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TOTAL SYNTHESIS OF AFRICANOL

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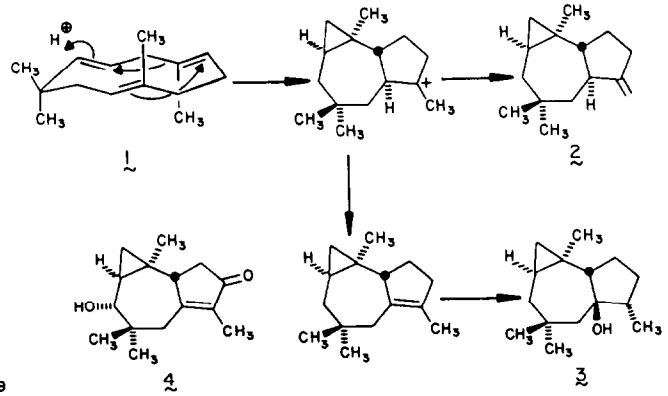
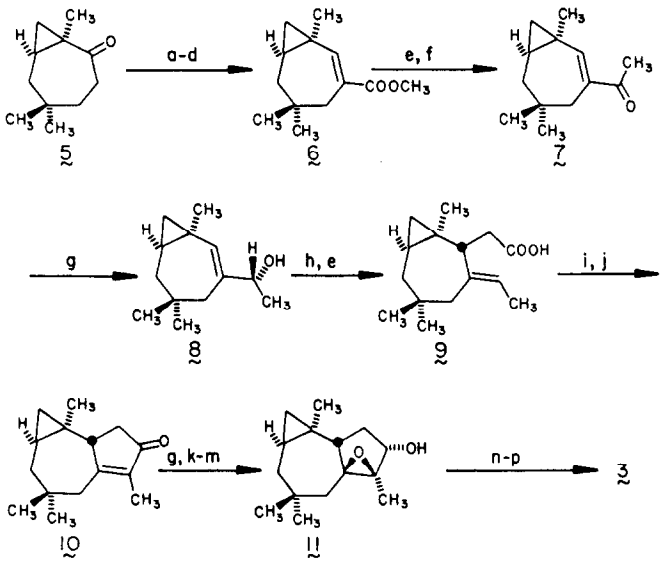
Summary: The first total synthesis of africanol has been achieved in 18 steps from ketone **5** by a route that for the most part is highly stereocontrolled.

Considerable effort has been expended to elucidate the interrelationship of humulene conformation and intramolecular cyclization leading to various sesquiterpene frameworks.[1] The most recent developments surround the biosynthetic origins of the africane natural products.[2] Implicated to date is a cationic closure of CT-**1** that eventuates in formation of $\Delta^{9(15)}$-africanene (**2**, source: soft corals Sinularia erecta[3] and S. polydactyla[4]), africanol (**3**; source: soft coral Lemnalia africana[5]), or africanone (source: leafy plant Lippia integrifolia[6]). Although **3** and **4**[7] have been arrived at by Lewis acid-catalyzed rearrangement of humulene-9,10- and 4,5-epoxides, respectively,[8,9] no successful de novo synthesis of a representative africane has yet been achieved, despite attempts in this direction.[10]

In this communication, we report a practical solution to the stereocontrolled synthesis of africanol (**3**). Our strategy for proper installation of the five consecutive chiral centers in **3** encompasses several notable facets: (1) recognition that ketone **5** and structurally related molecules are essentially locked into one preferred conformation[11]; (2) stereocontrolled reduction of the

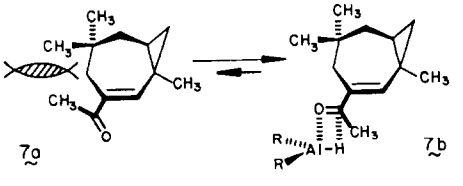


pendant acetyl function in **7** and complete transfer of this chirality in an ensuing [3.3]sigmatropic rearrangement; (3) avoidance of all complications stemming from potential cyclopropylcarbinyl cation formation[12]; and (4) proper introduction of the "angular" hydroxyl group so as to produce the cis-perhydroazulene system.



