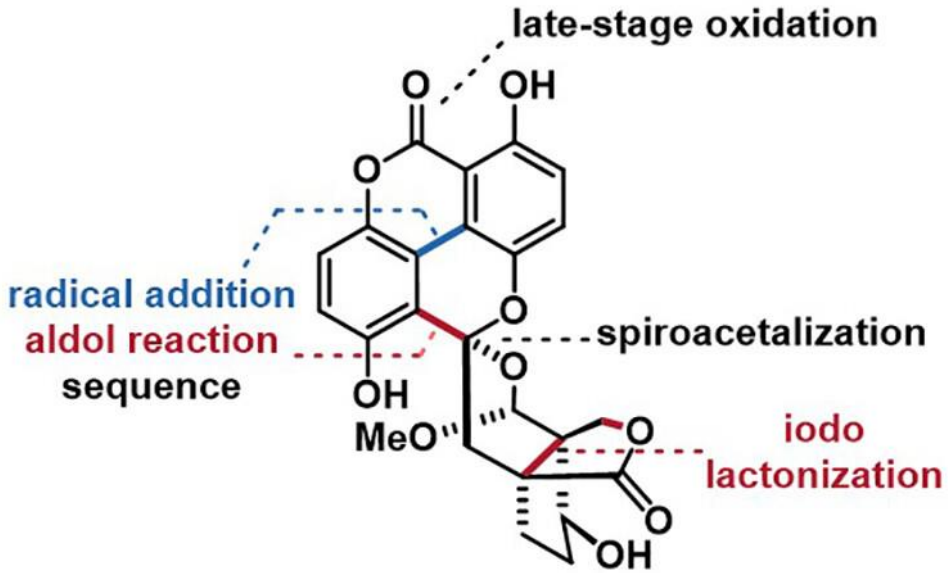
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Total Synthesis of Ganoapplanin Enabled by a Radical Addition/Aldol Reaction Cascade



ganoapplanin
[inhibitor of Ca^{2+} channels]

- isolated from *Ganoderma applanatum*
- 6/6/6/6 tetracyclic system
- dioxatricyclo[4.3.3.0]dodecane
- spiro bisacetal

J. Am. Chem. Soc. **2024**, *146*, 22937−22942

Thomas Magauer

- **Education:**

2002 – 2007: Undergraduate Studies
University of Vienna (Prof. J. Mulzer)

2007 – 2009: Graduate Studies
University of Vienna (Prof. J. Mulzer)

2010 – 2012: Postdoctoral Studies (Prof. A. G. Myers)
Harvard University

- **Work Experience:**

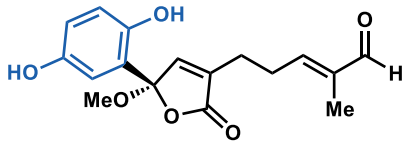
2012-2017: Assistant Professor
Ludwig Maximilian University of Munich

2017-now: Full Professor
University of Innsbruck, Austria

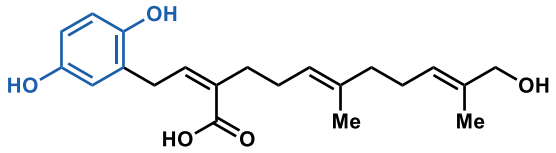
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Ganoderma meroterpenoids

linear *Ganoderma* meroterpenoids

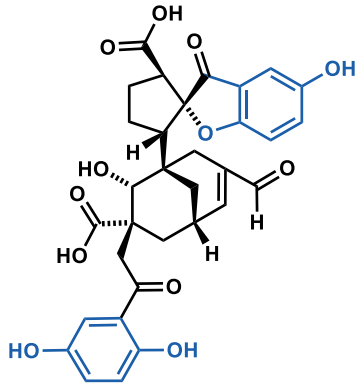


lucidulactone B (1)

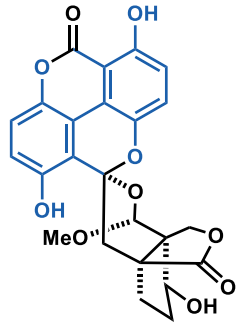


ganomycin A (2)

dimeric *Ganoderma* meroterpenoids



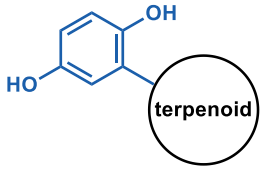
applanatunin A (9)

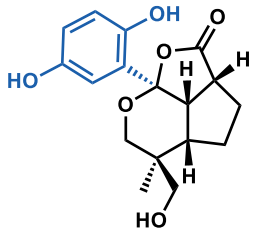


ganoapplanin (10)

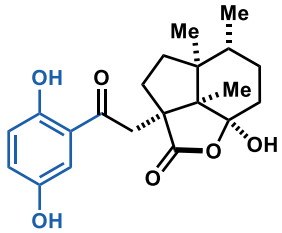
polycylic *Ganoderma* meroterpenoids

Pattern A



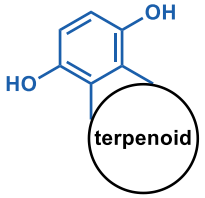


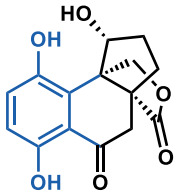
applanatunol B (3)



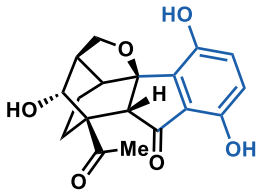
ganodermaone A (4)

Pattern B



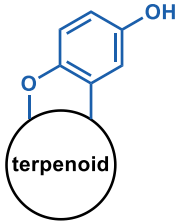


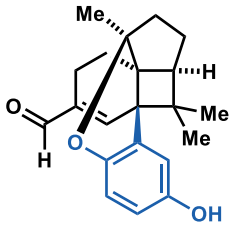
lingzhiol (5)



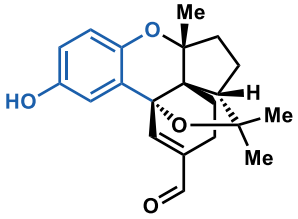
Lucidumone (6)

Pattern C





cochlearol B (7)

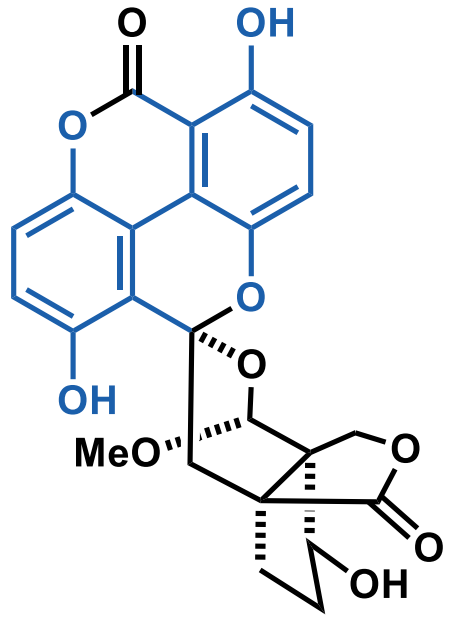


ganocin A (8)

Nat. Prod. Bioprospect., **2018**, *8*, 137–149, *Asian J. Org. Chem.* **2024**, *13*, e202300633

