ISCHIA SEPTEMBER 2006 ROCHE LECTURE

BETTER SCIENCE THROUGH SYNTHESIS:

NEW MEDICINAL LEADS BASED ON PHARMACOPHORE TARGETING OF NEW REACTIONS AND ON NOVEL DRUG DELIVERY SYSTEMS

WENDER GROUP - STANFORD UNIVERSITY

Dept. of Chemistry(H&S); Dept of Molecular Pharmacology (Medical School); Molecular & Genetic Medicine; Cancer Biology; Clinical Oncology Quantitative Chemical Biology; Neurobiology; Epithelial Biology; Imaging Institute

SOME RELEVANT LEAD REFERENCES

Paul Wender, Nicole Deschamps, Robert Sun "Rh(I)-Catalyzed C-C Bond Activation: Seven-Membered Ring Synthesis by a [6+1] Carbonylative Ring Expansion Reaction of Allenylcyclobutanes " *Angewandte Chemie Int. Ed.*, **2006**, *45(24)*, 3957.

Wender, Croatt, Witulski, "New Reactions and Step Economy: The Total Synthesis of (±)-Salsolene Oxide Based on the Type II Transition Metal-Catalyzed Intramolecular [4+4] Cycloaddition" *Tetrahedron* **2006**, *62*, 7505-7511.

Paul A. Wender,* Michael K. Hilinski, Nicolas Soldermann, Susan Mooberry "Total Synthesis and Biological Evaluation of 11-Desmethyl Laulimalide, a Highly Potent Simplified Laulimalide Analog" *Organic Lett.* **2006**, 1507.

Susan L. Mooberry, Deborah A. Randall-Hlubek, Rachel M. Leal, Sayee G. Hegde, Robert D. Hubbard, Lei Zhang and Paul A. Wender "Structure-Function Studies on a New Class of Microtubule Stabilizing Agents Based on Laulimalide" *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 8803-8808.

Erin A. Clark, Bradley S. Davidson, Paul A. Wender, Susan L. Mooberry "Laulimalide and Synthetic Laulimalide Analogs are Synergistic with Paclitaxel and 2-Methoxyestradiol" *Molecular Pharmaceutics* **2006**, 457-467.

Paul Wender, Mitchell P. Croatt, Nicole M. Deschamps "Metal-Catalyzed [2+2+1] Cycloadditions of 1,3-Dienes, Allenes, and CO' *Angewandte Chemie Int. Ed.*, **2006**, *45(15)*, 2459-2462.

Lisa Jones, Elena Goun, Rajesh Shinde, Jonathan Rothbard, C. Contag, P.Wender* "Releasable Luciferin-Transporter Conjugates: Tools for the Real Time Analysis of Cellular Uptake and Release" *J. Am. Chem. Soc.* **2006**, *128(20)*, 6526-6527.

Elena Goun, Rajesh Shinde, Karen Dehnert, Angie Adams-Bond, Paul Wender, Chris H. Contag, Benjamin L. Franc "Intracellular Cargo Delivery by an Octaarginine Transporter Adapted to Target Prostrate Cancer Cells Though Cell Surface Protease Activation" *Bioconjugate Chem.* **2006**, *17(3)*, 787-796.

Wender, Paul A.; Gamber, Gabriel G.; Williams, Travis J.; Rhodium(I)-Catalyzed [5+2], [5+2], and [5+2+1] Cycl;oadditions: New Reactions for Organic Synthesis in "Modern Rhodium-Catalyzed Organic Reactions" P. Andrew Evans Ed. Wiley-VCH Verlag Gmbh & Co. KgaA, Weinheim pp 263-299, **2005**.

Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L.; "Multicomponent Cycloadditions: The Four-Component [5+1+2+1] Cycloaddition of Vinylcyclopropanes, Alkynes, and CO" *J. Am. Chem. Soc.* **2005**, 2836-2837.

Jonathan B. Rothbard Theodore C. Jessop, Richard S. Lewis, Bryce A. Murray, Paul A. Wender "The Role of Membrane Potential and Hydrogen Bonding in the Mechanism of Translocation of Guanidinium-Rich Peptides into Cells" *J. Am. Chem. Soc.* **2004**, 9506-9507.

Wender, Paul A.; Baryza, Jeremy L.; Brenner, Stacey E.; Clarke, Michael O.; Craske, Madeleine L.; Horan, Joshua C.; Meyer, Tobias "Function Oriented Synthesis: The Design, Synthesis, PKC Binding and Translocation Activity of a New Bryostatin Analogue" *Current Drug Discovery Technologies* **2004**, 1, 1-11.

Samuel, Hearn, Mack, Wender, Rothbard, Kirisits, Mui, Wernimont, Roberts, Muench, Rice, Prigge, Law, McLeod "Delivery of Antimicrobials into Parasites" *Proc. Natl. Acad. Sci. USA* , **2003**, *100*, 14281-14286.

Paul A. Wender, Dennis J. Mitchell, Kanaka Pattabiraman, Erin Pelkey, Lawrence Steinman, Jonathan B. Rothbard "Molecular Transporters: The Design, Synthesis, and Evaluation of Molecules that Enable or Enhance Cellular Uptake" *Proc. Natl. Acad. Sci. USA* , **2000**, *97*, 13003-13008.

Jonathan B. Rothbard, Sarah Garlington, Qun Lin, Thorsten Kirschberg, Erik Kreider, P. Leo McGrane, Paul A. Wender and Paul A. Khavari, Conjugation of Arginine Oligomers to Cyclosporin A Facilitates Topical Delivery and Inhibition of Inflammation, *Nature Medicine* **2000**, *6*, 1253-1257.

OUR RESEARCH FOCUSES ON…

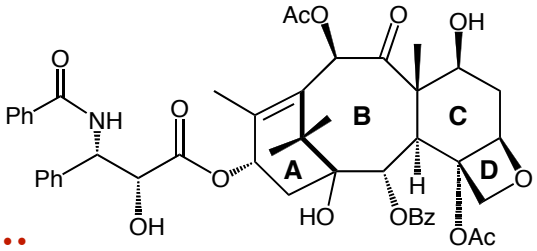
***NOVEL STRUCTURES…**

AS INSPIRATION FOR NEW REACTIONS, CATALYSTS, STRATEGIES

***UNIQUE AND POTENT ACTIVITY, FUNCTION…**

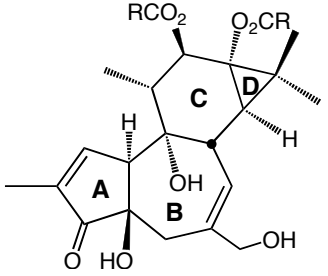
AS INSPIRATION FOR NEW THERAPEUTIC LEADS, MODES OF ACTION, MATERIALS

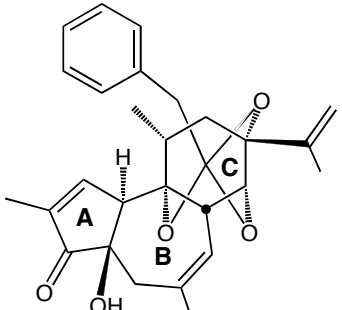
***INTEGRATION OF CHEM, BIO, MED**



TAXOL

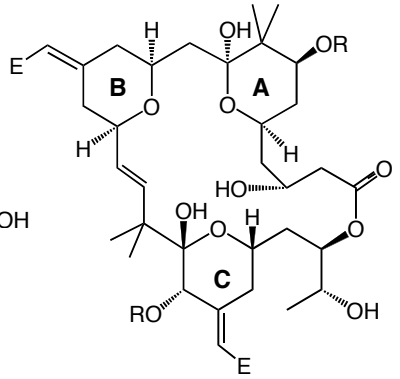
PHORBOL

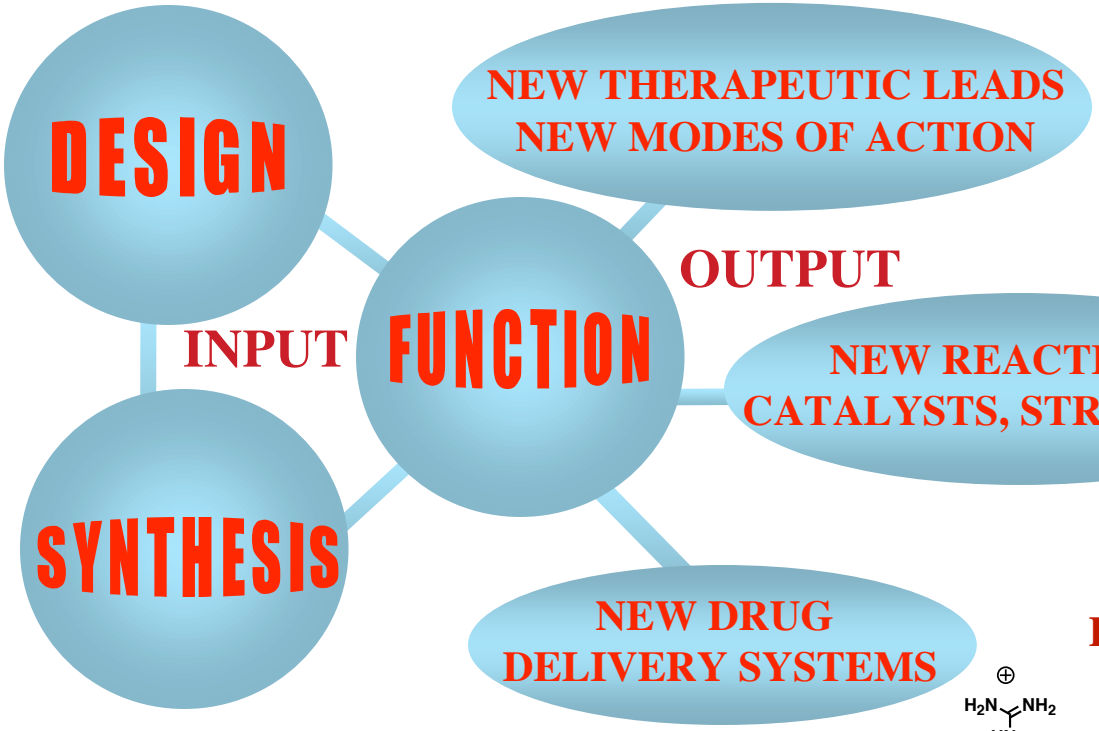




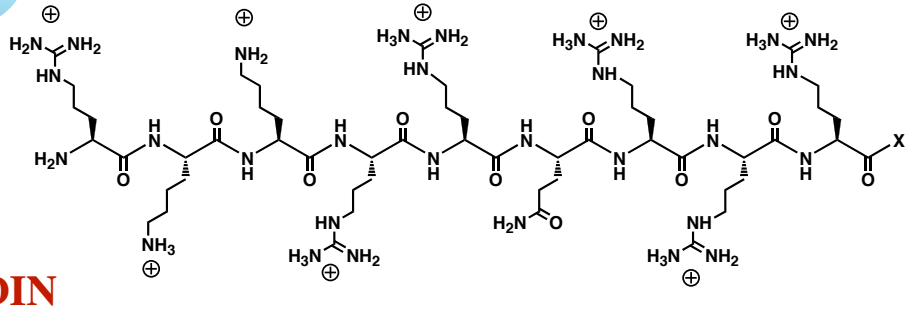
RTX

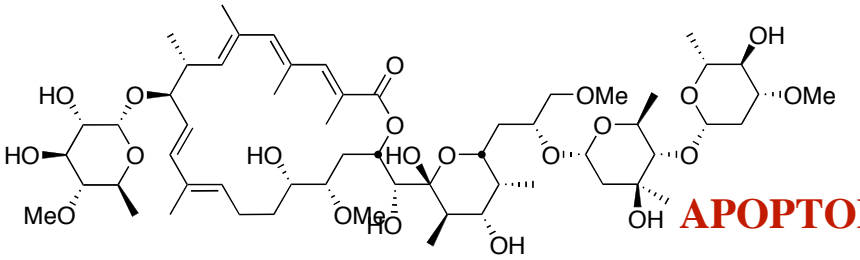
BRYOSTATIN





HIV TAT 9-MER





APOPTOLIDIN

TWO MAJOR PRIORITIES IN CHEMISTRY

FUNCTION ORIENTED SYNTHESIS

- •MEDICINAL AGENTS
- •MATERIALS
- •CATALYSTS
- •PROBES
- •IMAGING TOOLS
- •DIAGNOSTICS
- •SENSORS
- •NANODEVICES
- •ENERGY COLLECTION
- •ENERGY STORAGE
- •ENERGY CONVERSION
- •ENVIRONMENTAL

Wender, P.A.; Baryza, J.L.; Brenner, S.E.; Clarke, M.O.; Craske, M.L.; Horan, J.C.; Meyer, T. " **Function Oriented Synthesis:…"** *Current Drug Discovery Technologies*, **2004**, *1*, 1-11.

- •OVER 200 TOTAL SYNTHESES / YEAR IN ACS JOURNALS ALONE
- •MAKING MOLECULES IS NO LONGER THE BIGGEST CHALLENGE IN SYNTHESIS
- •THE MAJOR CHALLENGES NOW ARE TARGET DESIGN & SELECTION & ADVANCING SYNTHESIS TO MAKE SUCH TARGETS …

IN A PRACTICAL IF NOT IDEAL FASHION

*Wender, Miller **"Toward the Ideal Synthesis:** Connectivity Analysis & Multi-Bond Forming Processes" in *Organic Synthesis: Theory and Applications* T. Hudlicky (ed.), V. 2, 27, **1993**, JAI Press.
Wender, Wright, Handy, **"Toward the Ideal Synthesis"** *Chemistry & Industry*, **1997**, 765.

THE IDEAL SYNTHESIS AND STEP ECONOMY

- ONE STEP, 100 % YIELD
- READILY AVAILABLE STARTING MATERIALS
- OPERATIONALLY SIMPLE, SAFE AND ENVIRONMENTALLY SOUND
- RESOURCE (COST, TIME, MATERIAL, PERSONNEL) EFFECTIVE

*Wender, Miller, "Toward the Ideal Synthesis: Connectivity Analysis and Multi-Bond Forming Processes", in *Organic Synthesis: Theory and Applications* T. Hudlicky, ed., V. 2, pp 27-66, **1993**, JAI Press.
Wender, Dennis Wright, Scott Handy, "Toward the Ideal Synthesis," *Chemistry & Industry*, **1997**, 765.

WHY IS STEP ECONOMY SO IMPORTANT?

A 70 step synthesis, even if 100% selective & efficient, is still a 70 step synthesis.
70 steps take time, add cost, deplete resources, generate waste (solvent, etc)…

STEP ECONOMY:

REDUCES LENGTH, WASTE (SOLVENT, ATOM LOSS!!!), ENVIRONMENTAL IMPACT, DEVELOPMENT & EXECUTION TIME, SEPARATION SCIENCE, EFFORT, COST;

IMPROVES YIELD, SPEED, SCIENTIFIC ADVANCEMENT, SAFETY, RETURN ON INVESTMENT, AND MOST IMPORTANTLY **HUMAN ECONOMY**

Wender, P.A.; Baryza, J.L.; Brenner, S.E.; Clarke, M.O.; Craske, M.L.; Horan, J.C.; Meyer, T.
" Function Oriented Synthesis:…" *Current Drug Discovery Technologies*, **2004**, *1*, 1-11.

BRYOSTATIN: NOVEL STRUCTURE, UNIQUE FUNCTION

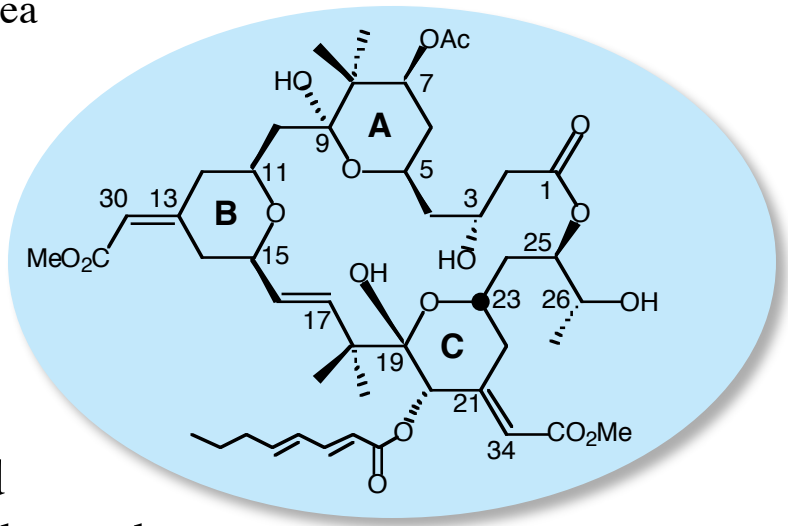
Underwater Treasures

Doctors Searching for Potential Cancer Cures Beneath the Sea

John McKenzie abc NEWS

"A treasure chest of potential medicine lies in the sponges, algae and coral that live beneath the sea. And doctors think some of them may even help cure cancer…"

BRYOSTATIN 1



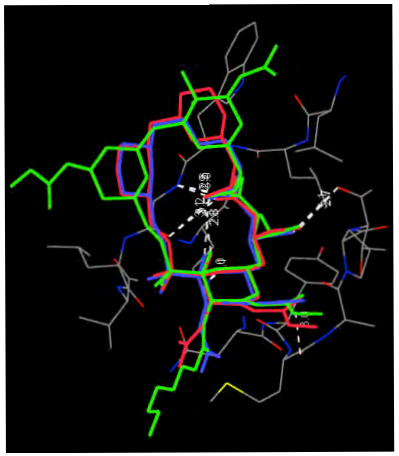
Louis Piaroulli…

his cancer was spreading through his bones and lymph nodes. Traditional chemotherapy had failed. Then, doctors tried again with the same chemotherapy drug, but they added bryostatin. Before adding bryostatin, Piaroulli's bones were riddled with cancer.

Five months after the treatment, there was no trace of the disease.

