Current Literature Presentation

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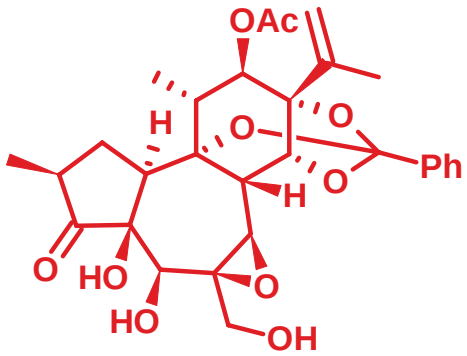
11/26/2011

Gateway synthesis of daphnane congeners and their protein kinase C affinities and cell-growth activities

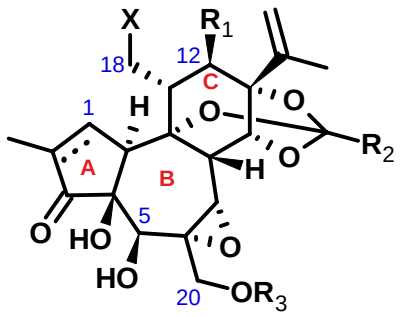


Wender, P. A., Buschmann, N., Cardin, N. B., Jones, L. R., Kan, C., Kee, J-M., Kowalski, J. A., Longcore, K. E., *Nature Chemistry,* **2011,** *3,* 615-619

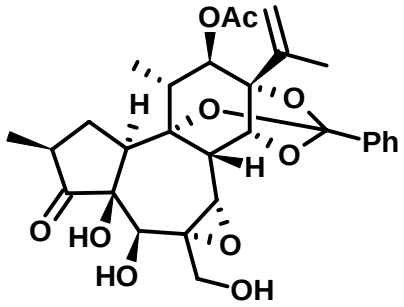
More than 129 of **Daphnane Diterpenoid Orthoesters** (**DDOs**) are identified*, and they occurr only in the plant families of Thymelaeaceae and Euphorbiaceae

A major subset of **DDOs**, is made up of at least 73 congeners that differ in the:

- functionality at C-12
- orthoester side chain
- A-ring oxidation and
- substitution at C-20



Yuanhuapin was first isolated in 1986 from the flowers of *Daphne genkwa,* and possessed significant anticancer activity

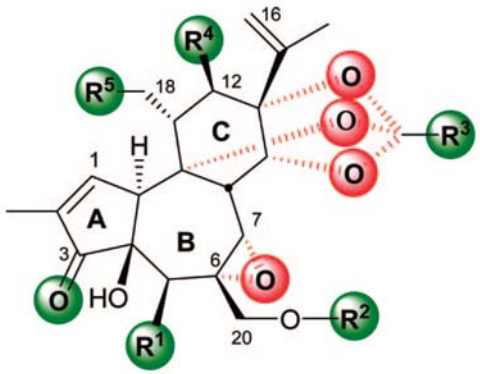


*up to the end of September, 2008
Chem. Rev. **2009,** *109,* 1092–1140

DDOs have been demonstrated to possess a wide range of biological activities:
•anticancer
•TRPV1 activating
•cholesterol-lowering
•antihyperglycemic
•irritant
•tumor-protoming activity

Anticancer Activity

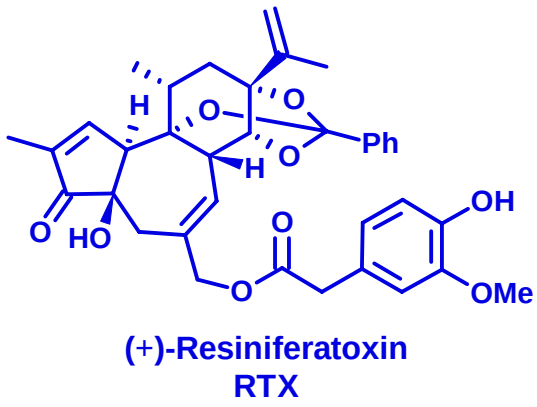
Several of **DDOs** display over a 1000-fold greater activity against
A549 human lung cancer cells relative to that of normal lung epithelial cells (MRC-5)



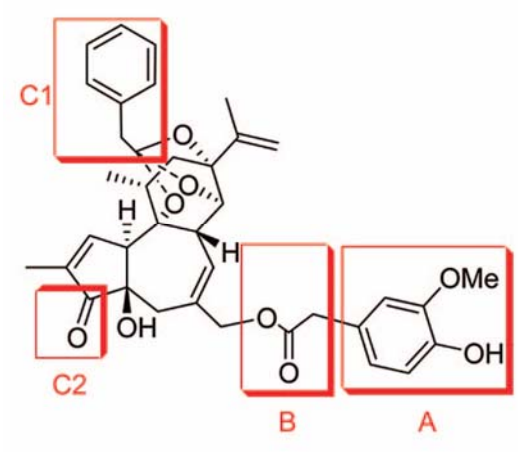
Groups in green: modification is allowed
Groups in red: modification is forbidden

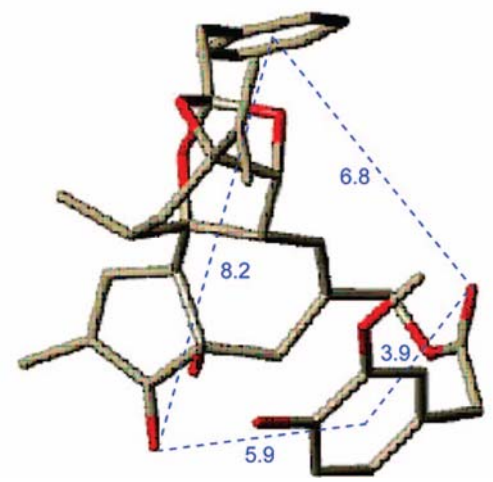
Chem. Rev. **2009,** *109,* 1092–1140

Activation of Transient Receptor Potential Vanilloid 1 (TRPV1) -capsaicin receptor-



(+)-Resiniferatoxin
RTX





*Principal **pharmacophores** and **active conformation** of **RTX***

RTX is most potent *TRPV1* agonist reported to date

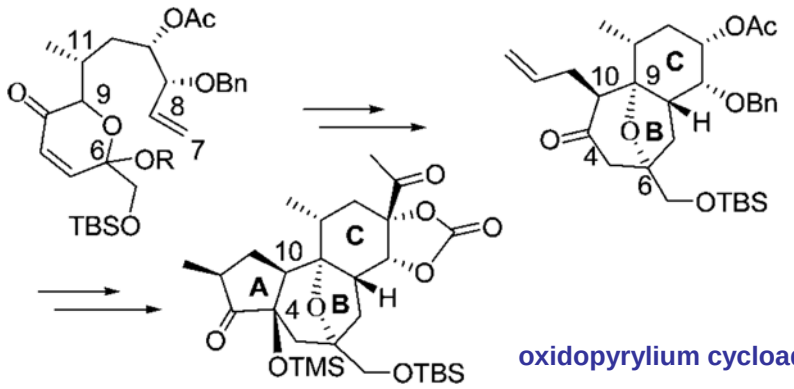
Two major therapeutic strategies for **RTX** analogues:

- optimize the **RTX**-related agonists to “desensitize” capsaicin sensitive nerves (to mitigate neuropathic pain)
- develop RTX-related antagonists for the pharmacological blockade of *TRPV1* where over expression of *TRPV1* is involved

Chem. Rev. **2009,** *109,* 1092–1140

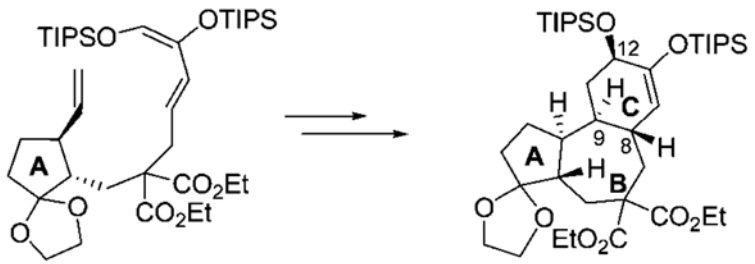
Strategies for construction of the daphnane diterpene skeleton

[X→BC→ ABC] approach



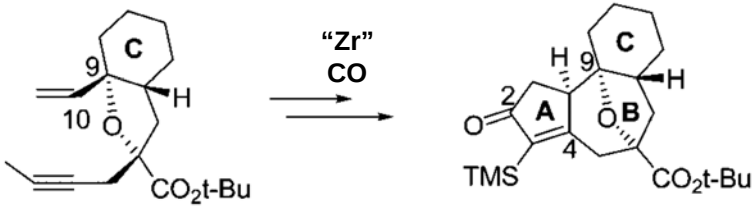
oxidopyrylium cycloaddition

[AX(Y)→ ABC] approach



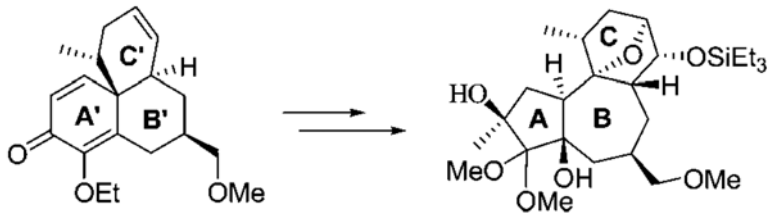
intramolecular Diels-Alder reaction

[CX(Y)→ ABC] approach



"Zr" or "Pd" mediated intramolecular enyne carbocyclization

[A'B'C'(666)→ ABC(576)] approach



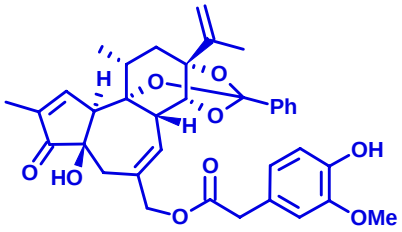
photorearrangement of a tricyclic cross-conjugated 2,5-cyclohexadienone

[X-BC-ABC] approach is welldefined and has proven to be very efficient in the first enantiocontrolled total synthesis of (+)-RTX

Chem. Rev. **2009,** *109,* 1092–1140

Wender, P. A.

J. Am. Chem. Soc. **1997,** *119,* 12976-12977

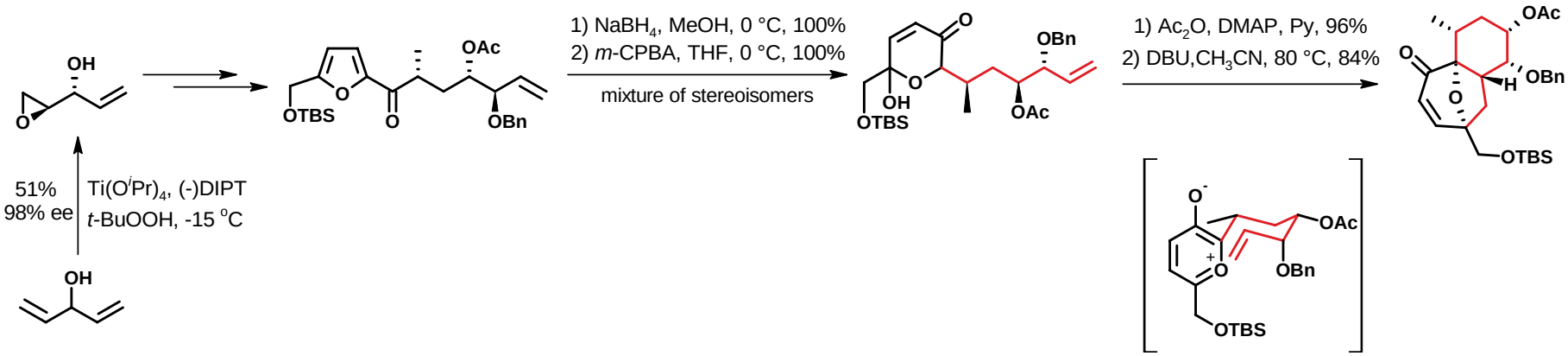


(+)-Resiniferatoxin
RTX

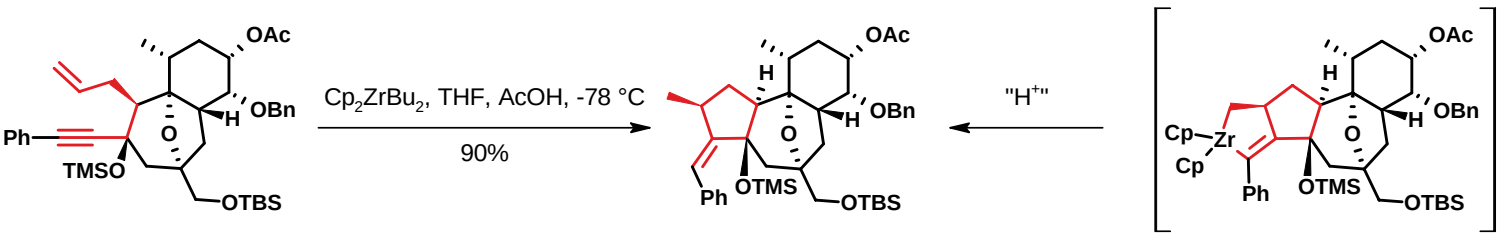
First Synthesis of a Daphnane Diterpene

Asymmetric Total Synthesis of (+)-Resiniferatoxin

Oxidopyrylium cycloadition:



Zirconocene-mediated cyclization:

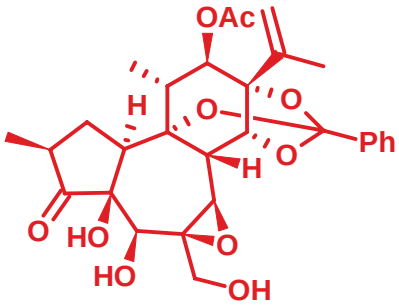


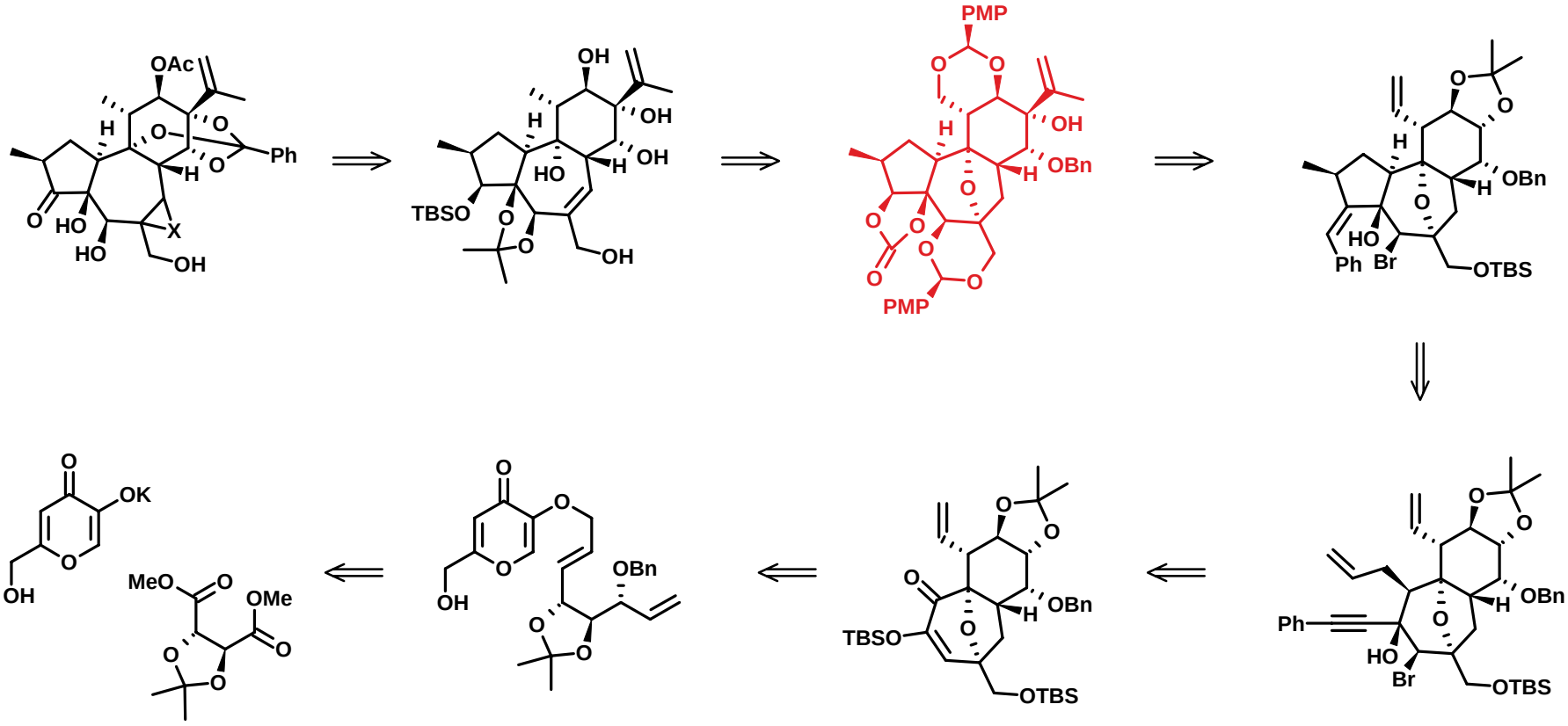
Wender, P. A.

Nature Chemistry, **2011,** *3,* 615-619

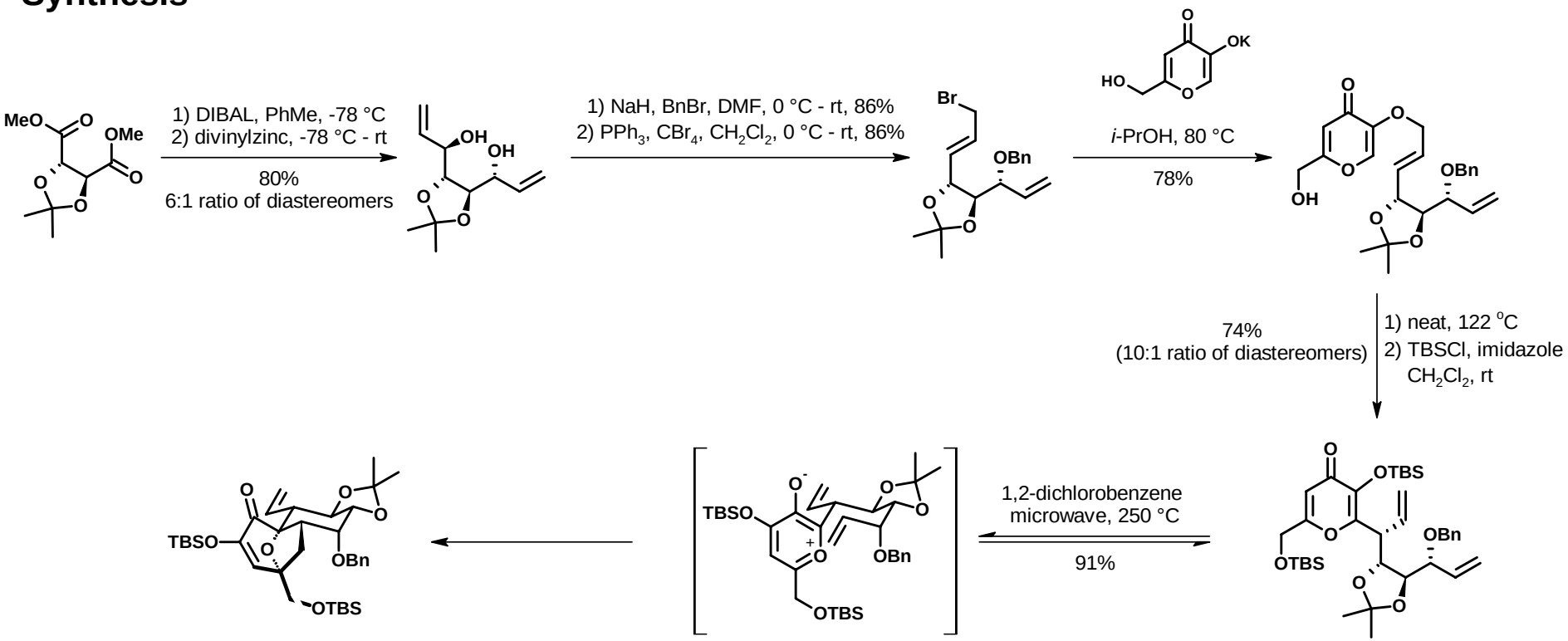
'**Gateway strategy**' designed to:

