JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Concise Total Synthesis of Trichodermamides A, B, and C Enabled by an Efficient Construction of the 1,2-Oxazadecaline Core

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Supporting Information

ABSTRACT: We report herein a facile and efficient method of the construction of the *cis*-1,2-oxazadecaline system, distinctive of (pre)trichodermamides, aspergillazine A, gliovirin, and FA-2097. The formation of the 1,2-oxazadecaline core was accomplished by a 1,2-addition of an α*C*-lithiated *O*-silyl ethyl pyruvate oxime to benzoquinone, which is followed by an oxa-Michael ring-closure. The method was successfully applied to the concise total synthesis of trichodermamide A (in gram quantities) and trichodermamide B, as well as the first synthesis of trichodermamide C.

The 1,2-oxazadecaline framework is a recurring structural motif of a number of secondary metabolites produced by terrestrial and marine fungi. Examples include trichodermamides A, B, and C (**1**−**3**) from *Trichoderma virens* (A[1,2] and B[1a]) and *Eupenicillium* sp. (C),[3] aspergillazine A (**4**) from *Aspergillus unilateralis*,[4] the unusual seven-membered epidithiodiketopiperazines pretrichodermamide A (**5**) from *Trichoderma*[5] and *Aspergillus*[6] *spp.*, *N*-methylpretrichodermamide B (**6**) and pretrichodermamide C (**7**) from *Penicillium sp.*,[7] gliovirin (**8**) from *Trichoderma virens*,[8] and FA-2097 (*N*-methylgliovirin, **9**) from *Eupenicillium abidjanum*.[9] In addition, the structurally related aspergillazines B−E (**10**−**13**) from *A. unilateralis* are presumed to arise from the reductive N−O bond cleavage of aspergillazine A (for B and C) and trichodermamide A (for D and E).[4] The structural similarity and coisolation of aspergillazines, trichodermamides, pretrichodermamides, and gliovirin, as well as the facile conversion[5] of **5** to **1**, suggest a common biogenetic origin of the naturally occurring 1,2-oxazadecalines.[10] The bioactivity of these fungal metabolites remains largely unexplored, primarily due to their scarcity. However, preliminary data attest to their potential as lead compounds for antibiotic and anticancer drug discovery that would be enabled by an efficient synthetic access. For example, gliovirin is a potent inhibitor of the expression of pro-inflammatory enzymes (COX-2, iNOS) and cytokines (TNF-α, IL-2) in T-cells and monocytes/macrophages[11] and was linked to the efficacy of *T. virens* as a commercial biocontrol agent of several pathogenic fungi.[12] FA-2097 (**9**) is highly active against several drug-resistant anaerobic bacteria, especially *Fusobacterium* and *Bacteroides* spp. Both trichodermamides B and C were shown to display significant cytotoxicity toward the human colorectal carcinoma HCT116 cells (IC_{50} = 0.32 and 0.68 μg/mL, respectively). Significant cytotoxicity was also reported for *N*-methylpretrichodermamide B. Curiously, trichodermamide A was shown to be completely inactive, indicating that C6-chloro and *N*-methyl groups may be important for the activity of these compounds.

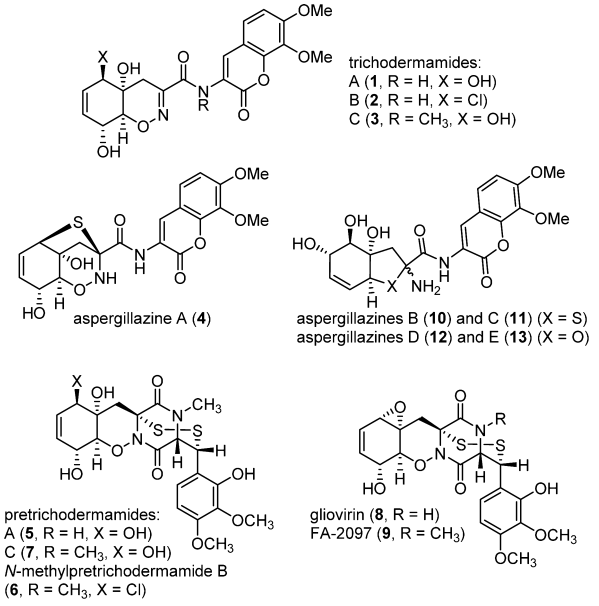


Figure 1. 1,2-Oxazadecaline fungal metabolites.

