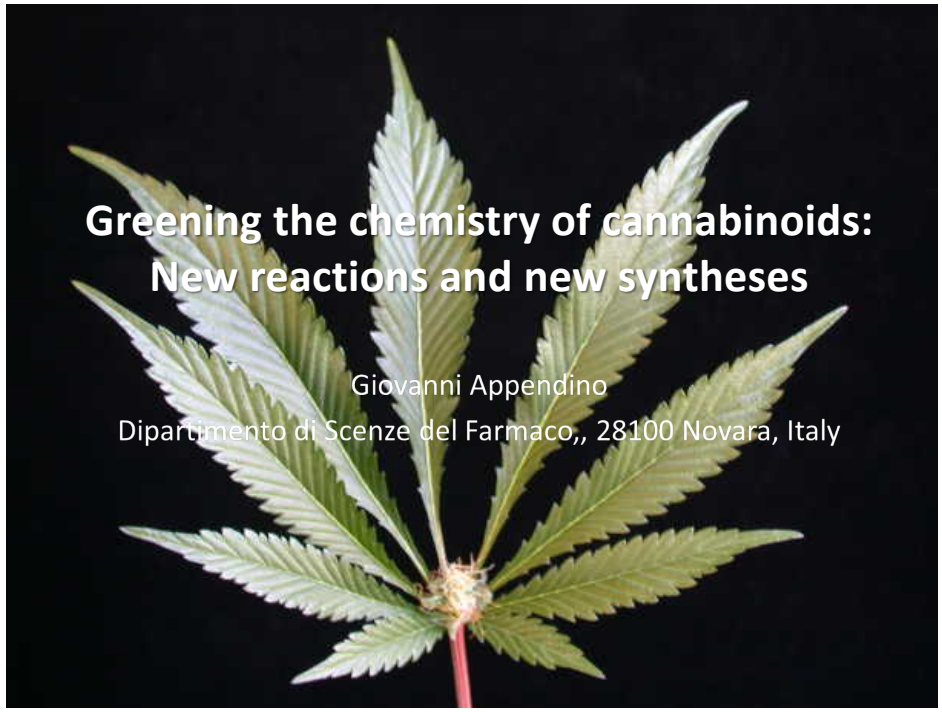
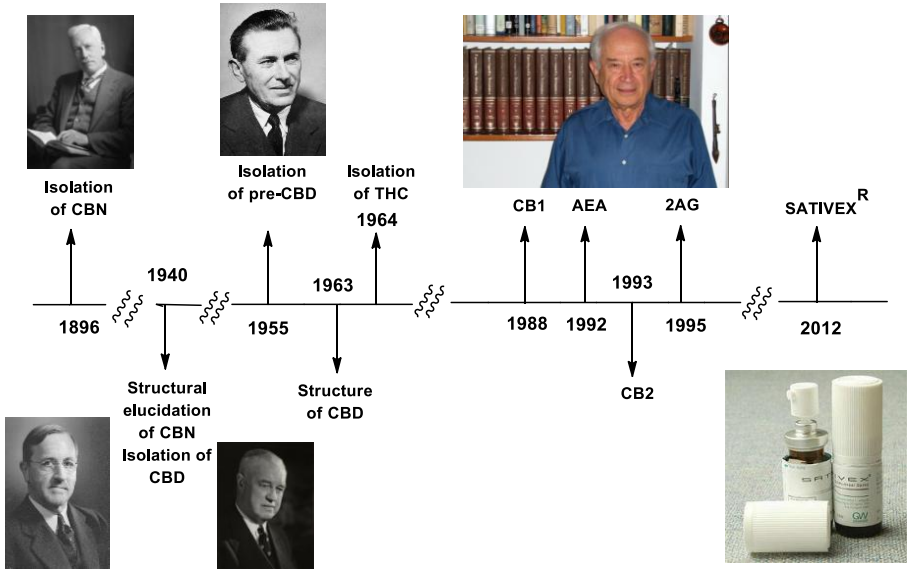


Timeline of cannabinoid research

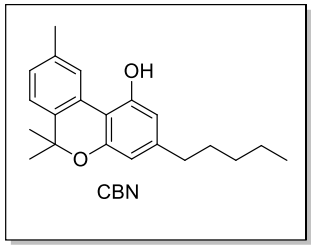


Phytocannabinoids: a confusing and tragic start in Cambridge

20 WOOD, SPIVEY, AND EASTERFIELD: CANNABINOL. PART I.

III.—*Cannabinol. Part I.*

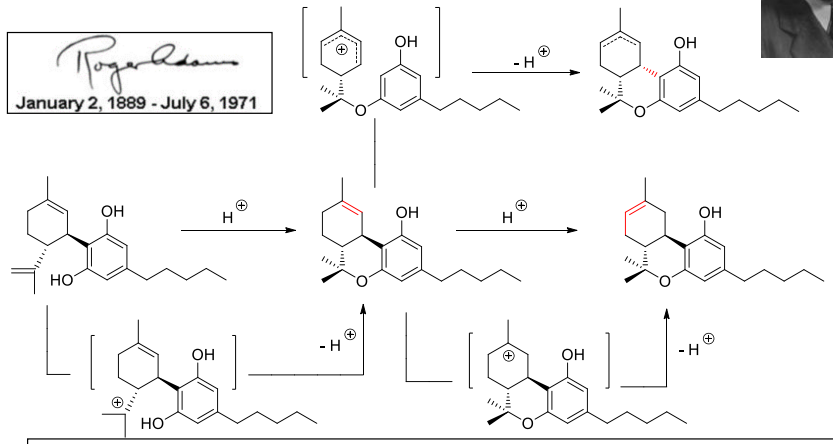
By Thomas Barlow Wood, M.A.; W. T. Newton Spivey, M.A.; Thomas Hill Easterfield, M.A., Ph.D.



T. H. Easterfield
(1866-1949)

Trinitrocannabinol, $C_{21}H_{28}(NO_2)_3O_2$.—This compound is produced on adding fuming nitric acid (5 c.c.), drop by drop, to a well cooled solution of crude cannabinol (8 grams), dissolved in glacial acetic acid (18 c.c.), the temperature being kept down by immersing the flask in ice cold water. After standing for several days, the crystals are collected; the yield is 20 per cent. (1·6 grams) of the crude cannabinol used. The compound is easily soluble in benzene, phenol, alcohol, and ether; it is also readily soluble in hot, but only sparingly in cold, glacial acetic acid, which is the most convenient solvent for its recrystallisation. It crystallises in bright yellow plates, which, when quickly heated, melt at 160° (uncorr.) with some decomposition.

