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Review

Total Syntheses of Chloropupukeananin and Its Related Natural Products

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Abstract: Chloropupukeananin is a natural product that inhibits HIV-1 replication and has antitumor activity. Its structure consists of a chlorinated tricyclo[4.3.1.$0^{3,7}$]decane core skeleton with an array of highly oxidized multifunctional groups. In the biosynthesis of chloropupukeananin, (+)-iso-A82775C and (−)-maldoxin are employed as biosynthetic precursors for the intermolecular Diels–Alder and carbonyl–ene reactions, followed by the migration of the *p*-orcellinate group. Chloropupukeanolides and chloropestolides are intermediates and isomers in biosynthesis; their unique chemical structures and biosynthetic pathways have attracted significant attention from synthetic chemists. In this review, I present the synthetic studies on chloropupukeananin and its related compounds that have been conducted thus far.

Keywords: biomimetic synthesis; Diels–Alder reactions; carbonyl–ene reactions; cascade reactions; enantioselective synthesis; natural products; total synthesis

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1. Introduction

Chloropupukeananin (**1**) was originally isolated in 2008 by Che et al. from *Pestalotiopsis fici* (an endophytic plant fungus) as an antimicrobial agent and inhibitor of HIV-1 replication (Figure 1) [1]. Simultaneously, iso-A82775C (**2**) and pestheic acid [2–4] (**3**) were also isolated and proposed as biosynthetic precursors of **1** (Scheme 1). Structurally, chloropupkeananin possesses a highly functionalized pupukeanane skeleton [5–9]. Significantly, both **1** and pupukeanane share a common skeleton despite possessing no biosynthetic relationship, as pupukeananes, which are marine sesquiterpenes from sponges, have exclusively been isolated with a single functional group.

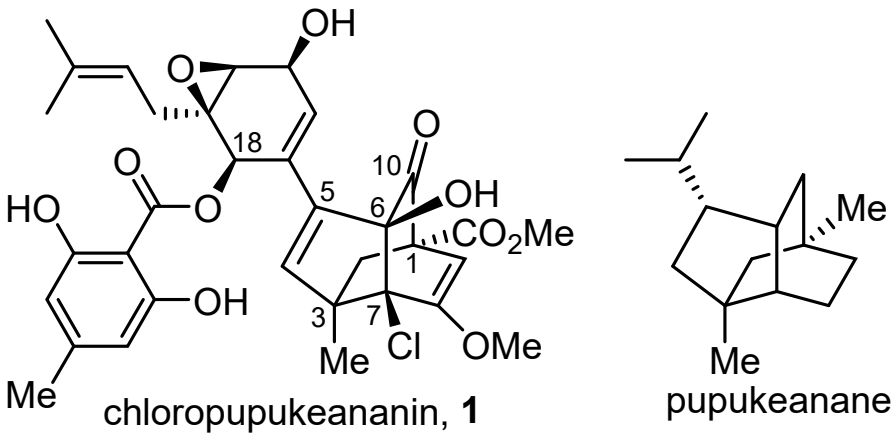
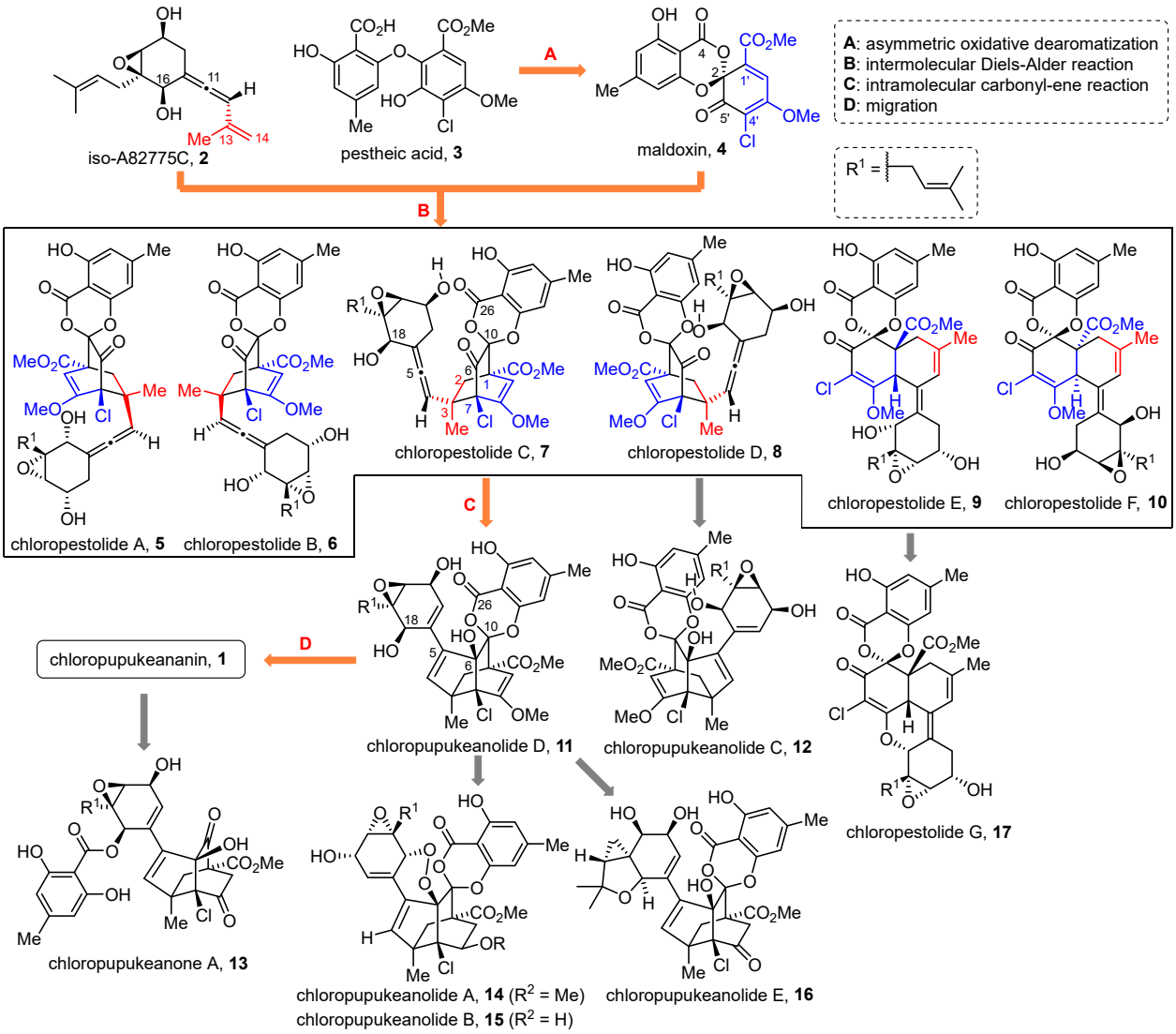


