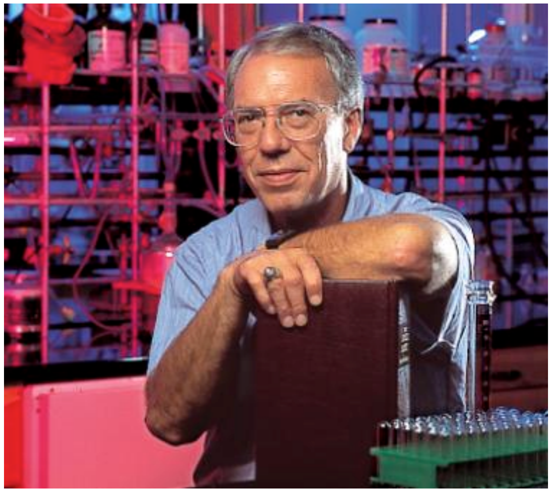
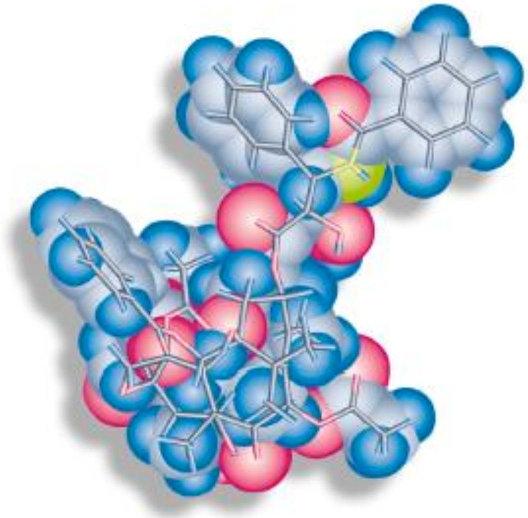




Robert A. Holton

Career-In-Review (CIR)

Jenny M. Baxter (Leighton Group)
May 25, 2007

Synthesis Literacy Group
Columbia University Chemistry

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

Career Snapshot

<u>1965</u> *B.S. at University of North Carolina*

<u>1971</u> *Ph.D. at Florida State University (Adv. Martin Schwartz)*

<u>1971-73</u> *Postdoc at Stanford University*

<u>1973-78</u> *Assistant Professor at Purdue University*

<u>1978-85</u> *Associate Professor at Virginia Tech*

<u>1985-present</u> *Professor at Florida State University*

Chief Scientific Officer and co-founder of Taxolog, Inc.

President and founder of MDS Research Foundation and Syncure, Inc.

Five Most Cited Papers (ISI Web of Science)

1. **HOLTON RA**, SOMOZA C, KIM HB, et al.
   FIRST TOTAL SYNTHESIS OF TAXOL .1. FUNCTIONALIZATION OF THE B-RING
   JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 116 (4): 1597 -1598 FEB 23 1994
   Times Cited: 398

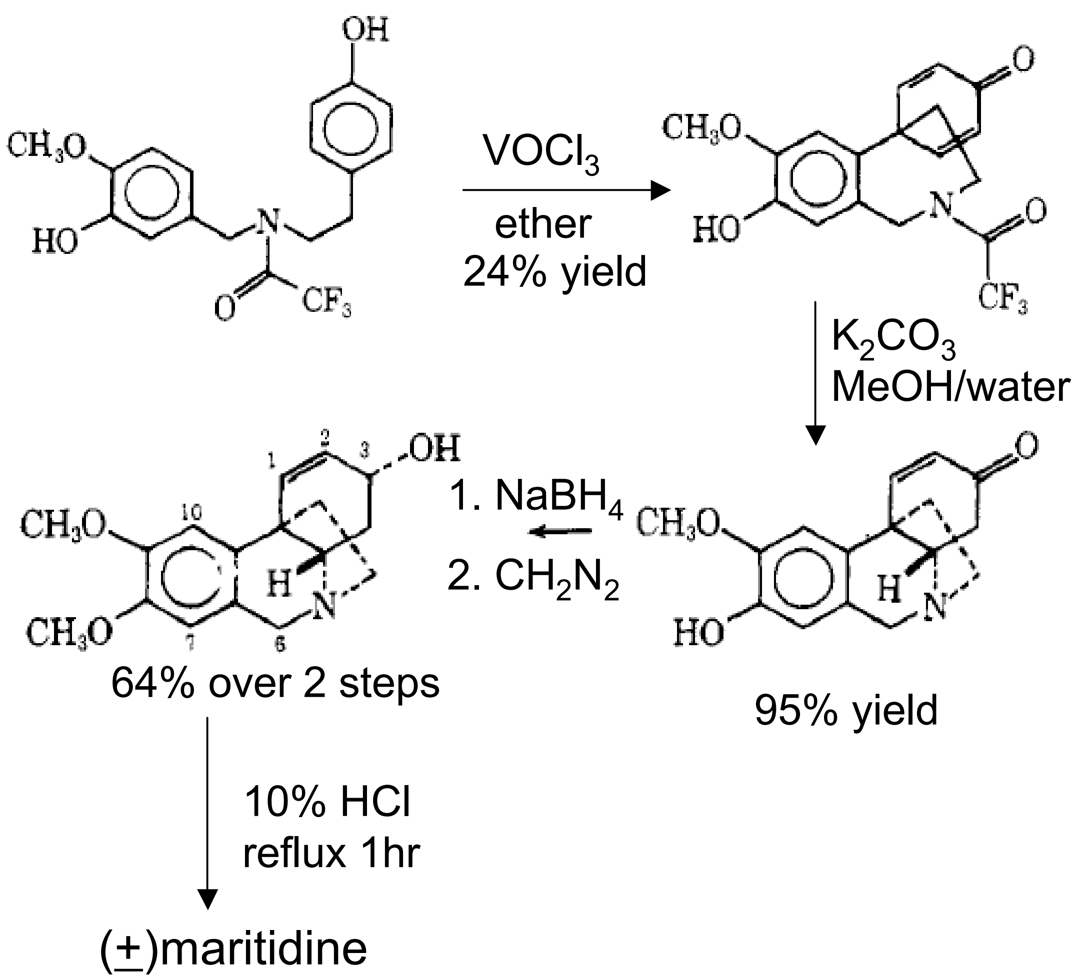
2. **HOLTON RA**, KIM HB, SOMOZA C, et al.
   FIRST TOTAL SYNTHESIS OF TAXOL .2. COMPLETION OF THE C -RING AND D-RING
   JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 116 (4): 1599 -1600 FEB 23 1994
   Times Cited: 328

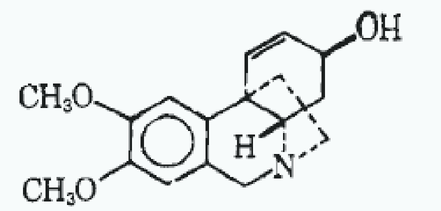
3. Rodi DJ, Janes RW, Sanganee HJ, et al.
   Screening of a library of phage -displayed peptides identifies human Bcl -2 as a taxol binding protein
   JOURNAL OF MOLECULAR BIOLOGY 285 (1): 197 -203 JAN 8 1999
   Times Cited: 107

4. **HOLTON RA**, JUO RR, KIM HB, et al.
   A SYNTHESIS OF TAXUSIN
   JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 110 (19): 6558 -6560 SEP 14 1988
   Times Cited: 106

5. 5. KRAFFT ME, **HOLTON RA**
   REGIOSPECIFIC PREPARATION OF THERMODYNAMIC SILYL ENOL ETHERS USING BROMOMAGNESIUM DIALKYLAMIDES
   TETRAHEDRON LETTERS 24 (13): 1345 -1348 1983
   Times Cited: 75

Biogenetic synthesis of maritidine





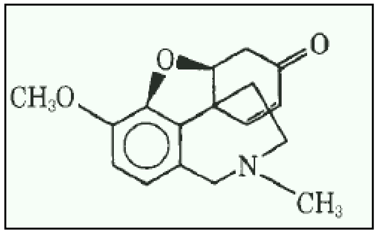
Key Points:

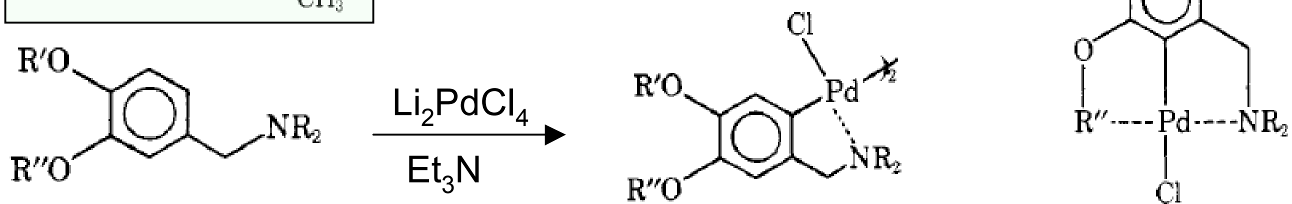
- Phenolic para coupling
- Second report of a biogenetic synthesis for this alkaloid class

Refs: JACS 1970, 92, 1090.
JACS 1969, 91, 2800.

