14-Step Synthesis of (+)-Ingenol from (+)-3-Carene

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Baran, P. S. *et al.*
Science **2013**, *341*, 878.

The Scripps Research Institute

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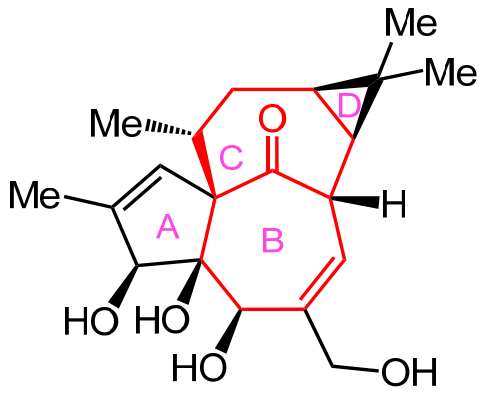
Introduction

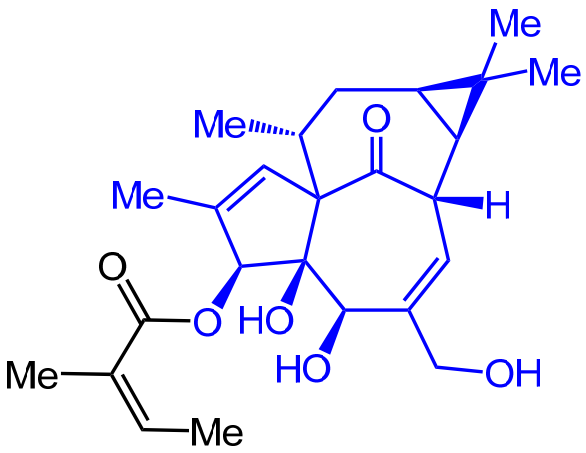


Ingenol (**1**)

Euphorbia

- Isolated from the genus *Euphorbia* in 1968
- The “inside-outside” bridged BC ring coupled with a broad spectrum of biological activities

