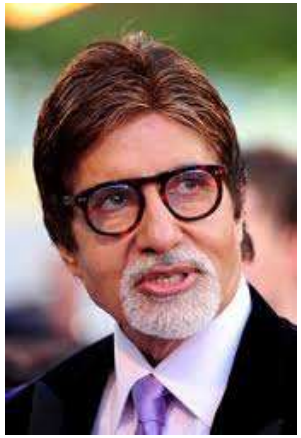
Molecules with Celebrity Status

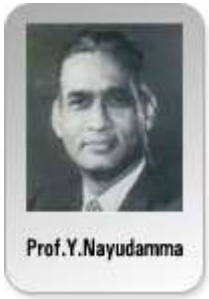


S. Chandrasekhar
CSIR-Indian Institute of Chemical Technology
Hyderabad, 500 007
Email: srivaric@iict.res.in

Foundation Day lecture
CSIR-CLRI
22nd April 2016

Salute to the Leaders……..


Dr. B.M.Das

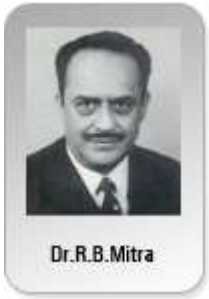

Prof.Y.Nayudamma


Prof.M.Santappa


Dr.N.Ramanathan


Shri.T.S.Krishnan


Dr.G.Thyagarajan


Dr.R.B.Mitra


Dr.K.V.Raghavan


Dr.T.Ramasami


Prof. Asit Baran Mandal

Celebrities ???

- The state of being well-known
- A famous person
- Or a group of people
- Occasionally an animal
- Sometimes fictional entities

Celebrities with ‘Class’ and ‘Mass’ Appeal

- Some celebrities have a mass following
- Some are admired by a selected group

Mona lisa by Leonardo Da vinci

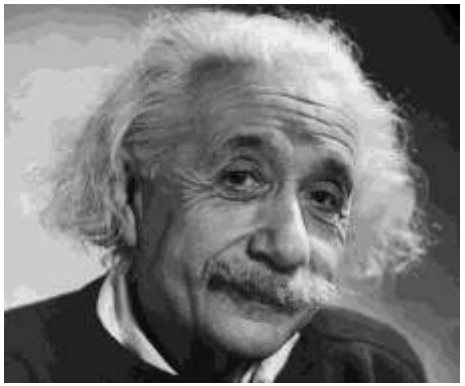
Group of Three Girls, 1935

Group of three girls by Amrita Shergill

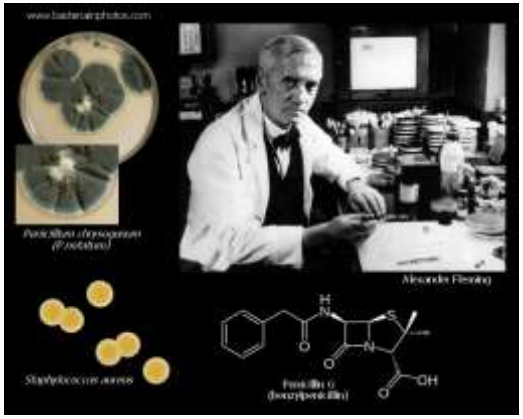
Sportsmen and Film personalities

Scientists

Isaac Newton and Albert Einstein

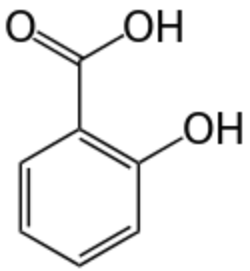


Watson & Crick and Alexander Fleming

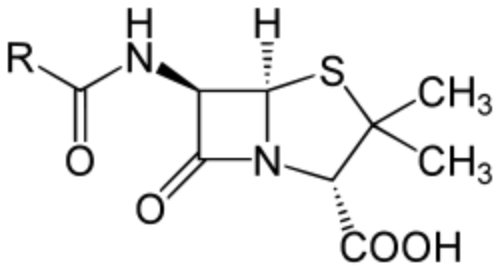


A P J Abdul Kalam and C N R Rao

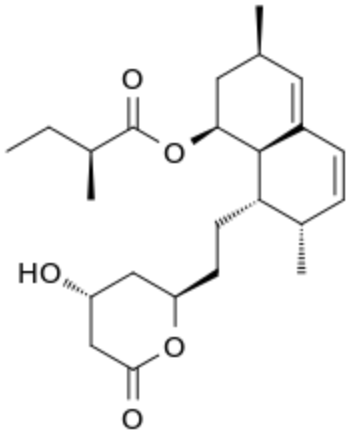
Famous Molecules



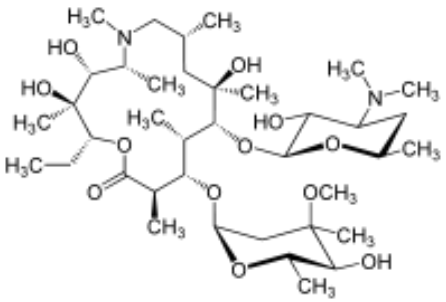
Salicylic acid



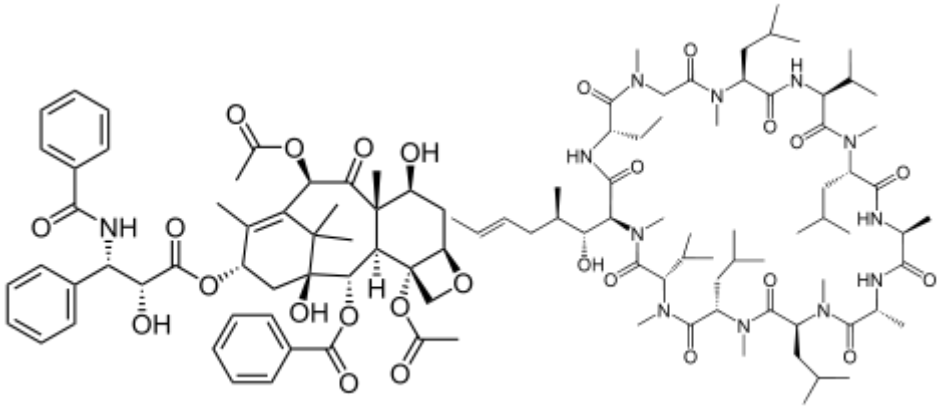
Penicillins



Lovastatin

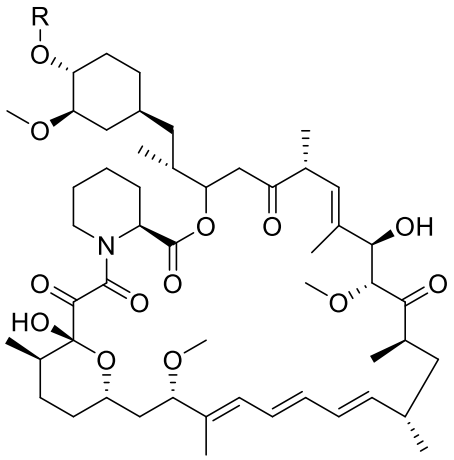


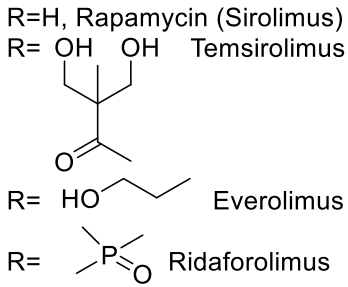
Azithromycin



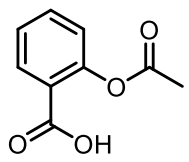
Paclitaxel

Cyclosporin

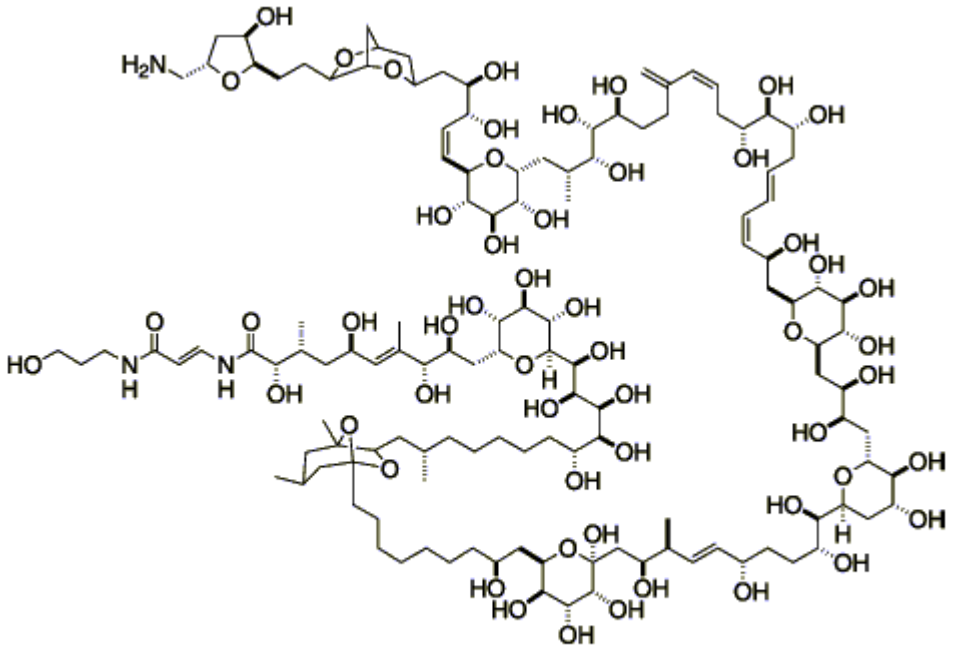




Celebrity Molecules



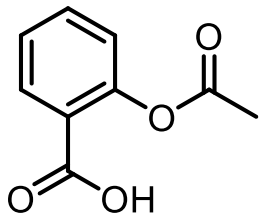
Aspirin



PALYTOXIN

- Aspirin is the smallest possible drug molecule
- Aspirin is known even to a layman
- Palytoxin is one of the most complex, large natural products
- Palytoxin structure is appreciated by a selected few

Aspirin

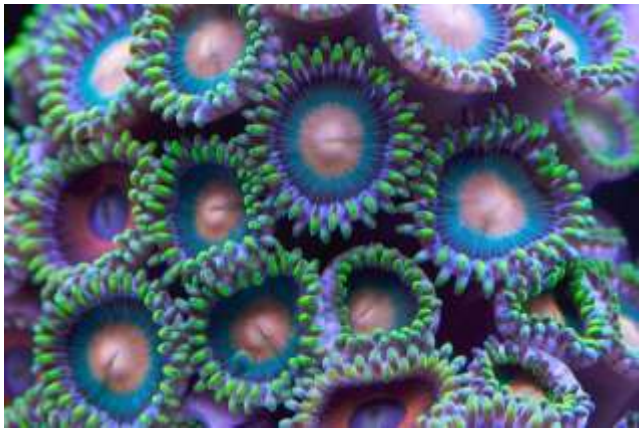


- 3500 Years ago Egyptian physicians prescribed herbal preparation for rheumatism and backpain.
- ~2500 years ago Hippocrates used willow bark extracts for pain, fever and child birth.

