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Article

Synthesis of (±)-Africanol

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Os compostos **1a** e **1b,** diastereoisômeros do africanol, foram obtidos como produtos exclusivos através de uma metodologia que empregou como etapa chave a reação de ciclização intramolecular, mediada por ^{n}BuLi, do iodeto vinílico **5**. Utilizando processo de ciclização semelhante com o composto **19**, obteve-se o álcool terciário **20** como único produto. O africanol pode ser obtido, juntamente com seus diastereoisômeros **1a** e **1b**, ao se efetuar a reação de ciclização intramolecular da cetona **21**, em presença de iodeto de samário.

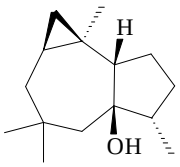
Two diastereomers of africanol, compounds **1a** and **1b**, were obtained exclusively through a methodology which employed, as the key step, the ^{n}BuLi mediated intramolecular cyclization of the vinyl iodide **5**. A similar cyclization of **19** provided exclusively the tertiary allylic alcohol **20**. Africanol could be prepared, along with its diastereomers **1a** and **1b,** when ketone **21** was submitted to the cyclization reaction promoted by samarium iodide.

Keywords: samarium iodide, cyclization, africanol, synthesis

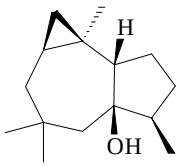
Introduction

Africanol **1**, a tricyclic sesquiterpene alcohol, was isolated in 1974 from the soft coral *Lemnalia africana* collected around the island of Leti, province of Maluku, Indonesia[1]. The structure of africanol, including its absolute configuration, was established by X-ray crystallography[2]. Substance **1** is a member of the africanane group of sesquiterpenoids, which includes several other compounds such as isoafricanol **2**, leptographiol **3** and isoleptographiol **4**, all of which were isolated in 1986 from a sapwood staining ascomycete fungus, *Leptographium lundbergii* Lag. et Melin[3].

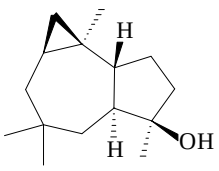
There are four syntheses of africanol described in the literature[4-7] of which the one described by Fan and White[7], is the shortest and most elegant. This route also provided the diastereomer isoafricanol **2**. Our initial approach to the synthesis of africanol consisted of the construction of a five membered ring on the bicyclo[5.1.0]octanone precursor **6**, employing methodology based on the intramolecular cyclization of a vinylic anion onto a carbonyl moiety[8] as the key step, as shown in the retrosynthetic analysis in Scheme 1.



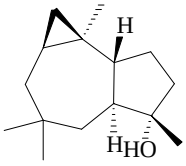
africanol **1**



isoafricanol **2**



leptographiol **3**



isoleptographiol **4**

Figure 1. Some sesquiterpenoids belonging to the africanane group

Experimental Section

General

Reagents and solvents were purified and dried using standard methods. Reactions involving organometallic reagents were carried out under argon in oven-dried

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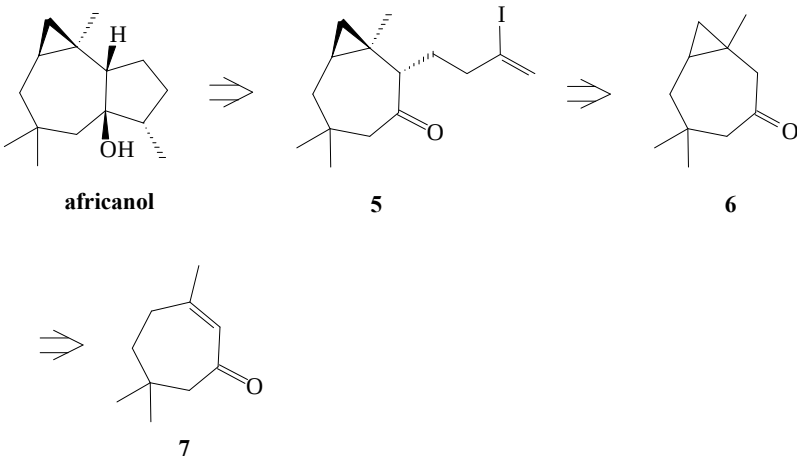


africanol **5** **6**

7

Scheme 1. Retrosynthetic analysis of africanol.

glassware. Reactions were monitored by thin-layer chromatography (TLC; E. Merck, Type 5554 plates) and gas chromatography (GC) with a Hewlett-Packard model 5880 A GC (flame ionization detector (FID, 25 m x 0.21 mm fused silica column coated with cross-linked SE-54) or 5890 GC (FID, 25 m x 0.20 mm capillary column cross-linked with 5% phenyl methyl silicone). Conventional and flash column chromatography were carried out with 70-230 and 230-400 mesh silica gel (E. Merck), respectively. Radial chromatography purifications were performed using a Chromatotron® model 7924 with plates of 1, 2 or 4 mm (silica gel 60, PF 254 with calcium sulphate, E. Merck 7749). Distillation temperatures, which refer to bulb-to-bulb (Kugelrohr) distillations, are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 spectrometer with internal calibration. ^{1}H NMR were recorded on $CDCl_3$ solutions using Bruker AC-200 or WH-400 spectrometers. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Deuterated solvents were used as lock and reference signal (^{1}H NMR reference signal relative to the proton resonance resulting from incomplete deuteration of the $CDCl_3$: δ 7.25). ^{13}C NMR spectra were determined as solutions either in $CDCl_3$ or in C_6D_6 with the spectrometers described above. The chemical shifts (δ) are reported in ppm relative to the center peak of $CDCl_3$ (δ 77.0) or C_6D_6 (δ 128.0). Low and high resolution mass spectra were obtained on Kratos/AEI 50 or MS 902 mass spectrometers. Combustion analyses were obtained with a Carlo Erba 1106 C, H, N analyzer.

3,6-Dimethyl-2-cyclohexenone (**9**)

To a solution of diisopropylamine (18.14 g, 179.3 mmol) in THF (450 cm^3) at –78 °C was added ^{n}BuLi in hexanes (108 cm^3, 171 mmol). After stirring for 30 min at 0 °C the solution was recooled to –78 °C followed by dropwise addition of 3-methyl-2-cyclohexenone (17.9 g, 163 mmol) in THF (100 cm^3). After 1 h at –78 °C iodomethane (69.4 g, 489 mmol) was added and the resulting mixture was stirred 1h at –78 °C and 3 h between –20 and –15 °C. Ether (600 cm^3) was added and the solution of the crude product was washed with water (2 x 100 cm^3) and saturated NaCl (2 x 70 cm^3), and dried over anhydrous $MgSO_4$. The solvent and excess iodomethane were removed by rotary evaporation and the product was distilled at reduced pressure (17 mmHg, 85-90 °C) to give 3,6-dimethyl-2-cyclohexenone (17.21 g, 85%); IR ν_{max}/cm^{-1} 2931, 1672, 1210, 1119 (film); ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 1.05 (d, *J* = 8 Hz, 3H), 1.56-1.68 (m, 1H), 1.87 (s, 3H), 1.92-2.03 (m, 1H), 2.13-2.36 (m, 3H), 5.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz,) δ 15.01, 24.12, 30.53, 30.64, 40.37, 126.05, 161.53, 202.05.

