Literature Report 3

Enantioselective Chemical Syntheses of the Furanosteroids (−)-Viridin and (−)-Viridiol

Reporter: Huanping Xie
Checker: Zhong Yan
Date: 2017-07-24

Bel, M. D.; Abela, A. R.; Ng, J. D.; Guerrero, C. A. *J. Am. Chem. Soc.* **2017**, *139*, 6819.

Contents

Biography

Carlos A. Guerrero

Areas of interest:

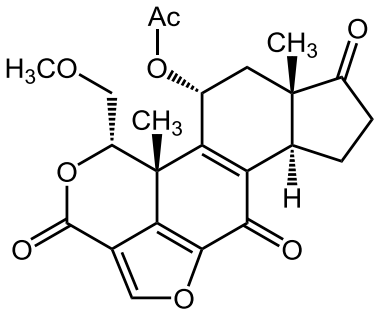
- offer solutions to longstanding problems in chemical synthesis that blend judicious synthesis planning with new and innovative bond constructions.
- expand the scope of known reactivity and possibly enable studies of biological phenomena.

Research experience:

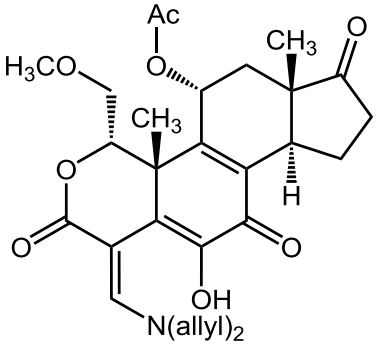
- **2011**- UC San Diego (assistant professor);
- **2008-2011** Princeton University (work with Professor Erik J. Sorensen);
- **2003-2008** Ph.D., Scripps Research Institute (Phil S. Baran);
- **2000-2004** B.S., Harvard University (Phil S. Baran).

Introduction

Furanosteroid natural products



Wortmannin



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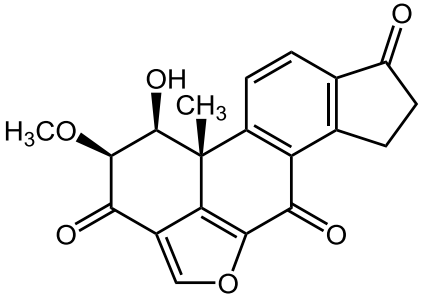
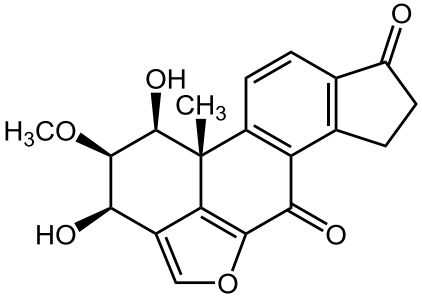


