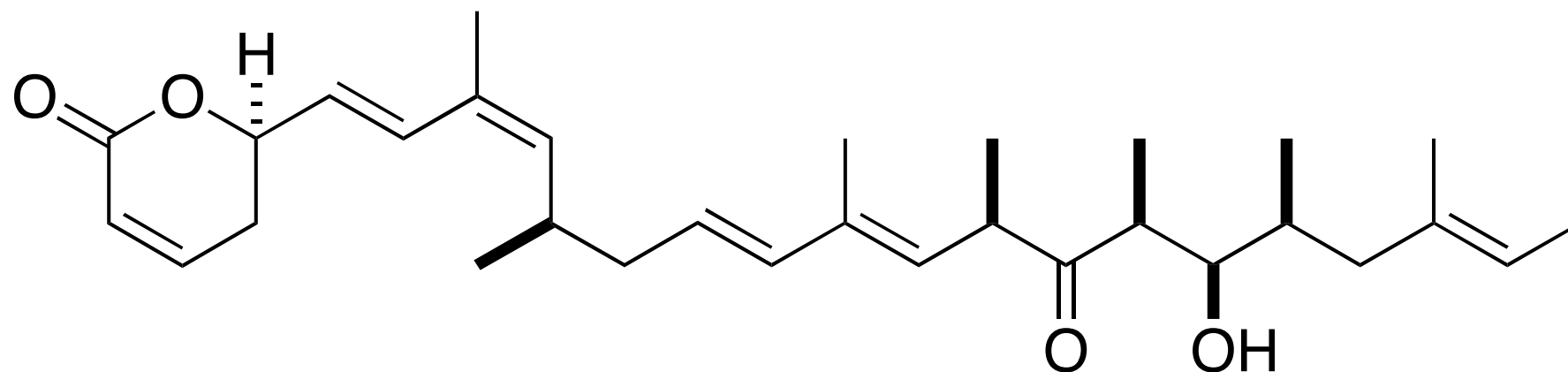
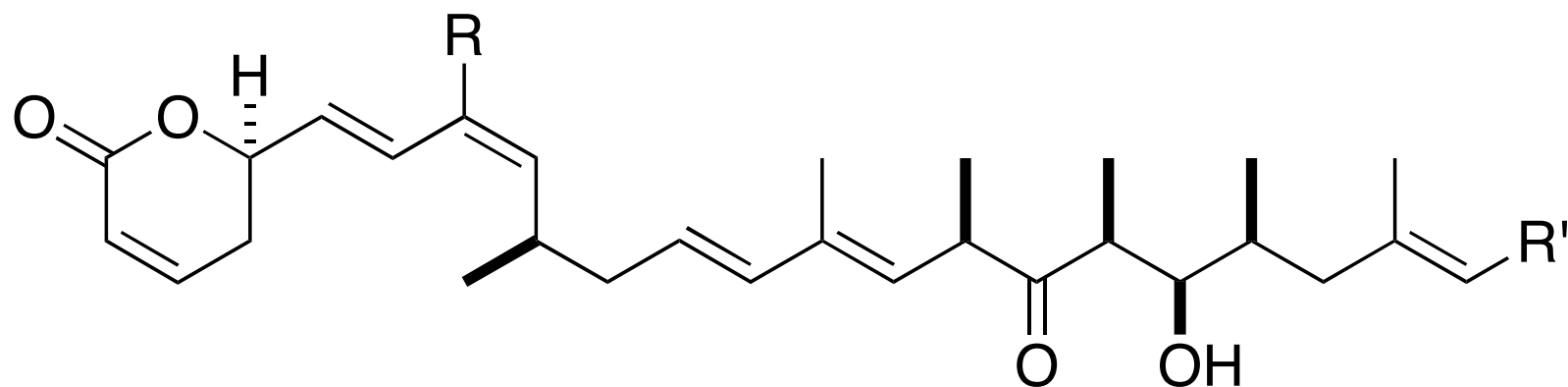


## Current Literature



**Anguinomycins and Derivatives: Total Syntheses,  
Modeling, and Biological Evaluation of the  
Inhibition of Nucleocytoplasmic Transport**  
Oliv Eidam, Ulrike Kutay, Karl Gademmann, et al,  
**JACS, ASAP, 2010**

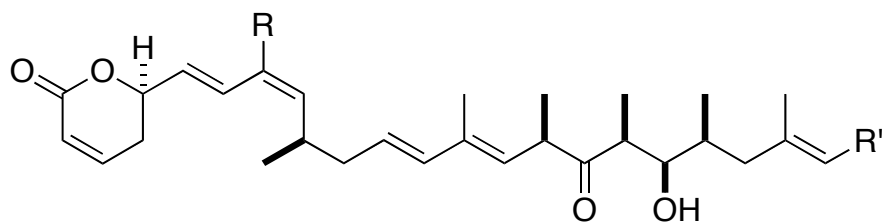
Junyan Han  
Dr. Wipf Group  
Jan. 23, 2010



