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Oxidative Indole Dearomatization for Asymmetric Furoindoline Synthesis by a Flavin-Dependent Monooxygenase Involved in the Biosynthesis of Bicyclic Thiopeptide Thiostrepton

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Abstract: The interest in indole dearomatization, which serves as a useful tool in the total synthesis of related alkaloid natural products, has recently been renewed with the intention of developing new methods efficient in both yield and stereoselective control. Here, we report an enzymatic approach for the oxidative dearomatization of indoles in the asymmetric synthesis of a variety of furoindolines with a vicinal quaternary carbon stereogenic center. This approach depends on the activity of a flavin-dependent monooxygenase, TsrE, which is involved in the biosynthesis of bicyclic thiopeptide antibiotic thiostrepton. TsrE catalyzes 2,3-epoxidation and subsequent epoxide opening in a highly enantioselective manner during the conversion of 2-methyl-indole-3-acetic acid or 2-methyl-tryptophol to furoindoline, with up to > 99% conversion and > 99% *ee* under mild reaction conditions. Complementing current chemical methods for oxidative indole dearomatization, the TsrE activity-based approach enriches the toolbox in the asymmetric synthesis of products possessing a furoindoline skeleton.

Thiostrepton is a parent member of thiopeptide antibiotics that exhibits potent anti-infective, antitumor and immunosuppressive activities.[1] It shares with other members in this family a characteristic macrocyclic framework that arises from complex post-translational modifications (PTMs) of a ribosomally synthesized precursor peptide to provide the 6-membered nitrogen heterocycle central to multiple azoles and dehydroamino acid residues (**Scheme 1A**).[2] In addition to sequence permutation of the precursor peptide for changes in amino acid constitution,[3] individualized PTMs are necessary for specializing the common thiopeptide framework to different thiopeptide antibiotics that are composed of over 100 naturally occurring chemical entities, thereby exemplifying a process of how nature develops structural complexity and diversity from a Ser/Thr and Cys-rich sequence.[4]

As characterized in the biosynthesis of thiostrepton, specific PTMs involve the incorporation of a biologically important, quinaldic acid (QA) moiety into the 27-membered, large side ring system conjugated with a typical 26-membered thiopeptide framework.[5] The formation of QA starts with the conversion of a precursor peptide-independent L-Trp residue via C2-methylation and subsequent C2'-transamination to produce 2-methyl-indole-3-pyruvic acid (**1, Scheme 1A**). This intermediate undergoes oxidative ring expansion, during which selective C2-N1 bond cleavage for indole ring opening is closely coupled with C2'-N1 bond formation for recyclization and the formation of a key quinoline ketone intermediate (**2**).[6] Followed by stereoselective reduction, the resulting quinoline alcohol is activated and appended onto the thiopeptide framework for side ring closure via epoxidation-mediated QA dearomatization.[7] Additional PTMs, e.g., thioamidation, glycosylation and central domain functionalization, can occur to give structurally related but more complex thiopeptides including thiopeptins and Sch40832.[8]

We have recently dissected the unusual ring expansion process in the formation of QA, where TsrE (with the accession No. ACN80667.1), a flavin adenine dinucleotide (FAD)-dependent, Class D monooxygenase,[9] plays a key role in the conversion of 2-methyl-indole-3-pyruvic acid (**1**) into the quinoline ketone intermediate (**2**). The activity of this flavoprotein relies on reduced $FADH_2$, which is recycled *in situ* from oxidized FAD using

