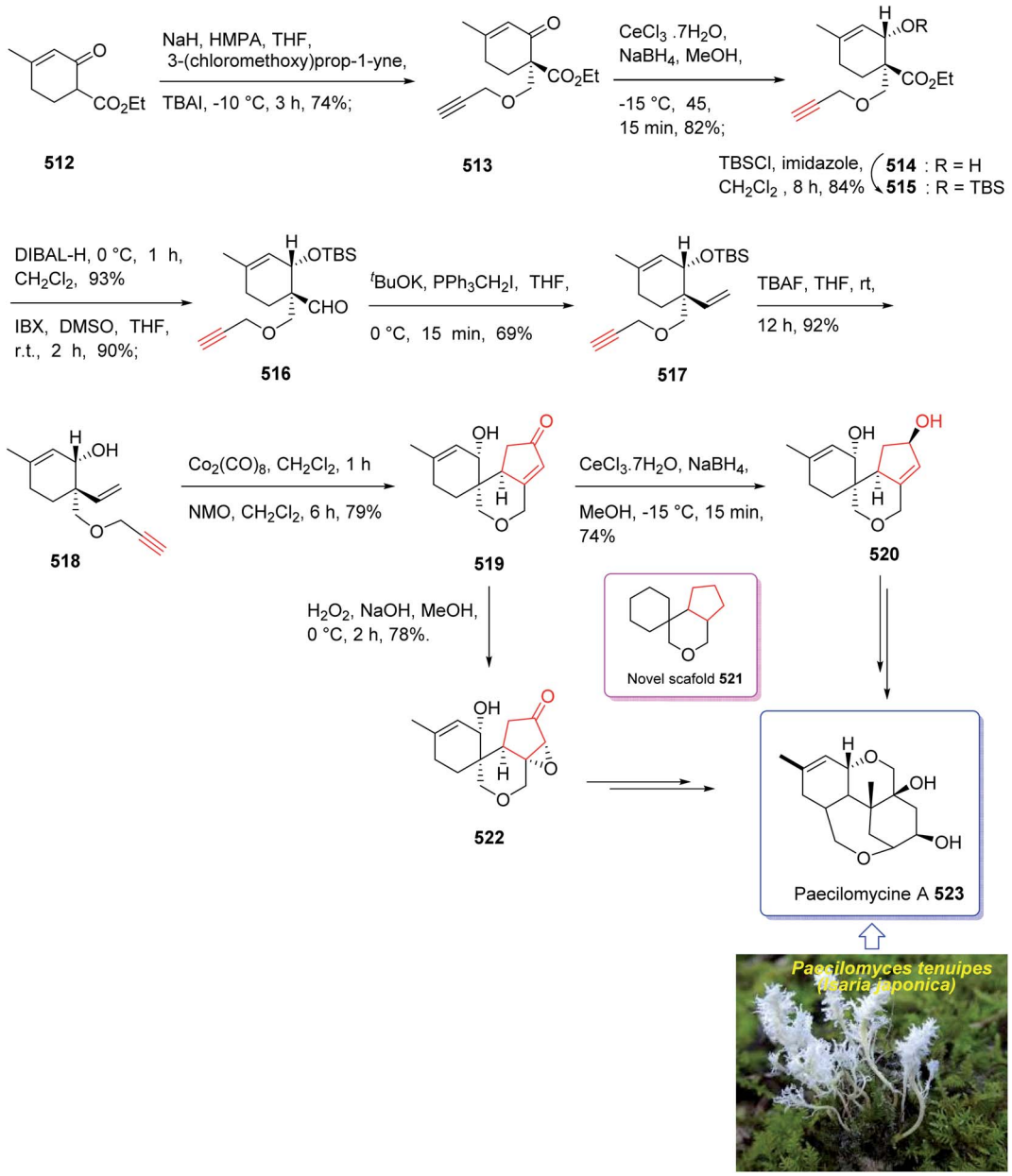
In 2000, Fenical research group isolated Mangicol A **504** (ref. 336) from a marine fungal *Fusarium heterosporum*. They reported it as a novel type of sesterterpene polyols with an exceptional spirotricyclic scaffold bearing a quaternary chiral carbon core.[336] Mangicol A **504**, among the other members of this class of naturally occurring compounds, has been found to be active anti-inflammatory agents, thus, has important therapeutic effect. Many unfinished efforts have been made for the total synthesis of this kind of compounds.[337–340] For instance, Uemura and co-workers in 2004 reported the total synthesis of core structure of mangicols A **504** in twenty-nine steps employing a Diels–Alder reaction of a macrocycle.[337] In 2012, Yu and co-workers[14,15,56,58,341] designed and effective pathway to obtain the spirotricyclic core analogue of mangicol A. This route involved asymmetric Pauson–Khand reaction and intramolecular Diels–Alder reaction as key steps. The total synthesis began from the BINOL-based catalytic asymmetric addition of enynal **498** to enyne **499** leading to formation of the optically active propargylic alcohol (*R*)-**500**. Treatment of the latter with *n*-BuLi followed by reaction with allyl bromide in DMSO afforded the corresponding diene–diyne substrate (*R*)-**501** as an appropriate precursor for PKR. Thus, the latter was subjected to the rhodium(I)-based catalyst and then to the PKR conditions ($[RhCl(CO)_2]_2$, CO, reflux, 24 h). The two cycloadditions of alkyne units took place to furnish compound **502**. The latter was converted after several steps to the desired natural product, the mangicol A **504** (Scheme 39).[342]