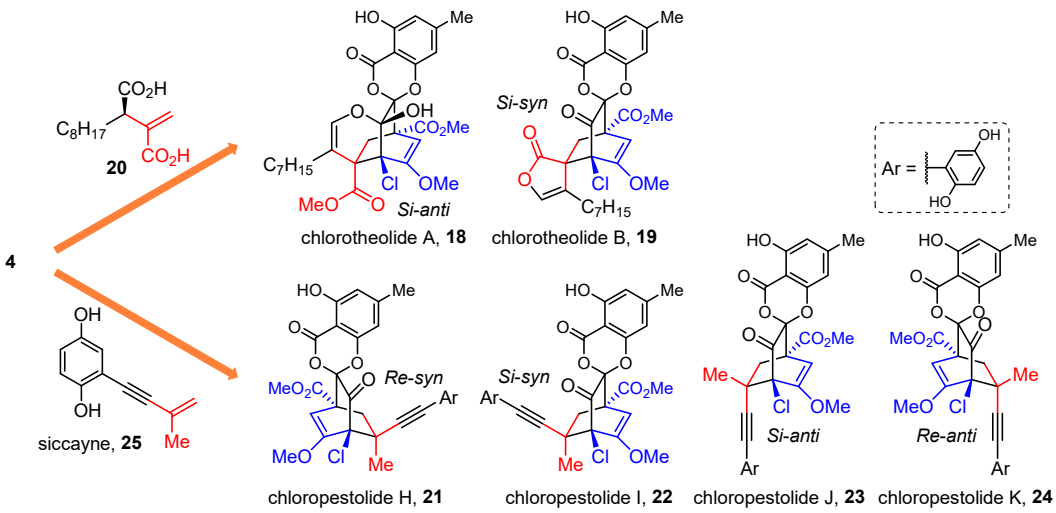
Figure 1. The chemical structure of chloropupukeananin and pupukeanane.



Scheme 1. The biosynthetic pathway of chloropupukeananin and its related natural products.

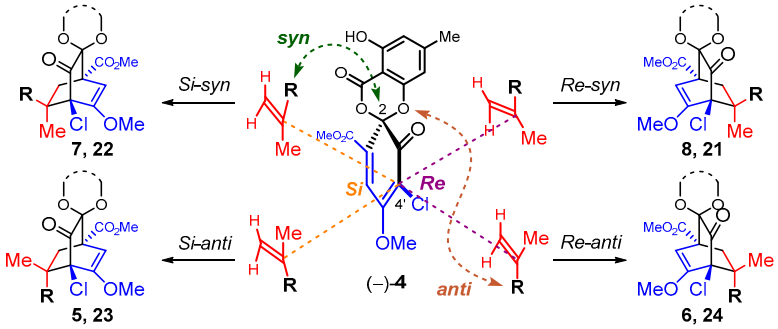
The isolation of chloropestolide A (**5**) [10] from the same fermentation medium as **1** in 2009 led Suzuki and Kobayashi to propose that the actual biosynthetic precursors of these compounds are **2** and maldoxin (4) [4], which is an oxidized form of **3** [11]. Although **4** had already been isolated without the determination of its optical rotation and stereochemistry, [4] (*R*)-**4** was assumed to be generated by asymmetric oxidative dearomatization in the biosynthesis of **1**. The subsequent biosynthetic pathway is as follows: the intermolecular reverse electron-demanding Diels–Alder reaction of **2** and **4** gives cycloadduct **5** and its isomers **6**–**8**, possessing a bicyclo[2.2.2]octane skeleton. Moreover, the normal-electron Diels–Alder reaction, using the vinylallene moiety of **2** as a diene, generates **9** and **10**. Intramolecular carbonyl–ene reactions between the C5 position in the allene moiety derived from **2** and the C6 ketone derived from **4** afford **11** and **12** with tricyclo [4.3.1.$0^{3,7}$]decane skeletons from **7** and **8**, respectively. Finally, the *p*-orsellinate moiety of **11** migrates to C18-OH to give **1**. In the continuing efforts by Che et al. to elucidate the biosynthetic pathway of **1** [12–16], all the aforementioned biosynthetic intermediates **6**–**12** (chloropestolides B-F and chloropupukenolides C and D) were isolated along with other degradation products **13**–**17**. Notably, optically active (*R*)-**4** was isolated from the related fungus, *P. theae*, [15] along with chlorotheolides A (**18**) and B (**19**) and 1-undecene-2,3-dicarboxylic acid (**20**), which is a proposed biosynthetic precursor of **18** and **19** (Scheme 2). To identify a biosynthetic gene cluster in chloropupukeananin-producing bacteria, chloropestolides H-K [16] (**21**–**24**),

which may be produced from **4** and siccayne **25**, were isolated using a prenyltransferase gene disruption strain.



Scheme 2. Natural products derived by the intermolecular Diels–Alder reaction of maldoxin.

The face selectivity of the intermolecular Diels–Alder reactions in biosynthesis requires further discussion. The isolation of chloropestolides (**5**–**8**, **21**–**24**) demonstrates the occurrence of all possible isomers in reverse electron-requested Diels–Alder reaction (Scheme 3). In the formation of these bicyclo [2.2.2]octane-containing cycloadducts, the dienophiles approach the *Re*- or *Si*-plane of C4′ of diene **4** in *syn*- or *anti*-orientation between the R group of the dienophiles (**2** or **25**) and the C2 acetal site of diene **4**. While the usual enzymatic reaction occurs selectively in nature, the current intermolecular Diels–Alder reaction of **4** displays poor selectivity. Therefore, enzymes may not be involved in the Diels–Alder reaction of **4**. However, it is reasonable to assume that enzymes are involved elsewhere in the series of biosynthetic reactions because the reaction sites are well controlled despite the presence of several functional groups. The chemical synthesis of the chloropupukeananin family via the Diels–Alder reactions of **4** and biosynthetic dienophiles helps elucidate the detailed mechanism of biosynthesis, especially the occurrence of an enzymatic Diels–Alder reaction. If the enzymatic Diels–Alder reaction does occur, this enzyme is the first example of an intermolecular Diels–Alderase that constructs a highly functional bicyclo [2.2.2]octane skeleton [17–20]. Because of the high synthetic convergence and the broad diversity of products in the intermolecular Diels–Alder reaction, artificial Diels–Alderases such as antibody catalysts [21], artificial enzymes [22], and supramolecules [23] have been developed. Recently, enzymes promoting the intermolecular Diels–Alder reactions to produce pseudodimeric resveratrols have been identified [24]. The identification of an intermolecular heterodimeric Diels–Alderase is expected to pave the way for the production of a variety of bioactive natural product-like compounds through its genetic modification [25].



Scheme 3. The facial selectivity of the intermolecular Diels–Alder reaction of maldoxin.

Therefore, chloropupukeananin has attracted significant research interest, and various studies have been conducted to elucidate its biosynthesis. In this review, reports on chloropupukeananin in the context of synthetic chemistry, the synthesis of biosynthetic precursors, the Diels–Alder reaction mimicking biosynthesis, and the total synthesis of chloropupukeananin, are presented.

2. Synthesis of the Biosynthetic Precursors of Chloropupukeananin

2.1. Pestheic Acid and Maldoxin

Pestheic acid (3) [2], also known as RES-1214-2 [3] and dihydromaldoxin [4], is a metabolite of chlorinated lichexanthone derivatives, such as chloroisosulochin (**26**) and chloroisosulochin dehydrate (**27**) [2], and it consists of *p*-orsellinate and methyl *p*-chlorobenzoate moieties (Figure 2). Maldoxin (**4**) was isolated from *Xylaria* species, which was collected from a Malaysian rain forest by Edwards et al., along with **3** and maldoxone (**28**) [4]. Similar to the biosynthesis of nidulin, [26,27] **3** and **28** can be generated by the oxidative dearomatization of **26,** followed by the hydrolysis of the resulting spiroketone **29**. The re-dearomatization of the methyl *p*-chlorobenzoate moiety of **3** produces **4**. These compounds exhibit biological activities; in particular, **3** is a promising selective endothelin A receptor antagonist.

