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Natural Product Synthesis

Biosynthesis and Chemical Synthesis of Presilphiperfolanol Natural Products

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biosynthesis · natural products · structure elucidation · terpenoids · total synthesis

Dedicated to Professor Richmond Sarpong on the occasion of his 40th birthday

Presilphiperfolanols constitute a family of biosynthetically important sesquiterpenes which can rearrange to diverse sesquiterpenoid skeletons. While the origin of these natural products can be traced to simple linear terpene precursors, the details of the enzymatic cyclization mechanism that forms the stereochemically dense tricyclic skeleton has required extensive biochemical, computational, and synthetic investigation. Parallel efforts to prepare the unique and intriguing structures of these compounds by total synthesis have also inspired novel strategies, thus resulting in four synthetic approaches and two completed syntheses. While the biosynthesis and chemical synthesis studies performed to date have provided much insight into the role and properties of these molecules, emerging questions regarding the biosynthesis of newer members of the family and subtle details of rearrangement mechanisms have yet to be explored.

1. The Presilphiperfolanol Natural Products

The presilphiperfolane (or prebotrydial) skeleton serves as an important branch point for the biosynthesis of many sesquiterpene natural products. As inherently high-energy structures, presilphiperfolanyl cations are especially prone to skeletal rearrangement by C–C bond migrations. While these intermediates are crucial for the formation of various downstream sesquiterpenes, natural products possessing an unmodified presilphiperfolane framework are rare in nature.

1.1. Isolation and Structural Elucidation

Currently, three presilphiperfolanols have been isolated and characterized: (−)-presilphiperfolan-8α-ol [(−)-**1**],[1] (−)-presilphiperfolan-9α-ol [(−)-**2**],[2] and (−)-presilphiperfolan-1β-ol [(−)-**3**][3,4] (Figure 1). Each of these natural products corresponds to the hydration product of a presilphiperfolanyl cation involved in terpene cyclization pathways. To date, naturally occurring stereoisomers of the structures (−)-**1**–**3** have not been reported. The structurally complex presilphiperfolanols are distinguished by their uncommon, compact tricyclo[5.3.1.$0^{4,11}$]undecane sesquiterpene skeleton, which bears five contiguous stereocenters, two all-carbon quaternary centers, and a tertiary hydroxy group. In addition to these readily apparent structural features, considerable ring strain is present in the tricyclic system,[5,6] thus allowing these compounds to undergo thermodynamically favorable skeletal rearrangements which lead to structurally diverse polycyclic sesquiterpenes. Computational studies have shown that the heat of formation (ΔH_f) of the presilphiperfolane skeleton is at least 7.1 kcal mol^{-1} greater than those for several isomeric sesquiterpene skeletons formed later in the biosynthetic sequence.[5]

(−)-Presilphiperfolan-8α-ol [(−)-**1**] was the first member of the family to be identified.[1] Bohlmann and co-workers isolated the compound from the flowering plants *Eriophyllum staechadifolium* and *Flourensia heterolepis* in 1981. The tricyclic structure and stereochemistry were assigned based on detailed ^{1}H NMR analysis employing chiral shift reagents. Subsequent work by Coates et al. provided an X-ray crystal structure of the *p*-nitrobenzoate ester derivative.[7]

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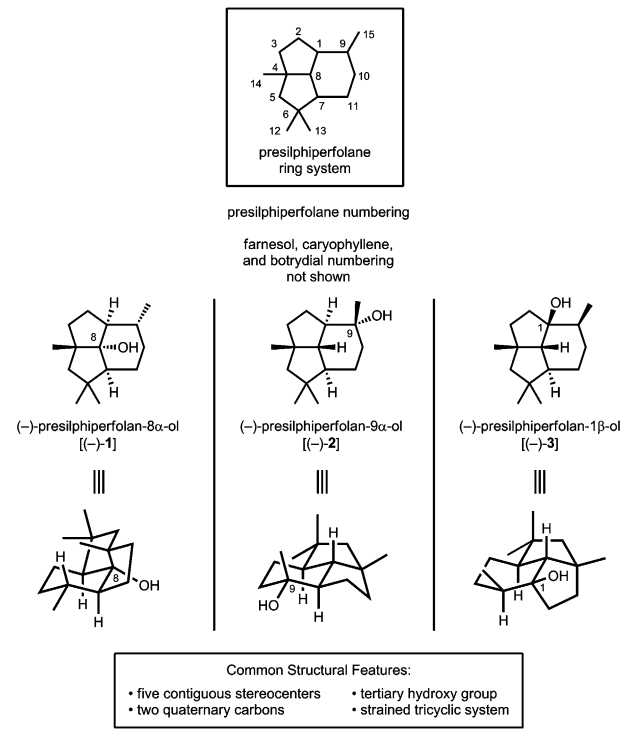

Figure 1. Presilphiperfolanol (prebotrydial) natural products.

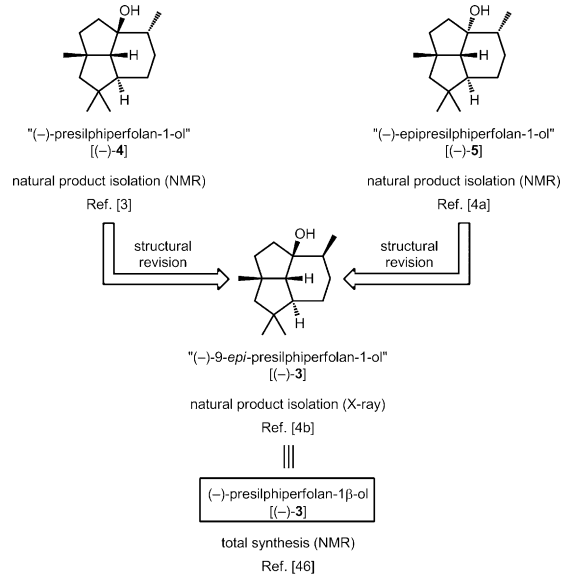

Figure 2. Structural reassignments of (–)-**3**.

(–)-Presilphiperfolan-9α-ol [(–)-**2**][2] was later discovered by Weyerstahl et al. in the wormwood *Artemisia lacinata* in 1993, and subsequently by Marco et al. in the related species *Artemisia chamaemelifolia* in 1996. The structure of (–)-**2** was determined based on NMR spectroscopic analysis and additionally confirmed by the total synthesis of (±)-**2** (see Section 2.2).[8]

In contrast to presilphiperfolanols (–)-**1** and (–)-**2**, the structure of (–)-presilphiperfolan-1β-ol [(–)-**3**][3,4] has been revised several times (Figure 2). The alcohol (–)-**3** was initially isolated by Melching and König in small quantities from the liverwort *Conocephalum conicum* in 1999,[3] but was incorrectly assigned the structure (–)-**4** based on NMR data. The same compound was isolated by Leitão and co-workers from the fern *Anemia tomentosa* var. *anthriscifolia* and reported as a unique natural product with the initial structure (–)-**5** from the analysis of NMR spectra.[4a] Subsequent collaborations between Leitão, Joseph-Nathan, and co-workers unambiguously determined that the isolated compound possessed the revised structure (–)-**3** by X-ray crystallography.[4b] Recently, the group of Stoltz proposed that the compounds isolated by König and Leitão are in fact the same natural product (–)-**3** based on synthetic studies, spectroscopic data, and analysis of the likely biosynthetic pathway (see Section 2.5).

In addition to the parent presilphiperfolanols, natural products with dehydrated or oxidized tricyclic skeletons have also been reported (Figure 3). Presilphiperfol-7(8)-ene (**6**)[9] presumably arises from the deprotonation of presilphiperfolanyl cation intermediates. Natural products such as the britanlins (**7**–**9**)[10] display additional oxidation at primary carbon atoms in the presilphiperfolane skeleton. Other isolated compounds, such as angelates **12** and **13**, show oxidation at multiple secondary carbon atoms in the tricyclic framework.[11] Oxidative ring cleavage is also possible as evidenced by the structures of botrydial (**10**)[12] and dihydrobotrydial (**11**).[12] All of these natural products arise from structural modification of the presilphiperfolanols, which exhibit a low level of oxidation.

