

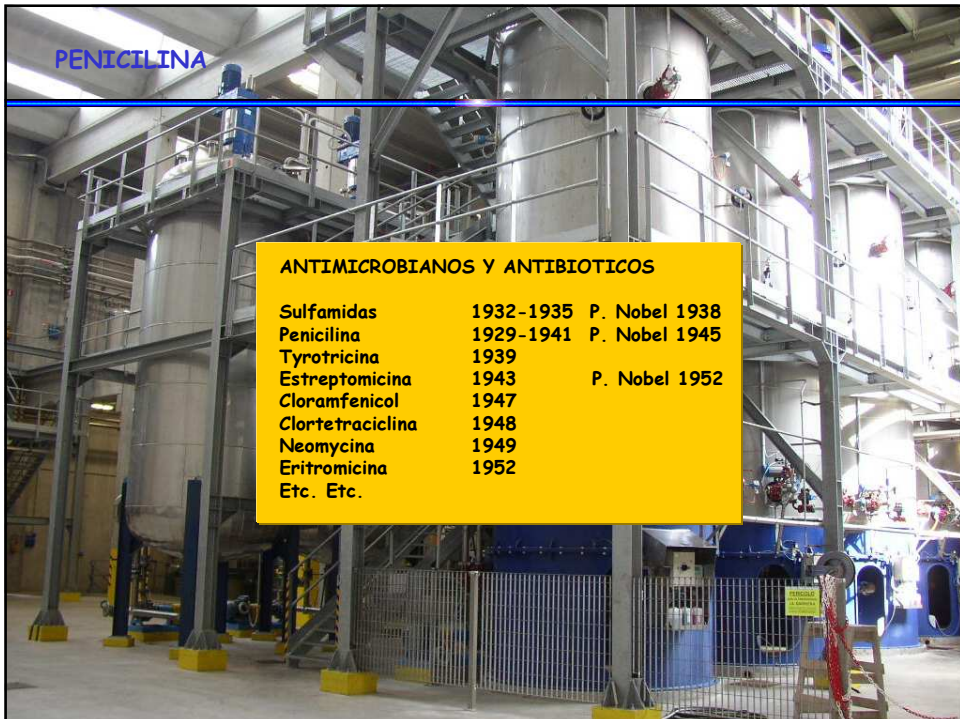


Universidades de Alcalá, Complutense y S Pablo-CEU
Doctorado Interuniversitario QUIMICA MEDICA

ESTRATEGIA EN SINTESIS DE FARMACOS

ANTIB BETA LACTAMICOS

Julio Alvarez-Builla



PENICILINA

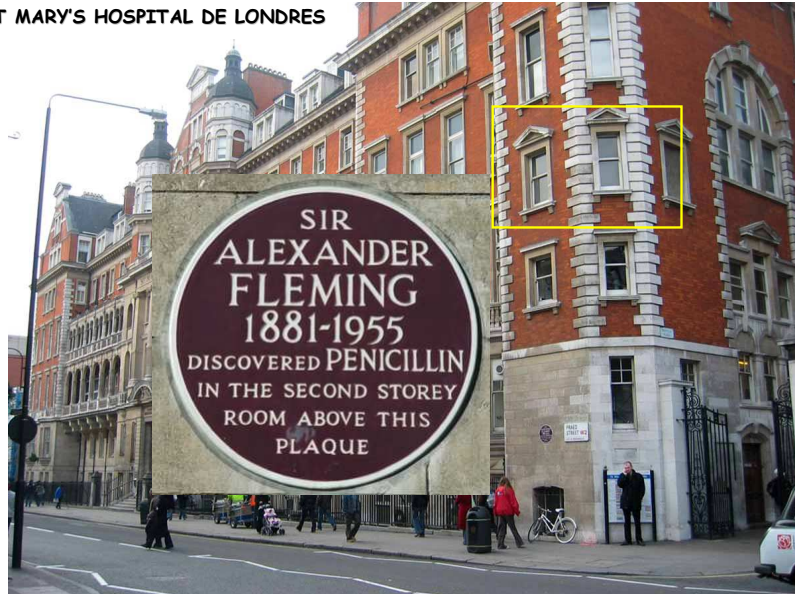
ANTIMICROBIANOS Y ANTIBIOTICOS

Sulfamidas	1932-1935	P. Nobel 1938
Penicilina	1929-1941	P. Nobel 1945
Tyroticina	1939	
Estreptomicina	1943	P. Nobel 1952
Cloramfenicol	1947	
Clortetraciclina	1948	
Neomycina	1949	
Eritromicina	1952	
Etc. Etc.		

PENICILINA

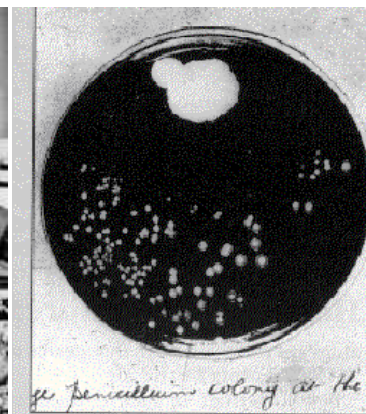
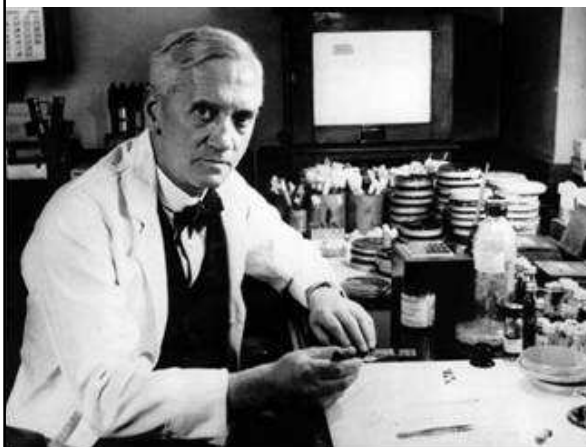
EL COMIENZO DE LA HISTORIA...

ST MARY'S HOSPITAL DE LONDRES



3

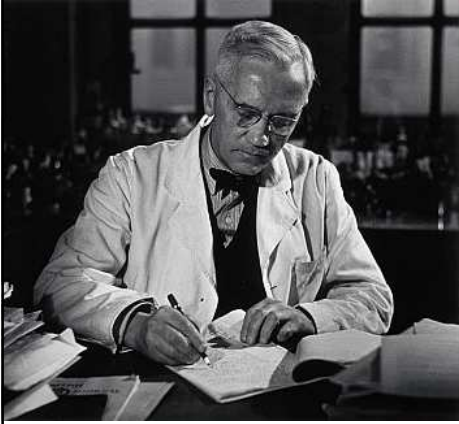
PENICILINA



Picture 2 Fleming's culture dish. The bacterial colonies are the small

A. FLEMING Y LA PLACA CON *S. AUREUS* CONTAMINADA CON *PENICILLIUM NOTATUM*

PENICILINA



On the antibacterial action of cultures of a *Penicillium*, with special reference to their use in the isolation of *B. influenzae*

1929 • Alexander Fleming

Fleming, Alexander. 1929. On the Antibacterial Action of Cultures of a *Penicillium*, with Special Reference to Their Use in the Isolation of *B. influenzae*. *British Journal of Experimental Pathology*, Vol. 10, pages 226-236.

WHILE WORKING WITH STAPHYLOCOCCUS variants a number of culture-plates were set aside on the laboratory bench and examined from time to time. In the examinations these plates were necessarily exposed to the air and they became contaminated with various micro-organisms. It was noticed that around a large colony of a contaminating mould the staphylococcus colonies became transparent and were obviously undergoing lysis.

Subcultures of this mould were made and experiments conducted with a view to ascertaining something of the properties of the bacteriolytic substance which had evidently been

formed in the mould culture and which had diffused into the surrounding medium. It was found that broth in which the mould had been grown at room temperature for one or two weeks had acquired marked inhibitory, bactericidal and bacteriolytic properties to many of the more common pathogenic bacteria.

CHARACTERS OF THE MOULD

The colony appears as a white fluffy mass which rapidly increases in size and after a few days sporulates, the centre becoming dark green and later in old cultures darkens to almost

5

PRECURSORES.....



38. LYON. — Ecole du Service de Santé Militaire. Actuellement Ecole Polytechnique.

Ernest Duchesne (1874-1912)

Medico militar francés

Presenta su Tesis Doctoral en 1897 en la Ecole du Service de Santé Militaire de Lyon sobre la interacción hongos-microbios (*P. glaucum*)

J. Lister, J. Tyndall (*P. glaucum*)

L. Pasteur (*P. notatum*)

Wikipedia



PENICILINA

CONTEXTO DE LA OBSERVACION

A COMIENZOS DEL S. XX NO HABIA
ANTIINFECCIOSOS UTILES

HIPOTESIS DE A. FLEMING

TODO ORGANISMO GENERA SUS
PROPIAS DEFENSAS CONTRA LA
INFECCION....

EL HONGO DEBIA GENERAR ALGUN
PRODUCTO QUE INHIBIA EL MICROBIO
(ANTIBIOTICO)



Penicillium notatum



PENICILINA



Penicillium notatum



PENICILINA



Sir William Dunn School
of Pathology, Oxford

1935 H. Florey es nombrado
Director

E. Lax
"The Mould in Dr. Florey's Coat"
Little Brown (2004)

DESCUBRIMIENTO DE FLEMING - CURIOSIDAD CIENTIFICA
H FLOREY RETOMA EL PROYECTO EN 1938



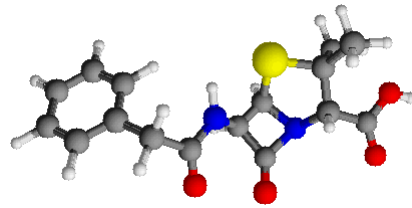
PENICILINA



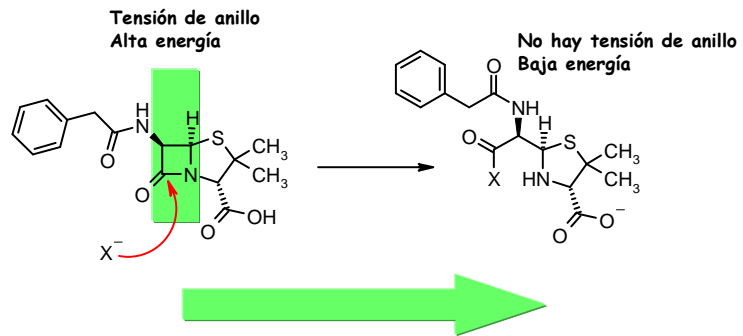
Sir William Dunn School of Pathology, Oxford

