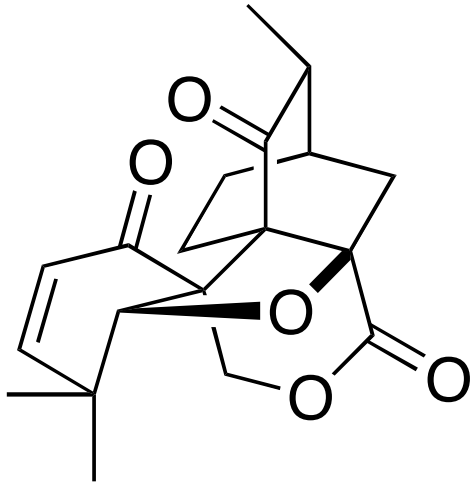
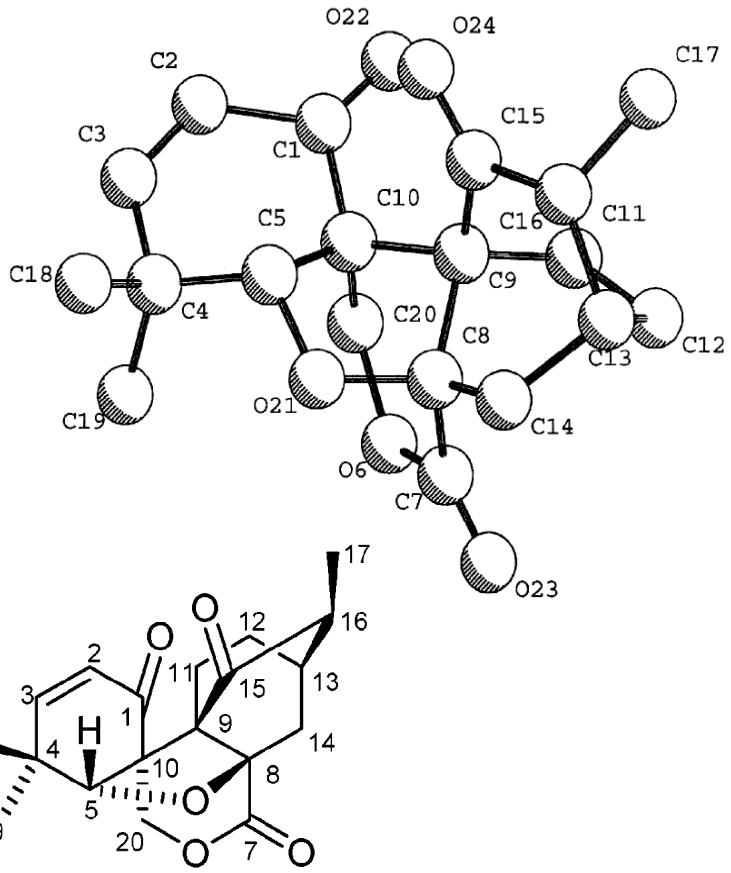
Towards Maoecrystal V: A Comparison of Recent Strategies

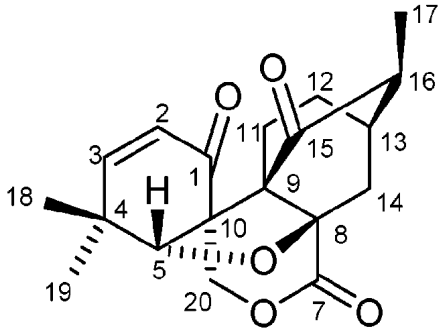


Current Literature: November 14, 2009

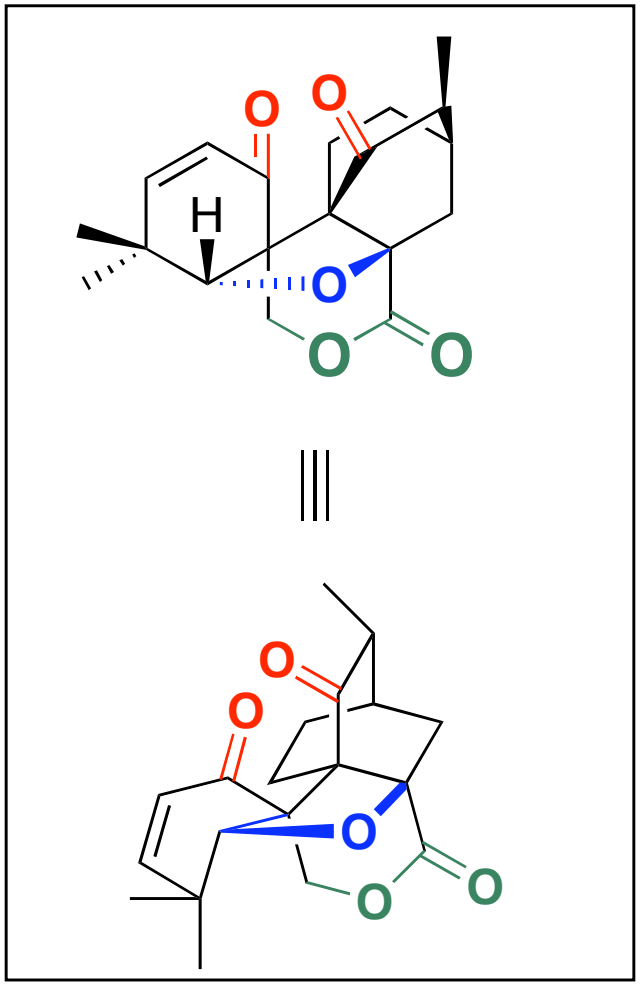
Melissa Sprachman

Maoecrystal V: Structural Representations



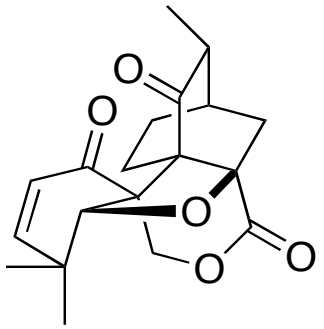


X-Ray Crystallographic Structure



Org. Lett. **2004,** *6,* 4327-4330.

