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Synthetic Studies on Polymaxenolides: Synthesis and Structure Elucidation of Nominal Epoxyafricanane and Other Africane-Type Sesquiterpenoids

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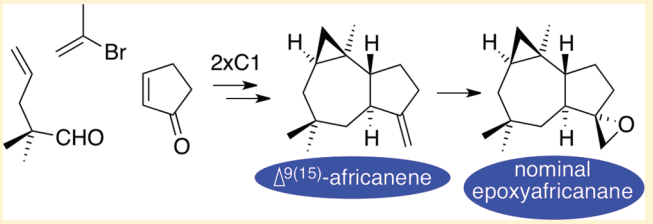
Supporting Information

ABSTRACT: A racemic total synthesis of the sesquiterpenoid unit of the hybrid marine natural product polymaxenolide has been achieved based on a three-component assembly followed by ring-closing metathesis as the key steps. However, the spectral data of our product synthesized from $\Delta^{9(15)}$-africanene by epoxidation were not identical with those of the natural product named epoxyafricanane. The structure confirmation of the synthetic nominal epoxyafricanane is described.



INTRODUCTION

Polymaxenolide (**1**) is the first hybrid compound from the marine environment isolated, by Slattery and co-workers in 2004, from the hybrid soft coral *Sinularia maxima* × *Sinularia polydactyla* collected from Piti Bomb Holes, Guam (Figure 1).[1] The relative configuration of **1** was determined by NMR experiments and X-ray crystallography.[1] This terpenoid is considered to be biogenetically synthesized from the africane-type sesquiterpenoid unit **2** possessing the bicyclo[5.3.0]decane structure and the cembranoid unit **3** (a diterpenoid) via C−C coupling followed by dehydrative cyclization (Figure 1).[1] In 2009, Kamel, Slattery, and co-workers isolated five new polymaxenolides from the same hybrid soft coral.[2] Their structures, including absolute configurations, were determined on the basis of detailed NMR and MS data analyses, experimental and theoretically calculated electronic circular dichroism, and X-ray crystallographic analysis.[2] There has been no comment on the absolute configuration of **1**. However, one would expect that polymaxenolide (**1**) has the absolute configuration as depicted in Figure 1 because of its structural similarity to the six isolated polymaxenolides.[1,2]

The structural complexity and uniqueness of the polymaxenolides, in conjunction with the proposed interesting biosynthesis, prompted us to synthesize them. In this article, we report the first racemic synthesis of the sesquiterpenoid unit **2**, claimed to have been isolated from the soft coral *Sinularia dissecta* in 1999 by the Venkateswarlu group.[3] We anticipated that **2** could be derived from $\Delta^{9(15)}$-africanene (**4**)[4,5] by a stereoselective epoxidation[3] (Figure 2). $\Delta^{9(15)}$-Africanene (**4**) would be obtained from ketone **5** by methylenation. In the original isolation studies, natural $\Delta^{9(15)}$-africanene (**4**) was reversibly transformed into ketone **5** by ozonolysis[4a] or by dihydroxylation followed by oxidative scission[4b] in order to confirm the structure of **4**. It was necessary for us to synthesize some other africane-type natural

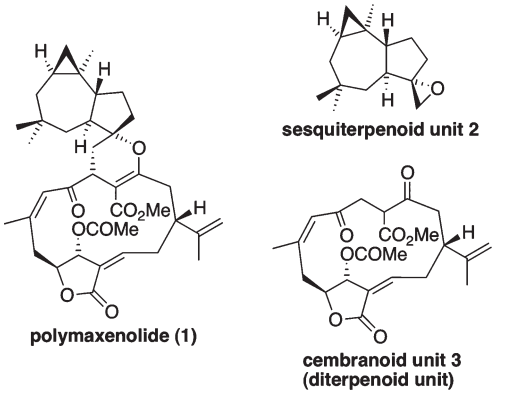


Figure 1. Structures of polymaxenolide (**1**) and its proposed biosynthetic precursors, i.e., the sesquiterpenoid unit **2** and the cembranoid unit **3**.

sesquiterpenoids, africane-9,15-diol **6**,[3,4b,6] another africane-9,15-diol **7**,[6] leptographiol (**8**),[7] and isoleptographiol (**9**),[7] in order to confirm the structure of **2** (Figure 2). The africanes, **4** and **6**−**9**, were isolated from several soft coral *Sinularia* or woods and have not become targets for total synthesis.[8] The first member of the africane-type sesquiterpenoids isolated from a natural source was (+)-africanol (**10**), obtained from *Lemnalia africana* in 1974 by the Braekman group (Figure 2).[9] Biosynthetic studies of the africane-type sesquiterpenoids and their chemical synthesis along the proposed biosynthetic pathway have been investigated.[9−16] Among them, Shirahama's synthesis[13] of (±)-africanol (**10**) from humulene in 1980 is the first example