2,5,5-Trimethylcyclohexanone (**10**)

To a flask containing copper (I) cyanide (5.64 g, 63.0 mmol) and THF (250 cm^3) at –78 °C was added MeLi in ether (43.0 cm^3, 60.4 mmol). After stirring 20 min at –10°C the solution was recooled to –78 °C and a second portion of MeLi (43.0 cm^3, 60.4 mmol) was added. After 30 min, chlorotrimethylsilane (13.69 g, 126.0 mmol) was added followed by addition of a solution of compound **9** (6.000 g, 48.32 mmol) and HMPA (22.58 g, 126.0 mmol) in THF (50 cm^3). The mixture was stirred 2 h at –78 °C and 3 h at room temp, then quenched with saturated aqueous NH_4Cl/NH_4OH (100 cm^3, pH 8). After 10 h at room temp the phases were separated and the aqueous layer was extracted with Et_2O (2 x 30 cm^3). The combined organic extracts were washed with water (2 x 30 cm^3) and concentrated under reduced pressure to 100 cm^3. The product was then stirred with 1 mol.L^{-1} HCl (10 cm^3) for 2 h at room temp. Ether (100 cm^3) was added, the phases were separated, and the organic layer was

washed with saturated $NaHCO_3$ (3 x 30 cm^3) and water (1 x 30 cm^3), and dried over $MgSO_4$. The filtrate was concentrated and purified by distillation at reduced pressure (10 mmHg, 60-65 °C) affording ketone **10** (5.61 g, 83%); compound **10** (Found: C, 77.13; H, 11.60. Calc. for $C_9H_{16}O$: C, 77.09; H, 11.50%); IR ν_{max}/cm^{-1} 2961, 1714, 1458, 1369, 1216, 1174 (film); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82 (s, 3H), 0.98 (d, *J* = 7 Hz, 3H), 1.00 (s, 3H), 1.39-1.56 (m, 2H), 1.58-1.68 (m, 1H), 1.88-1.99 (m, 1H), 2.08 (d, *J* = 13.6 Hz, 1H), 2.17 (d, *J* = 13.6 Hz, 1H), 2.20-2.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.40, 25.42, 31.61, 31.70, 36.87, 38.14, 44.20, 54.70, 213.20; MS *m/z* (relative intensity) 140 (M^+, 18), 96 (17), 95 (11), 83 (100), 82 (18), 69 (17).

cis-1-Trimethylsilyloxy-3,3-6-trimethylbicyclo [4.1.0]heptane (**11**)

To a solution of ketone **10** (2.10 g, 15.0 mmol) and hexamethyldisilazane (3.356 g, 18.73 mmol) in pentane (250 cm^3) at –25 °C was added iodotrimethylsilane (3.448 g, 17.23 mmol). After stirring 15 min at –25 °C and 4 h at room temp the mixture was filtered through celite eluting with petroleum ether, the organic phase was washed with saturated $NaHCO_3$ (3 x 30 cm^3), dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by distillation (1.2 mmHg, 34-36 °C) to give a mixture of thermodynamic and kinetic silyl enol ethers, 19:1 ratio determined by GC (3.02 g, 95%); thermodynamic silyl enol ether (Found: C, 68.20; H, 11.50. Calc. for $C_{12}H_{24}SiO$: C, 67.92; H, 11.32%); IR ν_{max}/cm^{-1} 2954, 2910, 1690, 1322, 1252, 1230, 1199, 1160 (film); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.18 (s, 9H), 0.90 (s, 6H), 1.24 (t, *J* = 6.4 Hz, 2H), 1.67 (brs, 3H), 1.87-1.96 (m , 4H); ^{13}C NMR (C_6D_6, 50.3 MHz,) δ 0.90, 16.31, 28.10, 28.25, 30.78, 30.92, 35.98, 44.58, 109.56, 142.46; MS *m/z* (relative intensity) 212 (M^+, 78), 197 (100), 183 (21), 144 (19), 141 (65), 75 (68), 73 (100).

The above mixture (3.000 g, 14.15 mmol) was dissolved in benzene (30 cm^3) and a solution of diethylzinc in hexanes (28 cm^3, 28 mmol) was added at 40 °C followed by the dropwise addition of CH_2I_2 (11.37 g, 42.45 mmol). After the addition was complete, a slow flow of O_2 was introduced into the headspace above the reaction mixture for 1 h. The resulting solid was removed by filtration over celite using hexane as eluent and the product was transferred to a separatory funnel containing ether (100 cm^3). The mixture was washed with saturated aqueous NH_4Cl/NH_4OH (2 x 30 cm^3, pH 8) and water (1 x 30 cm^3), and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/ether 92:8 v/v) to give compound **11** (2.72 g, 85%); compound **11** (Found: C, 68.78; H, 11.70. Calc. for $C_{13}H_{26}SiO$: C, 69.03; H, 11.50%); IR ν_{max}/cm^{-1} 3062, 2935, 2861, 1460, 1218, 1161, 1136, 1112 (film); ^1H NMR ($CDCl_3$, 400 MHz,) δ 0.23 (s, 9H), 0.29 (d, *J* = 4.6 Hz, 1H), 0.52 (d, *J* = 4.6 Hz, 1H), 0.77-0.93 (m, 1H), 0.88 (s, 3H), 1.00 (s, 3H), 1.06-1.15 (m, 1H), 1.36 (s, 3H), 1.60-1.76 (m, 3H), 1.89 (d, *J* = 14 Hz, 1H); ^{13}C NMR (C_6D_6, 50.3 MHz,) δ 1.57, 20.59, 21.43, 23.74, 25.55, 28.39, 29.51, 31.68, 33.97, 49.82, 59.55; MS *m/z* (relative intensity) 226 (M^+, 12), 211 (64), 197 (15), 169 (16), 121 (20), 96 (30), 75 (39), 73 (100).