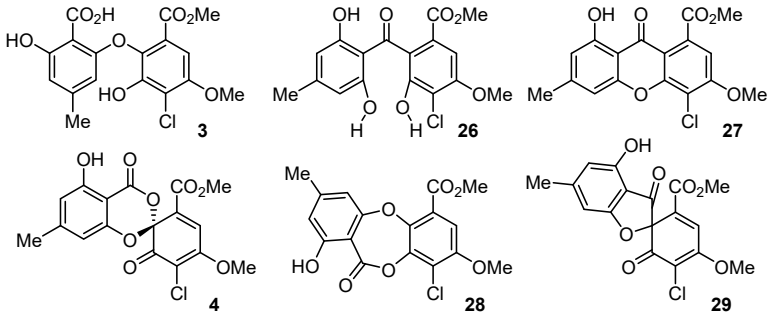
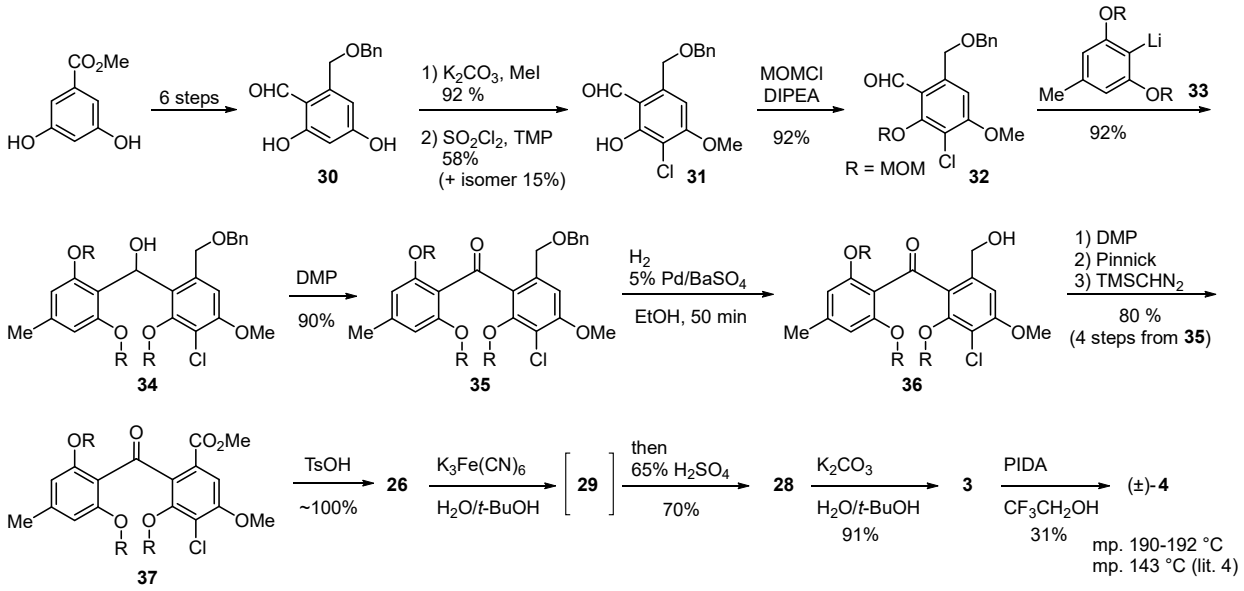


Figure 2. The chemical structure of pestheic acid, maldoxin, and these related natural compounds.

In 2012, Yu and Snyder reported the first total synthesis of pestheic acid and maldoxin based on a biosynthetic pathway (Scheme 4) [28]. The synthesis was initiated with a known six-step conversion of methyl 3,5-dihydroxybenzoate to salicylaldehyde **30**. Site-selective methylation followed by chlorination [29–31] using SO_2Cl_2 and 2,2,6,6-tetramethylpiperidine (TMP) afforded 3-chlorosalicyladehyde **31** (58% yield) and 5-chloride (15% yield). The use of a bulkier amine is essential because an undesired 5-chlorination was preferred when using *t*-butylamine (3-Cl:5-Cl = 1:2.6). After the MOM protection, the lithiated orcinol derivative **33** [32] was added to aldehyde **32** to produce alcohol **34** in 92% yield. Oxidation with Dess–Martin periodinane (DMP) gave benzophenone **35** in 90% yield. Over-reduction during the reductive removal of the benzyl group caused several issues. Various catalysts and reaction times were investigated, and reduction using the Rosenmund catalyst selectively afforded alcohol **36**. The resulting primary alcohol was converted to methyl ester **37** via a conventional three-step transformation. The removal of the MOM groups using TsOH produced chloroisosulochin **26**. Oxidation with $K_3Fe(CN)_6$ [33–35] in H_2O followed by continuous acidic hydrolysis furnished maldoxone **28**. The basic hydrolysis of **28** achieved a total synthesis of **3**. The oxidative dearomatization of **3** with iodobenzene diacetate (PIDA) afforded racemic **4** in 31% yield. The observed melting point of synthetic **4** is 193 °C, while that of natural **4** reported in the literature is 143 °C [4], indicating that the natural maldoxin is not racemic.

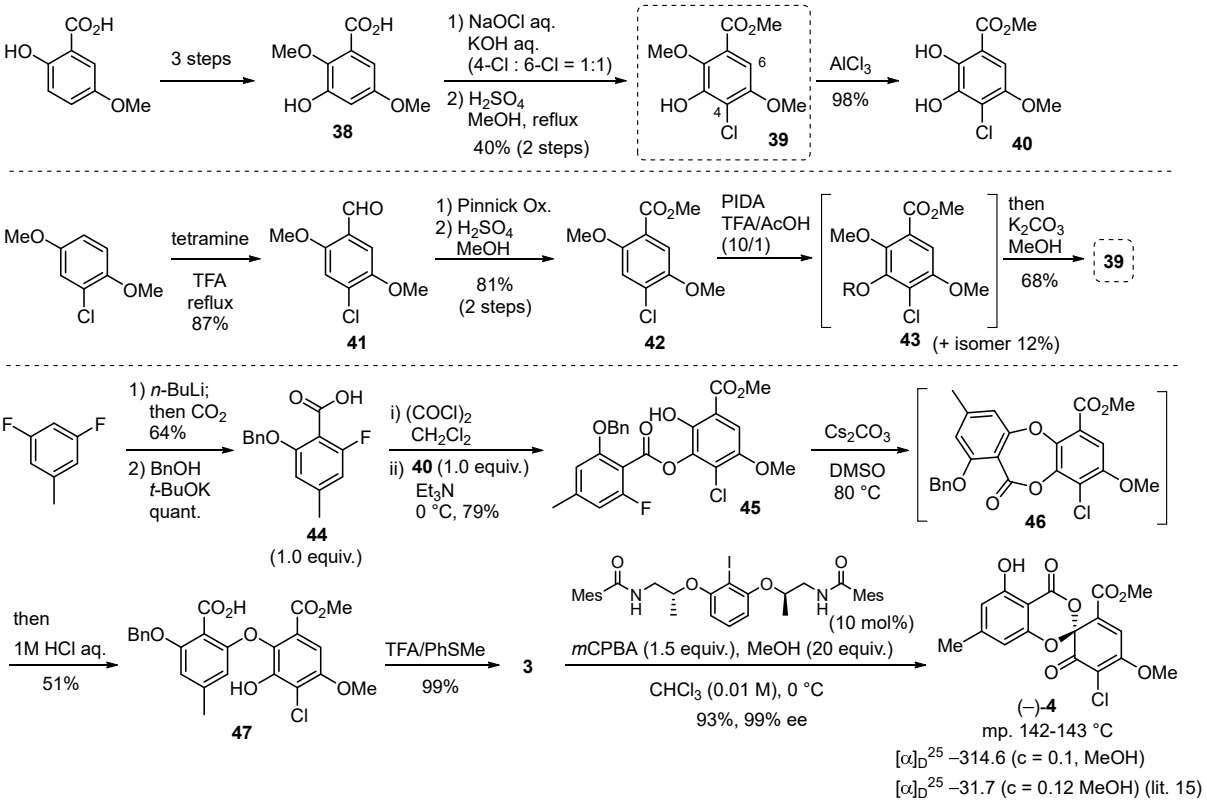


Scheme 4. Total synthesis of pestheic acid and *rac*-maldoxin by Yu and Snyder. MOM—methoxymethyl, DIPEA—diisopropylethylamine, DMP—Dess-Martin periodinane, PIDA—(diacetoxyiodo)benzene.

