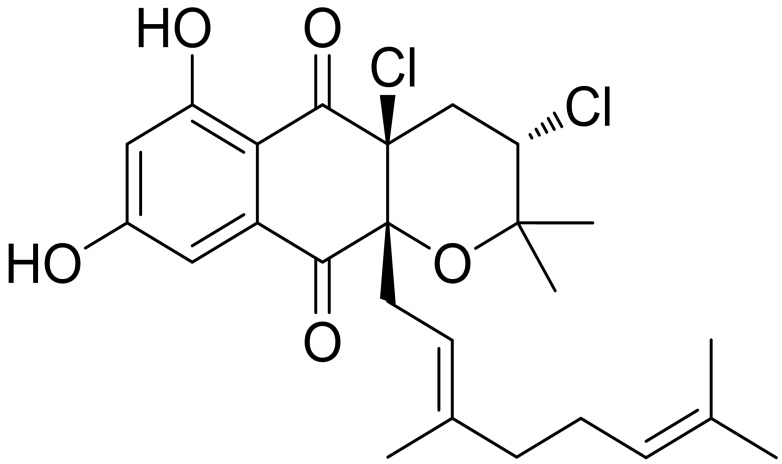
# Enantioselective Total Synthesis of (–)-Napyradiomycin A1 via Asymmetric Chlorination of an Isolated Olefin

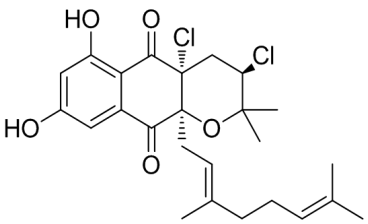
Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009,** *131,* 5744–5745.



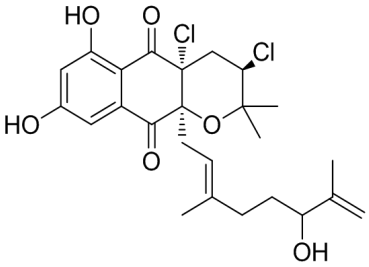

Zachary X. Giustra
Liu Group
July 1, 2015

# Previous Isolation and Characterization Studies

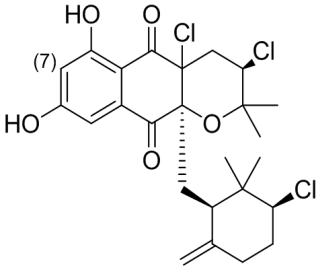
Originally isolated from the culture broth of terrestrial Streptomycetaceae bacterium *Chainia rubra* MG802-AF1.



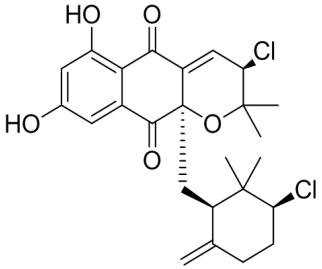
(+)-A1



A2



B1



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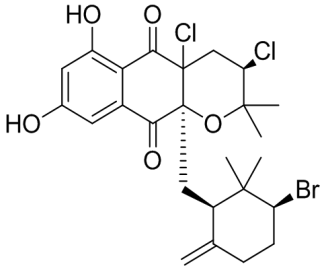

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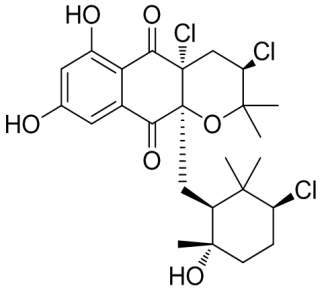
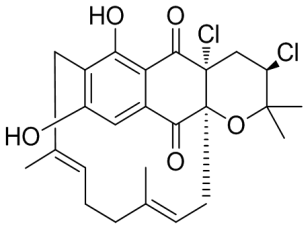
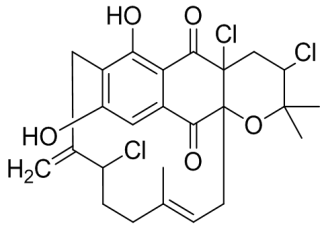


B4

C(7)-methylated variants of the B series later isolated from a marine strain of Streptomycetaceae bacteria.



C1

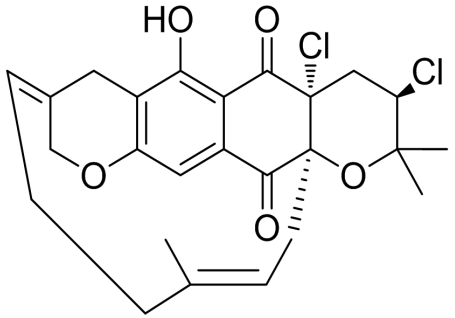


C2

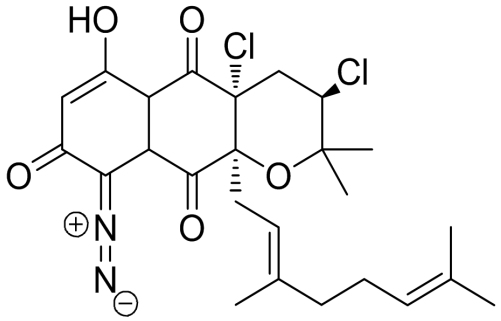
a) Shiomi, K.; Iinuma, H.; Hamada, M.; Naganawa, H.; Manabe, M.; Matsuki, C.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1986,** *39,* 487–493; b) Shiomi, K.; Nakamura, H.; Iinuma, H.; Naganawa, H.; Isshiki, K.; Takeuchi, T.; Umezawa, H.; Itaka, Y. *J. Antibiot.* **1986,** *39,* 494–501; c) Shiomi, K.; Nakamura, H.; Iinuma, H.; Naganawa, H.; Takeuchi, T.; Umezawa, H.; Itaka, Y. *J. Antibiot.* **1987,** *40,* 1213–1219.

Soria-Mercado, I. E.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. J. *J. Nat. Prod.* **2005,** *68,* 904–910.

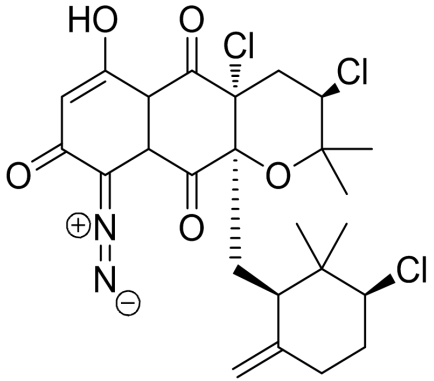
# Previous Isolation and Characterization Studies




**SR**




**7-demethyl SF2415A3**



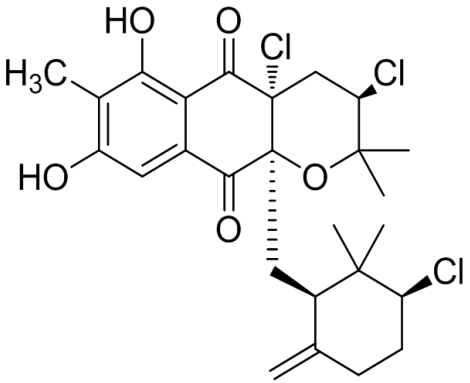

**7-demethyl A8019153**

More structurally diverse variants also isolated from *Streptomyces antimycoticus* NT17

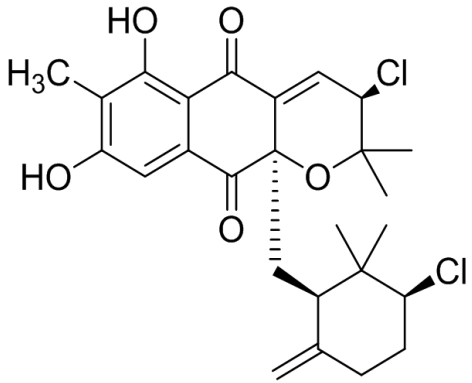


Motohashi, K.; Sue, M.; Furihata, K.; Ito, S.; Seto, H. *J. Nat. Prod.* **2008,** *71,* 595–601.

