Biosynthesis of the teleocidin-type terpenoid indole alkaloids

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Review

Biosynthesis of the teleocidin-type terpenoid indole alkaloids

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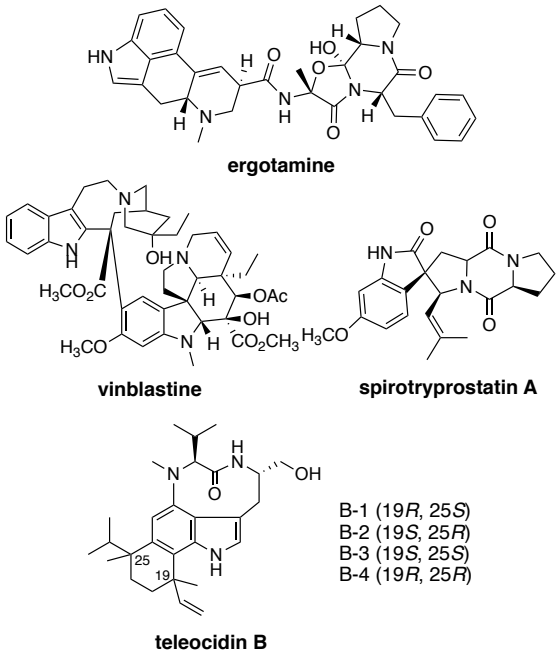
Teleocidin B is a terpenoid indole alkaloid with unique structures including indolactam and cyclic terpenoid, and is a strong protein kinase C activator. Its unique structure and bioactivity have drawn vast interest from chemists and biologists, and numerous isolation and bioactivity studies on this molecule have been performed. Recently, its biosynthetic enzymes were identified, and some of their crystal structures were reported. In this review, we describe the isolation of teleocidin derivatives, biosynthetic studies, and detailed analyses of biosynthetic enzymes, to clarify their biosynthetic reactions toward the enzymatic synthesis of bioactive teleocidin compounds.

1. Introduction

Terpenoid indole alkaloids include many bioactive compounds,[1] such as ergotamine (drug for thrombosis) isolated from ergot fungus,[2] vinblastine (anticancer) from a plant,[3] and spirotryprostatin A (antimitotic arrest agent) from a fungus (Scheme 1).[4] Teleocidin B is one of the well-known terpenoid indole alkaloids isolated from soil bacteria, *Streptomyces* spp.[5] Early studies showed that teleocidin B strongly activates protein kinase C (PKC),[6] a threonine kinase involved in signal transduction for cell proliferation.[7] Its unique structures, a nine-membered lactam and a C-11 cyclic terpene, have attracted keen interest from many natural product and synthetic chemists, and they have reported a number of isolation and synthetic studies. For the teleocidin biosynthetic studies, feeding experiments and chemical conversion have been performed, but its biosynthetic enzymes remained uncharacterized until our recent reports.[8] In this review, we mainly describe the studies of teleocidin, related to its isolation and biosynthesis.



