Communication

Total Synthesis of (+)-Pleuromutilin

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Supporting Information Placeholder

ABSTRACT: An 18-step synthesis of the antibiotic (+)-pleuromutilin is disclosed. The key steps of the synthesis include a highly stereoselective SmI_2-mediated cyclization to establish the eight-membered ring, and a stereospecific transannular [1,5]-hydrogen atom transfer to set the C10 stereocenter. This strategy was also used to prepare (+)-12-*epi*-pleuromutilin. The chemistry described here will enable efforts to prepare new mutilin antibiotics.

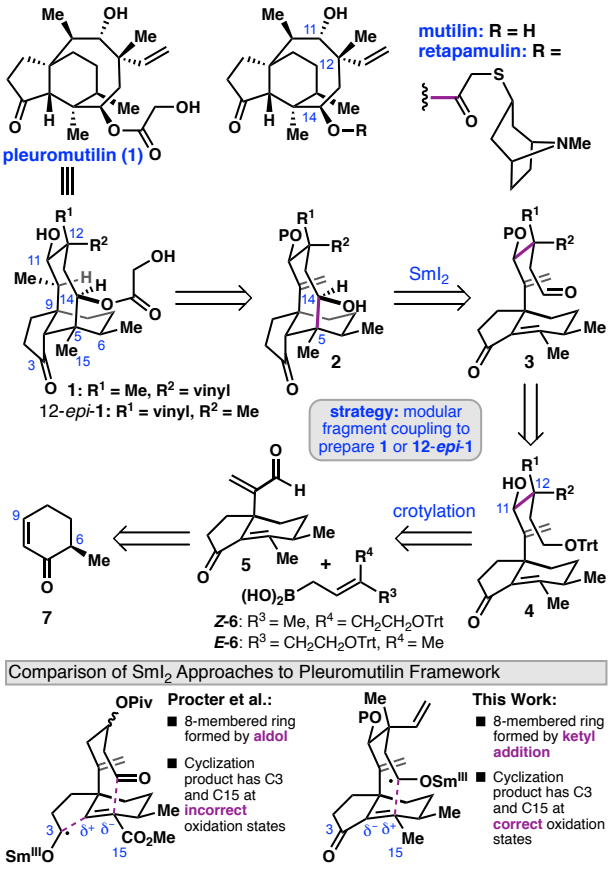
(+)-Pleuromutilin (**1**) is a diterpene natural product first isolated from the fungus *Clitopilus passeckerianus* in 1951 (Scheme 1).[1] (+)-Pleuromutilin binds to the peptidyl transferase center of bacterial ribosomes, preventing protein synthesis.[2] Semi-synthetic derivatives of **1** in which the C14 ester is modified have been identified as potent antibiotics; for example, retapamulin is an FDA-approved topical antibiotic.[3] Recently, derivatives of 12-*epi*-mutilin have been developed as broad-spectrum antibiotics with efficacy against gram-negative pathogens.[4] Given its promising antibacterial properties, four total syntheses of **1** have been reported to date, the most recent of which was disclosed by Herzon and coworkers in 2017.[5,6,7] Here we report an approach that enables the preparation of (+)-pleuromutilin and (+)-12-*epi*-pleuromutilin in 18 steps from (+)-*trans*-dihydrocarvone.

In considering a design plan for a synthesis of (+)-**1**, we targeted a modular approach in which a bifunctional hydrindane fragment (e.g. **5**) would be annulated to form the eight-membered ring through two sequential C–C bond forming steps. In particular, the C5–C14 and C11–C12 bonds, which each link vicinal stereogenic centers, were identified as strategic points of disconnection.

