Total Synthesis of *Illicium* Sesquiterpenes

Literature Seminar

2020/01/23

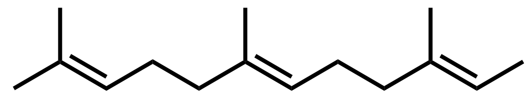
B4 Atsushi Iwai

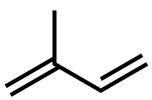
Contents

Contents

Sesquiterpene

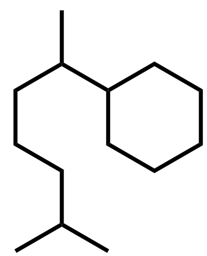
Sesquiterpene



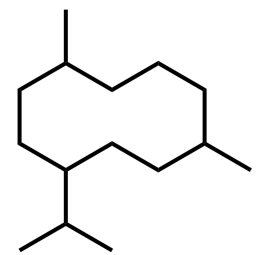


isoprene

× 3



bisabolan



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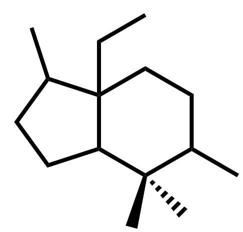
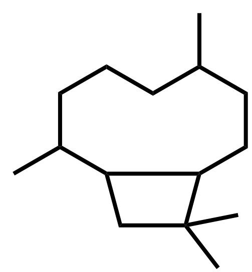


seco-prezizaane



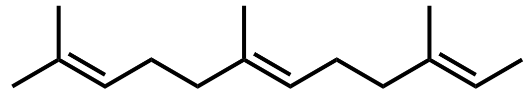
caryphyllan

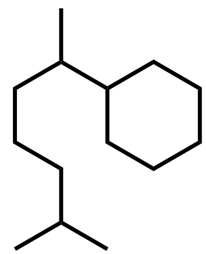
Introduction

Sesquiterpene

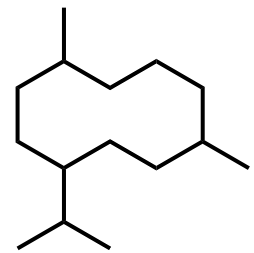
Illicium
(シキミ)

Sesquiterpene





bisabolan



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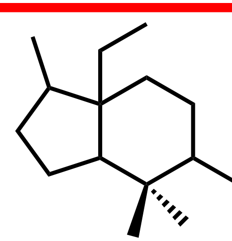

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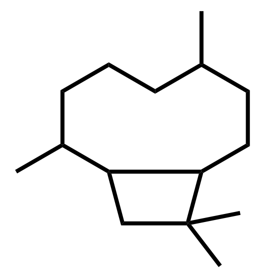
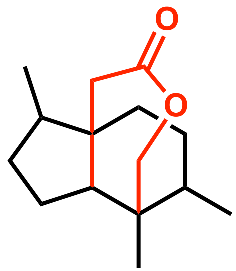


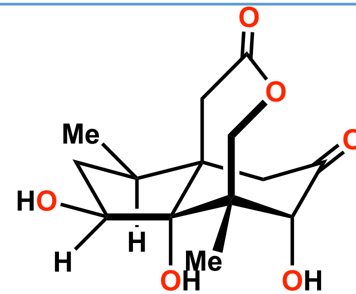
caryphyllan

Introduction

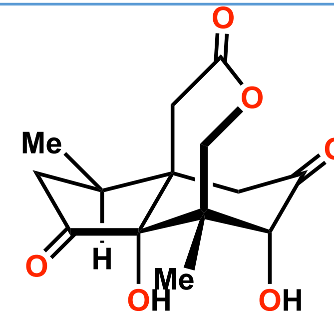
Illicium sesquiterpene family member subtypes



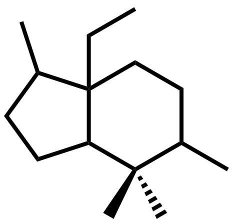
pseudoanisatinoids



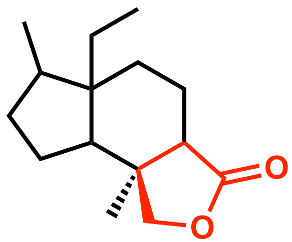
pseudoanisatin



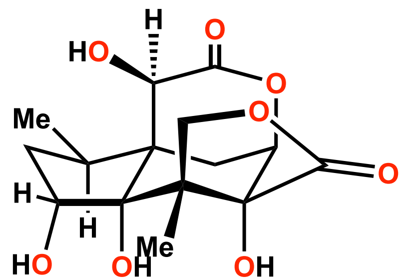
3-oxo-pseudoanisatin



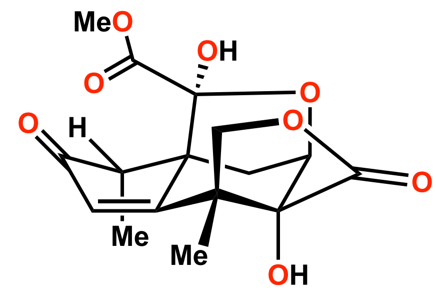
seco-prezizaane



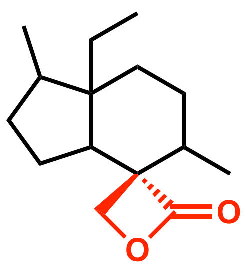
majucinoids



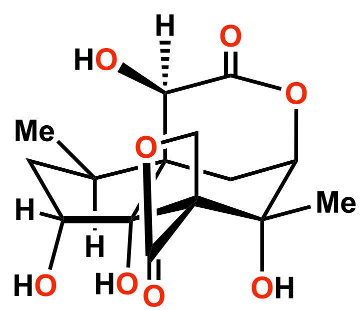
majucin



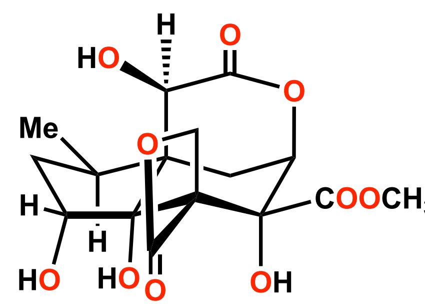
jiadifenin



anisatinoids



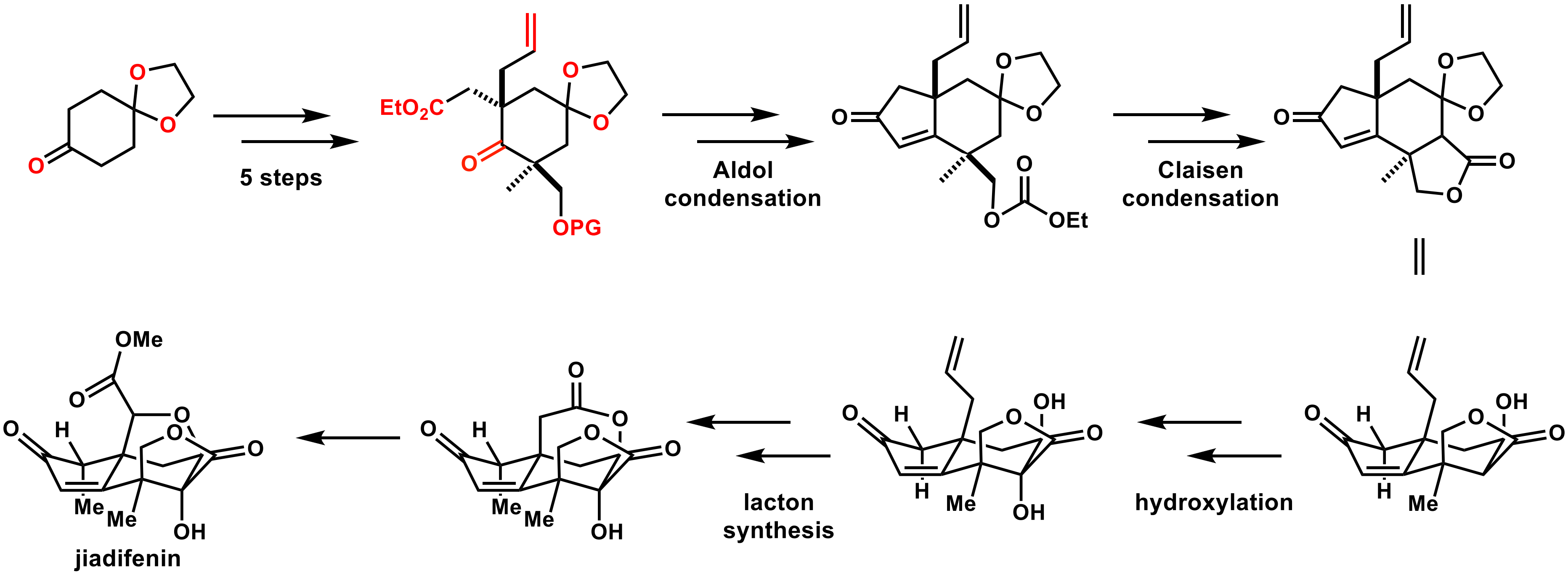
anisatin



veranisatins C

Introduction

Previous total-synthesis example

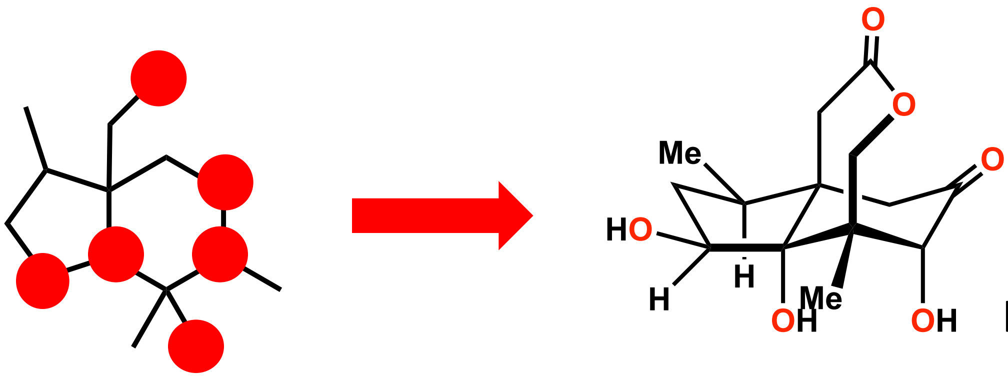


Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **2004**, *126*, 14358.

- Oxidized FG was installed at early stage.
- C-C bond formation reaction makes core skeleton of illicium sesquiterpene.

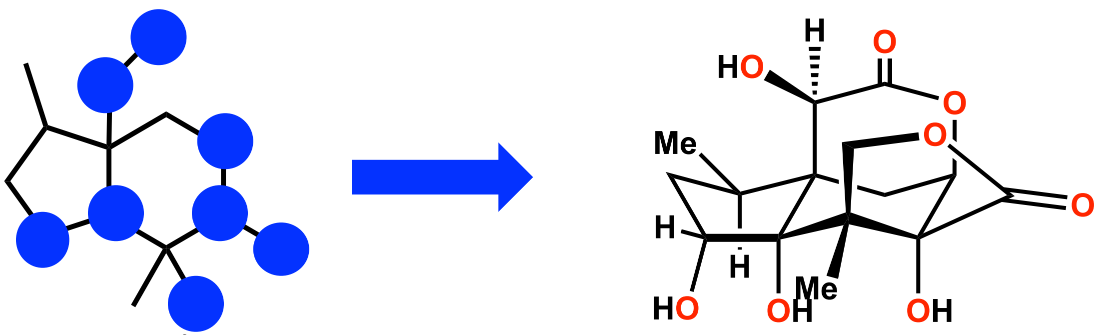
Introduction

Maimone's synthesis strategy by oxidation



seco-prezizaane

pseudoanisatin



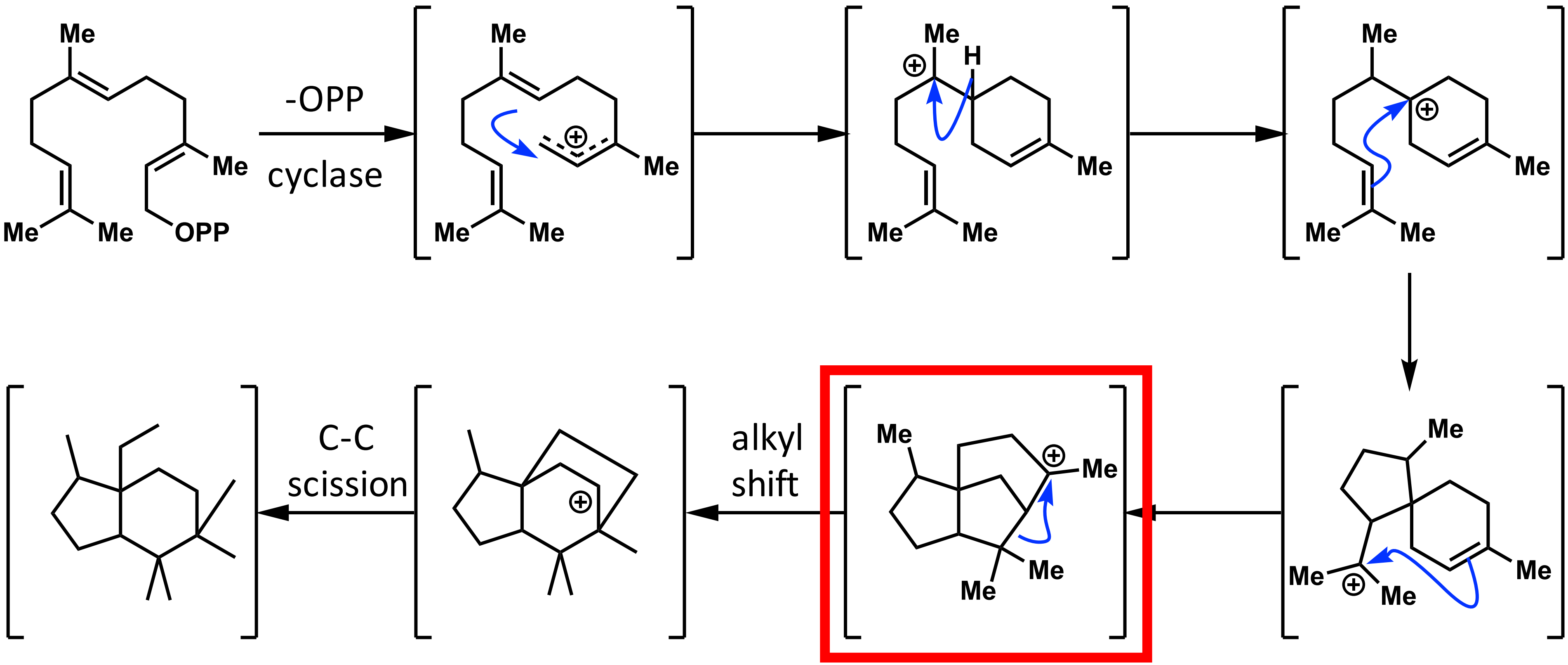
seco-prezizaane

majucin

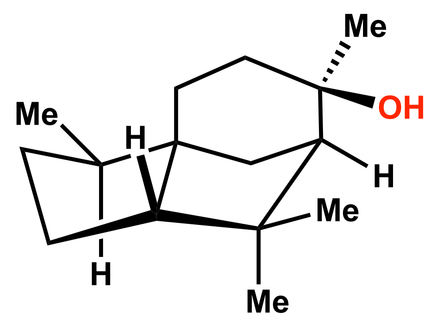
Direct C-H or C-C functionalization of seco-prezizaane skeleton would make short and diverse synthesis of illicium sesquiterpene.

Introduction

Proposed biosynthetic pathway



seco-prezizaane
skeleton



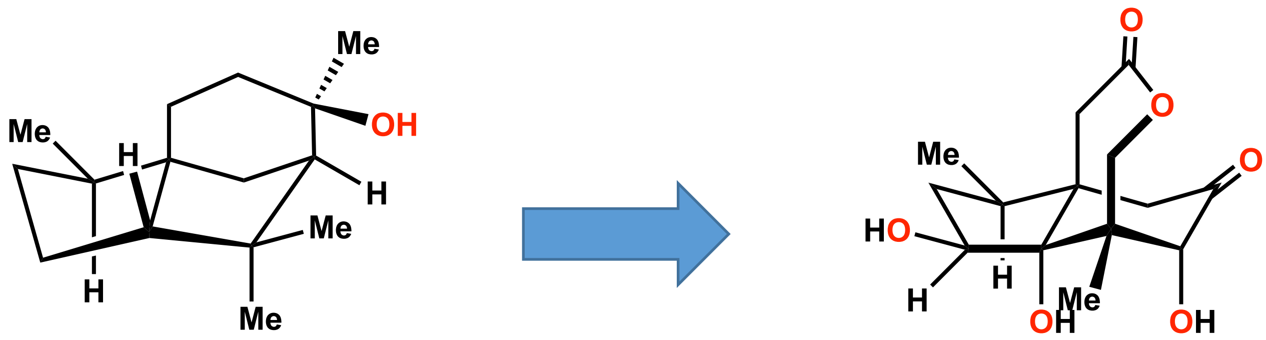
(+)-cedrol

$52 USD/kg

Fukuyama, Y.; Huang, J.-M. *Bioactive Natural Products (Part L)*; Studies in Natural Products Chemistry; Atta-ur-Rahman, Ed.; **2005**, Vol. 32, p 395.

Introduction

Synthesis strategy



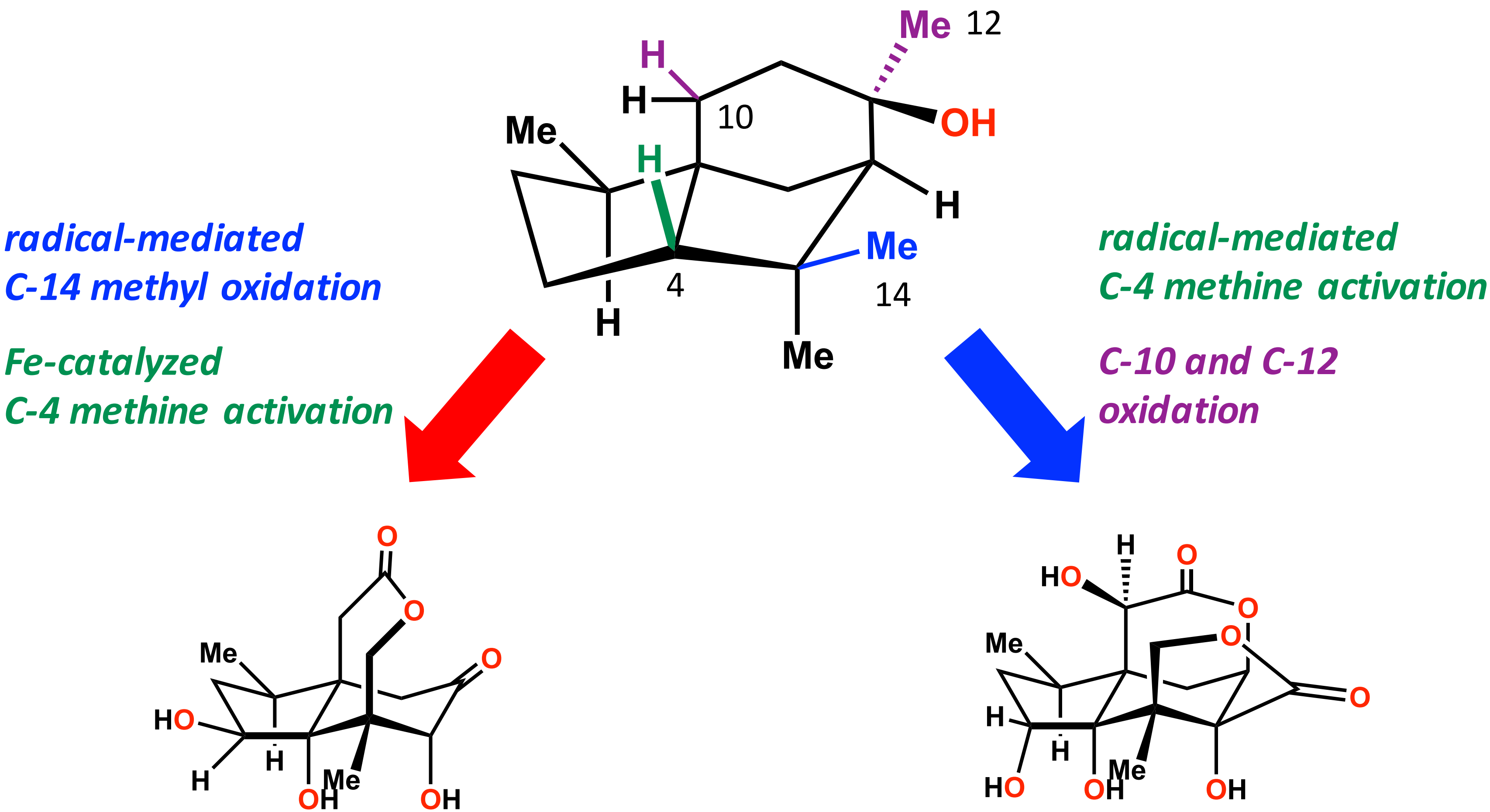
(+)-cedrol　　　　(+)-pseudoanisatin

$52 USD/kg

- Introduce position-selective hydroxyl groups based on nearby hydroxyl groups or carboxylic acids. (Redox-relay)
- Skeletal rearrangement by ring expansion and C−C cleavage .

Introduction

Synthesis strategy



(+)-pseudoanisatin

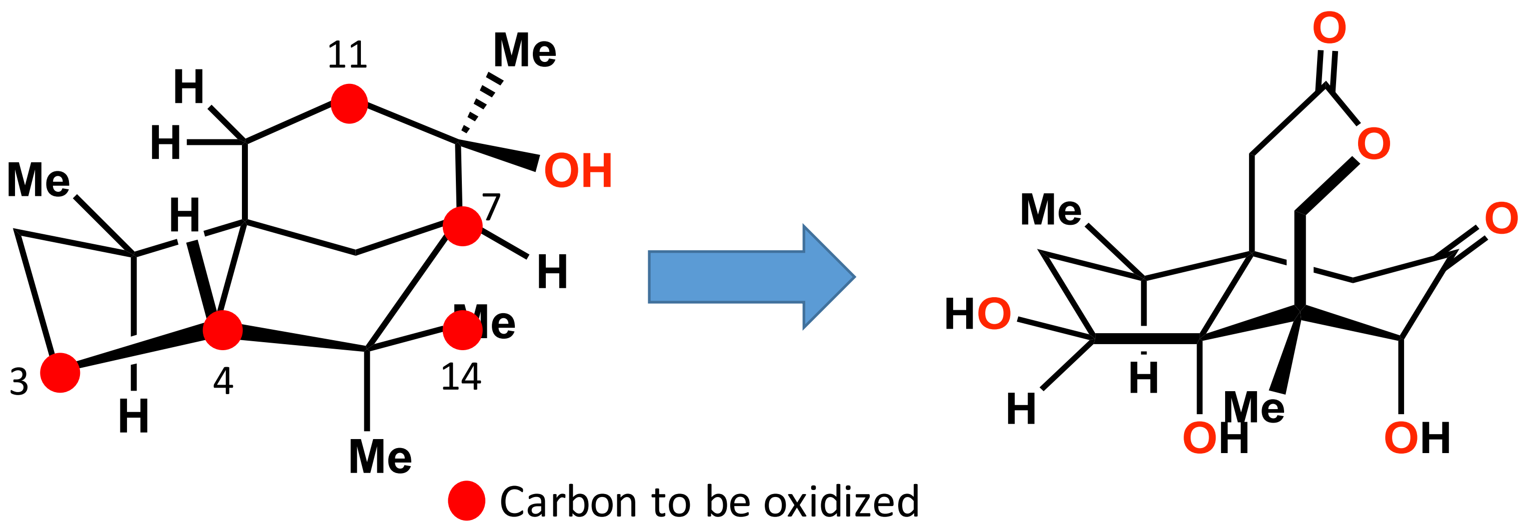
(-)-majucin

Synthesize differently according to oxidation order and location.

Contents

Pseudoanisatin

Key reaction



(1) C-14 oxidation by Suarez's radical-based method.

(2) Introduction of hydroxyl group to C-7 through acyloxylation with $CuBr_2$.

