Total Synthesis of (−)-Dendrobine


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Wipf Group Current Literature
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(-)-Dendrobine: Isolation and Biological Activity

- Most abundant sesquiterpene bases isolated from the ornamental orchid “Jinchai Shihu” (*Dendrobium nobile* Lindl.)
- Principle component of the Chinese medicinal tonic “Chin Shih Hu” and exhibits antipyretic, hypertensive, and convulsant activity
- Intriguing structure containing seven contiguous stereocenters
- Has served as a target to examine novel tactics and strategies for chemical synthesis
- 12 syntheses to date

Dendrobine: Previous Syntheses

- **Racemic Total Syntheses**
  - Kende, A. S. et al. *JACS* **1974**, 96, 4332. 15 steps, 1.1% yield
  - Roush, W. R. *JACS* **1978**, 100, 3599. 24 steps, 0.66% yield

- **Racemic Formal Syntheses**
  - Martin, S. F. et al. *JOC* **1991**, 56, 642. (Inubushi) 14 steps, 0.12% yield
  - Padwa, A. et al. *Org. Lett.* **2000**, 2, 3233. (Kende) 19 steps, 0.4% yield

- **Enantioselective Total Syntheses**
  - Sha, C.-K. et al. *JACS* **1997**, 119, 4130. 20 steps, 2.0% yield
  - Cassayre, S. Z. et al. *JACS* **1999**, 121, 6072. 13 steps, 1.8% yield

- **Enantioselective Formal Syntheses**
  - Mori, M. et al. *JOC* **1994**, 59, 5633. (Kende) 21 steps, 0.78% yield
Strategy is based on a key cascade reaction with an amine functioning as the linchpin

- Installs both the quaternary C11 center and the stereocenter at C3

Asymmetric Michael Reactions

- Catalytic activation:

  Enamine

  Enolate

  Iminium

- Enamine-Catalyzed Michael Reaction

Asymmetric Michael Reactions

- First catalytic asymmetric intramolecular Michael reaction of aldehydes

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{R} \\
\text{X} & \quad \text{R} \\
\text{R} &= \text{H, Me, Ph} \\
\text{X} &= \text{CH}_2, \text{NTs}
\end{align*}
\]  

10 mol% THF, rt, 15-24 h  
85-99%  
80-97% ee  
(8:1 dr - 49:1 dr)

- Complementary catalytic asymmetric intramolecular Michael reaction of aldehydes

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\text{X} & \quad \text{R} \\
\text{R} &= \text{H, Me, Ph} \\
\text{X} &= \text{CH}_2, \text{NTs}
\end{align*}
\]  

10 mol% acetone, 0 °C, 1-4 h  
93-100%  
97- >99% ee  
(8:1 dr - >19:1 dr)

Asymmetric Michael Reactions

- Complementary catalytic asymmetric intramolecular Michael reaction of aldehydes

\[
\begin{align*}
\text{ROC} & \xrightarrow{10 \text{ mol\%}} \text{MeO}_2\text{C} & \text{CF}_3\text{CO}_2^- \\
\text{CH}_3\text{CN}, 0^\circ\text{C}, 3\text{-}5 \text{ h} & \rightarrow & 89\text{-}100\% \\
\text{R}&=\text{Me, }n\text{-Bu, Bn, allyl}
\end{align*}
\]

- No examples of a Michael reaction involving β-substituted enones to generate quaternary centers

Fragment Synthesis

1. i-PrNO₂, TBAF
   THF, rt
   Me₂
   1. LiAlH₄, THF, 0 °C
   2. BzCl, DMAP, Et₃N
      DCM, 0 °C to rt
   3. AcOH, H₂O, 50 °C
   4. TBSCI, DMAP, im.
      DCM, 0 °C to rt
   5. HF-pyridine, THF
      0 °C to rt
   6. (COCl)₂, DMSO, Et₃N
      -78 °C to rt
   73% (4 steps)

76% (2 steps)

82% (2 steps)

**Synthesis of Key Intermediate**

1. **LDA, TMSCl, \( \Delta \)**
   - Reaction with (CH\(_2\))\(_4\)OTBDPS
   - Product: \( \text{B} \)
   - Yield: 88% (anti/syn = 2.2:1)

2. **TMSCHN\(_2\)**
   -反应(2 steps)
   - Product: TBDPSO\( \{\} \)
   - Yield: 95%

3. **HF-pyridine, THF, \( 0 \degree C \) to rt**
   - Reaction with TBDPSO\( \{\} \)
   - Product: TBDPSO\( \{\} \)
   - Yield: 81%

4. **PCC, Celite, DCM, rt**
   - Reaction with TBDPSO\( \{\} \)
   - Product: TBDPSO\( \{\} \)
   - Yield: 67% (d.r. = 2:1)

**Additional Reactions:**

- **EtMgBr, THF, \( 0 \degree C \) to rt**
  - Reaction with TBDPSO\( \{\} \)
  - Product: TBDPSO\( \{\} \)
  - Yield: 81%

- **TEMPO, Phl(OAc)\(_2\), DCM, 0 \degree C to rt**
  - Reaction with TBDPSO\( \{\} \)
  - Product: TBDPSO\( \{\} \)
  - Yield: 65% (d.r. = 2:1)
Intramolecular Enamine Michael Addition: Cyclization Studies

Preliminary cyclization studies revealed good stereocontrol at C11, and no stereocontrol at C3

Cyclization with N-methylbenzylamine gave same d.r. (2:1)

Cyclization and subsequent reduction provided a d.r.>10:1 and allows for introduction of the desired pendant amine
Intramolecular Enamine Michael Addition: Cyclization Studies

- The cyclization cascade can also be applied to other amines
Cascade Sequence: Mechanistic Proposals

endo

A

concave protonation

B

provides diastereomer

C

stereoselective C=C reduction

convex protonation

D

protonation
Cascade Sequence: Pathway D Favored

Convex protonation followed by reaction with pyrrolidine results in a 65% yield (d.r. 2:1) and (d.r. 5:1).

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Completion of (−)-Dendrobine

- 18 linear steps, 4.0% overall yield

Conclusions

- Asymmetric total synthesis of (-)-dendrobine was achieved in 18 linear steps, 4.0% overall yield
- Key features of the synthesis include:
  - Efficient construction of the central cyclohexane core by an Ireland-Claisen rearrangement
  - A conjugate enamine addition/hydrogenation sequence to install the quaternary center as well as the pendant methyl amino group
  - Regioselective ketone bromination followed by pyrrolidine formation
- The first report of an enamine conjugate addition to a β-disubstituted enone to generate a quaternary stereocenter