Quest for Scientific Excitement at the Multidisciplinary Interface of Chemistry and Biology

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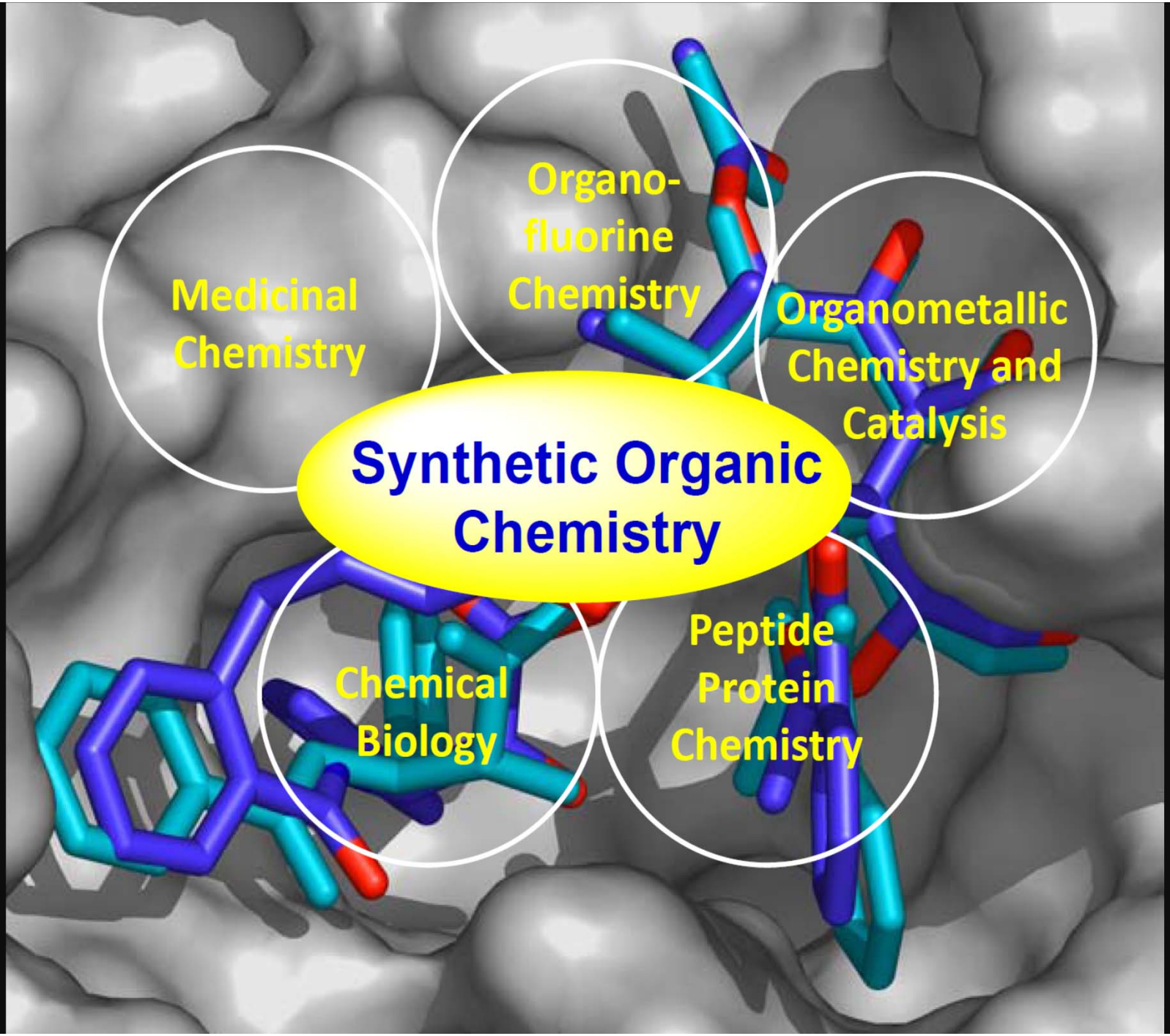
Department of Chemistry and ICB&DD

Stony Brook University

Stony Brook Symposium on
Chemical Synthesis in Life Sciences
Charles B. Wang Center, Stony Brook University
June 5-6, 2015


Medicinal Chemistry
Organo-fluorine Chemistry
Organometallic Chemistry and Catalysis
Synthetic Organic Chemistry
Chemical Biology
Peptide Protein Chemistry

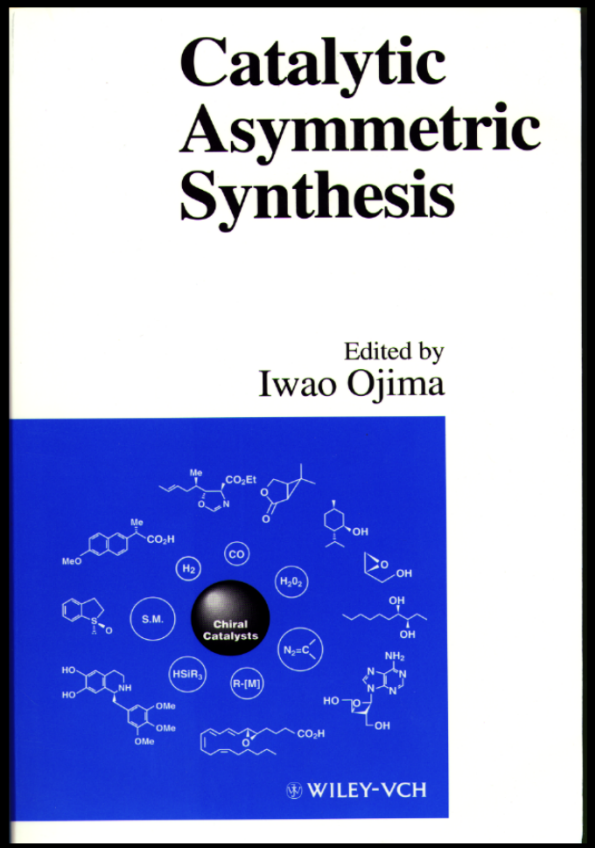
	Citation	Year
Catalytic asymmetric synthesis John Wiley & Sons	1958	**1993** **2000** **2010**
Transition metal-catalyzed carbocyclizations in organic synthesis I Ojima, M Tzamarioudaki, Z Li, RJ Donovan Chemical reviews 96 (2), 635-662	705	**1996**
Fluorine in medicinal chemistry and chemical biology I Ojima Wiley-Blackwell	422	**2009**
Biomedical frontiers of fluorine chemistry I Ojima, JR McCarthy, JT Welch	417	**1996**
Recent advances in tumor-targeting anticancer drug conjugates S Jaracz, J Chen, LV Kuznetsova, I Ojima Bioorganic & medicinal chemistry 13 (17), 5043-5054	346	**2005**
New and efficient approaches to the semisynthesis of taxol and its C-13 side chain analogs by means of β-lactam synthon method I Ojima, I Habus, M Zhao, M Zucco, YH Park, CM Sun, T Brigaud Tetrahedron 48 (34), 6985-7012	312	**1992**

(Google Scholar 6/3/2015)

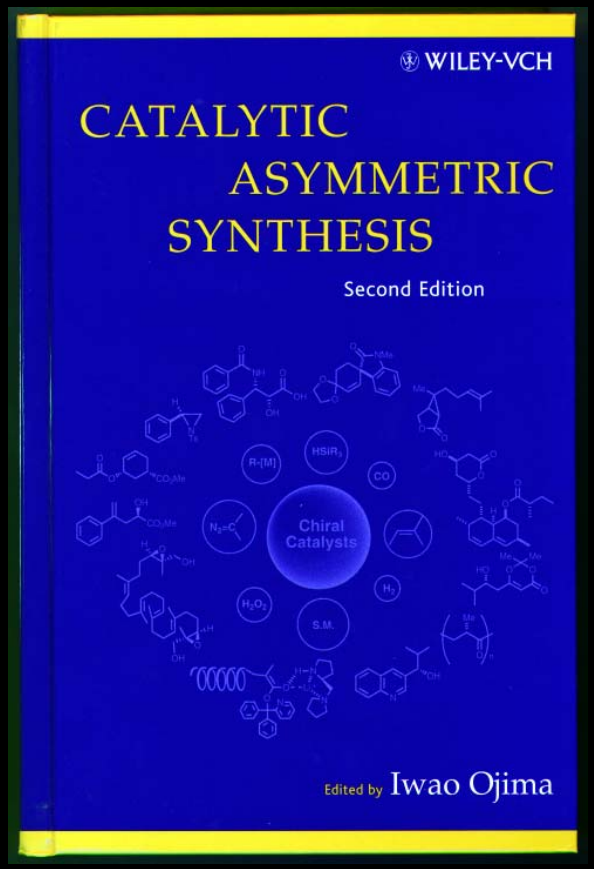
Recent advances in the. beta.-lactam synthon method I Ojima Accounts of chemical research 28 (9), 383-389	294	**2008**
A common pharmacophore for cytotoxic natural products that stabilize microtubules I Ojima, S Chakravarty, T Inoue, S Lin, L He, SB Horwitz, SD Kuduk, ... Proceedings of the National Academy of Sciences 96 (8), 4256-4261	286	**1999**
Recent advances in the hydrosilylation and related reactions I Ojima, Z Li, J Zhu Patai's Chemistry of Functional Groups	275	**1998**
Asymmetric synthesis of building-blocks for peptides and peptidomimetics by means of the β-lactam synthon method I Ojima, F Delaloge Chemical Society Reviews 26 (5), 377-386	264	**1997**
Functionalized single-walled carbon nanotubes as rationally designed vehicles for tumor-targeted drug delivery J Chen, S Chen, X Zhao, LV Kuznetsova, SS Wong, I Ojima Journal of the American Chemical Society 130 (49), 16778-16785	254	**2008**

(Google Scholar 6/3/2015)

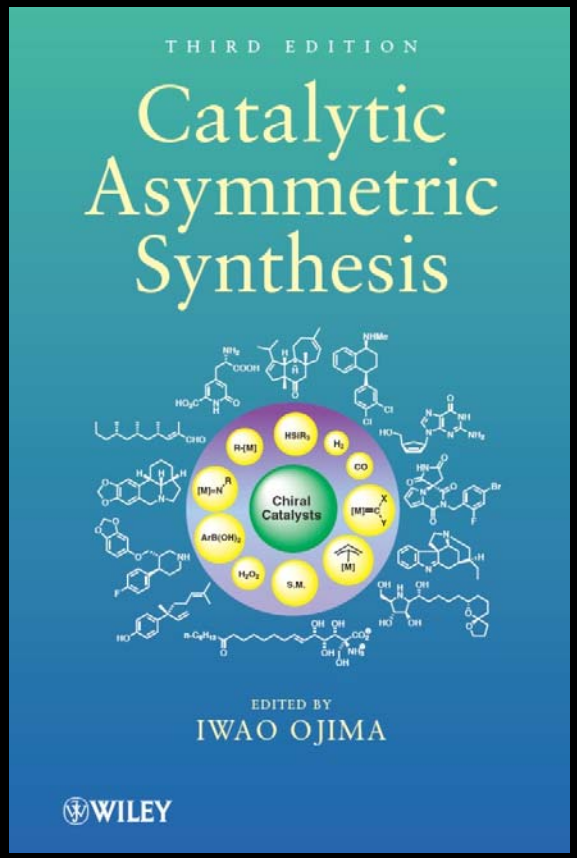
Catalytic Asymmetric Synthesis (CAS) in Perspective



1993

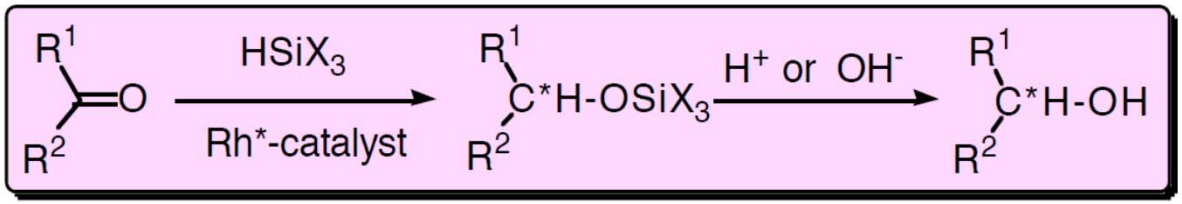


2000

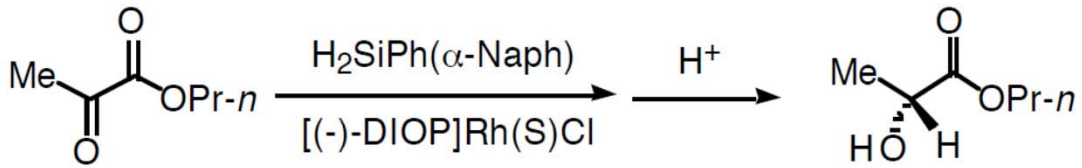


2010

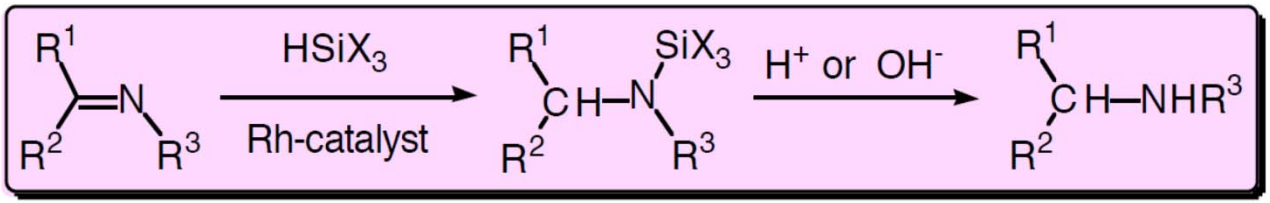
Discovery of Rh-Complex Catalyzed Hydrosilylation of Carbonyl Compounds and Imines and Applications to Regioselective and Asymmetric Reductions



Chem. Commun., 938 (l972)
Bull. Chem. Soc. Japan, **45**, 3506 (l972)
Chem. Lett., 223 (l974)
J. Organometal. Chem., **94**, 449 (l975)
J. Organometal. Chem., **l22**, 83 (l976)

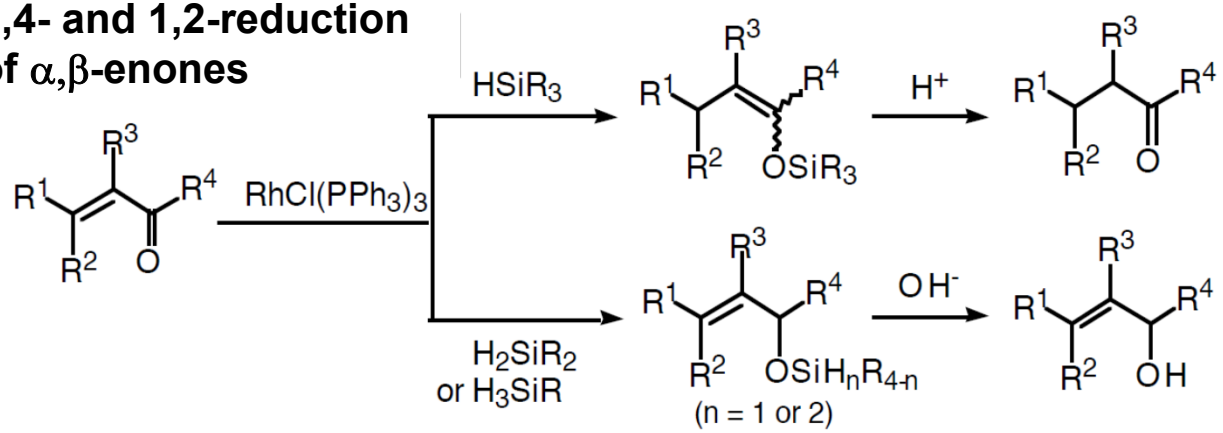


Tetrahedron Lett., l889 (l974)
J. Org. Chem., **42**, 1671 (1977)



Tetrahedron Lett., 2475 (l973)

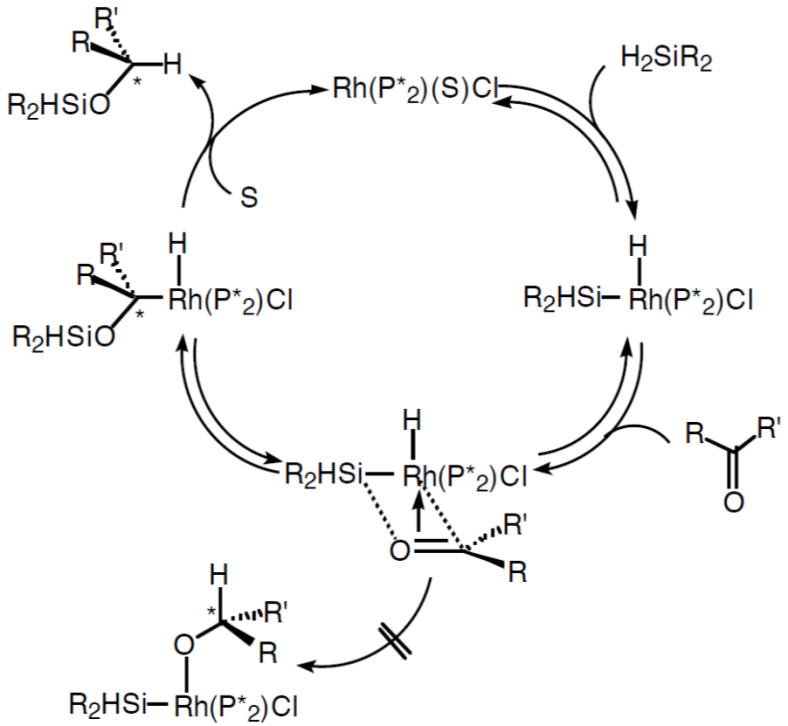
Selective 1,4- and 1,2-reduction of α,β-enones



Tetrahedron Lett., 5035 (1972)
Organometallics, 1, 1390 (1982)

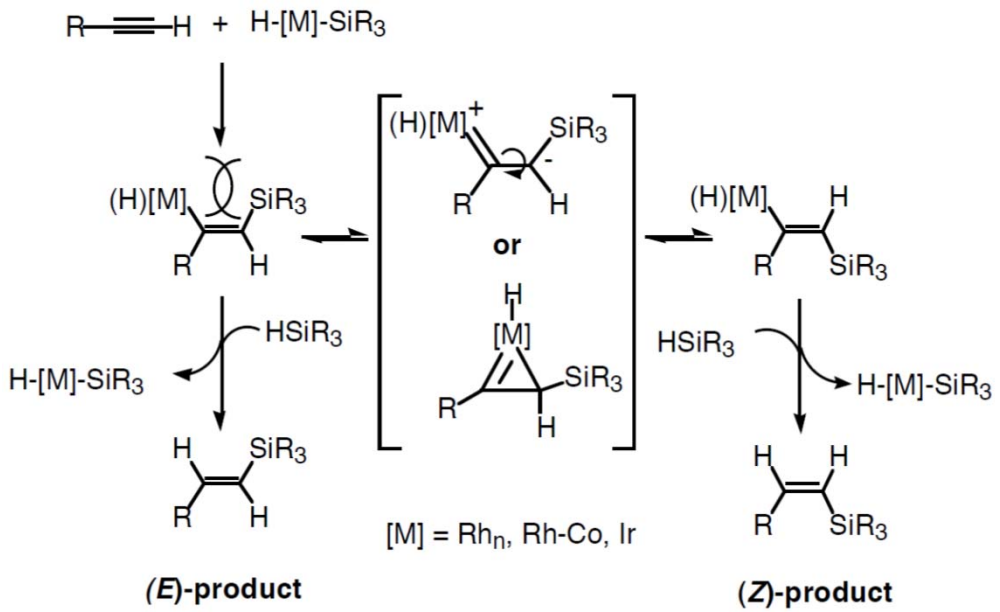
Mechanistic Studies on the Rh-complex Catalyzed Hydrosilylations

Ojima's Mechanism
--hydrosilylation of carbonyl compounds



Chem. Lett., 541 (1973)
J. Organometal. Chem., **94**, 449 (1975)
Organometallics, **1**, 1390 (1982)

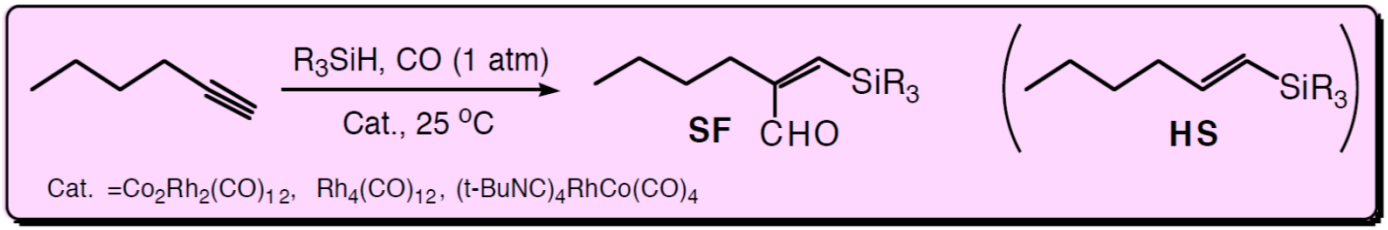
"Ojima-Crabree" Mechanism for *trans*-addition to 1-alkynes

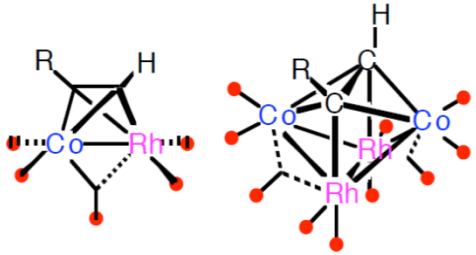


***(E)*-product** **(*Z*)-product**

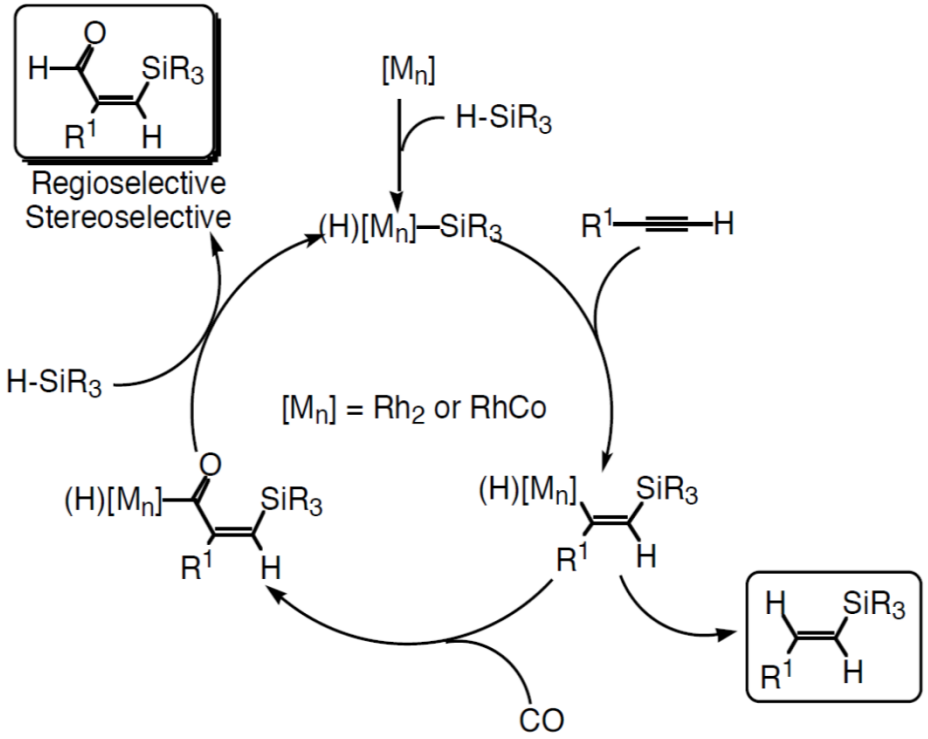
Organometallics, **9**, 3127-33 (1990)

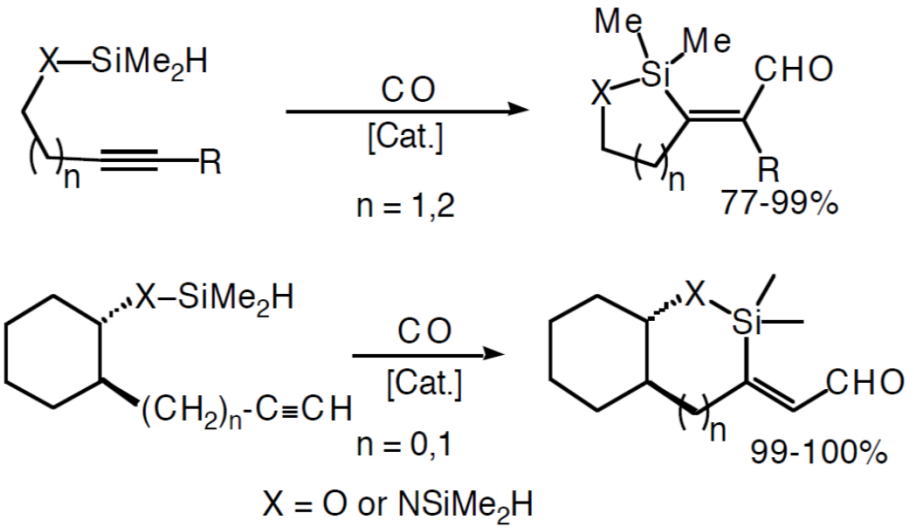
Discovery and Development of Novel Silylformylation Process Catalyzed by Rh Complexes and Rh-Co Mixed Metal Clusters





XXII Organosilicon Symposium, Philadelphia, April 7-8, 1989, PL7
Organometallics, **10**, 39 (1991). *J. Cluster Sci.*, **3**, 423 (1992). *Tetrahedron*, **49**, 5431 (1993).

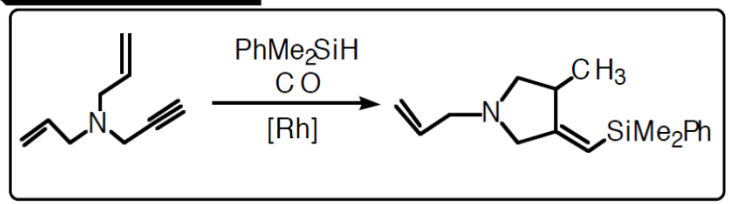


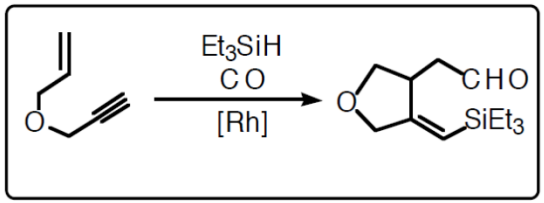


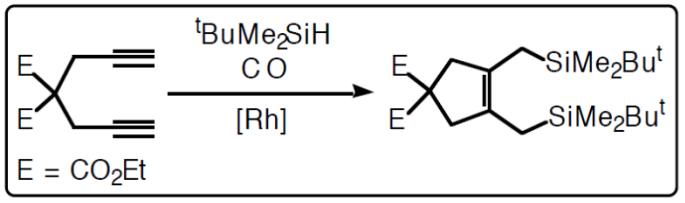
J. Am. Chem. Soc, **117**, 6797 (1995)

Discovery and Development of Novel Silylcarbocyclization (SiCaC) Processes

SiCaC-Type I

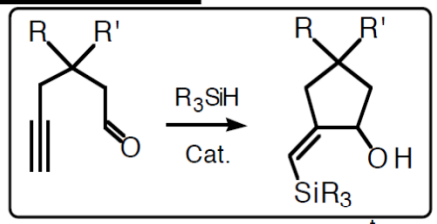






J. Am. Chem. Soc., **114**, 6580 (1992).
J. Am. Chem. Soc., **120**, 6690 (1998).

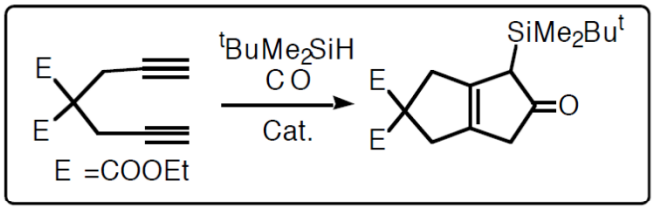
Hetero-SiCaC

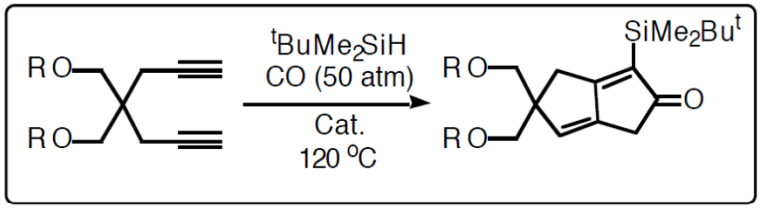


Cat. = $Rh(acac)(CO)_2$, $Rh(CN\text{-}Bu^t)_4Co(CO)_4$

J. Am. Chem. Soc., **116**, 3643 (1994).

SiCaC-Type II (SiCaB)

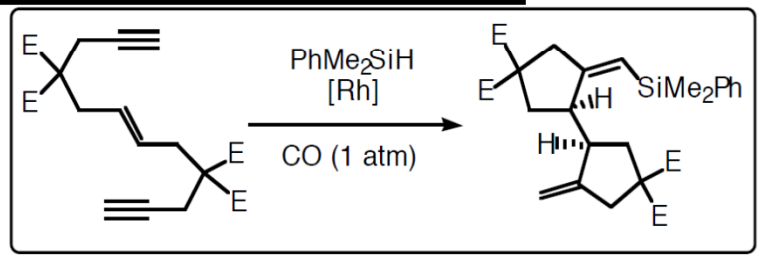




Cat. = $Rh_2Co_2(CO)_{12}$, $Rh(acac)(CO)_2$, $[Rh(CN\text{-}But)_4]CoCO_4$

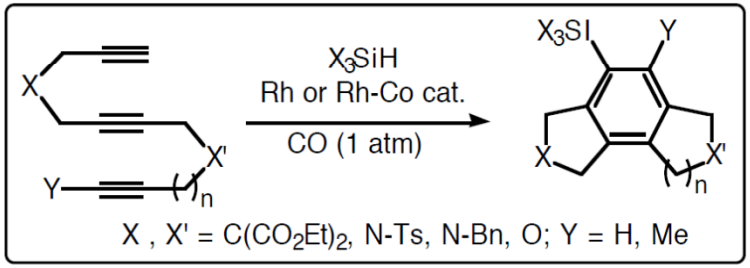
J. Org. Chem., **59**, 7594 (1994).
Organometallics, **15**, 5191 (1996).
J. Am. Chem. Soc., **120**, 6690 (1998).

Cascade SiCaC of enediyne



J. Organometal. Chem., **521**, 421 (1996)

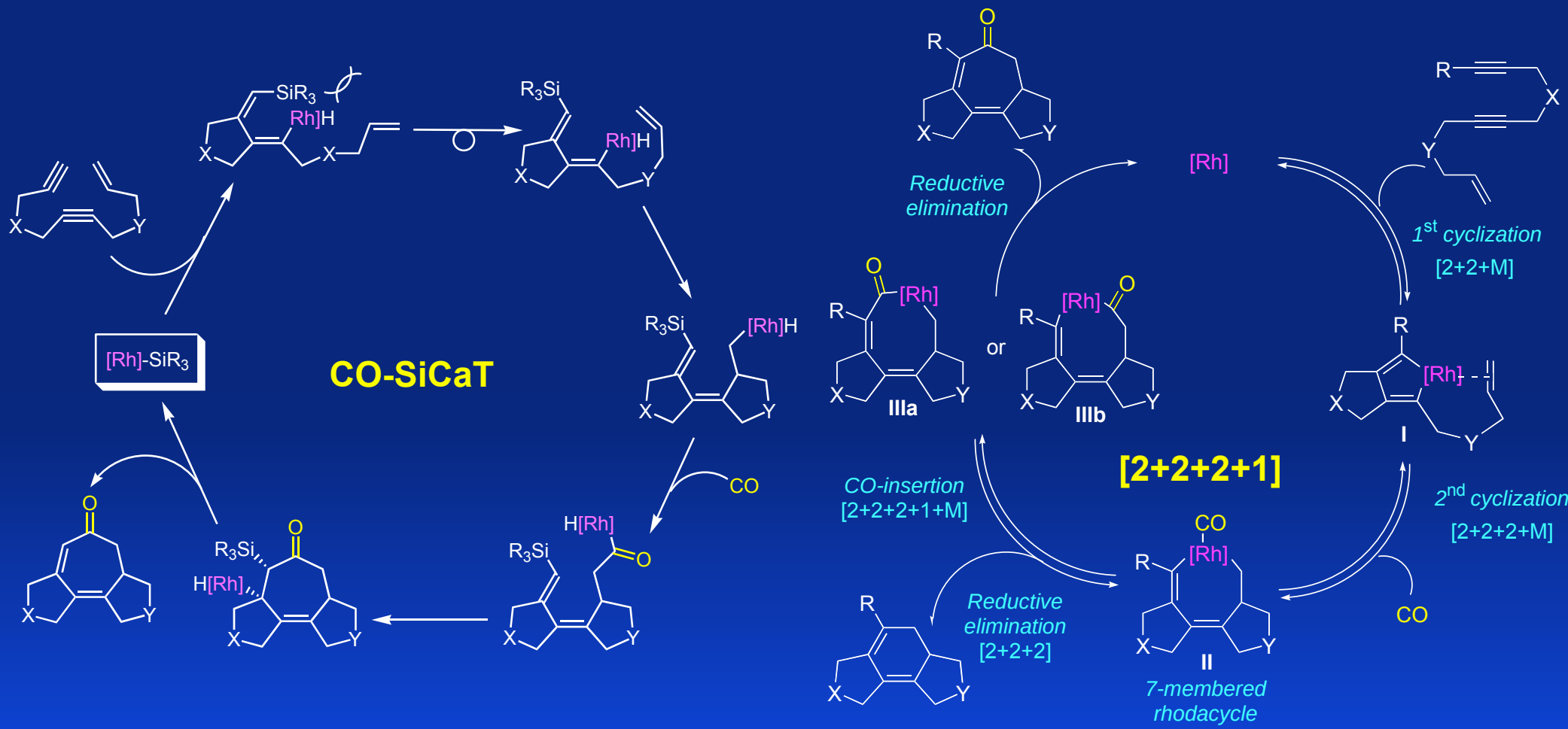
SiCaT of triynes



*J. Am.Chem. Soc.***121,** 3220 (1999).

