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An Approach to a Bislactone Skeleton: A Scalable Total Synthesis of (±)-Penifulvin A

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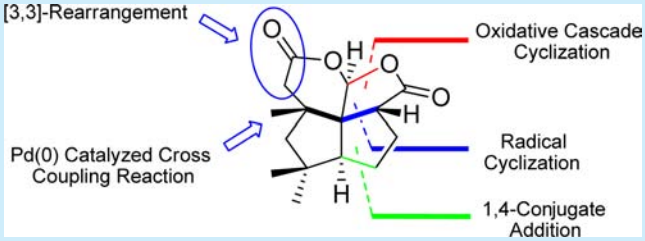
Supporting Information

ABSTRACT: An efficient and scalable total synthesis of the architecturally challenging sesquiterpenoid (±)-penifulvin A has been accomplished via a 12-step sequence with an overall yield of 16%. For the construction of this structurally complex tetracyclic molecule, the key steps used included 1,4-conjugate addition, a Pd(0) catalyzed cross-coupling reaction between an enol phosphate and trimethyl aluminum, Claisen rearrangement using the Johnson orthoester protocol, Ti(III)-mediated reductive epoxide opening−cyclization, Lewis acid catalyzed epoxy-aldehyde rearrangement, and finally a substrate controlled oxidative cascade lactonization process.



Penifulvin A (**1**, Figure 1), a novel sesquiterpenoid with significant insecticidal activity against the fall armyworm

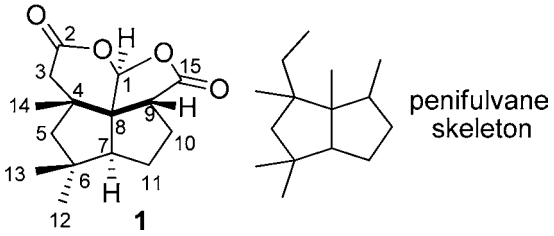


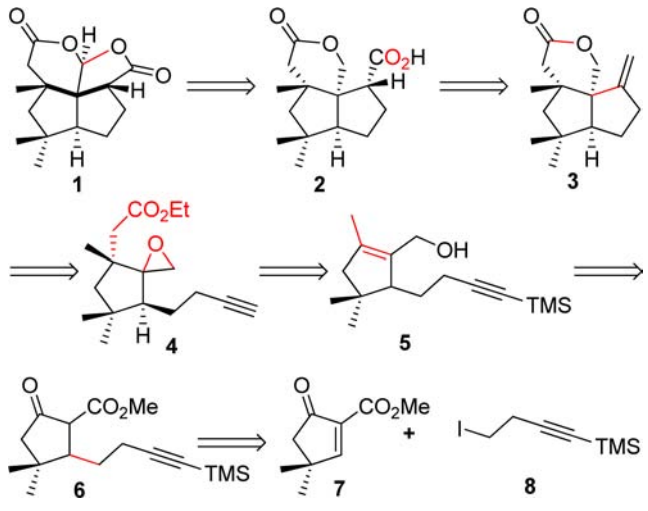
Figure 1. Structure of penifulvin A (**1**).

Spodoptera frugiperda, was isolated in 2006 by Gloer and co-workers from cultures of an isolate of *Penicillium griseofulvum* (NRRL 35584).[1] The structure was elucidated through a combination of spectroscopic methods and chemical correlation and confirmed by single-crystal X-ray crystallographic analysis which revealed a highly complex dioxa[5.5.5.6]-fenestrane skeleton possessing an intriguing arrangement of five contiguous stereogenic centers, among which two are vicinal quaternary stereocenters. The central quaternary carbon shares all four rings of the molecule. Additionally, there is one more quaternary carbon and a unique bislactone moiety in which a γ- and a δ-lactone share a chiral acylal center.