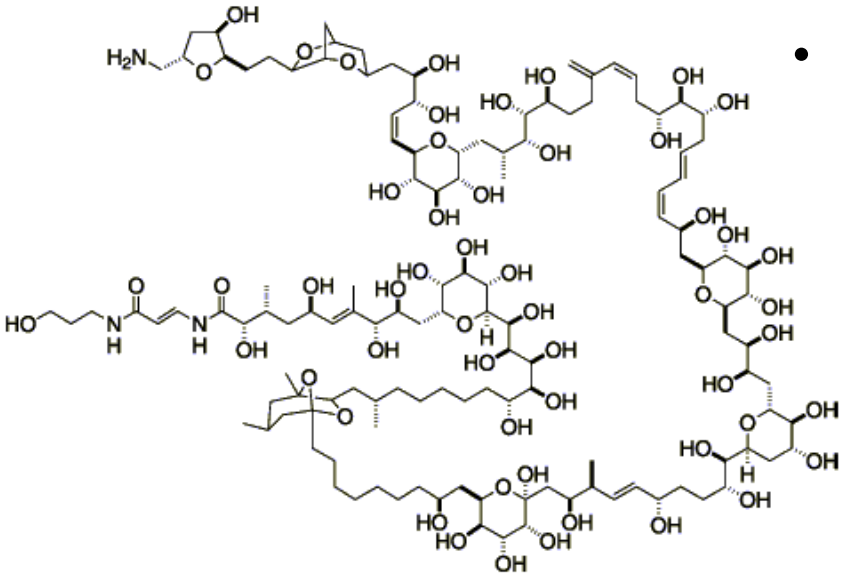
- Salicin, the major component extract comes from Saliceae, family of willow.
- Felix Hoffmann, from Bayer, was the first to synthesize and crystallise acetylsalicylic acid, branded as aspirin, in 1897.
- Aspirin can be synthesized by only one method which is the commercial method
- The yield of the reaction is ~99% with no side- or by-product formation.

- Paracetamol (tylenol; H. N. Morse-synthesis and J. von Mering-clinician) and ibuprofen (advil; Steward Adams head of a research team in Boots) are developed after aspirin.
- They are all COX (cyclooxygenase) inhibitors

Palytoxin



- Originally isolated from seaweed like soft coral *Palythoa* sp. near Hawaii
- It has 64 chiral centres and 8 double bonds
- It is one of the most toxic non-protein substance
- Total synthesis achieved by Kishi *et al*. in 1994
- It is an intense vasoconstrictor
- Yield 0.001% after joining 8 fragments



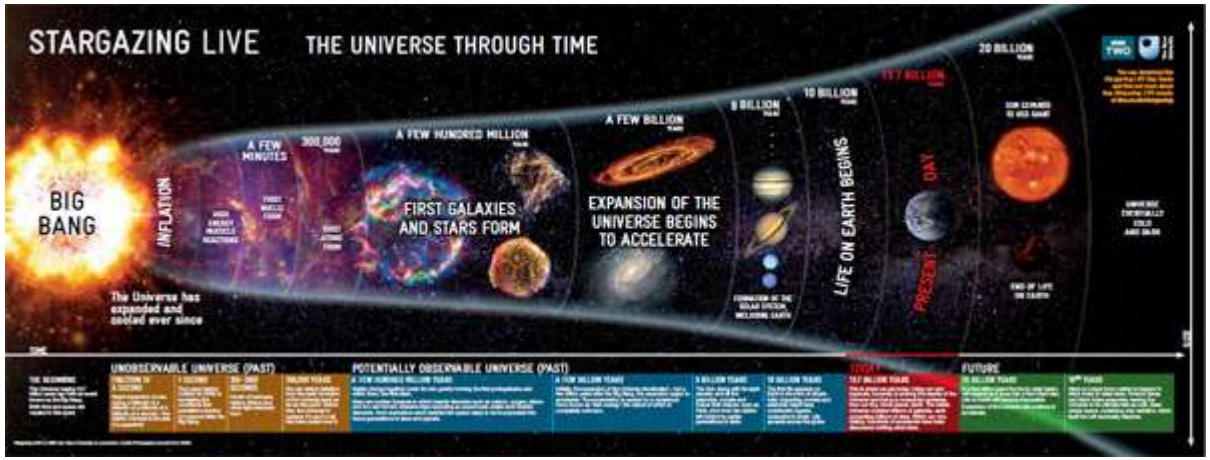
PALYTOXIN

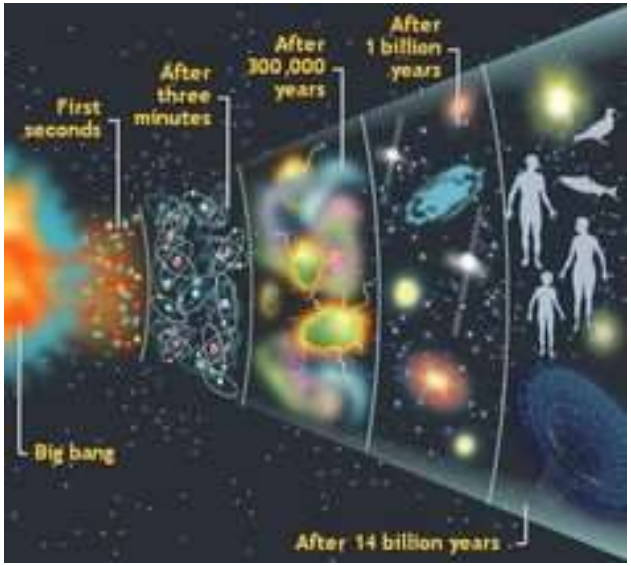
Big is not always dangerous, small can be equally lethal

Sting ray

- Steve Irwin, Australian Crocodile Man

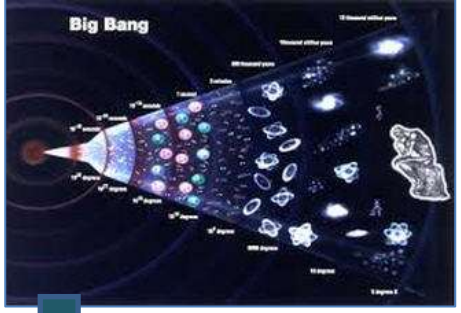
How did it begin?





- One of the theories states that it all started with a big bang.
- Hydrogen and Helium led to generation of other elements.
- Stars and Planets have deposits of all these elements in varying ratios.

Evolution of Humans !!!!!



Evolution


Evolution according to Darwin (Described in Origin of Species)
Chordates Living in Water (Fish)
Tetrapodes Living in both Water and Land (Amphibian)
Mammals Living on Land (Boar)
Partialy Bipedalled Primates (Half man-Half Animal)
Hominidae Dwarf (Phisicaly Less-Developed; Mentaly very wise)
Homo Erectus (Living in Jungle) Man with Axe weapon
Homo Sapiens (The Perfect Man)
Matsya Avtar
Kurma Avtar
Varah Avtar
Narsimha Avtar
Vaman Avtar
Parshuram Avtar
Ram Avatar
Evolution according to Dashavatar (Described in Vishnu Puraan)

Small is Beautiful & Useful

First generation computer

New computer

First generation laptops

New generation laptops

First generation cell phones

Smart phones

Major Causes of Mortality Worldwide

(2012 WHO report)

- **Cardio-Vascular Disease 31.5%**
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  - Brain stroke
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  - Breast
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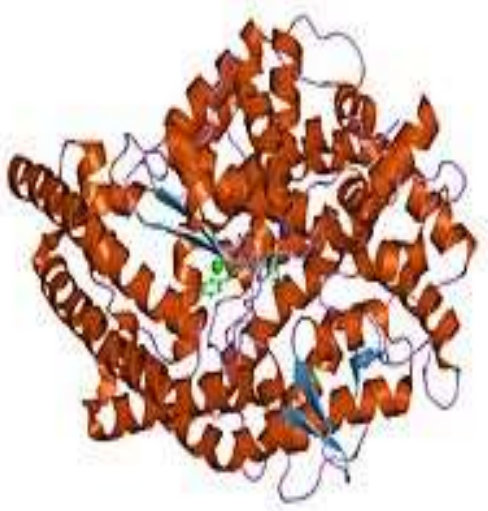
- Neuro-psychiatric Disorders 2.2%
  - Alzheimer's Disease and other Dementia
  - Parkinson's Disease
  - Depression and Schizophrenia
- Road accidents Unaccountable

History

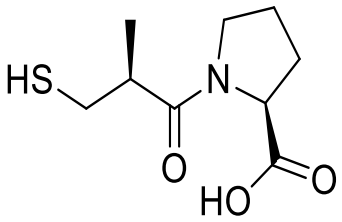
- Identification of ACE inhibitors for the treatment of cardiovascular illness began in the banana plantations of south-western Brazil.
- There were repeated instances of workers suffering sudden collapse and death. The cause was a bite from a snake (*Bothrops jararaca*).
- The toxin from *Bothrops jararaca* and several other snakes leads to a dramatic drop in blood pressure through vasodilation, which paralyses the victim.
- According to folklore, mongoose eats a herb and develops immunity to snake poison and hence not affected by it.
- Actually mongoose have **specialised acetylcholine receptors** that prevent snake toxin from binding to its cells.