3,6,6-Trimethyl-2-cycloheptenone (**7**)

To a flask containing anhydrous $FeCl_3$ (5.815 g, 35.85 mmol) in DMF (24 cm^3) at 0 °C under argon was added a solution of compound **11** (2.700 g, 11.95 mmol) in DMF (24 cm^3). After 4 h at room temp the reaction mixture was poured into a beaker with 1 $mol.L^{-1}$ HCl (30 cm^3) and ice. The mixture was transferred to a separatory funnel with ether (100 cm^3), the phases were separated and the aqueous phase was extracted with ether (2 x 30 cm^3). The combined organic extracts were washed with water (3 x 30 cm^3) and saturated NaCl (2 x 30 cm^3), and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the crude product was taken up in methanol (60 cm^3), $CH_3COONa.6H_2O$ (4.878 g, 35.85 mmol) was added and the solution refluxed for 4 h. The mixture then was diluted in ether (120 cm^3), washed with saturated $NaHCO_3$ and dried over $MgSO_4$. After removing the solvent under reduced pressure the crude product was purified by flash chromatography using CH_2Cl_2 as solvent affording cycloheptenone **7** (1.54 g, 85%); IR ν_{max}/cm^{-1} 2957, 1662, 1466, 1312, 1238, 1195 (film); ^1H NMR ($CDCl_3$, 400 MHz,) δ 0.91 (s, 6H), 1.47-1.52 (m, 2H), 1.85 (s, 3H), 2.20-2.28 (m, 2H), 2.32 (s, 2H), 5.75 (brs, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.35, 29.36, 31.77, 32.03, 41.41, 56.24, 129.68, 161.27, 201.58; MS *m/z* (relative intensity) 152 (M^+, 18), 137 (18), 109 (29), 95 (100), 82 (35), 68 (21), 67 (34); HRMS (M^+) Found: 152.1191. Calc. for $C_{10}H_{16}O$: 152.1196.

7,10,10-Trimethyl-1,4-dioxaspiro[4.6]7-undecene (**12**)

A solution of ketone **7** (1.40 g, 9.21 mmol), ethylene glycol (3.430 g, 55.26 mmol) and *p*-toluenesulfonic acid monohydrate (210 mg, 1.1 mmol) in benzene (15 cm^3) was refluxed in a flask connected to a Dean Stark trap for 15 h. The mixture was diluted with ether (50 cm^3), washed with saturated $NaHCO_3$ (2 x 20 cm^3) and water (1 x 20 cm^3), and dried over $MgSO_4$. The filtrate was concentrated in vacuo and purified by flash chromatography on basic alumina (petroleum ether/

ether 20:1 v/v) to give ketal **12** (1.53 g, 85%); IR ν_{max}/cm^{-1} 2952, 1675, 1454, 1365, 1228, 1104, 1073, 1044 (film); ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 0.92 (s, 6H), 1.68(s, 2H), 1.74 (s, 3H), 1.93 (d, *J* = 7.5 Hz, 2H), 2.35 (s, 2H), 3.90 (s, 4H), 5.46-5.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz,) δ 26.34, 29.90, 33.23, 39.71, 41.56, 52.98, 64.16, 108.28, 124.08, 134.47; MS *m/z* (relative intensity) 196 (M^+, 4), 127 (100), 113 (44), 95 (21), 83 (13), 81 (19), 69 (10), 67 (17), 41 (27); HRMS (M^+) Found: 196.1465. Calc for $C_{12}H_{20}O_2$: 196.1464.

cis-1,9,9-Trimethyltricyclo[4.5.1]4,7-dioxaspirododecane (**13**)

Compound **13** was prepared according to the cyclopropanation procedure reported for the preparation of **11**, starting from **12** (1.400 g, 7.14 mmol), benzene (40 cm^3), diethylzinc in hexanes (32.13 mmol) and diiodomethane (10.53 g, 39.31 mmol). The crude product was purified by flash chromatography on basic alumina (petroleum ether/ether 20:1 v/v) to give tricyclic **13** (1.33 g, 89%); IR ν_{max}/cm^{-1} 3057, 2951, 1470, 1364, 1328, 1231, 1176, 1105, 1044, 1020 (film); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (t, *J* = 4.8 Hz, 1H), 0.45 (dd, *J* = 8.8, 4.8 Hz, 1H), 0.62-0.72 (m, 1H), 0.91 (s, 3H), 0.93-1.02 (m, 1H), 1.07 (s, 3H), 1.13 (s, 3H), 1.43 (d, *J* = 8 Hz, 1H), 1.46 (d, *J* = 8 Hz, 1H), 1.73 (d, *J* = 14.4 Hz, 1H), 1.83 (dd, *J* = 15.2, 6.4 Hz, 1H), 2.02 (d, *J* = 15.2 Hz, 1H), 3.78-4.00 (m, 4H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.28, 20.69, 23.97, 25.53, 27.19, 32.30, 32.91, 43.33, 50.69, 63.10, 64.37, 112.00; MS *m/z* (relative intensity) 210 (M^+, 1), 153 (26), 139 (37), 128 (28), 127 (100), 113 (55), 87 (26), 86 (51), 67 (22), 55 (36), 41 (48); HRMS (M^+) Found: 210.1611. Calc. for $C_{13}H_{22}O_2$: 210.1615.

cis-1,5,5-Trimethylbicyclo[5.1.0]3-octanone (**6**)

A solution of ketal **13** (1.20 g, 5.71 mmol) and *p*-toluenesulphonic acid monohydrate (164 mg, 0.860 mmol) in acetone (7 cm^3) was stirred at room temp for 2 h. The crude product was diluted with ether (50 cm^3), washed with saturated $NaHCO_3$ (2 x 15 cm^3) and water (1 x 15 cm^3) and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give ketone **6** (0.92 g, 97%); IR ν_{max}/cm^{-1} 3057, 2957, 1700, 1464, 1192, 1101, 1060, 1023 (film); ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 0.25 (t, *J* = 4 Hz, 1H), 0.60-0.81 (m, 2H), 0.95 (s, 3H), 1.02 (brs, 4H), 1.08 (s, 3H), 2.00 (dd, *J* = 15, 5 Hz, 1H), 2.12 (d, *J* = 12 Hz, 1H), 2.15 (d, *J* = 15 Hz, 1H), 2.46 (d, *J* = 15 Hz, 1H), 2.52 (d, *J* = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz,) δ 14.79, 20.71, 23.72, 24.73, 26.83, 31.04, 34.55, 43.18, 49.01, 57.59, 210.18; MS *m/z* (relative intensity) 166 (M^+, 19), 123 (41), 110 (57), 109 (51), 95 (39), 82 (73), 67 (98), 41 (100); HRMS (M^+) Found: 166.1374. Calc. for $C_{11}H_{18}O$: 166.1366.