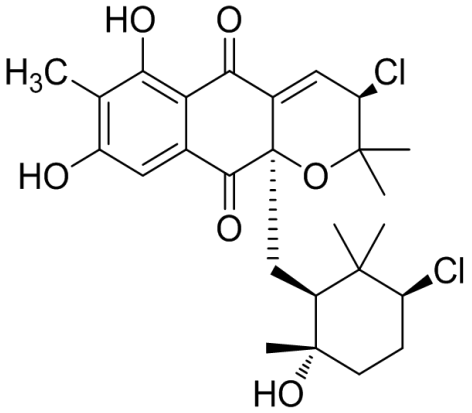
# Biological Activity




MRSA MIC:
1.90 μg/mL




VREF MIC:
1.95 μg/mL



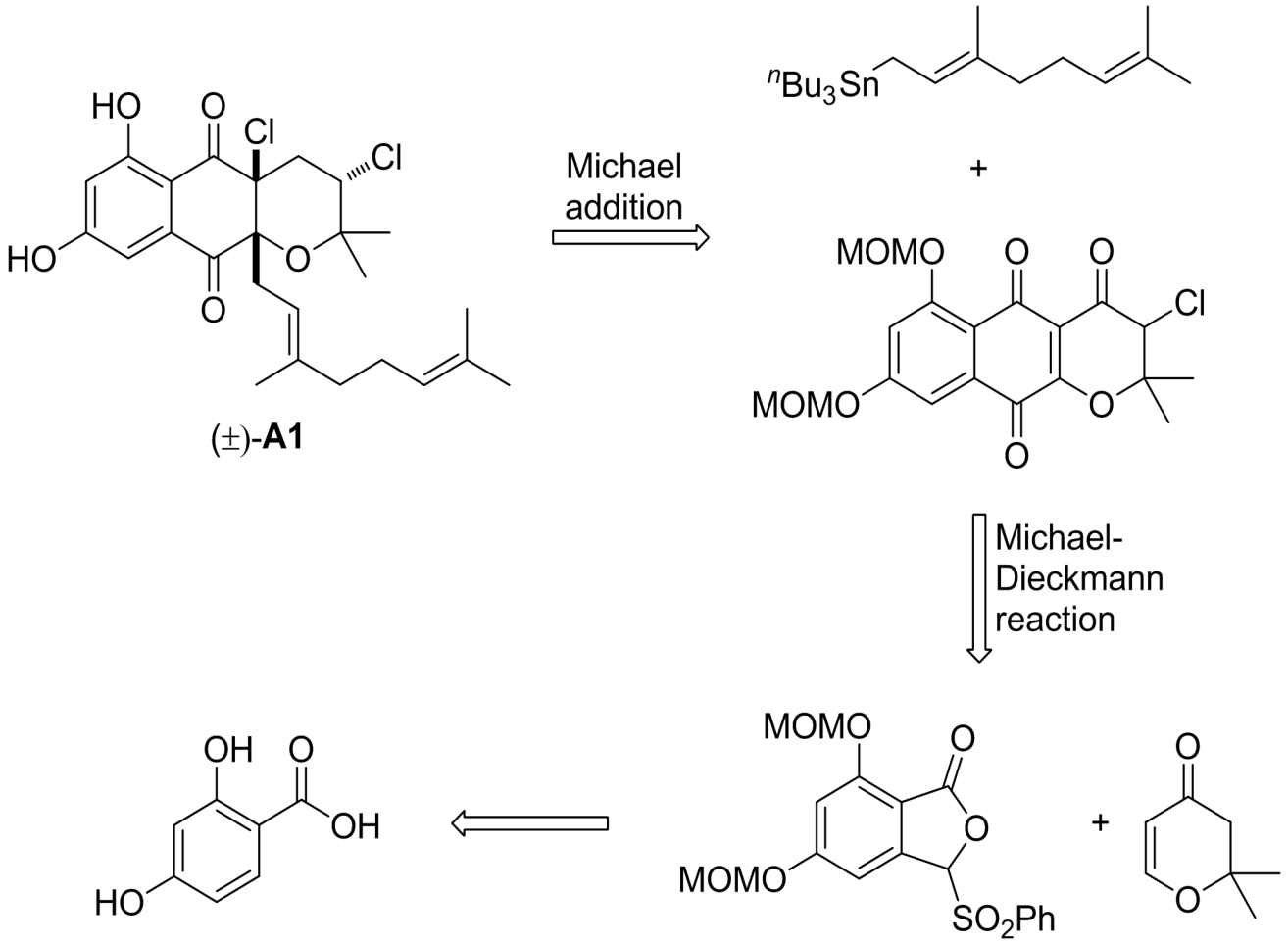

HCT-116 $IC_{50}$:
0.97 μg/mL

MRSA = methicillin-resistant *Staphylococcus aureus*
VREF = vancomycin-resistant *Enteracoccus faecium*

- Napyradiomycins generally display antibiotic activity against gram-positive bacteria.
- Cytoxic against human colon carcinoma HCT-116 cell line.

a) Shiomi, K.; Iinuma, H.; Hamada, M.; Naganawa, H.; Manabe, M.; Matsuki, C.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1986,** *39,* 487–493; b) Shiomi, K.; Nakamura, H.; Iinuma, H.; Naganawa, H.; Takeuchi, T.; Umezawa, H.; Itaka, Y. *J. Antibiot.* **1987,** *40,* 1213–1219.
Soria-Mercado, I. E.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. J. *J. Nat. Prod.* **2005,** *68,* 904–910.
Motohashi, K.; Sue, M.; Furihata, K.; Ito, S.; Seto, H. *J. Nat. Prod.* **2008,** *71,* 595–601.

# Previous Synthesis

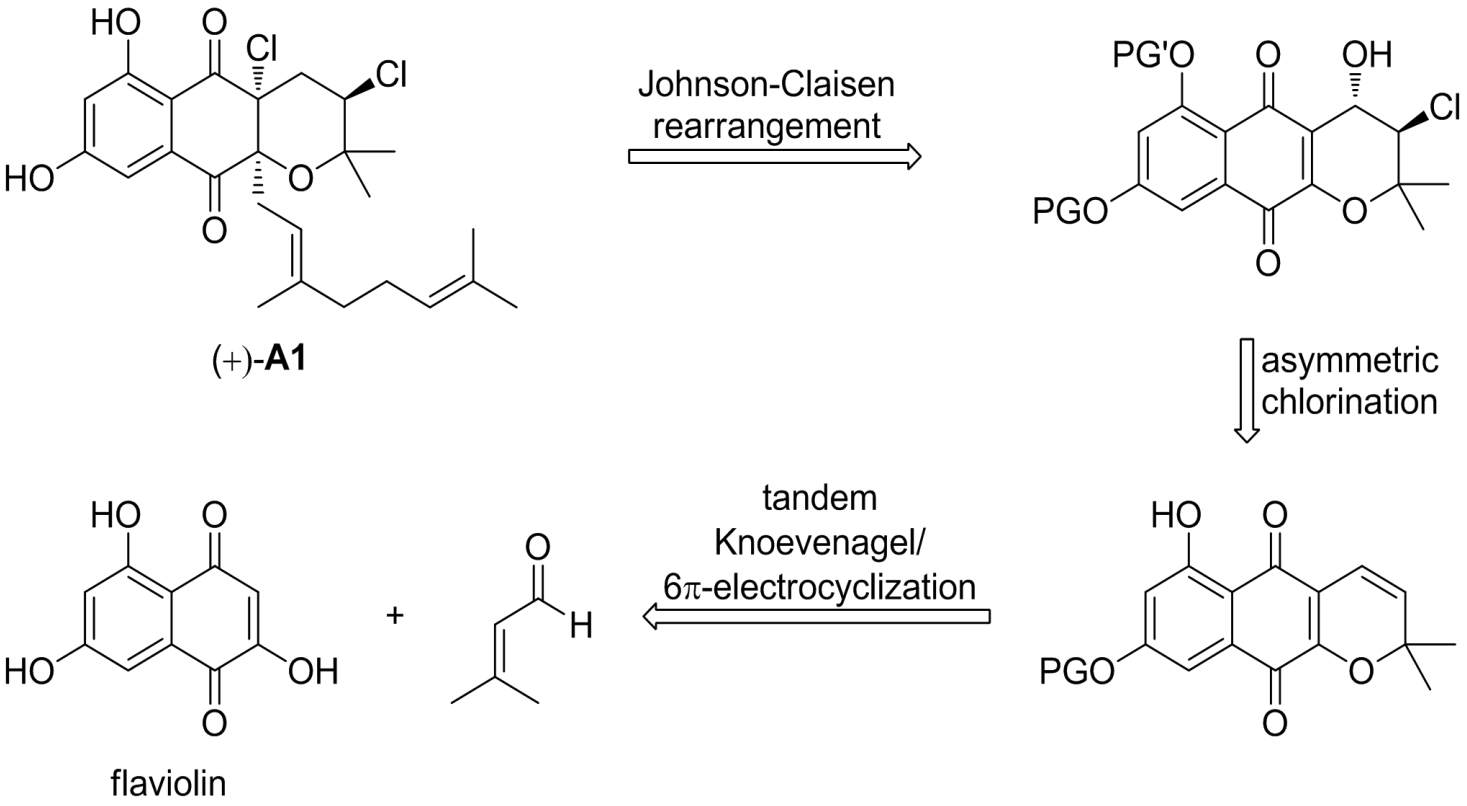



- Only (±)-**A1** had been synthesized previously.
- 13 steps longest linear sequence from 2,4-dihydroxybenzoic acid.