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Brian M. Stoltz obtained his BS in Chemistry and BA in German from Indiana University of Pennsylvania in 1993. He earned his PhD in 1997 under the direction of Prof. John L. Wood at Yale University. After an NIH-sponsored postdoctoral fellowship with Prof. E. J. Corey at Harvard University (1998–2000), he joined the faculty at Caltech in 2000. His research focuses on the design and implementation of new synthetic strategies for the synthesis of complex molecules, and the development of new synthetic methods.

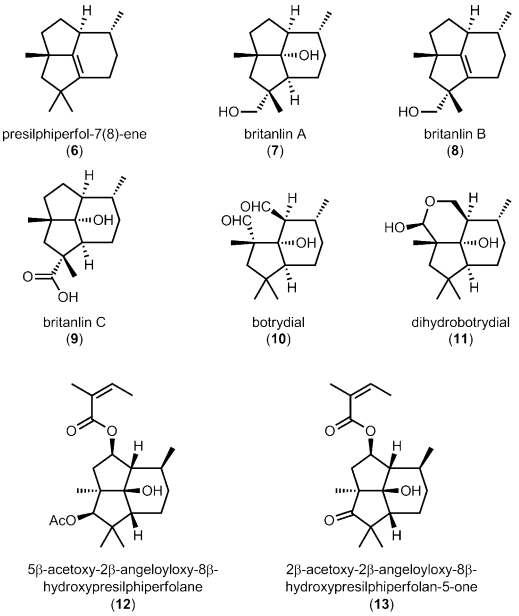


Figure 3. Natural products with dehydrated or oxidized presilphiperfolanol skeletons.

1.2. Biosynthesis of the Presilphiperfolanols

The co-isolation of the presilphiperfolanols with structurally related sesquiterpenes provided important clues for their biosynthetic origin. Bohlmann and co-workers observed that (−)-**1** was often found with various triquinane natural products.[1,13] The tricyclic alcohol (−)-**1** and β-caryophyllene (**14**) (Figure 4) were also isolated from the same natural sources in numerous reports.[9,14] These findings suggested that three classes of polycyclic sesquiterpenes were connected in a common biosynthetic pathway. In 1980, Bohlmann and Jakupovic explained these results by proposing that farnesyl pyrophosphate (FPP; **21**) undergoes enzymatic polycyclization to the caryophyllenyl cation **23** (Scheme 1 A).[13]

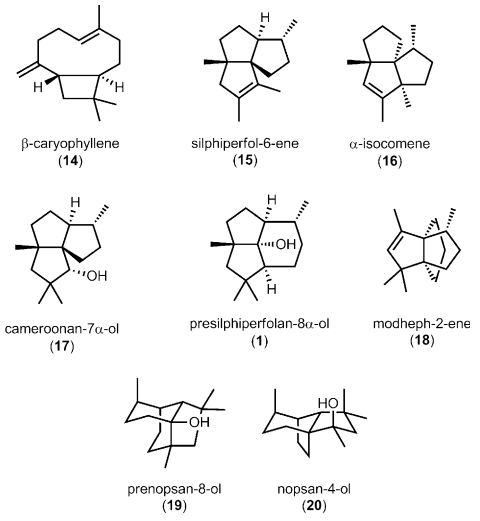
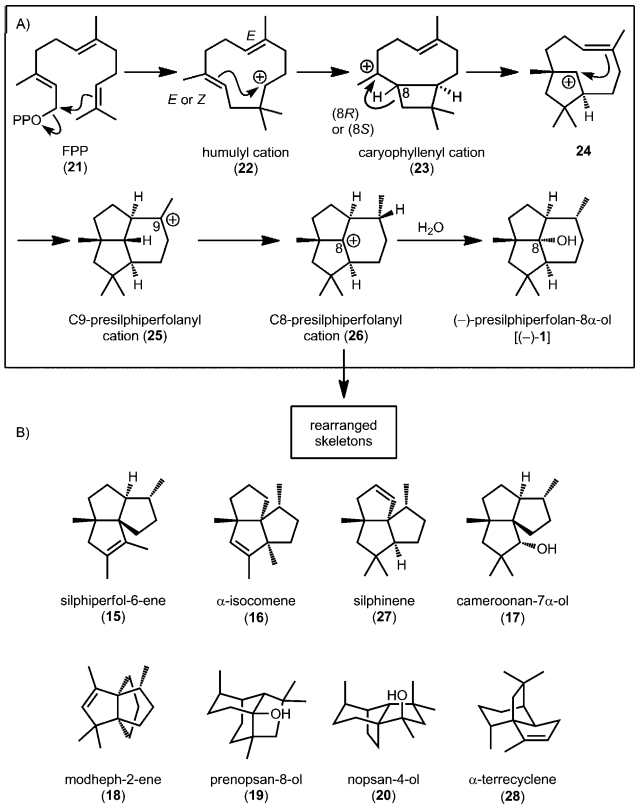


Figure 4. Selected co-isolated sesquiterpenes from rhizome *Echinops giganteus* var. *lelyi*.

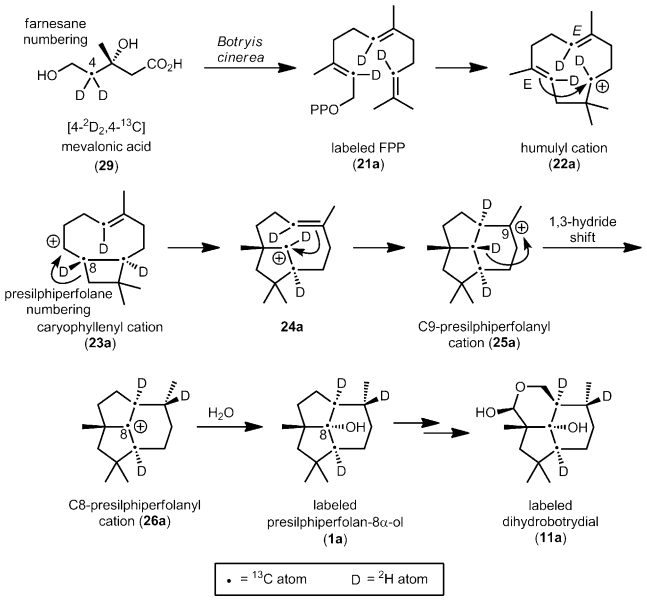


Scheme 1. A) Bohlmann mechanism for presilphiperfolane biosynthesis. B) Diverse rearranged sesquiterpene natural products.

Subsequent cyclobutane ring expansion and cation–alkene cyclization leads to the C8-presilphiperfolanyl cation **26**. From this common intermediate, rearrangement of the carbon skeleton by Wagner–Meerwein shifts can lead to the observed triquinanes.

Concurrent studies by Hanson and co-workers in 1981 helped elucidate the presilphiperfolane biosynthetic pathway.[15] In an effort to understand the biogenesis of the downstream metabolite dihydrobotrydial (**11**; Figure 3) from simple terpene building blocks, his group performed NMR studies with isotopically labeled mevalonic acid (**29**; Scheme 2). Linked ^{2}H and ^{13}C labels could be incorporated into this precursor, which was fed to the fungus *Botryis cinerea*. Subsequent analysis of the cyclized and oxidized dihydrobotrydial isolate **11a** revealed that three units of mevalonic acid (**29**) were incorporated into the molecule. Furthermore, the isotopic pair at C8 (presilphiperfolane numbering) became separated during the biosynthetic transformations while the other two pairs remained intact. This result provided the first evidence for an unusual 1,3-hydride shift linking the initially formed cation **25** to the isomeric C8-cation **26**. From this intermediate, Hanson reasoned that hydration and enzymatic oxidative cleavage of the less-substituted cyclopentane ring would lead to **10** and **11**.

