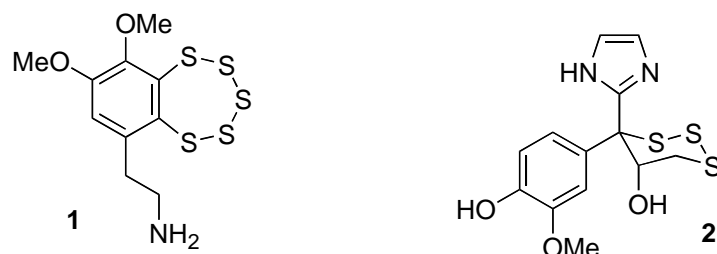


8.4 Dr G W Weaver, Department of Chemistry, Loughborough University Synthesis of Marine Polysulfide Natural Products

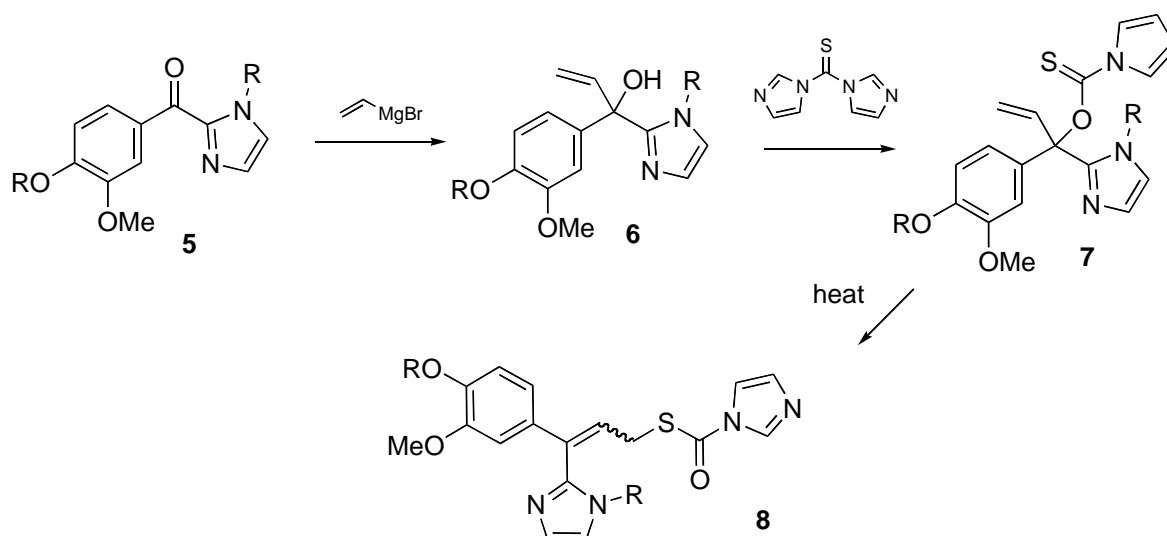
We are currently engaged in an EPSRC funded project to synthesise polysulfide natural products¹ such as the varacin **1**, and the Aplidium trithiane **2** shown below. These compounds, which have been isolated from marine organisms such as ascidians, have important biological properties including anti-tumour and anti-fungal activity.² We wish to make these compounds synthetically since only minute quantities are available from natural sources, and this involves harvesting the organisms and damaging the marine environment. The ability to synthesise these compounds will allow their structures to be confirmed, and allow detailed study of the mode of action as biological agents.³



We are investigating a number of routes to make both the benzopentathiepin **1**⁴ and the trithiane **2**. The synthesis of **1** involves the use of chromium arene complexes such as **3** and **4** in which the first two sulfur atoms can be attached to the aromatic ring by reaction with dialkyl disulfides. We also wish to develop an asymmetric synthesis of these type of molecules which can exhibit planar chirality due to the slow inversion of the pentathiepin ring. We have shown that reaction of the anion of fluoro complex **3** with dialkyl disulfides leads to formation of the synthetically useful di(alkylthio)arene complexes via electrophilic addition to the anion, followed by aromatic nucleophilic substitution of the fluorine atom. Compounds have been identified using a combination of mass spectrometry, NMR spectroscopy and X-ray crystallography. This work is due to be published in the near future. Mass spectrometry was essential for determining the composition of these compounds. The number of sulfur atoms present could not be determined by NMR spectroscopy.



Work towards the trithiane **2** currently involves the allylic alcohol **6**. We have been able to form this by Grignard addition to ketone **5**. We are currently investigating a [3,3]-sigmatropic rearrangement of thiocarbamate **7** to introduce the first key sulfur atom into the natural product framework. We then hope to attach further sulfur atoms and to effect cyclisation to form the trithiane ring by activation of the alkene double bond in **8**, and complete the synthesis of the natural product.



Mass spectrometry is essential for characterising these compounds, many of which are labile and will readily lose sulfur atoms. Attempts to obtain parent ions for a number of these compounds in-house have been unsuccessful, but the Swansea service has successfully detected the parent ion signal and determined its exact mass, confirming the molecular formulae of these labile compounds. Continued access to the service is vital for the future success of this project.