- develop a synthetic route to enable general access to DDOs and their analogues from a common precursor
- exploit this capability to investigate the SAR and their therapeutic potential

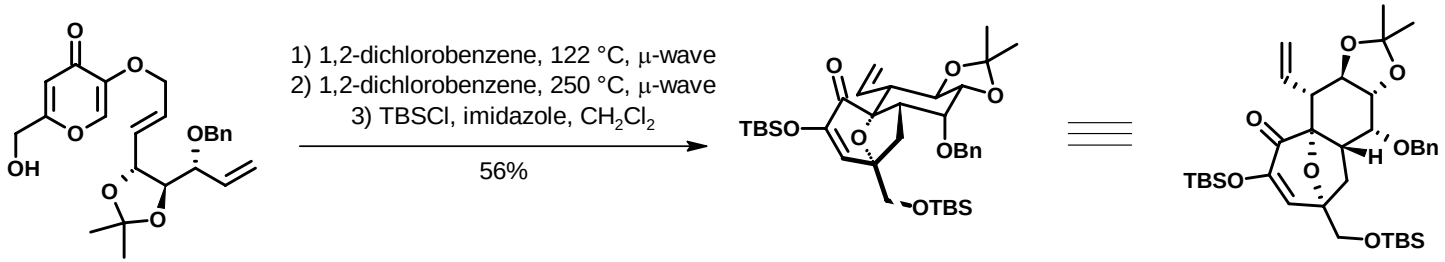


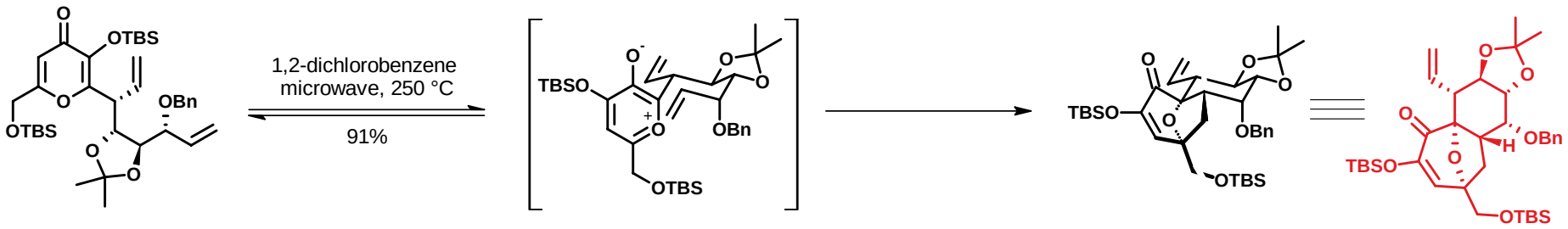


Synthesis

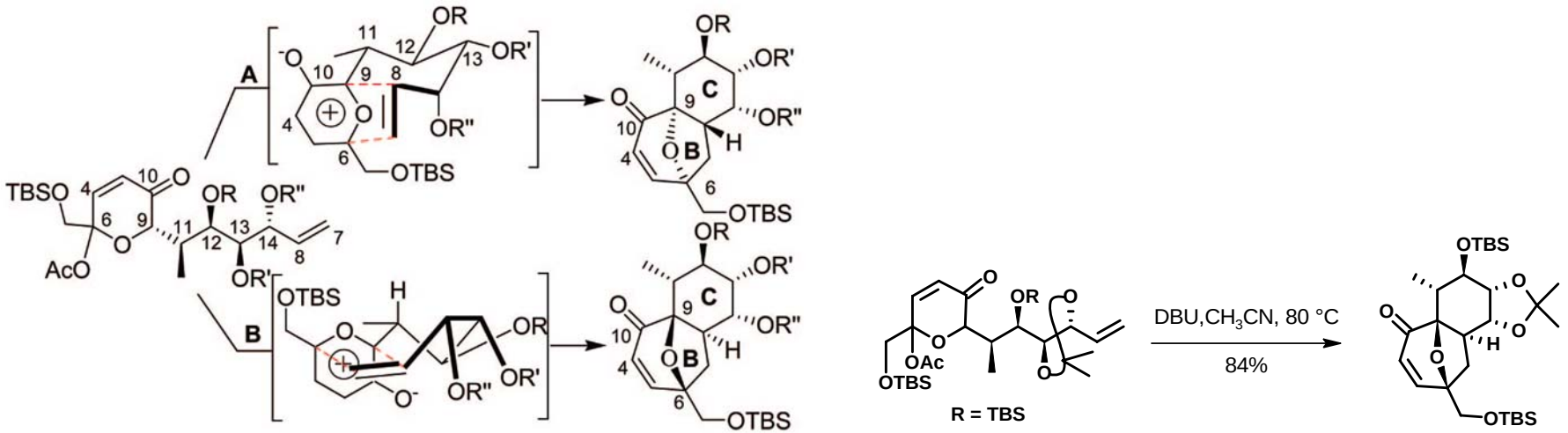


