# 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.* *131,* 5744–5745.

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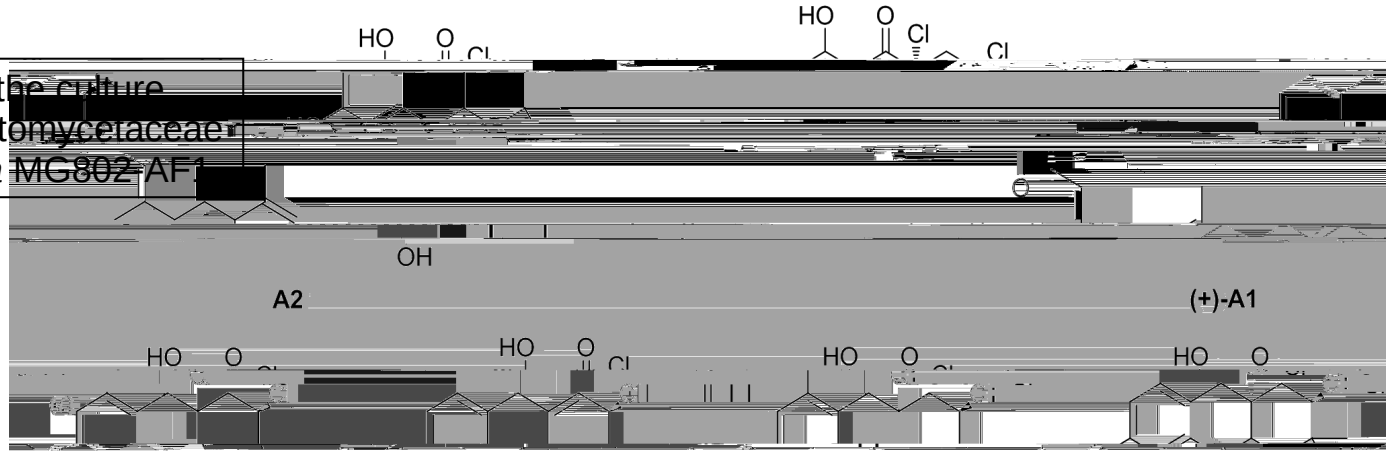
Liu Group
July 1, 2015

# Previous Isolation and Characterization Studies

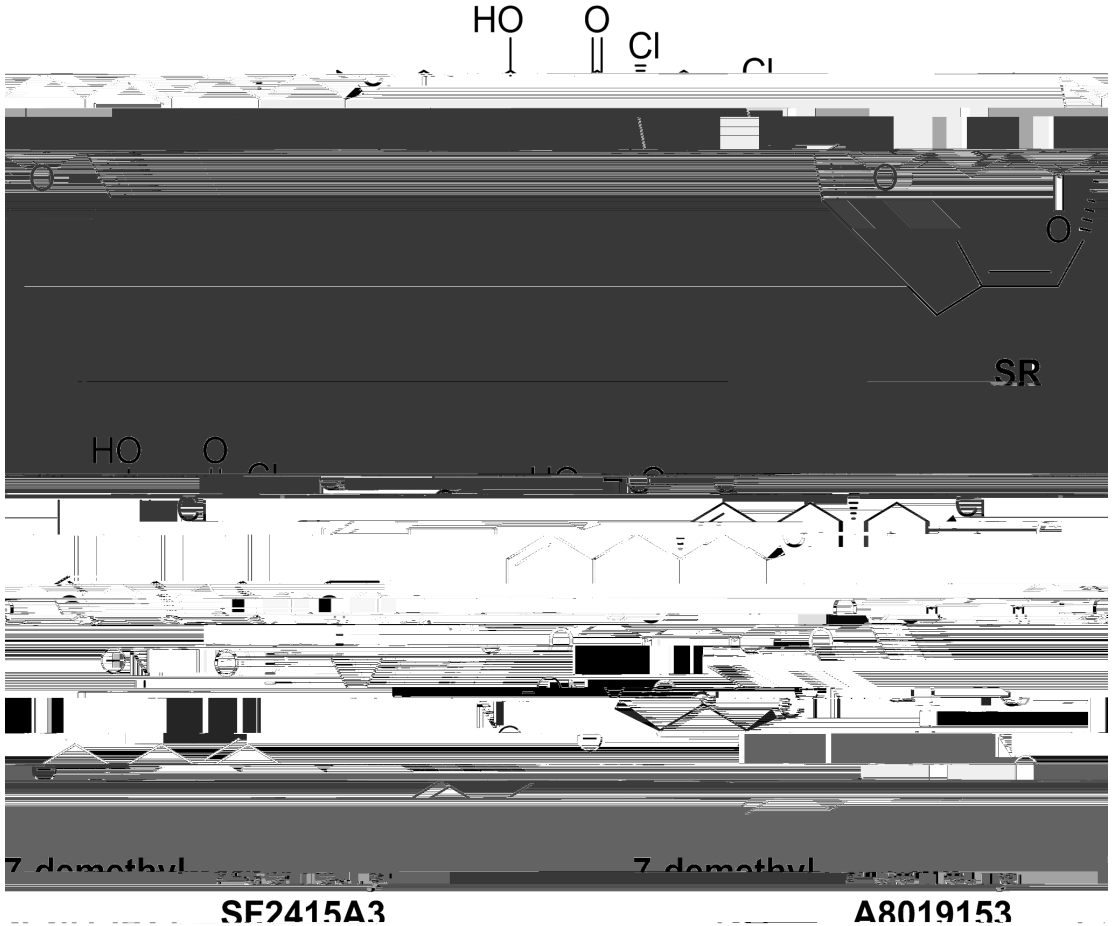
Originally isolated from the culture broth of terrestrial Streptomycetaceae bacterium *Chainia rubra* MG802-AF1




