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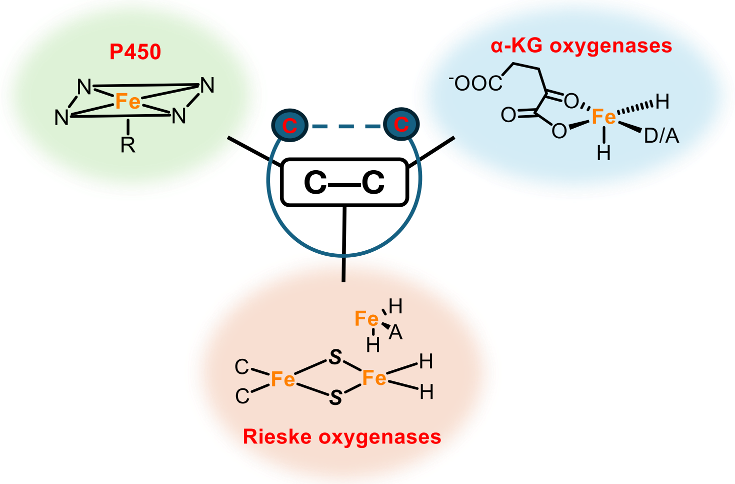

A survey of C–C bond formation strategies and mechanism deployed by iron-containing enzymes in natural products

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ABSTRACT

Developing effective carbon-carbon bond forming strategies is one of the central topics for organic chemistry, boosting the development of synthetic methods towards complex molecule preparation. Meanwhile, enzymes, biocatalysts existing in nature, can facilitate a stunning array of cyclization reactions through C–C bond formation, in which these late stage “decorations” are essential for inherent bioactivity and pharmaceutical use. In this review, we discuss how iron-containing enzymes catalyze intramolecular C–C bond formations found in natural products. Several of these enzymatic processes serve as foundations in developing chemo-enzymatic strategies in complex molecule synthesis.

KEYWORDS: natural product, biosynthesis, iron containing enzymes, C–C coupling, mechanism

INTRODUCTION

Natural products play a crucial role in the fields of medicinal chemistry and pharmaceutical chemistry.[1, 2] For example, due to their diversity and structural complexity, natural products offer a unique platform in understanding complex molecule properties and preparation, making them ideal candidates for the advancement of human health and longevity. In nature, the biosynthesis of these compounds entails multiple enzymatic transformations.[3-5] The structural diversity and heterogeneity of natural products, in many cases, are attributed to enzymes, that catalyze critical modifications such as hydroxylation, halogenation, epoxidation, cyclopropanation, and C–C bond formation.

Activating sp^3 carbon centers has never been trivial for organic chemists, especially in the studies that lead to carbon-carbon bond forming reactions. Given the plethora of sp^3 carbons in natural products, chemists continue to develop methods that employ sp^3 carbon activation step to enable C–C bond formations.[6-10] For example, since the first coupling reaction in 1855,[11] the discovery of coupling reactions has made an immense headway in natural product development.[12, 13]

In nature, several enzyme types enable C–C bond formations via sp^3 carbon center activation.[14] Despite their potential in biosynthesis and chemoenzymatic synthesis, a notable restriction is due to limited substrate scope and specific reaction conditions. Recent advancements in genome mining, mechanistic studies, and protein engineering have overcome some of these challenges.[15-18] These efforts not only enhance our comprehension of enzyme catalysis, but also expand their applications in organic synthesis.

Herein, we summarize recent discoveries of how iron-containing enzymes catalyze intramolecular carbon-carbon bond formations to afford cyclic ring installations in natural products. Enzymes discussed in this perspective belong to Fe/α-KG oxygenases, P450s and Rieske [2Fe-2S] enzyme families (Table1). These enzymes are found to deploy different strategies to generate a key species, while these reactive species are deployed to enable C-H activation and comprehend C–C bond formations.

Enzyme class					
Fe/α-KG		**Rieske [2Fe-2S]**		**P450s**	
Natural Product:	**Enzyme:**	**Natural Product:**	**Enzyme:**	**Natural Product:**	**Enzyme:**
kainic acid	KabC	streptorubin B	RedG	morphine	SalSyn
podophyllotoxin	DPS	metacycloprodigiosin	McpG	*(S)*-corytuberine	CYP8062
cycloclavine	EasH	premarineosins	MarG	staurosporine	StaP
okaramine E	OkaE	prodigiosin R1	RphG	himastatin	HmtT
anditomin	AndF/AndA			vancomycin	OxyC
hormaomycin	HrmJ				
belactosin A	BelL				

Table 1. Biocatalysts involved in certain natural product biosynthesis discussed in this review, categorized by their enzyme superfamily. (single column)

Fe/α-KG oxygenases

Fe/α-ketoglutarate dependent (Fe/α-KG) oxygenases constitute a subfamily of mononuclear nonheme iron enzymes. Fe/α-KG oxygenases share a prominent similarity in how they activate molecular oxygen (O_2) to yield an Fe(IV)-oxo, a.k.a., ferryl species. The majority of Fe/α-KG oxygenases (except halogenases) employ two histidines and one aspartic or glutamic acid, to coordinate iron. This arrangement leaves three coordination sites available for α-KG and O_2.[19, 20] During the reaction, following substrate and α-KG binding to the enzyme, addition of O_2 to Fe(II) leads to Fe(III)-superoxo (Fe(III)-OO•) species formation.

Interaction of Fe(III)-OO• with α-KG results in formation of the key ferryl species along with CO_2 and succinate. The Fe(IV)-oxo abstracts a hydrogen atom from the substrate, yielding a radical intermediate.[21, 22] The radical intermediate then triggers diverse reaction outcomes including hydroxylation, halogenation, desaturation, cyclization and rearrangement.[22-29] In this review, we focus on intramolecular C–C bond formation reactivity, a novel approach that brings structural complexity found in kainic acid, podophyllotoxin, cycloclavine, okaramine, anditomin, belactosins and hormaomycin biosynthesis.

Kainic acid **(1)** was first isolated from the Japanese red seaweed *Digenea simplex* in 1953.[30] Despite its seemingly simple chemical structure, kainic acid exhibits potent neuroexcitatory activity by acting as an agonist of glutamate receptors in the central nervous system (CNS).[31] Additionally, it is utilized as an anthelmintic agent, while its mechanism of action is not fully understood.[32] Due to its medicinal properties, various synthetic methods have been developed and summarized.[33-37] As mentioned in Zeng's report,[35] the three primary routes for the stereoselective synthesis of kainic acid are chiral pool synthesis, chiral auxiliary-induced synthesis, and catalytic asymmetric synthesis. The first enantioselective synthesis of **1** was completed by Oppolozer et. al. in 1982.[38] Beginning with a chiral glutamate precursor, a 1,6-diene intermediate was produced, which underwent a heat-driven cyclization to yield the pyrrolidine ring. In kainic acid (**1**) biosynthesis, an Fe/α-KG oxygenase KabC is responsible for catalyzing intramolecular cyclization of substrate (**2**), to yield kainic acid (**1**) (Fig. 1a).[39, 40] Moore and coworkers reported the kainic acid biosynthetic cluster and comprehended a gram scale chemo-enzymatic synthesis of kainic acid.[40] The mechanism of KabC catalyzed reaction was studied by Chang and co-workers. Combining mechanistic probe design, intermediate trapping, trasient kinetics, and product analysis, a plausible mechanism was proposed.[41] The reaction begins with an Fe(IV)-oxo triggered hydrogen atom transfer (HAT) at the C3 position. Following a radical triggered cyclization to install the C–C bond, an electron transfer (ET) step accompanied by a proton removal installs the C=C bond and furnishes kainic acid (Fig. 1b). Using a fluoro-containing substrate (**F-1**) redirects reaction outcome to partial hydroxylation (Fig. 1c), thus hinting at a possible involvement of a transient cation species in the KabC reaction.

