

Natural Product Synthesis

A Dialdehyde Cyclization Cascade: An Approach to Pleuromutilin**

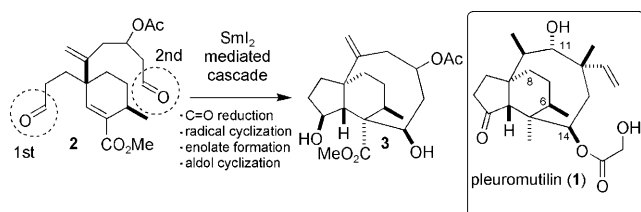
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Resistance to antibiotics is a major concern worldwide and has led to an urgent need to identify antibacterial agents with modes of action distinct from the established classes. The antibacterial natural product pleuromutilin (**1**) is such a candidate (Scheme 1).^[1] Pleuromutilin derivatives are known to bind to the peptidyl transferase site on the 50S ribosomal

the pleuromutilin framework in which a dialdehyde cyclization cascade is used to construct the core of the target in a single step, using a single reagent, with complete diastereocontrol at the four, contiguous stereocenters generated during the cascade.

We recently reported a new class of sequential cyclization of dialdehyde substrates, mediated by SmI_2 ,^[6] in which the aldehyde groups undergo cyclization in sequence.^[7] We proposed that dialdehyde substrates **2** would undergo a cyclization cascade upon treatment with SmI_2 to give concise, stereocontrolled access to the pleuromutilin framework **3**. Central to our approach was the belief that one aldehyde group in **2** would serve as a radical precursor while the other would wait in line to act as an electrophile later in the sequence.^[8] We envisaged that the first aldehyde group would be reduced by SmI_2 to the ketyl radical anion thereby triggering a 5-*exo*-trig radical cyclization. After reduction of the radical formed upon cyclization to a samarium enolate,^[9] the second aldehyde group would react with the enolate to form tricyclic system **3** (Scheme 1).^[10]

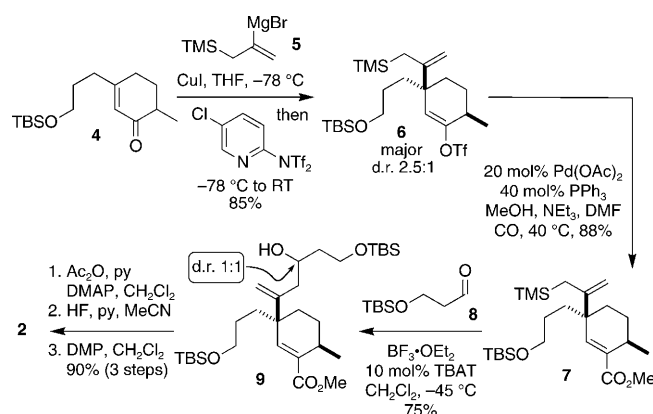
Dialdehyde cyclization substrate **2** was prepared according to the route outlined in Scheme 2. Addition of the organocopper reagent, derived from the Grignard reagent **5**,^[11] to enone **4**^[12] proceeded with moderate diastereoselectivity to give vinyl triflate **6** in 85% yield after trapping of the intermediate enolate with Comins' reagent.^[13] Palladium-catalyzed methoxycarbonylation then gave α,β -unsaturated ester **7** in 88% yield. Lewis acid mediated addition of aldehyde **8**^[14] to the allyl silane motif in **7** gave **9** as a 1:1 diastereoisomeric mixture at the new stereocenter. Subse-



Scheme 1. A SmI_2 -mediated cascade approach to pleuromutilin (**1**).

subunit of bacteria thereby preventing bacterial protein synthesis.^[2] 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 being developed. Although analogues of pleuromutilin are available by minor modification of the natural product, a concise approach to the core of pleuromutilin would allow the preparation of analogues of the natural product displaying improved pharmacokinetic properties.

The structure of pleuromutilin presents a significant synthetic challenge. Whereas Gibbons^[3] and Boeckman et al.^[4] have reported impressive syntheses of racemic pleuromutilin, neither route is well-suited for adaptation to provide analogues of **1**. Elegant studies by Zard and co-workers subsequently showed the potential of a concise approach to the antibacterial,^[5] and provided inspiration for our cascade approach to pleuromutilin. Herein we report a synthesis of



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

Tf = trifluoromethanesulfonyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, DMF = *N,N*-dimethylformamide, TBAT = tetra-*n*-butylammonium difluorotriphenylsilicate, DMAP = 4-dimethylaminopyridine, py = pyridine, DMP = Dess–Martin periodinane.

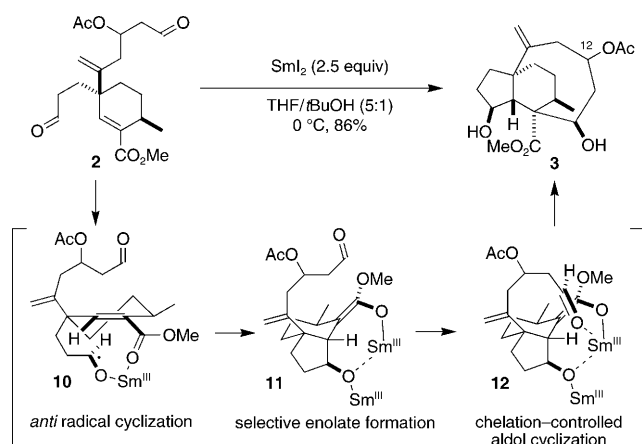
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quent acetylation, deprotection, and oxidation, using the Dess–Martin periodinane,^[15] gave dialdehyde **2** in 90 % overall yield (Scheme 2).

