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Total Synthesis of (-)-Pseudolaric Acid B

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Abstract

We report a full account of our work towards the total synthesis of pseudolaric acid B (**1a**), a diterpene acid isolated from the bark of *Pseudolarix kaempferi* Gordon (pinaceae). Pseudolaric Acid B (**1a**) is an antifungal and antifertility agent. Furthermore, its capacity of inhibiting tubulin polymerization makes it a lead compound for cancer therapy. Herein, we describe the use of a Ru or Rh catalyzed [5+2] intramolecular cycloaddition reaction of an alkyne and a vinylcyclopropane for the construction of the polyhydroazulene core of the molecule. Our first unsuccessful strategy towards the introduction of the quaternary center based on an epoxide opening with cyanide led to the discovery of a new TBAF mediated isomerization of 1,4 diene to 1,3 diene and a vinylogous eliminative opening of an epoxide to form a dienol. Our second strategy, based on the cyclization of an alkoxycarbonyl radical upon a diene system, succeeded in forming the quaternary center. Detailed studies showed the dependence of this underutilized approach for the synthesis of lactones from substrate structure and reaction conditions. In the late stage of the synthesis, the unique capacity of cerium organometallic reagents to add onto sensitive sterically hindered ketone was demonstrated. The easy formation of an oxo-bridged derivative was the major hurdle for the completion of the synthesis and showcased the intriguing reactivity of the complex core of the pseudolaric acids.

Introduction

Pseudolaric acids A-C (**1a–1c**), are diterpene acids isolated from the bark of *Pseudolarix kaempferi* Gordon (pinaceae).¹ The extract of the root bark of *Pseudolarix kaempferi* is a Chinese herbal medicine called *tujinpi* and is used against fungal infections of the skin and nails.¹ Pseudolaric acid B (**1a**) has been identified as a potent antifungal,^{2a} antifertility^{2b,2c} and cytotoxic agent,^{1d,2d} displaying much higher activity than pseudolaric acid A (**1b**) and C (**1c**). More recently, several other members of the pseudolaric acids family have been isolated, but none displayed significant activity.³ Pseudolaric acid B (**1a**) has been shown to be an agonist for transcriptional activation of PPAR (peroxisome proliferators-activated receptors) receptors, which are important for the membrane integrity and lipid metabolism of *Candida* species.^{4b} Furthermore, **1a** inhibits angiogenesis by diminishing the VEGF (vascular endothelial growth factor) secretion in tumor cells^{4a,4b} and has been shown to induce apoptosis through several pathways in human melanoma cells.^{4c–4g} Finally, **1a** inhibits the polymerization of tubulin in multi-drug resistant cancer cell lines and constitutes as such a potential lead for new cancer therapy.^{4h,4i} Because of these remarkable biological properties, combined with their low toxicity, the pseudolaric acids have attracted significant interest among the scientific community.

The compact tricyclic core of Pseudolaric acid B (**1a**) constitutes a challenge for modern synthetic chemistry. The 4 contiguous stereocenters, one of them quaternary (C10), and the

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unusual *trans*-substituted fused [5–7] ring system (polyhydroazulene) contributes to make any stereoselective approach towards the pseudolaric acids a daunting task. The many unsuccessful attempts towards a total synthesis of these natural products showcase these difficulties.^{5a-5h} In 2006, the first successful total synthesis of pseudolaric acid A (**1b**) was reported by Chiu.⁵ⁱ Key for this success was the development of an efficient carbene cyclization cycloaddition cascade to form the polyhydroazulene core of the molecule. Despite intensive optimization, the diastereoselectivity of the cyclization reaction never exceeded 1.6:1. Herein, we describe a full account of our work⁶, which highlights the challenges and surprises associated with the selective synthesis of such a densely-functionalized polycyclic compound.

Retrosynthesis

The polyhydroazulene constituting the core of the pseudolaric acids can be envisioned to be made by the metal-catalyzed [5+2] intramolecular cycloaddition of a vinylcyclopropane and an alkyne introduced by the Wender⁷ (with Rh catalysts) and Trost⁸ (with Ru catalysts) groups. One of the major challenges for this approach will be the stereoselective elaboration of the quaternary center at C10.

We intended to introduce the lactone ring and the fatty acid chain at a late stage of the synthesis in order to focus first in the challenging formation of the polyhydroazulene. These disconnections reveal **2** as a potential precursor (Scheme 1, **A**). In our first approach, we envisaged to access **2** using a Ru-catalyzed [5+2] cycloaddition reaction of linear precursor **3** via simultaneous C4–C10 and C5–C6 bond formations. This strategy would allow formation of the polyhydroazulene and quaternary center in one single synthetic transformation.

In the course of model studies (not shown), it became rapidly apparent that the Ru catalyst could not accommodate any substitution at the C10 position, probably because of the high steric hindrance. Consequently, it was necessary to introduce the quaternary center after the [5+2] cycloaddition had been performed. When considering the *trans* substitution of the oxygen at C4 and the ester at C10, we considered the possibility of cyanide opening of a tetrasubstituted epoxide derived from conjugated diene **5** (Scheme 1, **B**). The thermodynamically more stable conjugated diene **5** should be accessible from 1,4-diene **6** resulting from the Ru-catalyzed [5+2] cycloaddition of **7**.

We first concentrated our effort towards the synthesis of an adequate precursor **7** for the [5+2] cycloaddition. Iodide **11** and aldehyde **14** were considered to be adequate precursors to access **7** via a homologation-olefination sequence (Scheme 2).

The synthesis of iodide **11** began with the highly selective Noyori reduction of 2-acetyl butyrolactone (**8**) to generate the two adjacent stereocenters (Scheme 2, **A**).⁹ After TBS protection of the secondary alcohol **9**, the lactone was reduced with DIBAL-H. The resulting lactol was directly reacted with TMSCHN₂/LDA and TMSCl quench to give the corresponding protected alkyne **10**. For iodination of alcohol **10**, a one step procedure (PPh₃/I₂) was used in small scale, but a two step procedure (MsCl, then NaI), was more convenient for larger scale. Aldehyde **14** was obtained in 3 steps and 84% overall yield starting from *cis*butenediol (**12**) via mono-protection with TBDPSCl, Charette modification of the Simmons-Smith cyclopropanation¹⁰ and Moffat-Swern oxidation.

Reaction of iodide **11** with triphenylphosphoniummethylide provides the homologated phosphonium salt as a non-isolated intermediate. In situ conversion of this new phosphonium salt to ylide using the Schlosser modification of the Wittig olefination with aldehyde **14** gave, in this one pot operation, the desired vinyl cyclopropane **15** in 58% overall yield after TMS deprotection with good E selectivity (>10:1) (eq 1).¹¹ This high selectivity is important, as the *Z* olefins proved to be unreactive in the [5+2] cycloaddition.

(1)

The cyclization of **15** with $[\text{CpRu}(\text{CH}_3\text{CN})_3]^+\text{PF}_6^-$ (**17**) as catalyst proceeded only sluggishly, and full conversion was never observed even with 20 mol% catalyst. In contrast to this result, substrate **16** bearing a free acetylene was more reactive and was fully consumed under the reaction condition, although a 20 mol% catalyst loading was still required.

Initial experiments in methylene chloride led to the formation of two major products in a 1:1 ratio. Subsequently, one of them was identified as the desired [5+2] cyclization product **19**, with a diastereoselectivity of 9:1 – 15:1, as well as a conjugated diene **20** (eq 2).¹² The stereochemistry of the major diastereoisomer **19** was assigned based on the general selectivity of the Ru-catalyzed cycloaddition reaction and further confirmed via NOE experiments, although the weakness of the observed signals does not allow a certain assignment. The subsequent behavior of **19** in the synthesis, however, further corroborates this assignment (*vide infra*).

Fortunately, the ratio of products **19/20** could be increased to 3:1 by using acetone as solvent. In this case, a combined yield of 63% was obtained. With the more polar DMF, dehydration reactions became competitive and triene side products were dominant.

Following these preliminary results, several additives were examined in the [5+2] cycloaddition reaction. It was envisioned that an equimolar amount of a coordinating additive could bind to the Ru center and modulate its selectivity without hampering reactivity, as two free coordination sites on the Ru center should be sufficient for an efficient cycloaddition reaction. However, we were not able to identify any additive that could further increase the **19/20** ratio. Weak ligands (cyclopentanone, acetic acid, sulfolane, 2,4-diacetylpyridine, dimethylcarbonate, phosphate esters) simply showed no effects and stronger ligands (pyridine, bipyridine, triphenylphosphine oxide, triphenylphosphine sulfide, arylphosphines, DMPU, cyclooctadiene, excess acetonitrile) led to low turnover numbers, even if only one equivalent of ligand compared to the Ru catalyst was used. A particular behavior was observed for DMF

and DMA, which led to elimination products, and nitromethane, which favored the formation of **20** (**19**:**20** = 1:1.4).