N-N-Dimethylhydrazone derived from ketone **6**

A solution of ketone **6** (332 mg, 2.00 mmol) and *N,N*-dimethylhydrazine (480 mg, 7.99 mmol) in benzene (10 cm^3) was heated at reflux for 10 h under argon with azeotropic removal of water (Dean-Stark trap). The excess of dimethylhydrazine was distilled off with the solvent and the product was purified by distillation (0.4 mmHg, 65-69 °C) affording hydrazone **15** (392 mg, 94.2 %); IR ν_{max}/cm^{-1} 3059, 2953, 1624, 1467, 1366, 1196, 1021 (film); MS *m/z* (relative intensity) 208 (M^+, 14), 193 (8), 164 (13), 152 (12), 151 (100), 83 (7), 51 (11); HRMS (M^+) Found: 208.1931. Calc for $C_{13}H_{24}N_2$: 208.1939.

2[2-Trimethyltin-1-butene]1,5,5-trimethylbicyclo [5.1.0]3-octanone (**17**)

To a solution of diisopropylamine (114 mg, 1.13 mmol) in THF (1.5 cm^3) at –78 °C was added ^{n}BuLi in hexanes (0.83 cm^3, 1.1 mmol). After stirring 10 min at 0 °C a solution of hydrazone **15** (195 mg, 0.937 mmol) in THF (1 cm^3) was added. After 2 h at 0 °C iodide **14** (795 mg, 2.31 mmol) in THF (2 cm^3) was added and the resulting mixture was stirred 15 h at room temp. Ether (50 cm^3) was added and the organic layer was washed with water (2 x 10 cm^3). The solvent was removed under reduced pressure and the crude product was taken up in methanol (15 cm^3) and added to a round bottom flask containing phosphate buffer solution pH 7.2 (3 cm^3) and sodium periodate (796 mg, 3.72 mmol) in water (5 cm^3) at room temp. After stirring 48 h the reaction mixture was filtered, diluted with water (20 cm^3), extracted with CH_2Cl_2 (3 x 20 cm^3) and dried over $MgSO_4$. The filtrate was concentrated under vacuum and the crude product was purified by radial chromatography on silica gel (petroleum ether/dichloromethane 10:4 v/v) affording compound **17** (112 mg, 31%) and 23 mg of ketone **6. 17**: IR ν_{max}/cm^{-1} 3060, 2956, 1704, 1468, 1386, 1367, 915, 769 (film); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H), 0.16 (t, *J* = 6 Hz, 1H), 0.43-0.52 (m, 1H), 0.58 (dd, *J* = 8, 4 Hz, 1H), 0.72 (s, 3H), 0.82 (s, 3H), 0.85 (s, 3H), 1.19 (dd, *J* = 16, 12 Hz, 1H), 1.37-1.45 (m, 1H), 1.69-1.80 (m, 1H), 1.84 (ddd, *J* = 14.8, 6.0, 1.6 Hz, 1H), 1.96-2.13 (m, 5H), 4.98 (d, *J* = 2.8 Hz, 1H), 5.46 (dd, *J* = 2.8, 1.6, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz,) δ - 9.40, 16.98, 19.35, 21.96, 23.59, 25.07, 27.05, 32.41, 35.12, 38.86, 42.74, 53.78, 60.47, 124.87, 155.60, 209.34; MS *m/z* (relative intensity) 385 (0.3), 383 (0.5), 382 (0.4), 381 (0.7), 369 (95) 367 (72), 365 (40), 165 (100), 164 (30), 107 (48), 55 (20); M.S. (CI-NH_3) 383 (74), 385 (100), 389 (15).

2[2-Iodo-1-butene]1,5,5-trimethylbicyclo [5.1.0]3-octanone (**5**)

Iodine (73.2 mg, 0.288 mmol) in CH_2Cl_2 (6 cm^3) was added dropwise to a solution of ketone **17** (54 mg, 0.14 mmol) in CH_2Cl_2 (2 cm^3) at 0 °C under argon until the color of the resulting mixture was slightly pink. Ether (20 cm^3) was added and the organic layer was washed with 0.1 M solution of sodium thiosulphate (1 x 4 cm^3) and water (5 cm^3), and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the crude product was passed through a short pad of silica using CH_2Cl_2 as eluent to afford iodide **5** (48 mg, 97%); IR ν_{max}/cm^{-1} 3058, 2956, 2926, 1703, 1617, 1467, 1455, 1386, 892 (film); ^1H NMR ($CDCl_3$, 400 MHz,) δ 0.36 (t, *J* = 4.4 Hz, 1H), 0.65-0.73 (m, 1H), 0.78 (dd, *J* = 8.8, 4.4 Hz, 1H), 0.91 (s, 3H), 0.99 (s, 3H), 1.02 (s, 3H), 1.37 (dd, *J* = 14.8, 10.8 Hz, 1H), 1.73-1.83 (m, 1H), 1.93-2.08 (m, 2H), 2.15 (d, *J* = 5.6 Hz, 1H), 2.17 (d, *J* = 8.4 Hz, 1H), 2.27 (dd, *J* = 12, 1.8 Hz, 1H), 2.30-2.44 (m, 2H), 5.72 (brs, 1H), 6.02 (dd, *J* = 2.6, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz,) δ 16.97, 19.34, 22.07, 23.62, 25.19, 26.74, 32.40, 35.17, 42.70, 42.96, 52.86, 60.41, 112.17, 125.8, 209; HRMS (M^+) Found: 346.0813. Calc. for $C_{15}H_{23}IO$: 346.0804.

Tricyclic alcohol **18**

To a solution of vinyl iodide **5** (48 mg, 0.14 mmol) in THF (2 cm^3) at –78 °C was added ^{n}BuLi in hexanes (0.42 mmol, 0.32 cm^3). After stirring 30 min, ether was added (20 cm^3) and the product was washed with saturated $NaHCO_3$ (1 x 5 cm^3), water (1 x 5 cm^3) and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the crude product was passed through a short pad of silica gel using CH_2Cl_2 as eluent giving the tricyclic alcohol **18** (29 mg , 95%); IR ν_{max}/cm^{-1} 3055, 2950, 1650, 1183, 1101, 1062, 894 (film); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.18 (t, *J* = 4.0 Hz, 1H), 0.52 (dd, *J* = 8.4, 4.0 Hz, 1H), 0.73-0.84 (m, 1H), 0.91 (s, 3H), 1.10-1.30 (m, 2H), 1.12 (s, 1H), 1.16 (s, 3H), 1.32 (s, 3H), 1.41 (dd, *J* = 12.8, 6.0 Hz, 1H), 1.69-1.78 (m, 1H), 1.86-2.00 (m, 3H), 2.18-2.30 (m, 1H), 2.55 (ddd, *J* = 16.4, 7.6, 0.8 Hz, 1H), 4.91 (dd, *J* = 2.48, 1.6 Hz, 1H), 5.02-5.07 (m , 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.87, 22.10, 23.44, 25.24, 25.43, 25.58, 31.27, 34.31, 35.15, 44.10, 54.13, 54.37, 81.75, 106.00, 161.78; MS *m/z* (relative intensity) 220 (M^+, 0.7), 202 (12), 159 (20), 145 (29), 131 (31), 105 (30), 95 (23), 93 (25), 91 (41), 55 (20); HRMS (M^+) Found: 220.1837. Calc. for $C_{15}H_{24}O$: 220.1832.

