UCLA

Stereoselective Green Chemistry Strategies Using Crystal-to-Crystal Reactions: The Advantages of Molecular Nanocrystals

(Syntheses of complex structures with adjacent quaternary stereogenic centers)

Miguel A. Garcia-Garibay
University of California, Los Angeles
Dept of Chemistry and Biochemistry
mgg@chem.ucla.edu

C(N)SI

National Science Foundation

MCTP
Materials Creation Training Program

Nanotechnology

—Potential Benefits:

Drug delivery, solar energy conversion, catalysis, microelectronics, cosmetics, water and soil remediation, etc.

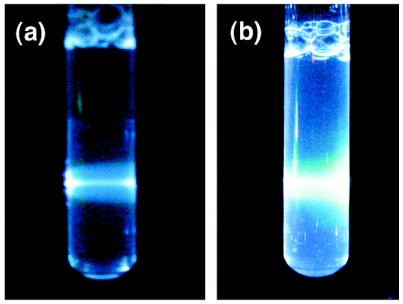
—Concerns:

Toxicology, bioaccumulation, oxidative stress (ROS), transport of pollutants, etc.

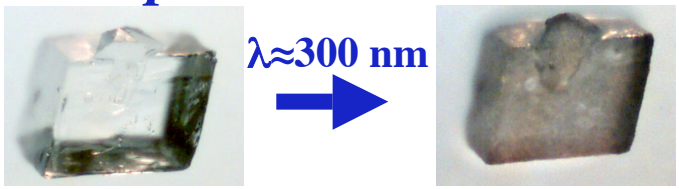
—Unknown:

????? Incentives for New Chemical Reactivity Paradigms (challenge your perspectives on chemical synthesis)

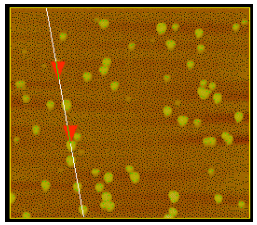
Challenging or Complex Chemical Processes in Molecular Crystals

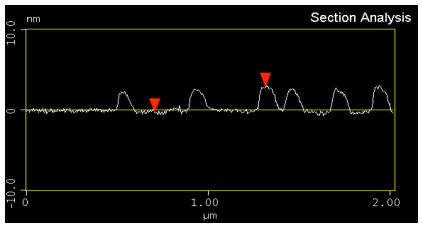


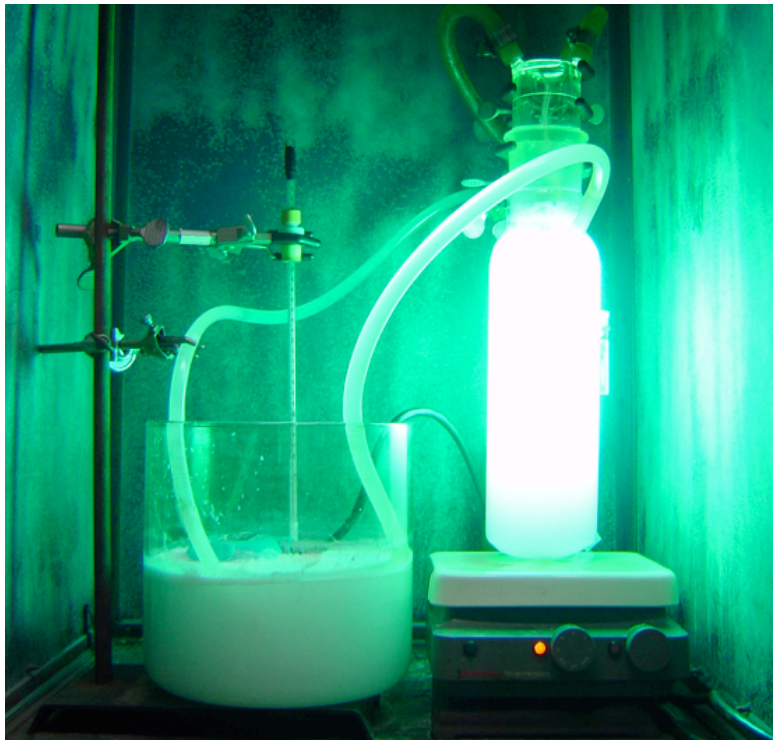
Loading: (a) 0.015 and (b) 1.8 mg/ml



100 % selectivity, but slow and inneficient (limited conversion)







Loading: 20 g / 5 L

Loading: 2 g/ 200 ml

Further scale up

Collect product by filtration, recycle water.

Pharmaceuticals (complex structures)

The top drugs worldwide (3000-4000 Tons/Year)*

Top 100
- **$85.2 billion**
- **50 single enantiomers, sales of $42.8 billion**

Top 300
- **$124.4 billion**
- **158 single enantiomers, sales of $64.7 billion**

Top 500 drugs
- **$135.9 billion total**
- **269 single enantiomers, sales of $71.1 billion.**

Enantiomers: *Chemical structures that differ only by the 3D atomic arrangement and have a relation like that of our hands.*

(Enzymes, DNA, sugars, biological receptors etc. are single enantiomers)

**Chem. Eng. News 1997*

Lundbeck Pharmaceuticals (1999)

(chemical complexity has a tremendous cost!)

Raw materials
Organic solvents: 990 tonnes
Other raw materials: 1,640 tonnes

Water
Crude water: 14,800 m³
Potable water: 7,900 m³

Energy
Oil: 4,450 MWh
Electricity: 3.300 MWh

Produced tonnes: 179

Wastewater:
Wastewater: 14,200 m³
Organic solvents: 0.3 tonnes
Organic matter: 36 tonnes

Atmospheric emissions
Organic solvents: 18 tonnes

Waste
Chemical waste: 1,255 tonnes

E factor = Materials Used / Product
= 14.7

www.lundbeck.com

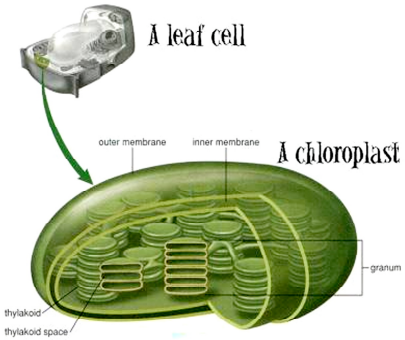
Major Sources of Waste

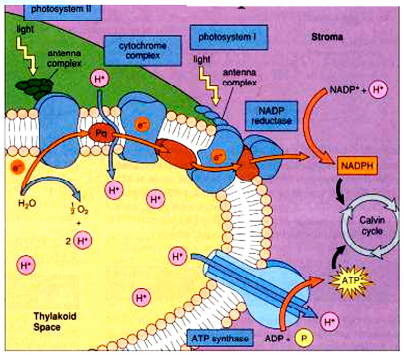
- **Stoichiometric Acids and Bases**
  (H_2SO_4, $AlCl_3$, $ZnCl_2$, BF_3, NaOH, NaOMe, etc.)
- **Stoichiometric Oxidants and Reductants**
  ($Na_2Cr_2O_7$, $KMnO_4$, MnO_2, $LiAlH_4$, $NaBH_4$, Zn, Fe/HCl, etc)
- **Solvent Loses**
  (air emissions and aqueous effluents)

	Ton	E-Factor
— Bulk Chemicals	10^4-10^6	< 1 - 5
— Fine Chemicals	10^2-10^4	5 - > 50
— Pharmaceuticals*	10 -10^3	25 - > 10

