Synthetic Methods and Applications at the Biomedical Interface

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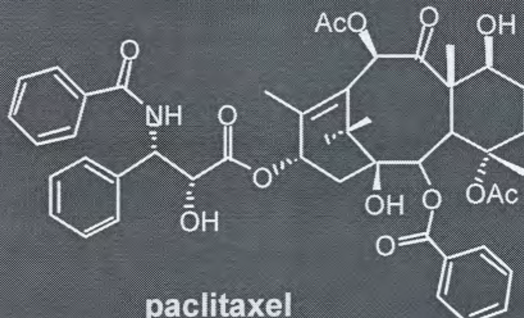
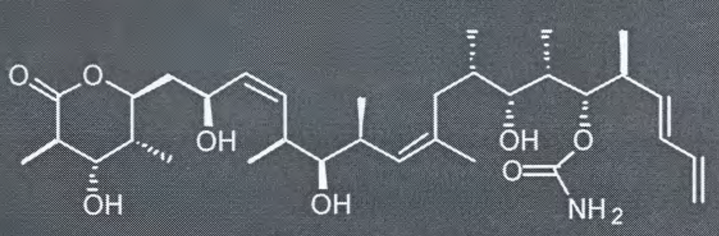
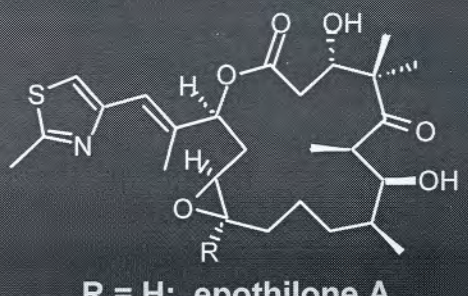
IASOC XI
Ischia, Italy
September 18-23, 2004



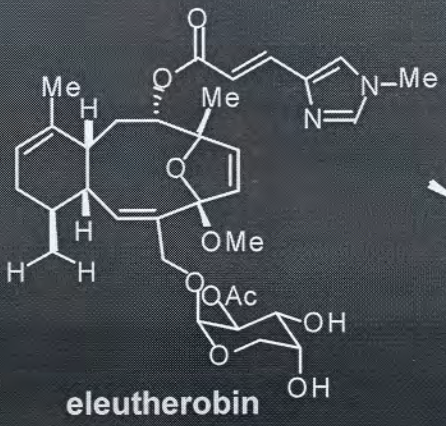
paclitaxel
(Taxol®)
(Taxus brevifolia)
pacific yew bark



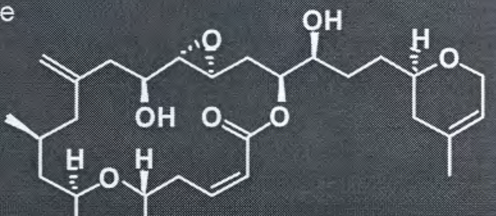
discodermolide
(Discodermia dissoluta)
marine sponge



R = H: epothilone A
R = Me: epothilone B
(Sorangium cellulosum)
myxobacterium

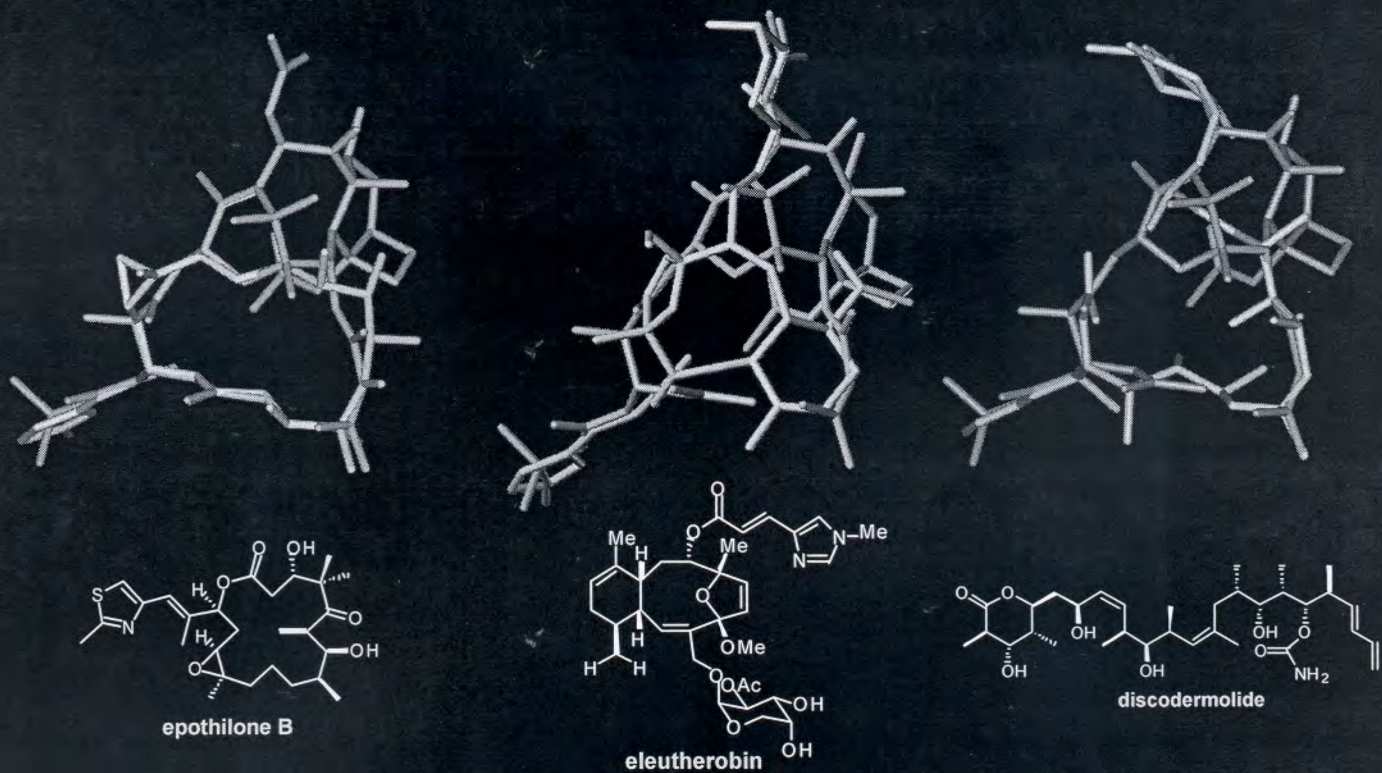


eleutherobin
(Eleutherobia)
soft coral
cf. Sarcodictyn (without sugar)



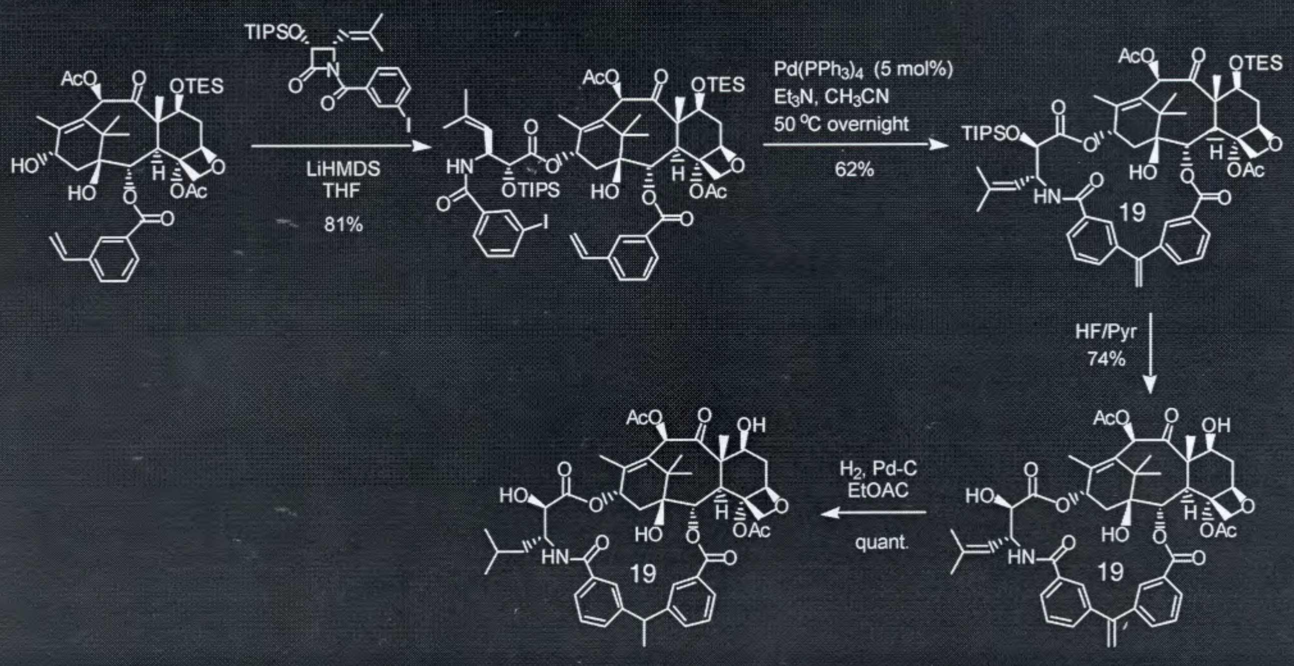
laulimalide
(Cacospongia mycofijiensis)
marine sponge

Overlays of Nonataxel, Epothilone B, Eleutherobin, and Discodermolide



cf. I. Ojima, S. Chakravarty, S. Lin, T. Inoue, S.D. Kuduk, L. He, S. D. Horwitz, S. J. Danishefsky, *Proc. Nat. Acad. Sci.* 96, 4256 (1999).

