The Tetracyclines

Prepared from the cultures of several species of *Streptomyces*

Once an enormously effective treatment for a wide range of bacterial infections

Mode of action is binding to the 30S ribosome of the bacteria, preventing attachment of the aminoacyl tRNA to the RNA-ribosome complex

Decades of clinical use have led to the emergence of widespread bacterial resistance

Analogs generally prepared via semisynthesis

First total synthesis of a tetracycline-like molecule reported by Woodward and a group from Pfizer

Synthetic approaches by Woodward, Shemyakin, Muxfeldt, Stork, and Myers

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Structure-Activity Relationships

-R1-R4 can be substituted or removed without effecting a substantial decrease in antimicrobial activity

-Configuration at C-5a and C-4 are crucial for activity

-Hypothesized that the principal active center is the C-11, C-12 diketone system of rings B and C
Woodward’s Approach

“The most formidable synthetic problems posed by the structure are concentrated in ring A: every carbon of the atom skeleton of that ring bears at least one substituent, and three of the four asymmetric centers of the molecule fall in the consecutive chain C4, C4a, C12a.” - Woodward

Korst, J. J.; Johnston, J. D.; Butler, K.; Bianco, E. J.; Conever, L. H.; Woodward, R. B.  
\[
\begin{align*}
\text{Cl-} & \quad \text{OH} \\
\text{O} & \quad \text{OMe} \\
\text{OH} & \quad \text{OMe} \\
\text{Cl} & \quad \text{OH} \\
\text{Cl} & \quad \text{O} \\
\text{H} & \quad \text{CO}_2 \text{Me} \\
\text{MeOH} & \quad \text{H}_2\text{SO}_4 \\
\text{NaH} & \quad \text{MeO}_2\text{C-CO}_2\text{Me} \\
\text{DMF} & \quad \text{MeOH} \\
\text{Mg} & \quad \text{OMe} \\
\text{OMe} & \quad \text{Cl} \\
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{CO}_2 \text{Me} \\
\text{nBu} & \quad \text{H}_2\text{O} \\
\text{Me}_2\text{NH} & \quad \text{H}_2\text{O} \\
\text{MeOH} & \quad \text{H}_2\text{O} \\
\text{MeO}_2\text{C-CO}_2\text{Me} & \quad \text{H}_2\text{O} \\
\text{H}_2\text{O} & \quad \text{H}_2\text{O} \\
\text{H}_2\text{O} & \quad \text{H}_2\text{O} \\
\end{align*}
\]
Stork’s Approach

1. Phl(OTf)$_2$, CH$_2$Cl$_2$, MeOH
   2. 5% HCl, THF

89% for 2 steps

1. MeMgBr, THF
   -78 °C to rt
   2. p-xylene

78% for 2 steps

1. EtOCHBrCH$_2$Br,
   Ph-NMe$_2$, CH$_2$Cl$_2$
   2. $^0$Bu$_3$SnH, AlBN, C$_6$H$_6$

81% for 2 steps

1. Ph(O Tf)$_2$, CH$_2$Cl$_2$, MeOH
   2. 5% HCl, THF

97% for 3 steps
45% for 10 steps
1. PhI(OTfA)₂, MeOH

2. HCl, H₂O

H+ transfer

H+ transfer

H+ transfer

H+ transfer
\[ R = \text{CO}_2\text{Me} \]
Myers’ Approach

(-)-6-deoxytetracycline

1. LiOTf, Ph-Me, 60 °C
2. TFA, CH2Cl2

Sommelet-Hauser Rearrangement
1. P(OMe)₃, MeOH, 70 °C
2. P(OMe)₃, MeOH, 70 °C

Mislow-Evans Rearrangement

[O]⁺
1. LDA, TMEDA, 
   -78 °C to 0 °C
2. HF, CH₃CN
3. H₂, Pd

1.% for 14 steps

pentacycline derivative
56% for 4 steps
6% for 15 steps

1. nBuLi, -100 °C
   to -70 °C
2. HF, CH₃CN
3. H₂, Pd

10-deoxysancycline
68% for 3 steps
7% for 14 steps

1. LDA, TMEDA, 
   -78 °C to 0 °C
2. HF, CH₃CN
3. H₂, Pd

(-)-6-deoxytetracycline
69% for 3 steps
7% for 14 steps

1. nBuLi, -100 °C
   to 0 °C
2. HF, CH₃CN
3. H₂, Pd
4. BBr₃, CH₂Cl₂ 
   -78 °C to rt

pyridone derivative
50% for 3 steps
5% for 14 steps