Pergamon

*Tetrahedron*, Vol. 53, No. 12, pp. 4271-4278, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00153-1

# Scanlonenyne, a Novel Halogenated $C_{15}$ Acetogenin from the Red Alga *Laurencia obtusa* in Irish Waters

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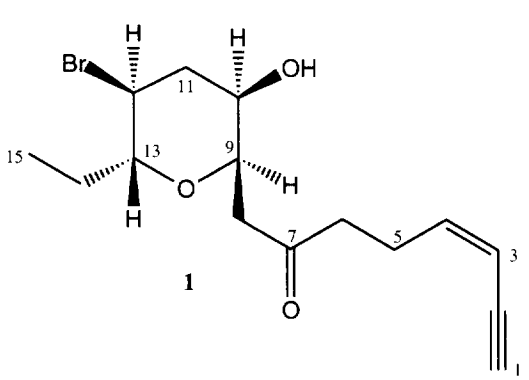
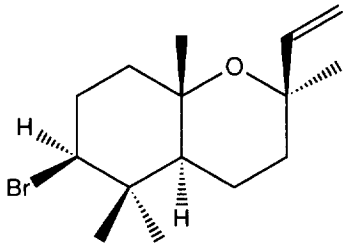
**Abstract:** A novel halogenated acetogenin with a ketonic moiety at C-7, named scanlonenyne, has been isolated from the red alga *Laurencia obtusa* collected in Irish waters. Its structure was determined by spectroscopic data. © 1997 Elsevier Science Ltd.

Species of the red algal genus *Laurencia* produce diverse halogenated secondary metabolites.[1,2] As species discrimination in *Laurencia* is complicated by high degree of morphological variation within individual species, halogenated secondary metabolites are considered to be a useful taxonomic feature at the species level.[3] *Laurencia obtusa* (Hudson) Lamouroux is widely distributed in the world and has been investigated for populations in England,[4,5] Italy,[6-10] Greece,[11] Turkey,[12-14] Spain,[15-20] Jamaica,[21,22] the Canary Isls,[23-27] the Aegean Sea,[28-31] the Red Sea,[32] California[11] and Japan.[33-38] *Laurencia obtusa* is a prolific source of diverse halogenated compounds, sesquiterpenes, diterpenes, triterpenes and $C_{15}$ acetogenins.

In our continuing chemotaxonomic studies[3] on species of genus *Laurencia*, we collected *L. obtusa* from Scanlon's Island, the western coast of Ireland. This sample contained a novel halogenated metabolite **1**, which we named scanlonenyne, along with a known halogenated sesquiterpene, 3β-bromo-8-epicaparrapi oxide (**2**), which has previously been obtained from the same species collected at Kimmeridge Bay, Dorset.[4]




**1**




**2**

We wish to report herein the isolation and structural elucidation of scanlonenyne (**1**) in full detail. This paper is the first report on chemical constituent from species of *Laurencia* found in Irish waters.

A combination of column and thin-layer chromatography of methanol extracts has led to the isolation of scanlonenyne (**1**) in 2.1% yield based on the extracts along with 3β-bromo-8-epicaparrapi oxide (**2**) (4.9%). Scanlonenyne (**1**), mp 80-81° (from pentane), $[\alpha]_D^{22}$ +40.8° (*c* 0.36; $CHCl_3$), was shown to have the molecular formula of $C_{15}H_{21}BrO_3$ on the basis of $^1H$ and $^{13}C$ NMR spectra as well as LR-FIMS and HR-EIMS. The IR spectrum showed the presence of hydroxyl ($\nu_{max}$ 3550 $cm^{-1}$), acetylenic ($\nu_{max}$ 3320 and 2100 $cm^{-1}$) and carbonyl ($\nu_{max}$ 1715 $cm^{-1}$) functionalities. The presence of a 2-penten-4-ynyl moiety, which is frequently encountered in *Laurencia*'s $C_{15}$ acetogenins, was readily recognized by $^1H$ NMR spectrum (δ 3.12 (1H, *br d*, *J*=2.0 Hz), 5.48 (1H, *ddd*, *J*=10.7, 2.0, 1.0 Hz) and 6.00 (1H, *ddd*, *J*=10.7, 6.8, 6.8 Hz)). The geometry of the double bond was evident to be *Z*-configuration from the chemical shift (δ 3.12) of the acetylenic proton and *J*-values (10.7 Hz, each) of the olefinic protons.[39] Combination of $^1H$ and $^{13}C$ NMR, $^1H$-$^1H$ COSY and HSQC experiments established the presence of partial structural units **A**-**D** (Figure 1). In