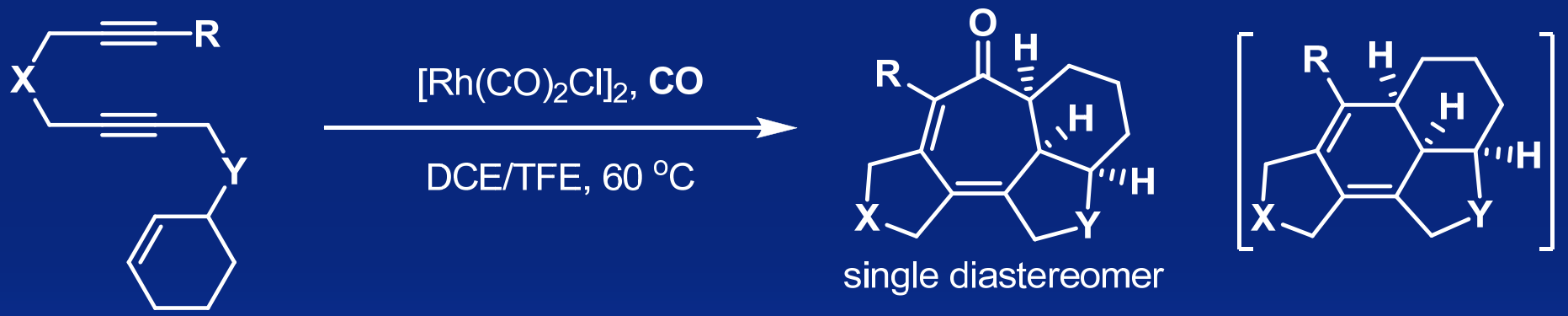
CO-SiCaT and [2+2+2+1] Cycloaddition:

Novel Carbonylative Tricyclization Processes of Enediynes



B. Bennacer, M. Fujiwara, S.-Y. Lee, I. Ojima, *J. Am. Chem. Soc*. **127**, 17756 -17767 (2005).
For SiCaC and CO-SiCaC, see A. T. Vu, S.-Y. Lee, J. V. McCullagh, A. Moralee, T. H. Hoang, I. Ojima, *J. Am. Chem. Soc*. **124**, 9164-9174 (2002). *For SiCaT and CO-SiCaT, see* I. Ojima, A. T. Vu, J. V. McCullah, A. Kinoshita, *J. Am. Chem. Soc*. **121**, 3230-3231 (1999). I. Ojima and S.-Y. Lee, *J. Am. Chem. Soc*., **122**, 2385-2386 (2000)

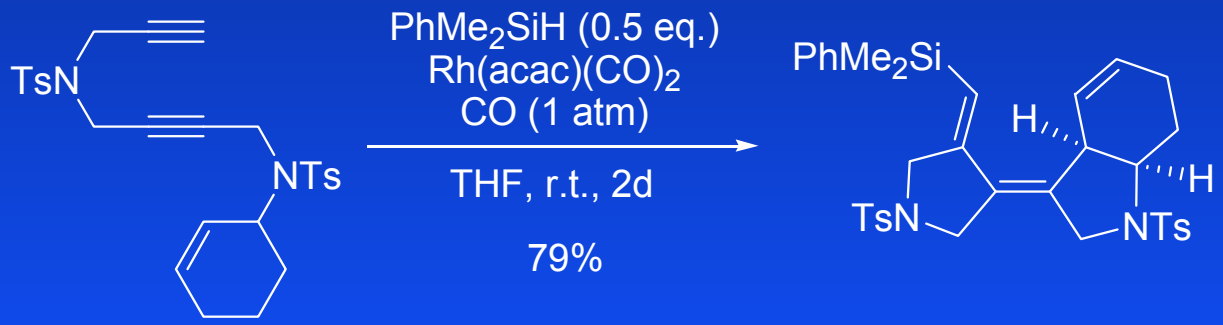
[2+2+2+1] of Enediynes to form Fused Tetracyclic Framework

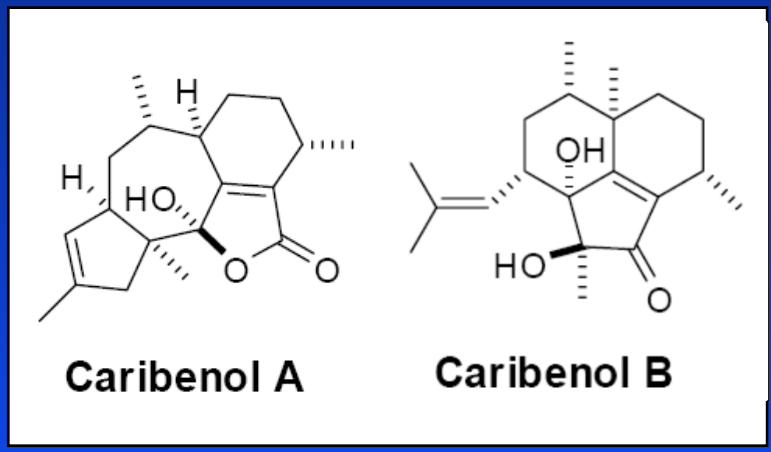


R = Me, Ph, TMS, $SiPhMe_2$; X,Y = $C(CO_2Et)_2$, O, NTs

J. J. Kaloko, Y.-H. G. Teng and I. Ojima, *Chem. Commun.* 4569-4571 (2009)

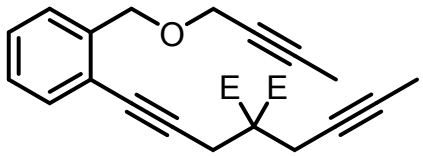
Bicyclization under CO-SiCaT conditions





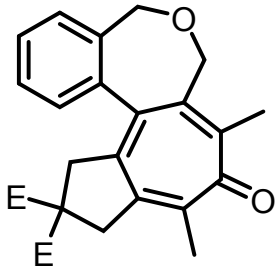
B. Bennacer, M. Fujiwara, S.-Y. Lee, I. Ojima, *J. Am. Chem. Soc*. **127**, 17756 -17767 (2005).

Synthesis of Colchicinoids

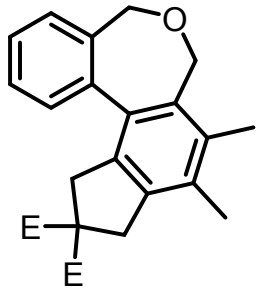


i) $[Rh(CO)_2Cl]_2$ (10 mol%)
CO (2 atm)
DCE, 50 °C, 48 h

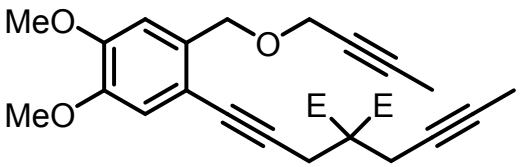
ii) μW, 80 °C, 30min



68%

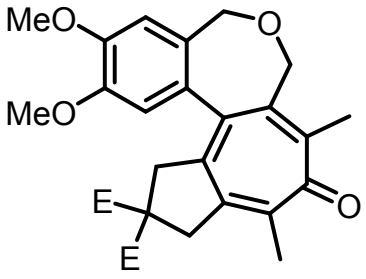


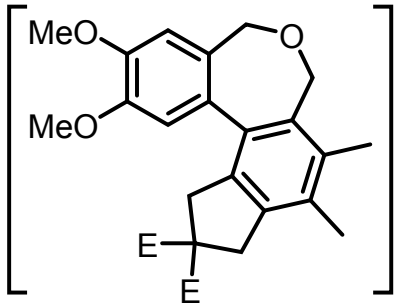
17%



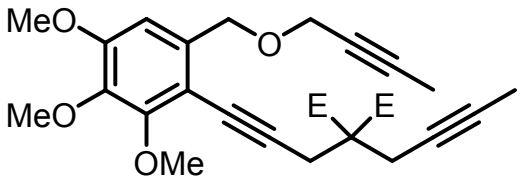
$[Rh(CO)_2Cl]_2$ (10 mol%)
CO (2 atm)
DCE, 50 °C, 48 h

80% conversion



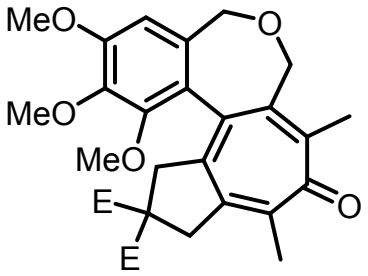


75% conversion yield

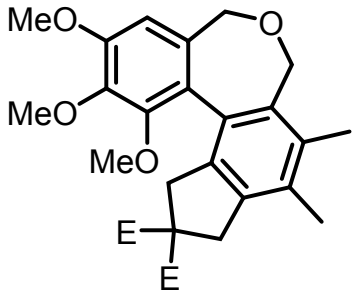


$[Rh(CO)_2Cl]_2$ (10 mol%)
CO (2 atm)
DCE, 50 °C, 72 h

93% conversion



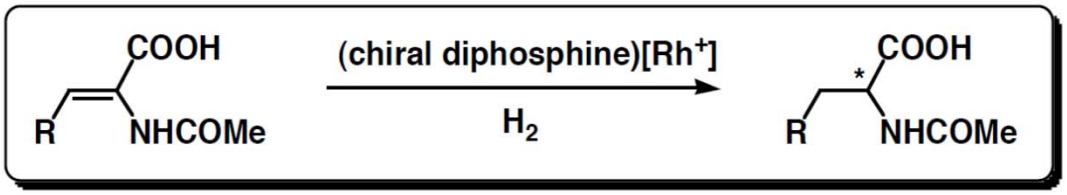
48%

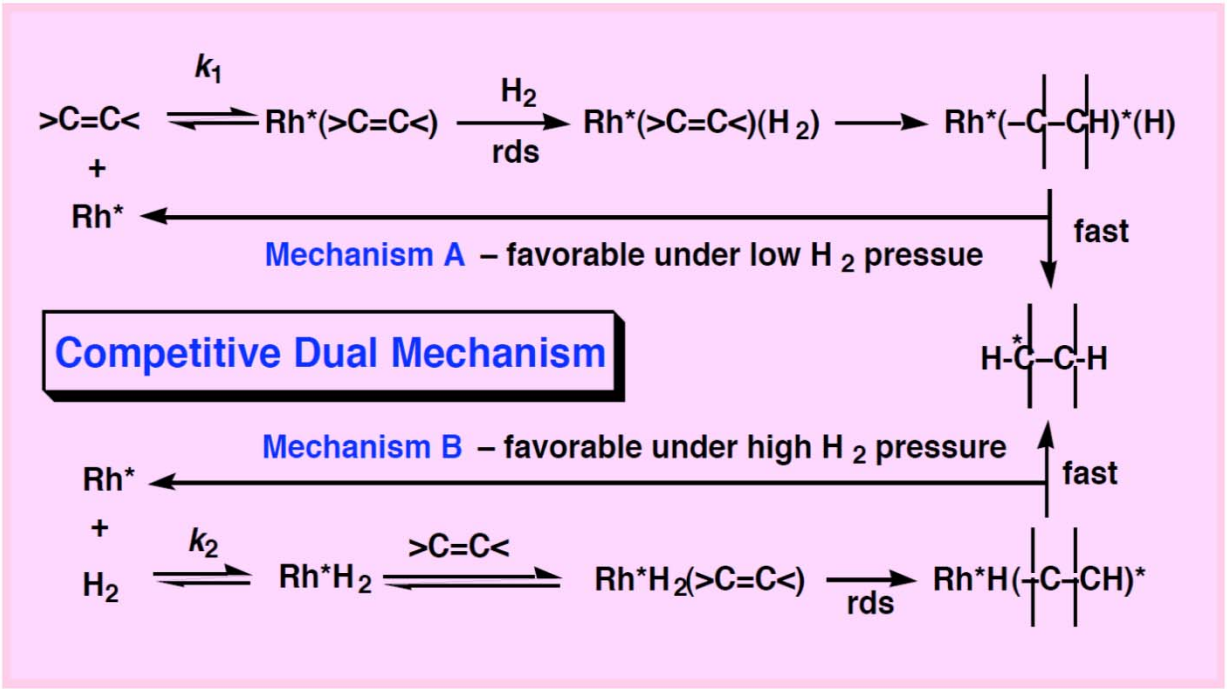


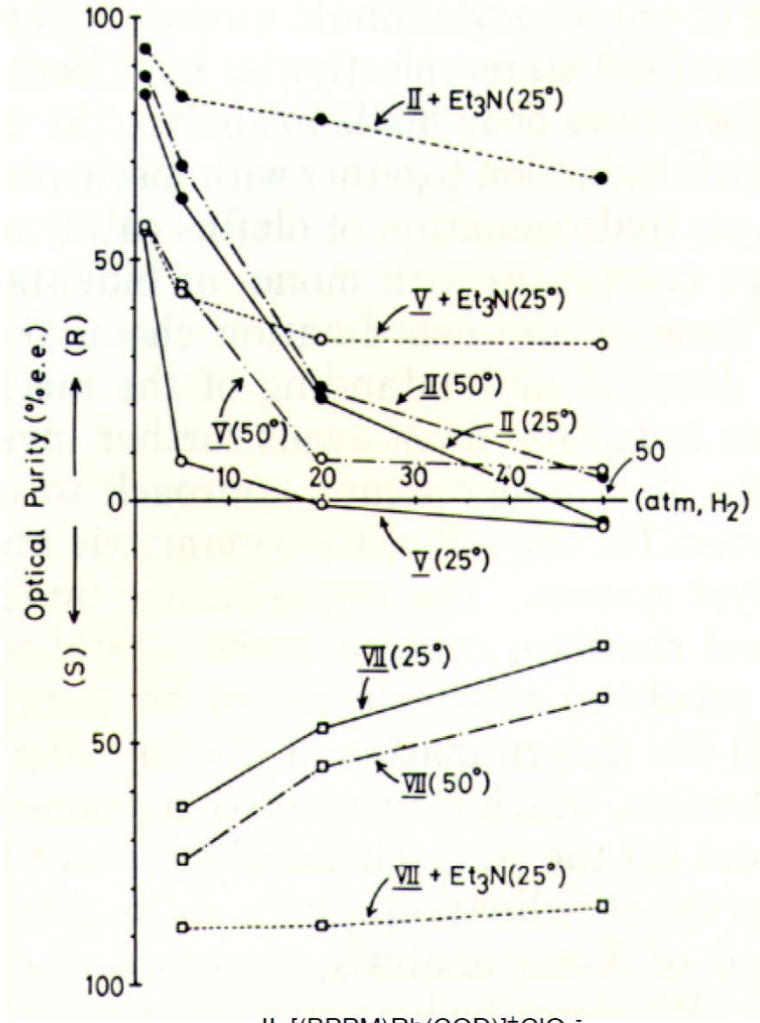
16%

Gary Y. H Teng

Mechanistic Studies on the Asymmetric Hydrogenation of Dehydroamino Acids
-- Proposal of dual mechanism depending on hydrogen pressure



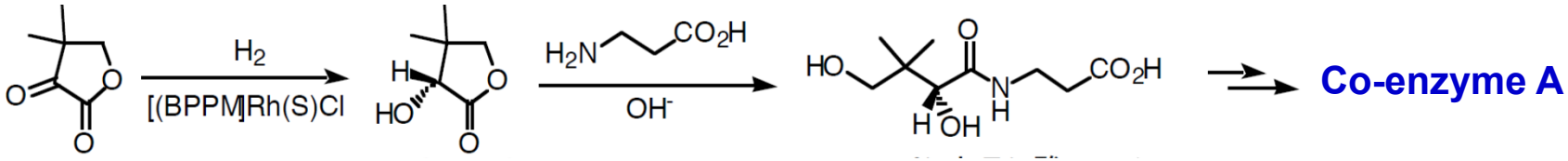




II, $[(BPPM)Rh(COD)]^+ClO_4^-$
V, $[((-)\text{-}DIOP)Rh(COD)]^+ClO_4^-$
VII, $[(diPAMP)Rh(COD)]^+ClO_4^-$

Chem. Lett., 495 (1979)
J. Org. Chem., **45**, 4728 (1980)

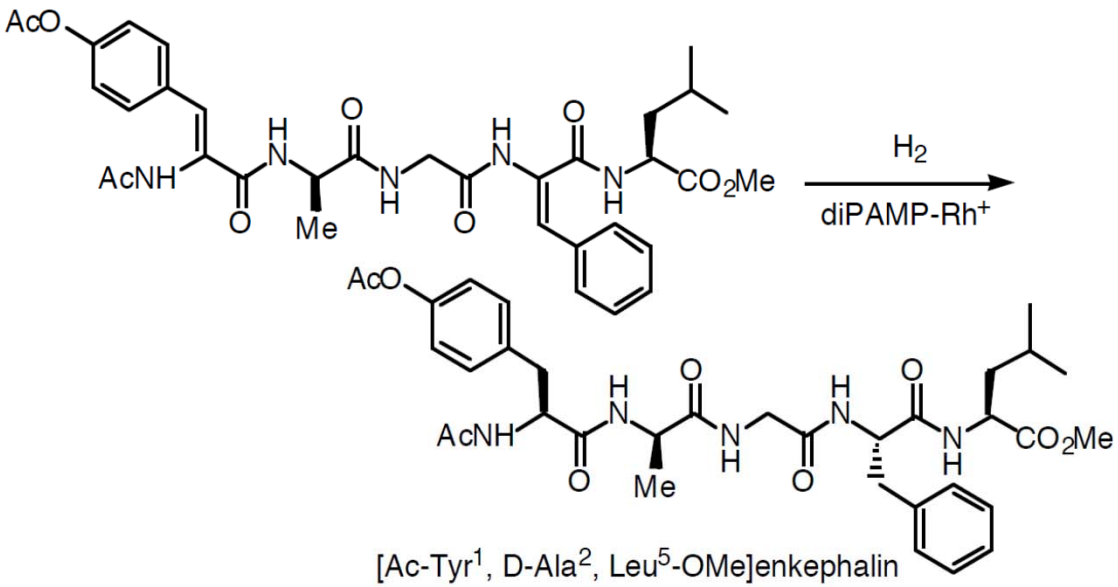
Application to the asymmetric synthesis of pantolactone and pantothenic acid



Pantolactone 87% ee
(>98% ee recrystal.)

pantothenic acid → calcium pantothenate
Vitamin B drug

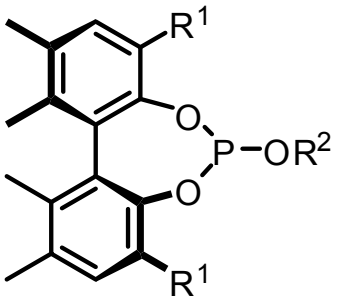
Application to the synthesis of analgesic brain peptide, enkephalin analogs



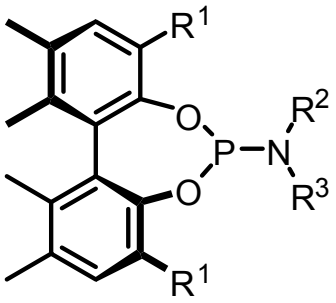
[Ac-Tyr^1, D-Ala^2, Leu^5-OMe]enkephalin

>98% (*S,R,S,S*)

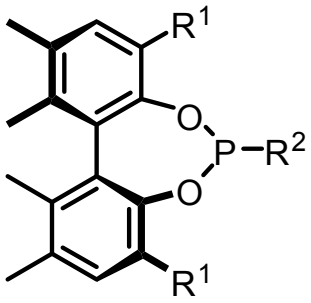
Chiral Biphenol-based Phosphorous Ligand Libraries



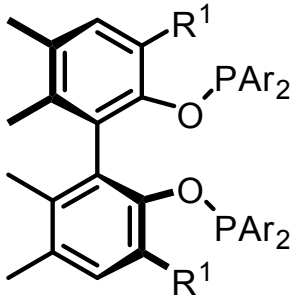
Phosphites



Phosphoramidites



Phosphonites



Diphosphonites (BOPs)

Exhibit excellent efficacy in asymmetric hydrogenation, conjugate addition, hydroformylation, allylic alkylation and allylic amination reactions

Hua, Z.; Vassar, V. C.; Ojima, I. *Org. Lett.* **2003**, *5*, 3831-3834.
Choi, H.; Hua, Z.; Ojima, I. *Org. Lett.* **2004**, *6*, 2689-2691.
Hua, Z,; Vassar, V. C.; Choi, H.; Ojima, I. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5411-5416.
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Chapsal. B. D.; Ojima, I. *NATO Science Ser.* **2008**, *246,* 29-54.
Shi, C.; Chien, C.-W.; Ojima, I. *Chem. Asian J.* **2011**, *6*, 674-680 (2011). [E. Nakamura special issue]
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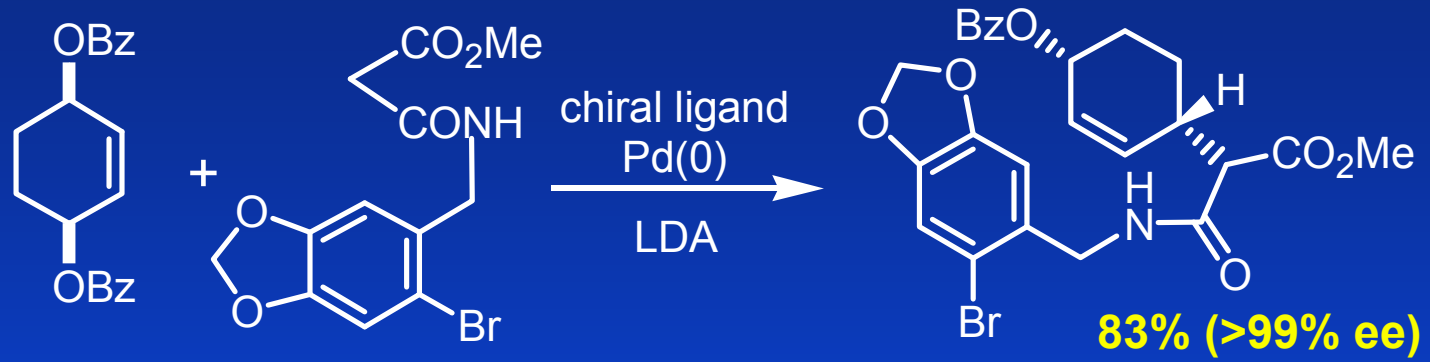
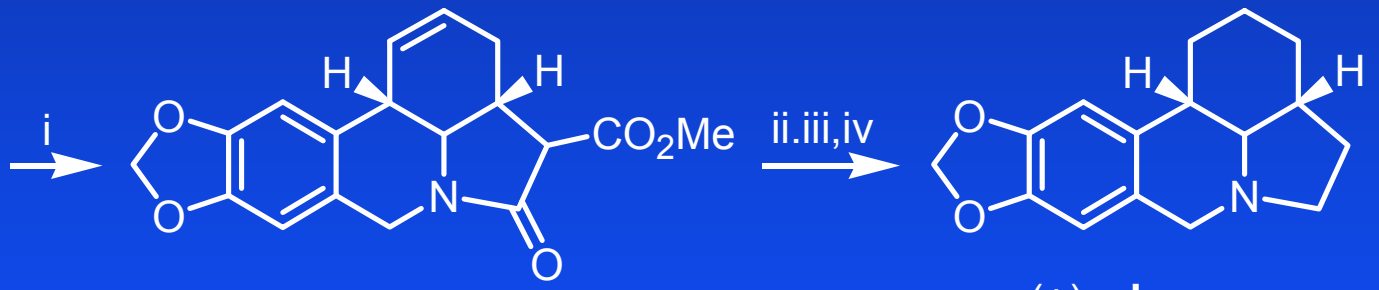
Y. Zang and I. Ojima, *J. Org. Chem*. **2013**, 78, 4013-4018.
C.-F. Lin, C.-W. Chien, and I. Ojima, *Org. Chem. Front*. **2014**, *1*, 1062-1066.
Y. Zang and I. Ojima, *Tetrahedron Lett.* **2015**, *56*, 3288-3292.

Highly Efficient Short Asymmetric Total Synthesis of (+)-γ-Lycorane



83% (>99% ee)



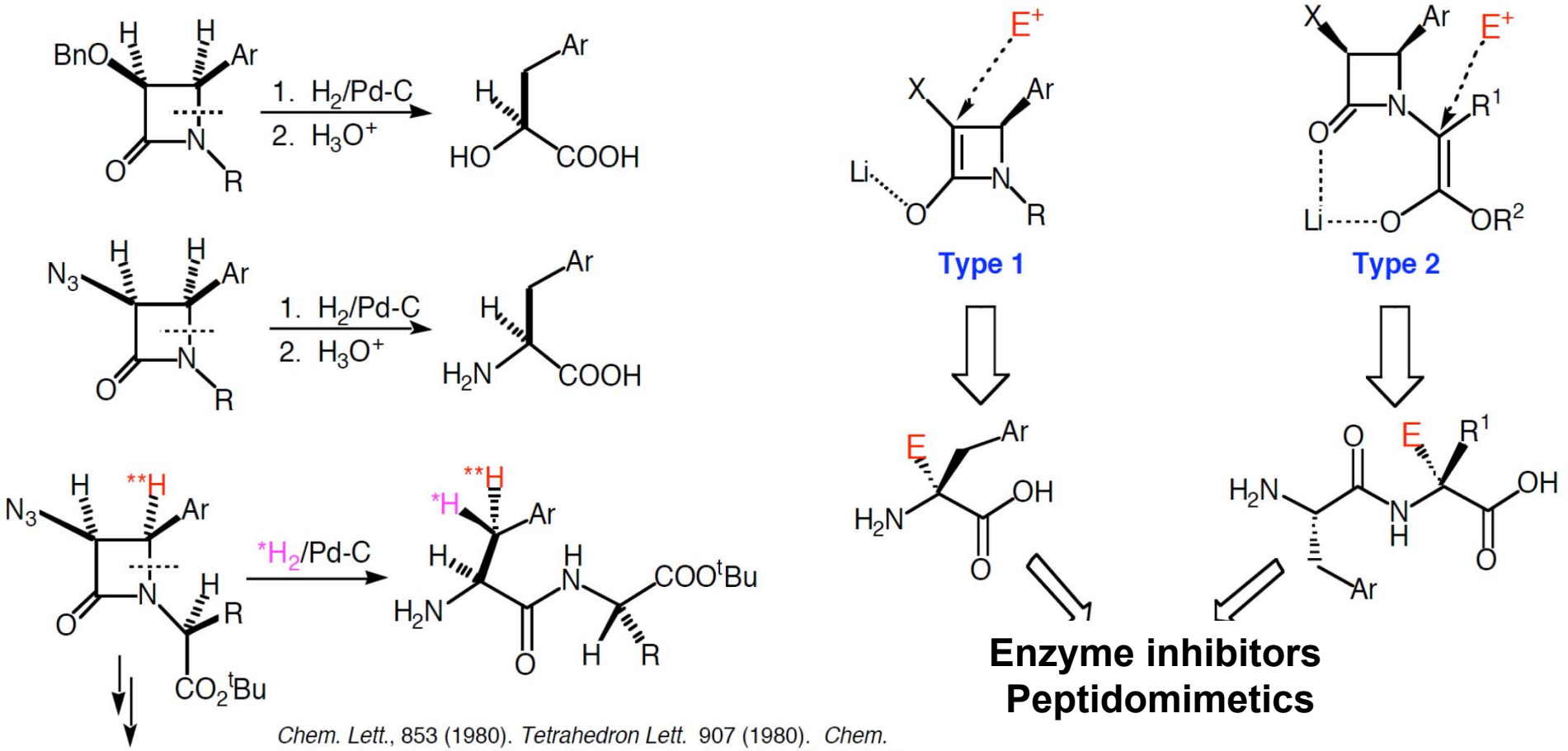
(+)-γ-**lycorane**

(>99% ee, 41% overall yield)

(i) $Pd(OAc)_2$-dppb, NaH, DMF, 50 ^{0}C, then *i*-Pr_2NEt, 100 ^{0}C;
(ii) NaCl, DMSO-H_2O, 160 ^{0}C;
(iii) H_2/Pd-C, MeOH; (iv) $LiAlH_4$, THF, 0 ^{0}C.

B. D. Chapsal and I. Ojima, *Org. Lett*. 8, 1395 -1398 (2006);
B. D. Chapsal, Z. Hua and I. Ojima", *Tetrahedron : Asymmetry*, 17, 642-657 (2006) [Jack Halpern Special Issue

Invention and Development of β-Lactam Synthon Method (1st-generation)



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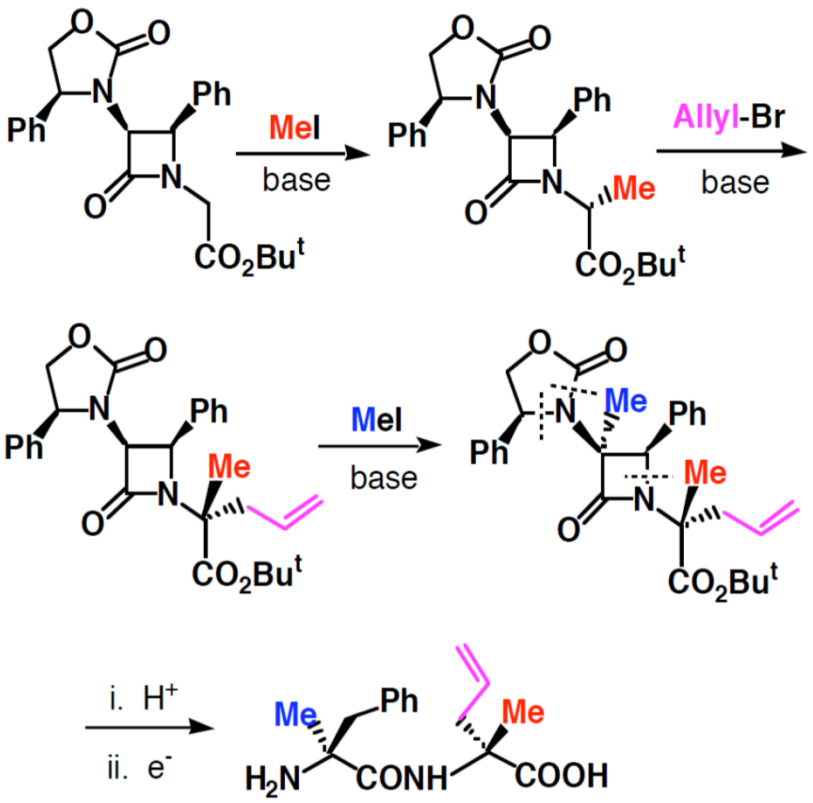
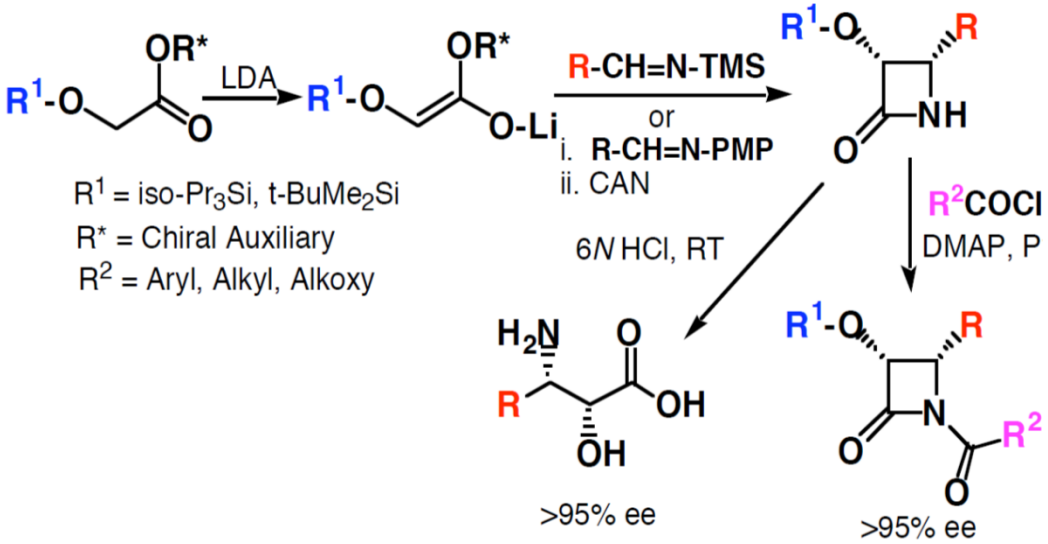
α,α'-Dialkyldipeptides through novel tandem trialkylation

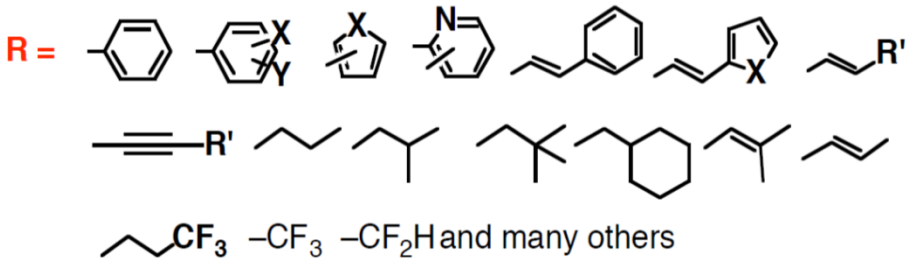
(impossible to synthesize by peptide coupling methods)