PENICILINA

REACTIVIDAD DE PENICILINA



www.acadabz.com

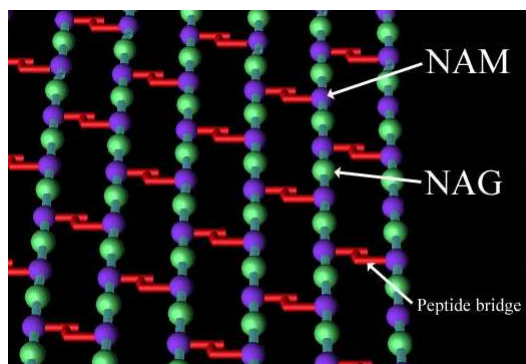
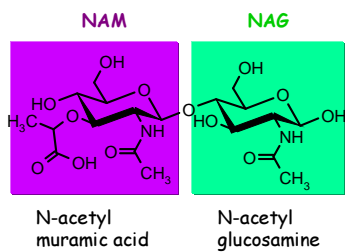


El proceso está favorecido por la disminución de energía del sistema

11

PENICILINA

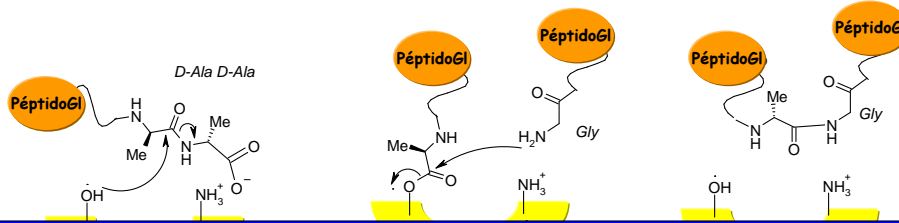
CUBIERTA DE PEPTIDO GLICANO



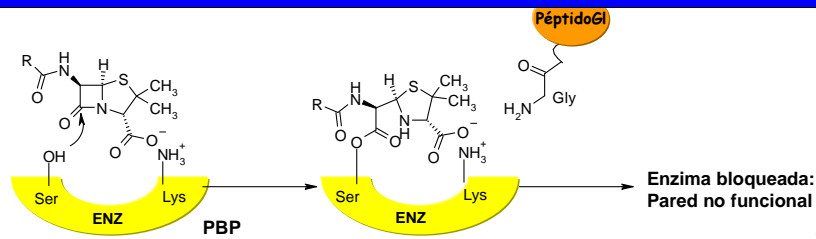
12

PENICILINA

ACTIVIDAD: INHIBICION DE PEPTIDO GLICANO SINTETASA



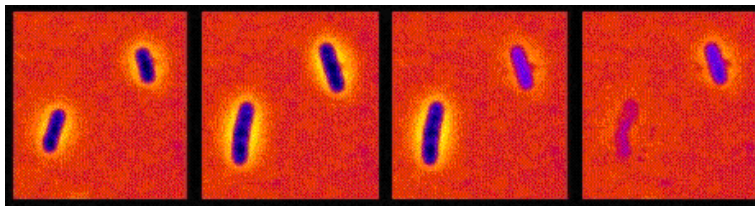
No hay ningún sistema similar en los mamíferos, por lo que las beta lactamas no son tóxicas



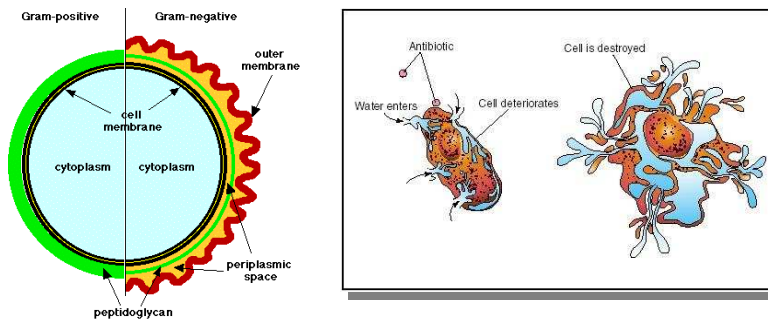
Enzima bloqueada:
Pared no funcional

13

PENICILINA



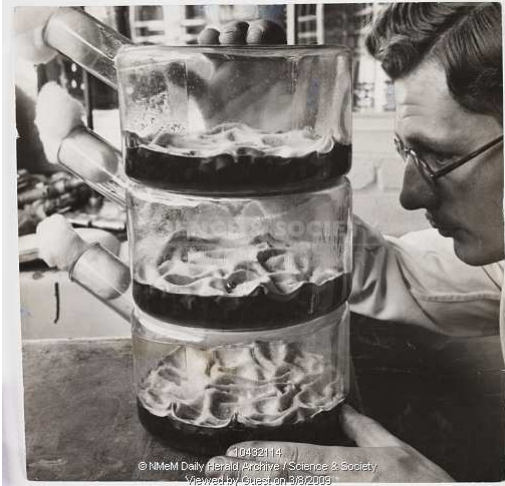
Penicillin kills bacteria by interfering with cell wall growth. These pictures show how bacteria growing in the presence of penicillin extend and eventually rupture because they are unable to divide. Photo courtesy of cellsalive.com



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PENICILINA

1er OBJETIVO: MÉTODOS DE PRODUCCIÓN



15

PENICILINA

1er OBJETIVO



RADCLIFFE INFIRMARY

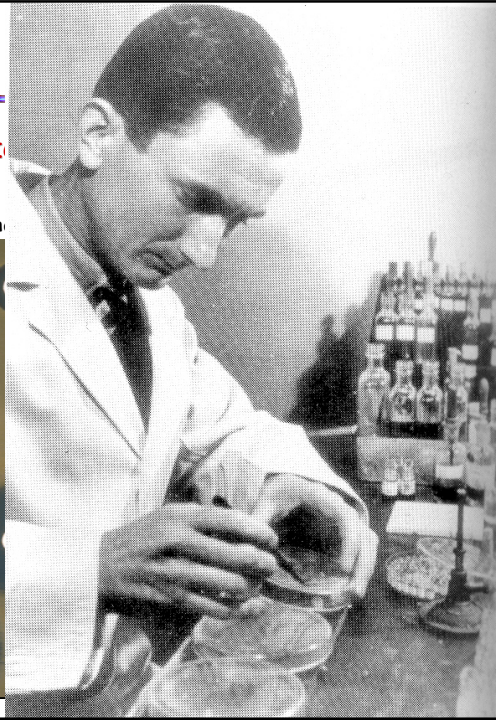
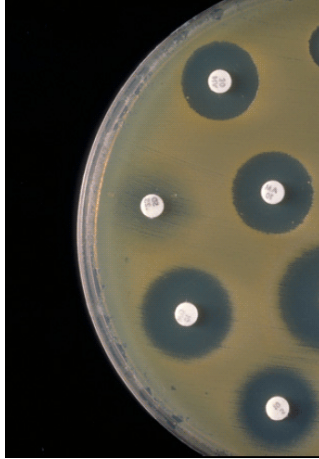


PENICILINA

1.2: CONTROL DE LA CONCENTRACION

1938-9

Heatley mejora la valoración de penicilina (h



PENICILINA

1.3: CALDO DE CULTIVO

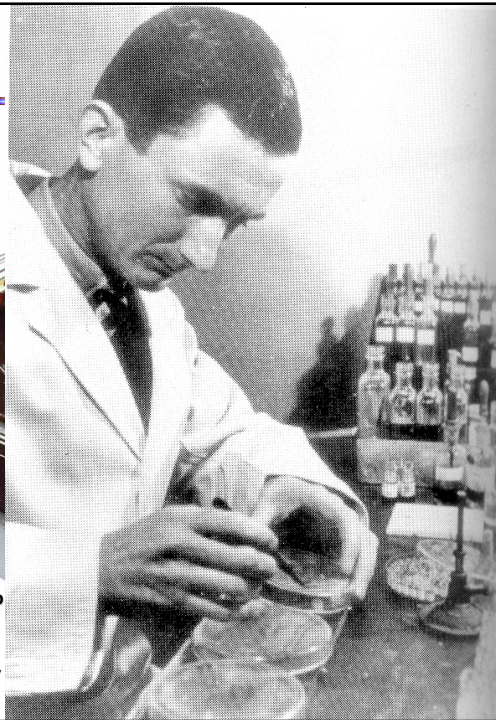


1938-9

Heatley mejora el medio de cultivo: extracto

1939

Heatley fué a Morrell's, una cervecera local, extracto de levadura fresco.



PENICILINA

2º OBJETIVO: ENSAYOS CON ANIMALES

1939 Florey: ensayos previos con ratones

1940 Abril-Mayo H. Florey, M. Jennings y J. ... ensayan penicilina sobre:

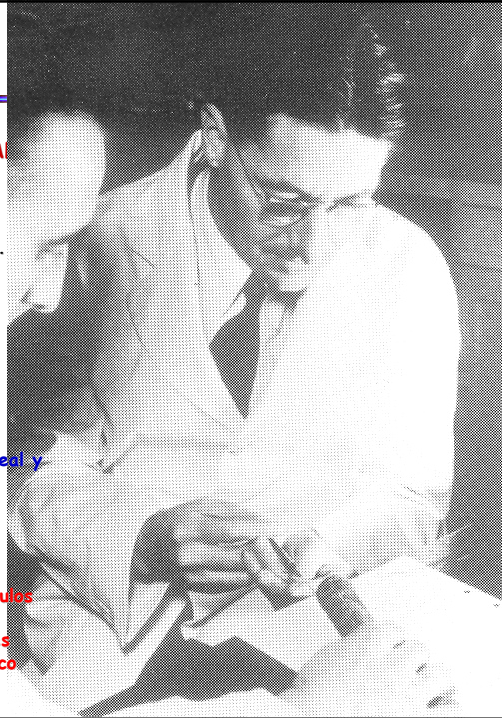
RATONES, RATAS, GATOS, CONEJOS
ABSORCIÓN, EXCRECIÓN Y TOXICIDAD

No sobre COBAYAS

VIA ORAL -mediante tubo al duodeno-
VIA PARENTERAL, intravenosa, intraperitoneal y
subcutánea.