Isolation and Structural Information



- Isolated from the leaves of *Isodon eriocalyx* (Chinese medicinal herb)
- Structural confirmation: 1D and 2D NMR, MS, X-Ray
- Inhibitory activity toward HeLa cells (IC_{50} = 0.02 µg/mL) [Compare to *cis*-platin: IC_{50} = 0.99 µg/mL)

Table 2. Cytotoxicity of Compound **1**

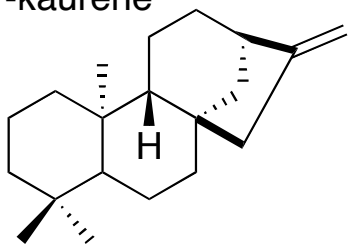
	IC_{50} (μg/mL)				
test substance	K562	A549	BGC-823	CNE	HeLa
1	6.43×10^4	2.63×10^5	1.47×10^4	nd[a]	0.02
cis-platin	0.38	1.61	0.25	2.31	0.99

[a] Not determined.

Copied from: *Org. Lett.* **2004,** *6,* 4327.

The *ent*-Kauranes (diterpenoids)

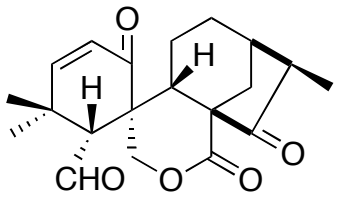
ent -kaurene



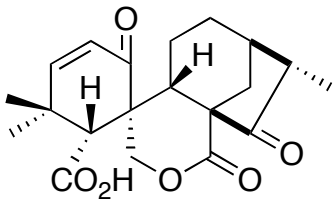
For a review see
Nat. Prod. Rep. **2006,** *23,* 673.

Related Structures:

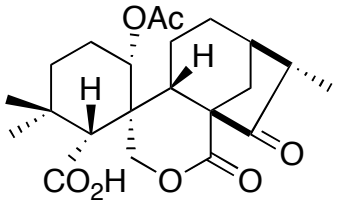
Epi-eriocalyxin A



Maoecrystal N



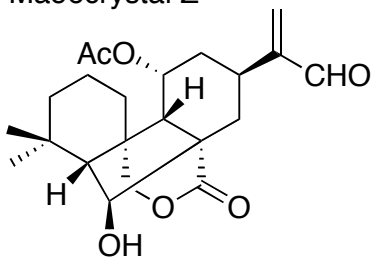
Maoecrystal O



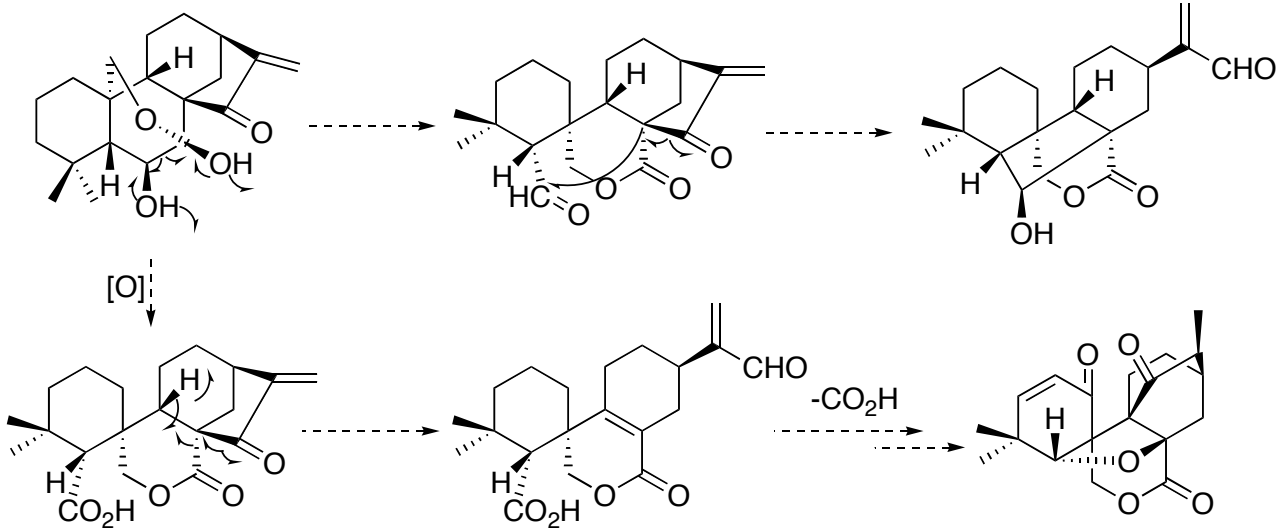
Acta Botanica Yunnanica, **1997,** *19,* 191.

Proposed Biogenetic Pathways for Maoecrystal V and Maoecrystal Z from a common 7,20-epoxy-*ent*-kaurane:

Maoecrystal Z

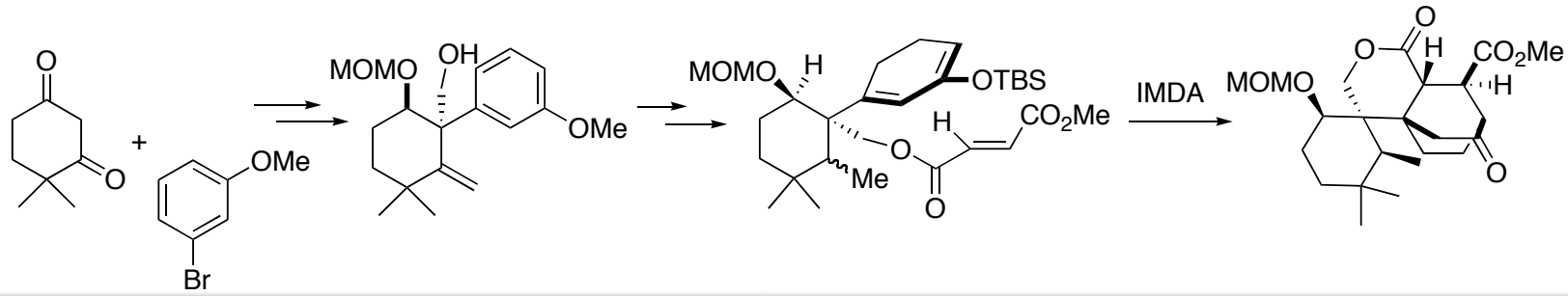


Org. Lett. **2006,** *8,* 4727.

