Total Synthesis

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Total Synthesis of Pseudolaric Acid A**

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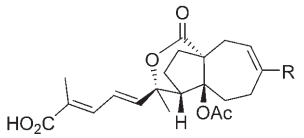
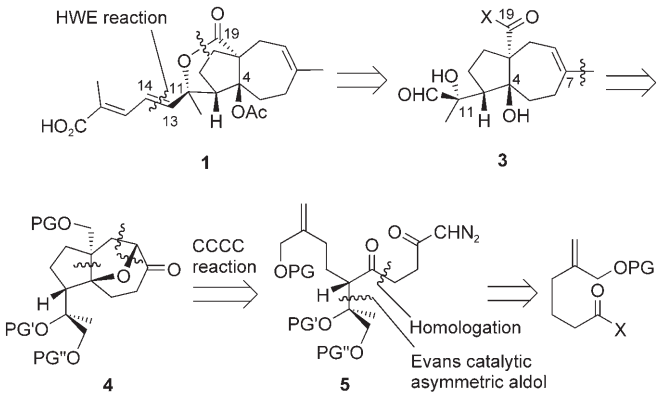


Scheme 1. Pseudolaric acid A (**1**), R = Me; pseudolaric acid B (**2**), R = CO_2Me

The pseudolaric acids A and B, first isolated in 1965, are the main biologically active constituents of *tujinpi*, a traditional Chinese medicinal herb in use since the 17th century for the treatment of dermatological fungal infections.[1] This medicinal preparation is harvested from the root bark of the tree *Pseudolarix kaempferi* Gordon (Pinaceae). The antifertile, antifungal, and cytotoxic properties of the pseudolaric acids have been recognized for quite some time.[2] However, the past few years have seen a resurgence of interest in these natural products for several reasons. The pseudolaric acids were identified as a new class of peroxisome proliferator-activated receptor (PPAR) agonists.[3] Additionally, pseudolaric acid B was found to activate c-Jun N-terminal kinase and caspase-3 in HeLa cells.[4] Studies recently disclosed the antiangiogenic effects of both pseudolaric acid A and B.[5,6] Our own studies revealed that pseudolaric acids A and B inhibit tubulin polymerization in vitro.[7] The resultant antimitotic activity and disruption of normal microtubule assembly appears to be their mode of anticancer action. Notably, pseudolaric acid B is able to circumvent the action of the P-glycoprotein (Pgp) efflux pump, which is responsible for the acquired resistance to many tubulin-binding agents, which allows pseudolaric acid B to maintain its activity, even on some multidrug-resistant cancers. We have further demonstrated the in vivo antitumor effects of pseudolaric acid B towards a liver cancer resistant to taxol in a murine xenograft model.

Structurally, the pseudolaric acids are novel diterpenoids with a highly oxygenated perhydroazulene skeletal framework (Scheme 1). The *trans* arrangement of the lactone and acetoxy group at the fused-ring junction is an unusual arrangement in natural perhydroazulenes, but is a representative structural feature of this family of compounds. The central δ-lactone is characterized by contiguous quaternary or tertiary stereocenters at all four tetrahedral carbon atoms. All of these structural elements congested within a relatively small space constitute the synthetic challenge at hand. The biological activity and molecular architecture of the pseudolaric acids have already attracted a number of synthetic efforts.[8–11] Herein, we describe our studies on pseudolaric acid A, which culminated in the first total synthesis of this natural product.[12]

Our retrosynthetic strategy towards pseudolaric acid A (**1**) is illustrated in Scheme 2, in which cleavage of the lactone functionality and a Wittig-type disconnection at C13–C14



Scheme 2. Retrosynthetic analysis of pseudolaric acid A. HWE = Horner–Wadsworth–Emmons; CCCC = carbene cyclization cycloaddition cascade; PG, PG′, PG″ = protecting groups.

