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BIOMIMETIC SYNTHESIS OF MARINE NATURAL PRODUCTS

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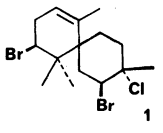
Abstract—The biosynthetic pathways to many halogenated marine natural products are based on bromonium ion initiated cyclisation reactions. We have shown that a bromonium ion initiated cyclisation reaction can be employed as the basis of a synthesis of 10-bromo-α-chamigrene from geranyl acetone in four steps. The stereochemistry of the product appears to be identical to that of a sample prepared from a natural product.

The most striking feature of the marine natural products literature is the frequency with which halogenated compounds have been described. At the time of writing this paper, we were aware of over 140 marine natural products which contain covalently bound halogen atoms. The majority of the halogenated marine metabolites contain bromine, with some of these compounds containing both bromine and chlorine, but relatively few compounds contain only chlorine and even fewer contain iodine.[1]

Since seawater is a halogen-rich environment, it is not surprising that marine organisms are capable of the synthesis of halogenated metabolites. However, it is remarkable that brominated compounds seem to be more abundant than chlorinated compounds, since seawater contains a much higher concentration of chloride ion [19,000 g/m^3] than of bromide ion [65 g/m^3]. It is possible that future research may reverse this generalisation, which is based on a small number of compounds reported by investigators who have often concentrated on those genera of marine organisms from which brominated metabolites had previously been obtained. Yet the selective manner of incorporation of chlorine and bromine into organic molecules which contain both halogens indicates a general ability of marine organisms to differentiate between halide ions during biosynthesis.

Sesquiterpenes containing both bromine and chlorine have been isolated from red algae of the genus *Laurencia*[1a] and from herbivorous molluscs, such as *Aplysia*, which eat *Laurencia*.[2] The dibromide **1**, recently isolated from an unnamed species of *Laurencia*,[3] is the simplest example of this class of compounds. It contains a chlorine atom and a bromine atom *trans* to one another on adjacent carbons atoms, with the chlorine atom situated at the more highly substituted carbon atom. This is precisely the arrangement which would be expected for the addition of a chloride ion (Cl^-) to the intermediate bromonium ion **2**, formed by addition of a bromonium ion (Br^+) to a trisubstituted olefinic bond. It is therefore reasonable to assume that the biosynthetic sequence involves a bromonium ion and a chloride ion.



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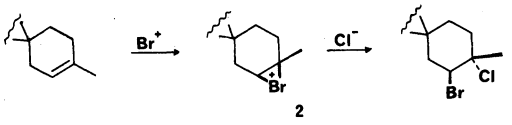

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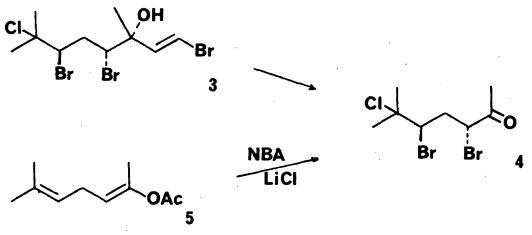
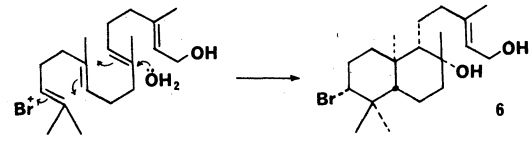
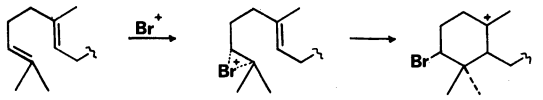
We made use of this hypothesis during the structural elucidation of the alcohol **3**.[4] We had found that oxidation of the alcohol **3** with Jones reagent gave a ketone **4** which contained two bromine atoms and one chlorine atom. Although we knew that bromine and chlorine atoms were located at C-5 and C-6, we could not assign the positions of the halogens from spectral data. The hypothesis predicted bromine at C-5 and chlorine at C-6. We were able to confirm this prediction by synthesis of the ketone **4**, using *N*-bromoacetamide as the source of a bromonium species in the presence of an excess of chloride ion. Treatment of the enol acetate **5** with N-bromoacetamide in tetrahydrofuran containing lithium chloride and a trace of hydrogen chloride gave a reasonable yield of the ketone **4**.