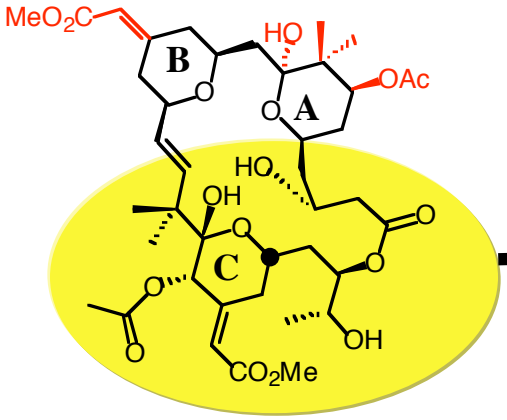
***"The response was exceptional and dramatic, and we would not have anticipated this response from chemotherapy alone,"* says Schwartz (Memorial Sloan-Kettering).**

BEYOND NATURAL PRODUCTS: DESIGN A *BETTER* TARGET



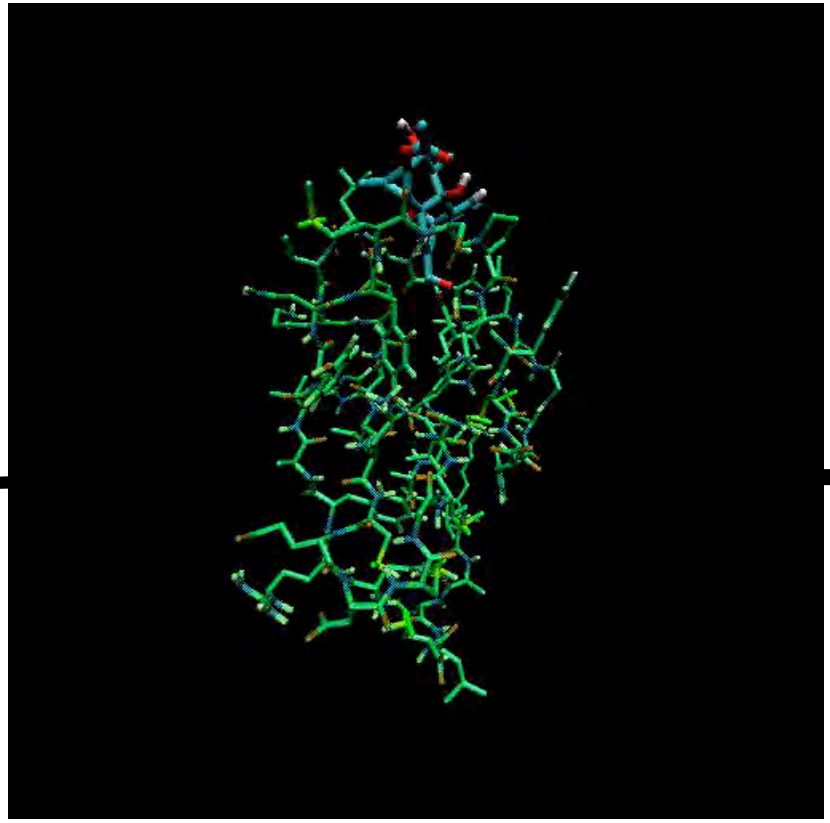
SIMPLER BUT FUNCTIONALLY SUPERIOR TARGETS= SHORTER (STEP ECONOMICAL) SYNTHESES

SPACER DOMAIN

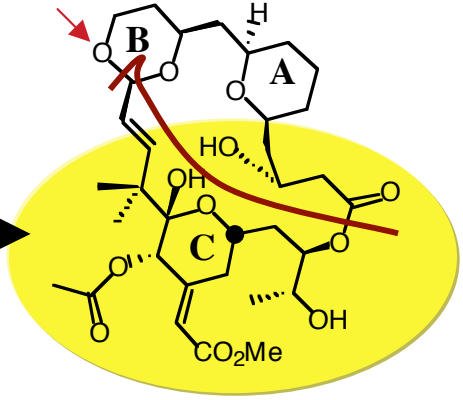


RECOGNITION DOMAIN

BRYOSTATIN



SIMPLER SPACER DOMAIN



RECOGNITION DOMAIN

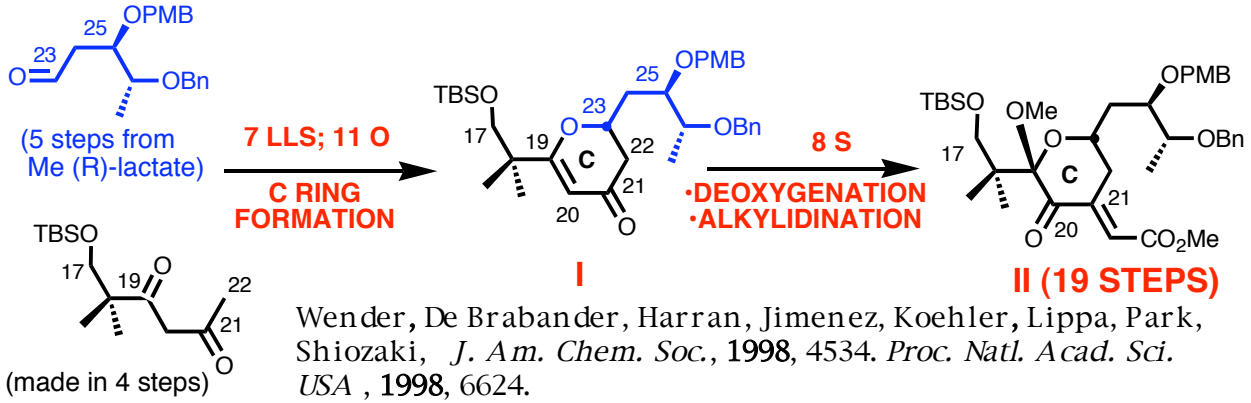
BRYOLOG

Wender, P.A.; Baryza, J.L.; Brenner, S.E.; Clarke, M.O.; Craske, M.L.; Horan, J.C.; Meyer, T. " Function Oriented Synthesis:…" *Current Drug Discovery Technologies*, **2004**, *1*, 1-11.

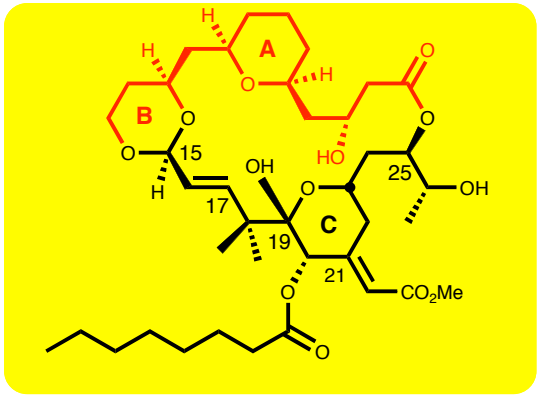
Wender, De Brabander, Harran, Jimenez, Koehler, Lippa, Park, Siedenbiedel, Pettit, *Proc. Natl. Acad. Sci.*, **1998**, 6624

Wender, Baryza, Bennett, Bi, Brenner, Clarke, Horan, Kan, Lacote, Lippa, Nell, Turner *J. Am. Chem. Soc.* **2002**, 13648

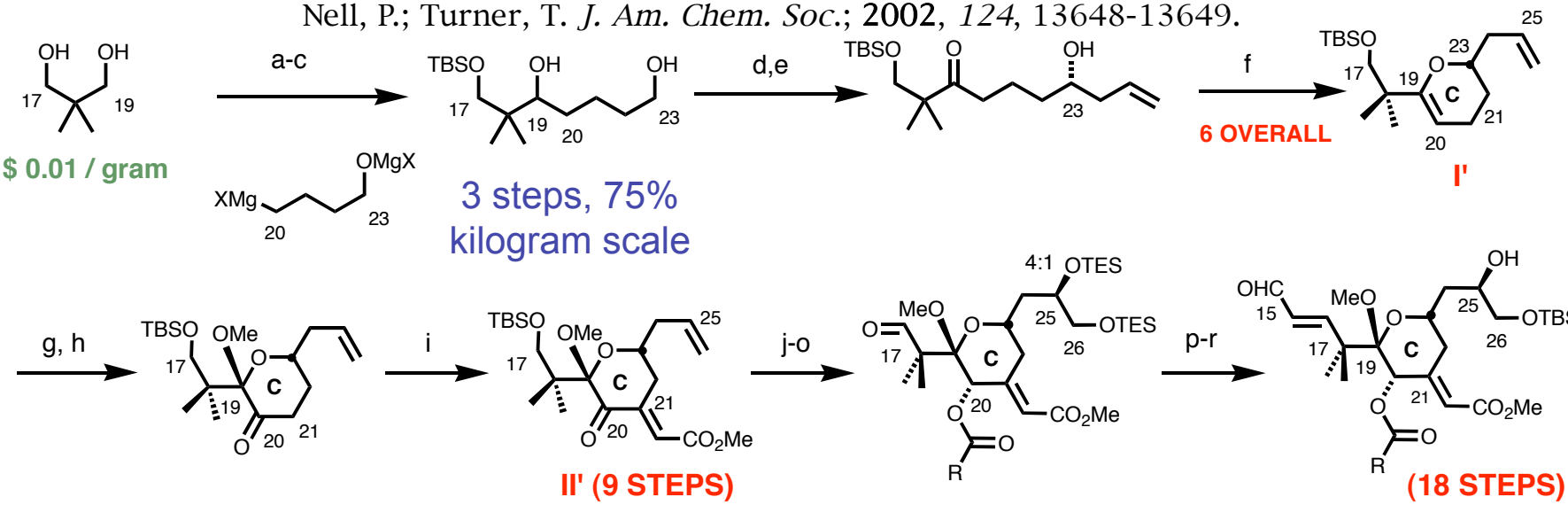
TOWARD A PRACTICAL (MANUFACTURING) SYNTHESIS OF "BRYOLOGS"



Wender, De Brabander, Harran, Jimenez, Koehler, Lippa, Park, Shiozaki, *J. Am. Chem. Soc.*, 1998, 4534. *Proc. Natl. Acad. Sci. USA*, 1998, 6624.



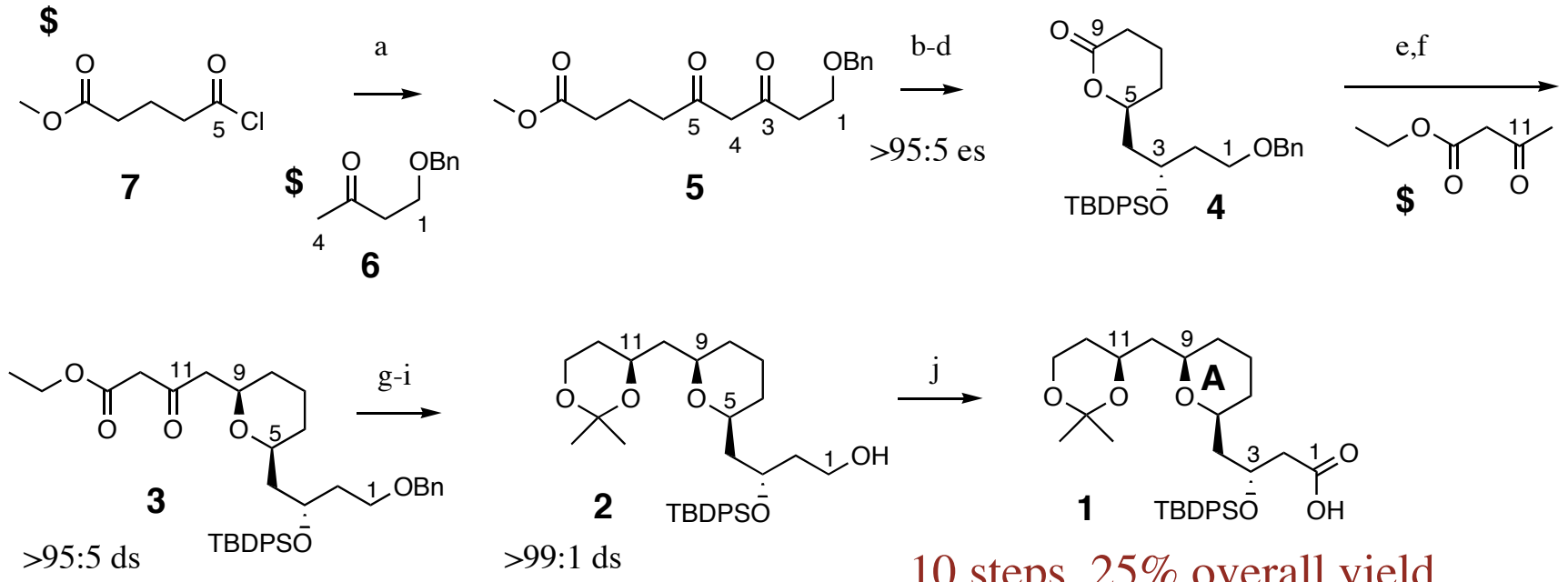
Wender, P. A.; Baryza, J.; Bennett, C.; Bi, C.; Brenner, S. E.; Clarke, M.; Horan, J.; Kan, C.; Lacote, E.; Lippa, Nell, P.; Turner, T. *J. Am. Chem. Soc.*; 2002, *124*, 13648-13649.



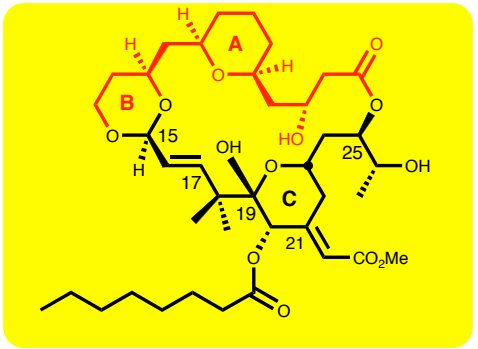
(a) NaH, TBDMSCl, THF, rt; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C; (c) 4-chlorobutanol, MeMgCl, -78°C; Mg, THF, reflux; -78°C, THF; 75% 3 steps; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, - 78°C; 75%; (e) 5 mol% $Ti(Oi\text{-}Pr)_4$, 10 mol% (R)-BINOL, $B(OMe)_3$, allylSnBu$_3$, 4 Å sieves, CH_2Cl_2, RT; 75%; (f) PTSA, 4 Å sieves, MePh; RT; 80% (g) MMPP, $NaHCO_3$, CH_2Cl_2, MeOH, 0°C; 75%; (h) 0.1 eq. TPAP, 3 eq. NMO, 4 Å sieves, CH_2Cl_2, MeCN, 0°C - RT; 81%(i) K_2CO_3, MeOH, (MeO)(OH)$CHCO_2$Me, - 78°C; 80%; (j) $CeCl_3$*$7H_2O$, $NaBH_4$, MeOH, -30 ∞C; (k) $C_7H_{15}CO_2H$, DIC, DMAP, CH_2Cl_2, RT; 79% 2 steps; (l) HF/pyridine, THF, RT.; (m) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT; 79% 2 steps; (n) $(DHQD)_2PYR$, $K_2OsO_2(OH)_4$, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH, H_2O, 0°C; 90%; (o) TESCl, pyr, CH_2Cl_2, rt; (p) 1-Br, 2-EtO-ethene, t-BuLi, $ZnMe_2$, -78°C; (q) HF, CH_3CN, H_2O, rt; (r) 1:3 TBSCl:imidazole, 9:1 CH_2Cl_2 : DMF; 40% 4 steps.

TOWARD A PRACTICAL (MANUFACTURING) SYNTHESIS OF "BRYOLOGS"

Paul A. Wender, Alexander V. M. Mayweg, Christopher L. VanDeusen *Organic Lett.* **2003**, 277-279



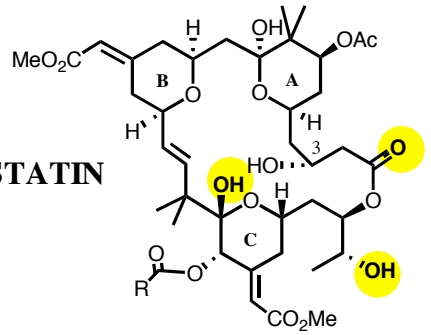
[a] Reagents and conditions: (a) LDA, 4-benzyloxy-2-butanone, −78 °C, 10 min, 68%; (b) Ru-(*S*)-BINAPCl$_2$, MeOH, H_2, (95 atm), 30 °C, 78 h, 92% (97% BORSM); (c) silica, PhMe, 12 h, reflux, 95%; (d) TBDPSCl, imidazole, DMF, 2 h, 85%; (e) ethylaceto-acetate, LDA (2 equiv), −78 °C; (f) Et_3SiH, TFA, −30 °C, 4 h, 70% over two steps; (g) Ru-(*R*)-BINAPCl$_2$, EtOH, H_2 (78 atm), 96 h, 91%; (h) H_2, $Pd(OH)_2$, Et_2O, 1 h, then $LiBH_4$, 1 h, 96%; (i) 2,2-dimethoxypropane, TsOH, DMF, then silica, DCM, 4 h, 93%; (j) TEMPO, NaOCl, $NaClO_2$, MeCN, 50 °C, 4 h, 92%.



