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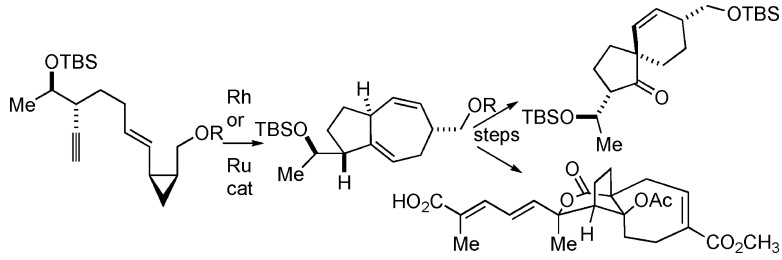

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Total Synthesis of (−)-Pseudolaric Acid B

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Abstract: We report a full account of our work toward the total synthesis of pseudolaric acid B (**1a**), a diterpene acid isolated from the bark of *Pseudolarix kaempferi Gordon* (pinaceae). Compound **1a** is an antifungal and antifertility agent. Furthermore, its capacity for inhibiting tubulin polymerization makes it a potential lead 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 for the introduction of the quaternary center based on an epoxide opening with cyanide led to the discovery of a new TBAF-mediated isomerization of a 1,4-diene to a 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 on substrate structure and reaction conditions. In the late stage of the synthesis, the unique capacity of cerium organometallic reagents to add to a sensitive, sterically hindered ketone was demonstrated. The easy formation of an oxo-bridged derivative was the major hurdle to the completion of the synthesis and showcased the intriguing reactivity of the complex core of the pseudolaric acids.

Introduction

Pseudolaric acids A−C (Figure 1) are diterpene acids isolated from the bark of *Pseudolarix kaempferi Gordon* (pinaceae).[1] The extract of the root bark of *P. kaempferi* is a Chinese herbal medicine called *tujinpi* that 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,c] and cytotoxic agent[1d,2d] and displays much higher activity than pseudolaric acid A (**1b**) and C (**1c**). More recently, several other members of the pseudolaric acid family have been isolated, but none displayed significant activity.[3] Pseudolaric acid B has been shown to be an agonist for transcriptional activation of peroxisome proliferator-activated receptors (PPARs), which are important for the membrane integrity and lipid metabolism of *Candida* species.[4b] Furthermore, **1a** inhibits angiogenesis by diminishing the secretion of vascular endothelial growth factor (VEGF) in tumor cells[4a,b] and has been shown to induce apoptosis through several pathways in human melanoma cells.[4c−g] Finally, **1a** inhibits the polymerization of tubulin in multidrug-resistant cancer cell lines and thus constitutes a potential lead for new cancer therapy.[4h,i] Because of these remarkable biological properties and the low toxicities of these compounds, the pseudolaric acids have attracted significant interest among the scientific community.

The compact tricyclic core of **1a** constitutes a challenge for modern synthetic chemistry. The four contiguous stereocenters, one of them quaternary (C10), and the unusual trans-substituted fused [5−7] ring system (polyhydroazulene) contribute to making any stereoselective approach toward the pseudolaric acids a daunting task. The many unsuccessful attempts toward

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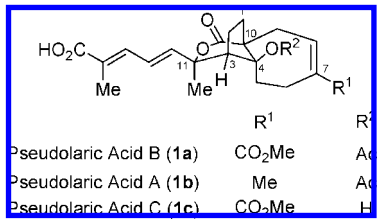


Figure 1. Structure of the Pseudolaric Acids.

a total synthesis of these natural products showcase these difficulties.[5a−h] In 2006, the first successful total synthesis of pseudolaric acid A was reported by Chiu.[5i] Key to 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 work,[6] which highlights the challenges and surprises associated with the selective synthesis of such a densely functionalized polycyclic compound.

Results and Discussion

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 Wender[7] (with Rh catalysts) and Trost[8] (with Ru catalysts) groups. One of the major challenges for this approach is the stereoselective elaboration of the quaternary center at C10.

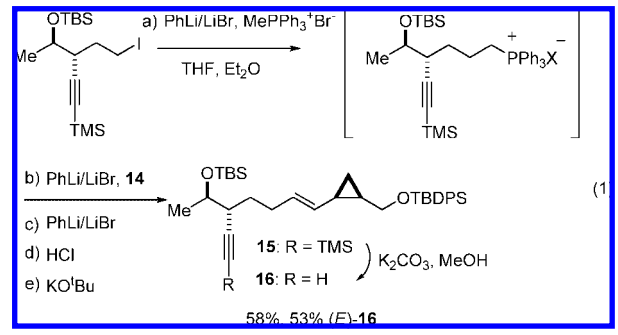
We intended to introduce the lactone ring and the fatty acid chain at a late stage of the synthesis in order to focus first on the challenging formation of the polyhydroazulene. These disconnections reveal **2** as a potential precursor (Scheme 1A). In our first approach, we envisaged accessing **2**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

In the course of model studies (not shown), it rapidly became apparent that the Ru catalyst could not accommodate any substitution at C10, 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 1B). The thermodynamically more stable conjugated diene **5** should be accessible from 1,4-diene **6** produced by the Ru-catalyzed [5 + 2] cycloaddition of **7**.