Tatsuta, K.; Tanaka, Y.; Kojima, M.; Ikegami, H. *Chem. Lett.* **2002,** 14–15.

# (+)-A1 Retrosynthesis




- Enantioselective chlorination to control stereochemistry of all subsequent steps.
- Required development of an asymmetric alkene chlorination protocol.
- Tricyclic core formed by cyclization of 3-methylcrotonaldehyde with flaviolin.



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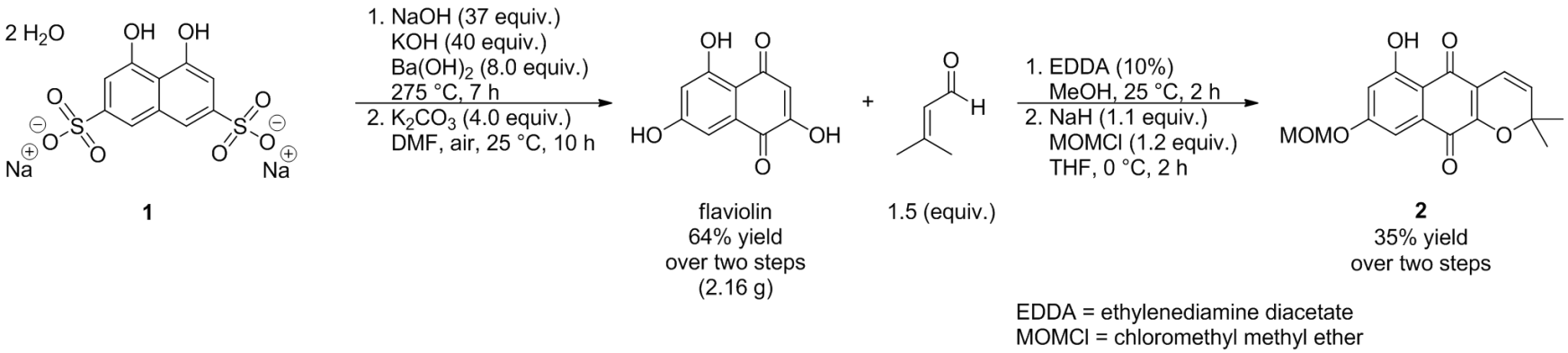
# Forward Synthesis




- Alkali fusion reaction performed using a eutectic salt bath of $KNO_3$, $NaNO_2$, and $NaNO_3$.
- Air-oxidation of the tetrahydroxynaphthalene intermediate produced the natural product flaviolin.
- Selective MOMCl protection achieved using the conditions shown; longer reaction times or higher MOMCl equivalencies led to bis-protection.



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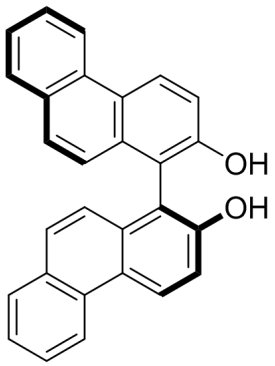
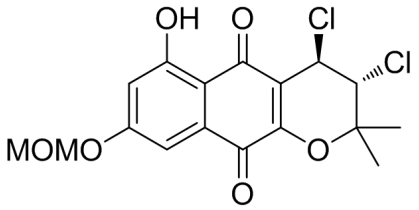
# Forward Synthesis




4.0 equiv.

1. $BH_3$•THF (4.0 equiv.)
   glacial AcOH (4.0 equiv.)
   THF, 25 °C, 20 min
2. **2** (1.0 equiv.), 1 h
3. $Cl_2$ ($CH_2Cl_2$), –78 °C, 20 min




**3**
93% yield
87% ee
(95% ee after recrystallization)

- Ligand *S*-enantiomer synthesized in four steps from 2-acetylphenanthrene.
- *Anti*-chlorination of the substrate alkene confirmed by X-ray crystallography.
- Absolute stereochemistry determined in the final product to be opposite that in naturally-occurring A1; use of ligand *R*-enantiomer led to natural configuration.
- Ligand could be recovered and recycled when THF was used as solvent; the ligand itself was chlorinated in all other solvents tested.



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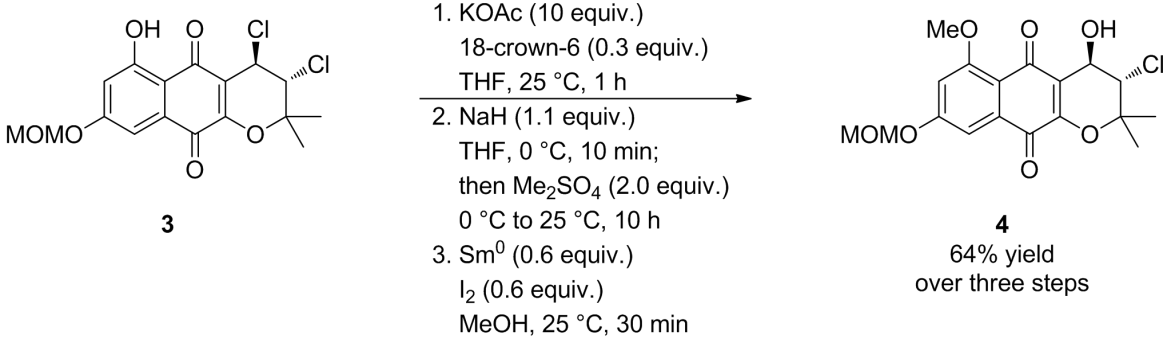
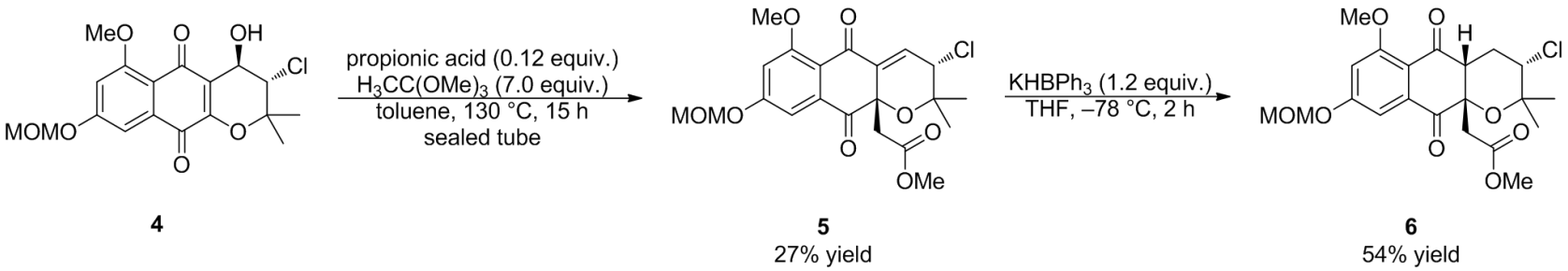
# Forward Synthesis




- Chloride displacement proceeded with retention of stereochemistry.
- Erosion of ee observed (5–8%) at reaction scales >0.026 mmol; step 1 run in a parallel series of ten reactions to bring material forward.




- Johnson-Claisen only variant of the Claisen rearrangement found effective.
- Reaction required prior methylation of the remaining aryl hydroxyl group.



