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A Hypothesis Concerning the Biosynthesis of the Obtusallene Family of Marine Natural Products via Electrophilic Bromination

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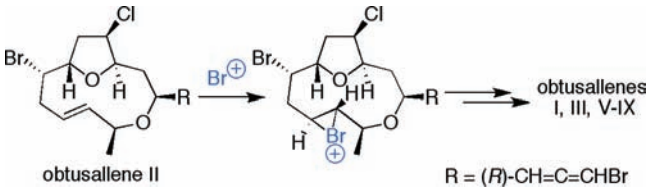
ABSTRACT



A hypothesis concerning the biosynthesis of the marine natural product family the obtusallenes is proposed. Multiple electrophilic bromination events are invoked.

Obtusallene I (**1**) (Figure 1) was reported in 1982 after isolation from the red algae *Laurencia obtusa* collected at Gökceada in the Aegean sea, and the structure was elucidated by NMR and by X-ray crystallographic methods.[1] Subsequently, 10-bromoobtusallene (**1a**),[2] obtusallenes II (**2**) and III (**3**),[3] obtusallene IV (**4**),[4,5] and obtusallenes V−IX (**5**−**9**) have all been reported.[6] The obtusallenes belong to a wider family of halogenated C_{15}-acetogenins isolated from red algae and seaweeds of the species *Laurencia*. Members of the wider family typically display a five- to nine-membered central acetogenic ring, with one bromine atom ***β*** to the acetogenic oxygen and an enyne or bromoallene unit.[7,8] In a series of experiments, Murai has shown that selected compounds can be derived from the straight-chain C_{15}-fatty acid derived lauredіol (**10**) via electrophilic bromoetherification.[9] Murai has also shown that the electrophilic bromine is generated enzymatically by the action of bromoperoxidase on bromide anion. Selected bromocyclizations in these systems have also been realized chemically.[10]

The obtusallenes are a subset of the family of metabolites isolated from *Laurencia* species, in that they are the only members of the family to be oxygenated at C_{14} and they contain a macrocyclic ring (we propose that these two facts are intimately related). With the exception of obtusallene IV, they all display a bromoallene unit with an *R* configuration (obtusallene IV is *S*) and the *S* C_4-configuration (*R* for obtusallene IV). The contiguous C_{15} chain of lauredіol **10** can be clearly identified in all of the obtusallenes as shown by the numbering on the structures. From the work of Murai, it seems reasonable to suggest that these compounds derive

(1) Cox, P. J.; Imre, S.; Islimyeli, S.; Thomson, R. H. *Tetrahedron Lett.* **1982**, *23*, 579−580.
(2) Öztunç, A.; Imre, S.; Wagner, H.; Norte, M.; Fernández, J. J.; González, R. *Tetrahedron* **1991**, *47*, 2273−2276.
(3) Öztunç, A.; Imre, S.; Lotter, H.; Wagner, H. *Phytochemistry* **1991**, *30*, 255−257.
(4) Guella, G.; Chiasera, G.; Mancini, I.; Öztunç, A.; Pietra, F. *Chem. Eur. J.* **1997**, *3*, 1223−1231.
(5) Ciavatta, M. L.; Gavagnin, M.; Puliti, R.; Cimino, G.; Matínez, E.; Ortea, J.; Mattia, C. A. *Tetrahedron* **1997**, *53*, 17343−17350.
(6) Guella, G.; Mancini, I.; Öztunç, A.; Pietra, F. *Helv. Chim. Acta* **2000**, *83*, 336−348.
(7) For a recently isolated member of the wider family, see: Aydogmus, Z.; Imre, S.; Ersoy. L; Wray, V. *Nat. Prod. Res.* **2004**, *18*, 43−49.
(8) For a recent synthesis of a member of the wider family, (+)-obtusyne, see: Crimmins, M. T.; Powell, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 7592−7595.
(9) Murai, K. In *Comprehensive Natural Product Chemistry*; Barton, D. H. R., Meth-Cohn, O., Nakanishi, K., Eds.; Pergamon: Elmsford, NY, 1999; Vol. 1, pp 303−324.
(10) Ishihara, J.; Shimada, Y.; Kanoh, N.; Takasugi, Y.; Fukuzawa, A.; Murai, A. *Tetrahedron* **1997**, *53*, 8371−8382.

