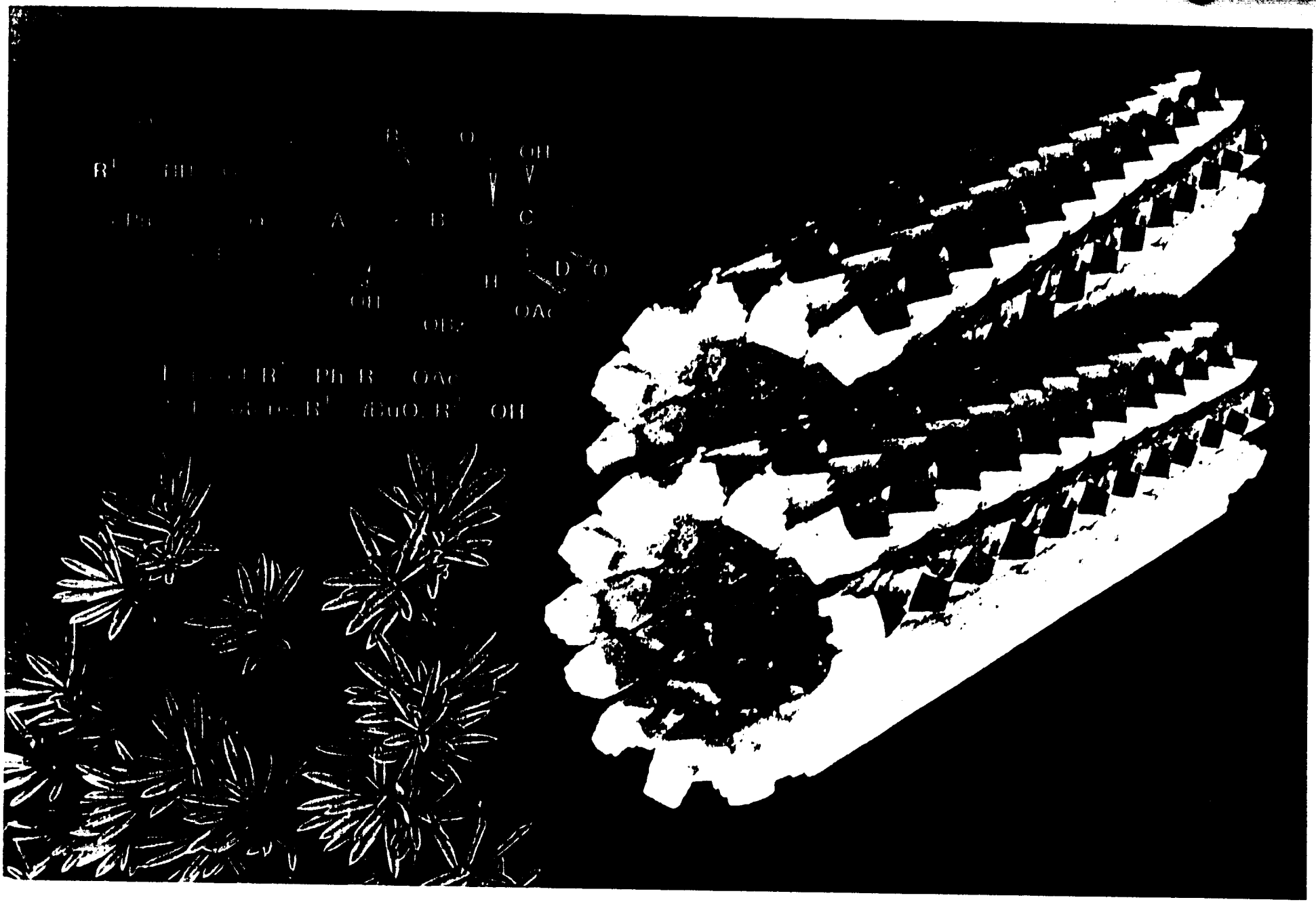
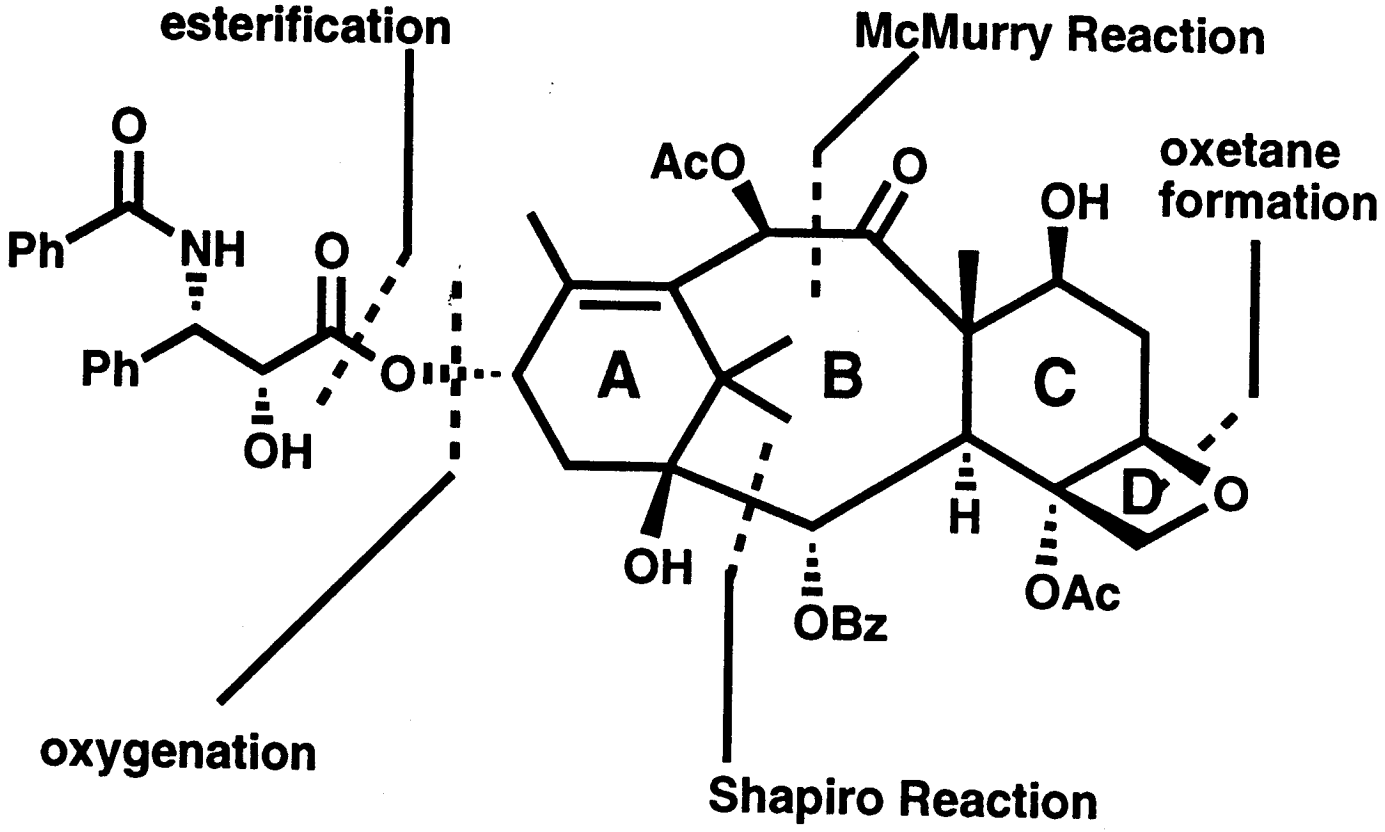
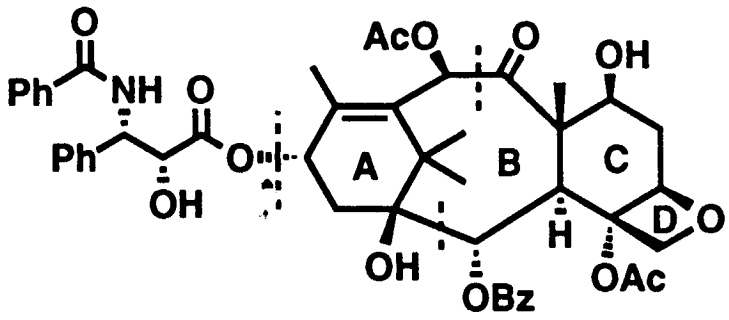


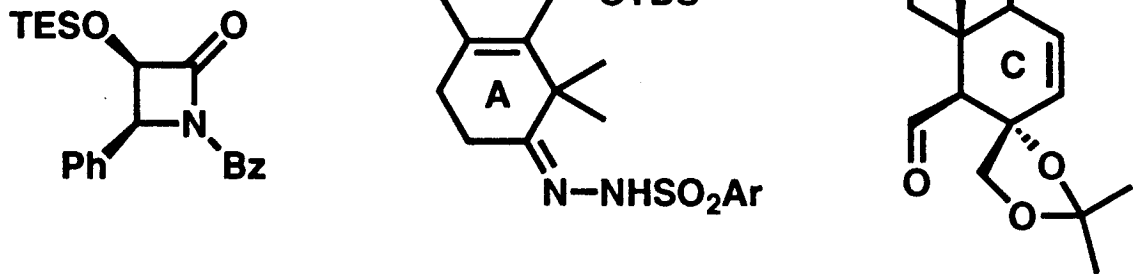
Strategic Bond Disconnections for Taxol



Nicolaou, et. al. *J. Chem. Soc., Chem. Commun.* 1992, 1117 - 1118.
Nicolaou, et. al. *Nature*, 1994, *387*, 630 - 634.

