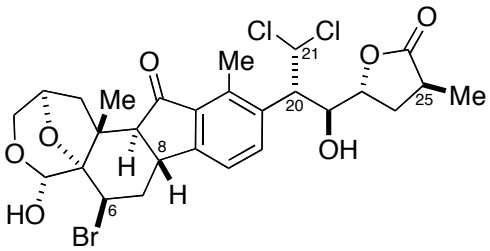
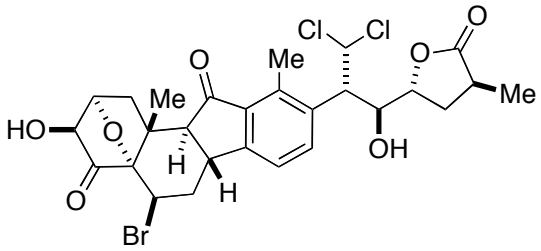


Nakiterpiosin (**1**)



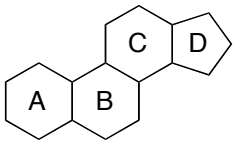
Nakiterpiosinone (**2**)

Chemical and Biological Studies of Nakiterpiosin and Nakiterpiosinone

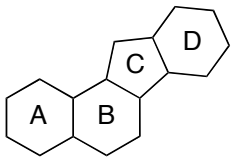
Shuanhu Gao, Qiaoling Wang, Lily Jun-Shen Huang, Lawrence Lum and Chuo Chen

J. Amer. Chem. Soc. **2009**, *ASAP*.

C-nor-D-homosteroids: Nakiterpiosin and Nakiterpiosinone



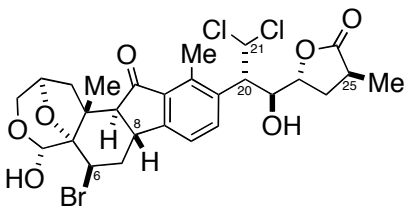
steroid



C-nor-D-homosteroid

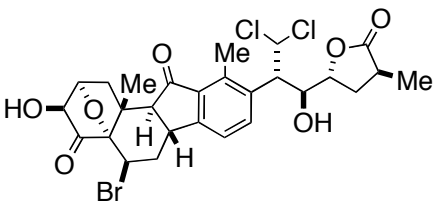
Terpios hoshinota

30 kg



Nakiterpiosin

0.4 mg



Nakiterpiosinone

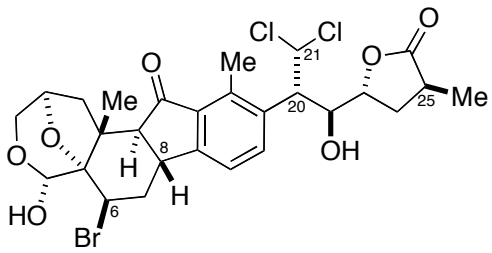
0.1 mg

"Both compounds inhibited the growth of P388 mouse leukemia cells with a mean Inhibitory concentration (IC_{50}) of 10 ng/mL."

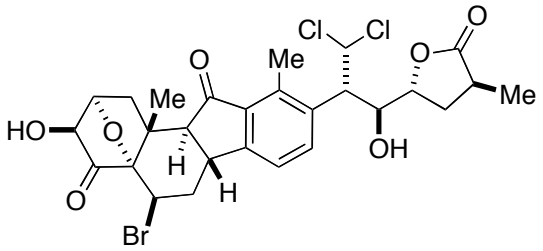
http://www.flmnh.ufl.edu/reefs/guamimg/porifera/Pages/Image81.html

Teruya, T. *et al. Tetrahedron*, **2004**, *60*, 6989.

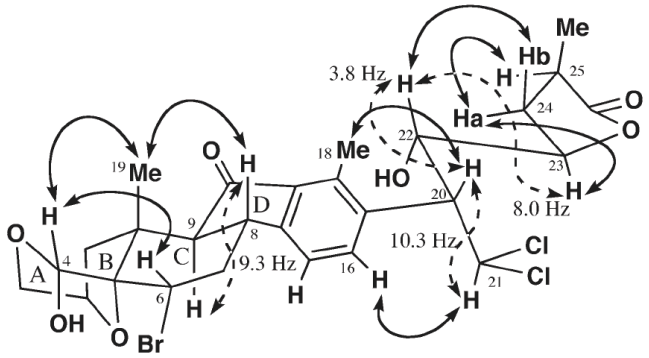
C-nor-D-homosteroids: Nakiterpiosin and Nakiterpiosinone

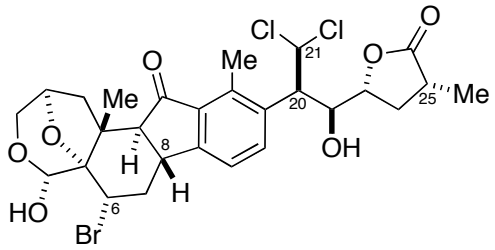


Nakiterpiosin (**1**)

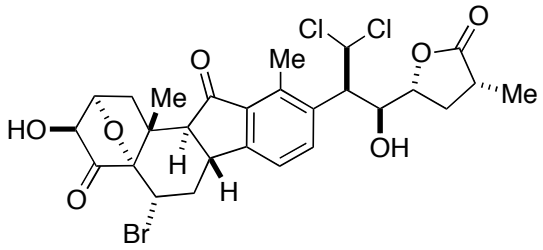


Nakiterpiosinone (**2**)



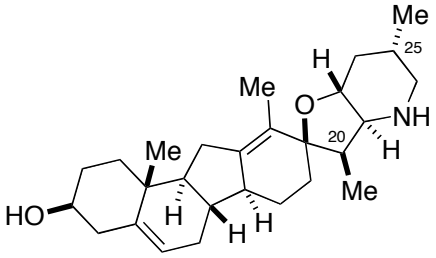


Originally Proposed Nakiterpiosin (**3**)

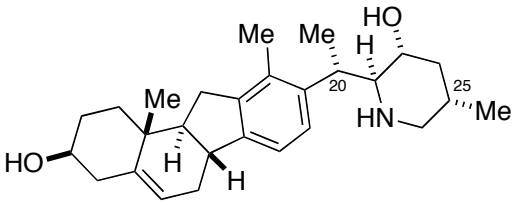


Originally Proposed Nakiteriosinpne (**4**)

- unusual stereochemistry at C-20 and C-25
- stereochemistry at C-6 and C-20 is arguable



