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Part II:**Early Work:**

10. Roger Adams: Structure Determination of Cannabinoids
11. Mechoulam: Structure Determination and Synthesis of THC

Stereospecific Syntheses:

12. Petrlik and Eschenmoser, Razdan
13. Rickards, Stoss, Studer
14. Kobayashi

Enantioselective Syntheses:

15. Evans
16. Trost
17. Carreira
18. Zhou

Reviews:

Progress in the Chemistry of Organic Natural Products. M. A. ElSohly *et al.*; Ch 1, *Phytochemistry of Cannabis sativa L.* & Carreira *et al.*; Ch 2 *Synthesis of Phytocannabinoids 2017*, Springer, pp 1-60.

Kassiou *et al.*; The evolving science of phytocannabinoids. *Nat. Reviews* **2017**, 2, 0101.

Appendino, Hanus, *et al.*; Phytocannabinoids: a unified critical inventory. *Nat. Prod. Rep.*, 2016, 33, 1357.

Ligresti *et al.*; From phytocannabinoids to cannabinoid receptors and endocannabinoids: pleiotropic physiological and pathological roles through complex pharmacology. *Physiol Rev.* **2016**, 96, 1593.

Adams; *Marihuana*, *Bul. N.Y. Acad. Med.* **1942**, 705.

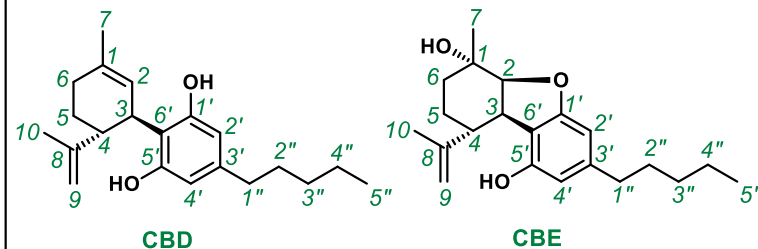
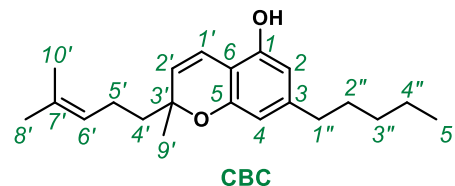
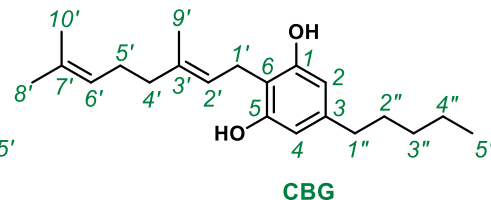
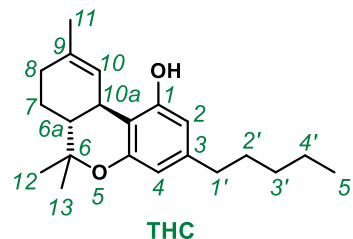


"The recorded medical literature is most confusing. The reports are contradictory, and the description of the drug varies from one which is habit-forming and which with constant use is as harmful to the system as morphine, to one which is almost completely innocuous with a stimulation not far remote from that of alcohol" - Roger Adams, February 9, 1942

Prefixes to know:

phyto- , plant
endo- , internal/within

phytocannabinoids
and their current
numbering
systems:

**Conditions and Diseases in which Activation of the Endo Cannabinoid System has Shown Benefit**

| | | |
|-------------------------------|-------------------------------|-------------------------------------|
| Emesis | Epilepsy | Obesity |
| Pain | Glaucoma | Anorexia |
| Inflammation | Schizophrenia | Parkinson's disease |
| Multiple sclerosis | Cardiovascular disorders | Insomnia |
| Autism | Stroke (Ischemia) | Alzheimer's disease |
| PTSD | Cancer | Metabolic syndrome related diseases |
| Obsessive compulsive behavior | Amyotrophic lateral sclerosis | Prion diseases |
| Tourette's syndrome | Depression | Psychosis |
| Anxiety | Panic | |

Surg. Neurol. Int. **2018**, 9, 91.

Cannabis sativa, an Abbreviated Cultural Timeline

Common Names:

- Arabic: Al-Bhango; Al Hashish; Al-Qanaap
- Chinese: Xian ma; ye ma
- Danish: Hemp
- Dutch: Hennep
- English: hemp; marihuana
- Finnish: Hamppu
- French: Chanvre
- German: Hanf
- Indian: Bhang; ganja
- Japanese: Mashinin
- Nepalese: Cares; gaanjaa
- Portuguese: Canhamo; maconha
- Russian: *Kannabis sativa*
- Spanish: grifa; marijuana
- Sweedish: Porkanchaa



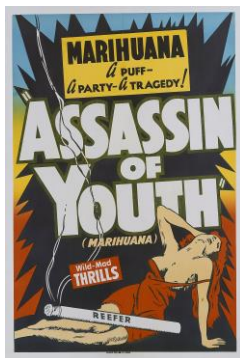
1937

United States introduces Marihuana Tax Act



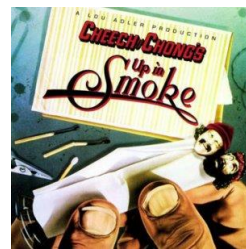
1942

Roger Adams correctly reports the structure of CBN and CBD, but misassigns THC



1951

Cannabis listed as a narcotic in United States



1978

Up in Smoke released



1988

endocannabinoid system identified

1985

Synthetic THC (Marinol; AbbVie) approved for use in the United States

1992

Endogenous cannabinoid discovered

2016

Human CB₁ receptor crystal structure obtained

1964

Structure of THC reported correctly by Mechoulam

1839

Cannabis plant introduced to Western medicine

1895

Wood, Spivey, and Easterfield become the first to isolate pure cannabinoid (CBN)

1932

Cahn reports the structure of CBN, but misassigns the C₅H₁₁ and hydroxyl group locations

2,700 to 10,000 BCE

oldest use of Cannabis is unknown

2,000 BCE

1,000-2,000 BCE

Cannabis as a textile fiber introduced to Europe from Egypt and western Asia

1122-249 BCE

Burial site, China, Chou Dynasty

1000 BCE

Debris pile, Gordion, Turkey

CE

200 BCE

China, Chou-Li mentions use of Cannabis fiber

900 CE

Hokkaido, Japan

1,000 CE

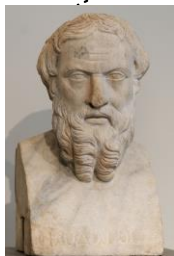
1320 CE
Lalibela Cave
Begemeder Province
Ethiopia

1545 CE
Cannabis fiber
introduced to
South America

today

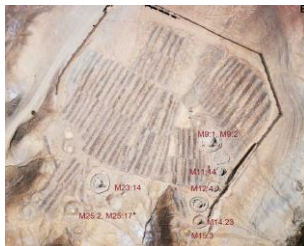
500 BCE

ritual and recreational inhalation of cannabis fumes documented in Herodotus's *The Histories*



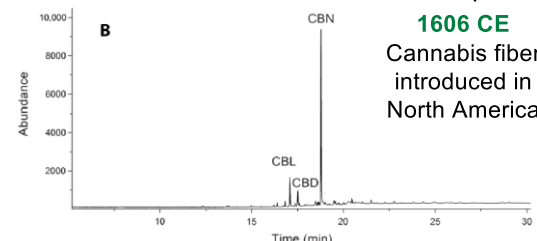
500 BCE

evidence of CBN found at the Jirzankal Cemetery *Sci. Adv.* 2019, 5, 1391.



1606 CE

Cannabis fiber introduced in North America



Cultivation:



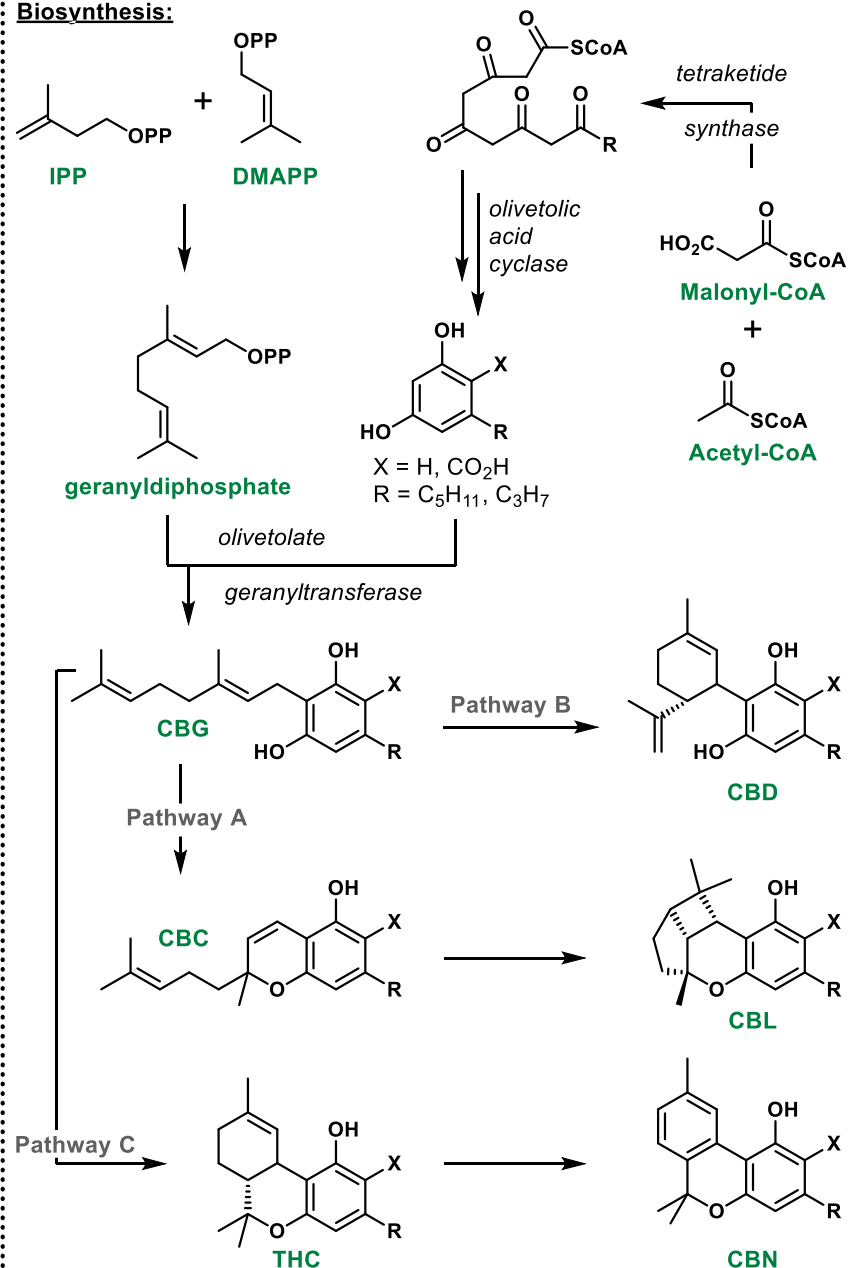
Field-grown *Cannabis sativa* L.: male plants (left), female plants (right)

- There is a debate over whether *C. sativa*, *C. indica*, and *C. ruderalis* are separate species, but it is now accepted that all are varieties of the highly diverse species *C. sativa* L.-*Cannabis sativa* is a dioecious species, i.e. male and female flowers develop on separate plants. Males are heterogametic (XY) while females are homogametic (XX).
- Determining sex in developing plants is difficult, and molecular tests are required.
- Indoor cultivation provides 3-4 crops per year, while outdoor cultivation produces just a single crop.
- THC content can be analyzed on a daily basis to ensure optimum levels. Typically, THC content increases gradually with plant age until the budding stage, whereupon it reaches a plateau for one to two weeks.

