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Total Synthesis of (±)-Cameroonan-7α-ol and Biomimetic Rearrangements to Related Nopsane Sesquiterpenes

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A total synthesis of the novel silphinane sesquiterpene alcohol (±)-cameroonanol (**6**-OH) from bicyclic enone **10** was accomplished by conjugate addition of crotylsilane, photochemical hydrobromination, intramolecular alkylation, and hydride reduction. The stereoisomers cameroonan-7*β*-ol (**18**-OH) and 9-epicamerooonanols (**19** and **20**) were separated from isomer mixtures and the 9-desmethyl-cameroonanols (**21**-OH and **22**-OH) were obtained by similar means. Solvolysis of **6**-OMs and **18**-OMs effected skeletal rearrangements to (±)-silphiperfol-6-ene (**5**), (±)-prenopsanol (**7**) and (±)-nopsanol (**8**), and (±)-silphiperfolan-7*β*-ol (**9**) in parallel with biogenetic schemes proposed for these naturally occurring sesquiterpenes. The nor analogues **21**-OMs and **22**-OMs underwent solvolytic rearrangments to a similar set of nor products. The increase in solvolytic rates for the 7*β*-mesylates **18**-OMs and **22**-OMs in comparison to the 7α epimers is attributed to concerted antiperiplanar Wagner−Meerwein rearrangements to the prenopsyl and norprenopsyl carbocations. Further analysis of the kinetic data and comparisons with solvolysis rates for the structurally related silphin-1*β*-yl and silphin-1α-yl mesylates (**28** and **29**) are presented. The rearrangements observed afford chemical precedent for the biogenetic pathways in the literature for these silphinane sesquiterpenes.

Introduction

The isolation, structure elucidation, and synthesis of the triquinane sesquiterpenes continue to be active areas of research.[1] The silphinane subclass of the numerous tricyclic skeletal types are usually characterized by a bicyclo[3.3.0]octane core angularly fused to, or bridged by, another three carbons. This sesquiterpene family is thought to be biogenetically derived from (*E*,*E*)-farnesyl diphosphate (**1**) by ring expansion of a caryophyllenyl ion, *π*-cyclization, and 1,3-hydride shift to generate the presilphiperfolanyl branch point intermediate $\mathbf{A}^+$, the precursor of (−)-presilphiperfolanol (**2**) (Scheme 1).[2−4] Rearrangement of $\mathbf{A}^+$ along path **a** through the silphinyl ion $\mathbf{B}^+$ accounts for silphinene (**3**) and the unnatural tricyclic sesquiterpene α-terrecylene (**4**). Wagner−Meerwein and methyl group rearrangements along path **b** through ion $\mathbf{C}^+$ provide a rationale for the origin of the silphiperfolenes (e.g. silphiperfol-6-ene, (−)-**5**).

Weyerstahl and co-workers recently reported the isolation of three new sesquiterpene alcohols, (−)-cameroonan-7α-ol (**6**-OH), (+)-prenopsan-8-ol (**7**), and (−)-nopsan-4-ol (**8**), from the essential oil of *Echniops giganteus var lelyi* rhizomes.[5] These natural products were isolated from a complex mixture of numerous biogenetically related silphinanes including five of the eight possible silphiperfolan-6-and 7-ols, one being the previously known (−)-silphiperfolan-7*β*-ol, **9**.[6] Cameroonanol and prenop-

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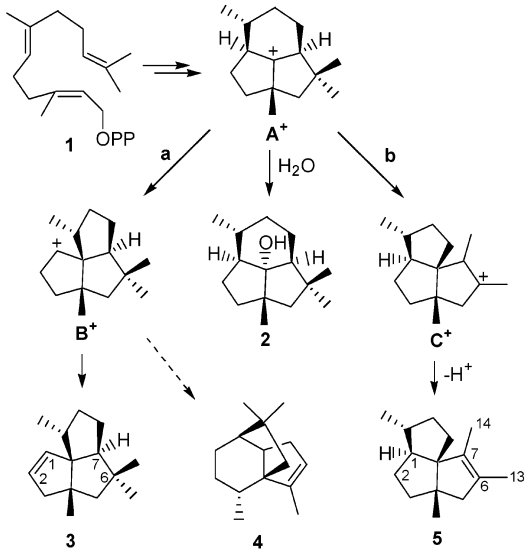

(1) For reviews, see: (a) Fraga, B. M. *Nat. Prod. Rep.* **2002**, *19*, 650; **2001**, *18*, 650; and previous reviews in this series. (b) Goldsmith, D. J. *The Total Synthesis of Natural Products*; Wiley-Interscience: New York, 2000; Vol 11. (c) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671.

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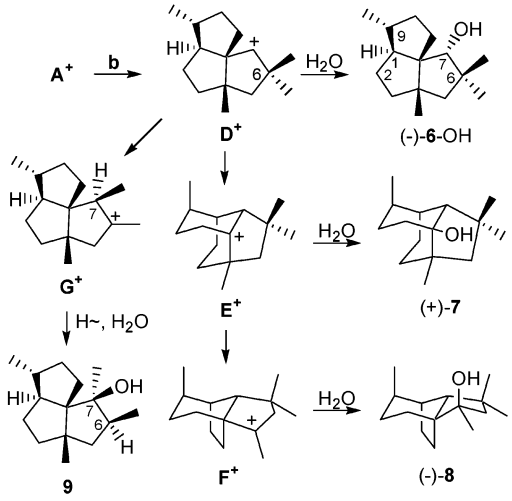

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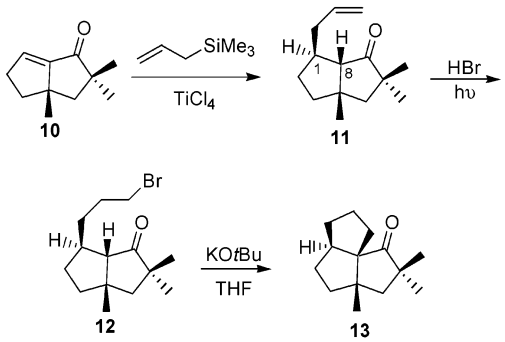

sanol were considered to be the main contributors to the strong patchouli-like, woody odor characteristic of the essential oil.

The structures and relative stereochemistry of these natural products were assigned mainly by NMR spectral methods.[5] The absolute configurations shown were based on the co-occurrence with silphinane sesquiterpenes of known configuration (e.g. **2** and **5**), and the biogenetic relationships presented in Schemes 1 and 2. The new skeletal types were proposed to arise from the presilphiperfolanyl ion $\mathbf{A}^+$ via path **b** through the cameroonanyl ion $\mathbf{D}^+$ ion by water capture on the α face, and further Wagner−Meerwein rearrangements to prenopsyl and nopsyl ions, $\mathbf{E}^+$ and $\mathbf{F}^+$. We report here the full details concerning the first total synthesis of (±)-cameroonanol[7] and in addition solvolytic rearrangements of the epimeric cameroonanyl mesylates to (±)-prenopsanol, (±)-nopsanol, (±)-silphiperfolan-7β-ol, and (±)-silphiperfol-6-ene, which validate these structures and biogenetic hypotheses.

Results and Discussion

Synthesis of Cameroonanols. The angular triquinane nucleus of cameroonanol was synthesized by conjugate addition to bicyclic enone **10** and intramolecular alkylation. We chose to prepare the norcameroonanone analogue **13** first for use as a model compound to avoid chromatographic separation of isomers (Scheme 3). Synthesis of norcameroonanone began with a five-step preparation of the known bicyclic enone **10**[8] from isobutyric acid.[9,10] Construction of the third ring of **13** was initiated by a Sakurai addition[11] (1 M $TiCl_4$, CH_2Cl_2, −78 °C) of allyltrimethylsilane to enone **10**, which gave exclusive formation of δ,ϵ-enone **11** (82%). The 1,8-anti stereochemistry of **11** was assigned based on the magnitude of the coupling constants for the C1 and C8 hydrogens (J = 3.6 Hz) and expectation of nucleophilic attack on the convex face of the enone.[12] Radical hydrobromination ($h\upsilon$, 254 nm, HBr, pentane)[13] of keto olefin **11** afforded bromo ketone **12** (60%) with only minor amounts (≤5%) of the Markovnikov product recognized by appropriate ^{1}H NMR absorptions for a C*H*BrCH$_3$ group (δ_H 4.2) in the unpurified product. Reaction of purified **12** with KOtBu (1.0 M in THF, 1.5 equiv) effected cyclization to norcameroonanone (**13**) in 98% yield.