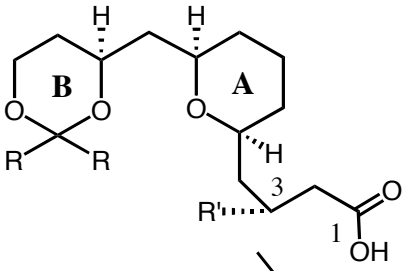
A PRACTICAL (MANUFACTURING) SYNTHESIS OF DESIGNED TARGET

•LATE STAGE CONVERGENCY
•MILD MACROACETALIZATION
•COMBINATORIAL SYNTHESIS

BRYOSTATIN

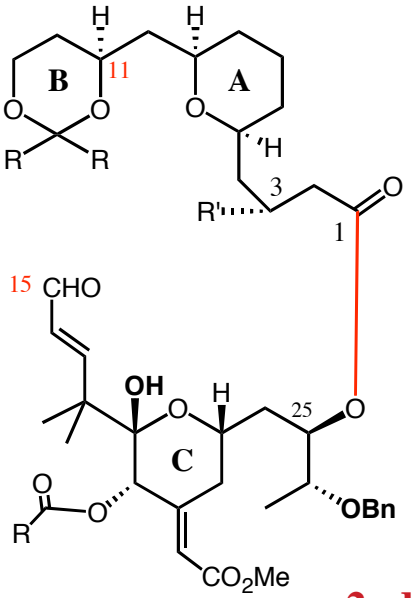


SPACER DOMAIN



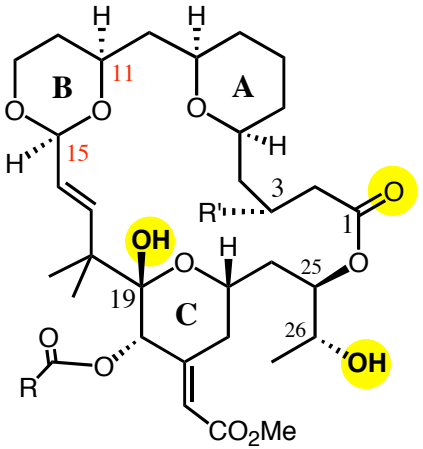
2,4,6-$Cl_3ArCOCl$,
Et_3N, rt, DMAP

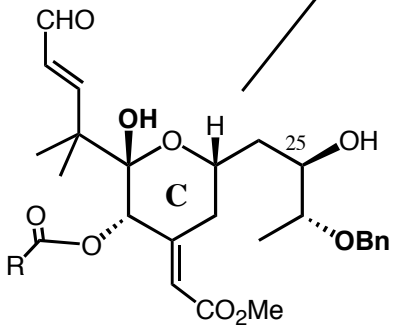
81%



1.Amberlyst resin
2. cat. $Pd(OH)_2/C$,
H_2

88%



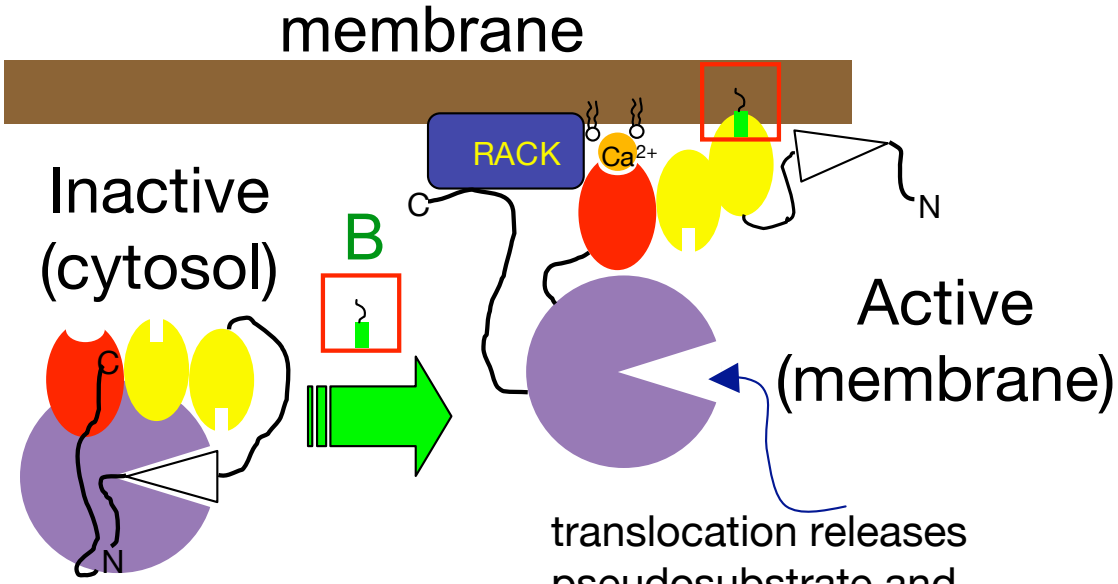


RECOGNITION DOMAIN

Scale up in progress
2nd gen. Synthesis J. Am. Chem. Soc. 2002
BRYOLOG ~ 25 STEPS
(BRYOSTATIN > 70 STEPS)

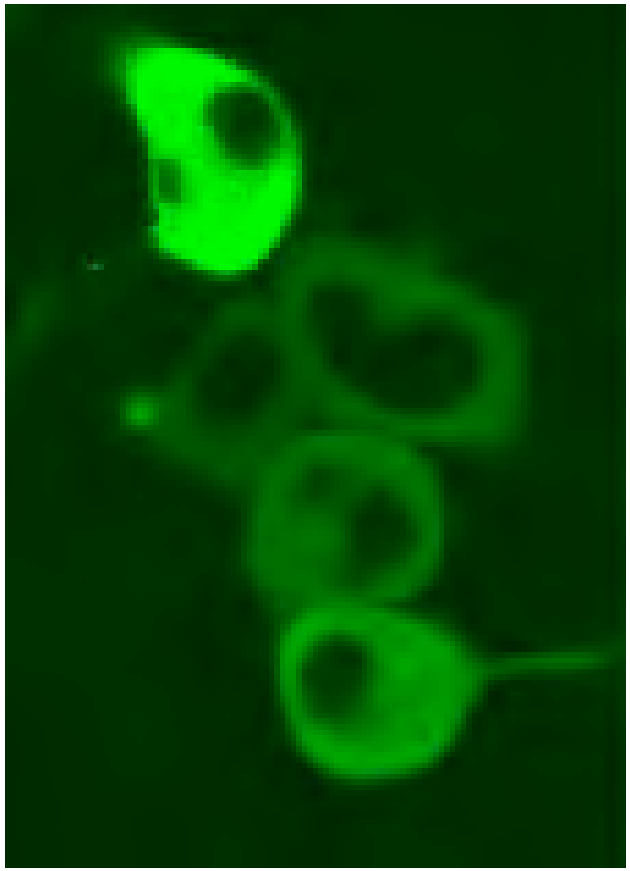
Wender, Baryza, Bennett, Bi, Brenner, Clarke, **Horan**, Kan, Lacote, Lippa, Nell, Turner, *J. Am. Chem. Soc.*; **2002**, *124*, 13648.
Wender, De Brabander, Harran, Jimenez, Koehler, Lippa, Park, Shiozaki, *J. Am. Chem. Soc.*, **1998**, 4534.
Wender, De Brabander, Harran, Jimenez, Koehler, Lippa, Park, Siedenbiedel, Pettit, *Proc. Natl. Acad. Sci. USA* , **1998**, 6624.
Wender, Hinkle, Koehler, Lippa, *Medicinal Research Reviews*, **1999**, 388.

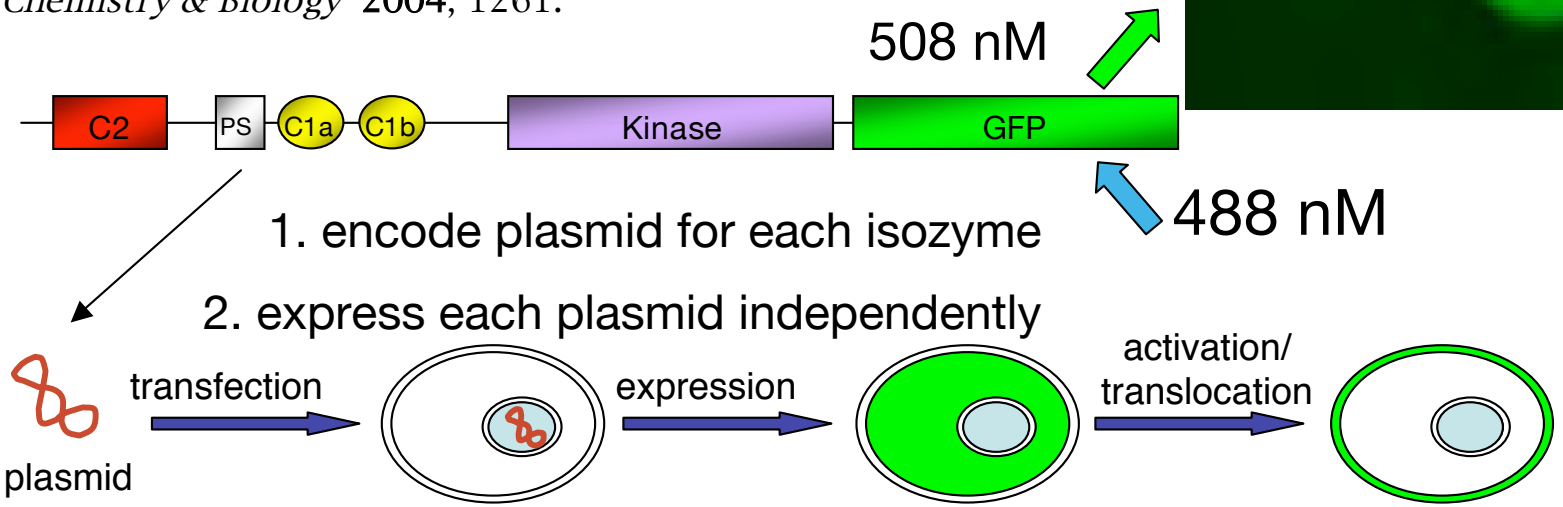
REAL TIME EVALUATION OF PKC TRANSLOCATION



Newton, Chem. Rev. 2001

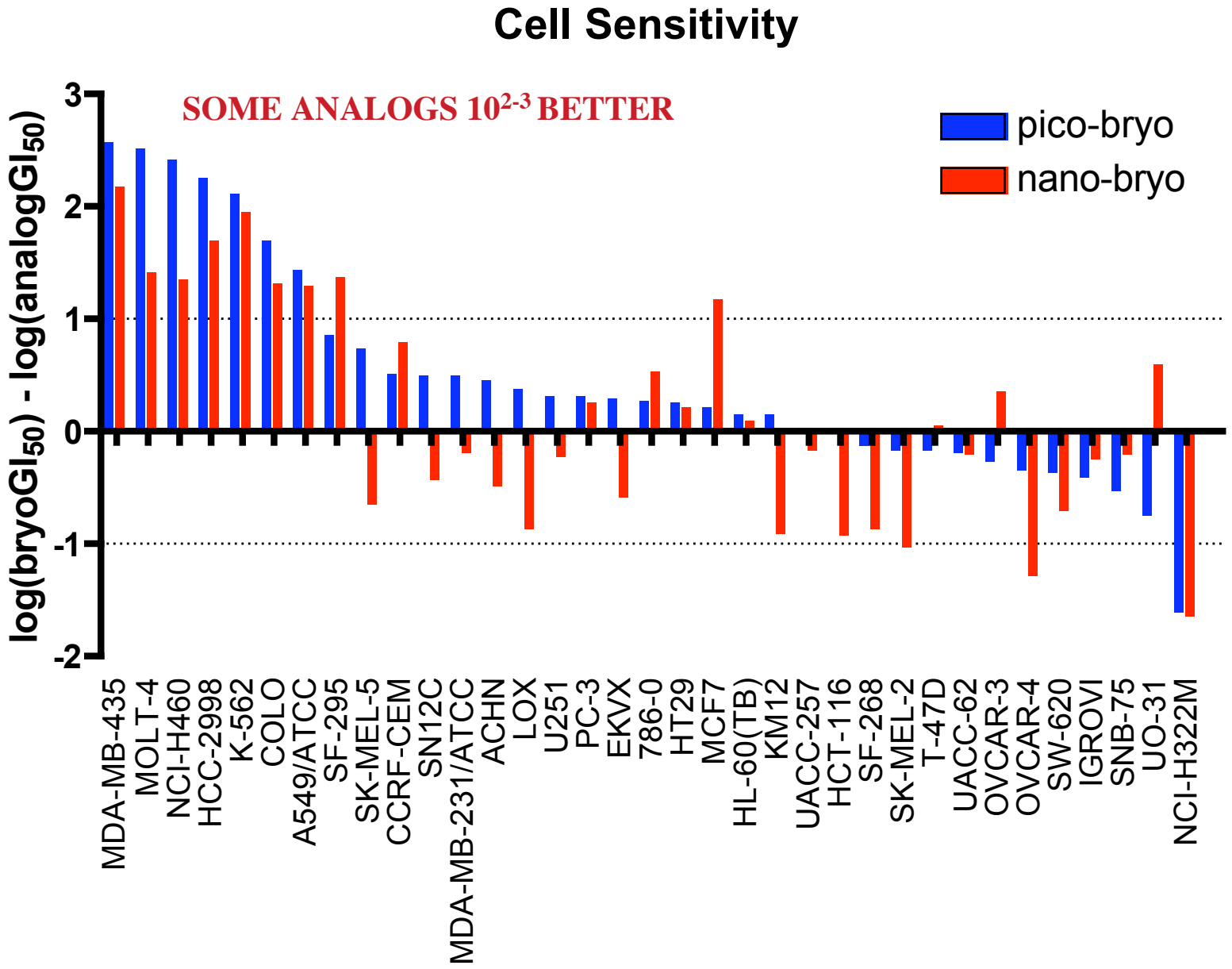
J. Baryza, S. Brenner, M. Craske, T. Meyer, P.Wender
Chemistry & Biology **2004**, 1261.





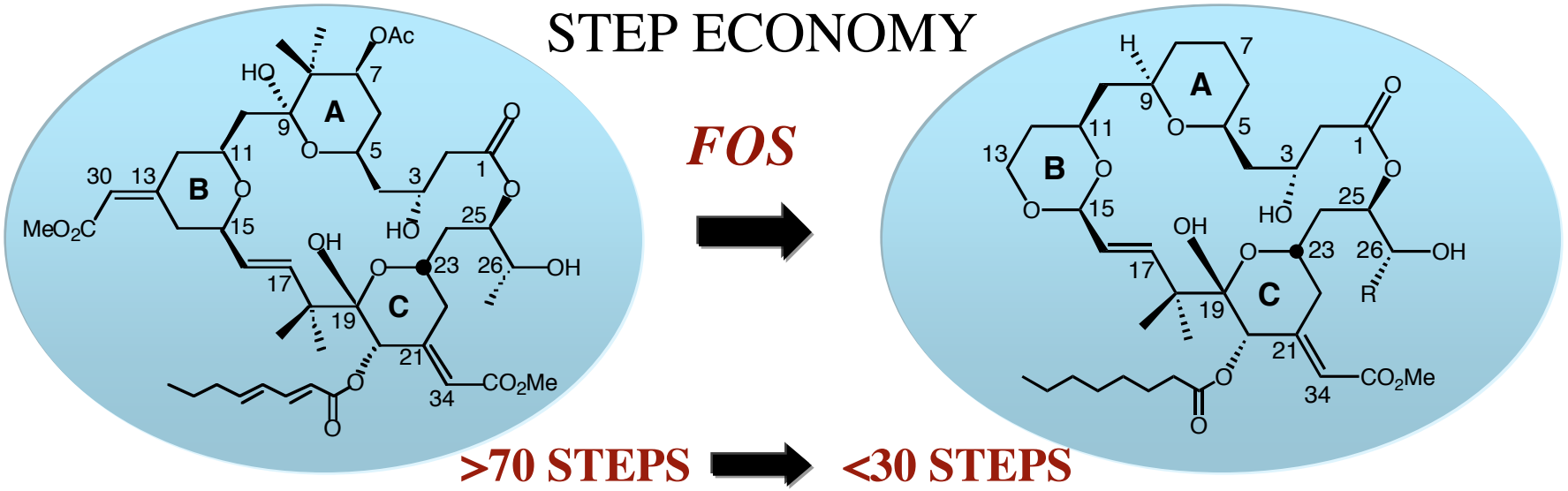
GROWTH INHIBITION IN HUMAN CANCER CELL LINES

Stanford / National Cancer Institute USA (Ven Narayanan)



FUNCTION ORIENTED SYNTHESIS: BETTER, AVAILABLE LEADS

STEP ECONOMY



>70 STEPS ➡ **<30 STEPS**

Wender, P.A.; Baryza, J.L.; Brenner, S.E.; Clarke, M.O.; Craske, M.L.; Horan, J.C.; Meyer, T. " FOS" *Current Drug Discovery Technologies*, **2004**, *1*, 1-11. *Chemistry & Biology* **2004**, 1261.

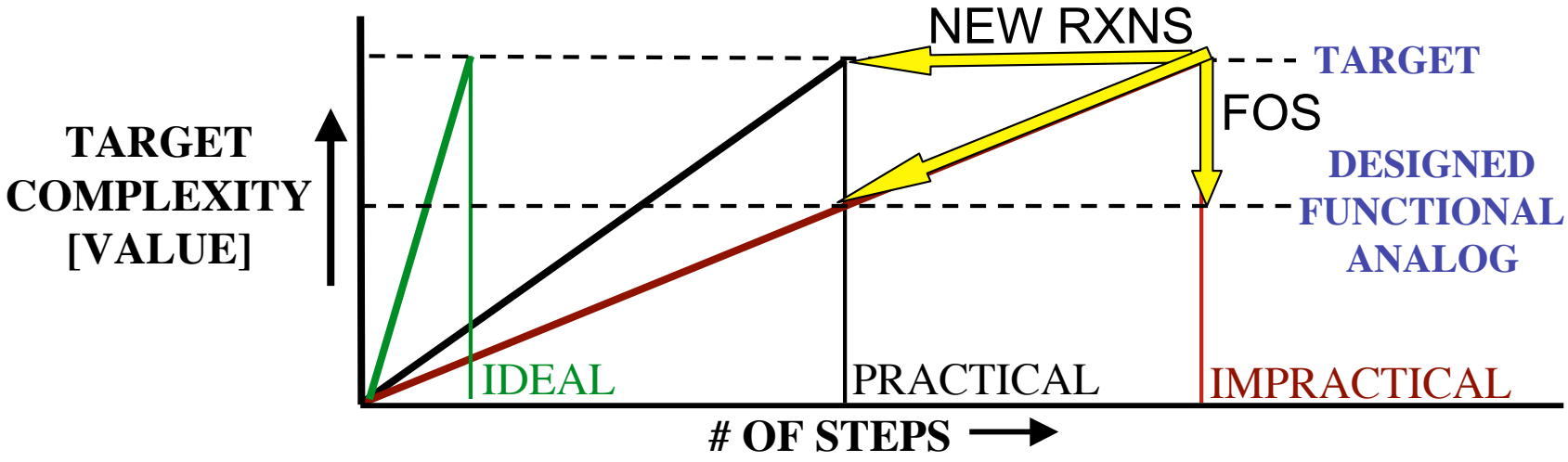
- **BRYOLOG AND BRYOSTATIN HAVE SIMILAR VIRTUAL STRUCTURES, SOLUTION STRUCTURES, PKC AFFINITIES**
- **BRYOLOGS ARE GENERALLY MORE POTENT (10-100 FOLD) THAN BRYOSTATIN IN HUMAN CANCER CELL GROWTH INHIBITION**
- **BRYOLOGS ARE COMPARABLE OR BETTER THAN BRYOSTATIN IN ANIMAL ASSAYS**
- **PICOLOG SYNTHESIS < 30 STEPS, ~ $3K/gm (BRYO $2.3M/ gm); NOW IN SCALE UP**