yields the stereochemically loaded aldehyde **3**. Redox interconversions at C11 and C19, and a crucial reductive cleavage reveal key oxatricyclic intermediate **4** as the precursor. In this way, the tertiary hydroxy acetate/hydroxy group at C4 is protected from dehydration and other side reactions in the form of the oxygen bridge. This oxatricyclic intermediate **4** could be obtained through an intramolecular carbene cyclization cycloaddition cascade (CCCC) reaction of acyclic diazoketone **5**.[13–15] This reaction would be the key step in the construction of the stereochemically defined perhydroazulene platform in the present synthetic strategy.[16] Diazoketone **5** could be constructed from three carbon fragments, as shown. The stereochemically defined southern portion of diazoketone **5** could be obtained from an Evans catalytic

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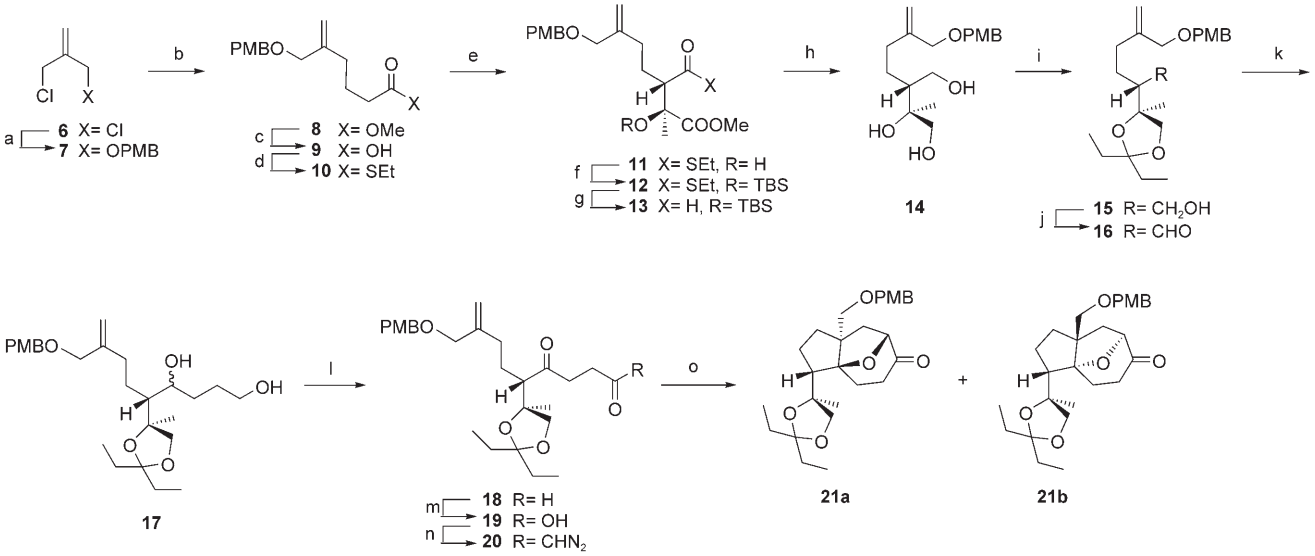
asymmetric aldol reaction,[17] another key reaction in this total synthesis.

Following this retrosynthetic analysis, and based on results from model studies,[12] we began the synthesis with commercially available allyl dichloride **6**. Reaction of **6** with sodium *p*-methoxybenzyl alcoholate produced a mixture of substitution products, the major one being 3-chloro-2-benzyloxymethylpropene (**7**; Scheme 3). Coupling **7** with the zinc homoenolate derived from methyl 3-iodopropionate smoothly afforded homologated ester **8**,[18] which was subsequently converted into thioester **10** via acid **9**.

The Evans catalytic asymmetric aldol reaction was employed to introduce the initial stereochemical elements in the molecule.[17] Thus, **10** was converted into its silyl enol ether and treated with methyl pyruvate under catalysis by the [Cu{(S,S)-*t*Bu-box}][OTf]$_2$ complex (Scheme 3). Substrate **10** is one of the more demanding cases for this reaction, because of the longer alkyl chain, which leads to a more hindered enol ether derivative. The use of the trimethylsilyl enol ether of **10** gave capricious results in the aldol reaction, but the use of the triethylsilyl enol ether led to consistent yields of aldol **11**, albeit at a noticeably slower reaction rate. The use of dichloromethane as the solvent was also critical, since the conversion rate was low in the more common solvent THF. The increased reaction rate in dichloromethane is indicative of a change in the rate-determining step from copper catalyst decomplexation to aldol condensation. In this manner, aldol diastereomer **11** bearing vicinal tertiary stereocenters was synthesized in a yield of 76% and with an *ee* value of 88%.[19] Protection of the newly generated tertiary alcohol was achieved using TBSOTf to give **12**.