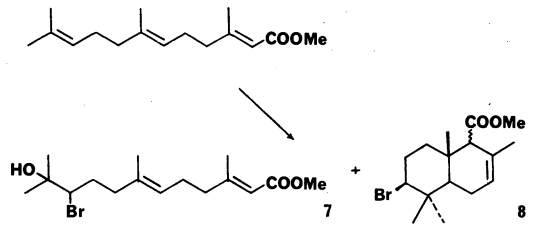
Recently we have been concerned with the cyclisation of linear isoprenoids, using a bromonium ion to initiate the cyclisation reaction in order to synthesise brominated metabolites. Invariably the biomimetic synthesis of the halogenated polycyclic terpenes appears to be the best "paper" synthesis, although careful choice of starting materials and some "non-biomimetic" modifications may be required. For example, it is difficult to imagine a more simple synthesis of aplysin-20 **6** than that which is assumed to be the biosynthetic route.[5] On closer examination, however, several potential difficulties emerge. Bromination must occur only at the terminal olefinic bond. The cyclisation reaction must be performed in such a way that a bicyclic, rather than monocyclic or tricyclic, product is favoured. Addition of water must occur to give an axial tertiary hydroxyl group. The reaction conditions must not cause a reaction at the primary allylic alcohol



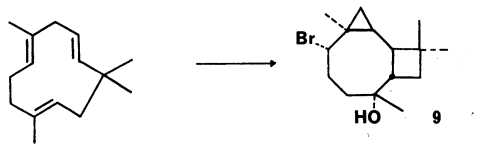
functionality. Without the aid of enzymes to overcome these restrictions, the synthetic chemist must modify his synthetic pathway to obtain *his* most efficient route. In this respect, a biomimetic synthesis does not follow the biosynthesis exactly, but uses the general principles and mechanisms on which the biosynthesis is based. Thus the basis of the biomimetic synthesis of the brominated terpenes is the bromonium ion initiated cyclisation reaction (Fig. 1).



The first example of a bromonium ion initiated cyclisation was reported by van Tamelen and Hessler.[6] During the preparation of the bromohydrin **7**, by the treatment of methyl farnesoate with *N*-bromosuccinimide in aqueous tetrahydrofuran, a small quantity of a mixture of cyclised products, such as the bromide **8**, was obtained. In this case, cyclisation had occurred despite the presence of a



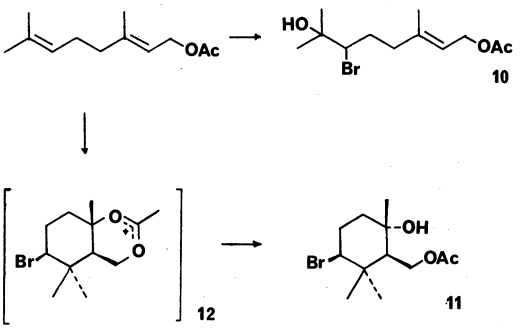
nucleophile. A more interesting example was provided by Sutherland and co-workers,[7] who obtained the tricyclic alcohol **9** in 20% yield by the reaction of humulene with *N*-bromosuccinimide in aqueous acetone. The higher yield in this reaction is undoubtedly due to the close proximity of olefinic bonds in a medium ring compound.



We began our research on bromonium ion initiated cyclisation reactions by investigating the efficacy of various brominating reagents, using a model system. We chose all *trans*-geranyl acetate as starting material, since it contained only two olefinic bonds of defined stereochemistry and, unlike geraniol, offered no opportunity for unwanted oxidation reactions. The reaction of geranyl acetate with *N*-bromosuccinimide in aqueous glyme (essentially the conditions used by van Tamelen) gave, as expected, an almost quantitative yield of the bromohydrin **10**. In order to encourage cyclisation, we required a reagent which would produce a bromonium ion without the simultaneous production of a nucleophilic counter ion. We proposed that the desired reagent system could be produced by mixing equivalent quantities of bromine with a Lewis acid, such as stannic bromide or aluminium bromide, in a polar but inert solvent. A similar reagent formed from an acyl chloride and a Lewis acid had been used by Kitahara and co-workers in cyclisation reactions.[8]