The synthesis of cameroonanone was carried out by using the procedures developed with the nor model compounds. Sakurai addition of (*Z*)- and (*E*)-crotyltrimethylsilanes[14] provided 1.1:1 and 1:1.8 mixtures[15] of anti and syn α-methylallyl isomers **14a** (1′α methyl) and **14b** (1′β methyl) according to GC and ^{1}H NMR analyses (Scheme 4). The bicyclo[3.3.0]octan-2-one adducts **14a**,**b**

(6) Coll, J. C.; Wright, A. D. *Aust. J. Chem*. **1989**, *42*, 1591.
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(9) Significant modifications were made in adapting the literature methods[8] to larger scale preparation of the critical enone intermediate **10**.[10] Alkylation of isobutyrate dianion with methallyl chloride afforded 2,2,4-trimethyl-4-pentenoic acid in yields of 46 (82%) and 52 g (92%) after vacuum distillation.[9a,b] Polyphosphoric acid-mediated cyclization (20 wt %, 90 °C)[9c] to 3,5,5-trimethyl-2-cyclopentenone by way of the lactone, 3,3,5,5-tetramethyldihydrofuran-2-one,[9d] proved to be convenient and cost-effective on a large scale (29.8 g, 64%). Conjugate addition of the Grignard reagent from β-bromopropionaldehyde propylene acetal (CuBr·Me$_2$S, THF, 0 °C)[9e,f,8] provided 26.5 g (93%) of the keto acetal adduct following vacuum distillation. Acetal hydrolysis and aldol cyclization were accomplished simultaneously (aq HCl−THF, reflux, 30 min).[8b] The crude mixture of ketol isomers (β-OH/α-OH ratio, 9:1) was dehydrated to enone **8** (9.8 g, 71% after flash chromatography) by mesylation (MsCl/Et$_3$N in CH_2Cl_2) and β-elimination (DBU in CH_2Cl_2).[8a] The following alternative procedures for conversion of 2,2,4-trimethyl-4-pentenoic acid to 3,3,5-trimethyl-2-cyclopentenone were evaluated and deemed less convenient: (i) P_2O_5 in CH_3SO_3H (40 h, rt, 0.60 g, 61%);[9g] (ii) $(COCl)_2$ or $SOCl_2$ followed by $AlCl_3$ (CS_2, reflux, 3.43 g, 58%).[9b,h] For experimental details, see Supporting Information and ref 10: (a) Creger, P. L. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 517. (b) Hayashi, Y.; Nishizawa, M.; Sakan, T. *Tetrahedron* **1977**, *33*, 2513. (c) Dorsh, M.; Jager, V.; Sponlein, W. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 798. (d) Bertrand, P. M.; Dulcere, J. P.; Gil, G.; Grimaldi, J.; Sylvestre-Panthet, P. *Tetrahedron Lett*. **1976**, *37*, 3305. (e) Stowell, J. C.; Keith, D. R.; King, B. T. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 59. (f) Stowell, J. C. *J. Org. Chem*. **1976**, *41*, 560. (g) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem*. **1973**, *38*, 4071. (h) Weyerstahl, P.; Marschall, H.; Schulze, M.; Schwope, I. *Liebigs Ann. Chem*. **1996**, 799.

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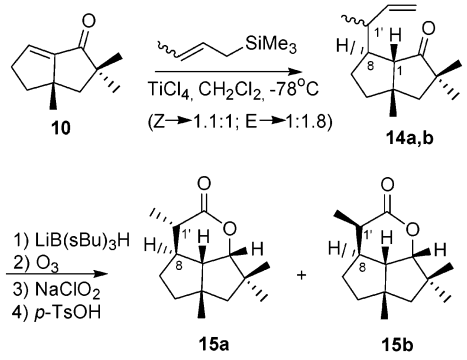
(12) For *cis*-3,3,5-trimethylbicyclo[3.3.0]octan-2-ones and -2-ols bearing substituents at C8, $^3J_{anti}$ = 0−5.1 Hz (5 compounds) and $^3J_{syn}$ = 8.1−9.8 Hz (3 compounds). See ref 10, p 34.

(13) Molander, G. A.; McKie, J. A. *J. Org. Chem*. **1991**, *56*, 4112.

(14) (a) Hayashi, T.; Kabeta, K.; Kumada, M. *Tetrahedron Lett*. **1984**, *25*, 1499. (b) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn*. **1976**, *49*, 1958. (c) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem*. **1986**, *51*, 3772. (d) Tokoyorama, T.; Pan, L. R. *Tetrahedron Lett*. **1989**, *30*, 197.

(15) The product ratio was corrected for the isomeric purity of the (*Z*)-crotylsilane (*Z*/*E* ratio 5:1).

SCHEME 4



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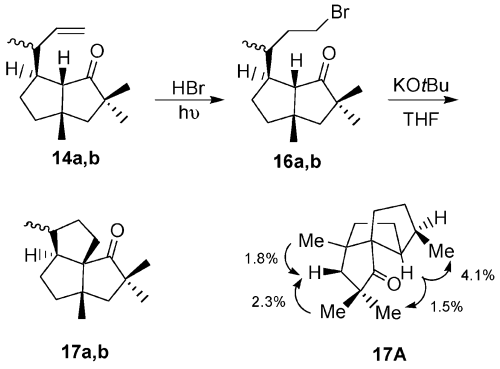
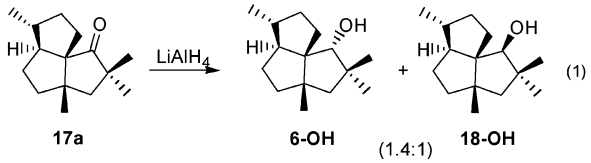


were shown to have the thermodynamically more stable cis ring junction stereochemistry.[16] Exposure of a 1:1 mixture of ketones **14a** and **14b** with KOH in CD_3OD led to 90% deuterium incorporation at C1 with no evidence for formation of the trans isomer by GC and NMR spectral comparisons. The 1,8-anti stereochemistry of **14a** and **14b** was assigned from the magnitude of the ^{1}H NMR coupling constants (J_{1-8} = 3.7, 4.9 Hz) for the C1 and C8 hydrogens as described above.[12] The relative configurations of the C1′-methyl group had been previously determined by comparison of coupling constants (H1′ and H8) for lactones **15a** and **15b** prepared from methallyl ketones **14a** and **14b** by LiB(^{s}Bu)$_3$H reduction, ozonolysis, sodium chlorite oxidation, and acid-catalyzed lactonization.[7,10]

Radical hydrobromination (*hν*, 254 nm, HBr) of 1:1 and 1:1.8 mixtures of methallyl ketones **14a** and **14b** afforded 1.2:1 and 1:1.8 mixtures of bromo ketones **16a** and **16b** (72−73%) which underwent clean cyclization to 1:1 and 1:1.6 mixtures (92% and 77%) of (±)-cameroonanone (**17a**) and (±)-9-epicameroonanone (**17b**) (Scheme 5). The consistent isomer ratios and spectral data observed for the bromo ketones and the cyclization products ensured that **14a** was converted into **17a** having the natural configuration at the secondary methyl group. The epimeric ketones were separated by silica gel chromatography, and the ^{1}H NMR (500 MHz, $CDCl_3$), ^{13}C NMR (126 MHz, $CDCl_3$ and C_6D_6), IR (CCl_4), and MS (EI, 70 eV) data for the less polar **17a** agreed with those presented in the literature for (−)-cameroonanone obtained by H_2CrO_4 oxidation of (−)-**6**-OH.[5a] The relative stereochemistry of **17a** was also confirmed by NOE experiments (750 MHz, C_5D_5N) as shown in **17A**.