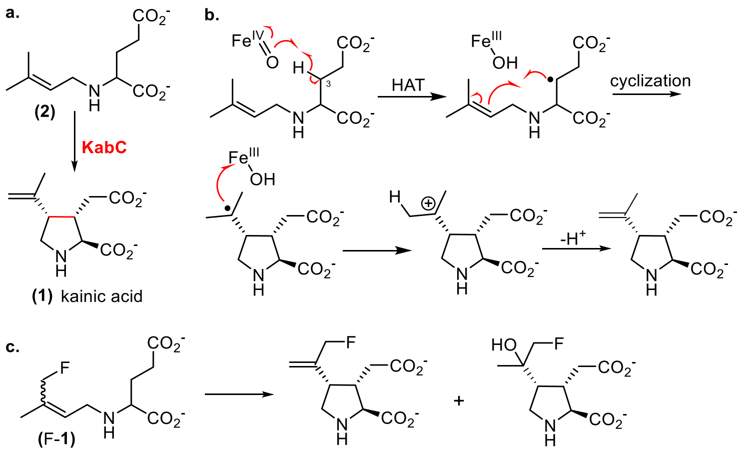

Figure 1. a) KabC catalyzes conversion of prekainic acid (**2**) to kainic acid (**1**); b) A proposed reaction mechanism of KabC; c) The fluorinated probe (**F-1**) redirects the reaction to partial hydroxylation. (single column)

Podophyllotoxin (**3**), a potent non-alkaloid toxin lignan derived from *Podophyllum* species, is one of the key clinical anticancer drugs used in cancer therapy. Isolated in 1880, podophyllotoxin's important medicinal applications leads to its inclusion in the World Health Organization's (WHO) list of essential medicines. Its role as a cancer therapeutic arises from its capacity to impede both viral and cellular DNA replication and destabilize microtubules, preventing cell division.[42] Due to its potent medicinal capabilities, multiple synthetic methods have been developed.[43-46] Hajra et al. achieved the total synthesis of podophyllotoxin with an overall yield of 27% starting from 6-bromopiperonal.[43] Their strategy involved generating a bromo-containing intermediate reminiscent of **4**, which yielded **3** via an intramolecular Heck coupling. A recent study utilizing a radical-based coupling strategy to forge a C-C bond between the C and E rings was established.[47] In 2015, a biosynthetic cluster accounts for podophyllotoxin was elucidated by Sattely et al.[48] In this process, a key cyclization is catalyzed by an Fe/αKG oxygenase 2-ODD-PH or DPS (Deoxypodophyllotoxin Synthase). Starting from (-)-yatein (**4**), this reaction leads to the formation of the C ring, a six-membered ring of deoxypodophyllotoxin (**5**), (Fig. 2a). Renata et al. developed a chemoenzymatic synthesis of podophyllotoxin (**3**). The synthesis was initiated by reacting oxazolidinone (**6**) with (**7**) to afford (**4**). Subsequently, DPS is employed to convert **4** to **5**.[49] Introduction of the benzylic alcohol was accomplished by a consecutive oxidation and asymmetric reduction to yield podophyllotoxin (**3**) (Fig. 2b). Around the same time, another chemo-enzymatic synthesis was published by Fuchs et al.[50] In their approach, they accomplished the synthesis of both podophyllotoxin (**3**) and epi-podophyllotoxin (**8**) (Fig. 2c). Using a racemic hydroxy-yatein isomers ((**9**) and (**10**)) as the substrates, (**10**) yields to a cyclized product (**8**), while the other diastereomer (**9**) undergoes hydroxylation (Fig. 2c). Light on the possible mechanism of this intramolecular C–C bond formation was shed by Chang et al. (Fig. 3).[51, 52] The reaction is initiated by HAT at C7 to form the substrate radical, in which it is likely converted to a cation intermediate by an electron transfer. As revealed by the protein structure and modelling, after rotation of the benzodioxole moiety, C–C bond formation takes place to furnish regio- and stereo-selective Csp^2–Csp^3 bond formation. The reinstatement of aromaticity is completed via a proton removal. During this work, a substrate bound protein structure reveals a U-shaped conformation of (-)-yatein and (+)-yatein within the active site, thus supporting the DPS's substrate promiscuity and regio- and stereo-selectivity.

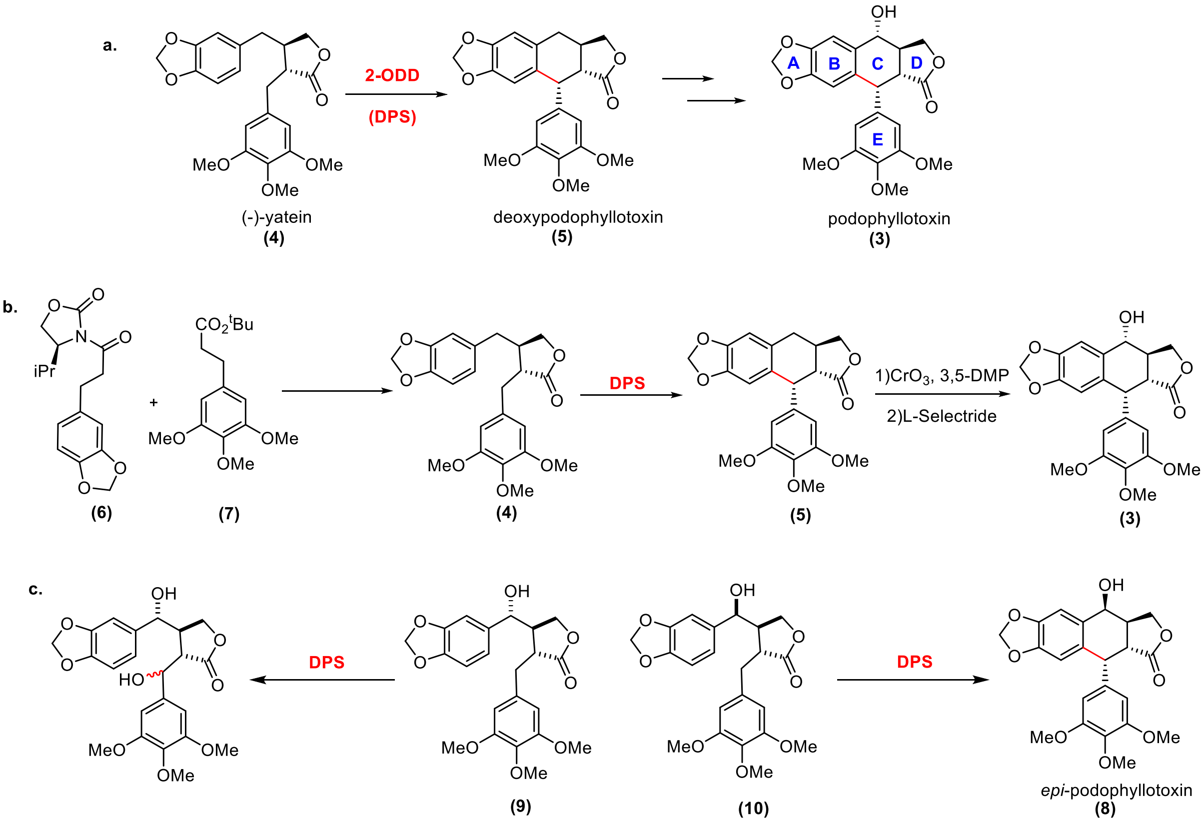

Figure 2. a) DPS (2-ODD) catalyzes formation of (**5**), which is a key intermediate in podophyllotoxin (bio)synthesis; b) and c) Chemo-enzymatic syntheses of podophyllotoxin. (double column)