Penifulvins, and other structurally related dioxa[5.5.5.6]-fenestranes like asperaculin A, have attracted the attention of many synthetic chemists.[2] However, only one total synthesis of penifulvin A has been reported to date by the Mulzer group[3] who later extended the elegant strategy to synthesize other members of the family.[4] The complexity toward the total synthesis of **1** arises from the highly compact architecture. A particularly worrisome issue is the construction of two vicinal quaternary stereocenters. Considering the construction of the quaternary centers as one of the main strategic goals, and the lack of many synthetic methods in accomplishing this, we undertook the challenge of synthesizing penifulvin A (**1**), having three such centers, involving a Ti(III)-mediated radical cyclization method to stereoselectively construct the most important central quaternary center of the molecule.[5]

Scheme 1 represents the retrosynthetic blueprint for the target penifulvin A (**1**). Retrosynthetically, **1** was planned to be derived from the intermediate **2** via an oxidative cascade lactonization process. Compound **2** could be obtained from **3** via a substrate controlled Lewis acid catalyzed rearrangement of

Scheme 1. Retrosynthetic Strategy



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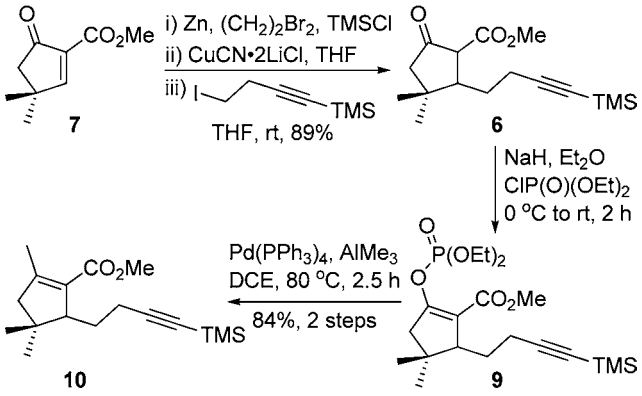
an epoxide intermediate, originating from the exocyclic double bond, to aldehyde followed by its oxidation. In the context of our synthetic plan, we hypothesized that it might be possible to construct both the δ-lactone and the right-hand-side cyclopentane ring in **3** synchronously from the epoxy-ester **4** through a $Cp_2Ti(III)Cl$-mediated radical cyclization. The latter could be assembled from the allyl alcohol **5** by a Claisen type rearrangement using the Johnson orthoester protocol followed by functional group manipulations. The construction of **5** would entail a Pd(0) catalyzed cross-coupling reaction followed by a direct hydride reduction of the ester group. The required ketoester **6** was projected to be readily available from **7** and **8** by a suitable 1,4-conjugate addition process.

Based on the above analysis, our synthesis commenced with the preparation of **6** by performing a cyano-cuprate mediated conjugate addition of 4-iodo-1-trimethylsilylbutyne (**8**)[6] to an enone **7**[7] as described in Scheme 2.[8] With keto-ester **6** in hand,

Scheme 2. Conjugate Addition and Subsequent Pd(0) Catalyzed Cross-Coupling Reaction To Access 10

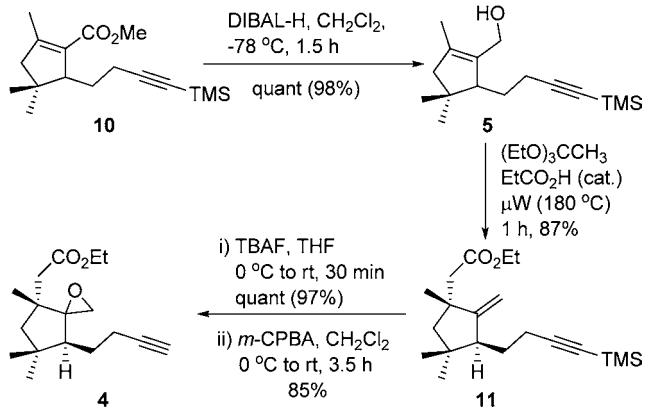


the stage was set for the insertion of a methyl group (14 Me). For that, **6** was treated with sodium hydride and diethyl chlorophosphate to give the enol phosphate **9**, which without purification was subjected to a $Pd(PPh_3)_4$ catalyzed cross-coupling reaction with trimethylaluminum in 1,2-dichloroethane (DCE) at 80 °C to give **10** in 84% overall yield.[9]