Africanol diastereomers **1a** *and* **1b**

A mixture containing alcohol **18** (27 mg, 0.12 mmol) in ethyl acetate (7 cm^3) and PtO_2 (20 mg) was kept under hydrogen pressure (50 psi) for 24 h. After filtering through a short pad of celite using petroleum ether as solvent the crude product was purified by radial chromatography on silica gel (petroleum ether/dichoromethane 5:1 v/v) giving 13.1mg of compound **1a** and 10.9 mg of its epimer **1b**. **1a**: IR ν_{max}/cm^{-1} 3605, 2923, 1725, 1465, 1374, 1108, 1041 (film); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (t, *J* = 4.8 Hz, 1H), 0.46 (dd, *J* = 8.9, 4.8 Hz, 1H), 0.69-0.80 (m, 1H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 3H), 0.99-1.10 (m, 2H), 1.12 (s, 3H), 1.22-1.30 (m, 1H), 1.24 (s, 3H), 1.33-1.42 (m, 2H), 1.52 (dd, *J* = 14.3, 2.15 Hz, 1H), 1.61-1.70 (m, 1H), 1.72-1.93 (m, 3H), 2.00-2.10 (m, 1H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 18.28, 18.36, 22.67, 24.03, 25.78, 25.83, 25.91, 32.87, 34.17, 35.64, 44.49, 49.99, 51.27, 52.39, 85.49; MS *m/z* (relative intensity) 222 (M^+, 11), 207 (16), 204 (43), 189 (45), 165 (43), 162 (79), 147 (54), 133 (51), 109 (100), 107 (65), 105 (53), 93 (60), 83 (84), 81 (69), 69 (87), 67 (58), 57 (46); HRMS (M^+) Found: 222.1981. Calc. for $C_{15}H_{26}O$: 222.1979. **1b**: IR ν_{max}/cm^{-1} 3602, 3054, 2922, 1461, 1374, 1115, 1041, 911 (film); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.11 (t, *J* = 3.9 Hz, 1H), 0.43 (dd, *J* = 8.8, 3.9 Hz, 1H), 0.67-0.77 (m, 1H), 0.83 (s, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.92 (brs, 1H), 1.03-1.14 (m, 2H), 1.09 (s, 3H), 1.23 (s, 3H), 1.27-1.42 (m, 1H), 1.43-1.56 (m, 2H), 1.56-1.76 (m, 3H), 1.84-1.95 (m, 2H); ^{13}C NMR (C_6D_6, 50.3 MHz,) δ 12.83, 18.31, 22.92, 23.71, 23.81, 25.45, 30.53, 34.12, 35.30, 44.08, 46.51, 52.33, 54.72, 84.22; MS *m/z* (relative intensity) 222 (M^+, 9), 204 (30), 189 (35), 165 (37), 123 (35), 109 (85), 107 (41), 98 (62), 83 (100), 81 (72), 69 (88), 67 (49), 55 (87); HRMS (M^+) Found: 222.1978. Calc. for $C_{15}H_{26}O$: 222.1972.

2[(Z)-2-Iodo-2-butene]1,5,5-trimethylbicyclo [5.1.0]3-octanone (**19**)

To a solution of diisopropylamine (97 mg, 0.96 mmol) in THF (2 cm^3) at 0 °C was added ^{n}BuLi in hexanes (0.63 cm^3, 0.82 mmol). After 10 min a solution of hydrazone **15** (100 mg, 0.480 mmol) in THF (1 cm^3) was added and the mixture was stirred 2 h at 0 °C followed by addition, at –78 °C of (*Z*)-1-bromo-3-iodo-1-butene (378 mg, 1.44 mmol) in THF (2 cm^3). The resulting mixture was stirred 1 h at –78 °C and 2 h at 0 °C. The product was diluted with ether (20 cm^3) and washed with water (5 cm^3), saturated NaCl (5 cm^3) and the solvent was removed under reduced pressure. The crude product was taken up in methanol (10 cm^3) and added to a round bottom flask containing phosphate buffer solution (2 cm^3, pH 7.2) and sodium periodate (410 mg, 1.92 mmol) in water (4 cm^3) at room temp. After stirring 48 h the mixture was filtered, diluted with water (15 cm^3), extracted with CH_2Cl_2 (3 x 20 cm^3)

and dried over $MgSO_4$. The product obtained was purified by radial chromatography on silica gel (petroleum ether/ether 5:1 v/v) giving compound **19** (91 mg, 55%); IR ν_{max}/cm^{-1} 3057, 2956, 1703, 1467, 1367, 1214, 1181, 1089, 810 (film); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.35 (t, *J* = 4.5 Hz, 1H), 0.61-0.71 (m, 1H), 0.75 (dd, *J* = 8.75, 4.5 Hz, 1H), 0.87 (s, 3H), 0.96 (s, 3H), 0.98 (s, 3H), 1.34 (dd, *J* = 15.0, 10.5 Hz, 1H), 1.99 (ddd, *J* = 15.0, 6.5, 1.65 Hz, 1H), 2.12-2.32 (m, 4H), 2.44 (s, 3H), 2.44-2.53 (m, 1H), 5.37-5.44 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.12, 19.51, 22.23, 23.78, 25.33, 32.46, 33.64, 34.41, 35.25, 42.62, 54.15, 60.29, 102.19, 133.09, 209; MS *m/z* (relative intensity) 346 (M^+, 0.4), 234 (39), 219 (81), 149 (64), 109 (47), 107 (100), 91 (68), 67 (48), 55 (70), 41 (77), 39 (50); HRMS (M^+) Found: 346.07864. Calc. for $C_{15}H_{23}OI$: 346.07857.