Many are Derived from Complex Natural Products

R.A Sheldon, *Chem. Ind.* **1992**, 903; **1997**, 12



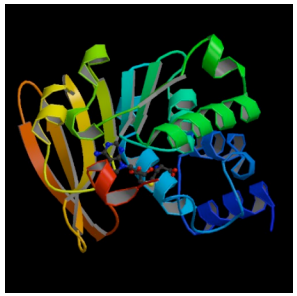


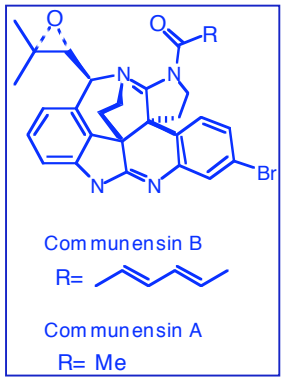
Photosynthesis

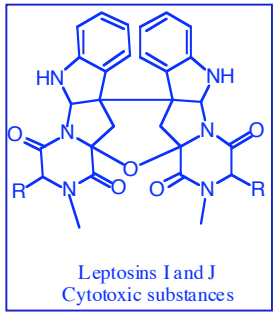
$CO_2 + H_2O + h\nu \rightarrow C_3H_6O_3 \rightrightarrows$ **Life**

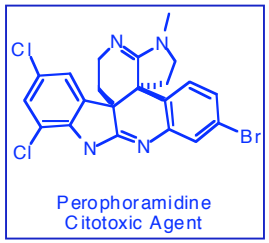
Biosynthesis

isoprenes
propionates
sugars
aminoacids,
etc…



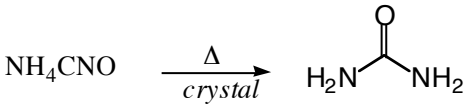




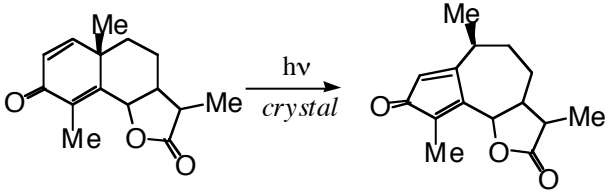


Secondary metabolites

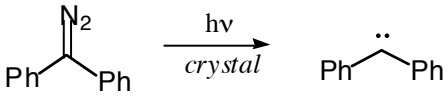
Wholer 1828: First "organic" compound synthesized



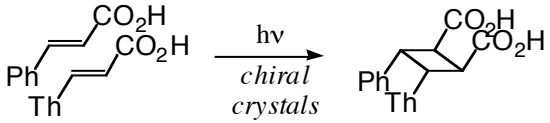
Pfizer 1849: First drug formulated in the US



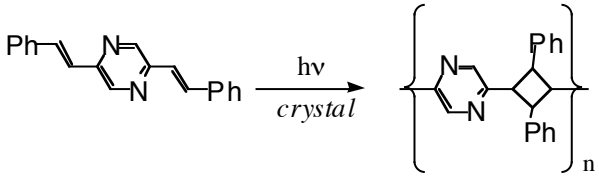
Murray et al. 1962: First triplet molecule observed



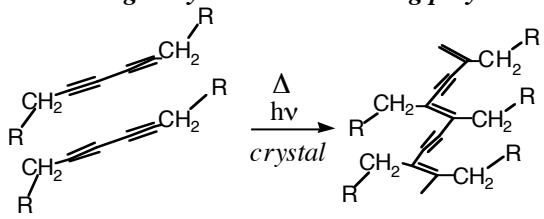
Schmidt et al. 1971: "Spontaneous" generation of optical activity



Hasegawa et al. 1972 : Single crystaline polymers



Wegner et al. 1971: Single crystalline conducting polymers



REACTIONS IN CRYSTALS

—Associations (components)
—Rearrangements
—Fragmentations

Have selectivities, specificities and efficiencies that rival those observed in enzymatic process

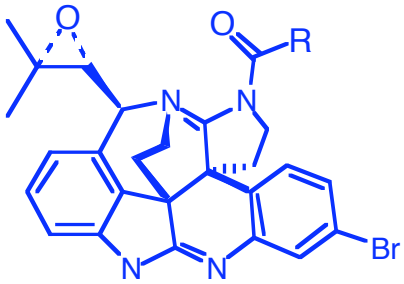
*****DPCP*****

How to take advantage of Photo-[Complex Organic]-Synthesis?

Where to start..? Need a Niche!

