Enantioselective Total Synthesis of the Reported Structures of \((-\)-9-\textit{epi}-Presilphiperfolan-1-ol and \((-\)-Presilphiperfolan-1-ol: Structural Confirmation and Reassignment, New Biosynthetic Insights

Allen Y. Hong and Prof. Brian M. Stoltz
Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering Division of Chemistry and Chemical Engineering California Institute of Technology 1200 E. California Blvd, MC 101-20 Pasadena, CA 91125 (USA)

Keywords

total synthesis; natural products; terpenoids; structure determination; asymmetric catalysis; allylation; ring contraction; rearrangement; cycloaddition; palladium; nickel

Presilphiperfolanols (also known as prebotrydials) are members of a family of natural products that are important biosynthetic precursors to diverse sesquiterpenoids (Figure 1).\[i, ii, iii, iv\] To date, four members of the group have been isolated: presilphiperfolan-1-ol (1),[v] 9-\textit{epi}-presilphiperfolan-1-ol (2),[vi] presilphiperfolan-8-ol (3),[ii] and presilphiperfolan-9-ol (4),[vii] with 1 and 2 being the most recently disclosed (Figure 1A).

The original proposal for the biosynthesis of the presilphiperfolane core and its rearrangement to related sesquiterpenes was reported independently by Bohlmann[li, iii] and Hanson.[iiiia] Subsequent studies by multiple research groups [iiib, iv, viii, ix] have provided further insight into this biosynthetic pathway. Farnesyl pyrophosphate (FPP) is commonly believed to undergo enzyme-catalyzed cyclization to caryophyllenyl cation 6,[ix] which undergoes further rearrangements to the C(9)- and C(8)-presilphiperfolanyl cations 7 and 8 (Figure 1B). Hydration of these cations affords the natural products 3 and 4 as single stereoisomers. To date, existing biosynthetic proposals have not accounted for the formation of 1 and 2, which possess an unusual C(9)-epimeric relationship. Neither 3 nor 4 have known naturally occurring epimers. From the tricyclic cation 8, further C-C bond migrations can lead to diverse sesquiterpenoid natural products (Figure 1C).[i-iv] In addition to their central biosynthetic role, the presilphiperfolanols possess antimycobacterial properties (e.g., 2)[x] and insect antifeedant properties (e.g., 4).[xi] Furthermore, unnatural presilphiperfolane analogs have demonstrated antifungal activity.[xii]

Although the presilphiperfolanols have garnered broad scientific interest in the natural product,[xiii] biosynthesis, [iii, ix, ix, xvii] synthetic [xiv] organic, [xvi, xvi] and fragrance [vii, xvi, xviii] literatures since their discovery, they have proven to be challenging targets for total synthesis. To date, only (\(\pm\))-presilphiperfolan-9-ol (4) has been prepared by total synthesis,[xvii] and no asymmetric routes toward any of the presilphiperfolanols have been reported. Within this context, our group became interested in developing an
enantioselective synthesis to enable further exploration of their biosynthetic relationships and biological activity.

The structurally complex presilphiperfolanols are distinguished by their rare, compact tricyclic terpenoid core, which bears five contiguous stereocenters, two all-carbon quaternary centers, and a tertiary alcohol (Figure 1A). In addition to these readily apparent structural features, considerable ring strain is built into the tricyclic system, allowing these compounds to undergo thermodynamically favorable skeletal rearrangements leading to numerous terpenes (Figure 1C). Our goal was to develop an efficient and general asymmetric route to access various members of the presilphiperfolanol family. In this communication, we describe the first asymmetric total syntheses of the reported structures of presilphiperfolanols 1 and 2. Our investigation has confirmed the structure of 2 and prompted us to reassign the structure of 1. Finally, in the context of this reassignment, we propose a new biosynthetic route to account for our observations.

Retrosynthetic analysis suggested that tricycle 9 could serve as an intermediate for the divergent synthesis of several members of the family (Figure 2). Two of the three rings could be forged simultaneously in an intramolecular [4+2] cycloaddition (via 10), thereby avoiding a more conventional sequential annulation strategy. Monocyclic precursor 11 could be prepared from an α-quaternary vinylogous ester 12 by a two-carbon ring contraction. The strategic application of our recently reported methodology for the synthesis of γ-quaternary acyclcyclopentenes and α-quaternary vinylogous esters would provide a solid starting point for our synthesis.