[5 + 2] Cycloaddition and Epoxide-Opening Strategy. We first concentrated our efforts toward 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 2A).[9] After TBS protection of the secondary alcohol **9**, the lactone was reduced with DIBAL-H. The resulting lactol was directly reacted with $TMSCHN_2$/LDA followed by a TMSCl quench to give the corresponding protected alkyne **10**. For iodination of alcohol **10**, a one-step procedure (PPh_3/I_2) was used in small-scale syntheses, but a two-step procedure (MsCl then NaI) was more convenient for larger-scale work. Aldehyde **14** was obtained in three steps and 84% overall yield starting from *cis*-butenediol (**12**) via monoprotection with TBDPSCl, Charette modification of the Simmons−Smith cyclopropanation,[10] and Moffat−Swern oxidation (Scheme 2B).

Reaction of iodide **11** with triphenylphosphoniummethylide provides the homologated phosphonium salt as a nonisolated intermediate. In situ conversion of this new phosphonium salt to an 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 was important, as the *Z* olefins proved to be unreactive in the [5 + 2] cycloaddition.



The cyclization of **15** using $[CpRu(CH_3CN)_3]^+PF_6^-$ (**17**) as the 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 these reaction conditions, although a 20 mol % catalyst loading was still required.

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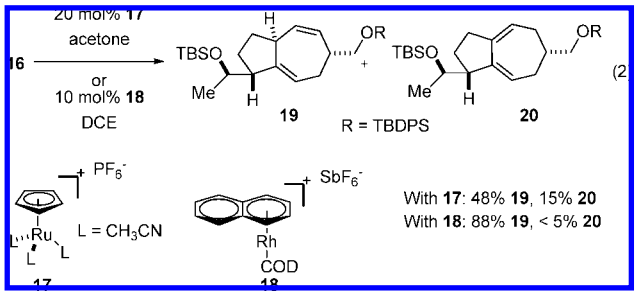
Initial experiments in methylene chloride led to the formation of two major products in a 1:1 ratio. Subsequently, one of them was identified as the desired [5 + 2] cyclization product **19**, with a diastereoselectivity of 9:1 to 15:1, while the other proved to be conjugated diene **20** (eq 2).[12]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



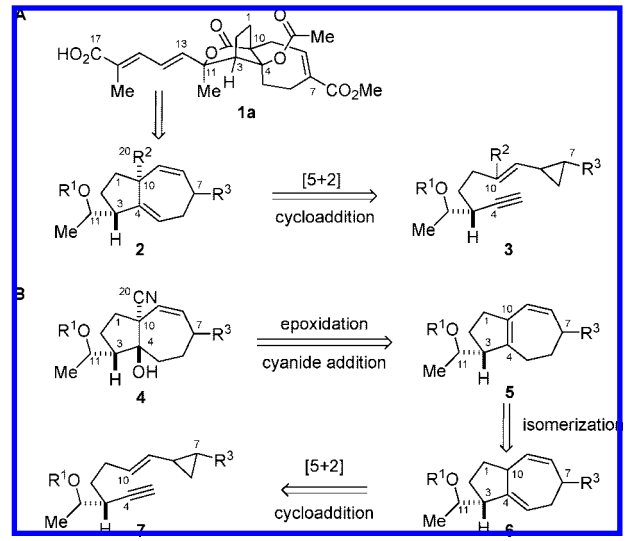
Fortunately, the **19/20** product ratio could be increased to 3:1 by using acetone as the solvent. In this case, a combined yield of 63% was obtained. With more polar DMF as the solvent, dehydration reactions became competitive and triene side products were dominant.

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 1 equiv of ligand with respect to the Ru catalyst was used. A particular behavior was observed for DMF and DMA, which led to elimination products, while nitromethane favored the formation of **20** (**19/20** = 1:1.4).

To explain the formation of **20**, we speculated that the insertion of a Ru intermediate into 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 then results in conjugated diene **20**. It is important to note that in a separate experiment, conversion of **19** to **20** in the presence of Ru catalyst

(12) The exact structure of **21** was difficult to ascertain because of the overlap of numerous signals in the NMR spectra. The drawn structure would be in accordance with the data available to date. Removal of the silyl protecting group of **20** led to a solid compound, but repeated attempts to recrystallize this product have not been successful to date.

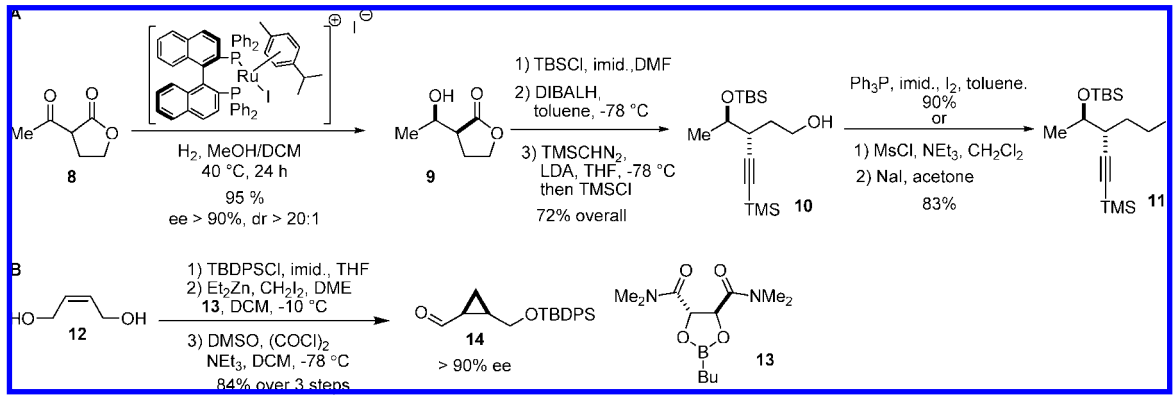
Scheme 1. Retrosyntheses of Pseudolaric Acid B (**1a**)



