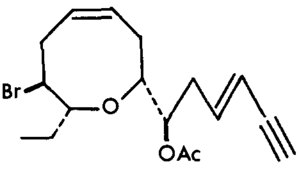
Tetrahedron Letters,Vol.22,No.47,pp 4729-4732,1981 0040-4039/81/474729-04$02.0
Printed in Great Britain

LAURENCENYNE, A PLAUSIBLE PRECURSOR OF VARIOUS NONTERPENOID C_{15}-COMPOUNDS,AND NEOLAURENCENYNE FROM THE RED ALGA LAURENCIA OKAMURAI

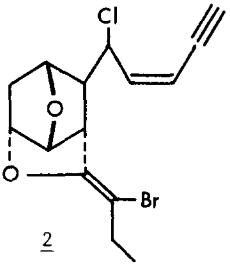
Hideo Kigoshi, Yoshikazu Shizuri, Haruki Niwa, and Kiyoyuki Yamada*
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464 Japan

Abstract: Structural elucidation of two new acetylenic polyenes, laurencenyne 5 and neolaurencenyne 6 isolated from Laurencia okamurai, together with their syntheses, was achieved, suggesting that laurencenyne 5 was a possible precursor of various nonterpenoid C_{15}-compounds in the marine red algae of the genus Laurencia.

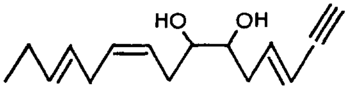
From red algae of the genus Laurencia there were isolated a number of acetylenic halogenated cyclic ethers based on a linear pentadec-3-en-1-yne carbon chain,[1)] such as laurencin 1[2)] and cis-maneonene A 2[3)]. Irie and his coworkers reported the isolation of trans- and cis-laurediol (3, 4) from Laurencia nipponica, and suggested that the diols, 3 and 4, might be the biosynthetic precursors of those acetylenic cyclic ethers.[4)]



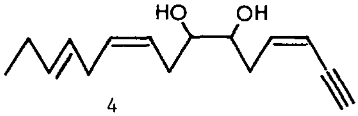
1



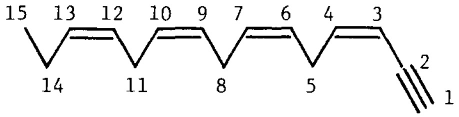
2



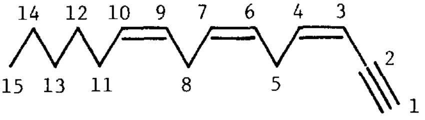
3



4



5



6

We have examined the constituents of Laurencia okamurai collected off the coast of Goza, Mie Prefecture, Japan in July and isolated two new acetylenic polyenes, laurencenyne 5 and neolaurencenyne 6, the structural elucidation of which is described in the present paper.

The ethyl acetate-soluble fraction of the acetone extract of fresh Laurencia okamurai was chromatographed on silica gel with hexane, hexane-benzene, benzene, and ethyl acetate, successively. The fraction eluted with hexane was separated by preparative HPLC [Zorbax ODS with EtOH-H_2O (9:1)], giving laurencenyne 5 (0.001%) and neolaurencenyne 6 (0.002%), which were further purified by preparative GLC[5)] to afford pure 5[6)] and 6[7)].

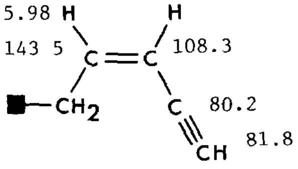
Laurencenyne 5:[8)] colorless liquid, $C_{15}H_{20}$; UV (MeOH) nm (ε) 224 (13,700), 231 (11,400, shoulder); IR (film) 3300 (acetylenic ν_{C-H}), 3010 (olefinic ν_{C-H}), 2140 ($\nu_{C\equiv C}$), 1645 ($\nu_{C=C}$, broad), 1610 ($\nu_{C=C}$), 725 (δ_{C-H} cis-disubstituted olefin) cm^{-1}; ^1H-NMR (100 MHz, CDCl$_3$) δ 0.98 (3H, t, J=7 Hz, H-15), 2.09 (2H, br.quint, J=7 Hz, H-14), 2.7 - 3.0 (4H, m, H-8, H-11), 3.12 (1H, d, J=2 Hz, H-1), 3.13 (2H, br.dd,J=7 Hz, H-5), 5.2 - 5.7 (7H, m, H-3, H-6, H-7, H-9, H-10, H-12, H-13), 5.98 (1H, dt, J=10, 7 Hz, H-4); ^{13}C-NMR (22.5 MHz, CDCl$_3$) δ 14.3 (q), 20.6 (t), 25.6 (t), 25.7 (t), 28.7 (t), 80.2 (s), 81.8 (d), 108.3 (d), 126.0 (d), 127.0 (d), 127.7 (d), 128.7 (d), 129.6 (d), 132.0 (d), 143.5 (d); MS (*m/e*) 200 (M^+).

