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A Concise Synthesis of the Molecular Framework of Pleuromutilin

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Abstract

Two syntheses of the tricyclic carbon skeleton of pleuromutilin are reported. Diastereoselective 1,4-conjugate additions were used to elaborate bicyclic precursors at an early stage of each route, while ring-forming olefin metatheses were executed to complete the pleuromutilin carbon framework. The congeners prepared are appropriately functionalized to enable access to diverse pleuromutilin analogues.

In 1951, Kavanagh and coworkers described the isolation of the diterpene pleuromutilin (**1**) from several species of basidiomycetes, including the edible mushroom *Pleurotus mutilus*.¹ In the period of 1962–1963, Arigoni² and Birch³ independently reported their creative insights that led to the elucidation of the complex molecular structure of pleuromutilin. These efforts and the subsequent X-ray crystallographic analysis of a bromoacetate derivative by Dobler and Duerr⁴ revealed that pleuromutilin possesses eight stereocenters and a unique “propellane-like” fusion of 5-, 6-, and 8-membered rings wherein the three rings share a common carbon-carbon bond (Figure 1). Not surprisingly, pleuromutilin stimulated creative advances in chemical synthesis.⁵ As of this writing, the groups of Gibbons^{5a} and Boeckman^{5b} achieved remarkable syntheses of the full structure of pleuromutilin; more recently, the groups of Paquette,^{5c} Trost,^{5d} Kahn,^{5f} Zard,^{5g} and Procter^{5h} reported creative strategies for constructing key elements of this complex natural product.

Pleuromutilin is the prototype of a class of antibiotics that inhibit bacterial protein synthesis by binding to the peptidyl transferase domain of the 50S ribosomal subunit.⁶ Although liver enzymes rapidly metabolize the pleuromutilins, these compounds are of considerable interest as antibiotics because they are unaffected by resistance to the macrolides, another class of 50S-targeting antibiotics.⁷ The ready availability of pleuromutilin through fermentation of microorganisms⁸ such as *Clitopilus*, *Octojuga*, and *Gerronema* fueled a substantial program at GlaxoSmithKline aimed at the development of new pleuromutilin-based antibiotics through semisynthetic modifications of the pleuromutilin structure.⁹ This effort led to the development of the topical antibiotic retapamulin (**2**), the first approved drug from the pleuromutilin class, and tiamulin (**3**), an antibiotic for use in veterinary medicine.¹⁰ Despite these significant developments, the potential of the pleuromutilin scaffold as a source for promising new antibiotics has not been fully developed.¹¹ As part of

a larger effort to expand the structural diversity of the pleuromutilin class of antibiotics through advances in *de novo* chemical synthesis, we achieved short syntheses of the pleuromutilin-like molecular scaffold from readily available hydrindane derivatives. The development of this approach for building the pleuromutilin scaffold is described herein.

Our plan for synthesis was informed by prior reports of the intrinsic challenge of annulating the pleuromutilin-like, eight-membered ring onto bicyclic precursors. For example, the barriers for achieving late-stage constructions of the C5–C14 and C9–C10 bonds undermined the development of otherwise attractive strategies.^{5d} Nevertheless, we were drawn to the idea of constructing the eight-membered medium ring by the method of ring-closing olefin metathesis (RCM)¹² for two reasons: (1) several reports demonstrated the feasibility of medium-ring formations by RCM,¹³ and (2) we anticipated that the types of bis-alkenes that would be required for the key cyclization step could be amenable to relatively short syntheses from convenient precursors. For example, the known enones **4**¹⁴ and **5**¹⁵ (Scheme 1) emerged as logical starting points for syntheses of bis-alkenes **6** and **7**, respectively; the relatively rigid structures of hydrindanones **6** and **7**, with their axially disposed side chains at C-5 and C-9, were anticipated to have a favorable effect on the planned olefin metatheses to afford compounds **8** and **9**, respectively. If successful, these ring closures would generate compounds possessing the complex, cyclic connectivity of pleuromutilin as well as alkenes that could serve our analogue development program. The transformations that brought this general plan to fruition are described below.

The idea that we might fashion the challenging C-9 quaternary stereocenter in the course of a 1,4-conjugate addition to the known bicyclic enone **4**¹⁴ was attractive; however, it was only after several attempts that we discovered that the combined action of vinylmagnesium bromide, copper bromide dimethyl sulfide complex and boron trifluoride etherate¹⁶ on enone **4** afforded the desired ketone **10** as a 2:1 mixture of diastereomers (Scheme 2). To set the stage for a second conjugate addition reaction, compound **10** was converted to the thermodynamic enol silane **11**, which was subsequently transformed to enone **12** via a Saegusa oxidation.¹⁷ We were pleased to observe that exposure of enone **12** to diethylaluminum cyanide¹⁸ resulted in the formation of *cis*-fused bicycle **13** in 89% yield as a single diastereoisomer whose structure was confirmed by X-ray crystallography.