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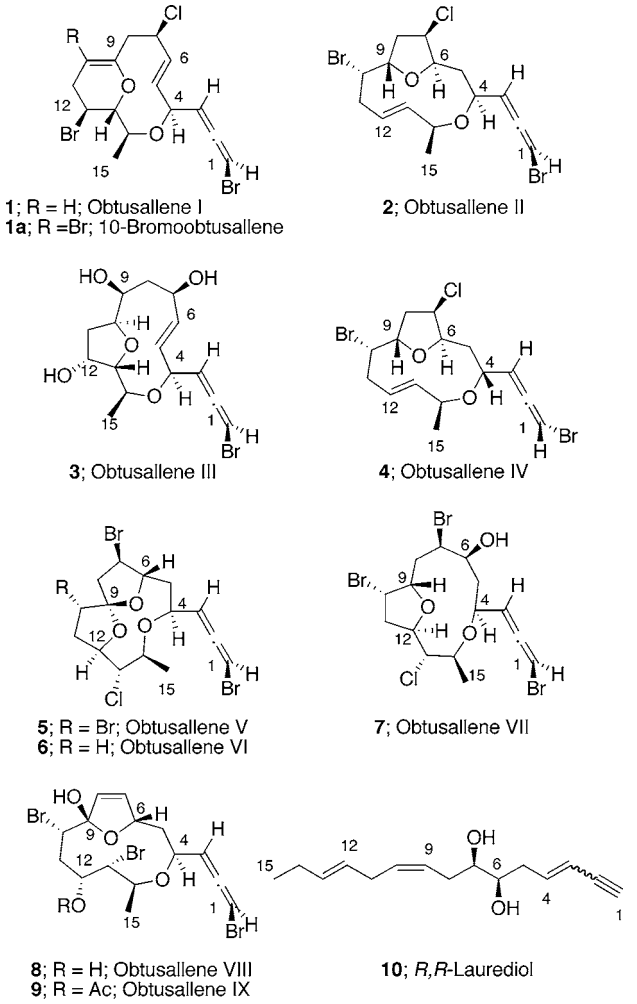
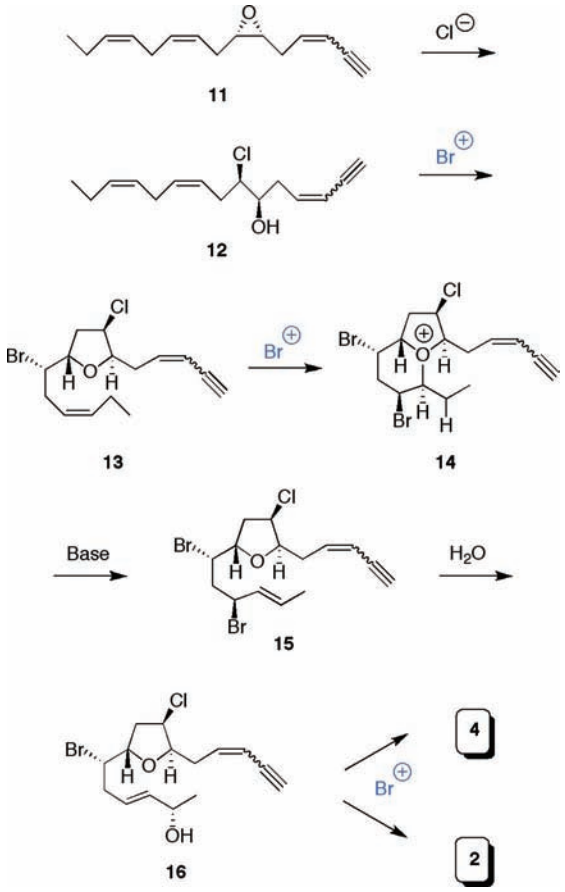


Figure 1. Obtusallene family.

from laurediol **10** (or a closely related precursor) and electrophilic bromination events. To date, however, no synthesis (or partial synthesis) of any obtusallene has been reported, and no biosynthetic hypotheses for the obtusallenes has been suggested.