Direct homologation of thioester **12** was surprisingly difficult. Nucleophilic addition to the thioester functionality was hampered by branching at the β carbon atom, and further complicated by the competitive reactivity of the proximate carbomethoxy functional group. Although the more reactive aldehyde derivative **13** could be obtained from thioester **12** through a Fukuyama reduction,[20] homologation of this substrate also failed. Under more forcing conditions, side products arose, apparently from reaction of both the ester and the aldehyde.[21] To circumvent these problems, the interfering ester functionality was removed by reduction. Direct treatment of **11** with LAH resulted in a significant portion of the hydroxyketone undergoing a retroaldol reaction. Therefore, the protected aldol **12** was subjected to exhaustive reduction instead. This reaction resulted in migration of the TBS group and led to isolation of a mixture of diols. However, after desilylation a single triol **14** was obtained as the sole product in good yield. Treatment of triol **14** with 3,3-dimethoxypentane resulted in the exclusive formation of desired dioxolane **15**, in which the alcohol derived from the thioester remained available for further elaboration.[22] Alcohol **15** was converted into aldehyde **16** by a Dess–Martin oxidation.

Homologation was then attempted on aldehyde **16**. Although aldehyde **16** has steric hindrance comparable to that in substrate **13,** but lacks the electrophilic group at the β position, it could be smoothly converted into diol **17** in 90% yield, using the variant of the Grignard reagent ClMgO-



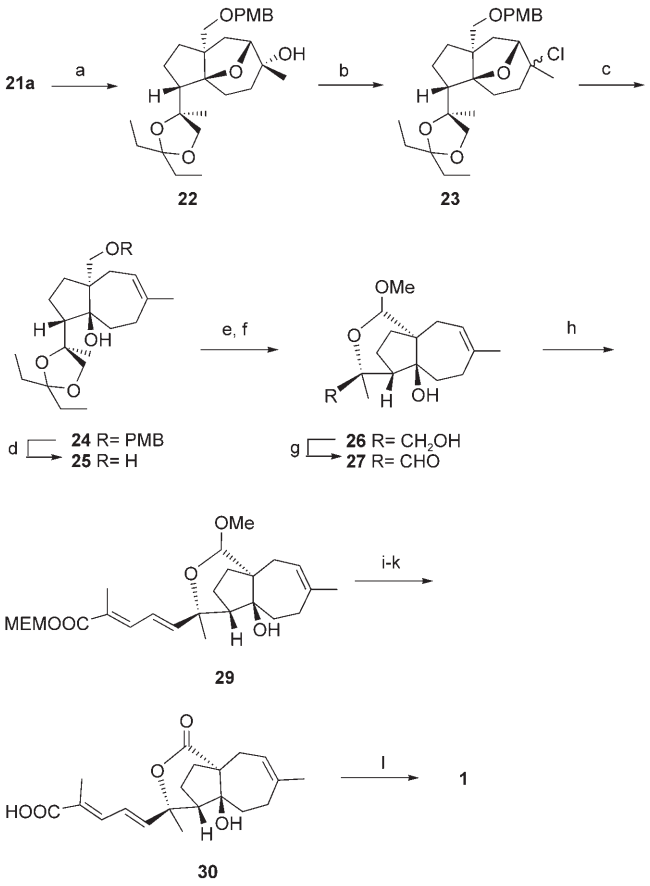
Scheme 3. Reagents and conditions: a) NaH, PMBOH, THF, reflux, 61%; b) $ICH_2CH_2CO_2Me$, Zn(Cu), CuCN, DMA, THF, 60°C, 12 h, 91%; c) 20% NaOH, MeOH, RT, 4 h, 96%; d) EtSH, DCC, DMAP, CH_2Cl_2, 3 h, 97%; e) 1. LDA, TESCl, THF, −78°C-RT; 2. [Cu{(*S*,*S*)-*t*Bu-box}][OTf]$_2$, methyl pyruvate, CH_2Cl_2, −78°C, 76%, 88% *ee*; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 97%; g) Et_3SiH, Pd/C, CH_2Cl_2, 81%; h) 1. LAH, THF, 0°C, 4 h; 2. TBAF, THF, RT, 2 h; i) 3,3-dimethoxypentane, PTSA, RT, 1 h, 66% from **12**; j) Dess–Martin periodinane, CH_2Cl_2, RT, 88%; k) $ClMgO(CH_2)_3MgCl$, THF, 0°C, 90%; l) Swern oxidation, 90%; m) $NaClO_2$, NaH_2PO_4, *t*BuOH, 2-methyl-2-butene, RT, 96%; n) 1. *i*BuOCOCl, Et_3N, THF/Et_2O, −20→0°C, 0.5 h; 2. CH_2N_2, Et_2O, 0°C–RT, 3 h, 71%; o) 3% [Rh_2{(*S*)-bptv}$_4$], $PhCF_3$, −40°C, 82% yield (50% **21a**, 32% **21b**). PMB = *p*-methoxybenzyl, DMA = *N*,*N*-dimethylacetamide, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, LDA = lithium diisopropylamide, TES = triethylsilyl, box = bis(oxazoline), Tf = trifluoromethanesulfonyl, TBS = *tert*-butyldimethylsilyl, LAH = lithium aluminum hydride, TBAF = tetra-*n*-butylammonium fluoride, PTSA = *p*-toluenesulfonic acid, bptv = α-(*tert*-butyl)-1,3-dihydro-1,3-dioxo-2*H*-benz[*f*]isoindole-2-acetato.

