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FEATURE ARTICLE

Oxazine ring construction: methods and applications to natural product synthesis

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Although natural products containing a 1,2-oxazine ring are rare, more examples in this family of natural products have been discovered since trichodermamides A and B were reported in 2003. In addition to their structural novelty, these natural products possess very interesting bioactivities that are strongly dependent on their structures, making them attractive targets for investigating structure-activity relationships (SAR). In this feature article, we summarized the methodologies developed in recent years for constructing the 1,2-oxazine rings. Racemic and enantioselective total syntheses of trichodermamides A and B, based on these methodologies, are reviewed in detail.

Keywords natural products, trichodermamides, 1,2-oxazine ring construction methodology, total synthesis

1 Natural products containing 1,2-oxazine rings

Although 1,2-oxazine (Figure 1, I) is a well-known intermediate for the synthesis of substituted pyrrolidines, piperidines, unnatural α-amino acids, and other organic compounds, its presence in natural products is rare. To our knowledge, only two classes of natural products possessing this unique structure have been discovered. In 1987, FR 900482 (Figure 1, IIa) was isolated from *Streptomyces sandaensis* No. 6897 as a mixture of two tautomers [1]. The compound contains a 1,2-oxazine as a hemiketal moiety. Its dihydro derivative FR 66979 was also isolated from the same strain (Figure 1, IIb). Both compounds showed promising antitumor activity. FK 973 and FK 317 (Figure 1, IIc and d) were obtained by chemical modification of FR 900482 in an effort to develop new drugs with reduced side effects and stronger antitumor activity. These compounds are structurally related to mitomycin C, a compound used in cancer therapy. The total syntheses of these natural products were reported by several groups, and will not be discussed in this feature article.

The trichodermamides (Figure 1, IIIa–c) represent the other class of natural products containing a 1,2-oxazine moiety. Trichodermamides A and B are modified dipeptides isolated as secondary metabolites from marine-derived fungal strains, *Trichoderma virens* CNL910 and CNK266, in 2003 [2]. More recently, trichodermamide C was isolated from a culture broth of the endophytic fungus *Eupenicllium* sp [3]. Aspergillazines A (Figure 1, IV) and its derivatives, a series of dipeptides co-occurring with trichodermamide A, were isolated from an Australian strain of *Aspergillus unilateralis* in 2005 [4]. Aspergillazine A may be considered as the sulfur-containing analogue of trichodermamides, in which the sulfur atom is incorporated into a more complicated tricyclic system. It was later found that trichodermamide A might be derived from pretrichodermamide A (Figure 1, V), a bridged epidithiodiketopiperazine discovered in 2006 [5]. Pretrichodermamide A resembles gliovirin, which was isolated in 1982 [6]. The only difference between the two compounds is that gliovirin has an epoxide moiety instead of a diol moiety at the ring junction position.

These products (from trichodermamides to gliovirin) share a very similar 1,2-oxazine core structure, which is incorporated into a highly oxygenated cyclohexene structure with contiguous stereocenters. It is believed that these compounds are biologically related. For instance, the coexistence of trichodermamide A and aspergillazines was observed by two different groups [4,7], and the conversion of pretrichodermamide A to trichodermamide A was also reported [5]. These compounds exhibit very interesting biological activities that are strongly dependent on their structures. A minor variation in structure leads to a dramatic change in bioactivity. For

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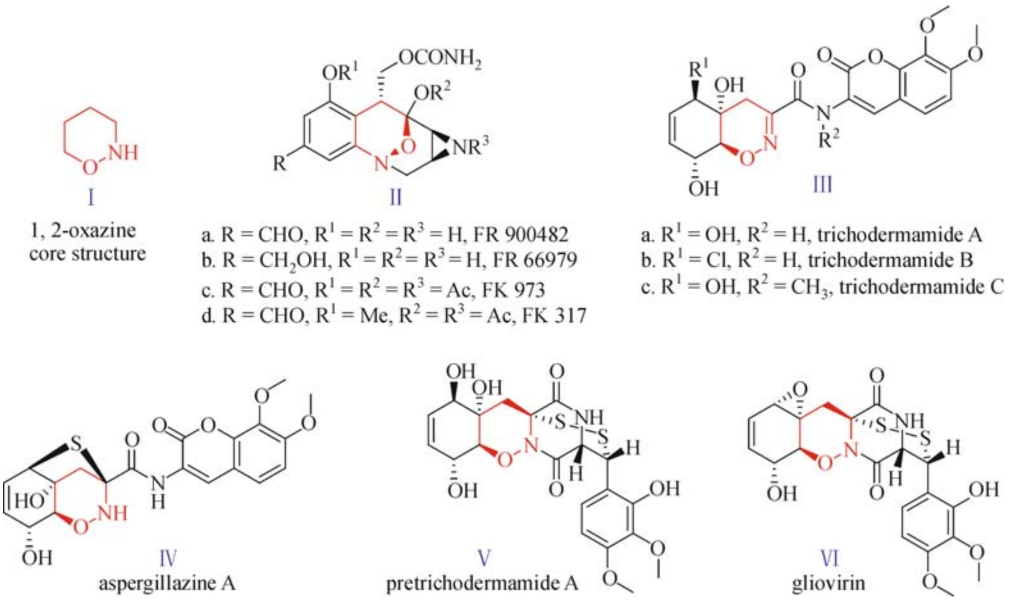


a. R = CHO, $R^1 = R^2 = R^3 = H$, FR 900482
b. R = CH_2OH, $R^1 = R^2 = R^3 = H$, FR 66979
c. R = CHO, $R^1 = R^2 = R^3 = Ac$, FK 973
d. R = CHO, $R^1 = Me$, $R^2 = R^3 = Ac$, FK 317

a. $R^1 = OH$, $R^2 = H$, trichodermamide A
b. $R^1 = Cl$, $R^2 = H$, trichodermamide B
c. $R^1 = OH$, $R^2 = CH_3$, trichodermamide C