***J. Am. Chem. Soc.* 2002,** 13648

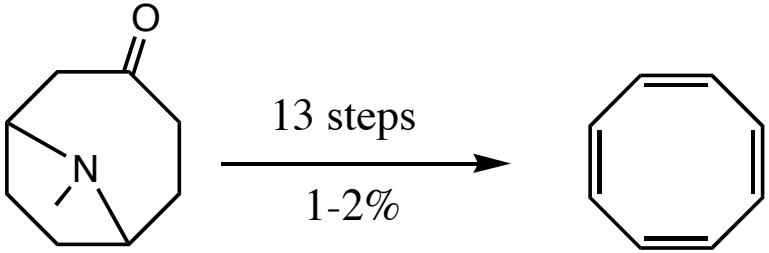
- **PRE-CLINICAL DEVELOPMENT CANDIDATE**

STEP ECONOMY AND FUNCTION ORIENTED SYNTHESIS:

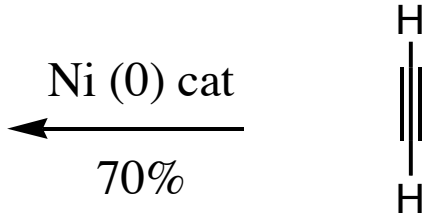
Wender, Brabander, Harran, Jimenez, Koehler, Lippa, Park, Siedenbiedel, Pettit *Proc. Natl. Acad. Sci. USA* **1998**, 6624; Wender, P.A.; Baryza, J.L.; Brenner, S.E.; Clarke, M.O.; Craske, M.L.; Horan, J.C.; Meyer, T. " **Function Oriented Synthesis"** *Current Drug Discovery Technologies*, **2004**, *1*, 1-11



Willstätter & Waser 1911

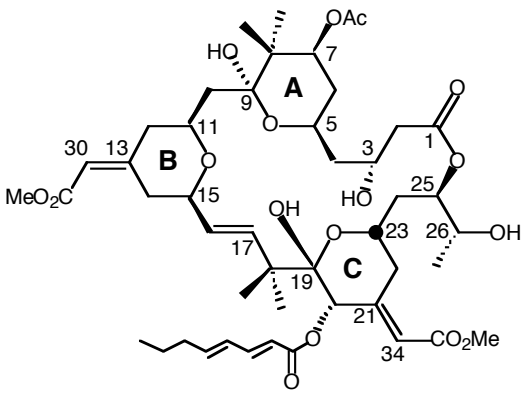


Reppe & Toepel 1940



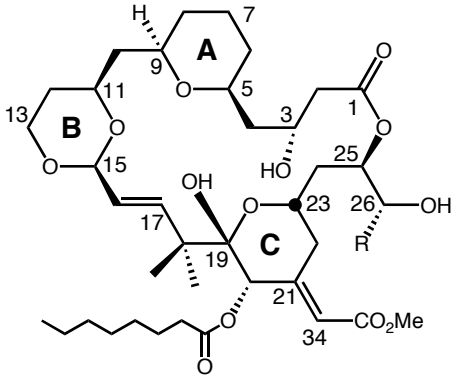
NOW…COMBINE NEW REACTIONS AND FOS…
INVENT NEW FUNCTIONAL TARGETS WITH NEW RXNS

PHARMACOPHORE TARGETING WITH NEW REACTIONS



>70 steps

FOS



<25 steps

FOS

NEW RXNS

NEXT LEVEL?

SIMPLER FASTER

•STEP ECONOMY TO KNOWN SCAFFOLDS
•STEP ECONOMY TO NEW SCAFFOLDS

DESIGN
HIGH THROUGHPUT IN SILICO

The virtual medicinal chemist

INPUT

FUNCTION
H-T SCREENS

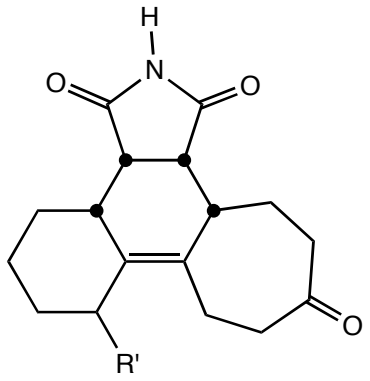
OUTPUT

SELECTIVE INHIBITORS AS MEDICINAL LEADS

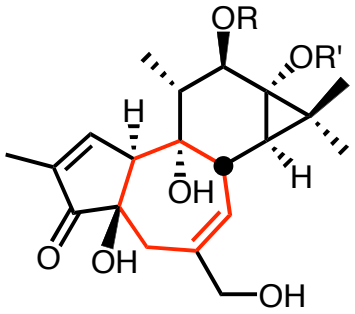
Real time cell & animal assays

SYNTHESIS
COMBI CHEM

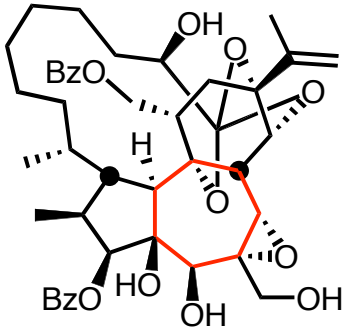
New reactions novel structures



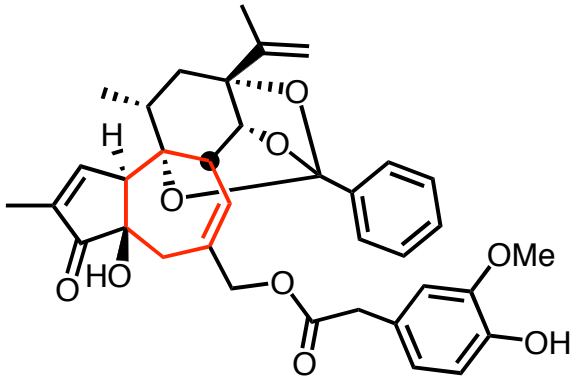
DESIGNING NEW REACTIONS FOR UNMET NEEDS



TUMOR PROMOTER
NANOMOLAR ACTIVITY

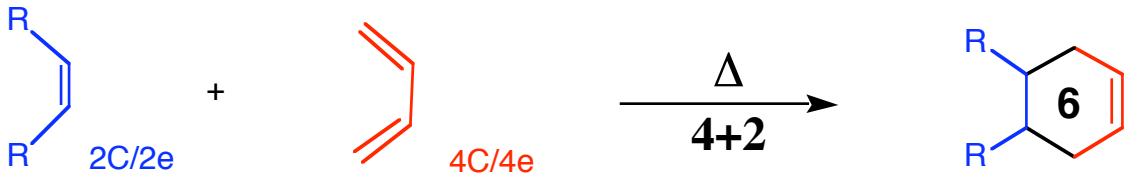


CANCER CHEMOTHERAPEUTIC LEAD
PICOMOLAR ACTIVITY



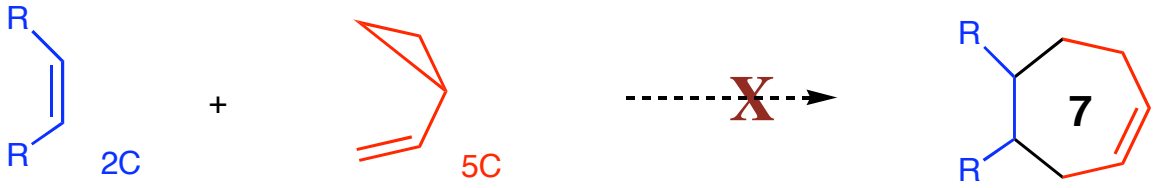
NEUROPATHIC PAIN
FEMTOMOLAR ACTIVITY

THE DIELS-ALDER CYCLOADDITION: A POWERFUL PROCESS FOR 6-MEMBERED RINGS



DESIGNING NEW REACTIONS: A HOMOLOG OF A [4+2] TO 6 IS A [5+2] TO 7

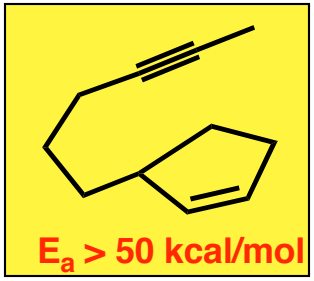
Sarel, Breuer *J. Am. Chem. Soc.* **1959**, 6522: Thermal reaction; VCP to CP 51.7kcal/M; Herges in "Chemical Structures" Springer-Verlag, 1988: "vinylcyclopropanes do not react even with the strongest dienophiles..."; *Chem. Ber.* **1986**, 829



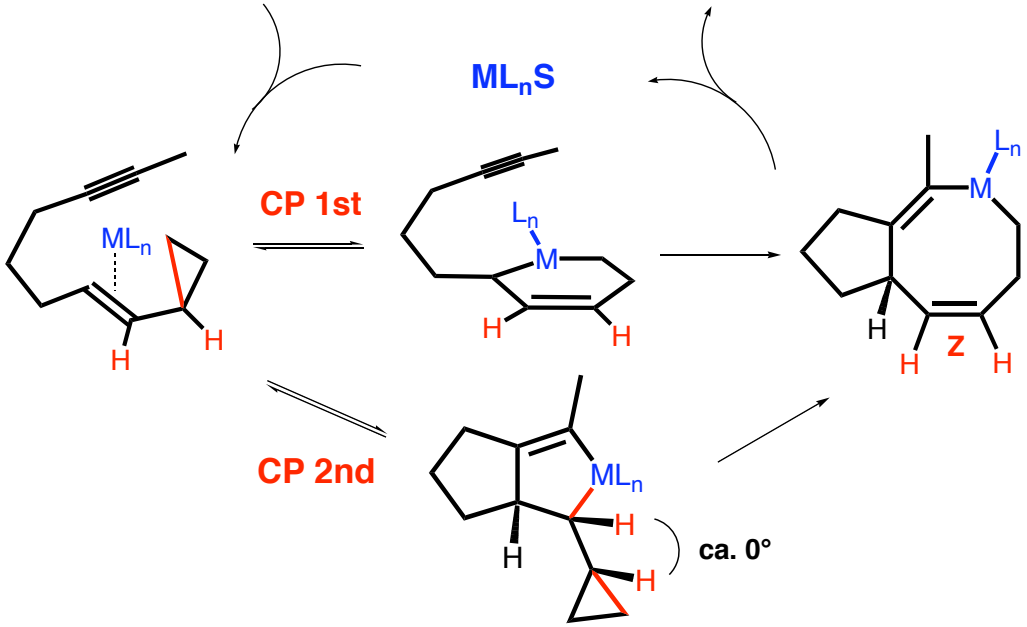
DESIGNING NEW REACTIONS: THE [5+2] CYCLOADDITION

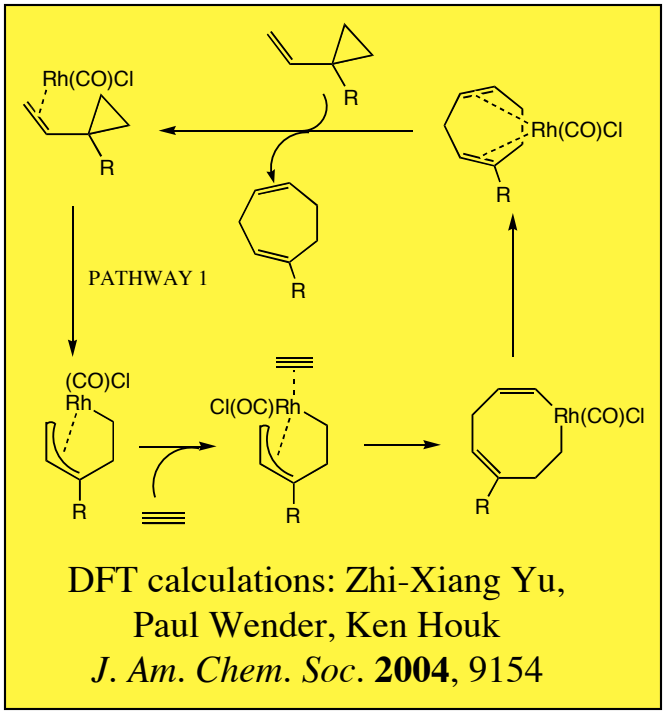
Wender, Takahashi, Witulski *J. Am. Chem. Soc.* **1995**, 4720; *J. Am. Chem. Soc.* **1998**, 1940

* **THERMAL REACTION DOES NOT WORK**



* **THEREFORE, SELECT SUITABLE METAL TO MEDIATE π-SYSTEM *ACTIVATION***
(MANY METALS REACT WITH CPs and / or VCPs; must suppress 2+2+2, VCP to CP)

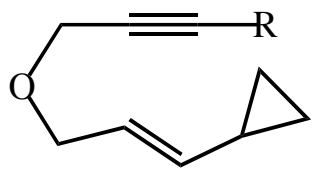




DFT calculations: Zhi-Xiang Yu,
Paul Wender, Ken Houk
J. Am. Chem. Soc. **2004**, 9154

A NEW REACTION: TRANSITION METAL CATALYZED [5+2] CYCLOADDITIONS

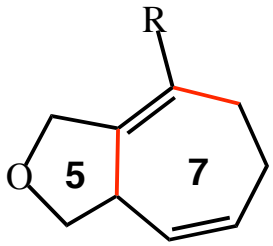
* **ALKYNES** (Wender, Takahashi, Witulski *J. Am. Chem. Soc.* **1995**, 4720; *J. Am. Chem. Soc*, **1998**, 10976)



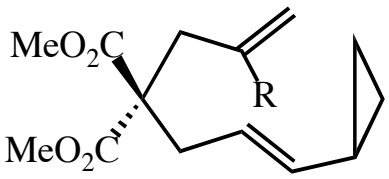
1-10 mol % $Rh(PPh_3)_3Cl$
1-10 mol % AgOTf

R= H, Me, CO_2Me, TMS, Ph

80-95 %



* **ALKENES** (*J. Am. Chem. Soc*. **2001**, *123*, 179; *J. Am. Chem. Soc*. **1998**, 1940; *Tetrahedron* **1998**, 7203)

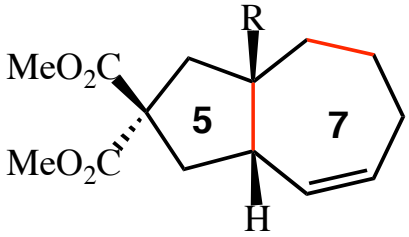


0.1 mol % $RhCl(PPh_3)_3$
0.1 mol% AgOTf

1.0M, PhMe, 110°C, 17h

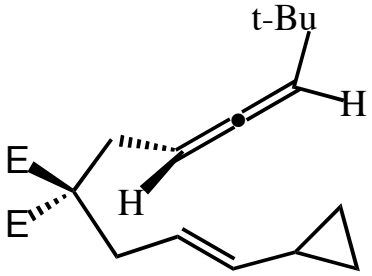
R= H, Me

86-91%, only *cis*



(exo selective)

* **ALLENES** (Wender; Glorius; Husfeld; Langkopf; Love *J. Am. Chem. Soc*., **1999**, 5348; *Organic Lett.* **2000**, 2323)



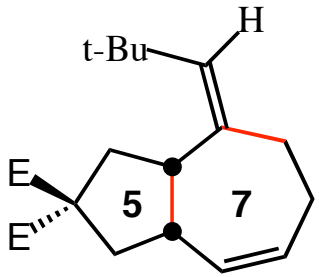
91% ee

1 mol % CAT

$PhCH_3$, 100 °C

3 h

96%, only *cis*



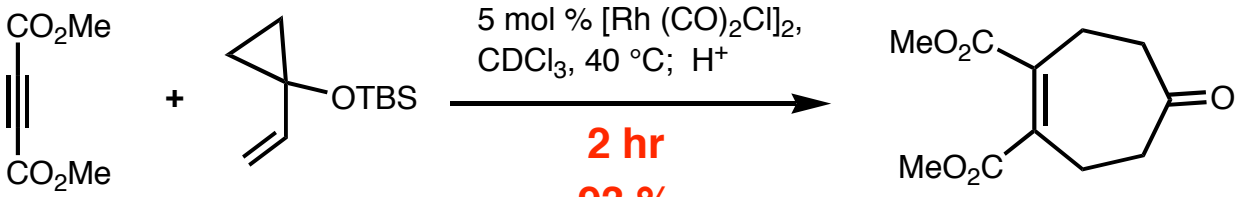
92% ee

INTERMOLECULAR TRANSITION METAL CATALYZED [5+2] CYCLOADDITIONS

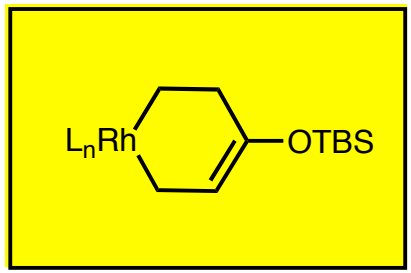
Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc*, **1998**, 10976.

