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# Asymmetric Synthesis of Natural *cis*-Dihydroarenediols Using Tetrahydroxynaphthalene Reductase and Its Biosynthetic Implications

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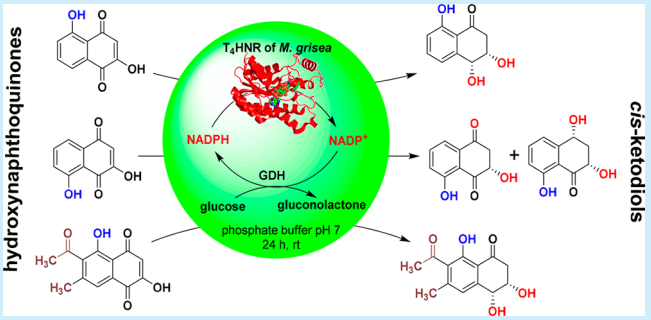
Supporting Information

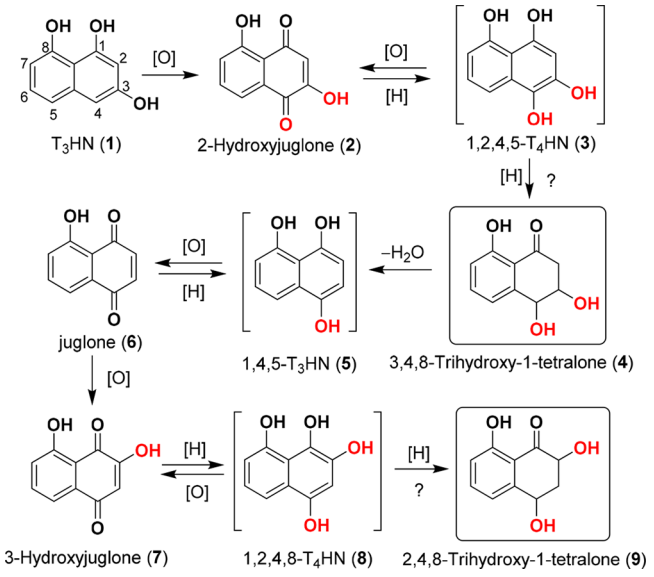
**ABSTRACT:** Asymmetric reduction of hydroxynaphthoquinones to secondary metabolites, (3*S*,4*R*)-3,4,8- and (2*S*,4*R*)-2,4,8-trihydroxy-1-tetralone, a putative biosynthetic diketo intermediate and a probable natural analogue, (3*S*,4*R*)-7-acetyl-3,4,8-trihydroxy-6-methyl-3,4-dihydronaphthalene-1(2*H*)-one, using NADPH-dependent tetrahydroxynaphthalene reductase ($T_4$HNR) of *Magnaporthe grisea* is described. This work implies the involvement of $T_4$HNR or related enzymes during the (bio)synthesis of other dihydroarenediols by reduction of the hydroxynaphthoquinone scaffold containing substrates.






Polyketide secondary metabolites containing a ketodiol substructure such as bicyclic dihydroarenediols are common in nature. Some are proposed to be derived from 1,6,8-trihydroxynaphthalene ($T_3$HN, **1**) formed during 1,8-dihydroxynaphthalene (DHN) melanin biosynthesis (Scheme 1).[1] An example is 3,4,8-trihydroxy-1-tetralone (3,4,8-THT, **4**) also known as 4-hydroxyvermelone,[2a,b] which was first isolated from *Pyricularia oryzae* and later from several other fungal species.[2] It shows inhibitory activity toward SHP2, a protein tyrosine phosphatase associated with several forms of cancer, and PTP1B, a negative regulator of the leptin and insulin signaling pathway, as well as phytotoxicity.[3a] Despite its common occurrence and rather simple structure, uncertainty remains regarding the stereochemistry of **4** due to conflicting reports in the literature.[3] Various synthetic[4] and biocatalytic methods[5] developed over the years for its preparation could not address this issue completely.