$(CH_2)_3MgCl$ reported by Normant et al.[23] Oxidation of both alcohols was accomplished under Swern conditions, followed by Lindgren oxidation to cleanly yield ketoacid **19**. Activation with isobutylchloroformate and treatment with diazomethane by using standard methods[24] afforded diazoketone **20**.

With chiral diazoketone **20** in hand, the carbene cyclization cycloaddition cascade reaction was studied.[14,15] This transformation would complete the stereochemical configuration of the molecule, as well as assemble the polycyclic carboskeleton of pseudolaric acid A from acyclic precursor **20** in one step. We have studied various model substrates in the context of this reaction.[12] With achiral dirhodium catalysts, the CCCC reaction of **20** was found to favor the formation of undesired diastereomer **21b**. For example, the CCCC reaction of **20** catalyzed by $[Rh_2(OAc)_4]$ at 0°C in CH_2Cl_2 generated a 61% yield of a 1:3 mixture of **21a**/**21b**. The preference for this mode of cycloaddition arose from the unfavorable interactions between the sterically demanding dioxolane and the PMB ether, which would be *syn* on the same face of the ring, in the transition state of the intramolecular cyclcoaddition leading to **21a** . We have examined various factors in this reaction, including catalysts, solvents, and temperature, and after optimization found that 3% of the chiral catalyst, developed by Hashimoto and co-workers, $[Rh_2\{(S)\text{-bptv}\}_4]$ in benzotrifluoride at −40°C, afforded the desired isomer **21a** as the major product.[25] Under these conditions, a 82% yield of the CCCC cycloadducts **21a** and **21b** was obtained in a ratio of 1.6:1, which translates to a 50% yield of the desired diastereomer **21a** to carry forward in the total synthesis. Thus, the remaining two stereocenters and the carbocyclic skeleton in pseudolaric acid A were efficiently constructed.

Our synthetic strategy was to mask the acetate group in pseudolaric acid A as an oxygen bridge to prevent dehydration or elimination side reactions, as observed in previous approaches. However, the oxabicyclic nucleus turned out to be quite robust and did not yield easily to reaction. Exploratory experiments on **21a** demonstrated that the construction of the final ring was difficult, if not impossible, in the presence of the bridging oxygen atom, because of rigidification of the carbobicyclic ring system. Thus, cleavage of the oxygen bridge in **21a** proved to be another challenge. This crucial transformation was finally achieved through a reductive elimination protocol (Scheme 4).[26] Ketone **21a** was treated with MeMgCl to give alcohol **22** as a single diastereomer. The diastereoselective *syn* approach of the nucleophile with respect to the oxygen bridge is well established. Conversion of the tertiary alcohol into the diastereomeric chlorides **23** was achieved using thionyl chloride. Both diastereomers of **23** underwent reductive elimination with sodium in refluxing diethyl ether with concomitant opening of the oxygen bridge to reveal perhydroazulene **24** in 78% yield over two steps from **21a**. At this stage, the central nucleus in pseudolaric acid A bearing all of the required stereocenters in their correct absolute configurations had been constructed.