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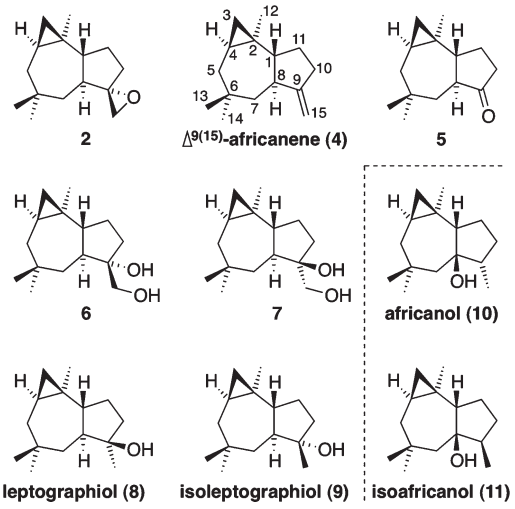
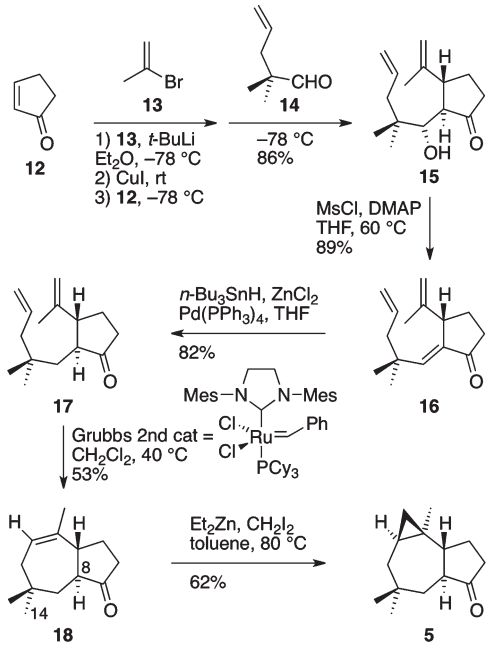


Figure 2. Some africanes and ketone **5**.

Scheme 1. Synthesis of Ketone 5



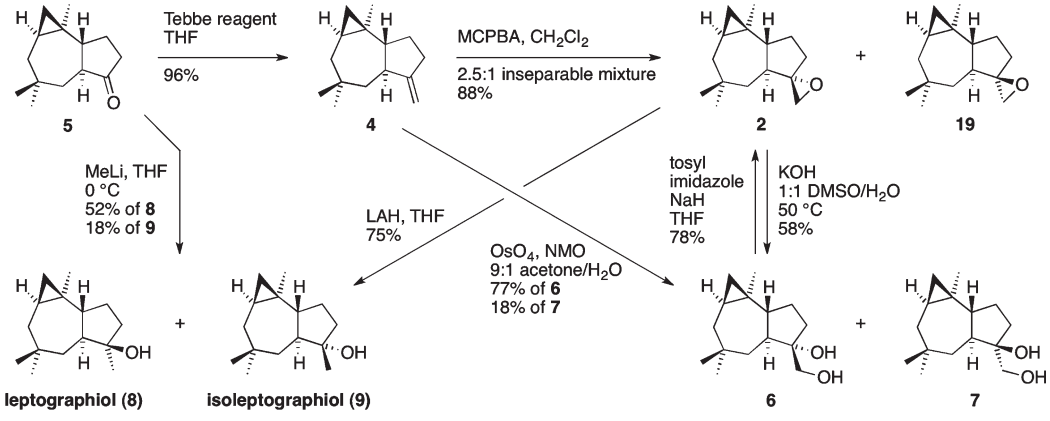
of the chemical synthesis of a natural africane. Following this synthesis, Paquette and Ham succeeded in the synthesis of (±)-africanol (**10**) in 1986.[17] In 1990, Tai and co-workers reported the first chiral synthesis of (+)-africanol (**10**) and (+)-isoafricanol (**11**);[18] however, these were obtained as minor components of the products. White,[19] Cossy,[20] and Marques[21] also reported the syntheses of (±)-africanol (**10**) and/or (±)-isoafricanol (**11**). Paquette reported the synthesis of a diastereomer of (+)-africanol (**10**) featuring ring-closing metathesis (RCM).[22] Recently, Hoveyda succeeded in the synthesis of (+)-africanol (**10**) using asymmetric ring-opening metathesis/RCM.[23]

