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Prediction of a New Pathway to Presilphiperfolanol

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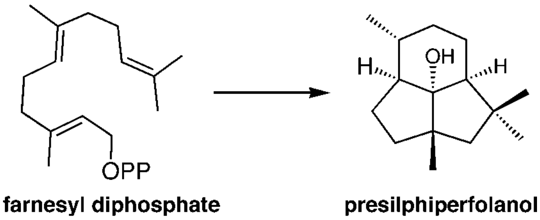
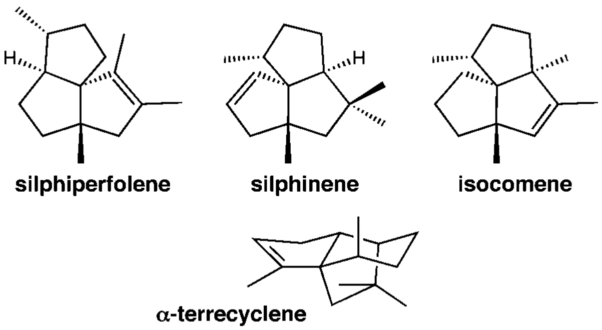
ABSTRACT



Quantum chemical calculations on the conversion of farnesyl diphosphate to presilphiperfolanol are described. On the basis of the results of this theoretical study, we predict a new mechanism for presilphiperfolanol formation that involves the intermediacy of nerolidyl diphosphate and an unusual reaction step in which a 1,2-alkyl shift and a transannular alkene attack are combined into a concerted process.

Presilphiperfolanol (abstract graphic and Scheme 1),[1] a sesquiterpene alcohol, occupies an interesting position in the intertwining biosynthetic pathways leading to sesquiterpene-derived natural products.[2] Presumably, this alcohol results from trapping the presilphiperfolanyl ion (**F**; Scheme 1) by water. Carbocation **F** is thought to be the precursor of a variety of sesquiterpene natural products, including the angular triquinanes silphiperfolene, silphinene, and isocomene,[1] which are some of the most stereodense sesquiterpenes known, each containing four contiguous stereogenic centers, two or three of which are quaternary all-carbon centers.[3] Rearrangement of the immediate precursor cation to silphinene also leads to the bridged polycycle α-terrecyclene.[1]



Presilphiperfolanol is produced from the universal sesquiterpene precursor farnesyl diphosphate (**FPP**, Scheme 1, box).[1,2] A reasonable mechanism for the **FPP**-to-presilphiperfolanol rearrangement is shown in Scheme 1 (center row to bottom row). This mechanistic scheme is representative of the sorts of mechanistic proposals found in the literature.[1] In particular, the intermediacy of the caryophyllenyl cation (**C**) has frequently been emphasized, but exactly how this carbocation is produced is not fully understood,[4] nor are the details of the interconversion of cation **C** to presilphiperfolanyl cation **F**. For example, whether or not the conversion

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(1) Isolation: (a) Bohlmann, F.; Zdero, C.; Jakupovic, J.; Robinson, H.; King, R. M. *Phytochemistry* **1981**, *20*, 2239−2244. Stereochemistry and mechanistic proposals: (b) Coates, R. M.; Ho, Z.; Klobus, M.; Wilson, S. R. *J. Am. Chem. Soc.* **1996**, *118*, 9249−9254, and references therein; (correction) *J. Am. Chem. Soc.* **1996**, *118*, 13117.

(2) Leading references on carbocation rearrangements in terpene biosynthesis: (a) Christianson, D. W. *Curr. Opin. Chem. Biol.* **2008**, *12*, 141–150. (b) Christianson, D. W. *Chem. Rev.* **2006**, *106*, 3412–3442. (c) Davis, E. M.; Croteau, R. *Top. Curr. Chem.* **2000**, *209*, 53–95. (d) Cane, D. E. *Comp. Nat. Prod. Chem.* **1999**, *2*, 155–200. (e) Cane, D. E. *Chem. Rev.* **1990**, *90*, 1089–1103.

