

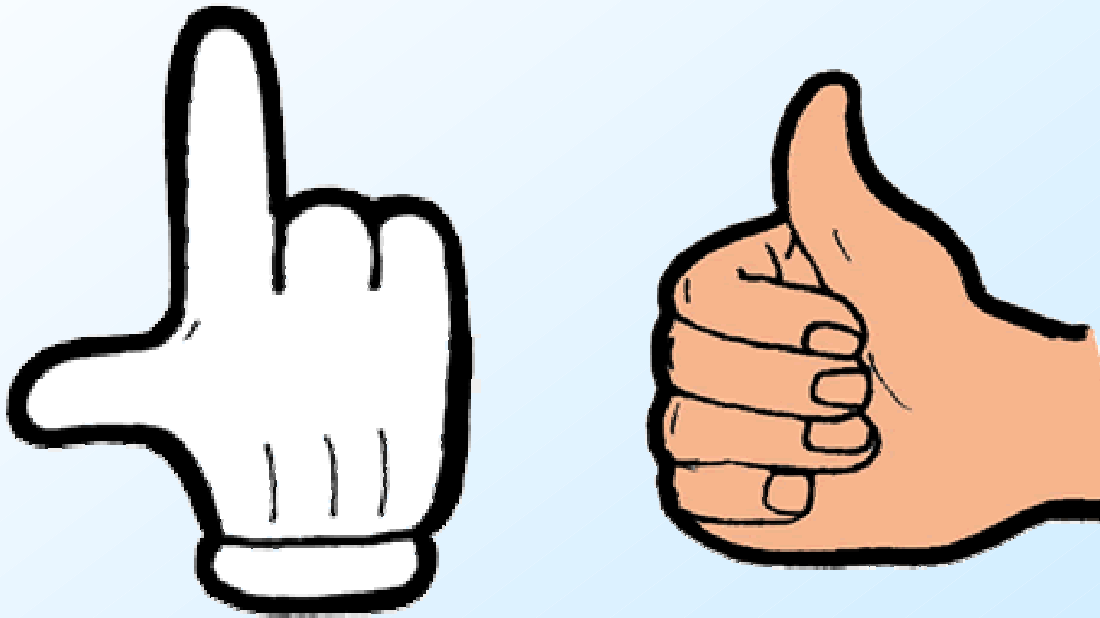
# Indexing and searching chemical structures and reactions with stereo-selectivity

**Andrew Lemon PhD**

- Binding is shape dependant
- Chiral Drugs
- IDBS Stereochemical descriptors
- Searching
- Reactions and Schemes
- Future Developments

IDBS provide Cheminformatics solutions

# Receptor mapping is shape dependant



## The rise of the Chiral Drug Industry

- “Combined US demand for chiral chemicals -- including the value of merchant sales and captive and contract production will rise 9.4 percent annually to \$15.1 billion in 2005, with real demand advancing six percent per year.”
- “Pharmaceutical applications will lead growth as regulatory requirements and competitive advantages promote the development of new and re-formulated drugs containing single isomer active ingredients.”

## Advantages of Chiral Drugs

- Single Isomer Compounds are more active and require lower doses and exhibit fewer side effects than racemic drugs
- Extending Patent Lifetimes – Marketing chiral versions of racemic drugs to extend patent times

# The importance of tracking stereochemistry

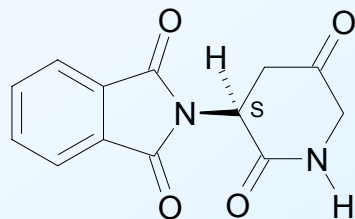
## FDA'S POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS

- “Geometric Isomers and diastereoisomers should with the rare exception of cases where *invivo* interconversion occurs be treated as separate drugs”
- “The stereoisomeric composition of a drug with a chiral center should be known and the quantitative isomeric composition of the material used in pharmacologic, toxicologic, and clinical studies known. Specifications for the final product should assure identity; strength, quality, and purity from a stereochemical viewpoint”