Introduction

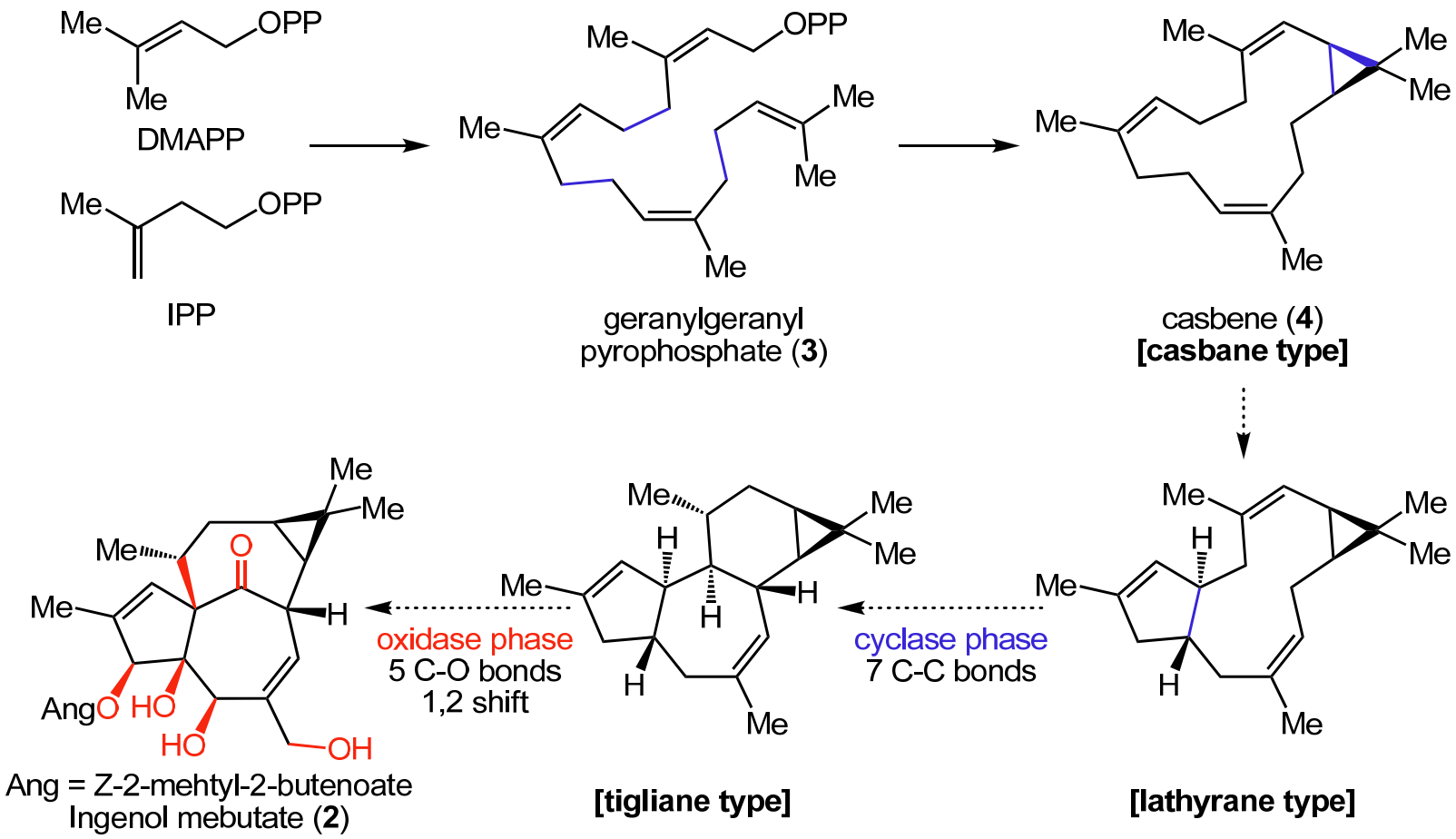


Ingenol mebutate (**2**)
(Picato)
[FDA approved 2012]

- Direct isolation: the isolation yields only 1.1 mg of **2** per kg of *E. peplus*
- Semisynthesis from ingenol: the yield of 275 mg of ingenol **1** per kg of dried seeds of *E. lathryis*

