Synlett N. Mori Letter

Formal Synthesis of Pseudolaric Acid B

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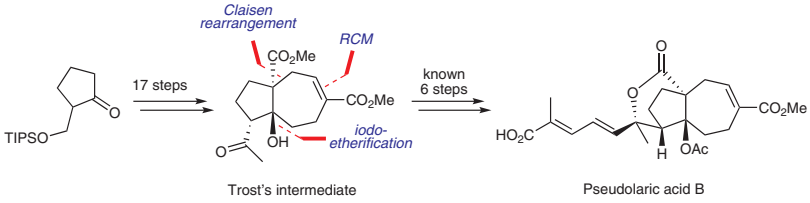

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Abstract A formal synthesis of pseudolaric acid B, a diterpene isolated from the root bark of *Pseudolarix kaempferi* Gordon (Pinaceae), to Trost's synthetic intermediate was achieved in 17 steps from a known ketone. Key features of this synthesis 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-workers[3] [26 steps for (–)-**1**] and Yang and co-workers[4] [16 steps for (±)-**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.

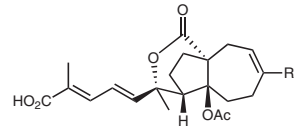


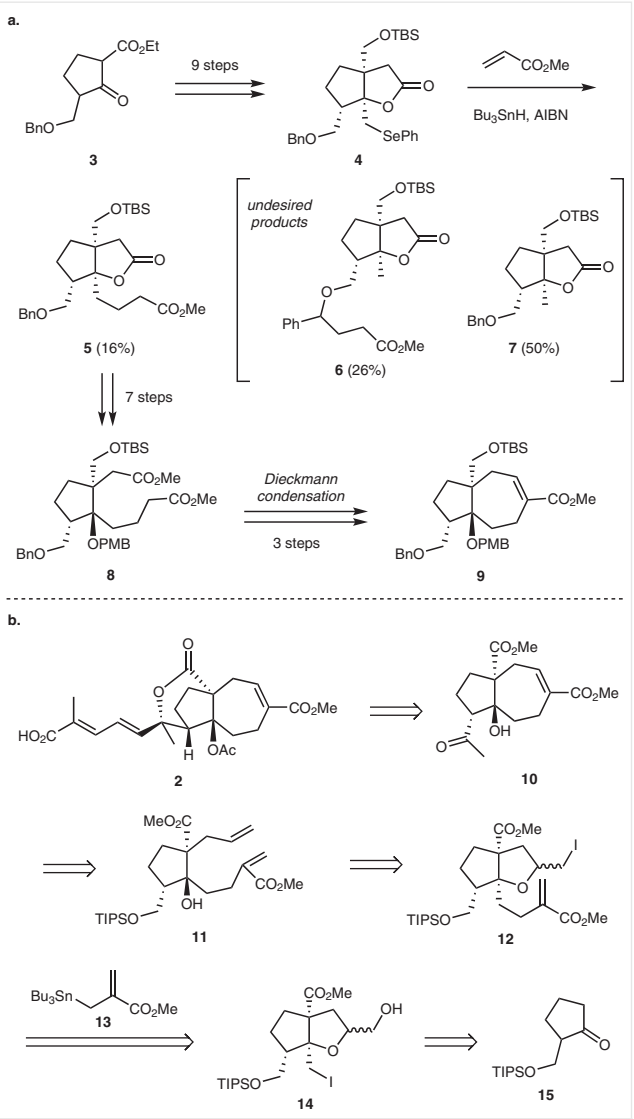
Figure 1 Structures of pseudolaric acids A (**1**) and B (**2**)

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** → **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 Bu_3SnH 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 Bu_3SnH, 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.

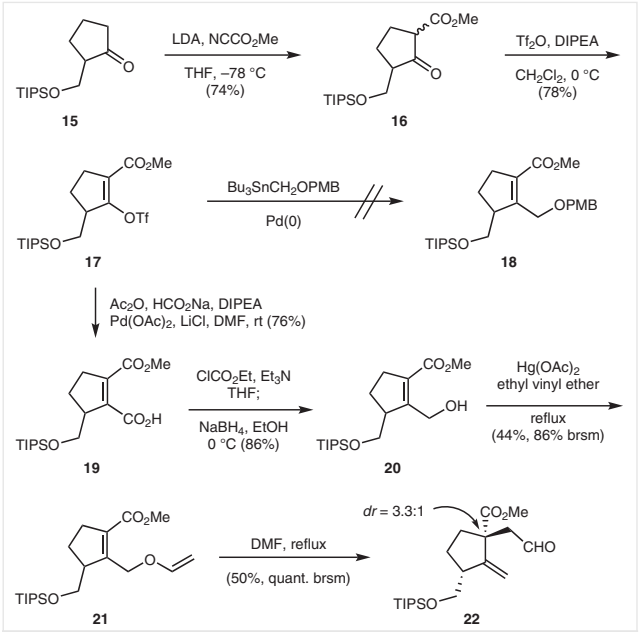
Our synthesis commenced with the preparation of aldehyde **22** (Scheme 2). Methoxycarbonylation of **15** provided a diastereomeric mixture of esters **16** (dr = 2:1), which were

converted into the enol triflate **17** in 78% yield. Because a Stille-type coupling[10] of **17** with Bu_3SnCH_2OPMB[11] was unsuccessful, we installed a hydroxymethyl group through palladium-catalyzed carboxylation[12] 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 $LiCH_2OPMB$ to **22**