RESULTS AND DISCUSSION

The synthetic route to ketone **5** followed Fürstner's synthesis[24] of dactylol, which is based on a three-component assembly followed by ring-closing metathesis (RCM) as the key steps (Scheme 1). A similar strategy was recently applied to the synthesis of bicyclo[5.3.0]decane and bicyclo[6.3.0]undecane natural products.[25] The three-component coupling of cyclopentenone **12**, 2-metallopropene derived from 2-bromopropene (**13**), and the commercially available aldehyde **14** afforded alcohol **15** as a single diastereomer in 86% yield. Mesylation of **15** gave olefin **16** directly in 89% yield. The relative configuration of three consecutive stereocenters in **15** and the *E*-configuration of the newly formed double bond in **16** were inferred from Snider's[26] and Vanderwal's[25] precedents. Selective hydrogenation of **16** with *n*-Bu_3SnH in the presence of $ZnCl_2$ and $Pd(PPh_3)_4$ provided **17** in 82% yield as a single diastereomer.[24,25,27,28] This reaction proceeded via palladium-catalyzed hydrostannation followed by kinetic protonation, providing 2,3-*trans*-cyclopentanone.[24,25,27,29] RCM of **17** using Grubbs' second generation catalyst[30] gave the bicyclo[5.3.0]decane derivative **18** in 53% yield. Cyclopropanation of **18** with $Et_2Zn-CH_2I_2$[21,22,31] exclusively afforded the desired ketone **5** in 62% yield. The data (^1H NMR, ^{13}C NMR, and mp) of **5** were identical with those of the naturally derived **5**.[4] The stereoselectivity of this cyclopropanation can be explained by the steric hindrance of the lower face of the *trans* bicyclic compound **18** caused by the 14-Me and H-8 groups.

The methylenation of **5** with Tebbe reagent[32] afforded $\Delta^{9(15)}$-africanene (**4**) in 96% yield (Scheme 2). The data of the synthetic **4** were identical with those of natural **4**.[4,33] This is the first synthesis of $\Delta^{9(15)}$-africanene (**4**), achieved in six steps and 20% overall yield without using any protecting groups. Epoxidation of **4** with MCPBA gave a 2.5:1 inseparable mixture of the

Scheme 2. Synthesis of 2 and Some Other Africanes



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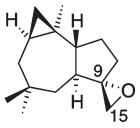

2

synthetic	isolated (ref. 3)
^{1}H NMR (500 MHz, $CDCl_3$)	^{1}H NMR (400 MHz, $CDCl_3$)
H-15: 2.61 (d, J = 4.6 Hz)	H-15: 3.46 (d, J = 13.5 Hz)
H-15: 2.86 (d, J = 4.6 Hz)	H-15: 3.57 (d, J = 13.5 Hz)
^{13}C NMR (125 MHz, $CDCl_3$)	^{13}C NMR (50 MHz, $CDCl_3$)
C15: 50.3	C15: 68.9
C9: 68.5	C9: 82.9

Figure 3. Representative NMR data of **2**.

sesquiterpenoid unit **2** and its epimer **19** in 88% combined yield.[3,34] Surprisingly, the ^{1}H NMR and ^{13}C NMR spectra of our synthetic **2** were not identical with those of the reported isolated sample,[3] especially in the epoxide region (Figure 3).[35]

Therefore, to confirm the structure of our synthetic **2**, we synthesized some additional africane-type natural sesquiterpenoids. First, $\Delta^{9(15)}$-africanene (**4**) was subjected to dihydroxylation using OsO_4 and NMO, giving a separable mixture of africane-9,15-diol **6** and another africane-9,15-diol **7** in 77% and 18% yields, respectively[34] (Scheme 2). The major diol **6** has been isolated from a natural source[3,6] and also derived from natural **4**.[3,4b,6] The minor diol **7** has also been isolated from a natural source[6] but has not yet been synthesized.[36] The spectral data of **6** and **7** were identical with those of natural **6** and **7**. In addition, the relative configuration of **6** was confirmed by X-ray crystallographic analysis[4b] (see Supporting Information). With the pure sample of **6** in hand, it was converted into the pure sample of **2** by treatment with tosyl imidazole[37] and NaH in 78% yield.[38] Furthermore, the obtained **2** was converted into diol **6** by epoxide opening with aqueous KOH in 58% yield. On the other hand, the treatment of ketone **5** with MeLi gave leptographiol (**8**)[7,39] and isoleptographiol (**9**)[7] in 52% and 18% yields, respectively,[34] the latter of which could be obtained from **2** by reductive opening of the epoxide with LAH in 75% yield. All of these experimental results confirm the structure of the synthetic sesquiterpenoid unit **2**.

CONCLUSION

We succeeded in the racemic total synthesis of the sesquiterpenoid unit **2** of polymaxenolide (**1**), featuring the three-component coupling of cyclopentenone **12**, 2-metallopropene derived from 2-bromopropene (**13**), and aldehyde **14** followed by ring-closing metathesis, methylenation, and epoxidation. The structure confirmation of **2** was realized by chemical correlation between **2** and **6** and between **2** and **9**. Although we are uncertain about the structure of the compound isolated from the soft coral *Sinularia dissecta*,[3] our results indicate that the structure of the natural product named epoxyafricanane was incorrectly assigned. Progress toward the total synthesis of polymaxenolide (**1**) using **2**, **4**, or **5** as the sesquiterpenoid unit is now underway.[40]