Scheme 1 Representative terpenoid indole alkaloids

2. Discovery of teleocidins

In 1960, Takashima and Sakai isolated a toxic substance against fish during the course of metabolite screening from *Streptomyces*, and named it teleocidin.[5] Arima, Hirata, and co-workers studied the spectral properties of the teleocidin compound by using ultraviolet, infrared, NMR, and MS spectrometric analyses, and identified its partial indolic structures.[9-10] In 1966, Hirata and co-workers determined its overall structure through an X-ray structural analysis of teleocidin B-4 bromoacetate.[11] Interestingly, in 1979, Moore and co-workers isolated a teleocidin-related compound, lyngbyatoxin A, from the cyanobacterium *Moorea producens*, as a causative agent for skin irritation.[12] In 1984, reverse-phase separation of teleocidin substances revealed that they consisted of six structurally and optically distinct compounds, including teleocidins A-1, A-2, B-1, B-2, B-3, and B-4 (Scheme 1 and 2).[13] Teleocidin A-1 is identical to lyngbyatoxin A, while A-2 is the C-19 stereoisomer of A-1.[14] The ^{13}C NMR chemical shifts at C-20 and C-21 were 21.7 and 151.9 ppm for B-4, and 26.5 and 147.6 ppm for B-1.[15] This difference is ascribable to a gauche effect between C-24 and the axially substituted methyl group C-20 for B-4, and the vinyl group C-21 for B-1, indicating that B-1 is a 19*S*, 25*R* stereoisomer. The corresponding ^{13}C NMR chemical shift difference and CD spectral analyses indicated that B-2 is the 19*S*, 25*R* stereoisomer, and B-3 is the 19*S*, 25*S* stereoisomer. The occurrence of different stereoisomers implies that the teleocidin biosynthetic reaction involves several variations in terpene scaffold synthesis. Interestingly, the compound with a vinyl group at C-25 and

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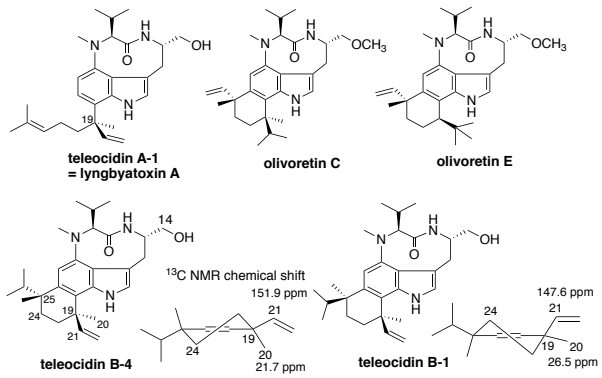
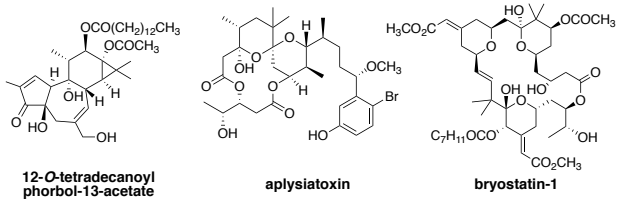


Scheme 2 Isolated teleocidin compounds

an isopropyl group at C-19, olivoretin C,[16] and the compound with a tertiary butyl group at C-19, olivoretin E, were isolated from *Streptomyces olivoreticuli* (Scheme 2).[17] The isolation of these compounds has contributed to the construction of the biosynthetic pathway of teleocidins.

