Stereochemistry and Reactions of Presilphiperfolanol: A Branch Point Marker in Triquinane Sesquiterpene Biogenesis

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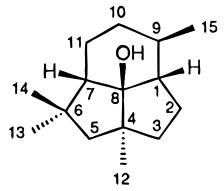
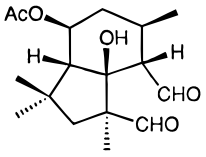
Abstract: The structure and stereochemistry of the tricyclic sesquiterpene alcohol (−)-presilphiperfolanol, a structural precursor for the angular and propellane triquinane sesquiterpenes, are established as (1*S*,4*S*,7*S*,8*S*,11*S*)-2,2,4,8-tetramethyltricyclo[5.3.1.$0^{4,11}$]undecan-11-ol [[2aS-(2aα,4aβ,5β,7aβ,7bβ)]-decahydro-1,1,2a,5-tetramethyl-7b*H*-cyclopenta[*cd*]inden-7b-ol, **1**] by an X-ray crystallographic analysis of its *p*-nitrobenzoate derivative **8a** and by correlation with (−)-silphiperfol-6-ene (**6**). Dehydration of **1** afforded a 2:1 mixture of presilphiperfol-1(8)- and 7-enes (**9** + **10**) which underwent epoxidation on both α and β faces. Acid-catalyzed dehydration with H_2SO_4−silica gel lead to competing ring contractions by migrations of C11 and C9 to C8 to give silphiperfolene (**6**) and α-terrecyclene (**12**) in a 98:1 ratio. Solvolysis of **8a** in 60% aqueous acetone provided a mixture of olefins (**9** + **10** + **6**) and **1** (9%) as the sole alcohol product. The similarity of the solvolysis rate (5.2×10^{-5} s^{-1} at 50 °C) to the literature value for *trans*-bicyclo[3.3.0]octan-1-yl *p*-nitrobenzoate indicates comparable levels of strain relief in the respective transition states.

Introduction

The isolation of a new sesquiterpene alcohol, presilphiperfolanol (**1**), from the California coastal succulent *Eriophyllum staechadifolium* (common name lizard tail) and from *Flourensia heterolepis* was reported by Bohlmann and associates in 1981.[1] The tricyclo[5.3.1.$0^{4,11}$]undecane structure and stereochemistry shown in **1** were deduced primarily from extensive analysis of



1

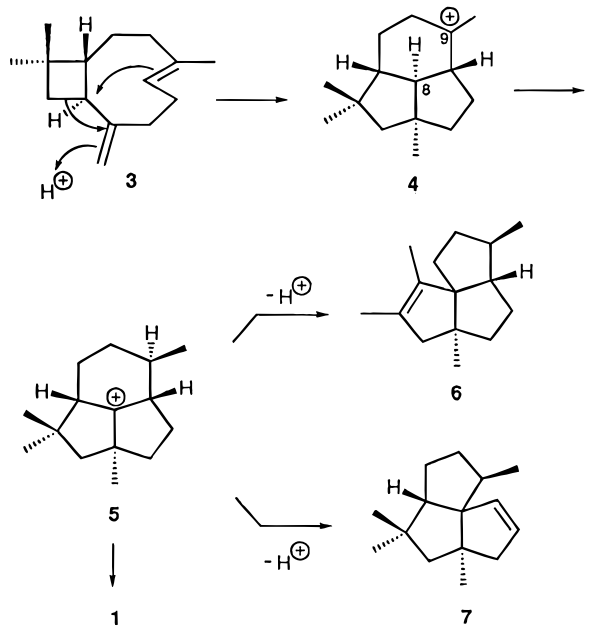


2

^{1}H NMR couplings and chemical shifts in mixtures of solvents and Eu(fod)$_3$ shift reagent as well its acid-catalyzed rearrangement to silphiperfol-6-ene (**6**).[1,2] However, the relative configurations at C7 and C8 lost in the correlation were considered uncertain, and no evidence to assign the absolute stereochemistry was available at that time.

It seems probable that presilphiperfolanol is the initial cyclization product on the biosynthetic pathway to botrydial (**2**) and dihydrobotrydial, antibiotics produced by *Botrytis cinerea*.[3] The structures assigned to these fungal metabolites based on chemical degradations and spectroscopic evidence[3] were confirmed by an X-ray crystallographic determination with dihydrobotrydial.[4] The absolute configuration was deduced from the negative Cotton effect observed in the CD spectrum of the δ-lactone derived by oxidation of dihydrobotrydial and application of the lactone sector rule.[5]

Scheme 1



The co-occurrence of silphiperfolene (**6**) and silphinene (**7**) with presilphiperfolanol in *F. heterolepis*,[1] and the co-existence of the triquinane sesquiterpenes−isocomene, modhephene, silphinene, and the silphiperfolenes−with caryophyllene in *Silphium perfoliatum* L.[6,7] lead Bohlmann to propose the biogenetic origin of the isomeric angular triquinane structures[8] by ring expansion, cyclization, and rearrangement of the

[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1996.

(1) Bohlmann, F.; Zdero, C.; Jakupovic, J.; Robinson, H.; King, R. M. *Phytochemistry* **1981**, *20*, 2239−2244. **Note Added in Proof.** The isolation and total synthesis of presilphiperfolan-9-ol (formally derived from **4**) have recently been reported: Marco, J. A.; Sanz-Cervera, J. F.; Morante, M. D.; García-Lliso, V.; Vallès-Xirau; Jakupovic, J. *Phytochemistry* **1996**, *41*, 837−844. Weyerstahl, P.; Marschall, H.; Schulze, M.; Schwope, I. *Liebigs Ann. Chem.* **1996**, 799−807.

(2) Semisystematic names for presilphiperfolane, silphiperfolane, and silphinane derivatives together with a common positional numbering scheme are used in this paper. Systematic IUPAC and *Chemical Abstracts* names are given in the abstract.

(3) Fehlhaber, H.-W.; Geipel, R.; Mercker, H.-J.; Tschesche, R.; Welmar, K.; Schönbeck, F. *Chem. Ber.* **1974**, *107*, 1720−1730.

(4) Lindner, H. J.; von Gross, B. *Chem. Ber.* **1974**, *107*, 3332−3336.