- **Isolation and Activity**

G. Applanatum (36 kg)



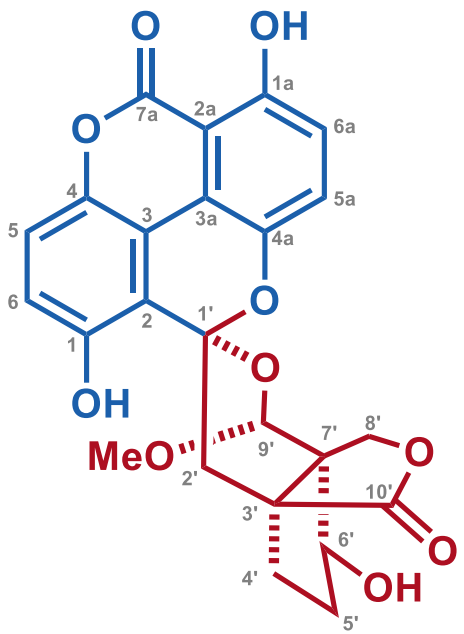
(±)-ganoapplanin (**10**) (15.6 mg)

inhibition of T-type voltage-gated Ca^{+} channels
(IC_{50} = 36.6 μM)

Org. Lett. **2016**, *18*, 6078−6081

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

- **Structure**



(±)-ganoapplanin (**10**)

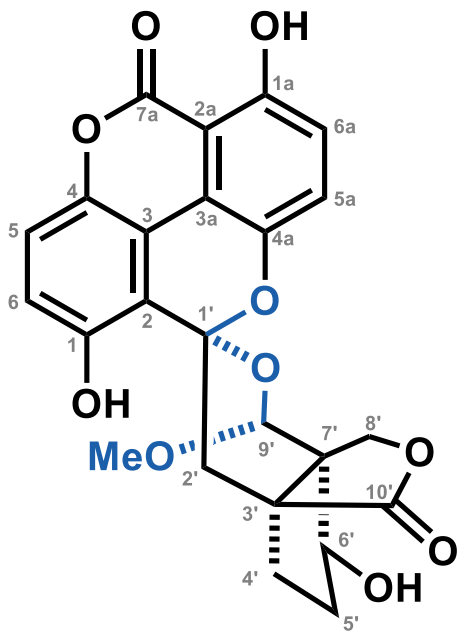
- Hydroquinone fragment

  6/6/6/6 tetracyclic system
- terpene fragment

  dioxatricyclo[4.3.3.0]dodecane
- Spiro bis-acetal skeleton
- Five stereocenters (two quaternary)

Org. Lett. **2016**, *18*, 6078−6081

- **Structure**



(±)-ganoapplanin (**10**)

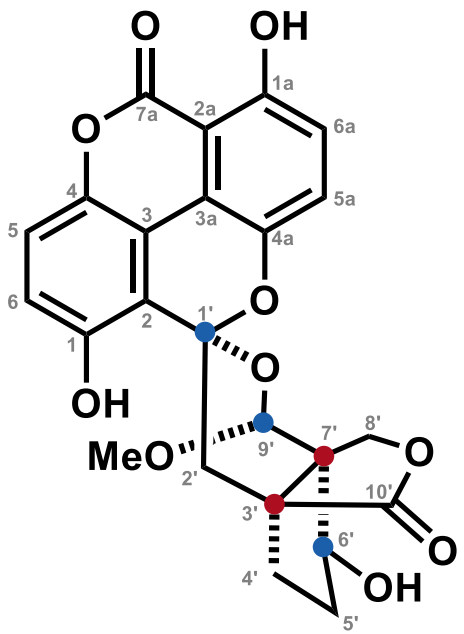
- Hydroquinone fragment

  6/6/6/6 tetracyclic system
- terpene fragment

  dioxatricyclo[4.3.3.0]dodecane
- Spiro bis-acetal skeleton
- Five stereocenters (two quaternary)

Org. Lett. **2016**, *18*, 6078−6081

- **Structure**



(±)-ganoapplanin (**10**)

- Hydroquinone fragment

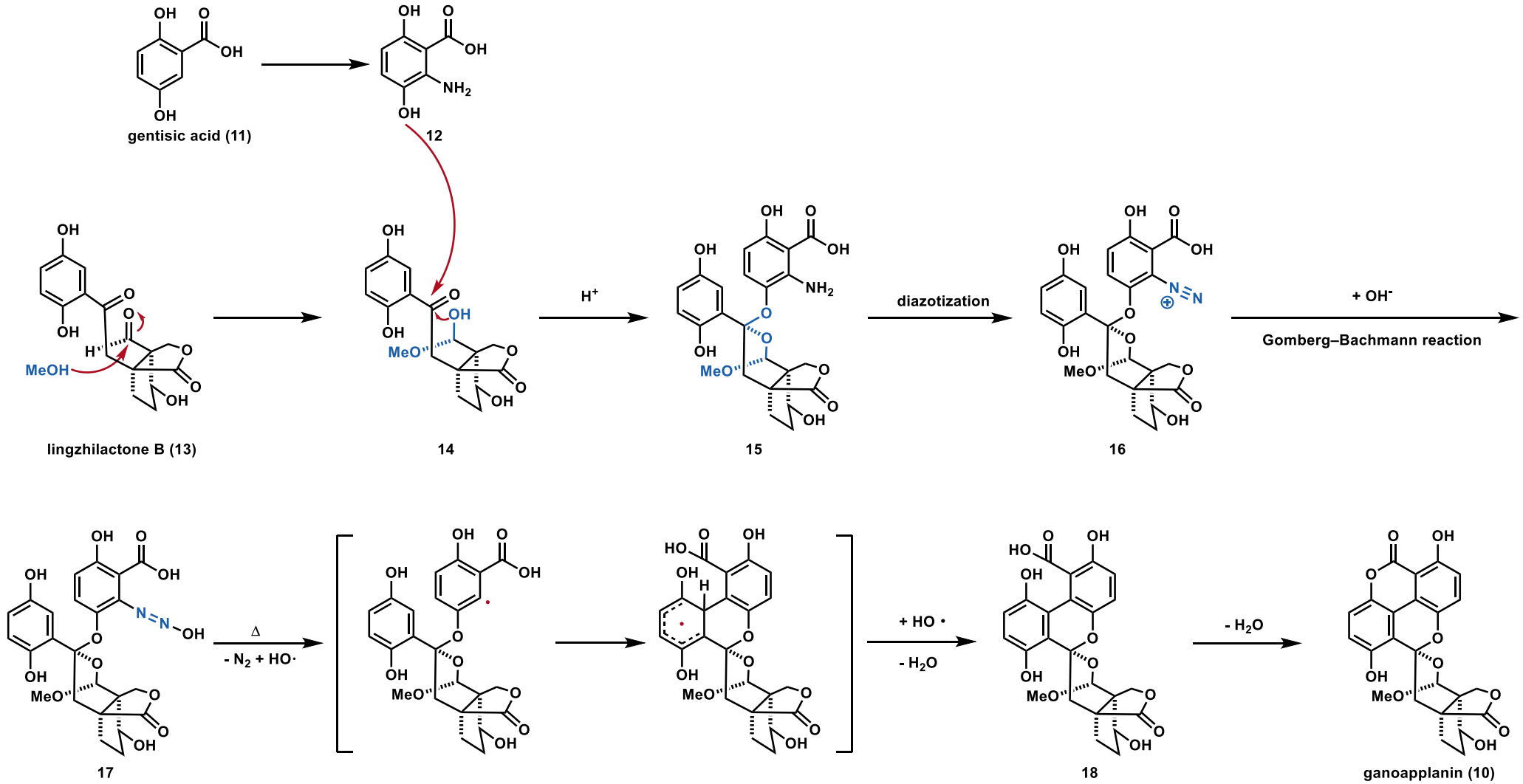
  6/6/6/6 tetracyclic system
- terpene fragment

  dioxatricyclo[4.3.3.0]dodecane
- Spiro bis-acetal skeleton
- Five stereocenters (two quaternary)