Tricyclic alcohol **20**

Tertiary alcohol **20** was prepared as described above for **18** from vinylic iodide **19** (35 mg, 0.10 mmol) and ^{n}BuLi in hexanes (0.23 cm^3, 0.3 mmol). The crude product was passed through a small pad of silica using CH_2Cl_2 as eluent affording the tricyclic alcohol **20** (21 mg, 95%); IR ν_{max}/cm^{-1} 3609, 3055, 2923, 1451, 1377, 1273, 1160, 1013 (film); ^{1}H NMR (C_6D_6, 400 MHz,) δ 0.13 (t, *J* = 4.2 Hz, 1H), 0.47-0.53 (m, 2H), 0.77-1.09 (m, 3H), 0.88 (s, 3H), 1.21 (s, 3H), 1.42 (s, 3H), 1.50-1.58 (m, 4H), 1.78 (dd, *J* = 13.75, 2.3 Hz, 1H), 1.87-1.93 (ddd, *J* = 13.75, 6.5, 2.3 Hz, 1H), 1.93-2.20 (m, 1H), 2.30-2.41 (m, 1H), 5.28-5.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz,) δ 12.00, 18.18, 22.17, 23.10, 25.36, 26.20, 30.18, 30.66, 34.49, 35.34, 44.41, 52.26, 86.35, 126.96, 146.25; MS *m/z* (relative intensity) 220 (M^+, 4), 202 (85), 187 (79), 177 (39), 160 (30), 159 (65), 145 (100), 119 (51), 105 (53), 91 (65), 55 (62), 41 (97); HRMS (M^+) Found: 220.1818. Calc. for $C_{15}H_{24}O$: 220.1810.

2[1-Butene]1,5,5-trimethylbicyclo[5.1.0]3-octanone (**21**)

To a solution of diisopropylamine (97 mg, 0.96 mmol) in THF (2 cm^3) at 0 °C was added ^{n}BuLi in hexanes (0.63 cm^3, 0.82 mmol). After 10 min a solution of hydrazone 15 (100 mg, 0.480 mmol) in THF (cm^3) was added and the mixture was stirred for 2 h at 0 °C followed by addition of 4-iodo-1-butene (175 mg, 0.961 mmol) in THF (cm^3). The mixture was stirred 17 h at room temp. The product was diluted with ether (30 cm^3) and washed with water (5 cm^3) and saturated NaCl (5 cm^3) and the solvent was removed under reduced pressure. The crude product was transferred to a round bottom flask containing acetic acid/THF/ water/ NaOAc (15:2:2:1 w/w) and stirred for 36 h at room temp. Ether (50 cm^3) was added and the organic layer was washed with water (3 x 5 cm^3) and saturated $NaHCO_3$ (2 x 5 cm^3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product obtained was purified by radial chromatography on silica gel (petroleum ether/ CH_2Cl_2 5:2 v/v) affording compound **21** (52 mg, 50%); IR ν_{max}/cm^{-1} 3060, 2956, 1704, 1641, 1455; ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 0.28 (t, *J* = 4.3 Hz, 1H), 0.56-0.66 (m, 1H), 0.71 (dd, *J* = 8.7, 4.3 Hz, 1H), 0.85 (s, 3H), 0.95 (s, 3H), 0.97 (s, 3H), 1.32 (dd, *J* = 14, 10 Hz, 1H), 1.51-1.63 (m, 1H), 1.80-1.91 (m, 1H), 1.92-2.03 (m, 3H), 2.07-2.24 (m, 3H), 4.87-5.00 (m, 2H), 5.67-5.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.00, 19.29, 21.89, 23.63, 25.16, 26.36, 31.91, 32.41, 35.16, 42.74, 53.98, 60.40, 114.80, 138.59, 209.61; MS *m/z* (relative intensity) 220 (M^+, 6), 205 (11), 179 (22), 164 (32), 161 (34), 123 (30), 112 (51), 109 (100), 108 (44), 95 (91), 81 (67), 67 (56), 55 (67); HRMS (M^+) Found 220.1828. Calc. for $C_{15}H_{24}O$: 220.1829.

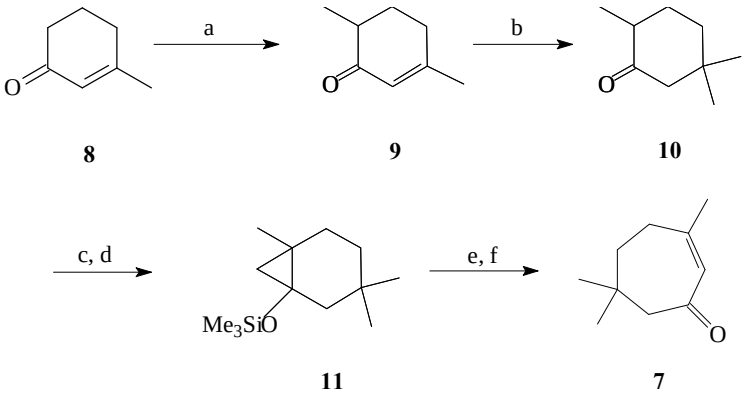
Africanol (**1**)

To a solution of SmI_2 (0.121g, 0.300 mmol) and HMPA (430 mg, 2.40 mmol) in THF (2 cm^3) at room temp was added a solution of ketone **21** (22 mg, 0.10 mmol) and *t*-butyl alcohol (22 mg, 0.30 mmol) in THF (2 cm^3). The mixture was stirred 4 h at 20 °C and another portion of SmI_2 (0.2 mmol) in THF (1.3 cm^3) was added and stirred for 24 h. The reaction was quenched with saturated $NaHCO_3$ (3 cm^3), the phases were separated and the aqueous layer was extracted with Et_2O (3 x 5 cm^3). The combined organic extracts were washed with water (2 x 3 cm^3) and saturated NaCl (1 x 3 cm^3) and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the product was purified by radial chromatography on silica gel (petroleum ether/dichloromethane 5:1 v/v) to give africanol **1** (5.1 mg), compound **1a** (5.12 mg) and compound **1b** (3.1 mg). **1**: IR ν_{max}/cm^{-1} 3483, 3078, 2965, 1461, 1387, 1267, 1109, 1087, 1024, 993 (CCl_4 solution); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.15 (t, *J* = 4.3 Hz, 1H), 0.47 (dd, *J* = 8.4, 4.0 Hz, 1H), 0.64-0.80 (m, 1H), 0.88 (d, *J* = 7.3 Hz, 3H), 0.95 (s, 3H), 1.01 (s, 3H), 1.10 (s, 3H), 1.24-2.11 (m, 11H); ^{13}C NMR ($CDCl_3$, 50.3 MHz,) δ 15.34, 18.25, 21.55, 22.97, 23.61, 26.02, 31.47, 31.75, 32.04, 34.32, 40.33, 45.16, 50.13, 55.94, 87.35; HRMS (M^+ - H_2O) Found: 204.1863. Calc. for $C_{15}H_{24}$: 204.1878.

