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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.

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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 $\text{Co}_2(\text{CO})_8$ 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 $\text{Co}(\text{II})$ salt through zinc or organo-magnesium to produce reactive $\text{Co}(\text{I})$ 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 $\text{Co}(\text{III})$ species enable improved selectivity and new transformations.²³

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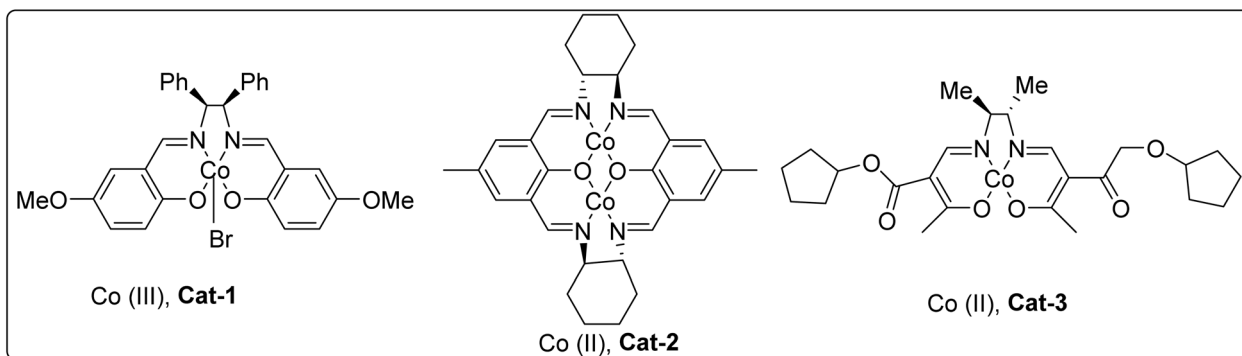


Fig. 1 Structure of Co(II), Co(III) complexes.

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

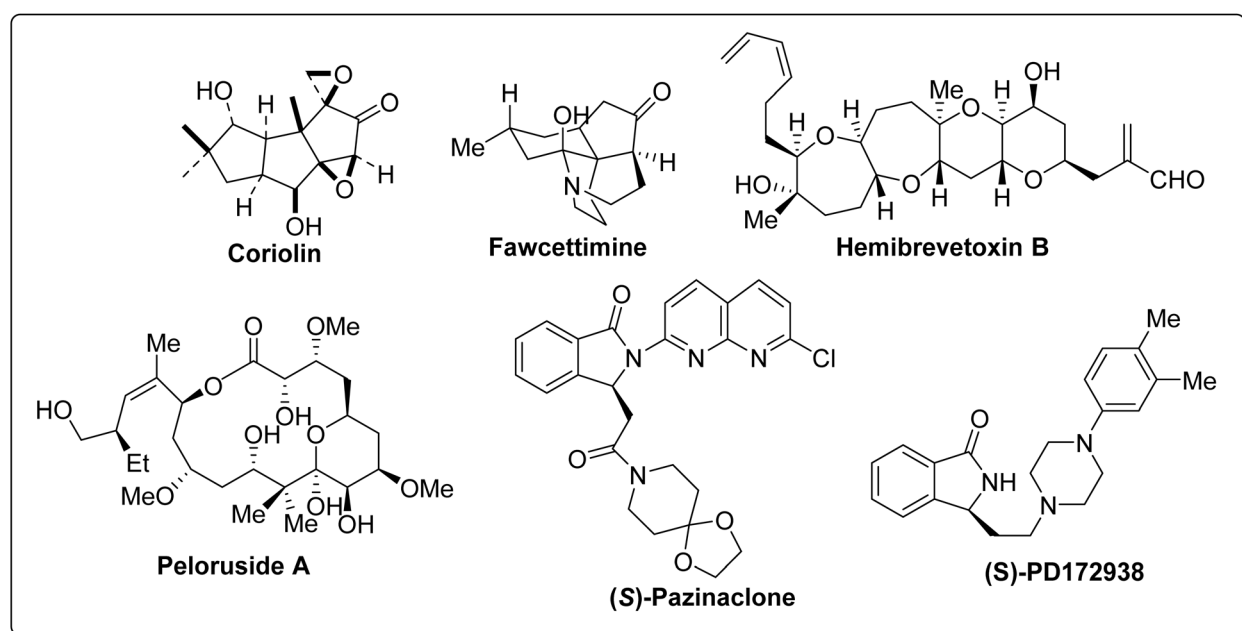


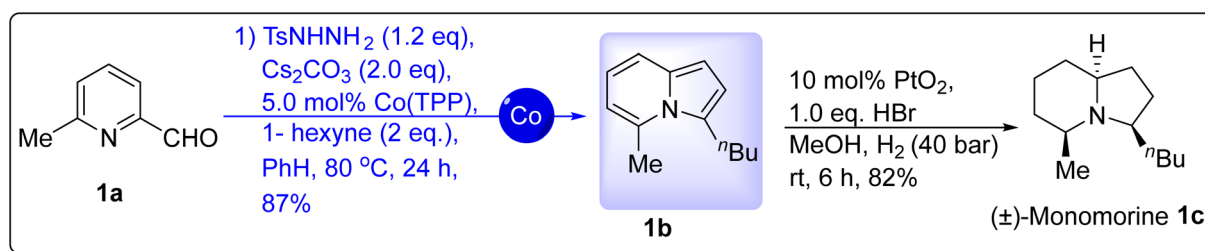
Fig. 2 Structures of few natural products and pharmaceuticals compounds synthesized by Co-catalysis.

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 (\pm)-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 (TsNHNH₂ (1.2 equiv.), Cs₂CO₃ (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 (\pm)-monomorine **1c** in 82% yield³⁸ (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 monoterpene 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)₂·4H₂O (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

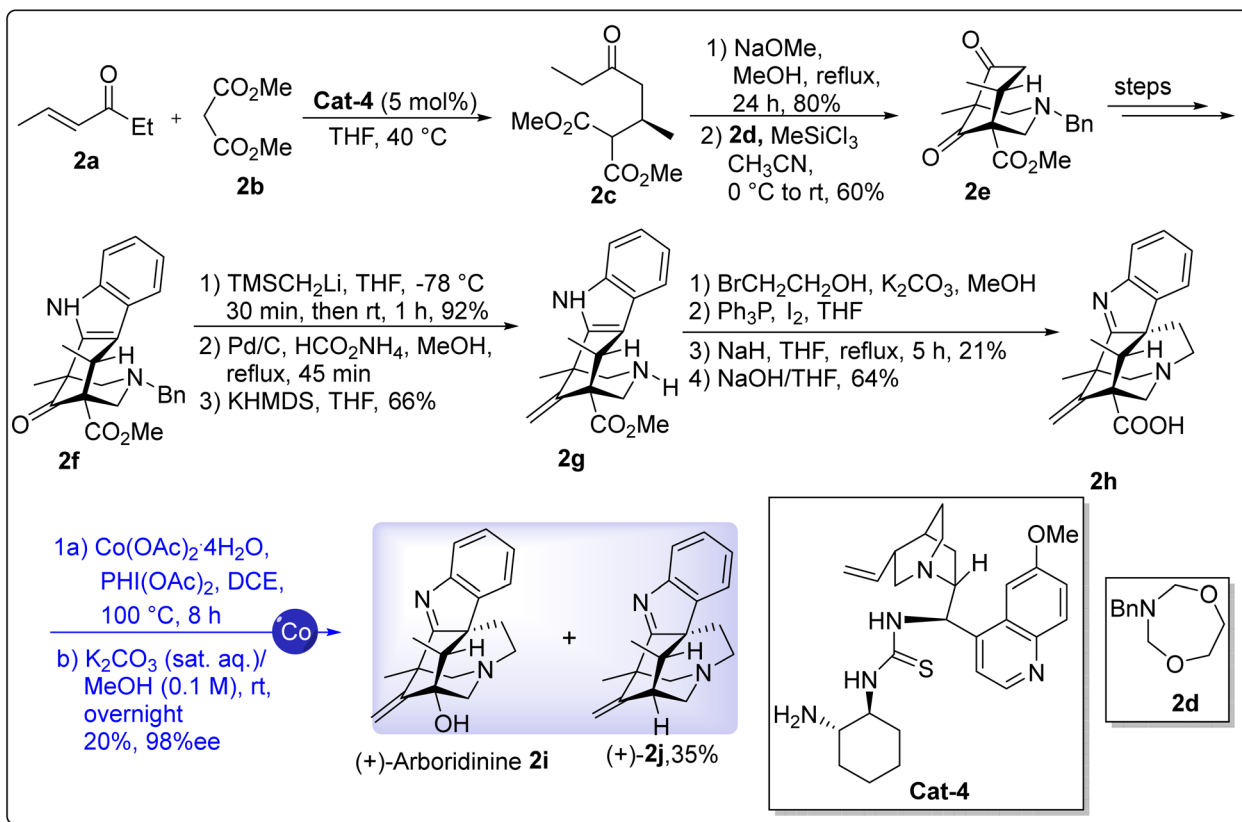
involving route proved uniquely effective at the congested bridgehead where other decarboxylative methods failed. The synthesis commenced with organocatalytic asymmetric Michael addition of dimethyl malonate **2b** to enone **2a** (Cat-4, THF) to furnish enantioenriched ketone **2c**. Dieckmann condensation 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 TMSCH₂Li delivered the silyl alcohol (92% yield), and subsequent debenzoylation 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)₂·4H₂O (0.1 equiv.) and PhI(OAc)₂ (1.5 equiv.) in DCE at 100 °C, 8 hours, followed by saponification (K₂CO₃/MeOH), delivered (+)-arboridinine **2i** (20% yield, 98% ee) alongside deoxyarboridinine **2j** (35%) from competitive hydrogen abstraction of the bridgehead radical intermediate⁴⁴ (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 monoterpene indole alkaloids. These compounds were derived from *Strychnos angustiflora* Benth and they have gained significant attention due to their biological activities including antimalarial, anti-inflammatory, 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 Co₂(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 POCl₃ at 80 °C formed the enamide **3e** as inseparable isomers in 62%. The carbonylative cyclization of **3e** with Co₂(CO)₈, ethyl chloroacetate, and K₂CO₃ in MeOH at 60 °C



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





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

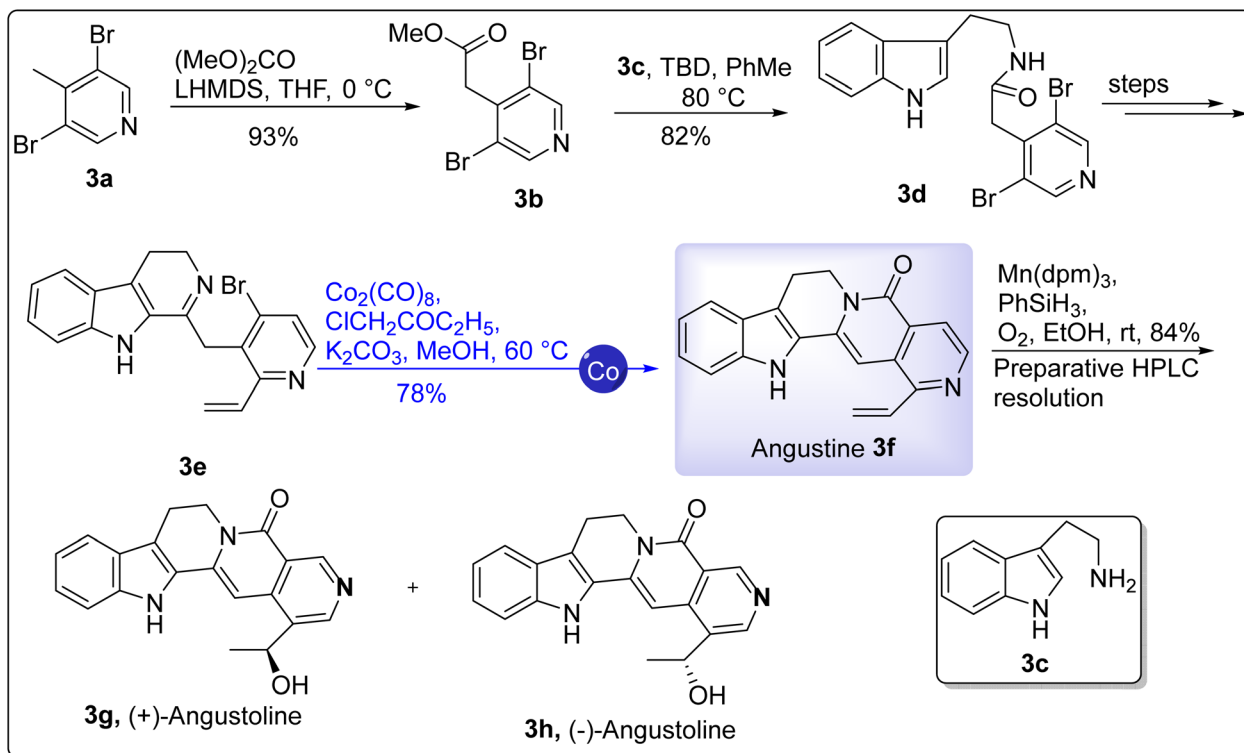
formed the natural product angustine **3f**, in 78% yield. Mukaiyama hydration $[\text{Mn}(\text{dpm})_3, \text{PhSiH}_3, \text{O}_2, \text{EtOH}, \text{r.t.}]$ converted **3f** to (\pm) -angustoline in 84% yield, which was resolved by preparative HPLC to give (+)-angustoline **3g** and (–)-angustoline **3h**. The anti-Zika virus (ZIKV) inhibitory activity of (–)-angustoline ($\text{IC}_{50} = 68.67 \mu\text{M}$) and (+)-angustoline ($\text{IC}_{50} = 17.91 \mu\text{M}$) 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 $\text{Cp}^*\text{Co}(\text{III})$ -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 $\text{Cp}^*\text{Co}(\text{I})$, 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 aryethylamine 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 $\text{Cp}^*\text{Co}(\text{III})$ -catalyzed C–H annulation conditions *i.e.*, $[\text{Cp}^*\text{Co}(\text{CO})\text{I}_2]$ (10 mol%), AgSbF_6 (20 mol%), $\text{Zn}(\text{OAc})_2$ (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 ($\text{Pd}(\text{OAc})_2$, 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





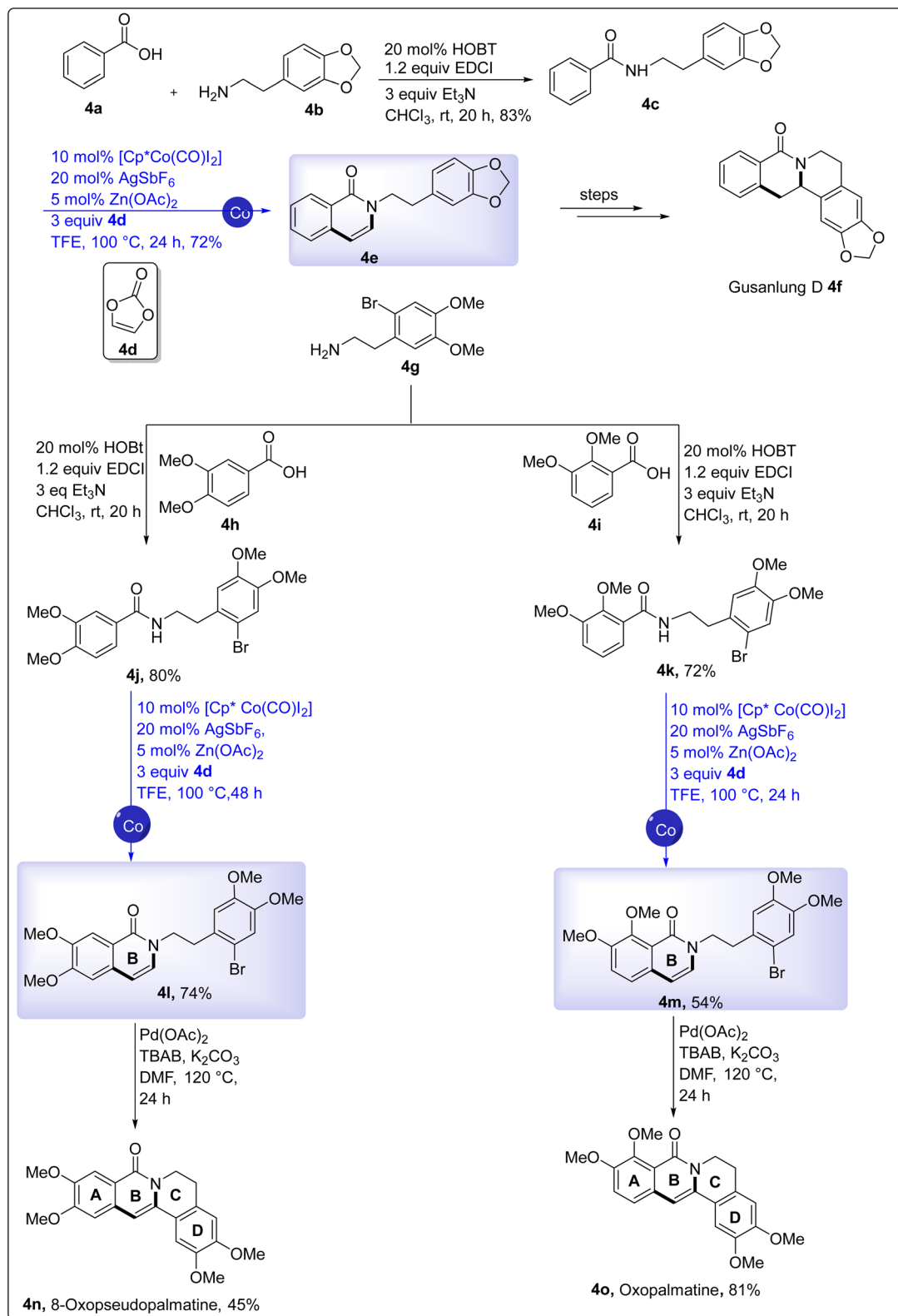
Scheme 3 Total synthesis of angustine **3f**, (+)-angustoline **3g** and (–)-angustoline **3h** (adapted from ref. 50).

diastereomer. Ozonolysis and subsequent $\text{Cu}(\text{BF}_4)_2/\text{Fe}(\text{BF}_4)_2$ -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 $\text{Co}(\text{salen}^{t\text{-Bu},t\text{-Bu}})\text{Cl}$ and PhSiH_3 in anhydrous acetone at 38 °C to provide the C-12 all-carbon quaternary center *via* the intramolecular $\text{Csp}^3\text{–Csp}^2$ 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*)-cryptostyline, 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 $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (10 mol%) and a chiral salicyloxazoline (Salox) ligand (15 mol%), $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (20 mol%) as the oxidizing agent, and $\text{PivONa} \cdot \text{H}_2\text{O}$ (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 $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (10 mol%), (*R,S*)-**L2** (15 mol%), $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (20 mol%), $\text{PivONa} \cdot \text{H}_2\text{O}$ (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



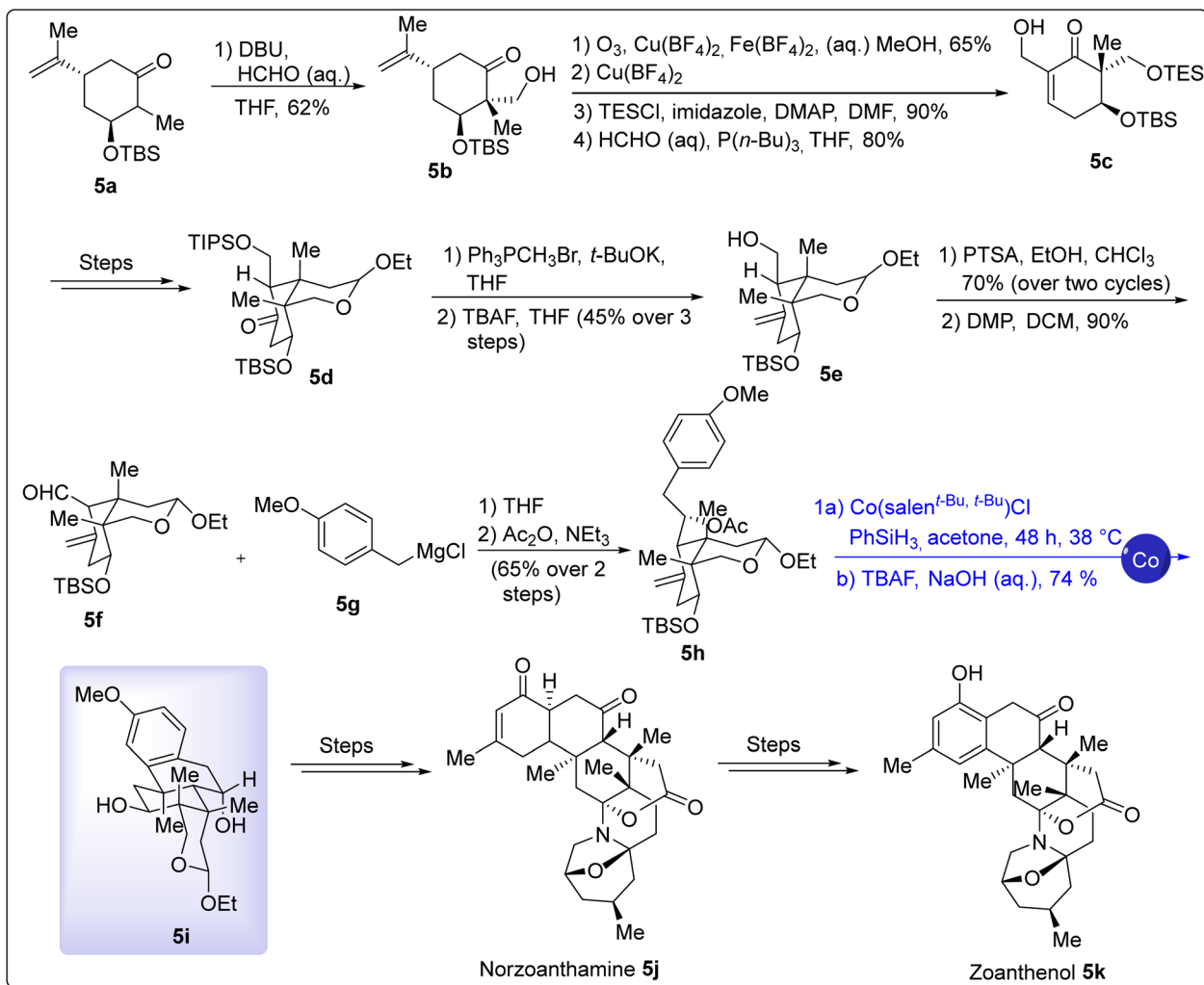


Scheme 4 Total synthesis of gusanlung D 4f, 8-oxopseudopalmatine 4n, and oxopalmatine 4o (adapted from ref. 52).

scale (1.42 g). Desilylation followed by hydrogenation using Pd/C, H₂, MeOH at 50 °C afforded 6c in 62% yield with >99%ee, from which PA₆ was removed using LiAlH₄ 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 CH₂O and NaBH₄ afforded (*S*)-laudanosine **6f** in 76% yield with 98% ee. Oxidative cyclization of **6f** using PIFA, HPA, BF₃·Et₂O, MeCN afforded (*S*)-sebiferine **6g** in 70% yield with 98% ee. Desymmetrization of **6h** using **6r** was conducted by employing Co(OAc)₂·4H₂O, (*R*)-**L1** to afford **6i** in 90% yield with 96% ee (1.52 g); sequential desilylation, hydrogenation, PA₆ 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 PA₆ removal afforded the precursor (58%, 99% ee) for (+)-NPS R-568 **6q** (Scheme 6).⁶⁸