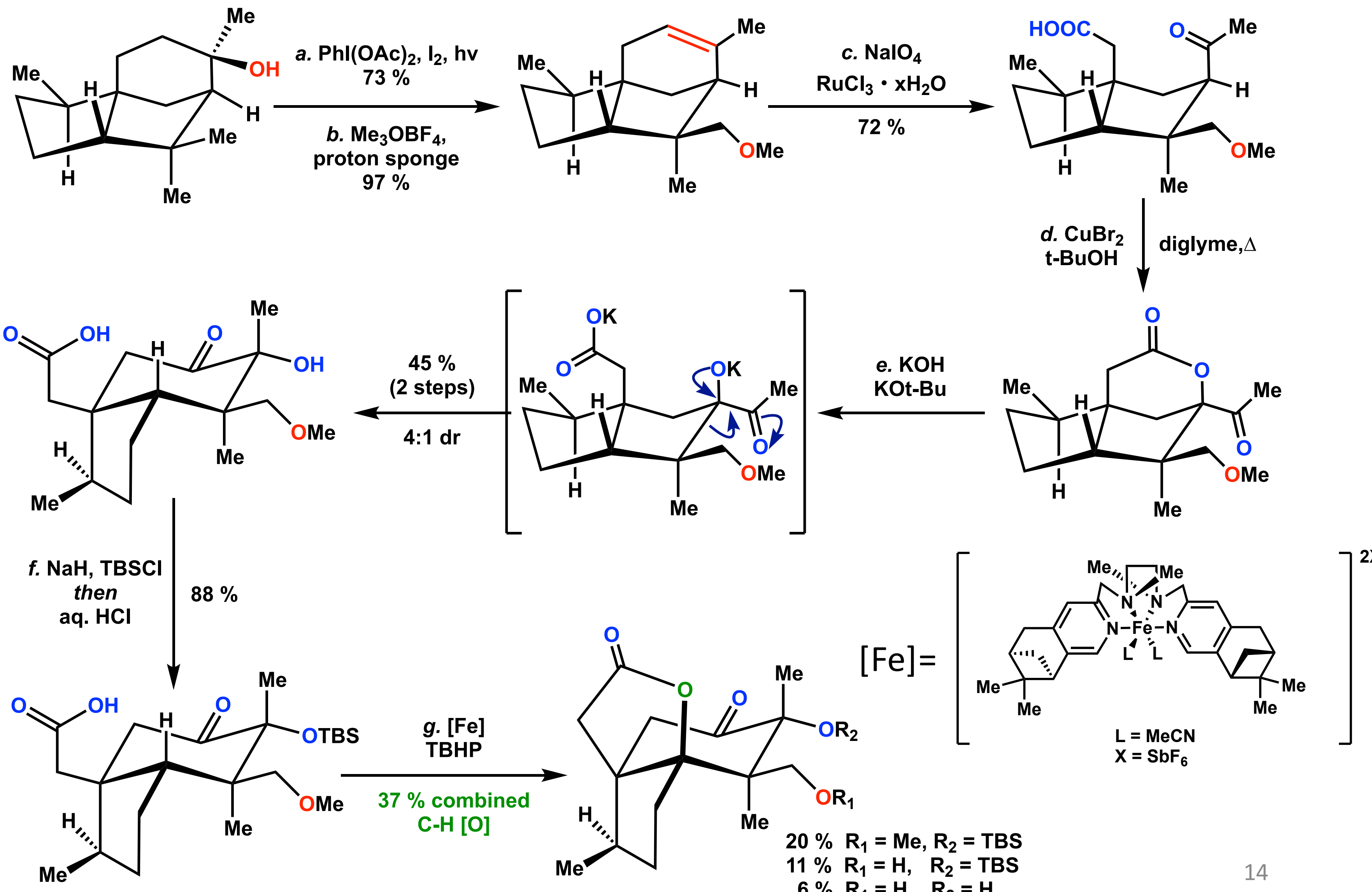
(3) α-Ketol rearrangement.

(4) Regioselective oxidation reaction using intramolecular carboxylic acid as directing group **at C-4 position**.

K. Hung, M. L. Condakes, T. Morikawa, T. J. Maimone, *J. Am. Chem. Soc.*, **2016**, *138*, 16616

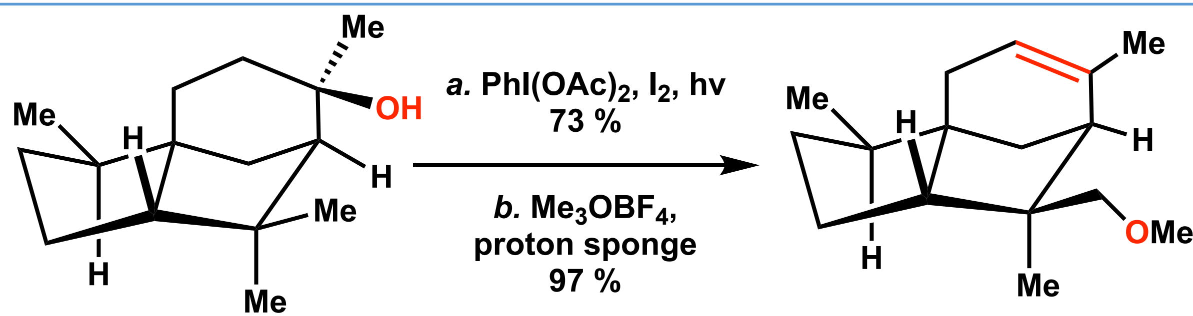
Pseudoanisatin

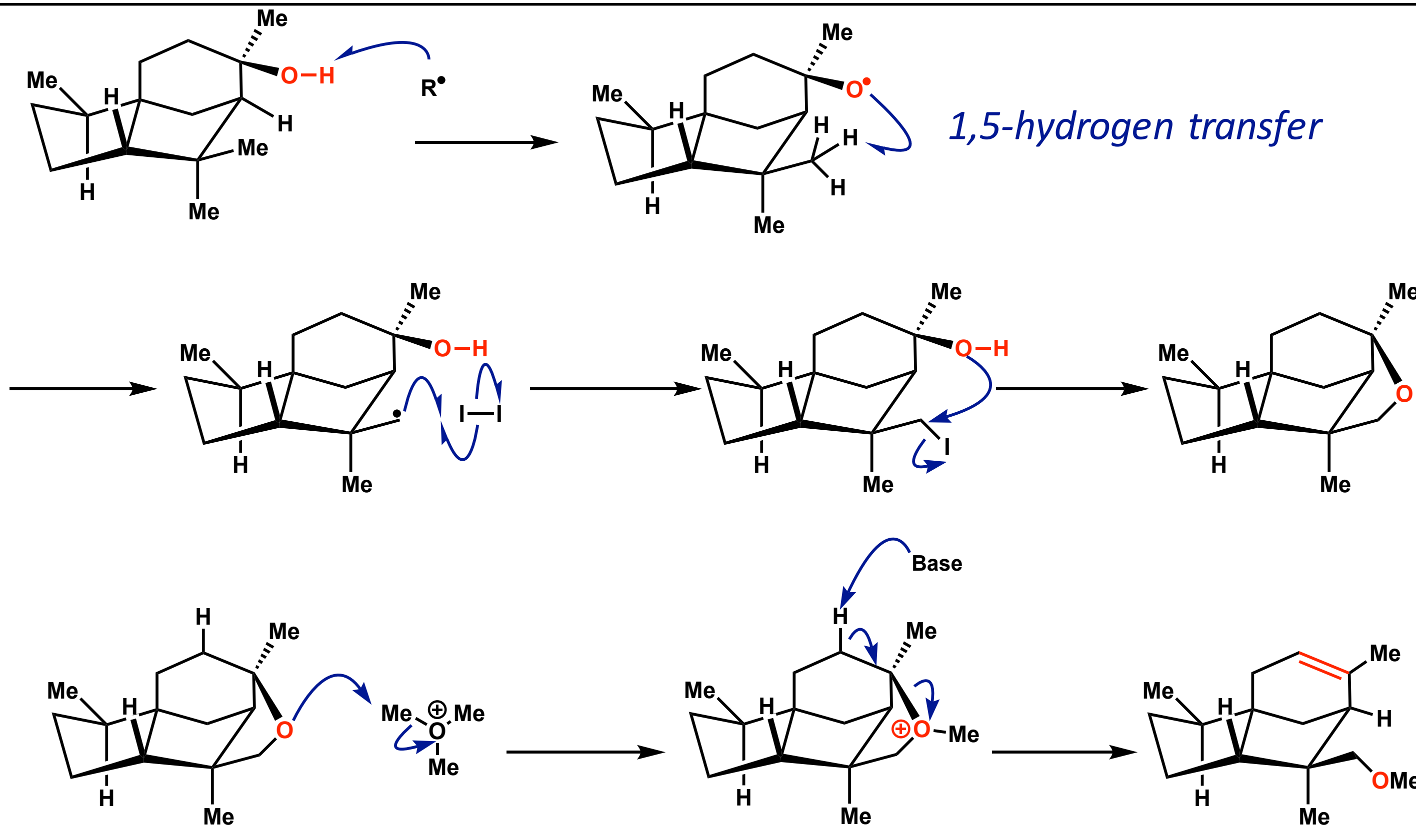
Synthesis scheme



Pseudoanisatin

Reaction mechanism

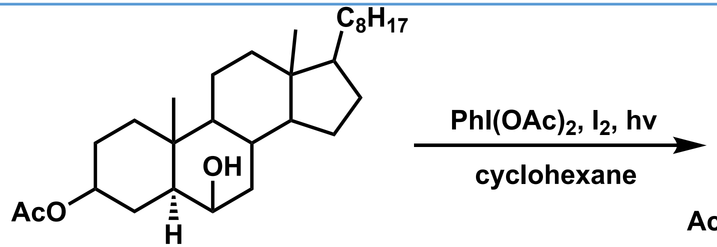




R. Baker, M.A. Brimble, J.A. Robinson, *Tetrahedron Lett.* , **1985**, *26*, 2115.

Pseudoanisatin

Suarez's radical-based method



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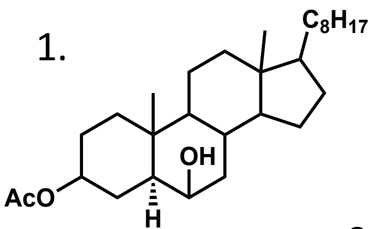

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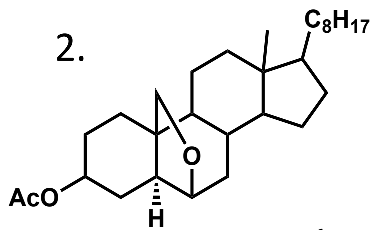

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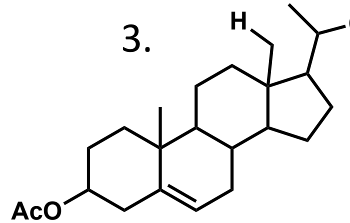

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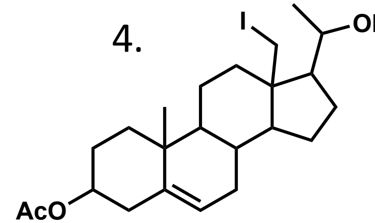

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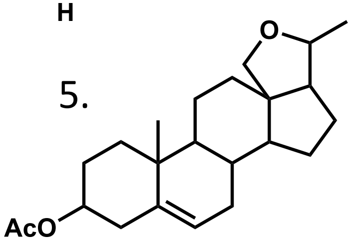

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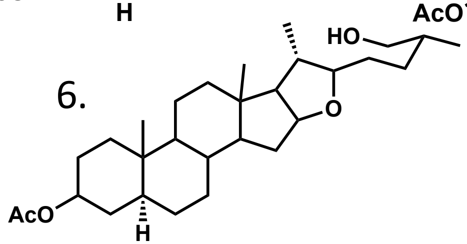

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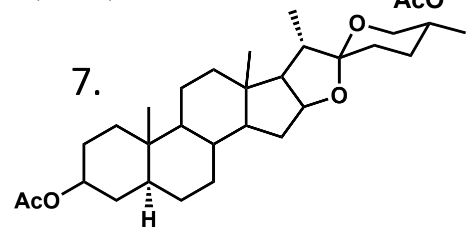
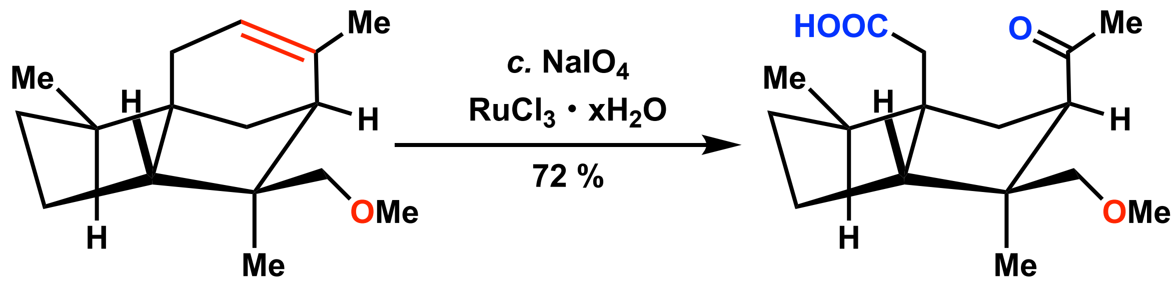


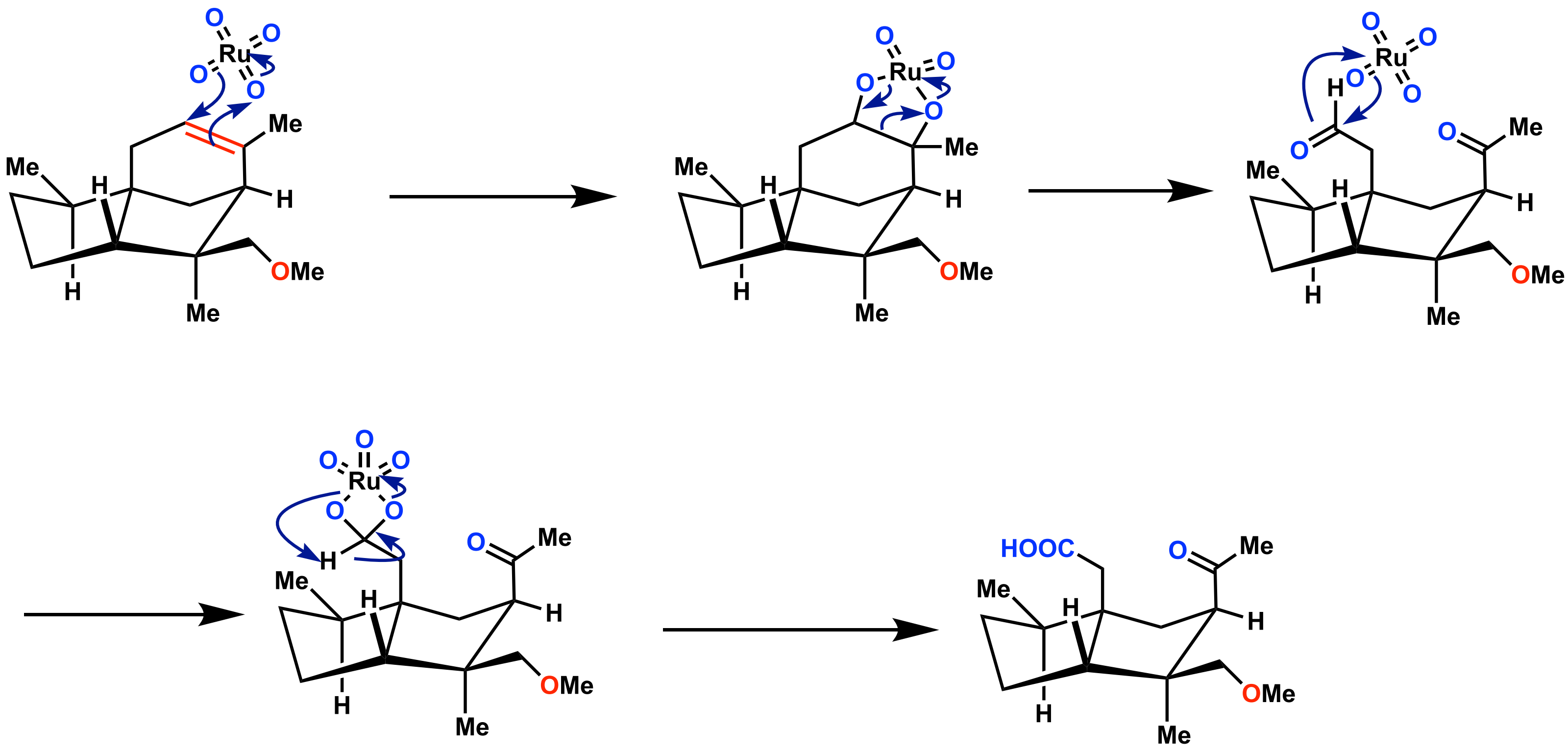
Entry	Alcohol (1 eq)	$PhI(OAc)_2/I_2$ (eq)	Time (min.)	Temperature (℃)	Product(Yield %)
1	1	1.1/1.0	50	40	2 (90)
2	1	1.1/0.0	120	40	No reaction
3	3	1.1/1.0	30	25	4 (53)
4	6	1.1/0.5	40	40	7 (90)

J.I. Concepcion, C.G. Francisco, R. Hernandez, J.A. Salazar, E. Suarez, *Tetrahedron Lett.* , **1984**, *25*, 1953.

Pseudoanisatin

Reaction mechanism

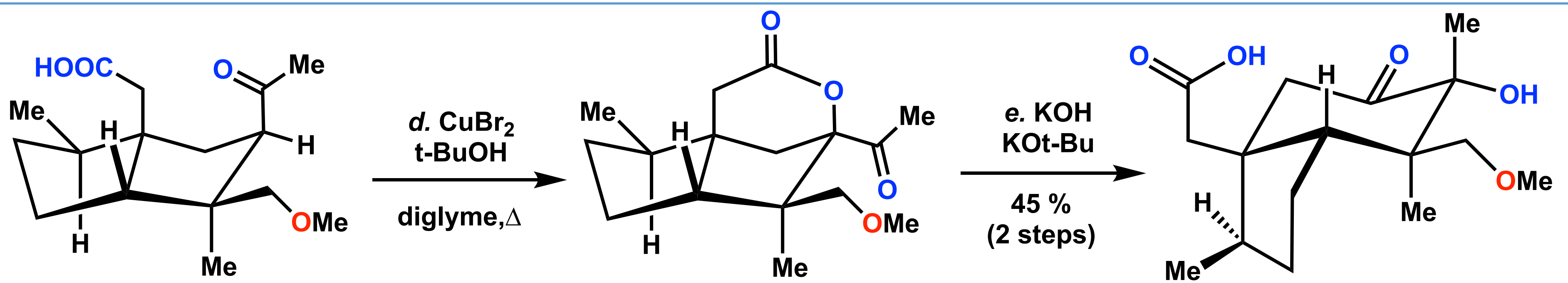


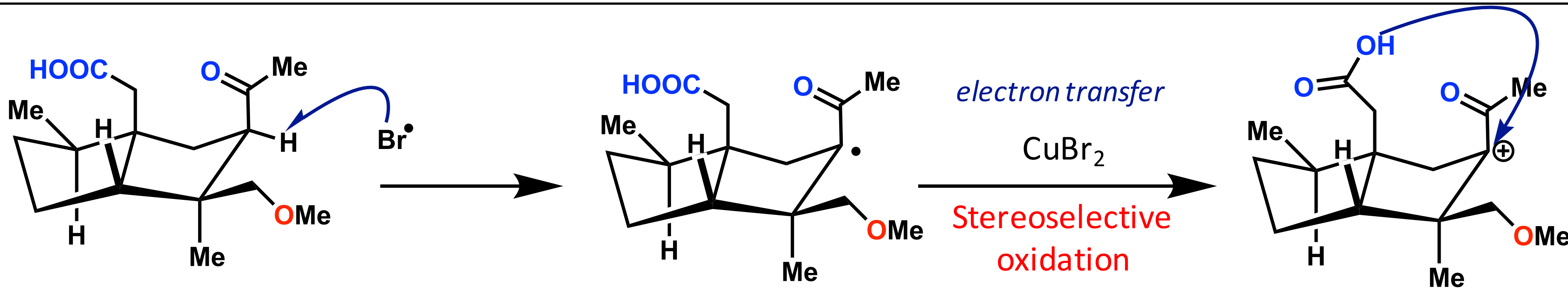


[O] was installed to two different position by 3 steps using C-6 -OH

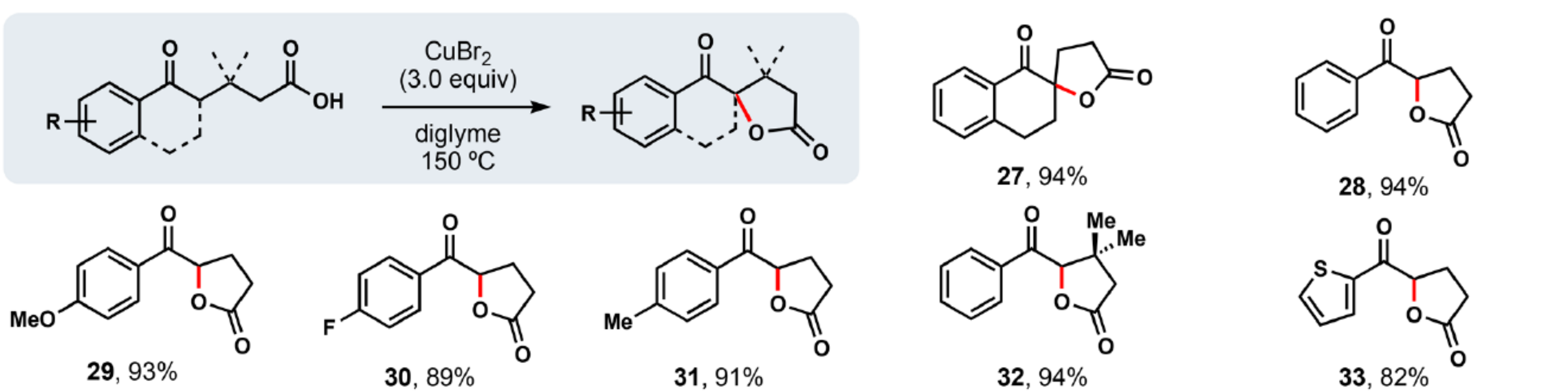
Pseudoanisatin

Reaction mechanism



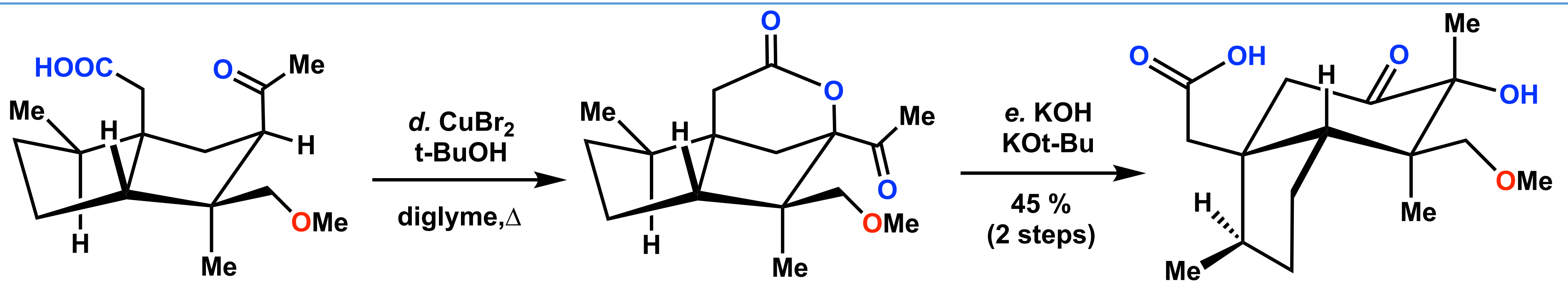


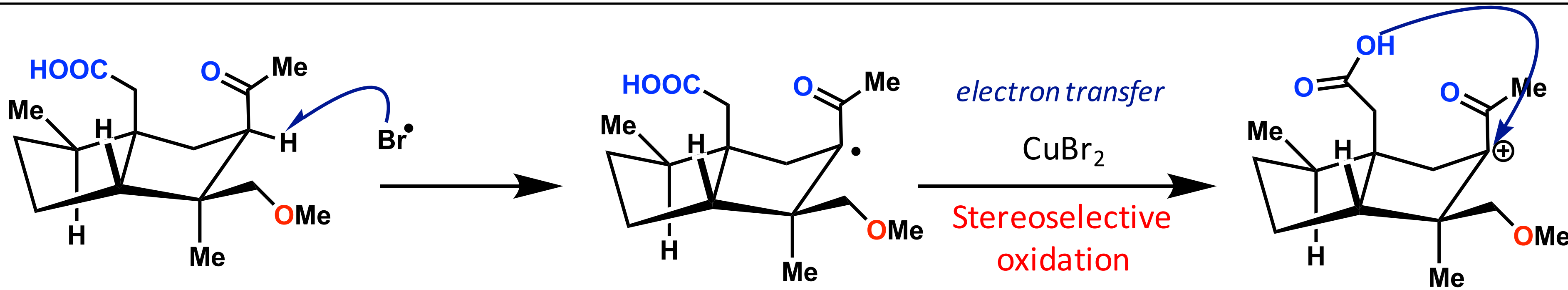
cf) substrate scope of oxidative lactonization (Maimone, T. J. et al. *JACS*, **2019**, *141*, 3083.)