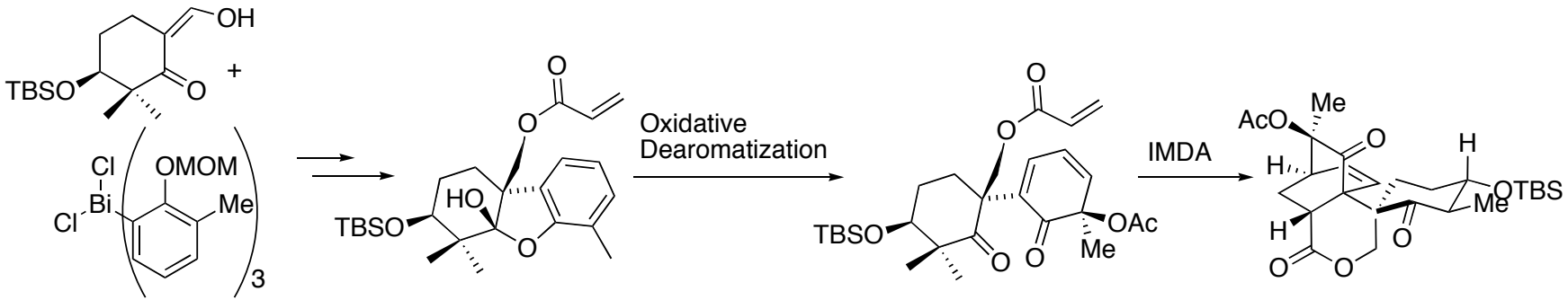


Summary of Routes

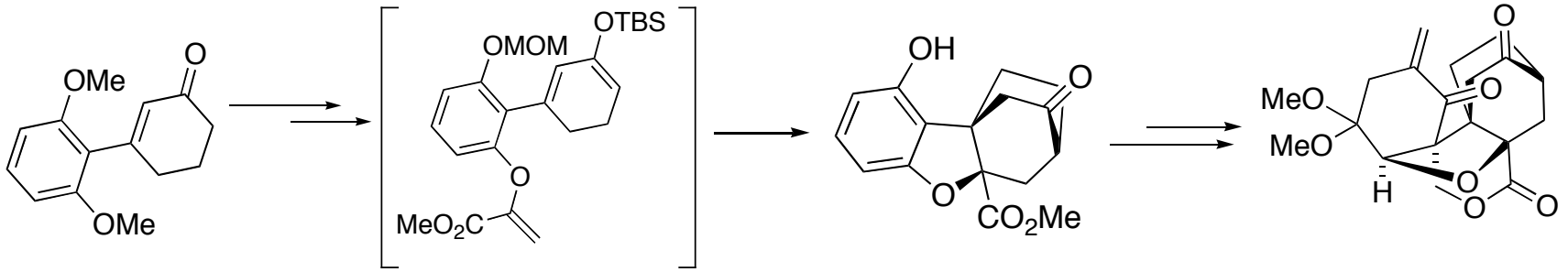
Danishefsky:
TL **2009,** *50,* 6586.



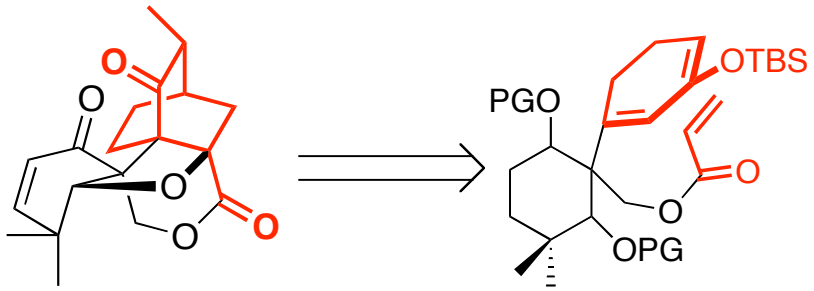
Baran (Li):
Org. Lett. **2009,** *11,* 4744 and *Org. Lett.* **2009,** *11,* 4770.

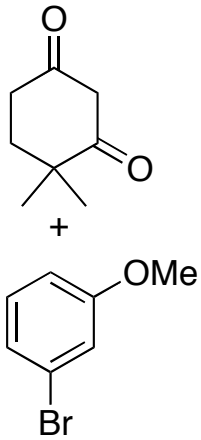


Nicolaou:
Chem. Commun. Advance

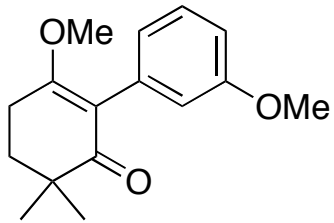


Danishefsky: "Pattern Recognition"

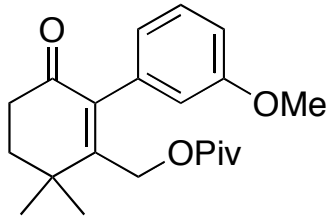




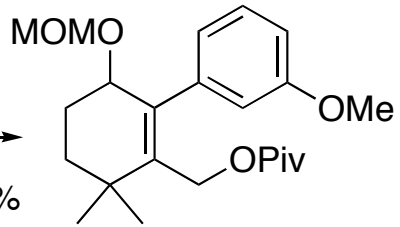
1. $Pd(OAc)_2$
ligand, K_3PO_4,
THF, 80 °C, 12 h
91%
2. $TMSCHN_2$, DIPEA
CH_3CN/MeOH, 9:1
quant.