Hybrid Synthesis via Intramolecular Heck Reaction



SB-T-14811

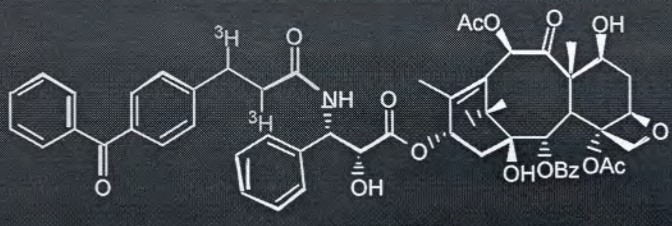
IC50	
LCC6-WT	LCC6-ADR
6 0 ± 0.4 nM	1.6 ± 0.07 μM

SB-T-14801

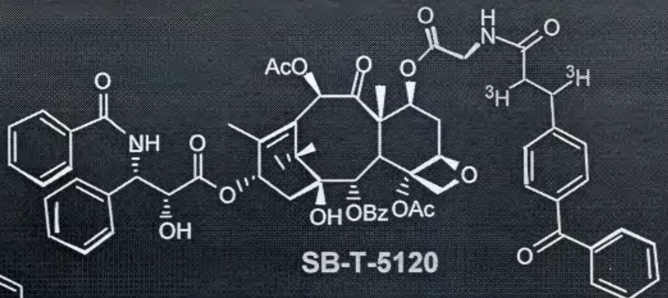
IC50	
LCC6-WT	LCC6-ADR
71 ± 8.8 nM	0.87 ± 0.02 μM

X. Geng, M. L. Miller, S. Lin, and I. Ojima, *Org. Lett.* **5** 3733-3736 (2003)

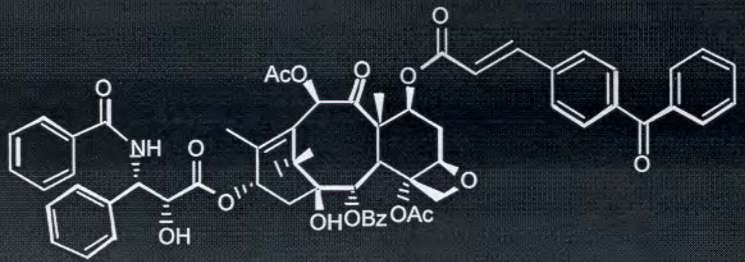
Photoreactive Paclitaxel Analogs



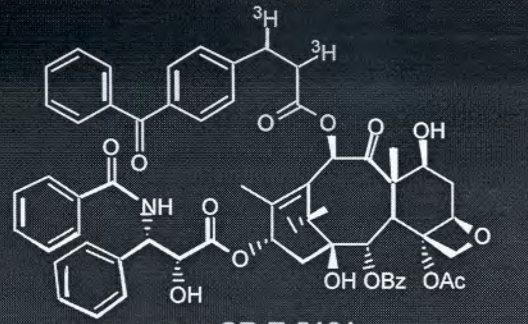
SB-T-5101



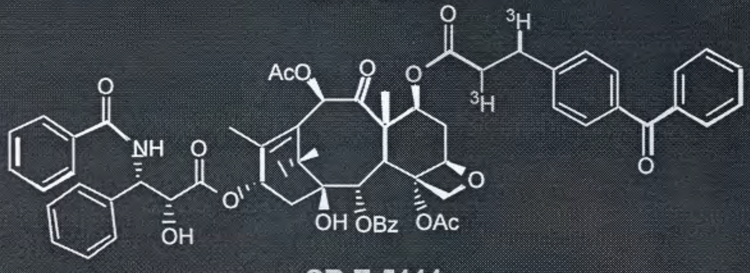
SB-T-5120



SB-T-5110



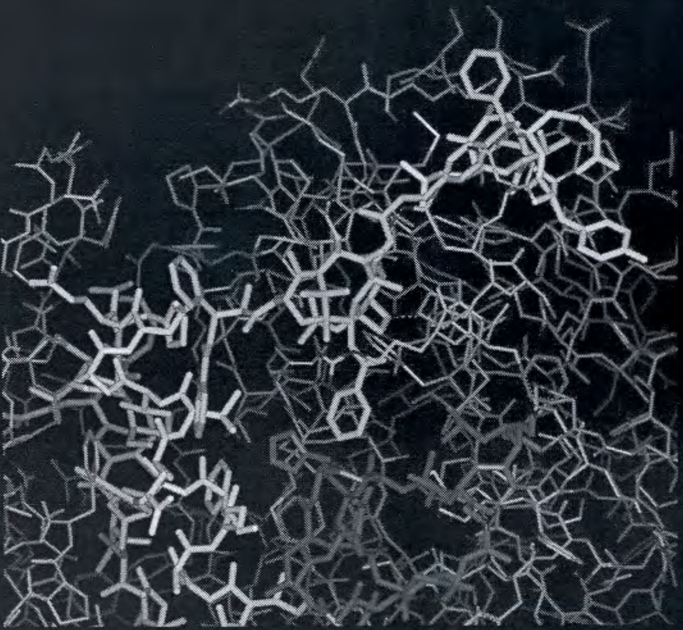
SB-T-5121



SB-T-5111

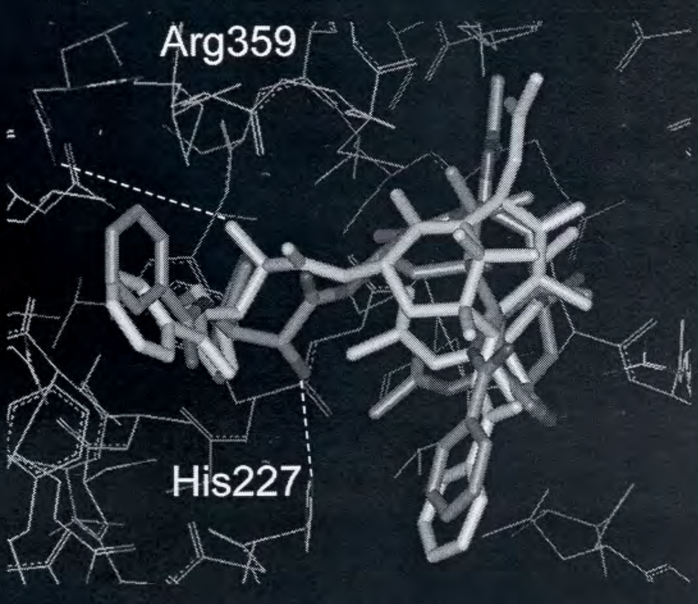
I. Ojima, P.-Y. Bounaud, D. G. Ahern, *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 1189.