Total Synthesis of (+)-Ingenol

Biosynthesis and bioengineering of ingenane diterpenoids



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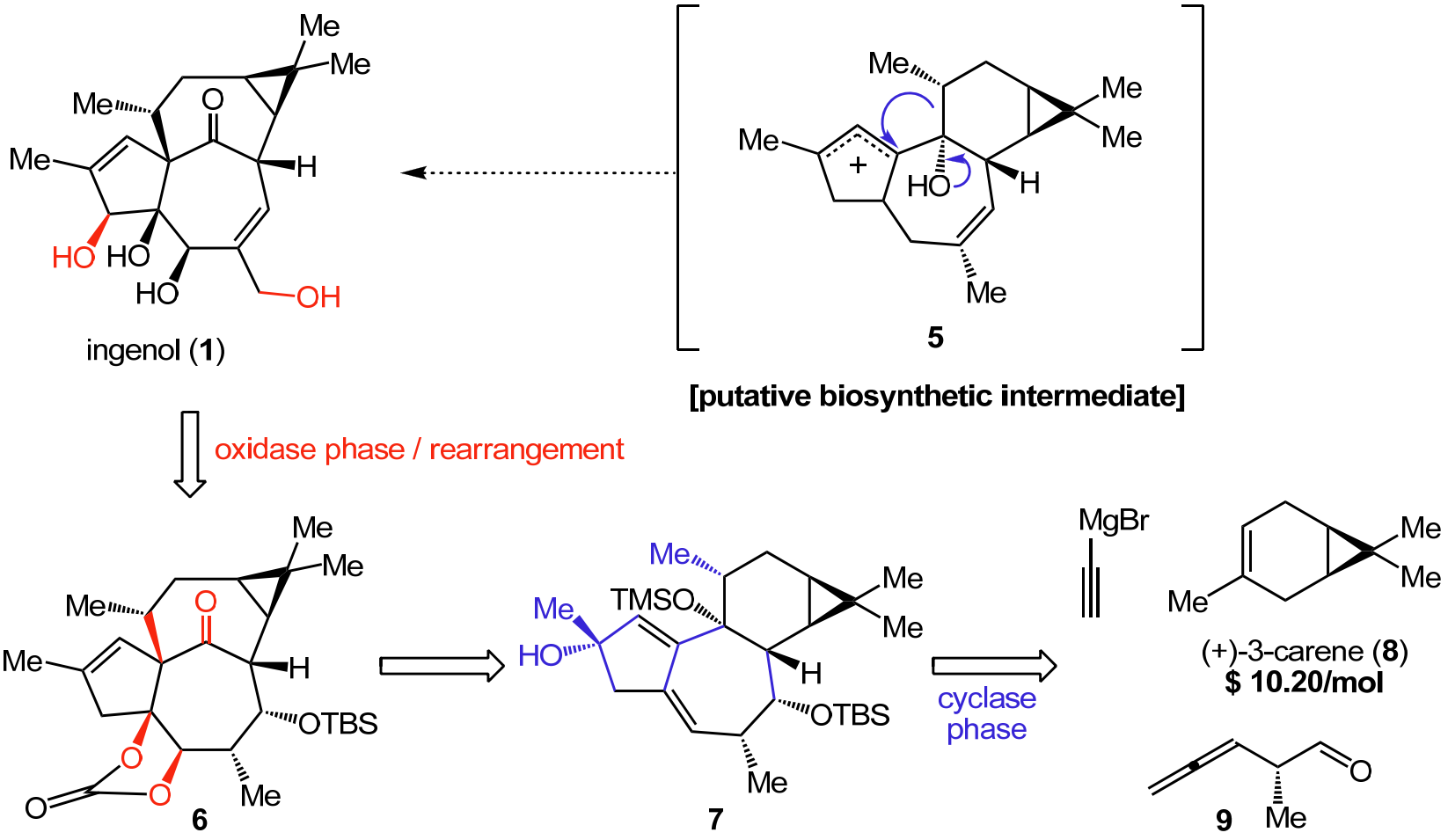
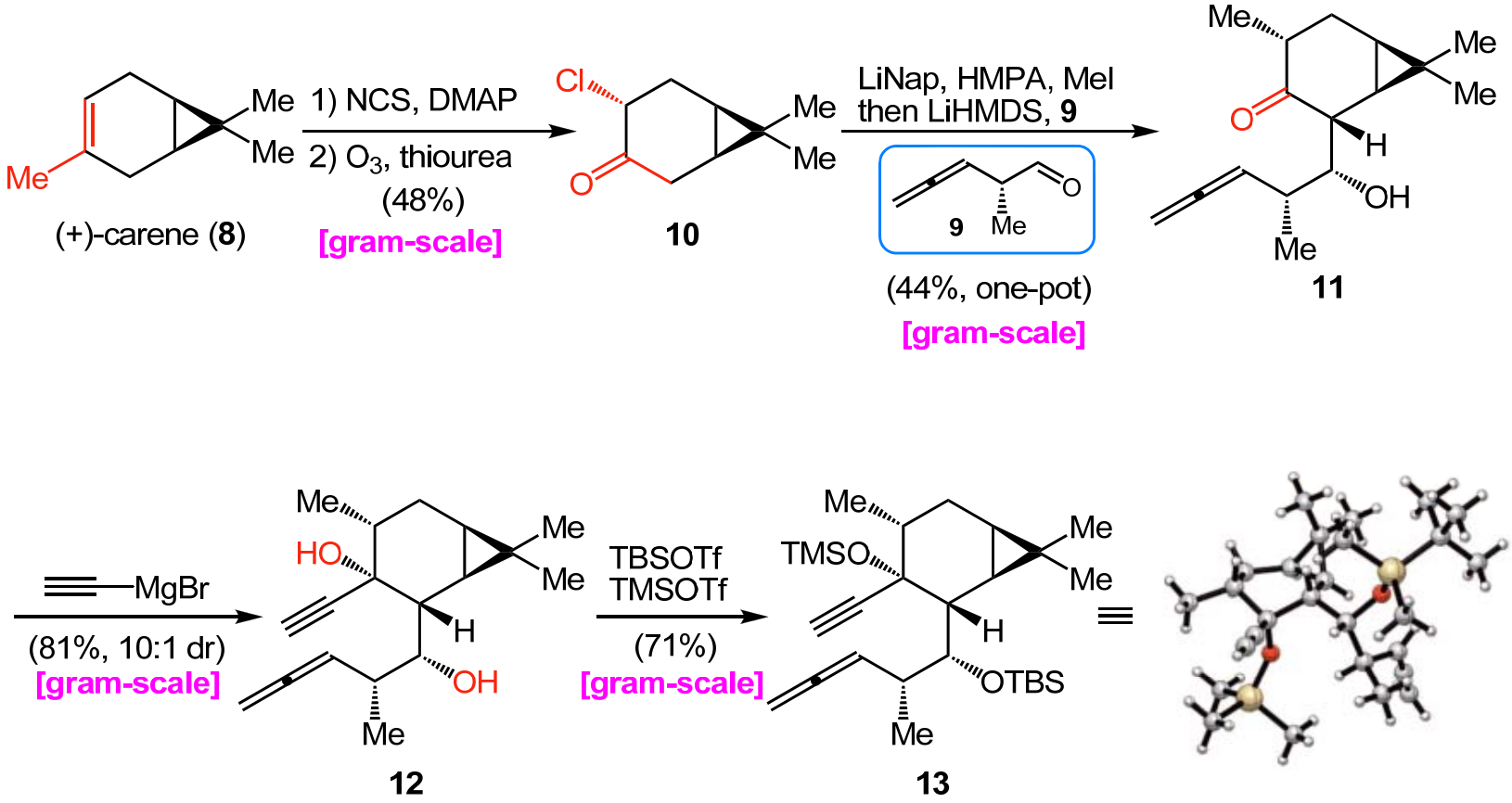
Total Synthesis of (+)-Ingenol