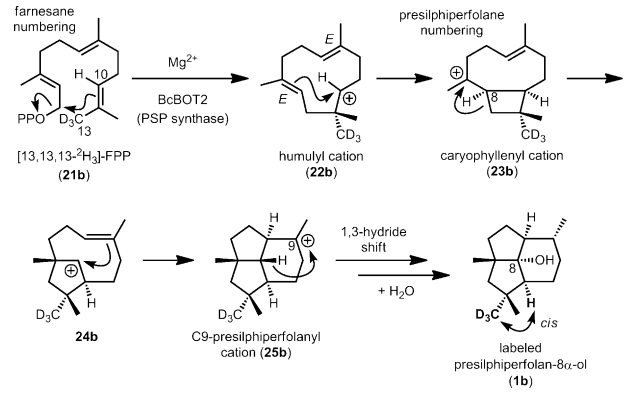
The Bohlmann–Hanson mechanism has been refined and expanded by numerous groups through biochemical, spectroscopic, and computational techniques in recent years. The groups of Collado, Cane, and Viaud worked together to



Scheme 2. Hanson mechanism for presilphiperfolane biosynthesis (representative isotope-labeling study).

identify the *BcBOT* gene cluster in *B. cinerea* responsible for the enzymatic conversion of **21** into **10**.[16] In these studies, it was demonstrated that the *BcBOT2* gene encoded an essential sesquiterpene cyclase while other genes in the cluster expressed cytochrome P450 monooxygenases responsible for the oxidation of the presilphiperfolane skeleton to **10** and related derivatives (Scheme 1B).

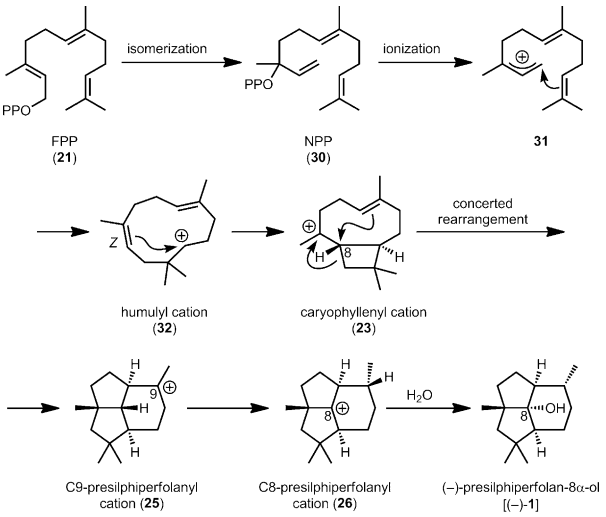
Subsequent work by Cane and co-workers focused on the incubation of isotopically labeled FPP derivatives with the isolated BcBOT2 enzyme to further elucidate the stereochemical details of the cyclization mechanism (Scheme 3).[17]



Scheme 3. Cane mechanism for presilphiperfolane biosynthesis (representative isotope-labeling study).

In total, Cane investigated four different FPP derivatives to probe the different cyclization steps, thus corroborating the earlier work of Bohlmann and Hanson. In a representative study, ^{2}H labeling at the C13-methyl group (farnesane numbering) translated to deuterium substitution at C14 (presilphiperfolane numbering) of presilphiperfolan-8α-ol isolate (**1b**). This study indicated that the *cis* relationship of the labeled C13-methyl group and the alkene proton at C10 is conserved throughout the terpene cyclization sequence, and led to the new proposal that the *cis*-caryophyllenyl cation **23b** is a key intermediate. While **14** (*trans* ring fusion) was co-isolated with (−)-**1** by Bohlmann, 2-*epi*-caryophyllene (**48**, Scheme 7, *cis* ring fusion)[18] was not observed.

Computational studies by Wang and Tantillo also sought to understand the presilphiperfolanol biosynthetic pathway.[19] Numerous theoretical terpene cyclization pathways were evaluated and a different mechanism was proposed on the basis of these results (Scheme 4). The key findings were



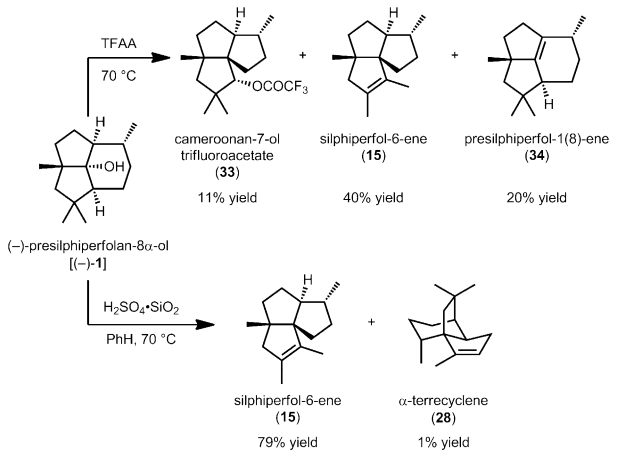
Scheme 4. Tantillo mechanism for presilphiperfolane biosynthesis (computational study).

the proposed isomerization of **21** to nerolidyl pyrophosphate (NPP; **30**), the conformer of **23** responsible for cyclization, the highly synchronous nature of the cation–alkene cyclizations leading from **23** to **25**, and the feasibility of the 1,3-hydride shift leading from **25** to **26**. Barquera-Lozada and Cuevas used molecular mechanics calculations to evaluate a similar mechanism for the conversion of **22** into the terrecylenyl cation precursor to α-terrecyclene (**28**; Scheme 1B).[20]

1.3. Structural Rearrangements of Presilphiperfolanols

The importance of the presilphiperfolanols in sesquiterpene biosynthesis has prompted more detailed investigations of the rearrangements leading to other related natural products.[7,9] A report by Weyerstahl et al. in 1998 described the constituents of the essential oil from the rhizome *Echinops giganteus* var. *lelyi* as containing a rich collection of biogenetically related sesquiterpenes (Figure 4).[9] Along with **14** and (−)-**1**, 18 unique tricyclic natural products were discovered. All of the tricyclic compounds could be traced to common presilphiperfolanyl cation intermediates through reasonable Wagner–Meerwein shifts. The co-occurrence of these compounds further supports the findings of Bohlmann.[1,13]

In conjunction with these natural product isolation studies, others have sought to understand the biosynthetic conversion of presilphiperfolane skeletons into those of other sesquiterpene natural products through chemical semisynthesis. Coates et al. successfully performed the rearrangement of (−)-**1** with TFAA at 70 °C to obtain the cameroonan-7-ol trifluoroacetate (**33**) in 11 % yield, silphiperfol-6-ene (**15**) in 40 % yield, and presilphiperfol-1(8)-ene (**34**)[21] in 20 % yield (Scheme 5).[5,7] Ionization of (−)-**1** with $H_2SO_4{\cdot}SiO_2$ in benzene at 70 °C provided **15** in 79 % yield and **28** in 1 % yield. The different distribution of sesquiterpene products obtained under these reaction conditions highlights the strong influence of reaction parameters on competing rearrangement pathways.



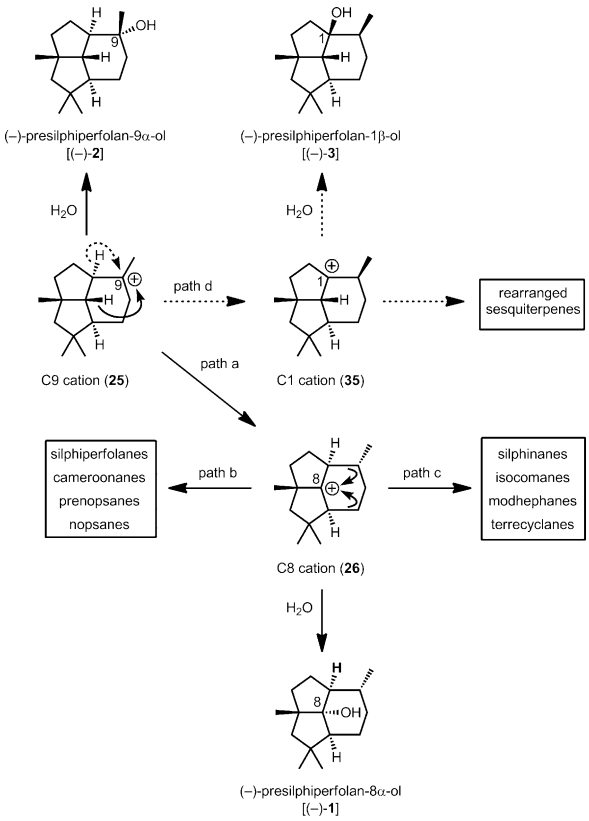
Scheme 5. Rearrangement of presilphiperfolan-8α-ol to other sesquiterpene skeletons. TFAA = trifluoroacetic anhydride.