Adams' THC: an anticipated natural product

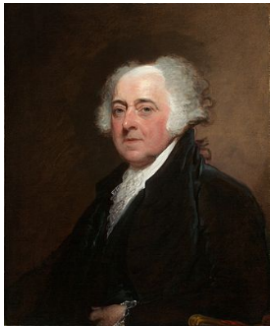


[Contribution from the Noyes Chemical Laboratory, University of Illinois]

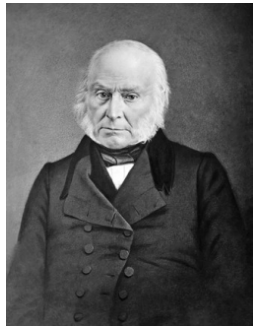
Structure of Cannabidiol. VII. A Method of Synthesis of a Tetrahydrocannabinol which Possesses Marihuana Activity[1]

By Roger Adams and B. R. Baker

1941: A descendent of two US Presidents becomes a «*suspect American citizen*» for FBI



John Adams
(1735-1826)



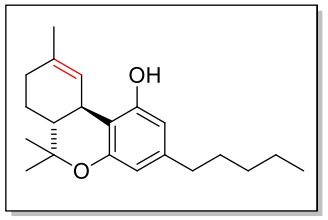
John Quincy Adams
(1767-1848)

Roger Adams
(1889-1971)

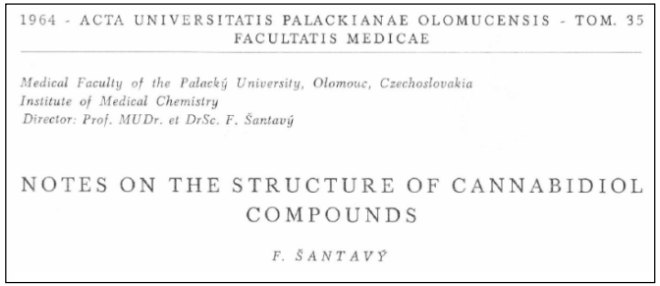
Lincoln's Birthday Committee for Democracy and Intellectual Freedom (anti-Nazi movement)

Lincoln's Birthday Committee for the Advancement of Science. (Communist organization)

1964: Šantavý established the structure of «Adams' THC» using CD data only



František Šantavý
(1915-1983)



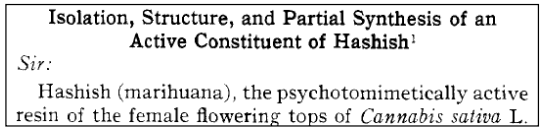
1964 - ACTA UNIVERSITATIS PALACKIANAE OLOMUCENSIS - TOM. 35
FACULTATIS MEDICAE

Medical Faculty of the Palacký University, Olomouc, Czechoslovakia
Institute of Medical Chemistry
Director: Prof. MUDr. et DrSc. F. Šantavý

NOTES ON THE STRUCTURE OF CANNABIDIOL COMPOUNDS

F. ŠANTAVÝ

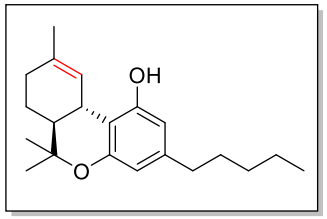
1964: actual isolation (but wrong absolute configuration) of Δ^9-THC

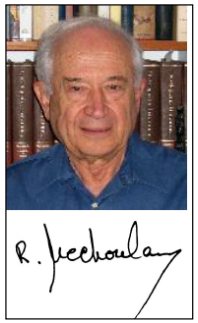


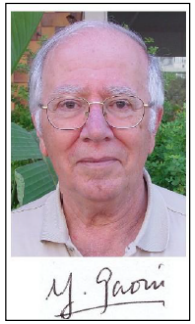
Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish[1]

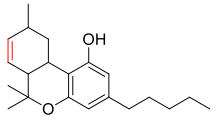
Sir:

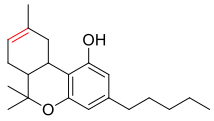
Hashish (marihuana), the psychotomimetically active resin of the female flowering tops of *Cannabis sativa* L.

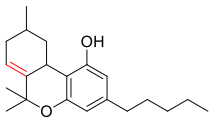


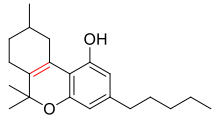






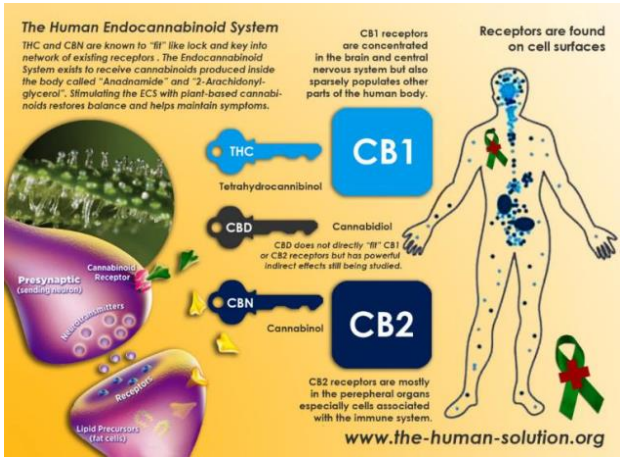


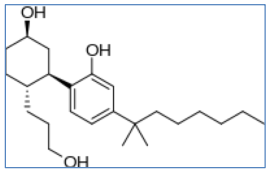




(Born 1930)