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

a) Shiomi, K.; Iinuma, H.; Hamada, M.; Naganawa, H.; Manabe, M.; Matsuki, C.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* *39,* 487–493; b) Shiomi, K.; Nakamura, H.; Iinuma, H.; Naganawa, H.; Isshiki, K.; Takeuchi, T.; Umezawa, H.; Itaka, Y. *J. Antibiot.* *39,* 494–501; c) Shiomi, K.; Nakamura, H.; Iinuma, H.; Naganawa, H.; Takeuchi, T.; Umezawa, H.; Itaka, Y. *J. Antibiot.* *40,* 1213–1219.
Soria-Mercado, I. E.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. J. *J. Nat. Prod.* *68,* 904–910.

# Previous Isolation and Characterization Studies




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



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

# Biological Activity


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

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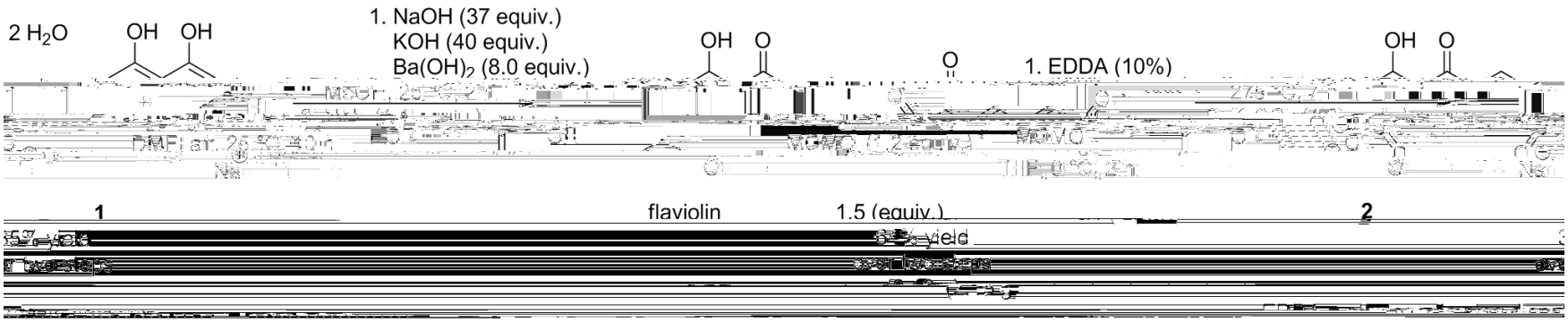
# Previous Synthesis

- Only (±)-A1 had been synthesized previously.

