A modular and enantioselective synthesis of the pleuromutilin antibiotics

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Antimicrobial resistance (AMR) threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi.

WHO Website (http://www.who.int/mediacentre/factsheets/fs194/en/)
Pleuromutilin and C14-Modified Derivatives

Natural products

(+)-pleuromutilin (1)  (+)-mutilin (2)

Isolation: Pleurotus mutilus (Clitopilus scyphoides)

Activity: Inhibition of protein synthesis in bacteria by binding to the peptidyl transferase component of the 50S subunit of ribosomes.

Veterinary antibiotics

R =

- tiamulin (DENEGARD®)
- valnemulin (ECONOR®)

Human topical antibiotic

- retapamulin (ALTABAX®, 3)
  anti-MRSA infections

Unlisenced

- azamulin
- BC-3781
- BC-3205

Retrosynthetic analysis of the mutilin scaffold

- Epimerization at C12 caused expression of activity against various Gram-negative pathogens (GNPs)
- Functionalization of the alkene at C12 extends the activity against GNPs

This approach maximizes the scope of accessible derivatives at positions 11 to 13

K. Thirring et al., U.S. Patent WO2015110481A1, **2015**
Total Synthesis of Pleuromutilin

Gibbons' synthesis (1982): • Racemic • 31 linear steps • Overall <0.6% yield


Boeckman's synthesis (1989): • Racemic • 27 linear steps • Overall 0.4% yield


Procter's synthesis (2013): • Non-racemic • 34 linear steps • Overall 0.7% yield

D. J. Procter et al. Chemistry, 2013, 19, 6718-6723
Synthesis of Coupling Fragment 7

1. Zn(CH₃)₂ (1.05 eq)  
   Cu(OTf)₂ (0.5 mol%)  
   Ligand (1.0 mol%)  
   then  
   CH₃Li (1.05 eq)  
   CH₃OC(O)CN (1.2 eq)

   MeO₂C═H
   Me

   9

2. CH₃I (5.0 eq)  
   t-BuONa (2.0 eq)  
   MeOH, 0 °C  
   71% (over 2 steps)  
   >20:1 dr, 97:3 er

   MeO₂C
   Me

   10

3. KHMDS (5.0 eq)  
   PhNTf₂ (2.0 eq)  
   THF/toluene (2:1)  
   -78 °C, 88%

   MeO₂C
   OTf

   11

4. Pd(PPh₃)₄ (4 mol%)  
   LiCl (5.0 eq)  
   Sn(C₂H₃)₄ (1.3 eq)  
   DMF, CO (1 atm)  
   40 °C, 83%

   MeO
   Me

   12

5. Cu(OTf)₂ (5.0 mol%)  
   (CH₂Cl₂)₂  
   60 °C, 88%

   MeO
   Me

   13

6. Et₂AlCN (3.0 eq)  
   THF, 0 °C  
   then  
   DIBAL-H (3.0 eq)  
   -78 °C

   MeO
   14

7. 0.01 M NaOH  
   MeOH/H₂O (5:1)  
   0 °C  
   65% (from 13)

   MeO
   Me

   15

8. TMSOTf (8.0 eq)  
   (TMSOCH₂)₂ (7.0 eq)  
   CH₂Cl₂, 30 °C  
   84%

   MeO
   Me

   16

9. MeLi (3.0 eq)  
   toluene, 0 °C

   MeO

   17

10. Boc₂O (4.0 eq)  
    80%

   Boc

   18

11. Boc

   7

12. Ligand

   [Chemical structure]
Synthesis of Diketone 25

1. Synthesis of 20:
   - NaHMDS (2.0 eq), PMBOCH₂Cl (2.0 eq)
   - THF, -78 to 0 °C, 60%, 7:1 dr

2. Reduction of 20 to 8:
   - LiAlH₄ (2.0 eq)
   - Et₂O, 0 °C, 71%
   - I₂ (1.1 eq), PPh₃ (1.1 eq), imidazole (2.0 eq)
   - THF, 70 °C, 74%