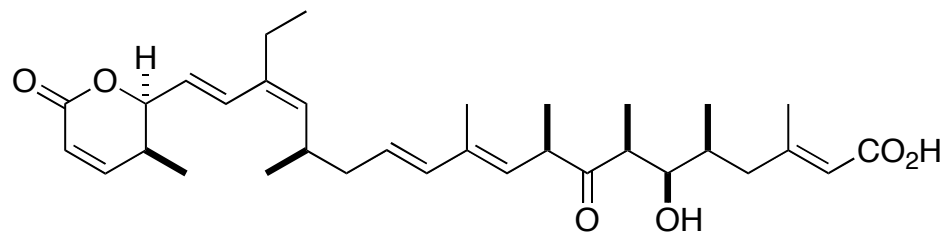
Anguinomycin A:  $R = \text{CH}_3$ ,  $R' = \text{CO}_2\text{H}$   
 Anguinomycin B:  $R = \text{C}_2\text{H}_5$ ,  $R' = \text{CO}_2\text{H}$   
 Anguinomycin C:  $R = \text{CH}_3$ ,  $R' = \text{CH}_3$   
 Anguinomycin D:  $R = \text{C}_2\text{H}_5$ ,  $R' = \text{CH}_3$

- Isolated from *Streptomyces* strains
- IC50 0.15 – 1.7 nM against normal and transformed rat cells
- Selective induce apoptosis of p-RB-inactivated tumor cells, while inducing growth arrest in normal cells
- Inhibits nucleocytoplasmic transport

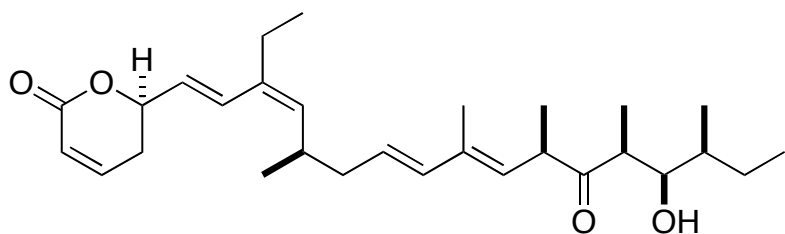
Hayakawa, Y, et al, *J. Antibiot.* 1987, 40, 1349; Hayakawa, Y, et al, *J. Antibiot.* 1995, 48, 954



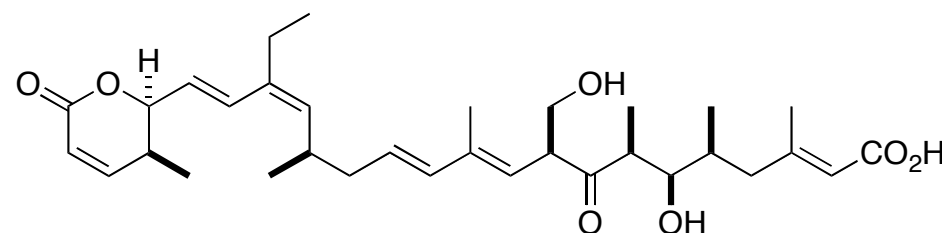
Anguinomycin A: R = CH<sub>3</sub>, R' = CO<sub>2</sub>H  
 Anguinomycin B: R = C<sub>2</sub>H<sub>5</sub>, R' = CO<sub>2</sub>H  
 Anguinomycin C: R = CH<sub>3</sub>, R' = CH<sub>3</sub>  
 Anguinomycin D: R = C<sub>2</sub>H<sub>5</sub>, R' = CH<sub>3</sub>  
 IC<sub>50</sub> = 0.1 -1.7 nM