(5) (a) Wolf, H. *Tetrahedron Lett.* **1966**, 5151−5156. (b) Legrand, M.; Bucourt, R.; *Bull Soc. Chim. Fr.* **1967**, 2241−2245.

(6) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259−265.

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Table 1. Selected Bond Angles from the X-ray Crystallographic Analysis of Presilphiperfolanyl *p*-Nitrobenzoate (**8a**)[a]

atom no.	bond angle (deg)	atom no.	bond angle (deg)
O1−C8−C1	106.7 (8)	C2−C1−C8	101.0 (10)
O1−C8−C4	101.3 (9)	C1−C2−C3	108.2 (11)
O1−C8−C7	108.1 (9)	C2−C3−C4	102.3 (11)
C2−C1−C9	117.1 (10)	C6−C7−C8	102.2 (10)
C8−C1−C9	112.3 (10)	C5−C6−C7	105.6 (10)
C1−C8−C7	125.2 (11)	C4−C5−C6	104.4 (10)
C8−C7−C11	111.1 (10)	C5−C4−C8	100.7 (10)
C6−C7−C11	121.7 (10)	C3−C4−C8	99.7 (9)
		C3−C4−C5	127.4 (11)

[a] See Figure 1 also.

caryophyllenyl ion[3] as shown in Scheme 1. Thus, the presilphiperfolanyl ion (**5**) occupies a key position on the biogenetic pathway to the silphinane sesquiterpenes by means of Wagner−Meerwein ring contractions and by a plausible relationship with caryophyllene.

Concurrent investigations by Hanson and associates on the biosynthesis of botrydial and related co-metabolites from [1-^{13}C] and [1,2-$^{13}C_2$]acetate as well as [4,5-$^{13}C_2$]mevalonate in *B. cinerea* cultures lead to the proposal that (*E*,*E*)-farnesyl diphosphate (FPP) is incorporated via C1−C2 cleavage together with C1−C11, C2−C10, and C2−C6 bond connections (FPP position numbers).[9] A similar schematic mechanism involving ring expansion−cyclization of the caryophyllenyl ion was postulated to explain the labeling patterns observed in the *B. cinerea* fermentation products. Further support for this scheme as well as evidence for a C8−C9 1,3-hydride shift (presilphiperfolane numbering) and water incorporation at C8 in botrydial biosynthesis was secured by means of biosynthetic experiments with various [^{3}H,^{14}C]- and [^{2}H]-labeled mevalonates and [^{18}O]water.[10]

The objectives of this research were as follows: (1) to confirm the structure of presilphiperfolanol (**1**) and to establish securely its relative and absolute stereochemistry; (2) to investigate its chemical derivatization, dehydration, and skeletal rearrangement reactions; and (3) to evaluate the carbocationic reactivity of the tricyclo[5.3.1.0^{4,11}]undecanyl structure in a kinetically controlled solvolysis.

Derivatization and Dehydration. Presilphiperfolanol was isolated from *E. staechadifolium* by extraction and repeated chromatography in a manner similar to the reported procedure (0.005% yield). ^{1}H and ^{13}C NMR spectra were completely assigned by means of DEPT, COSY, and HETCOR plots. The spectral data and assignments agree reasonably well ($\delta_H C_6D_6 \pm 0.1$ and $\delta_C CD_2Cl_2 \pm 0.5$) with the literature values except for three proton shifts, three carbon shifts, and two ^{13}C NMR assignments.[1,11]

The sterically hindered hydroxyl group of **1** was successfully derivatized by lithiation with *n*BuLi (THF−hexane, 25 °C, 1 h) and subsequent acylation with *p*-nitrobenzoyl chloride[12] and *tert*-butyl isocyanate[13] to the crystalline ester **8a** (65%) and carbamate **8b** (61%), respectively.

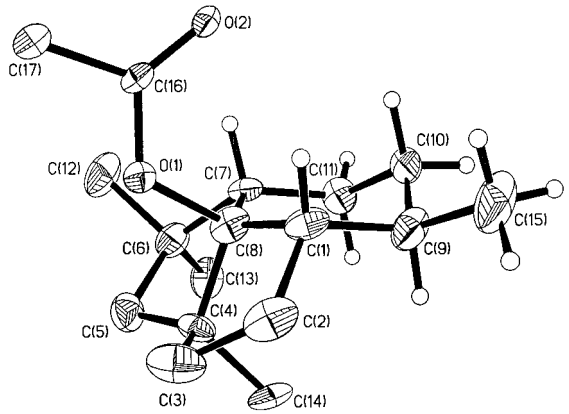
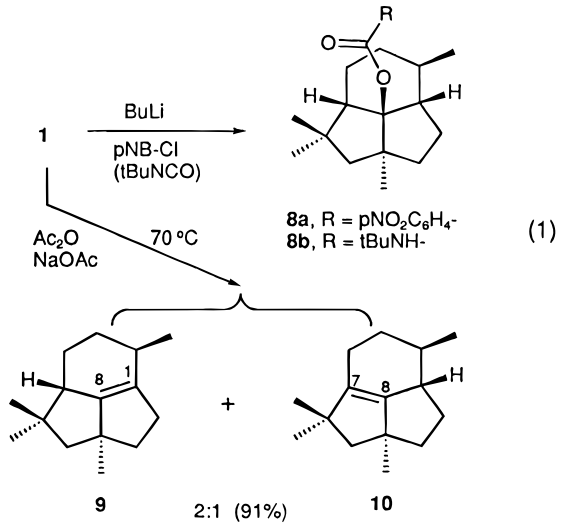


Figure 1. ORTEP plot of presilphiperfolanyl *p*-nitrobenzoate (**8a**) from the X-ray crystallographic analysis. *p*-Nitrobenzene ring (C18−C22, N1, O3, O4) and most hydrogen atoms on the cyclopentane rings are omitted for clarity.



(1)

Although an X-ray crystallographic analysis of **8a** was complicated by an elongated unit cell belonging to the primitive tetragonal $P4_32_12$ space group, satisfactory convergence was realized.[14] The ORTEP plot (Figure 1) shows the chair conformation of the six-membered ring, as well as the equatorial disposition of the C8 oxygen and C15 methyl group. The C2−C1−C9 (117.1(10)°), C1−C8−C7 (125.2(11)°), and C6−C7−C11 (121.7(10)°) bond angles (Table 1) around the cyclohexane ring junctions are considerably enlarged, and the O1−C8−C4 (101.3(9)°) bond angle is contracted to accommodate the fusion to the strained *trans*-bicyclo[3.3.0]octane moiety.

