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# Cobalt catalysis in organic synthesis: a powerful tool in the synthesis of natural products and pharmaceutically active compounds

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Cobalt-mediated catalysis has proven to be a potent and versatile method in the realm of present-day organic synthesis, facilitating the synthesis of biologically significant natural products and complex molecules. The field of natural product chemistry has always provided crucial advancements in the field of chemical science and pharmacology. Cobalt-mediated catalysis play a significant role towards the synthesis of biologically significant natural products, such as alkaloids, terpenoids, diterpenoids, polyketides, glycoside containing natural products, macrolides, as well as pharmaceutically active compounds such as nirmatrelvir, (*S*)-pazinaclone and MK-0371 *etc.* The present review focuses on the importance and applications of cobalt-mediated catalysis towards the synthesis of biologically significant natural products and pharmaceutical drugs, reported since 2018.



## 1 Introduction

Transition metals play a central role in modern organic synthesis, offering highly selective and efficient transformations that facilitate functional group modification, strategic bond construction and complex molecule assembly.[1–3] The abundance of third row transition metals in nature makes them more compatible for natural product synthesis than fourth and fifth row transition metal series. Nevertheless, the remarkable efficiency with which nature constructs diverse molecular architecture using these metals, highlights an underlying potential for first row transition metal chemistry.[4,5] Among these, cobalt occupies a distinctive position as the earliest and lightest member of the group 9 transition metals. As a naturally abundant 3rd transition element, cobalt has found striking applications in organic synthesis, most notably in catalytic transformations.[6]

The historical importance of cobalt catalysis can be traced to the work of Roelen in 1938, who implemented the hydroformylation of alkenes with $Co_2(CO)_8$ catalyst and emphasized the transformative ability of organometallic cobalt catalyst particularly in organic synthesis.[7] Cobalt catalysts were subsequently employed in the original industrial plants and later adopted in Russian facilities that have remained active since the 1950s. These systems closely resembled the cobalt carbonyl complexes first synthesized by Fischer in 1932, underscoring their foundational role in the development of modern catalytic chemistry.[8,9]

Cobalt catalysts represent an important class of transition metal systems in organic synthesis, distinguished by their remarkable characteristics, favorable environmental attributes and accessible mechanistic pathways.[10–12] The ability of cobalt to adopt many oxidation states facilitates the generation of reactive intermediates that are often inaccessible with late noble metals. A well-defined cobalt catalyst offers adjustable steric and electronic environments important for attaining precise control over stereoselectivity and reactivity.[13]

Cobalt catalysis operates through two distinct regimes: low valent and high valent catalysis. Low valent cobalt catalysis was initially described by Yoshikai in 2010, and subsequently expanded upon by Ackermann, Nakamura, and others, which include the reduction of Co(II) salt through zinc or organomagnesium to produce reactive Co(I) complexes, important for C–H activation.[12,14–24] In 2013, Matsunaga and Kanai introduced high valent Cp*Co catalysis exhibiting reactivity like rhodium and iridium complexes, thereby offering excellent functional group tolerance, air stability and low catalyst loading features.[25] The higher nucleophilicity and Lewis acid properties of Co(III) species enable improved selectivity and new transformations.[23]

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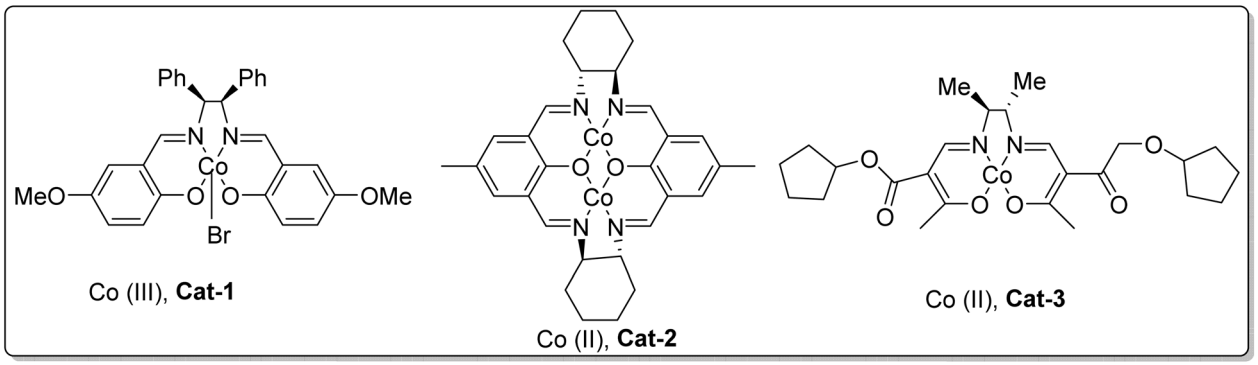



Fig. 1 Structure of Co(II), Co(III) complexes.

There have been significant developments towards natural products synthesis owing to their diverse biological profiles.[26–28] Cobalt catalysis has been highly successful towards the total synthesis of a variety of naturally derived molecules for the formation of complex molecular skeletons such as antitumor sesquiterpene coriolin,[29] and lycopodium alkaloids such as fawcettidine, fawcettimine, and lycoflexine.[30] Apart from the formation of complex molecular skeletons, cobalt catalysis has helped to design stereoselective transformation methods (Fig. 1). These advances led to the preparation of highly complex targets such as peloruside A and hemibrevetoxin-B, which highlight the utility of cobalt catalysis in modern organic synthesis (Fig. 2).[31,32]

The pharmaceutical relevance of cobalt catalysis extends to the direct construction of drug scaffolds and late-stage functionalization of bioactive molecules.[33] Cobalt catalyzed C–H activation has enabled the synthesis of a variety of drug frameworks[20,34] whereas pharmaceutically active isoquinoline alkaloids have been accessed through Co-catalyzed annulation reactions.[35,36] Recently, cobalt catalysts have been used in asymmetrical synthesis of pharmaceutically relevant compounds for instance (*S*)-PD172938 and (*S*)-pazinaclone. Cobalt catalysts with (*R*)-Salox-9 ligand have also been employed in enantioselective synthesis for the formation of chiral molecules, that are crucial for the synthesis of several drugs.[37] This review aims to provide a comprehensive outline of the applications of the cobalt catalysis towards natural product synthesis and pharmaceuticals, reported since 2018.

## 2 Cobalt-catalysis in total synthesis of natural products

### 2.1 Synthesis of alkaloids

**2.1.1. (±)-Monomorine.** (±)-Monomorine refers to the racemic mixture of indolizidine alkaloid type monomorine I, extracted from *Monomorium pharaonis*. Synthetic chemists have

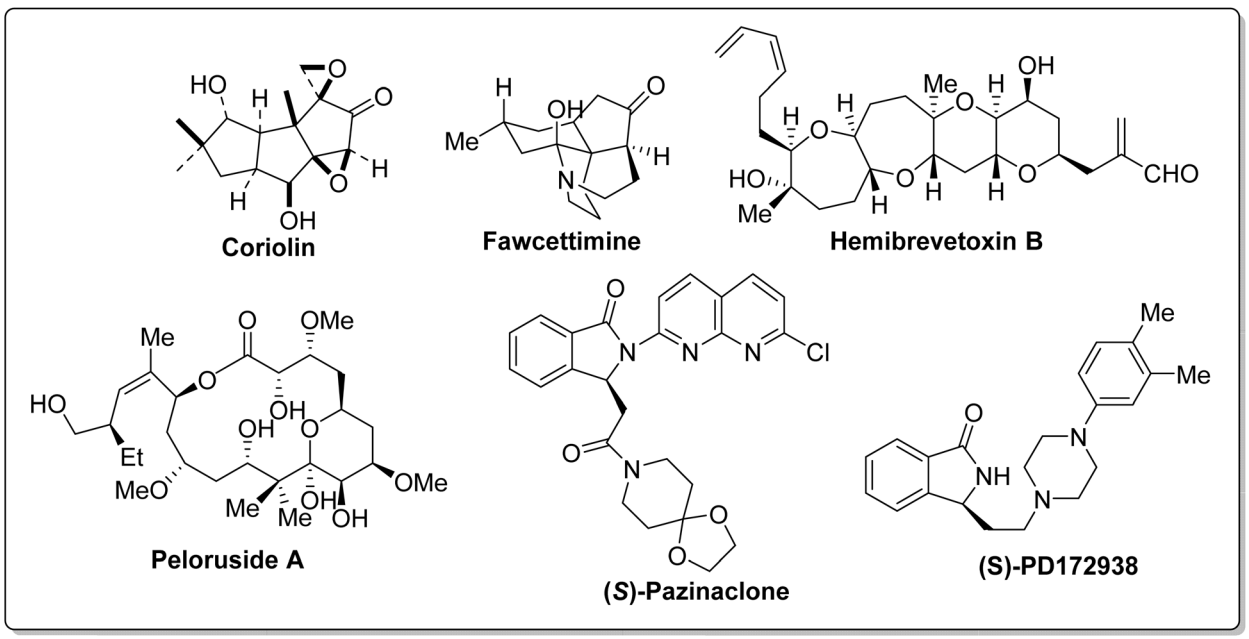
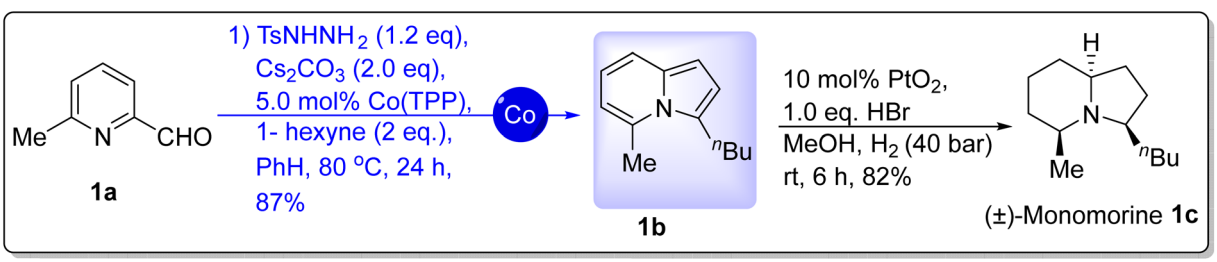



Fig. 2 Structures of few natural products and pharmaceuticals compounds synthesized by Co-catalysis.

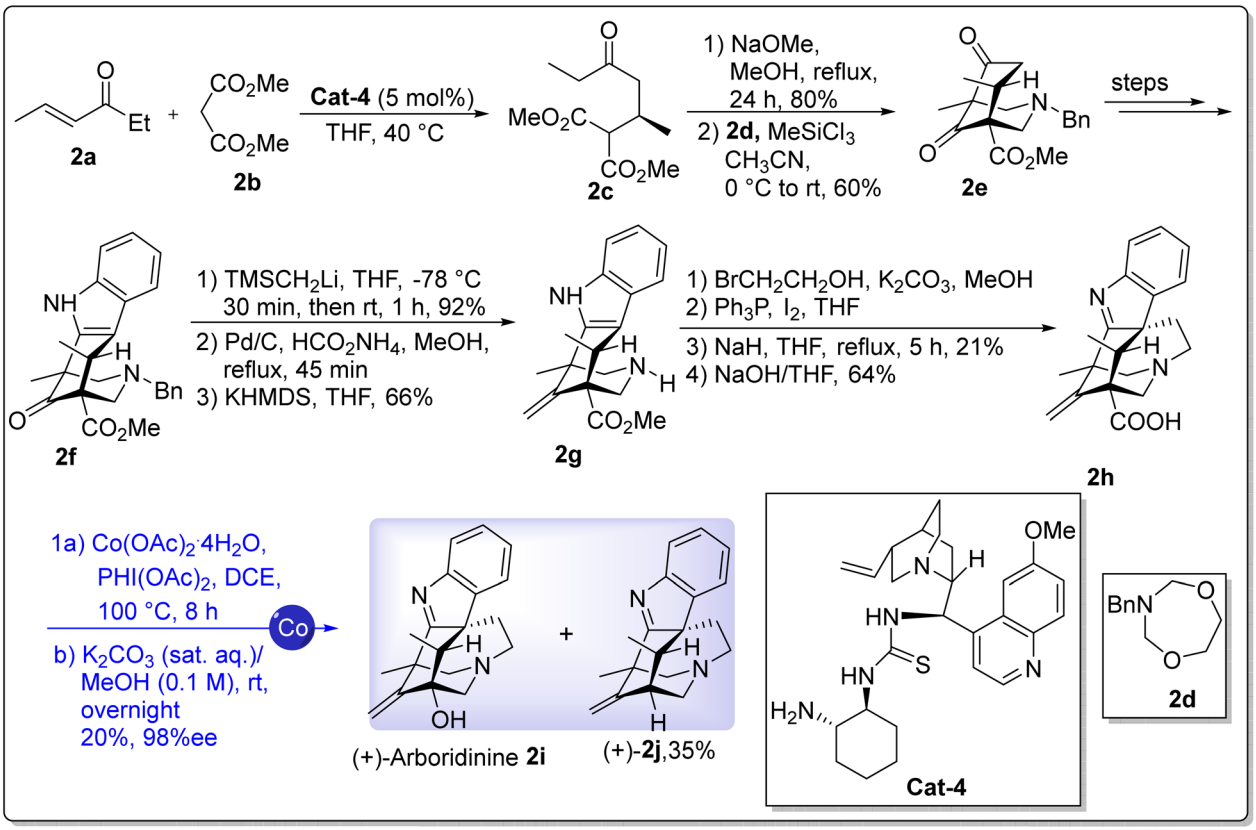
been interested in it for long time because it is biologically active pheromone and has challenging molecular architecture. Roy *et al.* in 2018, demonstrated short synthesis of (±)-monomorine started from commercially available compound **1a** which was subjected to a Co(II)-based metalloradical-catalyzed one-pot transannulation using Co(TPP) (5.0 mol%) under optimized conditions ($TsNHNH_2$ (1.2 equiv.), $Cs_2CO_3$ (2.0 equiv.), 1-hexyne (2.0 equiv.), PhH, 80 °C, 24 h). The *N*-tosylhydrazone in this reaction transformed the aldehyde group to 2-(diazomethyl)pyridine, which was subsequently activated by the Co(II) center to produce an α-Co(III)–carbene radical. A γ-Co(III)-vinyl radical was generated when this cobalt–carbene radical joined with the terminal alkyne. This radical then went through intramolecular radical cyclization to yield compound **1b** in 87% yield. TEMPO trapping and deuterium-labelling studies supported the radical mechanism, and Co(TPP) proved particularly effective because screening of other metal catalysts and metal–porphyrin complexes (Fe(TPP)Cl, Ni(TPP), Cu(TPP), and Pd(TPP)) produced no product. Compound **1b** was subsequently hydrogenated in methanol with platinum oxide and hydrobromic acid to produce (±)-monomorine **1c** in 82% yield[38] (Scheme 1).

**2.1.2. (+)-Arboridinine.** Arboridinine, a member of the Apocynaceae family, was isolated from the *Kopsia genus* of Malaysia in 2015 and is known for its unique pentacyclic structure. It belongs to the monoterpenoid indole alkaloid family, whose members are known for structural diversity. The specific biological properties of arboridinine itself remain unexplored due to limited material availability. Arboridinine possesses a sterically crowded pentacyclic indolenine framework bearing four contiguous stereocentres, two of which are quaternary, and a bridgehead tertiary alcohol. The molecule poses a significant synthetic challenge because of captivating structure coupled with its densely substituted cage system.[39–43] Zhang *et al.*[44] reported a 14-step enantioselective synthesis of (+)-arboridinine in 2019. The critical installation of the bridgehead hydroxyl at C11 relied on cobalt-catalyzed decarboxylative acetoxylation. Numerous alternatives including the Barton reaction, photoredox conditions, and Pb-, Ag-, Mn-, and CAN-mediated protocols failed at this sterically demanding bridgehead. The method employs $Co(OAc)_2 \cdot 4H_2O$ (10 mol%) with $PhI(OAc)_2$ as oxidant *via* a radical pathway: decarboxylative acetoxylation generates a bridgehead carbon radical intermediate, whose competitive hydrogen abstraction accounts for the formation deoxyarboridinine by-product. The employed cobalt involving route proved uniquely effective at the congested bridgehead where other decarboxylative methods failed. The synthesis commenced with organocatalytic asymmetric Michael addition of dimethyl malonate **2b** to enone **2a** (**Cat-4**, THF) to furnish enantioenriched ketone **2c**. Dieckmann condensation and stereoselective double-Mannich reaction afforded bicyclic ketone **2e** (60% yield), which was converted to ketone **2f** over a few steps. Next, Peterson olefination with $TMSCH_2Li$ delivered the silyl alcohol (92% yield), and subsequent debenzylation and KHMDS-mediated elimination furnished olefin **2g** (66% yield over 2 steps). *N*-Alkylation, iodination, and intramolecular dearomative annulation converted **2g** to the corresponding tetracyclic ester (21% over 3 steps), which upon saponification (NaOH, THF/MeOH, reflux, 12 h) afforded acid **2h** (64% yield). Treatment of **2h** with $Co(OAc)_2 \cdot 4H_2O$ (0.1 equiv.) and $PhI(OAc)_2$ (1.5 equiv.) in DCE at 100 °C, 8 hours, followed by saponification ($K_2CO_3$/MeOH), delivered (+)-arboridinine **2i** (20% yield, 98%ee) alongside deoxyarboridinine **2j** (35%) from competitive hydrogen abstraction of the bridgehead radical intermediate[44] (Scheme 2).

**2.1.3. Angustine and angustoline.** Angustine and angustoline are emblematic members of the indolopyridine alkaloids family, specifically classified within the Vallesiachotaman subclass of monoterpenoid indole alkaloids. These compounds were derived from *Strychnos angustiflora* Benth and they have gained significant attention due to their biological activities including antimalarial, antiinflammatory, renin inhibitory, antiviral and antiproliferative properties.[45–49] Peng *et al.* in 2020, have carried out the concise synthesis of these compounds, namely, angustine and angustoline, in five steps and six steps, respectively. The key reaction, cobalt-catalyzed carbonylative lactamization, formed the significant ring of the pentacycle. This reaction got failed by employing methyl chloroformate or dimethyl carbonate/*n*-BuLi system, resulting in decomposition or no reaction, and with the palladium-catalyzed carbonylation under CO. In this transformation, the catalytically active species is an alkylcobalt intermediate generated from $Co_2(CO)_8$ and ethyl chloroacetate. The synthesis began with 3,5-dibromo-4-methylpyridine **3a** which underwent esterification at –Me group to form **3b**, followed by aminolysis with tryptamine **3c**, and vinylation by the Suzuki reaction to form the amide **3d** in 51% overall yield, over three steps. The Bischler–Napieralski cyclization of **3d** with $POCl_3$ at 80 °C formed the enamide **3e** as inseparable isomers in 62%. The carbonylative cyclization of **3e** with $Co_2(CO)_8$, ethyl chloroacetate, and $K_2CO_3$ in MeOH at 60 °C




Scheme 1 Total synthesis of (±)-monomorine **1c** (adapted from ref. 38).

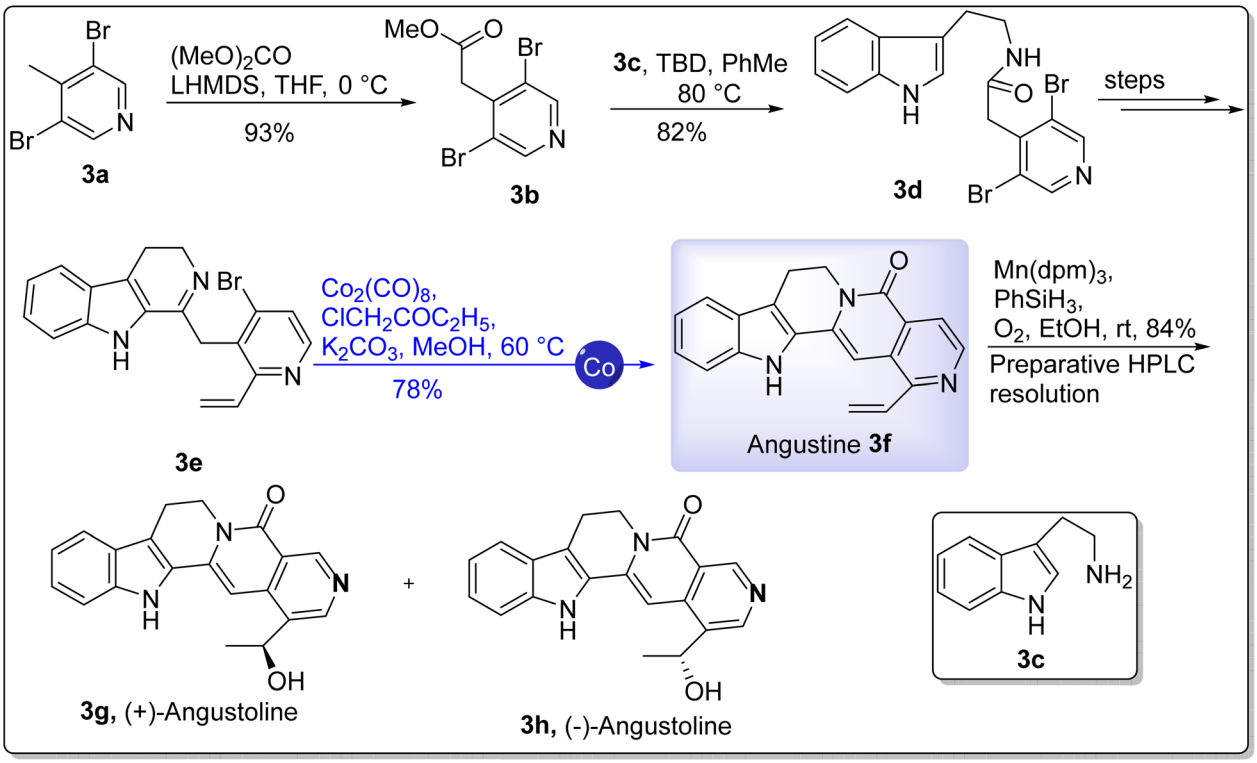



Scheme 2 Total synthesis of (+)-arboridinine **2i** (adapted from ref. 44).

formed the natural product angustine **3f**, in 78% yield. Mukaiyama hydration [$Mn(dpm)_3$, $PhSiH_3$, $O_2$, EtOH, r.t.] converted **3f** to (±)-angustoline in 84% yield, which was resolved by preparative HPLC to give (+)-angustoline **3g** and (−)-angustoline **3h**. The anti-Zika virus (ZIKV) inhibitory activity of (−)-angustoline ($IC_{50}$ = 68.67 μM) and (+)-angustoline ($IC_{50}$ = 17.91 μM) was also evaluated (Scheme 3).[50]

**2.1.4. Gusanlung D, 8-oxopseudopalmatine, and oxopalmatine.** Gusanlung D, 8-oxopseudopalmatine and oxopalmatine are all berberine alkaloids and vinylene incorporation through Co(III)-driven annulative process made it easy to synthesize these natural products. Li *et al.* in 2020, designed a three-step synthetic route to all three alkaloids, based on a Cp*Co(III)-catalyzed C–H annulation reaction with a vinylene carbonate. A KIE of 2.7 was indicative of C–H activation as a rate-determining step, and competitive experiments supported electrophilic C–H cyclocobaltation. The Co-catalyzed vinylene transfer ring-formation reaction involved the coordination of amide and cobalt followed by the formation of cyclocobaltation intermediate, vinylene carbonate insertion, reductive elimination, oxidative addition of the C–O bond to Cp*Co(I), and subsequent β-oxygen elimination to liberate $CO_2$ and regenerated Co(III). Compared to a related Rh(III) approach, this protocol was regioselective and applicable to acrylamides. Amide coupling of arylethylamine derivatives **4b** and **4g** with benzoic acids **4a**, **4h**, and **4i** using HOBt, EDCI, $Et_3N$, $CHCl_3$ conditions furnished the corresponding benzamides **4c**, **4j**, and **4k** respectively. C–H functionalization of **4c**, **4j**, and **4k** using Cp*Co(III)-catalyzed C–H annulation conditions *i.e.*, [Cp*Co(CO)$I_2$] (10 mol%), $AgSbF_6$ (20 mol%), $Zn(OAc)_2$ (5 mol%), TFE, at 100 °C for 24–48 h provided the isoquinolinones **4e**, **4l**, and **4m** respectively in a regioselective manner. The significant intermediate **4e** afforded gusanlung D **4f** over few steps,[51] while **4l** and **4m** underwent intramolecular Heck cyclization (Pd $(OAc)_2$, TBAB, $K_2CO_3$, DMF, 120 °C, 24 h) to forge the tetracyclic protoberberine framework, delivering 8-oxopseudopalmatine **4n** (45%) and oxopalmatine **4o** (81%) respectively (Scheme 4).[52]

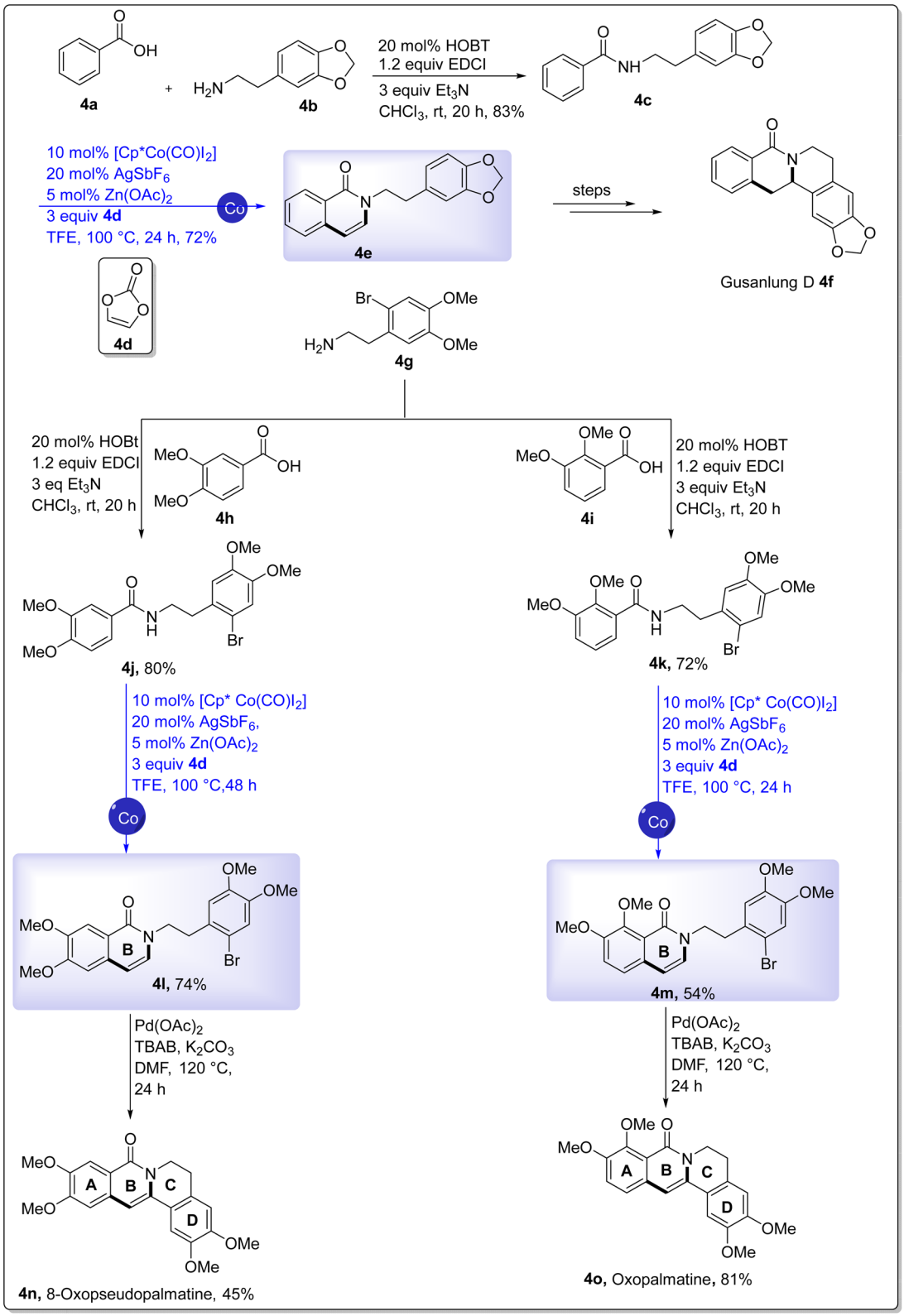
**2.1.5. Norzoanthamine and zoanthenol.** Among the various zoanthamine alkaloids derived from marine zoanthids, norzoanthamine and zoanthenol represent particularly significant discoveries. Norzoanthamine was first isolated by the research group of Uemura in the mid-1990s from colonies of the genus Zoanthus, collected near the Amami Islands, Japan.[53–57] The molecule showed promising therapeutic potential in the fight against bone deterioration and was effective in preventing skeletal weakening in experimental mouse models.[58] Chen *et al.* (2023) described the asymmetric total synthesis of norzoanthamine (**5j**) and the formal synthesis of zoanthenol (**5k**) *via* the use of radical reactions to form the complex core structure. The synthesis was initiated with the use of chiral ketone **5a**, which was obtained from (*S*)-(+)-carvone. The compound **5a** was subjected to hydroxymethylation with DBU and aqueous formaldehyde in THF to produce compound **5b** in 62% yield as the sole




Scheme 3 Total synthesis of angustine **3f**, (+)-angustoline **3g** and (−)-angustoline **3h** (adapted from ref. 50).