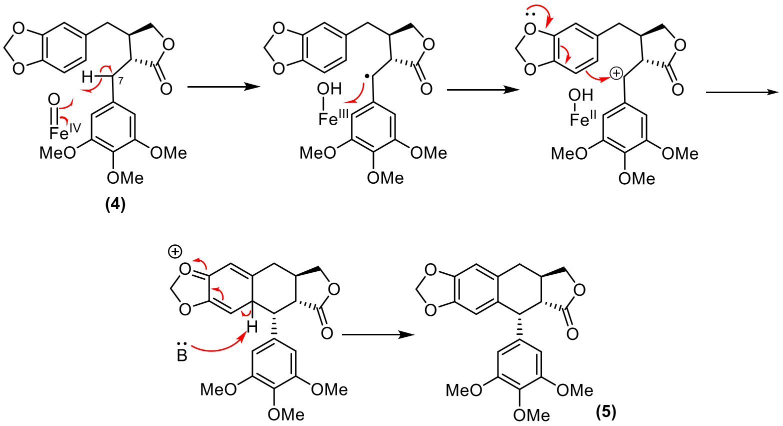

Figure 3. Proposed mechanism of Csp^2-Csp^3 cyclization catalyzed by DPS. (single column)

Cycloclavine (**11**) is an ergot alkaloid isolated from the seeds of *Ipomoea hildebrandtii vatke.*[53] It contains a five-fused ring system including a cyclopropane ring. Ergot alkaloids in general, exhibit significant effects on the central nervous system (CNS)[54] and cycloclavine, in particular, has been demonstrated to bind serotonin 5-HT2C receptor.[55] Except from its potential application as a pharmaceutical agent, cycloclavine has also shown promising insecticidal activity.[56] Due to its unique structure, it has drawn organic chemists's interest to develop various methods for its synthesis.[55, 57-61] Notably, a biomimetic approach enables an access to multiple clavine alkaloids, several of which are included to cycloclavine biosynthesis.[62] The first asymmetric total synthesis of (+)-cycloclavine was accomplished by Wipf et al in 2018.[55] Their approach involved the early synthesis of a bicyclic cyclopropane-containing intermediate through an intramolecular strain-promoted Diels-Alder reaction. In contrast, several groups have pursued the total synthesis of cycloclavine from an alternative perspective, in which a four-fused ring system was constructed and followed by cyclopropanation of olefinated intermediates.[58, 59, 63] Meanwhile, the biosynthesis of cycloclavine was elucidated by O'Connor et. al, in which its biosynthesis includes 8 enzymes starting from tryptophan as the substrate. One Fe/α-KG oxygenase, EasH, is included and catalyzes a cyclopropane ring formation (Fig. 4a).[64] The same group solved the crystal structure of the apo EasH, thus providing potential hint at the mechanism of the cyclopropane formation.[65] The proposed substrate for EasH is an iminium compound (**12**) which could tautomerize to a stable enamine (**13**). The reaction begins with an HAT to form a radical which then triggers cyclization via reacting with the enamine. An ET step is proposed to result in product (**14**) which is reduced by the downstream enzyme EasG to complete cycloclavine (**11**) biosynthesis (Fig. 4b). Additionally, QM/MM calculations support this proposed mechanism.[66]

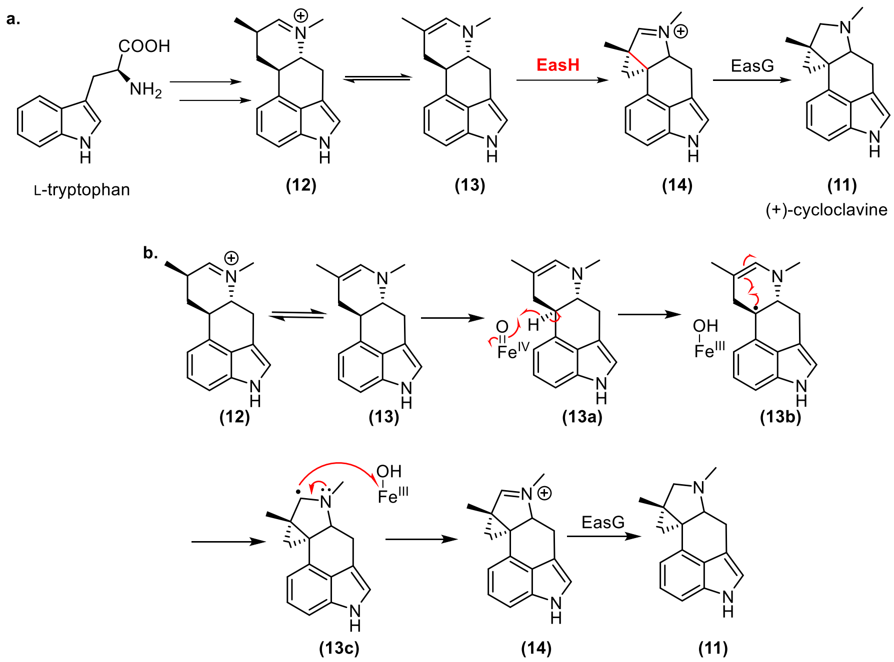

Figure 4. a) Key enzymes included in (+)-cycloclavine biosynthesis; (b) A proposed reaction mechanism of EasH. (single column)

Okaramines are indole alkaloids derived from *Penicillium simplicissimum AK-40* in the pulp of soybeans, a.k.a. okara.[67] Most of them contain a seven-fused ring varying carbon chain length with various functional groups. Okaramines show insecticidal potential through activating the L-glutamate-gated chloride channels specifically in the CNS of invertebrates.[68, 69] Azocine ring moiety, found in the majority of the members of okaramines is essential for the pesticide activity.[70] Multiple synthetic strategies have developed to conquer the synthesis of okaramines. [71, 72] In the course of elucidating the biosynthetic cluster, Lin et. al. characterized OkaE, an Fe/α-KG-dependent enzyme responsible for catalyzing the formation of the azetidine ring of okaramine E (**15**) (Fig. 5a).[73] To the best of our knowledge, a total synthetic method for Okaramine E has yet to be developed. The proposed mechanism for the four-membered ring formation initiates with HAT of **16**. The radical intermediate attacks the neighbouring olefin group and results in the C–C bond formation. OkaE is also proposed to catalyze the hydroxylation to complete okaramine E biosynthesis (Fig. 5b). However, the mechanism of OkaE has not been extensively investigated, making it an interesting subject for future research.