IT IS REMARKABLY GENERAL (1-3hr @ 25-40°C for most alkynes)

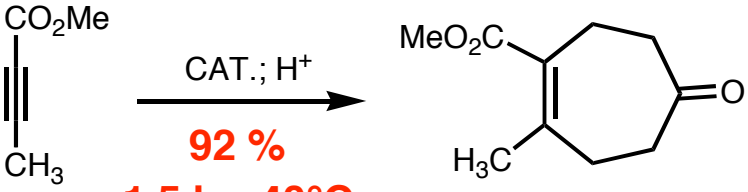
ONE MOLE SCALE



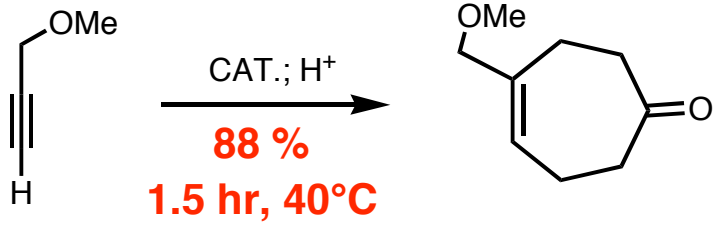
POSSIBLE RESTING STATE OF CATALYST



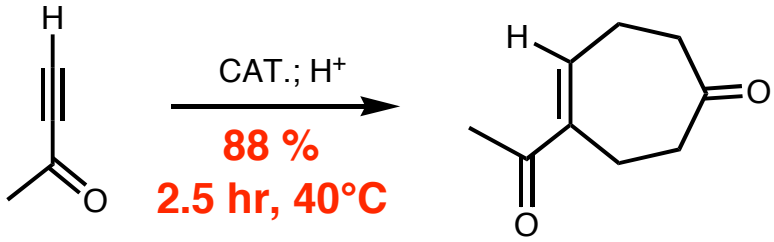
ALKYNYL ESTERS



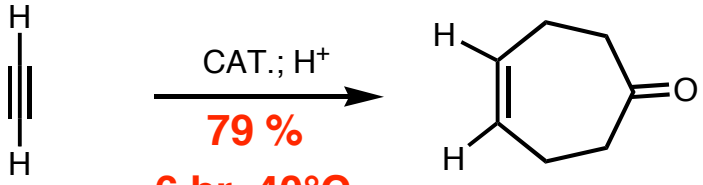
INTERNAL AND TERMINAL ALKYNES



ALKYNYL KETONES

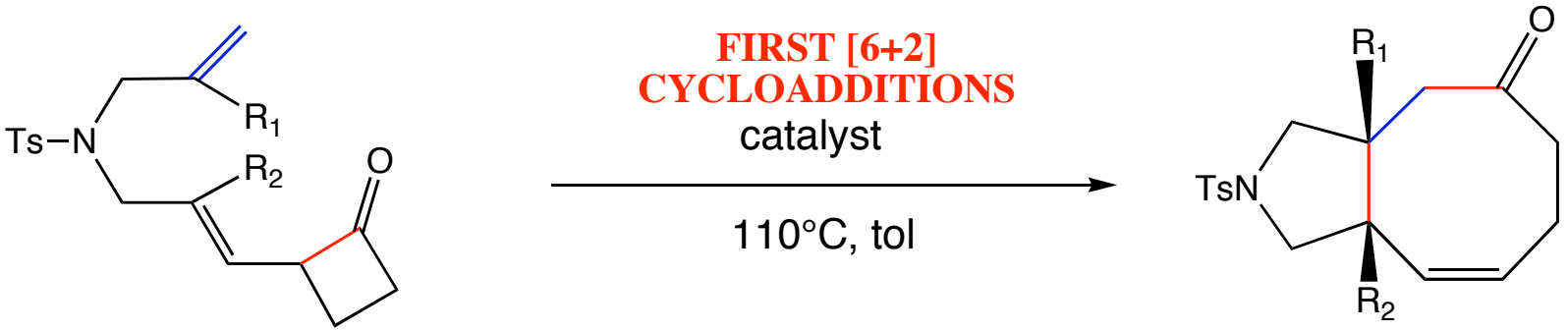


EVEN ACETYLENE



CC ACTIVATION: FROM VCPs to VCBs & A NEW REACTION

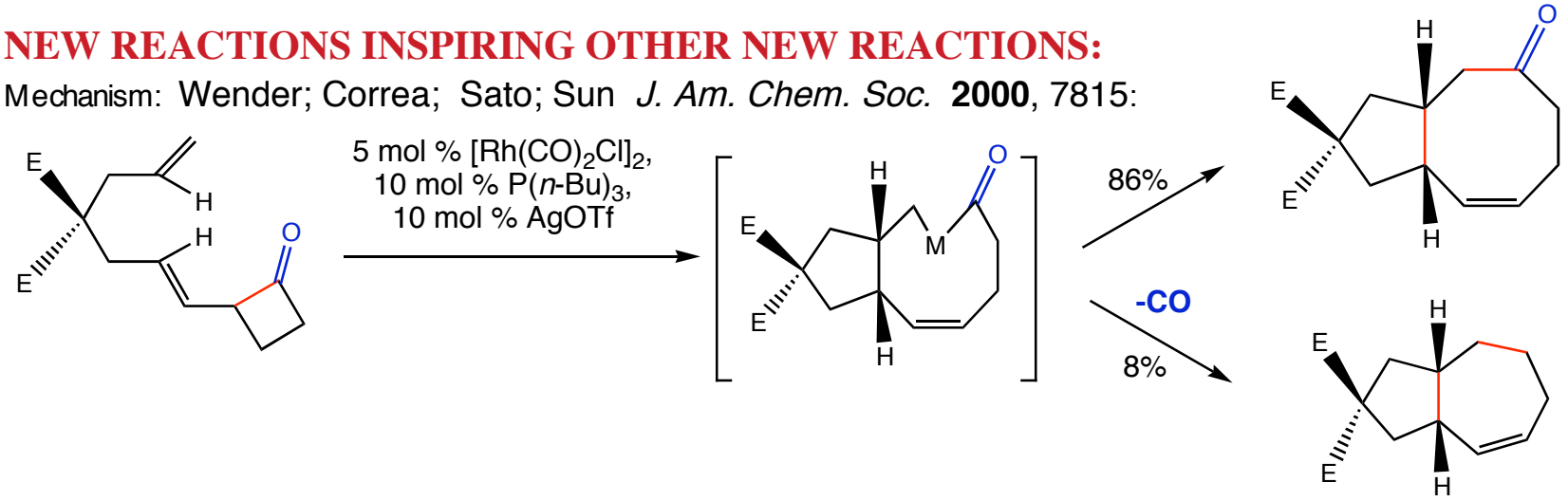
Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815.



R_1=R_2=H	**95%**	A, 3h	10 mol % $RhCl(PPh_3)_3$, 10 mol % AgOTf
R_1=H, R_2=Me	**78%**	B, 20h	10 mol % $RhCl(CO)(PPh_3)_2$, 10 mol % AgOTf

NEW REACTIONS INSPIRING OTHER NEW REACTIONS:

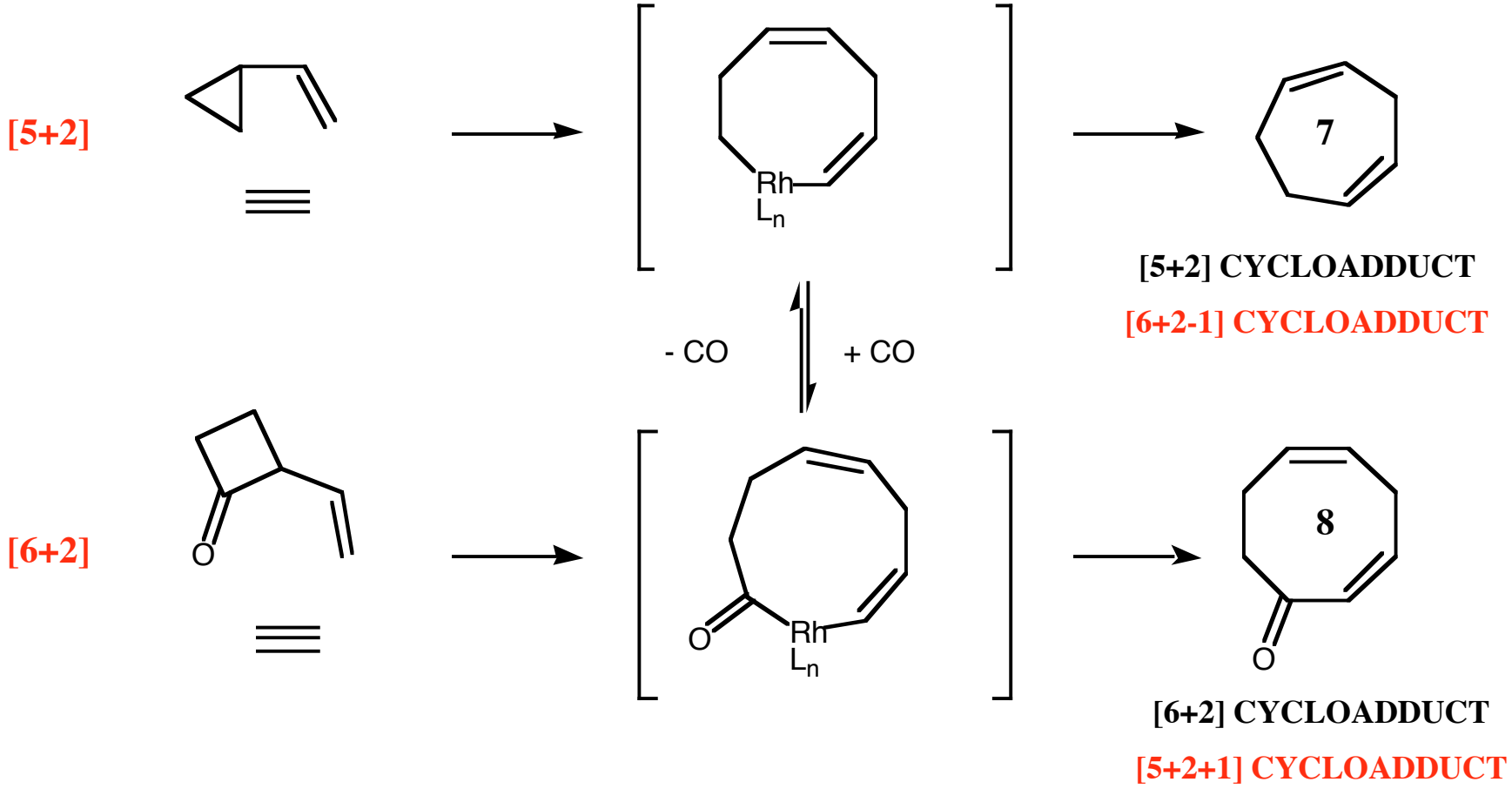
Mechanism: Wender; Correa; Sato; Sun *J. Am. Chem. Soc.* **2000**, 7815:



A NEW THREE COMPONENT CYCLOADDITION: TRANSITION METAL CATALYZED [5+2+1] CYCLOADDITIONS

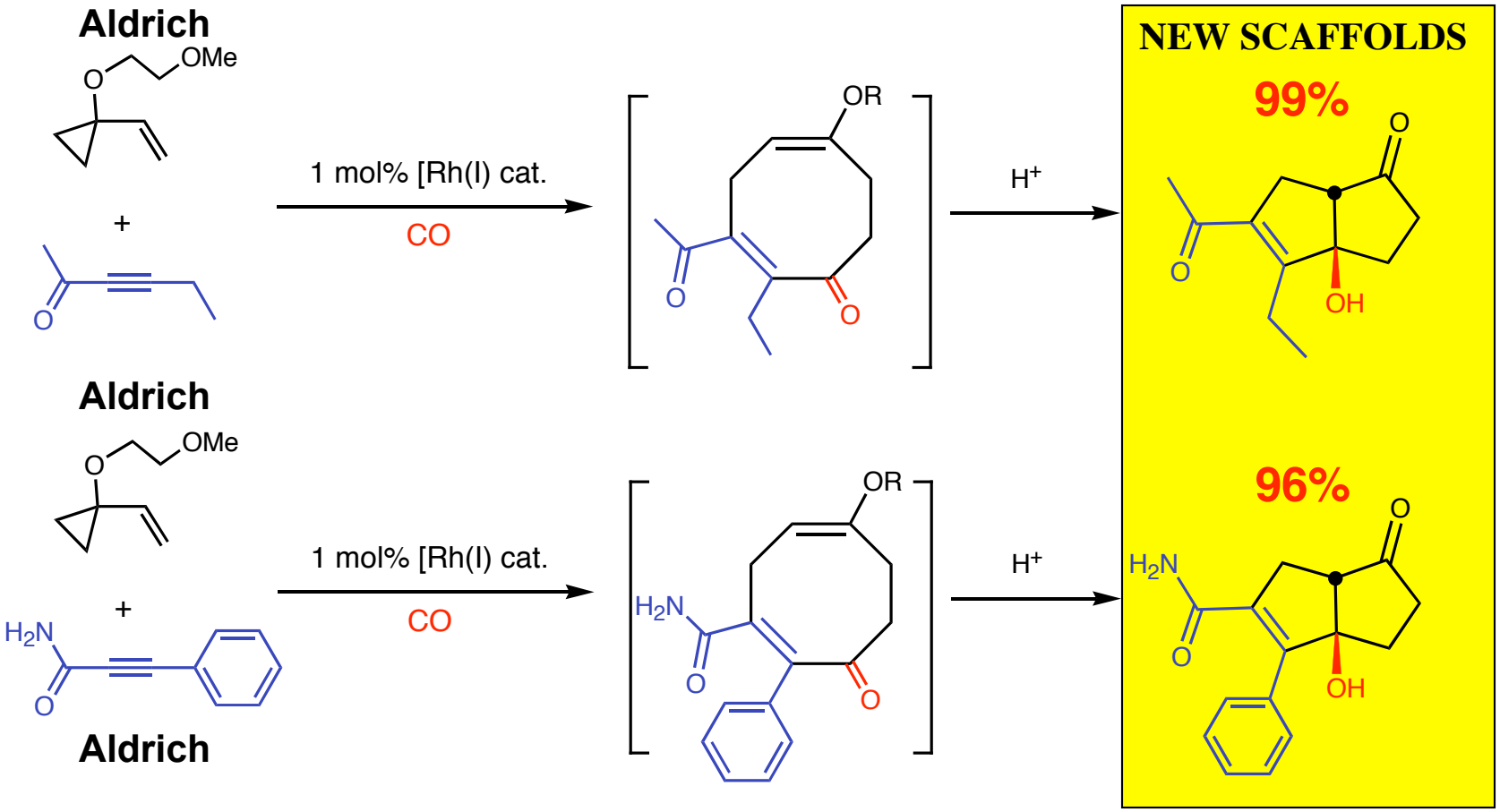
THUS FAR, [4+4], [4+2], [5+2], AND [6+2] CYCLOADDITIONS, OVERALL [M+N] CYCLOADDITIONS. COULD A 3rd COMPONENT OF 1, 2, etc ATOMS BE ADDED TO ACHIEVE [M+N+O] CYCLOADDITIONS?

NEW REACTIONS BEGET OTHER NEW REACTIONS



A NEW, THREE COMPONENT CYCLOADDITION: TRANSITION METAL CATALYZED [5+2+1] CYCLOADDITIONS

INTRAMOLECULAR [5+2] CYCLOADDITIONS: Wender, Takahashi, Witulski, *J. Am. Chem. Soc.* **1995** *117*, 4720.
INTERMOLECULAR [5+2] CYCLOADDITIONS: Wender, Rieck, Fuji, *J. Am. Chem. Soc*, **1998**, *120*, 10976.
[6+2] CYCLOADDITIONS: Wender, Correa, Sato, Sun, *J. Am. Chem. Soc.* **2000**, *122*, 7815.
[5+2+1] CYCLOADDITIONS: Wender, Gamber, Zhang, Hubbard, *J. Am. Chem. Soc.* **2002**, 2876.



1-5 mol% $[Rh(CO)_2Cl]_2$, dioxane, 60°C, 1-2 atm CO, conc. up to 0.5M;
Works with esters, amides, aldehydes, ketones; yields good to excellent; high regioselectivity

NEW REACTIONS, THE IDEAL SYNTHESIS, STEP ECONOMY, PHARMACOPHORE TARGETING

Representative New TM Catalyzed Reactions…New Strategies…New Structures…

Intramolecular [4+4] cycloaddition of bis dienes (1986)

Intramolecular [4+2] cycloaddition of diene-y[illegible]s (1989)

Intramolecular [4+2] cycloaddition of diene-alle[illegible] (1995)

Intramolecular [5+2] cycloaddition of VCPs & pi-s[illegible] (19[illegible]

Intermolecular [5+2] cycloaddition of VCPs & alkyn[illegible]

Intermolecular [6+2] cycloaddition of VCBs & [illegible]

Intra/intermolecular [5+2]/[4+2] cycloaddition[illegible]

Hetero [5+2] cycloaddition of cyclopropyl imines

Intermolecular [5+2+1] cycloaddition of VCPs, alky[illegible]

Intramolecular [2+2+1] cycloaddition of alkynes[illegible]

Intramolecular [4+2+1] cycloaddition of die[illegible]s, alkynes

Intramolecular [2+2+1] cycloaddition of alkenes, dienes[illegible])

Intermolecular [2+2+1] cycloaddition of alkenes, diene[illegible]CO ([illegible]4)

Intermolecular [5+1+2+1] cycloaddition of VCPs, alkynes, 2 C[illegible] (2005)

Carbonylative ring expansion [4+2+1]/[6+1] of allenylcyclobu[illegible]es (2006)

The allenyl Pauson-Khand [2+2+1] cycloaddition of bis-alkene[illegible], CO (2006)

Intramolecular [4+2+2] cycloadditions of dienes, alkenes, alkynes (2006)

Intermolecular [4+2+2] cycloadditions of dienes, alkenes, alkynes (2006)

Intermolecular [3+2] cycloadditions (unpub)

Can we exploit these new reactions to rapidly assemble new or novel FUNCTIONAL molecules

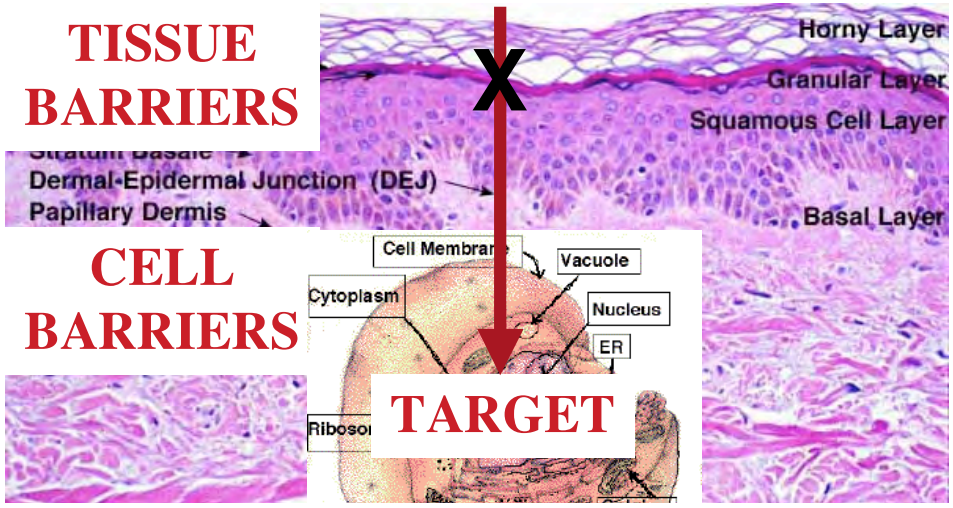
GRAND CHALLENGES: THE BARRIER PROBLEM

- Genomics (blueprint)
- Proteomics (targets)
- Systems Biology (pathways)
- Chemogenomics (ligands)

A CHALLENGE AHEAD…

THERAPY DEPENDS ON BREACHING BARRIERS…

DRUG / PROBE TRANSPORTER



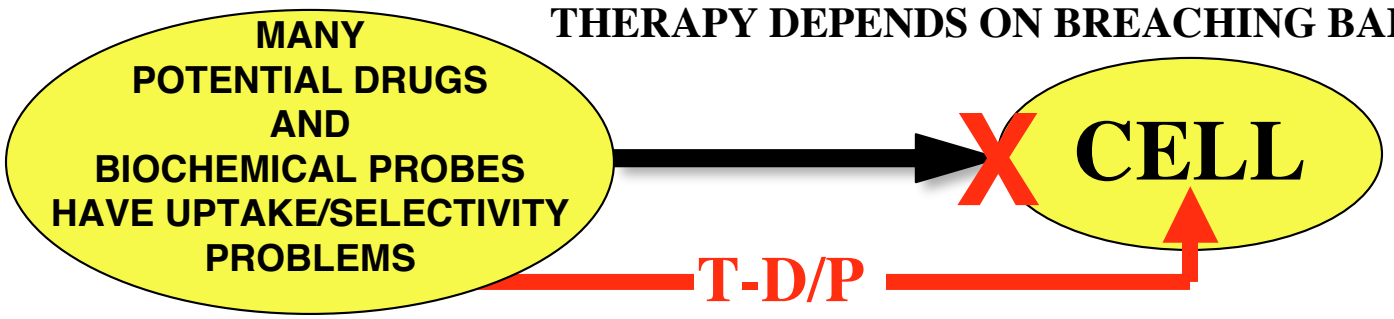
"The bilayer provides the basic structure of the membrane and serves as a relatively impermeable barrier to the flow of water soluble molecules" …most standard textbooks

Varmus, Klausner, et al. "Grand Challenges in Global Health" *Science*, **2003**, 398-399.