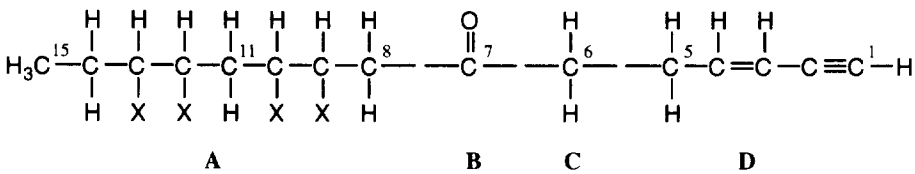



Figure 1. Partial structural units for scanlonenyne (**1**).

the $^{13}C$ NMR spectrum, the chemical shift (δ 47.68) of the methine carbon at C-12 in unit **A** indicated that a bromine atom is attached to this carbon. Therefore, in the unit **A**, the remaining substituents at C-9, C-10 and C-13 are oxygen atoms. In the $^1H$ NMR spectrum, the signal of the methine proton at C-10, which was observed as *dddd*, was changed into *ddd* by addition of $D_2O$, indicating that a hydroxyl group is attached to C-10. Connectivity of unit **C** was unable to be determined directly because of the overlap of two methylene signals at 2.58—2.68 (4H, *m*) in deuterated chloroform. Thus the $^1H$ NMR spectrum was measured in deuterated benzene. In this spectrum the overlapping two methylenes were observed separately at δ 2.55 (2H, *dddd*, *J*=14.7, 7.3, 7.3, 1.5 Hz; $H_2$-5), 2.10 (1H, *ddd*, *J*=17.6, 7.3, 7.3 Hz; H-6) and 2.00 (1H, *ddd*, *J*=17.6, 7.3, 7.3 Hz; H-6), whose signals showed a correlation in the $^1H$-$^1H$ COSY spectrum, establishing connection of unit **C** with unit **D**. Scanlonenyne (**1**), which has five degrees of unsaturation, must contain one oxide ring.

Confirmation of the partial structural units and determination of their connectivities were aided by HMBC experiments (Table 1). A long range correlation between the carbon at δ 70.56 (C-9) and methine protons at δ 3.60 (H-13) and a correlation between the carbon at δ 77.25 (C-13) and methine proton at 4.44 (H-9) confirmed connection of C-9 with C-13 through oxygen atom to form a tetrahydropyran ring system. Furthermore, correlations between the carbonyl carbon at δ 208.47 and methylene protons at δ 2.79 and 2.87 ($H_2$-8), methine proton at δ 4.44 (H-9) and methylene protons at δ 2.58–2.68 ($H_2$-6 and/or $H_2$-5) confirmed connection of unit **B** with units **A** and **C**. Thus, the planar structure **1** was unambiguously assigned for scanlonenyne.