Figure 1 Natural products containing the 1,2-oxazine core.

example, trichodermamide A showed only weak cytotoxicity against HL-60 cell line with an IC_{50} value of 89 μmol/L (38.5 μg/mL) [7] and remained inactive in other assays [2], while trichodermamide B displayed significant *in vitro* cytotoxicity against HCT-116 human colon carcinoma with an IC_{50} of 0.32 μg/mL [2]. The only structural difference between trichodermamides A and B is the replacement of a hydroxyl group at C-5 in A with a chlorine atom in B. Even more interestingly, trichodermamide C, which is the *N*-methylated derivative of trichodermamide A, exhibited similar cytotoxicity against HCT-116 human colon carcinoma (IC_{50} 0.68 μg/mL) as trichodermamide B [3]. Pretrichodermamide A only showed mild activity against *Mycobacterium tuberculosis* $H_{37}Ra$ with an MIC value of 12.5 μg/mL, while its epoxy-derivative, gliovirin, suppressed TNF-α synthesis, a major pro-inflammatory cytokine that regulates further cytokine induction in many human diseases including cancer, inflammation, and immune disorders [8]. The details of the structure-activity relationships of these compounds remain unknown.

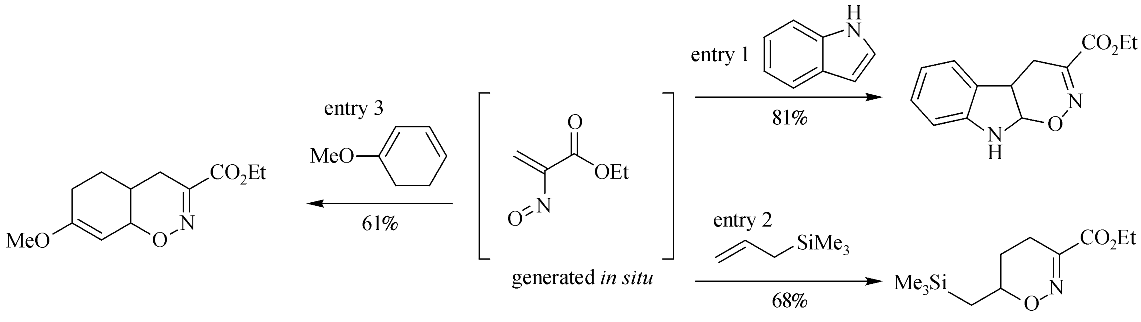
Despite their structural novelty and potent bioactivity, the total syntheses of these natural products were not extensively studied, partially due to the difficulties encountered in the stereoselective construction of the oxazine ring. Only a racemic total synthesis [9] and an enantioselective total synthesis [10] of trichodermamides were reported recently. We present here a brief review of the methodologies used for 1,2-oxazine ring construction and their application to the synthesis of trichodermamides.

2 Methods for oxazine ring construction

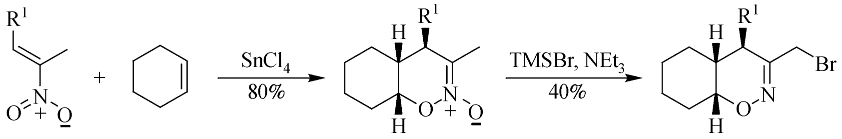
2.1 Hetero-Diels-Alder reaction

The hetero-Diels-Alder reaction is a well-known method to construct oxazines. The hetero-Diels-Alder reaction between nitrosoalkenes and activated alkenes has been studied since the 1970s [11]. Typical reactions are shown in Scheme 1.

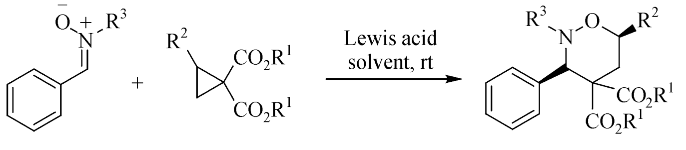
The reaction is a reverse electron-demand reaction and is



Scheme 1 Hetero-Diels-Alder reaction of nitrosoalkenes with activated alkenes.



Scheme 2 Hetero-Diels-Alder reaction of nitroalkenes with unactivated alkenes.



