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STRUCTURE OF A GUAIANE-TYPE SESQUITERPENE ETHER FROM "SAN-SHION"

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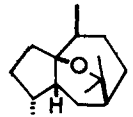
It has been reported that the benzene extract of "San-shion" (mountain Shion the roots of a *Ligularia* genus)[1,2] gives five volatile constituents (LA-LE, tentative names)[1] along with furanoligularenone[2] and ligularenolide [3] Four (LA, LC, LD, and LE) of the volatile constituents have been shown to be identical with cyperene, liguloxide, p-cymene, and limonene, respectively [1a,b] Recently, Fujita and Fujita[4] described the identity of LB with ogarukaya-ehter A, isolated from *Cymbopogon Georingii* (STEUD) A. CAMUS, and the structure (1) was proposed for ogarukaya-ether A based on biogenetic considerations [4b] We wish to report evidences leading to the structure (2) for LB

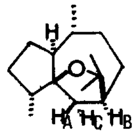
No hydroxy nor carbonyl absorptions were observed in the IR spectrum of LB, a colorless liquid, $C_{15}H_{26}O$ (M^+ at m/e 222), $[\alpha]_{578}=-45°$ (c = 2 2, $CHCl_3$) [1a,b] The PMR spectrum (in $CDCl_3$) shows the presence of two tertiary (δ 1 18 and δ 1 23, each 3H, s) and two secondary methyls (δ 0 87, 3H, d, J = 5 5 Hz and δ 0 89, 3H, d, J = 7 5 Hz) and the absence of olefinic proton. The absence of unsaturated carbon-carbon linkage was revealed by treatment of LB with CF_3CO_3H showing no consumption of the reagent A tricyclic saturated nature was thus suggested for LB in which an oxygen atom could exist as a part of ether linkage.[1a,c] The absence of signal due to $-O-\overset{|}{C}H-$ shows that the two carbon atoms attached to the ether oxygen must be both tertiary Dehydrogenation of LB with 10% Pd-C yielded S-guaiazulene (major product) and Se-guaiazulene (minor product). These observations[1] suggest that LB is related to a guaiane skeleton (3)[5] and lead to two alternative structures (A and B , without stereochemical considerations) for LB [1a, 5]

The presence of ABC-type spin-spin couplings was shown for 4 (1-epiguaioxide[6,7]) by the INDOR experiments[8] [H_A(6β-H δ 2.32, q, J = 13 and J = 6 Hz, H_B(7α-H)· δ 1 87, q, J = 8 and J = 6 Hz, H_C(6α-H) δ 1.63, d, J = 13 Hz] The same ABC-type spin-spin couplings were shown to be present in LB by the INDOR experiments (Fig 1) [H_A(6β-H) δ 2 28, q, J = 13 and J = 6 5 Hz, H_B(7α-H) δ 1.96, q, J = 9 and J = 6 5 Hz, H_C(6α-H) δ 1 69, d, J = 13 Hz, H_B couples further with the vicinal protons on $C_{(8)}$] The structure A can only account for these observations, excluding the structure B (with a proton on $C_{(5)}$) for LB.

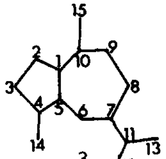
Six (4,[6,7] 5,[9] 6,[10] 7,[7] 8,[7] and 10[11]) among eight diastereomers (2 and 4-10, without consideration of their enantiomers) have been described for the structure A However, none of the spectral data of the six isomers were identical with those of LB. The structure of LB must therefore be represented by either 2 or 9 (or by one of their enantiomers)



1



2 (LB)



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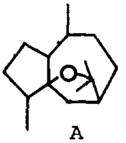
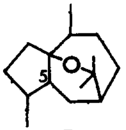
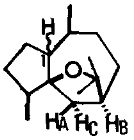


A

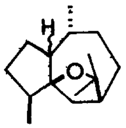


B



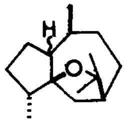
5 1β-H
(Guaioxide)

4 1α-H
(1-Epiguaioxide)



6 1β-H
(Bulnesoxide)

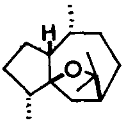
9 1α-H
(4-Epi-LB)