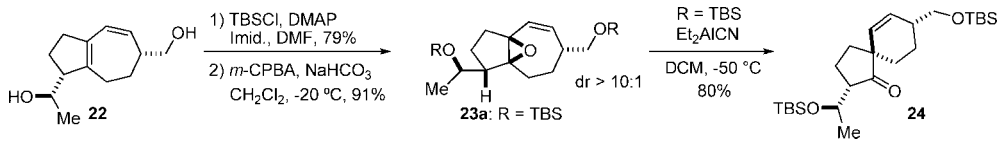
17 was not observed. Consequently, activation of the C−H bond had to occur from an intermediate in the catalytic cycle. For Rh catalysts, C−H activation is not so facile. When Wender's catalyst $[(C_8H_{10})Rh(COD)]^+SbF_6^-$ (**18**)[7o] was used, the desired product **19** was obtained exclusively 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^{t}Bu, DMSO; KO^{t}Bu, THF; LDA, THF). No reaction of the diene system occurred in the presence of Pd catalysts ($[Pd(CH_3CN)_2]_2^+(BF_4)^-_2$, CH_3CN; Pd/C, H_2, 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/mmol in TBAF) were 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 **21/22** ratio, and using 1.0 g of molecular sieves/mmol of 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 positions gave a mixture of elimination and simple deprotection products. Again, no isomerization product was obtained. An explanation for these observations would be an intramolecular deprotonation of the bisallylic 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 mmol (1.8 g) scale. On larger scales, resubmitting the mixture to KO^{t}Bu 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

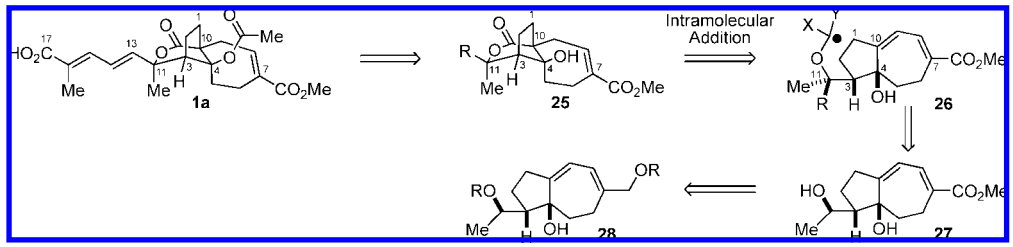
Scheme 2. Synthesis of Iodide **11** and Aldehyde **14**



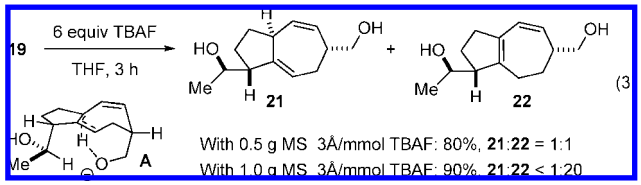
Scheme 3. Synthesis of Epoxide **23** and its Rearrangement to Ketone **24**



Scheme 4. Revised Retrosynthesis



TBAF-mediated isomerizations proceed to give completely different diene systems because they involve different isomerization mechanisms.



The research next was 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 ^{1}H NMR), but the obtained vinyl epoxide **23** proved to be unstable. The best results were obtained when the crude reaction mixture was directly filtered over deactivated (NEt_3) silica gel and used immediately.

The key formation of the quaternary center was first attempted via cyanide addition. Et_2AlCN 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 temperatures. No conversion was observed when nucleophilic activation of cyanide or weaker Lewis acids was used. Nevertheless, this sequence does provide a convenient diastereocontrolled entry into such spiro compounds, which are also a common motif in natural products.

Revised Retrosynthesis. At this point, it had become clear that the epoxide-opening strategy was not viable for introducing the quaternary center. As intermolecular addition of a nucleophile to form the quaternary center had proven to be very difficult, 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 alkoxycarbonyl selenide (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 (as in **27**) was envisioned 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 with a ketone at C11. In principle, side-chain introduction could be envisaged before or after formation of the quaternary center.