The asymmetric synthesis of (*R*)-**4** is essential for the total synthesis of the natural products in the chloropupukeananin family. In addition, an efficient and robust synthetic strategy to supply large quantities of **3** and **4** is required. In 2018, Suzuki et al. reported the asymmetric total synthesis of (−)-(*R*)-**4** via the intramolecular S_NAr etherification and asymmetric oxidative dearomatization of **3** using the Ishihara catalyst (Scheme 5) [36]. Herein, the right-hand benzoate moiety **40** was synthesized from 5-methoxysalicylic acid. After a three-step conversion to phenol **38** [37], chlorination with sodium hypochlorite proceeded nonselectively to afford a 1:1 mixture of 4-Cl and 6-Cl. Subsequent acidic esterification produced the 4-chlorobenzoate **39** (40% yield in two steps) [11]. The site-selective removal of the methyl group using $AlCl_3$ achieved the synthesis of the right-hand moiety **40**. As shown in Snyder's synthesis, the nonselectivity of the chlorination of these compounds is a fundamental issue that may necessitate alternative functionalization reactions. The alternative synthesis [38] was initiated with commercial 2-chloro-1,4-dimethoxybenzene, which was converted to methyl 4-chloro-2,5-dimethoxybenzoate **42** by three-step sequence (formylation, Pinnick oxidation, and acidic esterification). The oxidative nucleophilic substitution reaction [39,40] using PIDA in trifluoroacetic acid (TFA)/AcOH mixed solvent occurred selectively at the C3 position (C3/C6 = 6:1) to give **43**, which was directly subjected to basic hydrolysis to produce phenol **39** in 68% yield.

The left fragment **44** was prepared using two-step transformation: the lithiation of 3,5-difluorotoluene followed by carboxylation with CO_2 (64% yield) [41] and intermolecular S_NAr etherification of the resulting benzoic acid using KOBn (quantitative yield). The preparation of acyl chloride from the left-hand fragment **44** and the subsequent regioselective esterification with the right-hand fragment **40** afforded benzoate ester **45** in 79% yield. The intramolecular S_NAr reaction [42,43] was initiated by the treatment of benzoate **45** with Cs_2CO_3 (0.05 M, 80 °C) in DMSO, and the one-pot acid hydrolysis of the resulting 7-membered lactone **46** produced diaryl ether **47** in 51% yield. The synthesis of pestheic acid **3** was achieved by removing the Bn group of diaryl ether **47**. The asymmetric oxidative dearomatization [44–46] of **3** to maldoxin **4** using Ishihara catalysts has been thoroughly investigated. As a result, the optically pure (−)-(*R*)-**4** was successfully obtained with 93% yield using the (2*R*,2′*R*)-Ishihara catalyst (10 mol%), *m*CPBA (1.5 equiv.) as the co-oxidant, methanol (20 equiv.) as an additive, and chloroform (0.01 M) as the solvent [47–49]. The stereochemistry of (−)-(*R*)-**4** was confirmed by X-ray crystallographic analysis. The lev-

orotation of synthetic (*R*)-**4** indicates that natural **4** isolated from *P. theae* possesses the *R*-configuration. Moreover, as the melting point of synthetic **4** is 142–143 °C, the originally isolated natural **4** was likely to be optically pure.



Scheme 5. Enantioselective total synthesis of (−)-maldoxin by Suzuki et al. TFA—trifluoroacetic acid, DMSO—dimethylsulfoxide, mCPBA—3-chloroperbenzoic acid.

2.2. Iso-A82775C

As the name indicates, iso-A82775C is a diastereomer of the known natural product A82775C 48 [50] (Figure 3), isolated from an unknown terrestrial fungus collected in Egypt. Another natural diastereomer is Spartinoxide [51] (**49**), which is an enantiomer of **48**, isolated from a marine-derived fungus and identified as an inhibitor of human leukemia elastase. These compounds belong to a class of naturally occurring cyclohexene epoxides. Typically, these compounds (such as eutypoxides, asperpentyne, harveynone, panepoxydone, and isopanepoxydone) possess one prenyl chain; cyclohexene epoxides with two prenyl side chains are rare. To the best of our knowledge, only two natural products (other than compounds **2**, **48**, and **49**) have been reported: pestalofone A (50) [52] and biscogniene B (51) [53]. Significantly, one of the prenyl units of these compounds is oxidized and rich in sp^2 carbon. These oxidized prenyl side chains can undergo dimerization, forming a variety of natural products; for instance, pestalofones B and C have been isolated as dimeric natural products of iso-A82775C. Interest in the biological activity, as well as the biosynthetic pathway of these dimers, prompted investigations into the total synthesis of naturally occurring cyclohexene epoxides with prenyl side chains.