Next, our attention was shifted to the crucial construction of the quaternary stereocenter (C_4). Thus, **10** was treated with DIBAL-H and the resulting cyclopentenyl alcohol (**5**) was subjected to the Claisen rearrangement under the microwave assisted standard Johnson orthoester protocol[10] to furnish **11** with 85% overall yield over two steps (Scheme 3). The stereostructure of **11** was confirmed from the NOESY experiment. The NOE cross peak between C_7−H/C_3−H (penifulvin A numbering) indicated that these two were *syn* to each other. This was further confirmed by the strong NOEs between C_7−H/12-CH_3 and 13-CH_3/14-CH_3 (penifulvin A numbering; see Supporting Information). The relative stereochemistry observed in **11** was due to the steric crowding offered by the alkynyl chain, which directed the [3,3]-sigmatropic rearrangement from the less sterically hindered face of the double bond.

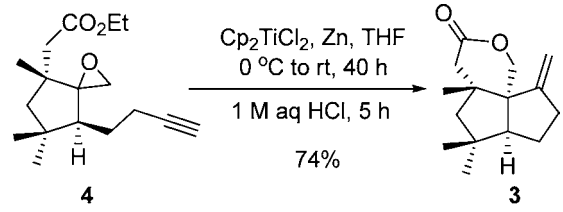
After the successful construction of the C_4-quaternary center, we next proceeded toward the construction of the most important central quaternary center (C_8) of the molecule. To achieve that, desilylation of **11** was followed by epoxidation with *m*-CPBA (Scheme 3) to set the stage for implementing the [Cp_2TiCl] (generated *in situ* from Cp_2TiCl_2 and activated Zn

Scheme 3. Claisen Rearrangement and Synthesis of 4



dust) mediated reductive epoxide opening[11] followed by 5-*exo*-dig cyclization onto the alkyne.[12] Construction of the δ-lactone ring was an important task during the radical cyclization process that could be achieved by the addition of 1 M aq HCl to the reaction mixture leading to the formation of lactone **3** from its counterpart in 74% overall yield (Scheme 4).

Scheme 4. Ti(III)-Mediated Reductive Cyclization of Epoxy-ester 4



The relative stereochemistry of **3** was confirmed by the NOE cross peaks between C_7−H/C_1−H, C_7−H/12-CH_3, and 13-CH_3/14-CH_3 (Figure 2; see also Supporting Information).

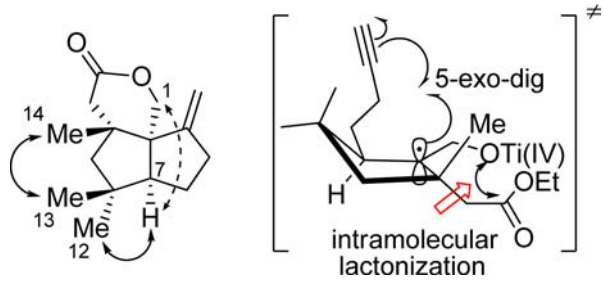


Figure 2. Characteristic NOEs of **3** and proposed transition state of the intermediate radical.

The remaining functionality that had to be constructed was the γ-lactone moiety. Based on the clue from the oxidative cascade cyclization step of (−)-penifulvin A synthesis by Mulzer et al.,[3] we came to a conclusion that we could also adopt a similar proximity based functional group manipulation strategy to construct the bislactone component of the molecule. Toward that objective, we surmised that the carboxylic acid **2** might be the optimal substrate to accomplish the final synthesis of penifulvin A (**1**).

