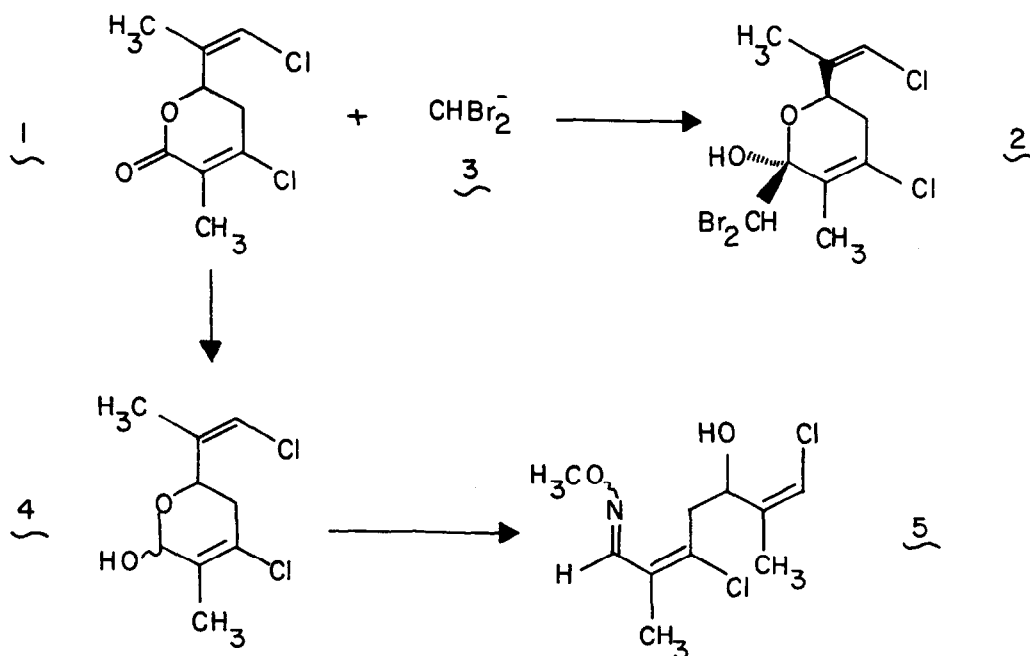


**Total Synthesis of Costatone: A Monoterpene from the
Red Seaweed: *Plocamium costatum***

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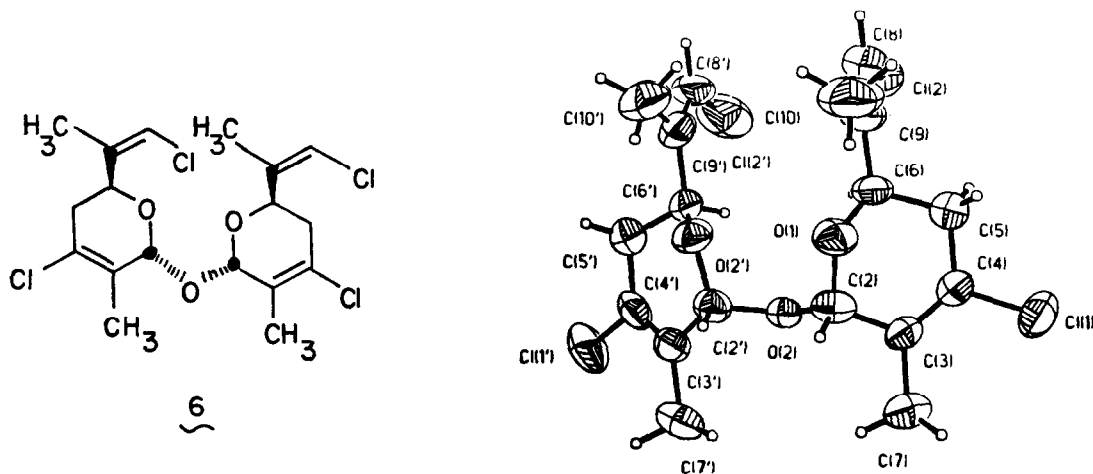
Abstract: The total synthesis of a unique, naturally occurring monoterpene hemiketal is described.

