SYNTHESIS OF SOME COMPLEX MOLECULES

Syllabus

Application of the above in the synthesis of following compounds:

Camphor
Longifoline
Cortisone
Reserpine
Vitamin D
Juvabione
Aphidicolin and
Fredericamysin A

1

The name *organic chemistry* came from the word organism.

Prior to 1828, all organic compounds had been obtained from organisms or their remains.

The scientific philosophy back then was that the synthesis of organic compounds could only be produced within living matter while inorganic compounds were synthesized from non-living matter.

A theory known as *"Vitalism"* stated that a "vital force" from living organisms was necessary to make an organic compound.

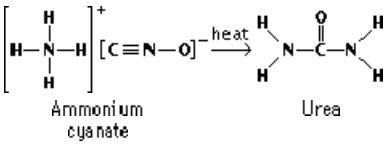
In 1828, a German chemist Friedrich Wöhler (1800-1882) amazed the science community by using the inorganic compound ammonium cyanate, NH_4OCN to synthesize urea, NH_2CONH_2 an organic substance found in the urine of many animals.

This led to the disappearance of the *"Vitalism"* theory.

2

TOTAL SYNTHESIS IN THE NINETEENTH CENTURY

- The birth of total synthesis occurred in the nineteenth century.
- Synthesis of Urea in 1828 marks the beginning of organic synthesis.



Ammonium cyanate — Urea

- The synthesis of acetic acid from elemental carbon by Kolbe in 1845 is the second major achievement in the history of total synthesis.

3

- But perhaps, after urea, the most spectacular total synthesis of the nineteenth century was that of (+)-glucose by E. Fischer. With its oxygen-containing monocyclic structure (pyranose) and five stereogenic centers (four controllable), glucose represented the state-of-the-art in terms of target molecules at the end of the nineteenth century.
- E. Fischer became the second winner of the Nobel Prize for chemistry (1902), after J. H. van't Hoff (1901).

Emil Fischer

4

TOTAL SYNTHESIS IN THE TWENTIETH CENTURY

•The twentieth century has been an age of enormous scientific advancement and technological progress.

•To be sure, we now stand at the highest point of human accomplishment in science and technology, and the twenty-first century promises to be even more revealing and rewarding.

•Advances in medicine, computer science, communication, and transportation have dramatically changed the way we live and the way we interact with the world around us.

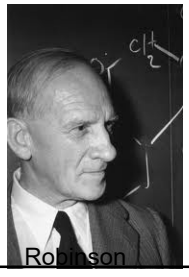
•Synthetic organic chemistry is perhaps the most expressive branch of the science of chemistry in view of its creative power and unlimited scope.

5

The Pre-World War II Era

•Some of the most notable examples of total synthesis of this era are α-terpineol (Perkin, 1904), camphor (Komppa, 1903; Perkin, 1904), tropinone (Robinson, 1917; Willstätter, 1901), haemin (H. Fischer, 1929), pyridoxine hydrochloride (Folkers, 1939), and equilenin (Bachmann, 1939).

•Particularly impressive were Robinson's one-step synthesis of tropinone (1917) from succindialdehyde, methylamine and acetone dicarboxylic acid and H. Fischer's synthesis of haemin.


Robinson


Richard Willstatter


H. Fischer

6

The Woodward Era

•In 1937 and at the age of 20, R. B. Woodward became an assistant professor in the Department of Chemistry at Harvard University where he remained for the rest of his life.

•The following compounds are amongst his most spectacular synthetic achievements: quinine (1944), patulin (1950), cholesterol and cortisone (1951), lanosterol (1954), lysergic acid (1954), strychnine (1954), reserpine (1958), chlorophyll a (1960), colchicine (1965), cephalosporin C (1966), prostaglandin F2a (1973), vitamin B12 (with A. Eschenmoser) (1973) and erythromycin A (1981).

•If Robinson introduced the curved arrow to organic chemistry (on paper), Woodward elevated it to the sharp tool that it became for teaching and mechanistic understanding and predict the outcome of chemical reactions.

7

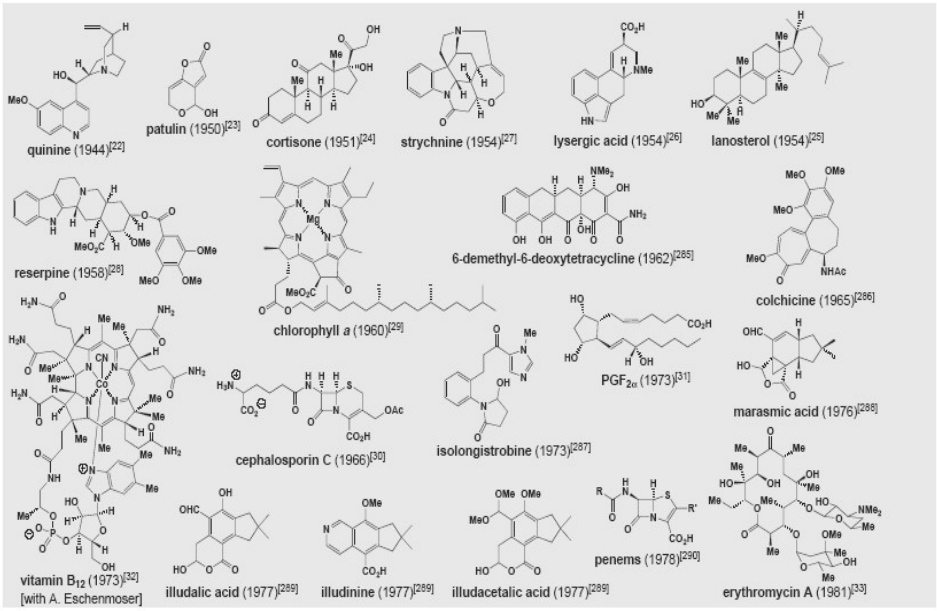


Figure 3. Selected syntheses by the Woodward Group (1944–1981).

8

The Corey Era

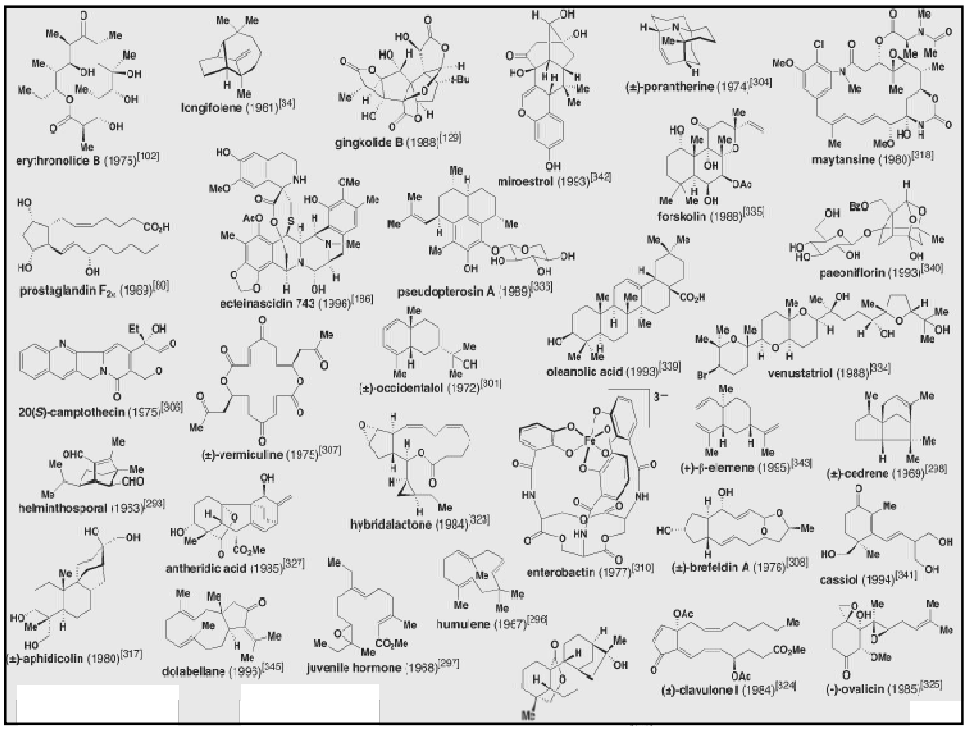
•In 1959 and at the age of 31, E. J. Corey arrived at Harvard as a full professor of chemistry from the University of Illinois.

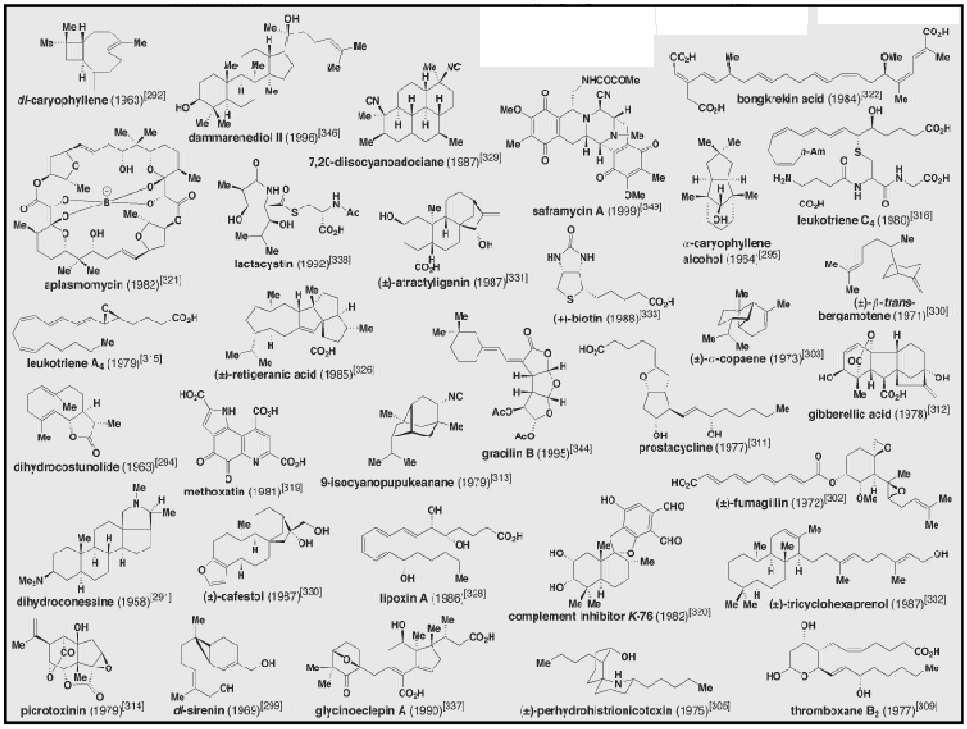
•Corey's pursuit of total synthesis was marked by two distinctive elements, **RETRO SYNTHETIC ANALYSIS** and the development of new synthetic methods as an integral part of the endeavor, even though Woodward (consciously or unconsciously) must have been engaged in such practices.

•It was Corey's 1961 synthesis of longifolene that marked the official introduction of the principles of retro synthetic analysis.

•Corey synthesized hundreds of natural and designed products within the thirty-year period stretching between 1960 and 1990, the year of his Nobel Prize.

9





- In addition to the Woodward and Corey schools, a number of other groups contributed notably to this rich period for total synthesis are G. Stork, A. Eschenmoser and Sir D. H. R. Barton.
- The Stork and Eschenmoser hypothesis for the stereospecific course of biomimetic cation cyclizations, such as the conversion of squalene into steroidal structures, stimulated much synthetic work (for example, the total synthesis of progesterone by W. S. Johnson, 1971).
- Stork's elegant total syntheses (for example, steroids, prostaglandins, tetracyclins) decorate beautifully the chemical literature and his useful methodologies (for example, enamine chemistry, anionic ring closures, radical chemistry, tethering devices) have found important and widespread use in many laboratories and industrial settings.

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•Similarly, Eschenmoser's beautiful total syntheses (for example, colchicine, corrins, vitamin B12, designed nucleic acids).

•His exquisite total synthesis of vitamin B12 (with Woodward), in particular, is an extraordinary achievement.

Gilbert Stork

Albert Eschenmoser

DHR Barton

13

Harvard University

University of Cambridge

14

There are three main branches of Organic Chemistry:

- Reaction mechanism
- Stereochemistry
- Organic Synthesis

Synthesis of a molecule is the central area of Organic Chemistry where the Chemist's art & imagination are involved in two parts-

- Proper Planning by Disconnection techniques (or Retrosynthetic pathway) of target molecules
- Chemical Instruments which are
  - Methods of C-C, C-N & N-N Bond formation by using various Name Reactions & Rearrangements
  - Protection & Deprotection of Functional groups/position/ring
  - Activation & Deactivation of Functional groups/position

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- Ring closure – Ring opening
- Ring expansion – Ring contraction
- Dehydrating agents
- Condensing agents

- **The ideal synthesis of an organic molecule involves**
  - Easily available cheap & most logical starting material
  - Have least number of steps
  - Highest possible overall yield
  - Highest purity
- **Synthesis of an Organic molecule is of two types**
  - For academic interest i.e. academic pleasure
  - Economic & commercial interest, most popular

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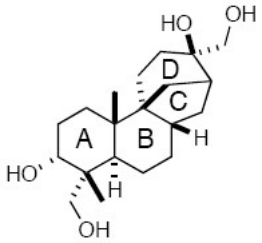
SYNTHESIS OF APHIDICOLIN

Aphidicolin is defined as a tetracyclic diterpene antibiotic with antiviral and antimitotical properties.

Isolated from the fungus *Cephalosporium aphidicola*.

Structure determined by X-ray crystallography and chemical degradation.

Synthetic challenges includes 8 stereocenters, especially the two adjacent chiral quaternary centers.