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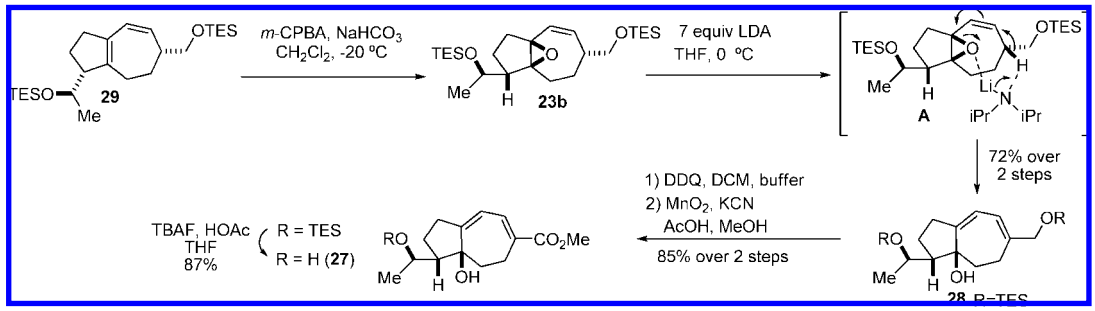
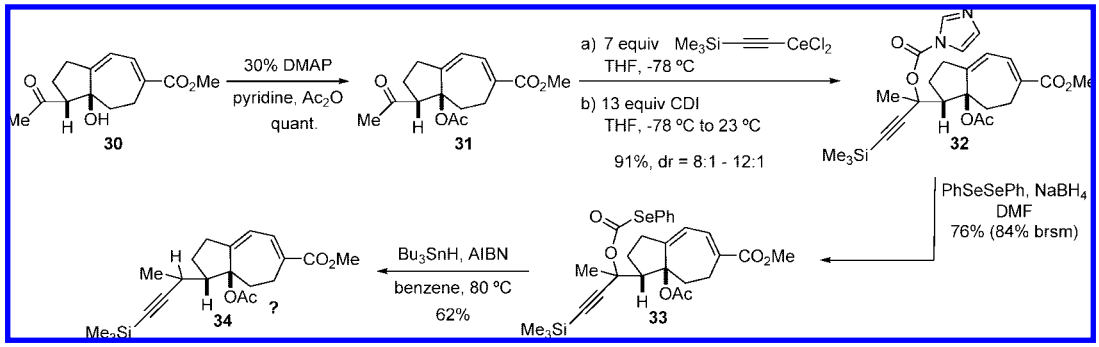
Scheme 5. Synthesis of Dienonate **27**



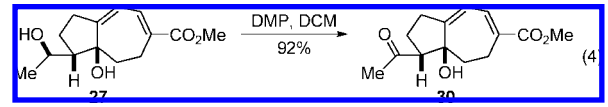
Scheme 6. Synthesis and Cyclization Attempts of Tertiary Alkoxycarbonyl Selenide **33**



Radical-Based Strategy. While the addition of any carbon nucleophile to vinyl epoxide **23** appeared to be a daunting task, an alternative approach to convert this compound into a more useful intermediate for the synthesis of pseudolaric acid B (**1a**) was sought. 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 LDA[17] resulted in the formation of dienol **28** (R = TES) (Scheme 5). Furthermore, only the major diastereoisomer of the epoxide reacts, greatly simplifying the purification of the obtained product. As such, it was found to be 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 silylation of diol **22** with TESCl in 82% yield) into dienol **28** (R = TES) constitutes an important step toward **1a**, as it introduced the tertiary hydroxy group at C4 with the correct stereochemistry. It also introduced the C7−C8 double bond and a double bond at C9−C10 that can serve as a handle for further functionalization. The methyl ester was introduced in a selective two-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 using 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 during column chromatography.

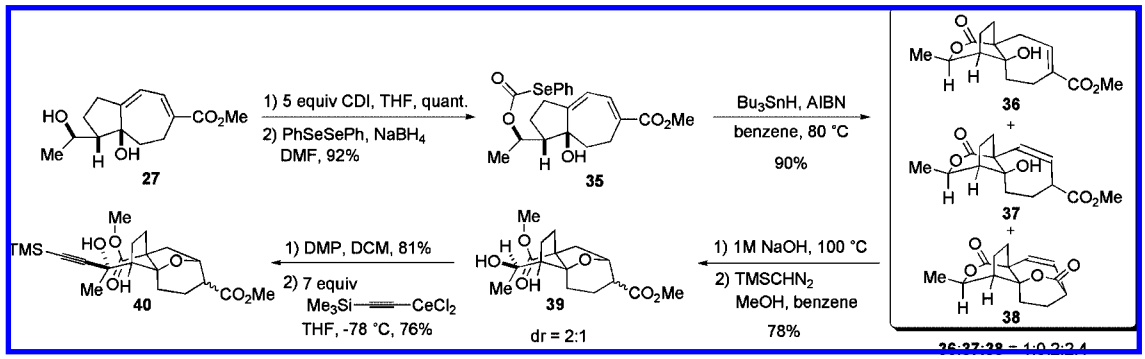
Obviously, the free propargylic alcohol was not a viable intermediate, so we decided to transform it in situ into an alkoxycarbonyl imidazole intermediate by quenching the addition reaction with carbonyldiimidazole (CDI). Gratifyingly, this approach proved to be highly successful, and **32** was obtained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

The conversion of **32** to alkoxycarbonyl selenide **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, in which the major product appeared to be the decarboxylation product **34**, as the phenyl group was absent but no changes had occurred in the structure of the diene, as shown by ^{1}H NMR spectroscopy. All further attempts were also unsuccessful. Initiation at room temperature using BEt_3/O_2 resulted in a complex mixture or reisolation of the starting material. An

(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 that are not compatible with sensitive substrates.

(17) The amount of LDA was 5−7 equiv. Although the reaction also proceeded when a smaller excess was used, this resulted in a longer reaction time that was detrimental to the yield.

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



attempt to activate the conjugated system with $Yb(OTf)_3$ 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 alkoxycarbonyl selenide **35** derived from **27** (Scheme 7).