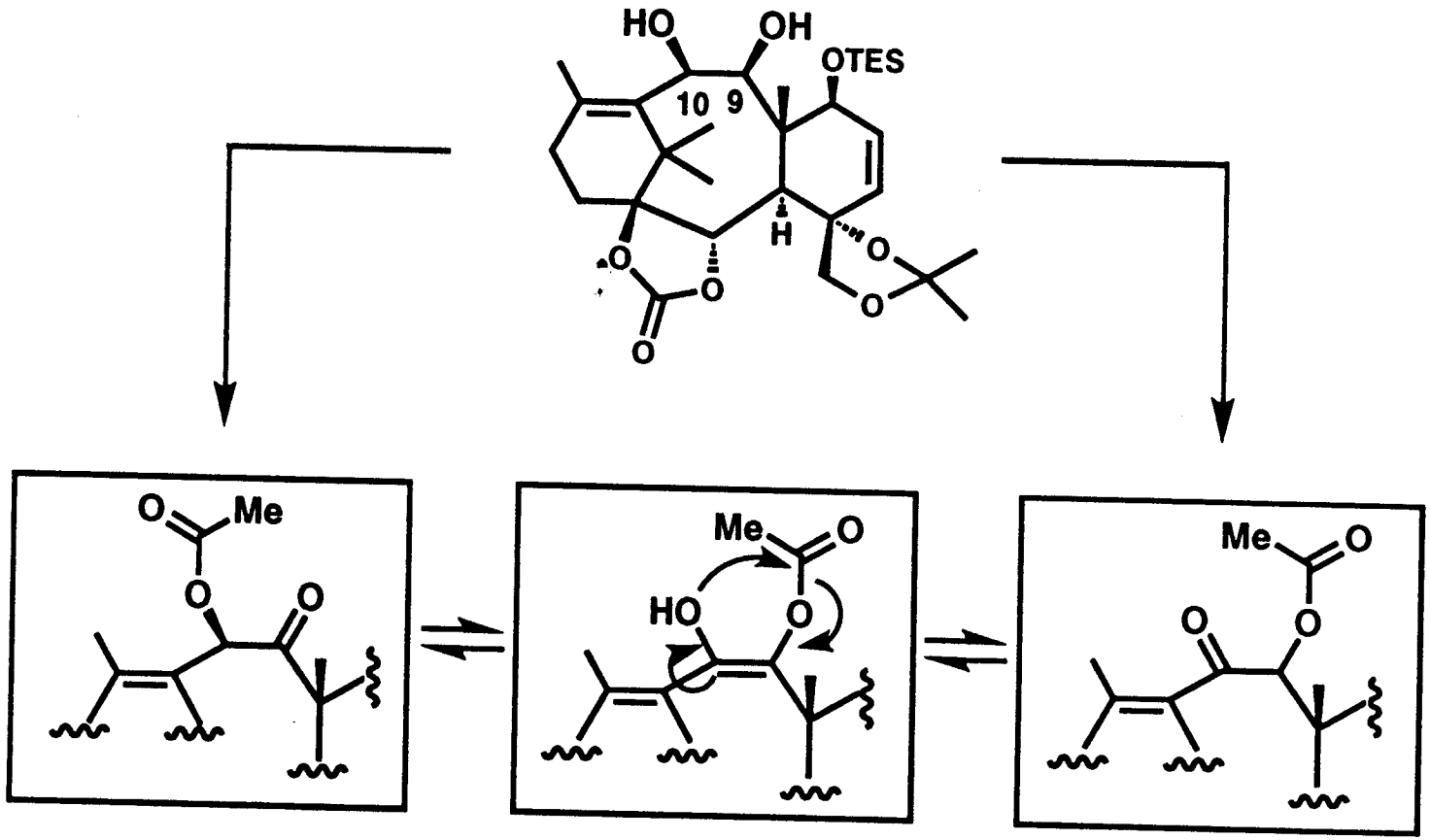
Retrosynthetic Analysis of Taxol



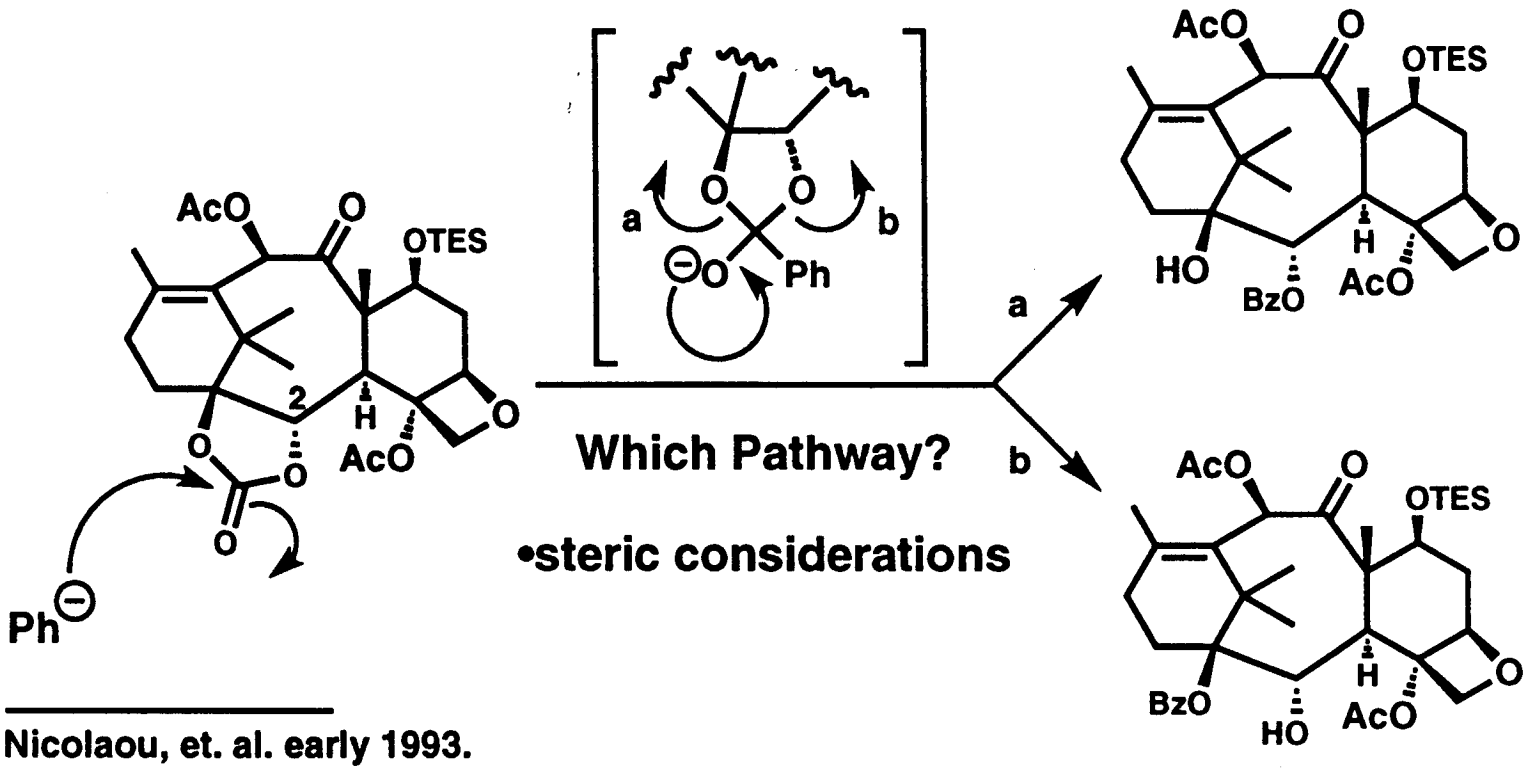


Nicolaou, et. al. *J. Chem. Soc., Chem. Commun.* 1992, 1117 - 1118.

