Total Synthesis of: Dysoxylactam A

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Background

• Dysoxylactam A is a class of compounds called cyclolipopeptides
  • Specifically it’s a macrocyclopolipopeptide
• It “dramatically reversed” multidrug resistance in cancer cells at noncytotoxic concentration
• Its mode of action involves inhibiting the function of P-glycoprotein
  • P-glycoprotein is a key mediator in multidrug resistance
Retrosynthetic approach:

\[
\begin{align*}
\text{O} & \quad \text{H} & \quad \text{OH} & \quad \text{H} & \quad \text{H} & \quad \text{O} & \quad \text{H} \\ \\
\text{HN} & \quad \text{O} & \quad \text{OH} & \quad \text{OH} & \quad \text{NH}_2 & \quad \text{O} & \quad \text{OH} & \quad \text{L-Valine}^* \quad \text{Fatty acid} & \quad L-\text{Valine}^* \quad \text{Amino Acid}
\end{align*}
\]

* D-Valine can also be used
Step 1

Regioselective epoxidation

Methyl linoleate

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$44.50 / 1g$, sigma

3.91 mmol

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\[ \text{NaHCO}_3 \] (1.5 equiv)

\[ \text{MCPBA} \] (0.9 equiv)

\[ \text{CH}_2\text{Cl}_2, 0 \, ^\circ \text{C}, 80 \, \text{min} \]

22%

Methyl 12S,13S-dihydroxyoctadeca-9Z-enoate

Step 2

Epoxide Reduction

\[
\text{NaOAc (7.9 equiv)} \quad \text{LiOH (1.4 equiv)}
\]

\[
\text{AcOH, } 80^\circ \text{C, 2 h} \quad \text{MeOH, rt, 2 h,}
\]

5.31 mmol

87%

Step 3

Oxidative Cleavage

Step 4a

Preparation of a Wittig reagent

(S)-1-Bromo-2-methylbutane
$66.60 / 1g$, sigma
45.2 mmol
Step 4b

Wittig reaction

\[
\text{O} \quad \text{O} \\
\text{NH}_2 \quad \text{OH} \\
\text{OH} \quad \text{OH} \\
\text{OH} \quad \text{OH}
\]

\[
\text{PPh}_3 + \text{methyl (Z)-12-oxododec-9-enoate} \rightarrow \text{THF, -78 °C, 24 h}
\]
Step 5

Methylation and nucleophilic addition

This step was inspired by the SI of the Dysoxylactam A paper.
Step 6

Ester Hydrolysis

Alternative route to the step 6 product

- Starting with the product from step 4b:

\[
\text{Me}_2\text{CuLi (1.73 equiv)} \rightarrow \text{Et}_2\text{O, -55 to -20 }^\circ\text{C, 4 h}
\]

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Note: The desired stereoisomer of this reaction would be isolated and the undesired stereoisomer would be re-epoxidized.

Alternative route to the step 6 product continued

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