Natural Product Synthesis

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Stereocontrolled Synthesis of Trichodermatide A**

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The development of shorter synthetic sequences for the synthesis of complex natural products represents significant progress in synthetic organic chemistry. Considering this, the development of a method capable of initially providing the core structure of a target molecule followed by the stereo-, regio-, and chemoselective introduction of functional groups at the desired positions of the core skeleton is an efficient and particularly attractive solution for the synthesis of complex organic compounds.[1]

In 2008, Pei et al. elucidated the structures of trichodermatides A–D (**1**–**4**, Figure 1), which were isolated from the marine-derived fungus *Trichoderma ressei*, and established

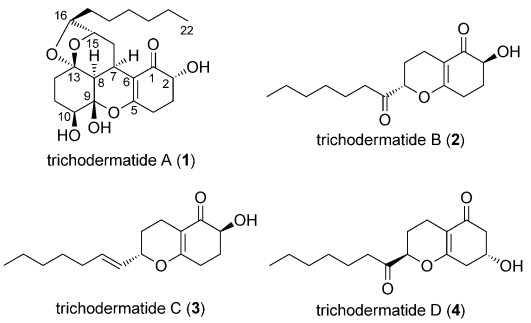
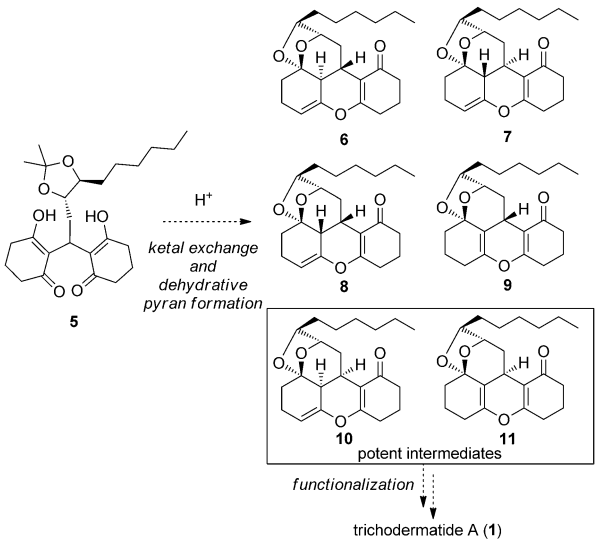


Figure 1. Structures of trichodermatides A–D (**1**–**4**).

their cytotoxicity against the A375-S2 human melanoma cell line.[2] Among them, trichodermatide A (**1**) is structurally distinct from the other members of this family (**2**–**4**). Trichodermatide A (**1**) incorporates a highly oxygenated pentacyclic structure with eight chiral centers containing a ketalic and hemiketalic carbon. Herein, we present the first stereocontrolled total synthesis of **1** utilizing a method for the efficient construction of core structure of **1** by a diastereoselective ketal-formation reaction and a cobalt-catalyzed hydration reaction of enol ether.

For the synthesis of the core of **1**, we planned to use ketal exchange and dehydrative pyran formation, both of which can be promoted under acidic conditions, from dimerized 1,3-cyclohexanedione derivative **5** in one pot (Scheme 1). Among



Scheme 1. Synthetic strategy for trichodermatide A (**1**).

compounds **6**–**11**, we expected that the synthetically potent intermediates **10** or **11**, both of which have stereogenic centers corresponding to that of **1**, would be selectively produced under thermodynamic conditions. We have previously reported a method for the construction of chiral quaternary carbon centers on the basis of the diastereoselective synthesis of the hemiketal and ketal derivatives of 2,2-disubstituted-1,3-cyclohexanediones.[3]

