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A copper-catalyzed asymmetric oxime propargylation enables the synthesis of the gliovirin tetrahydro-1,2-oxazine core†

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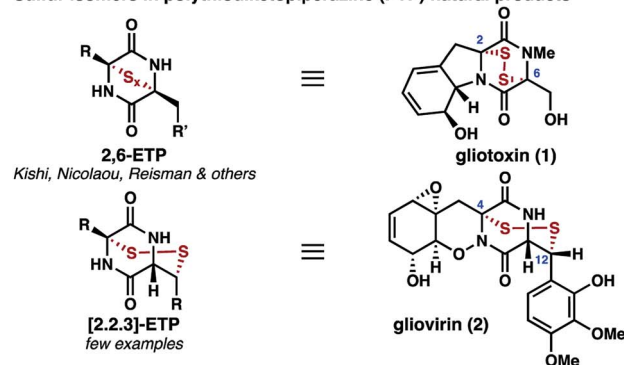
The bicyclic tetrahydro-1,2-oxazine subunit of gliovirin is synthesized through a diastereoselective copper-catalyzed cyclization of an *N*-hydroxyamino ester. Oxidative elaboration to the fully functionalized bicycle was achieved through a series of mild transformations. Central to this approach was the development of the first catalytic, enantioselective propargylation of an oxime to furnish a key *N*-hydroxyamino ester intermediate.

The fungal secondary metabolites gliovirin (**2**)¹ and pretrichodermamides A (**3**)² and E (**4**)³ are disulfide antibiotics that possess an unusual tetrahydro-1,2-oxazine (THO) core (Scheme 1). In addition to **2–4**, several related oxazine natural products have been isolated, including the monothiolated peniciadametizine B (**5**);⁴ however, these oxazine-containing natural products are rare relative to the biosynthetically related diketopiperazine natural products, hundreds of which have been isolated to date.⁵ In addition to their oxazine cores, **2–4** are unusual in that their disulfide linkages are joined to the carbon framework at C4 and C12, in contrast to the more common epipolythiodiketopiperazines (ETPs) such as gliotoxin (**1**).⁶ These fungal metabolites are proposed to be formed through thiolation of simple cyclic dipeptides followed by oxidative elaboration of the peripheral functionality.⁷ Perhaps because of the synthetic challenge posed by the combined oxazine and disulfide motifs, there have been no syntheses of gliovirin (**2**) or the related compounds **3** and **4** to date.

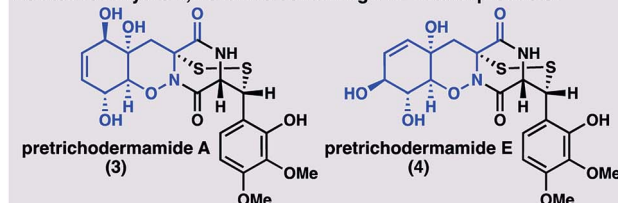
Whereas there are no syntheses of **2**, syntheses of related dihydro-1,2-oxazine (DHO) natural products, including trichodermamide A (**6**), have been reported by the groups of Joullie,⁸ Zakarian,⁹ and Larionov.¹⁰ These efforts relied upon cycloaddition chemistry or pericyclic rearrangement to install the DHO cores. As part of our larger program targeting the synthesis of polysulfide natural products,^{11,12} we envisioned a distinct approach to **2** that would involve late-stage diketopiperazine

and disulfide formation, thereby reducing the synthetic challenge to that of preparing key THO **7** (Scheme 2). Oxazine **7** was expected to be accessible from **8a** via epoxidation, desaturation, and functional group interconversion.

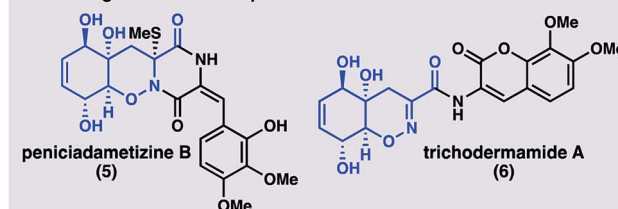
Sulfur isomers in polythiodiketopiperazine (PTP) natural products



Related tetrahydro-1,2-oxazine-containing PTP natural products:



Related degradative natural products:

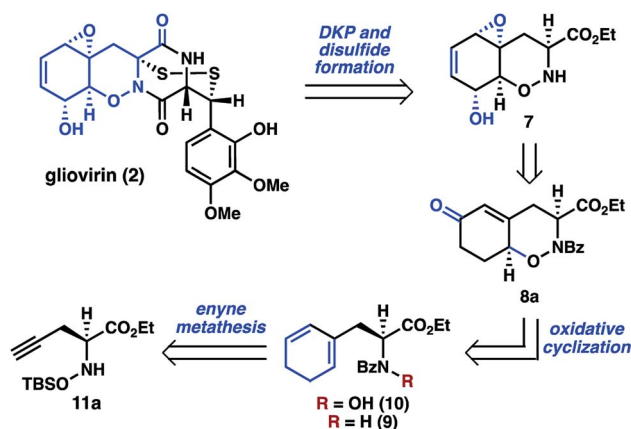


Scheme 1 PTP isomerism: gliovirin and related natural products.

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Scheme 2 Retrosynthetic analysis of tetrahydro-1,2-oxazine 7.

In a key synthetic step, the bicyclic THO **7** would be constructed by an intramolecular oxidative cyclization of *N*-hydroxydihydrophenylalanine derivative **10**. For the preparation of **10**, we considered two approaches: (1) *N*-oxidation of the corresponding dihydrophenylalanine **9**, or (2) initial installation of the N–O bond followed by construction of the cyclohexan-1,3-diene from the alkyne of **11a**. Given concerns about potential challenges of *N*-oxidation in the presence of the sensitive 1,3-cyclohexadiene motif, we elected to pursue a route where **10** would be accessed from α -propargyl *N*-hydroxyamino acid **11a** by an enyne metathesis reaction.

Having identified **11a** as an intermediate en route to **7**, a method to prepare this compound in enantioenriched form was desired. The most direct route to **11a** was envisioned to be an enantioselective propargylation of *N*-siloxyglyoxalate **12** (see Table 1). However, no examples of catalytic asymmetric addition of allyl nor propargyl nucleophiles to similar oxime substrates were found in the literature. The most promising lead was from Hanessian and coworkers, in which an excess of a chiral allylzinc reagent was added to an oxime.¹³ However, this method had not been extended to the corresponding propargylation.

Although there was no direct precedent for the catalytic asymmetric propargylation of oximes, we were inspired to

pursue this approach by recent studies describing Cu-catalyzed asymmetric propargylation of imines.^{14–16} We began by investigating the ability of chiral Cu complexes to catalyze the reaction between glyoxalate-derived oxime **12b** and allenyl boronate **13a**. Bidentate bisphosphines gave promising levels of enantioinduction, although the reactions produced **11b** in very low yield (Table 1, entries 1–2).¹⁷ In comparison, monodentate phosphoramidite ligands (e.g. **L3**) provided **11b** in improved yield, but with modest enantioselectivity (entry 3).

We hypothesized that the improved yield observed with the use of phosphoramidite ligands resulted from their increased ability to act as π -acceptors.¹⁸ It was envisioned that electron-deficient bis-phosphines would combine the benefits of greater π -acceptor ability to increase catalyst turnover while retaining the conformational rigidity of a bidentate ligand to promote asymmetric induction.¹⁹ Consistent with this hypothesis, fluorinated, commercially available, bisphosphines including DIFLUORPHOS (**L4**, entry 4) and BTFM-GARPHOS (**L5**, entry 5) both gave higher yields of **11b**, while also improving the enantioinduction.

In contrast to many metal-catalyzed cross-coupling reactions of boronates, a series of control experiments demonstrated that co-catalytic base was not required, and in fact, omitting base from the reaction led to an improvement in yield and ee (entry 6, Table 1). Use of neopentyl boronate **13b** further improved the yield. Although ester **12b** was used for the optimization process (due to the aryl UV chromophore aiding ee assay development), for the purpose of the synthesis, ethyl ester **11a** was accessed in similarly high yield and ee from *N*-siloxyglyoxalate **12a** (Scheme 3).