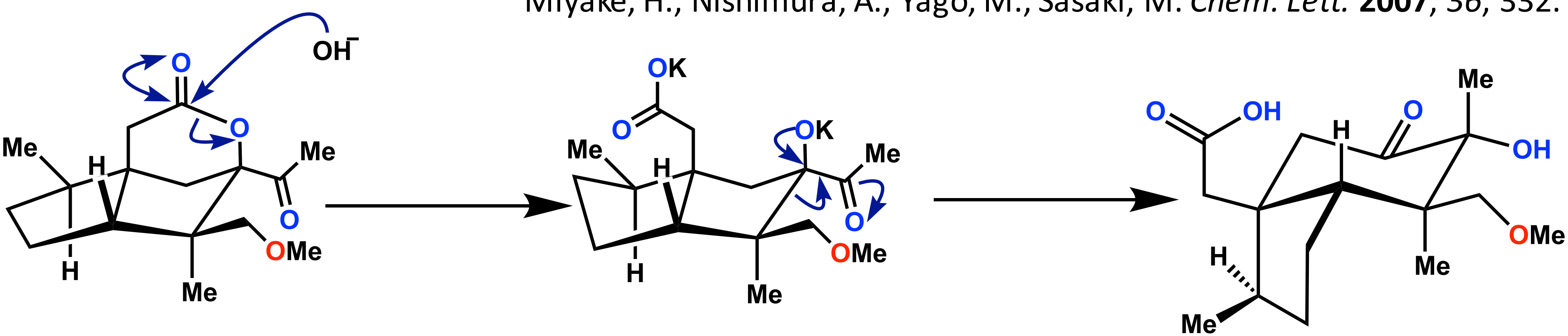
Pseudoanisatin

Reaction mechanism



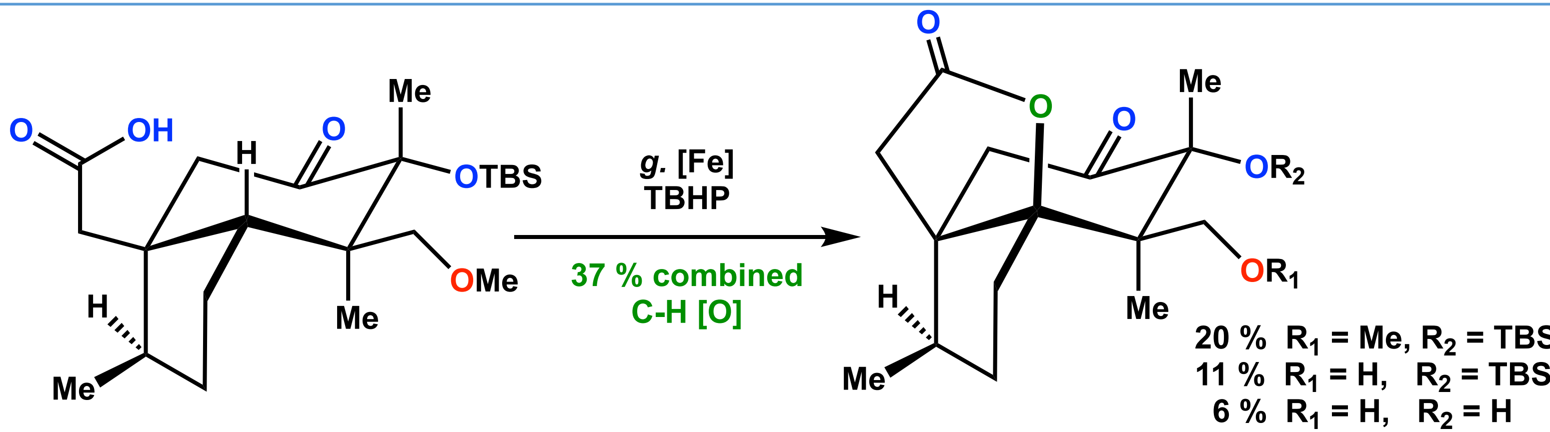


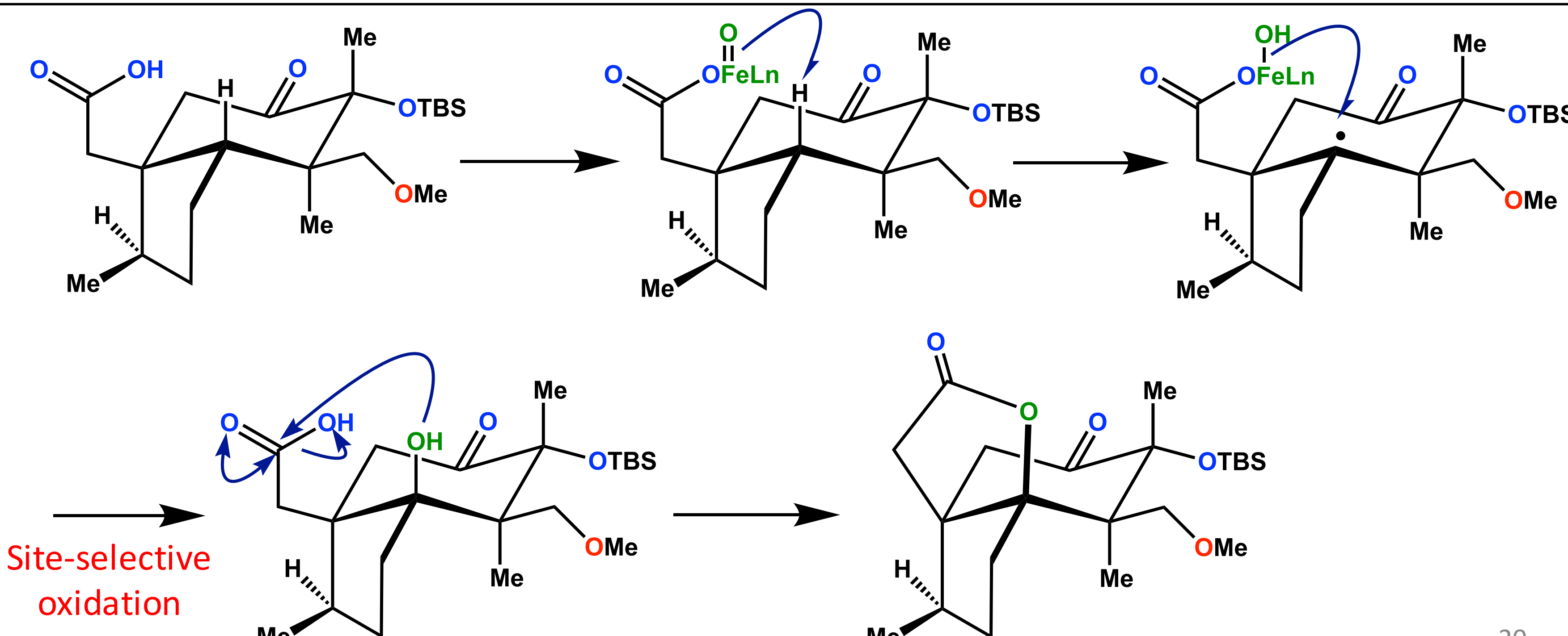
Miyake, H.; Nishimura, A.; Yago, M.; Sasaki, M. *Chem. Lett.* **2007**, *36*, 332.



Pseudoanisatin

Reaction mechanism

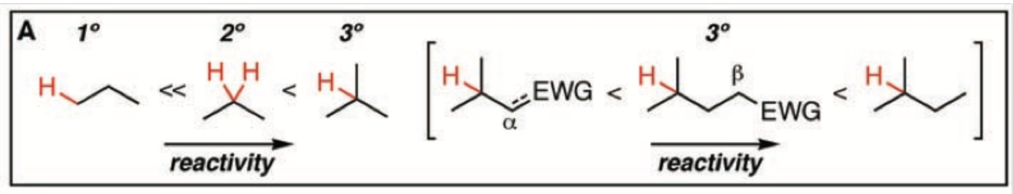


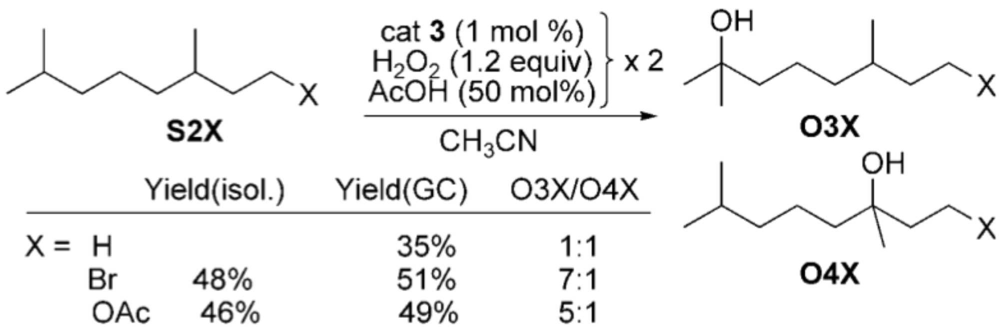


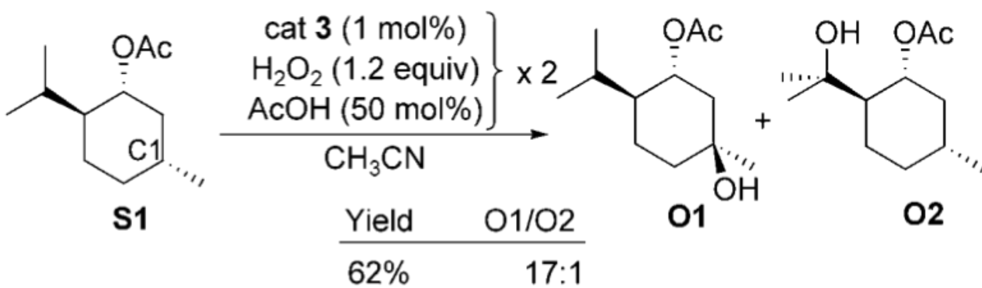
M. A. Bigi, S. A. Reed, M. C. White, *J. Am. Chem. Soc.*, **2012**, *134*, 9721.

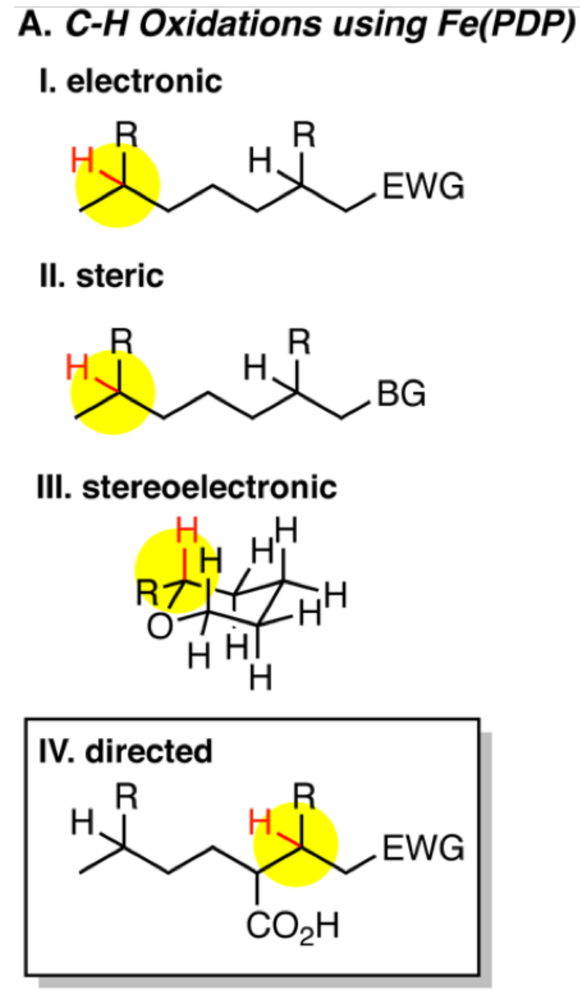
Pseudoanisatin

C-H oxidation by iron complexes









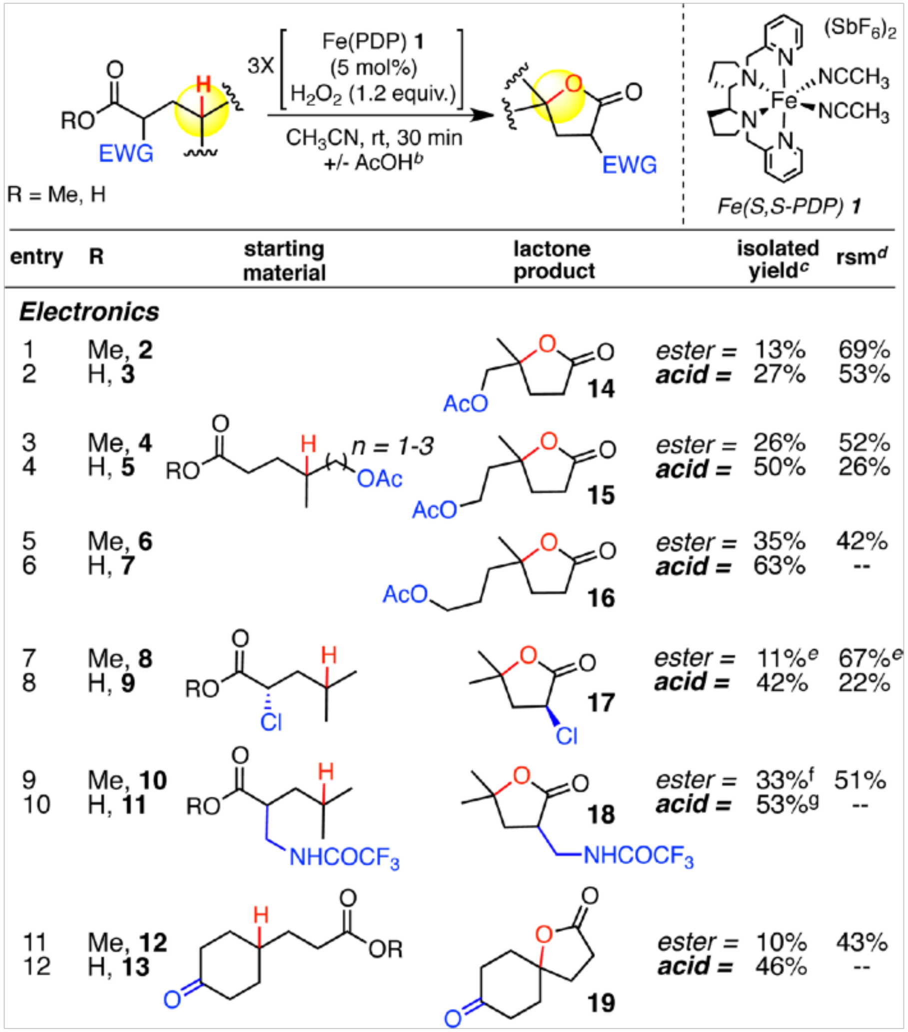
cat3 = [$Fe(CF_3SO_3)_2$((S,S,R)-mcpp)]

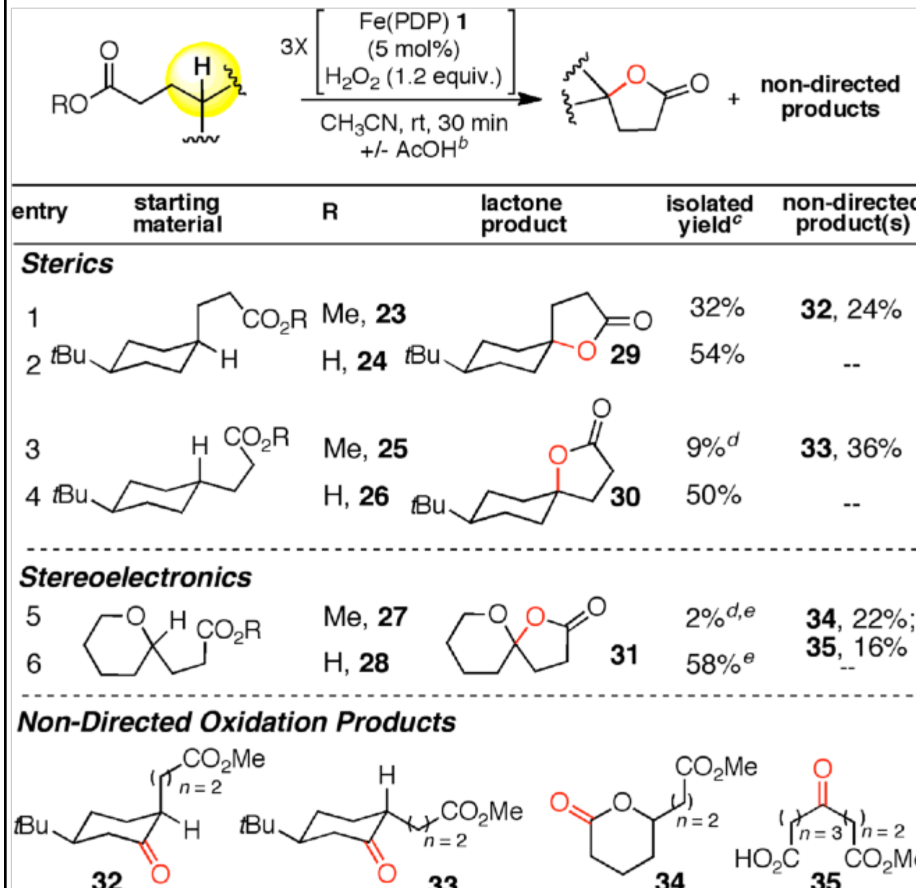
L. Gómez, I. Garcia-Bosch, A. Company, J. Benet-Buchholz, A. Polo, X. Sala, X. Ribas, M. Costas, *Angew. Chem. Int. Ed.*, **2009**, *48*, 5720.

M. A. Bigi, S. A. Reed, M. C. White, *J. Am. Chem. Soc.*, **2012**, *134*, 9721.

Pseudoanisatin

C-H oxidation by iron complexes



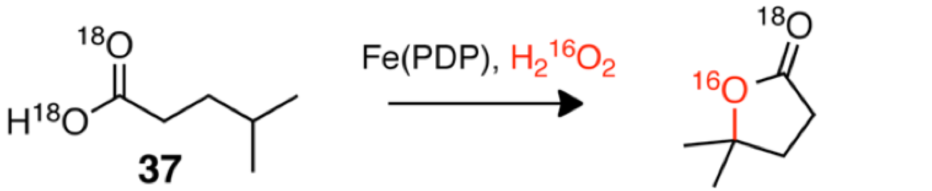


M. A. Bigi, S. A. Reed, M. C. White, *J. Am. Chem. Soc.*, **2012**, *134*, 9721.

Pseudoanisatin

C-H oxidation by iron complexes

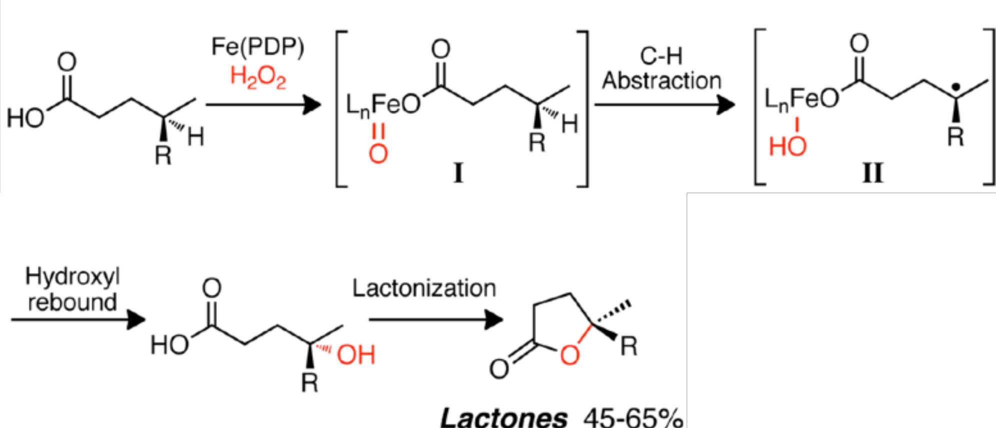
B. Labeling study supports hydroxyl rebound/lactonization.



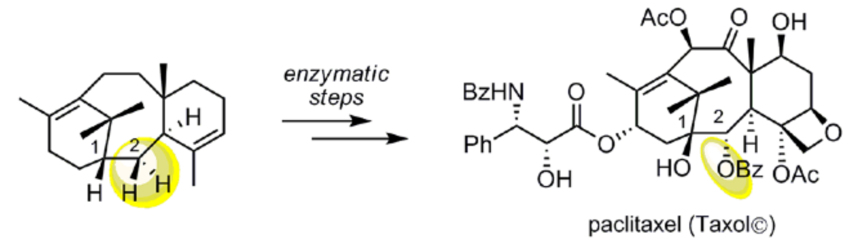
88% doubly ^{18}O labeled

87% singly ^{18}O labeled

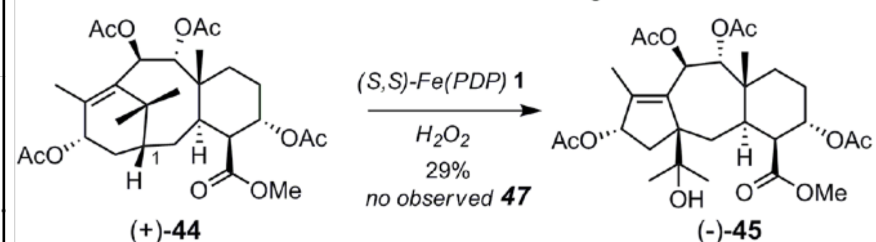
A. Proposed mechanism of Fe(PDP)-catalyzed C-H lactonization.



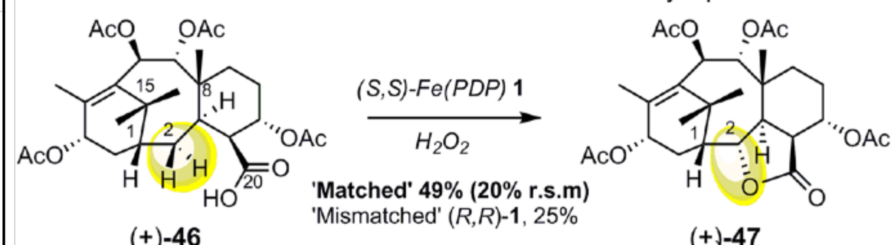
A. Biosynthesis of Taxol: oxidative tailoring of a hydrocarbon core



B. Non-directed: C—H abstraction at C1/rearrangement/OH rebound



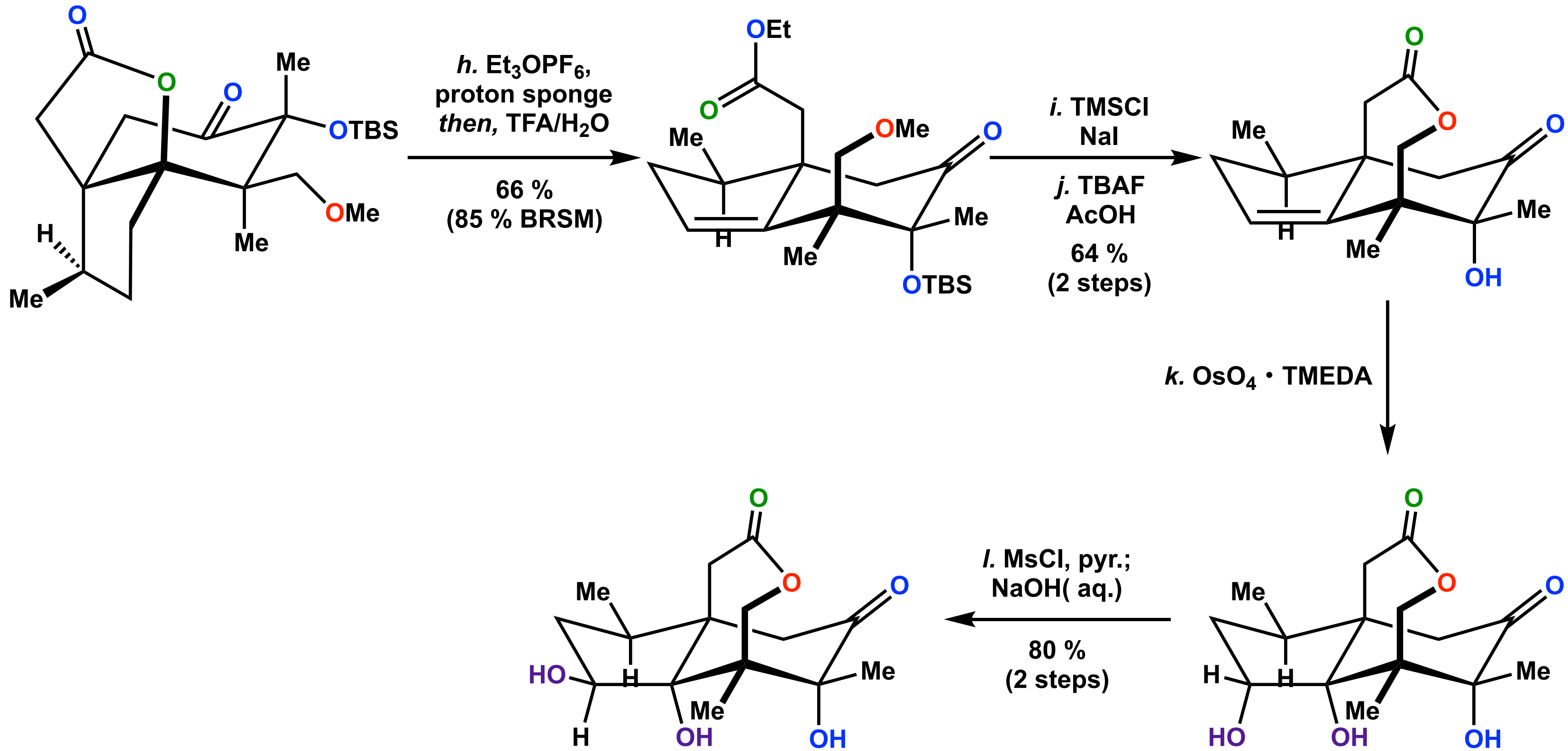
C. Directed oxidation leads to the C2 lactone as the major product