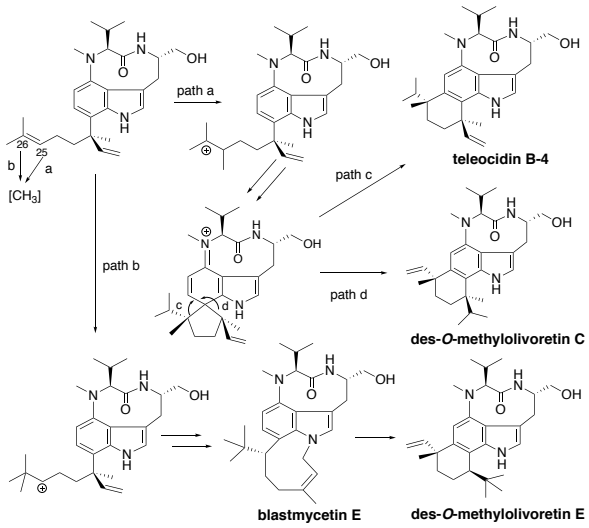
3. Biological activity of teleocidins



Scheme 3 Representative PKC activators

PKC turns into an activated form capable of phosphorylation after it is transferred from the cytosol to the cell membrane, bound to diacylglycerol and phosphatidylserine.[6] Since diacylglycerol is metabolized rapidly, PKC is activated for only a short term. However, some natural products, called PKC activators, keep activating PKC without being metabolized, leading to tumor cell proliferation.[18] In contrast to their toxic effects, PKC activators also act as therapeutic agents for Alzheimer's disease[19] and acquired immune deficiency syndrome.[20] So far, several natural products have been identified as PKC activators, exemplified by teleocidin B, 12-*O*-tetradecanoylphorbol-13-acetate (12-*O*-tetradecanoylphorbol 13-acetate, TPA), aplysiatoxin, and bryostatin-1 (Schemes 1 and 3).[21] Remarkably, bryostatin-1 acts as a tumor repressor through specific binding to PKC δ, one of the PKC subtypes,[22] suggesting that it is important to target the distinct PKC subtype for therapeutic effect. Through specific binding for each PKC subtype, we can understand their *in vivo* functions, as Irie and co-workers tested by using the aplysiatoxin analogs that they synthesized.[23] In addition, the chemical structure of PKC activator can be a model for the design of its inhibitor. For example, Sodeoka, Shibasaki, and co-workers synthesized phorbol ester-phosphatidyl-L-serine hybrid molecules, which block both the ligand and membrane binding sites of PKC and act as the inhibitors by blocking translocation.[24] This report illustrated that medicinally active compounds can be created based on the structures of PKC activators. Recently, PKC activation has become re-focused, as PKC β reportedly becomes inactivated by mutation in cancer cells, and the restoration of PKC function is regarded as a new therapeutic target.[25] Therefore, the PKC activators are also attracting attention, and the diverse structures of PKC activators are needed for use as chemical biology tools. Besides chemical synthesis, enzymatic synthesis is an effective way to build optically active and complex chemical structures in an environmentally friendly manner. To exploit their full potential for engineering studies, deep understanding of their reaction mechanisms is needed.

4. Early studies of teleocidin biosynthesis

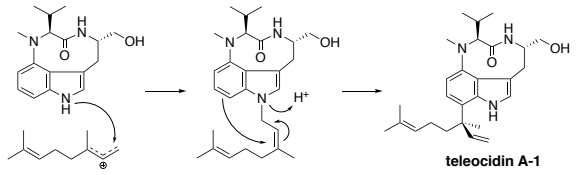


Scheme 4 Early hypothesis on the biosyntheses of the isolated teleocidin compounds

Early studies of teleocidin biosynthesis were performed with isotope feeding analyses. Irie, Koshimizu**,** and co-workers showed that L-valine, L-tryptophan, and L-methionine were incorporated into the indolactam V, a precursor of teleocidin, through utilizing ^{13}C-labeled amino acids for a feeding study, thus indicating that a peptide consisting of these three amino acids is cyclized to form the indolactam V scaffold.[26] However, ^{2}H-labeled *N*-methyl-L-valyl-L-tryptophan was not incorporated, while *N*-methyl-L-valyl-L-tryptophanol was incorporated. This result was consistent with the biosynthetic knowledge that the dipeptide intermediate was released as an alcohol, rather than a carboxylic acid, as described below.

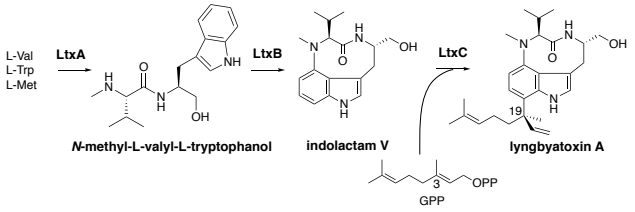
In 1991, the total synthesis of teleocidin B-4 was accomplished by Okabe and co-workers.[27] They showed that the treatment of 25-methylated teleocidin A-1 with boron trifluoride etherate yielded teleocidin B-4 and des-*O*-methylolivoretin C, suggesting the presence of cation-mediated pathway from teleocidin A-1 to teleocidin B-4. Based on this