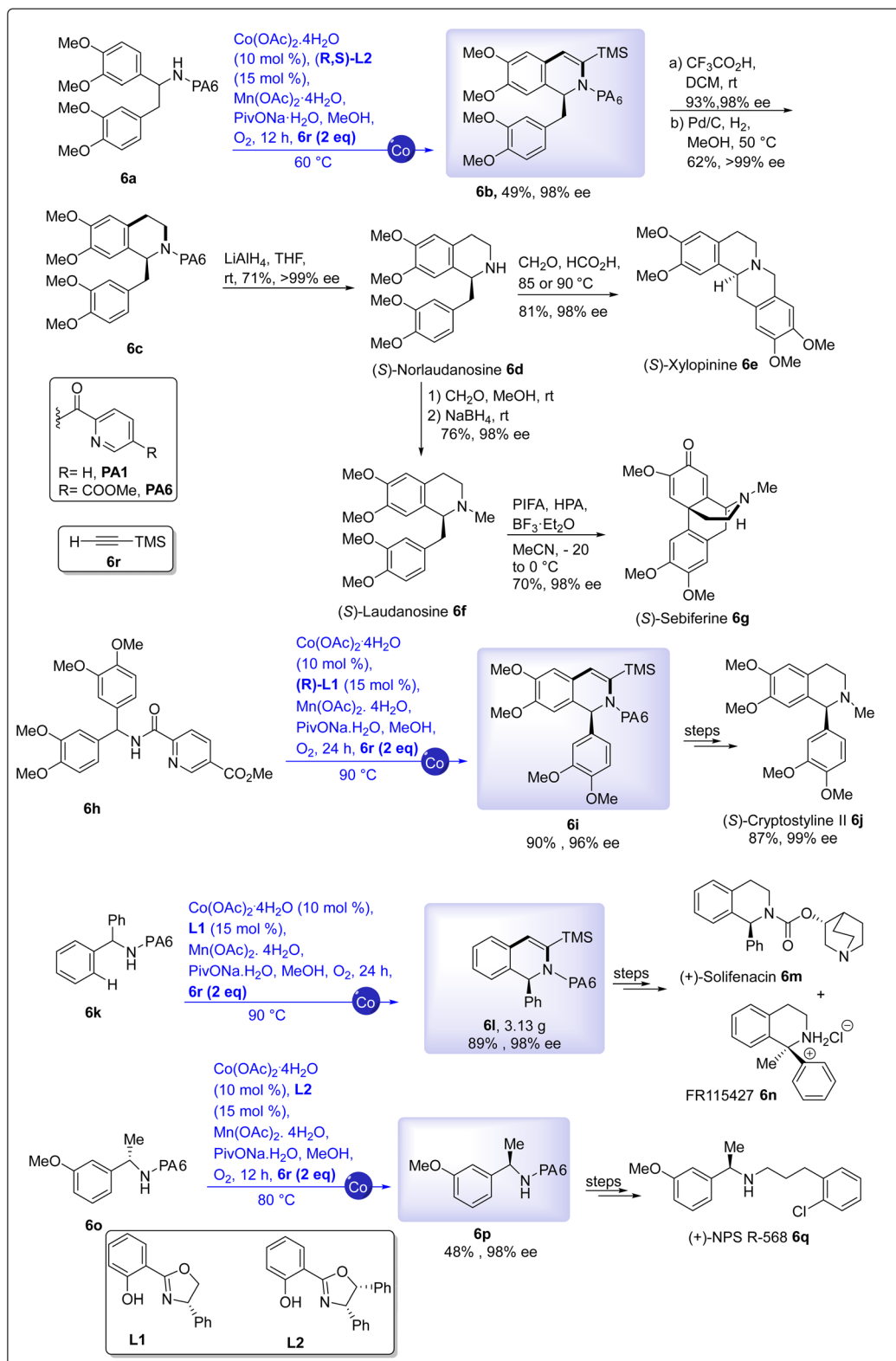
2.1.7. (±)-Halichonine B. Halichonine B, a sesquiterpene alkaloid extracted from the sponge *Halichondria okadai*, exhibits a C(sp³) rich framework characterized by unique quaternary methyl substitution. Biologically, halichonine B demonstrates potent cytotoxicity, notably triggering apoptosis in HL60 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 LiAlH₄ reduction afforded alcohol **7b**. Cobalt-catalyzed radical hydrocyanation (**Cat-5**, TsCN, PhSiH₃, 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 Me₂CuLi (Et₂O, –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 (IC₅₀ = 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



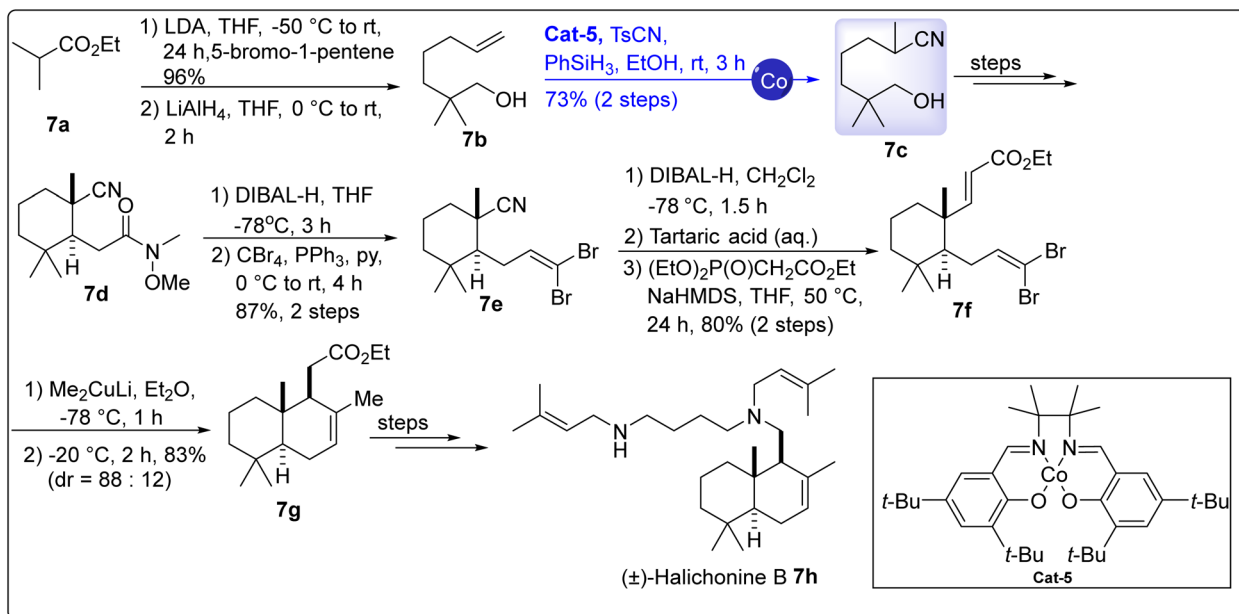


Scheme 6 Total synthesis of (*S*)-norlaudanosine **6d**, (*S*)-xylopinine **6e**, (*S*)-laudanosine **6f**, (*S*)-sebiferine **6g**, (*S*)-cryptostyline II **6j**, (+)-solifenacin **6m**, FR115427 **6n** and (+)-NPS R-568 **6q** (adapted from ref. 68).

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**, PhSiH₃, 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).

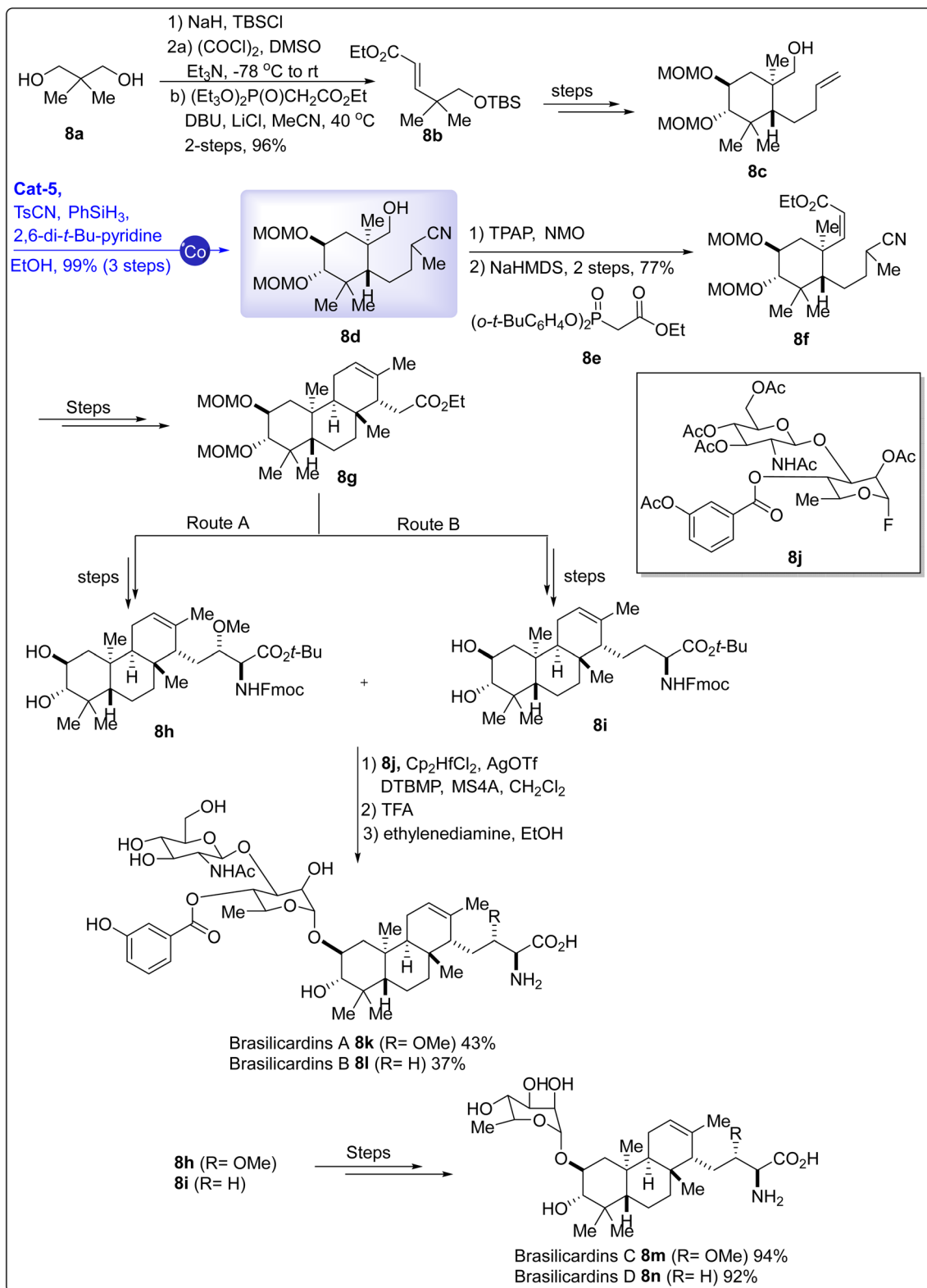
steps). Oxidation of **8d** with TPAP/NMO followed by Z-selective HWE olefination employing **8e** provided (Z)- α,β -unsaturated ester **8f** (77%, two steps). Next, **8f** was converted to tricyclic ester **8g**, from which, two routes installed the amino acid component: route A gave β -methoxy-substituted **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** [$\text{Co}_2(\text{CO})_8$ (1.05 equiv.), NMO (3.5 equiv.), CO (balloon), DCE, rt to $76\text{ }^{\circ}\text{C}$] afforded ketoester **9d** (40%, 98%ee after crystallization). This first PK reaction employed stoichiometric $\text{Co}_2(\text{CO})_8$ with NMO to build the CD ring required pre-complexation at room temperature which was gradually increased to $76\text{ }^{\circ}\text{C}$ as $\text{Co}_2(\text{CO})_8$ 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 [$\text{Co}_2(\text{CO})_8$ (10 mol%), TMTU (60 mol%), PhMe, $60\text{ }^{\circ}\text{C}$, CO (1 atm), 12 h] to furnish **9f** (21%) and C2 epimer **9g** (42%).

Thus, the second catalytic $\text{Co}_2(\text{CO})_8$ /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 ($\text{IC}_{50} = 0.58\text{ }\mu\text{M}$), 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 $\text{Co}_2(\text{CO})_8$ 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 $\text{Co}_2(\text{CO})_8$ (20 mol%) in toluene



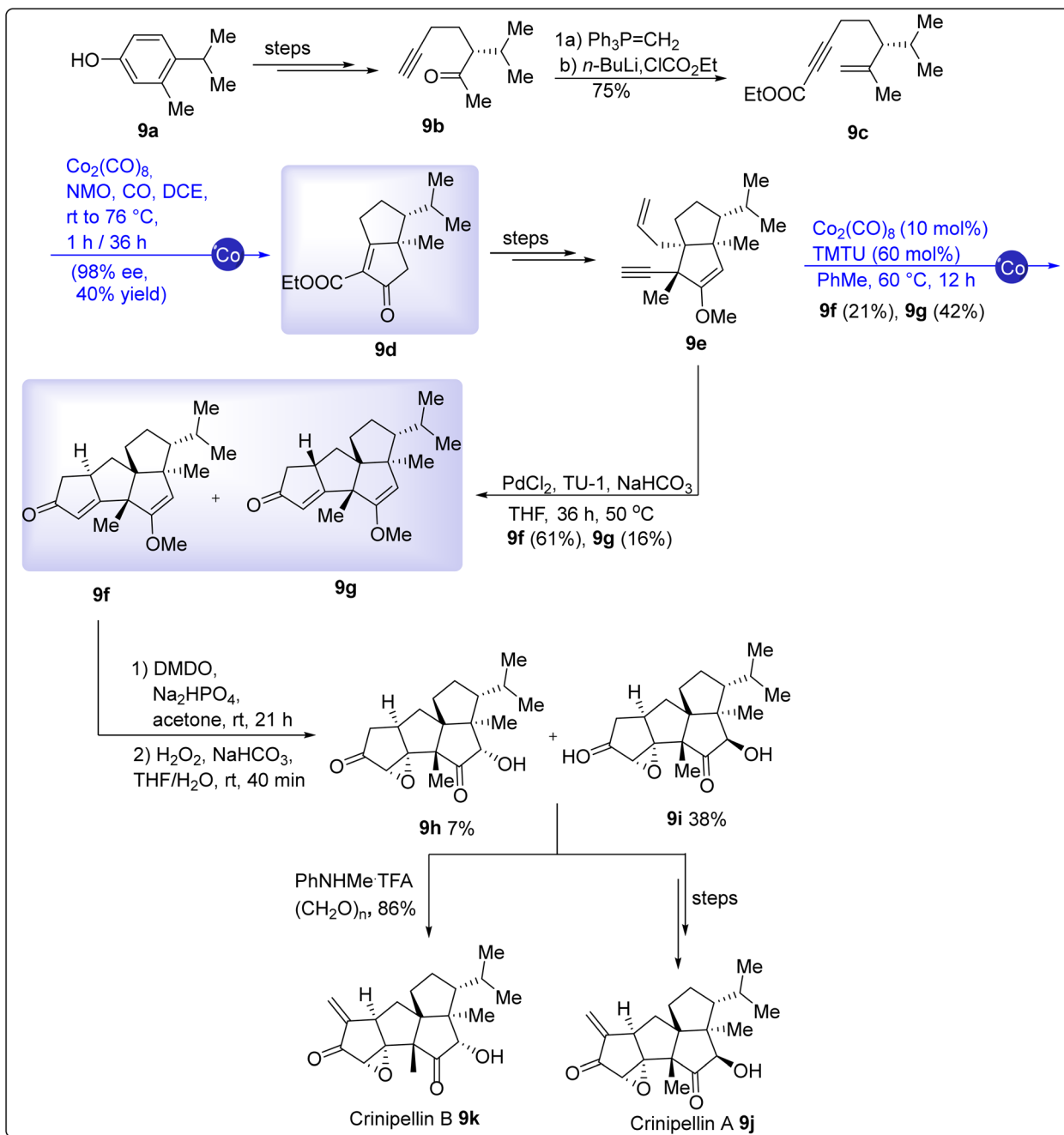


Scheme 8 Total synthesis of brasilicardins A **8k**, brasilicardins B **8l**, brasilicardins C **8m**, brasilicardins D **8n** (adapted from ref. 76).

(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





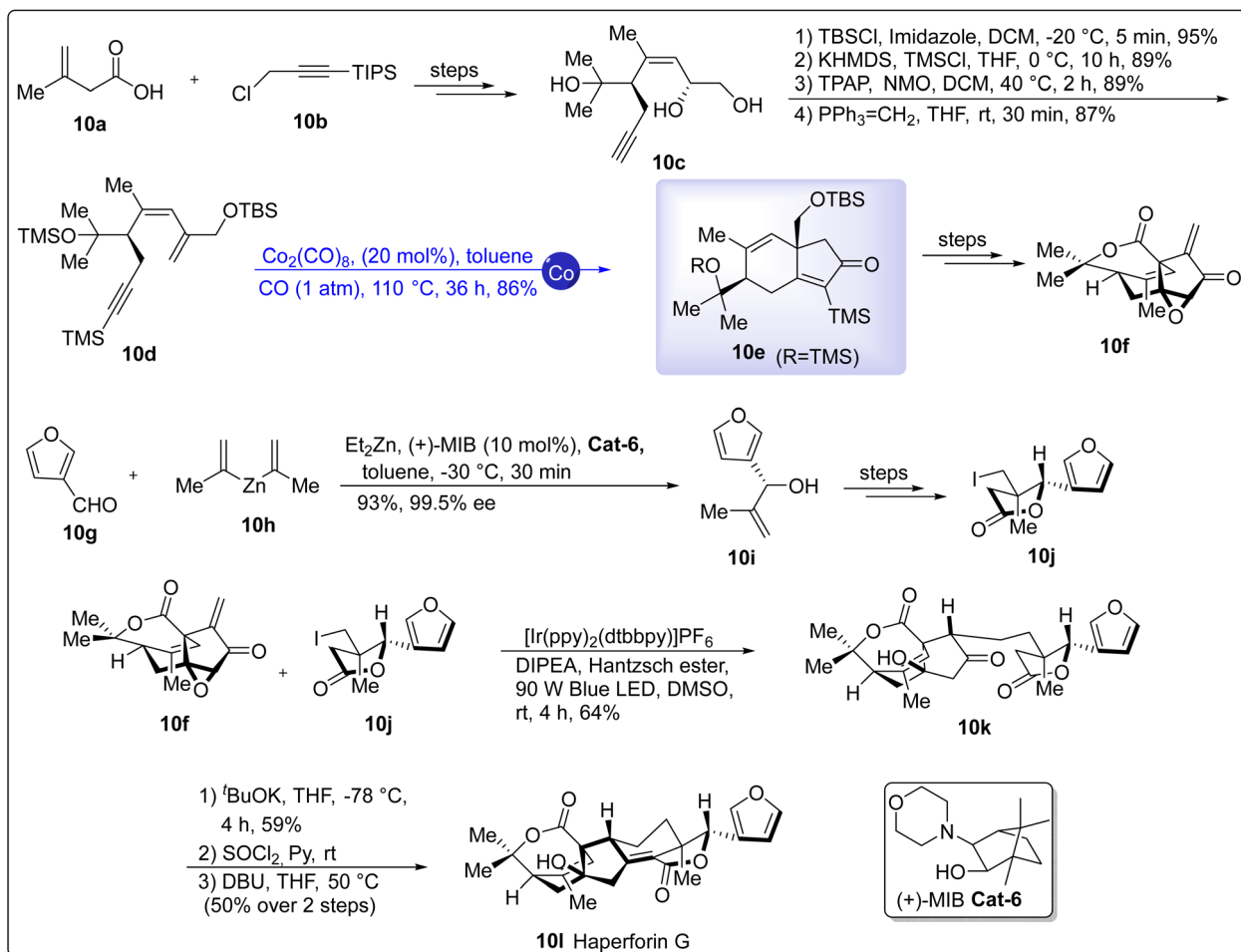
Scheme 9 Total synthesis of crinipellin A 9j and crinipellin B 9k (adapted from ref. 85).

coupling of **10f** and **10j** with $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (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 $\text{SOCl}_2/\text{pyridine}$ 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 $\text{Co}_2(\text{CO})_8$ under N_2O (1 atm) in DCE at 80°C for 22 h, affording tetracyclic enone **11f** in 59% yield with 93% ee. Alternative





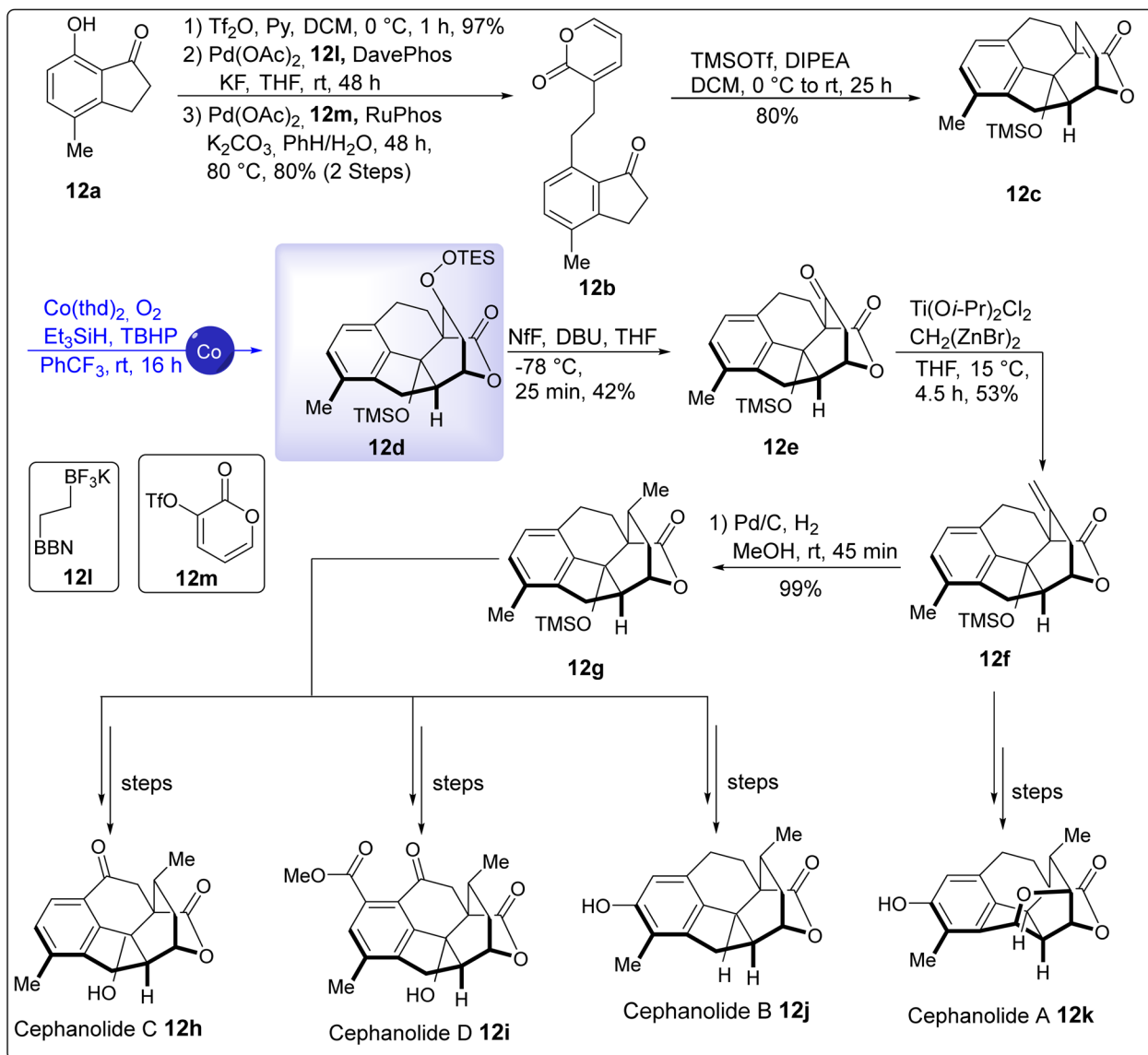
Scheme 10 Total synthesis of haperforin G 10l (adapted from ref. 92).

