Comparative Syntheses of Taxol

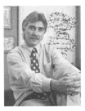
Ian Mangion
MacMillan Group Meeting
December 1, 2004

- The players:

Robert Holton, FSU
1993

K.C. Nicolaou, Scripps
1994

Sam Danishefsky, Columbia
1995

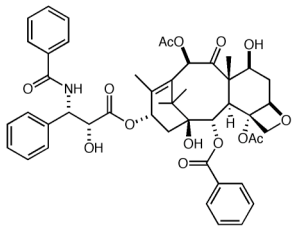


Paul Wender, Stanford
1996

Isao Kuwajima, Kitasato Inst.
1999

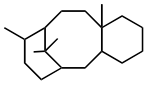
Teruaki Mukaiyama,
Science Univ. of Tokyo
1999

- The game:

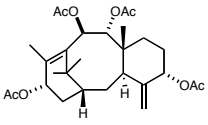


Structural Features of Taxanes

- Generally characterized by a common 6-8-6 tricyclic ring system, or related skeleton

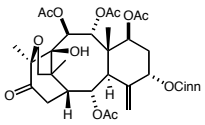


- Structure of Taxol elucidated 1971, but many others discovered both before and later

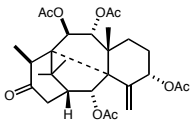


Taxusin

Holton - 1988
Kuwajima - 1996
Paquette - 1998



Taxigifine



Taxine A

- Useful reviews:

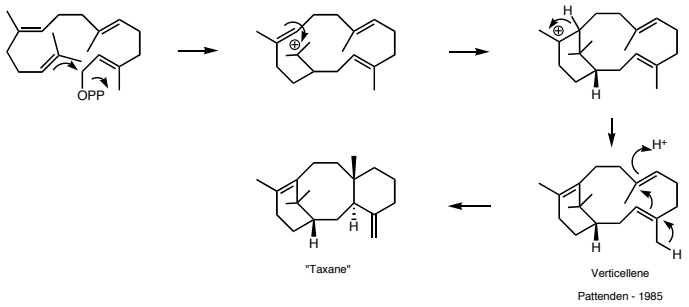
Kingston, D. G. I. *Chem. Comm.*, **2001**, 867 (general)

Miller, R. W. *J. Nat. Prod.*, **1980**, *43*, 425 (structures)

Farina, V., *ed. The Chemistry and Pharmacology of Taxol*; Elsevier Science, **1995**

Proposed Biosynthesis of Taxanes

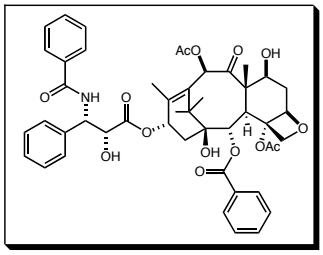
- Biosynthetic studies are lacking, but synthesis presumed to go through geranylgeranyl pyrophosphate



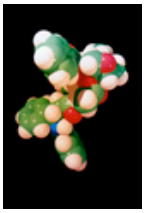
- Although this mechanism is generally accepted, attempts to convert Verticellene to taxanes have been unsuccessful; it is presumed particular oxygenations provide a conformational bias

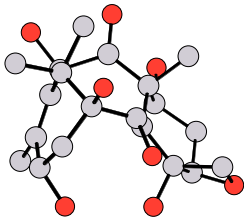
Biological Sources and Activity

- Knowledge of the biological potence of the yew tree goes back millenia



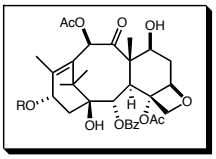
- While currently a massively successful drug, Taxol took many years to gain interest as a pharmaceutical agent
- Bioactivity of taxol discovered in 1962, but mode of action not found until 1979



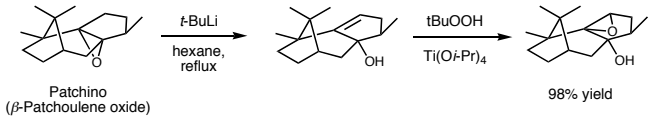


- Taxol acts as a microtubule stabilizer, interrupting cell division (now known in the Epothilones, Rhazinilam, etc)
- Currently used against metastatic ovarian and breast cancers, and being tested against other indications

The Holton Approach

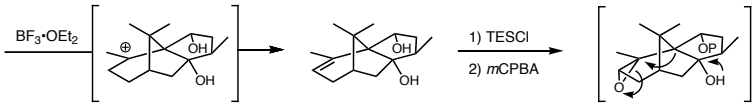


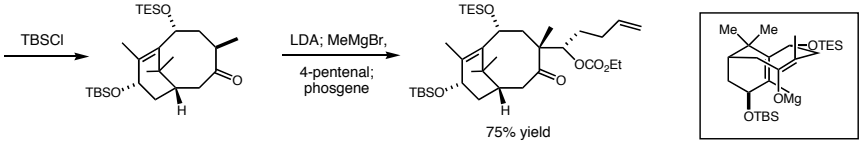
- Holton began on the premise of a ring expansion to make the required 8-ring



Patchino
(β-Patchoulene oxide)