Neolaurencenyne 6:[8] colorless liquid, $C_{15}H_{22}$; UV (MeOH) nm (ε) 224 (12,500), 231 (10,600, shoulder); IR (film) 3300 (acetylenic ν_{C-H}), 3010 (olefinic ν_{C-H}), 2130 ($\nu_{C\equiv C}$), 1640 ($\nu_{C=C}$, broad), 1610 ($\nu_{C=C}$), 730 (δ_{C-H} *cis*-disubstituted olefin) cm^{-1}; ^{1}H-NMR (100 MHz, CDCl$_3$) δ 0.90 (3H, br.t, J=6 Hz, H-15), 1.2 - 1.5 (6H, m, H-12, H-13, H-14), 2.07 (2H, m, H-11), 2.83 (2H, m, H-8), 3.11 (1H, d, J=2 Hz, H-1), 3.13 (2H, br.dd,J=7 Hz, H-5), 5.2 - 5.6 (5H, m, H-3, H-6, H-7, H-9, H-10), 5.97 (1H, dt, J=11, 7 Hz, H-4); ^{13}C-NMR (25 MHz, CDCl$_3$)[9] δ 14.0 (q), 22.5 (t), 25.7 (t), 27.2 (t), 28.7 (t), 29.3 (t), 31.5 (t), 81.7 (d), 108.1 (d), 125.7 (d), 127.3 (d), 129.8 (d), 130.5 (d), 143.5 (d); MS (*m/e*) 202 (M^+).

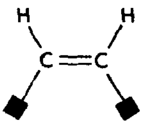
Structure of laurencenyne 5

On catalytic hydrogenation (H_2, Pt/EtOH, room temp., 2 h) laurencenyne 5 gave n-pentadecane, establishing the carbon skeleton of this compound. Laurencenyne 5 showed spectral properties characteristic of a conjugated *cis*-enyne system,[3,4,10] (C_1-C_4 in (I)) [UV (224 and 231 nm), IR (3300, 3010, and 2140 cm^{-1}) and ^{1}H-NMR (δ 3.12 and 5.98)], the presence of which was further corroborated by ^{13}C-NMR spectrum: carbon signals (δ 81.8, 80.2, 108.3, and 143.5) as shown in (I) corresponded very well to those of the *cis*-enyne unit present in various C_{15}-compounds.[3,11,12] Since the H-4 signal (δ 5.98) in the partial structure (I) was observed as a doublet of triplets ($J_{3,4}$=10 Hz, $J_{4,5}$=7 Hz) in the ^{1}H-NMR spectrum of 5, the olefinic carbon (C-4) was deduced to be adjacent to a methylene carbon (C-5) as depicted in (I). The ^{1}H- and ^{13}C-NMR spectra of 5 revealed the presence of eight vinyl hydrogens and eight olefinic carbons: among them two each are contained in the partial structure (I). Therefore there remained six vinyl hydrogens and six olefinic carbons to be characterized. In view of the fact that laurencenyne 5 has a linear pentadecane skeleton and that it possesses a methyl group (*vide post*), those six vinyl hydrogens and six olefinic carbons exist as three, unconjugated disubstituted double bonds in 5. Stereochemistry of these three double bonds was inferred to be *cis* based on the fact that there were no prominent bands around the region of 970 cm^{-1} (δ_{C-H} due to *trans*-disubstituted olefin) in the IR spectrum (partial structure (II)). Further, the presence of an ethyl group (III) on a double bond was deduced by ^{1}H- and ^{13}C-NMR spectral evidence.

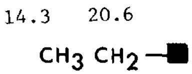
Among fifteen carbons in 5, thirteen carbons were characterized (partial structures: I, II, III). Each of the remaining two carbons was readily assigned as a diallylic methylene carbon (a di-π-methane carbon), considering their ^{1}H- and ^{13}C-NMR spectral properties [partial structure (IV)]. Thus the structure of laurencenyne was deduced to be 5.



