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A Concise Approach for the Total Synthesis of Pseudolaric Acid A

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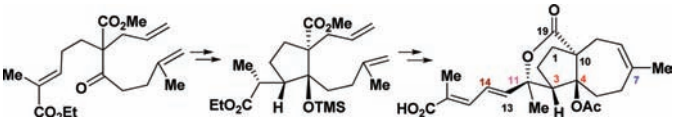
ABSTRACT



A new strategy for the stereoselective total synthesis of natural product pseudolaric acid A (1) was accomplished in 16 steps from commercially available starting material, featuring a samarium diiodide (SmI_2)-mediated intramolecular alkene-ketyl radical cyclization and a ring-closing metathesis (RCM) reaction to stereoselectively cast the unusual *trans*-fused [5−7]-bicyclic core of pseudolaric acid A (1).

Pseudolarix kaempferi (pinaceae)[1] is a Chinese folk medicine for the treatment of fungal infections of skin and nails.[2] To date, over 20 natural products including pseudolaric acid A (**1**) and structures **2**−**4** (Figure 1) have been isolated from extracts of its root bark.

The structure of pseudolaric acid A has been established by X-ray crystallographic analysis[3] combined with a circular dichroism (CD) excision chirality method.[4] The structure of pseudolaric acid A presents a significant challenge to synthesis: a rarely seen *trans*-fused [5−7]-bicyclic core substituted with an acetoxy group and a lactone at the ring junction. Preliminary biological assays show that pseudolaric acids exhibit significant biological activities against fungi and multidrug-resistant tumors.[1]

The structural complexity as well as biological significance of the pseudolaric acids has attracted synthetic interest worldwide; in particular, Chiu et al.[5] have synthesized

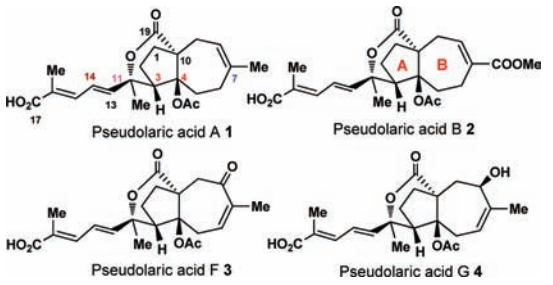


Figure 1. Pseudolaric acids A, B, F, and H.

(−)-**1** (26 steps) and Trost et al.[6] have synthesized (−)-**2** (28 steps), respectively, and several elegant model studies[7] have been reported. While the total syntheses of **1** and **2** have been achieved, the need to develop more concise routes remains in order to provide an ample supply of these valuable compounds for the purpose of facilitating further therapeutic investigations, since their availability from natural resource is limited.[1]

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At our laboratories, we aimed to develop a strategy to rapidly establish the *trans*-fused [5−7]-bicyclic core in a stereoselective manner, which would constitute a foundation for the synthesis of pseudolaric acids A and B. We also envisaged that the generated bicyclic core could be further elaborated by the installation of suitable functionalities so as to accomplish other family members of pseudolaric acids, such as **2**−**4** shown in Figure 1.

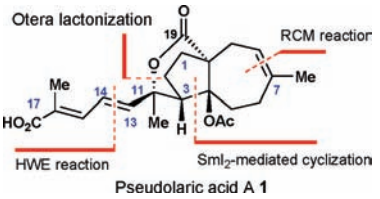
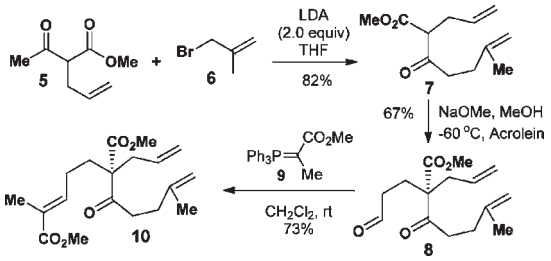


Figure 2. Synthetic analysis.