# 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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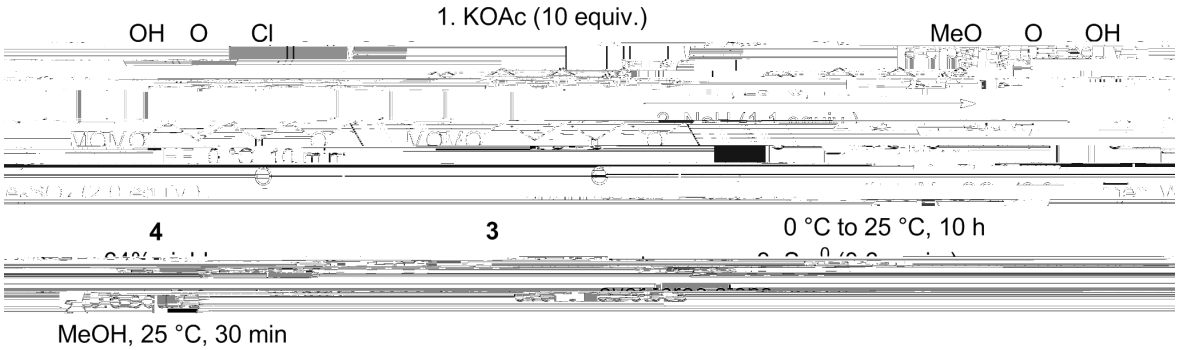
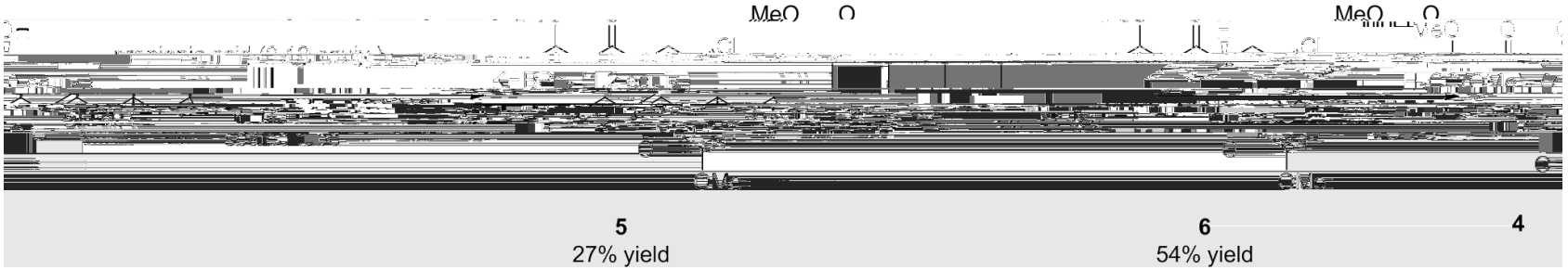
# Forward Synthesis

