Total Synthesis of (+)-Lycoricidine and (+)-Narciclasine

Daniel Olson, Tanner Bingham, Lucas Hernandez, David Sarlah
Department of Chemistry, Sarlah Group, University of Illinois at Urbana-Champaign

Introduction
Amaryllidaceae Isocarbostyril Alkaloids

- (+)-Narciclasine: Mean ICP = 0.049 µM
- (+)-Lyocoricidine: Mean ICP = 0.034 µM

Previous Work:
- (+)-Pancratistatin: 152 mg/kg
- (+)-Lycoricidine: 222 mg/kg
- (+)-Narciclasine: 136 mg/kg
- (+)-7-Deoxypancratistatin: 3 mg/kg

This Work:
- (+)-Narciclasine: 0.044 µM
- (+)-Lyocoricidine: 0.030 µM

Pharmacological Properties:
- Antibacterial
- Antivirus
- Anticancer
- Cytotoxicity
- Broad Therapeutic Window

Synthetic Challenges:
- Highly functionalized
- Four or six contiguous stereocenters

Methodology
Catalytic Cycle of Dearomatizing [4+2]-Cycloaddition

Mechanism:
- Decomplexation
- Re-complexation
- Reductive elimination
- Oxidative addition

Cycloaddition Set-Up:

Current Work
Total Synthesis of (+)-Narciclasine and (+)-Lyocoricidine

Previous Work
Total Synthesis of (+)-7-Deoxypancratistatin and (+)-Pancratistatin

Results
- (+)-Pancratistatin: 200 mg isolated, 12% overall yield
- (+)-7-Deoxypancratistatin: 1.6 g isolated, 19% overall yield
- (+)-Narciclasine: 1.8 g isolated, 15% overall yield
- (+)-Lyocoricidine: > 8.1 g isolated, 26% overall yield

- Syntheses start from benzene, a feedstock solvent
- Scalable routes provide material for further biological studies
- Modular synthesis allows for rapid access to analogues

Acknowledgments:
I’d like to thank the members of the Sarlah research group, David Sarlah for his supervision, and my graduate student advisor, Tanner Bingham, for his guidance and encouragement.

References:
1) J. Nat. Prod. 1993, 56 (10), 1682
3) J. Am. Chem. Soc., 2017, 139 (44), 15656
4) J. Org. Chem., 2010, 75 (1), 57