On Stereochemistry and Chirality

Interaction with plane polarized light

What is the relationship between R,S and d,l aka (±)?

Nomenclature

There isn't any!

All Isomers (same molecular formula)

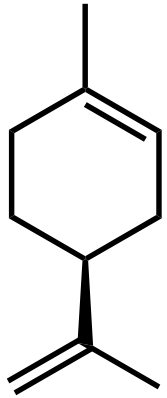
Stereoisomers

Identical	*Enantiomers*	*Diastereomers*
Same atom connectivity	Same atom connectivity	Same atom connectivity
Same spatial arrangement	Same spatial arrangement	Different spatial arrangement
Superimposable	Non-superimposable	Non-superimposable

Constitutional (Structural) Isomers

Same molecular formula; different atom connectivity

The Limonenes

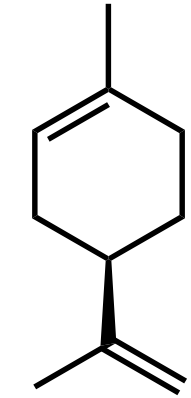


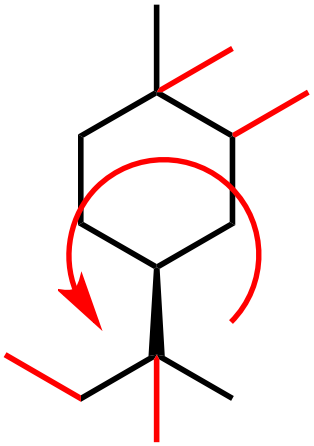
(-)-limonene

lemon

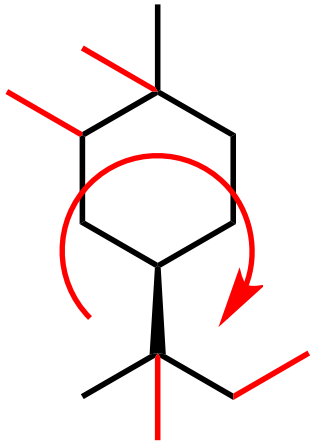
(+)-limonene

orange





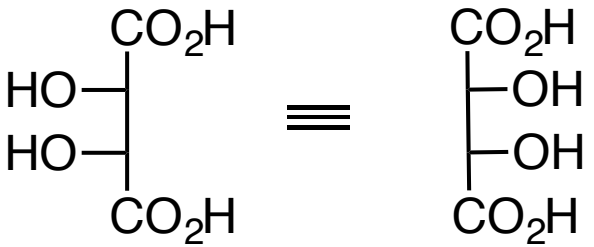
(S)



(R)

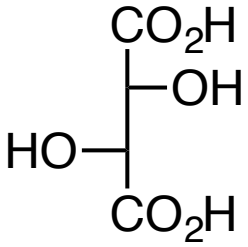
Meso Compounds

Meso – (middle or intermediate) - the achiral member(s) of a set of diastereoisomers which also includes one or more chiral members.

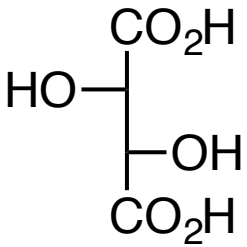


meso tartaric acid

R,S-stereoisomer



R,R-(+)-tartaric acid
"natural"

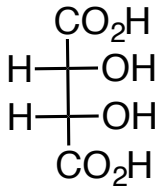


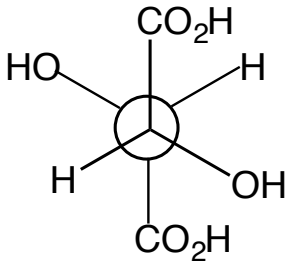
S,S-(-)-tartaric acid

Meso Tartaric Acid

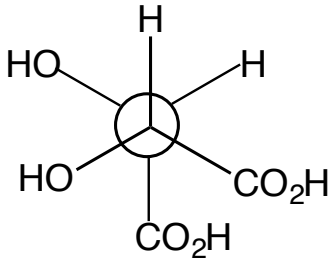
Why is meso tartaric acid not optically active?

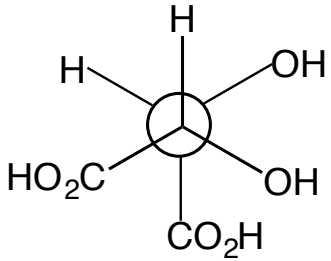
The Fischer projection is unstable; it is eclipsed and only a mnemonic device to test for a meso compound.