report and the structures of isolated teleocidin compounds, Irie and co-workers proposed the following biosynthetic pathway: C-25 of teleocidin A-1 is first methylated, and cyclized with induction by the cation resulting from the methylation, to yield the spiro intermediate (Scheme 4).[26] Subsequent C-C bond migration via path c yields teleocidin B-4, and path d yields des-*O*-methyl-olivoretin C. In addition, Irie's group readily synthesized des-*O*-methyl olivoretin E from blastmycetin E, a minor teleocidin metabolite with a t-butyl group through acid treatment.[26] Thus, the authors predicted the presence of a pathway including C-26 methylation, which leads to the olivoretin E scaffold via blastmycetin E (Scheme 4), although its biosynthetic pathway has not been determined yet. The isolation of blastmycetin E has the authors propose the pathway to yield teleocidin A-1 from the *N*-geranylated indolactam through aza-Claisen rearrangement (Scheme 5).



Scheme 5 Hypothetical teleocidin A-1 synthesis through aza-Claisen rearrangement

5. Elucidation of lyngbyatoxin A (=teleocidin A-1) biosynthesis



Scheme 6 Biosynthesis of lyngbyatoxin A

The development of DNA sequencing methods in the late 1990s accelerated the speed of biosynthetic studies, since we could easily obtain the DNA and amino acid sequences of enzymes. In 2004, Edwards and Gerwick identified the lyngbyatoxin A biosynthetic gene cluster (ltxABCD) from the cyanobacterial genome, and assayed the reaction of LtxC, a prenyltransferase that transfers a geranyl moiety to C-7 of indolactam V to yield lyngbyatoxin A (Scheme 6).[28] In this reaction, LtxC catalyzes reverse prenylation, a nucleophilic attack onto C-3 of GPP from the indole ring. Since LtxC was the first enzyme to catalyze the reverse prenylation with a C-10 prenyl chain, its substrate recognition and catalytic mechanism were intriguing. LtxC catalyzes stereoselective prenylation to produce the 19*R*-geranylated compound. The 19*S*-geranylated indolactam V, teleocidin A-2, was also isolated,[13] suggesting the presence of another prenyl transfer reaction with different stereoselectivity from LtxC. This research group also successfully demonstrated the C-N bond formation to yield the indolactam V by the P-450 oxidase LtxB, and showed that it also accepts unnatural analogs in which the valyl group is substituted with other aliphatic groups.[29] In addition, Read and Walsh demonstrated the synthesis of a dipeptide, *N*-methyl-L-valyl-L-tryptophanol, by the non-ribosomal peptide synthetase LtxA (domain structure MT-A-T-C-A-T-R, MT: methyltransferase, A: adenylation, T: thiolation, C: condensation, R: reductase).[30] The rare MT and R domains catalyze N-methylation and reductive release respectively, to produce the N-methylated peptide with C-terminal alcohol.

6. Elucidation of teleocidin B biosynthesis

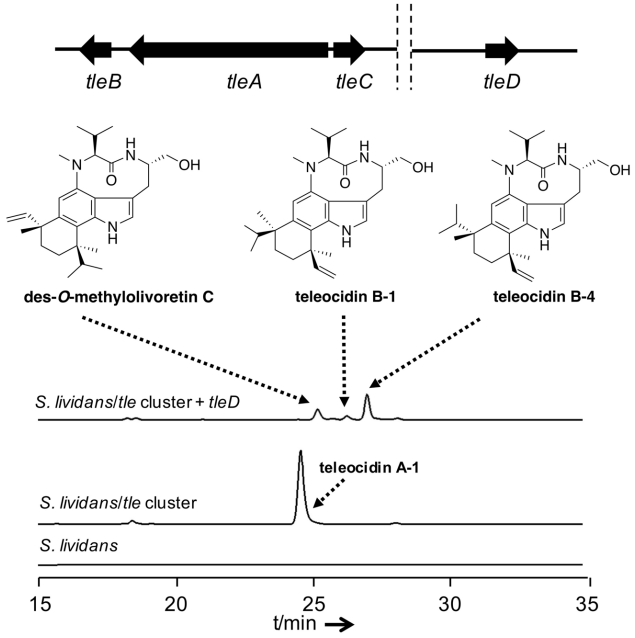
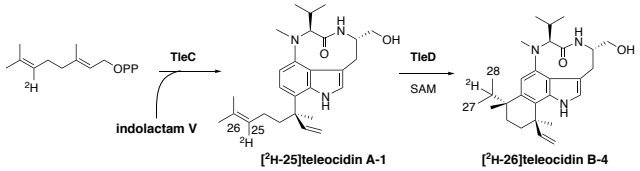