**Scheme 1. Proposed Biosynthetic Pathway for the Formation of 3,4,8- and 2,4,8-Trihydroxy-1-tetralones**[1a,b]




2,4,8-Trihydroxy-1-tetralone (**9**), another fungal ketodiol containing secondary metabolite isolated from *Penicillium diversum*, *Ceratocystis fimbriate*, and *Urnula craterium* exists in *cis*- and *trans*-form.[6a−c] It causes chocolate spot disease on *Vicia faba* and displays cytotoxic effects.[7] Both **4** and **9** have been proposed to be biosynthesized in melanin-producing fungi involving **1** as their precursor (Scheme 1).[1] Based on the study of mutant fungi and shunt metabolites isolated, Bell and Wheeler have proposed a diversity-oriented biosynthesis, which starts with the oxidation of **1** to 2-hydroxyjuglone (**2**) followed by reduction to **4** via intermediate 1,2,4,5-tetrahydroxynaphthalene (**3**).[1]

Furthermore, **4** may undergo dehydration to give 1,4,5-$T_3$HN (**5**), which upon oxidation can result in the formation of 3-hydroxyjuglone (**7**). Similarly, reduction of **7** might give **9** via intermediate 1,2,4,8-tetrahydroxynaphthalene (**8**) (Scheme 1).[1a] To clarify the absolute configuration of **4** and **9** and to elucidate their biosynthesis, we have employed NADPH-dependent tetrahydroxynaphthalene reductase ($T_4$HNR) from

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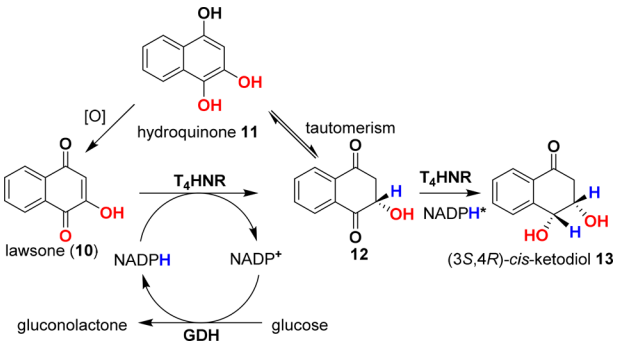
the plant-pathogenic fungus *Magnaporthe grisea* as a catalyst for the proposed reductions. Moreover, the enzyme was explored toward a variety of substrates which widened its application for the reduction of related compounds.

$T_4$HNR is one of the two naphthol reductases involved in the biosynthesis of DHN melanin. In its physiological reaction, it catalyzes the reduction of 1,3,6,8-tetrahydroxynaphthalene ($T_4$HN) to (*R*)-scytalone using NADPH as a cofactor (Scheme S4).[8a] $T_4$HNR has been used to catalyze the reduction of substituted tetralones, polyhydroxynaphthalenes, and hydroxynaphthoquinones such as flaviolin.[8a−c] Reduction of flaviolin to *cis*-4-hydroxyscytalone by $T_4$HNR established the role of this and related enzymes in the biosynthesis of *cis*-ketodiols.[8c] The work has been further expanded toward the synthesis of *trans*-4-hydroxyscytalone by combining $T_3$HNR with glucose dehydrogenase (GDH).[8d] A similar reduction of lawsone (2-hydroxy-1,4-naphthoquinone, **10**) as a model substrate provided the mechanistic details (Scheme 2).

**Scheme 2. $T_4$HNR-Catalyzed Reduction of Lawsone (10) to (3*S*,4*R*)-3,4-Dihydroxy-1-tetralone (13)[8e]**

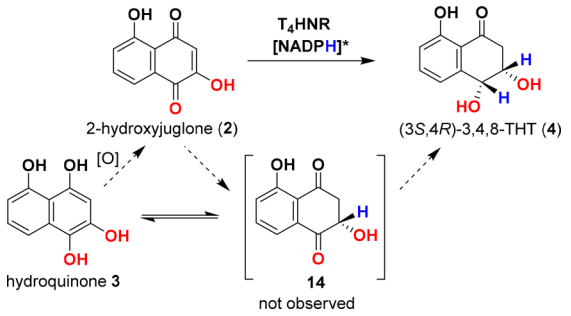



Reduction has been shown to involve two steps, with 1,4-diketo compound **12** as a surprisingly stable intermediate (Scheme 2). **12** can either tautomerize to hydroquinone **11** and then be oxidized back to lawsone, resulting in a redox cycle, or undergo further reduction to *cis*-ketodiol **13** catalyzed by $T_4$HNR in the presence of NADPH. (3*S*,4*R*)-3,4-Dihydroxy-1-tetralone (**13**) was obtained in 90% yield with a diastereomeric ratio ($dr_{cis/trans}$) of 99:1, and >99% ee.[8e] The other naphthol reductase enzyme, $T_3$HNR from *M. grisea*, which catalyzes the reduction of **1** to (*R*)-vermelone, did not catalyze this transformation (see Scheme S4).[8d]