Murai has concisely summarized the possible biosynthetic origins of laurediol supported by the isolation of various acyclic polyunsaturated compounds, ultimately leading back to *Z*,*Z*,*Z*-hexadeca-4,7,10-trienoic acid.[9] A key intermediate en route to laurediol has been suggested to be (Z)-6,7-epoxide **11**. Laurediol **10** can then be obtained by ring-opening of the epoxide with water. Our hypothesis commences with nucleophilic ring-opening of the epoxide **11** with chloride anion instead to provide *threo*-hydroxychloride **12** (Scheme 1). Subsequent bromonium ion formation at the C_9-C_{10} olefin followed by a 5-*exo* cyclization creates the tetrahydrofuran ring of **13**. A *second* bromonium ion formation at $C_{12}-C_{13}$ with an intramolecular attack of the nucleophilic oxygen of the tetrahydrofuran ring gives intermediate oxonium ion **14**, which can fragment to give the allylic bromide **15**. S_N2' displacement with water gives the C_{14}-alcohol **16**.[11] A subsequent delivery of a *third* electrophilic bromine to

Scheme 1. Proposed Biosynthesis of Obtusallenes II and IV



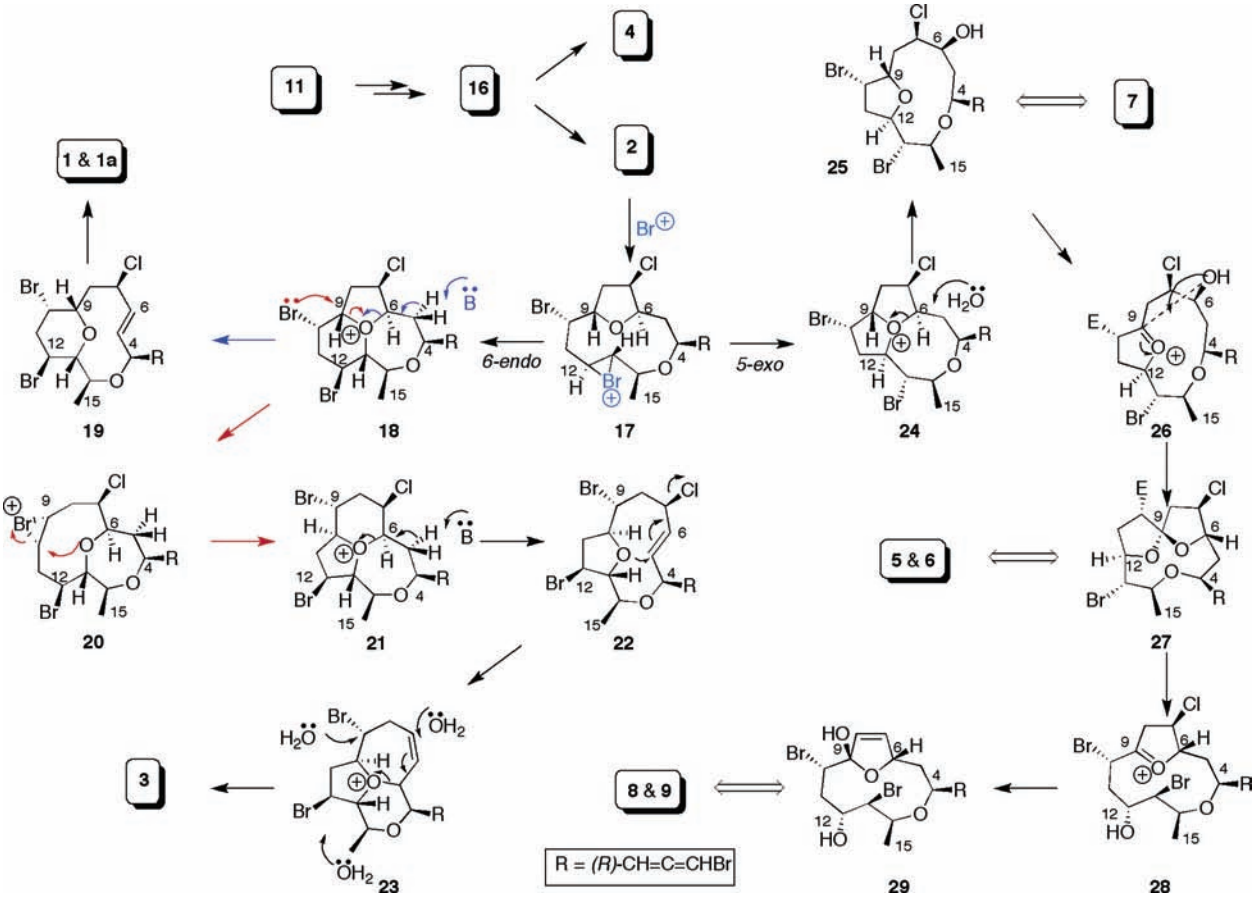
the enyne at C_1 allows for a macrobromoetherification with the newly created hydroxy group at C_{14} acting as the nucleophile attacking C_4. This step is particularly attractive since it simultaneously creates both the macrocycle and the bromoallene motif. We propose that this macrocyclisation is controlled by a gauche conformation of the bromo ether motif at C_9-C_{10} to preorganize the allylic alcohol side-chain for nucleophilic attack at C_4. Moreover, attack on one face of the enyne would lead to obtusallene IV (**4**), attack on the other would give obtusallene II (**2**).[12] The hypothetical overall transformation of epoxide **11** into obtusallenes II and IV therefore requires only chloride anion, electrophilic bromine, a nominal base, and water. Further, we herein propose that obtusallene II (**2**) is the biosynthetic precursor of all the remaining obtusallenes and they all derive from a common *fourth* bromination event (vide infra).

