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Published on Web 11/07/2007

Total Synthesis of (−)-Pseudolaric Acid B

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Received August 15, 2007; E-mail: bmtrost@stanford.edu

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 multidrug resistant cancer cell lines has revitalized interest in this natural product.[3]

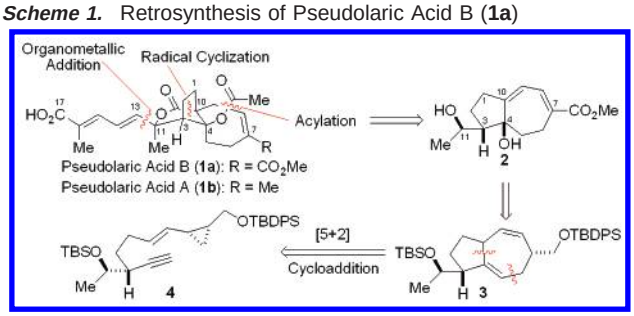
Pseudolaric acid B (**1a**) displays a compact tricyclic core which includes a fused [5−7] ring system (polyhydroazulene) with an unusual trans substitution pattern at the ring fusion site (C4−C10) and four contiguous stereocenters, one of them being quaternary (C10). Taken together, these structural features make pseudolaric acid B (**1a**) a challenging substrate for modern synthetic chemistry. As a result, several approaches toward the pseudolaric acids have been published.[4] In 2006, the unique successful synthesis of pseudolaric acid A (**1b**) based on a carbene cyclization cycloaddition cascade to build the polyhydroazulene core was reported.[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 Wender[5] and us,[6] 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**.

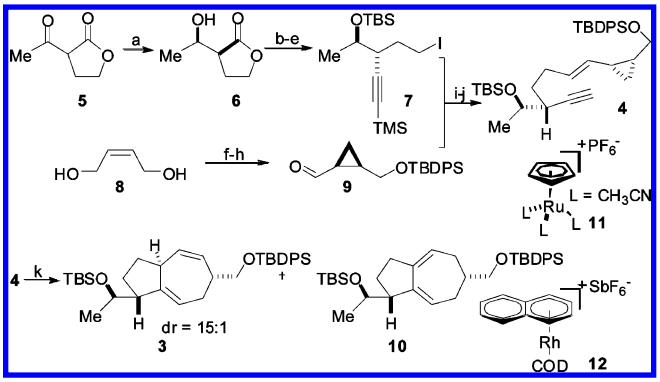
The synthesis of precursor **4** for the [5+2] cycloaddition reaction is shown in Scheme 2. Iodide **7** was synthesized in five steps and 62% overall yield from 2-acetylbutyrolactone (**5**), using Noyori reduction to install the adjacent stereocenters.[7] Aldehyde **9** was obtained in three steps 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 $[CpRu(CH_3CN)_3]^+PF_6^-$ (**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

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



Scheme 2. Synthesis of the Polyhydroazulene Core[a]



[a] Conditions: (a) 1.4 mol % $[RuI_2(p\text{-cymene})]_2$, 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 three 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) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, quant; (i) (1) $MePh_3P^+Br^-$, 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^{t}Bu, 23 °C; (j) K_2CO_3, MeOH, 58% over two steps (53% (*E*)-**4**); (k) 23 mol % $[CpRu(CH_3CN)_3]^+PF_6^-$ (**11**), acetone, 48% **3**, 15% **10** or 11 mol % $[(C_8H_{10})Rh(COD)]^+SbF_6^-$ (**12**), DCE, 88% **3**.