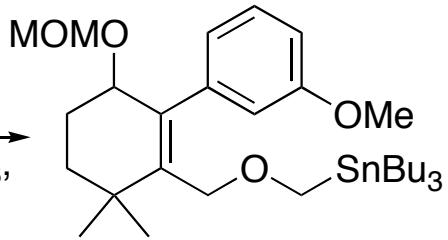
1. Bu_3SnCH_2OMOM,
BuLi, THF, -78 °C to -40 °C
30 min, 0.5% HCl workup, 75%
2. HCl/MeOH, 50 °C, 75%
3. PivCl, pyr, DCM, 12 h, 96%

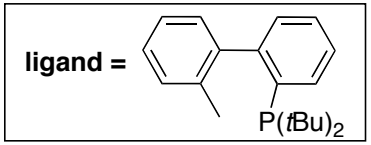


1. $NaBH_4$, $CeCl_3$
MeOH, 0 °C, 2 h, 93%
2. MOMCl,
DIPEA, DCM, 12 h, 95%



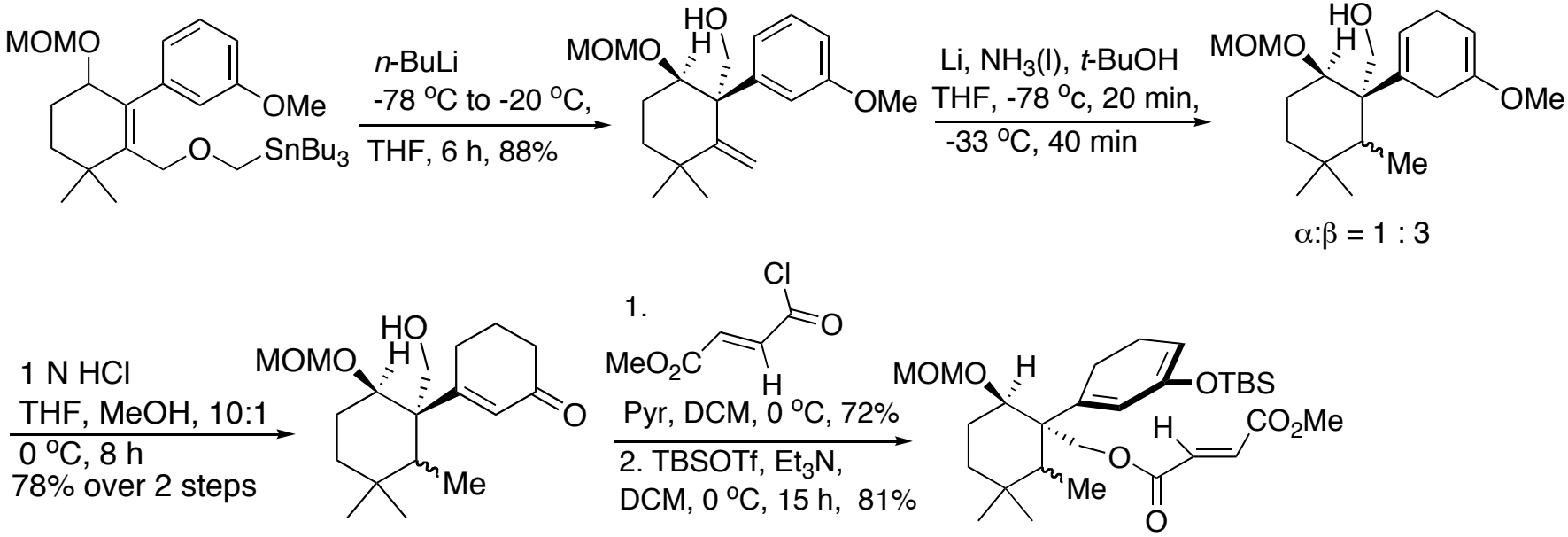
1. DIBALH, -78 °C
DCM, 30 min, 95%
2. KH, 18-crown-6, ICH_2SnBu_3,
0 °C, THF, 6 h, 90%



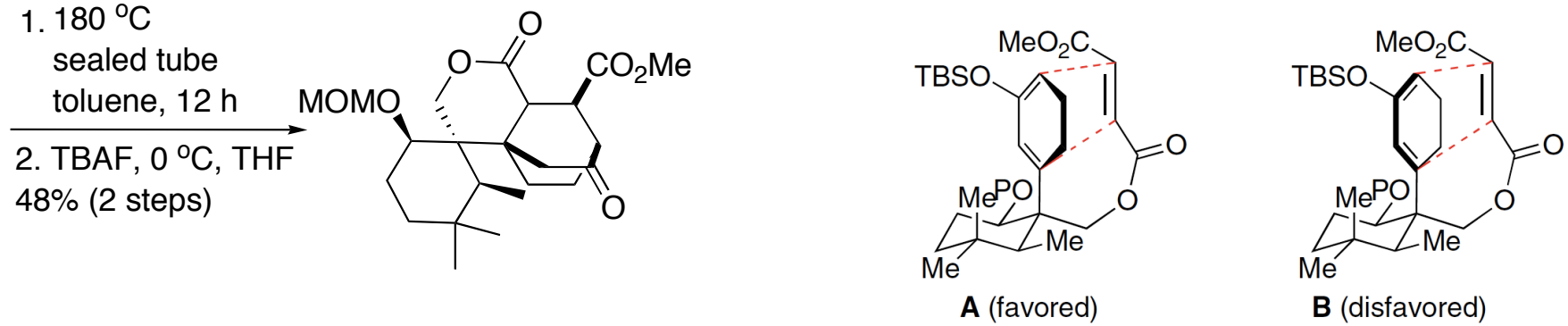


"Pattern Recognition:" *J. Org. Chem.* **2007,** *72,* 4293.