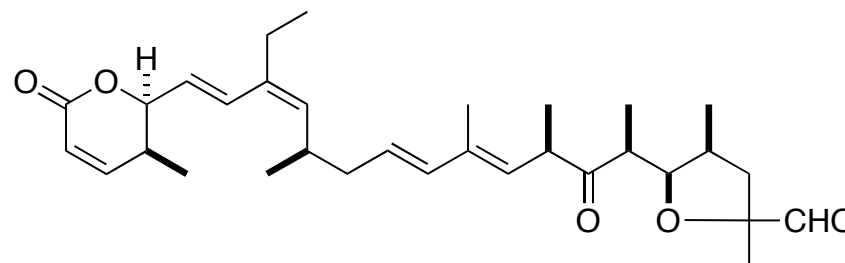
Leptomycin B (LMB)  
 over 1000 pubs



(-)-Callystatin A  
 IC<sub>50</sub> = 10PM



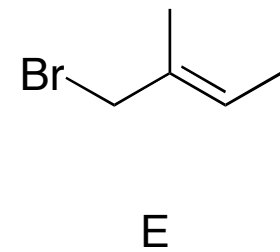
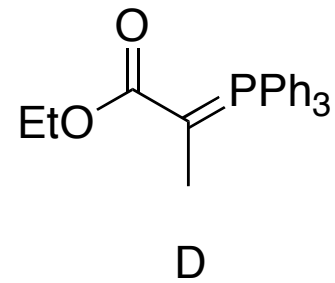
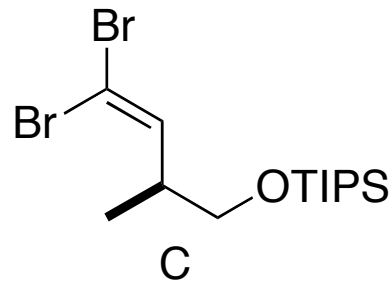