J. Am. Chem. Soc. , **112**, 770 (1990)

Highly efficient asymmetric synthesis of β-lactams and isoserines via novel chiral ester – enolate cyclocondensation





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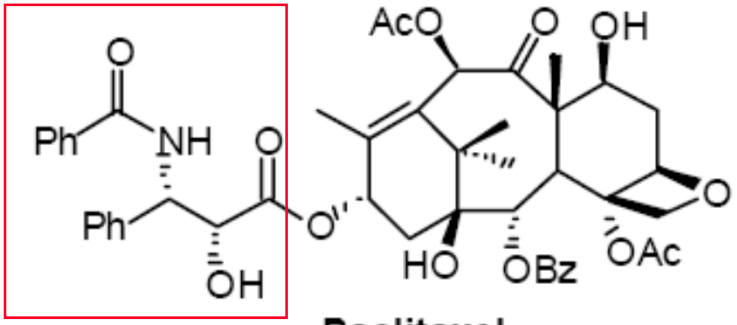
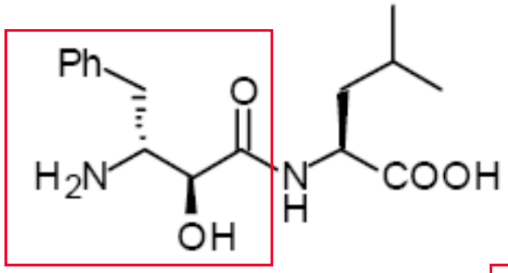
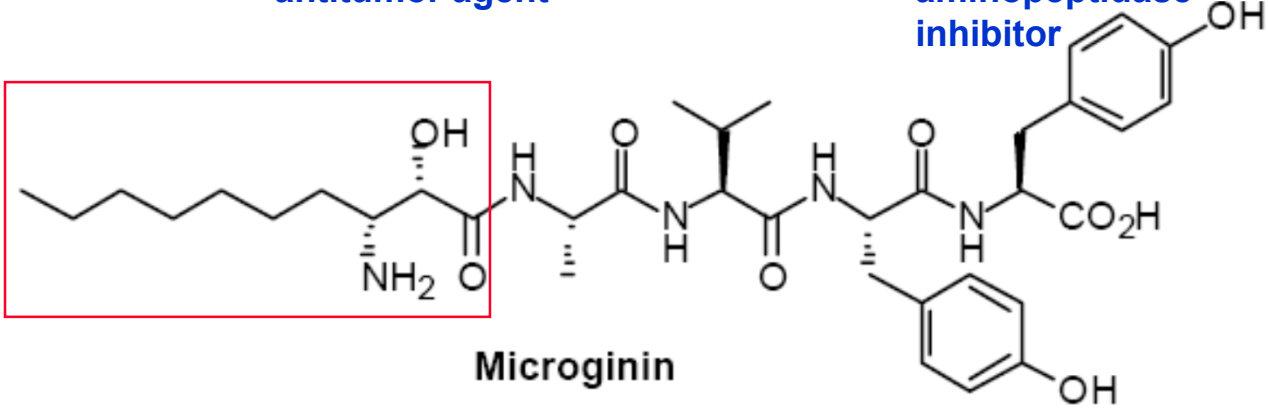
Biologically Active α-Hydroxy-β-Amino Acids



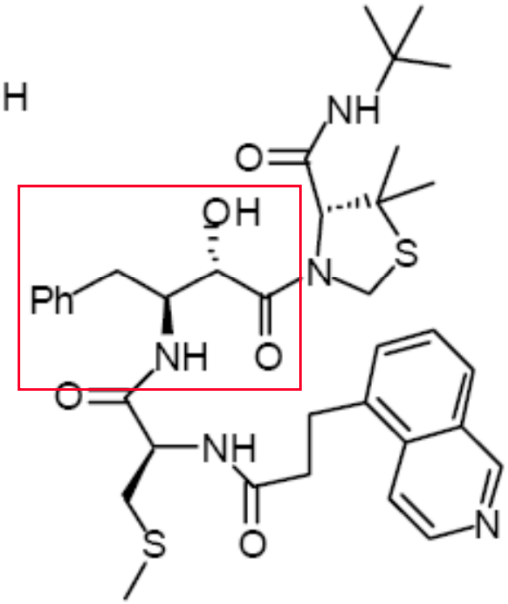
Paclitaxel
antitumor agent



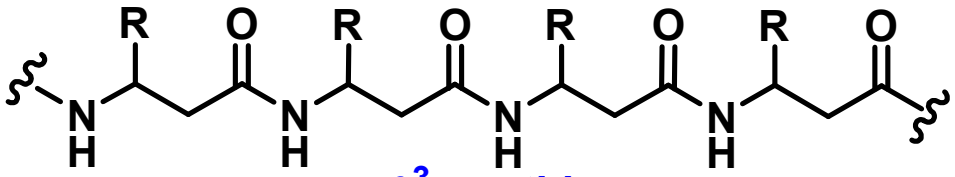
Bestatin
aminopeptidase inhibitor



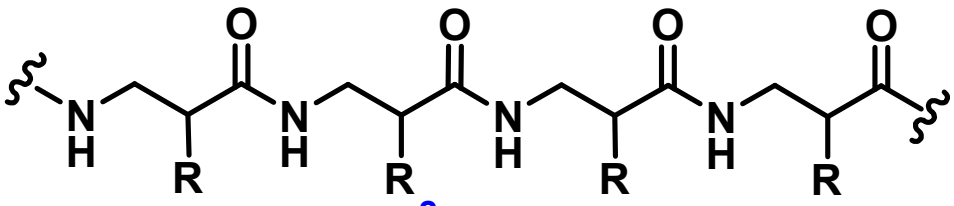
Microginin
ACE inhibitor



Kinostatin (KNI)-227
Anti-HIV agent

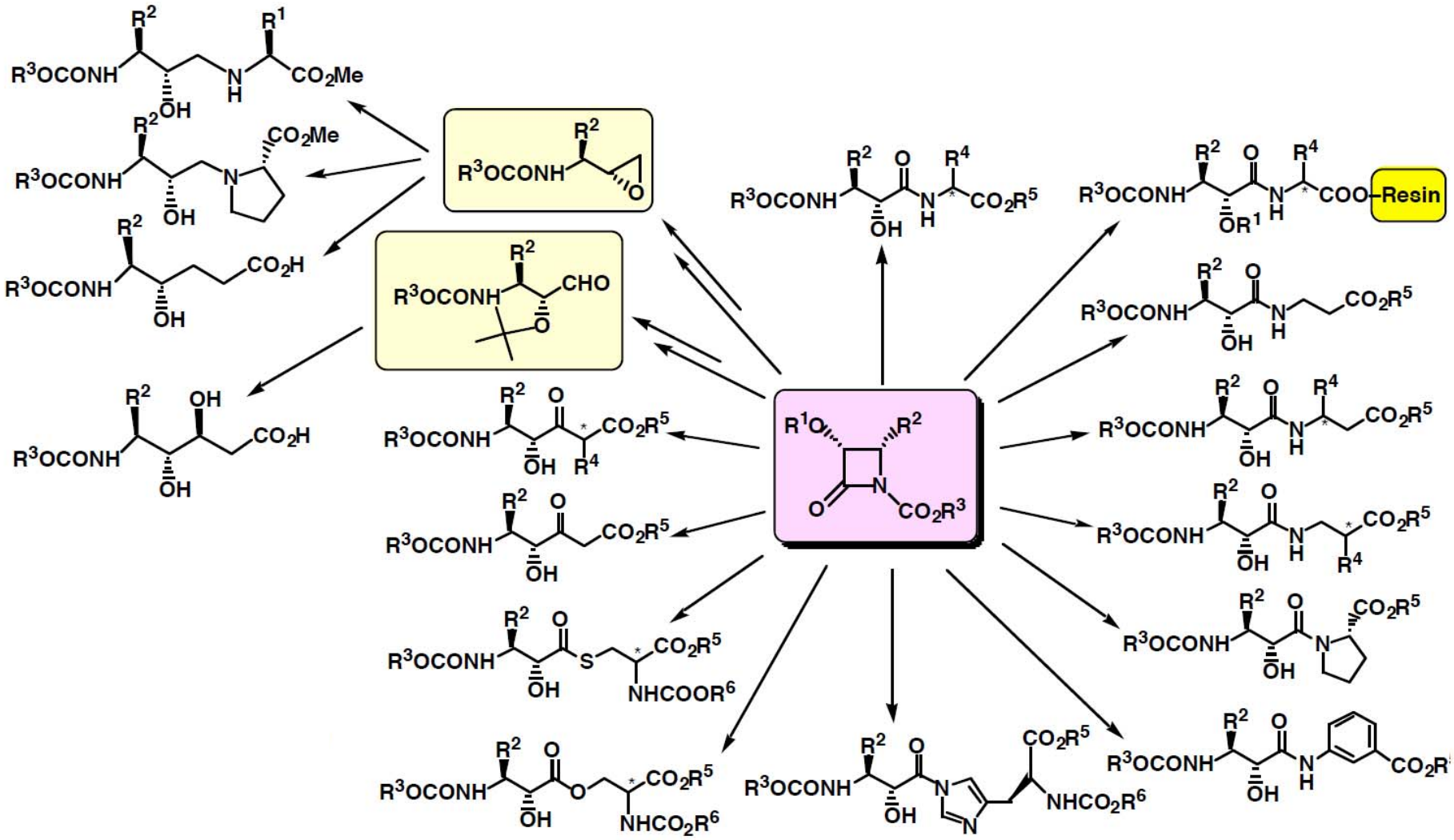


β^3-peptide



β^2-peptide

1-Carbalkoxy-3-hydroxy-4-R_f-β-lactams:
Versatile intermediates for fluoropeptides and fluoropeptidomimetics



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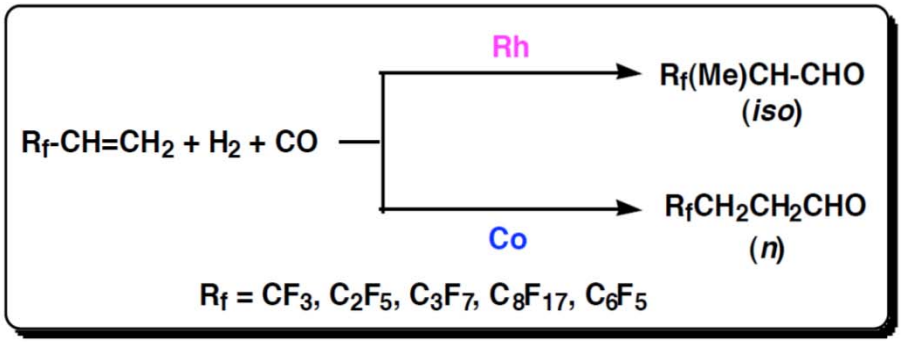
Applications of hydrocarbonylations of fluorine-olefins to the synthesis of fluoro-amino acids

Hydroformylation, Hydroesterification, Hydrocarboxylation, Amidocarbonylation



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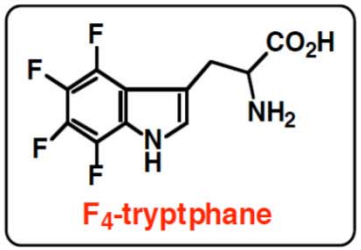
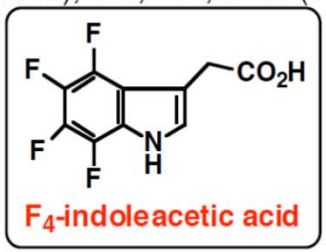
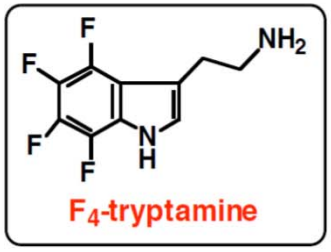
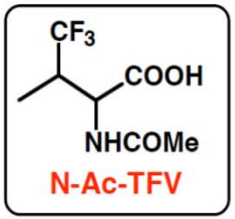
US Patent 4,370,504 (1983)

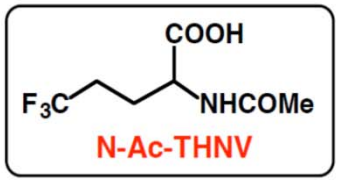


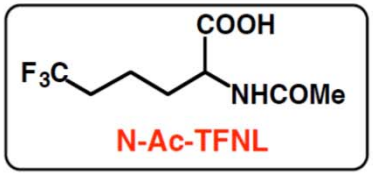


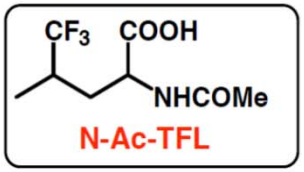


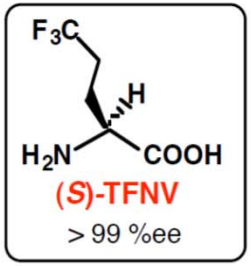
Synthesis of enantiopure fluoro-amino acids via enzymatic optical resolution

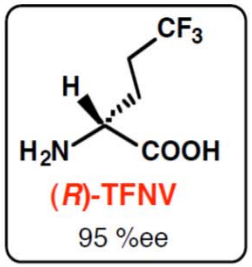


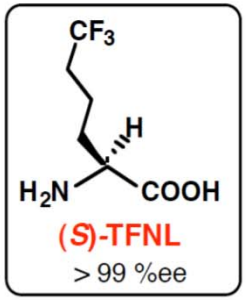


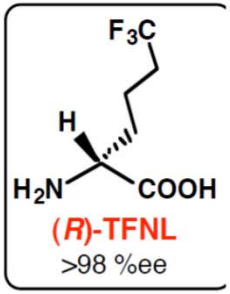












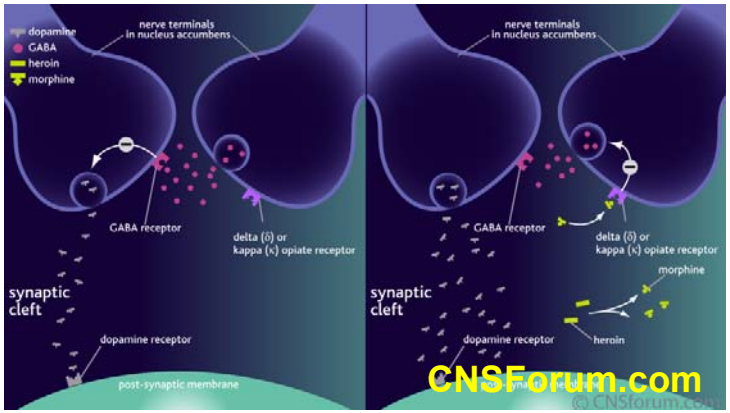
J. Org. Chem., **54**, 4511 (1989)

Enkephalins

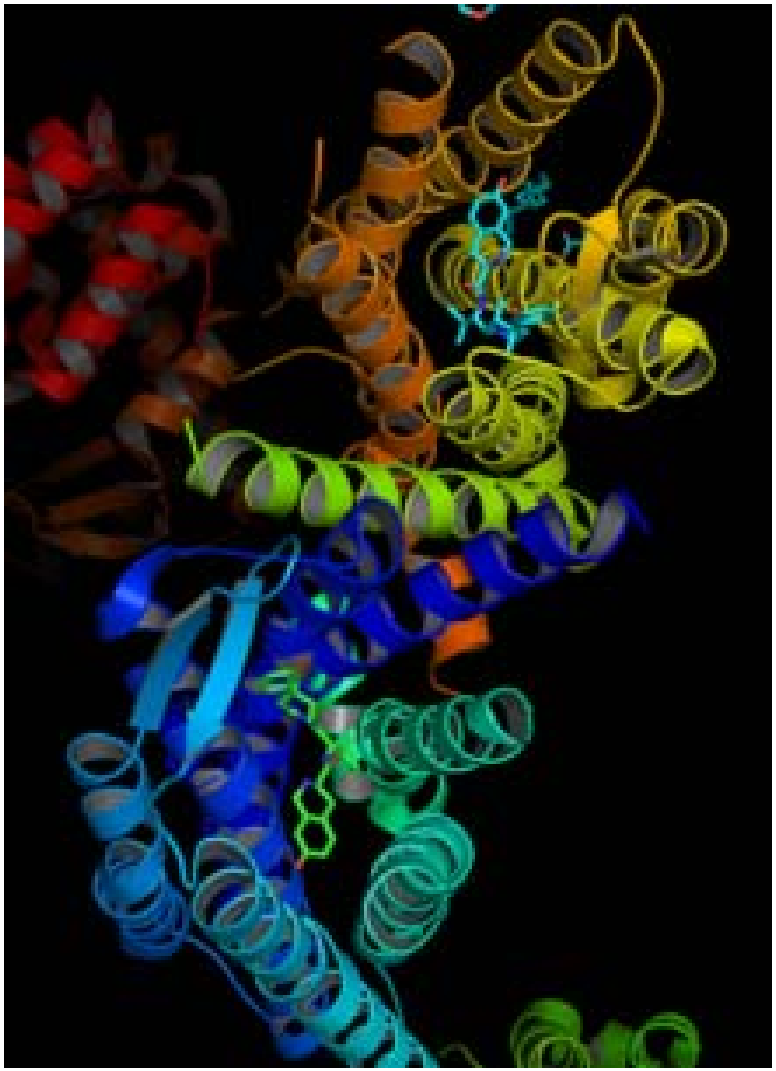
An enkephalin is involved in regulating nociception in the body. The enkephalins are termed endogenous ligands, or specifically endorphins, as they are internally derived and bind to the body's opioid receptors. Discovered in 1975, two forms of enkephalin were revealed, one containing Leu and the other containing Met. Both are products of the proenkephalin gene.

Met-enkephalin: Tyr-Gly-Gly-Phe-Met.
Leu-enkephalin: Tyr-Gly-Gly-Phe-Leu.

The receptors for enkephalin are the delta opioid receptors (GPCR family). The delta opioid receptor agonists produce analgesia, may act as antidepressant, and mimic ischemic preconditioning providing significant cardioprotection.



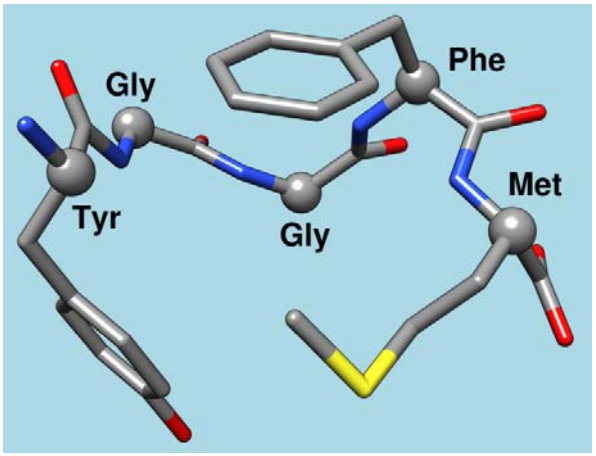
http://en.wikipedia.org/wiki/Enkephalin



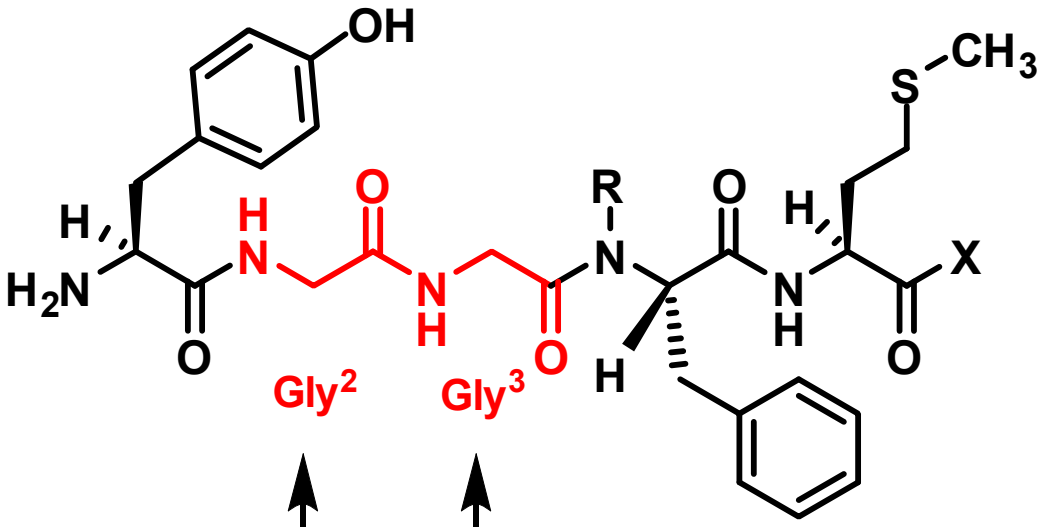
The human κ-opioid receptor (a GPCR) in complex with JDTic antagonist

http://en.wikipedia.org/wiki/G-protein-coupled_receptor

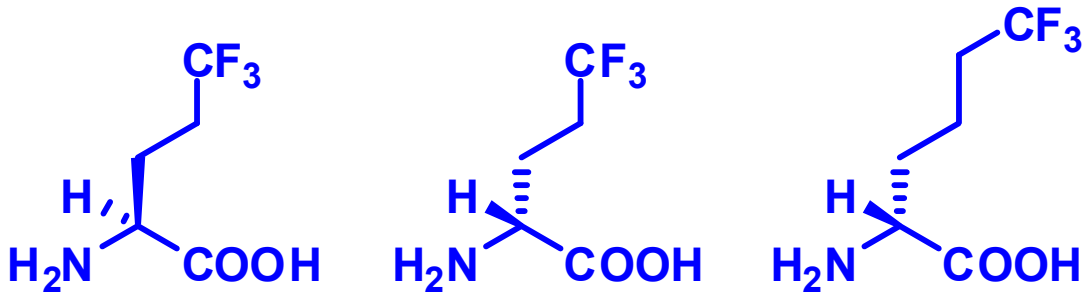
New Potent Enkephalin Analogs Containing Trifluoromethyl-Amino Acid Residues



http://en.wikipedia.org/wiki/Enkephalin



R = H, Me
X = OH, NH_2



I. Ojima and F.A. Jameison, J. D. Conway, K. Nakahashi, M. Hagiwara, T. Miyamae, and H. E. Radunz, *Bioorg. Med. Chem. Lett.*, **2**, 219-222 (1992)
I. Ojima, K. Nakahashi, *U.S. Pat.* 5,276,137 (1994)

In vivo Analgesic Activity of Fluoro-enkephalin analogs (*i.c.v.*)

Entry	Enkephalins	ED_{50} (10^{-9} mol/mouse)	
1	Methionine-Enkephalin	700	
2	(Morphine•HCl)	0.07	
3	Tyr-(D)Ala-Gly-Phe-Met-NH_2	0.05	
4	Sedapain™ (Morphine analog)	0.05	
5	Tyr-(L)TFNV-Gly-Phe-Met	120	
6	Tyr-Gly-(L)TFNV-Phe-Met	140	
7	Tyr-(L)TFNV-Gly-Phe-Met-NH_2	25	
8	Tyr-(D)TFNV-Gly-Phe-Met-NH_2	0.007	(100,000 x)
9	Tyr-(D)Nval-Gly-Phe-Met-NH_2	0.04	
10	Tyr-Gly-(L)TFNV-Phe-Met-NH_2	22	
11	Tyr-Gly-(D)TFNV-Phe-Met-NH_2	12	
12	Tyr-(D)TFNL-Gly-Phe-Met-NH_2	0.07	
13	Tyr-(D)TFNV-Gly-(N-Me)Phe-Met-NH_2	0.002	(350,000 x)

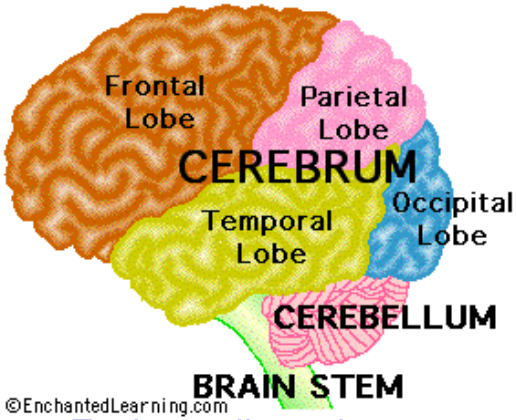
I. Ojima and F.A. Jameison, J. D. Conway, K. Nakahashi, M. Hagiwara, T. Miyamae, and H. E. Radunz, *Bioorg. Med. Chem. Lett.*, **2**, 219-222 (1992)
I. Ojima, K. Nakahashi, *U.S. Pat*. 5,276,137 (1994)

In vitro receptor-binding assay for fluoro-enkephalin analogs

Enkephalin	Receptor	Tissue	Ligand[a]	IC_{50} (nM)
[D-TFNV^2, Met^5-NH_2] enkephalin	*mu*	cerebrum[b]	[^{3}H]-PL-017	0.5
Methionine-enkephalin	*mu*	cerebrum[b]	[^{3}H]-PL-017	2
[D-TFNV^2, Met^5-NH_2] enkephalin	*delta*	cerebrum[b]	[^{3}H]-DPDPE	2
Methionine-enkephalin	*delta*	cerebrum[b]	[^{3}H]-DPDPE	1
[D-TFNV^2, Met^5-NH_2] enkephalin	*kappa*	cerebellum[c]	[^{3}H]-U-69593	400
Methionine-enkephalin	*kappa*	cerebellum[c]	[^{3}H]-U-69593	>10,000

[a] [^{3}H]-PL-017 = [^{3}H]Tyr-Pro-(N-Me)Phe-(D)Pro-NH_2; [^{3}H]-DPDPE = [^{3}H][(D)Pen^2, (D)Pen^5]enkephalin; [^{3}H]-U-69593 = [^{3}H](5á,7á,8â)-(-)-*N*-methyl-*N*-[7-(1-pyrrolidnyl)-1-oxaspiro(4,5)dec-8-yl]benzeneacetamide. [b] rat. [c] guinea pig.

- Remarkable enhancement in *in vivo* potency is not based on stronger binding to receptor sites, but mainly due to the extremely efficient inhibition of degradation/metabolism by aminopeptidases(s).
- enhancement of the rates of absorption and transport, arising from the lipophilicity of trifluoromethyl group can be taken into account.
- [D-TFNV^2, Met^5-NH_2]enkephalin crosses BBB (ED_{50}: 0.1 μM/mouse by *i.v.*; 0.2 μM/mouse by *s.c.*).



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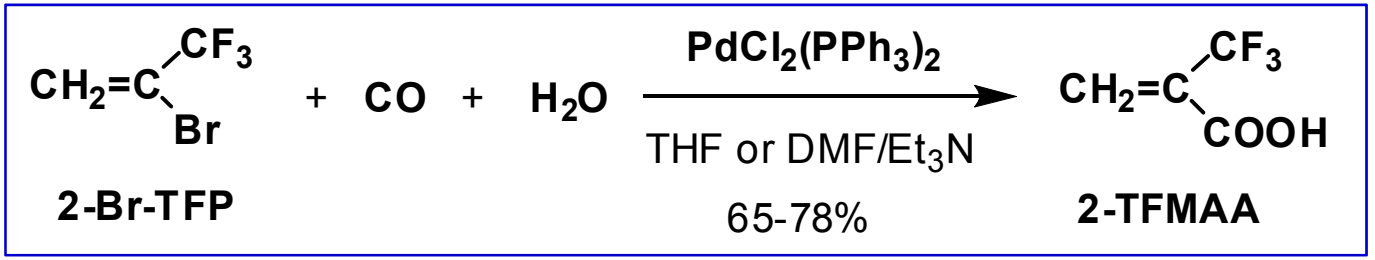
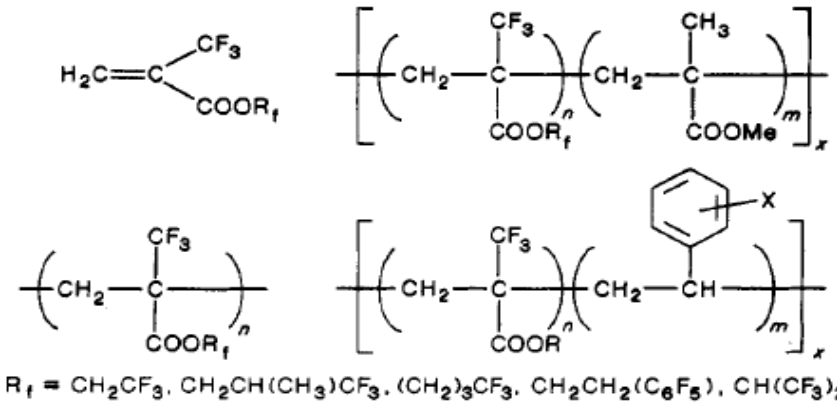
I. Ojima and F.A. Jameison, J. D. Conway, K. Nakahashi, M. Hagiwara, T. Miyamae, and H. E. Radunz, *Bioorg. Med. Chem. Lett.*, **2**, 219-222 (1992)
I. Ojima, K. Nakahashi, *U.S. Pat.* 5,276,137 (1994)

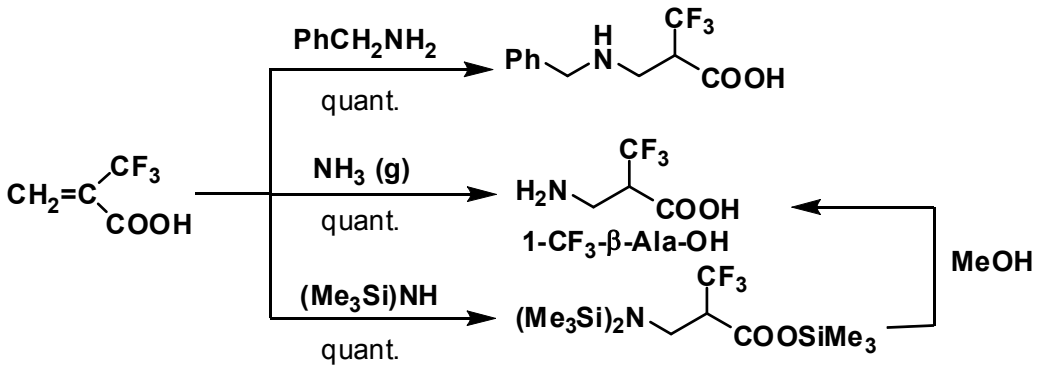
2-TFMAA: A highly versatile CF_3-building block



US Patent 4,581,452 (1985)

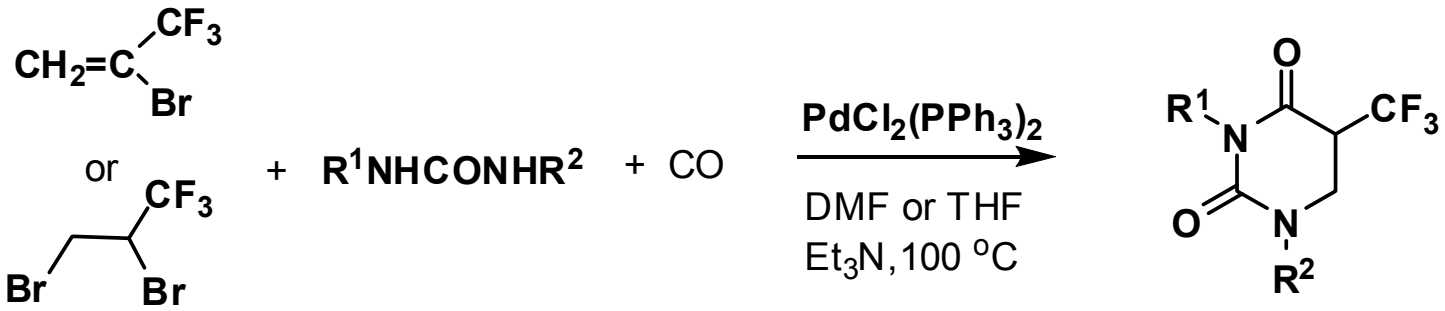


Jpn. Pat. 1676867 (1992)
Jpn. Pat. 173659 (1993)

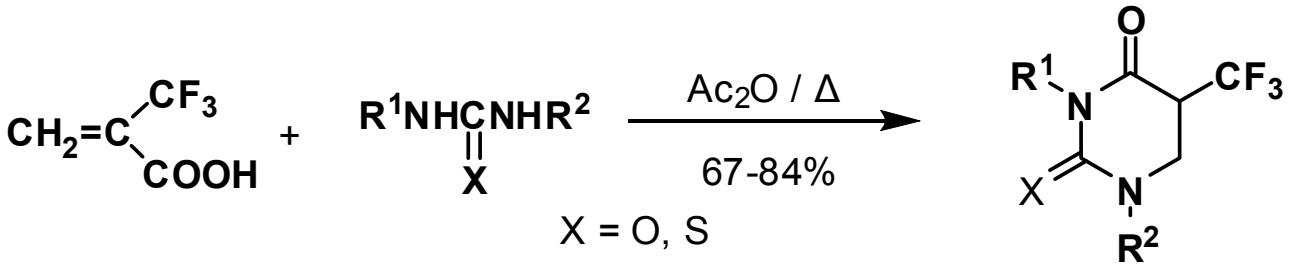


I. Ojima, *L'actualite chimique, France,* 171 (1987); I. Ojima, *Chem. Rev.*, **88**, 1011-1030 (1988)
I. Ojima, K. Kato, K. Nakahashi, T. Fuchikami, and M. Fujita, *J. Org. Chem.*, **54**, 4511 (1989)

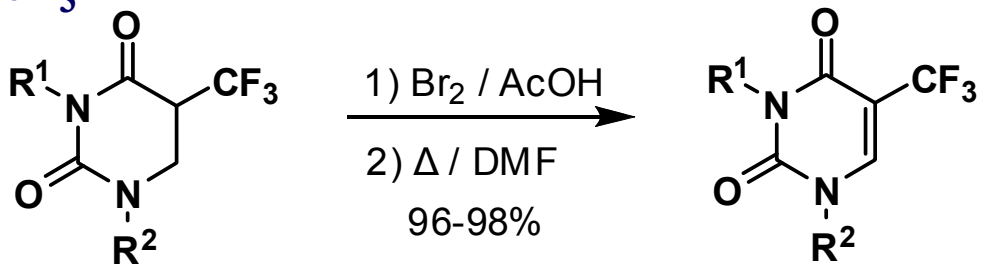
Pd-Catalyzed Ureidocarbonylation of 2-Br-TFP