Aromatic Palladation

narwedine

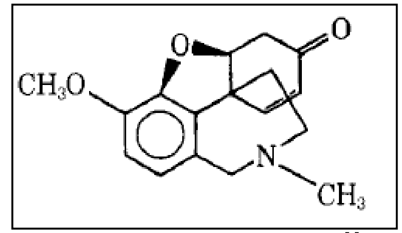




4a–g 6a–e 6f–g

Benzylic amine[8]				Palladium complex[8]			
No.	R	R′	R″	No.	6 isomer, %[a]	2 isomer, %[a]	% yield[b]
4a	C_2H_5	$-CH_2-$		**6a**	100	0	98
4b	C_2H_5	CH_3	H	**6b**	100	0	95
4c	C_2H_5	CH_3	$COCH_3$	**6c**	100	0	52
4d	C_2H_5	CH_3	CH_2OCH_3	**6d**	100	0	85
4e	C_2H_5	CH_3	$CH_2C_6H_5$	**6e**	100	0	58
4f[9]	C_2H_5	CH_3	$CH_2SC_6H_5$	**6f**	0	100	42
4g[10]	C_2H_5	CH_3	CH_2SCH_3	**6g**	0	100	95
4h[11]				**6h**			93

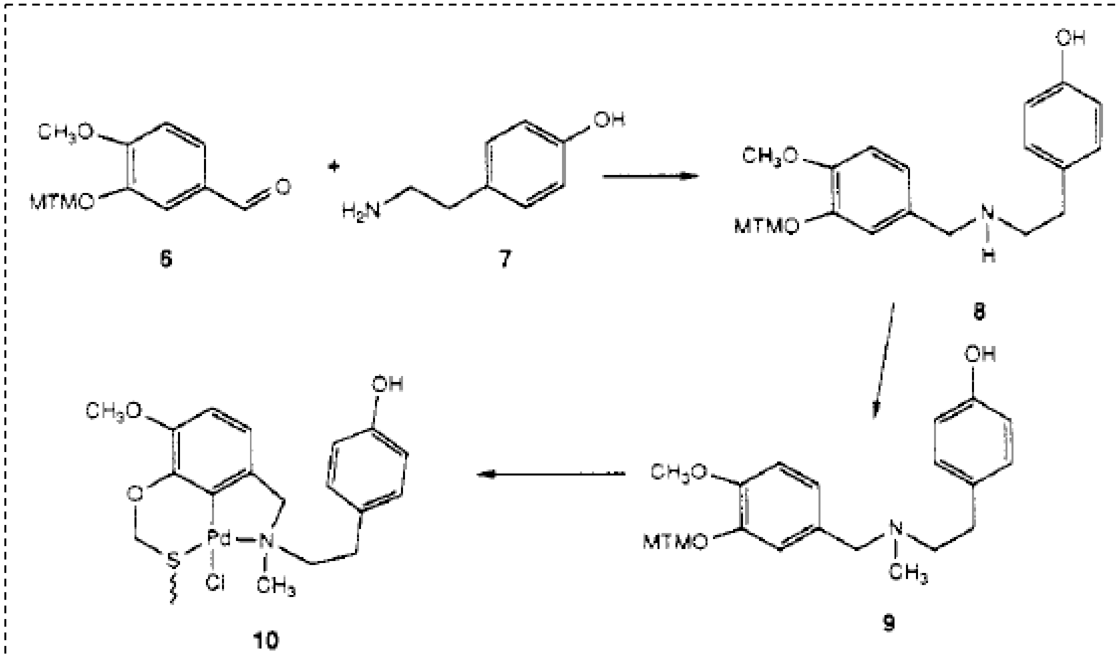
Synthesis of Narwedine

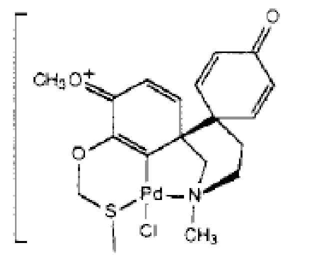


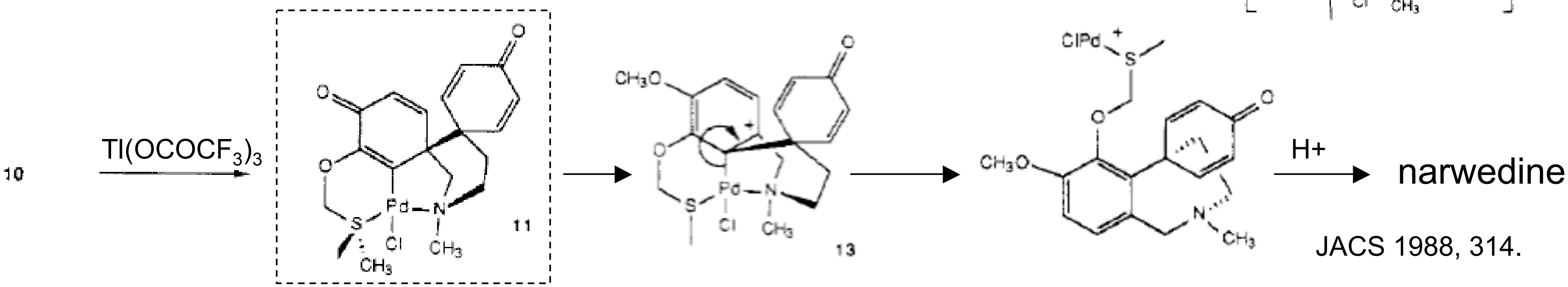
narwedine

Key Points:

- Ortho phenolic coupling
- Interesting rearrangement







JACS 1988, 314.

11 is obtained if reaction is quenched with water at low temp

Baxter 6 - CU Synthesis Lit Group - Holton

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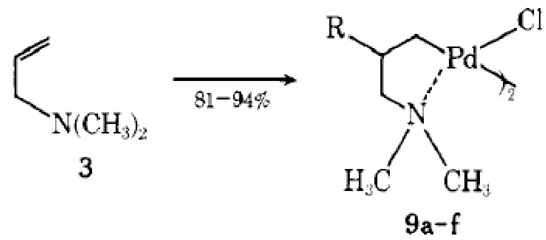
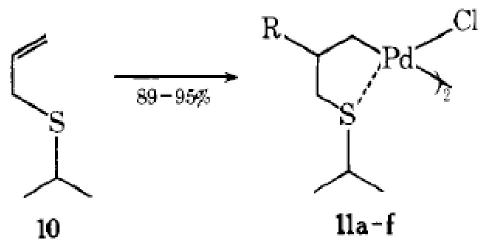
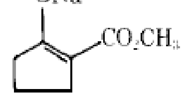
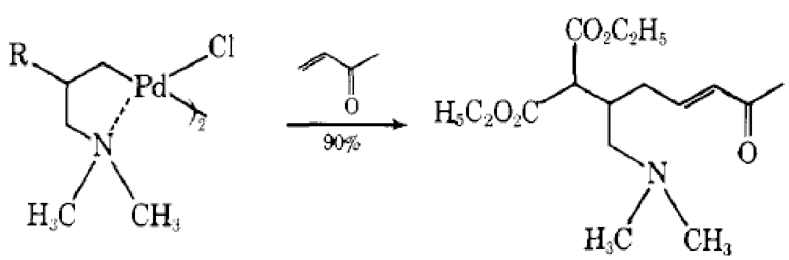
Carbopalladation





Nucleophile	Ole-fin	Palladium complex[11]	% yield[12]
$NaCH(COOC_2H_5)_2$	3	9a	91
	10	11a	95
$NaCH(COC_6H_5)_2$	3	9b	89
	10	11b	93
$NaCH(COCH_3)—CO_2C_2H_5$	3	9c	93
	10	11c	93
 ONa, CO_2CH_3	3	9d	91
	10	11d	94
$NaCH(COCH_3)COC_6H_5$	3	9e	93
	10	11e	92
$NaC(CO_2C_2H_5)_2(C_2H_5)$	3	9f	81
	10	11f	89



Key Points:

- **Heteroatom directed activation of alkene**
- **Nice tandem functionalization of alkene**

