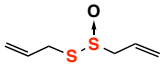
有機硫黄化合物の基礎と応用

大学院講義用資料
千葉大 高山廣光 (20180614)

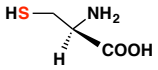
I: Introduction

$CH_3CH(CH_3)CH_2CH_2$-**SH**

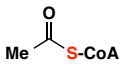
$CH_3CH=CH$-CH_2-**SH**



Allicin

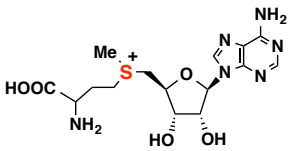


Cysteine

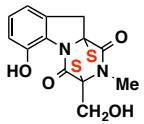


Acetyl coenzyme A

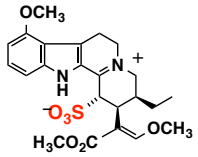
Lenthionine



***S*-Adenosyl methionine**



Gliotoxin
& β-lactams



Mitrasulgynine

II: Nomenclature

R–**SH** **thiol**

R–**SOH** **sulfenic acid**

R–**S(=O)OH** **sulfinic acid**

R–**S(=O)(=O)OH** **sulfonic acid**

R–**S**–R' **sulfide**

R–**S(=O)**–R' **sulfoxide**

R–**S(=O)(=O)**–R' **sulfone**

III: Charcteristics

N	O	F
P	**S**	Cl
As	Se	Br

S orbital

1s 2s 3s 2p 3p 3d □□□□□

空の d 軌道

dx^2, dx^2-y^2 σ 結合

dxy, dyz, dxz π 結合

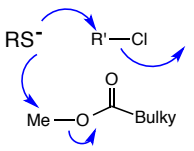
i. Less electronegativity compared with Oxygen

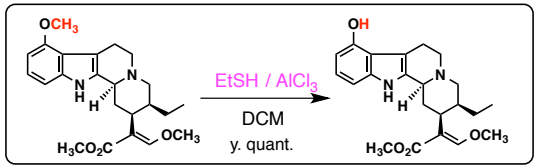
ii. Low affinity to H^+ ; Strong nucleophilicity

	p*K*a		p*K*a
MeSH	10.3	MeOH	15.5
EtSH	10.5	EtOH	16.0

basisity	RS^- <	RO^-
nucleophilicity	RS^- >	RO^-

S: highly polarizable ⟹ **soft base**
easily oxidized





Mitragynine

iii. Low bond energy

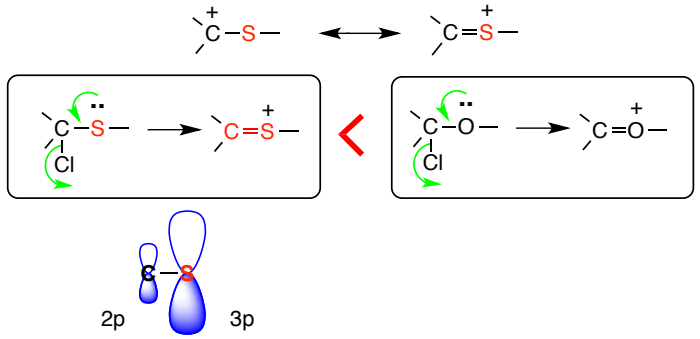
R'S—R

MeS-H (89 Kcal)

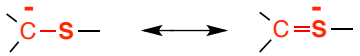
MeO-H (100 Kcal)

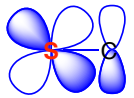
⇒ ラジカル反応を起こしやすい

iv. Electron-releasing conjugative effect

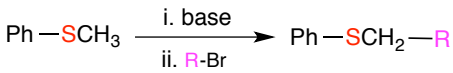


v. Electron-accepting conjugative effect





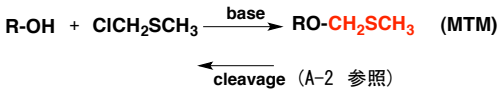
炭素原子の電子が
硫黄原子の空のｄ軌道に
流れこむことができるので
Ｓの隣のカルバニオンは安定



