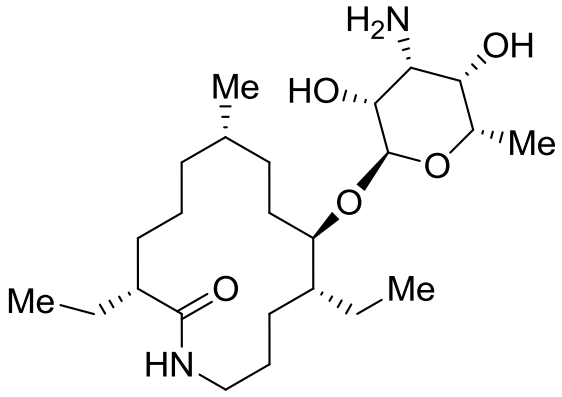
Applications of Zr-Catalyzed Carbomagnesation and Mo-Catalyzed Macrocyclic Ring Closing Metathesis in Assymetric Synthesis. Enantioselective Total Synthesis of Sch 38516 (Fluvirucin B_1)



Zhongmin Xu, Charles W. Johannes, Ahmad F. Houri, Daniel S. La, Derek A. Cognan, Gloria e. Hofilena and Amir H. Hoveyda

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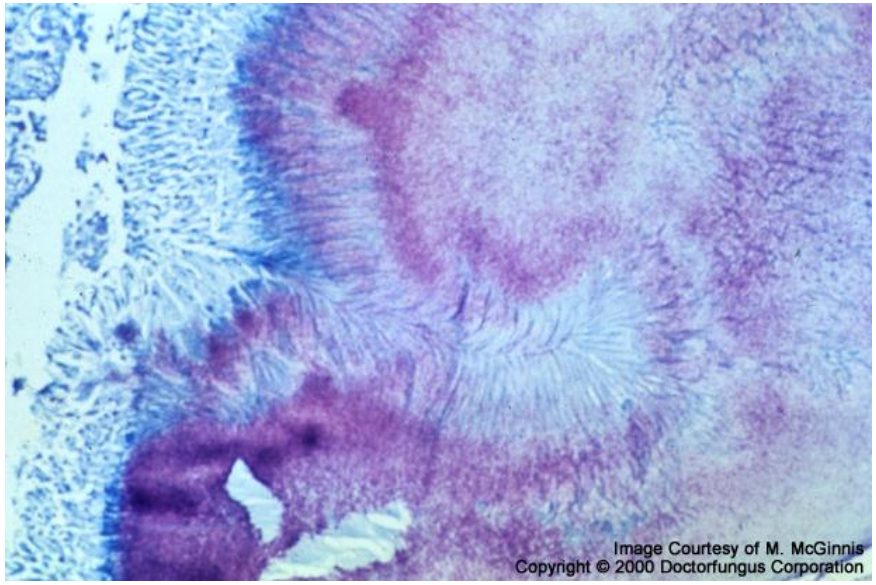
Presented by James Melnyk

Amir H. Hoveyda

- Born April 5th, 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.

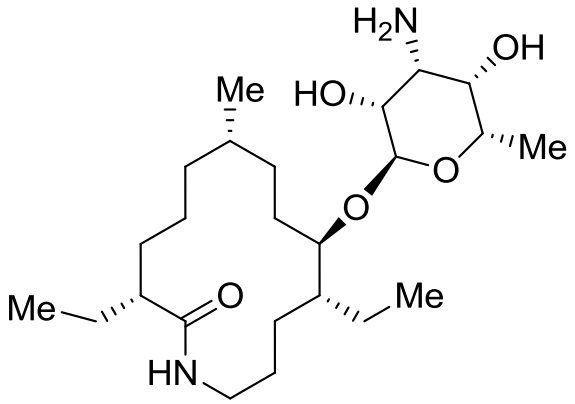
Sch 38516 (fluvirucin B_1)

