

Isolation and Bioactivity



- phainanoids A-F were isolated from *Phyllanthus hainanensis*
 - only native to Hainan island in China

Isolation and Bioactivity

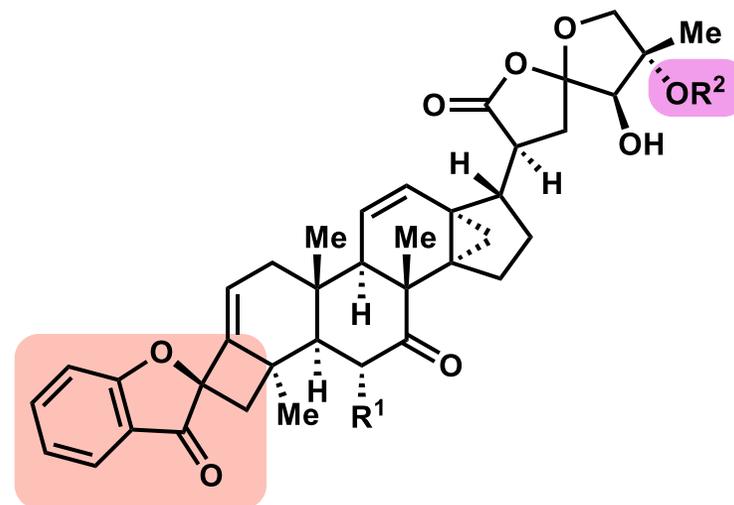


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- found to have potent immunosuppressive activity against T and B lymphocytes compared to clinically used cyclosporin A

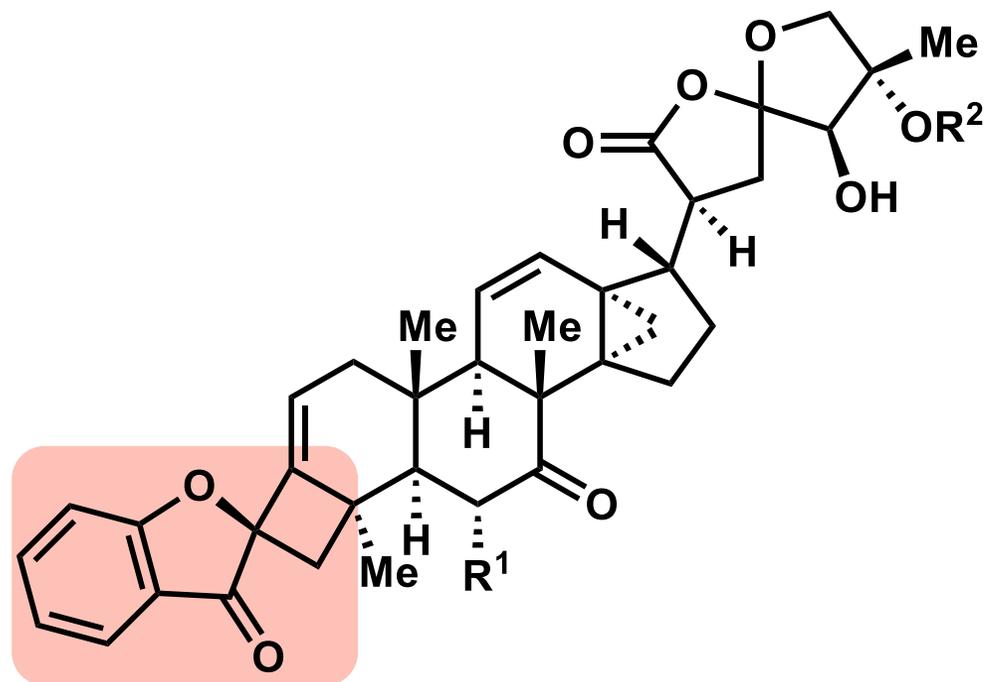
Isolation and Bioactivity



- phainanoids A-F were isolated from *Phyllanthus hainanensis*
 - only native to Hainan island in China
- found to have potent immunosuppressive activity against T and B lymphocytes compared to clinically used cyclosporin A
- structure-activity relationship postulated the 4,5-spirocycle is crucial for the bioactivity
 - OR² with methyl or acyl groups exhibited improved activities

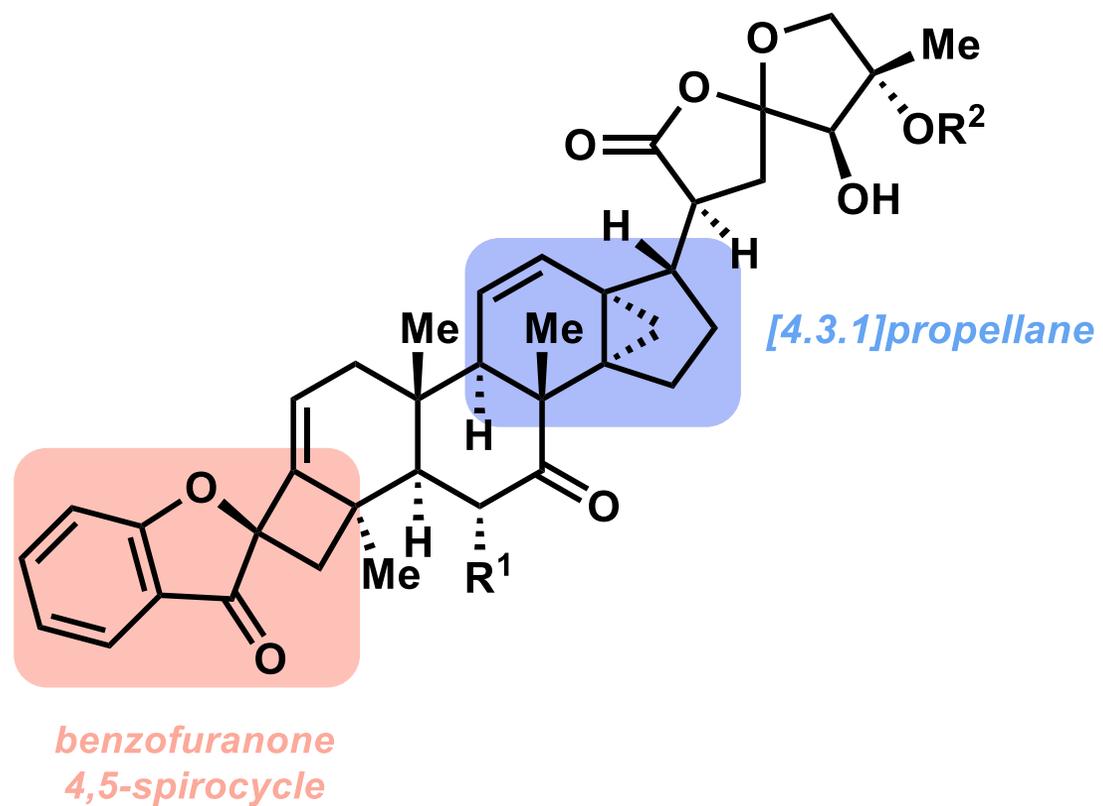


Structural Challenges

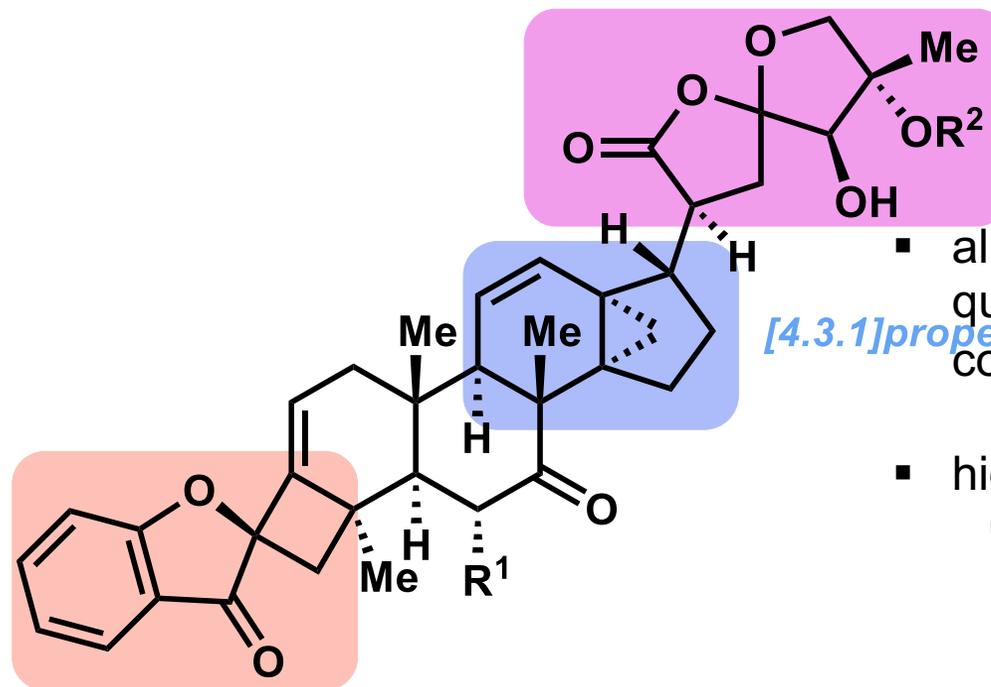


*benzofuranone
4,5-spirocycle*

Structural Challenges



Structural Challenges



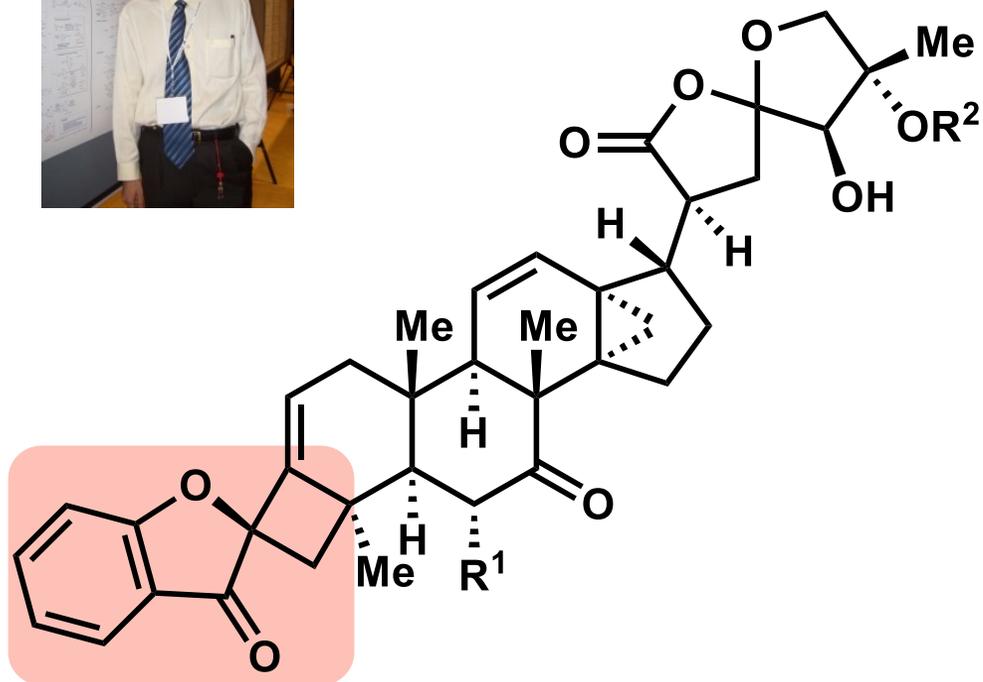
*benzofuranone
4,5-spirocycle*

5,5-oxaspirolactone

[4.3.1]propellane

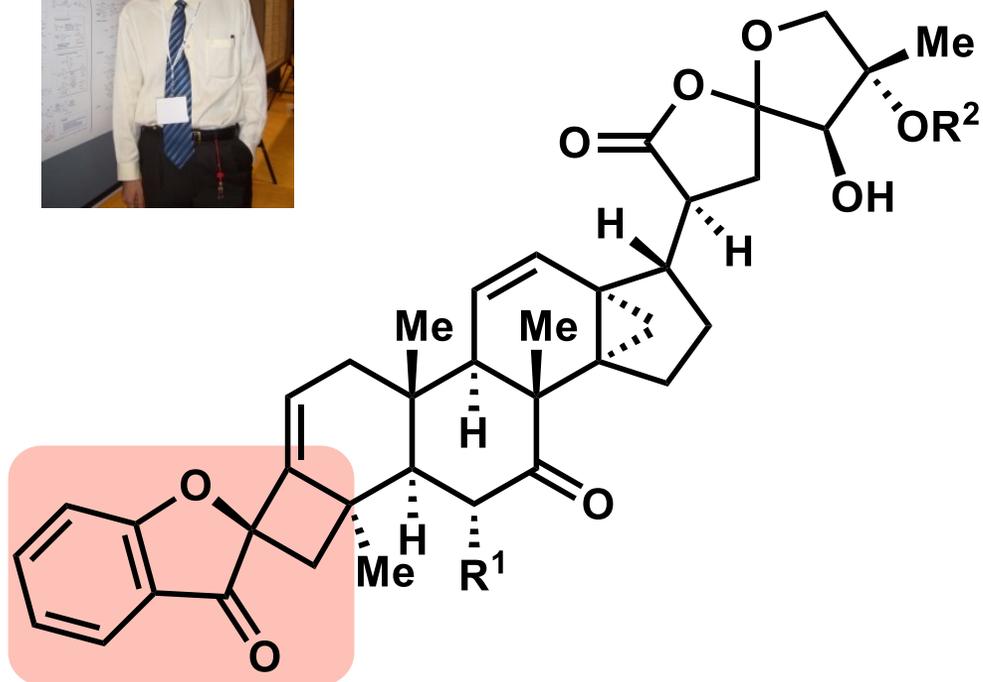
- all phainanoids have at least 8 quaternary centers, 3 of which are contiguous
- highly strained systems
 - alkylidene cyclobutene, vinyl cyclopropane

A Challenger Approaches: Dong's Approach to 4,5-spirocycle

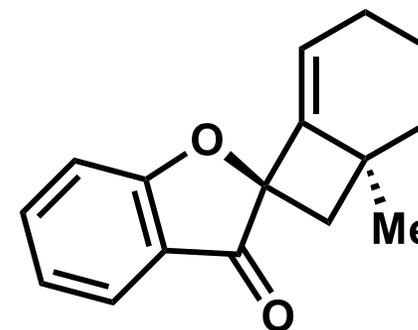


*benzofuranone
4,5-spirocycle*

A Challenger Approaches: Dong's Approach to 4,5-spirocycle



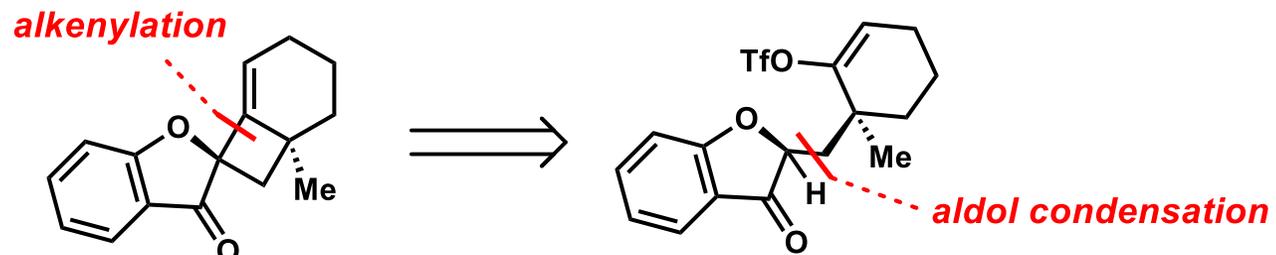
*benzofuranone
4,5-spirocycle*



Dong *et al.* constructed a model system for the 4,5-spirocycle of the phainanoids