SB-T-5111 connected to Arg282



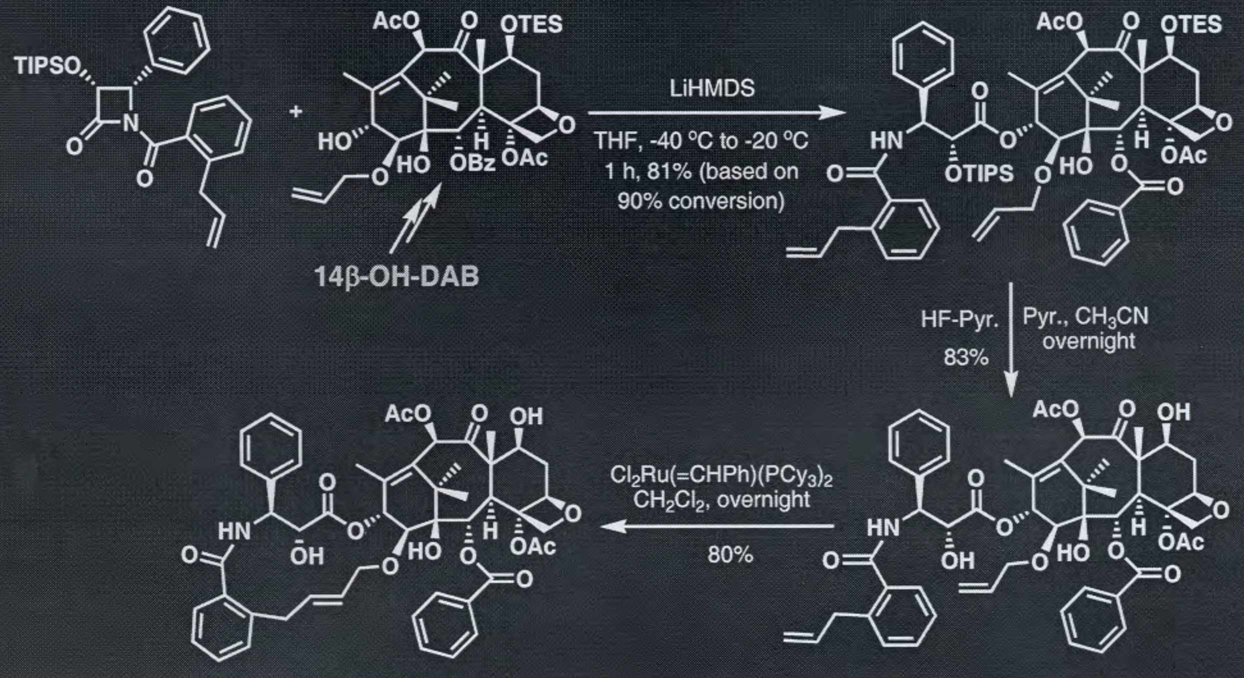
After minimization (Insight II, CVFF) of all β-tubulin (ca. 400 AAs), ca. 90 AA residues in 10Å radius are selected as model binding site

Paclitaxel with Model Biniding Site "REDOR-Taxol"



Fully minimized (Insight II, CVFF) with tubulin model binding site (Green: "REDOR-Taxol"). cf. "T-Taxol" (Yellow)

Synthesis of Conformationally Restricted Taxoid Mimicking Tubulin-Bound Paclitaxel Coformation

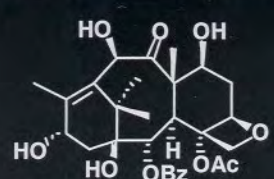


SB-T-2053

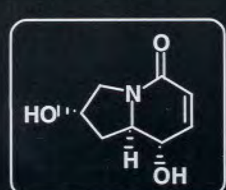
IC_{50} (LCC6-WT) 15 nM (Paclitaxel 4.5 nM)
Tubulin polymerization ability: > Paclitaxel

Liang Sun

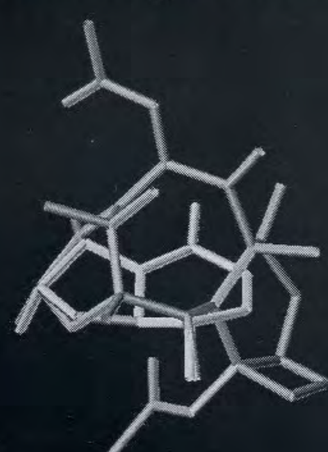
Synthesis of Taxoid Mimics with a Bicyclic Scaffold