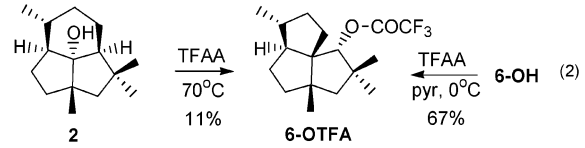
(16) Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311.

Reduction of (±)-cameroonanone **17a** with $LiAlH_4$ (Et_2O, 0 °C)[5a] afforded a 1.4:1 mixture of (±)-cameroonan-7α and 7*β*-ols (**6**-OH and **18**-OH, 86%) (eq 1), samples of

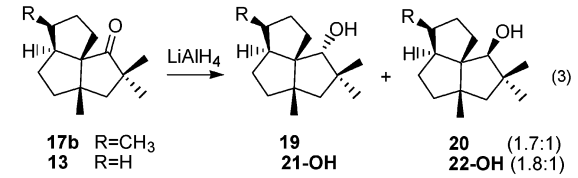


which were obtained in pure form by flash chromatography. The less polar (±)-**6**-OH (mp 48−49 °C) gave ^{1}H NMR (500 MHz, $CDCl_3$), ^{13}C NMR (126 MHz, $CDCl_3$ and C_6D_6), IR (CCl_4), and mass spectral (EI, 70 eV) data that agree precisely with those given in the literature for (−)-**1**-OH.[5a] Similar comparisons of the more polar isomer (±)-**18**-OH (mp 62−63 °C) with the unnatural cameroonan-7*β*-ol confirmed its identity as well. The cameroonanol epimers are readily distinguished by key ^{1}H NMR (500 MHz, $CDCl_3$) resonances: **6**-OH *δ* 0.91 (s, 3H, CH_3), *δ* 1.00 (d, 3H, J = 6.6 Hz, C9−CH_3), and *δ* 3.69 (d, 1H, J = 7.9 Hz, C*H*OH); **18**-OH *δ* 0.83 (s, 3H, CH_3), *δ* 0.92 (d, 3H, J = 6.6 Hz, C9−CH_3), and *δ* 3.36 (d, 1H, J = 6.8 Hz, C*H*OH). The configuration of the 7α-hydroxyl group in natural cameroonanol had been established previously by extensive NOE data.[5]

The proposed structure of the trifluoroacetate formed in the reaction of presilphiperfolanol with trifluoroacetic anhydride as **6**-OTFA[2a] was confirmed by GC, ^{1}H NMR, and ^{13}C NMR comparisons with the (±)-cameroonanyl esters independently prepared from the synthetic **6**-OH and **18**-OH (eq 2).



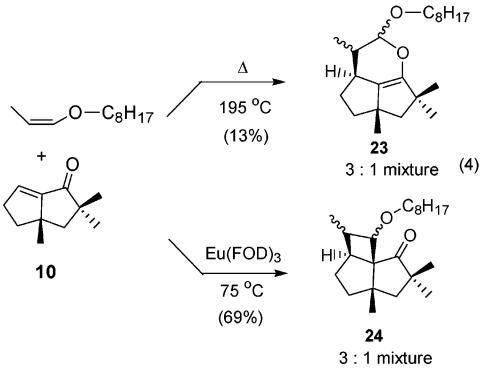
Reductions of 9-epicameroonanone **17b** and norcameroonanone **13** ($LiAlH_4$, Et_2O, 0 °C) similarly gave 1.7:1 and 1.8:1 mixtures of (±)-9-epicameroonan-7α and 7*β*-ols (**19** and **20**, 85%) and (±)-norcameroonan-7α and 7*β*-ols (**21**-OH and **22**-OH, 81%) that were fully characterized (eq 3). The configuration of the hydroxyl-bearing



stereogenic center of **21**-OH had been previously assigned based on ^{1}H NMR NOE analysis.[10] However, the structures of **19** and **20** are based solely on the similarity of product ratios observed above for the reduction of cameroonanones **17a** and **13**. Attempts to achieve higher selectivity in the reductions of ketones **17a** and **17b** with other reagents all favored the 7α isomers, but the enhancements in the proportion of (±)-**6**-OH were relatively small: 7α-OH/7*β*-OH ratios; Li/NH_3, 1.7:1 and 1.8:1; ^{i}Bu$_3$Al in benzene, 1.4:1 and 3.2:1, and AlH_3 in

Et_2O, 2.4:1 and 4.4:1. No reaction occurred with the selective, but sterically demanding $LiB(^sBu)_3H$.

Inverse Hetero-Diels−Alder Approach. The lack of stereocontrol observed in the crotylsilane Sakurai additions to bicyclic enone **10** prompted investigation of an inverse hetero-Diels−Alder reaction[17] to install the secondary methyl group with improved selectivity. It was thought that the angular methyl group of the bicyclic enone might direct the enol ether to react in an exo-fashion. In principle, hydrolysis of the dihydropyran adduct to the aldehyde followed by Wittig olefination would afford methallyl ketones **14a** and **14b**. However, the thermal inverse Diels−Alder reaction with cis *n*-octyl propenyl ether required high temperatures (195 °C) and resulted in low yields (13%) of the enol acetals as a 3:1 mixture (^{1}H NMR) of isomers (eq 4).



Lewis acids catalysis[18] of the inverse Diels−Alder reaction was also examined with $BF_3{\cdot}OEt_2$, Et_2AlCl, TMSOTf, $ZnCl_2$, $Dy(thd)_3$, $Yb(FOD)_3$, $Ag(FOD)_3$, and $Eu(FOD)_3$. The best results were obtained with $Eu(FOD)_3$ (neat, 75 °C), which gave a 3:1 mixture (^{1}H NMR) of epimeric cyclobutyl ether isomers in 69% yield (eq 4). Unfortunately epimerization occurred during ethanolysis (cat. HCl, refluxing ethanol) resulting in a 1.4:1 mixture of keto acetals. Since additional attempts to effect hydrolysis with aqueous acid or Me_3SiI were unpromising and photochemical cycloadditions[19] were unfruitful, this approach was not pursued any further.

Solvolytic Rearrangements of Cameroonanyl Mesylates. The ready access to quantities of (±)-cameroonanol prompted experiments to effect its skeletal rearrangement into prenopsanol (**7**), nopsanol (**8**), silphiperfol-6-ene (**5**), and silphiperfolan-7β-ol (**9**) along the lines of the biogenesis proposed for the four sesquiterpene natural products.[5a] (Schemes 1 and 2). It was anticipated that the epimeric cameroonanyl mesylates **6**-OMs and **18**-OMs would undergo solvolysis at appreciably different rates as observed previously for the structurally related silphinyl mesylate epimers **28** and **29** (eq 5).[2b] This expectation was borne out in preliminary reactions, and the reactivity difference (26-fold) was sufficient to quantify the rates and to determine the products from solvolyses conducted with a 1:1.5 mixture of the stereoisomers in 75% aqueous acetone (3:1 acetone-d_6:D_2O) at 25 and 70 °C.

(17) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651.
(18) Carruthers, W. Cycloaddition Reactions in Organic Synthesis; Pergamon Press: Exeter, UK, 1990.
(19) Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297.

TABLE 1. Kinetic Data for Solvolyses of Cameroonanyl, Norcameroonanyl, and Silphinyl Mesylates in 3:1 Acetone-d_6:D_2O at Various Temperatures[a]

entry	mesylate	config	temp (°C)	$k_{obs} \times 10^5$ (s^{-1})[b]	k_{rel}
1	**6**-OMs	7α	25	0.25[c]	(1)
2			55	10	
3			70	50	
4	**18**-OMs	7β	25	6.5 ± 0.5	26
5	**21**-OMs	7α	70	40	
6	**22**-OMs	7β	25	7.5 ± 0.5	
7	**28**[d]	1β	25	0.30 ± 0.5	(1)
8	**29**[d]	1α	25	310 ± 20	1000

[a] Kinetic measurements by integration of H7 (C*H*OMs) in ^{1}H NMR spectra recorded over 5 half-lives. [b] R-factor was ≥0.9 in all entries. The deviations given refer to reproducibility of duplicate runs. Other entries were single runs. [c] Extrapolated value. [d] Literature data from ref 2b. See eq 5.