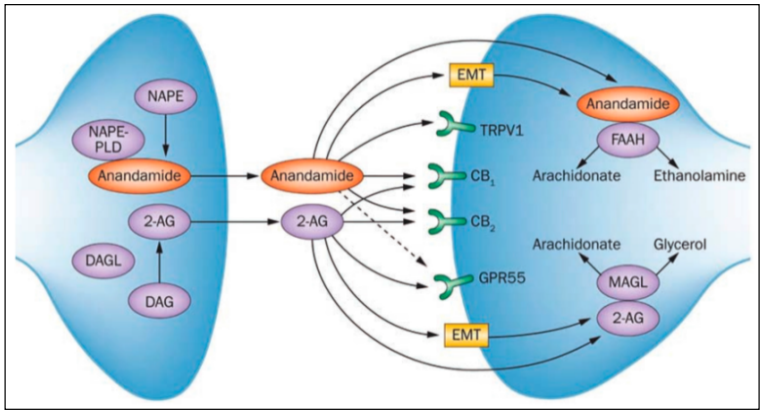
1988-1993: The cloning cannabinoid receptors (CB1,CB2)

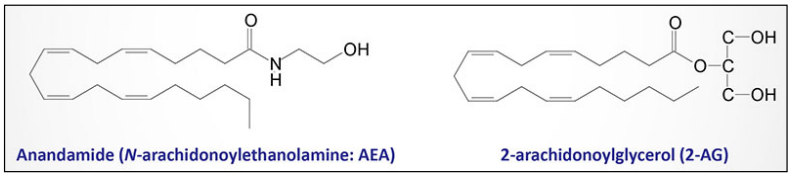




CP-55940

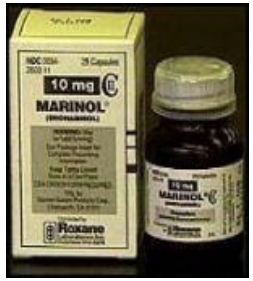
1992-1995: The discovery of endogenous cannabinoids





Anandamide (*N*-arachidonoylethanolamine: AEA) 2-arachidonoylglycerol (2-AG)

2018: *Cannabis sativa* as a mainstream medicinal plant



Outline of the cannabinoid project (2005-2018)

Cannabinoid diversity from biodiversity:

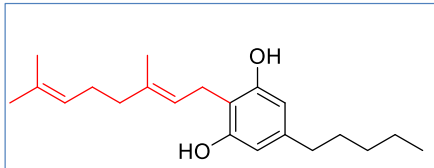
- ✓ *Multi-gram isolation of cannabinoids*
- ✓ *Disposal of THC-containing side-cuts*
- ✓ *Novel cannabinoids*
- ✓ *Interconversion of cannabinoids*

Cannabinoid diversity from ingenuity:

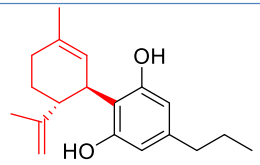
- ✓ *Semi-synthesis*
- ✓ *Total synthesis*
- ✓ *Biological analogues of cannabinoids*
- ✓ *Development of VCE-004.8 (OD status by FDA and EMA for scleroderma)*

Biological analogues of cannabinoids

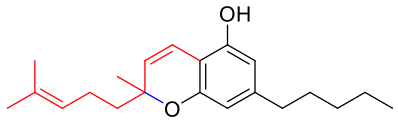
The "big four"



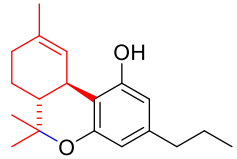
Cannabigerol (CBG)



Cannabidiol (CBD)

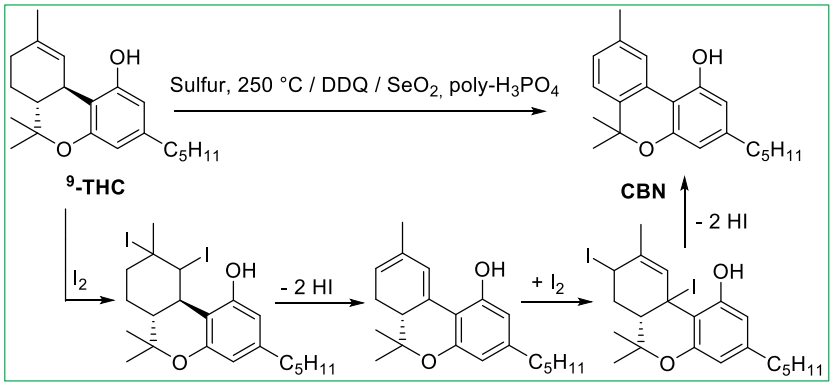


Cannabichromene (CBC)



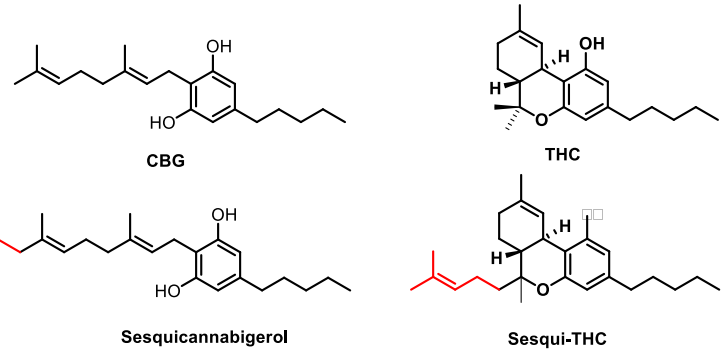
Δ^9-Tetrahydrocannabinol (THC)

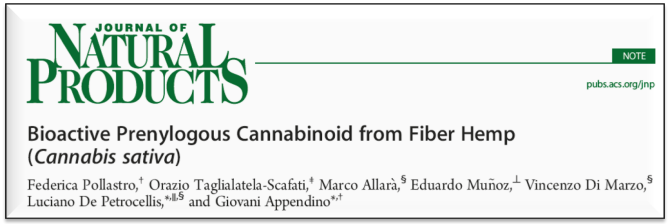
A smart disposal of THC



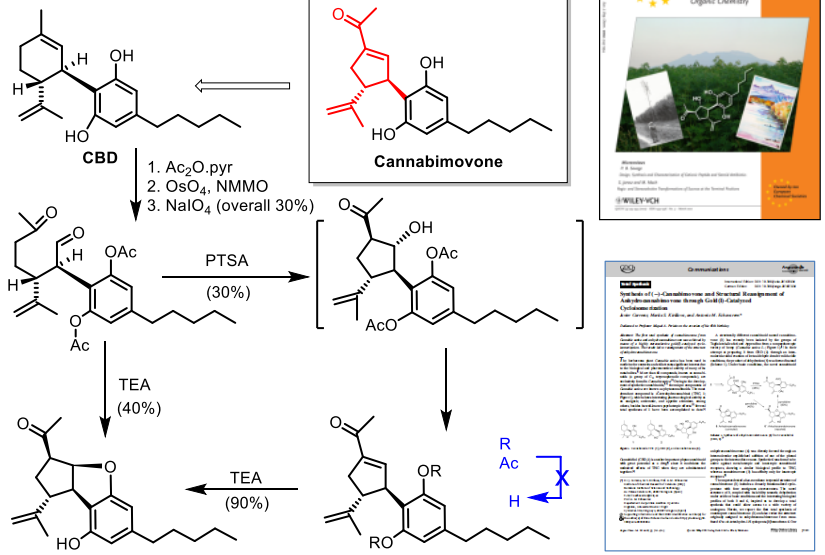
DOI: 10.1021/acs.jnatprod.7b00946
J. Nat. Prod. 2018, 81, 630−633