Inspection of the known X-ray crystal structure for obtusallene II (**2**) shows that the closest transannular contact

(11) One reviewer suggested that this process may occur with participation of the tetrahydrofuran oxygen atom.

(12) The overall stereochemical outcome (presumably stereoelectronically controlled) of the bromoetherification of enynes remains to be defined in the literature. The required stereochemistries of the obtusallene bromoallenes could arise *either* by *syn* addition to an *E*-enyne or by *anti* adddition to a Z-enyne. Since laurediol has been isolated with both *E* and *Z* enyne configurations (see: Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1972**, *13*, 2121−2124), this is an issue that will require experimental determination.

Scheme 2. Proposed Biosynthetic Conversion of Obtusallene II into the Other Obtusallenes



is between the THF ether oxygen and C_{12} at 2.79(2) Å. It seems reasonable to suggest that further bromonium ion formation could occur on the *exo* face of $C_{12}-C_{13}$ *trans* olefin of obtusallene II (**2**) followed by transannular attack of the THF ether oxygen. Exploring this postulate and allowing the THF oxygen to attack at either end of the $C_{12}-C_{13}$ bromonium ion **17** via a *6-endo* (C_{13}) or *5-exo* (C_{12}) process gives rise to two different tricyclic oxonium ions (Scheme 2). For the *6-endo* process, stereospecific bromonium ion ring-opening generates oxonium ion **18** with three contiguous chiral centers at $C_{12}-C_{14}$ with the same relative and absolute configurations reported (and confirmed by X-ray crystallography) for the $C_{12}-C_{14}$ fragment of obtusallene I (**1**). Fragmentation (blue pathway) can occur by *anti*-periplanar elimination of the pseudo-equatorial proton at C_5 to give pyran **19** with a new *E*-double bond at C_5-C_6. Subsequent facile *anti*-periplanar elimination of HBr across C_9-C_{10} gives rise to obtusallene I (**1**)[1] where all the stereochemistry is correctly set; *anti*-periplanar elimination of equatorial bromide from C_{12} cannot occur. 10-Bromoobtusallene (**1a**)[2] can be generated by further bromination of the reactive newly formed C_9-C_{10} enol ether of **1** at C_{10} followed by loss of a proton and regeneration of the (bromo)enol. Alternatively, from **18** (red pathway) fragmentation can occur by the participation of the *anti*-periplanar bromide at C_{10}, to form a new bromonium ion **20**. The newly formed ether oxygen can reattack at C_9 (to regenerate **18**) or attack at C_{10} to invert the stereochemistry at this position and stereospecifically relocate the bromine at C_9 giving **21**. *Anti*-periplanar fragmentation reveals new *trans* olefin **22** and a new tetrahydrofuran spanning C_{10} to C_{13}. Transannular attack of the new tetrahydrofuran oxygen on the allylic chloride generates new tricyclic oxonium ion **23**: attack by water, and invoking the principle of microscopic reversibility, generates the *R*-alcohol at C_7 and a *trans* olefin at C_5-C_6. Double S_N2 displacement of the two bromides at C_9 and C_{12} of with water with inversion of configuration gives obtusallene III (**3**), where the relative and absolute stereochemistries have been secured by X-ray crystallography.[3] It is clear that this mechanistic scheme successfully rationalizes the formation of obtusallene I (**1**), 10-bromoobtusallene (**1a**), and obtusallene III (**3**) using a common bromination event and subsequent rearrangement and correctly predicts the known stereochemistry.