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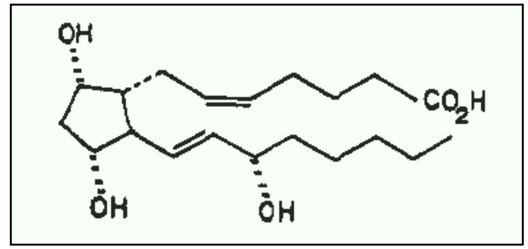
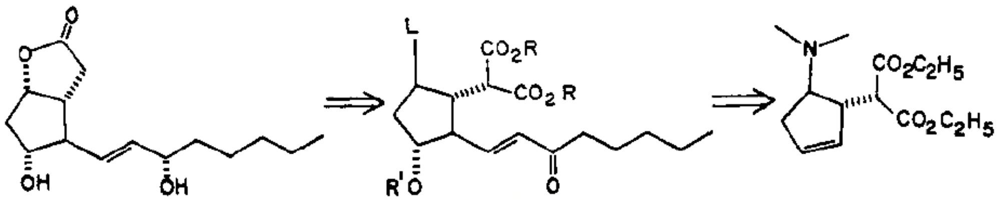
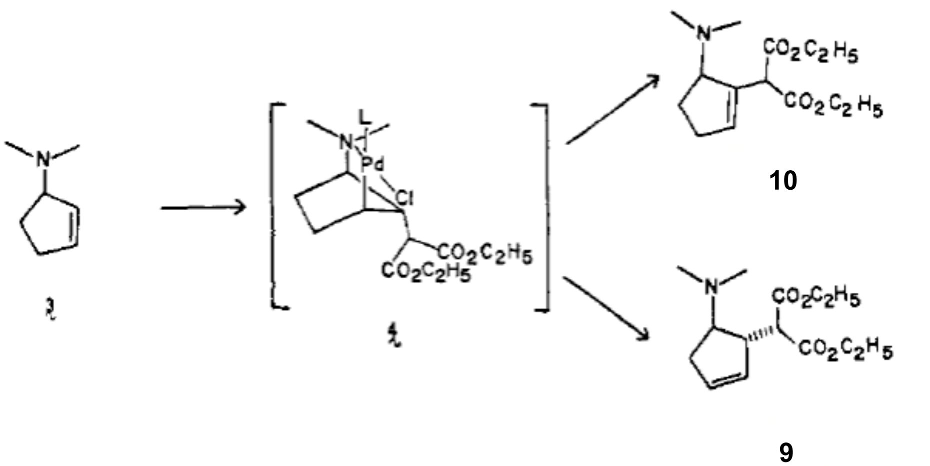
Prostaglandin

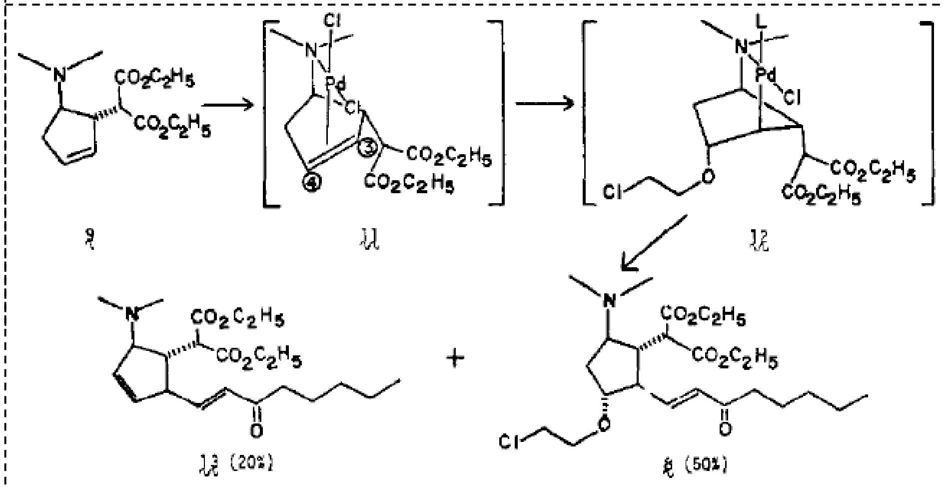




Key Points:

- Nitrogen chelate directed regiochemistry
- Relative stereochemistry directed by palladacycle





At 25°C: **10** is major product
At 0°C: **9** is obtained in 92% yield

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JACS 1977, 8083.

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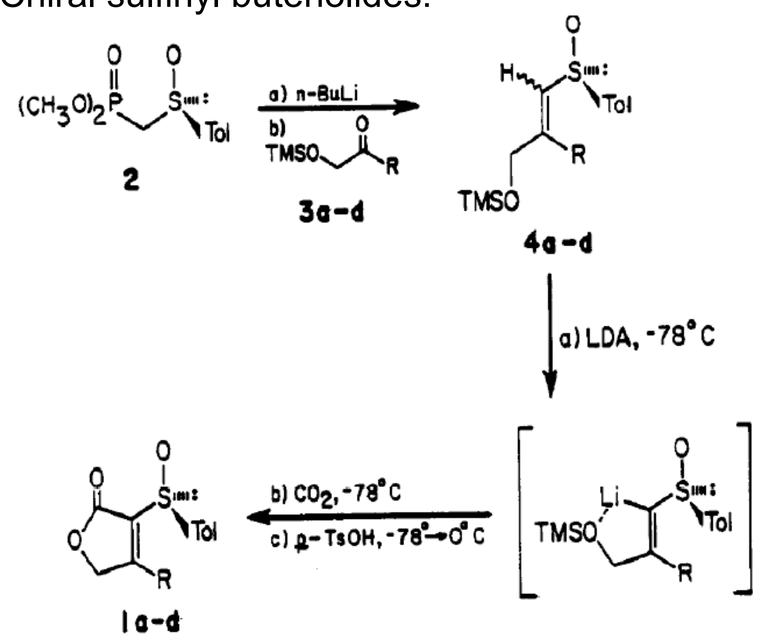
Enantioselective Synthesis of Aphidicolin

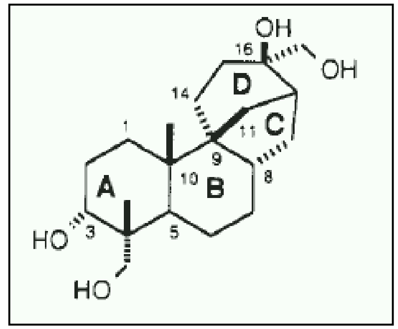
Chiral sulfinyl butenolides:



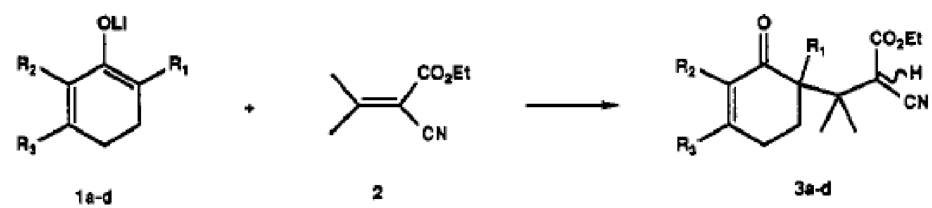
Key Points:

•Enantioselective preparation of 2-(*p*-tolylsulfinyl)-2-butenolides

•Formation of quaternary centers via Michael addition



Formation of vicinal quaternay centers:

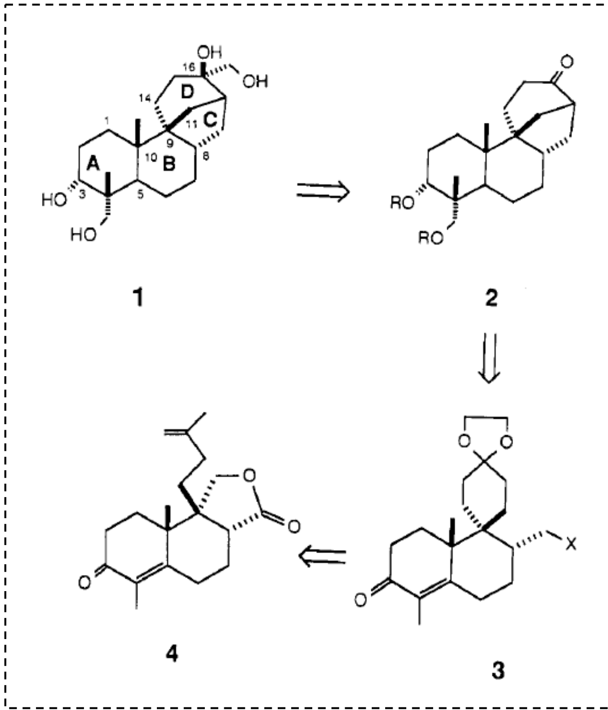


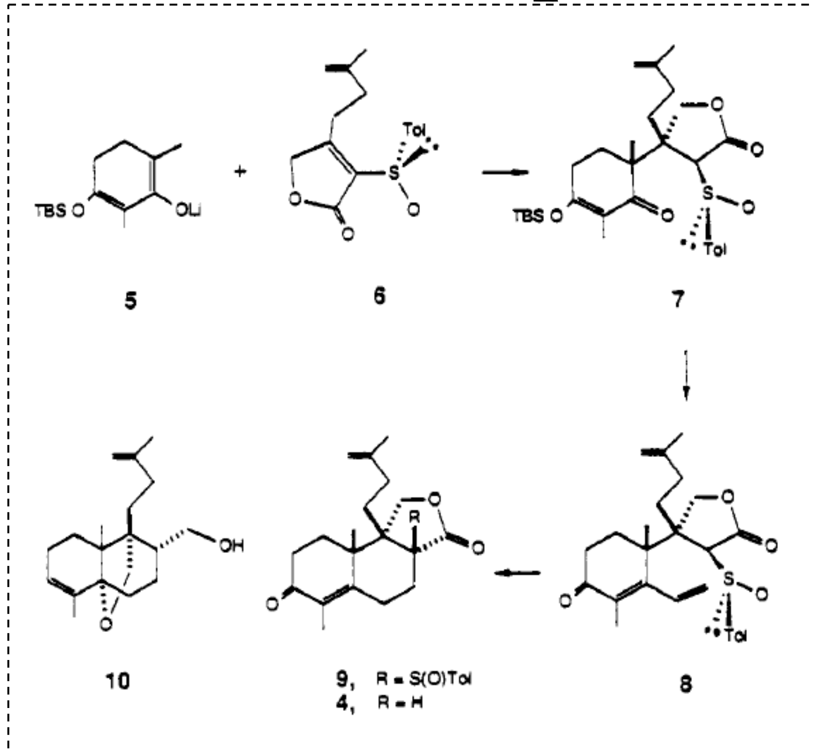
Refs: JOC 1986, 5480.
TL 1986, 2191.

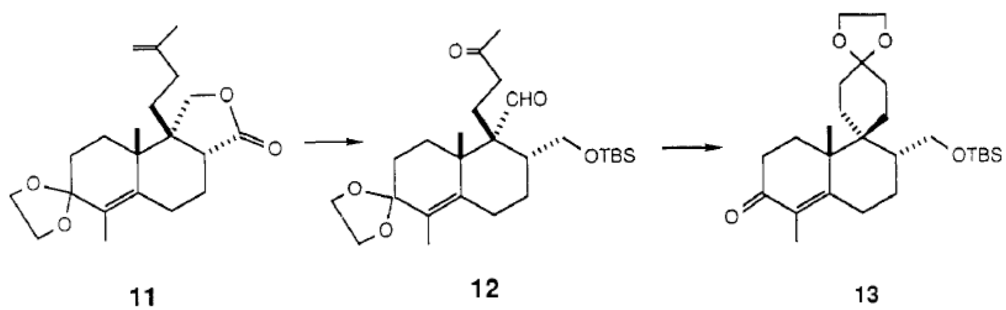
➢Chiral sulfoxides prepared via of menthol sulfinates
-both enantiomers are readily available

➢Two EWGs needed on Michael acceptor to overcome steric effects

Enantioselective Synthesis of Aphidicolin



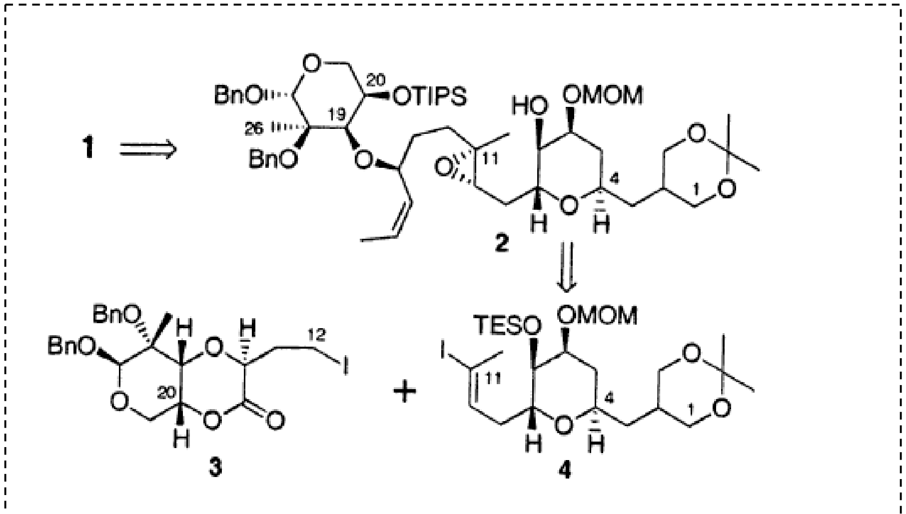




Key Points:

- •Formation of quaternary centers via Michael addition
- •Tandem Michael reaction to form B ring

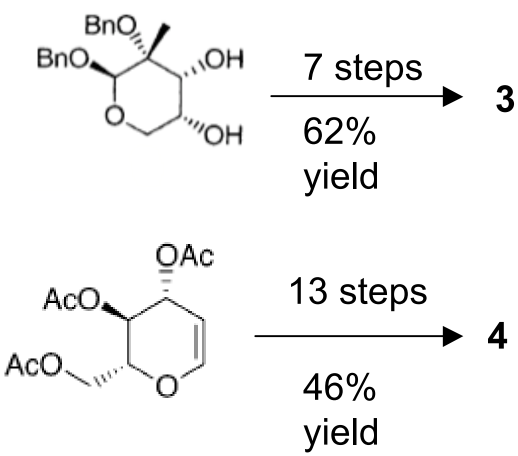
Total Synthesis of Hemibrevetoxin B

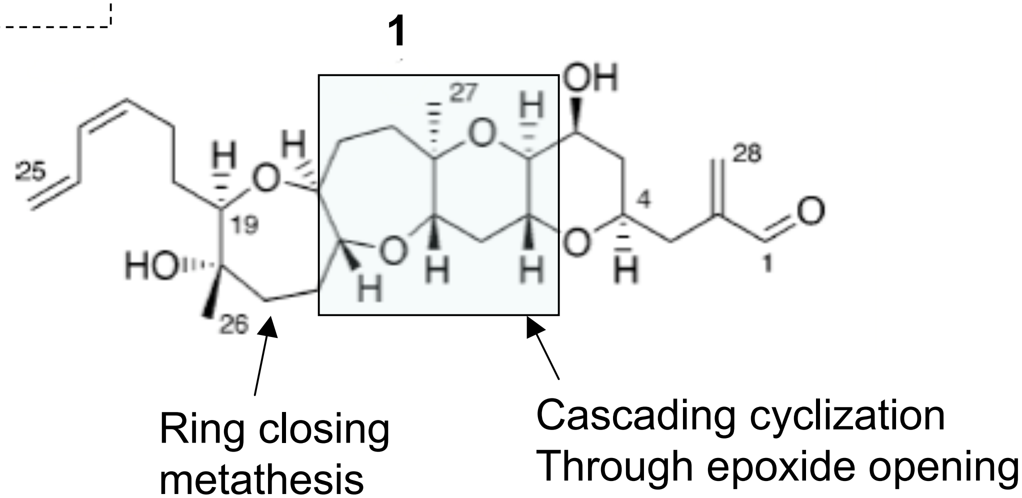


Key Points:

- First convergent synthesis
- Cascading cyclization as key step
- 6-endo epoxide opening

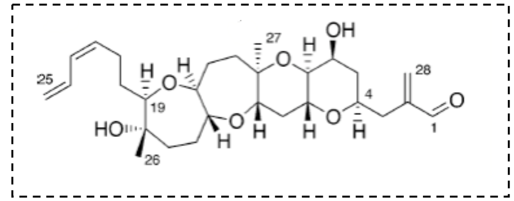
39 steps; 4% overall yield through longest linear sequence