(+)-Aphidicolin

17

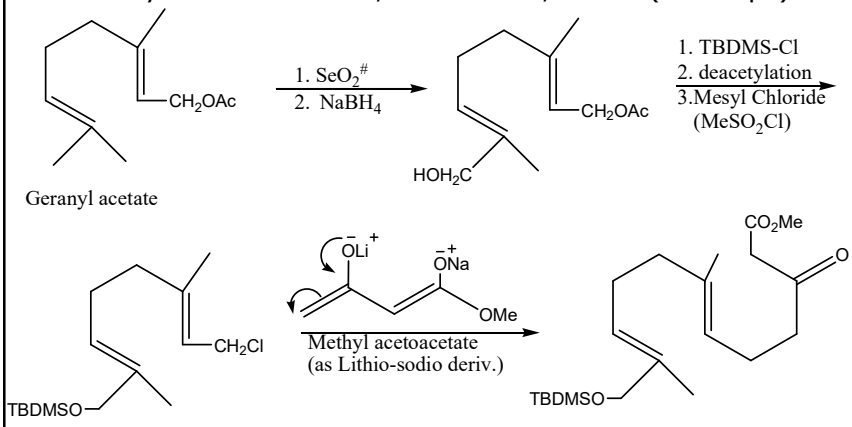
First shown to be active against DNA viruses, including Herpes simplex both in vitro and in the rabbit eye.

The drug may be useful for controlling excessive cell proliferation in patients with cancer, psoriasis (a chronic autoimmune disease) or other dermatitis with little or no adverse effect upon non-multiplying cells.

Pharmacological action: Antiviral agents, enzyme inhibitors.

18

EJ Corey et al. JACS 102, 1742-1744, 1980. (34 Steps)

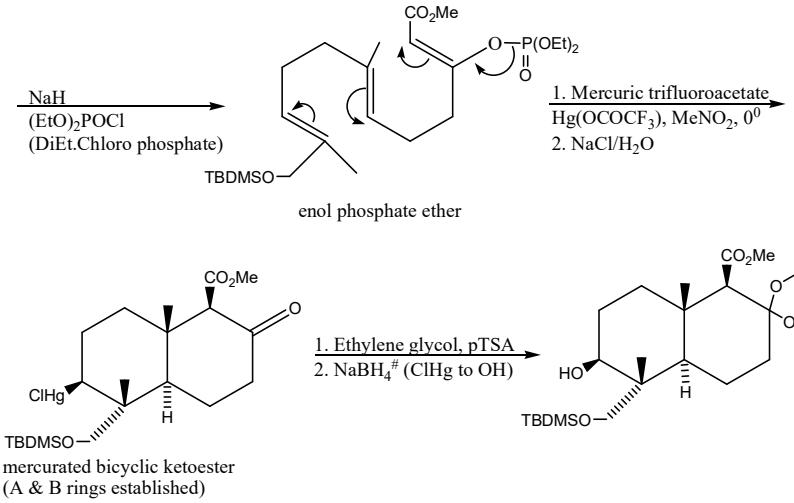


#SeO_2: 1. Oxidation of reactive -CH_3 & -CH_2 to aldehyde & ketone
2. Oxidation of -CH_2-CO— to -CO-CO—

$NaBH_4$: It is mild reducing agent than LAH, -CO or -CHO to -OH without touching the other reduciable gps like -COOR, epoxides, lactones, -COOH, -CN, -NO_2.

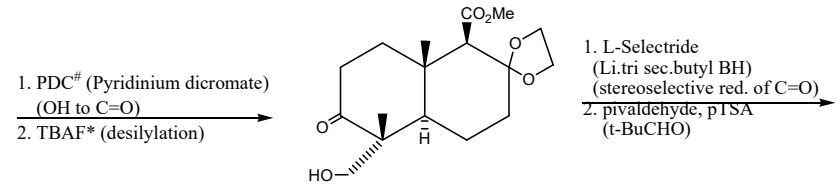
Can be used in protic solvents, therefore used widely in carbohydrate chemistry

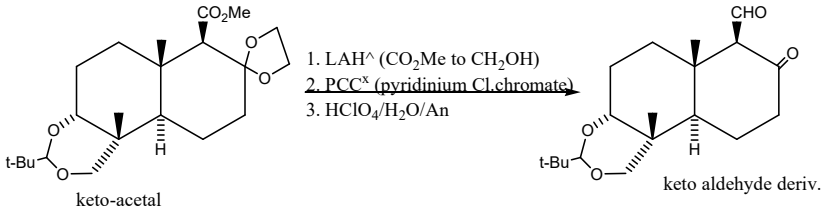
19



NaH, a strong base as proton abstractor, most notably is employed to deprotonate carbon acids such as 1,3-dicarbonyls

20





keto-acetal

keto aldehyde deriv.

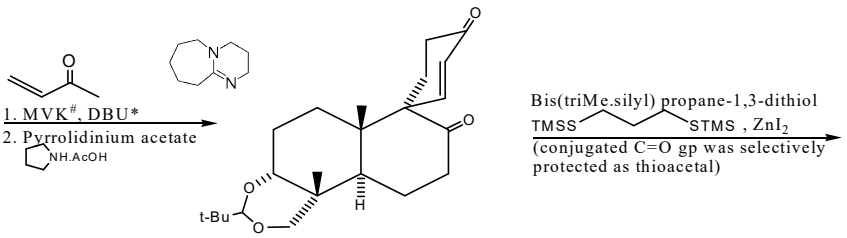
#PDC: $(C_5H_5NH)_2Cr_2O_7$, Cornforth Reagent, oxidises -OH to -CHO or -CO and less acidic than PCC

*Bu_4NF, a quarternary ammonium salt, a source of F^- ion to remove silyl ethers, also used as PTC and as a mild base. Since F^- is a strong H-bond acceptor, it is difficult to dehydrate sample, heating to 77^0C even at reduced pressure decomposes to hydrogen difluoride salt.

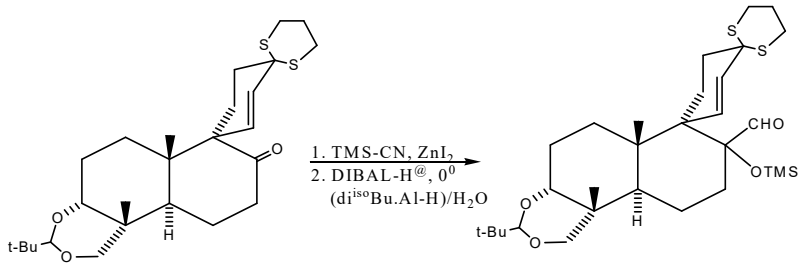
^LAH for reduction of RCOOR, -COOR to $-CH_2OH$ and $-CONH_2$ to $-CH_2NH_2$ in non aqueous solvents (unlik $NaBH_4$) but more poweful than $NaBH_4$ due to weaker Al-H bond than B-H bond in $NaBH_4$.

XPCC oxidises pri. -OH to -CHO & sec. -OH to ketone without further oxidation to acid. A disadvantage is that PCC is toxic to handle.

21



Robinson spiroannulation pdt.

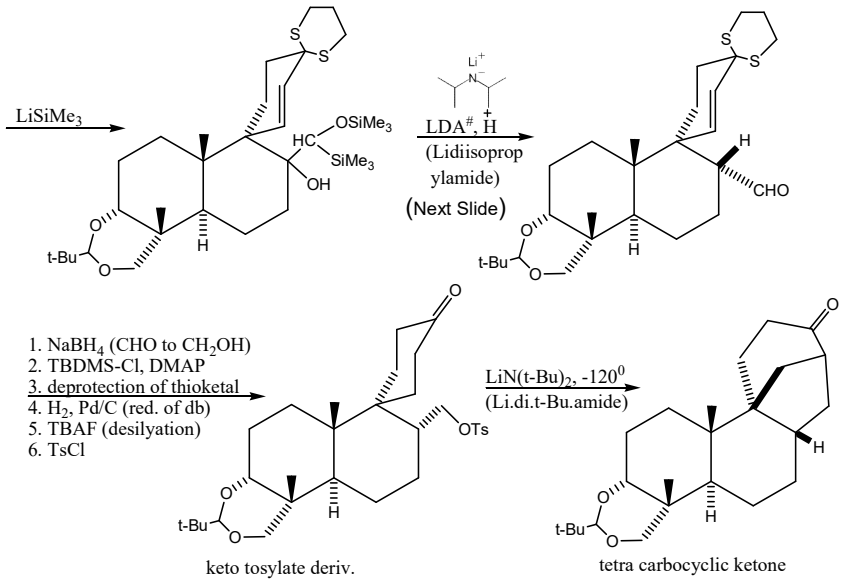


#Act as an alkylating agent since it is effective Michael Acceptor

*1,8-diazabicyclo[5.4.0] undec-7-ene. It is used in organic synthesis as a catalyst and complexing ligand and non-nucleophilic base.

@Reducing -COOR & -CN to-CHO, it reacts slowly with electron deficient compounds but more quickly on electron rich compounds, a electrophilic reducing agent

22

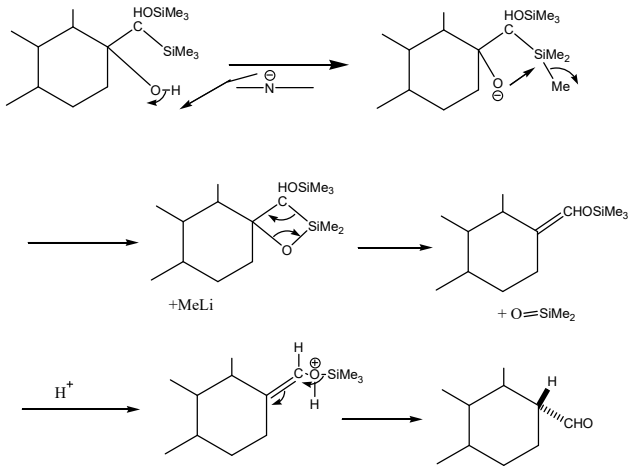


keto tosylate deriv.

tetra carbocyclic ketone

#LDA is a strong base used in deprotonation of weakly acidic compounds (abstract proton from activated -CH_3 & -CH_2 gps)

23



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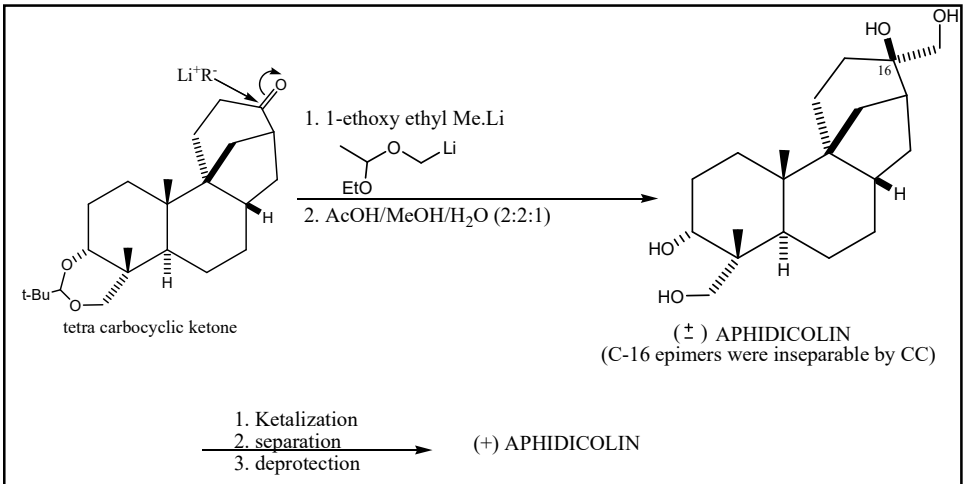


tetra carbocyclic ketone

(±) APHIDICOLIN
(C-16 epimers were inseparable by CC)

1. Ketalization
2. separation
3. deprotection

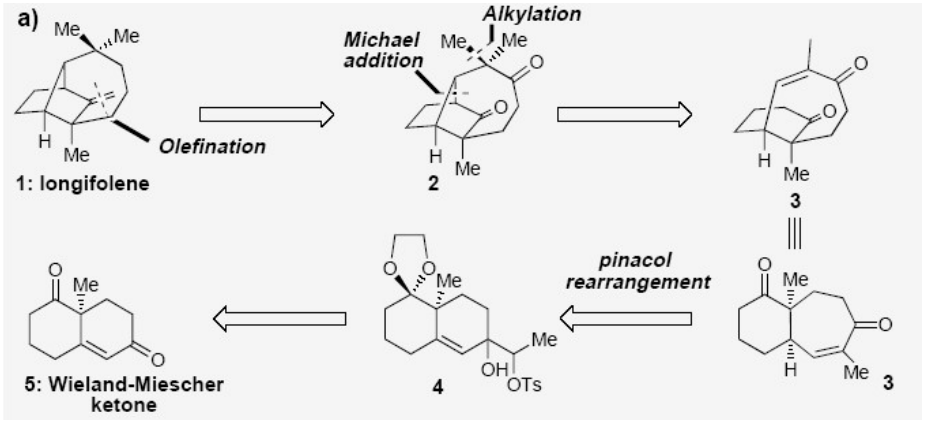
(+) APHIDICOLIN

25

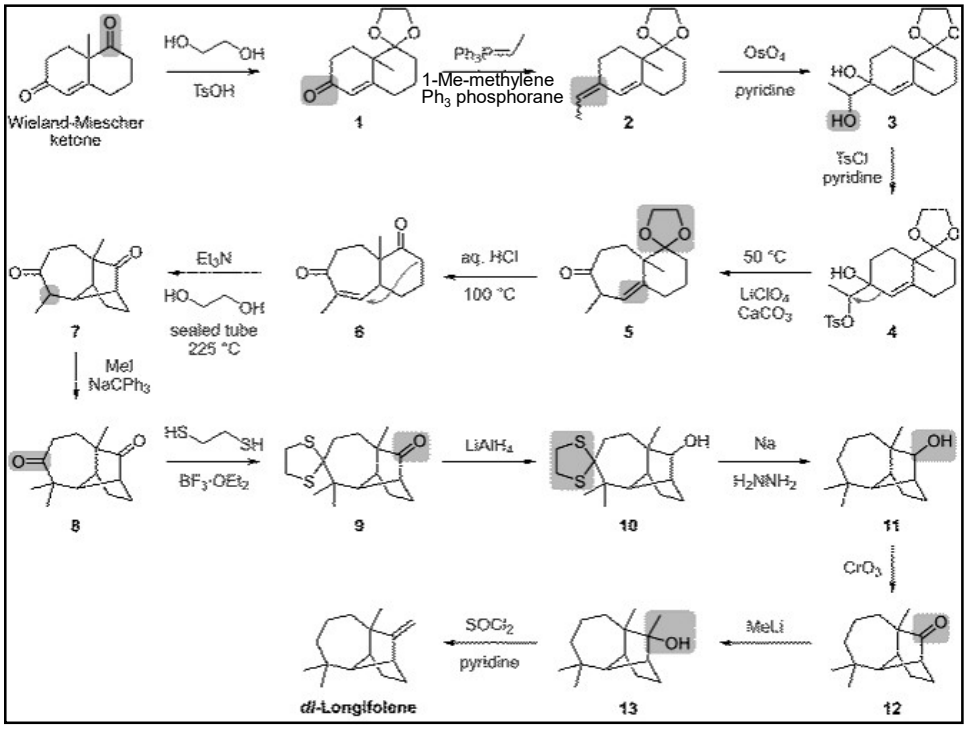
SYNTHESIS OF LONGIFOLENE (1961)

- The publication of the total synthesis of longifolene in 1961 by Corey et al. is of historical significance because Corey laid out the foundation of his systematic approach to retro synthetic analysis.
- Corey's longifolene synthesis exemplifies the identification and mental disconnection of strategic bonds for the purposes of simplifying the target structure.
- The total synthesis of longifolene itself, involves a Wittig reaction, an osmium tetraoxide mediated dihydroxylation of a double bond, a ring expansion, and an intramolecular Michael-type alkylation to construct the longifolene skeleton.

