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Synthesis of the Reported Structure of *trans*-Africanan-1α-ol

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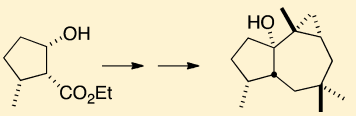
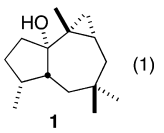
Supporting Information

ABSTRACT: A trisubstituted cyclopentane chiron has been prepared by dynamic kinetic reduction of a pulegone-derived β-keto ester. This chiron served as the starting material for the synthesis of the reported structure of the tricyclic sesquiterpene *trans*-africanan-1α-ol. The synthetic material was not congruent with the natural product.



INTRODUCTION

trans-Africanan-1α-ol[1] is a new sesquiterpene alcohol isolated from *Lippia integrifolia*, which grows wild in the province of Catamarca, Argentina. The indigenous population of Argentina and Paraguay use *Lippia integrifolia* in traditional medicine for the treatment of asthma. One of the unusual components of the essential oil of *L. intefriflia*, *trans*-africanan-1*a*-ol (eq 1) was

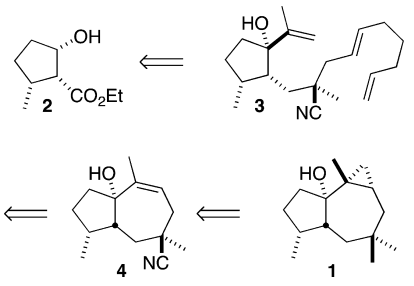


reported to have a tricyclic architecture **1** (eq 1), with five contiguous stereogenic centers, making it a challenge for total synthesis. We have completed the synthesis of **1** and have found that the material so prepared is not congruent with the reported natural product.

RESULTS AND DISCUSSION

We envisioned that the synthesis of **1** could start with the cyclopentanol **2** (Scheme 1). The *cis* ester group of **2** presented

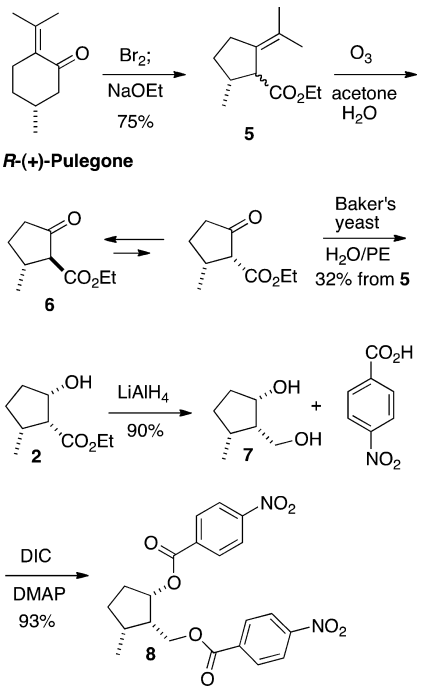
Scheme 1



a particular problem for diastereocontrol. We anticipated that after extension of the side chain 1,2-addition to the derived cyclopentanone would give the tertiary alcohol **3**, securing the angular stereogenic center. After relay ring-closing metathesis, Simmons–Smith cyclopropanation of the tertiary alcohol **4** would complete the preparation of **1**.

Preparation of 2. Enantioselective yeast reductions[2] of β-keto esters have been known for many years. However, the contrathermodynamic kinetic reduction of a cyclic β-keto ester had not been described.[3] We envisioned that yeast reduction of the ester **6** (Scheme 2), a mixture of equilibrating

Scheme 2



diastereomers, could preferentially convert the minor *cis* diastereomer to the corresponding secondary alcohol **2**.

The original yeast protocols needed saccharose and water[2b] or aqueous ethyl chloroacetate.[2a] Product recovery required either extraction of the product from the aqueous saccharose broth, or filtration, to wash the reaction products off the bulk

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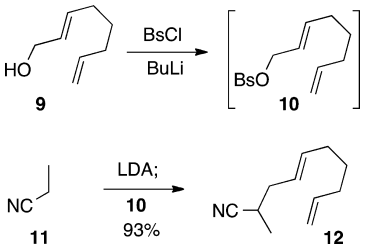
yeast. In 1997, Smallridge reported an improved procedure using yeast in water and light petroleum.[2c] This protocol had not been applied to cyclic β-keto esters.

The enantiomerically pure β-keto ester **6** was readily available from (*R*)-(+)-pulegone.[4] However, the reported ozonolysis conditions gave low material recovery. We found that simply carrying out the ozonolysis in aqueous acetone at 0 °C as described by Dussault[5] worked well. The crude product collected after extraction could be used directly in the yeast reduction.

The Smallridge protocol using Baker's yeast in a mixture of water and petroleum ether at room temperature took 3 days to go to completion. Simple filtration and washing of the yeast residue with acetone and petroleum ether followed by chromatography then delivered the *cis* β-hydroxy ester **2** as a single dominant diastereomer. The stereocenters were proved by X-ray crystallography of the derivative **8**.