98% yield



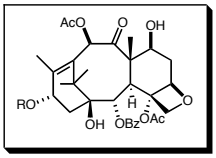


75% yield

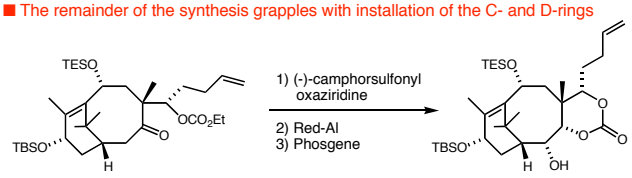
Holton, R. A. *et al.* *J. Am. Chem. Soc.* **1994**, *116*, 1597

- Source of selectivity in the aldol not commented upon, some compounds are mixtures of conformations
- Starting from a natural source, this approach quickly accesses much of the requisite functionality

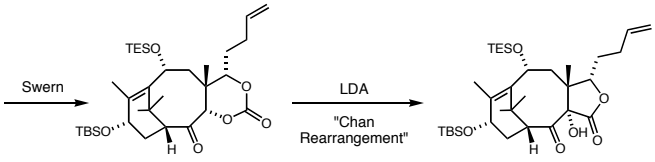
The Holton Approach



- The remainder of the synthesis grapples with installation of the C- and D-rings

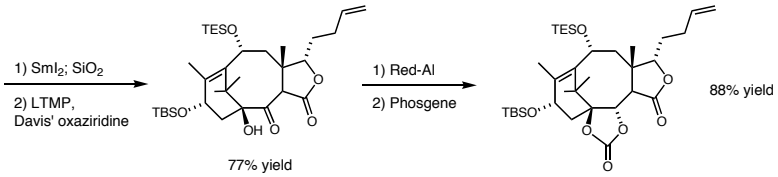


82% yield



95% yield

90% yield



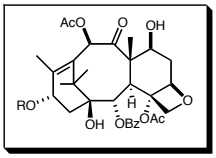
77% yield

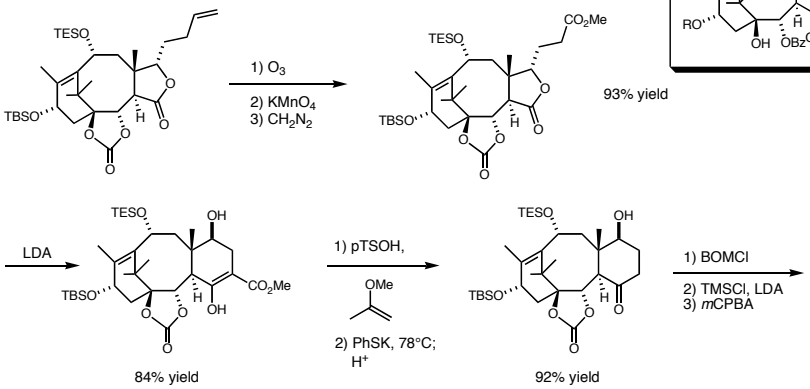
88% yield

Holton, R. A. *et al.* *J. Am. Chem. Soc.* **1994**, *116*, 1597

The Holton Approach

■ Functionalization of the C-ring proves lengthy

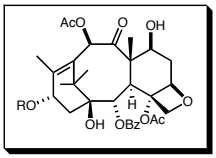


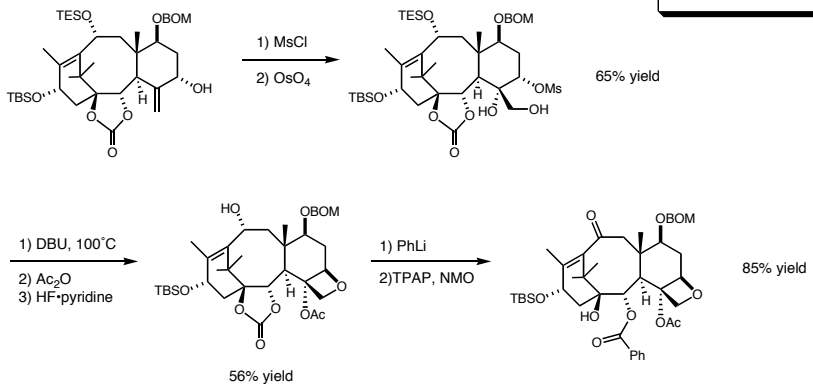


Holton, R. A. *et al. J. Am. Chem. Soc.* **1994**, *116*, 1599

The Holton Approach

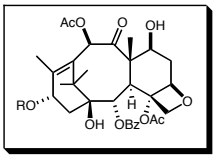
■ Introduction of the D-ring is largely uneventful



