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Total Synthesis of Jerangolid D

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Jerangolids A, B, D, E, and H (Figure 1) are secondary metabolites produced by the myxobacterium *Sorangium cellulosum* (strain So ce 307), a myxobacterium isolated in 1987 in the soil of Jerusalem.[1] In vitro tests suggested that jerangolid A (**1**) and D (**2**) might be potential antifungal agents (other jerangolid derivatives were not tested), since they exhibit interesting activities against the developing cells of *Hansenula anomala* and *Mucor hiemalis* (~70 ng/mL), *Pichia membranaefaciens*, *Debaryomyces hansenii*, and *Trichosporon terrestre* (0.1−0.4 μg/mL), and *Trichoderma hamata*, *Botritis cinerea*, and *Candida albicans* (4−7 μg/mL). The mechanism of their action is believed to be similar to that of ambruticin,[2] another well-known myxobacterium isolate. However, even in the case of ambruticin, its mode of the action is not clear. Despite their promising antifungal properties, no total synthesis of any member of this class of natural products has been disclosed so far.[3]

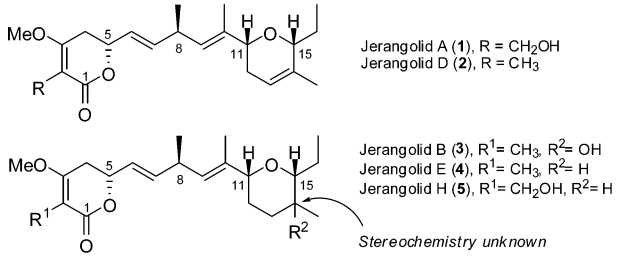


Figure 1. Members of the jerangolid natural products family.

Herein we report a short and convergent total synthesis of jerangolid D. At the onset of this project, it was decided that our approach to **2** should be easily adaptable to the synthesis of various structural analogues of **2**. Hence, it was envisioned that jerangolid D would derive from three fragments: lactone **6**, sulfone **7,** and dihydropyran **8** (Figure 2). These fragments would then be ultimately connected via a modified Julia and a Kocienski−Julia olefination.[4]

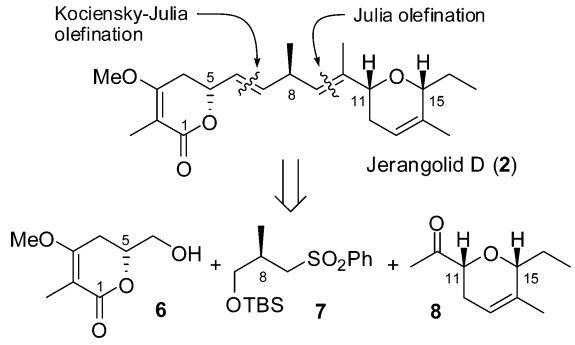
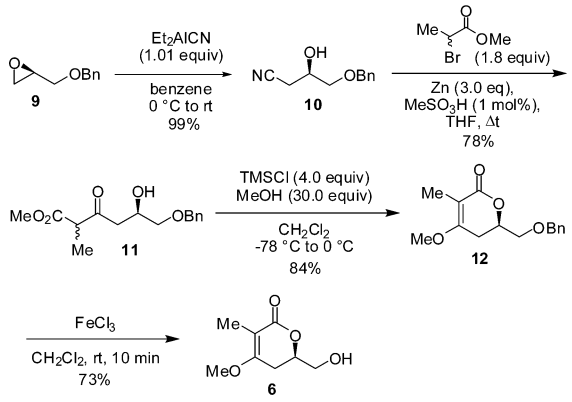


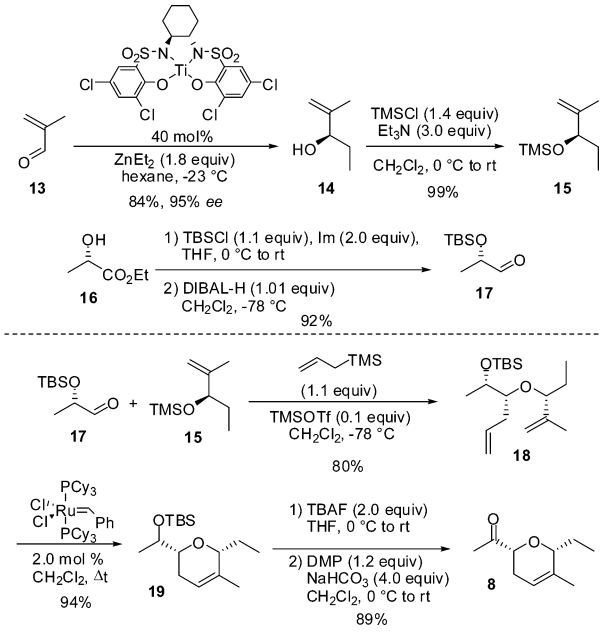
Figure 2. Retrosynthesis of jerangolid D.

The synthesis of lactone **6** is described in Scheme 1. Thus, Et_2AlCN mediated epoxide **9** opening[5] gave an easy access to the

Scheme 1. Synthesis of Lactone **6**



Scheme 2. Synthesis of Pyran **8**



β-hydroxynitrile **10**, which was reacted with methyl bromoacetate in the presence of activated zinc dust.[6] To our delight, the Blaise reaction proceeded smoothly and furnished the desired β-ketoester **11** in 78% yield. Interestingly, the free hydroxyl group was tolerated under the reaction's conditions.[7] The Lewis acid mediated one-pot cyclization/enol ether formation[8] furnished lactone **12** in 84% yield. Finally, $FeCl_3$-promoted deprotection of the benzyl group[9] completed the synthesis of the left-hand fragment **6**.