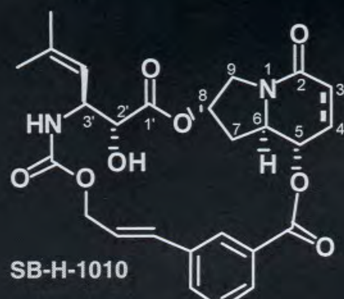


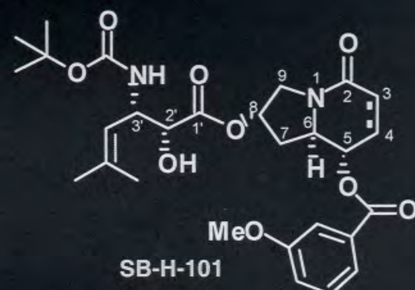
10-deacetylbaccatin III



scaffold mimicking baccatin framework

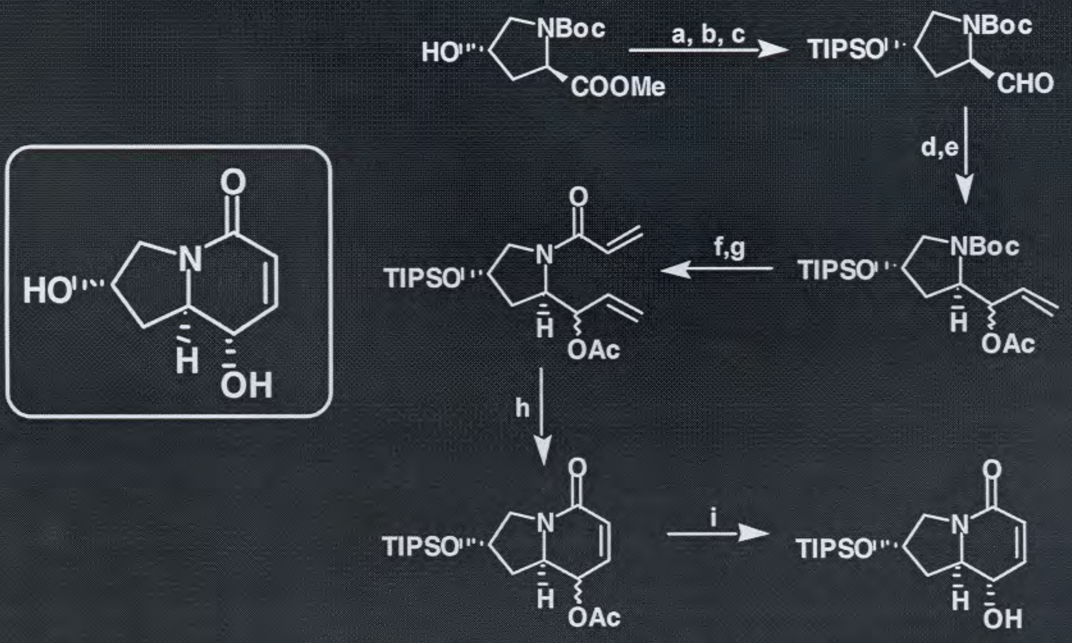






X. Geng, R. Geney P. Pera, R. J. Bernacki, and I. Ojima, *Bioorg. Med. Chem. Lett.* **14**, 3491-3494 (2004)

Synthesis of Enantiopure Bicyclic Scaffold

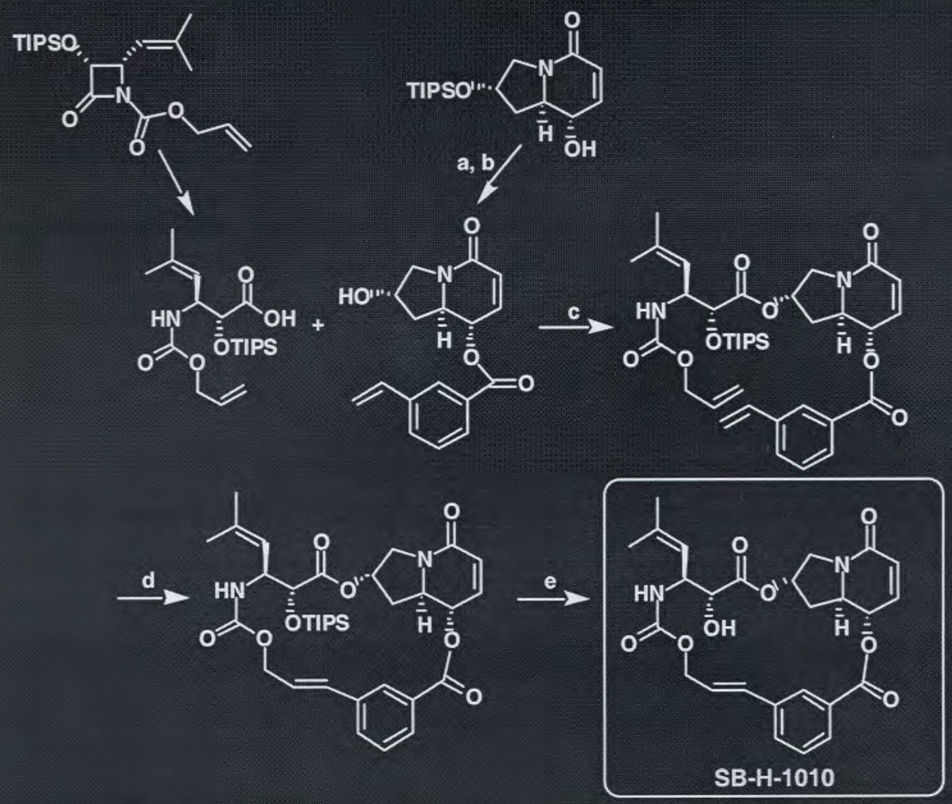


Deric X. Geng

a. TIPSCl (2.0 eq.), imidazole (2.4 eq.), DMF overnight, 97%; **b**. $LiBH_4$ (1.5 eq.), THF, 0 °C to r.t., overnight, quant.; **c**. SO_3-pyr. (3.0 eq.), Et_3N (7 eq.), DMSO, CH_2Cl_2, 0 °C, 1 h, 90%; **d**. vinylmagnesiumchloride (1.5 eq.), THF, -78 °C, 4 h, 80%; **e**. AcCl (2.0 eq.), Et_3N (4.0 eq.), DMAP, CH_2Cl_2, overnight, 85%; **f**. TFA, CH_2Cl_2, 1 h, 0 °C; **g**. acryloyl chloride (1.5 eq.), TEA (3.0 eq.), DMAP, CH_2Cl_2, overnight, 55% for two steps; **h**. $Cl_2Ru{=}CH_2Ph(PCy_3)_2$ (0.2 eq.) CH_2Cl_2, overnight, 90%; **i**. K_2CO_3 (1.2 eq.) THF/H_2O, 1 h, 80%.

X. Geng, R. Geney P. Pera, R. J. Bernacki, and I. Ojima, *Bioorg. Med. Chem. Lett.* **14**, 3491-3494 (2004)

Synthesis of Novel Macrocyclic Taxoid Mimic SB-H-1010

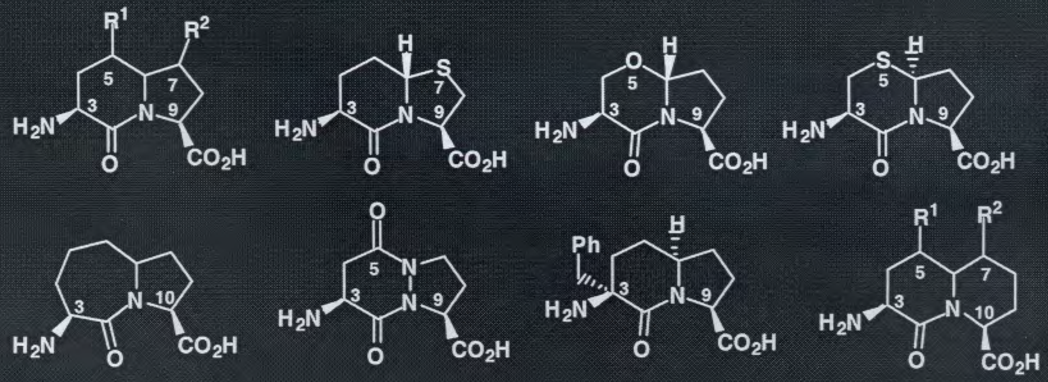


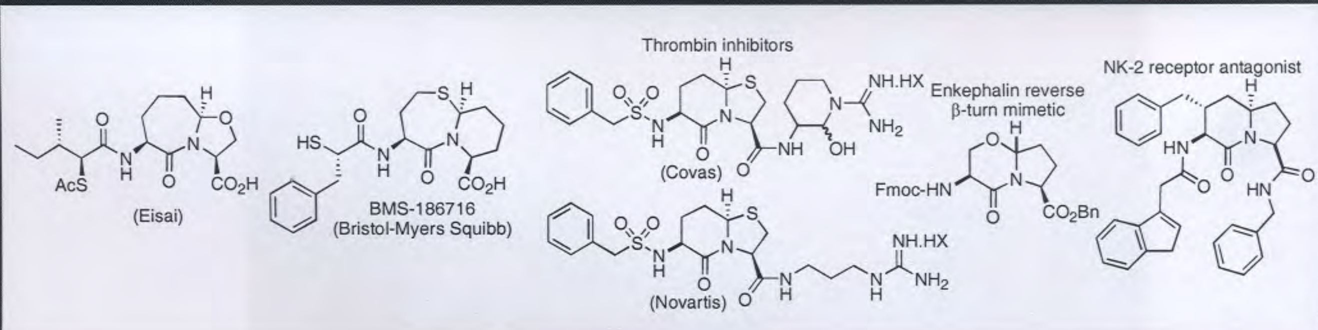
a. 3-vinylbenzoic acid (1.2 eq.), DIC (2 eq.), DMAP, CH_2Cl_2, 1 d, 90%;
b. HF-pyr., CH_3CN/pyr., 17 h, 80%;
c. amino acid (2 eq.), DIC (2 eq.), 4-pyrrolidin-1-yl-pyridine (0.5 eq.), CH_2Cl_2, 1 d, 80%;
d. $Cl_2Ru{=}CH_2Ph(PCy_3)_2$ (0.2 eq.), CH_2Cl_2, 2 d, 90%;
e. HF-Pyr., MeCN, Pyr. 80%.

IC_{50} (μM): LCC6 14
MCF7 8.1
(cf. Cisplatin: MCF7 3.5)

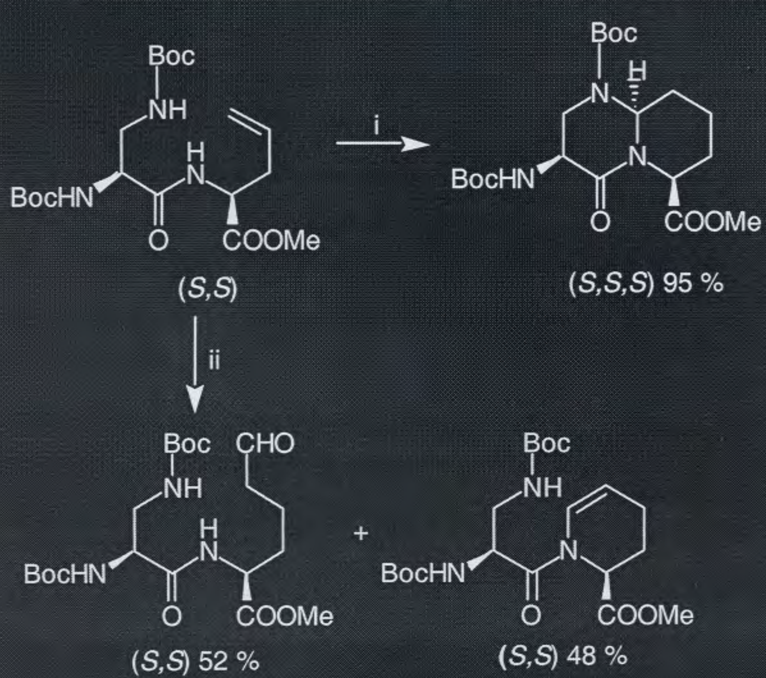
X. Geng, R. Geney P. Pera, R. J. Bernacki, and I. Ojima, *Bioorg. Med. Chem. Lett.* **14**, 3491-3494 (2004)

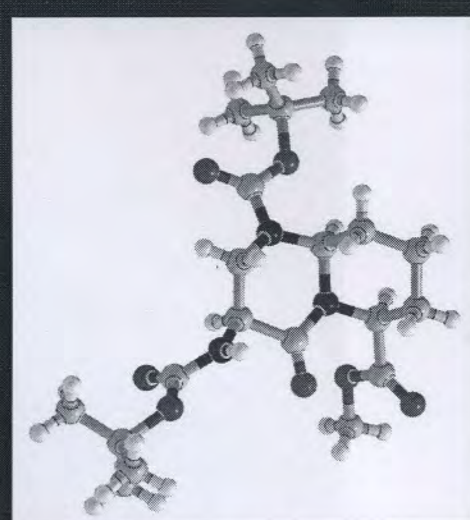
1-Azabicyclo[x.y.0]alkane amino acids and their congeners