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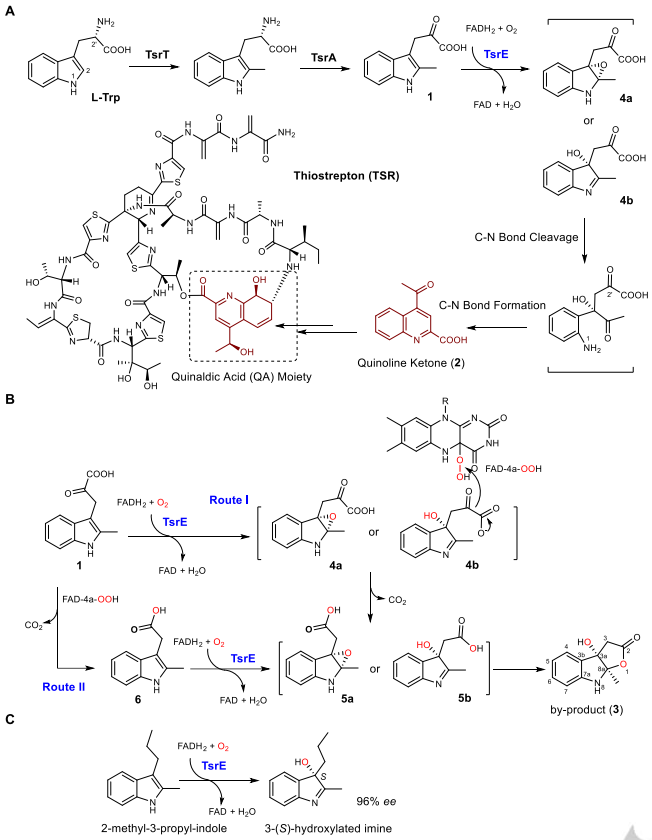
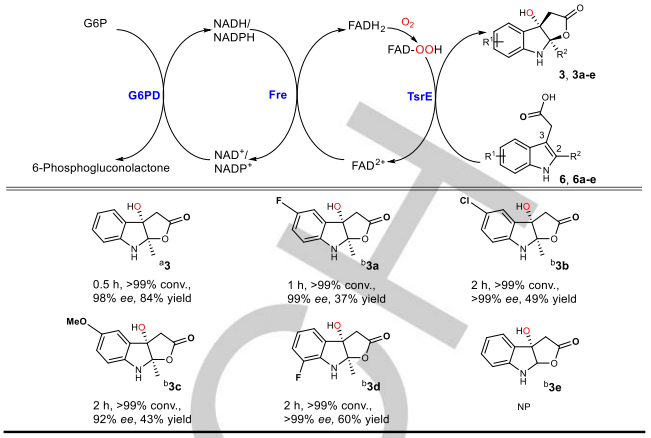


Scheme 1. Structures, biosynthetic pathway and enzymatic reactions associated with TsrE activity. Atom ^{18}O in panels B and C is indicated in red. (A) TSR and specific PTMs for processing L-Trp to the QA moiety within the side-ring system. (B) Proposed mechanism for the formation of by-product **3**. (C) Selective hydroxylation of 2-methyl-3-propyl-indole to a (3*S*) product.



Each reaction was conducted in a 25 mL mixture (with a 0.025 mmol scale) at room temperature. [a] **RC-I**: 1 mM substrate, 10 μM TsrE, 5 μM Fre, 100 μM FAD, 3 mM NADPH and 50 mM Tris-HCl (pH 7.5); [b] **RC-III**: 1 mM substrate, 10 μM TsrE, 5 μM Fre, 10 μM FAD, 50 μM NAD^+, 4 mM G6P, 0.1 U/mL G6PD and 50 mM Tris-HCl (pH 7.5).

Scheme 2. Enantioselective synthesis of 3a-hydroxy oxofuroindolines by TsrE.

reduced dihydronicotinamide adenine dinucleotide (phosphate) (NAD(P)H) in the presence of the flavin reductase Fre.[9b,10] In addition to **2**, careful analysis of the TsrE-catalyzed transformation revealed a minor compound, **3**, which proved to be a shunt product bearing a distinct dearomatized 3a-hydroxy oxofuroindoline scaffold. Following this unexpected observation, in this study, we demonstrated that TsrE catalysis is amenable for the effective asymmetric synthesis of a variety of furoindolines with a vicinal quaternary carbon stereogenic center by oxidatively dearomatizing indoles via enzymatic epoxidation and subsequent ring-opening in an enantioselective manner.