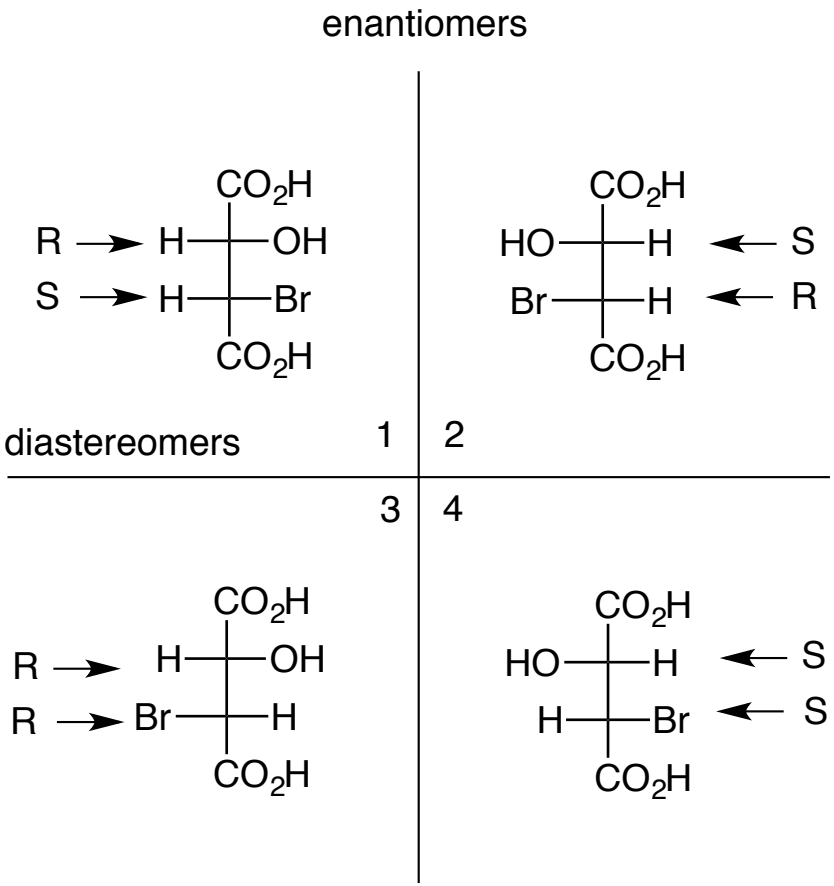
Anti staggered
Center of symmetry



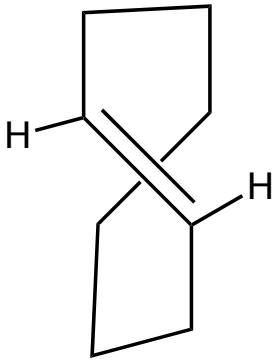


Gauche staggered
Racemic mixture

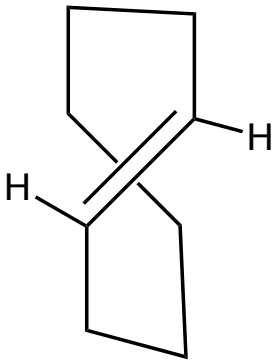
Enantiomers and Diastereomers



Other Sources of Chirality

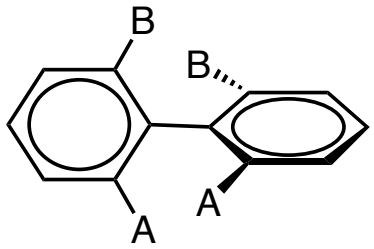


(R) "M"

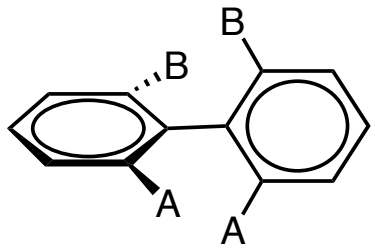


(S) "P"

trans - cyclooctene

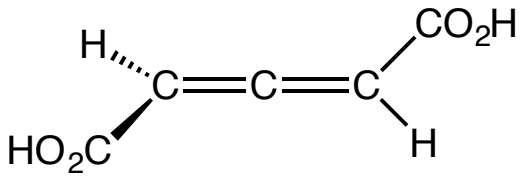


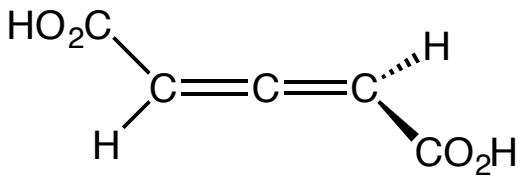
(R) "M"



