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Formal Synthesis of Pseudolaric Acid B

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Abstract A formal synthesis of pseudolaric acid B, a diterpene isolated from the root bark of *Pseudolarix kaempferi* Gordon (Pinaceae), to Trost's synthetic intermediate was achieved in 17 steps from a known ketone. Key features of this synthesis include a Claisen rearrangement and iodoetherification to construct quaternary stereocenters and ring-closing metathesis to form the seven-membered ring.

Key words pseudolaric acid B, total synthesis, diterpenes, cytotoxins, Claisen rearrangement, iodoetherification

More than 20 natural pseudolaric acids, including pseudolaric acids A (1) and B (2), have been isolated from the root bark of *Pseudolarix kaempferi* Gordon (Pinaceae) (Figure 1).¹ Among the members of this family, pseudolaric acid B (2) has significant medical potential, exhibiting potent antifungal, antifertility, and cytotoxic activities, even against multidrug-resistant cancer cell lines. These latter activities suggest that 2 might function as a potential lead for new anticancer agents. Structurally, pseudolaric acids A (1) and B (2) feature a distinctive tricyclic core with an unusual trans-fused [5-7] ring system. The complicated structures, as well as the important biological properties, of pseudolaric acids have fascinated both biochemists and synthetic chemists. In fact, Mafu et al.² recently identified an enzyme involved in the biosynthetic pathway of 2, and two total syntheses of 1 by Chiu and co-workers³ [26 steps for (-)-1 and Yang and co-workers⁴ [16 steps for $(\pm)-1$], and one total synthesis of **2** by Trost et al.⁵ [28 steps for (-)-**2**] have been reported. We previously attempted to improve on the synthesis of 2 by using a Dieckmann condensation as the key step to construct its trans-fused core framework.⁶ Here, we describe a formal synthesis of 2 by using a new synthetic strategy.





We previously synthesized model compound 9, containing the trans-fused bicyclic core of 2, in 20 steps, starting from the known compound **3**⁷ (Scheme 1a).⁶ However, the yield of the radical coupling reaction $4 \rightarrow 5$ was quite low due to undesirable side reactions; i.e., a 1,6-hydrogen shift to generate compound 6, and a direct reduction by Bu₃SnH to generate compound 7. To overcome these disadvantages, we designed an alternative approach for the synthesis of 2 (Scheme 1b). Pseudolaric acid B (2) can be accessed from Trost's intermediate 10 in six steps; we therefore chose 10 as our synthetic goal. Based on our retrosynthetic analysis, the seven-membered ring of 10 might be constructed through a ring-closing metathesis (RCM) reaction of diene **11**, obtained by a reductive opening of the tetrahydrofuran ring of the iodo ester 12. Installation of an unsaturated ester side chain onto 12 might be achieved through a radical coupling of iodo alcohol **14** with the allylstannane **13**.⁸ We expected that this Keck radical allylation, which proceeds in the absence of Bu₃SnH, would be effective in increasing the yield of the desired product. Compound 14 might be prepared from the known starting material 15,9 in which a TIPS protecting group replaces the previously employed Bn group to avoid the presence of troublesome benzylic hydrogens.

Our synthesis commenced with the preparation of aldehyde **22** (Scheme 2). Methoxycarbonylation of **15** provided a diastereomeric mixture of esters **16** (dr = 2:1), which were

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converted into the enol triflate **17** in 78% yield. Because a Stille-type coupling¹⁰ of **17** with Bu₃SnCH₂OPMB¹¹ was unsuccessful, we installed a hydroxymethyl group through palladium-catalyzed carboxylation¹² and subsequent reduction to afford the alcohol **20** in 65% yield over two steps. After the formation of a vinyl ether of alcohol **20**, Claisen rearrangement of the resultant product **21** in refluxing DMF for one hour gave aldehyde **22** [50%; quantitative based on recovered starting material (brsm)] in a 3.3:1 diastereomeric ratio, which was consistent with our previous results.⁶ Note that longer reaction times adversely affect the yield of **22**, owing to its decomposition in refluxing DMF (14% after 6 h).

