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Synthetic Approach for (+)-Africanol

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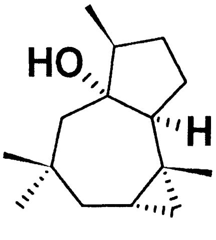
Syntheses of (+)-africanol(**1**) and (+)-isoafricanol(**2**) were attempted by reductive radical cyclization of (1<u>S</u>,2<u>S</u>,8<u>S</u>)-2-(4'-butenyl)-1,5,5-trimethyl-bicyclo[5.1.0]-3-octanone derived from (1<u>R</u>,2<u>S</u>,4<u>S</u>,8<u>S</u>)-4-alkoxy-1,6,6-trimethyl-tricyclo[6.1.0.0^{2,4}]nonane. This cyclization gave (+)-**1** and (+)-**2** as minor components, together with trans fused epimers as major components.

(+)-Africanol(**1**), isolated from the soft coral <u>Lemnalia africana</u>, is a novel tricyclic sesquiterpene alcohol, which include three, five and seven membered rings.[1a] The same compound was also isolated in 1986 from <u>Leptographium lundbergii</u> Lag. et Mel. with its stereoisomer, isoafricanol(**2**).[1b] Although racemic **1** has been synthesized by two different procedures,[2,3] optically active **1** has not yet been synthesized.



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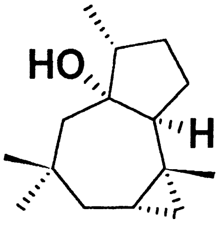

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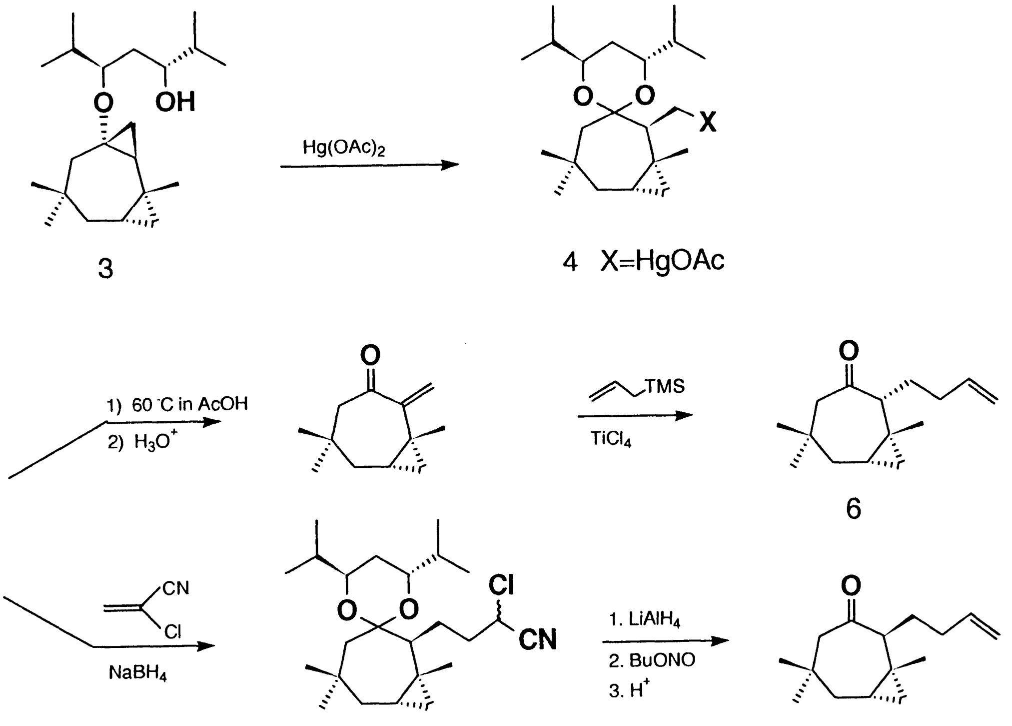
In this communication, we wish to report synthetic approach of (+)-**1** and (+)-**2** by using optically pure (1<u>R</u>,2<u>S</u>,4<u>S</u>,8<u>S</u>)-4-alkoxy-1,6,6-trimethyl-tricyclo[6.1.0.0^{2,4}]nonane(**3**), recently prepared by our group, as a starting material. As shown in Scheme 1, conversion of 3 to 1 and 2 was attempted by following procedures; 1) regio and stereo controlling ring opening of the alkoxy cyclopropane of 3 to give ketone(**4**) carrying $-CH_2X$ group, 2) chain elongation(allylation of $-CH_2X$ to $-(CH_2)_2-CH=CH_2$) of **4** to give 5, and 3) reductive ring closure of -$(CH_2)_2$-CH=CH_2 with carbonyl group to give **1** and **2**.

