Stereodivergent Total Synthesis of $\Delta^9$-Tetrahydrocannabinols

Michael A. Schafroth, Giuseppe Zuccarello, Simon Krautwald, David Sarlah, and Erick M. Carreira*


Ophélie Quinonero
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Literature precedents
Total Synthesis of $\Delta^9$-trans-Tetrahydrocannabinol

- First racemic synthesis reported by Gaoni et al
- 2% overall yield

Literature precedents

Total Synthesis of $\Delta^9$-trans-Tetrahydrocannabinol

- First enantioselective synthesis reported by Evans et al
- 21% overall yield

Diastereoisomers of $\Delta^9$-Tetrahydrocannabinols

More abundant diastereoisomer
Isolated from Cannabis sativa L.
Anti-nauseant / chemotherapy
Treatment of anorexia,
Management of neuropathic pain

[both diastereoisomers found in Nature]
A stereodivergent approach
Get them all!

Stereodivergent approach
- same starting material (SM)
- uniform synthetic sequence
- identical reaction conditions
- rapid access to any stereoisomer of natural product

Traditional approach
- different starting materials \( (\text{SM}_n) \)
and/or synthetic routes are required for diastereomeric targets
- diastereomer of natural product might not be accessible
Stereodivergent dual catalysis

Stereodivergent preparation of all stereoisomers of \( \Delta^9 \)-THC precursor (4)

**Conditions**
- 1.0 equiv 2, 3.0 equiv 3
- 3 mol% \([\text{Ir(cod)Cl}]_2\)
- 12 mol% \((P, \text{olefin})\)
- 15 mol% amine
- 5 mol% Zn(OTf)$_2$
- DCE (0.5 M), 25 °C, 20 h
Stereodivergent preparation of all stereoisomers of $\Delta^9$-THC

- **a)** Grubbs II cat.
- **b)** NaClO$_2$  
- **c)** Me$_3$SiCHN$_2$
- **d)** MeMgI, then ZnBr$_2$

Diagram:

- Initial compound (5)
- Steps:
  - **a)** Grubbs II cat.
  - **b)** NaClO$_2$  
  - **c)** Me$_3$SiCHN$_2$
  - **d)** MeMgI, then ZnBr$_2$

Resulting stereoisomers:

- (S,S)-4
- (R,S)-4
- (S,R)-4
- (R,R)-4

Uniform synthetic sequence of steps for all stereoisomers:

- [(S,S), (R,S)]
- [(S,R), (R,R)]
Conclusion

- Short and uniform synthetic route
  \( \rightarrow \) (12 % to 22 % overall yield for each stereoisomers)

- Key step: stereodivergent dual catalytic \( \alpha \)-allylation of linear aldehyde

- Combination of Iridium and amine catalysis

- Rapid access to different stereoisomers
  \( \rightarrow \) investigation of the pharmacology of all stereoisomers
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Thanks for your attention.