Stereodivergent Total Synthesis of Δ^9-Tetrahydrocannabinols

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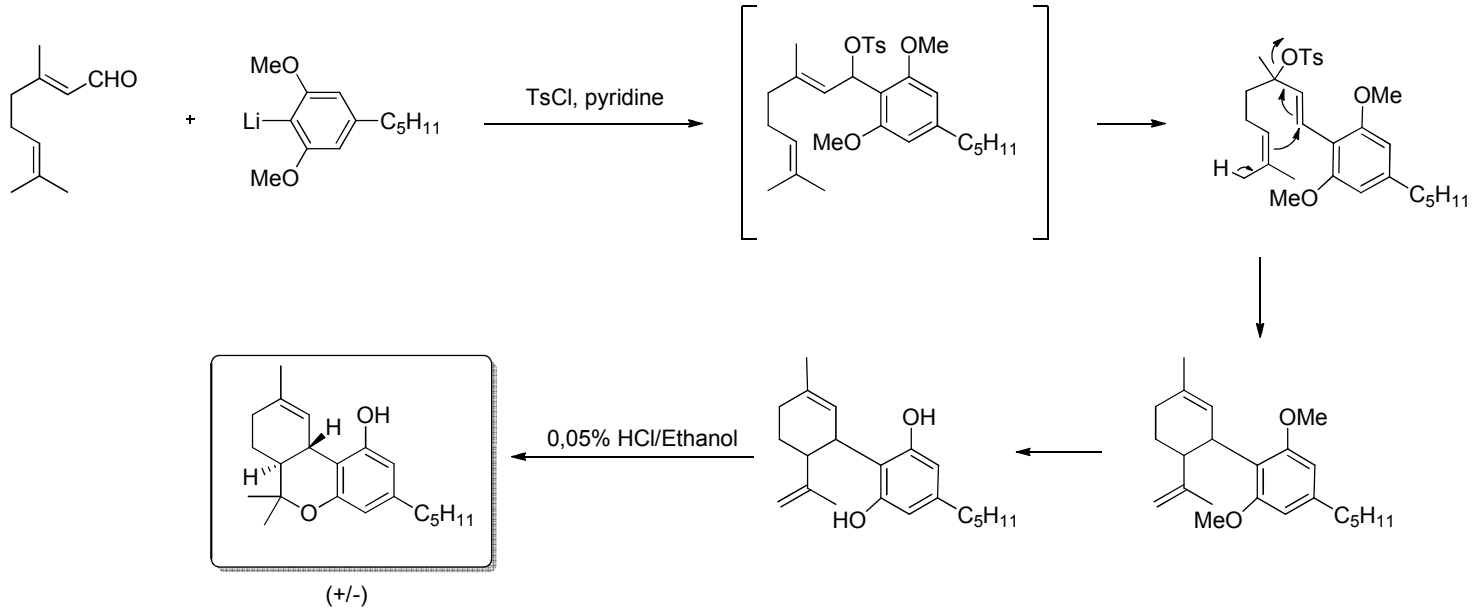
Ophélie Quinonero