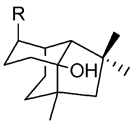
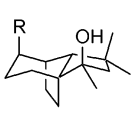
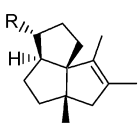
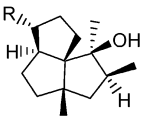
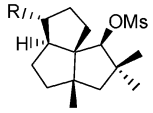
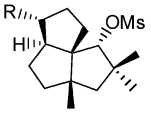
The first-order rates were determined by following the disappearance of the C7 carbinyl proton C*H*-OMs by integration of ^{1}H NMR spectra conducted at the specified temperatures (Table 1). Kinetic data were recorded over 5 half-lives and fit to the first-order rate expression. The rate constant for **6**-OMs at 25 °C was calculated by extrapolation from rate constants measured at 55 and 70 °C. Kinetic data for the norcameroonanyl mesylates **21**-OMs and **22**-OMs were determined in the same manner. The absolute and relative rates are presented in Table 1 along with data for the related silphinyl mesylates **28** and **29**.[2b]

Preparative solvolysis of the more reactive 7β isomer (**18**-OMs) for 24 h at 25 °C in 75% aqueous acetone with pyridine as buffer brought about rearrangement to a 7:1 mixture (47%) of (±)-prenopsanol (**7**) and (±)-silphiperfolene (**5**) as major products together with a small amount of (±)-silphiperfolan-7β-ol (**9**, ∼2%), and the slower reacting 7α mesylate **6**-OMs was recovered in pure form (66%) after chromatographic purification (Table 2). The actual product distributions were estimated by GC and NMR analyses before chromatography. However, the product ratios may be slightly skewed by small contributions from the products derived from partial solvolysis of the slower reacting 7α isomer (16% conversion of **6**-OMs).

Similar solvolysis of **6**-OMs at 70 °C gave rise to a mixture of (±)-prenopsanol (**7**, 18%), (±)-nopsanol (**8**, 6%), (±)-silphiperfol-6-ene (**5**, 18%), and (±)-silphiperfolan-7β-ol (**9**, 4%). The racemic rearrangement products were identified by comparison of their ^{1}H and ^{13}C NMR spectral data and mass spectral (EI) fragmentation patterns with those reported in the literature for the enantiopure compounds.[2a,5,6] Especially diagnostic were the 500-MHz ^{1}H NMR shifts for the methyl groups.[5a] The small, consistent discrepancies ($\Delta\delta \approx 0.06$) in the ^{1}H NMR data for nopsanol are likely attributable to differences in referencing the spectrum. It is noteworthy that (±)-**7** exhibited a woody fragrance consistent with that reported for the enantiomerically pure sesquiterpene alcohol.[5a]

Small amounts of other minor products were also partially characterized by spectral analyses of 2-component mixtures; however, efforts to identify them with certainty were unsuccessful. The spectral properties of two minor olefins (**A** and **B**, ∼2% each) isolated from the solvolysis of **18**-OMs as a 1.3:1 mixture are distinct from

TABLE 2. Structures and Isolated Yields of Products from Solvolysis of Cameroonanyl and Norcameroonanyl Mesylates in 75% Aqueous Acetone

Cameroonan-7-yl Mesylates				Products[b]							
											
	R	No.	Temp (°C)	No.	Yield (%)	No.	Yield (%)	No.	Yield (%)	No.	Yield (%)
	CH_3	**18-OMs**[a]	25	(±)-**7**	41	(±)-**8**	-	(±)-**5**	6	(±)-**9**	2
	H	**22-OMs**[c]	25	**25**	41	**26**	-	**27**	5	-	-
	CH_3	**6-OMs**	70	(±)-**7**	18	(±)-**8**	6	(±)-**5**	18	(±)-**9**	4
	H	**21-OMs**	70	**25**	25	**26**	8	**27**	24	-	-

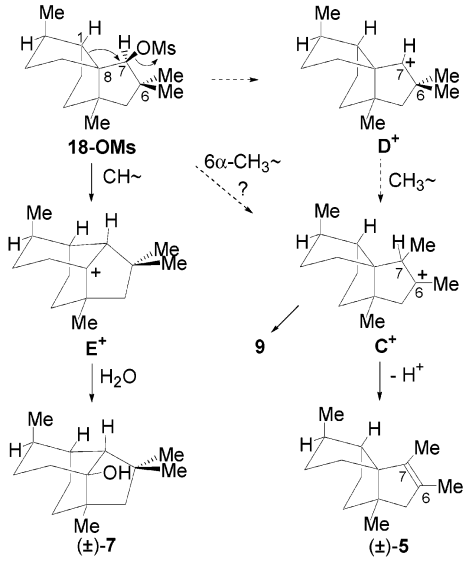
[a] Solvolysis conducted on a 1:1.5 mixture of **18**-OMs and **6**-OMs. [b] Product compositions prior to purification were estimated as follows: **18**-OMs, 7:1 of (±)-**7**, (±)-**5**; **22**-OMs, 17:2:1:1 of **25**, **27**, **D**, **E**; **6**-OMs, 6:5:2:1:1 of (±)-**5**, (±)-**7**, (±)-**8**, **B**, (±)-**9**; **21**-OMs, 9:8:4:4:1 of **27**, **25**, **26**, **D** + **E**, **F**. [c] Solvolysis conducted on 1:2 mixture of **22**-OMs and **21**-OMs.

those of the naturally occurring silphiperfol-6α- and 6β-7-enes.[20] The presence of two doublets for CHCH_3 and two vinyl hydrogens in the ^{1}H NMR spectrum suggests that **A** is probably one of the four possible unknown silphiperfolenes with an exocyclic double bond (i.e., silphiperfol-6,13- or 7,14-enes). The single vinyl proton appearing as a narrow quartet in the spectrum of unknown **B** indicates the likely presence of an endocyclic double bond bearing a methyl group and a mechanistically different origin.

A more polar fraction proved to be a 4:1 mixture of silphiperfolan-7β-ol (**9**, ~2%)[5a,6] and an unidentified tertiary alcohol **C** found to have significantly different NMR spectral properties than those of the four other known silphiperfolanols.[5a] GC co-injection experiments with authentic samples proved that **C** is different from presilphiperfolanol (**2**) and both of the silphin-1-ol epimers (**28** and **29**). A plausible structure consistent with the spectral data would be one of the two unknown silphiperfolan-7-ols having a 6α methyl configuration.

Selective solvolyses of norcameroonanyl mesylates **21**-OMs and **22**-OMs were carried out in the same manner, and the results are summarized in Tables 1 and 2. Chromatographic purifications gave norprenopsanol (**25**), nornopsanol (**26**), norsilphiperfol-6-ene (**27**), unknown olefins **D** and **E**, and an unidentified alcohol **F**. The similar rates and distributions of the major products indicate that the secondary methyl group has little effect on the course of the reaction. The identity of **27** was confirmed by comparison of its ^{1}H and ^{13}C NMR spectra with those of a sample prepared independently.[21] The structure of **25** was established by ^{1}H, ^{13}C, and HMBC NMR analyses. The identity of nornopsanol (**26**) was tentatively assigned based on analogy to solvolysis of **6**-OMs and similarities of its physical properties (TLC R_f, GC, ^{1}H NMR) to those of (±)-nopsanol (**8**). The structures of the three unidentified minor products **D**−**F**

SCHEME 6

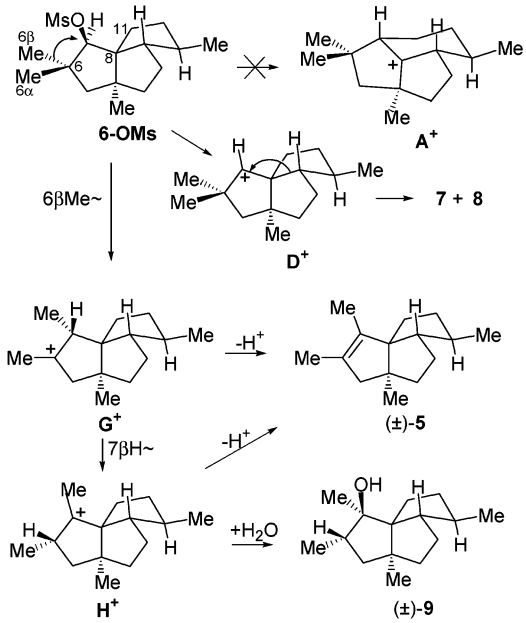


very likely correlate with **A**−**C** formed in the solvolyses of **6**-OMs and **18**-OMs.

