Natural Product Synthesis

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Total Synthesis of (±)-Trichodermamide B and of a Putative Biosynthetic Precursor to Aspergillazine A Using an Oxaza-Cope Rearrangement**

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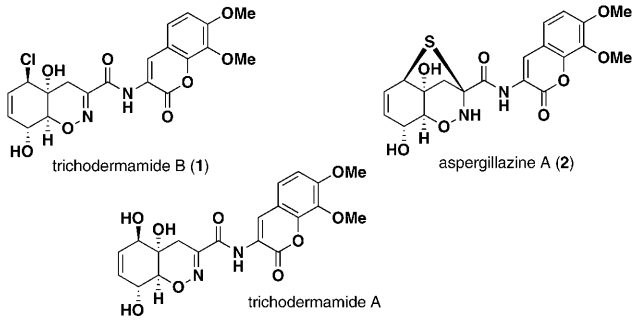
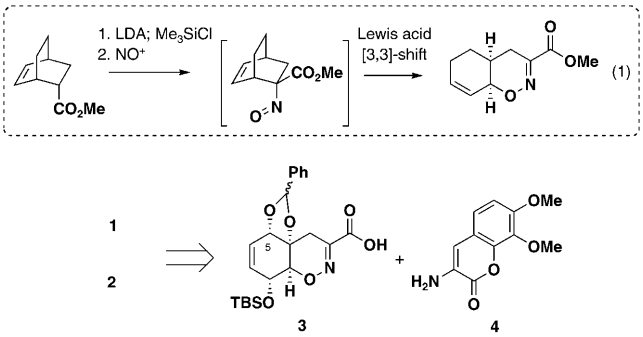
Dedicated to Professor Larry E. Overman on the occasion of his 65th birthday

Trichodermamides A and B are modified dipeptides recently isolated from a marine-derived fungus *Trichoderma virens*.[1] Trichodermamide A has been demonstrated to be identical to penicillazine,[2] obtained from a culture of another marine fungus, *Penicillium* sp. (strain #386) in 2000.[3] In contrast to trichodermamide A, which displayed no activity in bioassays, trichodermamide B (**1**) was found to have significant in vitro activity against HCT-116 human colon carcinoma (IC_{50} 0.32 μg mL^{-1}) and moderate antimicrobial activity against certain drug-resistant bacterial strains, indicating that the chlorine atom in **1** is essential for bioactivity. In 2005, a group of related metabolites, aspergillazines A–E, was characterized by Capon and co-workers.[2] Their biological evaluation was prevented by the lack of material available from biological sources.



The presence of a 4*H*-5,6-dihydro-1,2-oxazine fragment fused with a highly functionalized cyclohexene ring is a distinguishing structural attribute of these natural products, making them compelling targets for chemical synthesis.[4,5] Owing to the lack of mild methods for the direct assembly of the oxazine rings,[6,7] we recently developed a tandem reaction sequence that integrates nitrosation of ester enolates and a novel Lewis acid mediated hetero-Cope rearrangement, the oxaza-Cope rearrangement (Equation (1) in Scheme 1), which directly provides bicyclic oxazines from esters.[8,9] Herein, we report an application of this method to the first total syntheses of (±)-trichodermamide B and the putative biosynthetic precursor of aspergillazine A (**2**) from a common intermediate.



Scheme 1. Overall synthetic strategy. LDA = Lithium diisopropylamide.

Our strategy required a late-stage amide formation from functionalized carboxylic acid **3** and aminocoumarin **4**[5] (Scheme 1). Thus, acid **3** became our key sub-target. S_N2-type substitution at C5 served as the strategic basis for the divergent introduction of the appropriate functionality found in trichodermamide B and in aspergillazine A.

The preparation of the substrate for the key oxaza-Cope rearrangement began with the Diels–Alder reaction between 3-benzyloxy-2,2-dimethoxy-3,5-cyclohexadienone (**5**) and vinylene carbonate according to the method described by Liao and co-workers (Scheme 2).[10] Remarkably, hydrolysis of the carbonate with lithium hydroxide in aqueous THF resulted in a rapid, virtually complete inversion of stereochemistry at C7. Presumably, a retroaldol-aldol pathway is operative in this process, favoring the thermodynamically more stable *trans*-diol **9**.[11] Methyl ester **11** was obtained from **9** in seven straightforward steps in 78% overall yield.[12]