After epoxidation of the exocyclic double bond with *m*-CPBA, BF_3-etherate catalyzed epoxy-aldehyde rearrangement[13]

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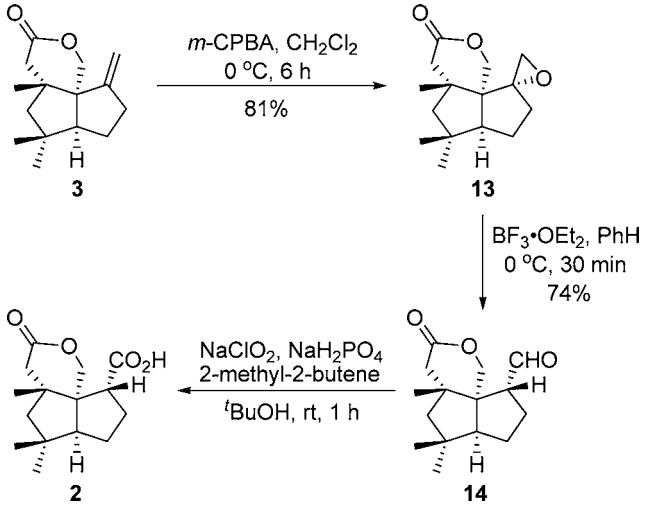
followed by Pinnick oxidation[14] delivered the requisite intermediate **2** (Scheme 5). The relative stereochemistry of

Scheme 5. Synthesis of Carboxylic Acid Fragment 2



the newly generated center C_9 in aldehyde **14** was confirmed by an NOESY experiment. The NOESY spectrum showed a strong dipolar coupling between C_9–H/14-CH_3 indicating the –CHO group was on the same side of the δ-lactone ring.

3D modeling (Figure 3) suggested that **3** adopts a conformation in which the C_4-Me group blocks the *si* face so

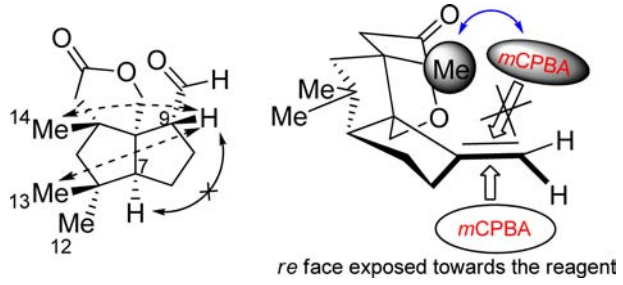


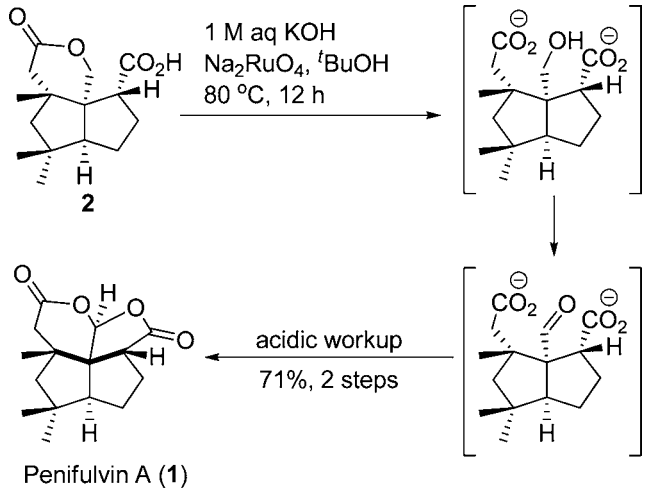
Figure 3. Characteristic NOEs in **14** and proposed model of **3** rationalizing the facial selectivity during epoxidation.

that the *re* face was anticipated to be more exposed toward *m*-CPBA, and thereafter a stereoselective 1,2-hydride shift fixed the C_9 stereocenter leading to the formation of the desired aldehyde **14**.