Viridin



Viridiol

Adward, A. E.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 1998.
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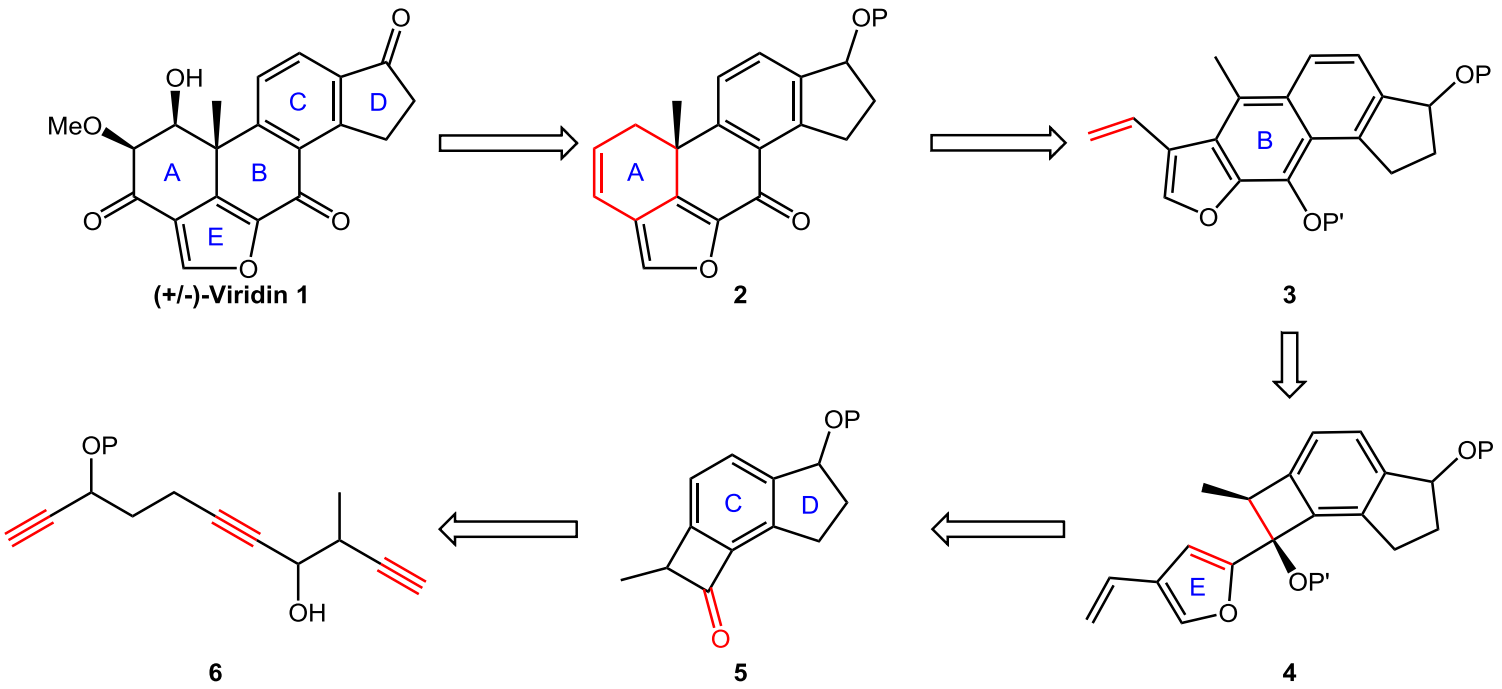
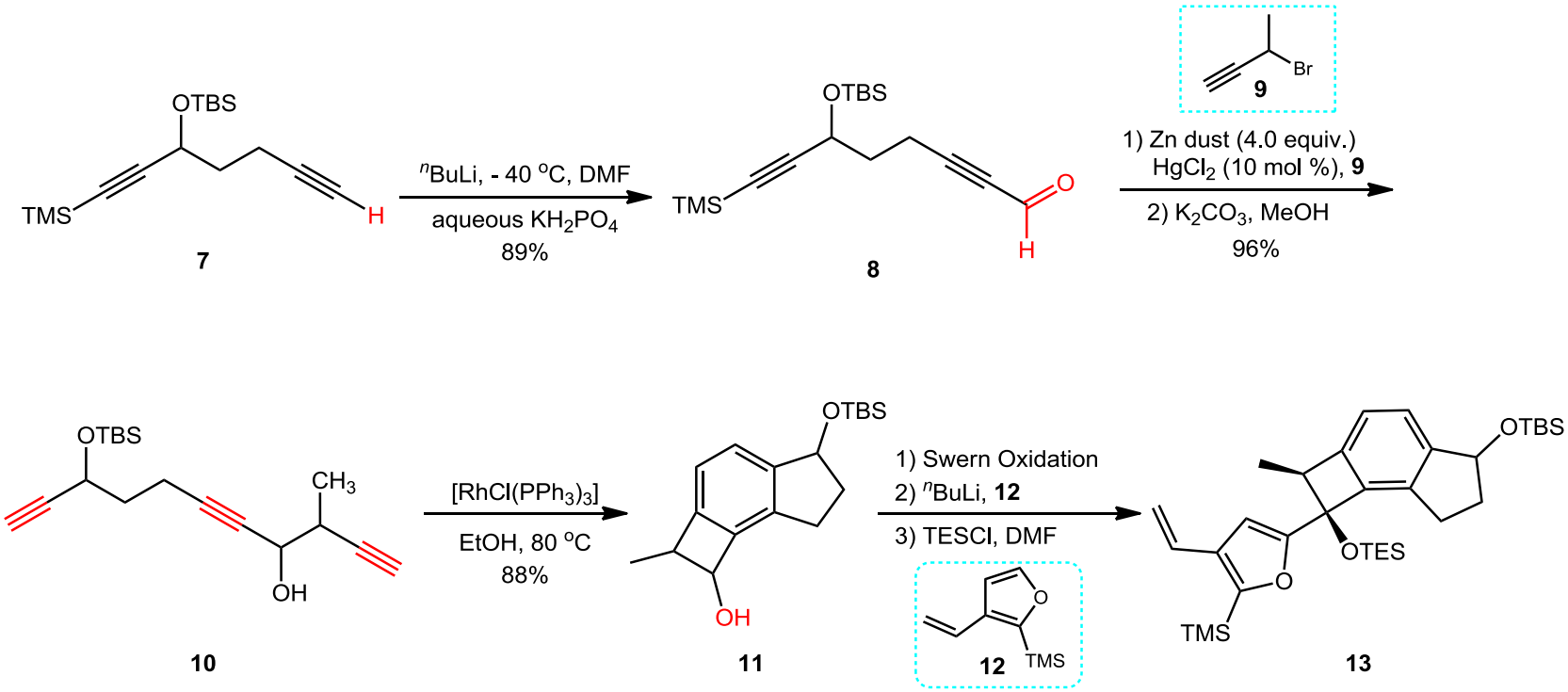
Retrosynthetic Analysis

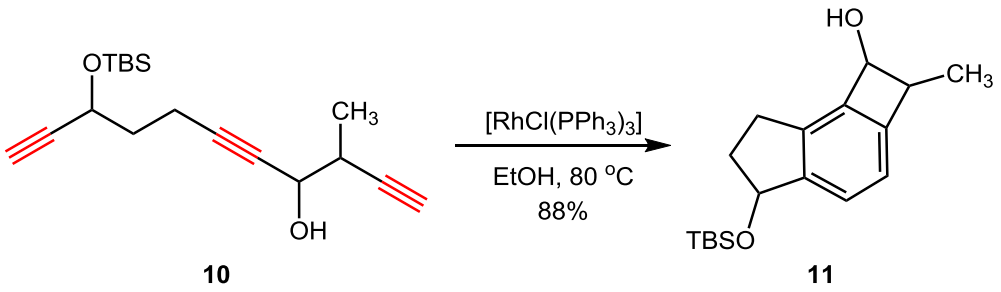


Adward, A. E.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 1998.