Dehydration of presilphiperfolanol with sodium acetate−acetic anhydride at 70 °C (Ac_2O, DMAP, pyridine, 80 °C) afforded a 2:1 mixture of presilphiperfol-1(8)-ene (**9**) and its 7-ene isomer (**10**). By means of repeated chromatography on $AgNO_3$-impregnated silica gel, the major component ($[\alpha]_D$ −125°) was isolated in pure form and the minor isomer ($[\alpha]_D$

(7) The co-occurrence of isocomene, modhephene, and caryophyllene in *Isocoma Wrightii* and the liklihood of their biogenetic relationship have been noted by Zalkow and co-workers in the initial discovery of these novel triquinane sesquiterpenes: (a) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456−457. (b) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D. *J. Chem. Soc., Chem. Commun*. **1978**, 420−421.

(8) For reviews, see: (a) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41−152, **1984**, *119*, 1−147. (b) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Berlin, 1987.

(9) (a) Hanson, J. R.; Nyfeler, R. *J. Chem. Soc., Chem. Commun.* **1976**, 72−73. (b) Bradshaw, A. P. W.; Hanson, J. R.; Siverns, M. *J. Chem. Soc., Chem. Commun.* **1977**, 819. (c) Bradshaw, A. P. W.; Hanson, J. R.; Nyfeler, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1469−1472.

(10) Bradshaw, A. P. W.; Hanson, J. R. Nyfeler, R.; Sadler, I. H. *J. Chem. Soc., Perkin Trans 1* **1982**, 2187−2192.

(11) $\delta_H{}^{C_6D_6}$ 0.98 (m, Hl), 1.26 (m, H7), 1.21 (m, H11β); $\delta_C{}^{CD_2Cl_2}$ 37.6 (d, C9), 34.6 (t, C10), 36.4 (q, C12), 28.6(q, C14, 21.6 (q, C15).

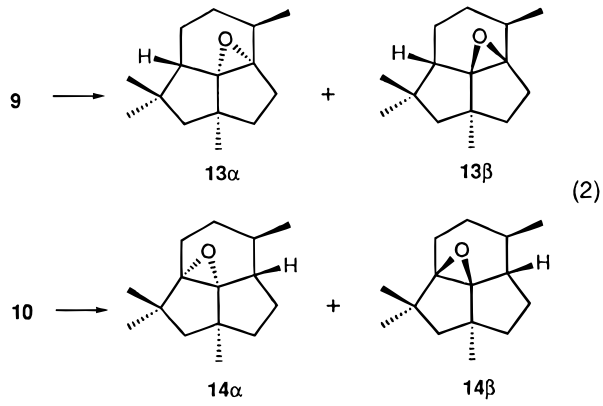
(12) Woodruff, R. A.; Kaiser, E. M. *J. Org. Chem.* **1970**, *35*, 1198−1199.

(13) (a) Nikiforov, A.; Jirovetz, L.; Buchbauer, G. *Liebigs Ann. Chem.* **1989**, 489−493. (b) Bailey W. J.; Griffith, J. R. *J. Org. Chem.* **1978**, *43*, 2690−2692.

(14) Crystal data for **8a**: crystal system, tetragonal; space group, $P4_32_12$; colorless; cell parameters, $a = b = 8.211(2)$, $c = 58.657(13)$; $z = 8$; $R1 = 0.1243$; GOF = 1.10.

+47.5°)was enriched to 80% purity. ^{1}H and ^{13}C NMR spectra together with DEPT, COSY, and HETCOR plots allowed definitive assignments for all carbon resonances; however, owing to extensive overlap of absorptions in the δ_H 1−2 region, some proton chemical shifts could not be determined precisely. The double bond position was assigned by the observation of H−H coupling cross peaks for the methine protons ($\delta_H C_6D_6$ 2.13 and 2.45 for C1 and C9) in the COSY plot for the minor isomer and the absence of cross peaks for the corresponding methine protons ($\delta_H C_6D_6$ 1.53 and 1.72 for C9 and C7, respectively) in the COSY of the major isomer. The dehydration of **1** to one presilphiperfolene isomer was previously reported by Bohlmann and co-workers.[1] Although the literature NMR data for this compound clearly correlate with our data for the major product, the structure was erroneously assigned as **10**.

Epoxidation of **9** and **10** (80% purity) with *m*-chloroperoxybenzoic acid (*m*-CPBA, CH_2Cl_2, 25 °C) afforded 1:3 (or 3:1) mixtures of **13**α + **13**β and **14**α + **14**β, which were characterized by GC/MS and ^{1}H NMR spectra (eq 2).



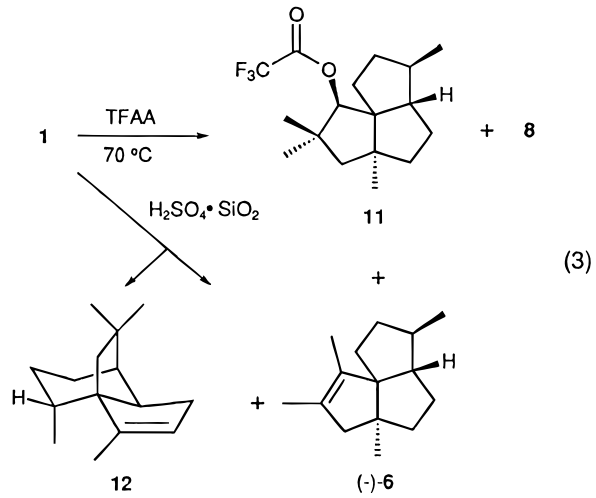
(2)

Reduction of the **13**α + **13**β epoxide mixture with lithium in ethylenediamine at 50 °C gave a four-component mixture (2:1:2:3 by GC) containing three $C_{15}H_{26}O$ isomers presumed to be tertiary alcohols.[15,16] The major product was identified as presilphiperfolanol by GC and GC/MS comparisons.

Carbocation Rearrangements and Reactivity. Reaction of **1** with trifluoroacetic anhydride (70 °C, 90 min) effected dehydration to presilphiperfol-1(8)-ene (**9**, 20%) together with ring contraction to trifluoroacetate **11** (11%) and (−)-silphiperfol-6-ene (**6**, 40%; $[a]_D^{26}$ −97.7°, lit.[6] $[a]_D^{26}$ −92.8°).