Table 1. $^{13}C$ NMR (100 MHz, DEPT), $^{1}H$ NMR (400 MHz) and HMBC data[a] for **1**

| C[b] | $^{13}C$ δ | $^{1}H$ δ | *J* (Hz) | long range correlations |
|---|---|---|---|---|
| 1 | 80.61 | 3.12 | *br d*, *J*=2.0 | |
| 2 | 82.28 | | | H-3 |
| 3 | 109.40 | 5.48 | *ddd*, *J*=10.7, 2.0, 1.0 | H-1, H-4, $H_2$-5 |
| 4 | 143.64 | 6.00 | *ddd*, *J*=10.7, 6.8, 6.8 | $H_2$-5 and/or $H_2$-6 |
| 5 | 24.29 | 2.6[c] | *m* | H-3, H-4, $H_2$-6 |
| 6 | 42.37 | 2.6[c] | *m* | H-4, $H_2$-6 |
| 7 | 208.47 | | | $H_2$-5 and/or $H_2$-6, $H_2$-8, H-9 |
| 8 | 41.20 | 2.87 | *dd*, *J*=16.6, 6.4 | $H_2$-6, H-9 |
| | | 2.79 | *dd*, *J*=16.6, 6.8 | |
| 9 | 70.56 | 4.44 | *ddd*, *J*=6.8, 6.4, 4.4 | $H_2$-8, $H_2$-11, H-13 |
| 10 | 67.12 | 3.92 | *dddd*, *J*=8.8, 4.8, 4.4, 4.0 | $H_2$-8, $H_2$-11, H-12 |
| 11 | 37.00 | 2.49 | *ddd*, *J*=14.2, 4.8, 4.4 | H-9, H-12, H-13 |
| | | 2.15 | *ddd*, *J*=14.2, 8.8, 8.8 | |
| 12 | 47.68 | 3.85 | *ddd*, *J*=8.8, 7.3, 4.4 | $H_2$-11, $H_2$-14 |
| 13 | 77.25 | 3.60 | *ddd*, *J*=8.8, 7.3, 3.4 | H-9, $H_2$-11, $H_2$-14, $H_3$-15 |
| 14 | 24.95 | 1.83 | *ddq*, *J*=14.2, 3.4, 7.3 | H-15, $H_3$-17 |
| | | 1.56 | *ddq*, *J*=14.2, 8.8, 7.3 | |
| 15 | 9.77 | 0.92 | *t*, *J*=7.3 | H-13, $H_2$-14 |
| OH | | 2.49 | *d*, *J*=4.0 | |

[a]Measured in chloroform-$d_1$.
[b]Assignment was made with the aid of HSQC spectrum.
[c]Four protons overlap at δ 2.58–2.68.

The relative configurations of the four asymmetric centers were determined through coupling constants of the $^{1}H$ NMR data. As shown in Figure 2, the $^{1}H$ NMR spectrum of **1** showed coupling constants with $J_{9,10}$=4.4 Hz, $J_{10,11\alpha}$=4.8 Hz, $J_{10,11\beta}$=8.8 Hz, $J_{11\alpha,12}$=4.4 Hz, $J_{11\beta,12}$=8.8 Hz and $J_{12,13}$=7.3 Hz, thus revealing that the tetrahydropyran ring adopts a typical chair conformation, on which hydroxyl, bromine atom and ethyl substituents are equatorial while $C_8$ side chain at C-9 is axial. These relative stereochemistries were also confirmed by the NOESY spectrum, which showed NOEs between $H_2$-8/$H_{ax}$-11, $H_2$-8/H-13, H-10/H-9,

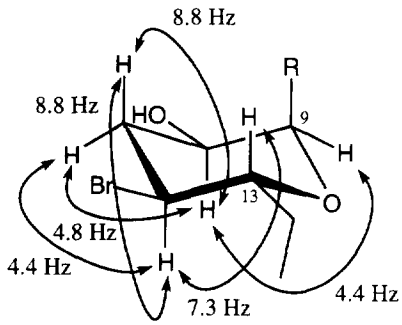
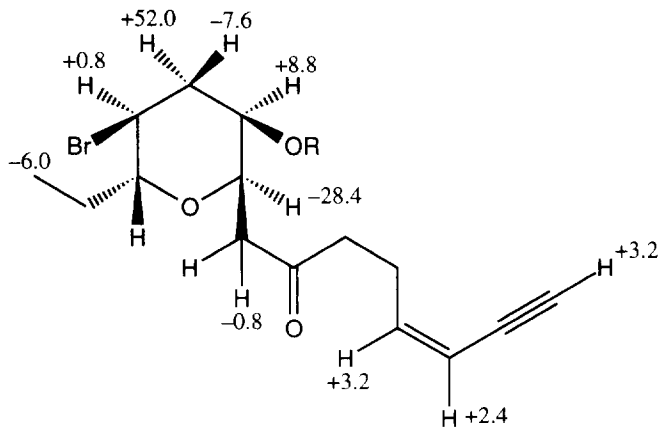



Figure 2. Coupling constants of the protons on oxane ring.