LA PENICILINA SE DESTRUYE
MAYORITARIAMENTE EN EL ESTOMAGO

C. G. Paine (Sheffield): toxicidad sobre globulos
blancos
P. Medawar: toxicidad sobre tejidos celulares
D. Gardner y J. Orr-Ewing: perfil terapéutico



PENICILINA

3er OBJETIVO: ENSAYOS CLINICOS (RADCLIFFE INFIRMARY)

1941 27 E
acepta rec
[PIRÓGENO]

PIROGENO
PENICILINA

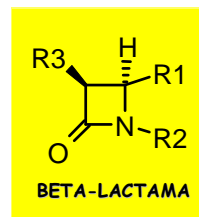
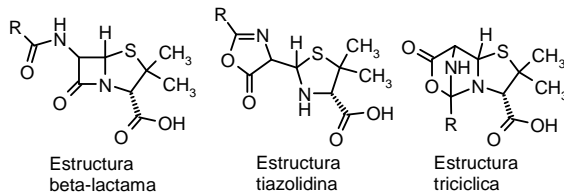
1941 12 F
estreptoco
100 mg ca

A las 24 h

El Dr. Cha
la llevaba

A los diez
estaba apo
vuelve a ap



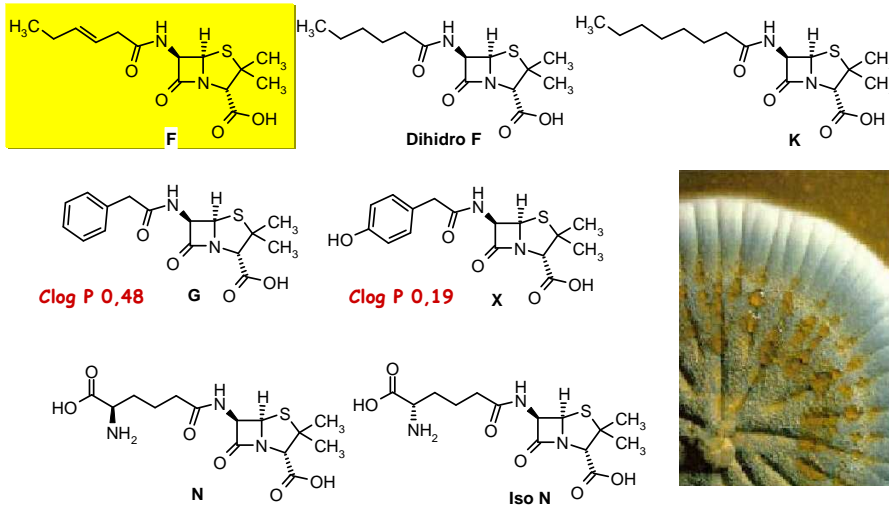


K. C. Nicolaou, T. Montagnon "Molecules that changed the world" (2008)
 R. Bentley, *J. Chem. Ed.* 2004, 81, 1462

21

PENICILINA

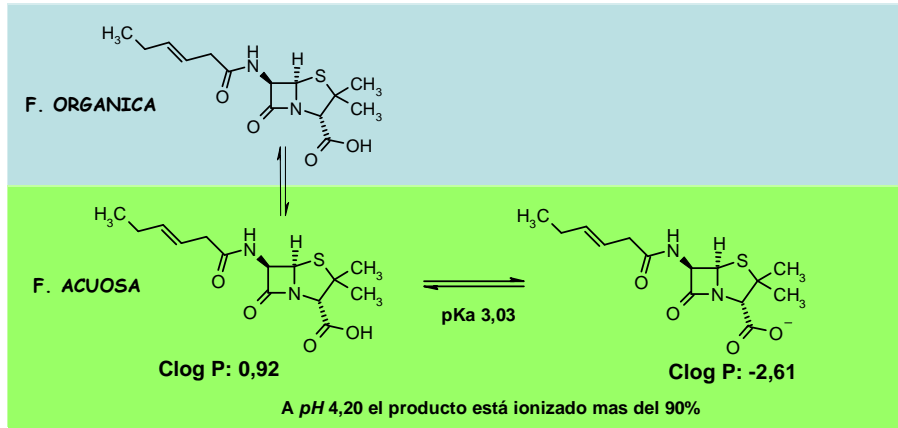
LA PENICILINA BRITANICA... (1939-43)



22

PENICILINA

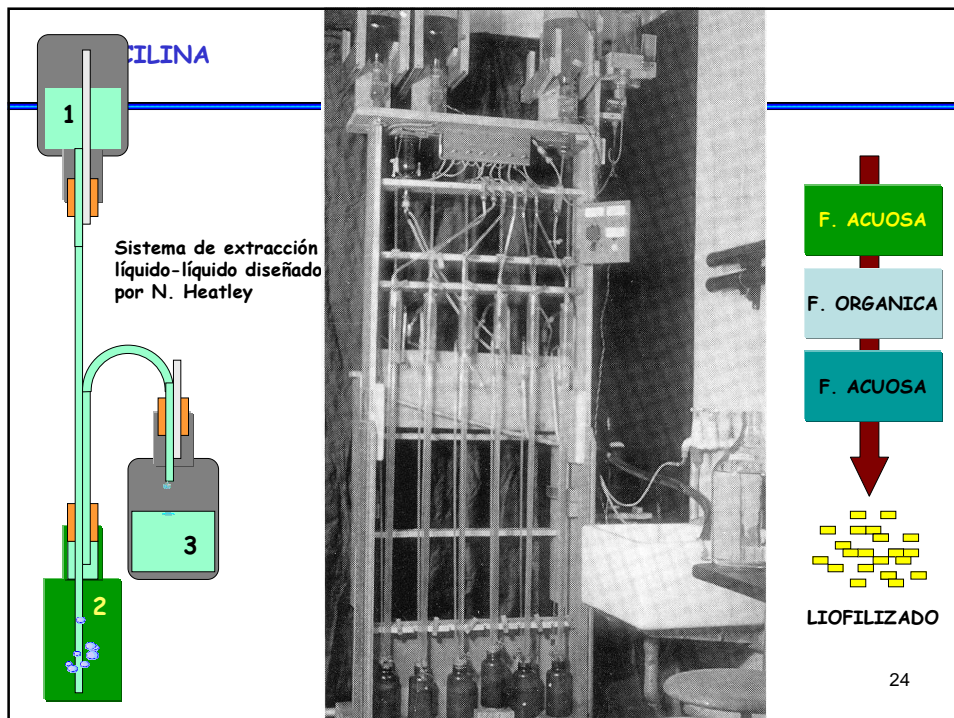
SOLUBILIDAD DE PENICILINA



Solo es estable en disolución acuosa a pH = 5-8

<http://www.chemaxon.com/marvin/sketch/index.html>

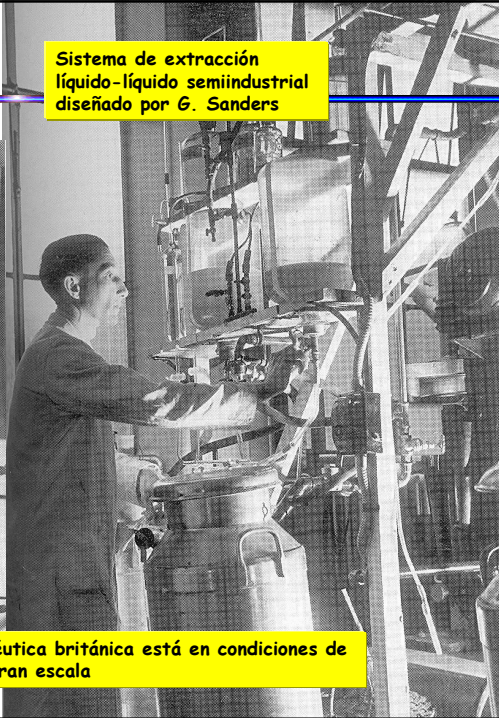
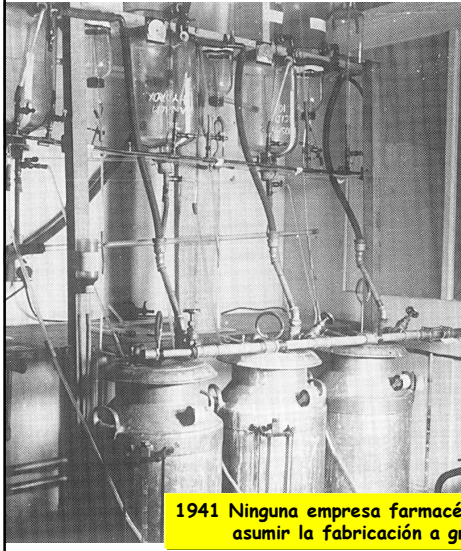
23



24

PENICILINA

Sistema de extracción líquido-líquido semiindustrial diseñado por G. Sanders



1941 Ninguna empresa farmacéutica británica está en condiciones de asumir la fabricación a gran escala

PENICILINA

UNA DISCREPANCIA CLAVE



1941
E. CHAIN PROPONE PATENTAR LA PENICILINA

H. FLOREY SE NIEGA A PATENTAR UN
DESCUBRIMIENTO MEDICO...

PENICILINA

COLABORACION EN PEORIA

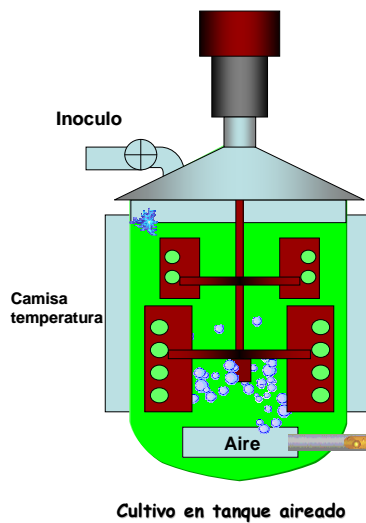


Northern Research Lab.



