Synthesis of the Tetrahydroisoquinoline Alkaloid (±)-Renieramycin G and a (±)-Lemonomycinone Analogue from a Common Intermediate

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Tetrahydroisoquinoline Antitumor Antibiotics

The tetrahydroquinoline family of antitumor antibiotics has been studied since naphthriydinomycin was isolated in 1974 by Kluepfel et al.

The two core structures of this family are the quinone A and the aromatic core B. To date, nearly 60 natural products in this family have been isolated, and hundreds of synthetic analogues have been reported.
Tetrahydroisoquinoline Antitumor Antibiotics


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Scott, J. D.; Williams, R. M. Chem. Rev. 2002, 102, 1669

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Tetrahydroisoquinoline Antitumor Antibiotics

Renieramycins: Isolation and Biological Activity

Renieramycines are isolated from various marine sponges belonging to genera *Reniera*, *Xestospongia*, *Haliclona*, *Cribrochalina*, and *Neopetrosia*.

The ring systems and their relative stereochemistry are identical with those of saframycins which exhibit strong cytotoxicity against cultured cells and antitumor activity against several experimental tumors.

Renieramycins A–D, and H have moderate antimicrobial activities. Renieramycin G has cytotoxicity against human cancer cells with MIC values of 0.5 and 1.0 µg/mL against KB and LoVo cell lines, respectively.
Total Synthesis of Renieramycins

Fukuyama: First Total Synthesis of (±)-Renieramycin A

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Total Synthesis of Renieramycins

Danishefsky: First Asymmetric Total Synthesis of Cribrostatin IV (Renieramycin H)

Pomeranz–Fritsch Cyclization

Lynchpin Mannich Cyclization

32 steps from

1.7% overall yield

Total Synthesis of Renieramycins

Williams: First Asymmetric Total Synthesis of (−)-Renieramycin G

23 steps from
CH$_2$OH
OMe
7.9% overall yield

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Lemonomycin was isolated in 1964 from *Streptomyces candidus*. However, the structure was not elucidated until 2000.

Lemonomycin contains the unusual aldehyde hydrate and the sugar moiety, and is the only member in this family of tetrahydroisoquinoline antibiotics.

Lemonomycin has interesting antibiotic activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*, as well as cytotoxicity against a human colon tumor cell line.
Total Synthesis of Lemonomycin

Stoltz: First Asymmetric Total Synthesis of (−)-Lemonomycin

15 steps from 3.1% overall yield

New Strategy for the 1,3-cis-Substituted Tetrahydroisoquinolines

Pictet–Spengler Approach

Intermolecular

Intramolecular

C1 Nucleophilic Addition Approach

Synthesis of Common Intermediate

1) OTIPS 9
   Cul (1.2 eq), Et₃N
   25 °C, 24 h
   MeO
   Me
   76% yield

2) Cul (0.2 eq), DMF
   100 °C, 1 h
   MeO
   Me
   79% yield

1) TFA, Et₃SiH,
   0 °C, 2 h
   MeO
   Me
   91% yield

2) H₂NNH₂, KOH,
   HOCH₂CH₂OH,
   150 °C, 3 h
   86% yield

1) TMSCl, Et₃N, THF, 0 °C, 2 h
2) H₂NNH₂, KOH,
   HOCH₂CH₂OH,
   150 °C, 3 h
   82% yield

Swern oxidn
88% yield

(±)-Renieramycin G

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\begin{align*}
\text{27} & \xrightarrow{40\% \text{ aq. formalin, } \text{ZnCl}_2, \text{HCl (g), reflux}} \text{28} & \text{yield 73\%} \\
\text{17} & \xrightarrow{\text{29, 18-crown-6, KHMDS, THF, } -78 \, ^\circ\text{C, 20 min.}} \text{30} & \text{yield 98\%} \\
\text{31} & \xrightarrow{\text{i) } t-\text{BuLi (2.2 eq.), THF, } -78 \, ^\circ\text{C, 10 sec. then BHT in THF}} \text{32} \\
\text{31} & \xrightarrow{\text{ii) } \text{HCl in Et}_2\text{O, } 0 \, ^\circ\text{C, 1 h}} \text{33 R = Bn, 65\% yield, two steps} \\
\text{33} & \xrightarrow{\text{NaBH}_3\text{CN, HCHO, AcOH, MeOH, } 25 \, ^\circ\text{C, 1 h}} \text{34 R = H, (X-ray)} \\
\text{34} & \xrightarrow{\text{1) Pd(OH)}_2, \text{MeOH, 1 atm H}_2, 6\, \text{h, (94\%)} \text{MeOH, 2) (NH}_4)_2\text{Ce(NO}_3)_6, \text{CH}_3\text{CN:HO}_2, 6:1, -5 \, ^\circ\text{C, 10 min. (55\%)}} \text{35} & \text{yield 74\%} \\
\end{align*}
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(±)-Lemonomycinone Amide

[Chemical reaction diagram showing the synthesis of Lemonomycinone Amide, including steps and yields.]
Summary

A general approach to both mono- and bistetrahydroisoquinoline alkaloids from a common advanced intermediate has been developed.

(±)-Lemonomycinone amide

18% yield (8 steps)

(±)-Renieramycin G

16% yield (9 steps)

(±)-Lemonomycinone amide