The C-9/C-10 Regiochemistry Problem

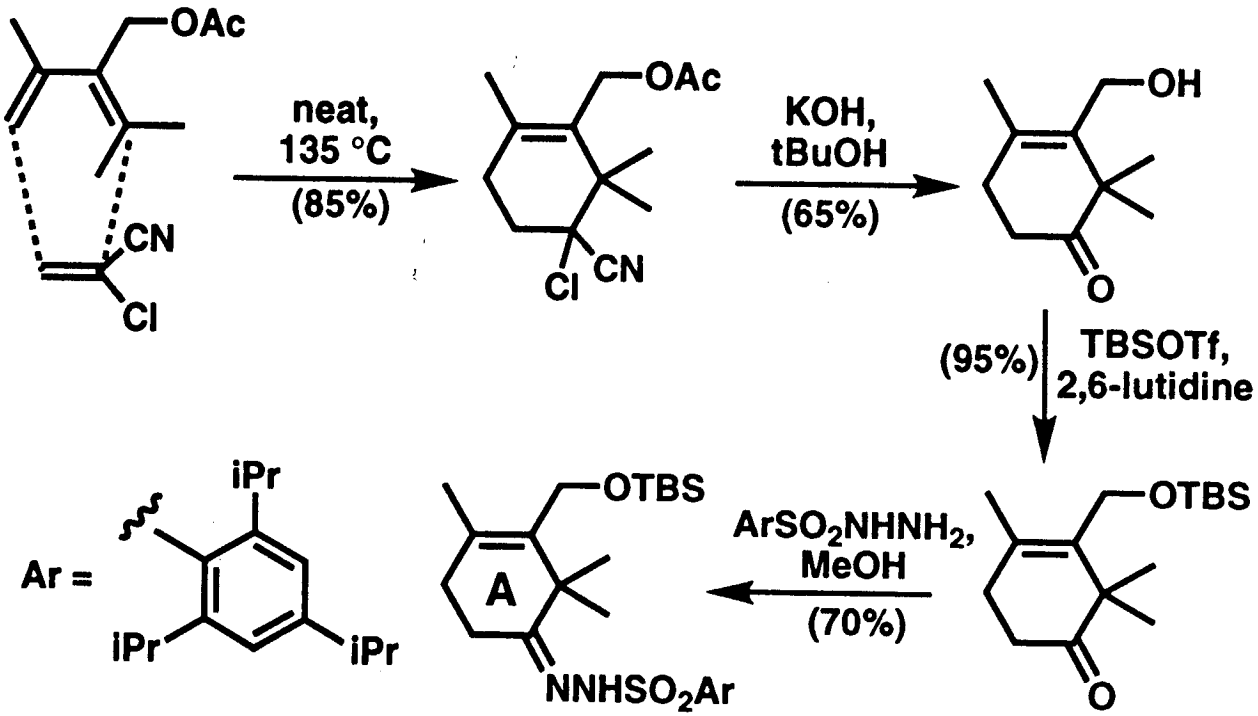


The C-2 Benzoate Problem



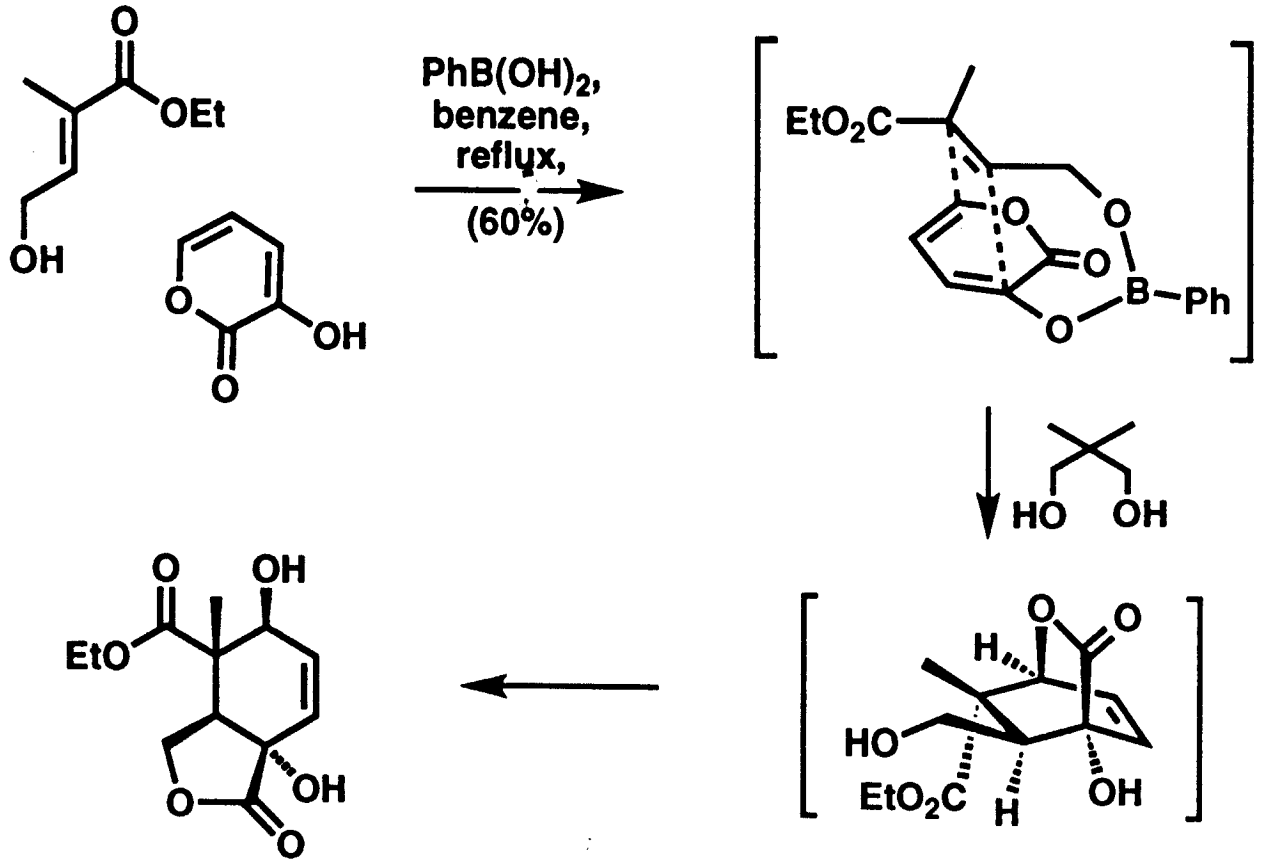
Nicolaou, et. al. early 1993.

Construction of Taxol's A-Ring System



Nicolaou, et. al. *J. Chem. Soc., Chem. Commun.* 1992, 1117 - 1118.
Nicolaou, et. al. *J. Chem. Soc., Chem. Commun.* 1993, 1024 - 1025.

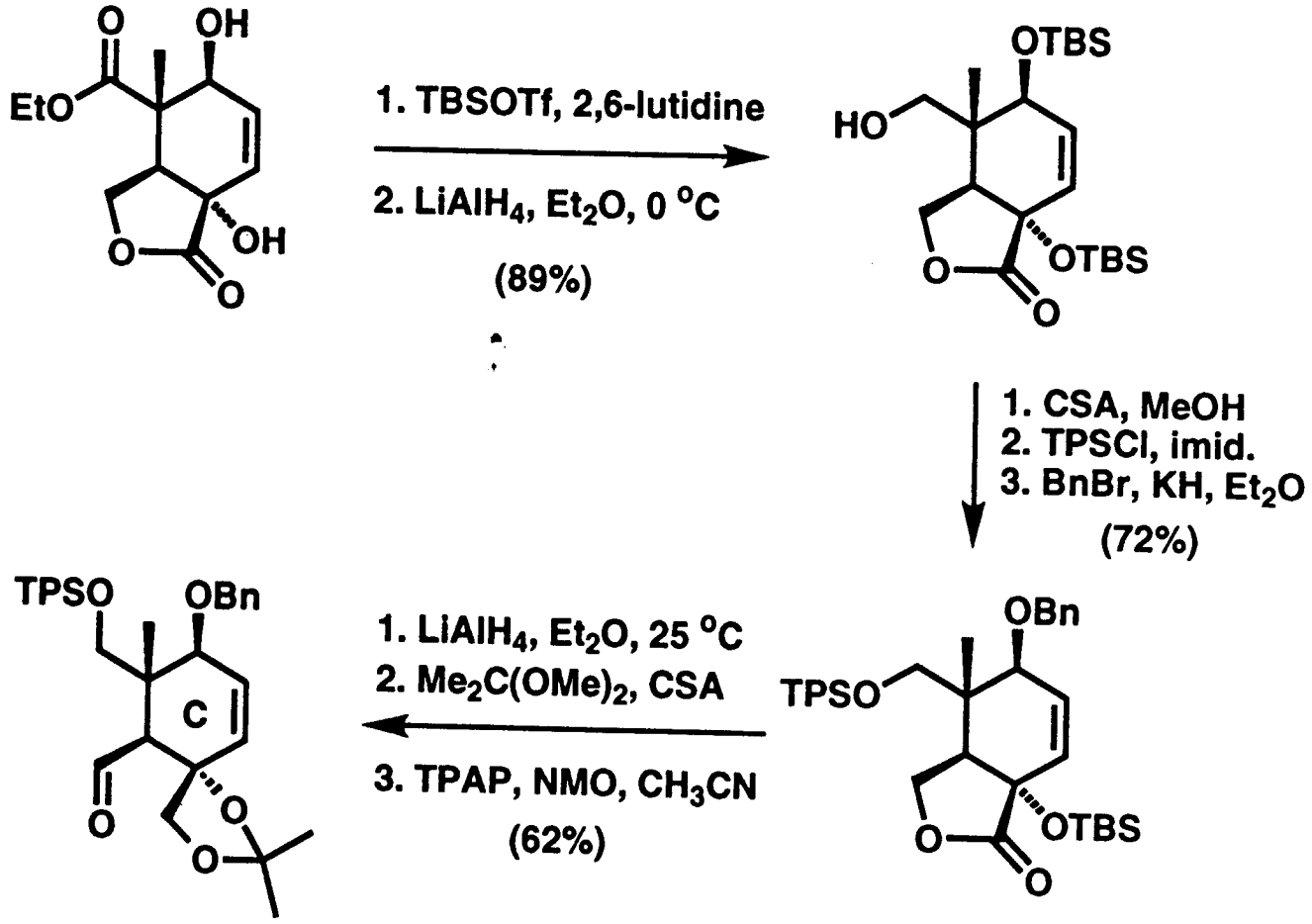
Construction of Taxol's C-Ring System
Template-Directed Diels-Alder Approach



precedent: Narasaka, et. al. *Synthesis*, 1171 (1991)

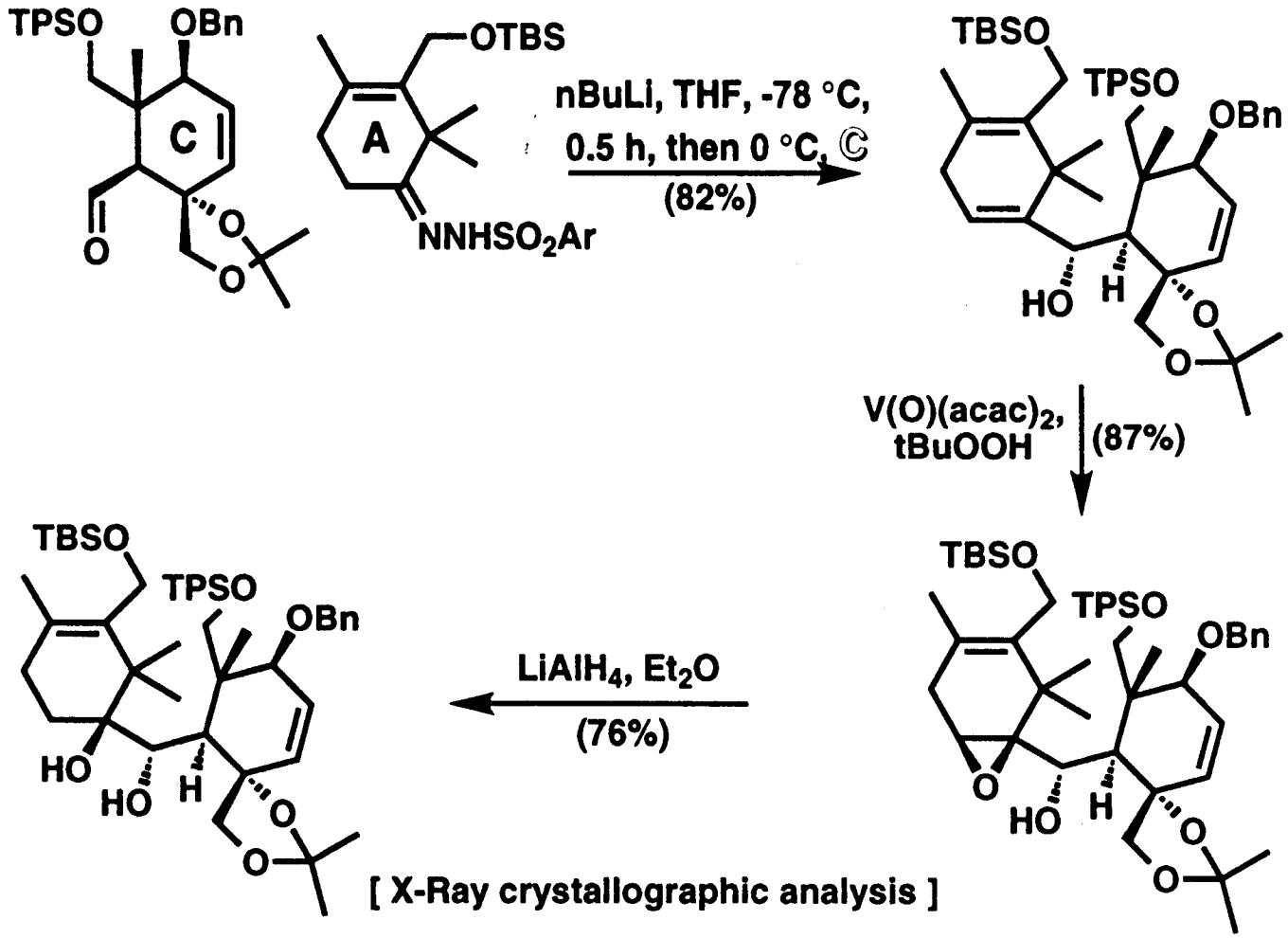
Nicolaou, et. al. *J. Chem. Soc., Chem. Commun.* 1992, 1118 - 1120.

Functionalization of Taxol's C-Ring System



Nicolaou, et. al. *Nature*, 1994, *307*, 630 - 634.