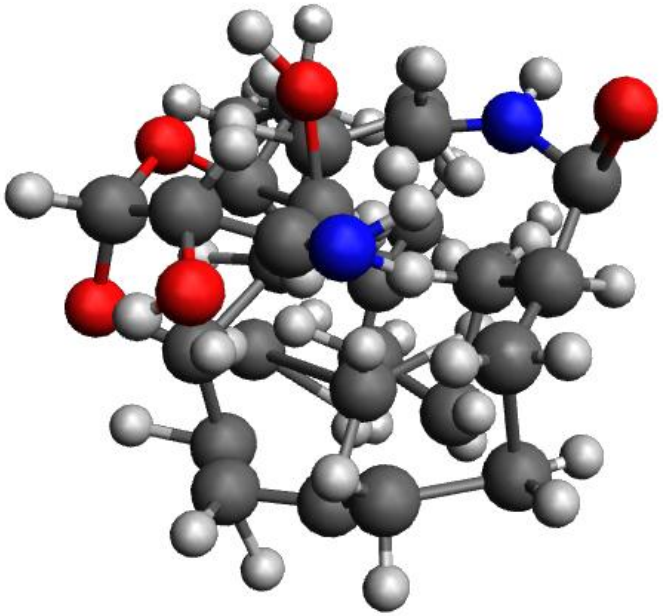
- Fluvirucin B_1 is a representative member of a noteworthy class of antifungal agents reported by Schering-Plough in 1990 from *Actinomadura vulgaris*, a bacterium found in soil.
- Detailed structure was established using X-ray crystallography.
- Fluvirucin B_1 is active against *Candida* (a strain of yeast), dermatophytes (a group of fungi responsible for skin diseases) and the influenza A virus.



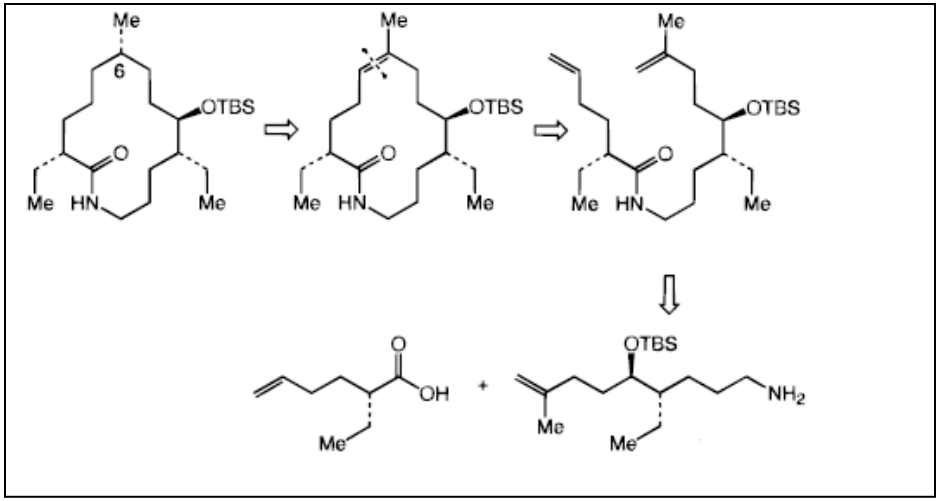
Culture of *Actinomadura*

Structure of Sch 38516 (Fluvirucin B_1)