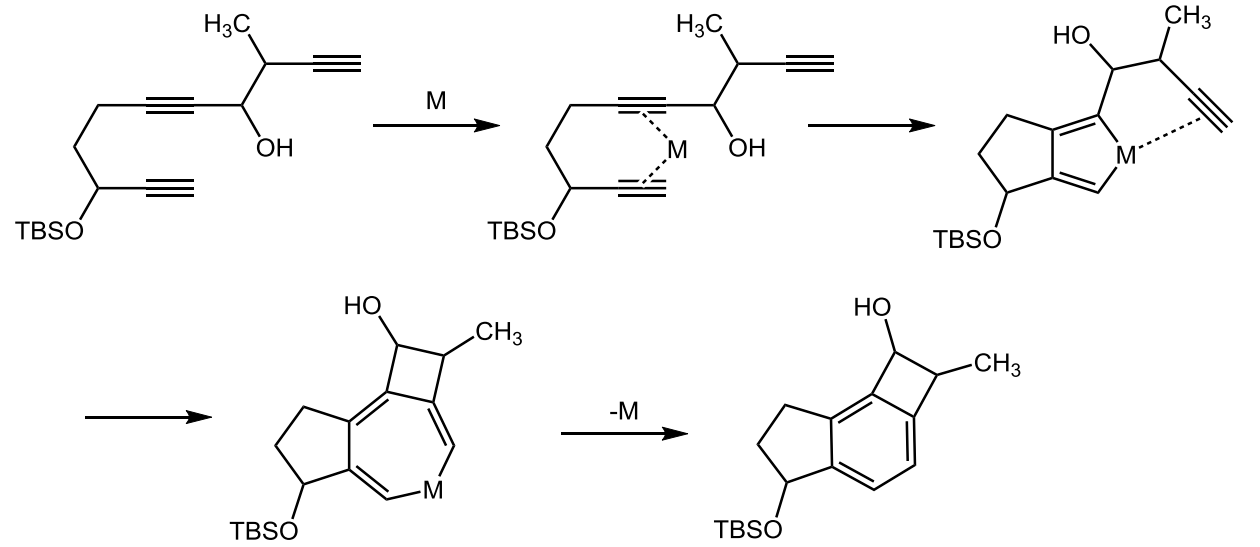
Synthesis of Benzocyclobutene 13



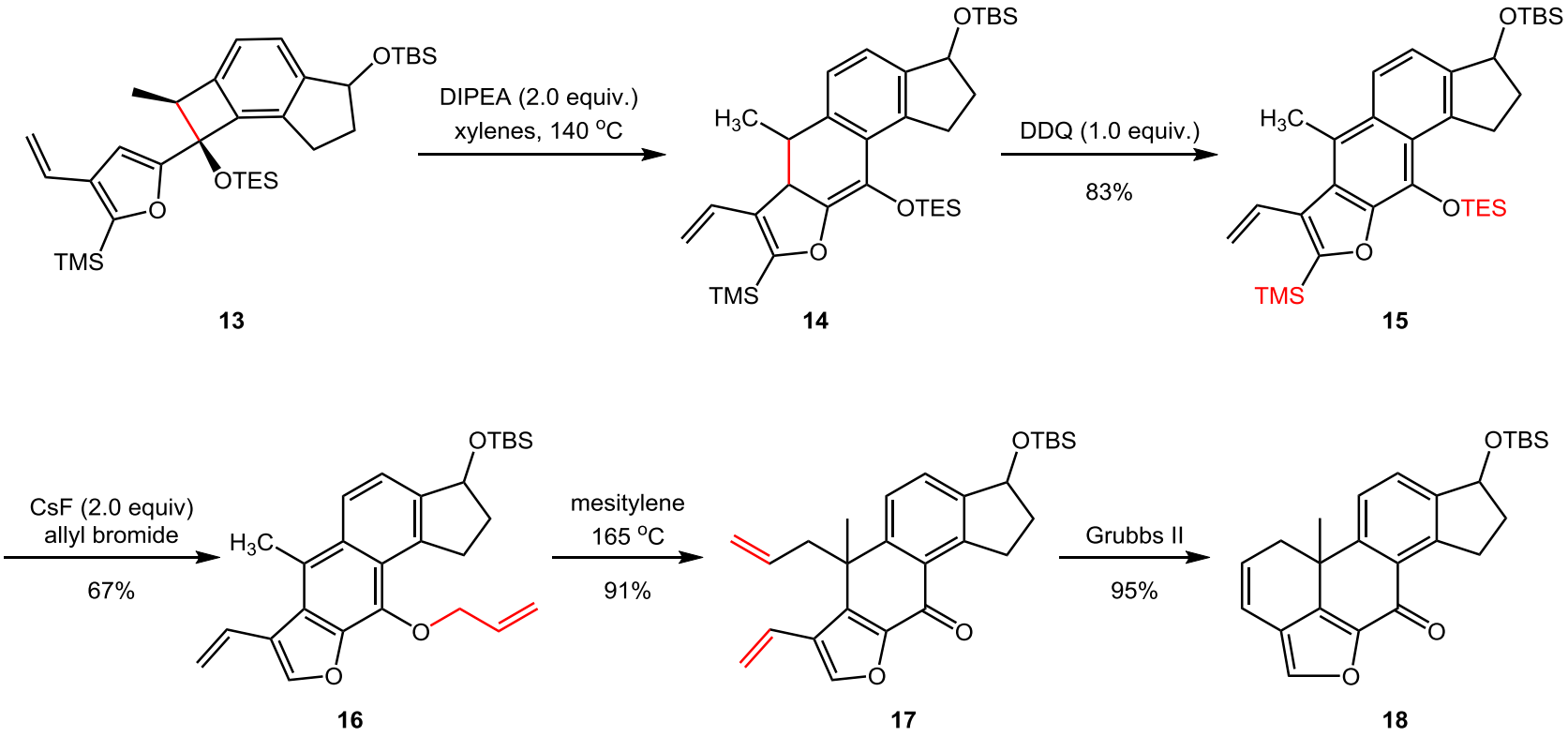
Alkyne Cyclotrimerization



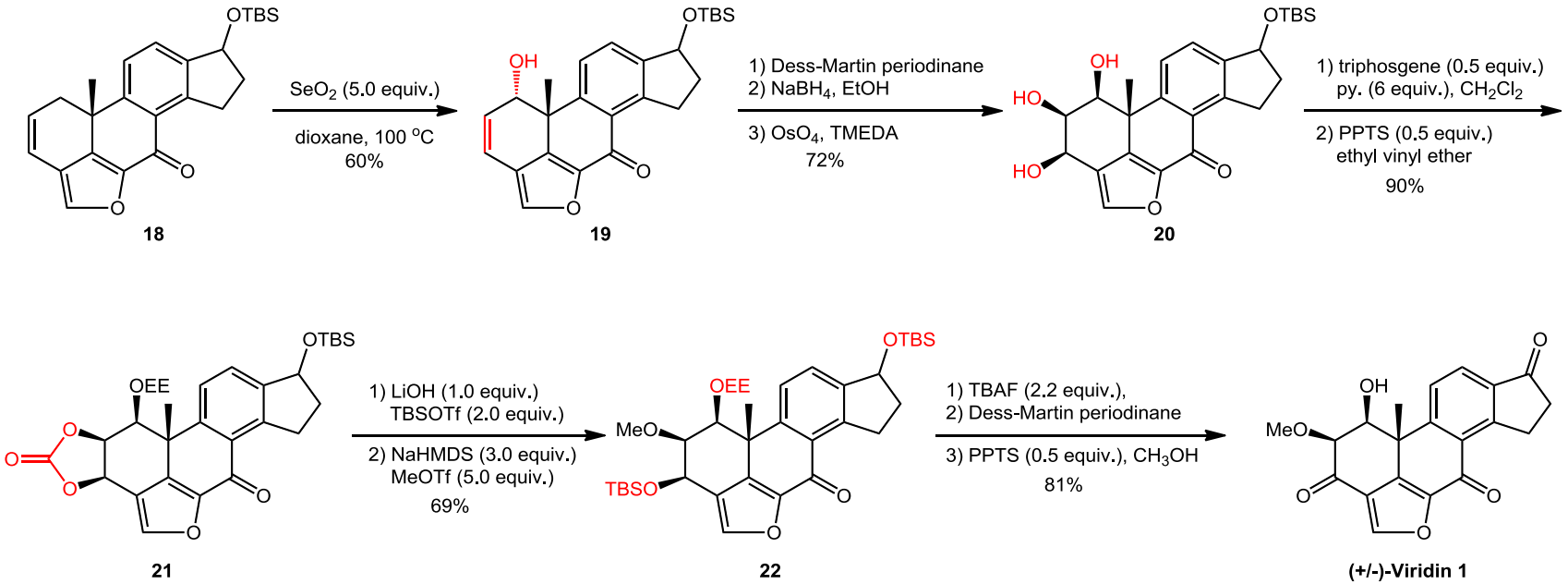
10 **11**



Synthesis of Pentacycle 18



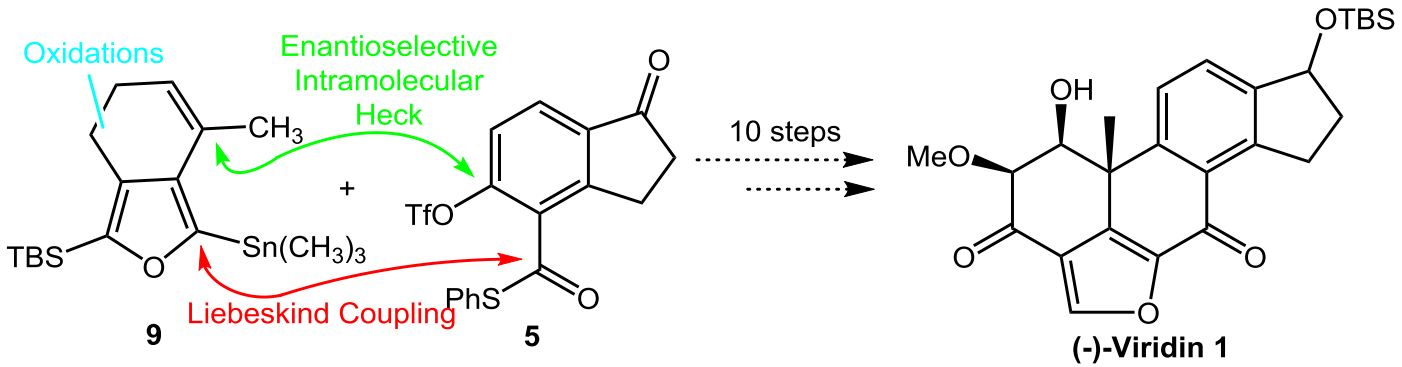
Synthesis of (+/-)-Viridin 1



18 **19** **20** **21** **22** **(+/-)-Viridin 1**

