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Total Synthesis of (–)-Pseudolaric Acid B

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Pseudolaric acids B and A (**1a** and **1b**, Scheme 1) are diterpene acids isolated from the extract of the root bark of *Pseudolarix kaempferi* Gordon (pinaceae), which is also used in *tujinpi*, a traditional Chinese medicine for the treatment of fungal infections of the skin and nails.¹ Pseudolaric acid B (**1a**) has been identified as a potent antifungal, antifertility and cytotoxic agent, displaying much higher activity than pseudolaric acid A (**1b**).² More recently, the discovery that pseudolaric acid B (**1a**) displays significant activity against multi-drug resistant cancer cell lines has revitalized interest in this natural product.³

Pseudolaric acid B (**1a**) displays a compact tricyclic core which includes a fused [5–7] ring system (polyhydroazulene) with an unusual *trans* substitution pattern at the ring fusion site (C4–C10) and 4 contiguous stereocenters, one of them being quaternary (C10). Taken together, these structural features make pseudolaric acid B (**1a**) a challenging substrate for modern synthetic chemistry. As a result, several approaches towards the pseudolaric acids have been published.⁴ In 2006, the unique successful synthesis of pseudolaric acid A (**1b**) was reported based on a carbene cyclization cycloaddition cascade to build the polyhydroazulene core.^{4h} Herein, we report the first asymmetric synthesis of pseudolaric acid B (**1a**) highlighting the use of a metal-catalyzed [5+2] cycloaddition and an intramolecular alkoxycarbonyl radical addition to construct the ring system.

The Rh and Ru catalyzed [5+2] intramolecular cycloaddition reaction of an alkyne and a vinylcyclopropane developed by Wender⁵ and us⁶ respectively is ideally suited for accessing the polyhydroazulene core of pseudolaric acid B (**1a**). To reveal this key structure in the natural product, we envisioned a late stage introduction of the C13–C17 side chain (Scheme 1). An intramolecular alkoxycarbonyl radical addition to the C9–C10 double bond of intermediate **2** was planned for the installation of the quaternary center. Adjustment of the oxidation state and double bond isomerization leads to 1,4-diene **3**, which would result from an intramolecular [5+2] cycloaddition reaction of easily accessible precursor **4**.

The synthesis of precursor **4** for the [5+2] cycloaddition reaction is shown in Scheme 2. Iodide **7** was synthesized in 5 steps and 62% overall yield from 2-acetylbutyrolactone (**5**), using Noyori reduction to install the adjacent stereocenters.⁷ Aldehyde **9** was obtained in 3 steps and 84% overall yield from *cis*-butenediol (**8**) via Charette cyclopropanation.⁸ Homologation of iodide **7**, followed by Schlosser-Wittig olefination with aldehyde **9** and deprotection gave vinylcyclopropane **4** with 10:1 *E/Z* selectivity.

We then proceeded to examine the key [5+2] cycloaddition reaction (Scheme 2). Using [CpRu(CH₃CN)₃]⁺PF₆[–] (**11**), 23 mol% catalyst was needed to obtain full conversion. The desired polyhydroazulene **3** was isolated with 15:1 diastereoselectivity but only 48% yield. Conjugated diene **10** was also obtained in 15% yield. We speculated that the insertion of the Ru catalyst in the labile bisallylic C–H bond leads to a Ru pentadienyl complex, which then deactivates the catalyst. Diene **10** then is a consequence of protonation upon work up. We expected Rh

catalysts to be less prone to this undesired side reaction. Indeed, $[(C_8H_{10})Rh(COD)]^+SbF_6^-$ (**12**)**5b** gave the desired product **3** exclusively in 88% isolated yield, although the reaction still required an unusually high catalyst loading (11 mol%).

A novel method for the regioselective isomerization of 1,4-diene **3** to a 1,3-diene **13** was then examined (Scheme 3). Activation of TBAF with molecular sieves provided a reagent that affected desilylation as well as isomerization to conjugated diene **13** in 94% yield.⁹ Protection of diol **13** allowed for a diastereoselective epoxidation of the tetrasubstituted double bond. Vinylogous eliminative opening of the resulting epoxide mediated by LDA completed the installation of the C4 alcohol of pseudolaric acid B (**1a**). Oxidation of the allylic silyl ether of the resultant diene **14** followed by deprotection provided diol **2**.

At this point, we turned towards introduction of the C13–C17 side chain and the quaternary center at C10 (Scheme 3). We intended to apply a rarely used alkoxycarbonyl radical cyclization¹⁰ to construct the quaternary center. The most direct approach would be to introduce a side chain precursor prior to cyclization. To examine this route, we synthesized alkoxycarbonyl selenium **15** bearing an alkyne group as side chain precursor in 4 steps from diol **2**. Cyclization of **15** resulted only in decomposition and decarboxylation. We concluded that formation of a tertiary propargylic radical was favored over cyclization. As an alternative strategy, secondary alkoxycarbonyl selenium **16** was synthesized. Gratifyingly, cyclization of **16** proceeded smoothly to give a mixture of double bond isomers. Treatment with DBU resulted in exclusive formation of the desired conjugated ester **17**.