The discovery of prenylogous cannabinoids

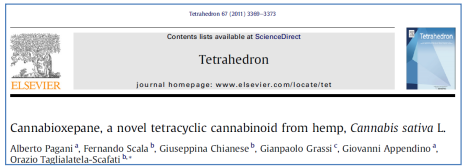


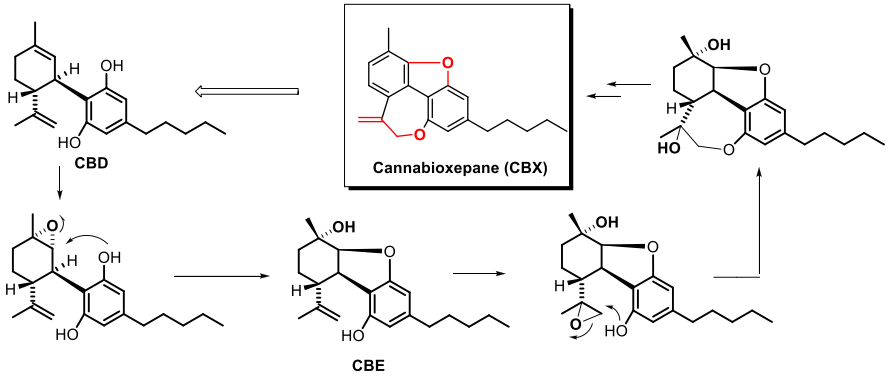


Polar cannabinoids

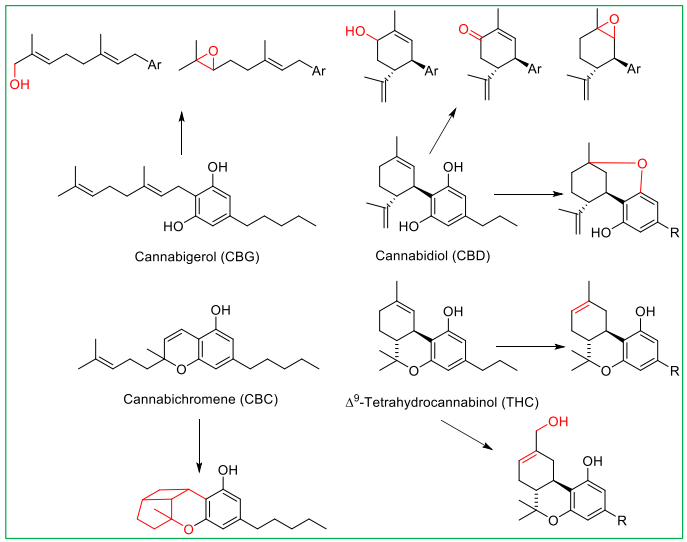


Discovery of a tetracyclic cannabinoid: Cannabioxepane (CBX)

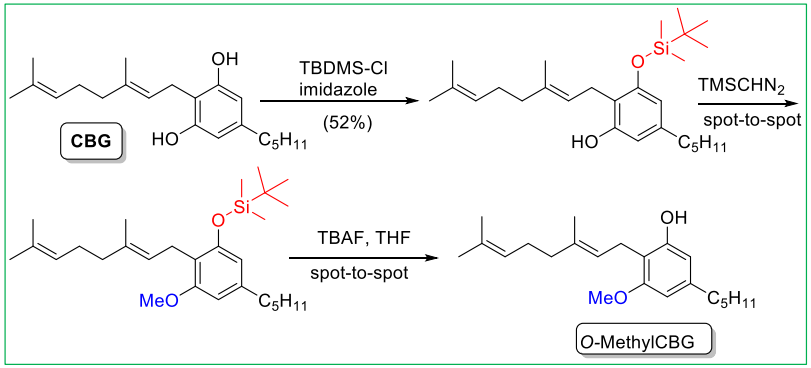




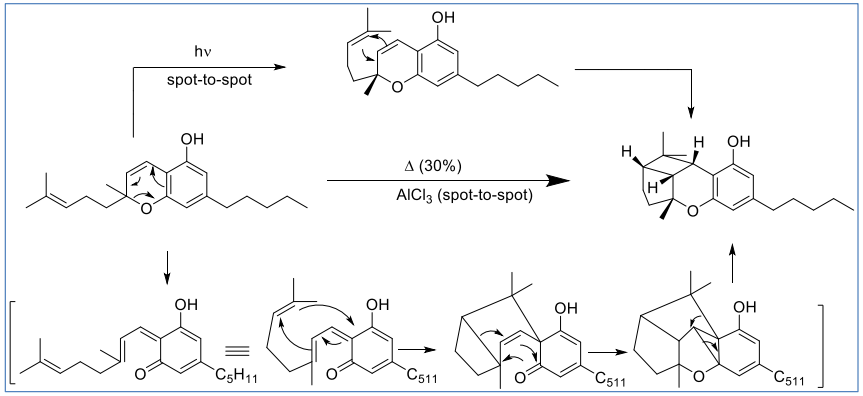
Minor cannabinoids can be obtained from the “big four”



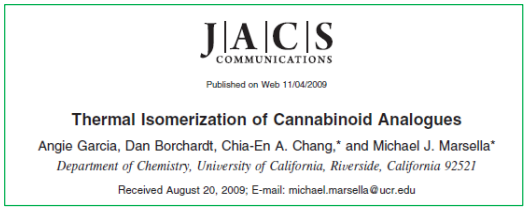
Some chemistry is simple….