(2)

To explain the formation of **20**, we speculated that the insertion of a Ru intermediate in the labile bisallylic C-H bond leads to a Ru pentadienyl complex, which then deactivates the catalyst. In fact, the low turnover observed for the reaction in the case of Ru catalysts seems to be related to the formation of **20**, as the isolated yield of **20** was in the same range as the catalyst loading. While not unexpected with Ru catalysts in general, this behavior was not observed in other Ru catalyzed [5+2] cycloaddition reactions. Protonation of the intermediate Ru-pentadienyl complex results then in conjugated diene **20**. It is important to note that conversion of **19** to **20** in the presence of Ru catalyst **17** was not observed in a separate experiment. Consequently, activation of the C-H bond had to occur from an intermediate in the catalytic cycle. For Rh catalysts, C-H activation is not so facile. When Wender's catalyst [(C₈H₁₀)Rh(COD)]⁺SbF₆⁻ (**18**)⁷⁰ was used, the desired product **19** was obtained exclusively in 88% isolated yield and 15:1 diastereoselectivity (18 g scale), although the reaction still required an unusually high catalyst loading (10 mol%) (eq 2).

We then focused on the isomerization of diene **19** and its further elaboration. At the beginning, several attempts to isomerize **19** to a conjugated diene were unsuccessful, as either no reaction (HCl, THF; PPTS, toluene, 110 °C; CSA, toluene, 110 °C) or decomposition (TFA, 0 °C) was observed under acidic conditions and decomposition occurred under common basic conditions (KO^tBu, DMSO; KO^tBu, THF; LDA, THF). No reaction of the diene system occurred in the presence of Pd catalysts ([Pd(CH₃CN)₂]₂⁺(BF₄)₂⁻, CH₃CN; Pd/C, H₂, benzene). Finally, a surprising solution to the isomerization problem was found when attempting the deprotection of the two silyl ether groups of **19**. As the removal of the silyl groups was slow with TBAF only, activated molecular sieves (3 Å, 0.50 g/mL TBAF) was added. This resulted in a fast deprotection, but the obtained product was in fact a 1:1 mixture of the expected product **21** and the conjugated diene **22** (eq 3). It was soon found that the amount of molecular sieves was crucial in determining the ratio **21**:**22** and using 1.0 g of molecular sieves/mmol TBAF led to the exclusive formation of conjugated diene **22**. It is interesting to note that submitting cyclization product **20** to the same reaction conditions simply resulted in a clean cleavage of the silyl groups without isomerization and the corresponding diastereoisomer of **19** with the

hydrogen at C10 and the hydroxymethyl group at C7 in *trans* position gave a mixture of elimination and simple deprotection products. Again, no isomerization product was obtained. An explanation to these observations would be an intramolecular deprotonation of the bis-allylic hydrogen via a “naked” alkoxide generated during the deprotection (**A** in eq 3). Such a process would be possible only with rigorous exclusion of water. The isomerization-deprotection sequence worked well up to a 3.2 mmole (1.8 g) scale. On larger scale, resubmitting the mixture to KO^tBu in THF was necessary to achieve full conversion. The fact that an anhydrous base is able to mediate the isomerization of **21** to **22** whereas no reaction was observed with **19** further supports the proposed mechanism. It is interesting to note that the Ru and TBAF mediated isomerizations proceed to give completely different diene systems due to different isomerization mechanisms.

The research was then focused on the functionalization of diene **22**. In order to obtain the desired diastereoselectivity for the epoxidation of **22**, it was necessary to protect the two hydroxy groups (Scheme 3). The subsequent epoxidation proceeded with good selectivity (10:1 by ¹H NMR), but the obtained vinyl epoxide **23** proved to be unstable. Best results were obtained when the crude reaction mixture was directly filtered over deactivated (NEt₃) silica gel and used immediately.

The key formation of the quaternary center was first attempted via cyanide addition. Et₂AlCN appeared to be the reagent of choice, as it has been reported to open similar 6,6-bicyclic tetrasubstituted vinyl epoxides with high regio- and diastereoselectivity.¹³ When epoxide **23** was treated with this reagent, however, the desired product was not observed. Instead, ketone **24**, resulting from a pinacol-like rearrangement via a cationic intermediate, was obtained in high yield (Scheme 3).¹⁴ Unfortunately, this ring contraction reaction appeared to be highly favored with any strong Lewis acid, even at low temperature. No conversion was observed when nucleophilic activation of cyanide or weaker Lewis acids were used. Nevertheless, this sequence does provide a convenient diastereocontrolled entry into such spiro compounds which also are a common motif in natural products.

Revised Retrosynthesis

At this point, it had become clear that the epoxide opening strategy was not viable to introduce the quaternary center. As an intermolecular addition of a nucleophile has proven very difficult for the formation of the quaternary center, the synthesis strategy was modified to include an intramolecular bond formation (Scheme 4). A radical cyclization was envisioned to introduce the quaternary center at C10 stereoselectively. An alkoxy carbonyl selenium (X = O, Y = SePh in **26**) was chosen as a radical precursor as there were rare examples of such an intermediate for radical lactonization reactions in the literature.¹⁵ A dienoate was envisioned as in **27** as the

radical acceptor which, in turn, would derive from the dienol **28**. The side chain would be introduced via the reaction of an organometallic reagent on a ketone at C11. In principle, side chain introduction could be envisaged prior or after quaternary center formation.

Radical Based Strategy

While the addition of any carbon nucleophile on vinyl epoxide **23** appeared a daunting task, an alternative approach was sought to convert this compound into a more useful intermediate for the synthesis of pseudolaric acid B (**1a**). Examination of a molecular model of vinyl epoxide **23** revealed that the oxygen atom of the epoxide and the allylic hydrogen of the alkene were in close proximity to each other. It was envisioned that opening of the epoxide to form a dienol should be possible via coordination of the oxygen atom and directed deprotonation (**A** in Scheme 5). Indeed, treatment of the epoxide formed from diene **29**¹⁶ with a large excess of LDA¹⁷ resulted in the formation of dienol **28** (R=TES) (Scheme 5). Furthermore, only the major diastereoisomer of the epoxide reacts, simplifying greatly the purification of the obtained product. As such, it was found most convenient to perform the epoxidation and opening in one reaction sequence to give dienol **28** (R=TES) in 72% overall yield.

The transformation of diene **29**, which is readily available by silylating diol **22** with TES-Cl in 82% yield, into dienol **28** (R=TES) constitutes an important step towards pseudolaric acid B (**1a**), as it introduced the tertiary hydroxy group at C4 with the correct stereochemistry. It also introduced the double bond at C7–C8 and a double bond at C9–C10 that can serve as a handle for further functionalization. The methyl ester was introduced in a selective 2 step oxidation sequence at the allylic position (Scheme 5). Finally, deprotection of the secondary TES group led to diol **27**.

The most direct approach is to introduce the side chain prior to cyclization. To achieve this goal, ketone **30** was synthesized in high yield form diol **27** via oxidation with Dess-Martin periodinane (DMP, eq 4). Introduction of the side chain was then attempted using different organometallic acetylide reagents, but clean conversion could not be obtained with free alcohol **30**.

Acylation of **30** proceeded smoothly to give acetate **31** in quantitative yield (Scheme 6). Although good conversion for acetylide addition could not be obtained with lithium or Grignard reagents, cerium acetylide gave full conversion of the starting material. Unfortunately, the obtained tertiary propargylic alcohol was unstable, decomposing both on standing and on column chromatography.

Obviously, the free propargylic alcohol was not a viable intermediate and we decided to transform it in situ to an alkoxycarbonyl imidazole intermediate by quenching the addition reaction with carbonyldiimidazole (CDI). Gratifyingly, this approach proved to be highly successful, and **32** was obtained in 91% yield and good diastereoselectivity (Scheme 6, dr = 8:1–12:1). Alkoxycarbonyl imidazole **32** was sufficiently stable to allow easy purification by column chromatography. The conversion of alkoxycarbonyl imidazole **32** to alkoxycarbonyl

selenium **33** proceeded smoothly in 76% yield. Unfortunately, when **33** was submitted to standard conditions for radical generation, no cyclization was observed. A complex mixture was obtained, the major product appeared to be decarboxylation product **34**, as the phenyl group was absent but no changes had occurred in the structure of the diene as shown by ^1H NMR spectroscopy. All further attempts were also not successful. Initiation at room temperature using BEt_3/O_2 resulted in a complex mixture or re-isolation of the starting material. An attempt of activation of the conjugated system with $\text{Yb}(\text{OTf})_3$ resulted in the elimination of HOAc and formation of triene products.

From the studies on substrate **33**, we concluded that fragmentation with loss of CO_2 to form a tertiary radical was favored over the desired cyclization reaction. As an alternate strategy, we synthesized the secondary alkoxy carbonyl selenide **35** derived from **27** (Scheme 7).

