Total synthesis of (-)-Curvulamine


(-)-Curvulamine was isolated from the fungi strain *Curvularia* associated with the white croaker fish.

- It was found to possess sub-micromolar minimum inhibitory concentrations against a variety of Gram-positive and negative bacteria.
- Its biogenetically related trispyrrole natural product cruindolizine 2 was found to lack these properties but possesses anti-inflammatory activity.
- Here is the first chemical synthesis of (-)-curvulamine in 10 steps.
Curvulamine could be trace back to diketon 4 via excision of a two-carbon nuleophile and redox manipulations. Then they envisioned construction tetracycle 4 from 5 and pyrrole 6.
Aldol condensation

1. **Aldol Condensation**
   - **Base** promotes the reaction between an aldehyde and a ketone.
   - **PhMe** (dichloromethane) as the solvent.
   - **DBU** (1,8-diazabicyclo[5.4.0]undec-7-ene) facilitates the condensation.

2. **Reaction Steps**
   - **c. NaH** with **TMSO**
   - **d. DIBAL** (diisobutylaluminum hydride)
   - **e. TMSCN** (trimethylsilylenetriphenylphosphorane)

3. **Products**
   - **N-Me-CO-OMe** (Me: methylene group)
   - **O-Me-CO-OMe** (Me: methylene group)
   - **O-Me-CO-OMe** (Me: methylene group)
   - **O-Me-CO-OMe** (Me: methylene group)
   - **TMSO-NC-CMe** (TMS: trimethylsilyl, NC: cyano group, CMe: methylene group)

4. **Chemical Reactions**
   - **NaHMDS** (sodium bis(trimethylsilyl)amide) in **THF** (tetrahydrofuran)
   - **DBU** in **PhMe** (dichloromethane)
   - **LiClO** (lithium perchlorate)
   - **TMSO** (trimethylsilyl oxide)
   - **DIBAL** (diisobutylaluminum hydride)
   - **TMSCN** (Trimethylsilylenetriphenylphosphorane)
5 + TMSO + NC-R → f. NaHMDS, LiCl, THF, -78 °C
Then add 5 then add NIS 64%

12 + g. hv (390nm) NaHCO₃ MeCN/tBuOH 55%

13 + h. Na₂CO₃ MeOH 96%
Cyanohydrin deprotection
epimerization

\[
\text{Base} \quad \xrightarrow{\text{Li, THF, -78°C}} \quad \text{17}
\]

allylic 1,3-strain minimization

\[
\text{Base} \quad \xrightarrow{\text{KHMDS, CICSO\text{Ph, DMAP, THF}}} \quad \text{71%}
\]
Enol ether hydrolysis

\[
\text{Et}_3\text{B} + \text{O}_2 \rightarrow \text{Et}_2\text{BOO}^\cdot + \text{Et}^\cdot
\]

Bu\_3SnH

Bu\_3Sn^-

CBS reduction condition

\[
\text{BH}_3^\cdot\text{DMS} \rightarrow \text{BH}_3 + \text{DMS}^\cdot
\]

\[
\text{BH}_3 + \text{THF} \rightarrow \text{BH}_3^\cdot\text{THF}
\]