Solvolysis of Caryophyllen-8*β*-yl Derivatives: Biomimetic Rearrangement−Cyclization to 12-Nor-8α-presilphiperfolan-9*β*-ol

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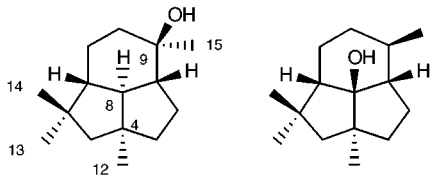
The solvolyses of caryophyllen-8*β*-yl *p*-nitrobenzoate (**14**-O*p*NB) and 15-norcaryophyllen-8*β*-yl tosylate (**15**-OTs) were investigated as potential model reactions for the biogenesis of the tricyclic presilphiperfolanol sesquiterpenes. Buffered solvolysis of **14**-O*p*NB in 60% aqueous acetone at 125 °C afforded caryophyllene (**3**) as major product, accompanied by small amounts of caryophyllen-8*β*-ol (**14**-OH) and 5,8-cyclocaryophyllen-4α-ol (**16**). In contrast, **15**-OTs underwent a stereospecific rearrangement−cyclization to 12-nor-8α-presilphiperfolan-9*β*-ol (**17**) upon solvolysis in 60% aqueous acetone at 75 °C. The structure and stereochemistry of this *trans*,*cis*,*trans*-tricyclo[6.2.1.$0^{5,11}$]-undecane derivative were established by NMR correlation spectroscopy and X-ray crystallography. Two different mechanisms (paths A and B) for the conversion of **15**-OTs to **17** by initial 1,2-migration of either the external or internal cyclobutane ring bonds (C10 and C1) followed by $\pi-\sigma$ cyclization onto the trans double bond are discussed.

Introduction

The presilphiperfolanol isomers **1** and **2** (Chart 1) are novel sesquiterpene alcohols that have in common the unusual tricyclo[6.2.1.$0^{5,11}$]undecane skeleton with trans, cis,trans and cis,trans,cis ring fusion stereochemistry, respectively. Presilphiperfolan-8*β*-ol (**2**) was isolated first from *Eriophyllum staechadifolia* and *Fluorensia heterolepis* by F. Bohlmann and associates in 1981,[1] and subsequently the natural product as well as its oxidative metabolites were found in other plant sources.[2] The structure and absolute configuration were recently confirmed in these laboratories by X-ray crystallography and chemical correlation.[3]

8α-Presilphiperfolan-9*β*-ol (**1**, Chart 1), which differs in stereochemistry at C8 and the position of the tertiary hydroxyl group, occurs in the essential oil of *Artemesia lacinata* Willd.[4] and *Artemesia chamaemelifolia*,[5] and its structure was confirmed by total synthesis of (±)-**2**.[4] These natural products can be regarded as trail markers along the pathway from (−)-*β*-caryophyllene (**3**) to the triquinane sesquiterpenes silphinene and silphiperfolene, a biogenetic relationship proposed by Bohlmann in 1980 (Scheme 1).[1,6,7] Chemically precedented hydride shift, methyl migrations, and Wagner−Meerwein rearrangements generate connections to the isocomene, modhephene, and terrecyclene sesquiterpene families.[3,8,9]

Chart 1



1 **2**

Concurrent investigations on the biosynthesis of dihydrobotrydial in *Botrytis cinerea* cultures[10] led Hanson to propose the same rearrangement−cyclization mechanism to produce **2** as an intermediate which undergoes oxidative metabolism to this sesquiterpene antibiotic. Furthermore, incorporation of [4-$^{2}H_2$,4-^{13}C]mevalonate into dihydrobotrydial and ^{2}H NMR analysis provided evidence for the occurrence of a 1,3-hydride shift from C9 to C8 and ruled out the plausible alternative of two consecutive 1,2-hydride shifts.

The key initiating step in the Bohlmann−Hanson biogenetic pathway to **2** is the cyclobutylcarbinyl ring expansion of the caryophyllen-8-yl ion (**4**) which gener-

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(1) Bohlmann, F.; Zdero, C.; Jakupovic, J.; Robinson, H.; King, R. M. *Phytochemistry* **1981**, *20*, 2239.

(2) (a) Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H. *Phytochemistry* **1981**, *20*, 2425. (b) Bohlmann, F.; Zdero, C. *Phytochemistry* **1981**, *20*, 2529. (c) Bohlmann, F.; Singh, P.; Jakupovic, J. *Phytochemistry* **1982**, *21*, 157. For oxidized derivatives of **2**, see: (d) Bohlmann, F.; Ziesche, J.; Gupta, R. K. *Phytochemistry* **1982**, *21*, 1331. (e) Bohlmann, F.; Zdero, C. *Phytochemistry* **1982**, *21*, 2537. (f) Zdero, C.; Bohlmann, F.; King, R. M.; Haegi, L. *Phytochemistry* **1990**, *29*, 509. (g) Weyerstahl, P.; Marshall, H.; Seelman, I.; Jakupovic, J. *Eur. J. Org. Chem.* **1998**, 1205.

(3) Coates, R. M.; Ho, Z.; Klobus, M.; Wilson, S. R. *J. Am. Chem. Soc.* **1996**, *118*, 9249.

(4) Weyerstahl, P.; Marschall, H.; Schulze, M.; Schwope, I. *Liebigs Ann. Chem.* **1996**, 799.

(5) Marco, J. A.; Sanz-Cervera, J. F.; Morante, M. D.; Garcia-Lliso, V.; Vallés-Xirau, J.; Jakupovic, J. *Phytochemistry* **1996**, *41*, 837.

(6) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259.