Figure 2 outlines our strategy on the disconnection of pseudolaric acid A (**1**). Key steps thereof include the formation of *trans*-fused bicyclic core by a SmI_2-mediated alkene−ketyl radical cyclization[8] and a RCM reaction.[9] The former has been widely applied in syntheses[10] given it may create not only high yield but also stereoselectivity,[11] and the latter has been regarded as one of the most powerful reactions in natural product synthesis.[12] The rest of the major challenges, namely the construction of lactone and side chain were intended to be addressed by a Cu-mediated oxidative deformylation,[13] an Otera lactonization[6,14] and a Horner−Wadsworth−Emmons (HWE) reaction.

We commenced from preparing the key intermediate **7** (Scheme 1). Diene **7** was synthesized in 82% yield via alkylation of the dianion derived from ketoester **5** with allyl bromide **6**.[15] Compound **7** then underwent a Michael addition with acrolein in the presence of NaOMe to give aldehyde **8** in 67% yield. Then, upon the treatment of aldehyde **8** with Wittig reagent **9**, **10** was obtained in 73% yield. We also envisaged that asymmetric synthesis of either enantiomer of intermediate **10** could in principle be achieved via the asymmetric Michael addition by **7**.[16]

Scheme 1. Synthesis of Intermediate **10**



We then explored the route for the synthesis of 2-hydroxycyclopentanecarboxylate **11a** (Scheme 2). Although SmI_2-mediated acyclic alkene−ketyl radical cyclization had been widely used to construct structurally diverse natural product scaffolds, the stereoselective synthesis of the *trans*-fused [5−7]-bicyclic core however remains rare.[17] As the stereochemical outcome of SmI_2-mediated cyclization tends to be highly solvent-, additive- and substrate-dependent,[18] we therefore attempted to apply this reaction to synthesize **11a**.

To this end, we initially profiled the SmI_2-mediated alkene-ketyl radical annulation reaction in the solvents of THF, acetonitrile, and DME, respectively. Unfortunately, poor diastereoselectivity was observed in all those cases with low yields (see the Supporting Information for details).

Based on the knowledge that additives such as HMPA or DMPU may increase the reduction potential of SmI_2 and cosolvents such as MeOH or ^{t}BuOH as proton source may affect the efficiency of quenching intermediate anions in reactions,[19] we carried out the SmI_2-mediated cyclization in the presence of HMPA (10 equiv) and ^{t}BuOH (10 equiv).

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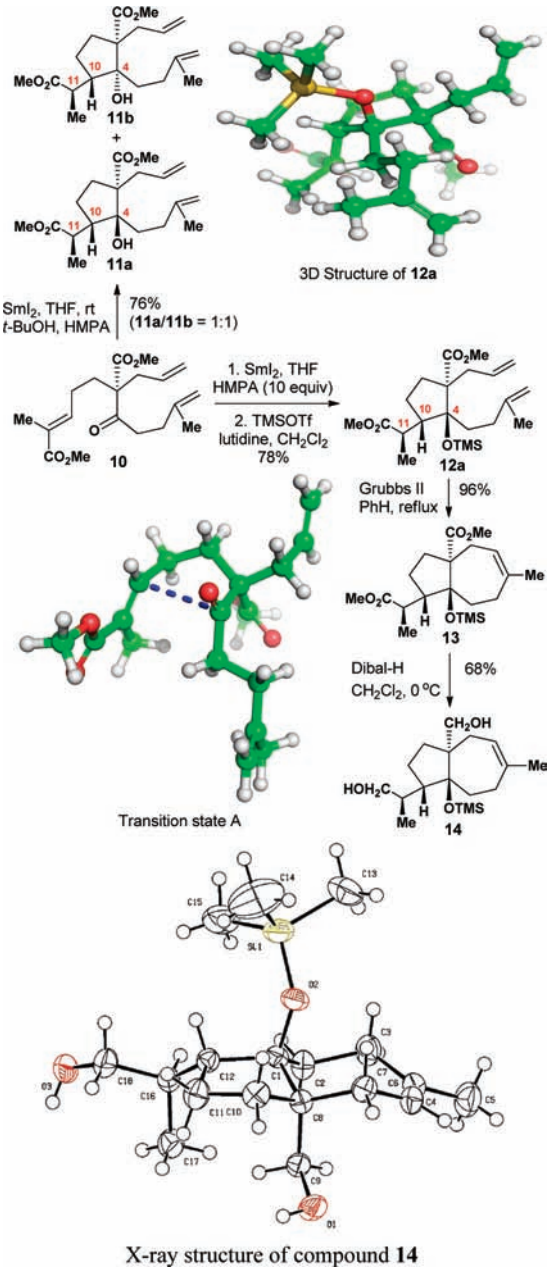
Scheme 2. Synthesis of Compound **13**

