PIEF-GA-2008-220720 SEQUENCING: Periodic Report & Final Report

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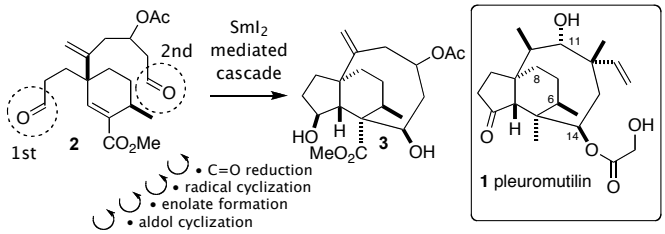
1. Introduction

Resistance to antibiotics is a major concern worldwide and has led to an urgent need to identify antibacterial agents with modes of action distinct from the established classes. The antibacterial natural product pleuromutilin **1** is such a candidate. Pleuromutilin derivatives are known to bind to the peptidyl transferase site on the 50S ribosomal subunit of bacteria thus preventing bacterial protein synthesis. The poor pharmacokinetic properties of the pleuromutilin class are, however, a major problem. Only recently has a pleuromutilin derivative been approved for use in humans: retapamulin (an ester derivative at C14) is used as a topical agent for bacterial skin infections and other pleuromutilin analogues are currently in development. Although analogues of pleuromutilin are available by minor modification of the natural product, a concise approach to the core of pleuromutilin would allow analogues of the natural product to be prepared that display improved pharmacokinetic properties and that can *not* be obtained from the natural product.

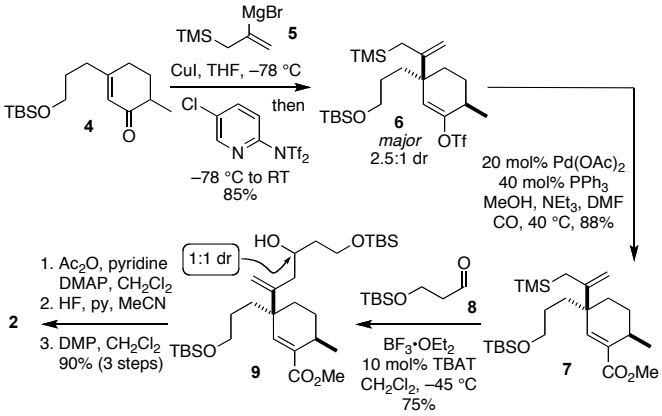


Scheme 1: A SmI_2–mediated 'sequencing' approach to pleuromutilin **1**

Our aim was to develop a synthesis of the pleuromutilin framework using a *sequencing* strategy: we proposed that a dialdehyde substrate **2** could undergo a cyclization cascade resulting in the construction of the core of pleuromutilin in a single step, using a single reagent, with complete diastereocontrol at the four, contiguous stereocentres generated during the cascade.

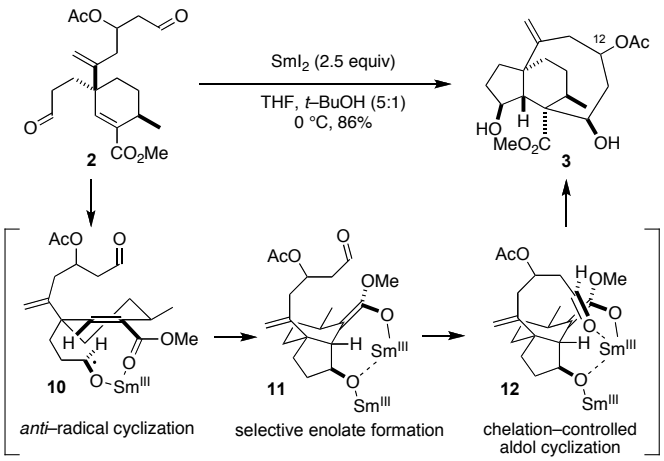
2. Results and discussion

After initial model studies carried out by the Fellow,[1,2] we prepared the cyclization substrate **2** using the route shown in Scheme 2.[3]



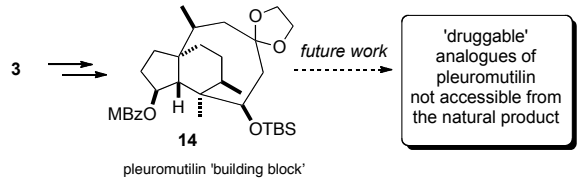
Scheme 2: Synthesis of dialdehyde cyclization substrate **2**.

Pleasingly, treatment of **2** with SmI_2 in THF and *t*–BuOH, at 0 °C resulted in a cyclization sequence to give **3** in 86%. Futhermore, the reaction proceeded with complete control at the four, contiguous stereocenters generated during the cascade. No by–products arising from the 'out-of-sequence' reduction of either aldehyde group were observed (Scheme 3).[3]



Scheme 3: A SmI_2–mediated dialdehyde, 'sequenced' cyclization for the stereocontrolled construction of the pleuromutilin framework

The exquisite control achieved in each stage of the cascade presumably arises from the chelation of intermediates to samarium: coordination to samarium controls the chemoselectivity of aldehyde reduction, the *anti*–diastereoselectivity of the cyclization of radical anion **10**, the formation of a single Sm(III)–enolate **11**, and diastereoselective aldol cyclization through transition structure **12**. We believe that pre–coordination of samarium to the proximal (or 1st) aldehyde group and the ester carbonyl groups leads to its selective reduction over the more–remote aldehyde. It is well appreciated that pre–coordination of Lewis acidic samarium to the carbonyl and unsaturated ester components in ketyl–olefin additions is important for promoting reaction and controlling the diastereoselectivity of such additions.[3]
The product of the sequenced reaction was then converted to a valuable pleuromutilin precursor **14** by a multi-step route (Scheme 4).[3]



Scheme 4: Synthesis of pleuromutilin 'building block' **14**

Summary and future work

We have exploited a SmI_2–mediated dialdehyde cyclization cascade in an approach to the pleuromutilin framework. The reaction proceeds with complete sequence integrity and with excellent control during the construction of four, contiguous stereocenters. The product of the cascade reaction can be converted to a valuable pleuromutilin precursor. Due to the resignation of the Fellow our plans to apply the approach in the asymmetric synthesis of pleuromutilin analogues not accessible from the natural product were not fulfilled.

Socio–economic impact of the project

We have developed new approaches to reaction *sequencing* that allow molecular complexity to be increased in a single step. This is an important, current area of organic synthesis and our studies have made a significant contribution to the field. The provision of new, sequential organic reactions will benefit the synthetic community including those working in the pharmaceutical, agrochemical and fine–chemicals industries in Europe, by allowing drugs and other active agents to be constructed rapidly saving time and other resources whilst potentially minimizing waste.
The Fellowship has also resulted in the development of a flexible approach to pleuromutilin analogues. Such an approach in important as resistance to antibiotics becomes a major concern worldwide. This project has paved the way for access to analogues of the natural product with drug–like properties that cannot currently be prepared and may lead to future therapeutics based on the pleuromutilin scaffold. The proposed work will therefore have widespread benefits for everyone in the European Community.

Publications arising from the project

1. Helm, M. D.; Sucunza, D.; Da Silva, M.; Helliwell, M.; Procter, D. J. *Tetrahedron Lett.* **2009**, *50*, 3224.
2. Helm, M. D.; Da Silva, M.; Sucunza, D.; Helliwell,M.; Procter, D. J. *Tetrahedron* **2009**, *65*, 10816.
3. Helm, M. D.; Da Silva, M.; Sucunza, D.; Findley, T. J. K.; Procter, D. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 9315.