PENICILINA

MÉTODOS DE PRODUCCIÓN EN PEORIA



LOS ACIERTOS DE PEORIA:
1) CULTIVO EN TANQUE



PENICILINA

LOS ACIERTOS DE PEORIA: 2) NUEVO MEDIO DE CULTIVO



LOS PRODUCTOS DEL MAIZ



Aceite de maiz



Almidón de maiz



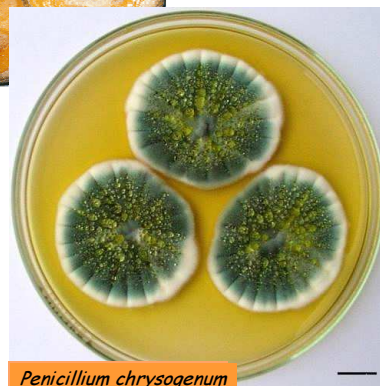
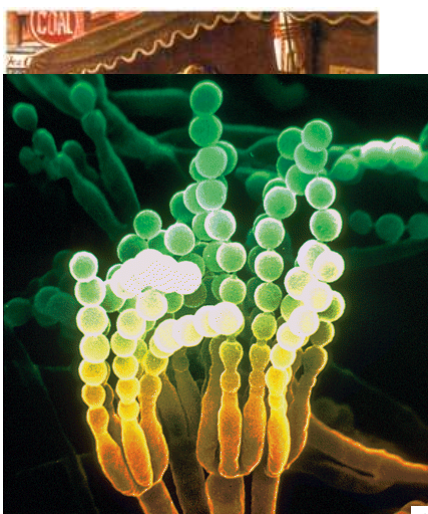
Resíduo: Corn steep liquor

900 U.I./ml de filtrado

-En Oxford-
(2 U.I./ml de filtrado)

PENICILINA

LOS ACIERTOS DE PEORIA: 3) OTRO PENICILLIUM

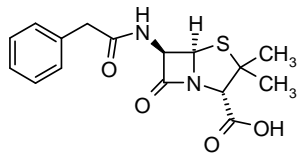


Penicillium chrysogenum

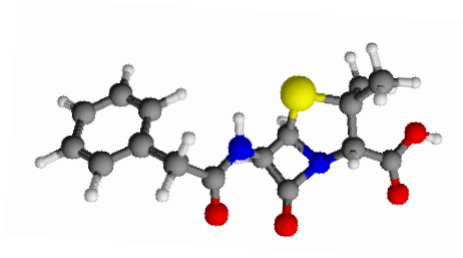
Producía 3000 veces mas penicilina que *P. notatum*

PENICILINA

LA PENICILINA NORTEAMERICANA....(1941-)



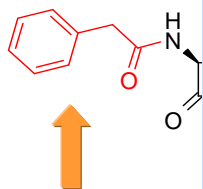
G ó bencilpenicilina



N. A. Meyers, "Happy Accidents" Arcade publishing 2007 pag 74-5

31

PENICILINA

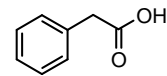


A partir de 1941

**Pfizer
Merck
Squibb
Eli & Lilly**

**Lederle
Abbott
Winthrop
Parke-Davis
Upjohn
Schenley**

**Ponen en marcha
la producción de
Penicilina**



ACIDO FENILACETICO

ó Bencilpenicilina

32

PENICILINA

Thanks to PENICILLIN
...He Will Come Home!



33

ANTIB BETA LACTAMICOS NC

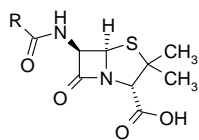
MEJORA DE LOS METODOS DE PRODUCCION

- 1) Fermentación aireada en tanques, en vez de en superficie
- 2) Uso de *Penicillium Chrysogenum* en vez de *P. notatum*.
- 3) nuevos medios de cultivo -cornsteep- en vez de extracto de levadura

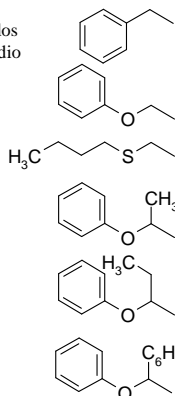
2. PENICILINAS BIOSINTETICAS



El resto acilo procede de los
ácidos presentes en el medio



R



Denomin.

G Bencilpenicilina
V Fenoximetilpenicilina
S Butiltiometilpenicilina
Feneticilina
Propicilina
Fenbencilina

CLog P

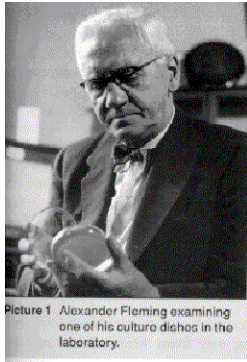
1,817

1,695

34

ANTIB BETA LACTAMICOS NC

PREMIO NOBEL DE MEDICINA, 1945



A. Fleming



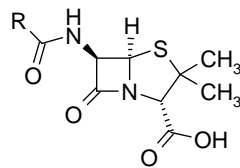
H. Florey



E. Chain

35

PENICILINA



Back

Emergency
Contact
656.555.1212



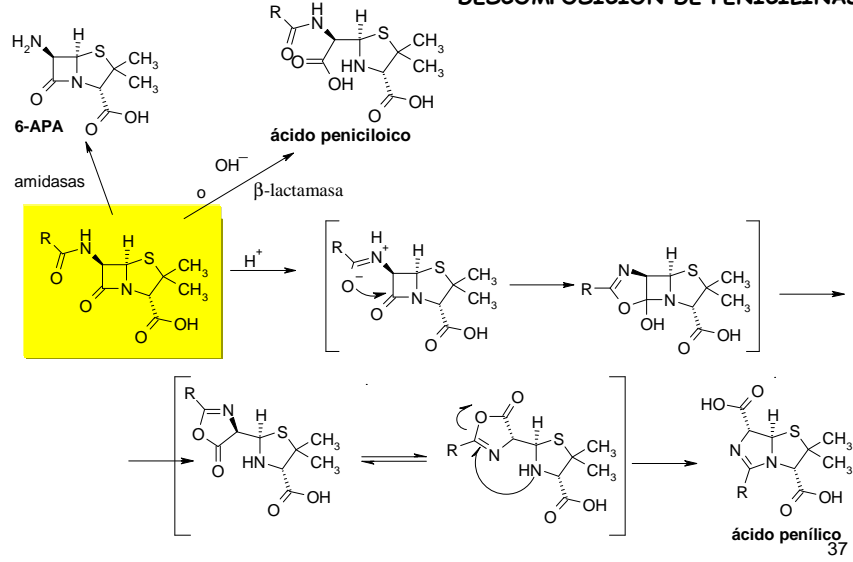
DIFICULTADES DE USO TERAPEUTICO

- 1) Baja estabilidad en medio ácido (via oral)
- 2) Espectro antimicrobiano estrecho (Gram +)
- 3) Desarrollo de resistencia por algunos microorganismos
- 4) Alergicidad en un porcentaje de pacientes (10%, anafilaxis 0,01%)
- 5) Farmacocinética inadecuada
 - Baja absorción oral
 - Excreción rápida (80% dosis eliminada en 3-4h)

36

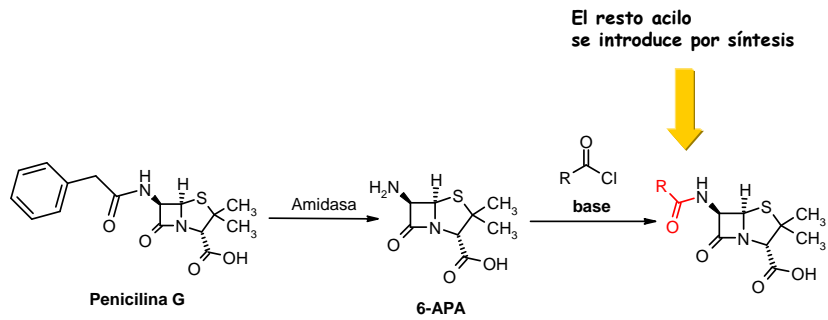
PENICILINA

DESCOMPOSICION DE PENICILINAS



PENICILINA

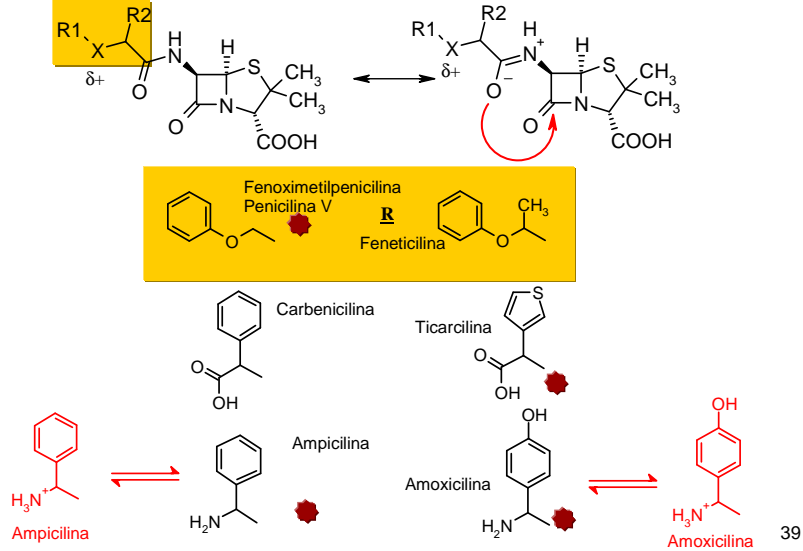
PENICILINAS SEMISINTETICAS



Todas las penicilinas a partir de este punto son SEMISINTETICAS

PENICILINA

3. PENICILINAS RESISTENTES AL MEDIO ACIDO



39

PENICILINA

ACTIVIDAD DE PENICILINAS

Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudomonas	Anaerobios
25	++	-	+/-	-	+

Bencilpenicilina

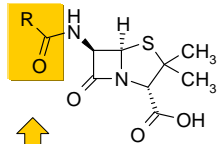
Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudomonas	Anaerobios
60	++	-	+/-	-	+

Fenoximetilpenicilina

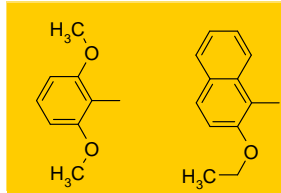
40

PENICILINA

4. PENICILINAS RESISTENTES A BETA LACTAMASAS

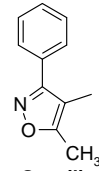


R CON IMPEDIMENTO ESTERICO

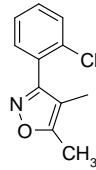


Metcilina

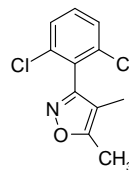
Nafcilina



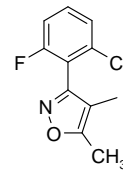
Oxacilina



Cloxacilina



Dicloxacilina



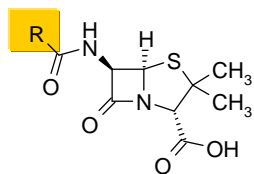
Floxacilina

Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudo-monas	Anaerobios
50	+	+	-	-	-

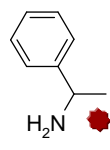
41

PENICILINA

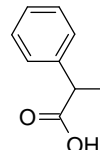
5. PENICILINAS DE AMPLIO ESPECTRO



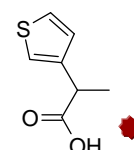
Grupos polares en R



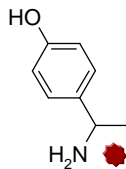
Ampicilina



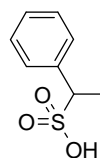
Carbenicilina



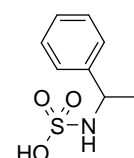
Ticarcilina



Amoxicilina



Sulbenicilina

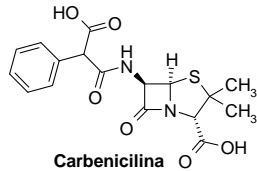


Suncilina

42

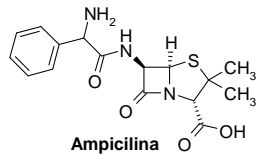
PENICILINA

ACTIVIDAD DE CARBOXY Y AMINOPENICILINAS



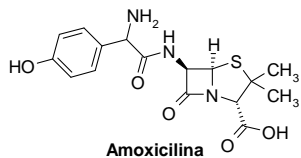
Carbenicilina

Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudomonas	Anaerobios
-	+/-	+	+	+	+



Ampicilina

Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudomonas	Anaerobios
30-50	+	+/-	+	-	+



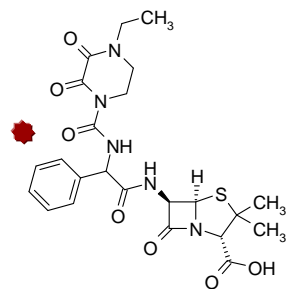
Amoxicilina

Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudomonas	Anaerobios
70-80	+	+/-	+	-	+

43

PENICILINA

5. PENICILINAS DE AMPLIO ESPECTRO



Piperacilina

Eficaz en neumonía, peritonitis...

