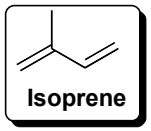
Classic Terpene Syntheses

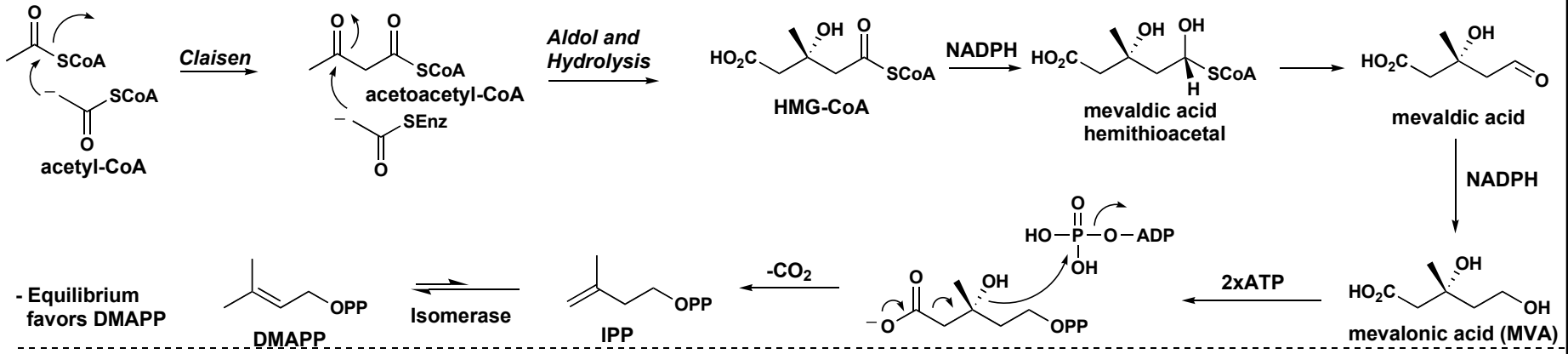
Tom Maimone

I. An Introduction to Terpenes

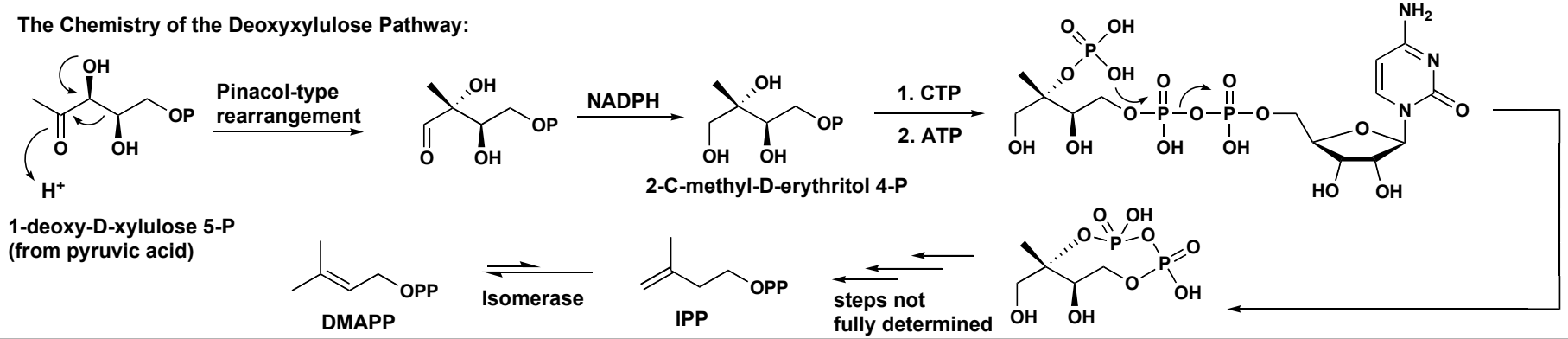
-Terpenes are an enormous class of natural products spanning well over 30,000 members
-They have been used throughout history for a broad variety of purposes including perfume, medicine, and flavoring
-Recognized early on as being composed of isoprene fragments
-Isopentyl diphosphate (IPP) and dimethyl allyl diphosphate (DMAPP) later found to be the actual building blocks
-There are 2 biosynthetic pathways for the production of IPP and DMAPP, the mevalonate pathway and the more recently discovered deoxyxylulose pathway



The Chemistry of the Mevalonate Pathway:



The Chemistry of the Deoxyxylulose Pathway:

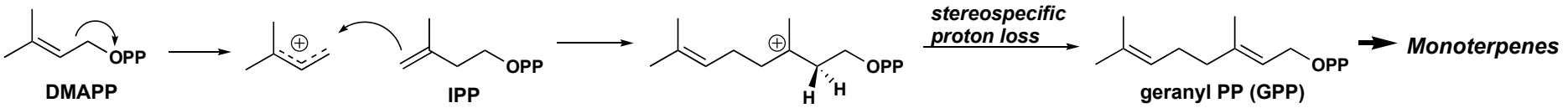


* For an excellent review on natural products and biosynthesis see: Dewick, P.M. *Medicinal Natural Products: A Biosynthetic Approach.* Wiley, **2002**.

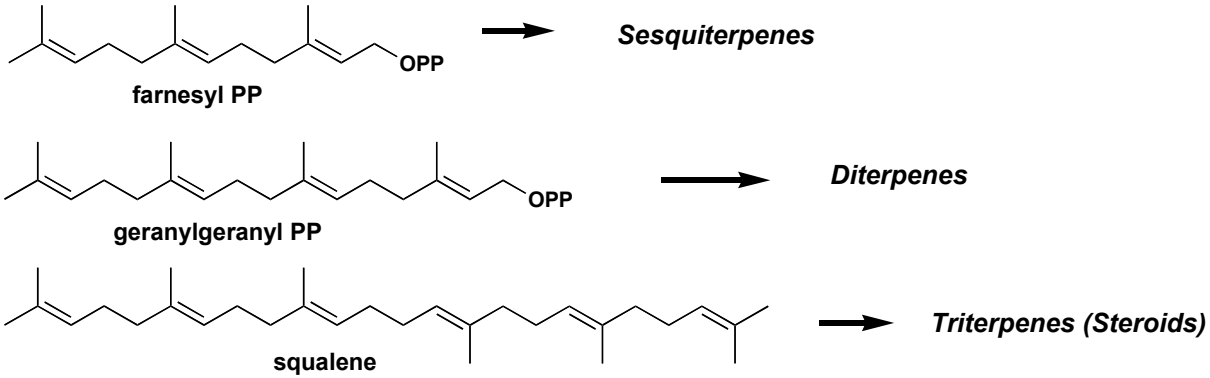
Classic Terpene Syntheses

Tom Maimone

- All terpenes are formed through the reactions of IPP and DMAPP:

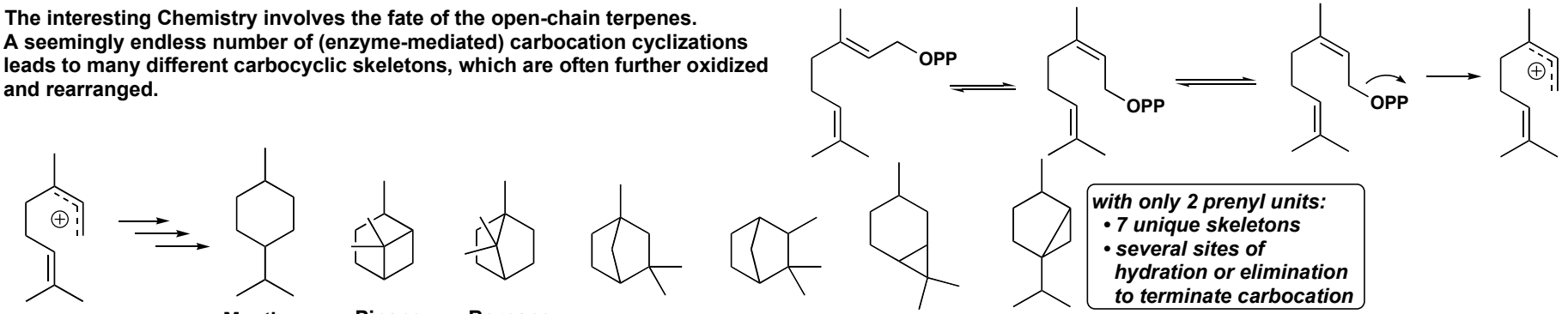


- repeat several times:



- Hemiterpenes (C_5)
- Monoterpenes (C_{10})
- Sesquiterpenes (C_{15})
- Diterpenes (C_{20})
- Sesterterpenes (C_{25})
- Triterpenes (C_{30})
- Tetraterpenes (C_{40})

- The interesting Chemistry involves the fate of the open-chain terpenes. A seemingly endless number of (enzyme-mediated) carbocation cyclizations leads to many different carbocyclic skeletons, which are often further oxidized and rearranged.