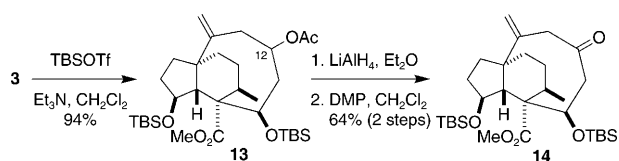
Pleasingly, treatment of **2** with SmI_2 in THF and *t*BuOH, at 0 °C resulted in a cyclization sequence to give **3** in 86 %. Furthermore, the reaction proceeded with complete control at the four contiguous stereocenters generated during the cascade. No by-products arising from the ‘out-of-sequence’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



Scheme 3. A SmI_2 -mediated dialdehyde cyclization cascade for the stereocontrolled construction of the pleuromutilin framework.

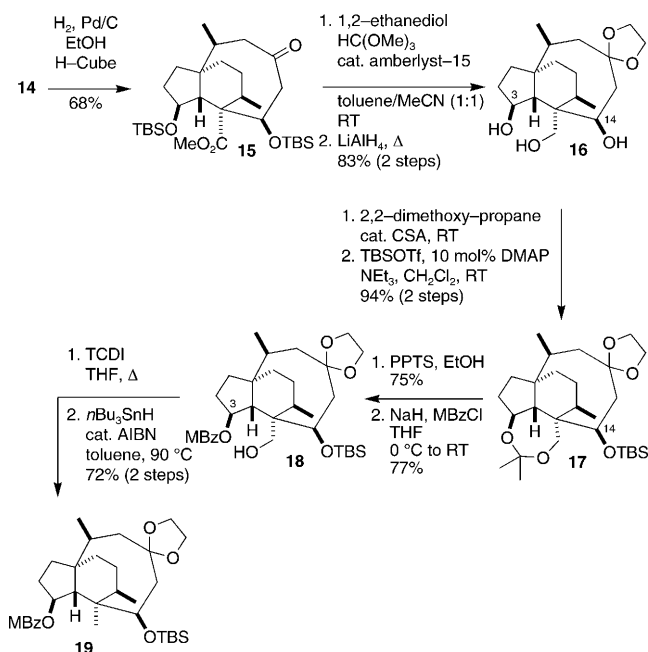
The exquisite control achieved in each stage of the cascade presumably arises from the chelation of intermediates to samarium: coordination to samarium controls the chemoselectivity of aldehyde reduction, the *anti* diastereoselectivity of the cyclization of radical anion **10**,^[16] the formation of a single Sm^{III} -enolate (**11**), and the diastereoselective aldol cyclization through transition-structure **12**. We believe that pre-coordination of samarium to the proximal (or first) aldehyde group and the ester carbonyl group leads to its selective reduction over the more remote aldehyde.^[17] It is well appreciated that pre-coordination of Lewis acidic samarium to the carbonyl group and unsaturated ester component in ketyl–olefin additions is important for promoting the reaction and controlling the diastereoselectivity of such additions.^[18]

To simplify the diastereoisomeric mixture of **3** (at C12), the product of the cascade was converted into the TBS ether **13**, then the C12 acetate was removed and the resulting secondary hydroxy group was oxidized using Dess–Martin periodinane to give ketone **14** in excellent yield (Scheme 4).



Scheme 4. Synthesis of ketone intermediate **14**.

To illustrate the value of the dialdehyde cyclization cascade for the synthesis of pleuromutilin analogues, we have converted ketone **14** into the versatile, orthogonally protected intermediate **19** (Scheme 5). Hydrogenation of the



Scheme 5. Synthesis of the pleuromutilin ‘building block’ **19**. CSA = 10-camphorsulfonic acid, PPTS = pyridinium *p*-toluenesulfonate, MBz = 4-methylbenzoyl, TCDI = 1,1'-thiocarbonyldiimidazole, AIBN = azobis(isobutyronitrile).

alkene in **14** proceeded with high diastereocontrol to give **15** and the C12 ketone was then protected as the corresponding cyclic ketal. The stereochemistry of **15** was confirmed by X-ray crystallographic analysis on a derivative.^[19] Unfortunately, reduction of the methyl ester could not be achieved without removal of the TBS ethers to give triol **16** in good yield. Selective acetal formation and protection of the C14 hydroxy group then gave **17**. Acetal hydrolysis and protection of the C3 hydroxy group with MBz group allowed deoxygenation of the primary hydroxy group, using standard conditions,^[20] to give the pleuromutilin ‘building block’ **19**^[21] in good yield.

In summary, 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 into a valuable pleuromutilin precursor. We are currently applying the approach in the asymmetric synthesis of pleuromutilin analogues that can not be accessed from the natural product by semi-synthesis.

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