EXPERIMENTAL SECTION

(±)-(2*R*,3*R*)-2-(1-Hydroxy-2,2-dimethylpent-4-enyl)-3-(prop-1-en-2-yl)cyclopentanone (15). To a solution of 2-bromopropene (0.242 mL, 2.00 mmol) in Et_2O (25.0 mL) was added a 1.60 M pentane solution of *t*-BuLi (2.50 mL, 4.00 mmol) at −78 °C. After 30 min at −78 °C, this yellow solution was warmed to rt, and CuI (190 mg, 1.00 mmol) was added with stirring. After 15 min at rt, this dark black solution was cooled to −78 °C, and cyclopentenone (0.164 mL, 2.00 mmol) was added with stirring. After 2 h at −78 °C, 2,2-dimethyl-4-pentenal (0.114 mL, 1.00 mmol) was added at −78 °C, and the resulting mixture was stirred at −78 °C for additional 3 h. Saturated aqueous solution of NH_4Cl was then added at 0 °C, and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10.2 g, hexane/EtOAc = 10:1) to afford **15** (203 mg, 86%) as a colorless syrup: R_f = 0.28 (hexane/EtOAc = 5:1); IR (neat, cm^{-1}) 3457, 3074, 2964, 1732, 1640, 1466, 1404, 1285, 1145, 1054, 997, 910; ^{1}H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.82 (s, 3H), 0.89 (s, 3H), 1.72 (s, 3H), 1.82 (ddd, J = 13.8, 11.7, 8.9 Hz, 1 H), 1.97 (dd, J = 13.5, 7.5 Hz, 1 H), 2.05 (ddd, J = 13.8, 9.0, 7.4 Hz, 1H), 2.12 (dd, J = 13.5, 7.8 Hz, 1 H), 2.21 (ddd, J = 18.9, 11.3, 8.9 Hz, 1 H), 2.29 (d, J = 11.7 Hz, 1 H), 2.38 (dd, J = 18.9, 8.9 Hz, 1 H), 2.56 (d, J = 11.5 Hz, 1 H), 2.82 (ddd, J = 11.7, 11.7, 6.3 Hz, 1 H), 3.31 (d, J = 11.5 Hz, 1 H), 4.90 (br s, 1H), 4.92 (br s, 1H), 5.03 (br d, J = 15.5 Hz, 1H), 5.04 (br d, J = 10.9 Hz, 1H), 5.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 18.1, 22.9, 23.6, 25.5, 38.3, 38.5, 43.5, 51.1, 53.0, 77.4, 114.2, 117.4, 135.2, 144.0, 219.0; LRMS (EI) m/z (M)$^+$ 236.2; HRMS (EI) m/z (M)$^+$ calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1776.

(±)-(2*E*)-2-(2,2-Dimethylpent-4-enylidene)-3-(prop-1-en-2-yl)cyclopentanone (16). To a solution of **15** (49.6 mg, 0.210 mmol) in THF (5.25 mL) were added 4-(dimethylamino)pyridine (128 mg, 1.05 mmol) and methanesulfonyl chloride (0.041 mL, 0.532 mmol) at rt, and the mixture was warmed to 60 °C (bath temperature). After 48 h at 60 °C, water was added at rt, and the mixture was extracted with hexane. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.50 g, hexane/EtOAc = 10:1) to afford **16** (40.8 mg, 89%) as a colorless syrup: R_f = 0.66 (hexane/EtOAc = 5:1); IR (neat, cm^{-1}) 3075, 2960, 2927, 1742, 1640, 1467, 1409, 1386, 1368, 1146, 997, 893; ^{1}H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 1.09 (s, 3H), 1.10 (s, 3H), 1.84 (s, 3H), 1.91−1.97 (m, 2H), 2.14 (br d, J = 7.5 Hz, 2H), 2.22 (m, 1 H), 2.30 (m, 1 H), 3.73 (br t, J = 3.7 Hz, 1H), 4.55 (br s, 1H), 4.82 (br s, 1H), 5.02 (br d, J = 18.9 Hz, 1H), 5.03 (br d, J = 9.5 Hz, 1H), 5.71 (m, 1H), 6.63 (d, J = 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 22.1, 25.2, 25.8, 26.8, 34.4, 37.2, 45.3, 47.3, 111.8, 117.6, 134.6, 136.5, 146.2, 147.3, 208.4; LRMS (EI) m/z (M)$^+$ 218.2; HRMS (EI) m/z (M)$^+$ calcd for $C_{15}H_{22}O$ 218.1671, found 218.1679.