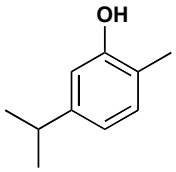
with only 2 prenyl units:
- ***7 unique skeletons***
- ***several sites of hydration or elimination to terminate carbocation***

***Take Home Message*: Complexity increases extremely rapidly with each addition prenyl unit**

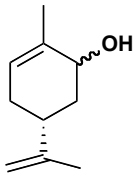
Classic Terpene Syntheses

Tom Maimone

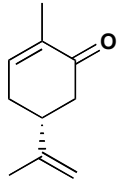
*II. Commercially available Terpene Building Blocks**



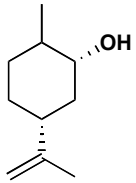
Carvacrol
$2.37/g



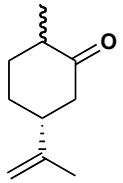
(-) carveol (isom. mix)
$1.326/g
(-) acetate $7/g



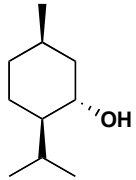
Carvone
(+) $1.76/g
(-) $0.20/g



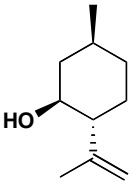
Dihydrocarveol
(-) $14/g
isomer mixture $1.6/g



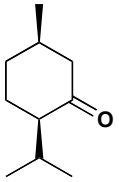
(+) Dihydrocarvone
isomer mixture $0.7/g



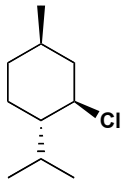
(+)-Isomenthol
$0.18/g



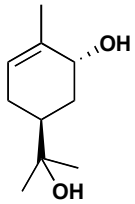
Isopulegol
(+) $95/g
(-) $25/g



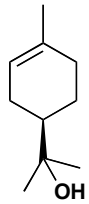
(-) Menthone
$ 0.54/g



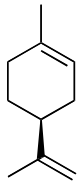
(-) Menthyl chloride
$ 16.4/g



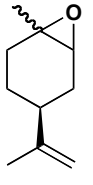
trans-p-menth-
6-ene-2,8-diol
$1.82/g



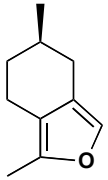
α-terpineol
(+) $38/g
(-) $0.4/g



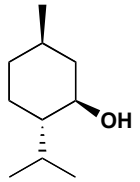
Limonene
(+) $0.09/g
(-) $0.23/g



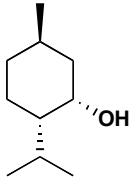
Limonene oxide
mixture of isomers
(+) $0.72/g
(-) $0.58/g



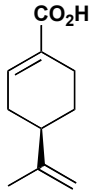
(+) Menthofuran
$3.88/g



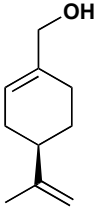
Menthol
(+) $2.2/g
(-) $0.19/g
many o-acetylated
derivatives available



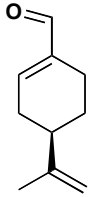
Neomenthol
(+) 11.5/g
(+) and (-) acetates
available



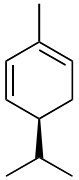
Perillic acid
$14/g



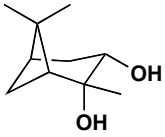
Perillyl alcohol
(+) $44/g
(-) $1.9/g



Perillaldehyde
(+) $53/g
(-) $2.88/g



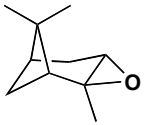
α-Phellandrene
$0.164/g



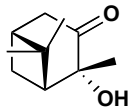
Pinanediol
(+) $20/g
(-) $17/g

α-Pinene
(+) $0.28/g
(-) $0.1/g

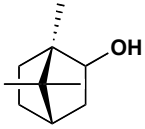
β-Pinene
(-) $0.04/g



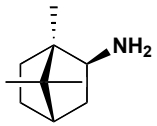
Pinene Oxide
$0.332/g



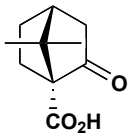
2-Hydroxy-3-pinanone
(+) $22/g, (-) $15/g



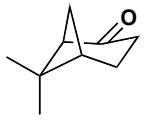
Isoborneol
$0.09g
O-acrylate $0.08/g



(-) Isobornylamine
$1360/g

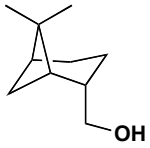


(+) Ketopinic acid
$60/g

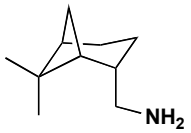


(+) Nopinone
$31/g

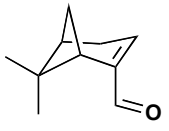
(-)-Nopol
$0.13/g
Benzyl ether
available



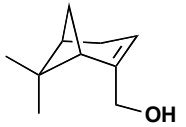
(-)-Myrtanol
$22.7/g



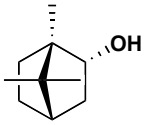
(-)-cis-Myrtanylamine
$12.9/g



(-)-Myrtenal
$2.24/g



(-)-Myrtenol
$2.07/g



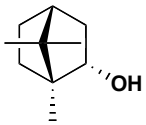
[(1S)-endo]-(-)-Borneol
$0.31/g

*Aldrich Prices (some prices are significantly lower from other suppliers)

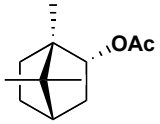
Baran Lab

Classic Terpene Syntheses

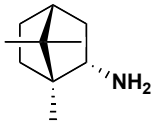
Tom Maimone



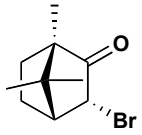
(+) Borneol
$53/g



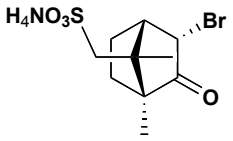
(-) Bornyl acetate
$0.18/g



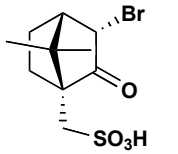
(+)-Bornylamine
$194/g



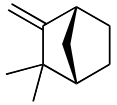
(-)-3-Bromocamphor
$4.6/g



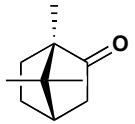
(+)-3-Bromocamphor-8-sulfonic acid ammonium salt $6/g



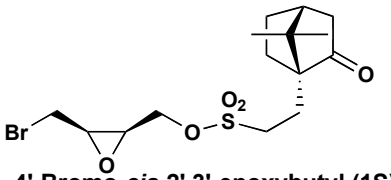
(+)-3-Bromocamphor-10-sulfonic acid hydrate
$57/g



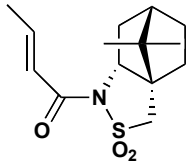
Camphene
(+) $0.045/g
(-) $0.055/g



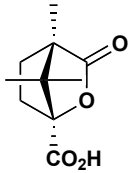
Camphor
(+) $0.205/g
(-) $5.49/g



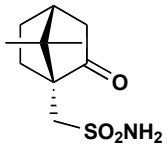
4'-Bromo-*cis*-2',3'-epoxybutyl (1S)-camphor sulfonate $217/g



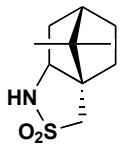
(2-Butenoyl)-2,10-camphorsultam
(+) or (-) $45/g



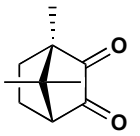
Camphanic acid
(+) $150/g , (-) $20/g
(-) acid chloride $22.6/g



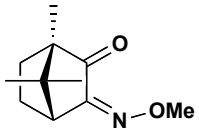
Camphorsulfonamide
$24/g either ent.



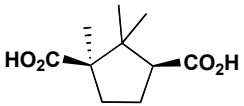
2,10-Camphorsultam
(+) $59/g, (-) $32/g



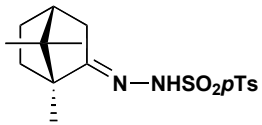
Camphorquinone
(+) $12.5/g , (-) $5.14/g



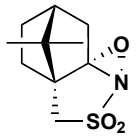
Camphorquinone 3-oxime
(+) $126/g , (-) $86/g



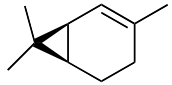
Camphoric acid
(+) $23.7/g, (-) $73.7/g



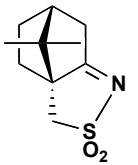
Camphor *p*-tosylhydrazone
(+) $1.4/g, (-) $8.8/g



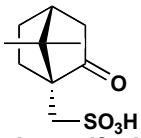
10-camphorsulfonyl oxaziridine
(+) $65/g, (-) $61/g



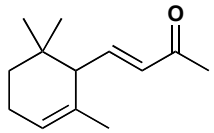
(+)-2-Carene
$3.3/g



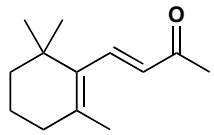
(-)-Camphorsulfonylimine
$26.80/g



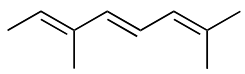
Camphor sulfonic acid
(-) $0.82/g, (+) $0.32/g
(-) Ammonium salt $0.92/g
sodium salt $0.25/g
(+) sulfonyl chloride $2.34/g
(-) sulfonyl chloride $10.0/g



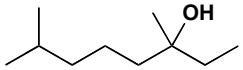
α-Ionone
$0.27/g



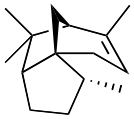
β-Ionone
$0.24/g



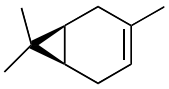
Alloocimene
$ $0.13/g



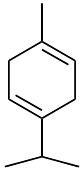
3.7Dimethyl-3-octanol
$4.13/g



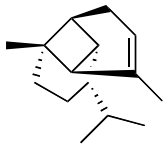
(-)- Cedrene
$46/g



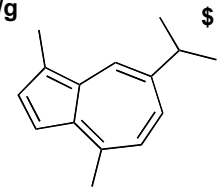
3-Carene
$0.056/g



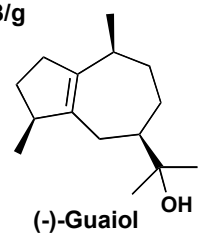
γ-terpinene
$0.39/g



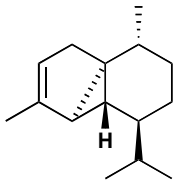
α-Copaene
$270/g



Guaiazulene
$3.1/g



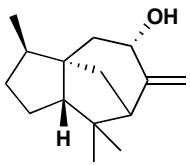
(-)-Guaiol
$700/g



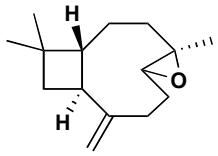
(-)-α-Cubebene
$ 1180/g

Classic Terpene Syntheses

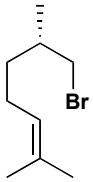
Tom Maimone



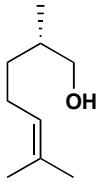
(+)-8(15)-Cedren-9-ol
$288/g



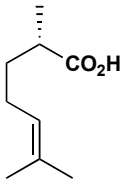
(-) Carophyllene oxide
$2/g



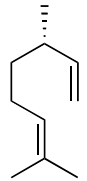
Citronellyl Bromide
(+) $6/g, (-) $30/g



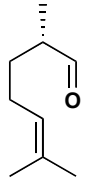
β-Citronellol
(+) $50/g, (-) $19/g
(dl) $0.13/g