21/10/2014

Literature precedents

Total Synthesis of Δ^9-trans-Tetrahydrocannabinol

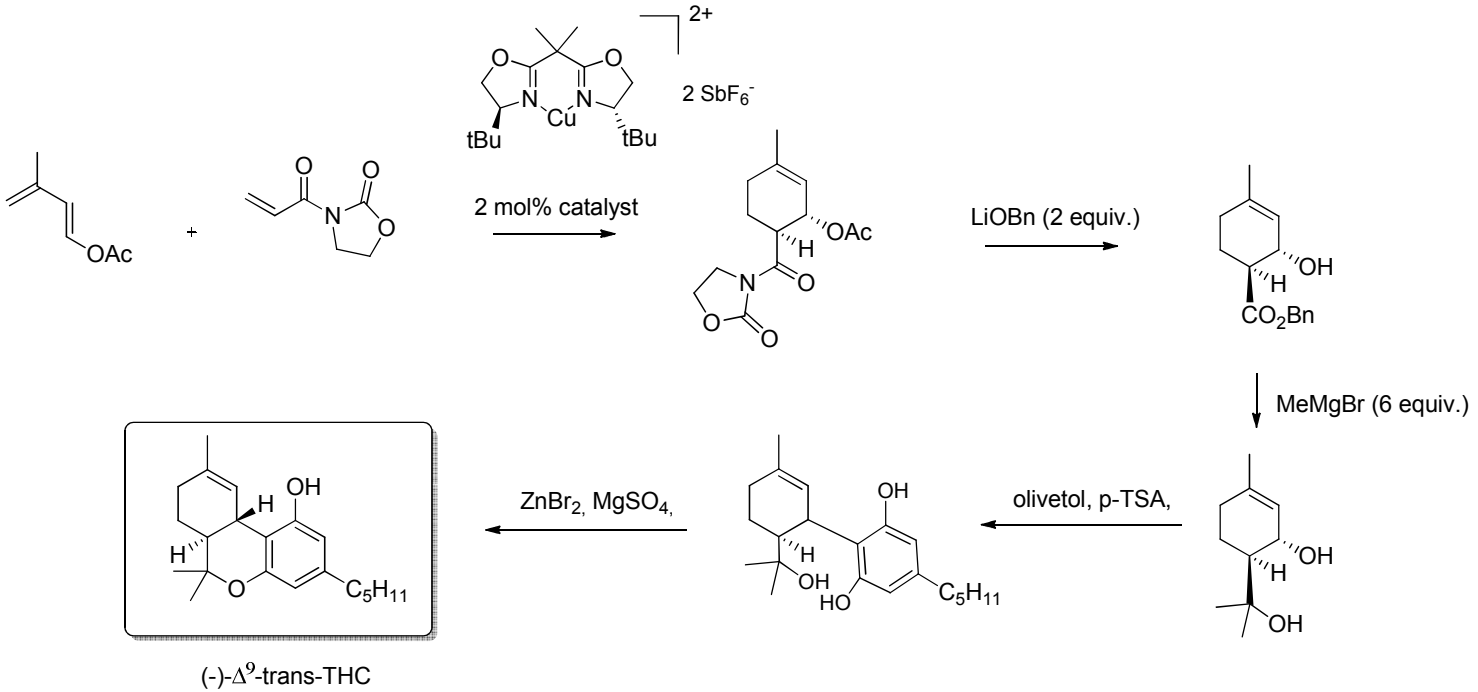


- First racemic synthesis reported by Gaoni *et al*
- 2% overall yield

R. Mechoulam, Y. Gaoni, *J. Am. Chem. Soc.* **1965**, *87*, 3273

Literature precedents

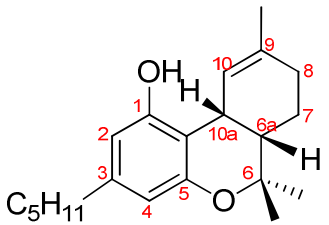
Total Synthesis of Δ^9-trans-Tetrahydrocannabinol



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

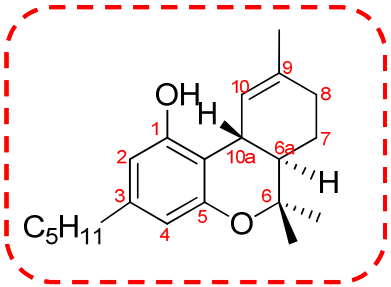
D.A. Evans, E.A. Shaughnessy, D.M. Barnes, *Tetrahedron Lett.* **1997**, *38*, 3193

Diastereoisomers of Δ⁹-Tetrahydrocannabinols



(6aS, 10aR)

(-)-Δ⁹-cis-tetrahydrocannabinol



(6aR, 10aR)

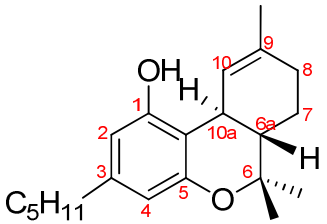
(-)-Δ⁹-trans-tetrahydrocannabinol

[both diastereoisomers found in Nature]

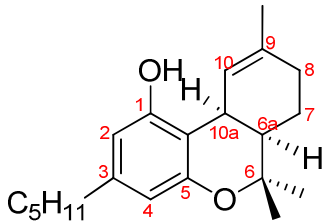
More abondant diastereoisomer

Isolated from *Cannabis sativa* L.