(±)-(2*S*,3*R*)-*trans*-2-(2,2-Dimethylpent-4-enyl)-3-(prop-1-en-2-yl)cyclopentanone (17). To a solution of **16** (269 mg, 1.23 mmol) in THF (4.13 mL) degassed with argon were added $ZnCl_2$ (369 mg, 2.71 mmol) and $(PPh_3)_4Pd$ (42.7 mg, 0.0369 mmol) at rt. This solution was again degassed with argon, tributyltin hydride (0.716 mL, 2.46 mmol) was added at rt with stirring, and the resulting mixture was stirred at rt for additional 1 h. Water was added at rt, and the mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on 10% w/w anhydrous K_2CO_3−silica gel (27.1 g, hexane/EtOAc = 10:1) to afford **17** (222 mg, 82%) as a colorless syrup: R_f = 0.62 (hexane/EtOAc = 5:1); IR (neat, cm^{-1}) 3075, 2960, 1742, 1640, 1466, 1409, 1368, 1282, 1146, 997, 911, 893; ^{1}H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.81 (s, 3H), 0.85 (s, 3H), 1.15 (dd, J = 14.1, 2.6 Hz, 1H), 1.59 (dd, J = 14.1, 6.3 Hz, 1H), 1.74 (s, 3H), 1.83 (m, 1H), 1.90 (dd, J = 13.5, 7.5 Hz, 1H), 1.95−2.04 (m, 3H), 2.13 (ddd, J = 18.9, 10.1, 10.1 Hz, 1H), 2.34−2.42 (m, 2H), 4.83 (brs, 1H), 4.86 (brs, 1H), 4.98 (br d, J = 16.9, 1H), 5.00 (br d, J = 8.9, 1H), 5.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 18.5, 25.5, 26.7, 26.8, 33.2, 36.8, 40.5, 47.2, 49.1, 52.7, 113.2, 116.8, 135.7, 144.7, 220.0; LRMS (EI) m/z (M)$^+$

220.2; HRMS (EI) m/z $(M)^+$ calcd for $C_{15}H_{24}O$ 220.1827, found 220.1833.

(±)-(3a*R*,8a*S*)-4,7,7-Trimethyl-3,3a,6,7,8,8a-hexahydroazulen-1-one (18). To a solution of **17** (57.2 mg, 0.260 mmol) in dry CH_2Cl_2 (26.0 mL) degassed with argon was added the Grubbs second generation catalyst (11.0 mg, 0.013 mmol). The resulting purple solution was again degassed with argon and warmed to 40 °C (bath temperature). After 1.5 h at 40 °C, the reaction mixture was cooled to rt, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (500 mg, hexane/EtOAc = 10:1) to afford **18** (26.4 mg, 53%) as a yellow syrup: R_f = 0.52 (hexane/EtOAc = 5:1); IR (neat, cm^{-1}) 2954, 1741, 1635, 1462, 1365, 1283, 1159, 1104, 1078; ^1H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.85 (s, 3H), 0.96 (s, 3H), 1.22 (dd, J = 13.7, 13.0 Hz, 1H), 1.80 (br d, J = 1.5 Hz, 3H), 1.80−1.89 (m, 3H), 2.03 (ddd, J = 13.7, 2.7, 2.3 Hz, 1H), 2.08 (m, 1H), 2.09−2.16 (m, 2H), 2.40 (m, 1H), 2.71 (ddd, J = 12.9, 12.6, 4.9 Hz, 1H), 5.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 21.3, 24.3, 24.7, 30.5, 33.4, 38.1, 40.7, 45.2, 45.8, 48.8, 124.8, 139.0, 221.1; LRMS (EI) m/z $(M)^+$ 192.1; HRMS (EI) m/z $(M)^+$ calcd for $C_{13}H_{20}O$ 192.1514, found 192.1519.

(±)-(1a*S*,4a*S*,7a*R*,7b*R*)-3,3,7b-Trimethyloctahydrocyclopropa[*e*]azulen-5-one (5). To a solution of **18** (48.0 mg, 0.250 mmol) in dry toluene (1.25 mL) were added 1.0 M hexane solution of diethylzinc (2.50 mL, 2.50 mmol) and diiodomethane (1.34 mL, 5.00 mmol) at rt. After 12 h at 80 °C (bath temperature), water was added at rt, the reaction mixture was extracted with hexane, and the organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10.3 g, hexane/EtOAc = 40:1) to afford **5** (32.0 mg, 62%) as colorless solids and the recovered **18** (2.6 mg, 15%) as a colorless syrup: R_f = 0.55 (hexane/EtOAc = 5:1); mp 61−63 °C (colorless crystals recrystallized from benzene; lit. 63 °C,[4a] 62−64 °C[4b]); IR (KBr, cm^{-1}) 2989, 1739, 1456, 1385, 1240, 1139, 1019, 877, 757; ^1H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.27 (dd, J = 4.6, 4.4 Hz, 1H), 0.54 (m, 1H), 0.63 (dd, J = 8.3, 4.4 Hz, 1H), 0.91 (s, 3H), 0.95 (dd, J = 13.1, 12.9 Hz, 1H), 1.00 (s, 6H), 1.06 (dd, J = 14.6, 10.8 Hz, 1H), 1.57 (ddd, J = 11.5, 11.5, 6.3 Hz, 1H), 1.77 (m, 1H), 1.86 (ddd, J = 14.6, 6.3, 2.6 Hz, 1H), 1.90 (ddd, J = 13.1, 2.9, 2.6 Hz, 1H), 1.97 (ddd, J = 12.6, 8.9, 6.3 Hz, 1H), 2.08−2.17 (m, 2H), 2.38 (dd, J = 18.6, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 18.8, 20.4, 22.0, 23.3, 23.48, 23.53, 33.2, 33.3, 38.9, 43.3, 45.7, 48.1, 49.7, 222.3; LRMS (EI) m/z $(M)^+$ 206.1; HRMS (EI) m/z $(M)^+$ calcd for $C_{14}H_{22}O$ 206.1671, found 206.1692.