## Why is this important?

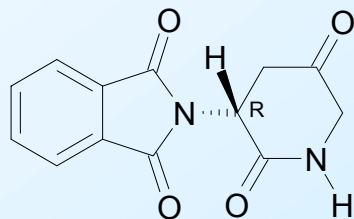
- Different isomers can have very different activity

Thalidomide



Potential anti-morning sickness treatment

Note: Still racemates under physio pH



Teratogenic

## Challenge to cheminformatics

- Track the chemical structures of compounds down to the enantiomeric level
- Store and represent both single enantiomers and mixtures of different diastereoisomers
- Resolve stereoisomers into different chemical entities

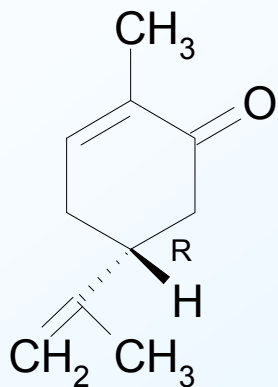


# IDBS Chemical Representation

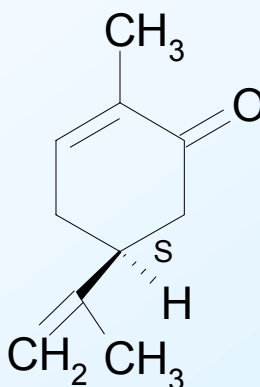
- Stereochemical descriptors
  - Stereocentres
    - R
    - S
    - R\*S
  - Bond stereochemistry
    - E (Trans)
    - Z (Cis)
    - E\*Z

## Specification of stereochemistry

Carvone



Spearmint

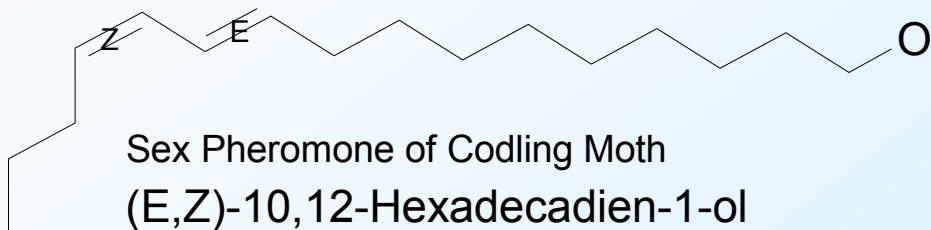


Caraway

- Calculated from Bond Markings using CIP Rules
- Calculated from 3D Coordinates
- Assigned to stereogenic atoms
- Chiral Flag Trigger

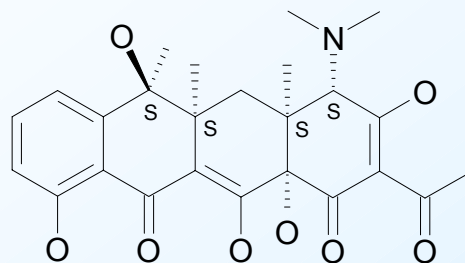
## Specification of stereochemistry

Bombykol

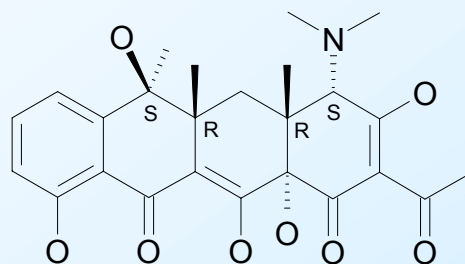


- Calculated from Bond arrangements
- Assigned to stereogenic bonds
- Chiral Flag Trigger

## Representation of Diastereoisomers



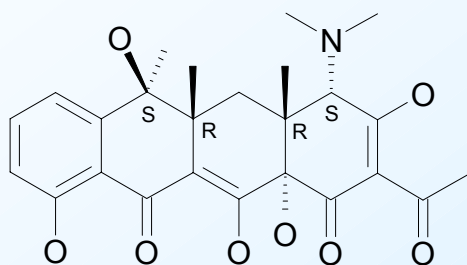
SSSS Tetracycline



SRRS Tetracycline

## Representation of mixtures of diastereoisomers

- Synthesis may generate specific mixtures of diastereoisomers
- n stereogenic centers generates  $2^n$  stereoisomers