On the basis of this strategy, the synthesis commenced with the preparation of aldehyde **12**, which corresponds to the side-chain portion of **1**, from L-tartaric acid according to known procedures.[4] Aldehyde **12** reacted with 1,3-cyclohexanedione in the presence of piperidine in ethanol to provide symmetric compound **5** in 89% yield (Scheme 2a). The key synthesis step, which involved the diastereoselective formation of a ketal from **5**, was the initial attempt to reflux benzene with *p*-toluenesulfonic acid (PTSA). Unfortunately, however, the isolated compound was not one of the anticipated products **6**–**11**, but was the unexpected bis(enol) ether **13**, in which each hydroxy group of the side chain had reacted with different carbonyl groups. In contrast, the reaction of **5** with a weak acid pyridinium *p*-toluenesulfonate (PPTS) resulted only in the formation of a 9-substituted-tetrahydrox-

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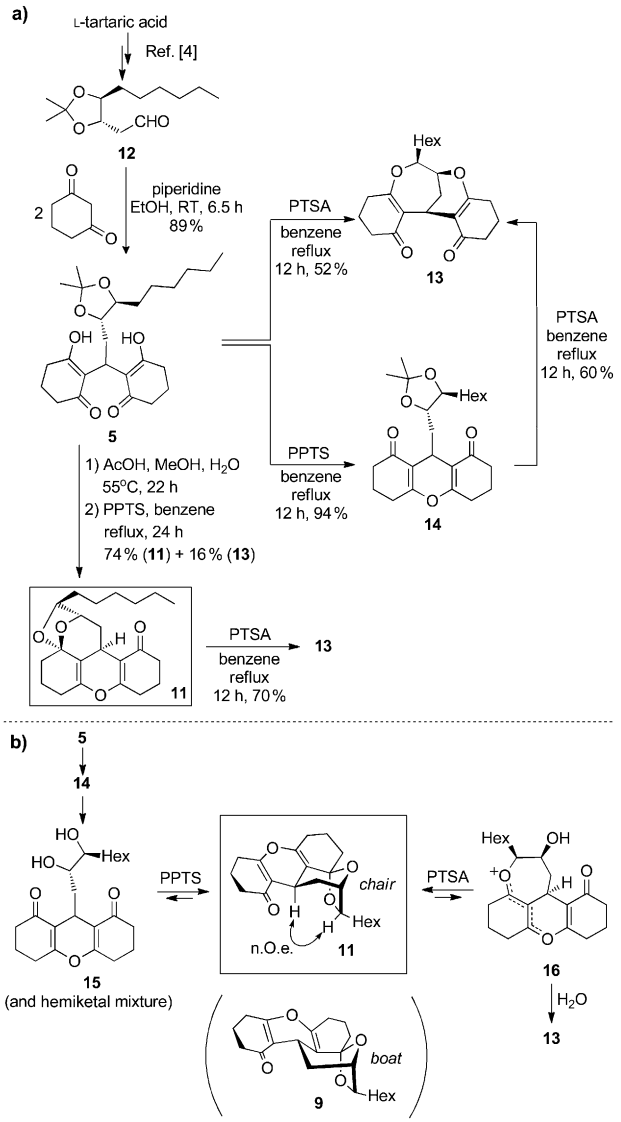
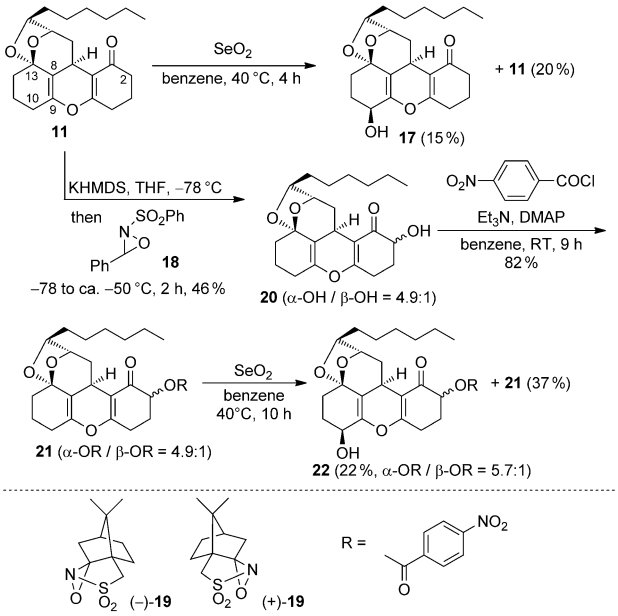