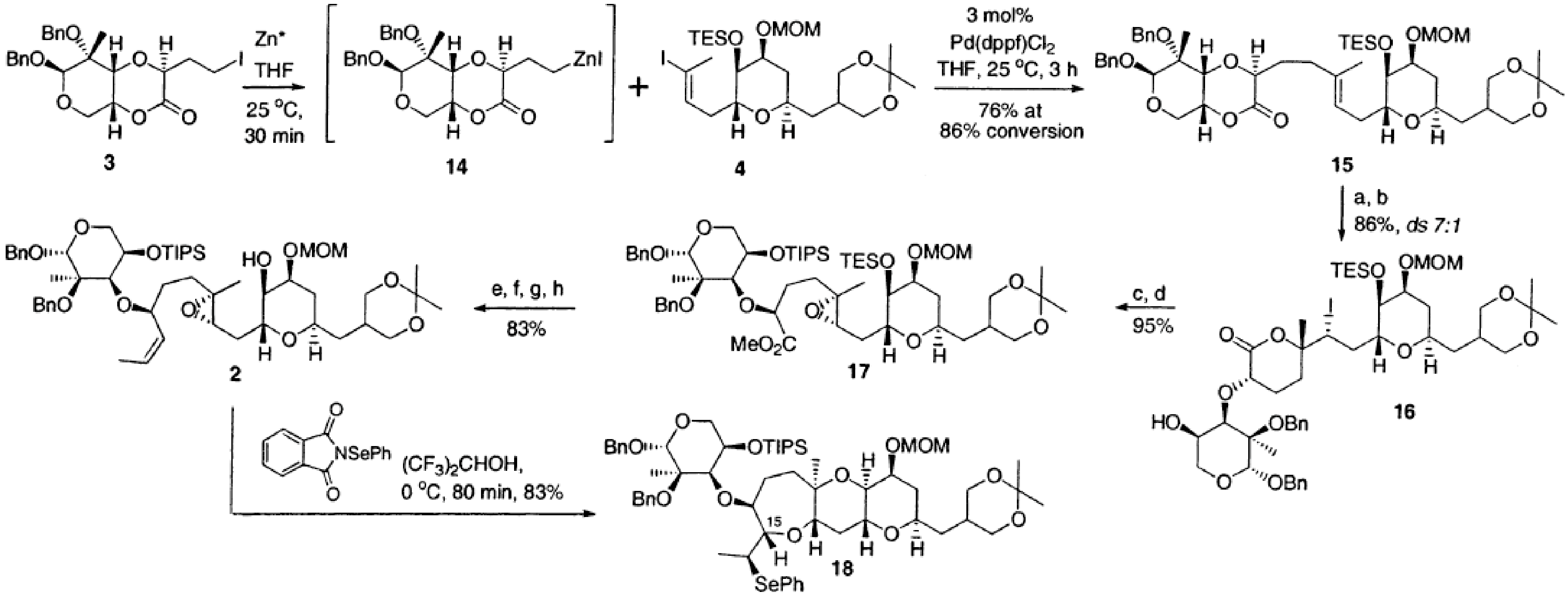




Ref: JACS 2003, 7822.

Total Synthesis of Hemibrevetoxin B

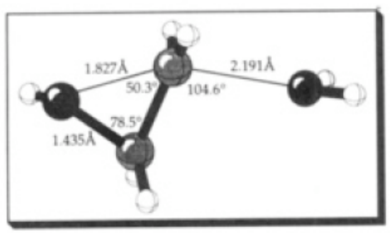




[a] Conditions: (a) LiOH, THF−H_2O (2:1), 0 °C, 20 min; (b) NIS, 2,6-lutidine, CH_2Cl_2, −10 °C, 3 h; (c) TIPSOTf, 2,6-lutidine, *t*-BuOAc, −10 °C, 15 min; (d) 1.1 equiv of MeONa/MeOH, CH_2Cl_2, −35 °C, 1 h; (e) $LiAlH_4$, THF, −78 °C, 1 h; (f) $(COCl)_2$−DMSO, *i*-Pr_2NEt, −78 to 0 °C, 30 min; (g) $Ph_3PEt^+Br^-$, NaHMDS, THF−DMPU (3:2), rt, 2 h; (h) 6 M aqueous HF−Py−MeCN, rt, 8 h.

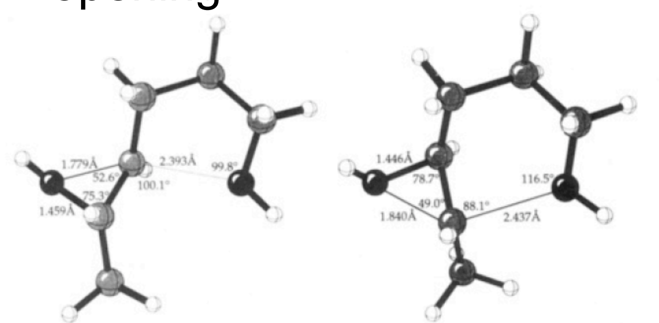
Total Synthesis of Hemibrevetoxin

Intermolecular epoxide opening



Ref: Houk *et al*. JACS, 1993, 8453.

Intramolecular epoxide opening



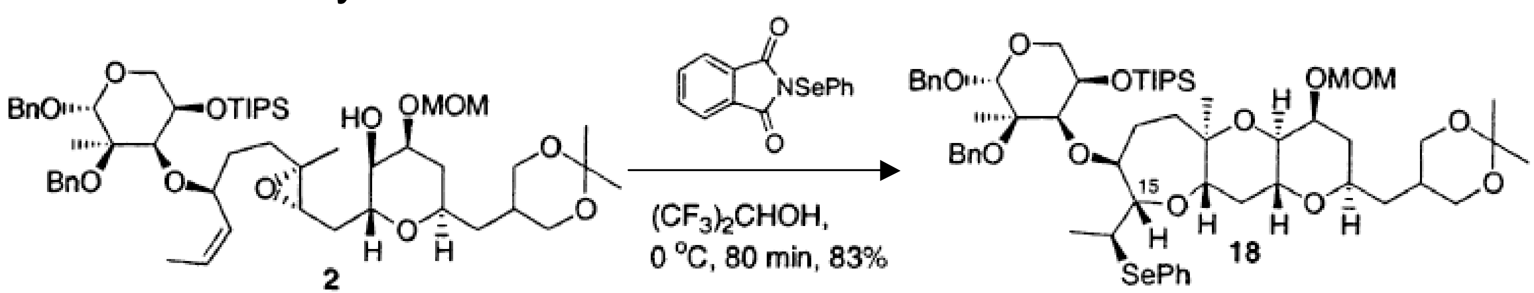
5-exo
Favored

6-endo
Disfavored

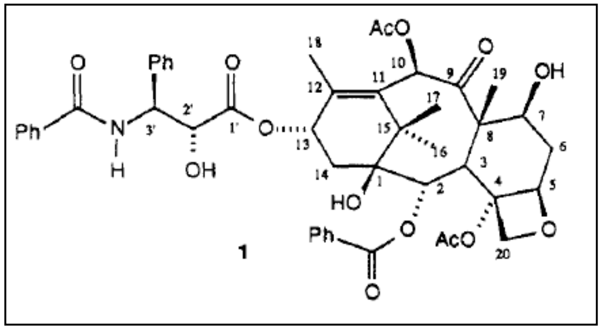
Key Points:

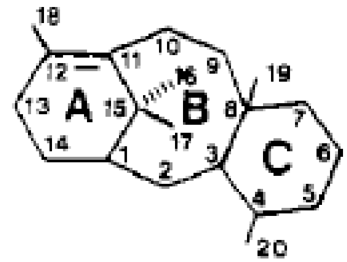
- Phenolic para coupling
- Second report of a biogenetic synthesis for this alkaloid class

Need 6-endo cyclization:



Taxol Synthesis - Taxane Skeleton



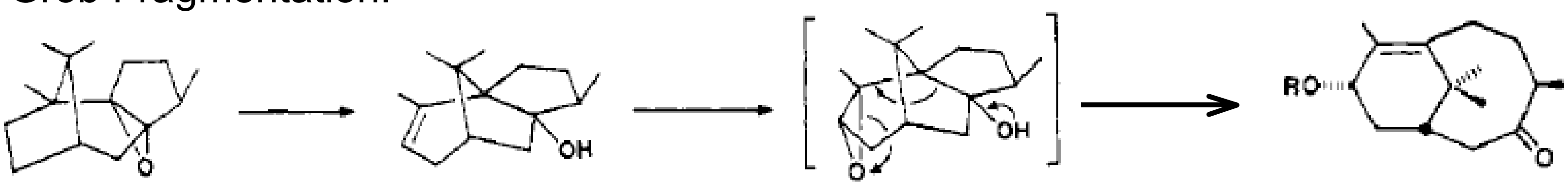


Key Points:

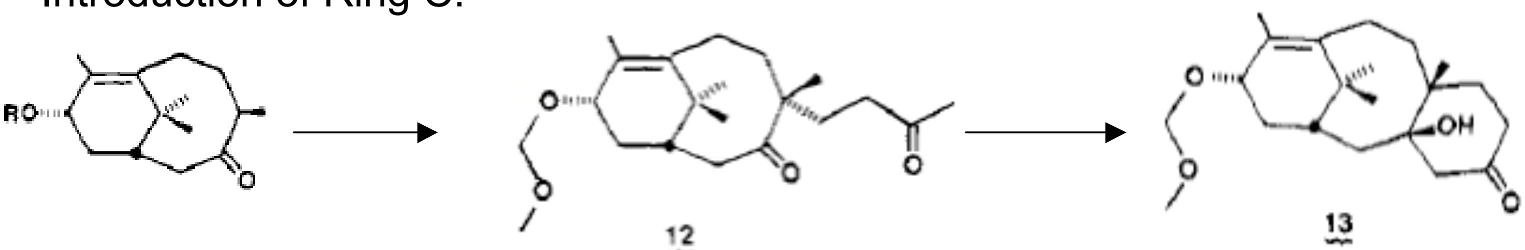
- Ring expansion via Grob fragmentation
- Initial step toward taxol

5 chemical steps
53% overall yield

Grob Fragmentation:



Introduction of Ring C:



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JACS 1984, 5731.