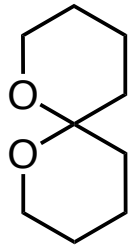
(S) "P"

atropisomerism

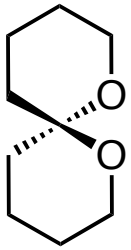




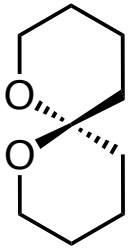
allene dicarboxylic acid



1,7-dioxaspiro[5.5]undecane

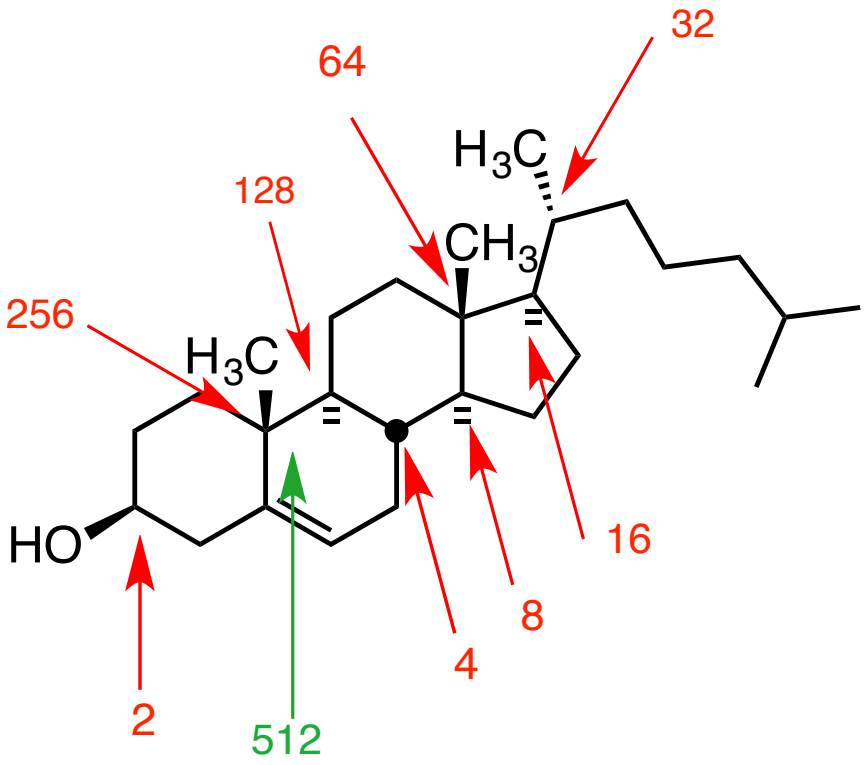


(*R*) "M"



(*S*) "P"

Cholesterol – How Many Stereoisomers are Possible?



256 centers of chirality (and stereochemistry)
2(S), 4(S), 8(S), 16(R), 32(R), 64(R), 128(S), 256(R)

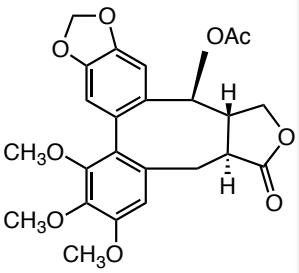
One double bond stereochemistry; no chirality
(*Although the double bond has two stereogenic carbons, only two double bond geometries are possible.*)

512 conceivable stereoisomers of cholesterol

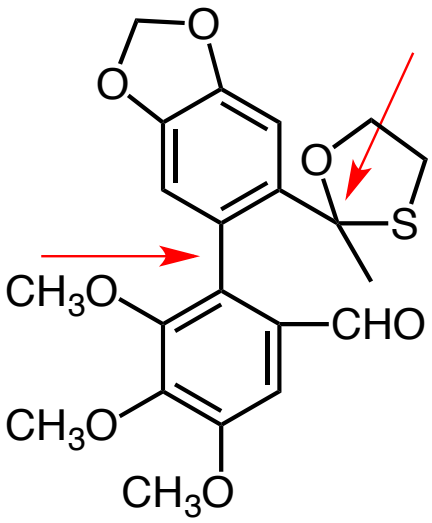
All other double bond isomers – namely, (E) -- are impossible to exist.