The construction of the right-hand portion **8** was based upon the diastereoselective three-component Sakurai condensation protocol[10] recently developed in our laboratory (Scheme 2). Accordingly, the readily available ether **15**[11] and aldehyde **17** were mixed with allyltrimethylsilane at −78 °C and a catalytic amount of

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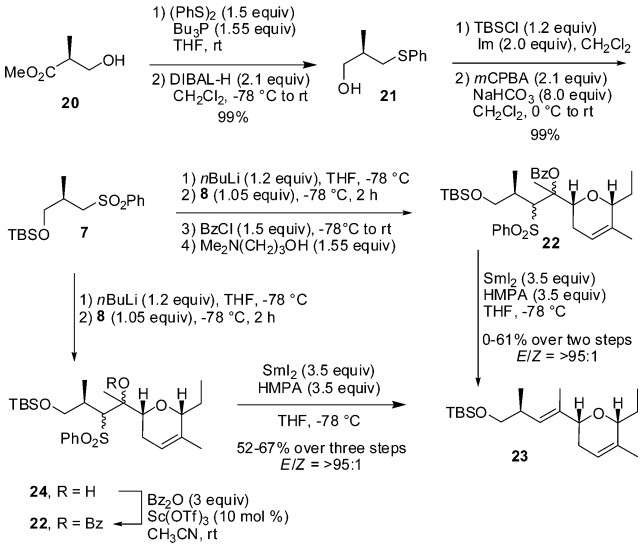
Scheme 3. Synthesis of Sulfone **7** and First Julia Coupling

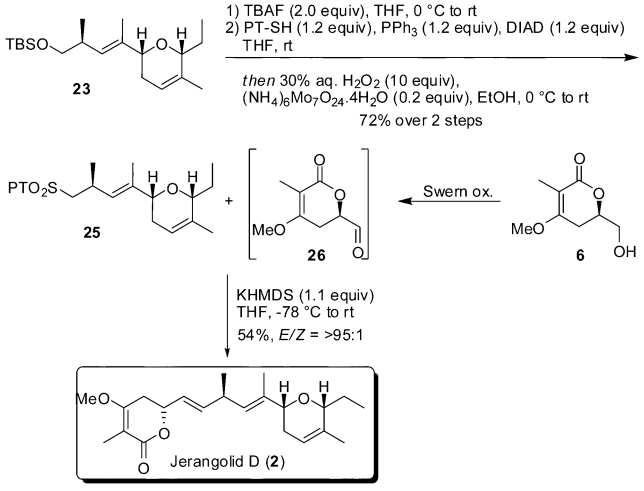


TMSOTf was added. The syn−syn adduct **18** was obtained as a single stereoisomer in 80% yield. Ring closing metathesis followed by TBS removal and oxidation of the resulting alcohol then accomplished the synthesis of the right-hand subunit **8**. The C7−C9 remnant **7** was prepared from the Roche ester **20** in four steps and 97% overall yield (Scheme 3).

Having established an easy access to all three fragments, we then focused our efforts on their union, and a Julia olefination reaction between sulfone **7** and ketone **8** was selected (Scheme 3). It was envisioned that the stereoselective formation of the trisubstituted C9−C10 olefin could be accomplished via the SmI_2-mediated reductive elimination[12] of the β-benzoyloxysulfones **22**. Initially, a one-pot condensation between **7** and **8** followed by the in situ benzoylation of the generated adducts was attempted. Surprisingly, this sequence proved to be irreproducible and therefore a two-steps procedure had to be used.[13] The SmI_2-mediated reductive elimination of the sulfones **22** then furnished the desired olefin **23** in good yield and excellent *E*/*Z* selectivity.

At this stage, only the coupling between fragment **23** and subunit **6** remained to complete the first total synthesis of jerangolid D (Scheme 4). Silylether **23** was thus transformed into the corresponding sulfone **25**. In parallel, alcohol **6** was oxidized into aldehyde **26**. Finally, fragments **25** and **26** were reacted under the standard Kociensky−Julia olefination conditions[14] yielding jerangolid D **2** in 54% yield and >95:1 *E*/*Z* selectivity.

Scheme 4. Completion of the Total Synthesis of Jerangolid D



In summary, we have accomplished the first total synthesis of jerangolid D in 22 steps (12 steps in the longest linear sequence) and 6.1% overall yield (14.5% in the longest linear sequence) starting from the commercially available epoxide **9**, Roche ester **20**, methacrylate **13**, and ethyl lactate **16**. While the synthesis of the left-hand fragment **6** was based upon a Blaise reaction (four steps, 46.7% overall yield), the Eastern ketone **8** was assembled using a diastereoselective multicomponent Sakurai condensation (eight steps, 51.2% overall yield). The synthesis of jerangolid D analogues as well as other members of the jerangolid family is currently in progress in our laboratory.

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Note Added after ASAP Publication: After this paper was published ASAP on February 23, 2007, the Supporting Information was updated with additional (and corrected) experimental details for **21A** and **23A** and NMR spectra for **19A** and **23**. Typographical errors and proton misassignments were also corrected. The revised Supporting Information was published March 7, 2007.

Supporting Information Available: Characterization data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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