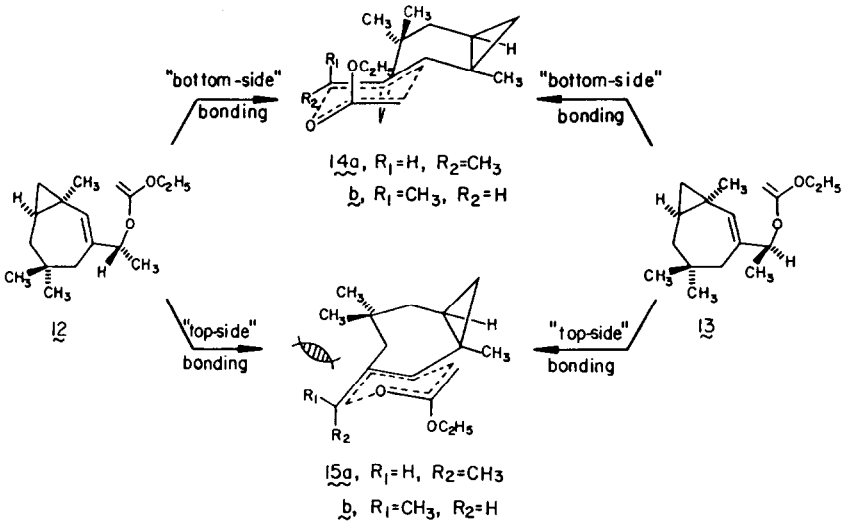
[a]NaH, (KH), O=C(OCH$_3$)$_2$, THF, Δ. [b]NaBH$_4$, C$_2$H$_5$OH, 0°C. [c]Ac$_2$O, Et$_3$N, cat DMAP, CH$_2$Cl$_2$, Δ. [d]DBU, C$_6$H$_6$, Δ. [e]KOH, 95% C$_2$H$_5$OH, Δ. [f]CH$_3$Li, ether, -78° → 0°C. [g]Dibal, CH$_2$Cl$_2$, -78°C. [h]CH$_3$C(OC$_2$H$_5$)$_3$, CH$_3$CH$_2$COOH, xylene, Δ. [i](COCl)$_2$, C$_6$H$_6$, 5°C. [j]SnCl$_4$, CH$_2$Cl$_2$, -78°C. [k]t-Bu(CH$_3$)$_2$SiCl, imidazole, THF, RT. [l]MCPBA, CHCl$_3$, -20°C. [m](n-Bu)$_4$N$^+$F$^-$, THF, RT. [n]CH$_3$SO$_2$Cl, (C$_2$H$_5$)$_3$N, CH$_2$Cl$_2$, -20°C. [o]Li, NH$_3$, THF, -78°C. [p]H$_2$, PtO$_2$, EtOAc.

Readily available ketone **5**[13] was conveniently transformed[14] via α,β-unsaturated ester **6** (65%) into the acetyl derivative **7** (67%).[15] The selection of **7** was founded on the expectation that its preferred conformation would eventually provide the configurational control required at the cyclopropylcarbinyl site in **3**. That is, molecular mechanics calculations reveal that conformation **7b** is 0.7 kcal/mol more stable than **7a** chiefly because of the illustrated nonbonded CH_3-CH_3 steric interaction. Additionally, molecular models of **7** suggested that approach of R_2AlH reducing agents toward **7b** would be preferentially relegated to "below-plane" because of steric shielding on the alternate surface by one of the geminal methyl groups. In actuality, Dibal reduction of **7** at -78°C delivered an 88:12 mixture of two easily separable carbinols, the major constituent of which was formulated as **8** for the above reasons.



The projected Claisen rearrangement of **8** (see **12**) is seen to be goverened by two chair-like transition state options. The

first (**14a**), involving C-C bond formation anti to the cyclopropane ring, does not experience the incipient 1,3-diaxial interaction so obvious in **15a** and should accordingly be favored. Since **9**



was formed exclusively, the level of chirality transfer in this instance is seen to be excellent. Isomer **13** (available from the minor alcohol) is not similarly advantaged because the appreciable nonbonded interactions in **15b** apparently bring into play a level of destabilization comparable to that present in **14b**. Under identical conditions, **13** gave rise to a 1:1 mixture of two carboxylic acids isomeric with **9**.

With the third chiral center introduced, the cyclization of **9** by means of alicyclic Friedel-Crafts chemistry[16] was next examined. Our expectation was that the intermediate tricyclic carbocation would experience β-elimination to establish the conjugated enone functionality at a rate considerably faster than hydride shift leading to the cyclopropylcarbinyl cation.[12] Significantly for our purposes, a stereochemically pure cyclopropane-substituted α,β-unsaturated ketone (**10**) was produced (53% isolated) following exposure of the acid chloride to $SnCl_4$ in dichloromethane solution at -78°C.

Low-temperature diisobutylaluminum hydride reduction of **10** gave rise to a 95:5 mixture of allylic alcohols. The predominant product was considered to be the α stereoisomer on the basis of steric approach control, a conclusion that was confirmed by eventual conversion to the natural product. This alcohol, after formation of its TBDMS ether, was sequentially oxidized with MCPBA at -20°C and desilylated with tetra-n-butylammonium fluoride. This sequence led in 56% yield to a 60:40 mixture of **11** and the α-epoxide. All attempts to enhance further the proportion of **11**, the separation of which

was achieved chromatographically, proved unsuccessful.

Removal of the OH group and regiospecific cleavage of the oxirane ring were realized by exposure of **11** to sulfene and reduction of the resulting mesylate with lithium in liquid ammonia (61%).[17] With access to the transposed allylic alcohol in this manner, hydrogenation of the trisubstituted cyclopentene double bond proceeded with the anticipated 100% stereoselectivity to give **3**. That africanol had indeed been produced was determined by careful comparison of 300 MHz ^{1}H NMR spectra recorded on synthetic and authentic samples.[18]

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18. We thank Dr. J. C. Braekman of the Universite Libre de Bruxelles for providing us with a generous sample of natural africanol.

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