Figure 1 Heterologous expression of teleocidin biosynthetic genes

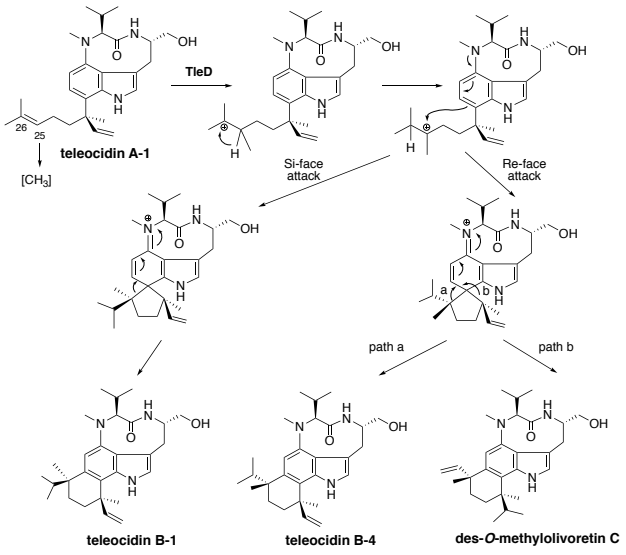
Recently, we identified the teleocidin B biosynthetic enzymes and validated some of their biosynthetic reactions biochemically.[8] We conducted genome sequencing of *Streptomyces blastmyceticus*, a producer of teleocidin B, and found a gene cluster containing *ltxABC* homologs (the *tle* cluster). The amino acid identities between LtxABC and TleABC are 47.8, 47.2, and 37.7%, respectively. The domain organization of TleA is identical with LtxA. The fosmid vector harboring the *tle* cluster was transferred to *Streptomyces lividans*, a heterologous expression host. We expected the



Scheme 7 TleD reaction with the deuterium-labeled substrate

transformant to produce teleocidin B, because the *tle* cluster was likely sufficient for teleocidin B production, due to the nature that microbial biosynthetic genes are usually clustered at one specific site. However, it only produced teleocidin A-1 (Figure 1), and not teleocidin B, indicating that enzyme responsible for methylation and cyclization was encoded outside of the *tle* cluster. Therefore, we focused on the *C*-methyltransferase (*C*-MT) that processes teleocidin A-1, with the expectation that we could find a gene encoding a cyclase around the C-MT gene. Thus, six C-MT genes co-transcribed with *tleC* (*ltxC* homolog) were identified from the genome sequence, and expressed with the *tle* cluster in the course of screening to seek the genes responsible for teleocidin B biosynthesis. As a result, the expression of one *C*-MT gene (named *tleD*) abolished teleocidin A-1 production, and yielded three new compounds. These were identified as teleocidin B-1, teleocidin B-4, and des-*O*-methylolivoretin C (Figure 1). These data clearly indicated that TleD is responsible for the methylation of the geranyl group of teleocidin A-1, leading to terpene cyclization. In addition, a 14-*O*-methyltransferase that converts teleocidins into olivoretins was also identified in this screen.