Scheme 40 Total synthesis of (±)-pentalenene **511**.

2.5. Sesquiterpenoids

Piers *et al.*[343] in 1984 reported total synthesis of (±)-pentalenene **511** using Pauson–Khand reaction. The natural product (±)-pentalenene **511**, belongs to the pentalenolactone family of sesquiterpenoid antibiotics. It was initially isolated in 1980 by Seto and Yonehara from *Streptomyces griseochromogenes*.[244] It has an interesting structure containing the parent hydrocarbon. In fact, (±)-pentalenene **511** has been found[344] to be a biosynthetic precursor of pentalenolactone.[327,345,346] Initially, several α,ω-allenynes **507** [1,2-dien-7-ynes **507a–d** ($n = 1$) and 1,2-dien-8-ynes **507e,f** ($n = 2$)] which were requisite for this total synthesis were provided *via* the Pd-catalyzed reaction of enyne **505** with the phosphates **506** in the presence of NaH in which the phosphate moiety was substituted. Unambiguously, cyclization of the bicyclic enone *via* the tertiary amine oxide-promoted PKR of enyne **507** was anticipated to proceed in the expected desired stereochemical sense. Consequently, intramolecular cobalt-catalyzed PKR of α,ω-allenynes **507** as an appropriate PKR precursor resulted in the formation of bicyclic dienones **509** and α-alkylidenecyclopentenones **511**, regioselectively, *via* formation and conversion of intermediate hexacarbonyldicobalt complex **508a** depending on the substitution pattern of the allenic moiety. It seemed likely that transformation of α-alkylidenecyclopentenones **509** into (±)-**511** after several steps is straightforward leading to the formation of the desired natural product (±)-pentalenene **511** (Scheme 40).[343,347]

