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). 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. recently identified an enzyme involved in the biosynthetic pathway of 2, and two total syntheses of 1 by Chiu and co-workers [26 steps for (−)-1] and Yang and co-workers [16 steps for (±)-1], and one total synthesis of 2 by Trost et al. [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. 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′ (Scheme 1a). 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 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) reaktion 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. 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 in which a TIPS protecting group replaces the previously employed Bn group to avoid the presence of troublesome benzyl hydrogens.

Our synthesis commenced with the preparation of aldehyde 22 (Scheme 2). Methoxycarbonylation of 16 (dr = 2:1), which were
converted into the enol triflate 17 in 78% yield. Because a Stille-type coupling 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, Claissen 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.

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 the solvent. For example, treatment of MeCN afforded the desired product 14, which could be obtained as a single diastereomer in 51% yield. For the installation of the unsaturated ester side chain, 14 was treated with the allylstannane 13 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 CH2Cl2 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 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 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. report-
ed that an organocerium reagent served as an excellent nucleophile in a similar transformation. To our delight, treatment of 30 with MeCeCl$_2$ followed by Dess–Martin oxidation successfully afforded Trost’s intermediate 29, prepared in this work agreed with those reported by the Trost group.

2. The $^1$H 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 ($21 \rightarrow 22$) 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, 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 as a chiral substrate.

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Supporting Information

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References and Notes

(13) Dimethyl 8a-Hydroxy-1-[(triisopropylsilyl)oxy)methyl]-2,3,4,7,8,8a-hexahydroazulene-3a,6(1H)-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, 755 cm⁻¹. ¹H 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]+ calcld for C₂₄H₄₂NaO₆Si: 477.2643; found: 477.2637.