Plausible conformations for the tricyclo[6.3.0.0^{1,5}]-undecane ring system of the epimeric cameroonanyl mesylates and rearrangement mechanisms are illustrated in Schemes 6 and 7. It seems reasonable to suppose that the 26-fold faster rate of the 7β isomer **18**-OMs reflects participation by the C1−C8 σ bond in the solvolytic transition state and concerted Wagner−Meerwein rearrangement to a more stable tertiary prenopsyl ion $\mathbf{E}^+$ that undergoes water capture to give (±)-**7**. In contrast, the rearrangement of the antiperiplanar C−C bond (C8−C11) in the less reactive **6**-OMs isomer corresponding in stereochemistry to natural cameroonanol, (−)-**6**-OH, would lead back to its hypothetical biogenetic antecedent, the presumably strained presilphiperfolan-8-yl ion $\mathbf{A}^+$ (Scheme 7). The parent trans-fused tricyclo[5.3.1.0^{4,11}]undecane nucleus is estimated to be strained by ca. 5 kcal/mol.[22] The absence of detectable amounts of presilphiperfolanol (**2**), the presilphiperfol-7- and 1(8)-

(20) Weyerstahl, P.; Marschall-Weyerstahl, H.; Schroder, M.; Brendel, J.; Kaul, V. K. *Phytochemistry* **1991**, *30*, 3349.
(21) Davis, C. E. Ph.D. Dissertation, University of Illinois, Urbana, IL, 2003.

SCHEME 7



ene isomers, and silphinene (**3**) in the product mixtures from both **6**-OMs and **18**-OMs was verified by GC co-injections with authentic samples, and these observations are consistent with the unfavorable nature of this rearrangement. Thus, heterolysis of **6**-OMs likely proceeds to a localized cameroonanyl ion $\mathbf{D}^+$ (or $\mathbf{D}^+/OMs^-$ ion pair) that undergoes successive skeletal rearrangements to the prenopsyl ion and nopsyl ions ($\mathbf{E}^+$ and $\mathbf{F}^+$) leading to the respective tertiary alcohols, (±)-(**7**) and (±)-(**8**).

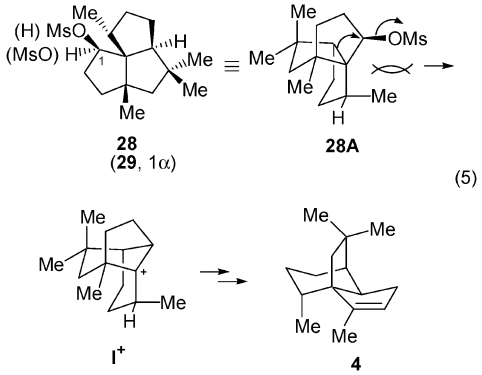
The most notable differences in the product distributions from **6**-OMs and **18**-OMs are the absence of the double rearrangement product nopsanol (±)-**8** in the products arising from solvolysis of the 7β mesylate and the increased proportion of methyl migration products, silphiperfolene (±)-**5** and silphiperfolan-7β-ol (±)-**9**, in the products from the less reactive 7α isomer. These differences might be caused in part by the temperature difference (room temperature vs 70 °C) and/or by the stereochemistry of the leaving group. Thus the solvent nucleophile might be delivered more rapidly to $\mathbf{E}^+$ from a hydrated mesylate anion in an $\mathbf{E}^+/OMs^-\cdots HOH$ ion pair generated by concerted rearrangement of **18**-OMs (Scheme 6). The increased amounts of (±)-**5** and (±)-**9** in the products from **6**-OMs indicate more favorable 6,7-methyl rearrangement (Scheme 7).

The 6β-methyl stereochemistry in silphiperfolan-7β-ol (**9**) must arise in 3 steps by initial migration of the 6β methyl group to C7, hydride shift of H7α to C6, and water capture on the same face (**6**-OMs → $\mathbf{G}^+$ → $\mathbf{H}^+$ → (±)-**9**, Scheme 7). Thus, it is the C6 geminal methyl trans to the mesylate leaving group that undergoes the initial 1,2 Nametkin rearrangement on the way to (±)-**9**. In addition, ionization of **6**-OMs to form a cameroonanyl ion $\mathbf{D}^+$ followed by rearrangement to the prenopsyl skeleton likely competes with migration of the C6-methyl group.

(22) Osawa, E.; Aigami, K.; Takaishi, N.; Inamoto, Y.; Fujikura, Y.; Majerski, Z.; Schleyer, P. v. R.; Engler, E. M.; Farcasiu, M. *J. Am. Chem. Soc.* **1977**, *99*, 5361.

It is curious that neither of the cameroonanol epimers **6**-OH or **18**-OH resulting from direct water capture of the cameroonanyl ion $\mathbf{D}^+$ was detected in the products. However, this ion is trapped as the trifluoroacetate in trifluoroacetic anhydride-induced dehydration of presilphiperfolanol **2** (eq 2),[2a] and its water capture is proposed to be the biogenetic origin of (−)-cameroonanol (Scheme 2).[5a]

Comparisons of the kinetic data in Table 1 afford some insights on the effects of methyl substitution patterns and stereochemistry upon the solvolytic reactivity of the cameroonanyl, norcameroonanyl, and silphinyl mesylates (eq 5). It should be noted that these compounds differ



only in the position of the methyl substituents and the relative configuration of the leaving groups on the tricyclo[6.3.0.0^{1,5}]undecane nucleus. The similarity of the absolute rate constants observed for the cameroonan-7α-yl mesylate (**6**-OMs) and its nor analogue **21**-OMs (5×10^{-4} vs 4×10^{-4} s^{-1} at 70 °C), and the corresponding 7β epimers **18**-OMs and **22**-OMs (6.5×10^{-5} and 7.5×10^{-5} s^{-1} at 25 °C), suggests that the C9 secondary methyl group has little effect on ionization rates and relative carbocation stabilities. The similar rates (2.5×10^{-6} and 3.0×10^{-6} s^{-1} at 25 °C) for the less reactive cameroonan-7α-yl and silphinyl-1α-yl mesylates **6**-OMs and **29**[23] are consistent with largely unassisted ionizations to localized cameroonanyl and silphinyl ions ($\mathbf{D}^+$ and $\mathbf{B}^+$) unaffected by the steric influences of the methyl groups. On the other hand, the much greater relative rate of the more reactive silphin-1β-yl mesylate **28** over its 1α epimer **29** ($k_{rel} = 1000$ at 25 °C) compared to that of the cameroonan-7β- and -7α-yl mesylates **18**-OMs and **6**-OMs ($k_{rel} = 26$ at 25 °C) evidently highlights an important difference in the transition state energies.[2b] One plausible factor is relief of steric interactions between the mesylate leaving group and the secondary methyl group in the transition state for heterolysis of **28** as it progresses toward the tertiary tricyclo[5.4.0.0^{4,8}]undecyl ion $\mathbf{I}^+$ and further Wagner−Meerwein rearrangement leading to α-terrecyclene **4**.