Preparation of 3. We anticipated that while propionitrile could be allylated,[6] the product would be of such low molecular weight that it could be difficult to handle. Alternatively, the nonvolatile nitrile **12** (Scheme 3) could be easily prepared from

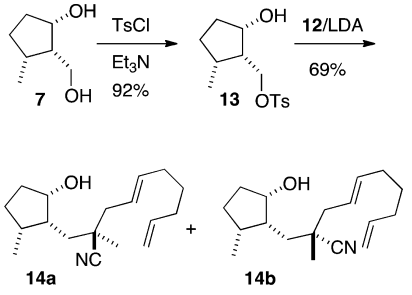
Scheme 3



the inexpensive butadiene telomer 2,7-octadienol **9**, setting the stage for relay ring-closing metathesis. The intermediate **10** was used directly without purification to alkylate[6] excess depronated propionitrile **11**.

Bond formation (Scheme 4) proceeded smoothly without protection of the secondary alcohol of **13**. The two

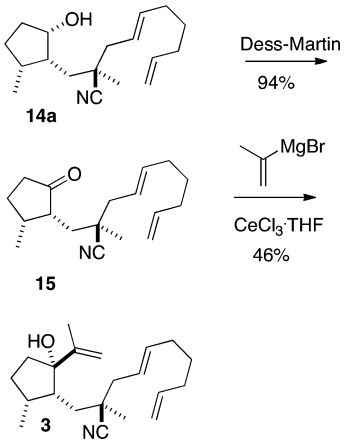
Scheme 4



diastereomers **14a** and **14b** could be readily separated by silica gel chromatography.

To establish the tertiary alcohol stereocenter, we oxidized the secondary alcohol **14a** with the Dess–Martin reagent. Addition of 2-propenylmagnesium bromide was not successful, even with the direct addition of anhydrous $CeCl_3$. With the addition of anhydrous $CeCl_3$ complexed with THF,[7] however, we were able to effect the 1,2-addition to the less hindered face of the ketone **15** to give **3** (Scheme 5). The complex was prepared by sonication of $CeCl_3$ in anhydrous THF. Workup with 5%

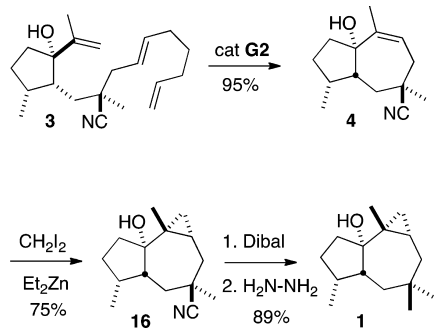
Scheme 5



NH_4Cl(aq) was important to achieve acceptable product recovery. The neat tertiary allylic alcohol **3** was sufficiently stable to be stored at room temperature for several weeks.

Preparation of 4. The relay ring-closing metathesis[8] (Scheme 6) proceeded smoothly to generate the cycloheptene

Scheme 6



ring. The nitrile **4** was crystalline, allowing us to assign the relative configurations of **14a** and **14b** (Scheme 4) by X-ray analysis. The diastereomeric nitrile **14b** and the products derived from it participated equally well in each of the subsequent transformations, leading also to **1**.

Synthesis of 1. We envisioned that the traditional Simmons–Smith reaction could set the cyclopropane ring. However, it had been reported that the hydroxyl group would direct the cyclopropane ring *syn* on a cyclohexene ring[9a] or *trans* on a cyclooctene ring.[9b] On the basis of a computationally derived model of our cycloheptene **4**, it appeared that the hydroxyl group should deliver the methylene on the bottom face on the alkene.[9c]

In the event, Simmons–Smith cyclopropanation[10] of the cyclic alkene **4** (Scheme 6) proceeded smoothly to give **16**, the relative configuration of which was again secured by X-ray crystallography. This became important because Dibal reduction followed by Wolff–Kishner deoxygenation[11] delivered a product tertiary alcohol **1** that was not congruent with the reported natural product. Although many of the structures of the africanane sesquiterpenes have been confirmed by total synthesis,[12,13] there is at least one other example[12g] of synthesis uncovering an incorrect structural assignment.

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CONCLUSION

The ready availability of the cyclopentane chiron **2** enabled the concise assembly of the tricyclic alcohol **1**. It is clear that the elucidation of the actual structure of *trans*-africanan-1α-ol will require further study. We expect that both the cyclopentane chiron **2** and the nitrile **12** will have many applications in target directed synthesis.