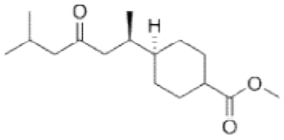
26

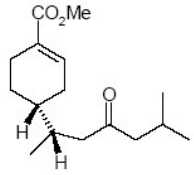

a)
Alkylation
Michael addition
Olefination
1: longifolene
2
3
pinacol rearrangement
5: Wieland-Miescher ketone
4
3

27


Wieland-Miescher ketone
TsOH
1
1-Me-methylene
Ph3 phosphorane
2
OsO4
pyridine
3
TsCl
pyridine
4
50 °C
LiClO4
CaCO3
5
aq. HCl
100 °C
6
Et3N
sealed tube
225 °C
7
MeI
NaCPh3
8
BF3·OEt2
9
LiAlH4
10
Na
H2NNH2
11
CrO3
12
MeLi
13
SOCl2
pyridine
di-Longifolene

Synthesis of the Natural Product Juvabione





R-(+)-Juvabione

•Juvabione is a biologically active compound that naturally occurs in the resin of balsam fir trees *(Abies balsam)*.

•The resin of this tree native to Canada and the North-East of the United States is known as Canada Balsam, which is used to preserve microscopy slides in biology, and forms the basis of glass scratch repair paste.

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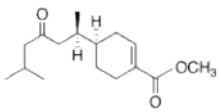
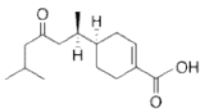
• **Juvabione** is the methyl ester of **todomatuic acid**, both of which are sesquiterpenes (C15) found in the wood of true firs of the genus *Abies*.

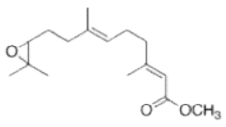
•Sesquiterpenes of this family are known as insect juvenile hormone analogues (IJHA) because of their ability to mimic juvenile activity in order to cut insect reproduction and growth.



(+)-Juvabione



Todomatuic Acid



Juvenile Hormone III

30

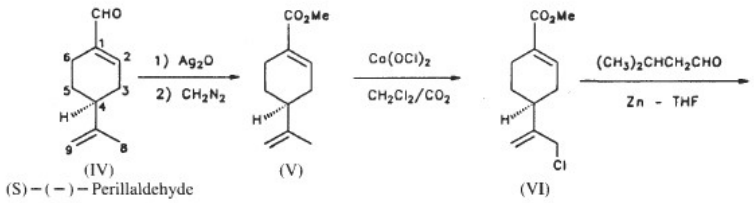
•The molecule itself is fairly straightforward, but it contains stereocentres.

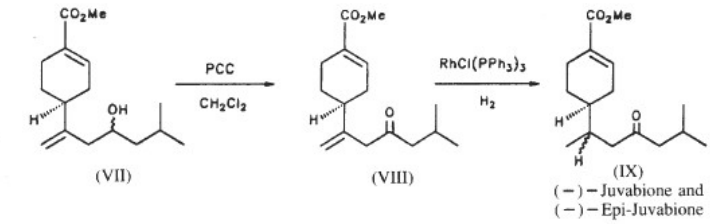
•The R-(+) isomer is biologically active, and it is easy enough to achieve this configuration by using natural raw materials in synthesis.

•Natural raw materials usually adapt R-(+) configuration, and for instance R-(+)-Limonene naturally contains the stereocentre of juvabione in its structure.

•S-(-)-juvabione has been synthesised using S-(-)-perillaldehyde, a compound derived from S-(-)-limonene. From this reaction it can be deduced that R-(+)-juvabione can be synthesised from the equivalent natural material, R-(+)-perillaldehyde:

31

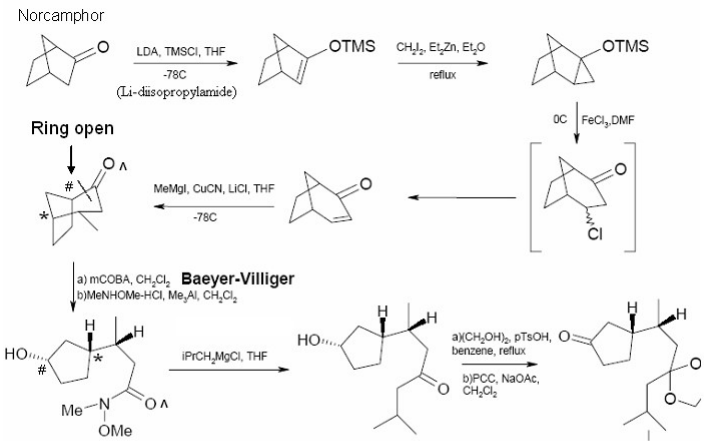




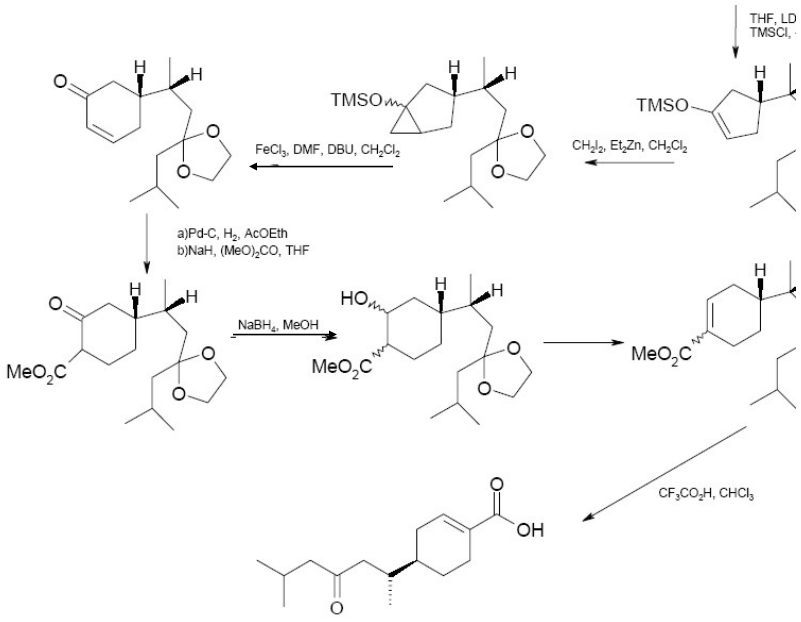
•This is a nice, clean and easy synthetic route.

•The most recent method describes the synthesis from racemic norcamphor. The beauty of this reaction is, that the reaction can yield either enantiomer of juvabione, depending on the reaction condition:

32


Norcamphor
LDA, TMSCl, THF
-78C
(Li-diisopropylamide)
OTMS
CH_2I_2, Et_2Zn, Et_2O
reflux
OTMS
0C
$FeCl_3$,DMF
Ring open
MeMgI, CuCN, LiCl, THF
-78C
Cl
a) mCOBA, CH_2Cl_2
b)MeNHOMe-HCl, Me_3Al, CH_2Cl_2
Baeyer-Villiger
HO
Me
N
OMe
$iPrCH_2MgCl$, THF
a)$(CH_2OH)_2$, pTsOH, benzene, reflux
b)PCC, NaOAc, CH_2Cl_2

1


THF, LD
TMSCl,
TMSO
TMSO
CH_2I_2, Et_2Zn, CH_2Cl_2
$FeCl_3$, DMF, DBU, CH_2Cl_2
a)Pd-C, H_2, AcOEth
b)NaH, $(MeO)_2CO$, THF
MeO_2C
$NaBH_4$, MeOH
HO
MeO_2C
MeO_2C
CF_3CO_2H, $CHCl_3$
OH
(+)-juvabione

36

SYNTHESIS OF RESERPINE (1958)

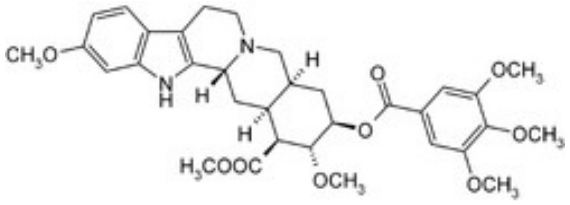
•Reserpine, a constituent of the Indian snakeroot *Rauwolfia serpentina (Sarpgandha)*, is an alkaloid with curative properties for the treatment of hypertension, as well as nervous and mental disorders.

•Reserpine was isolated in 1952 and yielded to structural elucidation in 1955 (Schlittler and co-workers) and to total synthesis in 1958 (Woodward et al.).

•The first total synthesis of reserpine, considered by some as one of Woodward's greatest contributions to synthesis.

37

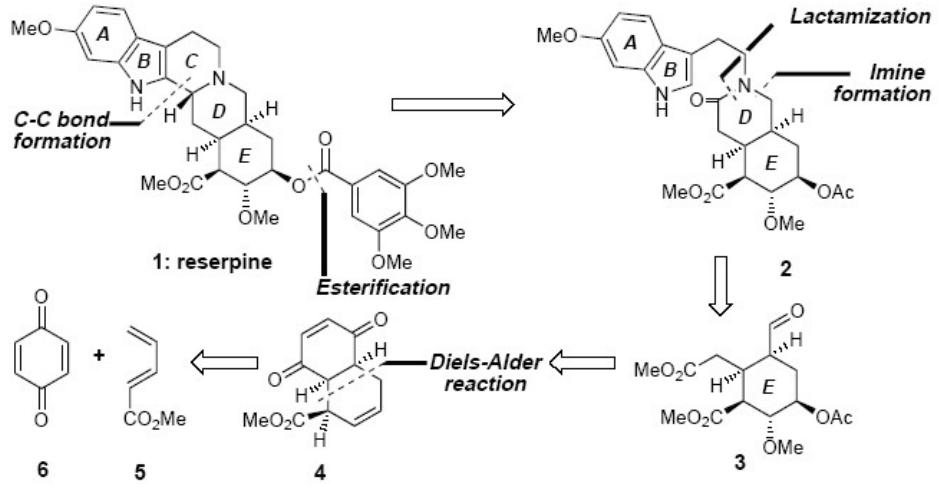
- It had been used for centuries in India for the treatment of insanity as well as fever and snakebites.
- Induces a period of sedation when intravenously injected into animals
- because of the development of better drugs for these purposes and because of its numerous side-effects, it is rarely used today.

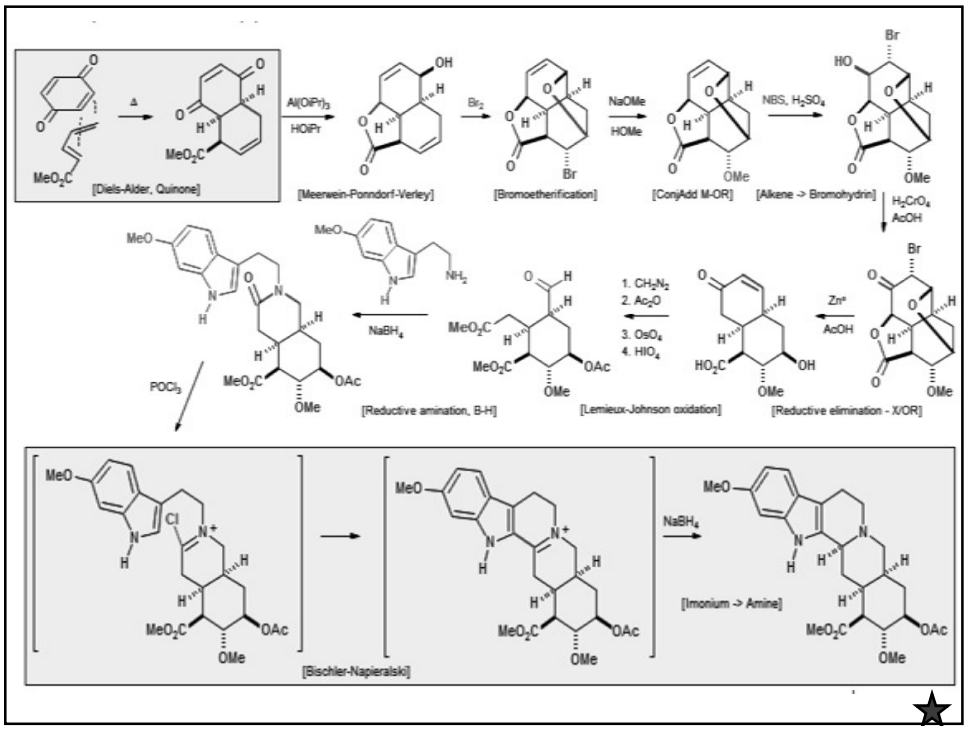


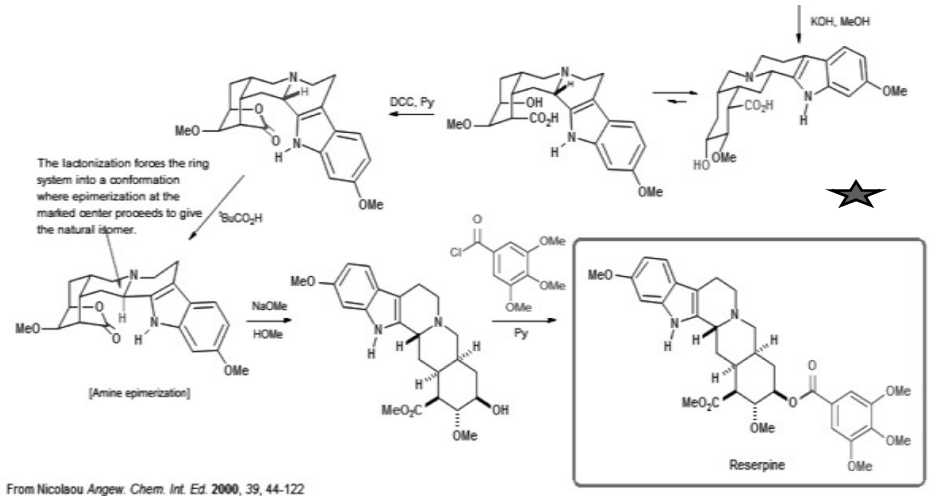
methyl-11,17-α -dimethoxy-18β-[(3,4,5-trimethoxybenzoyl) oxy]-3β,20-α -yohimban-16β-carboxylate

38

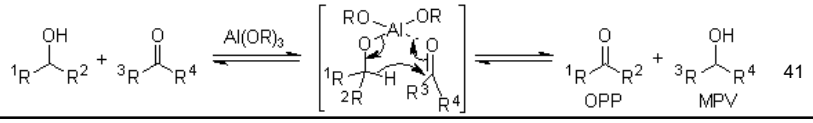
•Reserpine consisted of three parts: the indole (the AB unit), the trimethoxybenzene system, and the highly substituted E-ring cyclohexane.