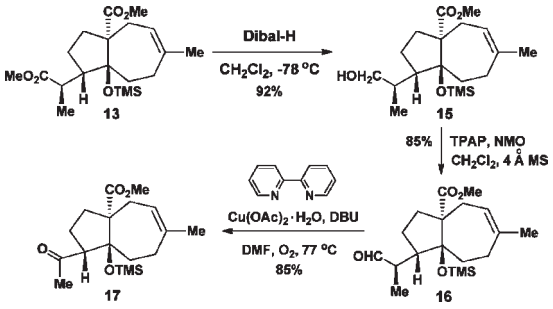


The annulated products**11a** and **11b** were obtained in 76% combined yield. While the yield for the annulated products was fine, the *trans*/*cis* stereoselectivity was unsatisfactory (ca. 1:1, *trans*/*cis*). We then ran the reaction in the presence of ^{t}BuOH (10 equiv) without addition of HMPA, and the reaction turned out to be very slow. We finally performed the annulation reaction in the presence of HMPA (10 equiv) without addition of ^{t}BuOH. To our delight, the desired product **11a** was formed as the major product (ca. 10:1, *trans*/*cis*). Subsequently, after the silylation with TMSOTf/lutidine, product **12a** was obtained in 78% yield in two steps.

The observed diastereoselectivity suggested that the dipolar repulsion[20] between Sm-associated ketyl radical anion and the ester group forced the transition state **A** as its favorable conformation as depicted in Scheme 2. As a result of that, **11a** came out as the major product.

With **12a** in hand, we moved on to construct the azulene **13** via RCM. To this end, **12a** was treated with Grubbs II catalyst to perform an RCM reaction. To our delight, the desired product **13** was formed in excellent yield. The stereochemistry of **13** has been confirmed via the X-ray crystallographic analysis of its derivative **14**, which was generated from **13** via Dibal-H reduction. We attributed this successful RCM reaction to the favorable conformation of substrate **12a**, in which the two-terminal olefins occupy equatorial positions, which would facilitate the proposed annulation (see 3D structure of **12a** in Scheme 2).

Scheme 3. Synthesis of **17**



We next focused on advancing the intermediate **13** (Scheme 3). To generate ketone **17**, it was essential to perform an oxidative one-carbon degradation of **13**. Scheme 4 illustrates our strategy involving a selective DIBAL-H reduction of **13** to alcohol **15**, an oxidative of the alcohol into aldehyde **16**, and a copper-dipyridine mediated oxidative deformylation to give **17** in 85% yield.[11]

Having assembled the [5,7]-bicyclic core structure, we turned our attention to completing the total synthesis as illustrated in Scheme 4. Thus, **17** was first treated with (trimethylsilyl)ethynyl)lithium to afford a tertiary alcohol **18**, which upon treatment with Otera catalyst [^{n}BuSn(NCS)$_2$]$_2$O[13] in toluene, generated lactone **19** after TBAF-mediated desilylation.

We then designed two reactions independent of each other to achieve the total synthesis (Scheme 4). We first explored olefin-exchange metathesis[21] as a key step toward the total synthesis. To this end, **19** was converted into its corresponding acetate **20** in 75% yield by treatment with Sc(OTf)$_3$/Ac$_2$O,[22] and the formed acetylene in **20** was selectively