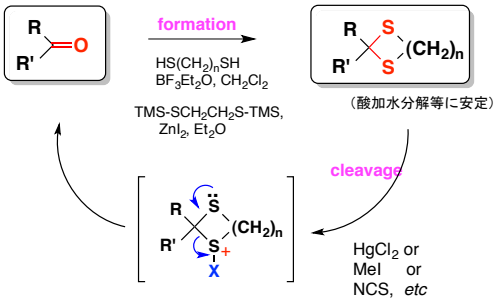
IV: Application to the Organic Syntheses

A: 保護基としての利用

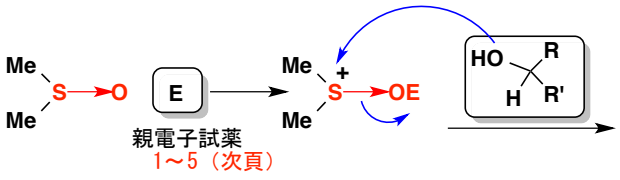
A-1 水酸基、カルボン酸



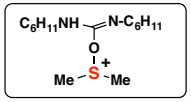
A-2 カルボニル化合物



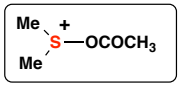
B: 酸化剤としての利用　活性化DMSO酸化



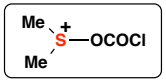
1. Pfitzner-Moffatt : DMSO, DCC, (pyridine-CF_3COOH)



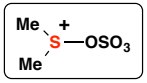
2. Albright-Goldman: DMSO-Ac_2O



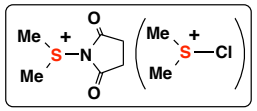
3. Swern: DMSO, $(CF_3CO)_2O$, Et3N, CH_2Cl_2
DMSO, $(COCl)_2$, Et3N, CH_2Cl_2



4. Parikh-Doering: DMSO, SO_3-pyridine

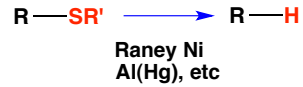


5. Corey-Kim: DMSO, Cl_2
DMS, NCS

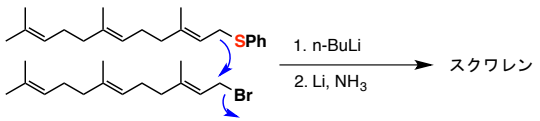


C：合成シントン、転位反応の利用

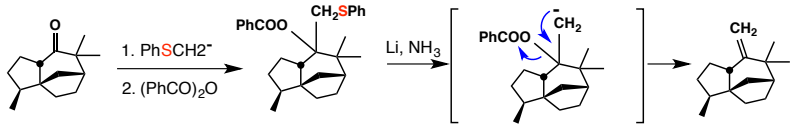
C-1.



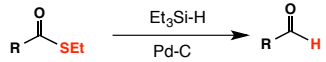
ex.1



ex.2

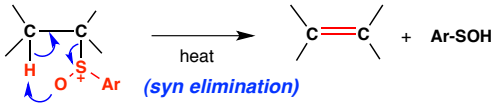


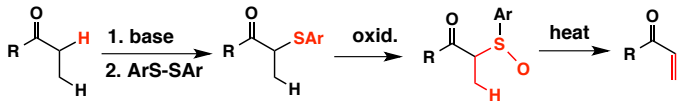
ex.3

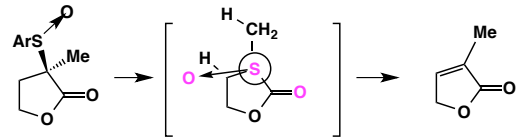


Application（US-7,8の不斉全合成）

C-2.

