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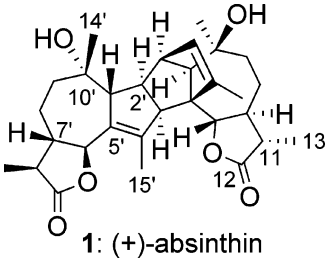
Total Synthesis of Absinthin

Weihe Zhang,[†,‡] Shengjun Luo,[†] Fang Fang,[†] Qingshou Chen,[†] Hanwei Hu,[†] Xueshun Jia,[‡] and Hongbin Zhai*,[†]

Laboratory of Modern Synthetic Organic Chemistry and State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China 200032, and Department of Chemistry, Shanghai University, Shanghai, China 200436

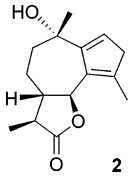
Received October 6, 2004; E-mail: zhaih@mail.sioc.ac.cn

(+)-Absinthin (**1**) was isolated by Herout[1] et al. as a main dimeric guaianolide from wormwood, *Artemisia absinthium* L., in 1953. The structural elucidation of this triterpene was completed in the 1980s using NMR spectroscopic[2] and X-ray crystallographic[3] analyses. The medicinally useful bitter herb, absinthium, has been used as stomachic tonic and anthelminthic.[4] Practitioners of traditional Chinese medicine (TCM) have successfully applied both fresh and dried plants of absinthium to treat acute bacillary dysentery.[5] In addition, Russian scientists discovered in 1977 that absinthin (10 mg/kg/day) given orally for 8 days to rats with experimental gastric ulcers alleviated the inflammation by 57% and stimulated regeneration of the stomach wall.[6]



1: (+)-absinthin

(+)-Absinthin was found to give rise to artabsin (**2**) upon heating.[7] Thus, biosynthetically, the triterpene might have been generated from the dimerization of two identical Diels−Alder partners **3**, which contains a cyclopentadiene system within the guaianolide skeleton. Moreover, diene **3** plausibly represents an intermediate in the thermolytic generation of **2** from **1**. The structural characteristics of **1** include a unique heptacyclic framework in which 14 stereocenters are densely imbedded. To our surprise, no reports have appeared so far addressing the synthesis of this novel sesquiterpene lactone dimer.



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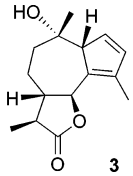

3

The structural complexity of **1** along with its physiological activity promoted us to embark on a novel, expeditious synthesis. Our overall synthetic strategy is outlined in Figure 1. Due to its intrinsic resemblance to artabsin (**2**), *O*-acetylisophotosantonic lactone[8] (**4**, a photolysis product of santonin[9]) was envisioned as an excellent starting material leading to (+)-absinthin. Lactone **4** can be modified to give the cyclopentadiene derivative (**5**), which is expected to produce **6** via a Diels−Alder-type dimerization. The remaining synthetic task is the inversion of the C10/C10′ configuration.

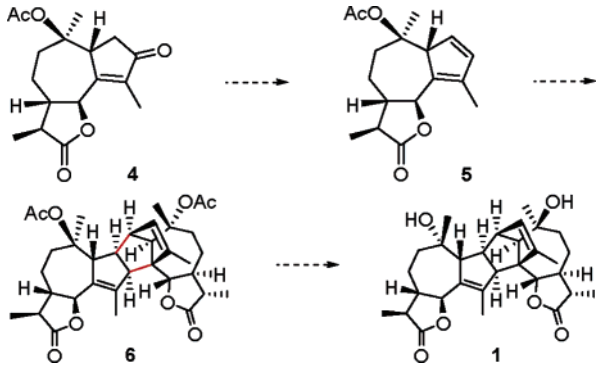

Figure 1. Proposed synthesis of (+)-absinthin (**1**).

