Total Synthesis of (−)-Virginiamycin M$_2$

Antibiotics from *Streptomyces*

- Type A and Type B streptogramins act in synergy; the *in vitro* activity of the mixture is at least 10 times greater than the sum of the individual activities.

- Both Type A and Type B streptogramins inhibit protein synthesis via action on the peptidyltransferase domain of 50S ribosomal subunits.

- The compounds bind specifically to non-overlapping regions of the ribosome in a 1:1 stoichiometry.

- Binding of Type A antibiotics increases the binding affinity for Type B antibiotics, but the opposite scenario does not occur.

Viriginiamycin Synthesis and Semisynthesis


Stereochemistry of vinylogous aldol product and diene controlled by chiral auxiliary; macrocycle closed via amide bond formation; 21 steps, 2.2% yield, 16 steps longest linear (numbers do not include auxiliary attachment).
Panek Group Retrosynthesis

Barbier-type Cyclization

Alkyne-alkyne reductive coupling

Panek group crotylation methodology
Terminal Alkyne Synthesis: Asymmetric Crotylation

Silane synthesis via Si-H insertion
(Davies et al. TL 1997, 38, 1741-1744.)

Application of optically active crotyl silanes toward vinylogous aldol products (Org. Lett. 2010, 12, 2112-2115.)


Alkyne-Alkyne Reductive Coupling

Stereoselective Synthesis of Functionalized Conjugated Dienes

\[
\begin{align*}
\text{Bu} & \quad \equiv \quad \equiv \\
\text{O} & \\
\text{Bu} & \quad \equiv \quad \equiv \\
\text{Ti(O-i-Pr)}_2 & \text{(1 equiv)} \\
\text{Et}_2\text{O}, -50 \, ^\circ\text{C}, 2 \text{ h} & \rightarrow \\
\text{Bu} & \quad \equiv \\
\text{O} & \\
\text{Bu} & \quad \equiv \\
\text{Bu} & \quad \equiv \\
\text{Ti(O-i-Pr)}_2 & \text{(1.25 equiv)} \\
\text{Et}_2\text{O}, -50 \, ^\circ\text{C}, 1 \text{ h} & \rightarrow \\
\text{Bu} & \quad \equiv \\
\text{O} & \\
\text{Bu} & \quad \equiv \\
\text{Bu} & \quad \equiv \\
\text{Ti(O-i-Pr)}_2 & \text{(0.8 equiv)} \\
\text{Et}_2\text{O}, -50 \, ^\circ\text{C}, 1 \text{ h} & \rightarrow \\
\text{Bu} & \quad \equiv \\
\text{O} & \\
\text{Bu} & \quad \equiv \\
\text{Bu} & \quad \equiv \\
\text{Ti(O-i-Pr)}_2 & \text{E}^+ (\text{H}^+) \\
\text{Et}_2\text{O}, -50 \, ^\circ\text{C}, 1 \text{ h} & \rightarrow \\
\text{Bu} & \quad \equiv \\
\text{O} & \\
\text{Bu} & \quad \equiv \\
\text{Bu} & \quad \equiv \\
\text{Ti(O-i-Pr)}_2 & \text{81\%} \\
\end{align*}
\]


Application to Polyketide Natural Product Synthesis

Application of Reductive Coupling

Synthesis of coupling partner:

1. Zn(OTf)$_2$, (-)-N-methylephedrine propyne, Et$_3$N 80%, 95% ee
2. TBSOTf, 2,6-lutidine, 96%


<table>
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<td>71%</td>
<td>0%</td>
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</table>

Most favorable substrate for synthesis
Proposed Alkyne-Titanium Intermediates

Unfavorable due to strain associated with a bridgehead alkene
Completion of the Synthesis

Barbier Cyclizations in Natural Product Synthesis


Model system of vinigrol (Matsuda et al., 1997).


Synthesis of Phorbol (Carrol and Little, 2000)


Synthesis of Kendomycin (Lowe and Panek, 2008)

-L1st example of Samarium-mediated Barbier cyclization for macrocycle closure in natural product synthesis (16-membered)


Summary and Outlook

- The antibiotic \((-\)-Virginiamycin \text{M}_2\) was synthesized in 19 steps and 6.0% overall yield from the optically active \((E)\) chiral silane. The longest linear sequence was 10 steps.
- Key transformations include application of crotyl silane addition toward a vinylogous aldol product, a regio- and stereo-selective titanium mediated alkyne-alkyne coupling reaction, and a samarium diiodide mediated Barbier-type cyclization.
- The 23-membered macrocycle is the largest ring reported to be synthesized by a Barbier type reaction to date.