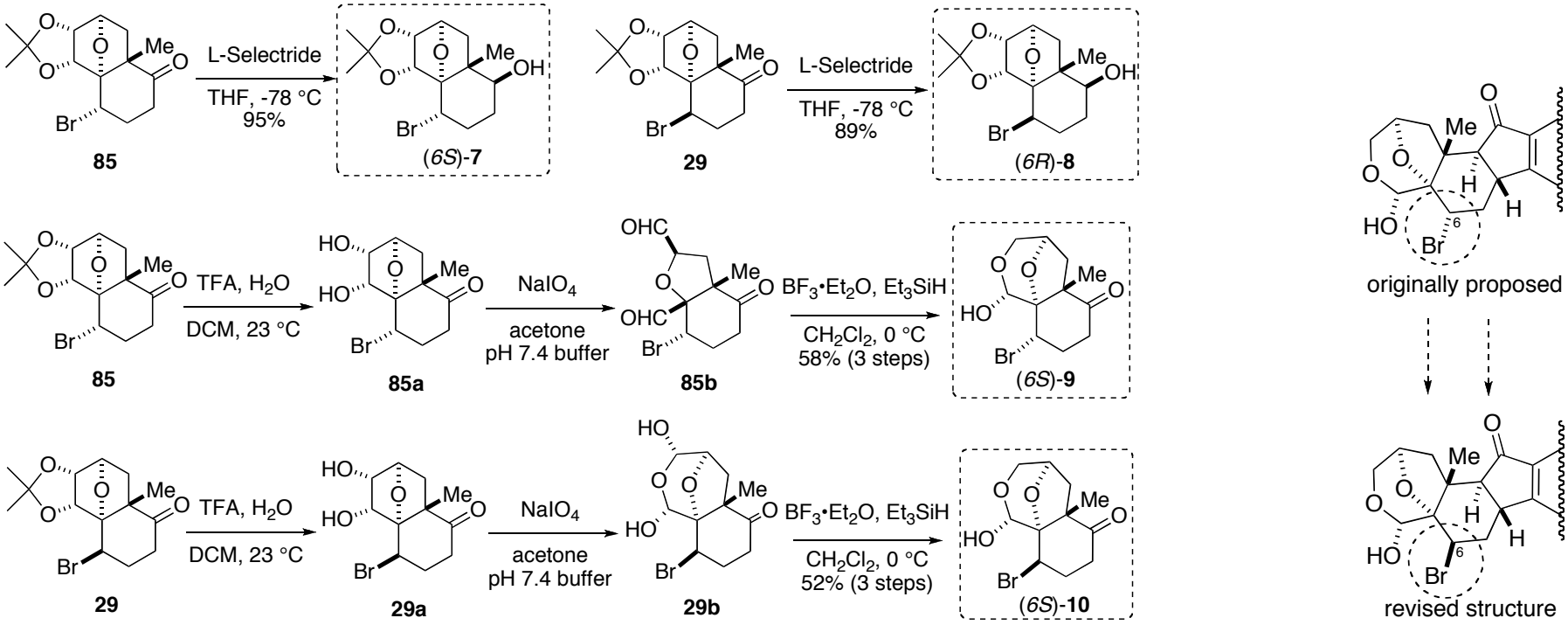
Cyclopamine (**5**)



Veratramine (**6**)

Teruya, T. *et al. Tetrahedron*, **2004**, *60*, 6989.
Gao, S. *et al. J. Amer. Chem. Soc.* ASAP

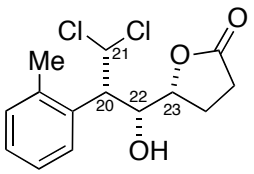
Probing the C-6 Configuration of Nakiterpiosin(one)



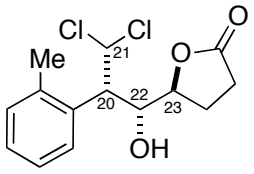
	Nakiterpiosin	Nakiterpiosinone	(6*S*)-**7**	(6*R*)-**8**	(6*S*)-**9**	(6*R*)-**10**
J_{H6-H7a}	2.7 Hz	2.3 Hz	12.2 Hz	3.2 Hz	11.6 Hz	3.2 Hz
J_{H6-H7b}	1.4 Hz	1.4 Hz	5.6 Hz	2.8 Hz	5.5 Hz	2.8 Hz

Gao, S. *et al. J. Amer. Chem. Soc.* ASAP

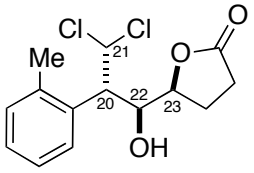
Investigating the Stereochemistry at C-20



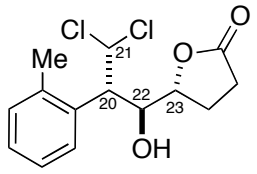
11 (syn-syn)
J_{H20-21} = 3.3 Hz



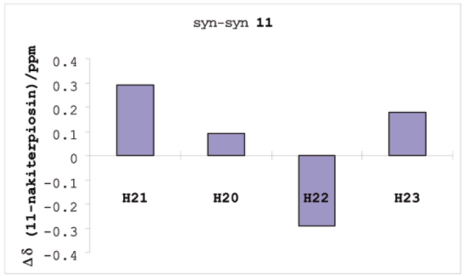
12 (syn-anti)
J_{H20-21} = 3.6 Hz

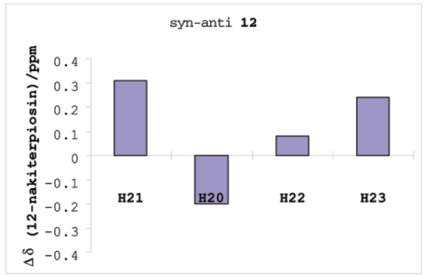


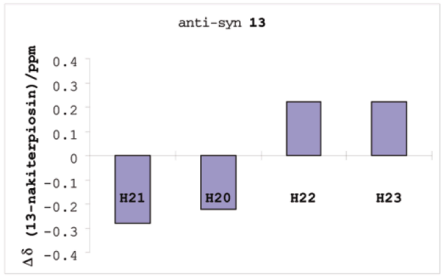
13 (anti-syn)
J_{H20-21} = 8.4 Hz

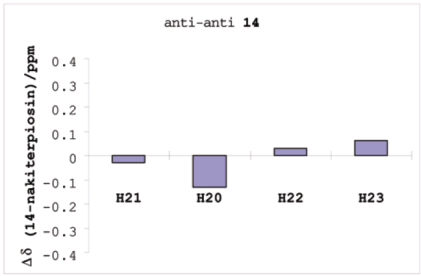


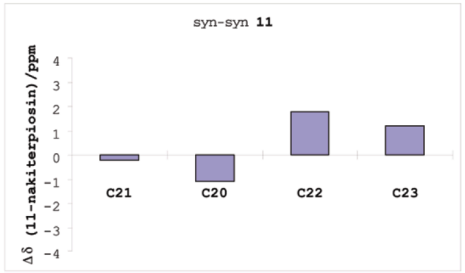
14 (anti-anti)
J_{H20-21} = 10.2 Hz

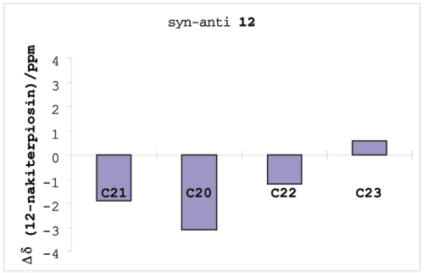


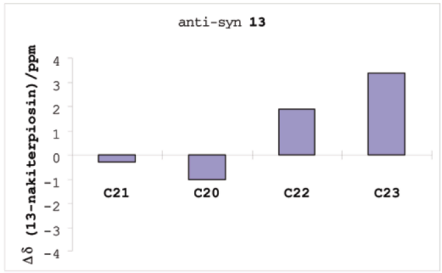


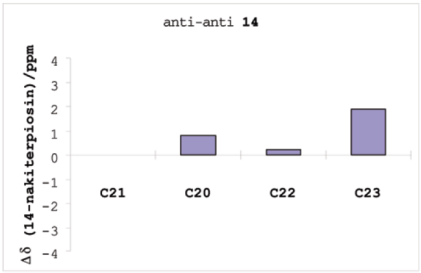


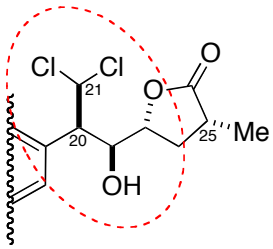






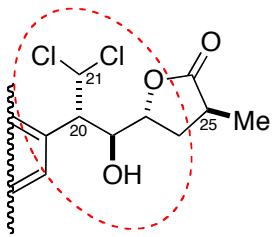






originally proposed
Nakiterpiosin(one)

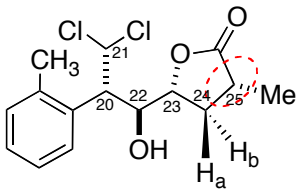
(J_{H20-21} = 10.3 (10.1) Hz)



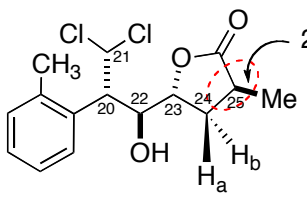
revised stereoshemistry at
C20-C22-C23 of
Nakiterpiosin(one)