H-10/$H_{eq}$-11 and H-12/$H_{eq}$-11. Furthermore, the modified Mosher's method[40] was applied to determine the absolute configuration of the secondary hydroxyl group at C-10. Scanlonenyne (**1**) was transformed to (*S*)- and (*R*)-MTPA esters, **1a** and **1b**, respectively. The Δδ values ($\delta_S$–$\delta_R$) obtained from these MTPA esters are shown in Figure 3. However, the systematic arrangement of the values was unable to be observed. One of the

methylene protons at C-11 was opposite of what was expected. It appears that the MTPA ester plane can not adopt the ideal conformation probably due to the intramolecular interaction of the MTPA ester with carbonyl group and/or conjugated enyne moiety in the molecule. Hence the application of the Mosher's method was insufficient to determine the absolute configuration of the asymmetric center at C-10 of scanlonenyne (**1**).




R=(*S*)- or (*R*)-MTPA

Figure 3. $\Delta\delta$ values ($\delta_S$–$\delta_R$) of MTPA esters are shown in Hz (400 MHz).

Further examination to confirm the absolute configuration and to evaluate the biological activity could not be carried out since scanlonenyne was very unstable and a large amount of sample decomposed during storage in a refrigerator.

Many halogenated $C_{15}$ acetogenins isolated from various *Laurencia* species have been suggested to be derived from (6*S*,7*S*)- or (6*R*,7*R*)-laurediol.[41] The ketone group at C-7 in scanlonenyne may arise from an enol which would be formed also from laurediol by dehydration between the OH group at C-6 and H-7.

Consequently, the structure of scanlonenyne must be represented by formula **1**, which includes the relative configuration of 9*R**, 10*R**, 12*S** and 13*R**. Scanlonenyne is the first example of halogenated $C_{15}$ acetogenins from *Laurencia* species with a ketonic functionality at C-7 as well as no functional group at C-6.

As described above, a number of halogenated secondary metabolites which belong to four structural classes, sesquiterpenoid, diterpenoid, triterpenoid and $C_{15}$ acetogenin, have been reported from *L. obtusa* collected at many locations in the world. It has been pointed out that a species of *Laurencia* producing diverse haloganated secondary metabolites may include several, different species or varieties,[42,43] and such a case demands re-examination at the morphological level required for taxonomy. The situation in which a 'species' of *Laurencia* has been known to produce diverse secondary metabolites may involve the following four cases at present. (1) Such a 'species' includes a different entity (entities), that is (are) undescribed or poorly known, superficially similar in gross morphology to the identified 'species' as demonstrated for the alga passing under the name *L. pacifica* Kylin in the Gulf of California[42] and for *L. okamurae* Yamada and *L. composita* Yamada in Japan.[3e] (2) Several "sibling species", which are morphologically identical, but chemically distinct, are involved in such a 'species' as reported for *L. pacifica* distributed along the coast of California.[43] (3) Misidentification of a species resulted in the alga passing under the name *L. obtusa* in Japan

when it was actually *L. saitoi* Perestenko.[38] (4) Several "chemical races" are included in a single species as in *L. nipponica* Yamada.[44] In consequence, re-examination of morphological features of the aforementioned populations of *L. obtusa* is apparently needed.