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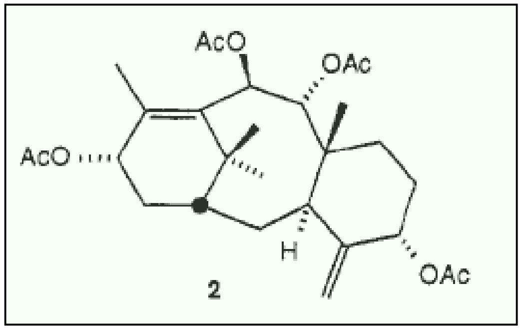
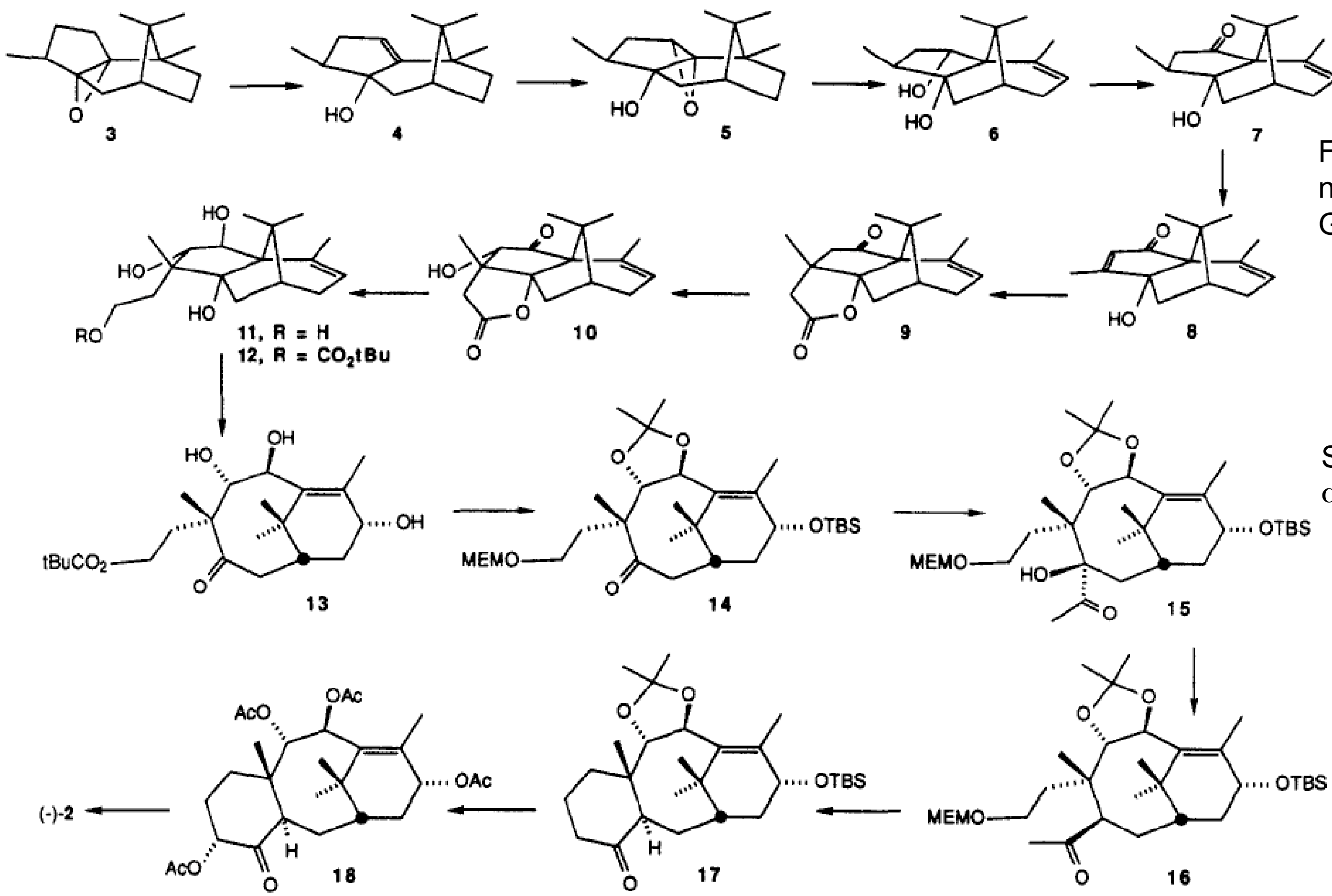


Synthesis of Taxusin

Key Points:

- Grob fragmentation effected on more functionalized substrate
- MEM ether directed alkylation



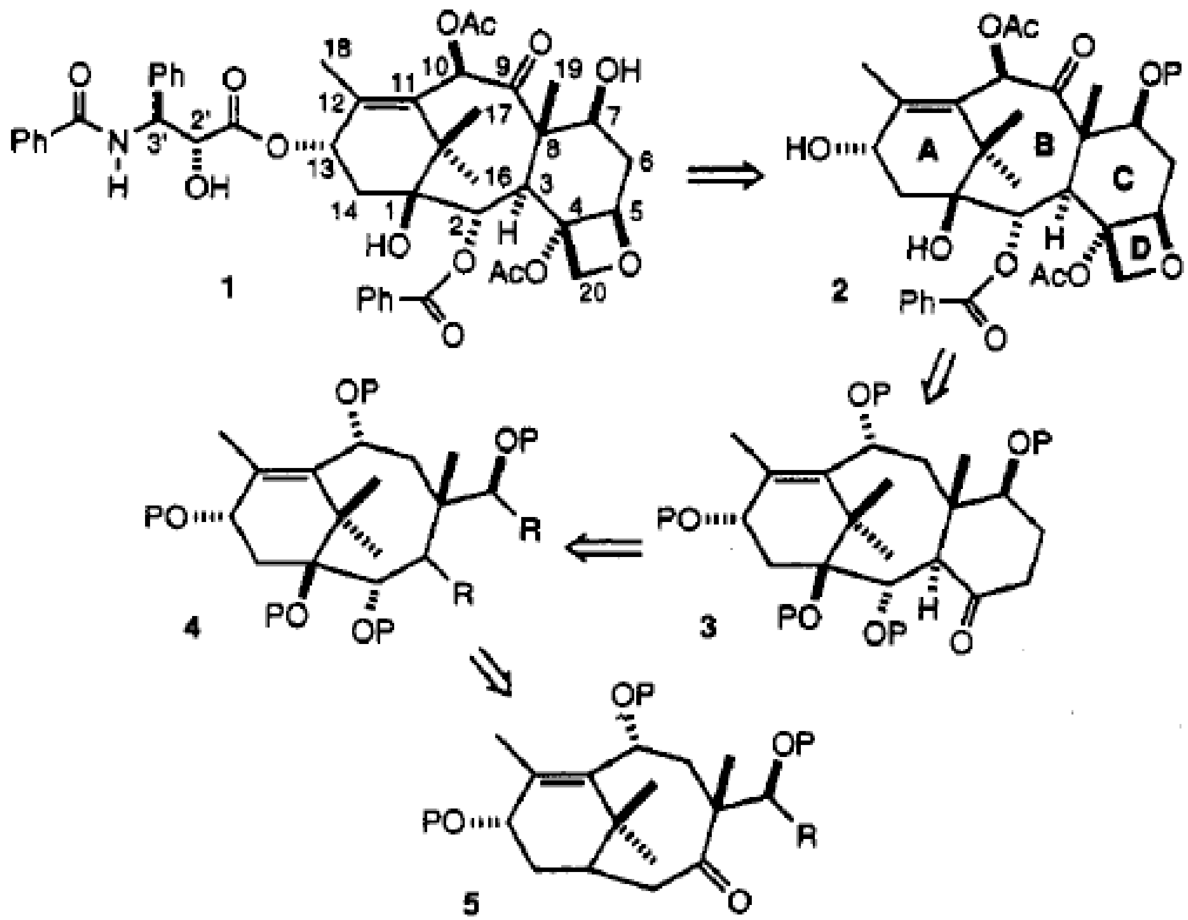
Functionality at C-6 and C-7 needed to be introduced before Grob fragmentation

Stereospecific addition of α-Methoxyvinyllithium

in THF: 1:1 mixture
in hexane: >30:1

JACS 1988, 6559.