Introduction to ACE Inhibitors

- Brazilian pharmacologist Sergio Henrique Ferreira isolated the pentapeptide in 1970 that is BPP5a (Bradykinin-potentialising peptide) IC_{50} = 1.2 µm.
- Its pharmacophore and that of a more stable analogue Teprotide, is a further optimised nonapeptide with blood pressure lowering properties.
- Captopril is the first highly specific enzyme inhibitor on the basis of rational drug design.



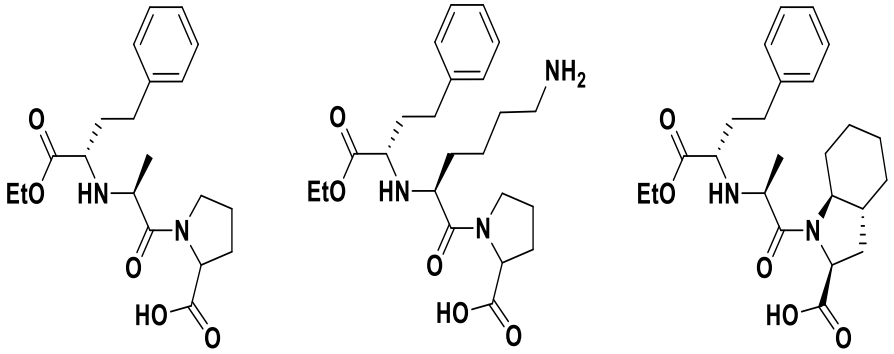
Structure of ACE



- The affinity of (*S,S*)-Captopril is around 100 times higher than of its (*R,S*)-configured isomer.

Second –Generation ACE Inhibitors

- The most common adverse effects of Captopril includes, skin rash and loss of taste, are the same as caused by mercapto-containing penicillamine.
- A group of researchers aimed at finding potent, selective ACE inhibitors that wouldn't contain a mercapto (SH) function and would have a weaker chelating function.
- They started working with substituted *N*-carboxymethyl-dipeptides. The results were two active inhibitors:



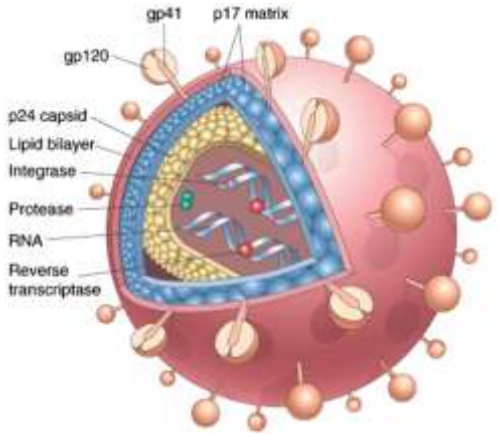
Enalapril Lisinopril Trandolapril

- ACE inhibitors and Angiotensin II receptor antagonist are given in combination and include
  - Losartan
  - Valsartan
  - Telmisartan

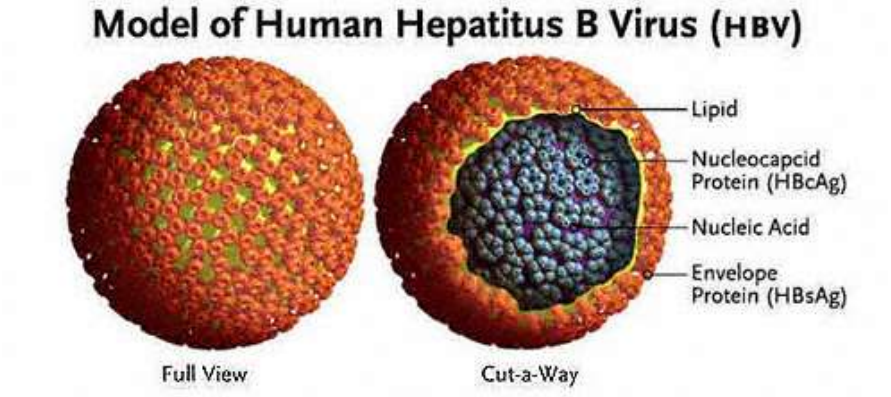
Crotalus horridus

- Commonly known as timber rattlesnake, canebreak rattlesnake or banded rattlesnake
- A venomous pit viper found in eastern parts of United States
- Produces high venom yield
- Venom comprises of
  - Type A-Neurotoxic
  - Type B-Hemmorrhagic and proteolyic
  - Type A +B
  - Type C-Relatively weak and contains none of the above components
- Enzymes present
  - Peptide that works as a myotoxin
  - Fibrinogen clotting enzyme
  - Bradykinin-releasing enzyme

Important RT viruses



HIV



Published in *The PRN Notebook*, Volume 9, Issue 3, September 2004 and *The PRN Notebook* Online at www.prn.org
Three-dimensional model of HBV created by Louis E. Henderson, PhD, Frederick Cancer Research Center.

❖ In order to confirm whether cDNA is synthesized or not, the reaction mixture was analyzed by checking the Amplification of Constitutive gene in the cDNA mix.

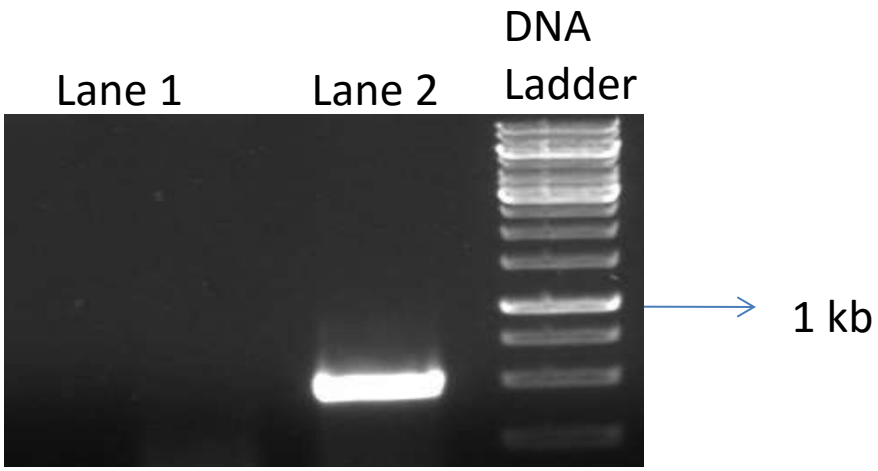
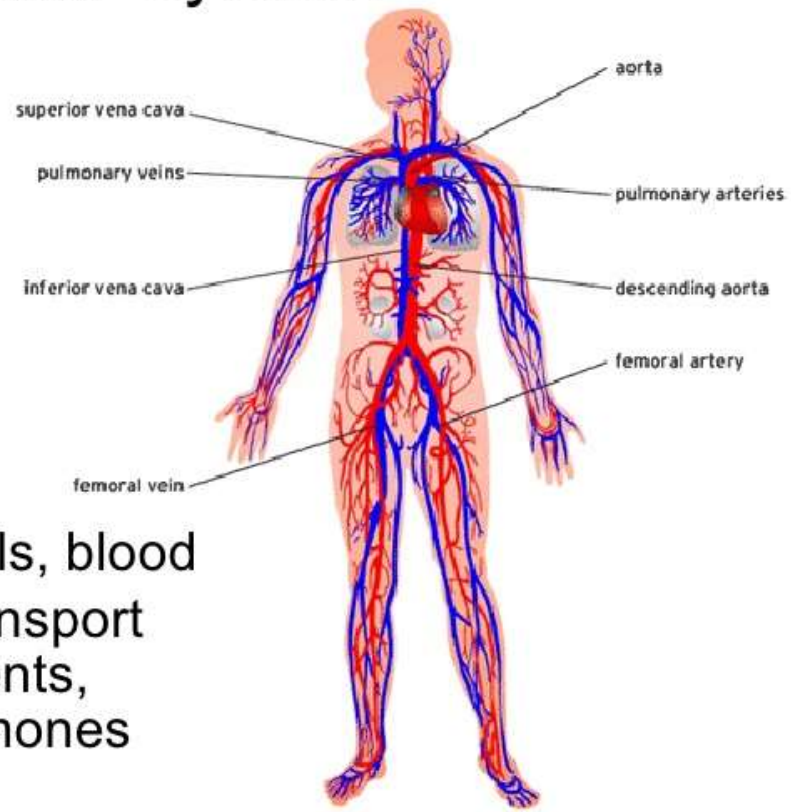


Figure 1: Lane 1 contains cDNA synthesized in presence of the Compound. There is no amplification of constitutive gene.
Lane 2 contains cDNA synthesized in presence of water . There is amplification of constitutive gene.

RESULT: The Absence of Amplification of constitutive gene in Reaction 1 confirms that the cDNA synthesis was inhibited, thus concluding that the compound inhibits Reverse transcriptase enzyme.