Geranyl acetate (>98% *trans*) was treated with one equivalent each of bromine and stannic bromide in nitromethane at 0°C for 5 min and then quenched with aqueous sodium bicarbonate solution. The NMR spectrum of the resulting viscous yellow oil contained several new peaks in the region of 1 ppm, indicating that cyclisation had occurred. After chromatography, we were able to isolate a crystalline alcohol **11**, isomeric with the bromohydrin **10**, in 16% yield. The NMR spectrum contained three methyl singlets at δ 0.98, 1.15 and 1.22, an acetoxy signal at 2.05, a double doublet at 4.00 (J = 12 and 5 Hz) due to a proton α to bromine, and a two-proton signal due to the methylene protons at 4.38 ppm. It was clear that cyclisation had occurred. Since moisture was rigorously excluded from the reaction mixture, the alcohol **11** must arise by hydrolysis of an intermediate ion **12** during work-up. The stereochemistry shown for the alcohol **11** is that which would be expected to arise from a concerted cyclisation reaction. The coupling constants of the proton α to bromine indicate that bromine is an equatorial substituent.

Examination of the other products obtained in the bromination reaction showed that some of the products contained more than one bromine atom, indicating addition of bromide ion. In order to minimize the formation of these unwanted products, we employed a reagent formed by mixing equivalent quantities of bromine and silver fluoroborate to obtain a 20% yield of the alcohol **11**.

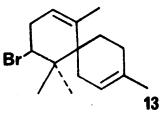


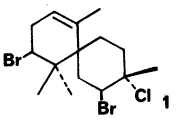
We now turned our attention to natural products from marine organisms. Among the halogenated marine natural products which had been described, the largest and most varied group were the halogenated chamigrenes, obtained from red algae of the genus *Laurencia*. There have been several biosyntheses proposed for individual compounds or groups of compounds.[9] We believe that the key step in any scheme for the biosynthesis of the halogenated chamigrenes is a bromonium ion initiated cyclisation reaction. It is not obvious, however, at which stage this reaction occurs. We were particularly interested in the biosynthesis of pacifenol **18** and johnstonol **19**, which are formed from prepacifenol **16** and prepacifenol epoxide **17** during the extraction of *Laurencia* species found at La Jolla and in the Gulf of California.[10]

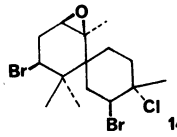
We have recently found an epoxide **15**, which we believe to be the biosynthetic precursor of prepacifenol **16**, among the constituents of the digestive gland of the sea hare *Aplysia californica*. The particular batch of *Aplysia* from which the epoxide **16** was isolated also contained very large quantities of pacifenol **18**, johnstonol **19** and acid-catalysed rearrangement products of these compounds. We deduced from the digestive gland content that the *Aplysia* had been grazing on *Laurencia* and had concentrated the halogenated metabolites so that even a

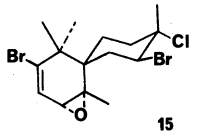
minor component such as the epoxide **15** was easily isolated.

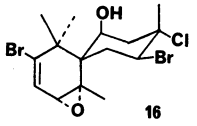
The compounds **1** and **14** have recently been isolated by Howard and Fenical[3] from an unnamed species of *Laurencia* from the Gulf of California. It does not seem unreasonable to propose that these metabolites might be precursors of the epoxide **15**. This scheme leads us back to 10-bromo-α-chamigrene (**13**), which is the simplest possible precursor to all other chamigrenes, particularly those related to the epoxide **20**, which cannot easily be formed from a precursor containing the vicinical bromochloride functionality. 10-Bromo-α-chamigrene (**13**) has not, however, been isolated from a natural source.†