As depicted in Scheme 1, santonin[9] (**7**), a commercially available material, was photolyzed with a high-pressure Hg lamp (150 W) in HOAc in a quatz reactor under a nitrogen atmosphere (16 °C, 7 h, 38.6%) to give *O*-acetylisophotosantonic lactone (**4**).[8] Shapiro reaction (200−1000 mol % LDA, THF) of the *p*-toluenesulfonylhydrazone of **4** at −78 °C, 0 °C, or room-temperature failed to produce diene **5**. Thus, reduction of the enone carbonyl was pursued. Treatment of **4** with $NaBH_4$ (105 mol %) in methanol at room temperature for 30 min afforded a pair of (equally useful) diastereomeric alcohols **8** in almost quantitative yield (99%).[10] Again, transformation of **8** to the corresponding sulfonates (OMs, OTs, or OTf) followed by base-promoted elimination did not produce the desired cyclopentadiene derivative. Therefore, Mitsunobu arylselenylation of **8** with *o*-nitrophenyl selenocyanate (130 mol %) and tributylphosphine (136 mol %) in THF at room temperature for 1 h produced in 72% yield selenides **9**, exposure of which to $NaIO_4$ (200 mol %) in MeOH−H_2O (2:1) at room temperature for 45 min led to the formation of the substituted cyclopentadiene (**5**) in 66% yield. Under the reaction conditions, the potential 2,3-rearrangement[11] did not materialize.

When stored neat under a nitrogen atmosphere at room temperature, diene **5** slowly underwent the desired biomimetic dimerization, a process that proceeded via a regio- and stereospecific Diels−Alder reaction. After 10 days, the heptacyclic product **6**, with the formation of two new bonds (C2−C2′ and C5−C3′, in red), was isolated in 72% yield, while the unreacted starting material was recycled. The two identical Diels−Alder partners **5**, approaching each other from their less hindered face (in view of the cyclopentadiene moieties), adopted a head-to-head orientation with regard to the lactone carbonyl groups (see **6**, C12/C12′, in green, Scheme 1), to minimize the steric interactions. The structure of the dimer was unambiguously confirmed using X-ray crystallographic analysis. Remarkably, the potential 1,5-H shift was not observed.

Saponification of **6** with 10% methanolic potassium hydroxide solution (excess) at 30 °C overnight followed by acidification to pH 2 with 6 M HCl smoothly furnished 10-*epi*-10′-*epi*-absinthin

[†] Shanghai Institute of Organic Chemistry.
[‡] Shanghai University.

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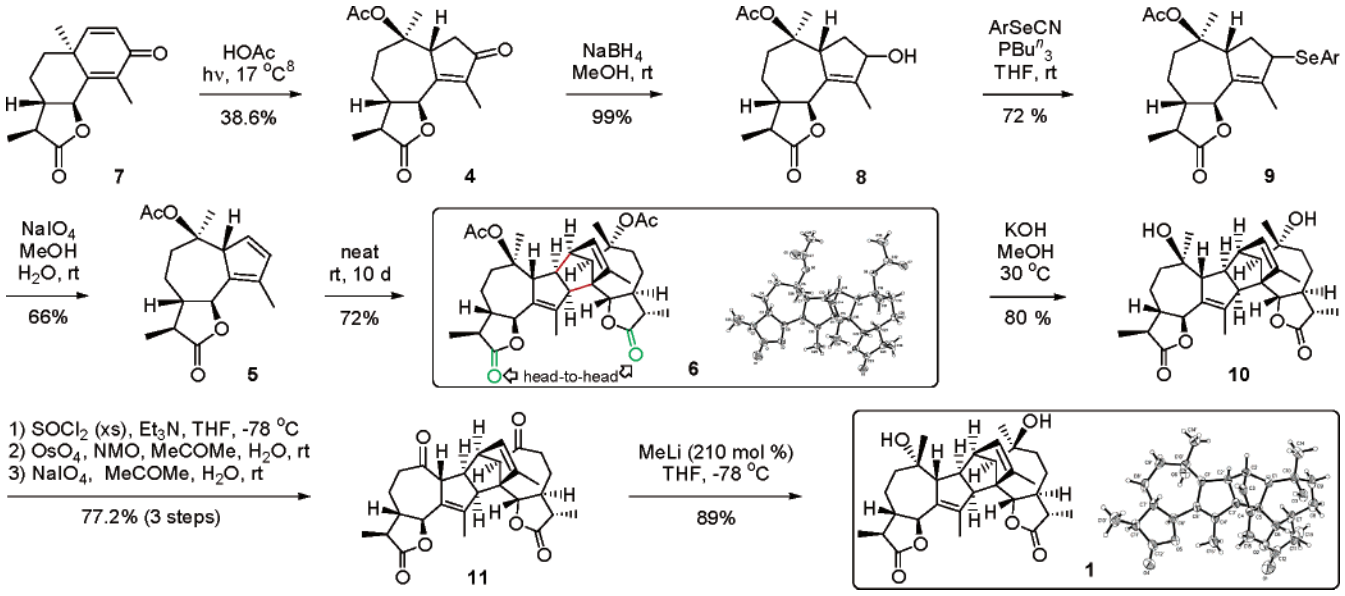
Scheme 1