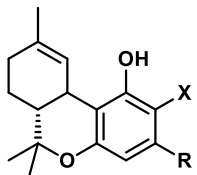
known constituents of *C. sativa* L.

| Chemical class | 2005 | 2015 |
|------------------------|------|------|
| Δ^9 -THC type | 9 | 23 |
| Δ^8 -THC type | 2 | 5 |
| CBG type | 8 | 16 |
| CBC type | 6 | 9 |
| CBD type | 7 | 7 |
| CBND type | 2 | 2 |
| CBE type | 5 | 5 |
| CBL type | 3 | 3 |
| CBN type | 7 | 11 |
| CBT type | 9 | 9 |
| Miscellaneous types | 14 | 30 |
| total cannabinoids | 72 | 120 |
| total non-cannabinoids | 419 | 445 |
| total | 491 | 565 |

Biosynthesis:



Biological activity of major phytocannabinoids



THC

X = H, R = C₅H₁₁

CB₁ K_i(nM) = 5.1-35,

CB₂ K_i(nM) = 3.1-8.5

Other Targets: GPR55, GPR18, TRPV1-4, TRPA1, 5HT_{3A}, PPAR_γ, and cytochrome P450

Δ⁸-THC

CB₁ K_i(nM) = 44-48,

CB₂ K_i(nM) = 39-44

X = H, R = C₃H₇

CB₁ K_i(nM) = 75

CB₂ K_i(nM) = 145-225

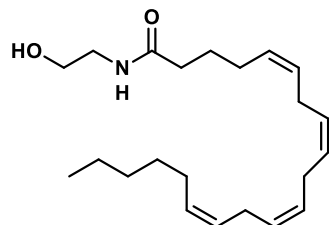
Other Targets: GPR55, TRPA₁,

TRPV2, TRPM8, 5HT_{3A}

X = CO₂H, R = C₅H₁₁

CB₁ K_i(nM) = 23-2200

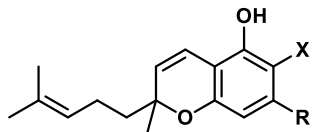
CB₂ K_i(nM) = 56-12500



anandamide

CB₁ K_i(nM) = 178-300,

CB₂ K_i(nM) = 344-535

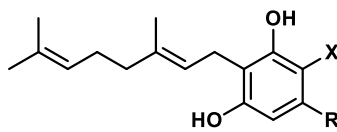


CBC

X = H, R = C₅H₁₁

no activity at CB₁ or CB₂

Other Targets: TRPV3-4, TRPA1, TRPM8,

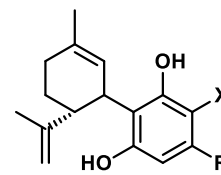


CBG

X = H, R = C₅H₁₁

no activity at CB₁ or CB₂

Other Targets: GPR55, 5HT_{3A}, TRPV1-2, TRPA1, TRPM8, GlyR₂, and anandamide uptake



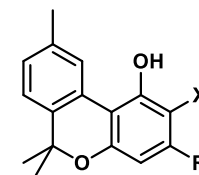
CBD

X = H, R = C₅H₁₁

CB₁ K_i(nM) = 4,000

CB₂ K_i(nM) = 4,200

Other Targets: GPR55, GPR18, TRPV1-3, TRPA1, 5HT_{3A}, PPAR_γ, GlyR_{1,3}, GABA_A, and anandamide uptake



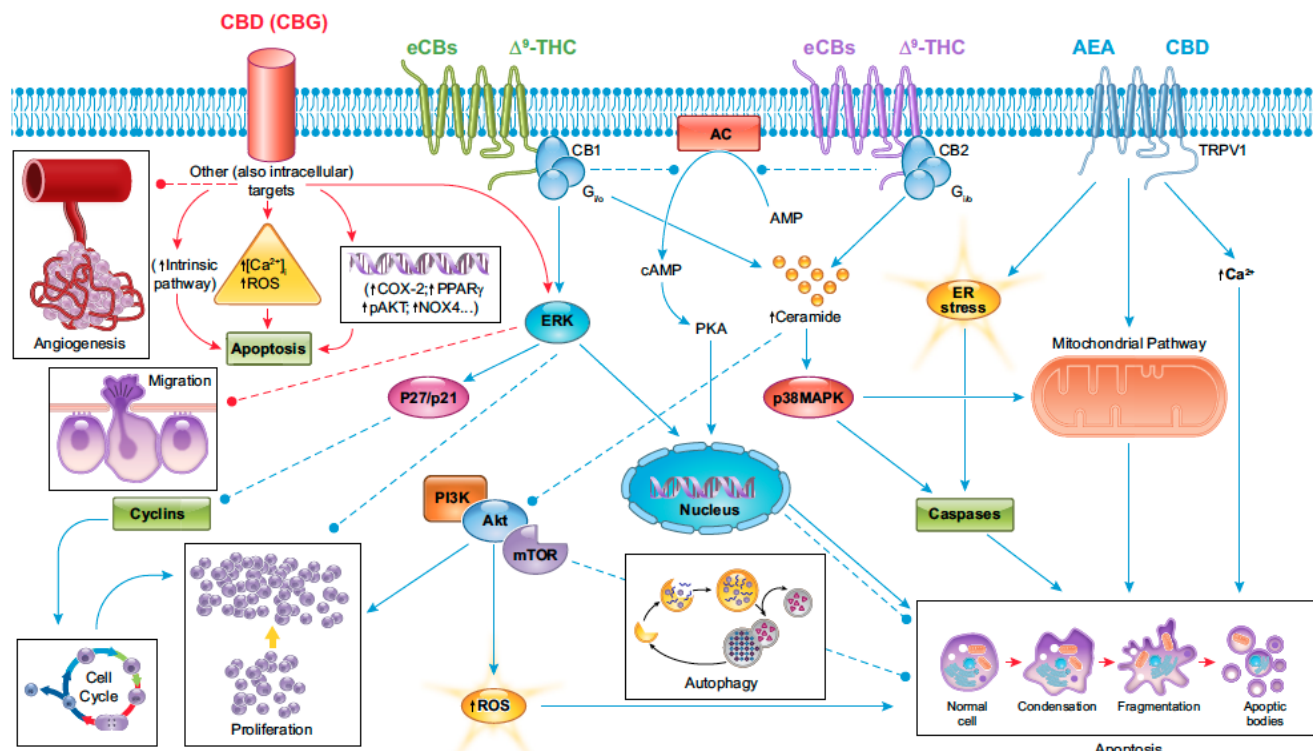
CBN

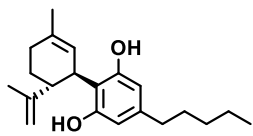
X = H, R = C₅H₁₁

CB₁ K_i(nM) = 12.7-125

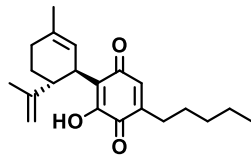
CB₂ K_i(nM) = 16.43-100

Other Targets: TRPA1, TRPM8

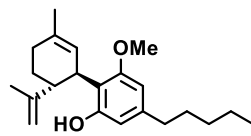




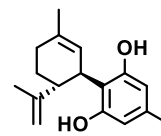
CBD



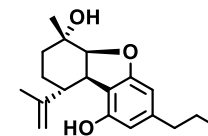
HU-313



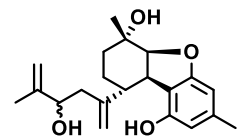
O-methylcannabidiol



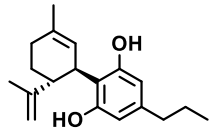
cannabidiolol



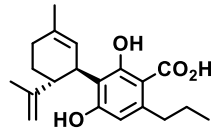
bisnor-cannabielsoin



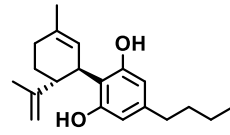
ferruginene A



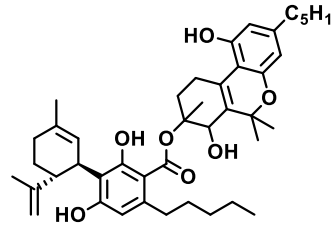
cannabidivarin (CBDV)