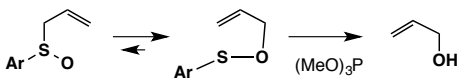




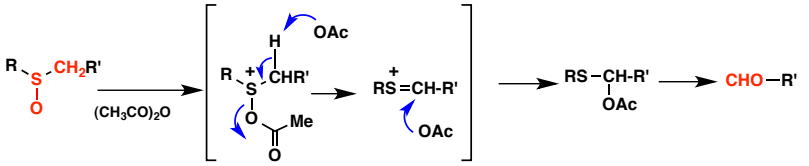


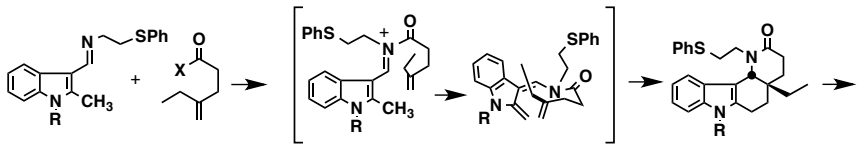
87% yield
位置選択的

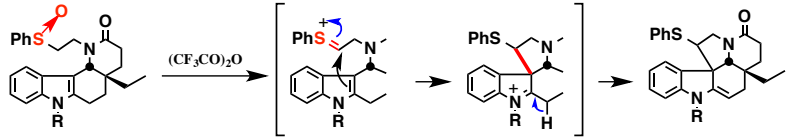
C-3. Evans Rearrangement (Allyl sulfoxide)