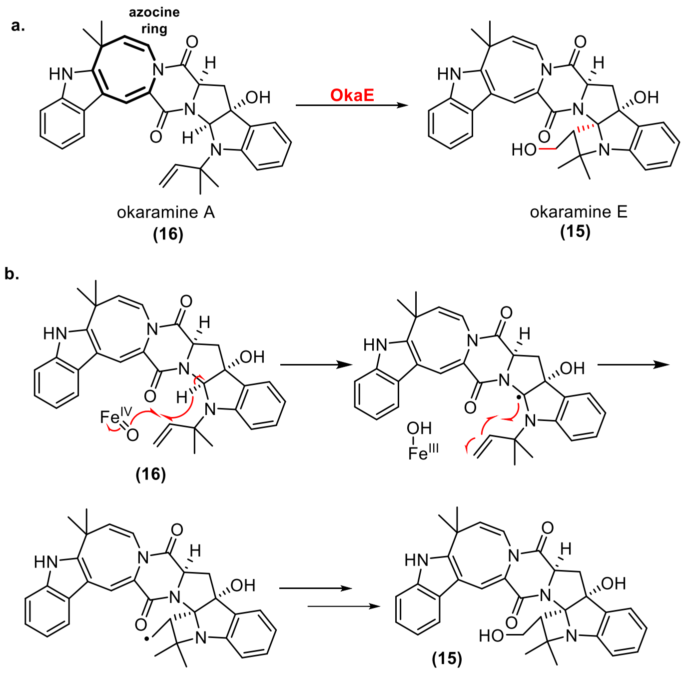

Figure 5. a) OkaE catalyzes cyclization reaction found in Okaramine E biosynthesis; b) A proposed reaction mechanism of OkaE. (single column)

Anditomin (**17**) is a meroterpenoid natural product isolated from *Aspergillus variecolor* in 1981.[74] The meroterpenoid superfamily shows promising medicinal applications. For instance, andrastin A is a potent anticarcinogen due to its ability to inhibit farnesyl transferase[75] and berkeleyone A shows anti-inflammatory activity by inhibition of caspase-1.[76] Although meroterpenoids have driven the attention of synthetic chemists to access their complex structures,[77, 78] their biosynthesis remain under explored. Early investigations of biosynthesis of anditomin suggested the involvement of an intramolecular Diels-Alder cycloaddition for the construction of the bicyclo[2.2.2]octane ring.[79] However, elucidation of anditomin's biosynthesis carried out by Abe et al has disproven this hypothesis,[80] In its biosynthesis, two Fe/α-KG dependent enzymes, AndA and AndF, are involved. The former facilitates desaturation and the assembly of the bicyclo[2.2.2]octane core to form andiconin (**20 → 19 → 18**) (Fig. 6a), while the latter orchestrates an intramolecular rearrangement to yield anditomin (**21 → 17**) (Fig. 6b). The mechanisms of AndA and AndF align with the common mechanism observed in Fe/α-KG enzymes. Following HAT, the radical undergoes sequential rearrangement, resulting in cyclized intermediate. Subsequently, with the assistance of a unknown reducing agent, intermediate (**19a**) is transformed into **18** (Fig. 7a).[80] Analogously, AndF catalyzed reaction also starts with HAT. It is followed by rearrangement, hydroxylation and consequent elimination to form anditomin (**17**) (Fig. 7b). The crystal structure of AndA in both its apo form and the complex with substrates, iron, and α-ketoglutarate (α-KG) support the above-mentioned mechanism.[81]

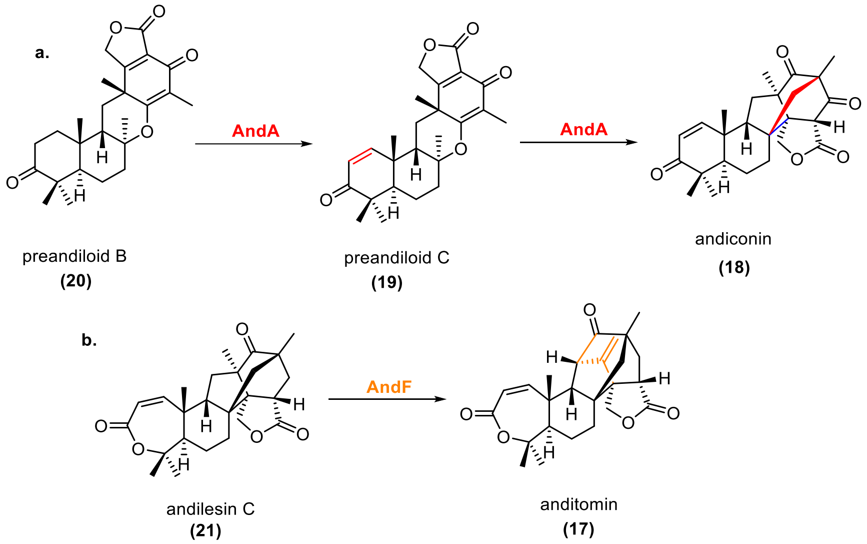

Figure 6. Enyzmatic reactions of a) AndA and b) AndF. (single column)

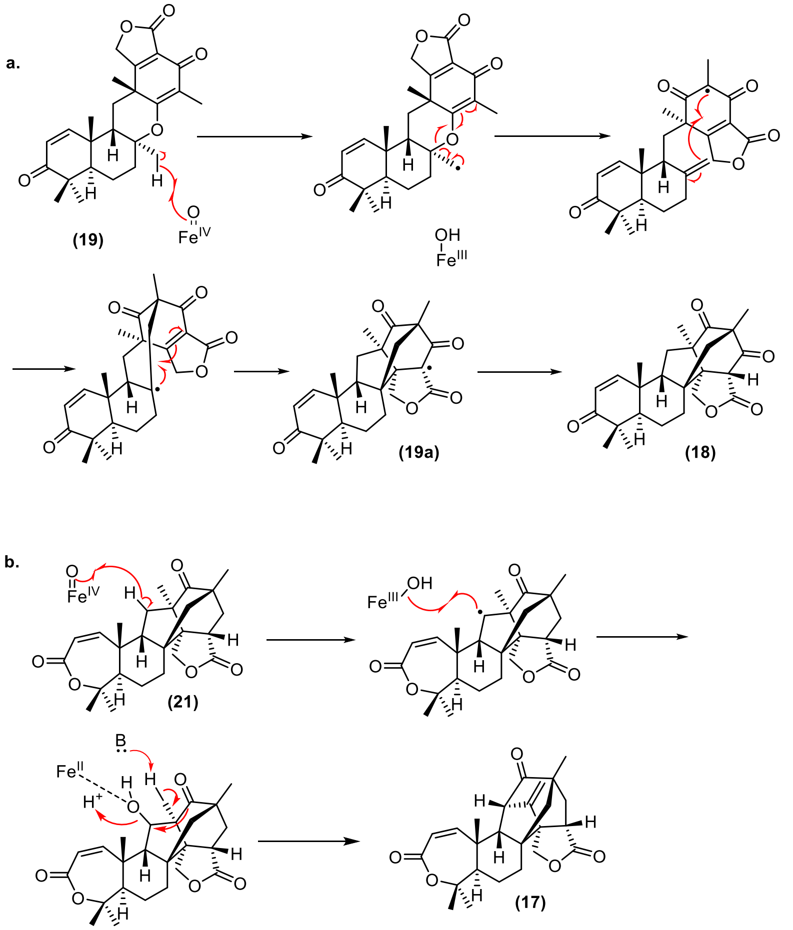

Figure 7. Proposed mechanisms of a) AndA and b) AndF catalyzed reactions. (single column)