(3) (a) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943–11948. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367. (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146.

(4) Tantillo, D. J. *J. Phys. Org. Chem.* **2008**, *21*, 561–570.

(5) Bradshaw, A. P. W.; Hanson, J. R.; Nyfeler, R.; Sadler, I. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, *n/a*, 2187–2192.

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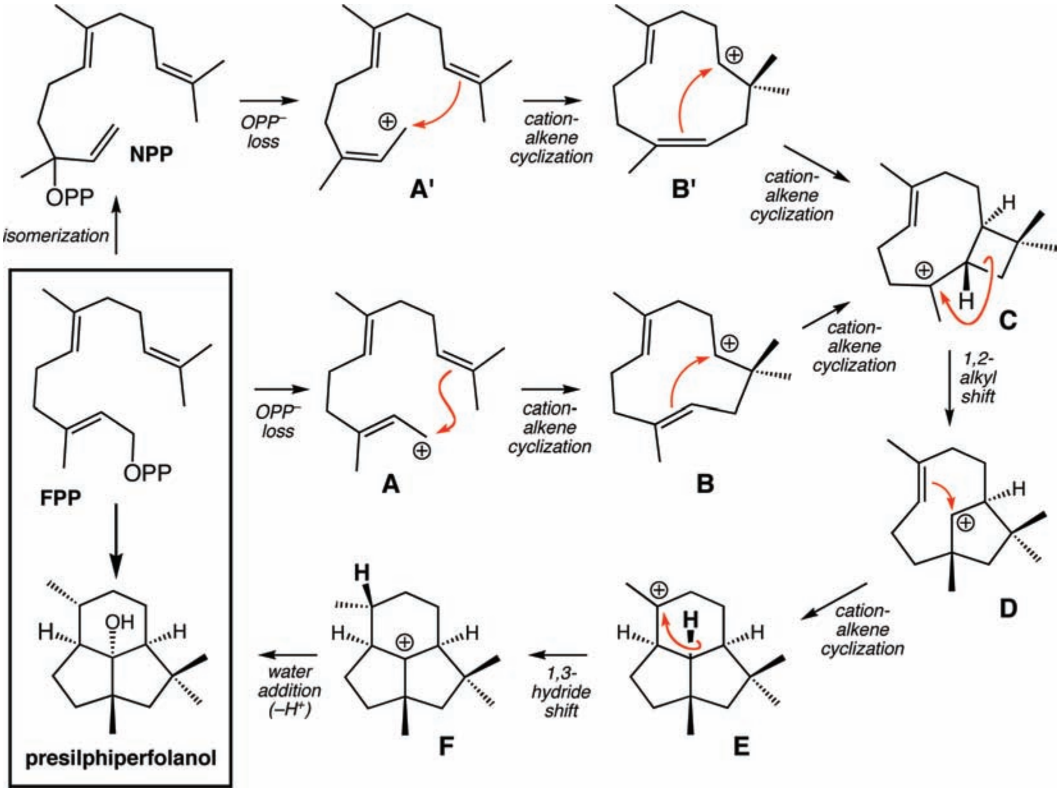
Scheme 1



of **C** to **E** is a concerted process or involves the intermediacy of a secondary carbocation is an open question. Moreover, the feasibility of the 1,3-hydride shift that converts cation **E** to cation **F** is unclear. Although experiments in which the migrating hydrogen was labeled confirm that this hydrogen ultimately ends up on the carbon shown,[5] direct transfer could be challenging for geometric reasons. Herein we describe quantum chemical calculations[6] aimed at assessing the inherent viability (i.e., in the absence of the enzyme) of the carbocation rearrangements shown in Scheme 1 and the implications of these results for the enzyme-catalyzed production of presilphiperfolanol (and the other sesquiterpenes derived from the presilphiperfolanyl ion).[7]