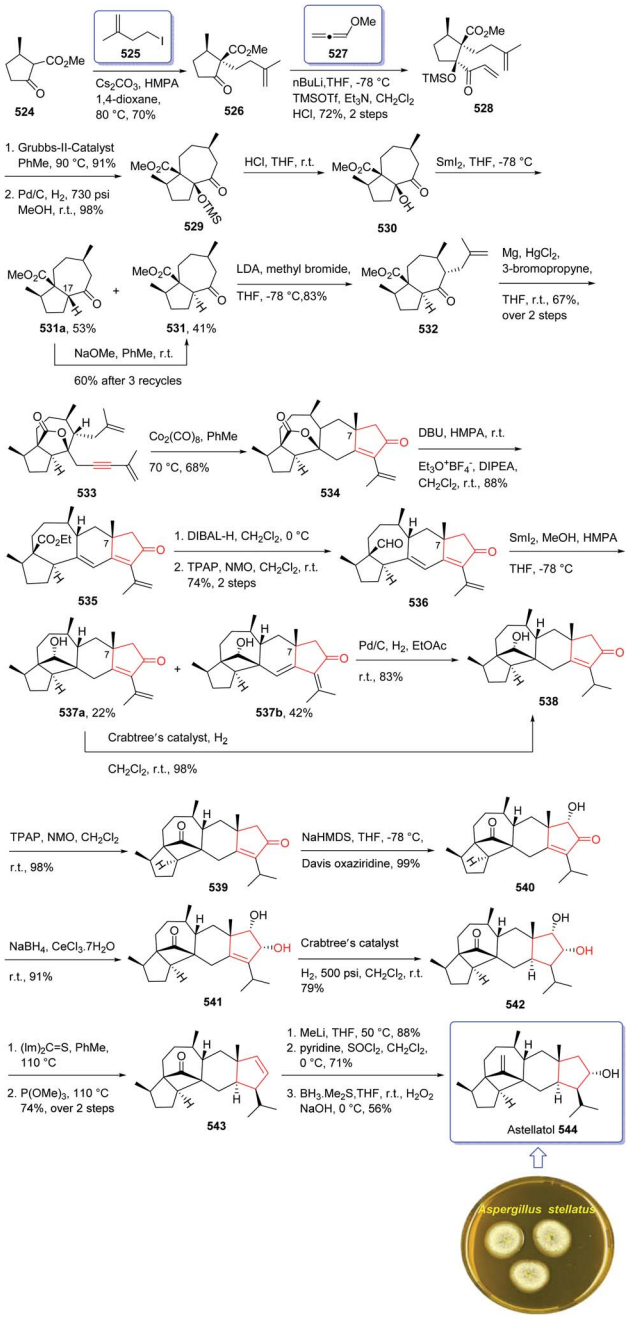


Scheme 41 Total synthesis of paecilomycine A **523**.

Paecilomycine A **523**, is a tricothecane derived naturally occurring sesquiterpenoid which was initially isolated in 2004 by Oshima and co-workers, among other *Paecilomyces tenuipes* and terpenoids from extract of cultured fruiting bodies of *Paecilomyces tenuipes* (*Isaria japonica*).[126,348] Paecilomycine A **523** showed an increased and inspiring neurite outgrowth in PC-12 cells and impressive neurotrophic activity.[126] The total synthesis of paecilomycine A **523** was reported by Mehta *et al.* in 2012 using intramolecular Pauson–Khand reaction.[349] This strategy commenced with ethyl 4-methyl-2-oxocyclohex-3-enecarboxylate **512** which was submitted to propargyloxymethylation using (propargyloxy) methyl chloride[350] to give **513**. The latter was subjected to stereoselective Luche reduction[351] in compound **513** to afford α-hydroxy compound **514**. The latter then after several steps including protection–deprotection and various functional group transformations such as Wittig olefination, was converted to **518** as an appropriate PKR precursor. In a key step, the latter underwent stereoselective intramolecular PKR in the presence of $Co_2(CO)_8$ and NMO in CH_2Cl_2 to provide the spiro-fused tricyclic hydroxy-enone **519**.

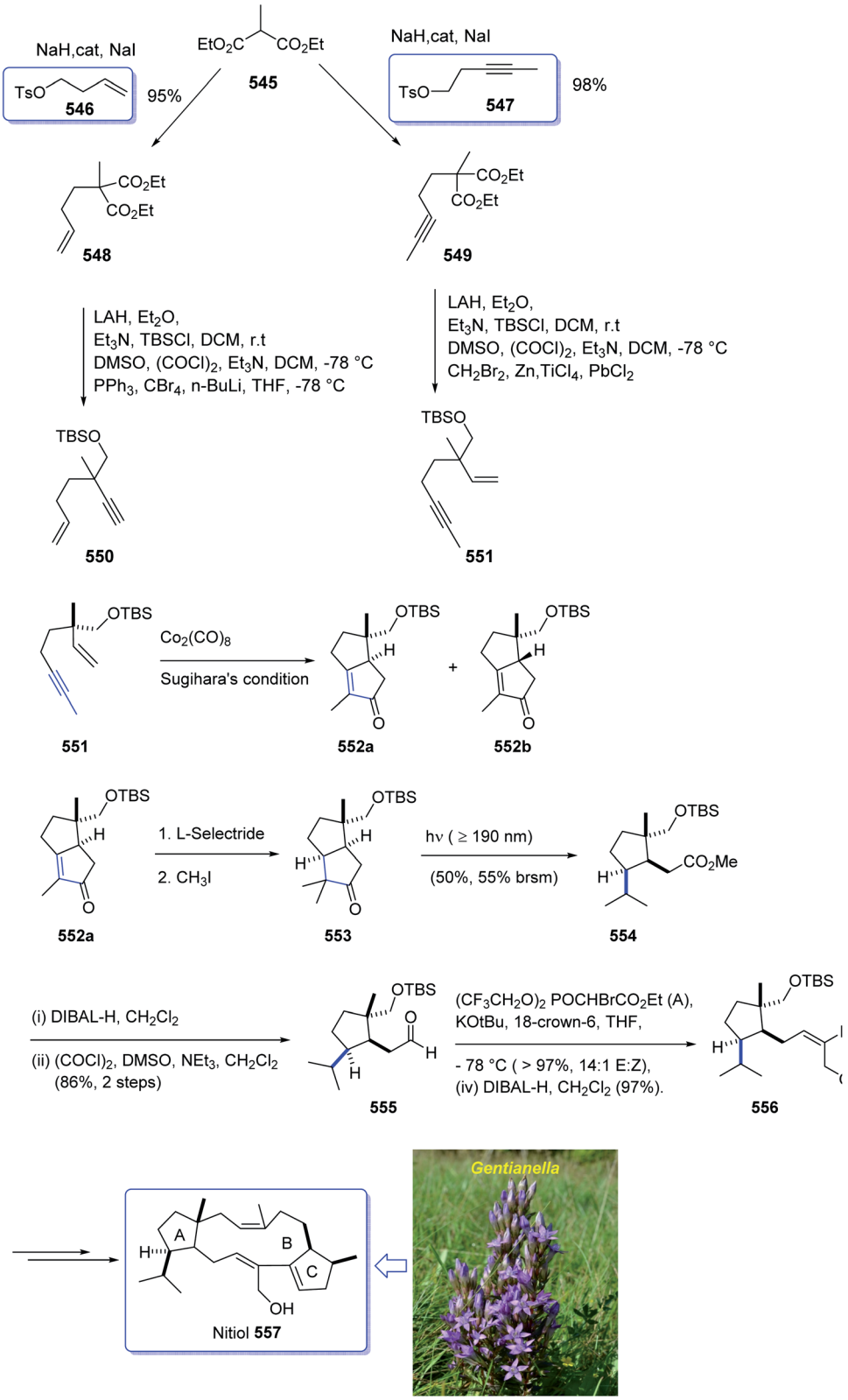
As a matter of fact, two derivatives were synthesized from **519**: (a) a tricyclic diol **520** obtained from stereoselective Luche reduction and (b) the respective epoxide **521** by nucleophilic epoxidation which was used for biological screening. Remarkably, all of the novel synthesized compounds **519**, **520**, **522** symbolizing the 2-oxa-spiro[5.5]undecane segment, which were already recognized to be neuroprotective in standard MTT and trypan blue for cell viability screening.[352–354] Interestingly, both compounds, **520** and **522** were converted to the desired natural product paecilomycine A **523**. The expedition for the synthesis of novel structure exhibiting neurotrophic activity, encouraged by paecilomycine A **523**, has resulted in the design and synthesis of a novel framework containing 2-oxa-spiro [5.5] undecane core (Scheme 41).[349]