We first determined the process of how the shunt product **3** is formed. An unstable oxygenated intermediate (**4a** or **4b**) can be observed at low temperature during the TsrE-catalyzed conversion of **1**.[9b] Thus, shunt product **3** might be produced through **5a** or **5b** by oxidative decarboxylation of the carbon side chain in the presence of O_2 and $FADH_2$, which react to form the oxidizing adduct FAD-4a-OOH, and subsequent addition of the newly formed carboxylate group to the indole ring for cyclization (**Scheme 1B, Route I**). The absolute configuration of **4b** or **5b** can be assigned as (3*S*), as supported by examining the TsrE-catalyzed hydroxylation of 2-methyl-3-propyl-indole (a synthetic mimic of **1**) that gives a (3*S*) product (**Scheme 1C**).[9b] Notably, this examination indicates the flexibility of TsrE catalysis. TsrE tolerates the indole substrate distinct from **1** by processing a shortened carbon side chain, leading to an alternative route in which the oxidative decarboxylation of **1** precedes TsrE-catalyzed oxygenation (**Scheme 1B**, **Route II**). To validate this route, we utilized 2-methyl-indole-3-acetic acid **6**, the decarboxylated derivative of **1**, as the substrate to test TsrE activity (**Scheme 2**). Remarkably, > 99% conversion and 98% *ee* were obtained in the prodution of **3**, a 3a-hydroxy oxofuroindoline with the assigned absolute configuration (3a*S*, 8a*R*; the stereoselectivity was further determined by the electronic circular dichroism calculation of **3a**, **Figure S3**). Using $^{18}O_2$ in this reaction led to the production of single ^{18}O-labeled **3** ([M - H]$^-$ *m/z*: calcd. 206.0709 for $C_{11}H_{11}NO_2{}^{18}O$, found 206.0697), consistent with the notion that TsrE catalyzes stereoselective oxygenation (**Figure S4**, further supported below by ^{18}O labeling in TsrE-catalyzed tryptophol dearomatization). This enzymatic transformation proceeded moderately under **RC-I**, the reaction condition used previously for the conversion of **1**,[9] with the steady-state kinetic parameters K_m at 0.4 ± 0.05 mM for **6**, k_{cat} at 18.1 ± 1.0 min^{-1} and k_{cat}/K_m at 50.2 $mM^{-1}min^{-1}$ (**Figure S1**). In contrast, the stereoselective chemical synthesis of **3** from **6** appears to be a challenge. By known chemical methods for oxidative asymmetric dearomatization, e.g., Sharpless oxidation and vanadium-dependent oxidation,[11] the conversion of **6** to **3** proved to proceed poorly, along with unexpected side reactions that can complicate the process for product purification and characterization.

Based on the above model reaction that TsrE catalyzes the oxidative asymmetric dearomatization of **6**, we examined the effects of indole substitution on enzymatic productivity and enantioselectivity. As a result, TsrE effectively converted four commercially available derivatives of **6** (i.e., **6a-d**, with the substitutions by F, Cl and CH_3O at C5, respectively, and the substitution by F at C7) to 3a-hydroxy oxofuroindolines (i.e., **3a-d**) with > 99%% conversion and 92-99% *ee* over a 1-2 hr reaction period under an optimized reaction condition (i.e., **RC-III**, see below for developing TsrE-catalyzed tryptophol dearomatization), indicating that TsrE catalysis is not sensitive to the substitution of the benzene ring by a group varying in size or electronical property (i.e., F, Cl and CH_3O). TsrE did not catalyze the transformation of indole-3-acetic acid, **6e**, validating the necessity of the C2-methyl group for TsrE catalysis (**Scheme 2**).