Synthesis of 5,6-dihydrothymine-f_3 via cyclocondensation of 2-Br-TFP with urea and thioureas

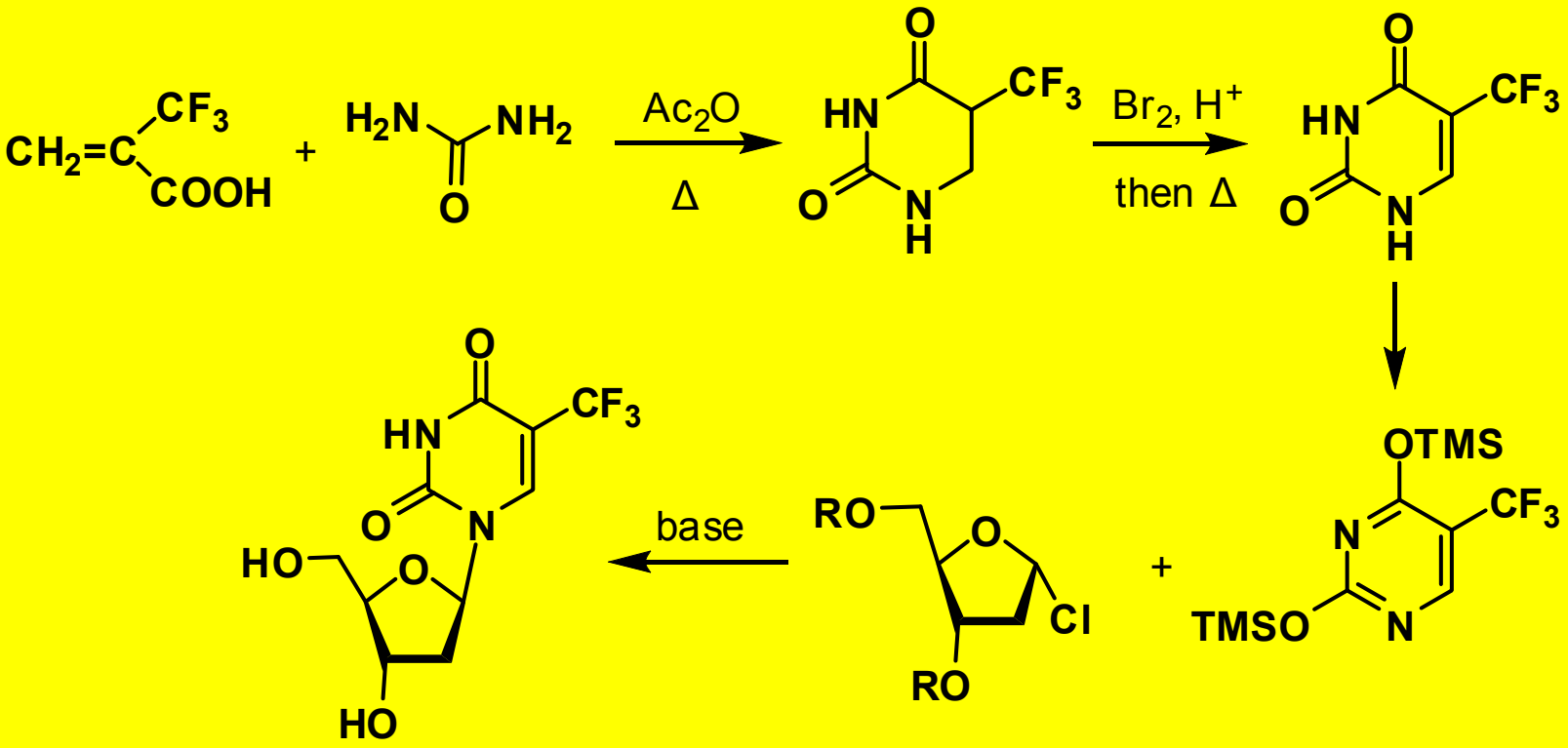


Preparation of thymine-f_3



T. Fuchikami and I. Ojima, *Tetrahedron Lett.*, **23**, 4099 (l982)
T. Fuchikami, A. Yamanouchi and I. Ojima, *Synthesis*, 766 (l984)
I. Ojima, T. Fuchikami, M. Fujita, *U.S. Pat.* 4581452 (1986)
I. Ojima, *Chem. Rev.*, **88**, 1011-1030 (1988)

Commercial Application to Trifluridine (*Viroptic*)

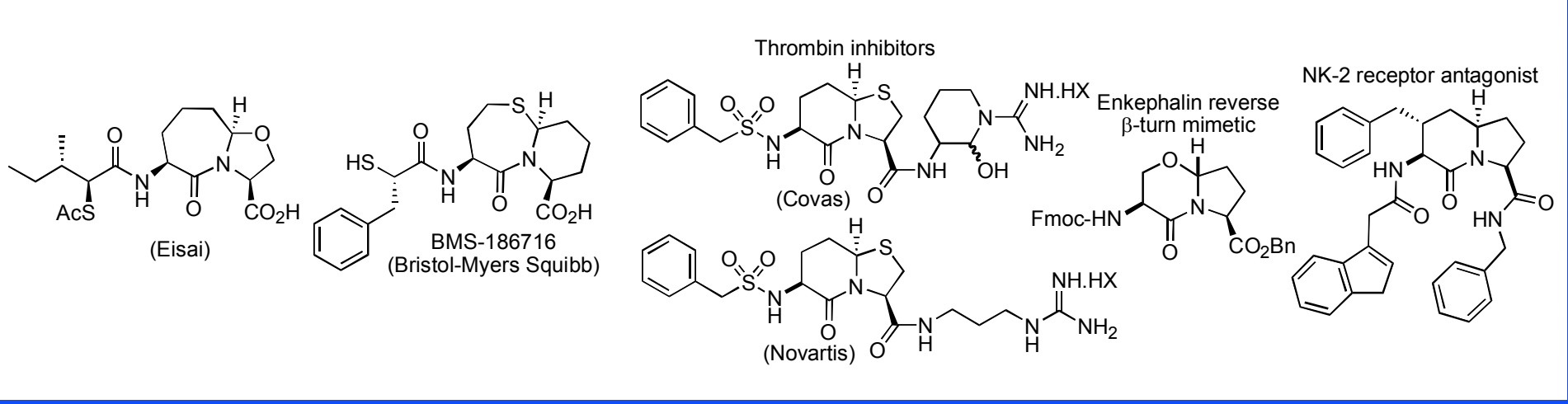


an anti-herpesvirus antiviral drug, used primarily on the eye

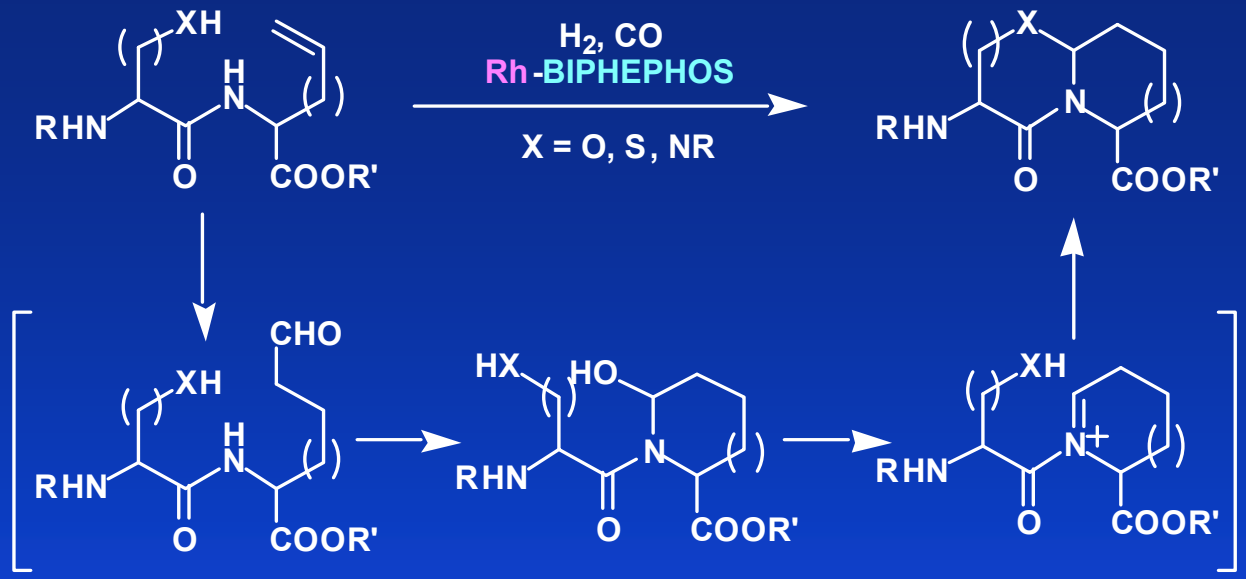
T. Fuchikami, A. Yamanouchi and I. Ojima, *Synthesis*, 766 (l984)

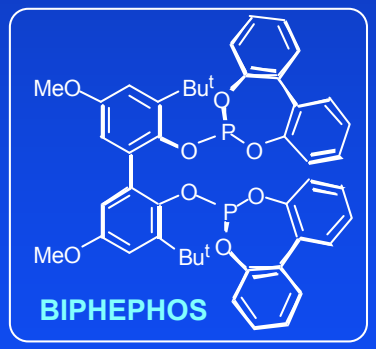
I. Ojima, T. Fuchikami, M. Fujita, *U.S. Pat.* 4581452 (1986)

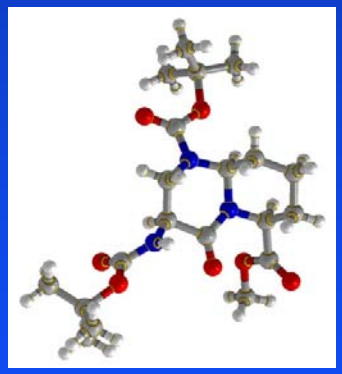
1-Azabicyclo[x.y.0]alkane amino acids and their congeners

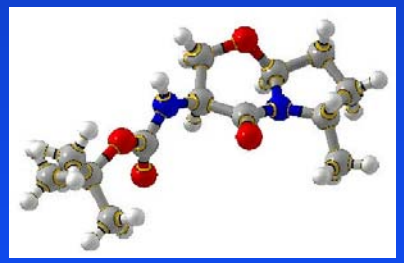


Cyclohydrocarbonylation (CHC) Approach



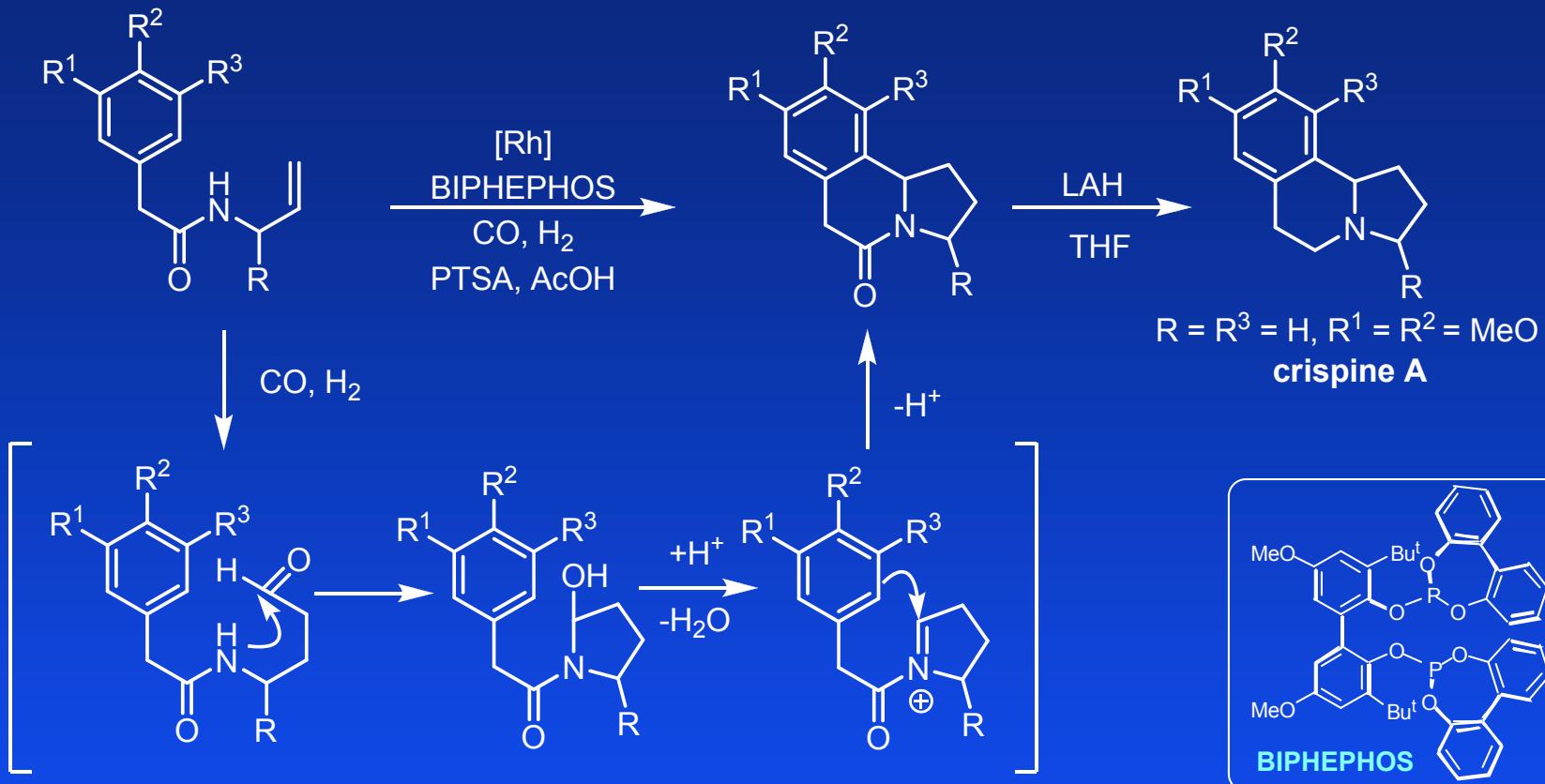


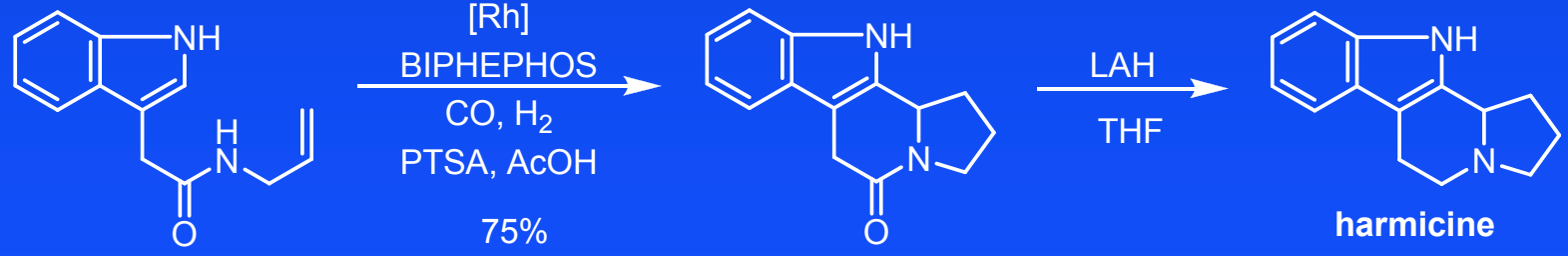




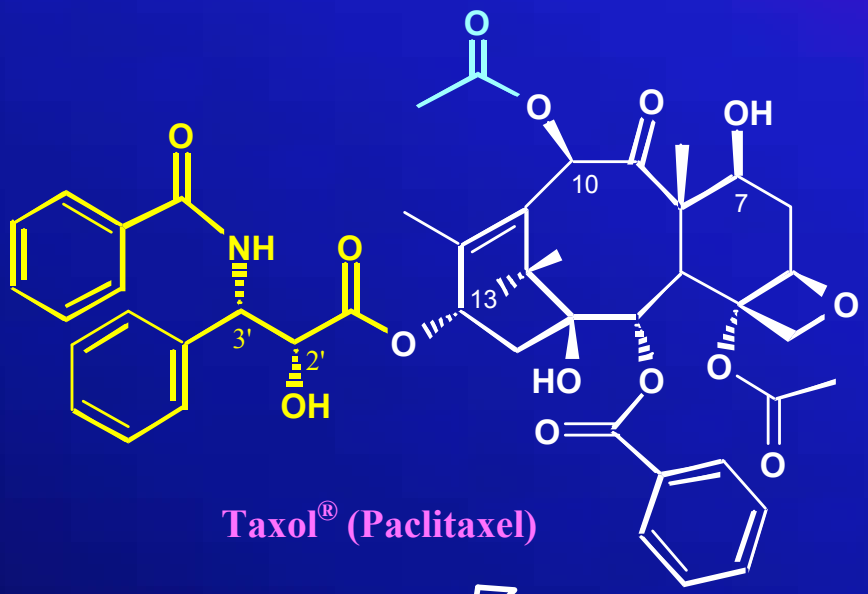
Ojima, M. Tzamarioudaki, M. Eguchi, *J. Org. Chem*. **1995**, *60*, 7078.
I. Ojima, D. M. Iula, M. Tzamarioudaki, *Tetrahedron Lett*., **1998**, *39*, 4599.
I. Ojima and E. S. Vidal, *J. Org. Chem.* **1998**, *63*, 7999.
N. Mizutani, W.-H. Chiou, I. Ojima, *Org. Lett*., **2002**, *4*, 4575.
W. H. Chiou, S.-Y. Lee, I. Ojima, *Can. J. Chem*. **2005**, *83*, 681.
W. H. Chiou, N. Mizutani, I. Ojima, *J. Org. Chem*. **2007**, *72*, 1871.
W.-H. Chiou, A. Schoenfelder, A. Mann, L. Sun, I. Ojima, *J. Org. Chem*. **2007**, *72*, 9418.

Cyclohydrocarbonylation (CHC) Approach (2)

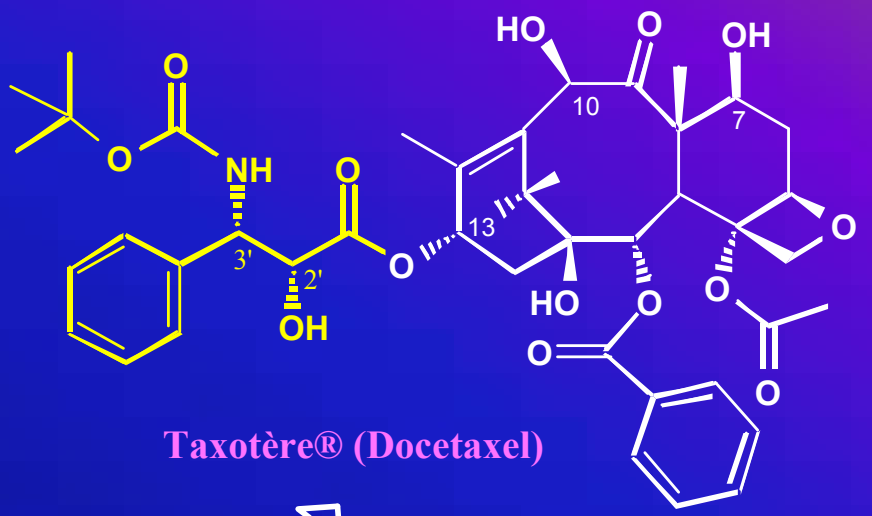




W.-H. Chiou, C.-C. Hsu, G.-H. Lin, S. J. Chaterpaul, and I. Ojima, *Org. Lett*. **11**, 2659-2662 (2009).

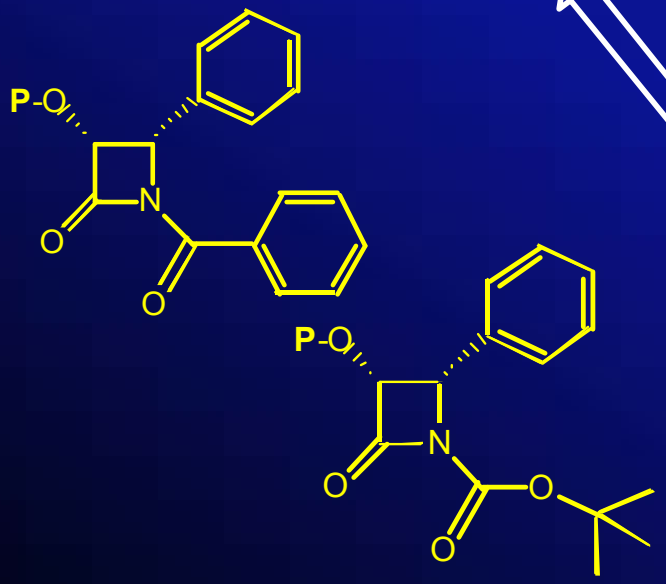


Taxol® (Paclitaxel)



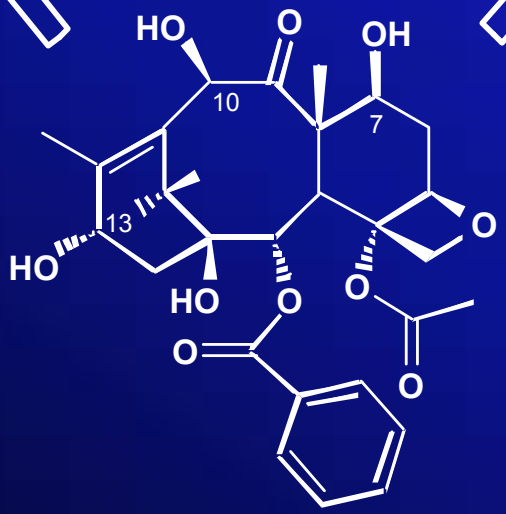
Taxotère® (Docetaxel)

Ojima-Holton Coupling



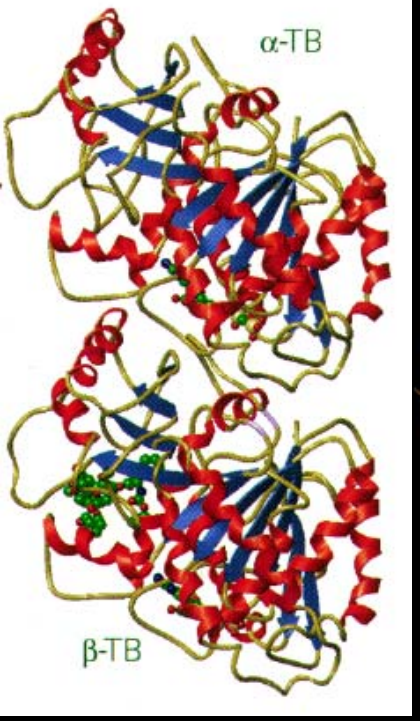
"Ojima Lactam"

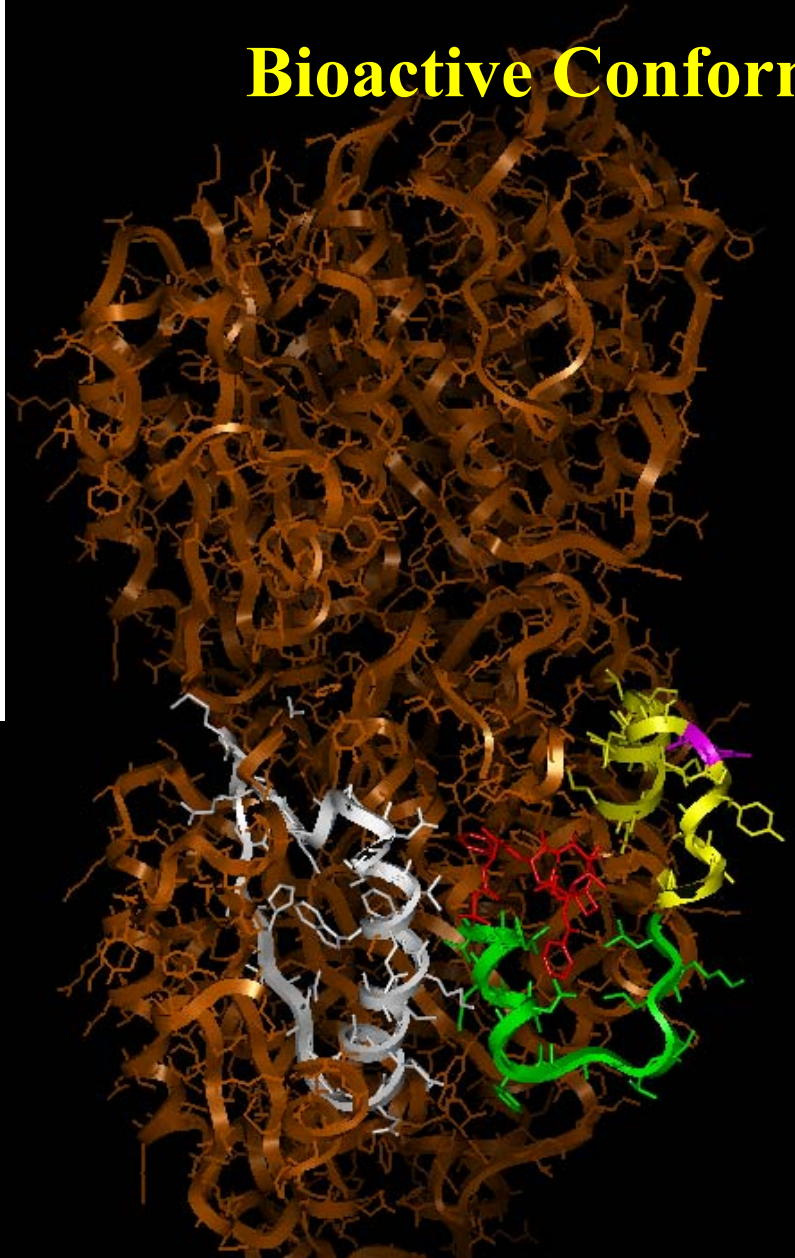
http://en.wikipedia.org/wiki/Ojima_lactam

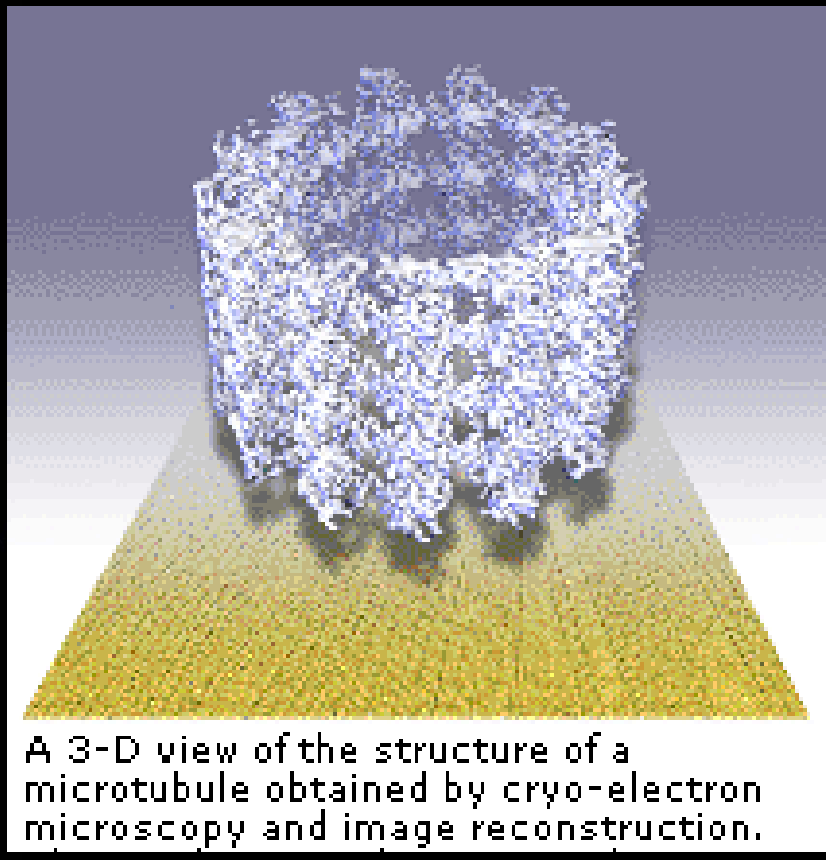


10-Deacetylbaccatin III (DAB)

Bioactive Conformation of Paclitaxel







A 3-D view of the structure of a microtubule obtained by cryo-electron microscopy and image reconstruction.

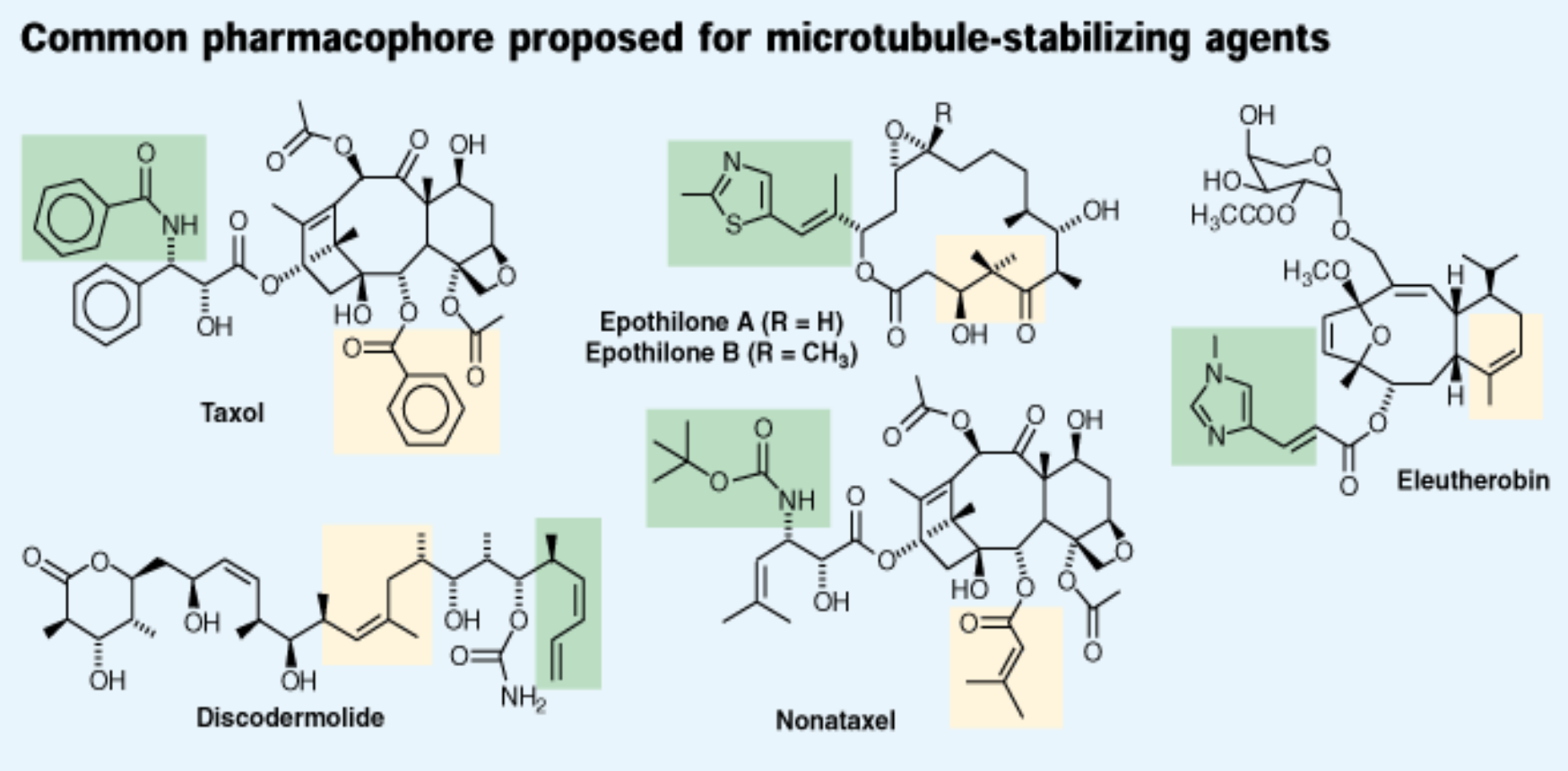
Nogales, E., Wolf, S. G., and Downing, K. H. *Nature* **391**, 199-203 (1998).
Rao, S., He, L., Chakravarty, S., Ojima, I., Orr, G. A., Horwitz, S. B. *J. Biol. Chem*., 274, 37990-37994 (1999).