(7) Caryophyllene and its relatives are named and numbered in this paper by standard semisystematic nomenclature[7a] as derivatives of the parent sesquiterpene hydrocarbon.[7b,c] Semisystematic names and consistent positional numbers based on the presilphiperfolanol sesquiterpenes are used in most cases for related tricyclic structures.[1,7b,c] Inevitably some structures in the same scheme (e.g. Scheme 1) may show these two different numbering conventions: (a) *IUPAC Nomenclature of Organic Chemistry*; Pergamon Press: Oxford, 1979; p 491. (b) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall: London, 1991. (c) *Dictionary of Natural Products*; Chapman and Hall: London, 1995.

(8) (a) Fitjer, L.; Monzó-Oltra, H. *J. Org. Chem.* **1993**, *58*, 6171. (b) Fitjer, L.; Majewski, M.; Monzó-Oltra, H. *Tetrahedron* **1995**, *51*, 8835.

(9) (a) Klobus, M.; Zhu, L.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 4327. (b) Coates, R. M.; Ho, J. Z.; Klobus, M.; Zhu, L. *J. Org. Chem.* **1998**, *63*, 9166.

(10) (a) Hanson, J. R. *Pure Appl. Chem.* **1981**, *53*, 1155. (b) Bradshaw, A. P. W.; Hanson, J. R.; Nyfeler, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1469. (c) Bradshaw, A. P. W.; Hanson, J. R.; Nyfeler, R.; Sadler, I. H. *J. Chem. Soc., Perkin Trans. I* **1982**, 2187.

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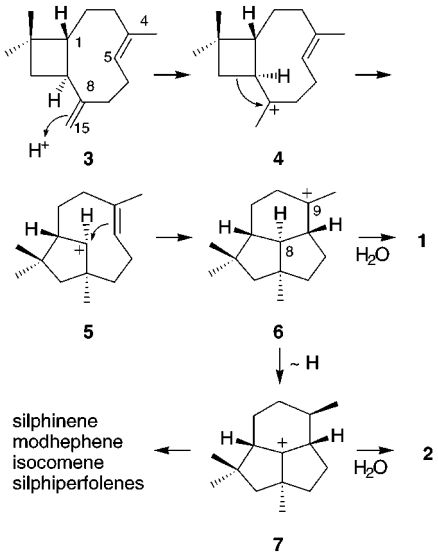
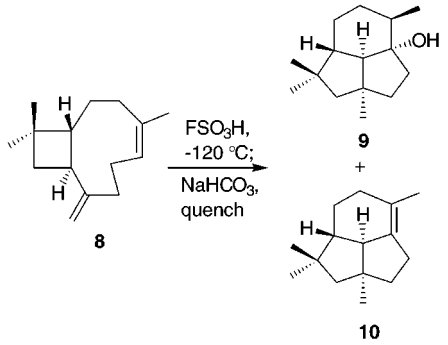
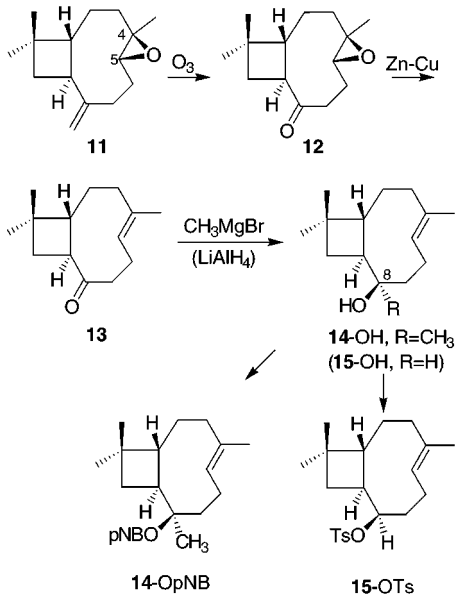
Scheme 1



Scheme 2



Scheme 3



ates the seemingly strained secondary cyclopentyl ion (**5**) bridged 1,3-trans by the (3*E*)-hexenyl chain. Although the acid-catalyzed and electrophile-induced reactions of caryophyllene have been extensively investigated,[11] most products arise by initial attack on the strained endocyclic double bond. Three examples are the complex cyclization−rearrangement processes leading to β-caryolanol,[12] clovene,[12] and neoclovene.[13] However, a recent reinvestigation of the caryophyllene rearrangements in H_2SO_4−ether with HPLC time-course analysis[14] demonstrated the occurrence of protonation at the exocyclic methylene group and cyclization to 5,8-cyclocaryophyllenes, structurally related to, but doubly epimeric with the natural sesquiterpene koraiol.[15] Cyclobutylcarbinyl to cyclopentyl rearrangements and cyclizations similar to those shown in Scheme 1 evidently occur in reactions of the cis endocyclic double bond isomer isocaryophyllene (**8**) with H_2SO_4 in ether,[16] under superacid conditions (FSO_3H, FSO_2Cl, −120 °C) (Scheme 2)[17] and with $FeCl_3$ on silica gel.[18]

The purpose of the present research was to determine the products formed from caryophyllen-8-yl (**4**) and 15-norcaryophyllen-8-yl carbocations having the natural (4*E*) double bonds in kinetically controlled solvolysis reactions. We have found that, while caryophyllen-8-yl *p*-nitrobenzoate (**14**-O*p*NB) undergoes primarily solvolytic elimination to β-caryophyllene, solvolysis of norcaryophyllen-8-yl tosylate (**15**-OTs) leads to efficient ring expansion and cyclization to 12-nor-8α-presilphiperfolan-9β-ol (**17**).