Our efforts towards synthesis of antihypertensive compound

Cardiovascular System

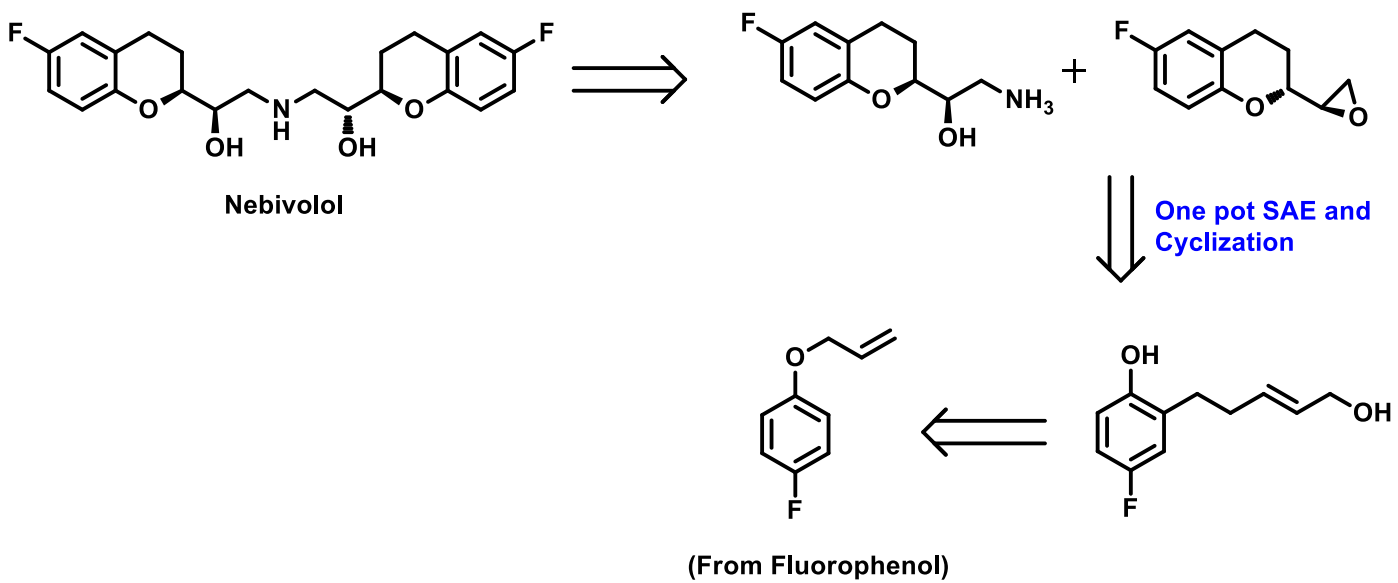


- Heart, vessels, blood
- Function: transport gases, nutrients, wastes, hormones

Nebivolol

- Potent and selective β1-adrenergic blocker with antihypertensive activity
- Approved by FDA in **2007**
- Activity greater than atenolol, pindolol and propranolol
- Synthesis reported using mostly step-wise process
- One-pot Sharpless Asymmetric Epoxidation/Cyclization
- Improved yields compared to reported procedures

Retrosynthesis



Tetrahedron, 2000, 56, 6339

Major Causes of Mortality Worldwide

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  - Breast
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- Neuro-psychiatric Disorders 2.2%
  - Alzheimer's Disease and other Dementia
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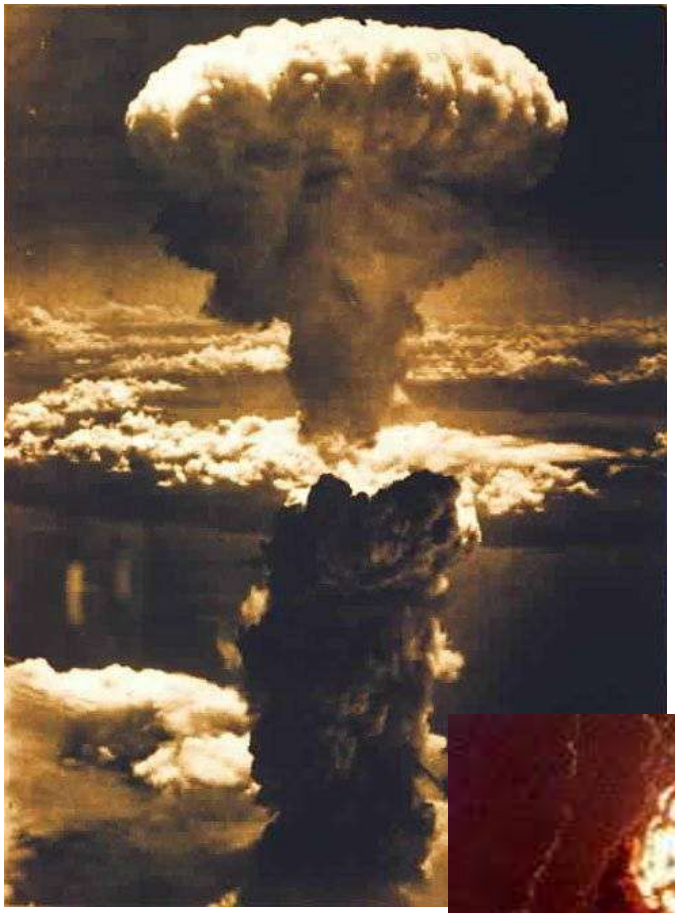
  - Depression and Schizophrenia
- Road accidents Unaccountable

World war I (1914-1918)

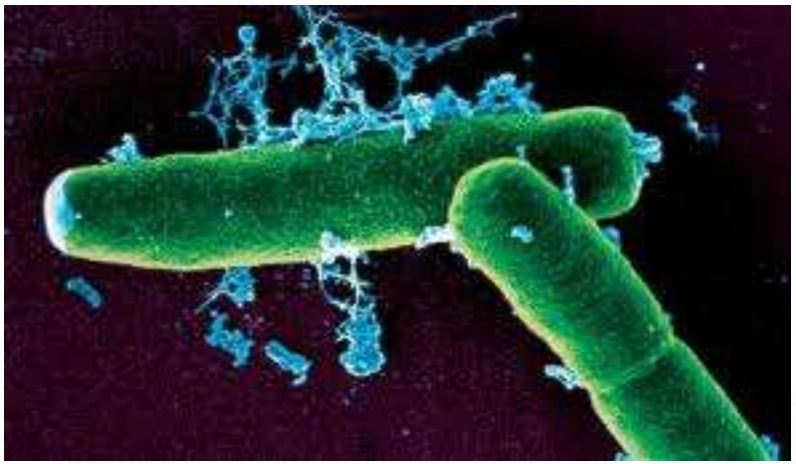
About 7 million deaths and ~20 million wounded

World war II (1939-1945)



Over 60 million deaths

Can *M. tuberculosis* be a threat to create havoc like world wars?



Mycobacterium tuberculosis

Nonmotile rod-shaped bacterium 2-4 micrometers in length and 0.2-0.5 micrometer in width.

??? Maybe 600 million When?

6 Ft. harmless bullet

Effect of TB around the world

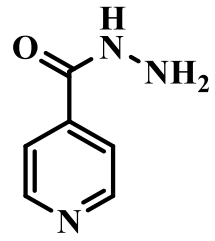
- Nearly 1/3rd of world's population is infected with Mtb. Globally 9.2 million new cases and 2-3 million deaths occur every year albeit widespread vaccination and chemotherapy.
- In 2007, there were an estimated 13.7 million chronic active cases globally, while in 2010 there were an estimated 8.8 million new cases.
- Distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests.
- India had the highest total number of TB cases worldwide in 2010, in part due to poor disease management within the private health care sector.

Image Courtesy: Amitabh Bachchan

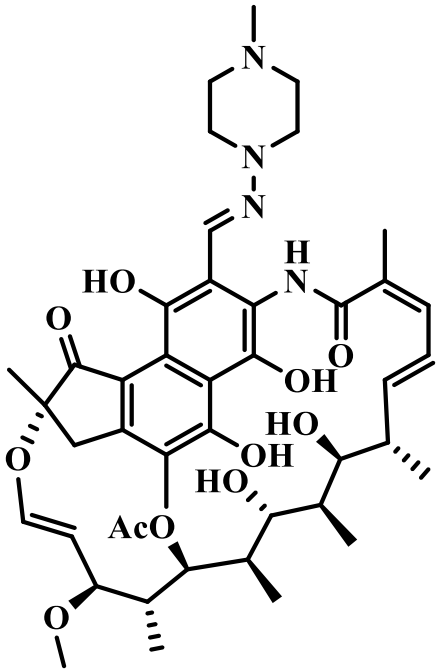
Chemotherapy

Current treatment includes first line drugs:

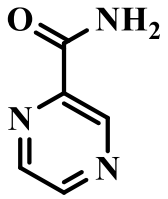
Isoniazid, Rifampicin, Pyrazinamide and Ethambutol, which cure most of the disease.



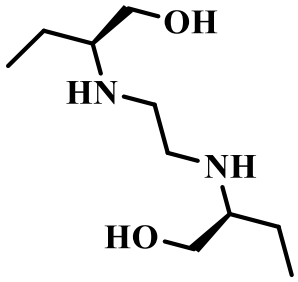
Isoniazid



Rifampin



Pyrazinamide

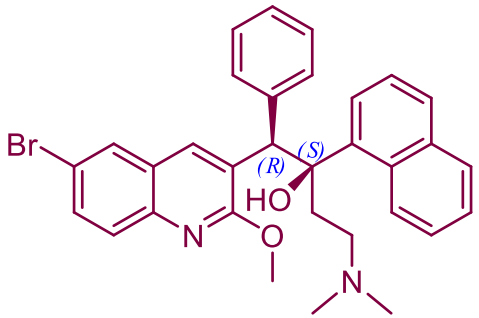


Ethambutol

New Tuberculostatic agent approved

- Many second line bacteriostatics, with established clinical efficacy and important side effects usually, are also used as per the case

- A search for new entities to treat *M. tuberculosis* and related strains in all their forms lead to the discovery of Bedaquiline [R207910 (TMC 207)] by Johnson & Johnson Pharmaceutical R & D. *Science* **307**, 223 (2005)



- Its novel mechanism is by acting on the proton pump of adenosine triphosphate (ATP) synthase of *M. tuberculosis* but not on other bacterial ATP systems.

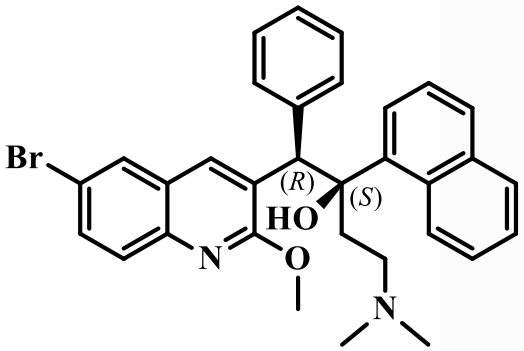
- From synthetic perspective the molecule is closely packed around two contiguous tri and tetra-substituted chiral carbons with aromatic motifs oriented in lowest energy conformations.