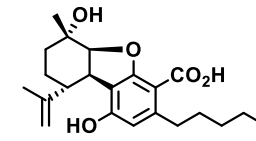
cannabidivarinic acid



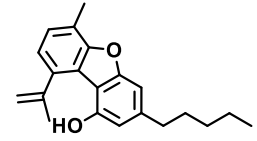
nor-cannabidiol



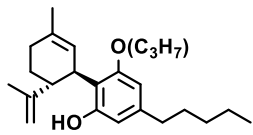
CBDA-THC ester



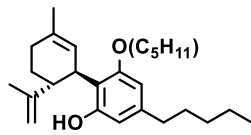
cannabielsoic acid B



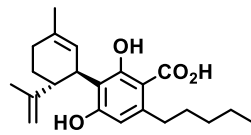
dehydrocannabifuran



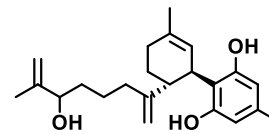
O-propylcannabidiol



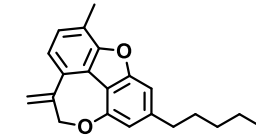
O-pentylcannabidiol



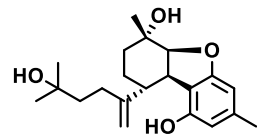
cannabidiolic acid



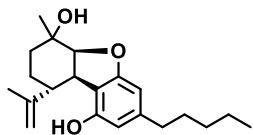
ferruginene C



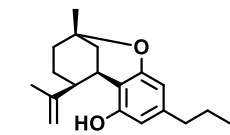
cannabioxepane



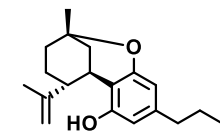
ferruginene B



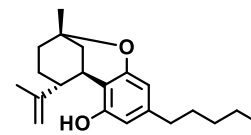
CBE



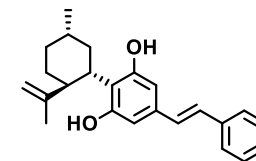
7-cis-isotetrahydrocannabivarin



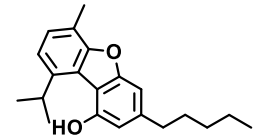
7-trans-isotetrahydrocannabivarin



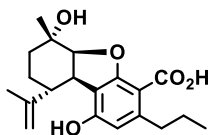
7-trans-isotetrahydrocannabinol



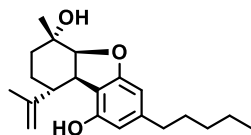
machaeridiol A



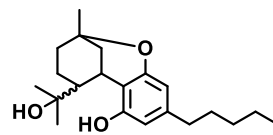
cannabifuran



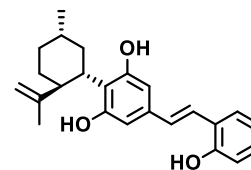
bisnor-cannabielsoic acid B



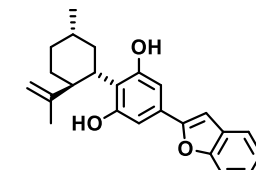
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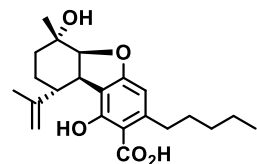
cannabiglendol



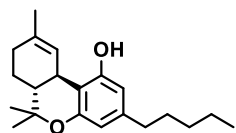
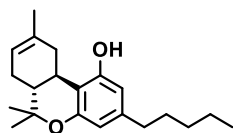
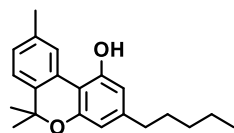
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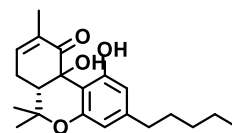
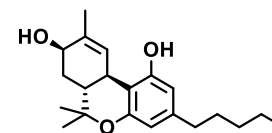
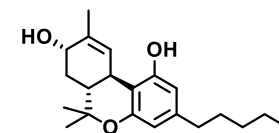
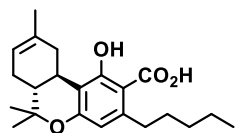
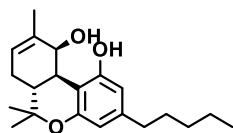
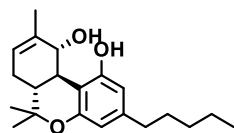
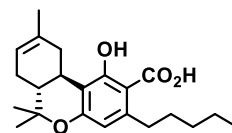
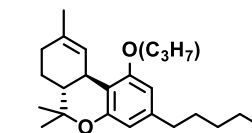
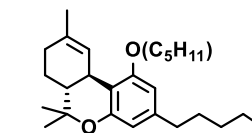
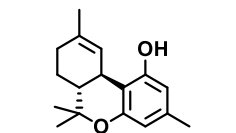
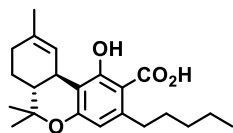
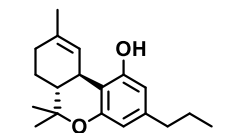
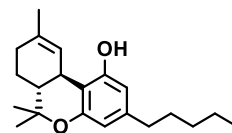
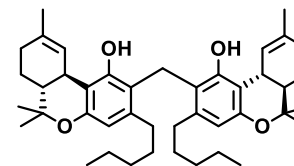
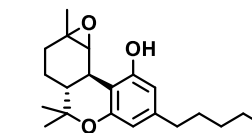
machaeridiol C



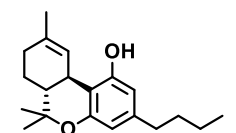
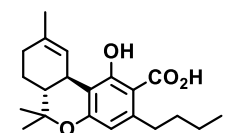
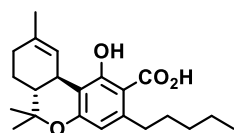
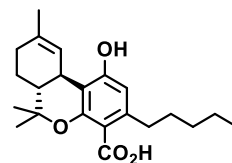
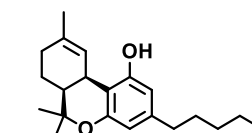
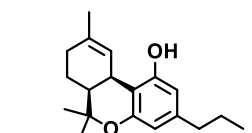
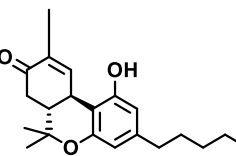
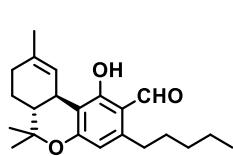
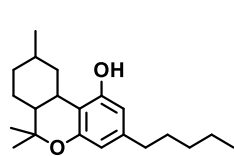
cannabielsoic acid A

 Δ^9 -THC Δ^8 -THC

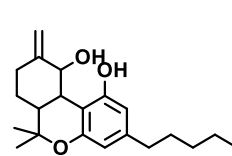
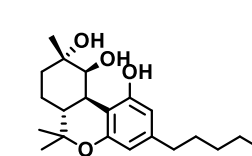
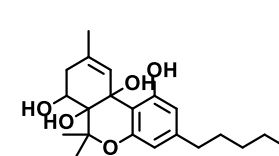
CBN

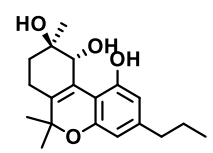
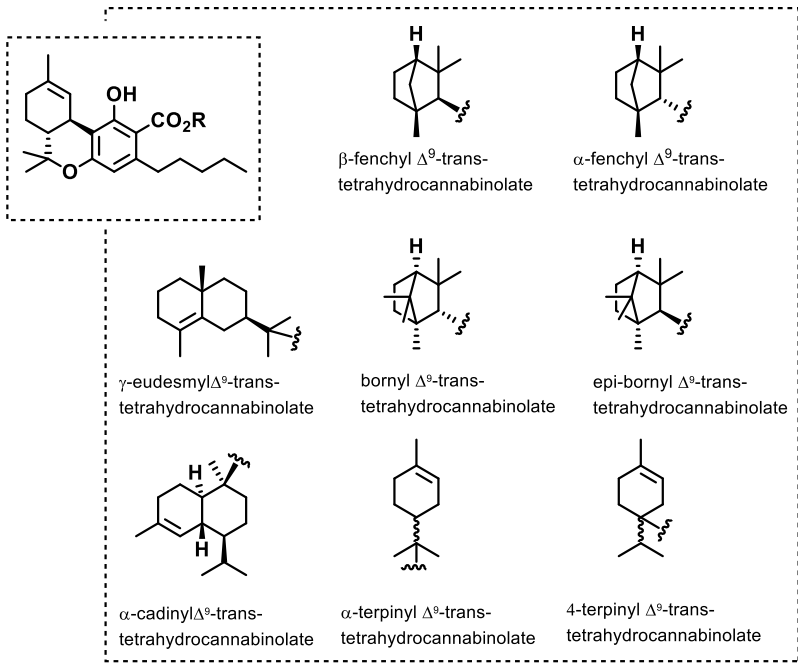
10-hydroxy-9-oxo- Δ^8 -THCA8 α - Δ^9 -trans-tetrahydrocannabinol8 β - Δ^9 -trans-tetrahydrocannabinoltrans- Δ^8 -THCA10 α -hydroxy trans- Δ^8 -THC10 α -hydroxy trans- Δ^8 -THC11-acetoxy- Δ^8 -THCAO-propyl- Δ^9 -trans-tetrahydrocannabinolO-pentyl- Δ^9 -trans-tetrahydrocannabinol Δ^9 -trans-tetrahydrocannabinol Δ^9 -trans-tetrahydrocannabinolic acid Δ^9 -trans-tetrahydrocannabivarin (THCV) Δ^9 -trans-tetrahydrocannabivarinic acidmethylen-bis Δ^9 -trans-tetrahydrocannabinol (cannabisol)

tetrahydrocannabinol epoxide

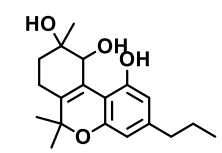
 Δ^9 -trans-nor-tetrahydrocannabinol Δ^9 -trans-nor-tetrahydrocannabinolic acid Δ^9 -trans-tetrahydrocannabinolic acid A Δ^9 -trans-tetrahydrocannabinolic acid B Δ^9 -cis-tetrahydrocannabinol Δ^9 -cis-tetrahydrocannabivarin8-oxo- Δ^9 -trans-tetrahydrocannabinol2-formyl- Δ^9 -trans-tetrahydrocannabinol

hexahydrocannabinol

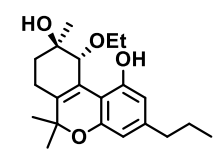
hydroxy- $\Delta^{9,11}$ -hexahydrocannabinol Δ^9 -trans-tetrahydrocannabinol glycol (cannabiripsol)6a,7,10a-trihydroxy- Δ^9 -tetrahydrocannabinol