Org. Lett. **2016**, *18*, 6078−6081

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

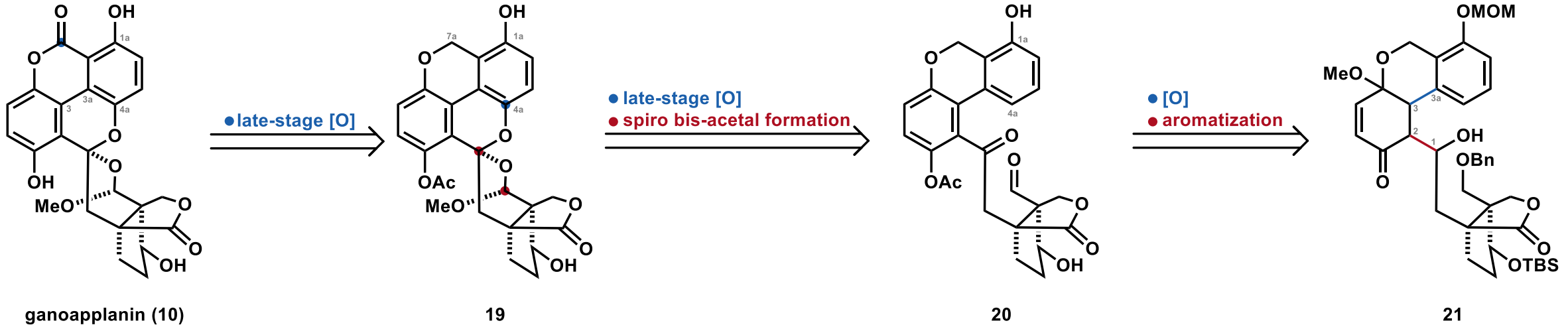
Proposed Biosynthesis



Org. Lett. **2016**, *18*, 6078−6081

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Retrosynthetic analysis

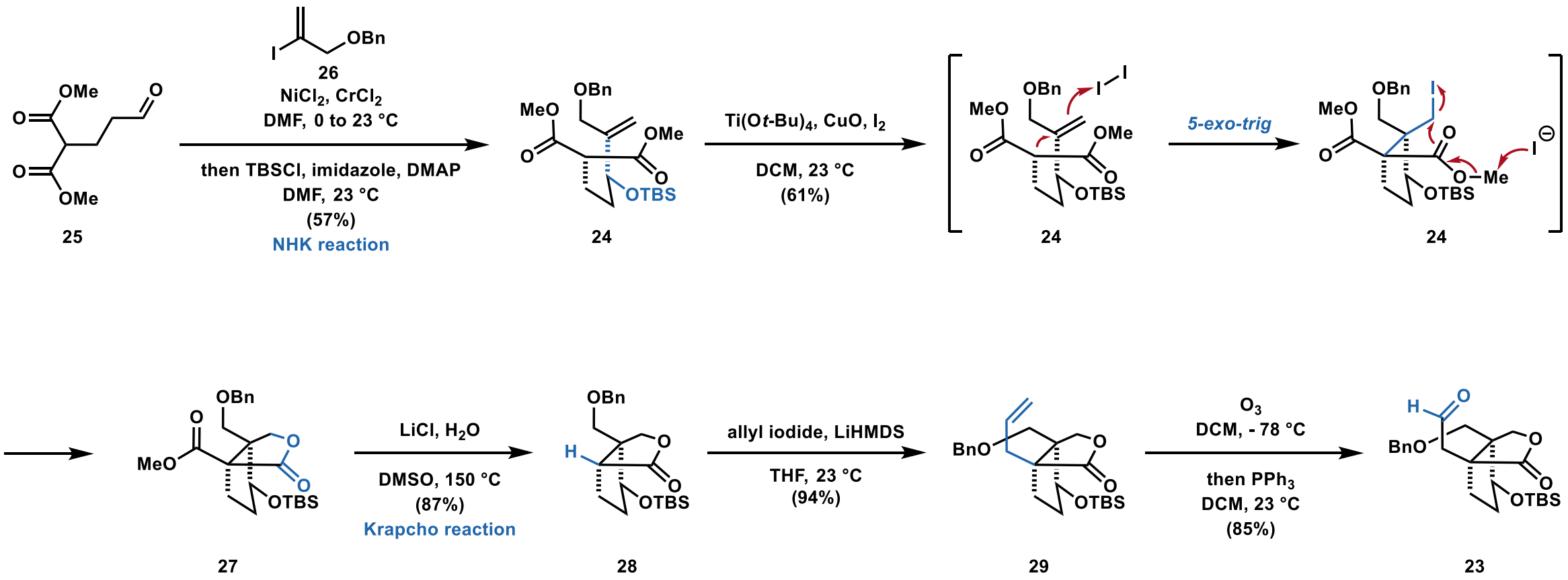


ganoapplanin (10) 19 20 21

22 23 24 25 26

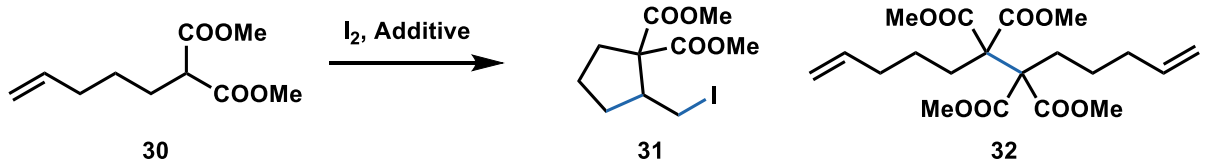
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Synthesis of the southern fragment



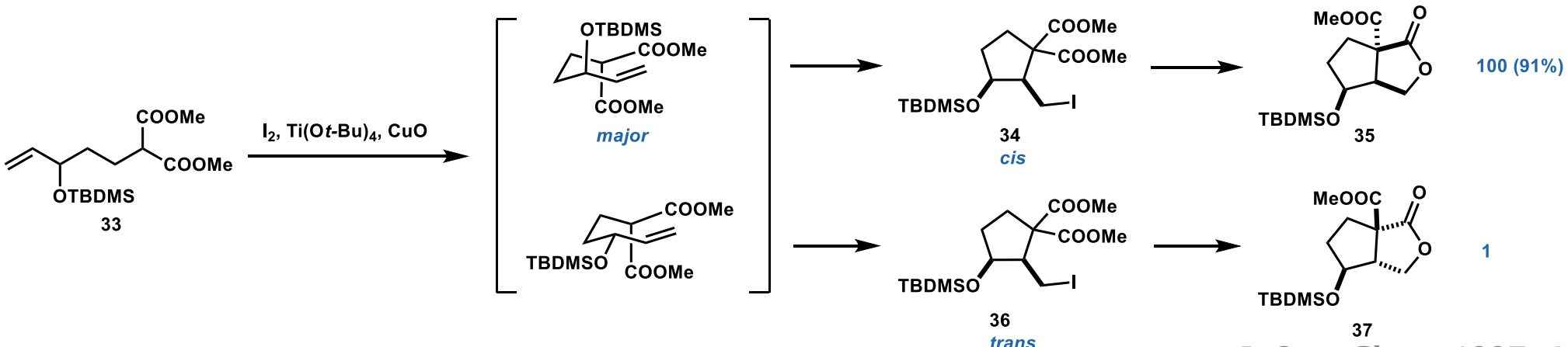
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Ti-mediated iodolactonization