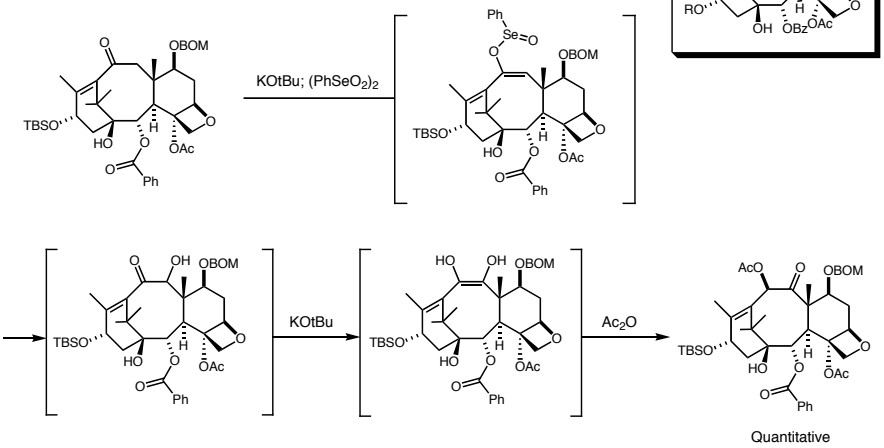


Holton, R. A. *et al. J. Am. Chem. Soc.* **1994**, *116*, 1599

The Holton Approach



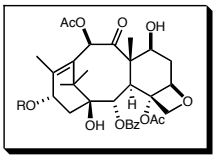
■ An interesting oxidation sets up the endgame



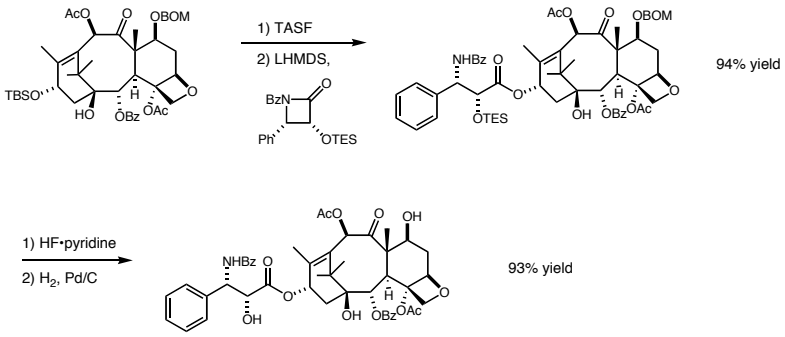
Holton, R. A. *et al. J. Am. Chem. Soc.* **1994**, *116*, 1599

Koji, Y. *et al. Tetrahedron* **1981**, *37*, 473 (oxidation)

The Holton Approach



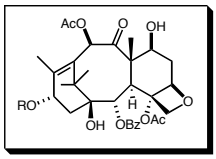
■ Completion of the synthesis is now readily achieved



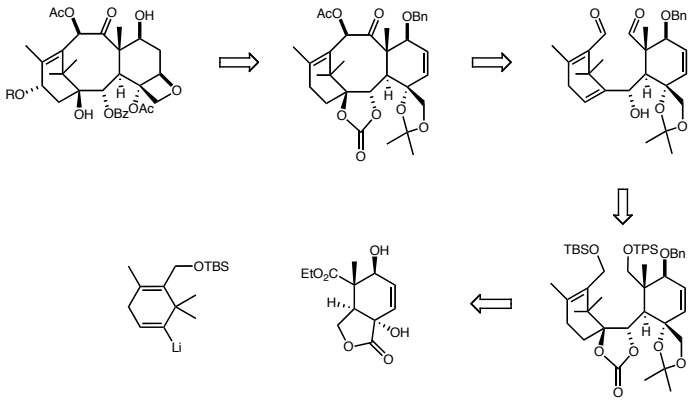
Holton, R. A. *et al. J. Am. Chem. Soc.* **1994**, *116*, 1599

■ Taxol is completed in ca. 41 steps in 2% overall yield from (-) patchino

The Nicolaou Approach

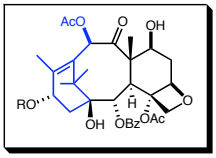


- The plan calls for a late 8-ring formation and a convergent A- and C-ring union

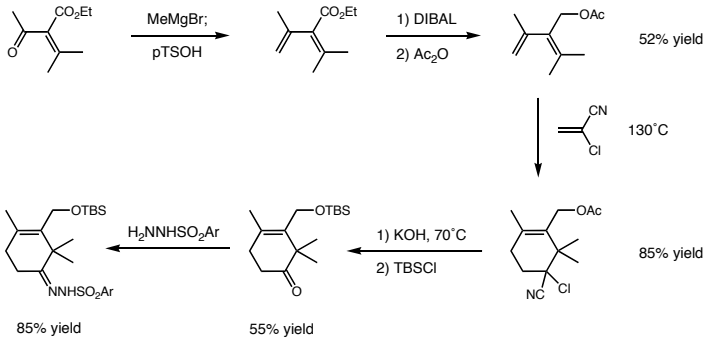


Nicolaou, K. C. *et al. Nature* **1994**, *367*, 630

The Nicolaou Approach

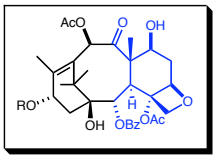


- Formation of the A-ring precursor occurs in 7 steps

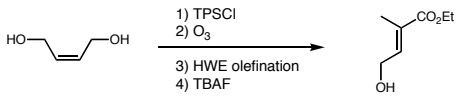


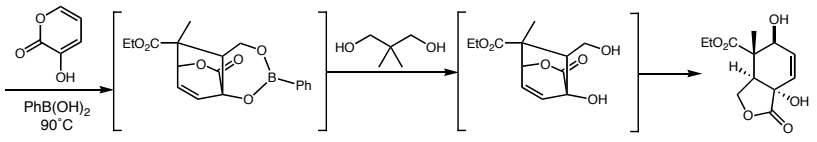
Nicolaou, K. C. *et al. Nature* **1994**, *367*, 630