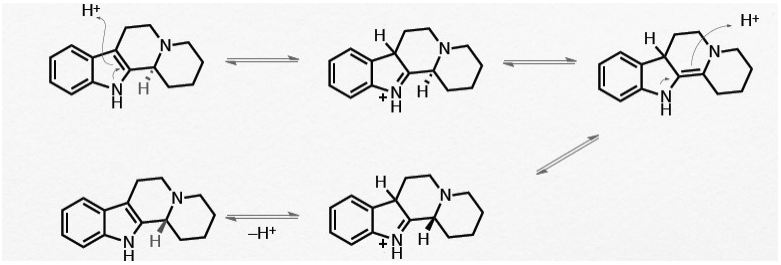




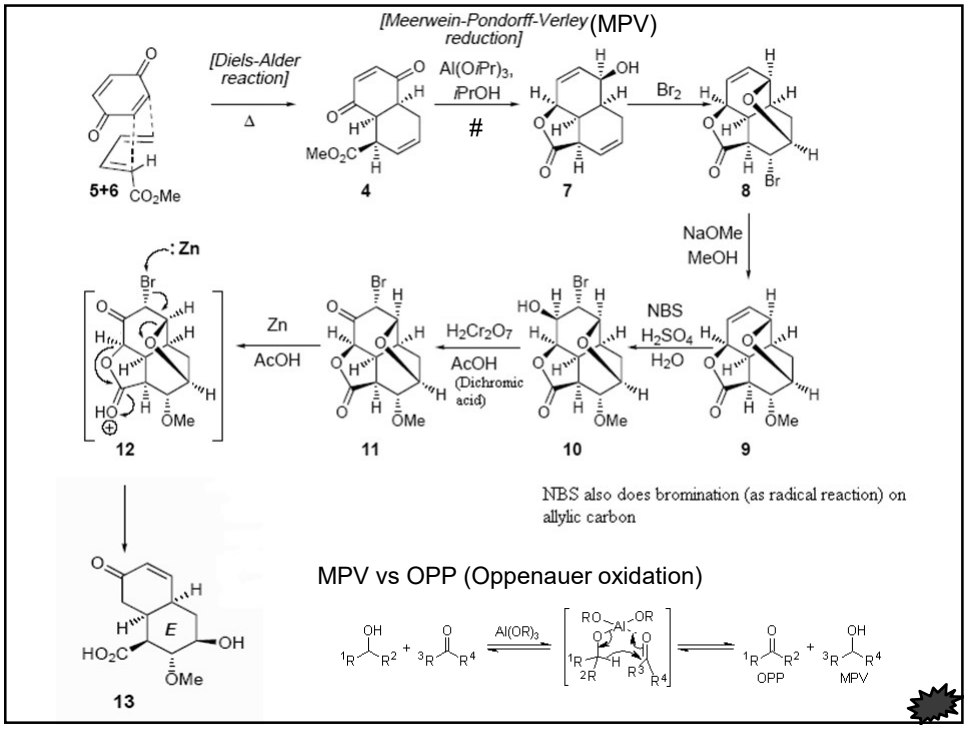
MPV (Meerwein Pondorff Valery Reduction) vs OPP (Oppenauer oxidation)

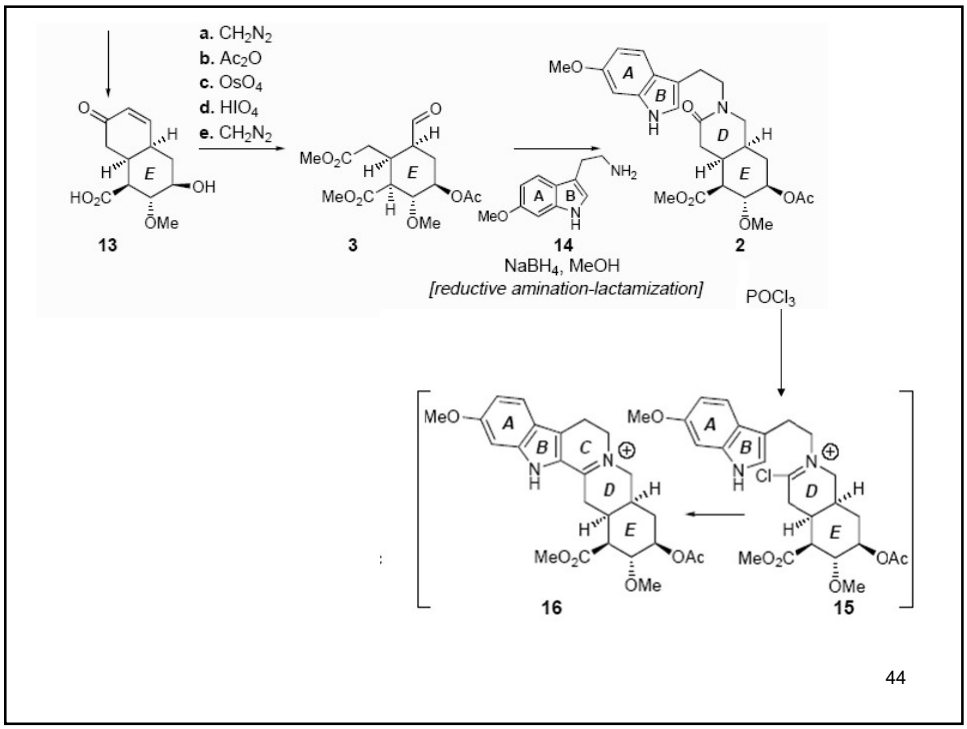


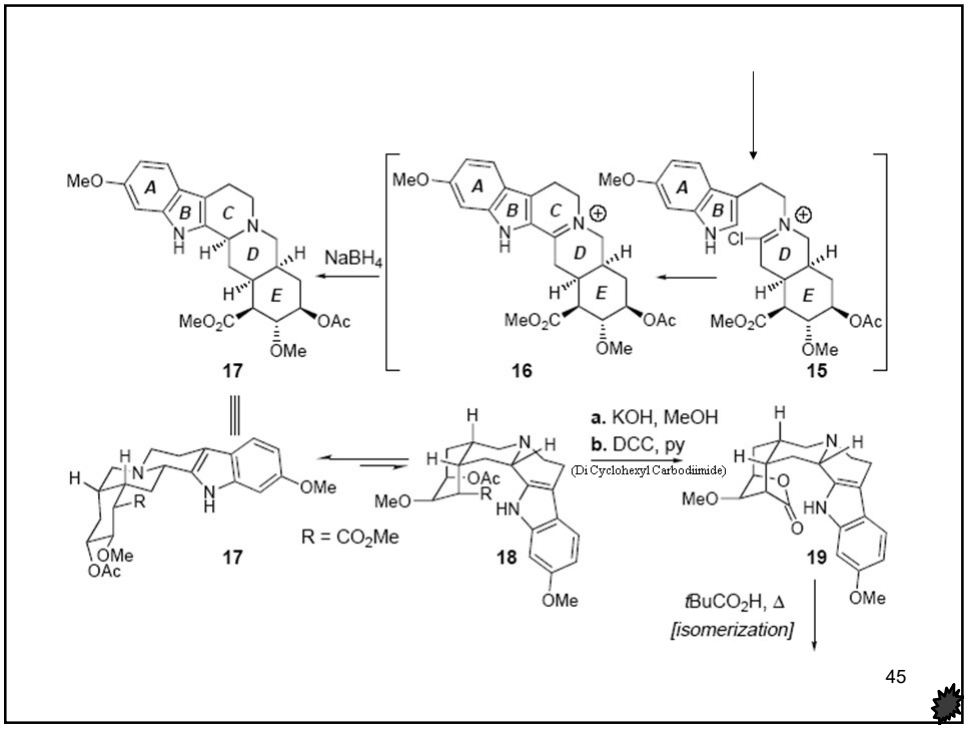
41

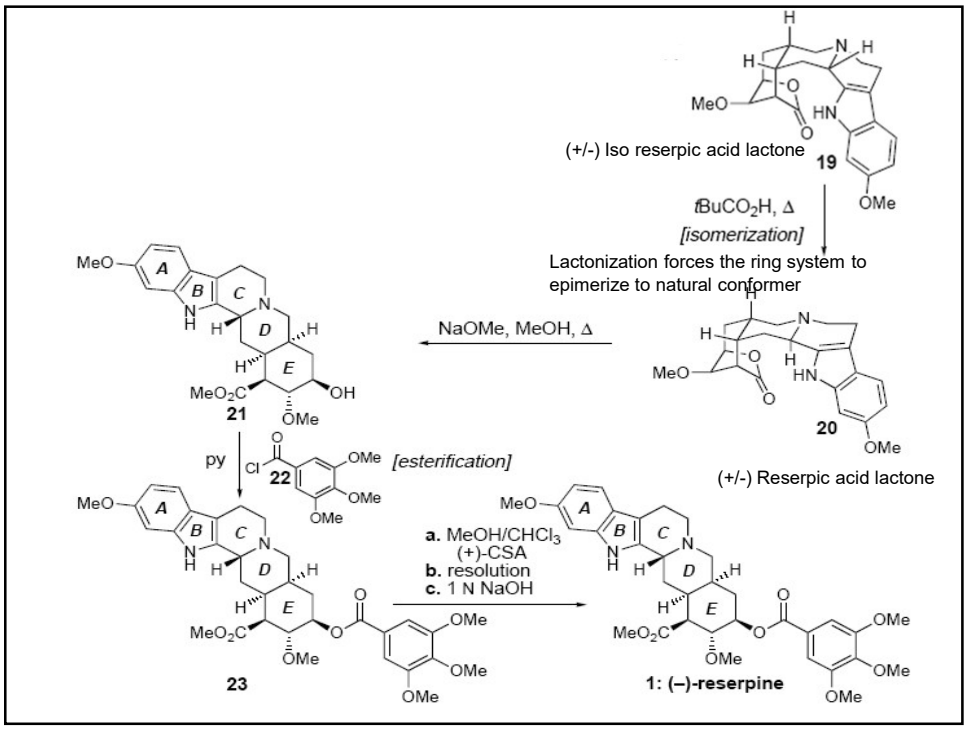


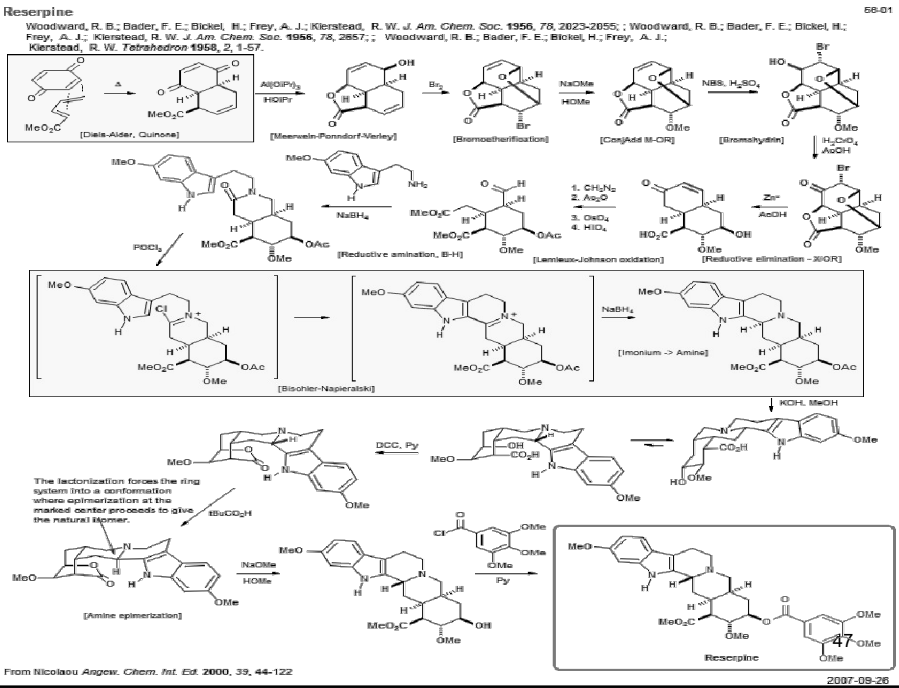
42


[Meerwein-Pondorff-Verley reduction] (MPV)
[Diels-Alder reaction]
Δ
Al(OiPr)3, iPrOH
#
Br2
NaOMe MeOH
NBS H2SO4 H2O
H2Cr2O7 AcOH (Dichromic acid)
Zn AcOH
5+6
4
7
8
9
10
11
12
13
NBS also does bromination (as radical reaction) on allylic carbon
MPV vs OPP (Oppenauer oxidation)
Al(OR)3
OPP
MPV

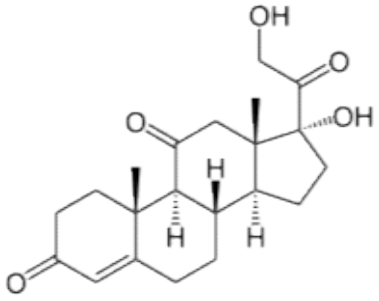

a. CH2N2
b. Ac2O
c. OsO4
d. HIO4
e. CH2N2
13
3
14
2
NaBH4, MeOH
[reductive amination-lactamization]
POCl3
16
15
44


NaBH4
17
16
15
a. KOH, MeOH
b. DCC, py
(Di Cyclohexyl Carbodiimide)
R = CO2Me
18
19
tBuCO2H, Δ
[isomerization]
45


(+/-) Iso reserpic acid lactone
19
tBuCO2H, Δ
[isomerization]
Lactonization forces the ring system to epimerize to natural conformer
NaOMe, MeOH, Δ
20
(+/-) Reserpic acid lactone
21
py
22
[esterification]
a. MeOH/CHCl3
(+)-CSA
b. resolution
c. 1 N NaOH
23
1: (–)-reserpine



SYNTHESIS OF CORTISONE



Cortisone (17-hydroxy-11-dehydrocorticosterone) is a steroid hormone.