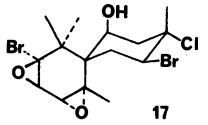


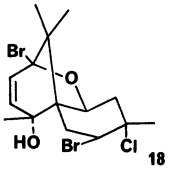


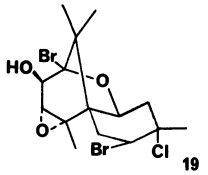


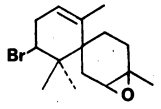




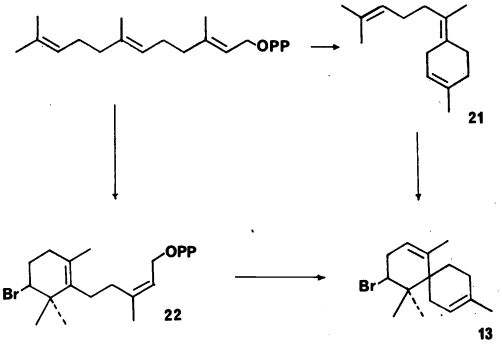






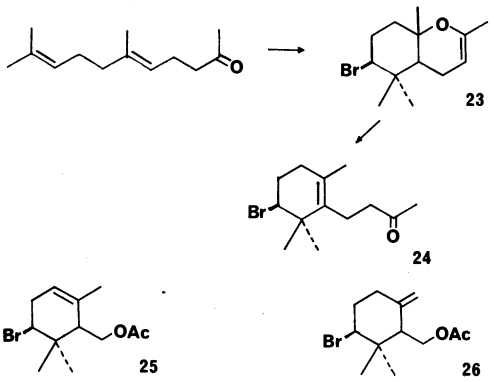


There are two possible biosynthetic routes from farnesyl pyrophosphate to 10-bromo-α-chamigrene (**13**), depending on the order in which the rings are formed. Cyclisation with loss of pyrophosphate gives γ-bisabolene (**21**) as an intermediate, while bromonium ion initated cyclisation gives a brominated monocyclofarnesyl pyrophosphate **22** as the intermediate.



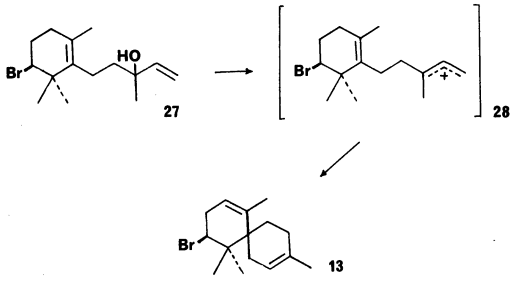
†10-Bromo-α-chamigrene has recently been identified as a *Laurencia* metabolite (W. Fenical, Personal communication).

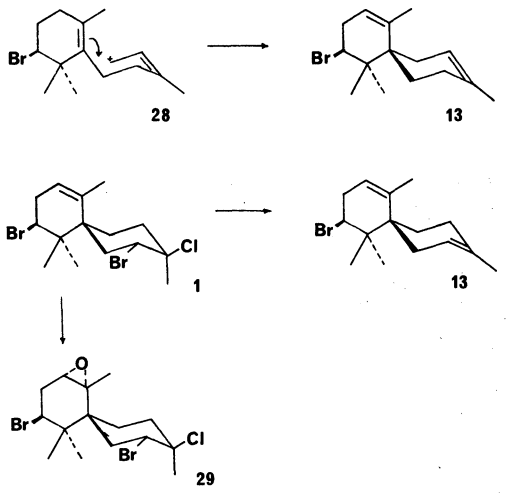
There are several reasons for not starting with a farnesol derivative for the synthesis, the most important being that cyclisation can give rise to a decalin ring system. We therefore selected geranyl acetone as starting material. Treatment of geranyl acetone with bromine and silver fluoroborate in nitromethane gave a bicyclic ether **23** in 20% yield. The infrared band at 1660 cm^{-1} indicated the presence of a vinyl ether, while the NMR spectrum, having sharp methyl singlets at δ 0.92, 1.05 and 1.16 ppm, showed that cyclisation had occurred. Use of the bromine-stannic bromide reagent for this reaction again gave a lower yield of vinyl ether **23** with polybrominated byproducts. Rearrangement of the vinyl ether **23** with *p*-toluenesulphonic acid in refluxing benzene solution resulted in the formation of the ketone **24** as the only isolable product. This result is in direct contrast with the dehydration of the alcohol **11**, which gave a mixture of the two olefins **25** and **26** and no trace of the tetrasubstituted olefin. We were now in a good position to synthesise a compound which could be regarded as being equivalent to the brominated monocyclofarnesyl pyrophosphate **22**.



