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Total Syntheses of Aplysin and Debromoaplysin Using a Diastereoselective, Sulfur Mediated Radical Cyclisation Strategy

David C. Harrowven,* Matthew C. Lucas
Department of Chemistry, The University, Southampton, S017 1BJ.

and Peter D. Howes
Enzyme Medicinal Chemistry 2, GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY.

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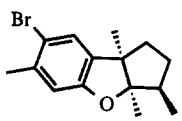
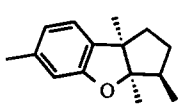
Abstract: Total syntheses of two marine sesquiterpenes, aplysin **1** and debromoaplysin **2**, are described. The key step involves a diastereoselective, sulfur mediated radical cyclisation of diene **5** to **7** which simultaneously creates the sterically demanding aplysin skeleton and establishes the relative configuration of the three contiguous stereogenic centres. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Terpenes and terpenoids; Natural products; Radicals and radical reactions; Cyclisations; Disulfides; Oxygen heterocycles.

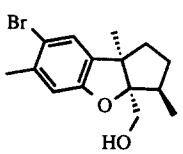
Aplysin **1** was one of the first halogenated sesquiterpenes to be isolated from marine organisms. Found in the sea hare *Aplysia* and the red alga *Laurencia*,[1] its antifeedant properties are believed to protect hosts from raptorial advances.[2] The co-occurrence of aplysin **1** and debromoaplysin **2** in all known natural sources has also prompted speculation that **2** is a biological precursor of aplysin and acts as an antioxidant by scavenging reactive halogens.[3] These factors, together with the unusual structural architecture, have generated considerable interest in this family of natural products (of which **3** and **4** are also members) and several total syntheses of **1** and **2** have been described.[3,4]



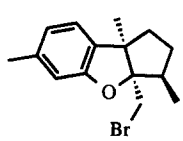
1 Aplysin



2 Debromoaplysin

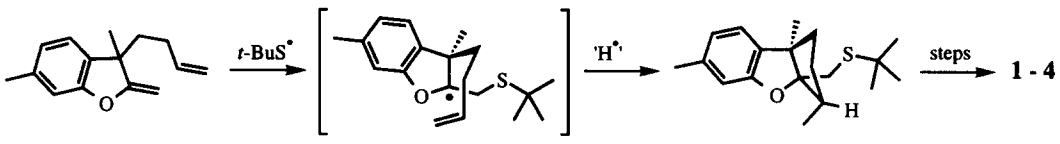


3 Aplysinol



4 Isoaplysin

The synthetic challenge presented by the aplysins rests in the construction of the sterically demanding tricyclic skeleton and the establishment of the three contiguous stereogenic centres. Our interest in naturally occurring arenes and radical reactions involving sulfur led us to consider the approach outlined in Scheme 1.[5,6] We hoped that an electrophilic thiyl radical generated in the presence of diene **5** would first add to the terminus of the enol ether giving **6**. A 5-*exo*-trig cyclisation through a chair-like transition state followed by a hydrogen atom quench would then provide **7**, an advanced precursor of all the aplysins.



5 **6** **7**

Scheme 1

Our synthesis of diene **5** began with acetate **8** which was smoothly transformed into acetophenone **9** through exposure to zirconium(IV) chloride under ultrasound irradiation.[7,8] Protection of the phenol as its methyl ether **10** and Willgerodt-Kindler oxidation to thioamide **11** provided access to thioester **12** through

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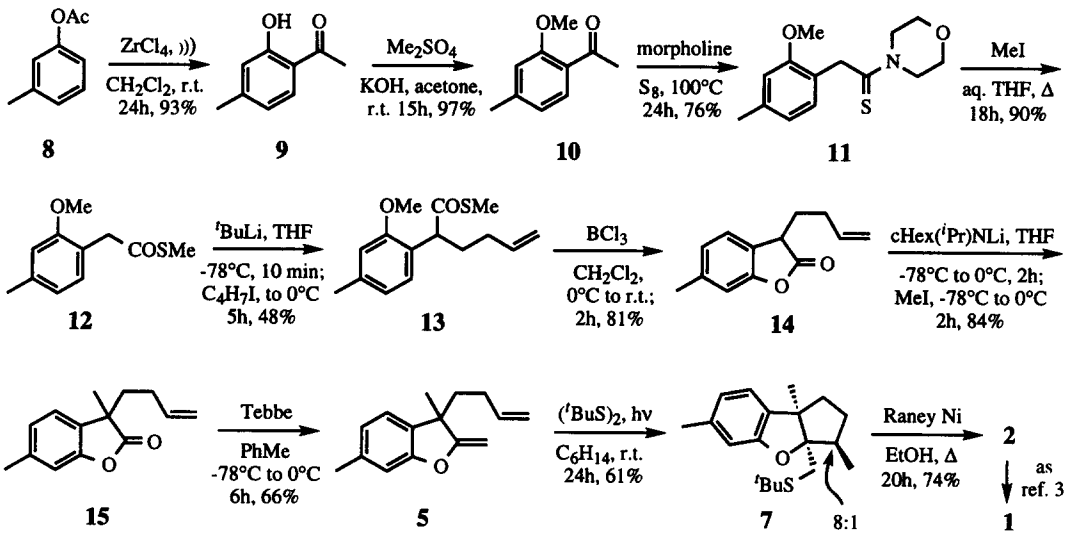
simultaneous alkylation and hydrolysis.[8] Sequential homoallylation to **13**, lactonisation to **14**, methylation to **15** and methylenation to **5** then allowed us to examine our key step. To our delight, irradiation of a hexane solution of **5** containing di-*t*-butyl disulfide gave tricycle **7** as an 8:1 mixture of diastereoisomers. A Raney nickel reduction of **7** completed the synthesis of debromoaplysin **2**, while exposure of **2** to bromine completed a total synthesis of aplysin **1**.[3]



Scheme 2

In conclusion, our approach to the aplysins has demonstrated further the utility of sulfur mediated radical cyclisation reactions in synthesis. That these cyclisations use reagents that are cheaper and less toxic than trialkylstannane based radical methodologies is noteworthy. We are currently exploring the conversion of sulfide **7** into aplysinol **3** and isoaplysin **4** so as to provide a general entry to this family of sesquiterpenes.

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