Gao, S. *et al. J. Amer. Chem. Soc.* ASAP

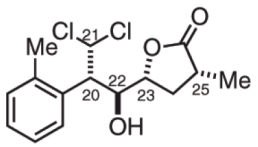
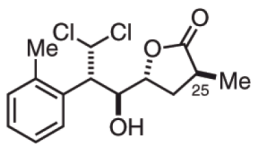
Studies of the C-25 Configuration of Nakiterpiosin(one)

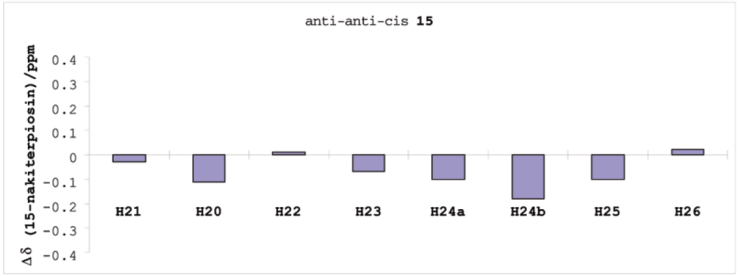


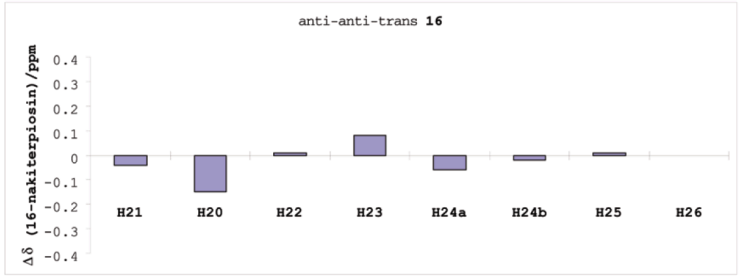
15 (anti-anti-cis)

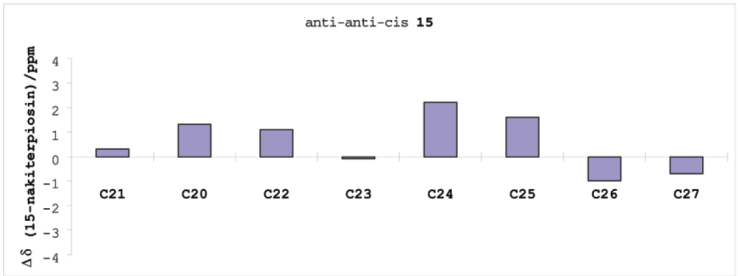


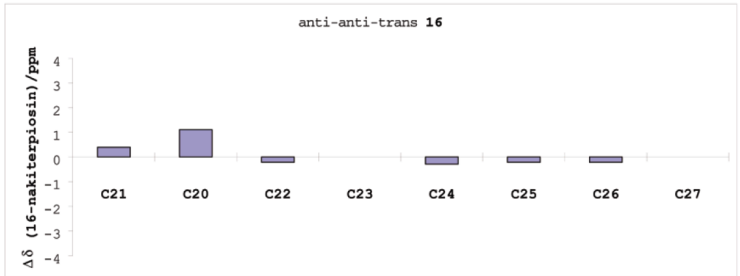
16 (anti-anti-cis)

	Nakiterpiosin	**Nakiterpiosinone**	 **15** (anti-anti-cis)	 **16** (anti-anti-trans)
$J_{H20-H21}$	10.3 Hz	10.1 Hz	10.2 Hz	10.1 Hz
$J_{H23-H24a}$	8.2 Hz	8.2 Hz	10.0 Hz	8.0 Hz
$J_{H23-H24b}$	3.7 Hz	3.7 Hz	5.8 Hz	3.9 Hz
$J_{H24a-H25}$	8.4 Hz	8.2 Hz	12.1 Hz	8.3 Hz
$J_{H24b-H25}$	N/A	9.2 Hz	8.8 Hz	9.4 Hz