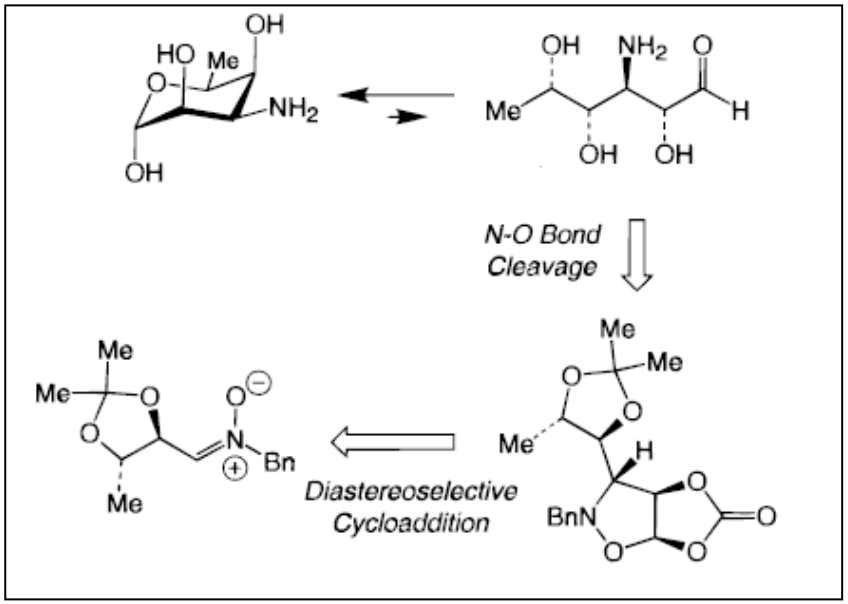




Retrosynthetic Analysis



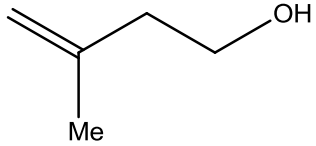
Macrolactam



Carbohydrate

- 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

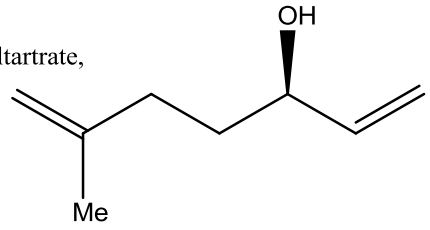
Fluvirucin B_1 Total Synthesis – Part 1



1

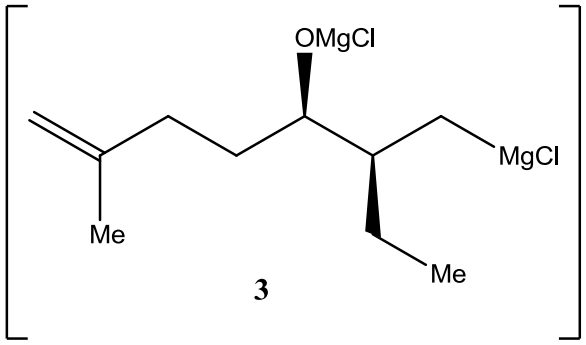
1. Ph_3P, I_2, Et_3N, CH_2Cl, 0°C - 22°C
2. *n*-BuLi, 2-propenal, THF, -78°C
3. $Ti(OiPr)_4$, *t*-BuOOH, (+)-dicyclohexyltartrate, 4Å Molecular Sieves

34% over three steps



2

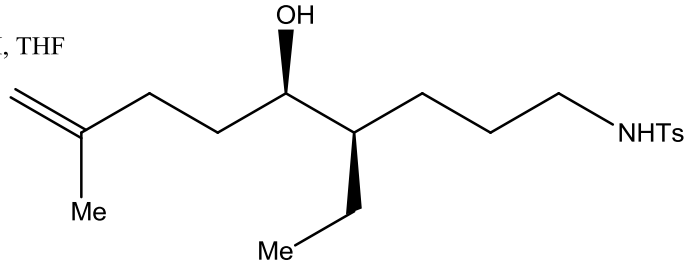
5 equiv. of EtMgCl, 5mol% Cp_2ZrCl_2, Et_2O, 22°C for 12h