In chemical structure, it is a corticosteroid closely related to corticosterone. It is used to treat a variety of ailments and can be administered intravenously, orally, intraarticularly or cutaneously.

Cortisone suppresses the immune system, thus reducing inflammation and attendant pain and swelling at the site of the injury. Risks exist, in particular in the long-term use of cortisone.

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Effects and uses

Cortisone and adrenaline are the main hormones released by the body as a reaction to stress. They elevate blood pressure and prepare the body for a fight response.

A cortisone injection can also be used to give short-term pain relief and reduce the swelling from inflammation of a joint, tendon in the joints of the knee, elbow and shoulder.

Cortisone may also be used to deliberately suppress immune response in persons with autoimmune diseases (Rheumatoid arthritis & Rheumatoid fever) or following an organ transplant to prevent transplant rejection.

Last, cortisone is a common treatment for a severe sore throat that occurs commonly with infectious mononucleosis (fever, sore throat and fatigue).

It is important to note that cortisone does not help lessen the duration of the virus, and is used purely to increase the comfort of a patient with trouble speaking or swallowing as a result of the mononucleosis-induced swollen throat.

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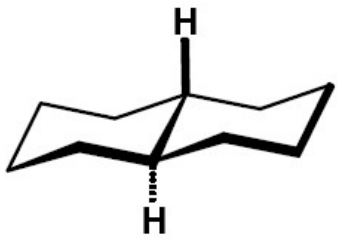
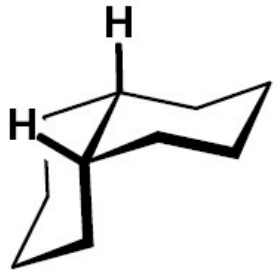
Configurational Isomers of decaline

- The six-membered rings are in fixed chair conformations
- Two cyclohexane rings can be joined in either a cis or a trans manner
- In cis-decalin, both groups at the ring-junction positions are on the same side of the two rings
- In trans-decalin, the groups at the ring junctions are on opposite sides



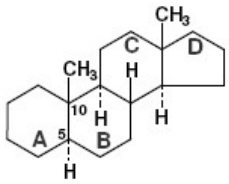
trans- configuration



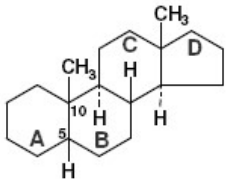
cis- configuration

50

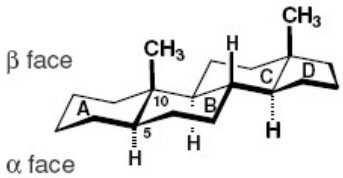
STEREOCHEMISTRY OF STEROIDS



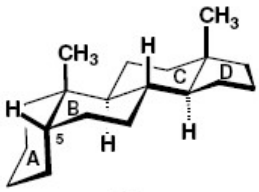
A/B *trans*
B/C, C/D *trans*



A/B *cis*
B/C, C/D *trans*



trans

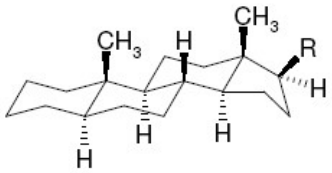


cis

51

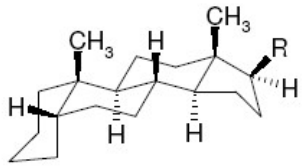
Configurational Isomers of Steroids

Three dimensional structure of three most common isomers



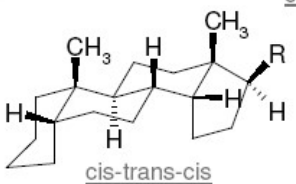
trans-trans-trans

sex hormones



cis-trans-trans

bile acids



cis-trans-cis

cardiac glycosides

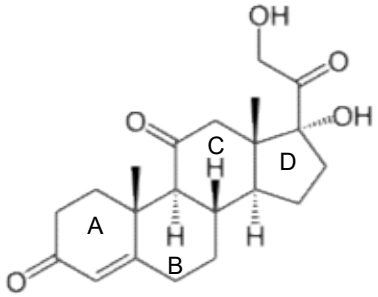
52

Side-effects

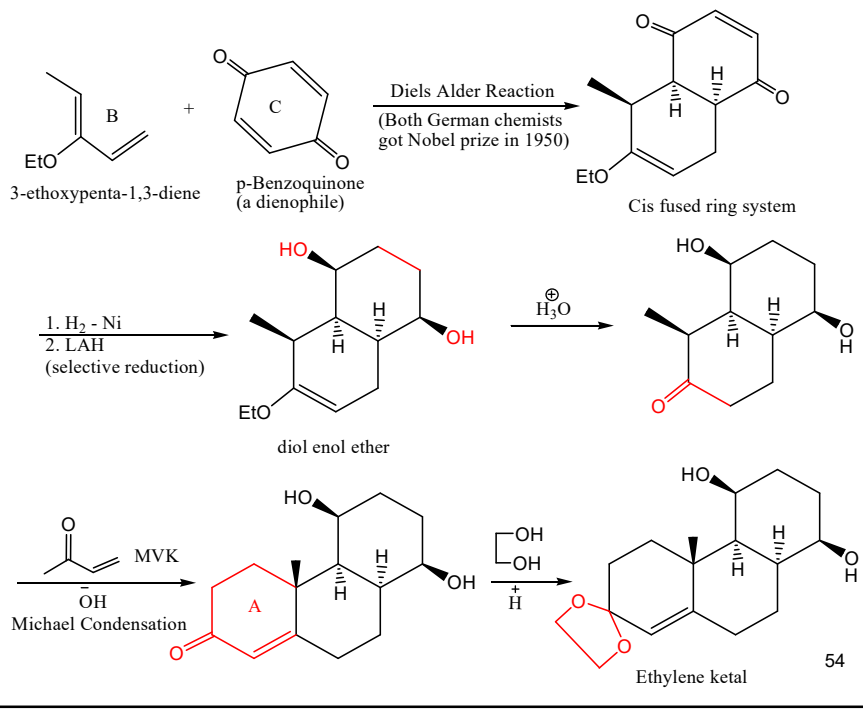
Oral use of cortisone has a number of potential side-effects: hyperglycemia, insulin resistance, diabetes mellitus, osteoporosis, anxiety, depression, cataracts and glaucoma among other problems.

Many partial synthesis are known but the total synthesis was given by Sarett (1952-53).