Synthesis and Stereochemistry of Caryophyllene Derivatives. Caryophyllen-8β-ol (**14**-OH)[19] and the previously unknown secondary alcohol 15-norcaryophyllen-8β-ol (**15**-OH) were prepared by addition of CH_3MgBr to 15-norcaryophyllen-8-one (**13**) and by $LiAlH_4$ reduction of this ketone by modified versions of the literature procedures (Scheme 3).[19,20] Ozonolysis of caryophyllene 4β,5β-epoxide (caryophyllene α-oxide, **11**) using Zn dust in aqueous acetic acid to reduce the ozonide afforded kobusone (**12**)[20] in 76% yield as a single stereoisomer. Reductive de-oxygenation to the 15-norketone **13** was accomplished in 85% yield by heating with Zn−Cu couple[19,21] in refluxing EtOH. Retention of the trans double bond configuration was verified by epoxidation (*m*CPBA, ether, NaOAc, rt) back to **12**.

Reaction of **13** with CH_3MgBr in ether at 0 °C afforded caryophyllen-8β-ol (**14**-OH) as a single isomer.[19] The

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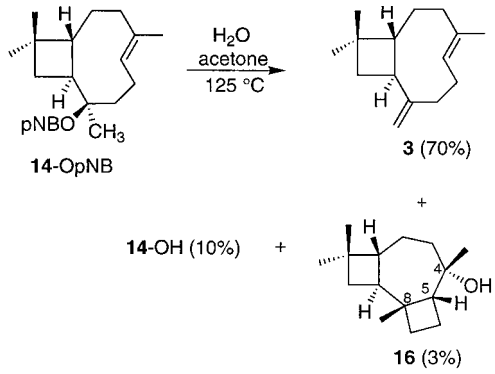
(21) (a) Kupchan, S. M.; Maruyama, M. *J. Org. Chem.* **1971**, *36*, 1187. (b) LeGoff, E. *J. Org. Chem.* **1964**, *29*, 2048.

Scheme 4

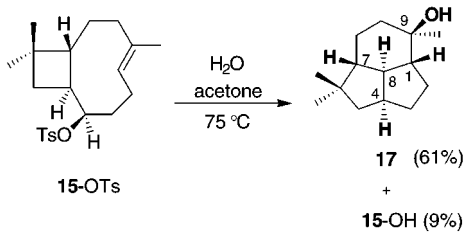


appearance of two sets of peaks for the methyl groups and vinyl proton (87:13 ratio) in the ^{1}H NMR spectrum and similar doubling of ^{13}C NMR signals is attributed to the presence of two slowly interconverting conformers. This phenomenon is precedented by the conformational behavior of caryophyllene itself,[22] and the stereochemical homogeneity of **14**-OH was supported by variable temperature ^{1}H NMR spectra (−80 to +100 °C). Assignment of the 8R (β-OH) stereochemistry to **14**-OH relies upon chemical correlations with caryophyllene 4β,8β-oxide (structure not shown).[19,23−25]

Reduction of **13** with $LiAlH_4$ in ether gave 15-norcaryophyllen-8β-ol (**15**-OH) the NMR spectra of which also showed line broadening indicative of conformational isomers. Conversion of the tertiary and secondary alcohols to the respective crystalline *p*-nitrobenzoate (**14**-O*p*NB, 62%) and tosylate derivatives (**15**-OTs, 83%) was best accomplished by lithiation with *n*BuLi or *t*BuLi in THF,[26] followed by reaction with *p*-nitrobenzoyl and tosyl chlorides. The 8β-configuration of **15**-OTs was established independently by an X-ray crystallographic determination (see Supporting Information).

Solvolysis of 14-OpNB and 15-OTs. Solvolysis of **14**-OpNB in 60% aqueous acetone in the presence of 3 equiv of pyridine at 125 °C for 3−4 half-lives afforded primarily caryophyllene (**3**, 70%), accompanied by smaller amounts of two tertiary alcohols, **14**-OH (10%) and the known 5,8-cyclocaryophyllen-4α-ol[14,27] (**16**, 3%; Scheme 4). Although the tricyclic alcohol was not isolated in pure state (~85% purity), its identity was securely established by ^{1}H and ^{13}C NMR spectral comparisons. The structure and stereochemistry of **16** are based upon an X-ray crystallographic analysis.[14] Several other minor alcohol products (1−3% each) were not isolated in sufficient purity or amounts to permit their identification.

Scheme 5



Buffered solvolysis of **15**-OTs in 60% aqueous acetone at 75 °C in a similar manner gave rise mainly to two alcohol products, **15**-OH (9%) and a crystalline tricyclic alcohol (**17**, mp 88−89 °C, 61%; Scheme 5). The 500 MHz ^{1}H NMR spectrum (C_6D_6) of the major product shows three singlets for the CH_3 groups (δ 1.24, 0.98, 0.81) and no peaks having chemical shifts $\delta > 1.98$, indicating the absence of carbinyl and vinyl protons. A signal at δ 76.2 ppm in the ^{13}C NMR spectrum and a weak band at ν_{max} 3610 cm^{-1} in the IR spectrum confirmed the presence of a tertiary OH group. The absence of signals from olefinic carbons in the ^{13}C NMR spectrum together with the identification of 4 CHs, 5 CH_2s, and 2 quaternary Cs from a DEPT 135 plot proved that the compound is a tricyclic tertiary alcohol.

Tricyclo[6.2.1.0^{5,11}]undecanol **17** and 15-nor-5,8-cyclocarophyllan-9-ol (**16** lacking the quaternary CH_3 at C8) which differ in the connectivity of the methine carbons [$CH(CH)_3$ vs $(CH)_4$] were considered as plausible candidate structures. The absence of four contiguous methine carbons was inferred from homonuclear and heteronuclear correlation NMR spectra. On the other hand, the presence of the $CH(CH)_3$ core was apparent from the HMBC and HMQC spectra in accord with **17**. The structure and stereochemistry of the compound as *trans,cis,trans*-(1β,4α,7β,8α)-4,10,10-trimethyltricyclo-[6.2.1.0^{5,11}]undecan-4β-ol or 12-nor-8α-presilphiperfolan-9β-ol (**17**) were ultimately proven by single-crystal X-ray diffraction analysis.