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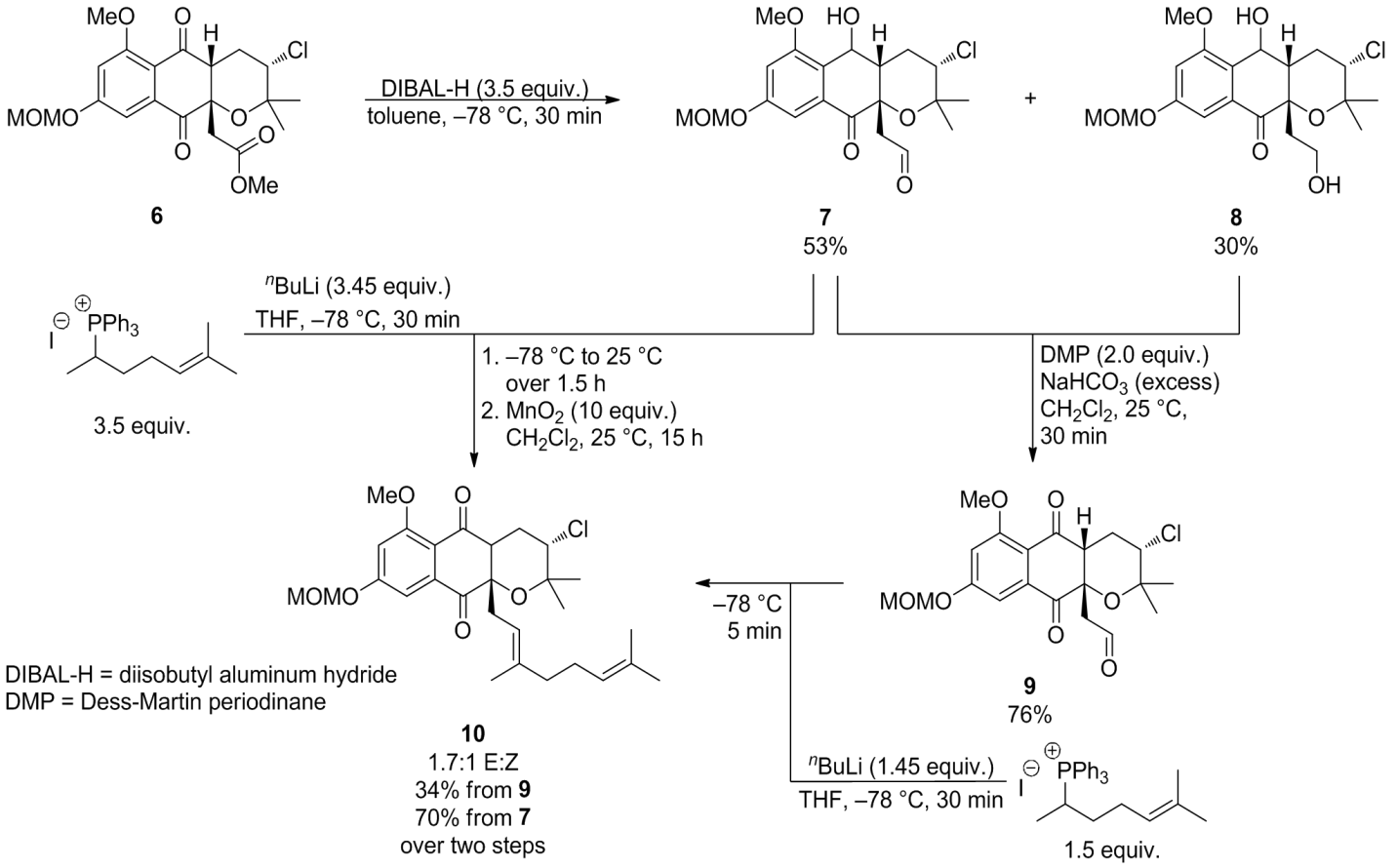
# Forward Synthesis




- Wittig reagent prepared from 5-chloropentan-1-ol in five steps.
- Mixture of **7** and **8** could be jointly oxidized to **9**, followed by Wittig reaction to **10**; longer Wittig reaction times resulted in olefination of the ketone groups in **9**.
- Other olefination reactions, including Julia-Kocienski and cross-metathesis, were ineffective.
- Alternatively, isolated **7** could undergo Wittig reaction followed by oxidation to give **10** in higher yield.



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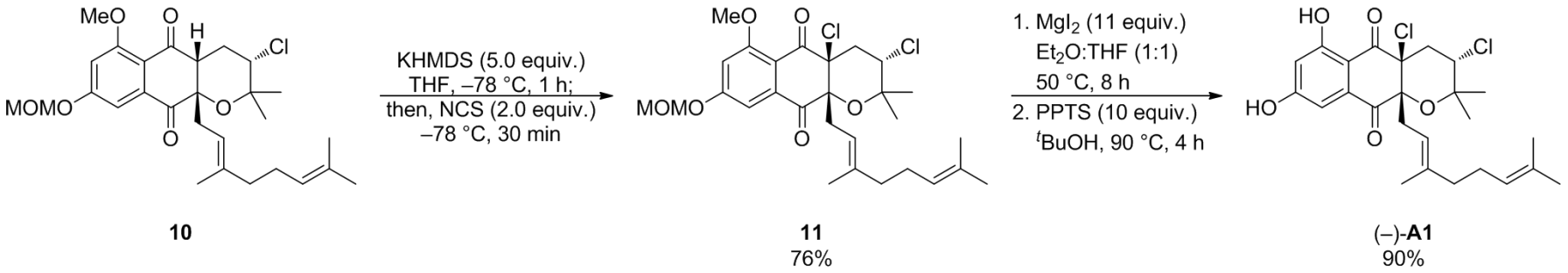
# Forward Synthesis




**10**

**11**
76%

(–)-**A1**
90%

KHMDS = potassium hexamethyldisilazide
NCS = *N*-chlorosuccinimide
PPTS = pyridinium *p*-toluenesulfonate

- Alkene isomers of **11** separable on preparative TLC.