Linking the A- and C-Rings

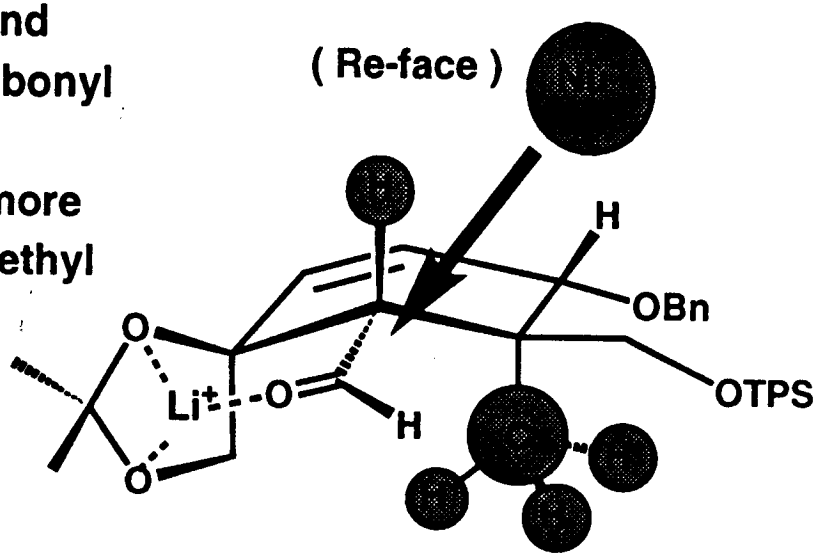


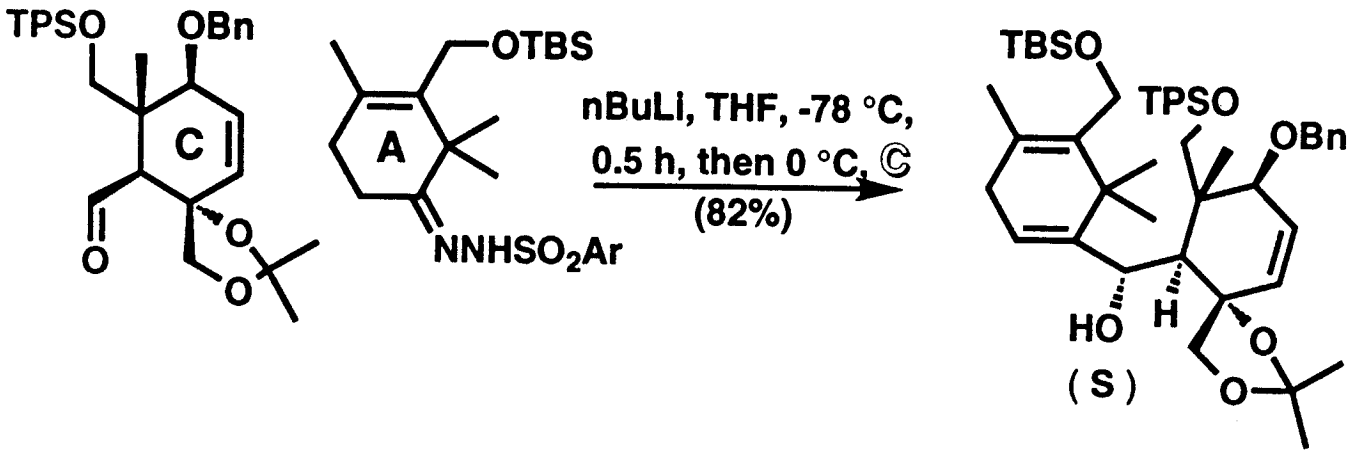
[X-Ray crystallographic analysis]

Nicolaou, et. al. *Nature*, 1994, *387*, 630 - 634.

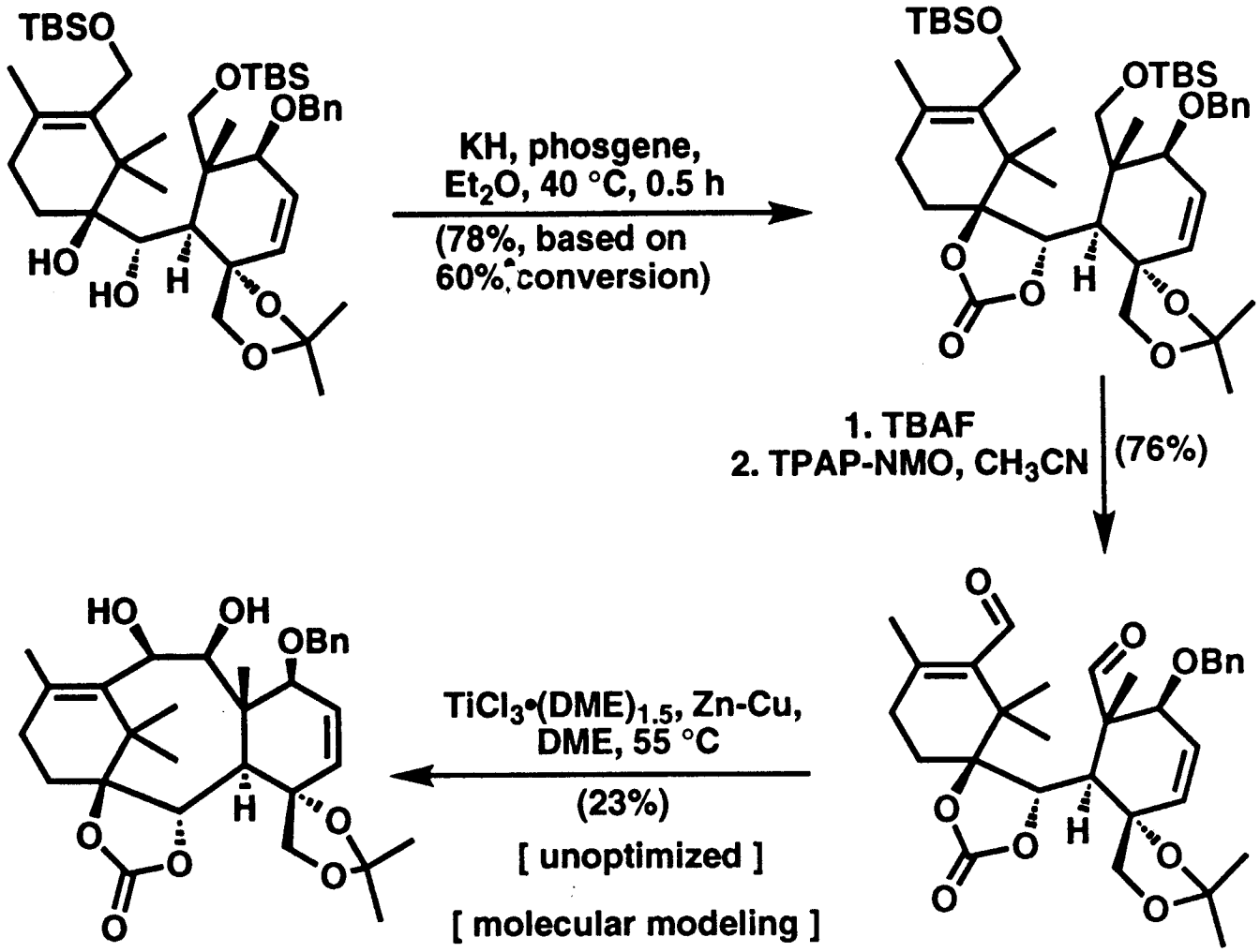
Stereoselectivity in the Shapiro Reaction

- Li^+ complexes the acetonide and aldehyde oxygens, fixing the cabonyl group in space.
- Nucleophile attacks from the more accessible face, opposite the methyl group.





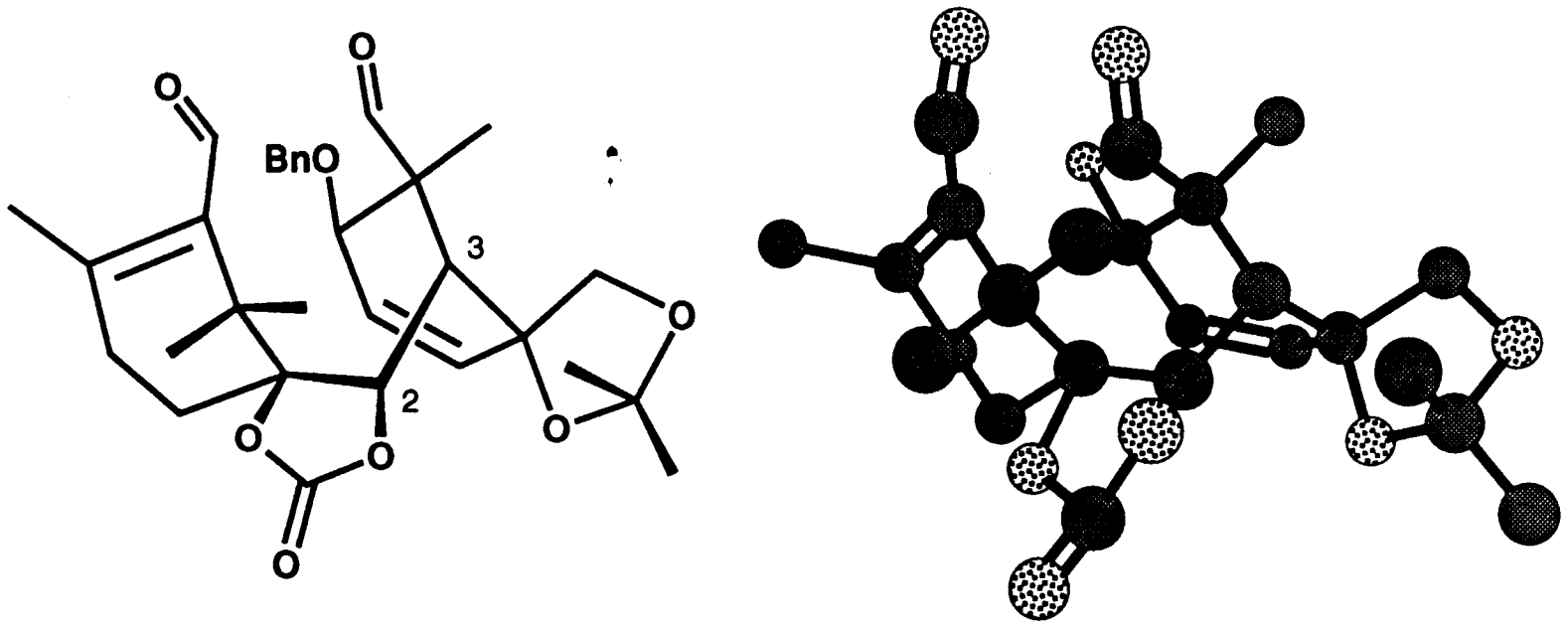
Preorganization and Closure of Taxol's B-Ring



precedent: Kende, et. al., *J. Am. Chem. Soc.* 1986, *108*, 3513 - 3515.