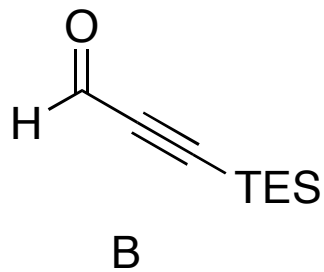
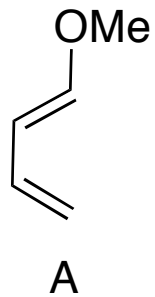
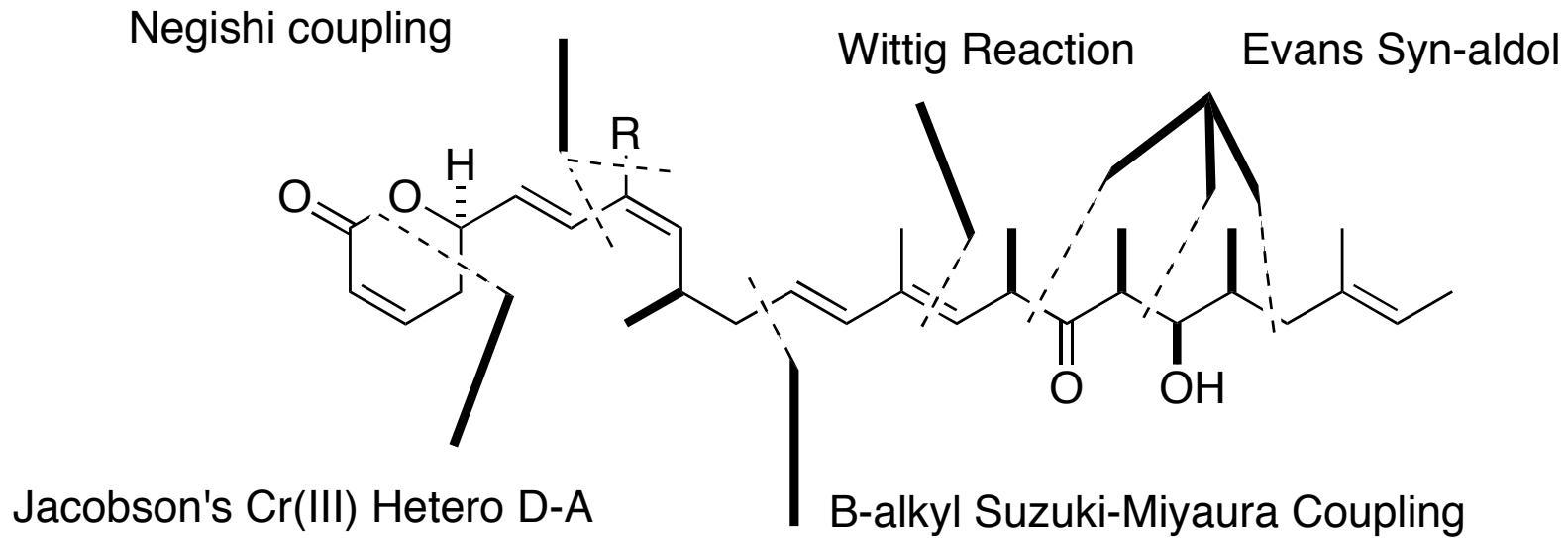
(-)-Kazusamycin A



Leptofuranin D

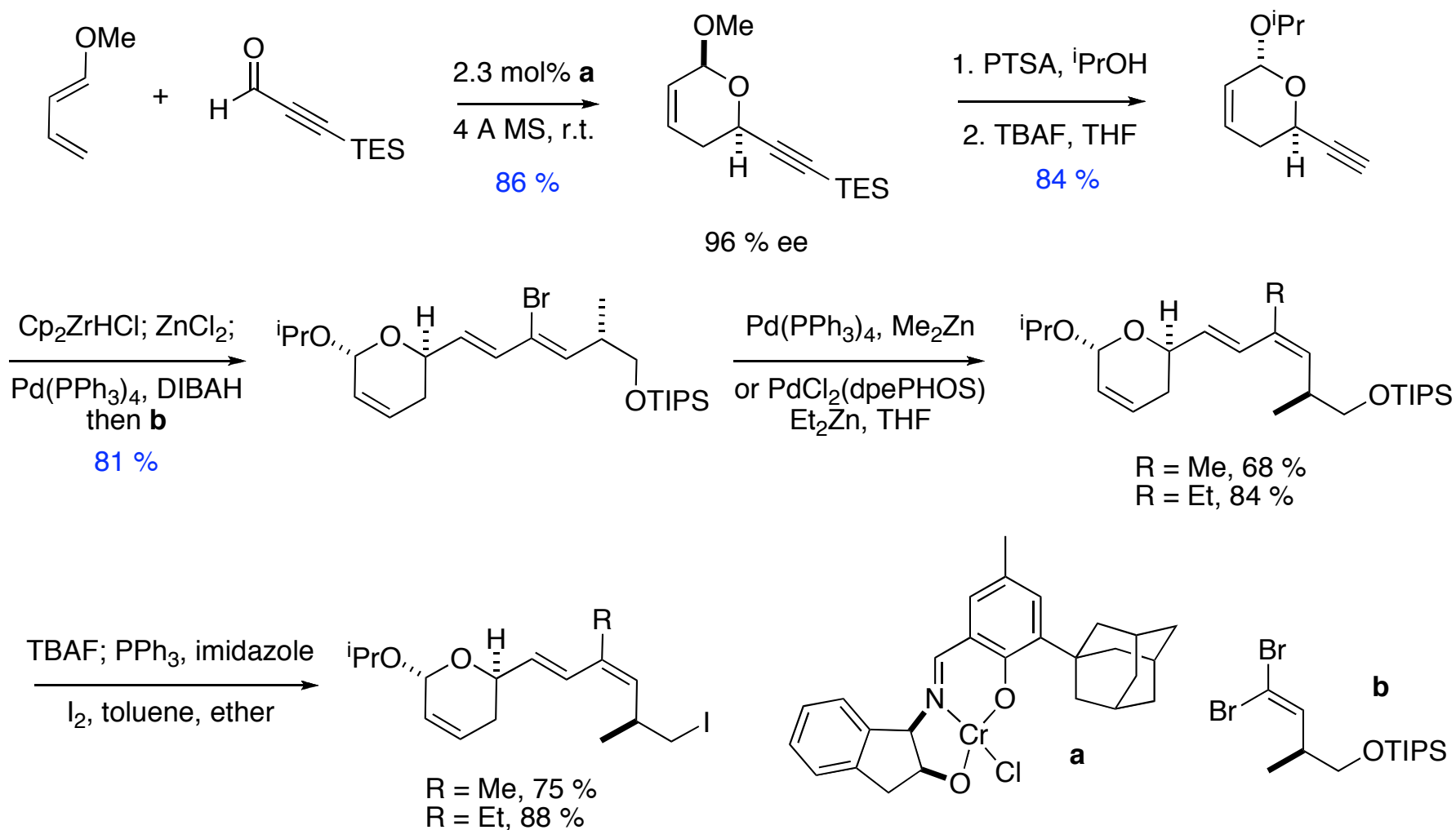
Highly Cytotoxic,  
 Structure Similar Polyketides