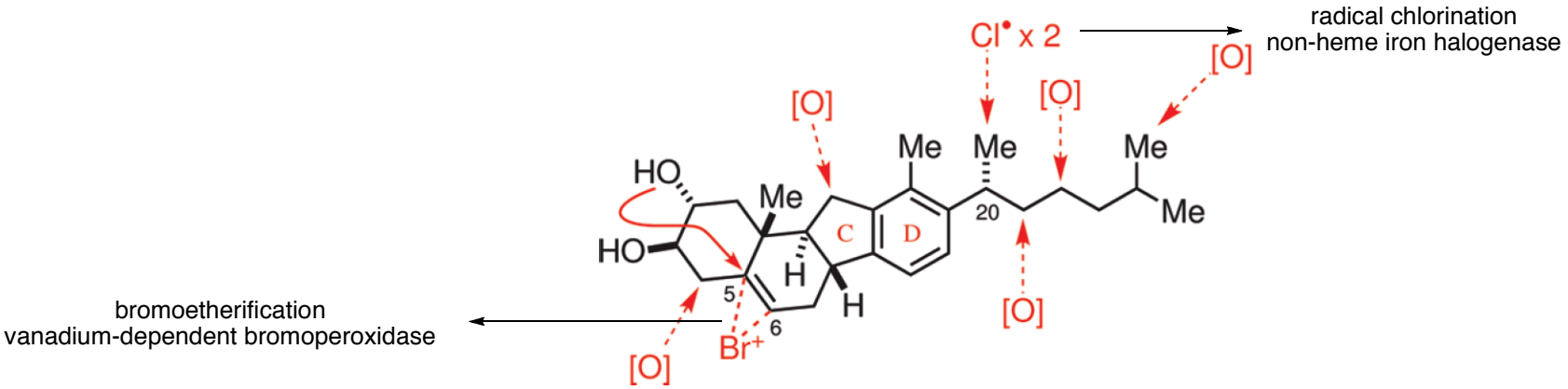




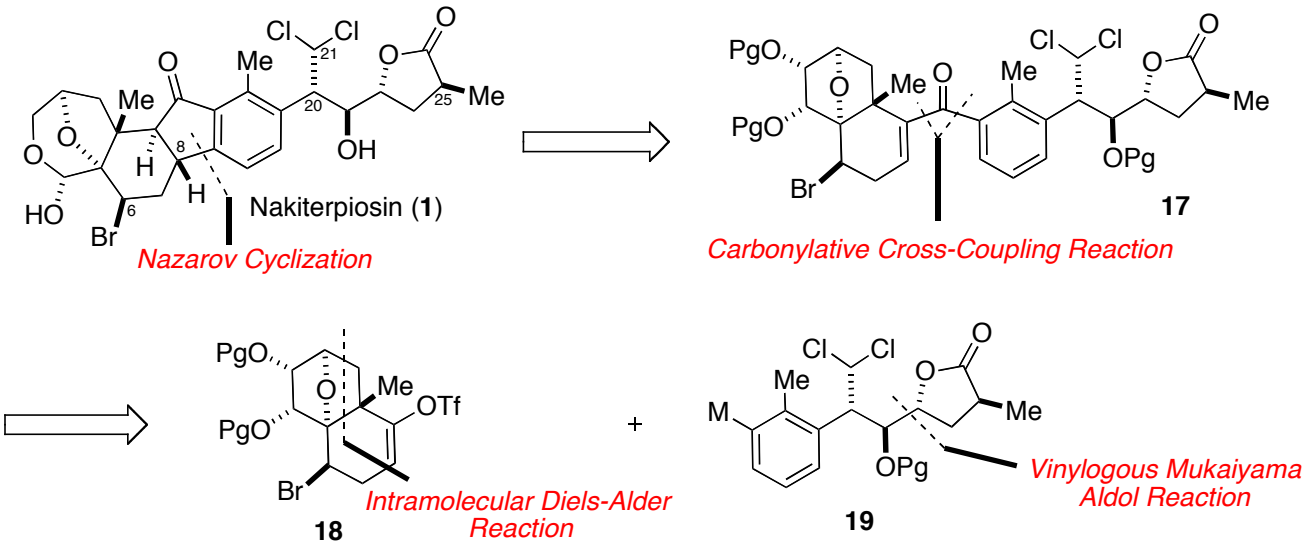


Gao, S. *et al. J. Amer. Chem. Soc.* ASAP

Proposed Biosynthesis and Synthetic Plan

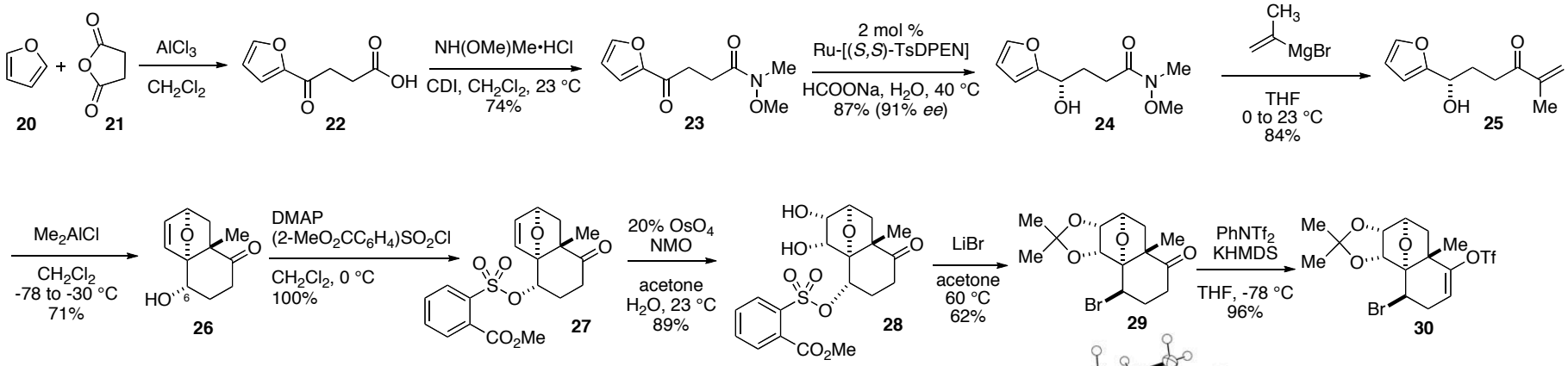


Retrosynthesic Analysis of Nakiterpiosin

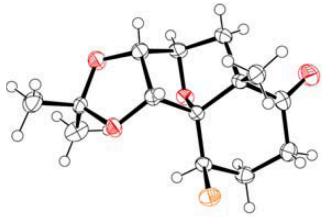


Gao, S. *et al. J. Amer. Chem. Soc.* ASAP

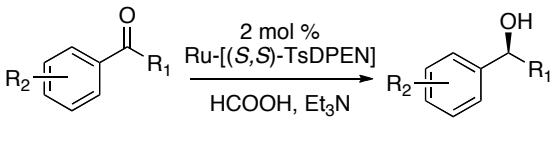
Synthesis of the Electrophilic Coupling Component **30**

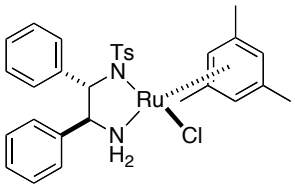


-Ts or Ns less reactive
- electron-deficient sulfonate
  is crucial for the S_N2 reaction



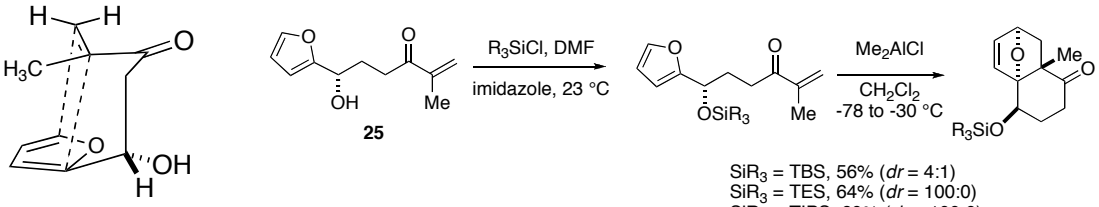
Noyori reduction





Ru-[(*S,S*)-TsDPEN](η^6-mesytilene)

Diels-Alder Reaction (exo *vs.* endo addition)

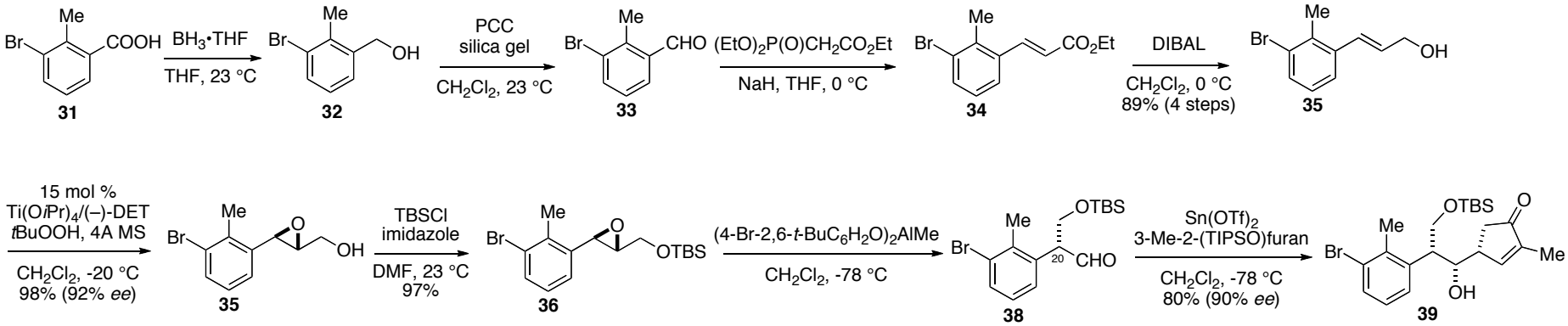


entry	Lewis acid	equiv	**25/26**	note
1	Me_2AlCl	2.5	0:100	
2	Me_2AlCl	1.0	30:70	
3	Me_2AlCl	0.1	100:0	
4	$MeAlCl_2$	1.0	15:85	with decomposition
5	$MeAlCl_2$	0.1	100:0	

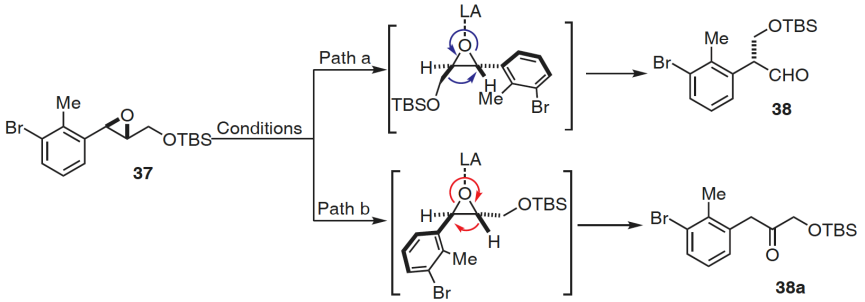
SiR_3 = TBS, 56% (*dr* = 4:1)
SiR_3 = TES, 64% (*dr* = 100:0)
SiR_3 = TIPS, 60% (*dr* = 100:0)

Gao, S. *et al. J. Amer. Chem. Soc.* ASAP
Fujii, A. *et al. J. Amer. Chem. Soc.* **1996**, *118*, 2521.