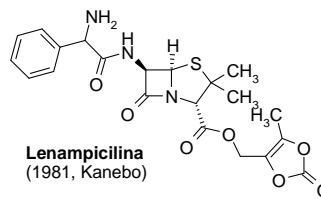
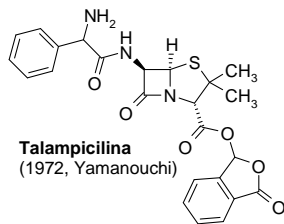
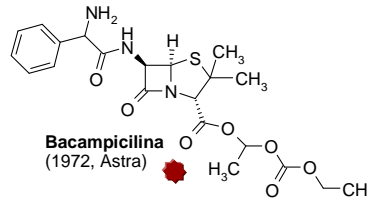
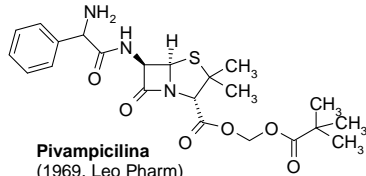
Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudomonas	Anaerobios
-	+	+	++	++	+

Derivados de Ampicilina, activos frente a *Pseudomonas Aeruginosa*

44

PENICILINA

7. PROFARMACOS DE PENICILINAS

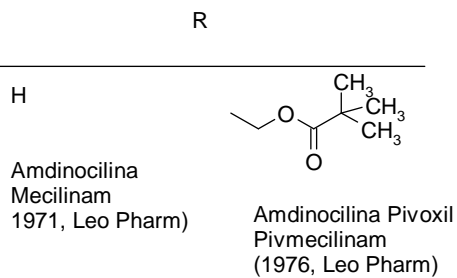
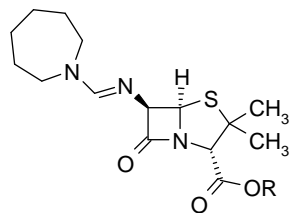


Formas de absorcion oral BIODISPONIBILIDAD ORAL= 90%

45

ANTIB BETA LACTAMICOS NC

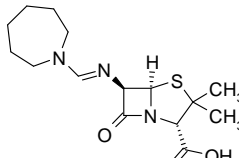
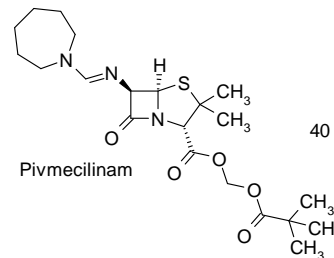
7. PROFARMACOS DE PENICILINAS



46

ANTIB BETA LACTAMICOS NC

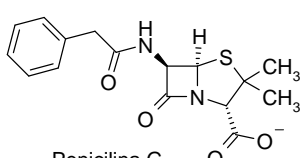
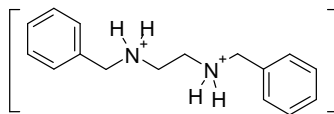
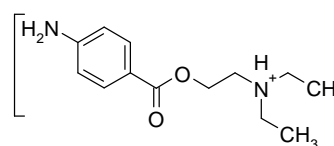
ACTIVIDAD DE AMIDINOPENICILINAS

	Absorcion oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudomonas	Anaerobios
 Mecilinam	0	-	-	++	-	-
 Pivmecilinam	40					

47

ANTIB BETA LACTAMICOS NC

8. SALES DE PENICILINAS

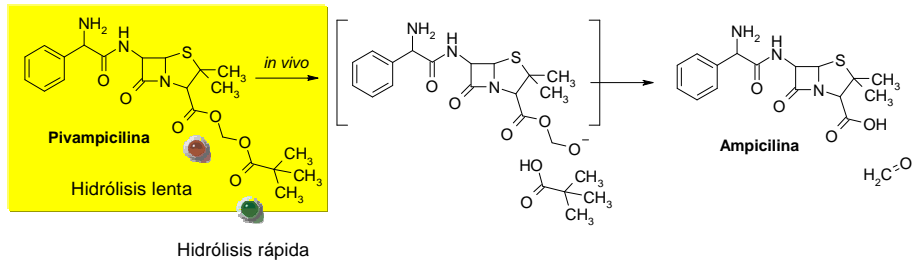
 Penicilina G	 Penicilina G Benzatina Concl. plasmatica máxima= 18 h. Semivida eliminación= 5 días	Pen ₂
	 Penicilina G Procaina Concl. plasmatica máxima= 2 h. Semivida eliminación= 5 h.	Pen

FORMULACIONES DE LARGA DURACIÓN

48

PENICILINA

7. PROFARMACOS DE PENICILINAS



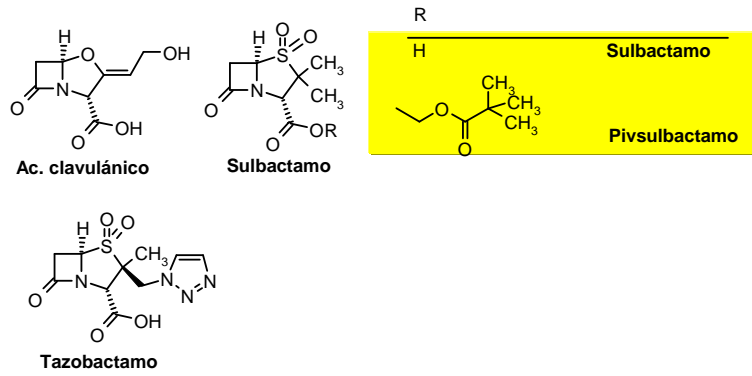
PENICILINA

7. PROFARMACOS DE PENICILINAS

	Ampicilina	Absorción oral % 30-50	Gram+	Resist. a lactamasas +/-	Enterobacteriaceas +	Pseudo-monas -	Anaerobios +
	Amoxicilina	Absorción oral % 70-80	Gram+	Resist. a lactamasas +/-	Enterobacteriaceas +	Pseudo-monas -	Anaerobios +
	Pivampicilina	Absorción oral % 85-95	Gram+	Resist. a lactamasas +/-	Enterobacteriaceas +	Pseudo-monas -	Anaerobios +
	Bacampicilina	Absorción oral % 85-95	Gram+	Resist. a lactamasas +/-	Enterobacteriaceas +	Pseudo-monas -	Anaerobios +

PENICILINA

9. INHIBIDORES DE BETA LACTAMASAS

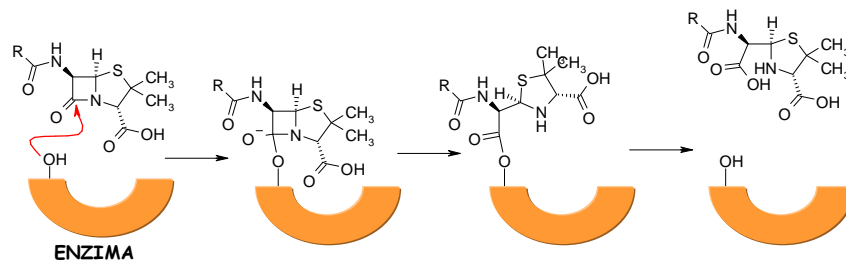


51

PENICILINA

9. INHIBIDORES DE BETA LACTAMASAS

TRES VIAS DE RESISTENCIA BACTERIANA A BETA LACTAMASAS:
A) MODIFICACION DE PBP_s EN LA ZONA DEL RECEPTOR
B) MODIFICACION DE LA PERMEABILIDAD DE MEMBRANAS
C) PRODUCCION DE BETA LACTAMASAS



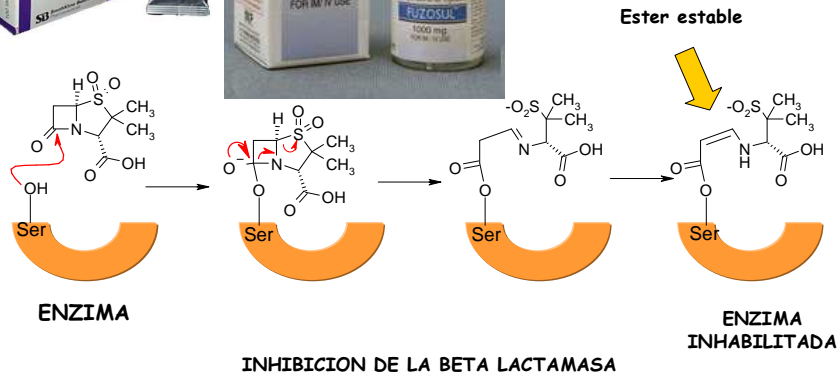
ACCION DE LA BETA LACTAMASA

52

PENICILINA



INHIBIDORES DE BETA LACTAMASAS

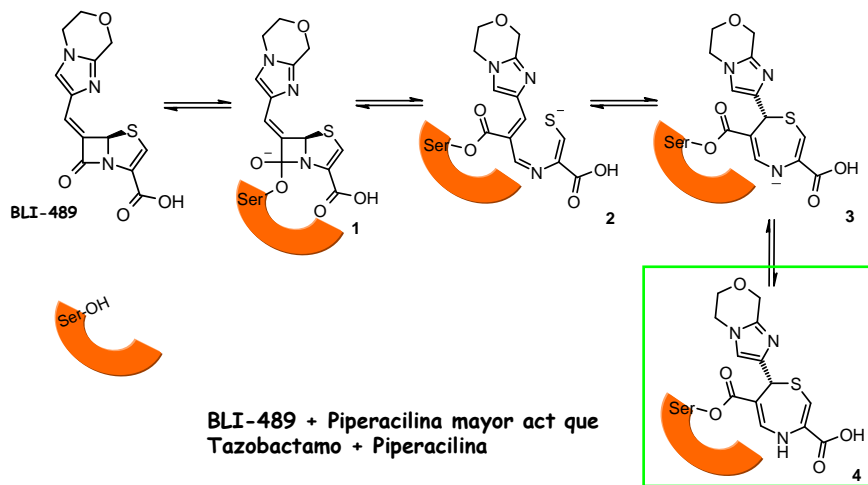


R. G. Micetich y col., *J. Med. Chem.* **1987**, 30, 1469

53

PENICILINA

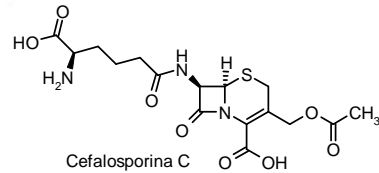
9. INHIBIDORES DE BETA LACTAMASAS



T. S. Mansour, P.A. Bradford, A. M. Venkatesan, *Ann. Rep. Med. Chem.* **2008**, 43, 247

54

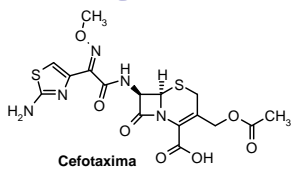
E. ABRAHAM LIDERA EL PROYECTO DE LAS CEFALOSPORINAS



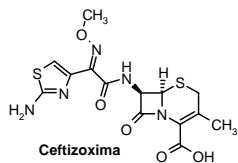
Aislado de *Cephalosporium acremonium* a partir de una alcantarilla de Cerdeña, en 1948 por Giuseppe Brotzu

Y ESTA VEZ SI SE PATENTAN...