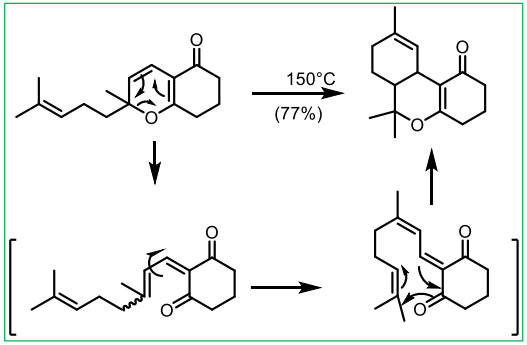


but other is not: is CBC violating W-H rules?



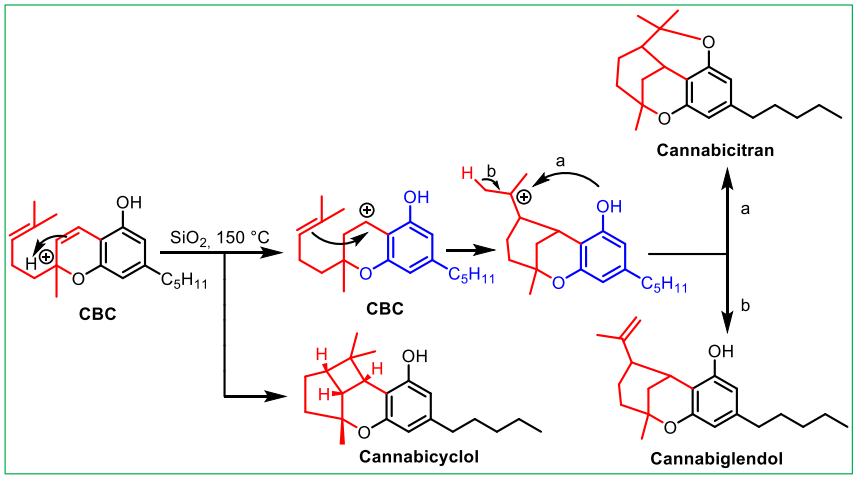
Can CBC be turned into THC?



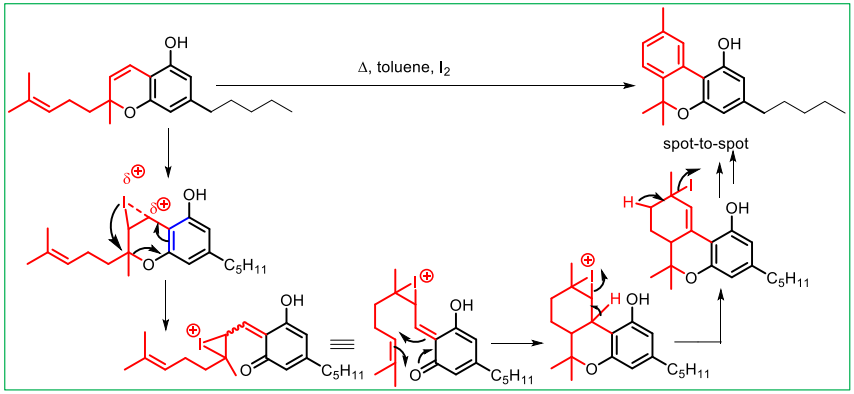


Garcia et al. *J. Am. Chem. Soc.* **2009**, *131*, 16640

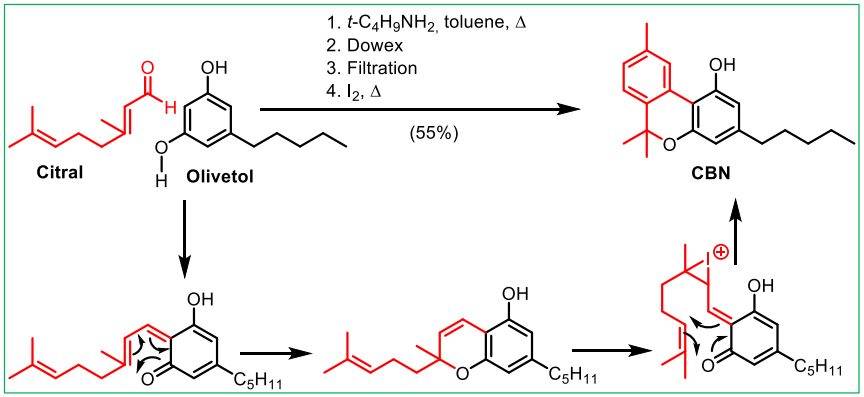
Definitely not..