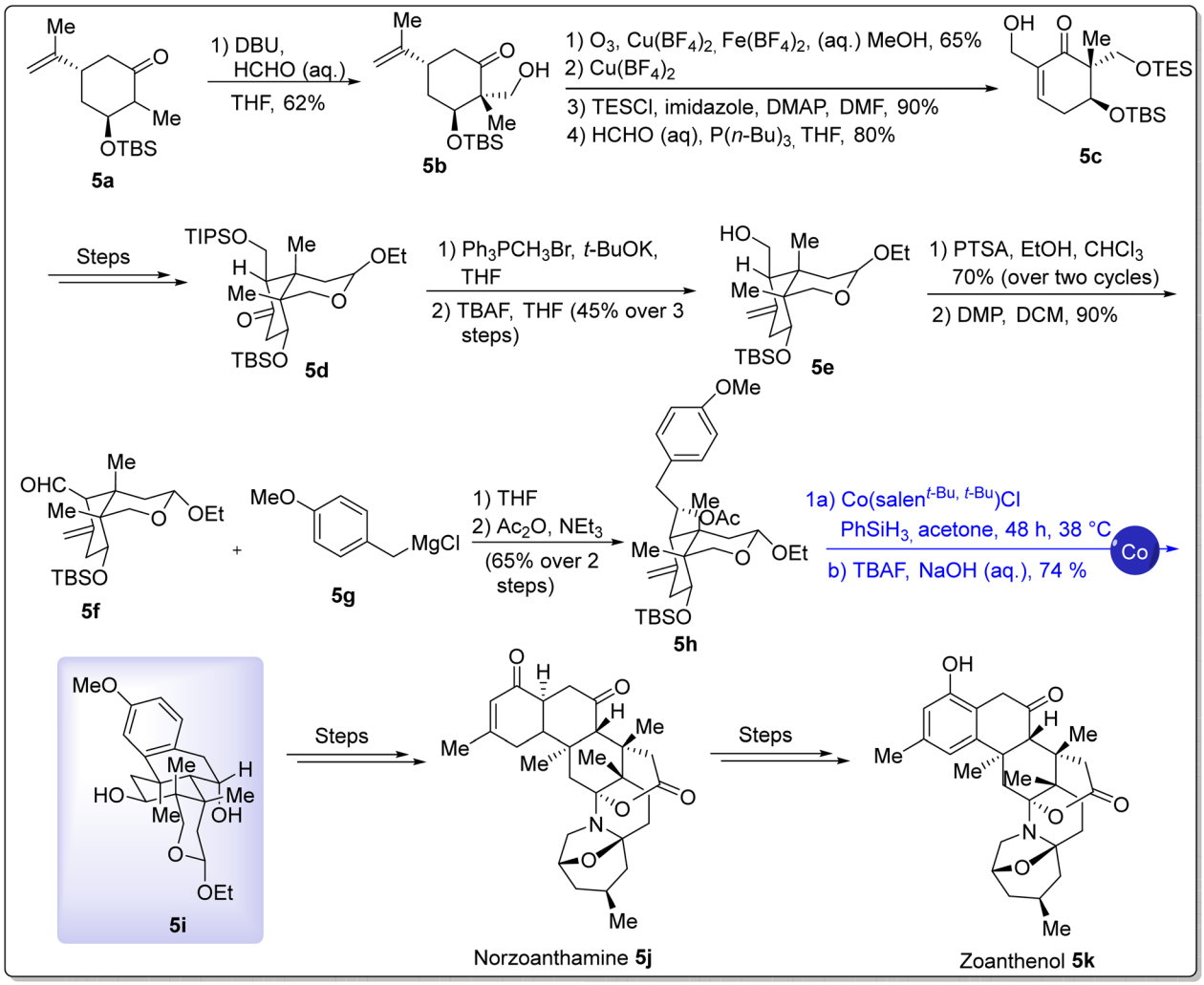
diastereomer. Ozonolysis and subsequent $Cu(BF_4)_2/Fe(BF_4)_2$-mediated fragmentation provided the corresponding enone in 65% yield, which after TES protection (90%) and Baylis–Hillman hydroxymethylation (80%) afforded enone **5c**. A series of reactions provided the bicyclic intermediate **5d**. Wittig olefination and subsequent TIPS removal provided alcohol **5e** in 45% yield. Next, PTSA-mediated isomerization was followed by Dess–Martin oxidation to provide the corresponding aldehyde **5f** in 90% yield. Addition of Grignard reagent **5g** to **5f**, followed by acetylation with $Ac_2O$ and $NEt_3$, provided ester **5h** in 65% yield over two steps. In the key step of the synthesis, the cobalt-catalyzed HAT radical cyclization was performed by treating **5h** with Co(salen$^{t\text{-Bu},t\text{-Bu}}$)Cl and $PhSiH_3$ in anhydrous acetone at 38 °C to provide the C-12 all-carbon quaternary center *via* the intramolecular $Csp^3$–$Csp^2$ radical cyclization, assembling the A–B–C ring system. The one-pot sequence, including subsequent treatment with TBAF and aqueous NaOH, provided diol **5i** in 74% yield as the sole diastereomer. This approach drew on Shenvi's cobalt-catalyzed radical hydroalkylation and Gao's HAT chemistry in the synthesis of viridin. A series of reactions were performed to achieve the total synthesis of norzoanthamine (**5j**). Zoanthenol (**5k**) was obtained *via* the formal synthesis method by using the established seven-step protocol by Miyashita's group to convert norzoanthamine hydrochloride (Scheme 5).[59]

**2.1.6. (*S*)-Norlaudanosine, (*S*)-xylopinine, (*S*)-laudanosine, (*S*)-sebiferine, (*S*)-cryptostyline II, (+)-solifenacin, FR115427 and (+)-NPS R-568.** Tetrahydroisoquinolines represent one of the most significant classes of alkaloids, chiral 1-substituted THIQ frameworks appear widely across natural products, drug molecules, and bioactive substances.[60–63] Their pharmacological relevance is exemplified by compounds such as (*S*)-cryptostylines, dopamine receptor D1 probes,[64–66] and solifenacin, a clinically used antispasmodic drug.[67] Wu *et al.* in 2023, synthesized THIQ alkaloids *i.e.*, (*S*)-xylopinine, (*S*)-sebiferine, (*S*)-cryptostyline II, (*S*)-norlaudanosine, (*S*)-laudanosine as well as asymmetrically constructed the intermediates, potentially leading towards (+)-NPS R-568, (+)-solifenacin and FR115427. They demonstrated that Co(II)-catalyzed enantioselective C–H/N–H annulation reactions between benzylamine picolinamides and alkynes proved as the chirality-inducing step. This formal (4 + 2) annulation employs $Co(OAc)_2\cdot 4H_2O$ (10 mol%) and a chiral salicyloxazoline (Salox) ligand (15 mol%), $Mn(OAc)_2\cdot 4H_2O$ (20 mol%) as the oxidizing agent, and $PivONa\cdot H_2O$ (50 mol%) in MeOH under $O_2$. Careful optimization of the reaction parameters suppresses competing dehydrogenative aromatization that would otherwise erode the C1 stereogenic center. The Co/Salox system also presented an environmentally friendly alternative to the use of precious metals such as Rh and Pd, and the reactions are successful with both electron-donating and electron-withdrawing substituents as well as heteroaromatic rings, operating on gram scale *via* desymmetrization and kinetic resolution with excellent enantioselectivities (up to 98% yield, >99%ee). The total synthesis commenced from **6a** which was subjected to C–H annulation reaction with trimethylsilylacetylene **6r** using $Co(OAc)_2\cdot 4H_2O$ (10 mol%), (*R*,*S*)-**L2** (15 mol%), $Mn(OAc)_2\cdot 4H_2O$ (20 mol%), $PivONa\cdot H_2O$ (50 mol%), MeOH, $O_2$ at 60 °C for 12 h to afford $C_1$-chiral 1,2-dihydroisoquinoline **6b** in 49% yield and 98%ee on a 5.0 mmol




Scheme 4 Total synthesis of gusanlung D **4f**, 8-oxopseudopalmatine **4n**, and oxopalmatine **4o** (adapted from ref. 52).

scale (1.42 g). Desilylation followed by hydrogenation using Pd/C, $H_2$, MeOH at 50 °C afforded **6c** in 62% yield with >99%ee, from which $PA_6$ was removed using $LiAlH_4$ in THF to give (*S*)-norlaudanosine **6d** in 71% yield with 99%ee. From **6d**, cyclization using formaldehyde and formic acid afforded (*S*)-xylopinine **6e** in 81% yield with 98%ee, while reductive amination




Scheme 5 Total synthesis of norzoanthamine **5j** and zoanthenol **5k** (adapted from ref. 59).

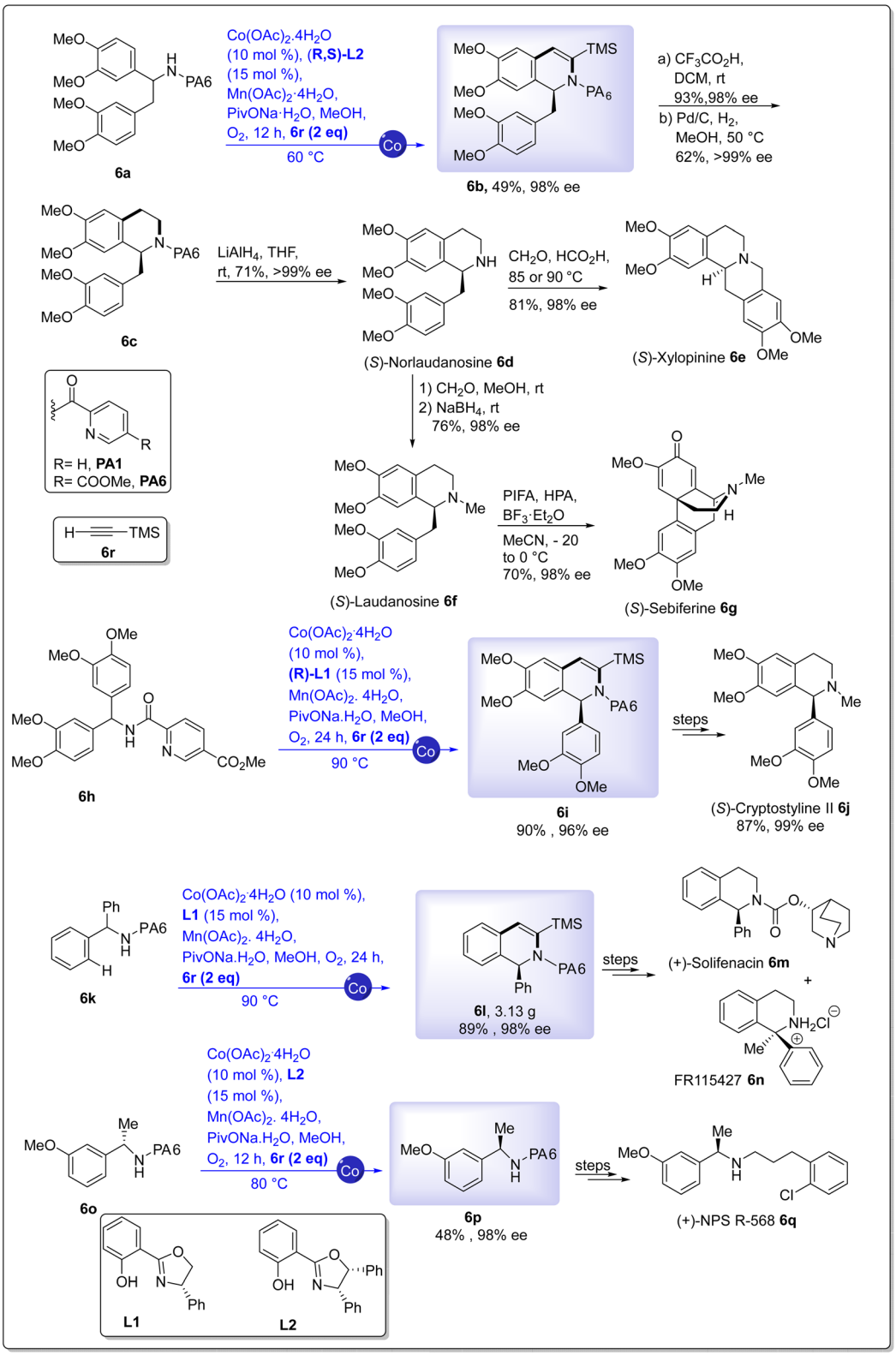
using $CH_2O$ and $NaBH_4$ afforded (*S*)-laudanosine **6f** in 76% yield with 98%ee. Oxidative cyclization of **6f** using PIFA, HPA, $BF_3 \cdot Et_2O$, MeCN afforded (*S*)-sebiferine **6g** in 70% yield with 98%ee. Desymmetrization of **6h** using **6r** was conducted by employing $Co(OAc)_2 \cdot 4H_2O$, (*R*)-**L1** to afford **6i** in 90% yield with 96%ee (1.52 g); sequential desilylation, hydrogenation, $PA_6$ removal, and *N*-methylation delivered (*S*)-cryptostyline II **6j** in 99%ee. Similarly, desymmetrization of **6k** with **6r** using (*R*)-**L1** gave **6l** in 89% yield with 98%ee (3.13 g), a common precursor for (+)-solifenacin **6m** and FR115427 **6n**. Finally, kinetic resolution of **6o** ((*R*,*S*)-**L2**, 80 °C) recovered **6p** in 48% yield with 98% ee (1.50 g), from which $PA_6$ removal afforded the precursor (58%, 99%ee) for (+)-NPS R-568 **6q** (Scheme 6).[68]

**2.1.7. (±)-Halichonine B.** Halichonine B, a sesquiterpene alkaloid extracted from the sponge *Halichondria okadai*, exhibits a C($sp^3$) rich framework characterized by unique quaternary methyl substitution. Biologically, halichonine B demonstrates potent cytotoxicity, notably triggering apoptosis in HL60 leukemia cells, highlighting its promise as an anticancer lead.[69–71] Yoshimura *et al.* in 2025 reported the total synthesis of (±)-halichonine B. A cobalt-catalyzed hydrocyanation served as the key C–CN bond-forming transformation. Starting from ethyl isobutyrate **7a**, C-alkylation and $LiAlH_4$ reduction afforded alcohol **7b**. Cobalt-catalyzed radical hydrocyanation (**Cat-5**, TsCN, $PhSiH_3$, EtOH, rt, 3 h) then delivered the branched nitrile **7c** with high regiocontrol (73%, 2 steps). Next, transformation of **7c** into **7d**, followed by DIBAL-H reduction and Corey–Fuchs reaction led to the synthesis of 1,1-dibromoalkene **7e** (87%, 2 steps). Cyano reduction and Horner–Wadsworth–Emmons olefination converted **7e** to dibromide **7f**, and treatment of **7f** with $Me_2CuLi$ ($Et_2O$, −78 to −20 °C) afforded bicyclic ester **7g** (83%). Bicyclic ester was treated over several steps to deliver final compound (±)-halichonine B **7h** (Scheme 7).[72]

## 2.2 Synthesis of terpenoids/diterpenoids

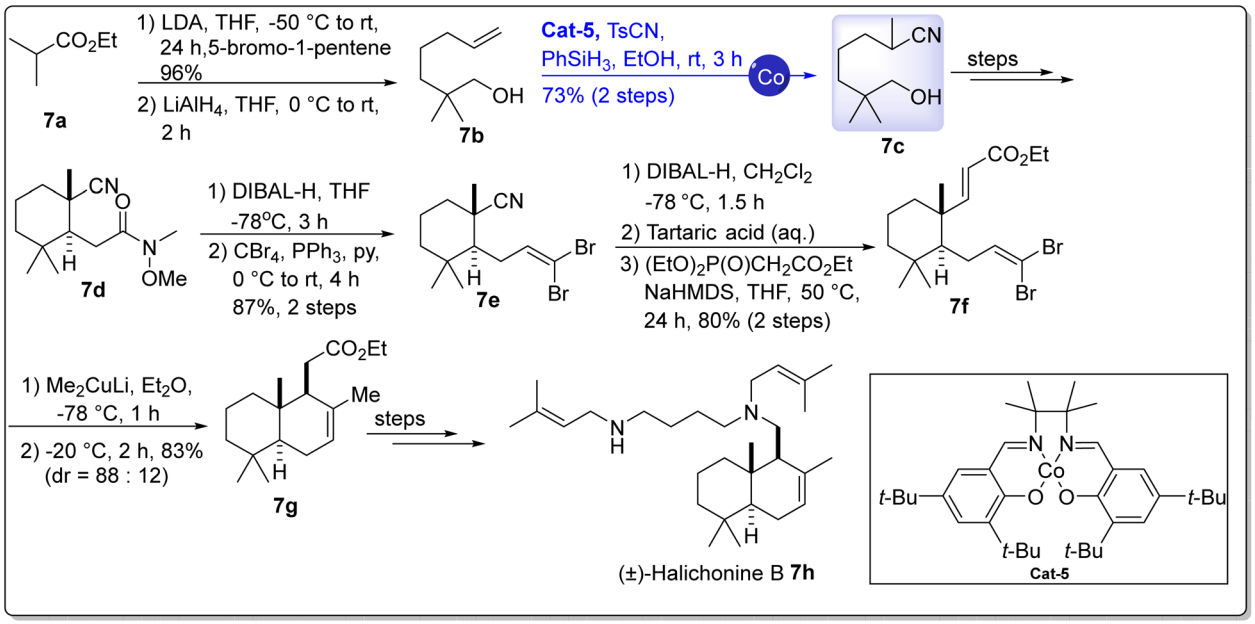
**2.2.1. Brasilicardins.** Brasilicardins A–D are diterpenoid metabolites produced by the actinomycete *Nocardia brasiliensis* IFM 0406. They show a variety of biological activities such as potent immunosuppressive activity ($IC_{50}$ = 0.05 nM).[73–75] Yoshimura *et al.* in 2018 reported the total synthesis of brasilicardins A–D constructing tricyclic ester **8g** as the common




Scheme 6 Total synthesis of (*S*)-norlaudanosine **6d**, (*S*)-xylopinine **6e**, (*S*)-laudanosine **6f**, (*S*)-sebiferine **6g**, (*S*)-cryptostyline II **6j**, (+)-solifenacin **6m**, FR115427 **6n** and (+)-NPS R-568 **6q** (adapted from ref. 68).

intermediate for all four congeners. From diol **8a**, monosilylation, Swern oxidation, and HWE olefination afforded ester **8b** (96%, two steps), which was treated over several steps to terminal alkene **8c**. Cobalt-catalyzed hydrocyanation using Co(II) catalyst **Cat-5**, $PhSiH_3$, TsCN, and 2,6-di-*tert*-butylpyridine in ethanol converted **8c** to secondary nitrile **8d** (99%, three

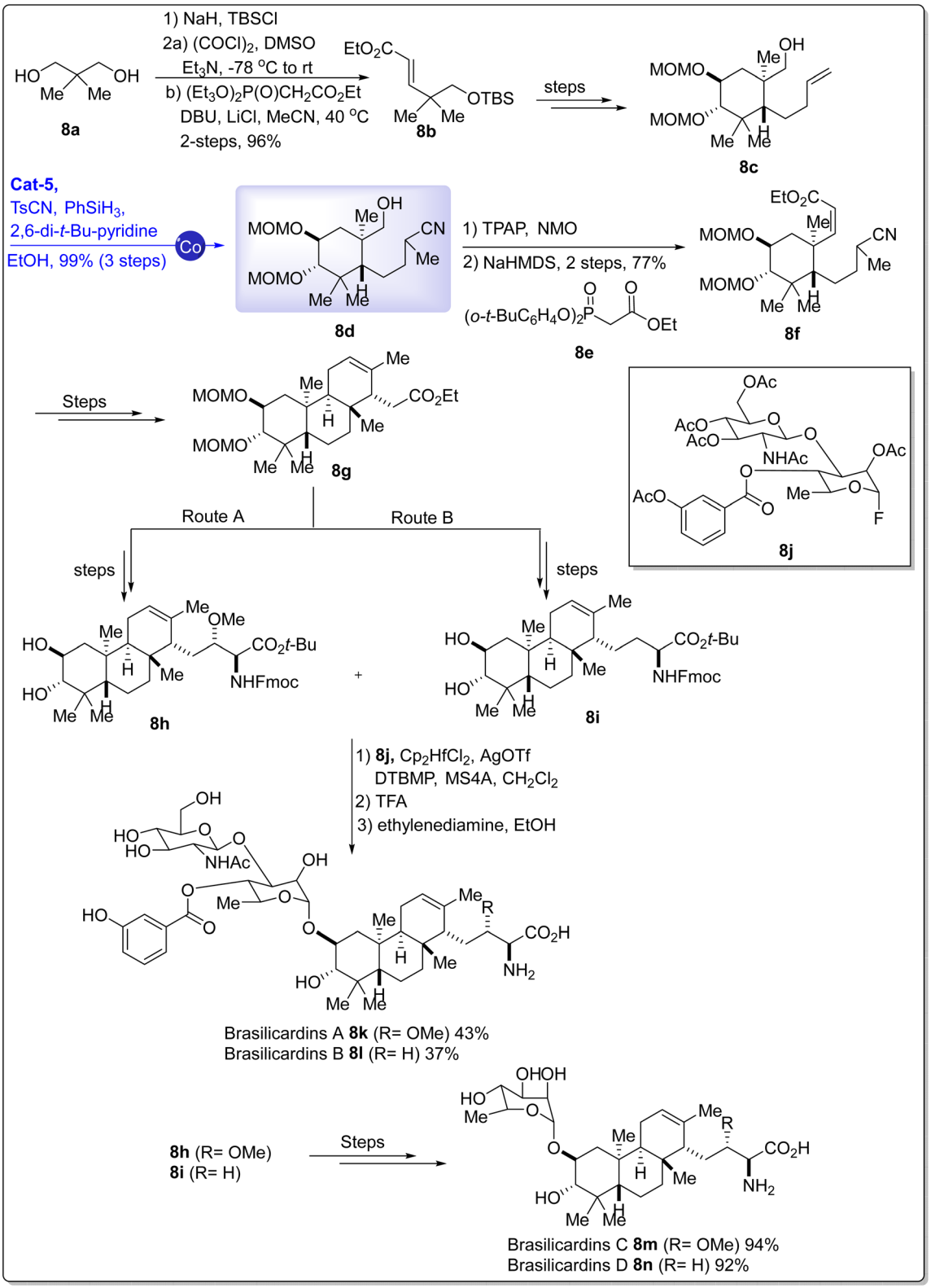



Scheme 7 Total synthesis of halichonine B **7h** (adapted from ref. 72).