In parallel, we applied TsrE-catalyzed oxygenation in the asymmetric dearomatization of tryptophols. Under **RC-I**, the

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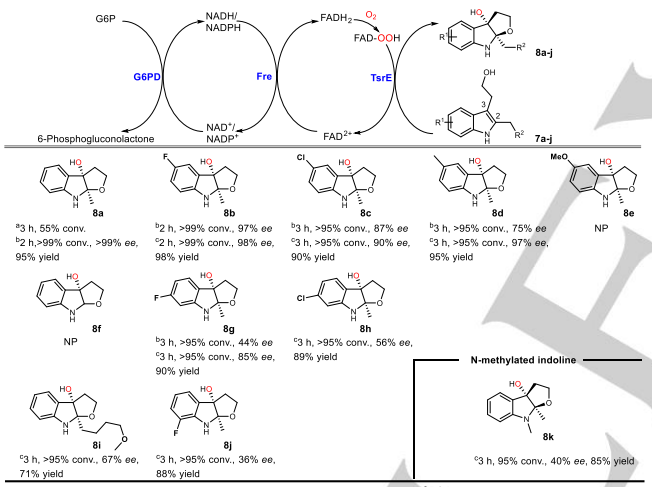
model substrate 2-methyl-tryptophol (**7a**) was transformed to 8a-methyl-3a-hydroxyfuroindoline, **8a**, but not completely (i.e., 55% conversion observed over a 3-hr reaction period). Kinetic analysis under **RC-I** revealed a k_{cat} value of 6.6 ± 0.1 min^{-1}, approximately 3-fold lower than that in the conversion of **6**, indicating that reduced $FADH_2$, which was rapidly produced given the high catalytic efficiency of the flavin reductase Fre, might not be completely used for **8a** production and instead tend to be oxidized by O_2 to FAD and H_2O_2. Consistently, either time elongation or increase in NADPH supply (e.g., 3:1 for the ratio of NADPH to the substrate **7a**) in the reaction mixture did not cause conversion improvement. H_2O_2 appears to have little affect on TsrE activity under **RC-I**, because the addition of catalase (e.g., 0.1U/ml or 1U/ml) did not improve the conversion rate. To alleviate the inconsistency in reduced $FADH_2$ production and TsrE-catalyzed oxygenation, we utilized glucose 6-phosphate dehydrogenase (G6PD), which provides NAD(P)H *in situ* by converting glucose 6-phosphate (G6P) to 6-phosphogluconolactone, for sustainable $FADH_2$ supply in the presence of Fre. Consequently, the two-enzyme system composed of G6PD and Fre was optimized to provide the reducing power matching TsrE activity for **7a** transformation, leading to a reaction condition (**RC-II**) giving > 99% conversion and 99% *ee* for **8a** production over a 2-hr reaction period (**Scheme 3**).



[a] 3 h, 55% conv. [b] 2 h, >99% conv., >99% *ee*, 95% yield

[b] 2 h, >99% conv., 97% *ee* [c] 2 h, >99% conv., 98% *ee*, 98% yield

[b] 3 h, >95% conv., 87% *ee* [c] 3 h, >95% conv., 90% *ee*, 90% yield

[b] 3 h, >95% conv., 75% *ee* [c] 3 h, >95% conv., 97% *ee*, 95% yield

[b] 3 h, >95% conv., 44% *ee* [c] 3 h, >95% conv., 85% *ee*, 90% yield

[c] 3 h, >95% conv., 56% *ee*, 89% yield

[c] 3 h, >95% conv., 67% *ee*, 71% yield

[c] 3 h, >95% conv., 36% *ee*, 88% yield

[c] 3 h, 95% conv., 40% *ee*, 85% yield

Each reaction was conducted in a 25 mL mixture (with a 0.025 mmol scale) at room temperature. [a] **RC-I**: 1 mM substrate, 10 μM TsrE, 5 μM Fre, 100 μM FAD, 3 mM NADPH and 50 mM Tris-HCl (pH 7.5); [b] **RC-II**: 1 mM substrates, 10 μM TsrE, 5 μM Fre, 100 μM FAD, 500 μM $NADP^+$, 4 mM G6P, 0.1 U/mL G6PD and 50 mM Tris-HCl (pH 7.5); and [c] **RC-III**: 1 mM substrates, 10 μM TsrE, 5 μM Fre, 10 μM FAD, 50 μM NAD^+, 4 mM G6P, 0.1 U/mL G6PD and 50 mM Tris-HCl (pH 7.5).