M. A. Bigi, S. A. Reed, M. C. White, *J. Am. Chem. Soc.*, **2012**, *134*, 9721.

Pseudoanisatin

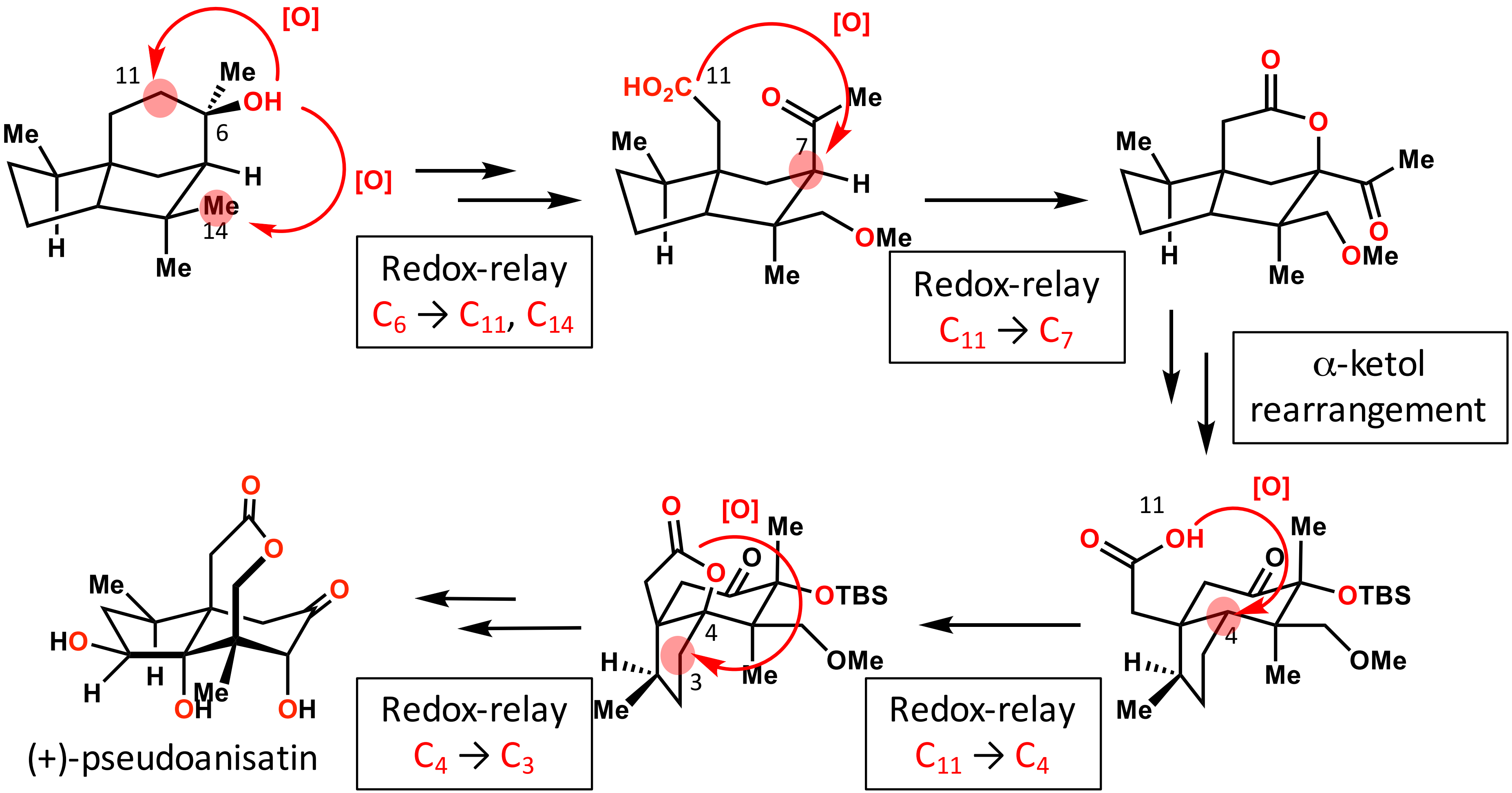
Synthesis scheme



(+)-pseudoanisatin

Pseudoanisatin

Summary of Pseudoanisatin synthesis

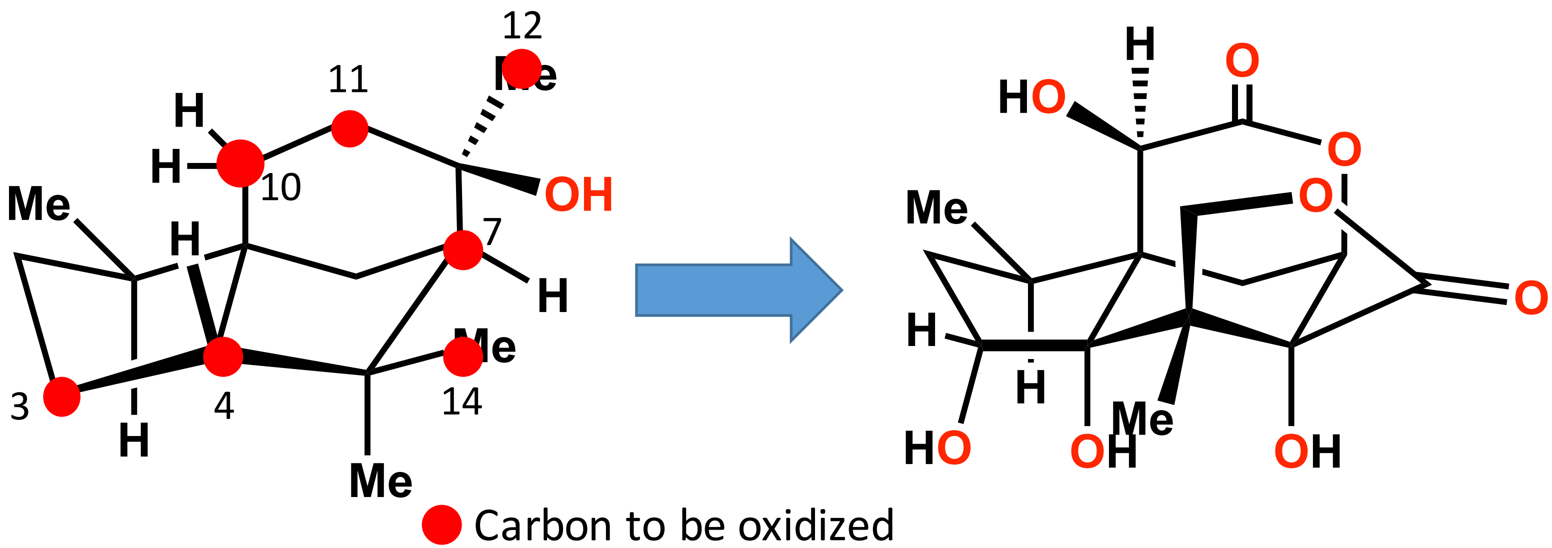


- (+)-Pseudoanisatin was synthesized by fully oxidative strategy.
- Is this strategy applicable for other illicium sesquiterpenes?

Contents

Majucin

Key reaction



(1) C-4 selective oxidation by Suarez's radical-based method.

(2) C-7 & C-12 oxidation by SeO_2 without H_2O.

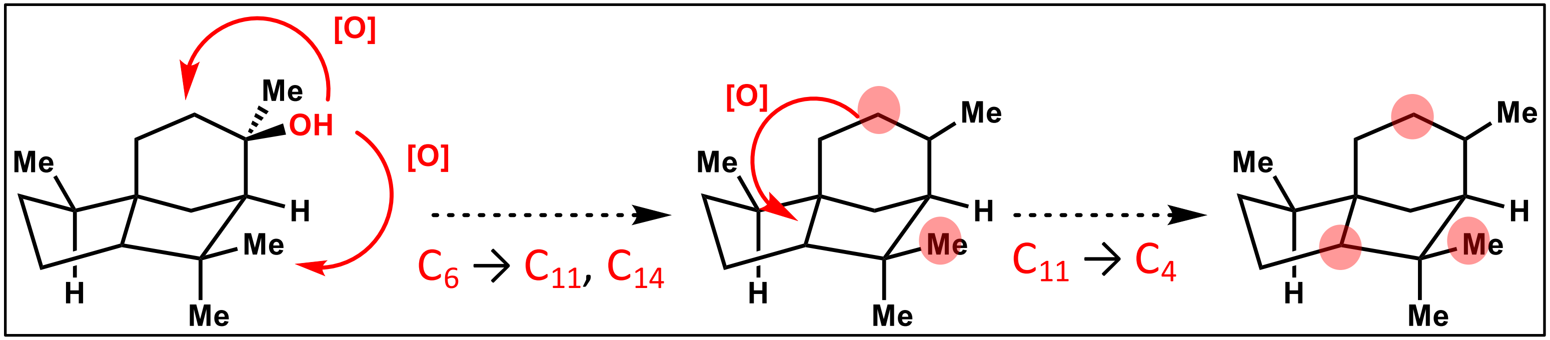
(3) α-ketol rearrangement.

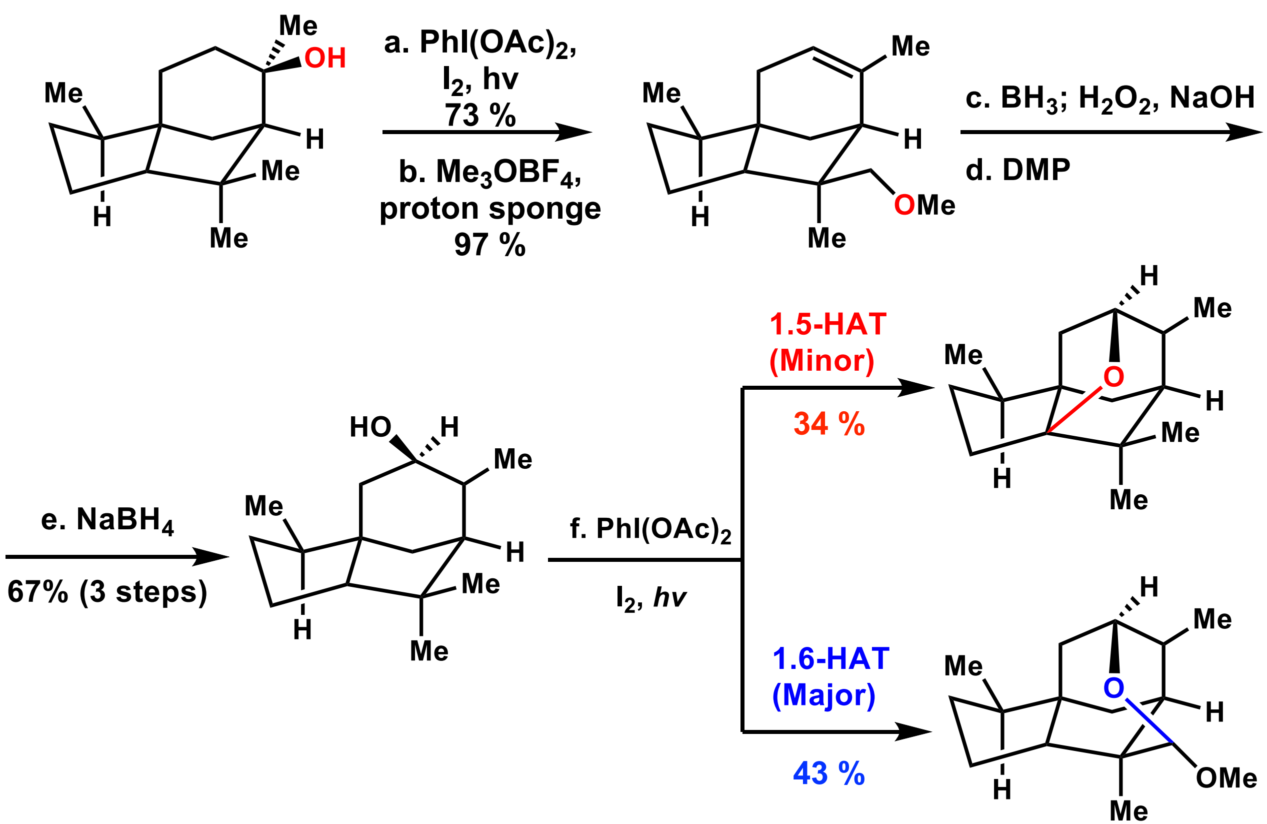
(4) C-10 oxidation.

M. L. Condakes, K. Hung, S. J. Harwood, T. J. Maimone, *J. Am. Chem. Soc.*, **2017**, *139*, 17783

Majucin

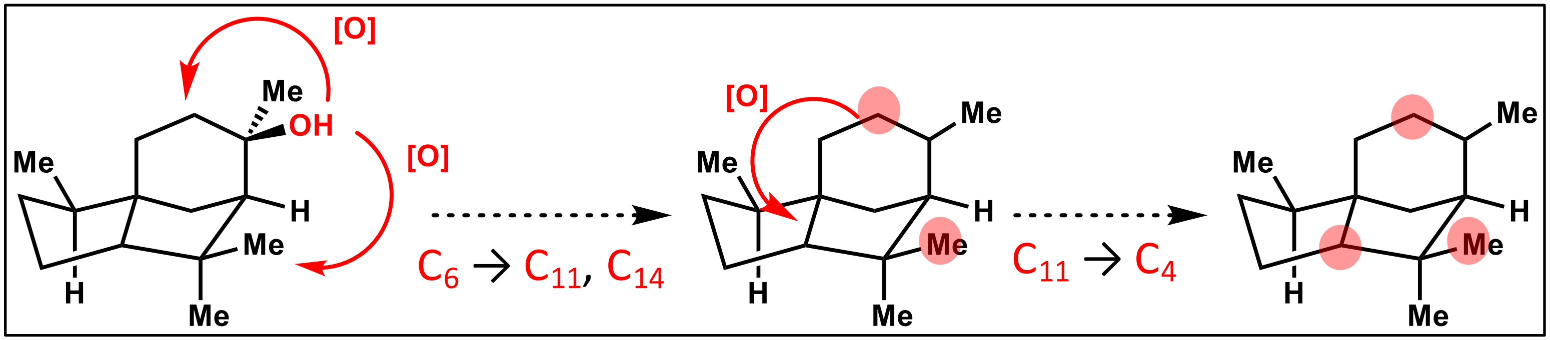
First trial: $C_6 \rightarrow C_{11}, C_{14} \rightarrow C_4$

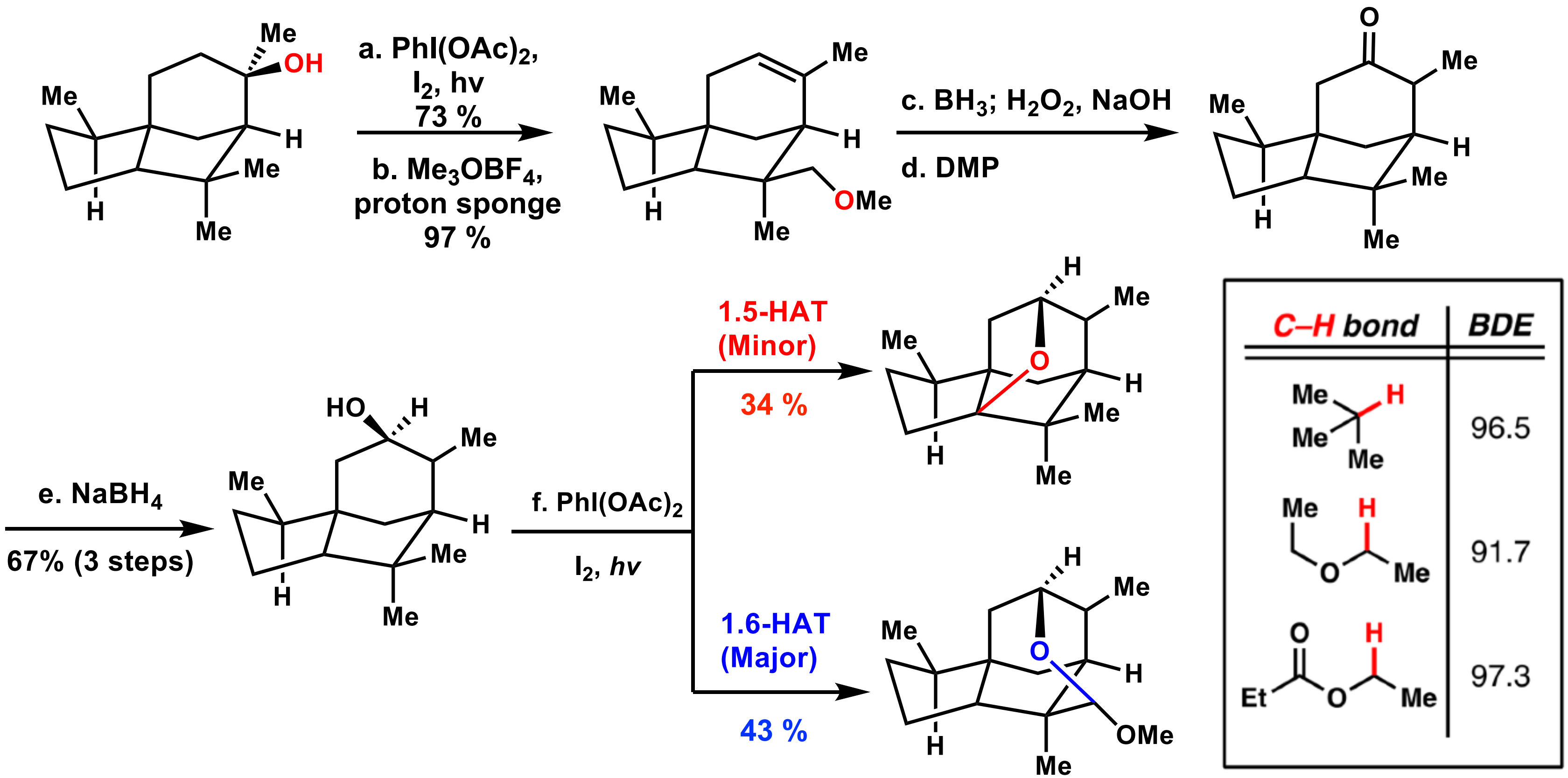




Majucin

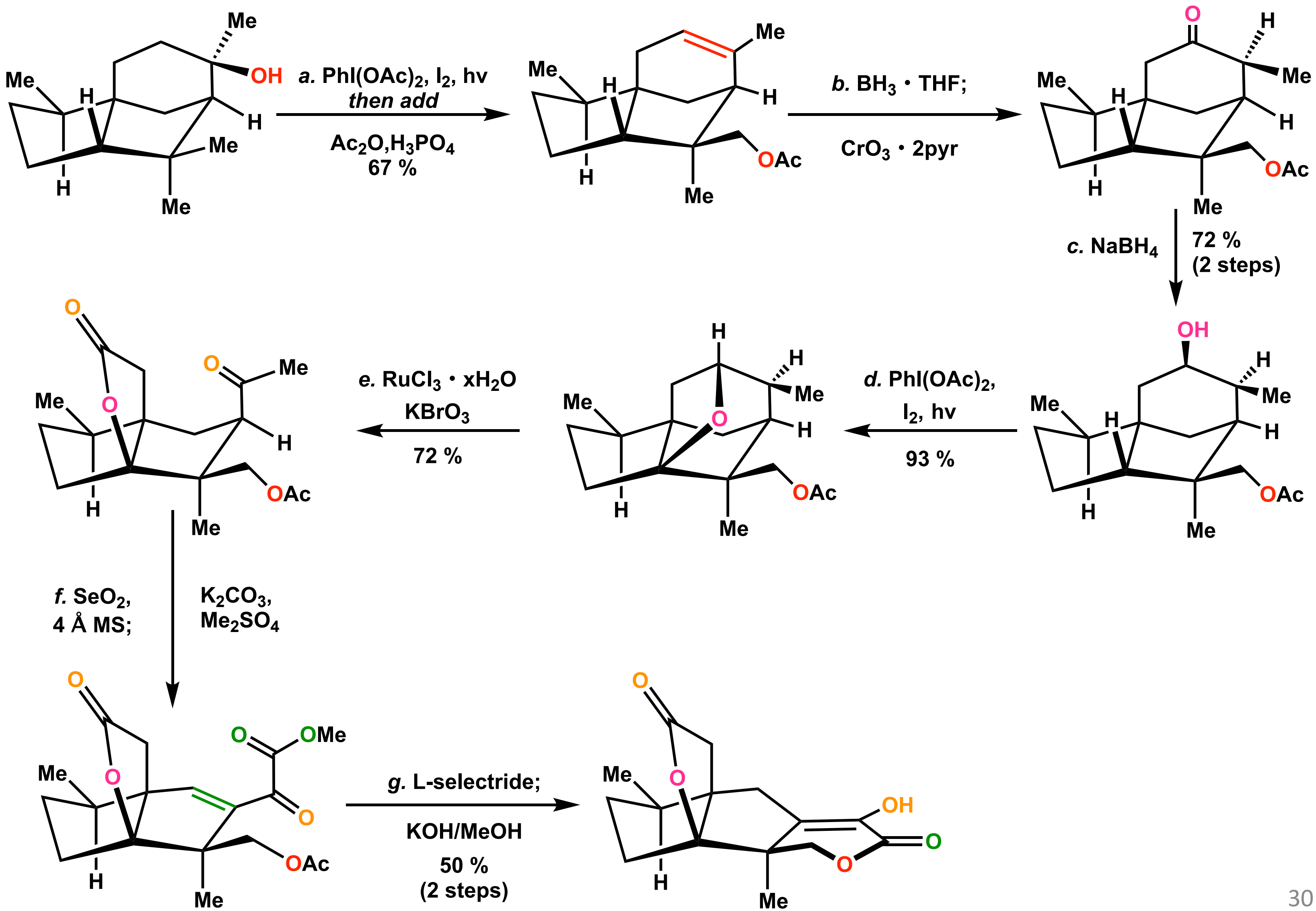
First trial: $C_6 \rightarrow C_{11}, C_{14} \rightarrow C_4$





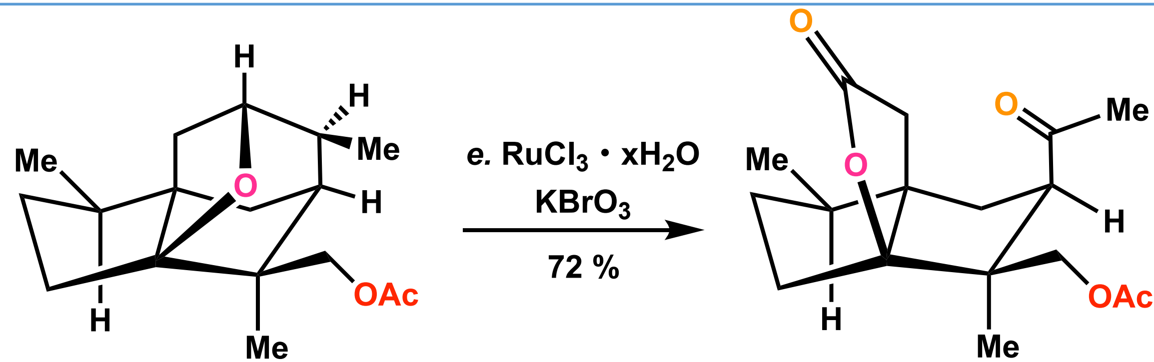
Majucin

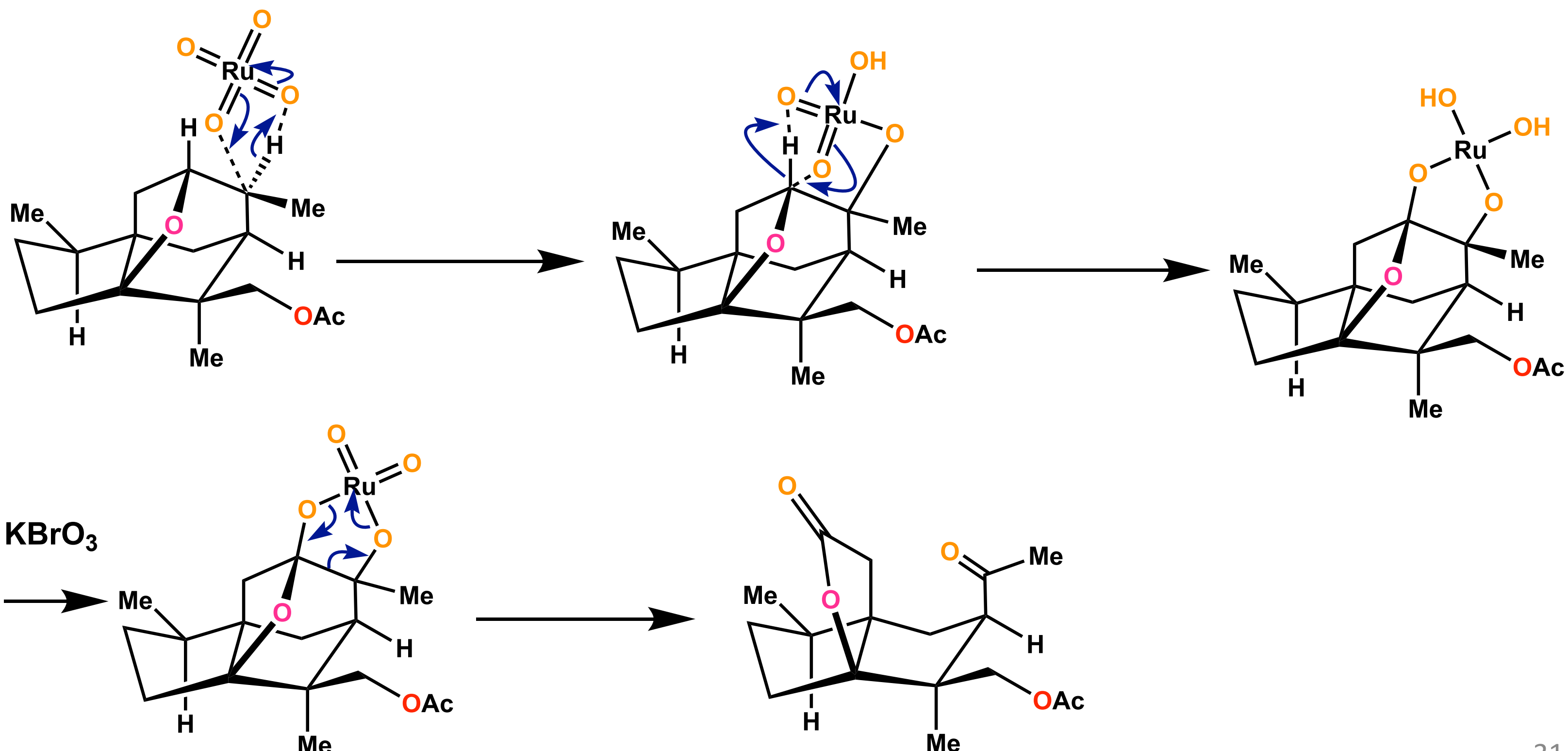
Synthesis scheme



Majucin

Reaction mechanism



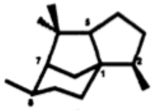
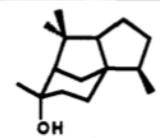
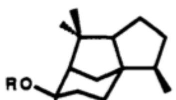
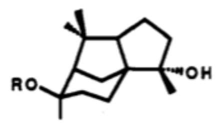
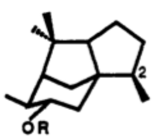
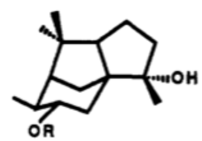
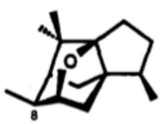
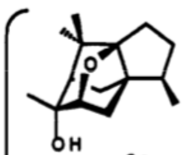
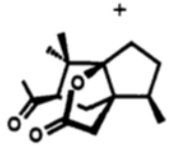


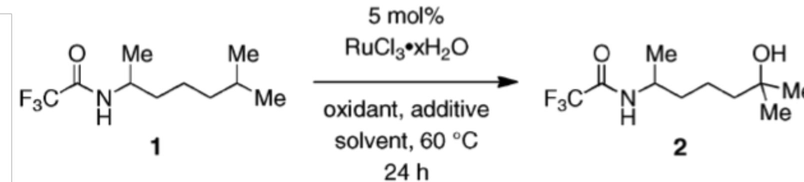
A. Tenaglia, E. Terranova, B. Waegel , *J. Org. Chem.*, **1992**, *57*, 5523.