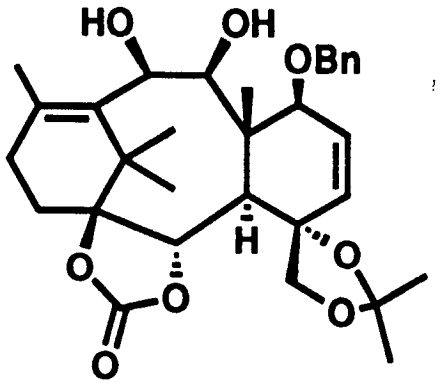
Nicolaou, et. al. *J. Chem. Soc., Chem. Commun.* 1993, 1024 - 1025.
Nicolaou, et. al. *J. Am. Chem. Soc.* 1994, *116*, 1591 - 1592.
Nicolaou, et. al. *Nature*, 1994, *387*, 630 - 634.

Proposed Ground State Conformation for the McMurry Cyclization

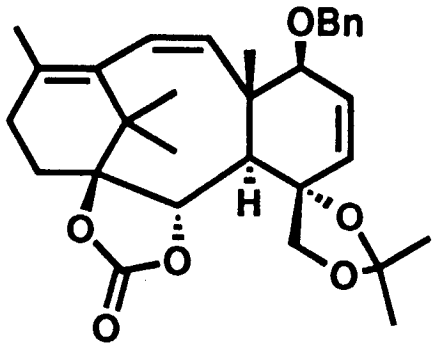


The model was generated using Chem3D (MM2)
The C7 benzyl and all hydrogens are omitted for clarity

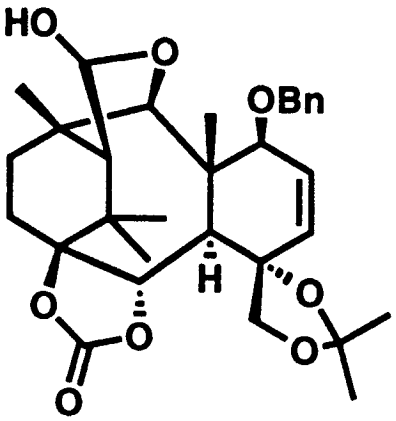
McMurry Coupling Products



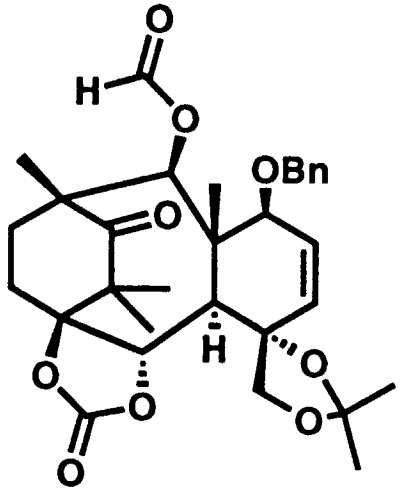
(23-25%)



(10%)

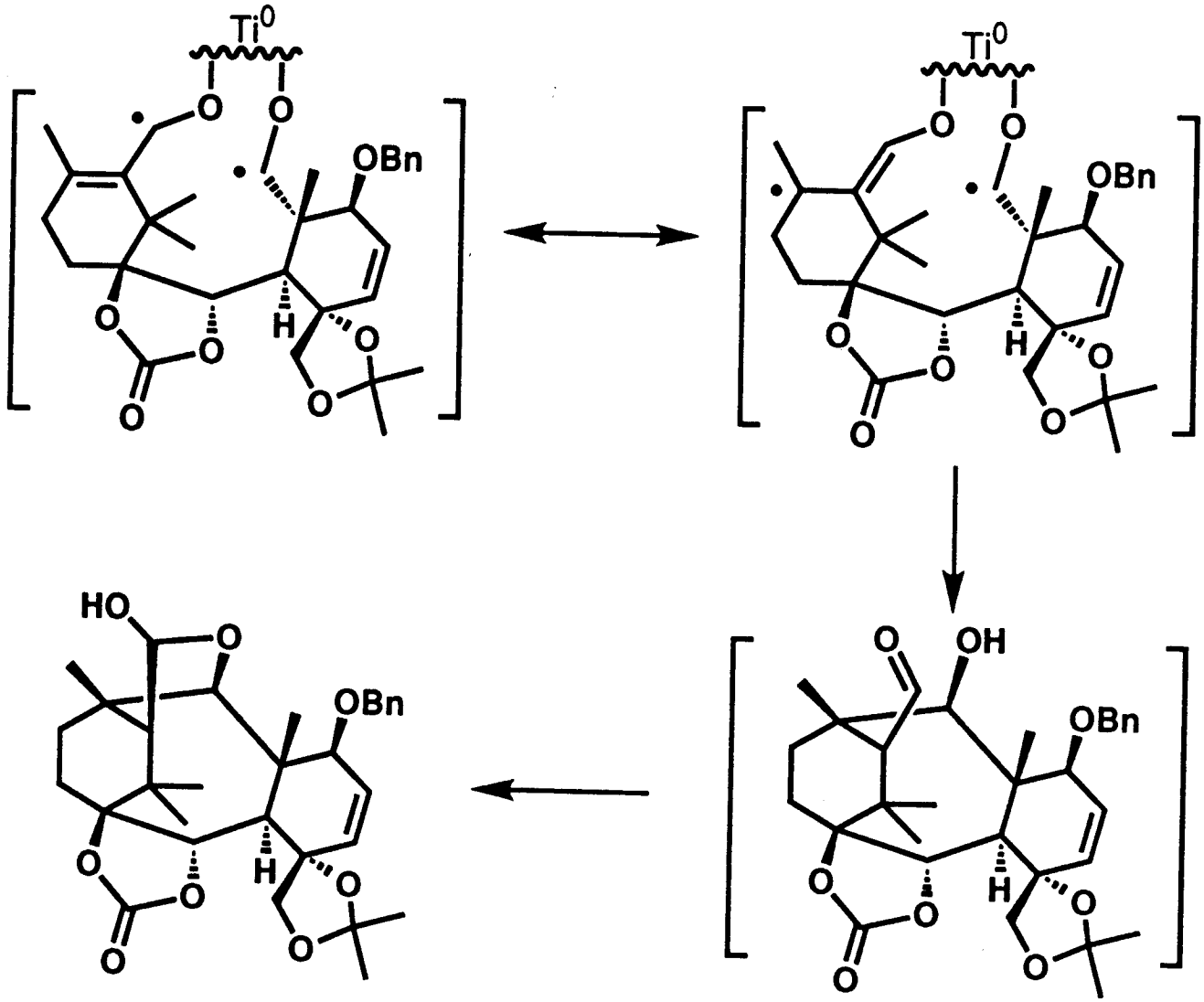


(40%)



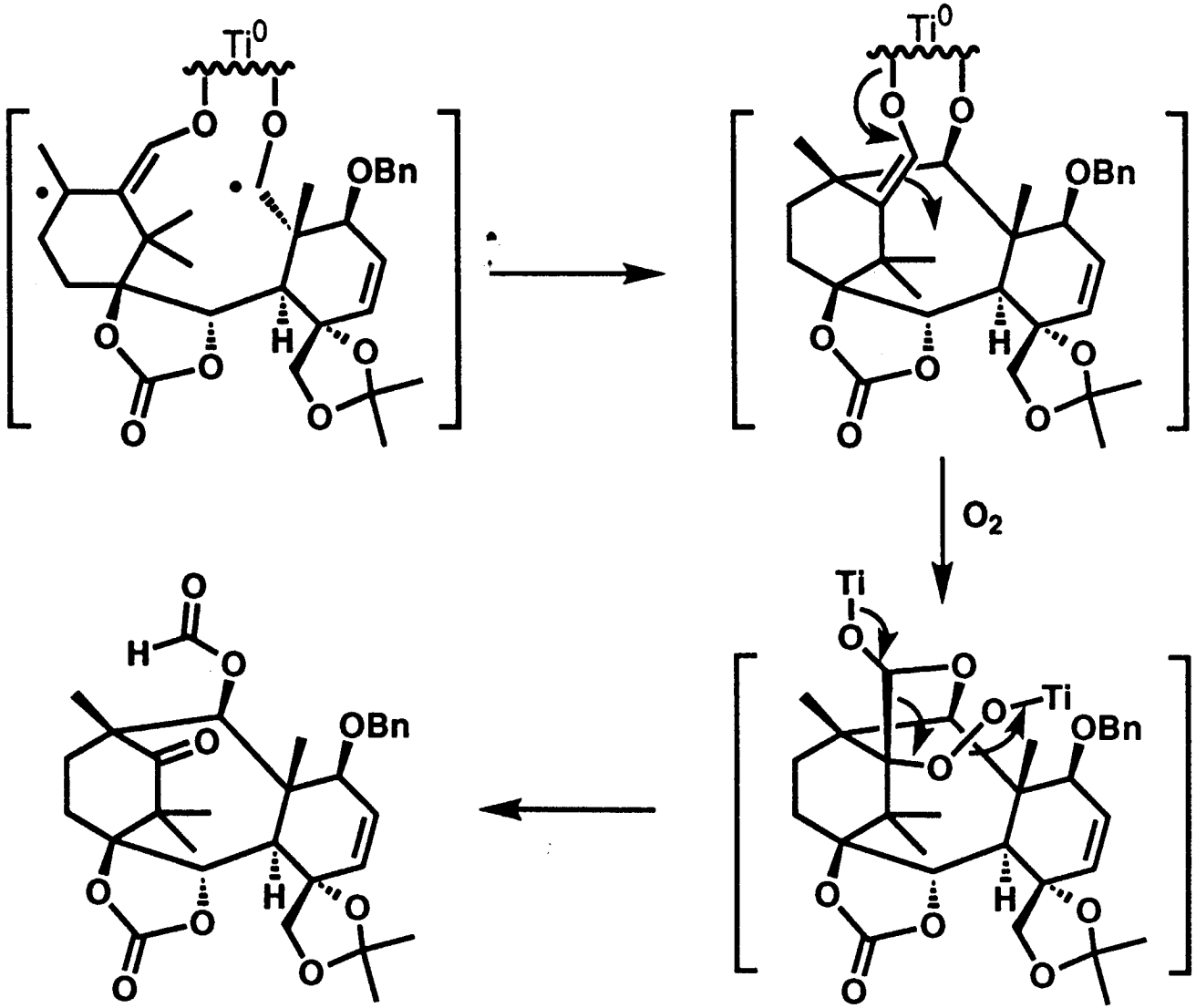
(15%)