To maximize our chances of achieving an efficient synthesis of RCM substrate **17**, we protected the keto group of **13** to give ketal **14** (Scheme 3). A regioselective hydroboration of the alkene in **14** was then followed by an *in situ* Suzuki coupling¹⁹ with 2-bromopropene, a sequence that afforded the homologated alkene **15** in 71% yield. While the nitrile group in **15** proved to be unreactive toward Grignard reagents, it was possible to produce aldehyde **16** by a reduction/hydrolysis sequence. Addition of vinylmagnesium bromide to the aldehyde afforded an epimeric mixture of secondary alcohols, which was oxidized to enone alkene **17** with the Dess-Martin periodinane (DMP).²⁰ By this sequence, diene **17** was produced in 50% yield over the three steps, requiring only one purification by column chromatography. When a solution of **17** and Grubbs' second-generation olefin metathesis catalyst (3×10^{-3} mol %) in dichloromethane was heated to reflux for 24 hours, the desired 8-membered ring formation took place and afforded compound **18**, a substance with the unique, tricyclic carbon skeleton of pleuromutilin. The yield for this ring closure was moderate, and we observed that related compounds having silyloxy groups at C-11 were unreactive toward ring-closing metathesis.²¹

With the aim of incorporating functional groups at C-11 of our pleuromutilin scaffolds, we developed syntheses of diene alcohols **23** and **24** (Scheme 4). In the wake of a copper-catalyzed 1,4-conjugate addition of Grignard reagent **19** to enone **5**, the putative intermediate **20** was directly transformed to bicyclic enone **21**²² via an acid-induced

cyclodehydration.²³ A diastereoselective conjugate addition of cyanide to the newly fashioned enone was then followed by a ketone protection step (**21**→**22**) and a nitrile reduction/Grignard addition sequence to give epimeric alcohols **23** and **24** as a 1:2 mixture of diastereomers that could be resolved by silica gel chromatography.

It was possible to convert alcohol **24** to the C-14 epimer **23** via a two-stage oxidation/reduction sequence (Scheme 5). It was also possible to independently transform alcohols **23** and **24** to esters **27** and **28**, respectively, by carbodiimide-mediated acylations with the known carboxylic acid **26**.²⁴ When a solution of ester **27** and the Hoveyda-Grubbs second-generation olefin metathesis catalyst²⁵ (2×11 mol%) in methylene chloride was heated to reflux, the pleuromutilin-like tricyclic alkene **29** was produced and isolated in 80% yield. Surprisingly, ester **28** did not undergo an analogous metathesis cyclization; even under dilute conditions, only slow dimerization of the substrate was observed.

A diastereoface-selective epoxidation of **29** with *m*-CPBA afforded the crystalline compound **31**, whose relative stereochemistry was confirmed by an X-ray crystallographic analysis (Scheme 6). Our intent is to utilize **31** in syntheses of antibacterial screening candidates that are epimeric to natural pleuromutilin at C-14.

To further investigate the disparate reactivity of esters **27** and **28**, a small family of related derivatives were constructed (Scheme 7). The outcomes of our attempts to achieve ring-forming olefin metatheses with these substrates mirrored our observations regarding esters **27** and **28**: the viability of the metathesis process seemed to hinge on the configuration at C-14. One possible explanation for the observation is that a destabilizing, non-bonded interaction between the hydroxy-derived group on C-14 and the methyl group on C-12 hinders the formation of metallocyclobutane **33**; this type of steric clash would not destabilize the transition state leading to metallocyclobutane **35**. Furthermore, a marked rate enhancement was observed in the ring-closing metathesis reactions of derivatives with bulky groups at C-14.²⁶ This could be interpreted as an alteration in the conformational bias of the molecule toward conformer **34b**, where the pendent olefins should be more ideally suited to engage the metathesis catalyst.

The transformations described herein constitute our initial attempt to expand the pleuromutilin class of antibiotics through the achievement of a rapid synthesis of the pleuromutilin molecular scaffold. This work is thus a contribution toward the larger aims of establishing how much of the full structure of pleuromutilin is required for antibiotic activity and elucidating the potential of this underdeveloped scaffold as a source for new antibiotics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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26. For RCM rates and yields of **27** and its analog with triethylsilyloxy at C-14, see supporting information. Compounds **23**, **24** and **25** were unreactive under same RCM conditions.

Fig. 1.
Pleuromutilin (1), Retapamulin (2) & Tiamulin (3)

Scheme 1.

An approach to the pleuromutilin framework featuring ring-closing olefin metatheses.

Scheme 2.
Synthesis of Nitrile **13**. HMDS = hexamethyldisilazane

Scheme 3.

Construction of Pleuromutilin Skeleton **18**. 9-BBN = 9-borabicyclononane; DIBAL = diisobutylaluminum hydride.

Scheme 4.

Synthesis of Bicycles **23** and **24**. DMAP = 4-dimethylaminopyridine; $p\text{-TsOH}$ = p -toluene sulfonic acid.

Scheme 5.

Construction of Pleuromutilin Skeleton **29**. DCC = *N,N'*-dicyclohexylcarbodiimide.

Scheme 6.

Synthesis and X-ray crystallographic analysis of epoxide **31** (C-14 side-chain has been partially omitted for clarity). *m*-CPBA = 3-chloroperoxybenzoic acid.

Scheme 7.
Proposed Conformational Bias in the Olefin Metathesis