Majucin

C-H oxidation by RuO_4

Table I. RuO_4-Catalyzed Oxidation of Cedrane and Derivatives

entry	starting compound	reaction conditions: temp (°C)	reaction conditions: time (d)	reaction conditions: $NaIO_4$ (equiv)	product(s)	yield (%)
1	 1	25	1.25	4	 1a	69
2	 2 R = H	70	1	4	 2a	29
3	3 R = Ac	55	1	4	3a	53
4	 4 R = Ac	55	5	7	 4a	33
5	5 R = CO_2Me	50	3	7.5	5a	35
6	 6	70	2	4	 6a +  6b	48 (6a), 20 (6b)
7	6a	70	2	4	6b	80
8	6	65	4	14	6b	80

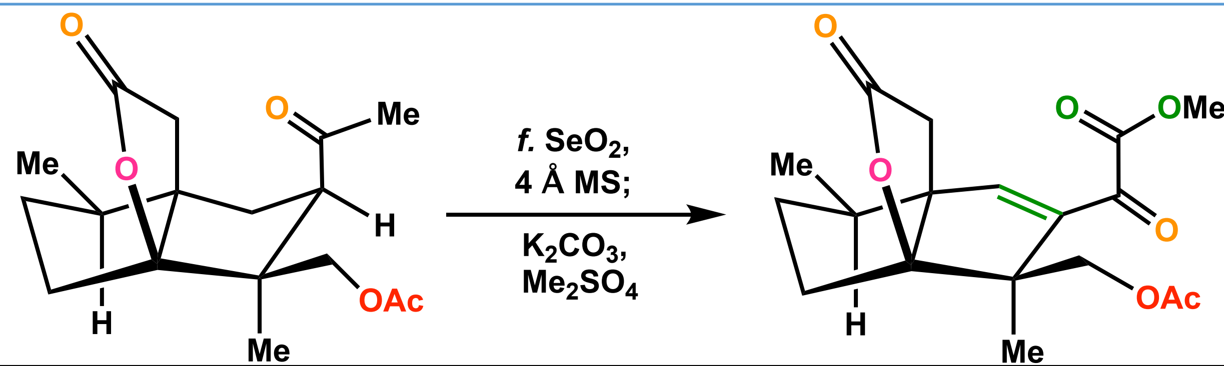


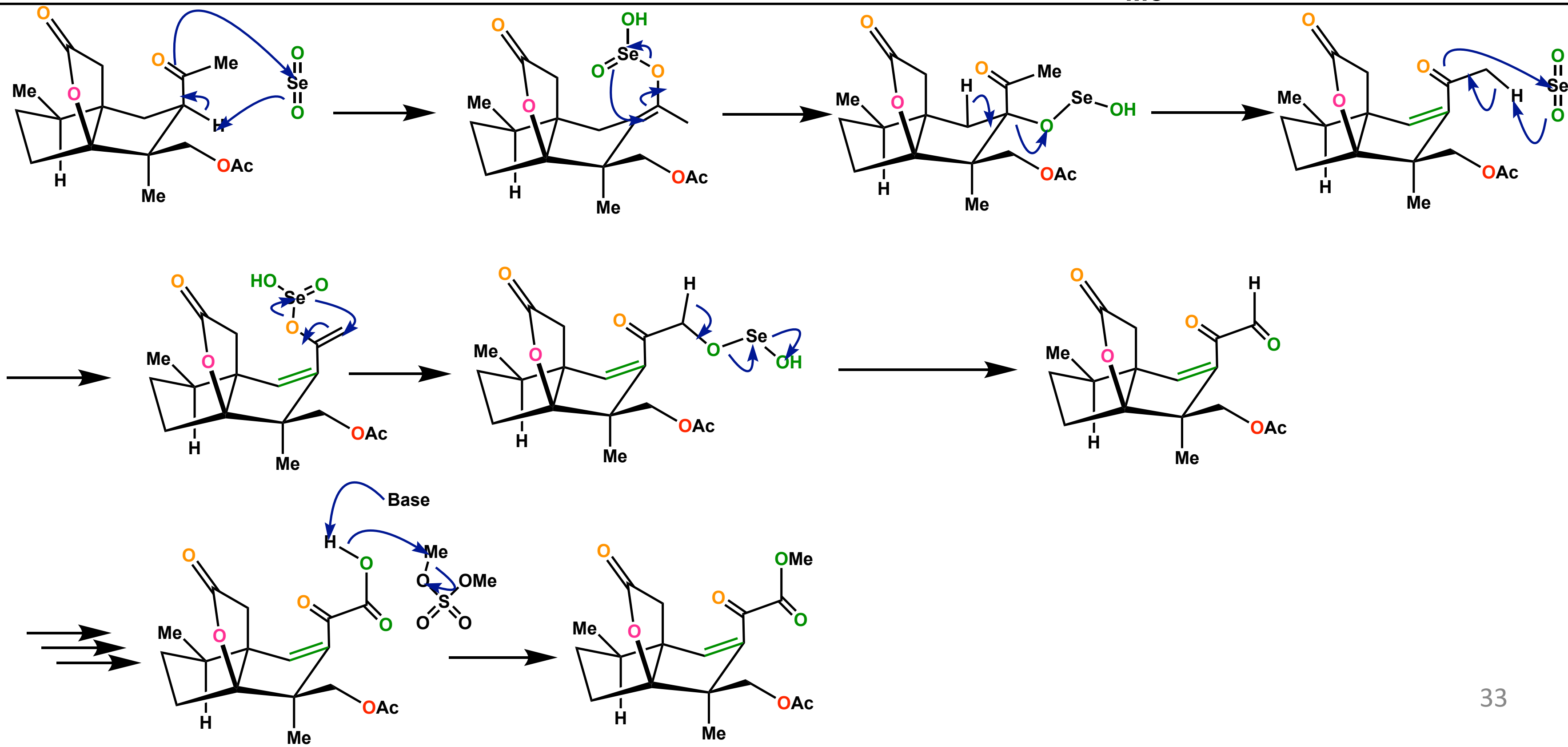
Entry	Oxidant	Solvent	Additive	Conv[b]
1	$NaIO_4$	$CCl_4/MeCN/H_2O$	none	25
2	$NaIO_4$	EtOAc/MeCN/aq. $H_2PO_4^-$	none	35
3	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	none	15
4	$NaIO_4$	EtOAc/MeCN/aq. $H_2PO_4^-$	pyridine	50
5	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	pyridine	70(62)
6	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	quinuclidine	<5
7	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	imidazole	20
8	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	pyridazine	25
9	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	pyrazine	<5
10	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	2,2-bpy	0
11	$KBrO_3$	EtOAc/MeCN/aq. $H_2PO_4^-$	pyr N-oxide	30
12	Oxone	EtOAc/MeCN/aq. $H_2PO_4^-$	pyridine	<5
13	NaOCl	EtOAc/MeCN/aq. $H_2PO_4^-$	pyridine	15
14	$KBrO_3$	$CCl_4/MeCN/H_2O$	pyridine	35
15	$KBrO_3$	$EtOAc/MeCN/H_2O$	pyridine	75(67)
16	$KBrO_3$	$MeOAc/MeCN/H_2O$	pyridine	80(73)
17	**$KBrO_3$**	**$MeCN/H_2O$**	**pyridine**	**75(74)**

A. Tenaglia, E. Terranova, B. Waegel ,
J. Org. Chem., **1992**, *57*, 5523.
E. McNeill and J. Du Bois,
J. Am. Chem. Soc., **2010**, *132*, 10202.

Majucin

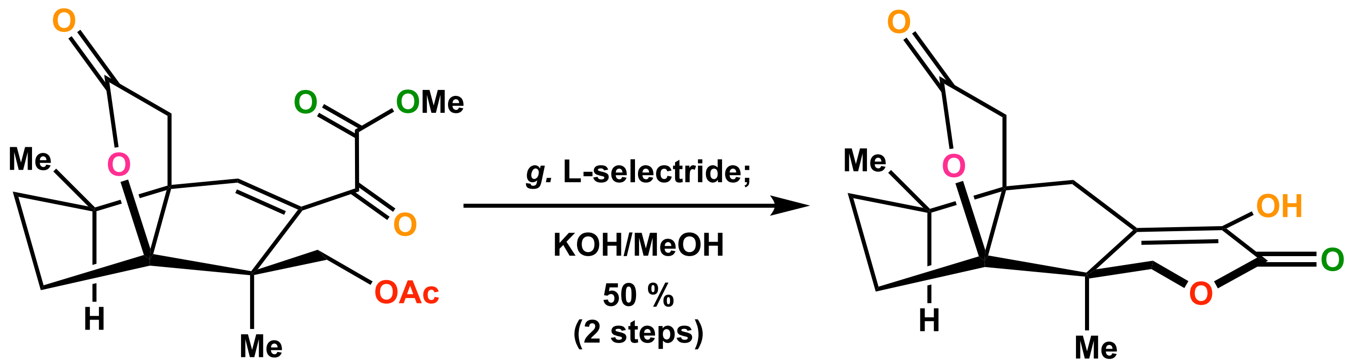
Reaction mechanism

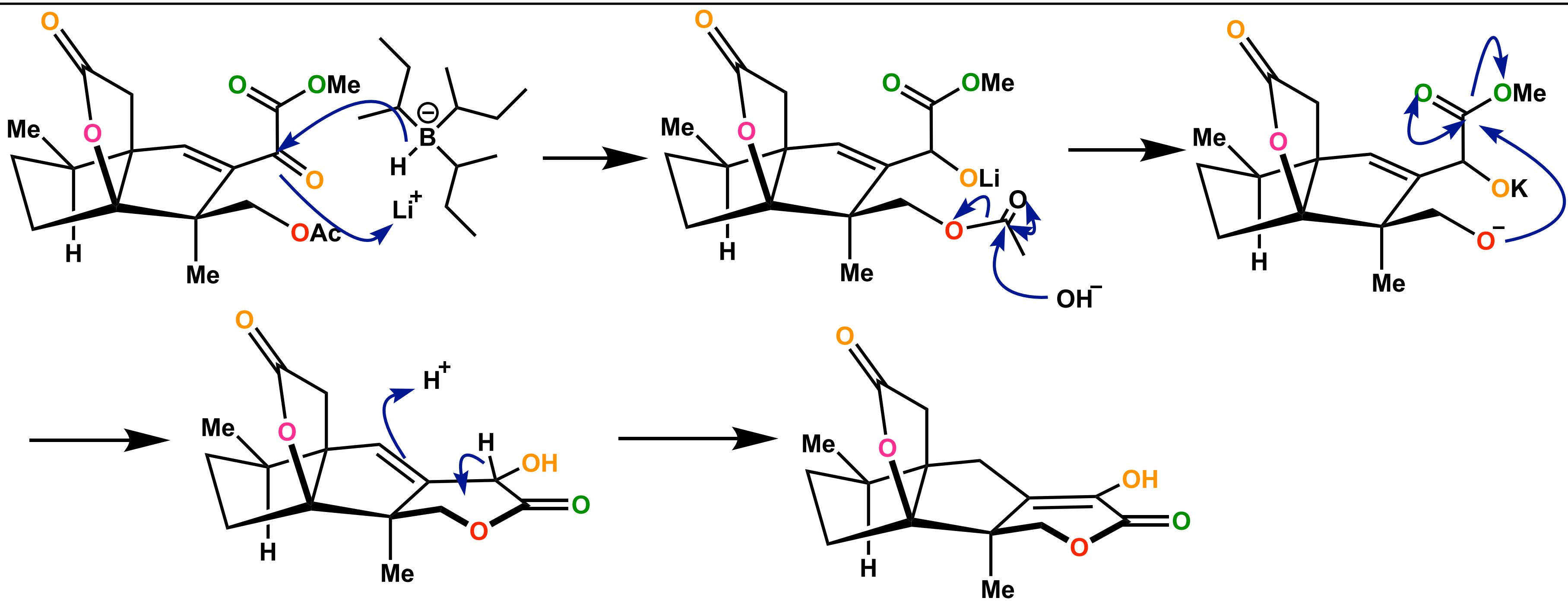




Majucin

Reaction mechanism

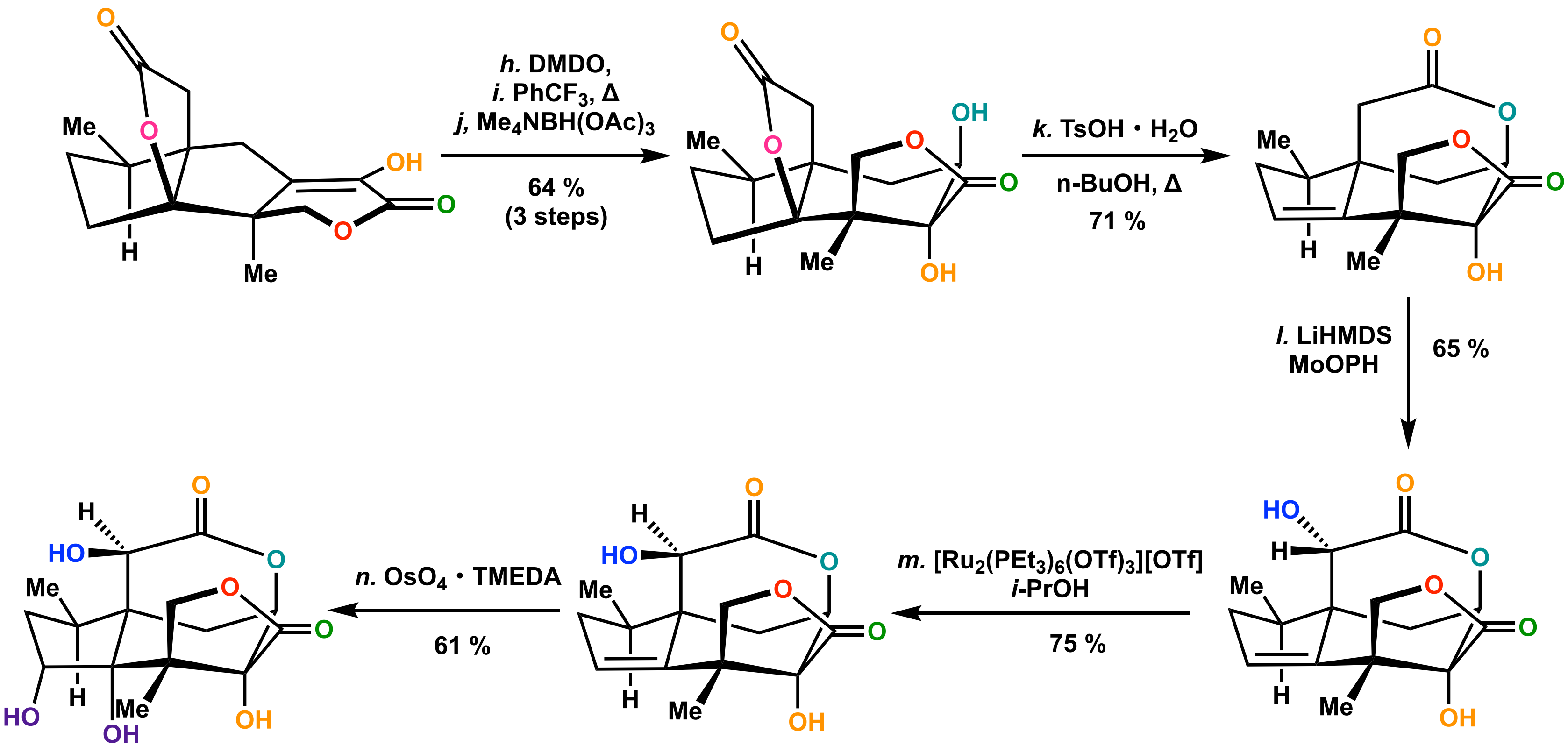




K. Hung, M. L. Condakes, L. F. T. Novaes, S. J. Harwood, T. Morikawa, Z. Yang, T. J. Maimone, *J. Am. Chem. Soc.*, **2019**, *141*, 3083.

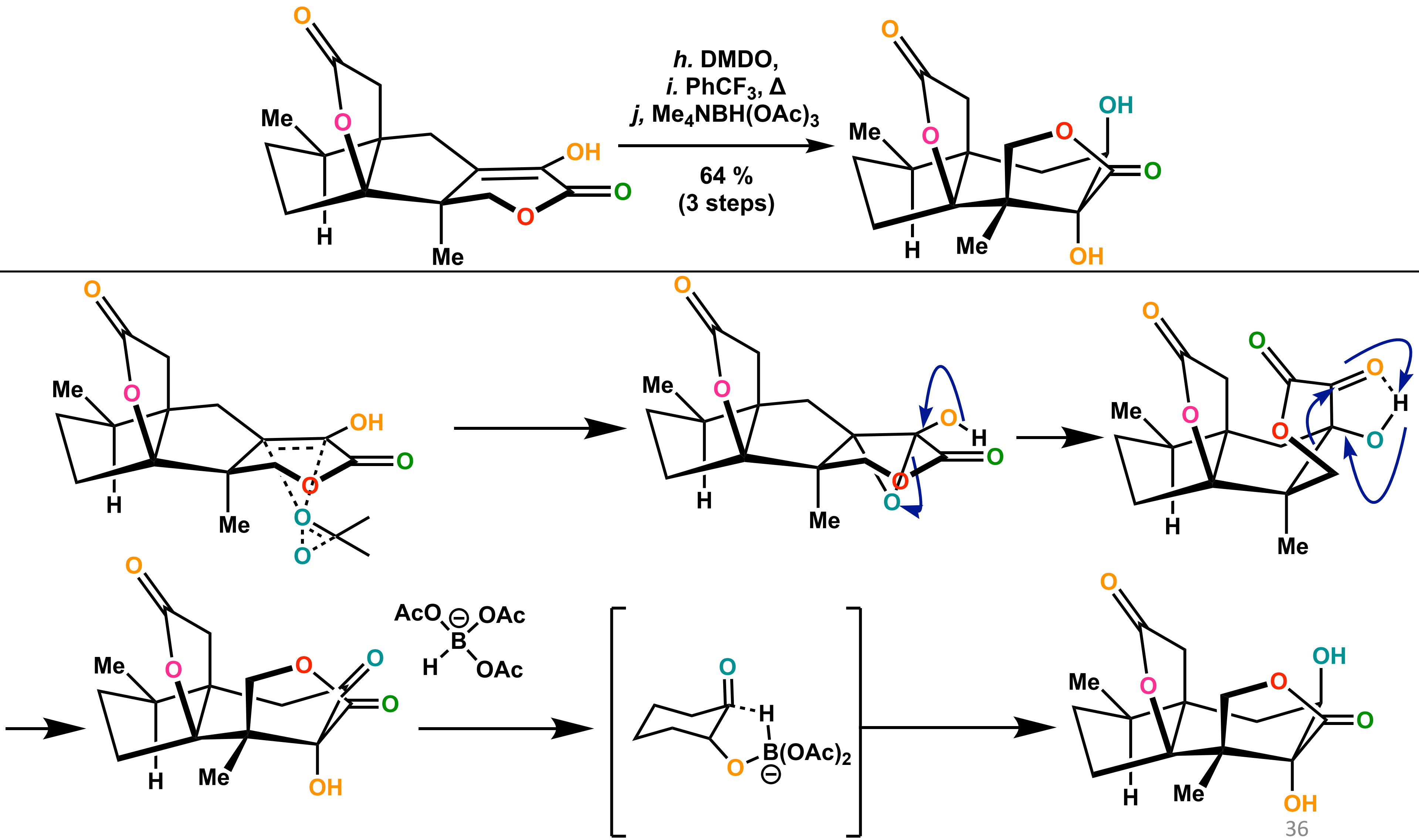
Majucin

Synthesis scheme



Majucin

Reaction mechanism



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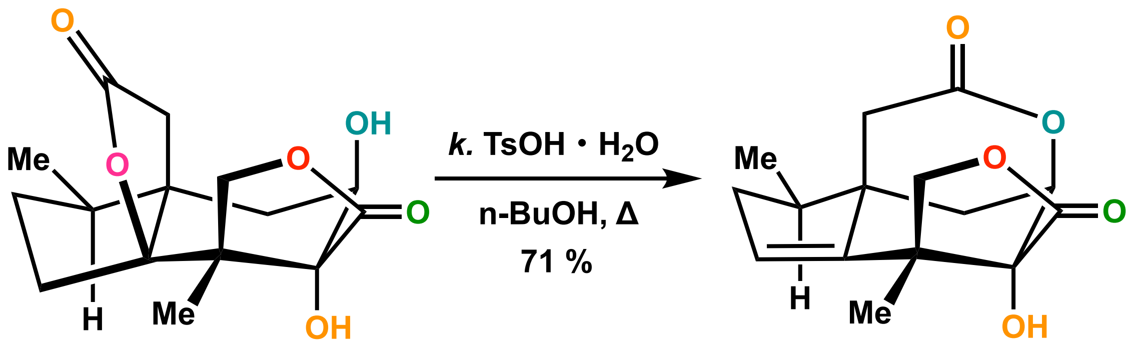
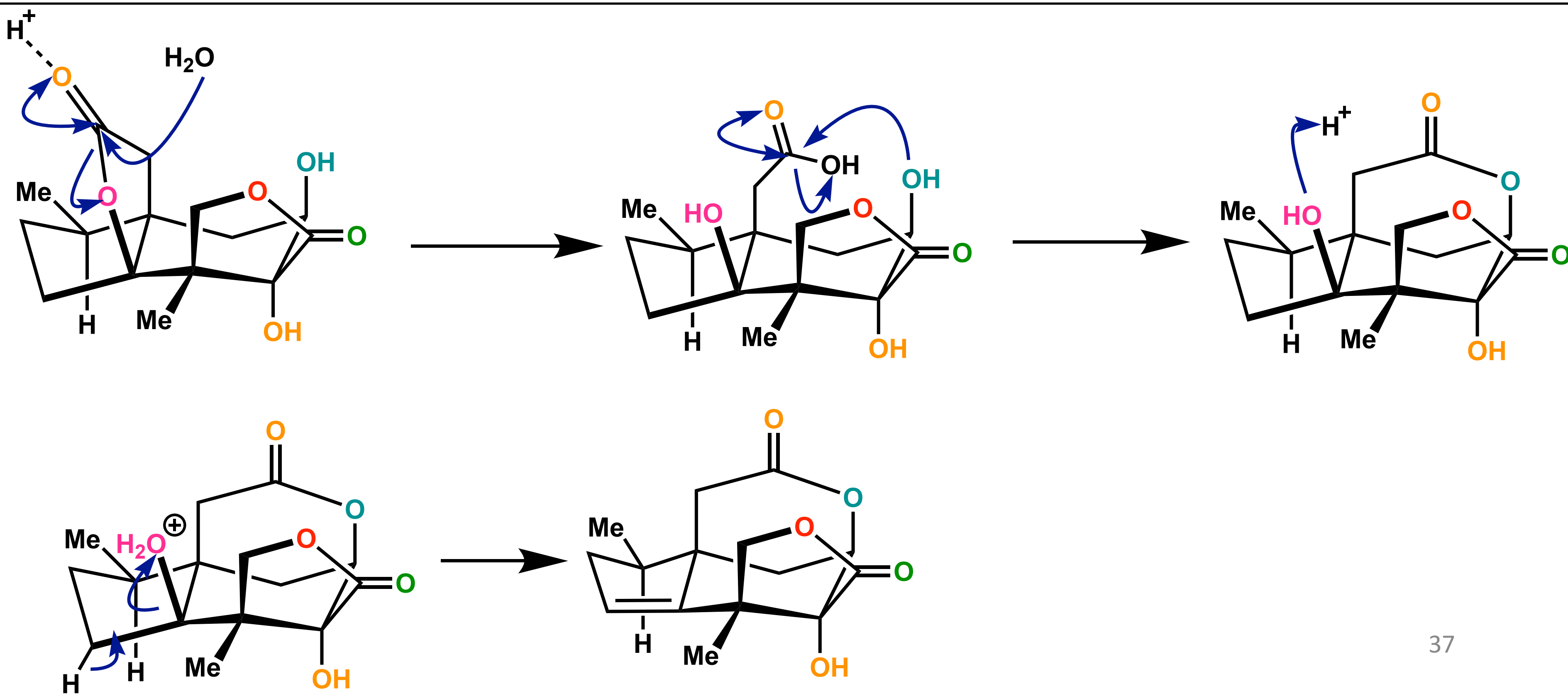
Reaction mechanism