The SHELXTL plot (Figure 1) shows the chair conformation of the six-membered ring, the equatorial disposition of the tertiary OH group, and the crownlike confor-

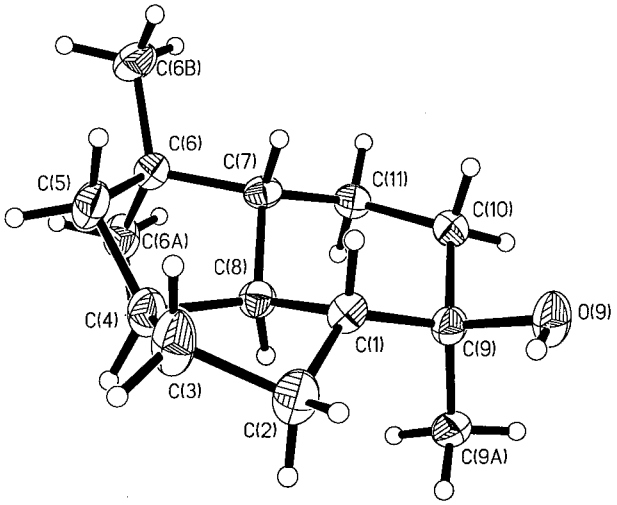


Figure 1. SHELXTL plot from X-ray diffraction analysis of tricyclic alcohol **17** from solvolysis of **15**-OTs showing 35% probability ellipsoids for non-H atoms and circles of arbitrary size for H atoms. The 1997 SHELXTL software package from Bruker AXS, Inc. (Madison, WI) was used.

(22) (a) Shirahama, M.; Osawa, E.; Chhabara, B. R.; Shimokawa, T.; Yokono, T.; Kanaiwa, T.; Amiya, T.; Matsumoto, T. *Tetrahedron Lett.* **1981**, *22*, 1527. (b) Guella, G.; Chiasera, G.; N'Diaye, I.; Pietra, F. *Helv. Chem. Acta* **1994**, *77*, 1203.

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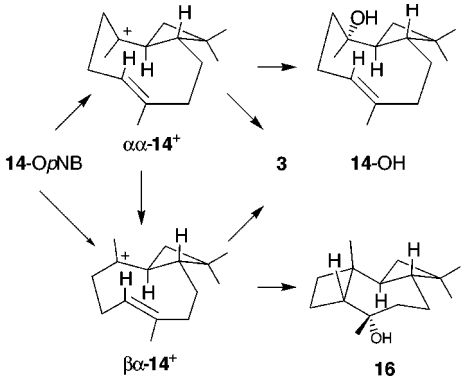
(25) Oxymercurations of **14**-OH[19] and 4,5-dihydrocaryophyllen-4β-ol[23] give rise to the same bridged ether, caryophyllene 4β,8β-oxide. The 4β,8β-configuration of the oxygen bridge follows from the X-ray crystal structure determination of caryophyllene 4β,5β-epoxide (**11**)[24] and its reduction with lithium ethylenediamine to 4,5-dihydrocaryophyllen-4β-ol.[23]

(26) Kaiser, E. M.; Woodruff, R. A. *J. Org. Chem.* **1970**, *35*, 1198.

(27) Tkachev, A. V. *Zh. Org. Khim.* **1990**, *26*, 1706; *Russ. J. Org. Chem. (Engl. Transl.)* **1990**, *26*, 1476.

Scheme 6

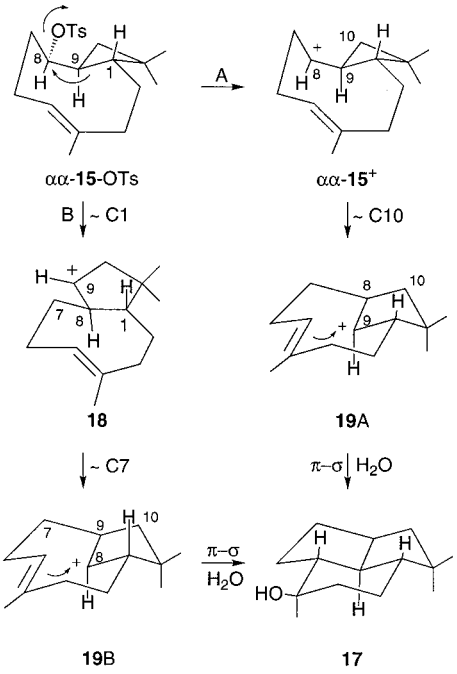


mation of the *cis*-bicyclo[3.3.0]octane moiety. The considerable distortion of several C−C−C bond angles no doubt reflects the strain associated with the trans,cis,trans ring fusions joining the five- and six-membered rings, a stereochemical arrangement estimated to be 2.4 kcal/mol more strained than the cis,trans,cis alternative in the parent tricyclo[6.2.1.0^{5,11}]undecane hydrocarbons.[28] Thus, the three bond angles exocyclic to the peripheral methines—C3−C4−C5 (122.8°), C2−C1−C9 (129.0°), and C6−C7−C11 (128.7°)—are substantially enlarged, whereas the two internal five-membered bond angles at the peaks of the crown—C1−C2−C3 (100.2°) and C5−C6−C7 (98.9°)—are somewhat compressed in comparison to the normal tetrahedral value. Also noteworthy are the expanded dihedral angles within the six-membered ring at the ring junctions—C7−C8−C1−C9 (−73.9°) and C11−C7−C8−C1 (73.2°)—instead of the expected dihedral angles of ±60°.