- Its fascinating biological activity and molecular complexity interested us to develop an asymmetric and practical synthesis.

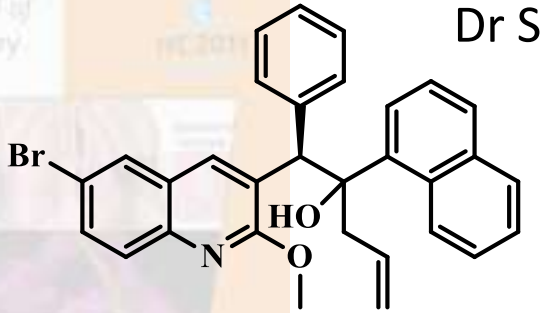
Practical synthesis of Bedaquiline and its isomer

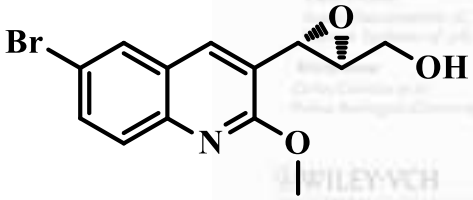
Dr Shyamkiran

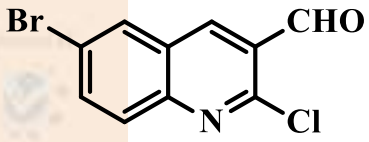
Retrosynthetic analysis:



R207910







Eur. J. Org. Chem. **2011**, *11*, 2057-2061

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  - Leukemia
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- Neuro-psychiatric Disorders 2.2%
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  - Parkinson's Disease
  - Depression and Schizophrenia
- Road accidents Unaccountable

Cancer is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012 . The most common causes of cancer death are cancers of:

- lung (1.59 million deaths)
- liver (745 000 deaths)
- stomach (723 000 deaths)
- colorectal (694 000 deaths)
- breast (521 000 deaths)
- oesophageal cancer (400 000 deaths)

Manisha Koirala

Yuvraj Singh

Mumtaz

Rajesh Khanna

Robert DeNiro

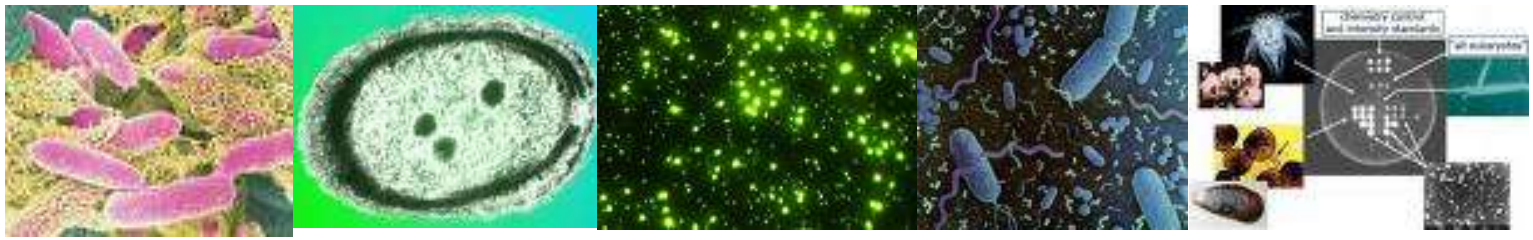
Lance Armstrong

Sources of Marine Natural Products

Marine Alge:

Marine Fungi:

Marine Bacteria:



MARINE SOURCES For Natural Products

Marine invertebrates:

Starfish

Fish

Green turtle

Marine worms

Mammals

Oceanic habitats:

Corals and reef fish

Coral

Treasure hunters

Collecting marine life in the search of the drugs

Emma Marris. *Nature*, **2006**, *443*, 904-905.

Marine medicines by PharmaMar

Ecteinascidia turbinata
A Caribbean and Mediterranean sea squirt, makes a compound that PharmaMar has brand-named Yondelis. Trials are also under way for ovarian cancer.

Aplidium albicans Another anticancer drug has been isolated from this sea squirt.

Conus magus
This cone snail paralyses its prey using a poison tipped barb (right). The poison is a painkiller many times more potent than morphine, and is now on the market as Prialt.

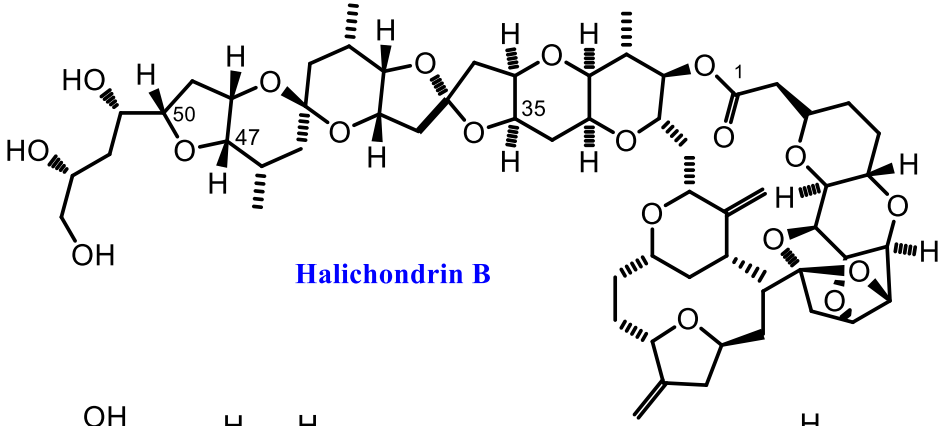
History of eribulin mesylate (Halaven®)

❖Synthetic analogue of halichondrin B; natural product from marine sponge *Halichondria okadai*

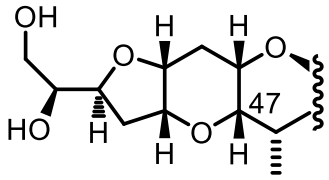
❖Tubulin-targeting agent

❖Eribulin could be effective in patients with disease that is resistant to other tubulin targeting-agents

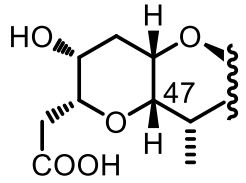
Halichondria okadai



Halichondrin B



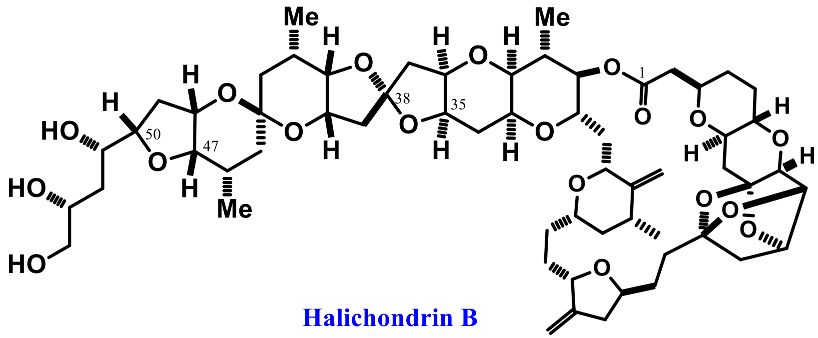
Homohalichondrin B



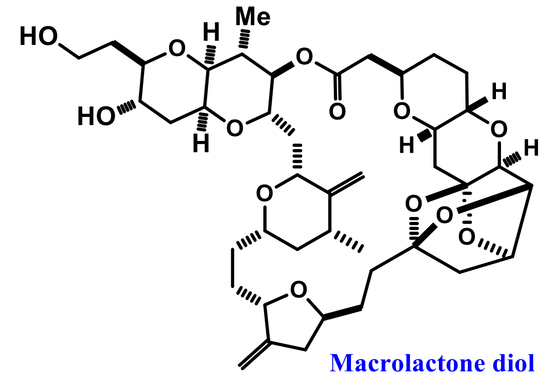
Norhalichondrin B

Ref: (a) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y. *J. Am. Chem. Soc.* **1985**, *107*, 4796-4798. (b) Hirata, Y.; Uemura, D. *Pure Appl. Chem*. **1986**, *58*, 701-710

History of eribulin mesylate (Halaven®)



Halichondrin B



Macrolactone diol

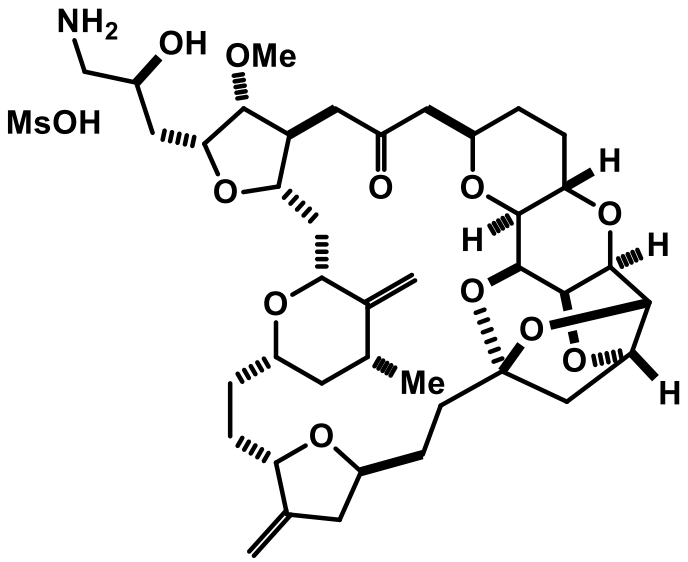
❖In 1992 samples of synthetic halichondrin B and several intermediates were provided by the Kishi group to the Eisai Research Institute with a goal of evaluating *in Vitro and in* V*iVo activity.*

❖*In a remarkable discovery, the macrocyclic* macrolactone diol **was found to** be within an order of magnitude as potent as the parent halichondrin B against DLD-1 human colon cancer cells (IC50 for **146) 4.6 nM).**

❖**Further study showed that halichondrin** B and **macrolactone diol both blocked cell cycle progression at the G2/M** phase, both caused microtubule destabilization, and both had similar profiles in the 60-cell-lines screen at the National Cancer Institute.