CHC Reaction of *N,N*-diBoc-(*S*)-amino-Ala-(*S*)-allylGly-OMe



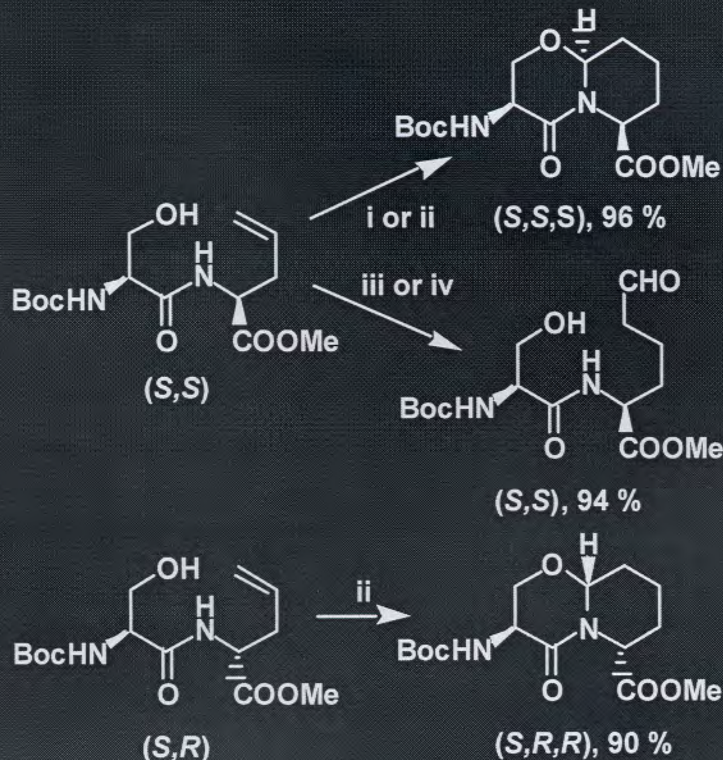


X-ray crystal structure
(Joseph W. Lauher)

Rh(acac)$(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%),
H_2 (2 atm), CO (2 atm), toluene, 65 PC, 20 h
(i) PTSA (10 mol%)
(ii) without PTSA.

N. Mizutani, W.-H. Chiou, and I. Ojima, *Org. Lett.*, **4**, 4575-4578 (2002)

CHC Reactions of Boc-(*S*)-Ser-(*S*)-allylGly-OMe and Boc-(*R*)-Ser-(*S*)-allylGly-OMe



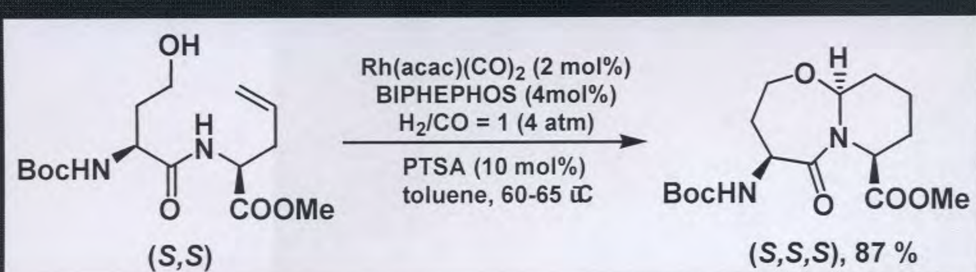
$Rh(acac)(CO)_2$ (2 mol%)
BIPHEPHOS (4 mol%)
H_2 (2 atm), CO (2 atm)
65 °C, 20 h

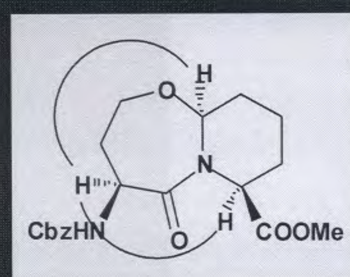
(i) toluene
(ii) toluene, PTSA (10 mol%)
(iii) toluene, DMAP (10 mol%)
iv) THF

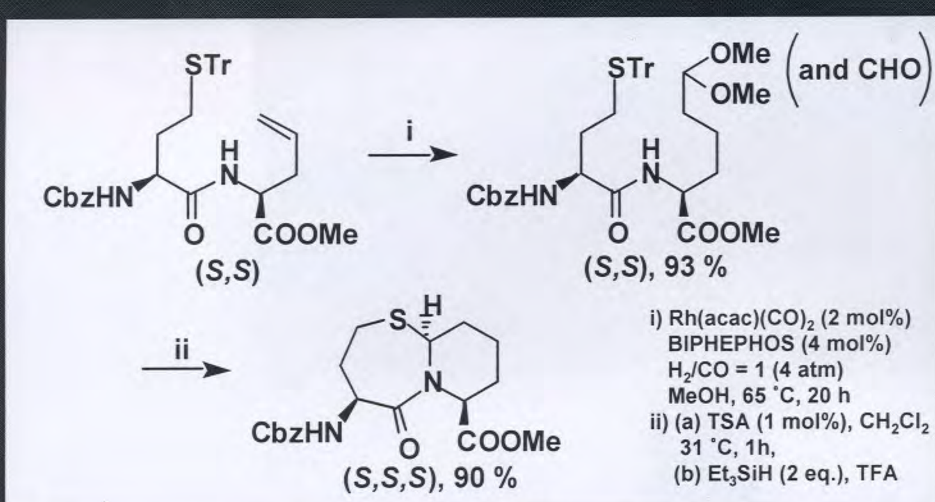
Stereochemistry---NOESY

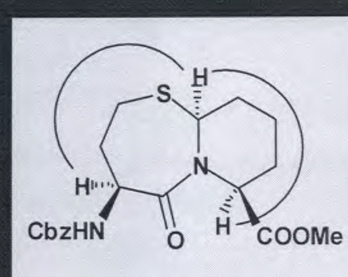
N. Mizutani, W.-H. Chiou, and I. Ojima, *Org. Lett.*, **4**, 4575-4578 (2002)