Discussion

β-Caryophyllene (**3**), the major product arising from solvolysis of **14**-O*p*NB is probably formed by intramolecular elimination within a caryophyllenyl$^+$/OpNB$^-$ ion pair.[29,30] Exocyclic elimination may be favored because of the increased angle strain associated with the competing endocyclic elimination to an (*E*,*E*)- or (*E*,*Z*)-4,7-nonadiene. Although the possibility that caryophyllen-8*β*-ol (**14**-OH) arises by acyl-oxygen cleavage of **14**-O*p*NB cannot be excluded, the sterically crowded environment of this tertiary ester and the formation of norcaryophyllen-8*β*-ol (**15**-OH) in the solvolysis of **15**-OTs are persuasive reasons to consider a heterolytic mechanism (Scheme 6). The observed retention of configuration can be rationalized by assuming that the initially formed α,α-caryophyllen-8-yl carbocation (αα-**14**$^+$)[31] undergoes water capture on the exposed *β*-face faster than conformational inversion to the *β*α-conformer (*β*α-**14**$^+$). Rapid *π*−*σ* cyclization of *β*α-**14**$^+$ followed by inversion of the seven-membered ring to *ββ*-**16**$^+$ (not shown) and nucleophilic hydration would then give rise to 5,8-cyclocaryophyllen-5α-ol (**16**). Evidently cyclobutyl ring expansion of the short-lived caryophyllenyl carbocation does not compete with proton elimination and solvent capture in the aqueous solvolysis medium.

Scheme 7



Two distinctly different mechanisms are proposed to explain the solvolytic ring expansion and cyclization of 15-norcaryophyllen-8*β*-yl tosylate (**15**-OTs) to **17** (Scheme 7). At the outset it should be noted that a mechanism involving ring expansion of the external cyclobutyl C−C bond (C10) concerted with tosylate departure must take place with inversion at C8. This course of events can be excluded for the simple reason that it must give rise to a *trans*,*trans*,*trans*-tricyclo[6.2.1.0^{5,11}]undecanol and not the observed trans,cis,trans stereochemistry.

Path A in Scheme 7 begins with unassisted ionization of the tosylate in its α,α conformation to generate the secondary cyclobutyl carbinyl ion αα-**15**$^+$, water capture of which on the exposed *β*-face would form **15**-OH with net retention of configuration. Ring expansion of the external cyclobutyl bond (C10) to the same *β*-face of C8 would generate the trans-bridged cyclopentyl ion **19A**, which would undergo immediate *π*−*σ* cyclization and nucleophilic capture to form **17** with the observed trans, cis,trans ring juncture stereochemistry. In this case cyclobutyl carbon C9 of **15**-OTs becomes the center methine of the CH(CH)$_3$ core, and the C10 to C8 rearrangement must take place with overall retention of configuration.

In path B, a concerted, antiperiplanar migration of the internal cyclobutyl bond (C-1) would produce a trans-fused bicyclo[6.3.0]undecenyl ion intermediate **18**. The isolation of a secondary chloride corresponding to **18** with a methyl group at C8 and a cis 4,5-double bond from reaction of **14**-OH with BCl_3 provides precedent for this mode of ring expansion.[18] Migration of C7 to C9 would lead to trans-bridged cyclopentyl ion **19B** which is identical to **19A** except that the carbocation site is now derived from the carbinyl carbon (C8) of **15**-OTs. Consequently the center methine of the CH(CH)$_3$ core would originate from C8 and the *π*−*σ* cyclization necessarily

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(30) Toteva, M. M.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 11434.

(31) The αα and *β*α notations for the conformations of **14**$^+$ shown in Scheme 6 signify the disposition of the C8 and C4 methyl groups with respect to the average plane of the cyclobutane ring, and their approximate synperiplanar and periplanar relationships with the C−H bond at C9.[14,22]

occurs syn to the preceding Wagner−Meerwein rearrangement.

Pathways A and B are in principle distinguishable by isotope labeling at C8 since the label would appear at different positions in **17**. However, this evidence is not presently available. Although the formation of **15**-OH might be regarded as evidence for the intermediacy of αα-**15**$^+$ on path A, this retentive substitution might also be explained by water capture of a bridged carbonium ion precursor to **18** on path B. While the formation of one or both secondary alcohols derived from intermediate **18** might be expected if rearrangement occurred by path B, the possibility exists that they were among the minor unidentified products from the solvolysis.

The solvolytic rearrangement−cyclization of **15**-OTs to **17** is remarkable for its complexity and stereospecificity. With the exception of the missing methyl group at C4, the tricyclic alcohol product is otherwise identical to the naturally occurring 8α-presilphiperfolan-9β-ol (**1**).[4,5] This transformation is the first example of the conversion of a caryophyllene derivative having the 4,5-double bond in the natural trans configuration to a tricyclo[6.2.1.0^{5,11}]-undecane with trans,cis,trans stereochemistry. Although the ring bond that participates in the cyclobutylcarbinyl−cyclopentyl rearrangement is unknown (path A or path B), the reaction provides chemical precedent for a biogenetic connection between caryophyllene and the presilphiperfolanols **1** and **2**.[1,10]

Experimental Section

General Aspects. All anhydrous reactions were performed in glassware that was flame-dried and assembled under N_2. Anhydrous ether and THF were distilled from Na/benzophenone; anhydrous CH_2Cl_2 was distilled from CaH_2. Pyridine was distilled from KOH and stored over KOH pellets. Bulb-to-bulb distillations were performed in a Buchi Kugelrohr apparatus. Boiling points are uncorrected. Melting points were determined in capillary tubes and are uncorrected. Flash column chromatography was performed by the method of Still.[32]