Lewis acid = Yb(OTf)$_3$, MgI$_2$
solvent = THF, CH$_2$Cl$_2$

Scheme 3 Homo [3 + 2] dipolar cycloaddition.

applicable only to certain substrates. The diene was limited to an electron-poor nitrosoacrylate that was not stable and needed to be generated *in situ*. The scope of the dienophiles was also limited to electron-rich heterocycles such as furan or indole (Scheme 1, entry 1) [12] or activated alkenes such as silyl enol ethers [13, 14], enamines [15], and allyltrimethylsilanes (Scheme 1, entry 2) [16]. The yields were moderate in many cases. More recently, Chan et al. reported that an *in situ* generated diene reacted with the nitrosoacrylate as the dienophile (Scheme 1, entry 3), and that the cyclization took place at the less activated terminal of the diene [17]. An enantioselective hetero-Diels-Alder reaction to form oxazine rings was realized in Reissig's group by attaching a chiral auxiliary to the alkenes [14].

In addition to nitrosoacrylates, nitroalkenes were also reported to react as electron acceptors in hetero-Diels-Alder reactions [18]. Since nitroalkenes are better electron acceptors than nitrosoacrylates, unactivated alkenes could be used as dienophiles. [4 + 2] Cyclization of nitroalkenes with olefins affords oxazine N-oxides in good yields, as shown in Scheme 2. The reaction is promoted by Lewis acids such as titanium tetrachloride and tin tetrachloride. The resulting 1,2-oxazine *N*-oxide may be converted to 1,2-oxazine in moderate yield by reduction followed by bromination in the presence of trimethylsilyl bromide and triethylamine [19]. This approach represents a novel strategy for the synthesis of C-3 functionalized 5,6-dihydro-4H-1,2-oxazines. The resulting bromomethyl derivatives are proven to be useful in synthesis.

2.2 Lewis acid-promoted homo [3 + 2] dipolar cycloaddition

Another method to construct oxazine rings is based on a homo [3 + 2] dipolar cycloaddition, which was systematically studied by Kerr et al. [20–22]. A facile cycloaddition of activated cyclopropanes with nitrones, which were formed *in situ* by the reaction of hydroxylamines with aldehydes, was accomplished using Yb(OTf)$_3$ [20] or MgI$_2$ [22] as the Lewis acid catalyst, as shown in Scheme 3. The three-component coupling allows for the formation of a diverse array of cycloadducts with excellent diastereoselectivities and yields.

2.3 Reverse Cope elimination

Dulcère and coworkers reported a novel approach to form 1,2-oxazines. It was found that nitroallenes could be selectively reduced into the corresponding hydroxylamines upon treatment with samarium iodide (SmI$_2$). The resulting hydroxylamines underwent facile cyclization at room temperature without assistance of catalysts to yield 3,6-dihydro-1,2-oxazines [23], as shown in Scheme 4. It was believed that the cyclization occurred through a reverse Cope elimination pathway via an intramolecular *N*-alkylated intermediate. The facile cleavage of the N–O bond in 3,6-dihydro-1,2-oxazines to generate 1,4-bifunctional groups makes this methodology useful in the synthesis of indolizidine alkaloids [23].

2.4 Addition of methoxyallenes to nitrones

The addition of lithium methoxyallenes to nitrones provided hydroxylamine derivatives that underwent rapid cyclization to 3,6-dihydro-1,2-oxazines. Reissig extensively investigated this type of reaction and discovered that it was highly diastereoselective, as shown in Scheme 5 [24–26].

The reaction between chiral nitrones and methoxyallenes yielded excellent *syn* stereoselectivity, which was governed by stereoelectronic effects in accordance with the Felkin-Anh model (Scheme 5, entry 1). When chiral nitrones were precomplexed with Et$_2$AlCl, excellent *anti* selectivity was achieved (Scheme 5, entry 2). The selectivity was governed by the transition state involving an aluminum complex formed by the chelation of the nitrone oxygen and the oxygen of the neighboring acetonide. This methodology is very efficient in preparing highly functionalized 1,2-oxazines. The resulting oxazines are versatile starting materials for stereoselective syntheses of polyfunctional compounds. The reaction is also an excellent tool for efficient chain elongation of carbohydrates.

2.5 Acid-catalyzed cyclization

Acid-catalyzed cyclization has also been investigated for the construction of oxazine rings. Synthesis of 4H-1,2-benzoxazines by means of a unique Friedel-Crafts-type reaction of nitroalkenes with benzene (used as solvent) in the presence of a superacid was reported by Shudo et al. [27]. Ohwada later expanded this method to synthesize substituted benzoxazines [28], as shown in Scheme 6.

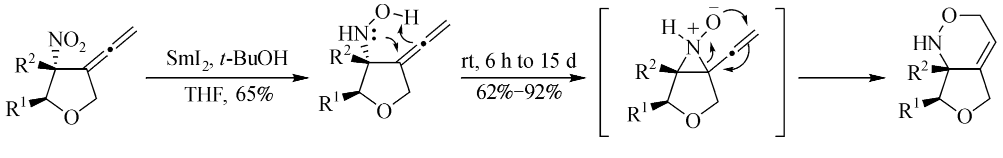
The intramolecular cyclization of 2-nitro-3-phenylpropanoate bearing an electron-withdrawing group on the benzene ring in chloroform and in the presence of trifluoromethanesulfonic acid, occurred smoothly to yield the corresponding 4H-1,2-benzoxazines. This reaction, however, was not compatible with benzene rings bearing electron-donating groups such as a methoxy group.