30 31 32

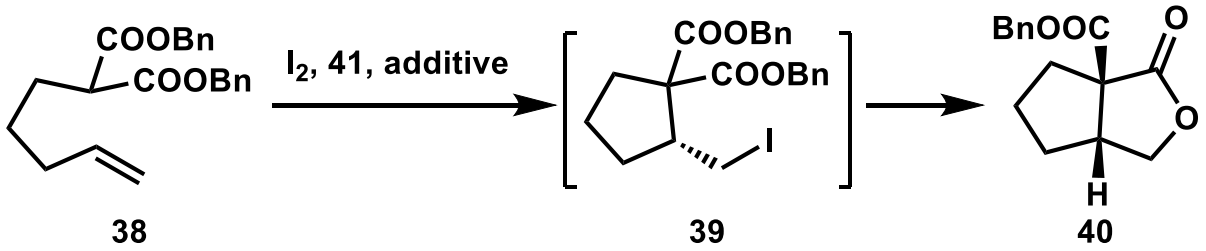
Entry	Adiitive	Yield(%)	
		31	32
1	LDA	60	60
2	$Ti(OtBu)_4$	74	(-)
3	$Ti(OtBu)_4$, CuO	83	(-)



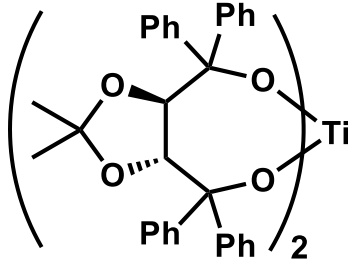
J. Org. Chem. **1997**, *62*, 7384-7389

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

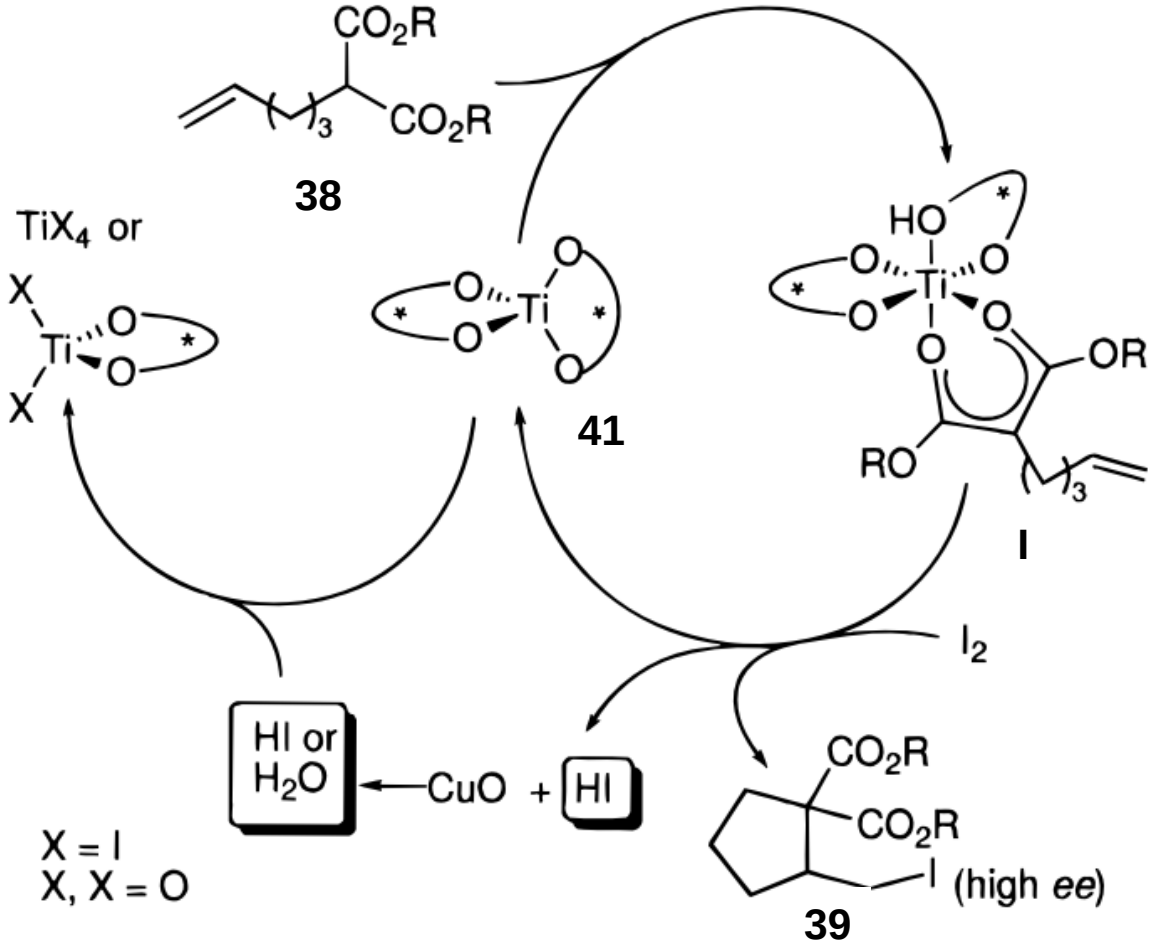
Ti-mediated iodolactonization



Entry	Adiitive	41(mol %)	Yield(%)	ee(%)
1	CuO	100	96	85
2	CuO	50	85	50



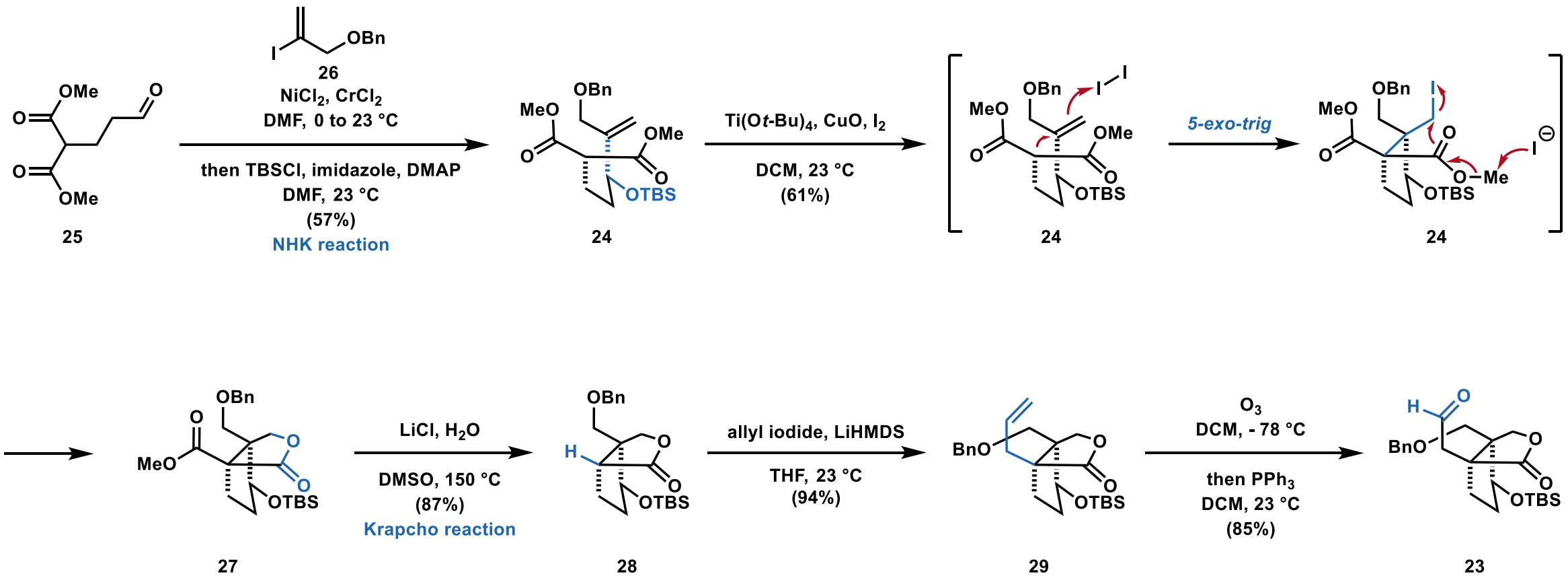
Ti(TADDOLate)$_2$ (41)