When alkoxycarbonyl selenide **35** was submitted to the standard reaction conditions for radical cyclization, a mixture containing three major products was obtained in 90% yield after extensive optimization. For successful cyclization, a 0.6:2.2:1 AIBN/Bu_3SnH/**35** ratio and slow addition of azobisisobutyronitrile (AIBN) were essential.[18] The best results were obtained with a relatively high concentration of Bu_3SnH, showing that the main problem was not (as is often the case) direct reduction of the carbonyl radical but rather decomposition of the formed allylic instead of the desired 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 was tentatively assigned as isomer **37**, whereas the other, lacking the methyl ester group, could have been 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 resulting 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**, which is diastereomeric at C7 and 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 DMP 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 **1a**. We first attempted to use basic conditions to promote β-elimination to the conjugated ester.[19] At low temperature, no reaction was observed with either 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 ($BF_3 \cdot OEt_2$, $Ti(O^iPr)_4$) or in elimination at the propargylic position (TMSOTf, TsOH). Finally, an attempt was made to promote lactonization using Otera's catalyst[20] prior to opening of the oxo bridge; however, 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 "pulls 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 **1a**. Because of the strong basic conditions needed for lactone opening, we needed a protecting group that was stable to base but 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 imidate with $Sc(OTf)_3$ (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 and when the standard conditions developed for the free alcohol **35** were used, only a small amount of conversion was observed in the case of PMB-protected **41** (entry 1 of 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 along with several unidentified impurities. Addition of DBU to the reaction mixture directly after completion of the cyclization allowed clean conversion of **44** to the desired product **43**, which could be isolated in 56% yield and ~90% purity (entry 3). To improve this yield, we decided to use azobis(dicyclohexylcarbonitrile) (**42**) as the initiator, as it is thermally more stable and allows

(18) In the optimized procedure, a reaction mixture containing 1.4 equiv of Bu_3SnH and 0.5 equiv of AIBN was heated at 90 °C, after which a solution containing 0.7 equiv of Bu_3SnH and 0.5 equiv AIBN was 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.

Scheme 8. Completion of the Synthesis

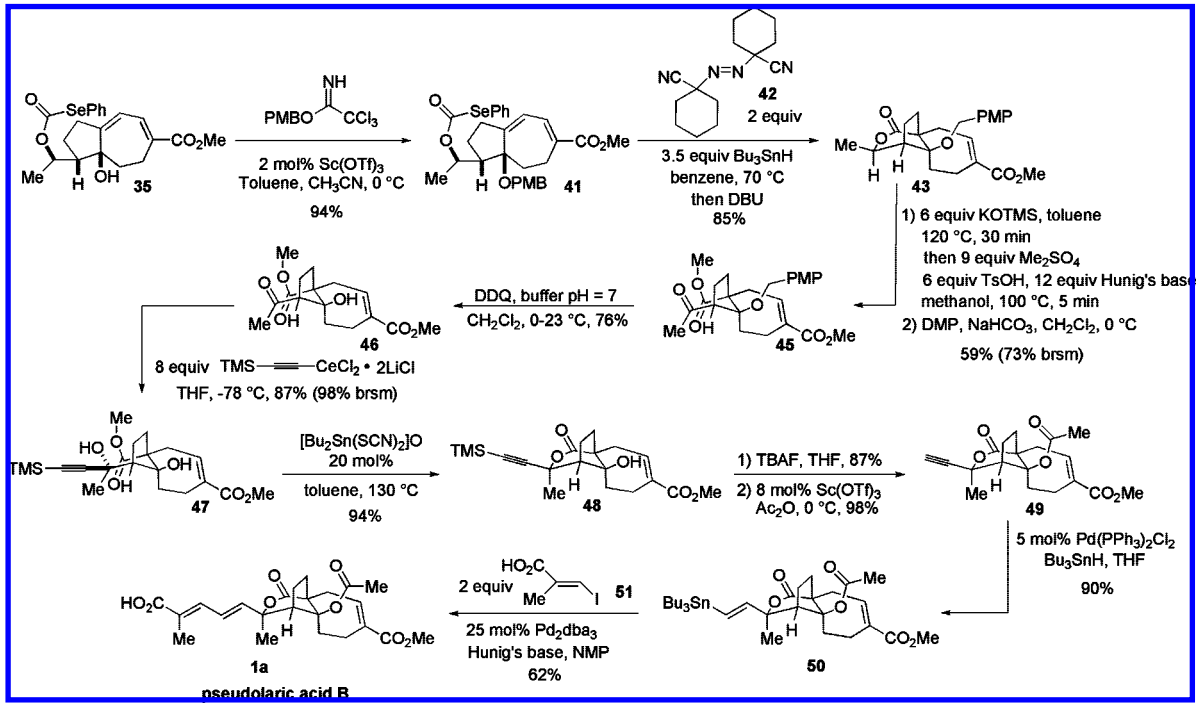
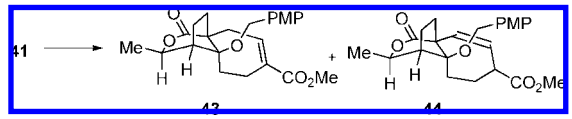


Table 1. Radical Cyclization of **41**



entry	conditions	products
1	2.2 equiv Bu_3SnH, 0.6 equiv AIBN, benzene, 80 °C	<20% conversion
2	3 equiv Bu_3SnH, 1.2 equiv AIBN, benzene, 80 °C	5−15% **43**, 30−50% **44**, several impurities
3	3 equiv Bu_3SnH, 1.2 equiv AIBN, benzene, 80 °C, then DBU	56% **43**, several impurities
4	1.4 equiv Bu_3SnH, 0.2 equiv **42**, toluene, 110 °C	5−15% **43**, 30−50% **44**, 20−30% impurity
5	3.5 equiv Bu_3SnH, 2.0 equiv **42**, benzene, 70 °C, then DBU	85% **43**, 92% purity

for cleaner, continuous generation of radicals.[21] When the reaction was conducted in refluxing toluene with only 0.2 equiv 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 spectrum. 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. Use of 2 equiv of **42** and 3.5 equiv 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 low rate of decomposition of **42** and not the rate of addition, all of the reagents could be mixed together at the beginning, leading to an operationally simpler procedure.

