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Progress Towards the Total Synthesis of Trichodermamides A and B: Construction of the Oxazine Ring Moiety

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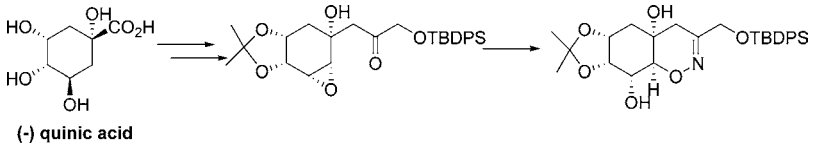
ABSTRACT



Trichodermamides are modified heterocyclic dipeptides that possess a unique 4*H*-5,6-dihydro-1,2-oxazine ring. Starting from affordable, easily available (–)-quinic acid, the enantioselective synthesis of this oxazine moiety was achieved by an intramolecular epoxide ring-opening reaction by an oxime.

Trichodermamides A and B (Figure 1) are modified heterocyclic dipeptides isolated from cultures of the marine-derived

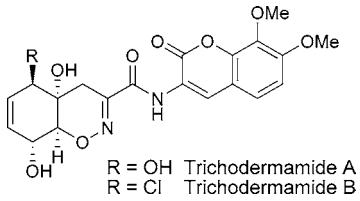


Figure 1. Trichodermamide family.

fungus *Trichoderma virens* in 2003.[1] Trichodermamide A was believed to have the same structure as penicillazine, which was isolated from a culture of the marine fungus *Penicillium* sp. (strain #386).[2] Both compounds possess a unique 4*H*-5,6-dihydro-1,2-oxazine ring merged with a highly functionalized cyclohexene ring, a heterocyclic core found for the first time in a natural product. Although trichodermamide A was found to be completely inactive in biological assays, trichodermamide B displayed significant in vitro cytotoxicity against HCT-116 human colon carcinoma with an IC_{50} of 0.32 μg/mL and moderate antimicrobial activities against amphoterocin-resistant *Candida albicans*, methacillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus faecium* with MIC values in the range of 15 μg/mL. More recently, Capon's group isolated aspergillazines A−E, which are structurally related to the trichodermamides, from an Australian strain of *Aspergillus unilateralis*.[3] However, the bioactivity of these compounds was not reported due to insufficient material for testing. To date, no total synthesis of these compounds has been reported. Therefore, this synthetically challenging and biologically interesting new class of metabolites led us to investigate their synthesis.

Strategically, the most challenging problem is the construction of the 4*H*-5,6-dihydro-1,2-oxazine ring incorporated into the highly functionalized cyclohexane moiety. When we began this study, we found few ways to form the oxazine ring. The most common approach was the hetero Diels−Alder reaction between vinylnitroso compounds generated

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in situ and alkenes with inverse electron demand.[4−7] Unactivated alkenes gave generally poor yields, and although electron-rich alkenes such as silyl enol ethers reacted more efficiently, the reaction could not be applied to our system because the regioselectivity would be reversed and the tertiary alcohol could not be installed properly. Furthermore, the enantioselective hetero Diels−Alder reaction of vinylnitroso compounds was not reported, and we wanted to synthesize trichodermamides enantioselectively. Only recently, the Zakarian group developed a novel strategy to construct the oxazine ring by a 1,2-oxaza-Cope rearrangement.[8] Here we report our synthetic approach toward the enantioselective construction of the oxazine ring, which will be further manipulated to afford trichodermamides A and B.