This prompted us to test if $T_4$HNR and $T_3$HNR from *M. grisea* can be used for the synthesis of **4** and **9** from the appropriate 2-hydroxynaphthoquinone substrates. $T_4$HNR and $T_3$HNR genes cloned into the pET19b vector were overexpressed in *E. coli* BL21 (DE3) to obtain $T_4$HNR-his and $T_3$HNR-his.[8a,d] These were used as cell-free extracts or after purification using Ni-NTA affinity chromatography (see Supporting Information). Next, we synthesized the assumed naphthoquinone substrates for the proposed enzymatic reduction, namely, **2** and **7** (see Supporting Information).[9] Incubation of **2** with $T_4$HNR in the presence of NADPH (regenerated through glucose/GDH system) in potassium phosphate buffer (50 mM, 1 mM EDTA, 1 mM DTT, pH 7.0) for 24 h under anoxic conditions showed 60% conversion toward **4** (determined by $^1$H NMR spectroscopy). On purification, we obtained the desired product **4** in 42% yield. Nevertheless, the diketo intermediate **14** was not observed in the $T_4$HNR-catalyzed reduction of **2**, even when the reaction was performed for a short period of time (4 h) and analyzed by $^1$H NMR spectroscopy and TLC.

This could be due to a rapid conversion of the expected diketo intermediate **14** toward its hydroquinone **3** followed by its oxidation back to **2**, resulting in an incomplete conversion toward the ketodiol product **4**. Although **14** could not be observed, the reduction of **2** to **3** by $T_4$HNR (Scheme 1) might involve a diketo intermediate **14**, which could be responsible for the formation of **4** during biosynthesis (Scheme 3).[1c]

**Scheme 3. $T_4$HNR-Catalyzed Reduction of 2-Hydroxyjuglone (2) to (3*S*,4*R*)-3,4,8-Trihydroxytetralone (4)**




*NADPH was regenerated using glucose/GDH.

We assigned the absolute configuration of **4** as (3*S*,4*R*) by comparing the CD spectra of **4** with that of **13** obtained from the reduction of **10** catalyzed by $T_4$HNR (Figure S2). Moreover, the optical rotation of the purified compound **4** ($[\alpha]_D^{25}$ = −36 (methanol)) matches exactly with that of the natural product isolated from *Pyricularia oryzae*.[2a] This unambiguously confirms the (3*S*,4*R*) stereochemistry of **4** and also supports similar biogenesis in fungi involving the reduction of **2** by $T_4$HNR or related enzymes (Scheme 2). In contrast, no reduction of **2** was observed by $T_3$HNR-his, discarding a role of this enzyme in the biosynthesis of **4**.

Next, we used **7** as a substrate for enzymatic reduction. Based on our previous results, we expected the formation of *cis*-ketodiol **16**. Compound **16** has been isolated from *P. diversum* along with **9**, hinting for similar transformation during the biosynthesis of the two secondary metabolites.[6a]

However, incubation of **7** with $T_4$HNR for 24 h in potassium phosphate buffer (50 mM, 1 mM EDTA, 1 mM DTT, pH 7.0) and NADPH (regenerated through glucose/GDH system) under anoxic conditions resulted in an incomplete conversion with the formation of three major products as analyzed by $^1$H NMR spectroscopy. Ketodiol **9** was isolated as a mixture of *cis* and *trans* with a $dr_{cis/trans}$ of 82:18 in 38% yield (Scheme 4). A small amount of *cis*-ketodiol **9** was purified by crystallization and characterized NMR spectroscopy and mass spectrometry (Supporting Information). Further investigations led to the isolation of a diketo intermediate (**15**), similar to **12**. **15** has not been isolated, chemically synthesized, nor proposed in any biosynthetic pathways. Nevertheless, it might be formed during the biosynthesis of secondary metabolites such as **9** and **16**. Incubation of **7** with $T_4$HNR for a shorter time (4 h) resulted in 87% yield of intermediate **15**, which proved to be even more stable than **12**. This may be due to the intramolecular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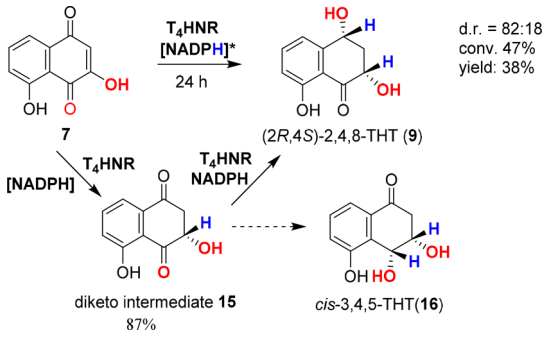
**Scheme 4. $T_4$HNR-Catalyzed Reduction of 3-Hydroxyjuglone (7) to 15 and 9**




