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TOTAL SYNTHESIS OF RACEMIC PERFORENONE AND 3-DEBROMO-PERFORATONE [1]

A G González J Darias J D Martín and M A Melián
Department of Organic Chemistry Universidad de La Laguna
Instituto de Productos Naturales Orgánicos CSIC Tenerife SPAIN

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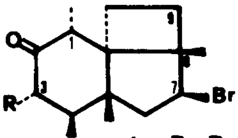
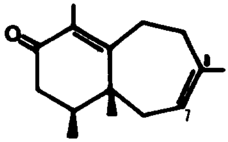
We have recently described [1] the structure and stereochemistry of perforatone (1a) and perforenone (2), metabolites isolated from the marine alga Laurencia perforata. The reported Δ^{7-8} double bond could not be definitely located on the cycloheptane ring in perforenone, nor the bromine atom at C-7 in perforatone as the spectroscopic and biogenetic considerations applied equally to the structures 3 and 4. However, now that the compounds 2 and 1b have been synthesized and proved identical to naturally occurring perforenone and 3-debromo-perforatone, respectively, these alternative structures can be dismissed.



1a, R = Br

1b, R = H



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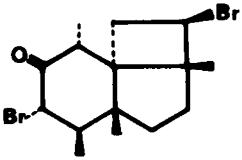

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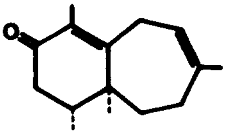

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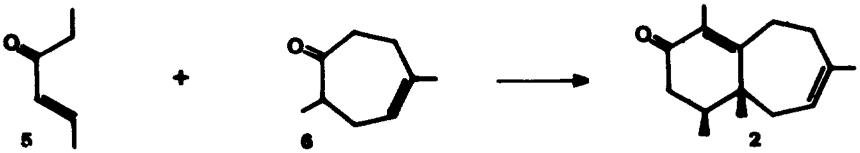
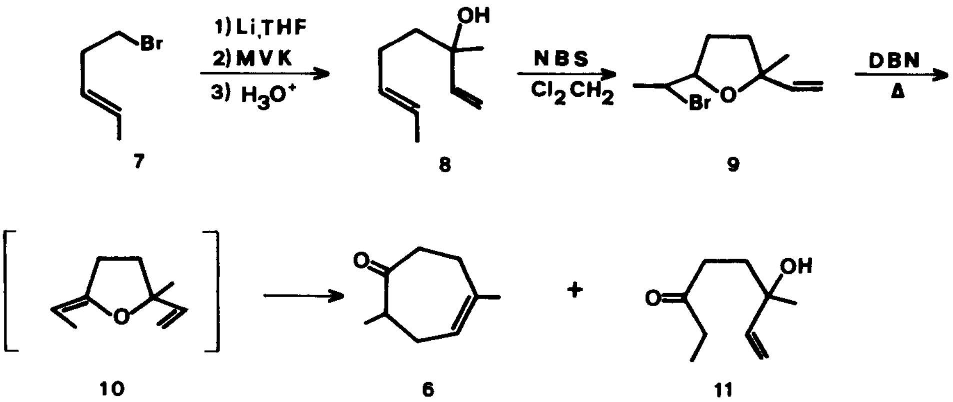
As a potential synthetic route to perforenone, a direct approach involving simultaneous introduction of the vicinal methyl groupings and the conjugated α-methyl ketone function via a Robinson annelation of trans-2-hexen-4-one (5) with the cycloheptanone (6) was considered.



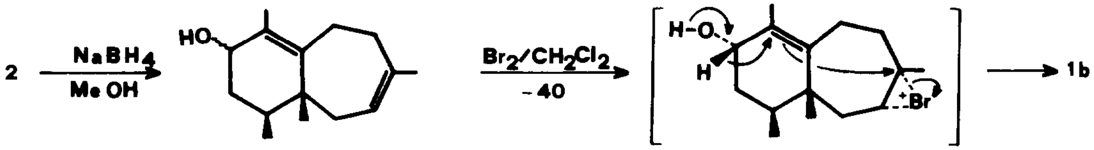
Thus the synthesis of compound (6) was the first objective. Trans-allyl-bromide (7) [Scheme 1] readily available in two stages from cyclopropylmethylketone [2] in 90% overall yield was converted to a lithium derivative using lithium metal (3-atom gr equiv) in dry THF at -40° and then adding methyl vinyl ketone (1.2 equiv) to give an 86% yield of the dienic alcohol (8) [3] after hydrolysis of the reaction mixture. 8 was treated with N-bromosuccinimide in methylene chloride at 0° for 1 hr (or at 25° for 10 min), yielding the tetrahydrofurane derivative (9). When the solvent was changed to CCl_4 no appreciable progress was observed even after reflux for 5 hr. Compound (9) in refluxing DBN undergoes dehydrobromination to an intermediate allyl vinyl ether (10) which rearranges directly to 6 (homogeneous by vpc) and 11, in 74% and 15% yield respectively. Compound (11) was obtained by



hydrolysis of the unrearranged compound (10) worked up with dilute mineral acid.

The annelation process was carried out by treating a suspension of the sodium enolate of 6 (from NaH 1 equiv) in dry THF with 1 equiv of 5 at 50° for 10 hr, to afford a 29% overall yield of a mixture of 2 and epimer (with a trans vicinal methyl grouping) in the ration 68:32. Compound (2) was identical with the natural sample. A mixture of synthetic and natural compounds showed a homogeneou peak on vpc analysis.

The synthesis of 3-debromo-perforatone (1b) from 2 has already been reported [1].



R E F E R E N C E S

1 Part 18 in the series "Marine Natural Products from the Atlantic Zone". For Part 17, see: A G González J Darias and J D Martin Tetrahedron Letters 3375 (1977)

2 M Julia S Julia and R Guegan Bull Soc Fr 1072 (1960)

3 All new compounds reported were homogeneous by tlc and gave satisfactory ir, nmr and exact mass spectra.