A notable structural feature common to trichodermamides, pretrichodermamides, and gliovirins is the unique and highly functionalized 1,2-oxazadecaline core containing four contiguous stereogenic centers. The synthetically challenging structure and the promising biological activity have attracted significant attention to these secondary metabolites,[13] albeit only trichodermamides A and B have been synthesized to date, by Zakarian and Lu (B),[14] employing the oxaza-Cope rearrangement,[15] and by Joulié and Wan (A and B), stereospecifically from (−)-quinic acid.[16]

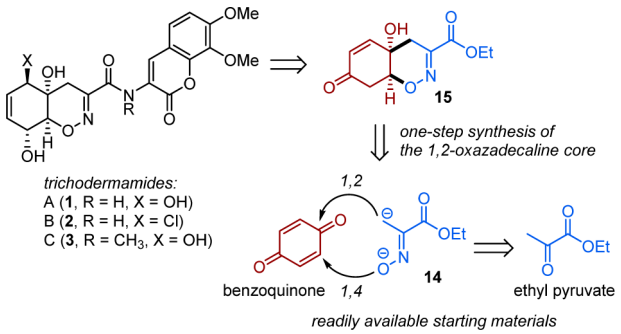
Herein, we report a novel, scalable approach to the construction of the 1,2-oxazadecaline ring system and its application to the concise total synthesis of trichodermamides A, B, and C. We envisioned that the synthesis of trichodermamides and the related natural products can be greatly simplified by developing an early stage 1,2-oxazadecaline core synthesis comprising a 1,2-addition of the *C*-terminus of the dianionic synthon **14** to benzoquinone, followed by an intramolecular oxa-Michael ring-closure en route to cis-fused

Received: May 19, 2015
Published: June 18, 2015

DOI: 10.1021/jacs.5b05205
J. Am. Chem. Soc. 2015, 137, 8050−8053

bicyclic enone **15** (Scheme 1). Although such a synthesis of the cis-fused 1,2-oxazadecaline system has not, to our knowledge,

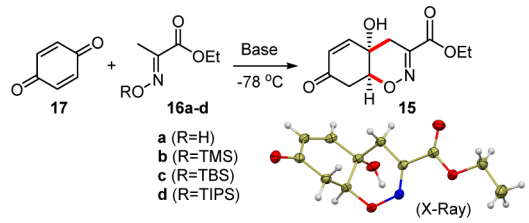
Scheme 1. Retrosynthetic Analysis of Trichodermamides



been reported in the literature, the precedents of 1,2-addition of αC-mono- and αC,O-bislithiated acetophenone oximes to ketones,[17] the efficiency of this approach, and the ready availability of benzoquinone and ethyl pyruvate made it an attractive direction for investigation.

Our initial experiments were met with limited success, as ethyl pyruvate oxime (**16a**) and benzoquinone (**17**) did not produce enone **15** under a variety of reaction conditions (Table 1). We

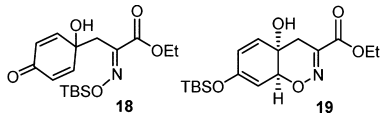
Table 1. Construction of the 1,2-Oxazadecaline Core of Trichodermamides from Benzoquinone and Ethyl Pyruvate Oximes 16a–d



entry	oxime	base	yield (%)[a]
1	**16a**	LDA	
2	**16a**	LHMDS	
3	**16a**	LiTMP	
4	**16b**	LiTMP	
5	**16c**	LiTMP	92
6[b]	**16c**	LiTMP	34
7[c]	**16c**	LiTMP	88
8	**16c**	KHMDS	11
9	**16c**	LiHMDS	6
10	**16d**	LiTMP	<5