Currently, the presilphiperfolane skeleton is believed to serve as the precursor to silphiperfolane, silphinane, isocomane, modhephane, terrecyclane, prenopsane, nopsane, and cameroonane skeletons (Scheme 1 B and Scheme 6).[9] The structural diversity of polycyclic skeletons produced from the presilphiperfolane skeleton underscores their fundamental biosynthetic importance in sesquiterpene cyclase pathways.

While past work has explored the formation of (−)-**2** and (−)-**1** in great detail, existing biosynthetic proposals have not accounted for the formation of (−)-**3**, the newest discovered member of the family (Scheme 5). The understanding of the mechanistic pathway leading to this natural product could additionally provide new insight into the formation of downstream rearranged sesquiterpene natural products.

1.4. Biological Activity of the Presilphiperfolanols

While the presilphiperfolanols have proven to be important biosynthetic precursors to a number of polycyclic sesquiterpenes, they also exhibit modest biological activity. As a relatively nonpolar low molecular weight alcohol, (−)-**2** has pleasant olfactory properties and has attracted interest as a fragrance compound.[2,22] The natural product (−)-**2**[2] has a pleasantly sweet and woody aroma with hints of coconut



Scheme 6. Rearrangement of presilphiperfolanols to other sesquiterpene natural products.

and celery. Synthetic (±)-**2**[8] possesses a slightly different olfactory profile with a strongly radiative, woody, resinous, and amber(gris) notes.

González-Coloma and co-workers discovered the insect antifeedant properties of (−)-**2** while screening a collection of polycyclic sesquiterpenoids.[23] The tricyclic alcohol displayed an EC_{50} of 19.5 nmol/cm^2 against the Colorado potato beetle *Leptinotarsa decemlineata* and 47.5 nmol cm^{-2} against the aphid species *Diuraphis noxia*. Direct injection or oral dosing of this compound with *L. decemlineata* beetles led to 47 % mortality after 72 hours. While the mode of action has not been fully elucidated, (−)-**2** is believed to be toxic to the insect's peripheral and central nervous system.

Leitão and co-workers have found that (−)-**3** possesses antimycobacterial properties.[24] The natural product is active against *Mycobacterium tuberculosis* (H37Rv) and *Mycobacterium smegmatis* (mc2155) strains with minimal inhibitory concentrations (MICs) of 100 μg mL^{-1} and 200 μg mL^{-1}, respectively. Currently, the basis for the observed antimycobacterial activity is unclear.

Non-natural presilphiperfolane analogues have also been investigated for their biological properties. The presilphiperfolane derivatives (−)-**4** and **36**–**46** were investigated as novel antifungal agents by Collado et al. (Figure 5).[25] Of these compounds, the alcohols **37** and **42** showed the most promising inhibition in fungal growth assays with *Botryis cinerea*. The tertiary hydroxy **37** showed complete suppression of fungal growth for four days with continued growth reduction

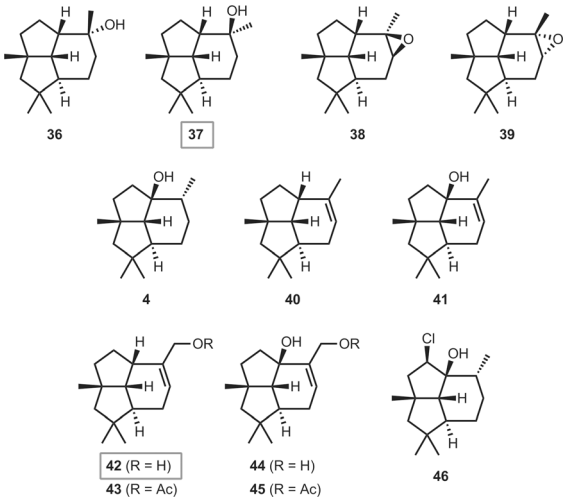


Figure 5. Natural and non-natural presilphiperfolanol analogues investigated for antifungal activity.

after seven days. The primary alcohol **42** effectively reduced the size of fungal colonies and triggered changes in fungal morphology. For both of these active tricyclic terpenoid compounds, the hydroxy groups are believed to be essential for inhibition, as the evaluation of the acetylated derivates such as **43** led to no observable activity.

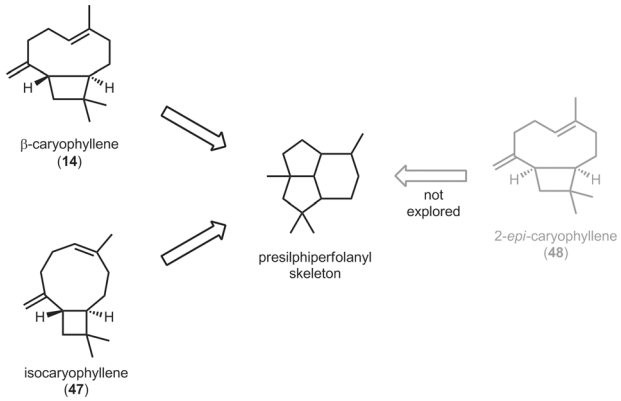
2. Synthetic Studies Toward the Presilphiperfolanol Natural Products

Although the presilphiperfolanols are vitally important to the biosynthesis of numerous polycyclic sesquiterpenes, reports of synthetic efforts directed toward these natural products have been scarce. A number of biomimetic synthetic approaches have aimed to convert advanced biosynthetic precursors into the tricyclic alcohols (−)-**1**–**3**, but these approaches have not been successful. More recently, research directed toward the chemical synthesis of the presilphiperfolanols has led to compounds which possess the tricyclic core of the targeted natural products and two completed total syntheses.

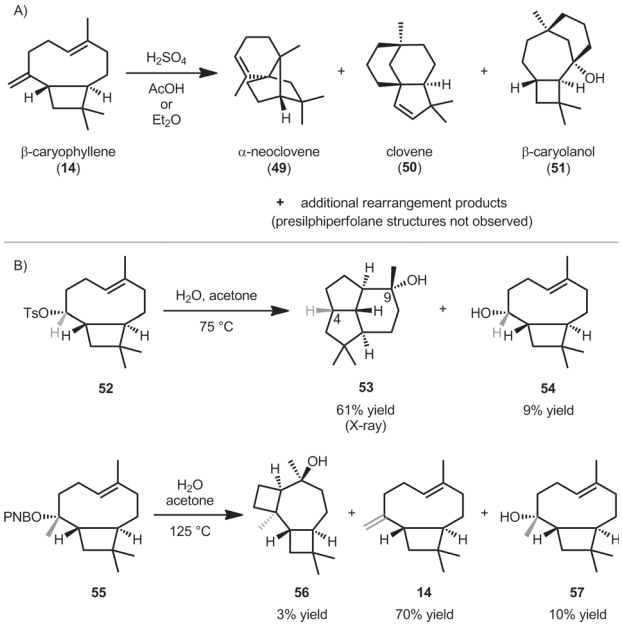
2.1. Biomimetic Cyclizations of β-Caryophyllene and Isocaryophyllene

Based on the substantial evidence for the biosynthetic conversion of **21** into caryophyllenyl cations en route to presilphiperfolanyl cations through cation–polyene cyclizations, many researchers have sought to achieve biomimetic syntheses of the presilphiperfolanols by rearrangement of β-caryophyllene (**14**) or isocaryophyllene (**47**; Scheme 7).[26] To date, however, these efforts have not resulted in the formation of any of the naturally occurring tricyclic alcohols (−)-**1**–**3**.