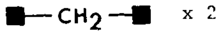
(I)



(II)



(III)



(IV)

Structure of neolaurencenyne 6.

Comparison of the spectral properties of laurencenyne 5 and neolaurencenyne 6 suggested that they were closely related and that the latter was a dihydro compound of the former. Catalytic hydrogenation of neolaurencenyne 6 afforded n-pentadecane, as in the case of laurencenyne 5. The presence of the partial structure (I) in neolaurencenyne 6 was deduced based on the spectral data. From the ^{1}H- and ^{13}C-NMR and IR spectral findings there must exist two unconjugated cis-disubstituted double bonds in 6. Since the chemical shift due to H-5 (partial structure (I)) of 6 was identical with that of the corresponding signal of laurencenyne 5, the methylene carbon (C-5) of the partial structure (I) in 6 was deduced to be adjacent to an olefinic carbon (C-6). In the ^{1}H-NMR spectrum of 6 there was observed a multiplet (2H) at δ 2.83 due to diallylic methylene protons. Above findings clearly defined the location of two cis-disubstituted double bonds in the linear pentadecane skeleton, and the structure of neolaurencenyne was deduced to be 6.

Syntheses of laurencenyne 5 and neolaurencenyne 6.

In order to confirm unambiguously the structures of laurencenyne 5 and neolaurencenyne 6, syntheses of laurencenyne and neolaurencenyne were performed as follows.
The coupling reaction of 1-bromo-2,5-octadiyne 7[13)] with the Grignard reagent 8[14)] (1.8 equiv) in the presence of CuCl (0.2 equiv) in dry THF under reflux for 4 h afforded the triyne 9[15a)] (67%), which was reduced by hydrogen (1 atm) over Lindlar catalyst (deactivated by quinoline) in benzene (room temp., 7 h) to give the desired all cis-triene 10[15a)] (68%). Exposure of 10 to methanolic d-camphorsulfonic acid (room temp., 45 min.) gave the triene alcohol 11[15a)] (98%), which was converted via sequential reaction with p-toluenesulfonyl chloride - pyridine (0 °C, 4.5 h) and sodium iodide - acetone (room temp., 12 h) to the triene iodide 12[15a)] (78% overall yield) and thence with triphenylphosphine (2.4 equiv) in acetonitrile (40 °C,36 h) into the desired phosphonium salt 13[15b)] (92%). Reaction of the phosphonium salt 13 with n-butyllithium (1.2 equiv) in THF containing HMPT (10 equiv) (-78 °C, 20 min.) gave the corresponding ylide solution, which was treated with propargylaldehyde (1.2 equiv) at -78 °C for 1 h and then at room temperature for 1 h. Extractive isolation and chromatography on silica gel with hexane afforded as the major product laurencenyne 5[15a,16)] (29%).
The stereochemical assignment of the newly formed double bond (C-3) in synthetic 5 was confirmed to be cis from the coupling constant ($J_{3,4}$=10 Hz) of H-4 (δ 5.98) in the ^{1}H-NMR spectrum.[16)] Preparative GLC gave pure synthetic laurencenyne 5[5)] as colorless liquid, which was completely identical with natural 5 in all respects (IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectra, HPLC and GLC retention times[6)] and TLC mobility).
Neolaurencenyne 6 was also synthesized by essentially the same procedure as described above. (3Z,6Z)-3,6-Dodecadien-1-ol 14[17)] was converted via sequential reaction with p-toluenesulfonyl chloride - pyridine and sodium iodide in acetone to the iodide 15[15a)] and thence with triphenylphosphine (6 equiv) in acetonitrile into the desired phosphonium salt 16[15b)] (79%

7 X = Br
9 X = C≡CCH$_2$CH$_2$O-THP

8

10 X = O-THP
11 X = OH
12 X = I
13 X = P$^+$Ph$_3$I$^-$

14 X = OH
15 X = I
16 X = P$^+$Ph$_3$I$^-$

overall yield), which was subjected to the Wittig reaction with propargylaldehyde (1.2 equiv) to give, after chromatography on silica gel, neolaurencenyne 6 15a) (30%). Synthetic and natural neolaurencenyne 6 were proved to be identical by comparison of the spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, and MS) and chromatographic behavior (HPLC and GLC 7) retention times and TLC mobility). The unambiguous syntheses of laurencenyne 5 and neolaurencenyne 6 confirm fully the structural and stereochemical assignment discussed above.