[a]Reaction conditions: oxime **16** (1 mmol), **17** (1 mmol), base (2 equiv), THF (c = 0.16M), −78 °C. [b]1 equiv of LiTMP was used. [c]Reaction was carried out on a 40.8 mmol (10 g of oxime **16c**) scale.

then turned our attention to *O*-silyl oximes **16b–d**. While *O*-TMS and *O*-TIPS oximes **16b** and **16d** were ineffective, *O*-TBS oxime **16c** afforded enone **15** in 92% yield with 2 equiv of LiTMP and in 34% yield with 1 equiv of LiTMP (entries 5 and 6), indicating that 2 equiv of base was required to overcome the coordination of the lithium base to the oxime.[17d] LiTMP proved to be the base of choice, as no or very little product was observed with other bases. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy prior to quenching with acetic acid revealed the presence of quinol **18** and silyl enol ether **19**, along with enone **15**, suggesting that **18** and **19** may be intermediates en route to **15**. The structure of enone **15** was confirmed by a single crystal X-ray crystallographic analysis. Further, the reaction was successfully scaled up to 10 g of oxime **16c**, setting the stage for the synthesis of trichodermamides.

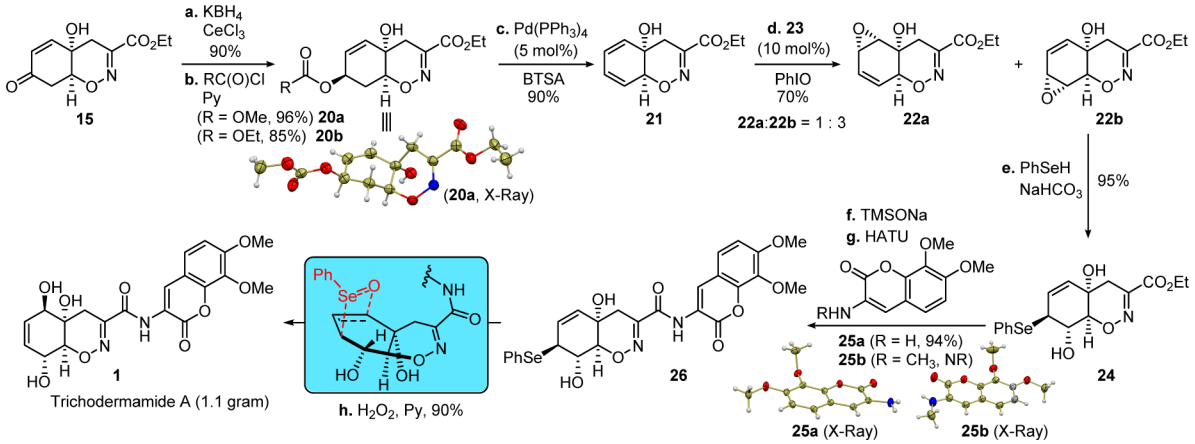


Our synthesis of trichodermamide A commenced from enone **15**, which was subjected to a modified Luche reduction that, under the optimized conditions, was carried out with potassium borohydride to improve the stereoselectivity and in the presence of acetic acid to suppress polymerization of the allylic alcohol (Scheme 2). Methyl and ethyl carbonates **20a** and **20b** were then prepared in 96% and 85% yields. The trans-configuration of the 1,4-dioxyalkene unit was confirmed by single crystal X-ray crystallographic analysis of **20a**. Treatment of carbonate **20b** with 5 mol % $Pd(PPh_3)_4$ in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BTSA)[18] delivered dienol **21** in 90% yield. Installation of the critical C9−OH stereocenter necessitated a regio- and stereoselective epoxidation of the distal double bond of the dienol. While 10 mol % $Ti(OiPr)_4$/*t*BuOOH afforded a 10:1 ratio of the proximal and distal epoxides **22a** and **22b**, a 1:1 ratio was observed with 10 mol % $VO(acac)_2$/$PhCMe_2OOH$. After additional optimization a 1:3 ratio of the proximal and distal