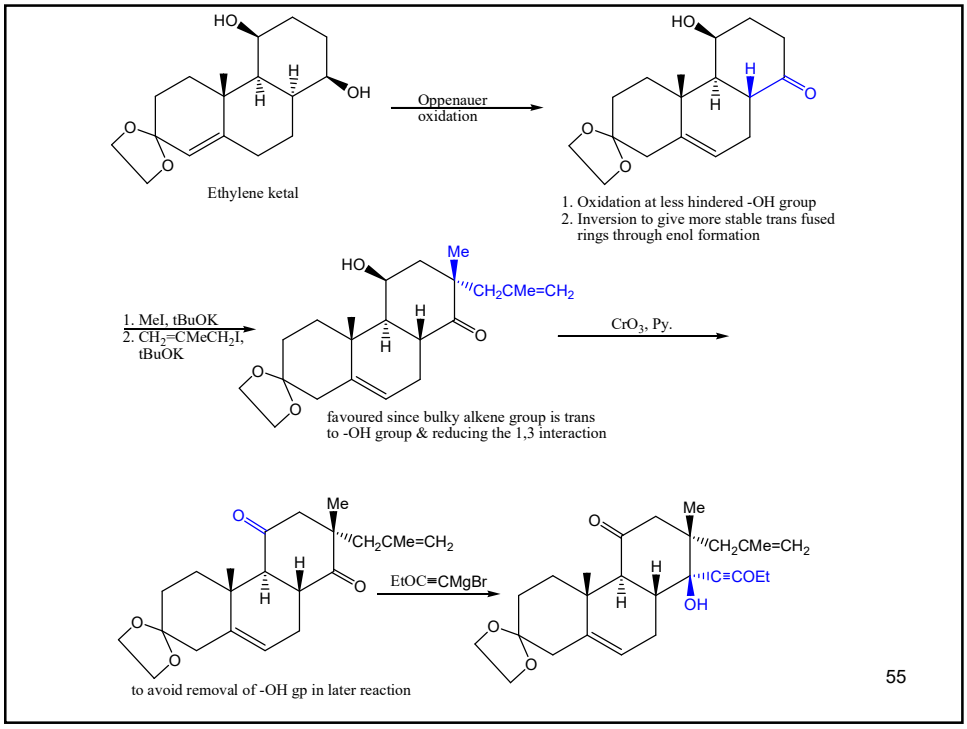
Type ring C ⟶ BC ⟶ ABC ⟶ ABCD

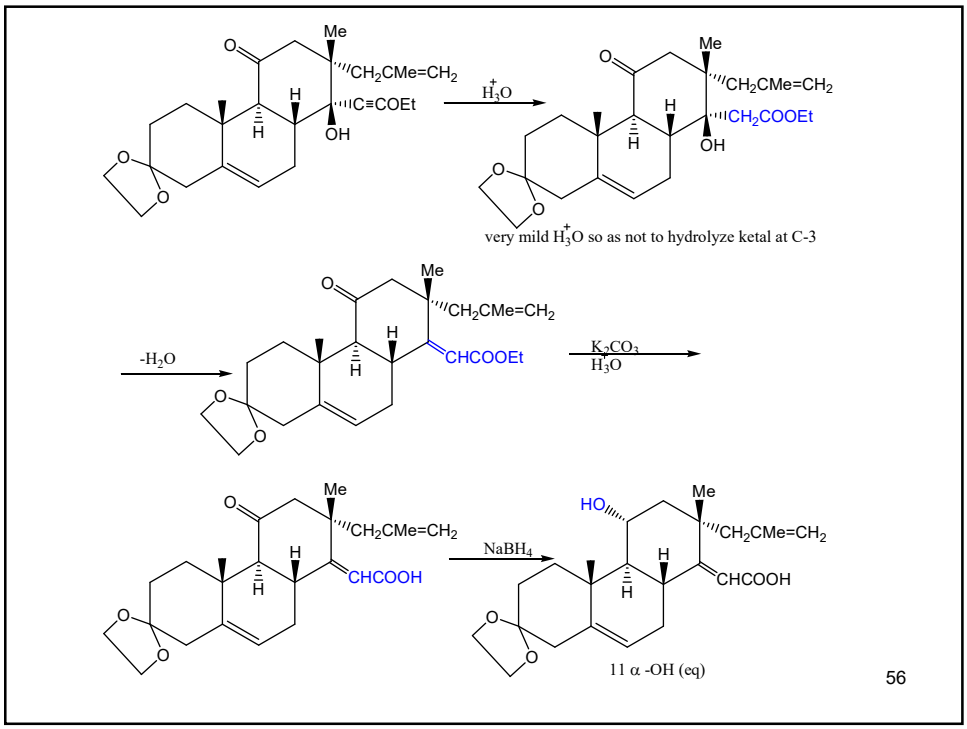


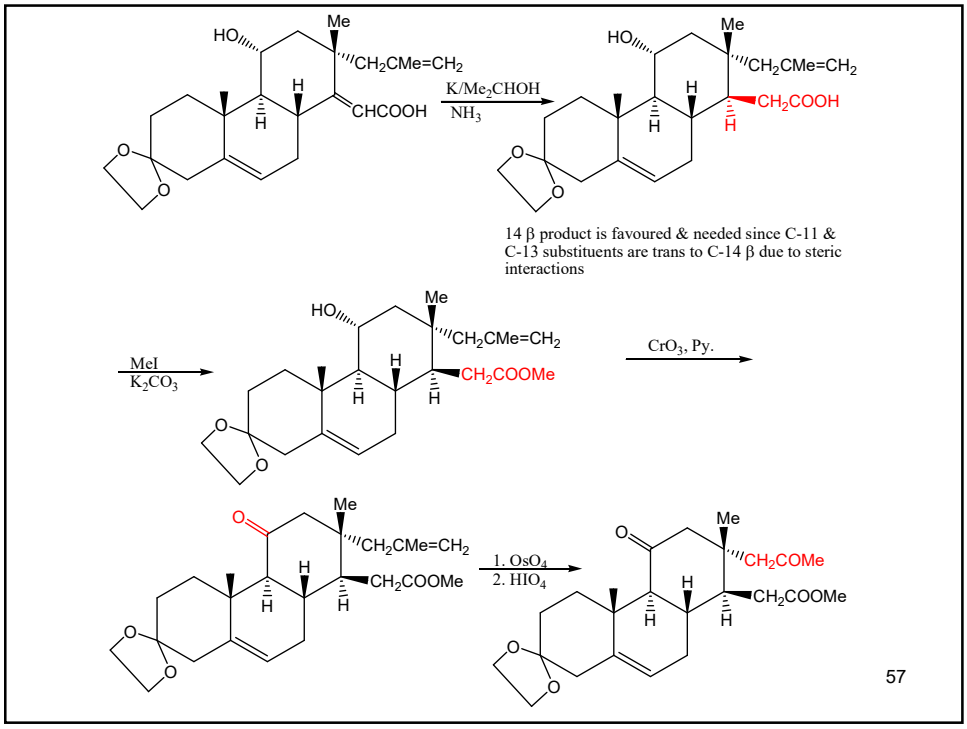
53

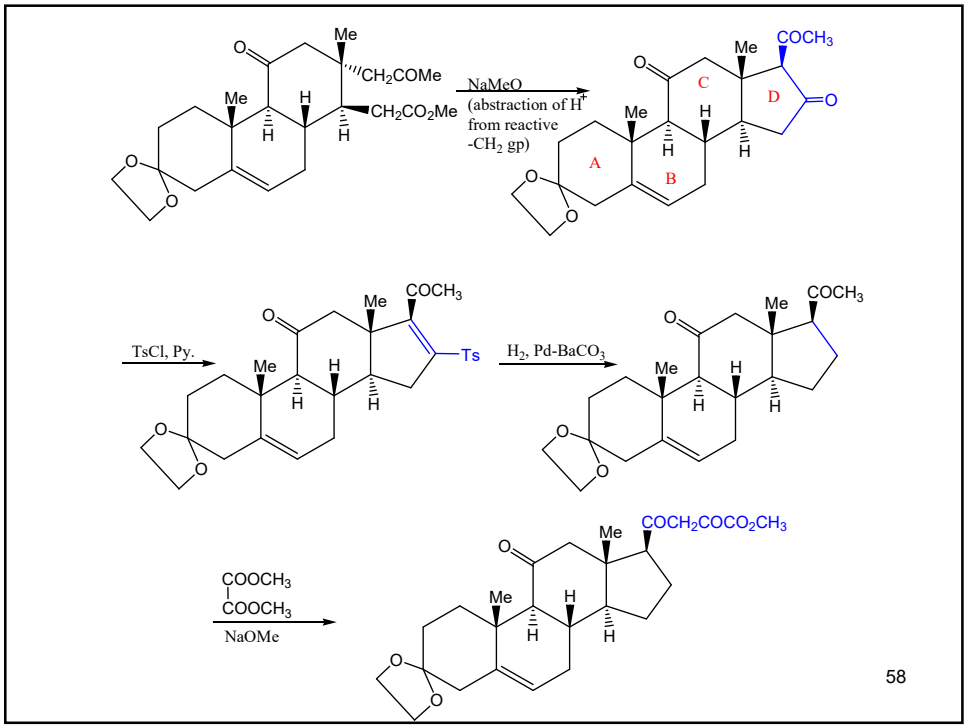


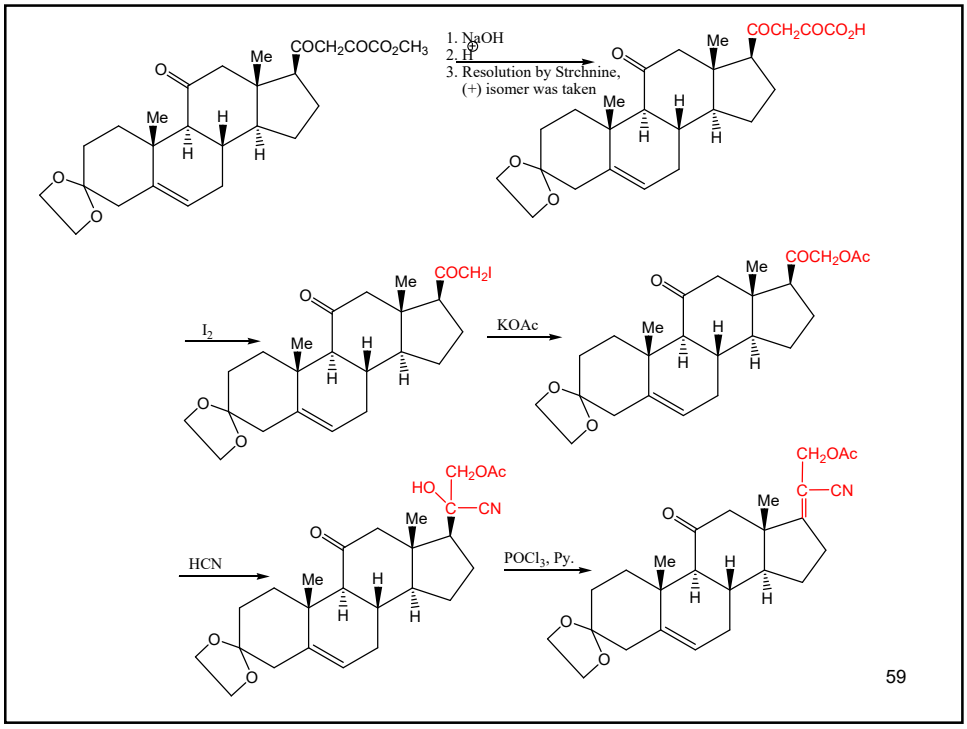
54

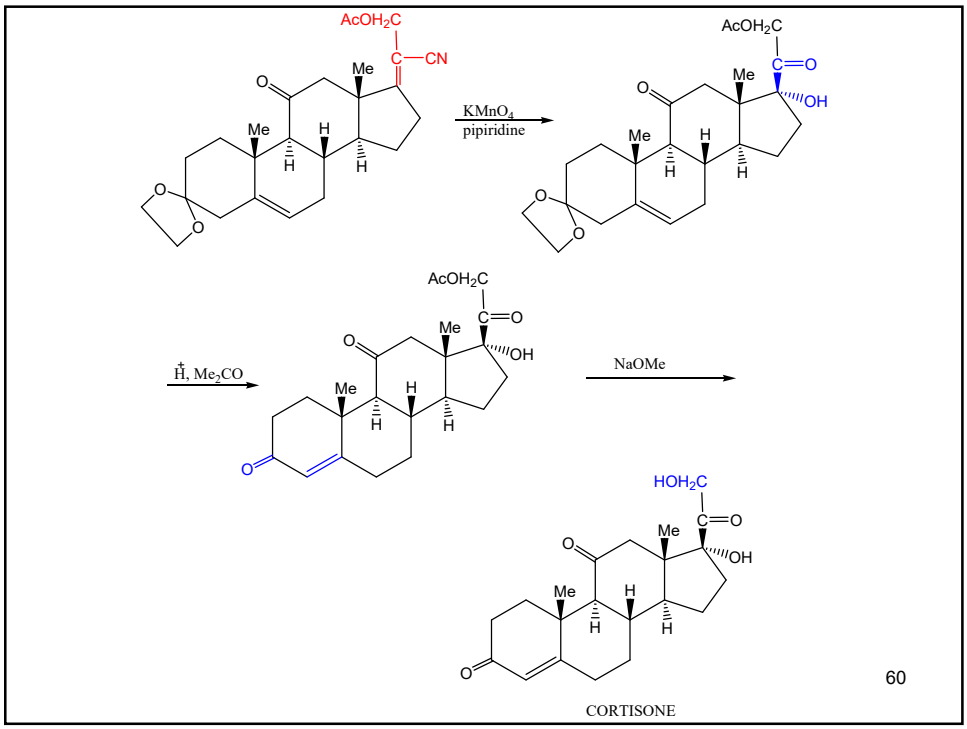

HO
OH
Oppenauer oxidation
Ethylene ketal
1. Oxidation at less hindered -OH group
2. Inversion to give more stable trans fused rings through enol formation
1. MeI, tBuOK
2. CH2=CMeCH2I, tBuOK
Me
CH2CMe=CH2
CrO3, Py.
favoured since bulky alkene group is trans to -OH group & reducing the 1,3 interaction
EtOC≡CMgBr
C≡COEt
to avoid removal of -OH gp in later reaction
55


CH2CMe=CH2
C≡COEt
OH
H3O+
CH2COOEt
very mild H3O+ so as not to hydrolyze ketal at C-3
-H2O
CHCOOEt
K2CO3
H3O
CHCOOH
NaBH4
HO
11 α -OH (eq)
56


HO
Me
CH2CMe=CH2
CHCOOH
K/Me2CHOH
NH3
CH2COOH
14 β product is favoured & needed since C-11 & C-13 substituents are trans to C-14 β due to steric interactions
MeI
K2CO3
CH2COOMe
CrO3, Py.
O
1. OsO4
2. HIO4
CH2COMe
57


CH2CO2Me
NaMeO
(abstraction of H+ from reactive -CH2 gp)
COCH3
C
D
A
B
TsCl, Py.
Ts
H2, Pd-BaCO3
COOCH3
COOCH3
NaOMe
COCH2COCO2CH3
58


COCH2COCO2CH3
1. NaOH
2. H+
3. Resolution by Strchnine,
(+) isomer was taken
COCH2COCO2H
I2
COCH2I
KOAc
COCH2OAc
HCN
HO
CH2OAc
C—CN
POCl3, Py.
59


AcOH2C
C—CN
KMnO4
pipiridine
C=O
OH
H+, Me2CO
NaOMe
HOH2C
CORTISONE
60

Angew. Chem. Int. Ed. 1999, 38, No. 5, 683-686

Asymmetric Total Synthesis of Fredericamycin A

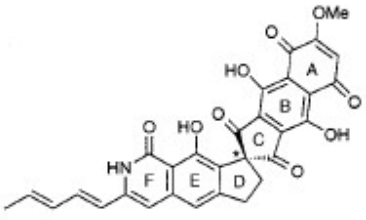
By Yasuyuki Kita et al.

•Fredericamycin A (1), isolated from ***Streptomyces griseus*** in 1981
•possesses potent antitumor activity

61

Its structure consists of two sets of peri-hydroxy tricyclic aromatic moieties

connected through a spiro quaternary carbon center,



fredericamycin A **1**

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•Its promising biological profile as well as its unprecedented unique structure has made it quite attractive as a lead compound for a novel type of chemotherapeutic drug for human cancers, and hence extensive attention is being focused on its total synthesis.
•In spite of the enormous efforts towards this goal, including the total syntheses of racemic Fredericamycin A by five research groups and a recently reported synthesis of optically pure Fredericamycin A by HPLC separation of a racemic intermediate of Fredericamycin A using a special chiral column.
•Kita et al. present the first asymmetric total synthesis of Fredericamycin A with definite absolute configuration of the spiro center, which elucidates the absolute configuration of natural Fredericamycin A, 17 years after its isolation.

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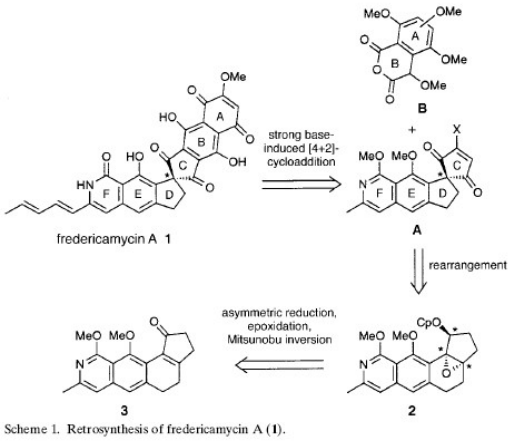
•Their synthetic strategy is based on the strong base-induced intermolecular cycloaddition of a suitably functionalized homophthalic anhydride (**B**) to an optically pure dienophile (**A**) corresponding to the CDEF moiety,
•in which the regiochemistry during the cycloaddition is known to be controlled by the substituent X on the dienophile.

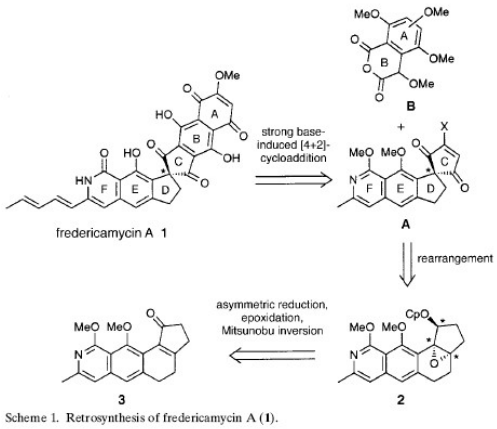


Scheme 1. Retrosynthesis of fredericamycin A (**1**).

64

The dienophile A could be prepared from the optically pure trans-epoxy camphanate (**2**) through the stereospecific rearrangement.

•Compd. **2** in turn could be prepared from the enone **3** by an asymmetric reduction of the keto group followed by the epoxidation of the olefin and Mitsunobu inversion of the hydroxy group.

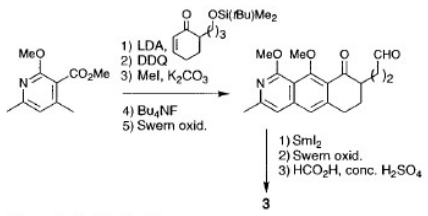


Scheme 1. Retrosynthesis of fredericamycin A (**1**).

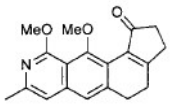
65

Synthesis of Fredricamysin A

The enone **3** was obtained from methyl 2-methoxy -4,6-dimethylpyridine-3-carboxylate.



Scheme 5. Synthesis of 3.