C&EN
CHEMICAL & ENGINEERING NEWS

Taxol And Friends Have Something In Common

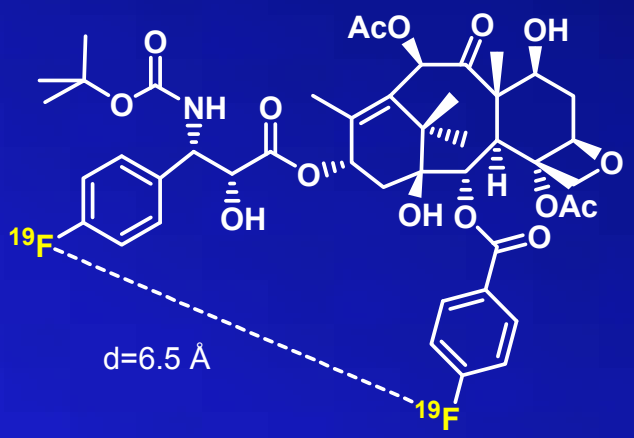
Researchers propose a structural basis for the anticancer activity of compounds that stabilize cell microtubules

Stu Borman

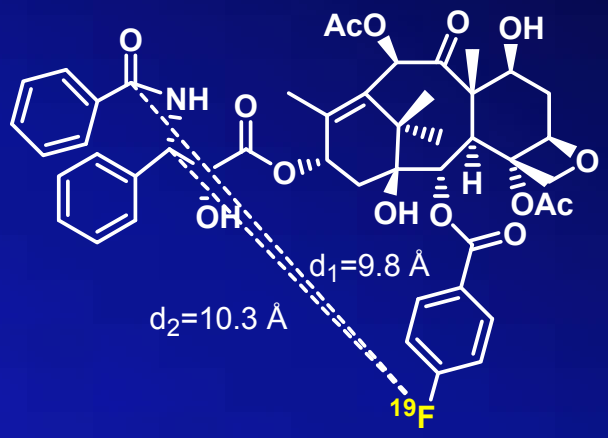


Ojima and coworkers propose that two corresponding structural regions (areas colored green and beige) in each of four classes of agents--Taxol, the epothilones,eleuthe-robin, and discodermolide--account for most of the compounds' antitumor activity. The researchers used nonatax [Adapted from *PNAS,* copyright 1999]

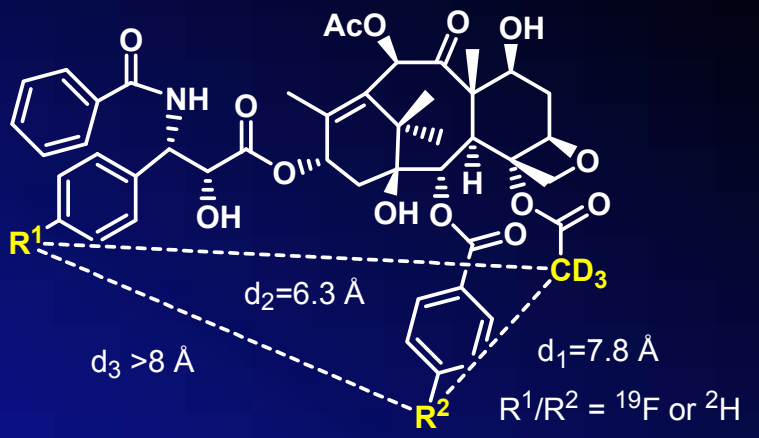
Solid State NMR Studies on F-Labeled Taxane – Microtubule Complexes



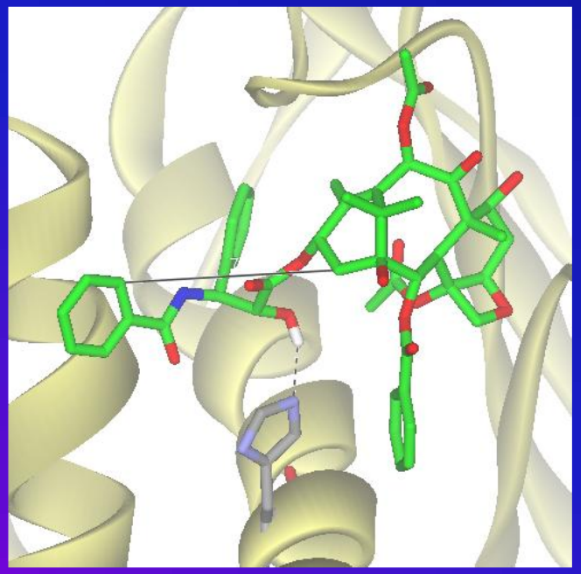
RFDR
(Radio Frequency Driven Recoupling)
Adv. Med. Chem., **4**, 69-124 (1999)



REDOR (^{19}F-^{13}C)
(Rotational Echo Double Resonance)
Biochemistry, ***39***, 281 (2000)
J. Am. Chem. Soc. 129, 361-370 (2007)



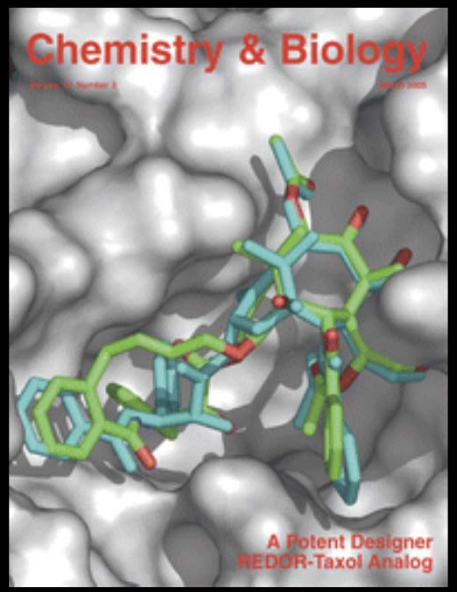
REDOR (^{19}F-^{2}H)

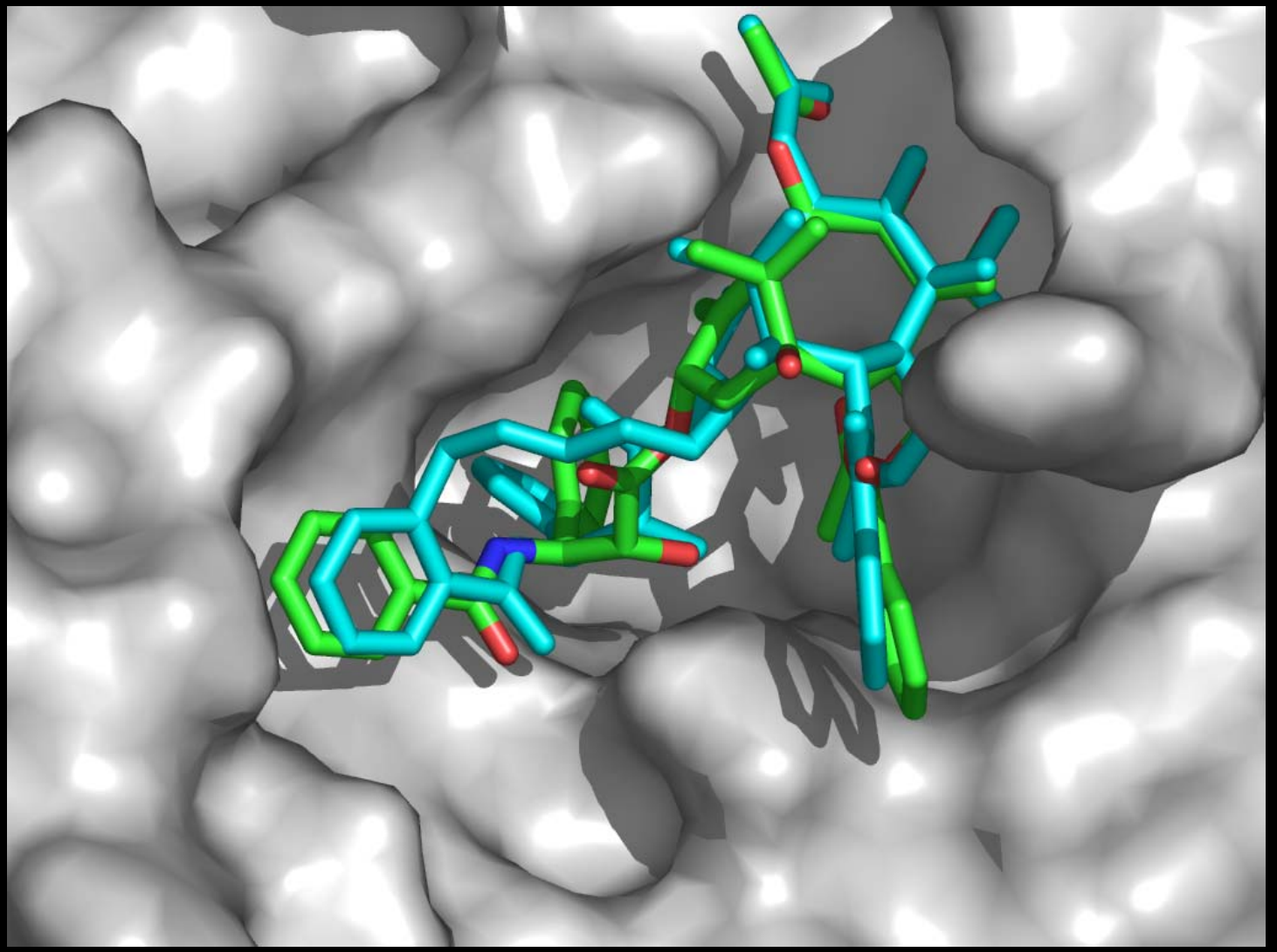


REDOR-Taxol-1JFF
(For clarity, only heavy atoms, C2'OH of REDOR-Taxol and His229 are shown.)

L. Sun, I. Ojima *et al. J. Org. Chem*. **73**, 9584–9593 (2008)
L. Sun, C. Simmerling and I. Ojima, *ChemMedChem.*, **4**, 719-731 (2009)

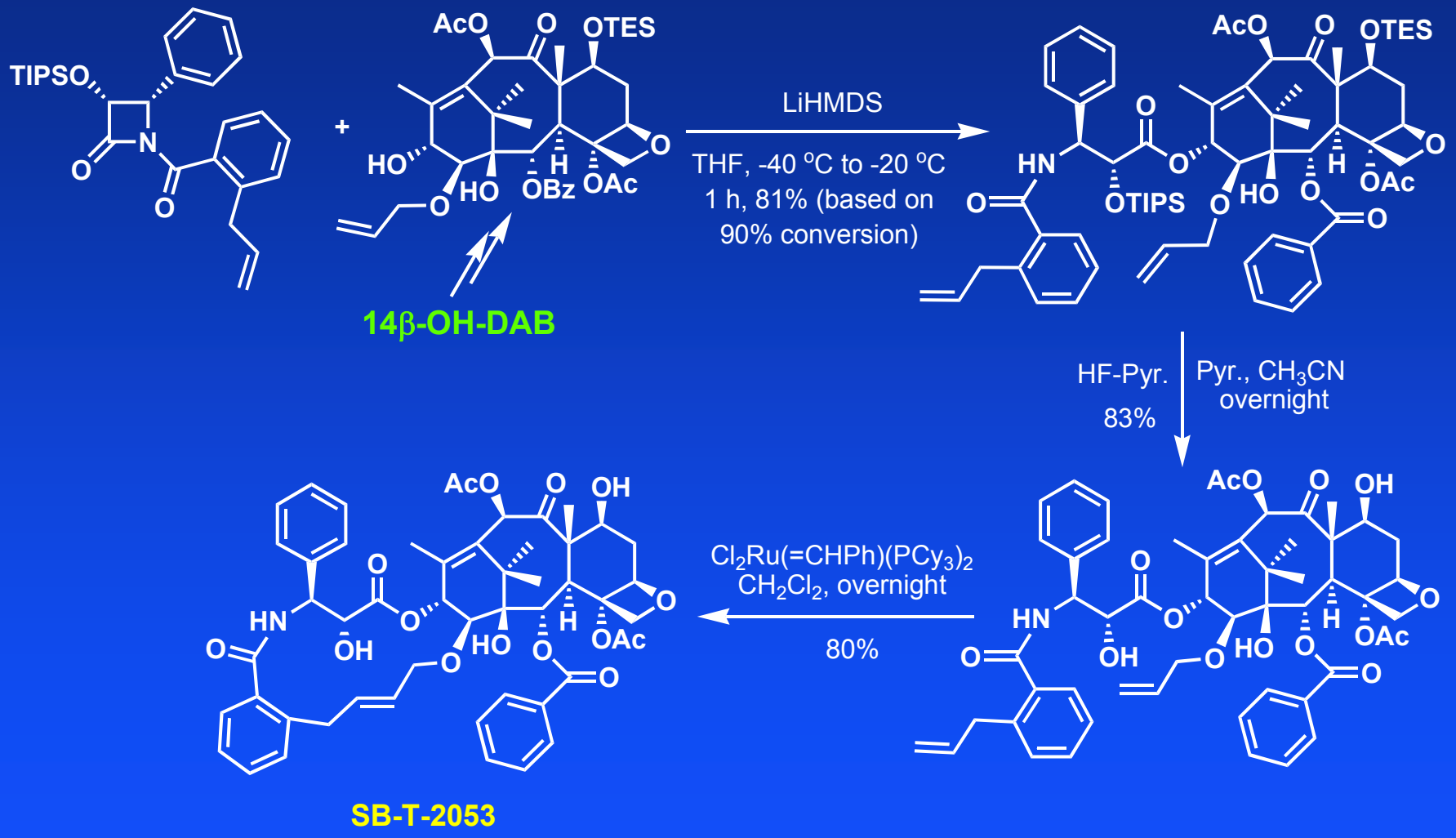
REDOR-Taxol: Crucial Bioactive Conformation





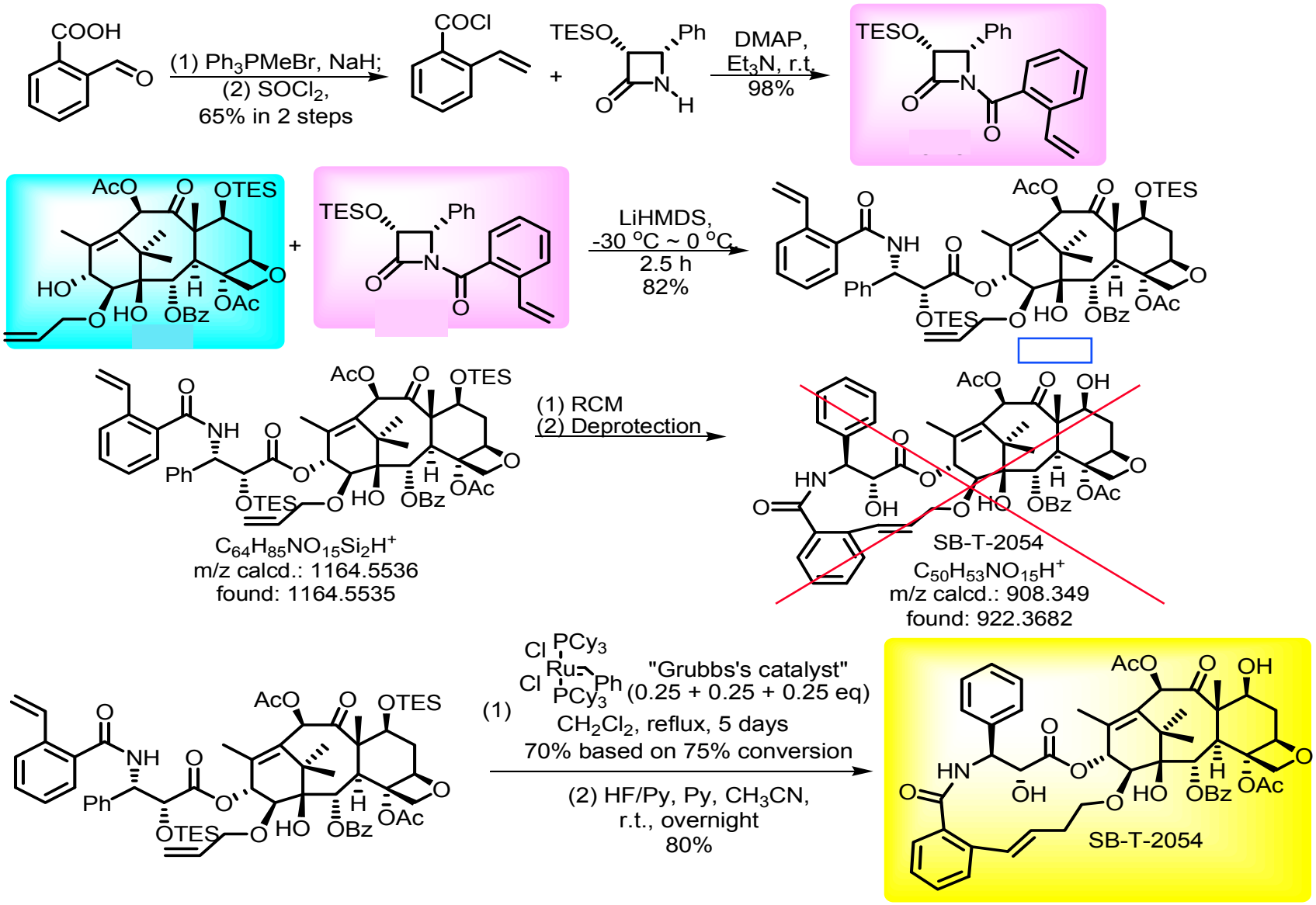
R. Geney, L. Sun, P. Pera, R. J. Bernacki, S. Xia, S. B. Horwitz, C. L. Simmerling, and I. Ojima, *Chem. & Biol*. **2005**, *12*, 339-348

Synthesis of Conformationally Restricted Taxoid Mimicking Tubulin-Bound Paclitaxel Coformation



R. Geney, L. Sun, P. Pera, R. J. Bernacki, S. Xia, S. B. Horwitz, C. L. Simmerling, and I. Ojima*, *Chem. & Biol.* **2005**, *12,* 339-348

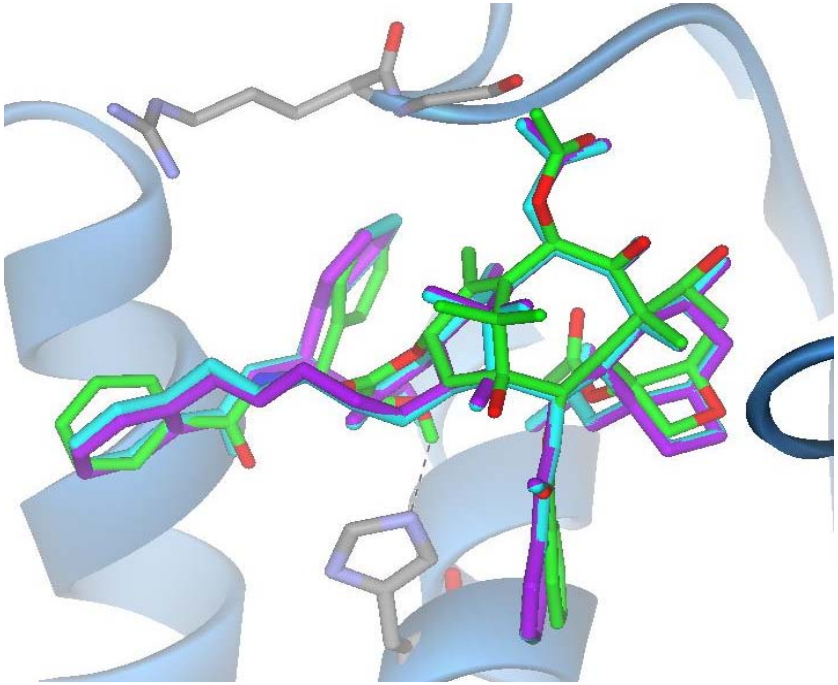
Synthesis of SB-T-2054



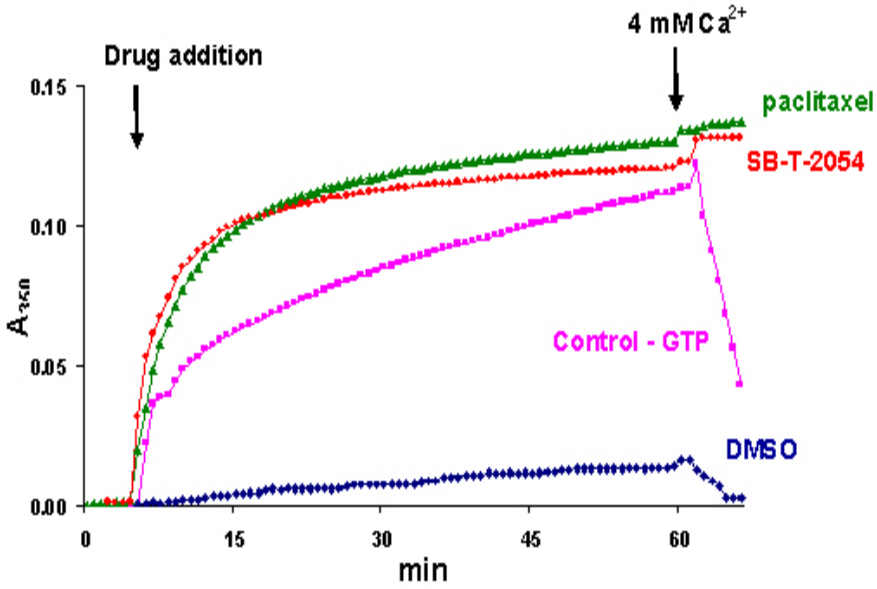
L. Sun, X. Geng, R. Geney, Y. Li, Z. Li, J. W. Lauher,S. Xia, S. B. Horwitz, J.M. Veith, P. Pera, R. J. Bernacki, I. Ojima, *J. Org. Chem*. **73** (2008) in press [A. I. Meyers Memorial Issue].

Biological evaluation of C14-C3'N linked macrocyclic taxoids

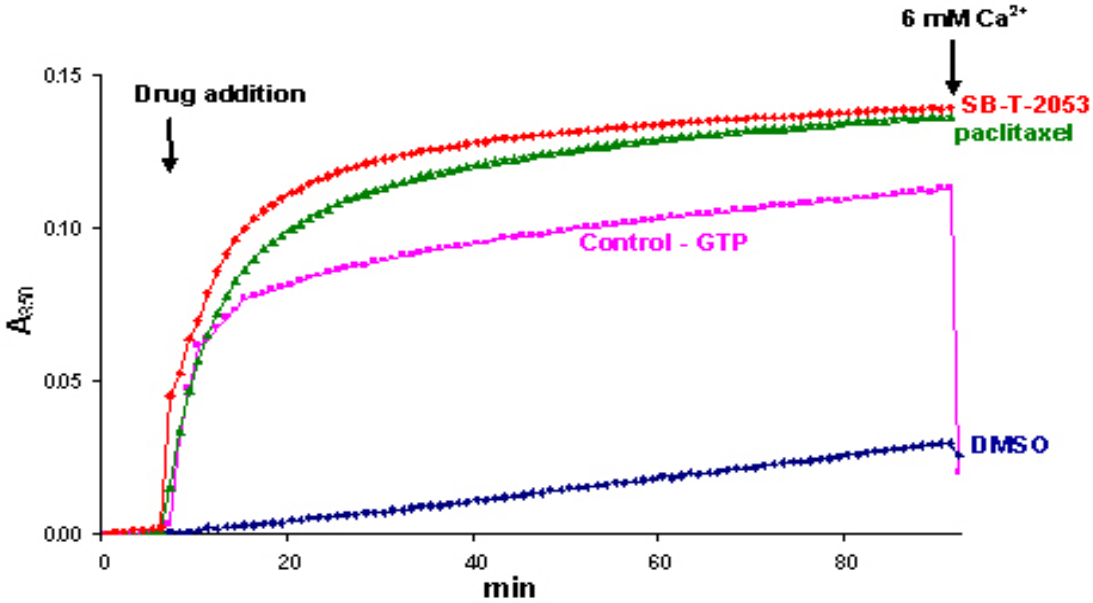
Compound	IC50 nM (±S.E.)[a] MCF7[b]	NCI/ADR[c]
Paclitaxel	3.0 ±0.3	518 ±71
SB-T-2053	42 ±2.3	1066 ±59
SB-T-2054	5.96 ± 0.83	240±68



Overlay of SB-T-2054 (magenta), SB-T-2053 (cyan) and REDOR-Taxol (green)

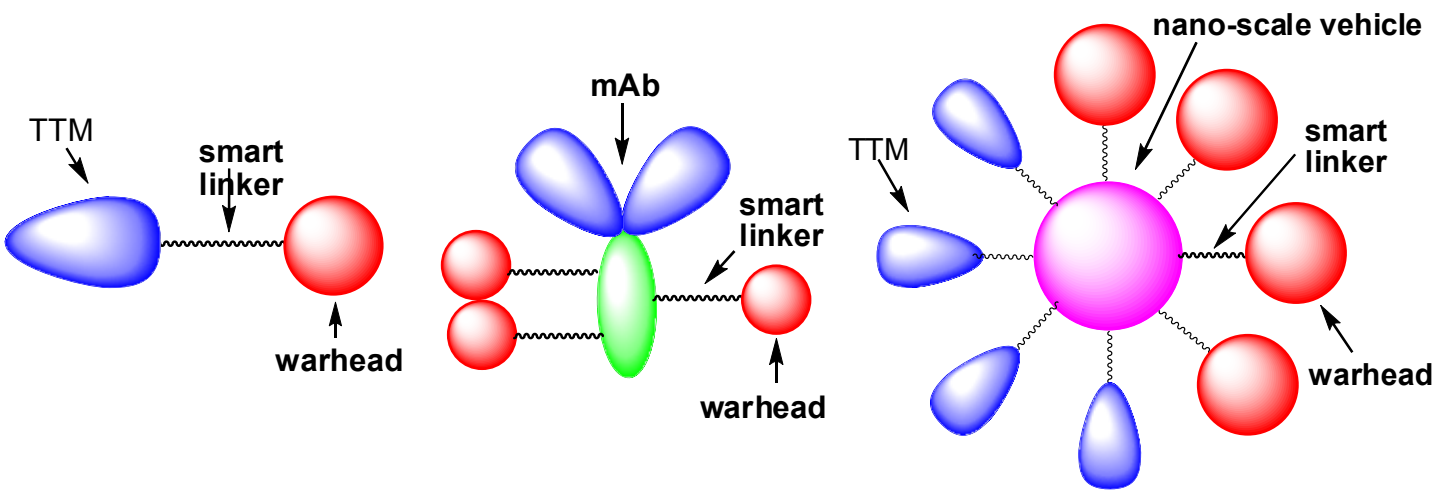


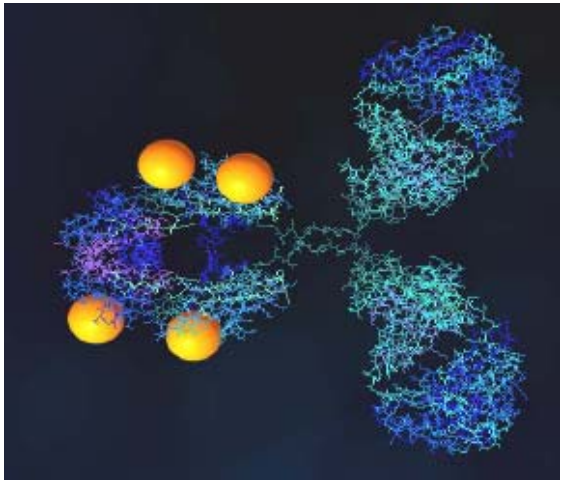
Liang Sun



J. Org. Chem. **73** (2008) in press. [A. I. Meyers Memorial Issue]

"Guided Molecular Missiles"
for Tumor-Targeting Drug Delivery





⇨ **Taxoid–Omega-3 Polyunsaturated Fatty Acid Conjugates**

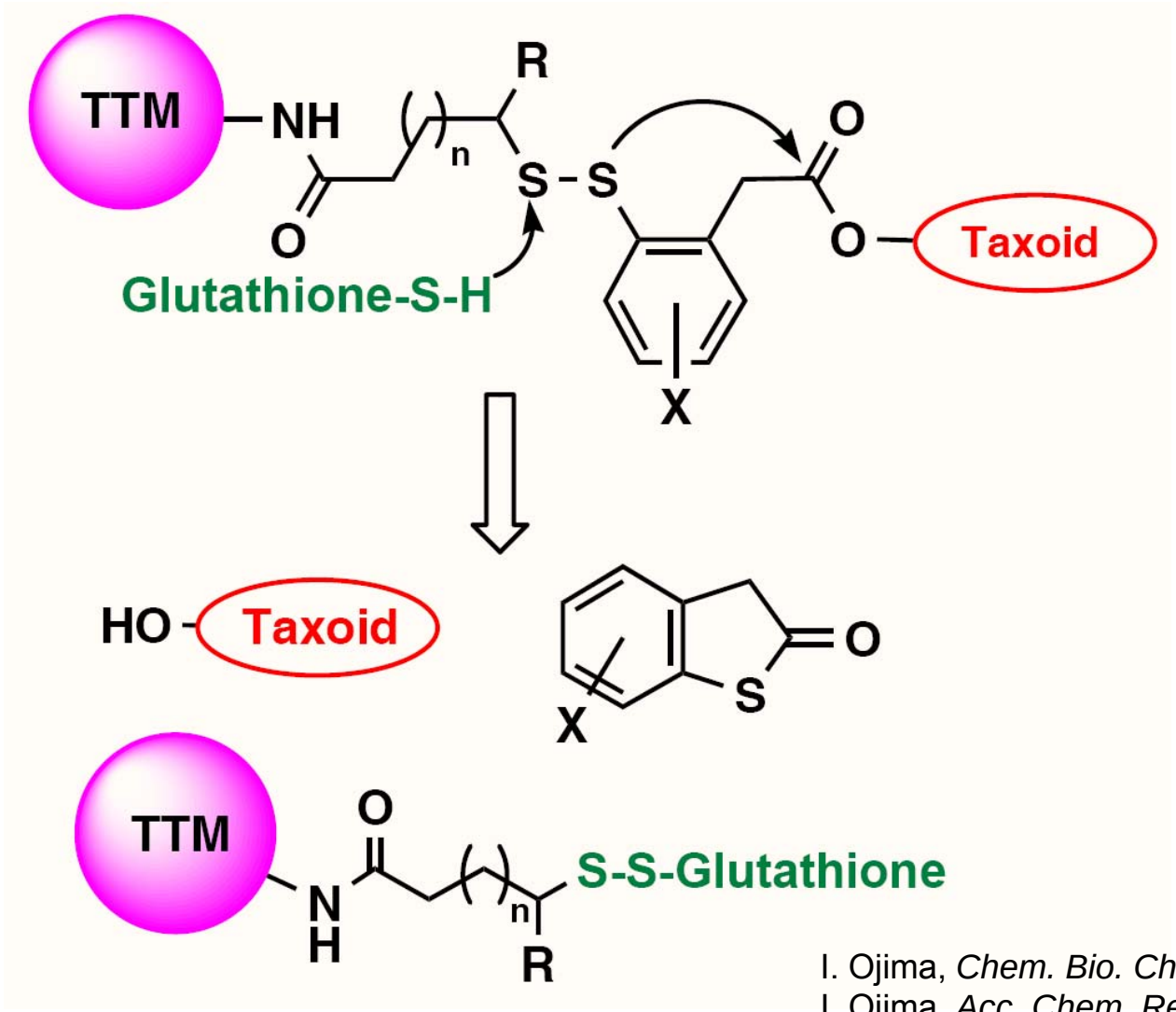
⇨ **Taxoid–Monoclonal Antibody Immunoconjugates**

⇨ **Taxoid–Vitamin Conjugates**

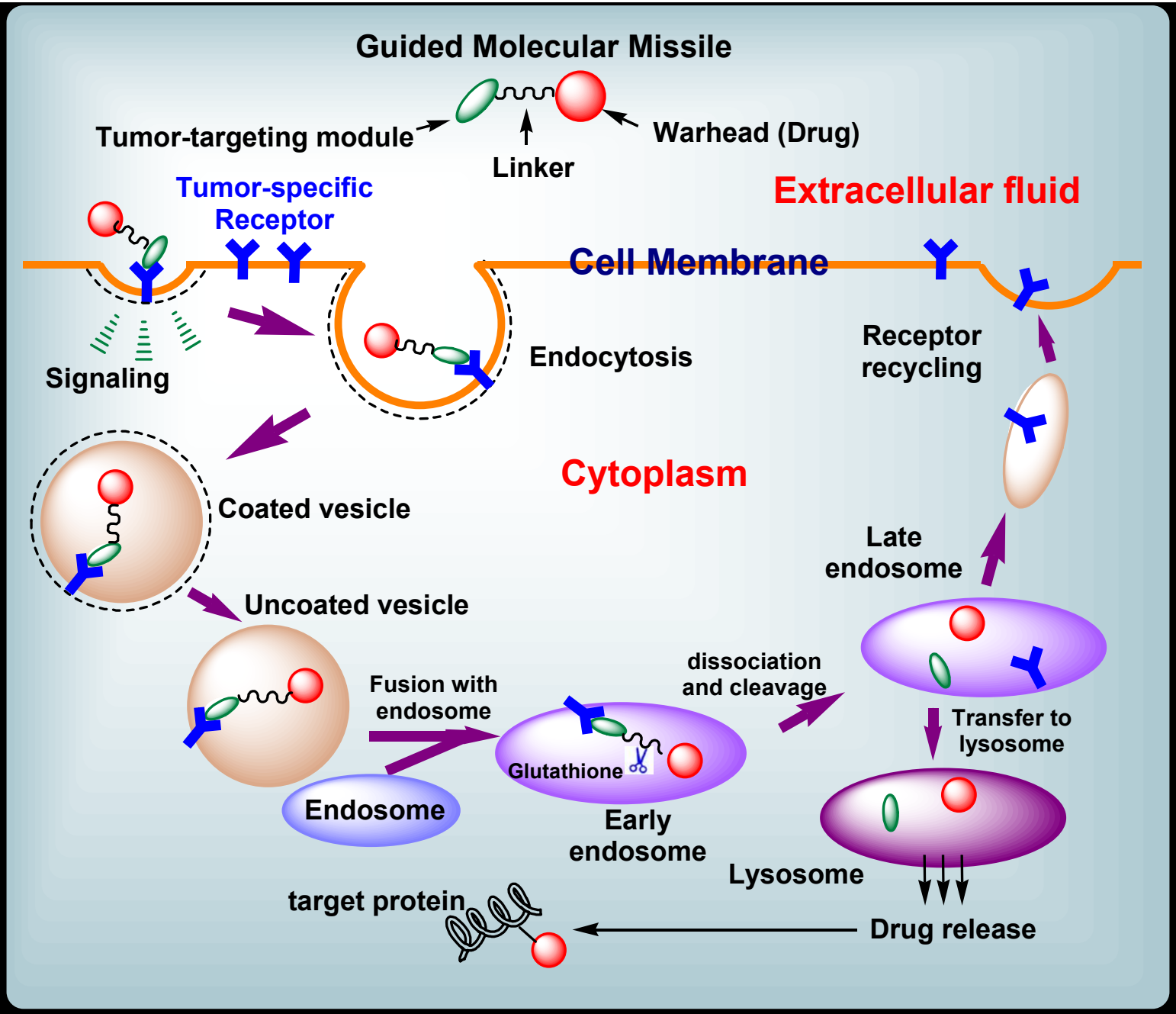
⇨ **Taxoid–Vitamin SWNT/Dendrimer Nano-Conjugates**

"*Guided Molecular Missiles for Tumor-Targeting Chemotherapy*", I. Ojima, *Acc. Chem. Res.* **41**, 108-119 (2008).
"*Functionalized Single-walled Carbon Nanotubes as Rationally Designed Vehicles for Tumor-Targeted Drug Delivery*", J. Chen, S. Chen, X. Zhao, L. V. Kuznetsova, S. S. Wong and I. Ojima, *J. Am. Chem. Soc*., **130**, 16778-16785 (2008).
"Mechanism-Based Tumor-Targeting Drug Delivery System. Validation of Efficient Vitamin Receptor-Mediated Endocytosis and Drug Release"S.Chen, X. Zhao. J. Chen, J. Chen, L. Kuznetsova, S. S. Wong, I. Ojima, *Bioconjugate Chem*. **21,** 979-987 (2010).
"Tumor-Targeting Drug Delivery of Chemotherapeutic Agents", I. Ojima, *Pure & Appl. Chem*. 83, 1685-1698 (2011).
"Tumor-targeting drug delivery of new generation taxoids", I. Ojima, E. S. Zuniga, W. T. Berger, and J. D. Seitz, *Future Med. Chem*., 4, 33-50 (2012).