Complex Natural Product Synthesis

—Compounds with adjacent stereogenic quaternary stereogenic centers

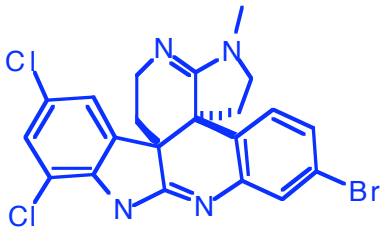


Communensin B

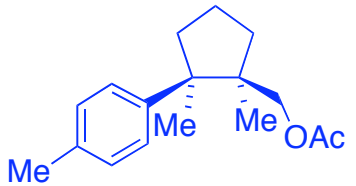
R= 

Communensin A

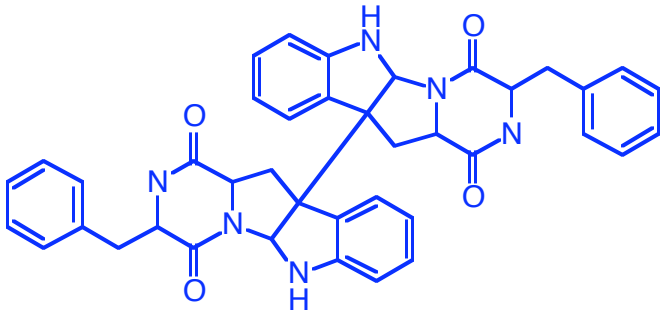
R= Me



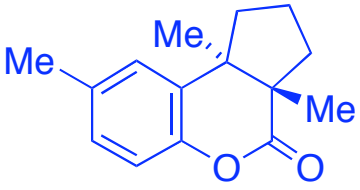
Perophoramidine
Citotoxic Agent



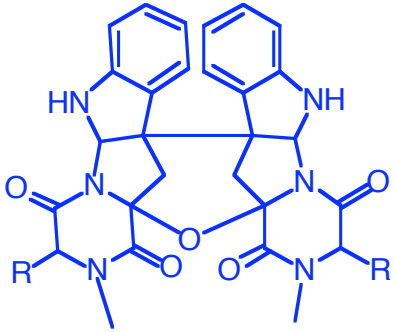
Tochuinyl Acetate
Citotoxic Agent



Psycholein
Antagonists to cholecystokinin
(CCK)B/gastrin receptor



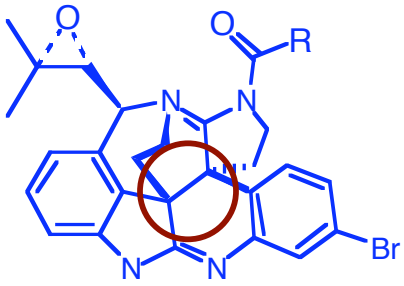
Herbertenolide
Citotoxic Agent



Leptosins I and J
Cytotoxic substances

Complex Natural Product Synthesis

—Compounds with adjacent stereogenic quaternary stereogenic centers

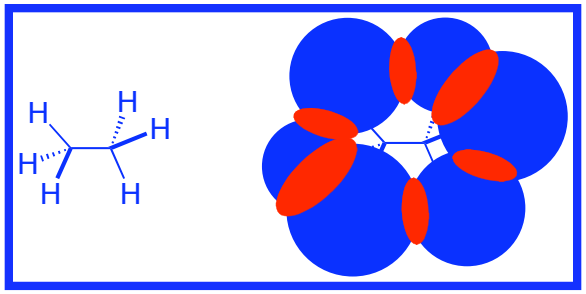


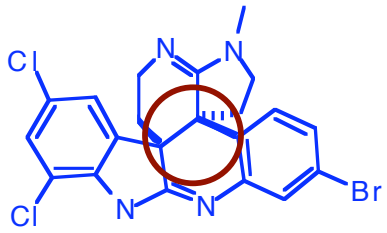
Communensin B

R= 

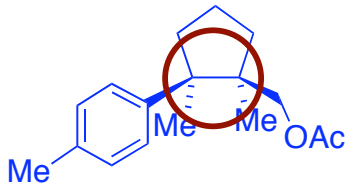
Communensin A

R= Me

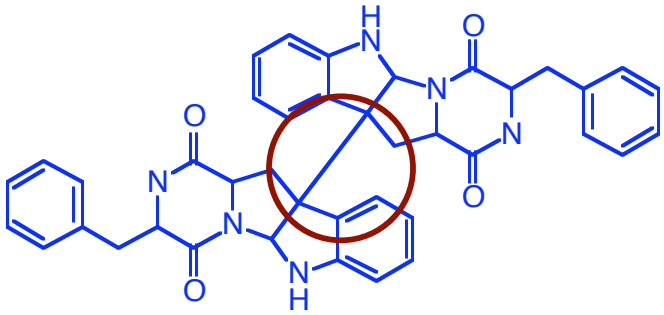




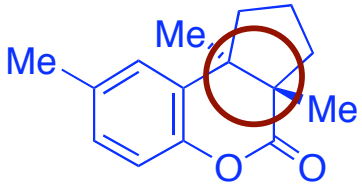
Perophoramidine
Citotoxic Agent



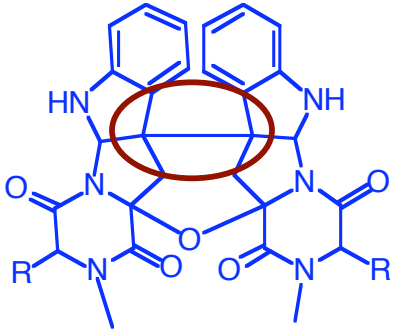
Tochuinyl Acetate
Citotoxic Agent



Psycholein
Antagonists to cholecystokinin
(CCK)B/gastrin receptor



Herbertenolide
Citotoxic Agent

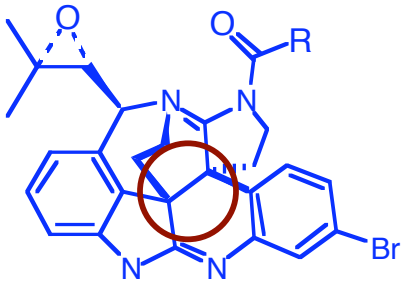


Leptosins I and J
Cytotoxic substances

1) ***Multiple steps***
2) ***Poor stereochemical control***
3) ***Difficult purification***
4) ***Low yields***

Complex Natural Product Synthesis

—Compounds with adjacent stereogenic quaternary stereogenic centers

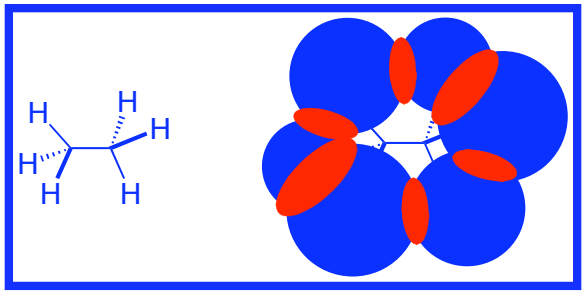


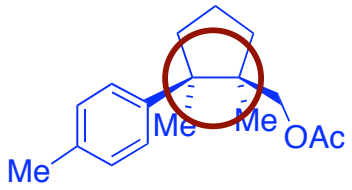
Communensin B

R= 

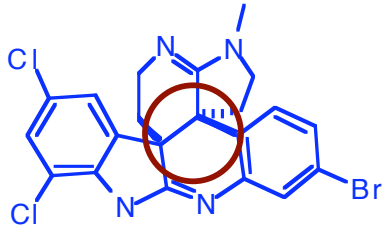
Communensin A

R= Me

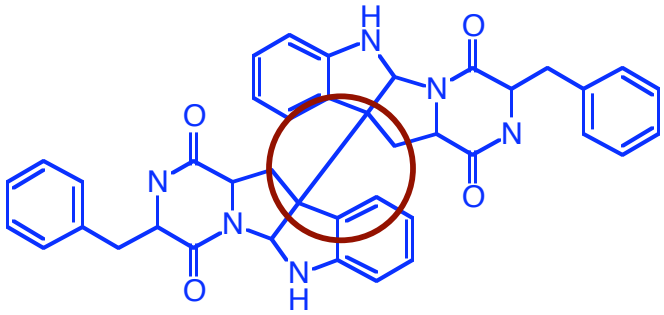




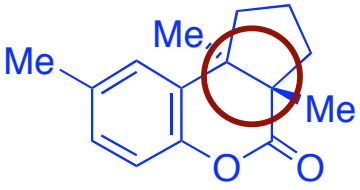
Tochuinyl Acetate
Citotoxic Agent



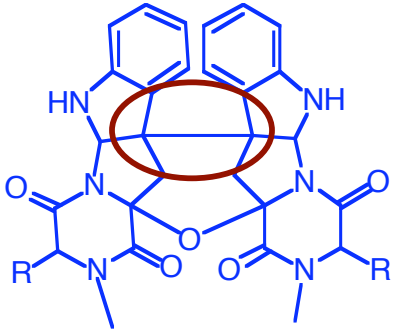
Perophoramidine
Citotoxic Agent



Psycholein
Antagonists to cholecystokinin
(CCK)B/gastrin receptor



Herbertenolide
Citotoxic Agent

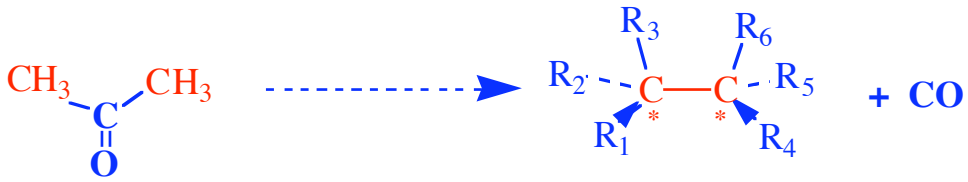


Leptosins I and J
Cytotoxic substances

E. J. Corey

"The asymmetric construction of molecules with adjacent quaternary centers represents a very challenging area in organic synthesis" ***Angew. Chem. Int. Ed.*** **1998, *37*, 388-401**