Jain, R.K. "The Next Frontier of Molecular Medicine: Delivery of Therapeutics" *Nature Med.* **1998**,

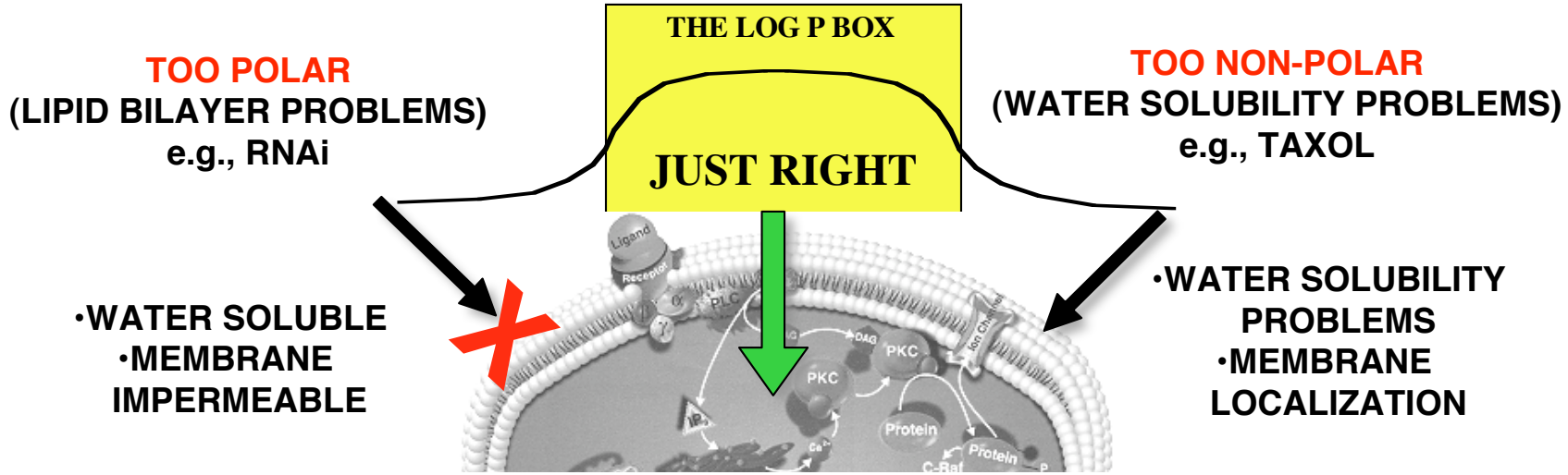
BREACHING BIOLOGICAL BARRIERS

Wender, P.; Mitchell, D.; Pattabiraman, K.; Pelkey, E.; Steinman, L.; Rothbard, J. *Proc. Natl. Acad. Sci. USA*, **2000**, 13003
Rothbard, Garlington, Lin, Kirschberg, Kreider, McGrane, Wender, Khavari, *Nature Medicine* **2000**, 1253



THE PROBLEM: MOST DRUGS MUST BE BOTH WATER & LIPID SOLUBLE FOR PASSIVE DIFFUSION INTO TISSUES AND CELLS

THINKING OUT OF THE log P BOX AND PHYSICAL PROPERTY HOMOGENEITY



BARRIER PROBLEMS ARE A MAJOR CAUSE OF HIT-TO-LAUNCH ATTRITION
A POTENTIAL FIX: MOLECULAR TRANSPORTERS

NATURAL CHEMICAL CODES FOR FACILITATED CELLULAR UPTAKE

* **Evolutionary pressures have produced mechanisms to prevent and promote uptake**

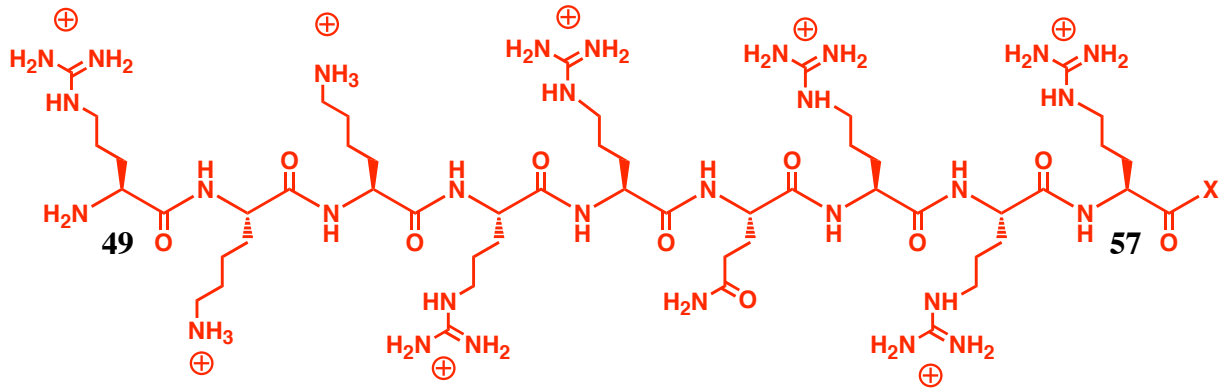
* **HIV tat and Antennapedia are transcription factors that cross biological membranes**

MEPVDPRLEPWKHPGSQPKTACTTCYCKKCCFHCQVCFTTKALGISYG**RKKRRQRRR**PPQGSQ
THQVSLSKQPTSQPRGDPTGPKE*KKKVERETETDPFD

* **HIV tat 49-57 is required for translocation (Frankel, Pabo 1988)**

SIGNIFICANTLY, IT IS CHARGED BUT EXHIBITS FACILITATED UPTAKE

arginine-lysine-lysine-arginine-arginine-glutamine-arginine-arginine-arginine



* **This works for the HIV tat protein, the "gold standard" in research**
  - **it would have limited use in therapy (cost of goods, metabolism, etc) and**
  - **it is not necessarily an optimized system**

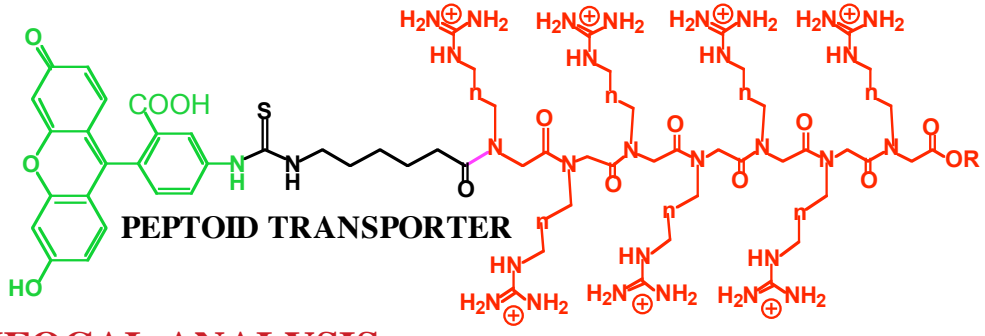
* **Design a *better* transporter; what's required in tat?**

Stanford (Engleman, Fathman, Kiley, Rothbard, Wender) -> CellGate

CHEMICAL CODES FOR CELLULAR UPTAKE

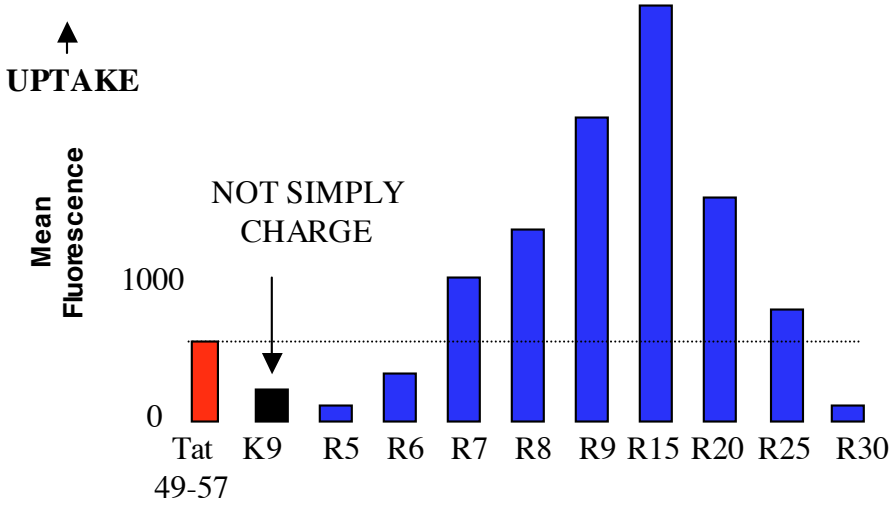
Wender, Mitchell, Pattabiraman, Pelkey, Steinman, Rothbard *Proc. Natl. Acad. Sci. USA* , 2000, *97*, 13003;
Rothbard, Garlington, Lin, Kirschberg, Kreider, McGrane, Wender, Khavari, *Nature Medicine* 2000, *6*, 1253-1257;
Mitchell, Kim, Steinman, Fathman, Rothbard, *J. Pept. Res.* 2000, 56(5), 318-325. ; *J. Med. Chem.* 2002, 3612-3618.
* Wender, Jessop, Pattabiraman, Pelkey, VanDeusen *Organic Letters* 2001, 322

Uptake of Peptide & Peptoid-aca-FITC conjugates into Human Jurkat T Cells

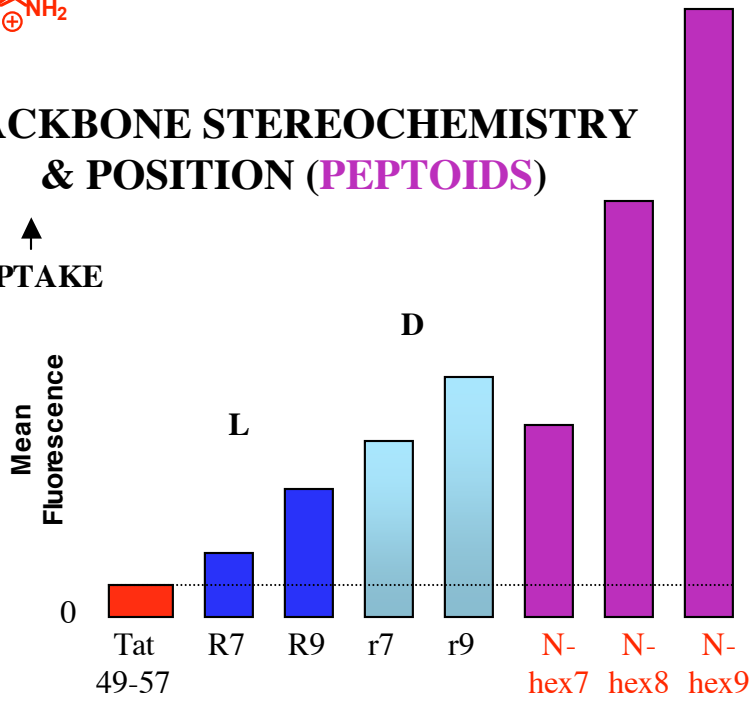


SUPERIOR SYSTEMS AND *COST OF GOODS

CONFOCAL ANALYSIS
HEAD GROUP TYPE & TRANSPORTER LENGTH



BACKBONE STEREOCHEMISTRY & POSITION (PEPTOIDS)



STEP ECONOMY THROUGH SYNTHESIS AND FUNCTION GUIDED DESIGN

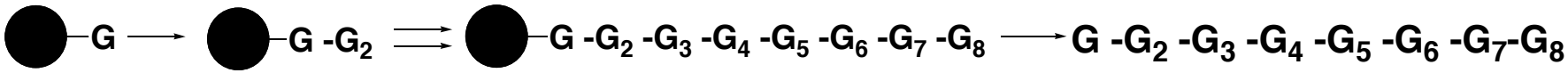
Wender, Jessop, Pattabiraman, Pelkey, VanDeusen *Organic Letters* **2001**, 3229.
Wender, Mitchell, Pattabiraman, PelkeySteinman, Rothbard *Proc. Natl. Acad. Sci. USA* , **2000**, 13003

LINEAR: TARGET OF n UNITS REQUIRES 2n STEPS; THUS EVERY 2 STEPS ADD 1 UNIT

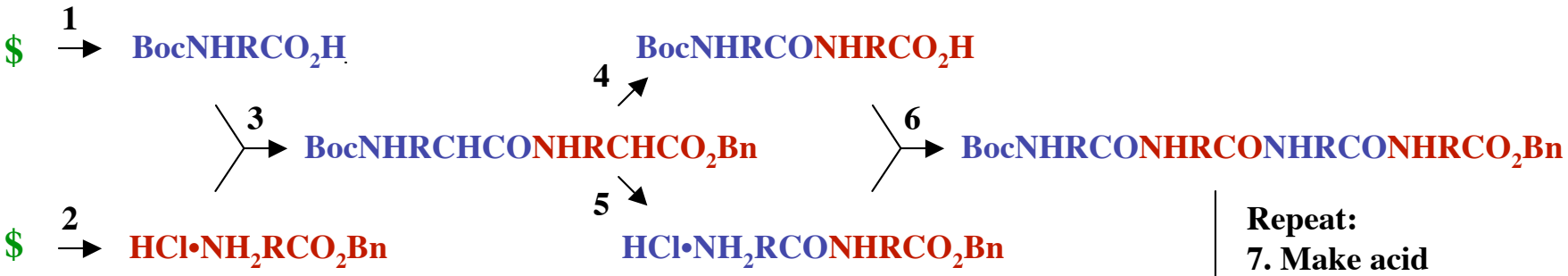
1. Activate
2. Couple

repeat

16 OPERATIONS OVERALL



SEGMENT DOUBLING: A TARGET OF 2^n UNITS REQUIRES 3n STEPS
THUS AN 8-MER (n=3) REQUIRES ONLY 9 STEPS; THUS EVERY 3 STEPS DOUBLE THE SIZE!



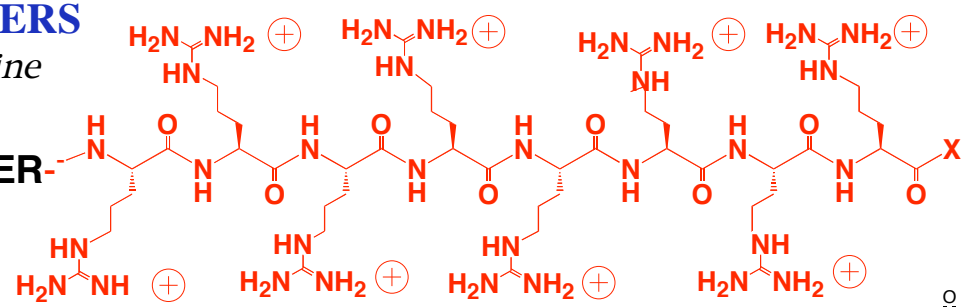
9 OPERATIONS OVERALL
NO RESIN, SOLN. SCALABLE
COST SAVINGS >100FOLD;
GMP SCALED IN US PHARMA

MOLECULAR TRANSPORTERS FOR CELLULAR UPTAKE

OLIGOARGININE TRANSPORTERS

Nature Medicine 2000,1253

DRUG--LINKER-

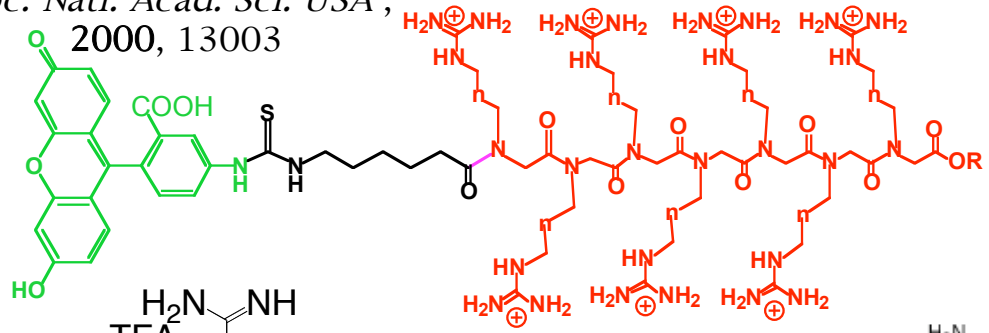


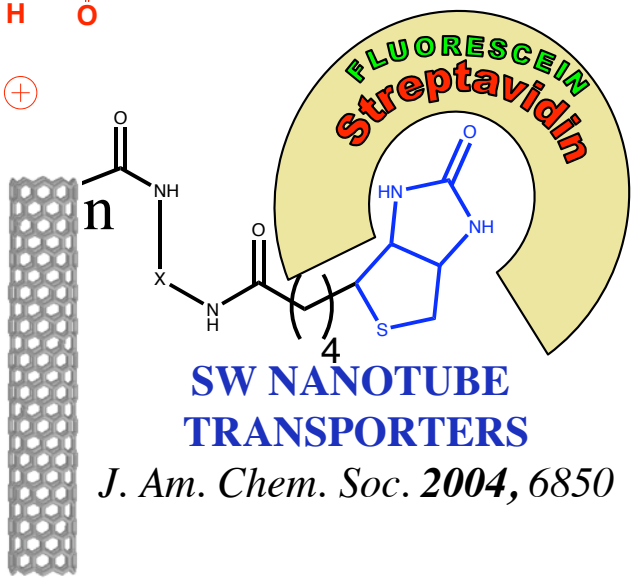
RXRXRXRXRXRXR SPACED ARG-TRANSPORTERS

J. Med. Chem. 2002, 3612

PEPTOID TRANSPORTERS

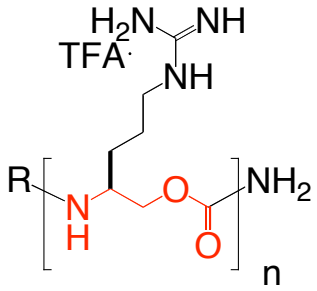
Proc. Natl. Acad. Sci. USA , 2000, 13003