Belactosin A (**22a**) and hormaomycin (**22b**) are peptide natural products that contain unique cyclopropyl ring. Belactosins are isolated from the broth of *Streptomyces sp.UCK 14* and present antitumor activity by inhibiting the cell cycle progression of cancer cells at G2/M phase.[82] Due to its potential medicinal applications, multiple total syntheses have been developed.[83-85] Hormaomycin is found in *Streptomyces griseoflavus*.[86] Both natural products are derived from amino acids and share structural similarity, especially the cyclopropane moiety which suggests a possibly common biosynthetic pathway.[87, 88] The biosynthesis of belactosins utilises ATP-grasp ligases whereas hormaomycin is formed using non-ribosomal peptide synthetases (NRPSs). Interestingly, both biosynthetic clusters have common iron containing proteins e.g., HrmI/BelK (heme oxygenase-like enzymes) and HrmJ/BelL (Fe/α-KG enzymes).[89, 90] BelK and HrmI catalyze the formation of L-6-nitronorleucine (**23**) from L-lysine (**24**), and HrmJ and BelL catalyze formation of the cyclopropane, (**25a**) and (**25b**).[89, 91] Compounds **25a** and **25b** have opposite stereochemistry of the cyclopropane moiety (Fig. 8c). The first asymmetric synthesis of a protected **25b** was published in 2009 by Charette et. al., via saponification and decarboxylation of a chiral α-nitrocyclopropyl lactone intermediate.[92] Additionally, during the first total synthesis of belactosin A, a cyclopropane containing protected amino acid was synthetized in 8 steps from a chiral epoxide.[84] In the course of belactosin A biosynthesis, it is noteworthy to highlight the recent identification of a molybdenum-dependent reductase, known as BelN. This enzyme catalyzes the reduction of the nitro moiety of **25b** to the amine.[93] Abe, Chang and their co-workers, in their recent study on BelL homologs, provided evidence on the stereoselective formation of each of the four cyclopropane diastereomers (**25a-25d**) by different BelL homologs (Fig. 8c).[94] Mechanistic studies of HrmJ are also elucidated. The reaction likely involves a nitronate intermediate, in which the nitro group increases the acidity of C6-proton (Fig. 9). Following Fe(IV)-oxo formation, the reaction proceeds with HAT at C4 position to result a radical species. At this point, the reaction can branch into three possible directions, radical catalyzed cyclization (path A), cation catalyzed cyclization (path B) or hydroxylation followed by nucleophilic attack (path C).[89, 91, 94] The deprotonation step was proven to be essential, as difluorinated analog (**26**) gave no reaction product.

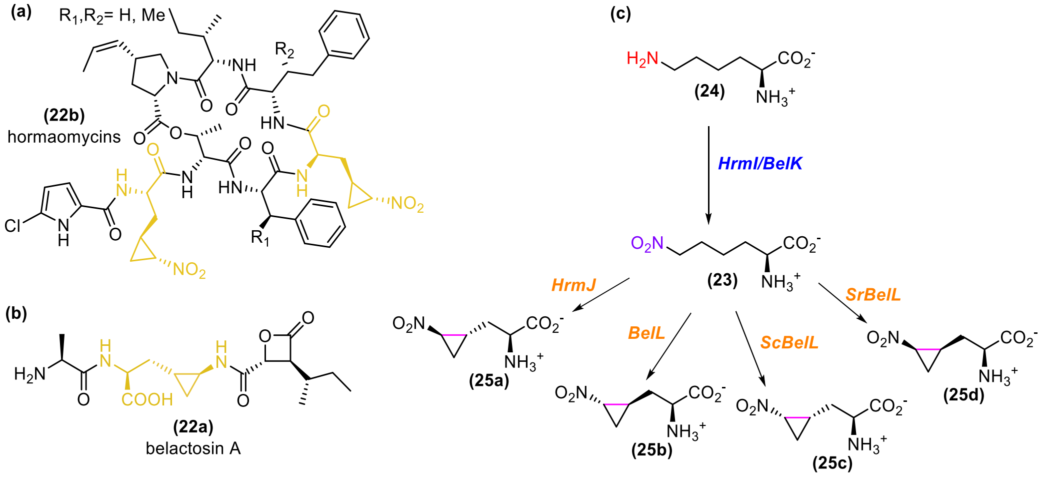

Figure 8. a) and b) Structures of hormaomycins and belactosin A; c) HrmJ and BelL homologs catalyse cyclopropanation where all four isomers are produced. (double column)

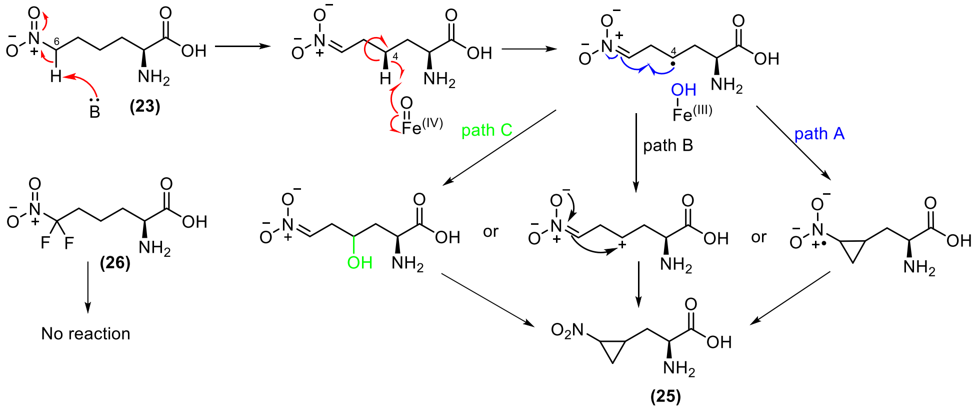

Figure 9. Mechanistic studies on the formation of the cyclopropane ring. (double column)

Rieske [2Fe-2S] oxygenases

Rieske oxygenases were first found in *Pseudomonas putida* [95, 96] and they are characterized by their abilities to degrade aromatic hydrocarbons, mostly catalyzing dihydroxylation.[97, 98] This family of enzymes contain the characteristic iron-sulfur cluster and depend on a reducing pair to promote electrons from NAD(P)H, to the cluster and consequently to the iron in the active site. The mononuclear iron is responsible for enabling substrate oxidation.[99] The [2Fe-2S] cluster is coordinated to two cysteins and two histidine residues.[100, 101] In addition to hydroxylation, rieske-oxygenases are found to catalyze a variety of reactions such as oxygenations, dealkylations and C–C coupling.[102, 103]

Streptorubin B (**27**) and metacycloprodigiosin (**28**) are heterocyclic natural products, part of the prodiginine alkaloids family. Prodiginines have been recognized since ancient times, and their initial interactions with humans occurred through an organism called *Serratia marcescens*, found in a farmer's polenta.[104] Historically, they have had a significant impact due to their ability to emit a blood like-reddish color on cereal grains and their products.[105] Several syntheses of **27** and **28** are known.[106-109] The first metacycloprodigiosin (**28**) synthesis featured a pyrrole-containing bicycle, a.k.a. the Wasserman pyrrole, as the primary intermediate originating from cyclododecanone.[108] Thomson and coworkers pursued a comparable strategy in 2014, employing the Wasserman pyrrole; however, the non-aromatic carbocycle of this intermediate was generated through a ring-closing metathesis of a linear chiral olefin.[107] Similar approach was followed in the synthesis of streptorubin B (**27**) core by Chen.[110] In contrast, Thomson accessed the 10-membered carbocycle of **27** via an anionic oxy-Cope rearrangement from a chiral cyclohexanol.[106] Noteworthy is the synthesis of **27** by Fürstner, which utilizes intramolecular platinum-catalyzed enyne metathesis as the key step to access the pyrrole containing bicyclic structure.[109] During their biosyntheses, both natural products share the same substrate, undecylprodigiosin (**29**). Two rieske-oxygenases RedG and McpG catalyze C–C coupling to yield **27** and **28** (Fig. 10a), forming 10- and 12-membered carbocycles.[111] Mechanistic insights of these enzymes has been proposed by Challis et al.[102, 112] Addition of O_2 to the Fe(II) center which is followed by ET and protonation produces Fe(III)-peroxo species (**29a**). This species catalyzes HAT at C7 which forms radical species (**29b**), prone to cyclization, yielding another radical species (**29c**). Subsequently, a second HAT restores the aromaticity and leads to **27** (Fig. 11). Other homologs that catalyze similar reactions are also known. In the biosynthesis of prodiginines, MarG and RphG yield premarineosins (**31**) and prodigiosin R1 (**33**) using **30** and **32** as the substrates, respectively (Fig. 10b).[103, 113, 114]

