Total Synthesis of (+)-Pleuromutilin

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(+)-Pleuromutilin is a diterpene natural product first isolated from the fungus Clitopilus passeckerianus in 1951 (+)-Pleuromutilin binds to the peptidyl transferase center of bacterial ribosomes, preventing protein synthesis.

Recently, derivatives of 12-epi-mutilin have been developed as broad-spectrum antibiotics with efficacy against Gram-negative pathogens.

Four total syntheses of 1 have been reported to date, the most recent of which was disclosed by Herzon and co-workers in 2017.

Here we report an approach that enables the preparation of (+)-pleuromutilin and (+)-12-epi-pleuromutilin in 18 steps from (+)-trans-dihydrocarvone.

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Retrosynthetic Route

**Strategy:** modular fragment coupling to prepare 1 or 12-epi-1

**Comparison of Sml$_2$ Approaches to Pleuromutilin Framework**

- **Procter et al.**
  - 8-membered ring formed by aldol
  - Cyclization product has C3 and C15 at incorrect oxidation states

- **This Work:**
  - 8-membered ring formed by ketenyl addition
  - Cyclization product has C3 and C15 at correct oxidation states
The image depicts a chemical reaction scheme with various chemical structures and reactions steps. The scheme includes the conversion of compound 12 through a sequence of reactions leading to the formation of products 13a and 13b.

1. **Conversion of 12 to 5**
   - Reaction with KH₂PO₄, NaI in DMSO at 95 °C yields 5 with 69% yield.

2. **Conversion of 5 to 13a and 13b**
   - Reaction with (R)-3,3'-Br₂-BINOL (20 mol %) in βBuOH, 3 Å MS at PhMe, 0 °C yields 13a and 13b with 80% yield and 99% brsm.
   - The ratio of 13a:13b is 1.2:1, with 13a being the desired product.

3. **Detailed Mechanism**
   - The reaction involves the use of a sulfonamide reagent and a boronic acid derivative.
   - The mechanism is supported by steric congestion and the preferred face of the reaction.

The scheme includes stereochemical analysis with the major and minor enantiomers indicated for compounds 5a and 5b.

- **5a**, Major enantiomer
- **5b**, Minor enantiomer

The overall scheme demonstrates the synthesis of 13a and 13b via a series of carefully controlled steps, illustrating the complexity and precision required in organic synthesis.
13) Sml\(_2\) (3 equiv) H\(_2\)O (6 equiv)
THF, 0 °C, 5 min
then TMSCl (5 equiv)
93% yield, 23:1 dr

14

rigorously deoxygenated

15

17

14

Sml\(_2\) conditions

15

rigorously deoxygenated

17

Sml\(_2\) (3 equiv) H\(_2\)O (6 equiv)
THF, 0 °C, 5 min
then TMSCl (5 equiv)
aqueous workup

16

Sml\(_2\) (3 equiv) THF, 0 °C, 10 min
then NH\(_4\)Cl (aq)
41% yield

MOMO
Redox Relay by Transannular [1,5]-HAT

Mn(dpm)$_3$ (10 mol %) 
PhSiH$_3$ (1.5 equiv)
TBHP (2 equiv) 
iPrOH, r.t.

X= H, 56% yield
X= D, 47% yield
> 98% D transfer
synthesis of 12-epi-1

\[
\text{(R)-3,3'-Br}_2\text{-BINOL (20 mol %)}
\]

\[
\begin{align*}
&5 \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
&\text{BuOH, 3 Å MS} \\
&\text{PhMe, 0 °C} \\
&85\% \text{ yield} \\
&2:1 \text{ 13c:13d}
\end{align*}
\]

12-epi

11-epi

\[
\text{SmI}_2 (3 \text{ equiv})
\]

\[
\text{H}_2\text{O (6 equiv)}
\]

\[
\text{THF, 0 °C, 5 min then TMSCl (5 equiv)}
\]

77\% \text{ yield, 17:1 dr}

4 steps

12-epi-1