Two unique, heterocyclic monoterpenes **1** and **2** were isolated from the Australian red algae, *Plocamium costatum*.^{1a,b} These natural products have been assigned the trivial names costatolide and costatone, respectively. Various naturally occurring monoterpenes isolated from *Plocamium* sp. are known to possess mutagenic activity and also to inhibit oxidative phosphorylation.² *In vitro* conversion of **2** into **1** has been effected with base treatment by analogy to the haloform reaction.³ We wish to report the reverse reaction, *i.e.* a conversion of **1** into **2**. Since the starting material costatolide (**1**) was previously synthesized in our lab,⁴ the conversion of **1** into **2** completes the first total synthesis of the hemiketal costatone (**2**).



The final step in the synthesis of **2** is addition of the anion of methylene bromide (**3**) to costatolide (**1**). This addition was successful only when a procedure similar to that described by Yamamoto⁵ was employed. Other procedures^{6,7} for addition of a methylene bromide anion equivalent gave no reaction at all. Once formed, crude **2** could be purified by passing it through a HPLC fitted with a Bondapak-CN column. Other attempts at purification led to decomposition of the product.

Treatment of **1** with Dibal at -78°C afforded a somewhat unstable lactol **4** almost quantitatively. When this lactol was treated directly with methoxyamine in pyridine, the O-methyloxime **5** was obtained in 67% overall from **1**. The purified lactol **4** upon standing was converted into a crystalline substance whose structure was determined by x-ray diffraction analysis to be the dimer **6**.⁸ A computer generated plot of **6** is given below.



Compound **6** crystallized in the monoclinic space group $P 2_1/n$ with measured cell constants of $a = 13.611(3)$, $b = 8.244(2)$, $c = 18.567(3)$ Å and $\beta = 91.04(2)^{\circ}$. The density was calculated to be 1.20 g cm^{-3} for four molecules in the unit cell. Reflection data was collected with a Nicolet R3m/E crystallographic system using the $\theta:2\theta$ scan collection technique and MoK_{α} radiation ($\lambda = 0.71069$ Å). After Lorentz and polarization corrections, 1748 of 2254 reflections (77.6%) were judged observed. No absorbance correction was made. The structure was solved by the SHELXTL

programs.⁹ Block diagonal least squares refinement was applied to all non-hydrogens. Hydrogen atoms were located in a subsequent Fourier difference map and placed in calculated positions in the final stages of refinement to a final R of 0.073.

The dimer **6** is a *meso* compound. The conformation adopted by **6** in the crystal lattice is such that the bridging oxygen atom lies in a mirror plane which bisects the molecule into two equivalent halves. This central oxygen is pseudoaxial to the two cyclohexene rings and trans to both propenyl substituents on C-6 and C-6'. The trans relationship of the bridging oxygen to the propenyl substituents in both rings incorporates the same stereochemistry found in the natural product **2** with respect to the propenyl group and the hemiketal hydroxyl group. It is likely that this diastereomer is thermodynamically most favorable since an anomeric effect¹⁰ operates on the exocyclic oxygen atom and also since the bulky propenyl groups are pseudoequatorial.

A procedure for preparation of costatone (**2**) from costatolide (**1**) is given as follows. To a solution of methylene bromide (0.19 g, 1.1 mmol) in 2 mL of dry THF at -78°C under N₂ was added dropwise over 10 min. lithium dicyclohexylamide prepared from dicyclohexylamine (0.18 mL, 1.0 mmol) and 1.52 M n-butyl lithium (0.66 mL, 1.0 mmol). The solution was stirred for 20 min. then costatolide (**1**) (0.044g, 0.020 mmole) dissolved in .25 mL of THF was added at -78°C. Stirring under N₂ was continued for 3 hr and then the reaction was quenched with 0.5 M citric acid solution (6 mL). After the usual ether work-up, costatone (**2**) was purified by HPLC (hexane:ether/95:5) with a Bondapak-CN column to afford 0.053 g (68%) of pure **2** whose spectra were identical to those reported for the naturally occurring substance.

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