We next sought to prepare diene **11**, beginning with the introduction of a hydroxymethyl group onto aldehyde **22** (Scheme 3). Unfortunately, the addition of LiCH₂OPMB to **22**



Scheme 1 Our (a) previous work⁶ and (b) current retrosynthetic analysis for pseudolaric acid B (2)



Scheme 2 Preparation of aldehyde 22

resulted in the formation of lactone 23. Therefore, 22 was first converted into the diene 25, which could be obtained as a single diastereomer about the quaternary center following separation by column chromatography on silica gel. Diene 25 was then dihydroxylated with OsO₄ under neutral conditions to afford diol 26 as a 1:1 mixture of diastereomers in good yield (96%). The next step of the reaction, the iodoetherification of 26, required optimization with respect to the solvent. For example, treatment of 26 with NIS in MeCN afforded the desired product 14 (dr = 1:1) in 78% vield, whereas the use of CH₂Cl₂ resulted in the oxidative cleavage of the 1.2-diol to regenerate aldehvde **22** in 51% yield. For the installation of the unsaturated ester side chain, **14** was treated with the allylstannane **13**⁸ and AIBN in refluxing benzene to afford alcohol 27 (dr = 1:1) in 59% yield. After iodination of alcohol 27 under Appel's conditions, the tetrahydrofuran ring of iodide **12** was reductively opened by treatment with Zn in EtOH at 60 °C to afford diene **11** as a single diastereomer in 82% yield.

The formal synthesis of **2** was accomplished by first subjecting **11** to RCM conditions, using the Grubbs second-generation catalyst, to construct the seven-membered ring of **28**¹³ in 86% yield (Scheme 4). The TIPS protecting group was then removed with TBAF/AcOH, giving alcohol **29** in 54% yield with 34% of unreacted **28** remaining. Note that in the absence of AcOH, the reaction was dominated by 1,4-addition of the tertiary alcohol to the unsaturated ester. After oxidation to the aldehyde **30**, nucleophilic addition of a methyl group was attempted. Unfortunately, the standard conditions proved fruitless (MeLi, THF, –78 °C: decomposition; MeMgBr, THF, –78 °C: no reaction). Trost et al.⁵ report-

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ed that an organocerium reagent served as an excellent nucleophile in a similar transformation. To our delight, treatment of **30** with MeCeCl₂¹⁴ followed by Dess-Martin oxidation successfully afforded Trost's intermediate **10**, in racemic form, from which pseudolaric acid B (**2**) has been obtained in six steps, thus completing a formal synthesis of

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Scheme 3 Preparation of diene 11



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2. The ¹H NMR and ¹³C NMR spectra of compound **10** prepared in this work agreed with those reported by the Trost group.

In conclusion, we have accomplished a formal synthesis of pseudolaric acid B (**2**) from the known ketone **15** to Trost's synthetic intermediate **10** in 17 steps (six more steps are required to obtain **2**). The key elements in the present synthesis include: (1) construction of the vicinal quaternary stereocenters via a Claisen rearrangement (**21** \rightarrow **22**) and stereoselective iodoetherification (**26** \rightarrow **14**) and (2) formation of the seven-membered ring through an RCM reaction (**11** \rightarrow **28**). This current synthesis is more efficient than our previous preparation,⁶ and could expand the opportunities for derivatization of pseudolaric acid B and related compounds as lead anticancer drugs by using (*S*)-2-(hydroxymethyl)cyclopentan-1-one¹⁵ as a chiral substrate.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690829.

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 A mixture of diene 11 (16.4 mg, 34.0 μmol) and the Grubbs second-generation catalyst (2.9 mg, 3.42 μmol) in benzene (1.5 mL) was refluxed for 5 h, then cooled to rt. The mixture was

then concentrated under reduced pressure, and the residue was purified by preparative TLC (hexane–EtOAc, 5:1) to give a colorless oil; yield: 13.3 mg (86%). IR (film): 3515, 2945, 2866, 1716, 1463, 1238, 1194, 1055, 882, 755, 681 cm^{-1, 1}H NMR (400 MHz, CDCl₃): δ = 6.96 (m, 1 H), 4.00 (dd, *J* = 9.6, 6.4 Hz, 1 H), 3.70 (s, 3 H), 3.59 (m, 1 H), 3.58 (s, 3 H), 2.85 (m, 1 H), 2.76 (m, 1 H), 2.58–2.45 (m, 2 H), 2.37 (dt, *J* = 2.8, 14.0 Hz, 1 H), 2.20 (m, 1 H), 2.08–1.85 (m, 4 H), 1.23 (m, 1 H), 1.12–1.00 (m, 21 H). ¹³C NMR (100 MHz, CDCl₃): δ = 174.64, 168.53, 140.74, 135.51, 82.74, 65.29, 58.91, 57.38, 51.88, 51.55, 34.71, 30.39, 29.82, 26.00, 20.35, 18.06, 11.97. HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₄H₄₂NaO₆Si: 477.2643; found: 477.2637.

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