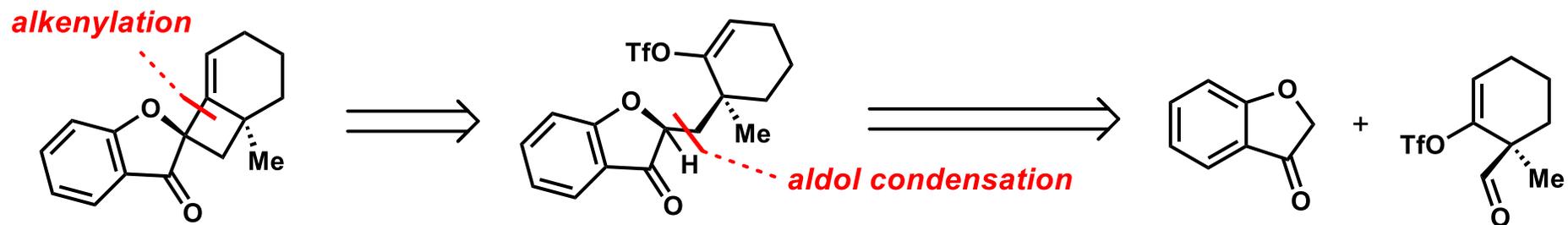
Dong's Approach to 4,5-spirocycle

Retrosynthesis



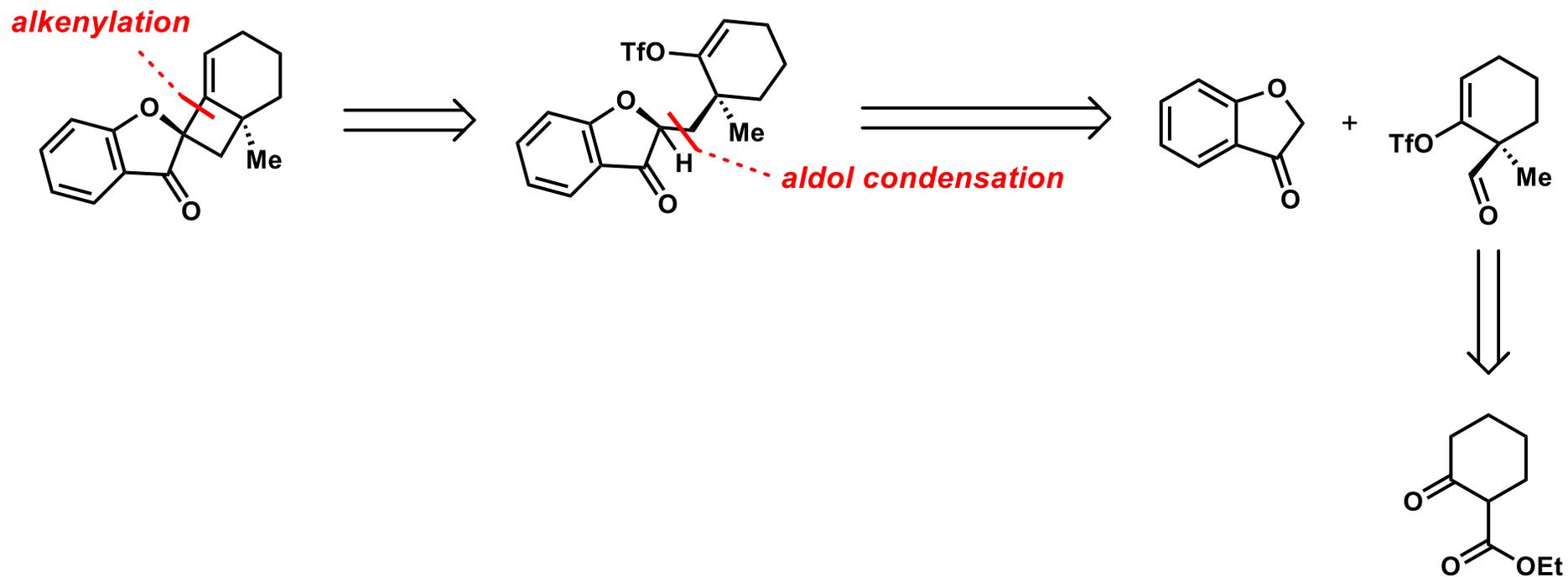
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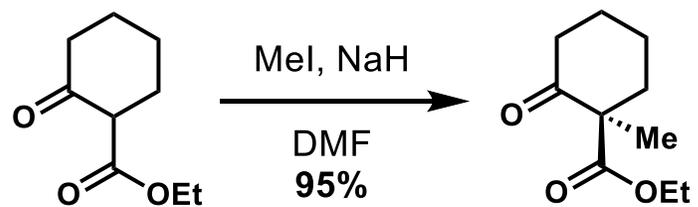


Dong's Approach to 4,5-spirocycle

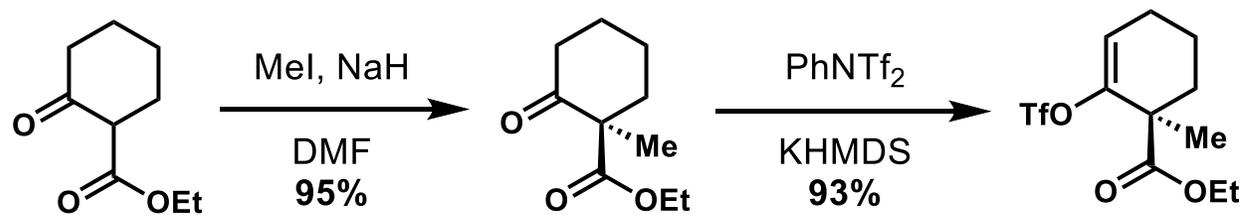
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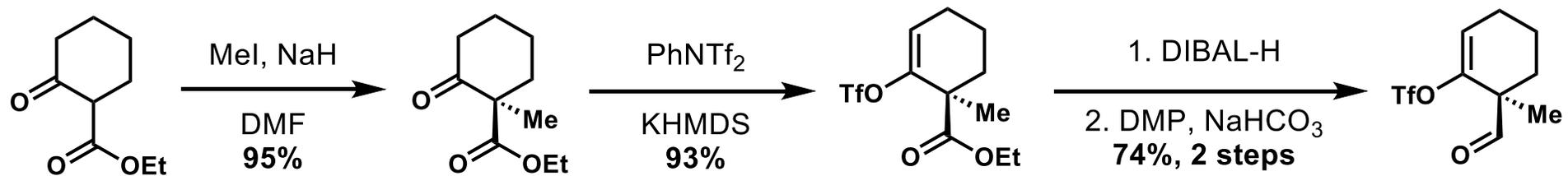
Dong's Approach to 4,5-spirocycle



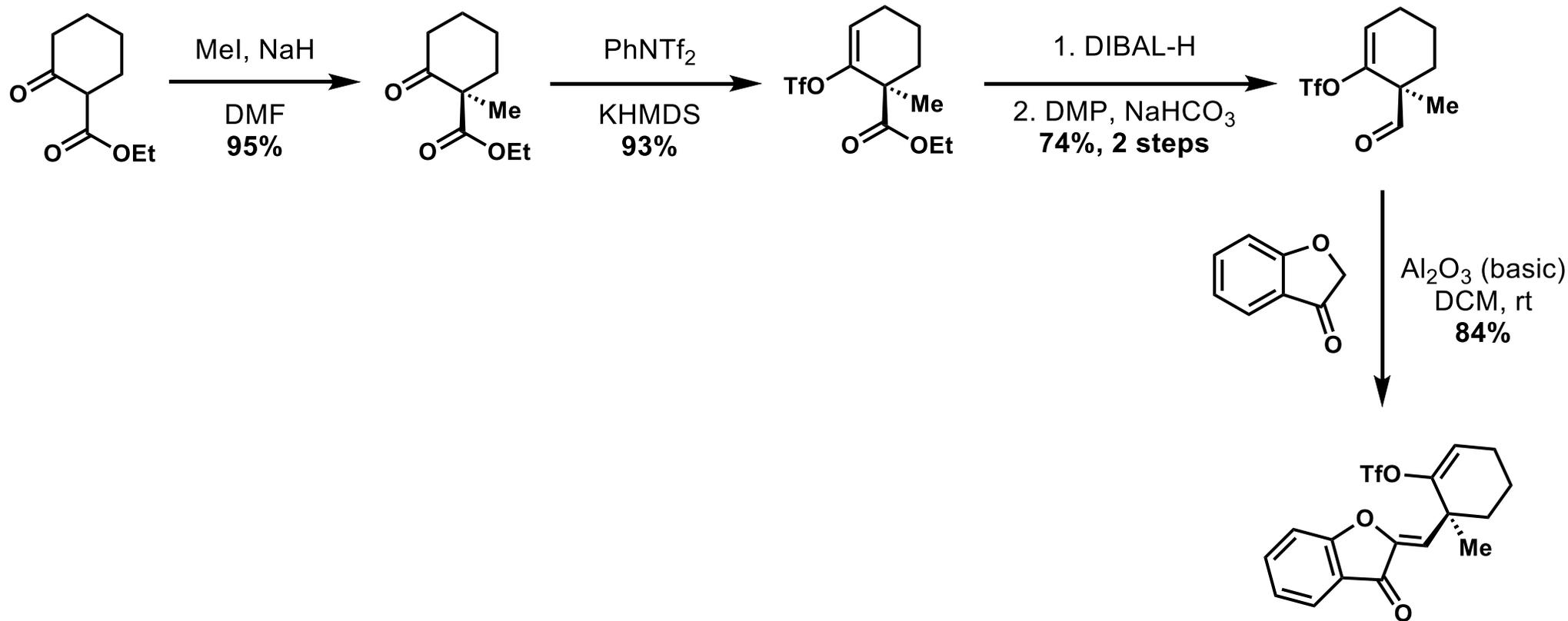
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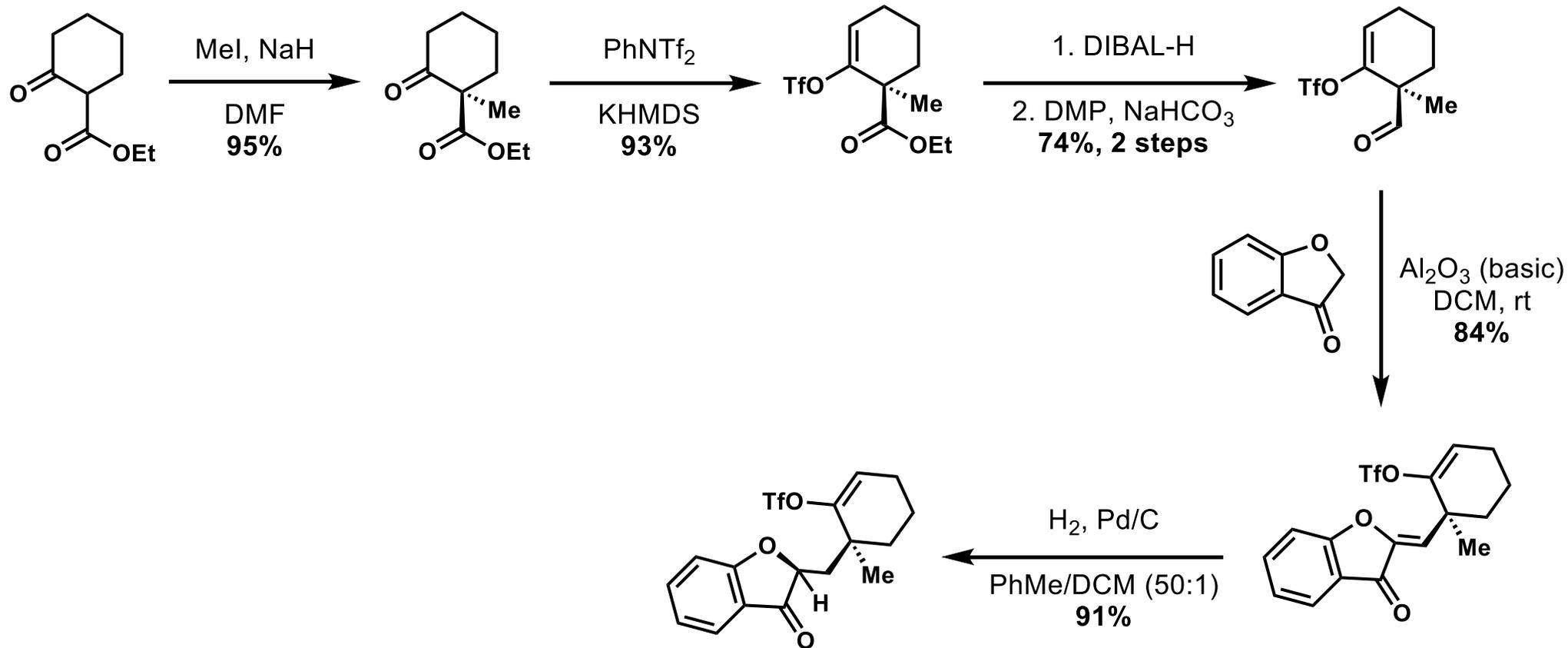
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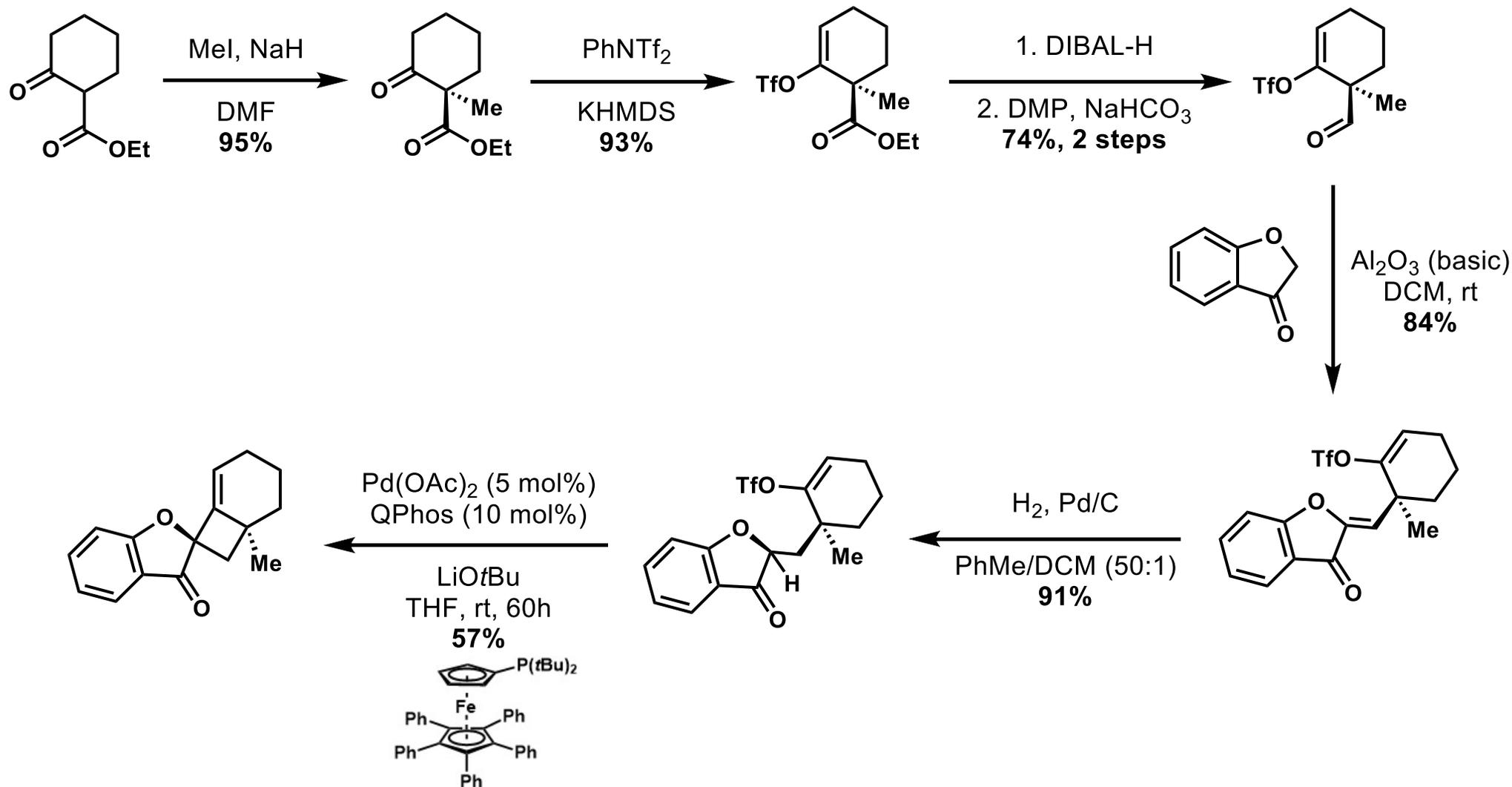
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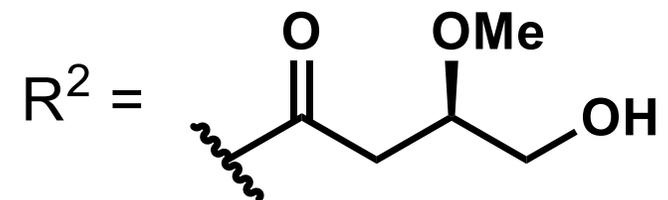
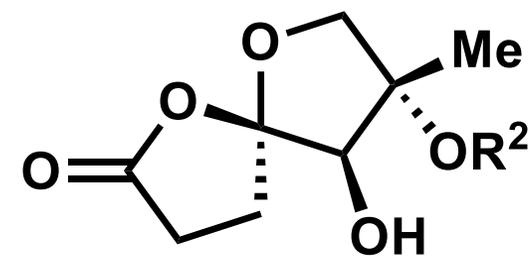
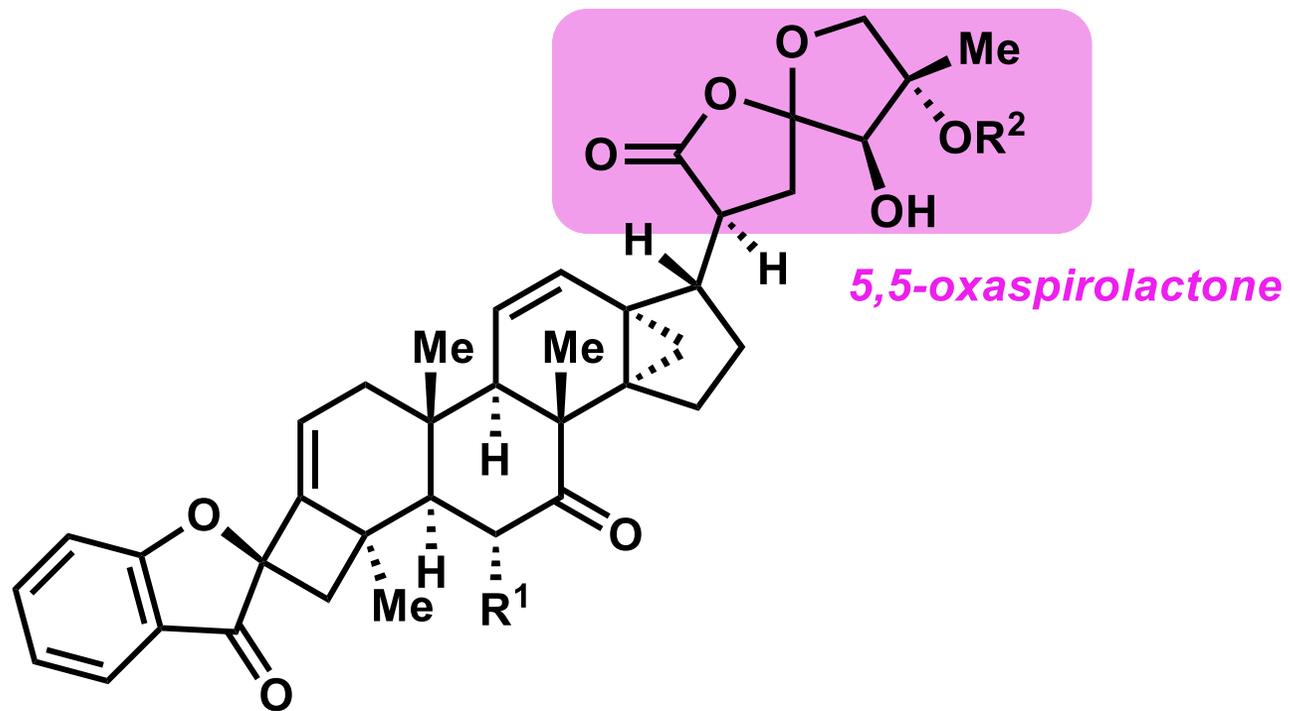
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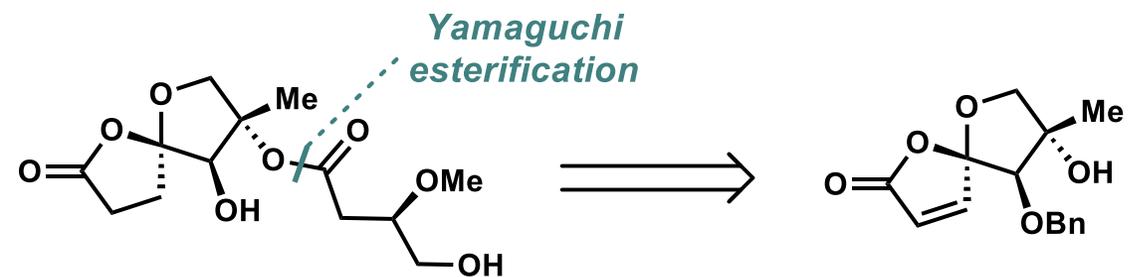


