Concise Total Synthesis of Variocolortides A and B through an Unusual Hetero-Diels-Alder Reaction

Christian A. Kuttruff, Hendrik Zipse, and Dirk Trauner

ACIE Early View, DOI: 10.1002/anie.201006154

Marija Manojlović

Wipf Group Current Literature Meeting
1-29-2011
Variecolortides A and B

- Isolated in 2007 from black mold, *Aspergillus variecolor*

- Modest cytotoxic and oxygen scavenging activity (μM range)

- Structural features: unprecedented anthraquinone methide moiety, diketopiperazine, spirocyclic N,O-acetal

Black mold, *Aspergillus variecolor*

Biomimetic Synthesis of Exiguamines A and B

Hemetsberger indole synthesis

1. NaOMe, MeOH
   N₃ → CO₂Me
   1. Pd black
      HCO₂NH₄, 94%
   2. Salcomine, O₂
      MeCN
   3. 1% HCO₂H in H₂O
      77%, 2 steps

1. BocHN
2. Stille coupling

Exiguamine B

Exiguamine A

Biosynthetic Analysis of Variecolortides – Is Diels-Alderase involved?

- 1989 – Monoclonal antibodies that catalyze Diels-Alder (DA) reaction
- 1999 – RNA (ribozymes) can catalyze DA reaction
- 2005 – Theoretical study of macrophomate synthase – stepwise process (Michael then aldol reaction) has more probable energetic profile than concerted process
- 2008 – Macrophomate synthase is a very efficient aldolase
- Existence of real Diels-Alderases still elusive

ACIE 2003, 42, 3078.
OBC 2008, 6, 4483.
JACS 2005, 130, 7789.
Hetero Diels-Alder Reactions of 1-oxa-1,3-butadiene

(-)-Reveromycin B

Camptothecin
Yao et al. OL 2008, 10, 5393.

Quassin and other quassinoids
Spino et al. JOC 1994, 59, 5596.
Hetero Diels-Alder Reactions of 1-oxa-1,3-butadiene


Snider and Lu, *JOC 1996, 61, 2839.*
Title Paper – Synthesis of Precursors

\[ \text{Me}_2\text{O} + \text{Cl} \rightarrow \text{NaH, THF} \rightarrow 52\% \rightarrow \text{Me}_2\text{OH} \rightarrow \text{AlCl}_3/\text{NaCl, 180 °C} \rightarrow 75\% \rightarrow \text{hydroxyviocristin} \]
Title Paper – Synthesis of Precursors

**Chemical Reactions:**

1. **Initial Reaction:**
   - Bromoindole reacts with allyltributyltin in the presence of PdCl2 and PPh3 to form an intermediate.

2. **Subsequent Reactions:**
   - The intermediate undergoes a series of reactions including:
     - Addition of isoprene to form a new bond.
     - Reaction with NCS to form a new functional group.
     - Reaction with 9-prenyl-tributylborane to form a new bond.

3. **Final Products:**
   - The final product is a conjugated diene, A.

**Additional Reactions:**

1. **Cbz Protection:**
   - Cbz protection of an amino group.

2. **Amination:**
   - Amination of the intermediate using EDCI, HOBt, DIPEA, followed by reduction with H2 and Pd/C, and then treatment with SOCl2.

3. **Amination with Piperidine:**
   - Amination with piperidine at 110 °C.

**Final Products:**

- **Isoechinulin B:** Resulting from the reaction of intermediate A with piperidine at 110 °C.

- **Neoechinulin B:** Resulting from the reaction of intermediate B with piperidine at 110 °C.
Computational Studies on Model System

Chemical Structures and Reactions:

1. 1,5H shift from (0.0) to TS[4+2] (+133.7)
2. 1,5H shift from (+55.1) to labile bond
3. 1,5H shift from (+16.7) to TS[4+2] (+74.2)
4. Reaction with o-DCB, air 180°C, 1.5 h, 73%
There is no reaction under more biological conditions (aqueous phosphate buffer at room temperature) => catalyst is needed in nature, possibly Diels-Alderase
Conclusions

- Variecolortides A and B were synthesized in concise manner (7 and 5 steps, respectively)

- Synthesis is mostly protecting group free (except for amide coupling reaction to form dipeptide)

- Unprecedented hetero-Diels-Alder reaction is used in a key step, and the concerted mechanism is strongly supported by DFT calculations

- The question of whether similar reaction occurs in nature is yet to be answered

- Further biological exploration of these natural product is ongoing.