Our synthetic efforts began with acylation/alkylation of commercial 3-isobutoxycycloheptenone 14 using isoprenol-derived carbamate 15 and methyl iodide under basic conditions (Scheme 1). This improved protocol enabled efficient access to β-ketoester 13 in a single synthetic operation and avoided employing the corresponding cyanoformate. With our desired functionality installed, we were poised to evaluate our asymmetric Pd-catalyzed decarboxylative alkylation on this novel substrate type containing a 2-vinyl allyl fragment. To our delight, treatment of β-ketoester 13 with catalytic Pd2(pmdba) and (S)-t-Bu3PHOX in toluene proceeded smoothly on 10 g scale, affording isoprenylated vinylogous ester 12 in 91% yield and 95% ee. Subsequent LiAlH4 reduction afforded an intermediate β-hydroxyketone, which underwent a base-mediated two-carbon ring contraction to provide multigram quantities of acyclcyclopentene 11 in 92% yield over two steps. After straightforward silyl dienol ether formation, we were able to examine our bicyclization strategy (via 10a: R = OTBS, R’ = CH2). The intramolecular Diels-Alder (IMDA) reaction proceeded efficiently with microwave irradiation despite the lack of an activated dienophile, affording tricycle 16 in 80% yield as a single diastereomer. The cis relationship of the C(7) and C(8) hydrogens was determined by NOESY experiments on cycloadduct 16. Unfortunately, in order to proceed toward targets 1 and 2, a trans relationship was required.

With a general and concise strategy to the tricyclic core, we next pursued the installation of the naturally-occurring substituents and stereochemistry present in the strained presilphiperfolanols. Our revised strategy aimed to install of the gem-dimethyl group at an earlier stage to potentially improve IMDA diastereoselectivity toward the desired trans product (via acyclcyclopentene 17, Scheme 2). Inspection of the possible IMDA transition states of the silyl dienol ether 10b suggested that nonbonding interactions from the C(6)-steric bulk could help favor the desired C(7)-stereochemistry (Scheme 2B). In TS-A, the steric elements would be oriented away from the bond-forming centers while cycloaddition via TS-B could only proceed with severe steric clash between the cyclopentene ring and the gem-dimethyl functionality. Additionally, the new gem-dimethyl
groups should decrease the C(5)-C(6)-C(7) bond angle while also providing greater conformational bias\textsuperscript{[xxxii]} for the desired cyclization with this uncommon IMDA substrate type.\textsuperscript{[xxxiii]}

Our efforts toward this end commenced with a regioselective 1,4-hydroboration/oxidation of the sterically hindered 2-substituted 1,3-diene 18 after carbonyl protection of 11 (Scheme 2A). While Pd\textsuperscript{[xxxiva]} Fe\textsuperscript{[xxxivb]} and Ni\textsuperscript{[xxxivc,d]} catalysts are known to effect this transformation, literature precedent suggested that the regioselective formation of linear product 19a would be most favorable with iron catalysis. To our surprise, the Ritter FeCl\textsubscript{3}(py-imine) catalyst system provided a disappointing 1:1:1 ratio of linear:branched products.\textsuperscript{[xxxivb, xxxv]} Investigation of Suzuki-Miyaura conditions with Pd(PPh\textsubscript{3})\textsubscript{4} and HBPin did not provide any reactivity\textsuperscript{[xxxiva, xxxv]}. Finally, we turned to Morken’s Ni(cod)/PCy\textsubscript{3} catalyst system.\textsuperscript{[xxxivc, xxxv]} Gratifyingly, we were able to obtain the separable allylic alcohols 19a and 19b in 81% combined yield in a 3.5:1 ratio (linear:branched) on multigram scale with 5 mol % catalyst loading. Doubling the catalyst loading led to a decrease in reaction time and a small improvement to 88% combined yield. To our knowledge, this is the first application of a regioselective metal-catalyzed 1,4-hydroboration in total synthesis.