Mechanistic Interpretation



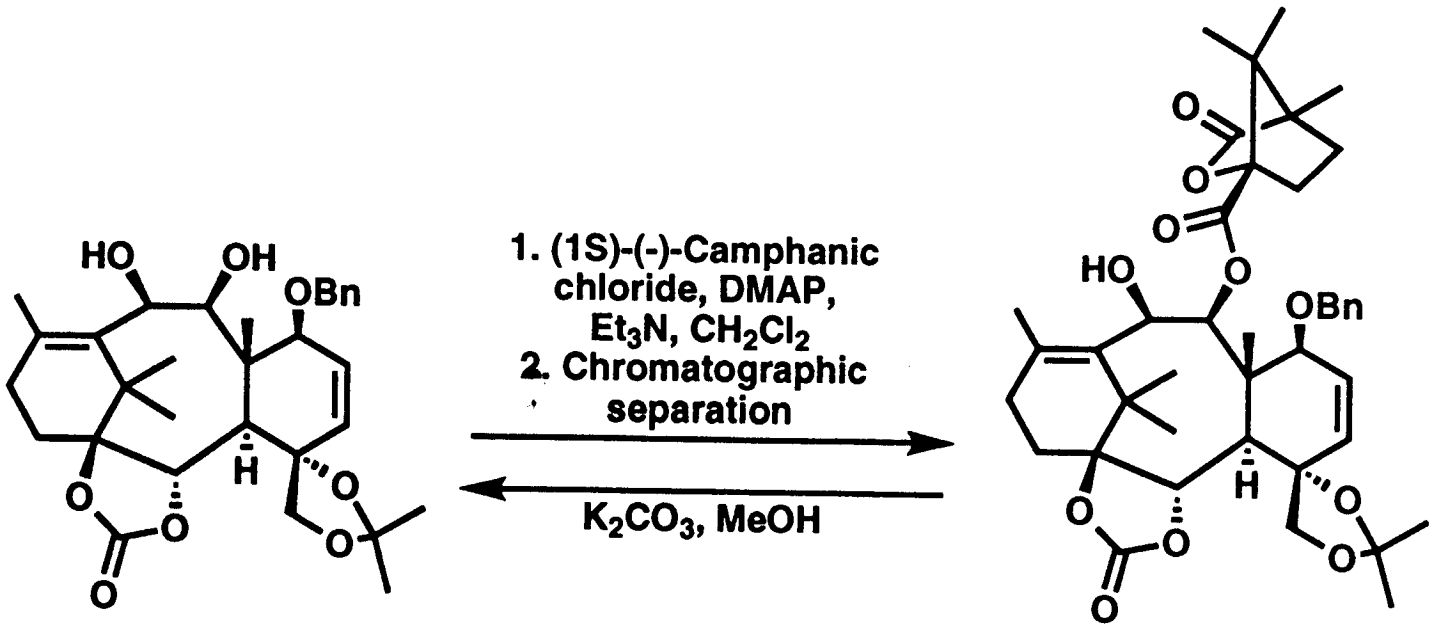
precedents: Kende, et. al., *J. Am. Chem. Soc.* 1986, *108*, 3513 - 3515.
McMurry *Chem. Rev.* 1989, *89*, 1513.

Mechanistic Interpretation



precedents: Kende, et. al., *J. Am. Chem. Soc.* 1986, *108*, 3513 - 3515.
McMurry *Chem. Rev.* 1989, *89*, 1513.

Resolution of Enantiomers

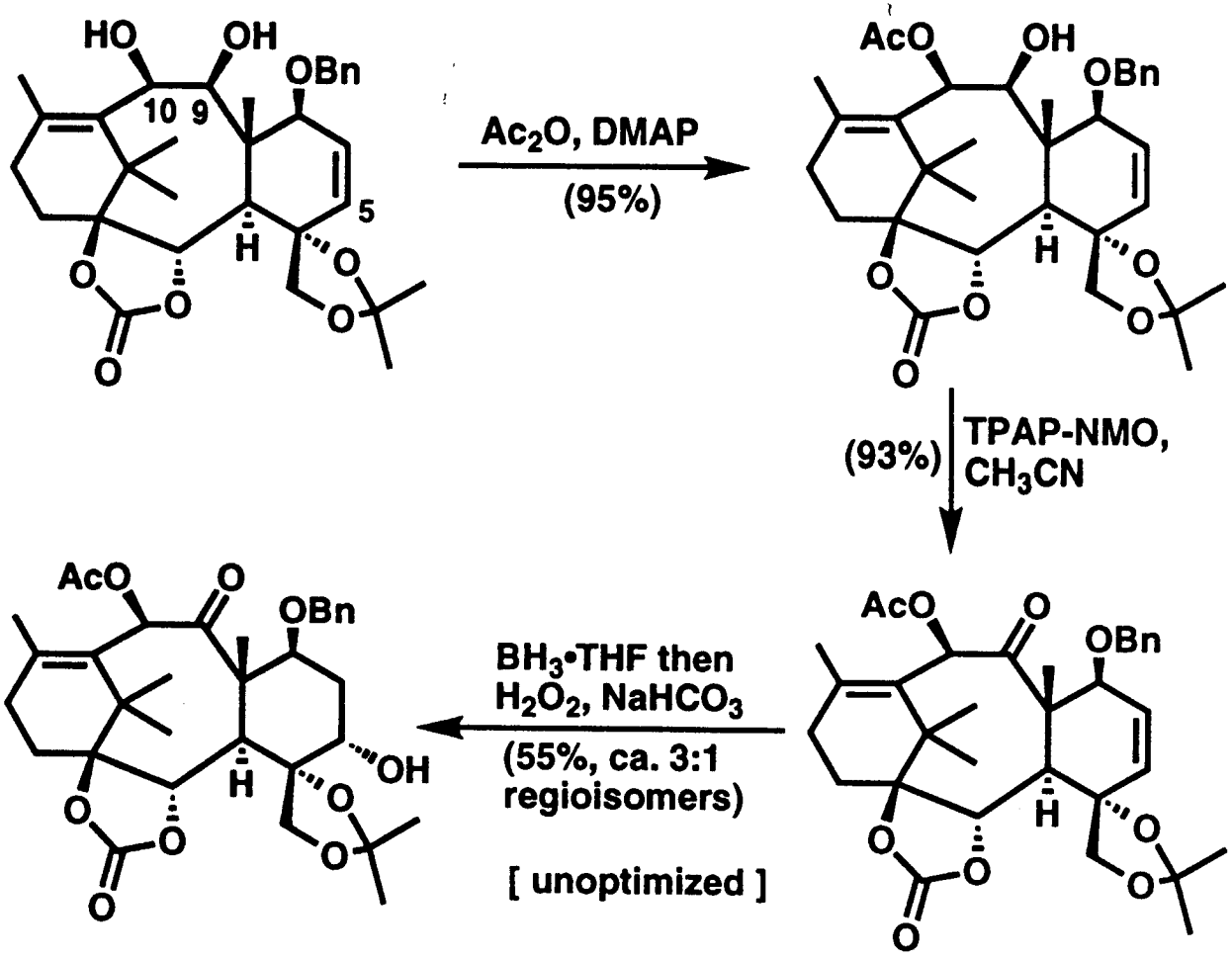


enantiomerically pure:
$[\alpha]_D^{22}$ +188° (0.5, $CHCl_3$) (90%)

more polar isomer: $[\alpha]_D^{22}$ +117° (41%)
less polar isomer: $[\alpha]_D^{22}$ -134° (41%)
[X-ray crystallographic analysis]

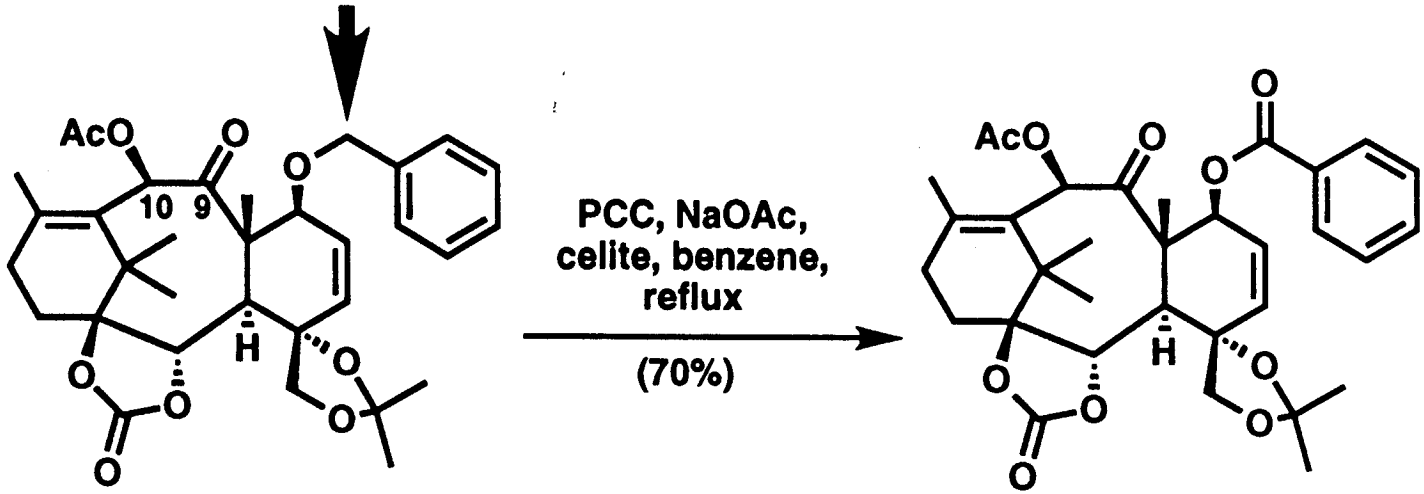
Nicolaou, et. al. *Nature*, 1994, *387*, 630 - 634.

Functionalization at C-5, C-9, and C-10



Nicolaou, et. al. *Nature*, 1994, *387*, 630 - 634.