steps). Oxidation of **8d** with TPAP/NMO followed by Z-selective HWE olefination employing **8e** provided (*Z*)-α,β-unsaturated ester **8f** (77%, two steps). Next, **8f** was converted to tricyclic ester **8g**, from which, two routes installed the amino acid component: route A gave β-methoxy-substituted **8h**; route B gave **8i**. Glycosylation of **8h** or **8i** with glycosyl donor **8j** ($Cp_2HfCl_2$, AgOTf) followed by global deprotection provided brasilicardins A **8k** (43%) and brasilicardins B **8l** (37%), while analogous sequences yielded brasilicardins C **8m** (94%) and D **8n** (92%) (Scheme 8).[76]

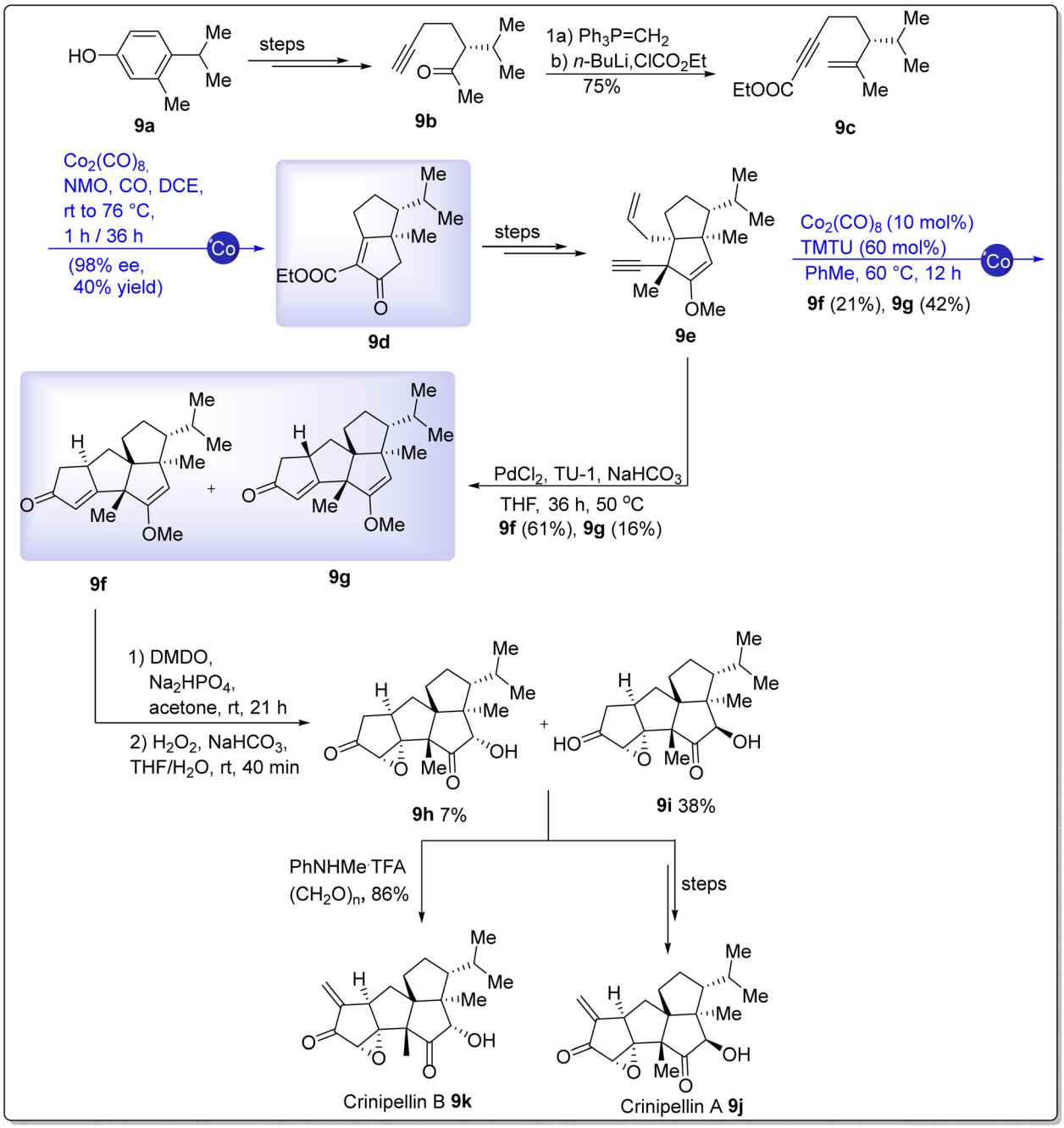
**2.2.2. Crinipellins.** In 1979, Steglich and coworkers discovered a number of analogous diterpenoids including crinipellin A from the *Crinipellis stipitaria*.[77,78] Crinipellin A and crinipellin B exhibit antibiotic properties along with a potential to suppress the syntheses of proteins, DNA and RNA in Ehrlich carcinoma cells. The α-methylene ketone functionality marks these natural products as candidate irreversible chemical probes in medicinal chemistry.[79–84] Huang *et al.* (2018) achieved asymmetric total synthesis of (−)-crinipellin A **9j** and (−)-crinipellin B **9k** in 17 and 18 steps, respectively, using two intramolecular Pauson–Khand (PK) reactions to construct the tetraquinane core. Phenol **9a** was converted over several steps to ketone **9b**, whose Wittig olefination and acylation (*n*-BuLi, $ClCO_2Et$) gave enyne ester **9c** (75%). Stoichiometric PK reaction of **9c** [$Co_2(CO)_8$ (1.05 equiv.), NMO (3.5 equiv.), CO (balloon), DCE, rt to 76 °C] afforded ketoester **9d** (40%, 98%ee after crystallization). This first PK reaction employed stoichiometric $Co_2(CO)_8$ with NMO to build the CD ring required precomplexation at room temperature which was gradually increased to 76 °C as $Co_2(CO)_8$ complexation is sluggish owing to the low electron density of the alkyne. The ketoester **9d** gave enyne **9e** over a number of steps, followed by catalytic PK reaction [$Co_2(CO)_8$ (10 mol%), TMTU (60 mol%), PhMe, 60 °C, CO (1 atm), 12 h] to furnish **9f** (21%) and C2 epimer **9g** (42%). Thus, the second catalytic $Co_2(CO)_8$/TMTU PK reaction was established which gave only 21% of the desired diastereomer, prompting a switch to a Pd-catalyzed protocol (61%). Epoxidation of **9f** with **9g** (DMDO/$Na_2HPO_4$, then $H_2O_2$/$NaHCO_3$) gave **9h** (7%) and **9i** (38%), which was followed by its advancement to crinipellin A **9k** (86%) crinipellin B **9j** (74%), respectively (Scheme 9).[85]

**2.2.3. (+)-Haperforin G.** (+)-Haperforin corresponds to structurally distinctive member of the limonoid family of tetranortriterpenoids, it was first isolated from the *Harrisonia perforata*, a plant rich in diverse bioactive limonoids.[86–90] It exhibits potent therapeutic activity as a selective inhibitor of human 11β-hydroxysteroid dehydrogenase type 1 ($IC_{50}$ = 0.58 μM), presenting a promising therapeutic strategy for managing metabolic disorders such as Alzheimer's disease, vascular inflammation, cardiovascular disease and glaucoma.[91] Its structural complexity and limited natural availability highlighted the importance of efficient synthetic development. Zhang *et al.* in 2020, accomplished a 20-step asymmetric total synthesis of (+)-haperforin G. A cobalt-mediated cyclisation served as the pivotal transformation, forging the cyclopentanone ring endowed with C10 all-carbon quaternary stereocenter (at bridgehead position) in a single operation. Optimization showed that stoichiometric $Co_2(CO)_8$ at 0.1 M afforded only 40% yield, whereas catalytic loading (20 mol%) at 0.01 M under CO balloon pressure raised the yield to 86% (d.r. > 20 : 1). The synthesis began with the formation of triol **10c** from commercially available 3-methylbut-3-enoic acid **10a** and alkyne **10b** over a number of steps. Successive transformations including silylation (TBSCl/imidazole (95%)), desilylation (KHMDS/TMSCl (89%)), TPAP/NMO oxidation (89%), and Wittig olefination (87%) converted **10c** to enyne **10d**. In the key cobalt step, **10d** was treated with $Co_2(CO)_8$ (20 mol%) in toluene




Scheme 8 Total synthesis of brasilicardins A **8k**, brasilicardins B **8l**, brasilicardins C **8m**, brasilicardins D **8n** (adapted from ref. 76).

(0.01 M) under CO (1 atm) at 110 °C for 36 h, affording PK product **10e** in 86% yield (d.r. > 20 : 1) (Scheme 10). Further treatment of **10e** over several steps gave enone **10f**. Separately, (+)-MIB (**Cat-6**)-mediated addition of vinyl zinc **10h** to aldehyde **10g** afforded allylic alcohol **10i** (93%, 99.5%ee) which was transformed to iodolactone **10j**, over a few steps. Photoredox

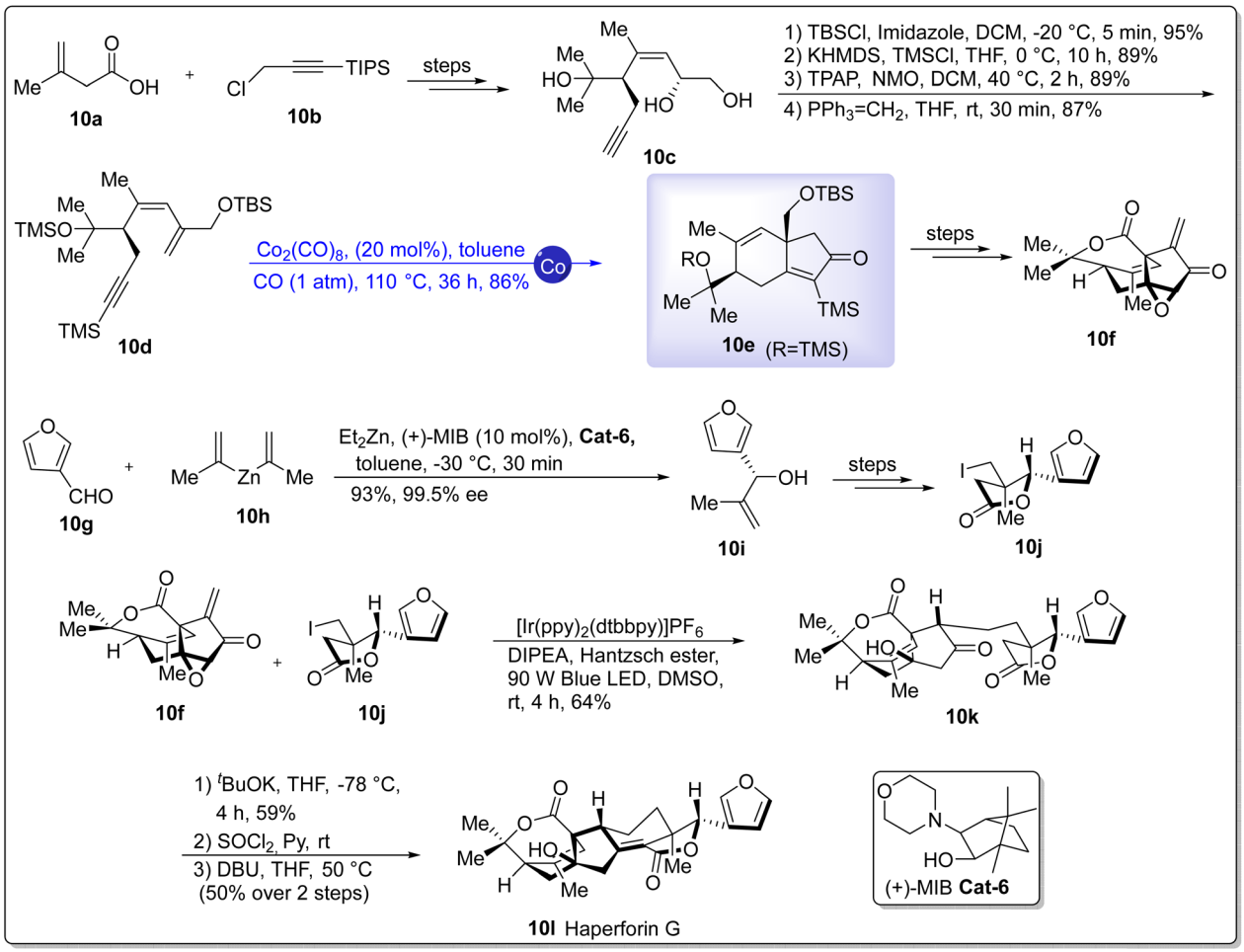



Scheme 9 Total synthesis of crinipellin A **9j** and crinipellin B **9k** (adapted from ref. 85).

coupling of **10f** and **10j** with $[Ir(ppy)_2(dtbbpy)]PF_6$ (2.5 mol%), DIPEA, and Hantzsch ester (90 W blue LED, DMSO) delivered **10k** as a single diastereoisomer (64%). Treatment of **10k** with *t*-BuOK (THF, −78 °C), followed by $SOCl_2$/pyridine and DBU, furnished (+)-haperforin G (**10l**) in 50% overall yield (Scheme 10).[92]

**2.2.4. (+)-Waihoensene.** Waihoensene possesses a densely functionalised *cis*-fused [6.5.5.5] tetracyclic framework featuring an angular triquinane motif, six consecutive stereocenters, four of them quaternary, and no heteroatom functionality.[93] It was first isolated by Weavers and co-workers in 1997 from *Podocarpus totara* var. *waihoensis*, a podocarp native to New Zealand.[94–96] Two total syntheses of (+)-waihoensene have been reported to employ an intramolecular cobalt-mediated Pauson–Khand (PK) reaction as the pivotal step to construct the angular triquinane core with its contiguous quaternary stereocenters. Qu *et al.* (2020) completed the synthesis in 15 steps and 3.8% overall yield, whereas Rosenbaum *et al.* (2021) achieved it in 14 steps (racemic) or 19 steps (enantioselective). In the Qu route, enyne **11e** was subjected to $Co_2(CO)_8$ under $N_2O$ (1 atm) in DCE at 80 °C for 22 h, affording tetracyclic enone **11f** in 59% yield with 93%ee. Alternative

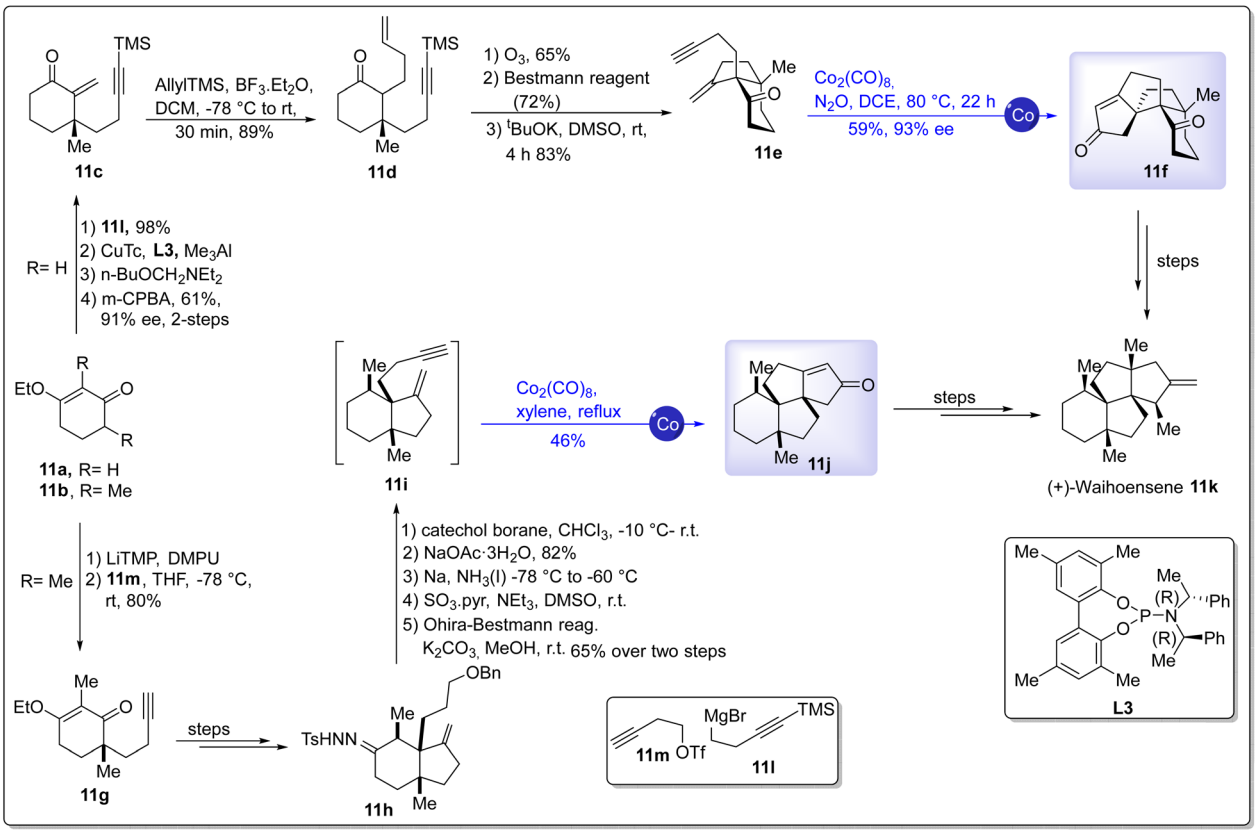
 




Scheme 10 Total synthesis of haperforin G **10l** (adapted from ref. 92).

promoters (TMANO, NMO, TMTU) and catalysts ($PdCl_2$/TMTU, $[Rh(CO)_2Cl]_2$) gave only 22–38% yield, underscoring the advantage of $N_2O$ in this sterically congested cyclization. In the Rosenbaum route, PK precursor **11i** was treated with stoichiometric $Co_2(CO)_8$ in refluxing xylene to furnish **11j** in 46% yield. In both cases, $Co_2(CO)_8$ first forms a cobalt–alkyne complex, followed by intramolecular alkene insertion and CO migratory insertion, thereby resulting in well-established (+)-waihoensene's framework. The Qu approach provides a higher-yielding PK step, whereas the Rosenbaum route utilizes the concise synthetic route through a radical cyclization/thermal PK strategy. In the Qu synthesis, enone **11a** (R = H) was converted to **11c** *via* Grignard addition of **11l** (98%) and Cu-catalyzed asymmetric conjugate addition (CuTc, **L3**, $Me_3Al$, *n*-$BuOCH_2NEt_2$) with *m*-CPBA oxidation (61%, 91%ee, two steps). Sakurai allylation of **11c** afforded **11d** (89%) followed by ozonolysis (65%), Ohira–Bestmann homologation (72%), and *t*-BuOK-mediated Conia-ene cyclization (83%), which resulted in enyne **11e**. The PK reaction of **11e** with $Co_2(CO)_8$ and $N_2O$ delivered tetracyclic enone **11f** (59%, 93%ee) which was converted to the natural product *i.e.*, (+)-waihoensene **11k** (90%, final step). In the Rosenbaum synthesis, alkylation of **11b** (R = Me) with homopropargylic triflate **11m** (LiTMP, DMPU, THF) afforded **11g** (80%). Radical cyclization of **11g** proceeded by epimerisation, and hydrazone formation gave **11h**, which was converted to enyne **11i** *via* catechol borane reduction (82%), Birch reduction (Na, $NH_3$(l)), Parikh–Doering oxidation ($SO_3$·pyr, $NEt_3$, DMSO), and Ohira–Bestmann alkynylation ($K_2CO_3$, MeOH, 65% over two steps). The PK reaction of **11i** with $Co_2(CO)_8$ in refluxing xylene furnished tetracyclic enone **11j** (46%). α-Alkylation (LiTMP, DMPU, then MeI; 63%), 1,4-addition of methyl cuprate (MeLi, CuCN, $BF_3{\cdot}OEt_2$; 70%) of **11j** followed by Wittig olefination ($Ph_3PCH_2Br$, KO*t*Bu, PhMe, 110 °C; 91%) completed (+)-waihoensene **11k** (Scheme 11).[97,98]

**2.2.5. (±)-Cephanolides A–D.** The benzenoid cephanolide diterpenoids (A–D) were first isolated by Yue and co-workers from *Cephalotaxus sinensis* in 2017.[99] Their intricate frameworks, closely similar to harringtonolide and fortalpinoid G, are significantly renowned for their potent biological activities *i.e.*, antitumor, antiviral and plant growth inhibitory properties[100–102] In 2021, Haider *et al.* demonstrated the total synthesis of (±)-cephanolides A–D *via* concise synthetic approach. The synthesis began with 7-hydroxy-4-methylindanone **12a**, which was used to form indanone–pyrone **12b** *via* triflation and Pd-catalyzed subsequent Suzuki couplings with **12l** and **12m** (80%, two steps). Enol ether formation and subsequent Diels–

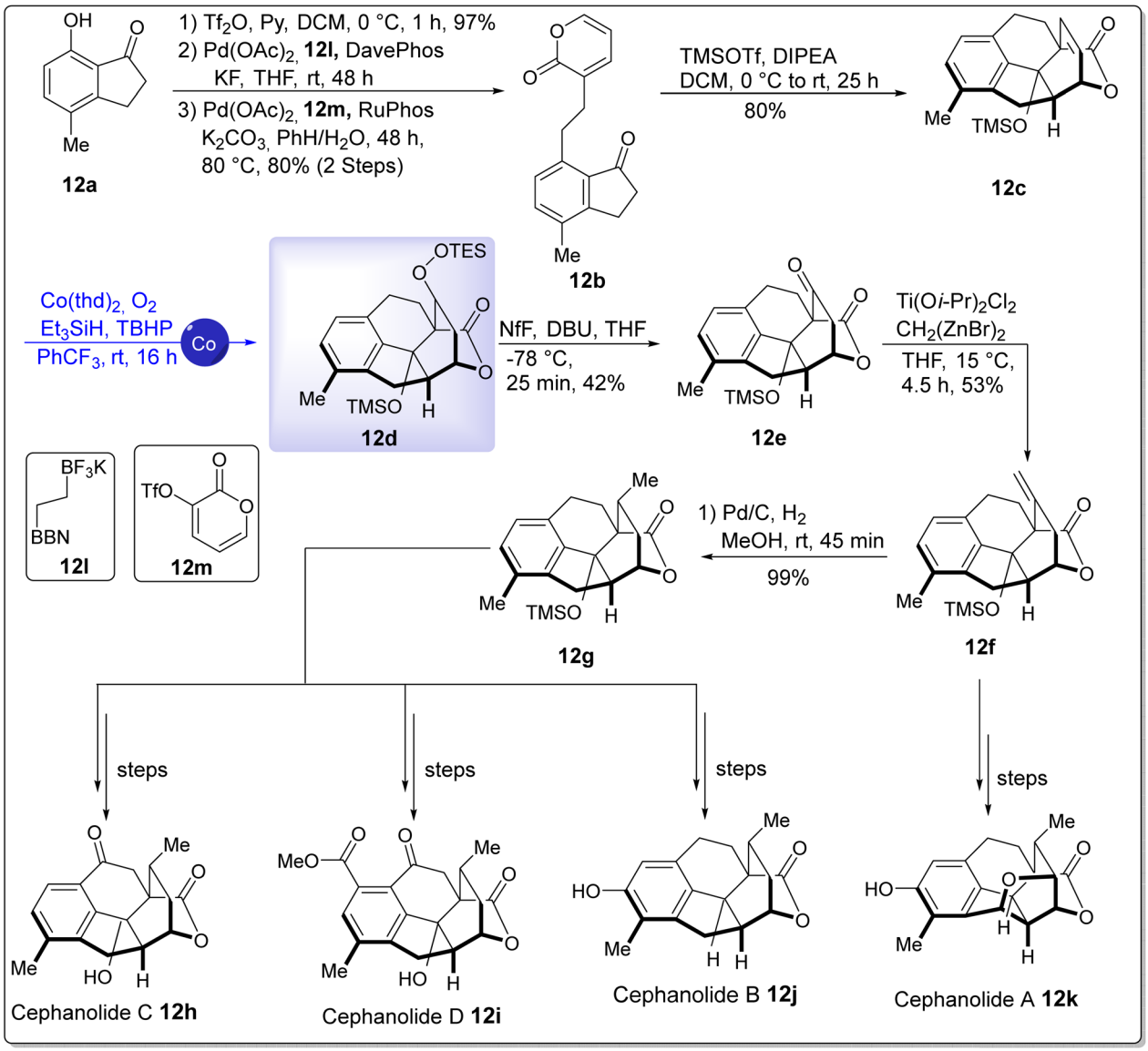



Scheme 11 Total synthesis of (+)-waihoensene **11k** (adapted from ref. 97 and 98).