4β,5β-Epoxy-15-norcaryophyllen-8-one (Kobusone, 12). Epoxy ketone **12** was synthesized by ozonolysis[20] of caryophyllene-4β,5β-oxide (**11**, 20 g, 91 mmol, 90% tech, Aldrich) in anhydrous CH_2Cl_2 (500 mL) at −70 °C followed by reduction with zinc dust (8.9 g, 136 mmol) and 50% aqueous acetic acid (250 mL), extractive workup, and recrystallization from pentane at −20 °C: yield, 15.4 g (76%), mp 62−63 °C (lit.[20a] mp 60−61 °C). The ^{1}H and ^{13}C NMR data for **12** are in good agreement with the literature values.[20b]

(*E*)-15-Norcaryophyll-4-en-8-one (13). The deoxygenation of **12** was performed by a modified literature procedure[19] with a different source of Zn−Cu couple[21b] which reduced the time and amount of Zn−Cu required. Reduction of **12** (25 g, 112.5 mmol) in EtOH (300 mL) with Zn−Cu couple (100 g, 1.5 mol) in EtOH (200 mL) at reflux under N_2 for 3 h gave 19.8 g (85%) of **13** as a colorless oil. The spectral data for the analytical sample purified by chromatography on silica gel and bulb-to-bulb distillation are consistent with the literature.[19] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.24 (1H, dd, J = 7.8, 6.5 Hz), 2.83 (1H, dt, J = 8.8, 8.5 Hz), 2.76−2.68 (2H, m), 2.49−2.36 (1H, m), 2.26−2.11 (3H, m), 2.05 (1H, dd, J = 10.7, 9.7 Hz), 1.75 (3H, s), 1.65−1.51 (5H, m), 1.01, 0.97 (2 × 3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.3, 138.10, 122.62, 52.55, 51.88, 40.73, 39.78, 35.67, 33.40, 29.28, 28.82, 23.07, 21.85, 15.90; IR (CCl_4) ν_{max} 1716, 1697 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.54; H, 10.77.

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(*E*)-Caryophyll-4-en-8β-ol (14-OH). The reaction of **13** (13.81 g, 66.9 mmol) in anhydrous Et_2O (110 mL) with 3 M ethereal CH_3MgBr (26.8 mL, 80.3 mmol) was carried out by the literature procedure.[19] Purification of the crude product (13.33 g, 85%) by flash chromatography using 15% EtOAc/hexane as eluant followed by bulb-to-bulb distillation at 102−103 °C (0.2 mmHg) provided the analytical sample. The ^{1}H and ^{13}C NMR spectra exhibited broad peaks attributable to slow interconversion of conformers. Variable temperature ^{1}H NMR spectra in toluene-d_8 (−80 to +100 °C) showed that **14**-OH exists in a conformational equilibrium. Two distinct sets of signals for the methyl groups and for the vinyl proton at 5.40 (t) and 4.98 (br d) for two conformers (87:13) were observed at −80 °C, and at +100 °C the spectrum simplified to a single set of well-resolved peaks, indicative of a pure stereoisomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.40 (1H, t, J = 7.6 Hz), 0.99 (3H, s), 0.90 (6H, s); vt NMR (toluene, 300 MHz, 100 °C) δ 5.40 (1H, t, J = 7.6 Hz), 1.82 (1H, dt, J = 12.5, 4.9 Hz), 1.67 (1H, br, s), 1.56 (3H, br, s), 0.99 (3H, s), 0.94 (6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.31, 122.07, 73.34, 51.99, 46.7, 40.93, 40.06, 37.1, 30.33, 29.69, 29.54, 23.07, 22.53, 15.93; IR (CCl_4) ν_{max} 3495, 2924, 2857, 1456, 1366 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 80.16; H, 11.87. The spectral data are consistent with the limited data available in the literature.[19]

(*E*)-Caryophyll-4-en-8-yl *p*-Nitrobenzoate (14-OpNB). The *p*-nitrobenzoylation reaction was performed by a general literature procedure.[3,26] Alcohol **14**-OH (10.4 g, 48.6 mmol) was stirred as a neat liquid under N_2 at room temperature as 1.6 M *n*-BuLi in hexane (60.7 mL, 97.1 mmol) was added. The solution was stirred for 6 h and then transferred over 30 min via a double-tipped needle into a solution of *p*-nitrobenzoyl chloride (27 g, 145.8 mmol) in anhydrous THF (136 mL) which was being stirred and cooled at 0 °C. After 20 h, excess acid chloride was removed by reaction with 3-(*N*,*N*-dimethylamino)-propylamine (15 mL, 0.15 mol) at 0 °C for 1 h, and satd NH_4-Cl (10 mL) was added. THF was evaporated and the residue was dissolved in 1:1 hexane/ether (100 mL). The organic layer was washed with 10% HCl (3 × 50 mL), satd. Na_2CO_3 (3 × 50 mL), and brine (1 × 50 mL); dried (Na_2SO_4); and concentrated to give a yellow oil (18.43 g). Purification by chromatography on silica gel with 10% EtOAc/hexane as eluant gave **14**-OpNB (10.8 g, 62%) as a viscous yellow oil, and 3.5 g of **14**-OH (ca. 90% based on ^{1}H NMR analysis) contaminated by 10% of *p*-nitrobutyrophenone. Crystallization from hexane afforded 6.15 g (35%) of **14**-O*p*NB: mp 102−103 °C (hexane); TLC R_f 0.30 (10% EtOAc/hexane). The ^{1}H and ^{13}C NMR spectra at room temperature showed line broadening, attributed to the presence of slowly interconverting conformers: $[\alpha]_D^{25}$ −108° (*c* 1.10, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35, (2H, d, J = 8.8 Hz), 8.29 (2H, d, J = 8.6 Hz), 5.34 (1H, br), 2.51 (1H, d, J = 12.3 Hz), 2.30 (1H), 2.13−1.96 (m, 3H) 1.80 (5H), 1.65 (5H), 1.49 (3H, s), 1.06, 0.98 (2 × 3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 150.30, 137.31, 135.94, 130.39, 123.65, 122.11, 87.29, 53.27, 47.78, 39.97, 39.91, 38.86, 38.23, 31.58, 30.46, 30.08, 26.02, 23.52, 23.03, 15.78; IR (CCl_4) ν_{max} 2805, 1690, 1506 cm^{-1}. Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.09; H, 7.86; N, 3.75.