Anti-nauseant / chemotherapy
Treatment of anorexia,
Management of neuropathic pain



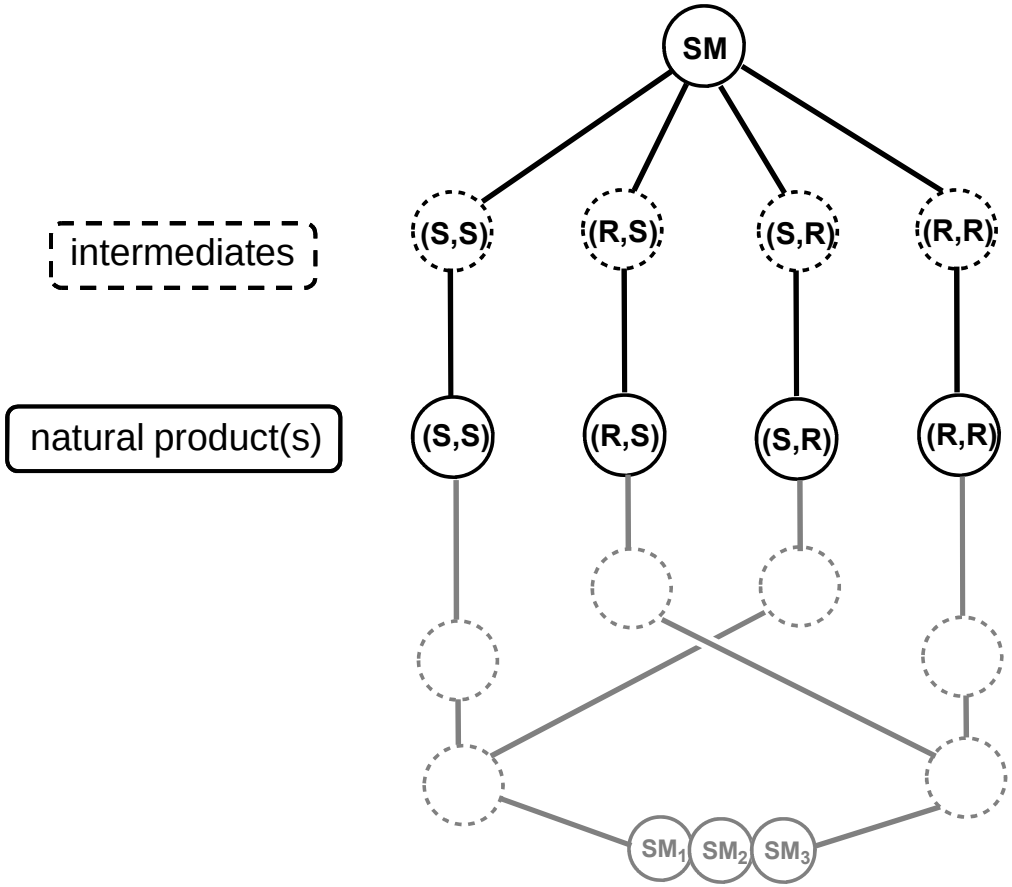
(6aS, 10aS)



(6aR, 10aS)

A stereodivergent approach

Get them all !