Scheme 1 Our (a) previous work[6] and (b) current retrosynthetic analysis for pseudolaric acid B (**2**)



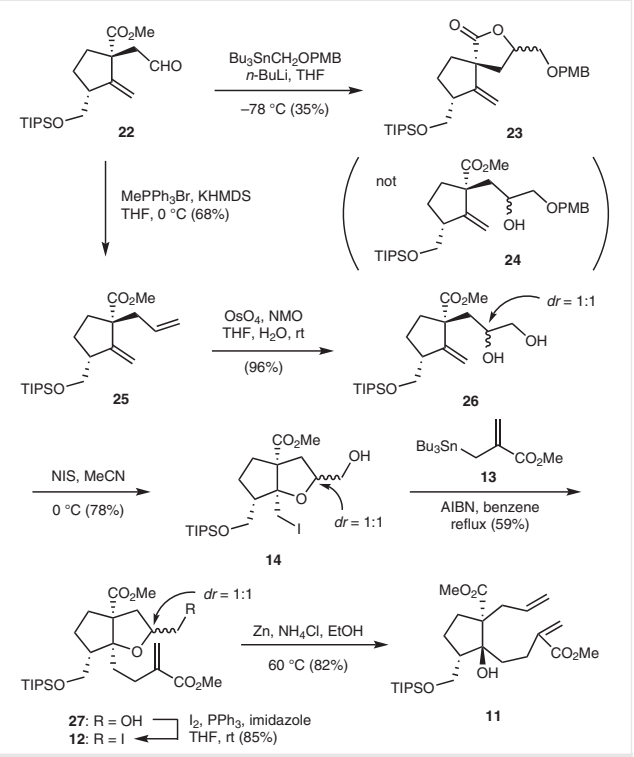
Scheme 2 Preparation of aldehyde **22**

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 OsO_4 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% yield, whereas the use of CH_2Cl_2 resulted in the oxidative cleavage of the 1,2-diol to regenerate aldehyde **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.

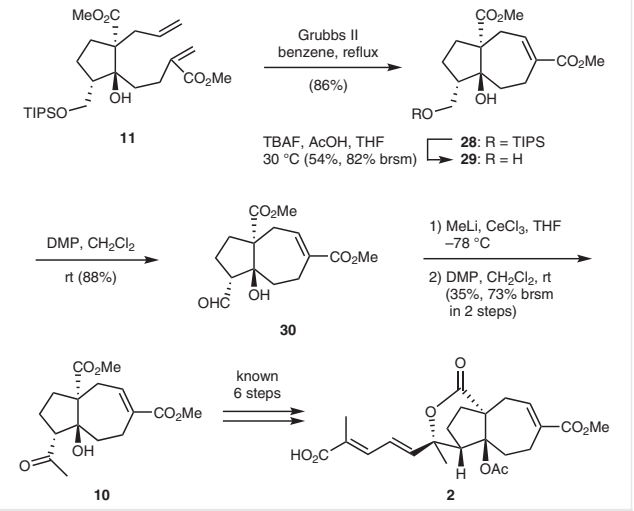
The formal synthesis of **2** was accomplished by first subjecting **11** to RCM conditions, using the Grubbs second-generation catalyst, to construct the seven-membered ring of **28**[13] in 86% yield (Scheme 4). The TIPS protecting group was then removed with TBAF/AcOH, giving alcohol **29** in 54% 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-

ed that an organocerium reagent served as an excellent nucleophile in a similar transformation. To our delight, treatment of **30** with $MeCeCl_2$[14] 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 **2**. The ^1H NMR and ^{13}C 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** → **22**) and stereoselective iodoetherification (**26** → **14**) and (2) formation of the seven-membered ring through an RCM reaction (**11** → **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-one[15] as a chiral substrate.



Scheme 3 Preparation of diene **11**



Scheme 4 Formal synthesis of pseudolaric acid B (**2**)

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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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(13) **Dimethyl 8a-Hydroxy-1-{[(triisopropylsilyl)oxy]methyl}-2,3,4,7,8,8a-hexahydroazulene-3a,6(1*H*)-dicarboxylate (28)**
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}. ^1H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{24}H_{42}NaO_6Si$: 477.2643; found: 477.2637.
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