EXPERIMENTAL SECTION

General. ^{1}H NMR (at 400 MHz) and ^{13}C NMR (at 100 MHz) spectra were obtained as solutions in $CDCl_3$, except as otherwise indicated. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" and for methylene and quaternary carbons as "u". High-resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI), except as otherwise indicated, and the errors between observed and theoretical monoisotopic molecular masses were typically ≤5 ppm. The infrared (IR) spectra were determined as neat oils or a solution in dichloromethane as indicated. R_f values indicated refer to thin layer chromatography (TLC) on 5.0 × 10 cm, 250 μm analytical plates coated with silica gel 60 F_{254}, developed in the solvent system indicated. Column chromatography was carried out by using silica gel 60 particle size 40−63 μm. The solvent mixtures reported are volume/volume mixtures. All glassware was oven-dried and reactions were carried out under a flow of nitrogen. MTBE is methyl *tert*-butyl ether. PE is petroleum ether.

Ethyl (1*R*,2*R*)-2-Methyl-5-(propan-2-ylidene)-cyclopentanecarboxylate (Ethyl Pulegenate) (5). Following the procedure of Marx,[4c] fresh NaOEt was prepared by dissolving Na (23.16 g, 1.007 mol) in EtOH (400 mL). Bromine was added dropwise into a mixture of pulegone (65.24 g, 428.5 mmol) and $NaHCO_3$ (10.82 g, 128.8 mmol) in Et_2O (350 mL) over 2 h at 0 °C with rapid stirring. Stirring was continued at 0 °C for another 2 h. The mixture was filtered with Et_2O (50 mL) through a pad of Celite into the freshly made NaOMe solution in EtOH (400 mL) at 0 °C. The reaction mixture was warmed to reflux overnight. The cooled reaction mixture was filtered with Et_2O (200 mL) through a pad of Celite. The crude product was concentrated and purified by bulb to bulb distillation (0.5 Torr, bp (pot) = 90 °C) to yield the ethyl ester **5** as a pale yellow oil (63.11 g, 75% yield). The ^{1}H and ^{13}C NMR data were consistent with those reported.[4c] TLC R_f (10% MTBE/PE) = 0.74.

Ethyl (1*R*,2*S*,5*R*)-2-Hydroxy-5-methylcyclopentanecarboxylate (2). Applying the protocol of Dussault,[5] a mixture of the distilled ethyl pulegenate **5** (14.05 g, 71.68 mmol) and 5% H_2O/acetone (450 mL) was bubbled with O_2/O_3 at 0 °C for 6 h, when Sudan III indicator was bleached. The reaction mixture was diluted with H_2O (200 mL) and stirred at rt until no more bubbles were observed and then partitioned between dichloromethane and H_2O. The combined organic extract was concentrated to yield the crude β-keto ester **6** as a pale yellow oil (14.58 g), which was used in the yeast reduction without further purification. The NMR data were consistent with the data reported.[4d] TLC R_f (5% MTBE/dichloromethane) = 0.72. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (q, 2H, J = 7.2 Hz), 2.70 (d, 1H, J = 11.8 Hz), 2.50−2.58 (m, 1H), 2.22−2.40 (m, 2H), 2.10−2.18 (m, 1H), 1.38−1.48 (m, 1H), 1.24 (t, 3H, J = 7.2 Hz), 1.13 (d, 3H, J = 6.5 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 14.1, 19.1, 36.3, 63.0; u 29.2, 38.6, 61.1, 169.1, 211.9. IR (film): 2963, 1755, 1726, 1459, 1374 cm^{-1}.

A mixture of the crude β-keto ester **6** (2.11 g), yeast (66.0 g), H_2O (52.8 mL), and petroleum ether (211 mL) was mechanically stirred at rt for 3 days. The resulting broth was diluted with acetone (200 mL) and filtered with petroleum ether (2.5 L). The filtrate was concentrated, and the residue was purified by chromatography followed by bulb to bulb distillation (0.5 Torr, bp (pot) = 110 °C) to give the β-hydroxy ester **2** as a colorless oil (0.580 g, 32% yield from the distilled ethyl pulegenate **5**). TLC R_f (5% MTBE/dichloromethane) = 0.51. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31−4.37 (m, 1H), 4.16 (q, 2H, J = 7.2 Hz), 3.80 (bs, 1H), 2.70−2.74 (dd, 1H, J = 4.6, 8.9 Hz), 2.33−2.42 (m, 1H), 1.78−1.90 (m, 2H), 1.66−1.77 (m, 1H), 1.53−1.63 (m, 1H), 1.25 (t, 3H, J = 7.1 Hz), 0.99 (d, 3H, J = 7.2 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 14.2, 18.8, 34.6, 52.5, 74.0; u 31.4, 33.4, 60.3, 174.5. IR (film): 3501, 2962, 2878, 1713, 1459 cm^{-1}. MS (m/z): 55, 69, 87, 101, 115, 127, 144, 171. HRMS calcd for $C_9H_{17}O_3$ 173.1178; obsd 173.1176. $[\alpha]_D$ −0.360 (c 3.89, $CHCl_3$).