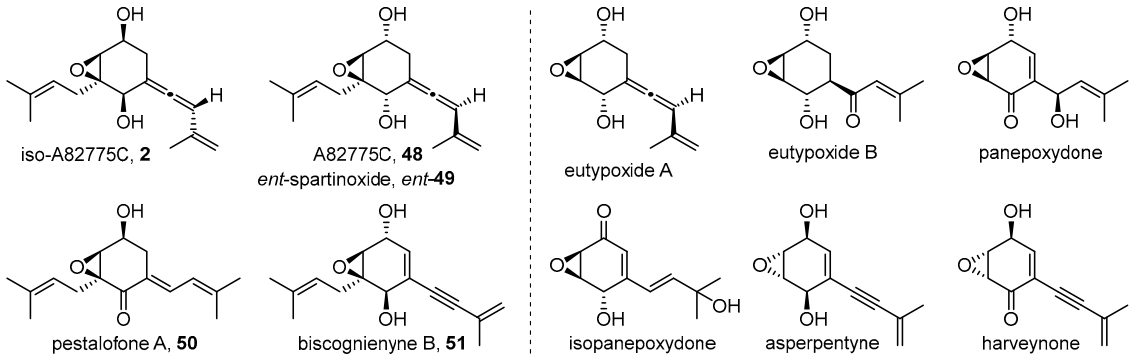
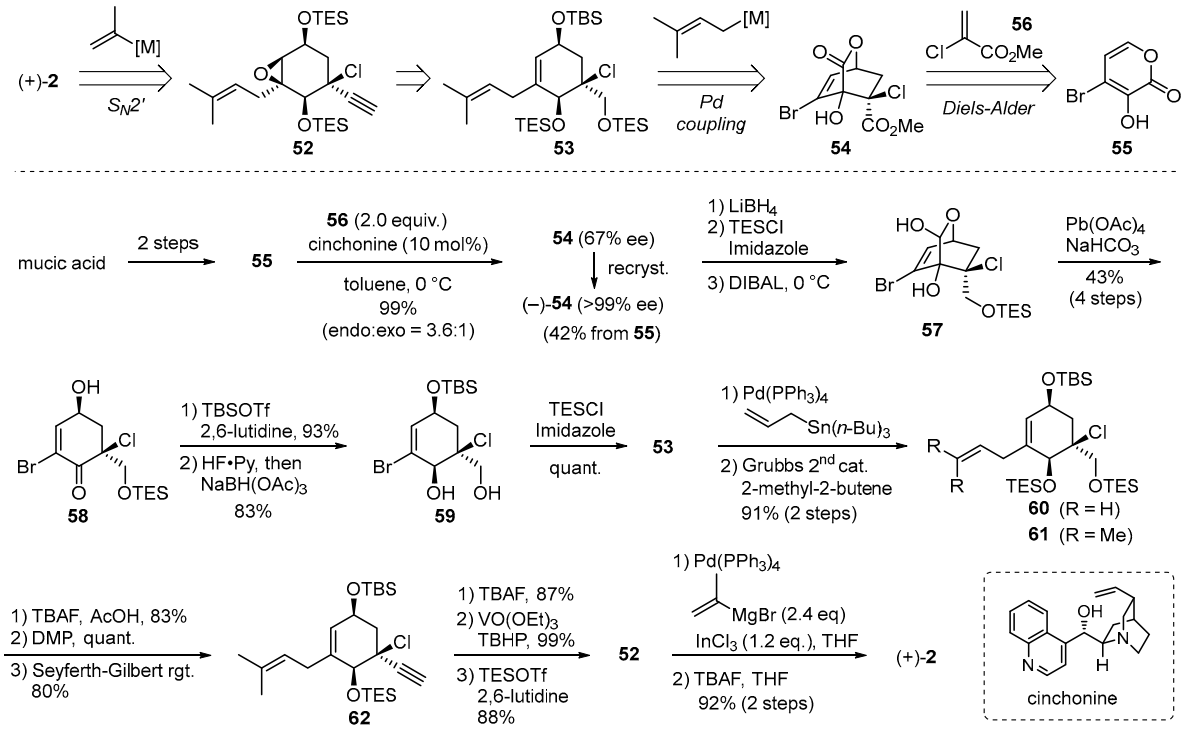


Figure 3. The chemical structure of iso-A82775C and its related natural products.

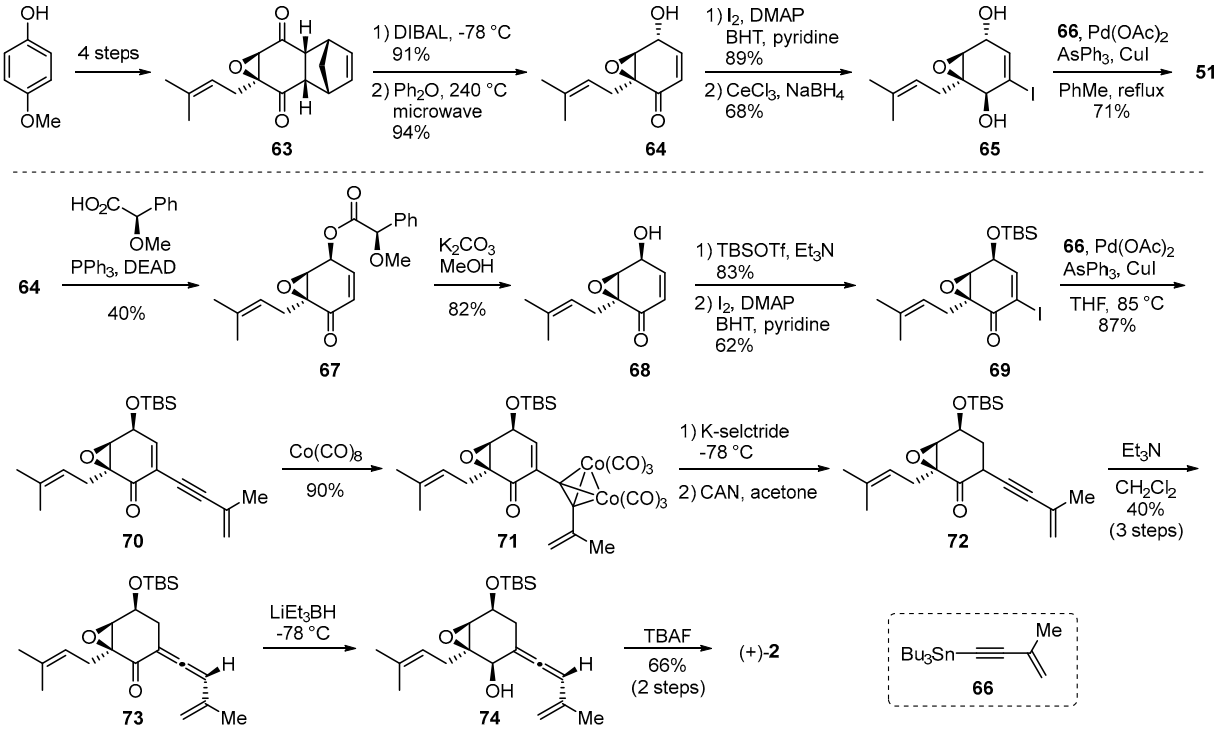
Suzuki et al. reported the enantioselective total synthesis of (+)-iso-A82775C in 2017, [54] which is the first report of the synthesis of naturally occurring cyclohexene epoxides with two prenyl side chains. The synthetic strategy is illustrated in Scheme 6. The installation of the labile axially chiral vinylallene to **52** would be achieved in the final stage of the total synthesis using a 2-propenyl metal reagent via an *anti*-S_N2' reaction. The stereoselective epoxidation of **53** and Pd-catalyzed prenylation would envision vinyl bromide **54**. Further, optically active **54** could be obtained via the base-catalyzed asymmetric Diels–Alder reaction reported by Okamura et al. [55–58] using pyrone **55** and 2-chloroacrylate **56**. First, **55** was prepared on a decagram scale from mucic acid using a modified two-step procedure [59,60]. By investigating the intermolecular Diels–Alder reaction using various cinchona alkaloids, the optimal result was obtained using 0.1 equiv of cinchonine in toluene at 0 °C to produce the desired *endo* cycloadduct **54** with 67% ee (*endo*:*exo* = 3.6:1). Recrystallization of **54** (67% ee) from EtOAc/*n*-hexane gave enantiomerically pure crystalline (−)-**54** (>99% ee, 42% yield from pyrone **55**), and the absolute stereochemistry of the product was determined via X-ray crystallographic analysis. Chemoselective reduction of the ester with $LiBH_4$, the protection of the resulting alcohol, and the reduction of the lactone moiety with DIBAL afforded α-hydroxylactol **57**. The Criegee oxidation of α-hydroxylactol **57** furnished α-bromoenone **58** in 43% overall yield from **54**. After the protection of the secondary alcohol, removal of the TES group, and one-pot hydroxyl group-induced reduction using $NaBH(OAc)_3$, 1,3-diol **59** was obtained as a single diastereomer [61]. Pd-coupling precursor **53** was obtained via the TES protection of 1,3-diol **59** in quantitative yield. Pd coupling reactions with various allyl metal reagents were conducted, but allylation occurred only under standard Stille conditions, quantitatively producing **60**. Stille coupling with prenylstannane reagents was unsuccessful, and prenylcyclohexene **61** was obtained only in trace amounts. However, the cross-metathesis of **60** with 2-methylbut-2-ene furnished prenylcyclohexene **61** in 91% yield. Selective deprotection, the Dess–Martin oxidation of the resulting primary alcohol, and subsequent Seyferth–Gilbert homologation gave propargylic chloride **62**. After the removal of the silyl-protecting groups of alkyne **62**, vanadium-catalyzed hydroxyl-directed epoxidation [62], and re-protection of the resulting diol, epoxide **52** was obtained as a single diastereomer. An *anti*-S_N2' reaction was first conducted with CuCN and isopropenyl-MgBr to afford the corresponding vinylallene as a single diastereomer; however, the conversion was low (~30%), probably because of the competitive deprotonation of the terminal alkyne. In contrast, the use of an organoindium reagent in the presence of a Pd-catalyst [63] resulted in the consumption of all the starting materials, and subsequent deprotection of the TES groups of the resulting allene gave (+)-**2** in 92% yield on a subgram scale.