SW NANOTUBE TRANSPORTERS

J. Am. Chem. Soc. ***2004,*** 6850

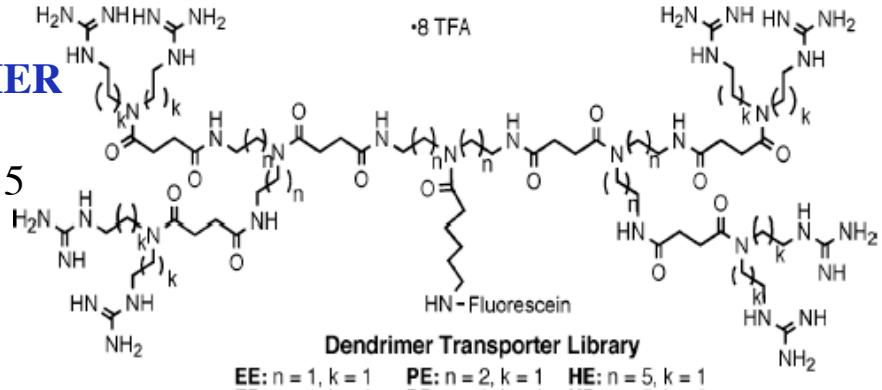


OLIGOCARBAMATE TRANSPORTERS

J. Am. Chem. Soc. ***2002*** 13382

ARBOREAL DENDRIMER TRANSPORTERS

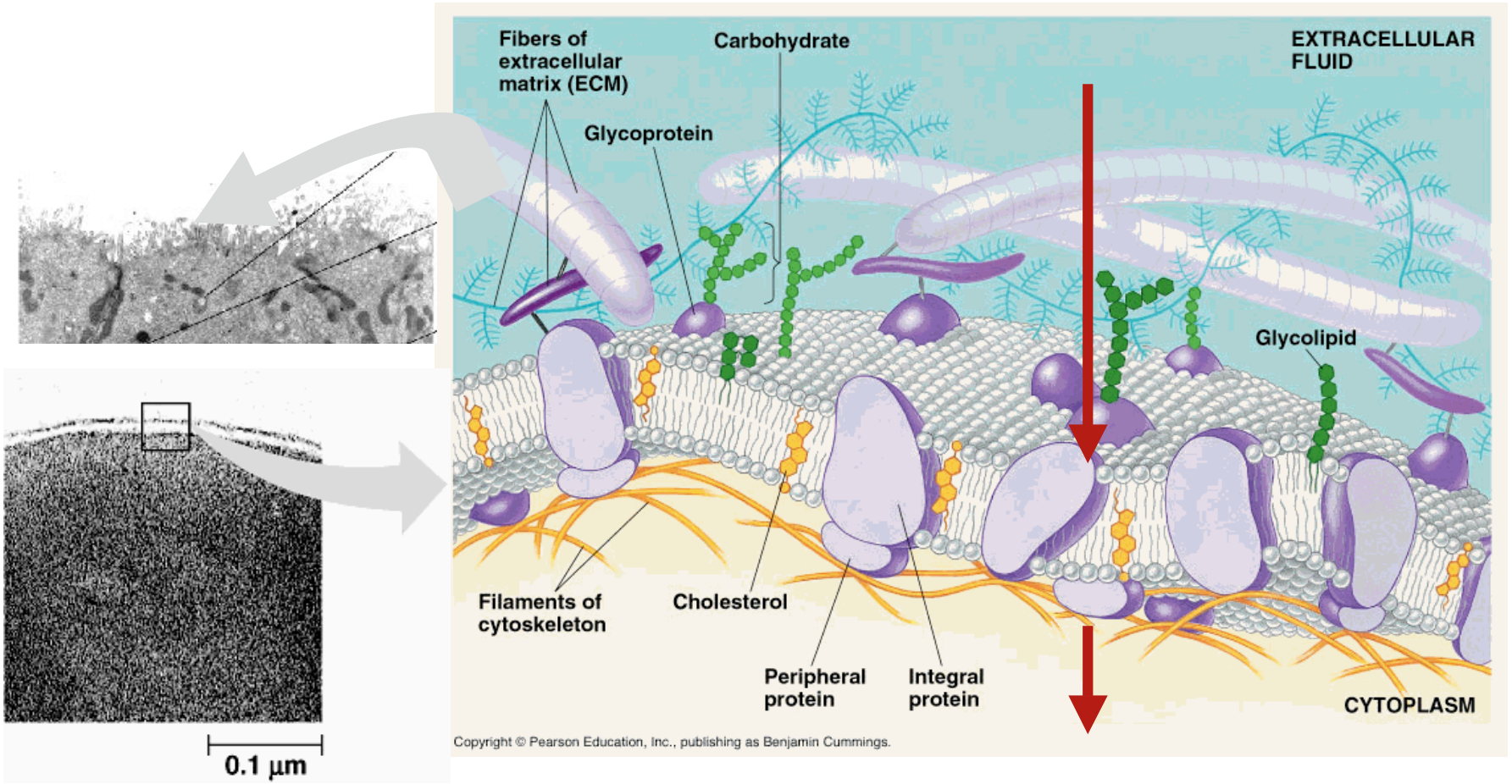
Organic Lett. ***2005***, 4815



AND OTHERS…

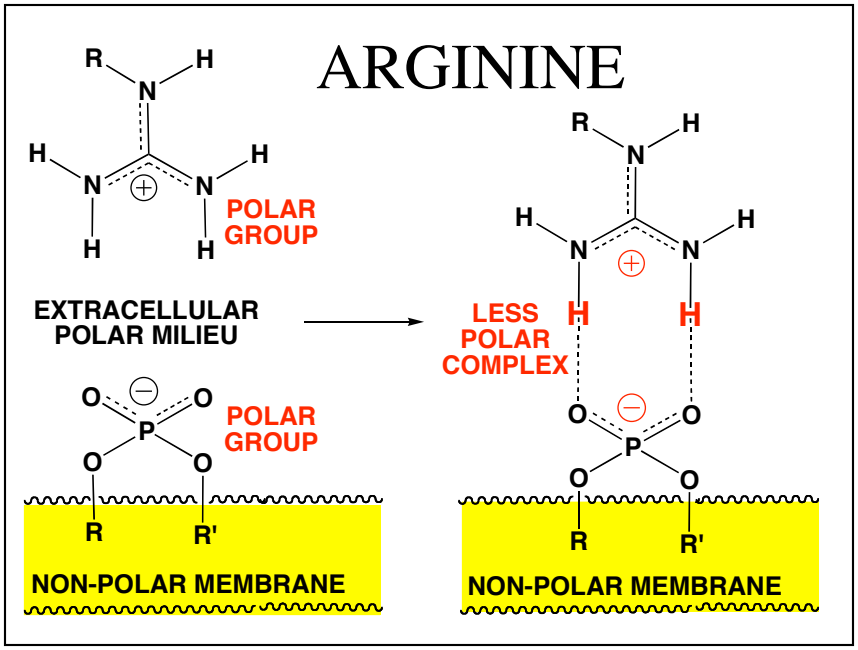
THE MEMBRANE BARRIER

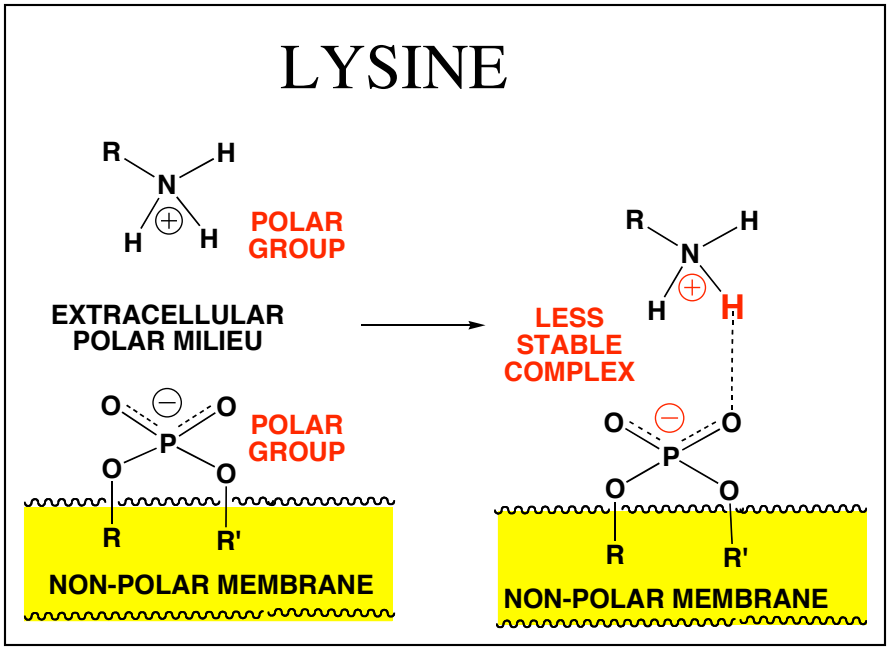
Singer-Nicolson (*Science* **1972**) fluid mosaic model
Vereb, Damjanovich, et al. *(PNAS* **2003***)* Dynamically structured mosaic model



"The bilayer provides the basic structure of the membrane and serves as a relatively impermeable barrier to the flow of water soluble molecules" …
Variations of this statement are found in most standard textbooks

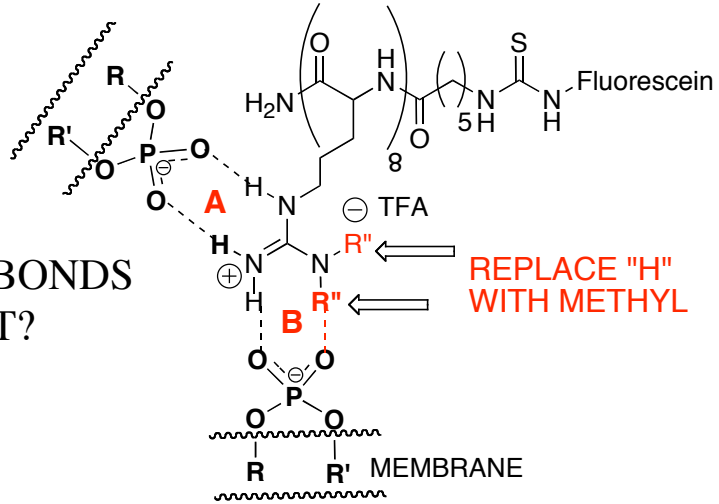
WHY ARGININE AND NOT LYSINE?

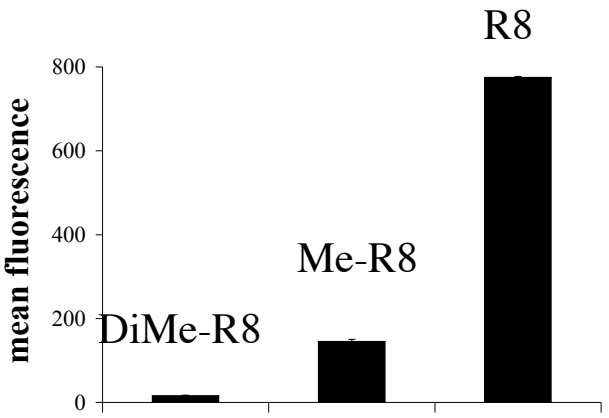




Rothbard, Jessop, Lewis, Murray, Wender *J. Am. Chem. Soc.* **2004**, 9506-9507.

ARE HYDROGEN BONDS THAT IMPORTANT?





TRANSPORTER-PEPTIDE CARGO UPTAKE INTO HEART TISSUE

PRECONDITIONING : BRIEF EPISODES OF ISCHEMIA DECREASE NECROSIS DURING PROLONGED ISCHEMIA
RACK PEPTIDES SIMULATE PRECONDITIONING WHEN INJECTED INTO CELLS BUT CANNOT ENTER BY DIFFUSION

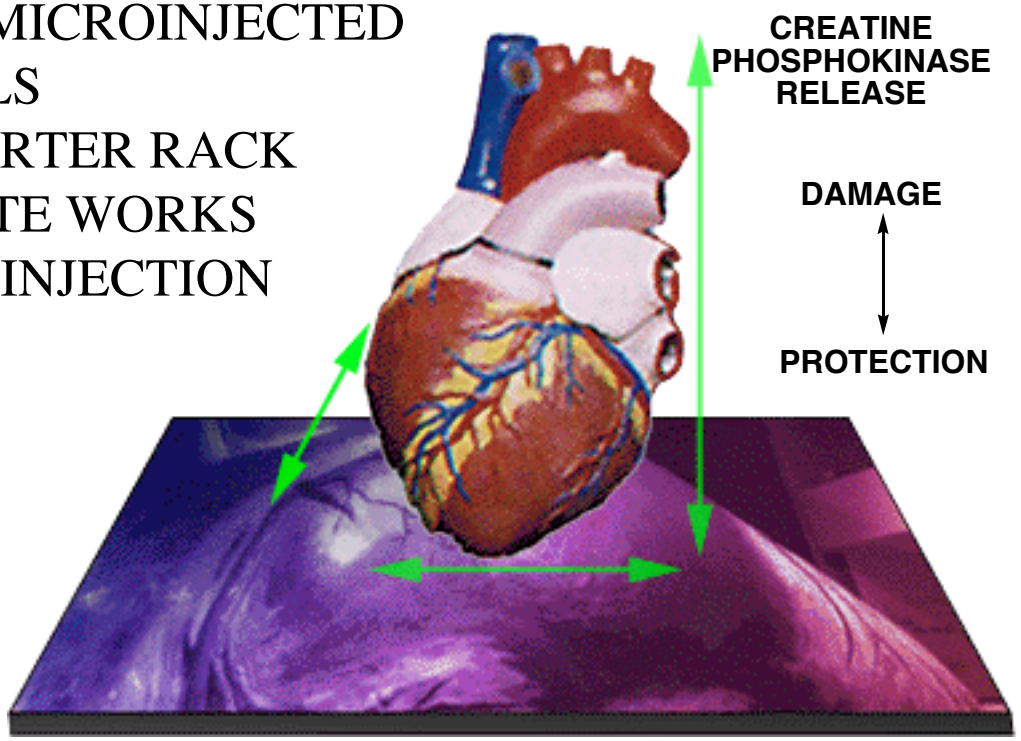
PEPTIDE DELIVERY TO PREVENT ISCHEMIC DAMAGE

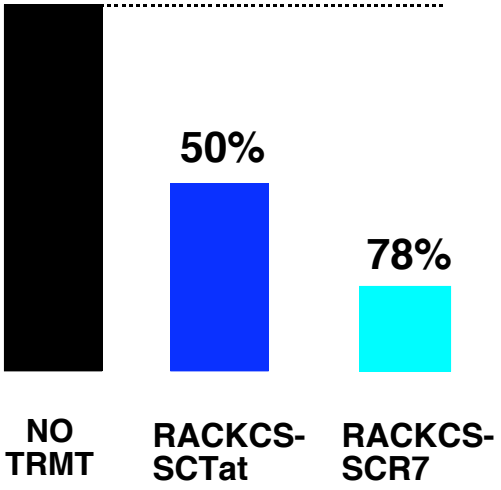
L. Chen, L. Wright, C-H. Chen, S. F. Oliver, P. A. Wender,* D. Mochly-Rosen*
CHEMISTRY & BIOLOGY, **2001**, 1123