*NADPH was regenerated using glucose/GDH.

hydrogen bonding between the keto group and the phenolic hydroxyl group, as shown by the chemical shift of the phenolic proton to $\delta$ 12.4 ppm (Scheme S7). It prevents the enolization of the ketone and hence the aromatization of **15** toward hydroquinone **8**, which has been proposed as the biosynthetic precursor for the formation of **9** (Scheme 1)[1a] The absolute configuration of **15** was determined to be (*S*) by comparison of the CD spectra of intermediates **12** and **15** (Figure S3). The absolute configuration of the diketo intermediate **12** has been assumed to be (*S*) based on the (3*S*,4*R*)-configuration of **13**, which has been assigned through VCD spectroscopy.[8c] Testing of **7** as a substrate with $T_3$HNR-his did not result in any product formation and hence rules out the involvement of this enzyme in the biosynthesis of **9**. Although both $T_4$HNR and $T_3$HNR of *M. grisea* catalyze the reduction of polyhydroxynaphthalenes using NADPH, they show only 46% sequence identity with each other. The interaction of sulfur atom of the C-terminal Met283 residue of $T_3$HNR has been proposed to be the reason for substrate discrimination, which might be responsible for no activity of this enzyme toward hydroxynaphthoquinones.[10]

To further explore the putative substrate range of the two naphthol reductases in the reduction of alkenones, we tested differently substituted naphthoquinone compounds **17** and **19**–**25** as possible substrates for the enzymatic reduction system. Recent isolation of teratosphaerones A (**17**) and teratosphaerones B (**18**) from the fungus *Teratosphaeria* sp. FL2137, which is associated with *Pinus clausa*, hinted the involvement of a reductase that may reduce both an alkene and a keto bond.[11] This motivated us to test $T_4$HNR for the reduction of **17** using NADPH. We synthesized **17** and incubated it with $T_4$HNR and with $T_3$HNR under conditions similar to those used for the reduction of hydroxynaphthoquinones for 24 h (see Supporting Information) (Figure 1). However, neither **18** nor any monoreduced intermediate was found in the reaction mixture.

We tested menadione (**19**), plumbagin (**20**), 2-methoxy-1,4-naphthoquinone (**21**), 2-methoxyjuglone (**22**), chloro-substituted naphthoquinones **23** and **24**, and methyl-substituted 2-hydroxy-3-methyl-1,4-naphthoquinone (**25**) with $T_4$HNR and $T_3$HNR (for the synthesis of **17** and **21**–**25**, see Supporting Information) (Figure 1). However, none of the substrates was reduced by any of the two enzymes, implying the involvement of another reductase of the short-chain dehydrogenase/reductase family for reducing such enone bonds. This also indicates the requirement of a hydroxyl

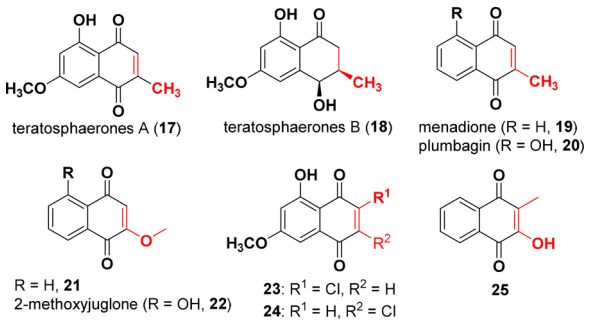
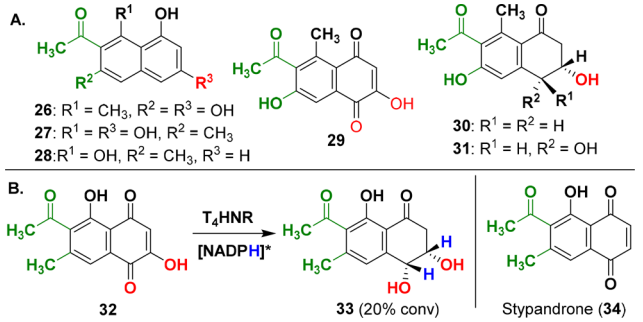