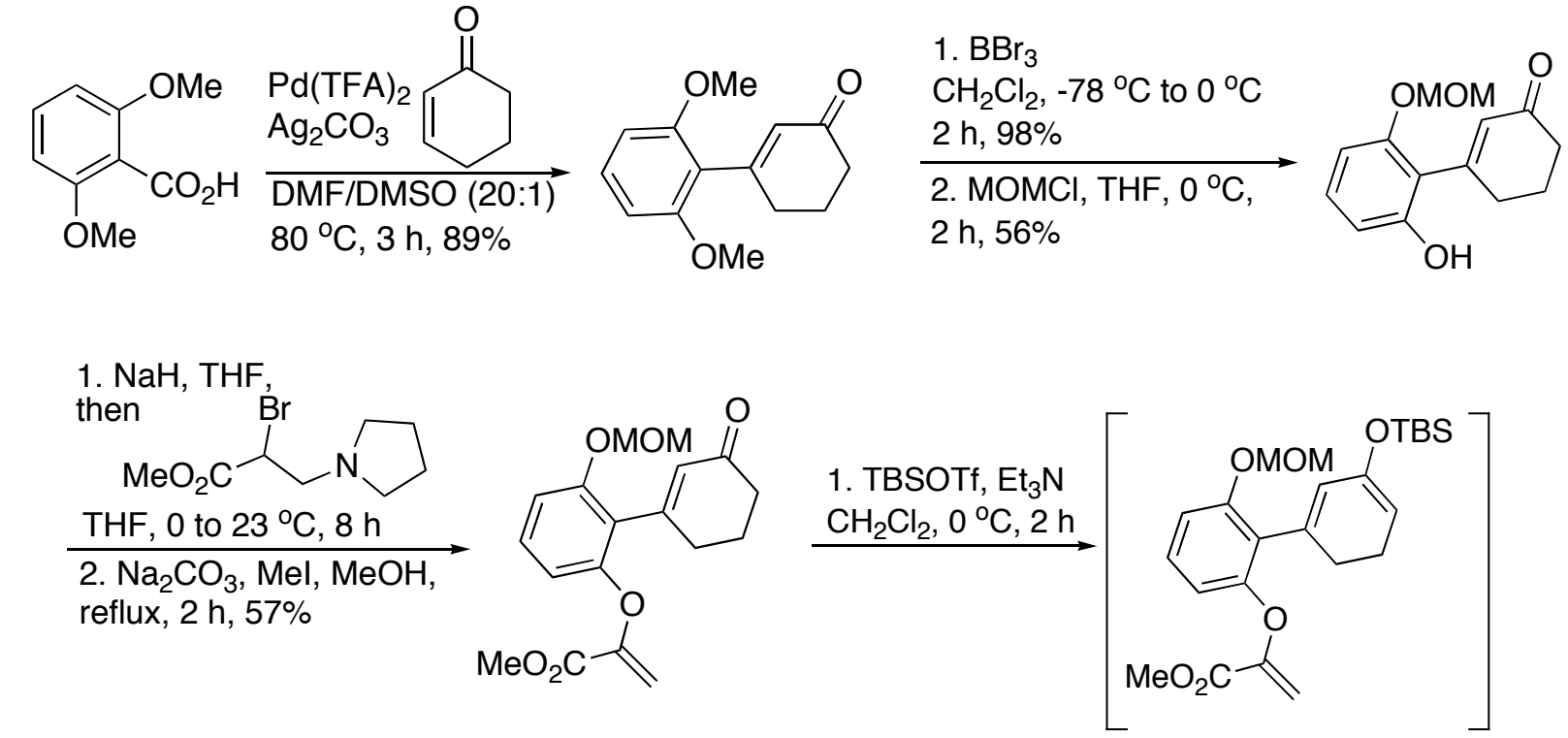
Danishefsky (cont.)



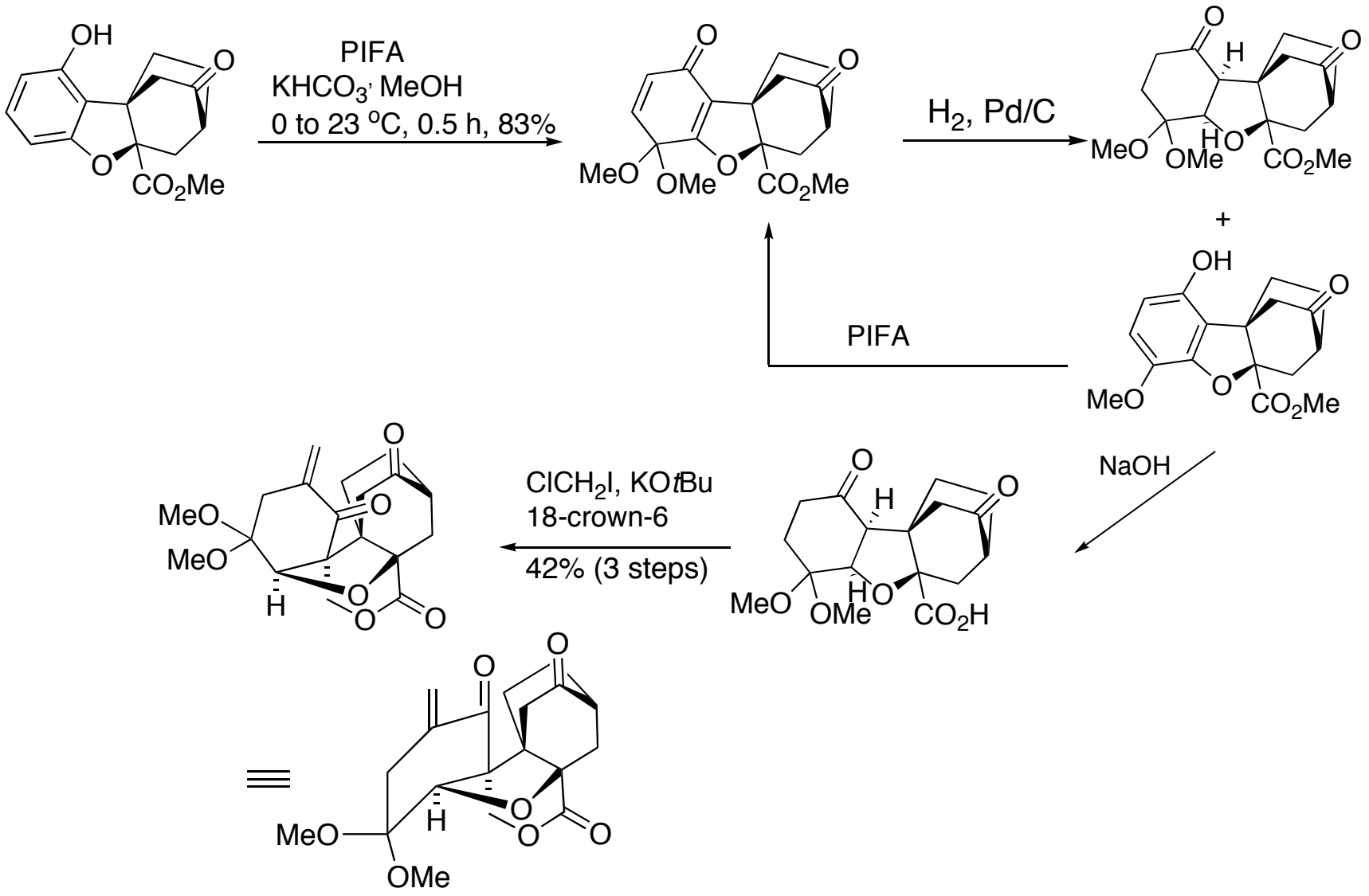
Incorrect Facial Selectivity from IMDA:



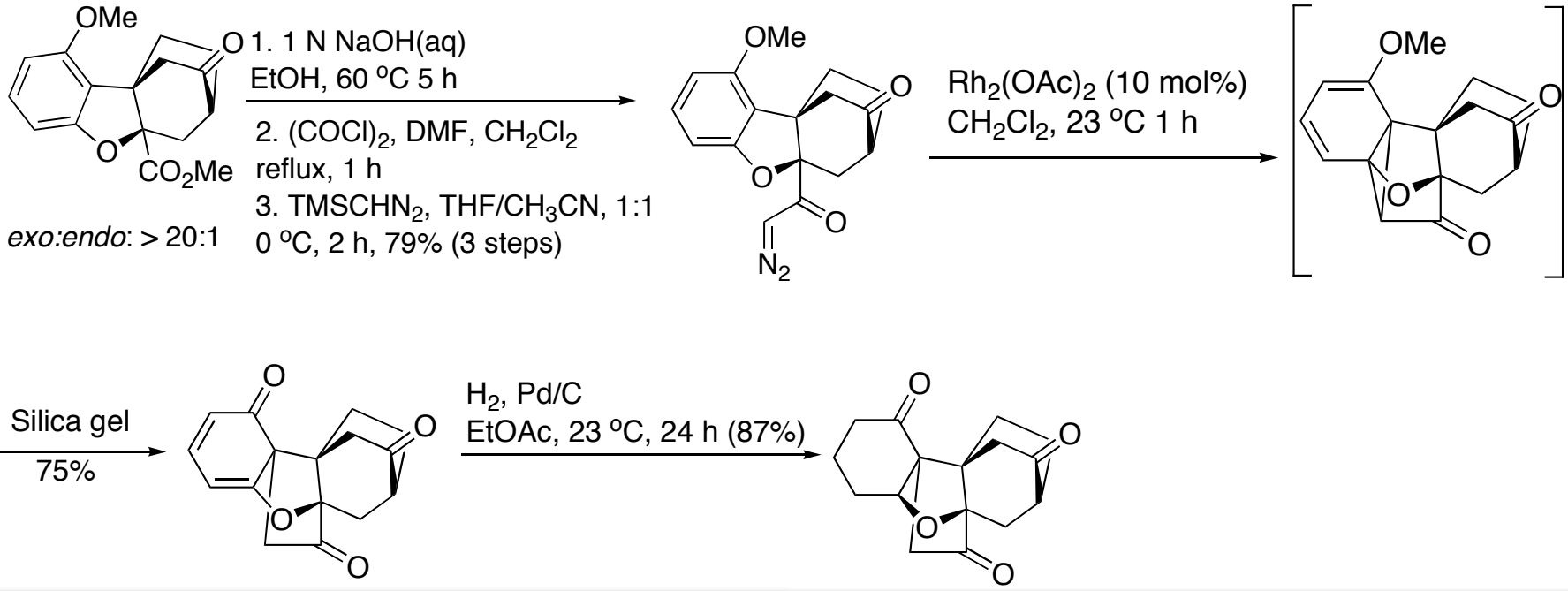
Nicolaou: "Core Structures for Evaluation"



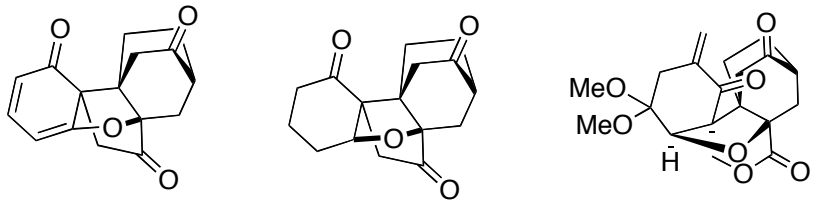
Nicolaou (cont.)