❖Armed with this information, the stage was set to develop a potential halichondrin-derived therapeutic.

Eribulin mesylate (Halaven®) structure and dosage



❖structures of the halichondrins were too complex to make them feasible as targets for scaled-up production by total synthesis.

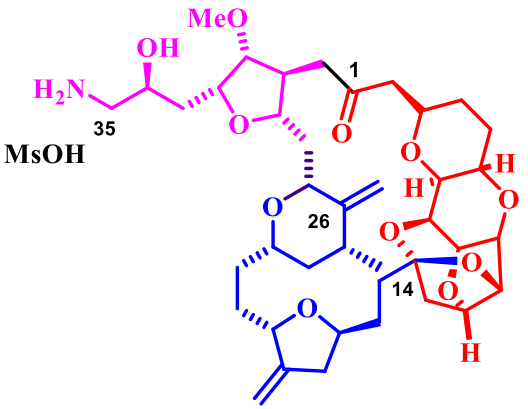
❖Eribulin mesylate is available as 1-mg vials for single-use infusion.

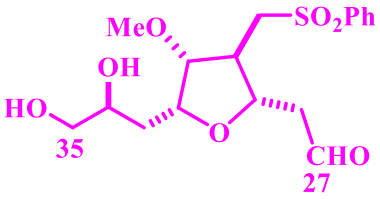
❖The average wholesale price of eribulin is $1037 for the 1-mg/2 mL vial.

❖Average dose is 2.4 mg which would amount to $2488, or $4977 per treatment cycle.

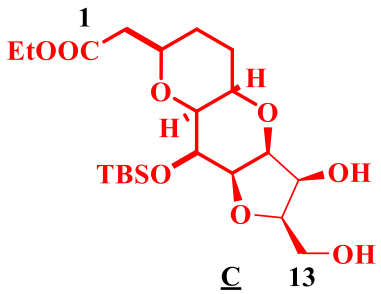
Towle MJ *et al*., "In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B". *Cancer Res.* **2001** , *61*, 1013–1021

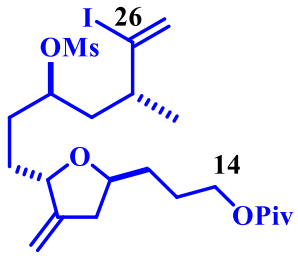
OUR RETRO-SYNTHETIC APPROACH





A





B

❖Practical and stereoselective synthesis of [6, 6, 5]-tricyclic core (C1-C13) of eribulin mesylate *Tetrahedron Letters* **2015**, *56*, 4280-4282

❖A practical synthesis of C14-C26 fragment of anticancer drug, eribulin mesylate *Tetrahedron Letters* **2015**, *56*, 4283-4285

❖Tandem organocatalytic approach to C28-C35 fragment of eribulin mesylate *Tetrahedron Letters* **2015**, *56*, 4286-4288

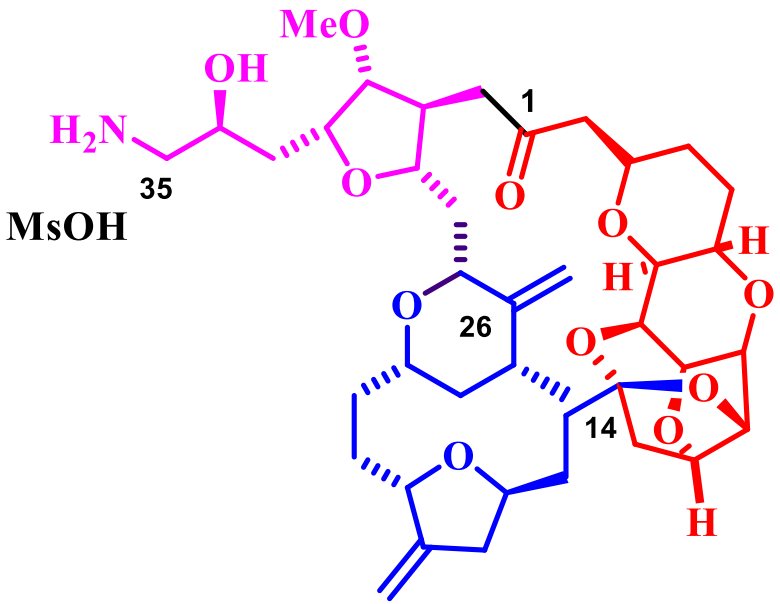
Ms. N. Lavanya

Dr. C. Rambabu

Dr. G. Vikram

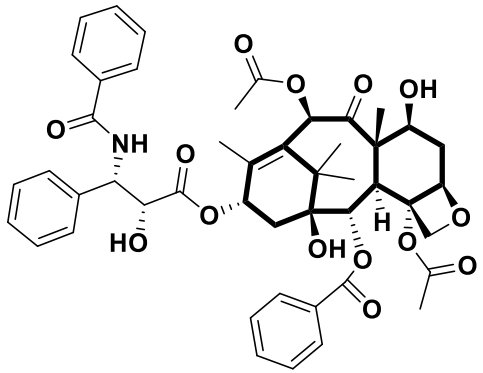
Mr. Lahu Chavan.

Mr. A. Sriram Murthy

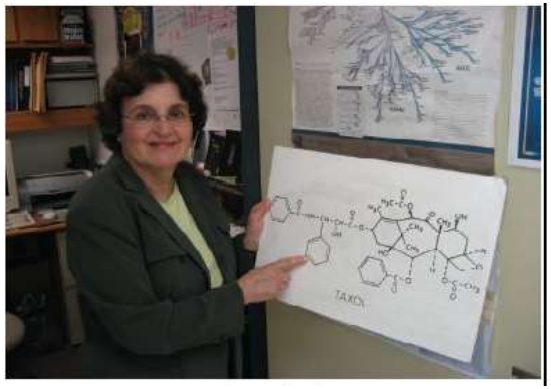


Dr. Prathama

Taxol



- Isolated from the bark of rare Pacific yew, *Taxus brevifolia* by M.E. Wall and M.C Wani.
- S. B. Horwitz established the mode of action, i.e., stabilization of microtubules.
- Opened up a new target towards finding a cure for cancer.
- First total synthesis achieved by K. C. Nicolaou *et al*. and R. Holton *et al.* in 1994.
- Nicolaou sent the publication to *Nature* whereas Holton to *J. Am. Chem. Soc.*
- Since *Nature* had a shorter turn around time K C Nicolaou got the honour of first total synthesis whereas Holton had actually achieved it earlier.

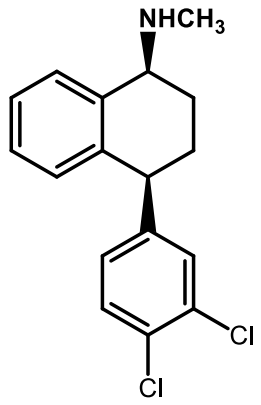


Major Causes of Mortality Worldwide
(2012 WHO report)

- Cardio-Vascular Disease 31.5%
  - Heart diseases
  - Brain stroke
- Infectious and Parasitic Disease 16.7%
  - Bacterial (Tuberculosis 2.7%)
  - Viral
  - Fungal
- Cancer 13.4%
  - Prostrate
  - Breast
  - Lung
  - Leukemia
- AIDS/HIV 3.5%
- **Neuro-psychiatric Disorders 2.2%**
  - Alzheimer's Disease and other Dementia
  - Parkinson's Disease
  - Depression and Schizophrenia
- Road accidents Unaccountable

Depression

- Very common psychiatric disorder
- 15% of life time common human suffers of this disease
- Women at high risk than men
- Common in young adults (15-40)
- No difference with caste-socio economic status
- Usually treated by psychotherapy, antidepressants, or a combination of the two or Electroconvulsive therapy

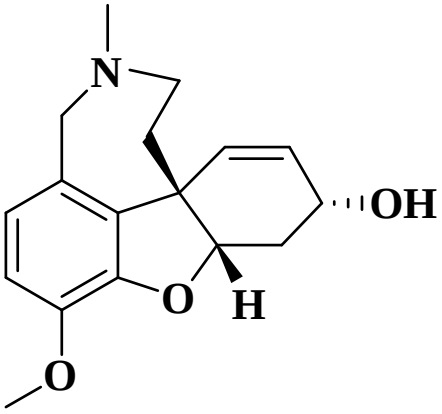


Sertraline
Antidepressant
5HT reuptake inhibitor
(A selective serotonin reuptake inhibitor
Tetrahedron, **2000***, 56,* 1111-1114

For years, the public believed that Diana was living a fairy tale life, married to her real life Prince Charming
While she was in fact fighting against depression

What is Alzheimer's disease?

- Alzheimer's disease is a brain disorder named for German physician Alois Alzheimer, who first described it in 1906.
- It causes large numbers of nerve cells in the brain to die.
- This affects the ability to remember things and think clearly. Doctors don't know what causes the disease. They do know that it usually begins after age 60 and nearly half of people age 85 and older may have Alzheimer's.