When alkoxy carbonyl selenide **35** was submitted to the standard reaction conditions for radical cyclization, a mixture containing 3 major products was obtained in 90% yield after extensive optimization. For successful cyclization, a ratio of 0.6:2.2:1 (AIBN , Bu_3SnH , **35**), and slow addition of AIBN were essential.¹⁸ Best results were obtained with relatively high concentration of Bu_3SnH , showing that the main problem is not, as often the case, direct reduction of the carbonyl radical, but rather decomposition of the formed allylic radical due to slow hydride abstraction. This also explains the high quantity of initiator needed for good conversion. Apart from the desired product **36**, two other compounds were isolated, one of them is tentatively assigned as isomer **37**, whereas the other, lacking the methyl ester group, could be bislactone **38**, resulting from a subsequent intramolecular lactonization. Separation of this mixture was not successful, and it was directly submitted to the next step.

It was our hope that the mixture resulting from the radical cyclization could be transformed to a single compound under hydrolysis conditions followed by methylation of the formed carboxylates. Indeed, when the mixture of **36–38** was subjected to forcing hydrolysis conditions (1 M NaOH , 100 °C, 24 h), followed by methylation with TMSCHN_2 , a new compound was obtained as a diastereomeric mixture (Scheme 7). The formed compound was identified as **39**, diastereomeric at C7, which resulted from an intramolecular attack of the tertiary alcohol at C4 onto the conjugate ester. We were never able to achieve the opening of the lactone(s) ring(s) without concomitant formation of the oxo bridge.

In principle, the oxo bridge could be used as a protecting group for the tertiary alcohol, provided it could be opened at a later stage. To test this hypothesis, the secondary alcohol of **39** was oxidized with Dess-Martin periodinane to give the corresponding ketone. Cerium acetylide addition proceeded in 76% yield to give the stable propargylic alcohol **40**.

The next task was to perform the opening of the oxo-bridge of **40** and the lactonization of the propargylic alcohol to give the complete tricyclic core of pseudolaric acid B (**1a**). We first attempted basic conditions to promote β -elimination to the conjugated ester.¹⁹ At low temperature, no reaction was observed, either with NaH , LiHMDS or LDA and higher temperature led to decomposition. In the case of LDA , racemization of the C7 center next to the methyl ester was observed, indicating that enolate formation was not the problem. An attempt to generate a silyl enolate prior to elimination only resulted in silylation of the propargylic alcohol.

We then turned to acid activation. Lewis acid either resulted in no reaction ($\text{BF}_3\cdot\text{OEt}_2$, $\text{Ti}(\text{O}^i\text{Pr})_4$) or in elimination at the propargylic position (TMSOTf , TsOH). Finally, an attempt was made to promote lactonization prior to opening of the oxo bridge using Otera's catalyst,²⁰ but no reaction was observed under standard conditions and higher temperature resulted in decomposition. Examination of a molecular model showed that the formation of the oxo bridge is “pulling away” the ester at C10 and the alcohol at C11, making lactonization unfavorable.

From these experiments we concluded that protection of the C4 alcohol could not be avoided for a successful synthesis of pseudolaric acid B (**1a**). Due to the strong basic conditions needed for lactone opening, we needed a protecting group stable to base but that could be removed under mild neutral conditions. For this reason, a PMB group was finally selected. Introduction of the PMB group was achieved in 94% yield using activation of the imide with $\text{Sc}(\text{OTf})_3$ (Scheme 8). For this reaction, low temperature and catalyst loading were essential to achieve good yields, as elimination of the tertiary alcohol was observed otherwise.

The protection of the alcohol seemed to slow down the radical cyclization, however, and using the standard conditions developed for the free alcohol **35**, only little conversion was observed in the case of the PMB protected **41** (entry 1, Table 1). It was found that a higher initiator loading (1.2 equiv) was necessary to achieve full conversion (entry 2). Under these conditions, a mixture of the double bond isomers **43** and **44** was observed as well as several non-identified impurities. Adding DBU to the reaction mixture directly after completion of the cyclization allowed clean conversion of **44** to the desired **43** which could be isolated in 56% yield and about 90% purity (entry 3). To improve this yield, we decided to use azobis (dicyclohexylcarbonitrile) (**42**) as initiator, as it is thermally more stable and allows for a cleaner, continuous generation of radicals.²¹ When the reaction was conducted in refluxing toluene with only 0.2 equivalents of **42**, full conversion was indeed achieved and the reaction was cleaner (entry 4). Unfortunately, the formation of other side products was favored, apparently via reaction of the benzylic position of the PMB protecting group, as shown by the disappearance of the characteristic two doublets of the PMB group in the ^1H NMR. We found after further optimization that this side reaction was minimized at lower temperature. In this case a higher loading of **42** was needed for full conversion. Using 2 equivalents of **42** and 3.5 equivalent of Bu_3SnH in benzene at 70 °C for 15 h followed by isomerization with DBU allowed the isolation of **43** in 85% yield and 92% purity (entry 5). As the radical generation is controlled by the slow rate of decomposition of **42** and not the rate of addition, all the reagents could be mixed together at the beginning, leading to an operationally simpler procedure.

The next task towards completion of the synthesis was to open the lactone of **43**. Several attempts using hydrolysis with base in water followed by extraction from an acidic solution and methylation with TMSCHN_2 were never successful and mainly led to removal of the PMB group and mostly isolation of bislactone **38**. We concluded that the main problem was the acidic conditions of work up and the subsequent methylation reaction. For a successful ring opening, direct methylation of the formed carboxylate salt was required, which precluded the use of excess base in water for the hydrolysis. We finally chose KOTMS as reagent, as the anhydrous salt is readily soluble in organic solvents. Furthermore, potassium was expected to give a dicarboxylate salt that was more soluble than barium for example, allowing for an easier subsequent methylation. Indeed reaction with KOTMS followed by methylation with dimethyl sulfate in the presence of bicarbonate resulted in successful formation of the desired alcohol in 50% yield together with isolated starting material (10%) and several side products, one of them resulting from methylation of the secondary alcohol at C11. Unfortunately, this protocol was difficult to reproduce on larger scale leading to lower yields (< 30%).

We hypothesized that a soluble buffer system after ring opening with KOTMS should be more efficient to control the pH of the reaction. Optimization studies led to the use of 6 equiv of TsOH and 12 equiv of Hünig's base in methanol as buffer. These conditions were designed to completely protonate any alkoxide present and leave only the carboxylates as the best nucleophiles in the reaction mixture. Indeed, the desired alcohol was formed in 65% yield (75% brsm) under these conditions and no methylation of the alcohol was observed (Scheme 8).

Dess-Martin periodinane then oxidized the alcohol to the corresponding ketone **45**. Buffering with NaHCO_3 and lowering the temperature to 0 °C were important to prevent decomposition

during the oxidation step. The problem of relactonization was easier to control when column chromatography was omitted prior to oxidation. In this case, the ketone **45** was obtained in 59% (73% brsm) over 2 steps.

Cerium acetylide addition was not compatible with the PMB protecting group, as β -alkoxide elimination was a major problem. For this reason, the PMB group was first removed with DDQ in 76% yield.

A few attempts were made to acylate the tertiary alcohol of **46**, but a considerable amount of elimination to the α,β -unsaturated ketone was observed and we decided to focus on **46** as substrate for the cerium acetylide addition.

First attempts towards cerium acetylide addition using the standard procedure were disappointing, as they resulted in a complex mixture. In a single case, however, we obtained a clean reaction to the desired product **47** in nearly quantitative yield! Thus, it appeared that this reaction was extremely sensitive to the quality of the cerium reagent, which led to major difficulties for reproducing this result. At this point, we became interested in a recent report of *Knochel* on the use of soluble ceriumlithium chloride reagents for addition reactions.²² Although we still encountered difficulties when using large quantities of Ce reagents, we found that on small scale (<1 mmol cerium), simply co-drying $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ with two equivalents of LiCl was successful in giving a clear solution of the reagent in THF. Importantly, the cerium acetylide addition was successful every time the clear solution was used as reagent and gave the desired addition product as a single diastereoisomer in 80–90% yield with 20–10% isolated starting material (Scheme 8). The optimal ratio of reagent to substrate was found to be 8:1, as lower ratios led to lower conversions. Inverse quenching of the reaction mixture with bicarbonate solution was important to prevent intramolecular attack of the tertiary alcohol onto the conjugate ester.

The lactonization of **47** was examined next. Basic conditions could not be used, as they led to exclusive formation of oxo bridge compound **40** (Scheme 9). Fortunately, the use of Otera catalyst²⁰ in toluene (30 min at 130 °C under microwave irradiation) resulted in formation of the desired lactone **48** in 94% yield. This perfect orthogonality between basic conditions and Otera catalyst is noteworthy and results probably from the unique ability of Otera catalyst to activate both the methyl ester and the alcohol. At this point, the stereochemistry of the propargylic position could be assigned by 1D NOE studies (Figure 2). Especially the strong NOE signal observed between the methyl group CH_3 13 and H 10 was crucial for the determination of the configuration of the propargylic center. The high selectivity of the addition step is explained by a Felkin-Ahn approach on ketone **46**, where the methyl ester group is blocking the other face of the carbonyl group.