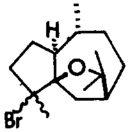


7 1β-H
(Liguloxide)

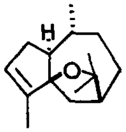
10 1α-H
(1-Epiliguloxide)

8
(10-Epiliguloxide)

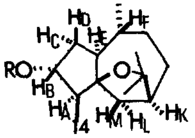




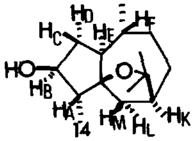
11



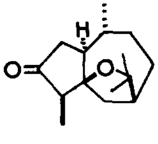
12



13 R = H
17 R = Ts



14



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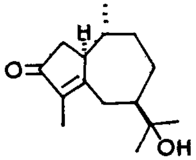


16

Treatment of LB in CCl_4 with NBS under reflux gave a monobromo derivative (11,[12] yield 18 %[13]), an oil, $C_{15}H_{25}OBr$ (M^+ at m/e 302 and m/e 300), PMR ($CDCl_3$). δ 0.92 (3H, diffused d), δ 1.20 (3H, s), δ 1.25 (3H, s), and δ 1.81 (3H, s, $C\underline{H}_3\text{-}\underset{|}{\overset{|}{C}}\text{-Br}$) The bromide (11) was heated under reflux with KOH-EtOH to give an olefin (12, y 60 %), an oil, $C_{15}H_{24}O$ (M^+ at m/e 220), PMR ($CDCl_3$) δ 0.88 (3H, d, J = 6 Hz), δ 1.20 (3H, s), δ 1.27 (3H, s), δ 1.74 (3H, s), and δ ca 5.65 (1H, m). Hydroboration of 12 yielded an alcohol (y· 64 %), mp 84-85°, $C_{15}H_{26}O_2$ (M^+ at m/e 238), ν_{OH} ca. 3250 cm^{-1}, PMR ($CDCl_3$) δ 0.85 (3H, diffused d), δ 1.04 (3H, d, J = 7 Hz), δ 1.17 (3H, s), δ 1.26 (3H, s), and δ 3.93 (1H, m) As a cis relationship between $C_{(3)}$-OH and $C_{(4)}$-H is required by the mode of formation, two alternative structures (13 and 14) are suggested for the alcohol The PMR spectra of the alcohol were measured using Eu(fod)$_3$-d$_{27}$ as a shift reagent (Fig 2) PMDR experiments led to the assignment of signals as shown in Fig 2, when a proton on $C_{(2)}$ cis to the hydroxyl group is designated as H_C (cf 13 and 14) The coupling constants in a first-order approximation are as follows $J_{A,14}$ = 7, $J_{A,B}$ = 7, $J_{B,C}$ = 2, $J_{B,D}$ = 8.5, $J_{C,D}$ = 13.5, $J_{C,E}$ = 8, $J_{D,E}$ = 10.5, and $J_{E,F}$ = 10 Hz The observations that $J_{D,E}$ was greater than $J_{C,E}$ and that a large shift was observed for H_E, favor the strucure 13 rather than 14 for the alcohol Thus, the structure 13 is suggested for the alcohol

The alcohol (13) was treated with Jones' reagent to give a five-membered ring ketone (15, y 77 %), mp 63-64°, $C_{15}H_{24}O_2$ (M^+ at m/e 236), $\nu_{C=O}$ 1740 cm^{-1}, PMR ($CDCl_3$) δ 0.89 (3H, d, J = 6 Hz, $C_{(10)}\text{-}C\underline{H}_3$), δ 1.03 (3H, d, J = 7 Hz, $C_{(4)}\text{-}C\underline{H}_3$), δ 1.16 (3H, s, $C_{(11)}\text{-}C\underline{H}_3$), δ 1.25 (3H, s, $C_{(11)}\text{-}C\underline{H}_3$), and δ ca. 2.20 (1H, q, J = 7 Hz, $C_{(4)}\text{-}\underline{H}$), the protons on $C_{(2)}$ (2H, δ ca. 2.0-2.5, m)