Total Synthesis of Taxol



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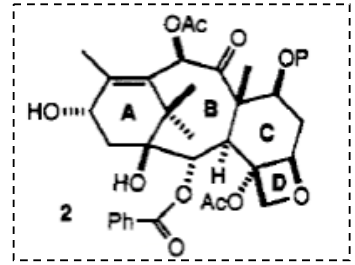
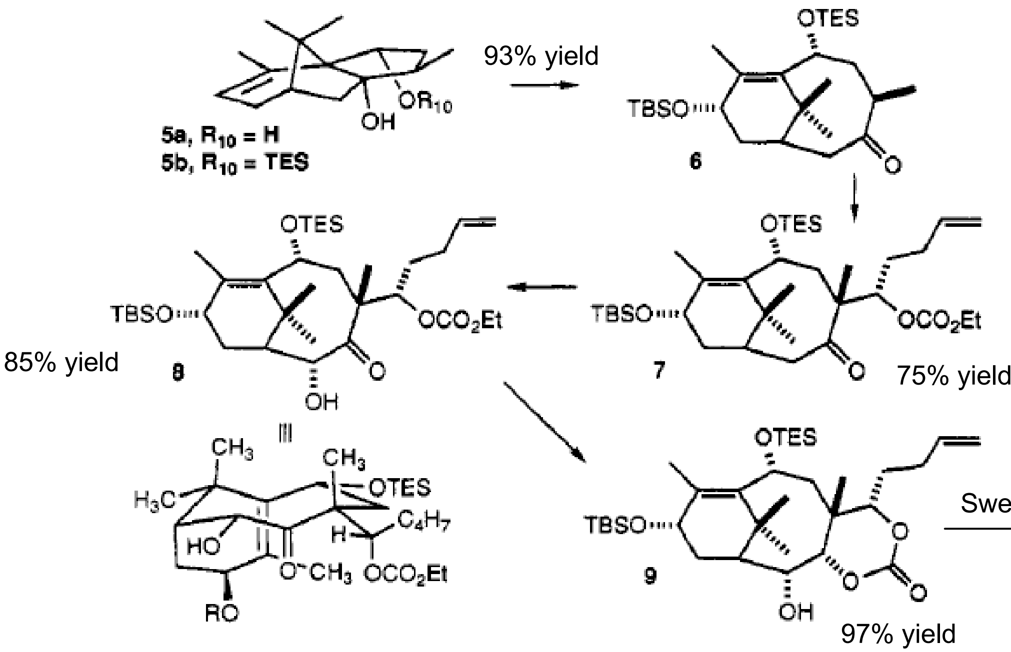
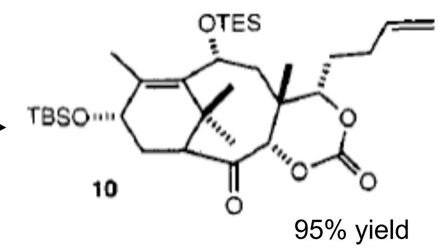
Total Synthesis of Taxol

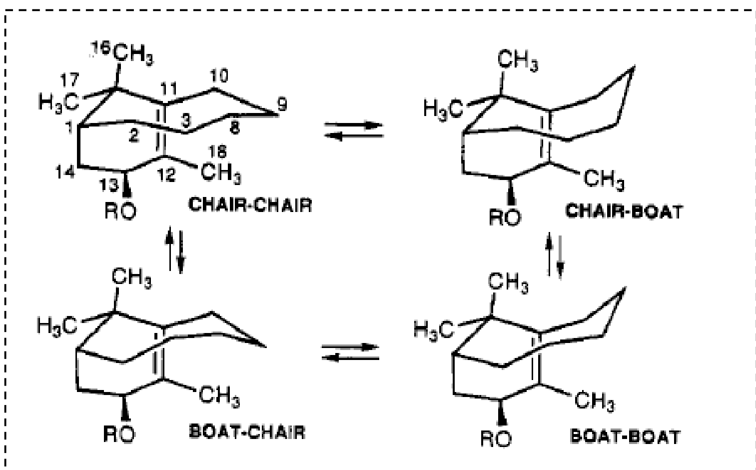




6 found to exist in chair-boat conformation
-chair-chair and boat-chair
only 2.5 kJ/mol less stable

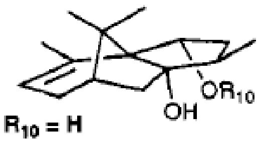
7 is a 6:1 mixture of chair-chair and boat-chair conf.





Introduction of bridgehead hydroxyl requires
boat-chair conformation

Total Synthesis of Taxol

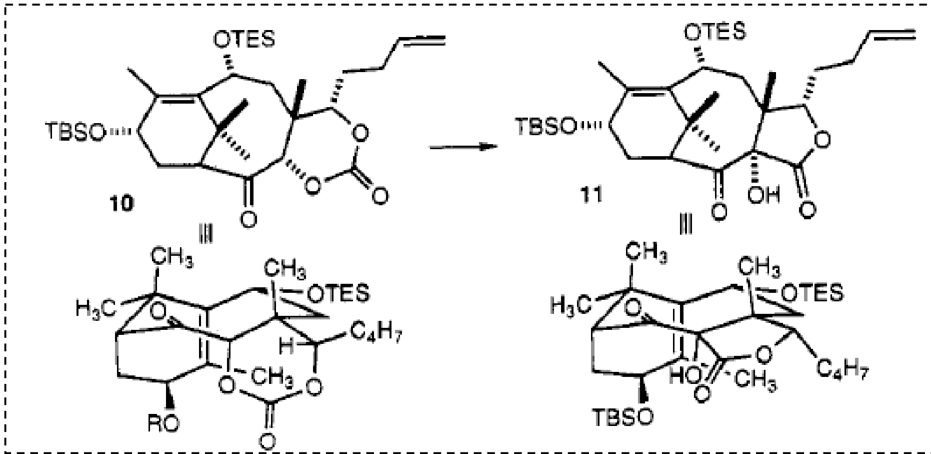


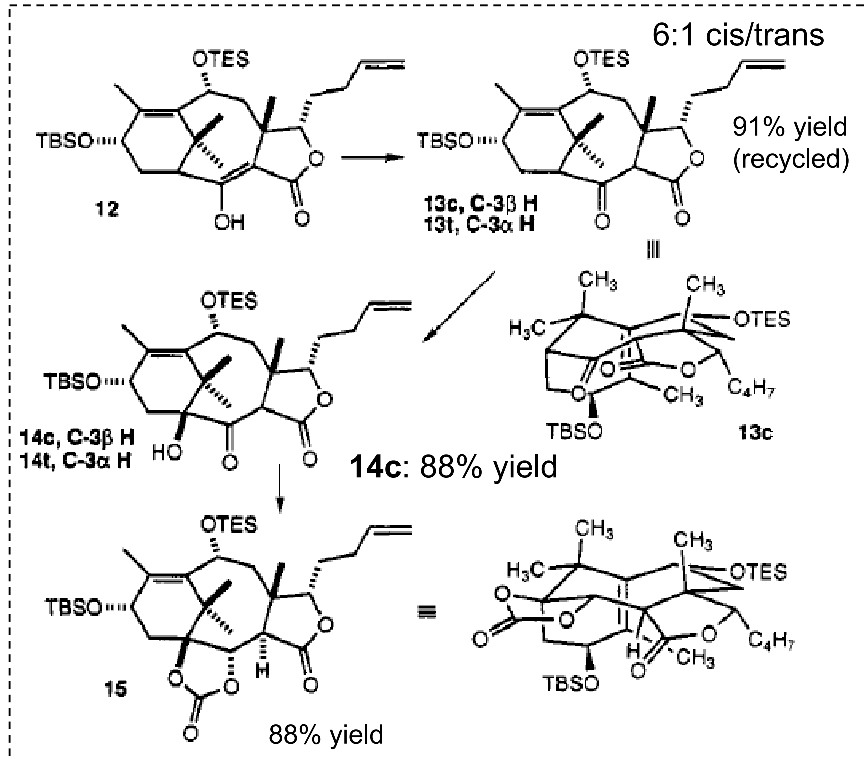
5a, R_{10} = H

5a to **15**: 12 steps
40% overall yield

Key Points:

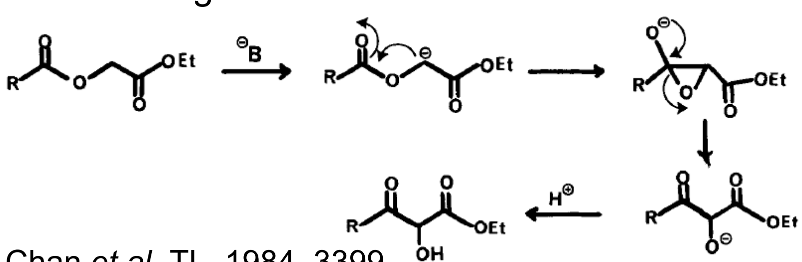
- First use of Chan rearrangement in a cyclic system
- Selective deprotonation





