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Total Synthesis of (±)-Cameroonanol

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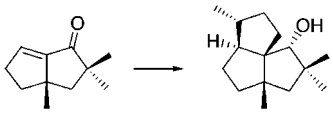
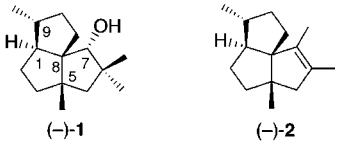
ABSTRACT



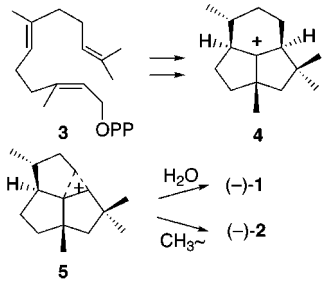
The structure and relative stereochemistry of the novel silphiperfolane-type sesquiterpene cameroonan-7α-ol (1) were confirmed by a total synthesis of (±)-1 from 3,3,5-trimethylbicyclo[3.3.0]oct-1(8)-en-2-one (6) by means of a Sakurai reaction with (*Z*)-crotylsilane, free radical hydrobromination, base-induced cyclization, and $LiAlH_4$ reduction.

The isolation and structure assignment of the novel tricyclic sesquiterpene alcohol (−)-cameroonanol (**1**) from the essential oil of *Echniops giganteus* var. *lelyi* rhizomes, and its association with the strong patchouli-like woody fragrance of the oil, were reported recently by P. Weyerstahl et al.[1] The co-occurrence of (−)-**1** with a myriad of related tricyclic sesquiterpenes (e.g., (−)-silphiperfol-6-ene, **2**) belonging to



the silphinane and silphiperfolane classes of triquinanes suggests a common biogentic origin from (*E*,*E*)-farnesyl diphosphate (**3**) through the presilphiperfolan-8-yl carbocation (**4**) branch point followed by ring contractions to the secondary silphinan-1-yl (not shown) and cameroonan-7-yl (**5**) ions[1,2−4] (Scheme 1). The formation of a secondary trifluoroacetate corresponding to **1**-OCO_2CF_3 in the trifluoroacetic anhydride-induced dehydrative rearrangement of presilphiperfolanol to **2**[2a] presaged the in vivo biosynthesis of this biogenetically significant natural product. The assignment of the structure and relative stereochemistry of (−)-**1** was based upon ^{1}H NMR, ^{13}C NMR, and NOE spectra of cameroonanol and its 7β epimer prepared from (−)-**1** by H_2CrO_4 oxidation and $LiAlH_4$ reduction together with considerations of likely biogenetic mechanisms.[1] This Letter discloses the first total synthesis of (±)-cameroonanol in four steps from the known bicyclic enone **6**[5] and independent spectral evidence confirming the aforementioned structural and configurational deductions.

Scheme 1



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(1) Weyerstahl, P.; Marschall, H.; Seelmann, I.; Jakupovic, J. *Eur. J. Org. Chem.* **1998**, 1205.
(2) (a) Coates, R. M.; Ho, Z.; Klobus, M.; Wilson, S. R. *J. Am. Chem. Soc.* **1996**, *118*, 9249. (b) Coates, R. M.; Ho, J. Z.; Klobus, M.; Zhu, L. *J. Org. Chem.* **1998**, *63*, 9166−9176.
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(5) (a) Paquette, L. A.; Leone-Bay, A. *J. Am. Chem. Soc.* **1983**, *105*, 7352. (b) Piers, E.; Renaud, J. *Synthesis* **1992**, 74.