## EXPERIMENTAL

**General.** The IR spectrum was measured on a JASCO IR-700 spectrophotometer. The $^1H$ and $^{13}C$ NMR spectra were obtained in $CDCl_3$ or $C_6D_6$ solution, with TMS as the internal standard by using a JEOL JNM-EX-400 spectrometer. The low and high resolution EI mass spectra were recorded on a JEOL JMS-DX303 spectrometer. Optical rotation was measured on a JASCO DIP-140 polarimeter. Silica gel (Merck, Kieselgel 60, 70—230 mesh) was used for column chromatography. Silica-gel plate (Merck, Kieselgel 60 $F_{254S}$) was used for preparative thin-layer chromatography.

**Collection, extraction and isolation.** *Laurencia obtusa* (Hudson) Lamouroux was collected at Scanlon's Island, Co. Clare, on May 6, 1993. Voucher specimens are deposited in the Herbarium of the Graduate School of Science, Hokkaido University (SAP 061954). The dried alga (77 g) was extracted with methanol and the methanol solution was concentrated *in vacuo* and partitioned between ether and water. The ethereal solution was washed with water, dried over anhydrous $Na_2SO_4$ and evaporated to leave a green oil (1.08 g). The extracts were fractionated by silica-gel column chromatography with a step gradient (hexane and ethyl acetate). The fraction eluted with hexane–ethyl acetate (9:1) was further chromatographed on a thin-layer plate with hexane-ethyl acetate (9:1) to give **2** as a colorless oil (50 mg), which was identified as 3β-bromo-8-epicaparrapi oxide by comparison of IR, $^1H$ NMR and mass spectral data together with optical rotation with those reported in the literature.[4] The fraction eluted with hexane–ethyl acetate (1:1) was further submitted to preparative thin-layer chromatography with toluene–ethyl acetate (4:1) to yield scanlonenyne (**1**) (20 mg).

**Scanlonenyne (1):** Mp 80-81° (pentane); $[\alpha]_D^{20}$ +40.8° (*c* 0.36); IR ($CHCl_3$), $\nu_{max}$ 3550, 3320, 3020, 2100, 1715, 1430, 1410, 1380, 1260, 1230, 1205, 1070, 930, 700 and 720 $cm^{-1}$; $^1H$ and $^{13}C$ NMR ($CDCl_3$), Table 1; $^1H$ NMR ($C_6D_6$), δ 0.86 (3H, *t*, *J*=7.3 Hz; $H_3$-15), 1.36 (1H, *m*; H-14), 1.72 (1H, *m*; H-14), 1.85 (1H, *ddd*, *J*=13.2, 10.3, 10.3 Hz; H-11), 2.00 (1H, *ddd*, *J*=17.6, 7.3, 7.3 Hz; H-6), 2.10 (1H, *ddd*, *J*=17.6, 7.3, 7.3 Hz; H-6), 2.10 (1H, *ddd*, *J*=13.2, 4.2, 4.2 Hz; H-11), 2.30 (1H, *dd*, *J*=16.1, 6.8 Hz; H-8), 2.39 (1H, *dd*, *J*=16.1, 6.4 Hz; H-8), 2.55 (2H, *dddd*, *J*=14.7, 7.3, 7.3, 1.5 Hz; $H_2$-5), 2.79 (1H, *br d*, *J*=2.0 Hz; H-1), 3.32–3.38 (3H, *m*; H-10, H-12 and H-13), 4.30 (1H, *br ddd*, *J*=6.8, 6.4, 5.4 Hz; H-9), 5.33 (1H, *dddd*, *J*=10.7, 2.4, 1.5, 1.0 Hz; H-3) and 5.68 (1H, *dddd*, *J*=10.7, 7.3, 7.3, 1.0 Hz; H-4); LR-FIMS (70eV), *m/z* (rel intensity) 330, 328 (100:83; $M^+$), 313, 311 (36:32; $M^+$–OH); LR-EIMS (70eV), *m/z* (rel intensity) 312, 310 (0.4:0.4; $M^+$–$H_2O$), 247, 245 (7.3:7.7; $M^+$–$C_5H_5$), 229 (12), 227 (13), 165 (44), 148 (45), 133 (38), 107 (83), 81 (92), 79 (100), 77 (86), 65 (63), 57 (65) and 41 (94); HR-EIMS, *m/z* 310.0547. Calcd for $C_{15}H_{19}{}^{79}BrO_2$, 310.0568 [M–$H_2O$].