Research by numerous groups has explored the rearrangement of **14** under acidic conditions (Scheme 8 A).[27,28] These reactions typically have led to complex mixtures with



Scheme 7. Strategy for the rearrangement of caryophyllenyl and isocaryophyllenyl skeletons.



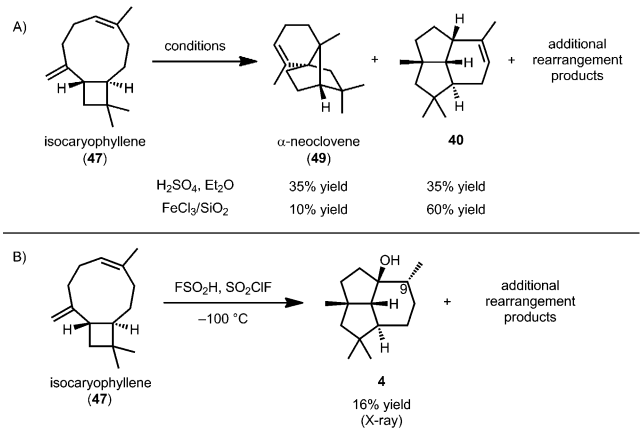
Scheme 8. Reported rearrangements of caryophyllene skeletons. PNB = *p*-nitrobenzoyl, Ts = 4-toluenesulfonyl.

product distributions which change over time. In this context, numerous rearrangement products such as α-neoclovene (**49**), clovene (**50**), and β-caryolanol (**51**) have been isolated and characterized. A supporting computational study was also performed to help understand the complex nature of the diverse rearrangement pathways.[28a] To date, however, presilphiperfolane structures have not been observed in any of these detailed studies.

More recently, Coates and co-workers studied the solvolytic rearrangement of β-caryophyllene-derived structures with intriguing results (Scheme 8 B).[28b] The ionization and rearrangement of the β-caryophyllene-derived tosylate **52** in water and acetone at 75 °C provided 12-*nor*-8 α-presilphiperfolan-9 β-ol (**53**) and the alcohol **54**. The compound **53** resembles (−)-**2**, but notably lacks the methyl group attached to C4 in the natural product. Rearrangement reactions employing β-caryophyllenyl precursors with the requisite

methyl group were also investigated. Subjection of the *p*-nitrobenzoate ester **55** to similar solvolytic rearrangement conditions at a higher temperature did not furnish (−)-**2**, but instead led to 5,8-cyclocaryophyllen-4α-ol (**56**), **14**, and **57**. The different product distributions under nearly identical reaction conditions suggests that the non-enzymatic cyclization is highly sensitive to the substitution of the caryophyllenyl framework and to the nature of the leaving group.

The rearrangement of isocaryophyllene (**47**) to presilphiperfolane-type structures has also been investigated.[25,29,30] Robertson and co-workers treated **47** with sulfuric acid in diethyl ether to obtain **49** and the tricyclic olefin **40**, which resembles the tricyclic core of the presilphiperfolanols (Scheme 9 A). Since these early studies, Collado et al. was able to favor the formation of **40** by employing silica-



Scheme 9. Reported rearrangements of isocaryophyllene (**44**).

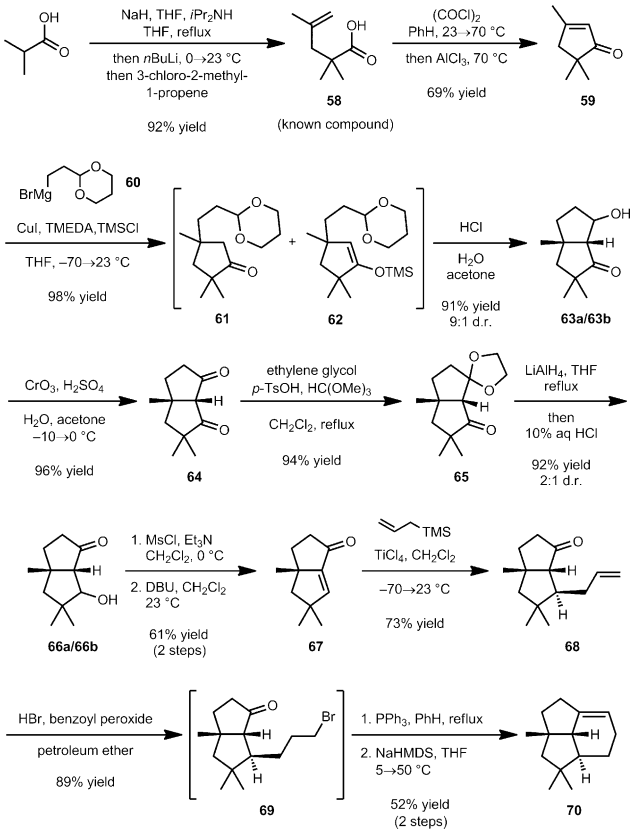
supported $FeCl_3$.[25b] Further work by Khomenko and co-workers has produced alcohol-containing tricyclic structures which more closely resemble the presilphiperfolanols.[30] Treatment of **47** with fluorosulfonic acid and sulfuryl fluorochloride at −100 °C and a subsequent careful quenching of the acidic solution led to the formation of **4** in 16% yield (Scheme 9 B). The structure was assigned based on ^1H and ^{13}C NMR studies and confirmed by single-crystal X-ray diffraction. Notably, this compound is the C9 epimer of (−)-**3** and identical to the structure originally assigned by König as "(−)-presilphiperfolan-1-ol" [(−)-**4**].

While the variation of the endocyclic double bond geometry of the caryophyllene skeleton has been explored in numerous contexts with **14** and **47**, biomimetic cyclizations with **48**[18] have not been explored. Since the compound was proposed as a key intermediate in Cane's biosynthetic proposal (Scheme 3),[17] successful chemical conversion into presilphiperfolane structures would provide further evidence for this hypothesis.

2.2. Weyerstahl Total Synthesis of (±)-Presilphiperfolan-9α-ol [(±)-2]

Driven by a keen interest in the biosynthetic importance, intriguing polycyclic structure, and olfactory properties of (−)-**2**, Weyerstahl and co-workers aimed to prepare the natural product by total synthesis.[8] Central to their synthetic approach was the design of an intramolecular olefination strategy for the construction of the tricyclic core.

Beginning from isobutyric acid, enolization and alkylation with methallyl chloride provided the functionalized pentenoic acid **58** (Scheme 10). Subsequent carboxylate activation with oxalyl chloride and cyclization with $AlCl_3$ provided the

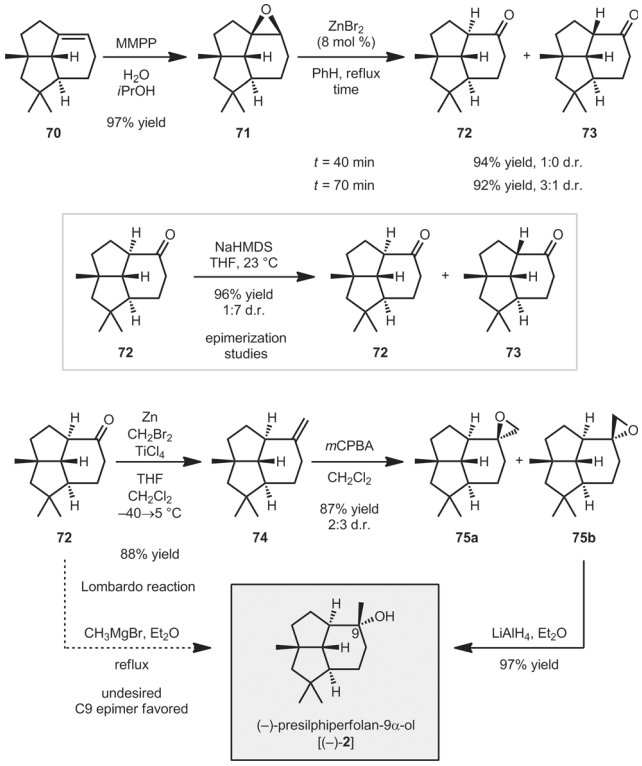


Scheme 10. Synthesis of the key tricyclic olefin intermediate **70**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MsCl = methanesulfonyl chloride, THF = tetrahydrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, TMS = trimethylsilyl, *p*-TsOH = *p*-toluenesulfonic acid.

