A Practical, Enantioselective Synthetic Route to a Key Precursor to the Tetracycline Antibiotics


![Chemical Reaction Diagram]

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Tetracycline Antibiotics

- Discovered in late 1940’s by fermentation methods
- The four fused ring system binds to the 30S subunit of the bacterial ribosome
- Used widely as broad-spectrum antibiotics for human and animals
- Extensive use over the past half century has led to widespread bacterial resistance by two major mechanisms: direct cleaning from the ribosome (TetM protein) or pumping out of the cell (TetA protein)
Crystal Structure of the Tetracycline-bound 30S

Biosynthesis of Tetracycline Antibiotics

- Much of the polar functionality important for binding lies in the AB fragment.
- D ring is tolerant to diverse modifications—important site to generate analogs to overcome bacterial resistance.
- Analogs without hydroxyl at C-6 are more resistant to degradation.

Past Synthetic Endeavors

**Sancycline**
25 steps, \(~\text{0.002\% yield}\)

**Terramycin**
22 steps, \(0.06\%\) yield

**Tetracycline (1)**
34 steps, \(0.002\%\)

**12a-deoxytetracycline (2)**
16 steps, 18-25\% yield
First Synthesis from the Myers Group

Key step: a generalized Michael-Dieckmann reaction sequence that forms the C ring of tetracyclines from the coupling of structurally varied carbanionic D-ring precursors with either of the AB precursors 4 or 5.

Synthesis of 4 and 5
Michael-Dieckmann Cyclization

\[ \text{Rational of化合} \]

\[ \text{Conditions: LDA, TMEDA, THF, -78 °C} \]

\[ \text{Yield: 81%} \]

\[ \text{Further treatment with HF, CH}_3\text{CN} \]

\[ \text{Yield: 85% (2 steps)} \]

\[ (-)-6-\text{Deoxytetracycline} \]
Synthesis of Analogs

- Compound 10 showed activity equal to or greater than tetracycline including strains with resistance to tetracycline, methicillin, and vancomycin.
Current Paper: Scalable Synthesis of the AB Core Intermediate

Brubaker, J. D; Myers, A. G. *Org. Lett.* 2007, 9, 3523.
Transition State

\[ \text{(S)-3} \]

\[ \text{(R)-3} \]
Intramolecular Diels-Alder Reaction

\[
\text{(S)-alcohol 7} \quad 1.3 \\
\text{(R)-alcohol 7} \quad 1 \\
\downarrow \\
95 \rightarrow 110 \, ^{\circ}\text{C} \\
\text{Endo (S)} \quad 6.2 \\
\text{Exo (S)} \quad 1.0 \\
\text{Endo (R)} \quad 3.5 \\
\text{Exo (R)} \quad 2.1
\]
Summary

➢ A highly efficient route to produce a common AB core intermediate in 9 steps and 21% overall yield from commercially available starting material for tetracycline antibiotics synthesis has been developed. The material has been produced in 40 g scale with 93% ee in a single batch after chromatography purification.

➢ The readily availability of this core intermediate would make possible the synthesis of a large number of tetracycline analogs to find more potent antibiotics for drug-resistant bacterium.

➢ The synthesis might be scaled up to multi-kilogram amounts.

➢ More Crystalline derivatives of the core intermediate should be studied to increase its optical purity.