**Figure 1.** Substituted naphthoquinones not accepted as substrates by the two naphthol reductases $T_4$HNR and $T_3$HNR.

group at position **2** of a naphthoquinone for a substrate to be accepted by NADPH-dependent $T_4$HNR, as in the case of **2** and **7**. This motivated us to test an additional substrate with substitution on the aromatic ring. Previously, we showed the stereoselective reduction of substituted trihydroxynaphthalene **26** and its oxidized hydroxynaphthoquinone **29** by $T_4$HNR using NADPH to a natural polyketide, (*R*)-GTRI-02 (**30**)[12] and (3*S*,4*R*)-ketodiol **31**, respectively (Scheme 5).[8b,c]

**Scheme 5. (A) Polyketidic Substrates (26–29) and Products Formed Using $T_4$HNR (30 and 31)[8c] and (B) $T_4$HNR-Catalyzed Reduction of 32 to 33 and a Natural Product Stypandrone (34)**




*NADPH was regenerated using glucose/GDH.

We hypothesized that the naturally occurring 6-hydroxymusizin (**27**) may also be reduced by $T_4$HNR and might be involved in the biosynthesis of its deoxygenated derivative musizin (**28**), also called nepodin. Compound **28** has been isolated from several fungal species and displays useful biological activities.[13] We synthesized **27** and incubated it with $T_4$HNR or $T_3$HNR in the presence of NADPH (generated using glucose/GDH system) (Supporting Information). However, no reduction of **27** was observed. Knowing the ability of $T_4$HNR to reduce hydroxynaphthoquinones, we oxidized **27** using $K_2CO_3$ in DMF to obtain naphthoquinone **32** in 80% yield (Supporting Information). Incubation of **32** with $T_4$HNR and NADPH gave the expected *cis*-ketodiol **33** in 20% isolated yield, whereas $T_3$HNR did not catalyze this transformation. The absolute configuration for **33** was assigned based on the comparison of CD spectra with *cis*-ketodiol **13** obtained from the enzymatic reduction of **10**. Biocatalytic synthesis of **33** using $T_4$HNR might lead to the formation of a toxic naphthoquinone, stypandrone (**34**), isolated from *Stypandra imbricata* and *Dianella revoluta*.[14a,b] Biosynthetic conversion of **33** to **34** should involve dehydration and an



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oxidation step. Alternatively, a monoreduced diketo intermediate in the reduction of **32** is dehydrated to **34**.

$T_4$HNR of *M. grisea* catalyzes the reduction of a number of 2-hydroxynaphthoquinones such as **10**, **2**, **7**, **29**, and **32**. We propose the involvement of this and related enzymes in the biosynthesis of further dihydroarenediols such as nodulones. Nodulones are a class of naphthalenones with a *cis*- or *trans*-ketodiol substructure (**35**−**41**). They have been isolated from endophytic fungi and display a diverse array of biological activities (Figure 2).[15−20]

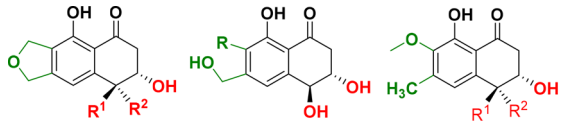


**Figure 2.** Various secondary metabolites from fungi with *cis*- and *trans*-ketodiol substructures.

In conclusion, we reported a regio- and stereoselective biomimetic, chemoenzymatic synthesis of natural products containing *cis*-ketodiol substructure, which are prone to water elimination due to the presence of *β*-hydroxy ketone group and are otherwise difficult to synthesize using purely nonenzymatic methods. Isolation of a new diketo intermediate, **15**, supports the two-step enzymatic reduction of 3-hydroxyjuglone, during biosynthesis. Moreover, unsuccessful reduction of alkenone substrates (**17**, **19**−**25**) indicates the requirement of a hydroxynaphthoquinone scaffold for the reduction by the naphthol reductases. The concept was successfully applied toward the reduction of substituted hydroxynaphthoquinone **32**, giving *cis*-ketodiol **33** that might be involved in the biosynthesis of stypandrone. We propose the involvement of $T_4$HNR or related enzyme in the (bio)synthesis of other dihydroarenediols such as nodulones **35**−**41**. This may give straightforward access to a variety of *cis*- and *trans*-ketodiols in a biomimetic fashion.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00500.

Protein expression and purification, experimental details, characterization data, copies of NMR spectra, and CD spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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