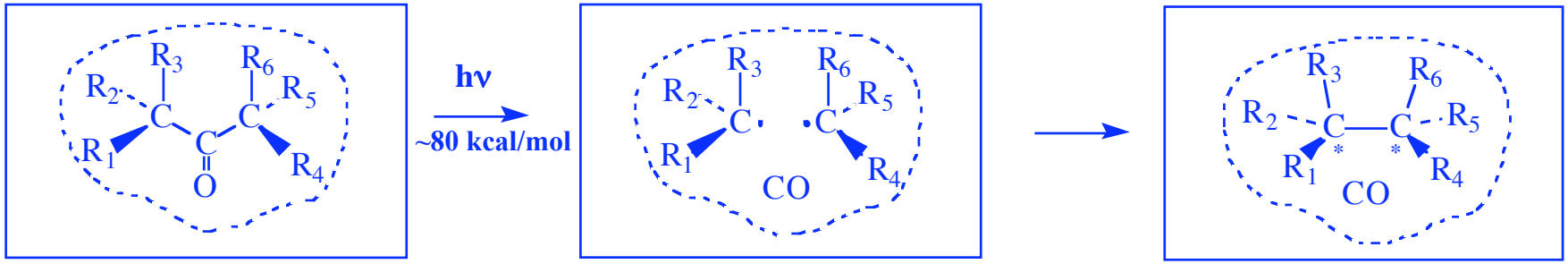
Solvent-Free Syntheses of Adjacent Stereogenic Quaternary Centers: General Strategy



a) Stereoselective ketone chemistry

b) Crystallization

—No solvent
—No separation
—No purification
—Works w/Sunlight



Close neighbors boundaries: (- - - -)

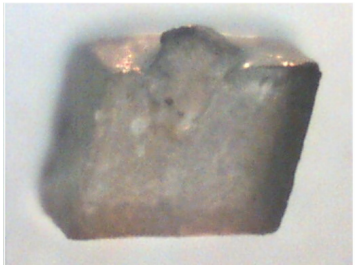
Reactant Crystal

—Highly Predictable Reaction
—Rigidity and Homogeneity lead to:

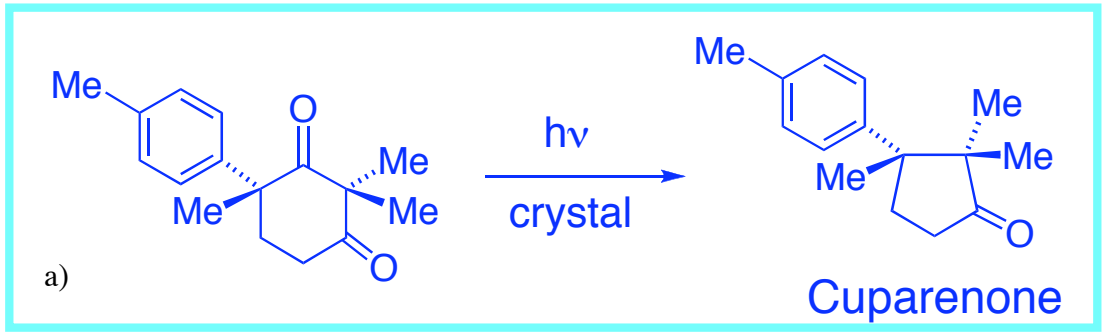
a) Stereoselectivity

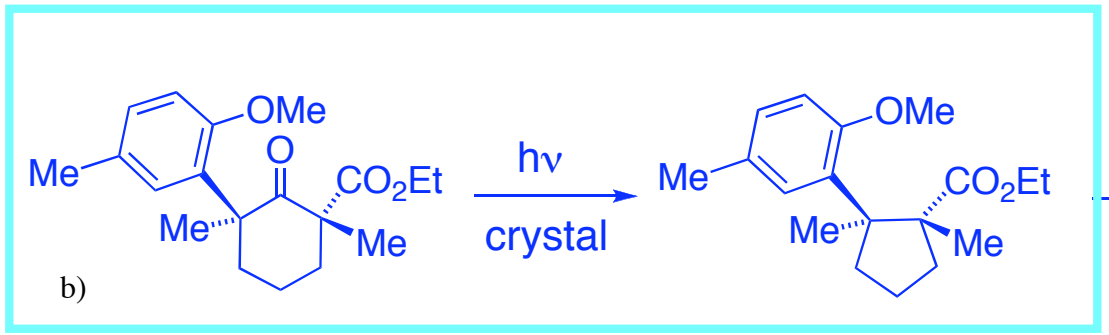
b) Stereospecificity

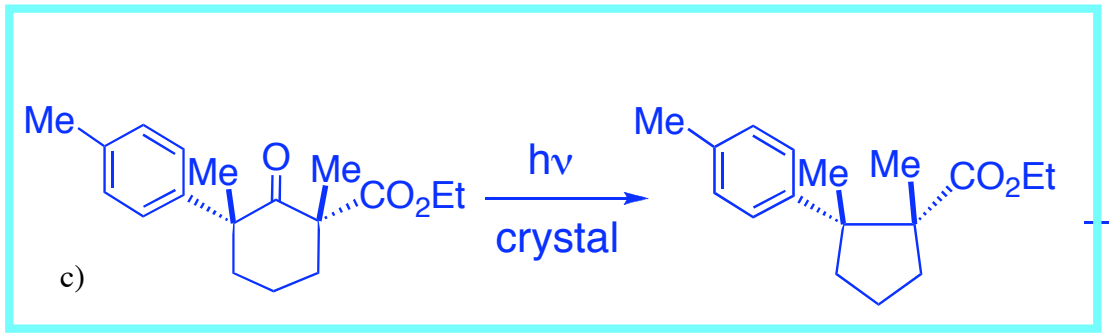
Product Crystal



Natural Product Syntheses Completed with Solid-to-Solid Reactions

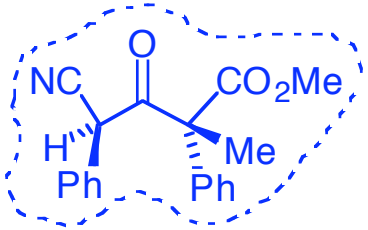






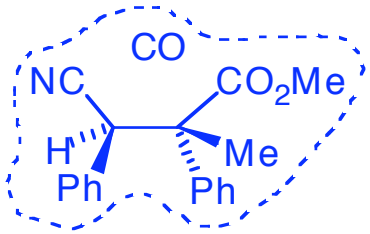
a) Arankumar et al., Angew. Chem. **2007**, b) Ng, D.; Yang, Z.; Garcia-Garibay. M. A., *Org. Letters*, **2004**, *6*, 645, d) Yang et al., in preparation

Reaction Stereoselectivity is determined by the similarity between the structures of the reactant and product



(+)-(2R,4S)

$[\alpha]_D$ = 120° (*c* 0,73, CHCl3)

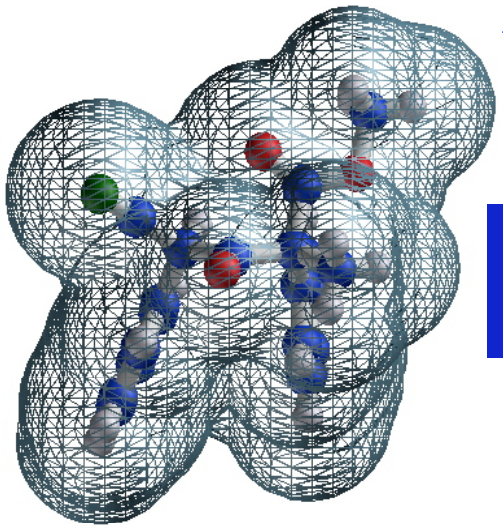


(+)-(2R,4S)

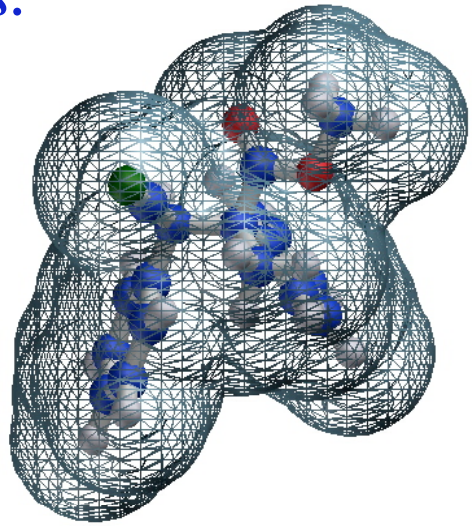
$[\alpha]_D$ = 128° (*c* 0,73, CHCl3)