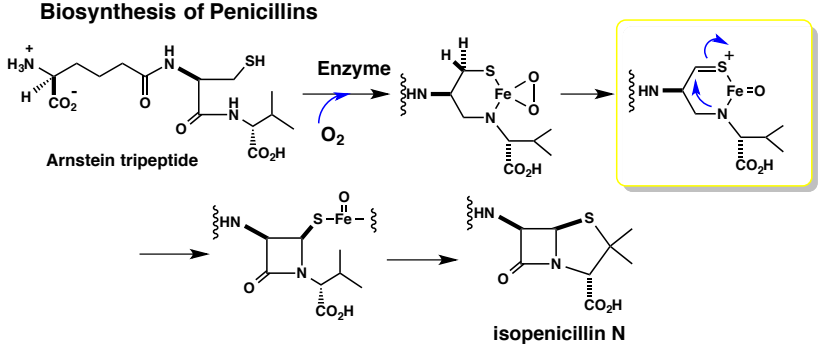
C-4. Pummere Reaction



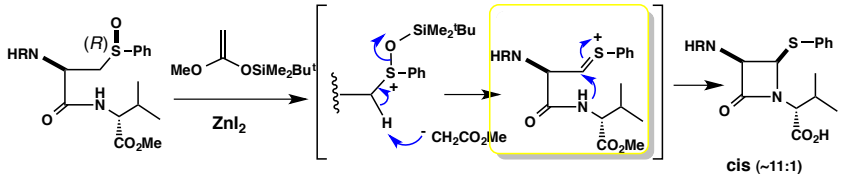




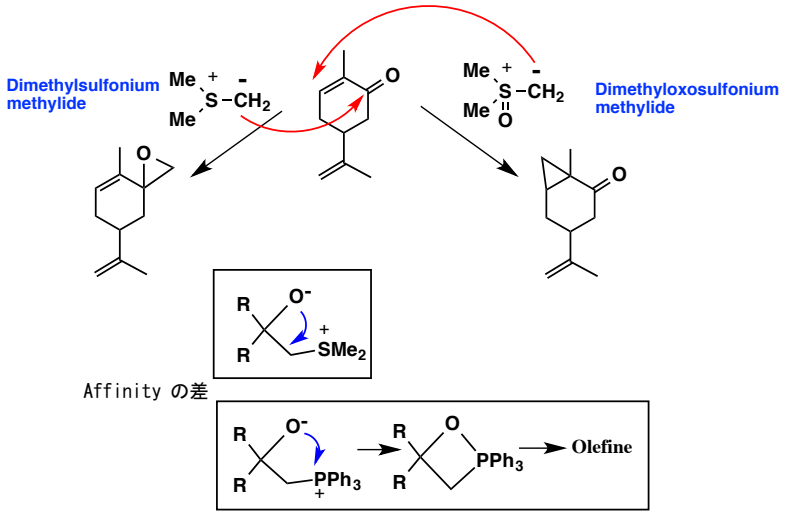
Biosynthesis of Penicillins



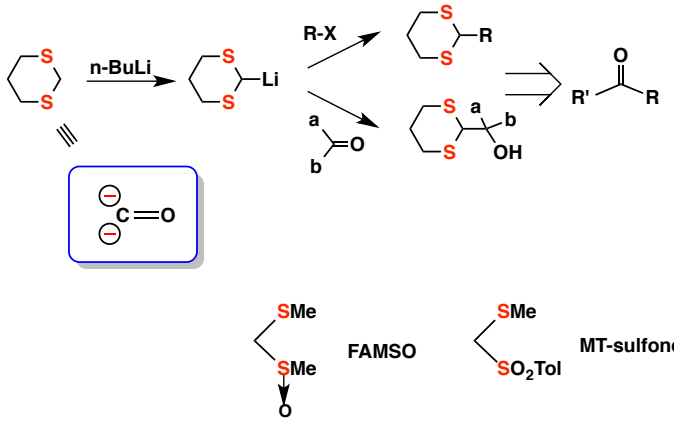
Biomimetic Synthesis of Penicillin Deriv.



C-5. イオウイリド

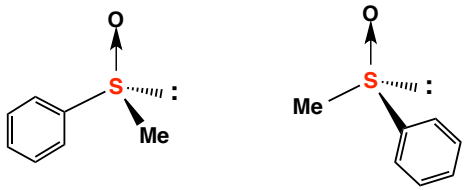


C-6. ジチオアセタール類　　Seebach, Corey: *Umpolung*

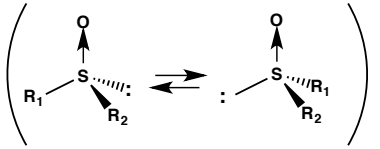


D：不斉合成への応用

D-1. Chiral Sulfoxide

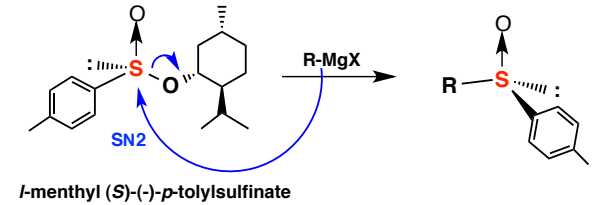


ラセミ化

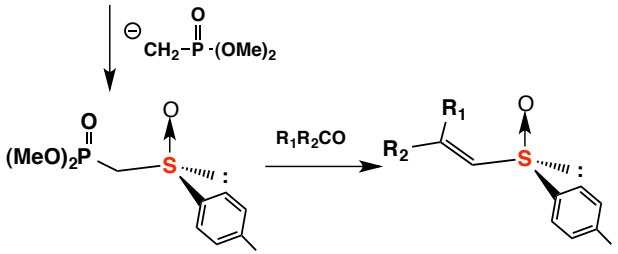


D-2. Preparation of chiral sulfoxide

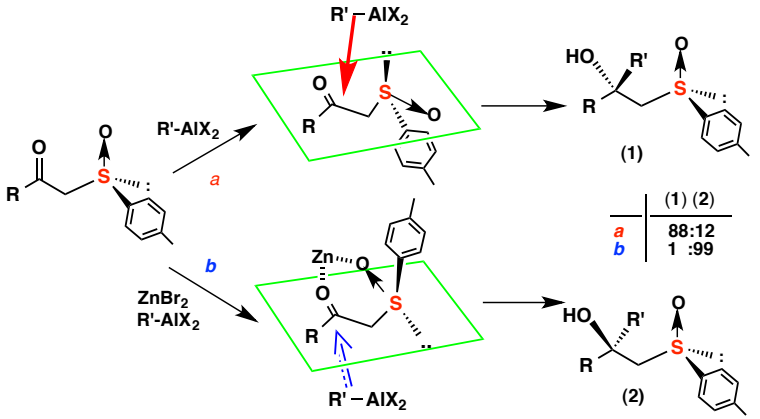
(Andersen 法)