To characterize the TleD reaction in detail, we prepared the His-tagged recombinant enzyme of TleD, and assayed its reaction *in vitro*, using teleocidin A-1 and *S*-adenosylmethionine (SAM) as substrates. In this reaction, we also observed the same products as seen in the expression study, indicating that TleD can facilitate the series of reactions from *C*-methylation to cyclization. To investigate the reaction mechanism of TleD, we conducted its reaction with 25-^{2}H labeled teleocidin A-1 that is derived from the TleC reaction with 6-D-GPP and indolactam V as substrates. The teleocidin B-4, obtained from the reaction using the ^{2}H-labeled teleocidin A-1, was purified and analyzed by ^{1}H NMR. As a result, the loss of the H-26 peak followed by the decoupling of the H-27 and -28 doublet peaks were observed, thus indicating that the deuterium atom is located at



Scheme 8 The terpene cyclization initiated with methylation by TleD

C-26 (Scheme 7). These data indicated that the hydride migrated from C-25 to C-26, as previously suggested by Irie's group.[26] There were no clear differences in the kinetic parameters between the TleD reactions with non-labeled and 25-^{2}H labeled teleocidin A-1, indicating that there are no isotope effects and this hydride shift is not a rate-limiting step.

Finally, the TleD reaction from teleocidin A-1 into the cyclized products was proposed (Scheme 8). First, C-25 is methylated, followed by the hydride shift from C-25 to C-26, resulting in the cation at C-25. The cation is attacked from C-7 of the indole ring to form the spiro-ring structure. The electron donating nature of the *N*-methyl group enriches the electron density in the indole, and enhances this nucleophilic attack. For this reaction, the *Re*-face attack was favored so that the bulky isopropyl and vinyl groups are located on the opposite faces, and the *Si*-face attack yields teleocidin B-1 as a minor product. The C-C bond migration via path a leads to teleocidin B-4, and path b leads to des-*O*-methylolivoretin C. No intermediates or shunt products derived from quenching with water or deprotonation were observed, indicating that the methylation and cyclization reactions occur spontaneously. This is the first example of terpene cyclization initiated by a cation generated with the methylation of olefin. The homolog of TleD has not been discovered in *M. producens*, with reflecting the structural difference between lyngbyatoxin A and teleocidin B. Recently, the 3D structure of TleD complexed with the substrates was elucidated by X-ray crystallography and a molecular dynamics simulation.[31] This study showed that teleocidin A-1 bends so that C-7 and C-25 are located in proximity to favor the Re-face attack, consistently with our proposed reaction scheme.

7. The molecular basis of prenylation by TleC

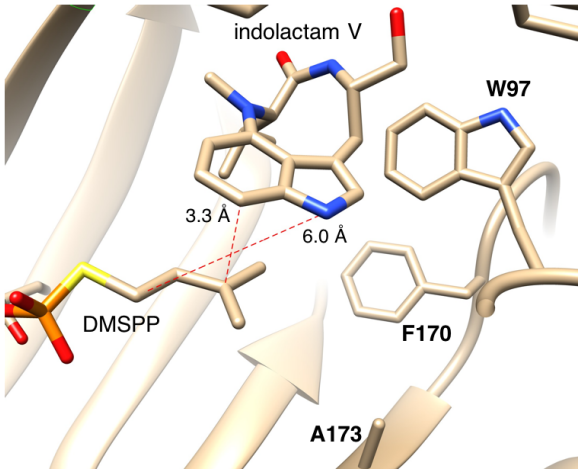


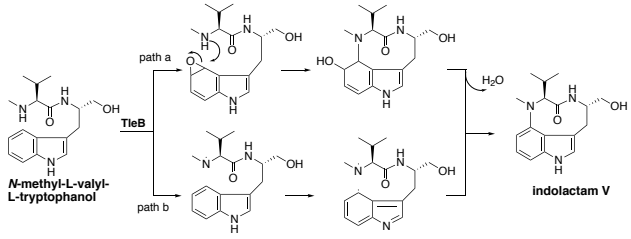
Figure 2 The active site structure of TleC