Synthesis of Azabicyclo[5.4.0] Systems by the CHC Process



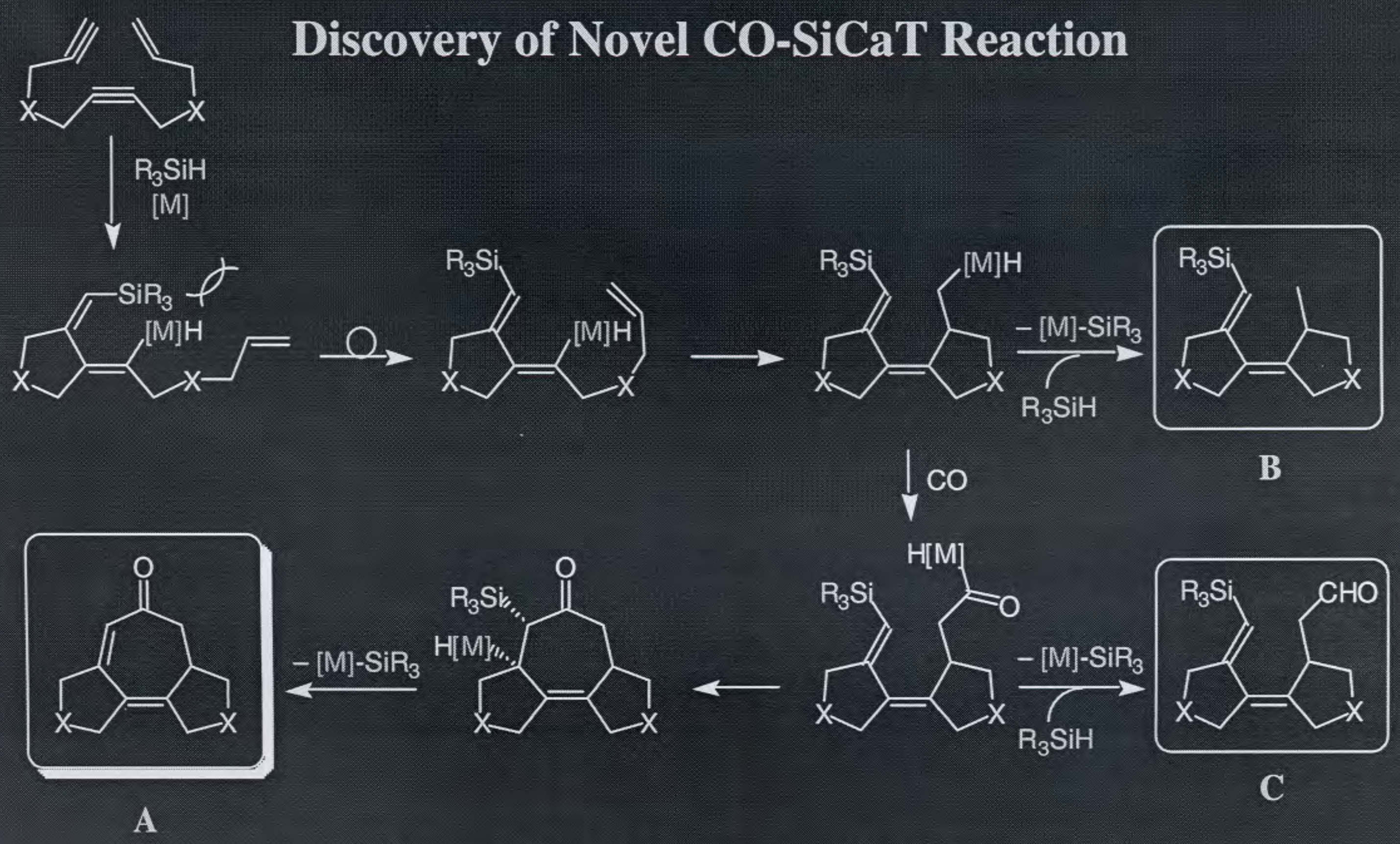






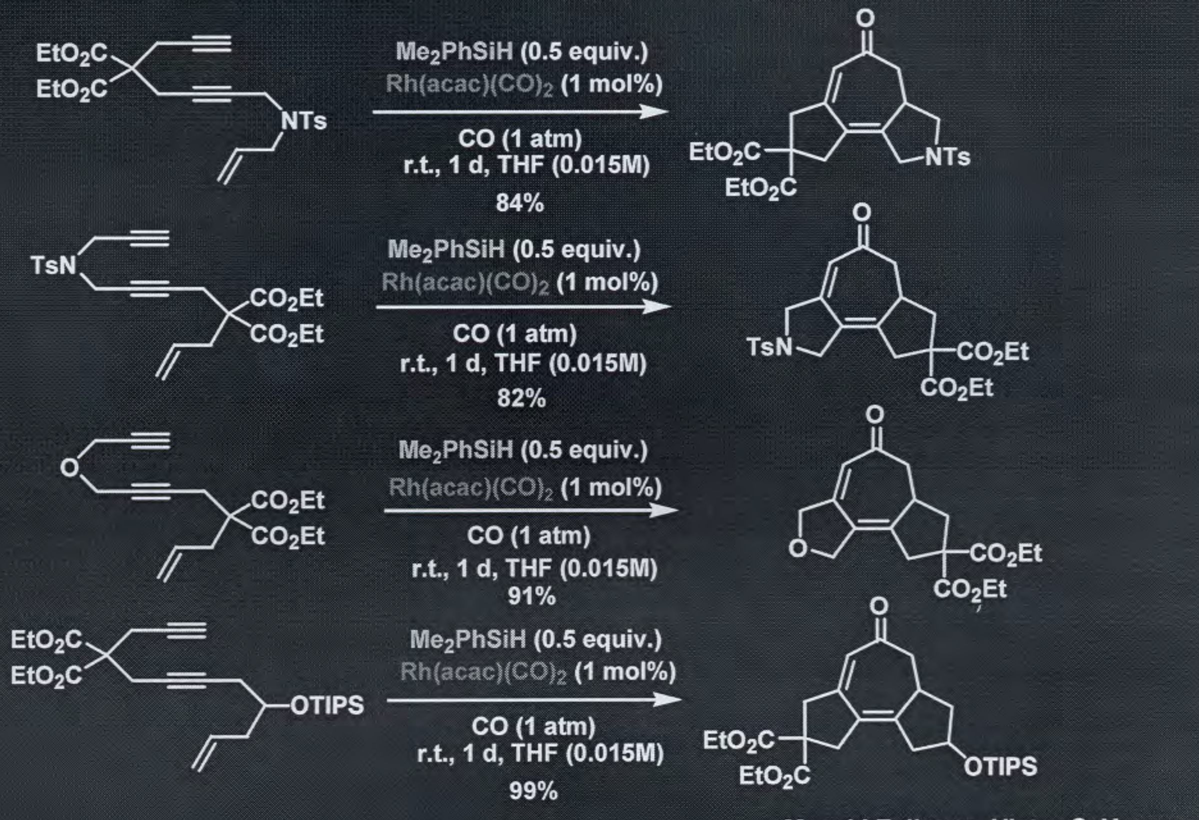
Wen-Hua Chiou

Discovery of Novel CO-SiCaT Reaction



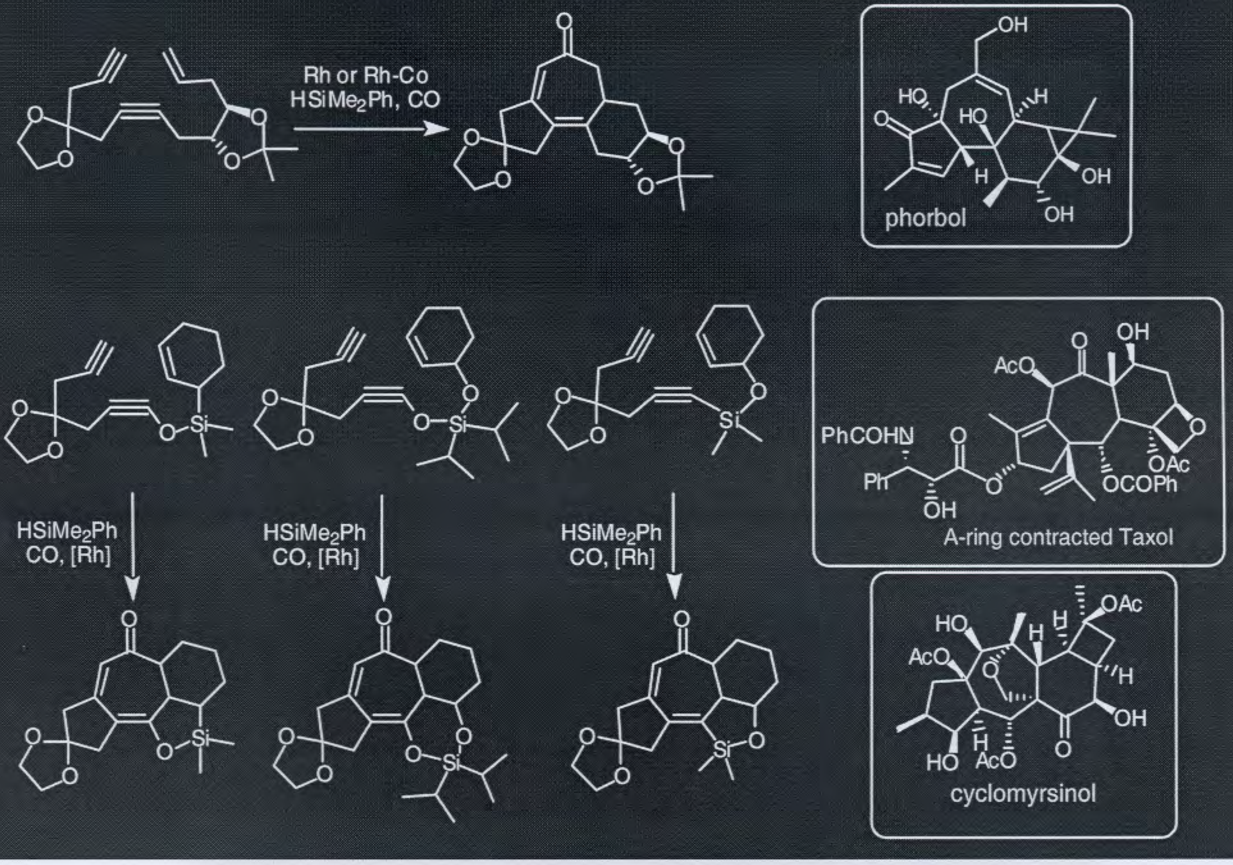
I. Ojima and S.-Y. Lee, *J. Am. Chem. Soc.*, **122**, 2385-2386 (2000)