2.6 Lewis acid-promoted 1,2-oxaza Cope rearrangement

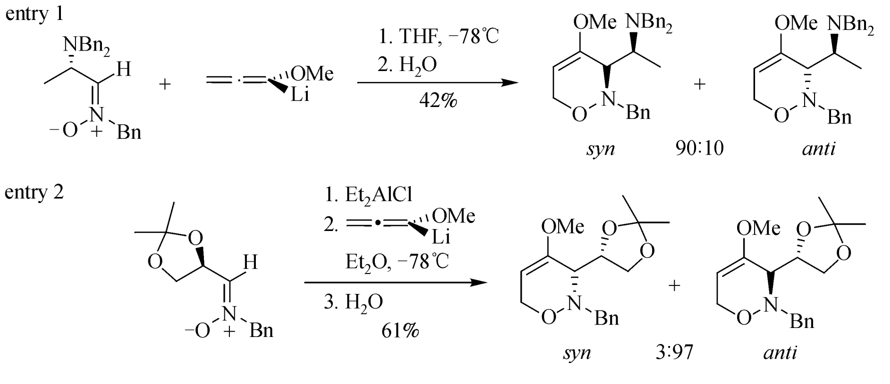
Recently, a new type of Cope rearrangement to construct the oxazine ring was developed by Zakarian et al. [29], as shown in Scheme 7. The key intermediate was converted to corresponding nitroso ester that underwent a [3,3]-sigmatropic rearrangement *in situ* to yield an oxazine ring. The oxazine ring was incorporated into a highly functionalized cyclohexene ring in moderate to good yield. The C-4 ring junction could be functionalized by choosing a properly substituted substrate. A racemic total synthesis of trichodermamide B based on this methodology was reported [9].

2.7 Nucleophilic substitution by oximes

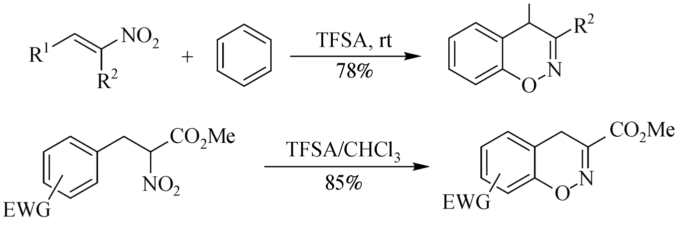
1,2-Oxazine ring formation reactions by nucleophilic substitutions are shown in Scheme 8. Intermolecular epoxide ring



Scheme 4 1,2-Oxazine synthesis by reverse Cope elimination.

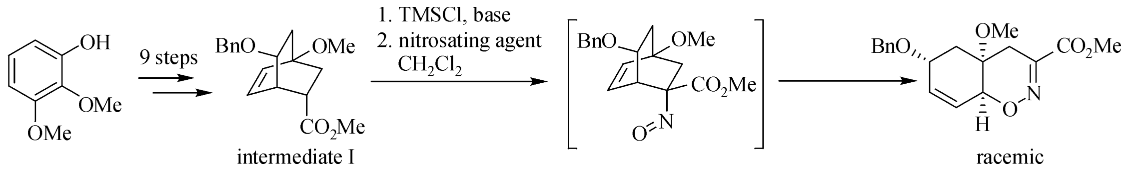


Scheme 5 Oxazine synthesis by [3 + 3] addition of methoxyallenes to nitrones.

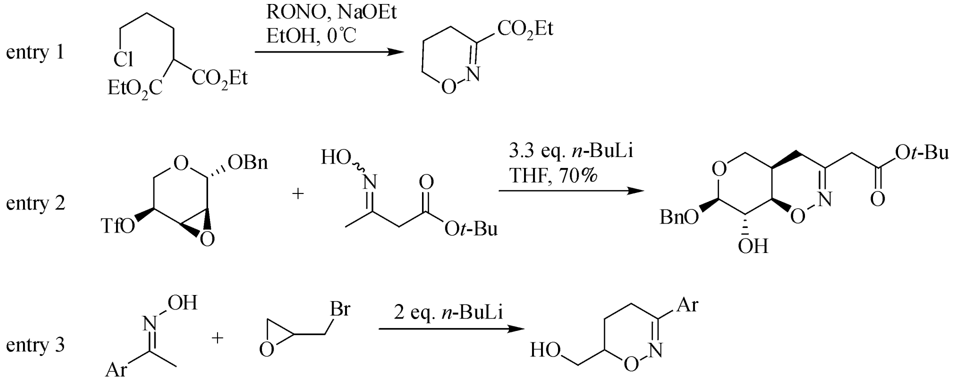


TFSA = trifluoromethanesulfonic acid

Scheme 6 Acid-catalyzed synthesis of 4H-1,2-benzoxazines.



Scheme 7 Tandem nitrosation/oxaza-Cope rearrangement.