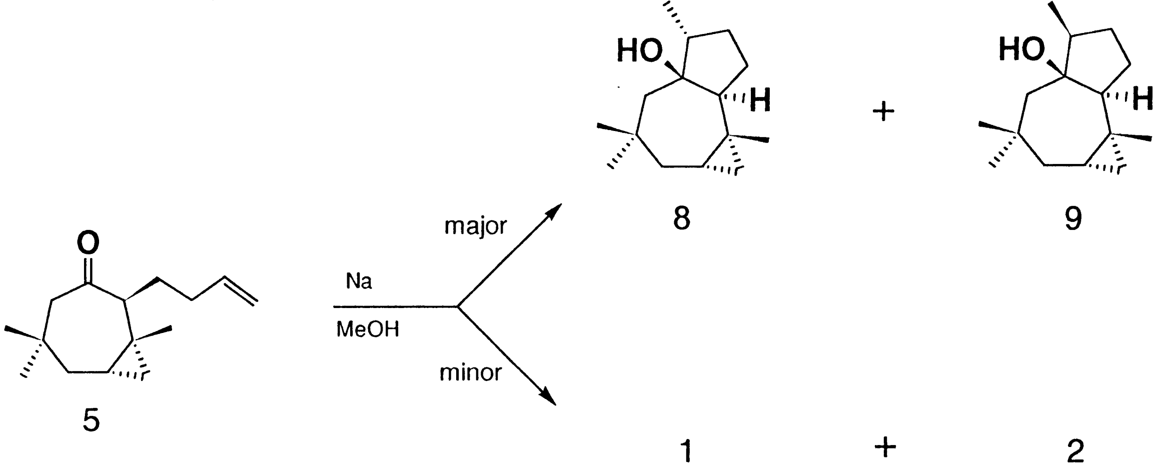


Scheme 1 .

The starting material, (1R,2S,4S,8S)-4-alkoxy-1,6,6-trimethyl-tricyclo[6.1.0.0^{2,4}]nonane(**3**) of this report was synthesized by ragio- and stereo-controlled cyclopropanations. Among several attempts, the selective ring opening of cyclopropyl ether moiety of **3** was only achieved by oxymercuration without accompanying racemization at 2-position of the product. By the treatment with mercuric acetate in acetic acid, **3** was converted to **4**(X=HgOAc) in a quantitative yield.

Straitforeword allylation of **4** was achieved by thermal elimination of mercury group at 60 °C(100%), deketalization(86.8%) followed by the treatment with allyltrimetylsilane and titaniumtetrachloride4) to give diastereomerically pure product(**6**, 65%). In this reaction, chirality at 2-position was once disappeared and then reintroduced. Unfortunately the structure of the product was 2-epimer of **5**.5)

Alternative allylation of **4** without epimerization at 2-position was achieved in four steps. Addition of 2-chloroacrylonitrile to **4** in the presence of sodium borohydride gave adduct(**7**) in 61.5%.6) Reduction of **7** with lithium alminiumhydride afforded aziridine,7) which was directory converted to terminal olefin by the treatment of butyl nitrite.8) Deketetalization of this product resulted diastereomerically pure **5**(72% for three steps).



Scheme 2.

When 5 was treated with sodium in methanol(cont. 3% of water), reductive cyclization of 5 was taken place in giving a mixture of four diastereomers of five membered ring fused compounds as shown in Scheme 2.9) Two major components were isolated from this mixture by MPLC on silica gel in 36% and 37% yields. These products were assigned to be trans fused **8** and **9** by NMR spectrum. Two minor products were also isolated in 2-3% yield and were identical with natural (+)-africanol and (+)-isoafricanol. Several attempts9) to obtain cis fused products as major components have not succeeded at present stage. Apart from the present subject, the following results were noteworthy in considering the steric control of this type ring closure. Irradiation of **5**(0.02 mol/l) with 254 nm light in HMPA exclusively gave **8**, the reduction of 5 with zinc/chlorotrimethylsilane gave **8** as a major product, while with titaniumtetrachloride/magnesium amalgam selectively gave **9**.10)

In the case of the cyclization of **6**(254 nm light in HMPA), a mixture of four compounds was obtained in a ratio of 2:2:1:1 in 85% yield. All of these products clearly had fused ring structure containing of three, five and seven membered rings, but were not identical with **1**, **2**, **8**, nor **9**. Thus, these were assigned to be 7a-epimers of natural africanol families.

The present study provided the first example of the preparation of (+)-**1** and (+)-**2** in an optically pure state, yet of its low chemical yield, and open a rout to the preparation of optically active tricyclic sesquiterpene frameworks consisting three, five, seven membered rings.

We thank Professor J. C. Braekman of the Universite Libre de Bruxelles for his generous gift of natural africanol. We also thank Professor L. A. Paquette of the Ohio State University who sent us spectral data of 4a,5-epi-africanol(**9**).

References

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10) ^{1}H-NMR and IR spectral data of synthesized **1**, **2**,and **9** was well consistent with reported one. Optical rotation of each compounds are as follows:
   1: $[\alpha]_D^{20}$ 61(c 0.1, $CHCl_3$), lit.$^{1)}$ $[\alpha]_D$ 59.5(c 0.474, $CHCl_3$).
   2: $[\alpha]_D^{20}$ 11(c 0.1, $CHCl_3$), lit.$^{2)}$ $[\alpha]_D^{23}$ 11.4(c 0.59, $CHCl_3$).
   8: $[\alpha]_D^{20}$ -9.8(c 0.2, CH_3OH). **9**: $[\alpha]_D^{20}$ 34.4(c 1.0, $CHCl_3$).

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