promoters (TMANO, NMO, TMTU) and catalysts (PdCl₂/TMTU, [Rh(CO)₂Cl]₂) gave only 22–38% yield, underscoring the advantage of N₂O in this sterically congested cyclization. In the Rosenbaum route, PK precursor **11i** was treated with stoichiometric Co₂(CO)₈ in refluxing xylene to furnish **11j** in 46% yield. In both cases, Co₂(CO)₈ first forms a cobalt-alkyne complex, followed by intramolecular alkene insertion and CO migratory insertion, thereby resulting in well-established (+)-waihonsene'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**, Me₃Al, *n*-BuOCH₂-NEt₂) 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 Co₂(CO)₈ and N₂O delivered tetracyclic enone **11f** (59%, 93%ee) which was converted to the natural product *i.e.*, (+)-waihonsene **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, NH₃(l)), Parikh–Doering oxidation (SO₃·pyr, NEt₃, DMSO), and Ohira–Bestmann alkylation (K₂CO₃, MeOH, 65% over two steps). The PK reaction of **11i** with Co₂(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, BF₃·OEt₂; 70%) of **11j** followed by Wittig olefination (Ph₃PCH₂Br, KO^tBu, PhMe, 110 °C; 91%) completed (+)-waihonsene **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–





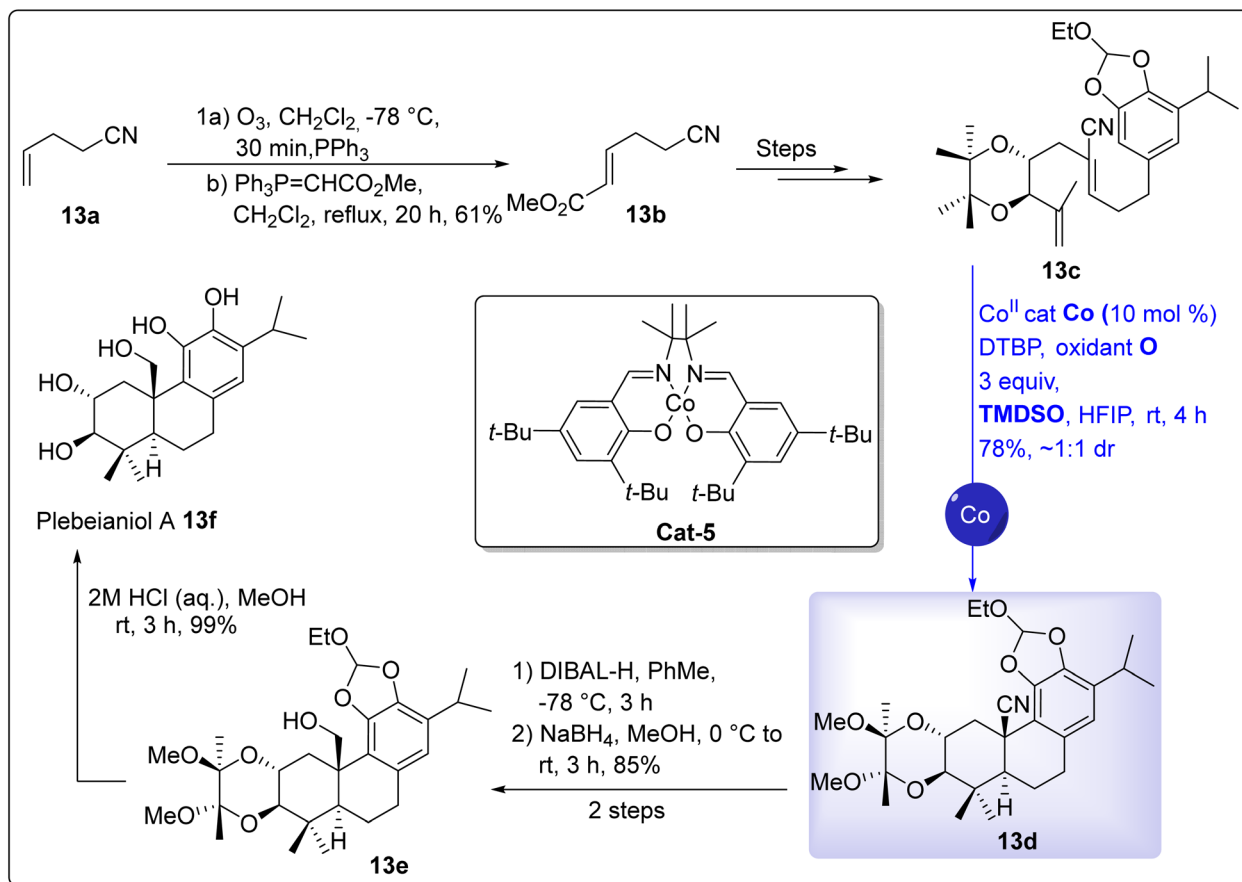
Scheme 12 Total synthesis of cephanolide A **12k**, cephanolide B **12j**, cephanolide C **12h**, and cephanolide D **12i** (adapted from ref. 103).

in 12 steps (30% overall yield), using cobalt-catalyzed asymmetric hydrovinylation as the stereo defining transformation. The cobalt method employed air-stable $\text{Co}(\text{II})$ 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** ($\text{Co}(\text{L4})\text{Cl}_2$ (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 ($(\text{CH}_2\text{O})_m$, 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** ($\text{Co}(\text{L5})\text{Cl}_2$, 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).

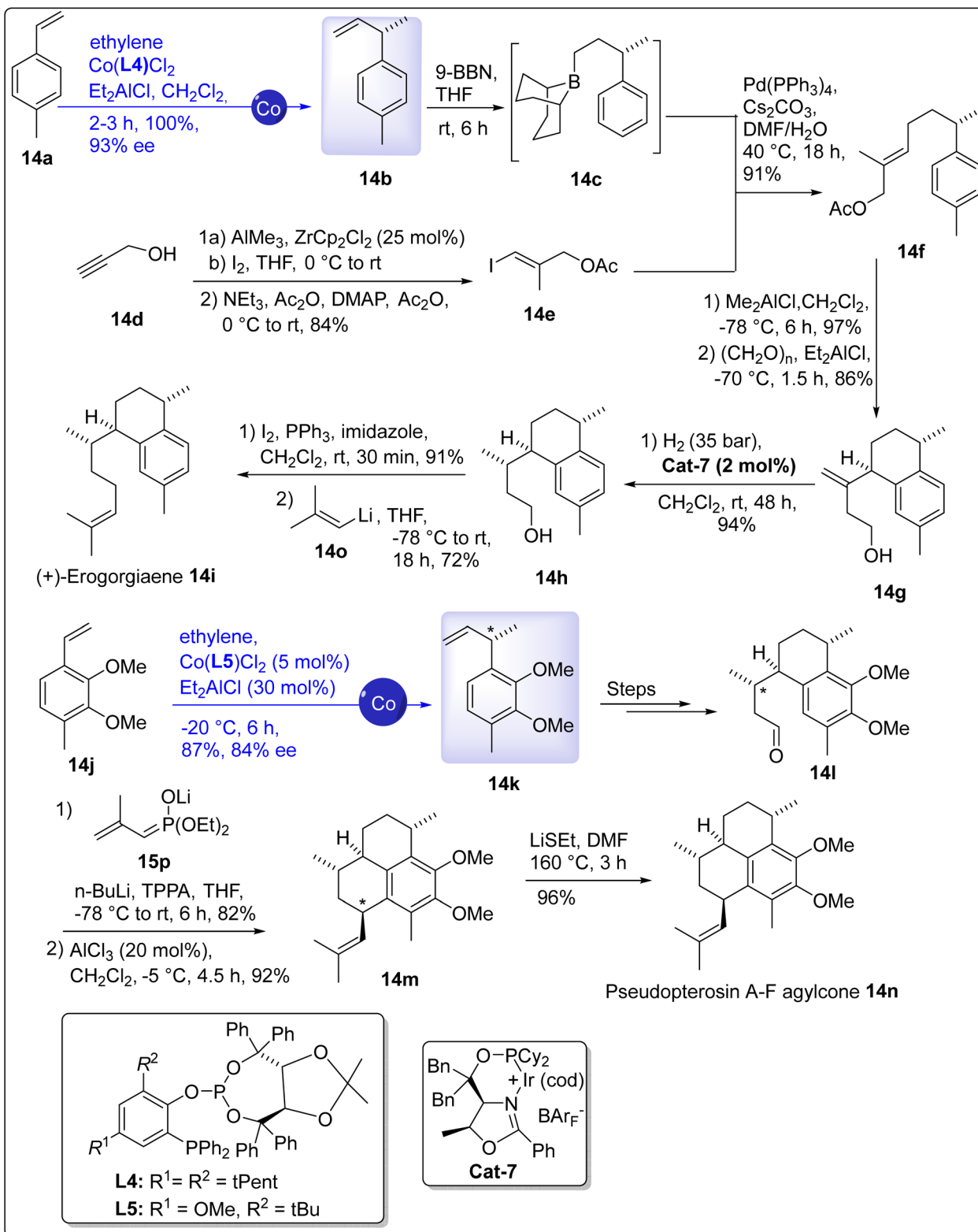
ever since, it has been the focus of extensive synthetic and pharmacological investigation. In addition to its known anti-inflammatory and immunosuppressive properties, it has also shown promise as a potential drug candidate for the treatment of cancer, specifically pancreatic cancer.¹²³ Fang *et al.* 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 , $40\text{ }^\circ\text{C}$) 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*-calamene **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 $\approx 28\text{ }\mu\text{M}$. 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



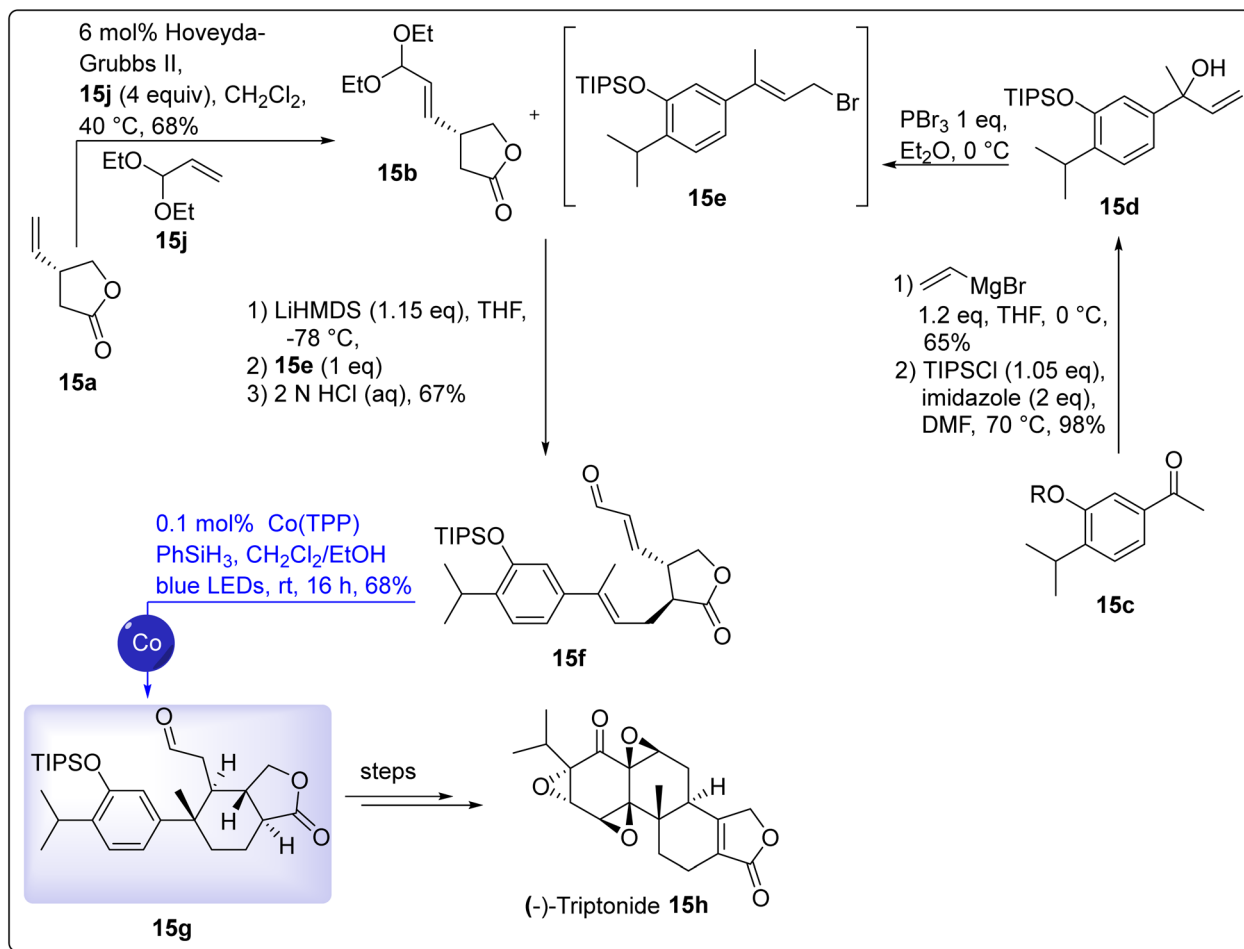


Scheme 14 Total synthesis of (+)-erogorgiaene 14i and the pseudopterosin A–F aglycone 14n (adapted from ref. 120).

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 [$\text{Co}(\text{acac})_2$, PhSiH_3 , O_2 , THF], followed by thermal transesterification (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 transactonization 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

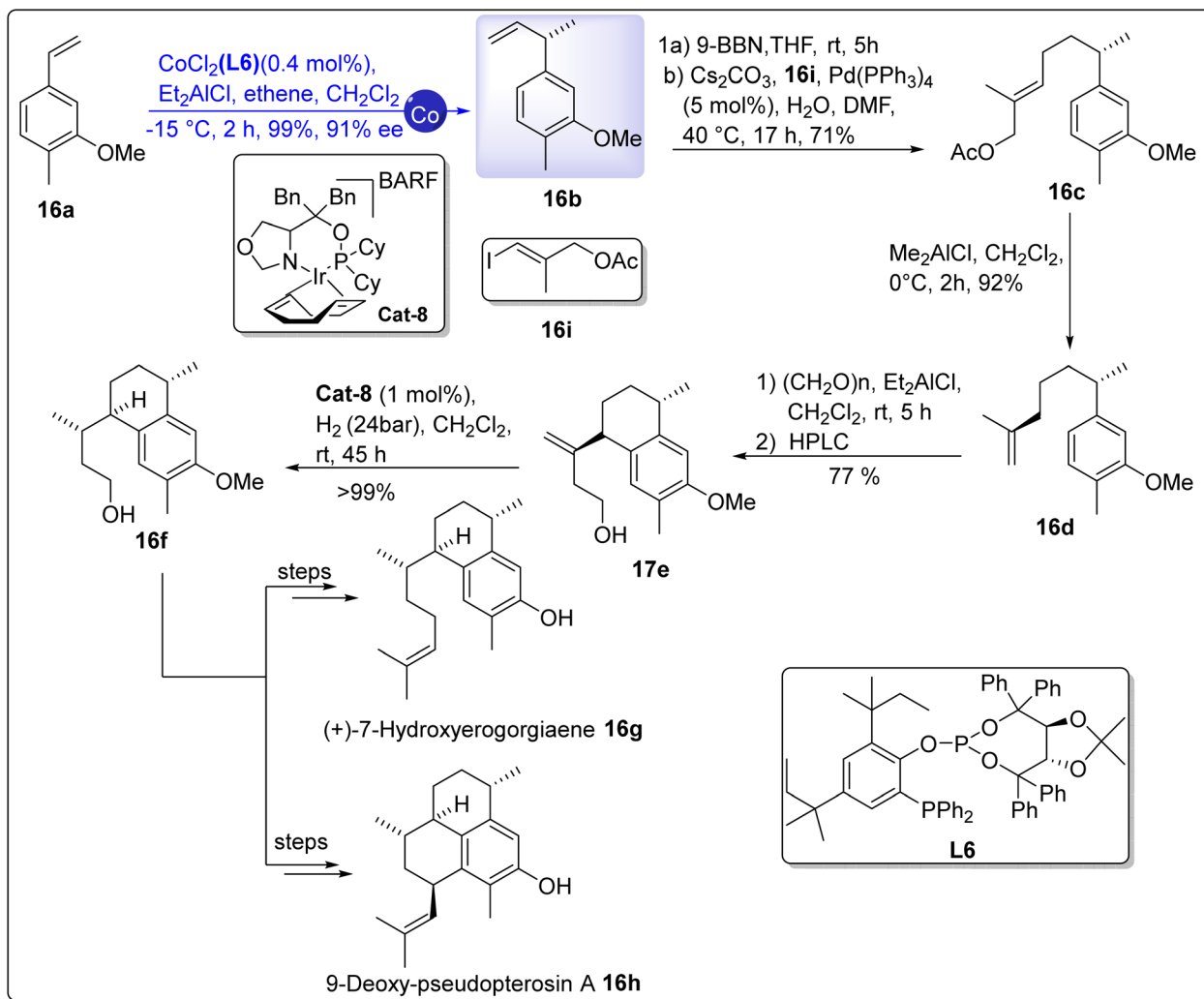
2.2.11. Pierisketone B. Pierisketone B belongs to a novel group of rearranged *ent*-kaurane diterpenoids, known for their tetracyclic 7/5/6/5 carbocyclic framework.^{134–136} These molecules possess bioactivities such as antitumor, antibacterial and anti-inflammatory activity which rendered it a primary 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·Me₂S-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** (Co₂(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





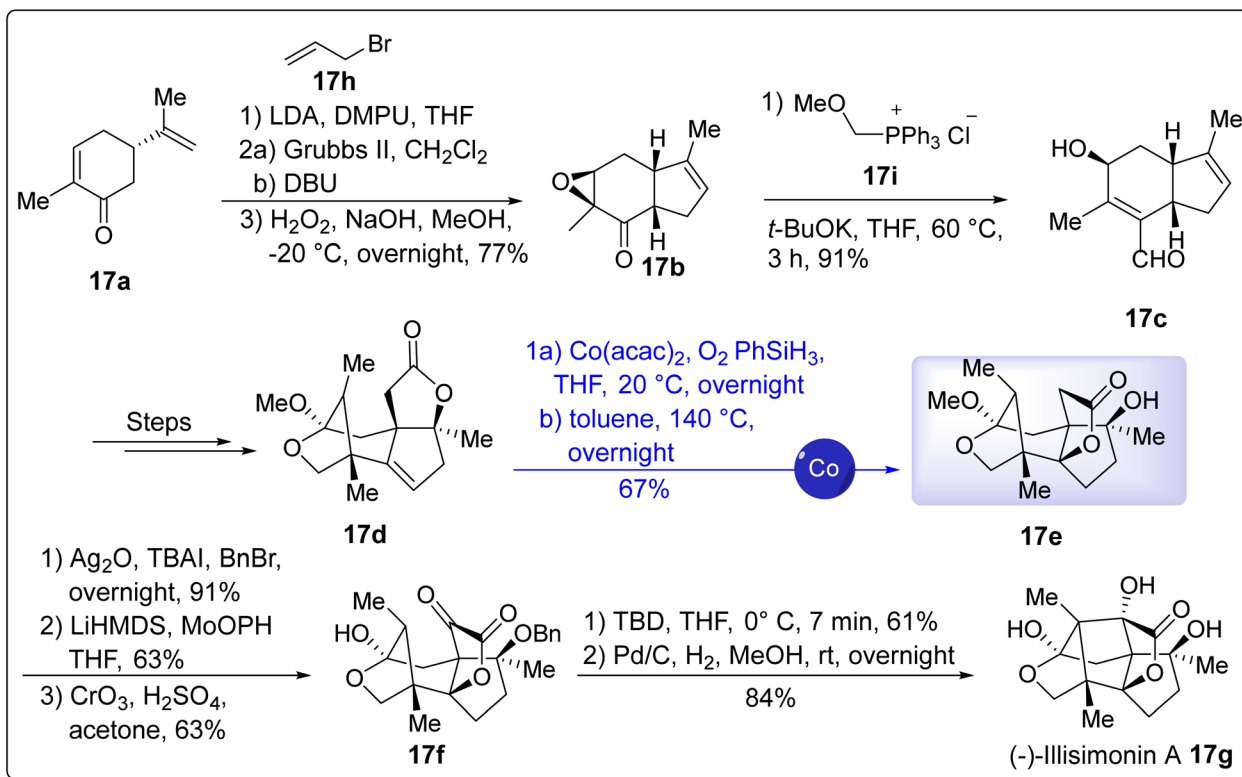
Scheme 16 Total synthesis of (+)-7-hydroxyergorgiaene **16g** & 9-deoxy-pseudopterosin A **16h** (adapted from ref. 125).