5.0% overall yield

Enantioselective Synthesis of (−)-Viridin 1



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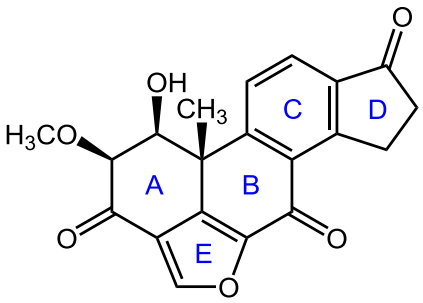
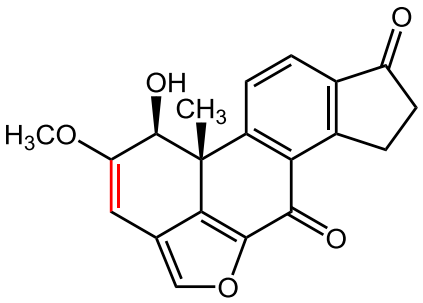
Retrosynthetic Analysis



(-)-Viridin 1



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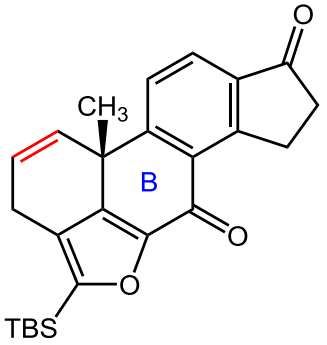

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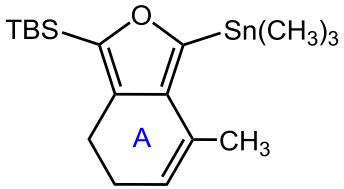
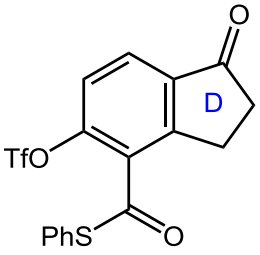


9

+



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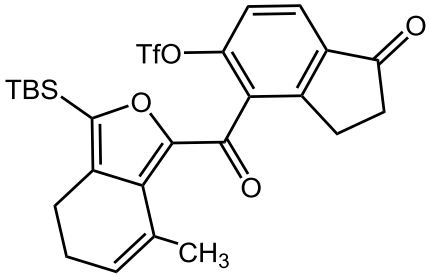

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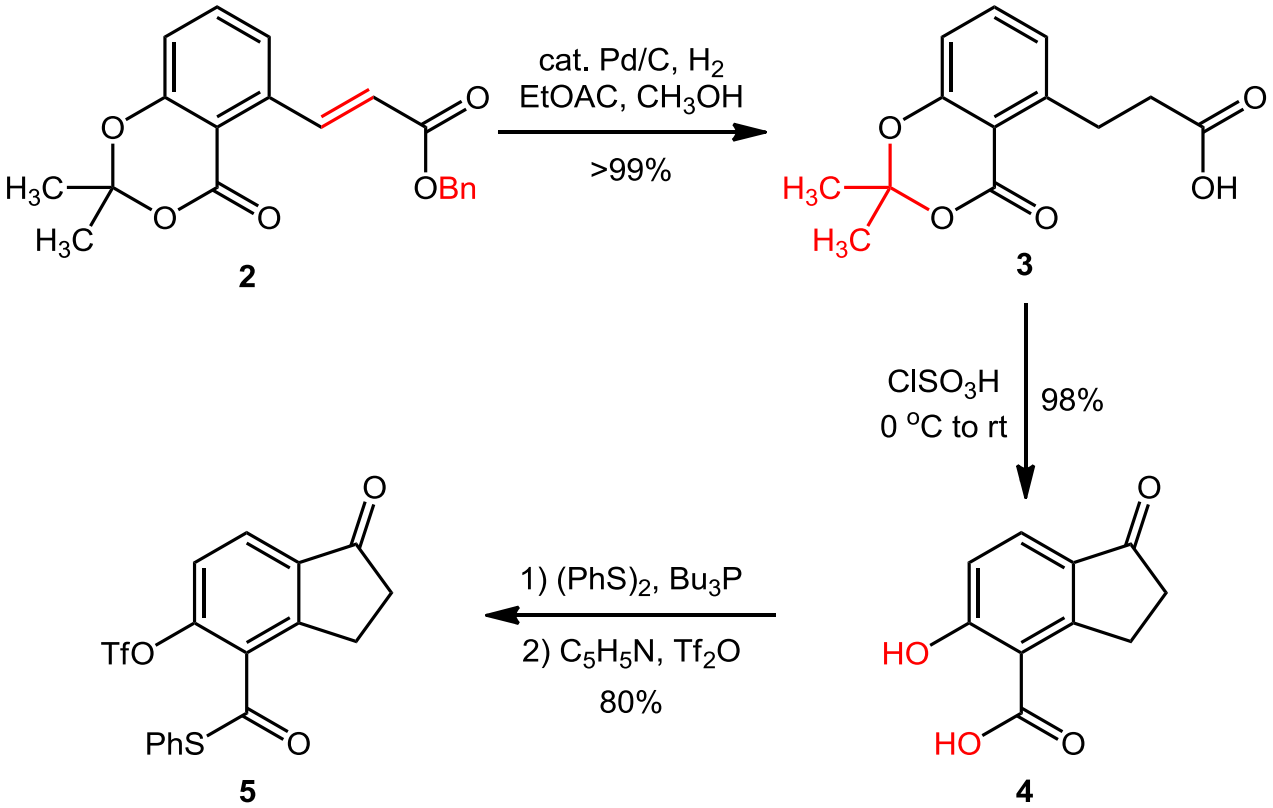
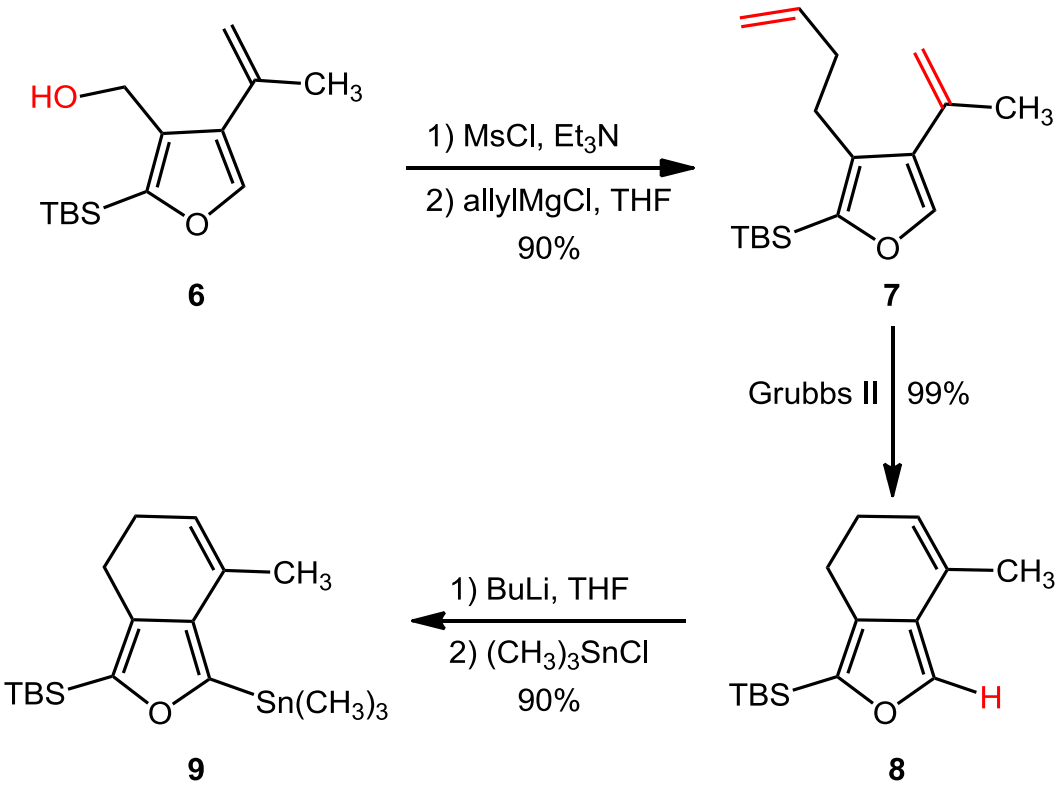
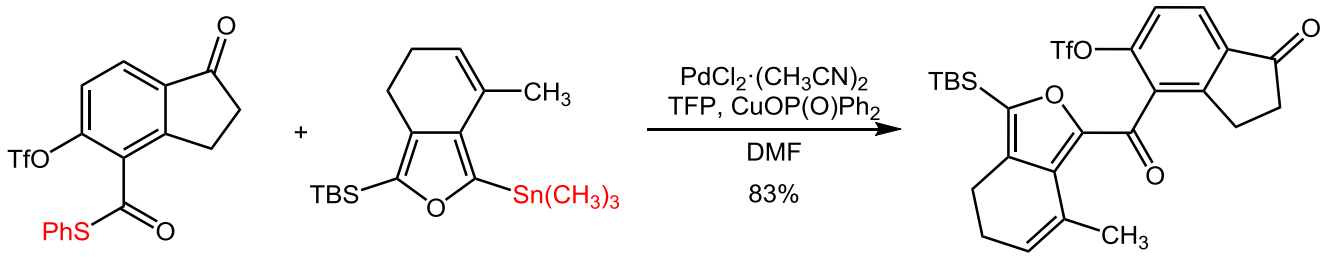
Preparation of Coupling Parter 5



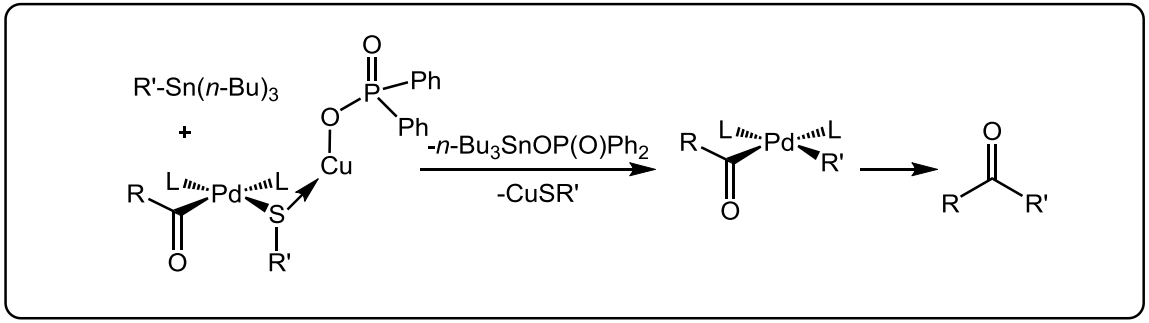
Preparation of Coupling Parter 9



Liebeskind Stannane-thioester Coupling

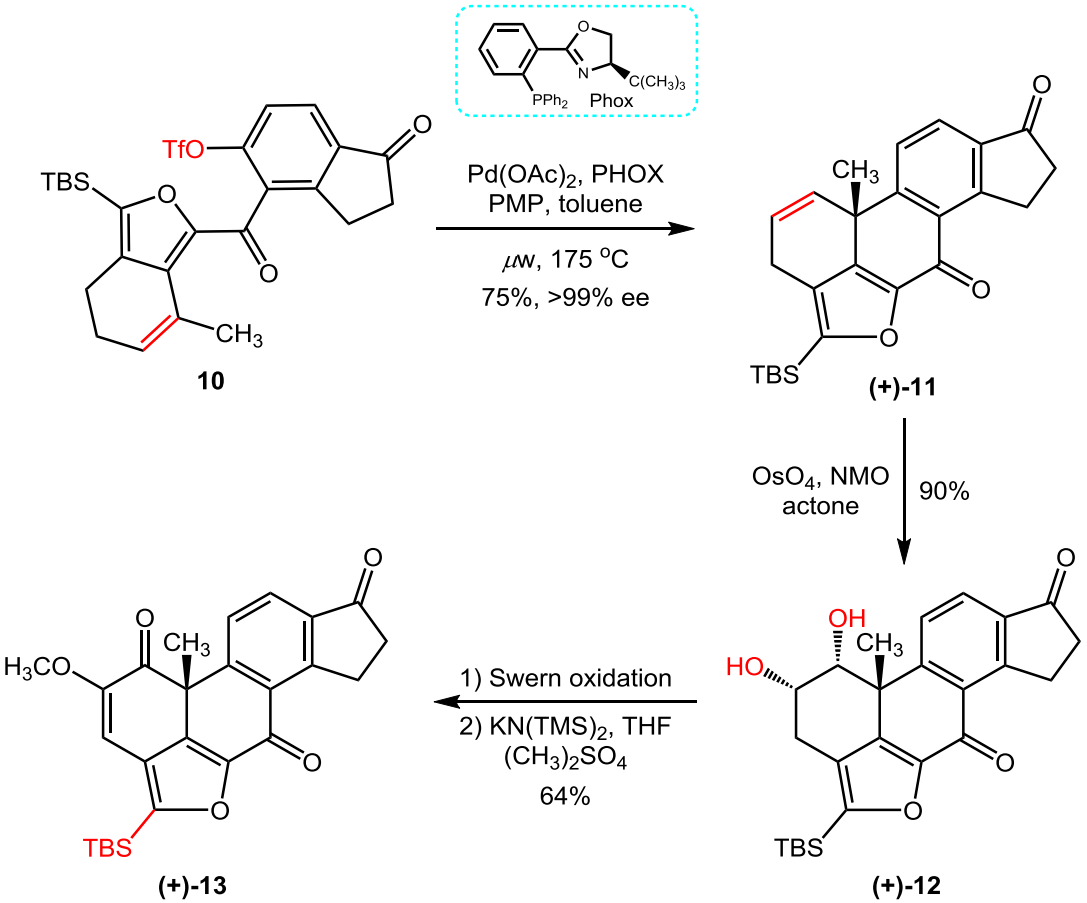


5 **9** **10**

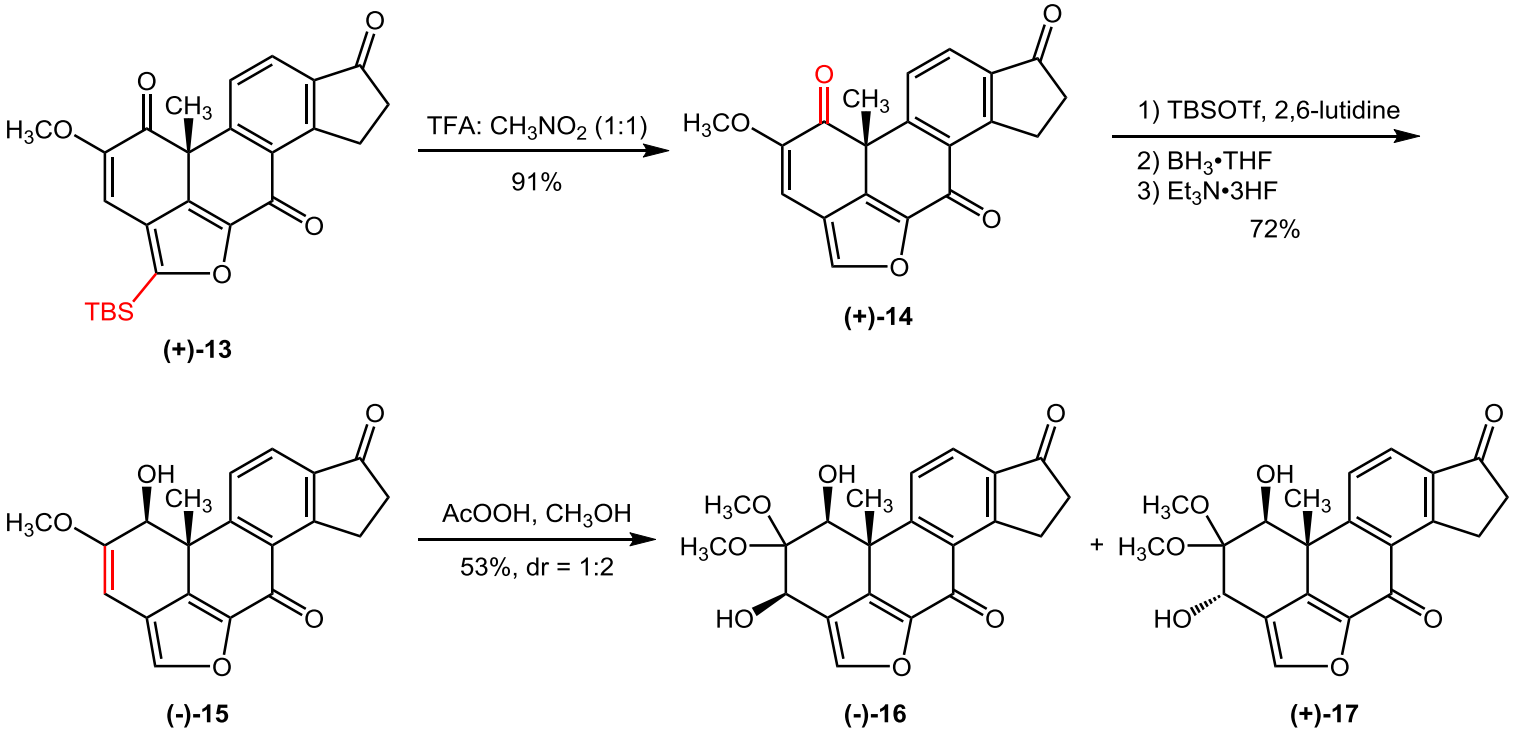


Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033.

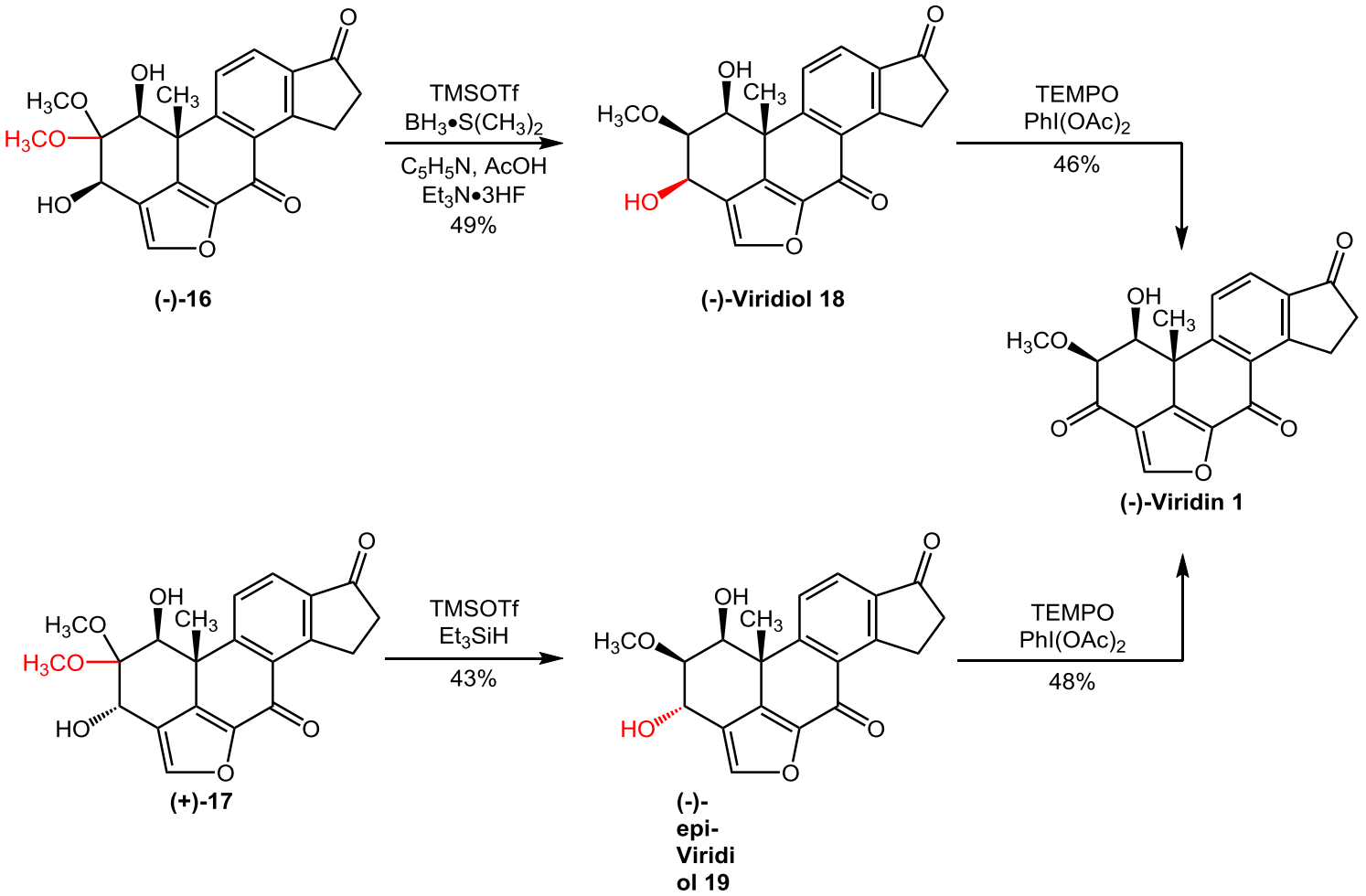
Enantioselective Synthesis of (+)-13



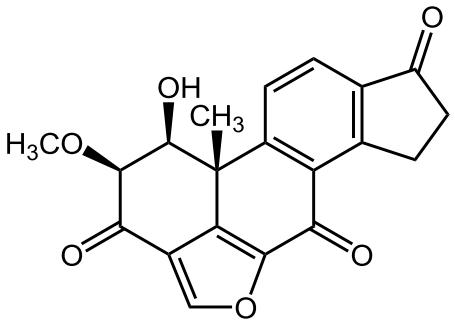
Enantioselective Synthesis of Ketals (-)-16 and (+)-17



Enantioselective Synthesis of (-)-Viridin 1



Summary



(±)-Viridin

- 13 Steps, 5.0% overall yield
- Alkyne Cyclotrimerization
- Thermal Electrocyclic Rearrangement

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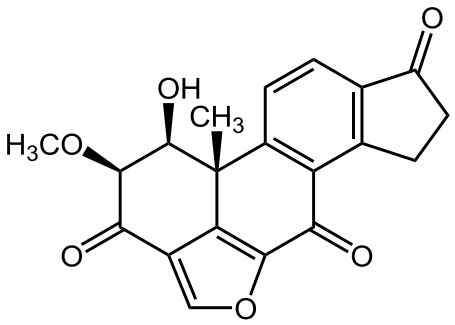

(-)-Viridin

- 18 Steps, 2.1% overall yield
- Enantioselective Heck reaction
- Liebeskind Coupling

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The First Paragraph

Wortmannin, viridin, and other furanosteroids have been the subjects of structural and limited biological studies for over seven decades. Unsurprisingly, wortmannin became the reagent of choice in fundamental biochemical studies of PI3Ks (phosphatidylinositol 3-kinases). In principle, viridin may also be a viable candidate for PI3K inhibition-based chemotherapy. Sorensen duly completed the first total syntheses of each viridin and viridiol in racemic form in 2004. Herein, we report our own enantioselective syntheses of (−)-viridin and (−)-viridiol.

The Last Paragraph

In summary, our synthesis of (−)-viridin up to fragments **5** and **9** is direct and efficient, permitting rapid assembly and late-stage functionalization of the A-ring. Thereafter, several novel and strategic maneuvers are executed including (1) an intramolecular, highly enantioselective Heck reaction to set the absolute stereochemical course of the synthesis; (2) double Swern oxidation to indirectly oxidize C3; (3) an epoxidation trapping sequence to install a hydroxyl group at C3; and (4) highly diastereoselective demethoxylation to address functionality at C2.

The Last Paragraph

Our syntheses of (−)-viridiol and (−)-viridin generate single enantiomers for the first time and proceed in 17 and 18 steps, respectively, from commercially available materials and thus compare favorably to prior art. More generally, by demonstrating the feasibility of a fragment coupling to approach access the viridin core, we have enabled the synthesis of analogues with deep-seated modifications to the C,D-ring system for medicinal chemistry investigations.

Acknowledgement

Thanks for your kind attention!

Synthesis of 2 and 6