3

6 equiv. of $TsN(CH_2CH_2)$, 5mol% CuI, THF

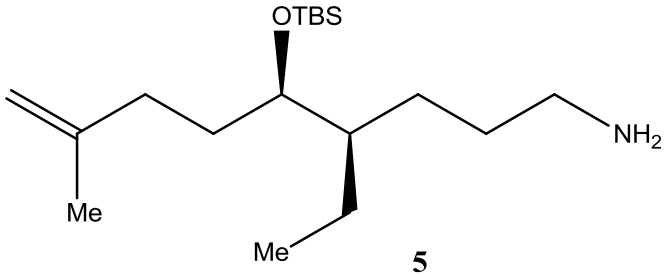
42% over two steps



4

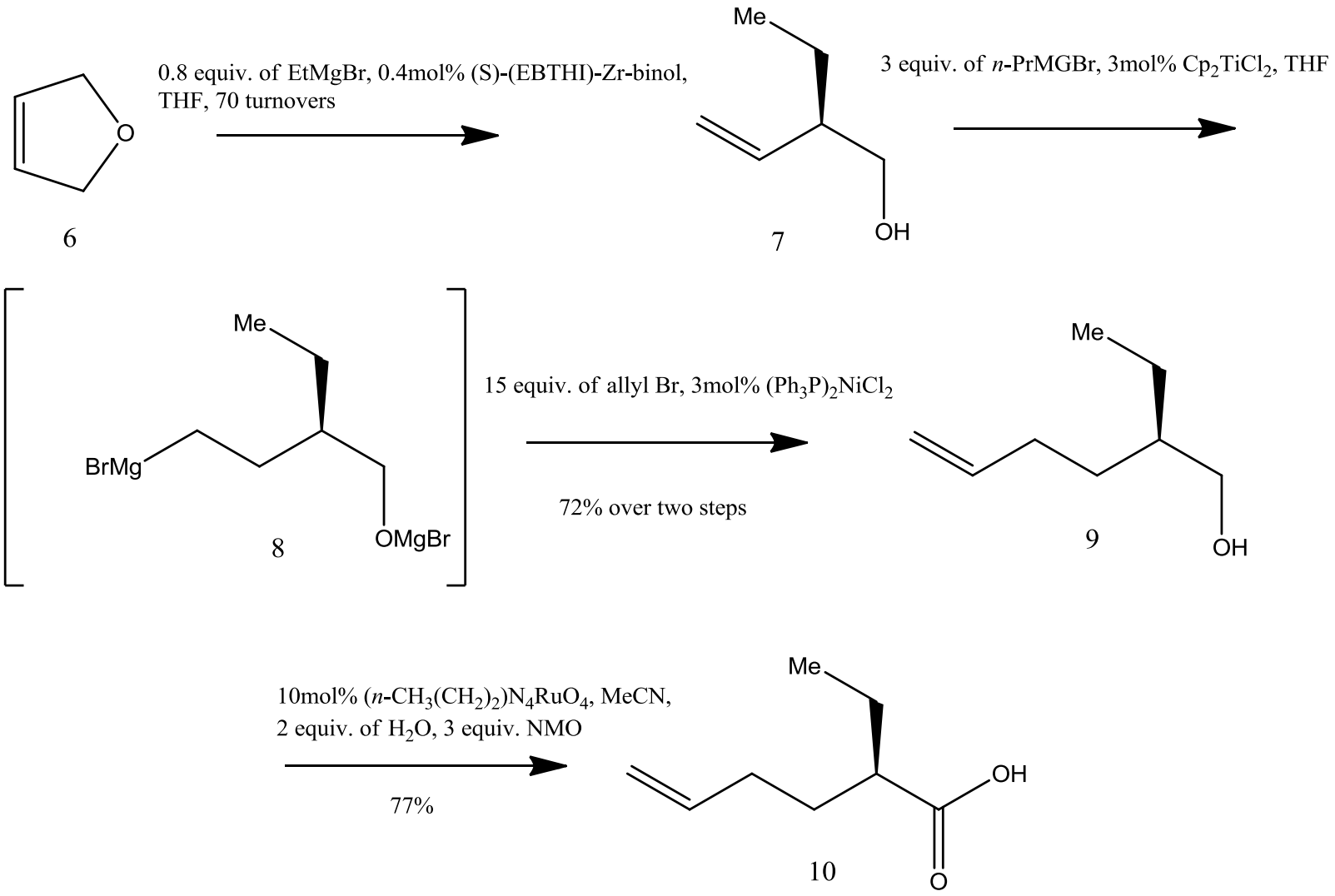
1. TBSOTf, Et_3N, CH_2Cl_2, -78°C
2. 7 equiv. of Na, NH_3, -50°C