100% ee

X-Ray Structures:



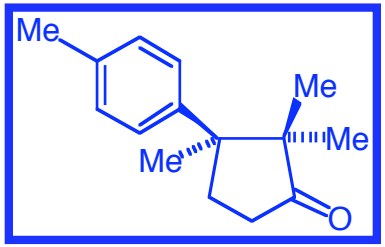
-reactant and product coexist in the same crystal lattice



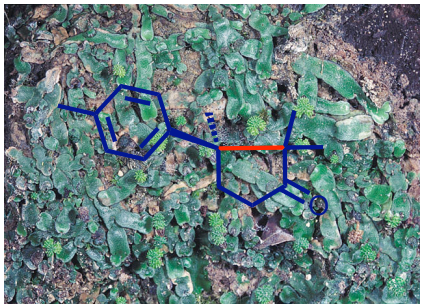
Crystal Rigidity => Reaction selectivity
Crystal Homogeneity => Reaction Specificity

Ellison, M. E.; Ng, D.; Dang, H.; Garcia-Garibay, M.A. *Organic Letters*, **2003**, *5*, 2531

Reported Syntheses of Cuparenone

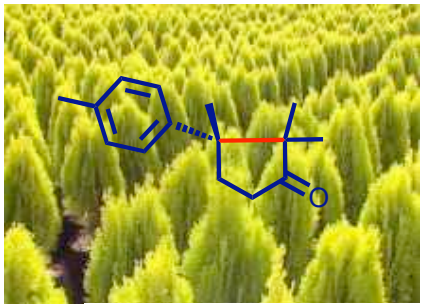


5 steps: 2 "pots" and one solid state reaction 60% total yield, both enantiomers obtained (key step ~100 yield)



(*S*)-(+)-α-Cuparenone

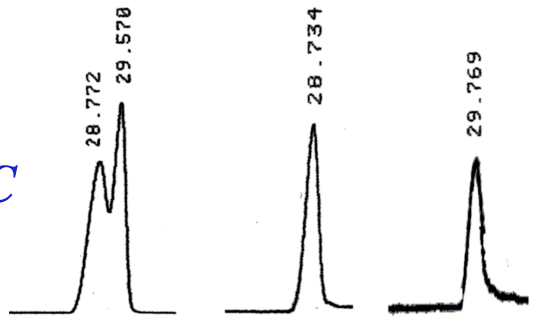
***"Mannia Fragrans"* Liverwort**



***"Mayur pankhi"* Tree**

(R)-(-)-α-Cuparenone

Chiral GC



Racemic ***S-(+)*** ***R-(-)***

Literature	No. of steps	Overall Yield (%) [%ee][§]
Posner *et al.*,[16] 1984	8	5 [71]
Taber *et al.*,[17] 1985	7	0.5 [96]
Kametani *et al.*,[18] 1985	14	5 [9]
Meyers *et al.*,[19] 1986	8	29 [97.6]
Greene *et al.*,[20] 1987	7	18 [99]
Asaoka *et al.*,[21] 1988	12	1.5
Takano, *et al.*,[22] 1989	13	0.5
Gharpure *et al.*,[23] 1989	6.5	6.5 [96]
Fadel *et al.*,[24] 1991	11	22
Nemoto *et al.*,[25] 1992	9	3
Canet *et al.*,[26] 1992	12	12
Honda *et al.*,[27] 1993	9	6
Maruoka *et al.*,[28] 1996	7	10 [70]
Kosaka *et al.*,[29] 1997	14	3.6
Nakashima *et al.*,[30] 2000	17	5.6
Satoh *et al.*,[31] 2003	9	32
Spino *et al.*,[32] 2004	9	12
Our work	5	60 [99]

[§] Only %ee values ex

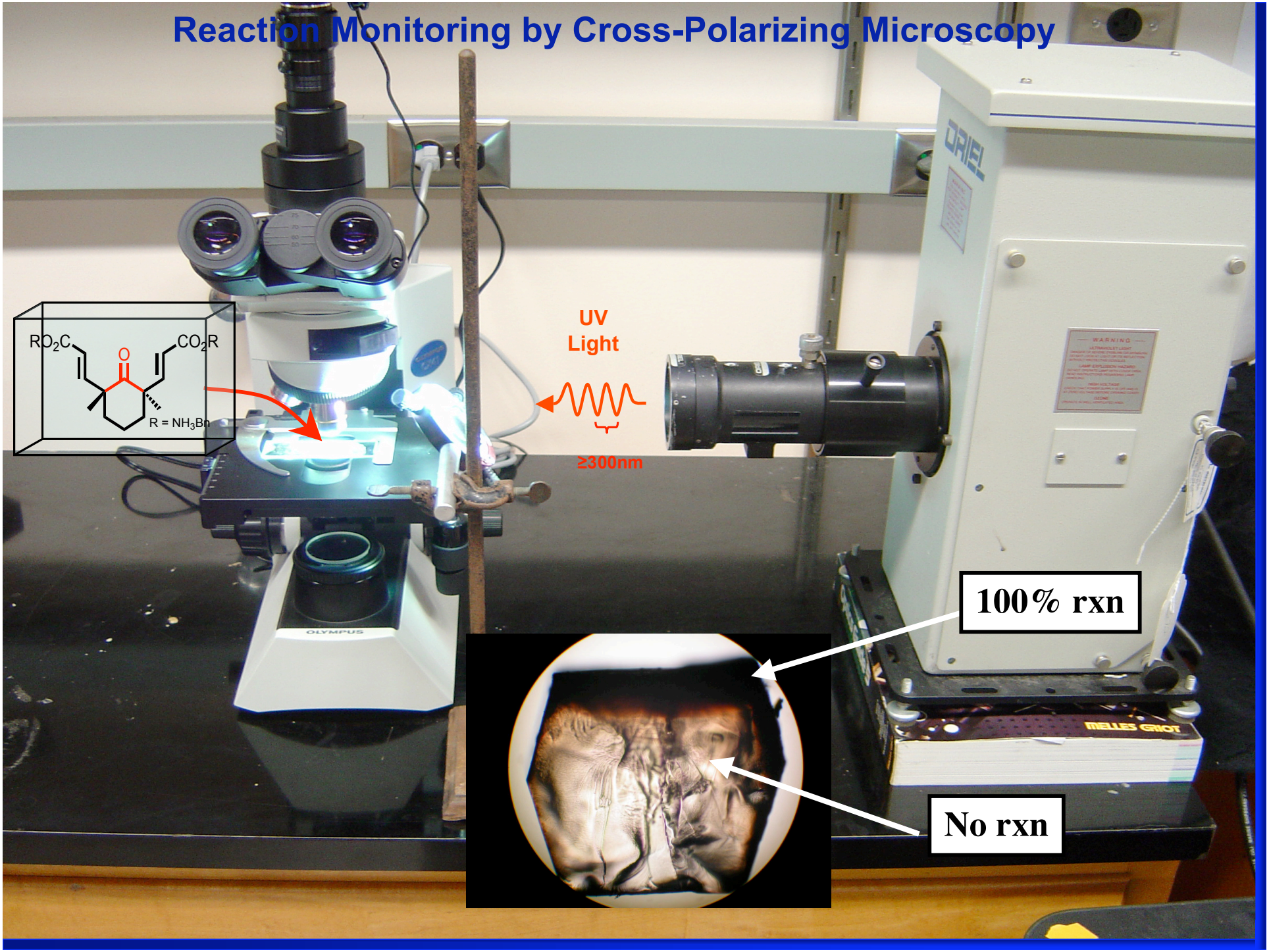
Why is it taking so long to develop solid state chemistry ?