Scheme 6. Enantioselective total synthesis of (+)-iso-A82775C by Suzuki et al. TES—triethylsilyl, DIBAL—diisobutylaluminium hydride, TBS—*tert*-butyldimethylsilyl, TBAF—tetra-*n*-butylammonium fluoride.

The concise total synthesis of *rac*-**51**, which is a naturally occurring cyclohexene epoxide with two prenyl side chains, was achieved by Han et al. in 2018 (Scheme 7) [64], along with the enantioselective total synthesis of (−)-**51** and its dimeric congener via biomimetic heterodimerization. The synthesis started with Mehta's four-step procedure [65] to convert *p*-methoxyphenol to tricyclic diketone **63**. The stereoselective reduction of the less hindered ketone [66] followed by the retro-Diels–Alder reaction afforded prenylated epoxyenone **64**. The following three-step conversion (α-iodination of enone, Luche reduction, and Stille coupling with alkynylstannane **66**) completed the synthesis of **51**. Similarly, Han et al. reported the total synthesis of (+)-**1** and (+)-**50** using a common synthetic intermediate, *rac*-**64** [67]. The Mitsunobu reaction of *rac*-**64** with *O*-methyl-D-mandelic acid furnished ester **67** and its diastereomer, which gave pure **67** in 40% yield on chromatographic separation. The removal of the *O*-methylmandelate group via methanolysis produced prenylated epoxyenone **68**, which is an epimer of **64**, with 97.5% ee. The protection of the secondary alcohol with a TBS group and α-iodination of the enone moiety furnished iodide **69**. The installation of the other prenyl unit via Stille coupling with alkynylstannane **66** was successful, following a procedure similar to the synthesis of **51**. Attempts to reduce enone **69** resulted in a 1,2-reduction instead of the desired 1,4-reduction, owing to conjugation with the alkyne moiety. Therefore, after converting the alkyne to dicobalt complex **71**, 1,4-reduction using K-selectride and the oxidative decobaltation of the resulting ketone with CAN successfully afforded β,γ-ynone **72**. The tautomerization of **72** was achieved by treatment with a catalytic amount of triethylamine [68], resulting in the desired axially chiral vinylallene **73** as a single diastereomer (40% yield, in three steps). The isomerization reaction proceeded in a 3:1 diastereomeric ratio, but the minor product was labile with an affinity for dimerization reaction at room temperature. The 1,2-reduction of ketone **73** occurred diastereoselectively with $LiBHEt_3$ to produce alcohol **74**. Desilylation with TBAF achieved the total synthesis of (+)-iso-A82775C (**2**) (66% yield, over two steps). The authors investigated the dimerization reactions of the synthetic iso-A82775C and its 16-

oxo derivative and found that, in contrast to biscognienyne B, these compounds did not undergo dimerization under any condition.



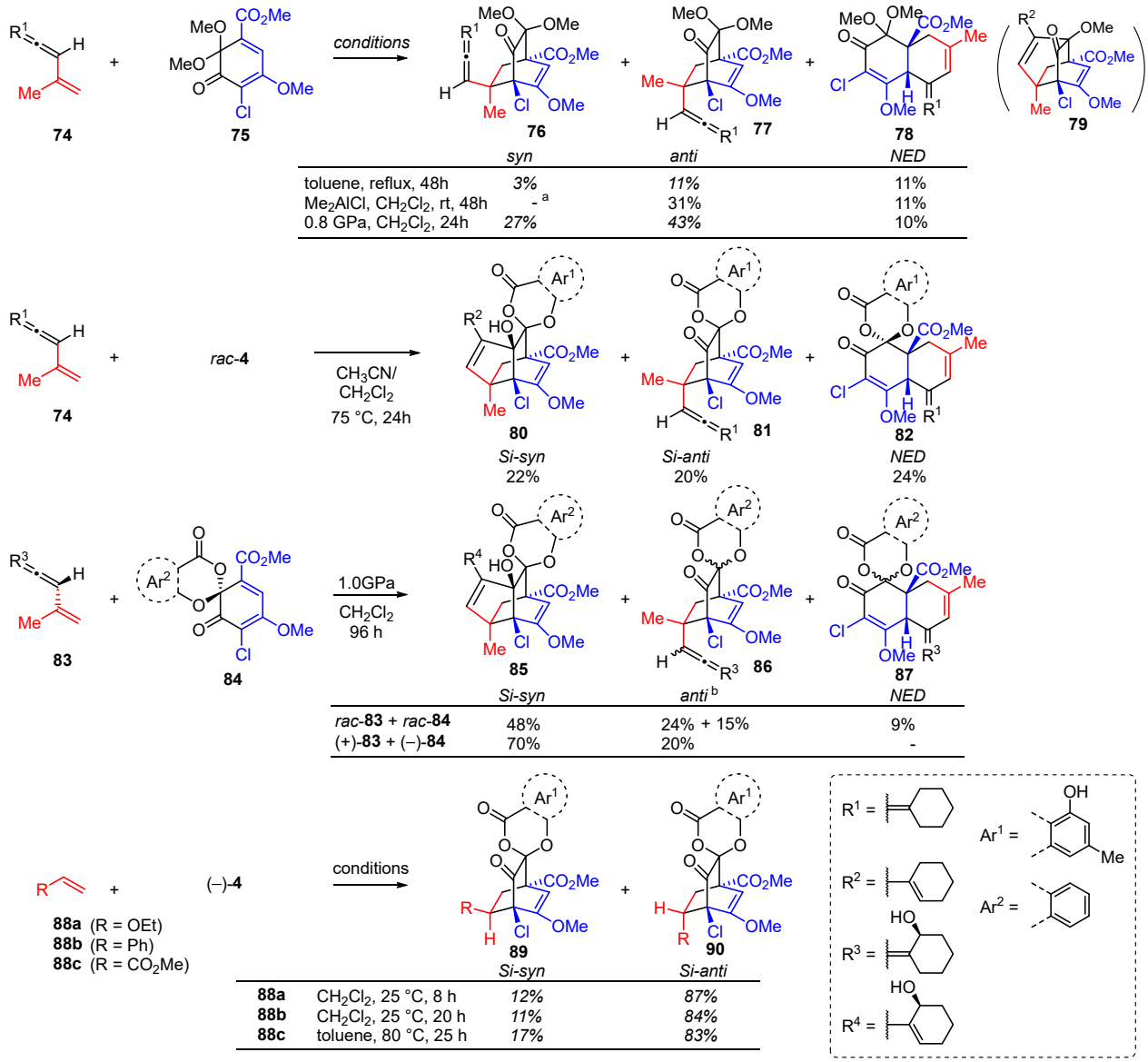
Scheme 7. Total syntheses of *rac*-biscognienyne B and (+)-iso-A82775C by Han et al. DMAP—4-dimethylaminopyridine, DEAD—diethyl azodicarboxylate, CAN—cerium ammonium nitrate.