The deprotection of the terminal acetylene proceeded uneventfully in 87% yield using TBAF in THF (Scheme 8). The acylation of the tertiary alcohol was attempted next. The use of DMAP and AcCl reported for the synthesis of pseudolaric acid A (**1b**) led to a very slow reaction (about 20% in 24 h).⁵¹

Fortunately, freshly dried $\text{Sc}(\text{OTf})_3$ in acetic anhydride as in solvent at 0 °C resulted in clean acylation of the tertiary alcohol 98% yield.²³

At this point, we chose a Stille coupling to complete the synthesis, as it allows the use of free acids for the coupling reaction. The iodide **51** needed for the Stille reaction is a known compound and was synthesized in two steps from diethyl methyl malonate using a literature procedure.²⁴

The hydrostannylation of the free alkyne in **49** proceeded in good yield, regio- and *trans*-selectivity as shown by ^1H NMR, but the formed stannane **50** was surprisingly unstable. Consequently, it was always prepared immediately prior to Stille coupling and purified over a short plug of deactivated SiO_2 .

First attempts for the Stille coupling were made with the most often used conditions, ligandless Pd(II) salts in DMF.²⁵ Both $\text{Pd}(\text{CH}_3\text{CN})\text{Cl}_2$ and $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ led to low yield (<30%) of pseudolaric acid B (**1a**). In both cases, protodestannylation and isomerization of the diene were serious issues. There is a single report in the literature of performing Stille coupling of an acid under basic conditions with $\text{Pd}_2(\text{dba})_3$ as catalyst and NMP as solvent.²⁶ Gratifyingly, these conditions were efficient to shut down both the destannylation and the isomerization side reactions and pseudolaric acid B (**1a**) was obtained in 62% yield after HPLC purification. 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).^{1e,2a}

Summary

We report the successful total synthesis of the highly biologically active and structurally intriguing pseudolaric acid B (**1a**). Vinylcyclopropane **16** was easily accessed in 7 linear steps and 33% overall yield from 2-acetyl-butyrolactone (**8**). The intramolecular cycloaddition of **16** constituted an efficient access to the polyhydroazulene core of pseudolaric acid B (**1a**). In this particular case, Rh catalyst **18** was superior to Ru catalyst **17**, as it displayed a lower tendency towards C-H insertion and subsequent isomerization of the diene product. Further elaboration of the polyhydroazulene core via a novel isomerization of a 1,4 diene to a 1,3 diene using TBAF and an interesting vinylogous opening of a vinyl epoxide with LDA as key steps resulted in alkoxycarbonyl seleniums **33**, **35** and **41**, but only secondary alkoxycarbonyl seleniums **35** and **41** were efficient precursors for the introduction of the quaternary center via a radical cyclization reaction. On the way to pseudolaric acid B (**1a**), a novel procedure for the opening of lactones and a highly selective cerium acetylide addition to a sensitive ketone were developed. Interesting observations were made on the orthogonality of cyclization conditions to generate diverse polycyclic ring systems from the polyhydroazulene core: intramolecular conjugate addition was preferred under basic conditions, whereas lactonization was observed exclusively using Otera's catalyst.

This work culminated in the total synthesis of pseudolaric acid B (**1a**) in 28 overall steps and 1.4% overall yield. Strength of our synthesis is the very high selectivity observed for the installation of the 4 stereocenters of the molecule via Noyori reduction, epoxidation, radical cyclization and cerium acetylide addition, which contributes together with the [5+2] cycloaddition to its efficiency. Furthermore, the late stage introduction of the acid side chain is also interesting from the point of view of analog synthesis. It should be noted that a new strategy for the syntheses of [6.5] spiro fused bicycles also emerged. Thus, the [5+2] cycloaddition can also initiate formation of other isomeric bicyclic skeleta which are also found among natural and other bioactive targets.

Experimental Section

(1*R*,3*aS*,6*R*)-1-[(*R*)-1-(*tert*-Butyl-dimethylsilyloxy)-ethyl]-6-(*tert*-butyl-diphenyl-silyloxymethyl)-1,2,3,3*a*,6,7-hexahydro-azulene (19) and (1*R*,6*S*)-1-[(*R*)-1-(*tert*-Butyl-dimethyl-silyloxy)-ethyl]-6-(*tert*-butyl-diphenyl-silyl-oxymethyl)-1,2,3,5,6,7-hexahydro-azulene (20)

$[\text{CpRu}(\text{CH}_3\text{CN})_3]^+\text{PF}_6^-$ (**17**) (1.9 g, 4.4 mmol, 0.23 equiv) was added in portions over 20 min to a solution of **16** (10.7 g, 19.1 mmol, 1.00 equiv) in acetone (distilled over drierite, 200 mL) at 0 °C. After 1 h at 23 °C, the reaction mixture was poured onto PET (1 L), filtered over

SiO₂, the plug was washed with PET/Et₂O 10:1 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (pentane/DCM 30:1–25:1–20:1–15:1–10:1–3:1, 1 kg SiO₂, collected fraction: 200 mL) to yield a first fraction (fractions 32–91) of diastereomerically pure **19** (4.59 g, 8.18 mmol, 43%), a second fraction (fractions 92–105) of **19** together with the *trans* diastereomer (534 mg, 0.952 mmol, 5%, dr (*cis:trans*) = 1:1.6, total **19**: 5.13 g, 9.15 mmol, 48%, dr = 15:1) and a third fraction (fractions 106–122) of **20** (1.60 g, 2.85 mmol, 15%), whose structure has tentatively been assigned as shown. All the isolated products were colorless, air-sensitive oils.

Using Rh catalyst

Rh catalyst **18** (2.0 g, 3.5 mmol, 0.11 equiv) was added in 4 portions of 500 mg every 10 min to a solution of **16** (18.2 g, 32.4 mmol, 1.00 equiv) in DCE (distilled over CaH₂, 320 mL) at 0 °C. After 1 h at 23 °C, the reaction mixture was poured into PET (300 mL), filtered over SiO₂, the plug was washed with PET/Et₂O 1:1 (1.5 L) and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (pentane/DCM 50:1–20:1–15:1–10:1–3:1, 1 kg SiO₂) to yield **19** (16.1 g, 28.7 mmol, 88%, dr = 15:1) as a colorless oil.

19: *R_f* 0.50 (pentane: DCM 3:1, Anisaldehyde); [α]_D (25 °C) = –12.9 (CHCl₃, c = 1.0); ¹H NMR (500 MHz, CDCl₃) δ 7.68–7.65 (m, 4H), 7.44–7.36 (m, 6H), 5.71–5.68 (m, 1H), 5.49–5.42 (m, 2H), 4.00–3.96 (m, 1H), 3.54–3.45 (m, 2H), 3.29 (br m, 1H), 2.47 (br m, 1H), 2.38 (br m, 1H), 2.23–2.19 (m, 2H), 2.07–2.01 (m, 1H), 1.68–1.56 (m, 2H), 1.38–1.21 (m, 1H), 1.12 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 9H), 0.84 (s, 9H), 0.02 (s, 3H), –0.02 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 150.4, 135.6, 133.9, 132.1, 130.0, 129.5, 127.6, 119.7, 69.6, 68.6, 52.0, 43.7, 40.4, 34.0, 28.8, 26.8, 25.8, 24.4, 22.3, 19.3, 18.0, –4.2, –4.8; IR ν 3070 (w), 3051 (w), 2999 (w), 2955 (s), 2930 (s), 2896 (m), 2858 (s), 1958 (w), 1888 (w), 1823 (w), 1770 (w), 1728 (w), 1694 (w), 1660 (w), 1590 (w), 1487 (w), 1472 (m), 1463 (m), 1446 (w), 1428 (m), 1390 (w), 1370 (m), 1361 (m), 1255 (m), 1187 (w), 1154 (m), 1112 (s), 1042 (m), 1007 (m), 954 (w), 939 (w), 910 (w), 882 (w), 834 (s), 807 (m), 774 (m), 739 (m), 701 (s), 667 (w), 613 (m), 506 (m), 487 (m); HRMS (EI): calcd for C₃₅H₅₂O₂Si₂: 560.3506 (M⁺), found : 560.3508; Anal. calcd for C₃₅H₅₂O₂Si₂: C, 74.94; H, 9.34. Found: C, 74.78; H, 9.43; further data: ¹H COSY, HSQC, NOE.

