Lundurines A, B & C

Lundurines A, B and C - isolated from *Kopsia tenuis*, a plant native to north of Borneo

Show interesting cytotoxicity properties

These alkaloids feature a unique polyhydropyrroloazocine and cyclopropyl moiety fused to the indoline ring

Reported total syntheses of Lundurine A and B were lengthy and involve over 20 linear synthetic steps

Thus difficult to synthesize useful quantities of final targets to study broad biological assays

In this paper, a more efficient total synthesis (12-14 steps) of Lundurine A, B and the first total synthesis of Lundurine C (racemic and enantiopure) were reported

\[\text{(-)-Lundurine A 1} \quad \text{(-)-Lundurine B 2} \quad \text{(-)-Lundurine C 3}\]
**Retrosynthesis**

1. **1-3**
   - Hydrogenation
   - Cyclopropanation

2. **4**
   - Au(I)-catalyzed hydroarylation
   - Ohira-Bestmann homologation

3. **5**

4. **7**
   - Condensation/Lactamization/Claisen rearrangement cascade

5. **8**

**Synthetic approach**

1. **7**
   - Condensation/Lactamization/Claisen rearrangement cascade
   - Toluene/py (1:2) reflux, 40 h (for 6a)

2. **8**
   - Toluene/Et$_3$N (1:2) reflux, 16 h (for 6b)

3. **R = H, 74% 6a**
   - R = c-C$_5$H$_9$, 84% 6b

4. **K$_2$CO$_3$**
   - MeOH, 25 °C, 3-5 h

5. **R = H, 88% 9a**
   - R = c-C$_5$H$_9$, 84% 9b

6. **AuCl (5 mol%)**
   - CH$_2$Cl$_2$, 25 °C, 5 h
R = H, 83% 10a
R = c-C₆H₅, 79% 89:11 er 10b
56%, >99:1 er (after recrystallization)

1) OsO₄, NMO acetone/H₂O 1.5-6 h, 25 °C
2) NaIO₄ acetone/H₂O 1.5-6 h, 25 °C

R = H, 80% 11a
R = c-C₆H₅, 88% 11b

TsNHNH₂ p-TsOH CH₂Cl₂, 25 °C 5-10 min

MeO
NHTs
BF₃·OEt₂ CH₂Cl₂, 2-3 h 80 °C
(+/-)-13, 91%
(-)-13, 79%

MeO
(+/-)-14a, 79%
(-)-14a, 80%

Toluene, 2 h 155 °C
(+/-)-14b, 96%
(-)-14b, 95%

1) n-BuLi, THF -78 to 23 °C
2) 130 °C 24-48 h

14b (20-25%)
15a: R = H 15b: R = CO₂Me (50-60%)
Mechanistic explanation

Synthesis of alcohol 20

\[ \text{MgBr} \rightarrow \text{MgBr} \]

**Enzymatic Kinetic Resolution:** To obtain the (S)-20

**Mechanism**

\[ \text{In(OTf)}_2 \rightarrow \text{In(OTf)}_2 \]

**Synthesis of azo compound 21**

\[ \begin{align*}
\text{Cl} & \quad \text{CO}_2\text{Me} \\
\text{CH}_3\text{CN}, 25 ^\circ \text{C} & \quad 4 \text{ h, 80%} \\
\rightarrow & \quad \text{N}_2 \quad \text{21}
\end{align*} \]

Mechanism
Both Z- and E- isomers are stable even at 100 °C for several hours. Curtin-Hammett principle is not applicable.
**Picket-Spengler type reaction:** under acidic conditions

![Chemical reaction scheme]

**Ohira-Bestmann reagent**

![Chemical structure of Ohira-Bestmann reagent]

R = H, 74% 6a  
R = c-C₅H₉, 84% 6b  
R = H, 88% 9a  
R = c-C₅H₉, 84% 9b

**Curtin-Hammett principle**

**Mechanism**

![Mechanism diagram]
Rare 8-endo-dig gold(I) catalyzed hydroarylation

Overall, an 8-endo-dig reaction?
Known to be catalysed by Au(III) catalysts in the presence of Ag salts
No explanation has been provided why Au(I) catalyzes the reaction
Johnson-Lemiex cleavage

Mechanism
Homodienyl Retro-Ene / Ene rearrangement

Mechanism

14a to 14b via Homodienyl Retro-Ene / Ene rearrangement