(±)-$\Delta^{9(15)}$-Africanene (4). To a solution of **5** (52.0 mg, 0.252 mmol) in THF (2.52 mL) was added 1.0 M toluene solution of the Tebbe reagent (0.328 mL, 0.328 mmol) at 0 °C, and the mixture was warmed to rt. After 10 min at rt, Et_2O (5.04 mL) and 1.0 M aqueous solution of NaOH (0.492 mL) were added at 0 °C, and the mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.00 g, hexane) to afford **4** (49.4 mg, 96%) as a colorless syrup: R_f = 0.95 (hexane); IR (neat, cm^{-1}) 3056, 2950, 1651, 1470, 1384, 1363, 1162, 1017, 875; ^1H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.19 (dd, J = 4.0, 4.0 Hz, 1H), 0.46−0.55 (m, 2H), 0.89 (s, 3H), 0.95 (s, 3H), 1.03 (dd, J = 13.1, 12.9 Hz, 1H), 1.04 (s, 3H), 1.10 (dd, J = 14.6, 10.5 Hz, 1H), 1.31 (ddd, J = 11.2, 11.0, 6.6 Hz, 1H), 1.55 (dddd, J = 12.1, 12.0, 11.2, 7.7 Hz, 1H), 1.67 (m, 1H), 1.73 (ddd, 1H, J = 13.5, 3.1, 2.3 Hz), 1.81 (ddd, 1H, J = 14.6, 6.3, 2.3 Hz), 2.25 (m, 1H), 2.37−2.45 (m, 2H), 4.71 (br s, 1H), 4.87 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 19.0, 20.5, 22.1, 23.3, 24.1, 27.7, 33.6, 33.7, 33.9, 42.2, 43.2, 51.3, 52.7, 104.4, 158.5; LRMS (EI) m/z $(M)^+$ 204.2; HRMS (EI) m/z $(M)^+$ calcd for $C_{15}H_{24}$ 204.1878, found 204.1891.

Epoxidation of (±)-$\Delta^{9(15)}$-Africanene (4) to Sesquiterpenoid Unit (±)-2 and Its Epimer (±)-19. To a solution of **4** (40.0 mg, 0.196 mmol) in CH_2Cl_2 (0.980 mL) was added 3-chloroperoxybenzoic acid (78.1 mg, 0.294 mmol) at rt. After 1 h at rt, saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with $CHCl_3$. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.00 g, hexane/EtOAc = 10:1) to afford a 2.5:1 inseparable mixture (judged by ^1H NMR spectrum) of **2** and **19** (38.0 mg 88% combined yield) as a colorless syrup. Data for each are shown below.

(±)-Africane-9,15-diol (6) and (±)-9-*epi*-Africane-9,15-diol (7). To a solution of **4** (49.4 mg, 0.242 mmol) in acetone (2.18 mL) and water (0.241 mL) were added OsO_4 (6.2 mg, 0.024 mmol) and 4-methylmorpholine *N*-oxide (144 mg, 1.21 mmol) at rt. After 3 h at rt, saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10.0 g, hexane/EtOAc = 1:1) to afford **6** (44.4 mg, 77%) and **7** (10.4 mg, 18%) as colorless solids. **6**: R_f = 0.53 (hexane/EtOAc = 1:2); mp 112−114 °C (colorless crystals recrystallized from hexane; lit. 112−114 °C[4b,6]); IR (neat, cm^{-1}) 3385, 3057, 2951, 2865, 1463, 1381, 1319, 1135, 1108, 1075, 1045, 912; ^1H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.18 (dd, J = 4.3, 4.0 Hz, 1H), 0.47 (m, 1H), 0.55 (dd, J = 8.3, 4.0 Hz, 1H), 0.89 (s, 3H), 0.90 (m, 1H), 0.99 (s, 3H), 1.03 (m, 1H), 1.03 (s, 3H), 1.32 (m, 1H), 1.52−1.61 (m, 2H), 1.61 (ddd, J = 12.8, 2.8, 2.6 Hz, 1H), 1.76−1.82 (m, 3H), 1.85 (br s, 1H), 2.01 (ddd, J = 12.8, 9.9, 2.8 Hz, 1H), 2.08 (br s, 1H), 3.43 (d, J = 10.8 Hz, 1H), 3.58 (d, J = 10.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 19.7, 20.4, 21.7, 23.5, 23.6, 23.9, 33.5, 34.0, 36.7, 43.5, 44.3, 48.0, 50.0, 65.3, 82.5; LRMS (EI) m/z $(M)^+$ 238.2; HRMS (EI) m/z $(M)^+$ calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1922. **7**: R_f = 0.51 (hexane/EtOAc = 1:2); mp 123−124 °C (colorless crystals recrystallized from hexane/acetone; lit. 122−125 °C[6]); IR (neat, cm^{-1}) 3430, 2950, 2855, 1457, 1382, 1261, 1103, 1078, 1063, 1041, 805; ^1H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.22 (dd, J = 4.3, 4.0 Hz, 1H), 0.48 (m, 1H), 0.54 (dd, J = 8.3, 4.0 Hz, 1H), 0.91 (s, 3H), 0.95 (s, 3H), 0.99 (s, 3H), 1.09 (dd, J = 14.6, 10.6 Hz, 1H), 1.17 (dd, J = 12.9, 12.6 Hz, 1H), 1.42 (ddd, J = 12.9, 2.3, 2.3 Hz, 1H), 1.59−1.75 (m, 6H), 1.81 (ddd, J = 14.6, 6.3, 2.3 Hz, 1H), 3.46 (br d, J = 10.9 Hz, 1H), 3.57 (br d, J = 10.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 19.7, 20.2, 21.8, 23.6, 23.9, 24.3, 33.4, 34.0, 37.4, 43.3, 44.1, 44.4, 49.8, 68.8, 82.9; LRMS (EI) m/z $(M)^+$ 238.2; HRMS (EI) m/z $(M)^+$ calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1932.