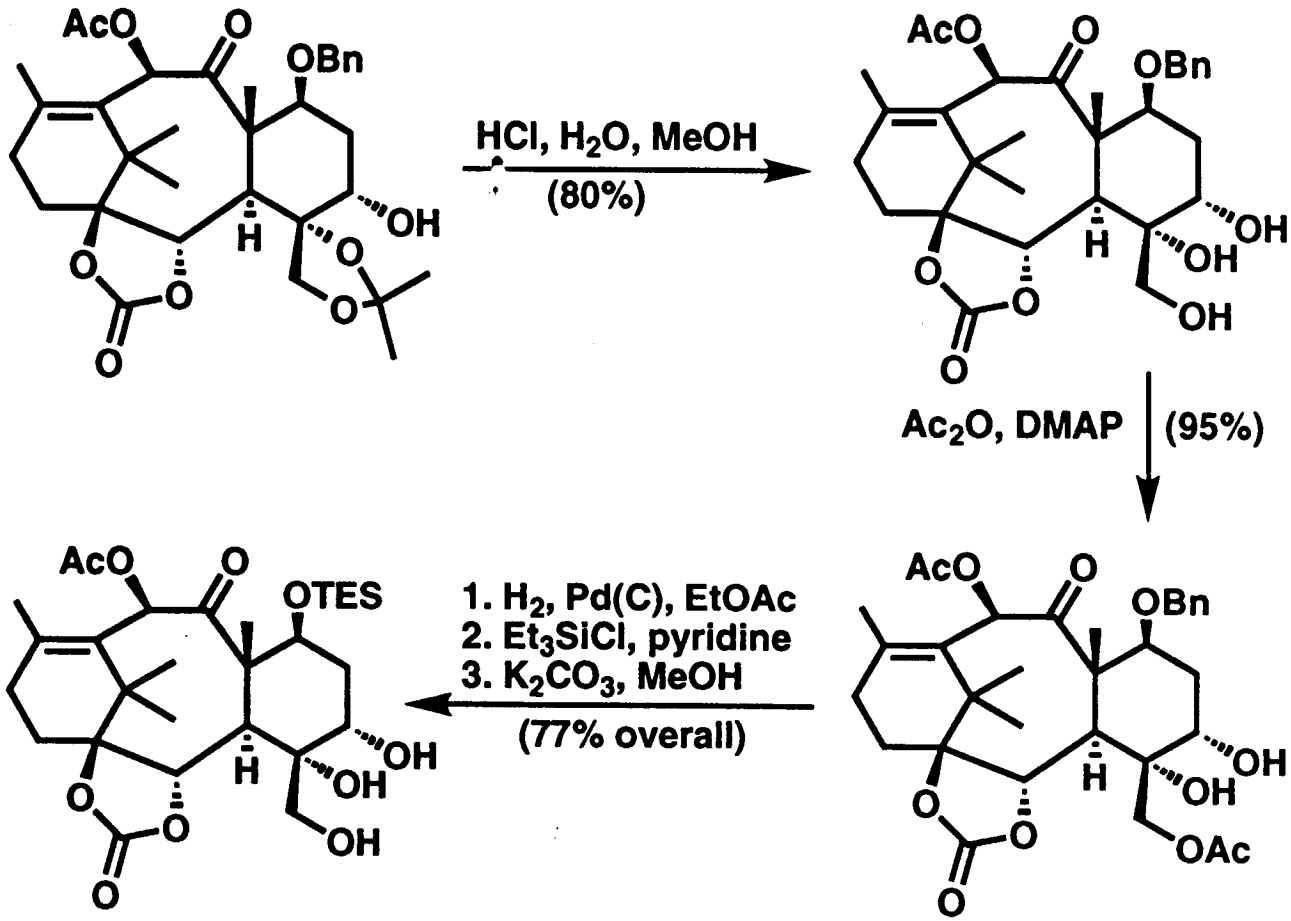
Confirming the Regio- and Stereochemistry at C-9/C-10



[X-ray crystallographic analysis]

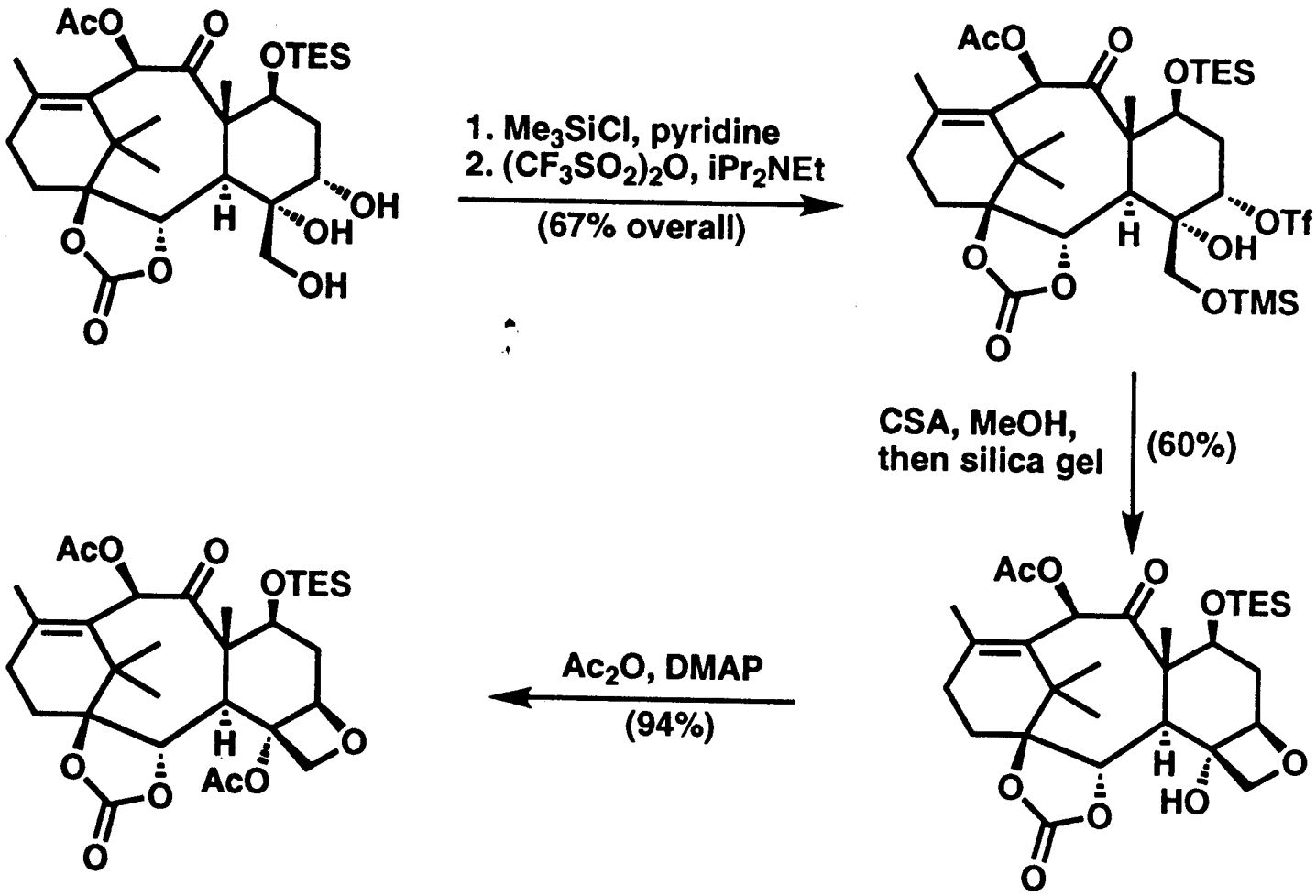
Nicolaou, et. al. *Nature*, 1994, *387*, 630 - 634.

Exchange of Protecting Groups



Nicolaou, et. al. *Nature*, 1994, *387*, 630 - 634.

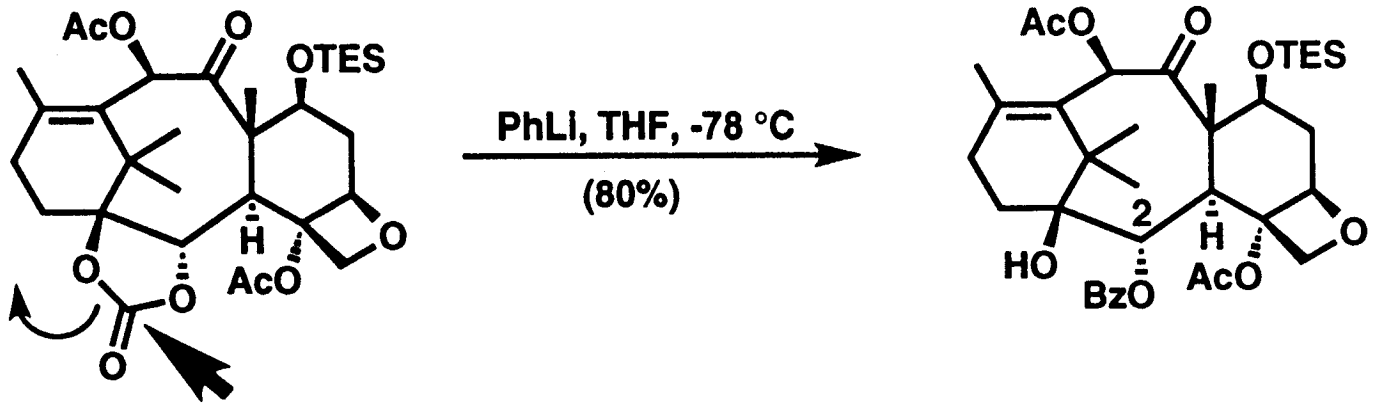
Installment of the Oxetane Ring



precedent: Potier, et. al. *Tetrahedron*, 1991, *47*, 9823 - 9838.
Danishefsky, et. al. *J. Org. Chem.*, 1992, *57*, 3274 - 3276.

Nicolaou, et. al. *Nature*, 1994, *387*, 630 - 634.

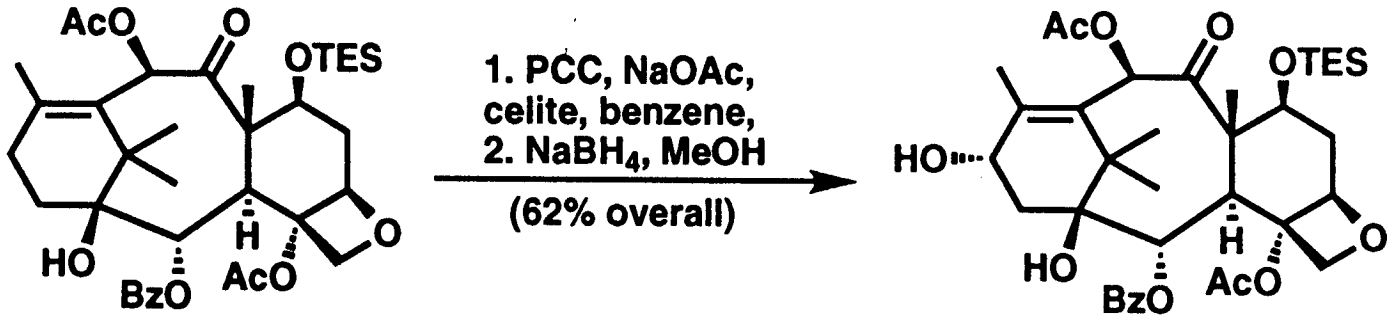
Regioselective Formation of the C-2 Benzoate



precedent: (with tBuLi) Wender, et. al. *J. Am. Chem. Soc.* 1989, *111*, 8957 - 8958.
(with symmetrical carbonates) Sivaram, S. et. al. *Synth. Commun.* 1990, 3273 - 3276

Nicolaou, et. al. *US Patent Appl*, 1993.
Nicolaou, et. al. *J. Chem. Soc., Chem. Commun.* 1994, 295 - 296.
Nicolaou, et. al. *J. Am. Chem. Soc.* 1994, *116*, 1591 - 1592.
Nicolaou, et. al. *Nature*, 1994, *387*, 630 - 634.