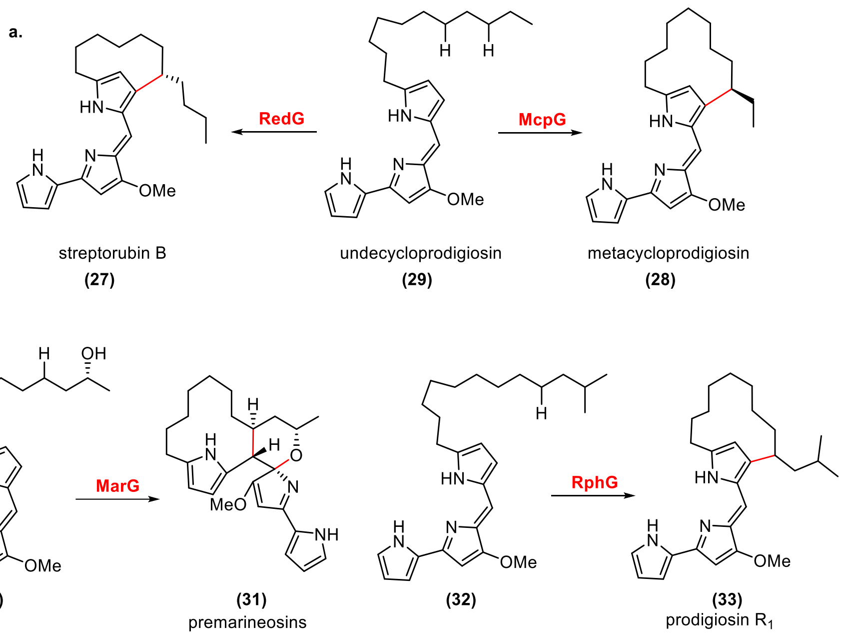

Figure 10. a) Undercycloprodigiosin reactions with RedG and McpG; b) MarG and RphG catalyze cyclization reactions to afford **(31)** and **(33)**. (double column)

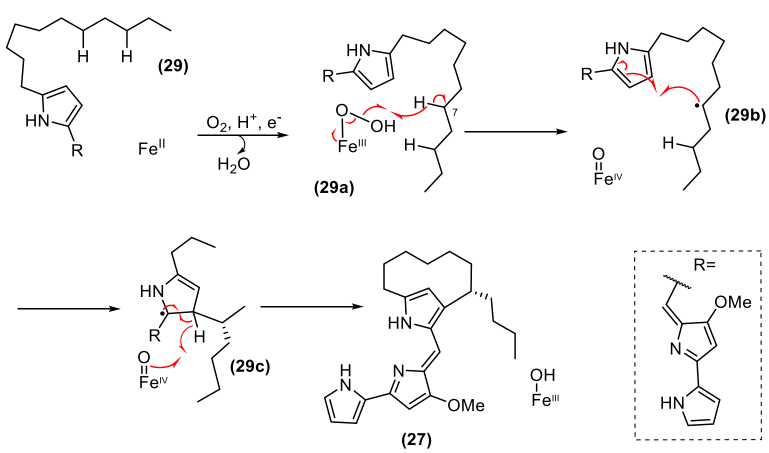

Figure 11. Mechanistic proposal for the action of RedG. (single column)

Cytochrome P450s

Cytochrome P-450, a.k.a CYP, composes enzymes that contain a heme-Fe center in the enzyme active site. Enzymes in this family can be found in all kinds of life including animals, humans, plants, bacteria and fungi.[115] For the majority of cytochrome P450s, the presence of a redox partner(s) is vital, acquiring it to transfer electrons to the heme center.[116, 117] The nomenclature of those enzymes is organized in a way to identify the basic characteristics of each species. The abbreviation CYP, shows the enzyme superfamily. A number code and a capital letter indicate the gene and sub-family, and lastly another number represents the individual gene.[118] P450s have been shown to act as platforms for multiple organic compounds oxidation.

In certain cases, one enzyme can react with one substrate, whereas many others have a broader substrate scope.[116] With regard to secondary metabolite production, CYPs catalyze hydroxylation, epoxidation, oxidation and C–C coupling with some of their catalytic actions and mechanisms being well-studied.[119, 120] Additionally, cytochrome P450s are also found to catalyze essential functions for life such as synthesis of hormones and cholesterol, and metabolism of various compounds including vitamin D, drugs and other xenobiotics.[117, 121]

Morphine (**34**) is a potent opiate analgesic and psychoactive drug derived from *Papaver somniferum*.[122] Morphine acts on the central nervous system to alleviate pain, although its use comes with a significant risk of addiction in which both physical and psychological dependence can develop rapidly.[122] It was first isolated in 1804 by Sertürner.[123] Like podophyllotoxin, morphine is also listed on the World Health Organization's List of Essential Medicines. Its biosynthesis initiates with tyrosine derivatives, i.e., dopamine and 4-hydroxyphenylacetaldehyde.[124] Over the years, various research groups have made significant contributions, collectively unravelling its biosynthesis.[124-126] Various modifications coordinated by NADPH-dependent reductases, P450s and a Fe/αKG-dependent enzyme enable the biosynthesis of morphine and its precursors, such as codeine and salutaridine.[124] In 2015, Smolke and coworkers achieved the morphine production on engineered yeast, which gives hope for developing a strategy for scalable morphine production.[127]

Salutardine (**35**), the first tetracyclic intermediate in morphine biosynthesis, is formed after an intramolecular phenol C–C coupling executed by salutaridine synthase (SalSyn, **33** → **35**), a P450 enzyme (Fig. 12a). SalSyn is most abundant in the stems of the plant, rather than in the leaves or its roots.[125] Despite all attempts, the native enzyme SalSyn was unstable and the protein isolation and characterization was not successful. Nevertheless, Kutchan and co-workers successfully expressed a recombinant enzyme in *Spodoptera frugiperda* Sf9 cells and characterized it as CYP719B1.[128] Another P450 that catalyzes the same cyclization on a similar scaffold is CYP80G2. It is involved in magnoflorine biosynthesis where *(S)*-Corytuberine (**36**) is formed using *(S)*-Reticuline (**37**) as the substrate (Fig. 12b).[129] Due to the importance of opium alkaloids in medicinal chemistry, various synthetic chemists have pioneered multiple phenol coupling strategies utilizing various metals and hypervalent iodine reagents[130-135], non-metallic oxidizing agents[136], electrochemical methods[137-141] , directed Grewe-type cyclizations[142, 143] or transition metal catalysis[144, 145]. Furthermore, Kroutil et. al. published a chemo-enzymatic synthesis of (+)-salutaridine from (*R*)-reticuline utilizing SalSyn at a late biocatalytic step.[146]

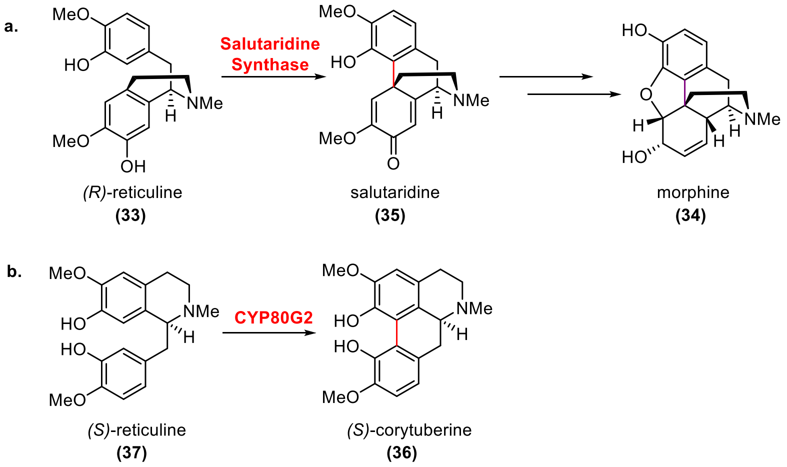

Figure 12. Examples of P450s catalyzed C–C bond formations found in tetracyclic opium alkaloids. (single column)