83% over two steps

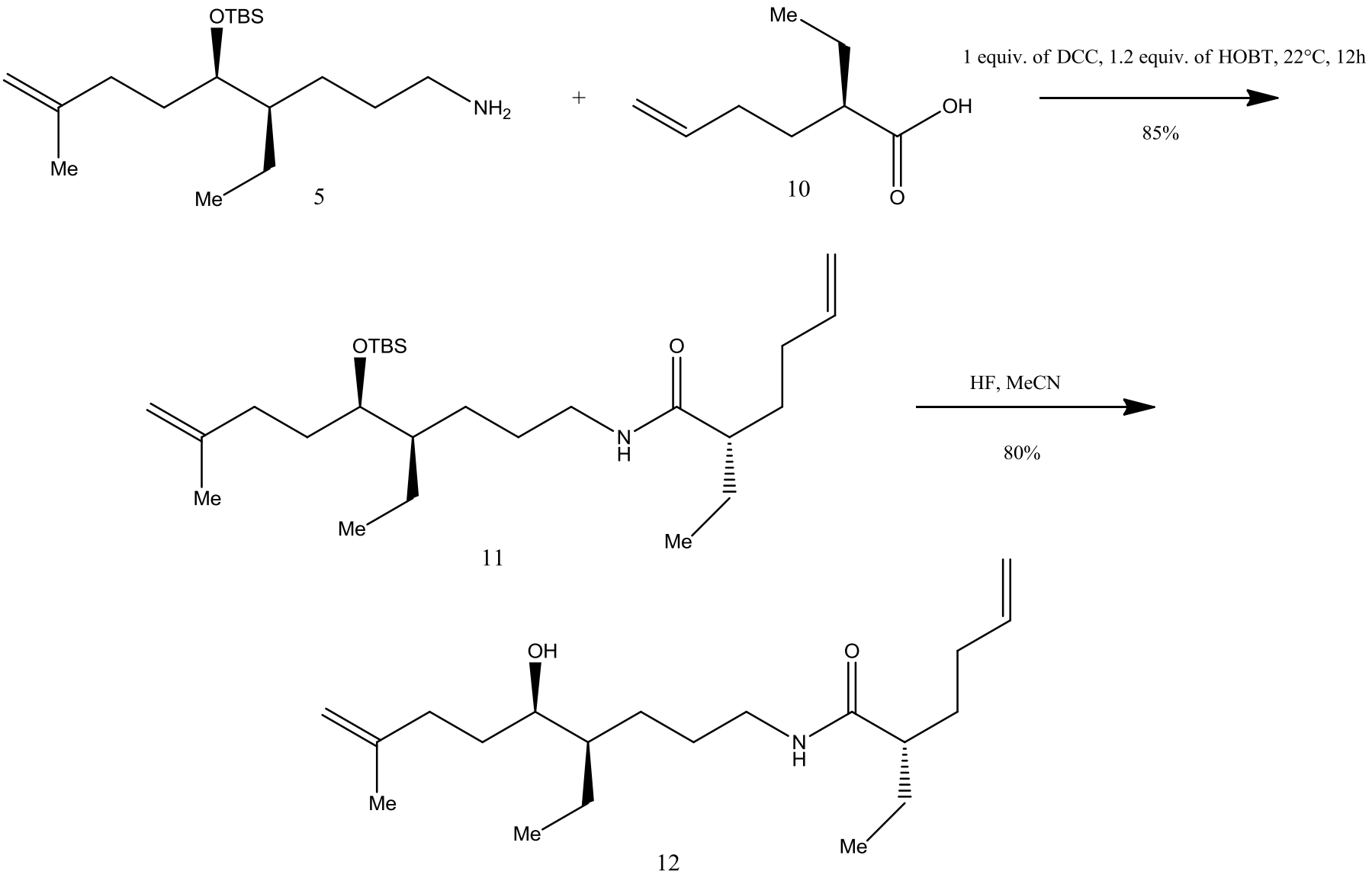


5

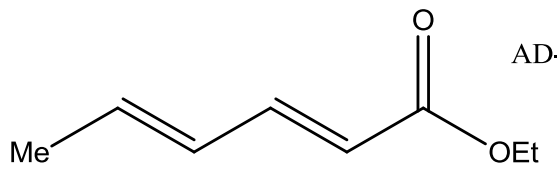
Fluvirucin B_1 Total Synthesis – Part 2



Fluvirucin B_1 Total Synthesis – Part 3

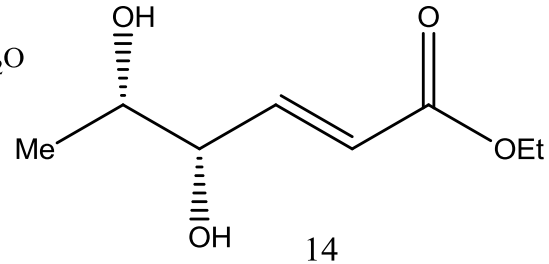


Fluvirucin B_1 Total Synthesis – Part 4



13

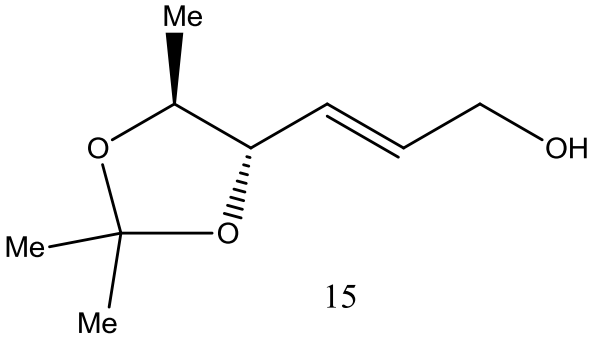
AD-mix-alpha, 1 equiv. of $MeSO_2NH_2$, *t*-BuOH, H_2O