Synthesis of the Eastern Hemisphere of Nakiterpiosin: Yamamoto's pinacol-type rearrangement



Yamamoto's rearrangement

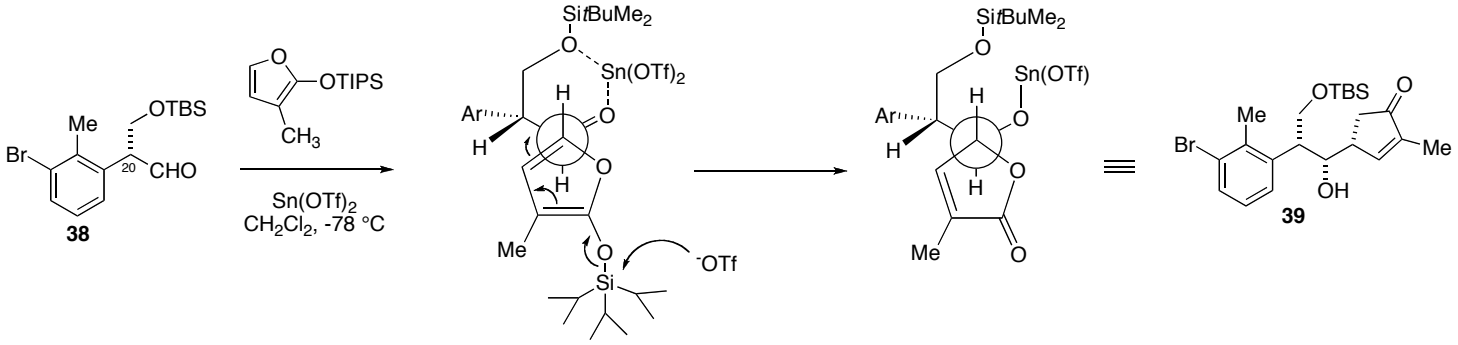


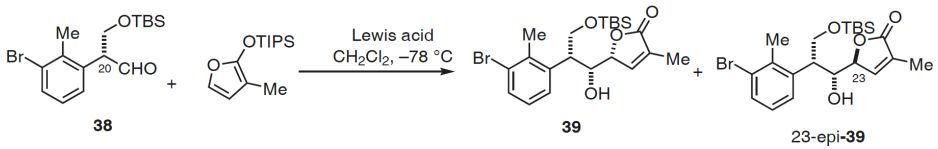
Entry	Lewis Acid	Equivalent	Temp.	**38**:**38a**	Conversion	Workup (Purification)	Note
1	(4-Br-2,6-^{t}BuPhO)$_2$AlMe	0.2	-78 °C	100:0	40%	NaF, H_2O (chromatography)	92% ee **37** →71% ee **38**
2	(4-Br-2,6-^{t}BuPhO)$_2$AlMe	2.0	-78 °C	100:0	100%	NaF, H_2O (chromatography)	92% ee **37** →71% ee **38**
3	(4-Br-2,6-^{t}BuPhO)$_2$AlMe	2.0	-78 °C	100:0	100%	1 N HCl (without purification)	92% ee **37** →90% ee **38**
4	Cr(TPP)(OTf)	0.05	83 °C	3:1	100%	---	92% ee **37** →78% ee **38**

Gao, S. *et al. J. Amer. Chem. Soc.* ASAP

Maruoka, K. *et al. J. Amer. Chem. Soc.* **1989**, *111*, 6431.

Synthesis of the Eastern Hemisphere of Nakiterpiosin: Mukaiyama Aldol

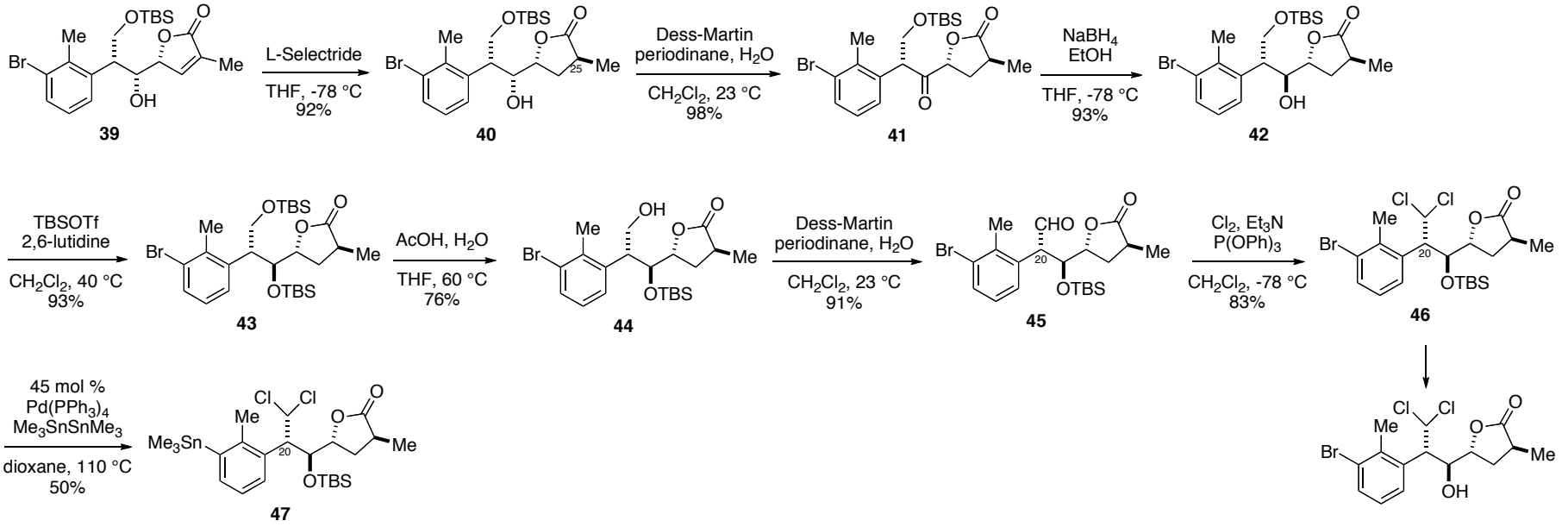




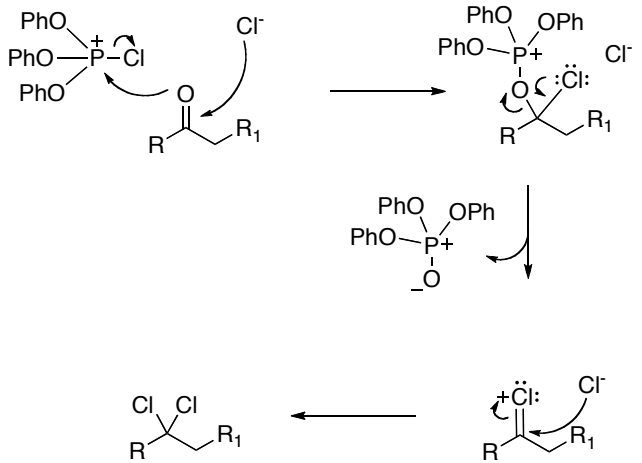
Entry	Lewis Acid	Equivalent	**39**:23-epi-**39**	Conversion	Note
1	$Yb(OTf)_3$	0.2	2.8:1	40%	—
2	$Sc(OTf)_3$	0.2	4:1	71%	—
3	$LiClO_4$	0.2	--	--	No reaction
4	$CrCl_3$	0.2	--	--	No reaction
5	$TiCl_4$	0.2	--	--	No reaction
6	$In(OTf)_3$	0.2	--	--	Messy
7	Ag(OTf)	0.2	--	--	Messy
8	$Cu(OTf)_2$	0.2	--	--	Messy
9	TMSOTf	0.2	100:0	24%	—
10	$Zn(OTf)_2$	0.2	100:0	37%	—
11	$ZrCl_4$	0.2	3:1	57%	—
12	Bi(OTf)3	0.1	11:1	56%	Ref. 3
13	$Sn(OTf)_2$	0.2	100:0	61%	—
14	$Sn(OTf)_2$	2.0	100:0	83%	90% ee **38** → 90% ee **39**
15	$BF3{\bullet}Et_2O$	1.5	4:1	100%	90% ee **38** → 90% ee **39**

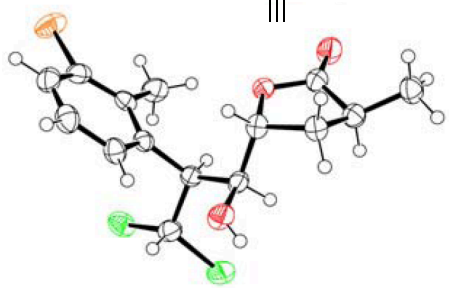
Gao, S. *et al. J. Amer. Chem. Soc.* ASAP
Ollevier, T. *et al. J. Org. Chem.* **2008**, *73*, 331.