Novel CO-SiCaT of Enediynes

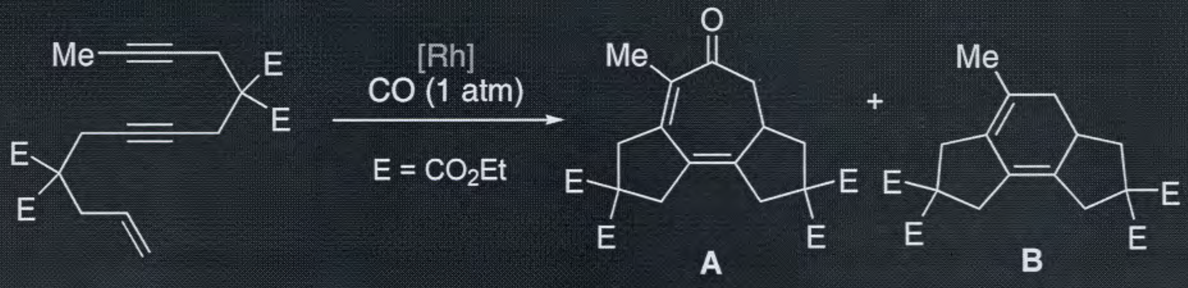


Masaki Fujiwara, Victor C. Vassar

Potential Target Skeletons for Applications of CO-SiCaT



Discovery of Novel [2+2+2+1] Cycloaddition Process

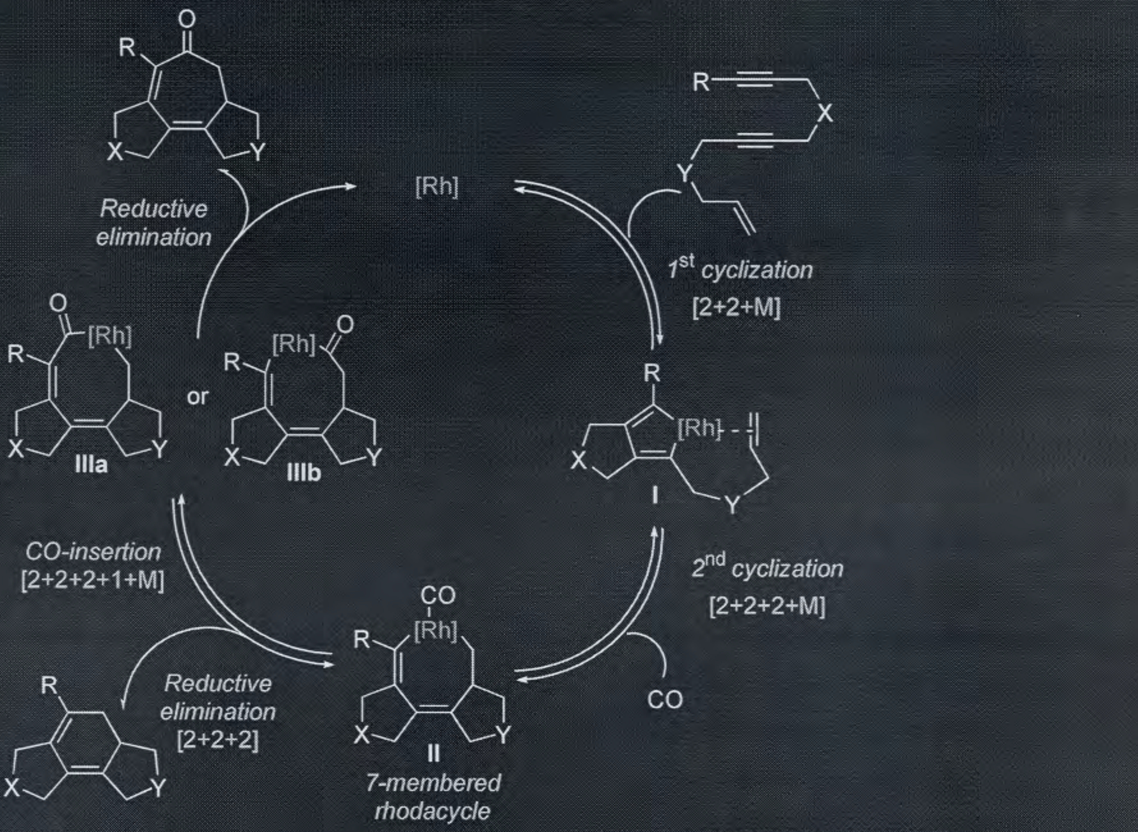


Entry	$PhMe_2SiH$	Catalyst	Solvent	Conditions	A	B
1	none	$[Rh(COD)Cl]_2$	toluene	50 °C, 24h	80	9
2	none	$[Rh(COD)Cl]_2$	$Cl(CH_2)_2Cl$	50 °C, 16h	88	<4
3	none	$Rh(acac)(CO)_2$	toluene	50 °C, 24h	49	20
4	0.5 equiv.	$[Rh(COD)Cl]_2$	toluene	70 °C, 24h	0	70
5	0.3 equiv.	$Rh(acac)(CO)_2$	toluene	70 °C, 3h	0	96
6	0.5 equiv.	$[Rh(COD)Cl]_2$	THF	50 °C, 24h	no reaction	

Masaki Fujiwara, Bibia Bennacer

B. Bennacer, M. Fujiwara, I. Ojima, *Org. Lett.* (2004) in press

Mechanism of Novel [2+2+2+1] Cycloaddition Process



B. Bennacer, M. Fujiwara, I. Ojima, *Org. Lett.* (2004) in press

Scope of Novel [2+2+2+1] Cycloaddition Process

Entry	Substrate	Conditions[1]	Yield (%)[2,3]
1		$Cl(CH_2)_2Cl$, 50 °C, 24 h	97 (93)
2		$Cl(CH_2)_2Cl$, 50 °C, 21 h	79 (77); 20 (17)
3		$Cl(CH_2)_2Cl$, 50 °C, 21 h	53 (52); 46 (43)
4		$Cl(CH_2)_2Cl$, 50 °C, 14 h	88 (85); 11 (8)
5		$Cl(CH_2)_2Cl$, 50 °C, 22 h	84 (83); 13 (11)
6		$Cl(CH_2)_2Cl$, 50 °C, 14 h	69 (62); 29 (26)
7		$Cl(CH_2)_2Cl$, 50 °C, 24 h	70 (66)
8	R = OMe	$Cl(CH_2)_2Cl$, 50 °C, 36 h	92 (87)
9	R = OBn	Toluene, 80 °C, 22 h	91 (86)
10	R = OAc	$Cl(CH_2)_2Cl$, 60 °C, 22 h	82 (75)
11	R R = $C(CH_3)_2$	$Cl(CH_2)_2Cl$, 60 °C, 24 h	78 (72)
12		Toluene, 50 °C, 32 h	59 (56); 32 (28)
13		$Cl(CH_2)_2Cl$, 50 °C, 21 h	53 (51)
14		$Cl(CH_2)_2Cl$, 50 °C, 24 h	>98 (97)

1) All reactions were run with 50-100 mg of enediyne (C = 0.1 M) under CO (1 atm) using 5 mol% of [Rh(COD)Cl]2. 2) 1H-NMR yields using mesitylene as internal standard. 3) Isolated yields based on an average of two runs.

B. Bennacer, M. Fujiwara, I. Ojima, *Org. Lett.* (2004) in press

One of the key problems with conventional chemotherapy:

Cytotoxicity: **In addition to killing cancer cells, anticancer drugs destroy healthy tissue, causing the side effects usually associated with this type of treatment.**

Possible solution

Tumor-Activated Prodrugs (TAPs) — **Combining powerful anti-cancer compounds with tumor-targeting molecules**

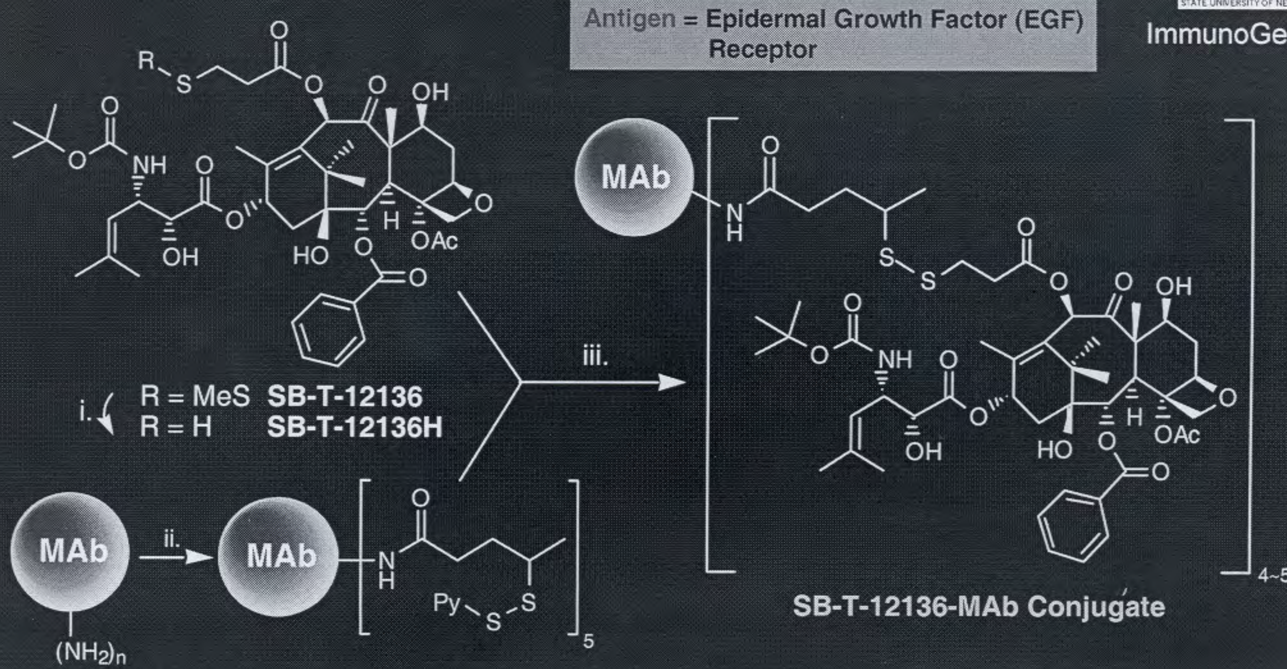
⟹ **Taxoid–Monoclonal Antibody Immunoconjugates**

Synthesis of Taxoid-MAb Conjugate

STONY BROOK
STATE UNIVERSITY OF NEW YORK

ImmunoGen, Inc.