J. Org. Chem. **1997**, *62*, 7384-7389

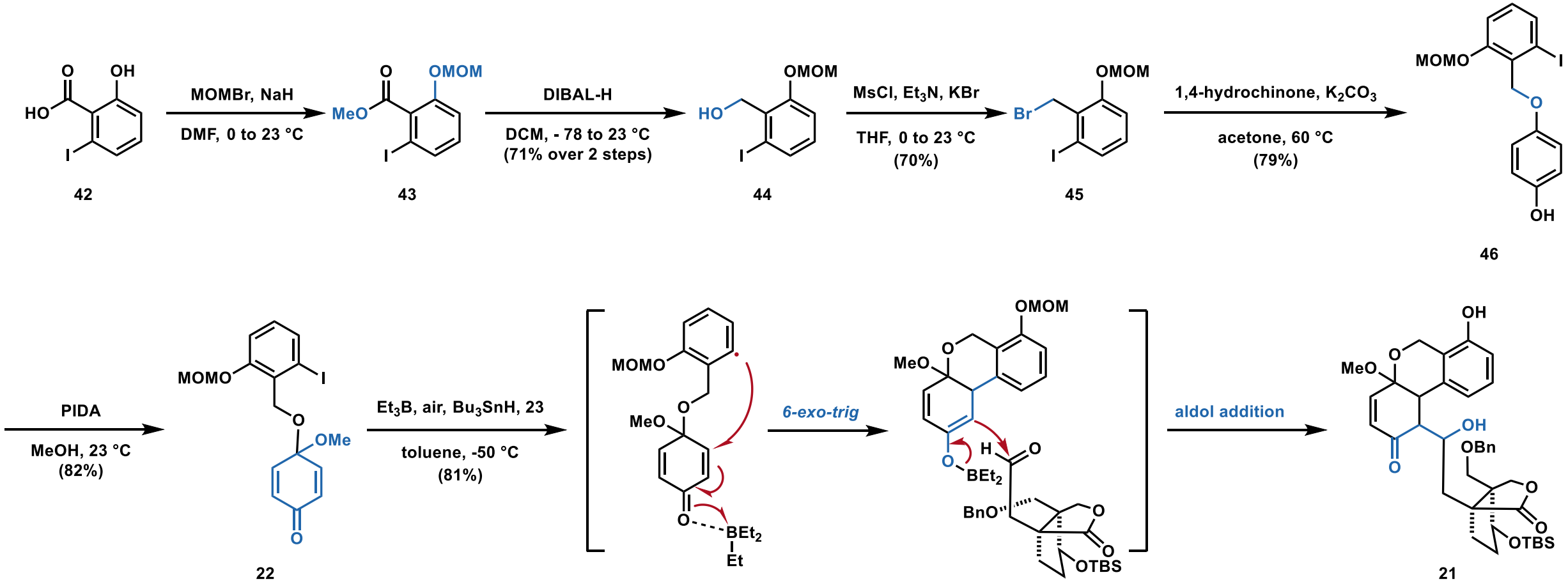
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Synthesis of the southern fragment

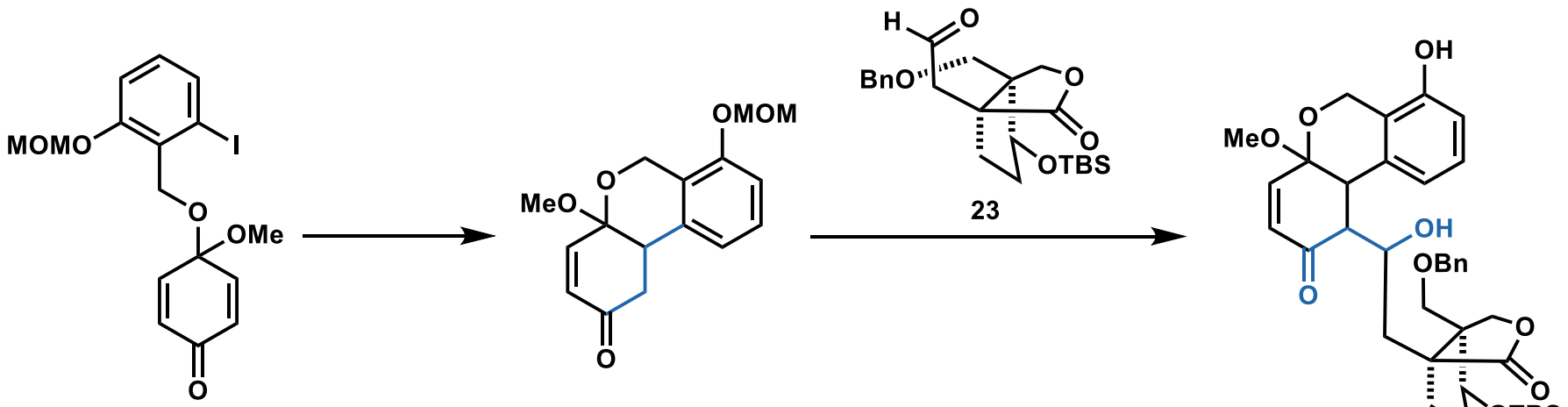


JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Synthesis of the northern fragment and radical 1,4-addition/aldol reaction sequence



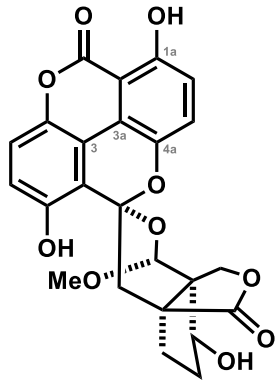
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

