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Total Synthesis of (−)-Penifulvin A, an Insecticide with a Dioxafenestrane Skeleton

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The fall armyworm (*Spodoptera frugiperda*) is native to the tropical regions of the western hemisphere from the United States to Argentina, and its larvae cause enormous damage by consuming foliage of a variety of field crops, including barley, buckwheat, cotton, corn, oat, rice, sugar cane, soybean, tobacco, wheat, and others.[1] In Florida, for example, the fall armyworm is the most significant pest of corn. As resistance to pesticides has been noted and is expected to become increasingly problematic from year to year, a way out of this dilemma would be the introduction of new environmentally benign pesticides. In this respect we were intrigued by a recent paper[2] in which Gloer and co-workers described a novel sesquiterpenoid named penifulvin A (**1**), isolated from the fungus *Penicillium griseofulvum* (syn. *P. patulum* Bain.; *P. urticae* bain). This metabolite, which belongs to a larger family of penifulvins A−E (Figure 1),[3] not only shows significant insecticidal activity in assays against the fall armyworm but also appeared, due to its unusual and complex molecular architecture, an attractive target for total synthesis. Furthermore, for procuring larger quantities, acquiring SAR data and elucidating the full bioprofile of the compound, a rational nonbiological access was of importance.

The overall structure of **1**, which has been secured by X-ray crystallographic analysis,[2] reveals a complex oxa-fenestrane[4] structure in which four rings share a central quaternary carbon. Additionally there are two more quaternary carbons, a γ- and a δ-lactone sharing the acylal center, and a total of five stereogenic centers congested on a 15 carbon skeleton. This ring system, whose absolute configuration is unknown, has not been described previously in literature. Herein we report the first total synthesis of racemic and optically active **1** from inexpensive *o*-tolylacetic acid (**2**) (Scheme 1).

For our key transformation, we focused on Wender's marvelous photoinduced cyclization of arene olefins[5] such as **3a** (optically active) and **3b** (racemic) (Scheme 3), both readily available from **2** (Scheme 2). Racemic carboxylic acid **3b** was obtained from the alkylation of the dianion. The stereogenic center in **3a** was introduced via Myers' alkylation[6] in 95% ee leading to amide **5** in two steps. As **5** undergoes racemization on basic hydrolysis, it was reduced to the alcohol.

The photoreaction of **3a,b** (Scheme 3) starts with a formal [3 + 2] cycloaddition to generate exciplex **E** which undergoes 1,3-bond formation to deliver the allylic regioisomers **6** and **7** (**6a:7a** = 55:45; **6b:7b** = 46:54). The stereochemical course of the addition is controlled by the stereogenic center in compound **3**. According to the A^{1,3}-strain model[7] steric interactions between the aromatic methyl and the R group are minimized. This effect strongly disfavors conformations such as **syn-3**, so that **anti-3** can be assumed to be the preferred conformation in the photocyclization.

The synthesis was completed in different ways for the racemic and the optically active series (Scheme 4). Thus, the optically active regioisomers **6a** and **7a** were separated by chromatography, and

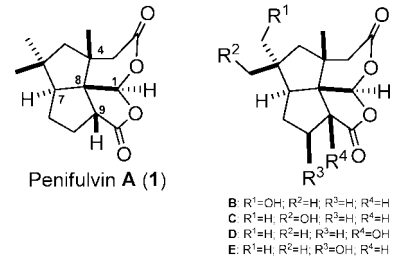
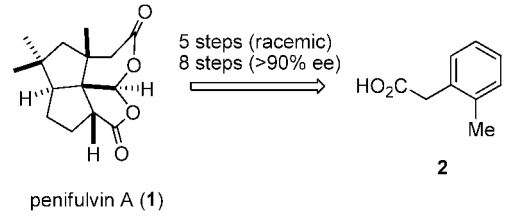
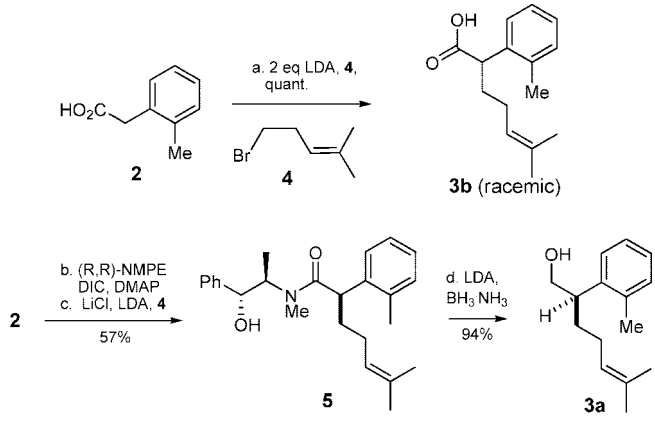


Figure 1. Structures of Penifulvins A−E.

Scheme 1. Retrosynthetic Overview



Scheme 2. Preparation of Photocyclization Precursors **3a** and **3b**[a]