New Self-Immolative Linkers for Taxoid Conjugates

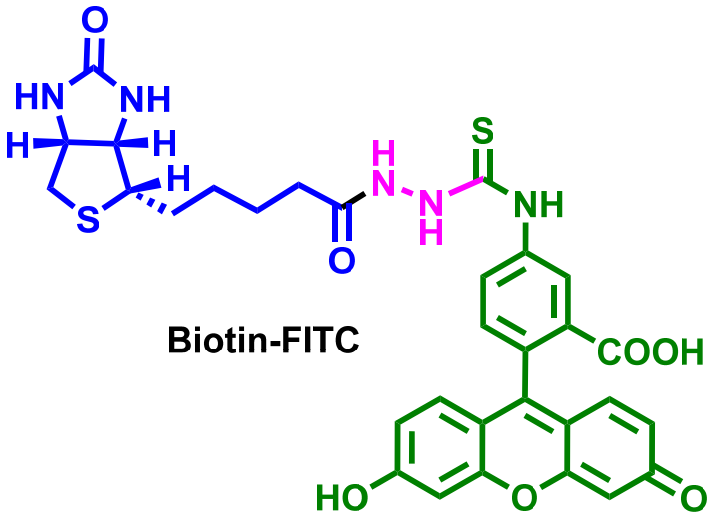


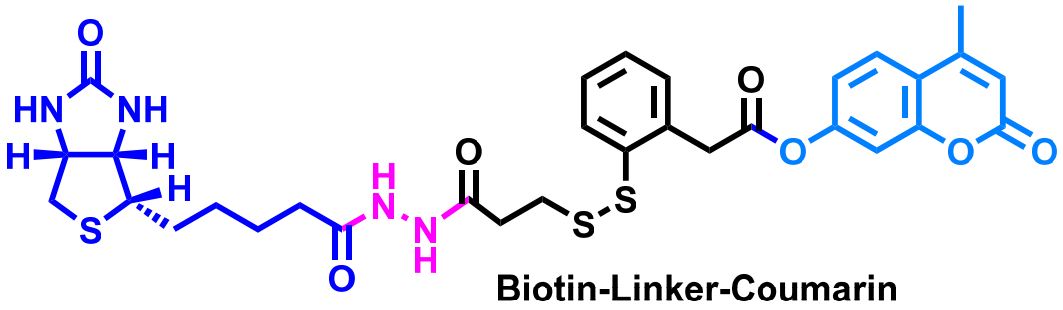
I. Ojima, *Chem. Bio. Chem.* **5**, 628-635 (2004).
I. Ojima, *Acc. Chem. Res.* **41**, 108-119 (2008).
US Patent 7282590 (2007), 7847119 (2010)

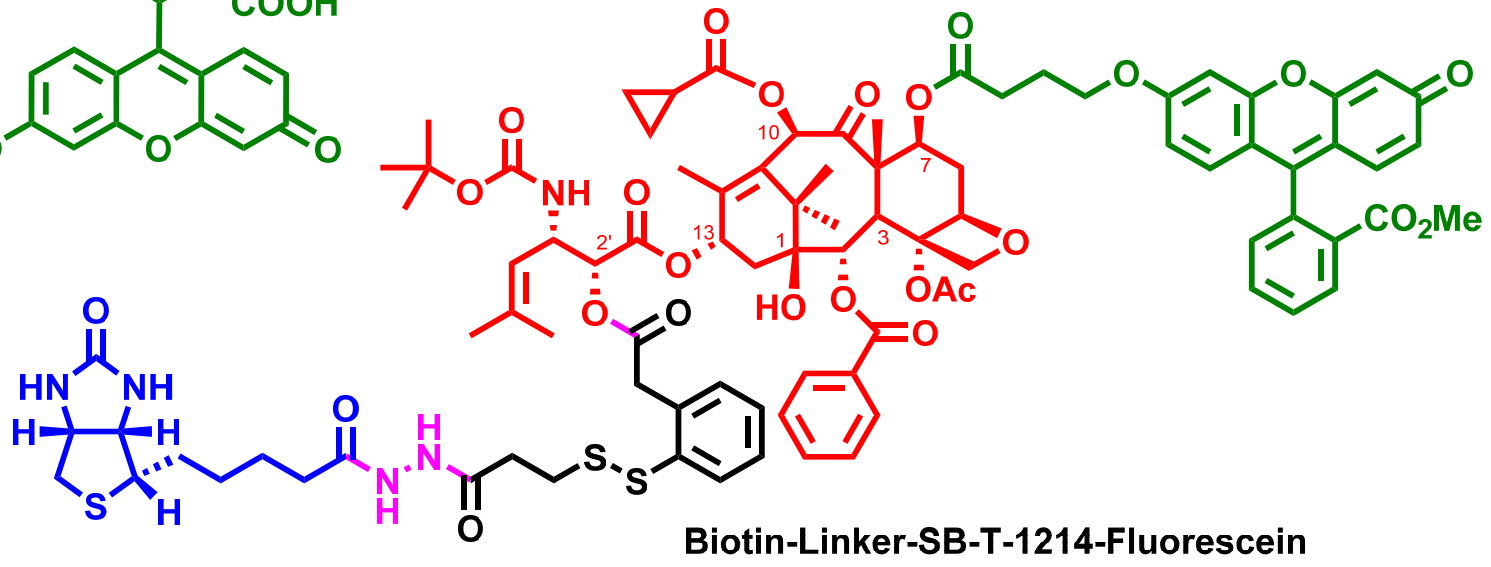


"Guided Molecular Missiles for Tumor-Targeting Chemotherapy", I. Ojima, *Acc. Chem. Res.* 41, 108-119 (2008).

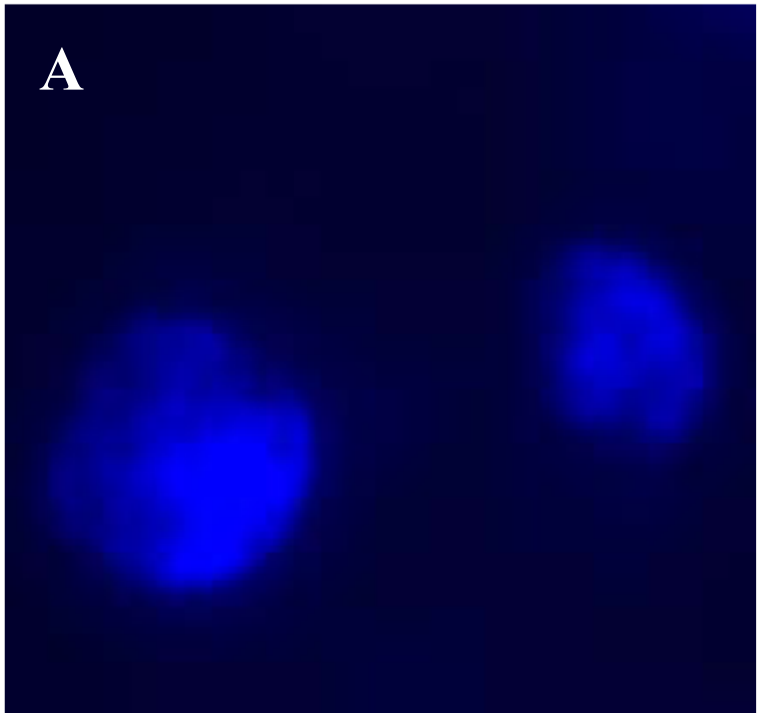
Monitoring the internalization and drug release using fluorescent and fluorogenic probes

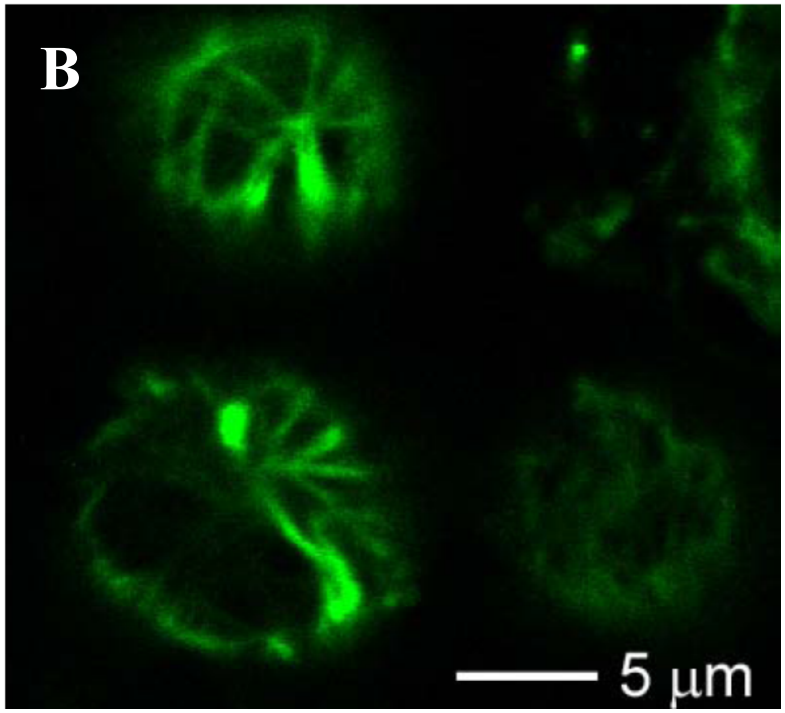




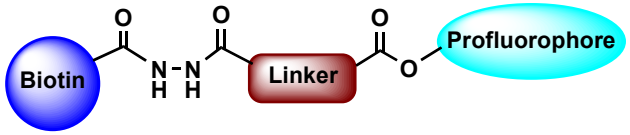


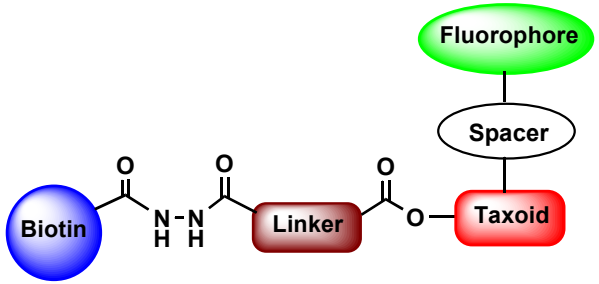
I,Ojima, *Acc. Chem. Res.* **41**, 108-119 (2008)
S.Chen, X. Zhao. J. Chen, J. Chen, L. Kuznetsova, S. S. Wong, I. Ojima, *Bioconjugate Chem*. **21,** 979-987 (2010).





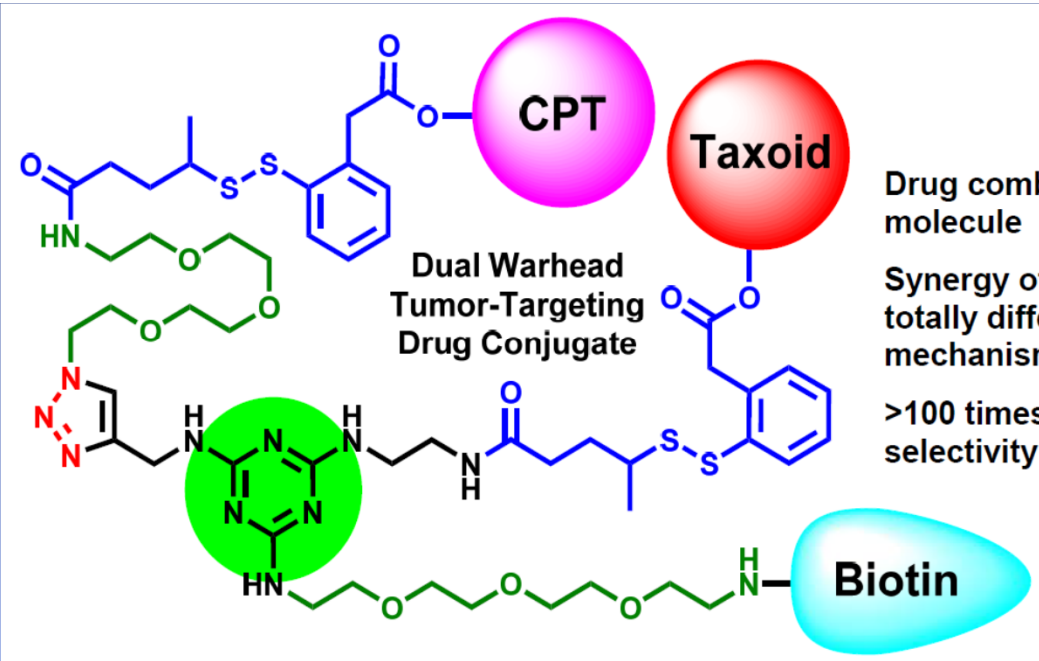
Drug Release





(**A**) epifluorescence CFM image of L1210FR cells that are first incubated with Biotin-Linker-Coumarin in the non-fluorescent form, and post-treated with glutathione to release the biotin and activate the dye to fluoresce blue. (**B**) CFM image L1210FR cells that are first incubated with Biotin-Linker-Taxoid-Fluorescein and post-treated with glutathione Et ester to release the Fluorescein-labeled Taxoid that are shown to bind to the microtubules inside the cancer cells.

I. Ojima, *Acc. Chem. Res.* **41**, 108-119 (2008)
S.Chen, X. Zhao. J. Chen, J. Chen, L. Kuznetsova, S. S. Wong, I. Ojima, *Bioconjugate Chem*. **21,** 979-987 (2010).



Drug combination in one molecule

Synergy of two drugs with totally different mechanism of action

>100 times higher selectivity for cancer cells

J. G. Vineberg, E. S. Zuniga, A. Kamath, Y.-J. Chen, J. D. Seitz, I. Ojima, *J. Med. Chem*. 57 (13), 5777-5791 (2014).

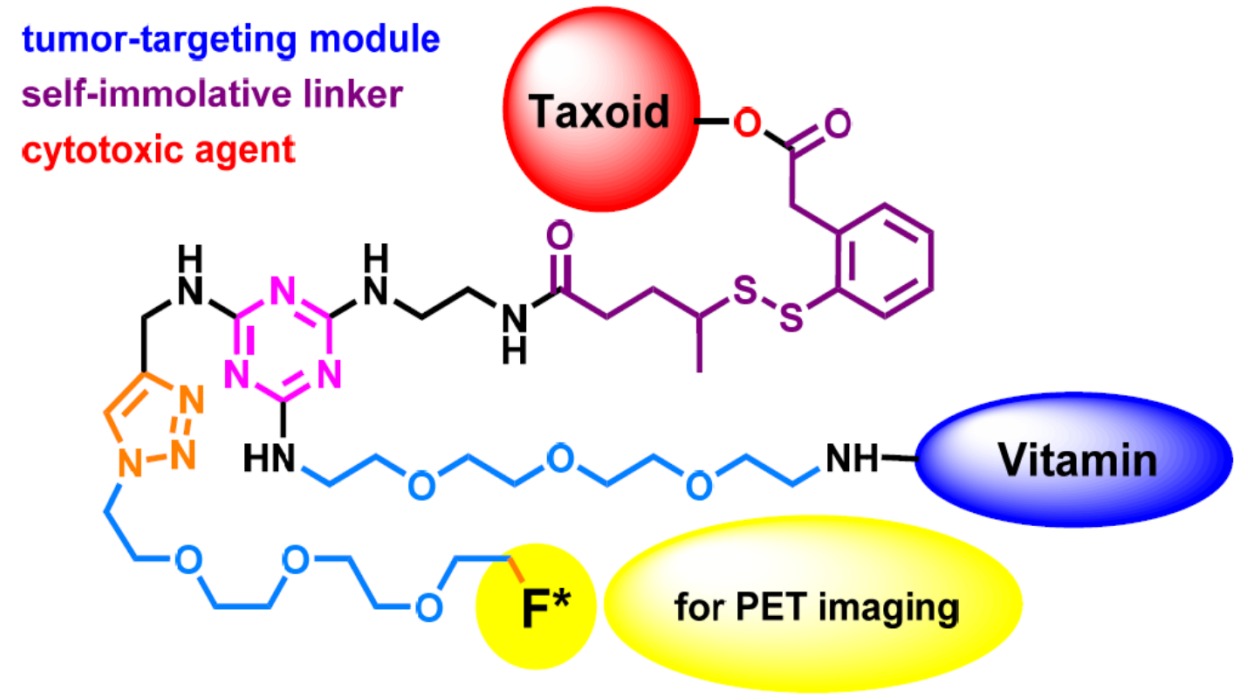
Theranostic Vitamin-Linker-Taxoid Conjugates

J. G. Vineberg, T. Wang, E. S. Zuniga, and I. Ojima, *J. Med. Chem*. 58, 2406–2416 (2015)

tumor-targeting module

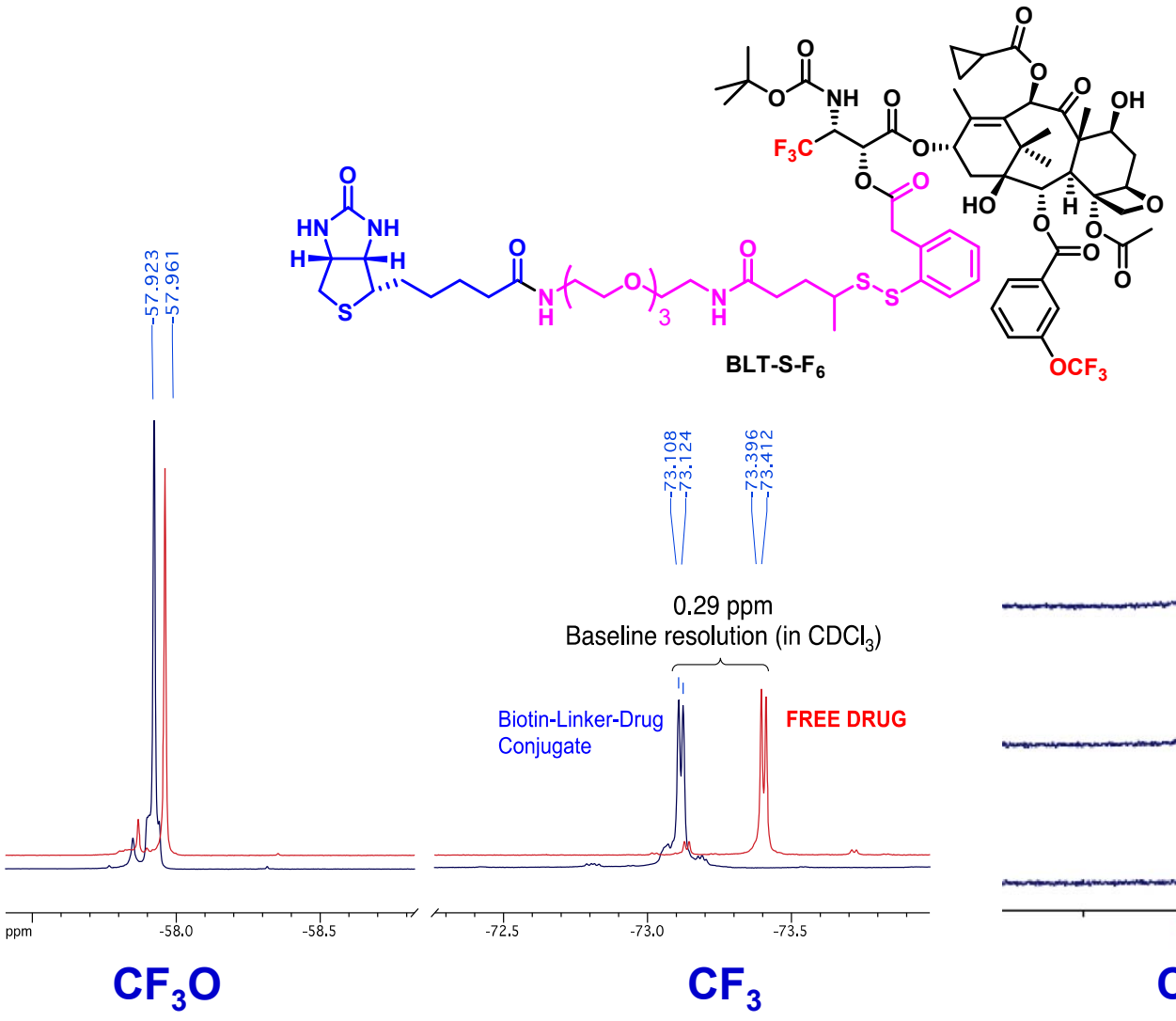
self-immolative linker

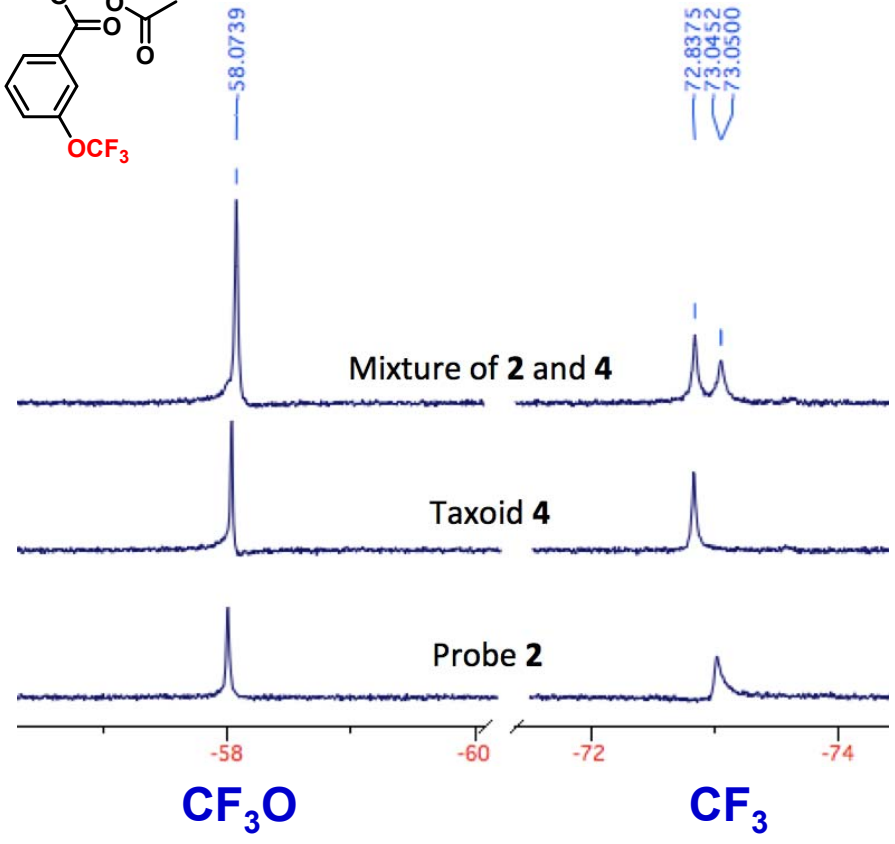
cytotoxic agent



^{19}F NMR Chemical Shift Dispersion in Novel Taxoid "3-FAB x 2 Probe"

Joshua Seitz, Longfei Wei

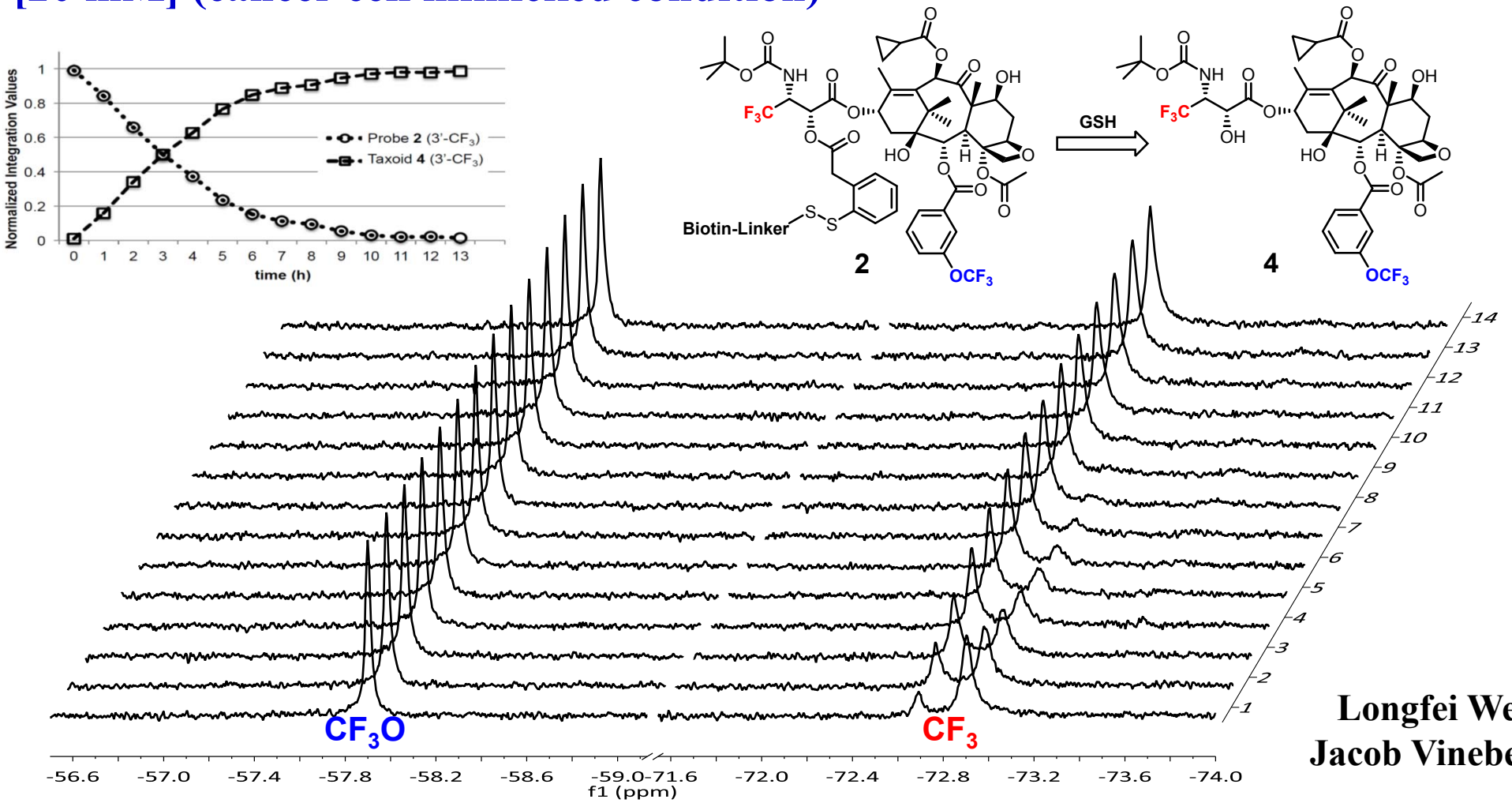




J. D. Seitz, J. G.Vineberg et al. *J. Fluor. Chem*. **171**, 148–161 (2015), *Bordeuax Fluorine Days Special Issue*

^{19}F NMR spectra (1024 scans) showing individual chemical shifts of 200 µM solutions of BLT-S-F_6 **2** and taxoid **4** in blood plasma-D_2O-ethanol-polysorbate 80 (86:10:2:2), and a 1:1 mixture of **2** and **4** in blood plasma-D_2O-ethanol-polysorbate 80 (84:10:4:2)

^{19}F NMR Monitoring of Drug Release in Blood Plasma with GSH (100 equiv.) [20 mM] (cancer cell mimicked condition)

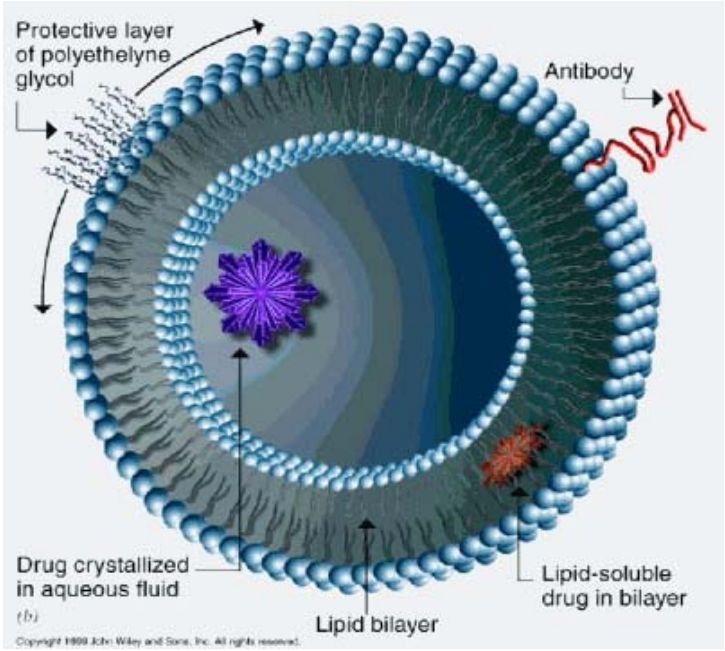


Longfei Wei
Jacob Vineberg

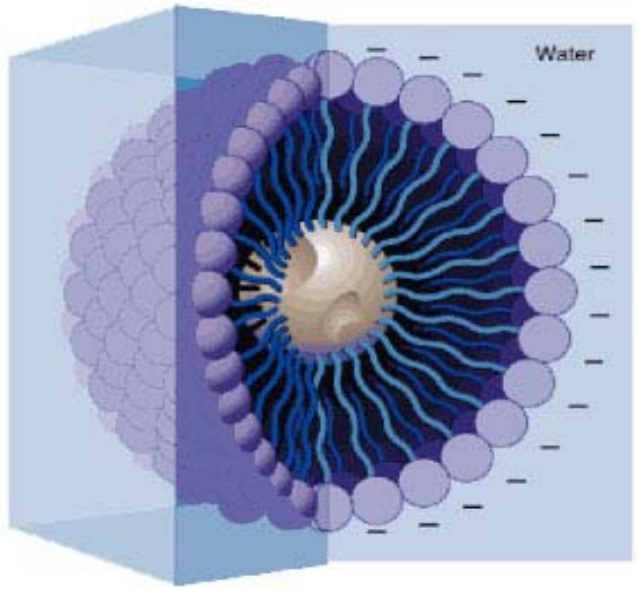
Time-resolved ^{19}F NMR spectra for the drug release of probe 2 (200 μM) in 86% blood plasma, 2% ethanol, and 2% Tween 80 in D_2O at 30 min after the addition of 100 equivalents of GSH at 37 °C with 1 h intervals (1024 scans/spectrum) for 13 h. The signals of 2-*m*-OCF_3 (*left*) and the 3'-CF_3 (*right*) are shown, which indicate full drug release after 13.5 h.

J. D. Seitz, J. G.Vineberg, L. Wei, J. F. Khan, B. Lichtenthal, C.-F. Lin and I. Ojima, *J. Fluor. Chem*. **171**, 148–161 (2015).