Alder cycloaddition (TMSOTf, DIPEA, DCM, 80%) gave **12c** as a single diastereomer. Radical hydration ($Co(thd)_2$, $O_2$, $Et_3SiH$, TBHP, $PhCF_3$, r.t.) afforded **12d**. This cobalt-catalyzed step was used to reduce the electron-deficient bridging olefin in **12c**. Standard electrophilic functionalization (hydroboration, epoxidation) proved ineffective on this olefin, whose reactivity is suppressed by the adjacent lactone functionality. The peroxide **12d** was converted to ketone **12e** (NfF, DBU, THF, −78 °C, 42%). Subsequent olefination ($Ti(O\textit{i}\text{-}Pr)_2Cl_2$, $CH_2(ZnBr)_2$, 53%) gave **12f** which was succeeded by hydrogenation (Pd/C, $H_2$, 99%, d.r. > 20 : 1) to give **12g**. Divergent sequences from **12g** furnished cephanolides C (**12h**), B (**12j**), D (**12i**) and A (**12k**) over a number of steps (Scheme 12).[103]

**2.2.6. Plebeianiol A.** Plants of the *Salvia genus* are renowned for producing a wide variety of biologically active abietane-type diterpenoids,[104,105] which are recognized for their diverse molecular architecture and notable pharmacological potentials, for instance antioxidants[106] and anti-inflammatory activities.[107,108] A noteworthy advancement occurred in 2015, when Liang, Wu, and coworkers identified an important abietane diterpenoid which was previously unknown, designated as Plebeianiol A, from *Salvia plebeia* R. Br. The compound denotes a novel structural framework and biochemical evaluation revealed that it has free-radical scavenging capacity and demonstrated inhibitory effects on ROS generation and NO production.[109] A novel 11-step synthesis of the natural product plebeianiol A, along with its revision, was also carried out by Johnson *et al.* in 2021, with an overall yield of 13%, utilizing cobalt-catalyzed MHAT-induced radical bicyclization, which afforded the tricyclic core of the natural product in one step, drawing on precedent from cationic biogenetic annulations towards abietanes synthesis. This reaction is compatible with highly oxygenated substrates, including unprotected diols. The ozonolysis of 4-pentenenitrile **13a**, followed by the Wittig reaction, afforded the acrylate ester **13b** in 61% which was transformed into **13c** over few steps. Bicyclization of **13c** with Co(II) catalyst **Cat-5**, TMDSO, DTBP, and oxidant (3 equiv.), in the presence of HFIP at room temperature, afforded the tricyclic nitrile **13d** in 78% yield, 1 : 1 dr. DIBAL-H reduction, followed by $NaBH_4$ reduction, afforded carbinol **13e** in 85% yield over two steps in conjugation with deprotection employing 2 M HCl in aqueous MeOH, that afforded the desired natural product, plebeianiol A **13f** in 99% yield (Scheme 13).[110]

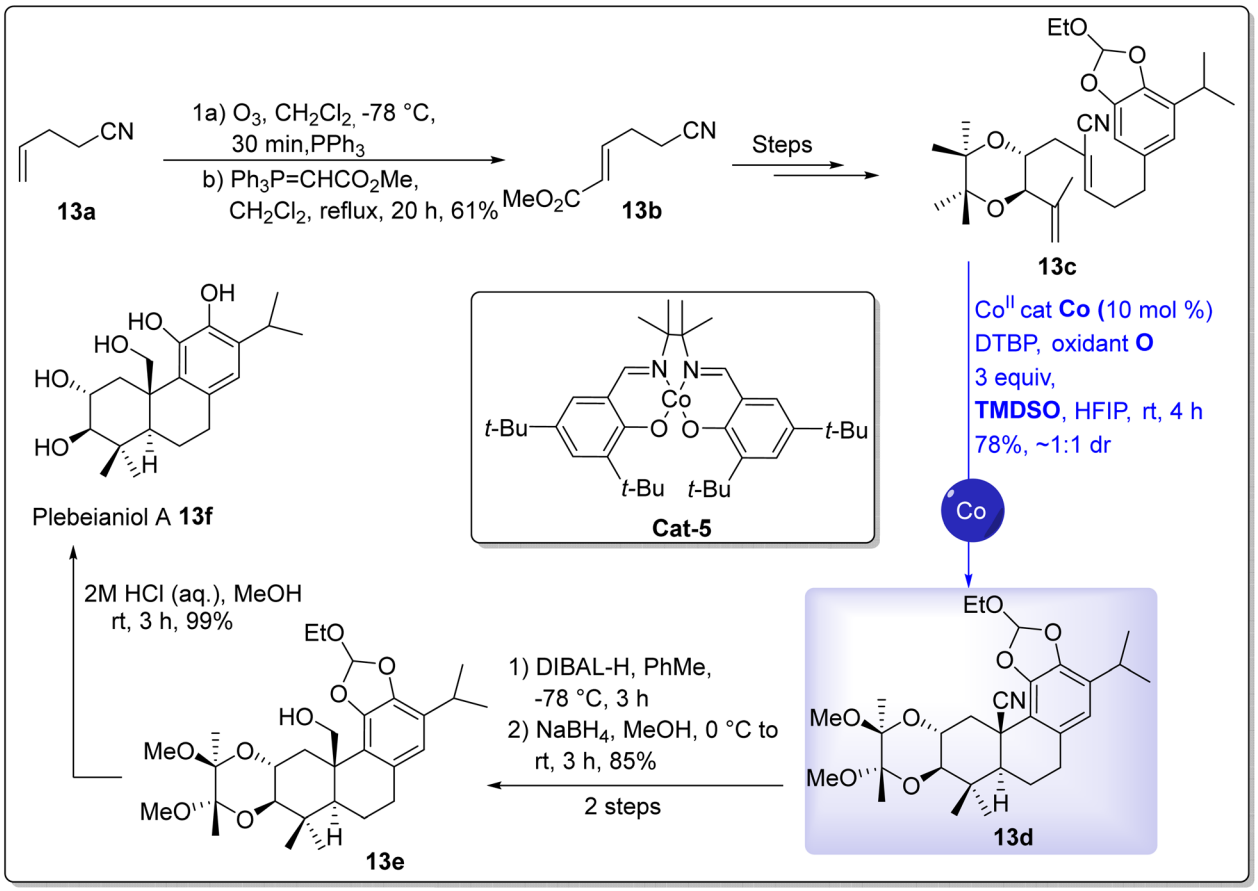
**2.2.7. (+)-Erogorgiaene and pseudopterosin A–F aglycone.** Pharmaceutically important terpenoids (+)-erogorgiaene and pseudopterosins belong to marine invertebrates *Pseudpterogorgia elisabethae*. (+)-Erogorgiaene demonstrates significant inhibitory activity towards *Mycobacterium tuberculosis*.[111–119] In addition, pseudopterosins emphasize their powerful analgesic, cytotoxic and anti-inflammatory characteristics, for instance pseudopterosin A displays broad-spectrum antibacterial activity and has shown neuromodulatory effects in mammalian tissues. Movahhed *et al.* completed synthesis of (+)-erogorgiaene **14i** in 7 steps (46% overall yield) and pseudopterosin A–F aglycone **14n**




Scheme 12 Total synthesis of cephanolide A **12k**, cephanolide B **12j**, cephanolide C **12h**, and cephanolide D **12i** (adapted from ref. 103).

in 12 steps (30% overall yield), using cobalt-catalyzed asymmetric hydrovinylation as the stereo defining transformation. The cobalt method employed air-stable Co(II) pre-catalysts was activated *in situ* by $Et_2AlCl$ to access **14k**. The corresponding Ni-based catalysts were oxygen-sensitive, demanding glovebox conditions that proved impractical and yielded inconsistent outcomes with the *ortho*-methoxy substrate **14j**. For erogorgiaene, hydrovinylation of 4-methylstyrene **14a** (Co(**L4**)$Cl_2$ (0.03 mol%), $Et_2AlCl$, $CH_2Cl_2$, −65 °C) gave **14b** in 98% yield (98–99%ee). With utilization of ligand *ent*-**L4** (0.03 mol%, −65 °C), 98–99%ee was reached. Hydroboration of **14b** (9-BBN) gave **14c**; Suzuki coupling with vinyl iodide **14e**, prepared from propargylic alcohol **14d** (84%), provided nuciferyl acetate **14f** (91%). Cyclization ($Me_2AlCl$, $CH_2Cl_2$, −78 °C) was followed by carbonyl–ene reaction ($(CH_2O)_n$, $Et_2AlCl$, −70 °C) which afforded alcohol **14g** (86%). Hydrogenation (**Cat-7**) furnished **14h** (94%), and iodination/coupling with isocrotyl-lithium **14o** afforded (+)-erogorgiaene **14i** (72%). For pseudopterosin A–F aglycone, hydrovinylation of **14j** (Co(**L5**) $Cl_2$, 5 mol%, $Et_2AlCl$, $CH_2Cl_2$, −20 °C, 6 h) gave **14k** (87%, 84%ee). Hydroboration–Suzuki coupling, Friedel–Crafts cyclization, and carbonyl–ene reaction afforded aldehyde **14l** followed by olefination with phosphonate **14p** (82%) and $AlCl_3$-mediated cyclization (20 mol%, −5 °C) that gave amphilectane **14m** (92%, d.r. = 95 : 5). Finally, demethylation (LiSEt, DMF, 160 °C) furnished pseudopterosin A–F aglycone **14n** in high yield (96%) (Scheme 14).[120]

**2.2.8. (−)-Triptolide.** (−)-Triptolide, despite its trace concentration of only 0.001% in *Tripterygium wilfordii* Hook F, remains as the most significant metabolite with considerable pharmacological activity.[121] Preparations derived from the plant, known as TwHF, have been used for centuries as part of traditional Chinese medicine for the treatment of autoimmune and inflammatory diseases.[122] In 1972, it was first isolated, and

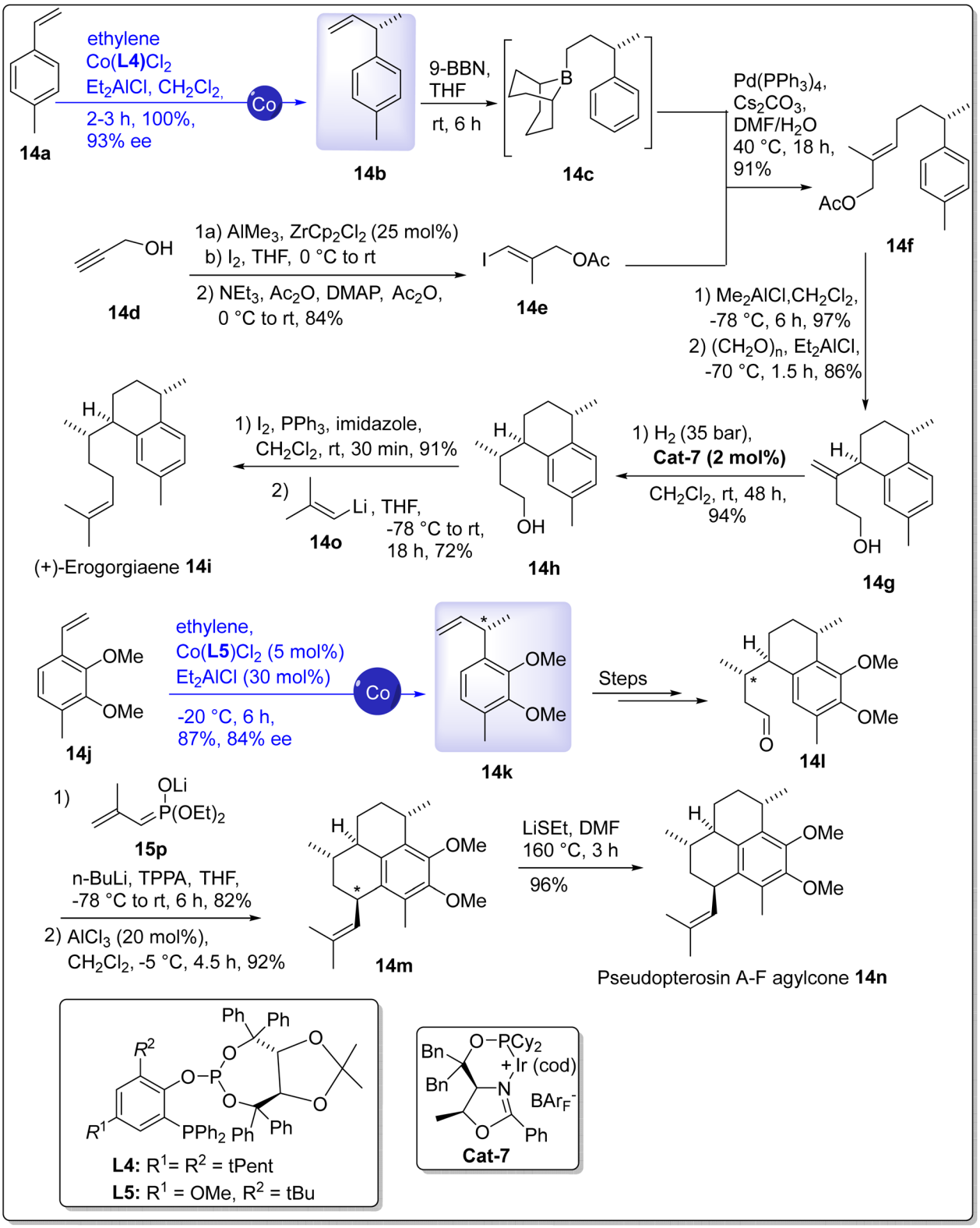



Scheme 13 Total synthesis of plebeianiol A **13f** (adapted from ref. 110).

ever since, it has been the focus of extensive synthetic and pharmacological investigation. In addition to its known anti-inflammatory and immunosuppressive properties, it has also shown promise as a potential drug candidate for the treatment of cancer, specifically pancreatic cancer.[123] Fang *et al.* reported the synthesis of (−)-triptonide from (*R*)-(−)-Taniguchi lactone **15a**, which involved the use of Co(TPP) as the catalyst for the MHAT-initiated radical cyclization reaction that forged the C5–C10 bond. Fe(III) catalysts only afforded the desired product with an isolated yield of 41%, while the use of Co(TPP) with blue LEDs (465 nm) at 0.1 mol% catalyst loading afforded **15g** with 68% yield as a single diastereomer. In the absence of blue LEDs, the substrate decomposed to unidentifiable side products, and no desired product was obtained (0% yield, 81% conversion by TLC). Cross metathesis between **15a** and acrolein diethyl acetal **15j** (Hoveyda–Grubbs II, $CH_2Cl_2$, 40 °C) afforded compound **15b** with 68% yield. TIPS protection of **15c**, Grignard addition, and $PBr_3$ treatment furnished **15d** and then **15e**. Alkylation of **15b** with **15e** (LiHMDS) and ketal hydrolysis (2 N HCl) afforded aldehyde **15f** with 67% yield as a single diastereomer. MHAT cyclization of **15f** (Co(TPP) (0.1 mol%), $PhSiH_3$ (1.5 equiv.), $CH_2Cl_2$/EtOH (10 : 1), blue LEDs, rt) gave **15g** (68%). Treatment of **15g** over several steps furnished (−)-triptonide **15h** (Scheme 15).[124]

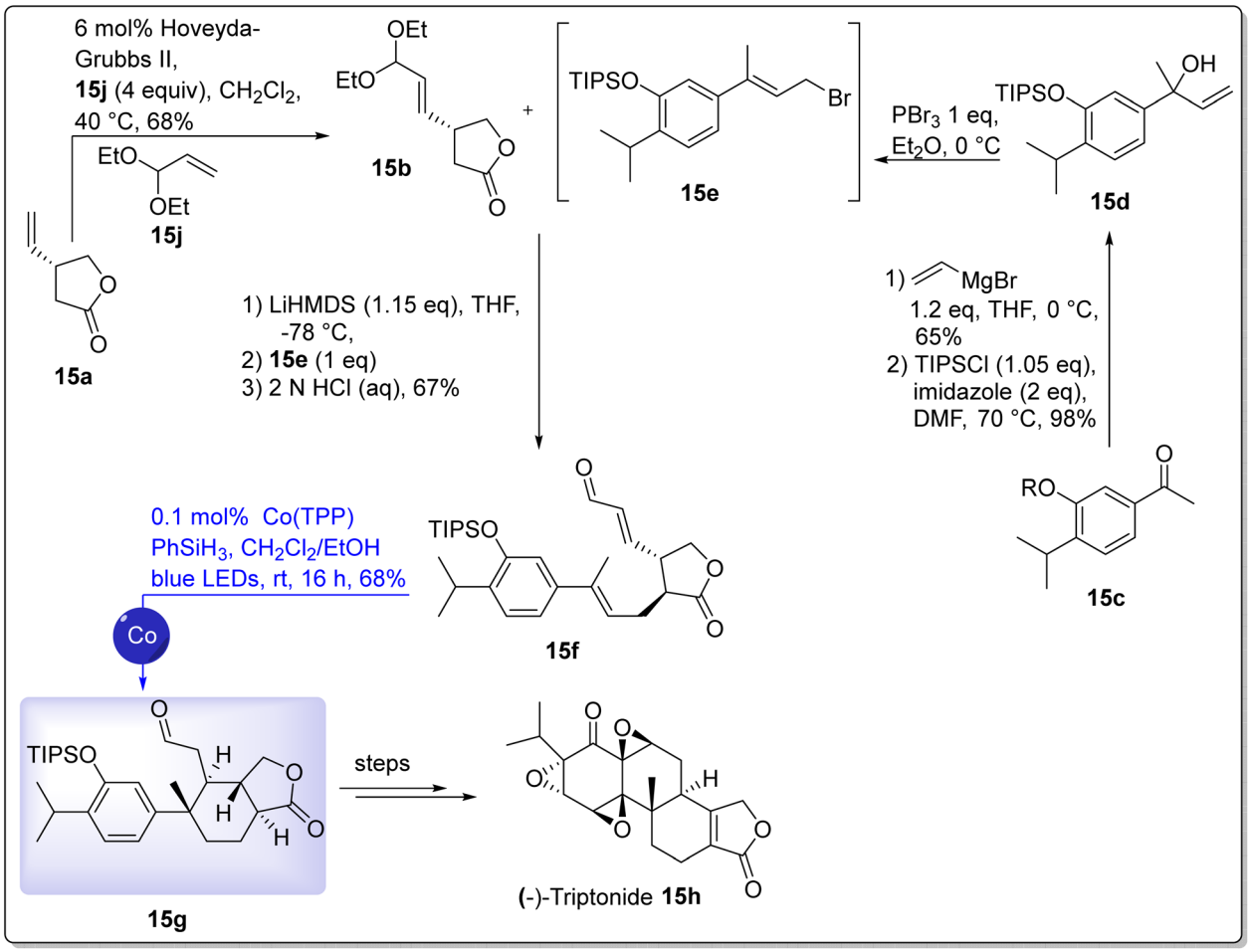
**2.2.9. 7-Hydroxyerogorgiaene and 9-deoxypseudopterosin A.** 7-Hydroxyerogorgiaene and 9-deoxypseudopterosin A are phenolic diterpenoids from the marine source *Pseudopterogorgia elisabethae* that illustrates antimicrobial activity against Gram-positive pathogens. Schumacher *et al.* described the enantioselective syntheses of (+)-7-hydroxyerogorgiaene **16g** (8 steps, 31% overall) and 9-deoxypseudopterosin A **16h** (9 steps, 28% overall) with an enantioselective cobalt-catalyzed hydrovinylation serving as the stereodefining transformation. The asymmetric hydrovinylation of styrene **16a** was mediated by catalyst, generated *in situ* from $CoCl_2$ and phosphoramidite ligand **L6** (0.4 mol%). This method delivered **16b** in 99% yield and 91%ee on multigram scale. Hydroboration/Suzuki coupling of **16b** with vinyl iodide **16i** gave **16c** (71%). Cyclization precursor **16c** was treated with $Me_2AlCl$ to afford *trans*-calamenene **16d** (92%, d.r. = 86 : 14). Carbonyl–ene reaction and HPLC separation provided **16e** (77%), and hydrogenation with iridium catalyst **Cat-8** furnished **16f** (>99%, d.r. = 95 : 5). From **16f**, (+)-7-hydroxyerogorgiaene **16g** and 9-deoxypseudopterosin A **16h** were obtained over a number of steps (Scheme 16).[125]

**2.2.10. (−)-Illisimonin A.** (−)-Illisimonin A was extracted by Yu and co-workers from the evergreen shrub *Illicium simonsii* that is frequently utilized in traditional Chinese medicine.[126] It exhibited neuroprotection in an SH-SY5Y oxygen–glucose deprivation resulting cell injury with half maximal effective concentration of ≈ 28 μM. Illisimonin A contains an unprecedented cage-like 5/5/5/5/5 pentacyclic scaffold. This compact ring network contains a strained *trans*-pentalene unit. Such




Scheme 14 Total synthesis of (+)-erogorgiaene **14i** and the pseudopterosin A–F aglycone **14n** (adapted from ref. 120).

motifs are exceedingly scarce among known natural products and present a major synthetic challenge.[126–132] Xu *et al.* in 2025, completed an asymmetric total synthesis of (−)-illisimonin A in 16 steps from (*S*)-carvone. The key cobalt-catalyzed step was Mukaiyama hydration of the trisubstituted olefin **17d** [$Co(acac)_2$, $PhSiH_3$, $O_2$, THF], followed by thermal trans-lactonization (toluene, 140 °C), giving γ-butyrolactone **17e** in 67% yield. Starting from (*S*)-carvone **17a**, α-allylation with **17h**,




Scheme 15 Total synthesis of (−)-triptonide **15h** (adapted from ref. 124).

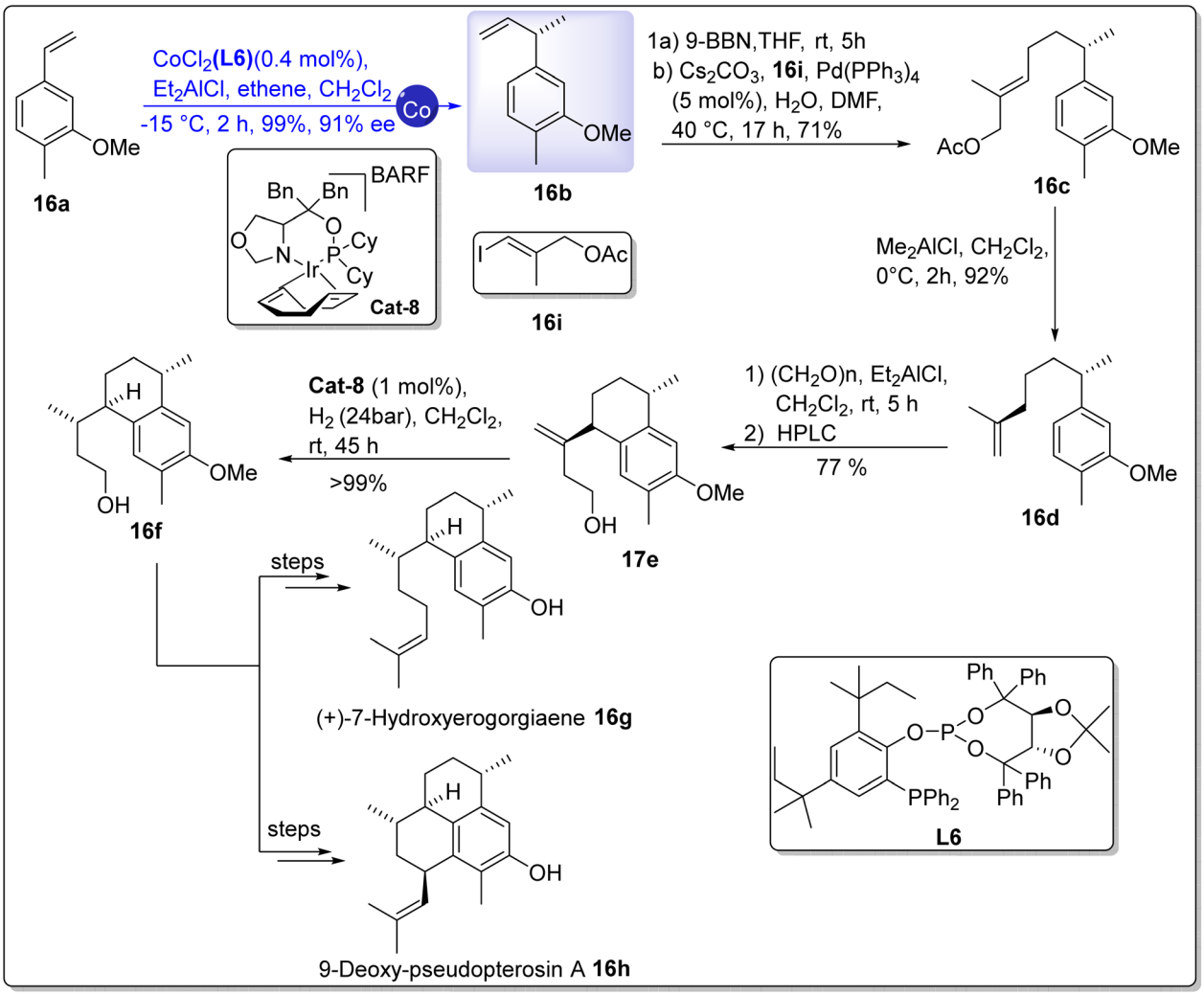
ring-closing metathesis with epimerization (67% over 2 steps) followed by nucleophilic epoxidation afforded **17b** (77%). Next, Wittig homologation of **17b** with **17i** then gave aldehyde **17c** (91%). Further, treatment of **17c** through several steps, resulted in the preparation of **17d**. In order to install the desired –OH group on C-4, $Co(acac)_2$-catalyzed Mukaiyama hydration of **17d** was carried out, followed by subsequent (one-pot) thermal translactonization to access **17e** (67%). Next, benzyl protection of **17e**, followed by MoOPH α-hydroxylation and Jones oxidation that gave **17f** in 63% yield. Then, **17f** was subjected to intramolecular aldol cyclization and hydrogenolysis to furnish (−)-illisimonin A **17g** in 84% yield (Scheme 17).[133]

**2.2.11. Pierisketone B.** Pierisketone B belongs to a novel group of rearranged *ent*-kaurane diterpenoids, known for their tetracyclic 7/5/6/5 carbocyclic framework.[134–136] These molecules possess bioactivities such as antitumor, antibacterial and anti-inflammatory activity which rendered it a primary focus of synthetic exploration.[137,138] Gu *et al.* completed the first total synthesis of (+)-pierisketone B (3.4% overall yield from the known enone **18a**), featuring an intramolecular Pauson–Khand reaction (PKR) to construct the bridged bicyclo [3.2.1] octane core. When the dihydro analogue of **18f** was subjected to PK reaction conditions, only traces of product were observed, underscoring the critical role of the conformational constraint in *Z*-enyne, facilitating the PKR reaction. The synthesis commenced with CuBr·$Me_2S$-catalyzed 1,4-vinylation of **18a** gave **18b** (58%) in conjugation with ozonolysis which afforded aldehyde **18c** (96%).[139] Julia–Kocienski olefination of **18c** with BT-sulfone **18d** (NaHMDS, −45 °C) provided *Z*-enyne **18e** (82%), and methylenation with Nysted reagent furnished **18f** (92%). PK reaction of **18f** ($Co_2(CO)_8$, *n*-BuSMe, PhMe, reflux) delivered **18g** (85%), whose structure was verified crystallographically. Elaboration of **18g** over several steps afforded **18h** followed by dimethylation to give **18i** (91%). Deoxygenation of **18i** and desilylation completed the total synthesis of (+)-pierisketone B **18j** (78%) (Scheme 18).[139]

## 2.3 Synthesis of polyketides

**2.3.1. (*R*)-Sarkomycin.** (*R*)-Sarkomycin, a cyclopentenone of prominent biological relevance was first isolated from *Streptomyces erythrochromogenes* in 1953.[140] Beyond its antibacterial properties, it exhibits potent inhibitory activity against diverse human cancer cell lines and malignancies. Cabré *et al.* reported an enantioselective synthesis of (*R*)-sarkomycin methyl ester in five steps, who were the first to use the Pauson–Khand reaction (PKR) for ring construction of this natural product. Within the PKR reaction of steric hindrance involving substituents of