Sesquiterpenoid Unit (±)-2. To a solution of **6** (30.0 mg, 0.126 mmol) in THF (0.629 mL) were added sodium hydride (8.3 mg, 0.19 mmol, 55% dispersion in paraffin liquid) and 1-(*p*-toluenesulfonyl)imidazole (56.0 mg, 0.252 mmol) at 0 °C, and the mixture was warmed to rt. After 1 h at rt, saturated aqueous solution of NH_4Cl was added at 0 °C, and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl soluion, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.00 g, hexane/EtOAc = 10:1) to afford **2** (21.7 mg, 78%) as a colorless syrup: R_f = 0.73 (hexane/EtOAc = 5:1); IR (neat, cm^{-1}) 2952, 1457, 1385, 1261, 1096, 1018, 954, 921, 875, 795; ^1H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.20 (dd, J = 4.3, 4.0 Hz, 1H), 0.50 (m, 1H), 0.56 (dd, J = 8.3, 4.0 Hz, 1H), 0.86 (s, 3H), 0.95 (s, 3H), 0.99 (m, 1H), 1.01 (s, 3H), 1.09 (dd, J = 14.6, 10.3 Hz, 1H), 1.33 (ddd, J = 12.9, 3.3, 3.3 Hz, 1H), 1.36 (ddd, J = 10.6, 10.6, 6.6 Hz, 1H), 1.62 (ddd, J = 13.2, 7.4, 2.3 Hz, 1H), 1.68 (m, 1H), 1.76−1.85 (m, 2H), 1.92 (ddd, J = 13.2, 11.5, 6.9 Hz, 1H), 2.07 (ddd, J = 10.6, 10.3, 3.3 Hz, 1H), 2.61 (d, J = 4.6 Hz, 1H), 2.86 (d, J = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 19.2, 20.2, 21.9, 23.3, 23.9, 26.0, 33.4, 33.90, 33.92, 41.0, 43.1, 47.5, 50.3, 52.4, 68.5; LRMS (EI) m/z $(M)^+$ 220.2; HRMS (EI) m/z $(M)^+$ calcd for $C_{15}H_{24}O$ 220.1827, found 220.1842.

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From (±)-2 to (±)-Africane-9,15-diol (6). To a solution of **2** (10.0 mg, 0.0454 mmol) in DMSO (0.227 mL) and H_2O (0.227 mL) was added potassium hydroxide (3.8 mg, 0.068 mmol) at rt, and the mixture was warmed to 50 °C (bath temperature). After 1 h at 50 °C, saturated aqueous solution of NH_4Cl was added at rt, and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.0 g, hexane/EtOAc = 2:1) to afford **6** (5.8 mg, 58%) as a colorless syrup.

