

Organic Synthesis

Copper-Catalyzed Double Additions and Radical Cyclization Cascades in the Re-Engineering of the Antibacterial Pleuromutilin

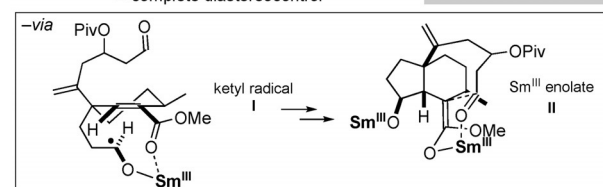
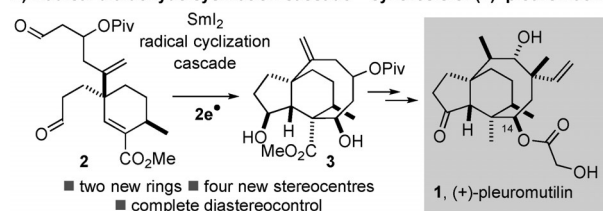
Rebecca E. Ruscoe, Neal J. Fazakerley, Huanming Huang, Sabine Flitsch, and David J. Procter*^[a]

Abstract: A general synthetic sequence involving simply prepared starting materials provides rapid access to diverse, novel tricyclic architectures inspired by pleuromutilin. Sm^{II}-mediated radical cyclization cascades of dialdehydes, prepared using a new, one-pot, copper-catalyzed double organomagnesium addition to β -chlorocyclohexenone, proceed with complete sequence selectivity and typically with high diastereocontrol to give analogues of the target core. Our expedient approach (ca. 7 steps) allows non-traditional, de novo synthetic access to analogues of the important antibacterial that can't be prepared from the natural product by semisynthesis.

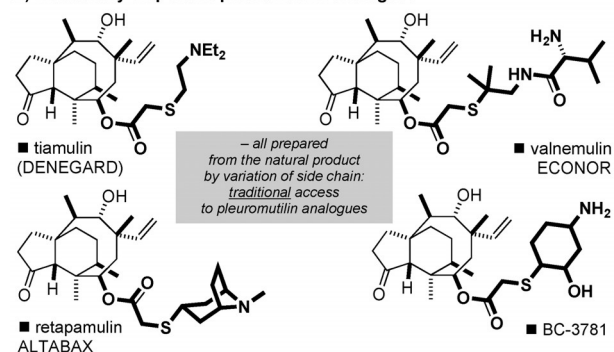
Cascade processes have the potential to assemble complex molecular architectures in a single synthetic operation.^[1] If such processes can be mediated by simple, commercial reagents and can be harnessed to deliver structures possessing important biological or physical properties they become even more desirable. We have recently exploited carbonyl reduction by the well-known electron-transfer reductant SmI₂^[2] to trigger cascade processes that deliver natural and unnatural product structural motifs.^[3,4] For example, we have prepared novel organic materials and bioactive targets using cascades involving phase-tag removal and cyclization.^[3b-d] In addition, we have developed radical cyclization cascades of dialdehydes^[4] and have used such a cascade^[4c,e] in the first enantiospecific total synthesis of the antibacterial natural product pleuromutilin (Scheme 1 A).^[4e] Electron-transfer reduction of dialdehyde **2** using SmI₂ gives **3** with complete diastereocontrol and excellent yield.^[4c,e] A dialdehyde cascade has since been employed by Reisman in an elegant synthesis of (–)-maoecrystal Z.^[5]

The natural product pleuromutilin is an important lead for the development of new antibacterials^[6,7] and much synthetic

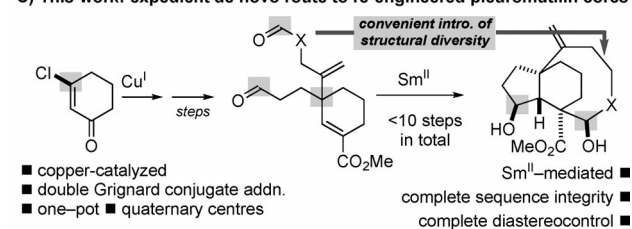
A) Radical dialdehyde cyclization cascade – synthesis of (+)-pleuromutilin