The relative energy differences between the tricyclo[6.3.0.0^{1,5}]undecane (cameroonane and silphinane), tricyclo[5.4.0.0^{4,8}]undecane (prenopsane and preterrecyclane), and tricyclo[4.3.0.2^{1,5}]undecane (nopsane and terrecyclene) ring systems and their methyl derivatives were estimated with use of ChemBats3D calculations (Table 3).[24] The cameroonane skeleton proved to be the most stable of all ring systems analyzed. The thermodynamic driving force for the cameroonanyl → prenopsyl rear-

TABLE 3. Relative Heats of Formation ($\Delta\Delta H_f$) Calculated for the Saturated Sesquiterpene Hydrocarbons (Parent, 9-nor-, and Tri-nor Derivatives) Using Chem 3D[24]

		relative energy ($\Delta\Delta H_f$, kcal/mol)		
entry	ring system	ring	9-nor	tri-nor
1	cameroonane	0	0	0
2	prenopsane	6.6	4.8	4.5
3	nopsane	8.5	6.7	7.8
4	silphinane	6.9	3.7	
5	preterrecyclane	11.3	10.1	
6	terrecyclane	12.3	9.0	
7	presilphiperfolane	19.4	19.2	10.8

rangement ($\mathbf{D}^+ \rightarrow \mathbf{E}^+$) likely arises from conversion of a localized secondary carbocation to a more stable tertiary carbocation. The energetic advantage in carbocation stability (2° vs bridgehead 3°) apparently compensates for formation of the less stable prenopsane ring system. The calculations suggest that the nopsane ring system is 1.9 kcal/mol less stable than the prenopsane skeleton that lies biogenetically upstream. It is plausible that the prenopsyl bridgehead carbocation $\mathbf{E}^+$ suffers from significant angle strain thereby further destabilizing this intermediate and rendering the nopsanyl carbocation $\mathbf{F}^+$ relatively more stable. In addition, the calculations indicate that the presilphiperfolane skeleton is substantially less stable than the cameroonane and prenopsane ring systems, consistent with previous computations reported for the tris-nor skeletons (ca. 5 kcal/mol as noted above).[22] The absence of solvolysis products having the presilphiperfolane skeleton is likely attributable to the prohibitive thermodynamic barrier to formation of the strained tricyclo[5.3.1.0^{4,11}] ring structure.

Conclusion

The first total synthesis of (±)-cameroonan-7α-ol was completed in four steps from the known bicyclo[3.3.0]-octen-2-one **10**. The structure and relative stereochemistry of this novel sesquiterpene were independently verified. Solvolysis of the cameroonanyl mesylates gave rise both to Wagner−Meerwein rearrangements to (±)-prenopsanol and (±)-nopsanol and to vicinal methyl migrations to (±)-silphiperfolan-7β-ol and (±)-silphiperfol-6-ene. The rate difference of the α- and β-mesylate epimers is rationalized via σ-bond participation. The nor analogues of cameroonanol and epicameroonanol were prepared, and the norcameroonanyl methanesulfonates underwent analogous solvolytic rearrangements. This work verifies the structures of cameroonanol, prenopsanol, and nopsanol, and provides evidence in support of the proposed biogenetic relationships of these sesquiterpene alcohols.

Experimental Section

HPLC separations were performed by using a refractive index detector with the following eluents, flow rates, and columns: (Method A) acetonitrile−H_2O (80:20) at 16 mL/min, using a Phenomenex Luna 5 μm C8 (2) semipreparative scale column; (Method B) Et_2O−hexane (5:95) at 16 mL/min, using a Dynamax-60A semipreparative scale column; and (Method C) Method B with Et_2O−hexane (2:98).

(1*S,5*S**,8*S**)-3,3,5-Trimethyl-8-[(1′*R* and 1′*S*)-(1′-methyl-2′-propen-1-yl)]bicyclo[3.3.0]octan-2-ones (14a,b).** This preparation is based on a procedure described by Sakurai.[11] A solution of bicyclic enone **10** (1.49 g, 9.0 mmol)[9,10] in CH_2Cl_2 (72 mL) was stirred and cooled at −78 °C as an aliquot of 1.0 M $TiCl_4$ in CH_2Cl_2 (9.0 mL, 9.0 mmol) was added dropwise over 7 min. After 10 min, a solution of (*Z*)-crotyltrimethylsilane (1.50 g, 11.7 mmol, *Z*:*E* = 5:1)[14] in CH_2Cl_2 (27 mL) was added dropwise over 10 min. The purple solution was stirred at −78 °C for 5 min and at 0 °C for 5 min. The $TiCl_4$ was hydrolyzed by adding water (24 mL). After 5 min, the heterogeneous mixture was extracted with ether (2 × 70 mL). The combined organic layers were washed with 10% HCl (60 mL), satd. $NaHCO_3$ (60 mL), and satd. NaCl (60 mL), dried ($MgSO_4$), and evaporated to give 1.88 g of crude product. Purification by flash chromatography (5:95 Et_2O−hexane) afforded 1.73 g (87%) of a 1:1 mixture of 1′α (anti) and 1′β (syn) methyl isomers (GC) as a clear, colorless oil. The following data were obtained by analyses and spectra of the isomer mixture: t_R = 12.08 min (1′α), 12.16 min (1′β) (Method B); TLC R_f 0.65 (15:85 Et_2O−hexane); ^{1}H NMR (500 MHz, $CDCl_3$) (1′α isomer) δ 1.01 (d, 3H, *J* = 6.4 Hz), 1.06 (s, 3H), 1.09 (s, 3H), 1.211 (s, 3H), 1.41−1.81 (m, 8H, α + β isomer), 1.72 and 1.76 (ABq, 2H, J_{AB} = 13.7 Hz), 1.96−2.11 (m, 3H, α + β isomer), 2.29 (d, 1H, *J* = 3.7 Hz), 4.95−5.01 (m, 4H, α + β isomers), 5.74 (9-line sym. m, 1H); (1′β-isomer) δ 1.06 (d, 3H, *J* = 6.8 Hz), 1.08 (s, 3H), 1.10 (s, 3H), 1.207 (s, 3H), 1.41−1.81 (m, 8H, α + β isomer), 1.74 and 1.78 (ABq, 2H, J_{AB} = 13.4 Hz), 1.96−2.11 (m, 3H, α + β isomers), 2.14 (sext, 1H, *J* = 7.3 Hz), 2.21 (d, 1H, *J* = 4.9 Hz), 4.95−5.01 (m, 4H, α + β isomer), 5.67 (ddd, 1H, *J* = 17.1, 10.3, 8.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) (1′α-isomer) δ 18.8, 26.4, 28.1, 28.9, 29.8, 41.6, 43.2, 44.3, 46.8, 48.8, 50.1, 61.8, 113.9, 143.8, 226.1; (1′β-isomer) δ 19.5, 26.6, 27.9, 29.2, 29.4, 41.7, 42.8, 44.4, 47.1, 49.6, 50.3, 62.4, 114.1, 142.4, 226.2; IR (CCl_4) 1734 (C=O); MS (EI, 70 eV) *m*/*z* 220. Kugelrohr distillation at 60−65 °C (0.30 Torr) gave an analytical sample. Anal. Calcd for $C_{15}H_{24}O$ (220.34): C, 81.76; H, 10.98. Found: C, 81.78; H, 11.06. A subsequent reaction carried out as described above with bicyclic enone **10** (0.50 g, 3.0 mmol) and (*E*)-crotyltrimethylsilane (0.50 g, 3.9 mmol) gave 0.57 g (86%) of a 1:1.8 (1′α-CH_3:1′β-CH_3) mixture of keto olefins. The ^{1}H NMR assignments for **14a**,**b** reported previously were incorrect; the corrected data are reported above.[7]

(1*S,5*S**,8*S**)-3,3,5,Trimethyl-8-[(1*R*′ and 1*S*′)-(1′-methyl-3′-bromopropyl)]bicyclo[3.3.0]octan-2-ones (16a,b).** The radical hydrobromination was based on that described by Molander.[13] A solution of **14a,b** (100 mg, 0.45 mmol, 1:1 isomer ratio) in HPLC grade pentane (30 mL, Aldrich) was placed in a 300-mL round-bottomed quartz flask fitted with a gas-dispersion tube (5 mm OD, 25−50 μm porosity) and sealed with a gas outlet connected to a trap followed by a satd. $NaHCO_3$ bath. The solution was purged with N_2 for 5 min. The flask was lowered into a photochemical reactor equipped with eight 254-nm bulbs symmetrically positioned around the flask. The gas dispersion tube was raised above the liquid level, and HBr flow was initiated (ca. 5 cm^3/min). Once HBr was observed to reach the neutralization bath, the gas-dispersion tube was lowered below the solution level, magnetic stirring was initiated, and the lamps were energized. After 13 min, the irradiation and HBr flow were terminated. The solution was purged with N_2 for 5 min, washed with satd. $NaHCO_3$ (4 mL) and satd. NaCl (4 mL), dried ($MgSO_4$), and evaporated to give 120 mg of crude bromo ketone. Purification by flash chromatography (2:98 EtOAc−hexane) afforded 105 mg (73%) (purity: 95%, 1:1 isomer ratio by GC) of bromo ketones as a clear, colorless oil. The NMR assignments for the individual isomers were made by comparison with spectra of the 1:1.8 isomer mixture: t_R = 15.64 min (1′α), 15.74 min (1′β) (Method B); TLC

(23) The silphin-1-ol epimers were previously designated with opposite configurations in reference to a different structure representation.[2b] Thus, silphin-1β-yl mesylate **28** was named silphin-1α-yl mesylate.