# Retro-Synthesis

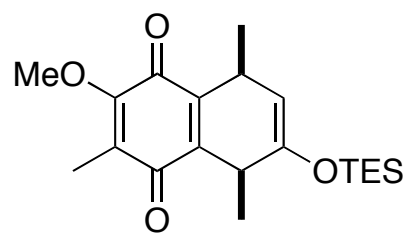
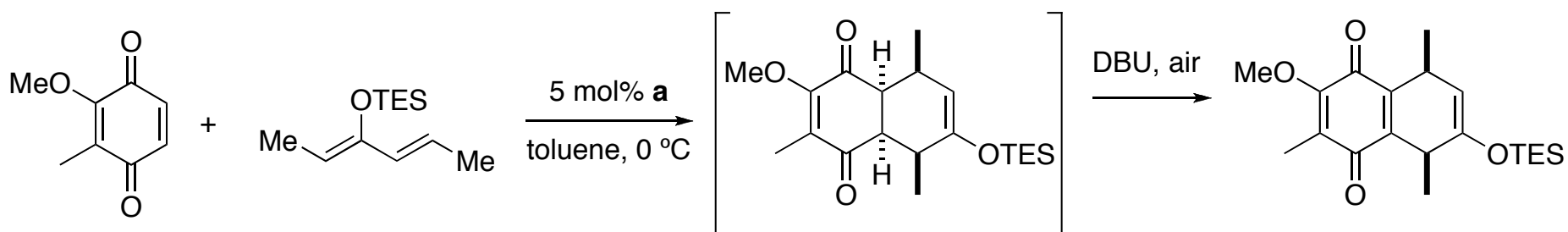


4

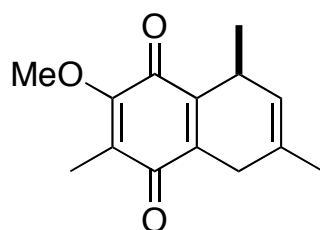
# Synthesis of C1-C11 Fragment



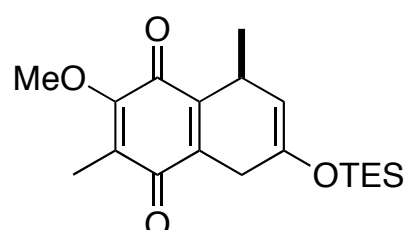
# Highly Enantio- and Regioselective Quinone Diels-Alder Reactions Catalyzed by a Tridentate Schiff Base CrIII Complex



