Hitachimycin (a.k.a. stubomycin): structural and synthetic studies

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Abstract - Stubomycin (a.k.a. hitachimycin) is a novel macrocyclic lactam antitumor agent. Herein we report the complete stereostructure of stubomycin, as well as progress towards the development of an efficient synthetic strategy.

In the early 1980's, Omura and Umezawa at the Kitasato Institute (Tokyo, Japan) independently reported the isolation and structural elucidation studies for hitachimycin (a.k.a. stubomycin), a novel macrocyclic lactam antitumor agent. The relative and absolute stereochemistry at two of the four stereogenic centers [i.e., C(8) and C(10)] however remained undefined. Herein we report the complete stereostructure of hitachimycin, as well as progress toward the development of an efficient synthetic strategy.

1 STRUCTURE ELUCIDATION

The complete structure of hitachimycin was derived through a combination of single crystal x-ray analysis, two-dimensional NMR studies, and molecular mechanics simulations (Macromodel). This combined effort led not only to the complete stereostructure, but also revealed that the solid state, solution and MM2 calculated conformations of hitachimycin were nearly identical.

2 SYNTHETIC STUDIES

2.1 Retrosynthetic analysis

[Diagram of retrosynthetic pathway]
2.2 Preparation of S- (+)-5-methoxy cyclopentenone

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\begin{align*}
\text{MeOH/\Delta} & \quad \text{(CH}_3\text{O})_2\text{CH/PTSA} & \quad \text{MeOH/\Delta} \\
\text{(-100\%)} & \quad \text{DIBAL} & \quad \text{(78\%)} \\
\end{align*}
\]

(2.8 : 1)

Separable by F.C.C.

X-RAY

2.3 Trans cuprate addition to 5-methoxy cyclopentenone

\[
\begin{align*}
\text{MeOH/pyr} & \quad \text{B} & \quad \text{OTBS} \\
\text{-78\°C / Et}_{2}\text{O/TMSCl} & \quad \text{+ LiI} \\
\end{align*}
\]

(77 - 90\%)


2.4 Aldehyde preparation

1) (±)-Tartaric Acid
2) 1N KOH

1) p-anisaldehyde
   Pre / Δ / HClO₄

2) NaBH₄ / MeOH
   -20°C
   (93%)

3) TiCl₄ / pyr
   (94%)

4) LAH / THF / 0°C - r.t
   (90%)

5) ig / imidazole / PPh₃
   Et₂O : CH₂CN
   (92%)

6) PPh₃ / CH₂CN / Δ
   (95%)

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1) 10% AgNO₃ / SiO₂
   Flash Chromatography
   (Ouant.)
   or fractional cryst.

2) 80% AcOH
   (95%)

3) MES-Cl / pyr
   (81%)

4) NaH / THF / 0°C-r.t
   (97%)

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1) THF / 0°C-Cr.L
   (98%)

2) MeO₂Cl / CH₂Cl₂ / KH / THF
   5%Bu₄N l / 18-crown-6 (cat)
   (97%)

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1) Na₂[Co(CN)₆] / -78°C
   DME

(88%)

2) TEOC-Cl / K₂CO₃ / THF
   (90%)
2.5 Union and progress towards completion of hitachimycin (a.k.a. stubomycin)

15 steps from β-phenylalanine

21.9% overall

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