(24) Computations were performed with use of CS ChemBats3D Ultra, Version 7.0.0, by CambridgeSoft, 2001.

R_f 0.64 (15:85 Et_2O−hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 6.6 Hz, 1′α), 0.94 (d, 3H, J = 6.2 Hz, 1′β), 1.08 (s, 6H, 1′α + 1′β), 1.101 (s, 3H, 1′β), 1.104 (s, 3H, 1′α), δ 1.21 (s, 3H, 1′β), 1.22 (s, 3H, 1′α), 1.43−1.79 (m, 12H), 1.74 and 1.81 (ABq, 2H, J_{AB} = 13.6 Hz, 1′α), 1.74 and 1.82 (ABq, 2H, J_{AB} = 13.6 Hz, 1′β), 1.93 (qd, 1H, J = 8.0, 5.3 Hz, 1′α), 2.00 (m, 2H), 2.07 (dddd, 1H, J = 14.0, 8.9, 8.0, 3.2 Hz, 1′α), 2.19 (d, 1H, J = 5.3 Hz, 1′β), 2.21 (d, 1H, J = 5.3 Hz, 1′α), 3.40 (m, 2H), 3.56 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) (1′α-isomer) δ 16.3, 26.7, 28.08, 29.1, 29.8, 32.3, 36.5, 38.7, 41.7, 44.5, 47.1, 49.4, 50.1, 62.5, 226.1 (C2); (1′β-isomer) δ 17.0, 26.8, 28.12, 28.9, 30.4, 32.4, 36.0, 38.0, 41.6, 44.6, 47.0, 48.9, 50.0, 61.4, 226.3; IR (CCl_4) 1731 (C=O); MS (EI, 70 eV) m/z 302. Kugelrohr distillation at 130−135 °C (0.09 Torr) gave a sample for elemental analysis. Anal. Calcd for $C_{15}H_{24}O$ (301.27): C, 60.00; H, 8.36. Found: C, 59.52; H, 8.25. HRMS (EI, 70 eV) calcd for $C_{15}H_{25}OBr$ 300.1089, found 300.1097 (Δ = −2.7 ppm). A subsequent reaction carried out as described above with a 1:1.8 (1′α-Me:1′β-Me) mixture of keto olefins (150 mg, 0.68 mmol) gave 148 mg (72%) of a 1:1.8 mixture of bromo ketones.

(±)-Cameroonanone and (±)-9-Epicameroonanone: (1*S,5*S**,8*S**,9*R**)- and (1*S**,5*S**,8*S**,9*S**)-3,3,5,9-Tetramethyltricyclo[6.3.0.0^{1,5}]undecan-2-ones (17a,b).** The cyclization was based on a procedure by Piers.[25] An aliquot of 1.0 M KOtBu (2.79 mL, 2.79 mmol) in THF was added dropwise over 4 min to a stirred solution of 613 mg (560 mg of pure ketone, 1.86 mmol, 1:1 1′-α:β isomer ratio) of **16a**,**b** in THF (42 mL). After 10 min, the excess base was neutralized by adding 10% HCl (6 mL). The solution was diluted with hexane (35 mL). The organic layer was washed with satd. $NaHCO_3$ (17 mL) and satd. NaCl (17 mL), dried ($MgSO_4$), and evaporated to give 387 mg of crude ketone that was a 1.2:1 mixture of **17a** and **17b** by GC. Purification by column chromatography (57 g SiO_2; 0.75:99.25 Et_2O−hexane) afforded 152 mg (37%) of colorless oil **17a**, 162 mg (40%) of colorless oil that was a 5:1 mixture of **17b**:**17a**, and 67 mg (15% corrected for purity) of colorless oil that was a 2:1 mixture of **17b**:**17a** that was 89% pure by GC. Two additional column chromatographies (25 g of SiO_2 and 32 g of SiO_2, respectively; 0.75:99.25 Et_2O−hexane) of the fractions containing a mixture of epimeric ketones afforded 15 mg (GC purity: 100%) of **17a** in addition to 16 mg (GC purity: 100%) and 82 mg (GC purity: 98%) of **17b**. HPLC purification (Method A) gave an analytical sample of **17b** (68 mg, GC purity: 100%). The NMR spectral data were identical with those previously reported for **17a**.[5a] (±)-**17b**: t_R = 12.67 min (Method B); TLC R_f 0.74 (15:85 Et_2O−hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, 3H, J = 6.8 Hz), 1.06 (s, 3H), 1.09 (s, 3H), 1.14 (m, 1H), 1.15 (s, 3H), 1.46 (m, 1H), 1.56−1.82 (m, 6H), 1.65 and 1.76 (ABq, 2H, J_{AB} = 13.6 Hz), 2.05 (m, 1H), 2.40 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.2, 24.5, 24.6, 27.4, 28.6, 29.9, 34.8, 37.9, 43.1, 45.2, 48.5, 49.2, 57.1, 71.5, 228.1; IR (CCl_4) 1728 (C=O); MS (EI, 70 eV) m/z 220. Kugelrohr distillation at 45−50 °C (0.65 Torr) gave an analytical sample. Anal. Calcd for $C_{15}H_{24}O$ (220.34): C, 81.76; H, 10.98. Found: C, 81.41; H, 11.06. A subsequent reaction carried out as described above with a 1:1.8 (1′α-Me:1′β-Me) mixture of bromo ketones (65 mg, 0.22 mmol) gave 37 mg (77%) of a 1:1.6 mixture of ketones **17a** and **17b**. Physical data for **17a** and additional NMR spectral data for **17b** are listed in the Supporting Information.

(±)-Cameroonan-7α and 7β-ols: (1*S,2*R**,5*S**,8*S**,9*S**)- and (1*S**,2*S**,5*S**,8*S**,9*S**)-3,3,5,9-Tetramethyltricyclo[6.3.0.0^{1,5}]undecan-2-ols (6-OH, 18-OH).** The reduction was performed according to the procedure described by Weyerstahl.[5a] A suspension of $LiAlH_4$ (22 mg, 0.579 mmol) in ether (3 mL) was stirred and cooled at 0 °C as (±)-cameroonanone (85 mg, 0.386 mmol) in ether (2 mL) was added dropwise over 1 min. After 30 min at 0 °C, the excess hydride was consumed by the sequential addition of water (22 μL), 15% NaOH (22 μL), and water (66 μL)[26] at 1-min intervals, and the suspended salts were allowed to stir at 0 °C for 30 min and room temperature for 15 min. The ethereal supernatant was pipetted from the white salts, and the salts were washed with ether (2 × 4 mL). The ethereal solution and washes were combined, dried ($MgSO_4$), and evaporated to give a white solid residue (79 mg) that was a 1.4:1 mixture of α:β-OH isomers by GC. Purification by column chromatography (8:92 Et_2O−pentane) gave 74 mg (86%) (isomer ratio of 1.4:1 by GC). Further column chromatography (2:98 Et_2O−pentane) followed by HPLC purification (Method B) of fractions containing a mixture of α:β alcohols afforded 34 mg (GC purity: 100%) of **6**-OH and 24 mg (GC purity: 99%) of **18**-OH as crystalline solids with mp 48−49 and 62−63 °C, respectively. The spectral data were identical with those previously reported[5a] except for coupling observed in the present case between the hydroxyl and the carbinol protons. Physical data for **6**-OH and **18**-OH are given in the Supporting Information.