Synthesis of the Nucleophilic Component **47**: Final Steps



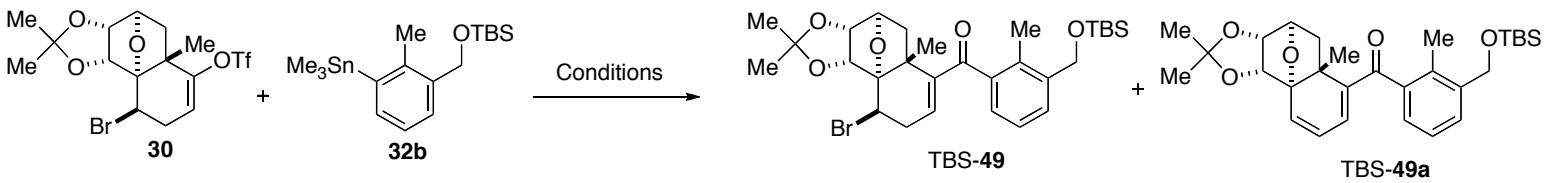
C-21 *gem*-dichloride formation

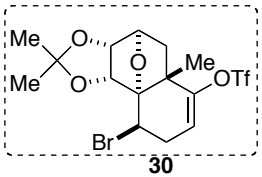




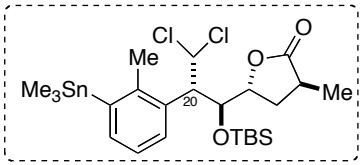
Gao, S. *et al. J. Amer. Chem. Soc.* ASAP
Spaggiari, A. *et al. J. Org. Chem.* **2007**, *72*, 2216.

Carbonylative Cross-Coupling Reaction: Optimization on the Model System **32b**





30



47

Entry	Pd	Ligand	Additive	Solvernt	Temp.	Time	TBS-**49**:**49a**	Note
1	0.3 eq, $Pd(OAc)_2$	0.6 eq, $P(Furyl)_3$	---	THF	23 °C	12 h	---	No reaction
2	0.3 eq, $Pd(OAc)_2$	0.6 eq, PPh_3	---	THF	23 °C	12 h	---	No reaction
3	0.3 eq, $Pd(OAc)_2$	0.6 eq, $P(Furyl)_3$	1.5 eq, CuCl	DMSO	55 °C	2 h	---	No reaction
4	0.3 eq, $Pd(OAc)_2$	0.6 eq, Ph_3As	1.5 eq, CuCl	DMSO	55 °C	2 h	---	No reaction
5	0.3 eq, $Pd(OAc)_2$	0.6 eq, $P(OMe)_3$	1.5 eq, CuCl	DMSO	55 °C	2 h	---	No reaction
6	0.3 eq, $Pd(OAc)_2$	0.6 eq, P(Cyhexane)$_3$	1.5 eq, CuCl	DMSO	55 °C	2 h	---	No reaction
7	0.3 eq, $Pd(OAc)_2$	0.6 eq, P(*t*-Bu)$_3$	1.5 eq, CuCl	DMSO	55 °C	2 h	---	No reaction
8	1.2 eq, $Pd(OAc)_2$	3 eq, Ph_3As	---	THF	23 °C	12 h	---	No reaction
9	1.2 eq, $Pd(OAc)_2$	3 eq, $P(OMe)_3$	---	THF	23 °C	12 h	---	No reaction
10	1.2 eq, $Pd(OAc)_2$	3 eq, $P(OPh)_3$	---	THF	23 °C	12 h	---	No reaction
11	1.1 eq, $Pd(PPh_3)_2Cl_2$	---	---	THF	50 °C	12 h	---	No reaction
12	1.0 eq, $Pd_2(dba)_3$	2.0 eq, $P(cy)_3$	1.5 eq, CuCl	DMSO	55 °C	2 h	---	No reaction
13	1.0 eq, $Pd_2(dba)_3$	2.0 eq, P(*t*-Bu)$_3$	1.5 eq, CuCl	DMSO	55 °C	2 h	---	No reaction
14	1.1 eq, $Pd(PPh_3)_4$	---	---	THF	50 °C	12 h	---	No reaction
15	1.1 eq, $Pd(PPh_3)_4$	---	6eq, CuCl; 6eq, LiCl	THF	50 °C	5 h	---	15% conversion
16	1.1 eq, $Pd(PPh_3)_4$	---	6eq, CuCl; 6eq, LiCl	DMSO	50 °C	70 min	0:100	100% conversion
17	2.0, eq, $Pd(PPh_3)_4$	---	6eq, CuCl; 6eq, LiCl	DMSO	60 °C	30 min	1:1	100% conversion
18	0.2 eq, $Pd(PPh_3)_4$	---	1.5 eq, CuCl	DMSO	55 °C	2 h	100:0	7% conversion
19	1.5 eq, $Pd(PPh_3)_4$	---	1.5 eq, CuCl	DMSO	55 °C	45 min	100:0	100% conversion

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Completion of the Synthesis of Nakiterpiosin