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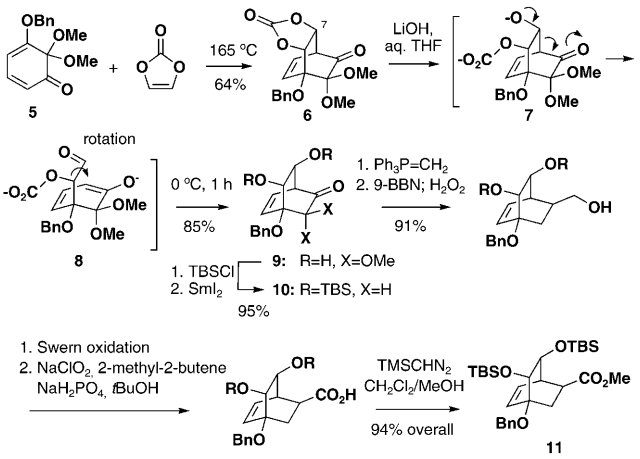
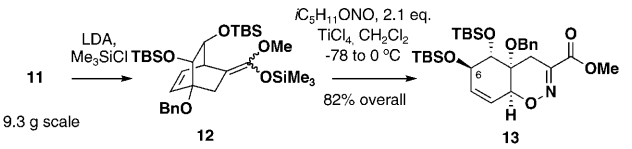


Scheme 2. Synthesis of the key substrate. 9-BBN = 9-Borabicyclo-[3.3.1]nonane, TBS = tributylsilyl, TMS = trimethylsilyl.

The crucial nitrosation/oxaza-Cope rearrangement employing **11** was studied next (Scheme 3). A mixture of isoamyl nitrite and silyl ketene acetal **12** derived from **11** was

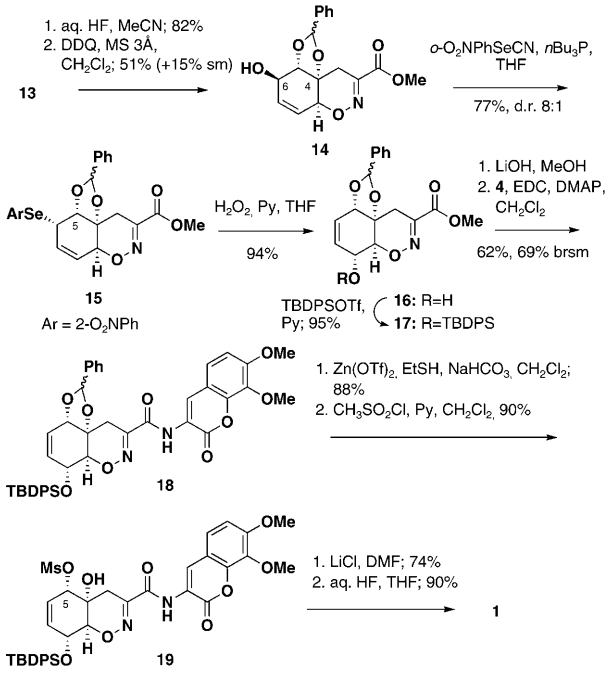


Scheme 3. The key oxaza-Cope rearrangement.

treated with titanium tetrachloride in dichloromethane at −78 °C, according to the standard reaction conditions.[8] The resultant blue solution of the intermediate nitrosoester was warmed to 0 °C, which effected the oxaza-Cope rearrangement to the desired oxazine **13**. We have found that the conversion was substantially higher when excess of the Lewis acid was used, however, partial debenzylation was also detected. The optimal stoichiometry for titanium tetrachloride was found to be 2.1 equivalents, giving an overall 82% yield of the desired product.

Subsequent transformations were aimed at allylic transposition of the hydroxy group at C6 with inversion of configuration (Scheme 4). Complete desilylation followed by oxidative formation of the benzylidene acetal afforded a approximately 1.7:1 mixture of diastereomers (**14**). The allylic alcohol was converted to the corresponding allylic selenide with inversion of configuration using the Grieco protocol.[13] The formation of about 10% of the allylic regioisomer was detected. With other protecting groups at C4 and C5 (triethylsilyl (TES), *tert*-butyldimethylsilyl (TBS)), the regioselectivity was substantially lower. Oxidation of the selenide followed by the in situ [2,3]-sigmatropic rearrangement of the intermediate selenoxide furnished **15**.[14]

After silylation of the allylic alcohol, the methyl ester was hydrolyzed with lithium hydroxide in advance of the amide formation (77%, 87% yields based on recovered starting material). In contrast to the model studies described recently



Scheme 4. Completion of the synthesis of trichodermamide B. DDQ = 2,3-Dicyano-5,6-dichloro-parabenzoquinone, sm = starting material, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, DMAP = 4-dimethylaminopyridine, Py = pyridine, brsm = based on recovered starting material, TBSDPOTf = *tert*-butyldiphenylsilyl trifluoromethanesulfonate.

by Taylor and co-workers,[5] we have found that amide **18** could be formed directly on treatment of the carboxylic acid and aminocoumarin **4** with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 4-dimethylaminopyridine (DMAP) in dichloromethane in 79% yield.

Removal of the benzylidene protecting group was effected with zinc triflate in the presence of ethanethiol in 88% yield. Mesylation of the diol regioselectively afforded **19** in 90% yield. The total synthesis of trichodermamide B was accomplished upon treatment of the mesylate with LiCl in DMF and subsequent desilylation, which provided the racemic natural product displaying identical physical data (UV, ^{1}H, ^{13}C NMR spectroscopy, HRMS-ESI) to those reported by Clardy, Fenical and co-workers.[1a]

Recently, Capon and co-workers proposed that aspergillazine A and trichodermamides could arise through a similar biosynthetic pathway, where a C5 thiol analog of trichodermamides functions as a putative biosynthetic precursor to **2** (Figure 1).[2] This hypothesis also stipulates that the proximity of the oximino and thiol groups predisposes the substrate for facile thiolane formation.

To gain further insight into the chemistry of aspergillazines, we used our synthetic strategy for the synthesis of the C5 thiol analogue of trichodermamides (**21**, Scheme 5). Displacement of the methanesulfonyl group in **19** with potassium thioacetate followed by desilylation smoothly provided **20** in 70% overall yield. The thioacetate was cleaved by treatment with hydrazine under mild conditions (0 °C, 15 min), cleanly delivering **21**. Thiol **21** did not undergo

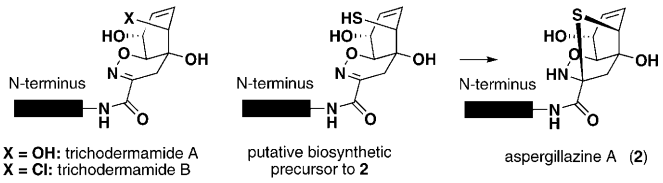
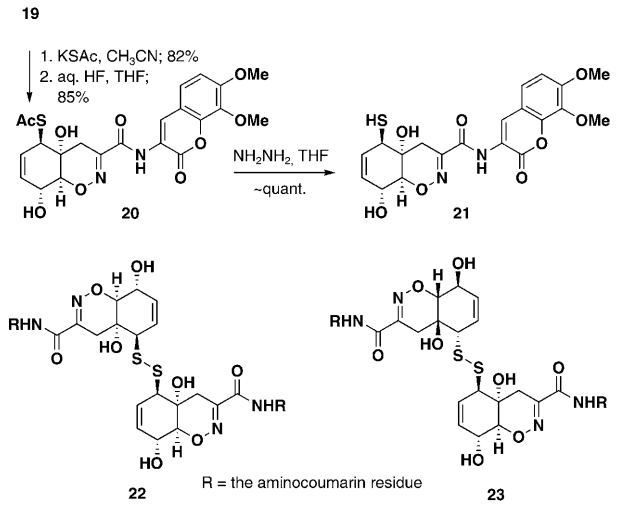


Figure 1. Proposed biosynthesis of aspergillazine A.



Scheme 5. Synthesis of putative biosynthetic precursor of aspergillazine A (top) and products of attempted final cyclization step (bottom)

a spontaneous cyclization to **2** and, under a variety of reaction conditions (DMSO or PhMe, $>130\,^{\circ}C$, CF_3CO_2H/DMSO 70 °C, CH_3CO_2H/H_2O 70 °C, Me_3Al, THF[15]) no ring closure was detected. The major products formed in these reactions were diastereomeric racemic disulfides **22** and **23**. These experimental results suggest that conversion of the putative biosynthetic precursor **21** into **2** is not spontaneous or even facile, as no ring closure is detected under rather harsh reaction conditions.

In conclusion, we reported a successful completion of the first total synthesis of trichodermamide B. An application of an efficient tandem nitrosation/oxaza-Cope rearrangement for the assembly of the characteristic bicyclic oxazine of trichodermamide B is one of the key transformations in the synthesis. Using a similar approach, we have also prepared thiol **21**, the proposed biosynthetic precursor of aspergillazine A. Based on our results, it appears that, if **21** is indeed involved in the biosynthesis of aspergillazine A, its cyclization to **2** is not spontaneous.

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