# 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.

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# Forward Synthesis

- Wittig reagent prepared from 5-chloropentan-1-ol in five epi8



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# Forward Synthesis

- Alkene isomers of



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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.
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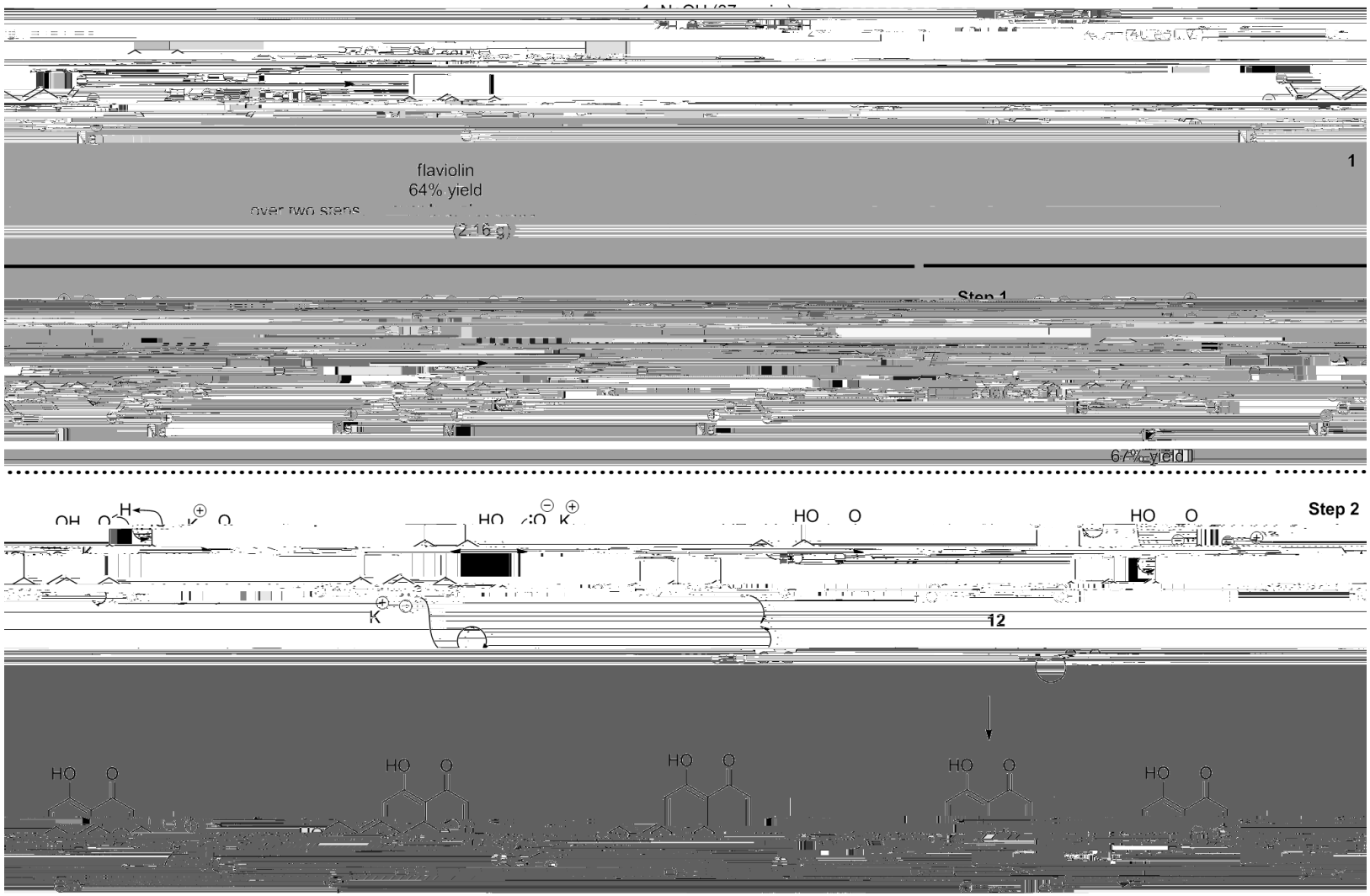
# Mechanisms



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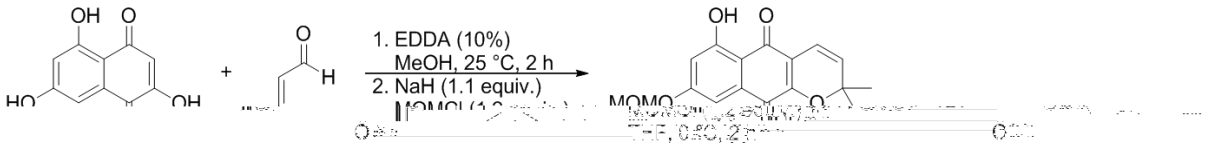
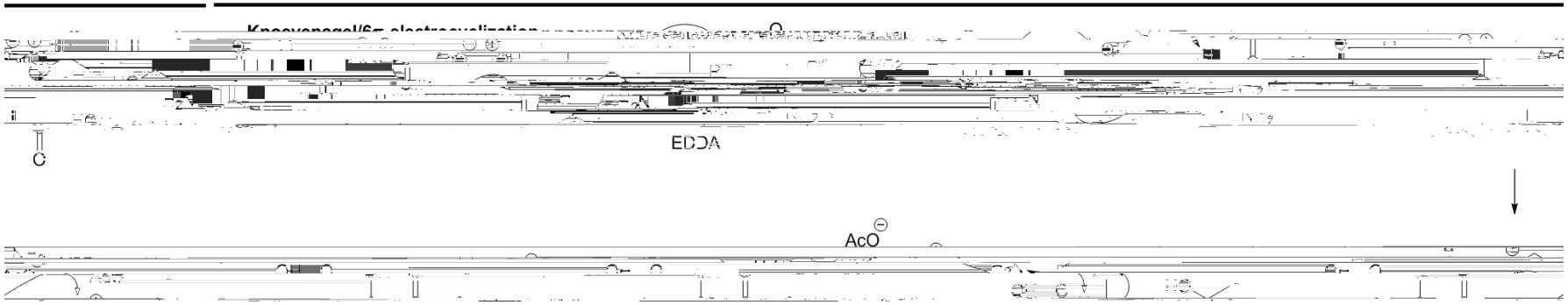