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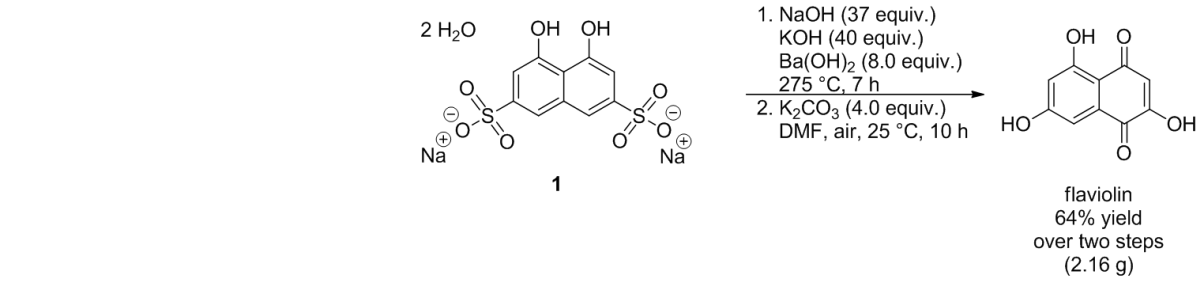
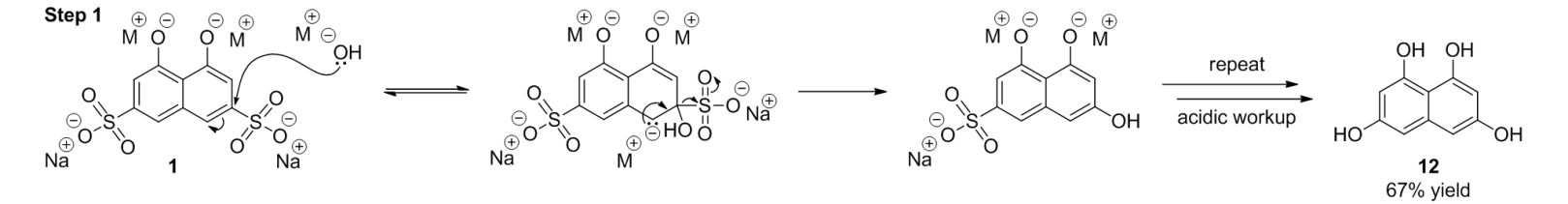
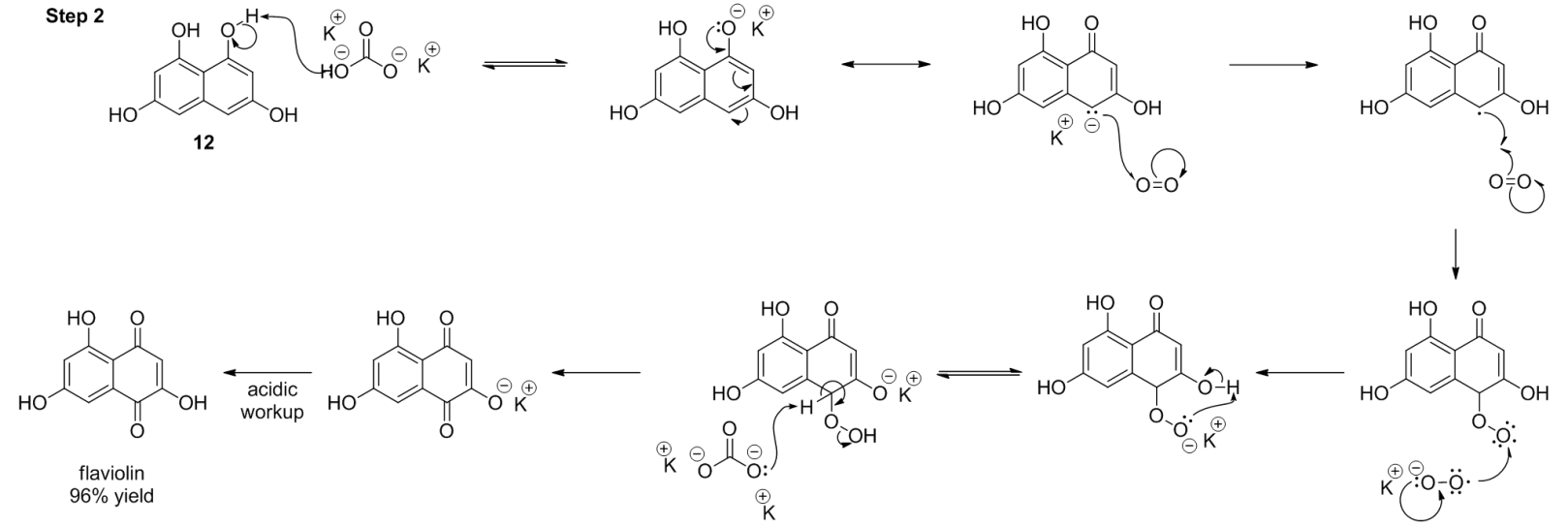
# Summary

- Asymmetric synthesis of (–)-Napyradiomycin A1 (enantiomer of naturally-occurring compound).
- 15 steps longest linear sequence.
- Protocol for enantioselective chlorination of isolated alkene developed to control stereochemistry for remainder of the synthesis.
- Quaternary stereocenter generated through Johnson-Claisen rearrangement.

# Mechanisms



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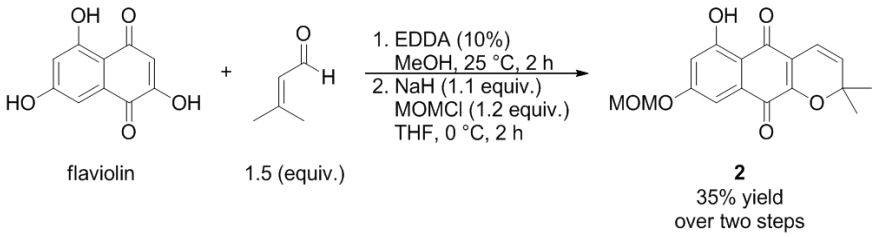
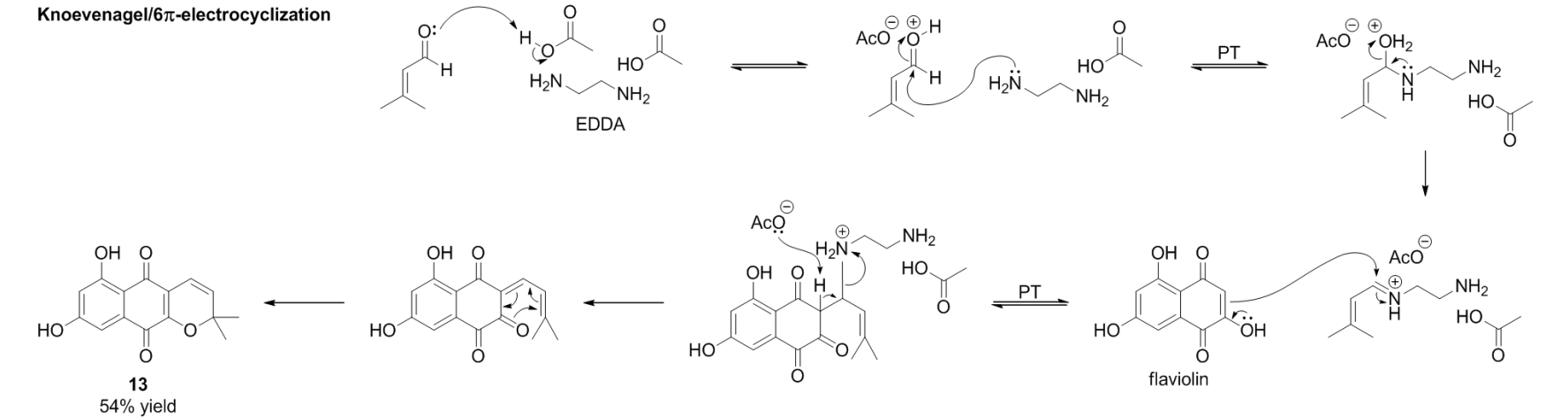
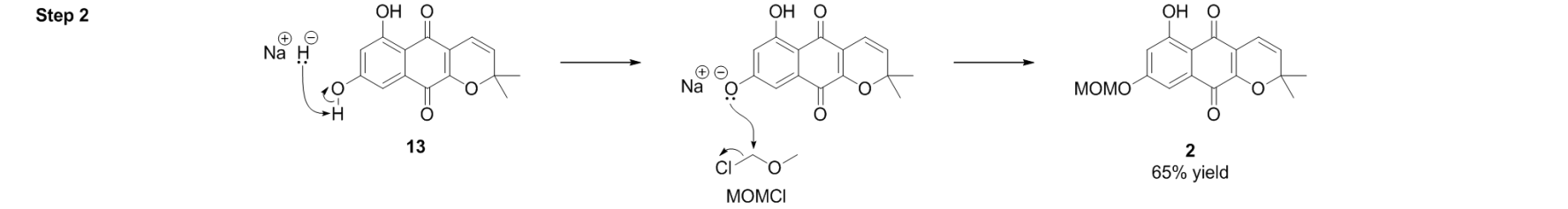
# Mechanisms



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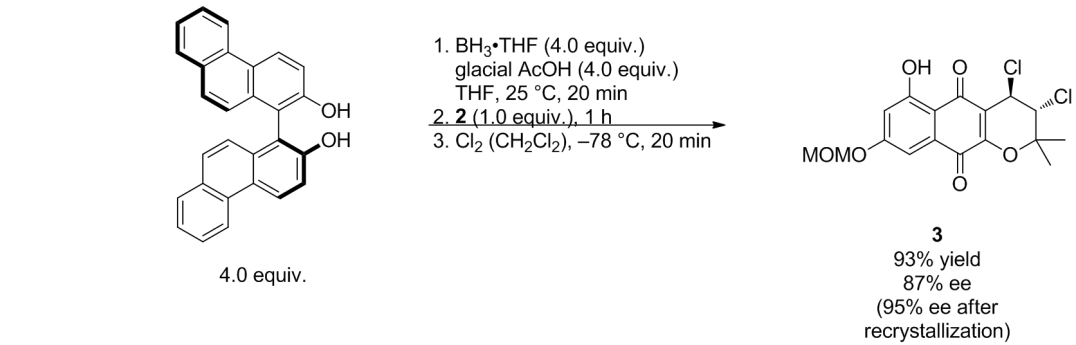