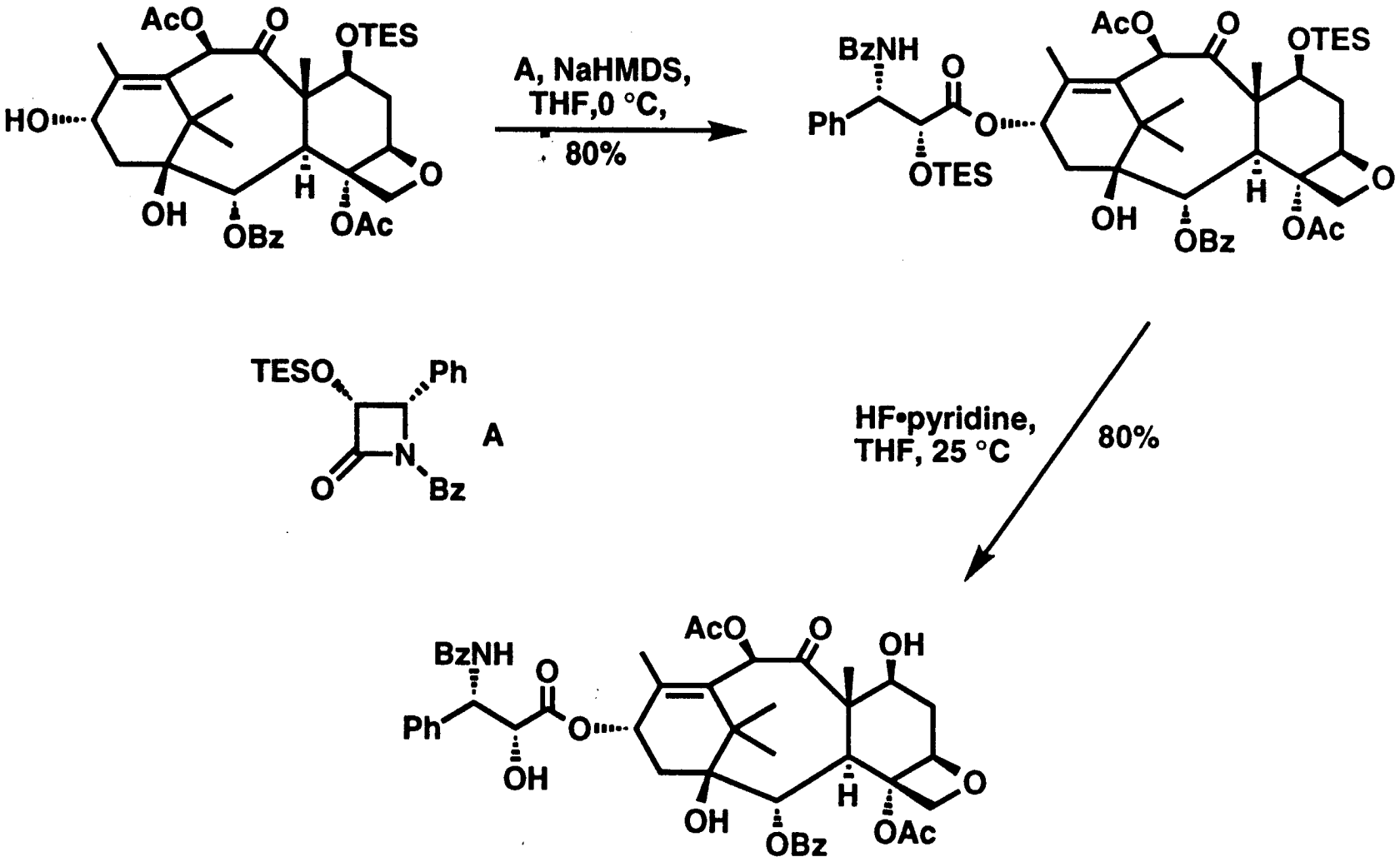
Oxygenation at C-13



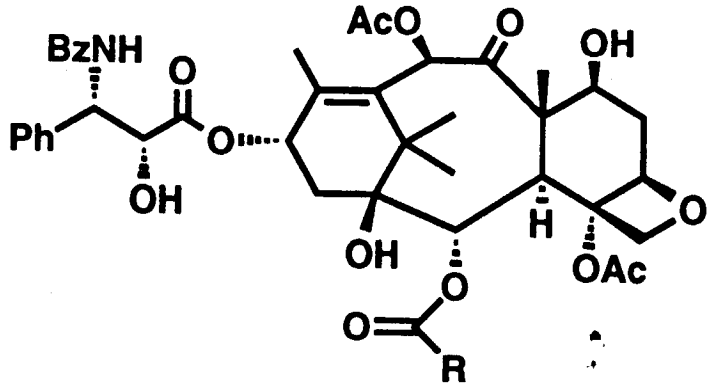
precedent (reduction): Potier, et. al. *C. R. Acad. Sc. Paris*, 1984, *299*, 1039 - 1043.

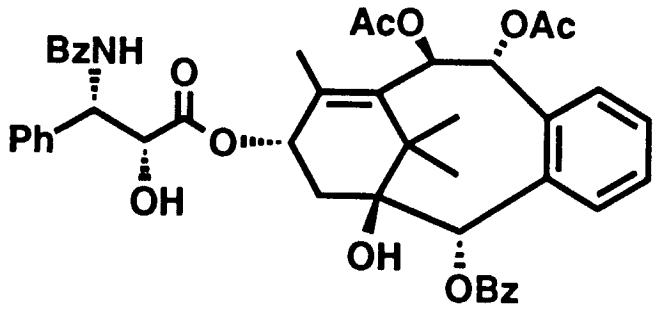
Nicolaou, et. al. *J. Chem. Soc., Chem. Commun.* 1994, 295 - 296.
Nicolaou, et. al. *J. Am. Chem. Soc.* 1994, *116*, 1591 - 1592.
Nicolaou, et. al. *Nature*, 1994, *387*, 630 - 634.

Total Synthesis of Taxol



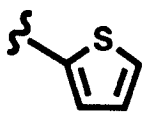
Synthetic Designed Taxoids





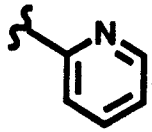
IC_{50} M : 1.9×10^{-6}
(antipode : inactive)

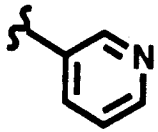
R =

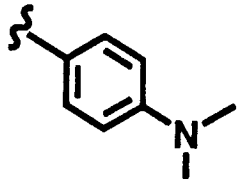


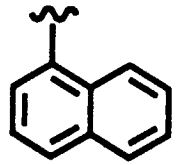
IC_{50} M : 3.8×10^{-7} 2.3×10^{-8} **2.9×10^{-9}** **Taxol : 3.2×10^{-9}**

R =







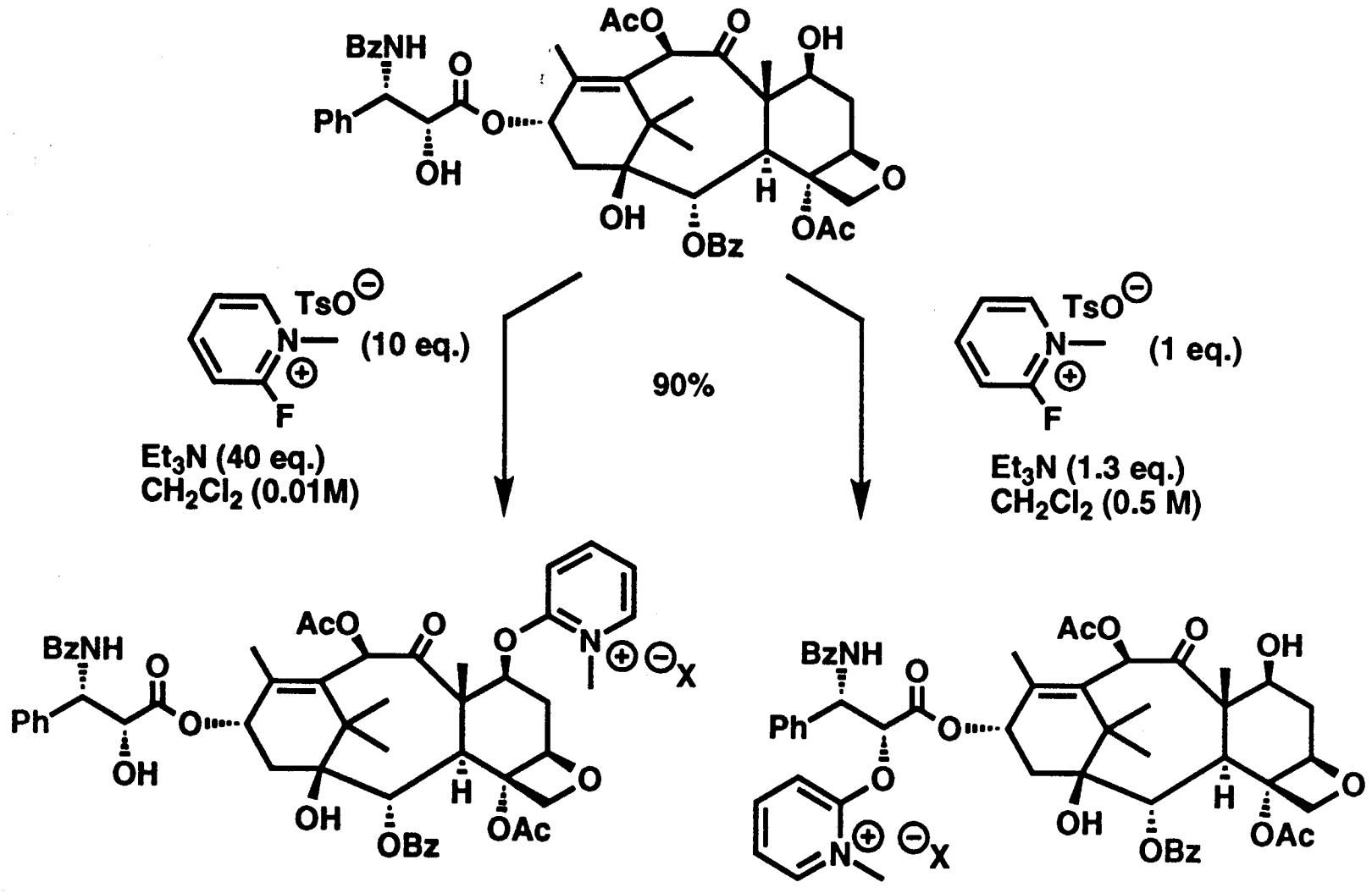


IC_{50} M : 2.8×10^{-8} 3.6×10^{-7} 1.7×10^{-5} 1.4×10^{-4}

IC_{50} values are averaged over 9 cell lines

Nicolaou, et. al. *Angew. Chem. Int. Ed. Engl.* 1994, *33*, 1581 - 1583.
Nicolaou, et. al. *J. Am. Chem. Soc.* 1994, *116*, 1591 - 1592.

Synthesis of Pyridinium Salts of Taxol



Taxol-7-methylpyridinium salt
(taxol-7-MPX)

Taxol-2'-methylpyridinium salt
(taxol-2'-MPX)

Nicolaou, et. al. *Angew. Chem. Int. Ed. Engl.* 1994, *33*, 1583 - 1587.
Gomez-Paloma, et. al. *Chem. Biol.*, 1994, *1*,