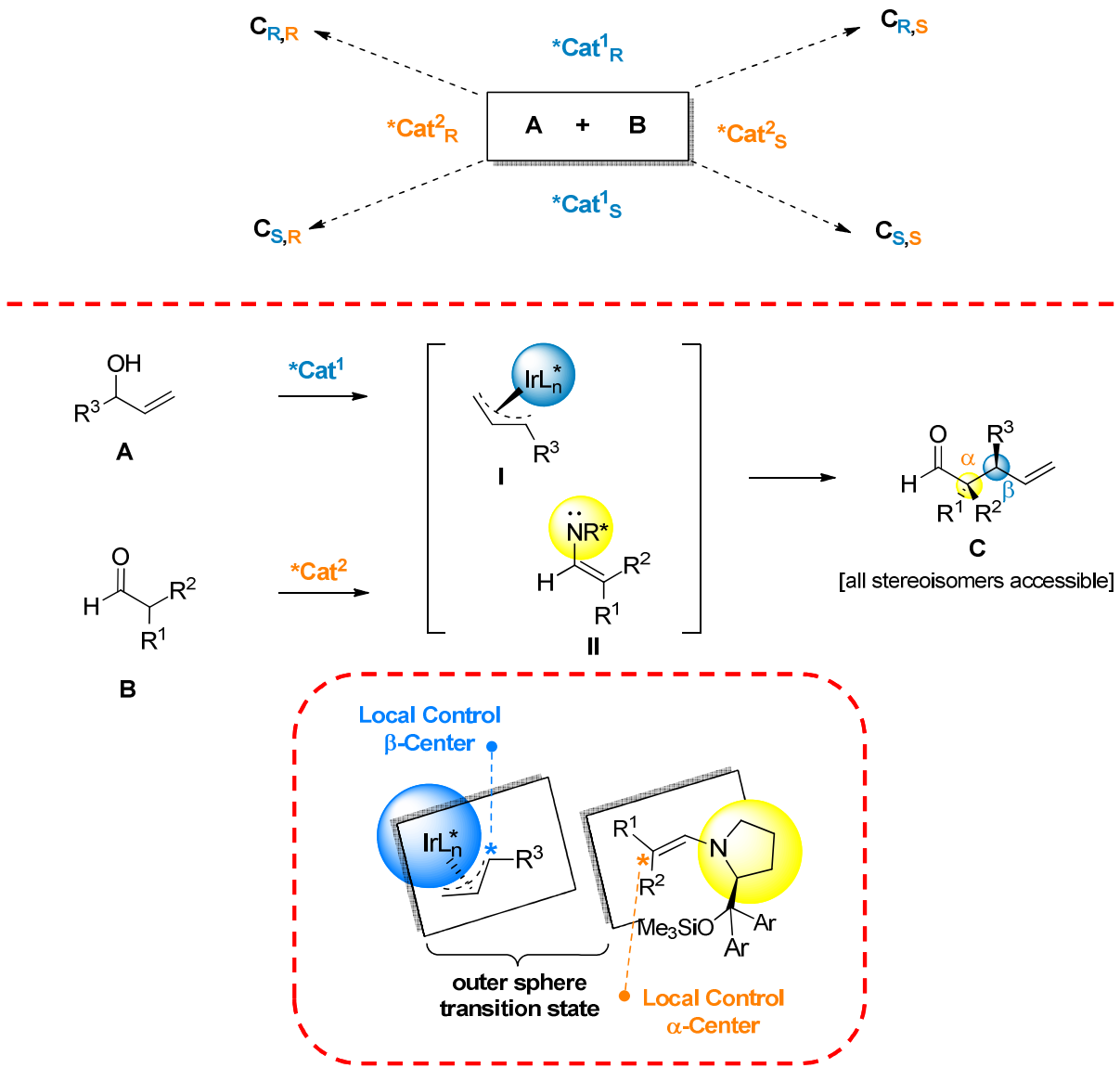
Stereodivergent approach

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

Traditional approach

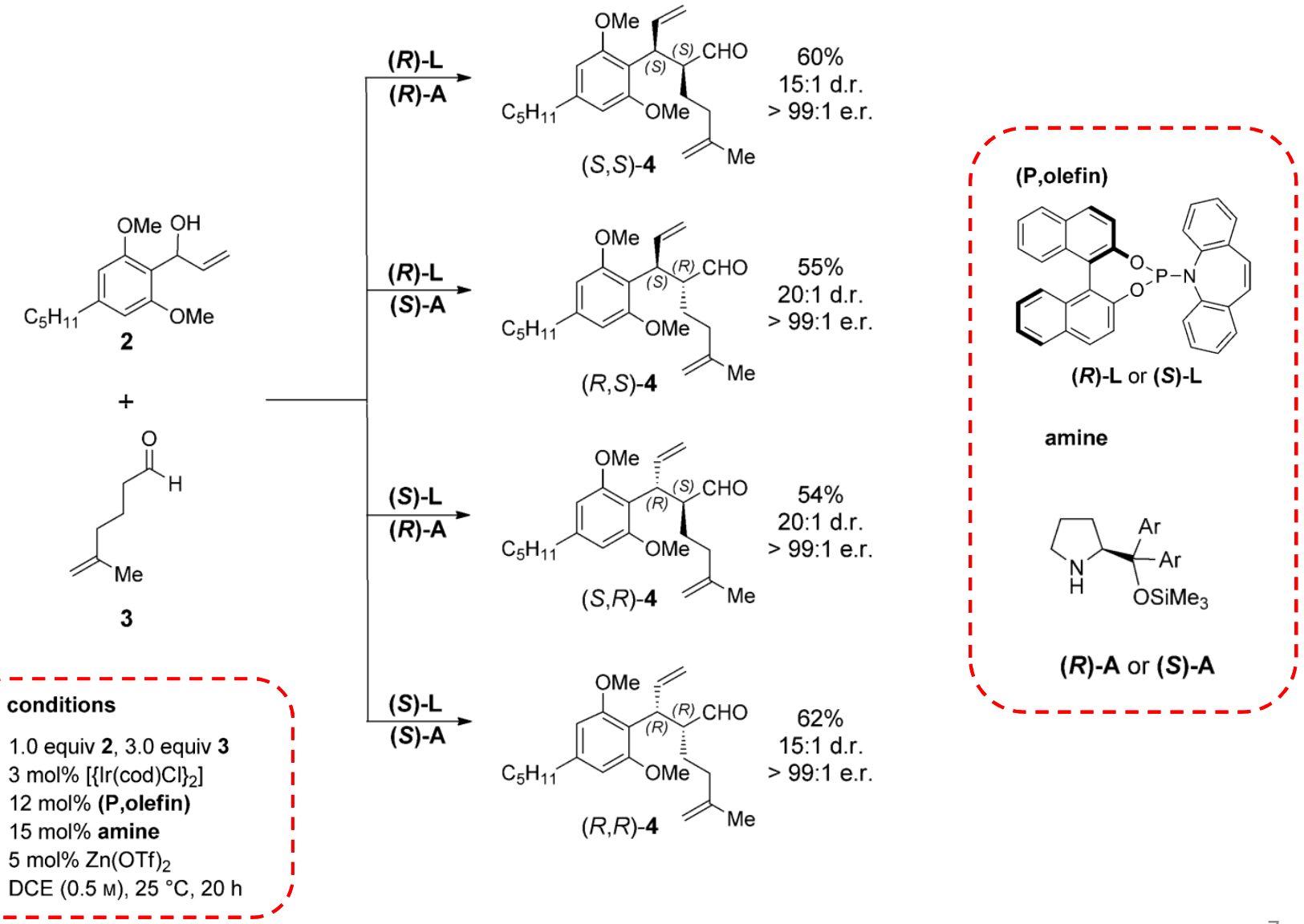
- different starting materials (SM_n) and/or synthetic routes are required for diastereomeric targets
- diastereomer of natural product might not be accessible