14

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

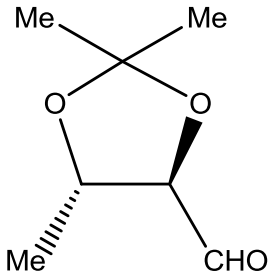
52% from 13



15

O_3, 8:1 CH_2Cl_2:MeOH, -78°C then Me_2S

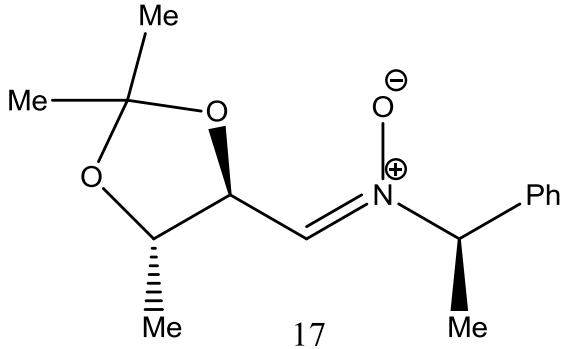
64% from 14



16

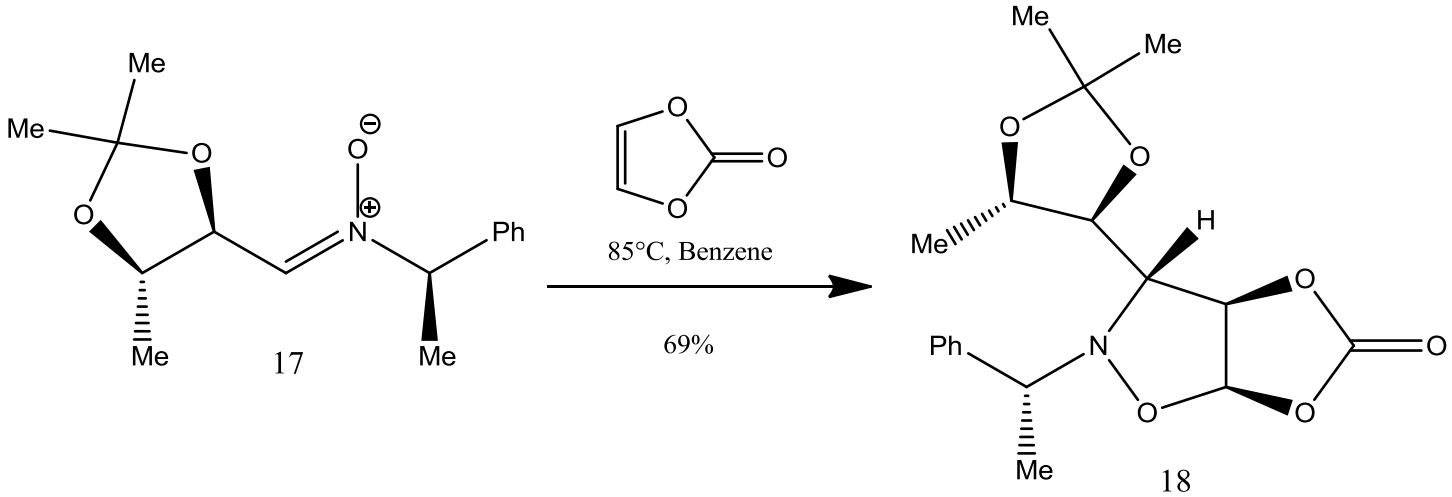
1.0 equiv. (R)-N-hydroxyl-alpha-methylbenzamine, 20h