(±)-Cameroonan-7α and 7β-yl Methanesulfonates: (1*S,2*R**,5*S**,8*S**,9*R**)- and (1*S**,2*S**,5*S**,8*S**,9*R**)-3,3,5,9-Tetramethyltricyclo[6.3.0.0^{1,5}]undecan-2-yl Methanesulfonates (6-OMs, 18-OMs).** A solution of MsCl (262 μL, 3.38 mmol) and a 1.5:1 mixture of α:β-cameroonanols (376 mg, 1.69 mmol) in pyridine (2.7 mL) was stirred at room temperature for 3 h. The reaction was stopped upon dilution with pentane (20 mL) and 5% HCl (5 mL). The organic layer was washed with 5% HCl (5 mL), satd. $NaHCO_3$ (5 mL), and satd. NaCl (5 mL), dried ($MgSO_4$), and evaporated to give 404 mg of crude oil. Column purification (20:79:1 Et_2O−pentane−Et_3N) afforded 357 mg (70%) of colorless oil that was a 1.5:1 mixture of α- and β-mesylates: TLC R_f 0.41 (15:85 EtOAc−hexane); ^1H NMR (500 MHz, $CDCl_3$) (**6**-OMs) δ 1.00 (d, 3H, J = 6.4 Hz), 1.018 (s, 3H), 1.021 (s, 3H), 1.17 (s, 3H), 1.21 (m, 1H), 1.34 (ddm, 1H, J = 13.0, 6.1 Hz), 1.37−1.90 (m, 9H), 2.09 (t, 1H, J = 8.4 Hz), 3.05 (s, 3H), 4.78 (s, 1H); (**18**-OMs) δ 0.94 (d, 3H, J = 6.4 Hz), 0.97 (s, 3H), 1.07 (s, 3H), 1.09 (s, 3H), 1.37−1.90 (m, 11H), 1.97 (ddd, 1H, J = 13.8, 8.4, 3.0 Hz), 3.05 (s, 3H), 4.56 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) (C7-αMs) δ 19.4, 25.1, 28.9, 31.8, 35.2, 35.2, 38.6, 38.8, 39.6, 43.8, 48.3, 52.4, 52.6, 66.9, 98.3; (C7-βMs) δ 19.0, 23.4, 26.3, 27.5, 27.9, 28.5, 36.3, 39.1, 41.8, 42.6, 49.5, 51.8, 61.2, 65.5, 96.9.

(±)-Silphiperfol-6-ene (5), (±)-Prenopsanol (7), and (±)-Silphiperfolan-7β-ol (9). This preparative solvolysis procedure is based on that described by Coates.[2b] A solution of **6**-OMs and **18**-OMs (316 mg, 1.05 mmol, α:β = 1.5:1) and pyridine (340 μL, 4.2 mmol) in 3:1 acetone-d_6:D_2O (6 mL) was stirred at 25 °C for 24 h while the reaction progress was monitored by ^1H NMR analysis of reaction aliquots. The solution was neutralized upon dilution with 5% HCl (10 mL) and Et_2O (40 mL). The organic layer was washed with satd. $NaHCO_3$ (10 mL) and satd. NaCl (10 mL), dried ($MgSO_4$), and evaporated to give 231 mg of crude oil that was an 11:7:1 mixture (^1H NMR) of **6**-OMs, prenopsanol, and silphiperfol-6-ene. Column purification (5:95 EtOAc:pentane) afforded 13 mg of colorless oil that was a 3.2:2.5:1 mixture (GC) of (±)-silphiperfol-6-ene (**5**, 6%) and unknown olefins **A** (2%) and **B** (2%), 3 mg of colorless oil that was a 4:1 (GC) mixture of silphiperfolan-7β-ol (**9**, 2%) and unknown alcohol C (<1%), 59 mg of (±)-prenopsanol (**7**, 41%), and 123 mg (66%) of **6**-OMs. Unknown olefin **A**: t_R = 9.64 min (Method B); TLC R_f 0.80 (pentane); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, 3H, J = 7.3 Hz), 0.96 (s, 3H), 4.69 (dt, ∼1H, J = 6.5, 1.7 Hz), 4.94 (m, 1H); GCMS (EI, 70 eV) m/z (rel intensity %) 204 (52), 189 (100), 175 (55), 161 (29), 147 (37), 133 (43), 119 (62), 105 (47), 91 (41), 77 (22). GC-HRMS (EI, 70 eV) calcd for $C_{15}H_{24}$ 204.1878, found 204.1886 (Δ = −3.9). Unknown olefin **B**: t_R = 9.38 min (Method B); TLC R_f 0.80 (pentane); ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.03 (s, 3H), 4.96 (app q, 1H, J = 1.5 Hz); GCMS (EI, 70 eV) m/z (rel intensity %) 204 (29), 189 (11), 175 (100), 162 (9), 147 (14), 133 (24), 121 (31), 105 (22), 91 (22), 77 (15). GC-HRMS (EI, 70 eV) calcd for $C_{15}H_{24}$ 204.1878, found

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204.1881 (Δ = −1.5). Unknown alcohol **C**: t_R = 11.42 min (Method B); TLC R_f 0.72 (1:3 EtOAc−hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.92 (d, 3H, J = 7.1 Hz), 0.94 (d, 3H, J = 6.9 Hz); GCMS (EI, 70 eV) *m*/*z* (rel intensity %) 222 (68), 207 (68), 189 (13), 165 (16), 151 (16), 137 (84), 126 (100), 95 (32), 83 (38), 69 (21), 57 (9). GC-HRMS (EI, 70 eV) calcd for $C_{15}H_{26}O$ 222.1984, found 222.1989 (Δ = −2.4). The tabulated physical data listed in the Supporting Information for silphiperfolan-7β-ol and prenopsanol agreed with those reported in the literature.[5a,6]

(±)-Silphiperfol-6-ene (5), (±)-Prenopsanol (7), (±)-Nopsanol (8), and (±)-Silphiperfolan-7β-ol (9). The solvolytic rearrangement of **6**-OMs (65 mg, 0.22 mmol) was carried out as described above except that the reaction was conducted at 70 °C for 2.5 h in a sealed tube, which upon workup gave 31 mg of colorless oil that was a 6:5:2:1:1 mixture (GC) of **5**, (±)-**7**, unknown olefin **B**, (±)-**8**, and (±)-**9**. Column purification (8:92 Et_2O−pentane) afforded 13 mg of colorless oil that was a 3:1 mixture (GC) of **5** (18%) and unknown olefin **B** (6%), 9 mg of colorless oil that was a 6:1 mixture (GC) of **7** (16%) and **9** (3%), and 5 mg of colorless oil that was a 4:2:1 mixture of **8** (6%), **7** (2%), and **9** (1%). The tabulated physical data reported in the Supporting Information for (±)-**5** and (±)-**8** compared favorably with those reported in the literature.[2a,5a]

Kinetic Measurements for Solvolysis of Cameroonanyl and Norcameroonanyl Methane-Sulfonates. The rate constants listed in Table 1 were obtained as described for cameroonanyl mesylate **18**-OMs. A 1.5:1 mixture of mesylates **6**-OMs and **18**-OMs (15 mg, 0.05 mmol) was dissolved in a 3:1 mixture of acetone-d_6−D_2O (1.0 mL) containing a small amount of benzene (∼3 mg) and loaded into a NMR tube. After the tube was sealed, the sample was allowed to stand at 25 °C while ^{1}H NMR spectra were taken at regular time intervals. The disappearance of the mesylate (C7-hydrogen signal) was monitored by comparison of the ^{1}H NMR signal from the remaining mesylate with that of benzene. The rate data were collected over a period of 5 half-lives and fit to a first-order rate expression. For solvolytic reactions conducted at 55 °C, the mesylate solution was placed in an oil bath at 55 °C. The progress of the reaction was monitored at regular time intervals by removing the NMR sample from the oil bath, quickly cooling to room temperature, and recording the ^{1}H NMR spectrum. Kinetic data for experiments conducted at 70 °C were obtained by placing the mesylate solution inside a thermostated probe (70 °C) of a NMR spectrometer. Kinetic data for **6**-OMs and **21**-OMs were obtained on the pure compounds while data for **18**-OMs and **22**-OMs were obtained by using mixtures of **6**-OMs + **18**-OMs and **21**-OMs + **22**-OMs, respectively.

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Supporting Information Available: Additional spectral data together with procedural information and characterization data for all other starting materials and products, general experimental details, and copies of ^{1}H NMR, HMBC, and HMQC spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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