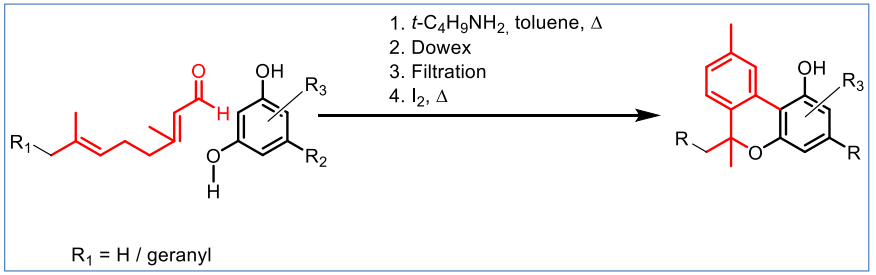
.. but iodine turns CBC into CBN

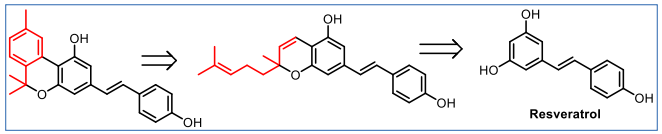


A one-pot outrageously simple total synthesis of CBN

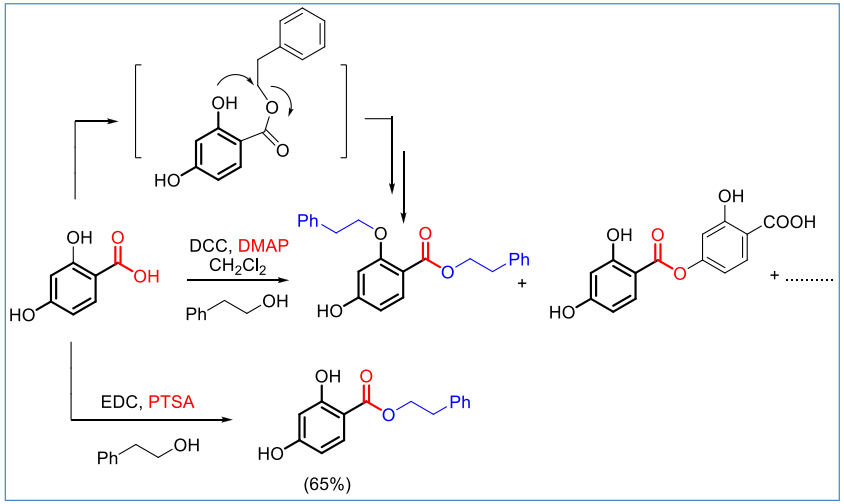


The prenylchromene-dibenzochromane rearrangement has general applicability

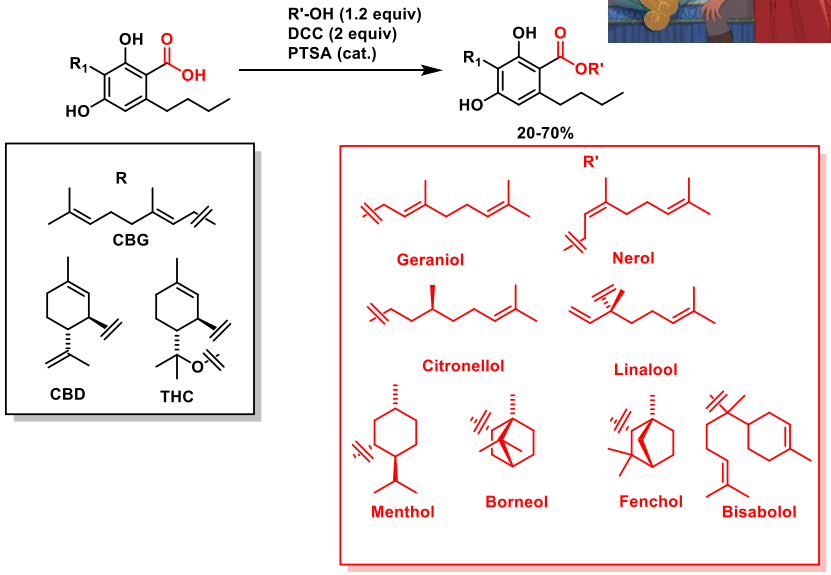




Development of a pyridine-free Holmberg esterification

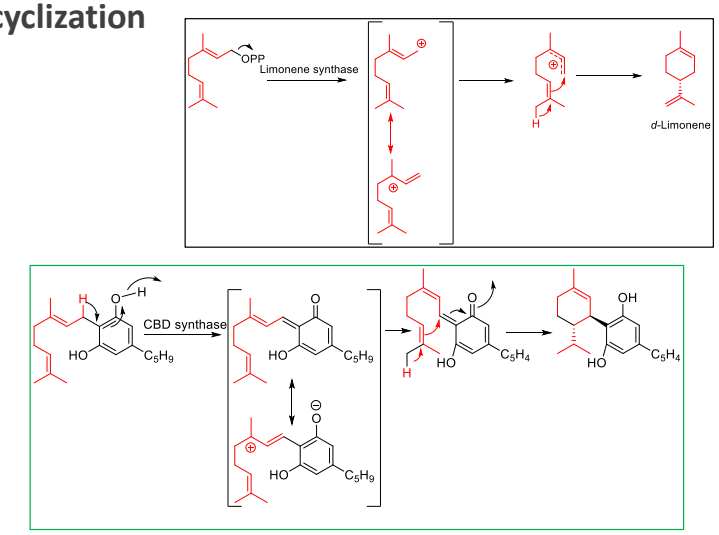


Synthesis of pre-cannabinoids esters



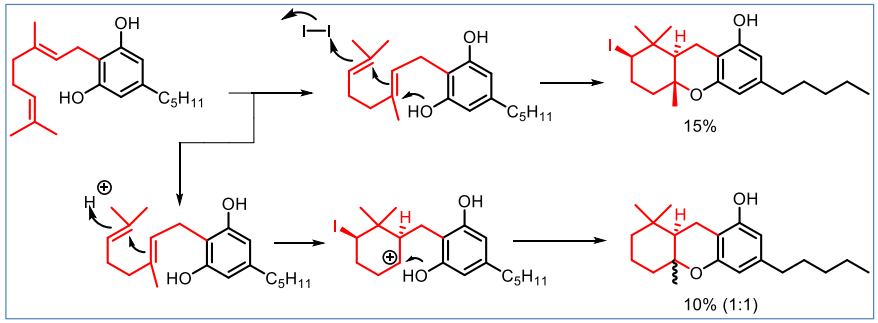
Cannabinoids diversity from ingenuity: non-natural cannabinoids

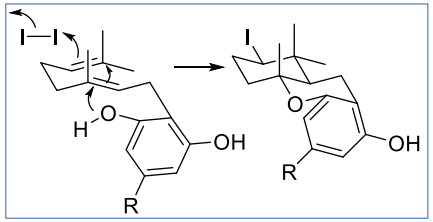
The path untaken: ionic vs electrophilic prenyl cyclization



Angew. Chem. Int. Ed. Engl. **2017**, *56*, 7935-7938

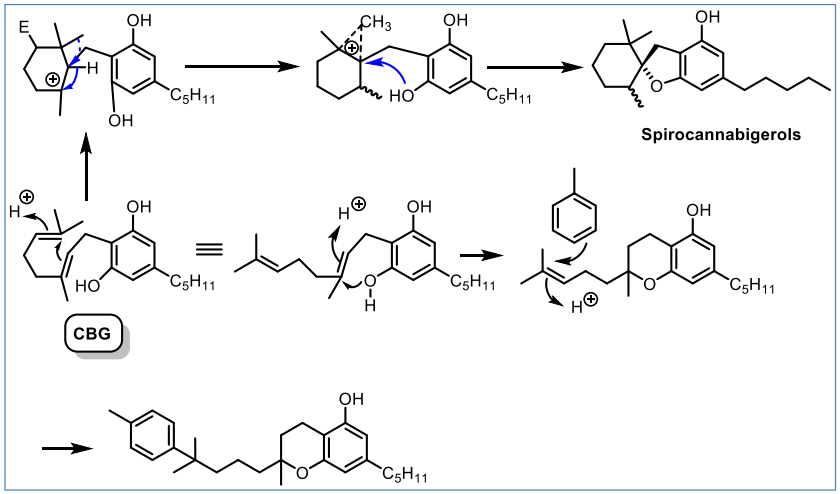
The cyclization of CBG: Iodine (concerted) *vs* proton (stepwise) trigger