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

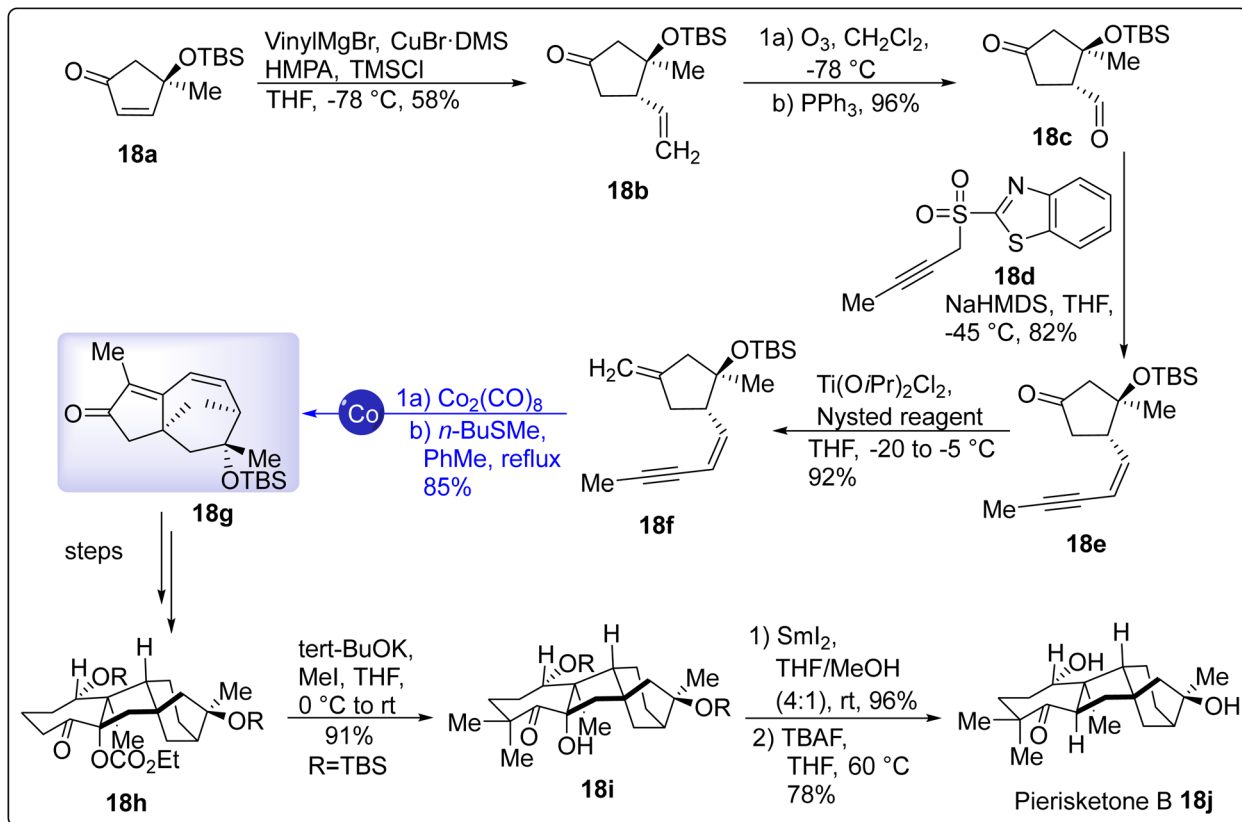
2.3.2. Monocillin VII. The resorcyclic acid lactones (RALs) are natural compounds that possess a β -resorcylate core fused to a 12-/14-membered macro lactone ring, obtained from numerous biological sources.¹⁴² Wei's group isolated a series of RALs from rice cultures of *Paecilomyces* sp. SC0924 including 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 acetone **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



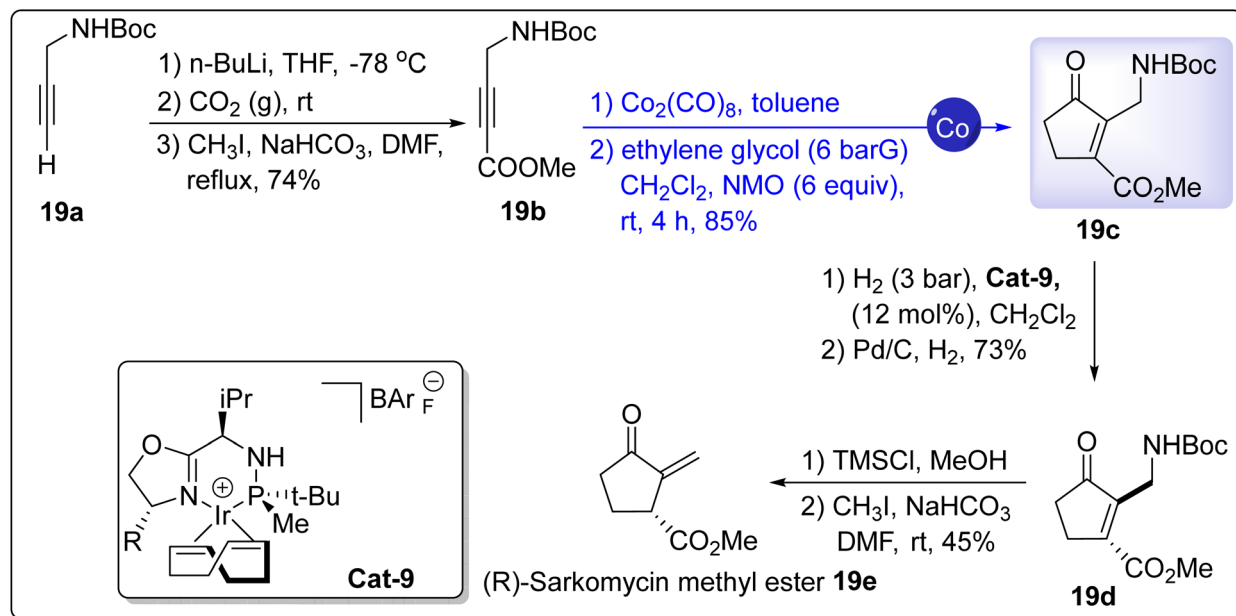
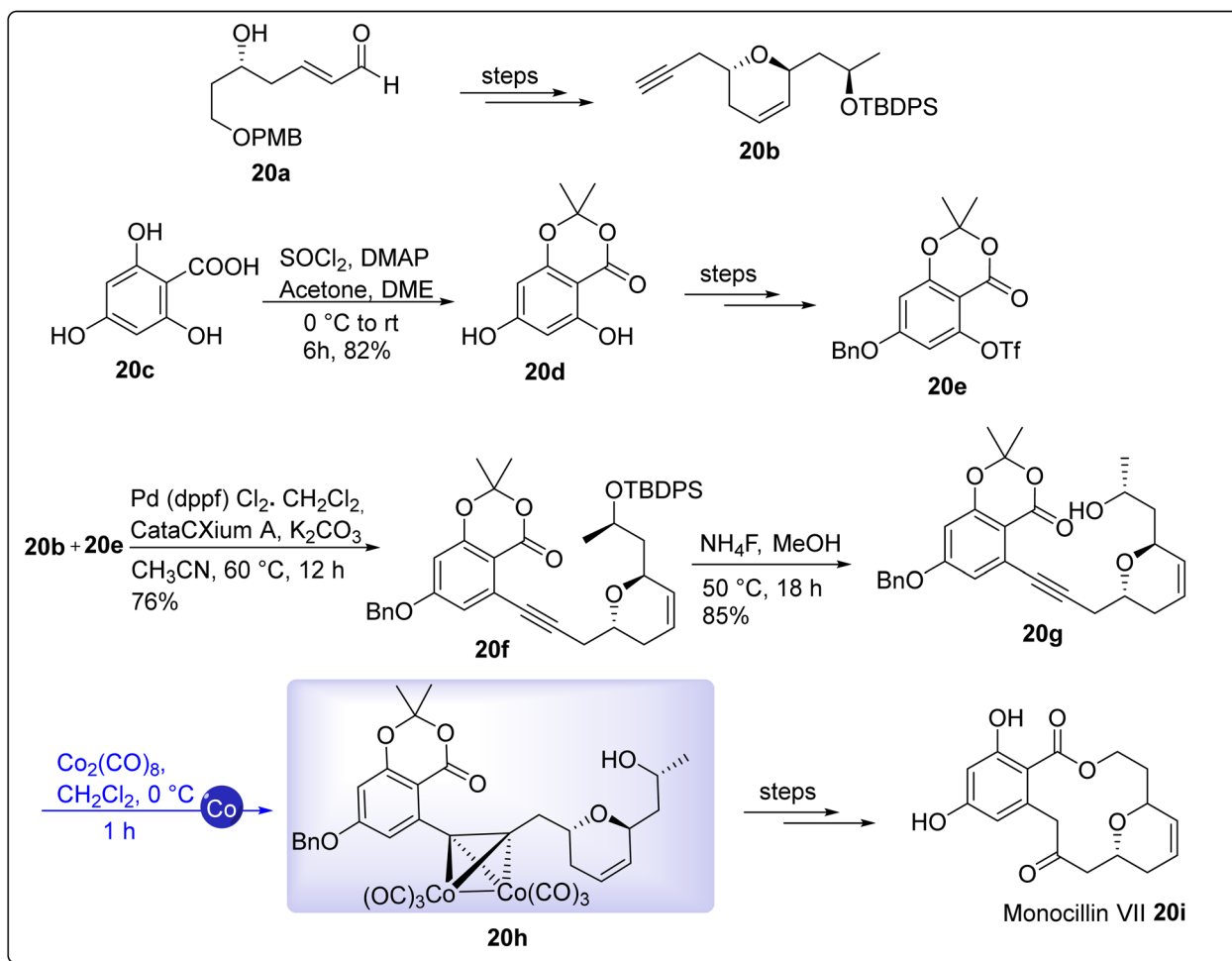


Scheme 17 Total synthesis of (-)-illisimonin A 17g (adapted from ref. 133).



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

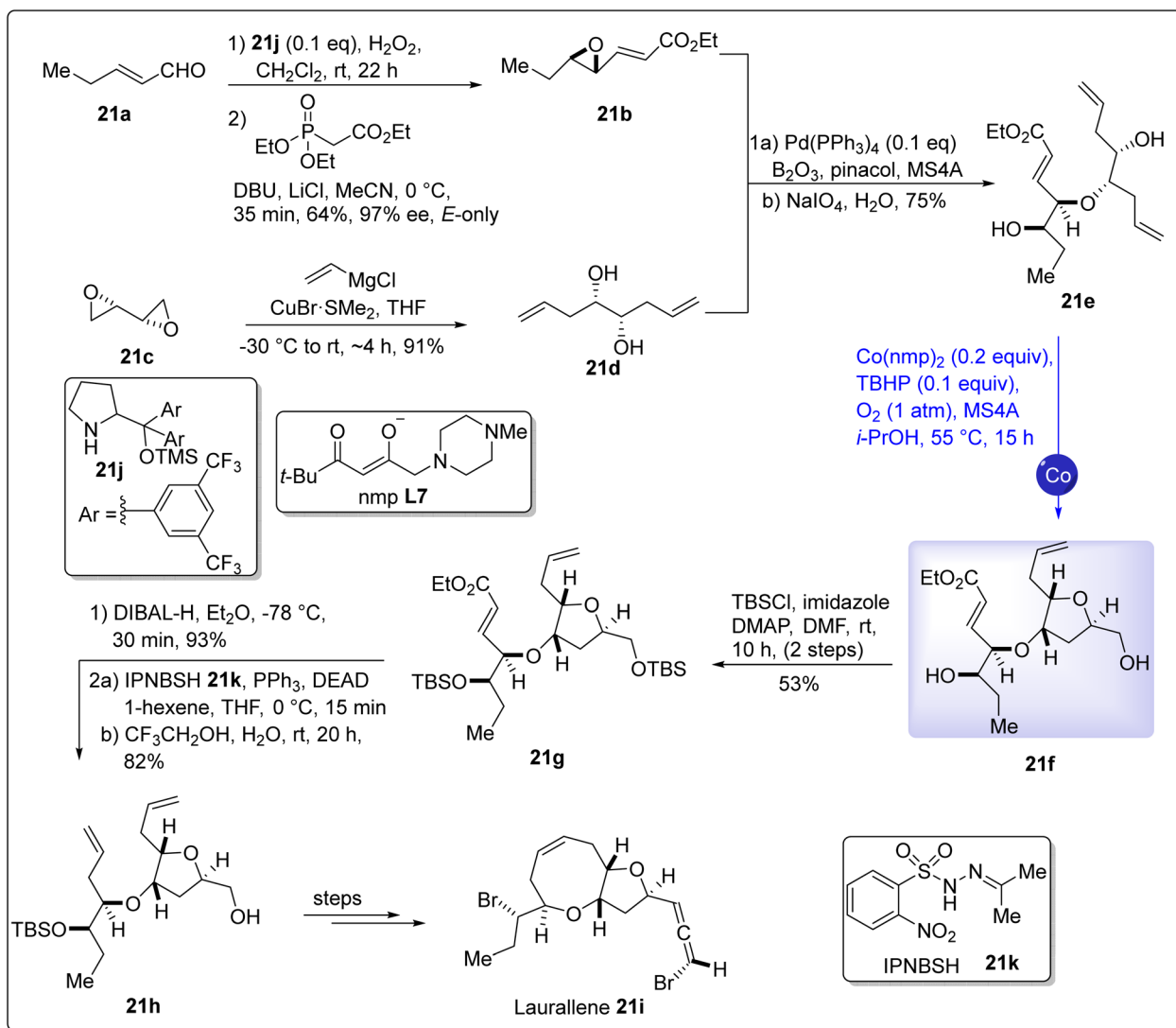


Scheme 19 Total synthesis of (*R*)-sarkomycin methyl ester **19e** (adapted from ref. 141).Scheme 20 Total synthesis of monocillin VII **20i** (adapted from ref. 144).

2.3.3. Laurallene. Laurallene, a marine-derived C₁₅ aceto-genin 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 NaIO₄ cleavage, provided branched ether **21e** (75%). In the next step, cobalt-mediated Mukaiyama oxidative cyclization of **21e** developed

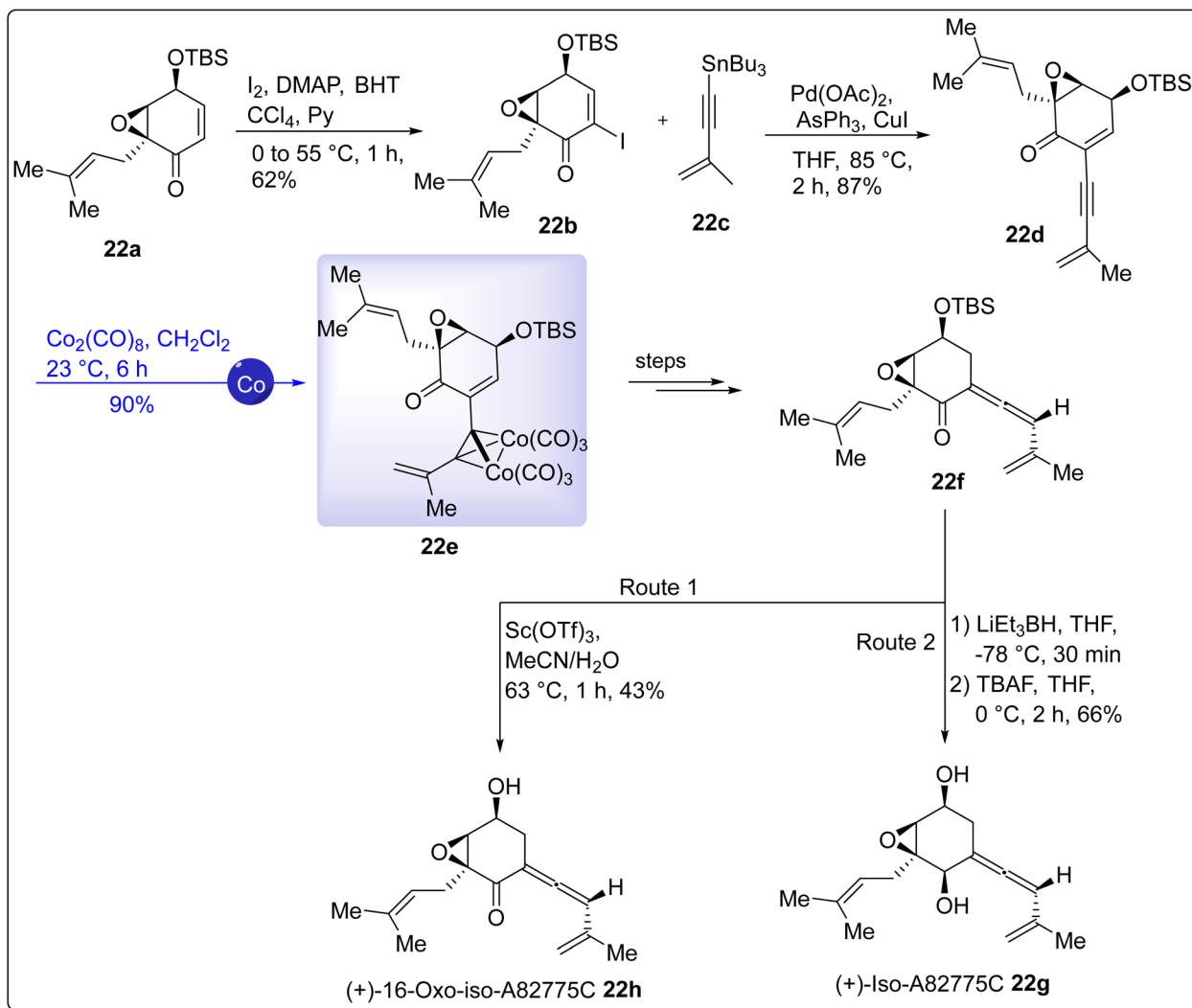
by Inoki and Mukaiyama, with a modification by Pagenkopf, utilizing Co(nmp)₂ catalyst (0.2 equiv.), TBHP (0.1 equiv.), O₂ (1 atm), MS 4A, *i*-PrOH at 55 °C furnished *trans*-THF **21f** as a single diastereomer, whose TBS protection gave **21g** (53%, two steps). Next, **21g** was subjected to DIBAL-H 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 chloropupekananin. 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, AsPh₃, 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 Co₂(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 Co₂(CO)₈ (1.0 equiv.) in CH₂Cl₂ 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 Et₃N-catalysed tautomerization furnished allene **22f** with complete diastereoselectivity (40%, three steps). From **22f**, Sc(OTf)₃-catalysed desilylation (MeCN/H₂O, 63 °C) furnished (+)-16-oxo-iso-A82775C **22h** in 43% yield, whereas chemoselective reduction with LiEt₃BH 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*-tetrahydrofuran 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, O₂, which was transformed into olefin **23d** over a few steps. Co–I cyclization of **23e** gave **23f** (61%, d.r. >20:1), whose

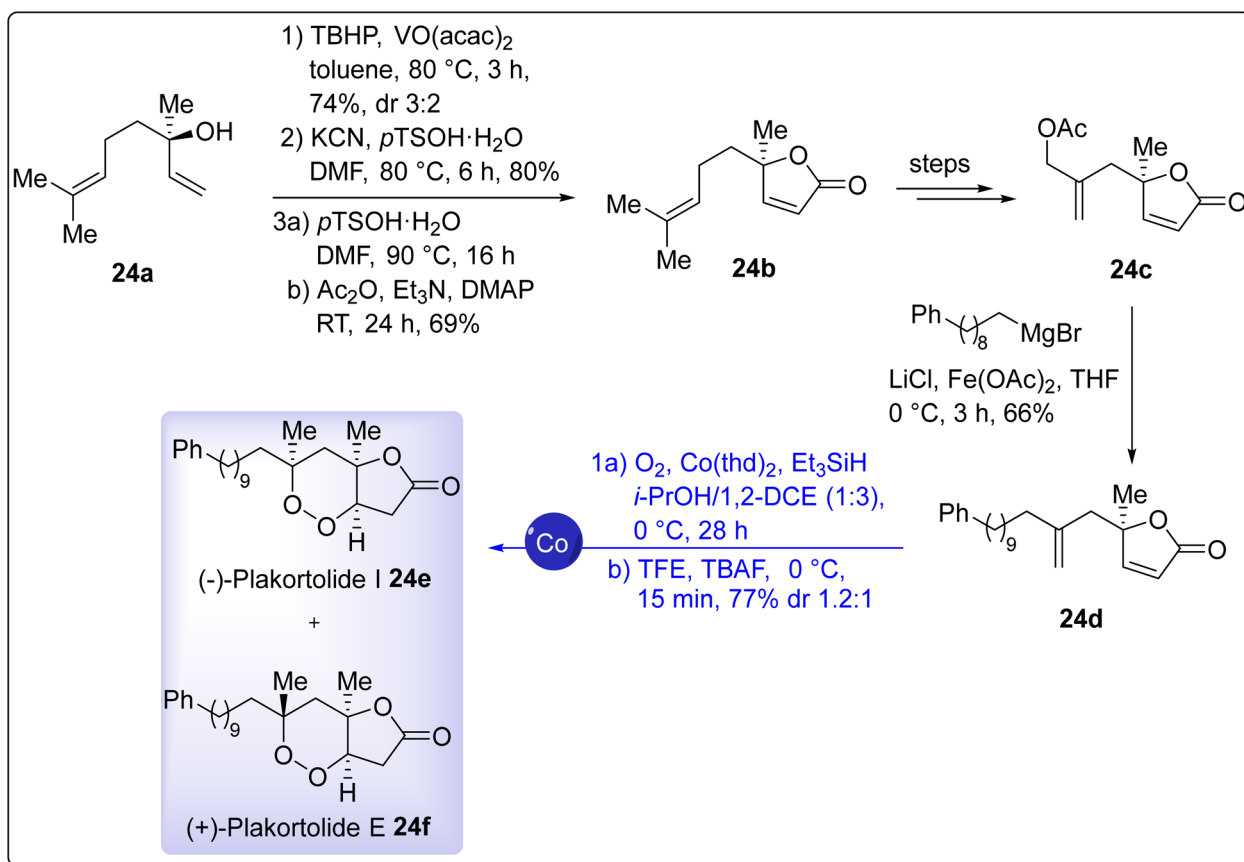


conjugation with DIBAL-H reduction (94%) and Takai olefination to furnish iodoolefin **23o**. Finally, coupling of **23j** and **23o/23o'** resulted in the synthesis of amphirionin-2 **23p** and its diastereomer **23q** respectively, over a few steps (Scheme 23).¹⁵²

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

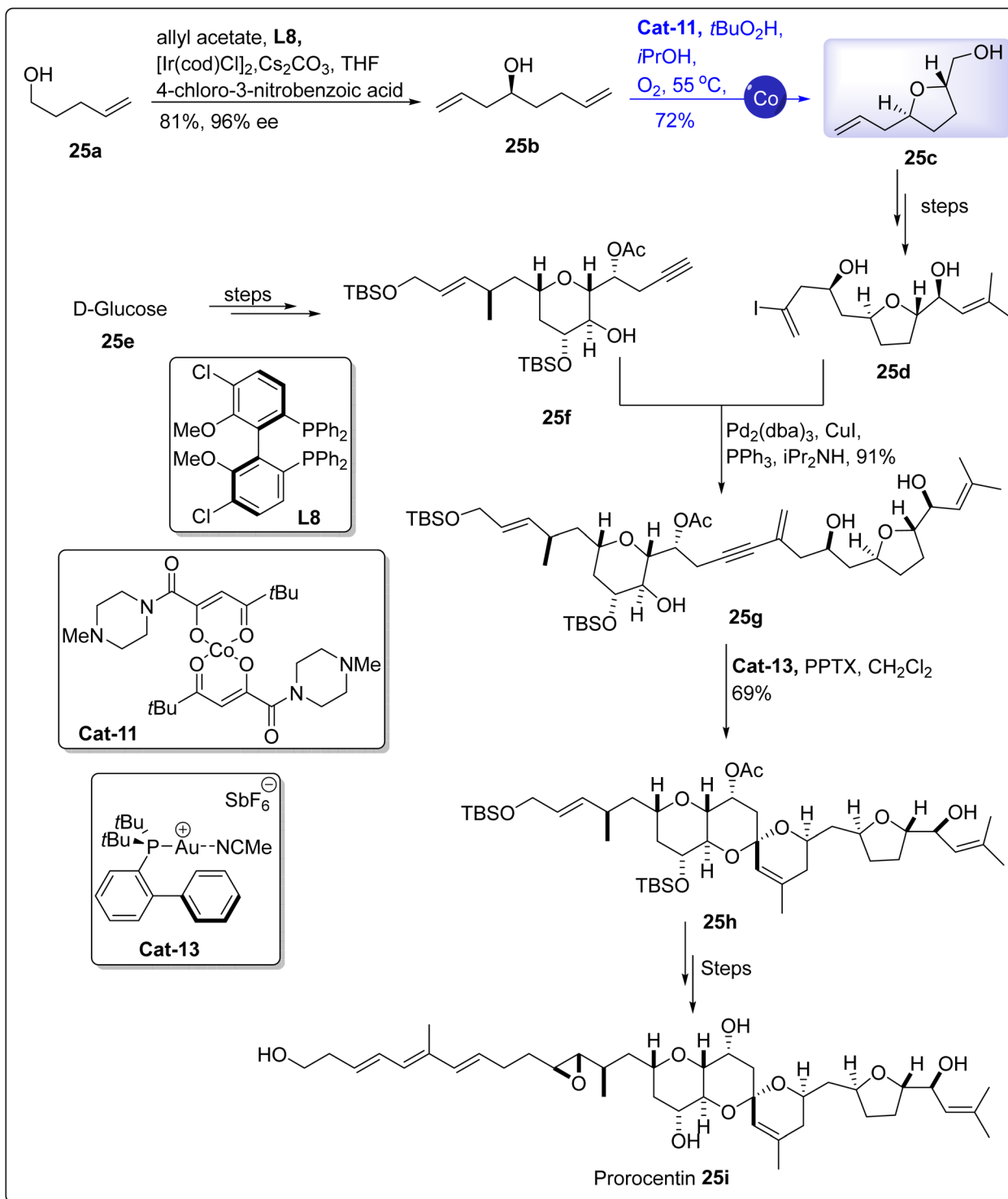
prevented the formation of by-products. However, the products were observed to be decomposed. At 0 °C, oxa-Michael addition was slowed and corresponding silyl peroxide was trapped. This challenge was handled by *in situ* TBAF/TFE desilylation, thereby preventing Weitz–Scheffer epoxidation. As a result, (–)-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**, Cs₂CO₃, THF) gave **25b** (81%, 96%ee) which was subjected to significantly selective cobalt-catalyzed oxidative etherification (Cat-13, *t*BuOOH, *i*PrOH, O₂, 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).