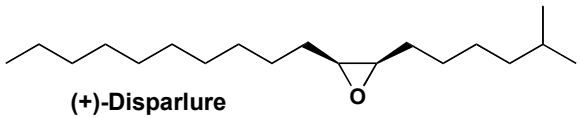
Citronellic acid
(+) $16/g, (-) $78,g
(+/-) $2/g



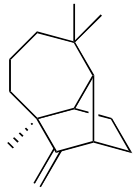
β-Citronellene
(-) $1.70/g



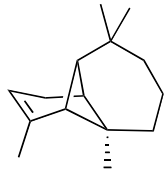
Citronellal
(+) $16.5/g,
(-) $13/g



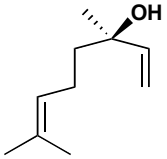
(+)-Disparlure
$812/g



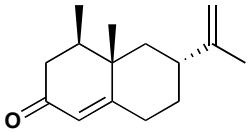
(+) Longifolene
$10.3/g



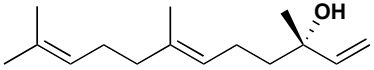
(+)-α-Longipinene
$342/g



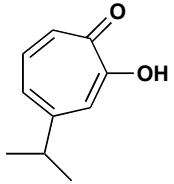
(-) Linalool
$0.63/g



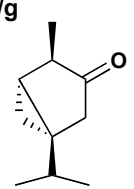
(+)-Nootkatone
$18/g



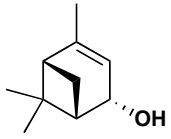
nerolidol
all trans $70/g
cis/trans $0.75/g



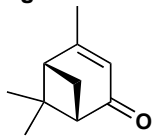
β-Thujaplicin
$8.6/g



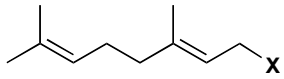
(-)-α-Thujone
$25/g
α,β–mix $5.5/g



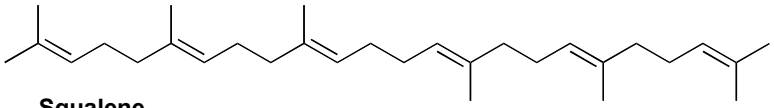
(*S*)-cis-Verbenol
$8/g



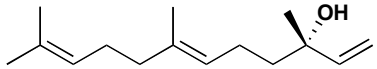
(-) Verbenone
$2.8/g



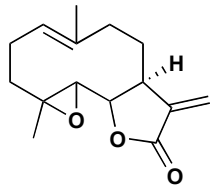
geraniol (X=OH)
$0.35/g
acetate $0.53/g
bromide $3.88
chloride $5.85
amine $23/g
acid $0.92/g



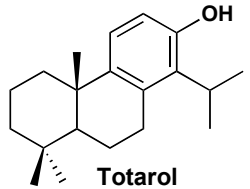
Squalene
$0.43/g



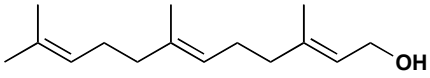
nerolidol
all trans $70/g
cis/trans $0.75/g



Parthenolide
$3724/g

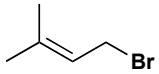


Totarol
$156/g



Farnesol
$1.1/g

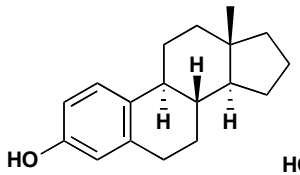
trans,trans
$ 10/g (also bromide,chloride, acetate)



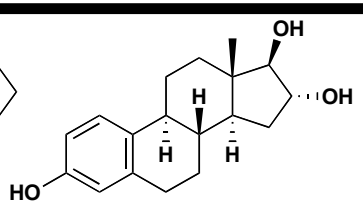
Prenyl Bromide
$2.1/g

Classic Terpene Syntheses

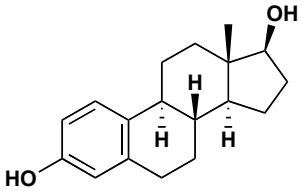
Tom Maimone



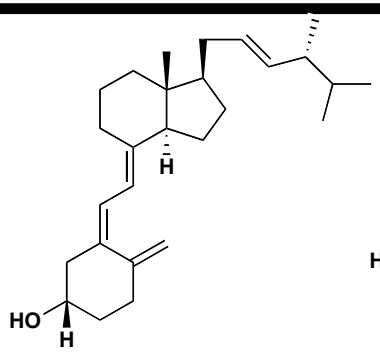
Estrone
$14.2/g



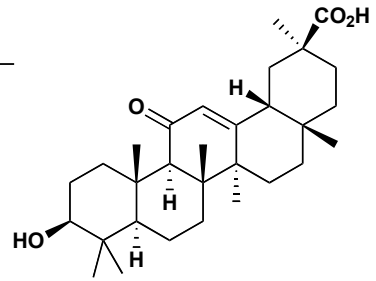
Estriol
$72/g



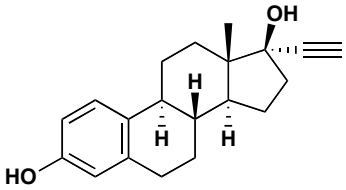
Estradiol
$24.6/g



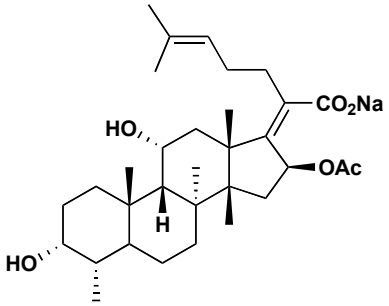
Ergocalciferol (D_2)
$15.7/g



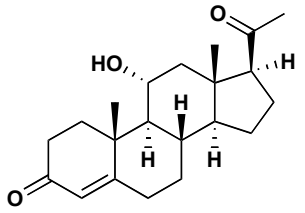
Glycyrrhetinic acid
$5.4/g



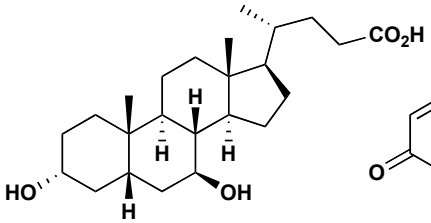
17α–Ethynylestradiol
$28.6/g



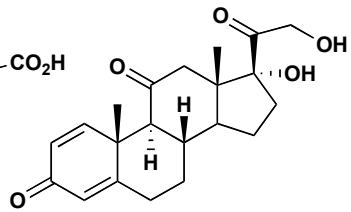
Fusidic acid
$108/g



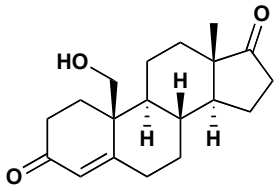
11α-Hydroxyprogesterone
$8.3/g



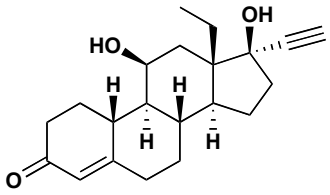
Ursodeoxycholic acid
$12.3/g



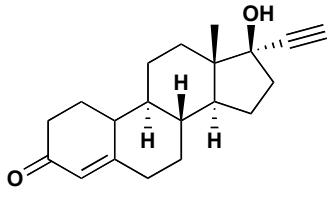
Prednisone
$13.4/g
several related
derivates available



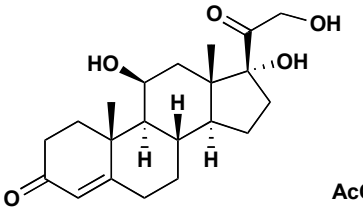
19-Hydroxy-4-androstene-
3,17-dione
$916/g



