11-Step Enantioselective Synthesis of (−)-Lomaiviticin Aglycon

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J. Am. Chem. Soc. ASAP DOI 10.1021/ja200034b

Melissa Sprachman
Current Literature
February 26, 2011
Isolation and Preliminary Biological Activity

The lomaiviticins (red solids) were isolated from the fermentation broth of an actinomycetes strain LL-371366, which was initially isolated from the core of a host ascidian.

The fermentation broth exhibited potent DNA-damaging activity (detected by biochemical induction assay) and was cytotoxic against a number of cancer cell lines.

Lomaiviticin A exhibited activity against a variety of cancer cell lines (IC₅₀ values of 0.01 – 98 ng/mL).

Related Natural Products: The Kinamycins

\[
\begin{align*}
\text{kinamycin A} & : R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = Ac \\
\text{kinamycin B} & : R_1 = H, R_2 = Ac, R_3 = H, R_4 = H \\
\text{kinamycin C} & : R_1 = Ac, R_2 = H, R_3 = Ac, R_4 = Ac \\
\text{kinamycin D} & : R_1 = Ac, R_2 = H, R_3 = Ac, R_4 = H \\
\text{kinamycin E} & : R_1 = Ac, R_2 = H, R_3 = H, R_4 = H \\
\text{kinamycin F} & : R_1 = H, R_2 = H, R_3 = H, R_4 = H \\
\text{kinamycin G} & : R_1 = Ac, R_2 = COiPr, R_3 = Ac, R_4 = Ac \\
\text{kinamycin H} & : R_1 = COiPr, R_2 = H, R_3 = Ac, R_4 = Ac \\
\text{kinamycin I} & : R_1 = COiPr, R_2 = H, R_3 = COiPr, R_4 = Ac \\
\text{kinamycin J} & : R_1 = Ac, R_2 = Ac, R_3 = Ac, R_4 = Ac
\end{align*}
\]


Model Systems and Construction of the Central Bond

Model Systems and Construction of the Central Bond

Key Findings:

- Fully stereoselective oxidative enolate coupling
- Stability of the lomaiviticin A core as the hydrate

Krygowski, E. S.; Murphy-Benenato, K.; Shair, M.D.
Herzon Group Forward Synthesis

1. Li, NH₃, 98%
2. (DHQD)₂PHAL
K₂OsO₄, K₃Fe(CN)₆
62%, 91% ee

O₂, Pd(OAc)₂
DMSO, 24 °C
92%

PPTS
CH₃CN, 24 °C to 50 °C
85%, 1:1 dr

1. TMSCH₂MgCl, CuI, TMSCl
then Pd(OAc)₂
82%

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Pd(OAc)₂
Ag₂CO₃ • PPh₃
toluene, 80 °C
95%

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End Game: Oxidative Dimerization

General Strategy

> 1500 experiments

Desired Product not formed

Both diastereomers and derivatives

TMSOTf, Et₃N

CH₂Cl₂, 0 °C

26%

PhH, 21 °C

12%

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Formation of Lomaiviticin Aglycon

\[
\text{formation of Lomaiviticin aglycon, reaction course, isolated, yield 39\%}
\]

\[
\text{TFA, TBHP, CH}_2\text{Cl}_2, -35 \degree \text{C, 12 h, 8 : 1}}
\]

\[
\text{formation of Lomaiviticin aglycon, reaction course, isolated, yield 41\%}
\]

\[
\text{TFA, CH}_3\text{OH, 50 \degree \text{C, 12 h, 8 : 1}}
\]
Proposed Mechanism of Action and Diazonium Character

The trend in "diazonium character" parallels the trend in antibiotic and antitumor activity.

\[ \begin{align*}
\text{9-diazofluorene} & : \nu = 1906 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.133 \text{ Å}
\end{align*} \]

\[ \begin{align*}
2,1\text{-naphthoquiniodiazide} & : \nu = 2056 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.111 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{9-diazofluorene} & : \nu = 2087 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.108 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{9-diazofluorene} & : \nu = 2101 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.107 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{9-diazofluorene} & : \nu = 2125 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.105 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{Isoprekinamycin} & : \nu = 2139 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.103 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{Kinamycin B} & : \nu = 2188 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.099 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{Model for Lomaiviticin A} & : \nu = 2212 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.100 \text{ Å}
\end{align*} \]

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\text{Lomaiviticin A} & : \nu = 2139 \text{ cm}^{-1} (C-N_2) \\
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\[ \begin{align*}
\text{Lomaiviticin A} & : \nu = 2218 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.100 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{Lomaiviticin A} & : \nu = 2220 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.100 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{Lomaiviticin A} & : \nu = 2221 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.100 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{Lomaiviticin A} & : \nu = 2222 \text{ cm}^{-1} (C-N_2) \\
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\text{Lomaiviticin A} & : \nu = 2223 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.100 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{Lomaiviticin A} & : \nu = 2224 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.100 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{Lomaiviticin A} & : \nu = 2225 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.100 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{Lomaiviticin A} & : \nu = 2226 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.100 \text{ Å}
\end{align*} \]

\[ \begin{align*}
\text{Lomaiviticin A} & : \nu = 2227 \text{ cm}^{-1} (C-N_2) \\
& : \text{N-N} = 1.100 \text{ Å}
\end{align*} \]

[ab initio] calculations at HF theory level using 6-31G and LanL2DZ basis sets.

Proposed Mechanism of Action (Continued)

The authors also provided experimental evidence for relative electrophilicities and a proposal that deazetation by nucleophilic attack followed by H-atom abstraction is a possible MOA.

\[
\text{HO} \quad \text{Cs}_2\text{CO}_3 \quad \text{THF, 0 °C} \quad 61\%
\]

\[
\text{HO} \quad \text{Cs}_2\text{CO}_3 \quad \text{NR}
\]

\[
\text{HO} \quad \text{Cs}_2\text{CO}_3 \quad \text{THF, 0 °C}
\]

\[
\text{Ns} \quad \text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4 \text{ buffer, pH 9}
\]

\[
\text{EtOH, reflux} \quad \text{quant.}
\]


A Second Proposal: 1-electron reduction

An alternative proposal involves 1-e⁻ reduction followed by H-atom abstraction.

Additionally, yields of solvent incorporation dropped with increasing equivalents of Bu₃SnH.

The authors estimate the rate constant for sp² radical addition to the aromatic solvent to be 10⁷ M⁻¹ s⁻¹. The reported rate constant for addition of phenyl radical to chlorobenzene is ~10⁶ M⁻¹ s⁻¹.

Experimental Evidence of DNA Strand Cleavage

The authors compared the DNA cleavage ability of kinamycin D to a variety of diazoflourene probes.

Summary and Outlook

Herzon and coworkers have completed the first synthesis of lomaiviticin aglycon in 11 linear steps. Several operations are amenable to large-scale preparative work. As of the online publication date, the group has synthesized 15 mg of lomaiviticin aglycon.

After exhaustive screening, the authors demonstrated the feasibility of an oxidative dimerization using Mn(hfacac)₃. Their report is the first use of this reagent in an oxidative enoxysilane coupling.

Herzon and coworkers previously reported the synthesis of the sugar residues (Org. Lett. 2009, 11, 4322-4325) and demonstrated formation of the glycosidic bonds on a model system. With the aglycon in hand, elaboration to form usable quantities of the natural products is a possibility.

The ability to produce useful quantities of the core may lead to analog development and future application to important antibiotics and/or cancer therapeutics.

Further probing of the lomaiviticins' MOA via some of the same assays used to study the kinamycins is also a possibility with synthetic access to the materials.