Nan's Approach to oxaspirolactone in Phainanoid F



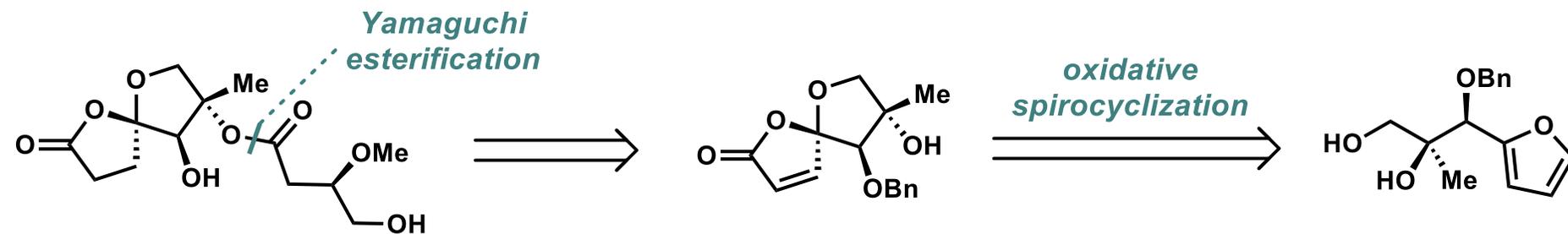
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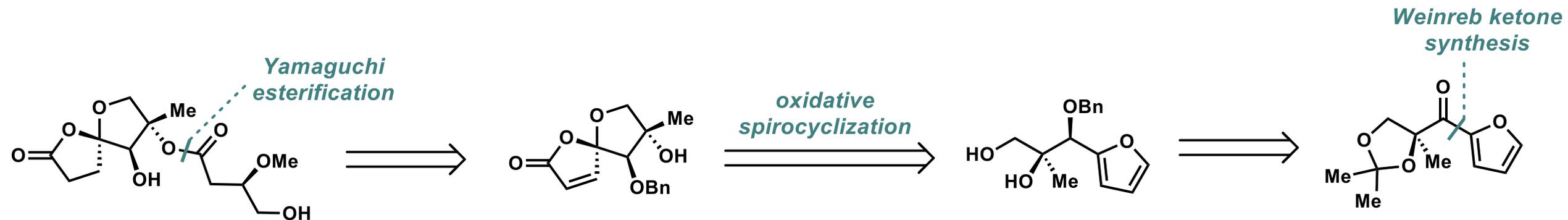
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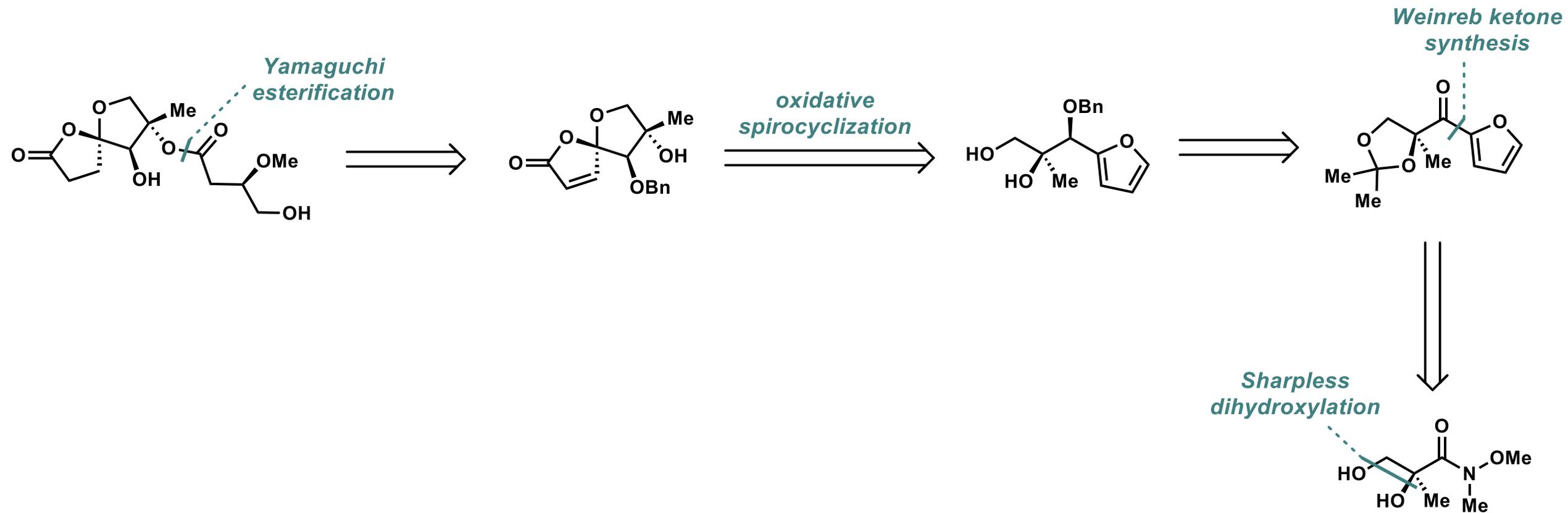
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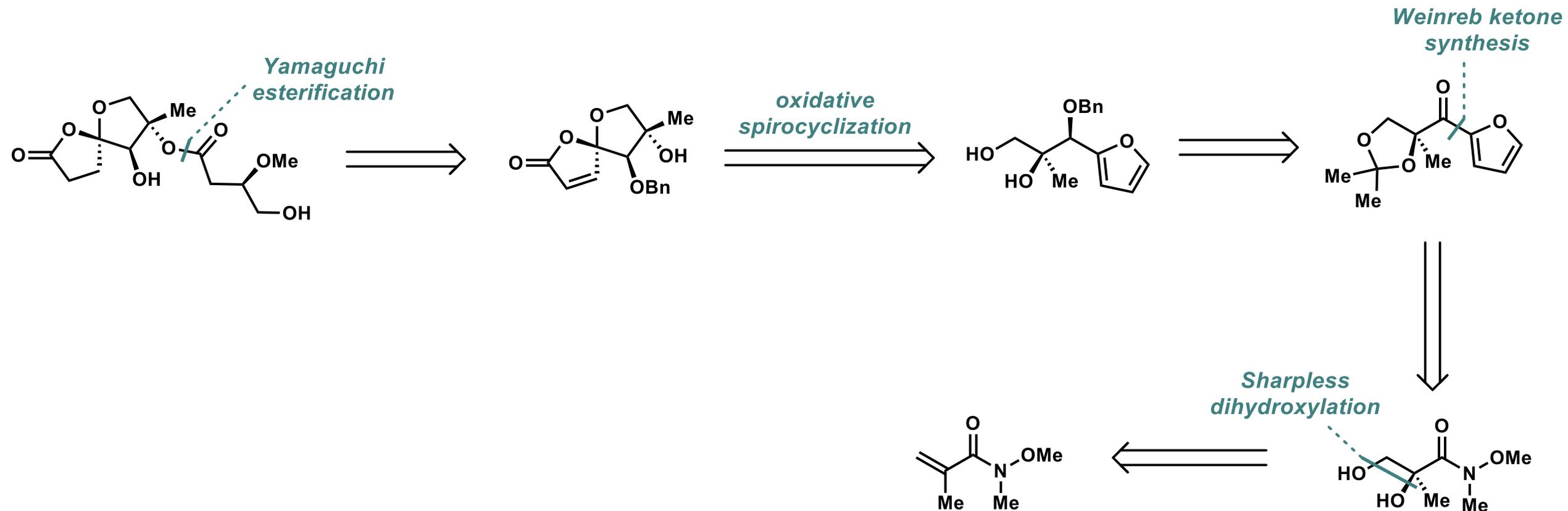
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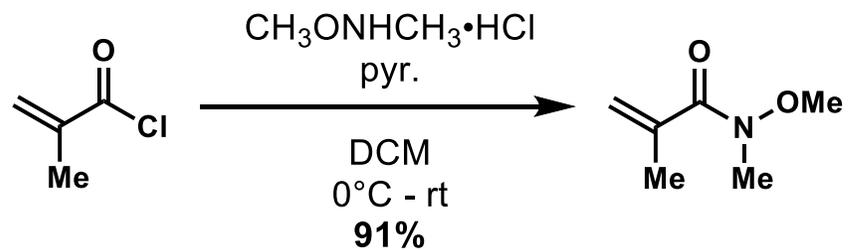
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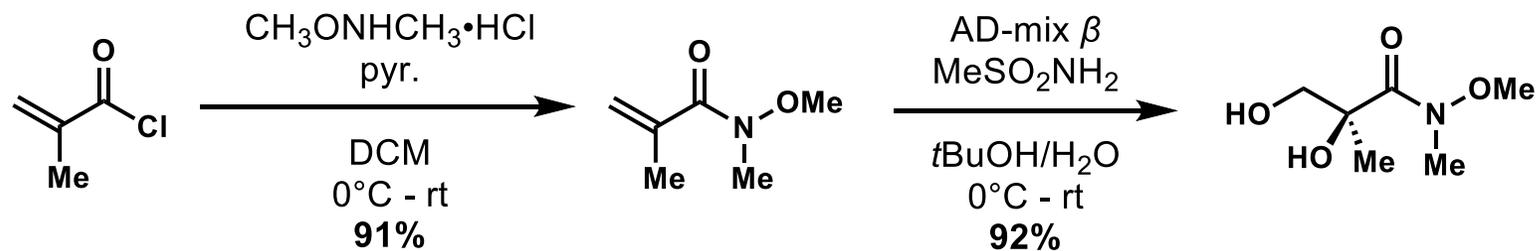
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Formation of furan derivative