Fig. 1

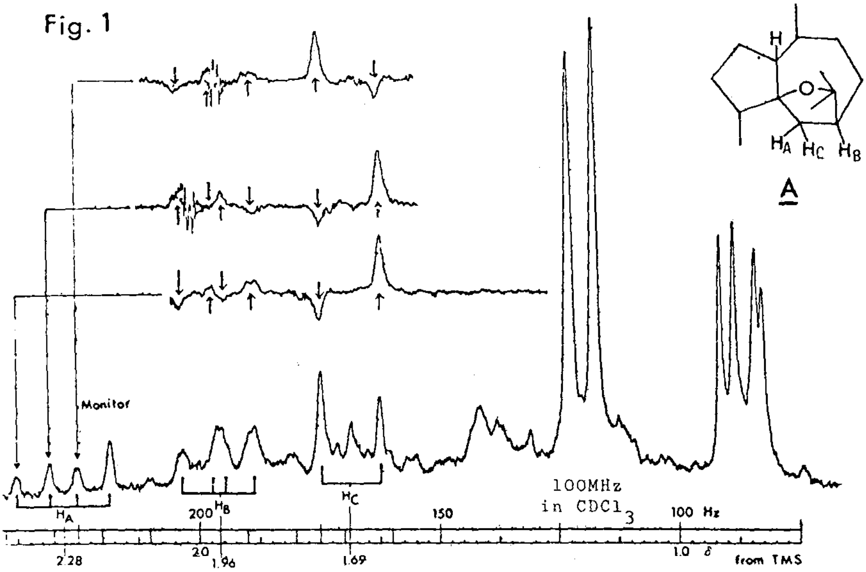
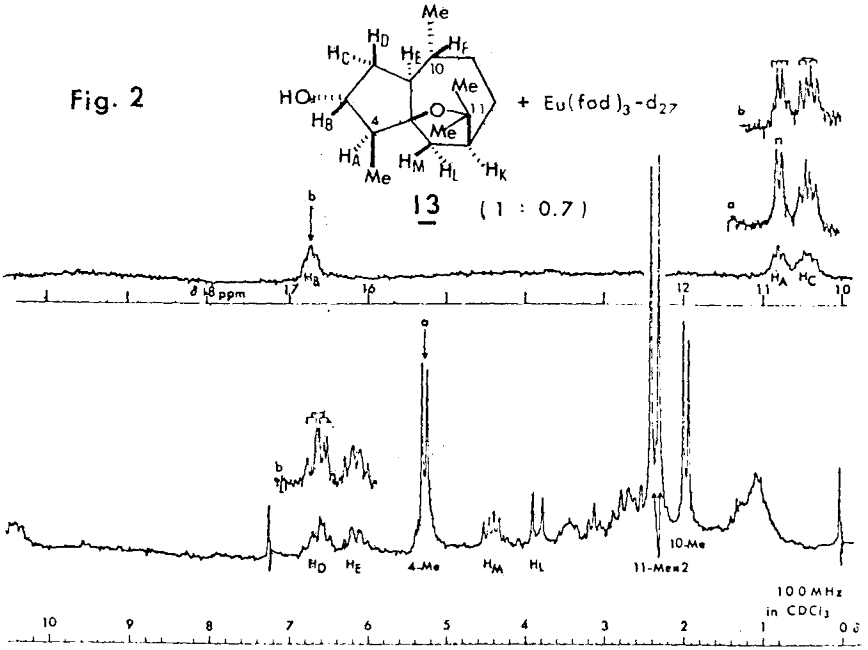

Monitor
H_A
H_B
H_C
200
150
100 Hz
100MHz in CDCl3
2.28
2.0
1.96
1.69
1.0 δ from TMS
H
O
H_A H_C H_B
A

Fig. 2


Me
H_D
H_F
H_C
H_E
10
Me
HO
11
H_B
4
Me
H_A
H_M
H_L
H_K
Me
13
+ Eu(fod)3-d27
(1 : 0.7)
b
a
δ 18 ppm
17
16
12
11
10
H_A
H_C
H_D
H_E
4-Me
H_M
H_L
11-Me×2
10-Me
100 MHz in CDCl3
10 9 8 7 6 5 4 3 2 1 0 δ