The Nicolaou Approach

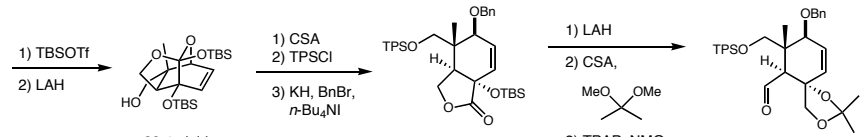


■ Formation of the C-ring precursor occurs in 13 steps





61% yield



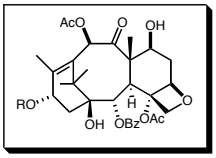
89% yield

76% yield

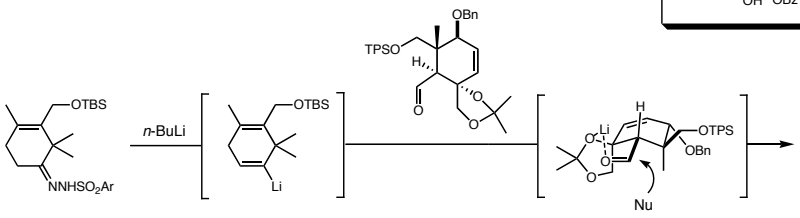
61% yield

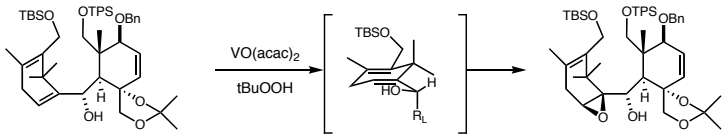
Nicolaou, K. C. *et al. Nature* **1994**, *367*, 630

The Nicolaou Approach



■ Union of the two fragments allows access to a mostly-formed skeleton



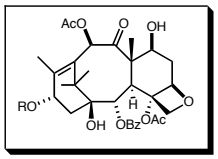


82% yield

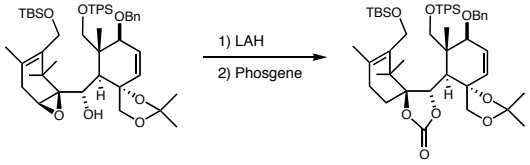
87% yield

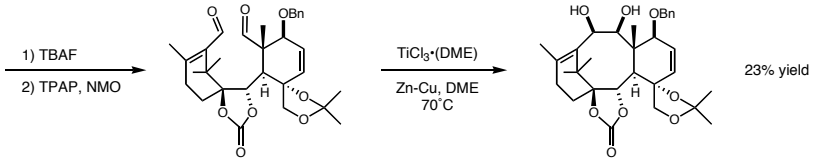
Nicolaou, K. C. *et al. Nature* **1994**, *367*, 630

The Nicolaou Approach



■ Closure of the B-ring proves...difficult

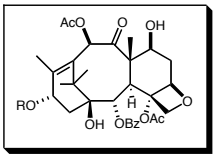




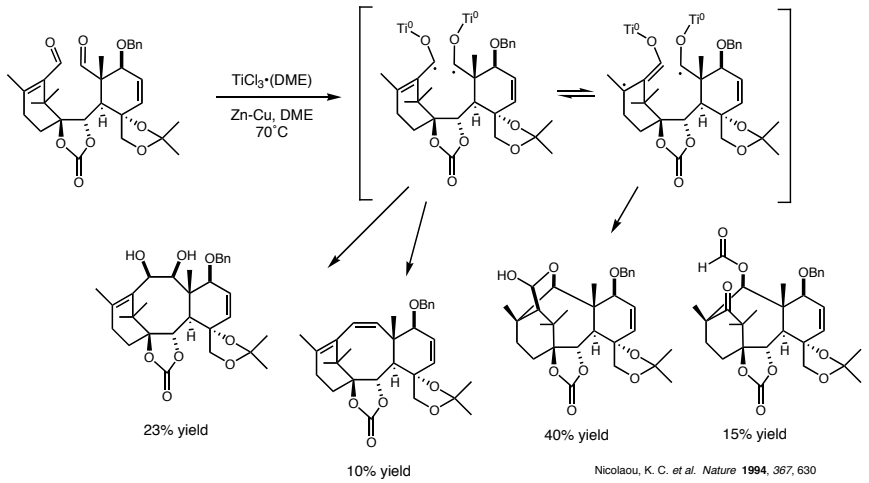
Nicolaou, K. C. *et al. Nature* **1994**, *367*, 630

■ McMurry coupling, based perhaps on precedent of verticellene, is heavily optimized to no avail