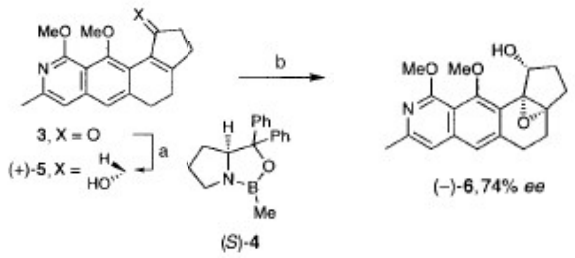


LDA (Li Diisopropyl Amide) is a strong base used for the deprotonation of weakly acidic compounds or abstract proton from reactive $-CH_3$ & $-CH_2$

DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone) is an oxidant for the dehydrogenation of alcohols, phenols and steroid ketones.

SmI_2 (Samarium Iodide) reduces –C=O to -OH

66

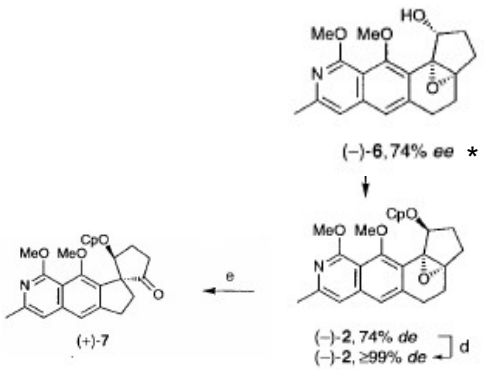


a) Chiral borane (S)-4, BH_3, Me_2S, THF, 0°C, 98%, gave (R)-Alcohol;

b) Sharpless oxidation afforded cis epoxy alcohol, $[VO(acac)_2]$, $tBuO_2H$, C_6H_6 , 0°C to rt, 81%;

Vanadyl acetylacetonate does epoxidation of allylic alcohol in combination with t-butyl hydroperoxide.

67



c) (-)CpOH (1*S*)-3-Oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid), Ph_3P, diethyl azodicarboxylate, toluene, 0°C to rt, under Mitsnobu Reaction gave a diastereomeric mixture of camphanate;
d) SiO_2 column chromatography, 59% from (-)-6;
e) BF_3. Et_2O, CH_2Cl_2 , 0°C, 94% required stereoselectivity of Spiro compd.;

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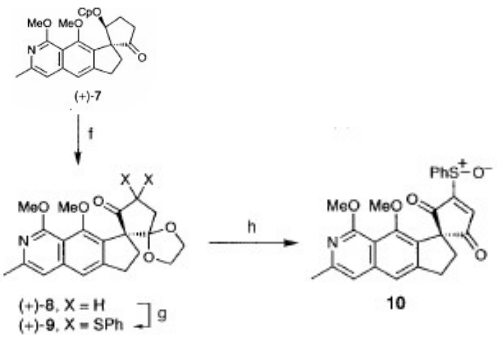

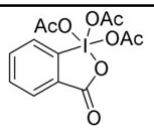

Dess Martin Periodinane (oxidising reagent)

f) 1. $(CH_2OTMS)_2$, TMSOTf, CH_2Cl_2 , 0°C to rt, 93%, 2. 10% NaOH, MeOH, rt, 97%, 3. Dess Martin periodinane, CH_2Cl_2 , rt, 98%; g) 1,1 Disulfenylation by $PhSSO_2Ph$, $LiN(TMS)_2$, THF, -78°C to rt, 98%; h) 1. Elimination of PhSH by 85% aq. CF_3CO_2H, 50°C, 92%, 2. Oxidation of sulfide by m-CPBA, CH_2Cl_2 , -40°C to rt, 93%.

(acac.acetylacetonate, Cp.(-)-camphanyl, m-CPBA.m-chloroperoxy benzoic acid, Tf.trifluoromethanesulfonyl, TMS.trimethylsilyl)

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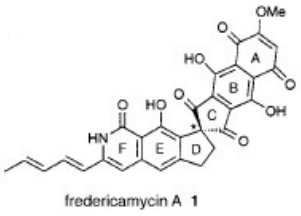
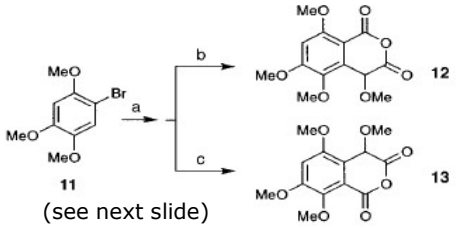
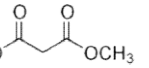
Synthesis of regioisomeric dine **12** and **13**



fredericamycin A **1**



(see next slide)



a) Dimethyl malonate, nBuLi, 2,2,6,6-tetramethylpiperidine, THF, -78°C, 3:2 mixture of regioisomers homophthalates, 58% in total; b) 1. **Bromination** by $LiN(TMS)_2$, NBS, THF, -78°C, 54%, 2. **Methanolysis** by AgOTf, 2,6-lutidine, MeOH, CH_2Cl_2 , **0°C**, 87%, 3. **Alk. Hydrolysis of the diester** by KOH, $EtOH/H_2O$, reflux, then 10% HCl, 98%, 4. Dehydration of dicarboxylic acid by trimethylsilyl(ethoxy) acetylene, CH_2Cl_2 , rt, 80%;

c) 1. **Bromination** by $LiN(TMS)_2$, NBS, THF, -78°C, 2. **Methanolysis** by NaOMe, $MeOH/CH_2Cl_2$, **-78°C to rt,** 60% over 2 steps, 3. **Alk. Hydrolysis by** KOH, $EtOH/H_2O$, reflux, then CF_3CO_2H, 71%, 4. Dehydration of dicarboxylic acid by trimethylsilyl (ethoxy) acetylene, CH_2Cl_2 , rt, 91%.

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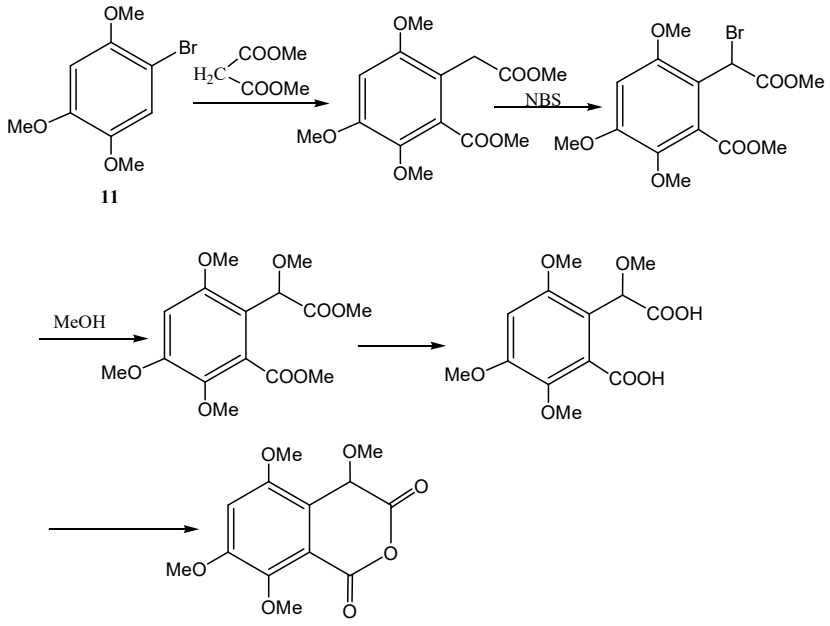

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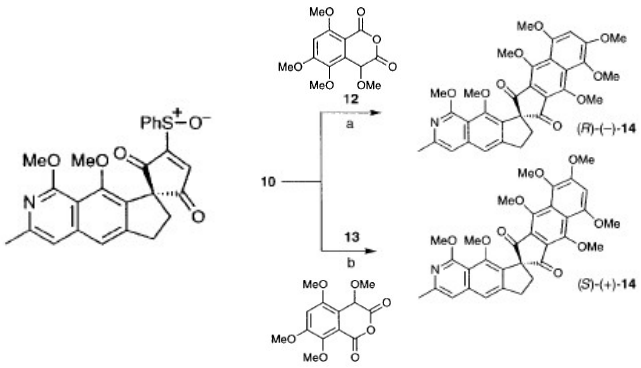
Intermolecular (4+2) Cycloaddition-



a) 1. NaH, THF, 0°C, 83%, generated **12** anion 2. MeI, K_2CO_3, DMF, rt, 85%; b) same as a, 76% over 2 steps;

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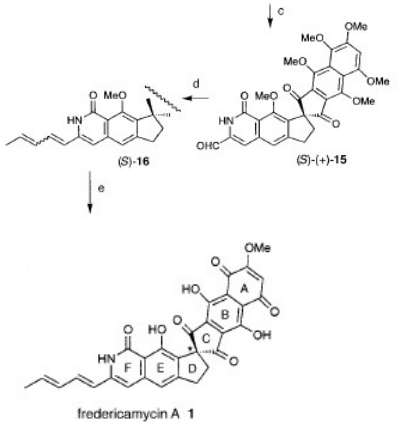
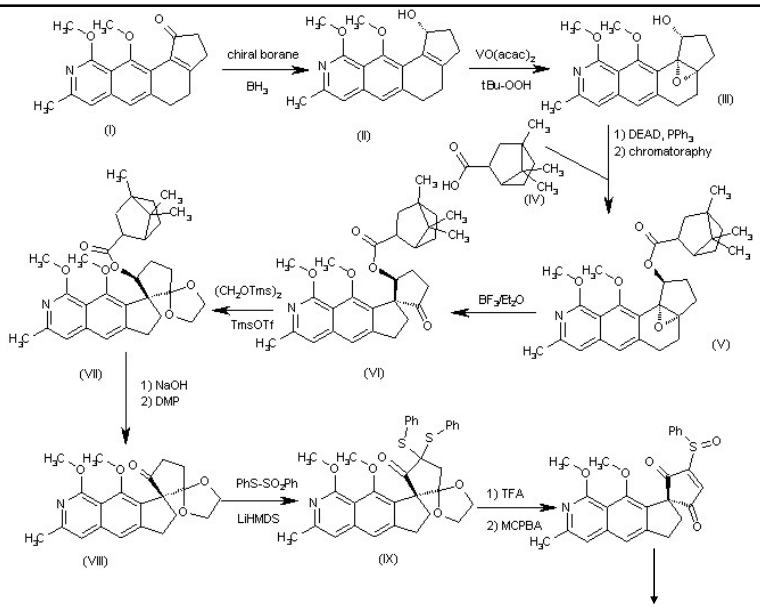
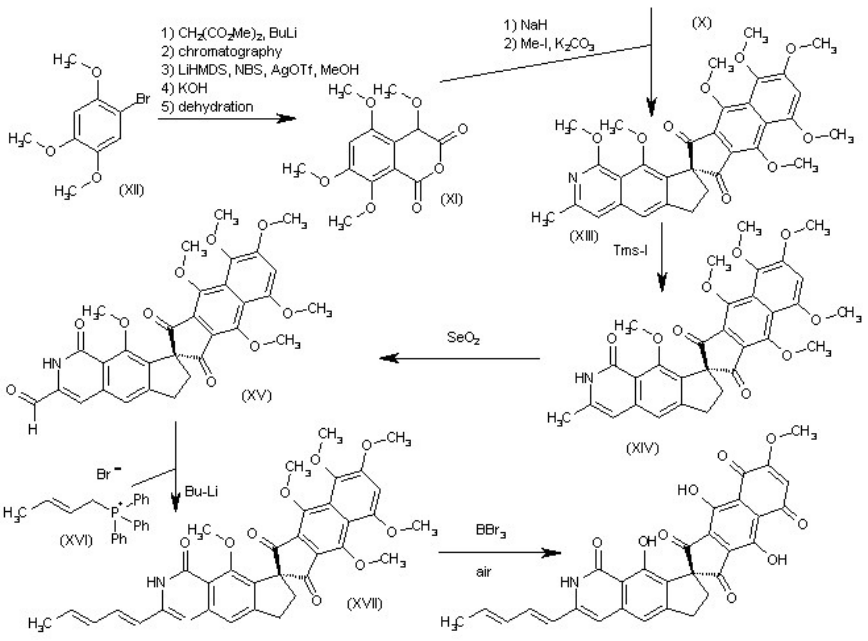


c) 1. Selective **Demethylation** by TMSI, CH_2Cl_2, rt, 74%, 2. SeO_2 , 1,4-dioxane, reflux, 76%; d) Wittig reaction by 2-butenyl(triphenyl) phosphonium bromide, nBuLi, THF, -78°C to rt, 46%; e) 1. BBr_3, CH_2Cl_2 , -78°C, 2. auto oxidation by air, THF/H_2O, rt, gave 5:1 mixture of EE & EZ-(S)—**16,** 3. Pure EE isomer separated by HPLC, 40% from(S)-**16**. 73



Vanadyl acetylacetonate does epoxidation of allylic alcohol in combination with t-butyl hydroperoxide.

DEAD (Diethyl azo dicarboxylate), a aza-dienophile and an dehydrogenating agent, converting alcohol to aldehyde, thiols to disulfides and hydrazo groups to azo groups. 74

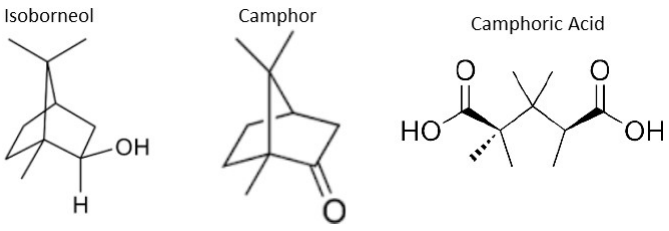


SYNTHESIS OF CAMPHOR

Camphor is a waxy, white terpenoid or transparent solid with a strong, aromatic odor with antimicrobial properties.

A natural product from the Camphor tree of Formosa & Japan.