One-flask Claisen/oxidopyrylium [5 + 2] cycloaddition



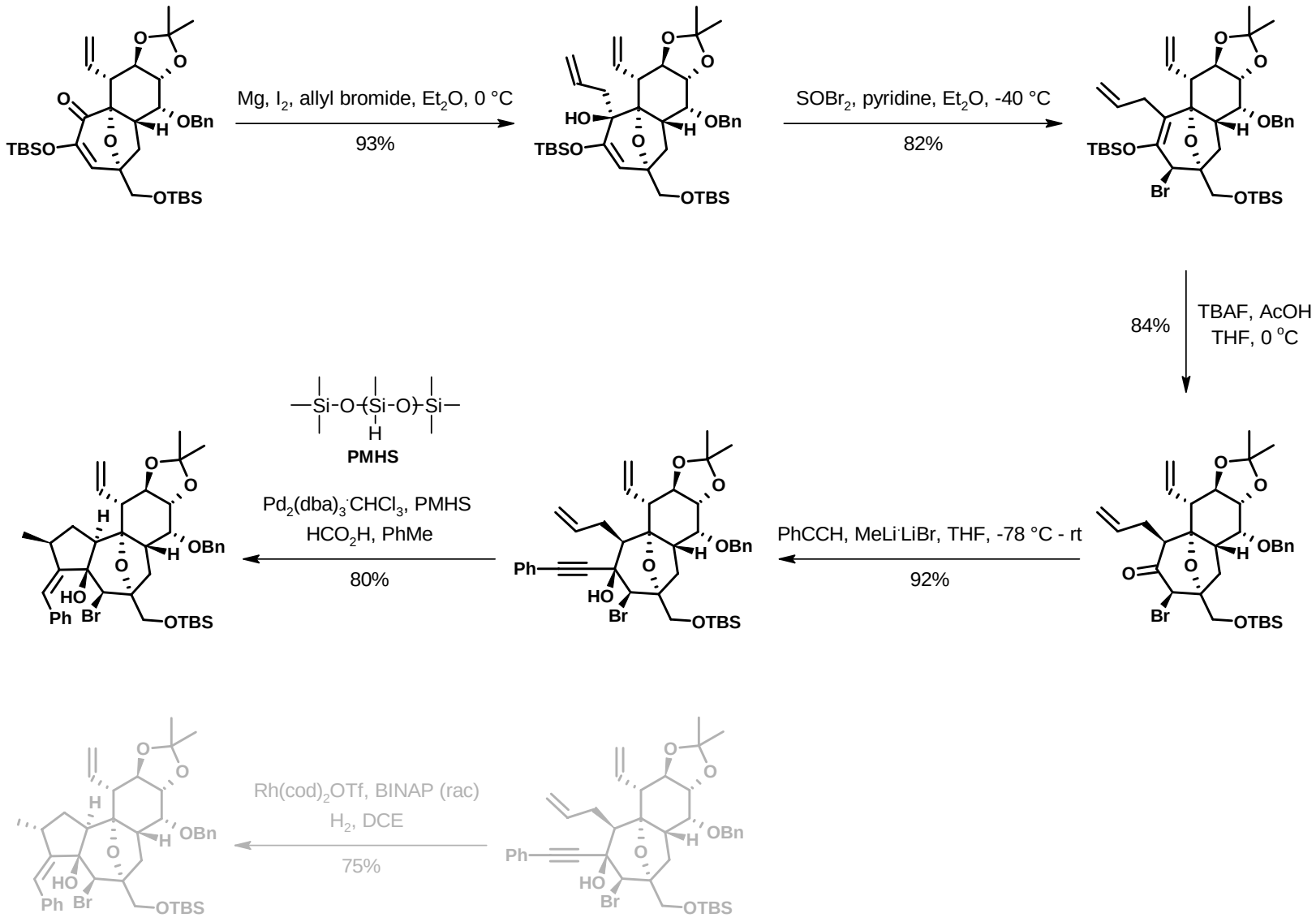


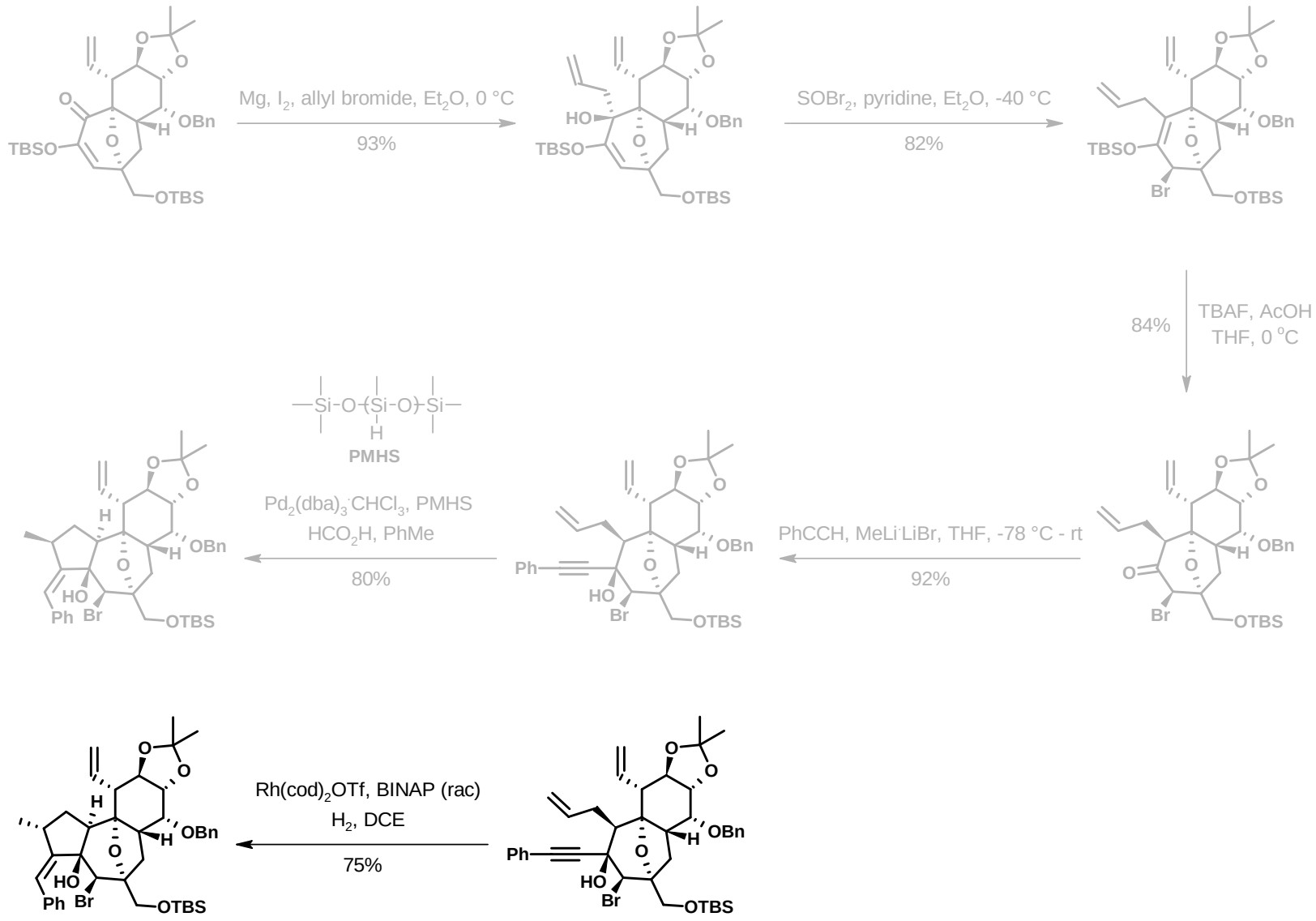
Org. Lett. **2006**, *8*, 5373-5376



Diastereoselectivity of the oxidopyrylium-alkene [5 + 2] cycloaddition was influenced largely by the substituents at C-12 and C-13