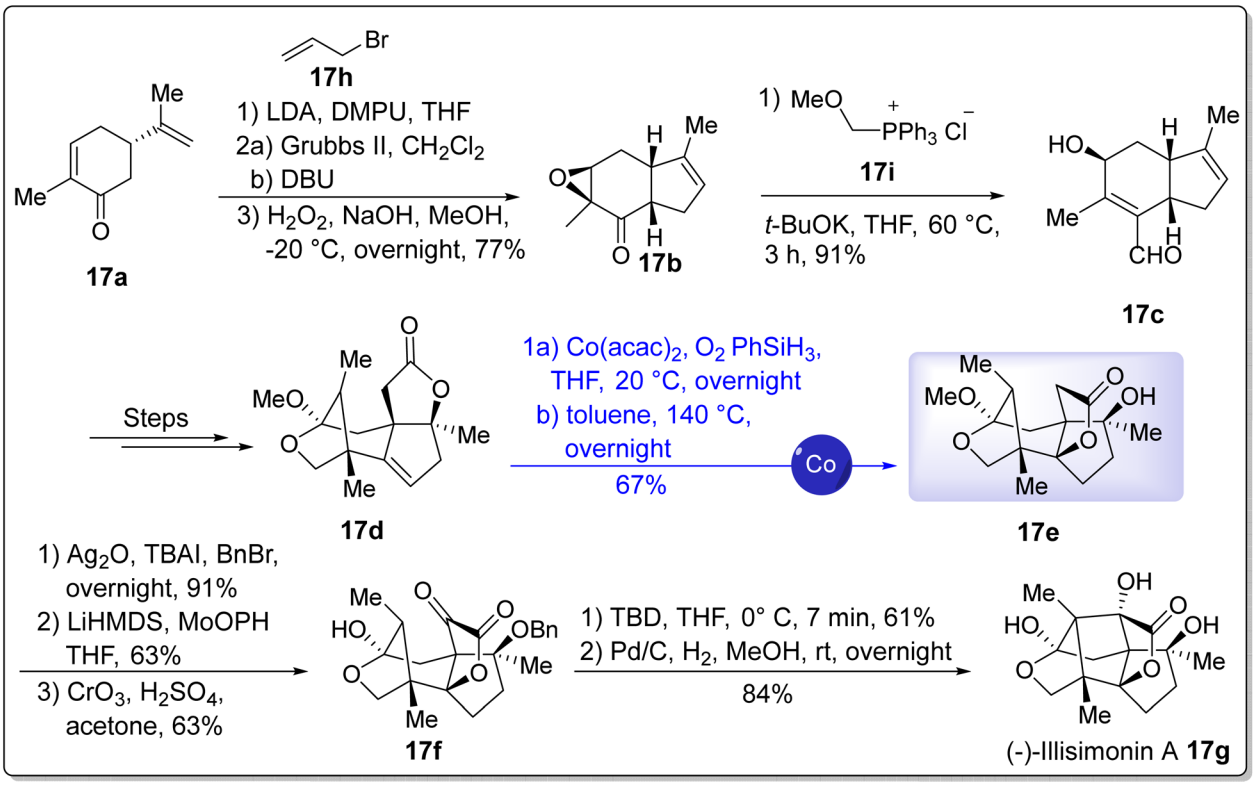
 



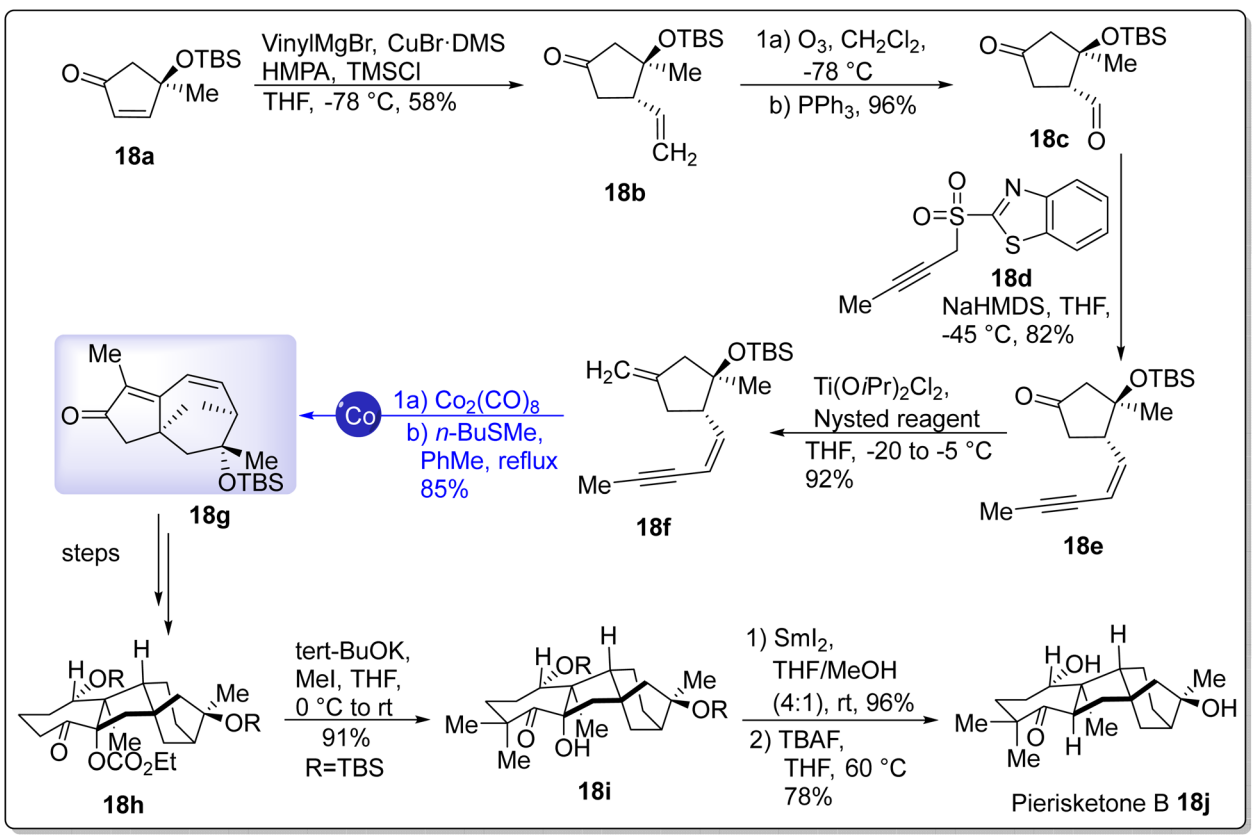

Scheme 16 Total synthesis of (+)-7-hydroxyerogorgiaene **16g** & 9-deoxy-pseudopterosin A **16h** (adapted from ref. 125).

internal alkynes, electronic effects direct the regioselectivity towards the electron withdrawing group *i.e.*, –OMe carbonyl will be directed to the β-position. Ethylene glycol was used as an additive to minimize the NMO activation, thereby giving 85% yield of **19c**. The synthesis initiated with the carboxylation and esterification of *N*-Boc-propargylamine **19a** to give alkyne **19b** in 74% yield. Subjecting **19b** to the Pauson–Khand reaction ($Co_2(CO)_8$, toluene, ethylene (6 barG), NMO (6 equiv.), 4 Å MS, ethylene glycol, $CH_2Cl_2$, rt, 4 h) provided cyclopentenone **19c** in 85% yield. Iridium-catalysed isomerization of **19c** followed by hydrogenation over Pd/C delivered **19d** in 73% yield and >99% ee. Finally, Boc removal and subsequent *N*-methylation/elimination afforded (*R*)-sarkomycin methyl ester **19e** in 45% yield with 98%ee (Scheme 19).[141]

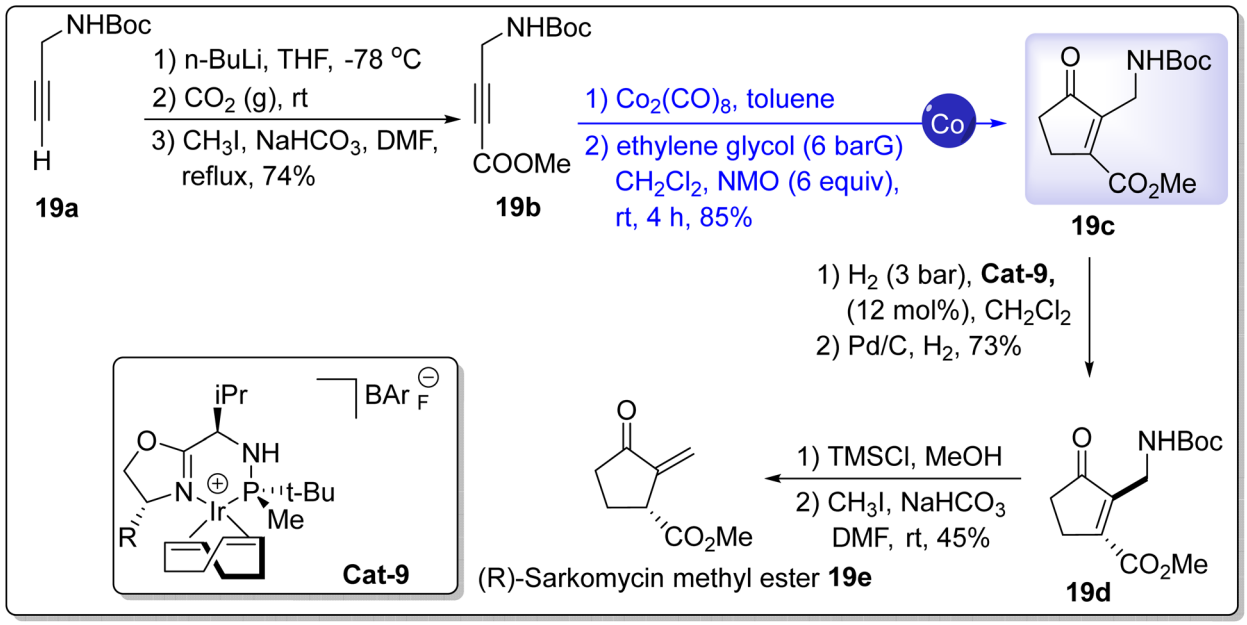
**2.3.2. Monocillin VII.** The resorcyclic acid lactones (RALs) are natural compounds that possess a β-resorcylate core fused to a 12-/14-membered macro lactone ring, obtained from numerous biological sources.[142] Wei's group isolated a series of RALs from rice cultures of *Paecilomyces* sp. SC0924 including monocillin VII. It displays moderate antifungal efficacy against *P. litchii* ($IC_{50}$ value 41.0 μM) and potent cytotoxicity against HeLa, A549, and MCF-7 cell lines, with $IC_{50}$ values of 3.9, 4.1, and 4.9 μM, respectively.[143] In 2019, Mallampudi *et al.* reported the first asymmetric total synthesis of monocillin VII **20k** in 16 longest linear steps *via* a convergent approach. Total synthesis commenced from the transformation of aldehyde **20a** into alkyne **20b** over a number of steps. The synthesis of second coupling partner *i.e.*, aryl triflate **20e** was initiated from acid **20c**, which was converted to acetonide **20d** under the presence of $SOCl_2$, DMAP, in acetone (giving 82% yield) followed by a sequence of steps to generate **20e**. Sonogashira coupling of **20b** and **20e** provided **20f** (76%), whose TBDPS removal gave **20g** (85%). The major hurdle was macrolactonization of seco-acid **20g** under De Brabander's conditions (NaH, THF, 0 °C) which were found to be highly unfavorable, yielding only 15% of desired product. On the other hand, the treatment of **20g** with $Co_2(CO)_8$ in $CH_2Cl_2$ at 0 °C for 1 hour gave the alkyne–dicobalt hexacarbonyl complex **20h** quantitatively. The resulting complex **20h** was then finally transformed to afford the target natural product monocillin VII **20i** (Scheme 20).[144]



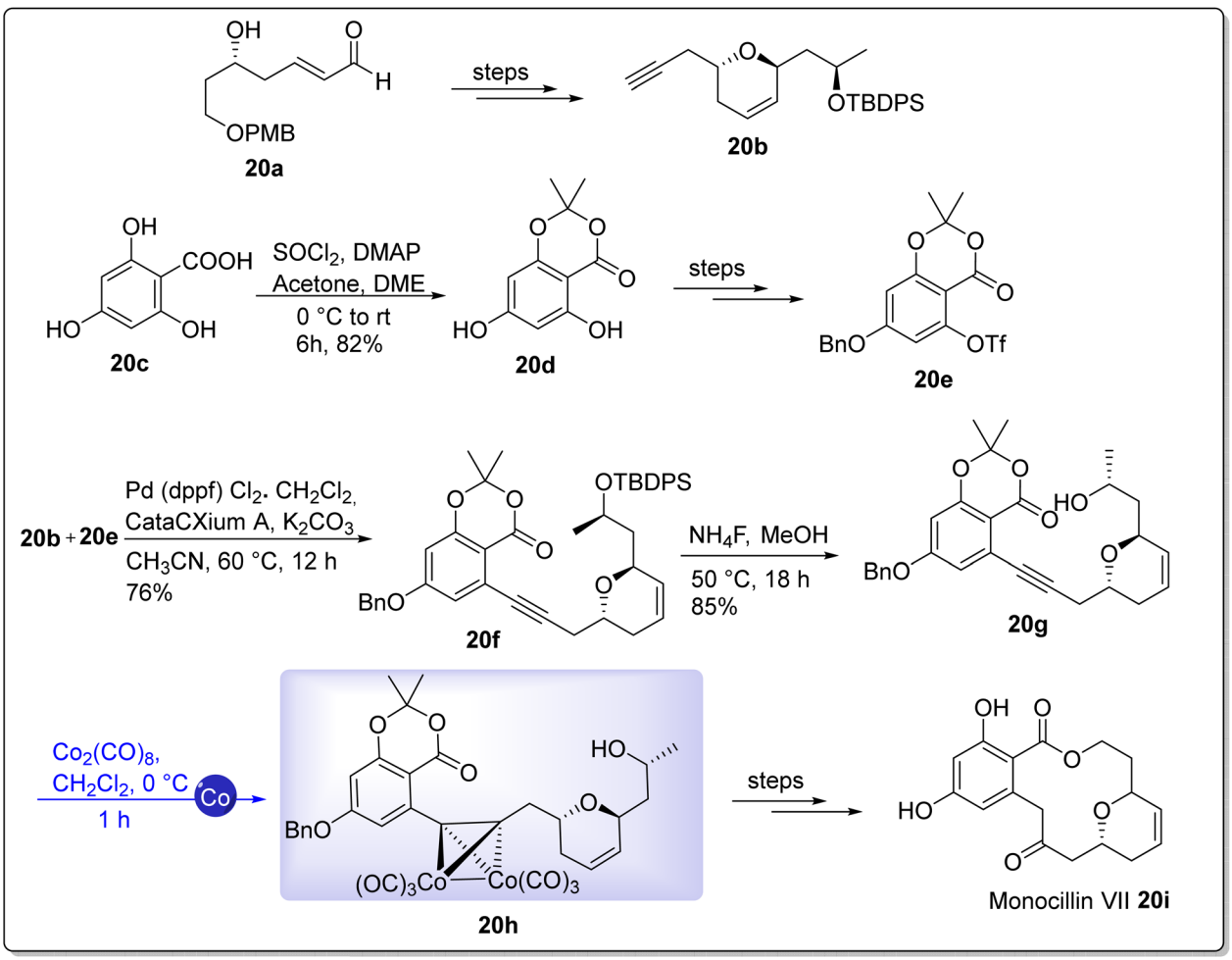

Scheme 17 Total synthesis of (−)-illisimonin A **17g** (adapted from ref. 133).




Scheme 18 Total synthesis of pierisketone B **18j** (adapted from ref. 139).



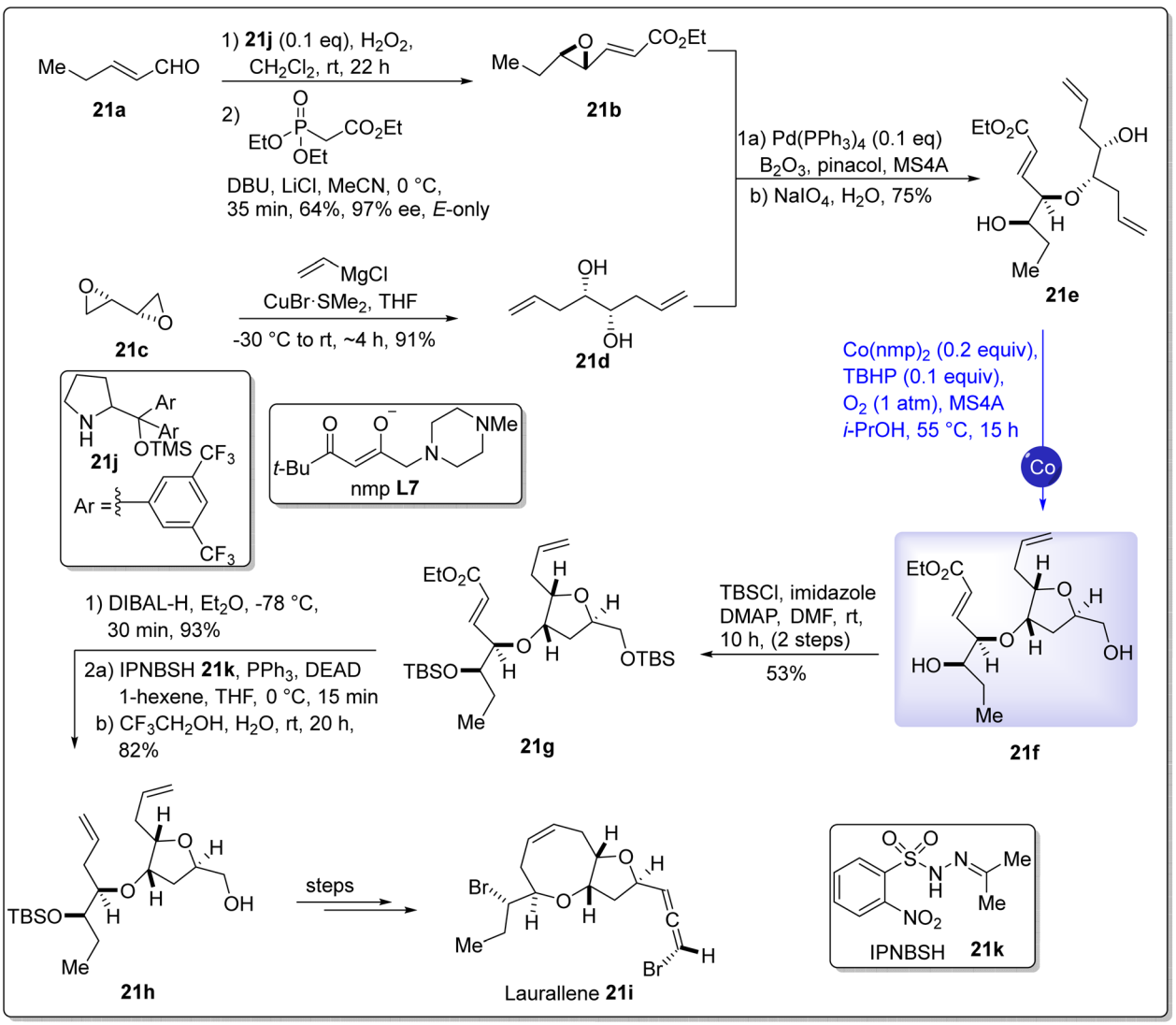

Scheme 19 Total synthesis of (*R*)-sarkomycin methyl ester **19e** (adapted from ref. 141).



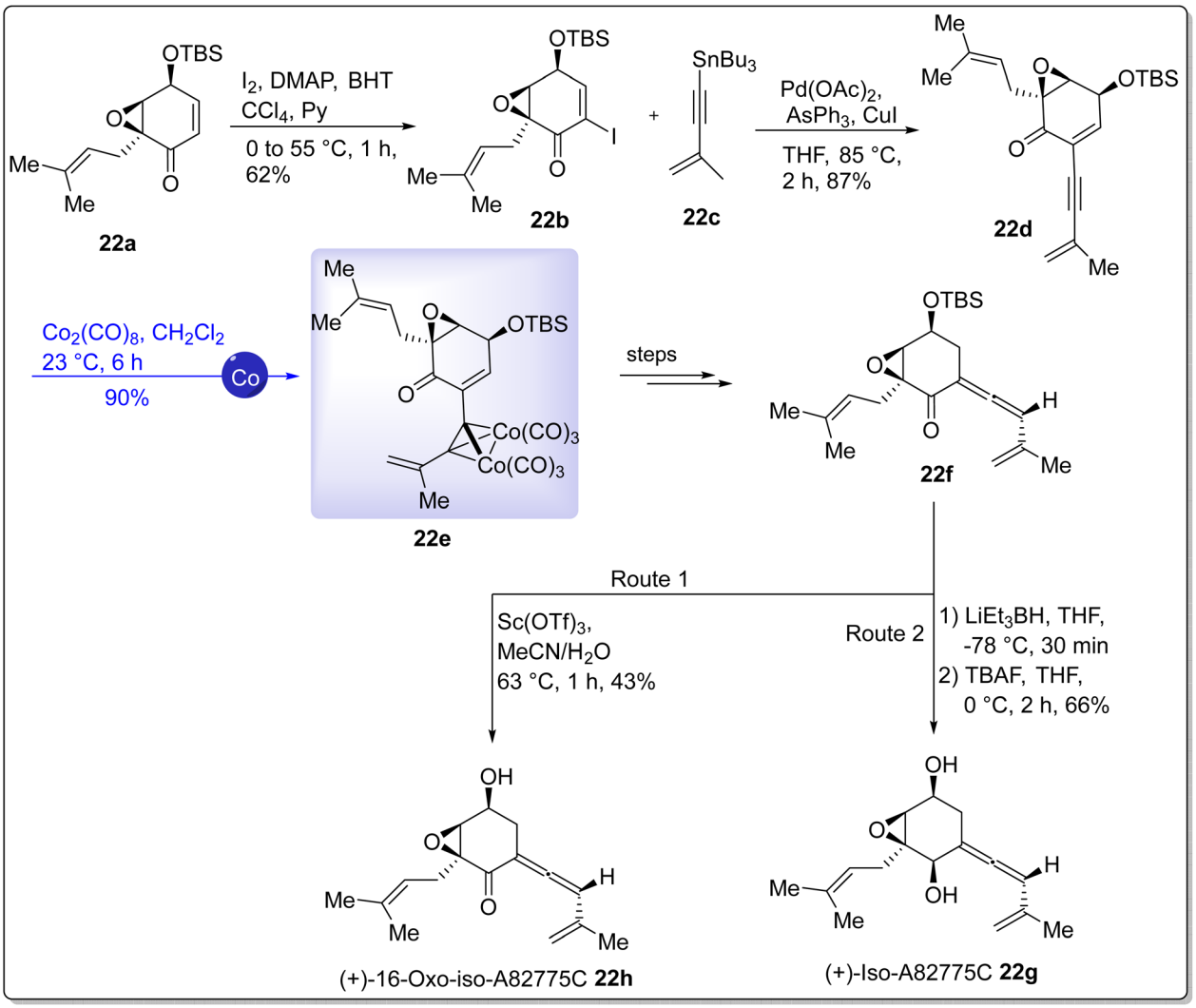

Scheme 20 Total synthesis of monocillin VII **20i** (adapted from ref. 144).

**2.3.3. Laurallene.** Laurallene, a marine-derived $C_{15}$ acetogenin isolated from the red alga *Laurencia nipponica* Yamada in 1979, exemplifies the lauroxane family bearing medium-ring ethers. Its rare 2,9-dioxabicyclo[6.3.0]undecene framework, featuring an exocyclic chiral bromoallene, has rendered laurallene a promising target for total synthesis.[145,146] Asymmetric total synthesis of laurallene by Yoshimura *et al.* involved a 13-step approach with an overall linear sequence of 3.3% yield. Cobalt-mediated Mukaiyama oxidative cyclization, with a modification by Pagenkopf, utilizing $Co(nmp)_2$ catalyst, constructs the *trans*-THF ring from diol-alkene **21e**. Yoshimura *et al.* used asymmetric epoxidation of *trans*-2-pentenal **21a**, followed by one-pot Horner–Wadsworth–Emmons olefination to obtain epoxy ester **21b** (64%, 97%ee). Copper-catalyzed opening of (*S*,*S*)-diepoxide **21c** furnished the second coupling partner *i.e.*, diol **21d** (91%). In the next step, Pd-catalyzed alkoxy substitution of **21b** with **21d**, followed by $NaIO_4$ cleavage, provided branched ether **21e** (75%). In the next step, cobalt-mediated Mukaiyama oxidative cyclization of **21e** developed by Inoki and Mukaiyama, with a modification by Pagenkopf, utilizing $Co(nmp)_2$ catalyst (0.2 equiv.), TBHP (0.1 equiv.), $O_2$ (1 atm), MS 4A, *i*-PrOH at 55 °C furnished *trans*-THF **21f** as a single diastereomer, whose TBS protection gave **21g** (53%, two steps). Next, **21g** was subjected to DIBAL-H reduction (93%) followed by Movassaghi reductive rearrangement to afford diene **21h** (82%), which was converted to laurallene **21i** *via* ring-closing metathesis, bromoallene installation, and C13-bromination (42%, three steps) (Scheme 21).[147]

**2.3.4. (+)-Iso-A82775C.** (+)-Iso-A82775C and its oxidized analogue (+)-16-oxo-iso-A82775C are important epoxyquinoid intermediates involved in the biosynthesis of structurally complex natural products such as pestalofones and chloropupukeananin. They are now important targets in synthetic and biosynthetic studies owing to their distinct cyclohexane frameworks and reactivity.[148] Kim *et al.* accomplished the total synthesis of (+)-iso-A82775C **22g** and (+)-16-oxo-iso-A82775C **22h** from *p*-methoxyphenol, with cobalt-mediated alkyne protection as the key reaction. α-Iodination of enone **22a**




Scheme 21 Total synthesis of laurallene **21i** (adapted from ref. 147).