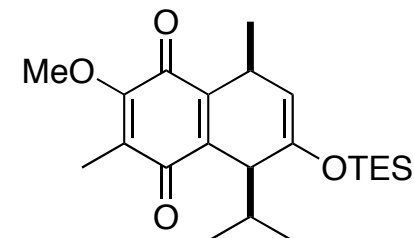
96 % ee  
12:1



93 % ee  
>30:1



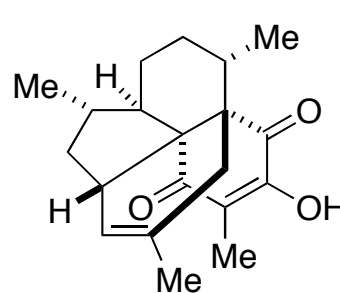
97 % ee  
25:1



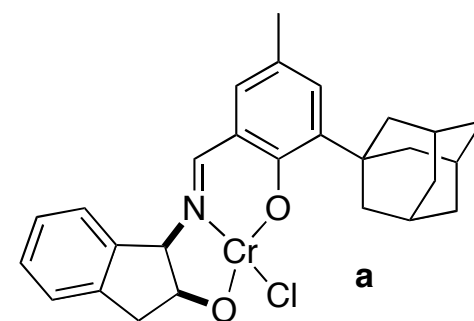
90 % ee  
9:1

E. Jacobson, et al, ACIE, 2005, 6043

E. Jacobson, et al, ACIE, 2005, 6047

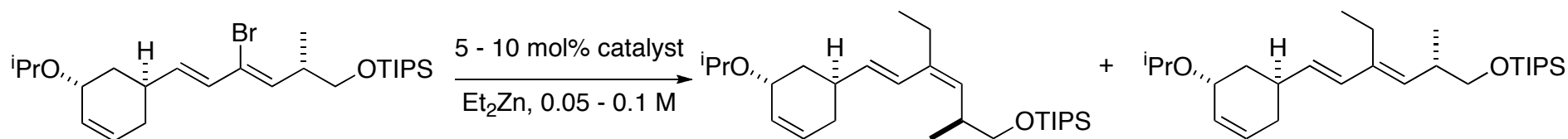


Colombiasin A



**a**  
6

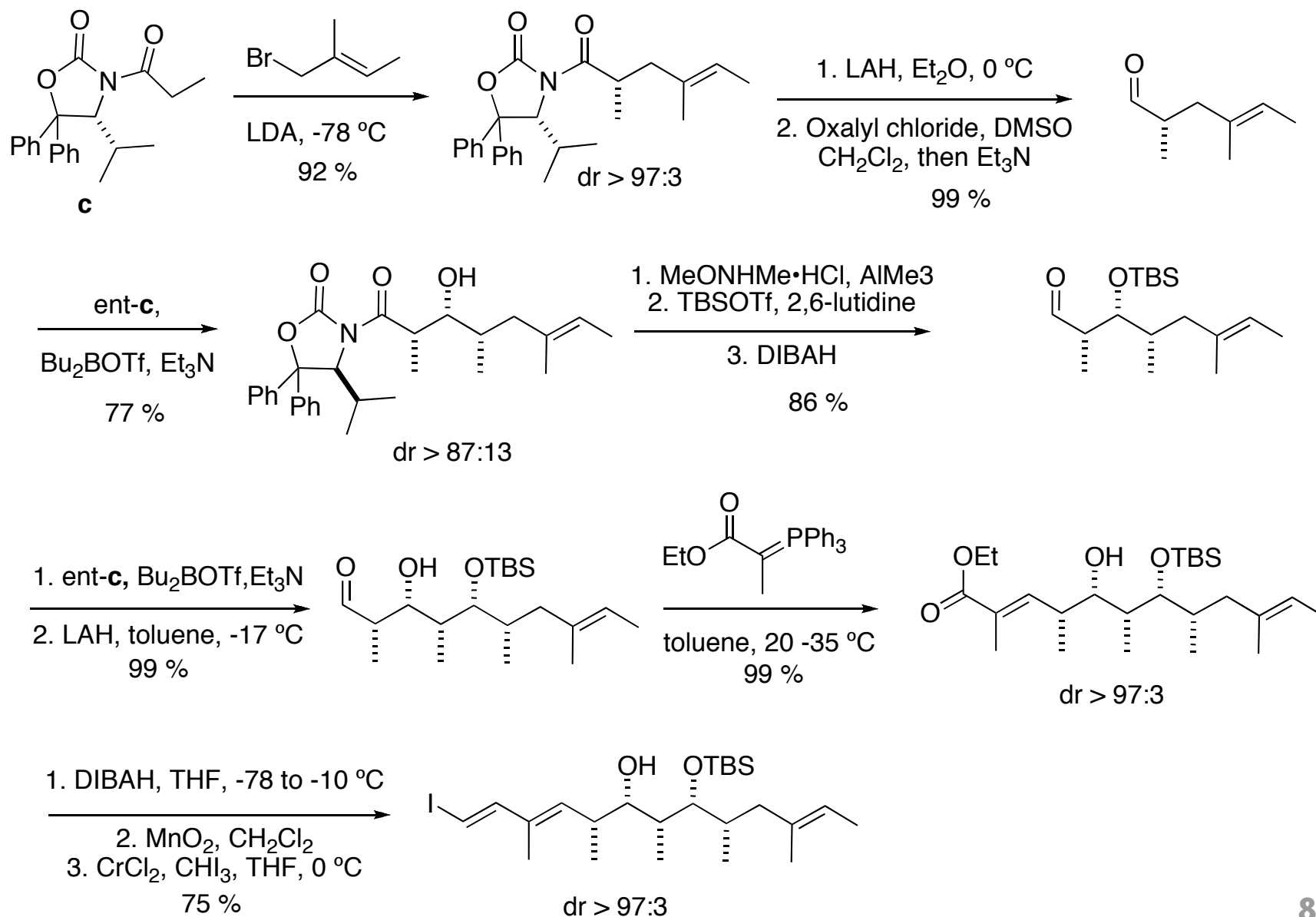
# Negishi Coupling with Selective Inversion and Retention of the Configuration



Catalyst	Equivalents (mol %)	Concentration	Reaction time	Ratio s.m./cis/trans	Yield
$\text{Pd}(\text{PPH}_3)_4$	5	0.06	24	0.14/1.00/0.38	n.d.
$\text{Pd}(\text{PPH}_3)_4$	10	0.1	28	0.16/1.00/0.17	n.d.
$\text{PdCl}_2(\text{PPh}_3)_2$	10	0.05	20	1.00/1.08/0.66	n.d.
$\text{Pd}(\text{PtBu}_3)_2$	10	0.05	3.5	0/0/1.00	75%
$\text{PdCl}_2(\text{DPEphos})$	5	0.08	14	0/1.00/0	84%
$\text{PdCl}_2(\text{DPEphos})$	10	0.08	14	0/1.00/0	84%
Trans-di(u-acetato)bis(o-tolylphosphino)benzyl dipalladium(II)	10	0.05	20	0/0/1.00	65%
Allyl[1,3-bis(mesityl)imidazol-2-ylidene]palladium chloride	10	0.05	20	0/0/1.00	77%