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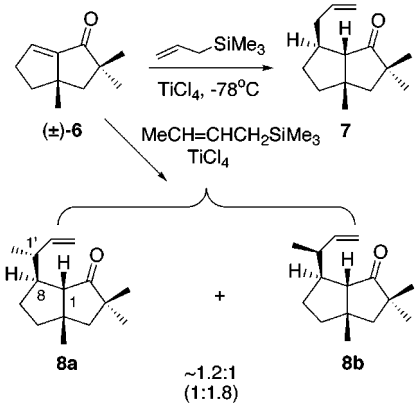
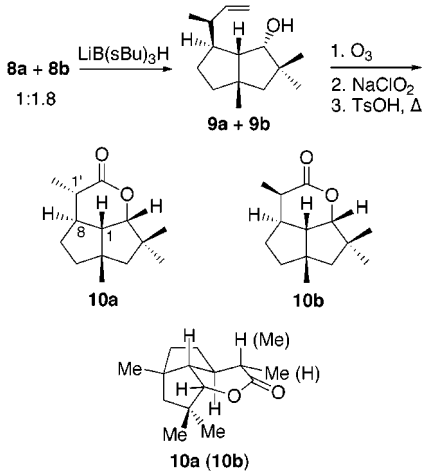
The additional carbons needed to form the third ring were introduced by stereoselective conjugate allylations of enone **6** by means of the Sakurai reaction[6] (Scheme 2). 3,3,5-Trimethylbicyclo[3.3.0]oct-1(8)-en-2-one (**6**) was prepared according to literature procedures[5] with significant modifications for large scale.[7] Reaction of **6** with allyltrimethylsilane (1 M $TiCl_4$, CH_2Cl_2, −78 °C, 20 min; 0 °C, 10 min; H_2O) afforded the single conjugate adduct **7** (82%).[8] Similar Sakurai reactions of **6** with (*Z*)- and (*E*)-2-buten-1-yltrimethylsilanes[9,10] gave 1.1−1.3:1 (87%) and 1:1.8 (86%) mixtures[11] of the corresponding anti and syn α-methylallyl isomers **8a** and **8b** according to GC and NMR analysis [^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (d, 3 H, J = 6.4 Hz, anti); 1.06 (d, 3 H, J = 6.8 Hz, syn)].

Scheme 2



The three bicyclo[3.3.0]octan-2-ones **7**, **8a**, and **8b** were shown to have the thermodynamically more stable cis ring fusion stereochemistry.[12] Treatment of a 1:1 mixture of **8a** and **8b** with KOH and MeOH-d_4 led to 90% deuterium incorporation at the C1 position ($\delta_H^{CDCl_3}$ 2.21 and 2.29 for **8a** and **8b**, respectively) with no evidence of isomer formation according to GC and NMR comparisons. Assignment of the 1,8-anti stereochemistry expected from attack on the convex face of **6** is based upon the coupling between the vicinal protons at C1 and C8 (^3J = 3.6, 3.4, and 5.1 Hz) in the 500 MHz ^{1}H NMR spectra.[13] The relative configurations of the methyl group in the methylallyl side chains of **8a** and **8b** were established by conversion of the 1:1.8 isomer mixture from the Sakurai reaction with the (*E*)-2-butenylsilane to lactones **10a** and **10b** (Scheme 3).

Scheme 3



Reduction of the **8a** and **8b** mixture with lithium tri-*sec*-butylborohydride (THF, 0 °C, 97%) gave a similar mixture of secondary alcohols **9a** and **9b** having a trans relationship of the hydroxyl and angular methyl groups (^3J for syn C1 and C2 hydrogens = 5.3 and 5.5 Hz).[13] Ozonolysis of the side chain double bond (O_3, MeOH, −78 °C; Me_2S; 87%) followed by $NaClO_2$ oxidation (aqueous tBuOH, 1 M $H_2PO_4^-$ buffer, pH ∼3.5, isoprene)[14] provided the hydroxy acids (1:1.8, 86%) which were cyclized (TsOH, PhH, reflux, 75 min) to a chromatographically separable mixture of δ-lactones (IR 1736 cm^{-1}) **10a** (13%) and **10b** (23%) accompanied by some of the major hydroxy acid component (19%). The equatorial configuration of the α-methyl group in the minor isomer and its axial orientation in the major isomer were established from the ^{1}H NMR coupling constants for the α (H1′) and β (H8) protons (**10a**, J = 12.2 Hz; **10b**, J = 5.0 Hz) in these conformationally fixed δ-lactones (**10a** and **10b**). The possibilities of epimerization or isomer ratio inversion during the conversion of the **9a** and **9b** mixture to lactones **10a** and **10b** were negated by converting **10b** back to **9b** (iBu_2AlH, toluene, −40 °C; $Ph_3P{=}CH_2$, THF). It follows that the minor α-methallyl adduct (**8a**) formed in the Sakurai reactive with (*E*)-crotylsilane (i.e., the major adduct produced with (*Z*)-crotylsilane) has side chain stereochemistry corresponding to that of cameroonanol.

Mixtures of **8a** and **8b** (1:1 and 1:1.8) obtained from the Sakurai reactions with (*Z*)- and (*E*)-crotyltrimethylsilanes were subjected to photochemically induced free radical hydrobromination (254 nm, HBr gas flow, rt, 13 min; 72−

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(7) (a) 2-(1,3-Dioxanyl)ethylMgBr−CuBr, THF, 0 °C, 4 h; 26.5 g, 93%. (b) 10% HCl, THF, 1:2 v/v, reflux, 30 min; 83%. (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 30 min; DBU, rt, 2 h; 71%.