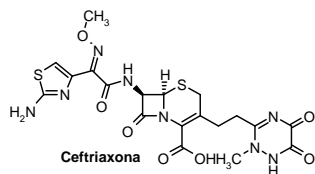
OTRAS BETA LACTAMAS: CEFALOSPORINAS DE 3ª GENERACION



Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudo-monas	Anaerobios
0	+/-	+	++	+/-	+



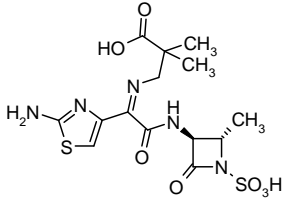
Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudo-monas	Anaerobios
0	+/-	+	++	+	+



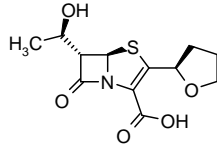
Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudo-monas	Anaerobios
0	+/-	+	++	+	+

ANTIB BETA LACTAMICOS

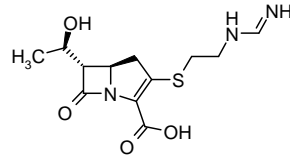
NUEVOS ANTIBOTICOS BETA-LACTAMICOS



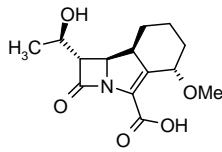
8 Azthreonam
Monobactama



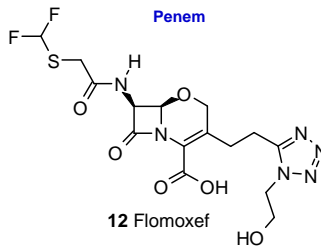
9 Furopenem
Penem



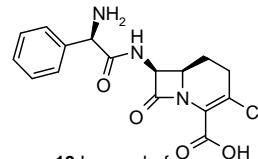
10 Imipenem
Carbapenem



11 Sanfetrinem
Trimem



12 Flomoxef
Oxacefem

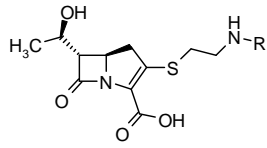


13 Loracarbef
Carbacefem

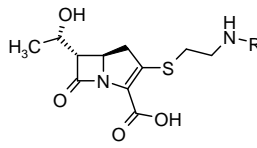
57

PENICILINA

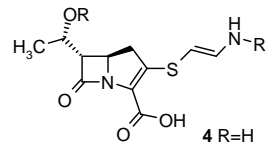
NUEVOS CARBAPENEMS



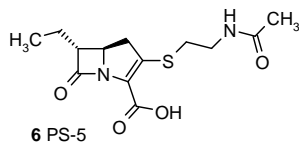
1 R=H Thienamicina
2 R=COCH₃ N-Acetilthienamicina



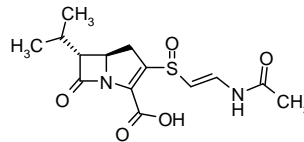
3 Epithienamicina



4 R=H
5 R=SO₃H



6 PS-5



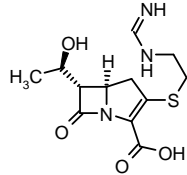
7 Carpetymicina

Thienamicina, *Streptomyces cattleya* (1974), muy resistente a beta-lactamasas.

58

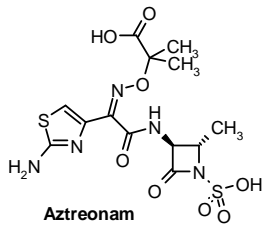
PENICILINA

OTRAS BETA LACTAMAS: CARBAPENEMS Y MONOBACTAMAS



Imipenem

Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudomonas	Anaerobios
0	+	+	+++	++	++



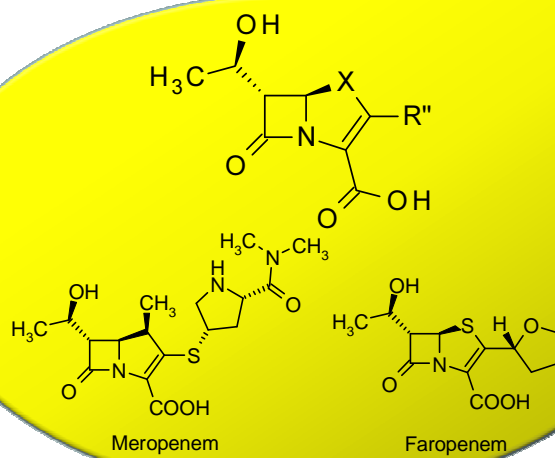
Aztreonam

Absorción oral %	Gram+	Resist. a lactamasas	Enterobacteriaceas	Pseudomonas	Anaerobios
0	-	+	+++	+	-

59

ANTIB BETA LACTAMICOS NC

CARBAPENEMS Y PENEMS: SINTESIS



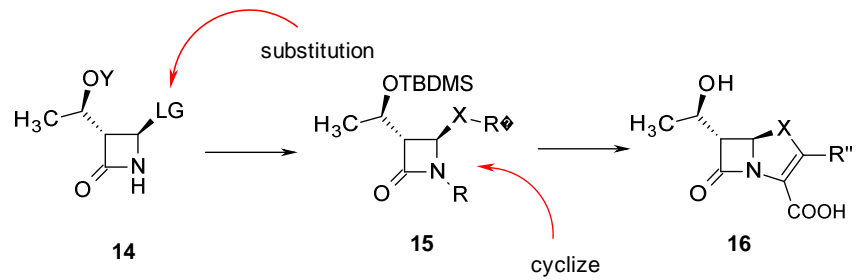
Meropenem

Faropenem

60

ANTIB BETA LACTAMICOS NC

CARBAPENEMS Y PENEMS: SINTESIS

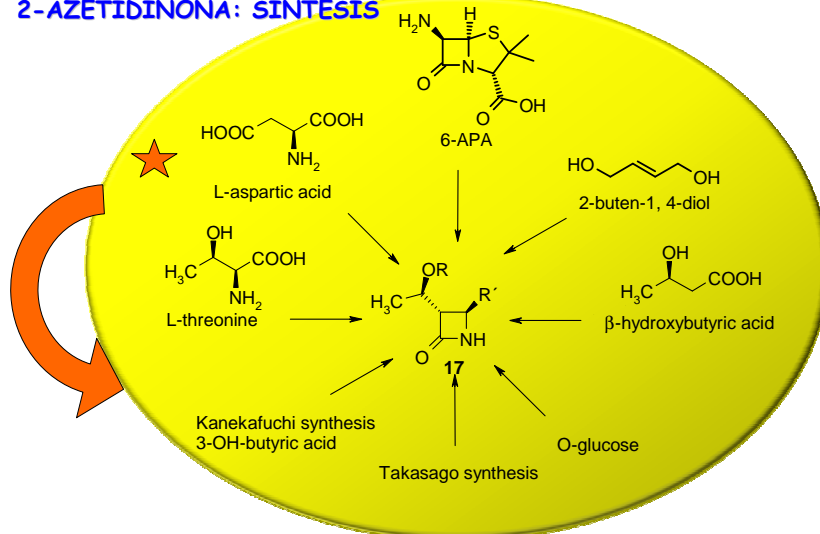


Estrategia general

61

ANTIB BETA LACTAMICOS NC

2-AZETIDINONA: SINTESIS

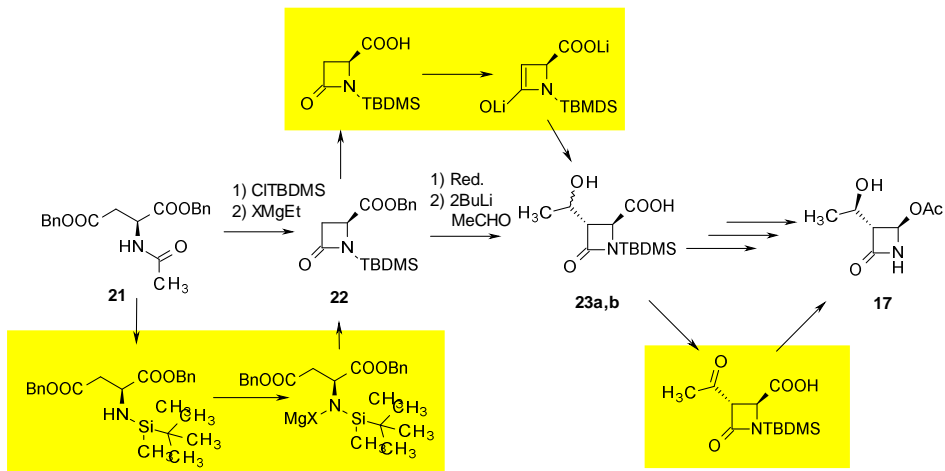


Sedelmeier, G, "Organic Synthesis Highlights II" Waldmann H. Ed., VCH, 1995, 277-288