Scheme 8 Oxazine ring formation by nucleophilic substitution.

opening reactions by oximes to form O-alkylated products were reported by several groups, though most afforeded low yields [30–33]. Intramolecular O-alkylation of oximes for the formation of the oxazine ring was first introduced by Woodward in 1979 (Scheme 8, entry 1) [34]. The oxime generated *in situ* attacks the carbon center with chlorine as the leaving group to form a 5,6-dihydro-4H-1,2-oxazine ring. Voelter later reported a similar methodology as shown in Scheme 8, entry 2. The oxime was used to open an intramolecular epoxide to incorporate an oxazine ring into a 6-membered ring with good yield and high diastereoselectivity [35]. This methodology was later applied to the regioselective synthesis of oxazine and oxazolopyridazinone structures (Scheme 8, entry 3) [36]. The enantioselective total syntheses of trichodermamides A and B were also based on such methodology [10].

3 Total synthesis of trichodermamides A and B

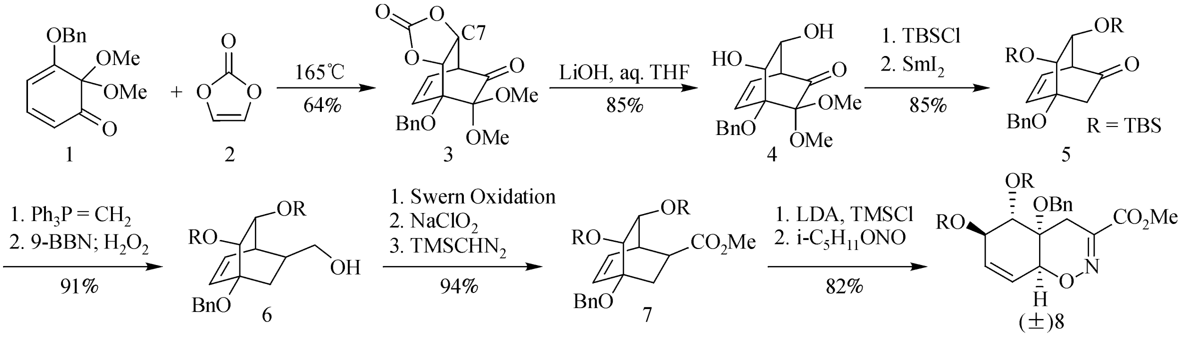
3.1 Racemic total synthesis of trichodermamide B

Based on the oxaza-Cope rearrangement methodology, Zakarian et al. reported a racemic total synthesis of trichodermamide B [9]. The construction of the highly functionalized oxazine ring core structure is summarized in Scheme 9.

The Diels-Alder reaction between functionalized cyclohexadiene 1, which was prepared using commercially available materials in four steps, and vinylene carbonate 2 yielded bicyclic compound 3. Upon treatment with LiOH, the loss of carbon dioxide from compound 3 was followed by a retroaldol-aldol reaction to yield compound 4 with complete inversion of the stereochemistry at C7. The diol was protected with TBS groups and the dimethoxy group at the α-position of the carbonyl group was removed with SmI_2 to yield compound 5 in excellent yield. Olefination followed by hydroboration gave the primary alcohol 6, which was oxidized to the corresponding acid in two steps and then converted to the methyl ester 7 in good yield. The key intermediate 7 was then treated with LDA and TMSCl to give a silyl ketene acetal, which was converted to nitrosoester at −78°C. The nitrosoester underwent a smooth oxaza-Cope rearrangement when the solution was warmed up to 0°C to produce the racemic oxazine core structure 8 in 82% yield.

Although compound 8 was highly functionalized, the location of the double bond and the hydroxy group were not in the desired positions, hence further manipulation was needed. Desilylation of compound 8 followed by oxidative benzylidene acetal formation yielded compound 9 as a mixture of two diastereomers in moderate yield, as shown in Scheme 10. The allylic alcohol was converted to the corresponding aryl allylic selenide 10 via a known procedure. Compound 10 then underwent a [2,3]-rearrangement upon treatment with H_2O_2 via the selenoxide intermediate to yield compound 11 with correct functional groups installed.

After the allylic alcohol being protected with TBDPSOTf, compound 11 was hydrolyzed to produce the corresponding acid, which was coupled with aminocoumarin 12 and EDCI to generate amide 13 in good yield. The benzylidene group was removed and the free allylic alcohol was converted to the



Scheme 9 Zakarian's racemic total synthesis of trichodermamide B (Part 1).

corresponding mesylate 14. When compound 14 was treated with LiCl, the chlorine atom was installed with stereochemistry inversion, followed by a desylation to yield (±)-trichodermamide B.