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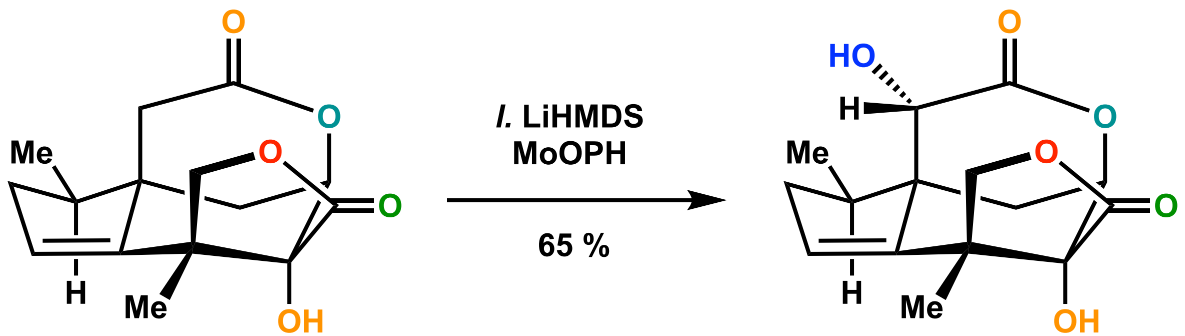

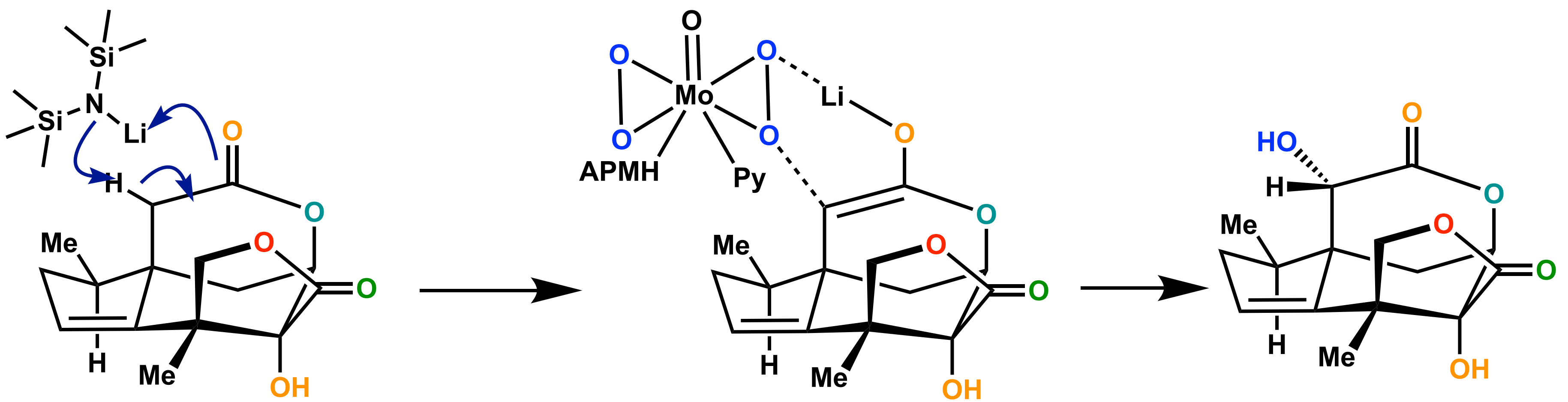

Majucin

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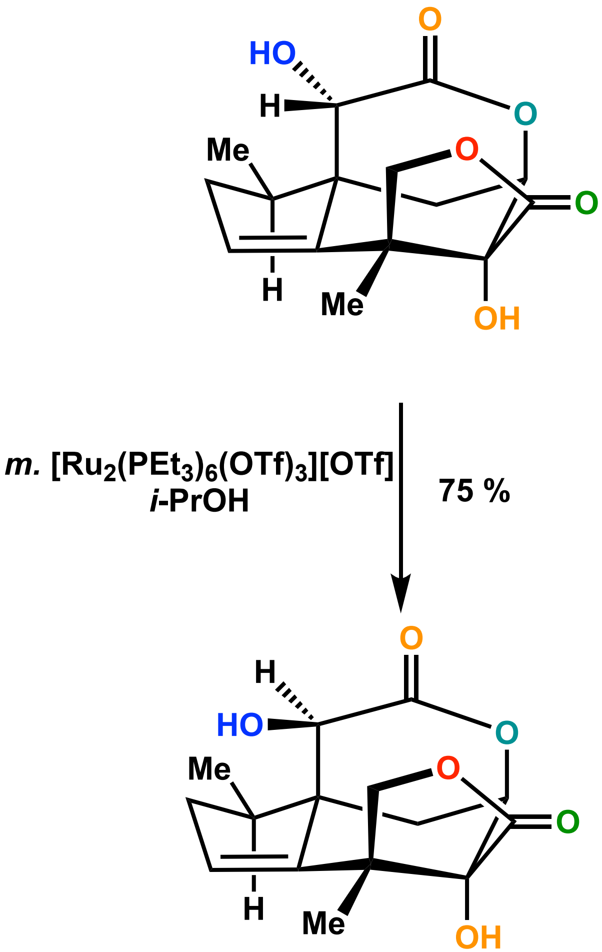
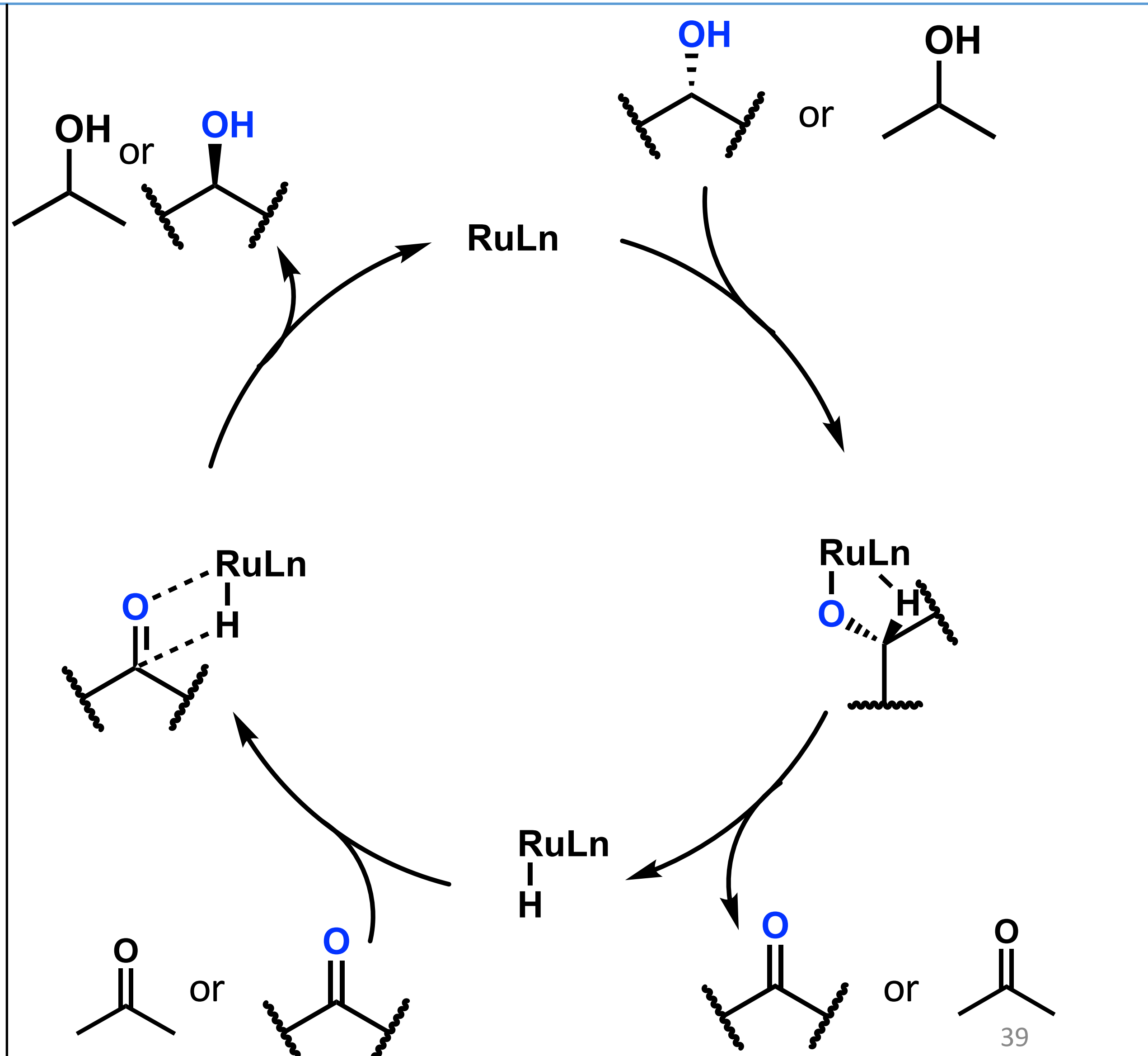


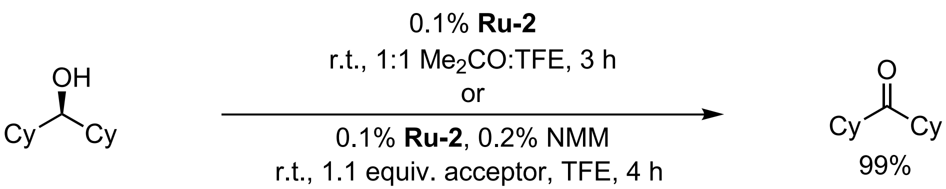
Almeida, M. L. S., Beller, M., Wang, G., Backvall, J., *Chem. Eur. J.*, **1996**, 1533.



Majucin

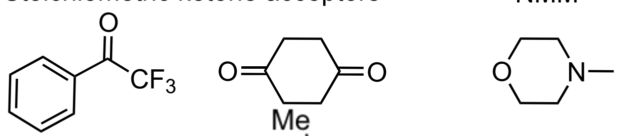
Transfer hydrogenation by Ruthenium complex

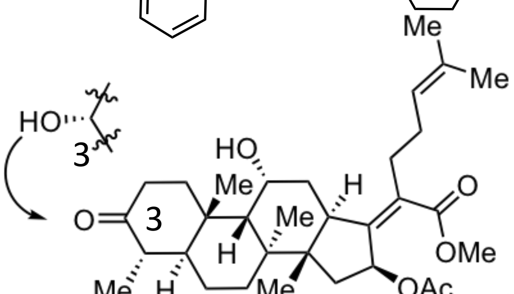
Oxidation



Stoichiometric ketone acceptors

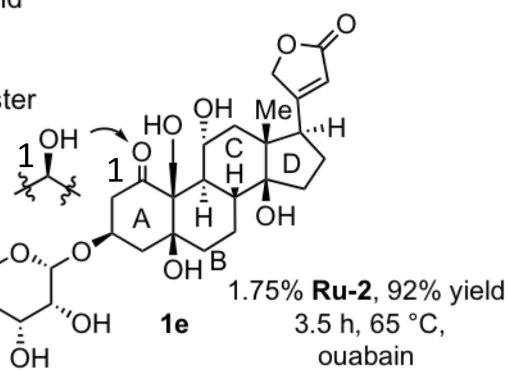
NMM





1f

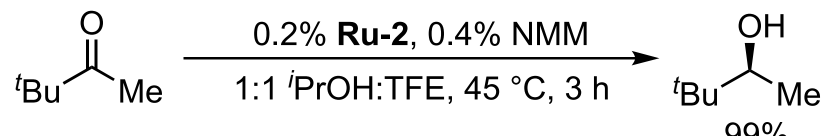
0.75% **Ru-2,** 97% yield
(or **Ru-3**, 95%),
4 h, 60 °C,
fusidic acid methyl ester



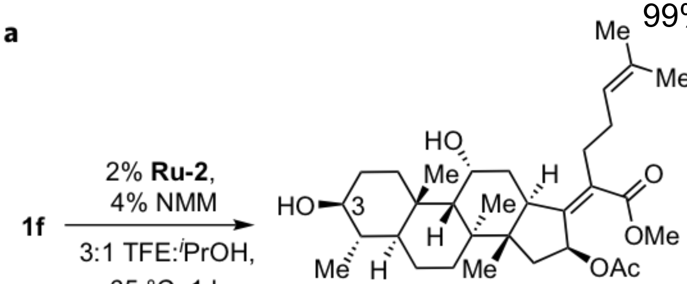
1e

1.75% **Ru-2**, 92% yield
3.5 h, 65 °C,
ouabain

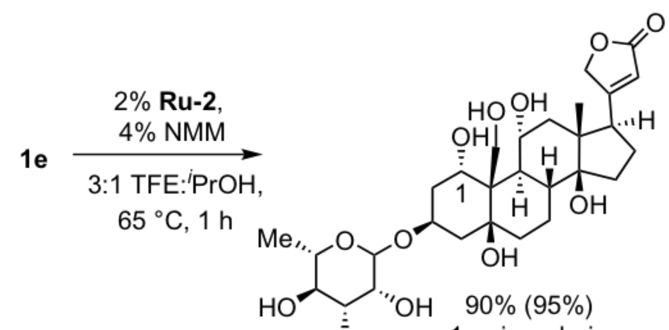
Reduction



a



3a 80% (84%)
3-epi-fusidic acid methyl ester
+ fusidic acid
methyl ester
(14%)



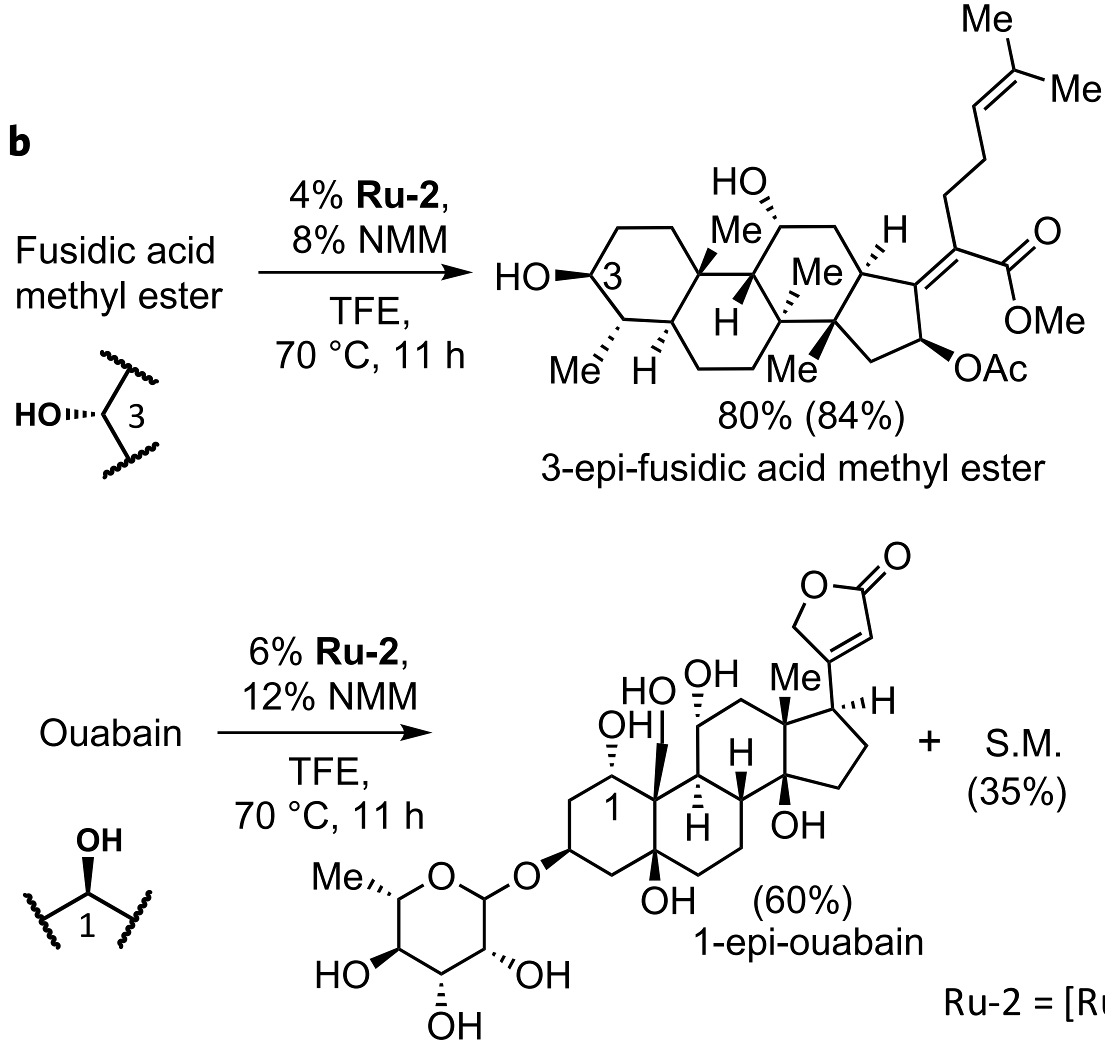
3b 90% (95%)
1-epi-ouabain

Ru-2 = $[Ru_2(PEt_3)_6(OTf)_3][OTf]$

Hill, C. K.; Hartwig, J. F. *Nat. Chem.* **2017**, *9*, 1213.

Majucin

Transfer hydrogenation by Ruthenium complex

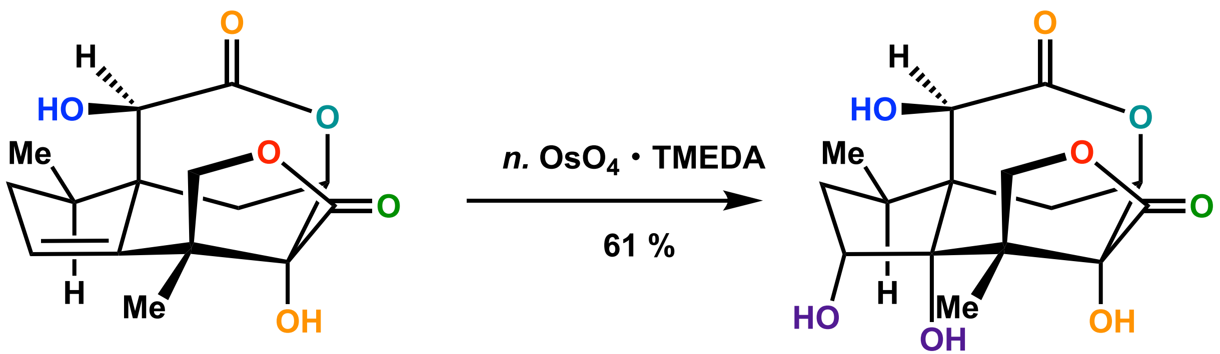


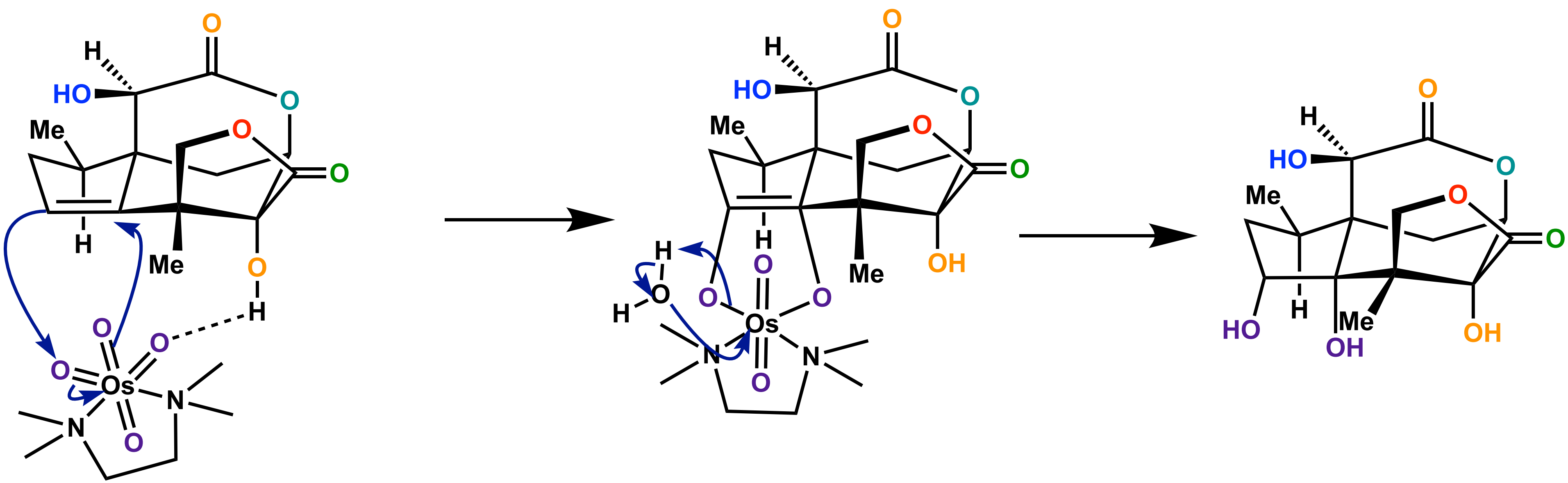
Ru-2 = $[Ru_2(PEt_3)_6(OTf)_3][OTf]$

Hill, C. K.; Hartwig, J. F. *Nat. Chem.* **2017**, *9*, 1213.

Majucin

Reaction mechanism

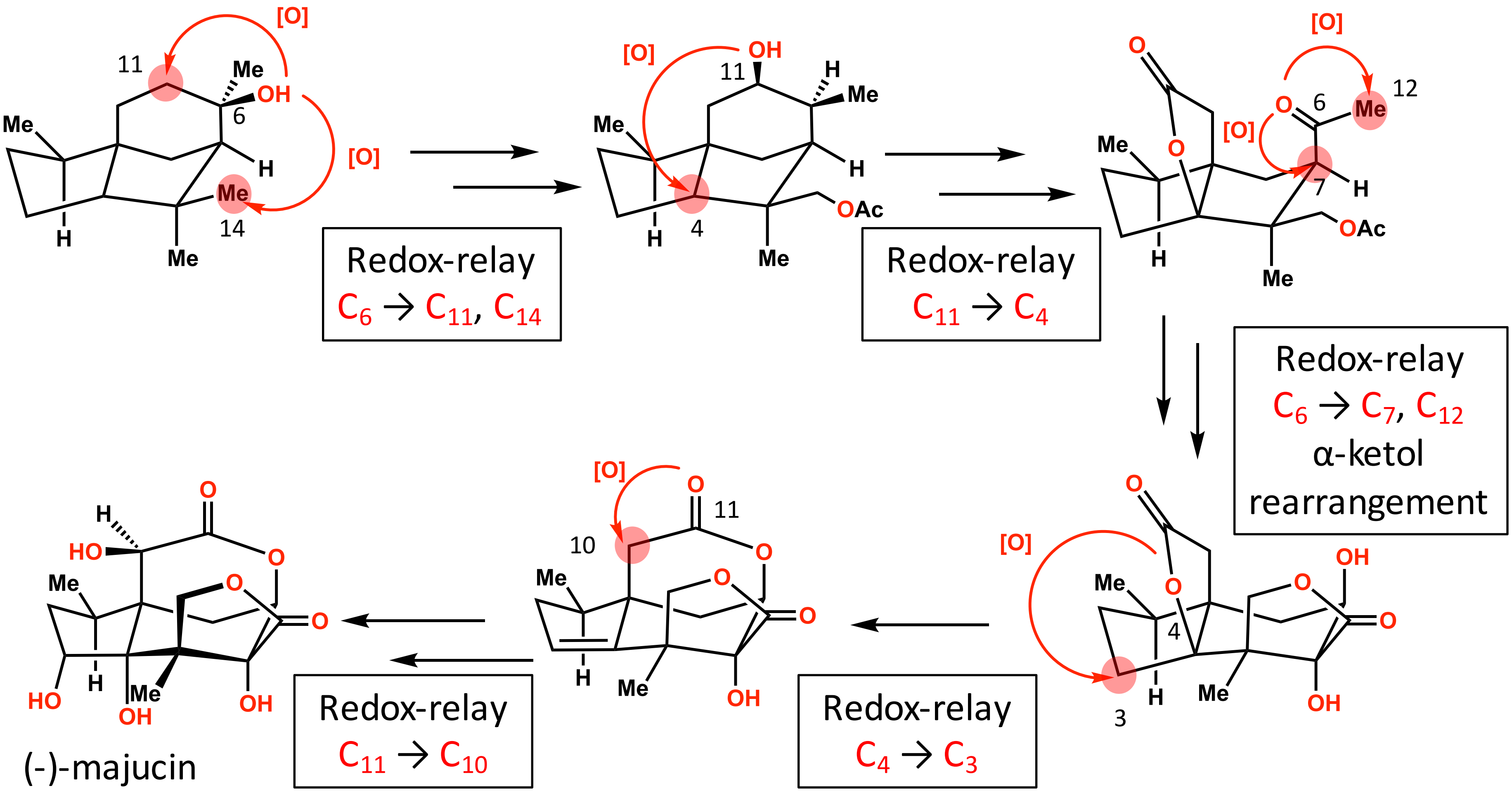




Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027.