20: *R_f* 0.40 (pentane: DCM 3:1, Anisaldehyde); [α]_D (25 °C) = –80.0 (CHCl₃, c = 1.0); ¹H NMR (500 MHz, CDCl₃) δ 7.70–7.68 (m, 4H), 7.46–7.34 (m, 6H), 5.47 (m, 1H), 5.42 (m, 1H), 3.78–3.75 (m, 1H), 3.56 (d, *J* = 4.8 Hz, 2H), 2.32–2.14 (m, 5H), 2.08–1.96 (m, 4H), 1.61–1.55 (m, 1H), 1.11 (d, *J* = 6.1 Hz, 3H), 1.06 (s, 9H), 0.84 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 135.6, 135.3, 133.9, 133.3, 129.5, 127.6, 124.1, 122.3, 68.4, 67.8, 48.1, 37.6, 34.5, 29.2, 26.8, 25.9, 23.8, 22.6, 22.2, 19.3, 18.1, –3.7, –4.8; IR ν 3074 (w), 3050 (w), 3029 (w), 2957 (m), 2929 (s), 2895 (m), 2857 (s), 1487 (w), 1472 (m), 1463 (w), 1428 (m), 1390 (w), 1375 (w), 1361 (w), 1264 (m), 1191 (w), 1112 (s), 1073 (m), 1018 (w), 1006 (m), 985 (w), 966 (w), 938 (w), 914 (w), 887 (w), 835 (s), 811 (m), 793 (m), 773 (m), 739 (m), 701 (s), 614 (w), 504 (m); HRMS (EI): calcd for C₃₅H₅₂O₂Si₂: 560.3506 (M⁺), found : 560.3488; further data: ¹H COSY, HSQC.

(*R*)-1-((1*R*,6*R*)-6-Hydroxymethyl-1,2,3,6,7,8-hexahydroazulen-1-yl)-ethanol (**22**)

TBAF (1 M in THF, 19 mL, 19 mmol, 6.0 equiv) was added over 10 min to a suspension of molecular sieves 3Å (flame-dried 4× in HV, 19 g) and **19** (1.82 g, 3.24 mmol, 1.00 equiv) in THF (190 mL) at 0 °C. After stirring 4 h at 23 °C, the reaction mixture was quenched with methanol (20 mL), filtered and the residues were washed with methanol (10 mL) and Et₂O (300 mL). The reaction mixture was washed with sat. NH₄Cl (3×200 mL) and brine (100 mL) and the combined water layers were extracted with Et₂O (3×300 mL). The combined organic

layers were dried over MgSO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/ Et_2O 1:1–0:1) to yield **22** (636 mg, 3.05 mmol, 94%) as a colorless oil. Larger scale (no full conversion): TBAF (1 M in THF, 100 mL, 100 mmol, 3.3 equiv) was added over 10 min to a suspension of molecular sieves 3 Å (dried 15 h at 200 °C in vacuo oven, 150 g) and **19** (16.8 g, 30.0 mmol, 1.00 equiv) in THF (1 L) at 0 °C. After stirring 16 h at 23 °C, the reaction mixture was quenched with methanol (200 mL), filtered and the residues were washed with methanol (500 mL). The solvent was removed under reduced pressure and Et_2O (600 mL) was added. The reaction mixture was washed with sat. NH_4Cl (3×200 mL) and brine (100 mL) and the combined water layers were extracted with Et_2O (3×300 mL). The combined organic layers were dried over MgSO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/ Et_2O 1:1–0:1) to yield **22** (5.35 g, 25.7 mmol, 86%, 6:1 mixture of double bond isomers) as a colorless oil. The mixture was dissolved in THF (140 mL) at 0 °C and a solution of KOtBu (8.0 g, 71 mmol, 2.8 equiv) in THF (40 mL) was added dropwise. After 50 min, the reaction mixture was poured onto sat. NaHCO_3 (200 mL) and extracted with Et_2O (3×200 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO_4 and the solvent was removed under reduced pressure to give pure **22** (5.15 g, 24.7 mmol, 96%, 82% from **19**) as a colorless oil. R_f 0.30 (Et_2O , Anisaldehyde); $[\alpha]_D^{25}$ (25 °C) = +107.5 (CHCl_3 , c = 1.0); ^1H NMR (500 MHz, CDCl_3) δ 5.82 (d, J = 11.6 Hz, 1H), 5.67 (dd, J = 11.5, 4.9 Hz, 1H), 4.08 (qd, J = 6.4, 2.3 Hz, 1H), 3.61 (dd, J = 10.5, 5.8 Hz, 1H), 3.58 (dd, J = 10.5, 7.2 Hz, 1H), 2.68 (br m, 1H), 2.58 (br m, 1H), 2.47–2.42 (m, 3H), 2.38–2.10 (m, 2H), 1.86–1.77 (m, 4H), 1.65 (br s, 1H), 1.15 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.9, 134.9, 132.6, 125.9, 67.4, 66.0, 57.9, 43.3, 37.2, 27.5, 26.9, 21.2, 20.5; IR ν 3384 (s), 3008 (w), 2925 (s), 2871 (s), 1644 (w), 1633 (w), 1626 (w), 1445 (m), 1434 (m), 1372 (m), 1350 (w), 1308 (w), 1261 (w), 1148 (w), 1117 (w), 1079 (m), 1029 (s), 949 (w), 913 (w), 861 (w), 834 (w), 737 (m), 666 (w), 645 (w); HRMS (EI): calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2$: 208.1463 (M^+), found: 208.1467; Anal. calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2$: C, 74.96; H, 9.68. Found: C, 75.02; H, 9.52; further data: ^1H COSY, HSQC, NOE.

(3S,3aS)-3-((R)-1-Triethylsilyloxy-ethyl)-6-triethylsilyl-oxymethyl-2,3,4,5-tetrahydro-1H-azulen-3a-ol **28, R=TES**

A suspension of **29** (2.60 g, 5.45 mmol, 1.00 equiv) and NaHCO_3 (1.2 g, 14 mmol, 2.4 equiv) in DCM (65 mL) was cooled to –20 °C and *m*-CPBA (95%, washed with buffer pH = 7 and dried in HV before titration, 1.4 g, 7.9 mmol, 1.3 equiv) was added. After 30 min, the cool solution was directly filtered through a plug of silica gel (deactivated with NEt_3), the plug was washed with PET/ Et_2O 10:1 and the solvent was removed under reduced pressure to give nearly pure epoxide **23b** (R=TES). Epoxide **23b** (R=TES) was used at once in the next step. R_f 0.60 (PET/ Et_2O 10:1, Anisaldehyde); ^1H NMR (400 MHz, benzene d_6) δ 5.76 (dd, J = 11.9, 2.4 Hz, 1H), 5.65 (dd, J = 11.9, 5.5 Hz, 1H), 4.00 (qd, J = 6.3, 1.8 Hz, 1H), 3.59–3.52 (m, 2H), 2.63 (br m, 1H), 2.43–2.36 (m, 1H), 2.27–2.24 (m, 1H), 2.04–1.86 (m, 4H), 1.68–1.62 (m, 1H), 1.46–1.27 (m, 2H), 1.06–0.95 (m, 21H), 0.65–0.63 (m, 12 H); ^{13}C NMR (125 MHz, benzene d_6) δ 136.3, 126.9, 75.3, 69.0, 68.8, 64.4, 53.0, 43.7, 33.9, 24.1, 22.2, 22.1, 21.3, 7.3, 7.3, 7.1, 5.8, 5.4, 4.8, 4.7. LDA (1 M in THF, freshly prepared from diisopropyl amine (7.4 mL, 41 mmol) and $^n\text{BuLi}$ (2.5 M in hexane, 24 mL, 41 mmol) in THF (36 mL), 41 mmol, 7.0 equiv) was added over 20 min to a solution of crude epoxide **52** in THF (120 mL) at –10 °C. The reaction was monitored by TLC (PET/ Et_2O 10:1). After 40 min, no **23b** (R=TES) was left and the reaction was quenched with sat. NH_4Cl solution (100 mL), extracted with Et_2O (3×150 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/ Et_2O 10:1–3:1) to yield **28** (1.93 g, 4.26 mmol, 72% over 2 steps) as a colorless oil. Compound **28** (R=TES) proved to be unstable in pure form, especially in larger scale and had to be kept frozen in benzene to prevent decomposition. R_f 0.20 (PET/

Et₂O 10:1, Anisaldehyde); [α]_D (25 °C) = -19.1 (CHCl₃, c = 1.0); ¹H NMR (500 MHz, CDCl₃) δ 5.82 (dm, *J* = 7.5 Hz, 1H), 5.64 (dm, *J* = 7.6 Hz, 1H), 4.11 (s, 2H), 4.07 (qd, *J* = 6.3, 3.3 Hz, 1H), 2.58–2.50 (m, 2H), 2.48–2.39 (m, 1H), 2.28 (dt, *J* = 18.1, 4.1, 1H), 2.08–1.88 (m, 2H), 1.91–1.88 (m, 1H), 1.81–1.74 (m, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 0.97 (t, *J* = 8.1 Hz, 9H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.62 (q, *J* = 7.8 Hz, 6 H), 0.52 (q, *J* = 8.0 Hz, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 152.2, 142.3, 118.7, 117.2, 80.8, 68.2, 67.5, 59.4, 32.9, 30.2, 25.0, 23.4, 22.9, 6.9, 6.8, 5.3, 4.5; IR ν 3363 (w), 2956 (s), 2912 (m), 2877 (m), 1738 (w), 1661 (w), 1634 (w), 1456 (m), 1434 (w), 1416 (m), 1372 (m), 1316 (w), 1261 (m), 1240 (m), 1192 (w), 1133 (m), 1112 (m), 1071 (s), 1016 (s), 971 (m), 921 (m), 894 (w), 870 (m), 802 (m), 740 (s), 673 (w); HRMS (EI): calcd for C₂₅H₄₆O₂Si₂: 434.3036 ([M-H₂O]⁺), found : 434.3031.