(1*S*,2*S*,3*R*)-2-(Hydroxymethyl)-3-methylcyclopentanol (7). To a gray suspension of $LiAlH_4$ (7.21 g, 176 mmol) in Et_2O (116 mL) was added a solution of the β-hydroxy ester **2** (7.49 g, 42.2 mmol) in Et_2O (60 mL) dropwise over 10 min at 0 °C. The resulting mixture was warmed to rt and stirred at rt for 4.5 h. Then H_2O/THF (1:9, 75 mL) was added dropwise over 17 min at 0 °C followed by stirring at rt for 1.5 h. 15% NaOH (aq, 7.5 mL) was added in one portion followed by stirring at rt for another 1.5 h. Water (22.5 mL) was added in one portion followed by stirring overnight. The reaction mixture was filtered with Et_2O through a pad of $MgSO_4$. The filtrate was concentrated, and the residue was purified by chromatography to yield the diol **7** as a colorless oil (5.09 g, 90% yield). TLC R_f (20% MTBE/dichloromethane) = 0.26. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.43 (q, 1H, J = 11.0 Hz), 3.88 (t, 1H, J = 4.4 Hz), 3.77 (dd, 1H, J = 4.4 Hz, 10.4 Hz), 3.16 (m, 2H), 2.03−2.14 (m, 2H), 1.87−1.97 (m, 1H), 1.69−1.82 (m, 2H), 1.39−1.49 (m, 1H), 0.97 (d, 3H, J = 6.8 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 16.6, 33.8, 47.8, 75.6; u 31.5, 33.3, 60.5. IR (film): 3354, 2952, 1458, 1338, 1040 cm^{-1}. MS (m/z) 53, 55, 57, 68, 70, 79, 81, 83, 94, 97, 112. HRMS calcd for $C_7H_{12}O$ 112.0888; obsd 112.0884. $[\alpha]_D$ + 37.3 (c 1.94, $CHCl_3$).

(Bis)-4-nitrobenzoate (8). To a mixture of the diol **7** (148 mg, 1.141 mmol), DMAP (72 mg, 0.59 mmol), and *p*-nitrobenzoic acid (1.93 g, 11.6 mmol) in dichloromethane (11.5 mL) was added *N*,*N*′-diisopropylcarbodiimide (2.99 g, 23.7 mmol) over 30 s at 0 °C. The resulting mixture was warmed to rt, stirred at rt for 2 h, and then filtered through a pad of silica gel with dichloromethane. The filtrate was concentrated, and the residue was stirred with NaOH (aq, 6 M, 20 mL) and dichloromethane (20 mL) at rt overnight and then partitioned between H_2O and dichloromethane. The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was purified by chromatography to yield the derivative **8** as a pale yellow solid (0.492 g). Recrystallization of a 0.160 g sample from EtOAc yielded 148 mg of pale yellow crystals (93% yield from **7**); mp = 128−129 °C. TLC R_f (20% MTBE/PE) = 0.29. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20−8.27 (m, 4H), 8.09−8.15 (m, 4H), 5.66 (dt, 1H, J = 2.7, 5.9 Hz), 4.55 (d, 2H, J = 7.6 Hz), 2.58−2.68 (m, 1H), 2.41−2.53 (m, 1H), 2.12−2.25 (m, 1H), 1.94−1.09 (m, 2H), 1.57−1.68 (m, 1H), 1.16 (d, 3H, J = 7.1 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 16.9, 33.4, 45.3, 78.0, 123.4, 123.5, 130.2, 130.6; u 31.5, 31.8, 62.6, 135.2, 135.5, 150.4, 164.0, 164.5. IR (film): 3424, 2967, 2076, 1722, 1643 cm^{-1}. $[\alpha]_D$ + 5.33 (c 2.21, $CHCl_3$).

(2*E*)-2-Methyldeca-4,9-dienenitrile (12). LDA was prepared by adding *n*-BuLi (2.5 M, 84.0 mL, 210 mmol) to a solution of diisopropylamine (30.5 mL, 218 mmol) in THF (450 mL) at −78 °C in one portion. Then a solution of propionitrile (14.3 mL, 200 mmol) in THF (50 mL) was added dropwise over 7 min. Stirring was continued at −78 °C for 1 h.