This correlation, in conjunction with the asymmetric synthesis of enantomerically enriched (−)-**6** from (*R*)-(+)-pulegone,[17] establishes the absolute configuration of (−)-presilphiperfolanol depicted in stereo formula **1**. Structure **11** assigned to the trifluoroacetate product is based upon appropriate ^{1}H and ^{13}C NMR spectra as well as the assumption that it arises from stereoelectronically favorable suprafacial 1,2-rearrangements of the C11 methylene and the $CF_3CO_2^-$ counterion. Conversion of **9** and **11** to **6** in separate experiments under the same conditions indicated that they are intermediates and, therefore, that **9** undergoes predominant protonation at the 1β position.

Dehydration of **1** with H_2SO_4−silica gel in benzene[18] at reflux temperature afforded silphiperfol-6-ene (**6**, 79%) accompanied by ∼1% of α-terrecyclene (**12**).[19] The latter was identified by GC and GC/MS comparisons with an authentic sample. α-Terrecyclene is presumably formed by three successive Wagner−Meerwein rearrangements as shown in eq 4: ring contraction by migration of C9, spiro bond rearrangement (C7 to C1), and finally C5 to C8 shift to generate the terrecyclanyl ion **16**.



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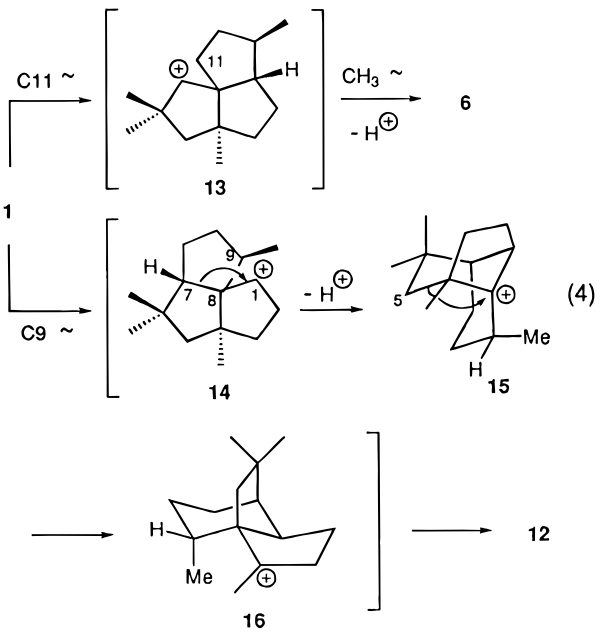
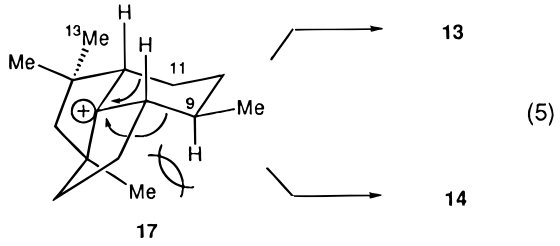


(4)

The preference for the initial ring contraction of C11 to give **13** over rearrangement of C9 to the silphinyl ion **14** ($\Delta\Delta G^{\ddagger}$ ∼2.7 kcal/mol) is attributed to the differing steric interactions that develop between the C9 methine and the angular methyl group in the competing transition states, as well as relief of the C11/C13 interaction in the migration of C11 (eq 5).



(5)

(15) Brown, H. C.; Ikegami, S.; Kawakami, J. H. *J. Org. Chem.* **1970**, *35*, 3243−3245.

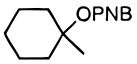
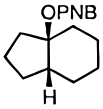
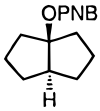
(16) Lithium−ethylenediamine reduction of 4,5,6,7-tetrahydroindane epoxide afforded *cis*- and *trans*-8-hydrindanols in a 58:42 ratio; see: Benkeser, R. A.; Rappa, A.; Wolsieffer, L. A. *J. Org. Chem.* **1986**, *51*, 3391−3393.

(17) Paquette, L. A.; Robert, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690−6693.

(18) Fitjer, L.; Monzó-Oltra, H. *J. Org. Chem.* **1993**, *58*, 6171−6173.

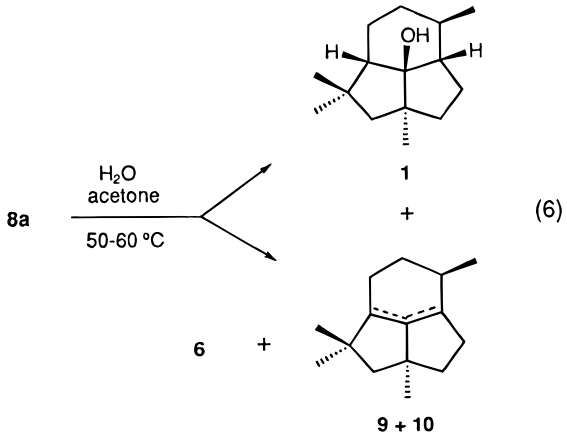
(19) Klobus, M.; Zhu, L.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 4327−4329.

Table 2. Rate Constants from Solvolysis of Presilphiperfolanyl *p*-Nitrobenzoate (**8a**) and Related Compounds in 60% Aqueous Acetone at Various Temperatures

p-nitrobenzoate	*t* (°C)	$k \times 10^5$ (s^{-1})	k_{rel} (50 °C)
8a	60	15.2 ± 0.1[a]	
	50	5.19 ± 0.06[a]	1900
	100	1.35 ± 0.01[a]	
	100	1.53[b]	
	50	0.00276[c]	(1.0)
	50	6.18[b]	2200
	80	2.11[b]	
	50	0.054[c]	19

[a] Average of two runs. [b] Data from ref 21. [c] Extrapolated values obtained by using $\Delta H^{\ddagger}$ 29.5 and 27.0 kcal/mol and $\Delta S^{\ddagger}$ −2.0 and −3.7 eu, respectively, reported in ref 21.