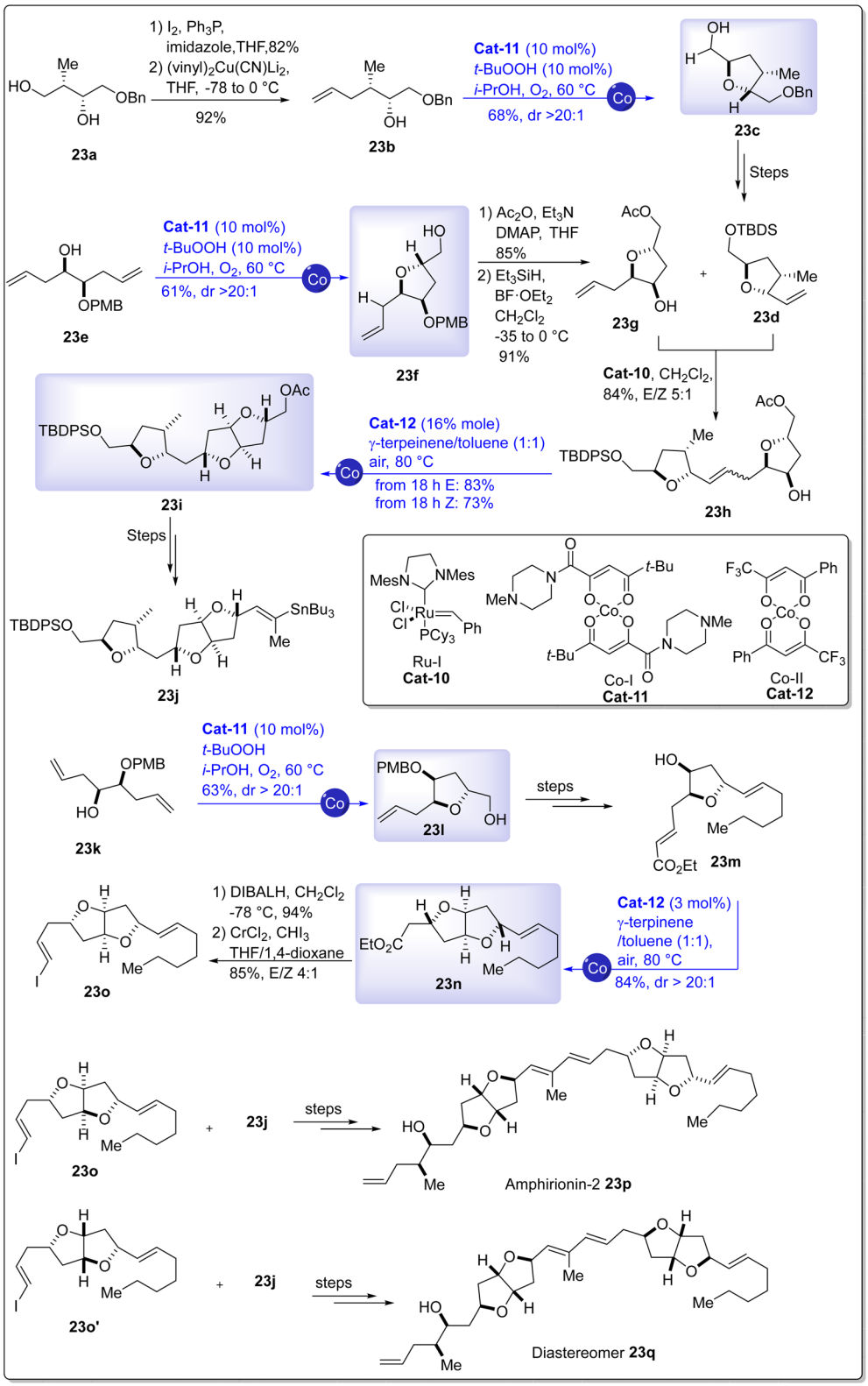



Scheme 22 Total synthesis of (+)-iso-A82775C **22g** and (+)-16-oxo-iso-A82775C **22h** (adapted from ref. 149).

afforded α-iodinated product **22b** in 62% yield. The Stille cross-coupling of **22b** with organostannane **22c** using Pd $(OAc)_2$, $AsPh_3$, and CuI in THF afforded enyne **22d** in 87% yield. The conjugate reduction of enyne enone **22d** failed because the alkyne π-system rendered the C10 position less-electron deficient, leading to exclusive carbonyl reduction at C16. Coordination of the alkyne with $Co_2(CO)_8$ to give dicobalt hexacarbonyl complex **22e** avoids the less electrophilicity tendency at C10 position as alkyne gets masked in this process, thereby leading to facile selective 1,4-reduction with K-selectride. Thus, treatment of **22d** with $Co_2(CO)_8$ (1.0 equiv.) in $CH_2Cl_2$ at 22 °C provided cobalt complex **22e** in 90% yield. Conjugate reduction of cobalt-complexed enone **22e** with K-selectride followed by CAN-mediated decomplexation, and $Et_3N$-catalysed tautomerization furnished allene **22f** with complete diastereoselectivity (40%, three steps). From **22f**, Sc $(OTf)_3$-catalysed desilylation ($MeCN/H_2O$, 63 °C) furnished (+)-16-oxo-iso-A82775C **22h** in 43% yield, whereas chemoselective reduction with $LiEt_3BH$ followed by TBAF desilylation afforded (+)-iso-A82775C **22g** in 66% yield, over two steps (Scheme 22).[149]

**2.3.5. Amphirionin-2.** The linear polyketide metabolite amphirionin-2 was isolated from cultured cells of the marine benthic dinoflagellate *Amphidinium* sp. KCA09051 strain. Amphirionin-2 demonstrated significant potent cytotoxic activity against the human non-small cell lung adenocarcinoma A549 cell line, human colon carcinoma caco-2 cell line and revealed anticancer efficacy *in vivo* toward murine tumor P388 cells (T/C 120% at 0.5 mg $kg^{-1}$).[150,151] The first total synthesis of amphirionin-2 **23p** and diastereomer **23q** was accomplished by Kato and co-workers in 2021, consisting of 17 linear steps (from diol **23a**), by relying on iterative cobalt-mediated Mukaiyama cyclization to synthesize the tetrahydrofuran rings. Afterwards, Hartung–Muakiyama cyclization illustrated that several radical terminators have the potential to trap the centered carbon radical intermediate to afford *trans*-tetrahydrofyran derivatives. Diol **23a** was converted to iodide (82%), then to γ-hydroxy olefin **23b** *via* vinyl cuprate addition (92%). Co–I-catalyzed cyclization of **23b** afforded **23c** (68%, d.r. >20 : 1) using cat-11, *t*-BuOOH, *i*-PrOH, $O_2$, which was transformed into olefin **23d** over a few steps. Co–I cyclization of **23e** gave **23f** (61%, d.r. >20 : 1), whose

further acetylation and PMB removal provided **23g**. Ru–I cross metathesis of **23d** and **23g** furnished **23h** (84%, *E*/*Z* 5 : 1), whose Co-II (16 mol%) catalyzed Hartung-Mukaiyama cyclization (γ-terpinene/toluene, air, 80 °C) gave **23i** (83% from *E*, 73% from *Z*). The compound **23i** was treated over several steps to access **23j**. Next, another Co-I cyclization of **23k** afforded **23l** followed by its transformation to **23m** over a few steps. Co-II (3 mol%) cyclization of **23m** afforded **23n** (84%, d.r. > 20 : 1) in

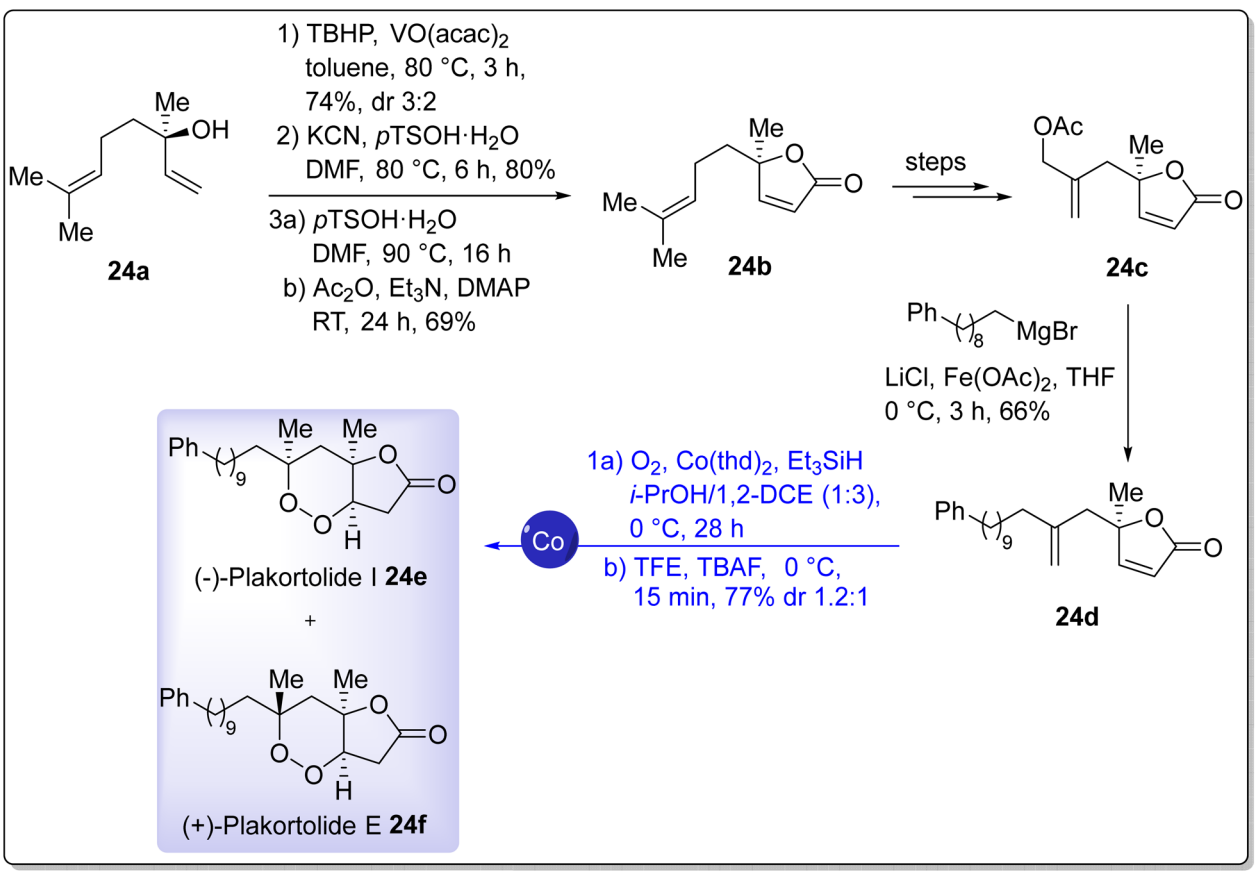



Scheme 23 Total synthesis of amphirionin-2 **23p** and its diastereomer **23q** (adapted from ref. 152).

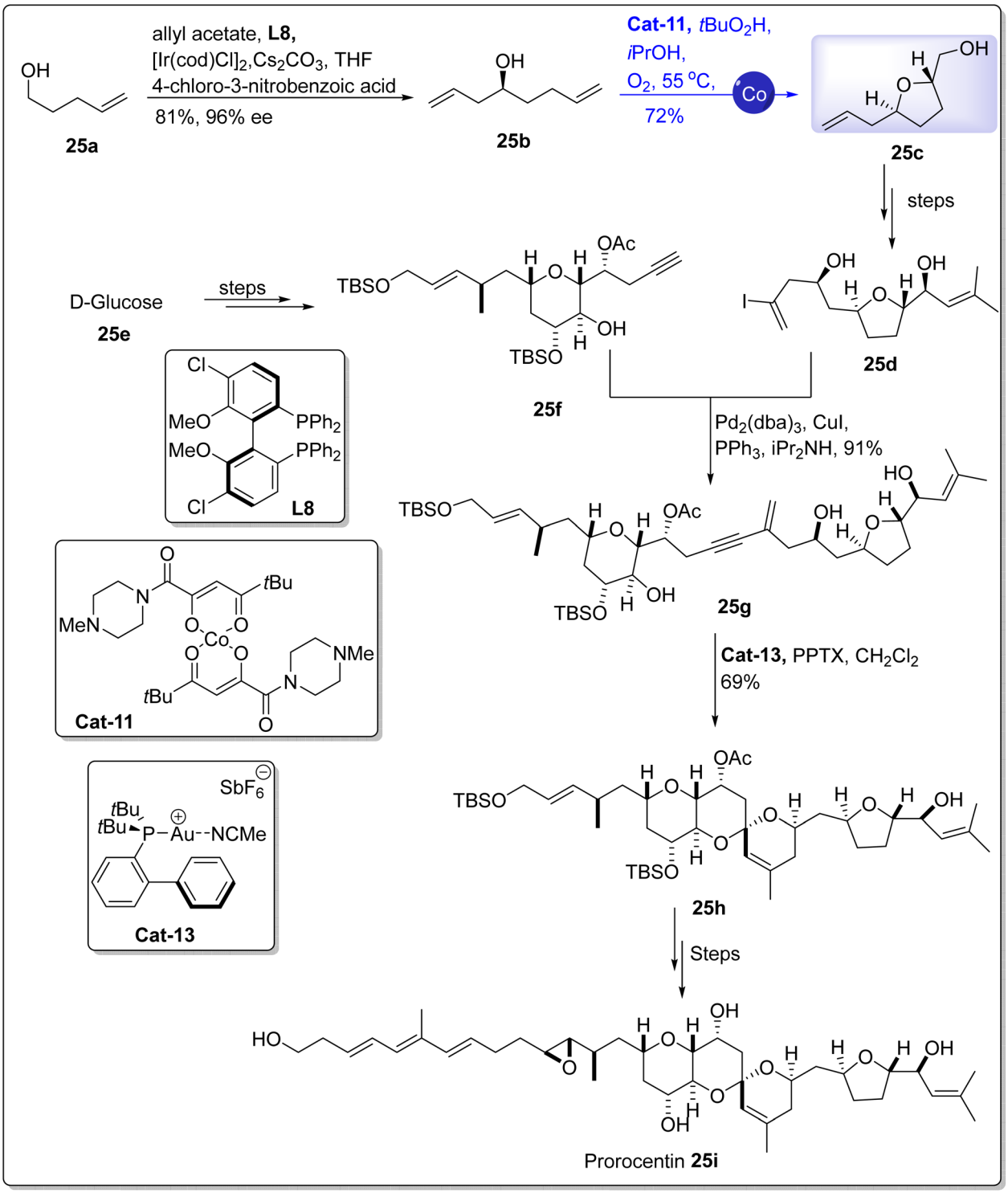
conjugation with DIBAL-H reduction (94%) and Takai olefination to furnish iodoolefin **23o**. Finally, coupling of **23j** and **23o**/**23o′** resulted in the synthesis of amphirionin-2 **23p** and its diastereomer **23q** respectively, over a few steps (Scheme 23).[152]

**2.3.6. Plakortolides E and I.** Endoperoxides are a structurally distinctive class of natural products isolated from both marine and terrestrial organisms. These compounds display diverse and relatively underexplored biological activities. Notably, polyketide-derived members such as plakinic acids, plakortides, and plakortolides have shown promising antitumor, antibacterial, and antifungal effects. The polyketide-derived endoperoxides plakortolides E and I were obtained from marine sponges.[153–155] Leisering *et al.* (2021) achieved a concise, seven-step route to both natural products starting from (*R*)-linalool **24a**, employing a tandem cobalt-mediated endoperoxide cyclization as the pivotal transformation. (*R*)-Linalool (**24a**) was converted to butenolide **24b** *via* vanadium-catalyzed epoxidation, cyanide opening, and one-pot hydrolysis/lactonization/elimination (69%). Butenolide **24b** was treated over few steps to access allyl acetate **24c**. Iron-catalyzed allylic substitution of **24c** afforded olefin **24d** (66%), which underwent cobalt-catalyzed hydro peroxidation followed by oxa-Michael addition. These conditions were not successful for the conversion of precursor, then addition of protic solvent (*i*-PrOH as co-solvent) facilitated the reactivity of olefin **24d** to afford the synthesis of desired natural products, which prevented the formation of by-products. However, the products were observed to be decomposed. At 0 °C, oxa-Michael addition was slowed and corresponding silyl peroxide was trapped. This challenge was handled by *in situ* TBAF/TFE desilylation, thereby preventing Weitz–Scheffer epoxidation. As a result, (−)-plakortolide I **24e** in 42% and (+)-plakortolide E in **24f** (77% combined, d.r. 1.2 : 1), were obtained *via* this endoperoxide formation (Scheme 24).[156]

**2.3.7. Prorocentin.** Prorocentin, a secondary metabolite generated by the strain *P. lima* PL021117001, was collected from the Northern Taiwan coastline. Prorocentin exhibits weak cytotoxicity towards two human cancer cell lines and shows no antimicrobial activity against *S. aureus*.[157] Zachmann *et al.* in 2023, reported the total synthesis of actual prorocentin from fragments **25d** and **25f**. The key cobalt-catalyzed step is an oxidative Mukaiyama cyclization, which resulted in 2,5-*trans*-disubstituted tetrahydrofuran **25c**. Krische allylation of **25a** ($(Ir(cod)Cl)_2$, **L6**, $Cs_2CO_3$, THF) gave **25b** (81%, 96%ee) which was subjected to significantly selective cobalt-catalyzed oxidative etherification (Cat-13, *t*BuOOH, *i*PrOH, $O_2$, 55 °C) to afford *trans*-THF **25c** (72%, d.r. > 20 : 1) as a single diastereomer, involving selective 5-*exo*-*trig* cyclization, even though the substrate bearing two chemically distinct olefin units adjacent to the hydroxyl group. The resulting THF **25c** was converted to vinyl iodide **25d** over a sequence of reaction steps. D-Glucose **25e** was converted to **25f** which was subjected to Sonogashira



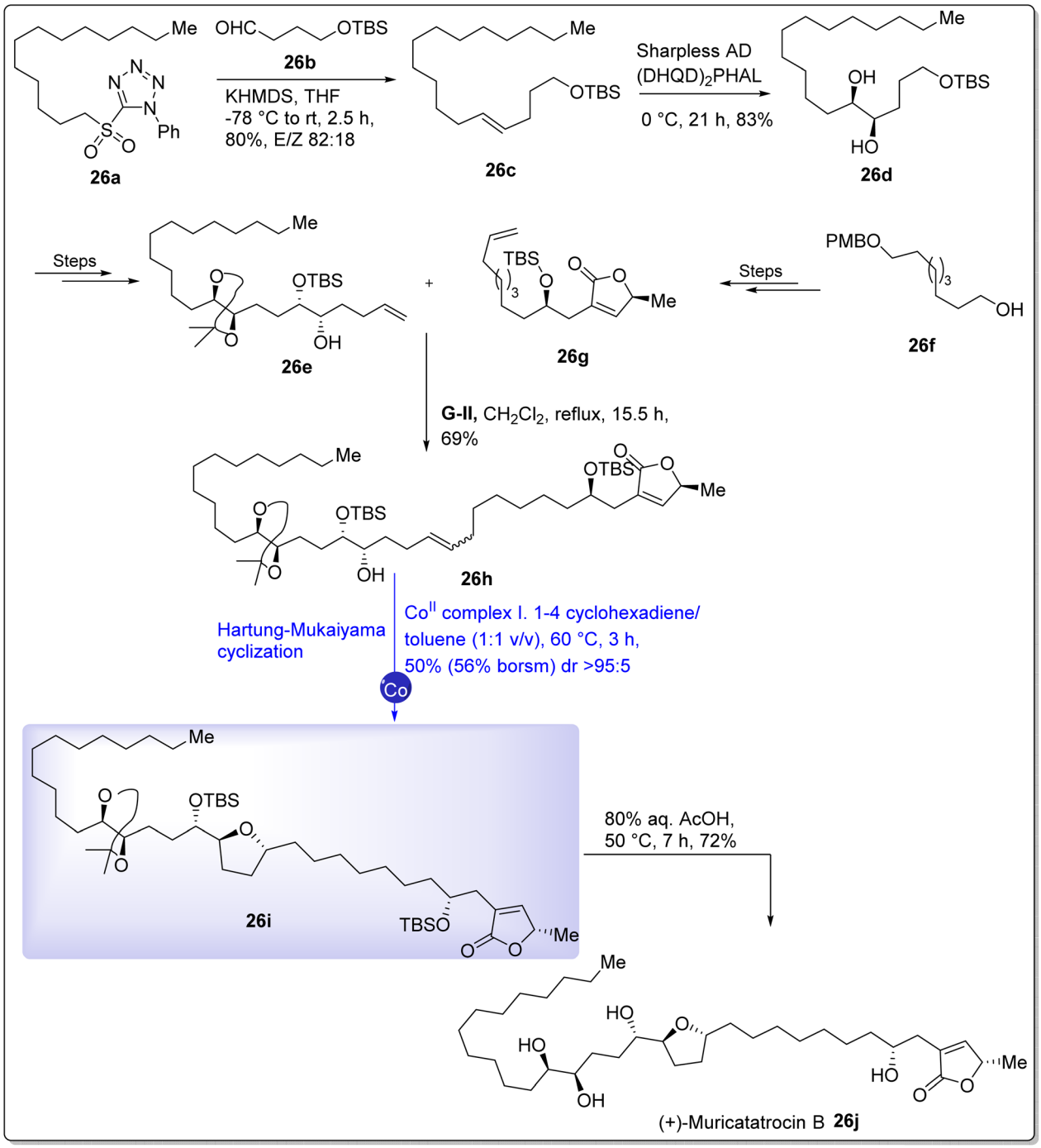

Scheme 24 Total synthesis of (−)-plakortolide I **24e** and (+)-plakortolide E **24f** (adapted from ref. 156).




Scheme 25 Total synthesis of prorocentin **25i** (adapted from ref. 158).

coupling with **25d** to access **25g** in 91% yield. Finally, its gold-catalyzed spirocyclization furnished product **25h** (69%) which was transformed to prorocentin **25i** over a number of steps (Scheme 25).[158]

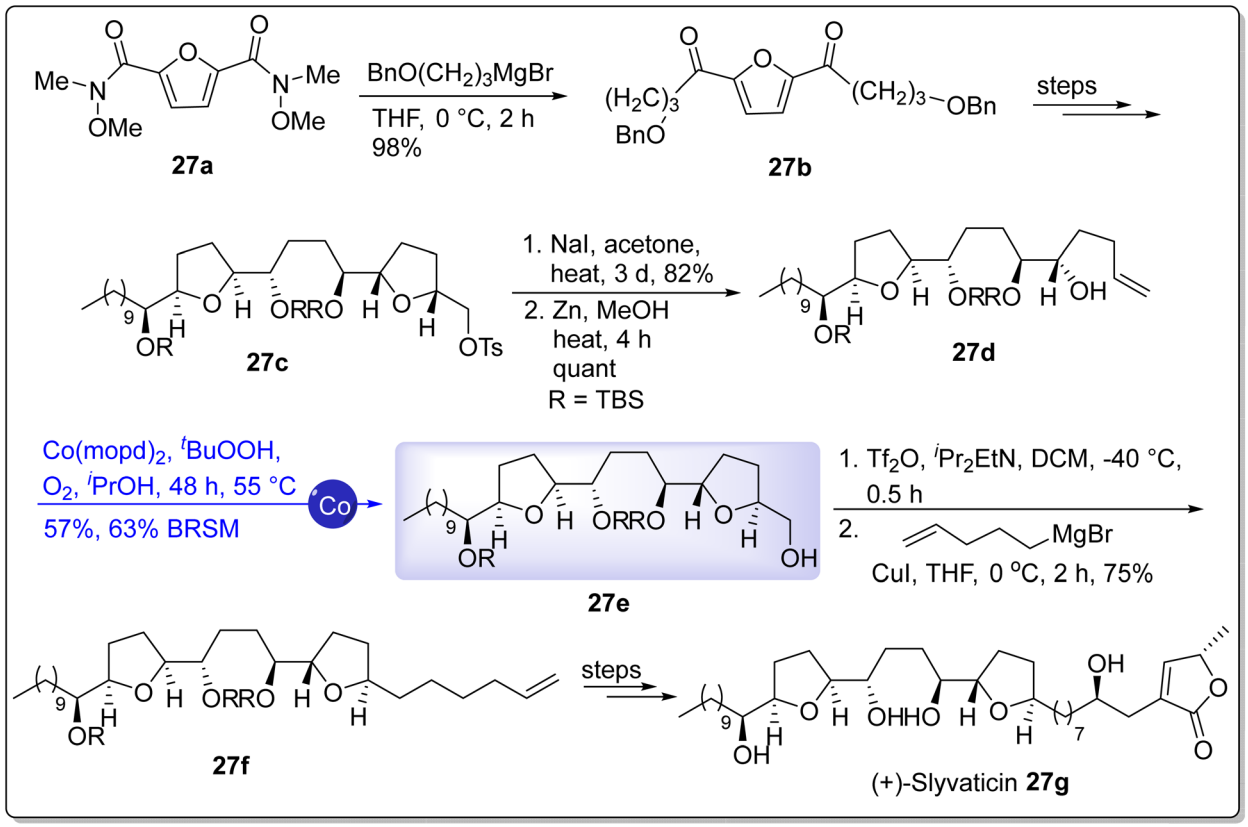
**2.3.8. (+)-Muricatetrocin B.** (+)-Muricatetrocin B, a naturally occurring product, was isolated by McLaughlin *et al.* from the ethanol extracts of the defatted seeds of *Annona muricata*.[159] This chemical has attracted significant attention because of its cytotoxic efficacy against A549 (lung), MCF-7 (breast) and HT-29 (colon) cancer cells.[160] Minami *et al.* in 2023, published an effective method to establish (+)-muricatetrocin B, which featured a late-stage Co(II)-catalyzed Hartung–Mukaiyama




Scheme 26 Total synthesis of (+)-muricatatrocin B **26j** (adapted from ref. 161).

cyclization to construct the core 2,5-*trans*-tetrahydrofuran ring. The total synthesis commenced from the synthesis of olefin **26e** which was obtained from sulfone **26a** on coupling with aldehyde **26b** under KHMDS in THF, gradually warming from −78 °C to rt to afford compound **26c**. Compound **26c** was converted to diol **26d** *via* Sharpless dihydroxylation and then diol **26d** was converted into olefin **26e** over a few steps. On the other hand, alcohol **26f** was transformed to **26g**, *via* few synthetic steps. In addition, the coupling partners *i.e.*, **26e** and **26g** were combined through second-generation Grubb's complex (G-II) using $CH_2Cl_2$ to synthesize hydroxy olefin **26h** in 69% yield. Finally, an important step of Hartung–Mukaiyama cyclization of hydroxy olefin **26h** was carried out to form tetrahydrofuran **26i** in 50% yield. Furthermore, in deprotection conditions (80% aq. AcOH at 50 °C), tetrahydrofuran **26i** synthesized final targeted natural product (+)-muricatetrocin B **26j** in 72% yield (Scheme 26).[161]

**2.3.9. Sylvaticin.** Sylvaticins are distinctive members of the annonaceae-derived acetogenins, important because of non-




Scheme 27 Formal total synthesis of (+)-sylvaticin **27g** (adapted from ref. 164).