Tetracycline

- 16 possible enantiomers of Tetracycline RRRR to SSSS

## Representation of mixtures of diastereoisomers

- Advanced stereochemical descriptors
  - R/S coupled descriptors
  - S/R coupled descriptors
  - R\*S
- R/S R/S S S represents 2 diastereoisomers RRSS and SSSS
- R\*S R\*S R/S S/R represents 8 possible diastereoisomers

## Searching

- Three level searching capability
  - Ignore
  - Relative (Bond Marks only)
  - Stereochemical
- All stereochemical descriptors can be used for searching
- Look for specific enantiomers or ranges of diastereoisomers
- Exact Match
- Substructure Searching
- SuperStructure Searching

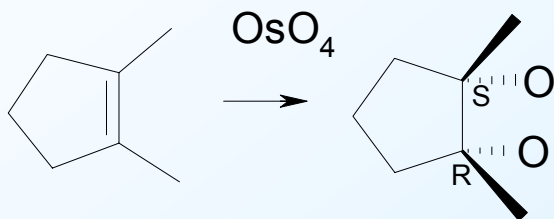
## Deployment

- IDBS Chemical Technology
  - Oracle DataCartridge (NT/2K, Solaris7,8, Linux, SGI)
  - IDBS Chemistry Client API
- StructureBase
- ReactionBase



## Indexing and Searching Reactions

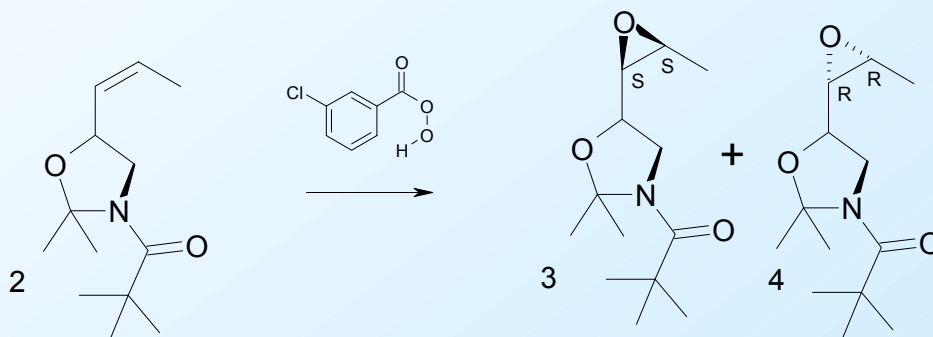
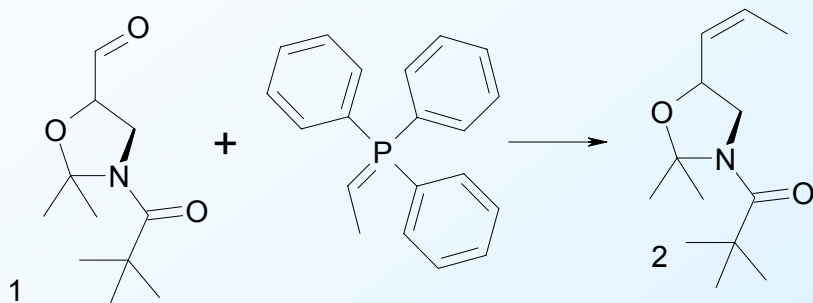
- Stereoselective Reactions



- Stereo descriptors available for describing reactions
  - Describe mixtures of possible products

# Indexing and Searching Reaction Schemes

- Stereoselective Reaction Schemes



- Search across multiple reactions in a reaction scheme
  - With stereoselectivity and transformation mapping

## Summary

- Use of stereochemical descriptors
- Representation of diastereoisomers
- Searching with stereoselectivity
- Deployment
- IDBS Offer Cheminformatics Solutions

## Future Developments

- Stereoselective Combinatorial Libraries
- Stereoselective Enumeration Services

## Acknowledgements

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