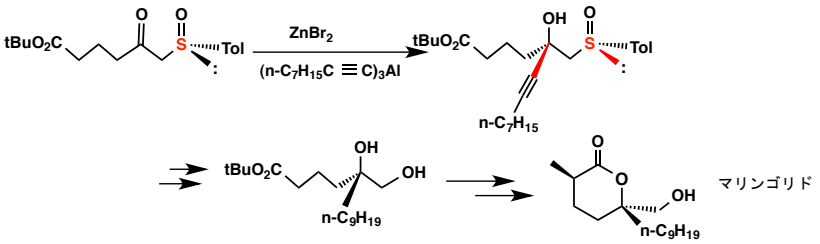
l-menthyl (*S*)-(-)-*p*-tolylsulfinate

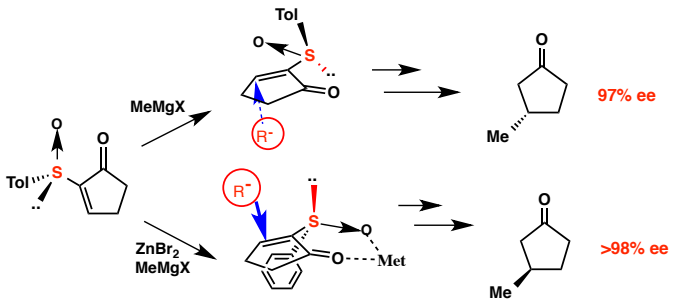


D-3. ジアステレオ面区別反応



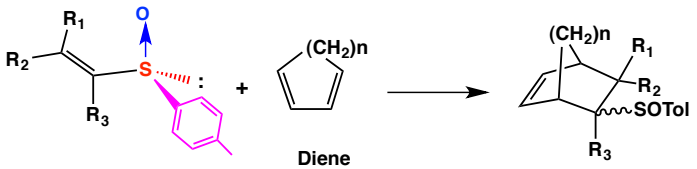
	(1)	(2)
a	88	12
b	1	99





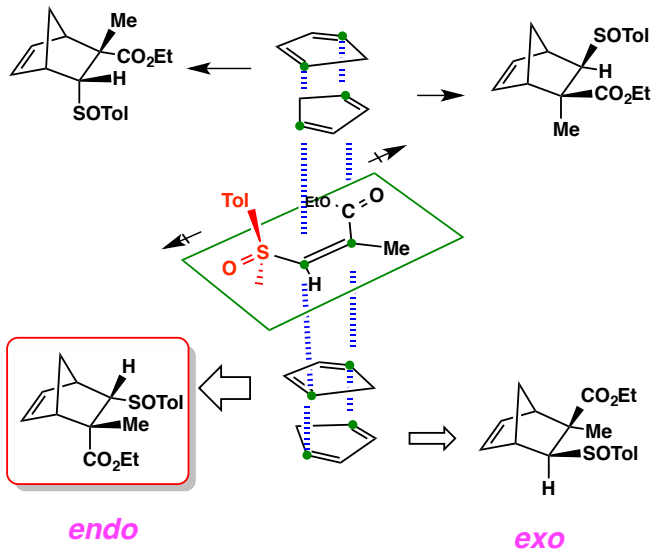
D-4. Asymmetric cycloaddition

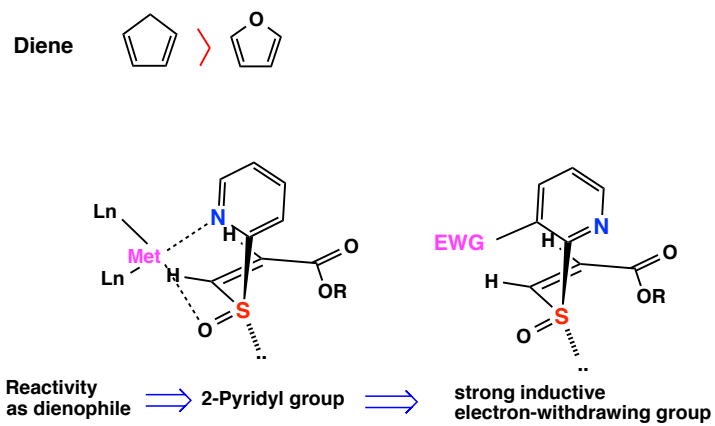
Diels-Alder reaction
(Chiral Auxiliary)