The Nicolaou Approach

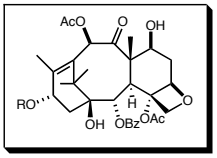


■ Mechanistic divergence leads to a multitude of products

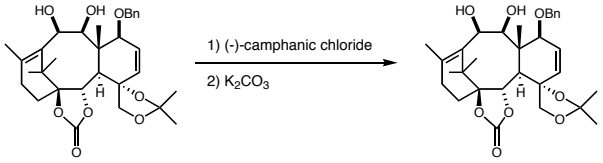


Nicolaou, K. C. *et al. Nature* **1994**, *367*, 630

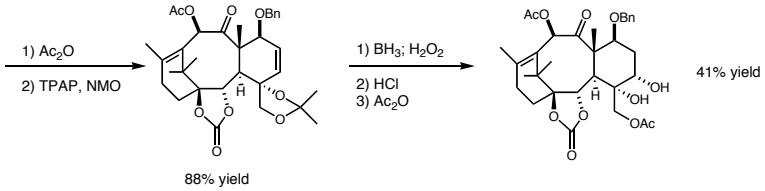
The Nicolaou Approach



■ Resolution of the racemic intermediate is now performed



38% total use of material



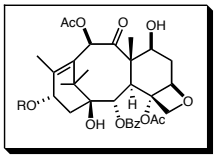
88% yield

41% yield

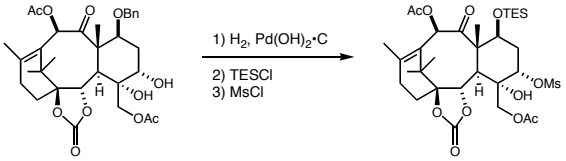
■ Hydroboration proceeds with 3:1 regioselectivity

Nicolaou, K. C. *et al. Nature* **1994**, *367*, 630

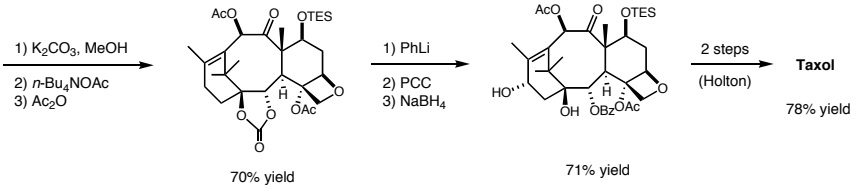
The Nicolaou Approach



■ Completion of the synthesis centers on installation of the D-ring



60% yield



70% yield

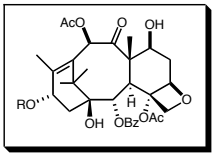
71% yield

78% yield

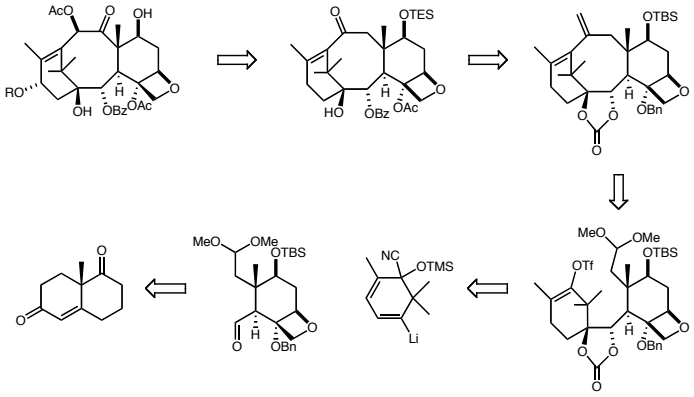
Nicolaou, K. C. *et al. Nature* **1994**, *367*, 630

■ The synthesis of taxol is complete in 51 steps in .03% yield from butene diol (average 85% yield vs. 91% Holton)

The Danishefsky Approach



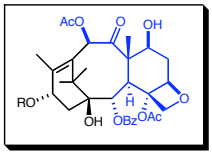
- Retrosynthesis focuses on exploitation of the Wieland-Miescher ketone



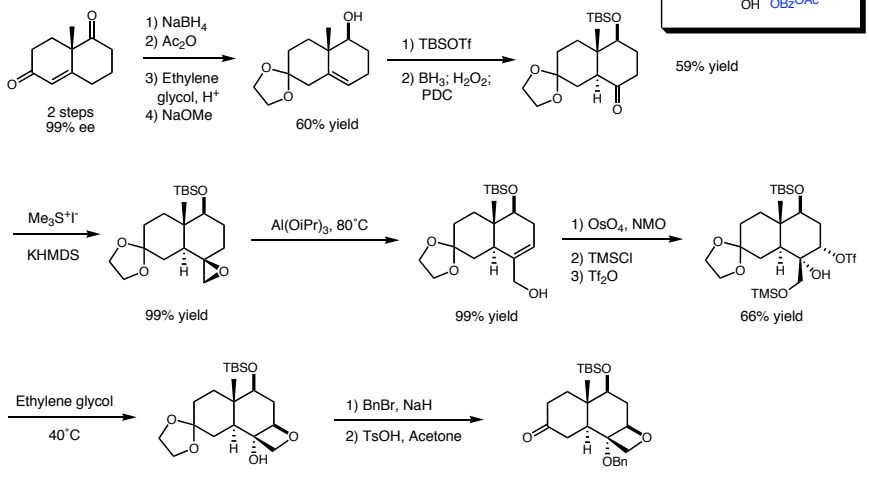
Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1996**, *118*, 2843

- "The sum of the components contain more than an ample number of carbons (20) to reach the ABC core (19)"