Intrigued by the report of an intramolecular epoxide ring-opening reaction by oximes,[9] we envisioned the installation of the oxazine ring and the secondary alcohol with the desired stereochemistry by the stereoselective formation of the epoxide. As shown in Figure 2, we planned to introduce the

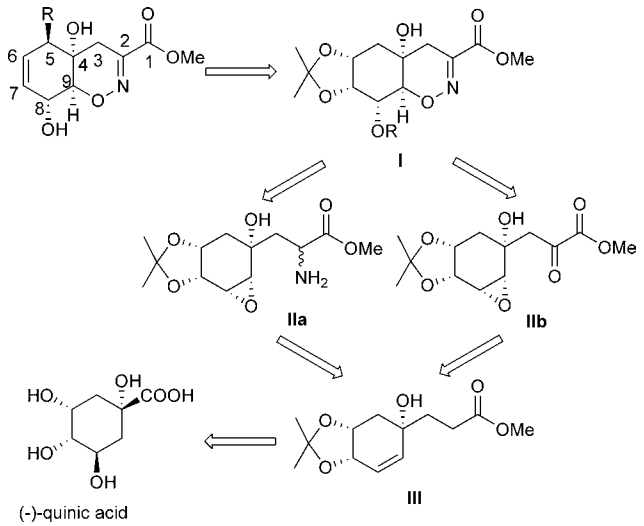
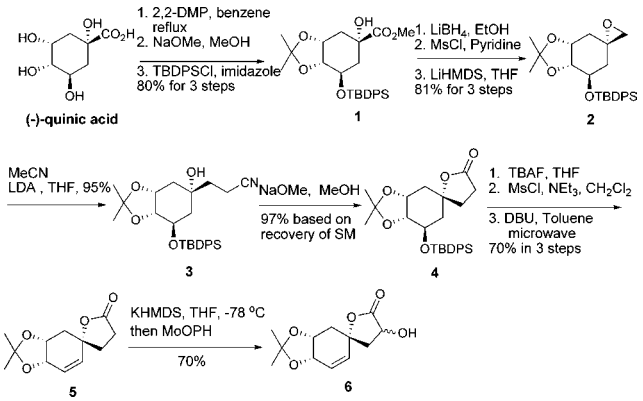


Figure 2. Retrosynthetic analysis of the oxazine-containing moiety.

double bond at a later stage by a Corey−Winter olefination,[10] and the hydroxyl group at the C5 position could be installed by allylic oxidation. The key intermediate **I** would be synthesized by the epoxide ring-opening reaction. The oxime could be introduced either by the oxidation of α-amino ester **IIa**[11] or by the traditional reaction between hydroxylamine and α-keto ester **IIb**. The epoxide moiety would be obtained stereoselectively by the directed epoxidation controlled either by the tertiary hydroxyl group or by the secondary hydroxyl group, and the α-functionality would be introduced by the oxidation of the enolate of compound **III**. We found that (−)-quinic acid was an appropriate starting material because it provided a tertiary hydroxyl functional group with the desired stereochemistry and a secondary hydroxyl group which could be further functionalized to the epoxide ring. In addition, it also had a diol moiety that could be manipulated by a Corey−Winter olefination.

As shown in Scheme 1, (−)-quinic acid was converted to the corresponding lactone acetonide, followed by the lactone

Scheme 1. Synthesis of the α-Functionalized Spiroketone



ring-opening reaction to give the ester, and then protection of the liberated secondary alcohol with TBDPS−Cl afforded **1** in an overall yield of 80% in three steps. Ester **1** was reduced to the corresponding alcohol using $NaBH_4$/LiCl. The diol was converted to epoxide **2** in two steps in good overall yield. The epoxide was then opened in 95% yield using acetonitrile as the nucleophile and LDA as the base to give the side chain elongation product **3**.[12] After treatment with NaOMe in MeOH, followed by neutralization with acetic acid, nitrile **3** was converted to the spirolactone **4** in 80% yield[13] (97% yield based on the recovery of starting material). Conversion of the nitrile to an ester and protection of the tertiary alcohol were realized in one step. Treatment of **4** with TBAF gave the free alcohol that was converted to a mesylate. Elimination of the mesylate group under microwave conditions gave the desired product **5** in an overall 70% yield. However, introduction of the azide at the α-position of lactone **5** could not be accomplished.