flaviolin 1.5 (equiv.)

**2**
35% yield
over two steps



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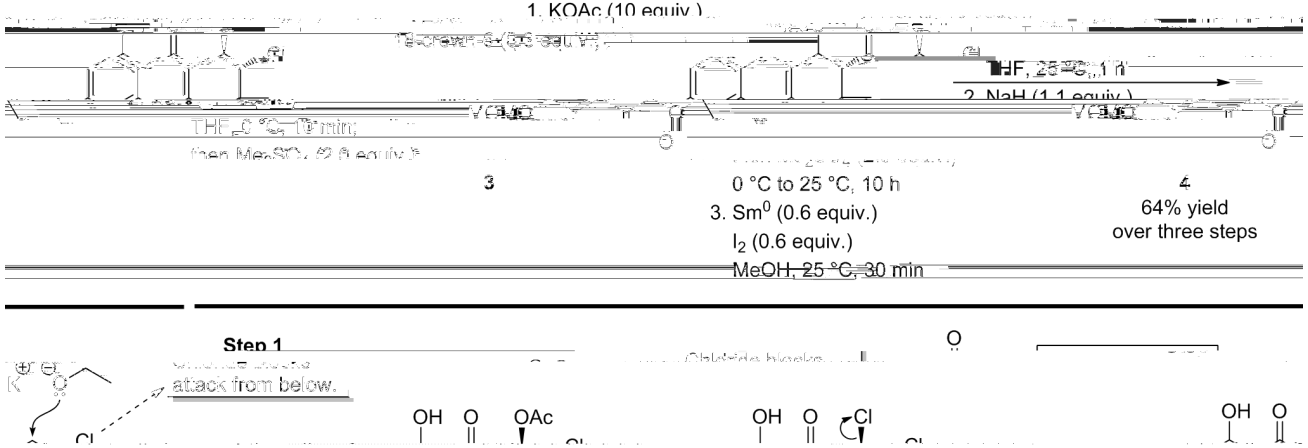




Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* *131,* 5744–5745.
Yanada, R.; Negoro, N.; Bessho, K.; Yanada, K. *Synlett* 1261–1263.

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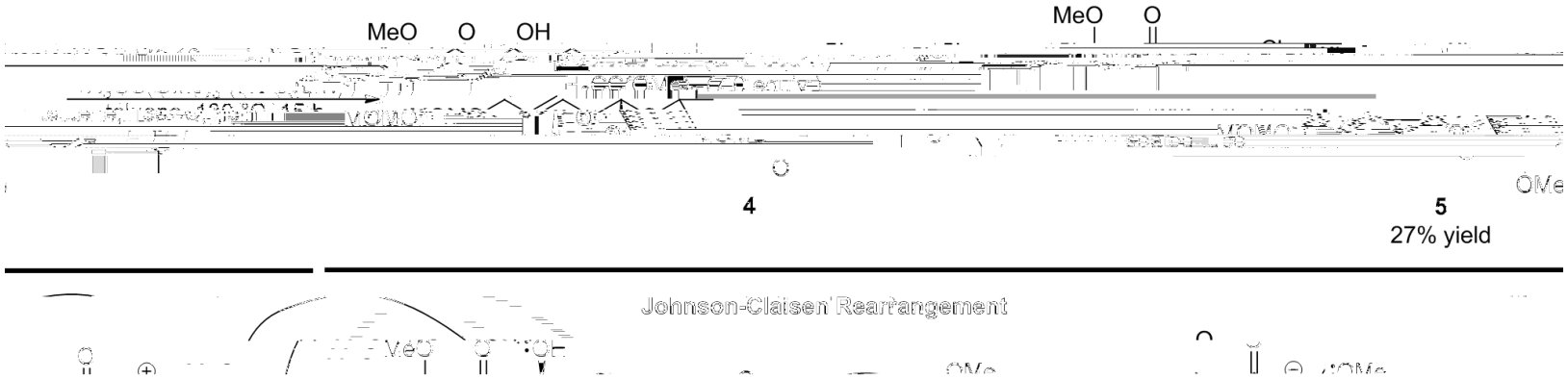