Less polar solvent: better selectivity but longer reaction time


Mg, I2, allyl bromide, Et2O, 0 °C
93%
SOBr2, pyridine, Et2O, -40 °C
82%
84%
TBAF, AcOH
THF, 0 °C
PhCCH, MeLi·LiBr, THF, -78 °C - rt
92%
Pd2(dba)3·CHCl3, PMHS
HCO2H, PhMe
80%
PMHS
Rh(cod)2OTf, BINAP (rac)
H2, DCE
75%
TBSO
OTBS
OBn
HO
Br
Ph
O


Mg, I2, allyl bromide, Et2O, 0 °C
93%
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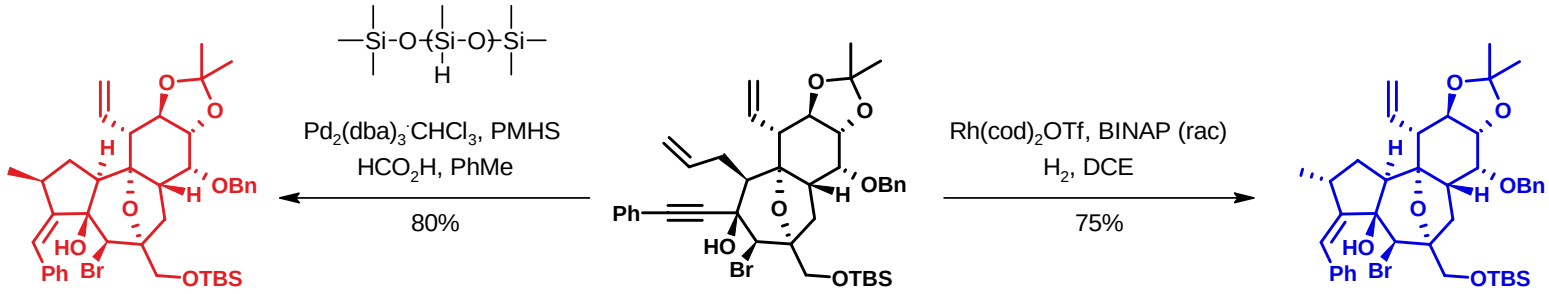
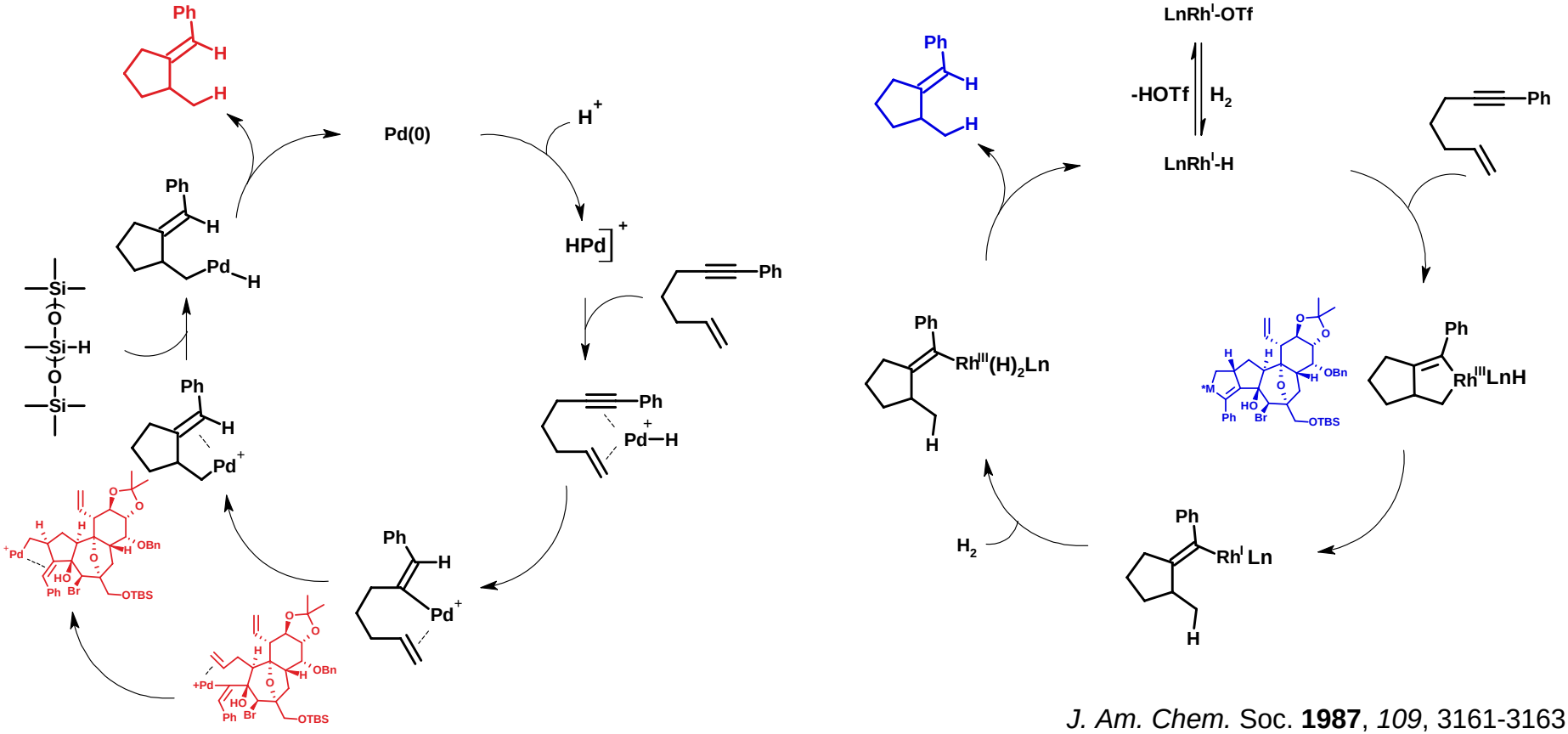
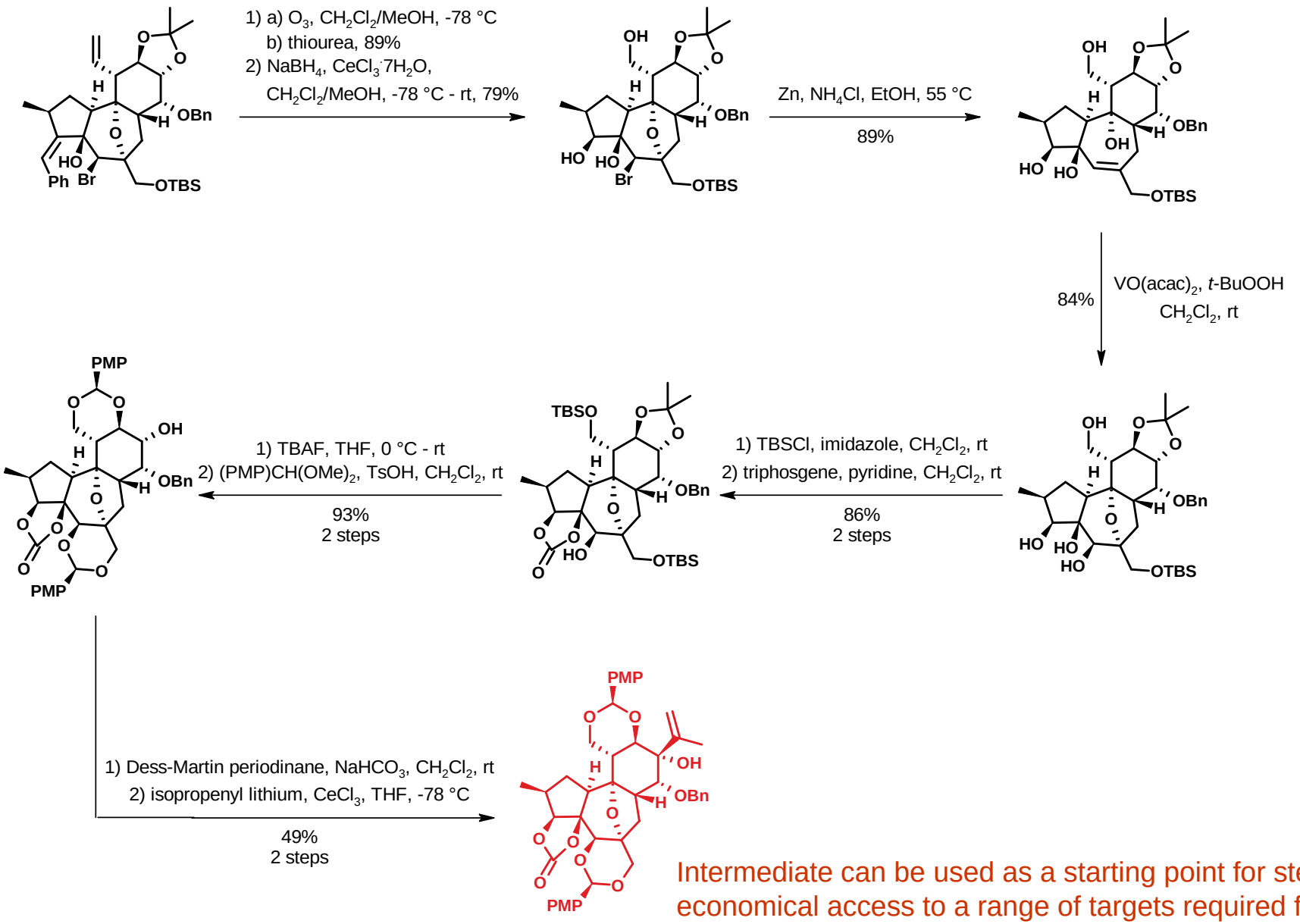
THF, 0 °C
PhCCH, MeLi·LiBr, THF, -78 °C - rt
92%
Pd2(dba)3·CHCl3, PMHS
HCO2H, PhMe
80%
PMHS
Rh(cod)2OTf, BINAP (rac)
H2, DCE
75%
TBSO
OTBS
OBn
HO
Br
Ph
O
H