epoxides **22a** and **22b** was obtained with 10 mol % *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-ethylenediaminomanganese(III) chloride (**23**) and iodosobenzene. The epoxidation occurred with complete stereoselectivity at the less hindered convex face of the dienol. The distal epoxide **22b** was converted to selenide **24** in a high yield (95%) on treatment with phenylselenol and $NaHCO_3$. The sensitivity of selenide **24** to acid and base necessitated saponification under mild conditions. Ultimately, we found that exposure of **24** to sodium trimethylsilanolate[19] followed by careful neutralization with MsOH resulted in a clean cleavage of the ethyl ester. The subsequent amide coupling with aminocoumarin **25a** was affected by HATU in the presence of *sym*-collidine in a high yield. Surprisingly, the related *N*-methylaminocoumarin **25b** proved resistant to amide coupling under a variety of conditions, indicating that an alternative strategy would be required for the synthesis of trichodermamide C. Oxidation of amide **26** to intermediate selenoxide triggered the [2,3]-sigmatropic rearrangement[20] that delivered trichodermamide A (**1**) in a high yield. The brevity of the synthetic route enabled preparation of 1.1 g of trichodermamide A in eight steps from enone **15** without the use of protecting groups and with only two chromatographic purifications. The selenoxide [2,3]-sigmatropic rearrangement was previously used by Zakarian and Lu in their synthesis of trichodermamide B.[14]

We next turned our attention to trichodermamides B and C (Scheme 3). Amide **27** that was envisioned as a common intermediate for both synthetic targets was accessed by a sequence of the ethyl ester cleavage with TMSONa and a HATU-mediated amide coupling with aminocoumarine **25a**. A completely regio- and diastereoselective epoxidation of the proximal C6−C7 double bond with peracetic acid delivered epoxide **28** in a nearly quantitative yield. Curiously, $Pd(PPh_3)_4$-catalyzed reaction of epoxide **28** with phenylselenol proceeded with overall inversion of configuration and afforded the undesired *trans*-selenohydrin **29** in a 96% yield, contrary to the

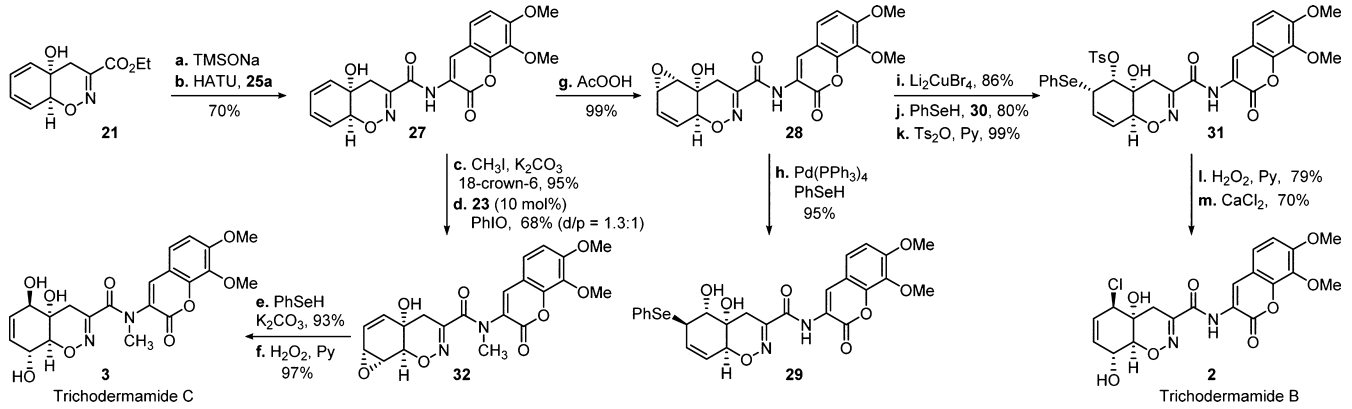
DOI: 10.1021/jacs.5b05205
J. Am. Chem. Soc. 2015, 137, 8050−8053