Subsequent phosphorylation and regioselective Cu-catalyzed allylic substitution\textsuperscript{[xxxvi]} provided the requisite gem-dimethyl acylcyclopentene 17 in 80% yield over two steps (Scheme 2B). After silyl dienol ether formation, the IMDA bicyclization proceeded smoothly under thermal or microwave-assisted conditions to provide a mixture of inseparable diastereomers 20a and 20b. A highly diastereoselective Rubottom oxidation of these products with DMDO\textsuperscript{[xxxvii]} provided α-hydroxyketones 21a and 21b in a 1:2 ratio as determined by \textsuperscript{1}H NMR. Chromatographic separation gave 21a in 27% yield and 21b in 61% yield over three steps. The structure of tricycle 21b was confirmed by single-crystal X-ray analysis.\textsuperscript{[xxxviii]}

With α-hydroxyketone 21a in hand, Wittig methylation proceeded efficiently to give allylic alcohol 22 in 90% yield (Scheme 3). While PtO\textsubscript{2}-catalyzed hydrogenation of olefin 22 afforded a separable mixture of targets 1 and 2, a diastereoselective synthesis of both target molecules could also be achieved. Tertiary alcohol-directed hydrogenation with Crabtree’s catalyst\textsuperscript{[xxxix]} produced the reported structure of presilphiperfolan-1-ol (1) in 92% yield and the structure was verified by single-crystal X-ray diffraction.\textsuperscript{[xxxviii]}

Alternatively, efficient formation of the reported structure of 9-\textit{epi}-presilphiperfolan-1-ol (2) was accomplished in 88% yield over three steps by silylation\textsuperscript{[xl]} of tertiary allylic alcohol 22 followed by PtO\textsubscript{2}-catalyzed hydrogenation and desilylation with TBAF.

Upon completing the synthesis of 1 and 2, we compared our spectral data with the reported data for the isolated compounds. Although the \textsuperscript{1}H and \textsuperscript{13}C spectra of synthetic 9-\textit{epi}-presilphiperfolan-1-ol (2) were in excellent agreement with reported data, the spectra for synthetic presilphiperfolan-1-ol (1) clearly were not.\textsuperscript{[xxxv]} In particular, the C(15) methyl hydrogens of synthetic 1 showed a \textsuperscript{1}H NMR resonance at 6 0.94 ppm compared the corresponding resonance of reported 1\textsuperscript{[v]} at 6 0.89 ppm. From the work of Joseph-Nathan and Leitão, the structure of reported 9-\textit{epi}-presilphiperfolan-1-ol (2) was unambiguously established by X-ray crystallography.\textsuperscript{[vib]} The structure of reported presilphiperfolan-1-ol (1) isolated by König was assigned based on NMR data\textsuperscript{[v, xli, xlii]} Overall, the spectral data of reported 1 more closely matches synthetic and reported 2\textsuperscript{[via]} than synthetic 1.

Given the significant discrepancy between our data and König’s data for 1, we sought to rationalize the formation of both 1 and 2 in the context of proposed mechanisms for presilphiperfolanol biosynthesis.\textsuperscript{[i-iv, viii]} While no proposals for the formation of 1 and 2 have been published, it is reasonable that presilphiperfolanols 1–4 are commonly derived

\textit{Angew Chem Int Ed Engl. Author manuscript; available in PMC 2013 September 17.}
from caryophyllenyl cation 6 (Figure 1B). Upon rearrangement to C(9)-presilphiperfolanyl cation 7, a divergent pathway can be envisioned (Figure 3). A simple 1,2-syn hydride migration to tertiary C(1)-cation 23 followed by hydration leads to 9-epi-presilphiperfolan-1-ol (2) with the 9β-methyl stereochemistry without invoking the intermediacy of unfavorable secondary carbocations.[viii] In contrast to this pathway, the formation of 9α-methyl-oriented presilphiperfolan-1-ol (1) seems unlikely since there is no obvious pathway from C(9)-cation 7 to C(1)-cation 24. Based on our NMR spectral data, X-ray crystal structure for 2, and new biosynthetic proposals, we believe the reported structure of natural presilphiperfolan-1-ol (1) is misassigned at C(9) and most likely is not a natural product. The nearly identical chemical shifts of reported 1 and 2 (1H and 13C NMR) suggest that the true structure of presilphiperfolan-1-ol (1) may actually be the same as 9-epi-presilphiperfolan-1-ol (2) with the 9β-methyl configuration (Figure 3). Since the reassignment can potentially lead to confusion, we suggest that the natural product structure represented by 2 be referred to as presilphiperfolan-1-ol or the more descriptive name 9β-presilphiperfolan-1α-ol in the future discussions.