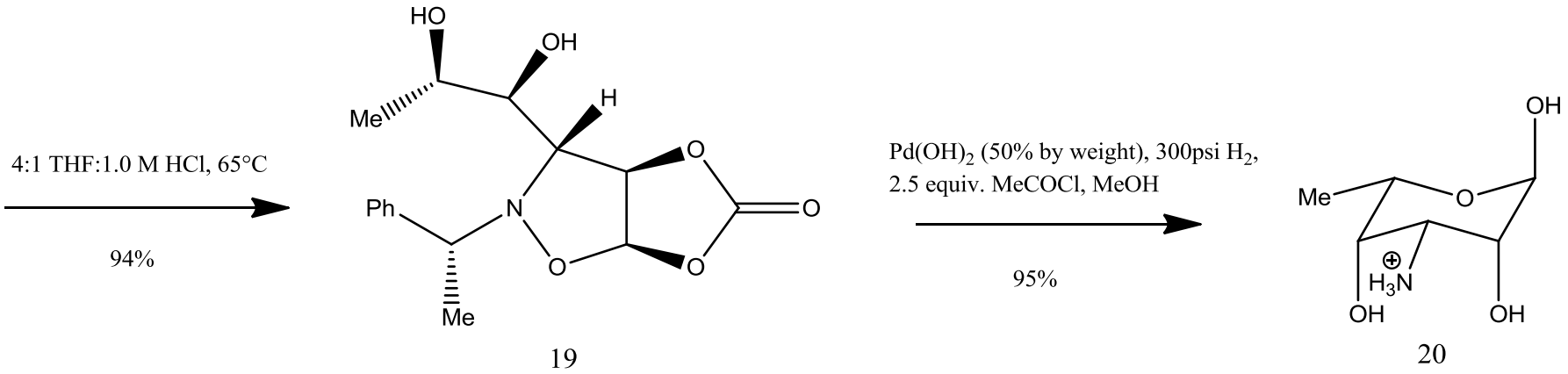
99%



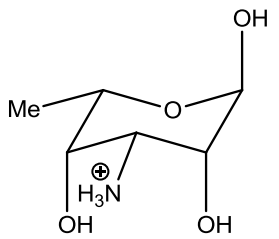
17

Fluvirucin B_1 Total Synthesis – Part 5





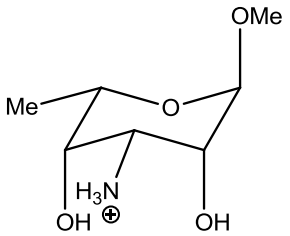
Fluvirucin B_1 Total Synthesis – Part 6



20

10% anhydrous HCl in MeOH

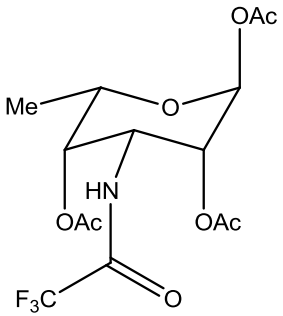
88%



21

1. 1.5 equiv. of CF_3COSEt, 1.5 equiv of Et_3N, MeOH
2. 10 equiv. of Ac_2O, pyridine, 5mol% (dimethyamino)pyridine
3. 1% H_2SO_4 in Ac_2O, 0°C, 1h

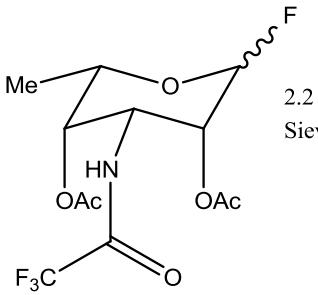
85% over three steps



22

1. 1.2 equiv. of PhSH, 0.7 equiv. of $SnCl_4$, 50°C, 1h
2. 1.3 equiv. of Et_2NSF_3, 1.5 equiv. NBS, 0°C