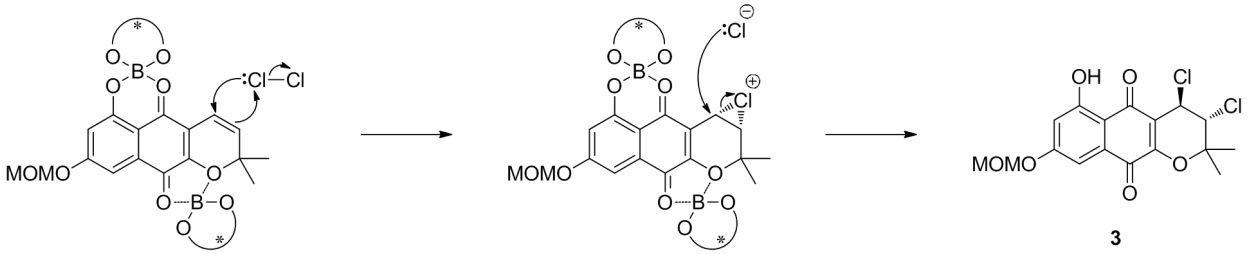


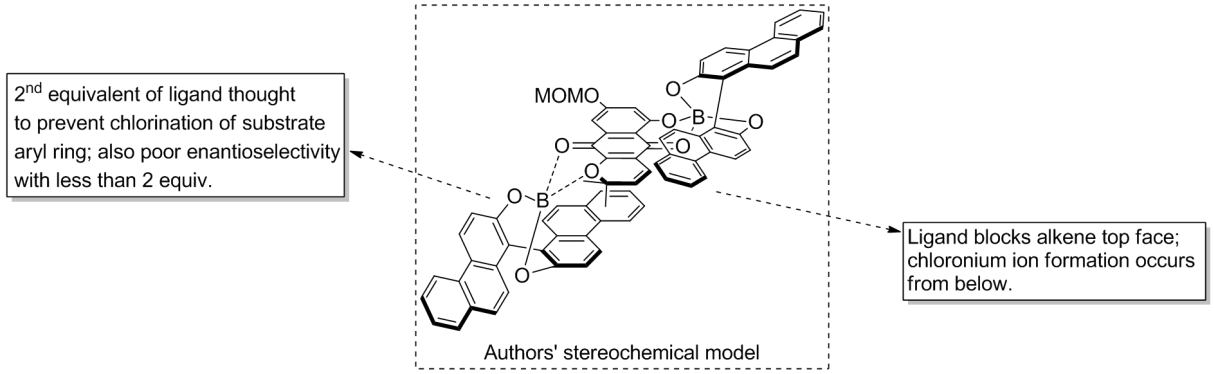




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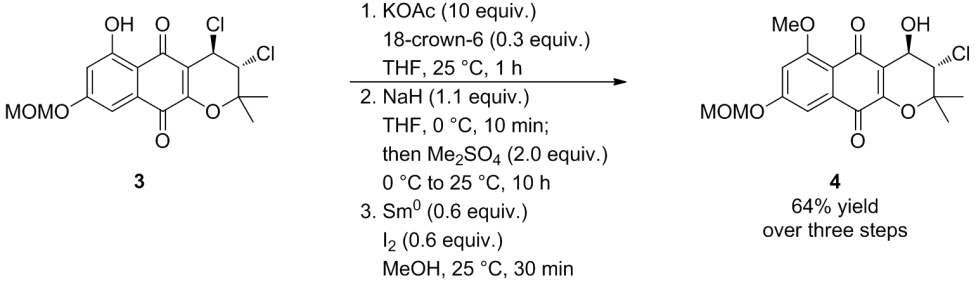