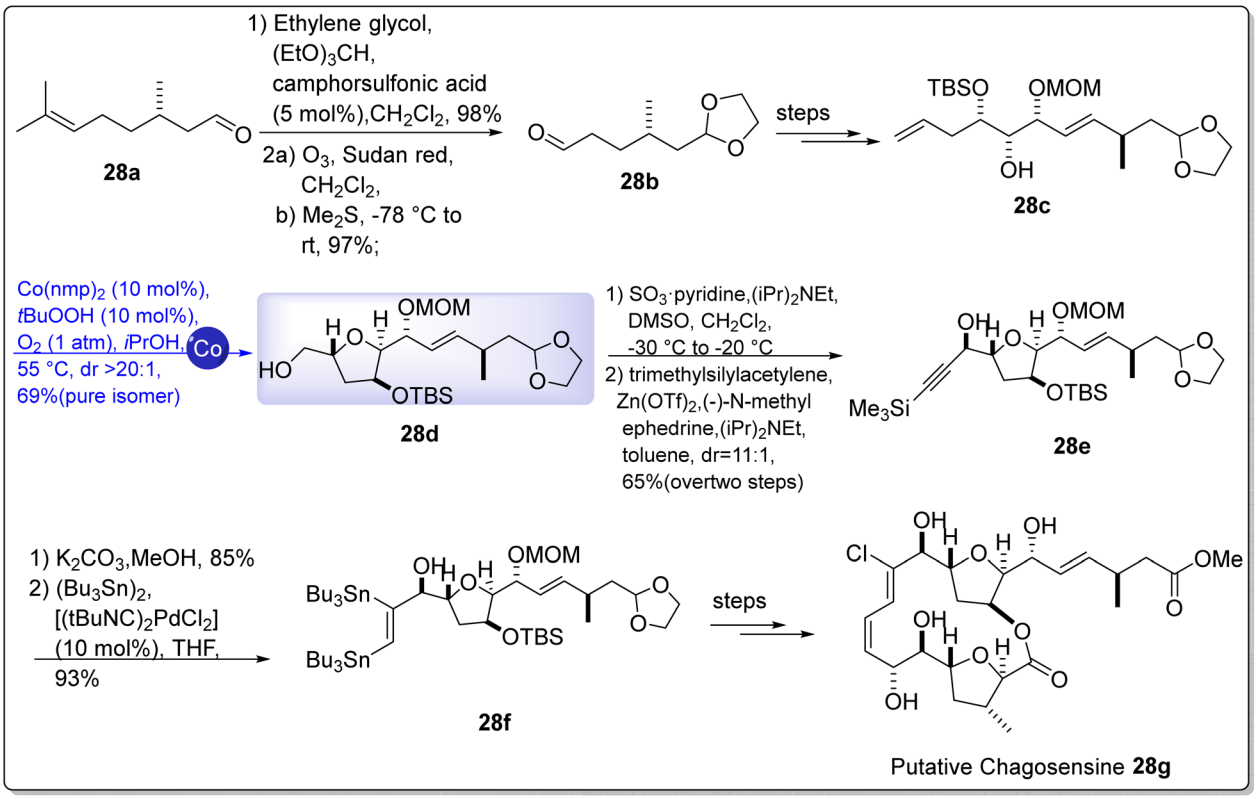
adjacent bis-THF motifs linked *via* 1,4-diol unit. Among them, *cis*-sylvaticin and sylvaticin are epimeric at a single THF ring yet both display notable anti-cancer abilities that have inspired synthetic researchers.[162,163] Dey and Prasad in 2025 described an enantiospecific formal total syntheses of (+)-*cis*-sylvaticin and (+)-sylvaticin from a $C_2$-symmetric furyl carbinol. The *cis*-THF rings were assembled by $OsO_4$-mediated oxidative cyclisation, whereas the *trans*-THF motif was installed through a cobalt-catalyzed Mukaiyama oxidative cyclization using $Co(modp)_2$ with *t*BuOOH and $O_2$, to generate *trans*-THF **27e**. The synthetic strategy initiated with the addition of $BnO(CH_2)_3MgBr$ to bis-Weinreb amide **27a**, which gave diketone **27b** in 98% yield which was further treated over several steps to achieve tetra-TBS ether **27c**. In the next step, Finkelstein reaction and Boord olefination afforded alkene **27d** which was followed by cobalt-catalyzed Mukaiyama cyclization using $Co(modp)_2$, *t*BuOOH, $O_2$ in *i*PrOH at 55 °C to furnish *trans*-THF **27e** (57%, 63% BRSM). In the next step, triflation and Grignard coupling (75%) delivered **27f** followed by its transformation to (+)-sylvaticin **27g** over few steps (Scheme 27).[164]

## 2.4 Synthesis of macrolides

**2.4.1. Chagosensine.** Marine sponges are renowned for harboring complex microbial colonies that serve abundant sources of bioactive natural products with notable structural complexity. Among these, the macrolide chagosensine, obtained from the calcareous sponge *Leucetta chagosensis* collected in the Gulf of Aqaba, showcased remarkable molecular diversity.[165,166] Heinrich *et al.* (2018) reported the total synthesis of putative chagosensine **28g**, wherein cobalt-catalyzed oxidative Mukaiyama cyclization was used to construct both *trans*-tetrahydrofuran rings. In this process, $Co(nmp)_2$ (10 mol%) with *t*BuOOH (10 mol%) and $O_2$ (1 atm) in *i*PrOH at 55 °C were employed. Although **28c** contains two distinct olefin sites, the cyclization proceeded with outstanding regio- and diastereoselectivity (d.r. > 20 : 1, regioselectivity >12 : 1). (*S*)-Citronellal **28a** was converted to **28b** *via* acetalization (98%) and ozonolysis (97%) followed by its conversion to alcohol **28c**, which was subjected to cobalt-catalyzed cyclization to afford **28d** (69%, pure isomer). Modified Parikh–Doering oxidation of **28d** with $(iPr)_2NEt$ and Carreira alkynylation provided **28e** (d.r. = 11 : 1, 65% over two steps). Next, resulting product **28e** was subjected to desilylation (85%) and palladium-catalyzed destination with $(Bu_3Sn)_2$ and $[(t\text{-BuNC})_2PdCl_2]$ (10 mol%) in THF resulted in bisstannane **28f** (93%), which was transformed to putative chagosensine **28g** over few steps (Scheme 28).[167]

**2.4.2. Halichondrin.** Halichondrin B, a prominent member of the halichondrin family, was isolated from a marine sponge. Structurally, it is a complex polyether macrolide featuring multiple fused cyclic ether rings and numerous stereocentres, and it displays potent antitumor activity. Notably, the clinically approved anticancer drug eribulin is a structurally simplified analogue of halichondrin B.[168,169] Nicolaou *et al.* in 2021

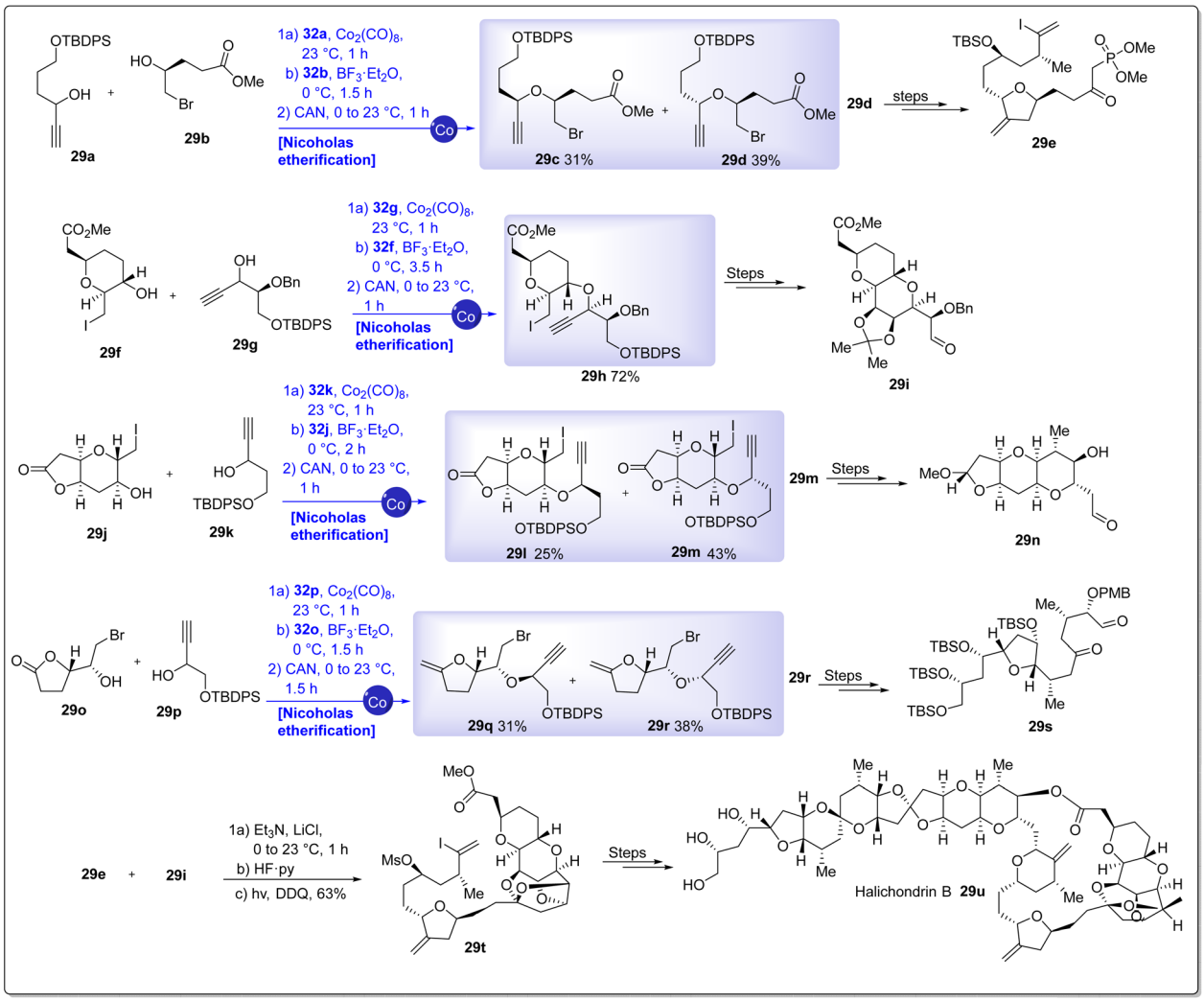



Scheme 28 Total synthesis of putative chagosensine **28g** (adapted from ref. 167).

reported a 25-step convergent route to halichondrin B, ranking amongst the most concise approaches to this target, till date. The key strategic innovation inverted the conventional ether-ring construction order: cobalt-mediated Nicholas etherification installed C–O bonds prior to radical-mediated C–C ring closure, thereby reversing the classical approaches in which C–C bonds preceded C–O cyclization. $Co_2(CO)_8$ coordinated the alkyne of a propargylic alcohol to form a hexacarbonyldicobalt complex. Treatment of the cobalt–alkyne complex with $BF_3\cdot Et_2O$ produced a cobalt complex, that upon exposure with alcohol generated ether–cobalt complex. Subsequent oxidative removal of the cobalt template with CAN delivered the propargylic ether. This cobalt etherification was applied uniformly to construct all four fragments of the natural product. Cobalt-catalyzed Nicholas etherification of propargylic alcohol **29a** with hydroxy bromide methyl ester **29b** ($Co_2(CO)_8$; $BF_3\cdot Et_2O$; CAN) afforded **29c** (31%) and **29d** (39%). Treatment of **29d** over few steps afforded tetrahydropyran **29h** (72%, 5 : 1 *dr*), which was later converted to aldehyde **29i** (70% overall). Analogously, **29j** and acetylene **29k** were also subjected to cobalt catalysis under similar conditions to afford **29l** (25%) and **29m** (43%), leading to compound **29n** (80%) over few steps. Similarly, **29o** and hydroxy acetylene **29p** gave **29q** (31%) and **29r** (38%) upon cobalt-catalyzed Nicholas etherification followed by conversion of **29r** to compound **29s** (55%). Next, coupling of **29e** and **29i** afforded **29t**, which was reacted over several steps to afford the synthesis of halichondrin B **29u** (Scheme 29).[170]

### 2.5 Synthesis of glycoside based natural products

**2.5.1. Varitriol.** Varitriol is a vinyl C glycoside with encouraging properties against several cell lines linked to cancer. *C*-Glycosides, valued for their biological activities and important *in vivo* stability, serve as significant motifs in natural products and drug design. Wang *et al.* in 2025 prepared varitriol **30c** *via* cobalt-catalyzed hydroglycosylation of a terminal alkyne, employing a bench-stable *ortho*-iodobiphenyl (oIB) sulfide as glycosyl donor. In this stereoconvergent process, a cobalt hydride, formed by the reaction of the Co(I) pre-catalyst with $(EtO)_3SiH$, underwent reaction with the terminal alkyne with *cis* selectivity. The resulting vinylcobalt intermediate was made to react with the oIB donor to produce alkene intermediate and an aryl radical that initiated an intramolecular $S_H2$ cyclization to release the glycosyl radical intermediate, whose recombination with alkene intermediate generated Co(III) species, whose subsequent reductive elimination from Co(III) delivered the *E*-configured vinyl *α-C*-glycoside along with the regeneration of Co(I). The less bulky bis(oxazoline) ligand **L9** is critical for regioselectivity outcome, as smaller bis(oxazoline) ligands gave appreciable quantities of 1,1-disubstituted regioisomers by-products. Coupling of oIB sulfide **30a** with aryl alkyne **30b** using $CoI_2$ (10 mol%), **L9** (12 mol%), $(EtO)_3SiH$ (3.0 equiv.), $K_3PO_4\cdot H_2O$ (3.0 equiv.) in DME at rt for 12 h under $N_2$ atmosphere, followed by ester hydrolysis (LiOH, MeOH, rt, 1 h), afforded varitriol **30c** in 36% overall yield (Scheme 30).[171]

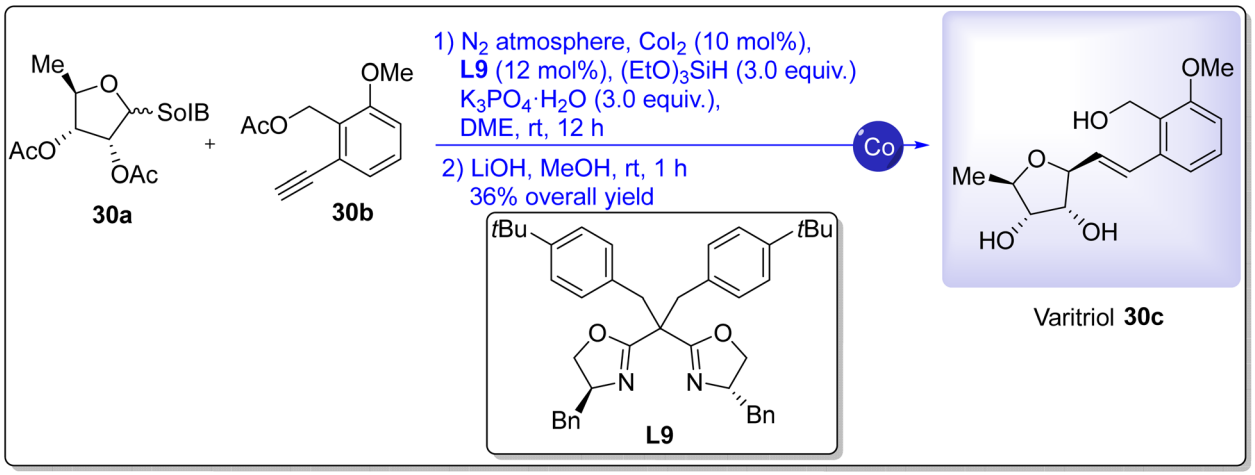



Scheme 29 Total synthesis of halichondrin B **29u** (adapted from ref. 170).

**2.5.2. Fortimicin B.** Fortimicin B belongs to a distinctive subgroup of aminoglycosides obtained from *Micromonospora* species, characterized by its unusual pseudodisaccharide framework.[172–174] Among its analogs, fortimicin B shows potent antibacterial activity with far lower kidney and ear toxicity, making it a promising scaffold for developing next-generation aminoglycoside antibiotics. In 2025, Lu *et al.* completed the asymmetric total synthesis of fortimicin B in 12 steps. The key cobalt-catalyzed step was a Cr(II)/Co(I)-mediated C–C bond coupling, based on the Takai–Utimoto protocol ($CrCl_2$, 4 equiv.; vitamin $B_{12}$, 20 mol%; DMF, 30 °C). This mild radical coupling replaced prior routes to access 6-*epi*-purpurosamine B fragment (up to 16 steps or 20 kbar pressure). Cu(II)-catalyzed IEDDA reaction of **31a** and **31b** gave **31c** (98%, 97%ee), which was treated over few steps to achieve glycosyl acceptor **31d**. Cr(II)/Co(I) coupling of aldehyde **31e** and alkyl bromide **31f** were treated *via* cobalt-catalyzed Takai and Utimoto's protocol involving $CrCl_2$ and vitamin B12 followed by Swern oxidation that delivered ketone **31g** (59%, two steps). The resulting ketone was treated over few steps to give glycosyl donor **31h**. Next, Au(I)-catalyzed glycosylation **31d** and **31h** afforded **31i** (76%, $\alpha:\beta$ = 6 : 1), which was treated over some steps to accomplish the synthesis of desired natural product *i.e.*, fortimicin B **31j** (76%) (Scheme 31).[175]

## 2.6 Synthesis of flavagline

**2.6.1. Rocaglaol.** Rocaglaol belongs to the flavagline family, whose members share a compact cyclopenta[*b*]benzofuran core bearing four to five contiguous stereocentres. It exemplifies this complexity while exhibiting diverse biological properties, for example anti-inflammatory, antiviral, and anticancer activities.[176] Notably, the benzofuran scaffold continues to inspire novel synthetic methodologies, exhibiting promising biologically active properties such as anti-HCV and anti-cancer activities.[177,178] Xu *et al.* in 2022, described a stereodivergent synthesis of eight rocaglaol stereoisomers *via* synergistic Co(II)(or Ni(II))/Ir dual catalysis. The chiral *N*,*N*′-dioxide–Co(II) complex enabled activation of the benzofuranone *via* Lewis acid-promoted enolization, while the activation of allylic electrophile was carried out by Ir-mediated oxidative addition, resulting in Ir-π-allyl

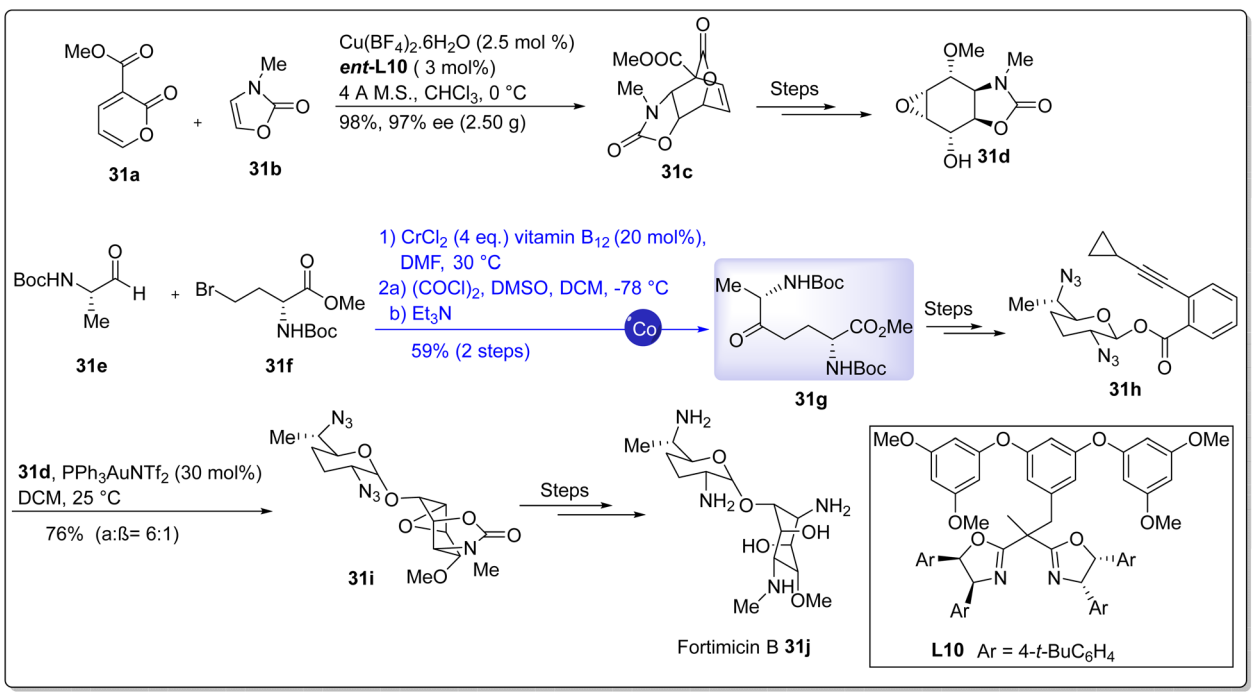



Scheme 30 Total synthesis of varitriol **30c** (adapted from ref. 171).