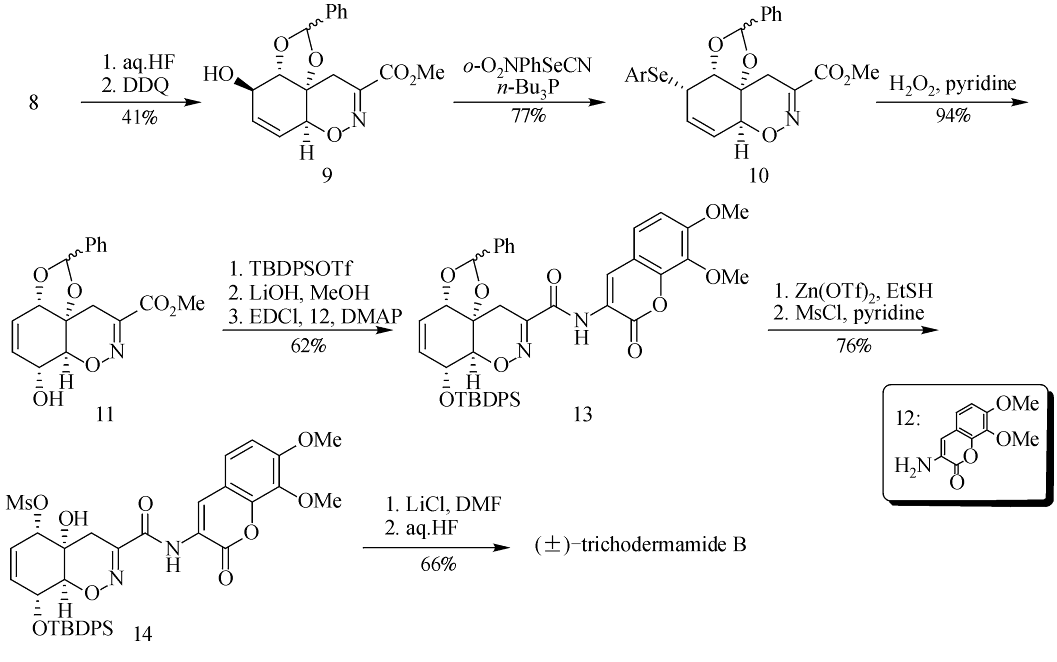
Racemic trichodermamide B was synthesized in 21 steps from a non-commercially available intermediate with a 3.3% overall yield.

3.2 Enantioselective total syntheses of trichodermamides A and B

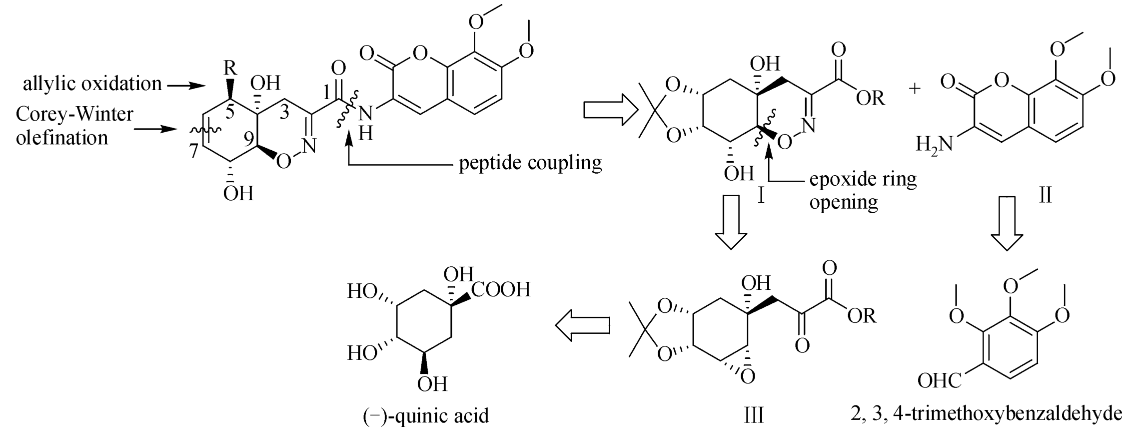
Joullié and coworkers completed the first enantioselective total syntheses of trichodermamides A and B at almost the same time as the racemic synthetic route was reported [10].

The retrosynthetic analysis of the Joullié's approach is shown in Scheme 11. The peptide bond disconnection split the trichodermamides into an oxazine ring moiety (I) and an aminocoumarin (II). The aminocoumarin II was synthesized from commercially available 2,3,4-trimethoxybenzaldehyde. We envisioned that the functionality at C5 (allylic alcohol for trichodermamide A or allylic chloride for B) and the double bond at C6-C7 could be introduced after construction of the oxazine ring. The oxazine ring could be synthesized stereoselectively by an intramolecular epoxide ring opening of intermediate III once the ketone moiety was converted into an oxime. Intermediate III was made from (–)-quinic acid, where the chiral tertiary alcohol would provide the C3 chiral ring junction in the trichodermamides.

As shown in Scheme 12, (–)-quinic acid was converted to the corresponding methyl ester 15 after protection of the three secondary alcohols. The methyl ester was reduced to a primary alcohol which was in turn mesylated and converted to