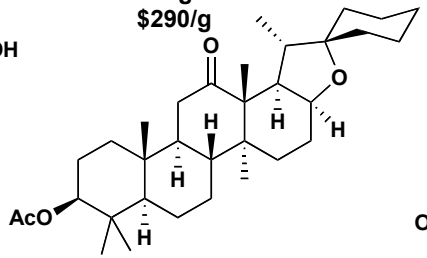
Norgestrel
$290/g



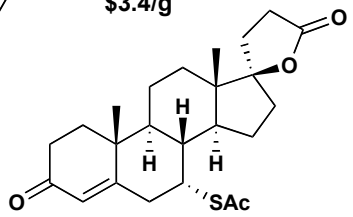
Ethisterone
$3.4/g



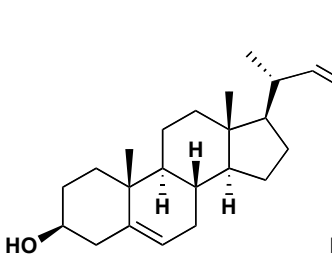
Hydrocortisone
$10/g



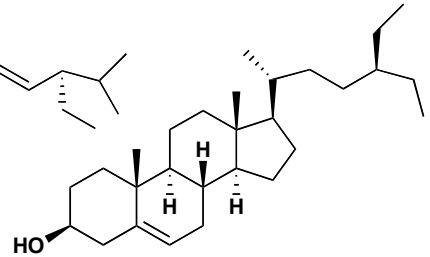
Hecogenin Acetate
$11.2/g



Spironolactone
$26/g



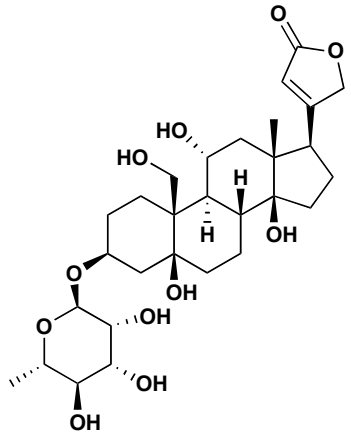
Stigmasterol
$12.5/g



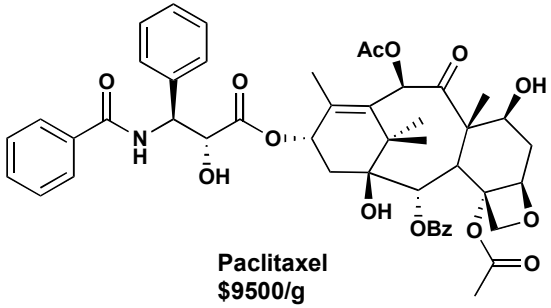
β-Sitosterol
$0.26/g

Classic Terpene Syntheses

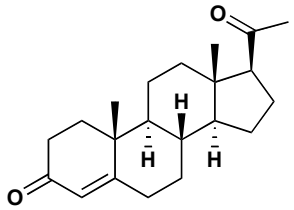
Tom Maimone



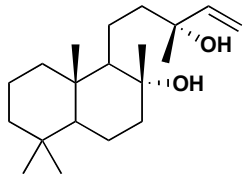
(-)-Oubain Hydrate
$75/g



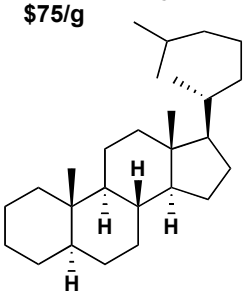
Paclitaxel
$9500/g



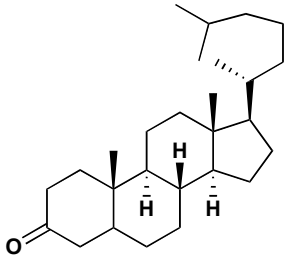
Progesterone
$2.24/g



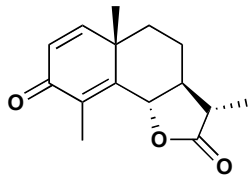
Sclareol
$32/g



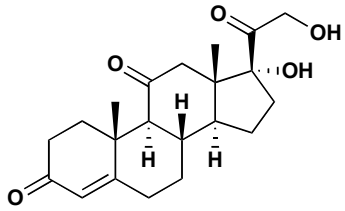
5-α-Cholestane
$60/g



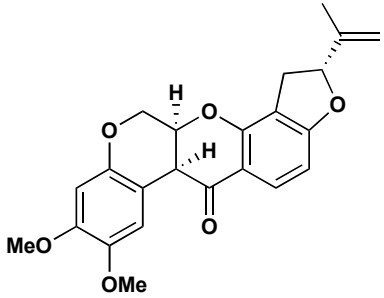
5-α-Cholestan-3-one
$20/g
(several unsaturated variants available)



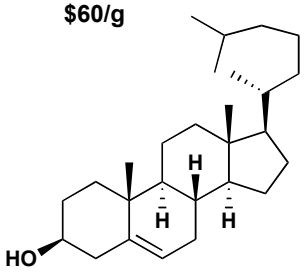
(-)-α-Santonin
$2.64/g



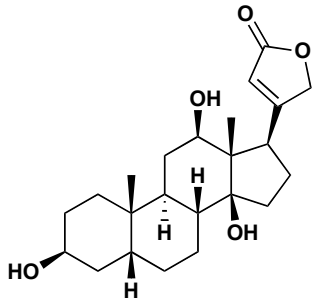
Cortisone
$22/g (several derivates available)



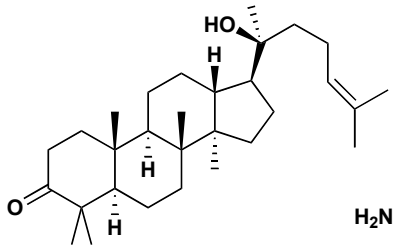
Rotenone
$4.16/g



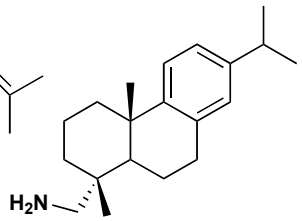
Cholesterol
$0.30/g
(many derivatives available)



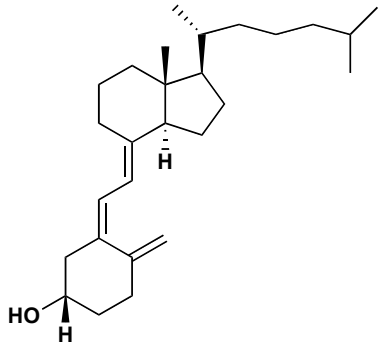
Digoxigenin
$586/g
(several derivatives available)



Dipterocarpol
$138/g



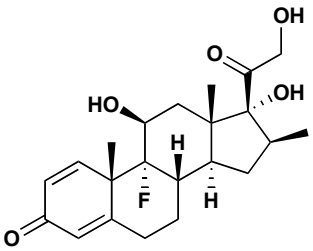
Dehydroabietylamine
(+) $0.27/g



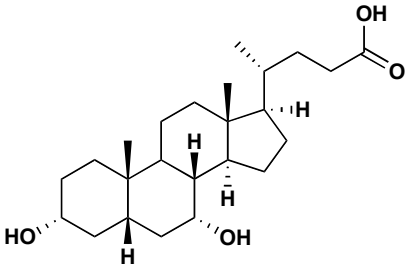
Cholecalciferol
$19.5/g

Classic Terpene Syntheses

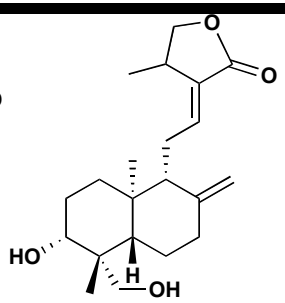
Tom Maimone



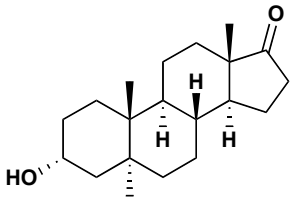
Betamethasone
$ 696/g



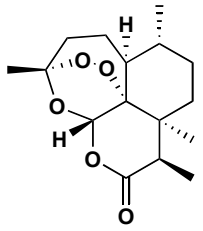
Chenodeoxycholic acid
$7.94/g



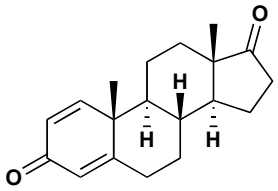
Andrographolide
$175.4/g



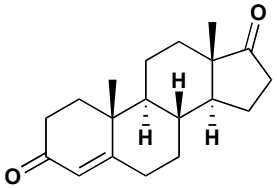
Androsterone
$45/g



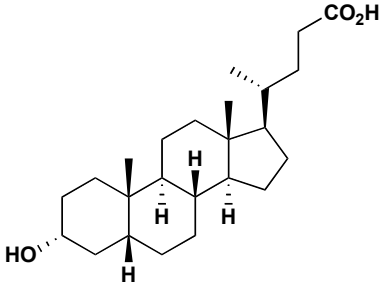
Artemisinin
$416/g



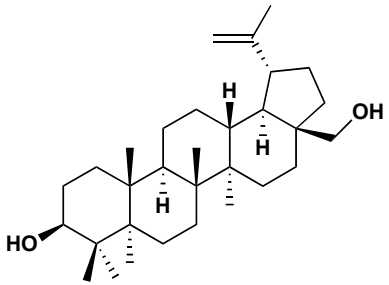
1,4-androstadiene-3,17-dione
$70/g



4-Androstene-3,17-dione
$7.44/g



Lithocholic acid
$1.24/g



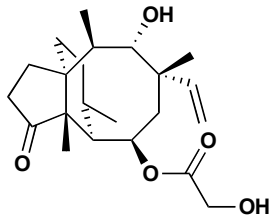
Betulin
$58.6/g

Classic Terpene Syntheses

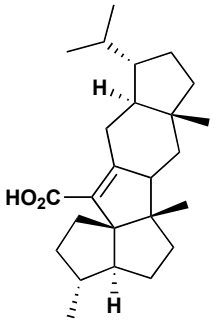
Tom Maimone

III. Synthesis Discussed

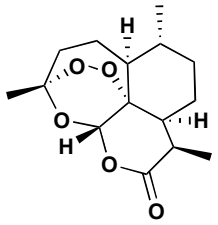
Disclaimer:
Natural Products arising from mixed biosynthetic pathways (terpene/alkaloid, terpene/polyketide) were not considered.



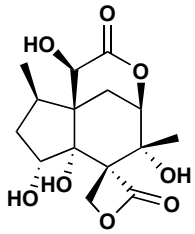
Pleuromutilin
Boeckman



Retigeranic acid
Corey

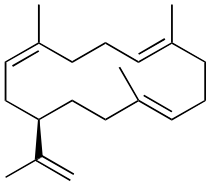


Qinghaosu
Hofheinz

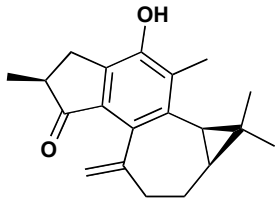


Anisatin
Kende

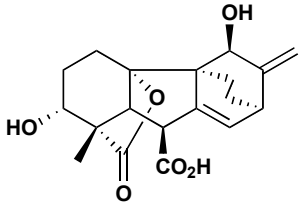
Molecules were chosen that are not typically covered in the synthetic organic chemistry classes at TSRI. The interested reader can find many more classic syntheses in the followiing locations.*



Cembrene
wender

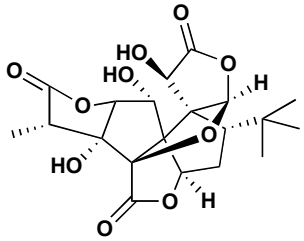


Jatropholones
A.B. Smith

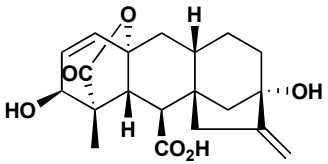


Antheridium-Inducing Factor (A_{An})
Corey

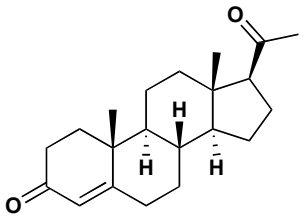
Some Classics not discussed:



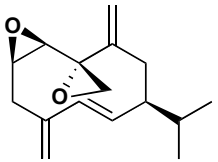
Ginkgolide B
Corey



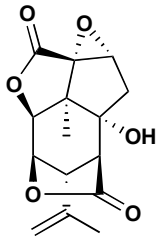
Gibberellic Acid
Corey



Progesterone
Johnson



Periplanone
Still

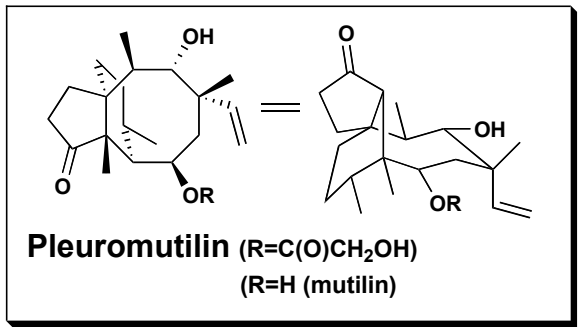


Picrotoxinin
Corey

* Nicolaou, K.C.; Sorensen, E.J. *Classics in Total Synthesis.* VCH, Weinheim, **1996**.
Corey, E.J.; Chen, X. *The Logic of Chemical Synthesis. Wiley, **1995.***
Ho, T.L. *Enantioselective Synthesis: Natural Products from Chiral Terpenes.* Wiley, **1992**.
Nicolaou, K.C.; Snider, S.A. *Classics in Total Synthesis II.* VCH, Weinheim, **2003**.

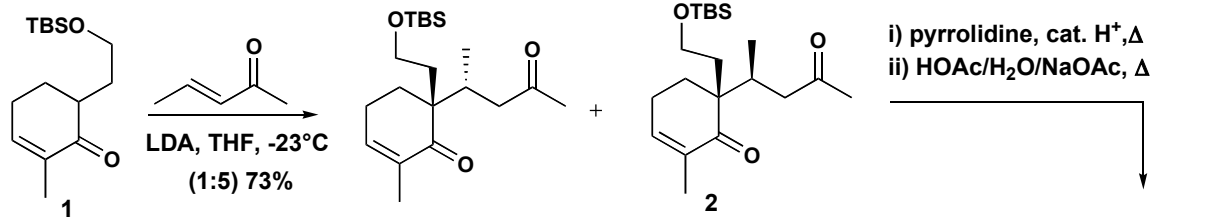
Classic Terpene Syntheses

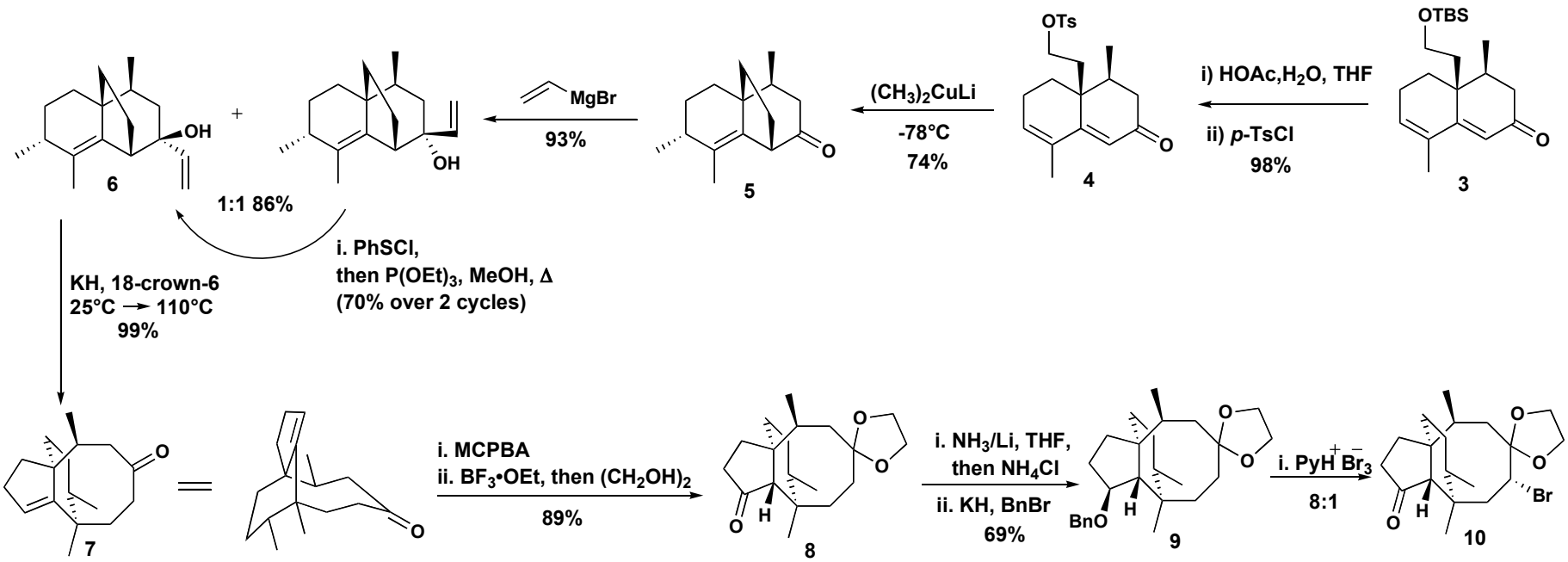
Tom Maimone



Pleuromutilin (R=C(O)CH_2OH)
(R=H (mutilin)

Boeckman et al. *J. Am. Chem. Soc.* **1989,** *111*, 8284-8286

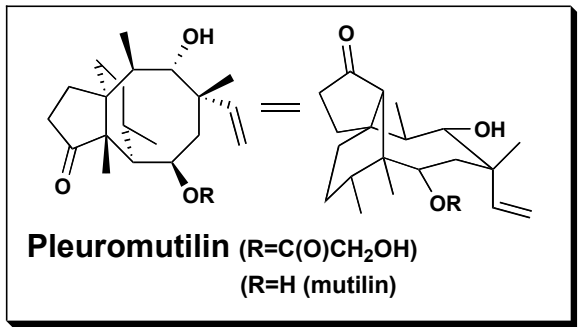




" The relative facility of the rearrangement in the present case may be due in part to the absence of side reactions such as retro ene porcesses owing to the presence of the allyl unit in a rigid framework"

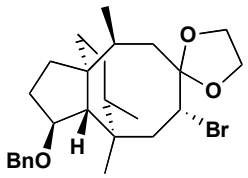
Classic Terpene Syntheses

Tom Maimone



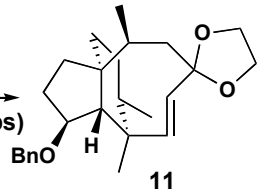
Pleuromutilin (R=C(O)CH_2OH)
(R=H (mutilin)

Boeckman et al. *J. Am. Chem. Soc.* **1989,** *111*, 8284-8286



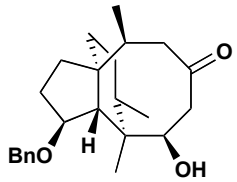
10

i. KO-*t*-Bu
67% (2 steps)



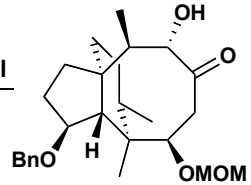
11

1M aq. TsOH
acetone, Δ
67%



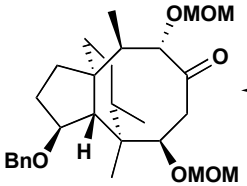
12

i. CH_3OCH_2Cl
iPr_2NEt_3
ii. TMSI, HMDS -20°C → 10°C, then $NaHCO_3$
iii. MCPBA, $NaHCO_3$
iv. aq. TBAF
62%



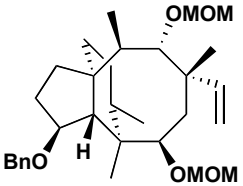
13

i. MOM-Cl



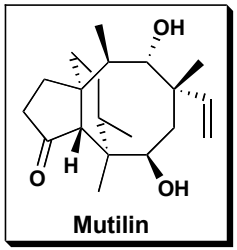
14

i.
ii. $SOCl_2$
iii. $CH_3CuB(CH_3)_3$
60% (5:1)



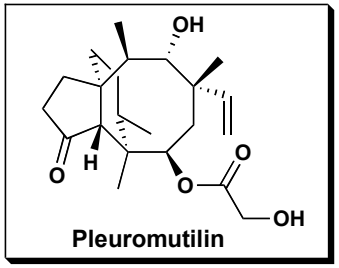
15

i. Li/NH_3
ii. PCC
iii. HCl-EtOH
80%



Mutilin

i. $AcOCH_2COOMs$, DMAP
ii. KOH, MeOH

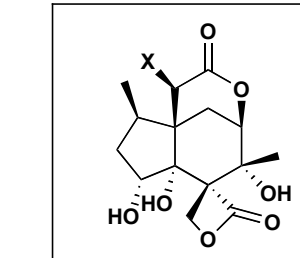


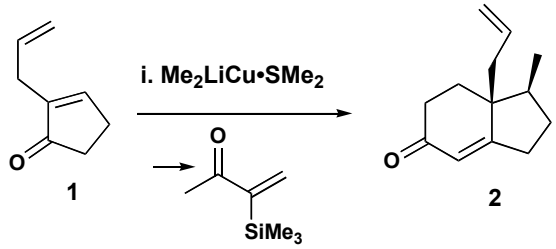
Pleuromutilin

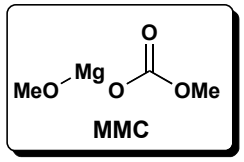
Classic Terpene Syntheses

Tom Maimone

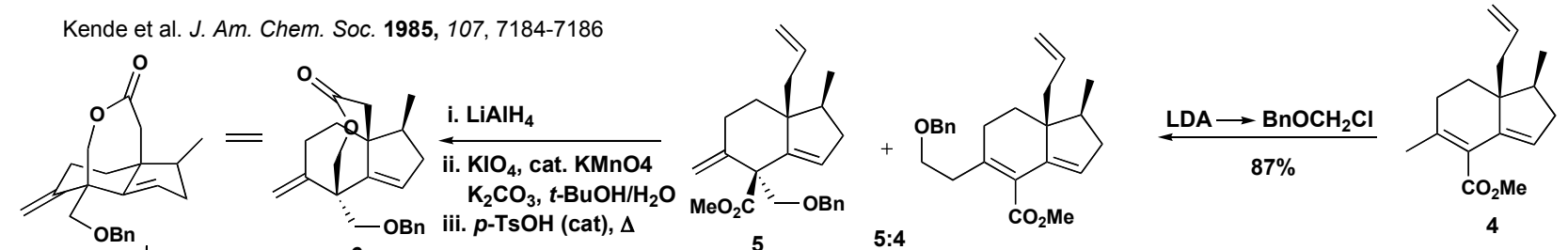
Deoxyanisatin (X=H)
X=OH (Anisatin)