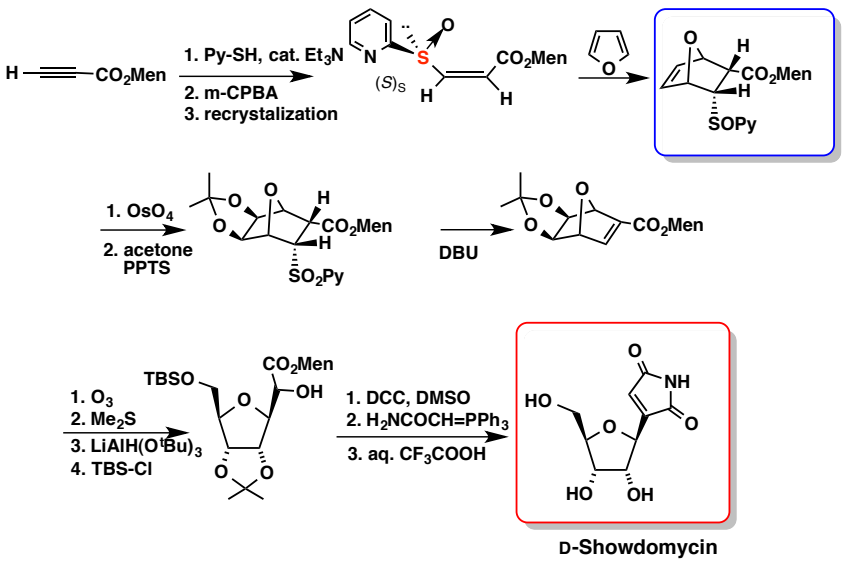


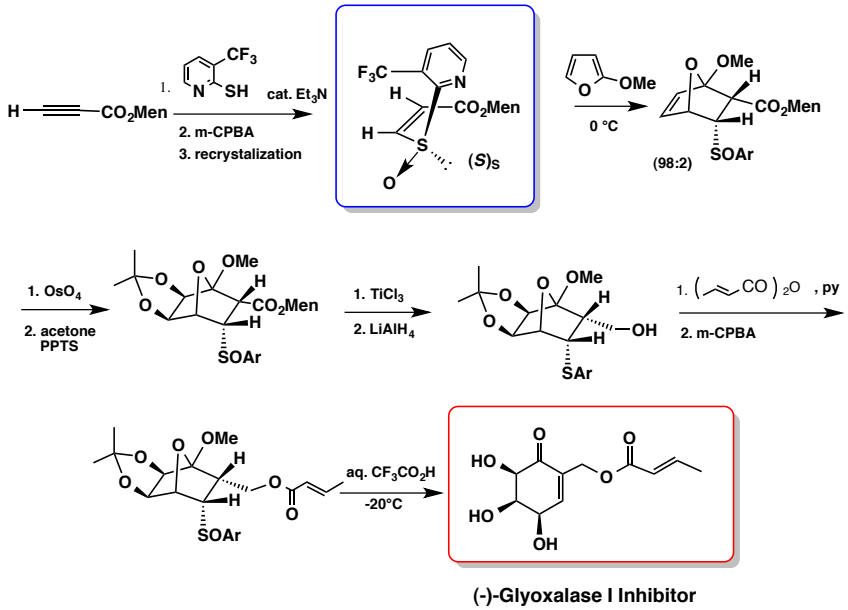
Dienophile **Diene**

Reactivity
Stereoselectivity
Enantioselectivity

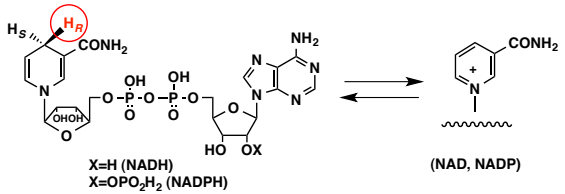

endo
exo

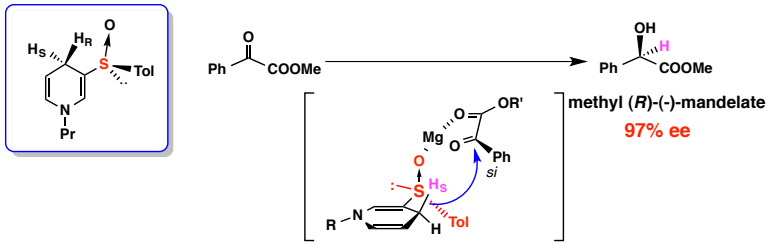

Diene
Reactivity as dienophile
2-Pyridyl group
strong inductive electron-withdrawing group


1. Py-SH, cat. Et3N
2. m-CPBA
3. recrystalization
1. OsO4
2. acetone PPTS
DBU
1. O3
2. Me2S
3. LiAlH(OtBu)3
4. TBS-Cl