Solvolysis of 14-OpNB. A suspension of **14**-O*p*NB (2.0 g, 5.38 mmol) in 60% aqueous acetone (160 mL, v/v) and pyridine (1.28 g, 16.2 mmol) in a 200-mL resealable tube was purged with N_2 and sealed tightly. The solid dissolved as the solvolysis mixture was magnetically stirred and heated to 125 °C. After 2 h at 125 °C, the tube was rapidly cooled in an ice-bath and hexane (20 mL) was added. The acetone was removed by rotary evaporation in an ice-bath, and more hexane was added. The organic layer was washed with 10% HCl (3 × 30 mL), satd $NaHCO_3$ (3 × 30 mL), and brine (50 mL); dried (Na_2SO_4); and concentrated to a yellow oil (1.16 g). The products were first separated into olefin and alcohol fractions by flash chromatography on silica gel. Elution with hexane afforded the olefin fraction as a colorless oil (863 mg, 72%) composed of two olefins in a 98.7:1.3 ratio according to GC analysis. The major olefin was identified as caryophyllene by GC, TLC, ^{1}H NMR, and ^{13}C NMR comparisons with an

authentic sample (99% purity by GC analysis).[13b] The minor olefin was not identified. Further elution with 5−10% ether/hexane afforded unreacted **14**-OpNB (40 mg, 2%), and elution with neat ether afforded the alcohol fraction (218 mg, 18%) consisting of three major alcohol products (A−C, GC ratio 19:65:15) and several minor alcohol products (15%). This mixture was combined with the same alcohol fraction (122 mg) from an identical 1-g scale solvolysis. The alcohol products were separated by flash chromatography on silica gel using 10% and 15% ether/hexane as eluant. Alcohol B (164 mg, 9%) was identical with **14**-OH based on TLC, GC, and ^{1}H NMR comparisons, and by vt NMR spectra (^{1}H and ^{13}C) at +80 °C. Minor alcohol A was isolated as a white solid (15 mg, 85% purity by GC, 1%) and was identified as (1*R*,4*R*,5*R*,8*R*,9*S*)-5,8-cyclocaryophyllan-4*β*-ol (**16**) by comparison of ^{1}H and ^{13}C NMR spectral data with the literature[14] and by direct comparison of the ^{1}H NMR spectrum with that of **16** in Supporting Information.[14] Particularly significant identification criteria were the overlapping doublet of triplets at *δ*H 2.31 and the coincidence of 12 ^{13}C NMR resonances within ±0.04 ppm. The other minor alcohol (C) was not isolated in pure form.

***(E)*-15-Norcaryophyll-4-en-8*β*-ol (15-OH).** A solution of $LiAlH_4$ (380 mg, 10 mmol) in anhydrous Et_2O (10 mL) was vigorously stirred at room temperature under N_2 as a solution of **13** (2.06 g, 10 mmol) in Et_2O (20 mL) was added via a cannula over 30 min. The reaction was stopped after 30 min by hydrolysis[33] at 0 °C. The salts were filtered and washed with ether; the filtrate was concentrated; and the residue was dissolved in CH_2Cl_2 (ca. 20 mL). The organic layer was washed with water (3 × 15 mL), dried (Na_2SO_4), and concentrated to give 1.97 g of a colorless oil. Purification by chromatography on silica gel with 20% EtOAc/hexane as eluant, followed by bulb-to-bulb distillation at 125 °C and 0.2 mmHg gave **15**-OH as a colorless oil (1.83 g, 88%) containing 3% of the cis isomer, according to GC analysis. The ^{1}H and ^{13}C NMR spectra at room temperature showed line broadening attributed to the presence of slowly interconverting conformers: $[\alpha]^{25}_D$ −26.7° (*c* 1.35, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 5.37 (1H, br), 3.65 (1H, br), 2.27 (1H, br), 2.06 (2H, br), 1.91 (2H, br), 1.70−1.29 (10H, br), 0.96, 0.95 (2 × 3H, 2s); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 125.0, 122.43, 73.20, 46.88, 44.85, 39.77, 37.73, 33.46, 33.42, 29.88, 28.34, 23.08, 22.56, 16.0; IR (CCl_4) ν_{max} 3441, 2936, 2776, 1346 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.72; H, 11.63.

