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Unusual oxidation behaviour of a propargylic alcohol

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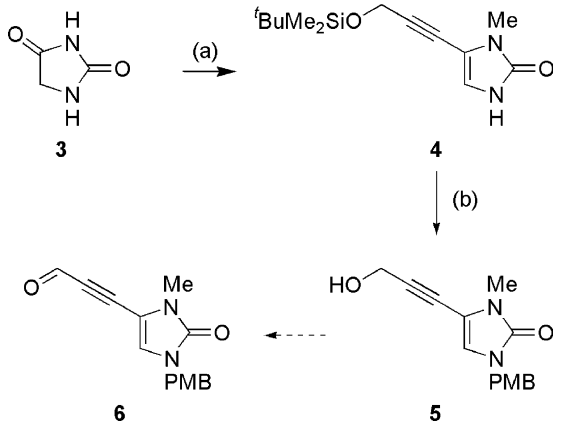
Abstract—Attempts to convert a propargylic alcohol bearing an imidazolone substituent to the corresponding aldehyde under Parikh–Doering conditions gave an α,β-unsaturated-β-methylsulfanyl aldehyde, which cyclised under mildly acidic conditions.

The marine sponge alkaloid agelastatin A (**1**), isolated in 1993,[1] is one of a series of pyrrole–imidazole alkaloids, which are biogenetically related to oroidin (**2**).[2] The synthetic interest shown in these alkaloids has culminated in two total syntheses[3a–d] and one formal synthesis[3e] of **1**; model studies towards the core cyclopentane unit have also been described (Fig. 1).[3f]

Our current investigations into a biogenetically-modelled[4] synthesis of **1** required the synthesis of alkynyl aldehyde **6** (Scheme 1). While the corresponding propargylic alcohol **5** could readily be prepared, oxidation of the alcohol to the aldehyde gave some unexpected products, which are the subject of this communication.

Synthesis of **5** commenced from hydantoin (**3**), which was selectively methylated at N-3 by reaction with dimethylacetamide dimethyl acetal.[5] Subsequent addition of the alkynyl Grignard reagent derived from TBS-protected propargyl alcohol, and elimination of the resulting tertiary alcohol afforded imidazolone **4** in moderate yield.[6,7] Protection of the remaining nitrogen and removal of the TBS group led to the desired alcohol **5**.



Scheme 1. Reagents and conditions: (a) (i) $MeC(OMe)_2NMe_2$, toluene, reflux, 83%; (ii) $^tBuMe_2SiOCH_2C{\equiv}CH$, BuMgCl, THF; (iii) TsOH, $CHCl_3$, 62% (two steps); (b) (i) *p*-$MeOC_6H_4CH_2Cl$, $KOBu^t$, DMF, 87%; (ii) TBAF, THF, 99%.

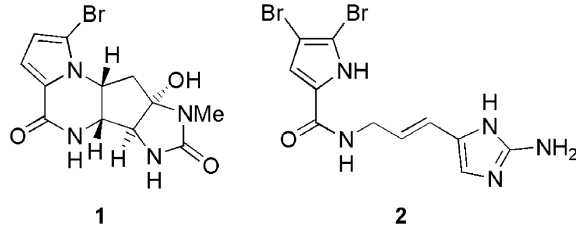


Figure 1. Agelastatin A (**1**) and oroidin (**2**).

Initially, Parikh–Doering oxidation[8] was employed in an attempt to prepare aldehyde **6**. On treatment of **5** with pyridine–sulfur trioxide and triethylamine in DMSO, aldehyde **7** was formed, in which a methylsulfanyl substituent has been added to the β-position of the desired ynal (Scheme 2).[9] Aldehyde **7** was obtained as a rapidly equilibrating 10:1 mixture of isomers, with the (*E*)-isomer predominating.