— *There was no incentives !*

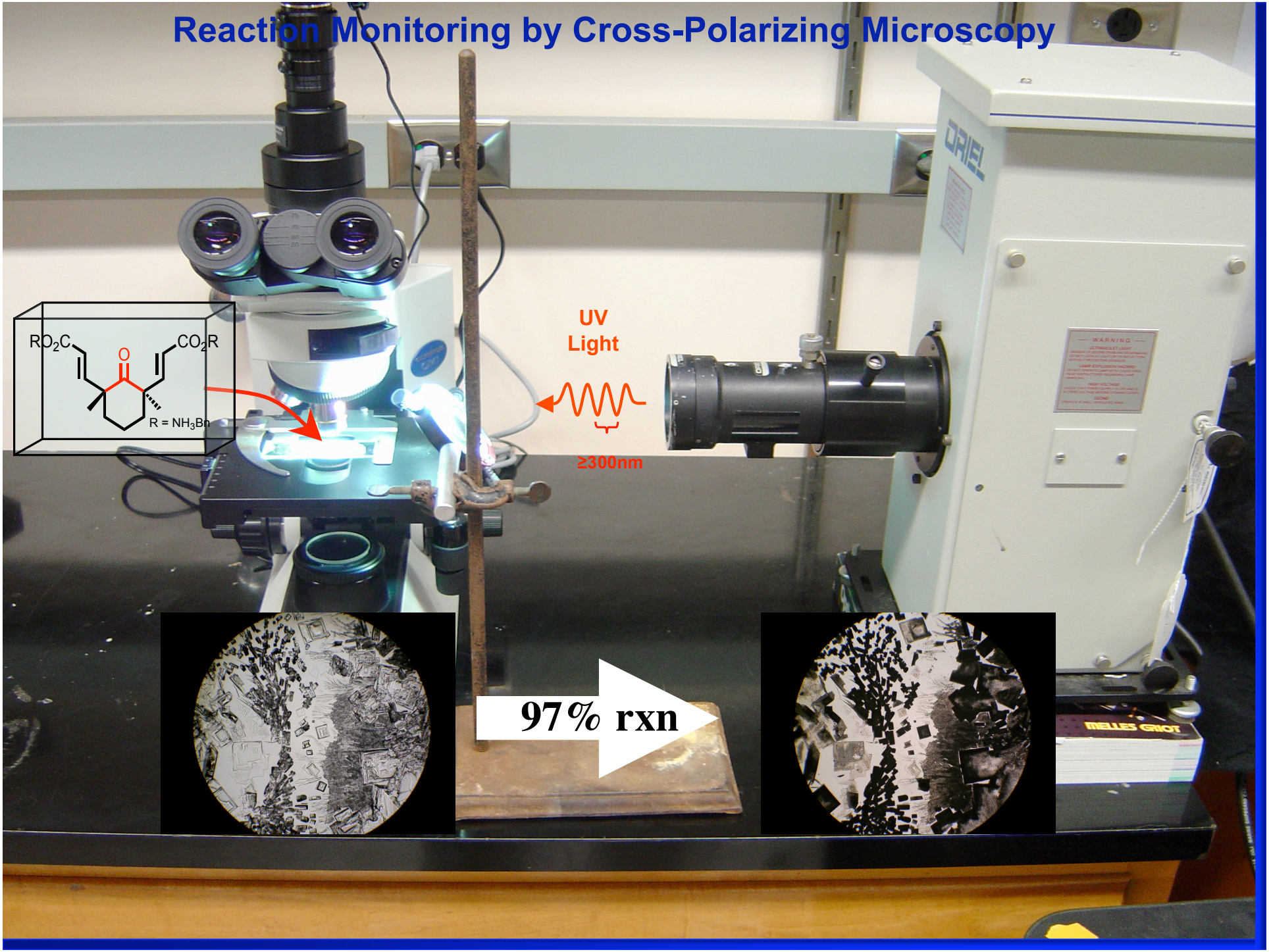
— *It is possible to "engineer" reactions in crystals*

— *Most problems in scale up and optimization seem surmountable … with nanocrystals*

Reaction Monitoring by Cross-Polarizing Microscopy



Reaction Monitoring by Cross-Polarizing Microscopy



Reduce the Crystal Size!

1. Nanocrystals of 100-500 nm retain the chemical influences of bulk crystals

2. As particle sizes approach the wavelength of individual photons : They are excited in nearly homogeneous manner

3. With strongly reduced birefringence, the interaction between particles and photons will approach those of molecules and photons

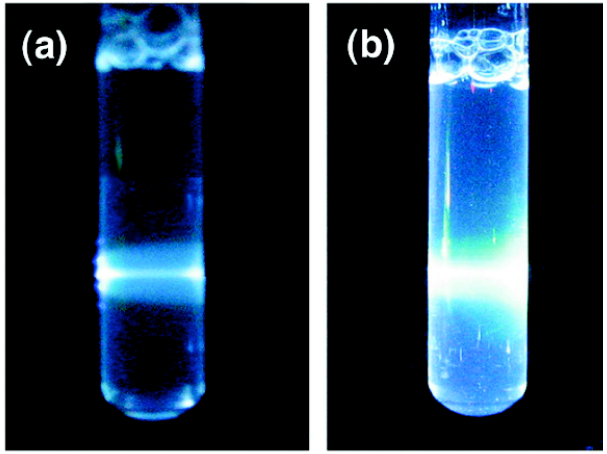
4. Small particles form stable suspensions that can be transported by fluids (H_2O)

5. With reduced birefringence, one can use transmission spectroscopy and monitor in situ

6. Absolute quantum and chemical yield measurements possible

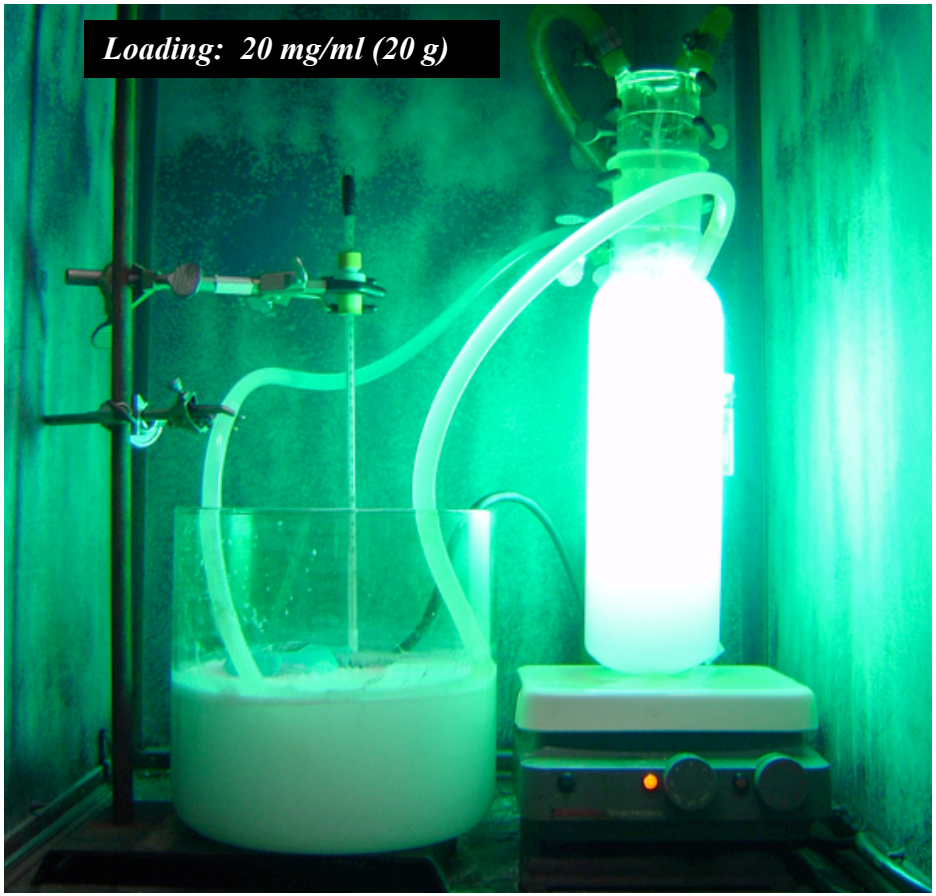
7. Free-flowing suspensions allow the easy scale up of solid state photochemical reactions by taking advantage of flow reactors