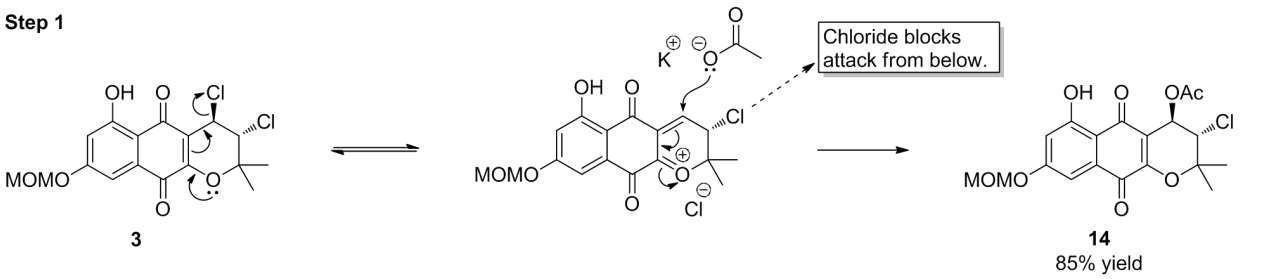


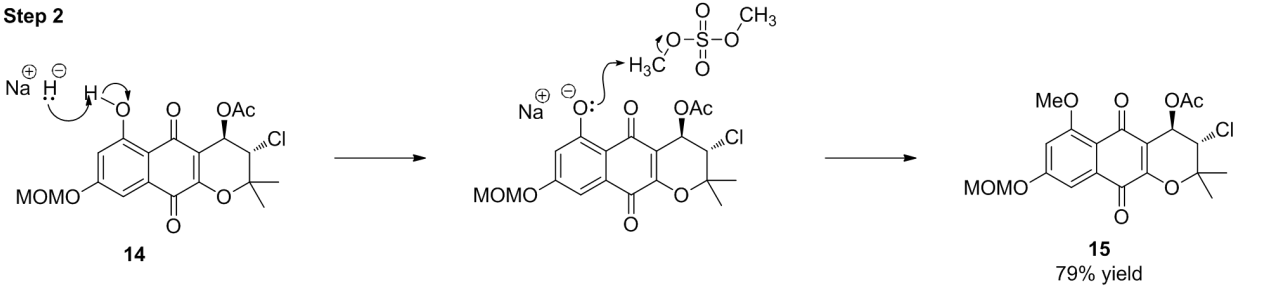


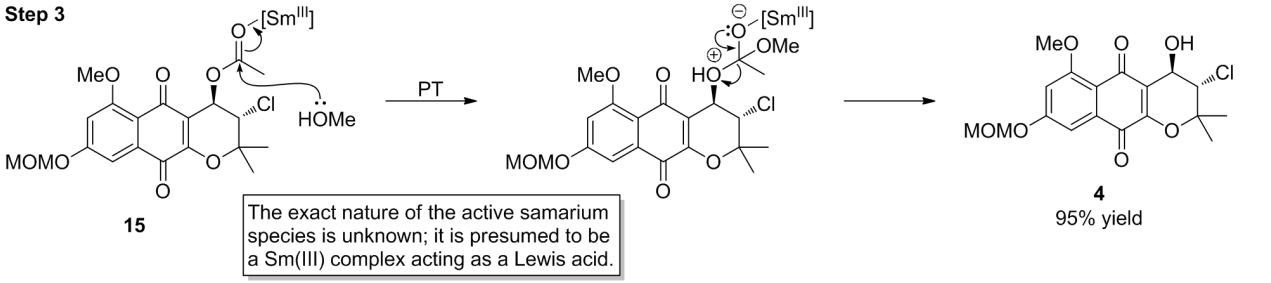




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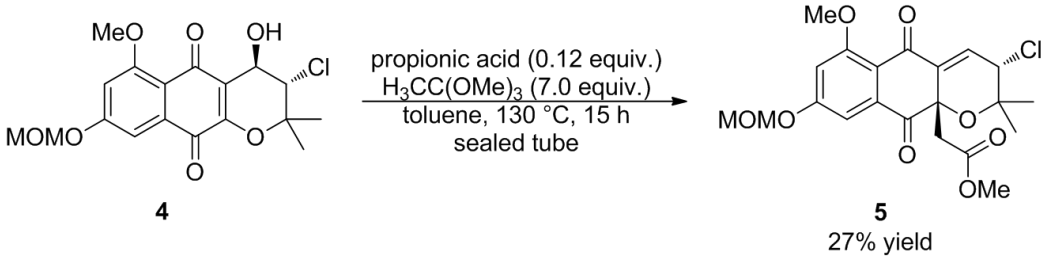
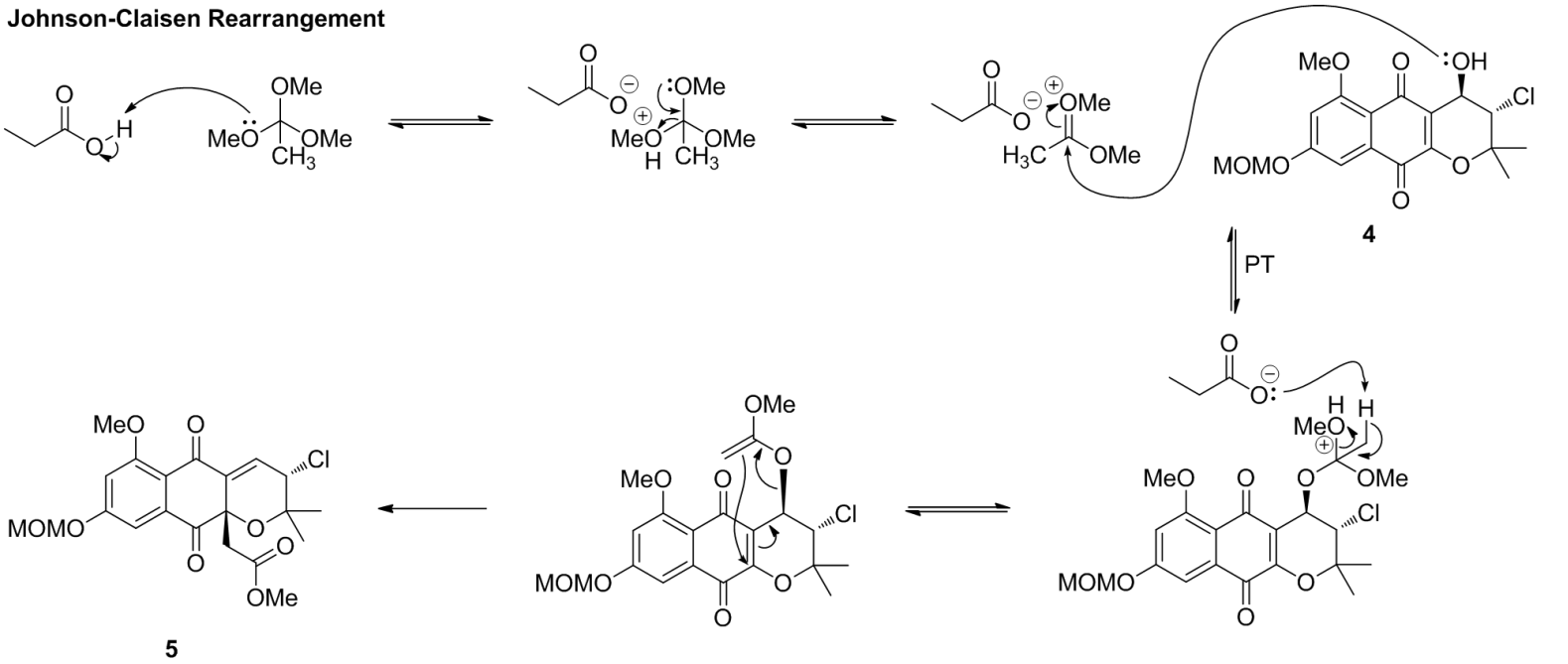
Yanada, R.; Negoro, N.; Bessho, K.; Yanada, K. *Synlett* **1995,** 1261–1263.

# Mechanisms



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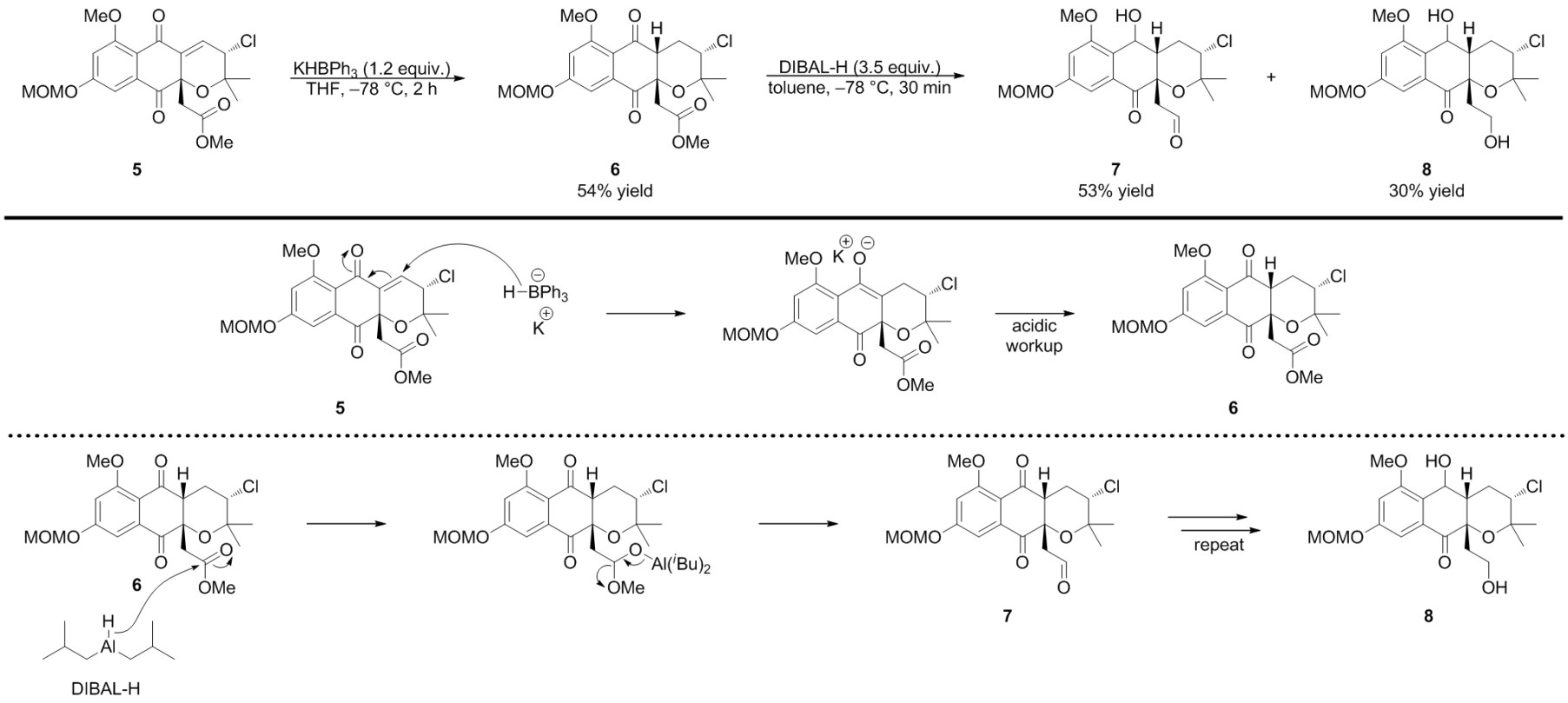




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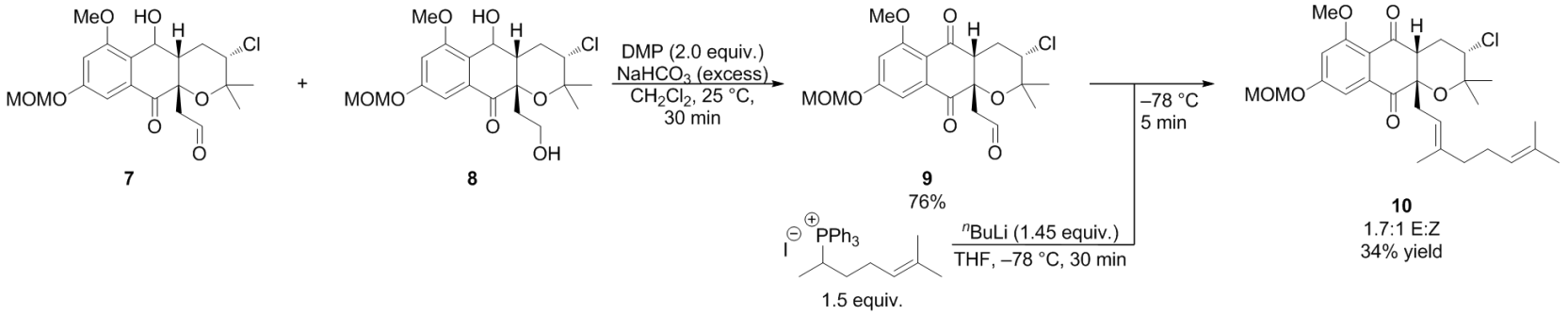