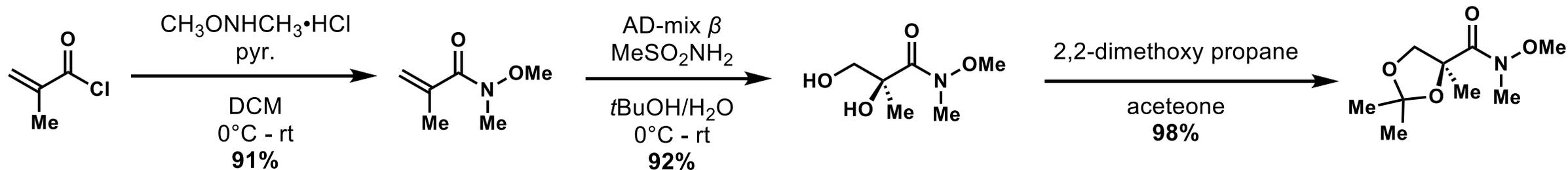
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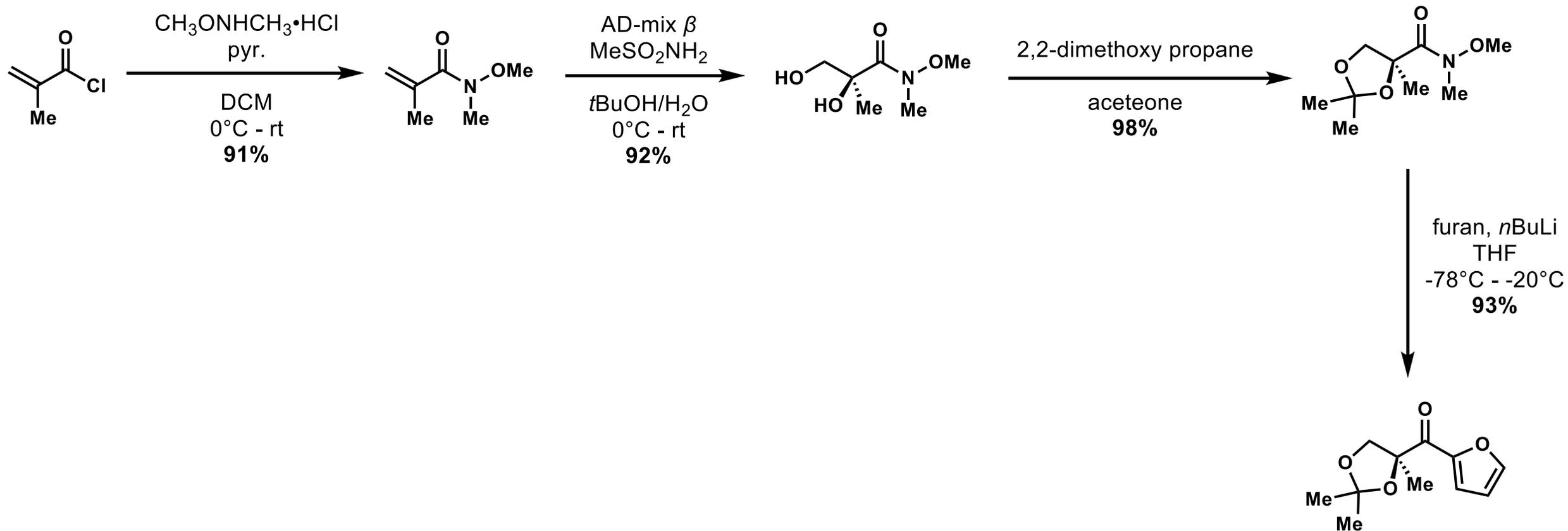
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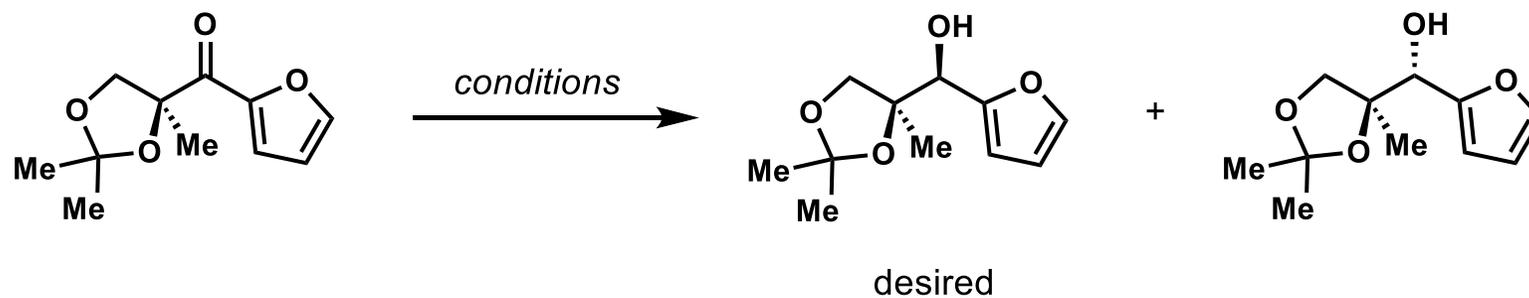
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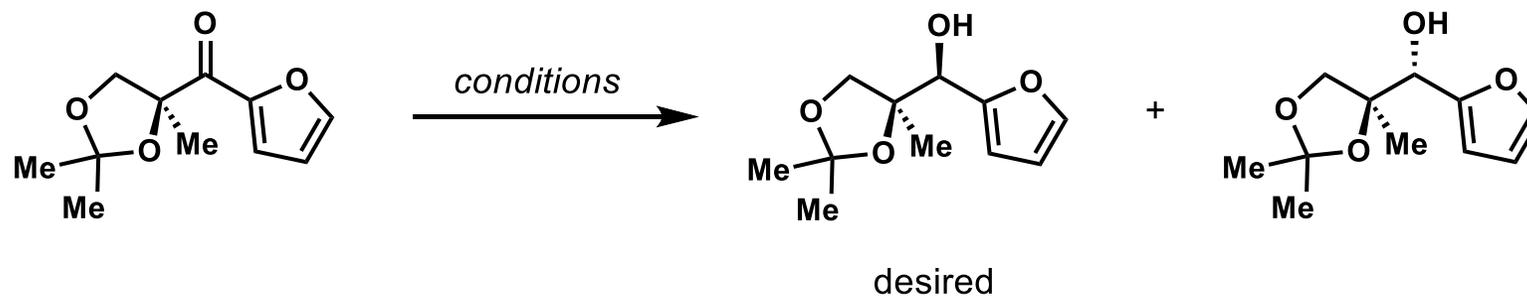
Attempt at selective reduction



conditions: *L*-selectride, CBS reduction

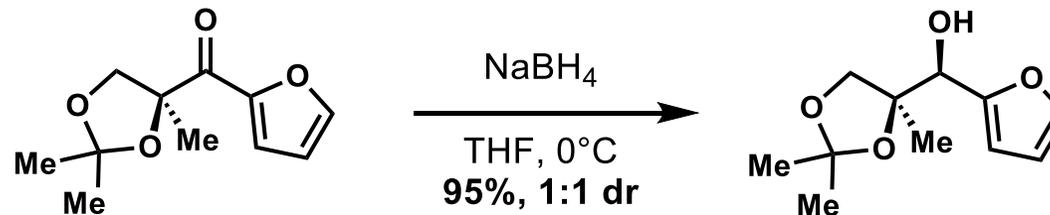
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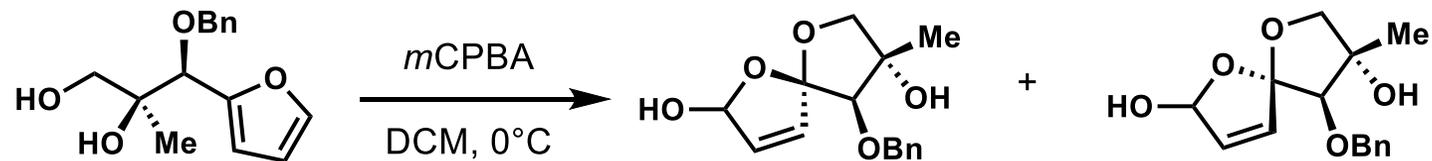
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Attempts at diastereoselective reduction favored the undesired, so they moved forward with separable 1:1 mixture of diastereomers



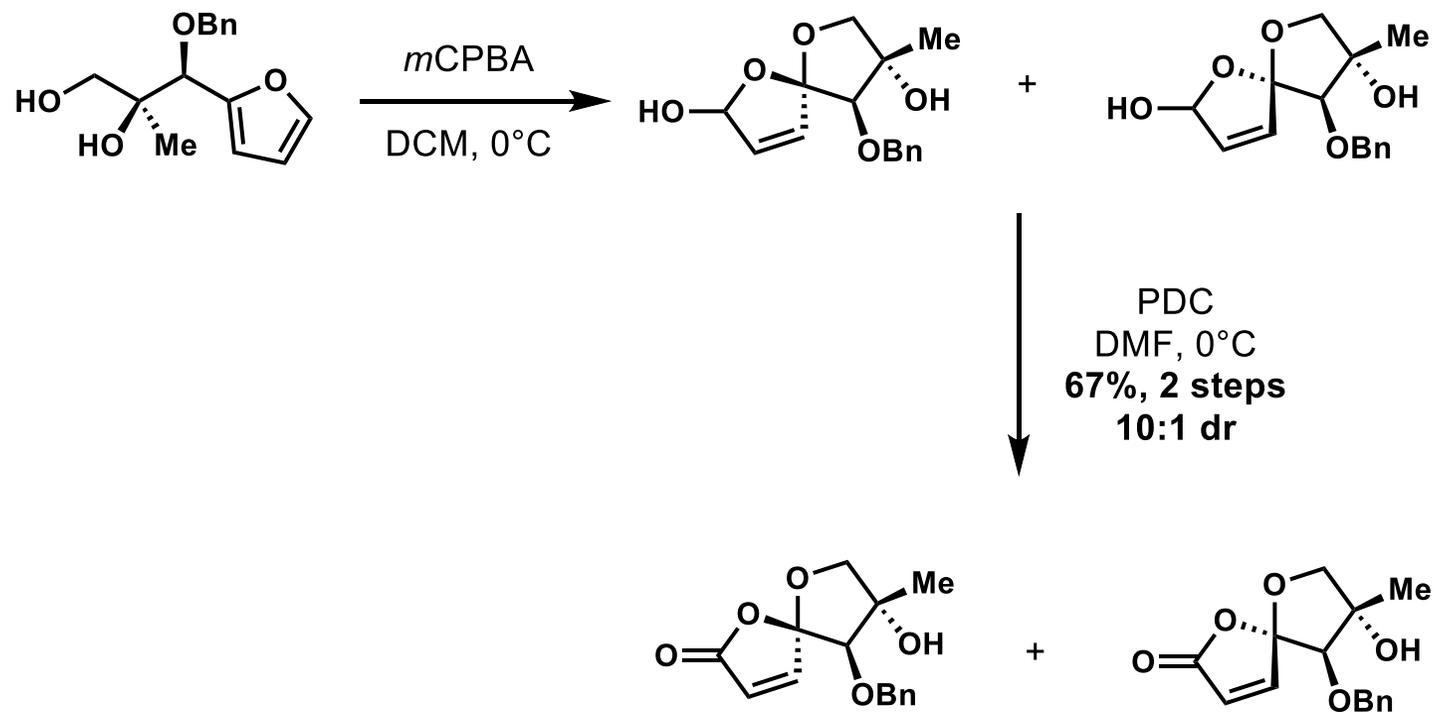
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Oxidative spirolactonization



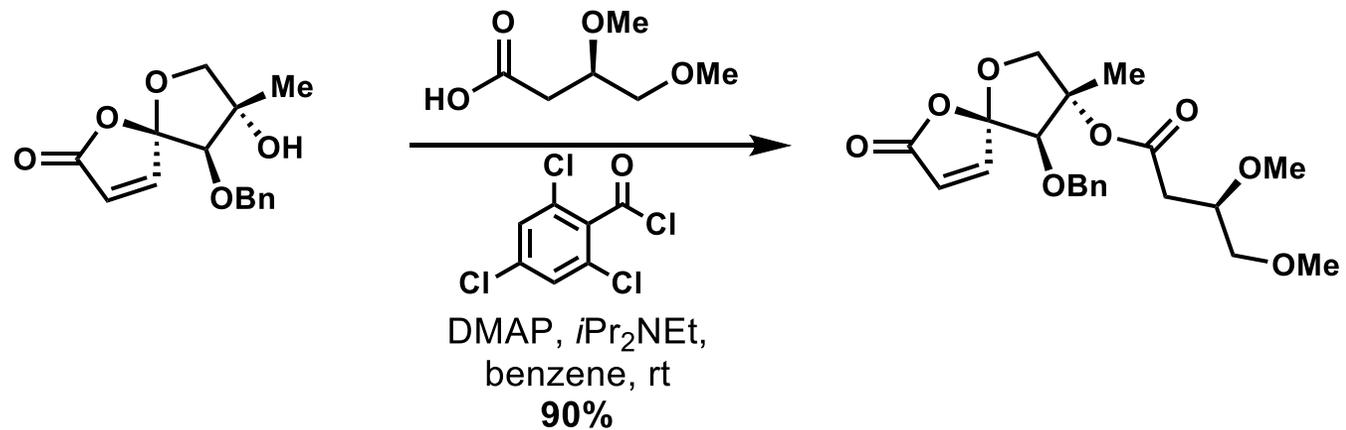
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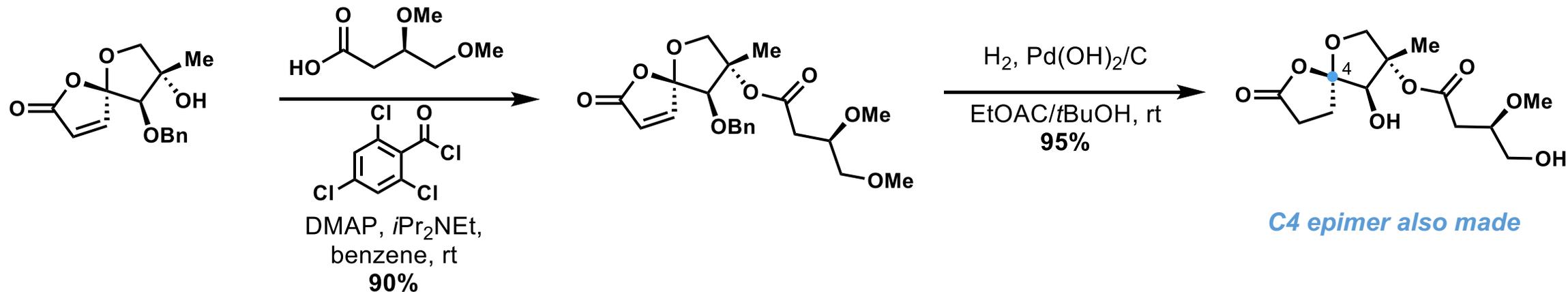
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Advancing to final product