1. DCC, DMSO
2. H2NCOCH=PPh3
3. aq. CF3COOH
D-Showdomycin


cat. Et3N
2. m-CPBA
3. recrystalization
0 °C
(98:2)
1. OsO4
2. acetone PPTS
1. TiCl3
2. LiAlH4
2. m-CPBA
aq. CF3CO2H
-20°C
(-)-Glyoxalase I Inhibitor

Asymmetric Reduction of Ketones with NADH Model Compounds Carrying a Chiral Sulfoxide Functin

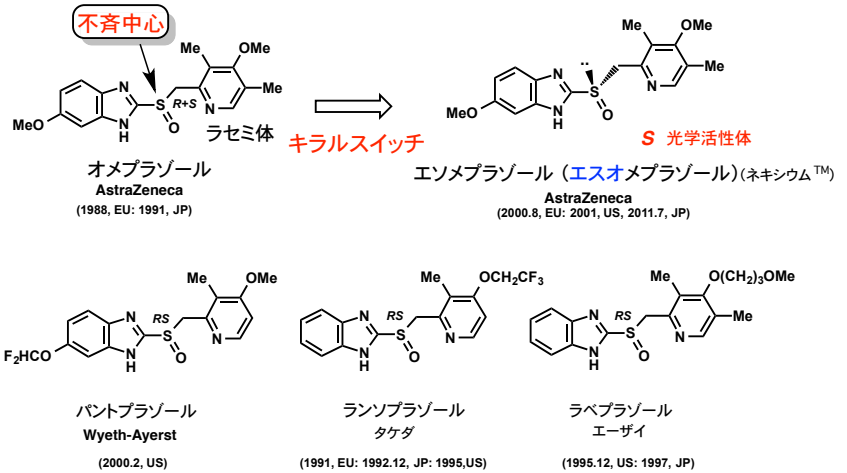




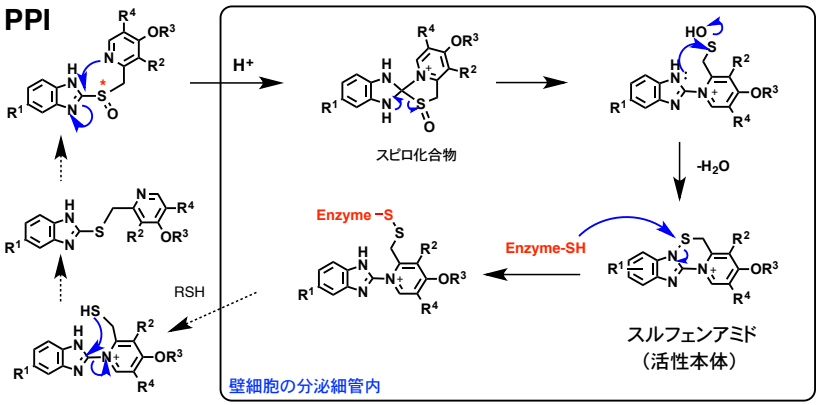
プロトンポンプ阻害薬（Proton Pump Inhibitor : PPI)

(プロトンポンプ = H^+,K^+-ATPaseとよばれる酵素)

