Total Syntheses of (−)-Majucin and (−)-Jiadifenoxolane A, Complex Majucin-Type Illicium Sesquiterpenes

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Wipf Group Current Literature
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The *Illicium* Family of Sesquiterpenes

- The *Seco*-prezizaane family of sesquiterpenes are produced by *Illicium* evergreen shrubs/trees
- 20 members possess the majucin core with different oxygenation patterns
- Several members enhance neurite outgrowth: (–)-jiadifenolide (10 nM), (–)-jiadifenin, (–)-ODNM
- Axon degeneration and neuronal atrophy accompany chronic neurodegenerative diseases. Small molecules that promote growth of neurons are of interest
**Isolation**: 1988 (Guangxi, China) by Sato

**Illicium majus** (Chinese flowering plant)

**Characterization**: 1D/2D NMR, IR, specific rotation, melting point, mass spectrometry, X-ray (des-C(3)-OH)

**Structural features**: fused γ-lactone, δ-lactone, and four stereodefined hydroxyl groups

**Synthesis**: Maimone (2017)

**Bioactivity**: None reported

Isolation: 2009 (Yunnan, China) by Fukuyama
Illicium jiadifengpi (Chinese flowering plant)
Characterization: 1D/2D NMR, IR, specific rotation, mass spectrometry
Structural features: fused γ-lactone, δ-lactone, two stereodefined tertiary hydroxyl groups, strained bridging tetrahydrofuran ring
Bioactivity: Promotes neurite outgrowth in primary cultured rat cortical neurons

Biosynthetic Pathway

This Work

(-)-jadifenoxolane A \(\rightarrow\) (−)-majucin \(\rightarrow\) (+)-cedrol

\[ \text{SN}_2 \]

~ $0.05 USD/g
Double Suárez Oxidation

**Mechanism?**

1. Phl(OAc)$_2$, I$_2$, hv

For HAT reactions
- Ideal arrangement of C-H—X is close to 180°
- Distance between X• and C-H is < 3Å

**References**

Double Suárez Oxidation

1. PhI(OAc)$_2$, I$_2$, hv

2. BH$_3$•THF

3. NaBH$_4$; 72% (2 steps)

4. PhI(OAc)$_2$, I$_2$, hv; 93%

chiral pool  (+)-cedrol

$\sim$ $0.05$ USD/g

Suárez oxidation

Suárez oxidation

>20 g scale

then add

Ac$_2$O, H$_3$PO$_4$; 67%

then add

CrO$_3$•2Pyr

5 g scale

RuO$_4$ Triple Oxidation

5. RuCl$_3$•xH$_2$O (3 x 0.3 eq), KBrO$_3$ (2 x 5.0 eq); 72% 

gram scale

3 x [O]

generates RuO$_4$ in situ

RuO$_4$ C-H oxidation

3°>2°>1°

(4x 3° C-H)

Regioselective for (C6) C-H

Rearrangement

6. SeO\(_2\) (3.5 eq), 4Å MS, diglyme, 130 °C, 4 h then K\(_2\)CO\(_3\) (3.0 eq), Me\(_2\)SO\(_4\) (1.5 eq), 1 h

Riley oxidation

7. L-selectride (1.2 eq), THF, -78 °C then add KOH (10 eq)/MeOH 0 °C, 30 min; 50% (2 steps)

8. DMDO (1.5 eq), 12 h

single diastereomer

9. PhCF\(_3\), 170 °C

[X-ray]

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Formation of the δ-Lactone Ring

10. Me₄NBH(OAc)₃
   (7 eq), MeCN/ AcOH
   -40 °C, 16 h
   64% (3 steps)

11. TsOH·H₂O (2.2 eq)
    n-BuOH, 150 °C
    25 h, 71%

12. LiHMDS (3 eq)
    MoOPH (5.0 eq)
    THF, -78 °C to 0 °C
    2.5 h; 65%

C(10)-epimerization?
Epimerization of C(10)-OH

- $\text{[Ru}_2(\text{PET}_3)_6(\text{OTf})_3][\text{OTf}]$ catalyzes the selective oxidation of secondary alcohols

\[
\begin{align*}
\text{OH} & \quad \begin{array}{c}
\text{Cy} \quad \text{Cy} \\
0.1\% \text{ Ru-cat} \\
1:1 \text{Me}_2\text{CO}:\text{TFE}, 3 \text{ h} \end{array} \\
& \quad \text{or} \\
\text{OH} & \quad \begin{array}{c}
\text{Cy} \quad \text{Cy} \\
0.1\% \text{ Ru-cat}, 0.2\% \text{ NMM} \\
\text{r.t.}, \text{ acceptor ketone} \\
\text{TFE}, 4 \text{ h} \end{array}
\end{align*}
\]

$\text{Ru-cat (1.88\%)}$

$\text{NMM (3.8 mol\%)}$

$\text{Me}_2\text{CO}$

65 °C, 3 h; 65%

$\text{Ru-cat (0.5\%)}$

$\text{NMM (1 mol\%)}$

$\text{Me}_2\text{CO}$

65 °C, 31 h; 88%

Catalyst is more selective for:
- electron rich 2° OH
- less hindered alcohols

Epimerization of C(10)-OH

• Ru complex catalyzes the reverse transfer hydrogenation from isopropanol to hindered ketones

\[
\begin{align*}
\text{Ru complex} & \quad \text{catalyzes} \quad \text{the} \quad \text{reverse} \quad \text{transfer} \\
\text{hydrogenation} & \quad \text{from} \quad \text{isopropanol} \quad \text{to} \quad \text{hindered} \\
\text{ketones} & 
\end{align*}
\]

• Ru complex catalyzes the site selective one-step epimerization of secondary alcohols in the absence of an acceptor

\[
\begin{align*}
\text{Ru complex} & \quad \text{catalyzes} \quad \text{the} \quad \text{site} \quad \text{selective} \quad \text{one-step} \\
\text{epimerization} & \quad \text{of} \quad \text{secondary} \quad \text{alcohols} \\
\text{in} \quad \text{the} \quad \text{absence} \quad \text{of} \quad \text{an} \\
\text{acceptor} & 
\end{align*}
\]

Epimerization of C(10)-OH/ Completion of the Syntheses

13. \([\text{Ru}_2(\text{PEt}_3)_6(\text{OTf}_3)][\text{OTf}]^+\) (0.1 eq)
   NMM (0.2 eq), TFE/ dioxane (1:1)
   120 °C, 18 h then add i-PrOH (3 eq)
   120 °C, 5 h; 65%

14. OsO₄•TMEDA (1 eq)
   DCM, -78 °C to 0 °C
   2 h; 61%

15. MsCl (5.0 eq), pyr (10 eq)
   DCE, rt to 80 °C, 15 h; 92%

* provided by Hartwig group;
Summary of Synthesis

13 oxidation reactions [O]
3 reduction reactions [R]
The first total synthesis of (−)-majucin (7.5 mg) was accomplished in 14 steps and 2.2% overall yield.

The first totals synthesis of (−)-jiadifenoxolane A (2.6 mg) was accomplished in 15 steps and 2.0% overall yield.

Exhaustive oxidation of (+)-cedrol scaffold (13 [O] reactions)
• Site-selective C(sp³)–H bond oxidation

However, 3 reductive steps were necessary for oxidation state and stereo-chemical adjustments.

First application of [Ru₂(PEt₃)₆(OTf)₃][OTf] catalyzed 2° alcohol epimerization in total synthesis.