Among terpenes as a wide-spread family of naturally occurring small compounds, sesterterpenoids probably are the most enthralling molecules with complicated architectures showing various biological potencies. Several members showed anticarcinogenic, antimicrobial, anti-inflammatory, and cytotoxic potencies.[355,356] One of these sesterterpenoids found to have a compound so-called astellatol **544**.[357,358] Initially, in 1989 Sadler and co-workers isolated astellatol **544** from extract of *Aspergillus stellatus* and elucidated its structure.[357] According to their structural determination, the left part of astellatol **544** structure possesses a crowded ring system with several stereogenic centers involving quaternary centers which makes its synthesis difficult. In addition, another major synthetic problem is the presence of highly substituted, notorious *trans*-hydrindane moiety on the right side.[359,360] Astellatol **544** possesses an executional bicycle [4.1.1] octane moiety, ten stereogenic centers, a cyclobutane involving two quaternary centers, an *exo*-methylene group, and a sterically hindered isopropyl *trans*-hydrindane moiety. Due to the structural complexity of astellatol **544**, its total synthesis has been very challenging and stimulating which took about 30 years to be successfully achieved.



Scheme 42 Total synthesis of astellatol **544**.

The total synthesis of astellatol **544** was successfully attempted by E. J. Corey and co-workers in 1985,[360] and later by Paquette,[361,362] Hudlicky,[363,364] and Wender.[365] In 2018, Xu *et al.* also accomplished **536** (ref. 366) and reported a brief and asymmetric synthesis of astellatol **544**. That was including a SmI_2-catalyzed reductive radical 1,4-addition.[367] This synthetic pathway started from the alkylation of the already reported chiral synthon **524** (ref. 368) with the homoallylic iodide **525** in the presence of Cs_2CO_3 and HPMA in dioxane under reflux to provide ketone **526**. The latter was attacked by the lithiated derivative of methoxypropadiene **527**,[369] which upon protection and hydrolysis gave the enone **528**. The latter after several steps



Scheme 43 Total synthesis of A-ring component of nitiol **557**.