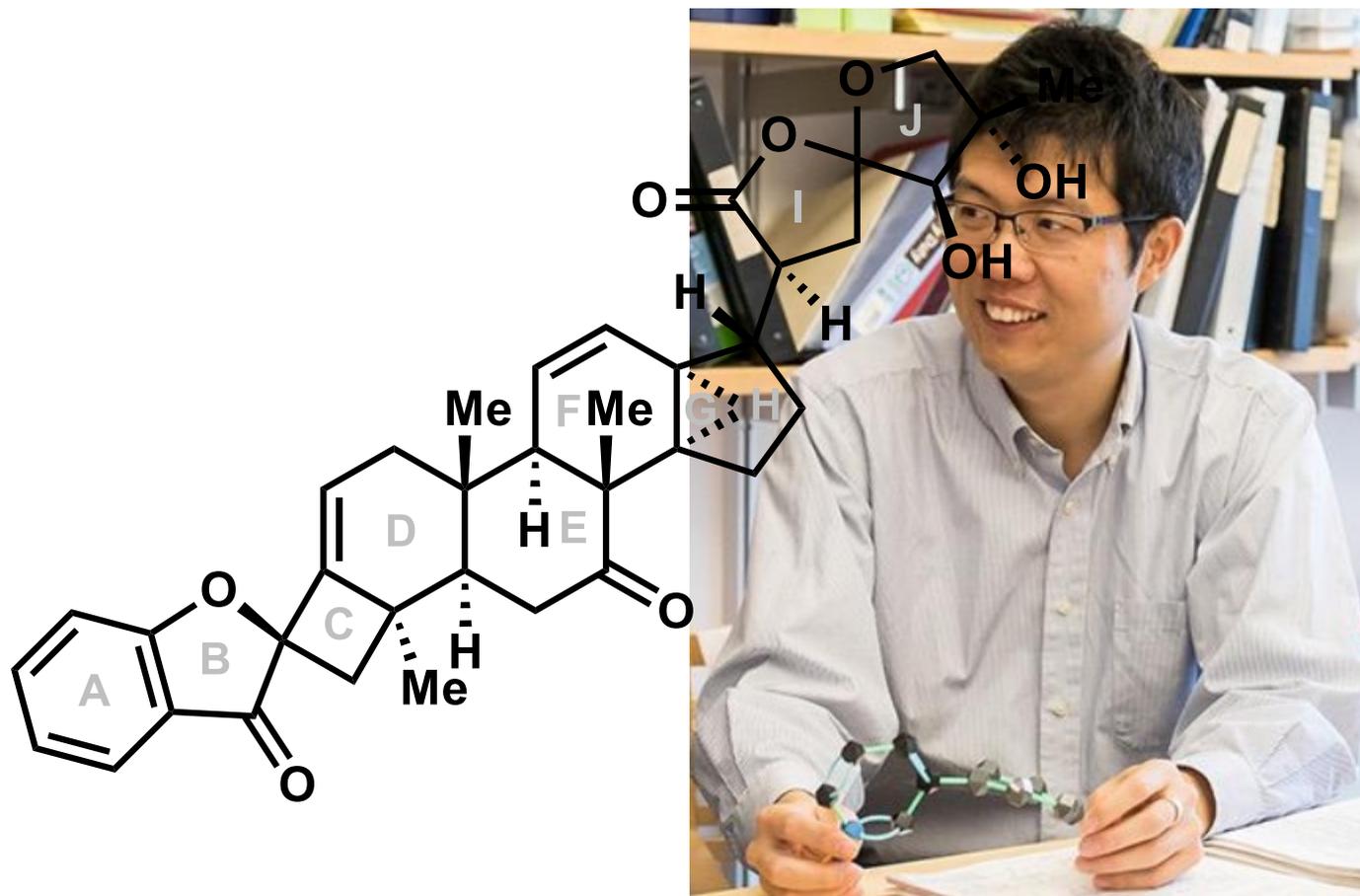


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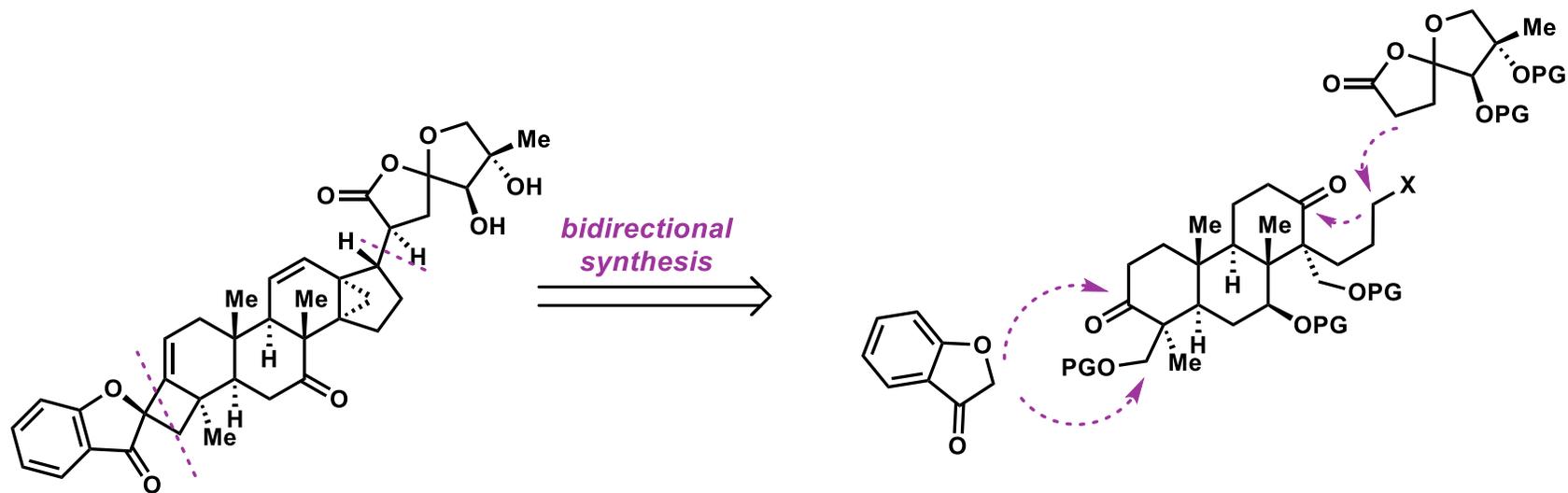


A Challenger Returns: Dong's Total Synthesis of Phainanoid A



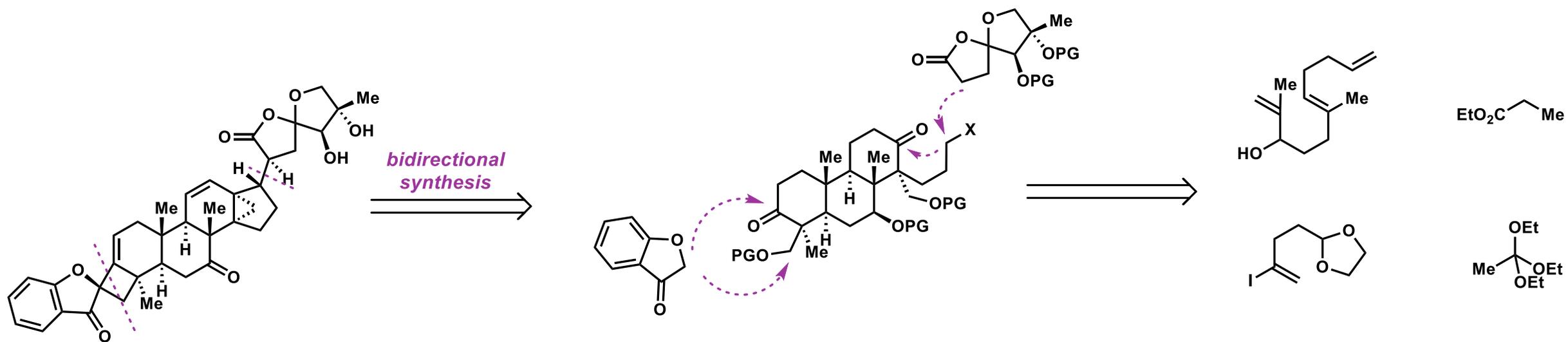
Dong's Total Synthesis of Phainanoid A

Retrosynthesis



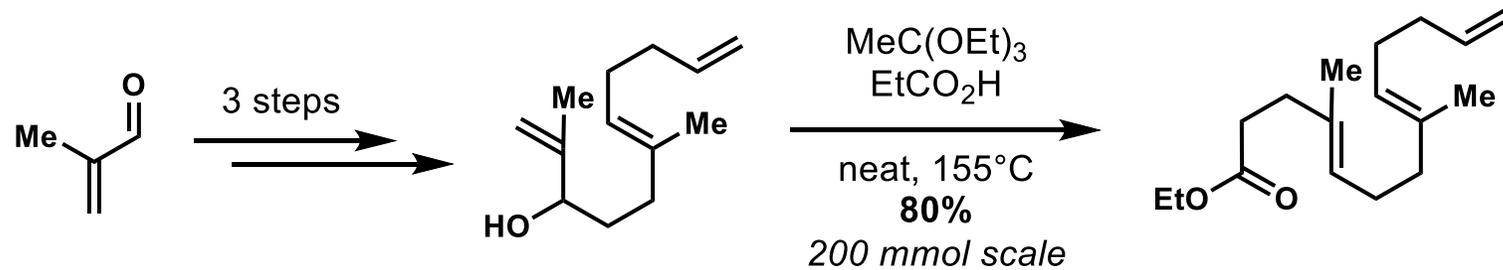
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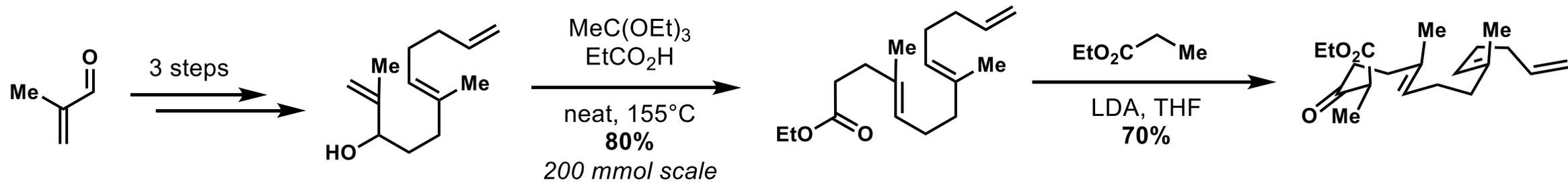
Dong's Total Synthesis of Phainanoid A

