SHORT PAPER

J. Chem. Research (S), 2000, 438–439

Acid catalysed rearrangement of $\Delta^{9,15}$-africanene: a cytotoxic sesquiterpene†

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Acid catalysed rearrangements of $\Delta^{9,15}$-africanene, a cytotoxic sesquiterpene isolated from the soft corals of the genus *Sinularia*, have been studied for the first time and a marked difference was observed between the compositions of the conversion products with and without refluxing conditions.

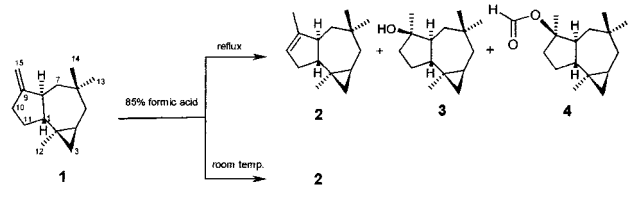
Chemical or biochemical transformation of an active molecule is a tool to obtain a more active molecule from its natural counterpart.[1] A recent review pointed out that approximately 60% of the anti-tumour and anti-infective agents that are commercially available or in late stages of clinical trials today are of natural origin.[2] Drugs of natural origin have been classified as original natural products, products derived semisynthetically from natural products or synthetic products based on natural product models, for example, irinotecan from camptothecin and etopophos from podophyllotoxin.

In continuation of our search for bioactive metabolites from marine sources, we have studied the different derivatives of a potent cytotoxic $\Delta^{9,15}$-africanene class,[3] and examined the chemical transformation of the above using 85% formic acid at different temperatures.

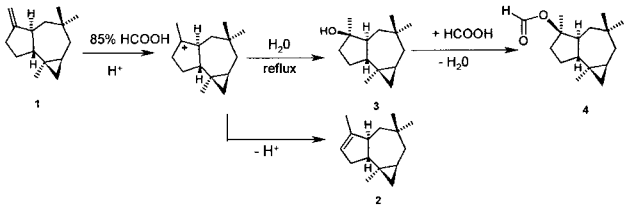
$\Delta^{9,15}$-africanene (**1**) is a tricyclic sesquiterpene isolated from various marine soft corals of *Sinularia* sp.[4,5] and some of its derivatives are also isolated from marine as well as terrestrial sources.[6–8] The absolute configuration of **1** was assigned by X-ray diffraction study of its derivatives.[4,5] Recently, its pharmacological activity was studied and it was found to be a potent cytotoxic.[9] The present study deals with the 85% formic acid catalysed rearrangement of $\Delta^{9,15}$-africanene to $\Delta^{9,10}$-africanene (**2**), leptographiol (**3**) and O-formyl leptographiol (**4**) (Scheme 1).

To investigate the course of acid catalysed[10, 11] transformation of **1** using 85% formic acid under different conditions, africanene (**1**) was treated with 85% formic acid at room temperature. While adding 85% formic to compound **1**, the reaction mixture turned to blue instantaneously and the resulting reaction mixture was stirred overnight. After usual work up, a single rearranged product $\Delta^{9,10}$-africanene (**2**) was isolated in 80% yield. This is a new analogue in this series. In contrast to this, under refluxing conditions at 80°C for one hour, compound **1** yielded compounds **2**, **3** and **4** in a 50:40:10 ratio. The structures of compounds **2**, **3** and **4** were determined by the study of spectral data and for **3** confirmed by literature comparison. The proposed mechanism is presented in Scheme 2.

Compound **2** was obtained as a colourless liquid, $[\alpha]_D^{25}$ +11.5 (c 1, $CHCl_3$). The ^{1}H NMR spectrum of compound **2** showed signals for the presence a trisubstituted double bond proton at δ 5.29 (br s, 1H), instead of the exocyclic methylene protons at δ 4.68 (br s, 1H) and 4.84 (br s, 1H) as observed for africanene. The tertiary methyls appeared at δ 1.05 (s, 3H), 0.95 (s, 3H) and 0.88 (s, 3H), a vinylic methyl appeared at δ 1.60 (s, 3H) and trisubstituted cyclopropane ring protons appeared at δ 0.52 (m, 2H) and 0.22 (m, 1H). The foregoing spectral data were similar to those of $\Delta^{9,15}$-africanene except for the presence of a trisubstituted double bond instead of exocyclic double bond. A similar conclusion was reached from its ^{13}C NMR spectral data. The ^{13}C NMR spectrum showed signals for trisubstituted double bond carbons at δ 143.1 (s) and 123.9 (d) instead of the exocyclic double bond carbons at δ 158.3 (s) and 104.5 (t) of $\Delta^{9,15}$-africanene. The foregoing spectral data revealed that the structure of compound **2** was $\Delta^{9,10}$-africanene, which is a new compound. Further, molecular modelling studies on the two possible isomers, the $\Delta^{8,9}$ and $\Delta^{9,10}$ compounds, revealed that compound **2** has 6 kcal/mol less free energy than $\Delta^{8,9}$ isomer ($\Delta^{8,9}$ isomer 33.22 and $\Delta^{9,10}$ isomer 27.34 kcal/mol respectively).