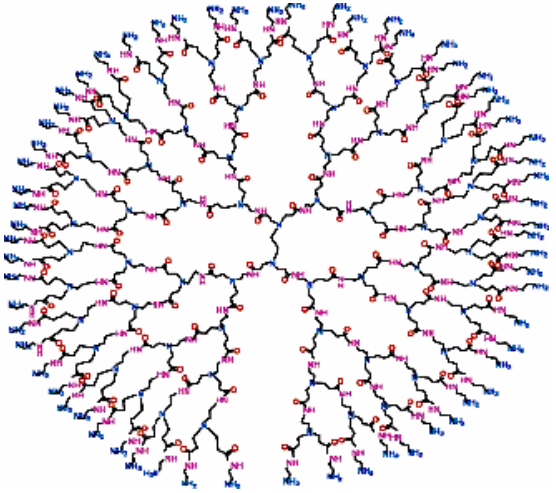
Liposome



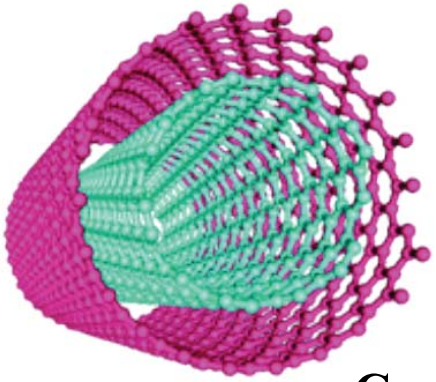
Micelle

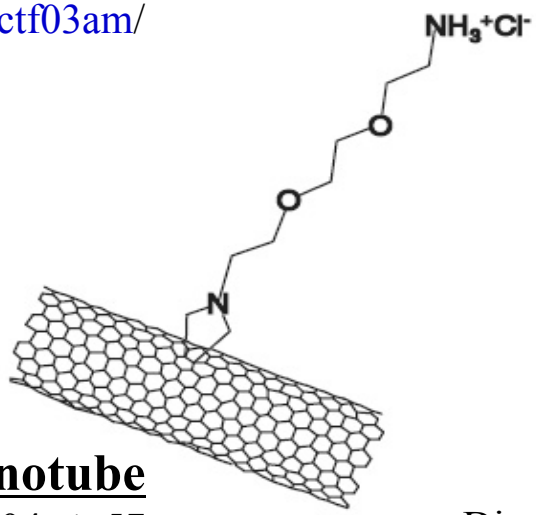


Dendrimer



http://www.uic.edu/classes/bios/bios100/lectf03am/

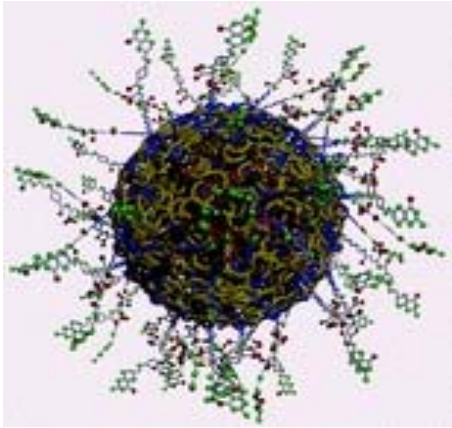




Carbon Nanotube

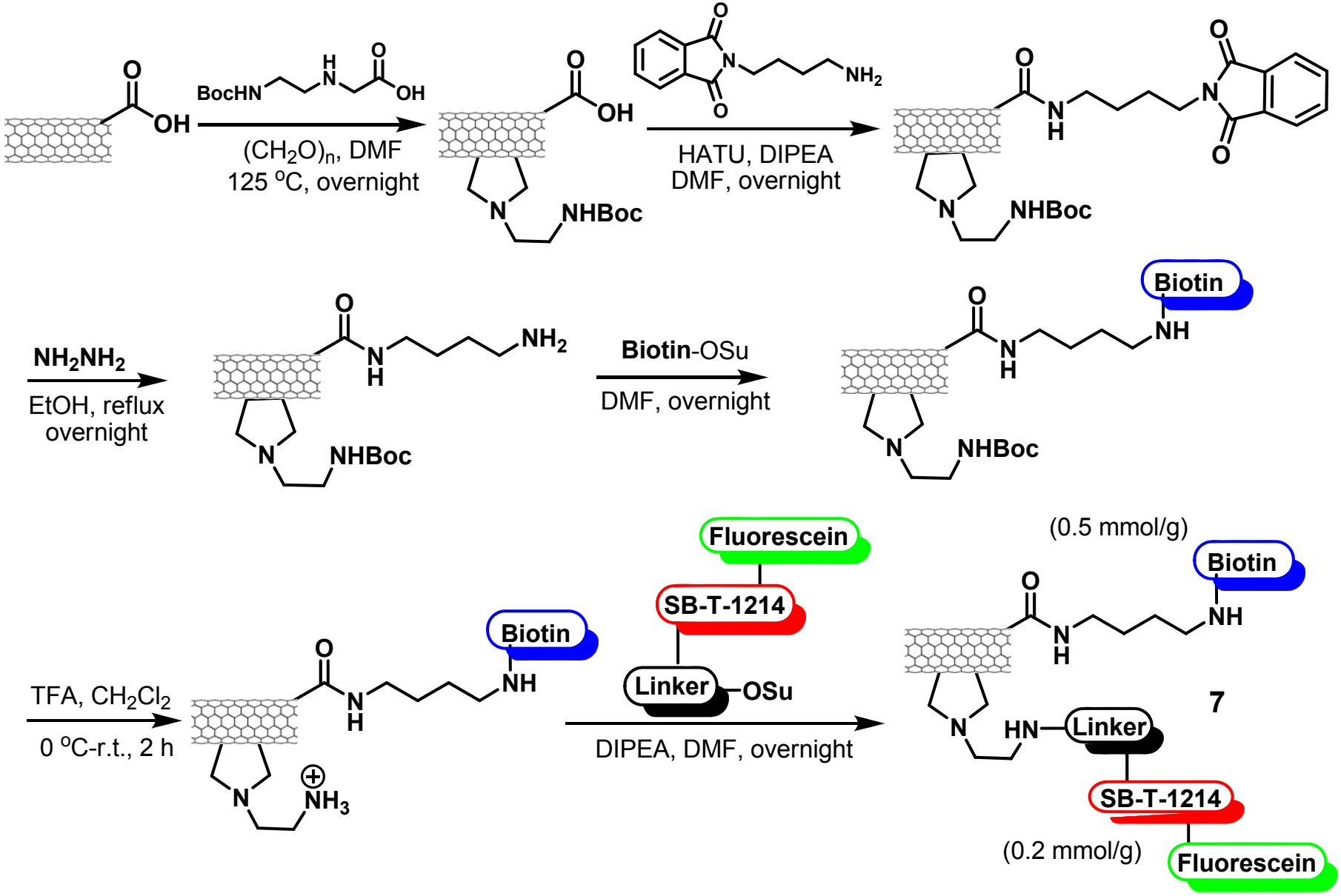
Bianco A. *Expert Opin.Drug Deliv.* **2004**, *1*, 57

Nanoparticle



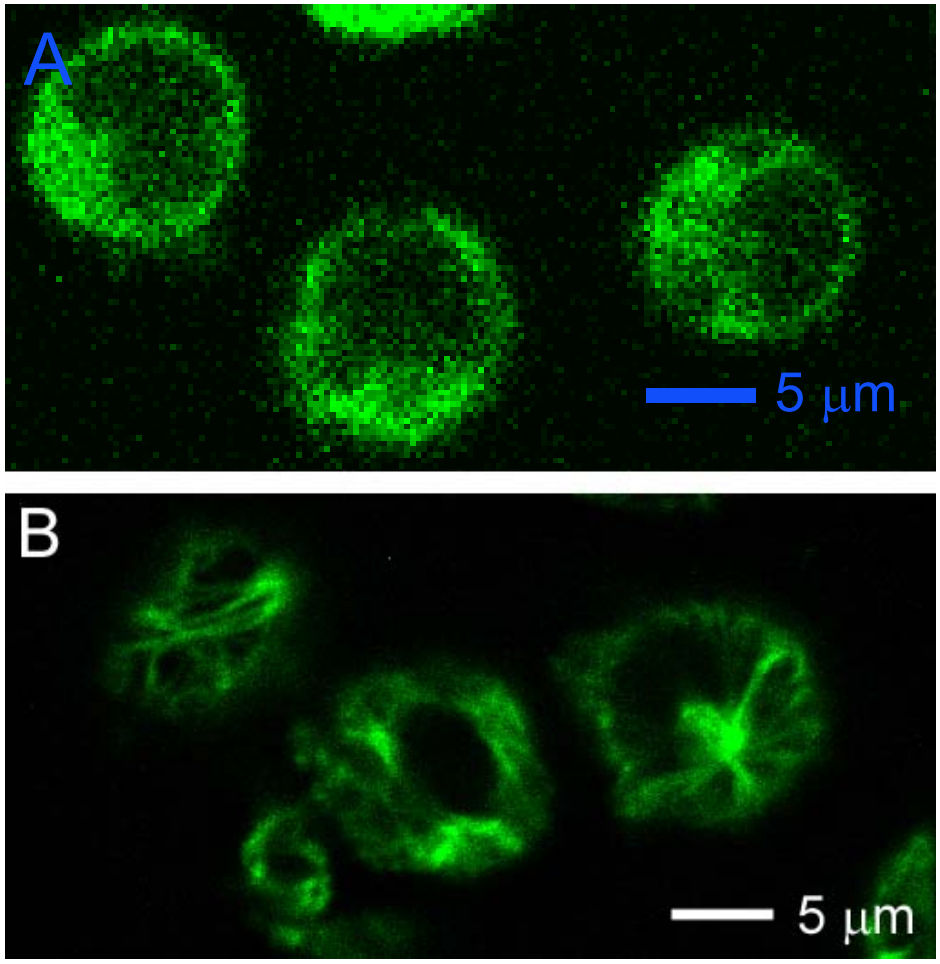
Dipanjan P. et al *Chem. Commun.*, **2003**, *19*, 2400

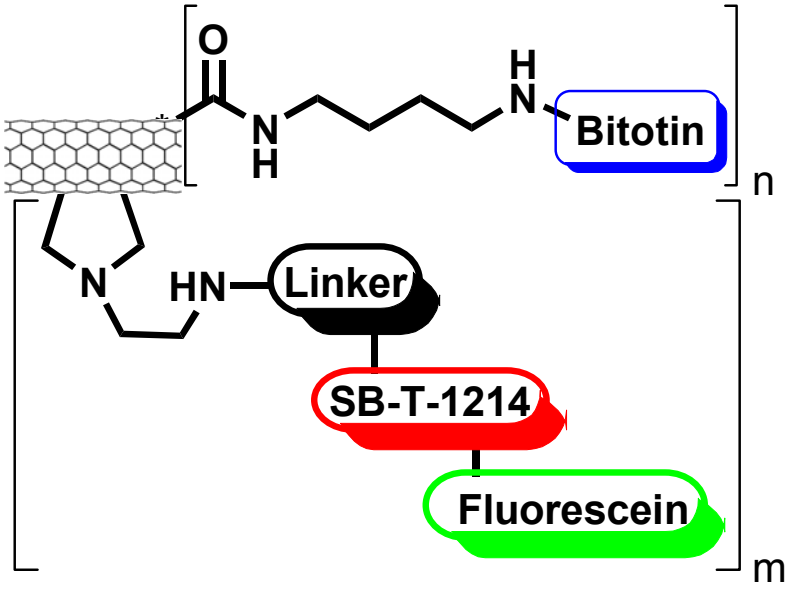
Synthesis of "Trojan Horse" Guided Molecular Missile



J. Chen S. Chen, X. Zhao, L. Kuznetsova, S. S. Wong, I. Ojima, *J. Am. Chem. Soc*. **130,** 16778-16785 (2008).

Internalization and Drug Release of Biotin-CNT-Linker-Taxoid-Fluorescein

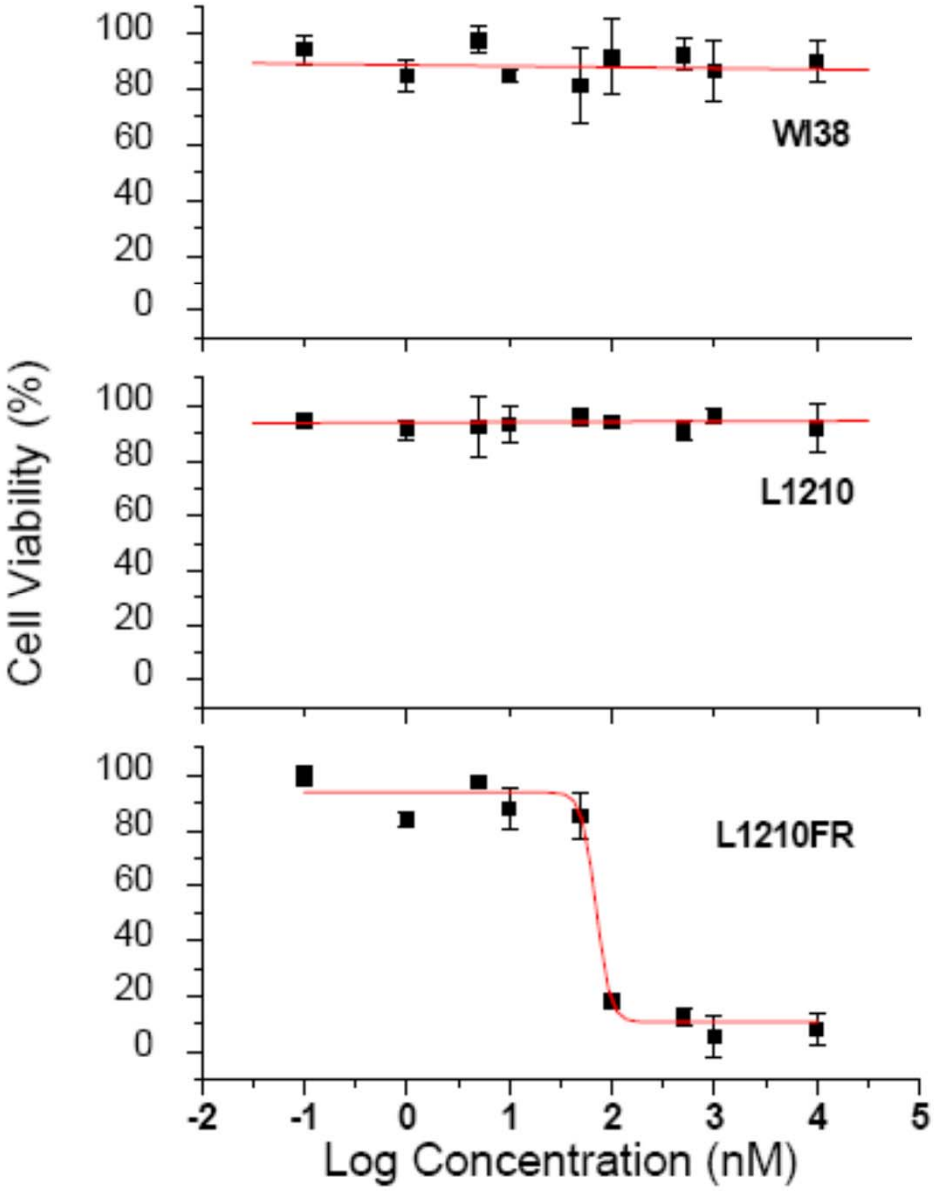




n: 0.50 mmol/g: 178 biotins/tube
m: 0.20 mmol/g: 71 taxoids/tube

CFM images of L1210FR cells treated with **biotin-CNT-taxoid-fluorescein** incubated in the absence (A) and in the presence (B) of GSH Et ester. The latter shows the presence of a microtubule network, polymerized by taxoid, after the disulfide bonds had been cleaved by the GSH ethyl ester.

J. Chen S. Chen, X. Zhao, L. Kuznetsova, S. S. Wong, I. Ojima, *J. Am. Chem. Soc*. **130,** 16778-16785 (2008).



Cytotoxicity of biotin-SWNT-taxoid-fluorescein conjugate against leukemia and normal cell lines (IC_{50})

L1210[a]	L1210FR[b]	WI38[c]
>50 µg/mL	0.36 µg/mL	>50 µg/mL

[a] mouse lymphocytic leukemia cell line.
[b] folate-receptor overexpressed L1210 leukemia cell line.
[c] human lung fibroblast cell line (normal human cells).

0.36 mg/mL = 51 nM of taxoids (max.)

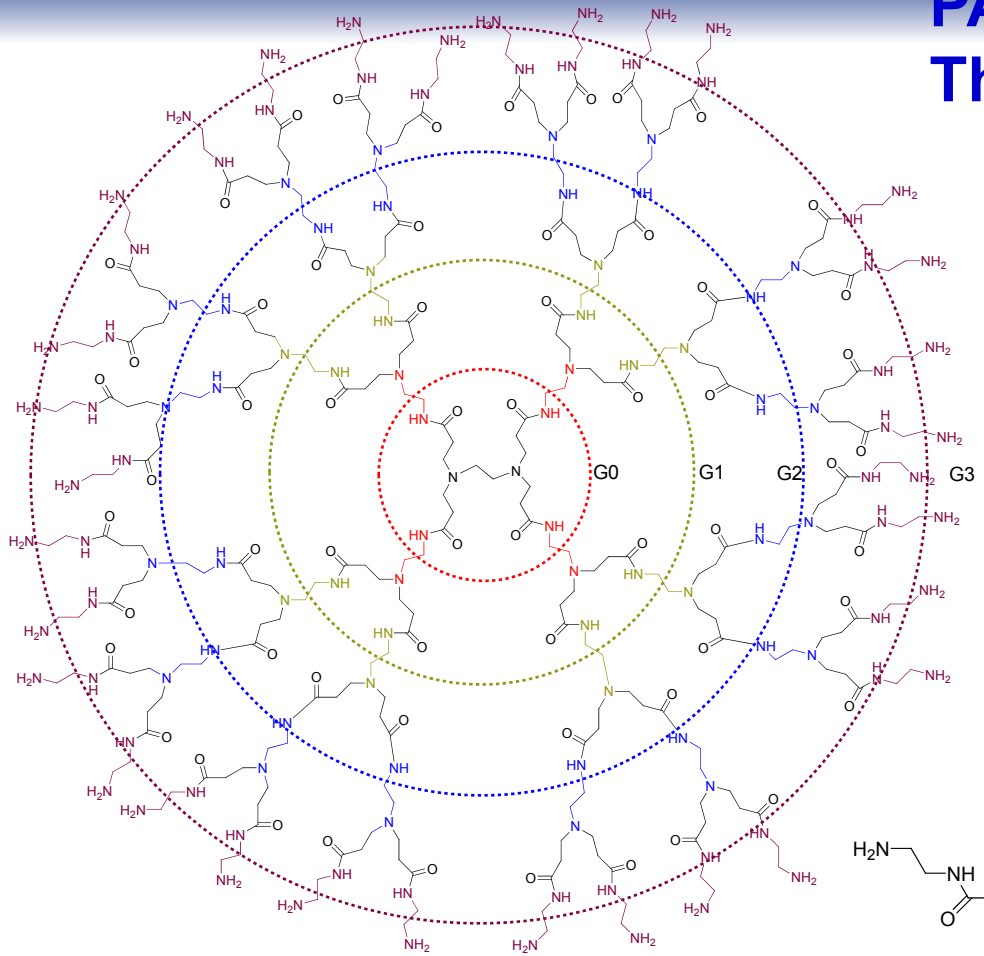
→ apparent IC_{50} of the released taxoid < 51 nM

cf. IC_{50} of SB-T-1214-fluorescein = 87.6 nM

→ Clear benefit of the "Trojan Horse" guided molecular missile strategy

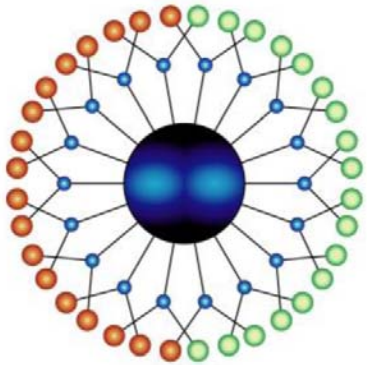
J. Chen S. Chen, X. Zhao, L. Kuznetsova, S. S. Wong, I. Ojima, *J. Am. Chem. Soc*. **130,** 16778-16785 (2008).

PAMAM Dendrimers and Those with Cystamie Core

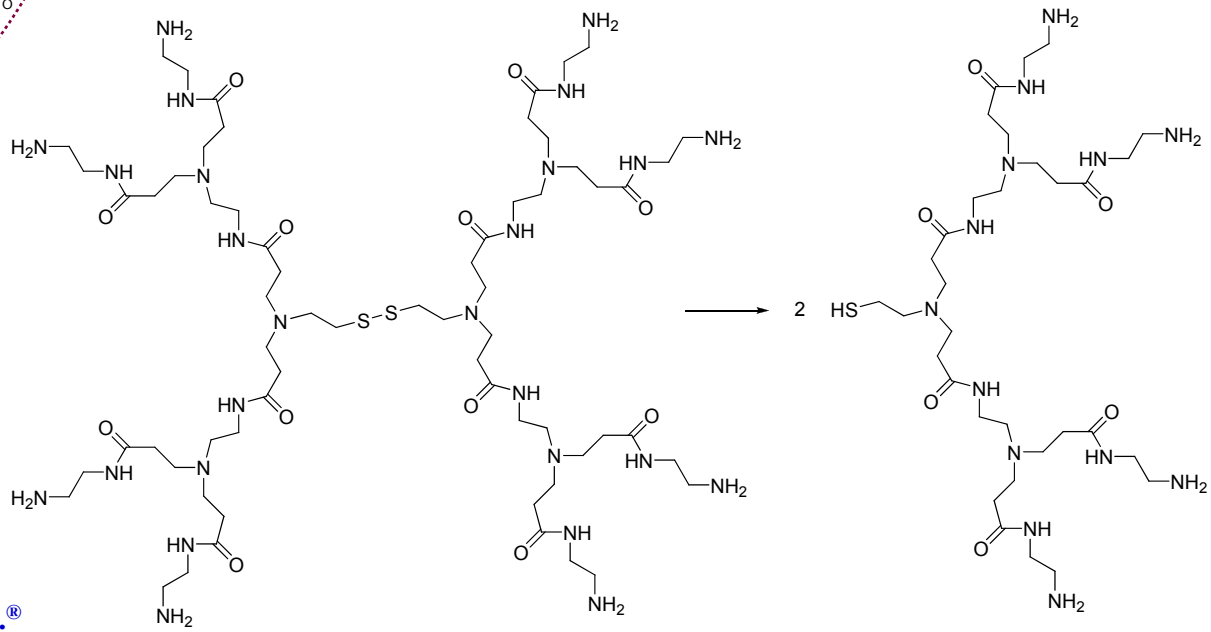


Generation 0 n=4
Generation 1 n=8
Generation 2 n=16
Generation 3 n=32

Symmetric Dendimer

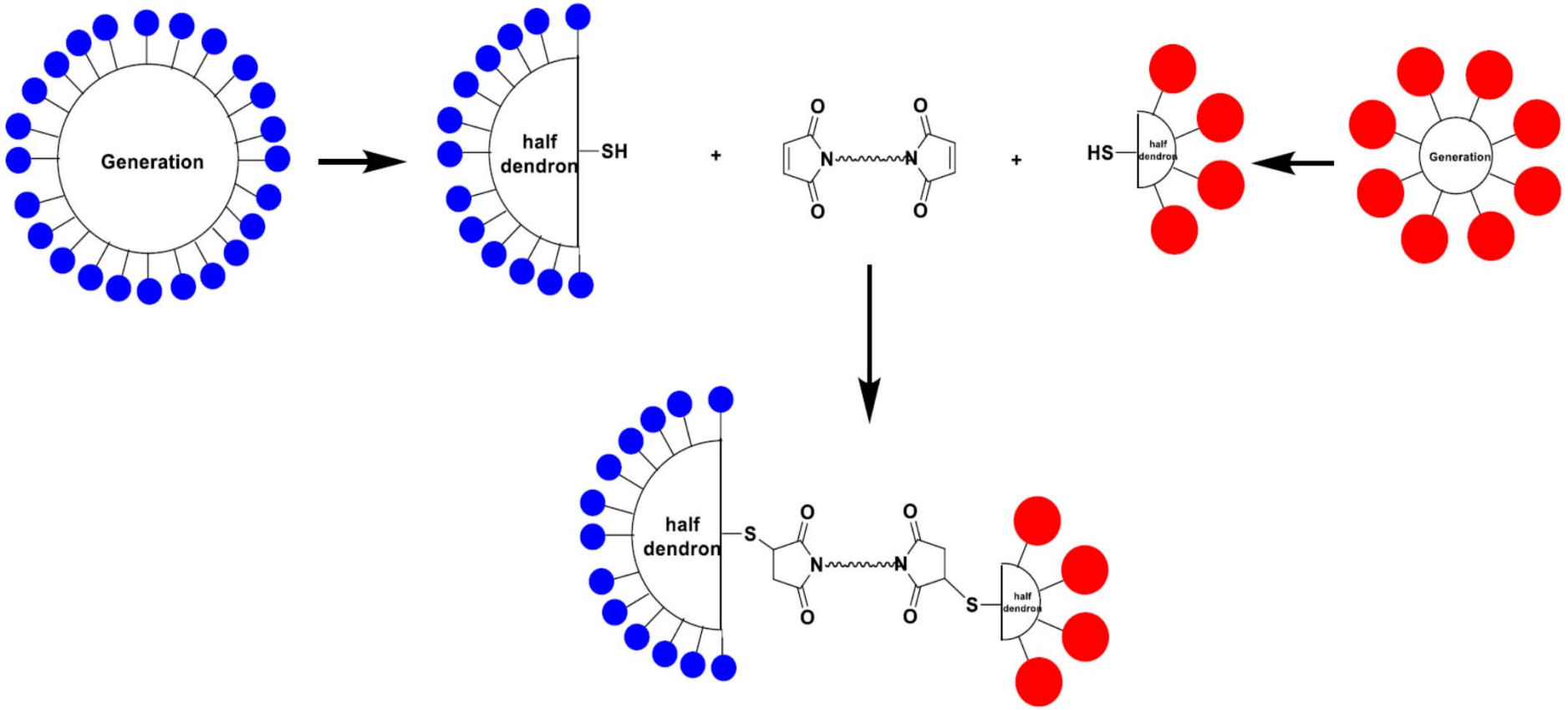


drug molecules
tumor-targeted molecules



Generation 1 (DNT-294)
Dendritic Nanotechnologies, Inc.®

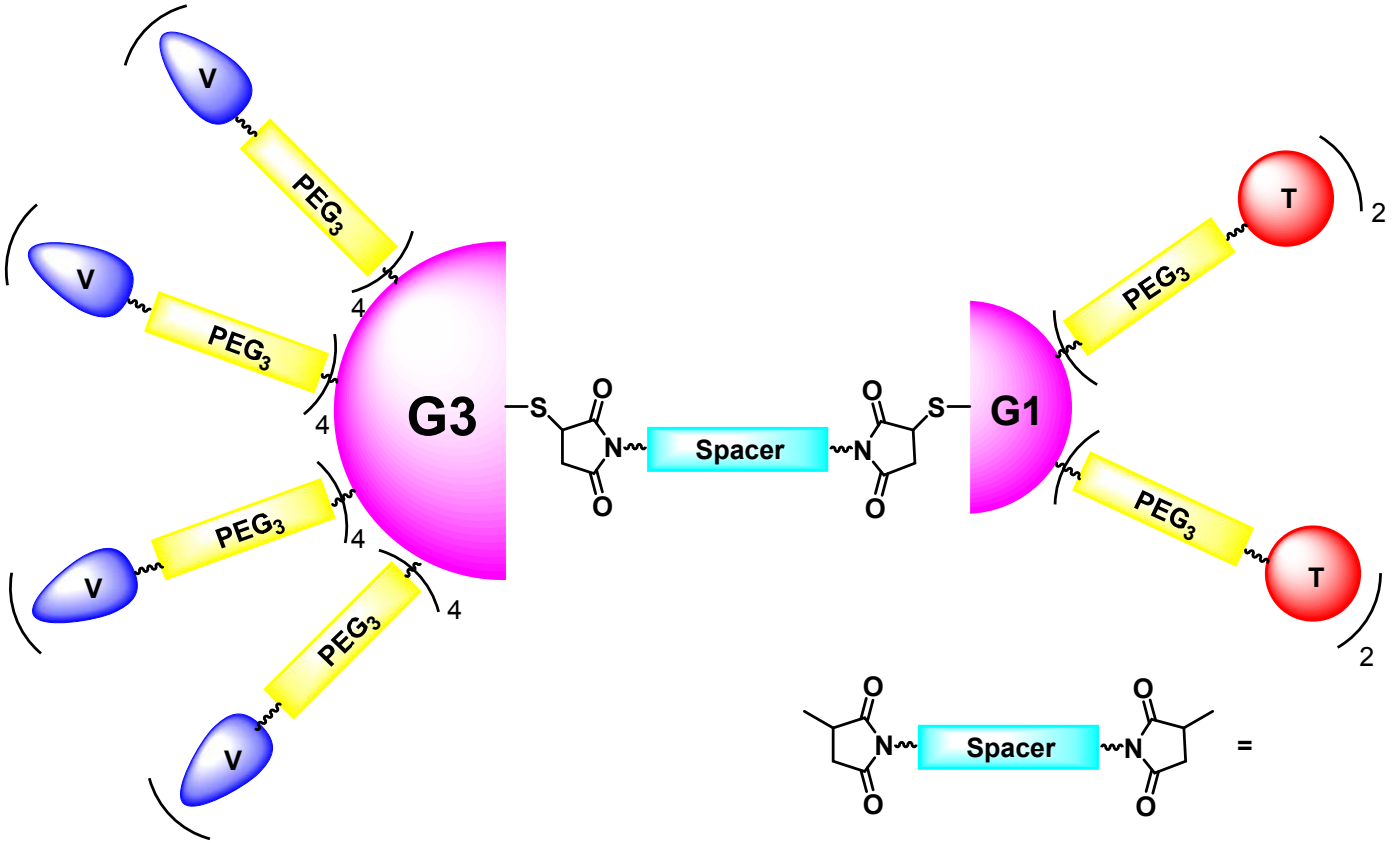
Construction of Asymmetric Bow-tie Dendimers with Different Generation Dendrons



G. T-S. Teng. Ph.D. Research Proposal, Stony Brook University (2010)

H. F. Gaertner, F. Cerini, A. Kamath, A.-F. Rochat, C.-A. Siegrist, L. Menin, O. Hartley, *Bioconj. Chem*. **2011**, *22*, 1103–1114

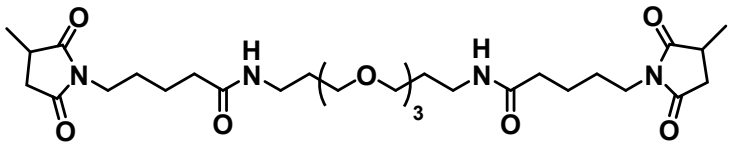
PAMAM Dendrimer-Based Tumor-Targeted DDS

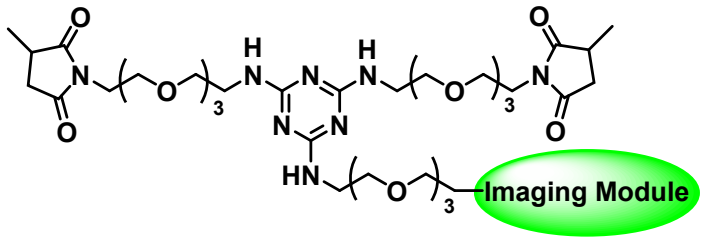


V = Vitamin B (Targeting module)

T = Taxoid (Warhead module)

PEG_3 = Polyethylene glycol trimer





Imaging

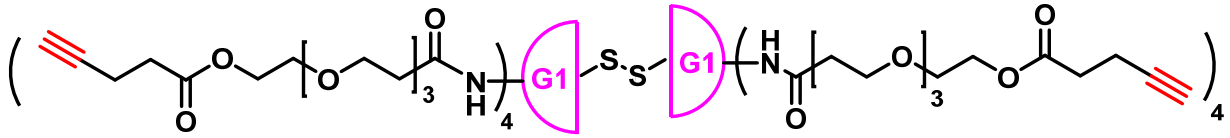
PET, SPECT, MRI

^{18}F, ^{64}Cu, ^{99m}Tc, Gd

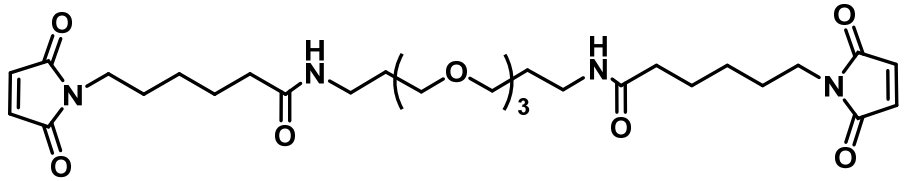
Tao Wang
Jacob Vineberg
Longfei Wei
Sungwon Kim (BNL)
Joanna Fowler (BNL)