cyclopentenone **59** in 69% yield. The conjugate addition of the organocuprate of **60** with TMSCl as an activator, and subsequent acidic deprotection and aldolization provided a mixture of the β-hydroxyketones **63a** and **63b** in 89% yield and 9:1 d.r. after two steps. A subsequent Jones oxidation afforded the diketone **64** in 96% yield. Selective protection of the less hindered carbonyl proceeded smoothly with *p*-TsOH, ethylene glycol, and trimethyl orthoformate in CH_2Cl_2 at reflux. Reduction of the remaining ketone in **65** with $LiAlH_4$ and subsequent acidic workup the provided β-hydroxyketones **66a** and **66b** in 92% yield and 2:1 d.r. Dehydration was

achieved by initial mesylation and elimination with DBU to give the bicyclic enone **67** in 61% yield over two steps. Alternatively, the elimination was achieved with Burgess' reagent[31] in 64% yield. A subsequent diastereoselective Sakurai allylation[32] afforded the ketone **68** in 73% yield. Regioselective radical hydrobromination of the terminal C=C bond and subsequent intramolecular Wittig reaction completed the tricyclic core of the target tricyclic molecule **70** in 52% yield over two steps.

With **70** in hand, a highly diastereoselective epoxidation with magnesium bis(monoperoxyphthalate) (MMPP)[33] afforded the epoxide **71** in 97% yield (Scheme 11). The epoxidation could also be achieved with *m*CPBA, but yields were typically lower. A subsequent stereospecific Meinwald



Scheme 11. Weyerstahl's completion of (±)-presilphiperfolan-9α-ol [(±)-**2**]. *m*CPBA = *m*-chloroperbenzoic acid, NaHMDS = sodium bis(trimethylsilyl)amide.

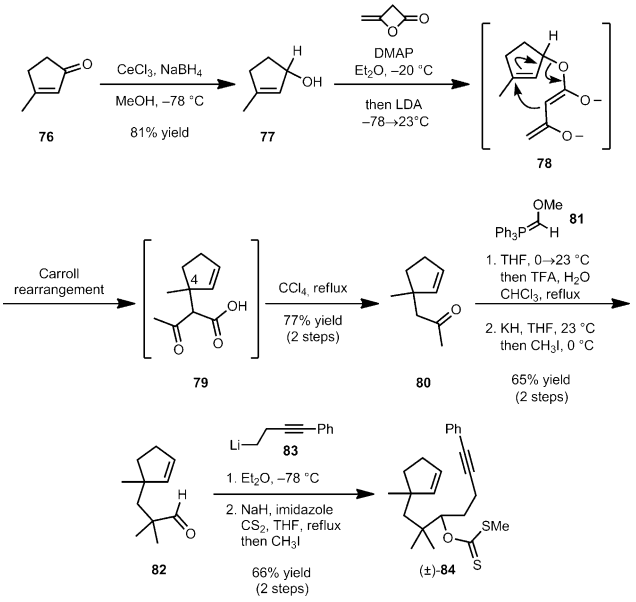
rearrangement catalyzed by $ZnBr_2$ was effective, thus giving the expected ketone **72** with α-H stereochemistry at C1 in 94% yield after 40 minutes. While these reaction conditions proved successful, longer reaction times led to significant C1 epimerization to the undesired ketone epimer **73**. The gradual conversion of **72** into its epimer **73** over time suggests that the desired ketone is thermodynamically unstable. This hypothesis was also supported by epimerization studies on **72** with NaHMDS, which provided a mixture of **72** and **73** in a 1:7 ratio of diastereomers.

With 14 of the 15 carbon atoms of the target compound installed, it was anticipated that the addition of MeMgBr to **72** could give (−)-**2** in a direct and straightforward manner. Unfortunately, this transformation predominantly led to the undesired C9 epimer with only trace amounts of the desired natural product (−)-**2**. The steric environment of the tricycle as well as the favorable Bürgi–Dunitz trajectory from the α face of the molecule dictated the facial bias of nucleophilic additions to the ketone of **72**. To arrive at the natural product through alternative means, the Lombardo reaction was employed to give the olefin **74** in 88% yield. A subsequent epoxidation with *m*CPBA gave a 2:3 ratio of the diastereomers **75a** and **75b** in 87% yield. After chromatographic separation, $LiAlH_4$ reduction **75b** provided (±)-presilphiperfolan-9α-ol [(−)-**2**] in 97% yield. The total synthesis was completed in 17 steps and 4.0% overall yield from commercial starting materials.

2.3. Piers Approach to the Synthesis of (±)-Presilphiperfolan-9α-ol [(±)-2]

Subsequent synthetic efforts toward the presilphiperfolanol natural products aimed to assemble the tricyclic framework in a more efficient manner by forging multiple rings in a single key step. In developing a novel approach to (−)-**2**, Piers employed a radical polycyclization strategy to enable rapid construction of central bonds in the core structure.[34,35]

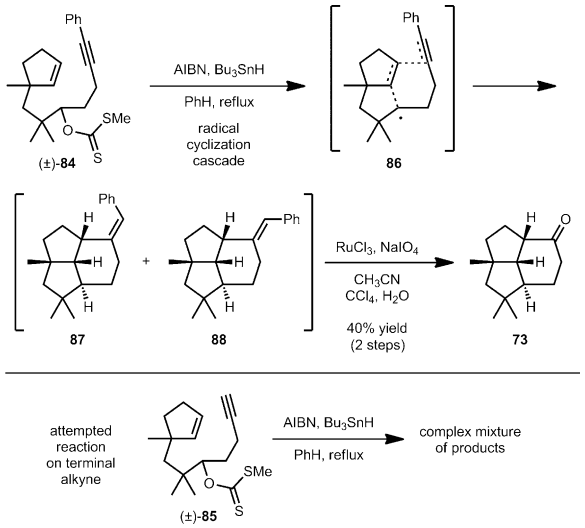
The synthesis proceeded from 3-methyl-2-cyclopentenone (**76**; Scheme 12). An initial Luche reduction[36] provided the alcohol **77** in excellent yield. The method of Wilson[37] was used to convert the allylic alcohol into the dianionic intermediate **78**, which undergoes a thermal Carroll rearrangement[38] and decarboxylation to form the functionalized cyclopentene **80** in 77% yield over two steps. With the C4 quaternary carbon atom installed, a Wittig homologation with the ylide **81**[39] and subsequent methyl enol ether



Scheme 12. Synthesis of the radical cyclization precursor **84**. DMAP = 4-(dimethylamino)pyridine, LDA = lithium diisopropylamide, TFA = trifluoroacetic acid.

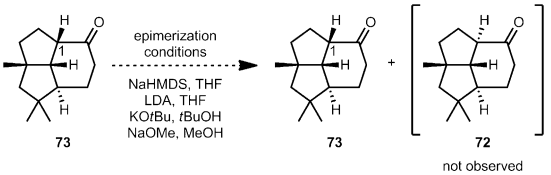
hydrolysis and α-methylation provided the aldehyde **82** in 65% yield. Addition of the alkyllithium reagent **83** to **82** and subsequent xanthate ester formation led to the radical cyclization precursor (±)-**84**.

The slow addition of Bu_3SnH and AIBN to (±)-**84** in benzene at reflux provided a mixture of the tricyclic olefins **87** and **88** (Scheme 13). Oxidative styrene C=C bond cleavage with $RuCl_3$ and $NaIO_4$[40] afforded (±)-*epi*-9-nor-presilphiperfolan-9-one (**73**)[8] in 40% yield over two steps. The disubstituted alkyne was essential for efficient cyclization since (±)-**85** only led to a complex mixture of volatile hydrocarbon products.