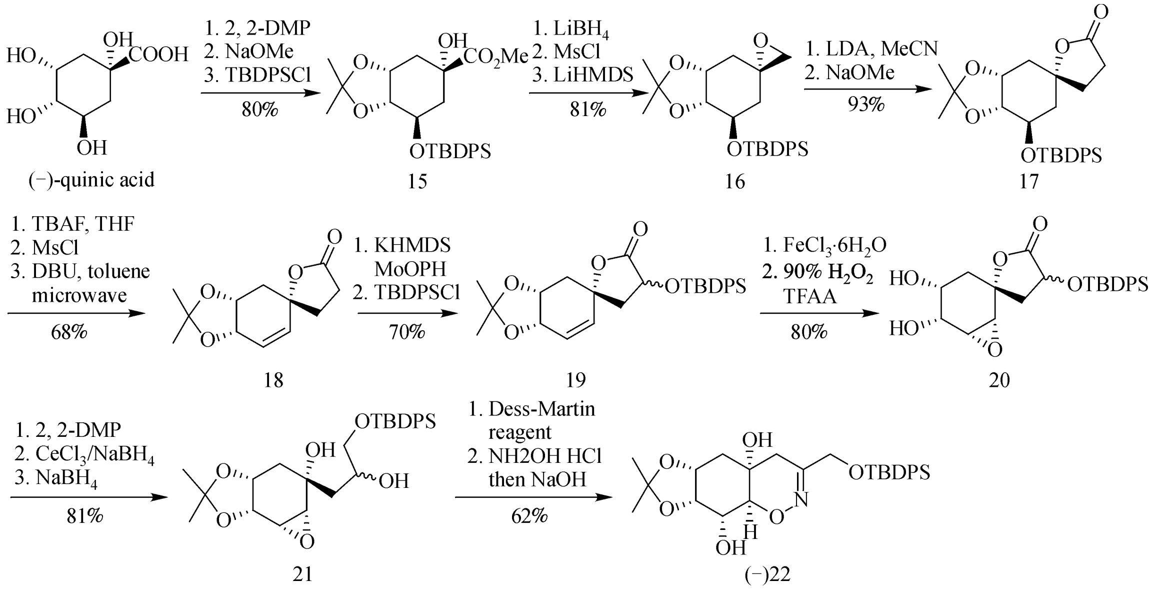
Scheme 10 Zakarian's racemic total synthesis of trichodermamide B (Part 2).



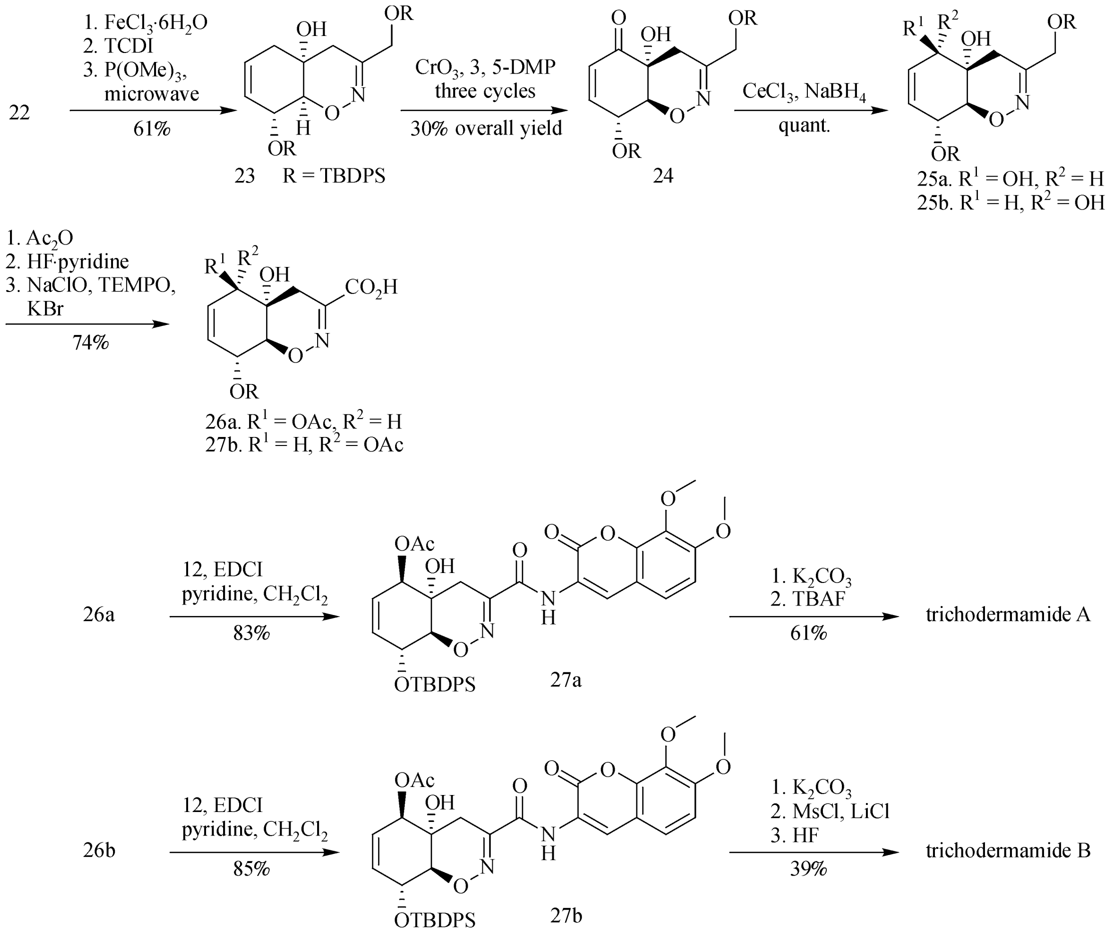
Scheme 11 Retrosynthetic analysis of trichodermamides in Joullié's approach.

epoxide 16. This epoxide was opened regioselectively at the primary position when treated with the anion of acetonitrile in order to provide the side chain elongated product which was then converted to spirolactone 17 in excellent yield. Removal of the TBDPS group followed by mesylation of the free secondary alcohol yielded the corresponding mesylate, which was then eliminated under microwave-assisted conditions to generate compound 18 in good yield. A hydroxyl group at the α-position of the lactone was installed by oxidation of the enolate of 18 using MoOPH (molybdenum pentoxide/pyridine/HMPA complex), followed by protection of the hydroxyl group with TBDPS to yield compound 19.