(1*R*,7*S*,8*S*,9*R*)-7-(4-Methoxy-benzyloxy)-9-methyl-11-oxo-10-oxa-tricyclo[6.3.2.0^{1,7}]tridec-3-ene-4-carboxylic acid methyl ester (43)

Tributyltin hydride (1.2 mL, 4.5 mmol, 3.5 equiv) was added to a solution of acyl selenium **41** (708 mg, 1.28 mmol, 1.00 equiv) and 1,1'-azo(biscyclohexanecarbonitrile) (**42**) (0.63 g, 2.6 mmol, 2.0 equiv) in benzene (120 mL) and the reaction mixture was degassed with two freeze-thaw cycles. After heating at 70 °C for 15 h, the reaction mixture was cooled to 23 °C. TLC (PET/AcOEt 2:1, CAN) showed the formation of two major products, identified as the desired **43** as well as its double bond isomer **44**.²⁷ DBU (12 mL) was added and the reaction was monitored by TLC. After 5 h, isomerization to the desired **43** was complete and the reaction mixture was diluted with Et₂O (100 mL), washed with 1 M NaHSO₄ (2×100 mL) and the combined aqueous layers were extracted with Et₂O (2×100 mL). The combined organic layers were washed with sat. NaHCO₃ solution (50 mL) and brine (50 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (50 g SiO₂ and 5 g KF,²⁸ PET/AcOEt 10:1–5:1–2:1–1:1) to yield **43** (447 mg, 1.09 mmol, 85%, > 92% pure by ¹H NMR) as a colorless foam. *R*_f 0.30 (PET/AcOEt 2:1, CAN); [α]_D (25 °C) = 101.9 (CHCl₃, c = 1.0); ¹H NMR (500 MHz, CDCl₃) δ 7.26 (d, *J* = 8.7 Hz, 2H), 7.23–7.18 (m, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.56 (qd, *J* = 6.4, 2.3 Hz, 1H), 4.39 (d, *J* = 10.4 Hz, 1H), 4.32 (d, *J* = 10.4 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 2.83 (dd, *J* = 14.9, 6.4 Hz, 1H), 2.76 (ddd, *J* = 14.5, 4.2, 1.6 Hz, 1H), 2.55 (dd, *J* = 14.5, 8.8 Hz, 1H), 2.52–2.41 (m, 2H), 2.34 (dd, *J* = 14.6, 5.9 Hz, 1H), 2.12–2.00 (m, 1H), 1.93–1.80 (m, 3H), 1.57 (ddd, *J* = 14.3, 12.4, 1.5 Hz, 1H), 1.35 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.8, 168.3, 159.1, 143.2, 134.3, 130.0, 128.7, 113.9, 83.6, 75.1, 62.1, 56.6, 55.3, 51.9, 45.7, 35.9, 27.1, 26.2, 19.1, 18.8, 18.8; IR ν 3062 (w), 2950 (m), 2870 (w), 1732 (s), 1714 (s), 1644 (w), 1614 (m), 1586 (w), 1514 (s), 1440 (m), 1384 (w), 1361 (w), 1324 (w), 1301 (m), 1271 (m), 1251 (s), 1204 (m), 1171 (s), 1123 (m), 1094 (m), 1070 (m), 1028 (m), 912 (w), 822 (w), 770 (w), 732 (m), 648 (w), 574 (w); HRMS (ESI): calcd for C₂₃H₂₈O₆Na: 423.1784 ([M + Na]⁺), found: 423.1798.

(1*S*,3*aR*,8*aS*)-8*a*-Hydroxy-1-((*S*)-1-hydroxy-1-methyl-3-trimethylsilylprop-2-ynyl)-2,3,4,7,8,8*a*-hexahydro-1*H*-azulene-3*a*,6-dicarboxylic acid dimethyl ester (47)

CeCl₃•7H₂O (0.30 g, 0.81 mmol, 9.0 equiv) and lithium chloride (68 mg, 1.6 mmol, 18 equiv) were dried under HV (< 0.05 Torr is essential for good drying),²⁹ warming up from 23 to 150 °C over 3 h (T increased of about 10 °C every 15 min), then at 150 °C for 2 h. During all this process, good stirring was essential to keep the mixture as a light homogenous powder. After cooling to 23 °C, THF (6 mL) was added and the suspension was vigorously stirred at 23 °C. After 4 h, a clear solution was obtained and the reaction mixture was cooled to -78 °C. In a separated flask, ⁿBuLi (2.5 M in hexane, 0.28 mL, 0.70 mmol, 8.0 equiv) was added to a solution of trimethylsilyl acetylene (distilled, 0.12 mL, 0.85 mmol, 9.8 equiv) in THF (2 mL) at -78 °C. After 30 min, this solution was transferred via canula to the CeCl₃•2LiCl solution at -78 °C. After 1 h, a solution of ketone **46** (27 mg, 0.087 mmol, 1.0 equiv) in cool (-78 °C, important!) THF (2 mL) was added *via canula*. After 1 h, the reaction was poured into sat. NaHCO₃ solution

(10 mL) and extracted with Et₂O (3×10 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (DCM/AcOEt 1:0–20:1–10:1–5:1–2:1) to yield **47** (31 mg, 0.076 mmol, 87%, dr > 20:1) as a colorless oil and reisolated **46** (3 mg, 0.01 mmol, 11%). *R_f* 0.50 (DCM/AcOEt 10:1, CAN/KMnO₄); [α]_D (25 °C) = –1.4 (CHCl₃, c = 1.0); ¹H NMR (500 MHz, CDCl₃) δ 6.97 (td, *J* = 5.9, 1.4 Hz, 1H), 4.80 (s, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 2.76 (d, *J* = 6.4 Hz, 1H), 2.70 (ddd, *J* = 14.4, 9.8, 4.5 Hz, 1H), 2.62–2.50 (m, 2H), 2.47 (dd, *J* = 9.9, 9.2 Hz, 1H), 2.21–2.12 (m, 1H), 2.12–2.06 (m, 1H), 1.97–1.85 (m, 2H), 1.85–1.76 (m, 1H), 1.67 (s, 3H), 1.67 (br s, 1H), 0.12 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 177.0, 168.2, 141.1, 133.9, 111.0, 85.9, 84.1, 69.6, 64.1, 60.0, 52.5, 52.0, 34.7, 33.1, 31.4, 31.1, 26.9, 20.8, 0.0; IR ν 3436 (m), 2954 (m), 2166 (w), 1714 (s), 1641 (w), 1455 (m), 1436 (m), 1372 (w), 1320 (m), 1276 (m), 1249 (s), 1200 (s), 1102 (m), 1065 (w), 987 (w), 933 (m), 865 (m), 843 (s), 757 (m), 700 (w), 625 (w); HRMS (ESI): calcd for C₂₁H₃₂O₆NaSi: 431.1866 ([M+Na]⁺), found: 431.1881.

(1*R*,7*S*,8*R*,9*S*)-7-Hydroxy-9-methyl-11-oxo-9-trimethylsilanylethynyl-10-oxa-tricyclo [6.3.2.0^{1,7}]tridec-3-ene-4-carboxylic acid methyl ester (48**)**

A solution of diol **47** (58 mg, 0.14 mmol, 1.0 equiv) and Otera's catalyst²⁰ (17 mg, 0.028 mmol, 0.20 equiv) in toluene (4 mL) was heated at 130 °C in a microwave oven for 30 min. The reaction mixture was poured directly on column chromatography (SiO₂, DCM/AcOEt 1:0–10:1–5:1) to yield lactone **48** (48 mg, 0.13 mmol, 94%) as a colorless solid. *R_f* 0.60 (DCM/AcOEt 10:1, CAN/KMnO₄); [α]_D (25 °C) = 44.4 (CHCl₃, c = 1.0); Mp 143–145 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.23–7.17 (m, 1H), 3.70 (s, 3H), 2.85 (ddt, *J* = 15.4, 6.2, 1.6 Hz, 1H), 2.66 (dd, *J* = 14.7, 8.6 Hz, 1H), 2.59–2.45 (m, 3H), 2.28–2.18 (m, 1H), 2.17 (d, *J* = 6.4 Hz, 1H), 2.08–1.98 (m, 2H), 1.91–1.79 (m, 2H), 1.79 (s, 3H), 1.75 (s, 1H), 0.17 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 173.6, 168.2, 142.7, 134.1, 105.0, 92.1, 80.3, 79.5, 55.0, 54.4, 52.0, 35.0, 33.5, 30.3, 27.2, 26.0, 19.7, –0.3; IR ν 3436 (m), 2957 (m), 2173 (w), 1715 (s), 1650 (w), 1436 (m), 1380 (w), 1347 (w), 1273 (s), 1252 (s), 1205 (m), 1176 (m), 1120 (m), 1076 (m), 1042 (w), 943 (w), 905 (w), 859 (s), 844 (s), 770 (w), 734 (w), 602 (w); HRMS (ESI): calcd for C₂₀H₂₈O₅NaSi: 399.1604 ([M+Na]⁺), found: 399.1600.

