Applications of Zr-Catalyzed Carbomagnesation and Mo-Catalyzed Macrocyclic Ring Closing Metathesis in Asymmetric Synthesis. Enantioselective Total Synthesis of Sch 38516 (Fluvirucin B₁)

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Presented by James Melnyk
Amir H. Hoveyda

- Born April 5\textsuperscript{th}, 1959
- 1981: B.A. Columbia University
- 1986: Ph.D. Yale University
  - Advisor: Stuart L. Schreiber
- 1986-90: Postdoctoral research – Harvard University
  - Advisor: David A. Evans
- 1990: Joined Boston College Faculty
- 1998: Vanderslice Millenium Professor
- Research focuses on the assymetric catalysis and assymetric olefin metathesis. More recently he is focused on the use of N-heterocyclic carbenes as ligands for copper catalyzed alkylations and conjugate additions.
Sch 38516 (fluvirucin B₁)

- Fluvirucin B₁ is a representative member of a noteworthy class of antifungal agents reported by Schering-Plough in 1990 from *Actinomadura vulgaris*, a bacterium found in soil.
- Detailed structure was established using X-ray crystallography.
- Fluvirucin B₁ is active against *Candida* (a strain of yeast), dermatophytes (a group of fungi responsible for skin diseases) and the influenza A virus.

Culture of *Actinomadura*
Structure of Sch 38516 (Fluvirucin B₁)
An attractive molecule for enantioselective synthesis due to the lack of stereogenic sites in the macrolactam structure thus making stereocontrol difficult.

Synthetic plan involves synthesizing the macrolactam and carbohydrate structures independently, and then subsequently coupling them together before the final ring closure of the macrolactam.
Fluvirucin B₁ Total Synthesis – Part 1

1. Ph₃P, I₂, Et₃N, CH₂Cl₂, 0°C - 22°C
2. n-BuLi, 2-propenal, THF, -78°C
3. Ti(OiPr)₄, t-BuOOH, (+)-dicyclohexyltartrate, 4Å Molecular Sieves

5 equiv. of EtMgCl, 5mol% Cp₂ZrCl₂, Et₂O, 22°C for 12h
34% over three steps

6 equiv. of TsN(CH₂CH₂), 5mol% CuI, THF
42% over two steps

1. TBSOTf, Et₃N, CH₂Cl₂, -78°C
2. 7 equiv. of Na, NH₃, -50°C
83% over two steps
Fluvirucin B₁ Total Synthesis – Part 2

0.8 equiv. of EtMgBr, 0.4 mol% (S)-(EBTHI)-Zr-binol, THF, 70 turnovers

3 equiv. of n-PrMgBr, 3 mol% Cp₂TiCl₂, THF

15 equiv. of allyl Br, 3 mol% (Ph₃P)₂NiCl₂

72% over two steps

10 mol% (n-CH₃(CH₂)₂)₄RuO₄, MeCN,
2 equiv. of H₂O, 3 equiv. NMO

77%
Fluvinucin $B_1$ Total Synthesis – Part 3

1 equiv. of DCC, 1.2 equiv. of HOBT, 22°C, 12h
85%

HF, MeCN
80%

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Fluvirucin B₁ Total Synthesis – Part 4

1. 2,2 dimethoxypropane, 5mol% p-TsOH
2. 2.5 equiv. of DIBAL-H, -78°C

52% from 13

O₃, 8:1 CH₂Cl₂:MeOH, -78°C then Me₂S

64% from 14

1.0 equiv. (R)-N-hydroxyl-alpha-methylbenzamine, 20h

99%
Fluvarucin $B_1$ Total Synthesis – Part 5

17 $\xrightarrow{85^\circ C, Benzene \text{, } 69\%}$ 18

4:1 THF:1.0 M HCl, 65°C $\xrightarrow{94\%}$ 19

Pd(OH)$_2$ (50% by weight), 300psi H$_2$, 2.5 equiv. MeCOCl, MeOH $\xrightarrow{95\%}$ 20
Fluvirucin B₁ Total Synthesis – Part 6

1. 1.5 equiv. of CF₃COSEt, 1.5 equiv of Et₃N, MeOH
2. 10 equiv. of Ac₂O, pyridine, 5mol% (dimethylyamino)pyridine
3. 1% H₂SO₄ in Ac₂O, 0°C, 1h

85% over three steps

1. 1.2 equiv. of PhSH, 0.7 equiv. of SnCl₄, 50°C, 1h
2. 1.3 equiv. of Et₂NSF₃, 1.5 equiv. NBS, 0°C

65% over two steps

2.2 equiv. of AgClO₄, 2.2 equiv. SnCl₂, 4Å Molecular Sieves, 1.1 equiv. of 12, Et₂O, -15°C to 22°C

92%
Fluvirucin $B_1$ Total Synthesis – Part 7

20\text{mol\%} \text{Mo}([\text{CHCMe}_3\text{Ph}]N(2,6-(i-\text{Pr})_2\text{C}_6\text{H}_3)(\text{OCMe(CF}_3)_2)_2, \text{Benzene, 22°C, 10h, 91\%}}$

1. $\text{H}_2, 10\text{\% Pd(C), EtOH}$
2. 20 equiv. of $\text{N}_2\text{H}_4, \text{MeOH, 24h, 69\%}
Conclusion

• First enantioselective synthesis of Sch 381516 (Fluvirucin B₁)
• Convergent synthesis involving three different starting materials and requiring a total of 21 steps
• Final Mo-catalyzed 14-membered lactam synthesis performed efficiently and with a high yield
• Route demonstrates the feasibility of a stereoselective synthesis of highly functionalized macrocycles containing olefins