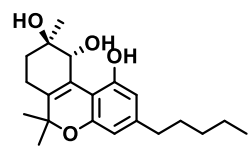
bis-nor cannabitril



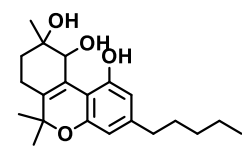
bis-nor-Cannabitril isomer



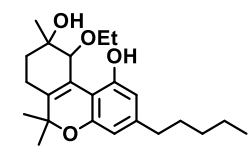
10-O-ethyl bis-nor-Cannabitril



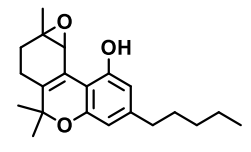
cannabitril



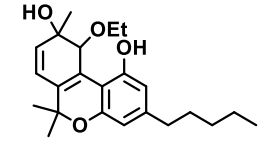
cannabitril isomer



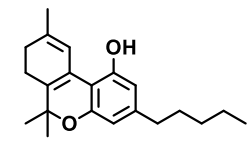
10-O-ethyl cannabitril isomer



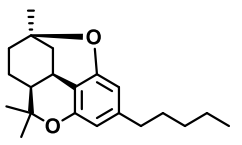
9,10-anhydrocannabitril



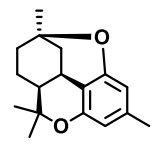
7,8-dehydro-10-O-ethylcannabitril



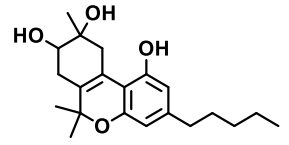
7,8-dihydrocannabinol



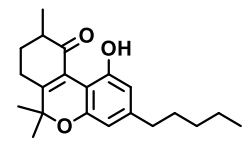
cannabicitran



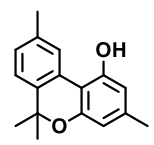
cannabiorcitrin



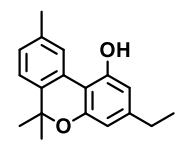
isocannabitril



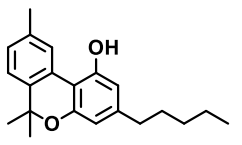
10-oxo-6,10-tetrahydrocannabinol



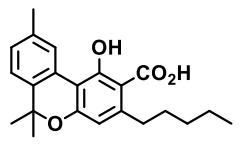
cannabiorcol



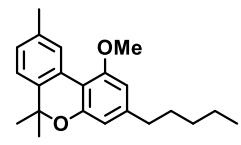
nor-cannabivarin



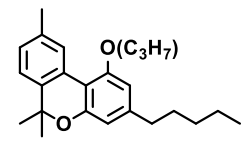
cannabinol



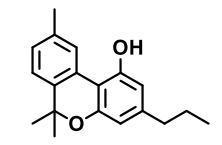
cannabinolic acid



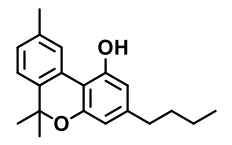
O-methylcannabinol



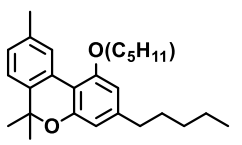
O-propylcannabinol



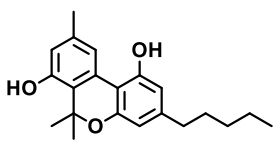
cannabivarin



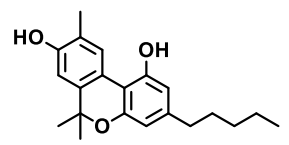
nor-cannabinol



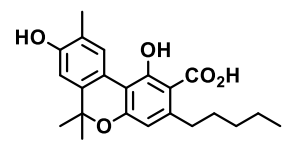
O-pentylcannabinol



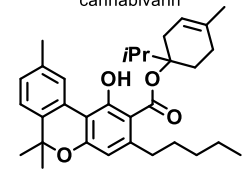
7-hydroxycannabinol



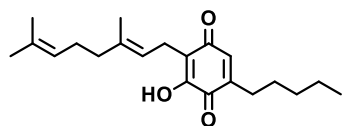
8-hydroxycannabinol



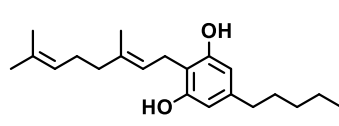
8-hydroxy cannabinolic acid



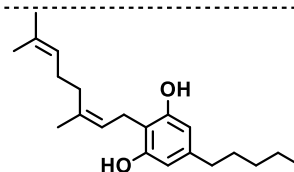
4-terpenyl cannabinate



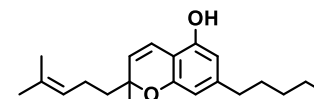
VCE-003



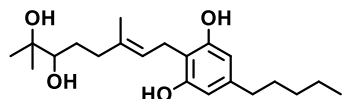
CBG



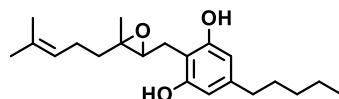
Cannabinerol



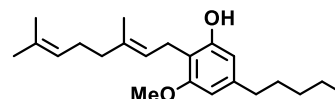
cannabichromene (CBC)



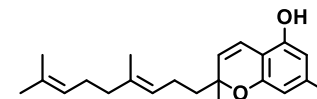
Carmagerol



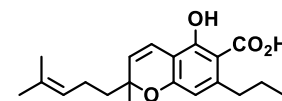
Epoxycannabigerol



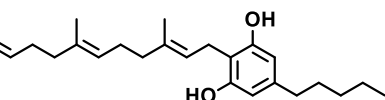
O-Methylcannabigerol



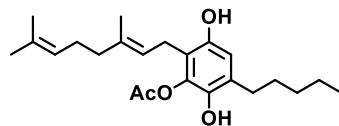
confluentin



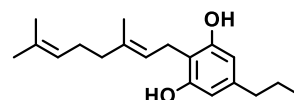
cannabichromevarinic acid



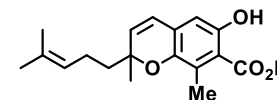
sesquicannabigerol



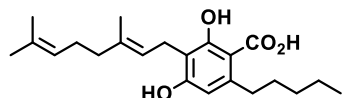
5-acetyl-4-hydroxycannabigerol



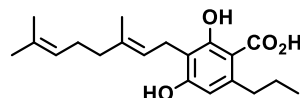
CBGV



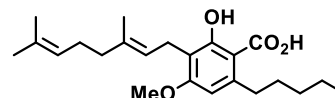
anthopogochromenic acid



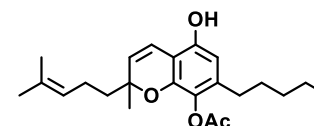
CBGA



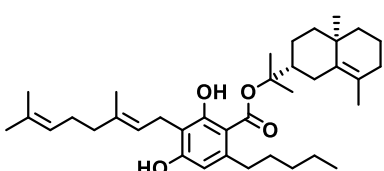
CBGVA



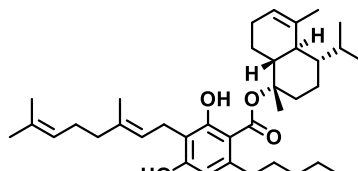
Cannabigerolic acid methylether



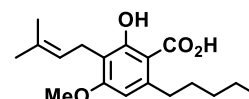
4-acetoxycannabichromene



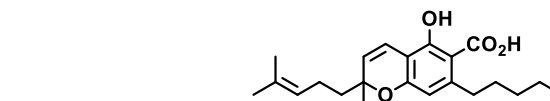
γ-Eudesmyl cannabigerolate



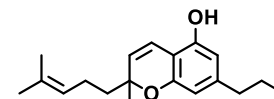
γ-Cadinyl cannabigerolate



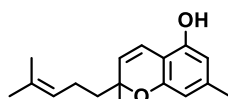
amorfrutin 2



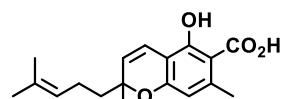
cannabichromenic acid



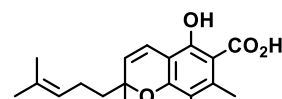
CBCV



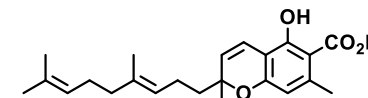
cannabiorcichromene



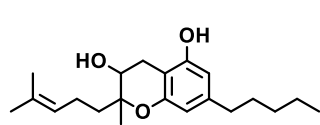
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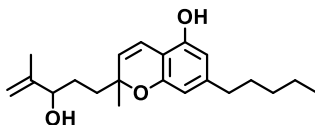
clorcannabiorcichromenic acid



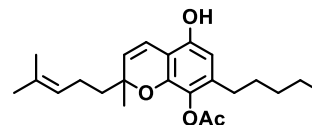
daurichromenic acid



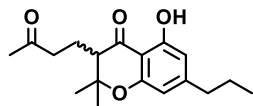
Cyclo-CBG



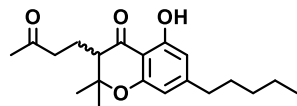
8'-hydroxyisocannabichromene



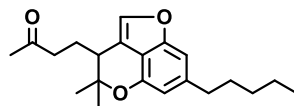
4-acetoxycannabichromene



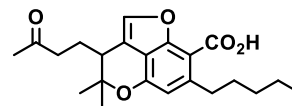
bisnor-cannabichromanone



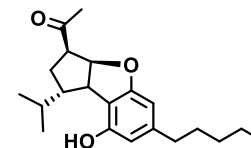
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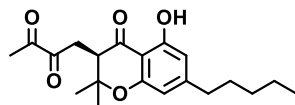
cannabicumaronone



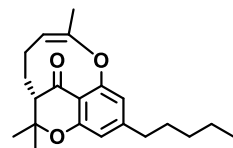
cannabicumaronic acid



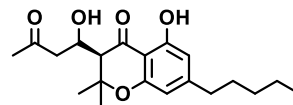
anhydrocannabimovone



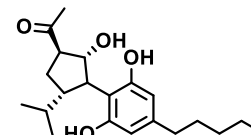
cannabichromanone C



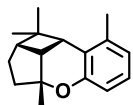
cannabichromanone D



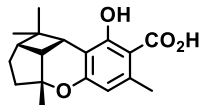
cannabichromanone B



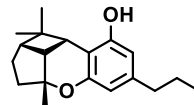
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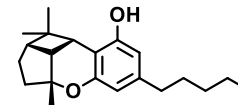
cannabiorcycloclol



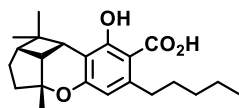
cannabiorcycloclolic acid



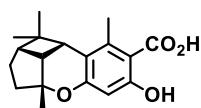
cannabicyclovarin



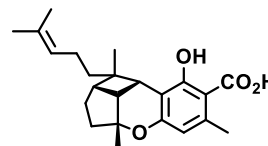
cannabicyclol (CBL)



cannabicyclolic acid



anthropogocycloclolic acid



rhododaurichromanic acid A

Adams; Marihuana,
Bul. N.Y. Acad. Med.
1942, 705.