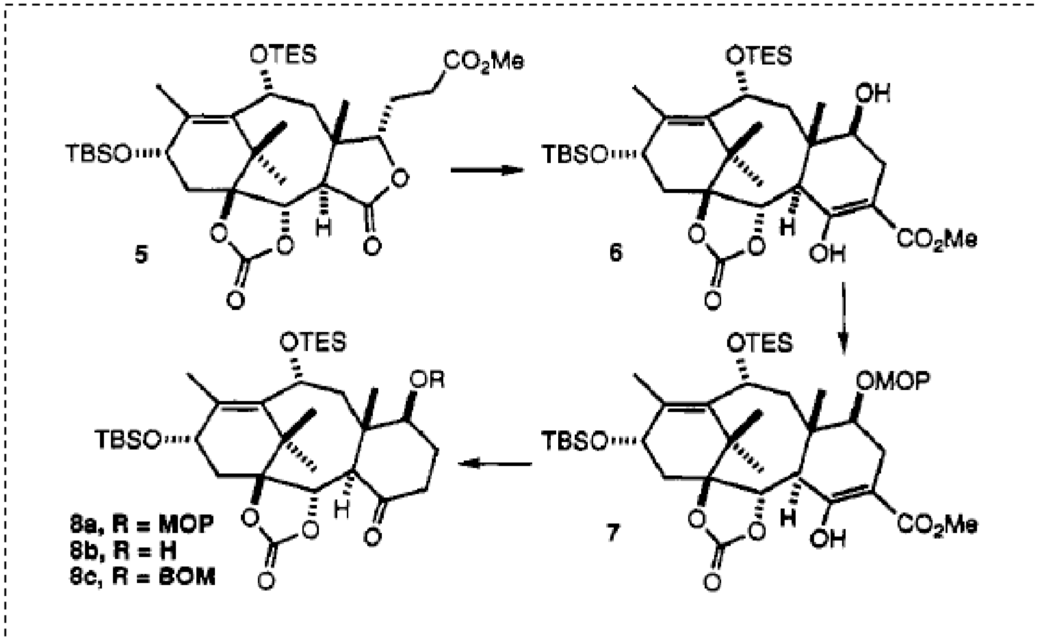
11 $\xrightarrow{SmI_2}$ 12

Chan rearrangement:



Chan *et al.* TL, 1984, 3399

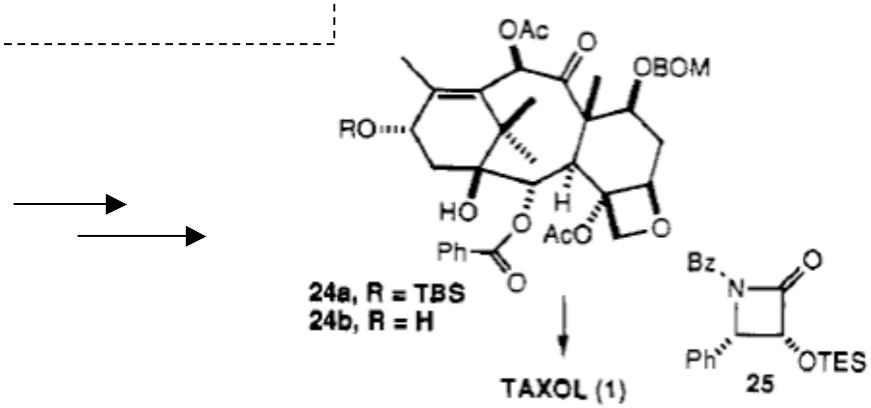
Total Synthesis of Taxol



Key Points:

- First use of Chan rearrangement in synthesis
- Selective deprotonation

8c



93% yield from **24b**

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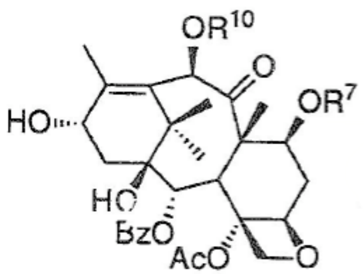
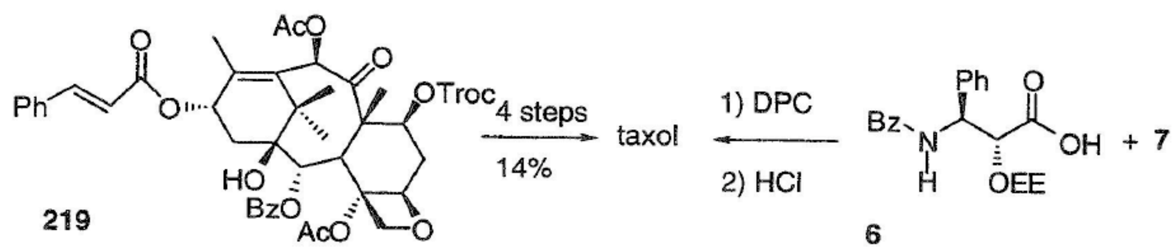
Side Chain Incorporation



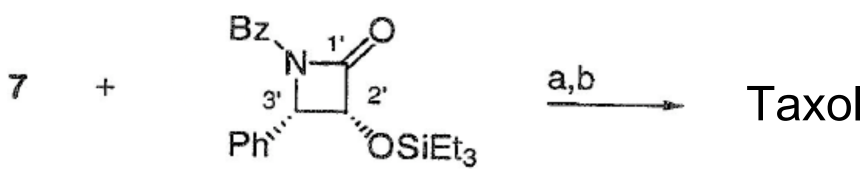
2 : R^{10} = H ,10-DAB
7: R^7 = TES, R^{10} = Ac

Key Points:

- Reaction with β-lactam is superior to other methods to install side chain
- Lithium alkoxide patent



80% yield, 50% conversion

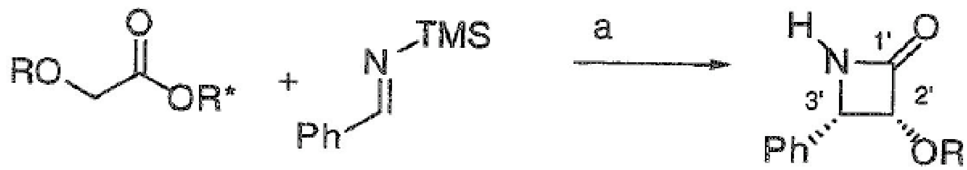


a) *n*-BuLi,THF, -45 °C, 1 h b) HF-pyridine-CH_3CN, 3 h 98%

BMS commercialized process used this method (LHMDS)

β-Lactam Synthesis

Ojima's and Georg's Chiral Synthesis of β-Lactams



221b 223a 222

a) LDA,THF -78 to 25 °C over 12 h

Ester	Chiral Auxiliary (R*)	R	%ee	major isomer	%yield	β-lactam
221a	(-)-(1*R*,2*S*)-2-phenyl-1-cyclohexanol	TBS	76	2'*R*,3'*S*	90	**222a**
221b	(-)-(1*R*,2*S*)-2-phenyl-1-cyclohexanol	TIPS	96	2'*R*,3'*S*	85	**222b**
221c	(+)-(1*S*,2*R*)-2-phenyl-1-cyclohexanol	TIPS	97	2'*S*,3'*R*	80	**222b**
221d	(-)-(1*R*,2*S*,4*R*)-menthol	Bn	15	2'R,3'S	18	**222d**
221e	(-)-(1*R*,2*S*,4*R*)-menthol	TBS	50	2'R,3'S	52	**222a**
221f	(-)-10-dicyclohexanyl-sulfamyl-D-isoborneol	TBS	94	2'*R*,3'*S*	97	**222a**

Chiral auxillary is expensive

COLUMBIA UNIVERSITY
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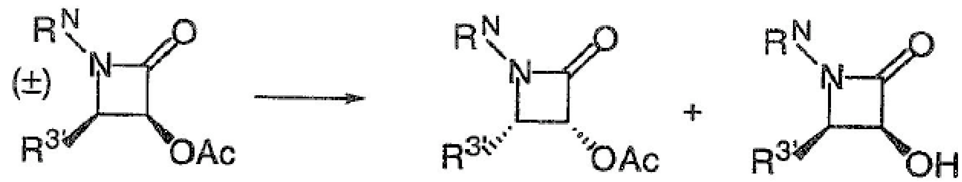
β-Lactam Resolution



(±)-**227** recovered **227** (-)-**228**

Enzyme source	(-)-227			(-)-228			Time (hrs)
	Yield(%)	α_{578}^{25} $CHCl_3$	%ee	Yield(%)	α_{578}^{25} MeOH	%ee	
BLAP	33	-40.0	78	37	-178.6	>95	3.0
BBLS	48	-46.9	>95	45	-178.7	>95	0.25
BCLS	53	-40.0	78	45	-175.6	>95	0.25
BTLS	55	-40.5	78	31	-179.4	>95	0.25
BPLS	62	-30.8	65	36	-175.8	>95	0.25
BY	70	-10.0	21	14	-140.0	80	14.0

- Enzymes are also expensive, but can be obtained from cheap source and used immediately (BBLS = Buffered Beef Liver Solution)

- Process used for initial deliveries of Taxolog's first two drug candidates (in Phase II)