At the same time, a solution of 2,7-octadienol (15.2 g, 120 mmol) in THF (200 mL) was cooled to −78 °C. *n*-BuLi (2.5 M, 44.0 mL, 110 mmol) was added dropwise over 3 min followed by benzenesulfonyl chloride (12.8 mL, 100 mmol) over 2 min. Stirring was continued at −78 °C for 15 min to generate (2*E*)-octa-2,7-dienyl 4-bromobenzenesulfonate (**10**) in situ. The reaction mixture was quickly poured into the stirring nitrile anion solution. The resulting mixture was stirred at −78 °C (~rt) overnight. The product was purified by chromatography followed by bulb to bulb distillation (0.5 Torr, bp (pot) = 100 °C) to yield the nitrile **12** as a colorless oil (15.2 g, 93% yield based on the limiting reagent BsCl). TLC R_f (5% MTBE/PE) = 0.40. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74−5.85 (m, 1H), 5.54−5.63 (m, 1H), 5.37−5.46 (m, 1H), 4.93−5.04 (m, 2H), 2.57−2.68 (m, 1H), 2.22−2.32 (m, 2H), 2.01−2.10 (m, 4H), 1.42−1.52 (m, 2H), 1.29 (d, 3H, J = 7.1 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 17.4, 25.9, 124.7, 135.0, 138.6; u 28.4, 31.8, 33.1, 36.9, 114.6, 122.7. IR (film): 2929, 2241, 1726,

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1642, 1451 cm^{-1}. MS (m/z): 55, 67, 81, 95, 109, 121, 134, 148, 162. HRMS calcd for $C_{11}H_{18}N$ (M + H) 164.1439; obsd 164.1433.

((1*S*,2*S*,5*R*)-2-Hydroxy-5-methylcyclopentyl)methyl 4-Methylbenzenesulfonate (13). Triethylamine (4.10 mL, 29.6 mmol) was added into a solution of the diol **7** (1.74 g, 13.4 mmol) in dichloromethane (14.0 mL) in one portion followed by the addition of TsCl (5.11 g, 26.8 mmol) in one portion. The reaction mixture was stirred at rt overnight, then quenched with HCl (aq, 1 M, 13.4 mL), and partitioned between dichloromethane and H_2O. The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was purifed by chromatography to yield the tosylate **13** as a thick yellow oil (3.51 g, 92% yield). TLC R_f (2% MTBE/dichloromethane) = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79−7.83 (d, 2H, J = 8.2 Hz), 7.33−7.37 (d, 2H, J = 8.2 Hz), 4.28−4.38 (m, 2H), 4.12−4.17 (dd, 1H, J = 5.7, 9.9 Hz), 2.45 (s, 3H), 2.09−2.22 (m, 2H), 1.87−1.97 (m, 2H), 1.78−1.87 (m, 2H), 1.66−1.76 (m, 1H), 1.43−1.55 (m, 1H), 0.90 (d, 3H, J = 6.8 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 17.1, 21.6, 33.2, 46.6, 73.6, 127.9, 129.9; u 32.1, 33.9, 68.8, 133.0, 144.8. IR (film): 3555, 2954, 1922, 1598, 1456 cm^{-1}. MS (m/z): 69, 82, 115, 139, 166. HRMS calcd for $C_{14}H_{20}O_4NaS$ 307.0980; obsd 307.0992. $[\alpha]_D$ − 5.56 (c 0.99, $CHCl_3$).

(2*R*,3*E*)-2-(((1*R*,2*S*,5*R*)-2-Hydroxy-5-methylcyclopentyl)-methyl)-2-methyldeca-4,9-dienenitrile (14a) and (2*S*,3*E*)-2-(((1*R*,2*S*,5*R*)-2-Hydroxy-5-methylcyclopentyl)methyl)-2-methyldeca-4,9-dienenitrile (14b). LDA was prepared by adding *n*-BuLi (15.0 mL, 2.5 M, 37.5 mmol) into a solution of diisopropylamine (5.70 mL, 40.7 mmol) in THF (40 mL) in one portion at −78 °C. A solution of the nitrile **12** (5.75 g, 35.3 mmol) in THF (40 mL) was added over 5 min. Stirring was continued at −78 °C for another 2 h. A solution of the tosylate **13** (2.50 g, 8.80 mmol) in THF (20 mL) was added in one portion. The resulting mixture was gradually warmed to rt, and stirring was continued for 4 h. The reaction mixture was concentrated, and the residue was purified by chromatography to yield the mixture of the nitriles **14a** and **14b** as a pale yellow oil (2.38 g, 98% yield). TLC R_f (2% MTBE/dichloromethane) = 0.27. The mixture (1.40 g) of **14a** and **14b** was further separated by silica gel chromatography to yield **14a** (0.35 g, 25% from **13**), **14b** (0.26 g, 18% from **13**), and a mixture of both (0.37 g, 26% from **13**). **14a**: TLC R_f (20% MTBE/PE) = 0.36. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72−5.86 (m, 1H), 5.44−5.69 (m, 2H), 4.90−5.04 (m, 2H), 4.38 (bs, 1H), 2.33−2.41 (dd, 1H, J = 6.5, 14.4 Hz), 2.16−2.23 (dd, 1H, J = 7.1, 13.7 Hz), 2.10−2.16 (dt, 1H, J = 3.1, 7.6 Hz), 1.99−2.10 (m, 5H), 1.86−1.98 (m, 2H), 1.76−1.85 (m, 1H), 1.65−1.76 (m, 2H), 1.40−1.53 (m, 4H), 1.30 (s, 3H), 0.96 (d, 3H, J = 7.2 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 17.5, 23.6, 35.8, 44.2, 74.4, 123.7, 136.0, 138.6; u 28.4, 31.4, 31.9, 33.1, 33.7, 34.5, 36.3, 43.7, 114.6, 125.3. IR (film): 3504, 3075, 2929, 2234, 1641 cm^{-1}. MS (m/z): 43, 55, 67, 81, 95, 105, 111, 119, 133, 146, 160, 242, 260, 274. HRMS calcd for $C_{18}H_{28}N$ 258.2222; obsd 258.2215. $[\alpha]_D$ + 17.4 (c 1.21, $CHCl_3$).