We next focused our attention on the introduction of the final hydroxyl group at the C_1 position. Introduction of the hydroxyl group in **2** should also install the expected stereochemical triad of the δ-lactone which would be suitable for further intramolecular lactonization to form the γ-lactone ring. A series of reactivity problems were encountered, and happily, this goal was successfully achieved by using sodium ruthenate (Na_2RuO_4) mediated oxidative cascade cyclization. First δ-lactone in **2** was hydrolyzed under basic conditions paving the way for the oxidation of the resulting open-ring δ-hydroxyl group to an aldehyde, in the same pot, with sodium ruthenate[15] which was followed by two consecutive intramolecular lactonizations under acidic conditions to provide the target (±)-penifulvin A in 71% overall yield (Scheme 6).

We believed that this cascade reaction would proceed stereoselectively to install the requisite *cis*-fused bislactone

Scheme 6. End Game towards the Total Synthesis of (±)-1



ring junction, which turned out to be the case. The selectivity observed during the hydroxyl group installation in the hemiacetal stage is believed to arise to avoid the flagpole–flagpole interaction (Figure 4).

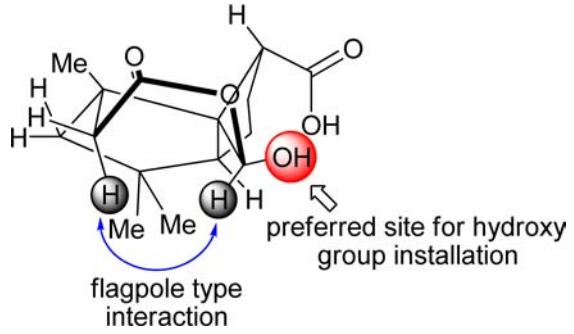


Figure 4. Model rationalizing the stereochemical triad during lactonization.

The spectroscopic data for the synthetic molecule were in full accord with those reported for the natural product and also presented by Mulzer et al. Finally, the formation of the target molecule in its desired stereochemistry was unambiguously confirmed by single crystal X-ray crystallographic analysis[16] (Figure 5).

In conclusion, we have developed an efficient route to penifulvin A in racemic form (12 steps, ~16% overall yield), confirming the earlier structural reassignment. The salient features of our effort involved the Pd(0) catalyzed cross-coupling reaction, Johnson orthoester Claisen rearrangement, reductive epoxide cleavage–cyclization by Ti(III), and Lewis acid catalyzed epoxide opening to aldehyde followed by sodium ruthenate mediated oxidative cascade lactonization as key steps. The synthetic route is characterized by high diastereoselectivity in the creation of all the stereogenic centers of the molecule either by reagent or by substrate control and required only one protecting group. All the reaction sequences are amenable for scale up and suitable for the synthesis of other related terpenoids.

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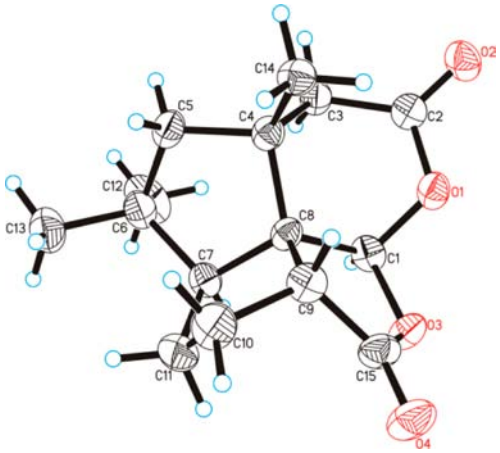

Figure 5. X-ray crystal structure of (±)-penifulvin A (**1**).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new compounds described herein, including CIF file (CCDC no. 981629) for racemic crystal of penifulvin A (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) The X-ray structure of racemic penifulvin A (having *Pbca* space group, CCDC no. 981629) is fully consistent with the X-ray structure of enantiopure (−)-penifulvin A (having $P2_12_12_1$ space group) provided by Gloer et al. (CCDC no. 284388; see ref 1).