Staurosporine (**38**) is an indolocarbazole alkaloid isolated from *Streptomyces sp.* TP-A0274 [147] and exhibits antitumor and antifungal properties.[148, 149] Functioning as an ATP-competitive kinase inhibitor, it features a non-selective binding affinity to various kinases.[150] Staurosporine synthesis has attracted the interest of multiple organic chemists.[151-156] The first total synthesis was accomplished by Danishefski et. al.[151] Various groups have pursued the construction of the indolocarbazole core scaffolds in various ways.[157] Common methods for connecting the two indole moieties together (similarly as the StaP reaction) are palladium[158-160], light[151, 161-164] or DDQ[165, 166] mediated reactions. The biosynthetic pathway of staurosporine starts with an P450 StaO catalzyed tryptophan oxidation to yield an imine, referred as indole-3-pyruvic acid (**39**) (Fig 13a). Dimerization of two molecules of **39** by StaD produces chromopyrrolic acid (**40**).[167, 168] Lastly, the cyclization and decarboxylation to assemble the indolocarbazole core is catalyzed by another P450, StaP (CYP245A1). A recombinant StaP in *E. Coli* yielded three different products, **41**, **42** and **43**, whereas addition of another enzyme, StaC can direct the reaction towards **42** that finally leads to Staurosporine (**38**).[168] Notably, Danishefski and coworkers accessed **38** via an intermediate that is comparable to the backbone structure of **40**. Subsequently, a radiation approach was deployed to form the central aromatic ring via connecting the two indole moieties. [151] Onaka and Nagano et. al., reported a 2.4 Å and 1.9 Å protein crystal structures of StaP in its apo- and substrate-bound form.[169] The proposed mechanism for the formation of the di-carboxy intermediate (**44**) begins with the generation of an indole-containing cation radical (**40a**), facilitated by the removal of one electron by the ferryl-oxoporphyrin complex (Fig. 13b). Due to potential hydrogen bonding and aromatic interactions of the substrate, hydroxylation is prevented. The cation radical intermediate (**40a**) prompts the cleavage of a proton, resulting in a more stable neutral radical species (**40b**). At this stage, two possible pathways are proposed. Either an ET and deprotonation of the neighbouring indole which then initiates the intramolecular radical coupling to yield compound (**40c**), or direct C–C coupling between the indoles that results in a cyclized radical species **40d** can take place. For the first possibility, the last step is a tautomerization to gain aromaticity and form the indolocarbazole scaffold. For the latter, an electron transfer which is followed by aromatization yields (**44**). [169]

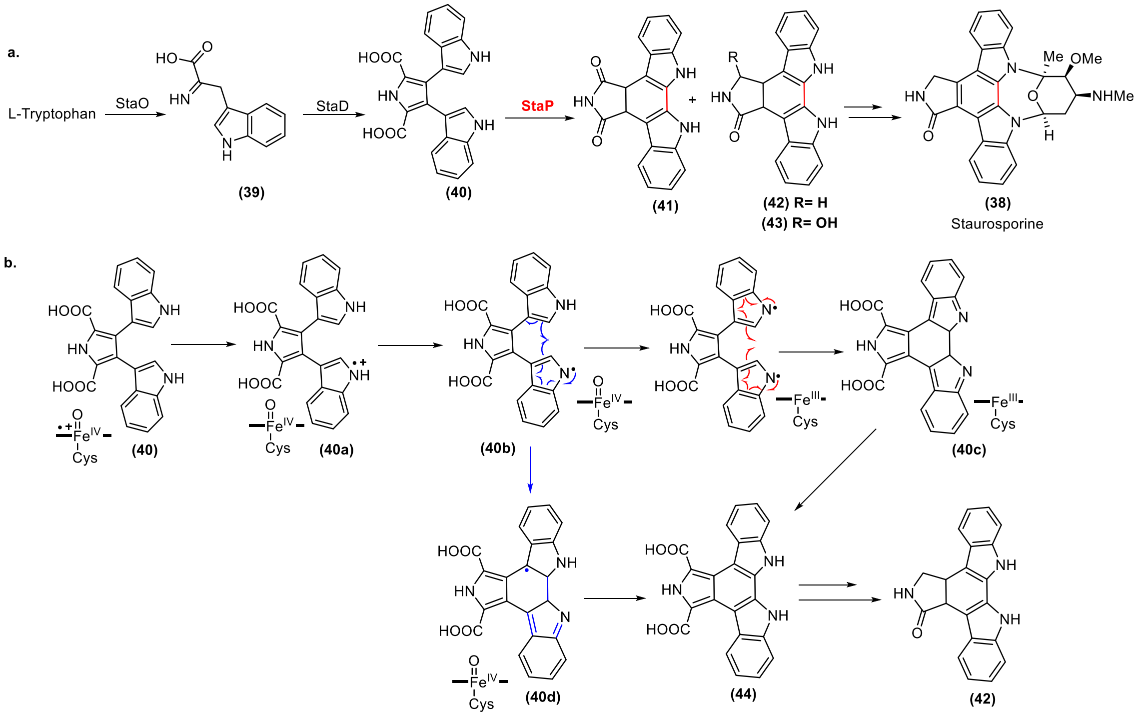

Figure 13. a) Key enzymes used in the biosynthesis of staurosporine; b) Proposed mechanisms of StaP catalyzed reaction. (double column)

Himastatin **(45)** is a dimeric depsipeptide produced in cultures of *Streptomyces hygroscopicus* found in soil in India and shows antibiotic and antitumor activity.[170, 171] Himastatin's structure contains multiple amino acids in their L or D form, such as tryptophan, valine, threonine and leucine, but also contains other small molecules like α-hydroxyisovaleric acid and 5-hydroxypiperazic acid. After the first total synthesis by Danishefski, the initial published structure of himastatin proved to be different than the natural compound, in which a reversed stereochemistry was observed on the tryptophan moiety (shown in blue) (Fig. 14).[172-174] Additionally, it was demonstrated that the chiral center on the tryptophan moiety is essential for himastatin's bioactivity.[175] Noteworthy is also a recent work of Movassaghi and coworkers on a biomimetic approach of the total synthesis of himastatin.[174] The pyrroloindole moiety of **45** was prepared in five steps starting from a tryptophan derivative. A key step in this process involved the utilization of N-bromosuccinimide (NBS) to induce the formation of the pyrrole ring. Similarly, Danishefski and coworkers completed their syntheses of the pyrroloindole utilizing NBS and oxidation with 2,2-dimethyldioxirane as their key steps for the pyrrole cyclization. [172, 173] Himastatin's biosynthesis was elucidated by Ju and co-workers and involves an unusual cytochrome P450 enzyme HmtT. It catalyzes the pyrroloindole formation in regio- and stereo-selective manner (Fig. 14).[176] While the protein crystal structure of HmtT is known,[177] studies on how HmtT catalyzes pyrroloindole formation requires further exploration.