B) Industrially-important pleuromutilin analogues



C) This work: expedient de novo route to re-engineered pleuromutilin cores



Scheme 1. A) Radical cyclization cascade of a dialdehyde in the first enantiospecific synthesis of (+)-pleuromutilin. B) Industrially-important pleuromutilin analogues and the traditional method of analogue synthesis. C) This work: Cu^I and Sm^{II} in a short route to re-engineered pleuromutilin cores.

effort has been focused on the synthesis of analogues with increased activity and a more favourable pharmacokinetic profile. A handful of compounds are widely used in veterinary medicine, a single analogue has been licensed for topical use on humans, and others are currently undergoing clinical evaluation. Crucially, all of the analogues licensed or in clinical trials are prepared from the natural product and vary only in the

[a] R. E. Ruscoe, Dr. N. J. Fazakerley, H. Huang, Prof. Dr. S. Flitsch, Prof. Dr. D. J. Procter
School of Chemistry University of Manchester
Oxford Rd, Manchester, M13 9PL (UK)
E-mail: david.j.procter@manchester.ac.uk

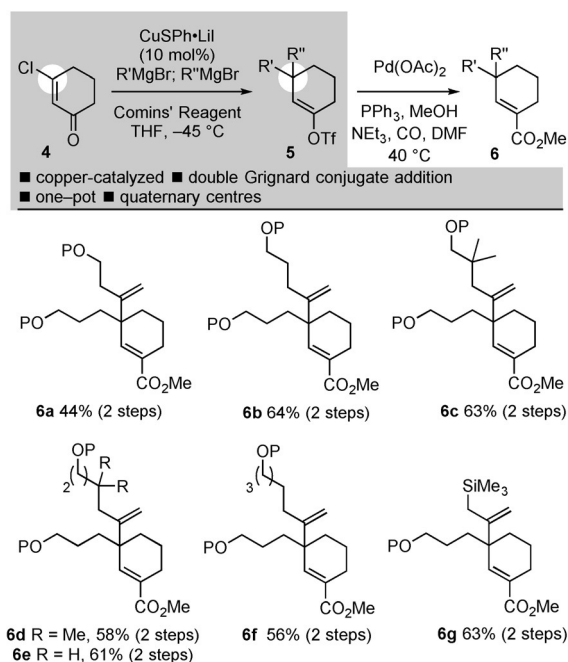
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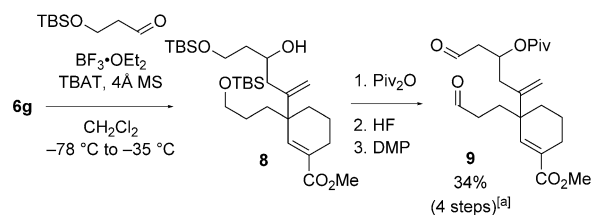
C14 side chain (Scheme 1B). As many of the undesirable properties of the pleuromutilins (e.g. poor solubility and poor pharmacokinetic properties) are associated with the core of the antibacterial natural product^[6,7] re-engineering of the pleuromutilin core is a crucial but long-neglected approach to analogues that is orthogonal to traditional approaches involving variation of the C14 side chain only (Scheme 1B). Importantly, our radical cascade approach to pleuromutilin allows us to consider the rapid de novo synthesis of simplified analogues that cannot be prepared from the natural product by semisynthesis—the approach universally adopted by industry in the pursuit of pleuromutilin analogues for use in humans.^[6,7]

Here we describe the development of a general synthetic sequence that rapidly converts simply prepared starting materials to diverse, novel tricyclic architectures inspired by pleuromutilin^[8] but that cannot be prepared from the natural product. Our studies have resulted in a new, one-pot, copper-catalyzed double organomagnesium addition to β -chlorocyclohexenone and have also allowed us to evaluate the scope of the radical cyclization cascade of dialdehydes.

We began our studies by developing a route to simplified analogues of dialdehyde substrate **2**. In our pursuit of an expedient route to re-engineered pleuromutilin cores, we developed a one-pot, sequential addition of two organomagnesiums to β -chlorocyclohexenone **4** catalyzed by CuSPh-LiI (10 mol%). In situ trapping of the enolate intermediate with Comins' reagent^[9] gave vinyl triflates **5** in good overall yield (Scheme 2). Thus, the framework of the cascade substrates **2** could be assembled in one-pot. To the best of our knowledge, the one-pot addition of two organometallic species to an



Scheme 2. One-pot, copper-catalyzed, double conjugate addition of organomagnesiums with enolate trapping in the expedient synthesis of unsaturated esters **6**. Comins' reagent = *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide); P = TBS, *tert*-butyl dimethylsilyl.