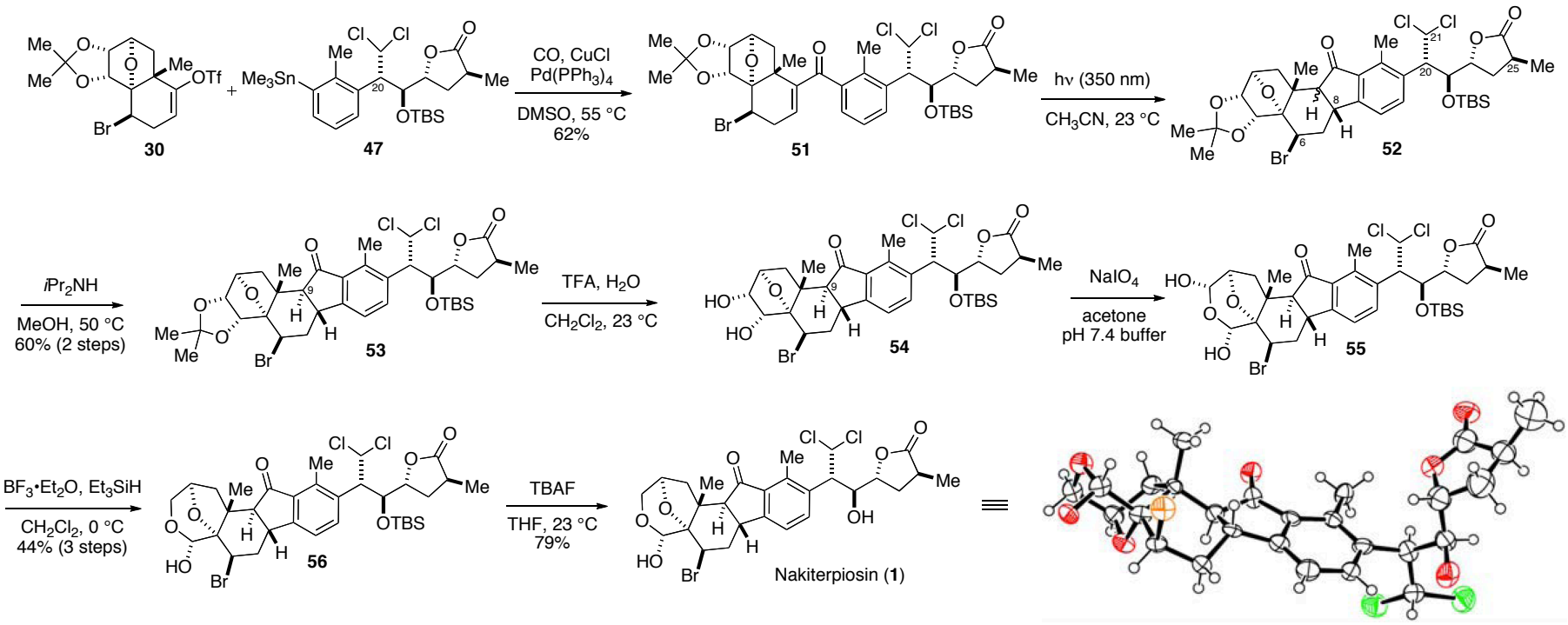
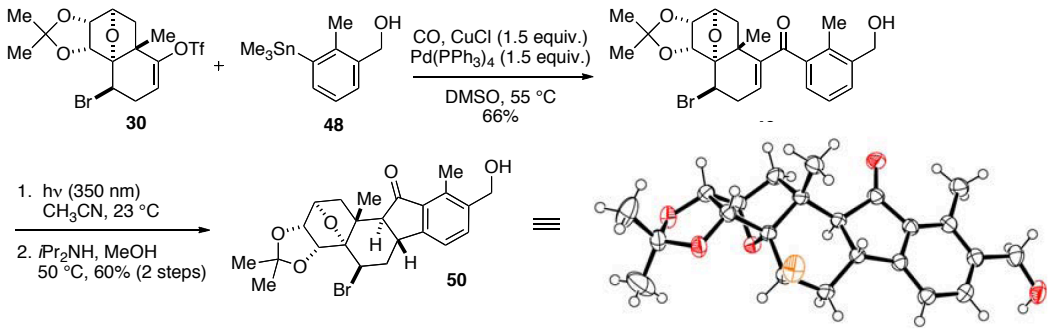
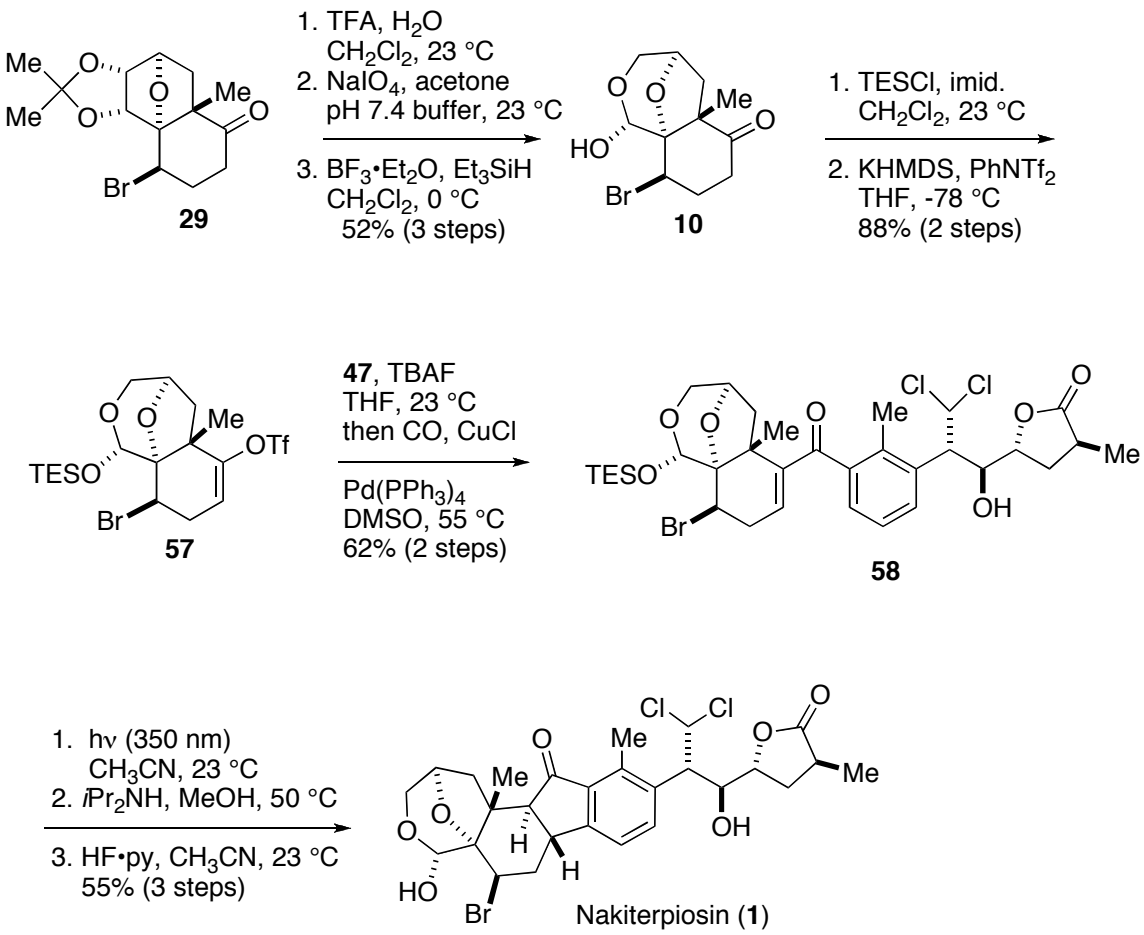


Photo-Nazarov Cyclization: Model Studies



Gao, S. *et al. J. Amer. Chem. Soc.* ASAP
Leitich, J. *et al. Eur. J. Org. Chem.* **2001**, 2719.

An Improved Synthesis of Nakiterpiosin: Second Generation Approach



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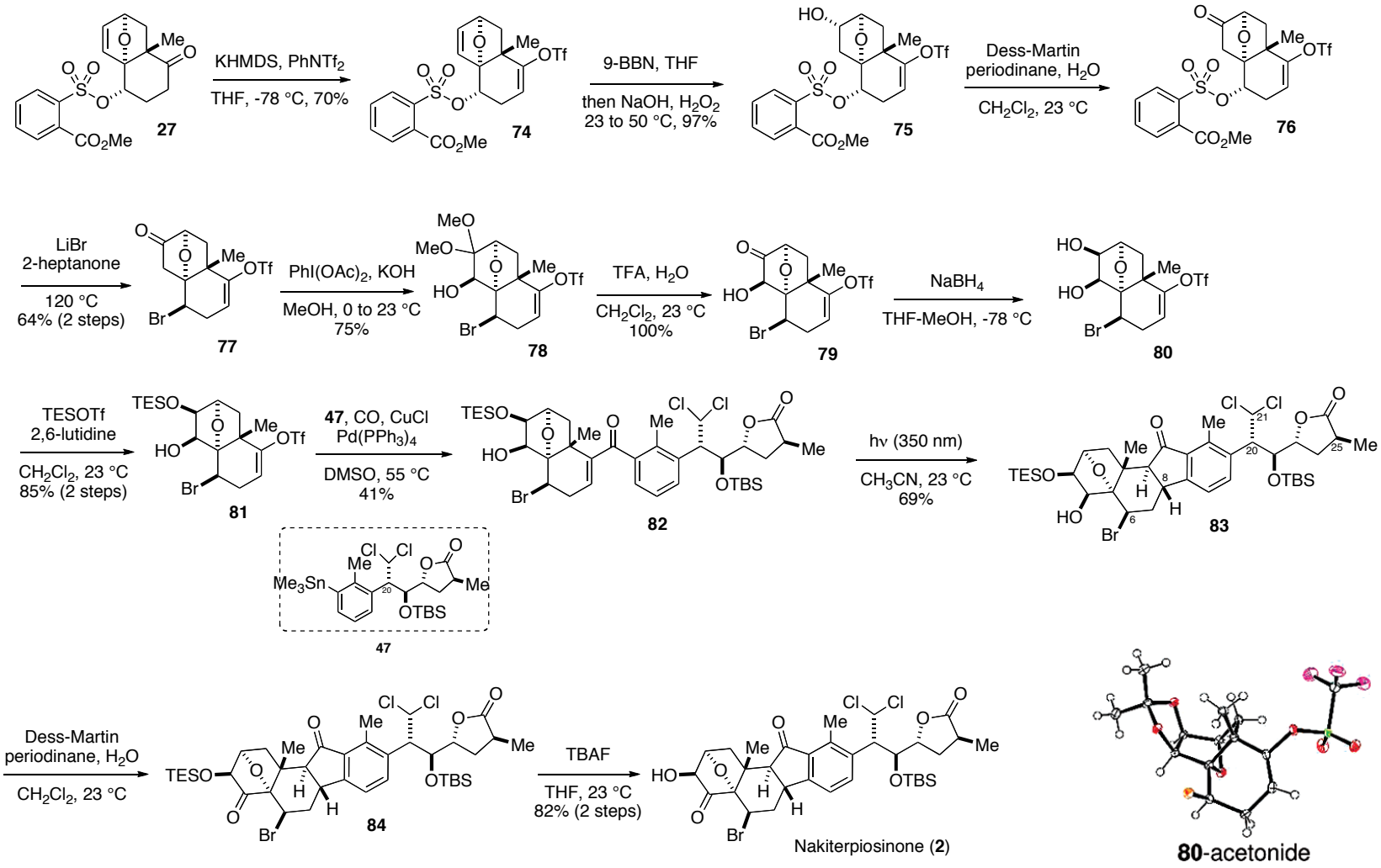
Synthesis of Nakiterpiosinone