14b: TLC R_f (20% MTBE/PE) = 0.26. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72−5.86 (m, 1H), 5.42−5.63 (m, 2H), 4.90−5.04 (m, 2H), 4.34 (bs, 1H), 2.33−2.41 (dd, 1H, J = 6.7, 13.6 Hz), 2.12−2.21 (m, 2H), 2.01−2.11 (m, 4H), 1.88−1.99 (m, 2H), 1.75−1.88 (m, 2H), 1.67−1.88 (m, 1H), 1.60−1.67 (dd, 1H, J = 4.2, 13.8 Hz), 1.41−1.53 (m, 3H), 1.33 (s, 3H), 0.97 (d, 3H, J = 7.3 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 17.5, 24.8, 35.7, 44.2, 74.7, 123.7, 136.0, 138.6; u 28.4, 31.4, 31.9, 33.1, 34.0, 34.3, 36.3, 42.5, 114.6, 125.1. IR (film): 3504, 3075, 2928, 2261, 2234, 1641, 1455, 973 cm^{-1}. MS (m/z): 43, 55, 67, 82, 95, 109, 119, 134, 146, 160, 174, 190, 200, 218, 242, 260, 274. HRMS calcd for (M−OH) = $C_{18}H_{28}N$ 258.2222; obsd 258.2225. $[\alpha]_D$ − 2.63 (c 1.52, $CHCl_3$).

(2*R*,3*E*)-2-Methyl-2-(((1*R*,2*R*)-2-methyl-5-oxocyclopentyl)-methyl)deca-4,9-dienenitrile (15). To a solution of the alcohol **14a** (0.268 g, 0.975 mmol) in dichloromethane (10.0 mL) was added Dess−Martin periodinane (823 mg, 1.94 mmol) in one portion. The resulting white suspension was stirred at rt for 2 h. The reaction mixture was filtered with Et_2O through a pad of Celite. The filtrate was concentrated, and the residue was purified by chromatography to yield the ketone **15** as a pale yellow oil (0.25 g, 94% yield). TLC R_f (2% MTBE/dichloromethane) = 0.58. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73−5.87 (m, 1H), 5.53−5.63 (m, 1H), 5.41−5.52 (m, 1H), 4.92−5.06 (m, 2H), 2.72−2.82 (m, 1H), 2.31−2.43 (m, 2H), 2.24−2.31 (m, 1H), 2.12−2.24 (m, 2H), 2.00−2.12 (m, 6H), 1.77−1.86 (m, 1H), 1.40−1.53 (m, 3H), 1.32 (s, 3H), 0.89 (d, 3H, J = 7.2 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 14.9, 24.8, 33.2, 51.9, 123.2, 136.4, 138.6; u 27.8, 28.4, 31.9, 33.1, 33.1, 33.4, 36.3, 42.0, 114.6, 124.0, 218.0. IR (film): 3463, 3075, 2929, 2360, 2233, 1740 cm^{-1}. MS (m/z): 43, 55, 67, 83, 98, 111, 123, 135, 149, 163, 258, 260, 273. HRMS calcd for (M − H) = $C_{18}H_{28}NO$ 274.2171; obsd 274.2174. $[\alpha]_D$ − 104 (c 1.02, $CHCl_3$).

(2*R*,3*E*)-2-(((1*R*,2*S*,5*R*)-2-Hydroxy-5-methyl-2-(1-methylethenyl)cyclopentyl)methyl)-2-methyldeca-4,9-dienenitrile (3). Isopropenylmagnesium bromide was prepared by adding a solution of 2-bromopropene (0.90 mL, 10.1 mmol) in THF (10 mL) into a suspension of Mg (367 mg, 15.1 mmol) and I_2 (catalytic amount) in THF (10 mL) dropwise over 5 min at reflux. The resulting mixture was heated at reflux for 4 h and then cooled to rt to give a pale gray solution.