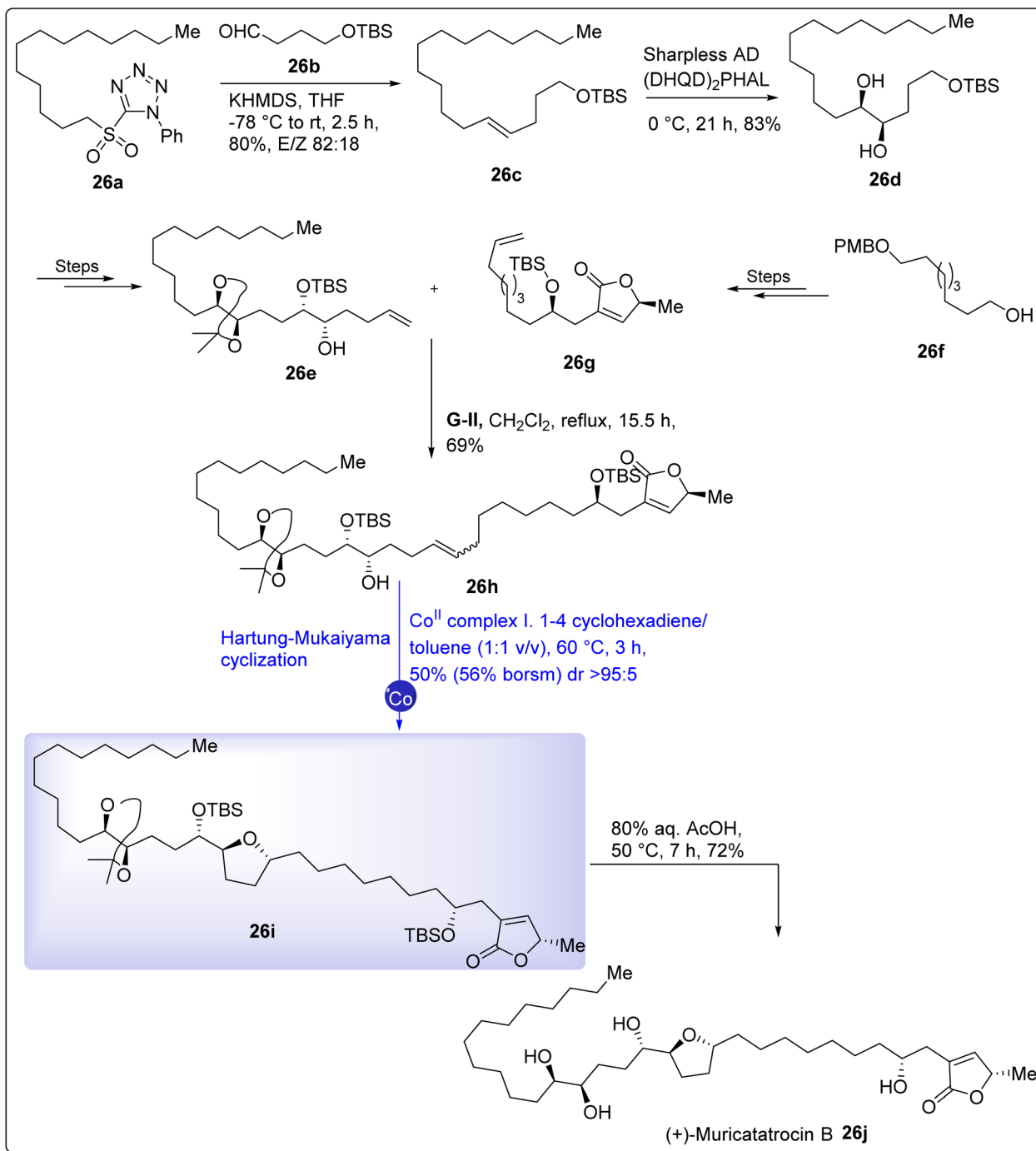
Scheme 25 Total synthesis of prorocentatin 25i (adapted from ref. 158).

coupling with **25d** to access **25g** in 91% yield. Finally, its gold-catalyzed spirocyclization furnished product **25h** (69%) which was transformed to prorocentatin **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



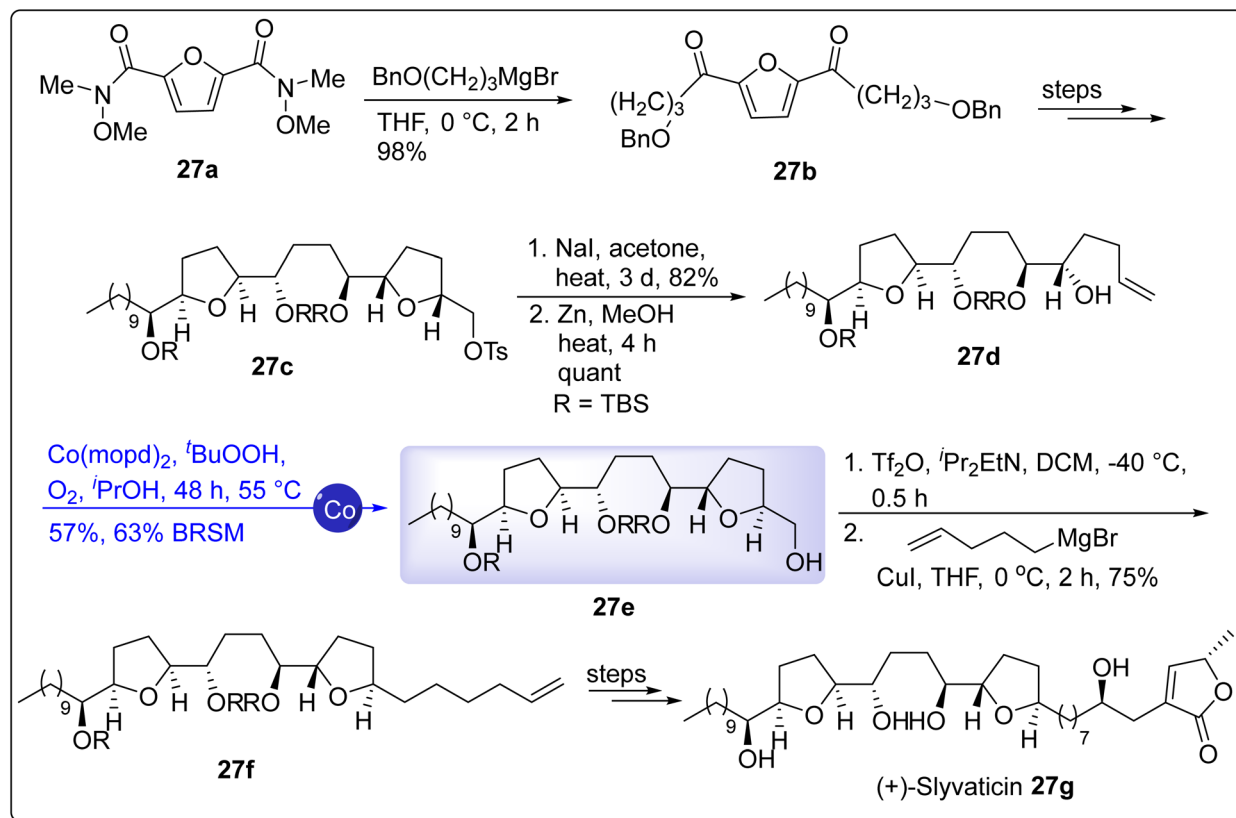


Scheme 26 Total synthesis of (+)-muricatetrocin B 26j (adapted from ref. 161).

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 Grubbs' 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

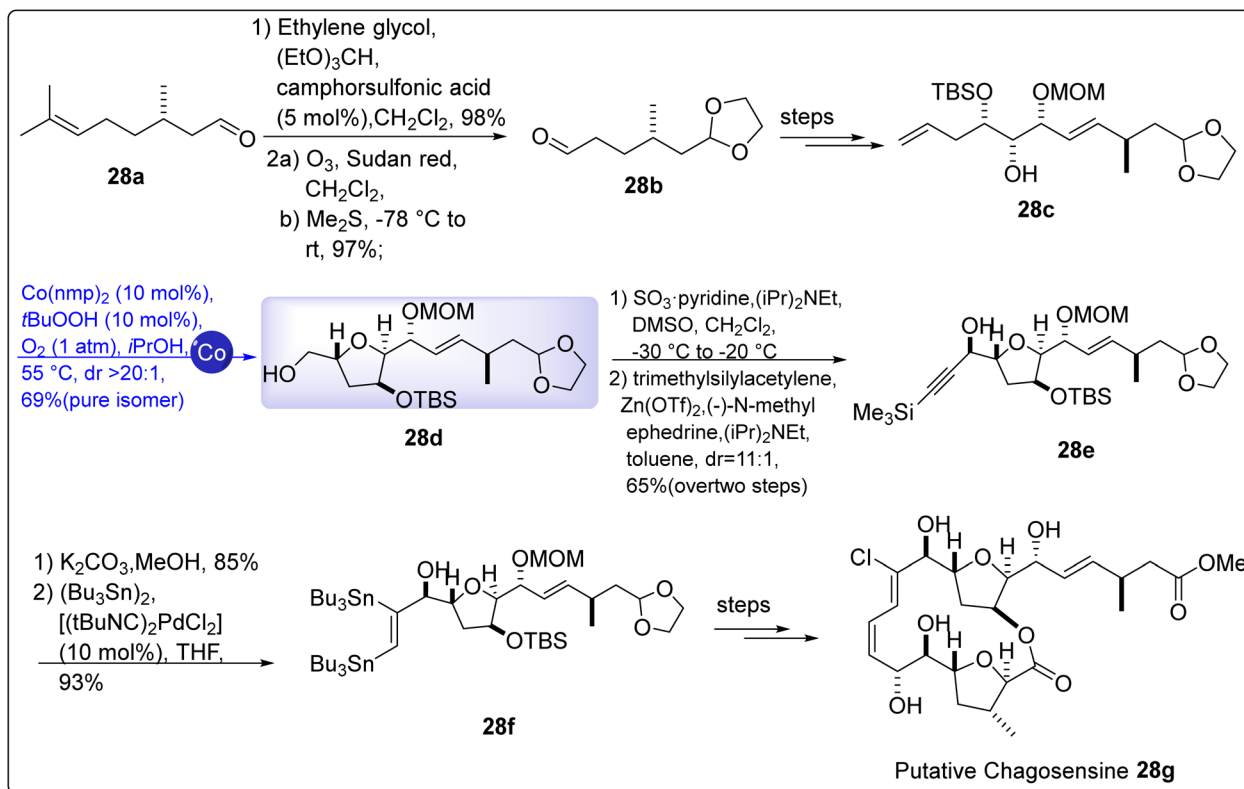
2.4 Synthesis of macrolides

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 (*i*Pr)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 $[(t-BuNC)_2PdCl_2]$ (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).

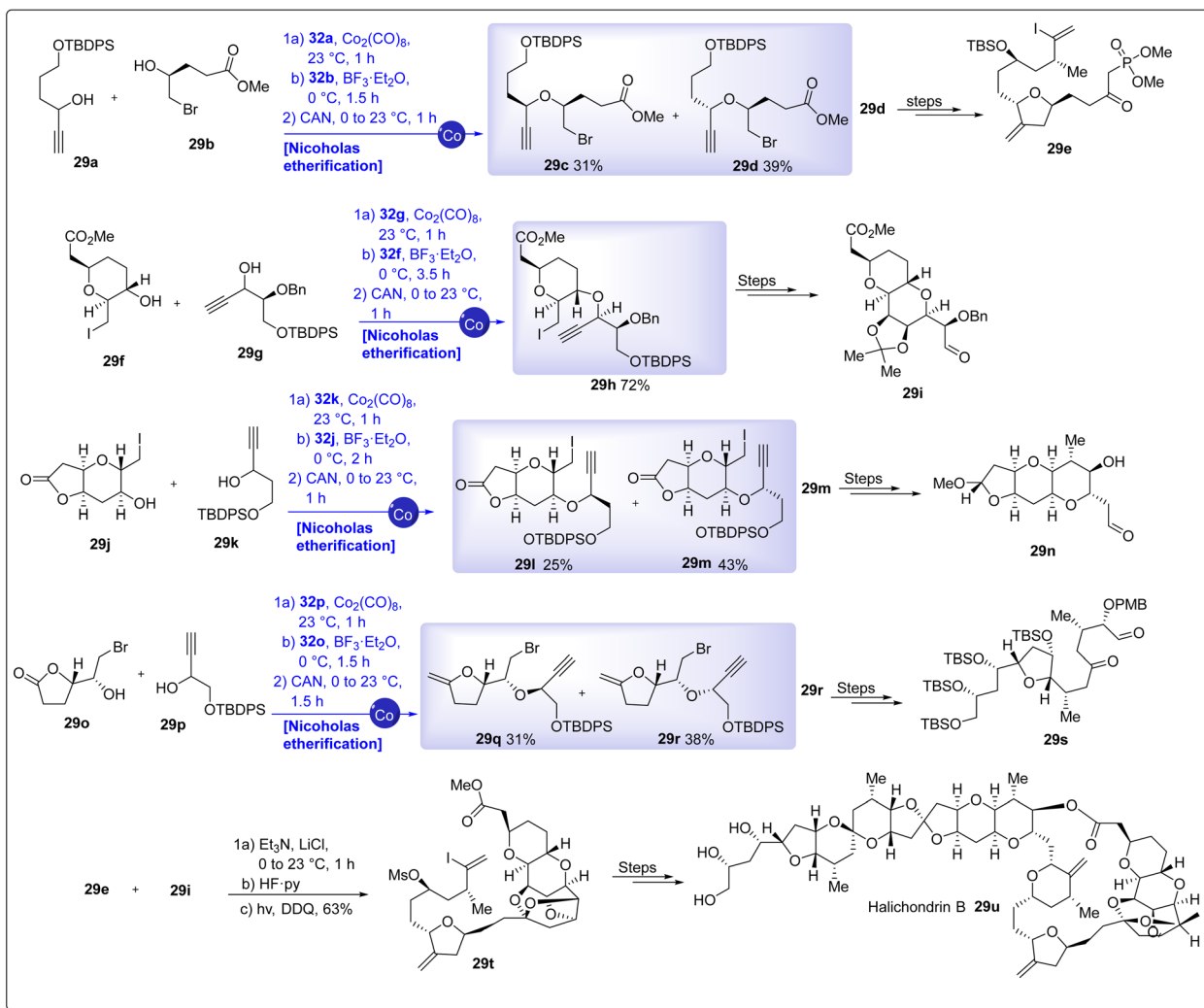
reported a 25-step convergent route to halichondrin B, ranking amongst the most concise approaches to this target, till date. The key strategic innovation inverted the conventional ethering construction order: cobalt-mediated Nicholas etherification installed C–O bonds prior to radical-mediated C–C ring closure, thereby reversing the classical approaches in which C–C bonds preceded C–O cyclization. Co₂(CO)₈ coordinated the alkyne of a propargylic alcohol to form a hexacarbonyldicobalt complex. Treatment of the cobalt–alkyne complex with BF₃·Et₂O 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** (Co₂(CO)₈; BF₃·Et₂O; 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 CoI₂ (10 mol%), **L9** (12 mol%), (EtO)₃SiH (3.0 equiv.), K₃PO₄·H₂O (3.0 equiv.) in DME at rt for 12 h under N₂ 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).

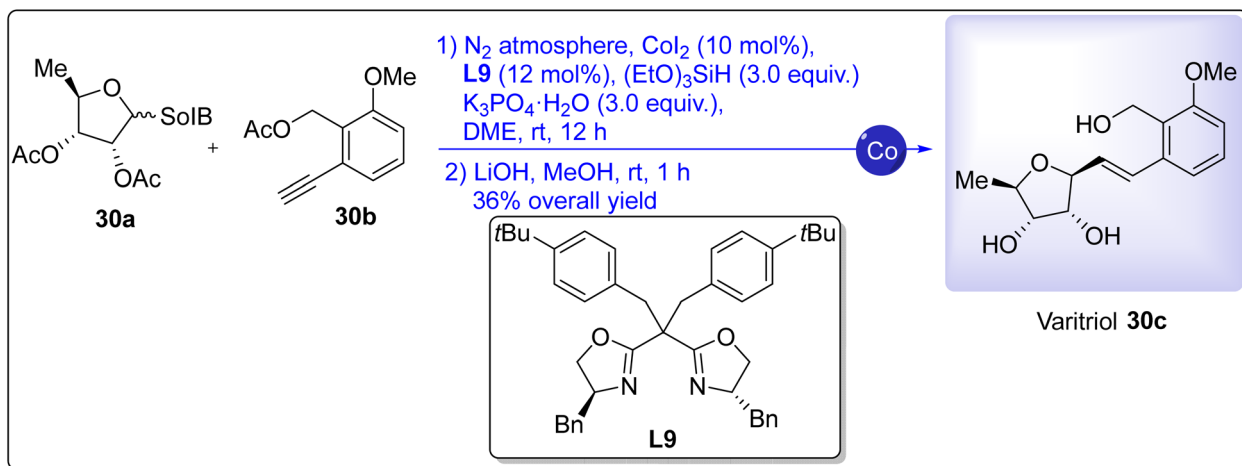
2.5.2. Fortimicin B. Fortimicin B belongs to a distinctive subgroup of aminoglycosides obtained from *Micromonospora* species, characterized by its unusual pseudodisaccharide framework.^{172–174} Among its analogs, fortimicin B shows potent antibacterial activity with far lower kidney and ear toxicity, 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 B₁₂, 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



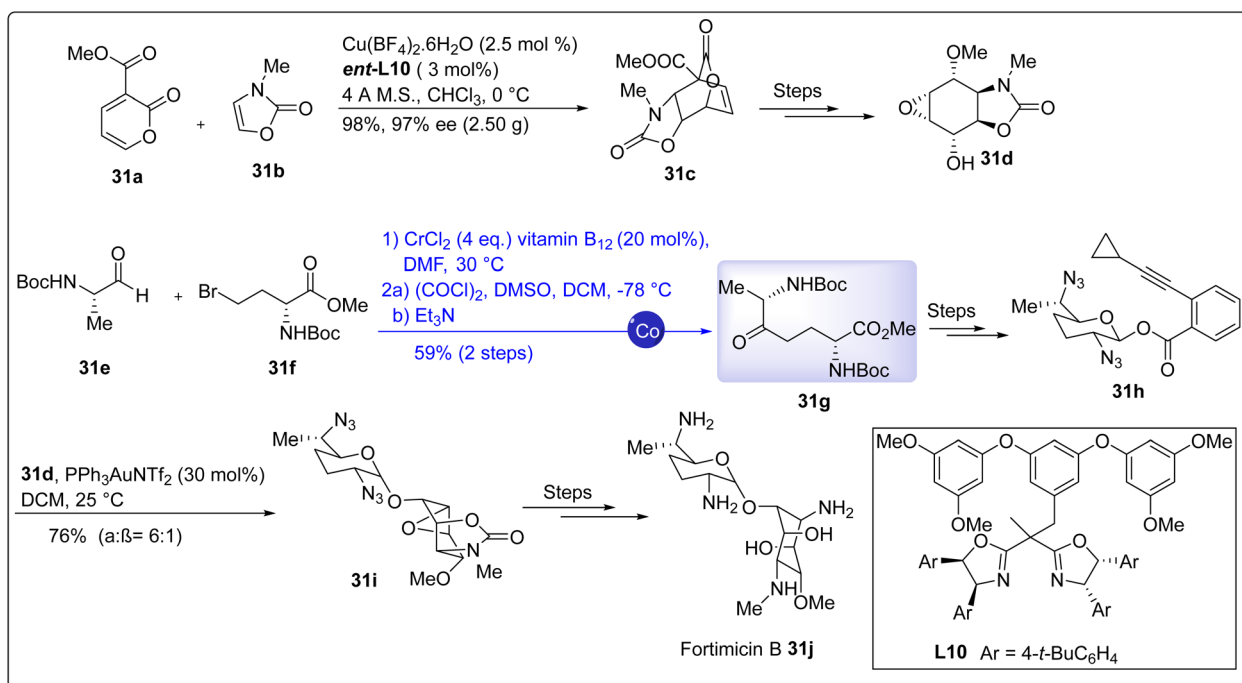
Scheme 30 Total synthesis of varitriol **30c** (adapted from ref. 171).

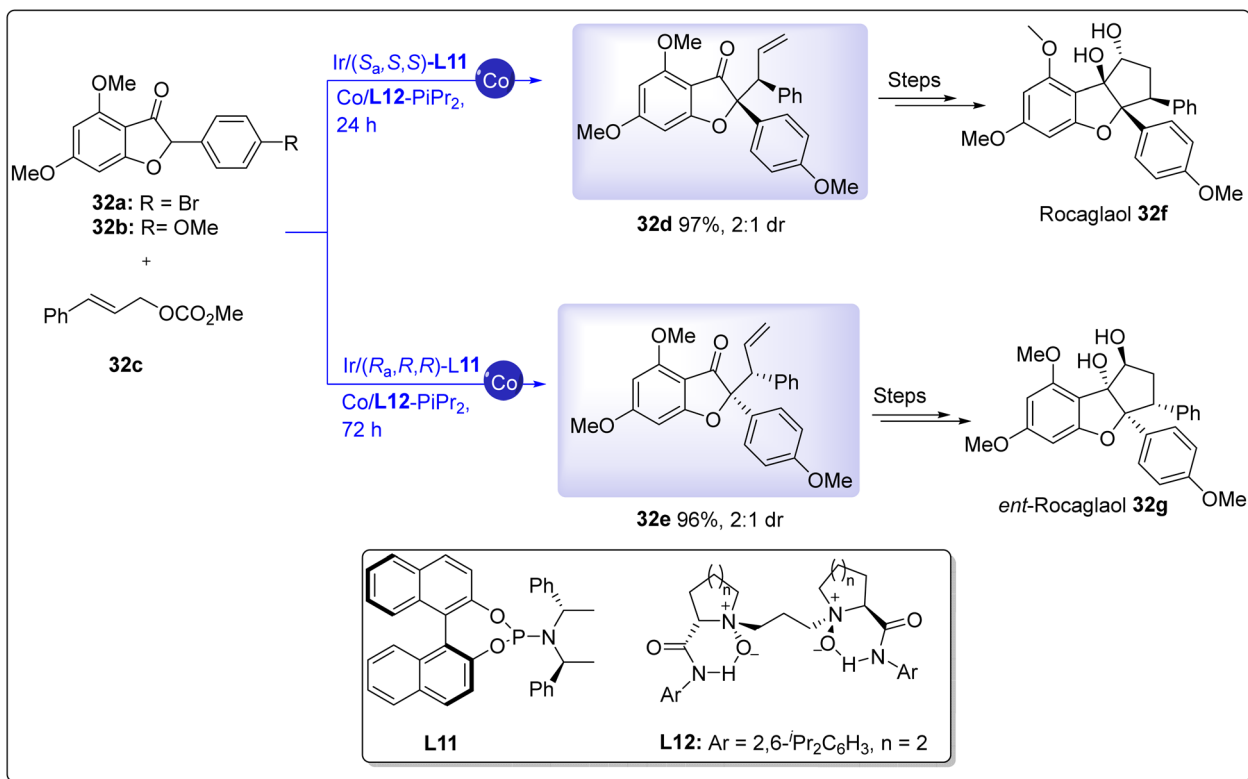
species. $Co(II)$ was found to be better than Cu-based catalysts (which gave 54% yield with 1.1 : 1 dr). Benzofuranones **32a** ($R = Br$) or **32b** ($R = OMe$) were reacted with carbonate **32c**, $Co(BF_4)_2 \cdot 6H_2O$ (10 mol%), **L11**- $PiPr_2$ (10 mol%), $(Ir(cod)Cl)_2$ (2 mol%), K_2CO_3 (1.3 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 roca-glalol **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

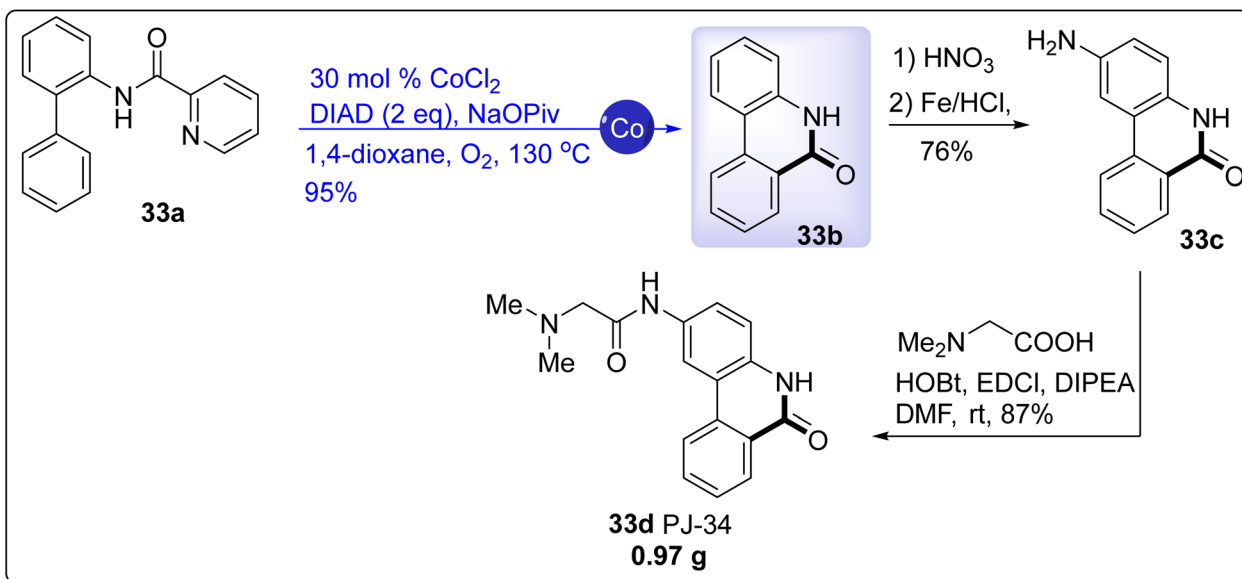
Scheme 31 Total synthesis of fortimicin B **31j** (adapted from ref. 175).