(**10**) in good yield (80%). At this stage, the possibility of direct configuration inversion at C10/C10′ of **10** was vigorously explored. Shi and co-workers[12] reported a simple and practical Mitsunobu approach to transform chiral *tert*-alcohols to aryl ethers with complete configuration inversion at elevated temperatures (80−100 °C). Mukaiyama's preparation[13] of inverted *tert*-alkyl carboxylates from chiral *tert*-alcohols involved a new type of oxidation−reduction condensation using 2,6-dimethyl-1,4-benzoquinone. However, neither of these methods seemed to operate on our substrate. Thus, after a three-step reaction sequence of (1) double kinetic dehydration {$SOCl_2$ (2600 mol %), Et_3N (2400 mol %), THF, −78 °C, 7 h} to form a bis(terminal alkene), (2) selective dihydroxylation at both terminal carbon−carbon double bonds {OsO_4 (6 mol %), NMO (400 mol %), MeCOMe−H_2O (8:1), rt, 3 h}, and (3) double cleavage of the two vicinal diols {$NaIO_4$ (400 mol %), MeCOMe−H_2O (2:3), rt, 2 h}, diol **10** was converted to dione **11** {$[\alpha]^{20}_D$ +404.4 (*c* 1.0, $CHCl_3$)} in 77.2% overall yield. Finally, chemo- and stereoselective methylation of **11** at the keto carbonyls (C10/C10′) {MeLi (1.7 M, in ether, 210 mol %), THF, −78 °C, 30 min} afforded in 89% yield (+)-absinthin (**1**) as colorless crystals {mp 165−166 °C (dec) (from benzene); lit.[1c] mp 165 °C (dec) (from benzene)}. The $[\alpha]^{20}_D$ data of **1** at different concentrations were found to be +107.0 (*c* 1.9, $CHCl_3$) and +103.5 (*c* 1.0, $CHCl_3$), which was prominently different from the reported value[1c] {$[\alpha]^{20}_D$ +180 (*c* 1.9, $CHCl_3$)}.[14] The structure of **1** was confirmed by X-ray crystallographic analysis. The ^1H and ^{13}C NMR spectroscopic data were in accord with those disclosed in the literature.[2]

In summary, (+)-absinthin (**1**) was efficiently constructed in nine steps and in 18.6% overall yield from *O*-acetylisophotosantonic lactone,[8] a known intermediate available in one step from santonin.[9] The present synthesis features Mitsunobu arylselenylation, oxidative elimination of allylic arylselenides, a biomimetic dimerization via regio- and stereospecific Diels−Alder reaction, and a four-step stereochemical inversion of the highly sterically congested tertiary alcohol. Completion of this synthesis has not only tackled the formidable synthetic challenges in assembling structurally complex (+)-absinthin but also paved an efficient synthetic route to a series of medicinally attractive absinthin analogues.

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Supporting Information Available: Experimental procedures, analytical data, and copies of ^1H and ^{13}C NMR spectra for **5**, **6**, **10**, **11**, and **1** (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Analytical data of the santonin (or α-santonin) sample used: mp 172−174 °C {lit.[4] mp 170−173 °C}; $[\alpha]^{20}_D$ −174.6 (*c* 2.0, MeOH) {lit.[4] $[\alpha]^{25}_D$ −170 ∼ −175 (*c* 2.0, alc)}.

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