1. extraction with organic solvent

2. filtration and solvent removal

"physiologically active oil, red in color"

fractionation of the portion boiling from 180-190 °C

"purified red oil"

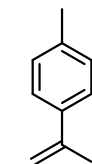
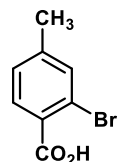


formaldehyde

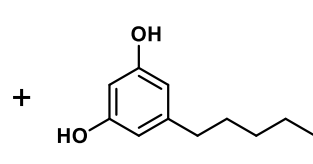
F "ozonization"

A "color tests" and acylation /etherification

formation of bis-ether and bis esters



p-cymene



olivetol

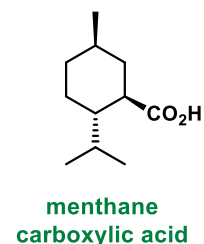
C pyrolysis with pyridine hydrochloride

cannabidiol (CBD)

B catalytic reduction resulting in the absorption of two moles of hydrogen without loss of the two phenols

tetrahydrocannabidiol

D oxidation



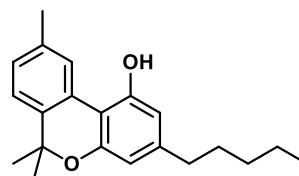
menthane carboxylic acid

E acidic conditions

tetrahydrocannabinol (THC)

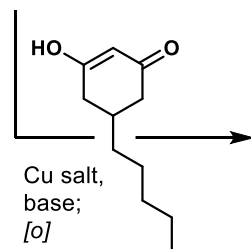
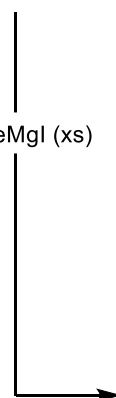
(low-rotating and high rotating, dependent on conditions used)

dehydrogenation

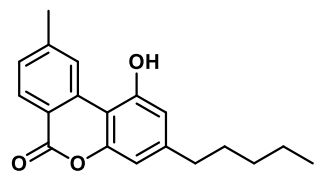


cannabinol (CBN)

MeMgI (xs)

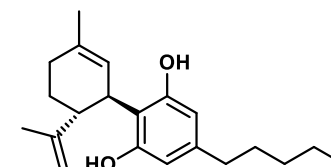
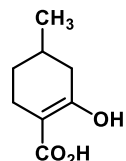


Cu salt, base; [o]

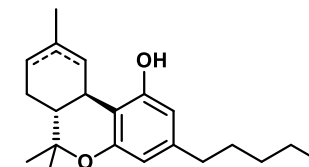


olivetol;

[o]



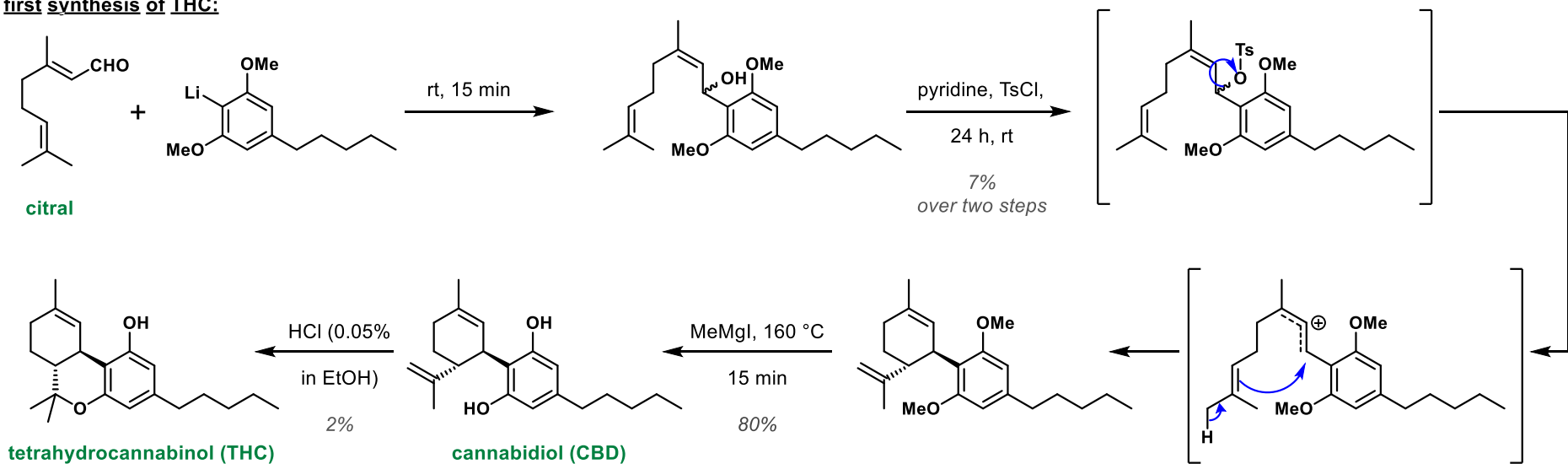
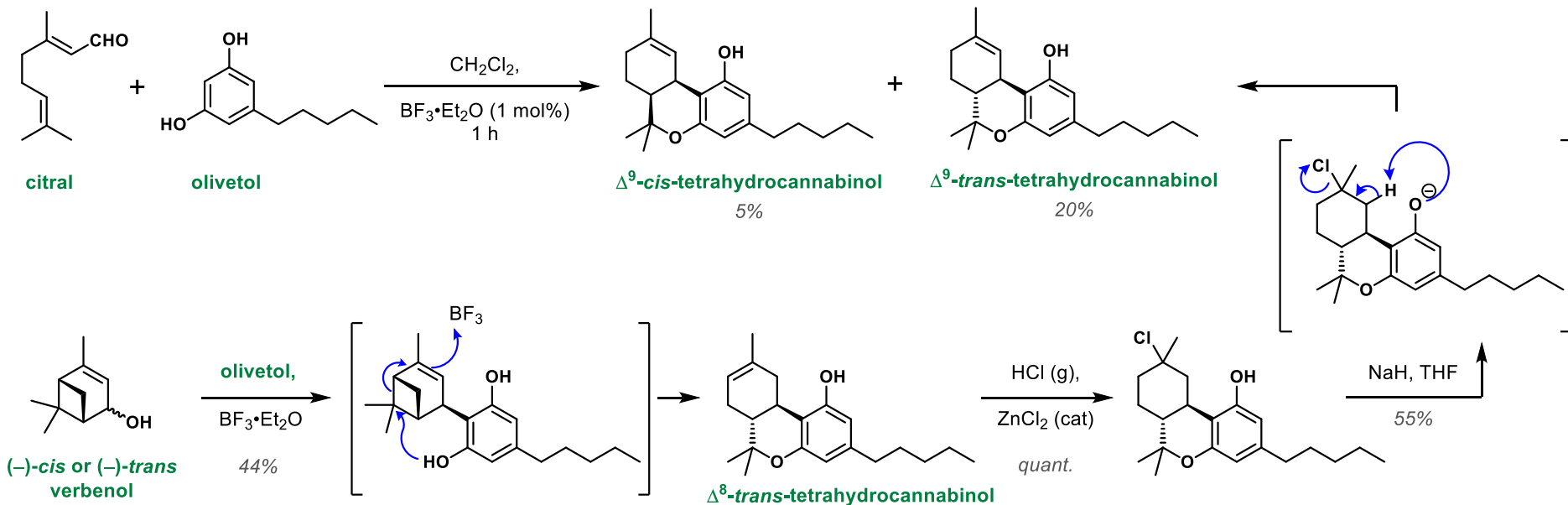
CBD

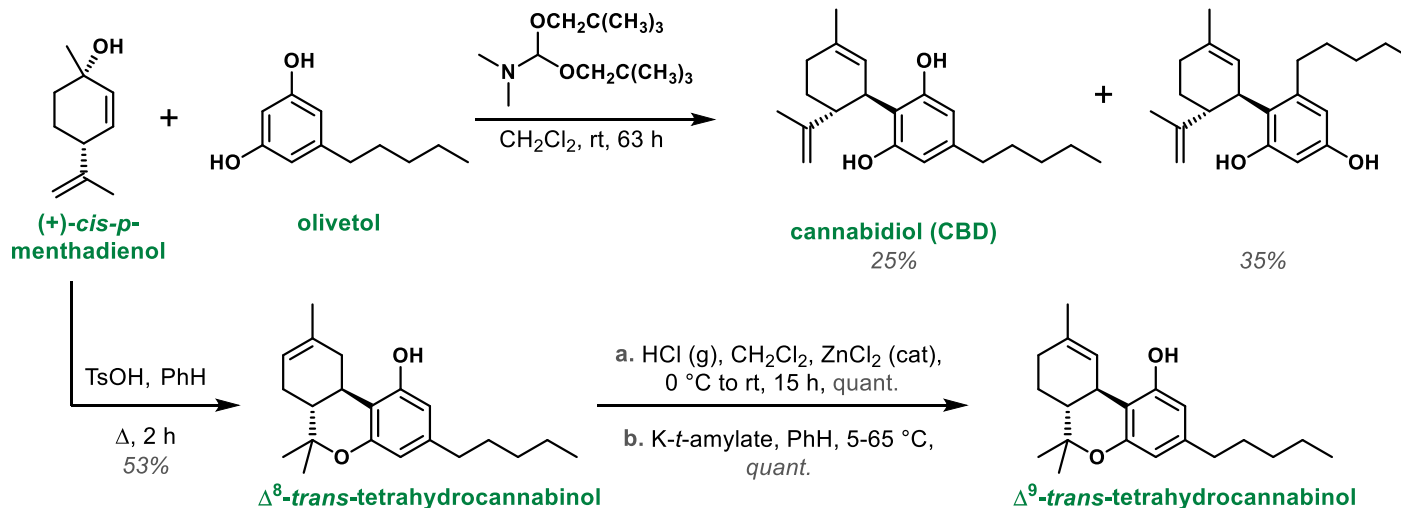
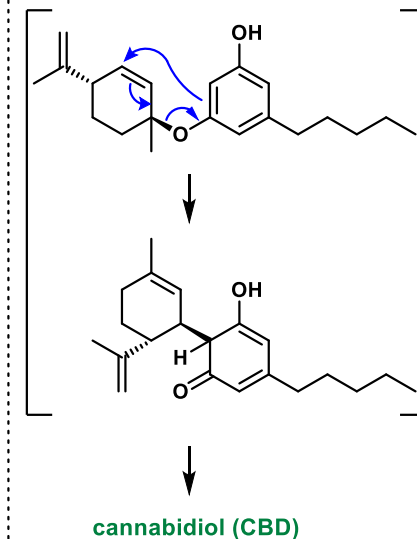