62

ANTIB BETA LACTAMICOS NC

2-AZETIDINONA: SINTESIS DE MERCK A PARTIR DE AC. ASPARTICO

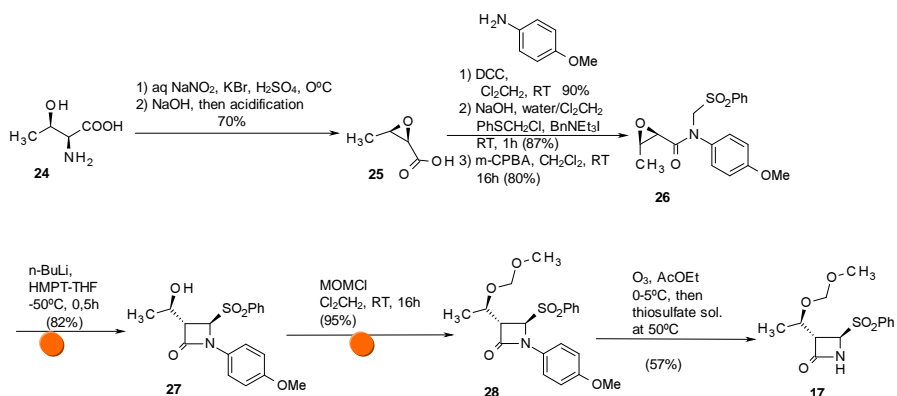


Reider, P. J., Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, 23, 2293

63

ANTIB BETA LACTAMICOS NC

2-AZETIDINONA: SINTESIS DE SANKYO A PARTIR DE L-TREONINA

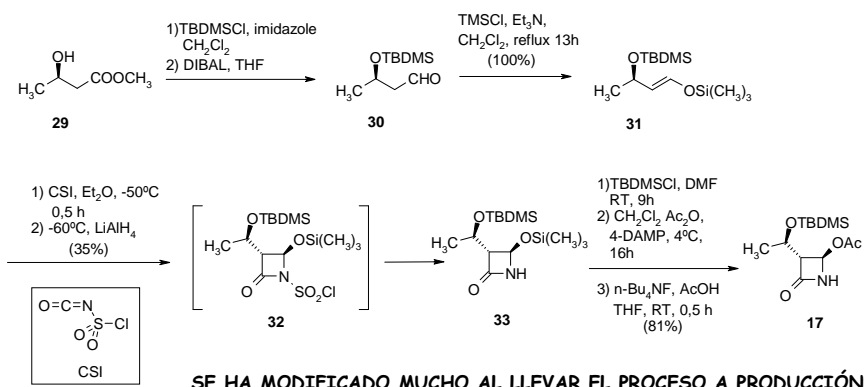


Yanagisawa, H. et al. *Tetrahedron Lett.* **1983**, 24, 1037

64

ANTIB BETA LACTAMICOS NC

2-AZETIDINONA: SINTESIS DE KANEGAFUCHI A PARTIR DE AC. 3-OH-BUTIRICO

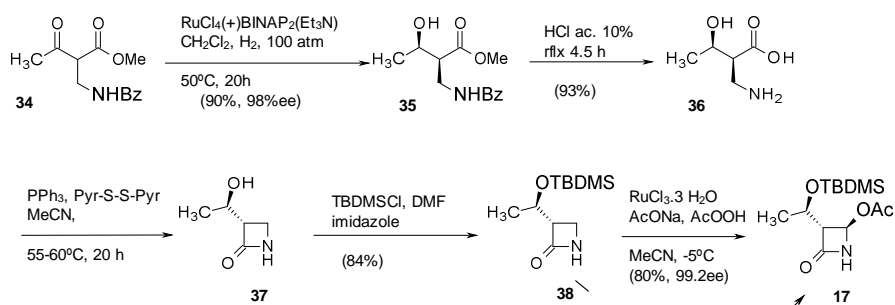


US 4791198 (1987), US 4861877 (1987), US 4914200 (1989)

65

ANTIB BETA LACTAMICOS NC

2-AZETIDINONA: APROXIMACION DE TAKASAGO

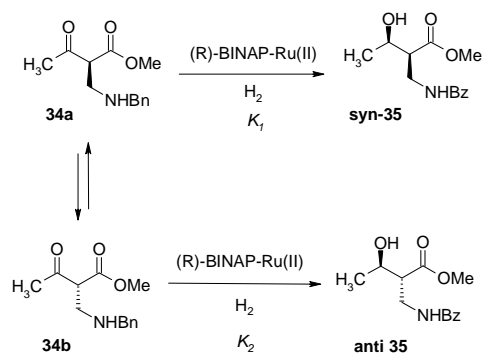


Saito, T., Komobayashi, H. Murahashi, S., US5629420 (1995)

66

ANTIB BETA LACTAMICOS NC

RESOLUCION CINETICA

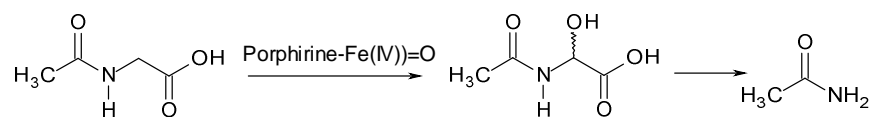


Mashima, K., et al. *J. Chem. Soc. Chem. Comm.* **1991**, 609

67

ANTIB BETA LACTAMICOS NC

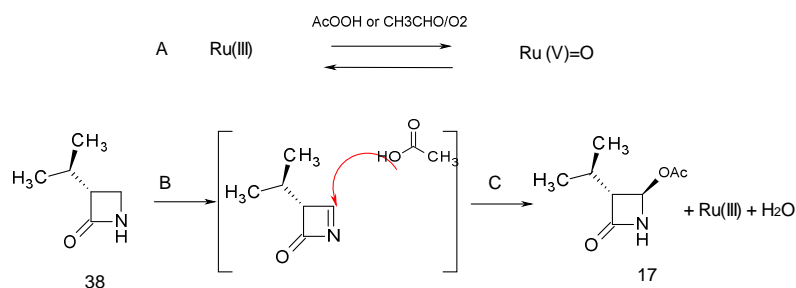
PROYECTO DE MURAHASHI, REACCIONES DE OXIDACION CIT P-450



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ANTIB BETA LACTAMICOS NC

OXIDACION DE MURAHASHI, REACCIONES DE OXIDACION RELACIONADAS CIT P-450



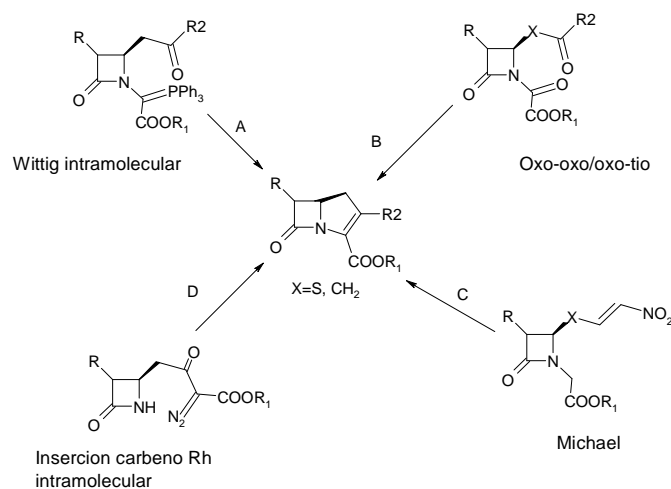
- Generación de especies de Ru(IV)=O, con ácido peracético, o posteriormente, con una mezcla acetaldehído/oxígeno.
- Abstracción de hidruro del C-4 de la lactama (protón + electrones)
- Ataque nucleófilo diastereoselectivo de ácido acético en C-4

Murahashi, S. I. et al. *Tetrahedron Lett.* **1991**, 32, 5991; *Tetrahedron Lett.*, **1991**, 32, 2145

69

ANTIB BETA LACTAMICOS NC

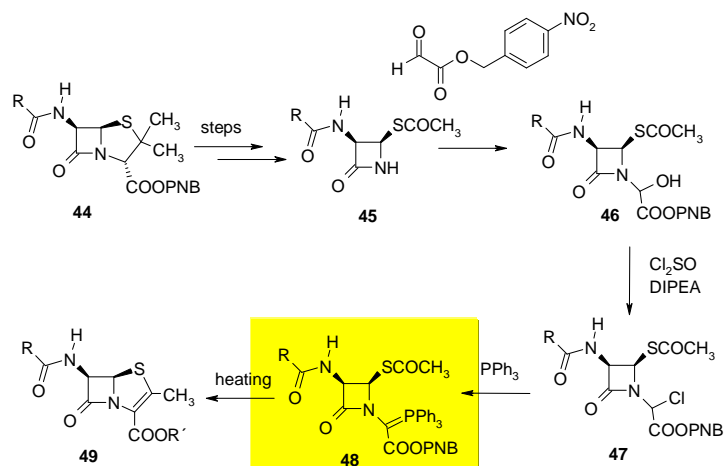
ESTRATEGIA GENERAL DE CONSTRUCCION DEL SISTEMA CICLICO



70

ANTIB BETA LACTAMICOS NC

SINTESIS DE WOODWARD DE PENEMS A PARTIR DE 6-APA

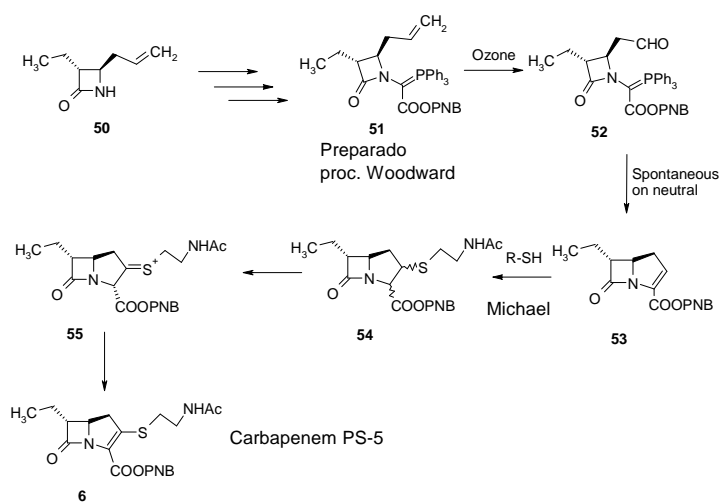


Woodward, R.B., et al. *J. Am. Chem. Soc.* **1980**, 102, 6, 2039

71

ANTIB BETA LACTAMICOS NC

SINTESIS DE CARBAPENEM PS-5, A PARTIR DE 6-APA

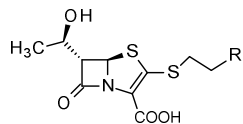


Bateson, J. H., et al. *J. Chem. Soc. Chem. Comm.* **1980**, 1084

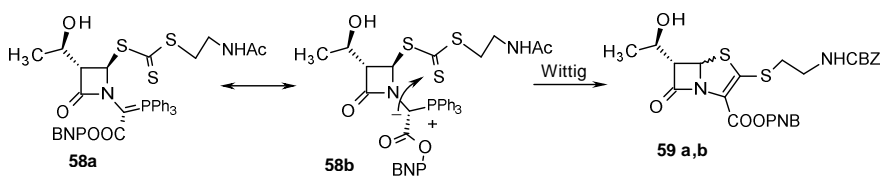
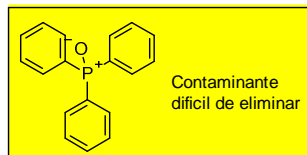
72

ANTIB BETA LACTAMICOS NC

SINTESIS DE BETA LACTAMAS



56 R= NH₂ Thiathienamicina
57 R= H



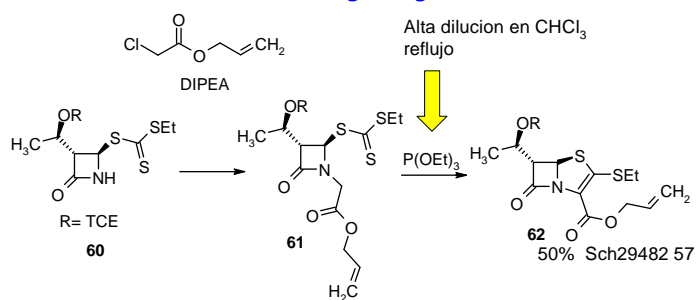
Los metodos de Wittig no pueden llevarse a escala industrial
La ciclación de **58** requiere altas temp y tiempos de reacción largos por lo que se produce epimerización de **59**.