Scheme 3. Enantioselective synthesis of 3a-hydroxyfuroindolines by TsrE.

We then utilized different tryptophol derivatives (i.e., **7b-d** and **7g**) to test TsrE activity under **RC-II**. Over a 2-3 hr period, these substrates were nearly completely converted to individual 8a-methyl-3a-hydroxyfuroindolines (i.e., **8b-d** and **8g**, > 95% conversion); however, compared to the conversion of **7a**, the enantioselectivity of this enzyme appeared to be decreased (i.e., with the *ee* values of 97%, 87%, 75% and 44% for **8b**, **8c, 8d** and **8g**, respectively). Analysis of the control reactions proceeding in the absence of TsrE revealed background products. Likely, overproduced $FADH_2$ can react with O_2, leading to an excess of FAD-4a-OOH that could mediate non-enzymatic oxidative dearomatization in a diastereoselective manner. To further balance $FADH_2$ production with TsrE-catalyzed oxygenation, for which the catalytic efficiency might be decreased by indole substitution, we reduced exogenous FAD usage. Remarkably, under **RC-III**, where the ratio between FAD and the enzyme was adjusted to 1:1, the conversions of **7b-d** and **7g** by TsrE provided expected products **8b-d** and **8g** with comparable conversion rates (i.e., > 95% for each reaction) and improved *ee* values (i.e., 98%, 90%, 97% and 85% for **8b**, **8c, 8d** and **8g**, respectively). This further optimized condition was thus applied to the dearomatizations of additional 2-methyl-tryptophol derivatives (i.e., **7e**, **7h**, **7j**, **7i**,**7f** and **7k**) to evaluate the selectivity of TsrE catalysis in substrate.

With the exceptions of **7e** and **7f** that cannot be converted, TsrE activity is sufficient for (nearly) completely converting the other 2-methyl-tryptophol substrates (i.e., **7h**, **7j**, and **7i**) into related 3-hydroxy-furoindoline products (i.e., **8h**, **8i** and **8j**); however, its stereoselectivity varies in a substrate-dependent manner (i.e., 36-67% *ee* values). Based on the observation that TsrE tolerates C5 substitutions by F, Cl and CH_3 but does not accept CH_3O substitution at the same position, the size of a substituent group, instead of its electronic property, likely plays a key role in substrate tolerance. In addition, the change in fluorination position from C5 to C6 and C7 decreases the enantioselectivity of this enzyme, likely due to the FAD-4a-OOH-associated, competitive oxidative dearomatization as aforementioned. Similar results were observed by changes in chlorination position. This nature is different from that observed above in the conversions of 2-methyl-indole-3-acetic acids, where either CH_3O substitution at C5 or fluorination at C7 has little effect on the enantioselectivity of TsrE, indicating that the terminal carboxylate group shared between **6, 6a-d** and the native substrate **1** is of importance to substrate binding at the active site of the enzyme. Without this group, as shown in **7a-j**, TsrE catalysis appears to be sensitive to substitution changes in the indole part of the substrate. As observed in the conversions of indole-3-acetic acids, C2-subsitution is necessary for TsrE activity, because oxidative indole dearomatization failed to occur by using the demethylated derivative **7f** as the substrate. At this position, enantioselectivity tends to decease with the extension of the length of substituent groups.