Scheme 13. Radical cyclization cascades with **84** and **85**. AIBN = 2,2′-azobis(2-methylpropionitrile).

Epimerization of the C1 methine hydrogen atom of **73** was necessary to proceed toward (−)-**2** (Scheme 14). Thermodynamic equilibration according to Weyerstahl's procedure[8] (Scheme 11) failed, thus returning only starting



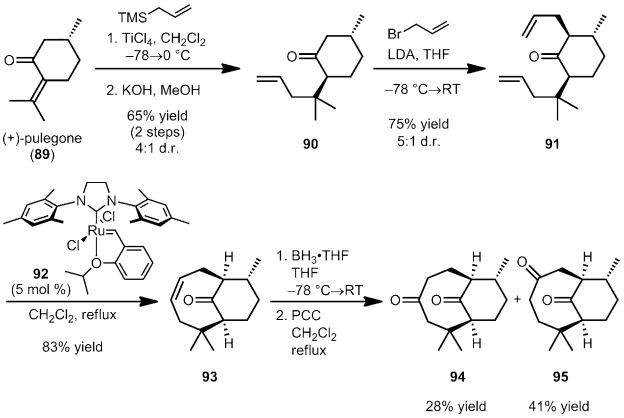
Scheme 14. Attempted epimerization of the C1 methine hydrogen atom of **73**.

material. Other strong bases such as LDA, KO*t*Bu, and NaOMe provided no trace of the desired ketone **72**. Because of the synthetic difficulties arising from the thermodynamic preferences of the tricyclic scaffold, the synthesis was not advanced further.

2.4. Ito Approach to the Synthesis of (−)-Presilphiperfolan-8α-ol [(−)-1]

While previous synthetic routes offered different strategies for the construction of the presilphiperfolanols, they did not provide access to the target natural products in enantioenriched form. To address this problem, Ito and co-workers devised a concise, enantiospecific approach to the synthesis of (−)-**1** from a chiral pool starting material.[41] The route aimed to forge the tricyclic core using two complementary transannular cyclization strategies.

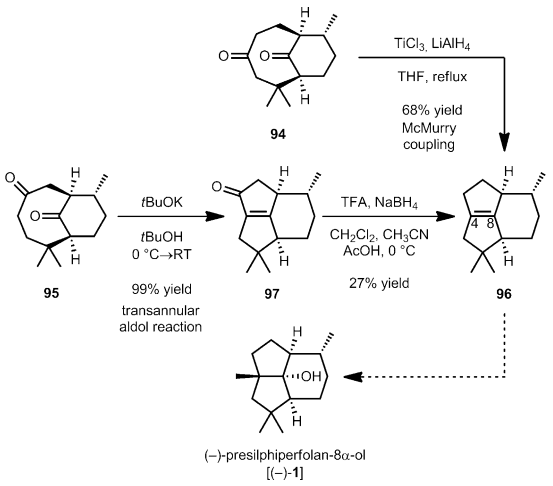
A Sakurai conjugate allylation[32,42] of (+)-pulegone (**89**) and subsequent base-mediated epimerization provided the ketone **90** in 65% yield and 4:1 d.r. over two steps (Scheme 15). Selective formation of the less-substituted,



Scheme 15. Construction of diketones **94** and **95** from chiral pool. PCC = pyridinium chlorochromate.

kinetic enolate and subsequent allylation provided the α,α′-dialkylated ketone **91** in 75% yield and 5:1 d.r. A key ring-closing metathesis event was achieved by treatment of **91** with the Grubbs–Hoveyda second-generation catalyst (**92**),[43] thus efficiently forging the necessary eight-membered ring in 83% yield. Hydroboration/oxidation of bicyclic alkene **93** led to a mixture of the diketones **94** (28% yield) and **95** (41% yield).

With isomeric diketones in hand, two transannular cyclization strategies provided rapid access to the presilphiperfolanol core by construction of the key C4–C8 bond (Scheme 16). The first strategy toward the tricyclic architecture employed **94** in a reductive coupling strategy. The application of McMurry conditions[44] provided the desired tetrasubstituted alkene **96** in 68% yield. The second strategy, which alternatively employed **95**, relied on an intramolecular aldol reaction to forge the same fully substituted C=C bond. Addition of the bicyclic compound to a solution of KO*t*Bu in *t*BuOH provided the enone **97** in excellent yield. Subsequent reductive deoxygenation using the Gribble protocol[45] provided **96** in 27% yield. Notably, the two routes provided efficient access to the tricyclic olefin core in seven or eight steps without the use of protecting groups. The all-carbon quaternary center at C4 and tertiary hydroxy group at C8 still must be installed in a stereoselective manner to advance **96** to (−)-presilphiperfolan-8α-ol [(−)-**1**].



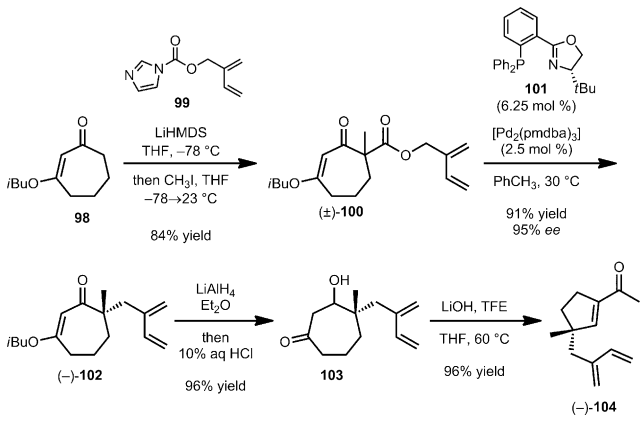
Scheme 16. Conversion of the diketones **94** and **95** into the tricyclic core **96**.

2.5. Stoltz Total Synthesis of (−)-Presilphiperfolan-1β-ol [(−)-3]

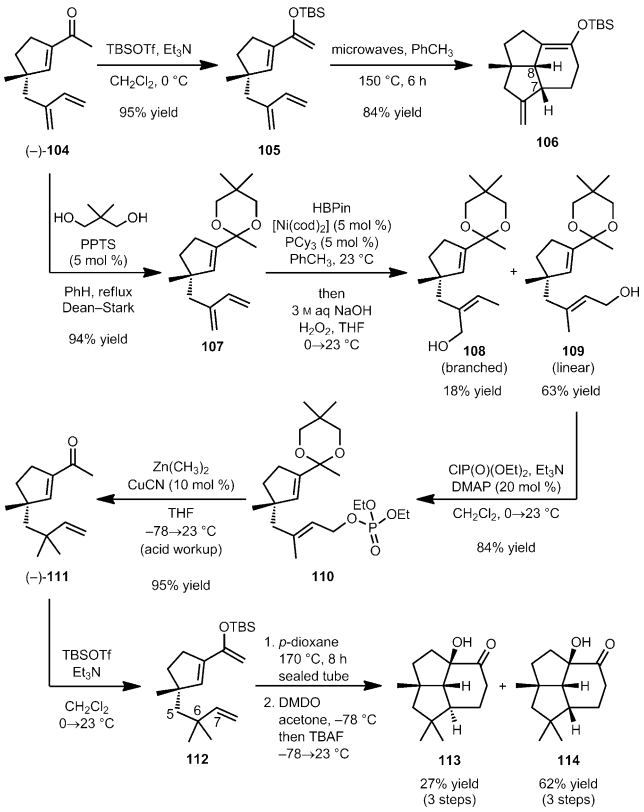
Motivated by the presilphiperfolanols' important role in sesquiterpene biosynthesis and the unique challenges posed by their strained, stereochemically dense architectures, the group of Stoltz initiated studies toward the total synthesis[46] of (−)-**3**[3,4] and (−)-**4** with the goal of developing a catalytic, asymmetric route. The application of an intramolecular Diels–Alder (IMDA) strategy was a key component of the overall strategy. At the outset of their investigations, the discrepancy of the structural assignments of "presilphiperfolan-1-ol" [(−)-**4**] and "9-*epi*-presilphiperfolan-1-ol" [(−)-**3**] was unknown (Figure 2), so synthetic efforts were directed toward both reported presilphiperfolanol compounds.[3,4]