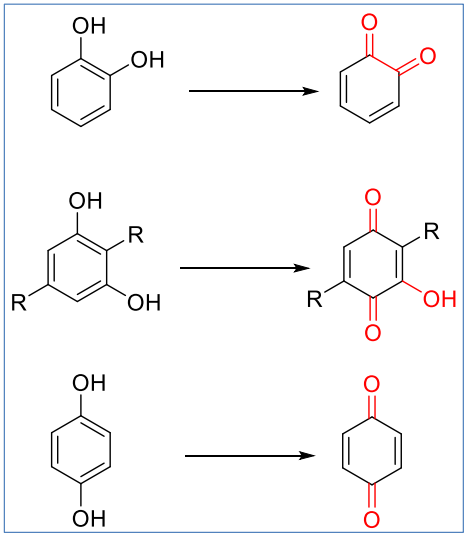
Bioorg. Med. Chem. Lett. **2018**,

The ionic cyclization of CBG: novel reaction courses via a corner-protonate cyclopropane



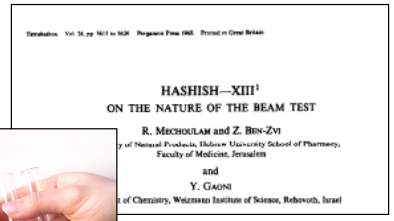
Bioorg. Med. Chem. Lett. **2018**,

The oxidation of benzenediols



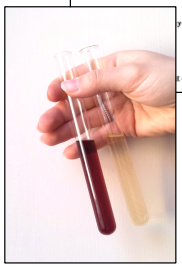
Cannabinoquinones: more than one reason to study them

Early discovery: first reported in 1968



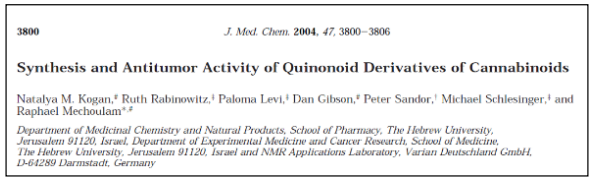
HASHISH—XIII[1]
ON THE NATURE OF THE BEAM TEST
R. Mechoulam and Z. Ben-Zvi
and
Y. Gaoni

Possible mammalian metabolites of cannabinoids



Forensic markers for recreational cannabis (Beam reaction)

Selective anti-cancer agents



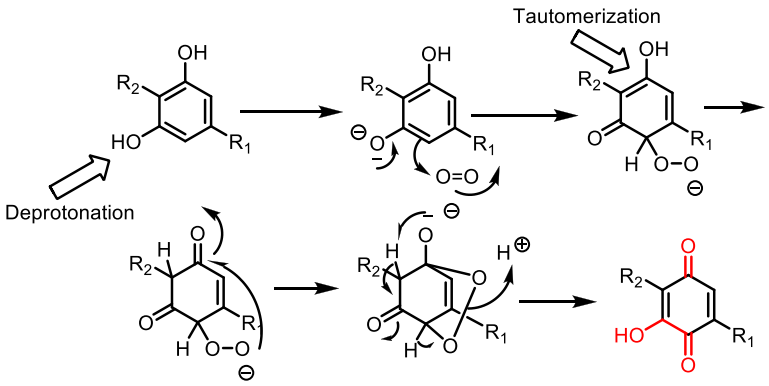
3800 *J. Med. Chem.* **2004**, *47*, 3800–3806

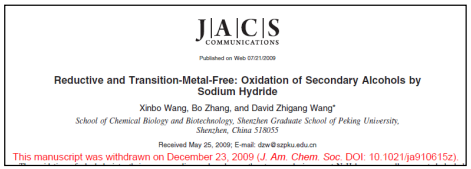
Synthesis and Antitumor Activity of Quinonoid Derivatives of Cannabinoids

Natalya M. Kogan,[#] Ruth Rabinowitz,[‡] Paloma Levi,[‡] Dan Gibson,[#] Peter Sandor,[‡] Michael Schlesinger,[‡] and Raphael Mechoulam*,[#]

Department of Medicinal Chemistry and Natural Products, School of Pharmacy, The Hebrew University, Jerusalem 91120, Israel, Department of Experimental Medicine and Cancer Research, School of Medicine, The Hebrew University, Jerusalem 91120, Israel and NMR Applications Laboratory, Varian Deutschland GmbH, D-64289 Darmstadt, Germany

“NaH oxidation” gives excellent analytical yields





J|A|C|S COMMUNICATIONS

Published on Web 07/21/2009

Reductive and Transition-Metal-Free: Oxidation of Secondary Alcohols by Sodium Hydride

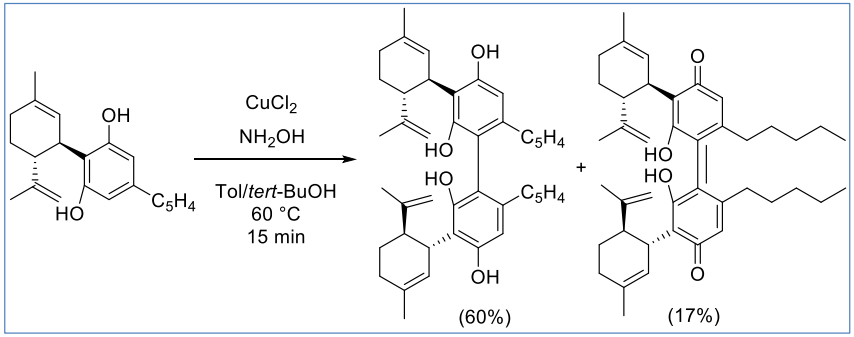
Xinbo Wang, Bo Zhang, and David Zhigang Wang*