THC

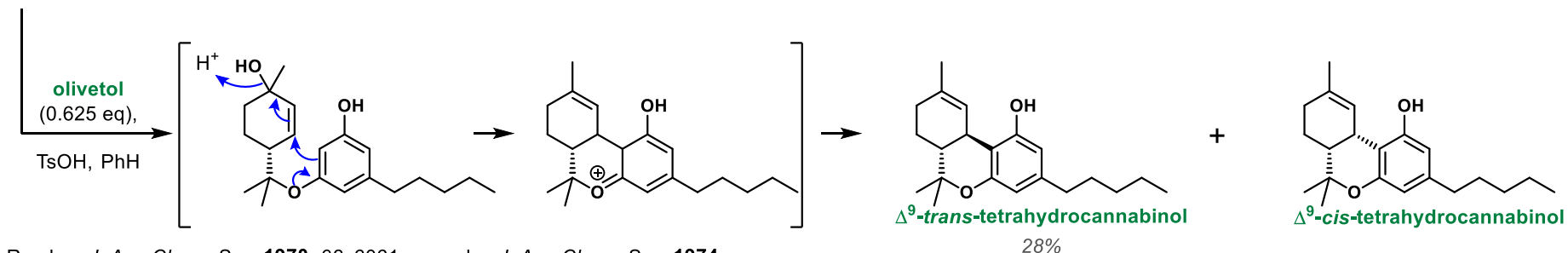
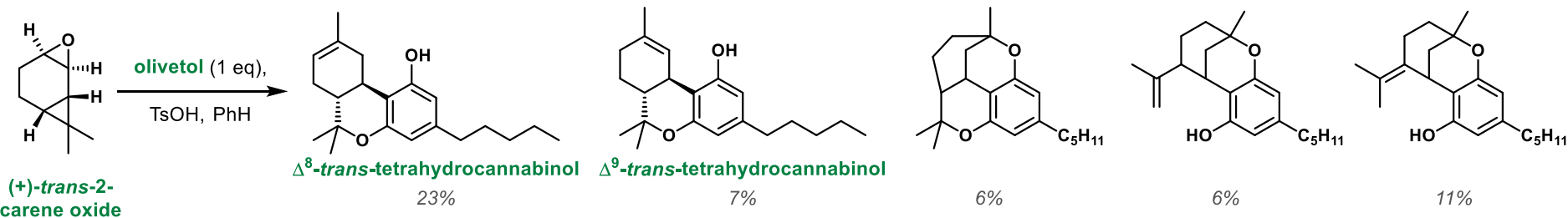
"The disappointment accompanying the discovery that cannabidiol had no marihuana activity was more than compensated by the observation that both the low-rotating and high-rotating tetrahydrocannabinols possess very marked marihuana potency"

- A. CBD contains two free phenols
- B. two aliphatic olefins are present
- C. composed of dihydrocymyl and olivetol residues
- D. dihydrocymyl residue attached adjacent to the isopropyl group
- E. olivetol residue attached between the phenols
- F. one of the two double bonds is terminal

first synthesis of THC:Mechoulam, *J. Am. Chem. Soc.* **1965**, *87*, 3273.**second generation by Mechoulam:**Petrzilka, *Helv. Chim. Acta* **1967**, *50*, 2111.; Mechoulam, *J. Am. Chem. Soc.* **1972**, *94*, 6159.

Petrilka & Eschenmoser:**possible mechanism:**

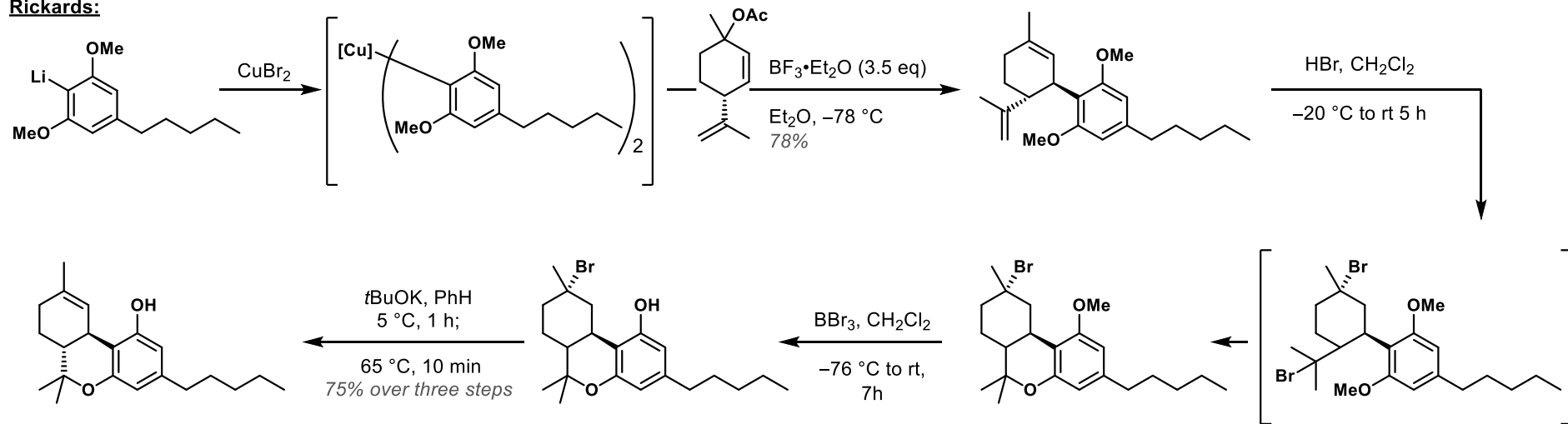
Petrilka & Eschenmoser, *Helv. Chim. Acta* **1967**, 50, 719.; *ibid.* **1967**, 50, 211.; *ibid.* **1969**, 52, 1102.

Razdan:

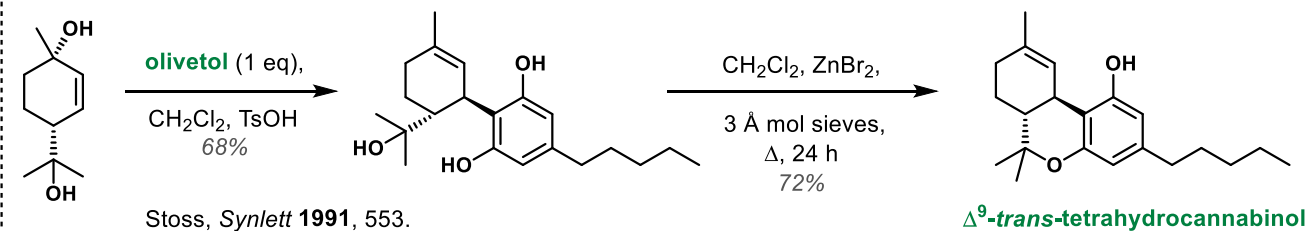
Razdan, *J. Am. Chem. Soc.* **1970**, 92, 6061.; see also *J. Am. Chem. Soc.* **1974**, 96, 5860.; *Experientia* **1972**, 28, 121.; *Tet. Lett.* **1979**, 8, 684.

28%

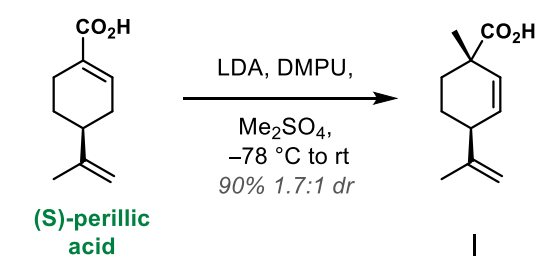
Rickards:

 Δ^9 -trans-tetrahydrocannabinolRickards, *J. Org. Chem.* **1984**, *49*, 572.

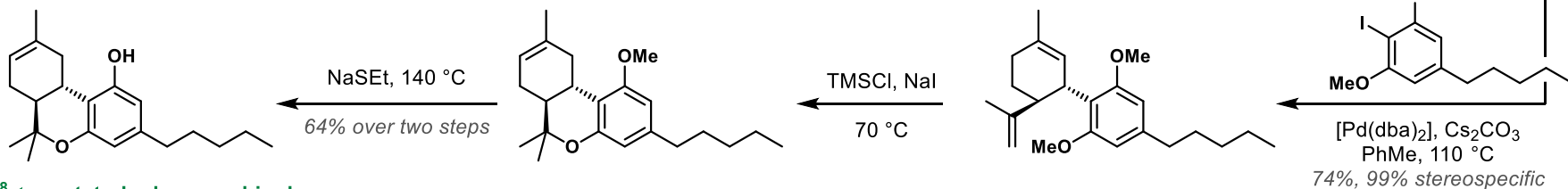
Stoss:

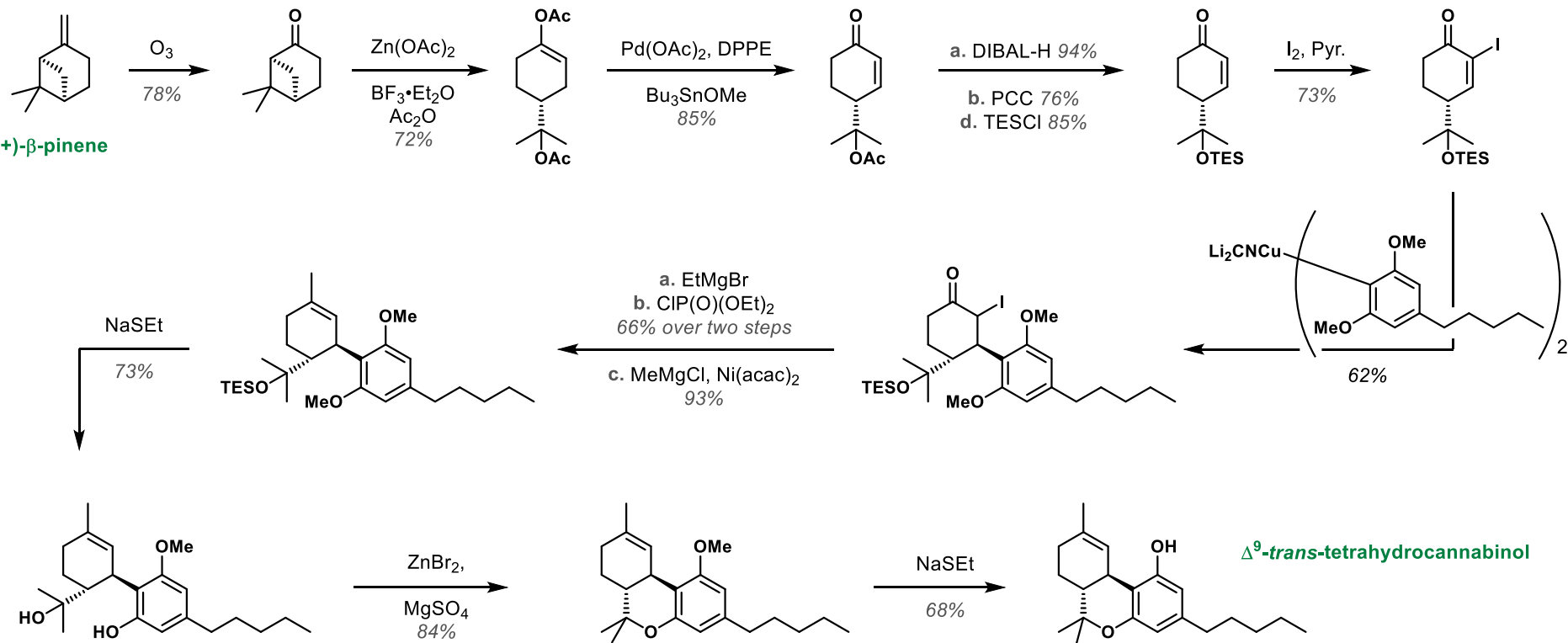
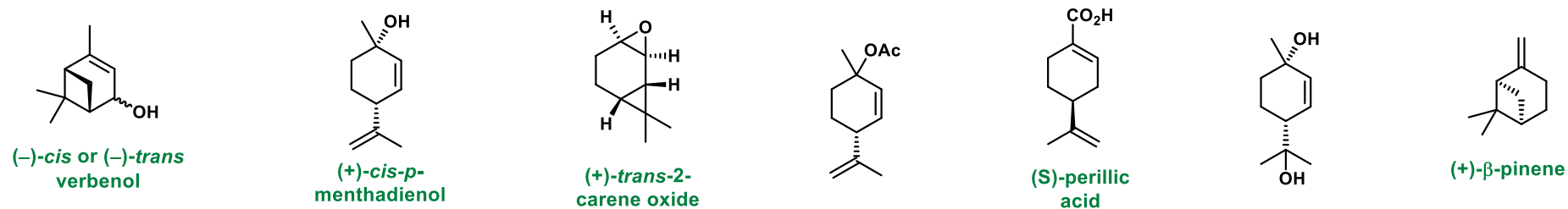
 Δ^9 -trans-tetrahydrocannabinol

Studer:

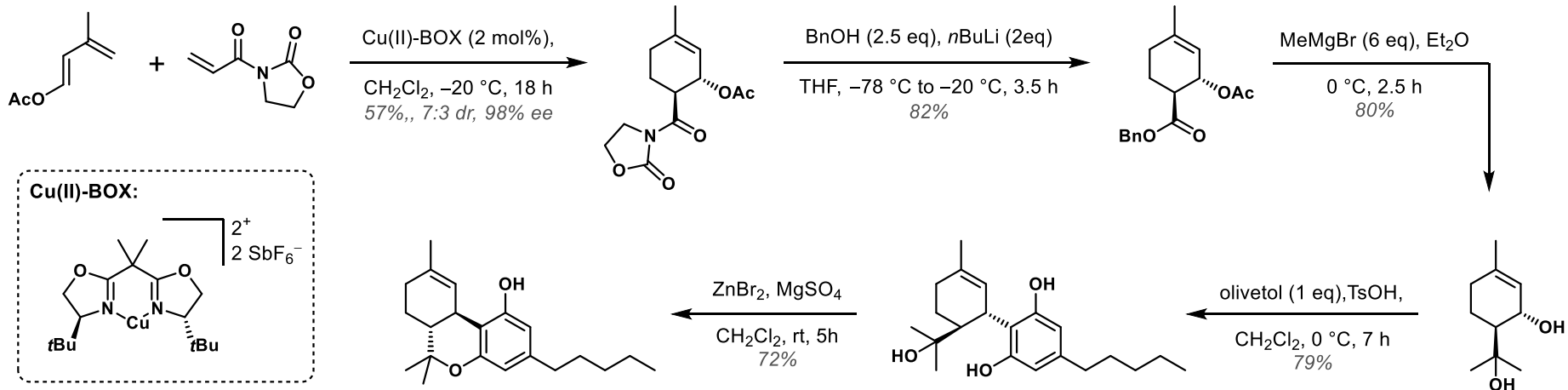


(S)-perillic acid

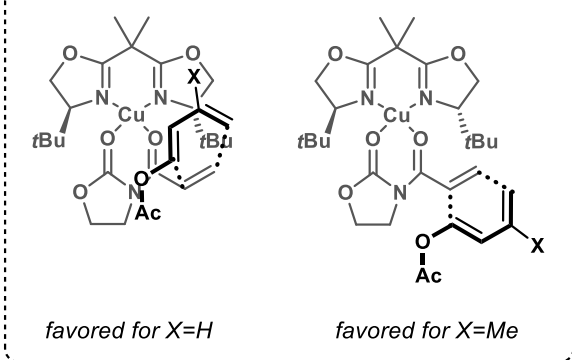
 $\text{ent-}\Delta^8$ -trans-tetrahydrocannabinolStuder, *Angew. Chem. Int. Ed.* **2015**, *54*, 8547.

Kobayashi:Kobayashi, *J. Org. Chem.* **2002**, 67, 8771.**Summary of chiral pool starting materials used:**

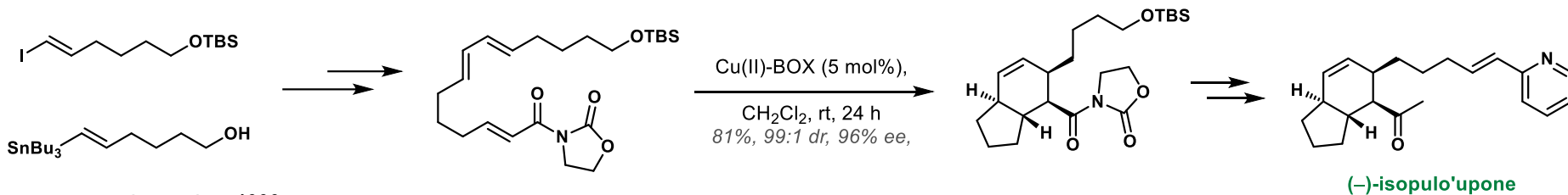
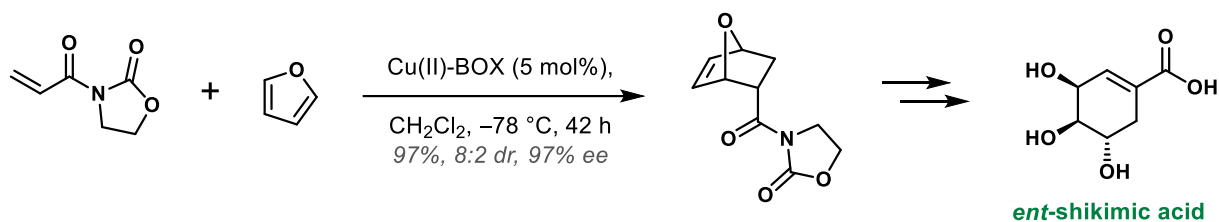
Evans (first enantioselective synthesis):

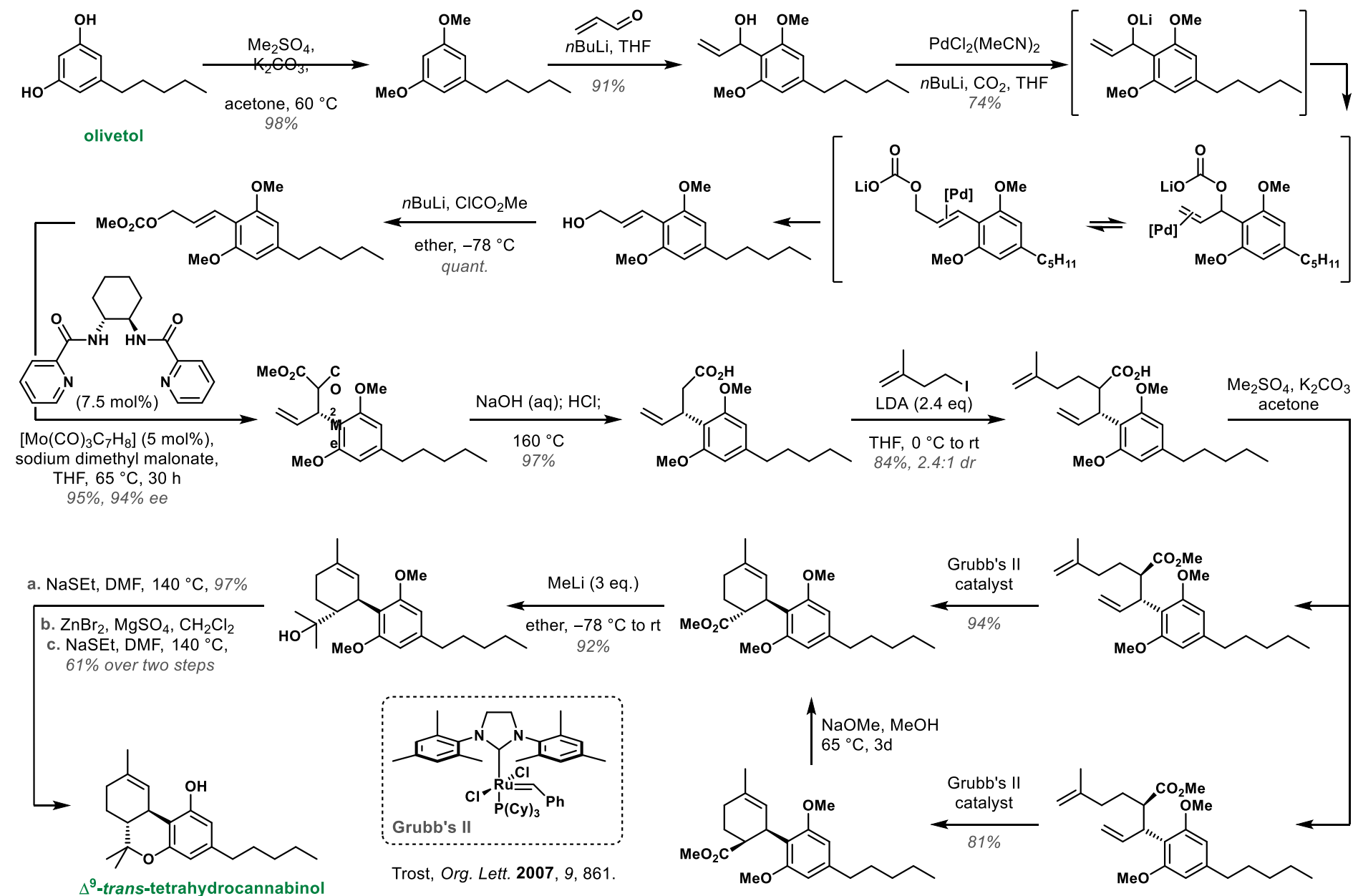
ent- Δ^9 -trans-tetrahydrocannabinolEvans, *Tet. Lett.* **1997**, 38, 3193.