A thick white suspension of anhydrous $CeCl_3$ (790 mg, 3.21 mmol) in THF (6.0 mL) was activated by sonication at rt for 4 h. The resulting milky suspension was cooled to 0 °C followed by adding the isopropenylmagnesium bromide solution (5.30 mL, 2.69 mmol) dropwise over 5 min. The resulting mixture was stirred at 0 °C for 1 h, turning to a dark brown suspension. This was cooled to −78 °C. Then the ketone **15** (230 mg, 0.842 mmol) in THF (12 mL) was added dropwise over 5 min. The resulting mixture was stirred at −78 °C for 1 h, then quenched with 5% NH_4Cl (aq, 18 mL), and partitioned between H_2O and dichloromethane. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography to yield the *ter*-alcohol **3** as a yellow oil (121 mg, 46% yield). TLC R_f (2% MTBE/PE) = 0.29. ^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72−5.86 (m, 1H), 5.38−5.61 (m, 2H), 4.90−5.10 (m, 4H), 2.41−2.54 (m, 1H), 2.26−2.34 (dd, 2H, J = 6.9, 13.7 Hz), 1.94−2.12 (m, 8H), 1.78 (s, 3H), 1.54−1.67 (m, 4H), 1.40−1.51 (m, 2H), 1.28 (s, 3H), 1.18 (s, 1H), 1.08 (d, 3H, J = 7.1 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 18.7, 19.5, 24.2, 34.4, 45.1, 123.7, 135.9, 138.6; u 28.4, 31.9, 32.5, 32.8, 33.1, 37.0, 37.7, 43.0, 86.8, 111.0, 114.6, 124.6, 148.8. IR (film): 3500, 3077, 2931, 2233, 1640 cm^{-1}. MS (m/z): 43, 55, 69, 81, 97, 109, 123, 135, 153, 164, 176, 190, 204, 218, 232, 246, 260, 274, 300, 314. HRMS calcd for (M + H) = $C_{21}H_{34}NO$ 316.2640; obsd 316.2639. $[\alpha]_D$ + 4.4 (c 0.79, $CHCl_3$).

(3*R*,3a*R*,5*R*,8a*S*)-1,2,3,3a,4,5,6,8a-Octahydro-8a-hydroxy-3,5,8-trimethylazulene-5-carbonitrile (4). A mixture of the *ter*-alcohol **3** (55.8 mg, 0.177 mmol) and Grubbs catalyst, second generation (3.0 mg, 0.0035 mmol), in dichloromethane (36.0 mL) was heated to reflux for 1 h. The reaction mixture was concentrated, and the residue was purified by chromatography to yield the cyclized nitrile **4** as pale yellow crystals (36.9 mg, 95% yield). TLC R_f (20% MTBE/PE) = 0.25; mp 90−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.58 (bs, 1H), 2.65 (d, 1H, J = 14.7 Hz), 2.11−2.31 (m, 3H), 2.03−2.11 (m, 1H), 1.91−2.03 (m, 1H), 1.81 (s, 3H), 1.41 (s, 3H), 1.1−1.2 (m, 1H), 0.93 (d, 3H, J = 6.2 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 18.5, 22.3, 29.3, 34.7, 45.5, 124.4; u 31.4, 36.0, 37.3, 38.3, 38.6, 83.4, 124.1, 145.5. IR (neat): 3484, 2936, 2231, 1722, 1452, 1373 cm^{-1}. MS (m/z): 42, 55, 79, 95, 108, 121, 135, 159, 177, 190, 204, 219. HRMS calcd for (M + H) = $C_{14}H_{22}NO$ 220.1701; obsd 220.1695. $[\alpha]_D$ − 97.4 (c 1.02, $CHCl_3$).

(1a*S*,3*R*,4a*R*,5*R*,7a*S*,7b*R*)-Decahydro-7a-hydroxy-3,5,7b-trimethyl-1*H*-cyclopropa[*e*]azulene-3-carbonitrile (16). Diiodomethane (0.11 mL, 1.35 mmol) was added into a solution of Et_2Zn (1 M in hexane, 0.66 mL, 0.66 mmol) over 2 min at 0 °C, and the stirring was continued at 0 °C for 30 min. To the resulting white suspension was added to a solution of the cyclized alkene **4** (25.2 mg, 0.115 mmol) in dichloromethane (1.64 mL) over 2 min. The reaction mixture was warmed to rt, and stirring was continued at rt for 1 h. The reaction mixture was quenched with 5% NH_4Cl (aq, 2.0 mL) and partitioned between H_2O and dichloromethane. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography to yield the cyclopropane **16** as

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colorless crystals (20.1 mg, 75% yield). TLC R_f (20% MTBE/PE) = 0.41. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35−2.47 (m, 1H), 2.13−2.26 (m, 2H), 2.04−2.13 (dd, 1H, J = 7.1, 13.9 Hz), 1.81−1.90 (m, 1H), 1.57−1.74 (m, 3H), 1.43−1.54 (m, 2H), 1.34 (s, 3H), 1.09 (s, 3H), 0.91 (d, 3H, J = 7.3 Hz), 0.86−0.96 (m, 1H), 0.77 (t, 2H, J = 4.8 Hz), 0.48 (dd, 1H, J = 4.4, 8.3 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 17.0, 22.5, 23.6, 29.0, 36.1, 45.3; u 17.7, 25.6, 33.3, 37.1, 37.6, 39.1, 39.6, 82.2, 124.6. IR (neat): 3489, 2961, 2232, 2075, 1643, 1454 cm^{-1}. MS (m/z): 55, 69, 79, 84, 91, 97, 107, 119, 125, 135, 148, 163, 176, 190, 204, 218, 233. HRMS calcd for (M + H) = $C_{15}H_{24}NO$ 234.1858; obsd 234.1851. $[\alpha]_D$ − 0.528 (c 1.00, $CHCl_3$).