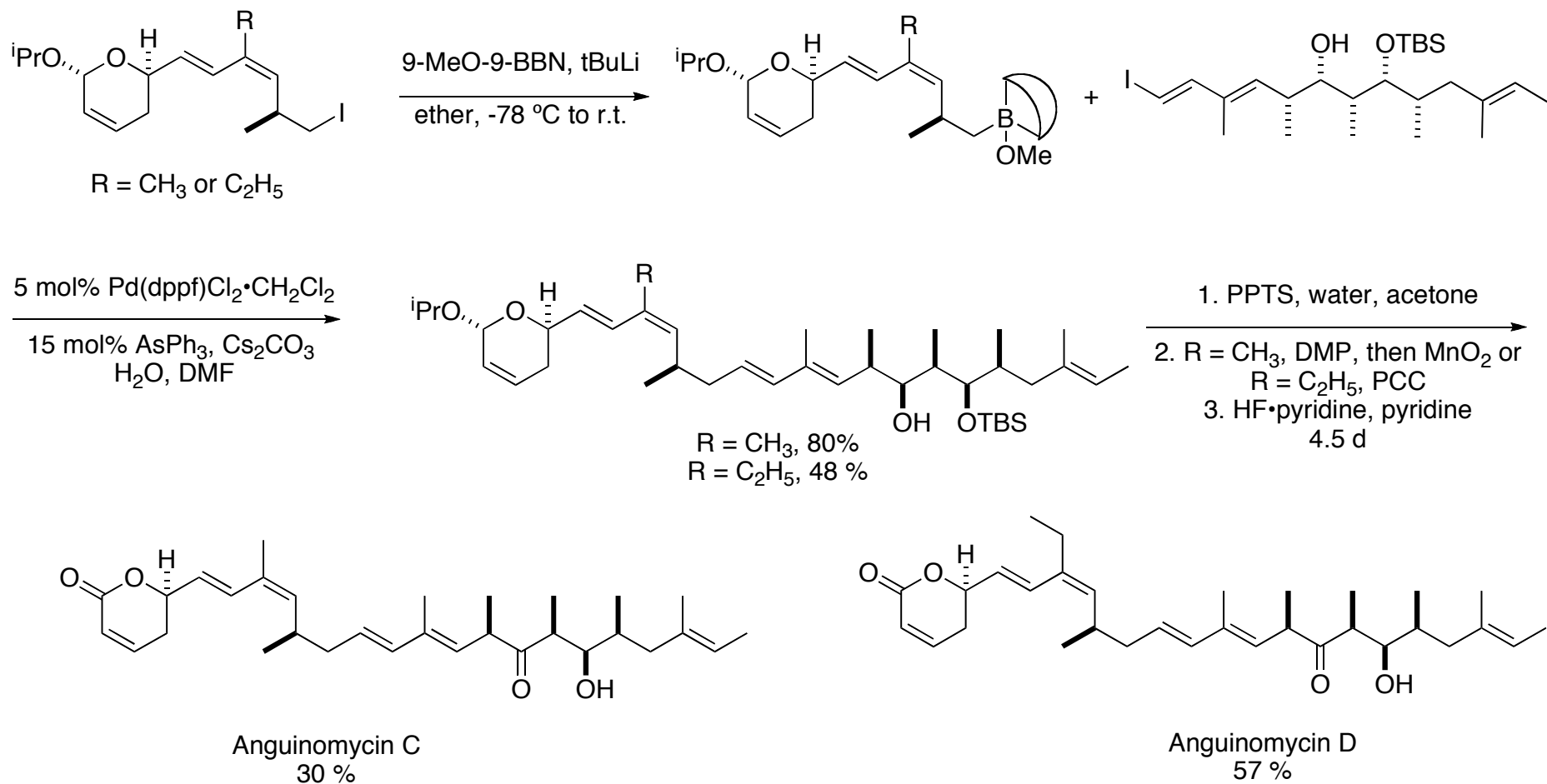
7

# Synthesis of C12-C24 Fragment

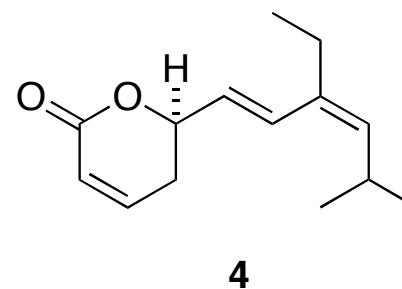
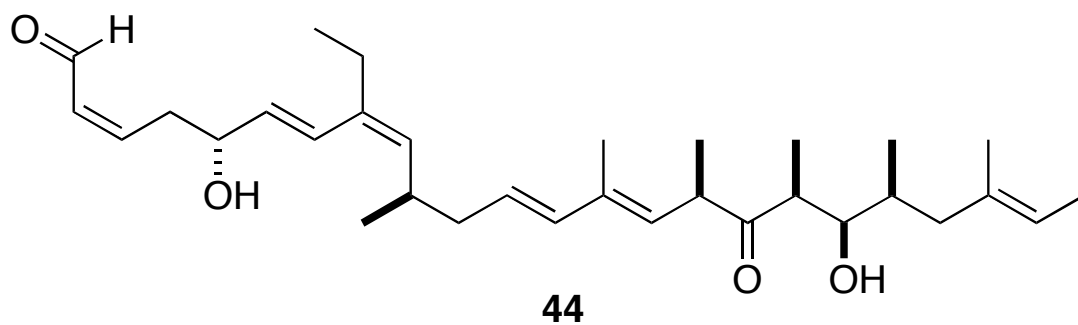
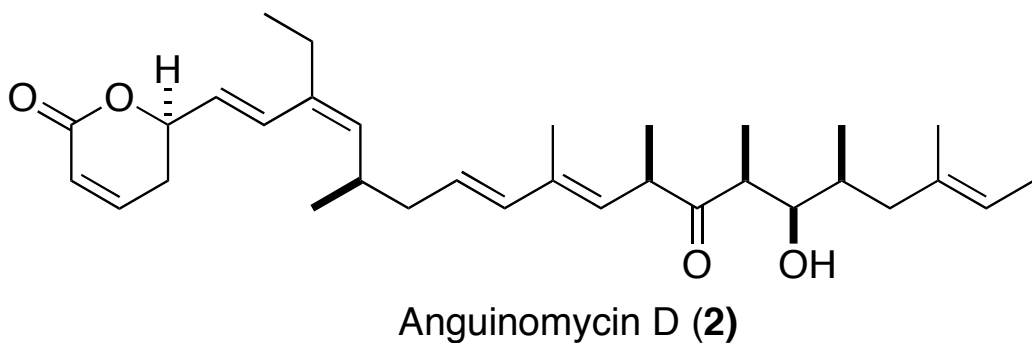
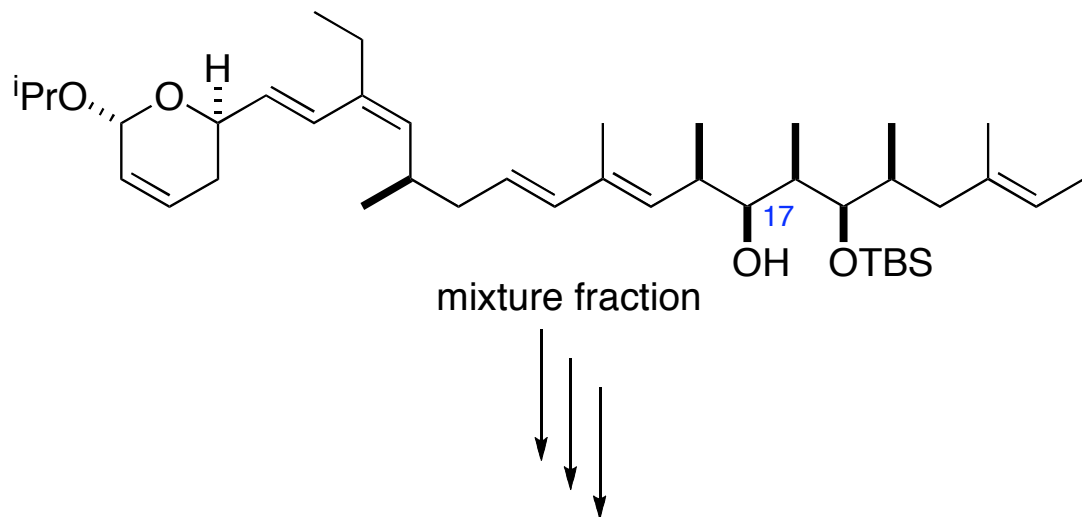