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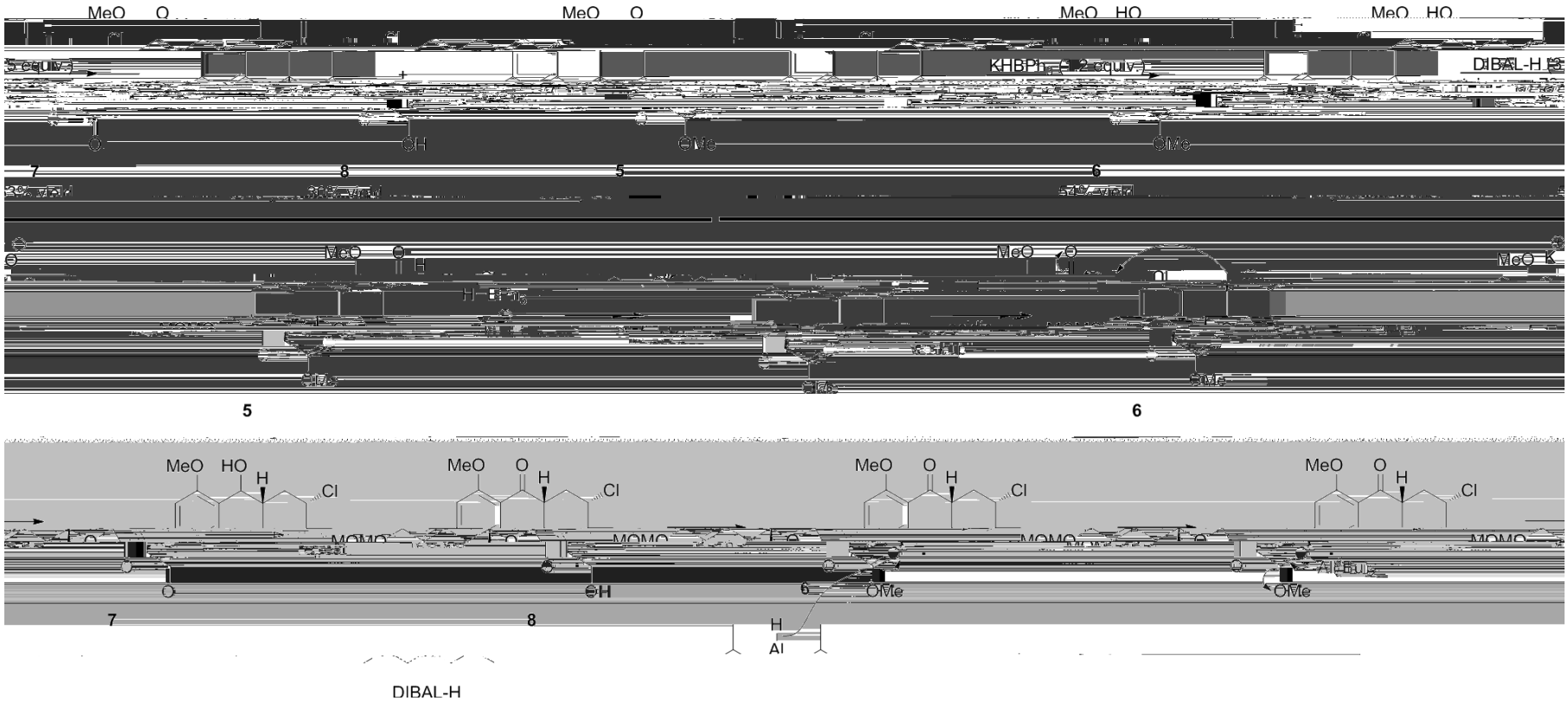




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