Hayashi, T. et al., *Chem. Pharm. Bull.* **1981**, 29, 3158

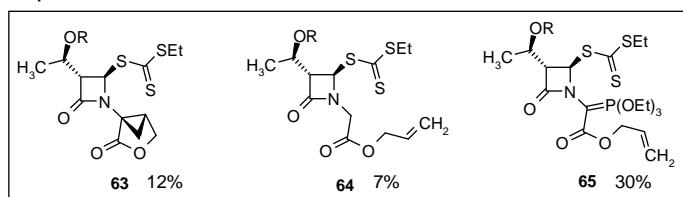
73

ANTIB BETA LACTAMICOS NC

SINTESIS CO-CO/CO-TIO (Shering Plough)



Impurezas

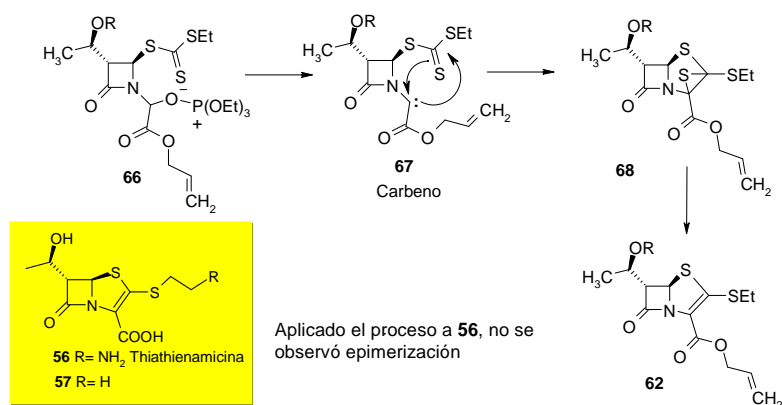


Afonso, A., et al. *J. Am. Chem. Soc.* **1982**, 104, 6138

74

ANTIB BETA LACTAMICOS NC

SINTESIS CO-CO/CO-TIO (Shering Plough)



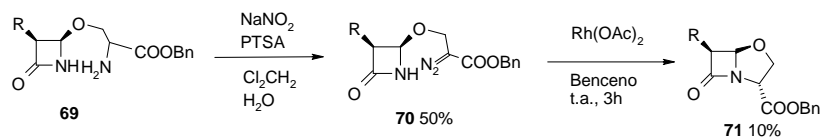
Método simplificado, hoy ha desplazado al de Woodward

Afonso, A., et al. *J. Am. Chem. Soc.* **1982**, 104, 6138

75

ANTIB BETA LACTAMICOS NC

SINTESIS POR CICLACIÓN DE CARBENO DE Rh



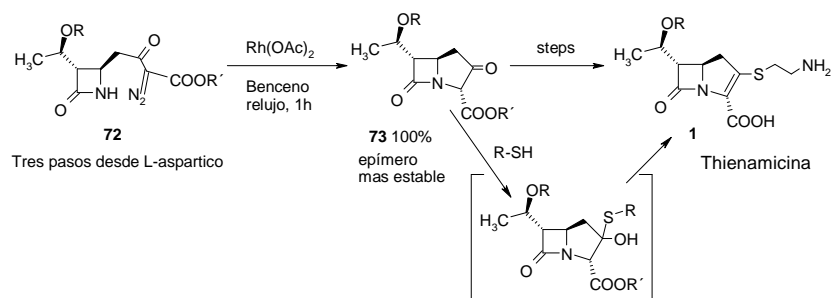
Primer ejemplo

Cama, L. D., Christensen, B. G., *Tetrahedron Lett.* **1978**, 44, 4233

76

ANTIB BETA LACTAMICOS NC

SINTESIS POR CICLACIÓN DE CARBENO DE Rh

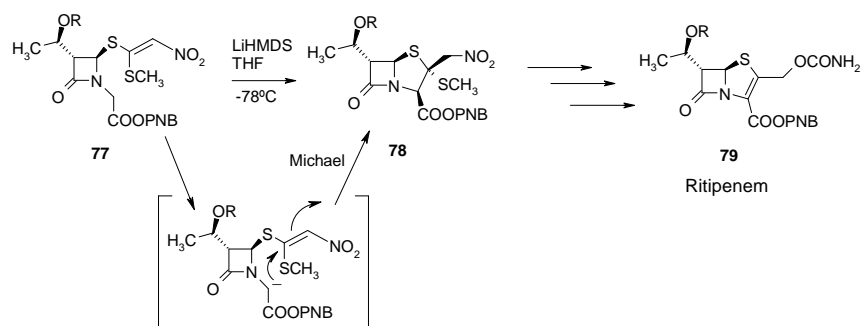


Marchand-Brynaert, J., Ghosez, L., *Tetrahedron Lett.* **1980**, 21, 3085

77

ANTIB BETA LACTAMICOS NC

SINTESIS POR CICLACIÓN VIA MICHAEL

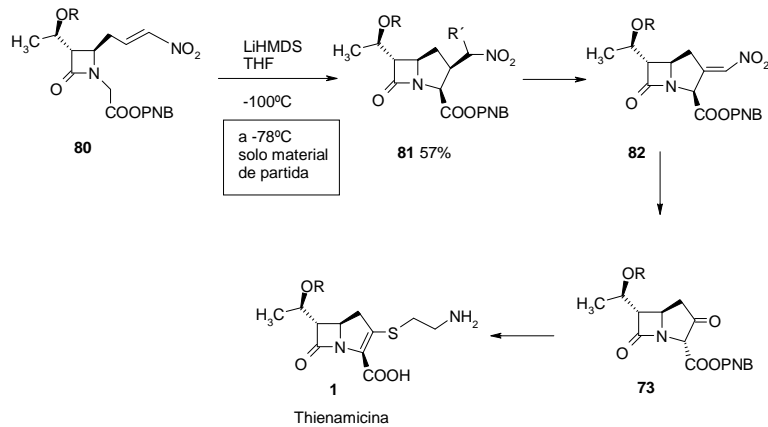


Hanessian, S., et al. *J. Am. Chem. Soc.* **1985**, 107, 1438

78

ANTIB BETA LACTAMICOS NC

SINTESIS POR CICLACIÓN VIA MICHAEL



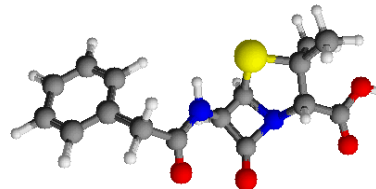
Hanessian, S., et al. *J. Org. Chem.* **1990**, 55, 3098

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PENICILINA



PREMIO NOBEL DE MEDICINA, 1945



Alexander Fleming
(1885-1955)

Howard W. Florey
(1898-1968)

Ernst B. Chain
(1906-1979)

80

PENICILINA

LOS HOMBRES DE LA PENICILINA

*"To sum it all up:
without Fleming, no Chain or Florey;
without Chain, no Florey;
without Florey, no Heatley;
without Heatley, no penicillin"*

Henry Harris, sucesor de Florey en la
Sir William Dunn School of Pathology

*Howard Florey and the development of
penicillin.*
Notes Rec R Soc Lond. 1999; 53: 243-52



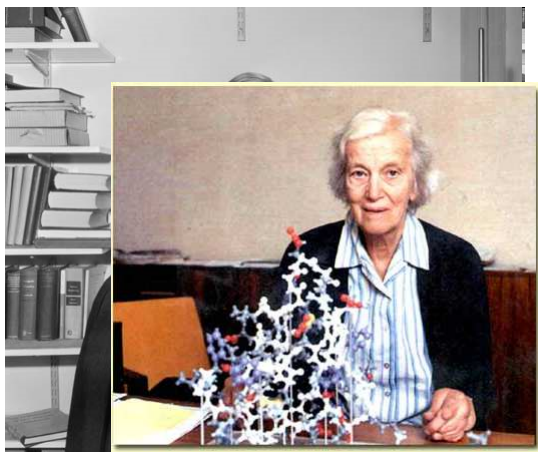
Norman C. Heatley
(1911-2004)
RETIRADO EN 1976
1990 DOCTOR H.C.
MEDICINA POR U. OXFORD

The Royal Society of Chemistry, 'International Historic Chemical Landmark'
at St Mary's Hospital, London 19 November 1999

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PENICILINA

PREMIO NOBEL DE QUIMICA, 1964



Dorothy C. Hodgkin
(1910-1994)



RESOLVIÓ, POR DIFRACCIÓN DE
RAYOS X LAS ESTRUCTURAS DE:

PENICILINA (CONFIRMACIÓN)
VITAMINA B12
INSULINA

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ANTIB BETA LACTAMICOS NC

LA PENICILINA ABRIÓ LA ERA DE LOS ANTIBIÓTICOS,
A PARTIR DE ELLA DISPONEMOS DE ANTIMICROBIANOS
EFICACES

DESPUES DE 60 AÑOS DESDE LA APARICIÓN DE LA PENICILINA

Se han investigado mas de 30.000 derivados semisintéticos de
Penicilina y Cefalosporina

Se han descubierto mas de 4000 metabolitos de microorganismos con
propiedades antibacterianas

Se han lanzado al mercado mas de 100 beta lactamicos (80% mercado)
de un mercado de mas 14.000 Millones de dólares, los beta lactámicos
son el 56%