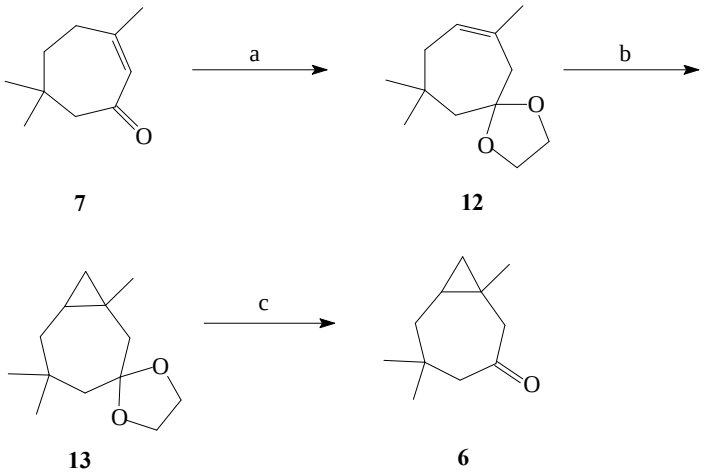
Results and Discussion

The cycloheptenone intermediate **7** was prepared as shown in Scheme 2, employing ring expansion of the silyloxybicyclo[4.1.0]heptane **11** as the key step.

Thus, alkylation of 3-methylcyclohex-2-en-1-one **8** with methyl iodide, at low temperature, afforded compound



Scheme 2. Reaction conditions: (a) LDA, THF, -78°C, 1h.; CH_3I, -78°C, 1h→-20°C, 3h (85%); (b) $Me_2Cu(CN)Li_2$, Et_2O, TMSCl, HMPA, -78°C, 2h→r.t. 3h; H_3O^+ (83%); (c) HMDS, TMSI, pentane, -25°C→r.t., 4h (95%); (d) Benzene, Et_2Zn, CH_2I_2, 40°C; O_2, 1h (85%); (e) $FeCl_3$, Py, DMF, O°C→r.t., 4h; (f) MeOH, NaOAc, reflux, 4h (85%).



Scheme 3. Reaction conditions: (a) $HOCH_2CH_2OH$, Benzene, PTSA, reflux, 15h (85%); (b) Benzene, Et_2Zn, CH_2I_2, 40°C; O_2, 1h (89%); (c) Acetone, PTSA, 20°C, 2h (97%).

9 in good yield. Conjugate addition of the higher order dilithium dimethylcyanocuprate to the α,β-unsaturated ketone **9** was carried out in the presence of the additives HMPA/TMSCl[9-11]. A ratio ranging from 15:1 to 19:1 of the thermodynamic versus kinetic enol silyl ethers was achieved when ketone **10** was treated with trimethylsilyl iodide and hexamethyldisilazane in pentane[12] at –25°C. Cyclopropanation of the resultant silyl enol ether mixture with diethylzinc and diiodomethane, in the presence of oxigen, gave **11** in high yield[13,14]. The ring expansion was then successfully carried out by treatment of compound **11** with $FeCl_3$ in pyridine/DMF[15].

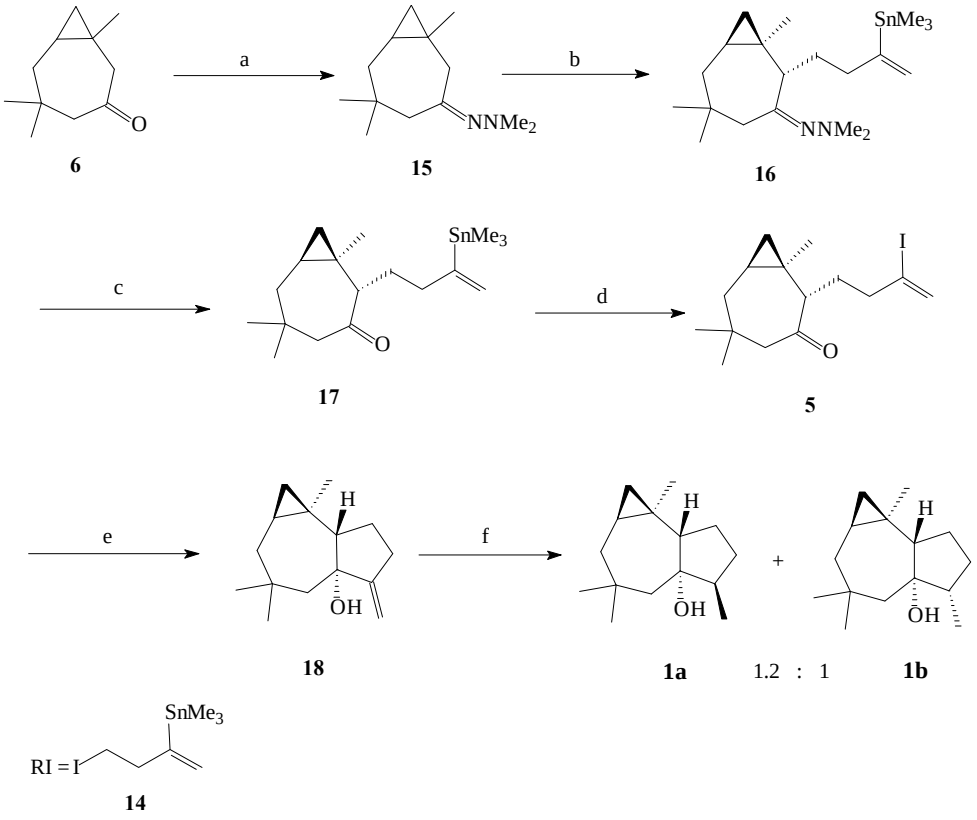
With the key precursor **7** in hand, a straightforward sequence of steps was employed to convert cycloheptenone **7** into bicyclic ketone **6** (see Scheme 3).

When ketone **7** was treated with ethylene glycol in the presence of PTSA in benzene, the ketal **12** was obtained as the only product. The migration of the double bond was confirmed by the ^1H NMR spectrum of **12**, which showed a multiplet for the vinylic hydrogen. Ketal **12** was subjected to the cyclopropanation conditions as before (diethylzinc and diiodomethane in the presence of oxygen[13,14]). Removal of the ketal protecting group of **13** by transketalization with PTSA in acetone generated bicyclic ketone **6**.

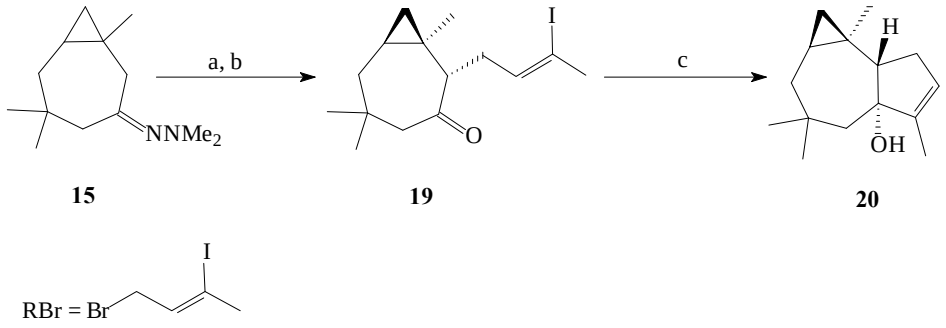
Several reaction conditions were tried in unsuccessful attempts to alkylate ketone **6** directly with iodide **14**, using LDA as base in THF/HMPA and varying the temperature of the reaction mixture from -78 °C to room temperature. This problem was surmounted by converting ketone **6** into its *N*,*N*-dimethylhydrazone derivative[16], (see Scheme 4) and sequential treatment of the derivative **15** with LDA in THF and the alkyl iodide **14**, yielding the desired alkylated product **16**. After oxidative cleavage of the hydrazone with sodium periodate in phosphate buffer solution[17], ketone **17** was obtained in 31% yield for the two steps. Vinyl iodide **5** was easily generated from vinylstannane **17** by treatment with a solution of iodine in methylene chloride[8].