-Selective oxidation of C-4 hydroxyl group of **28** or **54** is not possible
- C-3 epimerization of **28** lead to considerable decomposition
- Oxidation of diol **28** to diketone leads to diol cleavage

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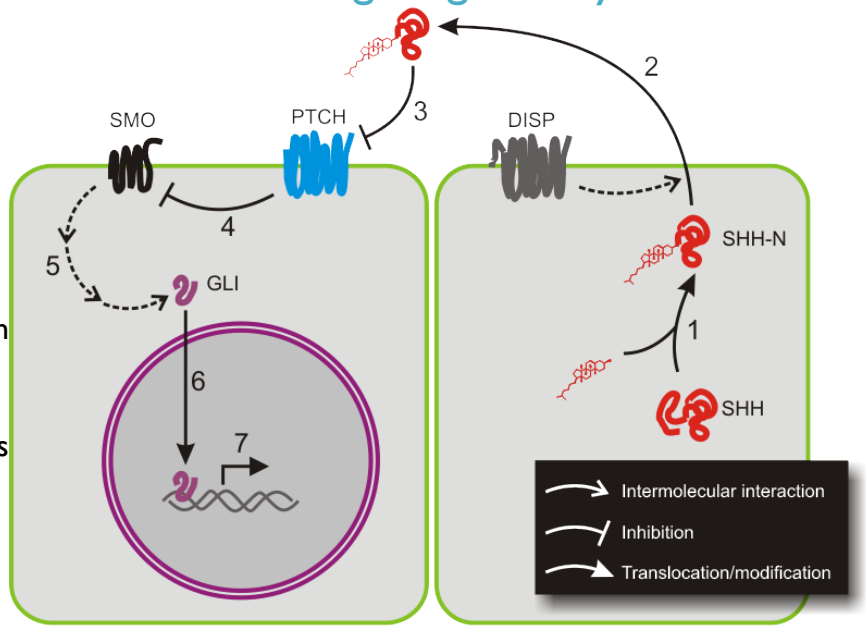
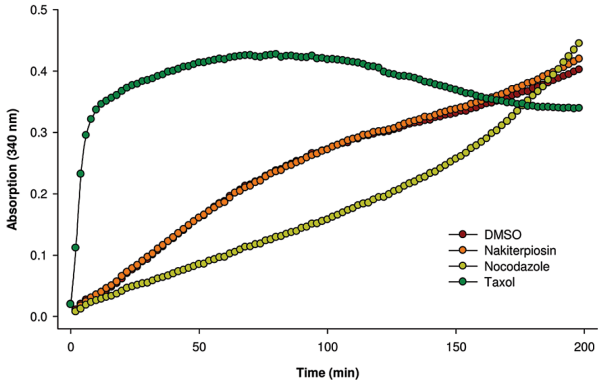
Biological Studies of Nakiterpiosin

Hedgehog Patway

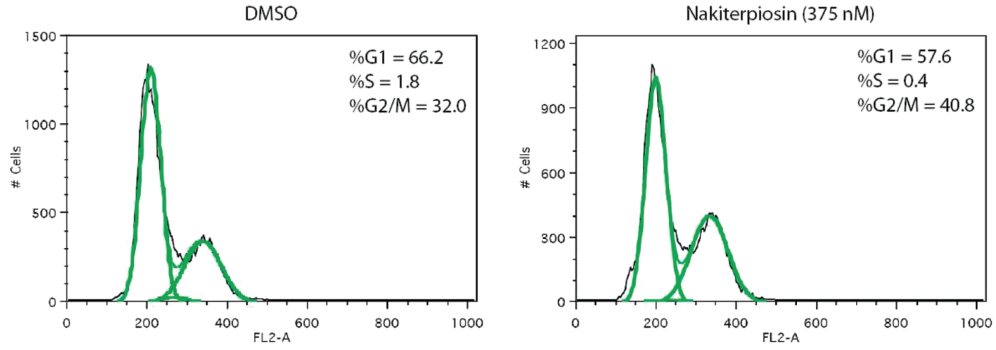
SHH = Sonic hedgehog
DISP = Dispatched protein
PTCH = Patched protein
SMO = Smoothened
GLI = transcription factors



Tubulin Polymerization Assay



DNA-profile of Nakiterpiosin Treated HeLa Cells



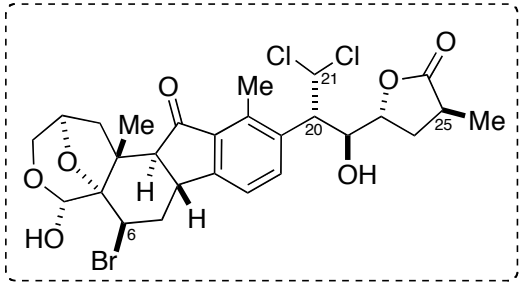
Gao, S. *et al. J. Amer. Chem. Soc.* ASAP
http://en.wikipedia.org/wiki/Hedgehog_signaling_pathway
Chen, J. *et al. Gen. and Develop.* **2002**, *16*, 2743.

Conclusions

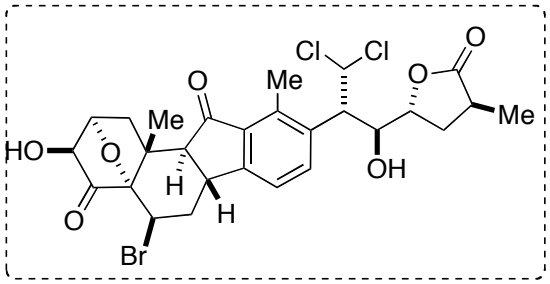
Extesive spectroscopic and synthetic analysis led to revision of previoulsy missasaigned stereochemistry

Nakiterpiosin and Nakiterpiosinone were succesfully sinthesized (the rout towards Nakiterpiosin was improved - 21 step - 5% overall yield)

Preliminary biological studies showed that Nakiterpiosin is antimitotic agent; the mechanisam is different from other well-established antimitotic agents (Taxol)



Nakiterpiosin



Nakiterpiosinone

Stereochemistry at C-6 was established through Noyori asymmetric hydrogenation

Lewis acid catalyzed *exo*-Diels-Alder furan cycloaddition used to establish A-ring

Sharpless Asymmetric Epoxydation followed by Yamamoto's pinacol type rearrangement was used to establish stereochemistry at C-20

Vinylogous Mukaiyama Aldol reaction installed C-22 and C-23 stereocenters

Carbonylative cross-coupling - Nazarov cyclization connecteded two hemispheres of Nakiterpiosin and Nakiterpiosinone