couple further with a $C_{(1)}$-H When 15 was passed through a column of alumina, 15 isomerized[14] to an α,β-unsaturated ketone (16, y almost quantitative), mp 57-58 5°, $C_{15}H_{24}O_2$ (M^+ at m/e 236), ν_{OH} ca 3250 and $\nu_{C=O}$ 1680 cm^{-1}, λ_{max}^{EtOH} 242 nm (ε = 9,000), PMR ($CDCl_3$) δ 1 03 (3H, d, J = 6 Hz, $C_{(10)}$-CH_3), δ 1 21 (3H, s, $C_{(11)}$-CH_3), δ 1 24 (3H, s, $C_{(11)}$-CH_3), and δ 1 67 (3H, s, $C_{(4)}$-CH_3), no olefinic proton signal was observed These spectral data provide further support for the presence of an ether linkage of $C_{(5)}$-O-$C_{(11)}$ (A) rather than $C_{(1)}$-O-$C_{(11)}$ (B)

Hydrogenation (in AcOEt-AcOH, PtO_2) of the olefin (12) gave 9 (4-epi-LB), an oil, $C_{15}H_{26}O$ (M^+ at m/e 222), PMR ($CDCl_3$) δ 0 85 (3H, diffused d), δ 0 95 (3H, d, J = 6 Hz), δ 1 19 (3H, s), δ 1 25 (3H, s), and δ 2 15 (1H, q, J = ca 5 and J = ca 12 Hz), as a sole product, no 2 was found to be formed. The alcohol (13) was coverted to a tosylate (17), which without separation was then treated with $LiAlH_4$ (in THF, under reflux) to give 9.

Finally, the ORD measurement on 15 showed a negative Cotton effect curve (a = -182), while that on 3-oxo-4-epiguaioxide (3-oxoliguloxide) a positive Cotton effect curve (a = +273[9])

These observations lead to the structure 2 including absolute configuration for LB Thus, all the diastereomers represented by A have now been recorded

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References

1) a) M Okazaki, Y Ishizaki, Y. Tanahashi, H Hirota, and T Takahashi, Yakugaku Zasshi, 94, 881 (1974) b) Y Ishizaki, M Okazaki, M Wada, Y Tanahashi, and T Takahashi, 12th Symposium on the Chemistry of Perfumes, Terpenes, and Essential Oils, Hamamatsu, 1968, Symposium papers, p 53 c) Y Tanahashi, S Tomoda, and T Takahashi, Bull Chem Soc Japan, 42, 2076 (1969)

2) F Patil, G Ourisson, Y Tanahashi, M Wada, and T Takahashi, Bull Soc Chim France, 1968, 1047

3) Y Ishizaki, Y Tanahashi, T. Takahashi, and K Tori, Tetrahedron, 26, 5387 (1970)

4) a) S Fujita and Y Fujita, Yakugaku Zasshi, 92, 1285 (1972) b) S Fujita and Y Fujita, 16th Symposium on the Chemistry of Perfumes, Terpenes, and Essential Oils, Hirosaki, 1972, Symposium papers, p 14

5) The presence of a five-membered ring in LB was received support from the formation of 15 No other formulations such as those involving a 4,10-oxide moiety or structures with a spirc carbon atom are compatible with the observed data described in the text

6) C. Ehret and G Ourisson, Bull Soc Chim France, 1968, 2629

7) H Ishii, T Tozyo, M Nakamura, and H Minato, Tetrahedron, 26, 2911 (1970)

8) e g a) E. B. Baker, J Chem Phys., 37, 911 (1962) b) R Kaiser, ibid , 39, 2435 (1963).

9) H. Ishii, T. Tozyo, M Nakamura, and H Minato, Tetrahedron, 26, 2751 (1970)

10) H Ishii, T. Tozyo, and M Nakamura, Tetrahedron, 27, 4263 (1971)

11) H Ishii, T Tozyo, M Nakamura, and E Funke, Chem, Pharm Bull (Tokyo), 20, 203 (1972)

12) The 4-bromo structure was deduced from its transformation to 15, via 12 and 13

13) A large amount (74%) of LB was recovered unchanged

14) A similar isomerization has been reported on 3-oxoguaioxide (ref. 10), 3-oxo-4-epiguaioxide (ref 9), and 8-acetoxy-3-oxo-4-epiguaioxide (ref 9)