Scheme 3. Sakurai coupling in the synthesis of a cascade substrate bearing an oxygenated tether. DMP = Dess–Martin periodinane; TBAT = tetrabutylammonium difluorotriphenylsilicate. [a] 1:1 mixture of diastereoisomers.

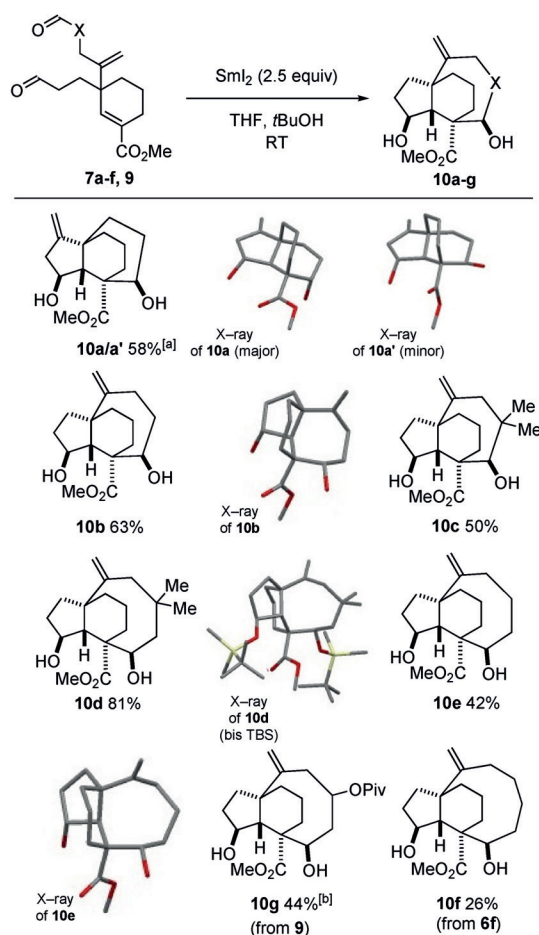
enone bearing a β -leaving group is unprecedented.^[10] Products of homo-double addition were not isolated. After partial purification of **5**, palladium-catalyzed methoxycarbonylation gave unsaturated esters **6 a–g**.

Unsaturated esters **6 a–f** were then converted to dialdehydes **7 a–f** in two straightforward steps (bis-desilylation and -oxidation—see Scheme 3 for illustrative conditions).^[11] Thus, cascade cyclization substrates **7 a–f** were accessible in only four steps from **4**. A cascade substrate bearing an oxygenated tether was constructed from **6 g** by Sakurai coupling^[12] with 3-[(*tert*-butyldimethylsilyl)oxy]propanal, protection of the resulting secondary alcohol as the pivaloate, followed by bis-desilylation and -oxidation to give dialdehyde **9** in good overall yield (6 steps from **4**) (Scheme 3).

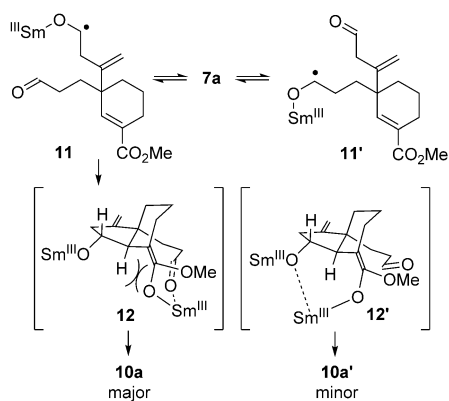
Pleasingly, in all cases, complete sequence integrity was observed in the cascade cyclizations of **7 a–f, 9** and synthetic pleuromutilin scaffolds containing 6, 7, 8, and even 9-membered right-hand rings (**10 a–g**) were obtained in moderate to good yield (Scheme 4). In all but one case, the cascades proceeded with complete diastereocontrol at the four newly-formed stereocentres. It is important to note that general approaches to such scaffolds from the natural product pleuromutilin would be impossible.^[6,7]