The next task on the way toward 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 unsuccessful and mainly led to removal of the PMB group, mostly with isolation of bislactone **38**. We concluded that the main problem was the acidic workup conditions and the subsequent methylation reaction. For a successful ring opening, direct methylation of the formed carboxylate salt was required; this precluded the use of excess base in water for the hydrolysis. We finally chose KOTMS as the 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 the barium salt, 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 a larger scale, leading to lower yields (<30%).

We hypothesized that use of a soluble buffer system after ring opening with KOTMS should be more efficient for controlling 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 the buffer. These conditions were designed to completely protonate any alkoxide present and leave only the

(21) Overberger, C. G.; Biletch, H.; Finestone, A. B.; Lilker, J.; Herbert, J. *J. Am. Chem. Soc.* **1953**, *75*, 2078.

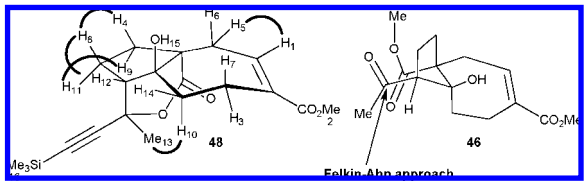


Figure 2. NOE studies on **48** and a model for acetylide addition to ketone **46**.

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).

DMP was then used to oxidize the alcohol to the corresponding ketone **45**. Buffering with $NaHCO_3$ and decreasing 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 that case, ketone **45** was obtained in 59% (73% brsm) over two steps.

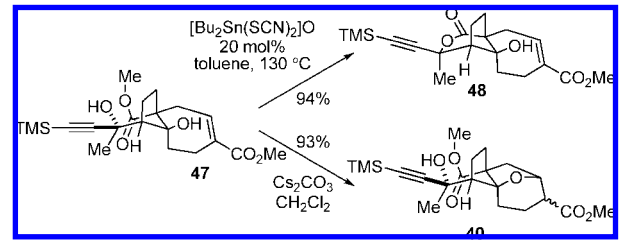
Cerium acetylide addition was not compatible with the PMB protecting group, as β-alkoxide elimination was a major problem. For this reason, the PMB group was first removed with DDQ in 76% yield.

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

The first attempts at 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 in reproducing this result. At this point, we become interested in a recent report of Knochel and co-workers[22] regarding the use of soluble cerium−lithium choride reagents for addition reactions. Although we still encountered difficulties when using large quantitites of Ce reagents, we found that on a small scale (<1 mmol cerium), simply codrying $CeCl_3 \cdot 7H_2O$ with 2 equiv 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 the 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 smaller 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's catalyst[20] 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's catalyst is noteworthy and probably results from the unique ability of Otera's catalyst to activate both the methyl ester and the alcohol. At this point, the stereochemistry of the propargylic position could be assigned by one-dimensional NOE

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



studies (Figure 2). The strong NOE signal observed between methyl group 13 and H10 was especially 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 blocks 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 (~20% in 24 h).[5i] Fortunately, freshly dried $Sc(OTf)_3$ in acetic anhydride solvent at 0 °C resulted in clean acylation of the tertiary alcohol in 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 with good 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 at the Stille coupling were made with the most often used conditions, namely, ligandless Pd(II) salts in DMF.[25] Both $Pd(CH_3CN)Cl_2$ and $Pd(PhCN)_2Cl_2$ led to low yields (<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 describing Stille coupling of an acid under basic conditions using $Pd_2(dba)_3$ as the catalyst and NMP as the solvent.[26] Gratifyingly, these conditions were efficient in shutting down both the destannylation and isomerization side reactions, and **1a** was obtained in 62% yield after HPLC purification. All of the physical and spectroscopic data (melting point, optical rotation, and ^1H and ^{13}C NMR, IR, and mass spectra) were in agreement with the published values for natural pseudolaric acid B.[1e,2a]

Summary

We have reported the successful total synthesis of the highly biologically active and structurally intriguing compound pseudolaric acid B (**1a**). Vinylcyclopropane **16** was easily accessed in seven linear steps and 33% overall yield from 2-acetylbutyrolactone (**8**). The intramolecular cycloaddition of **16** constituted an efficient access to the polyhydroazulene core of **1a**. In this particular case, Rh catalyst **18** was superior to Ru catalyst **17**,

(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, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47.
(25) Smith, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935.
(26) Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D. S.; Jung, C. K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S.; Jeon, K.; Park, J. H. *J. Org. Chem.* **2003**, *68*, 8080.

as it displayed a lower tendency toward 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 selenides **33**, **35**, and **41**, but only the secondary alkoxycarbonyl selenides **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, 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 for generating 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 **1a** in 28 overall steps and 1.4% overall yield. The strength of our synthesis is the very high selectivity observed for the installation of the four stereocenters of the molecule via Noyori reduction, epoxidation, radical cyclization, and cerium acetylide addition, which together with the [5 + 2] cycloaddition contributes to its efficiency. Furthermore, the late-stage introduction of the acid side chain is also interesting from the point of view of analogue synthesis. It should be noted that a new strategy for the synthesis of [6.5]spiro fused bicycles also emerged. Thus, the [5 + 2] cycloaddition can also initiate formation of other isomeric bicyclic skeletons that are also found among natural and other bioactive targets.