Galanthamine
Reversible inhibitor of Acetylcholinesterase (AChe) :
Used for the treatment of Alzheimer's disease
Tetrahedron Lett. **2009**, *50*, 4882-4884

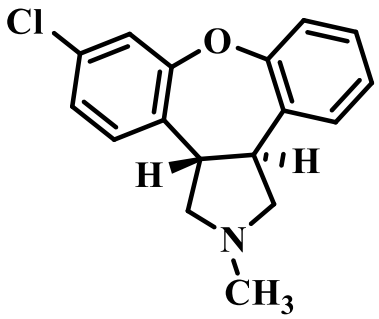
Alzheimer's disease usually affects people over 60

Trouble remembering recent events may be an early sign of Alzheimer's disease

Schizophrenia

- Originated from Greek *skhizein*-to split and *phren*-mind for splitting of mental functions
- Characterized by
  - Breakdown of thought processes
  - A deficit of typical emotional response
- Common symptoms
  - Auditory hallucination
  - Paranoid or bizarre delusions
  - Disorganized speech and thinking
- Affects ~1% population worldwide
- Accompanied by significant social and occupational dysfunction
- Thought mainly to affect cognition but also contributes to chronic emotional and behavioral problems

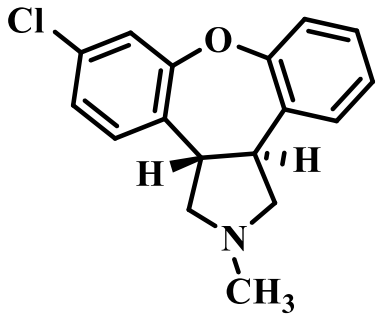
Paraveen Babi
Suffered from 'Paranoid Schizophrenia'.



Asenapine,
Org. Biomol. Chem.
2016, 000

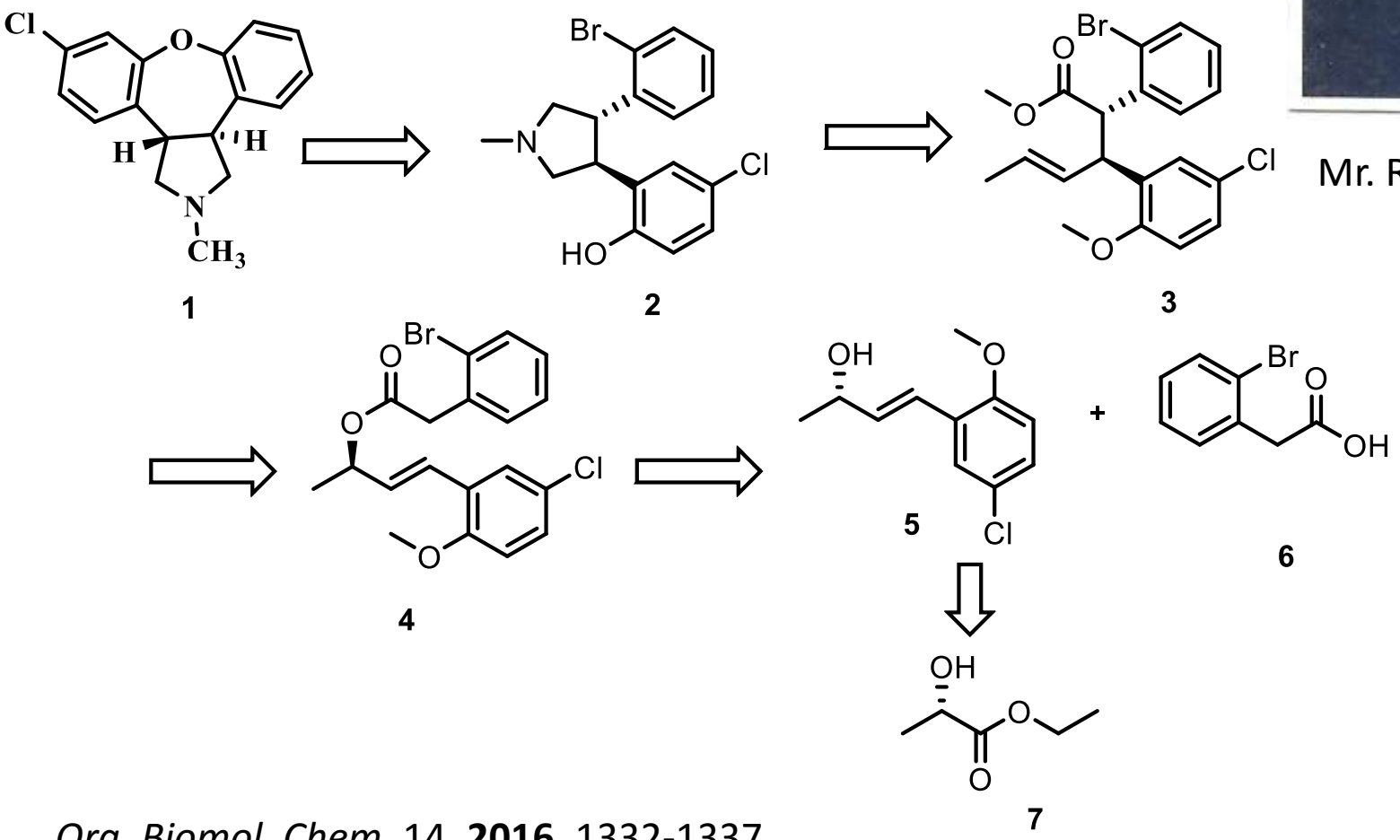
Asenapine

- (±) Asenapine approved by FDA for treatment of schizophrenia and acute manic or mixed episodes (bipolar disorders).
- Marketed by Schering-Plough
- Enhances the extracellular dopamine concentration in the mPFC (medial prefrontal Cortex).
- Also found to enhance the transmission of NMDA in the mFPC.



Retrosynthesis

Mr. Raghunath



Org. Biomol. Chem. 14, **2016**, 1332-1337

(*S*)-Ethyl lactate

Cervinomycin

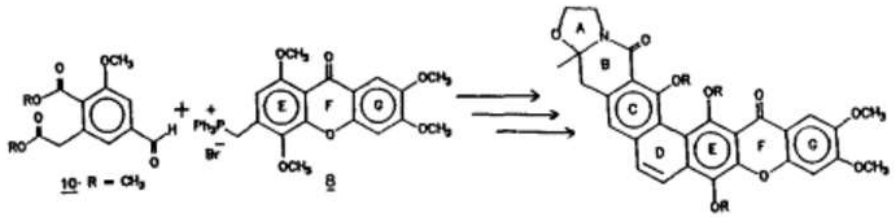
Total synthesis of cervinomycin A_1-trimethyl ether and cervinomycin A_2-methyl ether Original Research Article

Pages 5195-5198

Goverdhan Mehta, Shailesh R. Shah

Abstract | Close graphical abstract | PDF (188 K)

Graphic



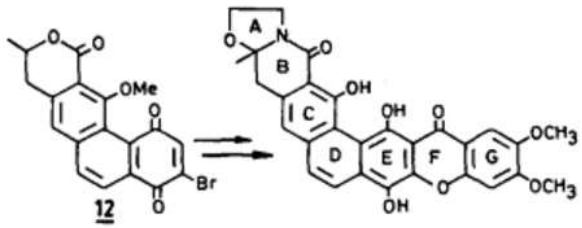
Total syntheses of (±) cervinomycins A_1 and A_2 Original Research Article

Pages 5199-5202

AV Rama Rao, J.S. Yadav, K Kishta Reddy, Velaparthi Upender

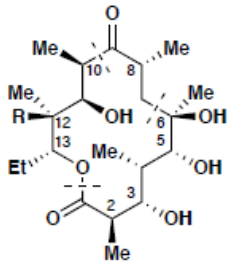
Abstract | Close graphical abstract | PDF (172 K)

Regiocontrolled total syntheses of cervinomycins A_1 (**1**) and A_2 (**2**) have been achieved from easily accessible 6-acetyl-2-bromo-1,4-dimethoxynaphthalene (**4**) via the key synthon **12**.

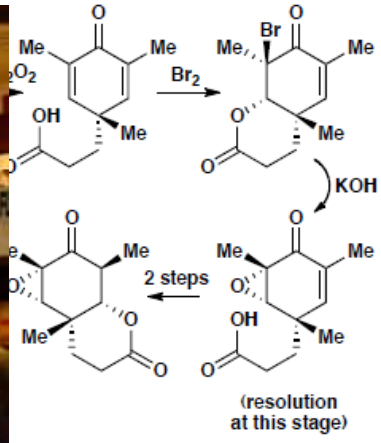


Erythronolide and Erythromycin

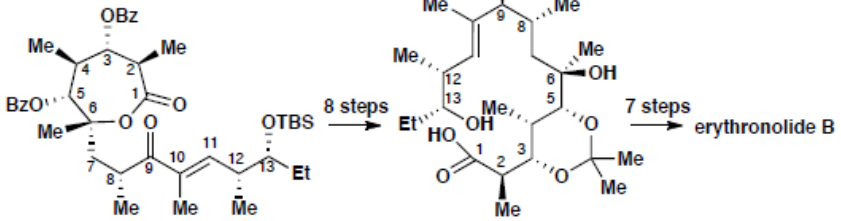
E. J. Corey (Harvard; 1978, 1979):
- First total syntheses of erythronolide B (***JACS*** 1978, ***100***, 4618 and 4620) and erythronolide A (***JACS*** 1979, ***101***, 7131), synthesized in (longest linear) 31 steps (ca. 0.8% overall, yields of the last epimerization-deprotection steps are not reported).
- 11 students worked on it, including K. C. Nicolaou.
- 50% yield for the macrolactonization, effectuated with a modified Corey-Nicolaou procedure (substituted imidazoles instead of pyridines).
- Key features: Cyclic stereocontrol (i.e. not a single aldol!); convergency amenable to the synthesis of both erythronolides A and B.
- Hard to retrosynthetically disconnect!
- "Classics-worthy" synthesis!