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

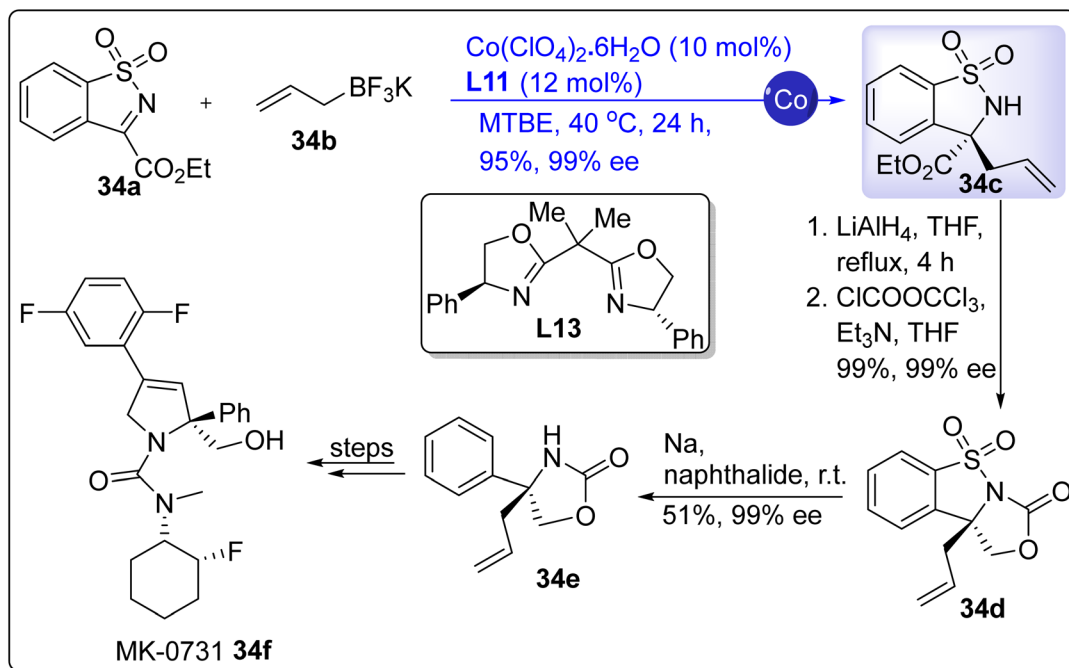
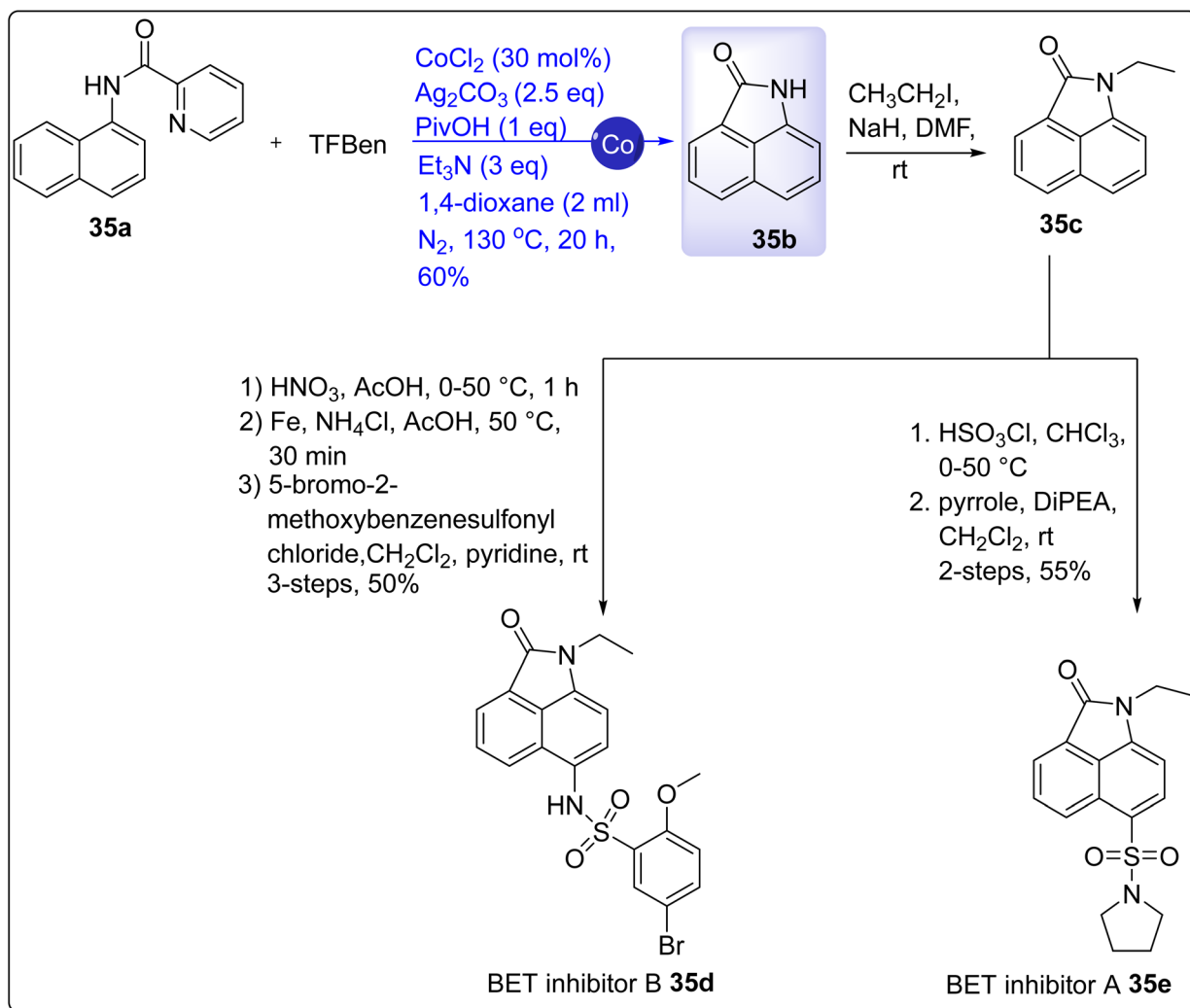
2.7.2 MK-0371. MK-0371, a potent inhibitor of the kinesin spindle protein, was synthesized by Wu and coworkers in 2018. They demonstrated the utility of Co(II)/bisoxazoline-catalyzed asymmetric allylation of cyclic ketimines with the synthesis of a key intermediate for MK-0731. The synthesis of MK-0371's intermediate was accomplished *via* highly enantioselective

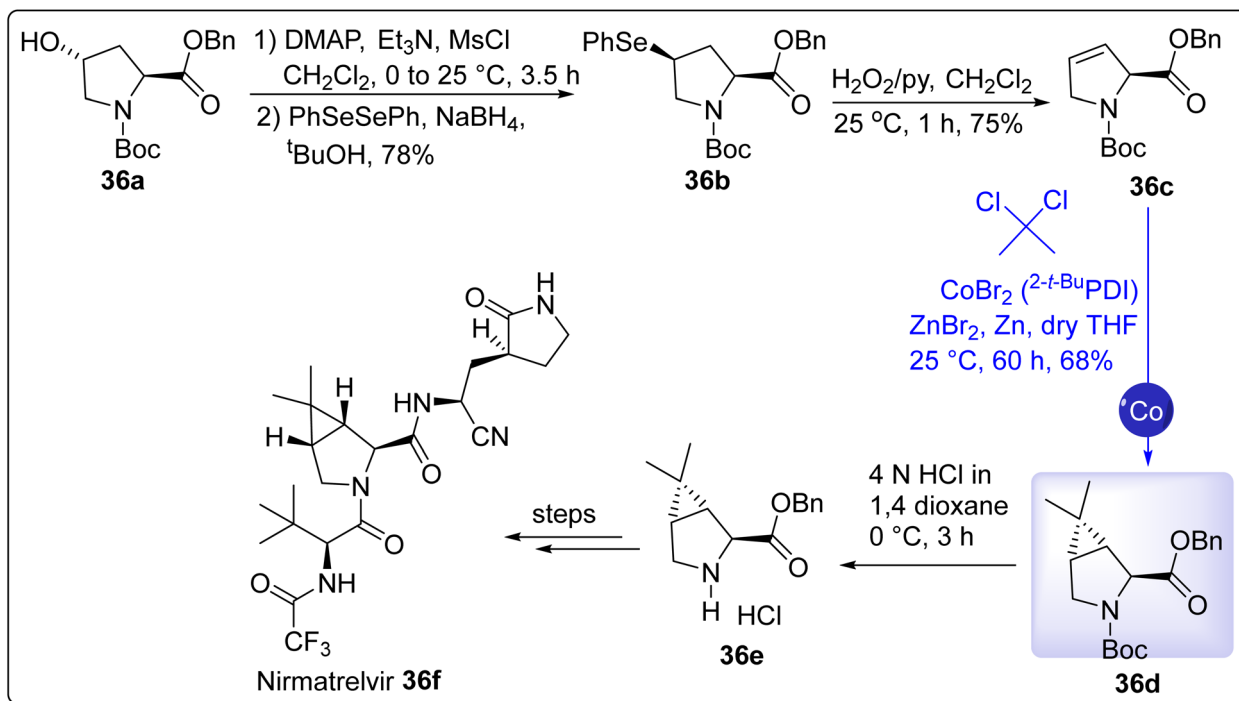
cobalt-catalyzed coupling. The initial step involved the reaction of ethyl ester sulfonamide **34a** with potassium allyl trifluoroborate **34b** in the presence of cobalt catalyst Co(ClO₄)₂·6H₂O to afford intermediate **34c** in 95% with 99% ee enantiomeric excess. Subsequent reduction of **34c** using LiAlH₄ 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).

Et₃N 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 PdCl₂/Cu(OAc)₂ system which required gaseous CO/O₂ 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 from the Co(I) complex, and subsequent hydrolysis released the product, while Co(II) is reoxidized to regenerate the catalyst. On gram scale, naphthylamide **35a** was treated with TFBen (1.75 equiv.), CoCl₂ (30 mol%), Ag₂CO₃ (2.5 equiv.), PivOH (1 equiv.), and Et₃N (3 equiv.) in 1,4-dioxane under N₂ at 130 °C for 20 h, furnishing **35b** in 60% yield. *N*-Alkylation (CH₃CH₂I, 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

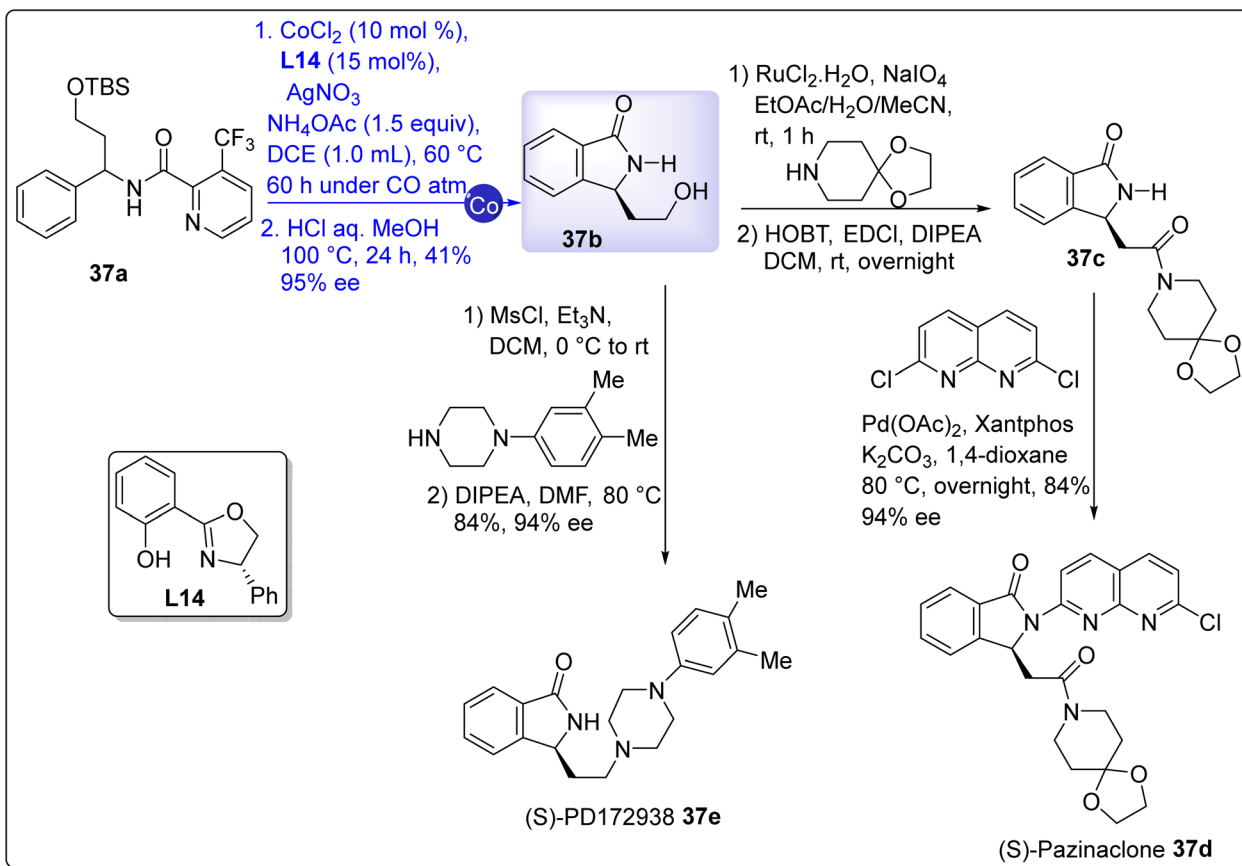
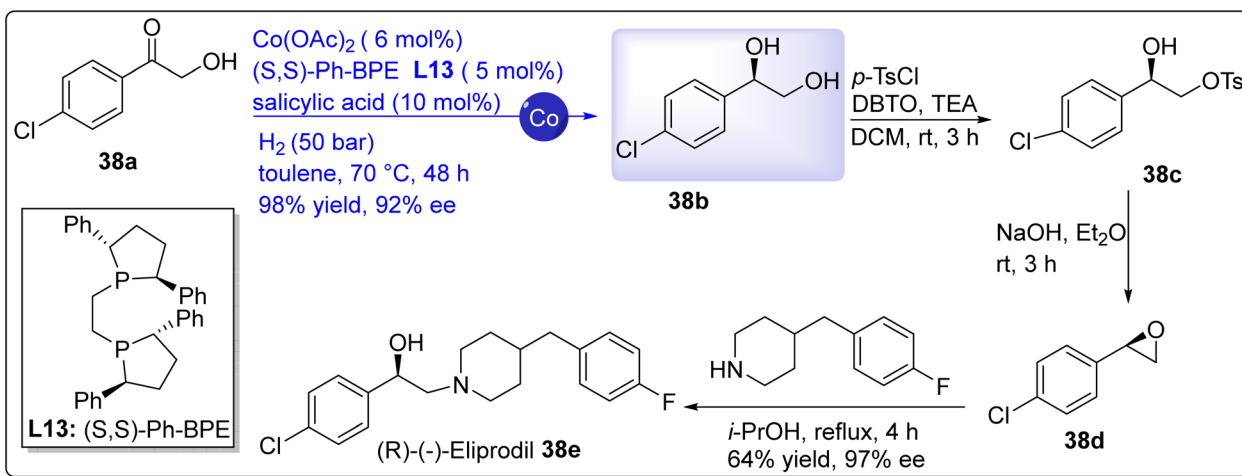
2.7.4. Nirmatrelvir. Nirmatrelvir, marketed as part of Paxlovid with ritonavir, is a tripeptide like inhibitor targeting the SARS-CoV-2 main protease. Shekhar *et al.* used Co(II)-catalyzed reductive dimethylcyclopropanation as the key step to introduce the *gem*-dimethylcyclopropane-fused proline core that enhanced protease inhibitory potency.¹⁸¹ Mesylation of hydroxy

proline benzyl ester **36a** followed by selenylation with diphenyl diselenide and NaBH₄ afforded selenide **36b** in 78% yield. Oxidative elimination of selenide **36b** with H₂O₂/pyridine then afforded alkene **36c** (75%). Co(II)-catalyzed dimethylcyclopropanation of **36c** using CoBr₂(2-*t*-BuPDI), Zn, 2,2-dichloropropane and ZnBr₂ 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)-pazinaclone, 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 CoCl₂ (10 mol%), Salox ligand **L12** (15 mol%), AgNO₃ (2.0 equiv.), and NH₄OAc (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-dioxo-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)-(–)-Eliprodiol. (R)-(–)-Eliprodiol is the enantiomer of the neuroprotective drug eliprodiol. 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)-(-)-eliprodiol **38e** (adapted from ref. 186).

catalyzed asymmetric hydrogenation of an α -hydroxy ketone. A nonredox $\text{Co}(\text{II})$ cycle is enabled with the use of an additive containing salicylic acid, which formed two hydrogen bonds with the substrate. Asymmetric hydrogenation of **38a** ($\text{Co}(\text{OAc})_2$ (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 ($p\text{-TsCl}$, 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 ($i\text{-PrOH}$, reflux, 4 h) delivered (R)-(-)-eliprodiol **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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References

- 1 S. K. Sinha, P. Ghosh, S. Jain, S. Maiti, S. A. Al-Thabati, A. A. Alshehri, M. Mokhtar and D. Maiti, Transition-metal catalyzed C–H activation as a means of synthesizing complex natural products, *Chem. Soc. Rev.*, 2023, **52**(21), 7461–7503.
- 2 S. Tabassum, A. F. Zahoor, K. G. Ali, M. Irfan, S. M. Hussain and R. Akhtar, Transition metal-catalyzed CH Alkylations as versatile tools for synthetic transformations: a review, *J. Iran. Chem. Soc.*, 2022, **19**(8), 3285–3315.
- 3 R. Ashraf, A. F. Zahoor, K. G. Ali, U. Nazeer, M. J. Saif, A. Mansha, A. R. Chaudhry and A. Irfan, Development of novel transition metal-catalyzed synthetic approaches for the synthesis of a dihydrobenzofuran nucleus: a review, *RSC Adv.*, 2024, **14**(21), 14539–14581.
- 4 J. E. Zweig, D. E. Kim and T. R. Newhouse, Methods utilizing first-row transition metals in natural product total synthesis, *Chem. Rev.*, 2017, **117**(18), 11680–11752.
- 5 P. Chirik and R. Morris, Getting down to earth: the renaissance of catalysis with abundant metals, *Acc. Chem. Res.*, 2015, **48**, 2495.
- 6 M. Hapke and G. Hilt, *Introduction to Cobalt Chemistry and Catalysis, Cobalt Catalysis in Organic Synthesis: Methods React.*, pp. , pp. 20201–20223.
- 7 S. Xiao, L. Ai, Q. Liu, B. Yang, J. Huang, W. Xue and Y. Chen, Total Synthesis of Natural Terpenoids Enabled by Cobalt Catalysis, *Front. Chem.*, 2022, **10**, 941184.
- 8 T. Momeni, V. Zadsirjan, M. Hadi Meshkatsadat and M. Pourmohammadi-Mahunaki, Applications of Cobalt-Catalyzed Reactions in the Total Synthesis of Natural Products, *ChemistrySelect*, 2022, **7**(48), e202202816.
- 9 C. Wu, J. Zhou, G. He, H. Li, Q. Yang, R. Wang, Y. Zhou and H. Liu, Ruthenium (ii)-catalyzed selective C–H bond activation of imidamides and coupling with sulfoxonium ylides: an efficient approach for the synthesis of highly functional 3-ketoindoles, *Org. Chem. Front.*, 2019, **6**(8), 1183–1188.
- 10 C. Gosmini, J.-M. Béguin and A. Moncomble, Cobalt-catalyzed cross-coupling reactions, *Chem. Commun.*, 2008, (28), 3221–3233.
- 11 G. Cahiez and A. Moyeux, Cobalt-Catalyzed Cross-Coupling Reactions, *Chem. Rev.*, 2010, **110**(3), 1435–1462.
- 12 K. Gao and N. Yoshikai, Low-Valent Cobalt Catalysis: New Opportunities for C–H Functionalization, *Acc. Chem. Res.*, 2014, **47**(4), 1208–1219.
- 13 H. Pellissier and H. Clavier, Enantioselective Cobalt-Catalyzed Transformations, *Chem. Rev.*, 2014, **114**(5), 2775–2823.
- 14 K. Gao, P.-S. Lee, T. Fujita and N. Yoshikai, Cobalt-Catalyzed Hydroarylation of Alkynes through Chelation-Assisted C–H Bond Activation, *J. Am. Chem. Soc.*, 2010, **132**(35), 12249–12251.
- 15 N. Yoshikai, Development of Cobalt-Catalyzed C–H Bond Functionalization Reactions, *Bull. Chem. Soc. Jpn.*, 2014, **87**(8), 843–857.
- 16 Q. Chen, L. Ilies and E. Nakamura, Cobalt-Catalyzed ortho-Alkylation of Secondary Benzamide with Alkyl Chloride through Directed C–H Bond Activation, *J. Am. Chem. Soc.*, 2011, **133**(3), 428–429.
- 17 L. Ilies, Q. Chen, X. Zeng and E. Nakamura, Cobalt-Catalyzed Chemoselective Insertion of Alkene into the Ortho C–H Bond of Benzamide, *J. Am. Chem. Soc.*, 2011, **133**(14), 5221–5223.
- 18 Q. Chen, L. Ilies, N. Yoshikai and E. Nakamura, Cobalt-Catalyzed Coupling of Alkyl Grignard Reagent with Benzamide and 2-Phenylpyridine Derivatives through Directed C–H Bond Activation under Air, *Org. Lett.*, 2011, **13**(12), 3232–3234.
- 19 W. Song and L. Ackermann, Cobalt-Catalyzed Direct Arylation and Benzylation by C=H/C=O Cleavage with Sulfamates, Carbamates, and Phosphates, *Angew. Chem.*, 2012, **124**(33), 8376–8379.
- 20 J. Li and L. Ackermann, Cobalt-Catalyzed C=H Arylations with Weakly-Coordinating Amides and Tetrazoles:



- Expedient Route to Angiotensin-II-Receptor Blockers, *Chem.-Eur. J.*, 2015, **21**(15), 5718–5722.
- 21 M. Moselage, N. Sauermann, S. C. Richter and L. Ackermann, C=H Alkenylations with Alkenyl Acetates, Phosphates, Carbonates, and Carbamates by Cobalt Catalysis at 23 °C, *Angew. Chem., Int. Ed.*, 2015, **54**(21), 6352–6355.
- 22 L. Ackermann, Cobalt-catalyzed C–H arylations, benzylations, and alkylations with organic electrophiles and beyond, *J. Org. Chem.*, 2014, **79**(19), 8948–8954.
- 23 M. Moselage, J. Li and L. Ackermann, Cobalt-Catalyzed C–H Activation, *ACS Catal.*, 2016, **6**(2), 498–525.
- 24 T. Yao, K. Hirano, T. Satoh and M. Miura, Nickel- and cobalt-catalyzed direct alkylation of azoles with N-tosylhydrazones bearing unactivated alkyl groups, *Angew. Chem.*, 2012, **124**(3), 799–803.
- 25 T. Yoshino, H. Ikemoto, S. Matsunaga and M. Kanai, A Cationic High-Valent Cp* Co III Complex for the Catalytic Generation of Nucleophilic Organometallic Species: Directed C=H Bond Activation, *Angew. Chem., Int. Ed.*, 2013, **52**(8), 2207–2211.
- 26 B. B. Toure and D. G. Hall, Natural product synthesis using multicomponent reaction strategies, *Chem. Rev.*, 2009, **109**, 4439–4486.
- 27 S. Munawar, A. F. Zahoor, S. M. Hussain, S. Ahmad, A. Mansha, B. Parveen, K. G. Ali and A. Irfan, Steglich esterification: A versatile synthetic approach toward the synthesis of natural products, their analogues/derivatives, *Heliyon*, 2024, **10**(1), 1–37.
- 28 P. Tang and Y. Qin, Recent applications of cyclopropane-based strategies to natural product synthesis, *Synthesis*, 2012, **44**, 2969–2984.
- 29 C. Exon and P. Magnus, Stereoselectivity of intramolecular dicobalt octacarbonyl alkene-alkyne cyclizations: short synthesis of dl-coriolin, *J. Am. Chem. Soc.*, 1983, **105**(8), 2477–2478.
- 30 N. Itoh, T. Iwata, H. Sugihara, F. Inagaki and C. Mukai, Total Syntheses of (±)-Fawcettimine, (±)-Fawcettidine, (±)-Lycoflexine, and (±)-Lycoposerramine-Q, *Chem.-Eur. J.*, 2013, **19**(26), 8665–8672.
- 31 J. M. Holland, M. Lewis and A. Nelson, Desymmetrization of a Centrosymmetric Diepoxide: Efficient Synthesis of a Key Intermediate in a Total Synthesis of Hemibrevetoxin B, *J. Org. Chem.*, 2003, **68**(3), 747–753.
- 32 M. A. McGowan, C. P. Stevenson, M. A. Schiffler and E. N. Jacobsen, An enantioselective total synthesis of (+)-peloruside A, *Angew. Chem.*, 2010, **49**(35), 6147.
- 33 S. Zhou, M. Wang, L. Wang, K. Chen, J. Wang, C. Song and J. Zhu, Bidentate directing-enabled, traceless heterocycle synthesis: Cobalt-catalyzed access to isoquinolines, *Org. Lett.*, 2016, **18**(21), 5632–5635.
- 34 M. M. Lorion, N. Kaplaneris, J. Son, R. Kuniyil and L. Ackermann, Late-Stage Peptide Diversification through Cobalt-Catalyzed C–H Activation: Sequential Multicatalysis for Stapled Peptides, *Angew. Chem.*, 2019, **131**(6), 1698–1702.
- 35 X.-Y. Wang, X.-B. Wang, Y. Tian, C. Peng, M.-S. Xie and H.-M. Guo, Cobalt-Catalyzed Asymmetric Dearomative [3 + 2] Annulation of Quinolines, Isoquinolines, and Pyridines, *ACS Catal.*, 2023, **13**(17), 11528–11540.
- 36 R. Hua, Isoquinolone syntheses by annulation protocols, *Catalysts*, 2021, **11**(5), 620.
- 37 Q.-J. Yao and B.-F. Shi, Cobalt(III)-Catalyzed Enantioselective C–H Functionalization: Ligand Innovation and Reaction Development, *Acc. Chem. Res.*, 2025, **58**(6), 971–990.
- 38 S. Roy, S. K. Das and B. Chattopadhyay, Cobalt (II)-based metalloradical activation of 2-(diazomethyl) pyridines for radical transannulation and cyclopropanation, *Angew. Chem.*, 2018, **130**(8), 2260–2265.
- 39 Y. Yang, W.-J. Zuo, Y.-X. Zhao, W.-H. Dong, W.-L. Mei and H.-F. Dai, Indole alkaloids from *Kopsia hainanensis* and evaluation of their antimicrobial activity, *Planta Med.*, 2012, **78**(17), 1881–1884.
- 40 K.-H. Lim and T.-S. Kam, Arbophylline, a novel heptacyclic indole with a cage skeleton incorporating an acetal moiety, *Tetrahedron Lett.*, 2006, **47**(49), 8653–8655.
- 41 K.-H. Lim, O. Hiraku, K. Komiyama, T. Koyano, M. Hayashi and T.-S. Kam, Biologically active indole alkaloids from *Kopsia arborea*, *J. Nat. Prod.*, 2007, **70**(8), 1302–1307.
- 42 K.-H. Lim, K. Komiyama and T.-S. Kam, Arboricine and arboricinine, unusual tetracyclic indole regioisomers from *Kopsia*, *Tetrahedron Lett.*, 2007, **48**(7), 1143–1145.
- 43 S.-H. Lim, K.-M. Sim, Z. Abdullah, O. Hiraku, M. Hayashi, K. Komiyama and T.-S. Kam, Leuconoxine, Kopsinitarine, Kopsijasmine, and Kopsinone Derivatives from *Kopsia*, *J. Nat. Prod.*, 2007, **70**(8), 1380–1383.
- 44 Z. Zhang, S. Xie, B. Cheng, H. Zhai and Y. Li, Enantioselective Total Synthesis of (+)-Arboridinine, *J. Am. Chem. Soc.*, 2019, **141**(17), 7147–7154.
- 45 L.-L. Song, Y.-L. Mu, H.-C. Zhang, G.-Y. Wu and J.-Y. Sun, A new indole alkaloid with anti-inflammatory from the branches of *Nauclea officinalis*, *Nat. Prod. Res.*, 2020, **34**(16), 2283–2288.
- 46 A. A. Agomuoh, A. Ata, C. C. Udenigwe, R. E. Aluko and I. Irenus, Novel indole alkaloids from *Nauclea latifolia* and their renin-inhibitory activities, *Chem. Biodiversity*, 2013, **10**(3), 401–410.
- 47 J. Sun, H. Lou, S. Dai, H. Xu, F. Zhao and K. Liu, Indole alkaloids from *Nauclea officinalis* with weak antimalarial activity, *Phytochemistry*, 2008, **69**(6), 1405–1410.
- 48 C. A. J. Erdelmeier, U. Regenass, T. Rali and O. Sticher, Indole Alkaloids with in vitro Antiproliferative Activity from the Ammoniacal Extract of *Nauclea orientalis*1, *Planta Med.*, 1992, **58**(01), 43–48.
- 49 Y.-P. Liu, Q.-L. Liu, X.-L. Zhang, H.-Y. Niu, C.-Y. Guan, F.-K. Sun, W. Xu and Y.-H. Fu, Bioactive monoterpene indole alkaloids from *Nauclea officinalis*, *Bioorg. Chem.*, 2019, 831–835.
- 50 X. Peng, M. Fu, J. Ou, R. Cao, H. Song, X.-Y. Liu and Y. Qin, Total synthesis of angustine and angustoline, *Tetrahedron Lett.*, 2020, **61**(15), 151757.



- 51 A. Padwa and A. G. Waterson, The thionium/N-acyliminium ion cyclization cascade as a strategy for the synthesis of azapolycyclic ring systems, *Tetrahedron*, 2000, **56**(52), 10159–10173.
- 52 X. Li, T. Huang, Y. Song, Y. Qi, L. Li, Y. Li, Q. Xiao and Y. Zhang, Co(III)-Catalyzed Annulative Vinylene Transfer via C–H Activation: Three-Step Total Synthesis of 8-Oxopseudopalmitine and Oxopalmitine, *Org. Lett.*, 2020, **22**(15), 5925–5930.
- 53 P. O. Guillen, K. B. Jaramillo, G. Genta-Jouve and O. P. Thomas, Marine natural products from zoantharians: bioactivity, biosynthesis, systematics, and ecological roles, *Nat. Prod. Rep.*, 2020, **37**(4), 515–540.
- 54 D. C. Behenna, J. L. Stockdill and B. M. Stoltz, The biology and chemistry of the zoanthamine alkaloids, *Angew. Chem., Int. Ed.*, 2008, **47**(13), 2365–2386.
- 55 F. Yoshimura, K. Tanino and M. Miyashita, Recent developments in the synthesis of zoanthamine alkaloids, *Tetrahedron Lett.*, 2014, **55**(18), 2895–2903.
- 56 C. B. Rao, A. S. R. Anjaneyula, N. S. Sarma, Y. Venkatateswarlu, R. M. Rosser, D. J. Faulkner, M. H. M. Chen and J. Clardy, Zoanthamine; a novel alkaloid from a marine zoanthid, *J. Am. Chem. Soc.*, 1984, **106**(25), 7983–7984.
- 57 S. Fukuzawa, Y. Hayashi, D. Uemura, A. Nagatsu, K. Yamada and Y. Ijuin, The isolation and structures of five new alkaloids, norzoanthamine, oxyzoanth amine, norzoanthaminone, cyclozoanthamine and epinorzoanthamine, *Heterocycl. Commun.*, 1995, **1**(2–3), 207–214.
- 58 A. H. Daranas, J. Fernández, J. Gavín and M. Norte, New alkaloids from a marine zoanthid, *Tetrahedron*, 1999, **55**(17), 5539–5546.
- 59 Y. Chen, Z. Xin, H. Wang, H. He and S. Gao, Asymmetric total synthesis of norzoanthamine and formal synthesis of zoanthenol, *Org. Chem. Front.*, 2023, **10**(3), 651–660.
- 60 J. Szawkało and Z. Czarnocki, Enantioselective synthesis of some tetracyclic isoquinoline alkaloids by asymmetric transfer hydrogenation catalysed by a chiral ruthenium complex, *Monatsh. Chem.*, 2005, **136**(9), 1619–1627.
- 61 K. W. Bentley, β -Phenylethylamines and the isoquinoline alkaloids, *Nat. Prod. Rep.*, 2006, **23**(3), 444–463.
- 62 P. M. Dewick, *Med. Nat. Prod.: a Biosynthetic Approach*, John Wiley & Sons, 2002.
- 63 A. N. Kim, A. Ngamthiporn, E. Du and B. M. Stoltz, Recent advances in the total synthesis of the tetrahydroisoquinoline alkaloids (2002–2020), *Chem. Rev.*, 2023, **123**(15), 9447–9496.
- 64 K. Leander, B. Luning, E. Ruusa, O. Theander, A. A. Lindberg, G. Jansen, B. Lamm and B. Samuelsson, Studies on Orchidaceae Alkaloids. XI. Three 1-Phenyl-1, 2, 3, 4-tetrahydroisoquinolines from *Cryptostylis fulva* Schltr, *Acta Chem. Scand.*, 1969, 23244–23248.
- 65 A. Brossi and S. Teitel, Synthesis and absolute configuration of cryptostylin I, II, and III, *Helv. Chim. Acta*, 1971, **54**(6), 1564–1571.
- 66 D. L. Minor, S. D. Wyrick, P. S. Charifson, V. J. Watts, D. E. Nichols and R. B. Mailman, Synthesis and molecular modeling of 1-phenyl-1, 2, 3, 4-tetrahydroisoquinolines and related 5, 6, 8, 9-tetrahydro-13BH-dibenzo [a, h] quinolizines as D1 dopamine antagonists, *J. Med. Chem.*, 1994, **37**(25), 4317–4328.
- 67 R. Naito, Y. Yonetoku, Y. Okamoto, A. Toyoshima, K. Ikeda and M. Takeuchi, Synthesis and antimuscarinic properties of quinuclidin-3-yl 1, 2, 3, 4-tetrahydroisoquinoline-2-carboxylate derivatives as novel muscarinic receptor antagonists, *J. Med. Chem.*, 2005, **48**(21), 6597–6606.
- 68 Y.-J. Wu, J.-H. Chen, M.-Y. Teng, X. Li, T.-Y. Jiang, F.-R. Huang, Q.-J. Yao and B.-F. Shi, Cobalt-Catalyzed Enantioselective C–H Annulation of Benzylamines with Alkynes: Application to the Modular and Asymmetric Syntheses of Bioactive Molecules, *J. Am. Chem. Soc.*, 2023, **145**(45), 24499–24505.
- 69 O. Ohno, T. Chiba, S. Todoroki, H. Yoshimura, N. Maru, K. Maekawa, H. Imagawa, K. Yamada, A. Wakamiya and K. Suenaga, Halichonines A, B, and C, novel sesquiterpene alkaloids from the marine sponge *Halichondria okadai* Kadota, *Chem. Commun.*, 2011, **47**(46), 12453–12455.
- 70 S.-J. Nam, C. A. Kauffman, L. A. Paul, P. R. Jensen and W. Fenical, Actinoranone, a cytotoxic meroterpenoid of unprecedented structure from a marine adapted *Streptomyces* sp, *Org. Lett.*, 2013, **15**(21), 5400–5403.
- 71 B. J. M. Jansen and A. De Groot, Occurrence, biological activity and synthesis of drimane sesquiterpenoids, *Nat. Prod. Rep.*, 2004, **21**(4), 449–477.
- 72 F. Yoshimura, M. Uchida, K. Aratame, H. Ouchi, M. Inai, M. Kondo, R. Takita and T. Kan, Total synthesis of (\pm)-halichonine B, *Org. Biomol. Chem.*, 2025, **23**(13), 3076–3080.
- 73 H. Shigemori, H. Komaki, K. Yazawa, Y. Mikami, A. Nemoto, Y. Tanaka, T. Sasaki, Y. In, T. Ishida, J. i. Kobayashi and A. Brasilicardin, A Novel Tricyclic Metabolite with Potent Immunosuppressive Activity from Actinomycete *Nocardia brasiliensis*, *J. Org. Chem.*, 1998, **63**(20), 6900–6904.
- 74 K. Komatsu, M. Tsuda, M. Shiro, Y. Tanaka, Y. Mikami and J. i. Kobayashi, Brasilicardins B–D, new tricyclic terpenoids from actinomycete *Nocardia brasiliensis*, *Bioorg. Med. Chem.*, 2004, **12**(21), 5545–5551.
- 75 H. Komaki, A. Nemoto, Y. Tanaka, H. Takagi, K. Yazawa, Y. Mikami, H. Shigemori, J. i. Kobayashi, A. Ando and Y. Nagata, Brasilicardin A, a new terpenoid antibiotic from pathogenic *Nocardia brasiliensis*: fermentation, isolation and biological activity, *J. Antibiot.*, 1999, **52**(1), 13–19.
- 76 F. Yoshimura, R. Itoh, M. Torizuka, G. Mori and K. Tanino, Asymmetric total synthesis of brasilicardins, *Angew. Chem., Int. Ed.*, 2018, **57**(52), 17161–17167.
- 77 J. Kupka, T. Anke, F. Oberwinkler, G. Schramm and W. Steglich, Antibiotics from basidiomycetes. (VII) crinipellin, a new antibiotic from the basidiomycetous



- fungus *crinipellis stipitaria* (fr.) pat., *J. Antibiot.*, 1979, **32**(2), 130–135.
- 78 C. Shinohara, T. Chikanishi, S. Nakashima, A. Hashimoto, A. Hamanaka, A. Endo and K. Hasumi, Enhancement of fibrinolytic activity of vascular endothelial cells by chaetoglobosin A, crinipellin B, geodin and triticone B, *J. Antibiot.*, 2000, **53**(3), 262–268.
- 79 G. Mehta and K. S. Rao, General transannulation approach to angular triquinanes. Total syntheses of (\pm)-pentalenene and (\pm)-epi-pentalenene, *J. Am. Chem. Soc.*, 1986, **108**(25), 8015–8021.
- 80 G. Mehta and K. S. Rao, Model studies towards Crinipellin diterpenes and paniculatin-type lycopodium alkaloids from a common triquinane precursor, *J. Chem. Soc., Chem. Commun.*, 1987, (20), 1578–1580.
- 81 C. E. Schwartz and D. P. Curran, New tandem radical cyclizations directed toward the synthesis of Crinipellin A, *J. Am. Chem. Soc.*, 1990, **112**(25), 9272–9284.
- 82 K. SrinivasáRao and M. SreenivasaáReddy, Synthetic approach to novel crinipellin diterpenes. Construction of the functionalised C 20-tetraquinane framework, *J. Chem. Soc., Perkin Trans. 1*, 1991, (4), 693–700.
- 83 A. S. Gybin, V. A. Smit, R. Caple, A. L. Veretenov, A. S. Shashkov, L. G. Vorontsova, M. G. Kurella, V. S. Chertkov and A. A. Karapetyan, The sequence of a stepwise AdE reaction and intramolecular Pauson-Khand cycloaddition as an entry into the synthesis of polycyclic compounds, *J. Am. Chem. Soc.*, 1992, **114**(14), 5555–5566.
- 84 L. V. Tino-Wooldridge, K. D. Moeller and C. M. Hudson, Intramolecular anodic olefin coupling reactions: a new approach to the synthesis of angularly fused, tricyclic enones, *J. Org. Chem.*, 1994, **59**(9), 2381–2389.
- 85 Z. Huang, J. Huang, Y. Qu, W. Zhang, J. Gong and Z. Yang, Total Syntheses of Crinipellins Enabled by Cobalt-Mediated and Palladium-Catalyzed Intramolecular Pauson-Khand Reactions, *Angew. Chem.*, 2018, **130**(28), 8880–8884.
- 86 Q. Khuong-Huu, A. Chiaroni, C. Riche, H. Nguyen-Ngoc, K. Nguyen-Viet and F. Khuong-Huu, New Rearranged Limonoids from *Harrisonia perforata*. III, *J. Nat. Prod.*, 2001, **64**(5), 634–637.
- 87 X.-H. Yan, P. Yi, P. Cao, S.-Y. Yang, X. Fang, Y. Zhang, B. Wu, Y. Leng, Y.-T. Di and Y. Lv, 16-nor Limonoids from *Harrisonia perforata* as promising selective 11 β -HSD1 inhibitors, *Sci. Rep.*, 2016, **6**(1), 36927.
- 88 Y. Tanaka, A. Sakamoto, T. Inoue, T. Yamada, T. Kikuchi, T. Kajimoto, O. Muraoka, A. Sato, Y. Wataya and H.-S. Kim, Andriolides H-P from the flower of andiroba (*Carapa guianensis*, Meliaceae), *Tetrahedron*, 2012, **68**(18), 3669–3677.
- 89 Z.-F. Zhou, H.-L. Liu, W. Zhang, T. Kurtan, A. Mandi, A. Benyei, J. Li, O. Tagliatalata-Scafati and Y.-W. Guo, Bioactive rearranged limonoids from the Chinese mangrove *Xylocarpus granatum* Koenig, *Tetrahedron*, 2014, **70**(37), 6444–6449.
- 90 C. Lv, X. Yan, Q. Tu, Y. Di, C. Yuan, X. Fang, Y. Ben-David, L. Xia, J. Gong and Y. Shen, Isolation and asymmetric total synthesis of perforanoid A, *Angew. Chem., Int. Ed.*, 2016, **55**(26), 7539–7543.
- 91 J. S. Scott, F. W. Goldberg and A. V. Turnbull, Medicinal chemistry of inhibitors of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), *J. Med. Chem.*, 2014, **57**(11), 4466–4486.
- 92 W. Zhang, Z. Zhang, J.-C. Tang, J.-T. Che, H.-Y. Zhang, J.-H. Chen and Z. Yang, Total synthesis of (+)-haperforin G, *J. Am. Chem. Soc.*, 2020, **142**(46), 19487–19492.
- 93 M. Bueschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal and L. E. Overman, Synthetic strategies toward natural products containing contiguous stereogenic quaternary carbon atoms, *Angew. Chem., Int. Ed.*, 2016, **55**(13), 4156–4186.
- 94 G. Mehta and A. Srikrishna, Synthesis of polyquinane natural products: An update, *Chem. Rev.*, 1997, **97**(3), 671–720.
- 95 Y. Qiu, W.-J. Lan, H.-J. Li and L.-P. Chen, Linear triquinane sesquiterpenoids: Their isolation, structures, biological activities, and chemical synthesis, *Molecules*, 2018, **23**(9), 2095.
- 96 D. B. Clarke, S. F. R. Hinkley and R. T. Weavers, Waihoensene. A new laurenene-related diterpene from *Podocarpus totara* var *waihoensis*, *Tetrahedron Lett.*, 1997, **38**(24), 4297–4300.
- 97 Y. Qu, Z. Wang, Z. Zhang, W. Zhang, J. Huang and Z. Yang, Asymmetric total synthesis of (+)-waihoensene, *J. Am. Chem. Soc.*, 2020, **142**(14), 6511–6515.
- 98 L. C. Rosenbaum, M. Häfner and T. Gaich, Total synthesis of the diterpene waihoensene, *Angew. Chem.*, 2021, **133**(6), 2975–2978.
- 99 Y.-Y. Fan, J.-B. Xu, H.-C. Liu, L.-S. Gan, J. Ding, J.-M. Yue and A. -J. Cephanolides, Cephalotane-Type Diterpenoids from *Cephalotaxus sinensis*, *J. Nat. Prod.*, 2017, **80**(12), 3159–3166.
- 100 J. G. Buta, J. L. Flippen and W. R. Lusby, Harringtonolide, a plant growth inhibitory tropone from *Cephalotaxus harringtonia* (Forbes) K. Koch, *J. Org. Chem.*, 1978, **43**(5), 1002–1003.
- 101 Z.-P. Ge, H.-C. Liu, G.-C. Wang, Q.-F. Liu, C.-H. Xu, J. Ding, Y.-Y. Fan and J.-M. Yue, 17-nor-Cephalotane-type diterpenoids from *Cephalotaxus fortunei*, *J. Nat. Prod.*, 2019, **82**(6), 1565–1575.
- 102 J. Du, M.-H. Chiu and R.-L. Nie, Two New Lactones from *Cephalotaxus fortunei* var. *alpnia*, *J. Nat. Prod.*, 1999, **62**(12), 1664–1665.
- 103 M. Haider, G. Sennari, A. Eggert and R. Sarpong, Total synthesis of the cephalotaxus norditerpenoids (\pm)-cephanolides A-D, *J. Am. Chem. Soc.*, 2021, **143**(7), 2710–2715.
- 104 Y.-B. Wu, Z.-Y. Ni, Q.-W. Shi, M. Dong, H. Kiyota, Y.-C. Gu and B. Cong, Constituents from *Salvia* species and their biological activities, *Chem. Rev.*, 2012, **112**(11), 5967–6026.
- 105 M. A. González, Aromatic abietane diterpenoids: Their biological activity and synthesis, *Nat. Prod. Rep.*, 2015, **32**(5), 684–704.