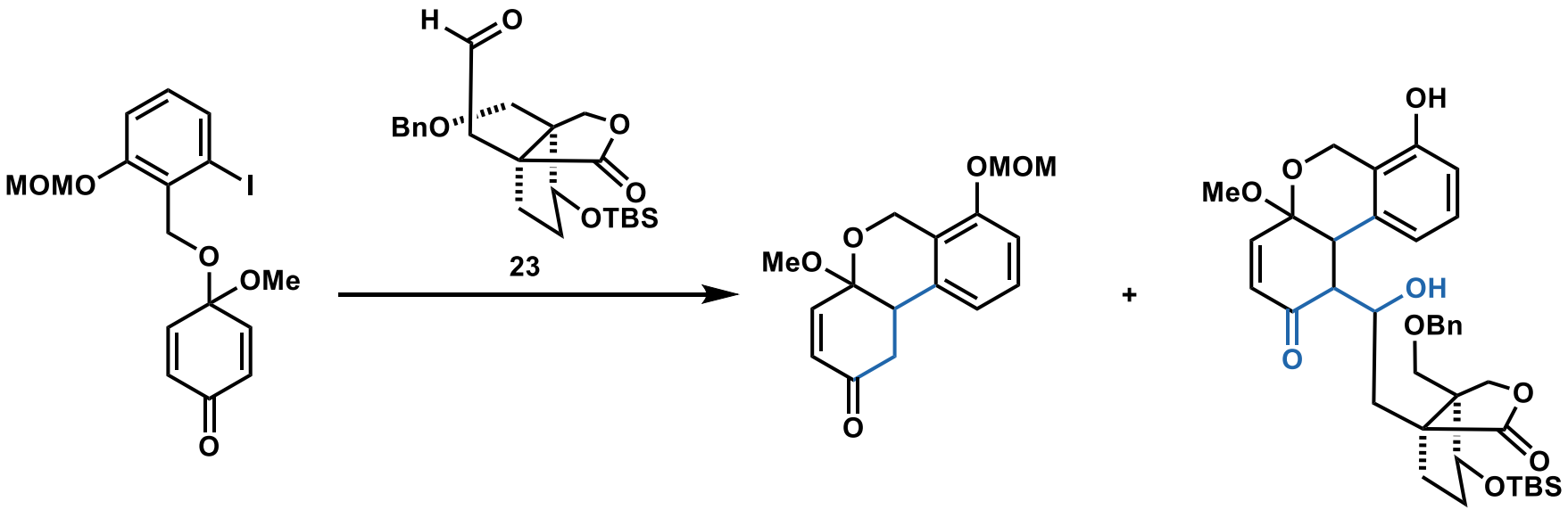


Entry	Conditions	Temp.	Result
1	*t*-BuLi, THF	- 78 °C	Decomposition
2	*t*-BuLi, HMPA, THF	- 78 °C	Decomposition
3	*i*PrMgCl, THF	0 °C	Decomposition
4	AIBN, $HSnBu_3$, toluene	50 °C	S11 (70%)
5	BEt_3, air, toluene	- 50 °C	Decomposition
6	$HSnBu_3$, BEt_3, air, toluene	- 50 °C	S11 (up to 90%)

Entry	Conditions	Temp.	Result
1	LDA, THF	- 78 to 23 °C	no consumption of S11 and 23
2	LiHMDS, THF	- 78 to 23 °C	no consumption of S11 and 23

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

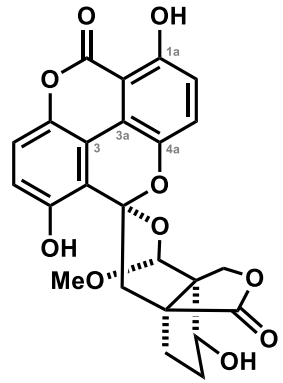




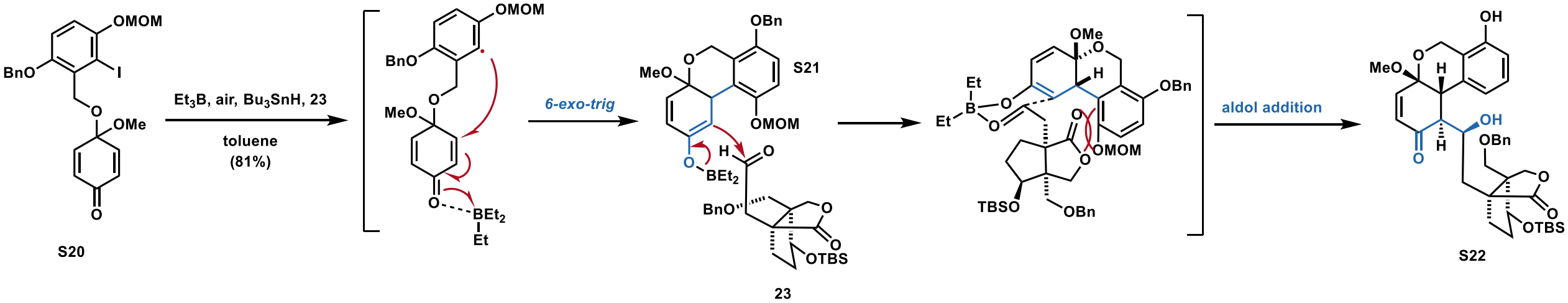
22 S11 21

Entry	Conditions	Temp.	Result
1	AIBN, $HSnBu_3$, toluene	50 °C	S11 (70%)
2	AIBN, $HSnBu_3$, BEt_3, toluene	50 °C	Decomposition
3	BEt_3, $HSnBu_3$, air, toluene	- 50 °C	21 (up to 81%) + S11

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

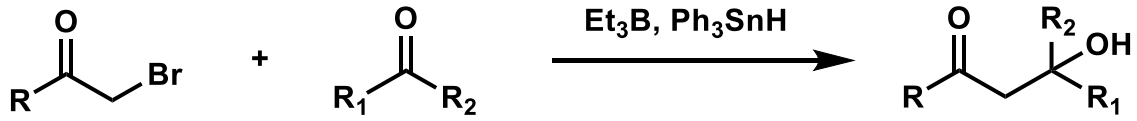


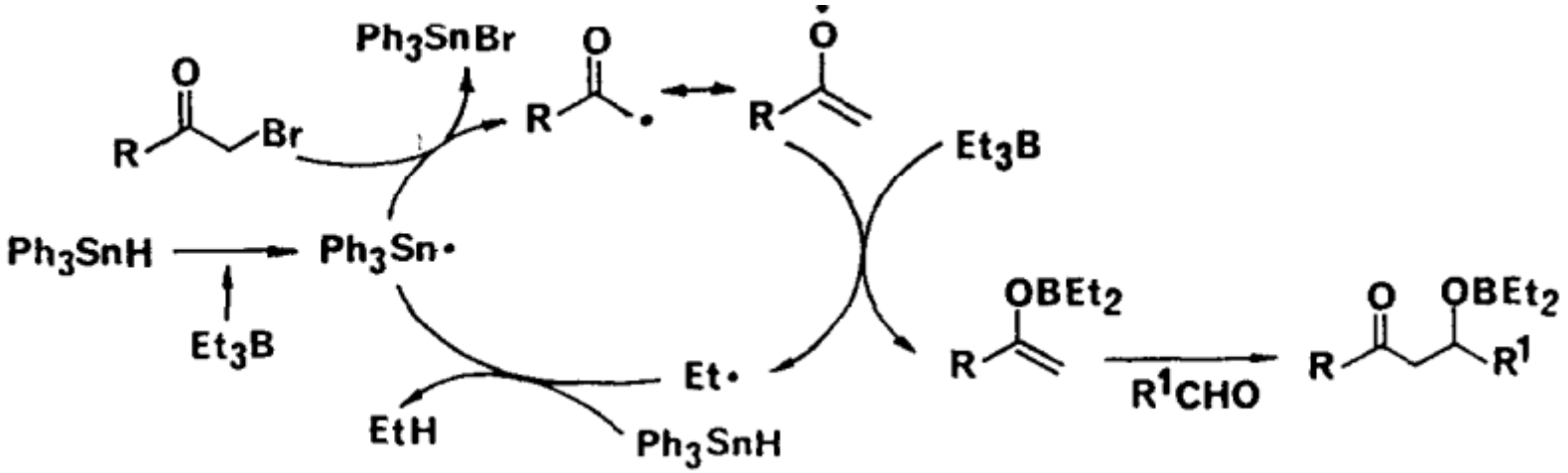
Radical addition followed by an intermolecular aldol reaction



Entry	Temp.	Result
1	- 78 °C	recovered 23 + S21 (not isolated), S22 not formed
2	- 50 °C	recovered 23 + S21 (40%), S22 not formed
3	0 °C	recovered 23 + S21 (not isolated), S22 not formed
4	23 °C	recovered 23 + decomposed, S22 not formed