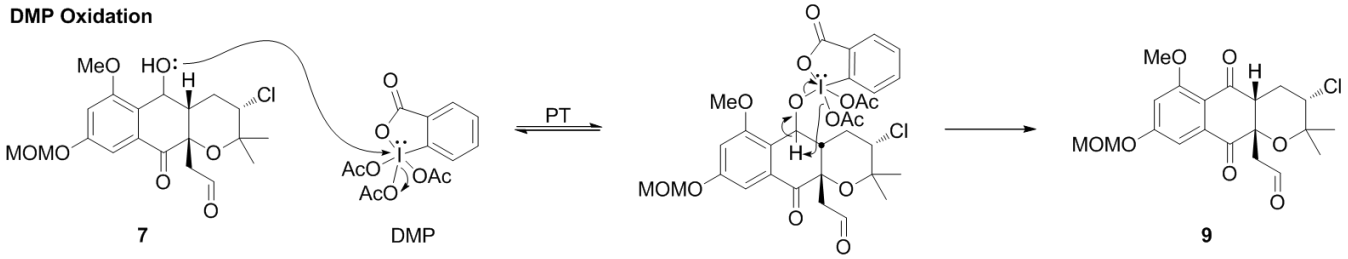


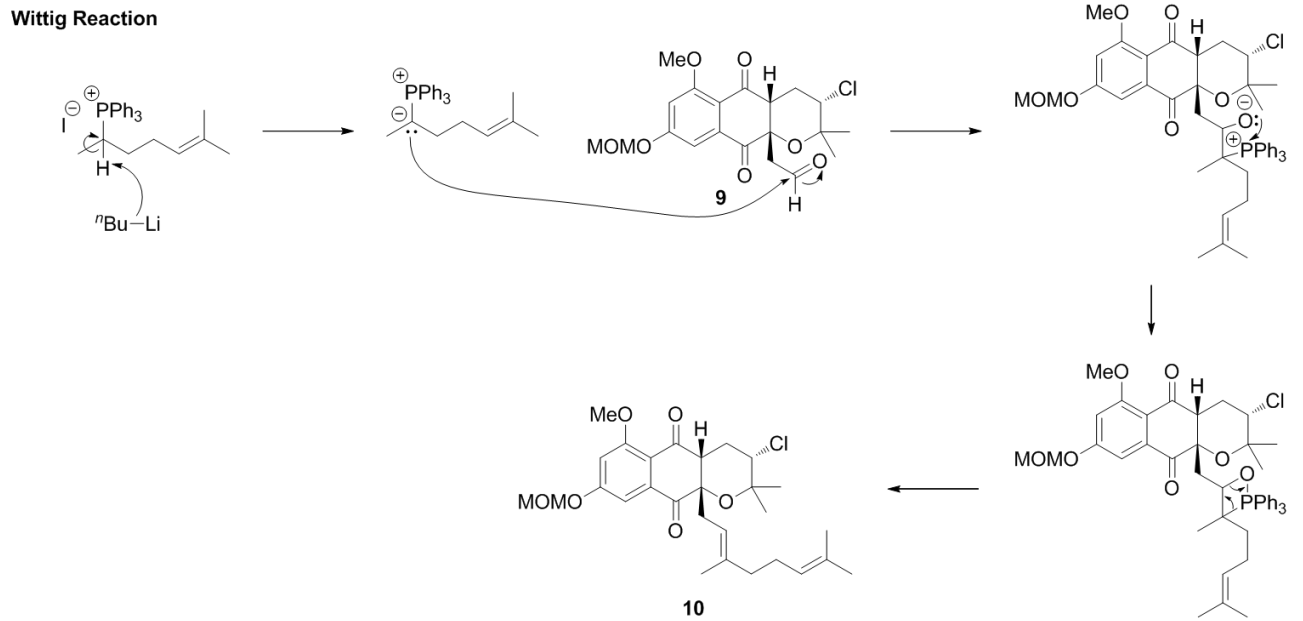




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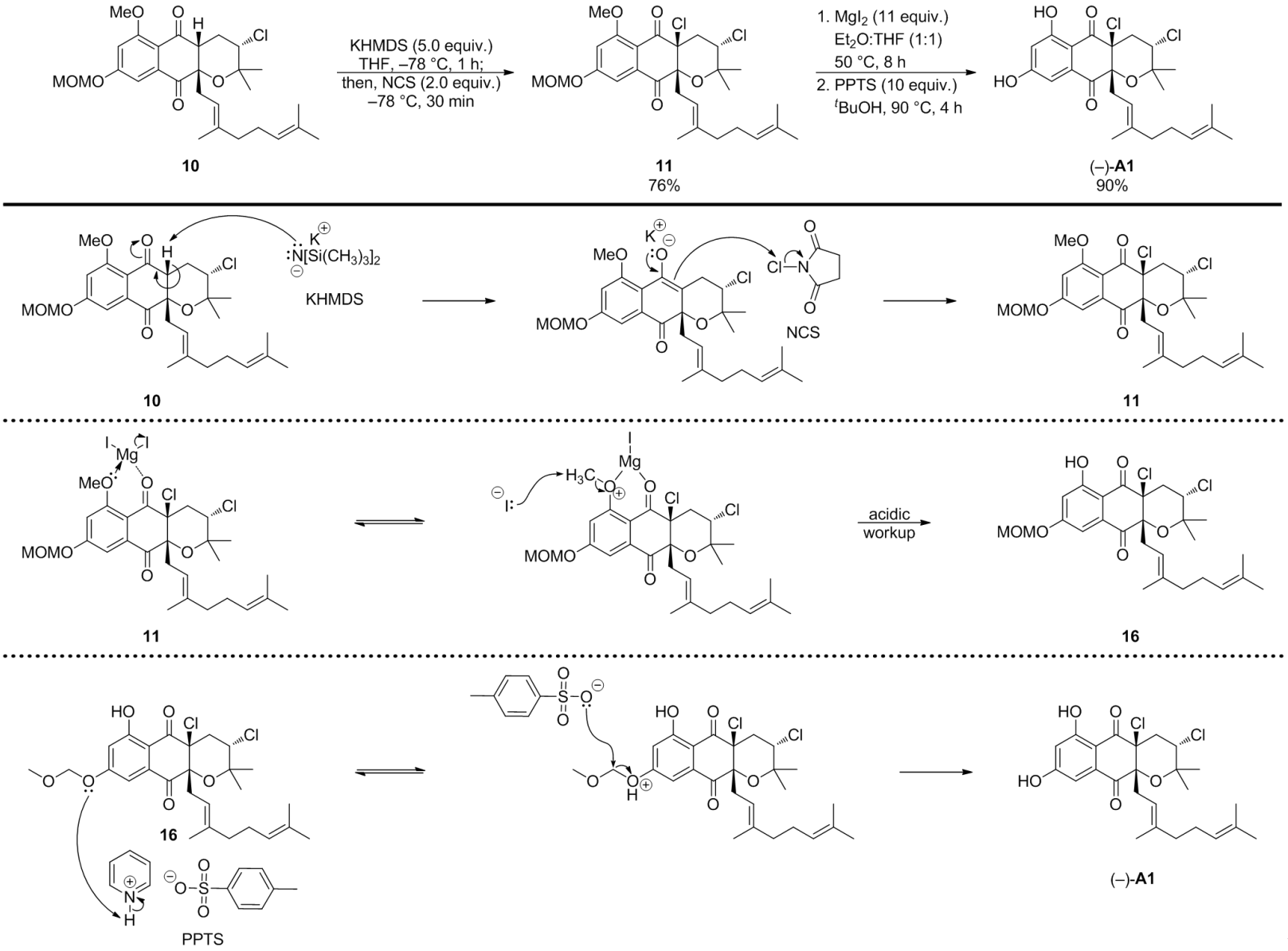
# Mechanisms






Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009,** *131,* 5744–5745.