Majucin

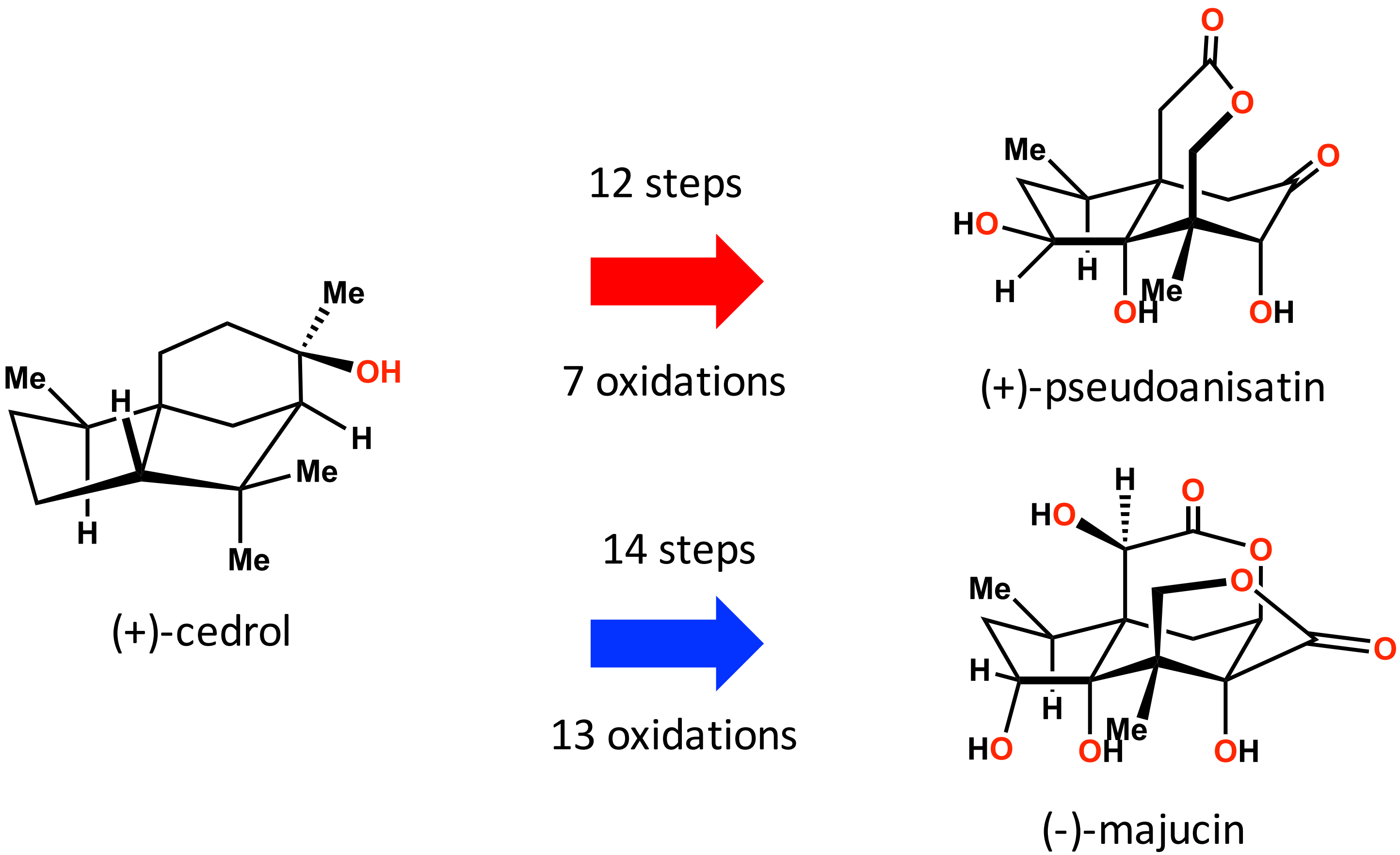
Summary of Majucin synthesis



- (-)-Majucin was synthesized by fully oxidative strategy.
- The strategy of pseudoanisatin is applicable for majucin.

Contents

Summary

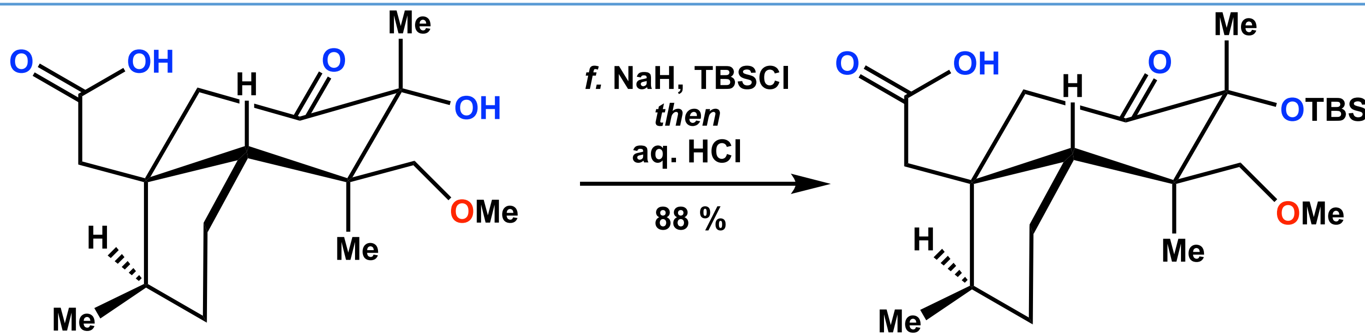


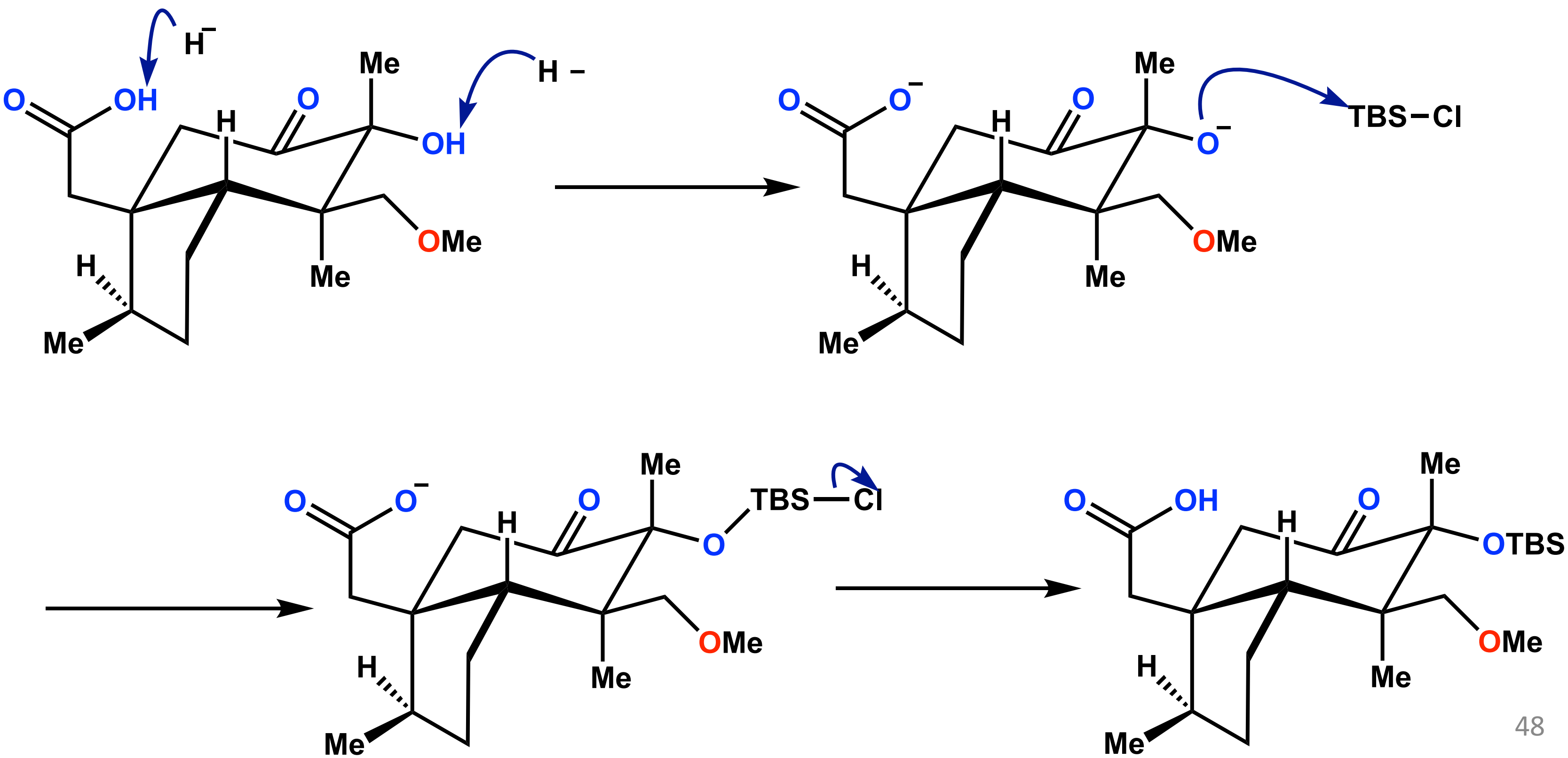
- Introduce position-selective hydroxyl groups by Redox-relay.
- Skeletal rearrangement by α-ketol rearrangement. (only one step)
- Two compounds could be synthesized using the same strategy.

Appendix

Pseudoanisatin

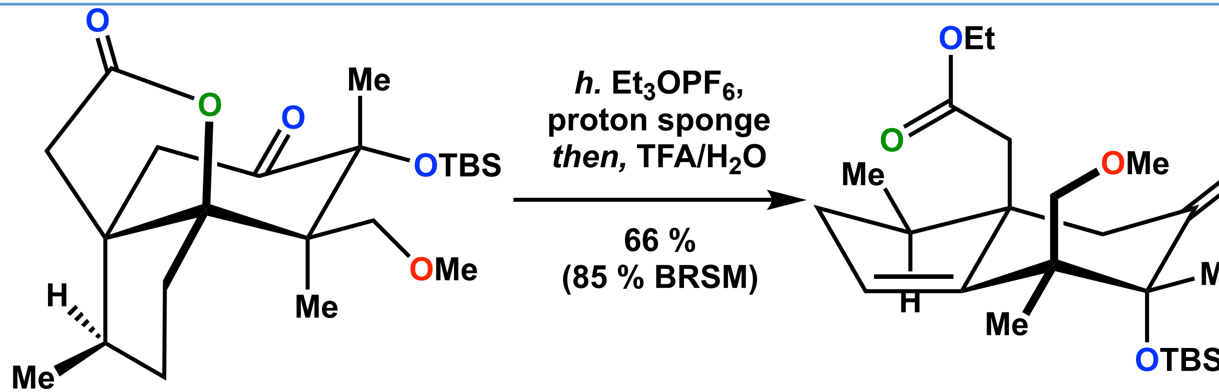
Reaction mechanism

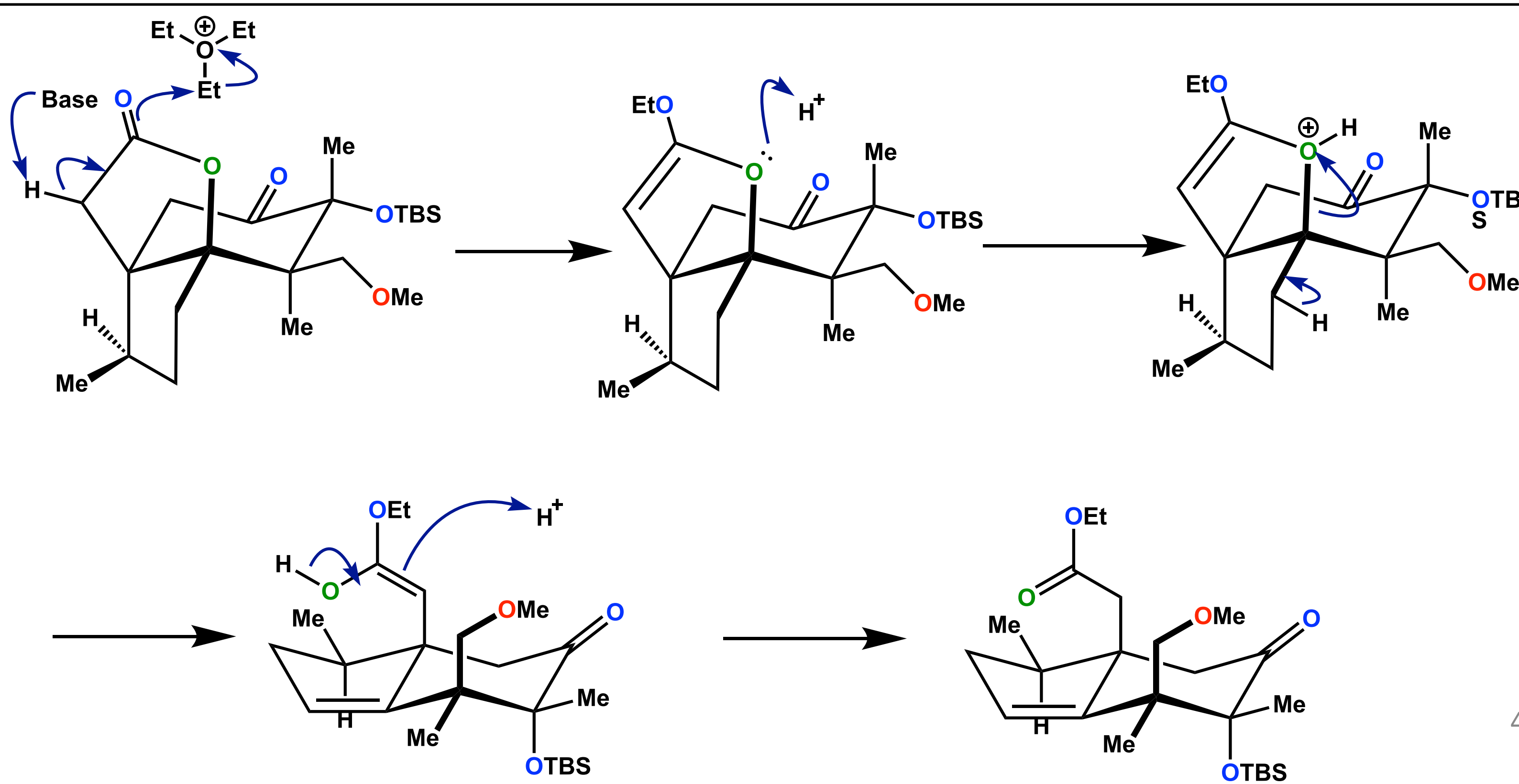




Pseudoanisatin

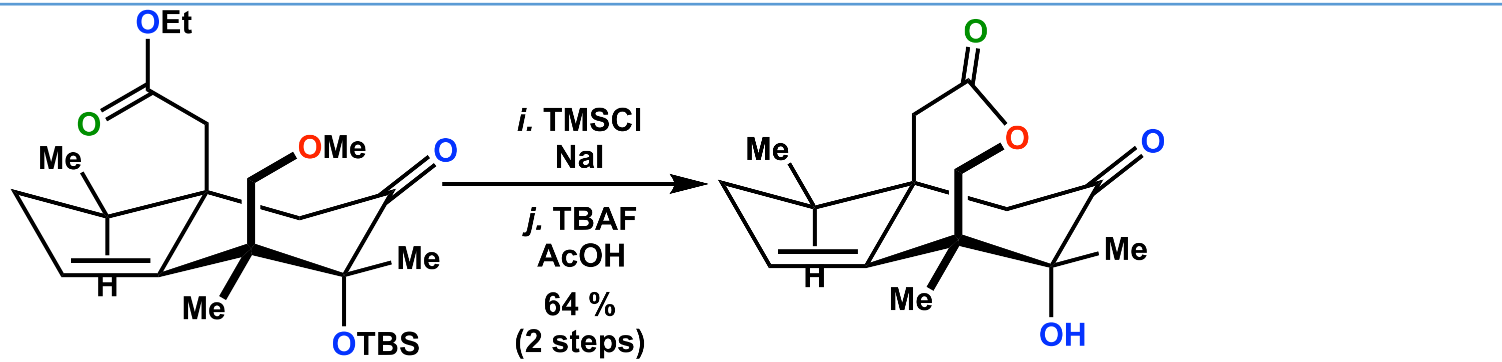
Reaction mechanism

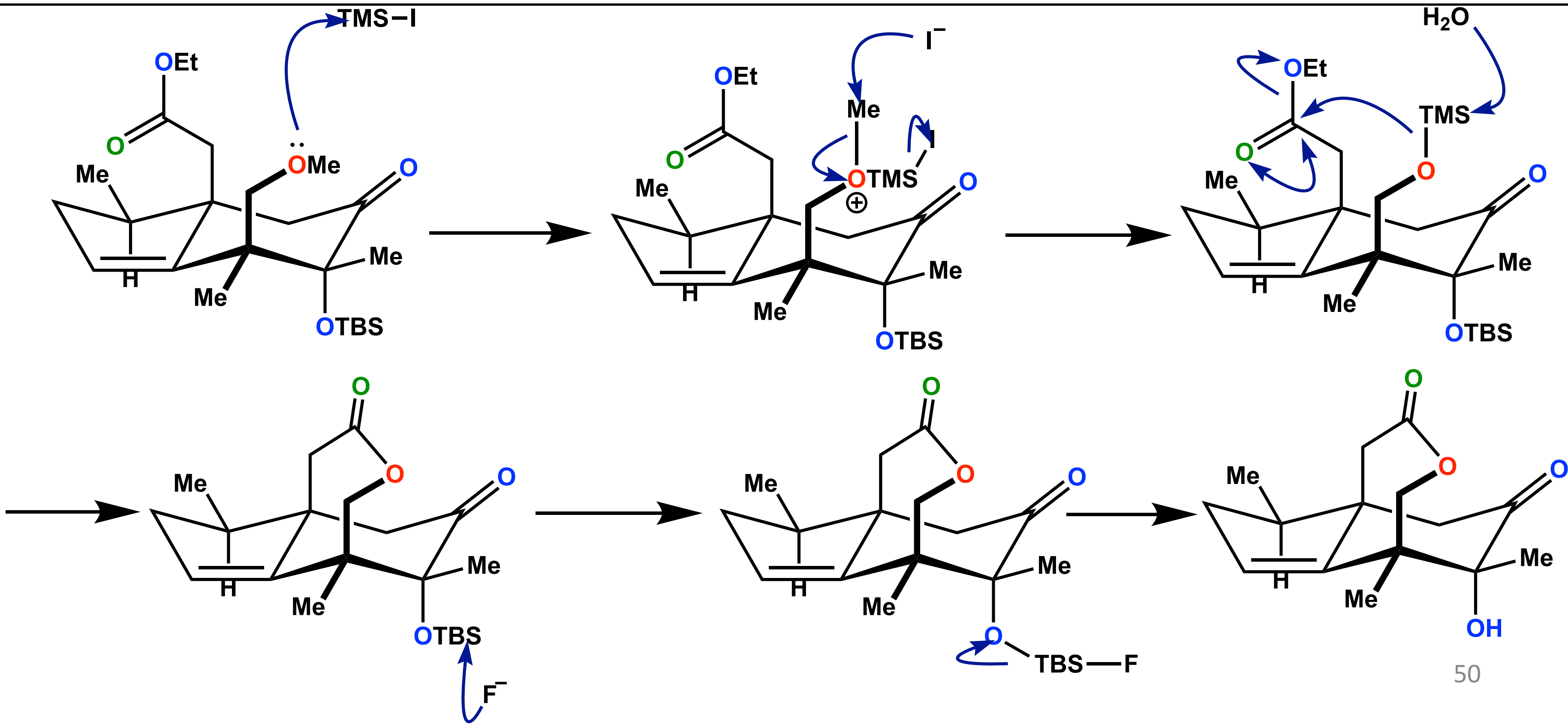




Pseudoanisatin

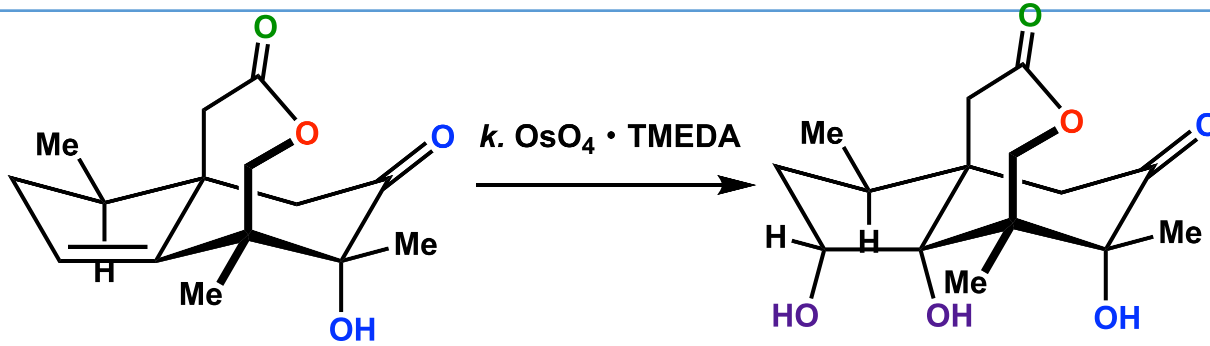
Reaction mechanism

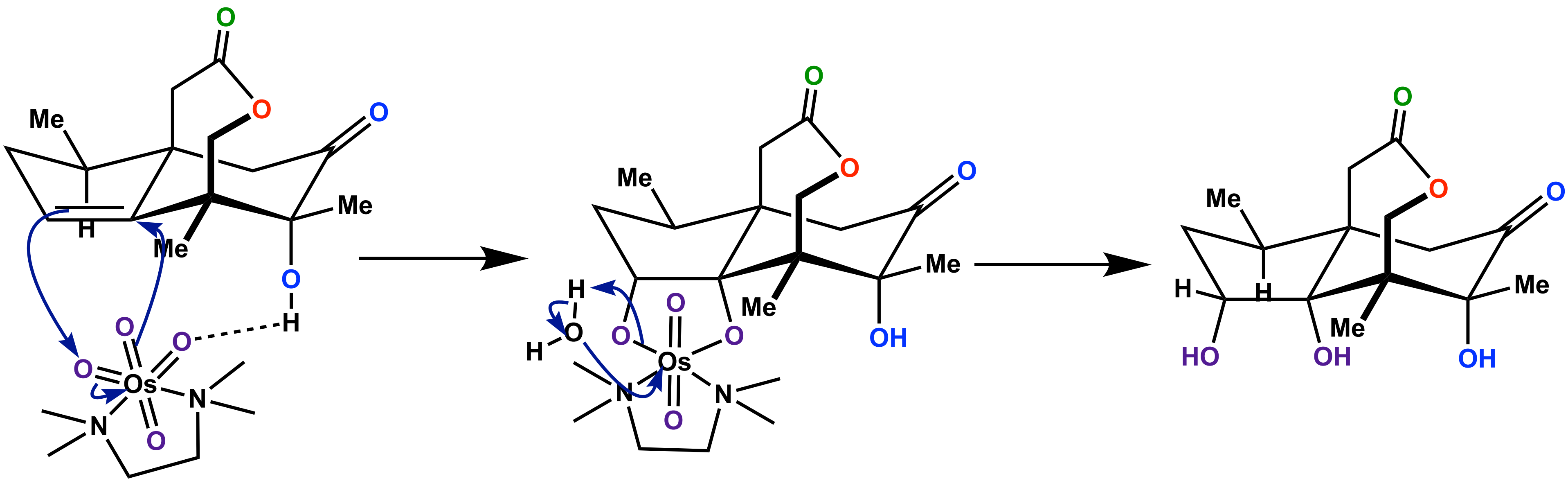




Pseudoanisatin

Reaction mechanism

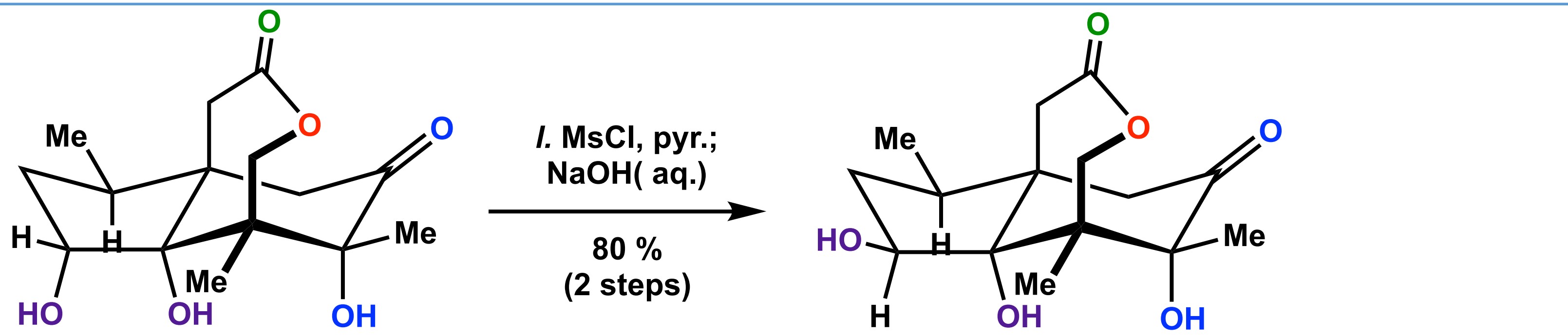


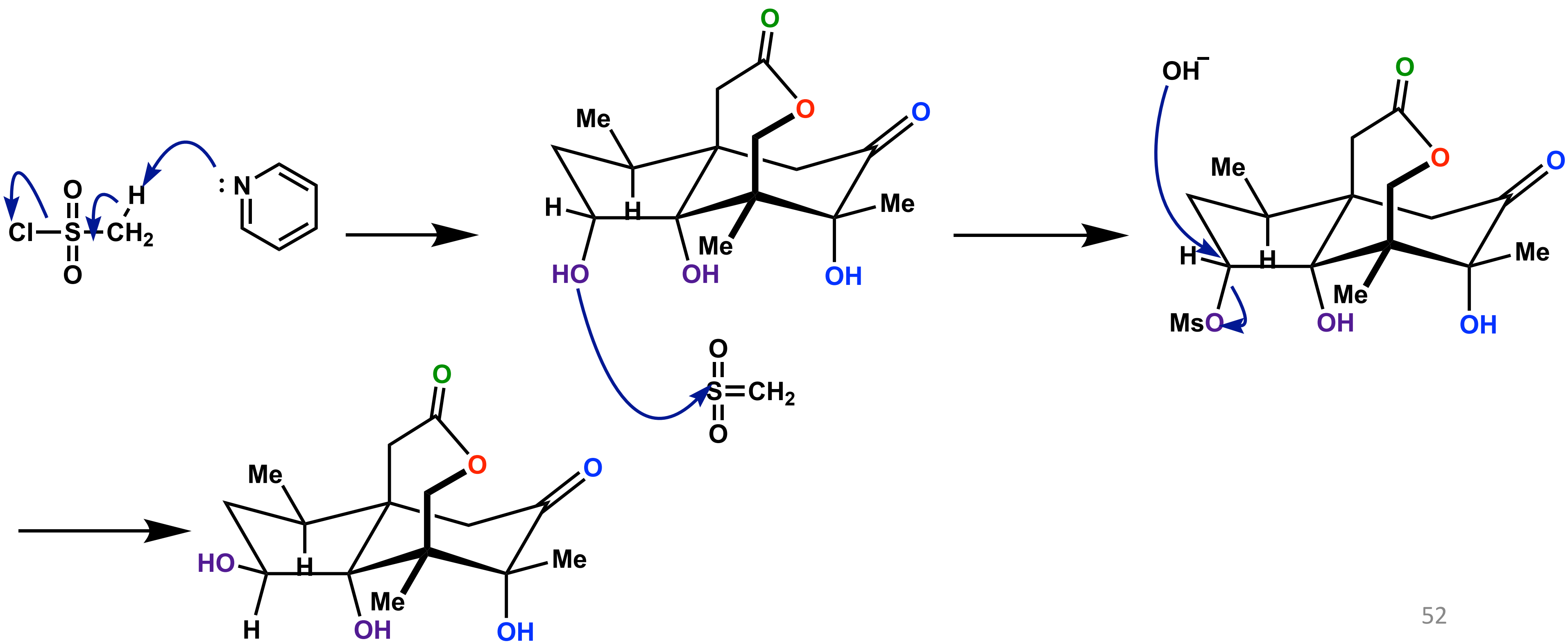


Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027.