3. Biomimetic Synthesis of Chloropupukeananin

3.1. Model Studies on the Intermolecular Diels–Alder Reaction

Synthetic studies using model compounds of biosynthetic precursors to elucidate the biosynthetic pathway of chloropupukeananin (Scheme 8) were independently conducted by Suzuki et al. and Yu and Snyder. Suzuki and Kobayashi reported the biomimetic Diels–Alder reaction with the simple model compounds **74** and **75** (both achiral compounds) in 2010 [11]. With these substrates, the Diels–Alder reaction barely occurred under heating and Lewis acid conditions, resulting in low yields of cycloadducts. Regarding selectivity, the ratio of *syn*- and *anti*-cycloadducts **76** and **77** (corresponding to chloropupukeananin and chloropestolide A, respectively) was 1:3, and a small amount of normal electron-demand (NED) cycloadduct **78** was obtained. The reaction under high-pressure conditions improved the yield and selectivity and produced a mixture of **76** and **77** (**76**:**77** = 1:1.6) in 70% yield.

Yu and Synder in 2011 reported the Diels–Alder reaction using the synthetic racemic **4** and the same achiral vinylallene **74** under the thermal conditions (75 °C, 24 h) [69]. This cycloaddition reaction displayed a selectivity of nearly 1:1:1 for *Si-syn*, *Si-anti*, and NED, giving tricyclic cycloadduct **80** (corresponding to chloropupukeanolide D) in 22% yield. This study reveals that the cyclic *p*-orsellinate moiety accelerates the intermolecular Diels–Alder reaction and completely controls the facial selectivity from the *Si face*.



Scheme 8. Model studies on the intermolecular Diels–Alder reaction toward the biomimetic synthesis of chloropupukeananin. All yields in italics are calculated by ^{1}H NMR. [a] carbonyl-ene isomer **79** derived from **76** was obtained (11% yield). [b] the whole structure could not be identified.

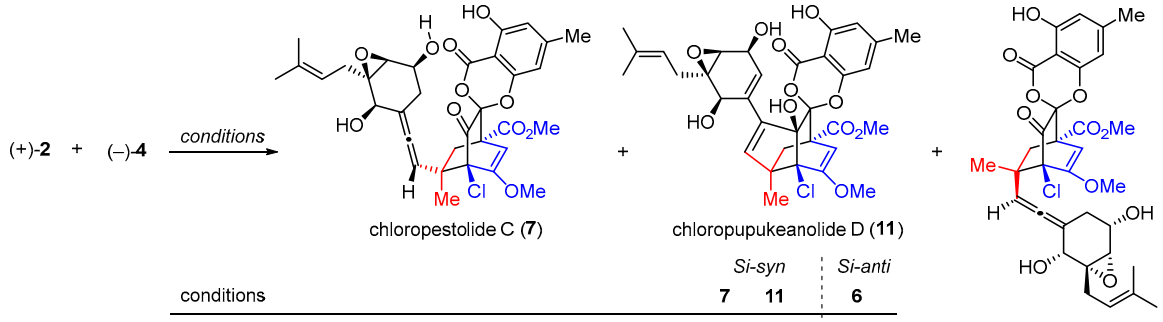
In 2013, Suzuki et al. reported synthetic studies with advanced model compounds **83** and **84**, cyclohexane possessing a vinylallene and its adjacent hydroxyl group as a model compound for Iso-A82775C, and a compound simplifying to a salicylate moiety instead of the *p*-orsellinate moiety of maldoxin, respectively [70]. Initially, using both racemic model compounds, the Diels–Alder reaction under high-pressure conditions (1.0 GPa, 96 h) afforded tricyclic compound **85** in 48% yield, and its structure was unambiguously confirmed via X-ray crystallographic analysis. However, the stereochemistry of the other products **86** and **87** (two *anti*- and one NED cycloadduct) could not be identified using NMR studies. Using optically pure model compounds (+)-**83** and (−)-**84** (a natural combination), the intermolecular Diels–Alder reaction furnished tricyclic compound **85** in 70% yield, along with *anti*-cycloadduct **86** in 20% yield. These results indicate that the hydroxyl group is important for *Si-syn* selectivity, probably because of the hydrogen bonding with the carbonyl groups of the maldoxin unit.

Furthermore, Suzuki et al. studied the thermal intermolecular Diels–Alder reaction of (−)-**4** with typical alkenes **88a–c** to acquire the trends of the facial selectivity of **4** [36]. In the

case of ethyl vinyl ether **88a** and styrene **88b**, the reactions occurred at room temperature and favored *Si-anti* cycloadducts **90**. However, in the case of methyl acrylate **88c**, the reaction required heating to 80 °C and showed a slightly lower *Si-anti* selectivity.

3.2. Syntheses of Chloropupukeananin and Its Related Natural Products

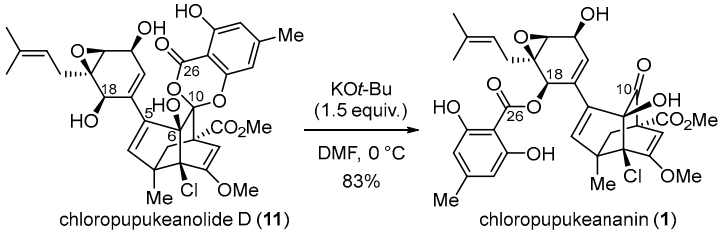
The total syntheses of the optically pure biosynthetic precursors (+)-**2** and (−)-**4** enabled the synthesis of chloropupukeananin via the intermolecular Diels–Alder reaction (Scheme 9) [38]. First, the reaction between (+)-**2** and (−)-**4** was performed under high-pressure conditions. The intermolecular Diels–Alder reaction and the subsequent carbonyl-ene reaction achieved a near-completion after 64 h, producing the desired *Si-syn* cycloadduct **7** (5%) and carbonyl-ene product **11** (71%), along with *Si-anti* cycloadduct **6** (17%). Similar to previous studies using enantiopure model compounds, no other cycloadducts were detected. To complete the intramolecular carbonyl-ene reaction, the products of the high-pressure reaction were heated to 60 °C at the atmospheric pressure, furnishing **11** and **6** in 69% and 21% isolated yields, respectively. The thermal conditions required for the Diels–Alder/carbonyl–ene cascade reactions at atmospheric pressure were also investigated. The intermolecular Diels–Alder reaction between (+)-**2** and (−)-**4** was performed under neat conditions (25 °C, 120 h). After the completion of the Diels–Alder reaction, the mixture was heated (60 °C, 68 h) to afford the target compounds **11** (57% yield) and **6** (25% yield).



conditions	*Si-syn* 7	*Si-syn* 11	*Si-anti* 6
1.0 GPa, CH_2Cl_2, 25 °C, 64 h	*5%*	*71%*	*17%*
1.0 GPa, CH_2Cl_2, 25 °C, 64 h; then 0.1 MPa, neat, 60 °C, 9 h	-	69%	21%
0.1 MPa, neat, 25 °C, 120 h; then 60 °C, 68 h	-	57%	25%