(±)-19. To a solution of **7** (5.0 mg, 0.021 mmol) in THF (0.11 mL) were added sodium hydride (1.4 mg, 0.031 mmol, 55% dispersion in paraffin liquid) and 1-(*p*-toluenesulfonyl)imidazole (9.3 mg, 0.042 mmol) at 0 °C and the mixture was warmed to rt. After 1 h at rt, saturated aqueous solution of NH_4Cl was added at 0 °C and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.0 g, hexane/EtOAc = 10:1) to afford **19** (3.5 mg, 75%) as a colorless syrup: R_f = 0.73 (hexane/EtOAc = 5:1); IR (neat, cm^{-1}) 2925, 2854, 1463, 1382, 1261 1075, 1038, 803; ^1H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.23 (dd, J = 4.3, 3.7 Hz, 1H), 0.51 (m, 1H), 0.56 (dd, J = 8.3, 3.7 Hz, 1H), 0.87 (s, 3H), 0.89 (m, 1H), 0.95 (s, 3H), 0.97 (s, 3H), 1.00 (m, 1H,), 1.09 (dd, J = 14.6, 10.6 Hz, 1H), 1.52 (ddd, J = 10.6, 10.6, 6.9 Hz, 1H), 1.64 (m, 1H), 1.74−1.84 (m, 3H), 1.92 (m, 1H), 2.12 (ddd J = 11.3, 10.6, 3.4 Hz, 1H), 2.62 (d, J = 5.1 Hz, 1H), 2.80 (d, J = 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 19.2, 20.4, 22.1, 23.3, 23.9, 25.3, 32.9, 33.0, 33.9, 38.9, 43.2, 44.2, 51.46, 51.52, 66.1; LRMS (EI) m/z $(M)^+$ 220.2; HRMS (EI) m/z $(M)^+$ calcd for $C_{15}H_{24}O$ 220.1827, found 220.1810.

(±)-Leptographiol (8) and (±)-Isoleptographiol (9) from Ketone 5. To a solution of **5** (20.0 mg, 0.0970 mmol) in THF (0.485 mL) was added a 1.12 M Et_2O solution of MeLi (0.113 mL, 0.126 mmol) at −78 °C, and the mixture was warmed to 0 °C with stirring. After 2 h at 0 °C, saturated aqueous solution of NH_4Cl was added at 0 °C, and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.00 g, hexane/EtOAc = 10:1) to afford **8** (11.2 mg, 52%) and **9** (3.9 mg, 18%) as colorless syrups. **8**: R_f = 0.33 (hexane/EtOAc = 5:1); IR (neat, cm^{-1}) 3442, 2925, 2853, 1463, 1382, 1262, 1075, 1017, 938, 920, 804; ^1H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.21 (dd, J = 4.3, 4.0 Hz, 1H), 0.45 (m, 1H), 0.53 (dd, J = 8.3, 4.0 Hz, 1H), 0.92 (s, 3H), 0.96 (s, 3H), 0.99 (s, 3H), 1.09 (dd, J = 14.6, 10.6 Hz, 1H), 1.10 (dd, J = 13.0, 12.9 Hz, 1H), 1.25 (s, 3H), 1.44 (ddd, J = 13.0, 2.6, 2.6 Hz, 1H), 1.57−1.64 (m, 3H), 1.67−1.75 (m, 3H), 1.77−1.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 19.6, 20.6, 21.8, 23.3, 23.7, 24.4, 25.6, 33.3, 34.0, 41.4, 43.2, 43.3, 48.0, 48.6, 81.3; LRMS (EI) m/z $(M)^+$ 222.2; HRMS (EI) m/z $(M)^+$ calcd for $C_{15}H_{26}O$ 222.1984, found 222.1985. **9**: R_f = 0.18 (hexane/EtOAc = 5:1); IR (neat, cm^{-1}) 3406, 2925, 2855, 1463, 1384, 1261, 1098, 1030, 803, 758; ^1H NMR (500 MHz, $CDCl_3$, TMS = 0.00) δ 0.17 (dd, 1H, J = 4.6, 4.6 Hz), 0.46 (m, 1H), 0.53 (dd, J = 8.3, 4.0 Hz, 1H), 0.92 (dd, J = 12.6, 12.6, 1H), 0.90 (s, 3H), 1.00 (s, 3H), 1.02 (m, 1H), 1.03 (s, 3H), 1.08 (s, 3H), 1.31 (ddd, J = 10.0, 10.0, 5.2 Hz, 1H), 1.52 (ddd, J = 12.6, 2.5, 2.3 Hz, 1H), 1.52 (m, 1H), 1.62 (ddd, J = 11.7, 11.7, 3.4 Hz, 1H), 1.66 (m, 1H), 1.73 (m, 1H), 1.79 (ddd, J = 14.6, 6.3, 2.3 Hz, 1H), 1.86 (ddd, J = 12.6, 10.0, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77.00) δ 19.7, 20.7, 21.8, 22.4, 22.9, 23.6, 24.1, 33.4, 34.0, 42.0, 43.5, 44.9, 48.5, 48.7, 80.2; LRMS (EI) m/z $(M)^+$ 222.2; HRMS (EI) m/z $(M)^+$ calcd for $C_{15}H_{26}O$ 222.1984, found 222.1983.

From (±)-2 to (±)-Isoleptographiol (9). To a solution of **2** (5.0 mg, 0.023 mmol) in THF (0.23 mL) was added $LiAlH_4$ (1.3 mg, 0.034 mmol) at 0 °C, and the mixture was warmed to rt. After 1 h at rt, saturated aqueous solution of NH_4Cl was added at 0 °C, and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.00 g, hexane/EtOAc = 5:1) to afford **9** (3.8 mg, 75%) as a colorless syrup.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra of all new compounds and crystallographic data of compound **6** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) For complete comparison, see Supporting Information.
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