Scheme 2. a) Synthesis of the framework of trichodermatide A. b) Mechanism and origin of diastereoselectivity. Hex = hexyl, PTSA = *p*-toluenesulfonic acid, PPTS = pyridinium *p*-toluenesulfonate, AcOH = acetic acid, n.O.e. = nuclear Overhauser effect.

anthene-1,8-dione ring, as represented by the conversion of **5** to **14**.[5,6] Furthermore, the reaction of **14** under the same conditions in the presence of PTSA also gave **13** in 60% yield. These results suggested that the reaction of **5** with a strong acid (PTSA) in the context of the ketal exchange reaction produced the undesired product **13**, and the tetrahydroxanthene-1,8-dione ring was cleaved under the same reaction conditions. In this reaction, the participation of the secondary hydroxy group(s) in cleaving the ring cannot be ruled out.[7]

Surprisingly, however, the pentacyclic compound **11** was afforded in 74% yield as a single diastereomer together with the undesired **13** (16% yield) by the reaction of **5** under weak acidic conditions (acetic acid) in aqueous methanol followed by treatment of the resulting intermediate with PPTS in refluxing benzene. By careful analysis of the reaction, it emerged that compound **5** was initially converted into **14** and the resulting acetonide was then hydrolyzed to give diol **15** (and its hemiketal mixture), which underwent a PPTS-catalyzed ketal formation reaction to provide the potent intermediate **11**. The diastereoselective production of **11** is presumably due to its greater thermodynamic stability compared with the interconvertible diastereomer **9**, because the ketal ring exists in a chair form in **11** and a boat form in **9** (Scheme 2b). Given that the reaction of **11** with PTSA under refluxing benzene gave **13** in 70% yield, the aforementioned formation of **13** from **5** with PTSA would also occur through compound **11** as a transient intermediate. The formation of bis(enol) ether **13** from **11** apparently involved a 7-membered ring cation intermediate **16**, by energetically unfavorable C–O bond activation by PTSA. Therefore, PPTS is likely an ideal reagent to avoid the acetal cleavage of **11**.

The remaining tasks involved the introduction of three hydroxy groups at the correct positions with the correct stereochemistry. There are two ways to introduce the required hydroxy groups onto **11**. Of the available methods, we initially decided to explore the introduction of the hydroxy group at the C10 position by applying an allylic oxidation strategy (Scheme 3).[8] The oxidation of **11** at the C10 position using

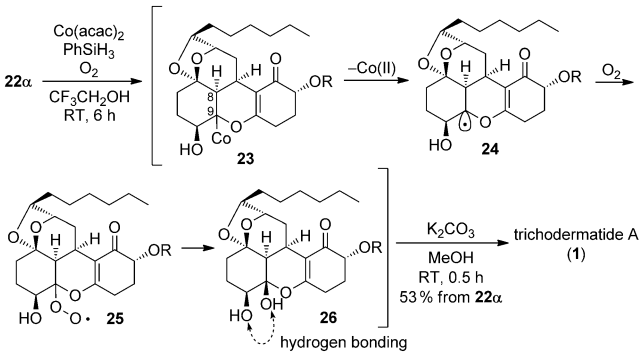


Scheme 3. Introduction of the hydroxy groups at C2 and C10. DMAP = *N*,*N*-dimethyl-4-aminopyridine, KHMDS = potassium hexamethyldisilazide.

a stoichiometric quantity of SeO_2 in benzene gave the desired alcohol **17** in a stereoselective manner, although the yield was only 15% with **11** being recovered in 20% yield. In spite of our best efforts,[9] the yield of **17** could not be improved. The diastereomer of **17** (C10-α-OH) was not detected because the α face of the C8–C9 olefin is probably shielded by the axially oriented C13-α-O ether bond. Although we could synthesize **17**, the difficulty of further conversion forced us to alter the route and investigate the introduction of hydroxy groups at the C2 position first.