(1a*S*,4a*R*,5*R*,7a*S*,7b*R*)-Decahydro-3,3,5,7b-tetramethyl-1*H*-cyclopropa[*e*]azulen-7a-ol (1). Diisobutylaluminum hydride (1.2 M in toluene, 0.18 mL, 0.22 mmol) was added into a solution of the cyclized nitrile **16** (12.1 mg, 0.0519 mmol) in Et_2O (0.52 mL) dropwise over 1 min at −78 °C. The resulting mixture was stirred at −78 °C for 1 h and then was quenched with $Na_2SO_4{\cdot}10H_2O$ (70 mg, 0.22 mmol). The reaction mixture was filtered with Et_2O through a pad of Na_2SO_4, and the filtrate was concentrated to yield the crude aldehyde **17** (13.2 mg). TLC R_f (20% MTBE/PE) = 0.51. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H), 2.05−2.31 (m, 4H), 1.56−1.67 (m, 2H), 1.45−1.56 (m, 4H), 1.27−1.34 (m, 1H), 1.24 (s, 3H), 0.98 (s, 3H), 0.94 (d, 3H, J = 7.1 Hz), 0.62−0.74 (m, 2H), 0.36−0.44 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 16.6, 21.6, 23.7, 25.7, 36.5, 44.6, 207.6; u 18.2, 26.0, 33.1, 33.3, 37.5, 39.1, 49.3, 82.1. This crude material was used in the next step without further purification.

A mixture of the above crude material (13.2 mg), hydrazine hydrate (80.3 mg, 1.60 mmol), and K_2CO_3 (72 mg, 0.52 mmol) in triethylene glycol (0.52 mL) was heated at 90−100 °C for 2 h and was then heated at 200 °C overnight. The reaction mixture was then cooled to rt. The reaction mixture was directly chromatographed to yield the alcohol **1** as a pale yellow oil (10.3 mg, 89% yield for two steps based on the cyclized nitrile **16**). TLC R_f (20% MTBE/PE) = 0.77. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17−2.26 (m, 1H), 2.01−2.13 (m, 2H), 1.75−1.86 (m, 1H), 1.64−1.73 (ddd, 1H, J = 2.5, 6.6, 14.2 Hz), 1.40−1.54 (m, 3H), 1.27−1.38 (m, 2H), 1.11−1.17 (m, 1H), 1.03 (s, 3H), 0.99 (s, 3H), 0.90 (d, 3H, J = 7.3 Hz), 0.89 (s, 3H), 0.70 (t, 1H, J = 4.5 Hz), 0.50−0.60 (m, 1H), 0.32−0.39 (dd, 1H, J = 4.1, 8.6 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ d 17.2, 22.6, 24.1(2), 34.1, 36.4, 43.6; u 17.4, 24.9, 33.0, 33.3, 38.8, 39.9, 42.2, 82.4. ^{1}H NMR (400 MHz, C_6D_6): δ 2.08−2.17 (m, 1H), 1.96−2.03 (m, 1H),1.86−1.95 (m, 1H), 1.56−1.82 (m, 4H), 1.38−1.49 (m, 2H), 1.20−1.28 (m,1H), 1.11−1.17 (m, 1H), 1.03 (s, 3H), 1.01 (d, 3H, J = 7.3 Hz), 0.97(s, 3H), 0.90 (s, 3H), 0.71 (t, 1H, J = 4.4 Hz), 0.49−0.58 (m, 1H), 0.29−0.33 (dd, 1H, J = 4.0, 8.8 Hz). ^{13}C NMR (400 MHz, C_6D_6): δ d 17.5, 23.0, 24.1, 24.3, 34.4, 36.9, 44.0 ; u 17.7, 25.0, 33.2, 33.7, 39.0, 40.2, 42.3, 82.0. IR (neat): 3426, 2962, 1640, 1410, 1260, 1090, 1021 cm^{-1}. MS (m/z) 43, 55, 69, 77, 83, 95, 109, 125, 138, 151, 165, 179, 207, 222. HRMS calcd for $C_{15}H_{26}O$ 222.1984; obsd 222.1992. $[\alpha]_D$ − 4.21 (c 1.26, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

X-ray structures, ^{1}H NMR and ^{13}C NMR spectra for all new compounds, and CIF files for **4**, **8**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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