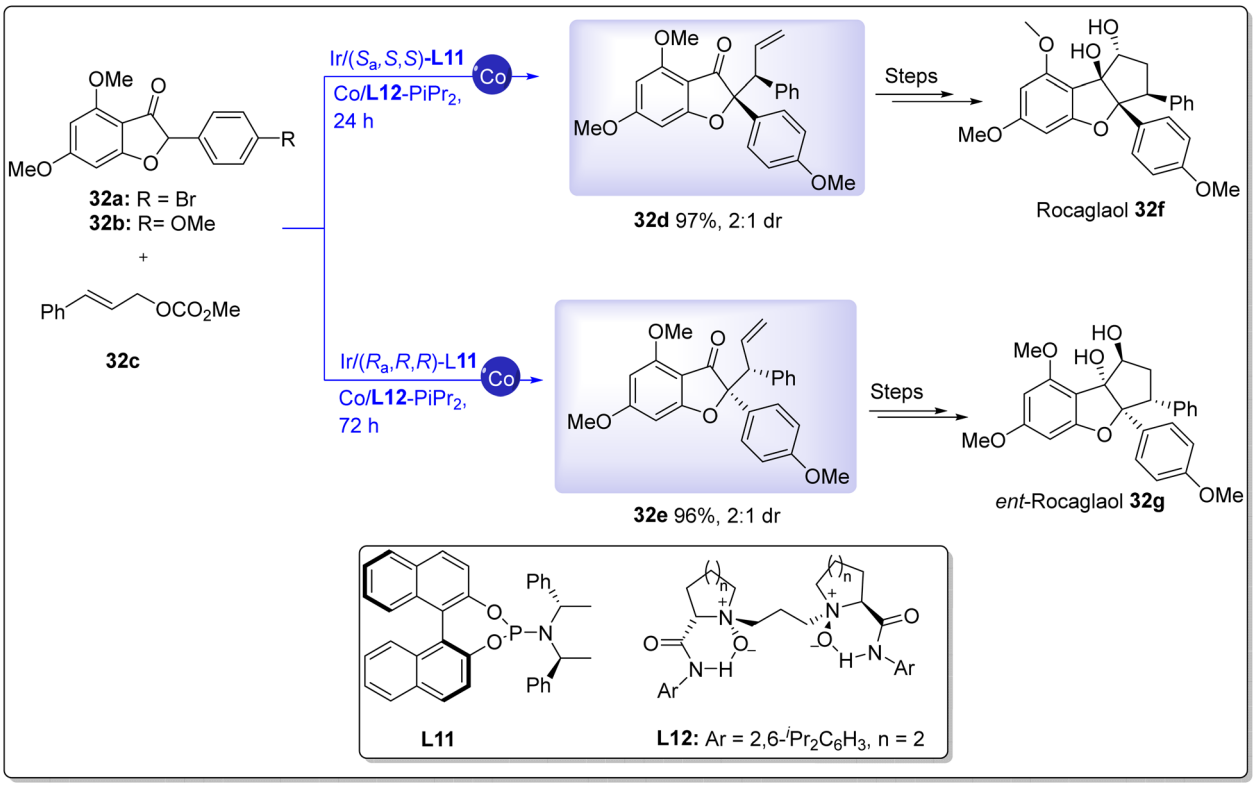
species. Co(II) was found to be better than Cu-based catalysts (which gave 54% yield with 1.1 : 1 dr). Benzofuranones **32a** (R = Br) or **32b** (R = OMe) were reacted with carbonate **32c**, $Co(BF_4)_2 \cdot 6H_2O$ (10 mol%), **L11**-PiPr$_2$ (10 mol%), $(Ir(cod)Cl)_2$ (2 mol%), $K_2CO_3$ (1.3 equiv.), DCM/DCE (1 : 1), 35 °C: ($S_a$,*S*,*S*)-**L12** to afford **32d** (97%, 2 : 1 dr) and employment of ($R_a$,*R*,*R*)-**L11** gave **32e** (96%, 2 : 1 dr). The resulting compounds **32d** and **32e** were independently treated over few steps to synthesized rocaglaol **32f** (58%, 19 : 1 dr) and **32g** (55%, 19 : 1 dr), respectively (Scheme 32).[179]

## 2.7 Total synthesis of pharmaceutically active compounds

**2.7.1. PARP inhibitor PJ-34.** PJ-34 functions by inhibiting PARP (poly (ADP-ribose) polymerase), a small molecule with therapeutic potential in oncology and neuroprotection. Ling and co-workers in 2018 efficiently synthesized PARP inhibitor PJ-34 *via* 3-step sequence started from compound **33a** which underwent cobalt(II)-catalyzed oxidative cyclization, featuring a Co(II)-catalyzed intramolecular C–H functionalization/carbonylation that directly constructs the phenanthridinone ring system. This strategy eliminates the need to use both toxic CO gas and stoichiometric metal oxidants (Ag or Mn salts), required in all previously reported Co-catalyzed C–H carbonylation methods, to form intermediate **33b** in 95%. The second step involved nitration of **33b** with $HNO_3$ followed by reduction using Fe/HCl to achieve compound **33c** in 76% yield. In the final step, coupling of **33c** with *N*,*N*-dimethylglycine *via* EDC, HOBt, and DIPEA in DMF furnished PJ-34 **33d** in 87% yield (Scheme 33).[180]

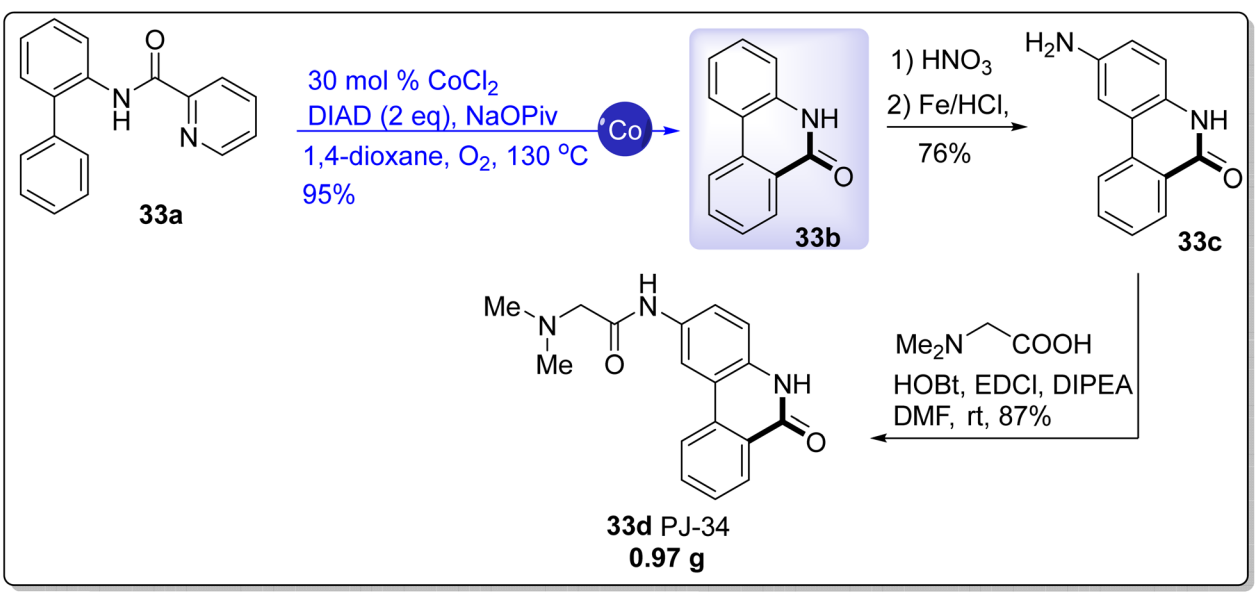



Scheme 31 Total synthesis of fortimicin B **31j** (adapted from ref. 175).

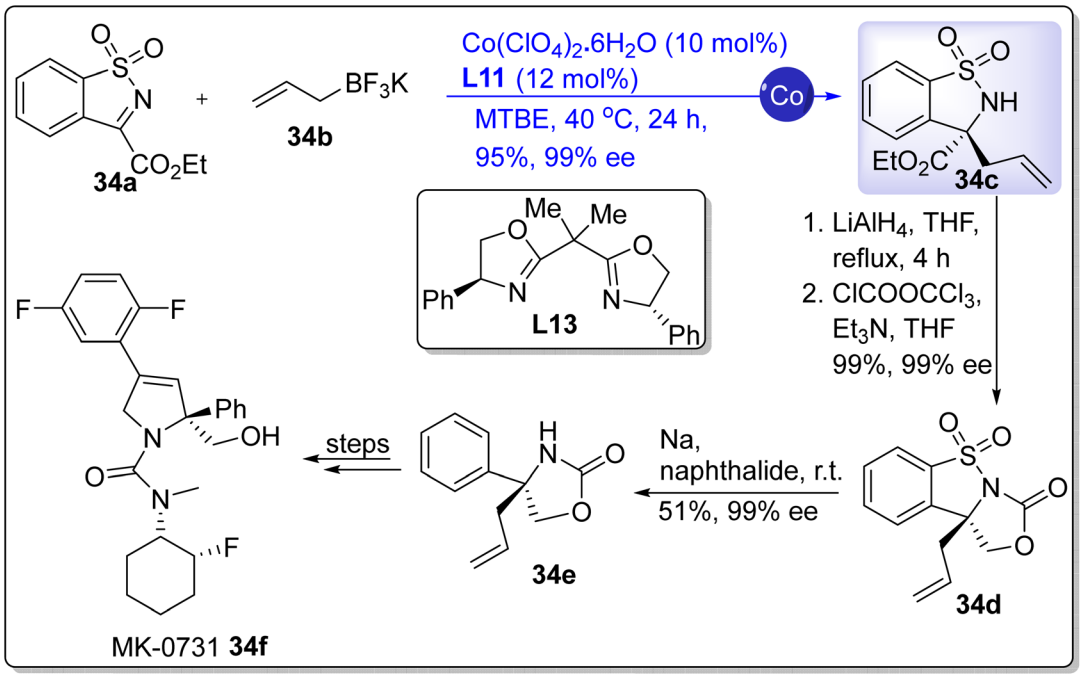



Scheme 32 Total synthesis of rocaglaol **30f** and *ent*-rocaglaol **32g** (adapted from ref. 179).

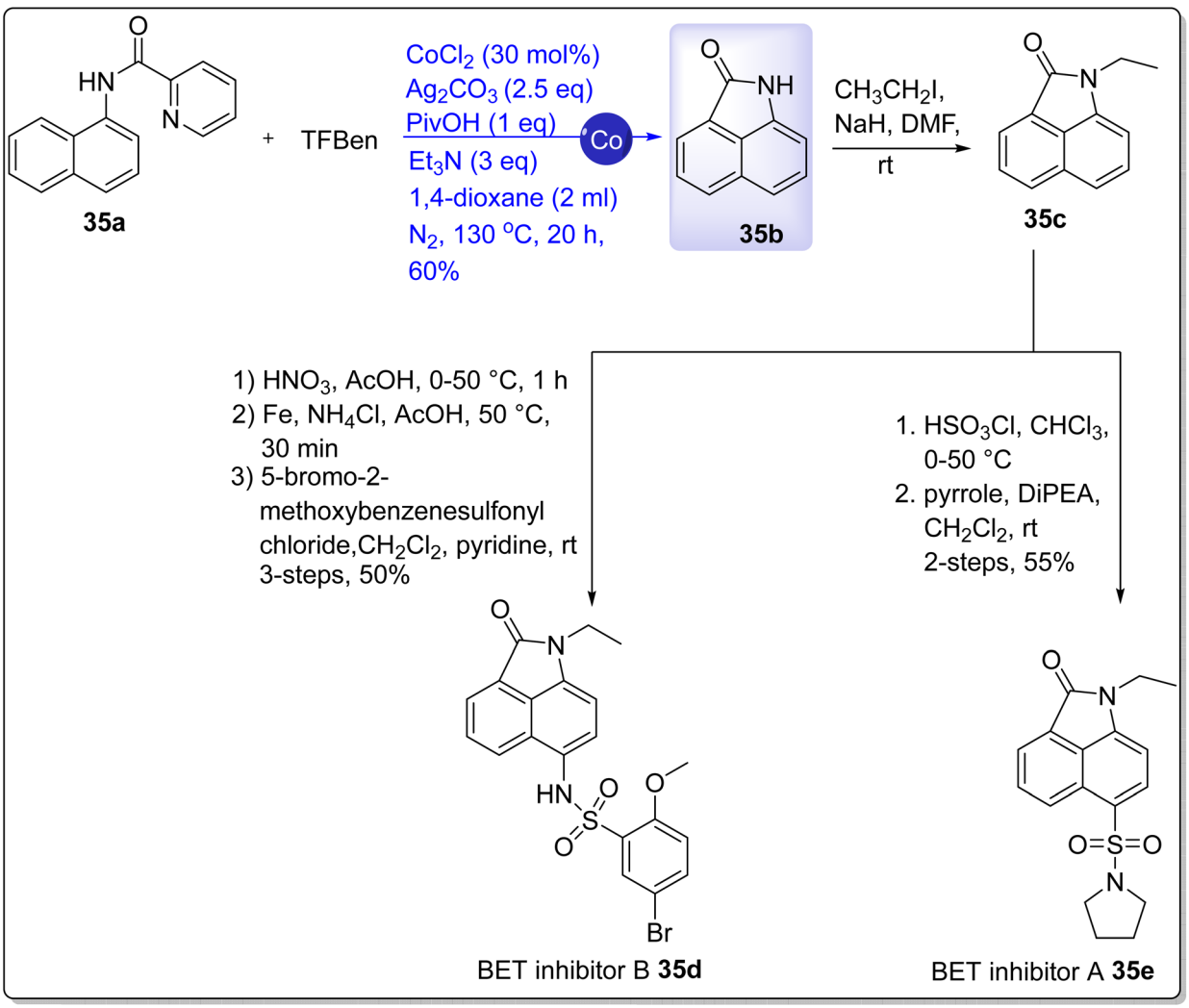
**2.7.2 MK-0371.** MK-0371, a potent inhibitor of the kinesin spindle protein, was synthesized by Wu and coworkers in 2018. They demonstrated the utility of Co(II)/bisoxazoline-catalyzed asymmetric allylation of cyclic ketimines with the synthesis of a key intermediate for MK-0731. The synthesis of MK-0371's intermediate was accomplished *via* highly enantioselective cobalt-catalyzed coupling. The initial step involved the reaction of ethyl ester sulfonamide **34a** with potassium allyl trifluoroborate **34b** in the presence of cobalt catalyst $Co(ClO_4)_2 \cdot 6H_2O$ to afford intermediate **34c** in 95% with 99%ee enantiomeric excess. Subsequent reduction of **34c** using $LiAlH_4$ in THF followed by acetylation with trichloro acetyl chloride and



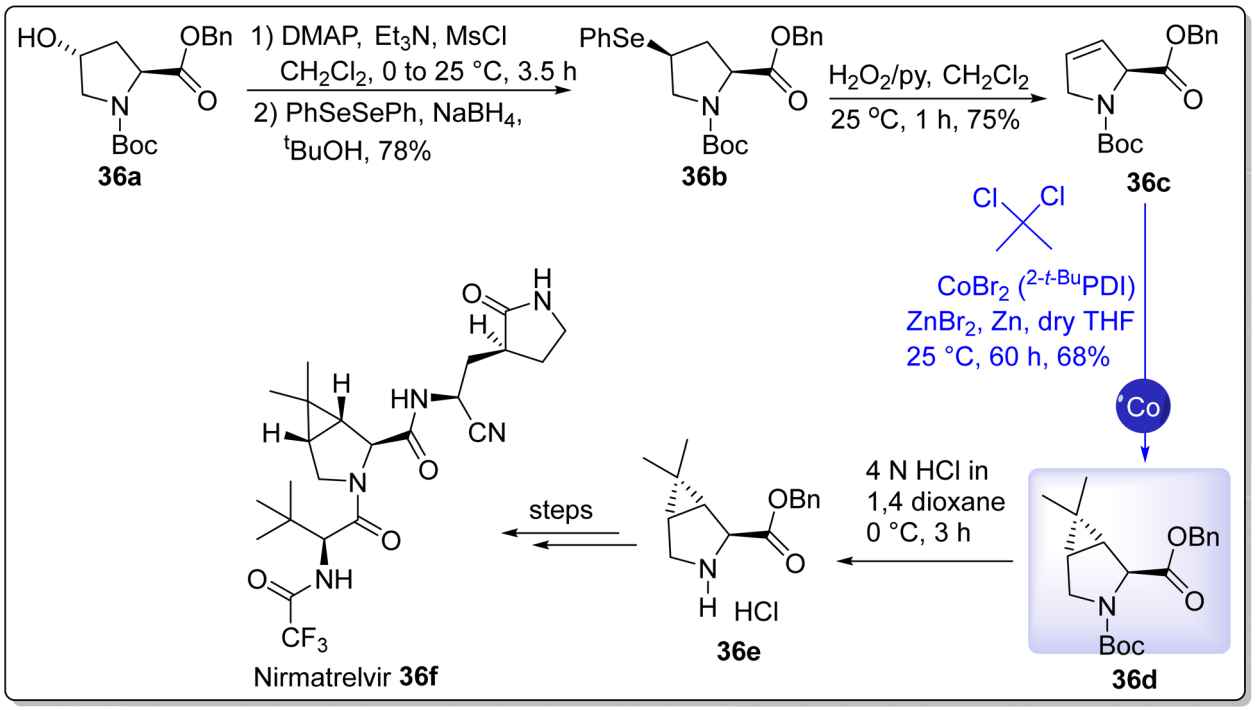

Scheme 33 Total Synthesis of PARP inhibitor PJ-34 **33d** (adapted from ref. 180).




Scheme 34 Total synthesis of MK-0731 **34f** (adapted from ref. 181).




Scheme 35 Total synthesis of BET inhibitor A **35e** and BET inhibitor B **35d** (adapted from ref. 182).




Scheme 36 Total synthesis of nirmatrelvir **36f** (adapted from ref. 183).

$Et_3N$ furnished compound **34d** in 99% yield with 99%ee. Then the treatment of **34d** with sodium naphthalide at room temperature formed compound **34e** in 51% yield with 99%ee. Finally, **34e** was converted to MK-0371 **34f** *via* several synthetic steps (Scheme 34).[181]

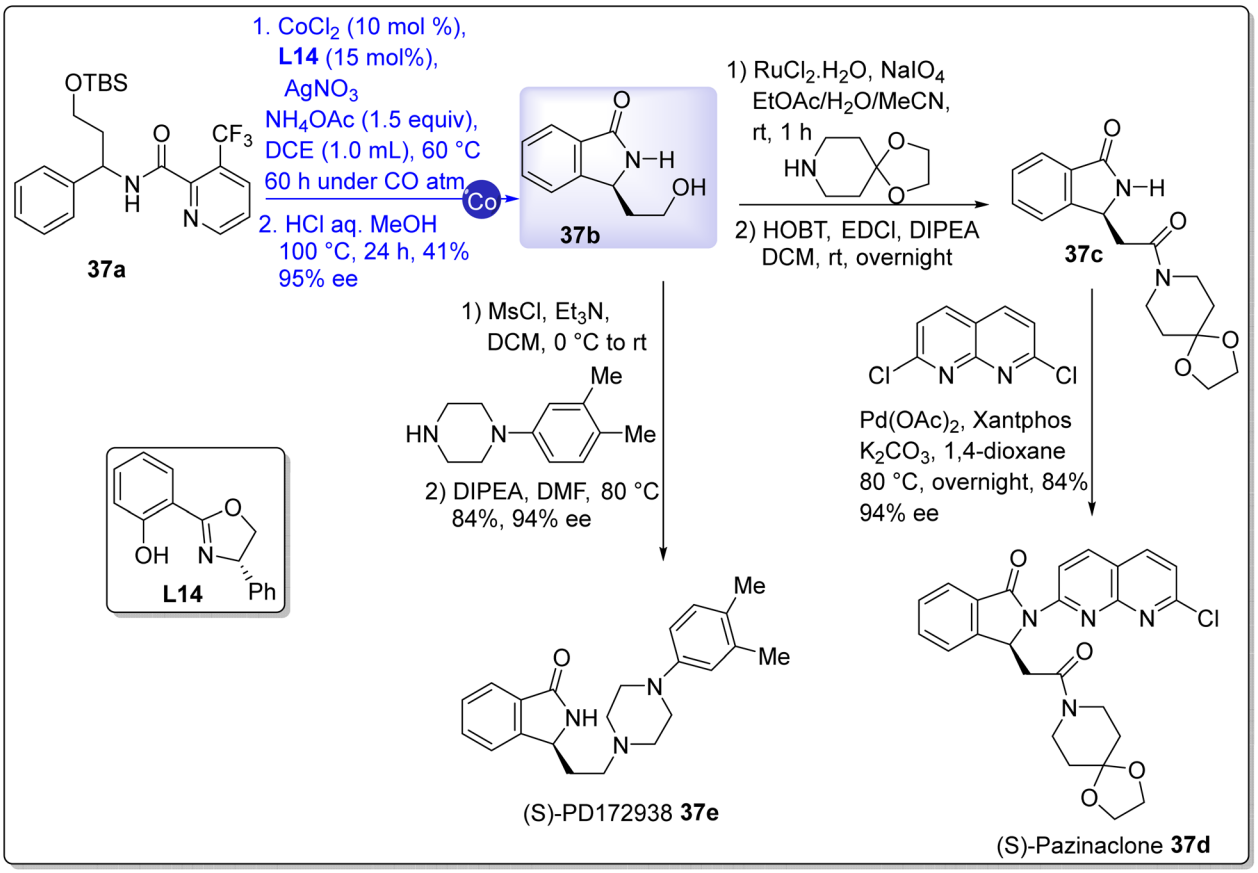
**2.7.3. BET inhibitor A and B.** Ying *et al.* developed a cobalt-catalyzed C–H carbonylation of naphthylamides using TFBen as a CO source and applied this approach to synthesize BET inhibitors **A** and **B**.[180] The cobalt system afforded free (NH)-products directly, unlike the $PdCl_2/Cu(OAc)_2$ system which required gaseous $CO/O_2$ and only afforded *N*-alkyl products (37–71%). In the catalytic cycle, Co(II) is oxidized to Co(III) by Ag(I), enabling C8–H activation; CO coordination and reductive elimination form the Co[I] complex, and subsequent hydrolysis released the product, while Co(I) is reoxidized to regenerate the catalyst. On gram scale, naphthylamide **35a** was treated with TFBen (1.75 equiv.), $CoCl_2$ (30 mol%), $Ag_2CO_3$ (2.5 equiv.), PivOH (1 equiv.), and $Et_3N$ (3 equiv.) in 1,4-dioxane under $N_2$ at 130 °C for 20 h, furnishing **35b** in 60% yield. *N*-Alkylation ($CH_3CH_2I$, NaH, DMF, rt) of **35b** gave **35c**. For BET inhibitor **B**, **35c** was subjected to nitration, iron reduction, and sulfonamide formation to afford **35d** in 50% yield (three steps). Furthermore, **35c** also underwent chlorosulfonation and reaction with pyrrole/DiPEA to furnish BET inhibitor A **35e** in 55% yield (two steps) (Scheme 35).[182]

**2.7.4. Nirmatrelvir.** Nirmatrelvir, marketed as part of Paxlovid with ritonavir, is a tripeptide like inhibitor targeting the SARS-CoV-2 main protease. Shekhar *et al.* used Co(II)-catalyzed reductive dimethylcyclopropanation as the key step to introduce the *gem*-dimethylcyclopropane-fused proline core that enhanced protease inhibitory potency.[181] Mesylation of hydroxy proline benzyl ester **36a** followed by selenylation with diphenyl diselenide and $NaBH_4$ afforded selenide **36b** in 78% yield. Oxidative elimination of selenide **36b** with $H_2O_2$/pyridine then afforded alkene **36c** (75%). Co(II)-catalyzed dimethylcyclopropanation of **36c** using $CoBr_2$(2-tBuPDI), Zn, 2,2-dichloropropane and $ZnBr_2$ in dry THF at 25 °C (60 h) resulted in bicyclic amino acid **36d** (68%). Furthermore, Boc deprotection of amino acid **36d** with 4 N HCl in 1,4-dioxane at 0 °C gave amine hydrochloride **36e**, which over several steps afforded nirmatrelvir **36f** (Scheme 36).[183]

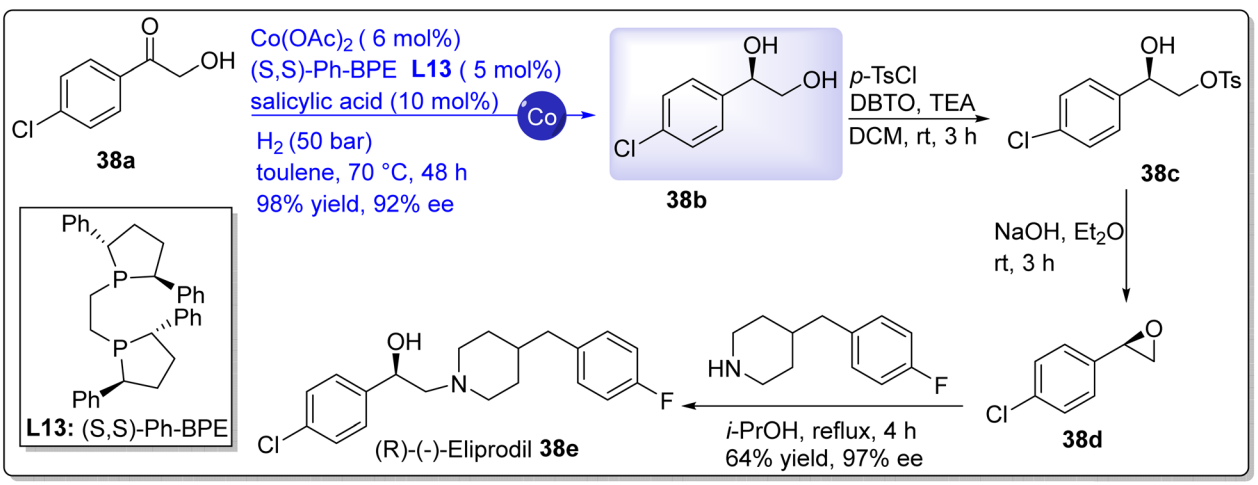
**2.7.5. (*S*)-Pazinaclone and (*S*)-PD172938.** (*S*)-PD172938 is a selective dopamine D4 receptor ligand, having notable pharmacological relevance. In contrast, (*S*)-pazinazclone, has been explored as benzodiazepine receptor agonist for the management of the anxiety disorders.[184] Teng *et al.* in 2024, demonstrated the first cobalt-catalyzed enantioselective C–H carbonylation by preparing both targets from common intermediate **37b**. Kinetic resolution of **37a** with $CoCl_2$ (10 mol%), Salox ligand **L12** (15 mol%), $AgNO_3$ (2.0 equiv.), and $NH_4OAc$ (1.5 equiv.) under CO (1 atm) (used as C1 source) in DCE at 60 °C for 60 h, gave **37b** in 41% yield with 95%ee. Mesylation of **37b** followed by substitution reaction with 6,7-dimethyl-1,2,3,4-tetrahydroisoquinoline gave (*S*)-PD172938 **37e** (84%, 94%ee). Next, oxidation reaction of **37b** and amide coupling with 1,4-dioxa-8-azaspiro[4.5]decane delivered **37c** (59%, 95%ee over two steps) whose Buchwald–Hartwig coupling provided (*S*)-pazinaclone **37d** (84%, 94%ee) (Scheme 37).[185]

**2.7.6. (*R*)-(−)-Eliprodil.** (*R*)-(−)-Eliprodil is the enantiomer of the neuroprotective drug eliprodil. Song *et al.* demonstrated its efficient synthesis in 2025. They described a four-step synthesis of **38e**, including the first earth-abundant metal-




Scheme 37 Total synthesis of (*S*)-pazinaclone **37d** and (*S*)-PD172938 **37e** (adapted from ref. 185).




Scheme 38 Total synthesis of (*R*)-(−)-eliprodil **38e** (adapted from ref. 186).

catalyzed asymmetric hydrogenation of an α-hydroxy ketone. A nonredox Co(II) cycle is enabled with the use of an additive containing salicylic acid, which formed two hydrogen bonds with the substrate. Asymmetric hydrogenation of **38a** ($Co(OAc)_2$ (6 mol%), (*S*,*S*)-Ph-BPE (5 mol%) with salicylic acid (10 mol%), $H_2$ (50 bar), toluene, 70 °C, 48 h) resulted in diol **38b** (98% yield, 92%ee) followed by its tosylation (*p*-TsCl, DBTO, TEA, DCM, rt) to obtain **38c**, whose base-mediated epoxidation (NaOH, $Et_2O$) afforded **38d**. Finally, the ring-opening of **38d** with 4-(4-fluorobenzyl)piperidine (*i*-PrOH, reflux, 4 h) delivered (*R*)-(−)-eliprodil **38e** in 64% yield with 97%ee (Scheme 38).[186]

## 3 Conclusion

The current review summarizes the applications of cobalt catalysis towards the synthesis of diverse classes of natural products and pharmaceutically active compounds, reported since 2018. Cobalt catalysis has made significant progress in the synthesis of natural products and biologically relevant compounds and has established itself as a crucial step for forming bonds between atoms within multi-step synthetic sequences. Diverse classes of natural products including alkaloids, terpenoids/diterpenoids, polyketides and macrolides along with glycoside-based natural products and several pharmaceuticals have been reviewed to be obtained by employing cobalt catalysis as one of the key steps in corresponding synthetic schemes. The thorough analysis unveiled that the asymmetric cobalt catalysis, involving the use of chiral ligands, led to significantly high yields of corresponding products with significant stereochemical control. Future research advances will likely require the development of more efficient asymmetric cobalt-catalytic approaches, which are primed to deliver high levels of enantiomeric control for future synthetic and biologically active targets.

## Conflicts of interest

The authors declare no conflicts of interest.

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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