Biogenetic significance of the isolation of laurencenyne 5 is apparent: laurencenyne 5 might be an intermediate in the earlier stage of the biosynthetic pathway to various halogenated cyclic ethers than laurediols (3 and 4). Previously, laurinterol and debromolaurinterol were reported to be characteristic major metabolites of Laurencia okamurai collected at various places in Japan: 18) although laurinterol was isolated from L. okamurai employed in the present study, it was a minor component (0.002%) and the major metabolite was found to be a chamigrane-type compound, prepacifenol 19) (0.03%).

Acknowledgments. The authors are grateful to Professor W. Kida, Mie University, for identification of the alga. Financial support from the Ministry of Education, Science, and Culture (Grant-in-aid for Scientific Research No. 447025) is gratefully acknowledged.

REFERENCES AND NOTES

1. Review: a) D. J. Faulkner, Tetrahedron, **33**, 1421 (1977); b) R. E. Moore in "Marine Natural Products", Vol. I, P. J. Scheuer, Ed., Academic Press, Inc., New York, 1978, Chapter 2.
2. a) T. Irie, M. Suzuki, and T. Masamune, Tetrahedron Lett., 1091 (1965); b) T. Irie, M. Suzuki, and T. Masamune, Tetrahedron, **24**, 4193 (1968); c) A. F. Cameron, K. K. Cheung, G. Ferguson, and J. M. Robertson, Chem. Commun., 638 (1965).
3. S. M. Waraszkiewicz, H. H. Sun, and K. L. Erickson, Tetrahedron Lett., 3021 (1976).
4. E. Kurosawa, A. Fukuzawa, and T. Irie, Tetrahedron Lett., 2121 (1972).
5. Conditions: a column of 6 mm x 1.5 m of 10% SILAR 10C, 135 °C, He flow rate 65 ml/min..
6. The retention time was 6.5 min. under the conditions employed. 5)
7. The retention time was 4.7 min. under the conditions employed. 5)
8. Satisfactory exact mass spectral data were obtained.
9. A signal due to C-2 was not observed.
10. T. Irie, M. Izawa, and E. Kurosawa, Tetrahedron, **26**, 851 (1970).
11. a) B. M. Howard, W. Fenical, K. Hirotsu, B. Solheim, and J. Clardy, Tetrahedron, **36**, 171 (1980). b)S. M. Waraszkiewicz, H. H. Sun, K. L. Erickson, J. Finer, and J. Clardy, J. Org. Chem., **43**, 3194 (1978).
12. J. J. Sims, A. F. Rose, and R. R. Izac in "Marine Natural Products", Vol. II, P. J. Scheuer, Ed., Academic Press, Inc., New York, 1978, Chapter 5.
13. A. A. Kraevskii, M. G. Pleshakov, I. K. Sarycheva, and N. A. Preobrazhenskii, Zh. Obshch. Khim., **33**, 1835 (1963); J. Gen. Chem. USSR, **33**, 1787 (1963).
14. Prepared in situ from 1-tetrahydropyranyloxy-3-butyne and EtMgBr in dry THF.
15. a) Satisfactory IR, ^{1}H-NMR, ^{13}C-NMR, MS, and exact MS spectral data were obtained using purified, chromatographically homogeneous samples; b) Satisfactory IR and ^{1}H-NMR spectral data were obtained for each compound, which was used for the next reaction without further purification.
16. The C-3 trans isomer (17) of 5 was also obtained as the minor product (5%) in the Wittig reaction: a very strong band was observed at 960 cm^{-1} in the IR spectrum (film); the H-4 signal of this isomer was observed at δ 6.25 as a doublet of doublets ($J_{3,4}$=16 Hz and $J_{4,5}$=6.5 Hz).

17

17. T. Kajiwara, J. Sekiya, Y. Odake, and A. Hatanaka, Agr. Biol. Chem., **41**, 1481 (1977).
18. M. Suzuki and E. Kurosawa, Bull. Chem. Soc. Jpn., **52**, 3352 (1979).
19. J. J. Sims, W. Fenical, R. M. Wing, and P. Radlick, J. Am. Chem. Soc., **95**, 972 (1973).

(Received in Japan 17 August 1981)