-prazole: benzimidazole誘導体の潰瘍薬

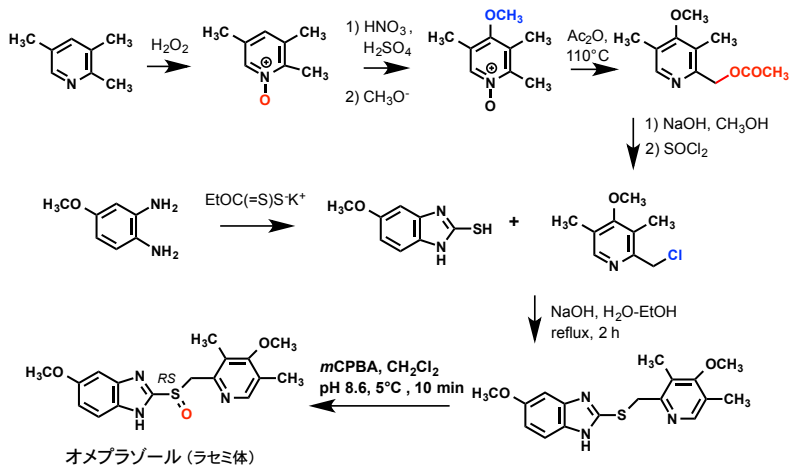


オメプラゾールの作用機序（一種のプロドラッグ）



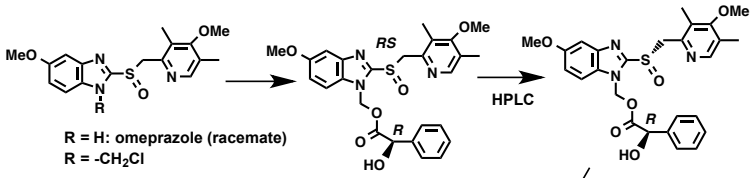
PPIは血中から壁細胞に取り込まれ、分泌細管内に移行する。その酸性環境下においてプロトン化されてたPPIは特異な分子内転位反応を起こし、スルフェンアミド（活性本体）になる。これがH+,K+-ATPaseのSH基とジスルフィド結合を形成することにより不可逆的に酵素を阻害する。

Synthesis of Omeprazole

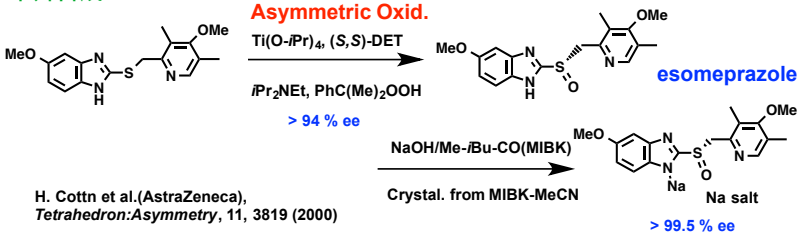


光学活性エソメプラゾールの合成

1) ジアステレオマー誘導体として分離



2) 不斉合成

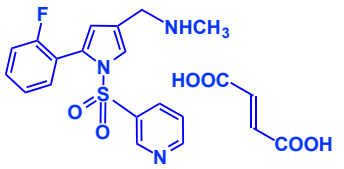


H. Cottn et al.(AstraZeneca),
Tetrahedron:Asymmetry, 11, 3819 (2000)

新薬 P-CAB (Pottasium-competitive acid blockers)

カリウムイオン競合型アシッドブロッカー

2014.12承認(日本), 2015.2発売(日本)



研究開発:武田薬品、
販売:武田薬品、大塚製薬共同販売

一般名:ボノプラザン フマル酸塩
商品名:タケキャブ

平成28年度
日本薬学会創薬科学賞

PPIと同様にプロトンポンプ(PP)(H^+,K^+-ATPase)に作用するが、作用機序が異なる。

⇒ PPをカリウムイオンと競合的かつ可逆的に阻害し、酸分泌を抑制する。PPIのような、酸による活性化を必要とせず、原体のまま作用するので、腸溶製剤などの製剤化を必要とせず、服用初日からほぼ最大薬効を示す。