Pseudolaric Acid B (1a**)**

A solution of acetylene **49** (9.0 mg, 26 μmol, 1.0 equiv) and Pd(PPh₃)₂Cl₂ (1.0 mg, 1.4 μmol, 0.050 equiv) in THF (0.3 mL) was degassed with 2 freeze-thaw cycles. Bu₃SnH (distilled, 12 μL, 45 μmol, 1.7 equiv) was added dropwise, whereas the color changed from yellow to orange. After 15 min, the solvent was removed under high vacuo and the crude product purified via a short column chromatography (SiO₂, deactivated with NEt₃, PET/DCM 1:0–1:1–0:1) to give crude stannane **50** (15 mg, 23 μmol, 90%, 90% pure by ¹H NMR) which was used immediately in the next step.

Following a reported procedure,³⁰ stannane **50** (17 mg, 27 μmol, 1.0 equiv) was dissolved in NMP (distilled, 0.4 mL) and Hunig's base (distilled, 30 μL, 0.17 mmol, 6.3 equiv) was added, followed by iodide **51** (12 mg, 57 μmol, 2.1 equiv). The reaction mixture was degassed with 2 freeze-thaw cycles and Pd₂dba₃ (3.5 mg, 3.8 μmol, 0.28 equiv) was added. The reaction was monitored via TLC (PET/AcOEt 5:1, 0.5% AcOH). After 17 h, no further conversion was observed and Pd₂dba₃ (3.5 mg, 3.8 μmol, 0.28 equiv) was added. After further 5 h, TLC showed that only traces from stannane **51** were remaining and the reaction mixture was diluted with AcOEt (10 mL) and washed with 1 M NaHSO₄ (2×5 mL). The combined aqueous layers were extracted with AcOEt (2×10 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 20:1–5:1–3:1–1:1, 0.5% AcOH) to yield crude pseudolaric acid B (**1a**) as a yellowish solid. Purification via preparative

HPLC (flow: 10 mL/min, detection at 265 nm, PET/AcOEt (0.5% AcOH in AcOEt): from 85:15 to 1:1 over 20 min, 20 min at 1:1, from 50:50 to 5:95 over 20 min, t_R = 31.1 min) finally gave pure pseudolaric acid B (**1a**) (7.2 mg, 0.017 mmol, 62%) as a colorless solid.

R_f 0.25 (PET/AcOEt 1:1, 0.5% AcOH, UV); $[\alpha]_D$ (24 °C) = -22.5 (MeOH, c = 0.9) (lit. -25.9 (MeOH, c = 0.9); Mp 143–144 °C (Lit. 139–141 °C, 145–146 °C); ^1H NMR (500 MHz, CDCl_3) δ 7.26 (d, J = 11.2 Hz, 1H), 7.24–7.18 (m, 1H), 6.55 (dd, J = 15.0, 11.5 Hz, 1H), 5.92 (d, J = 14.9 Hz, 1H), 3.72 (s, 3H), 3.31 (d, J = 4.70 Hz, 1H), 3.08 (dd, J = 13.8, 6.5 Hz, 1H), 2.90 (dd, J = 15.0, 6.3 Hz, 1H), 2.75 (dd, J = 15.2, 8.9 Hz, 1H), 2.61 (dd, J = 15.5, 4.3 Hz, 1H), 2.16–2.10 (m, 1H), 2.13 (s, 3H), 1.96 (s, 3H), 1.92–1.67 (m, 5H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.1, 172.8, 169.4, 168.0, 144.5, 141.7, 138.7, 134.4, 127.7, 121.7, 90.1, 83.7, 55.2, 52.0, 49.2, 33.3, 30.7, 28.4, 27.7, 24.3, 21.8, 20.1, 12.6; IR ν 3500–2500 (br m), 2955 (m), 2924 (m), 1740 (s), 1709 (s), 1680 (m), 1642 (m), 1611 (w), 1438 (m), 1415 (m), 1386 (w), 1278 (s), 1259 (s), 1208 (s), 1165 (s), 1072 (m), 1030 (m), 983 (w), 952 (w), 801 (w) 742 (w) Lit. 3500–2700, 1740, 1720, 1682, 1635, 1605; HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{28}\text{O}_8\text{Na}$: 455.1682 ($[\text{M}+\text{Na}]^+$), found: 455.1664.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. a Li ZL, Pan DJ, Hu CQ, Wu QL, Yang SS, Xu GY. *Acta Chim. Sin* 1982;40:447. b Li ZL, Pan DJ, Wu QL, Xu GY. *Acta Chim. Sin* 1982;40:757. c Zhou BN, Ying BP, Song GQ, Chen ZX, Han J, Yan YF. *Planta Med* 1983;47:35. [PubMed: 17405089] d Hamburger M, Shieh H, Pezzuto J, Cordell GA, Zhou BN. *Planta Med* 1988;579. [PubMed: 17265379] e Hamburger MO, Shieh HL, Zhou BN, Pezzuto JM, Cordell GA. *Magn. Reson. Chem* 1989;27:1025.
2. a Li EG, Clark AM, Hufford CD. *J. Nat. Prod* 1995;58:57. [PubMed: 7760078] b Wang WC, Lu RF, Zhao SX, Gu ZP. *Acta Pharmacol. Sin* 1988;9:445. c Zhang YL, Lu RZ, Yan AL. *Acta Pharmacol. Sin* 1990;11:60. d Pan DJ, Li ZL, Hu CQ, Chen K, Chang JJ, Lee KH. *Planta Med* 1990;56:383. [PubMed: 2236294]
3. a Li ZL, Chen K, Pan DJ, Xu GY. *Acta Chim. Sin* 1989;47:258. b Yue J, Yang S, Ding J, Xiao D, Yuan S. 2002patent US 6887895 c Yang SP, Dong L, Wang Y, Wu Y, Yue JM. *Bioorg. Med. Chem* 2003;11:4577. [PubMed: 14527554] d Peng L, Guo H, Wang W, Zhang J, Li N, Han J, Zhou N, Hu Y, Zhang T, Liu Z, Guo D. *J. Nat. Prod* 2007;70:533. [PubMed: 17291040]
4. a Li MH, Miao ZH, Tan WF, Yue JM, Chao Z, Lin LP, Zhang XW, Jian D. *Clin. Cancer Res* 2004;10:8266. [PubMed: 15623602] b Tan WF, Zhang XW, Li MH, Yue JM, Chen Y, Lin LP, Ding J. *Eur. J. Pharmacol* 2004;499:219. [PubMed: 15381043] c Gong XF, Wang MW, Tashiro S, Onodera S, Ikejima T. *Arch. Pharm. Res* 2005;28:68. [PubMed: 15742811] d Gong XF, Wang MW, Wu Z, Tashiro S, Onodera S, Ikejima T. *Exp. Mol. Med* 2004;36:551. [PubMed: 15665588] e Gong XF, Wang MW, Tashiro SI, Onodera S, Ikejima T. *Exp. Mol. Med* 2006;38:428. [PubMed: 16953122] f Wu WY, Guo HZ, Qu GQ, Han J, Guo DA. *Am. J. Chin. Med* 2006;34:887. [PubMed: 17080552] g Ko JKS, Leung WC, Ho WK, Chiu P. *Eur. J. Pharmacol* 2007;559:1. [PubMed: 17258704] h Wong VKW, Chiu P, Chung SSM, Chow LMC, Zhao YZ, Yang BB, Ko BCB. *Clin. Cancer Res* 2005;11:6002. [PubMed: 16115945] i Liu B, Chen H, Lei ZY, Yu PF, Xiong B. *J. Asian Nat. Prod. Res* 2006;8:241. [PubMed: 16864430]