Stereodivergent dual catalysis

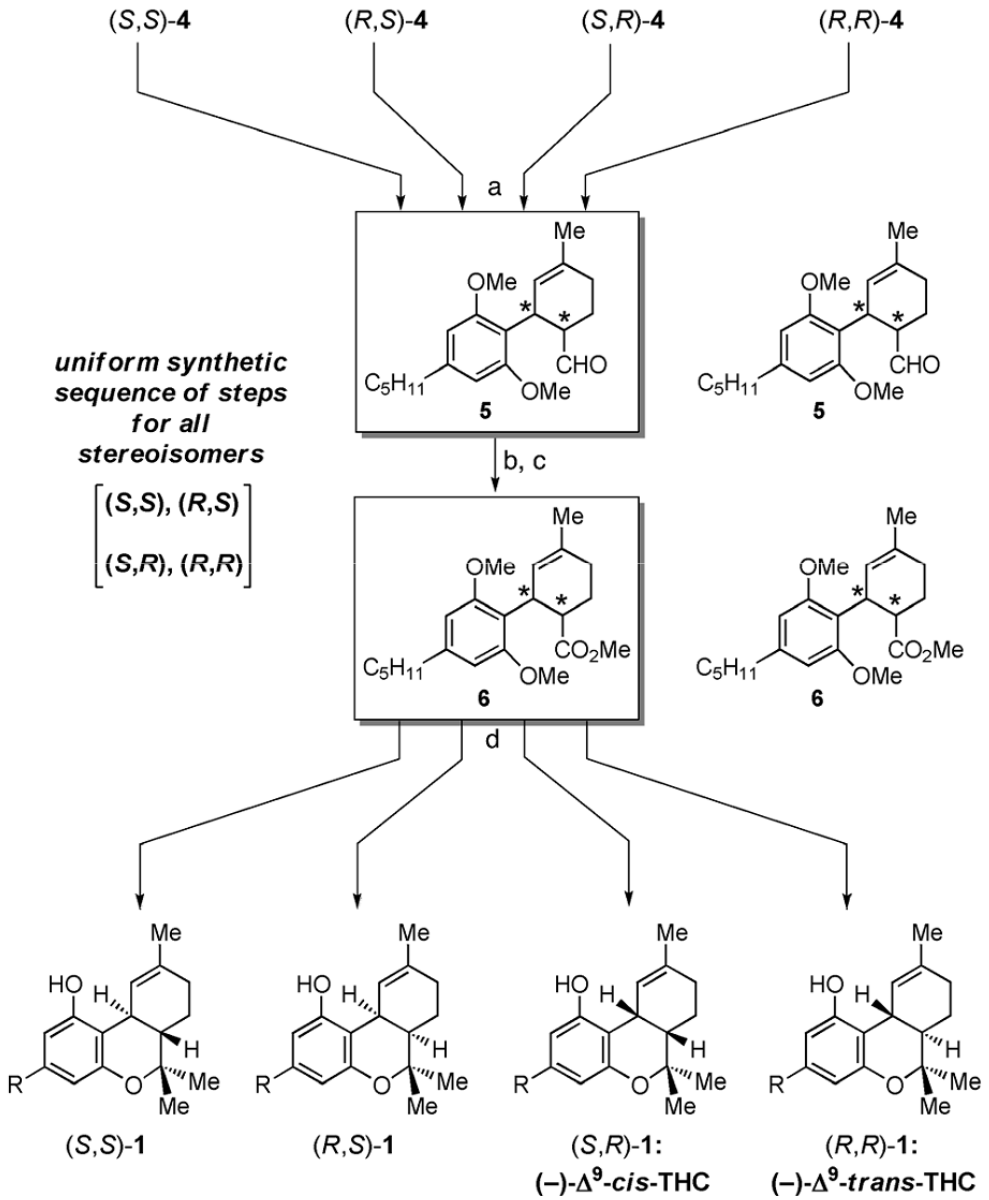


S. Krautwald, D.Sarlah, M.A. Schafroth, E.M. Carreira, *Science* **2013**, *340*, 1065

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



Stereodivergent preparation of all stereoisomers of Δ^9-THC



a) Grubbs II cat.

b) $NaClO_2$ **c)** Me_3SiCHN_2

d) MeMgI, then $ZnBr_2$

Conclusion

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

- Key step : **stereodivergent dual catalytic α-allylation** of linear aldehyde

- Combination of **Iridium and amine catalysis**

- Rapid access to differents stereoisomers
  → investigation of the **pharmacology** of all stereoisomers

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Thanks for your attention.