Scheme 2. Synthesis of Trichodermamide A[a]



[a]Reagents and conditions: a. KBH_4, $CeCl_3$, AcOH/THF (1:1), 0 °C; b. MeOC(O)Cl or EtOC(O)Cl, pyridine, PhMe/CH_2Cl_2 (2:1); c. $Pd(PPh_3)_4$ (10 mol %), *N,O*-bis(trimethylsilyl)acetamide (BTSA), PhMe; d. *N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-ethylenediaminomanganese(III) chloride (**23**) (10 mol %), PhIO, cyclohexane/$PhCF_3$ (1:1); e. PhSeH, $NaHCO_3$, THF, 0 °C; f. TMSONa, CH_2Cl_2, 3 Å MS, then MsOH; g. **25a** or **25b**, HATU, *sym*-collidine, DMF; h. H_2O_2, pyridine, THF, 0 °C.

Scheme 3. Synthesis of Trichodermamides B and C[a]



[a]Reagents and conditions: a. TMSONa, CH_2Cl_2, 3 Å MS, then MsOH, MeOH; b. **25a**, HATU, *sym*-collidine, DMF; c. MeI, 18-crown-6, K_2CO_3, acetone, 40 °C; d. *N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-ethylenediaminomanganese(III) chloride (**23**) (10 mol %), PhIO, CH_2Cl_2; e. PhSeH, K_2CO_3, THF, 0 °C; f. H_2O_2, pyridine, THF, 0 °C; g. AcOOH, $NaHCO_3$, CH_2Cl_2; h. $Pd(PPh_3)_4$ (10 mol %), PhSeH, PhMe; i. Li_2CuBr_4, THF; j. PhSeH, 1,8-bis(dimethylamino)naphthalene (Proton Sponge, **30**), THF, 0 °C; k. Ts_2O, pyridine, 0 °C; l. H_2O_2, pyridine, THF, 0 °C; m. $CaCl_2$, DMSO.

observed retention of configuration in the Pd-catalyzed reaction of phenylselenol with an unhindered allylic carbonate.[21] Epoxide **28** was, therefore, first treated with Li_2CuBr_4 to give the corresponding *trans*-bromohydrin that, on treatment with phenylselenol and 1,8-bis(dimethylamino)naphthalene (**30**) and subsequent tosylation, afforded the desired *cis*-selenotosylate **31** in a 68% yield over three steps. The selenoxide [2,3]-sigmatropic rearrangement was induced by the oxidation of selenide **31**. Finally, a nucleophilic displacement of the tosylate with $CaCl_2$ in DMSO afforded trichodermamide B (**2**) in 11 steps from ketone **15**.

For the synthesis of trichodermamide C, amide **27** was first subjected to the *N*-methylation that under the optimized conditions proceeded in 95% yield with iodomethane in the presence of 18-crown-6 and K_2CO_3. The Mn(salen)-catalyzed epoxidation of the distal C8−C9 double bond was followed by a trans-selective ring-opening of the intermediate distal allylic epoxide with phenylselenol. The oxidatively induced selenoxide rearrangement completed the first synthesis of trichodermamide C (**3**) in 9 steps from enone **15**.

In conclusion, we have developed a new gram-scale synthesis of the cis-fused 1,2-oxazadecaline enone **15** from readily available starting materials, ethyl pyruvate and benzoquinone, and successfully applied it to the short syntheses of trichodermamides A, B, and C. The strategies described herein should prove useful for the future synthesis of related 1,2-oxazadecaline natural products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental and spectral details for all new compounds and all reactions reported. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05205.

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DOI: 10.1021/jacs.5b05205
J. Am. Chem. Soc. 2015, 137, 8050−8053

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the NIGMS (SC3GM105579), the Welch Foundation (AX-1788), the Max and Minnie Tomerlin Voelcker Fund, and UTSA is gratefully acknowledged. Mass spectroscopic analysis was supported by a grant from the NIMHD (G12MD007591).

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DOI: 10.1021/jacs.5b05205
J. Am. Chem. Soc. 2015, 137, 8050−8053