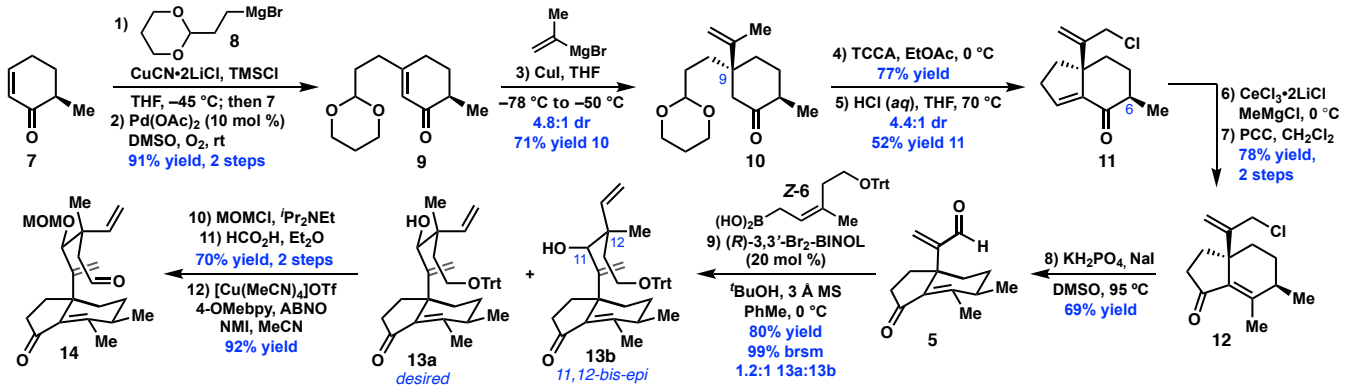
Applying this general plan in a retrosynthesis, (+)-**1** was simplified to **2**, which was further disconnected through the C5–C14 bond to aldehyde **3** (Scheme 1). In the forward sense, we envisioned forming the eight-membered ring through a late-stage SmI_2-mediated ketyl radical cyclization of **3**.[8] It is important to distinguish this approach from the SmI_2-mediated cascade cyclization employed in Procter's synthesis of **1**,[5c,d] which formed the C3–C4 bond by a ketyl radical conjugate addition, and the C5–C14 bond—and 8-membered ring—by intramolecular aldol cyclization. To enable the cascade reaction, Proctor employed an ester as a precursor to the C15 methyl, and required several additional steps to adjust the oxidation states at C3 and C15. In contrast, a SmI_2 cyclization of **3** was expected to provide **2** with C3, C14, and C15 in the correct oxidation states for advancement to **1**.

Aldehyde **3** was anticipated to arise from enone **4**, which, depending on the targeted stereochemistry at C12, could be prepared by crotylation of enal **5** with either *Z*- or *E*-boronic

Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of a cyclization substrate.



acid **6**.[9] Thus, through appropriate design of the crotylation reaction, either **1** or **12-*epi*-1** would be accessible through this route. Hydrindanone enal **5** was mapped back to enone **7** via sequential conjugate addition reactions and functional group interconversions.

The synthesis began with the preparation of enone **7** in one step from (+)-*trans*-dihydrocarvone.[10] Conjugate addition of the cuprate derived from **8**, followed by Pd-catalyzed desaturation furnished **9** (Scheme 2). A second conjugate addition furnished the C9-quaternary stereocenter; however, attempts to promote an intramolecular aldol condensation under Brønsted- or Lewis-acid catalysis resulted in the formation of undesired Prins-type products. Hypothesizing that electronic deactivation of the isopropenyl group would mitigate this non-productive reactivity, **10** was converted to the allylic chloride using trichloroisocyanuric acid (TCCA).[11] Indeed, treatment of the ketal with HCl at 70 °C provided enone **11** as a 4.4:1 mixture of diastereomers at C6; the major diastereomer was isolated in 52% yield. 1,2-Addition of methylmagnesium chloride was achieved with the aid of $CeCl_3$•2LiCl[12] and the diastereomeric mixture was submitted to pyridinium chlorochromate (PCC) to effect an oxidative transposition.[13] Kornblum oxidation[11] of **12** delivered enal **5** in 8 steps from **7**.

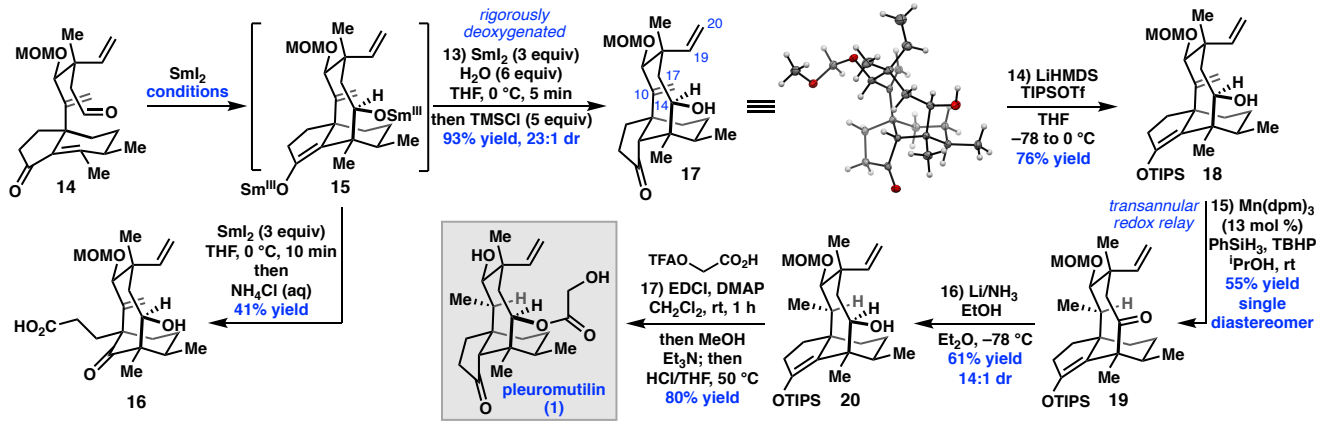
With enal **5** in hand, the first of two key C–C bond constructions required to form the bridging eight-membered ring was investigated. Reaction of **5** with boronic acid ***Z*-6**[14] under the conditions developed by Szabó and coworkers provided a mixture of diastereomers **13a** and **13b** (Scheme 4).[9b] While the reaction proceeded with excellent selectivity for *syn* crotylation—consistent with a closed transition state—the catalyst did not discriminate between the diastereofaces of the aldehyde during the nucleophilic attack. Use of the *S* catalyst provides a 1:1.4 mixture of **13a** and **13b**.[15] A brief investigation of alternative catalytic asymmetric crotylation conditions proved unfruitful. Separation of the diastereomers by column chromatography, followed by protection of **13a** as the methoxymethyl (MOM) ether, cleavage of the trityl ether, and oxidation under the conditions developed by Stahl[16] delivered aldehyde **14**.