Remarkably, in the cascade cyclization of **7 a**, a substrate in which both aldehydes are attached to three-carbon tethers, complete sequence integrity was observed in the dialdehyde cyclization cascade: the aldehyde on the tether containing the sp^2 -hybridized alkene carbon atom undergoes initial coupling (Scheme 5).^[4] This most likely results from the restricted conformation ('Thorpe–Ingold Effect') of the alkene-containing tether resulting in more facile cyclization. Thus reversible formation of radical anion **11**^[13] leads selectively to a Sm^{III} -enolate^[14] that undergoes aldol cyclization through closed transition structure **12** to give major product **10 a**. The minor diastereoisomer **10 a'** may arise from open aldol transition-structure **12'**. The low diastereoselectivity observed in the second stage of this particular cascade may result from unfavorable 1,3-*trans*-diaxial interactions in the closed transition-structure **12** leading to the relative stereochemistry typically formed in the cascades (vide infra). The relative stereochemistry of **10 a** and **10 a'** was determined by X-ray crystallographic analysis (Scheme 4).^[15]

Pleasingly, cascade substrate **7 b**, designed to deliver a 5,6,7-tricyclic architecture, underwent highly selective reaction with SmI_2 to give **10 b** as a single diastereoisomer in 63% yield (Scheme 4). Remarkably, efficient cascade cyclization was also



Scheme 4. Selective cascade cyclizations to six-, seven-, eight-, and nine-membered ring-containing analogues of the pleuromutilin scaffold. [a] 2:1 mixture of diastereoisomers. [b] 1:1 mixture of diastereoisomers at the centre bearing the OPiv group.

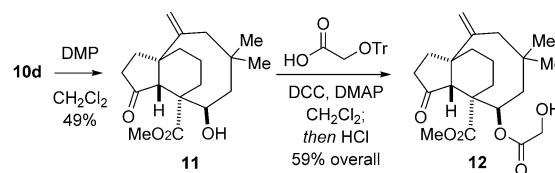


Scheme 5. Challenging the sequence integrity of the dialdehyde cascade: Cyclization of **7a** using SmI_2 .

observed for related substrate **7c** despite significant steric crowding adjacent to the second aldehyde group, and **10c** was isolated in 50% yield as a single diastereoisomer. *gem*-Di-substitution in the longer tether of cascade substrates resulted in more efficient cascade cyclization. For example, *gem*-dimeth-

yl-substituted 5,6,8-tricyclic cascade product **10d** was formed in 81% yield while products possessing less-substituted eight-membered rings **10e** and **10g** were isolated as single diastereoisomers in 42 and 44% yields, respectively. In a bid to identify the limits of the dialdehyde cascade process, we attempted to construct a nine-membered ring in the final stage of the cascade. The construction of nine-membered carbocycles is challenging and, to our knowledge, the formation of nine-membered carbocycles by using a SmI_2 -mediated aldol reaction is unprecedented.^[16] Impressively, treatment of substrate **7f** with SmI_2 gave the 5,6,9-tricyclic architecture and **10f** was isolated as a single diastereoisomer in 26% yield. The relative stereochemistry in the cascade products was determined by X-ray crystallographic analysis of **10a,a'**, **10b**, and **10e** and a derivative of **10d**^[15] and inferred for the remainder.

To illustrate the potential of our concise route to pleuromutilin analogues, diol **10d**, possessing a 5,6,8-tricyclic scaffold, was treated with one equivalent of Dess–Martin periodinane^[17] to give C3 ketone **11**. Installation of the C14 glycolate ester^[8b] gave **12** and completed a seven-step synthesis of a model pleuromutilin analogue (Scheme 6).



Scheme 6. Concluding a seven-step synthesis of pleuromutilin analogue **12**. DCC = *N,N*-dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine.

In summary, a general synthetic sequence involving simply prepared starting materials provides rapid access to diverse, novel tricyclic architectures inspired by pleuromutilin. At the heart of the short route, Sm^{II} -mediated radical cyclization cascades of dialdehydes, prepared using a new one-pot, copper-catalyzed double organomagnesium addition to β -chlorocyclohexenone, proceed with complete sequence selectivity and typically with high diastereocontrol. Our expedient approach (ca. 7 steps) allows non-traditional, *de novo* synthetic access to analogues of the important antibacterial natural product that can't be prepared from the natural product by semisynthesis.

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Keywords: cyclization • domino reactions • electron-transfer • radical reactions • samarium

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