5. a Pan BC, Chang HY, Cai GL, Guo YS. *Pure Appl. Chem* 1989;61:389. Higuchi, RI. Trimethylenemethane cycloadditions in perhydroazulene construction: studies directed toward the total synthesis of pseudolaric acid B and the total synthesis of isoclavukerin A. Stanford university; Stanford: 1995. c Chiu P, Chen B, Cheng KF. *Tetrahedron Lett* 1998;39:9229. d Hu YH, Ou LG, Wang XL, Bai DL. *Chin. Chem. Lett* 1999;10:281. e Jiang XT, Ou LG, Han DM, Zhai YF, Bai DL. *Chin. Chem. Lett* 2001;12:113. f Chiu P, Chen B, Cheng KF. *Org. Lett* 2001;3:1721. [PubMed: 11405695] g Chen B, Ko RYY, Yuen MSM, Cheng KF, Chiu P. *J. Org. Chem* 2003;68:4195. [PubMed: 12762718] h Wu BG, Karle JM, Watkins EB, Avery MA. *Tetrahedron Lett* 2002;43:4095. i Geng Z, Chen B, Chiu P. *Angew. Chem., Int. Ed* 2006;45:6197.
6. Trost BM, Waser J, Meyer A. *J. Am. Chem. Soc* 2007;129:14556. [PubMed: 17985906]
7. a Wender PA, Takahashi H, Witulski B. *J. Am. Chem. Soc* 1995;117:4720. b Wender PA, Rieck H, Fuji M. *J. Am. Chem. Soc* 1998;120:10976. c Wender PA, Sperandio D. *J. Org. Chem* 1998;63:4164. d Wender PA, Husfeld CO, Langkopf E, Love JA, Pleuss N. *Tetrahedron* 1998;54:7203. e Wender PA, Husfeld CO, Langkopf E, Love JA. *J. Am. Chem. Soc* 1998;120:1940. f Wender PA, Dyckman AJ. *Org. Lett* 1999;1:2089. g Wender PA, Fuji M, Husfeld CO, Love JA. *Org. Lett* 1999;1:137. h Wender PA, Dyckman AJ, Husfeld CO, Kadereit D, Love JA, Rieck H. *J. Am. Chem. Soc* 1999;121:10442. i Wender PA, Glorius F, Husfeld CO, Langkopf E, Love JA. *J. Am. Chem. Soc* 1999;121:5348. j Wender PA, Zhang L. *Org. Lett* 2000;2:2323. [PubMed: 10930274] k Wender PA, Dyckman AJ, Husfeld CO, Scanio MJC. *Org. Lett* 2000;2:1609. [PubMed: 10841491] l Wender PA, Gamber GG, Scanio MJC. *Angew. Chem., Int. Ed* 2001;40:3895. m Wender PA, Barzilay CM, Dyckman AJ. *J. Am. Chem. Soc* 2001;123:179. [PubMed: 11273617] n Wender PA, Pedersen TM, Scanio MJC. *J. Am. Chem. Soc* 2002;124:15154. [PubMed: 12487573] o Wender PA, Williams TJ. *Angew. Chem., Int. Ed* 2002;41:4550. p Yu ZX, Wender PA, Houk KNJ. *Am. Chem. Soc* 2004;126:9154.
8. a Trost BM, Toste FD, Shen H. *J. Am. Chem. Soc* 2000;122:2379. b Trost BM, Shen HC. *Org. Lett* 2000;2:2523. [PubMed: 10956537] c Trost BM, Shen HC. *Angew. Chem., Int. Ed* 2001;40:2313. d Trost BM, Shen HC, Schulz T, Koradin C, Schirok H. *Org. Lett* 2003;5:4149. [PubMed: 14572271] e Trost BM, Shen HC, Horne DB, Toste ED, Steinmetz BG, Koradin C. *Chem. Eur. J* 2005;11:2577.
9. Mashima K, Kusano KH, Sato N, Matsumura Y, Nozaki K, Kumobayashi H, Sayo N, Hori Y, Ishizaki T, Akutagawa S, Takaya H. *J. Org. Chem* 1994;59:3064.
10. Charette AB, Juteau H, Lebel H, Molinaro C. *J. Am. Chem. Soc* 1998;120:11943.
11. Wang Q, Deredas D, Huynh C, Schlosser M. *Chem. Eur. J* 2003;9:570.
12. The exact structure of **21** was difficult to ascertain, due to numerous signal overlapping in NMR spectra. The drawn structure would be in accordance with the data available so far. Removal of the silyl protecting group of **20** lead to a solid compound, but repeated attempts to recrystallize this product were not successful up to now.
13. Neef G, Eckle E, Muller-Fahrnow A. *Tetrahedron* 1993;49:833.
14. For similar rearrangements of vinyl epoxides, see: aJung ME, Damico DC. *J. Am. Chem. Soc* 1995;117:7379. bDeng XM, Sun XL, Tang Y. *J. Org. Chem* 2005;70:6537. [PubMed: 16050727].
15. a Singh AK, Bakshi RK, Corey EJ. *J. Am. Chem. Soc* 1987;109:6187. Bachi MD, Bosch E. *J. Org. Chem* 1992;57:4696.
16. In a second synthesis campaign, the TBS group was replaced by a TES group as it had become apparent that removal of the bulkier TBS group would require the use of harsh conditions not compatible with sensitive substrates.
17. 5–7 equivalent. Although the reaction also proceeded with lower excess, this resulted in a longer reaction time that was detrimental for the yield.
18. In the optimized procedure, a reaction mixture containing 1.4 equiv of Bu₃SnH and 0.5 equiv of AIBN was heated at 90 °C and a solution of 0.7 equiv of Bu₃SnH and 0.5 equiv AIBN was then added over 15 min.
19. For an example of similar eliminative opening, see: Jotterand N, Vogel P. *Synlett* 1999:1883..
20. Otera J, Danoh N, Nozaki H. *J. Org. Chem* 1991;56:5307.
21. Overberger CG, Bilech H, Finestone AB, Lilker J, Herbert J. *J. Am. Chem. Soc* 1953;75:2078.
22. Krasovskiy A, Kopp F, Knochel P. *Angew. Chem., Int. Ed* 2006;45:497.
23. Ishihara K, Kubota M, Kurihara H, Yamamoto H. *J. Am. Chem. Soc* 1995;117:4413.

24. Baker R, Castro JL. J. Chem. Soc., Perkin Trans. 1 1990:47.
25. Smith AB, Ott GR. J. Am. Chem. Soc 1998;120:3935.
26. Song HY, Joo JM, Kang JW, Kim DS, Jung CK, Kwak HS, Park JH, Lee E, Hong CY, Jeong S, Jeon K, Park JH. J. Org. Chem 2003;68:8080. [PubMed: 14535786]
27. At this point, removal of the solvent and column chromatography (SiO₂/KF 10:1, PET/AcOEt 10:1 –5:1–2:1–1:1) allowed the isolation of the desired product **43**, but the major product was the non-conjugated ester **44**. Direct *in situ* isomerization of the double bond was more convenient however
28. Harrowven DC, Guy IL. Chem. Commun 2004:1968.
29. A slightly modified literature procedure was used: Krasovskiy A, Kopp F, Knochel P. Angew. Chem., Int. Ed 2006;45:497..
30. Song HY, Joo JM, Kang JW, Kim DS, Jung CK, Kwak HS, Park JH, Lee E, Hong CY, Jeong S, Jeon K, Park JH. J. Org. Chem 2003;68:8080. [PubMed: 14535786]

	R^1	R^2
Pseudolaric Acid B (1a)	CO_2Me	Ac
Pseudolaric Acid A (1b)	Me	Ac
Pseudolaric Acid C (1c)	CO_2Me	H

Figure 1.
Structure of the Pseudolaric Acids.

A **B**

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

Scheme 2.
Synthesis of Iodide **11** and Aldehyde **14**.

Scheme 3.
Epoxide Opening and Synthesis of Diene **27**.

Scheme 4.
Revised Retrosynthesis.

Scheme 5.
Synthesis of Dienonate **27**.

Scheme 6.
Synthesis and Cyclization Attempts of Tertiary Alkoxy carbonyl Selenium **33**.

Scheme 7.
Synthesis and Cyclization of Secondary Alkoxycarbonyl Selenium **35**.

Figure 2.
NOE Studies on **48** and Model for Acetylide Addition on Ketone **46**.

Scheme 8.
Completion of the Synthesis.

Scheme 9.
Selective Cyclization of Diol **47**.

Table 1

Radical Cyclization of **41**.

entry	conditions	products
1	2.2 equiv Bu ₃ SnH, 0.6 equiv AIBN, benzene 80 °C	< 20% conversion
2	3 equiv Bu ₃ SnH, 1.2 equiv AIBN, benzene 80 °C	5–15% 43 , 30–50% 44 , several impurities
3	3 equiv Bu ₃ SnH, 1.2 equiv AIBN, benzene 80 °C then DBU	56% 43 , several impurities
4	1.4 equiv Bu ₃ SnH, 0.2 equiv 42 , toluene 110 °C	5–15% 43 , 30–50% 44 , 20–30% impurity
5	3.5 equiv Bu ₃ SnH, 2.0 equiv 42 , benzene, 70 °C then DBU	85% 43 , 92% purity