School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen, China 518055

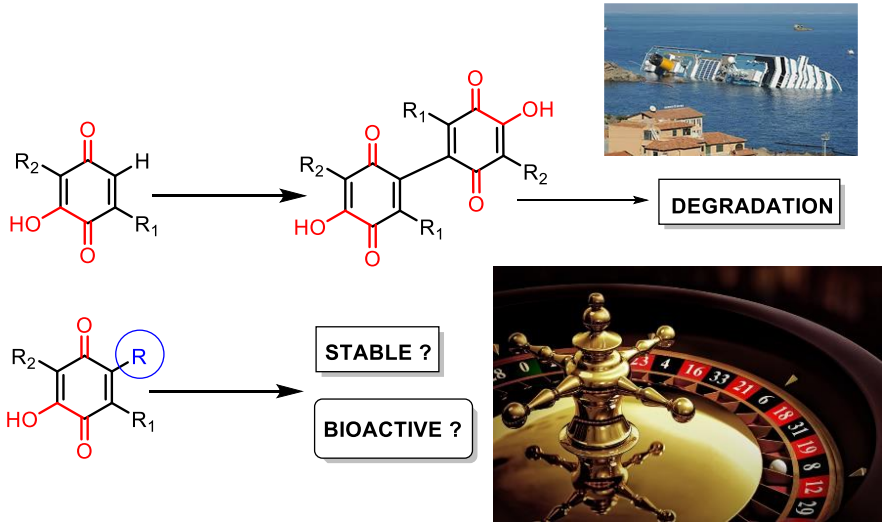
Received May 25, 2009; E-mail: dzw@szpku.edu.cn

This manuscript was withdrawn on December 23, 2009 (*J. Am. Chem. Soc.* DOI: 10.1021/ja910615z)

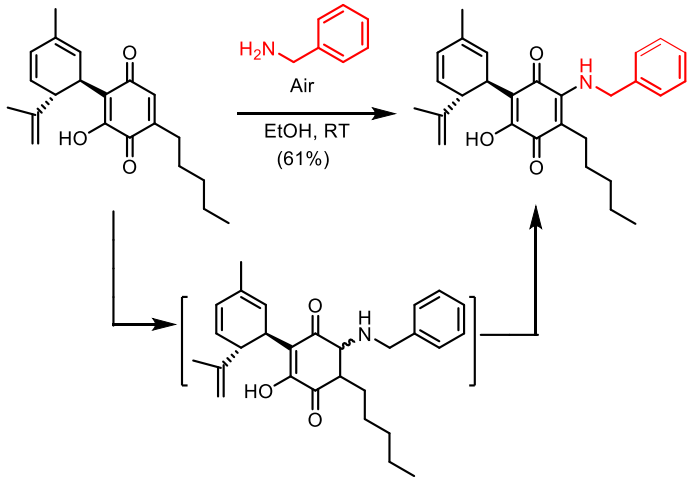
Most oxidants replicated the NaH-air reaction profile except $CuCl_2$-NH_2OH



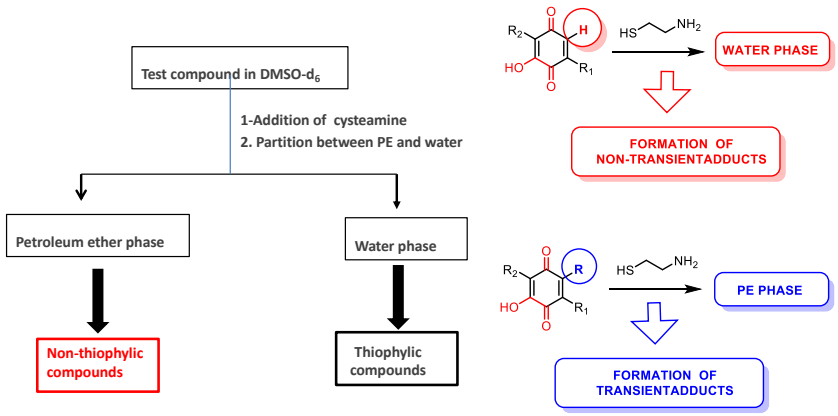
Cannabinoquinoids as a thermodynamic illusion. Possible strategies of chemical stabilization



The substituent at C-2: 3. The aza-Michael strategy



Substitution at C-2 changes the chemical profile



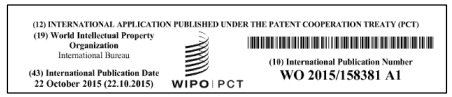
Angew. Chem. Int. Ed. **2011**, *50*, 467-471

Cannabinoquinoids: A winning ticket in the bioactivity lottery

Molecular:

CB1 neutrals but CB2 actives

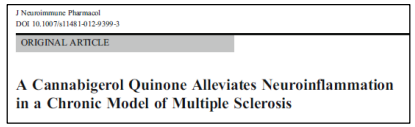
Powerful activators of PPAR-γ

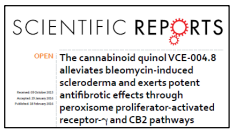

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
(19) World Intellectual Property Organization
International Bureau
(43) International Publication Date
22 October 2015 (22.10.2015)
WIPO | PCT
(10) International Publication Number
WO 2015/158381 A1

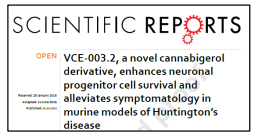
Cellular:

Non-cytotoxic

Neuroprotectants


J Neuroimmune Pharmacol
DOI 10.1007/s11481-012-9399-3
ORIGINAL ARTICLE
A Cannabigerol Quinone Alleviates Neuroinflammation in a Chronic Model of Multiple Sclerosis


SCIENTIFIC REPORTS
OPEN
The cannabinoid quinol VCE-004.8 alleviates bleomycin-induced scleroderma and exerts potent antifibrotic effects through peroxisome proliferator-activated receptor-γ and CB2 pathways


SCIENTIFIC REPORTS
OPEN
VCE-003.2, a novel cannabigerol derivative, enhances neuronal progenitor cell survival and alleviates symptomatology in murine models of Huntington's disease

Pre.clinical

Active in various animal models of neurodegenerative diseases

I am not saying that life should be without

amazement, but let's make that come from life

and sensations, not from chemicals

(paraphrasis from Kathleen Desmaisons, author of *The Sugar Addict's Total Recovery Program*)

FP 6 – 512696

VIVACELL
Biotechnology España

emerald
HEALTH BOTANICALS