The commercial vinylogous ester **98** was treated with the carbamate **99** with subsequent addition of CH_3I, which gave rise to the racemic α-quaternary β-ketoester (±)-**100** in 84% yield (Scheme 17). With the requisite isoprenyl fragment in place, the application of the group's previously developed palladium-catalyzed asymmetric allylic alkylation methodology,[47,48] with $[Pd_2(pmdba)_3]$ and (*S*)-*t*Bu-PHOX (**101**), smoothly provided the enantioenriched vinylogous ester (−)-**102** in 91% yield and 95% *ee*. Conversion of the compound into the acylcyclopentene (−)-**104** was achieved by employing a recently developed two-carbon ring contraction sequence.[49] Treatment of (−)-**102** with $LiAlH_4$ in Et_2O and the resulting acid workup provided the intermediate β-hydroxyketone **103**, which undergoes retro-aldol fragmentation and aldol cyclization in the presence of LiOH and TFE in THF at 60 °C. In this manner, (−)-**104** was obtained in 92% yield over two steps.

With the key all-carbon quaternary stereocenter of the target installed, the planned IMDA bicyclization was evaluated (Scheme 18). Silylation of (−)-**104** and heating in the presence of microwave irradiation led to the exclusive



Scheme 17. Construction of the enantioenriched acylcyclopentene **104**. LiHMDS = lithium bis(trimethylsilyl)amide, pmdba = 4,4′-methoxybenzylideneacetone, TFE = 2,2,2-trifluoroethanol.



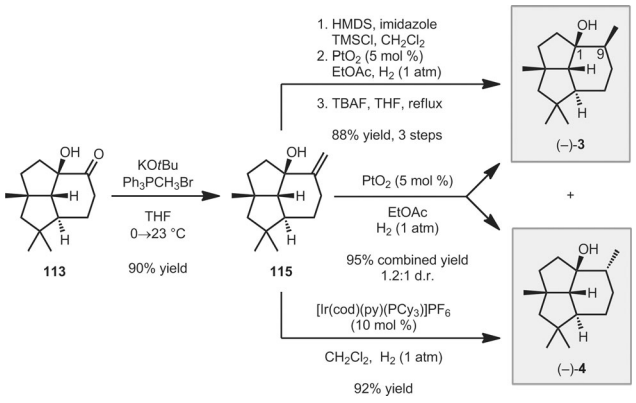
Scheme 18. Investigation of IMDA bicyclizations with **104** and **111**. cod = 1,5-cyclooctadiene, DMAP = 4-(dimethylamino)pyridine, DMDO = dimethyldioxirane, HBPin = pinacolborane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane), PPTS = pyridinium *p*-toluenesulfonate, PCy_3 = tricyclohexylphosphine, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

formation of the undesired tricyclic silyl enol ether **106** without any trace of the desired product containing the α-oriented C–H methine hydrogen atom at C7. Based on these results, modification of the IMDA strategy was necessary to complete the synthesis of (−)-**3**.

Subsequent efforts focused on the construction of the acylcyclopentene (−)-**111**, a compound having the *gem*-dimethyl substituents at C6, as an alternative IMDA precursor (Scheme 18). Following ketal formation, nickel-catalyzed regioselective 1,4-hydroboration/oxidation[50] of the

diene **107** provided the allylic alcohols **108** and **109** in 81% combined yield and a 1:3.5 ratio favoring the desired isomer. Phosphorylation and copper-catalyzed allylic substitution followed by acid workup led to (−)-**111**. Silylation and heating produced a mixture of intermediate tricyclic silyl enol ethers. Treatment of these compounds with DMDO led to diastereoselective epoxidation, thus providing the α-hydroxyketone **113** in 27% yield and α-hydroxyketone **114** in 62% yield.

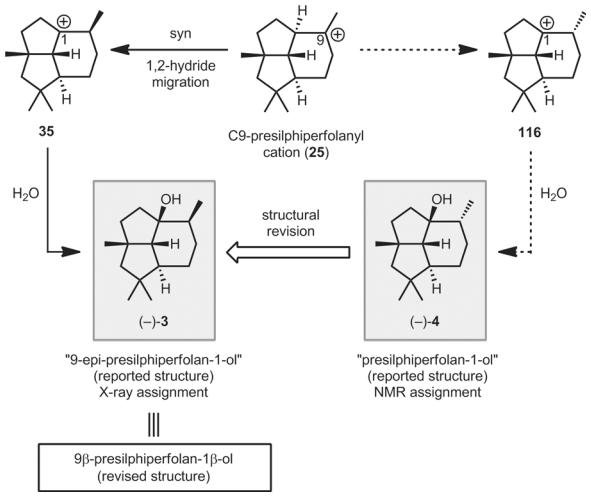
Methylenation of **113** using Wittig conditions led to the formation of the tricyclic alkene **115** in 90% yield (Scheme 19). Hydrogenation using Adams' catalyst provided a separable mixture of (−)-**3** and (−)-**4** in 95% combined



Scheme 19. Completion of (−)-presilphiperfolan-1β-ol [(−)-**3**] and synthesis of (−)-**4**.

yield and 1.2:1 d.r. Diastereoselective formation of (−)-**3** could be achieved by employing a bulky trimethylsilyl group on the C1 hydroxy group, while preferential formation of (−)-**4** could be achieved by using the sterically sensitive Crabtree catalyst. The total synthesis of (−)-**3** was completed in 15 steps and 7.9% overall yield while (−)-**4** was completed in 13 steps and 8.3% overall yield.[46]

Upon completion of the synthesis of (−)-**3** and (−)-**4**, subsequent comparison of spectral data for the synthetic presilphiperfolanols and the reported natural products led to unanticipated findings, which prompted structural reevaluation and a new biosynthetic proposal. While the synthetic sample of (−)-**3** matched literature reports,[4] synthetic (−)-**4** clearly showed significant discrepancies with reported ^{1}H and ^{13}C NMR spectra.[3] To explain these results, the Stoltz research group examined possible biosynthetic routes toward (−)-**3** and (−)-**4** (Scheme 20). In accordance with previous biosynthetic proposals,[1,2,5,7,13–15,17,19,20] **21** can undergo polycyclization and rearrangement to **25** (Schemes 1–4). A *syn* 1,2-hydride migration provided a reasonable path to (−)-**3** (Scheme 20), but the formation of (−)-**4** through similar hydride shifts was difficult to rationalize. Thus, inspection of the likely biosynthetic pathway in conjunction with spectroscopic data for the synthetic compounds suggested that the true structure of (−)-presilphiperfolan-1β-ol is (−)-**3** while (−)-**4** currently does not correspond to a known natural product.[46]



Scheme 20. Proposed biosynthesis of (−)-**3** and structural revision of the reported (−)-**4**.

3. Conclusion

The presilphiperfolanol terpenoids have been studied intensely in natural products, biosynthesis, computational, and fragrance chemistry research, but reports documenting synthetic efforts toward these molecules have been relatively scarce. Early studies of the biomimetic rearrangement of β-caryophyllene, isocaryophyllene, and their derivatives have provided structures resembling the presilphiperfolanol natural products. More recent work by several research groups has provided unique strategies for accessing the strained tricyclic presilphiperfolanol core through total synthesis. To date, (±)-**2**[2] has been prepared in racemic form and (−)-**3**[3,4] has been prepared in enantioenriched form, but (−)-**1**[1] has remained elusive to total synthesis.

Understanding of the biosynthetic relationships between presilphiperfolanes and related sesquiterpenes continues to grow and synthetic chemistry has made contributions in this area by not only providing access to members of the natural product family, but by also suggesting new biosynthetic rearrangement pathways. Much remains to be learned about the biosynthetic rearrangement pathways connecting the strained, high-energy structures of the presilphiperfolanols to diverse sesquiterpene natural products, and chemical synthesis can greatly aid these research efforts.

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