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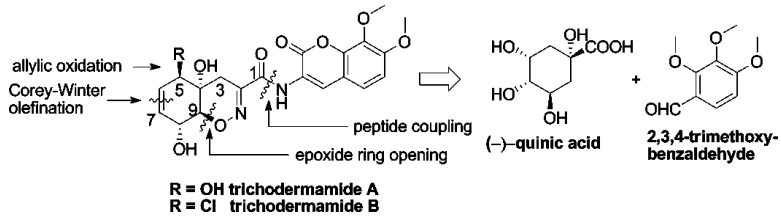
J. Am. Chem. Soc., **2008**, 130 (51), 17236-17237 • DOI: 10.1021/ja807011b • Publication Date (Web): 04 November 2008



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Enantioselective Total Syntheses of Trichodermamides A and B

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Trichodermamides A (**1**) and B (**2**), isolated as the secondary metabolites from marine-derived fungal strains in 2003,[1] represent a series of novel structurally related natural products, such as pretrichodermamide A,[2] apergillazines A−E,[3] and gliovirin[4] (Figure 1).

These natural products all possess a rare oxazine moiety incorporated into a more complex ring system. Among them, trichodermamide B (**2**) shows significant in vitro cytotoxicity against HCT-116 colon carcinoma (IC_{50} 0.32 μg/mL),[1] and gliovirin suppresses synthesis of TNF-α, a major proinflammatory cytokine that regulates further cytokine induction in many human diseases including cancer and inflammation and immune disorders.[5] Trichodermamide C, which is the *N*-methylated derivative of trichodermamide A, also showed significant antitumor activities.[6] It is believed that these compounds are biologically related, and the conversion of pretrichodermamide A to trichodermamide A (**1**) was observed.[2] Interestingly, despite their structural novelty and potent bioactivity, no enantioselective total synthesis of either of these compounds has been reported. Only a few model studies[7−9] and most recently a racemic total synthesis of trichodermamide B were reported.[10] We wish herein to report the first enantioselective total syntheses of trichodermamides A (**1**) and B (**2**).

The trichodermamides were disconnected into an oxazine ring moiety which could be obtained from intermediate **3** and an aminocoumarin (**4**), as shown in Scheme 1. The structural complexity of the trichodermamides lies in the rare oxazine moiety incorporated into a highly functionalized cyclohexene ring with four contiguous stereocenters. We envisioned that the functionality at C5 could be introduced at a later stage by allylic oxidation followed by further manipulation, and the double bond at C6−C7 could be introduced by Corey−Winter olefination. The oxazine ring could be synthesized by an intramolecular epoxide ring opening of intermediate **3** once the ketone moiety was converted into an oxime. Intermediate **3** was to be made from (−)-quinic acid, where the chiral tertiary alcohol would provide the C-3 chiral ring junction in the trichodermamides. The aminocoumarin **4** was to be synthesized from commercially available 2,3,4-trimethoxybenzaldehyde.

Starting from (−)-quinic acid, the previously reported precursor **5** for the epoxide installation was made in 13 steps,[8] as shown in Scheme 2. The stereoselective epoxidation was challenging and finally achieved using CF_3CO_3H as the oxidant,[11] which was prepared in situ using 90% H_2O_2 and trifluoroacetic anhydride. A two-step reduction[12] of lactone **6** with the migration of the TBDPS group to the primary alcohol led to the diol, which was oxidized under Dess−Martin conditions to give ketone **7**. Treatment of **7** with hydroxylamine generated the oxime in situ, which underwent an intramolecular epoxide ring opening upon addition of NaOH to give oxazine **8** as a single diastereomer in 65% yield. The secondary alcohol was protected with a TBDPS group, and the acetonide was removed to give the diol for the Corey−Winter olefination. The

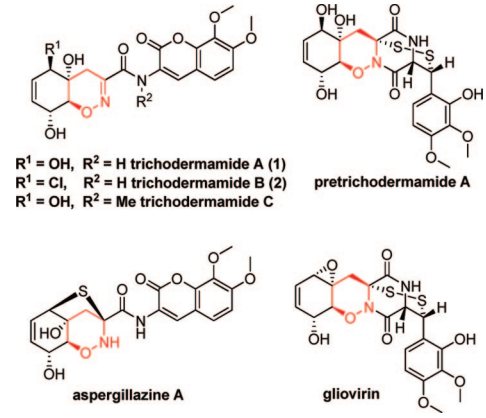
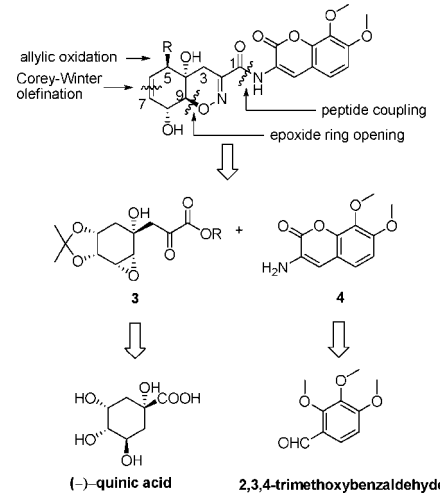


Figure 1. Trichodermamides A (**1**) and B (**2**) and related natural products.

Scheme 1. Retrosynthetic Analysis

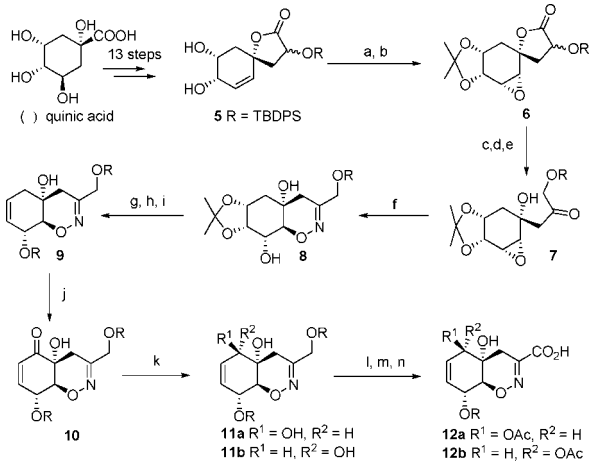


olefination gave a low yield under normal reflux conditions, but by using microwave-assisted conditions the yield of **9** was increased to 83%.

The allylic oxidation was problematic due to the existence of two allylic positions prone to oxidation. Many conditions including SeO_2, $Pd(OH)_2$/TBHP,[13] $Rh_2(Cap)_4$/TBHP,[14] and $Mn(OAc)_3$/TBHP[15] were screened, but all were fruitless. We finally found that treating **9** with excess CrO_3/3,5-dimethylpyrazole[16] gave enone **10** in ∼30% yield after two recycles. Luche reduction of **10** gave two chromatographically separable diastereomers **11a** and **11b** in a 1:1 ratio, both needed for the syntheses of trichodermamides A and B. The allylic alcohol was protected as its acetate, followed by selective removal of the TBDPS group at the primary position. The free primary alcohol was oxidized into the corresponding acid to give **12a** and **12b** in excellent yield. This completed the synthesis of the oxazine moiety.

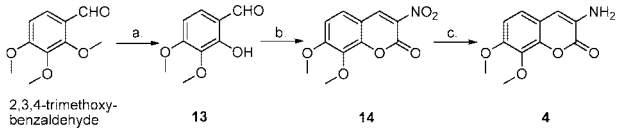
10.1021/ja807011b CCC: $40.75

Scheme 2. Synthesis of the Oxazine Moiety[a]



[a] Reagents and conditions: (a) TFAA, 90% H_2O_2, Na_2HPO_4, CH_2Cl_2, 95%; (b) TsOH, 2,2-DMP, acetone, 99%; (c) $NaBH_4$, $CeCl_3$, EtOH, −15 °C, 80%; (d) $NaBH_4$, EtOH, 95%; (e) Dess−Martin reagent, CH_2Cl_2, 95%; (f) $NH_2OH\cdot HCl$, NaOAc, EtOH/H_2O then NaOH, 65%; (g) TBDPSCl, imidazole, CH_2Cl_2, quant.; (h) $FeCl_3\cdot 6H_2O$, CH_2Cl_2, 85%; (i) 1,1′-thiocarbonyldiimidazole, toluene, reflux, 95%; then $P(OMe)_3$, μW, 150 °C, 84%; (j) CrO_3, 3,5-dimethoxy pyrazole, CH_2Cl_2, −15 °C, 29% after 2 recycles; (k) $NaBH_4$, $CeCl_3$, EtOH, quant.; (l) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 96%; (m) HF·pyridine, pyridine/THF, 80%; (n) TEMPO, NaOCl, KBr, $NaHCO_3$, MeCN/H_2O, 96%.

Scheme 3. Synthesis of Aminocoumarin **4**[a]

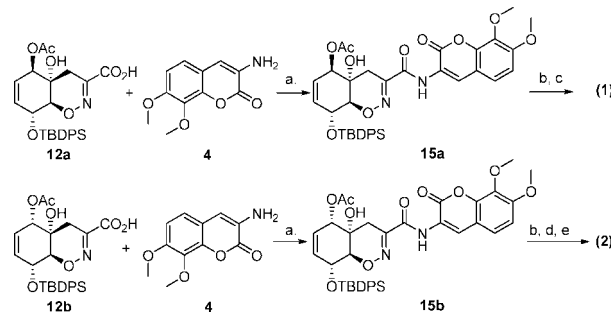


[a] Reagents and conditions: (a) $AlCl_3$, benzene, reflux, 85%; (b) $NO_2CH_2CO_2Me$, piperidine, benzene, Dean−Stark trap, reflux, 84%; (c) H_2, Pd/C, cyclohexene, reflux, 80%.

Aminocoumarin **4** was synthesized from 2,3,4-trimethoxybenzaldehyde, as shown in Scheme 3. Selective demethylation of trimethoxybenzaldehyde gave compound **13**, which was condensed with nitroacetate to give nitrocoumarin **14** in 84% yield. Hydrogenation of **14** finished the construction of aminocoumarin **4**.

The coupling reaction between aminocoumarin **4** and acids **12a** and **12b** was known to be difficult due to the low nucleophilicity of the amino group which is conjugated with the aromatic system, as indicated by a model study from another group.[9] After screening many coupling reagents, the coupling reaction was performed using EDCI in 30% pyridine/CH_2Cl_2 solution[17] with over 80% yield, as shown in Scheme 4. Removal of the protecting groups on **15a** gave trichodermamide A (**1**), the structure of which was confirmed by its crystal structure and other spectroscopic data. Removal of the acetate group on **15b** gave the corresponding allylic alcohol, which was converted into the corresponding allylic chloride in good yield when treated with mesyl chloride and excess lithium chloride. The removal of the TBDPS group completed the total synthesis of trichodermamide B (**2**).

Scheme 4. Completion of the Total Syntheses[a]



[a] Reagents and conditions: (a) EDCI, 30% pyridine, CH_2Cl_2, 83%; (b) K_2CO_3, MeOH, 72%, (c) TBAF, THF, 85%; (d) MsCl, NEt_3, LiCl, CH_2Cl_2, 60%; (e) HF, THF, 90%.

In conclusion, the first enantioselective total syntheses of trichodermamides A (**1**) and B (**2**) were realized starting from readily available (−)quinic acid. The longest linear sequence is 31 steps for trichodermamide A and 32 steps for trichodermamide B, with an average 85% yield for each step. The successful completion of the syntheses will allow for the expedient preparation of other related natural products and the investigation of their structure/activity relationships. These endeavors are currently being pursued.

Acknowledgment. Dedicated to Professor R. O. Hutchins for his many contributions to Chemistry and Education. We thank NSF (CHEM-0515443) for support of this work. We thank Professor Fenical for providing an authentic sample of trichodermamide A for comparison. We also thank Professor Taylor for a helpful discussion on the conditions for the coupling reaction.

Supporting Information Available: Experimental procedures and compound characterization data for all new key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA807011B