Experimental Section

(1*R*,3a*S*,6*R*)-1-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-6-(*tert*-butyldiphenylsilanyloxymethyl)-1,2,3,3a,6,7-hexahydroazulene (19) and (1*R*,6*S*)-1-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-6-(*tert*-butyldiphenylsilanyloxymethyl)-1,2,3,5,6,7-hexahydroazulene (20). $[CpRu(CH_3CN)_3]^+PF_6^-$ (**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 into PET (1 L) and filtered over SiO_2; the plug was washed with 10:1 PET/Et_2O, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (30:1−25:1−20:1−15:1−10:1−3:1 pentane/DCM, 1 kg SiO_2, collected fraction: 200 mL) to yield a first fraction (fractions 32−91) of diastereomerically pure **19** (4.59 g, 8.18 mmol, 43%) and a second fraction (fractions 92−105) containing **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); the third fraction (fractions 106−122) contained **20** (1.60 g, 2.85 mmol, 15%), whose structure has tentatively been assigned as shown in eq 2. All of the isolated products were colorless, air-sensitive oils.

Synthesis of 19 Using Rh Catalyst. Rh catalyst **18** (2.0 g, 3.5 mmol, 0.11 equiv) was added in four 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 CaH_2, 320 mL) at 0 °C. After 1 h at 23 °C, the reaction mixture was poured into PET (300 mL) and filtered over SiO_2; the plug was washed with 1:1 PET/Et_2O (1.5 L), and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (50:1−20:1−15:1−10:1−3:1 pentane/DCM, 1 kg SiO_2) to yield **19** (16.1 g, 28.7 mmol, 88%, dr = 15:1) as a colorless oil.

Data for **19**. R_f: 0.50 (3:1 pentane/DCM, anisaldehyde). $[\alpha]_D$ (25 °C): −12.9 ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 (cm^{-1}): 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 $C_{35}H_{52}O_2Si_2$, m/z 560.3506 (M^+); found, 560.3508. Anal. Calcd for $C_{35}H_{52}O_2Si_2$: C, 74.94; H, 9.34. Found: C, 74.78; H, 9.43. Additional data: ^{1}H COSY, HSQC, NOE (see the Supporting Information).

Data for **20**. R_f: 0.40 (3:1 pentane/DCM, anisaldehyde). $[\alpha]_D$ (25 °C): −80.0 ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 (cm^{-1}): 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 $C_{35}H_{52}O_2Si_2$, m/z 560.3506 (M^+); found, 560.3488. Additional data: ^{1}H COSY, HSQC (see the Supporting Information).

(*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 3 Å molecular sieves (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 the mixture was stirred for 4 h at 23 °C, the reaction was quenched with methanol (20 mL); the mixture was filtered, and the residues were washed with methanol (10 mL) and Et_2O (300 mL). The reaction mixture was washed with saturated 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 (1:1−0:1 PET/Et_2O) to yield **22** (636 mg, 3.05 mmol, 94%) as a colorless oil. On a 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 3 Å molecular sieves (dried 15 h at 200 °C in an oven in vacuo, 150 g) and **19** (16.8 g, 30.0 mmol, 1.00 equiv) in THF (1 L) at 0 °C. After the reaction mixture was stirred for 16 h at 23 °C, the reaction was quenched with methanol (200 mL); the mixture was filtered, and the residues were washed with methanol (500 mL). The solvent were removed under reduced pressure, and Et_2O (600 mL) was added. The reaction mixture was washed with saturated 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 (1:1−0:1 PET/Et_2O) 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 saturated $NaHCO_3$ (200 mL) and extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine (100 mL) and 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 °C): +107.5 ($CHCl_3$, c = 1.0). ^{1}H 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 (cm^{-1}): 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 $C_{13}H_{20}O_2$, m/z 208.1463 (M^+); found, 208.1467. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.02; H, 9.52. Additional data: ^{1}H COSY, HSQC, NOE (see the Supporting Information).

(3*S*,3a*S*)-3-((*R*)-1-Triethylsilanyloxyethyl)-6-triethylsilanyloxymethyl-2,3,4,5-tetrahydro-1*H*-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 pH 7 buffer 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 10:1 PET/Et_2O, 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 (10:1 PET/Et_2O, anisaldehyde). ^{1}H 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, 12H). ^{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}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 **23b** in THF (120 mL) at −10 °C. The reaction was monitored by TLC (10:1 PET/Et_2O). After 40 min, no **23b** (R = TES) was left, and the reaction was quenched with saturated NH_4Cl solution (100 mL) and extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (10:1−3:1 PET/Et_2O) to yield **28** (1.93 g, 4.26 mmol, 72% over two steps) as a colorless oil. Compound **28** (R = TES) proved to be unstable in pure form, especially on larger scales, and had to be kept frozen in benzene to prevent decomposition. R_f: 0.20 (10:1 PET/Et_2O, anisaldehyde). $[\alpha]_D$ (25 °C): −19.1 ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$): 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 Hz, 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, 6H), 0.52 (q, J = 8.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): 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 (cm^{-1}): 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 $C_{25}H_{46}O_2Si_2$, m/z 434.3036 ($[M - H_2O]^+$); found, 434.3031.