***(E)*-15-Norcaryophyll-4-en-8*β*-yl Tosylate (15-OTs).** Alcohol **15**-OH (1.76 g, 8.45 mmol) was stirred as a neat liquid and cooled at 0 °C under N_2, as 1.51 M *n*-BuLi in hexane (11.3 mL, 11.9 mmol) was added. After 3 h at room temperature. tosyl chloride (5.62 g, 29.6 mmol) in anhydrous THF (25 mL) was added via cannula over 10 min. The heterogeneous reaction mixture was stirred overnight at room temperature. Excess tosyl chloride was allowed to react with 3-(*N*,*N*-dimethylamino)propylamine (15 mL, 150 mmol) at room temperature for 1 h, and satd NH_4Cl (5 mL) was added. The solution was diluted with 1:1 hexane/ether (75 mL). The organic layer was washed with 10% HCl (2 × 20 mL), satd $NaHCO_3$ (2 × 25 mL), and brine (25 mL); dried (Na_2SO_4); and concentrated to give a yellow solid (3.66 g). Flash column chromatography on silica gel (500 g) using 15% EtOAc/hexane as eluant and recrystallization from hexane afforded 1.81 g (83%) of **15**-OTs as white crystals, mp 88−89 °C. The 8*β*-stereochemistry was confirmed by X-ray crystallography (see Supporting Information). TLC R_f 0.6 (5% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.84 (2H, d, *J* = 8.3 Hz), 7.37 (2H, d, *J* = 8.3 Hz), 5.35 (1H, t, *J* = 7.8 Hz), 4.52 (1H, d, *J* = 8.3 Hz), 2.45 (3H, s), 1.57 (3H, s), 0.87, 0.86 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 144.39, 135.06, 134.44, 129.64, 127.73, 122.88, 85.38, 45.84, 45.59, 39.41, 37.18, 32.79, 32.09, 29.70, 28.47, 22.82, 22.66, 21.61, 15.83; IR (CCl_4) ν_{max} 2953, 2926, 2858, 1371 cm^{-1}. Anal. Calcd for $C_{21}H_{30}O_3S$: C, 69.57; H, 8.34; S, 8.85. Found: C, 69.66; H, 8.40; S, 8.80.

Solvolysis of 15-OTs. A solution of **15**-OTs (750 mg, 2.07 mmol) in 60% aqueous acetone (56 mL, v/v) and pyridine (487 *μ*L, 454 mg, 6.21 mmol) was purged with N_2, sealed under nitrogen in a 100-mL, resealable glass tube, and heated at 75 °C for 45 min. The reaction was stopped by rapid cooling to 0 °C, and 1:1 hexane/ether (75 mL) was added. The organic layer was washed with satd $CuSO_4$ (3 × 15 mL), water (3 × 25 mL), and brine (25 mL); dried (Na_2SO_4); and concentrated to give a yellow oil (480 mg). The product mixture was first separated into olefin and alcohol fractions by chromatography on silica gel. Elution with 2% EtOAc/hexane afforded the olefin fraction (36 mg, 7%) which was a complex mixture that was not further characterized. Elution with 5% EtOAc/hexane gave recovered **15**-OTs (61 mg, 8%), and elution with 10−50% EtOAc/hexane gave the alcohol fraction (336 mg, 85%) which consisted of one major alcohol **17** (74%), **15**-OH (9%), and four other minor alcohols, based on GC analysis. Further purification by rechromatography using 10% EtOAc/hexane as eluant afforded **15**-OH (40 mg, 9%) which was identified by comparison with an authentic sample, and **17** (238 mg, 61%). Recrystallization from pentane afforded **17** (149 mg, 40%) as colorless crystals suitable for single-crystal X-ray analysis: mp 107−109 °C; $[\alpha]^{25}_D$ −29.7° (*c* 0.50, EtOH); ^{1}H NMR (C_6D_6, 750 MHz) *δ* 1.98 (2H, m), 1.86 (1H, dt, *J* = 10.9, 4.5 Hz), 1.81 (1H, ddd, *J* = 13.4, 3.8, 2.1 Hz), 1.68 (1H, dd, *J* = 12.1, 7.3 Hz), 1.61 (1H, m), 1.52 (1H, m), 1.42 (2H, dt, *J* = 12.3, 4.2 Hz), 1.29 (1H, qd, *J* = 11.9, 4.6 Hz), 1.22 (1H, dd, *J* = 12.2, 9.2 Hz), 1.21 (1H, br), 1.19 (1H, ddd, *J* = 7.5, 4.9, 2.7 Hz), 1.11 (3H, s), 1.07−1.04 (2H, m), 0.98 (3H, s), 0.79 (3H, s); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 2.11 (1H, m), 2.01 (1H, ddd, *J* = 12.1, 7.5, 4.8 Hz), 1.89 (1H, m), 1.87 (1H, dt, *J* = 9.0, 4.6 Hz), 1.76 (1H, m), 1.70 (1H, dd, *J* = 12.4, 7.7 Hz), 1.51 (1H, app. dt, *J* = 11.2, 4.6 Hz), 1.44 (1H, s, OH), 1.39 (1H, ddd, *J* = 17.1, 12.2, 4.9 Hz), 1.24 (3H, s), 1.20 (2H, m), 0.98 (3H, s), 0.81 (3H, s); ^{13}C NMR (C_6D_6, 125 MHz) *δ* 75.4 (C), 59.8 (CH), 58.5 (CH), 56.5 (CH), 51.5 (CH_2), 47.3 (C), 46.1 (CH_2), 36.0 (CH), 35.6 (CH_2), 32.1 (CH_2), 27.2 (CH_3), 27.1 (CH_2,), 21.7 (CH_3,), 20.4 (CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 76.2 (C), 59.7 (CH), 58.3 (CH), 56.3 (CH), 51.2 (CH_2), 47.3 (C), 45.6 (CH_2), 35.7 (CH), 35.4 (CH_2), 31.7 (CH_2), 27.1 (CH_3), 26.9 (CH_2), 21.7 (CH_3,), 20.3 (CH_3); IR (CCl_4) ν_{max} 3611, 2950, 2860 cm^{-1}; EIMS (relative intensity) *m*/*z* 208 (M^+, 26), 193 (17, M^+-CH_3), 175 (19) 150 (25) 175 (37), 123 (100), 109 (31), 95 (48), 81 (62), 71 (66), 55 (28), 43 (99). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H 11.61. Found: C, 80.67; H 11.41.

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Supporting Information Available: Detailed procedures for preparation **12**, **13**, and **14**-OH; and X-ray crystallographic data and SHELXTL figures for **15**-OTs and **17**; spectra for **17** (^{1}H and ^{13}C NMR, DEPT 90 and 135, COSY, HMQC, HMBC, IR, and EIMS) (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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