was transformed to multigram quantities of **533**, as an appropriate precursor for PKR. Pleasantly, the substrate **533** underwent PKR using $Co_2(CO)_8$, in 2015 by Yang *et al.*[370] to afford the expected cyclized product **534**. After several steps, compound **534** was converted to alkene **543**. Then, the latter was converted to the desired natural product astellatol **544** in two steps. In the

first step, alkene **543** was reacted with MeLi at 50 °C to give the tertiary alcohol, which successfully subjected to elimination in the presence of $SOCl_2$/pyridine conditions which leading to the *exo*-methylene functionality on the cyclobutane framework. In the second step, a hydroboration-oxidation occurred to give astellatol **544** in 56% yield. As a result, the total synthesis of the rare sesterterpenoid, astellatol **544**, was achieved in twenty-five steps and 0.63% overall yield starting from chiral synthon **524** (Scheme 42).[366,371]

A concise and asymmetric total synthesis of A-ring component of nitiol **559** including diastereoselective Pauson–Khand cycloaddition was reported by Dake in 2001.[372] It was actually an attempt towards the total synthesis of the natural product, nitiol **558**.[105,360,373] In 1995, Cordell and co-workers found out that the plant so-called *Gentianella* (G.) is a regular remedial plant that cultivates in the Andes area. Its extract contains several compounds with diverse structures showing various biological activities, extensively employed as folk medicine for the treatment of hepatitis, and obesity.[374,375] Nitiol **558** was initially extracted from this whole plant and was separated several times and purified *via* different techniques by Kawahara research group in 1999 resulting in the isolation of, novel sesterterpenoid.[376] Interestingly, its structural elucidation was made by the same group in the same year.[376] Primary biological screening showed that compound **558** behaves as an active enhancer of interleukin-2 in human T cell lines.[376] The total synthesis of nitiol **558** was accomplished and reported by Dake and co-workers in 2001.[372] The important steps in this strategy are an asymmetric Pauson–Khand cycloaddition and a norrish type 1 fragmentation reaction.[105,360,373] The total synthesis started from diethyl methylmalonate **545** which upon alkylation with the appropriate tosylate in the presence of sodium hydride and catalytic amount of sodium iodide in DMF gave 2,2-disubstituted malonates **548** and **549**.[377,378] The required enyne **551** and **550** were prepared *via* standard procedures involving, LAH reduction, TBSCl protection, oxidation, Corey–Fuchs or Nozaki reactions. Compound **551** was then subjected to Sugihara's conditions[15,379,380] to provide desired bicyclooctenes **552a** and **552b** in satisfactory yields (57–74%). The prepared cyclopentenone **552a** then underwent conjugate reduction by utilization of lithium tri(*sec*-butyl) borohydride followed by quenching with methyl iodide to afford **553** in high isolated yield in pure form. Delightfully, this process afforded trisubstituted cyclopentane **554** in 50% yield. In this step, the ester functional group of **554** was transformed into an aldehyde **555** under typical conditions, in two steps including reduction using diisobutylaluminum hydride and Moffatt–Swern oxidation in 86% overall yield. The latter upon treatment with Kogen's Horner-Wadsworth-Emmons-type reagent **A**[381] gave the trisubstituted vinyl bromide **556** in excellent yield (>97%) and high stereoselectivity ($E : Z$, 14 : 1). Finally, the latter after several steps was converted to the desired natural products **557** in 40% overall yield (Scheme 43).[372]

3. Conclusion

In conclusion, in this review, we tried to draw the attention of readers, especially synthetic organic chemists to one of the most useful name reactions in organic chemistry so-called Pauson–Khand reaction (PKR). We presented a brief summary of the catalytic PKR. As we mentioned there are just a few organic transformations that complement so much molecular complexity in one step as the PKR. The products of PKRs are cyclopentenones, which can be readily converted into various functionalized cyclopentanes, which exist as structural elements in the scaffolds of several natural products. Then, we discussed the merits and drawbacks, observed for PKR, during the years. As mentioned, the intramolecular PKR (IPKR) was developed. In addition, various transition metal catalysts were introduced. We showed that by using modified (chiral) catalysts and reaction conditions, the products of PKR can be synthesized, asymmetrically. Thus the asymmetric variant of this important name reaction, nowadays is quite possible, leading to optically active products. Asymmetric PKRs can be achieved by using different approaches, including use of chiral ligands and chiral metal complexes. Comprehension of the reaction mechanism will allow accurate prediction of the stereochemical outcome of the reaction. Thus, we focused on the applications of PKR in the total synthesis of natural products trying to encourage synthetic chemists to rely on this reaction when designing their synthetic pathways leading to total synthesis of an appropriate natural products. In addition, the content of this review has been arranged based on the family and types of plants, which the certain natural product has been isolated from and their biological activities were also mentioned. That makes this review in addition to organic synthetic chemists, useful and readable to natural products chemists, pharmacists and botanists.

Conflicts of interest

There are no conflicts to declare.

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