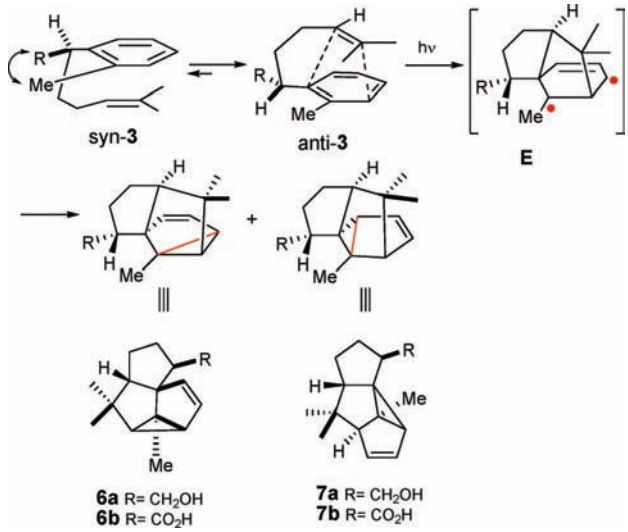


[a] Reagents and conditions: (a) 2 LDA, −78 °C, THF, 5-bromo-2-methyl-2-pentene (**4**); (b) (*R*,*R*)-N-MPE, DIC, DMAP, DCM; (c) LiCl (6 equiv) LDA, **4**, THF, rt, 24 h; (d) LDA, BH_3NH_3, THF. (*R*,*R*)-N-MPE = (*R*,*R*)-N-methylpseudoephedrine, DIC = diisopropyl carbodiimide, DMAP = dimethylaminopyridine, DCM = dichloromethane, LDA = lithium diisopropyl amide.

6a was reduced under Birch-like conditions (Scheme 4) to give triquinanyl alcohol **8**, which was oxidized to carboxylic acid **9**. Ozonolytic cleavage of the double bond generated the nonisolable dialdehyde **10** which immediately cyclized to lactol **11**.[8] Oxidation gave **1**, whose spectral data were in full accord with those of an authentic sample (see Supporting Information). The optical rotation of our material was $[\alpha]_D^{20} = -127$ (*c* 0.35, $CHCl_3$) compared to a

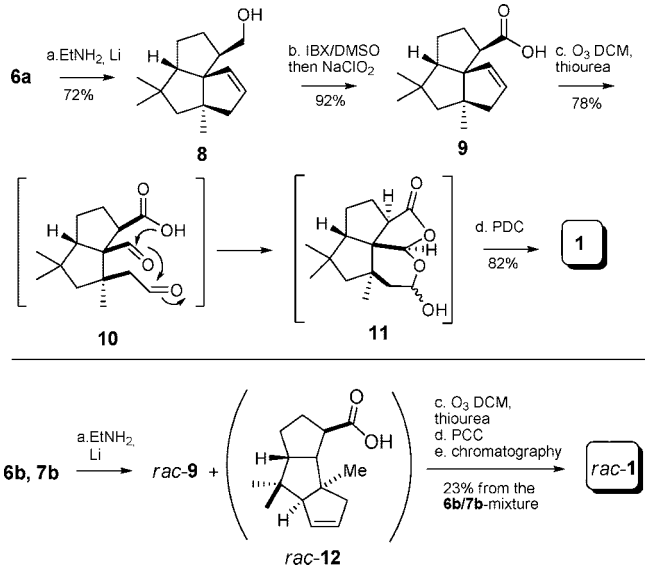
 10.1021/ja8083048 CCC: $40.75

Scheme 3. Photocyclization of **3a,b**[a]



[a] Conditions: *hν*, pentane, 22 °C, 2 h (Series **a**: R = CH_2OH, optically active, 70% yield. Series **b**: R = CO_2H, racemic, 62% yield).

Scheme 4. Completion of the Synthesis[a]



[a] Reagents and conditions: (a) $EtNH_2$, Li, THF, −78 °C, 7 h; (b) IBX, DMSO, 22 °C, 20 min, then $NaClO_2$, 2-methyl-2-butene, *tert*-BuOH, NaH_2PO_4, 1 h; (c) O_3, DCM, −78 °C, 2 min, then thiourea, 22 °C, 40 min; (d) PDC (4 equiv), DCM, 22 °C, 20 min, then AcOH (20 equiv), 20 min. IBX = 2-iodoxybenzoic acid, DMSO = dimethylsulfoxide, DCM = dichloromethane, PDC = pyridinium chlorochromate.

value of $[\alpha]_D^{20} = -133$ (*c* 0.50, $CHCl_3$) of the authentic sample.[9,10] This result also confirms the absolute configuration (1*S*, 4*R*, 7*S*, 8*S*, 9*R*) of **1**.

In the racemic series, the mixture of **6b** and **7b** was carried through the sequence without separation. Thus, reduction of this mixture under Birch-like conditions was directly followed by ozonolysis and oxidation, and *rac*-**1** was finally obtained in pure form by column chromatography and crystallization. Compound *rac*-**12** was not isolated.

In conclusion we have disclosed a concise synthesis of penifulvin A in racemic and optically active form from *o*-tolylacetic acid in altogether 5 steps (14% overall yield) and 8 steps (8% overall yield), respectively. Apart from the photocyclization which leads to readily separable regioisomers, the synthesis is stereo- and regiocontrolled, does not require protecting groups or purification of intermediates, and is scalable. Precursor **2** can be modified by introducing substituents onto the aromatic ring and/or the aliphatic side chain, so that a variety of analogues, among them penifulvins B−E, should be available for performing SAR tests in the insecticidal role.

Acknowledgment. We thank Hanspeter Kählig, Susanne Felsinger, and Lothar Brecker for NMR analysis; Gerald Wagner for assistance; Professor J. B. Gloer, Iowa State University, for fruitful discussions and a generous sample of **1**; and the Austrian Science Fund (FWF) for financial support.

Supporting Information Available: Detailed experimental procedures and characterization of new compounds and comparison NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Lactol **11** was formed as a mixture of anomers.

(9) The rotation of $[\alpha]_D^{20} = -3.5$ (*c* 0.17, MeOH), reported for **1** in ref 2 is wrong. We corrected the value by measuring an authentic sample, which was kindly provided by Professor J. B. Gloer.

(10) The enantiomeric excess of our synthetic sample of **1** was determined via the chiral ^1H NMR shift reagent ($[Eu(hfc)_3]$ to be >90%.

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