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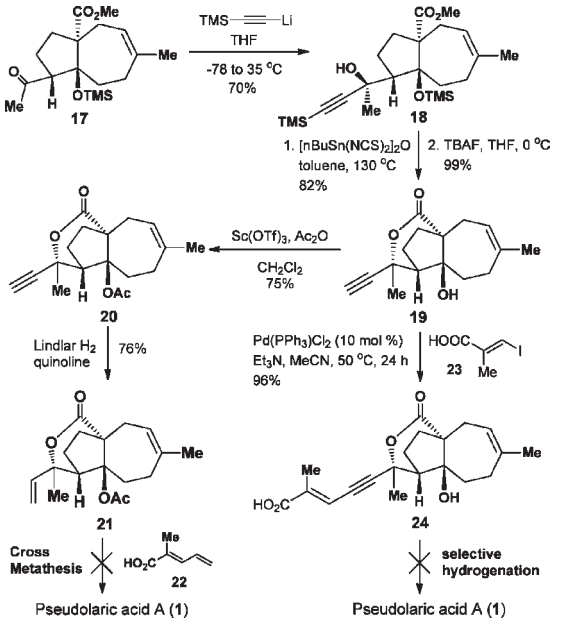
Scheme 4. Synthesis of Compound **20**



hydrogenated to give **21** in 76% yield. While various cross-metathesis conditions were screened for the coupling of **21** and **22**, unfortunately, none generated the desired pseudolaric acid A (**1**). In most of these cases, only the homocoupling product of **22** was obtained.

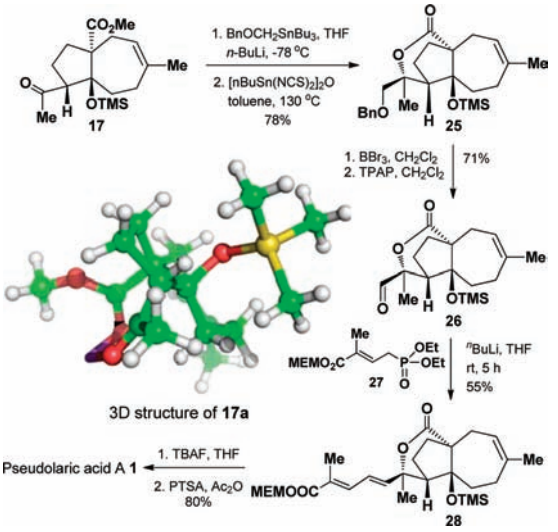
We then attempted a strategy to make pseudolaric acid A via a Sonogashira reaction, followed by selective hydrogenation as key steps. To this end, acetylene **19** was coupled with vinyl iodide **23** under the typical Sonogashira reaction conditions. As a result, enyne **24** was generated in 96% yield. However, when enyne **24** was subjected to the action of several known selective hydrogenation protocols, the desired product could not be generated.

We ultimately elected to synthesize the target molecule **1** via an HWE reaction as the key reaction (Scheme 5). To this end, ketone **17** was reacted with $BnOCH_2Li$[23] to give a tertiary alcohol in 87% yield, which subsequently underwent lactonization by the treatment with Otera catalyst to furnish lactone **25** in 78% yield in two steps.

The observed diastereoselectivity thereof was presumably attributed to the chelation of catonic lithium with ketone and the carbonyl of methyl ester (see **17a** in Scheme 5), which guided the nucleophile to attack the ketone from its top face with less steric hindrance.

Finally, a deprotection[24]–oxidation[25] sequence efficiently transformed **25** to **26**, which was then reacted with an HWE reagent **27** to afford product **28**. After TBAF desilylation followed by acetylation with in situ removal of MEM group, the target product **1** was obtained in 80% as a racemic form. The synthetic material has been fully characterized, and its ^{1}H NMR and ^{13}C NMR spectra are identical to those of the natural products.[5]

Scheme 5. Total Synthesis of Pseudolaric Acid A



In summary, we have developed a concise approach for the stereoselective synthesis of **1** with the unusual trans-fused [5−7]-bicyclic core in 16 steps involving a SmI_2-mediated intramolecular alkene ketyl radical cyclization and a ring closing metathesis (RCM) reaction as key steps. The work described herein exhibits a robust synthetic strategy for the rapid construction of the core structure of pseudolaric acids, which expectedly may be exploited to yield various analogues of pseudolaric acids. Asymmetric total synthesis of pseudolaric acid A based upon these key findings is currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR spectra, as well as X-ray data for compound **14** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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