With the ring-opened compound **24** in hand, the final functionalizations were accomplished as follows. Oxidative removal of the PMB group in **24** yielded the deprotected alcohol **25**, which was further oxidized to the aldehyde.



Scheme 4. Reagents and conditions: a) MeMgCl, THF, 0°C, 96%; b) $SOCl_2$, DMPU, 0°C–RT; c) Na, Et_2O, reflux, 78% over 2 steps from **22**; d) DDQ, CH_2Cl_2/H_2O, RT, 86%; e) Dess–Martin periodinane, CH_2Cl_2, RT, 91%; f) MeOH, CSA, RT, 95%; g) Dess–Martin periodinane, CH_2Cl_2, RT, 93%; h) (*E*)-$(EtO)_2POCH_2CH{=}C(CH_3)CO_2MEM$ **28**, *n*BuLi, THF, 83%; i) 60% AcOH, 60°C, 1 h; j) Dess–Martin periodinane, CH_2Cl_2; k) 3 N HCl/THF, RT, 66% over 3 steps from **29**; l) AcCl, DMAP, 80%. DMPU = 1,3-dimethylhexahydro-2-pyrimidinone, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, CSA = camphorsulfonic acid, MEM = 2-(methoxyethoxy)methyl.

Subsequent treatment with camphorsulfonic acid in methanol to deprotect the diol also induced spontaneous acetalization, engaging only the tertiary alcohol, to give the mixed acetal **26** in excellent yield as a single diastereomer. With this transformation we had achieved the construction of the final ring in pseudolaric acid A, opportunely leaving the primary alcohol free for oxidation to aldehyde **27** by Dess–Martin periodinane, in preparation for the Wittig homologation. In the event, the Horner–Emmons reagent **28**, the methoxymethyl diethylphosphonate of (*E*)-2-methylbut-2-enoate, reacted with aldehyde **27** under basic conditions to yield compound **29**.[10a] As expected, only the (*E*,*E*)-diene **29** was obtained. Hydrolysis of the mixed acetal and oxidation gave the lactone functionality, and acid-induced deprotection of the MEM group afforded acid **30**. Finally, acetylation of the hindered tertiary alcohol at C4 afforded pseudolaric acid A (**1**). The spectroscopic data of pseudolaric acid A obtained from this synthesis was in accordance with the natural product;[27] for example, the optical rotation of the synthetic

material is $[\alpha]_D^{20} = -37.1°$, and that of natural pseudolaric acid is $[\alpha]_D^{20} = -39.6°$.[28] Pseudolaric acid B (**2**) has been documented to be available from **1** by chemical transformations.[29]

In conclusion, we have accomplished the synthesis of pseudolaric acid A. The highlights of this synthetic route are the Evans catalytic asymmetric aldol reaction to establish the absolute stereochemistry of the first two tertiary carbon stereocenters, the carbene cyclization cycloaddition cascade reaction to install the remainder of the stereochemical elements and the polycyclic framework, as well as a reductive elimination protocol to unmask the oxatricyclic structure to reveal the perhydroazulene nucleus and facilitate cyclization to construct the final lactone ring. The present synthetic approach is amenable for the preparation of analogues and derivatives of pseudolaric acids that will be useful to the evaluation of the biological potential of these kinds of compounds.

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[28] According to the optical rotation, the synthetic material has an *ee* value of 94% . From the initial 88% *ee* obtained in Evans asymmetric aldol reaction, some enantiomeric enrichment has occurred, apparently in the chiral $[Rh_2\{(S)\text{-bptv}\}_4]$-induced CCCC reaction.
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