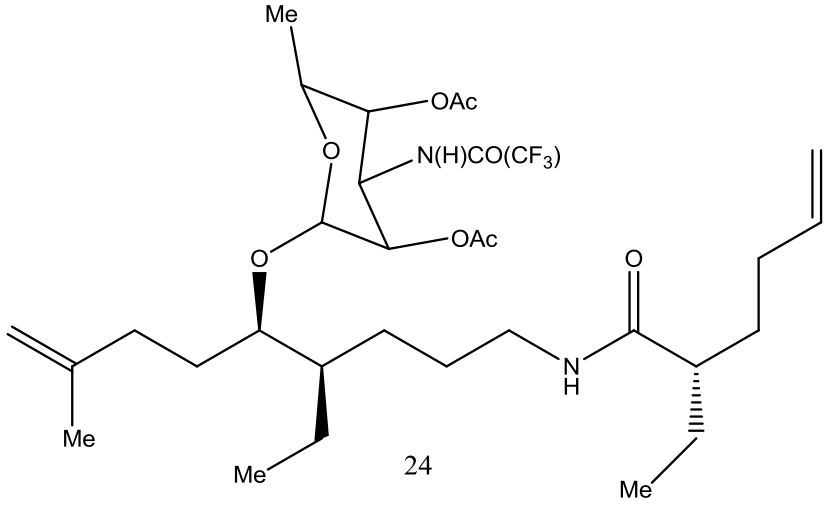
65% over two steps



23

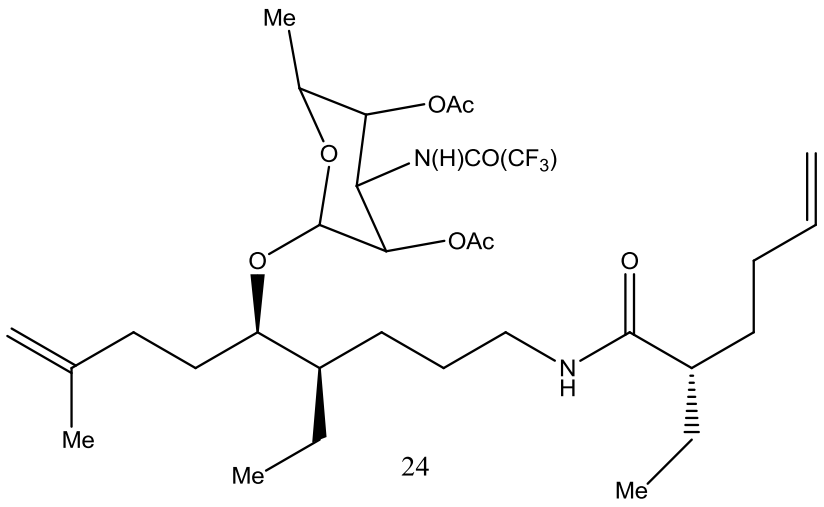
2.2 equiv. of $AgClO_4$, 2.2 equiv. $SnCl_2$, 4Å Molecular Sieves, 1.1 equiv. of **12**, Et_2O, -15°C to 22°C

92%



24

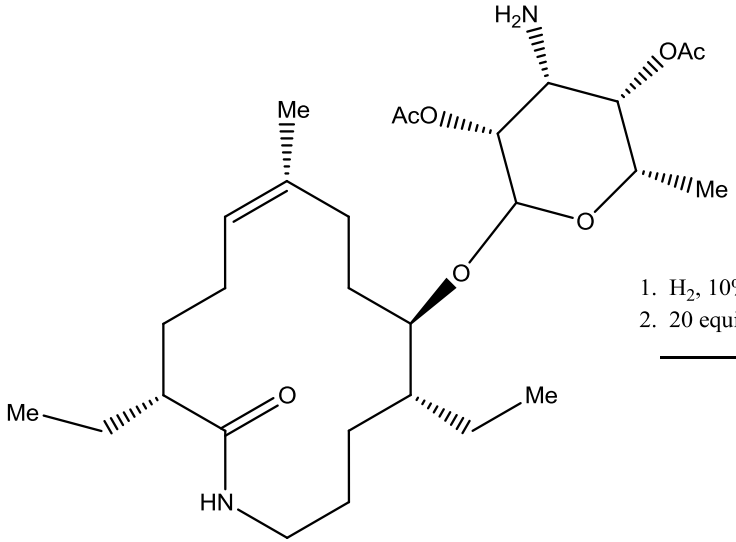
Fluvirucin B_1 Total Synthesis – Part 7



24

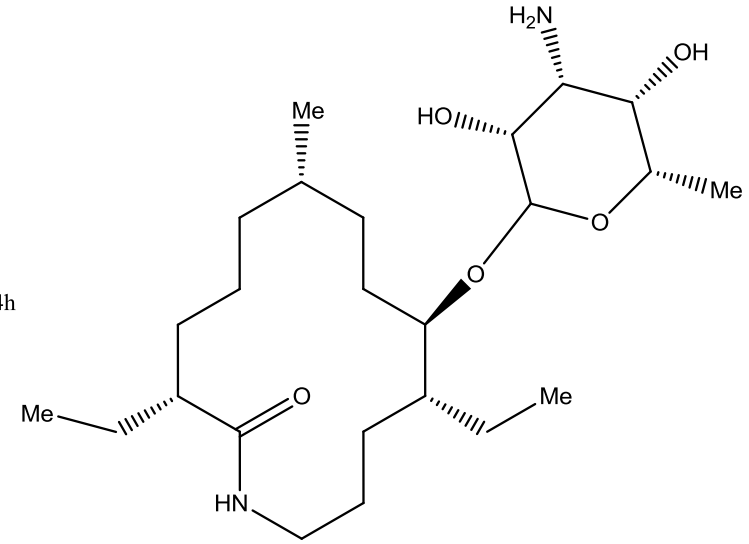
20mol% Mo(CHCMe$_2$Ph)N(2,6-(*i*-Pr)$_2$C$_6$H$_3$)(OCMe(CF$_3$)$_2$)$_2$, Benzene, 22°C, 10h

91%



1. H_2, 10% Pd(C), EtOH
2. 20 equiv. of N_2H_4, MeOH, 24h

69%



Conclusion

- First enantioselective synthesis of Sch 381516 (Fluvirucin B_1)
- 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