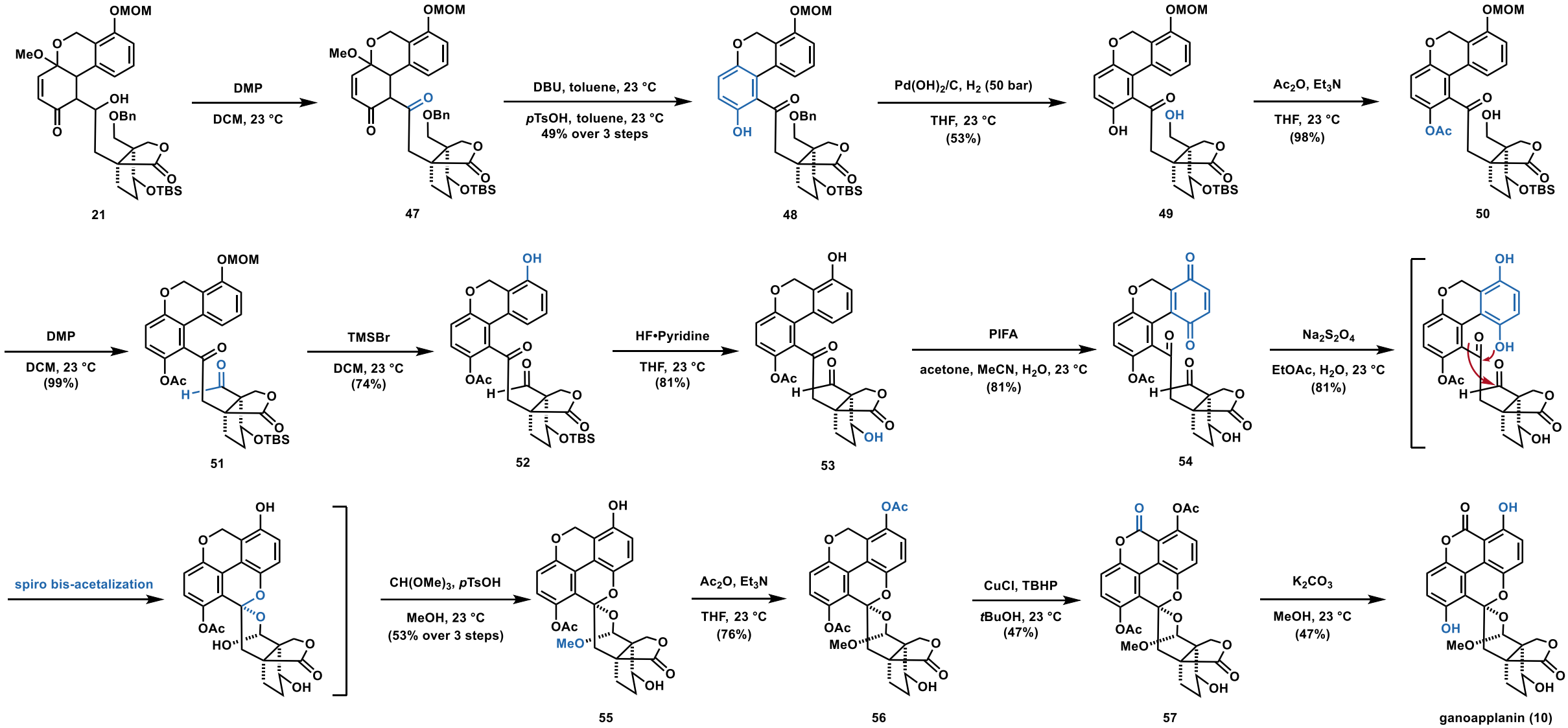
- **Et_3B-Mediated Reformatsky type reaction**