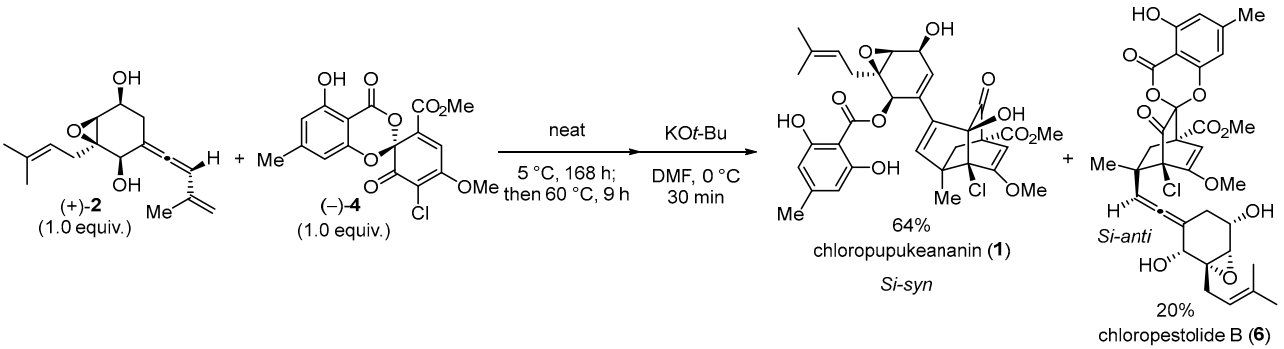
Scheme 9. The intermolecular Diels–Alder/carbonyl–ene cascade reaction using (+)-iso-A82775C and (−)-maldoxin. All yields in italics are calculated by ^{1}H NMR.

The migration of the *p*-orsellinate group of **11**, which was the final step in the biosynthetic pathway of chloropupukeananin, was conducted under basic conditions (Scheme 10). Migration was accomplished by the nucleophilic attack on C26 in the *p*-orsellinate group by the secondary alkoxide moiety at the C18 position generated from **11** using a strong base. This was followed by the elimination of the *p*-orsellinate group from the tetrahedral intermediate. The total synthesis of **1** was achieved by the treatment of **11** with KO*t*-Bu in DMF.



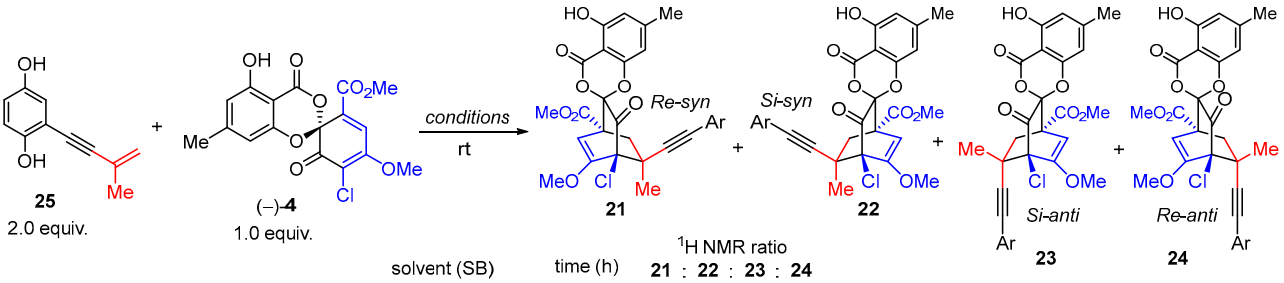
Scheme 10. Migration reaction of *p*-orsellinate group of chloropupukeanolide D. DMF—*N*,*N*-dimethylformaminde.

Further, the one-pot biomimetic transformation of (+)-**2** and (−)-**4** to (+)-**1** was accomplished as part of an alternative synthetic approach (Scheme 11); this was easily achieved because the Diels–Alder/carbonyl–ene cascade reaction did not require any reagents or solvents. The cascade reaction at atmospheric pressure (neat, 5 °C, 7 days; thereafter, 60 °C, 9 h) and subsequent migration reaction of the *p*-orsellinate group (KO*t*-Bu, DMF) provided (+)-**1** in 64% yield, along with **6** in 20% yield.



Scheme 11. One-pot biomimetic synthesis of chloropupukeananin.

The synthesis of chloropestolides H-K (**21**–**24**) via the intermolecular Diels–Alder reaction of siccayne [71] (**25**) and (−)-**4** was also achieved by Suzuki et al. (Scheme 12) [38]. The intermolecular Diels–Alder reaction using common organic solvents was studied, and the reaction in CH_2Cl_2 produced a quantitative mixture of the four cycloadducts **21**–**24** (**21**:**22**:**23**:**24** = 14:44:36:6). As expected, owing to the nature of (−)-**4**, a preference for the *Si* face was observed, and **22** and **23** were isolated with 39% and 34% yields, respectively. The use of other solvents afforded a mixture predominantly comprising *Si-anti* **23**. Significantly, the ratio of cycloadducts, particularly **22**:**23**, depended on the solvent basicity (SB), [72,73] with the ratio of **23** to **22** increasing as the SB value increased. In a solvent-free reaction, a mixture of **25** and (−)-**4** was maintained undisturbed at room temperature for 24 h to complete the Diels–Alder reaction, affording a mixture of **21**–**24** (**21**:**22**:**23**:**24** = 9:32:51:8). A high-pressure reaction in CH_2Cl_2 at 1.0 GPa for 1 h provided a mixture of the same ratio as that in the reaction under atmospheric pressure conditions (**21**:**22**:**23**:**24** = 15:46:33:6). Under high-pressure conditions, the intermolecular Diels–Alder reaction between **25** and (−)-**4** was significantly accelerated, but the facial selectivity remained unaffected.



solvent (SB)	time (h)	^{1}H NMR ratio **21** : **22** : **23** : **24**
CH_2Cl_2 (0.178)	48	14 : 44 : 36 : 6 (39) (34)
CH_3CN (0.286)	48	10 : 28 : 53 : 9
acetone (0.475)	48	6 : 20 : 64 : 10
EtOAc (0.542)	48	6 : 16 : 71 : 7
EtOH (0.658)	48	3 : 7 : 80 : 10
neat	24	9 : 32 : 51 : 8
CH_2Cl_2 in 1.0 GPa	1	15 : 46 : 33 : 6

Scheme 12. The intermolecular Diels–Alder reaction using siccayne and (−)-maldoxin. Isolated yield in parentheses. SB—solvent basicity.

4. Conclusions

This review outlines synthetic studies on the natural product chloropupukeananin and its analogs. Based on synthetic studies using model compounds, the biosynthetic pathway of chloropupukeananin was speculated to involve the intermolecular Diels–Alder reaction between maldoxin and iso-A82775C, carbonyl-ene reaction, and the migration reaction of the *p*-orsellinate group. Additionally, enantioselective syntheses of both biosynthetic precursors, (−)-maldoxin and (+)-iso-A82775C, were achieved. Combining these findings, the one-pot total synthesis of chloropupukeananin mimicking the biosynthetic pathway was accomplished (overall 4.5% yield, 19 steps from 3-bromo-2-hydroxypyrone). As a further bonus, the total synthesis of chloropestolides B, I, and J, and chloropupukeanolide D was achieved.

However, this synthetic approach preferentially gives *Si-syn* and *Si-anti* isomers among the possible cycloadducts in intermolecular Diels–Alder reactions, and it is difficult to synthesize natural products derived from other cycloadducts. Controlling the facial selectivity is possible by using computational chemistry, careful examination of reaction conditions (such as solvents and additives), and modifications to the biosynthetic precursors themselves to create appropriate reaction substrates. Chemical syntheses of natural/non-natural analogs of chloropupukeananin provide a wide variety of bioactive compounds. Additionally, these chemical syntheses are expected to contribute significantly to the identification and elucidation of the function of enzymes involved in chloropupukeananin biosynthesis. I hope that this review will provide new insight into the total synthesis of complex natural products.

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