Pseudoanisatin

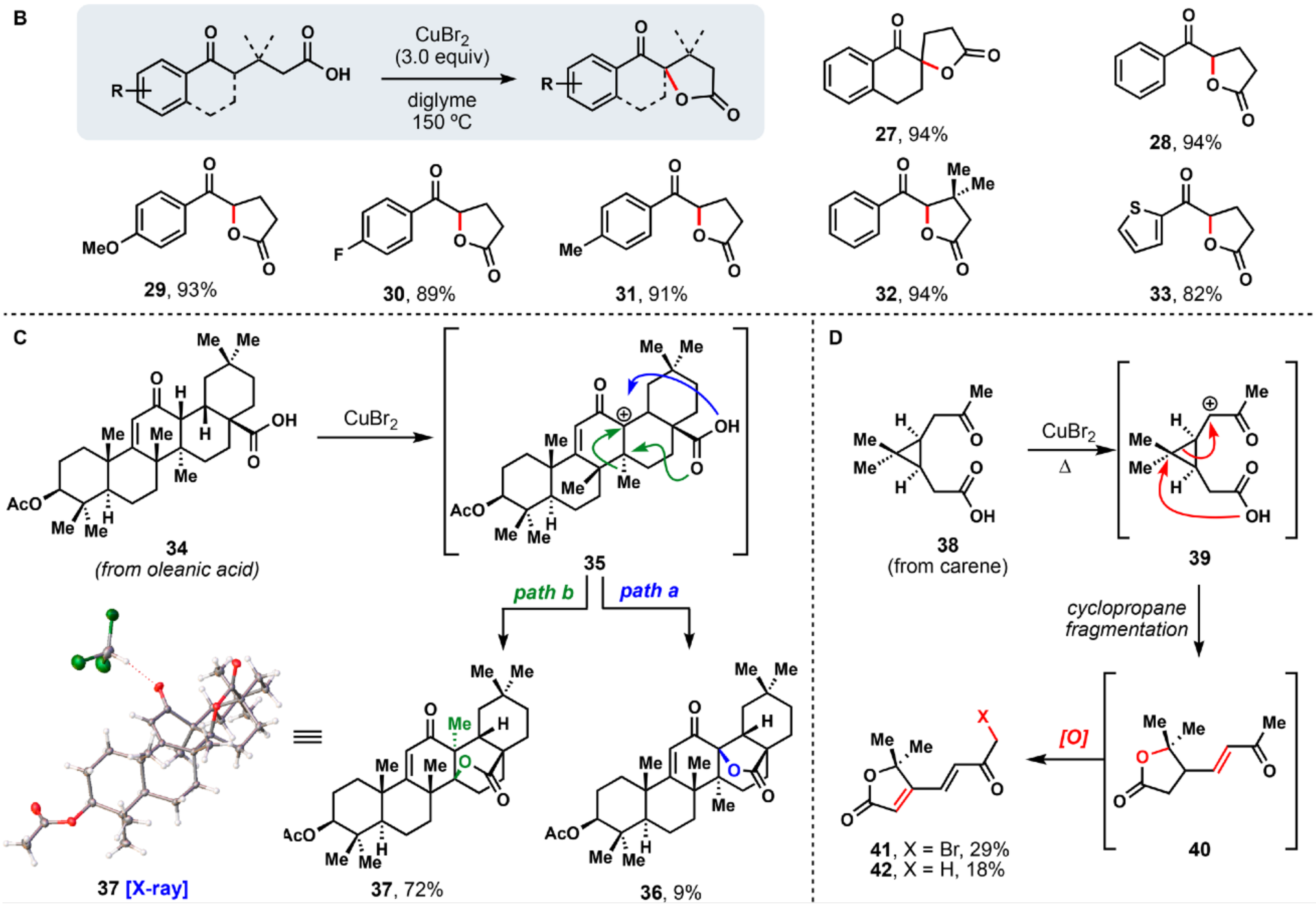
Reaction mechanism





Pseudoanisatin

Acyloxylation with $CuBr_2$

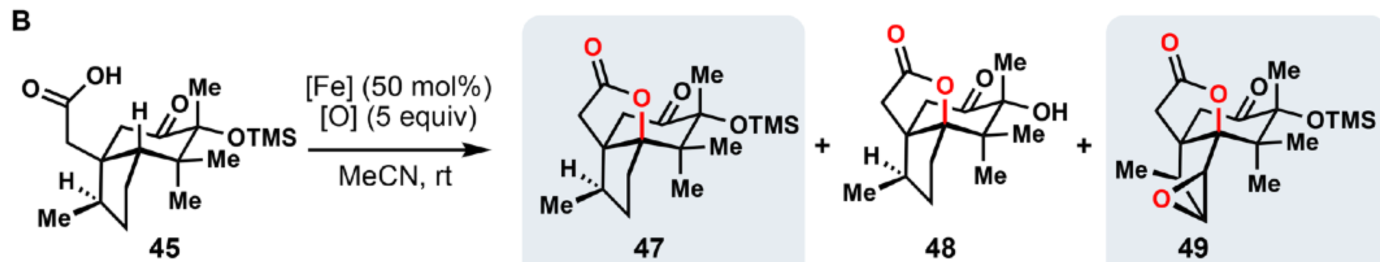


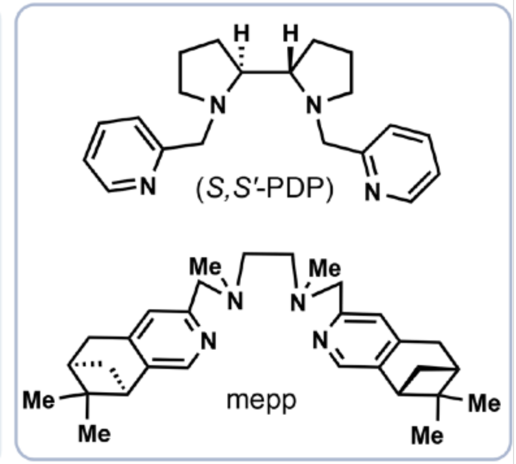
K. Hung, M. L. Condakes, L. F. T. Novaes, S. J. Harwood, T. Morikawa, Z. Yang, T. J. Maimone, *J. Am. Chem. Soc.*, **2019**, *141*, 3083.

Pseudoanisatin

C-H oxidation by iron complexes

B



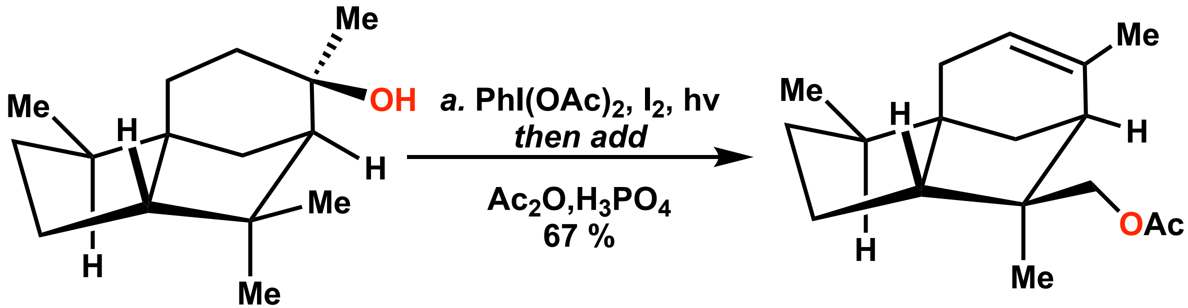


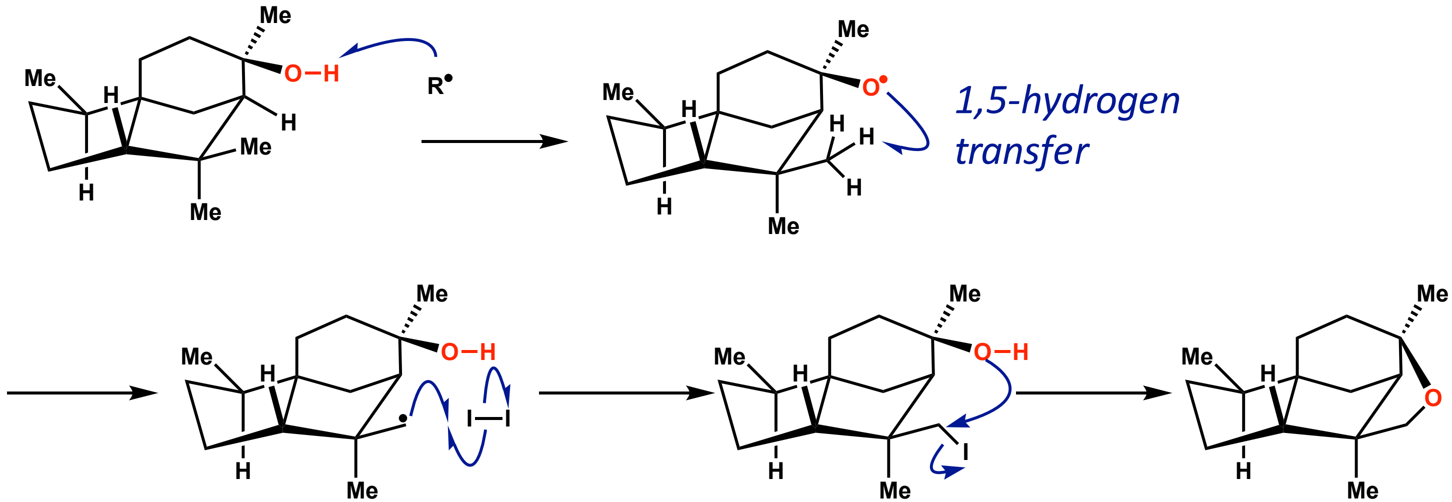
Entry	Conditions	47	48	49
1	Fe(mep)(MeCN)$_2$(SbF$_6$)$_2$, H_2O_2	22%	30%	4%
2	Fe(*S,S′*-PDP)(MeCN)$_2$(SbF$_6$)$_2$, H_2O_2	25%	0%	0%
3	Fe(mep)(MeCN)$_2$(SbF$_6$)$_2$, TBHP	21%	10%	4% (17% RSM)
4	Fe(*R,R′*-PDP)(MeCN)$_2$(SbF$_6$)$_2$, H_2O_2	16%	0%	0% (46% RSM)
5	Fe(mepp)(MeCN)$_2$(SbF$_6$)$_2$, H_2O_2	26%	0%	0% (30% RSM)

K. Hung, M. L. Condakes, L. F. T. Novaes, S. J. Harwood, T. Morikawa, Z. Yang, T. J. Maimone, *J. Am. Chem. Soc.*, **2019**, *141*, 3083.

Majucin

Reaction mechanism





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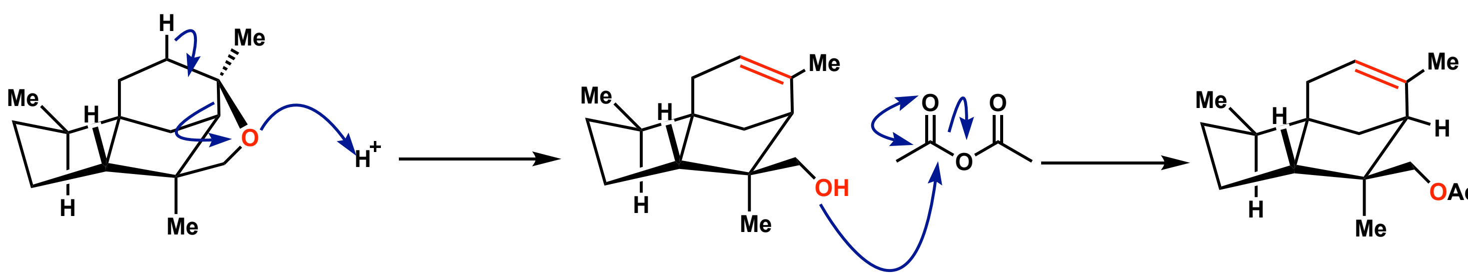

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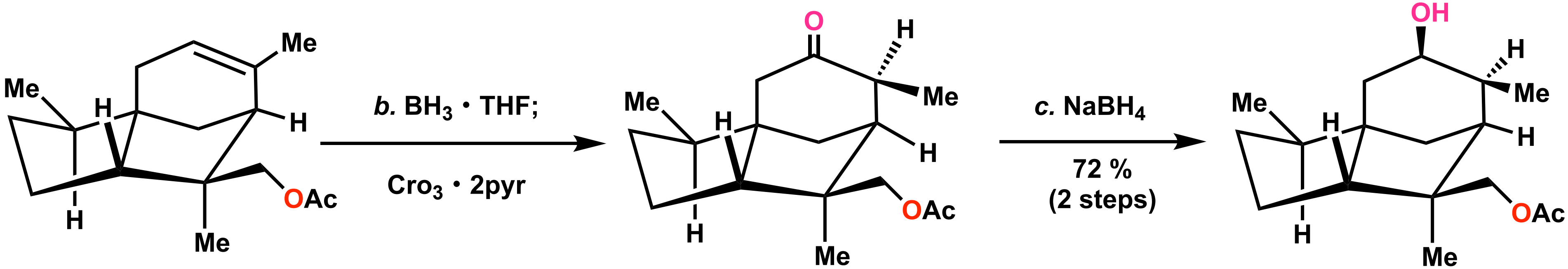
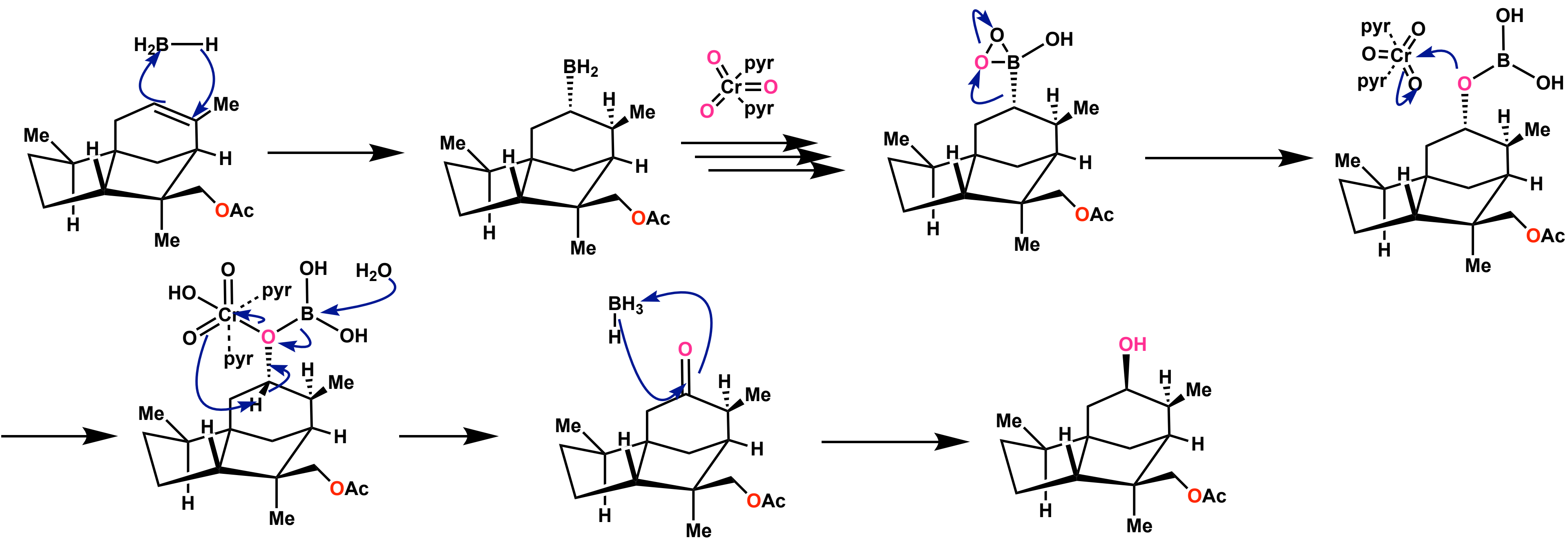
Reaction mechanism





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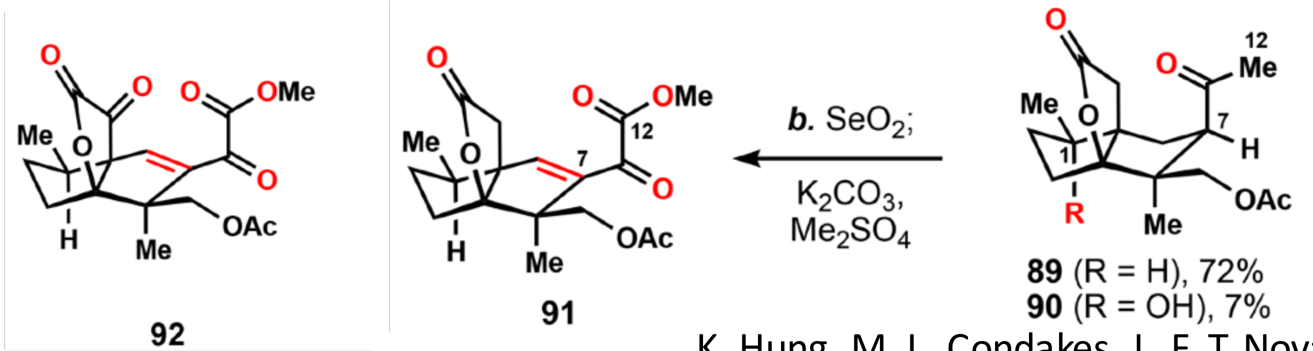
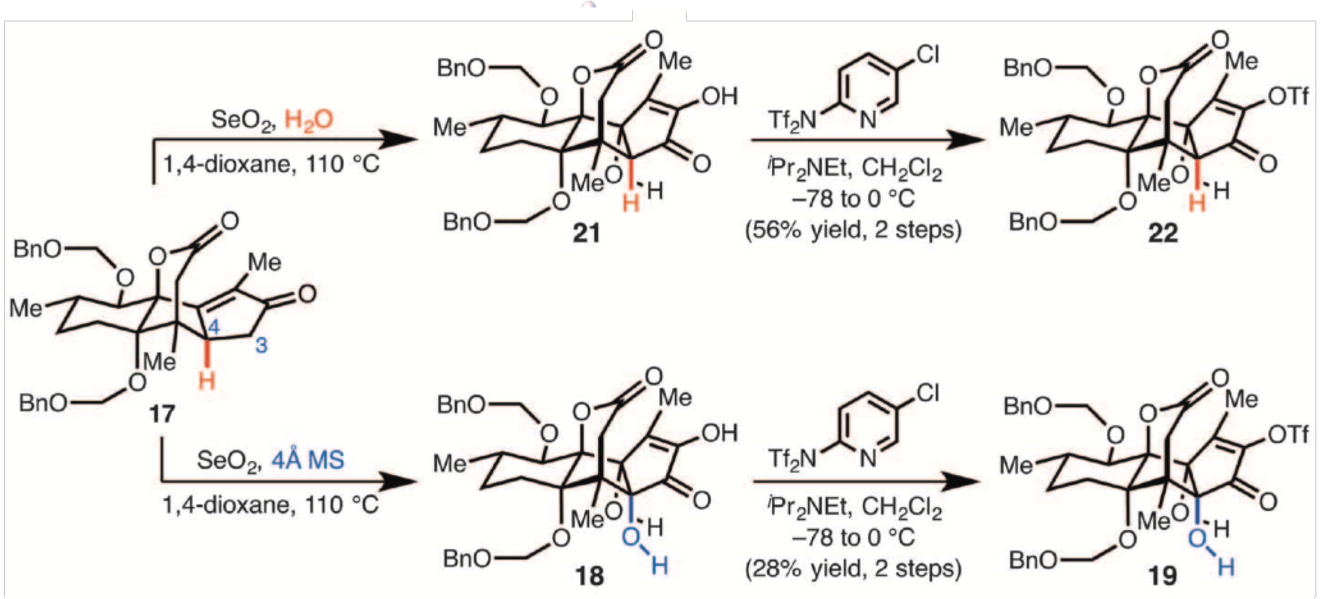
Oxidation by Se_2O under no H_2O condition



with 4 Å MS: 55% **91**, 0% **92**
without 4 Å MS: 43% **91**, 15% **92**

K. Hung, M. L. Condakes, L. F. T. Novaes, S. J. Harwood, T. Morikawa, Z. Yang, T. J. Maimone, *J. Am. Chem. Soc.*, **2019**, *141*, 3083.



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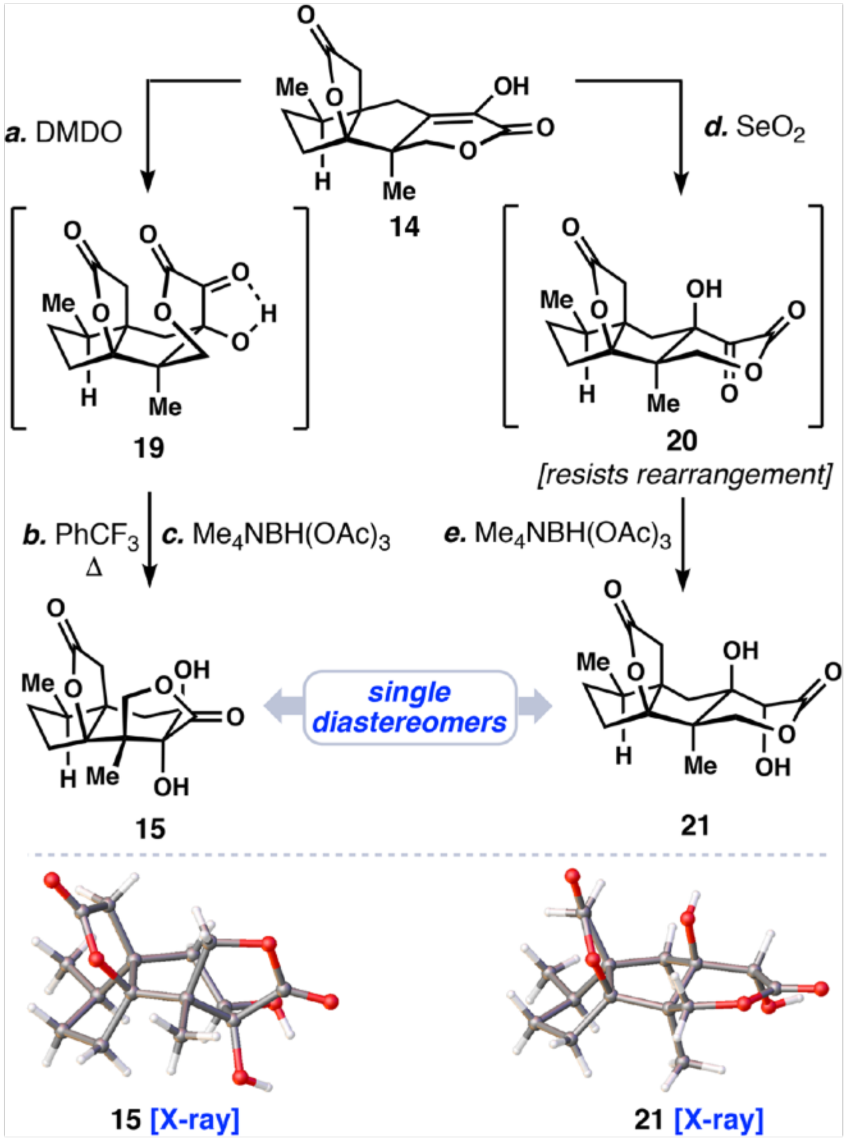
Stereochemical considerations for the α-Ketol rearrangement



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