HO_2C-DYGIPDAHC-SS-CR_7-$CONH_2$ ⟶ HO_2C-DYGIPDAHC-SH + HS-CR_7-$CONH_2$

RACK-TRANSPORTER CONJUGATE → **RACK PEPTIDE ("DRUG")** + **TRANSPORTER**

- THE RACK PEPTIDE ITSELF MUST BE MICROINJECTED INTO CELLS
- TRANSPORTER RACK CONJUGATE WORKS WITHOUT INJECTION



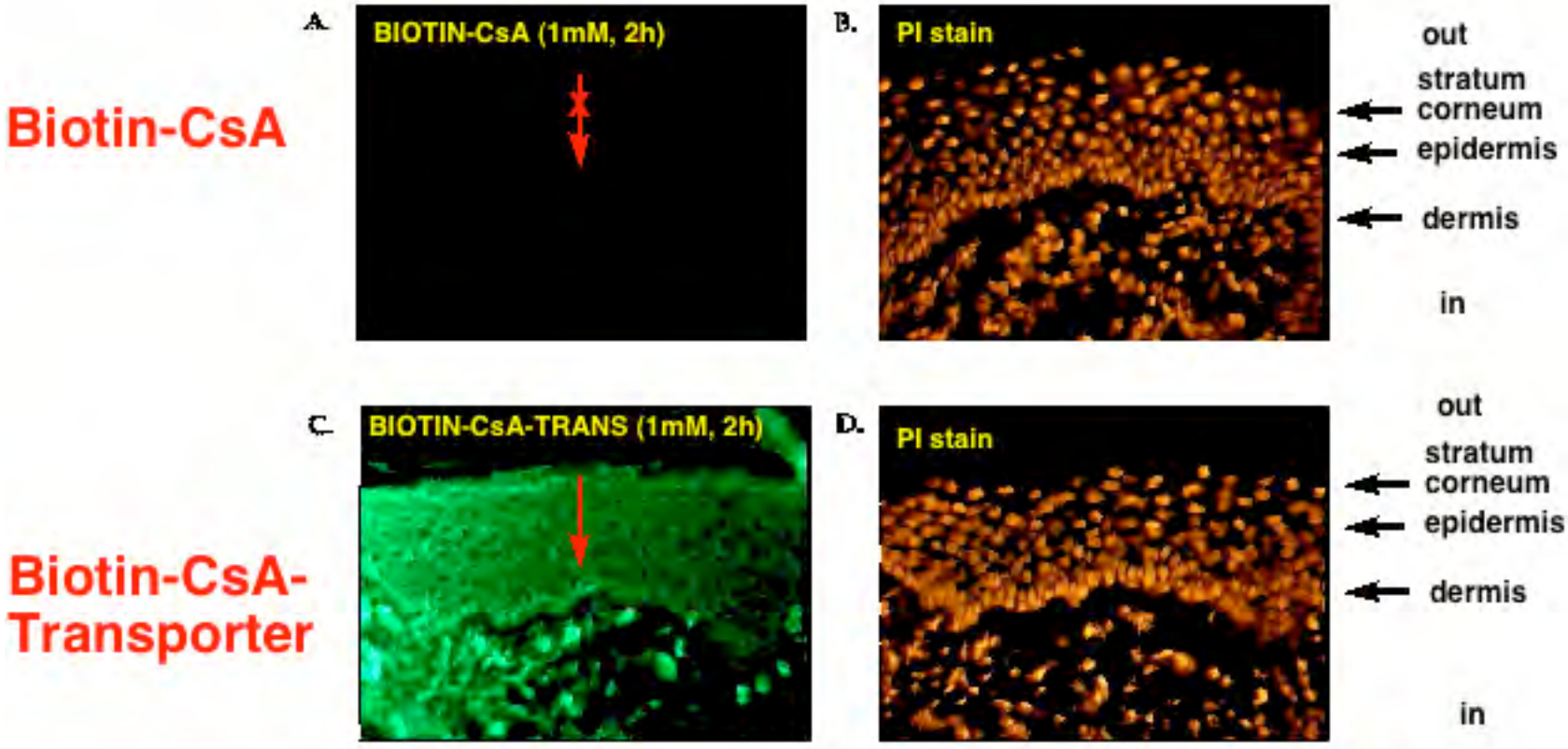


BASIS FOR NEW COMPANY, 2003

TRANSPORTER ENABLED DRUG UPTAKE IN HUMAN SKIN

Paul Wender, Dennis Mitchell, Kanaka Pattabiraman, Erin Pelkey, Lawrence Steinman, Jonathan Rothbard *Proc. Natl. Acad. Sci. USA* , 2000, 13003-13008; Jonathan Rothbard, Sarah Garlington, Qun Lin, Thorsten Kirschberg, Erik Kreider, P. Leo McGrane, Paul Wender, Paul Khavari, *Nature Medicine* 2000, 1253-1257

UPTAKE OF BIOTINYLATED CYCLOSPORIN (A) AND BIOTINYLATED CYCLOSPORIN TRANSPORTER CONJUGATE (C) IN HUMAN SKIN GRAFTED ON IMMUNE DEFICIENT MICE. PANELS B AND D ARE CONTROLS USING PROPIDIUM IODIDE TO VISUALIZE ALL CELLS.



HUMAN TRIALS ESTABLISHED SAFETY AND THERAPEUTIC LEVELS OF CONJUGATE:

T-L-CsA -> T-L + CsA (pH based release)

ASSAY NEEDED TO QUANTIFY RELEASE IN ANIMALS

REAL TIME QUANTIFICATION OF TISSUE PENETRATION, CELL UPTAKE, RELEASE & INTRACELLULAR FUNCTION IN TRANSGENIC MICE

Rothbard, Garlington, Lin, Kirschberg, Kreider, McGrane, Wender, Khavari *Nature Medicine* 2000, 1253.
L. Jones, E. Goun, R. Shinde, J. Rothbard, C. Contag, P. Wender* *J. Am. Chem. Soc.* 2006, *128(20)*, 6526.

Luc-RL-Trans (Luciferin-Releasable Linker-Transporter)

Stratum corneum

Animals can be re-used!

Luc-RL-Trans

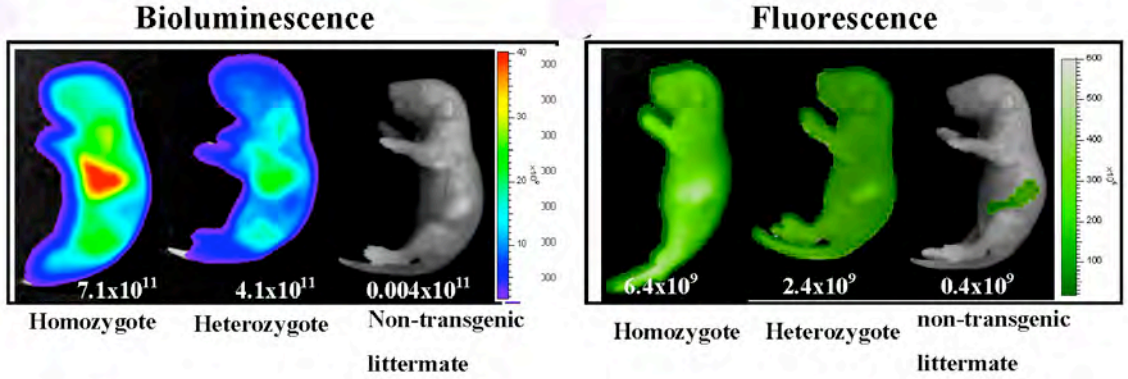
↓ Cell membrane

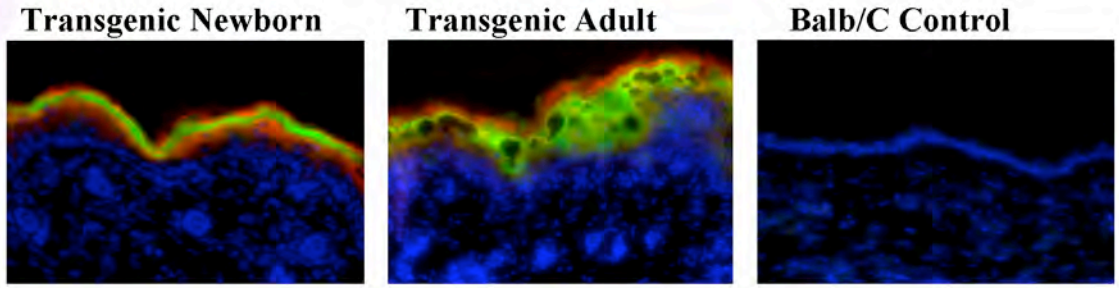
Luc-RL-Trans

↓ Intracell release

Luc + RL + Trans

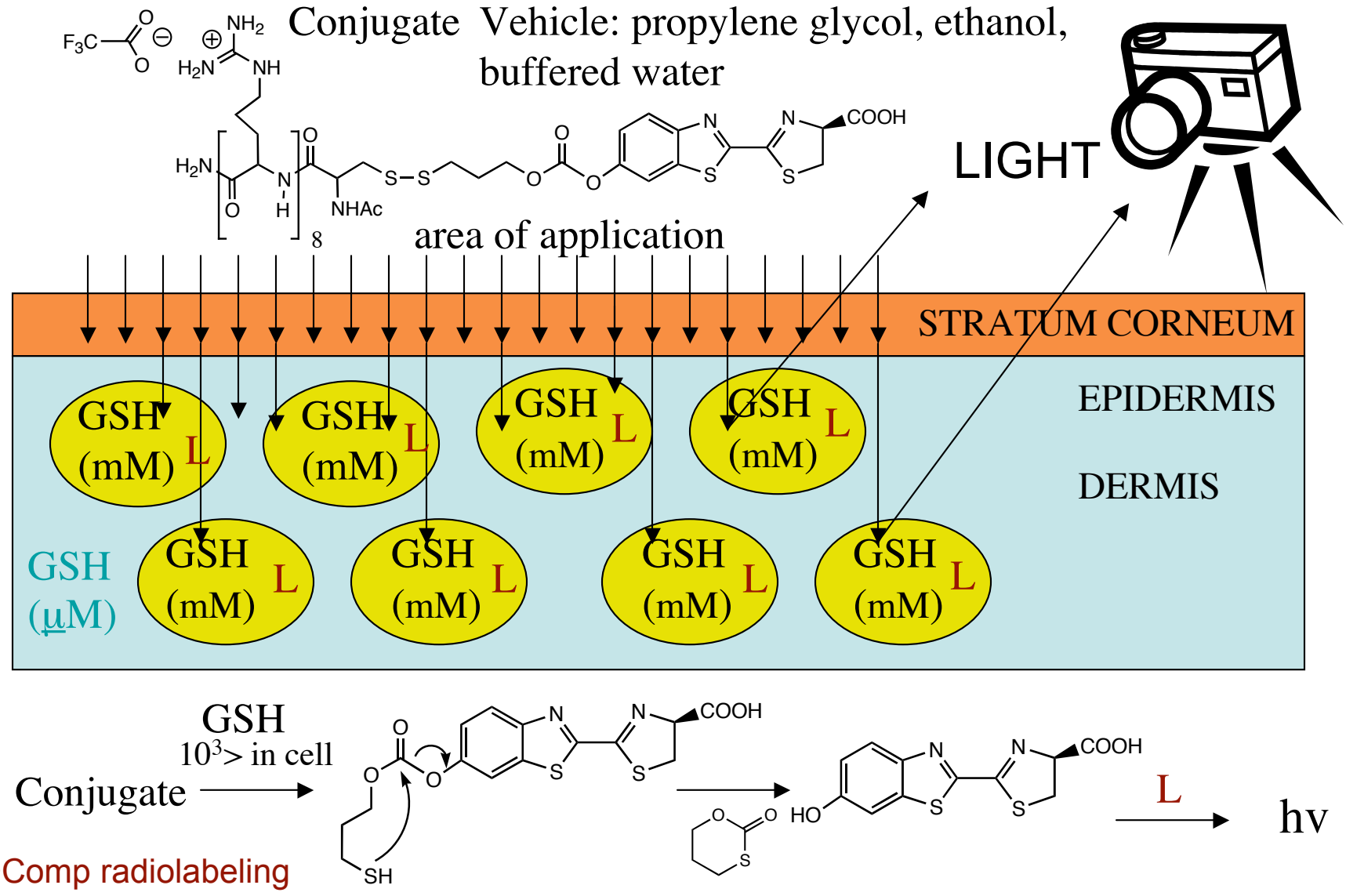
↓ luciferase





DESIGN STRATEGY FOR REAL TIME DERMAL UPTAKE

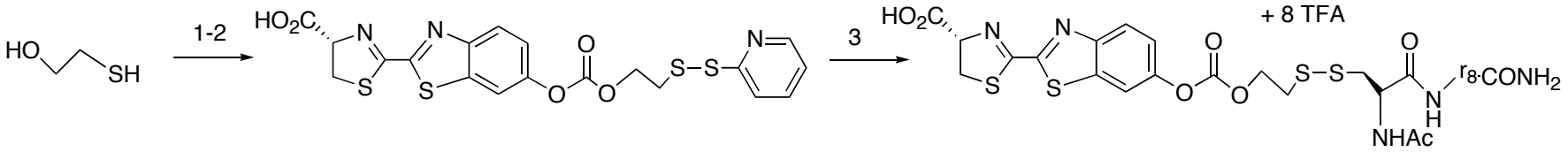
L. Jones, E. Goun, R. Shinde, J. Rothbard, C. Contag, P. Wender* *J. Am. Chem. Soc.* 2006, *128(20)*, 6526.



SYNTHESIS OF NEW BIO-RELEASABLE CONJUGATES

L. Jones, E. Goun, R. Shinde, J. Rothbard, C. Contag, P. Wender* *J. Am. Chem. Soc.* 2006, *128(20)*, 6526.

R8-CARBONATE 5 SYNTHESIS: 3 STEPS, OVERALL YIELD 40%



1. 2-aldrithiol, MeOH, 97%; 2. i) Phosgene,pyr, tol, ii) Luciferin, NaOH, H_2O, 70%; 3.AcHN-Cys-arg8-$CONH_2$, DMF, 59%

- $C_{67}H_{124}N_{36}O_{15}S_4$
- NO PROTECTING GROUPS
- GENERAL AND SCALABLE

REAL TIME QUANTIFICATION OF CELL UPTAKE IN TRANSFECTED PC3M CELLS

Luc-RL(SS)-Trans

↓ *Cell Entry*

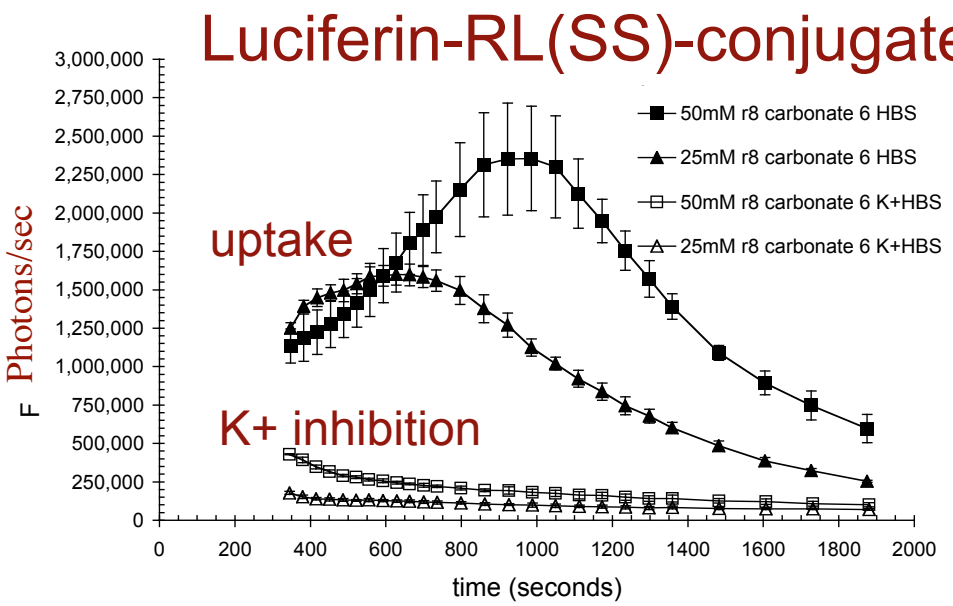
Luc-RL(SS)-Trans

↓ *GSH (in cell)*

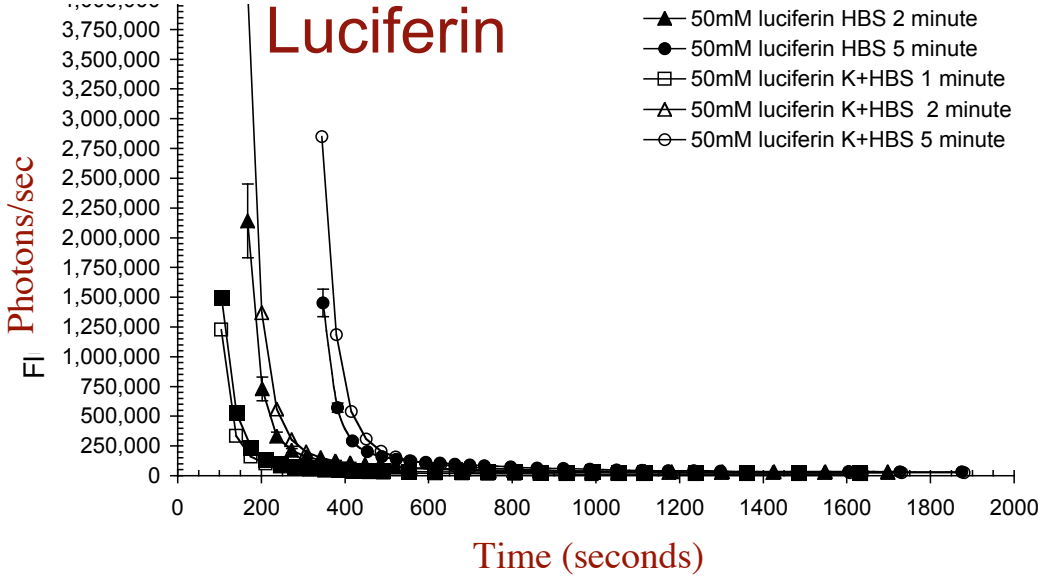
Luc + RLSH + HS-Trans

↓ *Luciferase*

Light



L. Jones, E. Goun, R. Shinde, J. Rothbard, C. Contag, P. Wender* *J. Am. Chem. Soc.* 2006, *128(20)*, 6526.



POINTS OF IMPORTANCE:

- UPTAKE & RELEASE ARE RAPID
- UPTAKE/RELEASE DOSE DEPENDENT
- UPTAKE IS INHIBITED BY K+
- UPTAKE/RELEASE MAX. IN MINUTES
- SIGNAL FROM CONJUGATE IS ~ ALL FROM BIORELEASE
- UPTAKE/RELEASE IS REPRODUCIBLE
- UPTAKE OF LUCIFERIN SHOWS DIFFERENT KINETICS

TWO MAJOR PRIORITIES IN CHEMISTRY

FUNCTION ORIENTED SYNTHESIS

- MEDICINAL AGENTS
- MATERIALS
- CATALYSTS
- PROBES
- IMAGING TOOLS
- DIAGNOSTICS
- SENSORS
- NANODEVICES
- ENERGY COLLECTION
- ENERGY STORAGE
- ENERGY CONVERSION
- ENVIRONMENTAL

Wender, P.A.; Baryza, J.L.; Brenner, S.E.; Clarke, M.O.; Craske, M.L.; Horan, J.C.; Meyer, T. " **Function Oriented Synthesis:…"** *Current Drug Discovery Technologies*, **2004**, *1*, 1-11.

- OVER 200 TOTAL SYNTHESES / YEAR IN ACS JOURNALS ALONE
- MAKING MOLECULES IS NO LONGER THE BIGGEST CHALLENGE IN SYNTHESIS
- THE MAJOR CHALLENGES NOW ARE TARGET DESIGN & SELECTION & ADVANCING SYNTHESIS TO MAKE SUCH TARGETS …

IN A PRACTICAL IF NOT IDEAL FASHION

*Wender, Miller **"Toward the Ideal Synthesis:** Connectivity Analysis & Multi-Bond Forming Processes" in *Organic Synthesis: Theory and Applications* T. Hudlicky (ed.), V. 2, 27, **1993**, JAI Press.
Wender, Wright, Handy, **"Toward the Ideal Synthesis"** *Chemistry & Industry*, **1997**, 765.