Towards D/E/F core



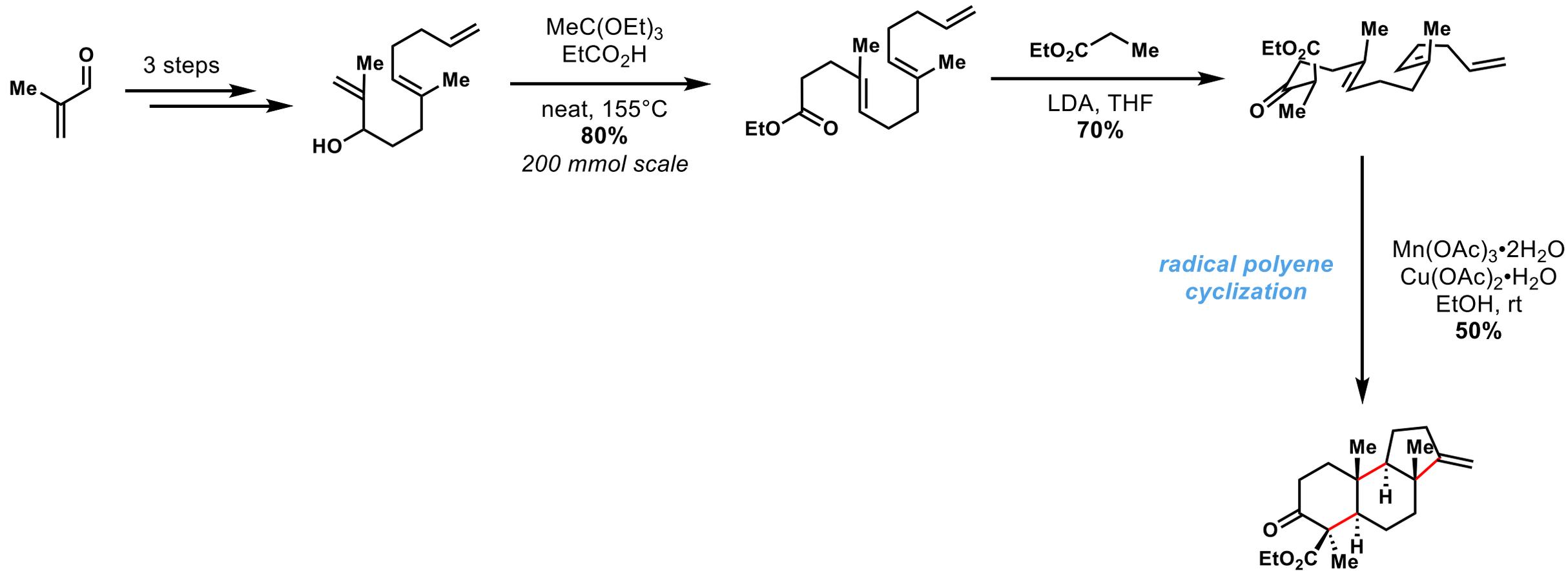
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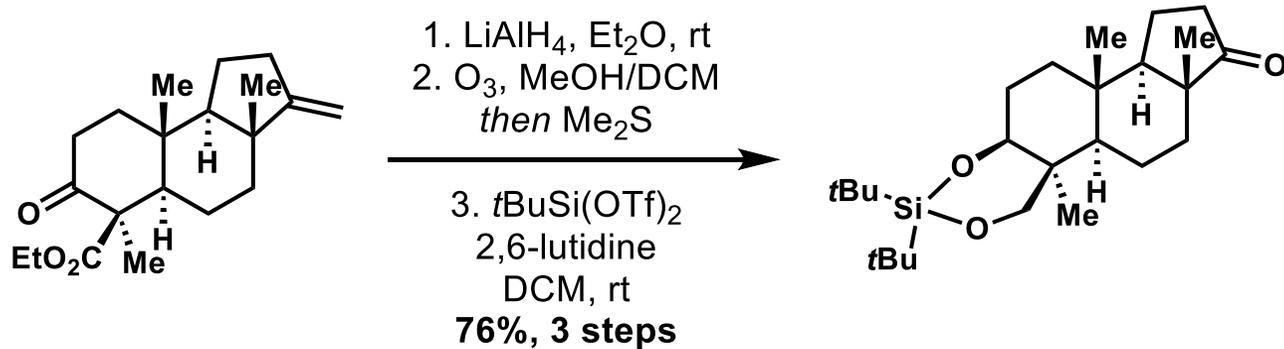
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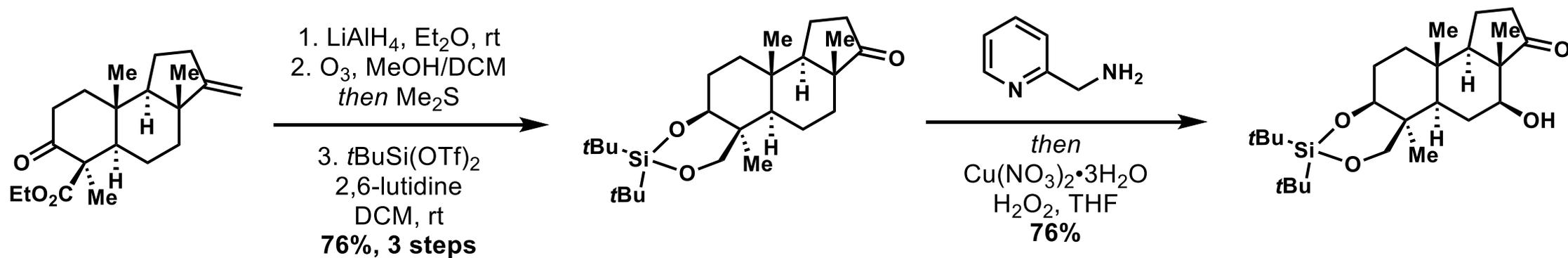
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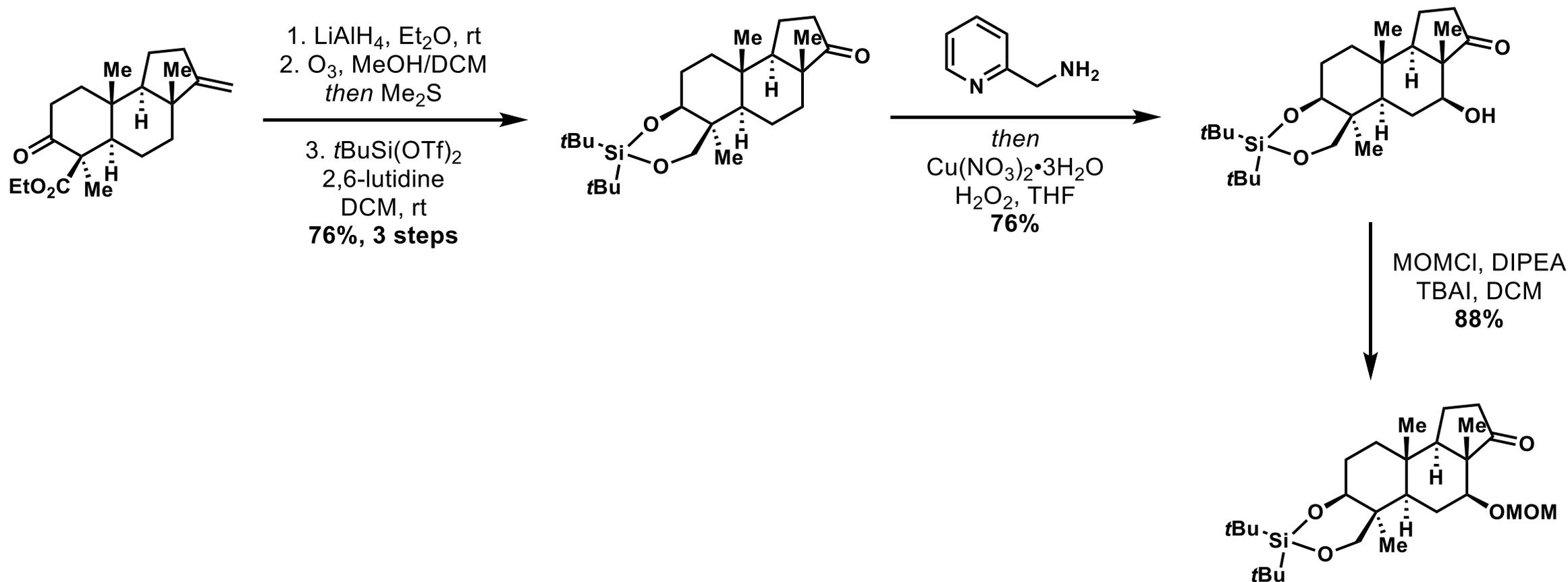
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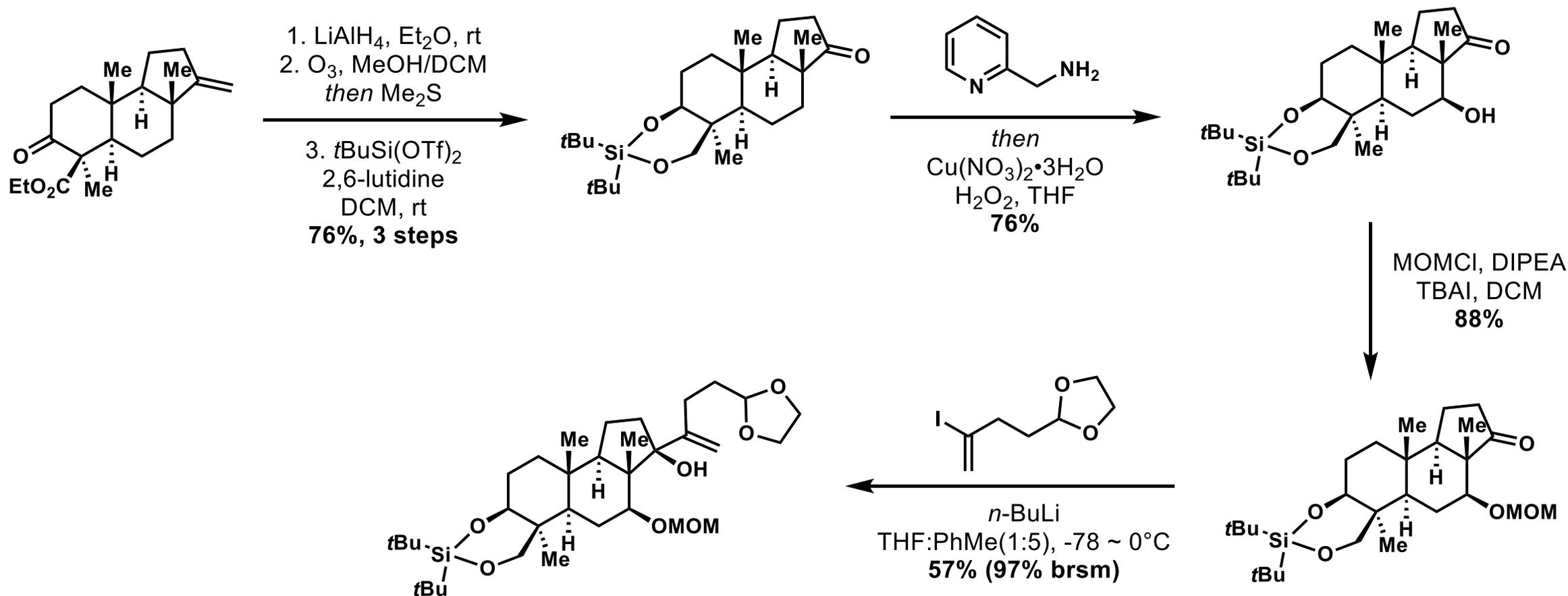
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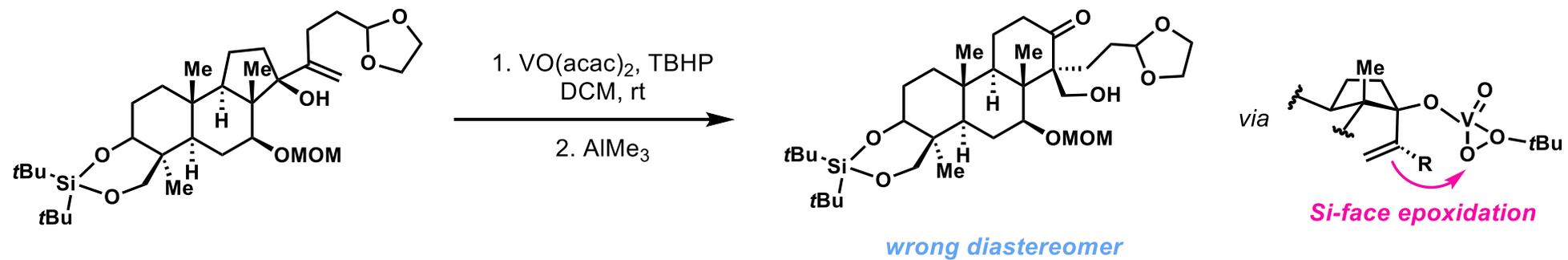
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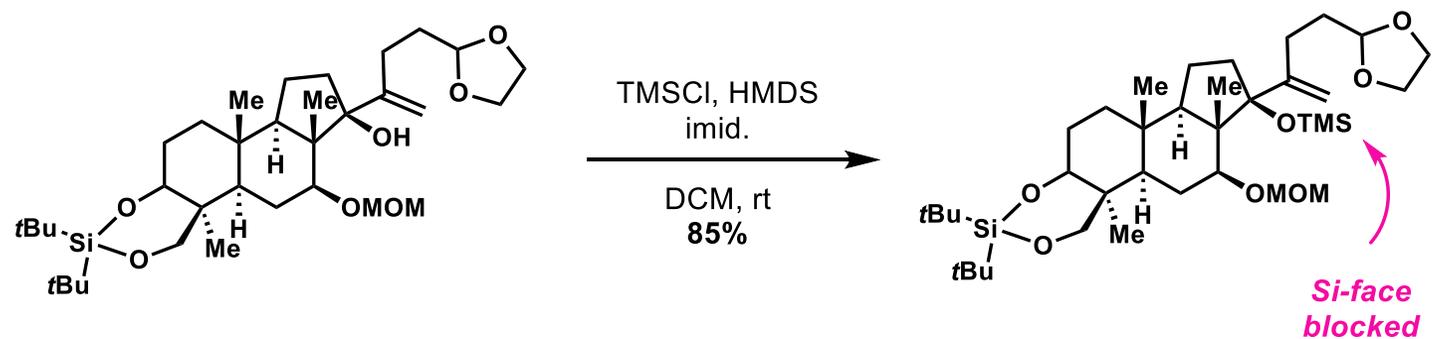
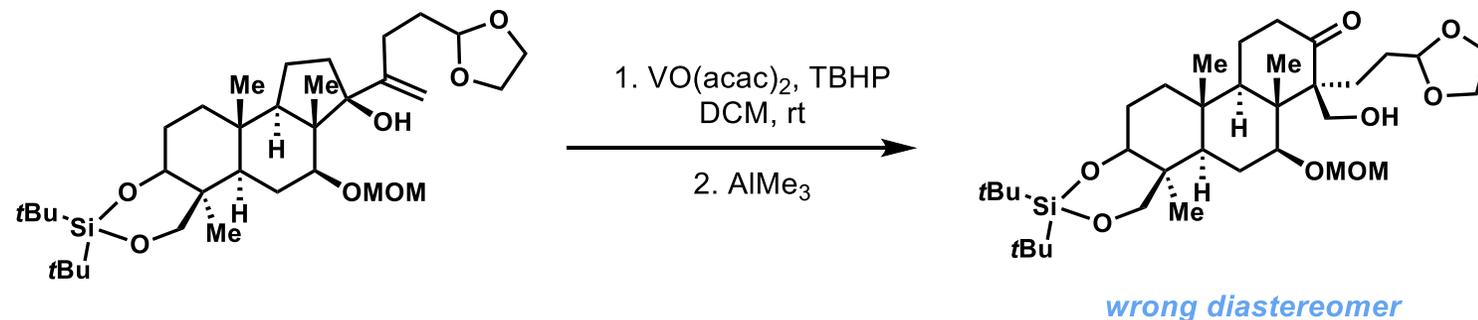
Dong's Total Synthesis of Phainanoid A