Scheme 1



Scheme 2
Mechanism for the formation of reaction products

Compound **3** was obtained as colourless liquid and its IR spectrum showed a strong absorption band at 3610 cm^{-1} indicating the presence of hydroxyl functionality. The ^{1}H NMR spectrum of compound **3** showed signals for four tertiary methyls at δ 1.18 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H) and 0.90 (s, 3H) and trisubstituted cyclopropane protons appeared at δ 0.17 (m, 1H) and 0.50 (m, 2H). The foregoing spectral data was reminiscent of that of $\Delta^{9,15}$-africanene (**1**) except for the presence of an additional methyl at δ 1.18 and the absence of exocyclic methylene signals at δ 4.68 (br s, 1H) and 4.84 (br s, 1H). A literature survey and the foregoing spectral data revealed the structure of compound **3** as 9β-hydroxy africanane, leptographiol, which has previously been isolated from the fungus *Leptographilum lundbergii*[12]. Compound **3** was matched in all respects with leptographiol (optical rotation, ^{13}C NMR *etc.*). To our knowledge this is the first report of the synthesis of this molecule.

Compound **4** was obtained in a minor quantity as an oil. Its ^{1}H NMR spectrum showed signals for the presence of a formyl group at δ 7.98 (s, 1H), four tertiary methyls at δ 0.90

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

(s, 3H), 0.95 (s, 3H), 1.03 (s, 3H) and 1.30 (s, 3H) and the trisubstituted cyclopropane protons at δ 0.17 (m, 1H) and 0.50 (m, 2H). The foregoing spectral data revealed that compound **4** was O-formyl 9β-hydroxy africanane or O-formyl leptographiol, which is a new compound in the africanene series. This was confirmed by acid hydrolysis of compound **4,** which yielded leptographiol (**3**).

Experimental

Optical rotations were measured with a JASCO DIP-370 polarimeter. UV and IR spectra were recorded on Shimadzu and Perkin-Elmer 240C instruments. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 200 MHz spectrometer using TMS as internal standard. Chemical shifts are reported in parts per million, and coupling constants (*J*) are expressed in Hertz. Mass spectra were recorded on VG Auto Spec-M instrument.

Reaction of $\Delta^{9,15}$-africanene with formic acid: $\Delta^{9,15}$-africanene (100 mg) was taken in a 25 ml round bottom flask, and an excess (3 ml) of 85% formic acid was added. The reaction mixture turned to pink instantaneously. The reaction mixture was then refluxed for 1 hour at 80 °C under an inert atmosphere. The reaction mixture was neutralized with 10% $NaHCO_3$ solution and extracted into ethyl acetate. The resultant gummy liquid was chromatographed on a 20% w/w $AgNO_3$ impregnated silica gel column using hexane through hexane-ethyl acetate mixtures as eluents to yield compounds **2**, **3** and **4**. In a separate experiment the above reaction mixture was stirred overnight at room temperature to yield exclusively the single rearranged product **2** in 80 % yield.

Acid hydrolysis of O-formyl leptographiol (4): Compound **4** (5 mg) was taken in a 10 ml round bottom flask containing 3 ml of 10 % HCl: methanol (30:70) and stirred overnight. The reaction mixture was neutralized with 10% $NaHCO_3$ solution, and extracted into ethyl acetate and concentrated to yield leptographiol (**3**) (3.5 mg).

$\Delta^{9,10}$-africanene **(2)***:* Obtained as viscous liquid; $[\alpha]^{25}_D$ +11.5° (c 1, $CHCl_3$); IR (neat) ν_{max} 2900, 1710, 1375, 820 cm^{-1}, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.29 (br s, 1H), 2.60 (m, 1H), 2.31 (m, 2H), 2.05 (m, 1H), 1.60 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H), 0.88 (s, 3H), 0.52 (m, 2H) and 0.22 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 52.8 (C-1), 19.3 (C-2), 23.5 (C-3), 22.0 (C-4), 43.5 (C-5), 33.7 (C-6), 49.0 (C-7), 46.8 (C-8), 143.1 (C-9), 123.9 (C-10), 32.2 (C-11), 24.3 (C-12), 14.9 (C-13), 34.1 (C-14), 21.9 (C-15); EIMS *m/z* 204 [M$^+$] (10), 189 (8), 161 (5), 135 (5), 119 (12), 107 (52), 105 (30), 91 (28), 69 (100), 41 (72); HREIMS *m/z* 204.1882 (calcd for $C_{15}H_{24}$, 204.1878).

O-formyl leptographiol (**4**)*:* Obtained as viscous liquid, $[\alpha]^{25}_D$ +21.5 ° (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.98 (s, 1H), 2.55 (m, 1H), 2.00–2.40 (m, 3H), 0.90 (s, 3H), 0.95 (s, 3H), 1.03 (s, 3H), 1.30 (s, 3H), 0.17 (m, 1H) and 0.50 (m, 2H); EIMS *m/z* 250 [M$^+$] (4), 205 (22), 204 (65), 189 (58), 175 (15), 161 (55), 147 (32), 81 (95), 55 (73), 41 (100); HREIMS *m/z* 250.3842 (calcd for $C_{16}H_{26}O_2$, 250.3848).

We thank the Department of Ocean Development for financial assistance, the Director IICT and Dr J.S. Yadav, Head, Organic Division-I for their encouragement. One of the author (NSR) thankful to CSIR (New Delhi) for providing a fellowship. IICT communication No. 4524.

Received 3 June 2000; accepted 17 September 2000
Paper 00/355

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