It is optically active, (+) & (-) forms occur naturally, so does racemic camphor which is usual form of Camphor



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•**Camphor**, 1,7,7-trimethylbicyclo [2.2.1] heptane, is a ketone related to bicyclic terpenoids
•which was already known in ancient times.
•It was used in a medicine, as a repellent, in cooking and in religious ceremonies.
•Camphor possesses a strong aromatic odor and forms colorless crystals (m.p. 178-179°C).
•By chemical properties camphor represents typical ketone, thus it is reduced to two stereoisomeric alcohols – borneol and isoborneol.
Camphor (topical) suggested uses include treating pain, warts, cold sores, hemorrhoids, osteoarthritis, anti-itch, to increase local blood flow, and as a counterirritant.
Camphor is an FDA-approved topical antitussive (anti-cough).
Camphor is an FDA-approved topical analgesic and anesthetic used to relieve pain.

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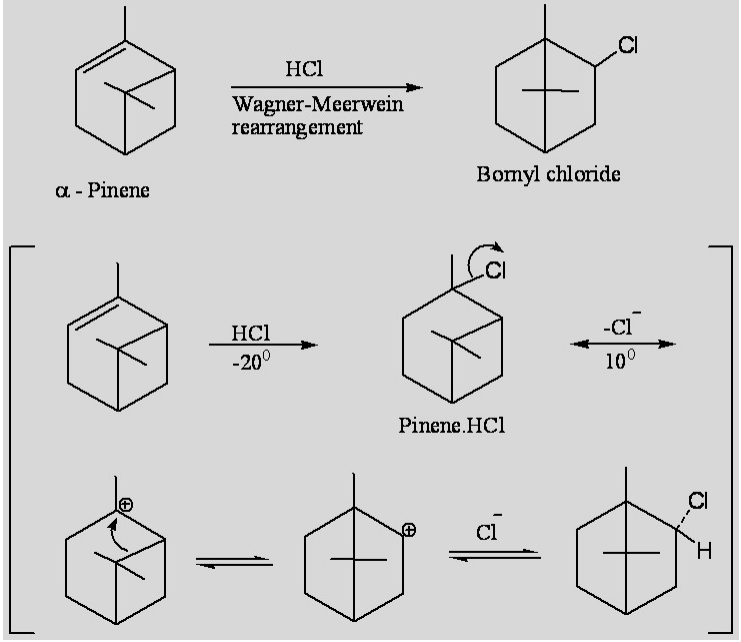
STEP I

Carbocation 1,2-rearrangement reactions where a H, alkyl or Aryl group migrates from one carbon to a neighbouring carbon.



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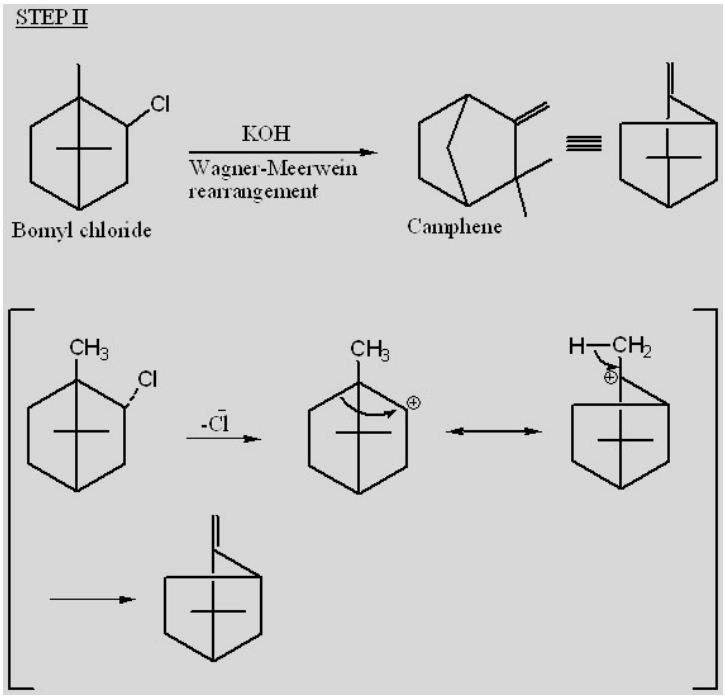
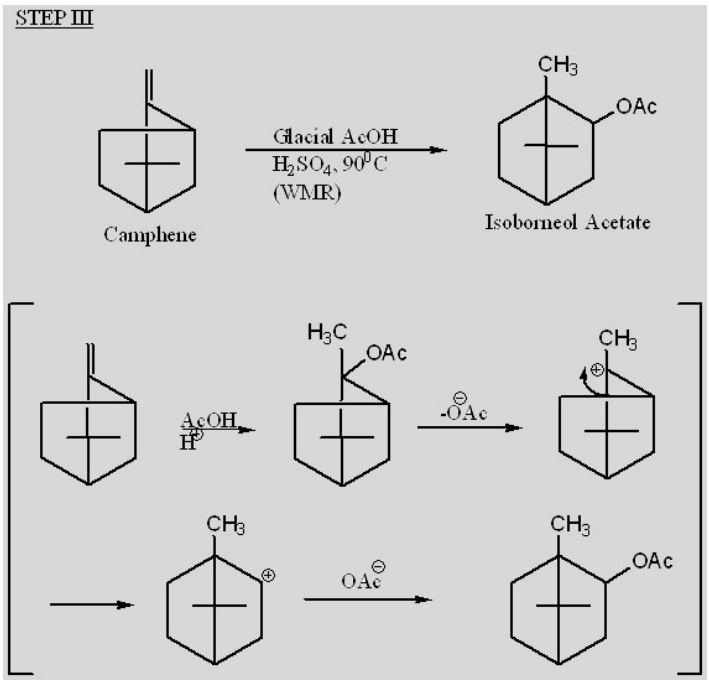
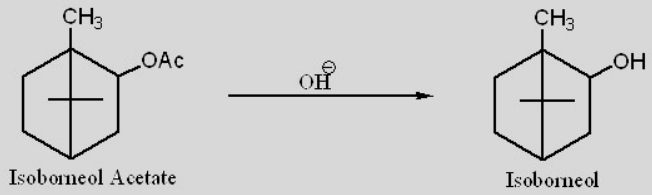

STEP II
Cl
KOH
Wagner-Meerwein rearrangement
Bornyl chloride
Camphene
CH3
Cl
-Cl
CH3
H—CH2

79


STEP III
Glacial AcOH
H2SO4, 90°C
(WMR)
Camphene
CH3
OAc
Isoborneol Acetate
H3C
OAc
AcOH
H⊕
-OAc
CH3
CH3
OAc⊖
CH3
OAc

80

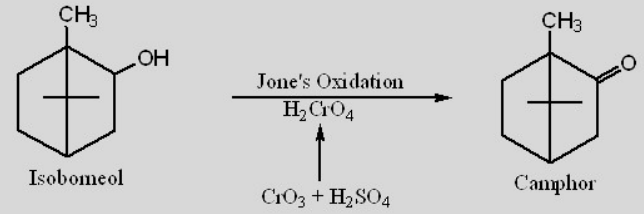
STEP IV



Isobornеol Acetate

Isobornеol

STEP V



Isobornеol

Camphor

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SYNTHESIS OF VITAMIN D

Vitamin D is antirachitic.

It controls the Calcium & Phosphorous metabolism in bone.

Initially this compound was named Calciferol by Medical Research Council (MRC) and Vitamin D_1 by Windaus (1931).

Later it was shown to be a molecular compound of Calciferol & Lumisterol (one molecule each).

Windaus (1932) therefore, renamed it as Vitamin D_2 but MRC retained Calciferol.

Chemical Society (1951) has proposed the name Ergocalciferol.

82

Vitamin D insufficiency can result in thin, brittle bones, while sufficiency prevents rickets in children and osteomalacia in adults, and, together with calcium, helps to protect older adults from osteoporosis.

Vitamin D also modulates neuromuscular function, reduces inflammation, and influences the action of many genes that regulate the proliferation, differentiation and apoptosis of cells.

83

Vitamin D is a generic term and indicates a molecule of the general structure shown for rings A, B, C, and D with differing side chain structures.

The A, B, C, and D ring structure is derived from the cyclopentanoperhydrophenanthrene ring structure for steroids.

Technically vitamin D is classified as a seco-steroid.

Seco-steroids are those in which one of the rings has been broken

In vitamin D, the 9,10 carbon-carbon bond of ring B is broken, and it is indicated by the inclusion of "9,10-seco" in the official nomenclature.

84

Vitamin D prevents Osteoporosis, Depression, Prostate cancer, Breast cancer, and even effects -Diabetes & Obesity..
Vitamin D is synthesised when sunlight touches your skin.
◆ The healing rays of natural sunlight (that generate vitamin D in your skin) cannot penetrate glass. So you don't generate vitamin D when sitting in your car or home.
◆ It is nearly impossible to get adequate amounts of vitamin D from your diet. Sunlight exposure is the only reliable way to generate vitamin D in your own body.
◆ A person would have to drink *ten tall glasses* of vitamin D fortified milk each day just to get minimum levels of vitamin D into their diet.
◆ The further you live from the equator, the longer exposure you need to the sun in order to generate vitamin D. Canada, the UK and most U.S. States are far from the equator.
◆ People with dark skin pigmentation may need 20 - 30 times as much exposure to sunlight as fair-skinned people to generate the same amount of vitamin D.
That's why prostate cancer is epidemic among black men -- it's a simple, but widespread, sunlight deficiency.

85

◆ Sufficient levels of vitamin D are *crucial for calcium absorption* in your intestines. Without sufficient vitamin D, your body cannot absorb calcium, rendering calcium supplements useless.
◆ Chronic vitamin D *deficiency cannot be reversed overnight*: it takes months of vitamin D supplementation and sunlight exposure to rebuild the body's bones and nervous system.
◆ Even weak *sunscreens (SPF=8) block* your body's ability to generate vitamin D by 95%. This is how sunscreen products actually cause disease - by creating a critical vitamin deficiency in the body.
◆ It is impossible to generate too much vitamin D in your body from sunlight exposure: your body will self-regulate and only generate what it needs.
◆ "Rickets" is the name of a bone-wasting disease caused by vitamin D deficiency.
◆ Obesity impairs vitamin D utilization in the body, meaning obese people *need twice* as much vitamin D.
◆ Vitamin D deficiency can cause ~ schizophrenia.
◆ Your risk of developing serious diseases like diabetes and cancer is *reduced 50% - 80%* through simple, sensible exposure to natural *sunlight 2-3 times each week*.

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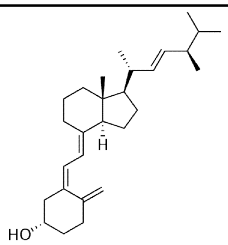
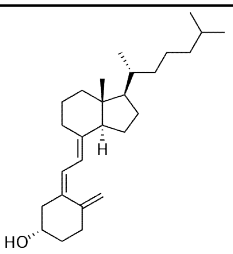
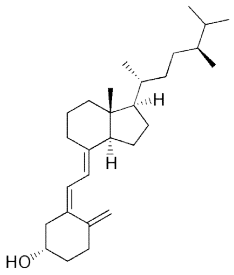


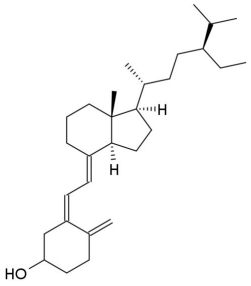
Vitamin D2, ergocalciferol (made from ergosterol)



Vitamin D3, cholecalciferol (made from 7-dehydrocholesterol in the skin).



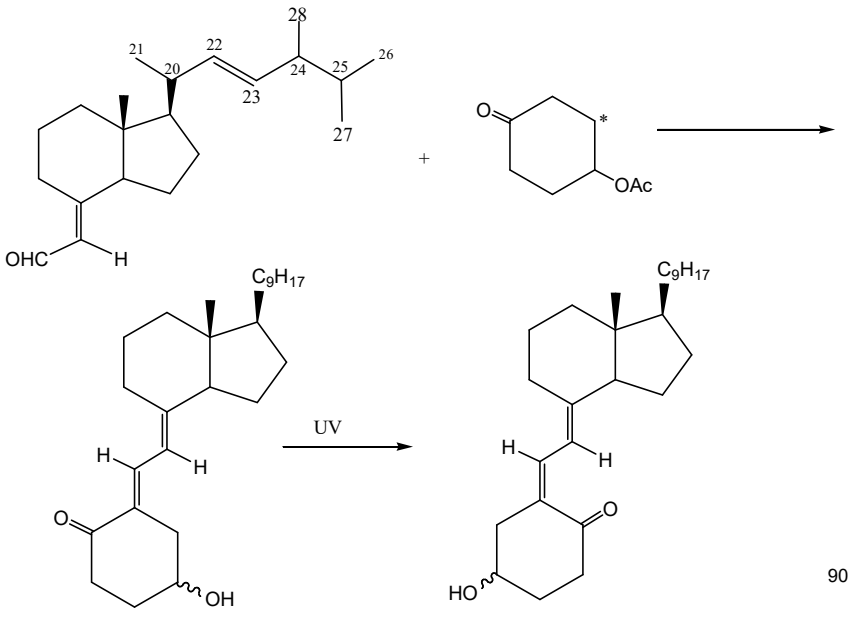
Vitamin D4, 22-dihydroergocalciferol



Vitamin D5, sitocalciferol (made from 7-dehydrositosterol)

87

Lythgoe et al (1958) gave the partial synthesis



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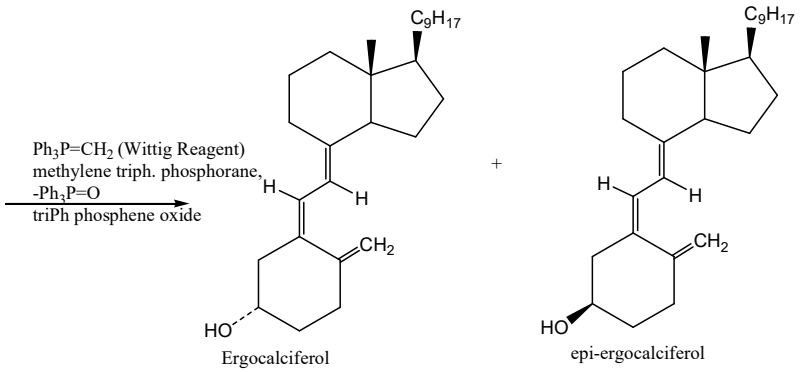

Ergocalciferol epi-ergocalciferol

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