The examination of N1 substitution was conducted by converting **7k** to provide insights into the oxygenation mechanism of TsrE catalysis (**Scheme 4**). TsrE-catalyzed oxygenation could facilitate indole dearomatization through two routes. **Route a** depends on the selective hydroxylation at C3 to produce intermediate **9**, which can result from deprotonation of the nitrogen hydrogen to drive double bond shift and thus increase C3 nucleophilicity for the attack to the peroxyl group of FAD-4a-OOH. In contrast, **Route b** requires deprotonation of the oxidizing adduct, yielding FAD-OO^- for nucleophilic attack to C2 of the indole ring during the formation of **10**, a 2,3-epoxidated intermediate. Facile tautomerization can occur between **9** and **10** in solution during the conversions of the native substrate **1** and the above tested **6**- and **7**-related derivatives, thereby perturbing intermediate trapping and characterization. As a result, the conversion of **7k** proceeded effectively in the presence of TsrE, given the expected product **8k** with 95% conversion and 40% *ee*. These results indicate that TsrE catalysis could prefer regio- and stereoselective 2,3-epoxidation over 3-hydroxylation to initiate the asymmetric dearomatization of indoles.

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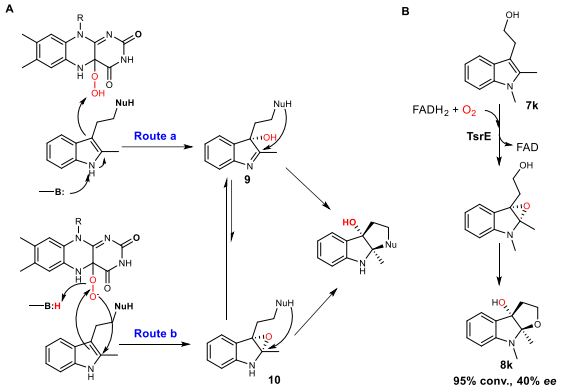

Scheme 4. Investigation into the catalytic mechanism of TsrE. (A) Two possible routes to furoindolines. (B) Conversion of **7k** into **8k**.

Finally, we tested the scale-up feasibility of TsrE-catalyzed oxidative dearomatization using the model substrates **6** and **7a**. In a 16-fold enlarged, 400 mL reaction mixture, TsrE completely transformed substrate **6** (75.6 mg and 0.4 mmol) or **7a** (70.1 mg and 0.4 mmol) into product **3** or **8a** over a 1.5-2.0 hr period at room temperature, with an *ee* value and a yield comparable with those obtained in a 25 mL reaction mixture. These enzymatic transformations were conducted under revised **RC-III**, where the only change is using glucose dehydrogenase and glucose to replace expensive G6PD and G6P for NADH supply.

In conclusion, following the unexpected TsrE-catalyzed shunt reaction during investigations into the formation of the QA moiety installed the side ring system of the thiopeptide antibiotic thiostrepton, we developed an effective enzymatic approach for the oxidative dearomatization of indoles in the asymmetric synthesis of a variety of furoindolines with a vicinal quaternary carbon stereogenic center. This approach, which relies on the 2,3-epoxidation of 2-methyl-indole-3-acetic acid or 2-methyl-tryptophol in a highly stereoselective manner and subsequent epoxide opening under mild reaction conditions, complements chemical methods for oxidative indole dearomatization and thus enriches the toolbox in the asymmetric synthesis of natural products possessing a furoindoline skeleton.[11,12]

Acknowledgements

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Keywords: Indole dearomatization • Furoindoline • Flavin-dependent monooxygenase • Thiostrepton • Quinaldic acid

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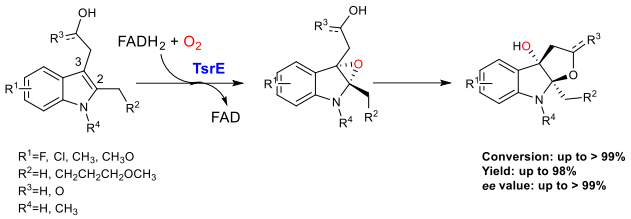

An enzymatic approach for oxidative indole dearomatization is reported. TsrE, a flavin-dependent monooxygenase involved in the biosynthesis of bicyclic thiopeptide antibiotic thiostrepton, catalyzes 2,3-epoxidation and subsequent epoxide opening during the conversion of 2-methyl-indole-3-acetic acid or 2-methyl-tryptophol to furoindoline, with up to > 99% conversion and > 99% *ee* under mild reaction conditions.