(8) All new compounds reported herein gave spectra (NMR, IR, and MS) and analytical data (elemental and/or GC analyses) that confirmed their purity and structural identity (see Supporting Information).

(9) 9) (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.

(10) Tokoyorama, T.; Pan, L.-R. *Tetrahedron Lett*. **1989**, *30*, 197.

(11) The product ratios have been corrected for the isomeric purity of the (*Z*)-butenylsilane (*Z*/*E* ratios 5:1 to 6:1).

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

(13) 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 (five compounds) and $^3J_{syn}$ = 8.1−9.8 Hz (three compounds). See: Duffy, B. C. Ph.D. Dissertation, University of Illinois, Urbana, IL, 1999; p 34.

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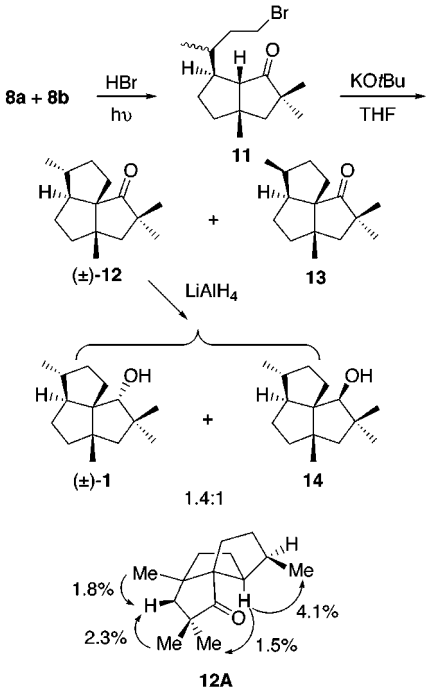
Scheme 4



73%)[15] (Scheme 4). Base-induced cyclizations of the resulting mixtures of bromo ketones **11** [1:1 and 1:1.8 ratios; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, 3 H, J = 6.6 Hz, anti 1′-CH_3), 0.94 (d, 3 H, J = 6.2 Hz, syn 1′-CH_3)] with 1 M KOtBu/THF (rt, 1.5 equiv, 10−15 min) afforded 1:1 and 1:1.6 mixtures (83% and 77%) of (±)-cameroonanone (**12**) and (±)-9-epicameroonanone (**13**). The isomeric ketones were isolated in pure form by flash chromatography on silica gel (0.75% ether−pentane). The ^{1}H NMR (500 MHz, $CDCl_3$), ^{13}C NMR (126 MHz, $CDCl_3$), IR (CCl_4), and MS (EI, 70 eV) data agree well with the corresponding literature data for (+)-**12**.[1] The relative stereochemistry of (±)-**12** was verified independently by NOE experiments (750 MHz, C_5D_5N) illustrated in **12A**, together with assignments for the geminal methyls (δ_H 1.04, 1.09) by HMBC cross-peaks.

Reduction of (±)-**12** with $LiAlH_4$ (ether, 0 °C)[1] afforded a chromatographically separable 1.4:1 mixture (86%) of (±)-cameroonan-7α-ol ((±)-**1**, mp 48−49 °C) and (±)-cameroonan-7β-ol (**14**, mp 62−63 °C). The spectral data for (±)-**1** [^{1}H NMR (500 MHz, $CDCl_3$), ^{13}C NMR (126 MHz, $CDCl_3$), IR (CCl_4), and MS (EI, 70 eV)] match well with the corresponding literature data for (−)-**1**.[1]

Conversion of (±)-**1** and (±)-**14** to the trifluoroacetate derivatives ($(CF_3CO)_2O$; py; 0 °C; 67% and 49%) followed by spectral and GC comparisons with the secondary trifluoroacetate obtained from the reaction of natural presilphiperfolan-8-ol with trifluoroacetic anhydride[2a] established the identity of the rearrangement product as cameroonan-7α-yl trifluoroacetate.

The total synthesis of (±)-cameroonanol confirms the structure and relative stereochemistry of this novel sesquiterpene alcohol and opens up possibilities for studies of the biogenetic rearrangements of the cameroonanol epimers.

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Supporting Information Available: Experimental procedures together with analytical and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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