Concomitant to the development of the enantioselective propargylation shown in Table 1, we investigated the elaboration of compound **14**, as a racemate, to oxazine **7**. Initial attempts to generate the desired 1,3-cyclohexadiene **15a** through enyne metathesis proceeded in low yield due to catalyst deactivation and alkyne oligomerization; however, slow addition of **14** to a solution of 1,5-cyclooctadiene and second generation Hoveyda–Grubbs catalyst (Mes-HGII) in benzene produced the desired product, **15**, in excellent yield (Scheme 3).²⁰

With access to *N*-hydroxydihydrophenylalanine derivative **15a**, we investigated the formation of the THO motif by an oxidative cyclization. The intramolecular oxidative radical addition of hydroxamic acids to generate cyclic hydroxamates was first observed by Perkins²¹ and later systematically studied by Alexanian.^{22–24} Furthermore, during the course of our work, the intermolecular addition of phthalimide *N*-oxyl radical (PINO) to activated alkenes was reported to be initiated by base metal catalysis, visible light, or conventional radical initiators.^{25–28} While this reactivity encouraged us, there were three issues that remained uncertain: (a) the regioselectivity of cyclization across the diene (i.e. 5-*exo* vs. 6-*endo*); (b) the diastereoselectivity of the C–O bond formation with respect the adjacent stereocenter; and (c) whether *N*-alkylhydroxamic acids would engage in similar reactivity previously observed in *N*-arylhydroxamic acids. With our cyclization substrate **15a** in hand we found that following *in situ* deprotection, silica-mediated autooxidation provided a mixture of allylic hydroperoxides **16** which could be converted to the corresponding

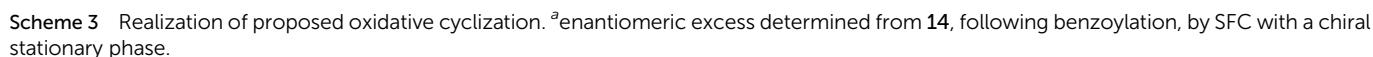
Table 1 Optimization of Cu-catalyzed oxime propargylation^a

Entry	B(OR ²) ₂	[Cu], L	Yield ^b (%)	ee ^c (%)
1	Bgly (13a)	Cu(CO ₂ <i>i</i> -Pr) ₂ , L1 ^d	2	63
2	Bgly (13a)	Cu(MeCN) ₄ BF ₄ , L2 ^d	7	72
3	Bgly (13a)	Cu(MeCN) ₄ BF ₄ , L3 ^d	70	30
4	Bgly (13a)	Cu(MeCN) ₄ BF ₄ , L4 ^d	11	80
5	Bgly (13a)	Cu(MeCN) ₄ BF ₄ , L5 ^d	24	82
6	Bgly (13a)	Cu(MeCN) ₄ BF ₄ , L5	30	95
7	Bgly (13a)	[Cu(L5)(MeCN) ₂]BF ₄	50	92
8	Bneo (13b) ^e	[Cu(L5)(MeCN) ₂]BF ₄	87	96

^a Reactions conducted under inert atmosphere on 0.05 mmol scale for 24 h. ^b Determined by ¹H NMR versus an internal standard.

^c Determined by SFC using chiral stationary phase. ^d Li(Ot-Bu) (9.5 mol%) was added to the reaction. ^e 2.0 equivalents used in place of 1.4 equivalents.





Taken together, these data might suggest that **20a** and **20b** can interconvert through an unusual vinylogous Payne rearrangement under Lewis acidic conditions.³⁸ Finally, chemoselective cleavage of the *N*-benzoyl protecting group revealed **22**,³⁹ our desired substrate for subsequent late stage diketopiperazine formation and thiolation.

Conclusions

In conclusion, an approach to the bicyclic THO subunit of gliovirin (**22**) is reported. As part of these studies, a Cu-catalyzed asymmetric propargylation of a glyoxylate-derived oxime **12** was developed to prepare enantioenriched α -propargyl hydroxylamino acid **11**. The key oxazine motif was formed through a mild, Cu-catalyzed, intramolecular oxidative cyclization, which demonstrates that simple *N*-acyl hydroxamic acids can undergo a diastereoselective cyclization with dienes. Although the early introduction of the heterocyclic oxazine motif was initially viewed as an advantage of this synthetic approach, it ultimately proved to be a liability. In particular, compounds **17–22** were found to be acutely sensitive to base and acid, likely resulting from facile elimination to cleave the N–O bond.⁴⁰ This study may serve to guide future work targeting the realization of the total synthesis of gliovirin and related THO natural products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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