For the *5-exo* process, attack of the THF ether oxygen at C_{12} in **17** gives rise to tricyclic intermediate **24**. In this case, molecular modeling reveals that there are no *anti*-periplanar groups available to initiate a fragmentation. Instead, S_N2 attack by water with inversion of configuration at C_6 (an *S* configuration at C_6 for obtusallenes is a signature for this) leads directly to bicyclo[8.2.1]tridecane **25**. This has the same carbon framework and identical absolute and relative stere-

ochemistries for all eight stereocenters as reported for obtusallene VII (**7**)[6] (structure deduced by ^{1}H NMR). However, the relative position of the chlorine and bromine atoms at C_7 and C_{13}, respectively, are interchanged. *Anti*-periplanar elimination of HBr from **25** across C_9-C_{10} (*anti*-periplanar elimination of bromide from C_{13} cannot occur), followed by electrophilic bromination or protonation (E = H, Br) of the resulting enol ether gives rise to intermediate **26**. This is subject to intramolecular attack by the new hydroxyl group at C_6 generating spiroketal **27**. The two possible products (E = H, Br) correspond to the correct carbon framework and identical absolute and relative configuration for all eight stereocentres reported for obtusallene V (E = Br) (**5**) and VI (E = H) (**6**).[6] However, once again, the C_7 and C_{13} chlorine and bromine are seen to be interchanged. Finally, collapse of the spiroketal in the opposite sense with liberation of the alcohol at C_{12} generates intermediate **28**. Capture by water and elimination of HCl gives **29** with the carbon framework as reported for obtusallene VIII (**8**).[6] In this case, the predicted constitution is correct but the stereochemistry at C_{13} is inverted. Acetylation of the free secondary alcohol gives obtusallene IX (**9**).

In conclusion, we have proposed an internally self-consistent hypothesis for the biosynthesis of the obtusallene family. Multiple electrophilic bromination events are invoked. The hypothesis correctly predicts the stereochemistries of obtusallenes I−IV whose structures have been unambiguously solved by X-ray crystallography. Interestingly, while the published structures of obtusallenes V−VII—as solved by NMR spectroscopy—show a bromine atom at C_7 and a chlorine atom at C_{13}, the hypothesis predicts that the obtusallenes V−VII should bear the bromine atom at C_{13} and the chlorine atom at C_7. Therefore, there is a need to investigate these bromonium ion-driven interconversions experimentally in order to confirm or correct the reported structures and to elucidate the biosynthetic pathway.

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