The cyclisation of the brominated monocyclofarnesyl pyrophosphate **22** is assumed to proceed via an allylic carbonium ion **28**. We considered that we could generate the same carbonium ion by treatment of the vinyl alcohol **27** with acid. We therefore prepared the vinyl alcohol in good yield by reaction of the ketone **24** with vinyl magnesium bromide in tetrahydrofuran solution. Treatment of the vinyl alcohol with *p*-toluenesulphonic acid in refluxing benzene gave a mixture of products whose major constituent was the desired 10-bromo-α-chamigrene (**13**). A sample of the synthetic 10-bromo-α-chamigrene (**13**) was compared with a sample prepared from the dibromide **1** by reductive elimination of the vicinal halogens. They were shown to have identical spectral data and identical retention times on gas–liquid chromatography.

There is no simple method to determine the stereochemistry of the 10-bromo-α-chamigrene (**13**). One





of the subtleties of chamigrene chemistry is that migration of the double bond in the manner shown gives rise to the optical enantiomer. Introduction of bromine at the 10-position creates a second chiral centre, so that a similar migration of the double bond results in a pair of diastereoisomers which should be separable. Examination of molecular models allows the prediction that cyclisation of the vinyl alcohol **27** would occur with formation of the new bond *anti* to the bromine atom being preferred. On the other hand, the sample of 10-bromo-α-chamigrene prepared by Howard and Fenical should be the opposite diastereoisomer, since it is likely that the 2-bromine atom directs the approach of *m*-chloroperbenzoic acid in the formation of epoxide **29** from dibromide **1**. Therefore, even ignoring the fact that the synthetic product is racemic and the sample from natural sources is probably optically active, the major product from the cyclisation and the 10-bromo-α-chamigrene (**13**) from the natural product **1** should not be identical. At present our only explanation of the apparent identity is that the two samples of 10-bromo-α-chamigrene (**13**) are not separable by gas-liquid chromatography.

We now attempted to obtain a 10-bromo-α-chamigrene by bromonium ion-initiated cyclisation of γ-bisabolene (**21**), which had been synthesised by a method which allowed the separation of E and Z isomers. E-γ-Bisabolene was treated with all the reagent systems which had proved successful in the model reaction, but we could not detect any 10-bromo-α-chamigrene (**13**) in the reaction mixtures. The product mixtures were extremely complex and did not contain any easily recognisable products containing only one bromine atom. This negative result is not entirely unexpected, since the transition state required for this reaction is more sterically hindered than the corresponding transition state in the cyclisation of geranyl acetone.

What can we learn about the biosynthesis of the halogenated chamigrenes from these results? We have shown that without the aid of enzymes to maintain the correct geometry of the transition state the bromonium ion initiated cyclisation of a linear polyene is preferred to a similar cyclisation of γ-bisabolene. This work simply reinforces the opinion of those who have been concerned with the biosynthesis of sesquiterpenes that γ-bisabolene is not involved in the biosynthesis of chamigrenes and other more complex sesquiterpenes.

Our studies of biomimetic synthesis have shown that bromonium ion-initiated cyclisation reactions provide a very useful route to relatively complex molecules containing arrangements of atoms difficult to synthesise by alternate methods. The synthesis of 10-bromo-α-chamigrene (**13**) serves to illustrate the efficacy of biomimetic systhesis. The problem of assigning the stereochemistry of the product serves to illustrate the stereochemical subtleties to be encountered in the chamigrene system, a problem which has occasionally been overlooked in structural determinations. Finally, we have synthesised many of the compounds which will be required for future biosynthetic studies, although we acknowledge that our studies are of little biosynthetic significance.

Acknowledgements—The bulk of the experiments described were performed by Larry Wolinsky. Those experiments concerning the addition of bromonium chloride to olefins were performed by Martha Stallard, who was also involved, with Chris Ireland, in the structural elucidation of *Aplysia* metabolites.

We are particularly indebted to Dr. Bill Fenical, who, with Bruce Howard, has provided data and compounds which influenced the direction of the research and enabled its completion.

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