In principle, caryophyllenyl cation **C** could be formed directly from **FPP** (via **A** and/or **B**; Scheme 1, center) or indirectly by initial isomerization of **FPP** to nerolidyl diphosphate (**NPP**; via **A′** and/or **B′**; Scheme 1, top). Both of these pathways were explored computationally. It is unclear whether or not cations such as **A** or **A′** are actually formed as discrete intermediates in sesquiterpene synthase active sites,[8] so the remainder of our mechanistic discussion begins with cations **B** and **B′**. We were able to locate both isomeric humulyl cations **B** and **B′**, and **B** is lower in energy than **B′** by ~9 kcal/mol.[9] Ring closure to cation **C** can occur for either **B** or **B′** (with a low barrier; Figure 1), but these two reactions lead to different conformers of **C**.[10]The conformer of **C** that is productive for subsequent reactions

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(6) The *GAUSSIAN 03* program suite was used for all calculations: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, revision B.04; Gaussian, Inc.: Wallingford, CT, 2004. Geometries were optimized at the B3LYP/6-31+G(d,p) level: Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652; Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377; Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789; Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627. All structures were characterized by frequency calculations, and reported energies include zero-point energy corrections (unscaled). Single point energies for all structures were also computed at the mPW1PW91/6-31+G(d,p) level as recommended in Matsuda, S. P. T.; Wilson, W. K.; Xiong, Q. *Org. Biomol. Chem.* **2006**, *4*, 530−543. These energies include unscaled zero-point energy corrections from B3LYP/6-31+G(d,p) frequency calculations. Intrinsic reaction coordinate (IRC) calculations were used to verify the identity of transition structures: Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523−5527; Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363−368. Structural drawings were produced using *Ball & Stick*: N. Müller, N.; Falk, A. *Ball & Stick, molecular graphics application for MacOS computers*, version 3.7.6; Johannes Kepler University: Linz, Austria, 2000.

(7) This report is part 4 in our "Theoretical Studies on Farnesyl Cation Cyclization" series. For parts 1−3 and leading references to related work, see: (a) Gutta, P.; Tantillo, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 6172–6179. (b) Hong, Y. J.; Tantillo, D. J. *Org. Lett.* **2006**, *8*, 4601–4604. (c) Lodewyk, M. W.; Gutta, P.; Tantillo, D. J. *J. Org. Chem.* **2008**, *73*, 6570−6579.