Evans' azidation[14] failed under all conditions tried. Other azidation conditions also failed. Bromination only gave a trace amount of α-bromo lactone. Finally, treatment of compound **5** with 3 equiv of KHMDS to form the corre-

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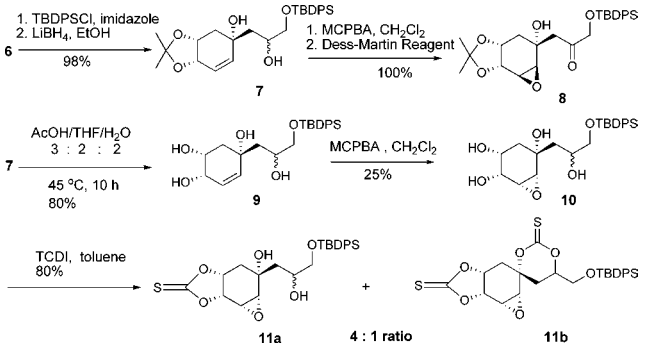
sponding enolate, followed by oxidation with a molybdenum pentoxide−pyridine−HMPA complex (MoOPH), gave the corresponding α-hydroxyl lactone **6** in 70% yield as a mixture of diastereomers.

Unfortunately, the five-membered spirolactone **6** was very stable and could not be esterified under several conditions. Alternatively, after protection of the secondary alcohol with TBDPS, **6** was opened easily when reduced by $LiBH_4$, with the migration of the TBDPS group to the primary alcohol to afford **7** in almost quantitative yield, as shown in Scheme 2.

Scheme 2. Attempts to Install the Epoxide with the Desired Stereochemistry



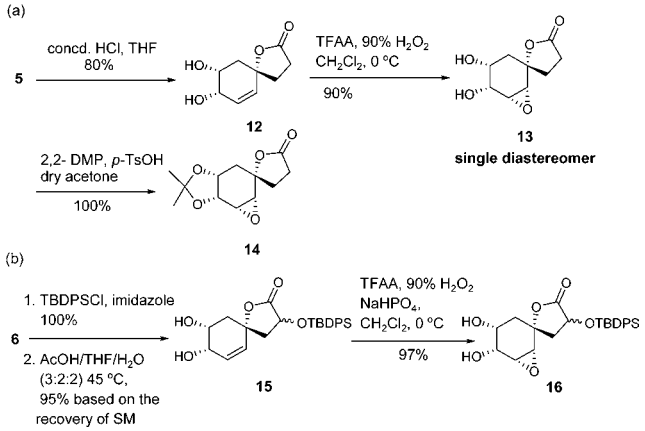
Our initial strategy was to use the tertiary alcohol at C-4 to direct the epoxidation; however, compound **7** was inert to Sharpless epoxidation conditions.[15] When treated with *m*CPBA in CH_2Cl_2, followed by Dess−Martin oxidation, a single diastereomer **8** was obtained. However, a detailed ^1H NMR study showed that the epoxide was formed anti to the tertiary alcohol. This stereochemistry was verified when oxidation with DMDO, which is reported to have no hydroxyl directing effect, provided the same diastereomer **8**. We attribute the failure of the *m*CPBA to direct epoxidation to the weak H-bonding-directing effect of the tertiary alcohol that was unable to control the approach of the oxidant from the concave face.

One way to circumvent this problem was to remove the acetonide protecting group and use the secondary alcohol as the directing group (Scheme 2). The acetonide was cleaved under acidic conditions to give **9** with retention of the TBDPS group on the primary alcohol.[16] However, Sharpless epoxidation failed again even when more reactive $VO(OEt)_3$/*t*-BuOOH was used.[17]

When treated with *m*CPBA under various conditions, **9** decomposed and epoxide **10** was formed in only 25% yield. Other conditions, such as H_2WO_4/30% H_2O_2[18] and $MnSO_4$/30% H_2O_2/$NaHCO_3$,[19] were also fruitless. Furthermore, when compound **10** was treated with TCDI, undesired dithiocarbonate **11b** was also formed with the desired monothiocarbonate **11a**, which made this approach less favorable.