The acetonide on 19 was removed to afford a secondary alcohol, which was to be used as the directing group when introducing an epoxide functionality stereoselectively. While several attempts failed, this goal was finally realized using CF_3CO_3H as the oxidant. This reagent was prepared *in situ* using 90% H_2O_2 and trifluoroacetic anhydride. After re-protection of the diol as an acetonide, the lactone was selectively reduced in two steps with migration of the TBDPS group to the primary alcohol to generate compound 21 in 81% overall yield. The epoxide functional group remained intact during the reduction. The free alcohol on compound 21 was oxidized into the corresponding ketone. Treatment of the ketone with hydroxylamine generated the corresponding oxime *in situ*, which underwent an intramolecular epoxide ring opening upon addition of NaOH to yield oxazine 22 as a single diastereomer. After this preliminary result was published [37], Taylor et al. reported a similar methodology



Scheme 12 Enantioselective construction of the oxazine moiety.



Scheme 13 Completion of the enantioselective total synthesis.

in a study of trichodermamides [38] on a model system lacking other functionalities and stereocenters.

After successful construction of the oxazine moiety, the next goal was to install other functionalities onto the cyclohexane structure. The secondary alcohol on 22 was protected with a TBDPS group and the acetonide was removed to yield the diol, which was to be used in a Corey-Winter olefination. The olefination proceeded in a low yield under normal reflux conditions, but a good yield of 23 was obtained under microwave-assisted conditions.

The allylic oxidation was problematic due to the existence of two allylic positions prone to oxidation. It was finally discovered that treating 23 with excess CrO_3/3,5-dimethylpyrazole generated enone 24 in approximately 30% yield after three cycles [39]. Luche reduction of 24 produced two separable diastereomers, 25a and 25b, in a 1 : 1 ratio, both of which are required for the syntheses of trichodermamides A and B. The allylic alcohol was protected as its acetate and the TBDPS group at the primary alcohol was then selectively removed. The free primary alcohol was then oxidized into the corresponding acid to generate 26a and 26b in excellent yield, completing the installation of all functionalities on the oxazine moiety.

The coupling reaction between aminocoumarin 12 and acids (26a and 26b) was achieved using EDCI in 30% pyridine/CH_2Cl_2 solution in over 80% yield [40], as shown in Scheme 13. Removal of the protecting groups from 27a yielded trichodermamide A. Removal of the acetate group from 27b generated the corresponding allylic alcohol, which was converted into the corresponding allylic chloride in one step when treated with mesyl chloride in the presence of excess lithium chloride. The removal of the TBDPS group completed the total synthesis of trichodermamide B.

4 Conclusion

Several new methods for constructing 1,2-oxazines have been developed in the past three decades. Only two of them have been applied to the total synthesis of the trichodermamides: the oxaza-Cope rearrangement was the key reaction in the racemic total synthesis of trichodermamide B, while a diastereoselective intramolecular epoxide ring opening reaction via an oxime generated *in situ* led to the enantioselective total synthesis of trichodermamides A and B. The structural complexity and interesting biological activities of trichodermamides and its related natural products still make those compounds very challenging targets for the discovery of new methodologies and development of more efficient synthetic routes.

Xiaobo WAN was born in Lasa, Xizang Autonomous Region, People's Republic of China. He got his B.S. degree from Nankai University. He got his Ph.D. in polymer chemistry and physics at Nanjing University under the guidance of Professor Gi Xue in 2000. He then went to the University of Pennsylvania for his second Ph.D. in organic chemistry under the guidance of Professor Madeleine M. Joullié. He is now working at Arkema Inc. as a postdoctoral research scientist. His research interests are in the areas of natural product synthesis, design and synthesis of new organic materials for polymeric devices.

Madeleine M. JOULLIÉ was born in Paris, France, but grew up in Rio de Janeiro, Brazil. She came to the United States to study chemistry and obtained a B.S. degree in chemistry from Simmons College in Boston. She went to the University of Pennsylvania, earning an M.S. degree in 1950 and a Ph.D. in 1953, under the guidance of Professor Allan R. Day. Madeleine Joullié then joined the faculty at Penn, where she was one of the first woman professors to earn tenure in chemistry in the Ivy League. Her research interests are in the areas of heterocyclic, medicinal, and natural products chemistry. Her laboratory has focused on the chemistry of the cyclopeptide alkaloid and didemnin families of natural products, as well as the development of compounds for the visualization of latent fingerprints as a forensic tool in law enforcement. She has held several visiting professorships, is currently the class of 1970 Professor of Chemistry at the University of Pennsylvania, just completed her second term on the Board of Directors of the American Chemical Society, and now serves on the board of the Chemical Heritage Foundation.

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