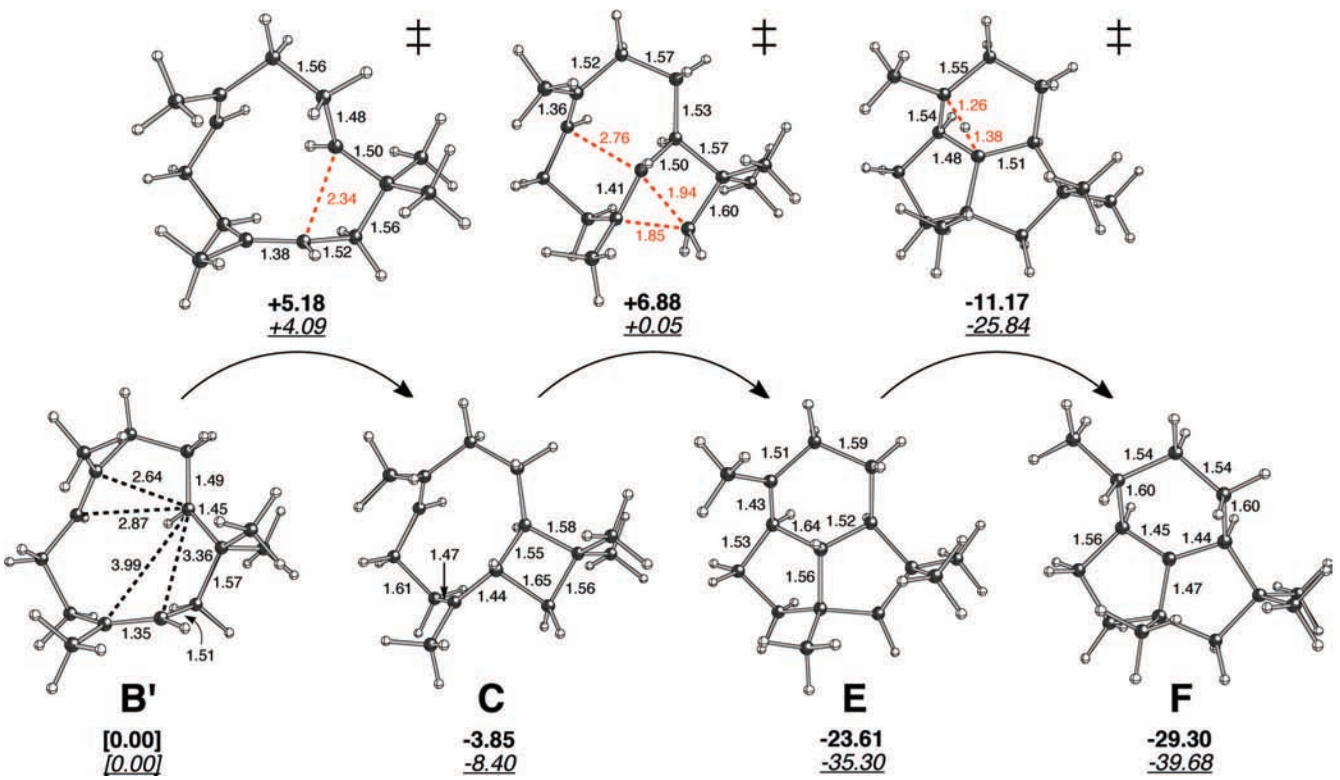

Figure 1. Predicted pathway for formation of presilphiperfolanyl cation **F**. All energies shown are relative to that of **B′** (kcal/mol; **bold**, zero point-corrected electronic energies with B3LYP/6-31+G(d,p); *underlined italics*, mPW1PW91/6-31+G(d,p)//B3LYP/6-31+G(d,p) electronic energies corrected with zero point energies from B3LYP/6-31+G(d,p)); selected distances are shown in Å.

leading to presilphiperfolanyl cation **F** is that formed directly from **B′**; this conformer, along with **B′** and the **B′**-to-**C** transition structure, are shown at the lefthand side of Figure 1; structures of **B**, the conformer of **C** that follows it, and the corresponding transition structure for ring closure can be found in the Supporting Information.[10] Thus, if the **FPP**-to-**B** pathway is followed in the enzyme, a significant conformational change would have to occur for cation **C** before the reaction cascade could continue. Even if such a conformational change does not have an inherently high barrier, the flipping over of the carbocation center that would be involved seems to us to be unlikely in the presence of an active site that conforms at all rigidly to the shape of the productive conformer of cation **C**. Thus, we propose, to our knowledge for the first time, that enzymatic production of presilphiperfolanol and other sesquiterpenes derived from the presilphiperfolanyl cation, likely involves the intermediacy of **NPP**.

Conversion of cation **C** to presilphiperfolanyl cation **F** likely involves cation **D** and/or cation **E**. We searched for both of these cations, but were only able to locate **E** as a minimum. Interestingly, we were able to locate a transition structure that connects cations **C** and **E** directly (Figure 1, center), thereby providing a reaction manifold that avoids formation of secondary cation **D**.[11,12] In this transition structure, the 1,2-alkyl shift and alkene attack occur not only in a concerted process, but with a substantial degree of synchrony.[4] Moreover, the barrier for this process is not predicted to be at all prohibitive (~8 to 11 kcal/mol from

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(8) In our studies of various sesquiterpene-forming reactions, we have located open farnesyl and nerolidyl cations as minima for some conformations, but not others;[7] further details will be reported in due course. For the system described herein, a productive conformer of **A** was located that is 4.5 kcal/mol lower in energy than **B′** (Figure 1) at the B3LYP/6-31+G(d,p) level (see Supporting Information for details), but attempts to find a productive conformer of **A′** led to structures with six-membered rings. We are not comfortable speculating as to whether or not cations such as **A** and **A′** are formed as intermediates in terpene synthase active sites at this time, since these cations would be formed in the mechanistic step where pyrophosphate departs and is therefore close in space to the putative carbocation center that is generated. These cations are therefore most likely to be influenced by the departed pyrophosphate group that is not included in the models reported herein.