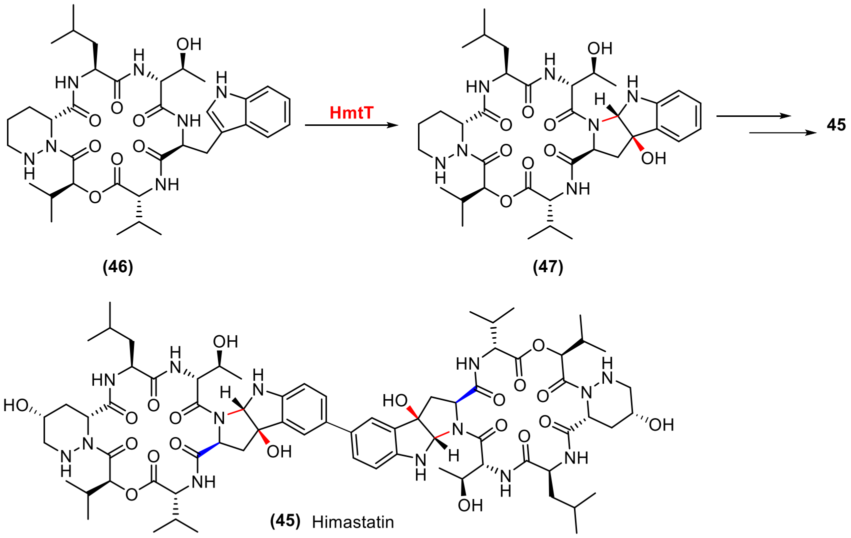

Figure 14. HmtT catalyzes coupling reaction towards Himastatin biosynthesis. (single column)

Vancomycin is a ribosomal glycopeptide produced by *Amycolatopsis orientalis*. It is an antibiotic used to treat various bacterial infections, including methicillin-resistant *Staphylococcus aureus*.[178] Despite its approval for clinical use in the United States in 1958, the elucidation of vancomycin's structure did not occur until 1985.[179] Due to its multiple stereocenters and structural complexity, multiple synthetic groups were devoted towards its total synthesis.[180-189] Its biosynthetic cluster mainly constitutes three NRPSs, VpsA, VpsB and VpsC, which are deployed to assembly different amino acids.[190] It's non-protein amino acids such as β-hydroxytyrosine and 4-hydroxyphenylglycine are synthetized prior to NRPSs action. After the assembly of the linear peptide chain, the peptide is subjected to glycosylations and C–C couplings.[191] A P450 enzyme, OxyC, is responsible for a C–C coupling between two phenol moieties (Fig 15a). During the chemical synthesis of vancomycin, a few methods have been deployed to achieve the bi-aryl coupling of ring A and B, such as vanadium oxytrifluoride (VOF_3) mediated oxidative coupling[185] and Suzuki couplings[181, 186, 188]. The protein structure of OxyC was solved by Schlichting[192] while Seyedsayamdost and co-workers demonstrated a chemo-enzymatic synthesis of vancomycin and its derivatives.[193] The proposed mechanism of the C–C bond formation is initialized by HAT at the phenol position. The radical is tautomerized to the alpha carbon (**48a**). Subsequently, this intermediate undergoes a C–C coupling and results in another radical species (**48b**). Intermediate **48b** is stabilized by two hydroxy groups. Finally, deprotonation and electron transfer lead to the formation of vancomycin aglycon (**50**) (Fig. 15b).[193]

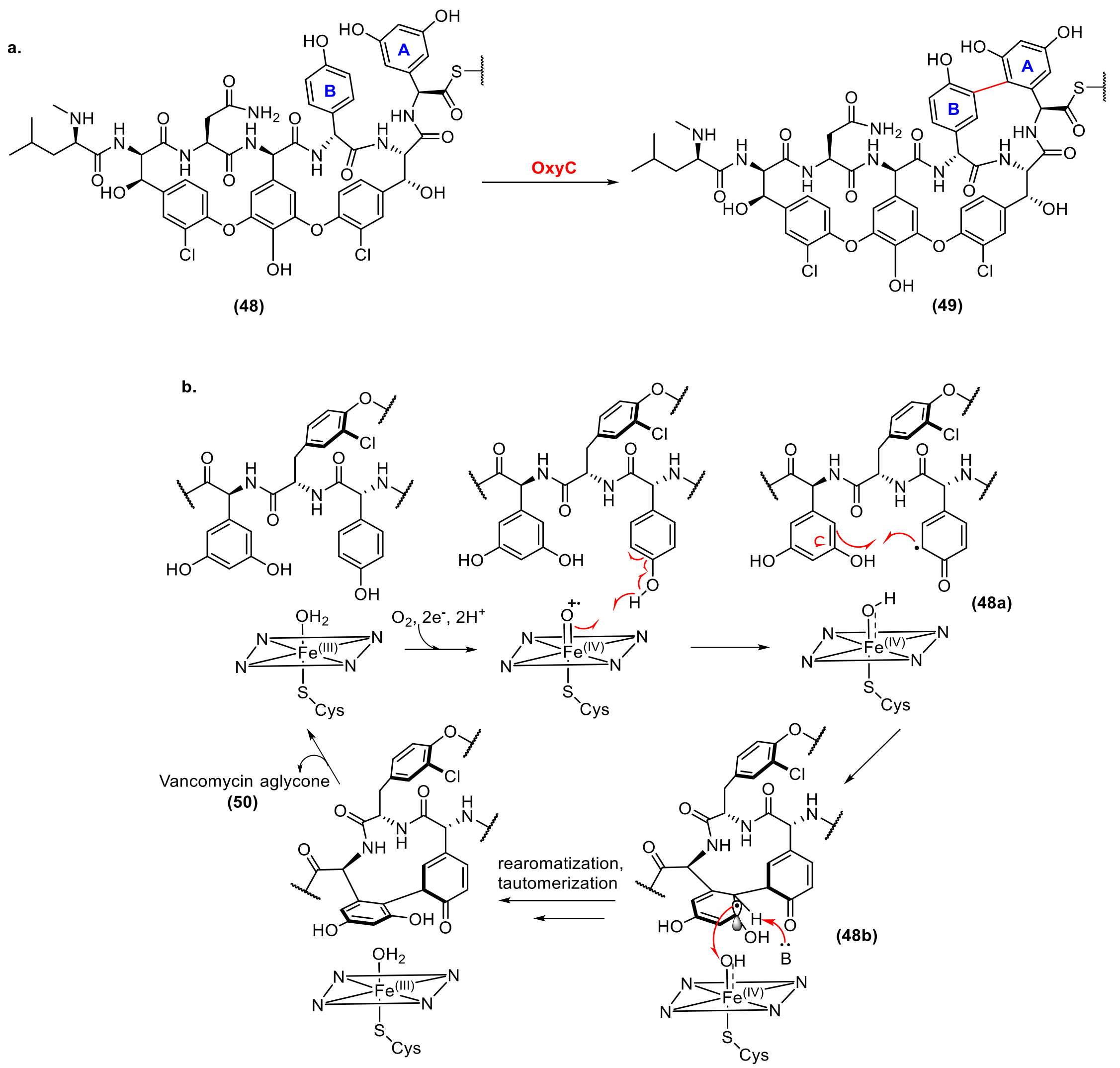

Figure 15. a) OxyC catalyzed aromatic C–C coupling and b) its proposed mechanism. (double column)

CONCLUSION:

Nature has offered remarkable machineries for constructing structurally complex compounds, surpassing the capabilities of current organic synthetic methods. Specifically, stereo- and regio-selective C–C bond formations have yielded crucial bioactive compounds and essential drugs. Comprehending the natural product biosynthesis and their corresponding mechanisms are proving to be essential for uncovering new reactivities and expanding the toolbox for synthetic and biosynthetic methodologies. Moving forward, we anticipate that elucidation of pathways associated with novel natural products and the characterization of corresponding enzymatic reactions will continue to shed light for the development of new drugs, chemo-enzymatic syntheses and other applications. The knowledge of fundamental studies will also contribute to pharmaceutical field and medicinal chemistry.

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