The Danishefsky Approach

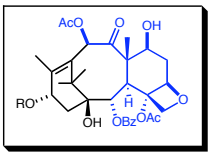


- Functionalization of the starting ketone occupies the initial steps

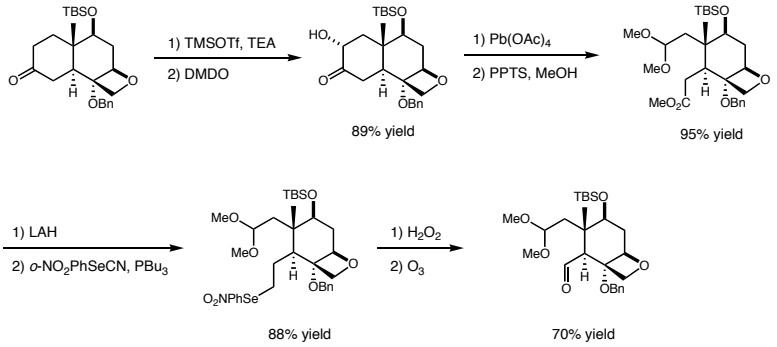


Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1996**, *118*, 2843

The Danishefsky Approach

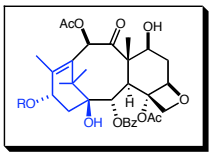


■ The inegrity of the oxetane is maintained throughout the remainder of the route

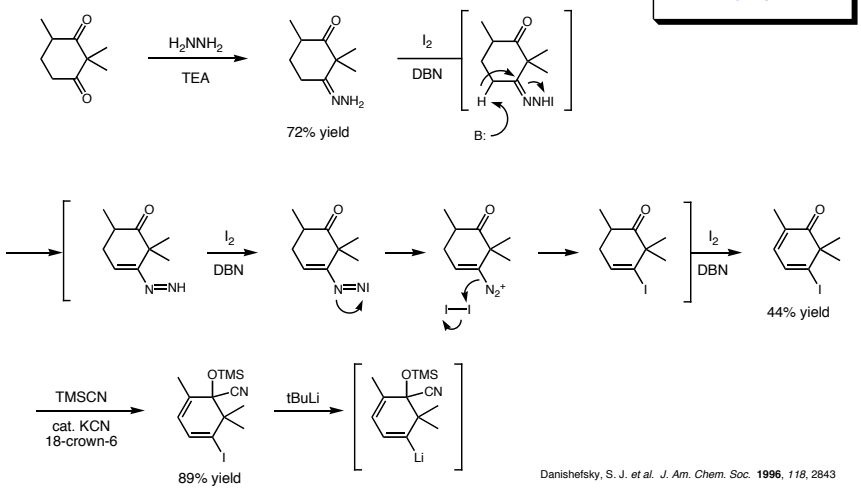


Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1996**, *118*, 2843

The Danishefsky Approach

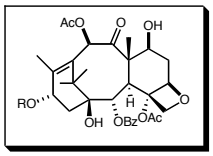


■ Introduction of the A-ring resembles Nicolaou's approach

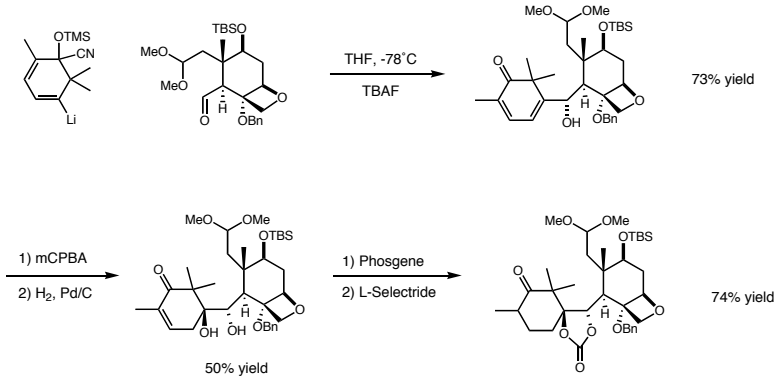


Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1996**, *118*, 2843

The Danishefsky Approach

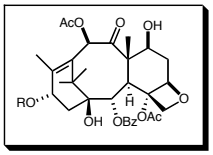


- Coupling of the fragments provides one diastereomer, perhaps analogous to the Nicolaou precedent