Nicolaou: Simplified structure/interesting approach to the THF

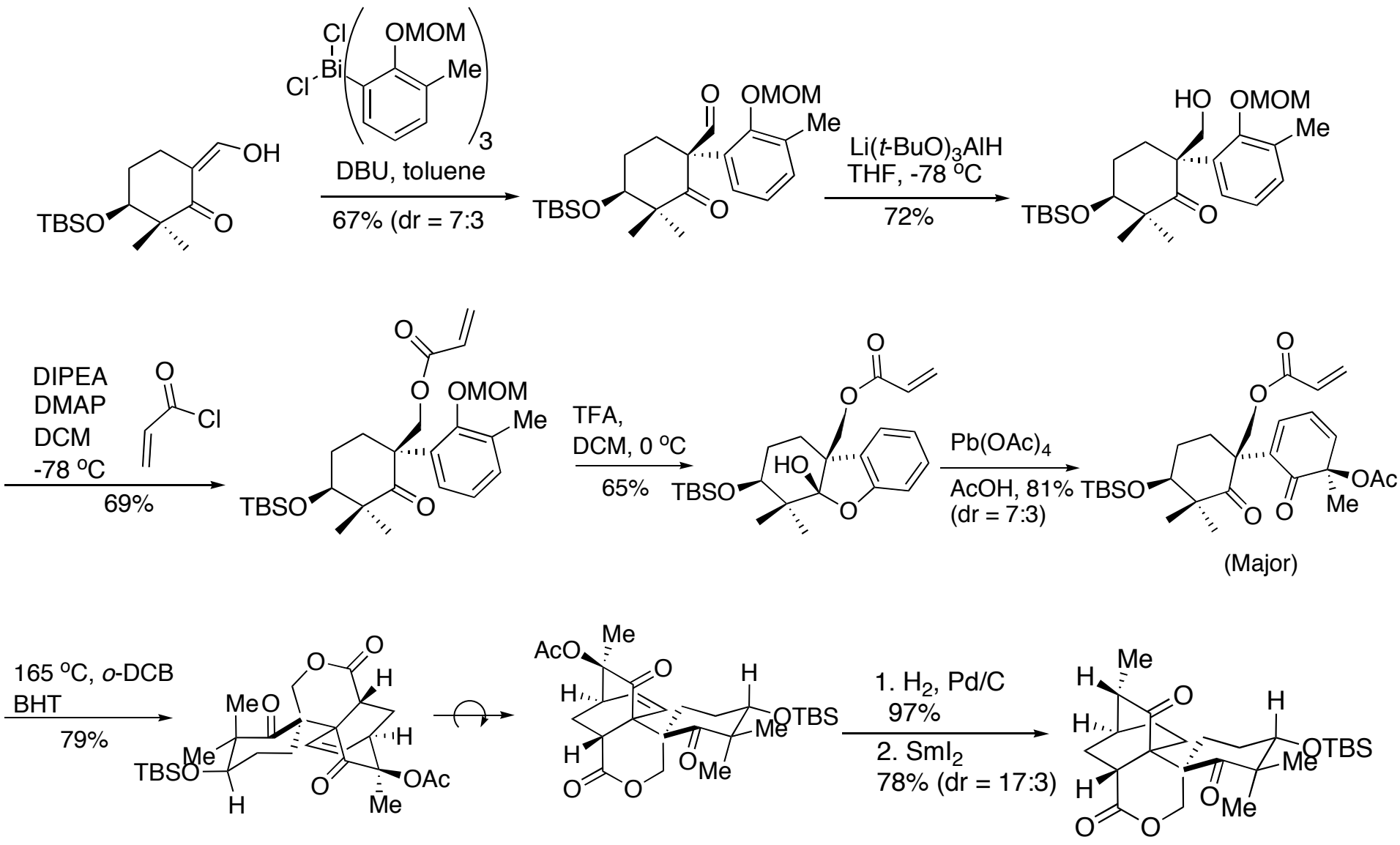


Tested three "core" structures against cell lines:



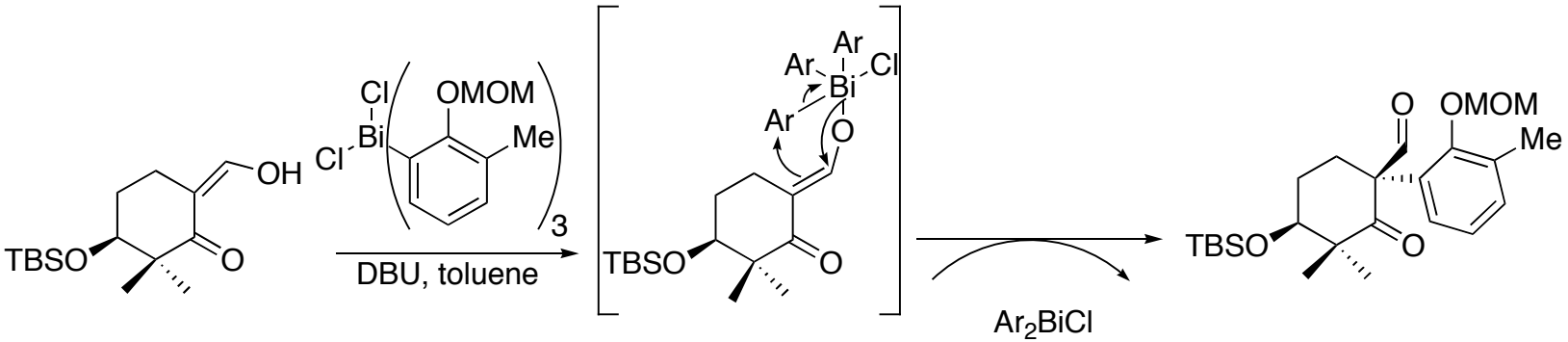
Only "**C**" showed moderate (but non-selective) activity against human tumor cell lines.