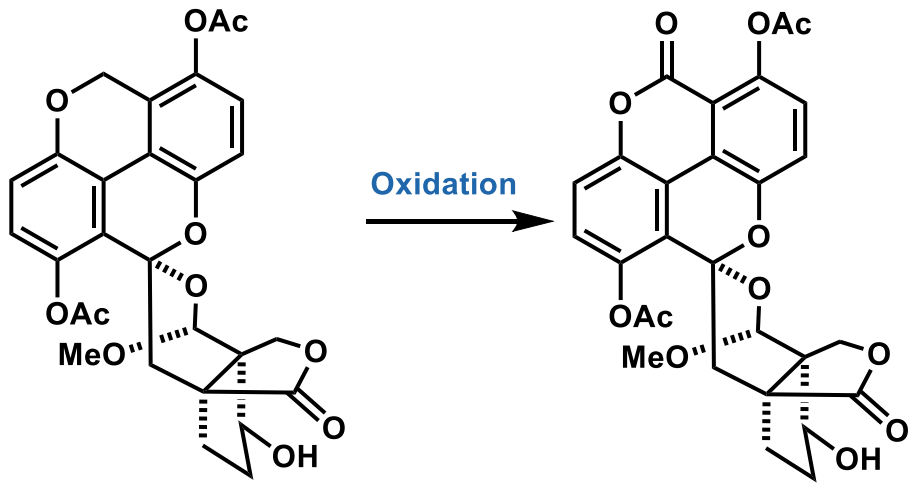


Tetrahedron Lett., **1988**, *29*, 1041-1044

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

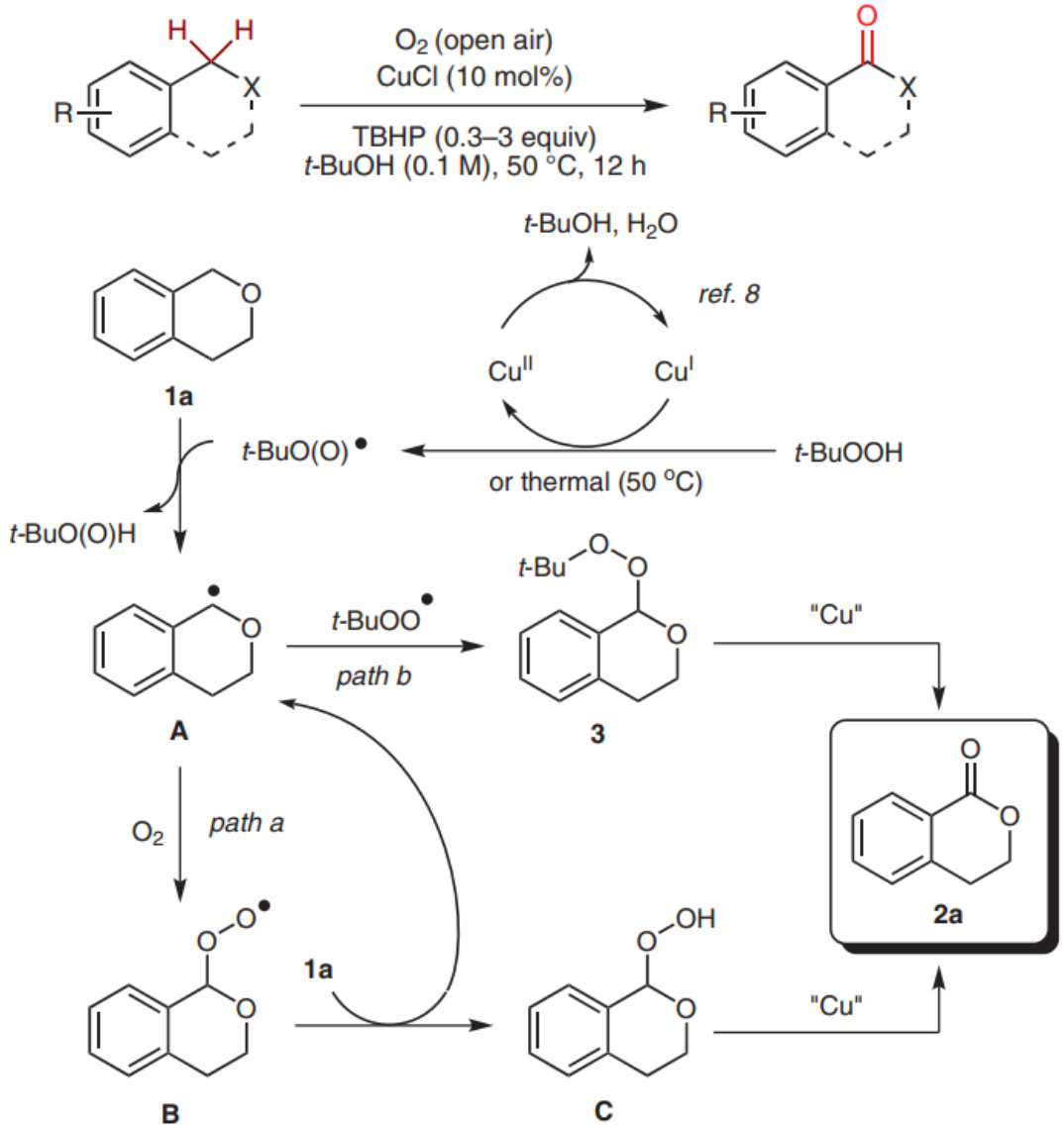


JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY



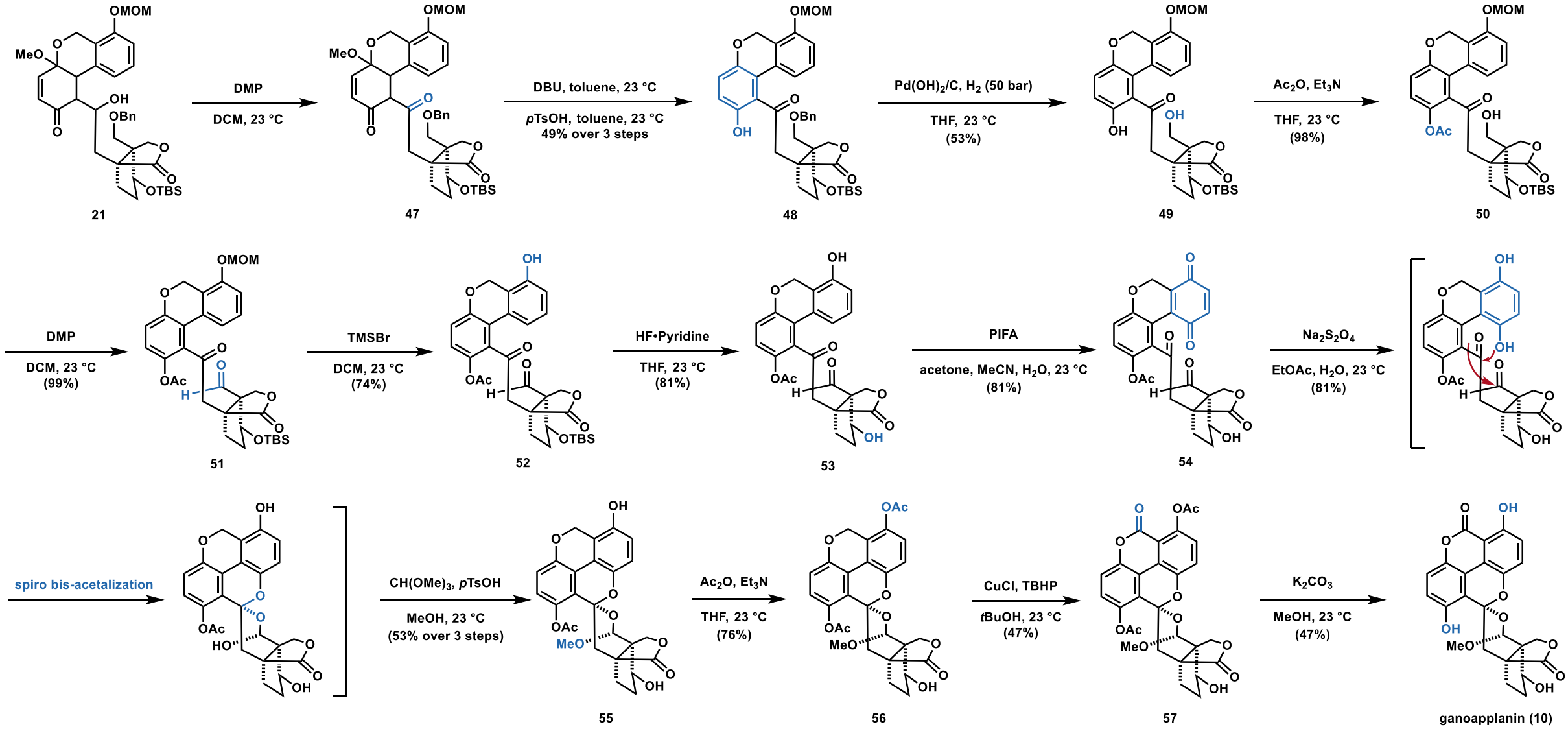
56 57

Entry	Conditions	Result
1	Jones reagent	Decomposition
2	DDQ, MeOH	Decomposition
3	DDQ, TBHP	Decomposition
4	DDQ, CuCl, tBuOH	47%

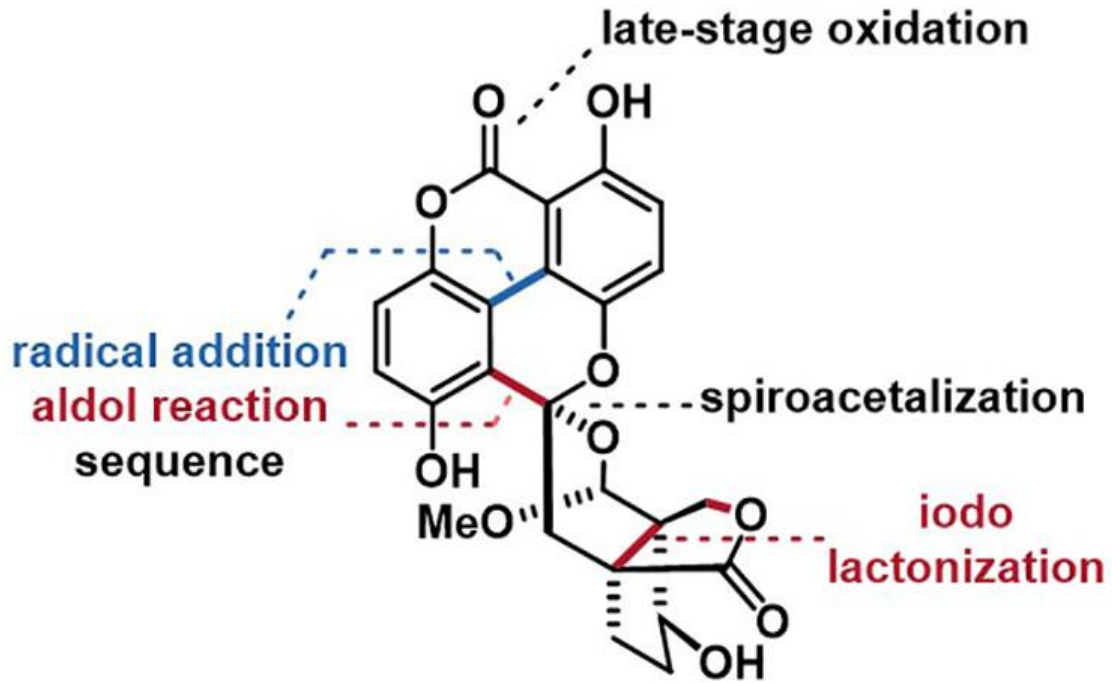


. *Synlett* **2017**, *28*, 1576−1580

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY



JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication



ganoapplanin
[inhibitor of Ca^{2+} channels]

- isolated from *Ganoderma applanatum*
- 6/6/6/6 tetracyclic system
- dioxatricyclo[4.3.3.0]dodecane
- spiro bisacetal

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

THANKS!