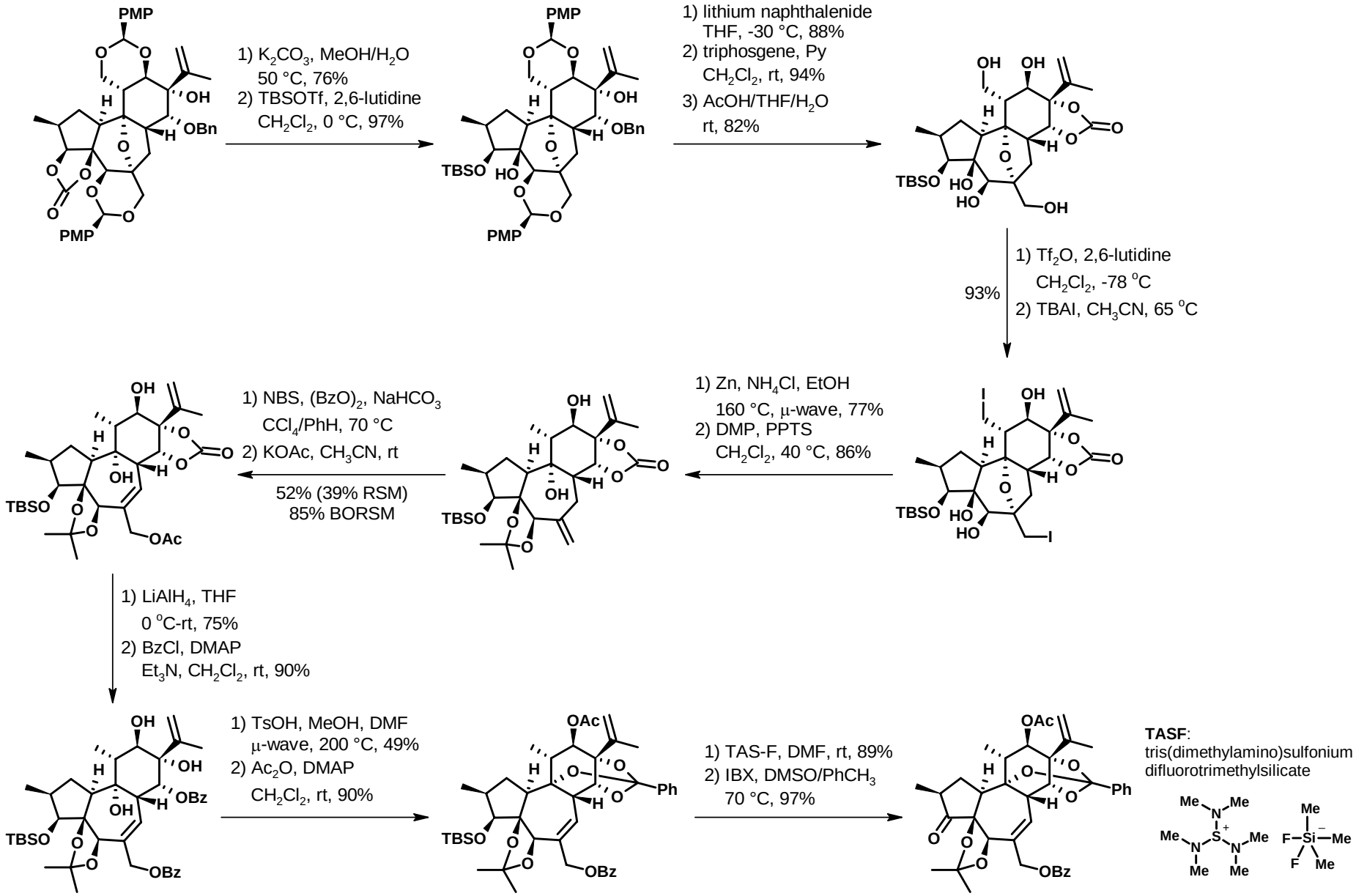


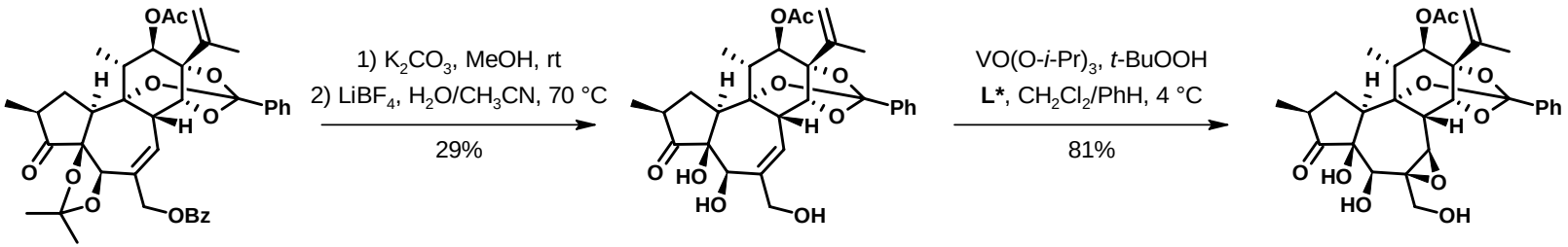


J. Am. Chem. Soc. **1987**, *109*, 3161-3163
J. Am. Chem. Soc. **1996**, *118*, 6625-6633
J. Am. Chem. Soc. **2004**, *126*, 7875-7880

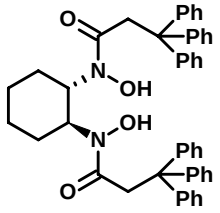


Intermediate can be used as a starting point for step economical access to a range of targets required for understanding SAR of daphnane derivatives


1) K_2CO_3, MeOH/H_2O
50 °C, 76%
2) TBSOTf, 2,6-lutidine
CH_2Cl_2, 0 °C, 97%
1) lithium naphthalenide
THF, -30 °C, 88%
2) triphosgene, Py
CH_2Cl_2, rt, 94%
3) AcOH/THF/H_2O
rt, 82%
93%
1) Tf_2O, 2,6-lutidine
CH_2Cl_2, -78 °C
2) TBAI, CH_3CN, 65 °C
1) Zn, NH_4Cl, EtOH
160 °C, μ-wave, 77%
2) DMP, PPTS
CH_2Cl_2, 40 °C, 86%
1) NBS, $(BzO)_2$, $NaHCO_3$
CCl_4/PhH, 70 °C
2) KOAc, CH_3CN, rt
52% (39% RSM)
85% BORSM
1) $LiAlH_4$, THF
0 °C-rt, 75%
2) BzCl, DMAP
Et_3N, CH_2Cl_2, rt, 90%
1) TsOH, MeOH, DMF
μ-wave, 200 °C, 49%
2) Ac_2O, DMAP
CH_2Cl_2, rt, 90%
1) TAS-F, DMF, rt, 89%
2) IBX, DMSO/$PhCH_3$
70 °C, 97%
TASF:
tris(dimethylamino)sulfonium
difluorotrimethylsilicate

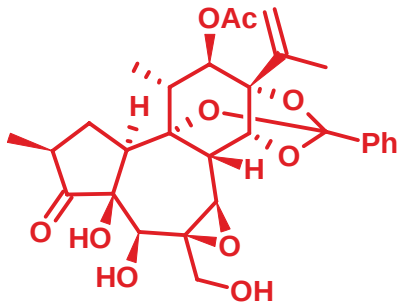


L*: (1*S*,2*S*)-*N*,*N*'-dihydroxy-*N*,*N*'-bis(3,3,3-triphenylpropionyl)-1,2-cyclohexanediamine



The synthesis employed:

- Claisen rearrangement and oxidopyrylium-alkene [5+2] cycloaddition for construction of **BC** rings
- palladium-catalysed cyclization for construction of **A** ring



Biological Activity

Anticancer Activity

DDOs were found to be a very potent inhibitors of DNA topoisomerase I (topo I). Anticancer activity of these class of compound is comparable to (or even better than) the activity of **hydroxycamptothecin** (**hCPT**), one of the most powerful DNA topo I inhibitors in clinical use.

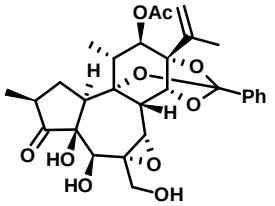
Protein Kinase C Binding Activity

DDOs are known to activate protein kinase C (PKC). PKC control the function of other proteins through the phosphorylation of hydroxyl groups of serine and threonine amino acid residues (serine/threonine kinases), and thus regulates a diverse set of cellular processes including proliferation, apoptosis, cell survival and migration. Activation of PKC could have implications for treating diseases including cancer, Alzheimer's and human immunodeficiency virus AIDS.

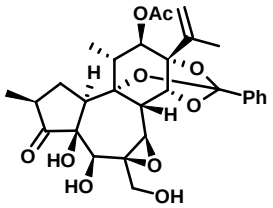
	PKC affinity, K_i (nM)*	Cellular growth inhibition†	
		A549 EC_{50} (nM)	K562 EC_{50} (nM)
1‡	0.48±0.07	150±30	7±1
2	343±6	>10,000	>10,000
3	1.6±0.1	1500±60	87±5

*K_i values determined in duplicate experiments. †half-maximum effective concentration (EC_{50}) values determined in triplicate experiments. All errors shown are standard errors of the mean. ‡A sample of yuanhuapin **1** was provided by J-M. Yue, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China.

A549 cells (human lung carcinoma)
K562 (human chronic myelogenous leukaemia)



1
Yuanhuapin



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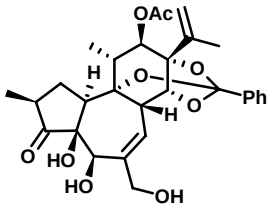

3

1 and **3** were identified as highly potent ligands for PKC and promising antiproliferative agents