Keywords: Agelastatin; Oroidin; Imidazolone; Parikh–Doering oxidation; Conjugate addition; Nazarov.
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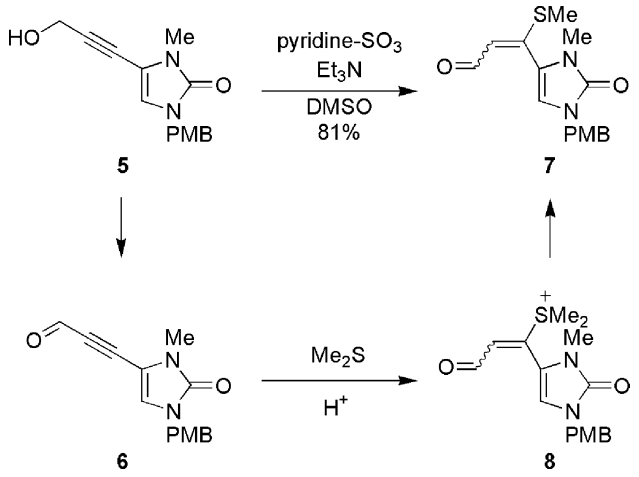
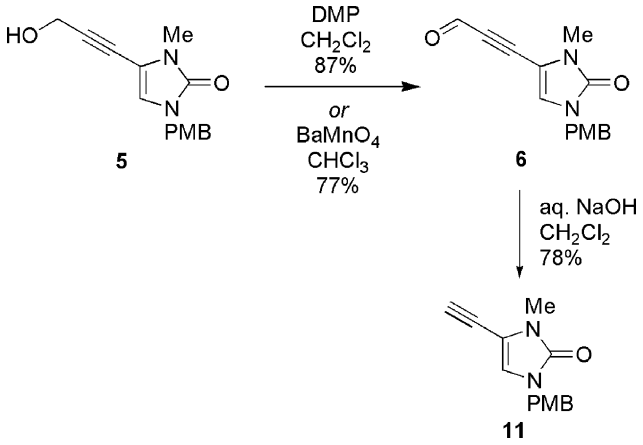


Scheme 2. Attempted Parikh–Doering oxidation of **5**.



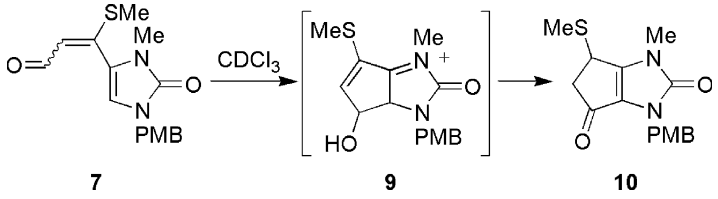
Scheme 4. Preparation and subsequent cleavage of **6**.

We presume that under these conditions the desired aldehyde **6** is initially formed, but is sufficiently reactive towards soft nucleophiles that dimethyl sulfide adds at the β-position to form sulfonium ion **8** (after protonation of the allenolate). Removal of a methyl group by one of the nucleophiles in the reaction mixture then gives the observed product **7**.

Aldehyde **7** proved somewhat unstable to mildly acidic conditions. On dissolution in $CDCl_3$ was slowly converted to bicyclic ketone **10** (Scheme 3),[9] presumably through protonation of the aldehyde, cyclisation to bicyclic cation **9** (a process which could be considered as either a nucleophilic attack of the imidazolone on the protonated aldehyde, or a Nazarov cyclisation) followed by loss of a proton and tautomerisation to afford the observed product **10**.

Oxidation of alcohol **5** to aldehyde **6** was successfully achieved by treatment either with Dess–Martin periodinane (DMP) followed by a sodium thiosulfate work-up,[10] or with barium manganate[11] (Scheme 4). The aldehyde **6** showed some instability to aqueous alkali, and if a sodium hydroxide work-up[10] was used following DMP oxidation, terminal alkyne **11** was the only product isolated, in 58% yield. Alternatively, aldehyde **6** could be cleanly deformylated by treatment with 1.3 M sodium hydroxide solution in a two-phase reaction mixture.

In conclusion, some unexpected reactions have been observed in attempts to oxidise the propargylic alcohol **5**. Efforts are under way to discover whether these reactions have any generality, and to complete a total synthesis of **1**.



Scheme 3. Acid-catalysed cyclisation of **7**.

Acknowledgements

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References and notes

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NC*H*=C), 5.85 (1H, d, *J* 7.4, C=C*H*CHO), 4.45 (2H, s, CH_2Ar), 3.23 (3H, s, OCH_3), 2.96 (3H, s, NCH_3), 1.44 (3H, s, SCH_3); compound **10**: δ_H (400 MHz, $CDCl_3$): 7.38 (2H, d, *J* 8.6, 2 × ArH), 6.79, 2H, d, *J* 8.6 (2 × ArH), 4.89 (1H, d, *J* 14.5) and 4.82 (1H, d, *J* 14.5, CH_2Ar), 4.12 (1H, dd, *J* 6.1, 1.3, C*H*SCH_3), 3.73 (3H, s, OCH_3), 3.37 (3H, s, NCH_3), 3.19 (1H, dd, *J* 18.1, 6.2) and 2.68 (1H, dd, *J* 18.1, 1.0, COCH_2), 1.68 (3H, s, SCH_3).

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