# Completion of the Synthesis

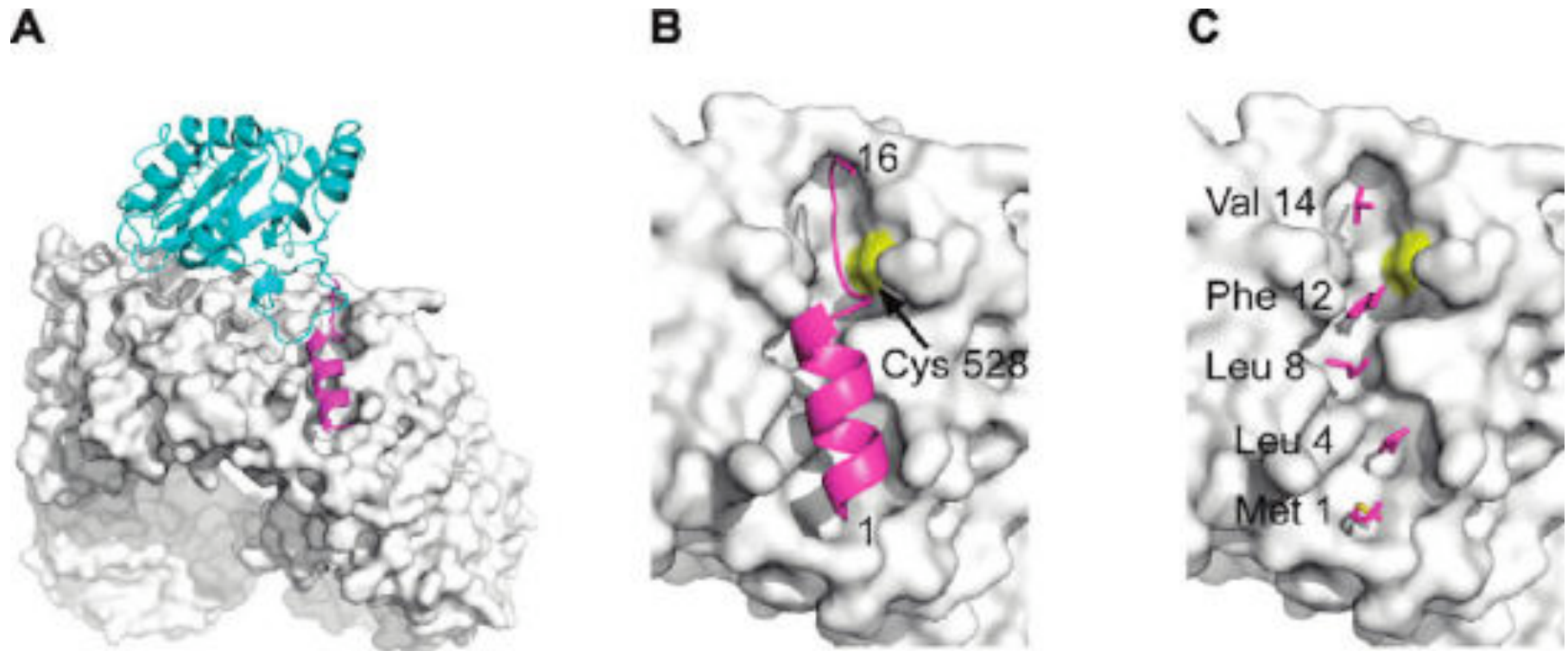


# Compounds Generated Using a Mixture of Diastereoisomers at C17





# Chromosome maintenance region 1 (CRM1) and SNUPN Complex



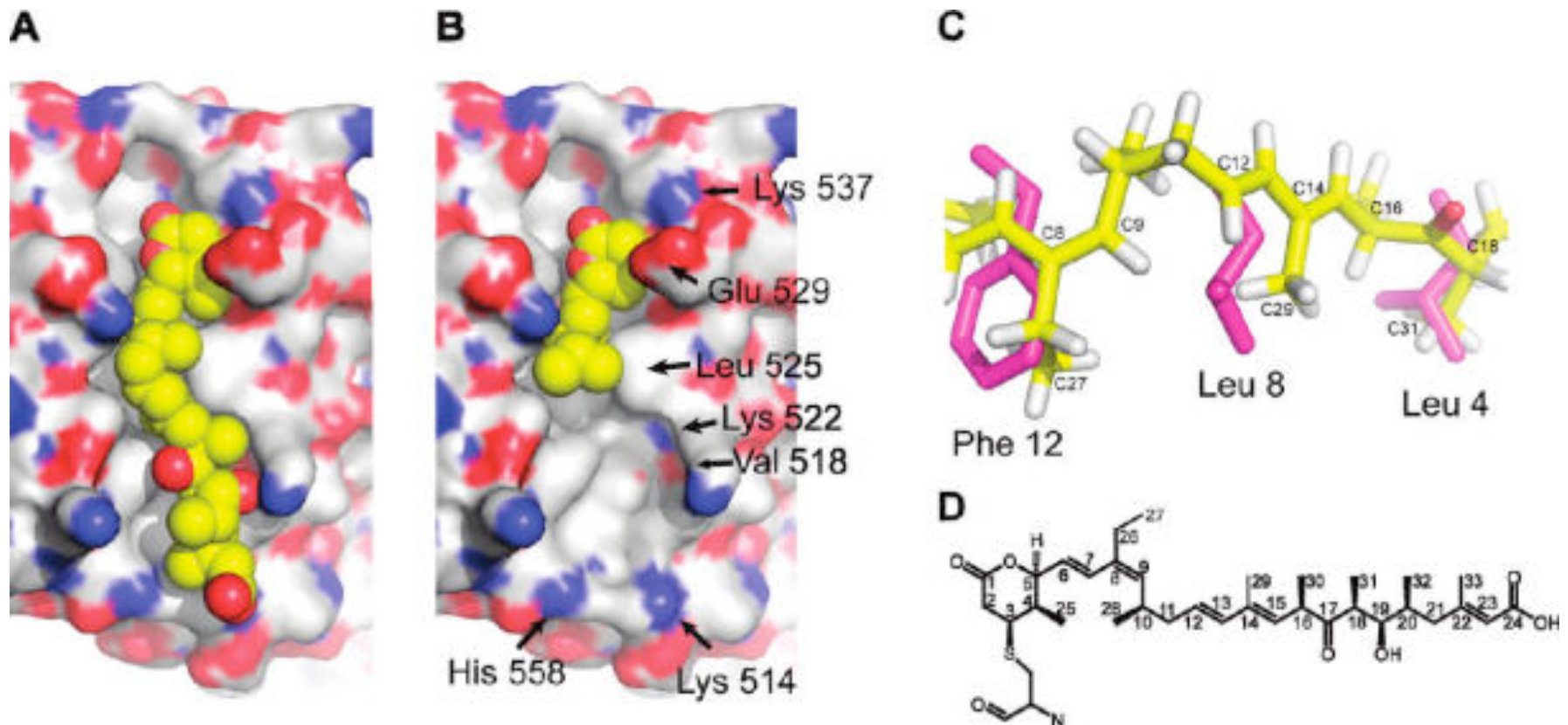
**A. X-Ray structure of the CRM1-SNUPN complex**

**B. Close-up view on the N-terminal nuclear export signal (NES) of SNUPN**

**C. Hydrophobic residues of SNUPN NES define five pockets in the CRM1 groove**

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# Models of CRM1-Inhibitor Complex



Sphere models of Leptomycin B adduct (**A**) and compound **4** adduct (**B**).  
**C**. Superposition of LMB adduct with NES residues of SNUPN. LMB depicted in yellow with hydrogen white.  
**D**. Atom numbering of LMB adduct.

# Conclusion

- Total synthesis of Anguinomycin C (6.7%) and D (6%) were obtained in 18 steps (longest linear sequence).
- Inhibitors of CRM1, shut down protein export at  $> 10$  nm
- Structure basis for this inhibition.  
Lactone ring and side chain effects.