Solvolysis of **8a** in 60% aqueous acetone at 50 °C afforded a 12:3:1 mixture of **9** + **10** + **6** (86%) together with **1** (9%) (eq 6). No other alcohol products were detected by GC and ^{1}H



(6)

NMR spectral analyses. The exclusive formation of **1** probably reflects the greater thermodynamic stability of the 1,8-*cis*/4,8-*trans*/7,8-*cis* stereochemistry. Molecular mechanics calculations[20] predict that the parent *cis*, *trans*, *cis*, tricyclo[5.3.1.0^{4,11}]-undecane, is more stable than the *trans*, *cis*, *trans*, isomer by 2.4 kcal/mol, despite the presence of the strained *trans*-bicyclo-[3.3.0]octane moiety in the former. In contrast, solvolyses of *trans*- and *cis*-bicyclo[3.3.0]octanyl *p*-nitrobenzoates (pNBs) give exclusively the less strained *cis*-tertiary alcohol (3−5% + olefins) while *cis*-hydrindan-3a-yl pNB afforded a 60:40 mixture (9% + olefins) of *cis* and *trans* tertiary hydrindanols.[21]

The rates of solvolysis of **8a** at 50 and 60 °C and for calibration purposes 1-methyl-1-cyclohexyl pNB at 100 °C were determined titrimetrically in 60% aqueous acetone. The rate constants are presented in Table 2 along with comparable kinetic data for *trans*-bicyclo[3.3.0]octan-1-yl and *cis*-hydrindan-3a-yl pNBs from the literature.[21] The solvolysis rate for presilphiperfolanyl pNB (**8a**) is very similar to the rate reported for the *trans*-bicyclo[3.3.0]octyl analog, and it is ∼100 times faster than the *cis*-hydrindanyl bicyclic model. Evidently the strain relieved in the transition state leading to the presilphiperfolanyl ion is similar to that associated with the *trans*-bicyclo[3.3.0]-octyl analog.

Experimental Section

General Aspects.[22] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. In a few cases when CD_2Cl_2 or C_6D_6 was used, the solvent is specified. *J* values are given in hertz. Mass spectra were recorded on a Varian 70−4F or 70-VSE mass spectrometer. GC analyses were carried out on a Varian 3700 equipped with a 30-m RTX-5 fused-silica capillary column using helium as carrier gas. Peaks were detected by a flame ionization detector. The standard operation conditions were as follows: 290 °C injector temperature, 300 °C detector temperature. The GC temperature program used was the following: 100 °C for 2 min, 12 °C/min to 275 °C, and then hold for 10 min. The carrier gas flow rate was 1.25 mL/min. $AgNO_3$-impregnated silica gel (15%, w/w) was prepared by a literature procedure.[23]

Isolation of Presilphiperfolanol (1). The aerial parts of *E. staechadifolium* were collected at the Bodega Bay Marine Reserve of the University of California in July 1992, June 1994, and August 1995. The species identification was confirmed by Dr. Peter G. Connors, senior museum scientist at the reserve. The plant material including branches and flowers was air-dried and ground to a powder with a Waring blender.

The ground plant material (2.0 kg) was extracted twice with 1:1 petroleum ether−diethyl ether (9 L) for 48-h periods. The combined extracts were concentrated to 200 mL, diluted with methanol (800 mL), and stored at −20 °C to precipitate lipid material. Filtration, concentration, and three chromatographies on silica gel with 6:1 or 8:1 hexane−ether as eluant afforded 91 mg of a yellow oil containing **1** (∼90% purity by ^{1}H NMR analysis). The purity was increased by brief exposure to ozone (CH_2Cl_2, −78 °C, 0.5 min; and then Me_2S) and another chromatography on silica gel: yield, 58 mg (98% purity); TLC R_f 0.42 (6:1) hexane−ether).

Repetition of the preceding extraction and purification procedures 6 times afforded 666 mg (0.005%) of **1**. With a few exceptions (see text), the following optical and spectral data correspond well with the literature:[1] $[\alpha]_{26}^{\circ}$ (λ) −19.0 (589 nm), −25.5 (577 nm), −28.8 (546 nm), −45.6 (436 nm) (c = 0.50, $CHCl_3$); IR (neat) 3519 (OH), 1456, 1375, 1161, 978, 890, 870 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.83 (d, 3H, J = 6, CH_3, H-15), 0.98 (m, 1H, H-1), 1.10 (s, 3H, CH_3, H-14), 1.14 (d, 1H, J = 11, H-5β), 1.15 (s, 3H, CH_3, H-13), 1.16(ddd, 1H, J = 15, 9, 4, H-3β), 1.21 (m, 1H, H-11β), 1.22 (m, 1H, H-7), 1.23 (s, 1H, OH) 1.26 (m, 1H, H-9), 1.36 (s, 3H, CH_3, H12), 1.44 (ddd, 1H, J = 12, 6, 3, H-11α), 1.46 (ddd, 1H, J = 12, 6, 3, H-10α), 1.48 (ddd, 1H, J = 12, 6, 3, H-10β), 1.77 (dddd, 1H, J = 14, 9, 8, 4, H-2α), 2.06 (ddd, 1H, J = 14, 9, 8, H-3α), 2.14 (d, 1H, J = 11, H-5α), 2.29 (dddd, 1H, J = 14, 9, 8, 0.5, H-2β); ^{13}C NMR (C_6D_6) δ 21.78 (CH_3, C-15), 27.09 (CH_2, C-11), 27.95 (CH_3, C-13), 28.09 (CH_3, C-14), 33.28 (CH_2, C-2), 34.02 (CH_2, C-3), 34.53 (CH_2, C-10), 36.46 (CH_3, C-12), 37.47 (CH, C-7), 48.01 (C-6), 49.37 (CH_2, C-5), 50.17 (CH, C-1), 52.48 (CH, C-9), 56.29 (C-4), 96.22(C-8); ^{13}C NMR (CD_2Cl_2) δ 21.6, 27.2, 27.8, 28.0, 33.2, 34.0, 34.6, 36.4, 37.6, 48.0, 49.4, 50.2, 52.4, 56.5, 97.1. MS (EI, 70eV) *m*/*z* (rel intensity) 222 (M^+, 10), 207 (M − CH_3, 35), 204 (M − H_2O, 6), 189, (M − CH_3, 20), 161 (M − C_3H_7, 11), 41 (100). Anal. Calcd for $C_{15}H_{26}O$: C, 81.08, H, 11.71. Found: C, 81.04, H 11.76.