- 106 R. Inatani, N. Nakatani and H. Fuwa, Antioxidative effect of the constituents of rosemary (*Rosmarinus officinalis* L.) and their derivatives, *Agric. Biol. Chem.*, 1983, **47**(3), 521–528.
- 107 D. Poeckel, C. Greiner, M. Verhoff, O. Rau, L. Tausch, C. Hörnig, D. Steinhilber, M. Schubert-Zsilavec and O. Werz, Carnosic acid and carnosol potently inhibit human 5-lipoxygenase and suppress pro-inflammatory responses of stimulated human polymorphonuclear leukocytes, *Biochem. Pharmacol.*, 2008, **76**(1), 91–97.
- 108 F. Maione, V. Cantone, S. Pace, M. G. Chini, A. Bisio, G. Romussi, S. Pieretti, O. Werz, A. Koeberle and N. Mascolo, Anti-inflammatory and analgesic activity of carnosol and carnosic acid in vivo and in vitro and in silico analysis of their target interactions, *Br. J. Pharmacol.*, 2017, **174**(11), 1497–1508.
- 109 B.-B. Zhang, B.-Q. He, J.-B. Sun, B. Zeng, X.-J. Shi, Y. Zhou, Y. Niu, S.-Q. Nie, F. Feng and Y. Liang, Diterpenoids from *Salvia plebeia* R. Br. and their antioxidant and anti-inflammatory activities, *Molecules*, 2015, **20**(8), 14879–14888.
- 110 L. K. Johnson, S. W. Niman, D. Vrubliauskas and C. D. Vanderwal, Stereocontrolled synthesis and structural revision of plebeianiol A, *Org. Lett.*, 2021, **23**(24), 9569–9573.
- 111 T. J. Heckrodt and J. Mulzer, in *Natural Products Synthesis II: Targets, Methods, Concepts*, ed. J. Mulzer, Springer Berlin Heidelberg, Berlin, Heidelberg, 2005, pp. 1–41, DOI: [10.1007/b96886](https://doi.org/10.1007/b96886).
- 112 F. Berru , M. W. B. McCulloch and R. G. Kerr, Marine diterpene glycosides, *Bioorg. Med. Chem.*, 2011, **19**(22), 6702–6719.
- 113 A. D. Rodr guez and C. Ram rez, Serrulatane Diterpenes with Antimycobacterial Activity Isolated from the West Indian Sea Whip *Pseudopterogorgia elisabethae*, *J. Nat. Prod.*, 2001, **64**(1), 100–102.
- 114 S. A. Kolesnikova, A. I. Kalinovsky, S. N. Fedorov, L. K. Shubina and V. A. Stonik, Diterpenes from the Far-eastern brown alga *Dictyota dichotoma*, *Phytochemistry*, 2006, **67**(19), 2115–2119.
- 115 S. A. Look, W. Fenical, R. S. Jacobs and J. Clardy, The pseudopterogens: anti-inflammatory and analgesic natural products from the sea whip *Pseudopterogorgia elisabethae*, *Proc. Natl. Acad. Sci. U. S. A.*, 1986, **83**(17), 6238–6240.
- 116 S. A. Look, W. Fenical, G. K. Matsumoto and J. Clardy, The pseudopterogens: a new class of anti-inflammatory and analgesic diterpene pentosides from the marine sea whip *Pseudopterogorgia elisabethae* (Octocorallia), *J. Org. Chem.*, 1986, **51**(26), 5140–5145.
- 117 S. A. Look and W. Fenical, The seco-pseudopterogens, new anti-inflammatory diterpene-glycosides from a caribbean gorgonian octocoral of the genus *pseudopterogorgia*, *Tetrahedron*, 1987, **43**(15), 3363–3370.
- 118 V. Roussis, Z. Wu, W. Fenical, S. A. Strobel, G. D. Van Duyne and J. Clardy, New anti-inflammatory pseudopterogens from the marine octocoral *Pseudopterogorgia elisabethae*, *J. Org. Chem.*, 1990, **55**(16), 4916–4922.
- 119 I. I. Rodr guez, Y.-P. Shi, O. J. Garc a, A. D. Rodr guez, A. M. S. Mayer, J. A. S nchez, E. Ortega-Barria and J. Gonz lez, New Pseudopterogen and seco-Pseudopterogen Diterpene Glycosides from Two Colombian Isolates of *Pseudopterogorgia elisabethae* and Their Diverse Biological Activities, *J. Nat. Prod.*, 2004, **67**(10), 1672–1680.
- 120 S. Movahhed, J. Westphal, A. Kempa, C. E. Schumacher, J. Sperlich, J.-M. Neud rfl, N. Teusch, M. Hochg rtel and H.-G. Schmalz, Total Synthesis of (+)-Erogorgiaene and the Pseudopterogen A-F Aglycone via Enantioselective Cobalt-Catalyzed Hydrovinylation, *Chem.-Eur. J.*, 2021, **27**(45), 11574–11579.
- 121 L. Tong, Q. Zhao, E. Datan, G.-Q. Lin, I. Minn, M. G. Pomper, B. Yu, D. Romo, Q.-L. He and J. O. Liu, Triptolide: reflections on two decades of research and prospects for the future, *Nat. Prod. Rep.*, 2021, **38**(4), 843–860.
- 122 Y.-Z. Chen, Q. Gao, X.-Z. Zhao, X.-M. Chen, F. Zhang, J. Chen, C.-G. Xu, L.-L. Sun and C.-L. Mei, Meta-analysis of *Tripterygium wilfordii* Hook F in the immunosuppressive treatment of IgA nephropathy, *Intern. Med.*, 2010, **49**(19), 2049–2055.
- 123 K. Morris, A. William and G. Richard, Triptolide and triptolidide, novel antileukemic diterpenoid triepoxides from *Tripterygium wilfordii*, *J. Am. Chem. Soc.*, 1972, **94**(20), 7194–7195.
- 124 X. Fang, N. Zhang, S.-C. Chen and T. Luo, Scalable total synthesis of (–)-triptonide: serendipitous discovery of a visible-light-promoted olefin coupling initiated by metal-catalyzed hydrogen atom transfer (MHAT), *J. Am. Chem. Soc.*, 2022, **144**(5), 2292–2300.
- 125 C. E. Schumacher, M. Rausch, T. Greven, J. M. Neud rfl, T. Schneider and H. G. Schmalz, Total synthesis and antibiotic properties of amino-functionalized aromatic terpenoids related to erogorgiaene and the pseudopterogens, *Eur. J. Org. Chem.*, 2022, **2022**(26), e202200058.
- 126 S.-G. Ma, M. Li, M.-B. Lin, L. Li, Y.-B. Liu, J. Qu, Y. Li, X.-J. Wang, R.-B. Wang, S. Xu, Q. Hou and S.-S. Yu, Illisimonin A, a Caged Sesquiterpenoid with a Tricyclo [5.2.1.0.1, 6] decane Skeleton from the Fruits of *Illicium simonsii*, *Org. Lett.*, 2017, **19**(22), 6160–6163.
- 127 T. F. Jamison, S. Shambayati, W. E. Crowe and S. L. Schreiber, Cobalt-mediated total synthesis of (+)-epoxydictymene, *J. Am. Chem. Soc.*, 1994, **116**(12), 5505–5506.
- 128 I. B. Seiple, S. Su, I. S. Young, C. A. Lewis, J. Yamaguchi and P. S. Baran, Total synthesis of palau' amine, *Angew. Chem.*, 2010, **122**(6), 1113–1116.
- 129 S. V. Pronin and R. A. Shenvi, Synthesis of highly strained terpenes by non-stop tail-to-head polycyclization, *Nat. Chem.*, 2012, **4**(11), 915–920.
- 130 P. Hu and S. A. Snyder, Enantiospecific total synthesis of the highly strained (–)-presilphiperfolan-8-ol via a Pd-



- catalyzed tandem cyclization, *J. Am. Chem. Soc.*, 2017, **139**(14), 5007–5010.
- 131 W. Zhang, Z.-X. Zhou, X.-J. Zhu, Z.-H. Sun, W.-M. Dai and C.-C. Li, Asymmetric total synthesis of the highly strained 4 β -acetoxypobotryane-9 β , 15 α -diol, *J. Am. Chem. Soc.*, 2020, **142**(47), 19868–19873.
- 132 C. H. McCulley and D. J. Tantillo, Predicting rearrangement-competent terpenoid oxidation levels, *J. Am. Chem. Soc.*, 2020, **142**(13), 6060–6065.
- 133 B. Xu, Z. Zhang and M. Dai, Total Synthesis of (–)-Illisimonin A Enabled by Pattern Recognition and Olefin Transposition, *J. Am. Chem. Soc.*, 2025, **147**(21), 17592–17597.
- 134 H.-D. Sun, S.-X. Huang and Q.-B. Han, Diterpenoids from *Isodon* species and their biological activities, *Nat. Prod. Rep.*, 2006, **23**(5), 673–698.
- 135 P. S. Riehl, Y. C. DePorre, A. M. Armaly, E. J. Groso and C. S. Schindler, New avenues for the synthesis of entkaurene diterpenoids, *Tetrahedron*, 2015, **71**(38), 6629–6650.
- 136 M. Liu, W.-G. Wang, H.-D. Sun and J.-X. Pu, Diterpenoids from *Isodon* species: an update, *Nat. Prod. Rep.*, 2017, **34**(9), 1090–1140.
- 137 A. Riaz, B. Saleem, G. Hussain, I. Sarfraz, B. Nageen, R. Zara, M. Manzoor and A. Rasul, Eriocalyxin B biological activity: a review on its mechanism of action, *Nat. Prod. Commun.*, 2019, **14**(8), 1934578X19868598.
- 138 Y. Zhang, S. Wang, M. Dai, J. Nai, L. Zhu and H. Sheng, Solubility and bioavailability enhancement of oridonin: a review, *Molecules*, 2020, **25**(2), 332.
- 139 Q. Gu, G. D. Walby, M. D. Wood and S. F. Martin, Total Synthesis of (+)-Pierisketone B, *J. Am. Chem. Soc.*, 2025, **147**(33), 29631–29635.
- 140 H. Umezawa, Studies on anti-tumor substances produced by microorganisms. III. On sarkomycin produced by a strain resembling to *Streptomyces erythrochromogenes*, *J. Antibiot., Ser. A*, 1953, 6147–6152.
- 141 A. Cabré, H. I. a. Khaizourane, M. Garçon, X. Verdagner and A. Riera, Total synthesis of (R)-Sarkomycin methyl ester via regioselective intermolecular pauson–khand reaction and iridium-catalyzed asymmetric isomerization, *Org. Lett.*, 2018, **20**(13), 3953–3957.
- 142 X. Ma, B. Bolte, M. G. Banwell and A. C. Willis, Total syntheses of the resorcylic acid lactones paecilomycin F and cochliomycin C using an intramolecular Loh-type α -allylation reaction for macrolide formation, *Org. Lett.*, 2016, **18**(17), 4226–4229.
- 143 L. Xu, P. Wu, J. Xue, I. Molnar and X. Wei, Antifungal and cytotoxic β -resorcylic acid lactones from a *Paecilomyces* species, *J. Nat. Prod.*, 2017, **80**(8), 2215–2223.
- 144 N. A. Mallampudi, B. Srinivas, J. G. Reddy and D. K. Mohapatra, Total synthesis and structural revision of monocillin VII, *Org. Lett.*, 2019, **21**(15), 5952–5956.
- 145 A. Fukuzawa and E. Kurosawa, Laurallene, new bromoallene from the marine red alga *Laurencia nipponica* Yamada, *Tetrahedron Lett.*, 1979, **20**(30), 2797–2800.
- 146 Z.-F. Zhou, M. Menna, Y.-S. Cai and Y.-W. Guo, Polyacetylenes of marine origin: chemistry and bioactivity, *Chem. Rev.*, 2015, **115**(3), 1543–1596.
- 147 F. Yoshimura, T. Okada and K. Tanino, Asymmetric total synthesis of laurallene, *Org. Lett.*, 2019, **21**(2), 559–562.
- 148 G. Mehta and S. Sengupta, Progress in the total synthesis of epoxyquinone natural products: An update, *Tetrahedron*, 2017, **73**(44), 6223–6247.
- 149 G. Kim, T. Kim and S. Han, Total synthesis of (+)-Pestalofone A and (+)-Iso-A82775C, *J. Org. Chem.*, 2020, **85**(10), 6815–6821.
- 150 K. Kumagai, M. Minamida, M. Akakabe, M. Tsuda, Y. Konishi, A. Tominaga, M. Tsuda, E. Fukushi and J. Kawabata, Amphirionin-2, a novel linear polyketide with potent cytotoxic activity from a marine dinoflagellate *Amphidinium* species, *Bioorg. Med. Chem. Lett.*, 2015, **25**(3), 635–638.
- 151 I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, High-field FT NMR application of Mosher's method. The absolute configurations of marine terpenoids, *J. Am. Chem. Soc.*, 1991, **113**(11), 4092–4096.
- 152 S. Kato, D. Mizukami, T. Sugai, M. Tsuda and H. Fuwa, Total synthesis and complete configurational assignment of amphirionin-2, *Chem. Sci.*, 2021, **12**(3), 872–879.
- 153 A. Qureshi, J. Salvá, M. K. Harper and D. J. Faulkner, New cyclic peroxides from the Philippine sponge *Plakinastrella* sp., *J. Nat. Prod.*, 1998, **61**(12), 1539–1542.
- 154 A. Rudi, R. Afanii, L. G. Gravalos, M. Aknin, E. Gaydou, J. Vacelet and Y. Kashman, Three new cyclic peroxides from the marine sponge *Plakortis aff simplex*, *J. Nat. Prod.*, 2003, **66**(5), 682–685.
- 155 K. W. L. Yong, B. Barnych, J. J. De Voss, J.-M. Vatele and M. J. Garson, Plakortolide stereochemistry revisited: The checkered history of Plakortolides E and I, *J. Nat. Prod.*, 2012, **75**(10), 1792–1797.
- 156 S. Leisering, A. Mavroskoufis, P. Voßnacker, R. Zimmer and M. Christmann, Synthesis of Plakortolides E and I Enabled by Base Metal Catalysis, *Org. Lett.*, 2021, **23**(12), 4731–4735.
- 157 C.-K. Lu, H.-N. Chou, C.-K. Lee and T.-H. Lee, Prorocentin, a New Polyketide from the Marine Dinoflagellate *Prorocentrum lima*, *Org. Lett.*, 2005, **7**(18), 3893–3896.
- 158 R. J. Zachmann, K. Yahata, M. Holzheimer, M. Jarret, C. Wirtz and A. Fürstner, Total syntheses of nominal and actual prorocentin, *J. Am. Chem. Soc.*, 2023, **145**(4), 2584–2595.
- 159 M. J. Rieser, X. P. Fang, J. E. Anderson, L. R. Miesbauer, D. L. Smith and J. L. McLaughlin, Muricatetrocins A and B and Gigantetrocin B: Three New Cytotoxic Monotetrahydrofuran-Ring Acetogenins from *Annona muricata*, *Helv. Chim. Acta*, 1993, **76**(7), 2433–2444.
- 160 S. Bäurle, U. Peters, T. Friedrich and U. Koert, Synthesis of (4R, 12S, 15S, 16S, 19R, 20R, 34S)-Muricatetrocin and (4R, 12R, 15S, 16S, 19R, 20R, 34S)-Muricatetrocin, Two Potent Inhibitors of Mitochondrial Complex I, *Eur. J. Org. Chem.*, 2000, **2000**(12), 2207–2217.
- 161 R. Minami, T. Kasai, K. Murata and H. Fuwa, Total synthesis of (+)-muricatetrocin B via a late-stage Co-



- catalyzed Hartung–Mukaiyama cyclization, *Org. Lett.*, 2023, **25**(31), 5745–5749.
- 162 A. Neske, J. R. Hidalgo, N. Cabedo and D. Cortes, Acetogenins from Annonaceae family. Their potential biological applications, *Phytochemistry*, 2020, 174112332.
- 163 A. Bermejo, B. Figadère, M.-C. Zafra-Polo, I. Barrachina, E. Estornell and D. Cortes, Acetogenins from Annonaceae: recent progress in isolation, synthesis and mechanisms of action, *Nat. Prod. Rep.*, 2005, **22**(2), 269–303.
- 164 S. Dey and K. R. Prasad, Formal Total Synthesis of cis-Sylvaticin and Sylvaticin, *Org. Lett.*, 2025, **27**(21), 5476–5479.
- 165 S.-K. Kim, *Handbook of Anticancer Drugs from Marine Origin*, Springer, 2014.
- 166 T. Řezanka, L. Hanuš and V. M. Dembitsky, Chagosensine, a new chlorinated macrolide from the Red Sea sponge *Leucetta chagosensis*, *Eur. J. Org. Chem.*, 2003, **2003**(20), 4073–4079.
- 167 M. Heinrich, J. J. Murphy, M. K. Ilg, A. Letort, J. Flasz, P. Philipps and A. Fürstner, Total synthesis of putative chagosensine, *Angew. Chem., Int. Ed.*, 2018, **57**(41), 13575–13581.
- 168 D. Uemura, K. Takahashi, T. Yamamoto, C. Katayama, J. Tanaka, Y. Okumura and Y. Hirata, Norhalichondrin A: an antitumor polyether macrolide from a marine sponge, *J. Am. Chem. Soc.*, 1985, **107**(16), 4796–4798.
- 169 Y. Hirata and D. Uemura, Halichondrins-antitumor polyether macrolides from a marine sponge, *Pure Appl. Chem.*, 1986, **58**(5), 701–710.
- 170 K. C. Nicolaou, S. Pan, Y. Shelke, D. Das, Q. Ye, Y. Lu, S. Sau, R. Bao and S. Rigol, A reverse approach to the total synthesis of halichondrin B, *J. Am. Chem. Soc.*, 2021, **143**(24), 9267–9276.
- 171 J. X. Wang, Y. Yao, Y. Wang and D. Niu, Cobalt-Catalyzed Hydroglycosylation of Alkynes for the Synthesis of Vinyl α -C-Glycosides, *Angew. Chem.*, 2025, **137**(11), e202423631.
- 172 I. Kawamoto, T. Oka and T. Nara, Cell wall composition of *Micromonospora olivoasterospora*, *Micromonospora sagamiensis*, and related organisms, *J. Bacteriol.*, 1981, **146**(2), 527–534.
- 173 R. Okachi, S. Takasawa, T. Sato, S. Sato, M. Yamamoto, I. Kawamoto and T. Nara, Fortimicins A and B, new aminoglycoside antibiotics II. Isolation, physico-chemical and chromatographic properties, *J. Antibiot.*, 1977, **30**(7), 541–551.
- 174 R. S. Egan, R. S. Stanaszek, M. Cirovic, S. L. Mueller, J. Tadanier, J. R. Martin, P. Collum, A. W. Goldstein and R. L. De Vault, AC Sinclair, EE Fager, and LA Mitscher, *J. Antibiot.*, 1977, 30552.
- 175 Y. Lu, X. Y. You, Q. Zhang, Q. T. Lu, J. L. Hou and Q. Cai, Enantioselective Total Synthesis of Fortimicin B, *Angew. Chem.*, 2025, **137**(22), e202424235.
- 176 F. Thuaud, Y. Bernard, G. Turkeri, R. Dirr, G. Aubert, T. Cresteil, A. Baguet, C. Tomasetto, Y. Svitkin and N. Sonenberg, Synthetic analogue of rocaglaol displays a potent and selective cytotoxicity in cancer cells: involvement of apoptosis inducing factor and caspase-12, *J. Med. Chem.*, 2009, **52**(16), 5176–5187.
- 177 A. Mushtaq and A. F. Zahoor, Benzyltriethylammonium chloride (BTEAC) catalyzed efficient synthesis of novel benzofuran-pyrazole hybrids: design, synthesis and in silico evaluation as potential anti-HCV agents, *ARKIVOC*, 2025, 1–17.
- 178 A. Irfan, A. F. Zahoor, A. Rasul, S. A. Al-Hussain, S. Faisal, S. Ahmad, R. Noor, M. T. Muhammed and M. E. A. Zaki, BTEAC catalyzed ultrasonic-assisted synthesis of bromobenzofuran-oxadiazoles: Unravelling anti-HepG-2 cancer therapeutic potential through in vitro and in silico studies, *Int. J. Mol. Sci.*, 2023, **24**(3), 3008.
- 179 Y. Xu, H. Wang, Z. Yang, Y. Zhou, Y. Liu and X. Feng, Stereodivergent total synthesis of rocaglaol initiated by synergistic dual-metal-catalyzed asymmetric allylation of benzofuran-3 (2H)-one, *Chem*, 2022, **8**(7), 2011–2022.
- 180 F. Ling, C. Zhang, C. Ai, Y. Lv and W. Zhong, Metal-Oxidant-Free Cobalt-Catalyzed C (sp²)-H Carbonylation of ortho-Arylanilines: An Approach toward Free (NH)-Phenanthridinones, *J. Org. Chem.*, 2018, **83**(10), 5698–5706.
- 181 L. Wu, Q. Shao, G. Yang and W. Zhang, Cobalt-Catalyzed Asymmetric Allylation of Cyclic Ketimines, *Chem.-Eur. J.*, 2018, **24**(6), 1241–1245.
- 182 J. Ying, L.-Y. Fu, G. Zhong and X.-F. Wu, Cobalt-catalyzed direct carbonylative synthesis of free (NH)-benzo [cd] indol-2 (1 H)-ones from naphthylamides, *Org. Lett.*, 2019, **21**(14), 5694–5698.
- 183 C. Shekhar, R. Nasam, S. R. Paipuri, P. Kumar, K. Nayani, S. Pabbaraja, P. S. Mainkar and S. Chandrasekhar, Total synthesis of antiviral drug, nirmatrelvir (PF-07321332), *Tetrahedron Chem*, 2022, 4100033.
- 184 A. Suneja, V. Bisai and V. K. Singh, Asymmetric Syntheses of Medicinally Important Isoindolinones (S)-PD 172938, (R)-JM 1232, and Related Structures, *J. Org. Chem.*, 2016, **81**(11), 4779–4788.
- 185 M. Y. Teng, Y. J. Wu, J. H. Chen, F. R. Huang, D. Y. Liu, Q. J. Yao and B. F. Shi, Cobalt-Catalyzed Enantioselective C–H Carbonylation towards Chiral Isoindolinones, *Angew. Chem., Int. Ed.*, 2024, **63**(10), e202318803.
- 186 Y. Song, Y. Zou, T. Chen, Z. Zhang and W. Zhang, Cobalt-Catalyzed Asymmetric Hydrogenation of α -Hydroxy Ketones Enabled by a Carboxylic Acid Additive Promotion Strategy, *Angew. Chem., Int. Ed.*, 2025, e202504159.