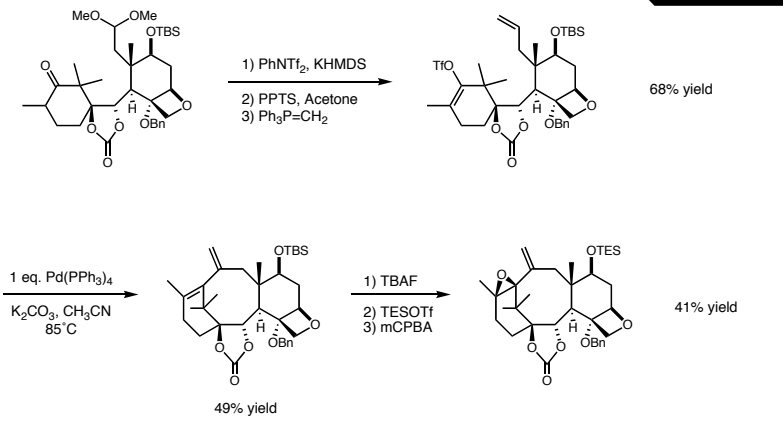


Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1996**, *118*, 2843

The Danishefsky Approach

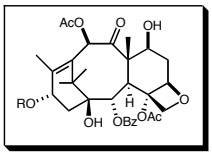


- Functionalization is then performed to set up an impressive Heck reaction

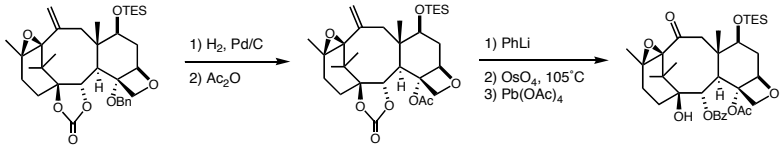


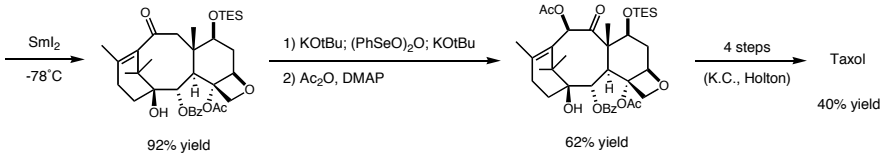
Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1996**, *118*, 2843

The Danishefsky Approach



■ Completion of the synthesis relies on a few known methods

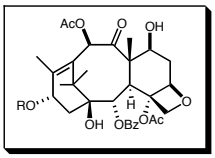




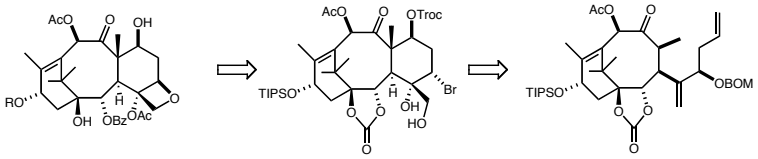
Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1996**, *118*, 2843

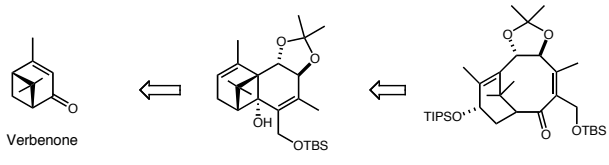
■ Danishefsky's synthesis requires 47 steps, 0.2% yield from Wieland-Mieschler ketone

The Wender Approach



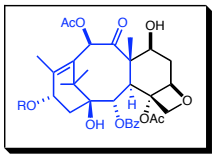
■ Wender's design relies upon manipulation of pinene



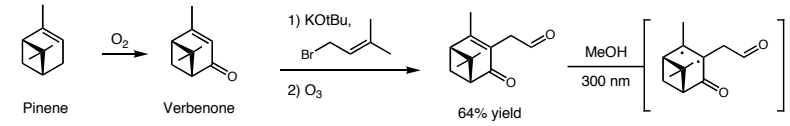


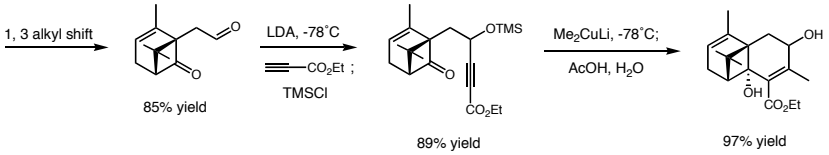
Wender, P. A. *et al. J. Am. Chem. Soc.* **1997**, *119*, 2755

The Wender Approach



- Starting from the air oxidation product of pinene, Wender attempts to introduce the A- and B-rings independently of the C-ring

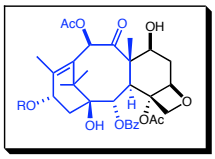




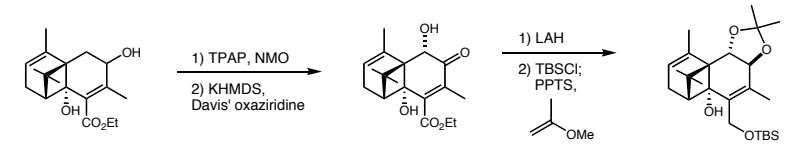
Wender, P. A. *et al. J. Am. Chem. Soc.* **1997**, *119*, 2755
Erman, W. F. *J. Am. Chem. Soc.* **1967**, *89*, 3830 (verbenone photochemistry)

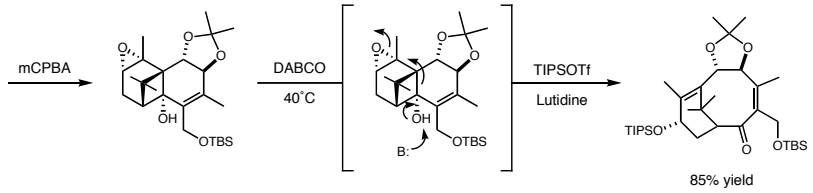
- Photochemical rearrangement occurs without loss of enantiopurity

The Wender Approach



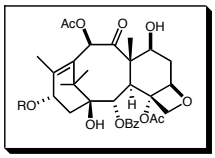
- An epoxide-opening ring expansion sets the B-ring in place