Presilphiperfolan-8-yl *p*-Nitrobenzoate (8a). A solution of **1** (111 mg, 0.5 mmol) in THF (1.0 mL) was stirred at room temperature as 400 μL (0.6 mmol) of 1.51 M *n*-BuLi was added. The resulting solution was stirred for 1 h at room temperature before adding 4-nitrobenzoyl chloride (204 mg, 1.0 mmol) in THF (2 mL).[12] The suspension was stirred for 1 h. Dilution with 6:1 hexane−ether (20 mL), washings with 10% HCl and saturated Na_2CO_3 (10 mL each), drying ($MgSO_4$), and concentration afforded a brown oil. Purification by flash chromatography with 8:1 hexane−ether as eluant furnished 120 mg (65%)

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of slightly yellow crystals. Recrystallization from hexane at −20 °C gave colorless cubic crystals, one of which was subjected to X-ray analysis:[14] mp 190−191 °C; IR (CCl_4) 2956, 1724 (C=O), 1528, 1346, 1274, 1115, 1101, 780 cm^{-1}. ^1H NMR δ 0.93 (d, 3H, J = 6, CH_3, H-15), 1.01 (s, 3H, CH_3, H-12), 1.09 (s, 3H, CH_3, H-13), 1.14 (s, 3H, CH_3, H-14), 1.27 (m, 3H, H-9, H-10α, H-3α), 1.30 and 2.05 (ABdd, 2H, J = 12, H-5α and H-5β), 1.51 (dq, 1H, J = 13, 3, H-11α), 1.59 (ddt, 1H, J = 13, 12, 3, H-2α), 1.74 (ddd, 1H, J = 13, 11, 3, H-11β), 1.80 (ddd, 1H, J = 12, 10, 4, H-10β), 2.03 (1H, H-7), 2.14 (dt, 1H, J = 13, 9, H-2β), 2,37 (ddd, 1H, J = 10, 9, 4, H-3β), 2.62 (dd, 1H, J = 12, 8, H-1); ^{13}C NMR (C_6D_6) δ 21.54, 27.33, 27.60, 28.60, 33.16, 33.22, 33.87, 35.81, 38.18, 43.84, 46.06, 47.80, 49.07, 47.84, 112.08, 123.59, 130.00, 137.53, 150.35, 163.34; MS (EI, 70eV) *m/z* (rel intensity): 204 (95), 189 (20), 175 (46), 119 (100). Anal. Calcd for $C_{27}H_{29}NO_4$: C 71.16, H 7.81, N 3.77. Found: 71.17, H 7.81, N 3.76.

Presilphiperfolanyl *tert*-Butylcarbamate (8b). Lithiation of **1** (50 mg, 0.225 mmol) in hexane (150 μL) at room temperature with *n*-BuLi in hexane (167 μL, 1.6 M, 0.267 mmol) was carried out as described above. After 50 min, *tert*-butyl isocyanate (35 mg, 0.36 mmol) was added by syringe.[13] After 1 h, the product was isolated in a manner similar to that for **8a**. Flash chromatography with hexane−ether 10:1 as eluant afforded 44 mg (61%) of a pale yellow oil which crystallized at −20 °C: mp 156−157 °C; ^1H NMR (C_6D_6) δ 0.95 (d, 3H, J = 6.6, CH_3, H-15), 1.15 (s, 9H, *t*-Bu), 1.16 (s, 3H, CH_3, H-12), 1.17 (s, 3H, CH_3, H-13), 1.19−1.38 (m, 3H), 1.30 (s, 3H, CH_3, H-14), 1.50 (dq, 1H, J = 3.2, 12.9), 1.60−1.68 (m, 2H), 1.77−1.89 (m, 2H), 2.05−2.14 (m, 2H), 2.35 (dt, 1H, J = 13.4, 8.8), 2.56 (m, 1H), 2.79 (bt, 1H, J = 8.8).

Presilphiperfol-1(8)- and -7-enes (9 and 10). A solution of **1** (30 mg, 0.15 mmol), 4-(dimethylamino)pyridine (18 mg, 0.18 mmol), and acetic anhydride (100 μL) in pyridine (300 μL) was stirred and heated at 80 °C for 5 h. The solution was cooled to room temperature, diluted with 20 mL of 6:1 hexane−ether, and washed with 10% HCl and saturated Na_2CO_3 (10 mL each). The organic layer was dried ($MgSO_4$) and concentrated. Column chromatography with hexane as eluant afforded 28 mg (86%) of a 2:1 mixture of **9** and **10** as a colorless oil. Another flash chromatography using 15% $AgNO_3$-impregnated silica gel with hexane as eluant gave 11 mg of **9** (97% pure by GC), and 4 mg of **10** (80% pure by GC, the other 20% was **9**). For **9**: $[\alpha]_D^{26}$ = −125.0° (c = 0.20, $CHCl_3$); IR (neat) 2947, 1455, 1373, 1384, 1064, 659 cm^{-1}; ^1H NMR δ 0.93 (d, 3H, J = 7, CH_3, H-15), 1.02 (s, 3H, CH_3, H-14), 1.05 (s, 3H, CH_3, H-13), 1.21 (s, 3H, CH_3, H-13), 1.29 (m, 1H, H-3β) 1.31 (m, 1H, H-10β), 1.35 (ddd, 1H, J = 13, 8, 4, H-2β), 1.51 (dqd, 1H, J = 8, 7, 3, H-9), 1.56 (dd, 1H, J = 9, 4, H-7), 1.64 (d, 1H, J = 11, H-5β), 1.71 (d, 1H, J = 11, H-5α), 1.75, (ddd, 1H, J = 12, 9, 4, H-3α), 1.92 (ddd, 1H, J = 13, 8, 3, H-10a), 1.93 (ddd, 1H, J = 12, 8, 3, H-2α), 1.97 (ddd, 1H, J = 19, 7, 4, H-11β), 2.05 (ddd, 1H, J = 19, 9, 3, H-11α); ^{13}C NMR δ 20.21 (CH_3, C-15), 21.19 (CH_3, C-11), 26.11 (CH_3, C-12), 28.30 (CH_3, C-13), 31.42 (CH_3, C-14), 33.07 (CH_2, C-2), 35.21 (CH_2, C-10), 35.79 (CH, C-9), 40.08 (CH_2, C-3), 43.68 (CH, C-7), 48.79 (C-6), 52.46 (C-4), 55.09 (CH_2, C-5), 131.08 (C-1), 155.84 (C-8); MS, *m/z* (rel intensity) 204 (M^+, 39.2), 189 (M − CH_3, 74.4), 175 (M − C_2H_5, 17.9), 161 (60.1), 119 (100); HRMS calcd for $C_{15}H_{24}$ 204.1878, found 204.1874. For **10** (80% pure by GC): $[\alpha]_D^{26}$ = +12.8° (c = 0.23, $CHCl_3$, corrected to 100% purity, $[\alpha]_D$ = +47.3°); IR (neat) 2927, 2846, 1455, 1370, 1259, 1099, 802, 622 cm^{-1}; ^1H NMR δ 0.98 (d, J = 6.9 Hz, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.31 (m, 3H), 1.72 (m, 4H), 1.96 (m, 1H), 2.14 (m, 1H), 2.28 (m, 2H), 2.69 (m, 1H); ^{13}C NMR δ 20.20, 24.06, 24.76, 25.42, 30.81, 31.13, 35.14, 36.82, 45.72, 47.38, 48.98, 54.13, 77.20, 131.52, 161.08; MS, *m/z* (rel intensity) 204 (M^+, 7.8), 189 (M − CH_3, 48.4), 119 (100); HRMS calcd for $C_{15}H_{24}$ 204.1878, found 204.1875.

Presilphiperfol-1(8)-ene Epoxides (13α and 13β). A solution of **9** (10 mg, 0.5 mmol) in 10 mL of CH_2Cl_2 was stirred and cooled at 0 °C as *m*-CPBA (110 mg, 55%, 0.346 mmol) was added in one portion. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was washed with aqueous saturated 15% aqueous NaOH (10 mL), saturated aqueous Na_2CO_3 (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$) and evaporated at reduced pressure. Purification by flash chromatography using hexane−ether (20:1) as eluant provided 7 mg (65%) of epoxides as colorless oil. GC/MS analysis and the ^1H NMR spectrum showed that resulting product was a 3:1 (or 1:3) mixture of epoxides **13**α and **13**β (90−95% purity). The ^1H chemical shifts of major isomer are in agreement with those in literature.[1] For the major epoxide: ^1H NMR δ 0.91 (s, 3H, CH_3), 0.93 (d, J = 6.6 Hz, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); MS, *m/z* (rel intensity) 220 (22), 165 (100), 136 (21), 121 (37), 110 (54). For the minor epoxide; ^1H NMR δ 0.62 (s, 3H, CH_3), 0.76 (d, J = 6.3 Hz, 3H, CH_3), 0.85 (s, 3H, CH_3), 1.04 (s, 3H, CH_3); MS, *m/z* (rel intensity) 220 (84), 205 (7), 192 (37), 178 (26), 165 (100). Only 12 of the 30 observable resonances in the ^{13}C NMR spectrum could be definitively assigned to major isomer. Those 12 peaks have δ 61.15, 48.42, 43.53, 40.96, 36.85, 31.93, 29.04, 28.99, 27.96, 27.50, 24.61, and 19.00. The other 18 peaks have δ 70.63, 55.95, 47.56, 45.83, 44.78, 41.12, 34.77, 32.31, 30.96, 30.19, 24.64, 23.10, 22.43, 22.12, 21.00, 19.42, 18.98, and 18.89.

Presilphiperfol-7-ene Epoxides (14α and 14β). Olefin **10** (10 mg, 0.05 mmol, 80% pure with 20% **9**) was converted to the epoxides (7.1 mg, 66%), in the same way described for **9**. The ^1H NMR spectrum showed that the product was a mixture of 3:1 mixture of presilphiperfol-7-ene epoxides (80%) together with a 3:1 mixture of presilphiperfol-1(8)-ene epoxides (20%) based on ^1H NMR analysis. For the major epoxide: ^1H NMR δ 0.86 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.96 (d, J = 6.3 Hz, 3H, CH_3). For the minor epoxide: ^1H NMR δ 0.72 (s, 3H, CH_3), 0.86 (d, J = 7.5 Hz, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.06 (s, 3H, CH_3). Since the epoxides were not be separated by GC, the GC/MS data reported are not assignable to **14**α and **14**β individually: MS, *m/z* (rel intensity) 220 (42), 205 (18), 192 (60), 177 (24), 165 (100), 149(32), 136 (26).

Reduction of the 13α + 13β Mixture with Lithium in Ethylenediamine. This procedure was based on a literature method.[15] A solution of **13**α + **13**β (5 mg, 0.023 mmol) and ethylenediamine (5 mL) under nitrogen was stirred at room temperature, as freshly cut lithium pieces (80 mg, 11 mol) were added. The blue reaction mixture was stirred vigorously and heated at 50 °C for 4.5 h. After being cooled to 0 °C, H_2O (1mL) and ether (15 mL) were added, and the organic layer was washed with 3% HCl (3 × 10 mL), H_2O (10 mL), and 5% Na_2CO_3 (5 mL). Removal of solvent gave an oily residue which was purified by chromatography on silica gel to give a four-component mixture (2.9 mg, 57%, 2:1:2:3 by GC). GC analysis showed that no epoxide was present. GC/MS analysis (baseline resolution) established presumptive molecular ions at *m/z* 222 for three of the four components, consistent with the expected $C_{15}H_{26}O$ elemental composition. The following data also show characteristic differences in the fragmentation patterns for the four products (elution order): GC/MS, *m/z* **A** 222 (4), 204 (28), 189 (7), 176 (8), 166 (24), 148 (23), 135 (100), 124 (28), 109 (21); **B** 222 (18), 204 (69), 189 (16), 176 (12), 166 (52), 148 (94), 135 (53), 124 (100), 109 (59); **C** 220 (16), 205 (14), 192 (7), 177 (4), 165 (100), 149 (17), 135 (7), 122 (14), 107 (18); **D** (1) 222 (29), 207 (52), 204 (20), 189 (31), 162 (15), 149 (64), 140 (61), 111(58), 69 (100). Peak **D** was identified as presilphiperfolanol by co-injection GC and GC/MS comparisons with the natural product.