A model study was then carried out to optimize the conditions for the directed epoxidation (Scheme 3a). The

Scheme 3. Model Study of the Directed Epoxidation and Its Application in the Real System



acetonide moiety on lactone **5** was cleaved, and the liberated hydroxyl group was used as the directing group. All of the directed epoxidation methods mentioned above were tried, but again all failed. However, we were delighted to find that with TFAA/90% H_2O_2[20] a single diastereomer **13** was obtained in 90% yield. The stereochemistry was confirmed by X-ray structure analysis of the corresponding diol-protected compound **14** (Figure 3). The optimized conditions

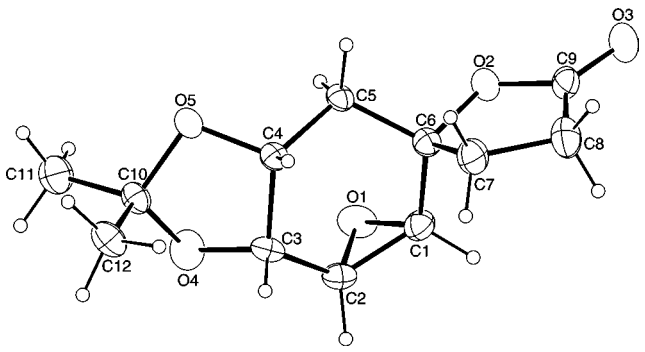


Figure 3. Crystal structure of the epoxide **14**.

were modified by adding Na_2HPO_4 as the buffer[21] and applied to compound **15**, which was synthesized in two steps from compound **6**. The desired epoxide **16** was obtained in excellent yield (Scheme 3b).

The diol moiety was then reprotected to give compound **17** in quantitative yield (Scheme 4). The reduction of the

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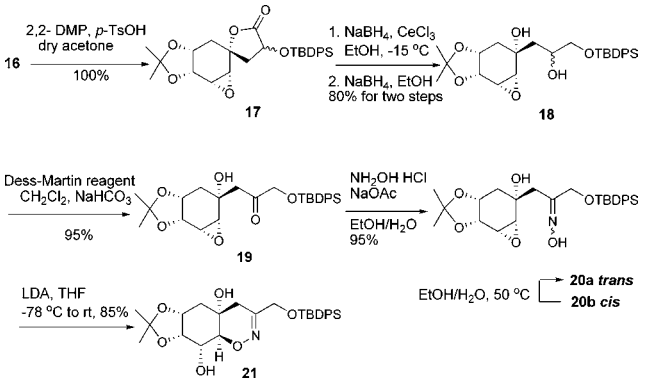
Scheme 4. Construction of the Oxazine Moiety



lactone in the presence of the epoxide moiety was challenging as the epoxide would not survive most conditions used for lactone reduction. After several conditions were tried and failed, the reduction of the lactone to lactol using $NaBH_4$/$CeCl_3$ as the reducing reagent[22] followed by $NaBH_4$ reduction successfully solved the problem, as shown in Scheme 4. The secondary alcohol of **18** was then oxidized to the ketone by the Dess−Martin reagent in excellent yield to give a single diastereomer **19**. The ketone **19** was converted to the oxime (trans/cis = 2:1) in excellent yield when treated with hydroxylamine. This cis isomer can be partially isomerized to the trans isomer when heated in EtOH/H_2O. The trans isomer **20a** cyclized easily when treated with LDA in THF to give the desired oxazine **21** in 85% yield.

In conclusion, starting with affordable, easily available (−)-quinic acid, we stereoselectively synthesized the oxazine moiety, which will be further manipulated to complete the total synthesis of trichodermamides A and B.

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Supporting Information Available: Experimental procedures and characterization of compounds **17**, **19**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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