To complete the synthesis, opening the lactone was necessary for the introduction of the side chain (Scheme 4). To prevent lactonization back to **17**, KOTMS was used for the hydrolysis of the lactone followed by methylation with dimethyl sulfate under buffered conditions and immediate oxidation. Removal of the PMB group was necessary before introduction of an acetylene as side chain precursor, as elimination to the conjugated ketone was observed otherwise. Using soluble $RCeCl_2 \cdot 2LiCl$ ¹¹ was essential to allow full conversion at $-78^\circ C$. At higher temperature a retro-aldol reaction became favored. Complete selectivity was observed in the formation of the C11-alcohol, as expected by a Felkin-Ahn approach on ketone **18**. Lactonization to tricycle **19** was achieved using Otera's catalyst.¹² Deprotection of the terminal acetylene, acetylation, hydrostannylation, and Stille coupling with known iodide **21**¹³ completed the total synthesis of pseudolaric acid B (**1a**). All physical and spectroscopic data were in agreement with the published values for natural pseudolaric acid B (**1a**) (melting point, optical rotation, 1H and ^{13}C NMR, IR and mass).^{2a,2c}

In summary, we report the asymmetric synthesis of pseudolaric acid B (**1a**) based on a metal-catalyzed [5+2] cycloaddition reaction to build the polyhydroazulene core directly from a simple linear precursor and a selective access to a 1,3-diene from the initially formed 1,4 diene. An efficient alkoxycarbonyl radical cyclization and a highly selective cerium acetylide addition were additional key steps towards the stereoselective formation of the tricyclic core of pseudolaric acid B (**1a**).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Retrosynthesis of Pseudolaric Acid B (**1a**)

Scheme 2.

Synthesis of the Polyhydroazulene Core^a

^aConditions: (a) 1.4 mol% $[\text{RuI}_2(p\text{-cymene})]_2$, 2.8 mol% (*R*)-BINAP, 1800 psi H_2 , methanol, CH_2Cl_2 , 40 °C, 95%, >95:5 dr, >90% *ee*. (b) TBSCl, imidazole, DMAP, DMF. (c) DIBALH, toluene, -78 °C. (d) TMSCHN_2 , LDA, THF, -78 °C, then TMSCl , 73% over 3 steps. (e) PPh_3 , I_2 , imidazole, toluene, 90%. (f) TBDPSCl, imidazole, THF, 92%. (g) Et_2Zn , DME, CH_2I_2 , Charette's auxiliary,⁸ CH_2Cl_2 , -10→23 °C, 91%, >90% *ee*. (h) $(\text{COCl})_2$, DMSO, NEt_3 , CH_2Cl_2 , quant. (i) 1) $\text{MePh}_3\text{P}^+\text{Br}^-$, PhLi/LiBr , THF; 2) 7, 0 °C, then PhLi/LiBr ; 3) 9, -78 °C, then PhLi/LiBr , 23 °C; 4) HCl , -78 °C, then KO^tBu , 23 °C. (j) K_2CO_3 , MeOH, 58% over 2 steps (53% (*E*)-4). (k) 23 mol% $[\text{CpRu}(\text{CH}_3\text{CN})_3]^+\text{PF}_6^-$ (11), acetone, 48% 3, 15% 10 or 11 mol% $[(\text{C}_8\text{H}_{10})\text{Rh}(\text{COD})]^+\text{SbF}_6^-$ (12), DCE, 88% 3.

Scheme 3. Introduction of the Quaternary Center^a

^aConditions: (a) TBAF, 3 Å MS, THF, 94%. (b) TESCl, imidazole, DMAP, DMF, 85%. (c) *m*-CPBA, NaHCO₃, CH₂Cl₂, -20 °C. (d) LDA, THF, 0 °C, 72% over 2 steps. (e) DDQ, pH=7 buffer, CH₂Cl₂. (f) MnO₂, KCN, AcOH, MeOH, 85% over 2 steps. (g) TBAF, AcOH, THF, 87%. (h) Dess-Martin periodinane, CH₂Cl₂, 85%. (i) Ac₂O, pyridine, DMAP, quant. (j) TMS-C≡C-Cl, THF, -78 °C, then CDI, -78→23 °C, 91%, 8:1 dr. (k) Ph₂Se₂, NaBH₄, DMF, 76% (84% brsm). (l) CDI, THF, quant. (m) Ph₂Se₂, NaBH₄, DMF, 92%. (n) PMBOC(NH) CCl₃, 2 mol% Sc(OTf)₃, toluene, 0 °C, 94%. (o) Bu₃SnH, 1,1'-azo(biscyclohexane carbonitrile), benzene, 70 °C, then DBU, 23 °C, 85% (92% purity).

Scheme 4. Completion of the Synthesis^a

^aConditions: (a) KOTMS, toluene, 120 °C, 30 min, then Me₂SO₄, buffer (TsOH, Hünig's base 1:2), 100 °C, 5 min. (b) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, 0 °C, 59% over 2 steps (73% brsm). (c) DDQ, pH=7 buffer, CH₂Cl₂, 76%. (d) TMS-C≡C-Cl₂·2LiCl, THF, -78 °C, 87% (98% brsm). (e) Otera's catalyst,¹² toluene, 130 °C, 30 min, 94%. (f) TBAF, THF, 0→23 °C, 87%. (g) Ac₂O, 8 mol% Sc(OTf)₃, 0 °C, 98%. (h) Bu₃SnH, 5 mol% Pd(PPh₃)₂Cl₂, THF, 90%. (i) Iodide **21**, 25 mol% Pd₂dba₃, Hünig's base, NMP, 62%.