At this stage, attention turned to the second key C–C bond construction: a SmI_2-mediated cyclization to form the eight-membered ring (Scheme 3). When **14** was treated with a freshly-prepared solution of SmI_2 in THF at 0 °C, then quenched with aqueous ammonium chloride, carboxylic acid **16** was obtained as a single diastereomer. Presumably **16** arises from exposure of Sm^{III}-enolate **15** to oxygen, resulting in formation of an α-peroxyketone and subsequent oxidative ring scission.[17] Although the ring scission was deleterious, it nonetheless confirmed that C–C bond formation occurred with high diastereoselectivity.

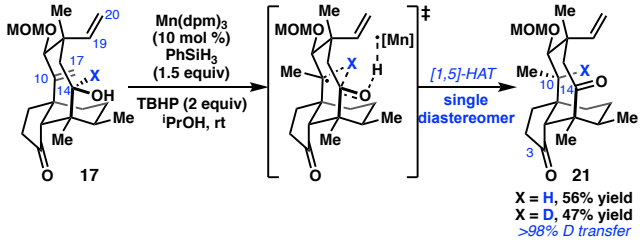
In an effort to prevent the unwanted formation of **16**, a variety of conditions were evaluated. After substantial optimization, it was found that dropwise addition of SmI_2 (3 equiv) to **14** and 6 equiv H_2O as a solution in THF at 0 °C, under rigorously anaerobic conditions, followed by quenching first with trimethylsilyl chloride (TMSCl), then aqueous workup delivered tricycle **17** in 93% yield as a separable 23:1 mixture of diastereomers (Scheme 3). The addition of H_2O was found to be critical to minimize undesired side-product formation and achieve high diastereoselectivity; reactions conducted in the absence of H_2O afforded **17** with 1:1 dr at C14.

To complete the synthesis of (+)-**1**, chemoselective reduction of the C10–C17 exocyclic olefin and installation of the glycolate ester were required. Unfortunately, standard hydrogenation conditions employing cationic transition metal complexes gave rapid and exclusive reduction of the more sterically-accessible C19–C20 vinyl group. Instead, we turned to hydrogen-atom transfer (HAT) reactions, seeking to leverage the thermodynamic preference for formation of a 3°carbon-centered radical.[18] Indeed, use of tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese (III) ($Mn(dpm)_3$) in the presence of phenylsilane and *tert*-butyl hydroperoxide (TBHP) in degassed, anhydrous isopropanol resulted in highly diastereoselective reduction of the C10–C17 olefin (Scheme 4).[19] We were surprised to discover, however, that alkene reduction was accompanied by oxidation of the C14 alcohol. This redox relay process delivered diketone **21** in 55% yield as a single diastereomer. Only

Scheme 3. Completion of the synthesis of (+)-pleuromutilin (1).



Scheme 4. Redox relay by transannular [1,5]-HAT.