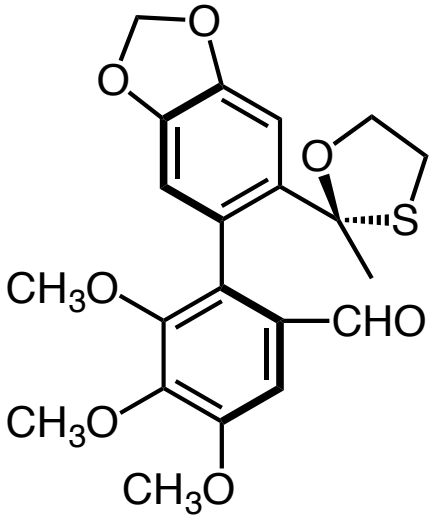
2^n stereoisomers; 2^{n-1} pairs of enantiomers

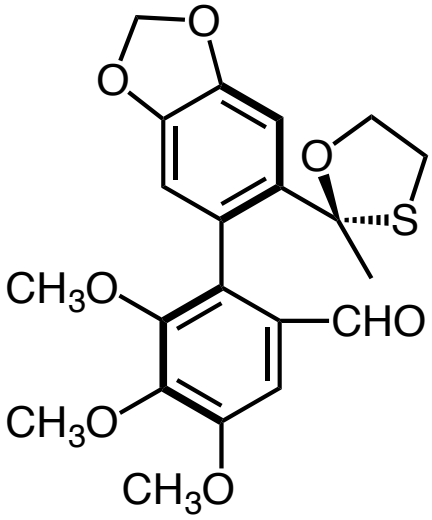
More on Atropisomerism



Steganacin







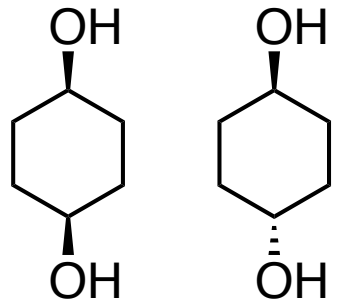
two racemic compounds
3:1 ratio

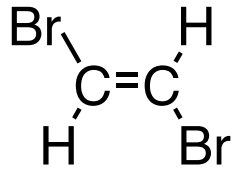
The Ambient Temperature Ullmann Reaction and Its Application to the Total Synthesis of (±)-Steganacin; Frederick E. Ziegler*, Irene Chliwner, Kerry W. Fowler, Sheldon J. Kanfer, Stephen J. Kuo, and Nanda D. Sinha*; J. Am. Chem. Soc.*, **1980**, *102*, 790.

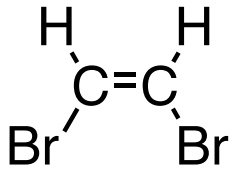
Stereogenic Atoms (Stereocenters)

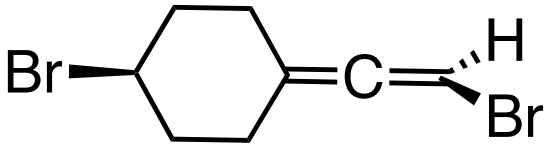
"An atom bearing several groups of such nature that an interchange of two groups will produce a stereoisomer." Mislow & Siegel - 1984

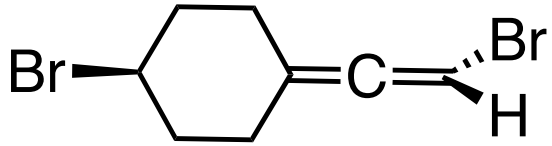
Stereocenters that are not chiral centers.





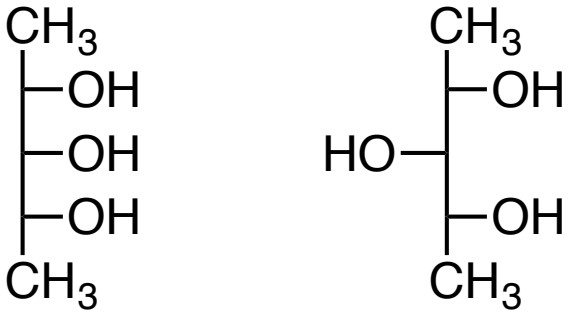






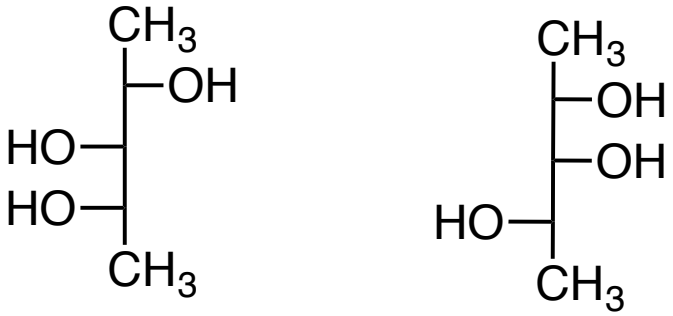
Chiral Atom (Chiral Center)

"An atom holding a set of ligands in a spatial arrangement which is not superimposable on its mirror image."



meso stereoisomers

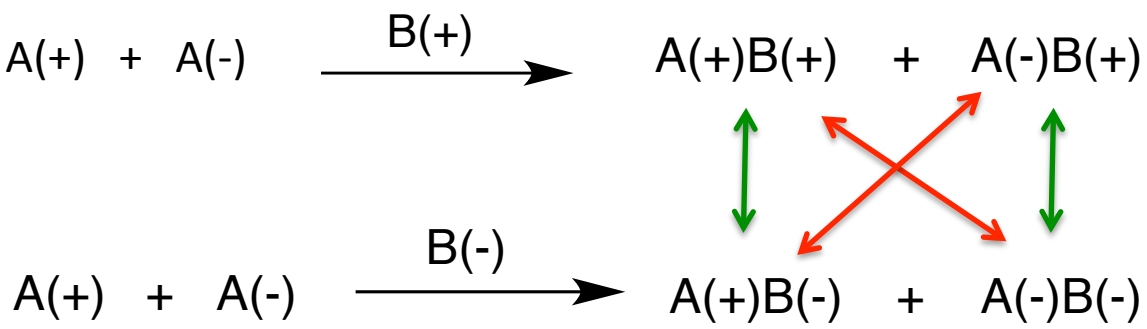
C_2 and C_4 chirotopic and stereogenic;
C_3 stereogenic and achirotopic



identical

C_2 and C_4 chirotopic and stereogenic;
C_3 chirotopic and nonstereogenic

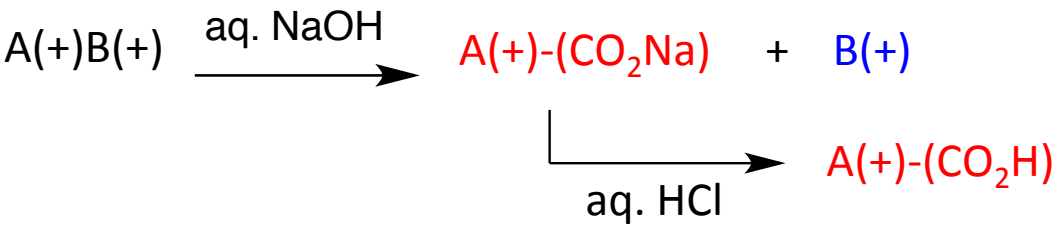
Resolution - I

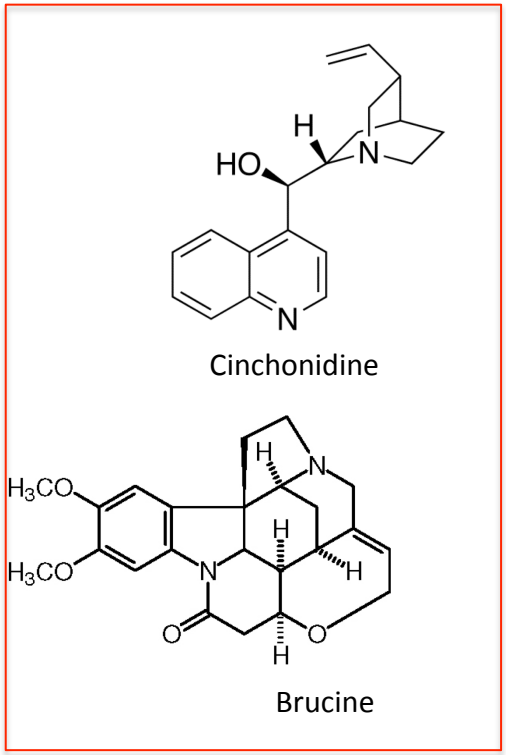


Assume A(+)B(+) less soluble than A(-)B(+)

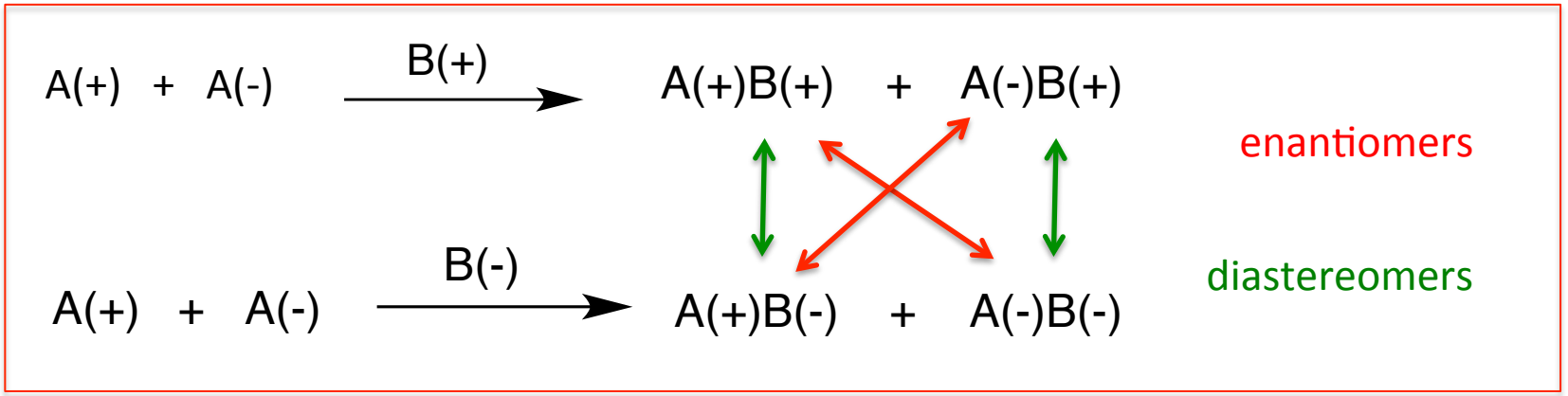
A(+)B(+) precipitates from solution

Isolate A(+)B(+) water soluble ether soluble





Resolution - II



What if A(-)-(CO_2H) is desired? Then use B(-) as the resolving agent.

Then A(-)B(-) is less soluble than A(+)B(-).

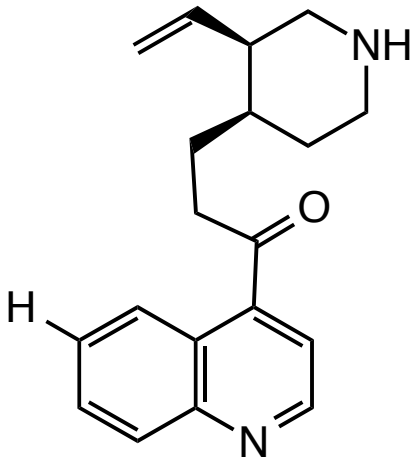
A(-)B(-) precipitates from solution.

Isolate A(-)B(-) water soluble ether soluble

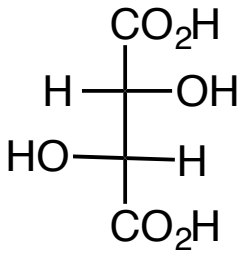
A(-)B(-) $\xrightarrow{\text{aq. NaOH}}$ A(-)-(CO_2Na) + B(-)

A(-)-(CO_2Na) $\xrightarrow{\text{aq. HCl}}$ A(-)-(CO_2H)

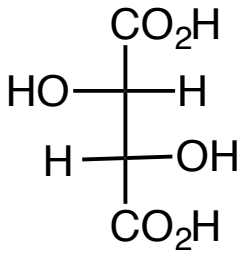
Resolution – III (Pasteur 1853)



(+)-**C**inchotoxine

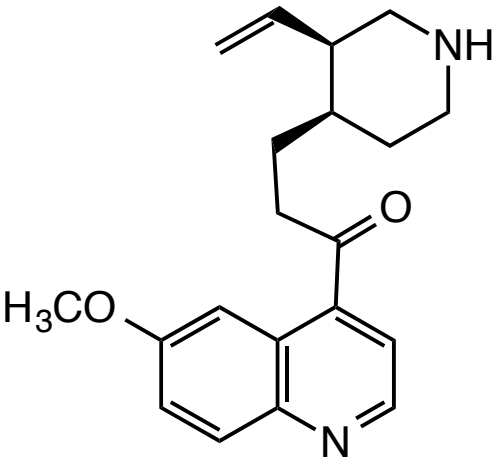


R,R-(+)



S,S-(-)

(+/-)-**T**artaric Acid



(+)-**Q**uinotoxine

(-)-**T**/(+)-**C** n-salt insoluble

(+)-**T**/(+)-**C** p-salt soluble

(-)-**T**/(+)-**Q** n-salt soluble

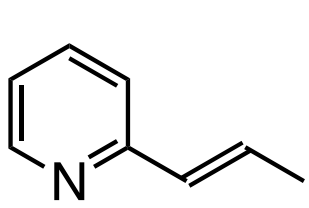
(+)-**T**/(+)-**Q** p-salt insoluble

(+)-A/+)-B or (-)-A/(-)-B = p(aired) salt

(-)-A/(+)-B or (+)-A/(-)-B = n(on-paired) salt

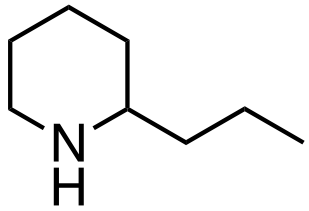
Resolution - IV

Albert Ladenburg
(1842 – 1911)



Na

C_2H_5OH



d,l - coniine

d-tartaric acid

1886 – resolution
of racemic coniine

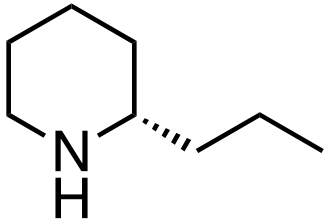
d-tartaric acid
l-coniine

less soluble

+

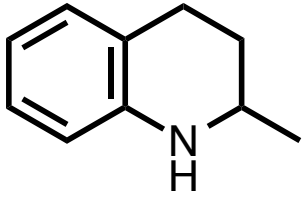
d-tartaric acid
d-coniine

d-(S)-coniine



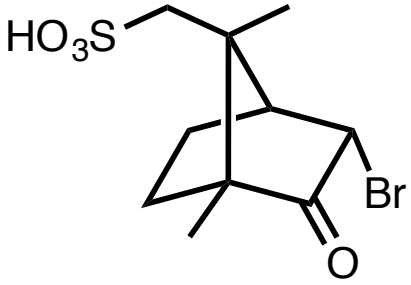
Resolution – V *The Method of Pope & Peachey - 1899*

Sir William Jackson Pope
(1870 – 1939)



d,l - B

d,l-Tetrahydroquinaldine
[d,l-2-Methyl-1,2,3,4-tetrahydroquinoline]



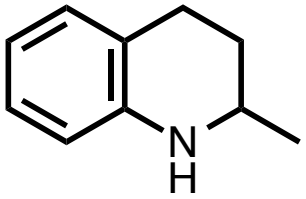
d - A

Dextrorotatory Reychler's Acid
[[(1R)-(endo,anti)]-(+)-3-Bromocamphor-8-sulfonic acid]

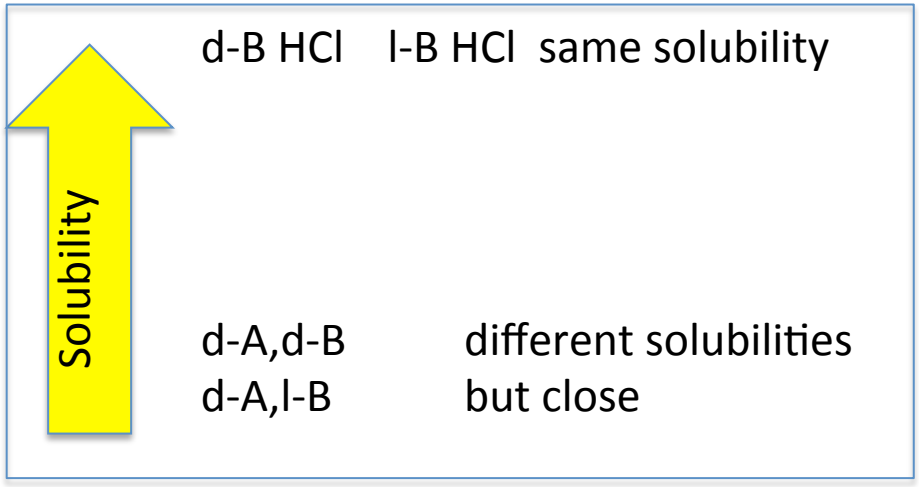
How do you maximize the difference in solubility of the two diastereomers?

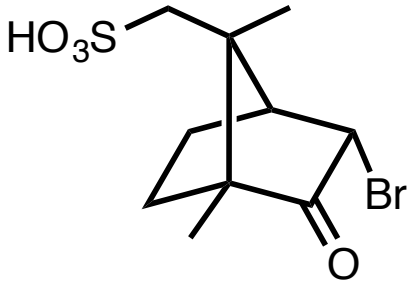
How do you minimize the use of resolving agent?

Resolution – VI *The Method of Pope & Peachey - 1899*



d,l - B





d - A

In solution

d-A + HCl + 2 d,l-B —(mix, conc. sol'n)→ d-A,l-B + d-A,d-B + d-B HCl + l-B HCl

Precipitates d-A,l-B (cool)

d-B HCl In solution

Resolution - VII

Is there a down side to resolution?

You bet!

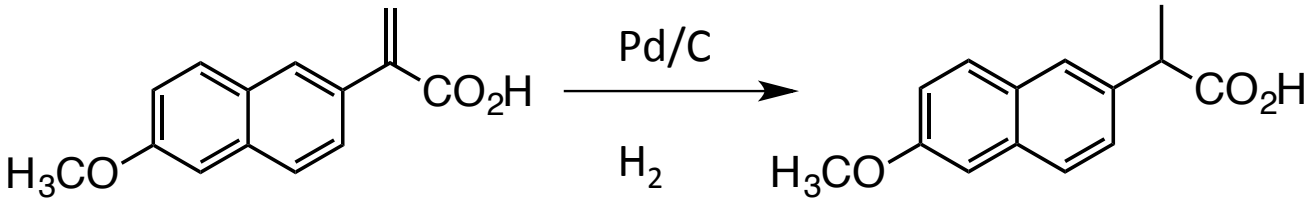
The yield will always be less than 50%.

Can not predict which enantiomer will be isolated.

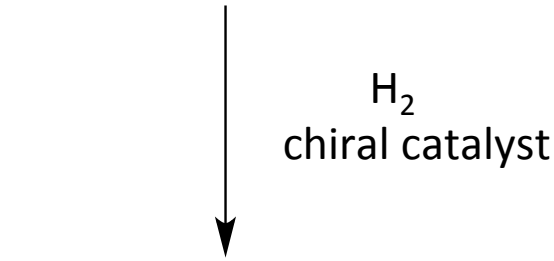
Mirror image resolving agents are not always available.

Trial and error may be required.

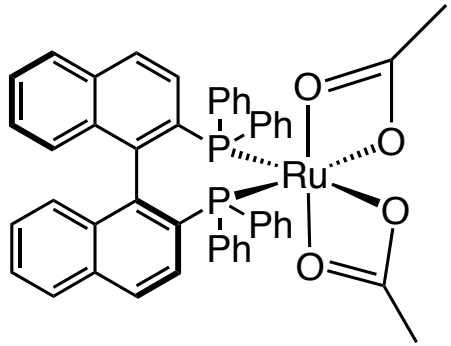
Asymmetric Reactions – A Better Way



racemic naproxen



(S)-Naproxen (97% ee)



(S)-BINAP-Ru(OAc)$_2$

The End