(9) At the B3LYP/6-31+G(d,p) level. This comparison is based on the conformers of **B** and **B′** that are productive for ring closure to form **C**. A detailed study on the various conformers available to humulyl cations and their interconversions will be described in due course. Humulyl cation conformer **B** was also discussed in ref 7a.

(10) The barrier for ring closure of **B** is computed to be 2.2 kcal/mol and the conformer of **C** that is formed is 3.9 kcal/mol lower in energy than that shown in Figure 1 (at the B3LYP/6-31+G(d,p) level). The transition structure for this reaction is also earlier than that for **B′**; see the Supporting Information and refs 4 and 7a for details and additional discussion.

(11) For other examples of complex concerted rearrangements that may avoid possible secondary carbocation intermediates, see refs 4, 7b and 7c.

(12) A similar transformation has been proposed previously for a nonbiological process; see: Koizumi, T; Harada, K.; Mochizuki, E.; Kokubo, K.; Oshima, T. *Org. Lett.* **2004**, *6*, 4081−4084 and Wang, S. C.; Tantillo, D. J. *J. Org. Chem.* **2007**, *72*, 8394–8401.

C; Figure 1). Note that the C−C bond that breaks during the migration is elongated in **C** due to hyperconjugation. To our knowledge, the concerted conversion of **C** to **E** by such a transition structure has not been previously proposed.

As described above, conversion of cation **E** to cation **F** has been proposed to occur by a direct 1,3-hydride shift (Scheme 1). Our calculations suggest that such a process is indeed energetically feasible, having a predicted barrier from **E** of ∼9 to 13 kcal/mol (Figure 1). This barrier is comparable to that reported previously for the degenerate 1,3-hydride shift of the 2,4-dimethyl-2-pentyl cation,[13] and we do not observe any unusual geometric parameters that would indicate that the transition structure for the **E**-to-**F** hydride shift is significantly more strained than those in simpler systems.

Thus, we propose that production of the presilphiperfolanyl cation **F** likely proceeds via cations **B′**, **C**, **E**, and **F**. Although the magnitude of the exothermicity associated with the interconversion of some of these cations varies significantly (but predictably[6]) depending on the level of theory used for energy calculations, the qualitative conclusions of our study do not: (1) the **B′**-to-**F** cascade that we propose is significantly exothermic overall (due, in large part, to the conversion of two π bonds to two new σ-bonds); (2) isomerization of **FPP** to **NPP** is likely; (3) conversion of **C** to **E** is concerted; (4) direct 1,3-hydride transfer is energetically feasible. These conclusions are consistent with all known experiments on this rearrangement, and we look forward to additional experiments that will provide further tests of our mechanistic proposal.[14]

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Supporting Information Available: Coordinates and energies for all structures and additional details on calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] This value is 8.5 kcal/mol based on experiment and ∼3 to 11 kcal/mol based on quantum chemical calculations at various levels of theory, some of which suggest that an extremely shallow symmetrically bridged minimum occurs along the reaction coordinate; for leading references, see: Vrcek, I. V.; Vrcek, V.; Siehl, H.-U. *J. Phys. Chem. A* **2002**, *106*, 1604–1611. Note that two consecutive 1,2-hydride shifts would, here, lead to a diastereomer of cation **F**.

[14] Theoretical studies on subsequent rearrangements of the presilphiperfolanyl cation are ongoing and will be reported in due course.