Acid-Catalyzed Rearrangements of 1. A. With Trifluoroacetic Anhydride. A solution of **1** (20 mg, 0.1 mmol) in trifluoroacetic anhydride (1 mL) was stirred and heated at 70 °C for 90 min. After it was cooled to room temperature, pentane (15 mL) was added. The solution was washed with 10% aqueous Na_2CO_3 (2 × 30 mL). Concentration and purification by preparative TLC with hexane as developing solvent gave (11.1 mg, 40%), **9** (4 mg, 20%), and trifluoroacetate **11** (3.3 mg, 11%). A commercial preparative TLC plate (Merck, precoated PLC silica gel TLC plate without fluorescence indicator, 200 × 200 × 2 mm) was used. The following IR and ^1H NMR data for **6** are in agreement with literature data.[6] For **6**: $[\alpha]^{26}$ (λ) −97.7° (589 nm), −100.0 (577 nm), −110.1 (546 nm), −195.0 (436 nm) (c = 0.16, $CHCl_3$) (Lit.[6] $[\alpha]^{24}$ (λ) −92.8° (589 nm), −96.6 (577 nm), −110.5 (546 nm), −194.0 (436 nm) (c = 0.8, $CHCl_3$)); IR (neat) 2953, 2870, 1455, 1373 cm^{-1}; ^1H NMR: δ 0.93 (d, 3H, J = 7, CH_3, H-15), 0.99 (s, 3H, CH_3, H-12), 1.51 (m, 3H, H-13), 1.54 (m, 3H, CH_3, H-14), 1.06−1.80 (m, 12H), 1.95 (d, 1H, J = 16, H-5α), 2.22 (d, 1H, J = 16, H-5β); ^{13}C NMR δ 10.83, 14.15, 19.55, 24.70, 28.92, 29.86, 36.56, 40.02, 41.23, 49.53, 52.16, 58.90, 71.67, 127.34, 135.99; MS (EI, 70 eV) *m/z* (rel intensity) 204 (M^+, 33), 189 (M −

CH_3, 16), 175 (M − C_2H_5), 57 (100); HRMS calcd for $C_{15}H_{24}$ 204.1878, found 204.1879.

For **11**: IR (neat) 2953, 2870, 1783 (CF_3C═O), 1221, 1162, 870 cm^{-1}; ^1H NMR δ 0.96 (s, 3H, CH_3, H-12), 0.98 (d, 3H, J = 6, CH_3, H-15), 1.06 (s, 3H, CH_3, H-13), 1.13 (s, 3H, CH_3, H-14), 1.24−1.38 (m, 2H), 1.42−1.73 (m, 8H), 1.87 (m, 2H), 2.11 (t, 1H, J = 8), 5.17 (s, 1H); ^{13}C NMR δ 19.12, 24.95, 25.21, 29.00, 31.78, 35.19, 35.54, 39.64, 39.66, 43.58, 49.24, 52.57, 52.92, 77.21, 95.08. The signals for the trifluoromethyl and carbonyl carbons were too weak to be observed. MS (EI, 70eV) *m*/*z* (rel intensity) 204 (M^+, 33), 189 (M − CH_3, 16), 175 (M − C_2H_5), 57 (100); HRMS calcd for $C_{15}H_{24}$ 204.1878, found 204.1879.

B. With H_2SO_4−Silica Gel. A suspension of **1** (22 mg, 0.1 mmol) and 5% (w/w) of concentrated sulfuric acid on Woelm 32−64-mm silica gel[19] (200 mg, 0.1 mmol) in benzene (1.2 mL) was stirred and heated at 70 °C for 3 h. It was cooled to room temperature and filtered, and pentane (15 mL) was added. The solution was washed with 10% aqueous Na_2CO_3 (2 × 10 mL). Concentration gave 16 mg (79%) of colorless oil, GC analysis of which showed two trace components in addition to **6** in a 1:98:1 ratio. The third eluting peak was identified as α-terrecyclene (**12**) by co-injection analyses and GC/MS comparisons with an authentic sample.[19] The IR and ^1H NMR spectra are indistinguishable from those obtained for **6** in part A. The identity of the other trace component is unknown: GC/MS, *m*/*z* 204 (14), 175 (100), 147 (7), 133 (14), 122 (23), 109 (24), 91 (6), 77 (7).

Solvolysis of Presilphiperfolan-8-yl *p*-Nitrobenzoate (8a) A. Product Isolation. A solution of **8a** (37.1 mg, 0.10 mmol) in 10.0 mL of 60% aqueous acetone was placed in a 10-mL resealable pressure tube (Aldrich Chemical Co.) under nitrogen. The solution was stirred and heated at 50 °C in an oil bath for 24 h. The progress of the solvolysis was followed by TLC. The pressure tube was cooled to room temperature, and the solution was concentrated under reduced pressure to remove most of the acetone. The products were extracted into CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with 10% Na_2CO_3 (1 mL) and brine (1 mL) before drying ($MgSO_4$). Removal of solvent afforded 24 mg of colorless oil. GC analysis showed the presence of **9** and **10**, **6**, and **1** in 12:3:1:1 ratio.

The products were separated into two main fractions by flash chromatography on silica gel with pentane−ether 9:1 as eluant. The olefin fraction (17.5 mg, 86%) was a 12:3:1 mixture of **9**, **10**, and **6** according to GC analysis. The second fraction (2 mg, 9%) contained a single alcohol (**1**). Further identification of the four products was accomplished by ^1H NMR spectral analysis for olefin mixture and **1** and GC co-injection analysis with authentic samples and GC/MS comparisons with the authentic mass spectra.

B. Kinetics. Two consecutive solvolysis runs with **8a** were carried out as described in part A (0.10 mmol in 10 mL of solvent).[21,24] The bath temperature was maintained at 50.0 ± 0.1 °C. Six 1.00-mL aliquots were taken at ∼3-h intervals by rapidly chilling the tube in ice water, removing the aliquots by pipet, and reheating quickly to 50 °C. Titration with 0.00110 M NaOH (methyl orange indicator) and graphical plots gave the following rate constants: 5.14×10^{-5} and 5.25×10^{-5} s^{-1}. Calibration runs with cyclohexyl *p*-nitrobenzoate agreed well with the literature (see Table 2).

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Supporting Information Available: A list of positional and thermal parameters, and summaries of crystal data and structure refinement bond lengths and angles, and an ORTEP plot for **8a** (8 pages). See any current masthead page for ordering and Internet access instructions.

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