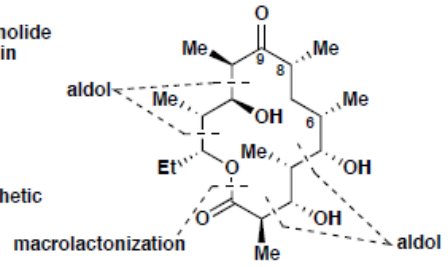
erythronolide A (R=OH)
erythronolide B (R=H)



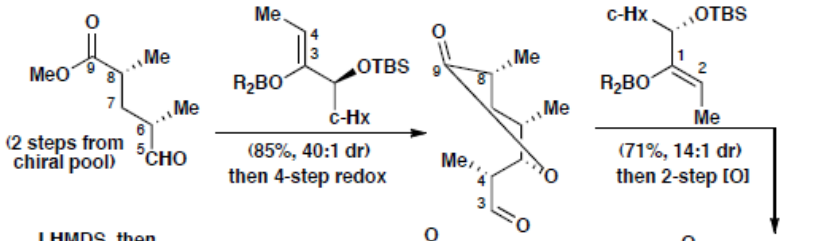
olide A synthesis simply uses a coupling
protected hydroxyl group at C12)

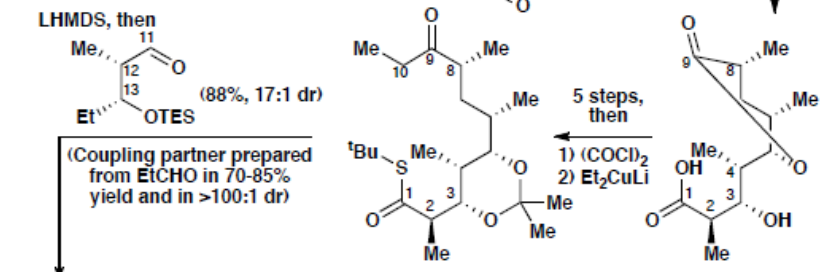


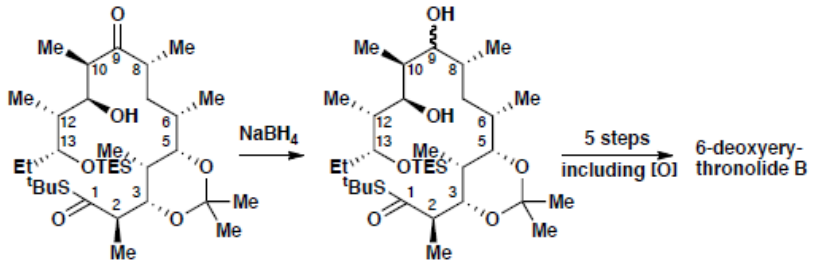
S. Masamune (MIT; 1981):
- First total synthesis of 6-deoxyerythronolide B (***JACS*** 1981, ***103***, 1568), synthesized in (longest linear) 22 steps (<7 % overall; missing yields for the last few steps).
- 4 students worked on it.
- 41 % yield for the macrolactonization, effectuated with Masamune's own *t*-butylthioester method, using CuOTf.
- Key feature: Aldol, aldol, aldol... a synthetic mimic of a polyketide synthase.
- Textbook-style retrosynthesis!
- Excellent demonstration of his own methodology.



6-deoxyerythronolide B

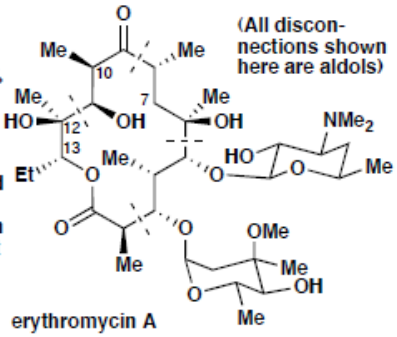




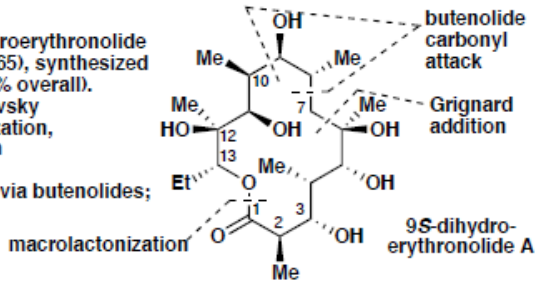


Erythronolide and Erythromycin

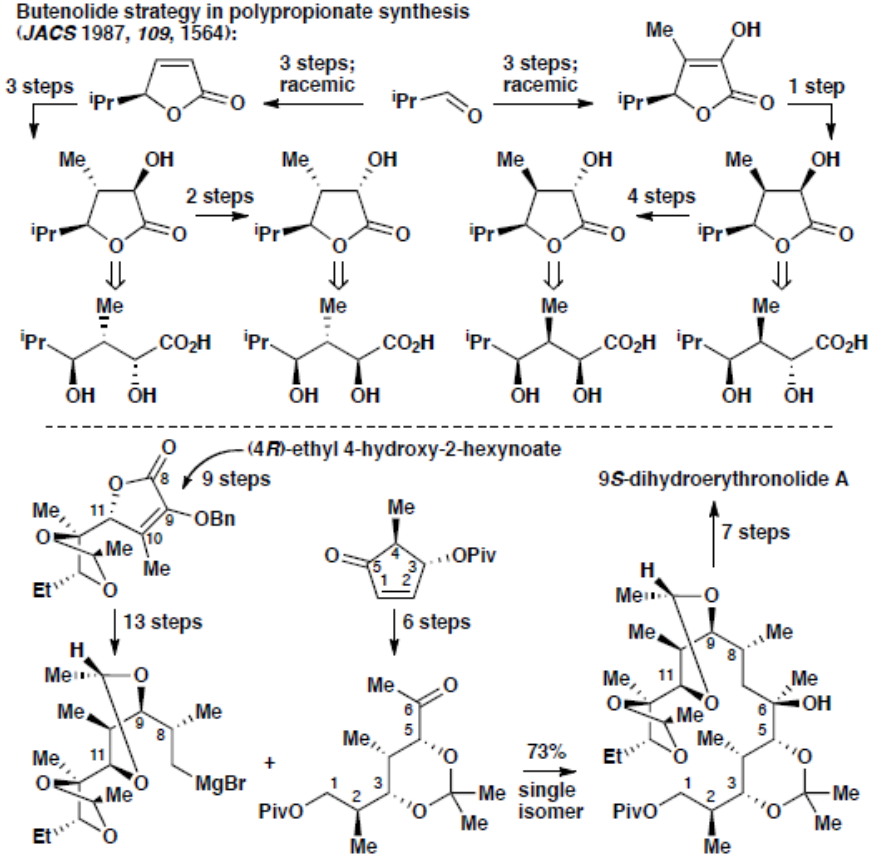
R. B. Woodward (Harvard; posthumous, 1981):
- First and only total synthesis of erythromycin A (*JACS* 1981, *103*, 3210, 3213 and 3215), synthesized in (longest linear) 52 steps (0.0089% overall, of which the last 10 steps, required for the glycosidations, yielded 1.54%).
- 48 students worked on it, including R. M. Williams.
- 70% yield for the macrolactonization, effectuated with a Corey-Nicolaou macrolactonization.
- Key features: Aldols using asymmetric induction via dithiadecalins; interestingly convergent; first detailed study on the structural requirements of the erythronolide seco acid macrolactonization.
- The end of the "Woodwardian era"...



G. Stork (Columbia; 1987):
- First total synthesis of 9*S*-dihydroerythronolide A (*JACS* 1987, *109*, 1564 and 1565), synthesized in (longest linear) 30 steps (1.3 % overall).
- Only one student: S. D. Rychnovsky
- 64 % yield for the macrolactonization, effectuated with a Keck-Steglich macrolactonization.
- Key features: Aldols performed via butenolides; convergent synthesis.



Butenolide strategy in polypropionate synthesis (*JACS* 1987, *109*, 1564):



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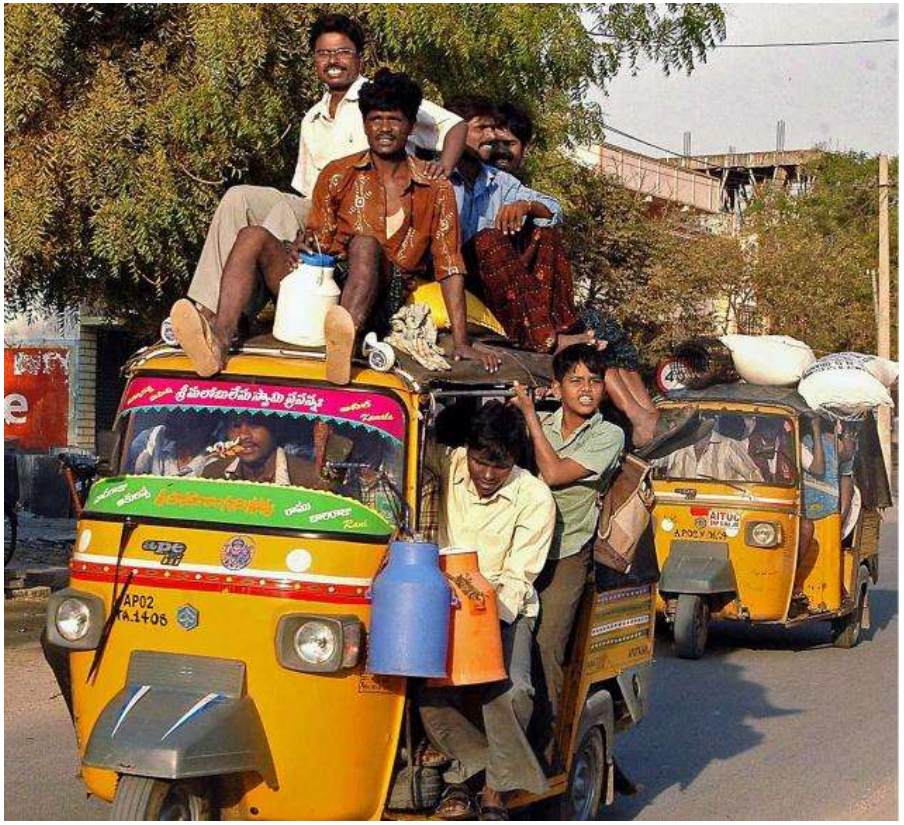
  - Leukemia
- AIDS/HIV 3.5%
- Neuro-psychiatric Disorders 2.2%
  - Alzheimer's Disease and other Dementia
  - Parkinson's Disease
  - Depression and Schizophrenia
- **Road accidents Unaccountable**

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THANK YOU