Baran: Oxidative Deramotization and IMDA

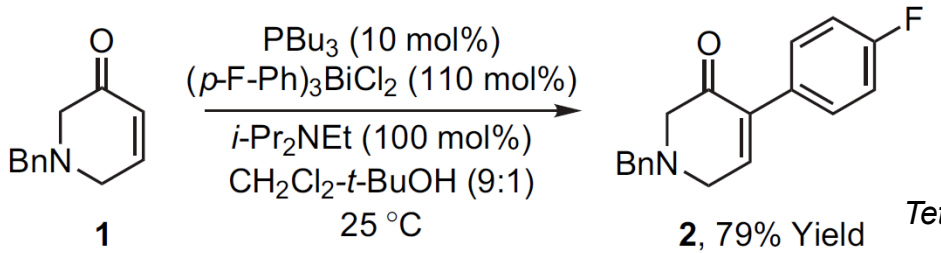


Reactions of Note

Arylation with a Bi(V) species:

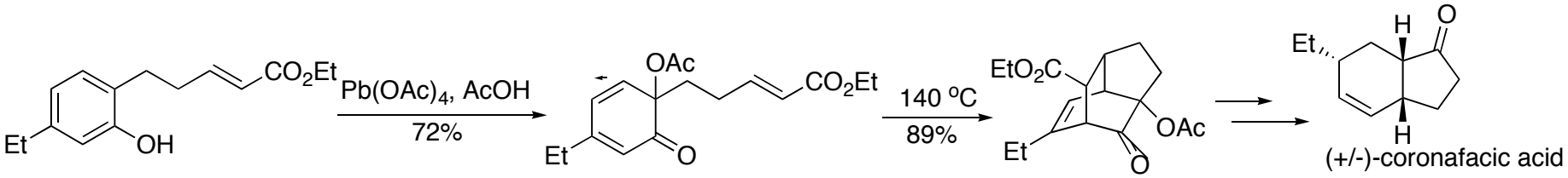


Applications of Bi(V) species include phenol oxidation alpha-arylation:



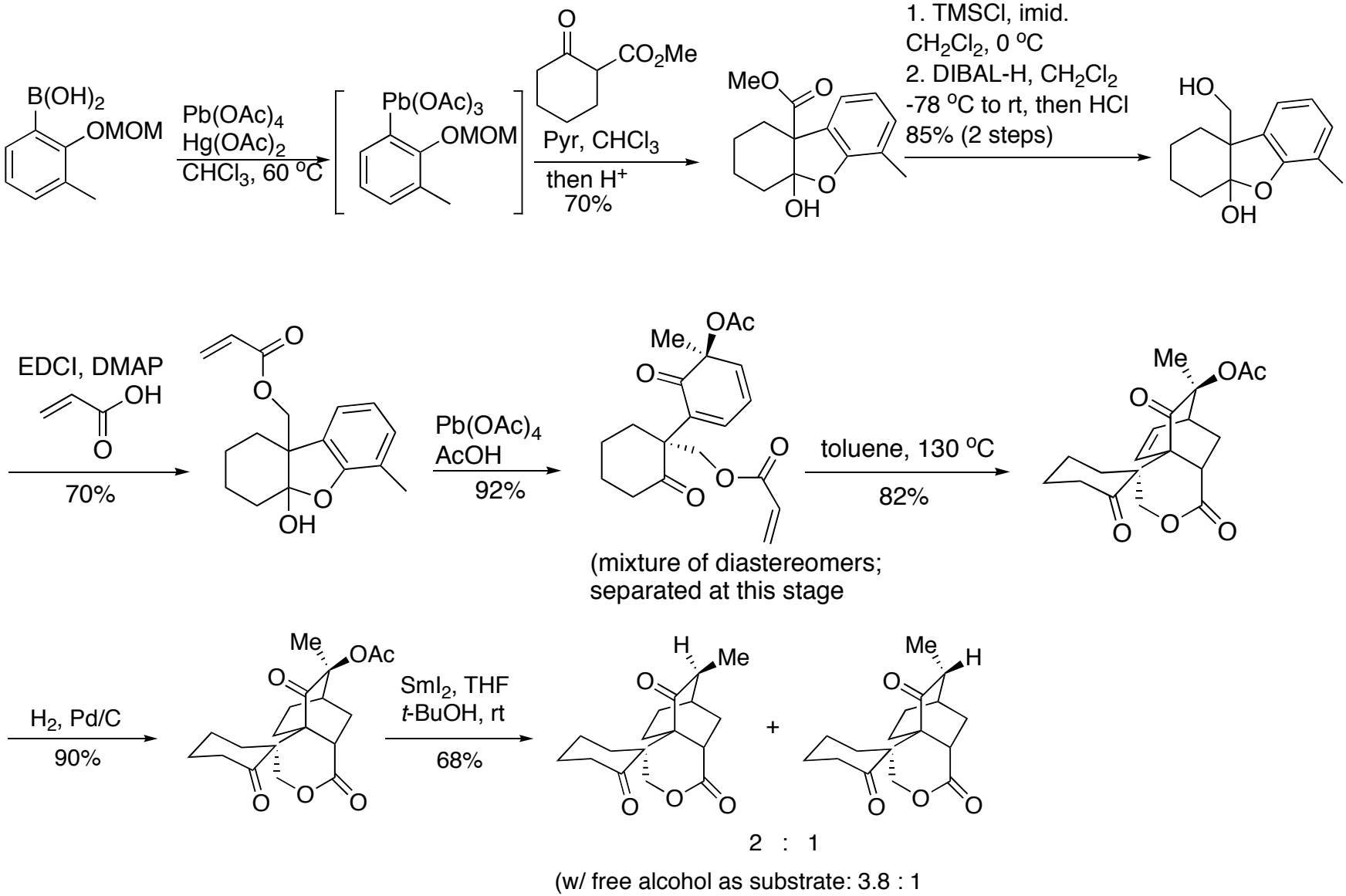
Tetrahedron **2006,** *62,* 10594.

Wessely oxidation/Diels Alder:



J. Chem. Soc., Chem. Commun. **1990,** 739.

Li (Same Approach?)



Summary and Outlook

- Several groups have reported approaches to Maoecrystal V, all involving a dearomatization and IMDA reactions.
- Only Nicolaou and coworkers have successfully installed the key THF moeity.
- Although Baran and coworkers pose an enantioselective approach, the need for improved diastereoselectivities is apparent.
- Even the advanced Maoecrystal V intermediate (Nicolaou) did not exhibit comparable biological activity to that of the natural compound; is a viable total synthesis necessary for making a useful therapeutic?