Ring expansion



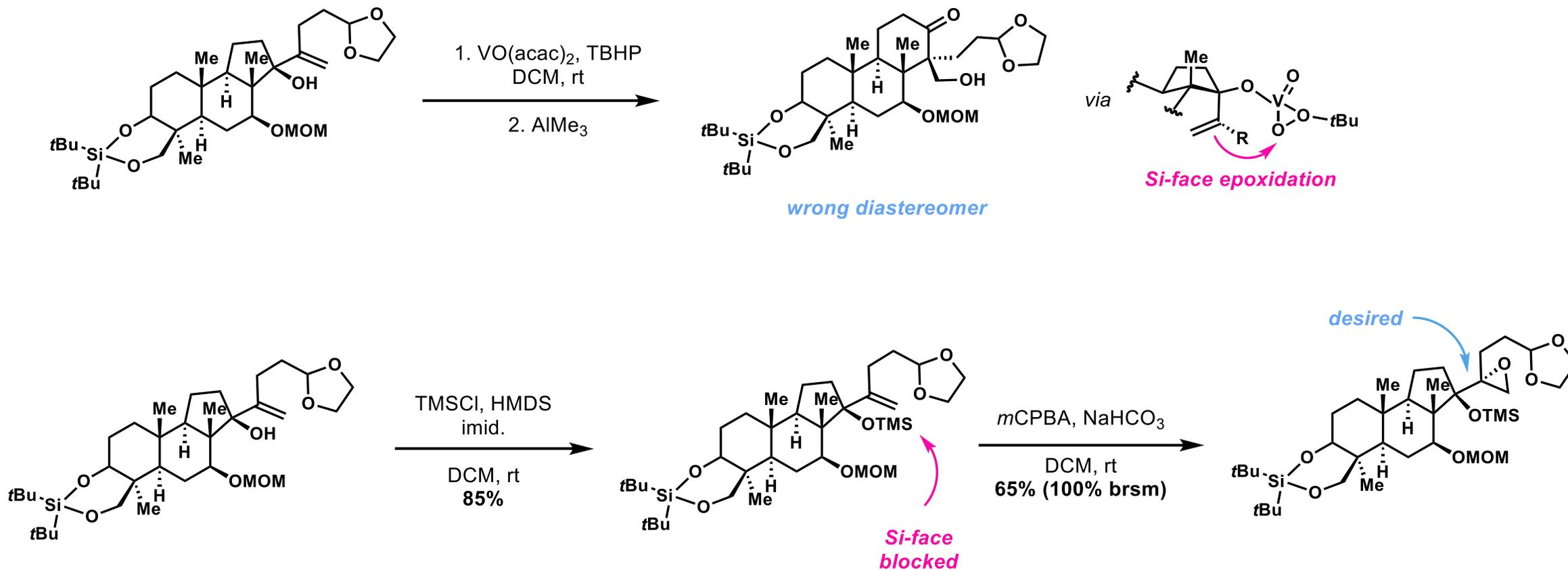
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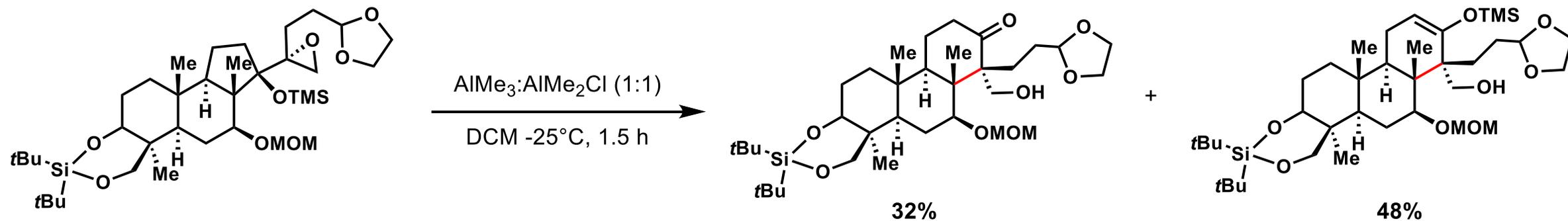
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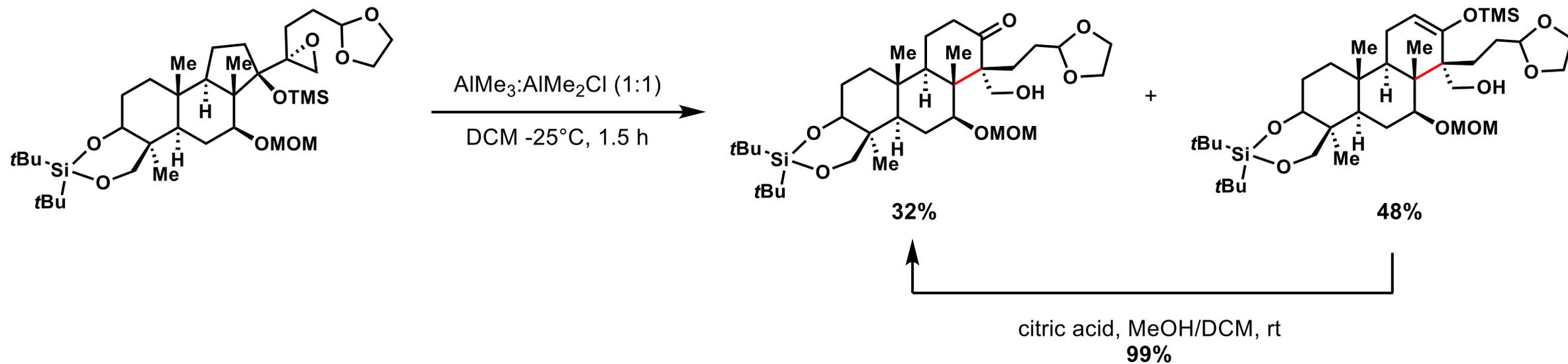
Dong's Total Synthesis of Phainanoid A

Completing the D/E/F core



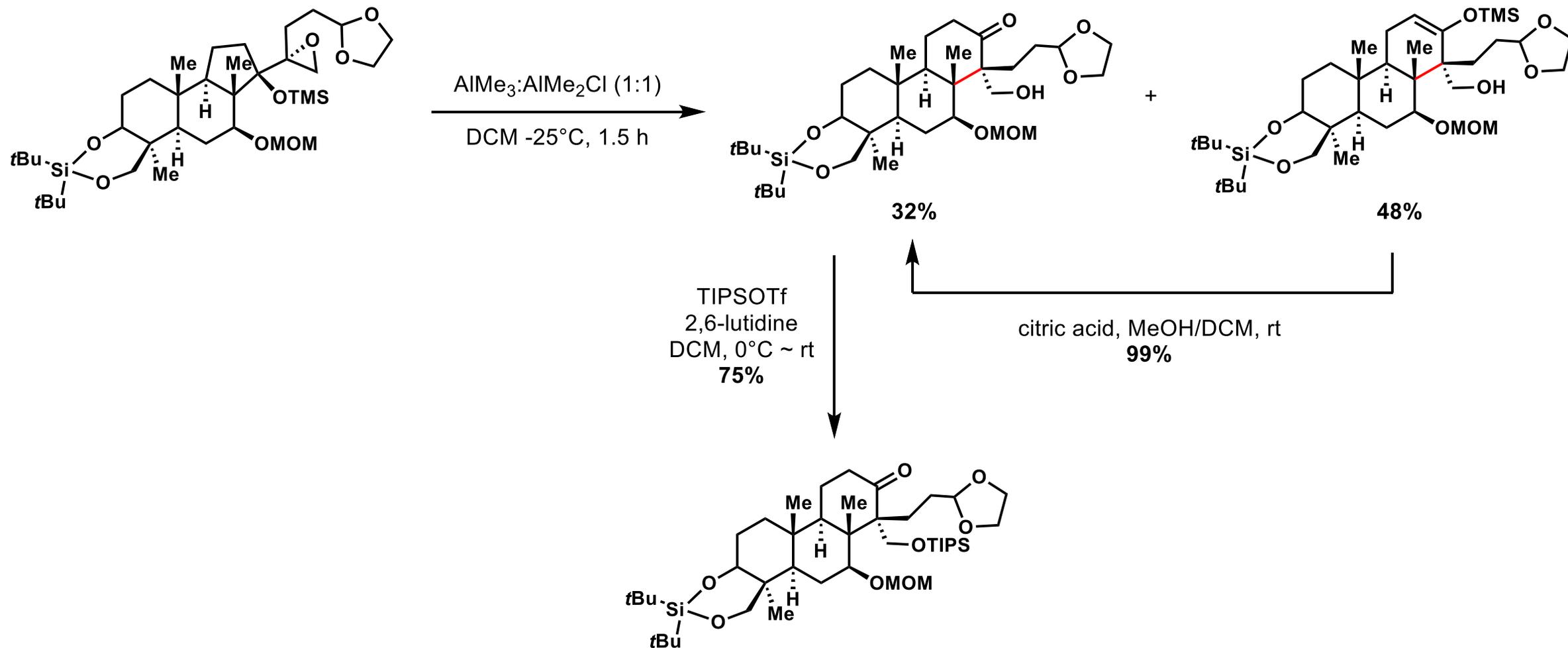
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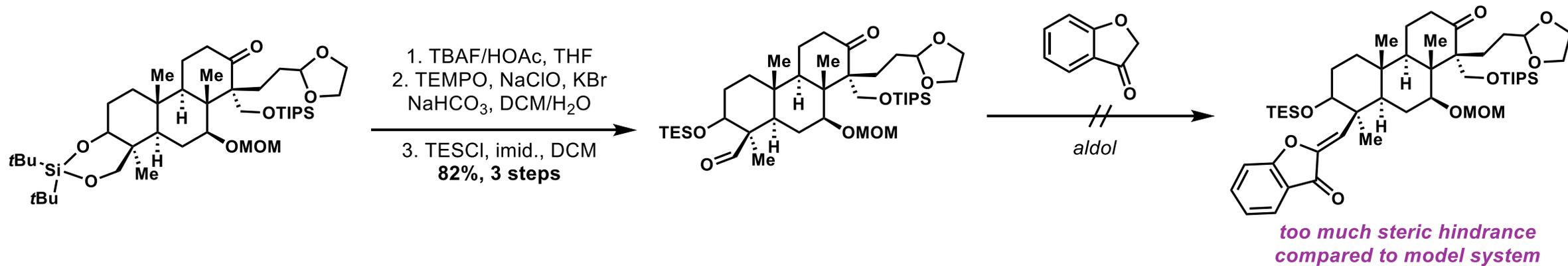
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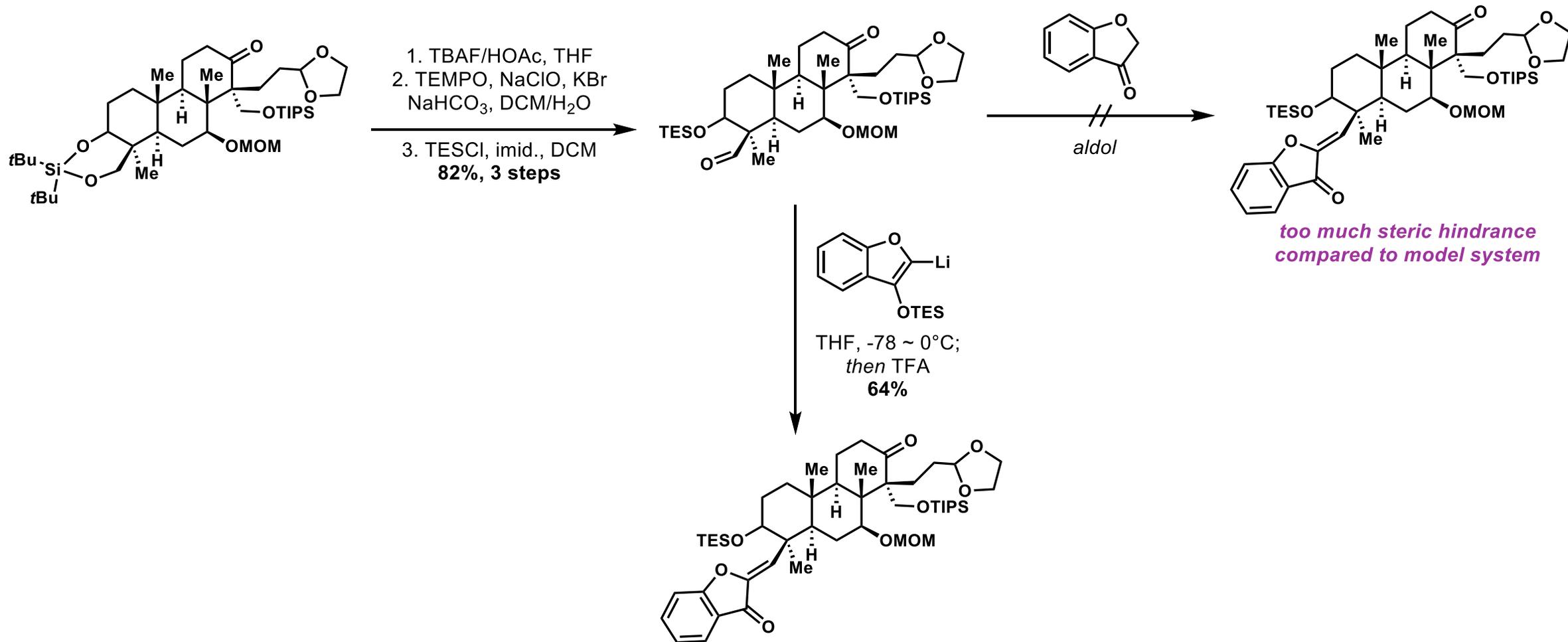
Dong's Total Synthesis of Phainanoid A

Aldol problem?



Dong's Total Synthesis of Phainanoid A

Solved



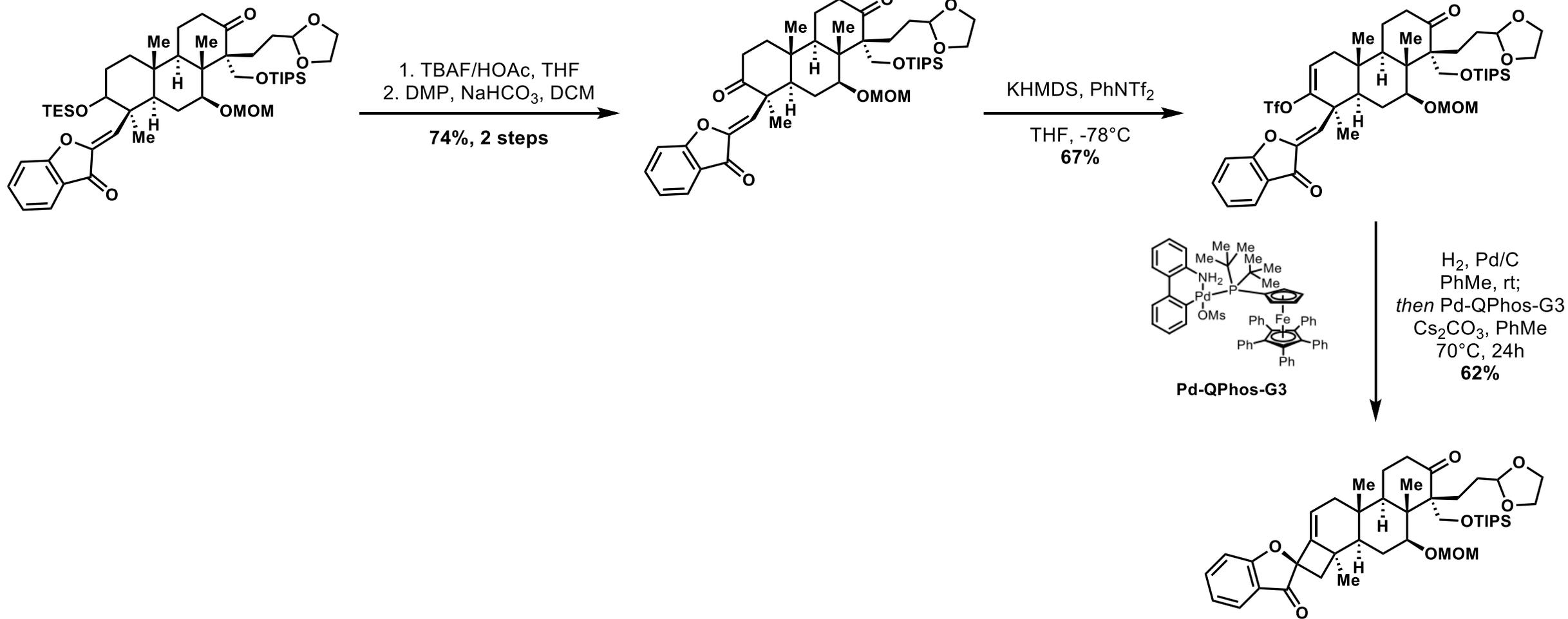
Dong's Total Synthesis of Phainanoid A

Completing southwest hemisphere



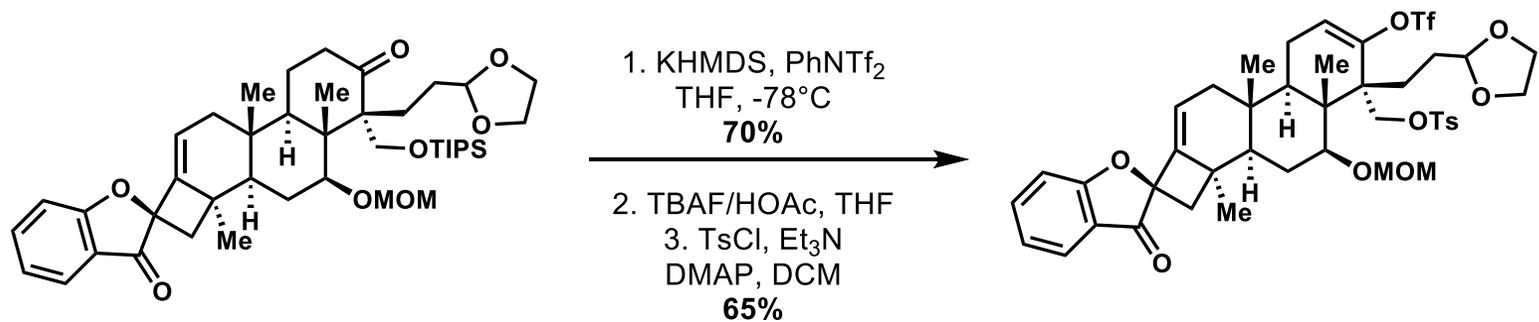
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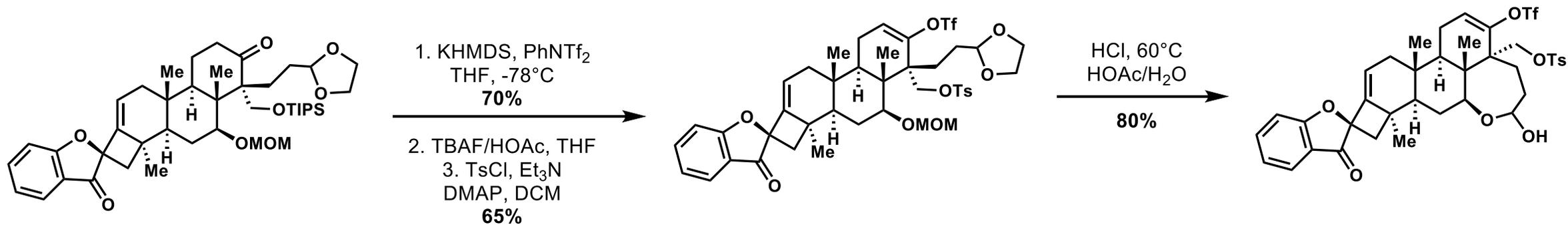
Dong's Total Synthesis of Phainanoid A