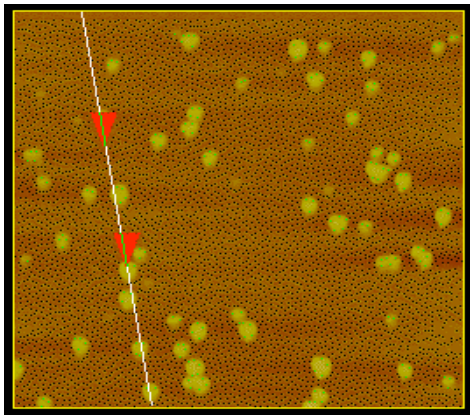
8. With suspensions made in water, the use of solid state chemistry will allow for the synthesis of complex structures by very desirable Green Chemistry methods

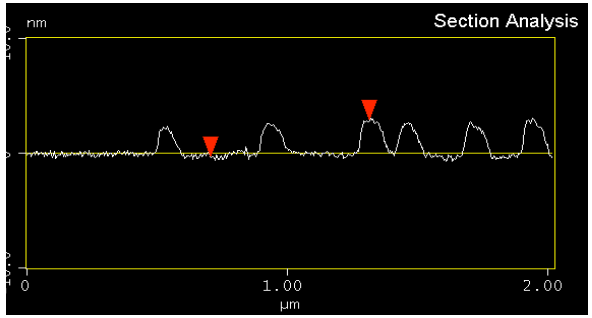


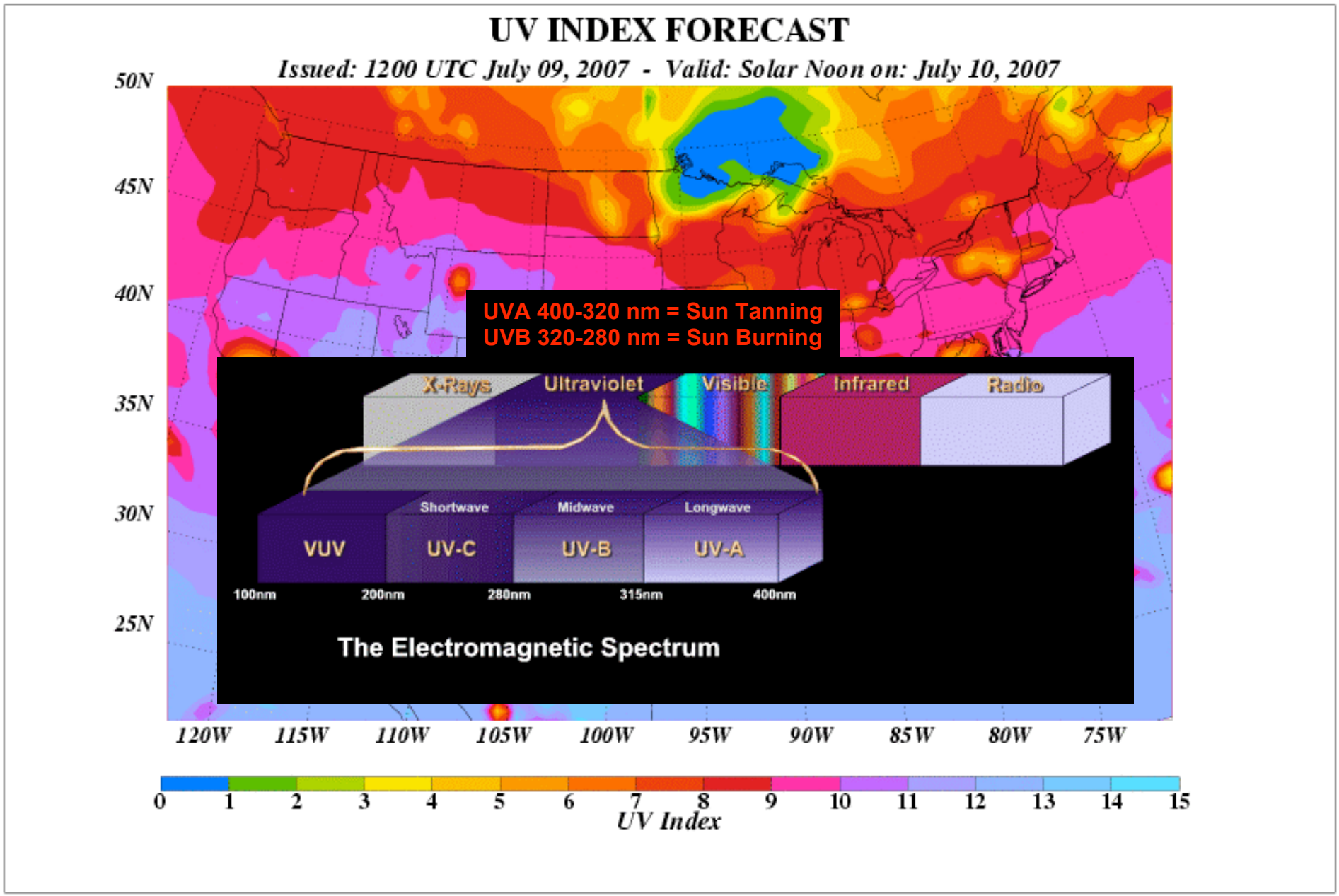
Loading: (a) 0.015 and (b) 1.8 mg/ml

Loading: 20 mg/ml (4 g)



