Total Synthesis of (-)-Δ⁹-trans-Tetrahydrocannabinol via Mo-Catalyzed Asymmetric Allylic Alkylation Reaction

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Overview

- Introduction
- Previous Syntheses
- Retrosynthetic Scheme
- Synthetic Scheme and Key Reactions
- Conclusion
(-)-Δ⁹-trans-Tetrahydrocannabinol (Δ⁹-THC) was first isolated in 1964 from female Cannabis sativa L.

- Is the primary psychomimetic component of marijuana
- Has been shown to possess analgesic properties and is used by chemotherapy patients
- Δ⁹-THC and its analogs have been shown to bind selectively to cannabinoid receptors CB1 and CB2

**Previous Syntheses**

- Δ⁹-THC has been synthesized multiple times but only once from achiral starting materials (Evans et. al. *J. Am. Chem. Soc.* **1999**, *121*, 7582)
- Evans’ synthesis derived chirality from an asymmetric catalyzed Diels-Alder reaction
- Using these synthetic schemes, it would be difficult to produce a large number of analogs
Evans’ Key Step

-20°C, 18h
trans:cis: 73:27
98% ee, 57% yield

Retrosynthetic Scheme
OH

\[
\text{C}_6\text{H}_5\overset{\text{OMe}}{\text{O}} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe}
\]

\[
\text{C}_6\text{H}_5\overset{\text{MeO}}{\text{O}} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe}
\]

\[
\text{C}_6\text{H}_5\overset{\text{Ar}}{\text{O}} \quad \text{Ar} \quad \text{Ar} \quad \text{Ar} \quad \text{Ar}
\]

\[
\text{C}_6\text{H}_5\overset{\text{OMe}}{\text{O}} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe}
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\text{C}_6\text{H}_5\overset{\text{OMe}}{\text{O}} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe}
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\text{C}_6\text{H}_5\overset{\text{OMe}}{\text{O}} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe}
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Summary

- 13 Steps, 21% Overall yield starting from commercially available olivetol (6)
- Evans’ Synthesis accomplished the synthetic scheme in 5 steps with 21% overall yield from the key step’s starting materials
- Further demonstrates the applications of the Mo-Catalyzed Asymmetric Allylic Alkylation to total synthesis