3. Synthesis of 7 and 8:
   - KHMDS (3.5 eq), Comin’s reagent (1.3 eq)
   - THF, -78 °C, 81%
   - t-BuLi (4.4 eq)
   - Et₂O, -45 °C
   - 1M HCl, THF
   - 0 °C, 48%

4. Further transformations:
   - Ni(cod)₂ (1.1 eq), IPr (1.0 eq), Et₃SiH (3.0 eq)
   - THF, 60%, >20:1 dr, >20:1 rr
   - TBAF (5.0 eq), THF

   - 1) DMP (4.0 eq)
   - DCM, 96%
   - 2) SmI₂ (4.0 eq)
   - THF/MeOH (2:1)
   - 98% (over 2 steps)
   - >20:1 dr

5. Completion of the synthesis:
   - 24
   - 25
Synthesis of (+)-12-epi-mutilin and (+)-11,12-di-epi-mutilin

Na (excess)  
EtOH, >20 °C, 52%  
C14: >20:1 dr  
C11: equatorial/axial, 3:1 dr

then  
conc. HCl (excess)  
THF/MeOH (1:1)  
96% (for 4), 81% (for 26)

<table>
<thead>
<tr>
<th>conditions</th>
<th>28 : 27</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sml₂, H₂O</td>
<td>1.3 : 1</td>
<td>80%</td>
</tr>
<tr>
<td>2. LiEt₃BH</td>
<td>1 : &gt;20</td>
<td>81%</td>
</tr>
</tbody>
</table>

Na (excess)  
EtOH, >20:1 dr  
then  
conc. HCl (excess)  
92% (for 28 to 4)  
81% (for 27 to 26)
Synthesis of (+)-12-epi-pleuromutilin, (+)-pleuromutilin and (+)-11,12-di-epi-pleuromutilin

(+)-12-epi-mutilin (4)

TFA-N (6.0 eq)
EtOAc, -78 °C, 65%

A

TFAO
(3.3 eq)
EDC·HCl (3.3 eq)
DMAP (3.3 eq), DCM
then MeOH, NaHCO₃
91%

(+)-12-epi-pleuromutilin (29)
1.1% overall yield

TrO
(3.3 eq)
EDC·HCl (3.3 eq)
DMAP (3.3 eq), DCM
then MeOH, NaHCO₃, 98%

30

Et₂Zn (1.03 eq)
DMF, 100 °C
then conc. HCl
33% for 1
56% for 29

(+)-pleuromutilin (1)
0.4% overall yield

TrO
(6.0 eq)
EDC·HCl (6.0 eq)
DMAP (16 eq)
DMF, 81%, 8:1 rr

B

conc. HCl
THF/MeOH
(4:1), 82%

(+)-11,12-di-epi-pleuromutilin (32)
2.3% overall yield

(+)-11,12-di-epi-mutilin-ketal (31)
Conclusion

17-20 steps

\[
\text{(+)-12-\textit{epi}-mutilin (4)} \quad 3.6\% \text{ overall yield}
\]

\[
\text{(+)-11,12-\textit{di-epi}-mutilin (26)} \quad 3.0\% \text{ overall yield}
\]

\[
\text{(+)-pleuromutilin (1)} \quad 0.4\% \text{ overall yield}
\]

\[
\text{(+)-12-\textit{epi}-pleuromutilin (29)} \quad 1.1\% \text{ overall yield}
\]

\[
\text{(+)-11,12-\textit{di-epi}-pleuromutilin (32)} \quad 2.3\% \text{ overall yield}
\]
Questions?
Epiperization at C12 quaternary stereocenter

Tandem conjugate addition–acylation

Polarized Nazarov Cyclization

(D=electron-donating group; E=electron-withdrawing group)

Conjugate Hydrocyanation

Exo-Selective Reductive Macrocyclization of Ynals