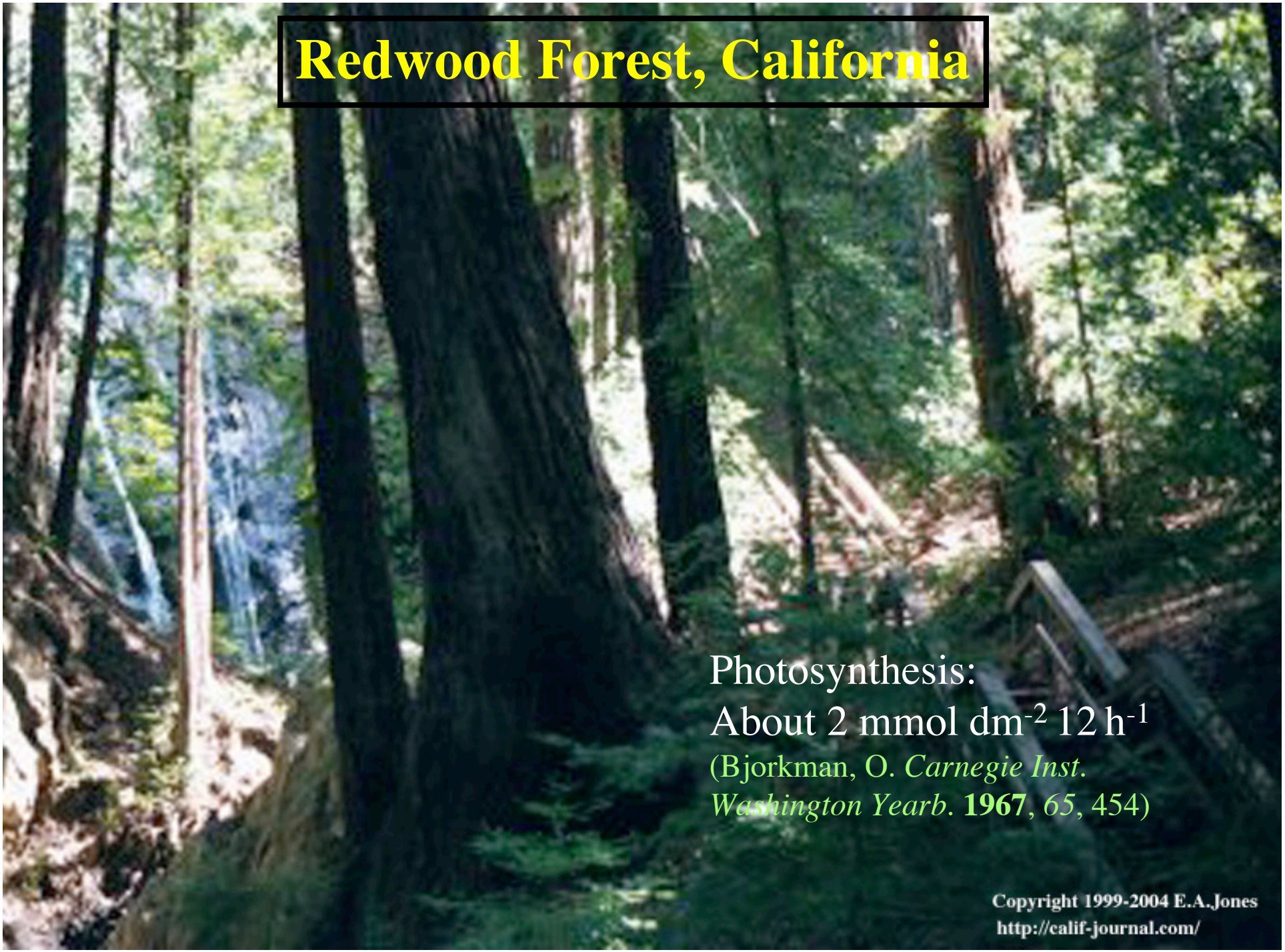






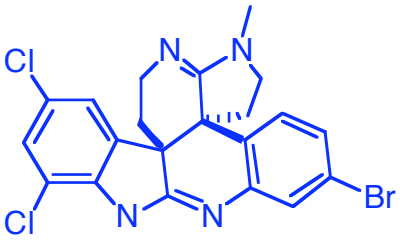
How efficient is decarbonylation in sunlight?

Mortko, C. J.; Garcia-Garibay, M. A
J. Am. Chem. Soc. **2005**, *127*, 7994

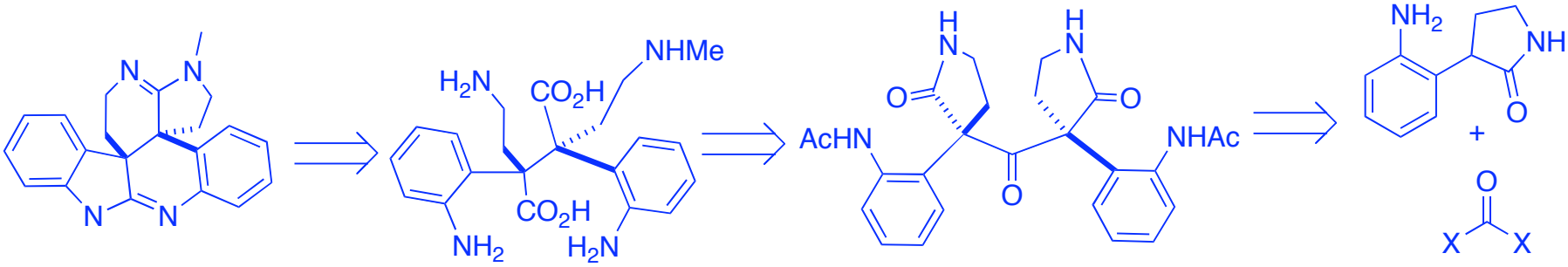

Redwood Forest, California
Photosynthesis:
About 2 mmol dm^{-2} 12 h^{-1}
(Bjorkman, O. *Carnegie Inst. Washington Yearb.* **1967**, *65*, 454)
Copyright 1999-2004 E.A.Jones
http://calif-journal.com/


01/Feb/2005
2 x 100mg (0.75 mmol), 5h
=> ca. 0.9 mmol dm^2 12 h^{-1})

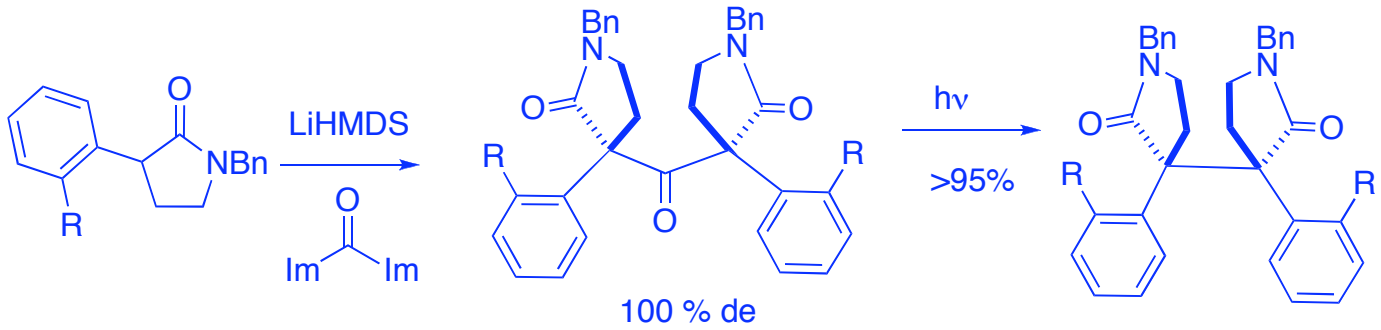
In Progress



perophoramidine



perophoramidine
skeleton model study



100 % de

Conclusions I

Advantages:

a) A Challenging transformation made easy
b) High selectivity
c) High specificity
d) No solvent

Disadvantages:

a) Must be and stay crystalline
b) Highly substrate specific

i.e., Very Much Like Most Enzymatic Processes!
Potential Applications? Specialty Chemicals

Conclusions II

—Solid state photochemical synthesis can be highly selective (there are many reactions amenable to development in the crystalline state)

—Nanocrystals make solid state reactions highly efficient

—Water suspensions make scale up easy to implement. Flow reactors are possible

—Complex structures, high yields, no workup (filtration), no purification

Solar and Arc Lamp reactors

Precipitate and Filter