The reaction of the cross-conjugated potassium dienolate of **11**, which was kinetically generated with the Davis reagent (**18**),[10] gave **20** as an inseparable diastereomeric mixture (α-OH/β-OH = 4.9:1) in 46% yield. In anticipation of improvements in diastereoselectivity, both enantiomers of the chiral oxaziridine (−)-**19** and (+)-**19**[11] reacted with the potassium dienolate of **11**. However, the selectivity decreased in the reaction with (−)-**19**, whereas the major product of the reaction with (+)-**19** was β-OH; the origin of this diastereoselectivity is not clear. As the C10-oxidized compound could not be afforded by the reaction of **20** with SeO_2, the hydroxy group was protected as the *p*-nitrobenzoate under standard conditions (82% yield, inseparable diastereomeric mixture, α-OR/β-OR = 4.9:1; R = *p*-nitrobenzoyl). The oxidation of **21** with SeO_2 proceeded to provide **22** in 22% yield with unreacted **21** recovered in 37% yield. A separation of the diastereomers was carried out at this stage.

The introduction of the third hydroxy group by the hydration of enol ether also proved problematic. In particular, standard aqueous acidic conditions did not give any desired products. After several efforts, we finally discovered the Co-catalyzed hydration reaction developed by Isayama and Mukaiyama (Scheme 4).[12,13] The reaction of **22α** in the presence of $Co(acac)_2$ (acac = acetyl acetonate) and phenylsilane in trifluoroethanol under O_2 atmosphere afforded **26** with satisfactory and chemo-, regio-, and stereoselectivity. The reaction in THF, a commonly used solvent in cobalt catalysis, barely hydrated the enol ether moiety in **22α**. After exchanging trifluoroethanol for methanol, *p*-nitrobenzoate was hydrolyzed under basic conditions to afford trichodermatide A (**1**) in 53% yield from **22α**. The spectral data of the resulting synthetic **1** were compared with those reported in the literature.[2]



Scheme 4. Proposed mechanism for the conversion of **22α** into **26** and for the total synthesis of trichodermatide A (**1**). acac = acetylacetonate, R = *p*-nitrobenzoyl.

The postulated origin of selectivity that is consistent with experimental data and literature precedent is explained as follows: By comparing the two olefins, the cobalt hydride species likely reacts with nucleophilic enol ether (C8–C9) more readily than the electron-deficient enone (C5–C6). The axially oriented α ether oxygen on C13 could induce an α facial approach of cobalt hydride by coordination; because of this, C8 stereochemistry would be controlled.[14] The observed regioselectivity can account for the generation of a C9 radical stabilized by the adjacent oxygen atom, which would result from the cobalt–carbon bond cleavage in **23**. The C9 radical in **24** would subsequently react with molecular oxygen to afford the peroxyradical **25**, which would be then converted into **26** by the cobalt catalyst and phenylsilane. The stereochemistry of the C9 hydroxy group is fixed at the β position by intramolecular hydrogen bonding with C10-β-OH because of its hemiketal character. To the best of our knowledge, this is the first example of the application of a Co-catalyzed hydration reaction to an enol ether.

In summary, we have described the first synthesis of trichodermatide A (**1**), which involves a short sequence beginning with L-tartaric acid. The highly efficient intramolecular ketal formation reaction furnishes the pentacyclic core of **1** by controlling two of the eight stereogenic centers. Additional short sequences, including cobalt-catalyzed enol ether hydration, successfully functionalize the core of **1** by controlling the remaining four stereogenic centers. These short step sequences should pave the way to a biological development of **1** by efficiently synthesizing its analogues and a molecule probe.

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