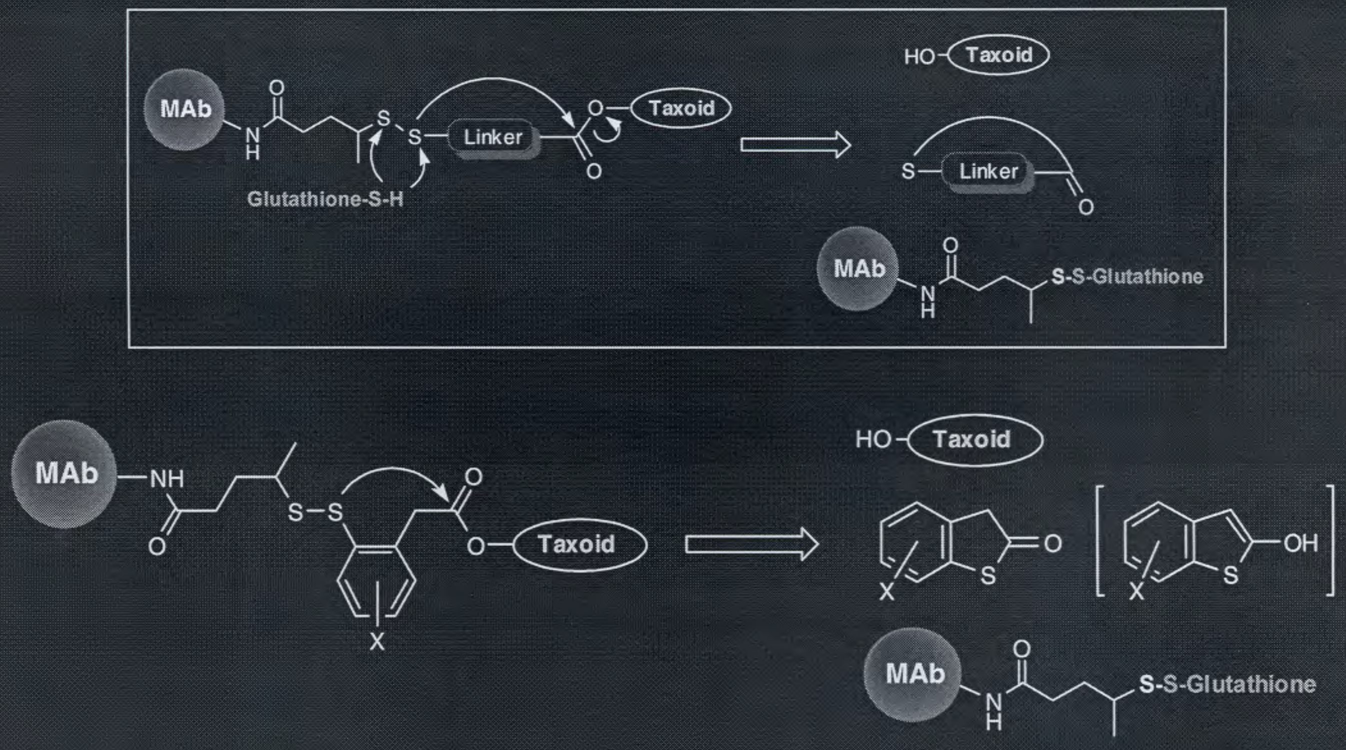
Antigen = Epidermal Growth Factor (EGF) Receptor



(i) dithiothreitol (DTT); (ii) *N*-succinimidyl-4-(2-pyridyldithio) pentanoate (SPP, 10 equiv in ethanol), 50 mM potassium phosphate buffer, pH 6.5, NaCl (50 mM), EDTA (2 mM), 90 min; (iii) 50 mM potassium phosphate buffer, pH 6.5, NaCl (50 mM), EDTA (2 mM), **SB-T-12136H** (1.7 equiv per dithiopyridyl group, in EtOH), 24 h.

I. Ojima et al. *J. Med. Chem.*, **2002**, *45*, 5620-5623.

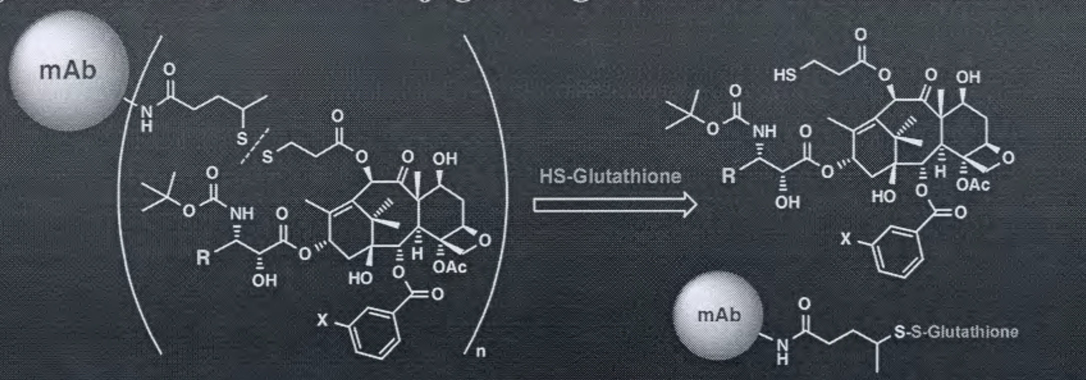
New Linkers for the Second-Generation Taxoid-mAb Conjugates



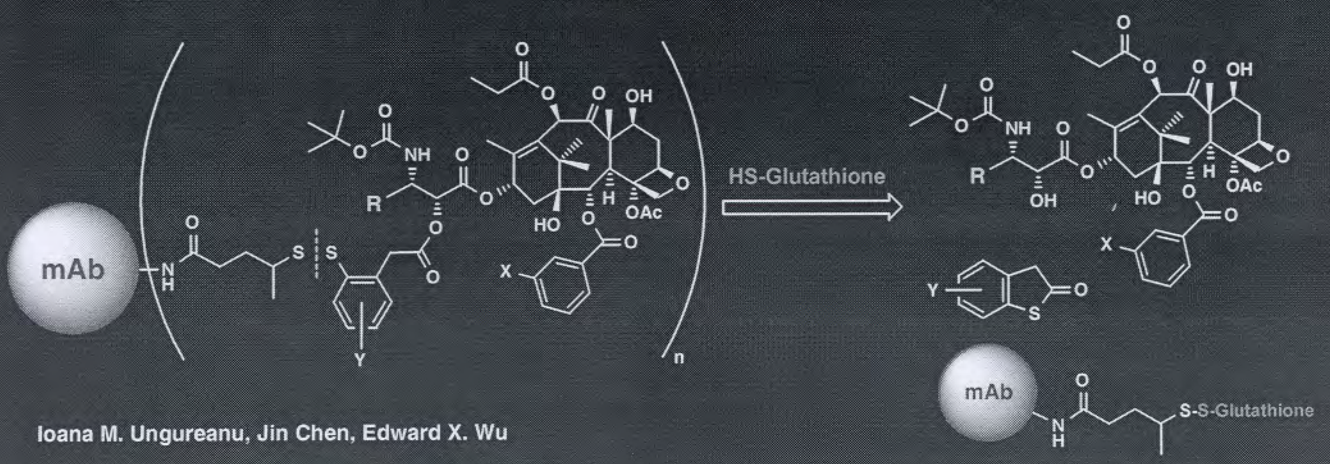
Iwao Ojima, *Chem. Bio. Chem.* **5**, 628-635 (2004)

Ioana M. Ungureanu, Jin Chen

First-generation Taxoid-mAb conjugate --- generation of 10-modified taxoid



Second-generation Taxoid-mAb conjugate --- release of the original taxoid



Ioana M. Ungureanu, Jin Chen, Edward X. Wu

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$$$$

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New York State Science & Technology Foundation
Indena SpA
Rhone-Poulenc Rorer (Aventis)
ImmunoGen, Inc.
Mitsubishi Chemical Corporation
Japan Halon Co., Ltd.
Ajinomoto Co., Inc.
Yuki Gosei Yakuhin K. K.
Central Glass Co., Ltd.

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