As described above, the reverse geranylation by TleC is a rare reaction in nature, and its mechanism has not been clarified. To obtain the insight into the TleC reaction for engineering, we solved the X-ray crystal structures of TleC and MpnD, a prenyltransferase that catalyzes the reverse prenylation of the C5 dimethylallyl group on indolactam V.[32,33] The comparison of

these two enzymes complexed with substrates yielded beneficial knowledge about the substrate recognition. While indolactam V and the pyrophosphate of GPP were fixed by salt bridge, electrostatic interaction, and hydrogen bond networks, the prenyl group of GPP was fixed through hydrophobic interactions with the enzyme and the indole ring of indolactam V. Among the residues for the hydrophobic interaction, Trp97, Phe170, and Ala173 in TleC (Figure 2) were substituted with Tyr80, Trp157, and Met159 in MpnD. Remarkably, Trp97 flipped by 70° when the substrates bound to the active site cavity, and the volume of the cavity increased to accommodate the geranyl group. The importance of these residues was tested by site-directed mutagenesis, to exchange the amino acid residues between the two enzymes. TleC A173M exhibited an increased preference for DMAPP, and notably lost the preference for GPP, indicating that the single mutation altered TleC into an MpnD-type prenyltransferase that prefers C-5 DMAPP. Interestingly, the TleC W97Y/A173M double mutant newly produced teleocidin A-2, implying the altered regulation of stereochemistry through these mutations in the active site. The reaction mechanism of TleC was also elucidated from the structure. In the complexed structure, the distance from the C-3 of DMSPP to the C-7 of indolactam V (3.3 Å) was closer than that from the C-1 of DMSPP (6.0 Å) (Figure 2). These data clearly indicated that the direct C-7 reverse prenylation is more plausible than the previously proposed pathway which includes N-1 regular prenylation followed by aza-Claisen rearrangement (Scheme 5).[26]

8. Summary

As described above, teleocidin biosynthesis is intriguing, in that the reaction between the electron-rich indole and the cation-generating terpene moiety generates diverse C-C bond forming chemistry. While the peptide formation, the prenyl chain transfer, and its cyclization were investigated in detail, the mechanism of C-N bond formation by TleB remained enigmatic. Edwards and Gerwick proposed an epoxide-based mechanism,[28] but Walsh proposed a radical-based mechanism (Scheme 9).[34] This C-N bond formation mechanism awaits to be clarified, based on the enzyme structure. We showed that the TleC mutant produces teleocidin A-2,[33] but the dedicated enzyme responsible for this reaction remains unknown. TleD was shown to methylate C-25, but there should be a methyltransferase enzyme that catalyzes C-26 methylation to produce the olivoretin E structure. The elucidation of these unknown biosynthetic pathways, based on biochemical and structural analyses, will lead to the further exploitation of biocatalysts to build terpenoid indole alkaloid scaffolds.



Scheme 9 Proposed mechanism of C-N bond formation by TleB

The indolactam structures also draws interest from synthetic researchers. In 2002, the core of teleocidin was synthesized via two steps of C-H activation with a palladium catalyst.[35] In 2016, the concise eight step total synthesis of indolactam V was accomplished, by using copper-mediated amino acid arylation as the starting reaction.[36] The knowledge from the biosynthetic pathway will also accelerate the development of synthetic methods, such as biomimetic synthesis. The development of gene expression, exemplified by the recent success in the construction of a teleocidin A-1 production system in *Escherichia coli,*[37] has opened the door to the biosynthesis of teleocidin compounds in practical yields. The combination of chemical and biosynthetic methods will contribute to furnishing the structural diversity of teleocidin compounds by complementing the weak points of each method. This would lead to the rational creation of a teleocidin compound library. Considering the notable biological activities of teleocidins and their analogues, pharmaceutically important terpenoid indole alkaloids may be discovered in the constructed library.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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