Elaboration of northeastern hemisphere



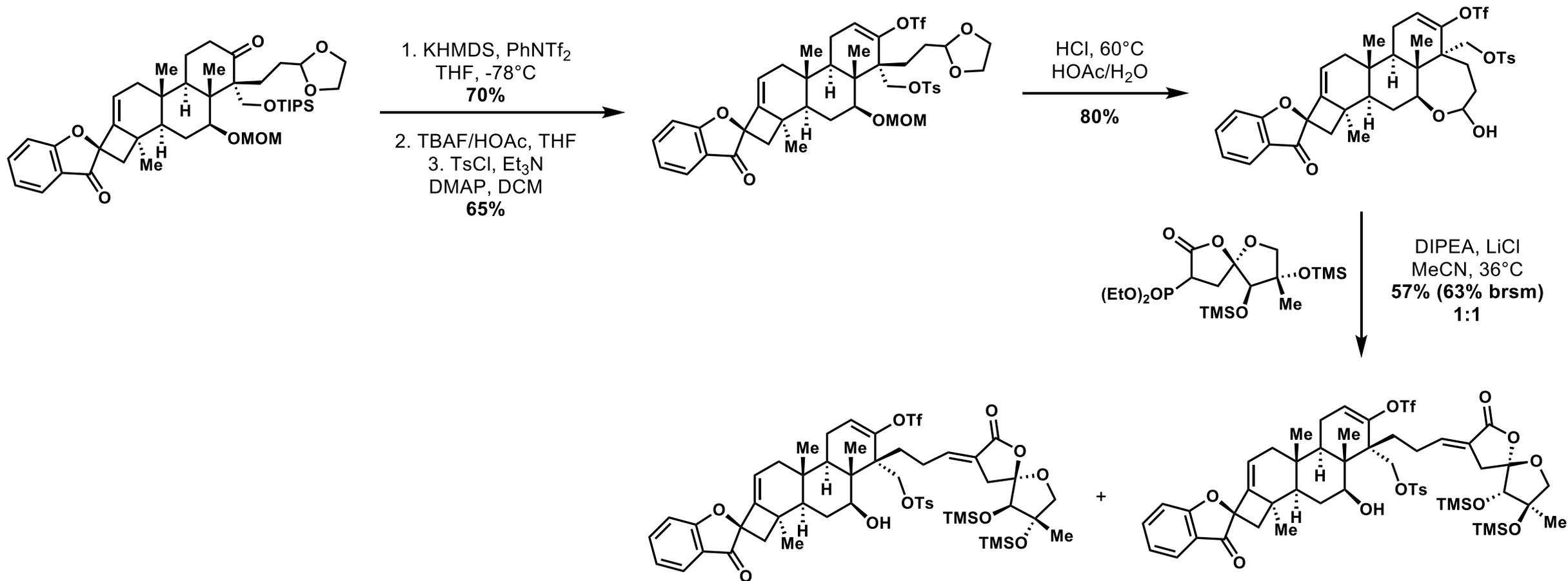
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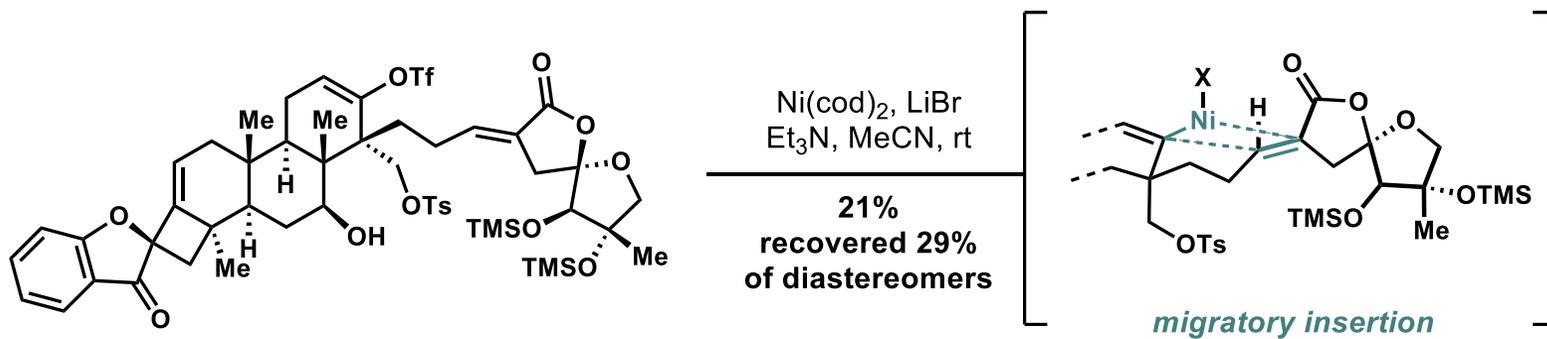
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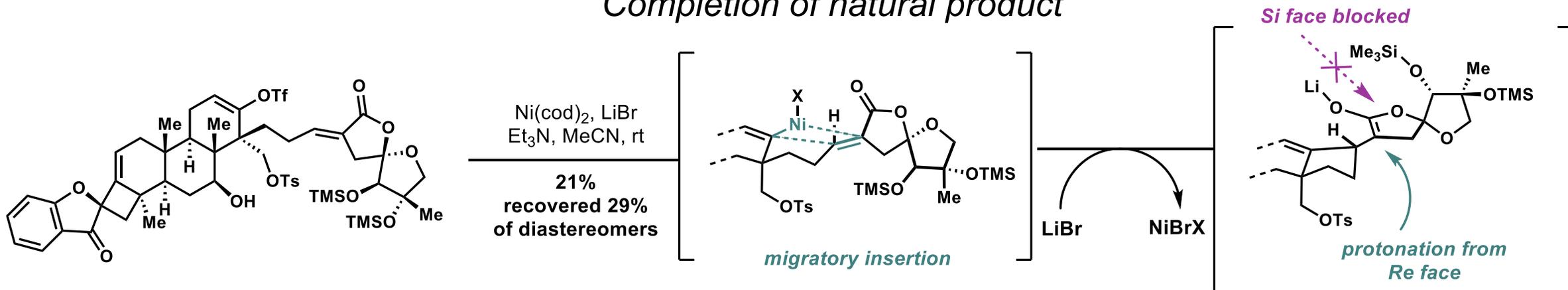
Dong's Total Synthesis of Phainanoid A

Completion of natural product



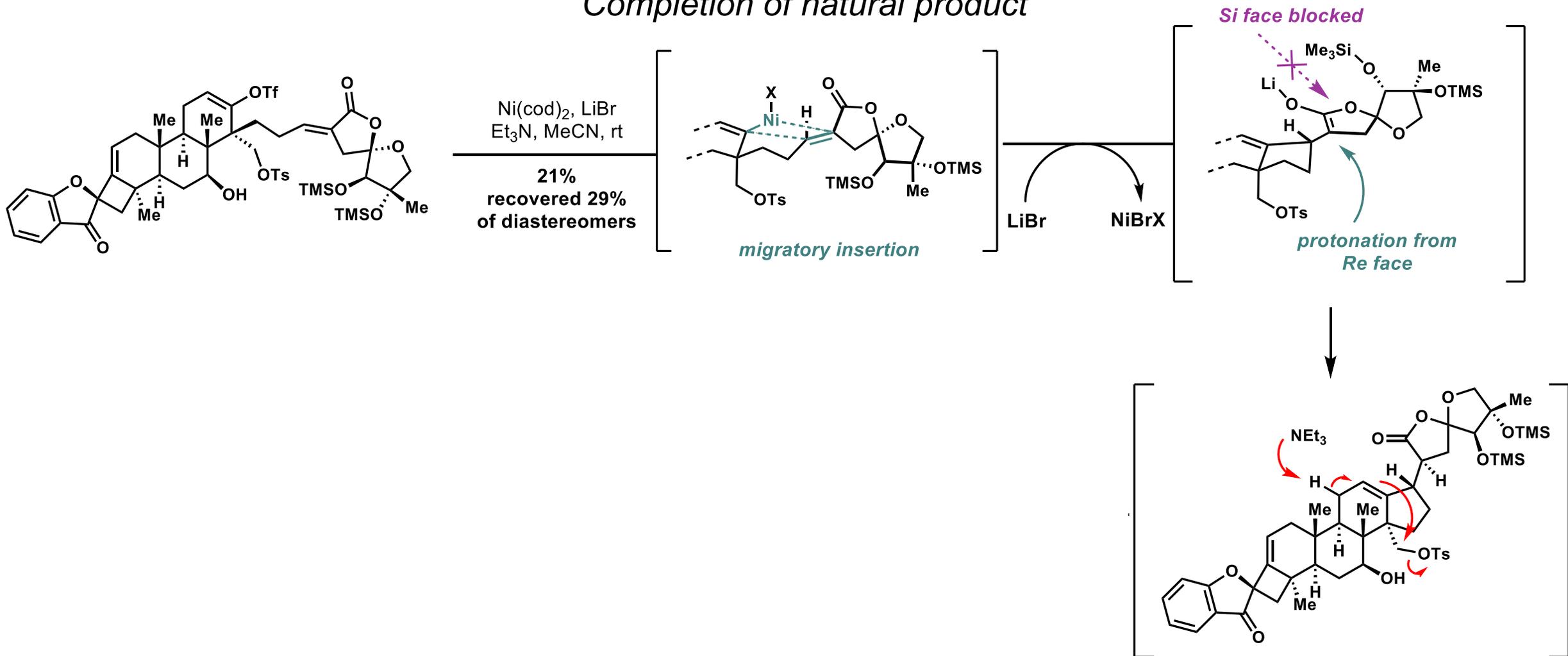
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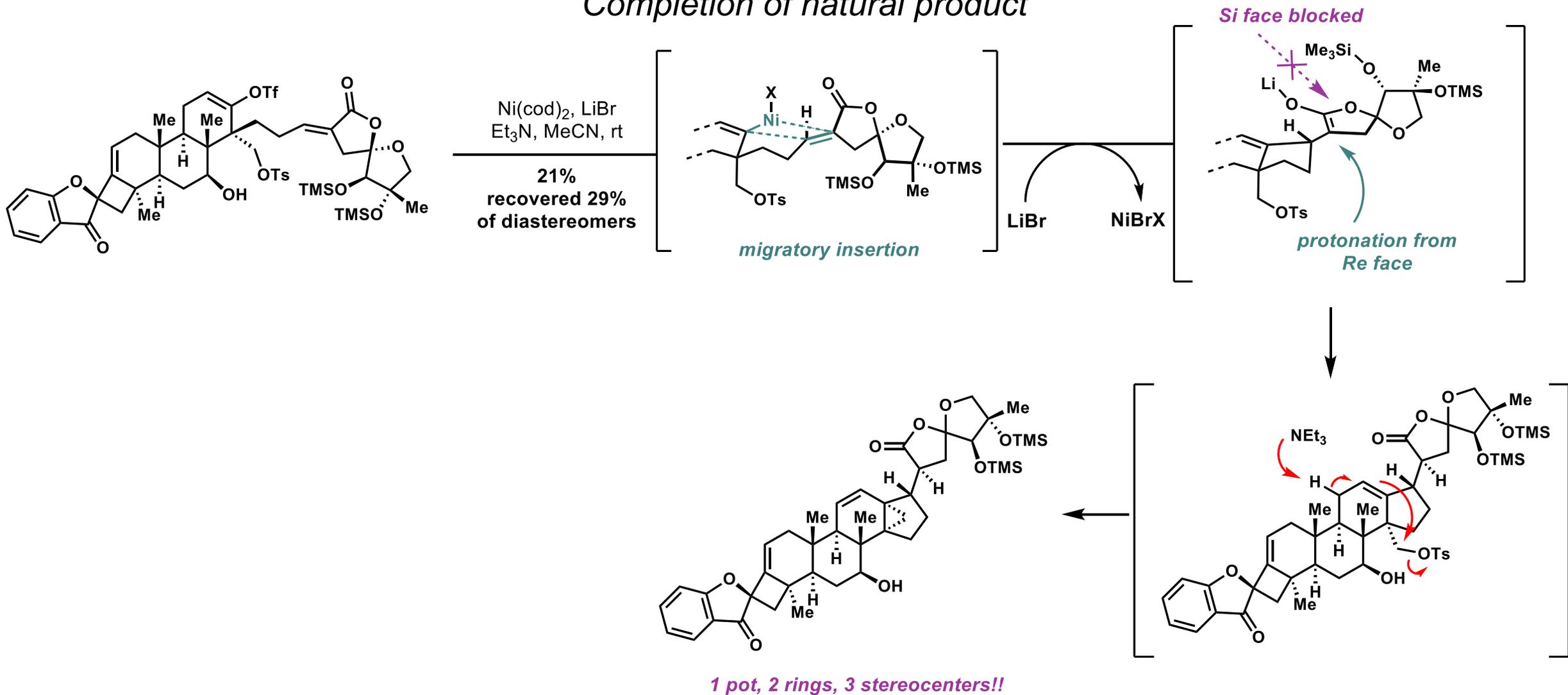
Dong's Total Synthesis of Phainanoid A

Completion of natural product



Dong's Total Synthesis of Phainanoid A

Completion of natural product



A Challenger Succeeds: Dong's Total Synthesis of Phainanoid A