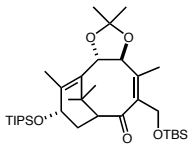


Wender, P. A. *et al. J. Am. Chem. Soc.* **1997**, *119*, 2755

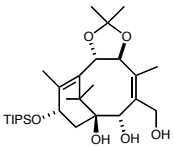
The Wender Approach



■ The acetonide enforces a desireable conformation for stereochemical control

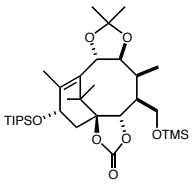


KOtBu, O_2, $P(OEt)_3$;
NH_4Cl, MeOH; $NaBH_4$



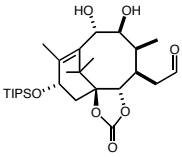
91% yield

H_2, Crabtree's cat.;
TMSCl, pyridine;
Triphosgene

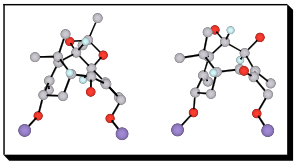


98% yield

1) PCC;
2) Ph_3P=CHOMe
3) 1N HCl

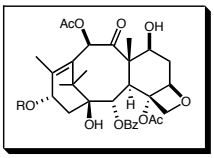


79% yield



Wender, P. A. *et al. J. Am. Chem. Soc.* **1997**, *119*, 2755
Wender, P. A. *et al. J. Am. Chem. Soc.* **1997**, *119*, 2757

The Wender Approach



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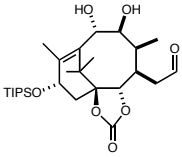
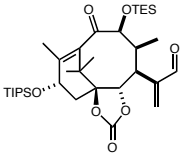


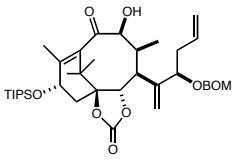
1) TESCl
2) Dess-Martin;
Me_2NCH_2I, TEA



90% yield

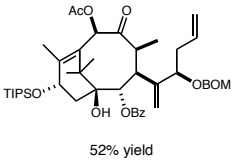
1) $ZnCl_2$


2) BOMCl
3) NH_4Cl



82% yield

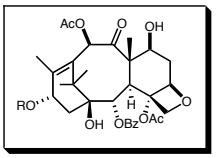
1) PhLi, Ac_2O
2)

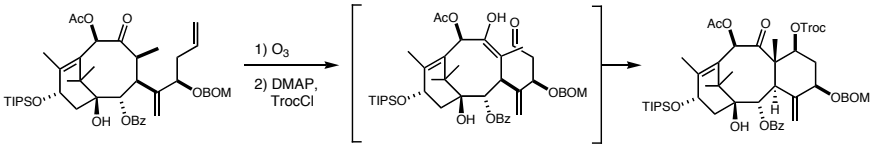
52% yield

Wender, P. A. *et al. J. Am. Chem. Soc.* **1997**, *119*, 2757

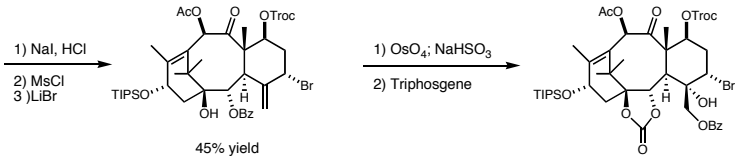
The Wender Approach



■ The intramolecular aldol reaction only proceeds without the carbonate

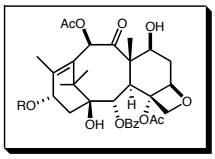


62% yield

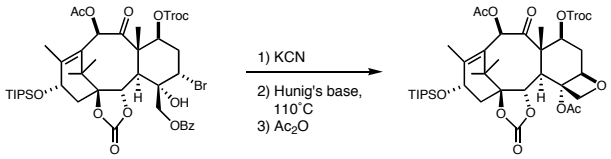


Wender, P. A. *et al. J. Am. Chem. Soc.* **1997**, *119*, 2757

The Wender Approach



■ Completion of the synthesis now requires oxetane formation



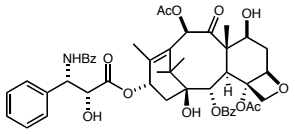
55% yield

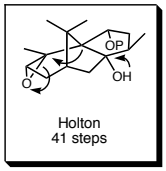
Wender, P. A. *et al. J. Am. Chem. Soc.* **1997**, *119*, 2757

■ Wender's synthesis invloves 37 steps, 0.2% yield overall from verbenone

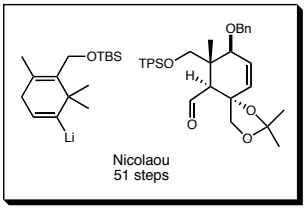
Conclusions

- While synthesis is not a practical approach to solve problems of Taxol's supply, fascinating chemistry has been discovered in pursuit of an optimal route

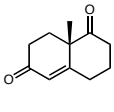




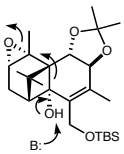
Holton
41 steps



Nicolaou
51 steps



Danishefsky
47 steps



Wender
37 steps

- Taxol represents one of the greatest synthetic achievements in organic chemistry