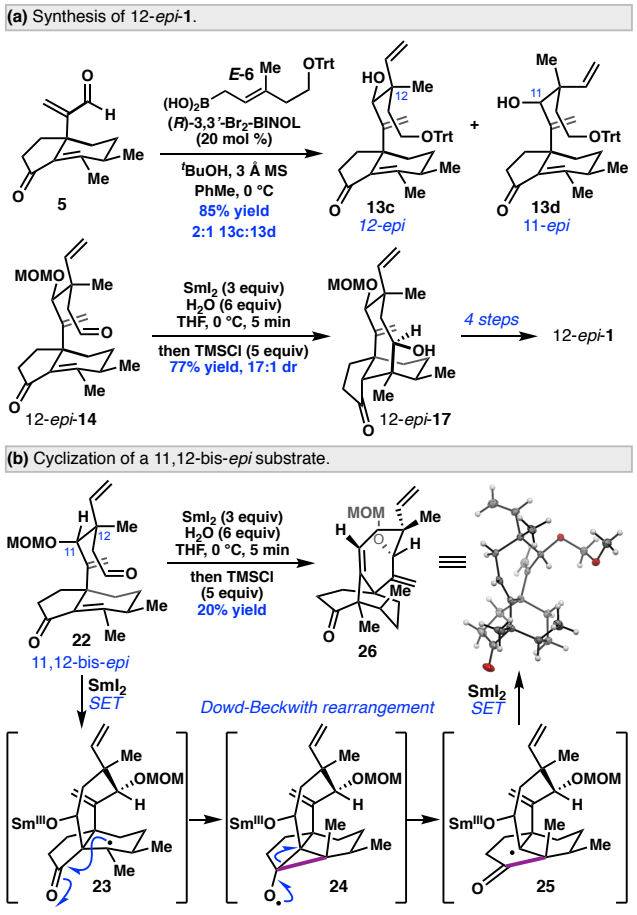


trace products arising from competing C19-C20 vinyl reduction were observed. Substrates in which the C14 alcohol is protected gave only 6–10% conversion after 6 h, and the resulting C10 stereocenter was formed as a mixture of diastereomers. To test if this reaction proceeds by a transannular [1,5]-HAT process,[20] deuterium-labeled substrate **17-*d*** was prepared and exposed to the optimized reaction conditions (Scheme 4). Tricycle **21-*d*** was formed as a single diastereomer with complete transfer of the deuterium label. The observation that substrates in which the C14 alcohol is protected perform poorly under the HAT conditions suggests that cleavage of the O–H bond to form the C14 ketone serves as a driving force for this transformation.[21]

Having solved the problem of chemoselective alkene reduction, the selective reduction the C14 ketone in the presence of the C3 ketone was now required. Ultimately, selective reduction of diketone **21** proved untenable. Instead, triisopropylsilyl (TIPS) enol ether **18** was prepared and submitted to radical reduction to obtain ketone **19** as a single diastereomer (Scheme 3). To complete the total synthesis, **19** was submitted to excess lithium in ammonia, which furnished alcohol **20** as a separable 14:1 mixture of diastereomers. Subsequent one-pot acylation with 2-(2,2,2-trifluoroacetoxy)acetic acid followed by trifluoroacetate methanolysis, then acidic hydrolysis effected global deprotection to deliver (+)-**1**.

A key design aspect of our strategy was the ability to easily vary the stereochemistry of the cyclization substrates at C11 and C12. In particular, given the recent interest in derivatives of C12-*epi*-mutilin as broad-spectrum antibiotics,[4] we sought to demonstrate that the 12-*epi*-mutilin framework could be prepared. To this end, enal **5** was subjected to crotylation with ***E*-6** under the previously developed conditions, to deliver **13c** and **13d** as a 2:1 mixture in 85% combined yield (Scheme 5, a). Elaboration of **13c** to 12-*epi*-**14** proceeded without difficulty.[15] Exposure of 12-*epi*-**14** to the optimal conditions for the SmI_2 cyclization furnished 12-*epi*-**17** in

Scheme 5. Reactivity of diastereomeric cyclization substrates.



77% yield and 17:1 dr. 12-*epi*-**17** was smoothly advanced four steps to complete the synthesis of 12-*epi*-**1**.[15]

In contrast, attempts to cyclize aldehyde **22**, prepared from crotylation product **13b**, revealed that the C11 stereochemistry exerts a pronounced effect on reactivity (Scheme 5, b). Subjection of **22** to the SmI_2-mediated cyclization conditions provided tricycle **26** as the major product in 20% yield.[22] It is proposed that conformational gearing to minimize $A^{1,2}$ strain at C11 reverses the regioselectivity of the Sm-ketyl addition to the enone, producing radical **23**. Subsequent Dowd-Beckwith rearrangement proceeding through cyclopropane **24** delivers the product bearing a bridgehead olefin.

In summary, the total syntheses of (+)-pleuromutilin and (+)-12-*epi*-pleuromutilin were each completed in 18 steps (longest linear sequence) from (+)-*trans*-dihydrocarvone. These syntheses were enabled by a modular approach, which employed a highly diastereoselective SmI_2-mediated radical cyclization to form the eight-membered ring. In addition, we uncovered a transannular [1,5]-HAT that effects a stereospecific redox relay to set the C10 stereocenter. The brevity and modularity of the route will enable the design and synthesis of new fully synthetic variants of mutilin antibiotics.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI: xx.xxxx/jacs.xxxxxxxxx.

Crystallographic data for **16**, **17**, and **26** (CIF)

Experimental procedures and characterization and spectral data for all compounds (PDF)

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Author Contributions

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22. The aldehyde derived from **13d** underwent the analogous cyclization.

TOC graphic: