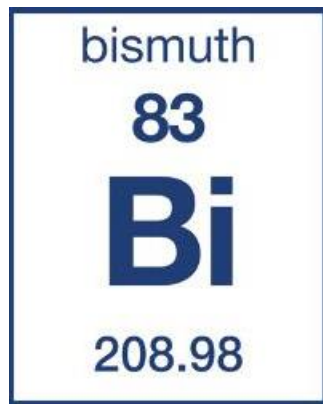


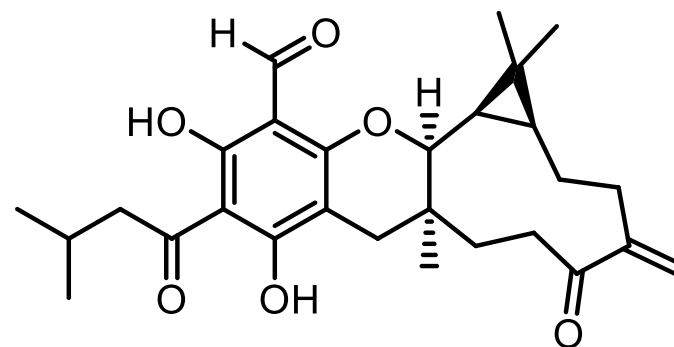
4th National SCI/RSC Retrosynthesis Competition

We Mean Bismuth



SBM CDT 2016

Target Molecule:



Eucalrobosone D

Jonathan Golec
Richard Surgenor

Jessica Reynolds
Jimmy Wang

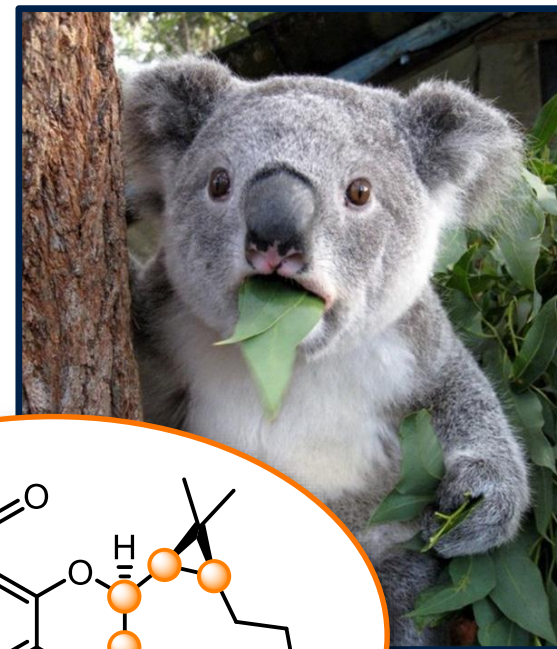


Eucalrobosone D



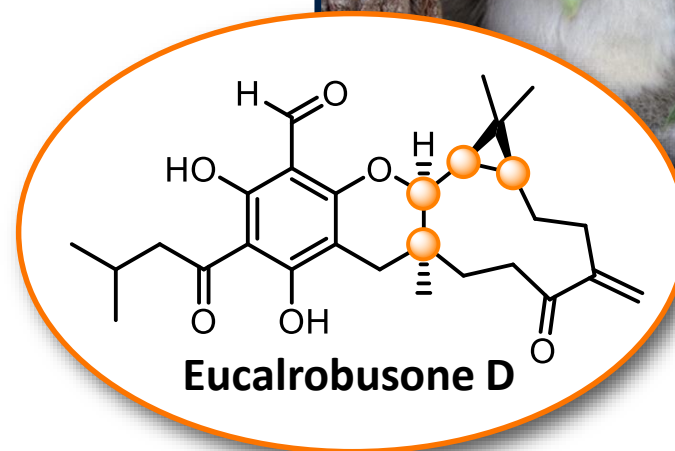
Isolation and purification

- Isolated from leaves of *Eucalyptus robusta*.^[1]
- Extracted with EtOH, then chromatographic purification afforded a white solid.
- 18.2 mg extracted from 15 kg leaves.
- *In Vitro* Activity vs. HepG2 cells ($26.78 \pm 2.31 \mu\text{M}$).



Structural Features

- Formyl phloroglucinol meroterpenoid.
- Fused grandinol/bicyclogermacrene-like system.
- 10 membered carbocyclic ring.
- 4 contiguous stereogenic centres.

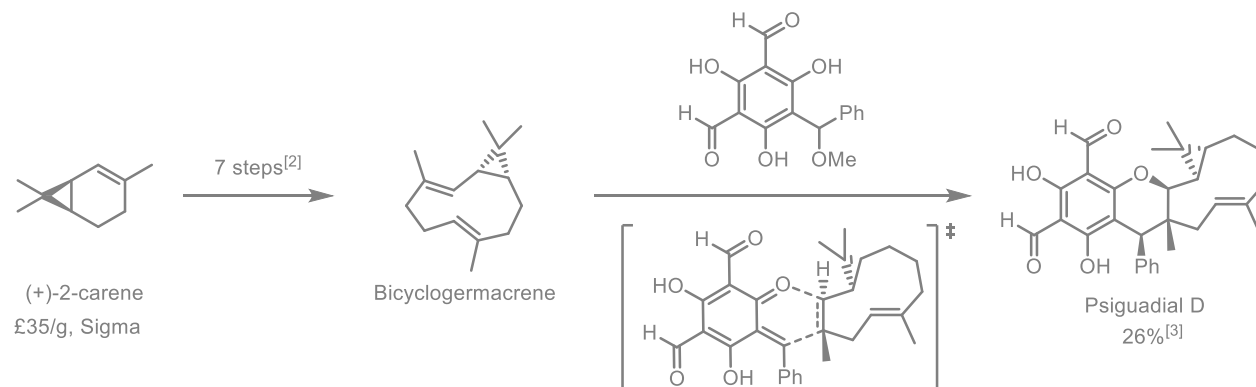
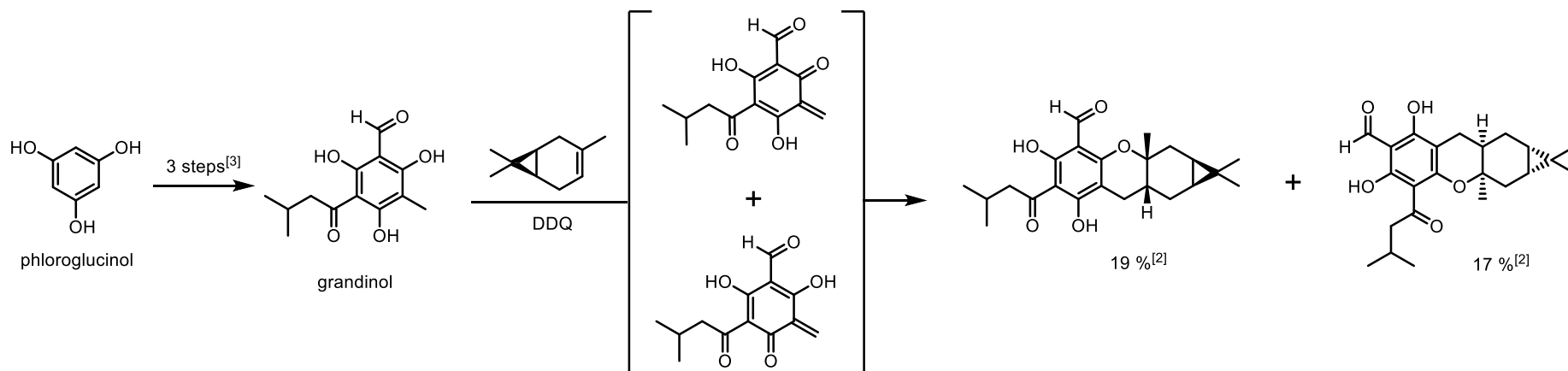


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Previous Approaches



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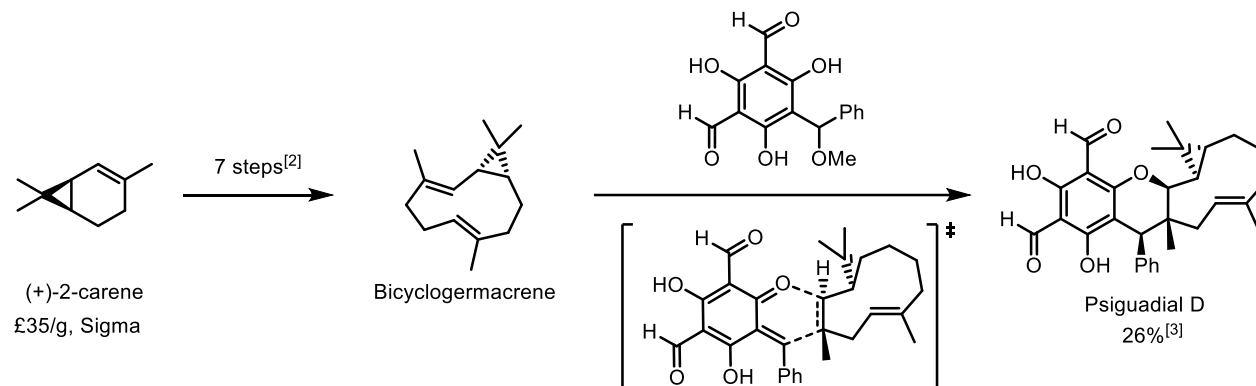
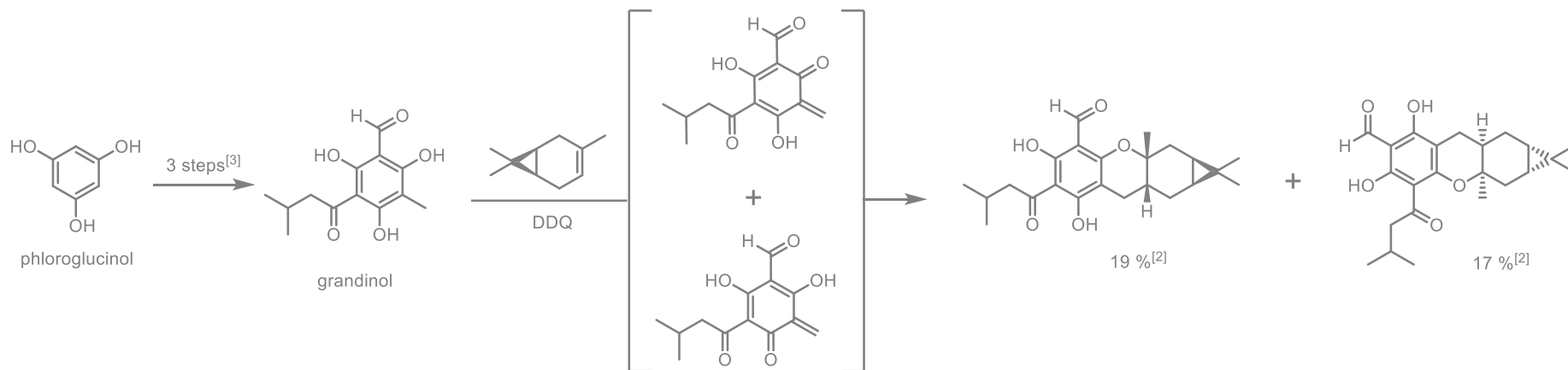
2. S. B. Bharate, K. K. Bhutani, S. I. Khan, B. L. Tekwani, M. R. Jacob, I. A. Khan and I. P. Singh, *Bioorg. Med. Chem.*, 2006, **14**, 1750–1760.

3. D. N. Tran and N. Cramer, *Chem. - Eur. J.*, 2014, **20**, 10654–10660.

Previous Approaches



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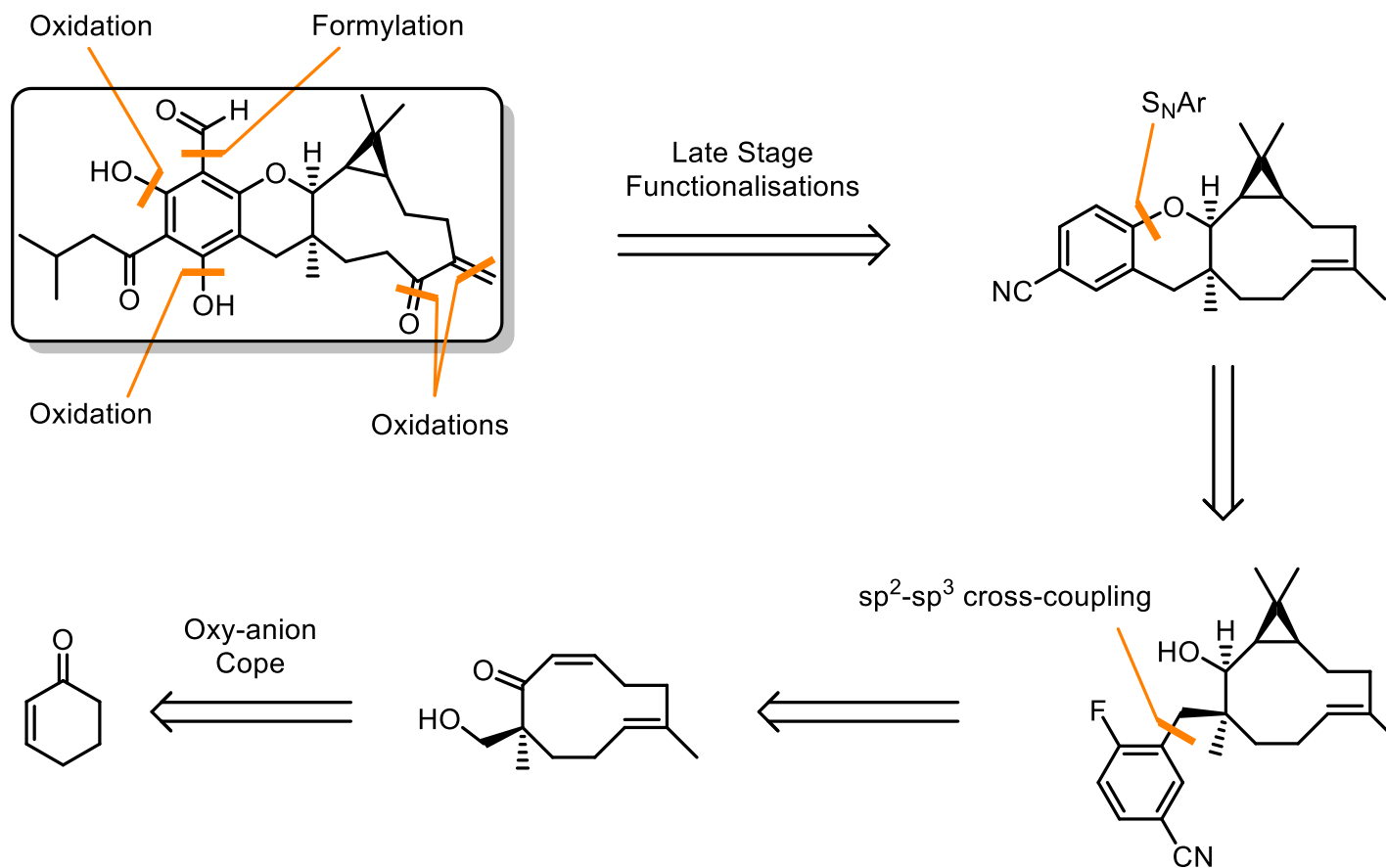
2. S. B. Bharate, K. K. Bhutani, S. I. Khan, B. L. Tekwani, M. R. Jacob, I. A. Khan and I. P. Singh, *Bioorg. Med. Chem.*, 2006, **14**, 1750–1760.

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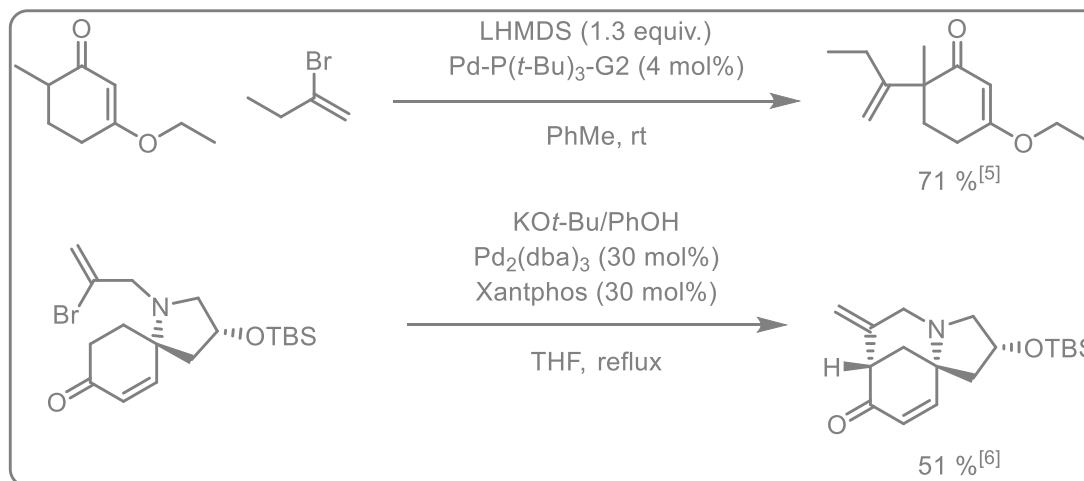
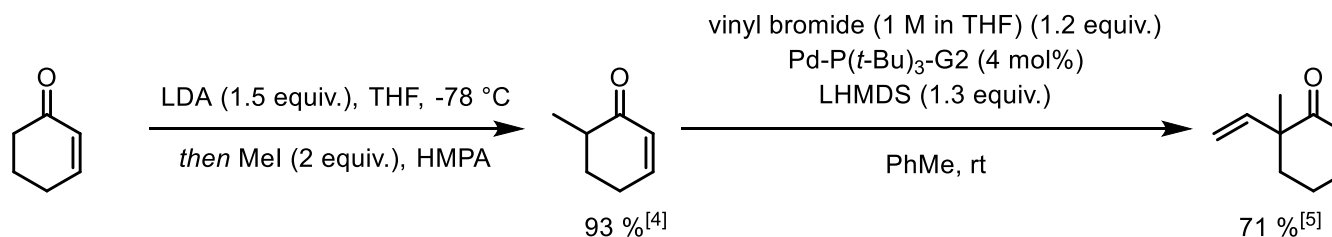
Retrosynthetic Analysis



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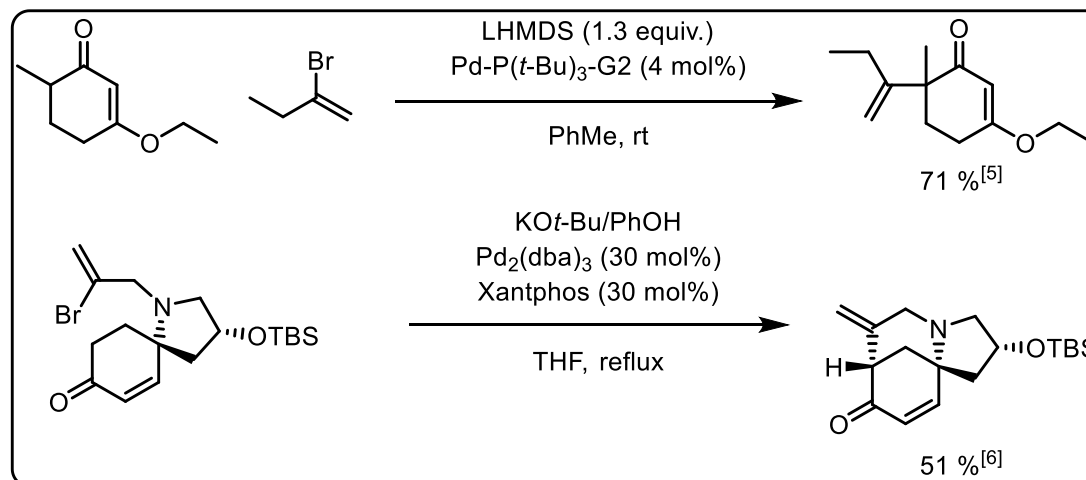
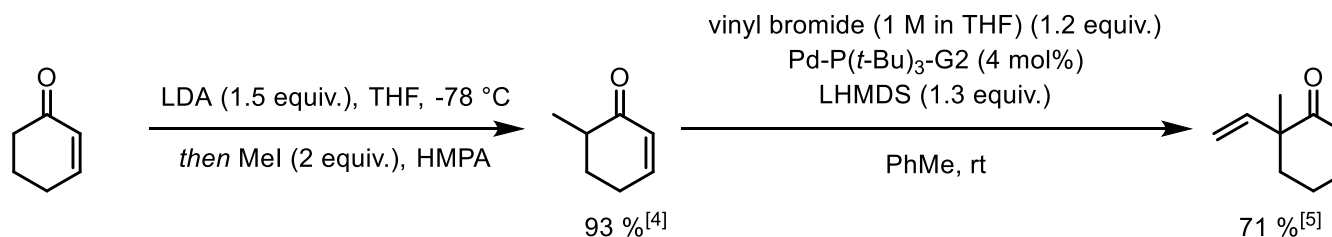


Oxy-Anion Cope


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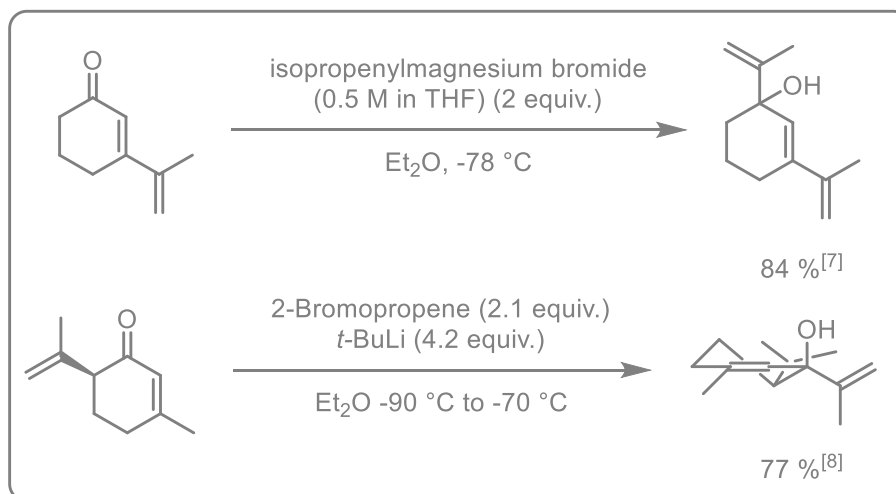
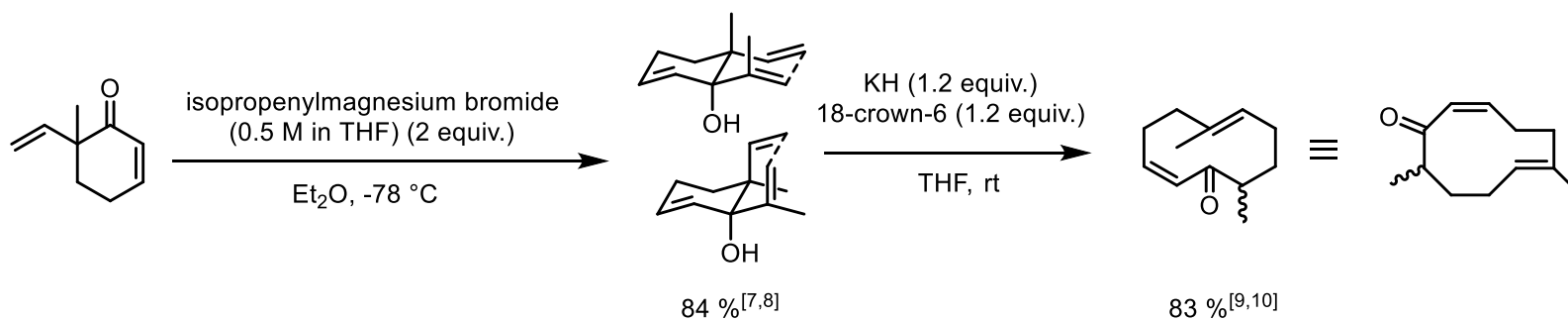
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5. T. Johnson, F. Pultar, F. Menke and M. Lautens, *Org. Lett.*, 2016, **18**, 6488–6491.
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Oxy-Anion Cope


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4. F. A. Marques, C. A. Lenz, F. Simonelli, B. H. L. N. S. Maia, A. P. Vellasco and M. N. Eberlin, *J. Nat. Prod.*, 2004, **67**, 1939–1941.
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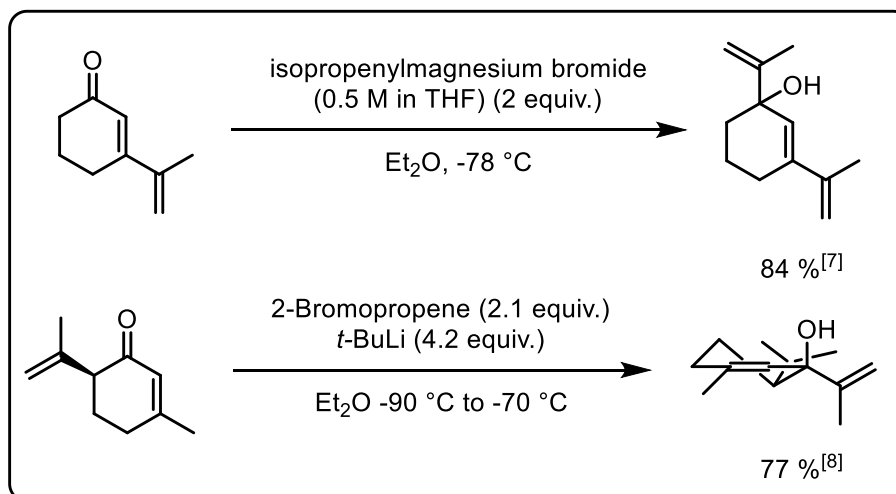
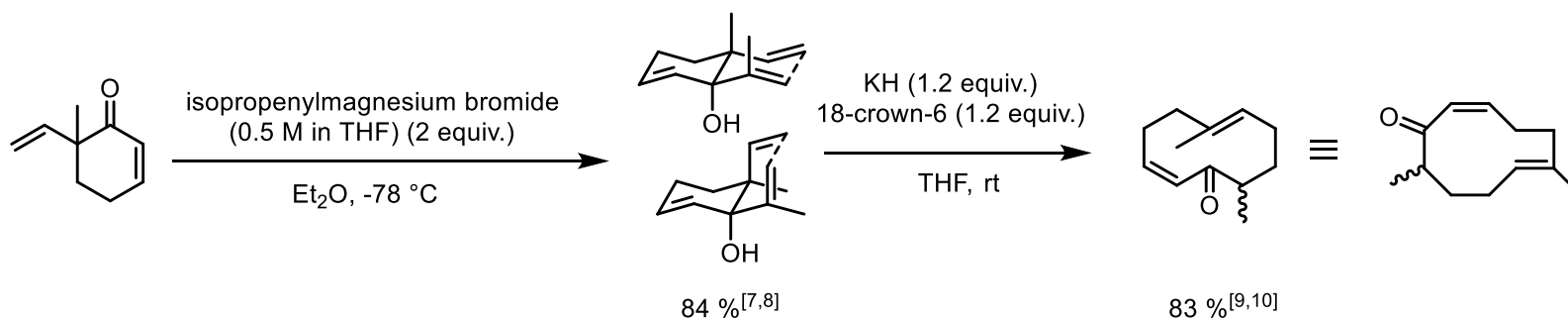

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 10. D. L. J. Clive, C. G. Russell and S. C. Suri, *J. Org. Chem.*, 1982, **47**, 1632–1641.

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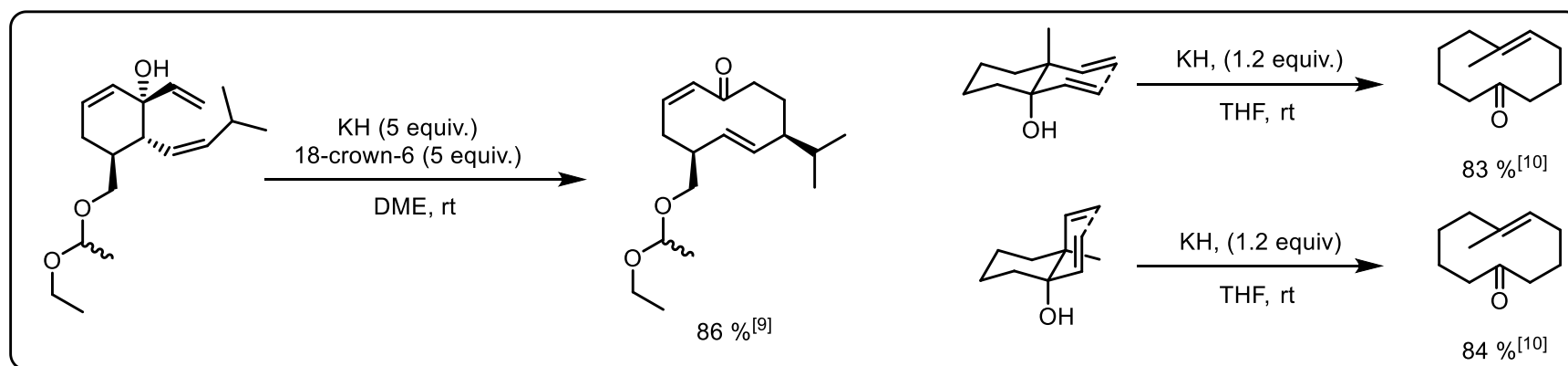
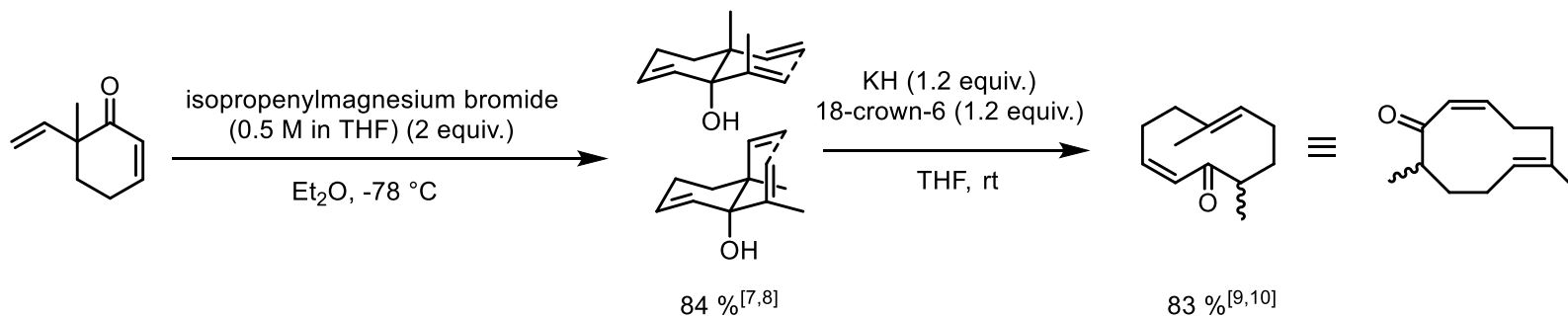

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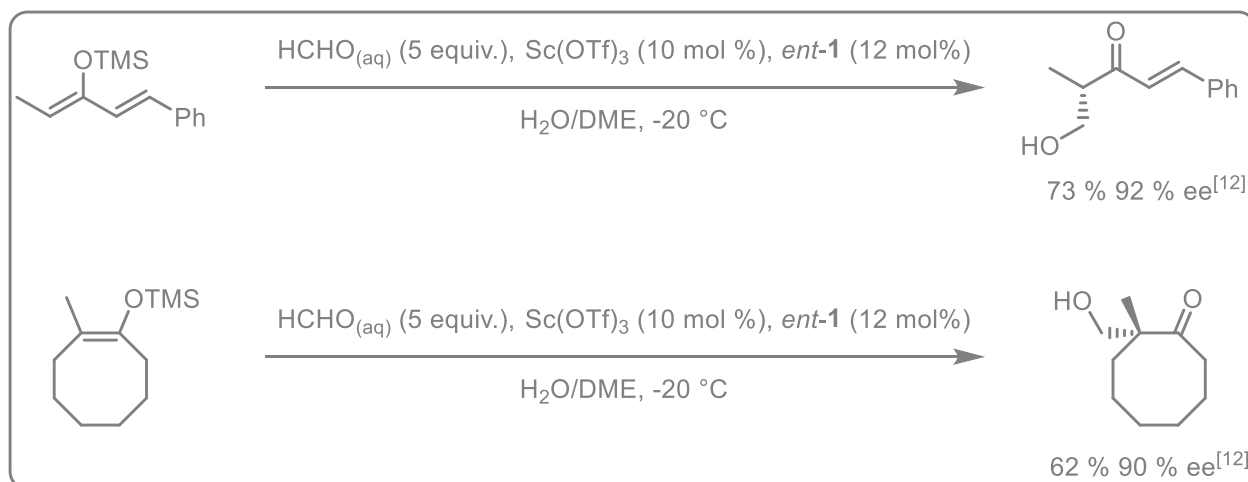
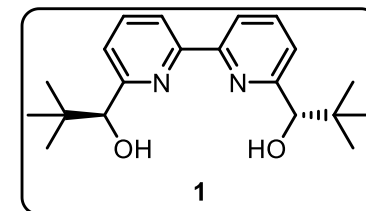
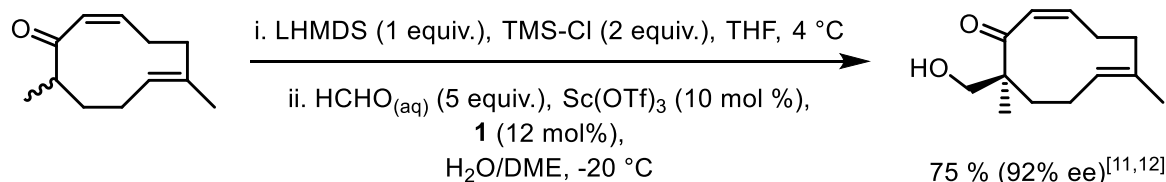
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Asymmetric hydroxymethylation



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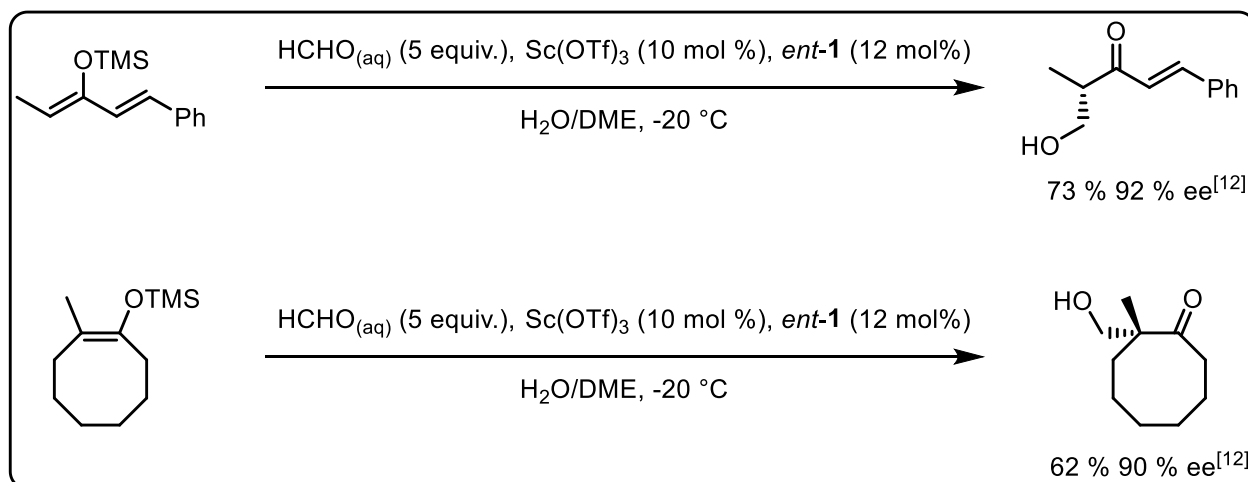
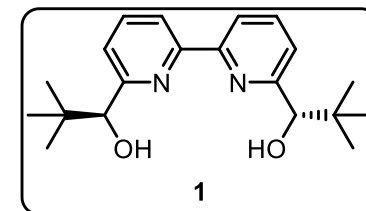
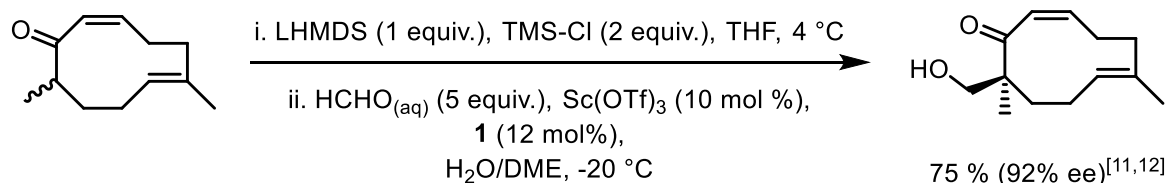
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Asymmetric hydroxymethylation



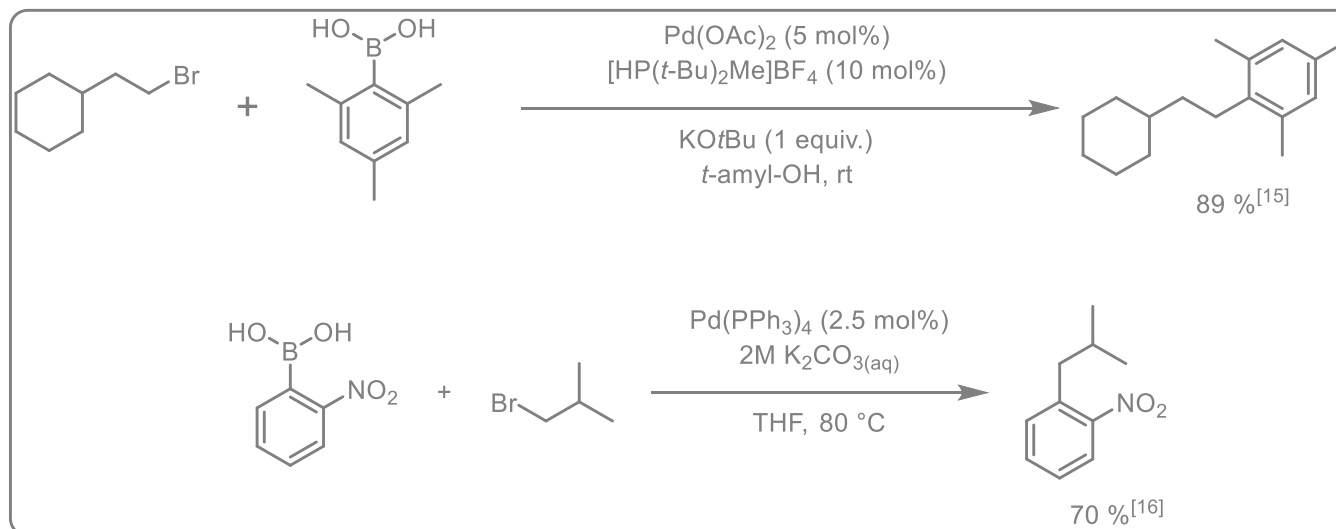
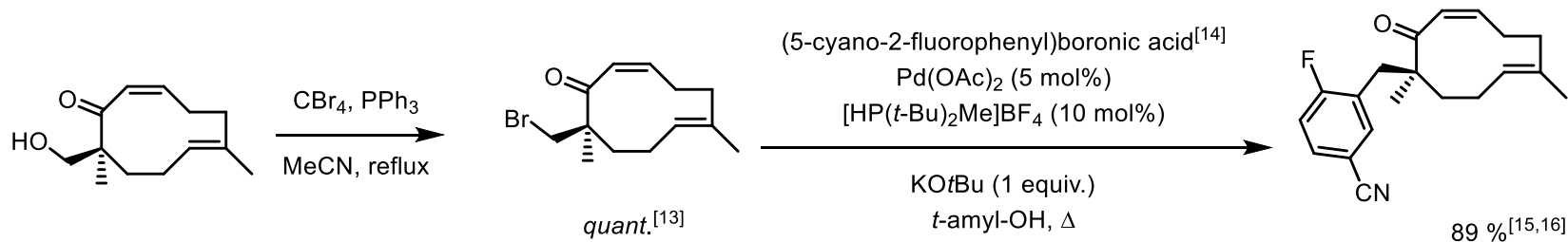
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sp²-sp³ Suzuki Coupling



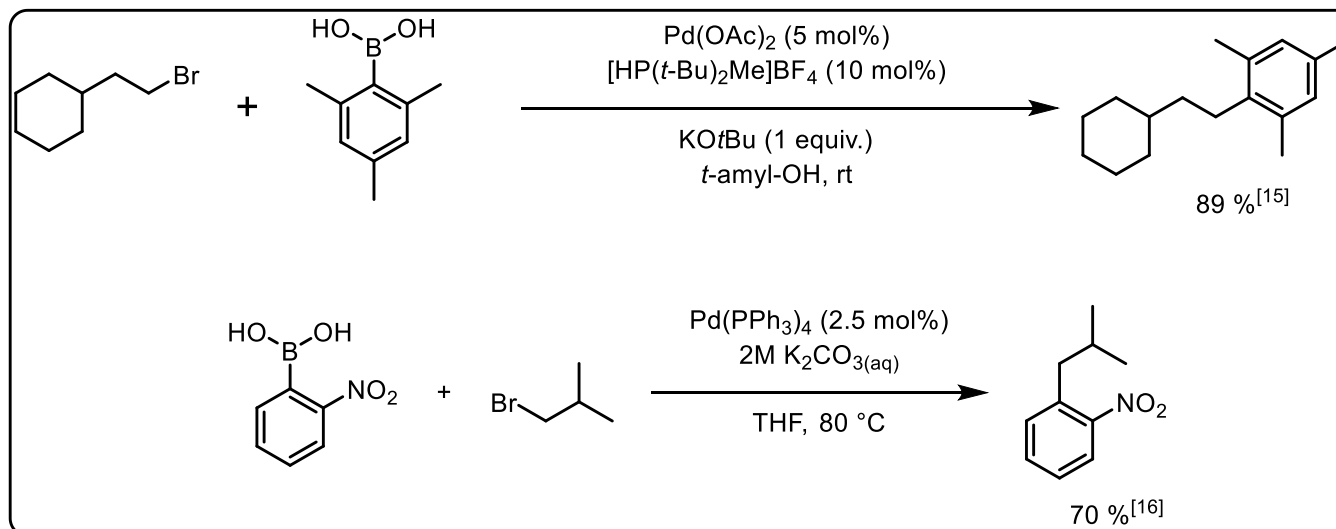
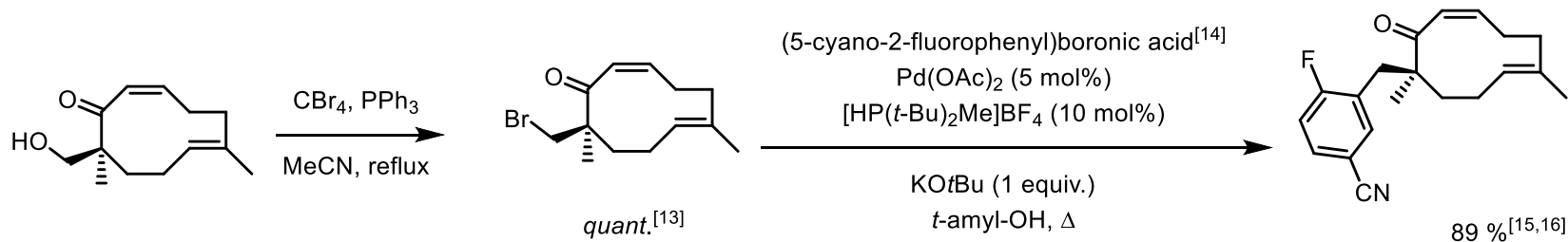
13. J. A. Miller, G. M. Ullah, G. M. Welsh and P. Mallon, *Tetrahedron Lett.*, 2001, **42**, 2729–2731.

14. Can be purchased (£20/g, Fluorochem) or synthesised in 1 step from 4-Fluorobenzonitrile (US Pat. US200373849 A1, 2003.)

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sp^2 - sp^3 Suzuki Coupling


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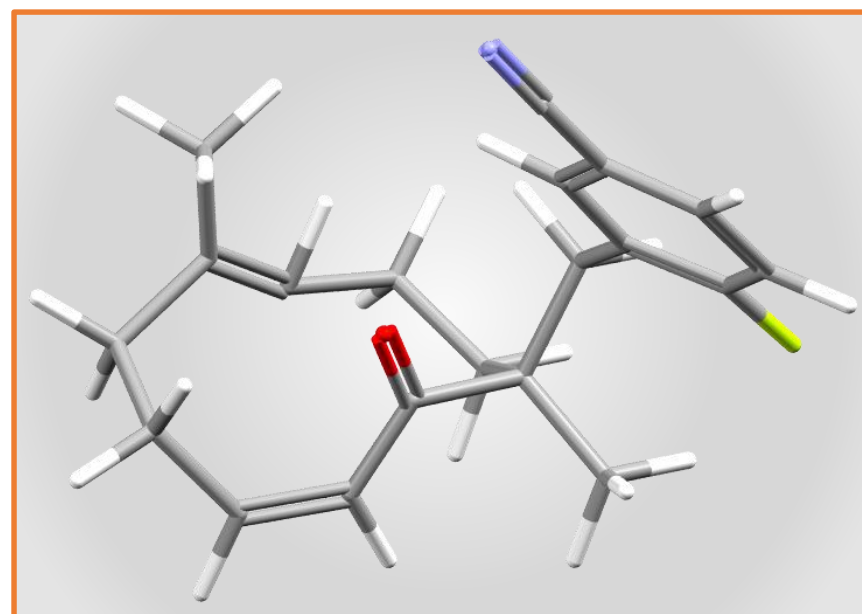
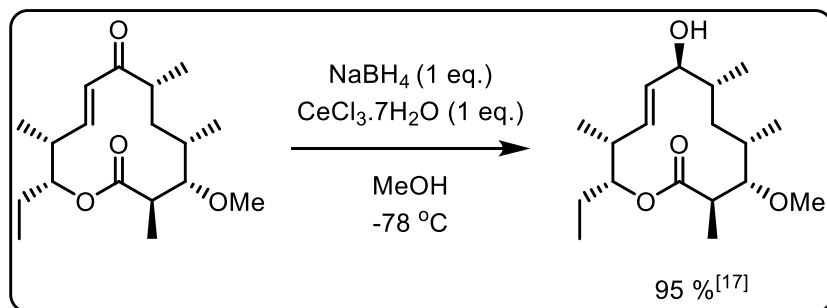
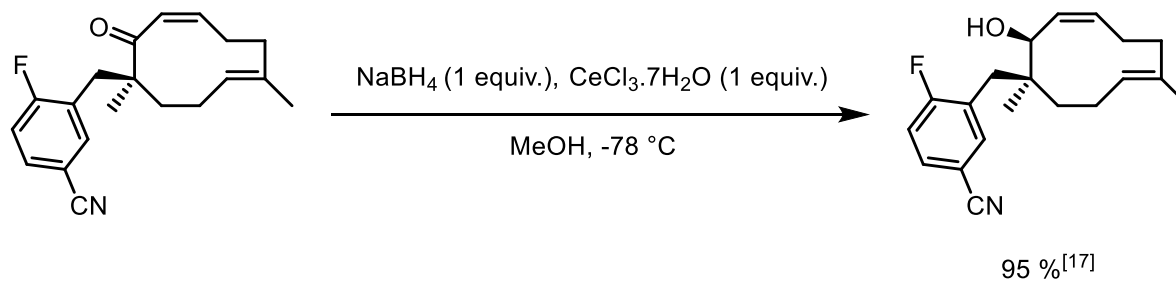
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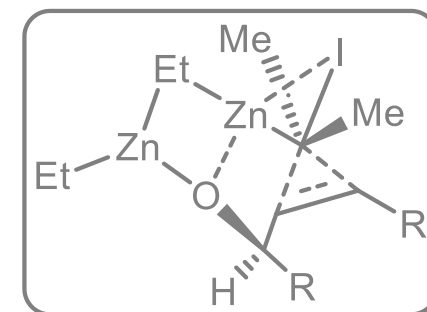
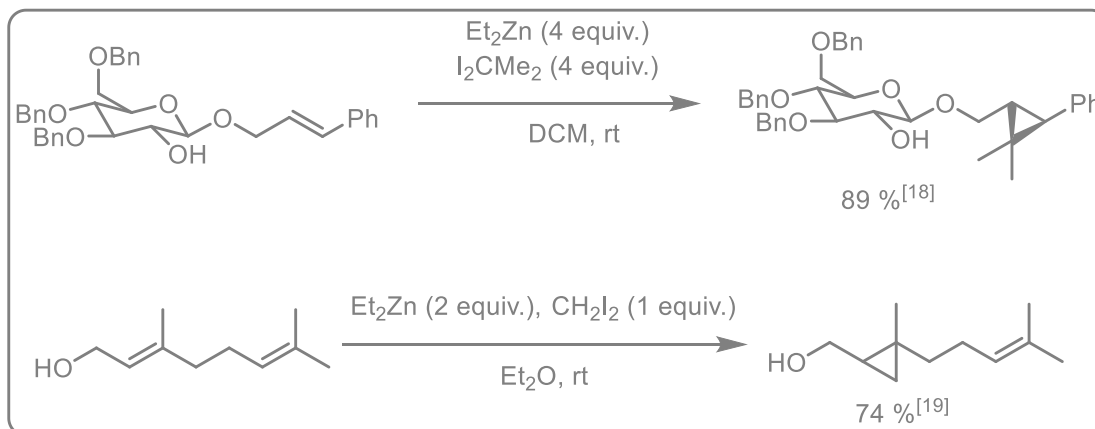
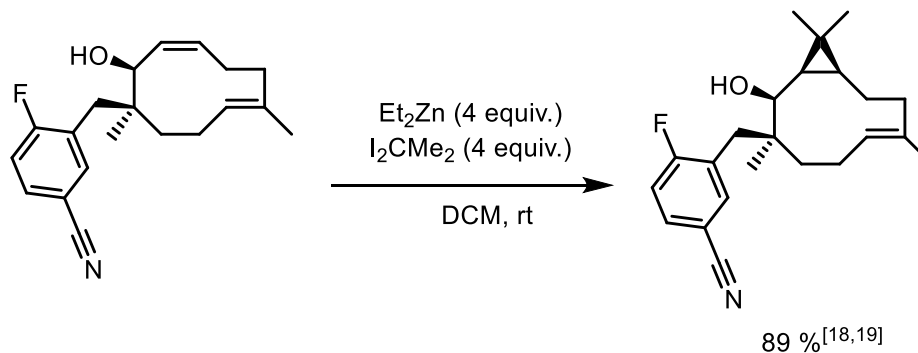
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Luche reduction



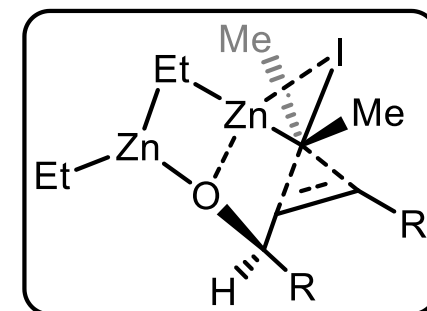
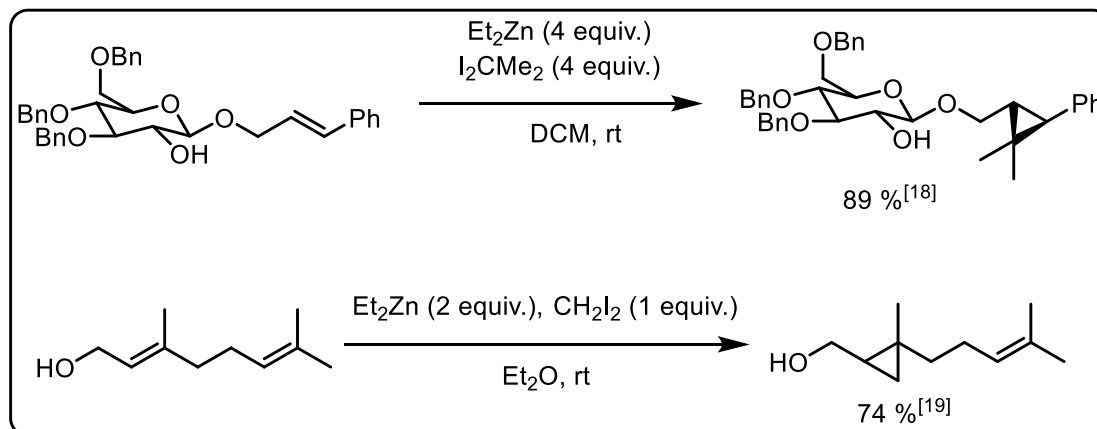
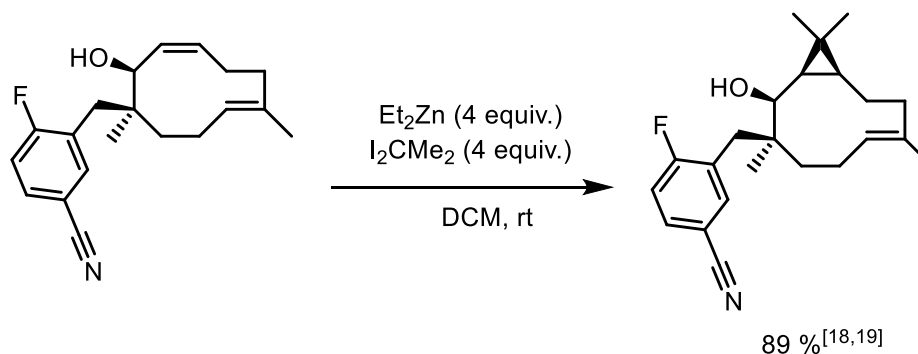
Directed cyclopropanation



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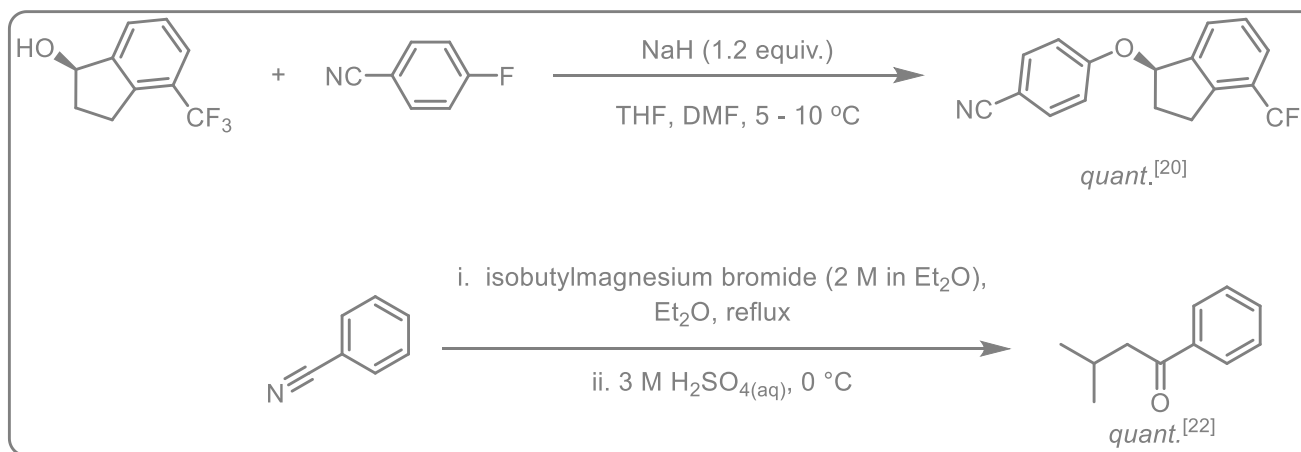
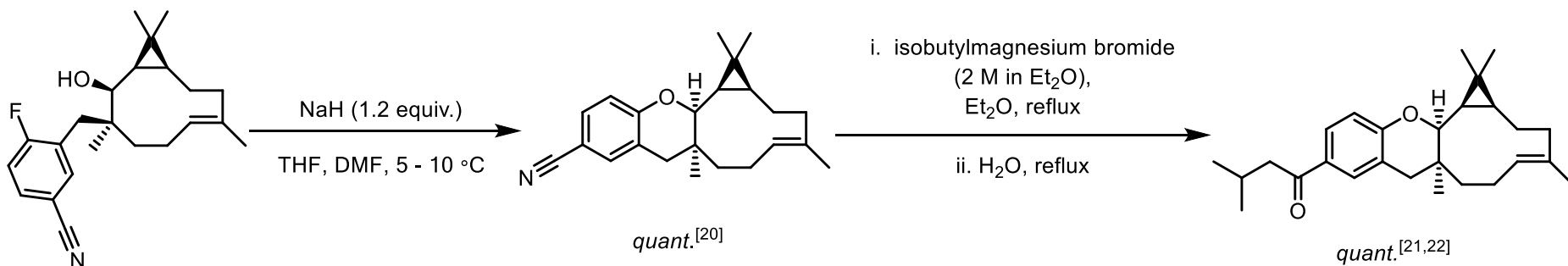
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Directed cyclopropanation


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 18. A. B. Charette and N. Wilb, *Synlett*, 2002, 2002, 176–178.

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S_NAr, Nitrile alkylation

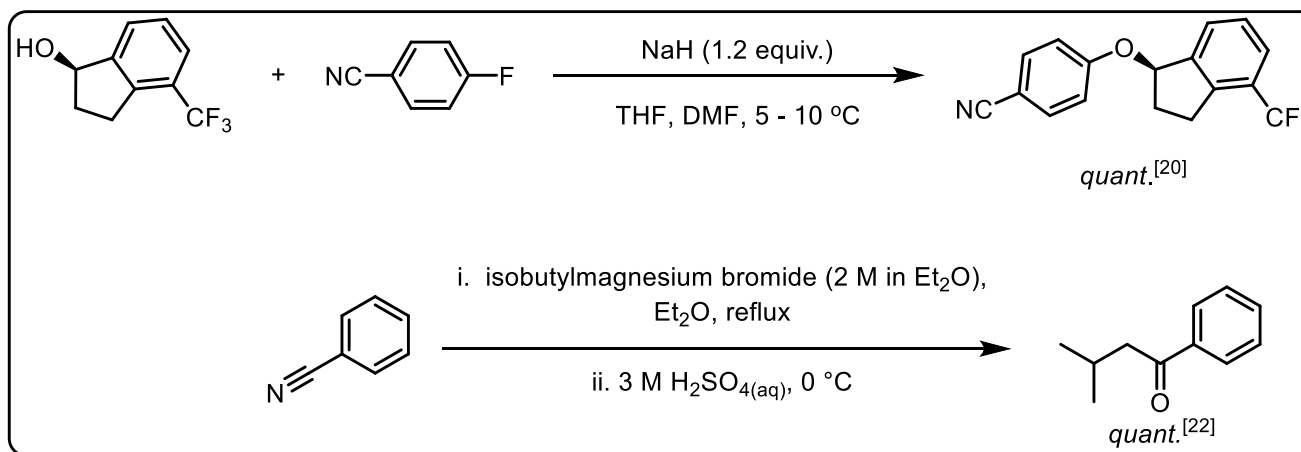
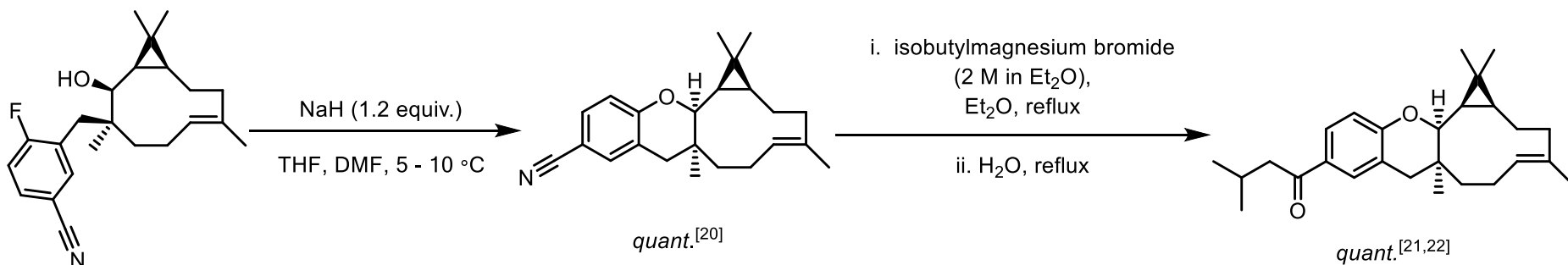


20. R. Takano, M. Yoshida, M. Inoue, T. Honda, R. Nakshima, K. Matsumoto, T. Yano, T. Ogata, N. Watanabe, M. Hirouchi, T. Yoneyama, S. Ito and N. Toda, *ACS Med. Chem. Lett.*, 2015, **6**, 266–270.

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S_NAr, Nitrile alkylation

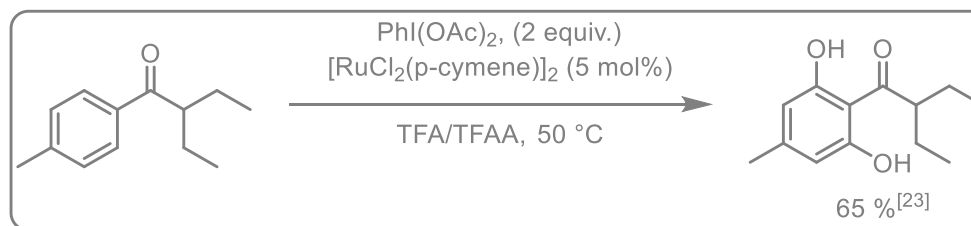
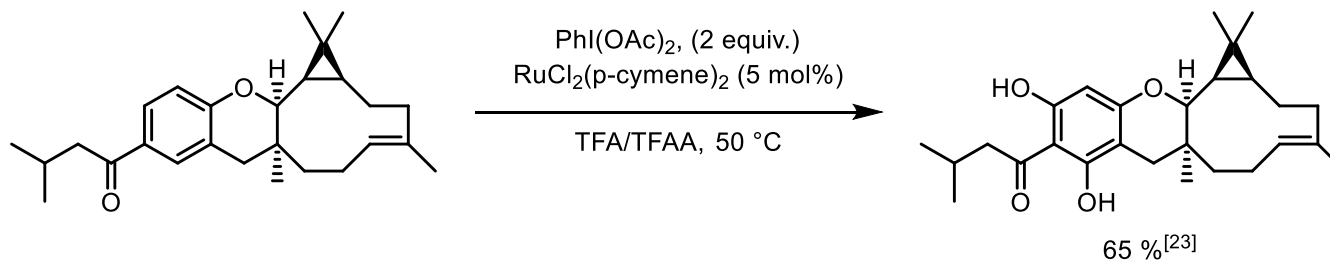


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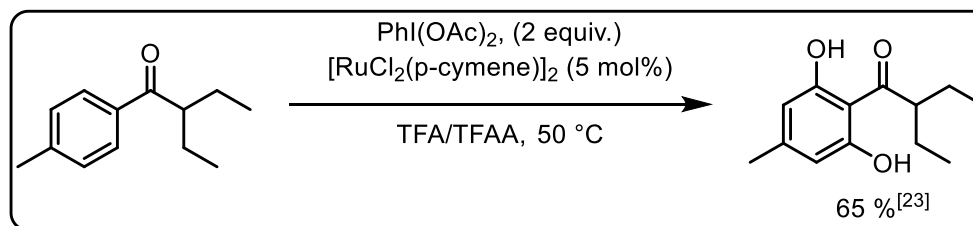
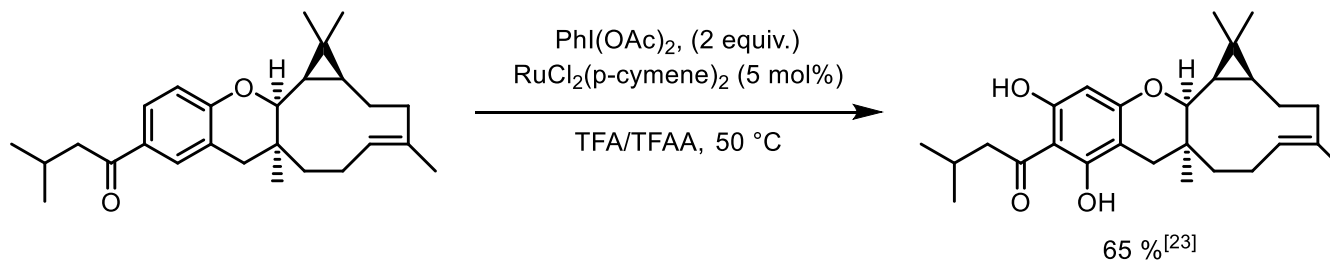
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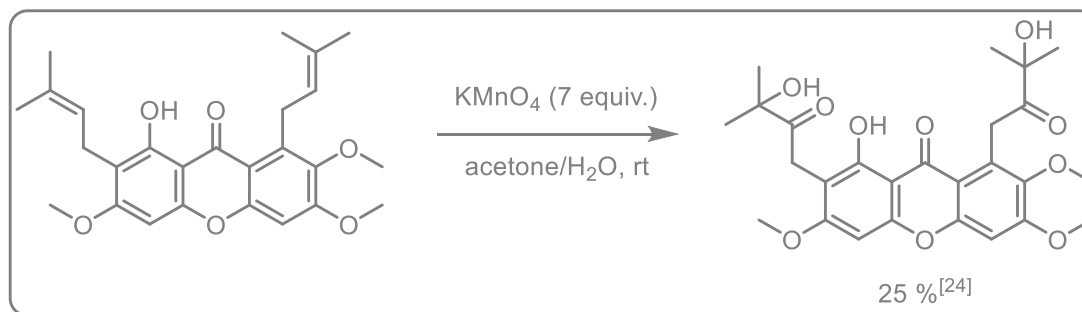
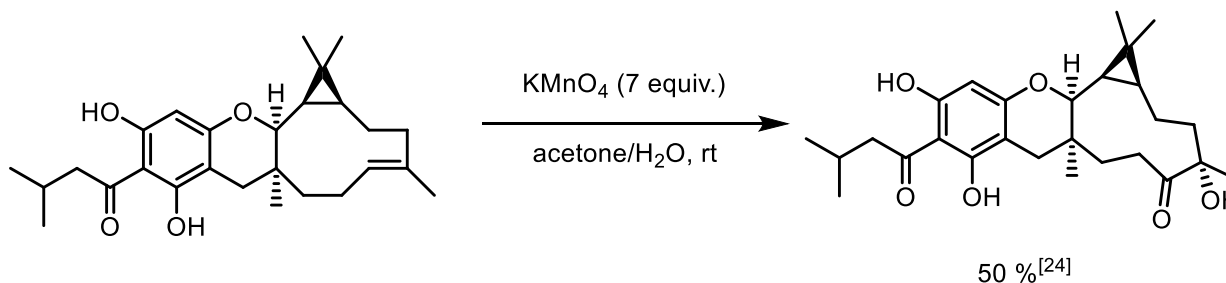
Late-Stage Oxidations



Late-Stage Oxidations



Late-Stage Oxidations

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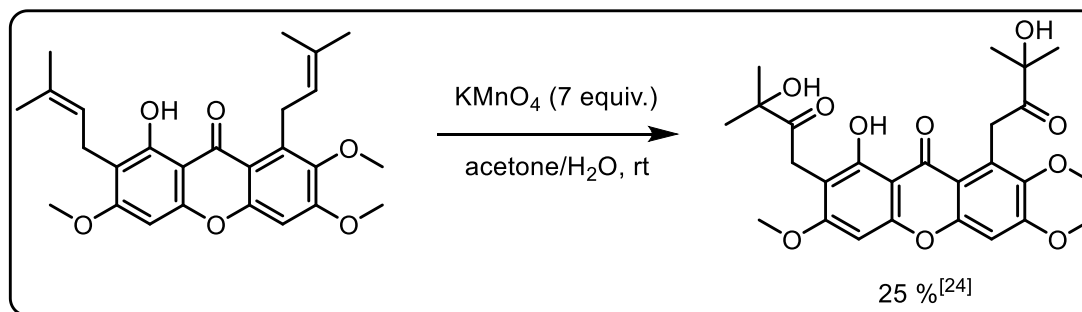
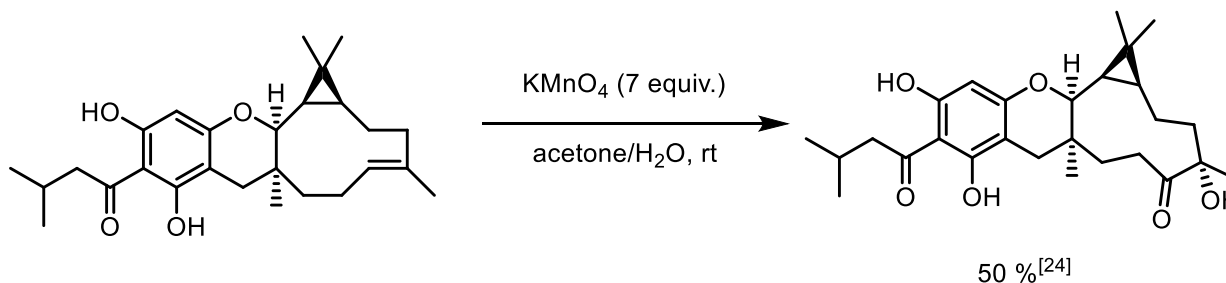
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27. US Pat., 20150132259, 2015.

Late-Stage Oxidations



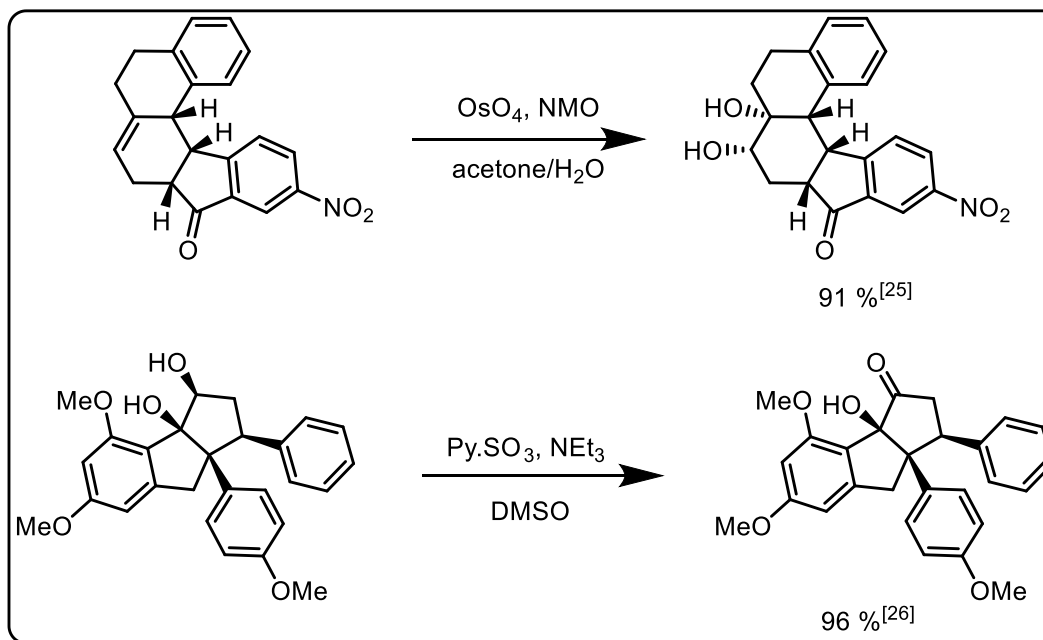
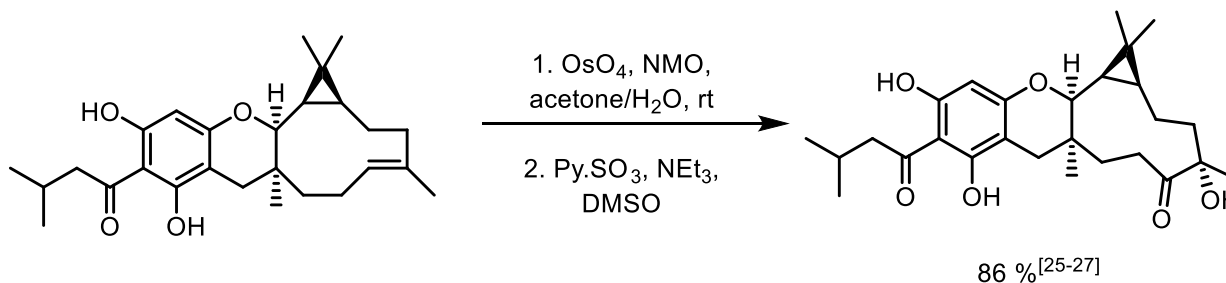
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Late-Stage Oxidations



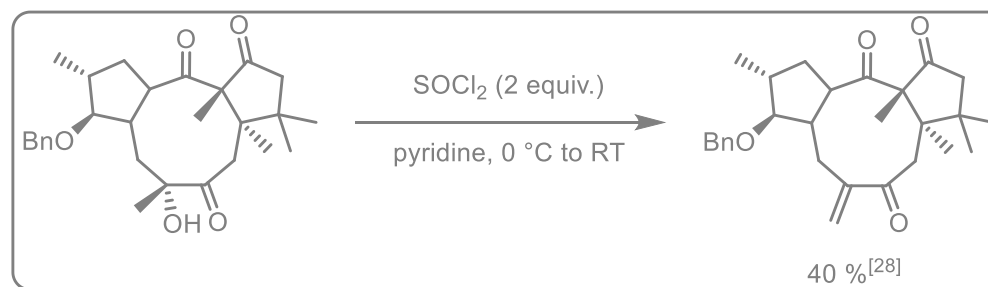
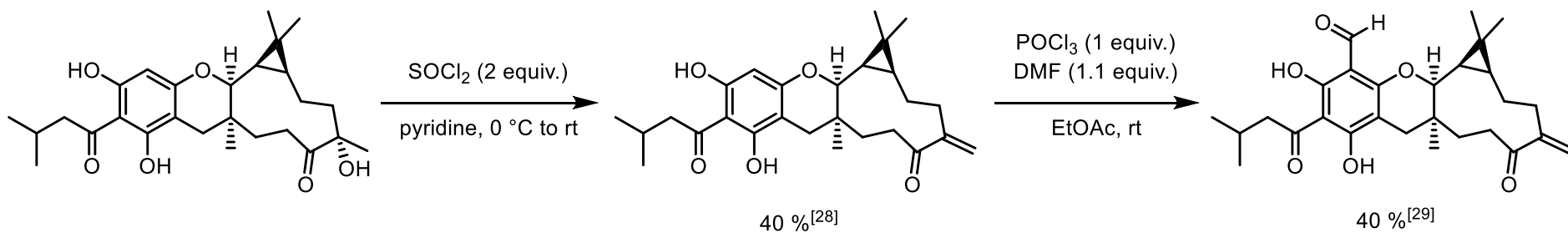
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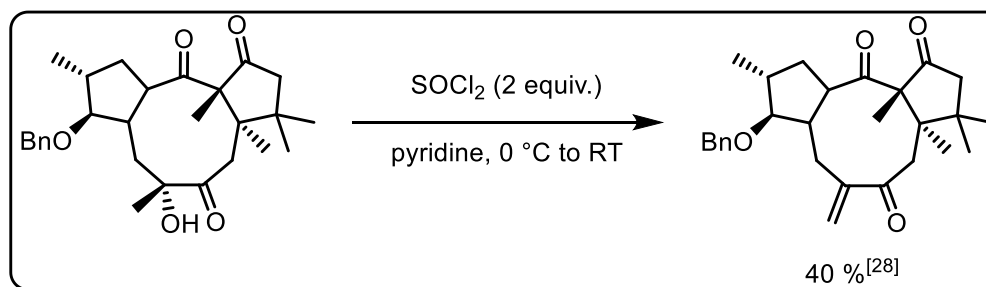
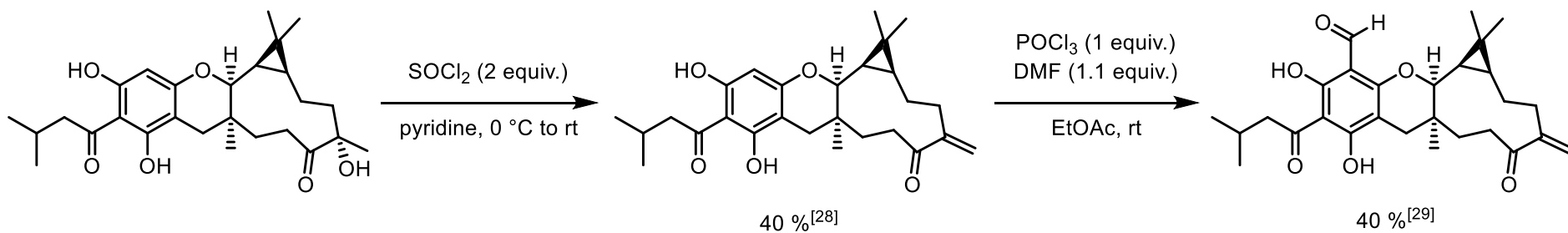
Final Steps



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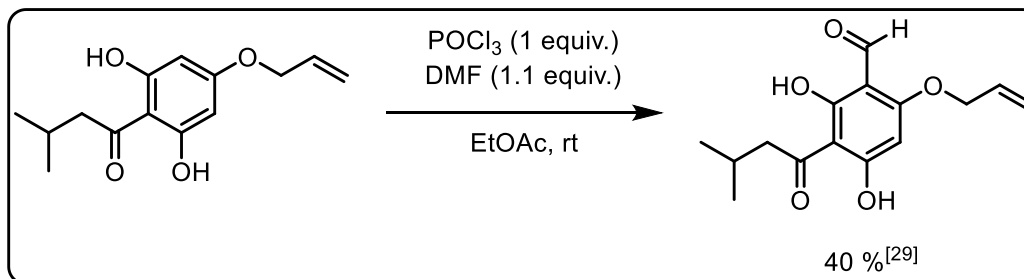
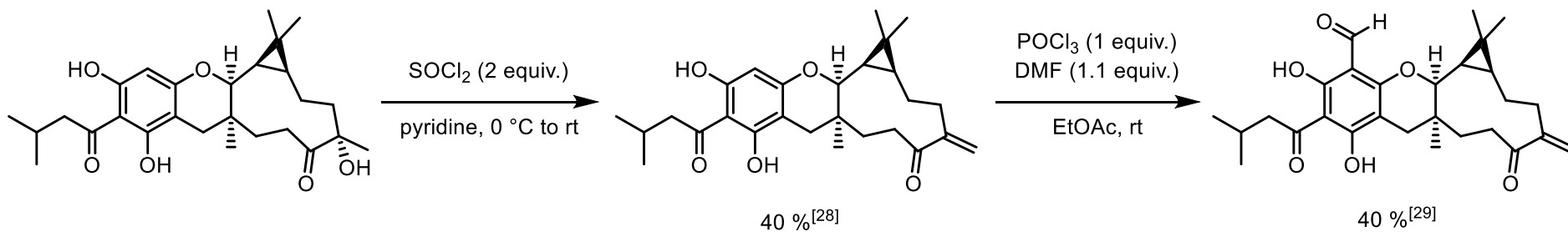
Final Steps



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Final Steps



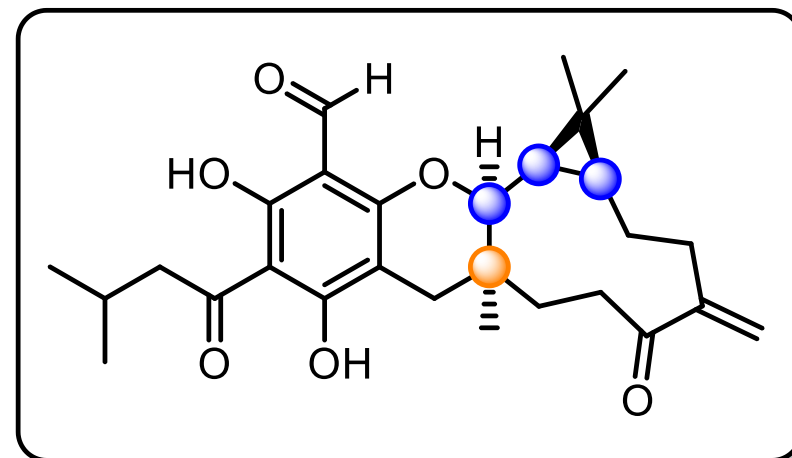
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Summary

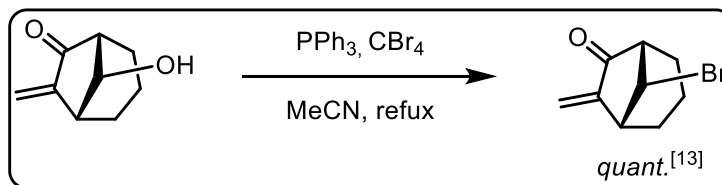


- 15 step, protecting group free synthesis of Eucalrobosone D in 1.4 % estimated overall yield.
- Single catalytic enantioselective step sets first stereocentre. Subsequent stereochemistry set through substrate control.

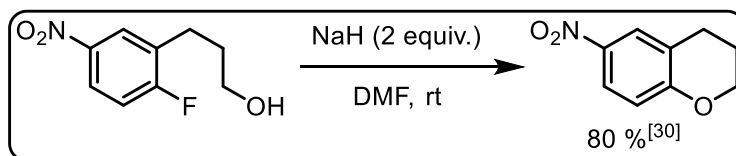


Thank you for listening! 😊

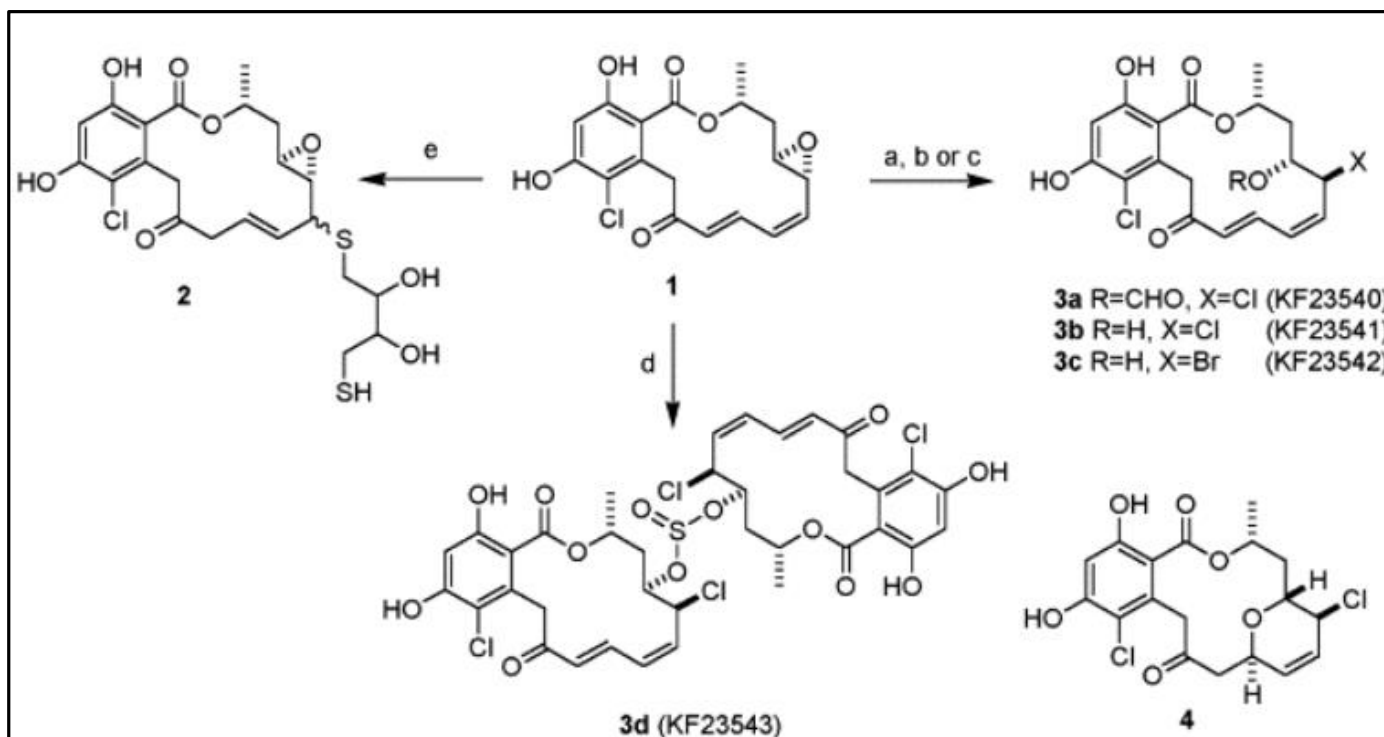
Appendix I



Appendix II



Appendix III



Scheme 1.

Reagents and conditions: (a) POCl₃, DMF, 0 °C to rt, 24 h, 51%; (b) concd HCl, dioxane, 0 °C to rt, 6 h, 45%;
 (c) concd HBr, dioxane, 0 °C to rt, 6 h, 56%; (d) SOCl₂, DMF, 0 °C to rt, 12 h, 62%; (e) DTT, 50% DMSO,
 37 °C, 2 h.

Appendix IV