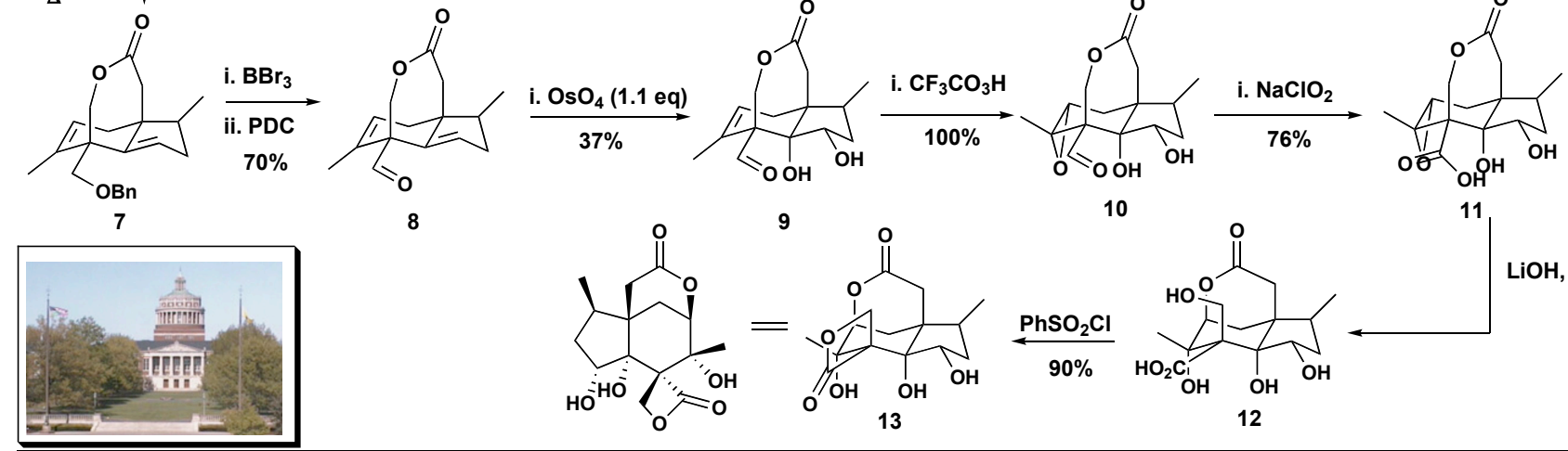






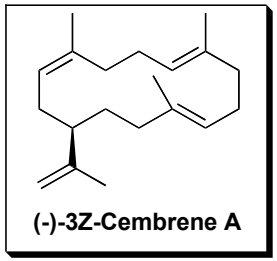
Kende et al. *J. Am. Chem. Soc.* **1985,** *107*, 7184-7186

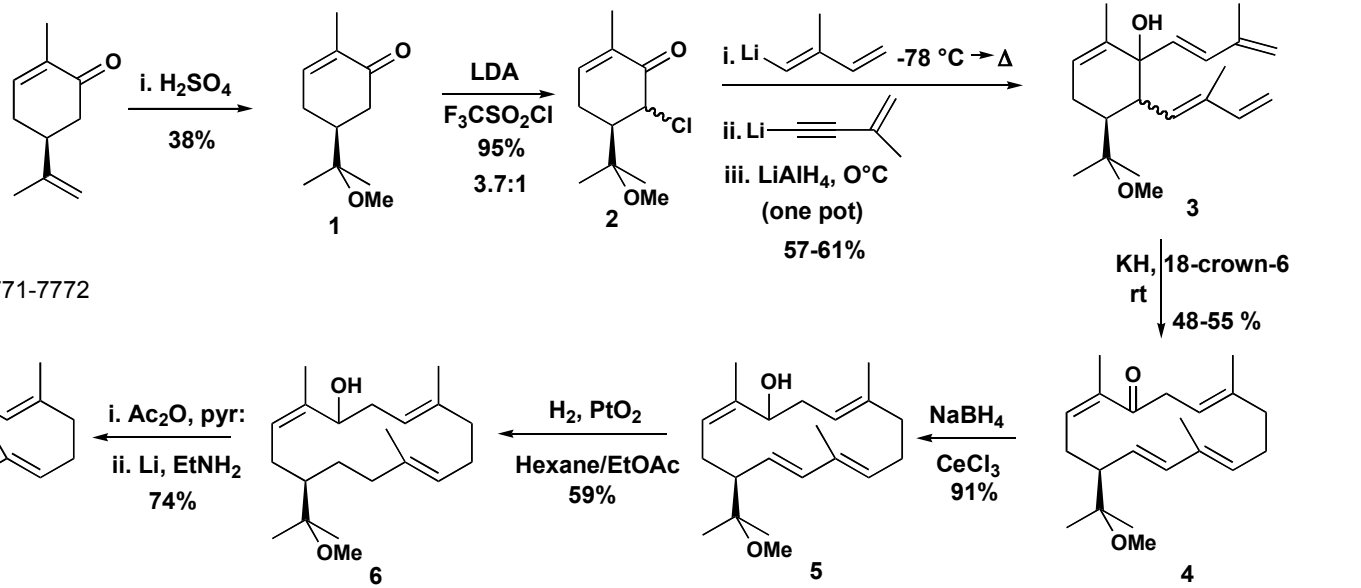




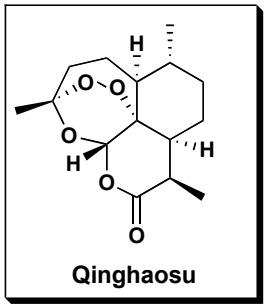
Classic Terpene Syntheses

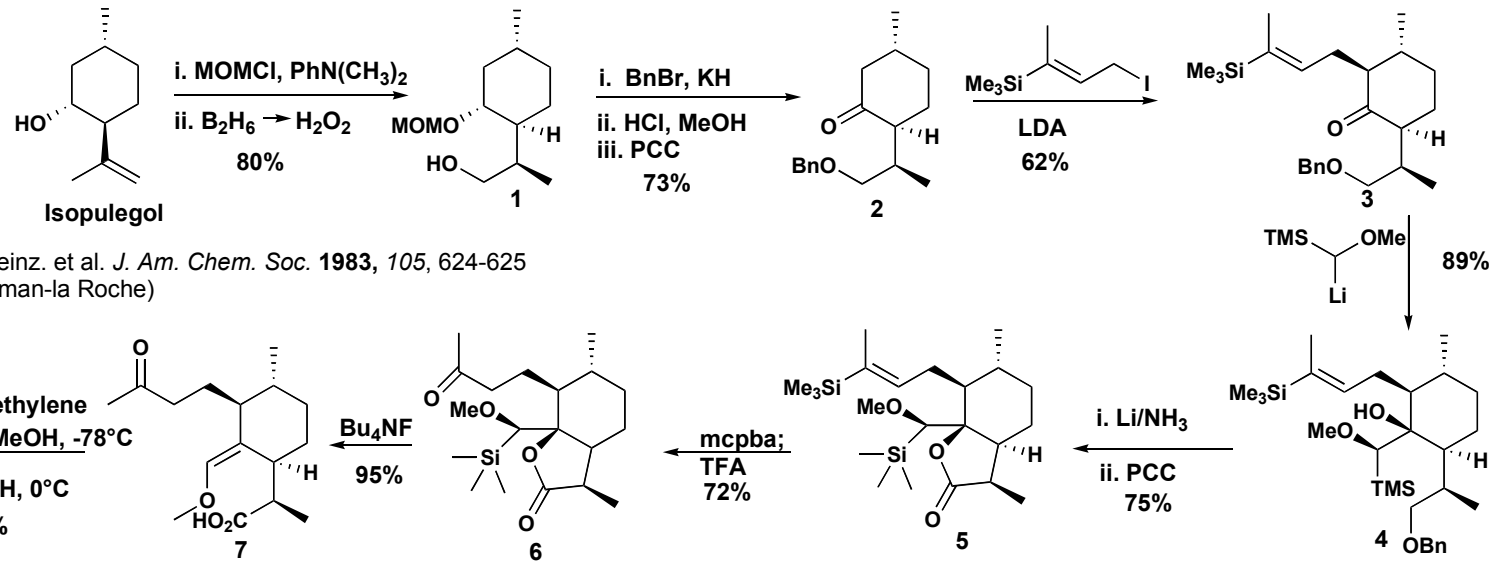
Tom Maimone





Wender et al. *J. Am. Chem. Soc.* **1985,** *107*, 7771-7772

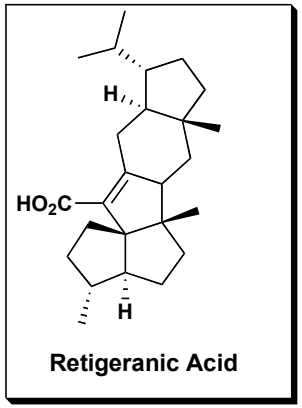




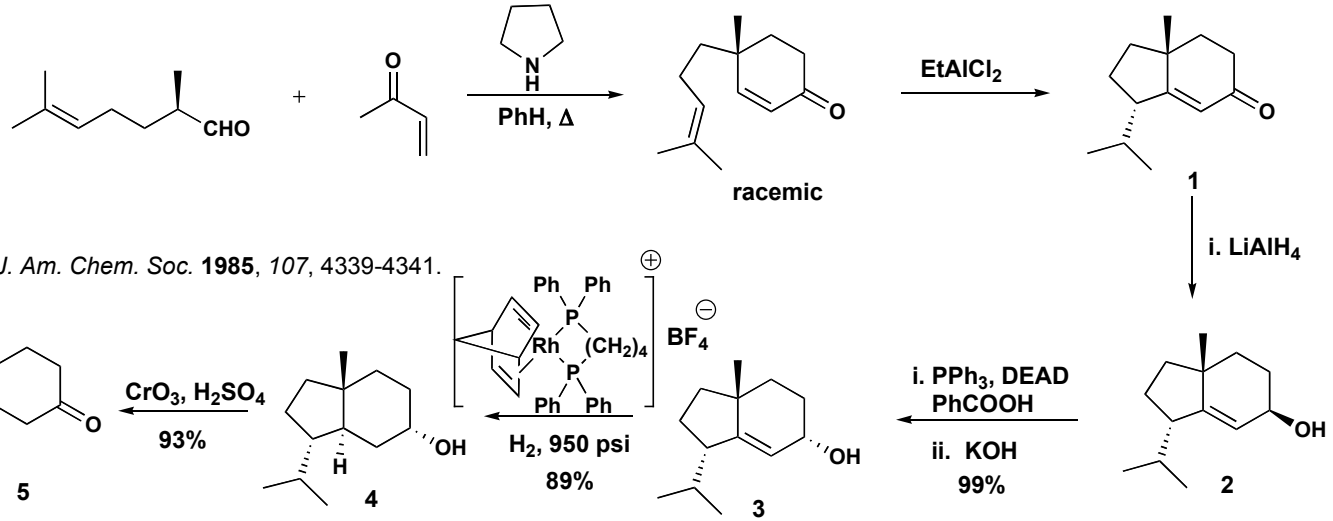
Hofheinz. et al. *J. Am. Chem. Soc.* **1983,** *105*, 624-625
(Hoffman-la Roche)

Classic Terpene Syntheses

Tom Maimone



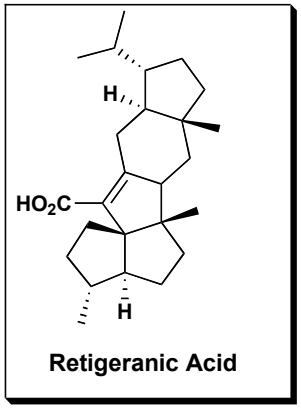
Retigeranic Acid



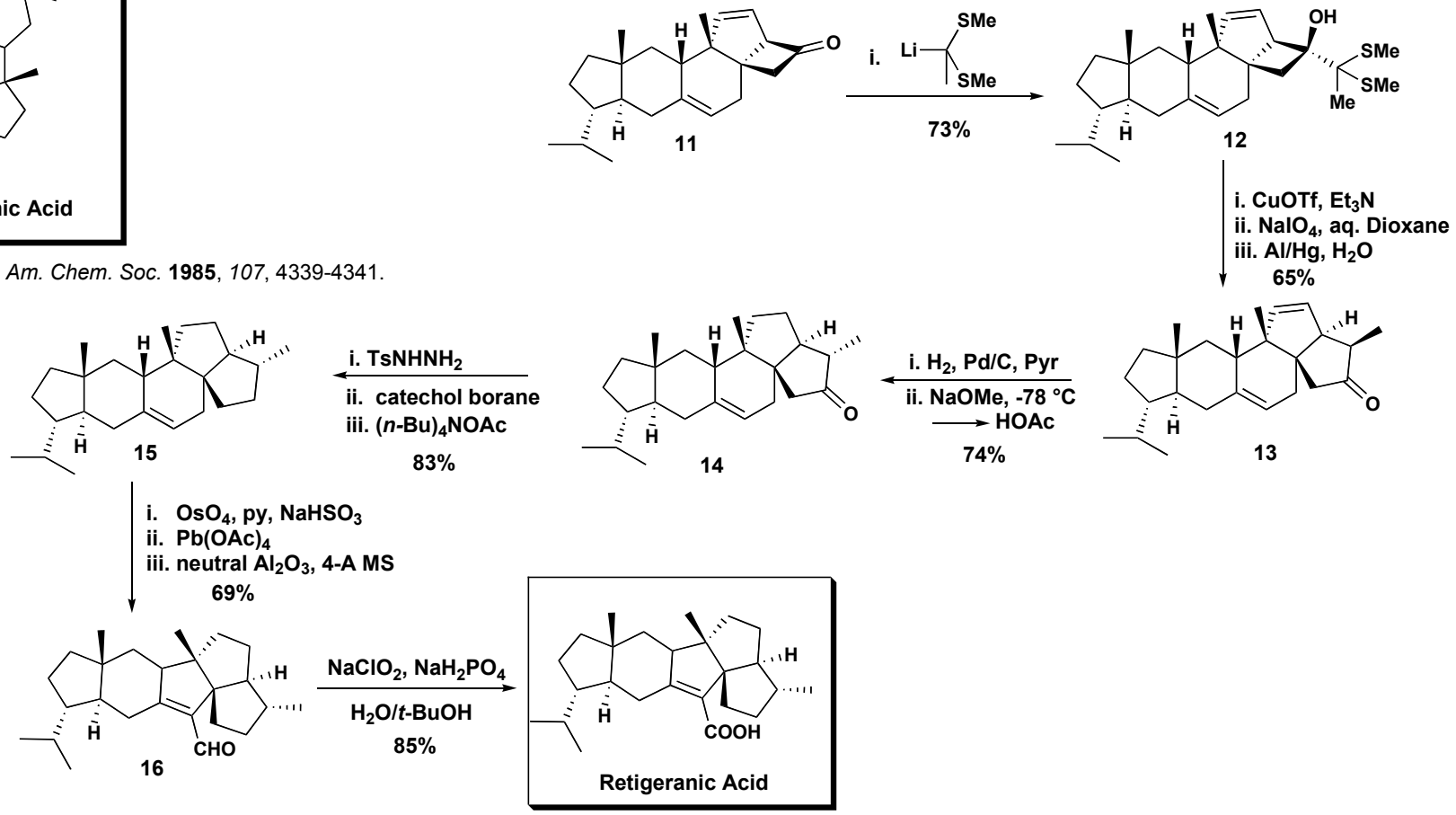
Corey et al. *J. Am. Chem. Soc.* **1985**, *107*, 4339-4341.

Classic Terpene Syntheses

Tom Maimone

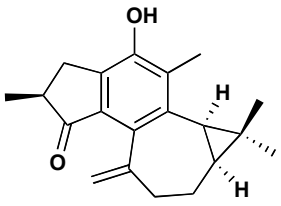


Corey et al. *J. Am. Chem. Soc.* **1985**, *107*, 4339-4341.