The alkylation of hydrazone **15** occurred regioselectively and with high stereoselectivity (> 30:1 ratio as determined by GC) giving, as the major diastereomer, the product derived from alkylation of the ring on the same side as the adjacent methyl group. The synthesis of the tricyclic carbon skeleton was completed by treatment of the vinyl iodide with ^{n}BuLi to effect lithium-halogen exchange, with the resulting anion undergoing an intramolecular cyclization to **18**. The relative configuration of the tricyclic alcohol **18** was assigned after hydrogenation of the exo-methylene function, which gave compounds **1a** and **1b**, diastereomers of africanol. Pure samples of **1a** and **1b** could be obtained by chromatography of the mixture on silica gel. Compounds **1a** and **1b** exhibited ^{1}H NMR spectra data identical with those of the same two substances previously prepared by Tai and coworkers[6].

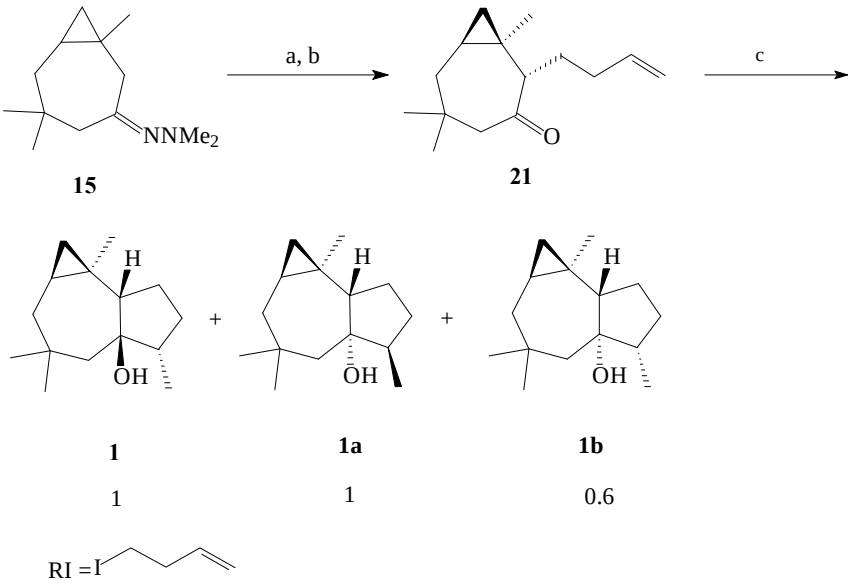
In an analogous sequence of reactions, hydrazone **15** was alkylated with (*Z*)-1-bromo-3-iodo-2-butene, followed by cyclization to give compound **20** (see Scheme 5). The only product obtained displayed the *trans* ring junction. The product **20** exhibited a H^{1} NMR spectrum identical with that of the same compound prepared by Paquette and Ham[5].



Scheme 4. Reaction conditions: (a) Benzene, Me_2NNH_2, reflux, 10h (94%); (b) THF, LDA, O^{o}C, 2h; RI, O^{o}C→r.t., 15h; (c) MeOH, phosphate buffer solution (pH 7.2), $NaIO_4$, 48 h (31% from 15); (d) CH_2Cl_2, I_2, O^{o}C (97%); (e) ^{n}BuLi, THF, -78^{o}C, 30 min. (95%); (f) PtO_2, EtOAc, H_2, 50 psi, 24 h, 20^{o}C (90%).



Scheme 5. Reaction conditions: (a) THF, LDA, O^{o}C, 2h; RBr, -78^{o}C, 1h→0^{o}C, 2h; (b) MeOH, phosphate buffer solution (pH 7.2), $NaIO_4$, 48 h (55% from 15); (c) ^{n}BuLi, THF, -78^{o}C, 30 min. (95%).



Scheme 6. Reaction conditions: (a) THF, LDA, 0^oC, 2h; RI, $0^oC \rightarrow 20^oC$, 17 h; (b) HOAc, THF, H_2O, NaOAc (15:2:2:1 w/w) (50% from 15); (c) THF, HMPA, SmI_2, t-BuOH, 20^oC, 28 h (60%).

The results outlined above revealed that the ^{n}BuLi mediated cyclizations of the keto iodides **5** (Scheme 4) and **19** (Scheme 5) were higly stereoselective and produced only the corresponding *trans* fused alcohols **18** and **20**, respectively. Thus, in each case, the intermediate alkenyl-lithium function (formed by lithium iodine exchange) attacks the carbonyl carbon from the side opposite to the cyclopropyl (angular) methyl group. It is evident from molecular modelling that, in each of the modes of cyclization that could lead to the *cis*-fused epimers of **18** and **20**, the transition states for cyclization would experience significant steric hindrance (1,3-diaxial type interaction) between the alkenyl-lithium moiety and the angular methyl group. On the other hand, the transition states leading to **18** and **20** appear to be relatively free of steric compression.

In view of the results described above, it was decided to prepare compound **21** and treat it with samarium iodide in the presence of HMPA. It was expected that the samarium iodide would generate the ketyl radical which would be complexed with HMPA[18], prior to attack on the terminal double bond.

Having made **21** by alkylation of the anion of **15** with 4-iodo-1-butene, the cyclization was attempted. The reaction produced a mixture of the compounds **1a** and **1b**, along with africanol, in a ratio of 1:0.6:1, respectively. The formation of isoafricanol was not observed.

Conclusion

The methodology presented herein was very effective up to the preparation of bicyclic ketone **6**. The regioselective and highly stereoselective alkylation of hydrazone **15** allowed the preparation of the key compounds **5**, **19** and **21** in reasonable yields. However, cyclization of intermediates **5** and **19** by treatment with ^{n}BuLi gave products with *trans* instead of the desired *cis* ring junctions. This problem was overcome by using a samarium iodide cyclization of olefin **21**, in which the radical intermediate yielded a mixture of products from both *cis* and *trans* ring closure.

Acknowledgments

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