In summary, the first total syntheses of the reported structures of presilphiperfolanol 1 and 2 have been achieved in 13-15 steps and 7.9-8.6% overall yield from commercially available vinylogous ester 14. This work constitutes the first asymmetric total synthesis of any member of the presilphiperfolanol family. In addition to demonstrating the synthetic utility of functionality-rich acyclic cyclopentenes 11 and 17 generated from our Pd-catalyzed allylic alkylation/ring contraction methodology, we exploited a range of methods to concisely construct the fully substituted carbocyclic core of our targets. Analysis of spectral data and evaluation of likely presilphiperfolanol biosynthetic pathways prompted us to reassign the structure of reported 1 to 2. Our synthetic route provides access to 1, 2, and synthetic analogs, enabling investigation of their biological activity. Extension of the synthetic strategy to the remaining members of the family, investigations of the biosynthetic pathway, and biomimetic rearrangement to other natural products are currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank NIH-NIGMS (R01GM080269-01), Roche, Abbott Laboratories, Amgen, Boehringer Ingelheim, the Gordon and Betty Moore Foundation, and Caltech for awards and financial support. Prof. Suzana G. Leitão (Universidade Federal do Rio de Janeiro) generously provided NMR spectra for natural 2. Dr. Lawrence Henling is gratefully acknowledged for X-ray crystallographic structure determination. The Bruker KAPPA APEXII X-ray diffractometer used in this study was purchased via an NSF CRIF:MU award to Caltech (CHE-0639094). Prof. Sarah Reisman, Dr. Scott Virgil, Dr. Douglas C. Behenna, Robert J. Ely and Fang Gao (Boston College), and Jessica Y. Wu (Harvard University) are acknowledged for helpful discussions and suggestions. Dr. David VanderVelde and Dr. Scott Ross are acknowledged for NMR assistance.

References


Universität Hamburg: Apr. 1999 Isolierung, Strukturaufklärung und stereochemische Untersuchungen neuer sesquiterpenoider Verbindungen aus vier Chemotypen des Lebermooses Conocephalum conicum.


Substituted allylic carbamates have been used by Trost to achieve O-acylation of enolates under different reaction conditions. See: Trost BM, Xu J. J. Org. Chem. 2007; 72:9372–9375. [PubMed: 17963405]


A related IMDA cycloaddition for the construction of an analogous tricyclic system with an activated alkyne has been reported. See: Evanno L, Deville A, Bodo B, Nay B. Tetrahedron Lett. 2007; 48:4331–4333.


Our IMDA substrate does not fit neatly into the Type I or Type II IMDA classification, making prediction of the reaction outcome less straightforward.


See Supporting Information for additional details and experimental procedures.
[xxxviii]. CCDC 889569 (1) and CCDC 889570 (21b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via. [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)
[xli]. Unfortunately, attempts to obtain samples or spectra of naturally isolated presilphiperfolan-1-ol (1) were unsuccessful.
[xlii]. An X-ray crystal structure for a synthetic compound with the same structure as our synthetic 1 (prepared from isocaryophyllene) was reported by Khomenko and associates (see ref. xvb). Our NMR data for synthetic 1 matches the spectral data for Khomenko’s synthetic 1 but not the spectral data for König’s reported natural 1.
Figure 1. Presilphiperfolanyl (Prebotrydialyl) Cations as Key Intermediates in the Biosynthesis of Diverse Sesquiterpenes
Figure 2. Synthetic Strategy Toward the Presilphiperfolane Core
Figure 3. Biosynthetic Proposal for the Formation of 2, and Structural Revision of 1
Scheme 1. Gram-Scale Synthesis of Acylocyclopentene 11 and IMDA
Scheme 2. Revised Synthetic Approach to Presilphiperfolane Core
Scheme 3. Synthesis of the Reported Structures of 9-epi-Presilphiperfolan-1-ol (2) and Presilphiperfolan-1-ol (1)