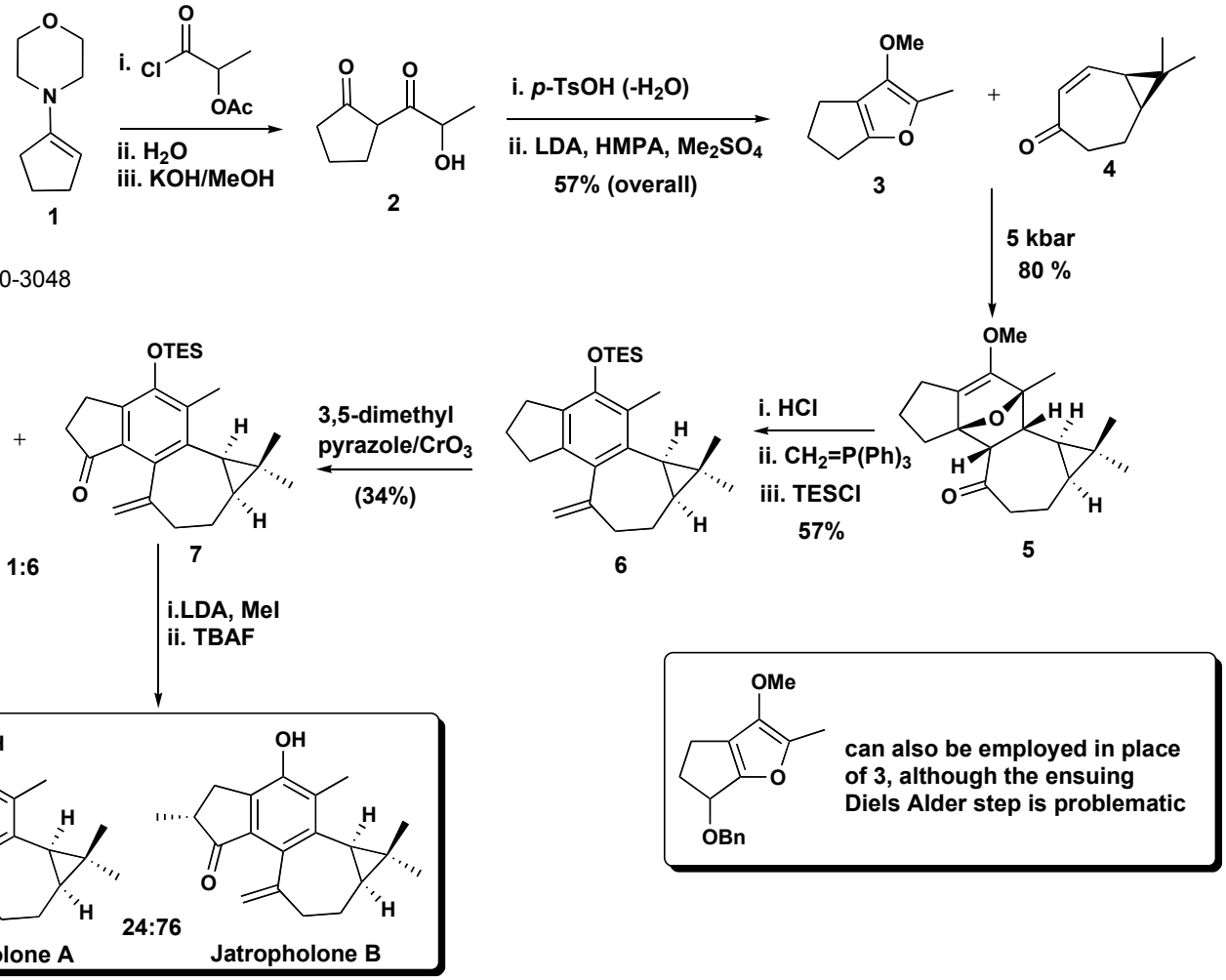
Classic Terpene Syntheses

Tom Maimone



Jatropholones

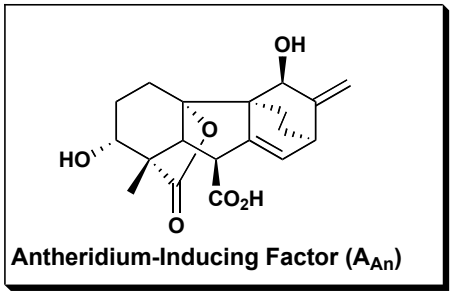
A.B Smith et al. *J. Am. Chem. Soc.* **1986,** *108*, 3040-3048



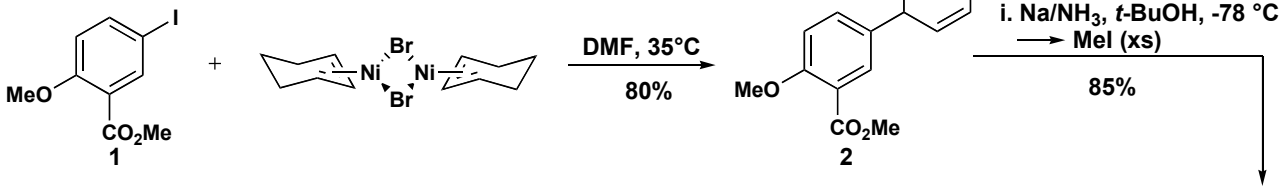
can also be employed in place of 3, although the ensuing Diels Alder step is problematic

Classic Terpene Syntheses

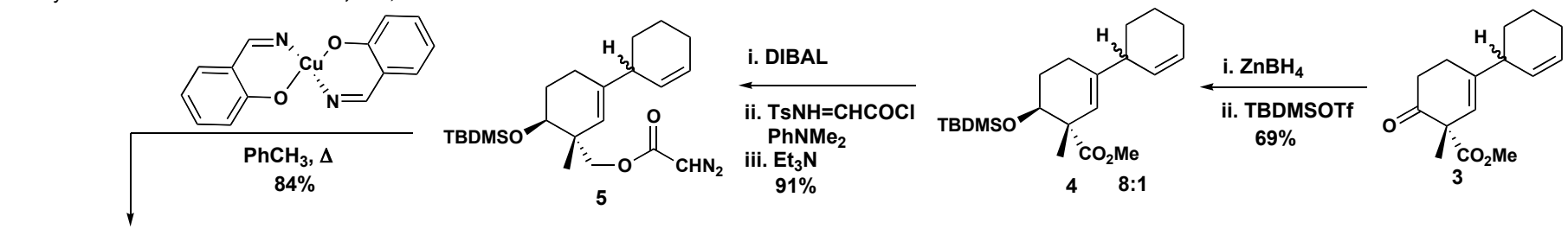
Tom Maimone

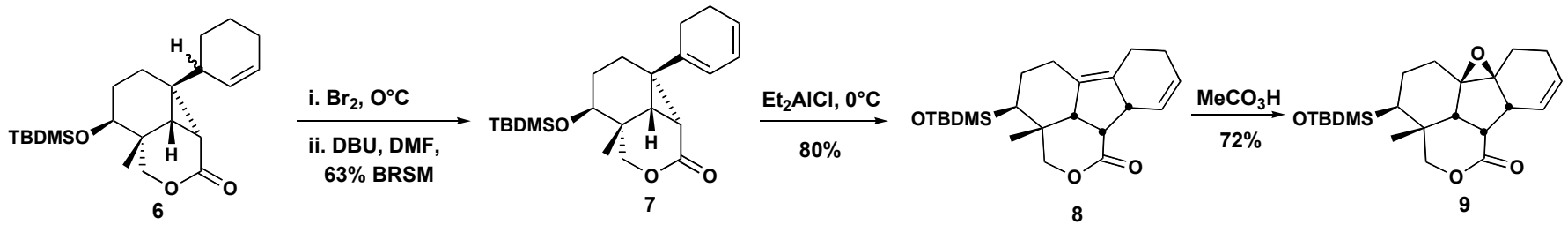


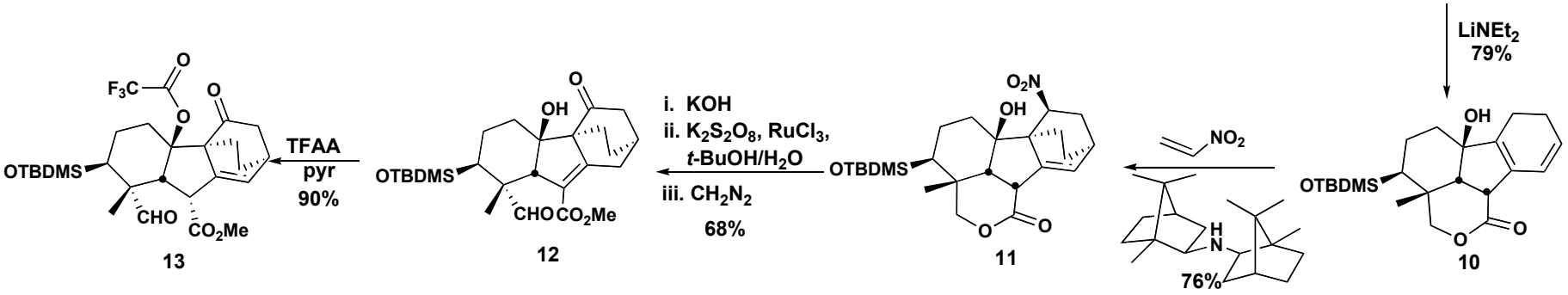
Antheridium-Inducing Factor (A_{An})



Corey et al. *J. Am. Chem. Soc.* **1985,** *107,* 5574-5576

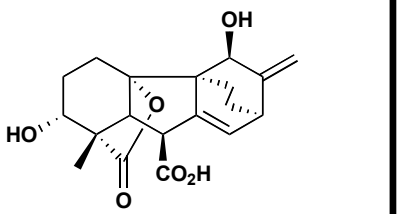






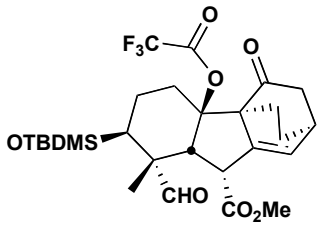
Classic Terpene Syntheses

Tom Maimone



Antheridium-Inducing Factor (A_{An})

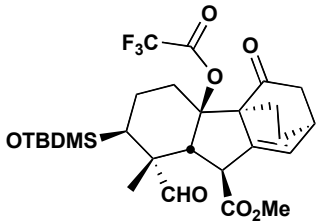
Corey et al. *J. Am. Chem. Soc.* **1985,** *107,* 5574-5576



13

DBU

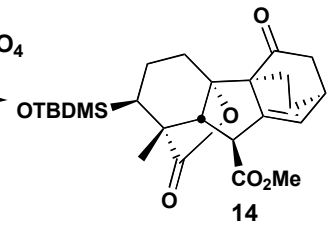
90%



i. $NaClO_2$, NaH_2PO_4
H_2O/*t*-BuOH

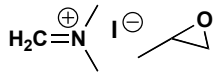
ii. 2,6-lutidine
CF_2CF_3OH

95%



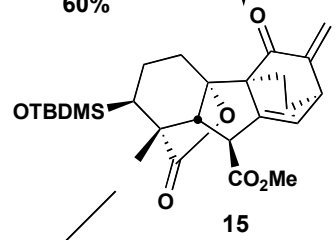
14

i. Et_3N, TMSCL, LDA
ii. (*i*-Pr)$_2$NEt, MeI



iii. aq. K_2CO_3

60%

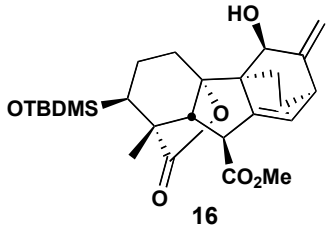


15

i. HF-Py
ii. PDC
iii. $NaBH_4$
iv. LiOH

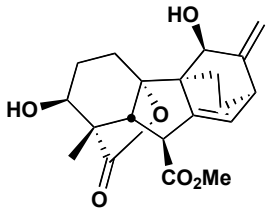
$NaBH_4$

91%

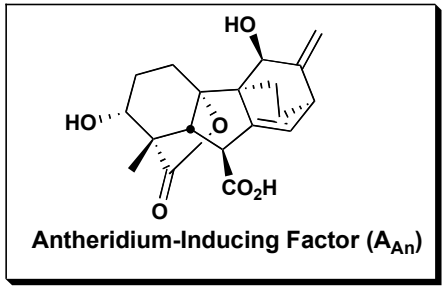


16

HF-Py



Originally Proposed structure (methyl ester)



Antheridium-Inducing Factor (A_{An})