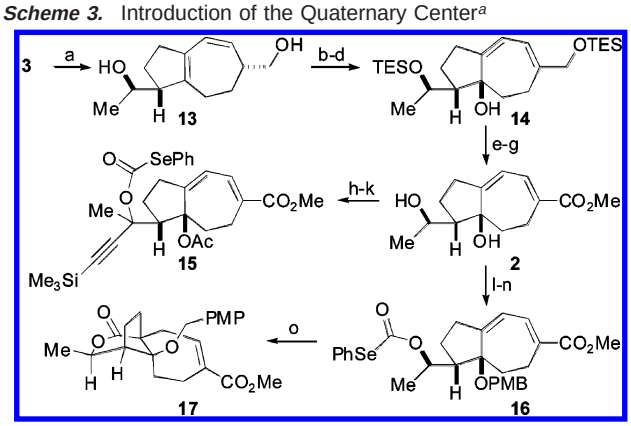
of protonation upon work up. We expected Rh catalysts to be less prone to this undesired side reaction. Indeed, $[(C_8H_{10})Rh(COD)]^+SbF_6^-$ (**12**)[5b] gave the desired product **3** exclusively in 88% isolated yield, although the reaction still required an unusually high catalyst loading (11 mol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

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 toward introduction of the C13−C17 side chain and the quaternary center at C10 (Scheme 3). We

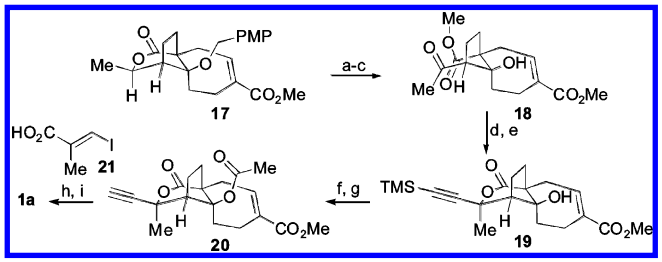
10.1021/ja076165q CCC: $37.00

Scheme 3. Introduction of the Quaternary Center[a]



[a] Conditions: (a) TBAF, 3 Å MS, THF, 94%; (b) TESCl, imidazole, DMAP, DMF, 85%; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, −20 °C; (d) LDA, THF, 0 °C, 72% over two steps; (e) DDQ, pH = 7 buffer, CH_2Cl_2; (f) MnO_2, KCN, AcOH, MeOH, 85% over two steps; (g) TBAF, AcOH, THF, 87%; (h) Dess−Martin periodinane, CH_2Cl_2, 85%; (i) Ac_2O, pyridine, DMAP, quant; (j) TMSC≡$CCeCl_2$, THF, −78 °C, then CDI, −78 → 23 °C, 91%, 8:1 dr; (k) Ph_2Se_2, $NaBH_4$, DMF, 76% (84% brsm); (l) CDI, THF, quant; (m) Ph_2Se_2, $NaBH_4$, DMF, 92%; (n) PMBOC(NH)CCl_3, 2 mol % $Sc(OTf)_3$, toluene, 0 °C, 94%; (o) Bu_3SnH, 1,1′-azo(biscyclohexane carbonitrile), benzene, 70 °C, then DBU, 23 °C, 85% (92% purity).

Scheme 4. Completion of the Synthesis[a]



[a] Conditions: (a) KOTMS, toluene, 120 °C, 30 min, then Me_2SO_4, buffer (TsOH, Hünig's base 1:2), 100 °C, 5 min; (b) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C, 59% over two steps (73% brsm); (c) DDQ, pH = 7 buffer, CH_2Cl_2, 76%. (d) TMSC≡$CCeCl_2$·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) Ac_2O, 8 mol % $Sc(OTf)_3$, 0 °C, 98%; (h) Bu_3SnH, 5 mol % $Pd(PPh_3)_2Cl_2$, THF, 90%; (i) Iodide **21**, 25 mol % Pd_2dba_3, Hünig's base, NMP, 62%.

intended to apply a rarely used alkoxycarbonyl radical cyclization[10] 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 four 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 $RCeCl_2$·2LiCl[11] was essential to allow full conversion at −78 °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,c]

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 toward the stereoselective formation of the tricyclic core of pseudolaric acid B (**1a**).

Acknowledgment. We thank the NSF and the NIH (Grant GM13598) for their generous support of our programs. J.W. thanks the Swiss National Science Foundation and the Roche Research Foundation for postdoctoral fellowships. A.M. thanks the German Academic Exchange Service (DAAD) for a postdoctoral fellowship. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California, San Francisco, supported by the NIH Division of Research Resources. We thank Johnson Matthey for a generous supply of palladium and ruthenium salts.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA076165Q