Total Synthesis of (+)-Isatisine A

Karadeolian, A.; Kerr, M. A. Angew. Chem., Int. Ed. 2010, Early View DOI: 10.1002/anie.200906632

Christopher J. Rosenker
Wipf Group - Current Literature
January 23, 2010
Isatis indigotica Fort.

- leaves of *Isatis indigotica* Fort. (Cruciferae); also known as Indigo-colored Woad Leaf
  - Used in traditional Chinese medicine for treating viral diseases (i.e. influenza, viral pneumonia, and hepatitis)
  - Isolated several different compounds from the leaves and roots

Isolation of isatisine A

- Isolated from the leaves of *Isatis indigotica* Fort. (Cruciferae)
  - Collected from Anhui province, China
  - Group sought an active anti-HIV agent
  - 50 kg provided 64 mg of acetonide
    - Characterized by 1D and 2D NMR, HRMS, $[\alpha]_D$, and X-ray crystallography
    - Absolute stereochemistry was not determined
    - 37.8 $\mu$M EC$_{50}$ anti-HIV-1 for acetonide
    - Acetonide artifact of isolation??


Images copied from Google Maps and http://4.bp.blogspot.com/_ZgtV2LusUZ8/SJspyUMZUAI/AAAAAAAAAIR/En5ImwHXHaQ/s1600-h/leaves.jpg
Structure of isatisine A

Retrosynthetic analysis

- Passes through acetonide isolation artifact
- Elegant stereospecific cycloaddition approach to tetrahydrofuran
  - Starting with chiral cyclopropane allows for synthesis of single enantiomer

Homo 3+2 cycloadditions using cyclopropanes

- Overall reactions provided compounds in high diastereoselectivity
- Other groups have performed reaction asymmetrically using chiral ligands

Young, I.; Kerr, M. Org. Lett. 2004, 6, 139.
Application of methodology

Interestingly, opening of the cyclopropane by the amine was not observed.

Johnson’s work

- Inspired by seminal work by Kerr, Johnson applied methodology to aldehydes
- Reaction occurs with inversion of stereochemistry at cyclopropane

Johnson’s work

observed stereochemistry

observed stereochemistry

Preparation of Starting Materials

Total synthesis of Isatisine A

- Cycloaddition is unsuccessful when cyclopropane has pendant hydroxyl group
  - Authors speculate necessity of π-donor for cycloaddition

Total synthesis of Isatisine A

• Dehydrocarboxylation reaction additionally affords single diastereomer

**Total synthesis of Isatisine A**

- Inconsequential epimeric mixture
- Indole alkylation occurs through acyl iminium
- Reversible alkylation provides 3:1 mixture of diastereomers
- Eventually cyclization occurs in competition with acid mediated decomposition

---

![Chemical Structures]

Total synthesis of Isatisine A

Isolated natural product is antipodal to synthesized product
Starting from opposite cyclopropane enantiomer would provide natural enantiomer
Total synthesis completed in 14 steps and 5.8% overall yield from cyclopropane

Isatisine A acetonide

1N HCl, MeOH

Isatisine A 82%

Isolated acetonide product $[\alpha]^{14}_D = -283$ (c= 0.46, MeOH)
synthetic acetonide product $[\alpha]^{25}_D = +271$ (c= 1.6, MeOH)

Conclusions

- Completed the total synthesis of Isatisine A in 14 steps and 5.8% overall yield from cyclopropane
- Established the absolute stereochemistry
- Successful application of synthetic methodology
  - Methodology provides access to substituted tetrahydrofurans and pyrrolidines asymmetrically
- Work including synthesis and biological evaluation of natural product derivatives is ongoing

(+)-isatisine A