(1*R*,7*S*,8*S*,9*R*)-7-(4-Methoxybenzyloxy)-9-methyl-11-oxo-10-oxatricyclo[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′-azobis(cyclohexanecarbonitrile) (**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 the reaction mixture was heated at 70 °C for 15 h, it was cooled to 23 °C. TLC (2:1 PET/AcOEt, 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; the reaction mixture was diluted with Et_2O (100 mL) and washed with 1 M $NaHSO_4$ (2 × 100 mL), and the combined aqueous layers were extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (50 g SiO_2 and 5 g KF,[28] 10:1−5:1−2:1−1:1 PET/AcOEt) to yield **43** (447 mg, 1.09 mmol, 85%, >92% pure by ^{1}H NMR) as a colorless foam. R_f: 0.30 (2:1 PET/AcOEt, CAN). $[\alpha]_D$ (25 °C): 101.9 ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 (cm^{-1}): 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 $C_{23}H_{28}O_6Na$, m/z 423.1784 ($[M + Na]^+$); found, 423.1798.

(1*S*,3a*R*,8a*S*)-8a-Hydroxy-1-((*S*)-1-hydroxy-1-methyl-3-trimethylsilanylprop-2-ynyl)-2,3,4,7,8,8a-hexahydro-1*H*-azulene-3a,6-dicarboxylic Acid Dimethyl Ester (47). $CeCl_3 \cdot 7H_2O$ (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 was essential for good drying),[29] warmed from 23 to 150 °C over 3 h (T was increased by ∼10 °C every 15 min), and then maintained at 150 °C for 2 h. During this whole process, good stirring was essential to keep the mixture as a light homogeneous powder. After the mixture was cooled 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 separate flask, ^{n}BuLi (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 $CeCl_3 \cdot 2LiCl$ 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 mixture was poured into saturated $NaHCO_3$ solution (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (1:0−20:1−10:1−5:1−2:1 DCM/AcOEt) 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 (10:1 DCM/AcOEt, CAN/$KMnO_4$). $[\alpha]_D$ (25 °C): −1.4 ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$): 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

(27) At this point, removal of the solvent and column chromatography (10:1 SiO_2/KF, 10:1−5:1−2:1−1:1 PET/AcOEt) allowed the isolation of the desired product **43**, but the major product was the nonconjugated ester **44**. Direct in situ isomerization of the double bond was more convenient, however.

(28) Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, 1968.

(29) A slightly modified version of the procedure given in ref 22 was used.

(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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 (cm^{-1}): 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 $C_{21}H_{32}O_6NaSi$, *m/z* 431.1866 ($[M + Na]^+$); found, 431.1881.

(1*R*,7*S*,8*R*,9*S*)-7-Hydroxy-9-methyl-11-oxo-9-trimethylsilanylethynyl-10-oxatricyclo[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 catalyst[20] (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 onto a chromatography column (SiO_2, 1:0−10:1−5:1 DCM/AcOEt) to yield lactone **48** (48 mg, 0.13 mmol, 94%) as a colorless solid. R_f: 0.60 (10:1 DCM/AcOEt, CAN/$KMnO_4$). $[\alpha]_D$ (25 °C): 44.4 ($CHCl_3$, $c = 1.0$) Mp: 143−145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 (cm^{-1}): 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 $C_{20}H_{28}O_5NaSi$, *m/z* 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 $Pd(PPh_3)_2Cl_2$ (1.0 mg, 1.4 μmol, 0.050 equiv) in THF (0.3 mL) was degassed with two freeze−thaw cycles. Bu_3SnH (distilled, 12 μL, 45 μmol, 1.7 equiv) was added dropwise, during which the color changed from yellow to orange. After 15 min, the solvent was removed under HV, and the crude product was purified via short column chromatography (SiO_2, deactivated with NEt_3, 1:0−1:1−0:1 PET/DCM) to give crude stannane **50** (15 mg, 23 μmol, 90%, 90% pure by ^{1}H NMR), which was used immediately in the next step.

In accord with a reported procedure,[26] 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 two freeze−thaw cycles, and Pd_2dba_3 (3.5 mg, 3.8 μmol, 0.28 equiv) was added. The reaction was monitored via TLC (5:1 PET/AcOEt, 0.5% AcOH). After 17 h, no further conversion was observed, and Pd_2dba_3 (3.5 mg, 3.8 μmol, 0.28 equiv) was added. After an additional 5 h, TLC showed that only traces of stannane **51** remained, and the reaction mixture was diluted with AcOEt (10 mL) and washed with 1 M $NaHSO_4$ (2 × 5 mL). The combined aqueous layers were extracted with AcOEt (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (20:1−5:1−3:1−1:1 PET/AcOEt, 0.5% AcOH) to yield crude pseudolaric acid B (**1a**) as a yellowish solid. Purification via preparative HPLC [10 mL/min flow rate, 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 **1a** (7.2 mg, 0.017 mmol, 62%) as a colorless solid.

R_f: 0.25 (1:1 PET/AcOEt, 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). ^{1}H 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 (cm^{-1}): 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 $C_{23}H_{28}O_8Na$, *m/z* 455.1682 ($[M + Na]^+$); found, 455.1664.

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

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