endo and exo selectivities:

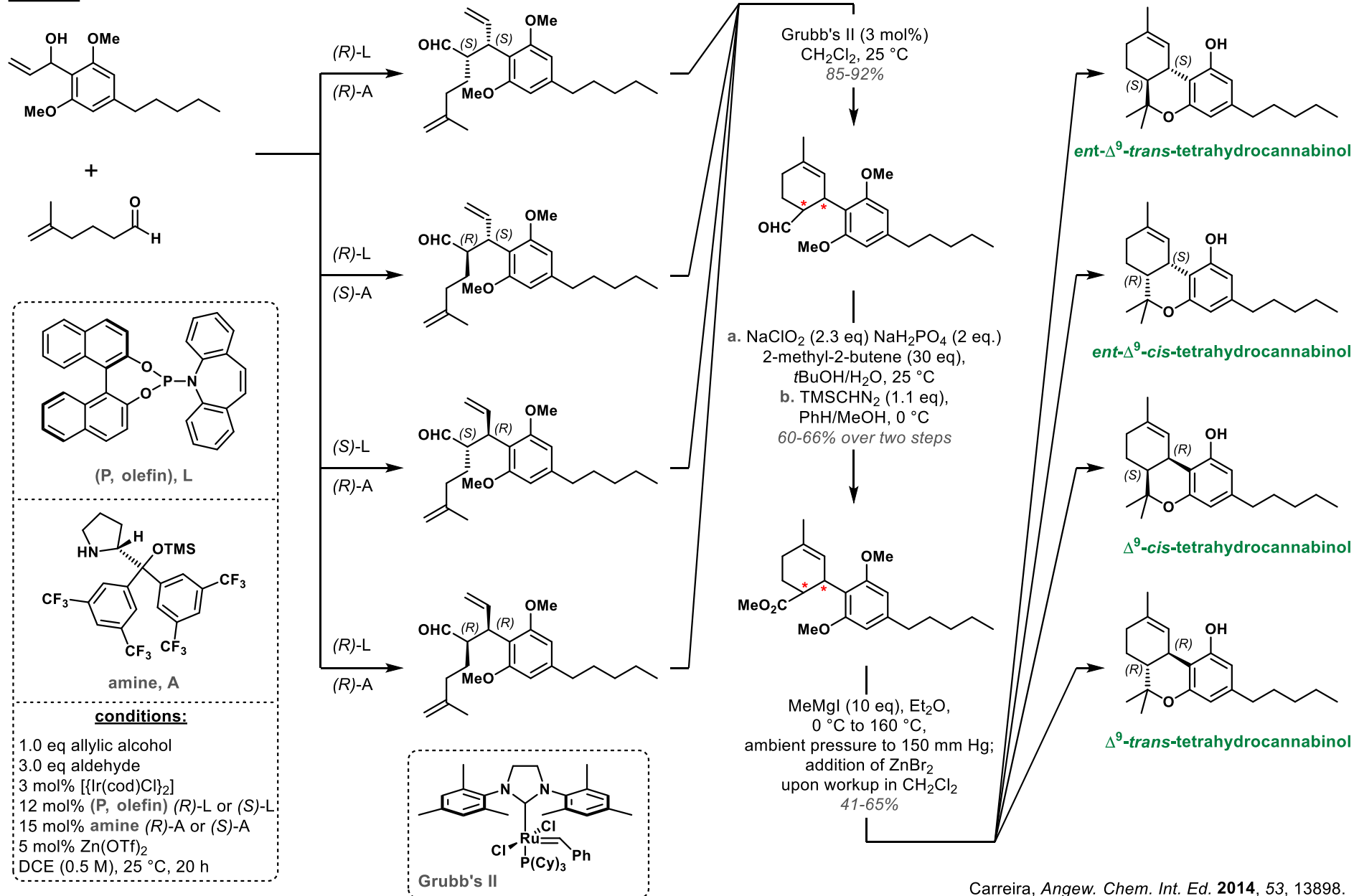


examples:

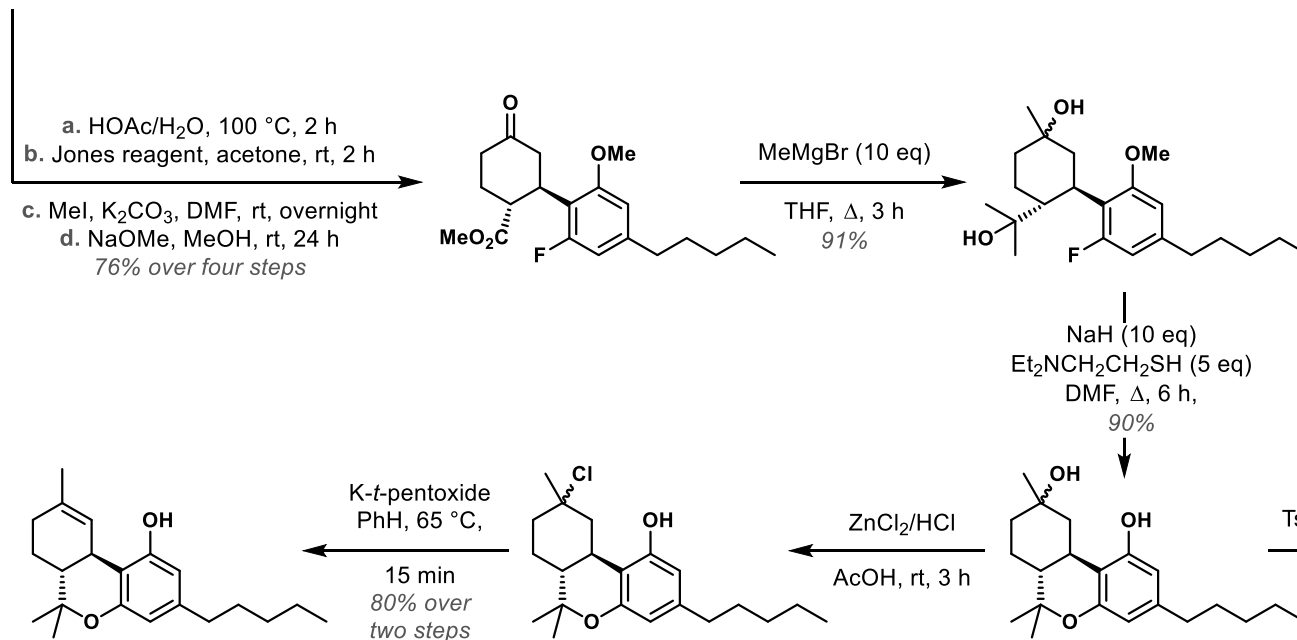
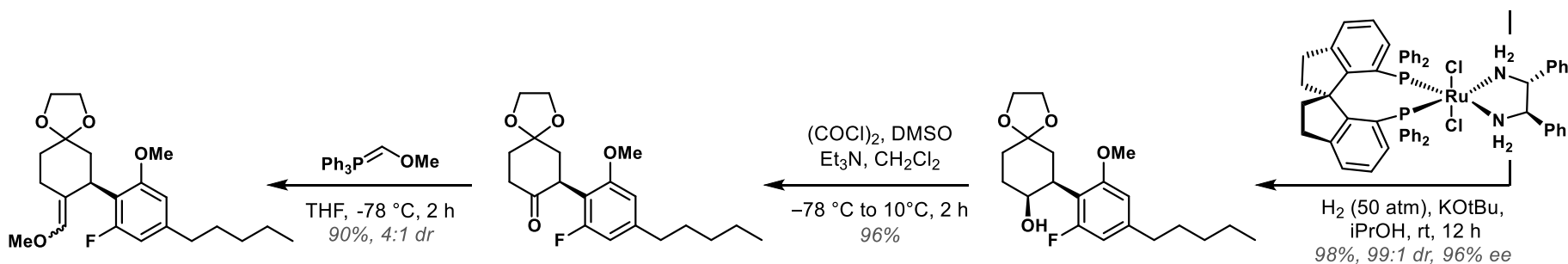
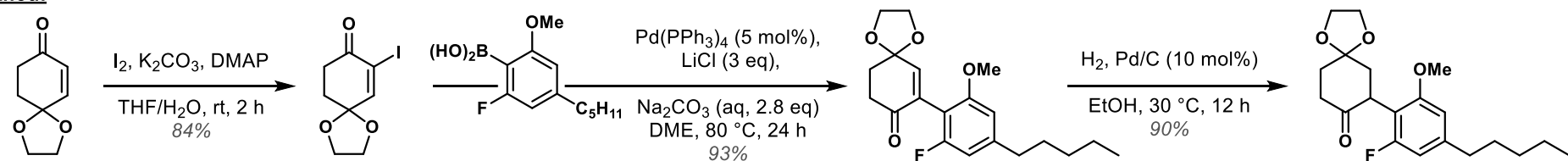
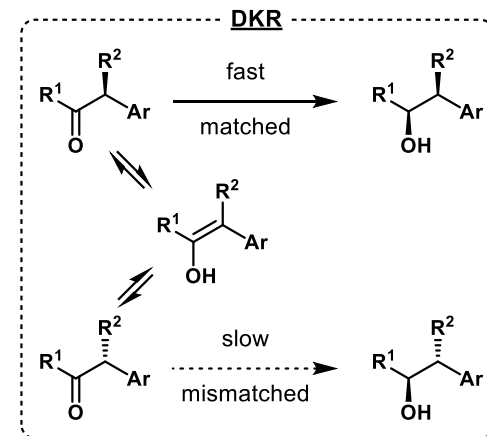
Evans, *J. Am. Chem. Soc.* **1999**, 121, 7582.

Trost:

Carreira:



Zhou:

 Δ^9 -*trans*-tetrahydrocannabinolZhou, *Org. Lett.* 2013, 15, 764. Δ^8 -*trans*-tetrahydrocannabinol