**Preparation of (*S*)-MTPA ester of scanlonenyne (1).** (*S*)-MTPA ester was prepared by using (–)-MTPA instead of (–)-MTPA chloride.[45] A solution of **1** (1.0 mg) in dry methylene chloride (0.5 mL) was

treated with (–)-MTPA (2.2 mg), dicyclohexylcarbodiimide (11.6 mg) and 4-dimethylaminopyridine (2.1 mg), and the mixture was allowed to stand at room temperature for 50 h and evaporated to dryness. The residue was chromatographed on a silica-gel plate with toluene–ethyl acetate (4:1) to afford pure (*S*)-MTPA ester **1a** (1.0 mg); $^1$H NMR ($CDCl_3$), δ 0.871 (3H, *t*, *J*=7.3 Hz; $H_3$-15), 1.935 (1H, *ddq*, *J*=14.6, 2.9, 7.3 Hz; H-14), 2.180 (1H, *ddd*, *J*=12.7, 11.2, 11.2 Hz; H-11), 2.619 (1H, *ddd*, *J*=12.7, 4.9, 4.9; H-11), 2.790 (1H, *dd*, *J*=16.1, 9.8 Hz; H-8), 3.096 (1H, *br d*, *J*=1.5 Hz; H-1), 3.752 (1H, *ddd*, *J*=11.2, 9.3, 4.9 Hz; H-12), 4.633 (1H, *ddd*, *J*=9.8, 4.9, 4.4 Hz; H-9), 5.218 (1H, *ddd*, *J*=11.2, 4.9, 4.9 Hz; H-10), 5.467 (1H, *dddd*, *J*=10.7, 1.5, 1.0, 1.0; H-3) and 5.942 (1H, *ddd*, *J*=10.7, 7.3, 7.3, 1.0 Hz; H-4).

**Preparation of (*R*)-MTPA ester of scanlonenyne (1).** (*R*)-MTPA ester was prepared according to the same procedure as in the case of preparation of (*S*)-MTPA ester **1a**. **1** (1.0 mg) was treated with (+)-MTPA (2.1 mg), dicyclohexylcarbodiimide (11.0 mg) and 4-dimethylaminopyridine (2.1 mg) in dry methylene chloride (0.5 mL) to yield pure (*R*)-MTPA ester **1b** (1.0 mg); $^1$H NMR ($CDCl_3$), δ 0.886 (3H, *t*, *J*=7.3 Hz; $H_3$-15), 1.924 (1H, *ddq*, *J*=14.6, 2.9, 7.3 Hz; H-14), 2.050 (1H, *ddd*, *J*=12.7, 11.2, 11.2 Hz; H-11), 2.638 (1H, *ddd*, *J*=12.7, 4.9, 4.9; H-11), 2.792 (1H, *dd*, *J*=16.1, 8.3 Hz; H-8), 3.088 (1H, *br d*, *J*=1.5 Hz; H-1), 3.750 (1H, *ddd*, *J*=11.2, 9.8, 4.9 Hz; H-12), 4.704 (1H, *ddd*, *J*=8.3, 5.4, 5.4 Hz; H-9), 5.196 (1H, *ddd*, *J*=11.2, 5.4, 5.4 Hz; H-10), 5.461 (1H, *dddd*, *J*=10.7, 1.5, 1.0, 1.0; H-3) and 5.944 (1H, *ddd*, *J*=10.7, 7.3, 7.3, 1.0 Hz; H-4).

## ACKNOWLEDGMENT

We are grateful to Dr. Ikuko I. Ohtani, Nagoya University, for valuable discussions on the results obtained from the modified Mosher's method.

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(*Received in Japan* 8 *January* 1997; *accepted* 3 *February* 1997)