Asymmetric PAMAM Dendrimer DDS Construction

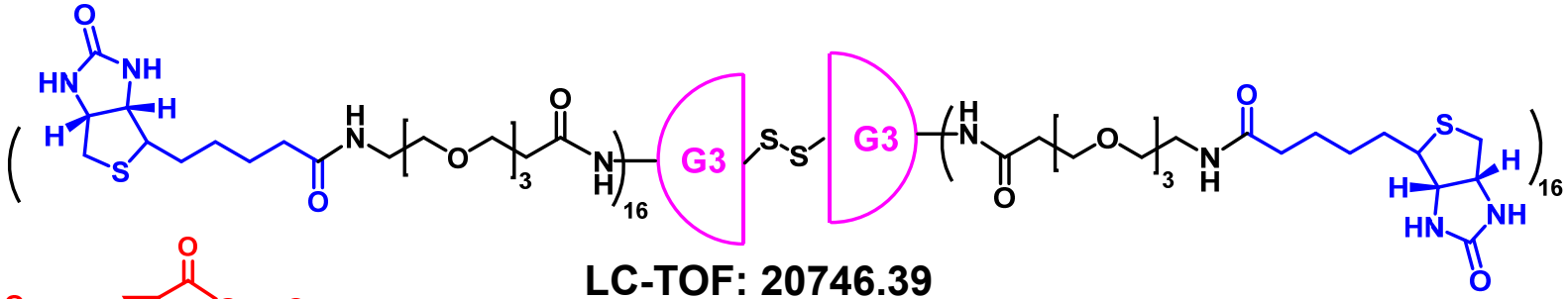
G1 construct



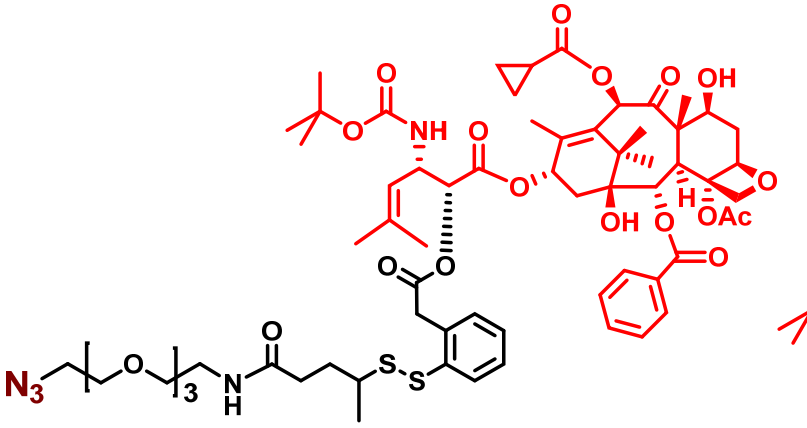
Bismaleimide Linker

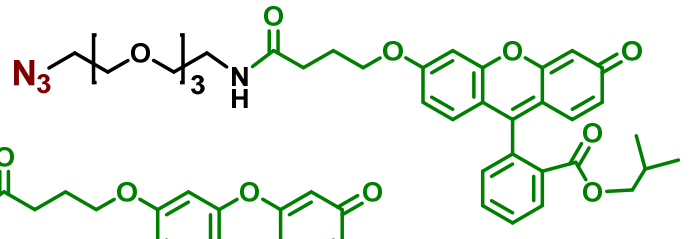


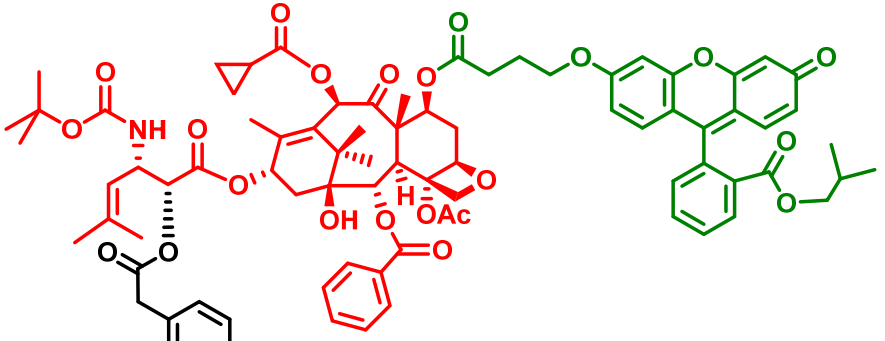
G3 construct

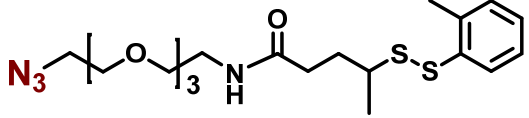


LC-TOF: 20746.39









Warhead and Fluorescent Probe constructs

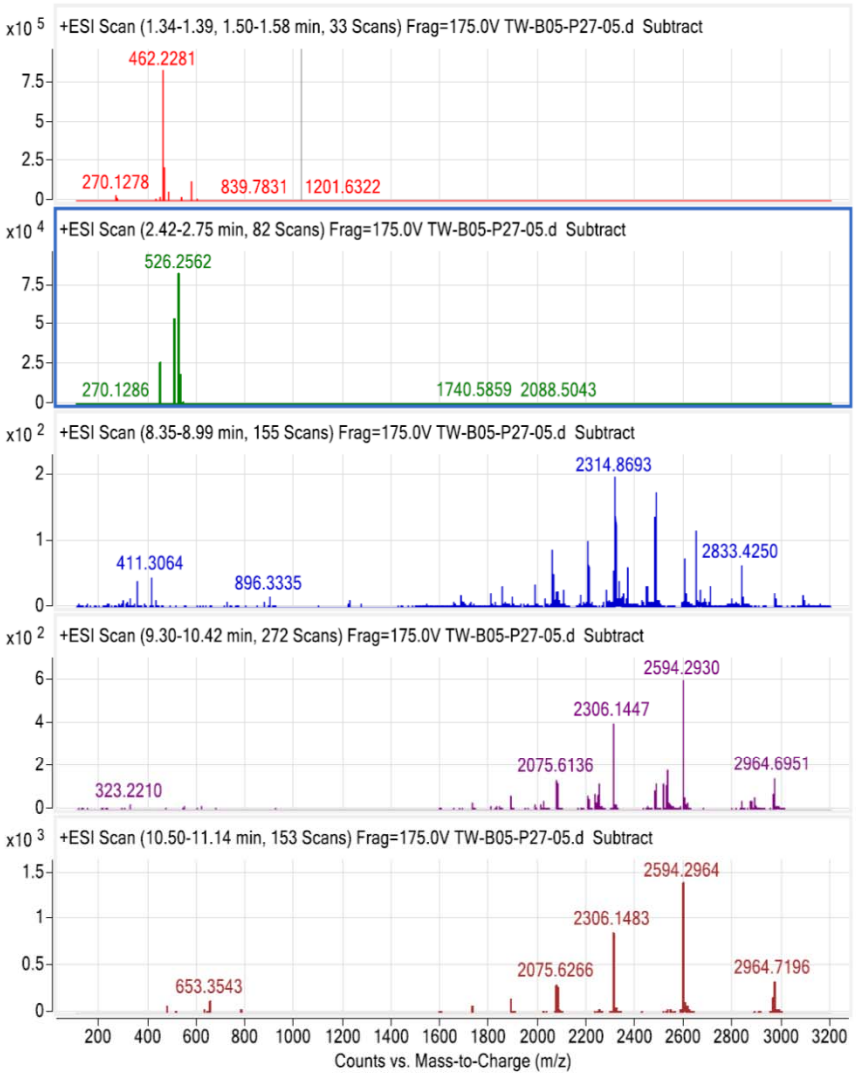
Tao Wang
Longfei Wei

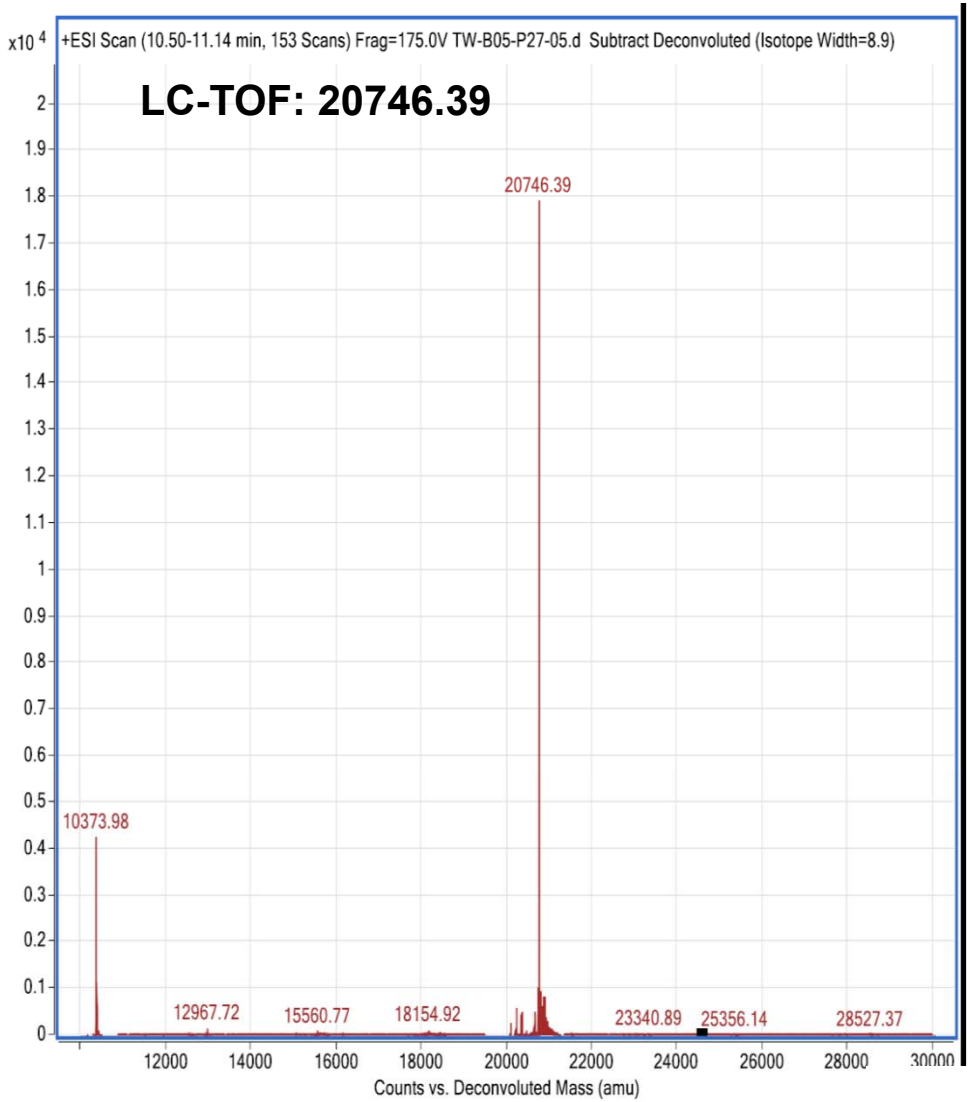
LC-TOF Analysis

Chemical Formula: $C_{912}H_{1604}N_{218}O_{252}S_{34}$
Exact Mass: 20730.99
Molecular Weight: 20746.01

G3 Construct

Tao Wang



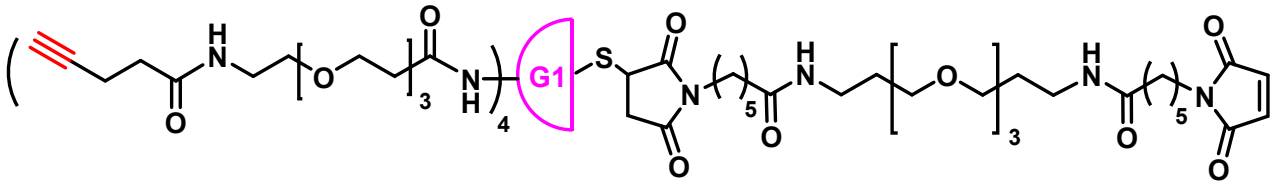


Click-Ready Asymmetric PAMAM Dendrimer Construct Synthesis

G1 construct —(**Bismaleimide Linker** (10 equiv.); TCEP (3 equiv.), MeOH, r.t.)→ **G1-maleimide construct**

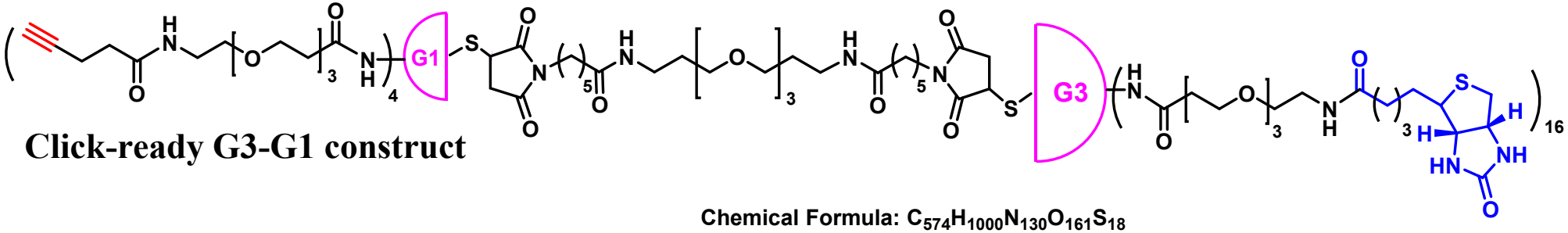
G3 construct —(**G1-maleimide construct** (2 equiv.); TCEP (3 equiv.), MeOH/H_2O (1/1), r.t.)→ **Click-ready G3-G1 construct**

G1-maleimide construct



Chemical Formula: $C_{118}H_{197}N_{21}O_{35}S$
Exact Mass: 2500.40
Molecular Weight: 2502.01
LC-TOF: 2503.40

Click-ready G3-G1 construct

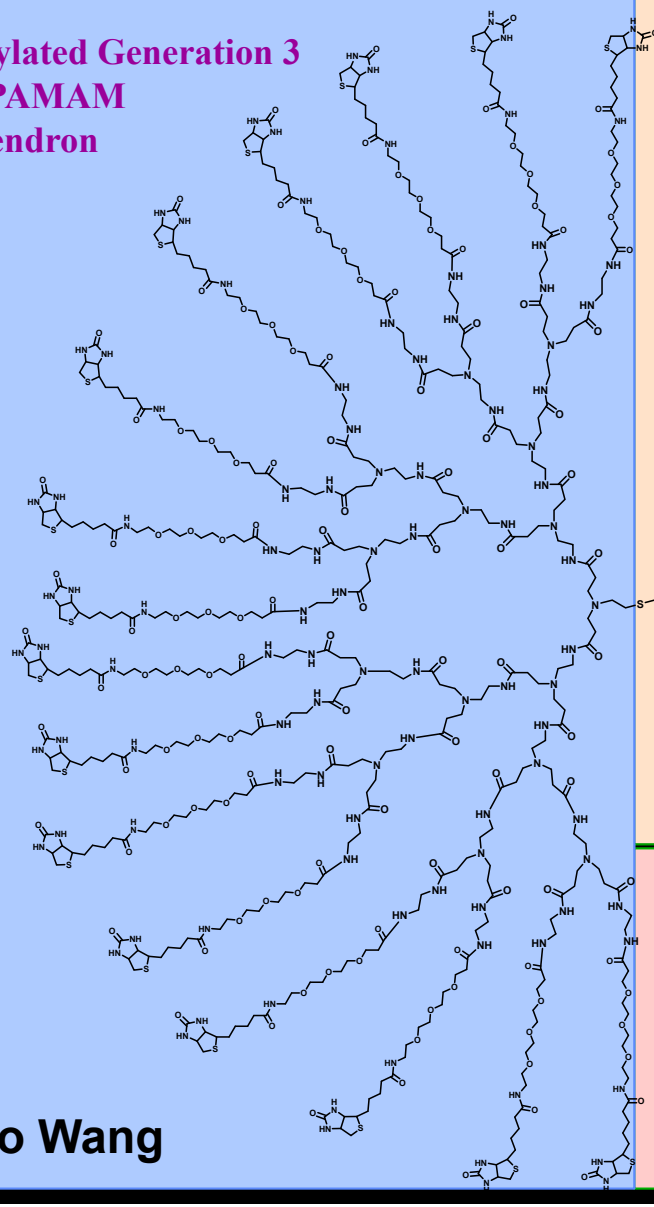


Chemical Formula: $C_{574}H_{1000}N_{130}O_{161}S_{18}$
Exact Mass: 12866.90
Molecular Weight: 12876.03
LC-TOF: 12876.20

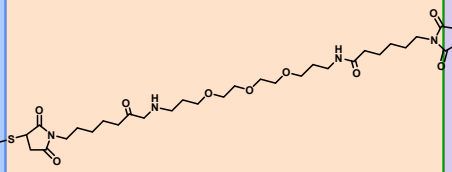
Tao Wang

$(Biotin)_{16}$-D_3-linker-D1-$(Alkyne)_4$ Template

Biotinylated Generation 3
PEG-PAMAM
half dendron

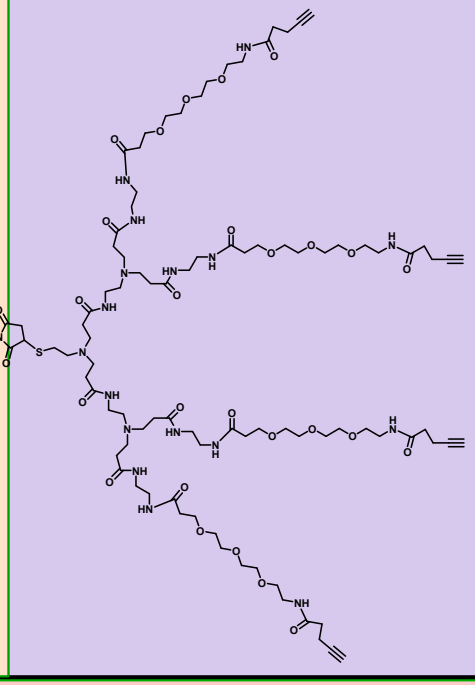


Bis (maleicimido)
PEGylated Linker

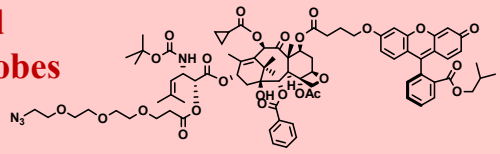


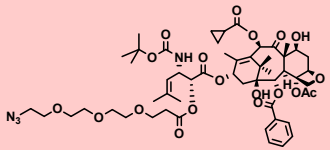
Click-reactions:
70-88% yields

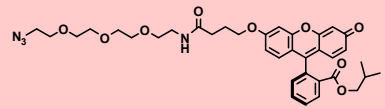
"Click-ready" Generation 1
PEG-PAMAM
half dendron



"Click-ready" PEGylated
Drug and Fluorescent Probes

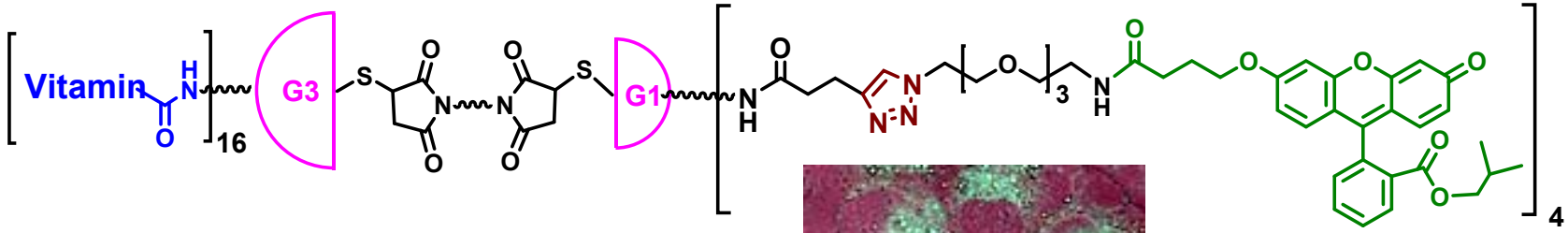




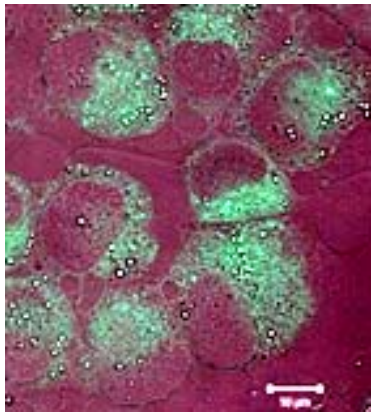


Tao Wang

Asymmetric Dendimer–Based Tumor-Targeting Conjugates



ABTD-3



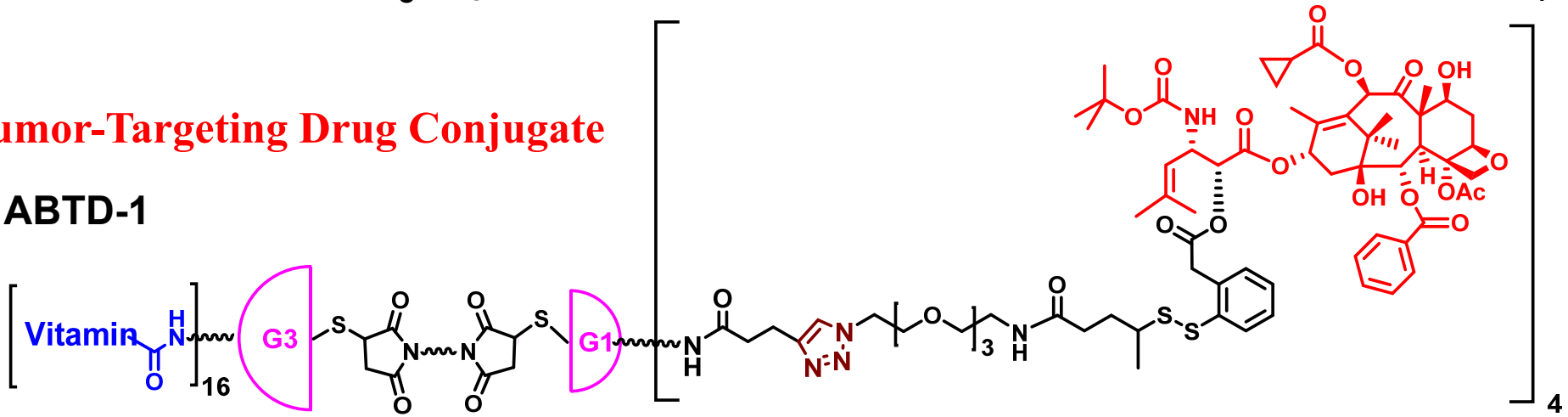
fluorescein

Fluorescent Probes

ABTD-2

Tumor-Targeting Drug Conjugate

ABTD-1



Tao Wang

Exceptional Potency (IC_{50}) and Cancer Cell Specificity of ABTD-1

Multiple binding of the tumor-targeting module to biotin receptors

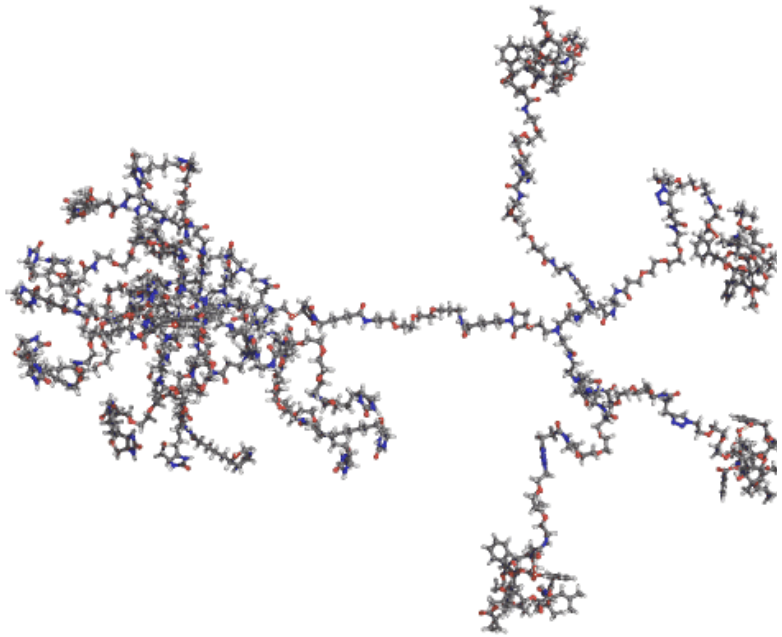
	ID-8	MX-1	WI-38
Paclitaxel	21.2 ± 4.30	3.83 ± 0.59	17.5 ± 5.2
SB-T-1214	1.89 ± 0.30	2.90 ± 0.47	4.14 ± 0.82
BLT-S	7.84 ± 1.85	26.7 ± 3.44	519 ± 90.3
BLT-S + GSH-OEt*	5.91 ± 0.32	1.52 ± 0.34	N.D.
ABTD-1	7.84 ± 1.85	2.05 ± 0.91	582 ± 48.8
ABTD-1 + GSH-OEt*	0.62 ± 0.07	0.12 ± 0.05	N.D.
ABTD-3	> 5000	> 5000	N.D.

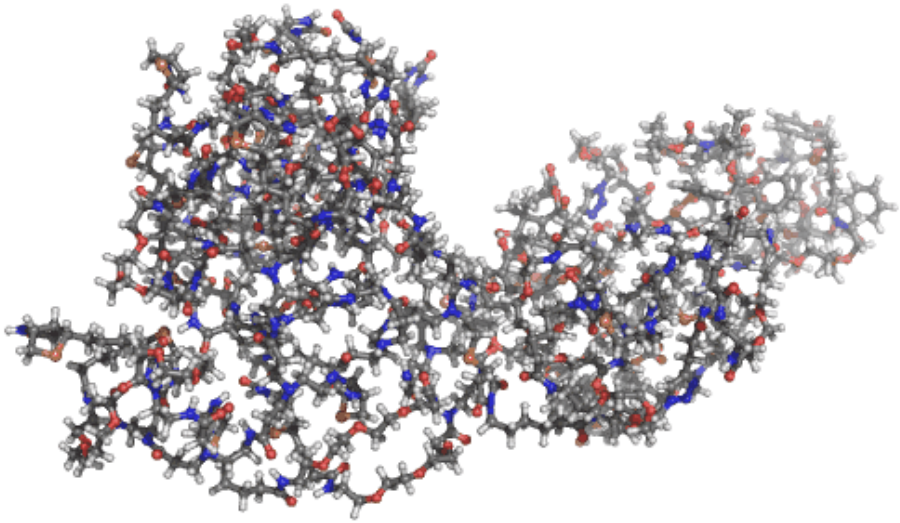
Concentration of compound that inhibits 50% (IC_{50}, nM) of different types of cells after 72 h of drug exposure at 37 ^{o}C under 5 % CO_2.

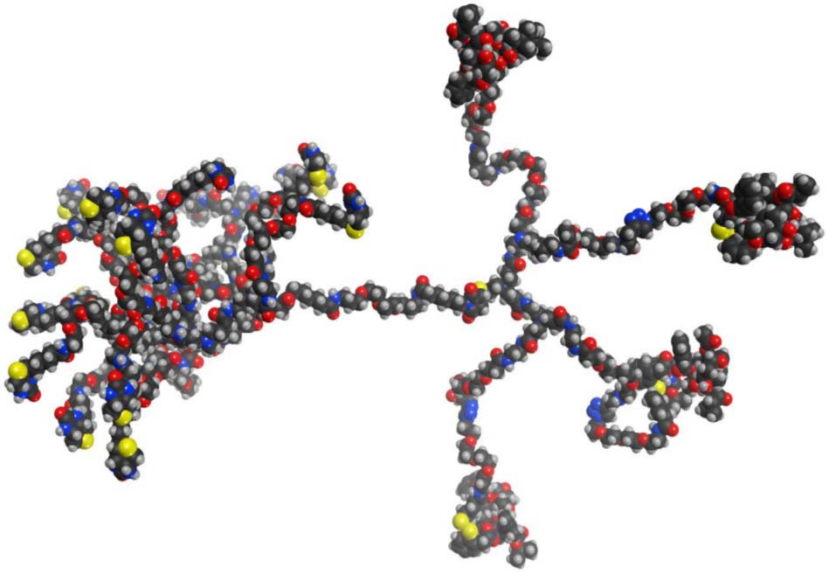
*24 h of drug exposure, followed by thorough washing with DPBS, and 48 hours incubation with 6 eq glutathione-OEt at 37 ^{o}C under 5 % CO_2.

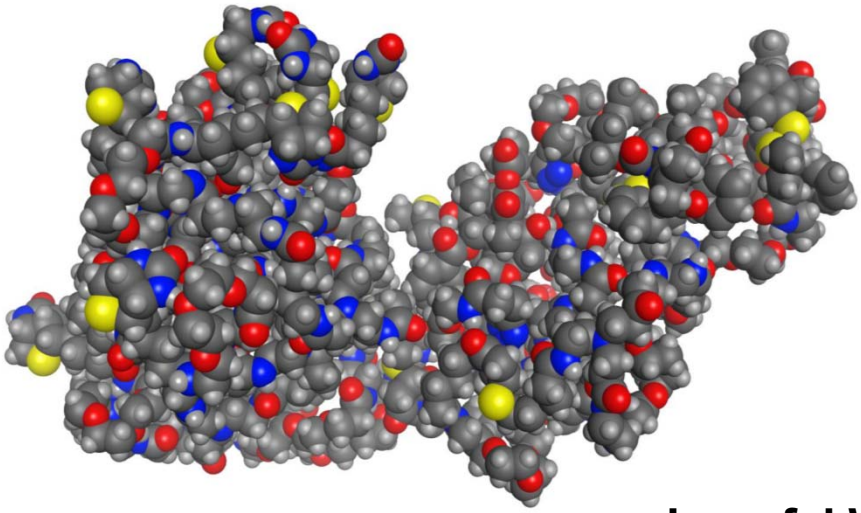
Tao Wang

Molecular Structure of ABTD-1 Tumor-Targeting Dendrimer Conjugate



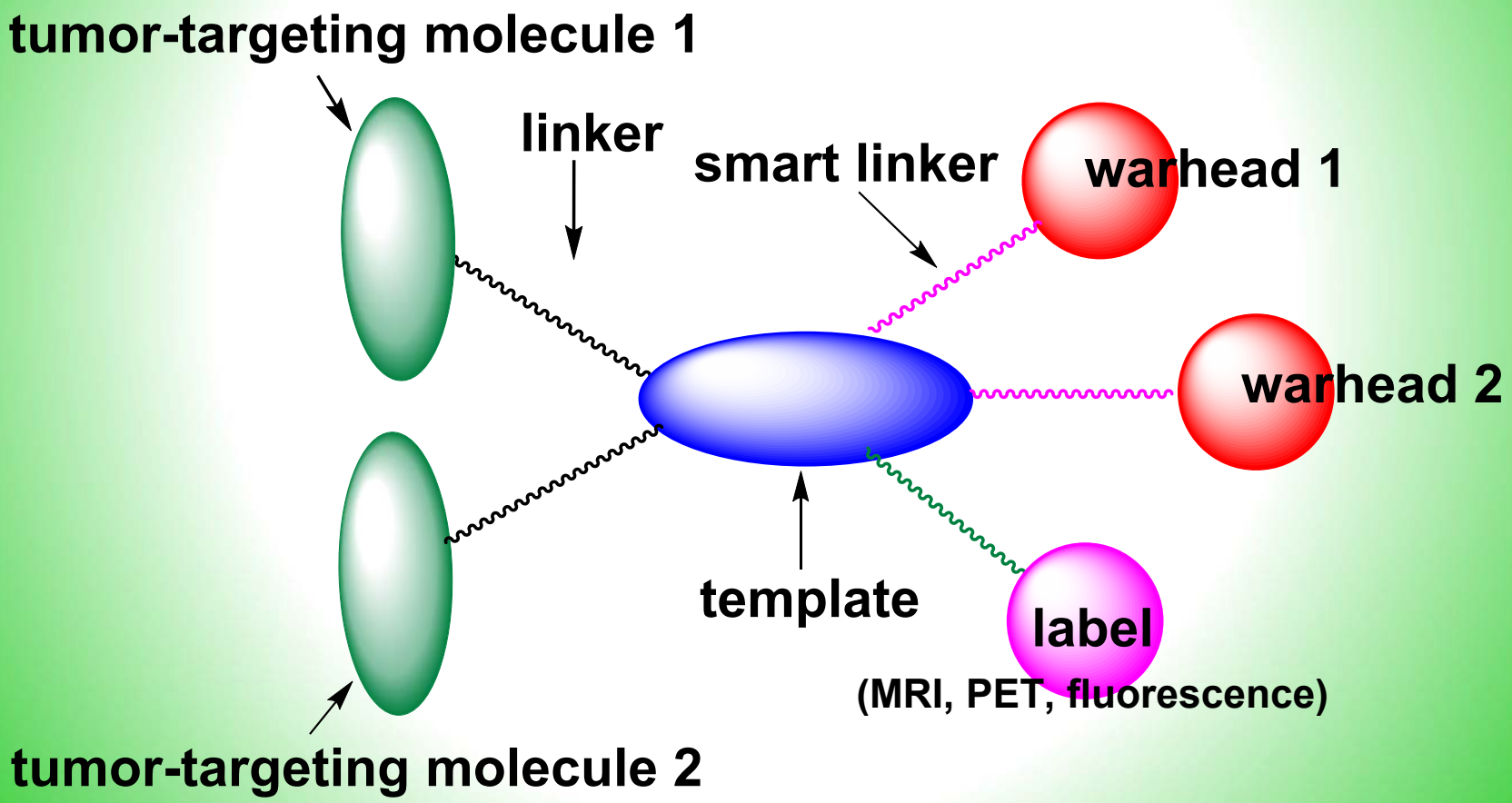






Longfei Wei

New Generation Tumor-Targeting Anticancer Agents
-Basic structure of the multi-functional conjugates: tailor-made "nano medicine"-



Acknowledgments

$$$$

National Institutes of Health (NCI, NIAID, NIGMS)
National Science Foundation
Department of Defense (DTRA)
New York State Office of Science, Technology and Academic Research (NYSTAR) Faculty Development Award
ACS-Petroleum Research Fund
Arthur C. Cope Funds (ACS)
John S. Guggenheim Memorial Foundation
New York State Science & Technology Foundation
Japan Health Science Foundation
Indena SpA
Rhone-Poulenc Rorer (Sanofi-Aventis)
ImmunoGen, Inc.
Mitsubishi Chemical Corporation
Japan Halon Co., Ltd. (Tosoh F-Tech, Inc.)
Ajinomoto Co., Inc.
Yuki Gosei Yakuhin K. K.
Central Glass Co., Ltd.

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AT STONY BROOK UNIVERSITY

Stony Brook University

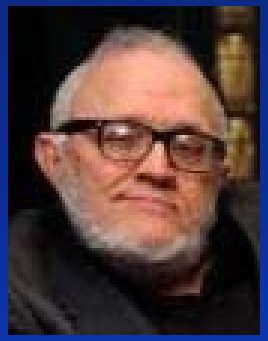
Acknowledgments


Benjamin Hsiao


Robert Filler

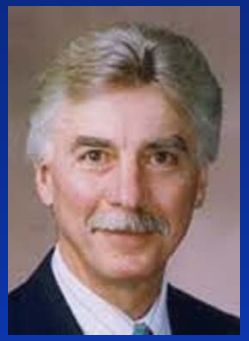

John Welch

(ACS F-Chem Award)


S. Danishefsky


Koji Nakanishi

(E. B. Hershberg Award)


Paul Wender


Albert Meyers

(A. C. Cope Scholar Award)


Susan Horwitz


Ralph Bernacki


E. Bombardelli


A. Commerçon


C. Ferlini


C. Simmerling


Stan. Wong


Peter Tonge


Ric. Slayden


Jacqueline Kampf


Patricia Marinaccio


Kimberly Johnson-Hillock


Roxanne Brockner


Yoko Ojima