Retrosynthetic Analysis



Total Synthesis of (+)-Ingenol

[Cyclase Phase]: 7 steps, 7 C-C bonds, 5 stereocenters



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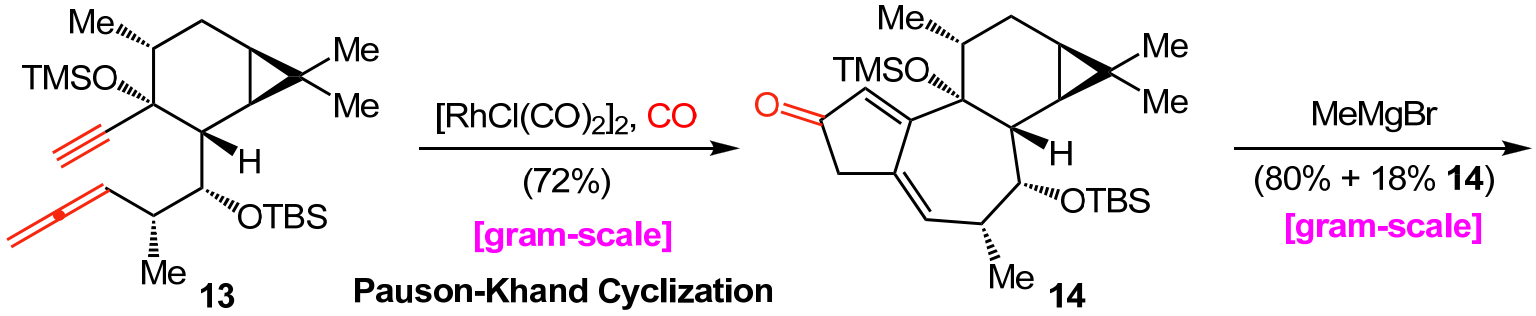
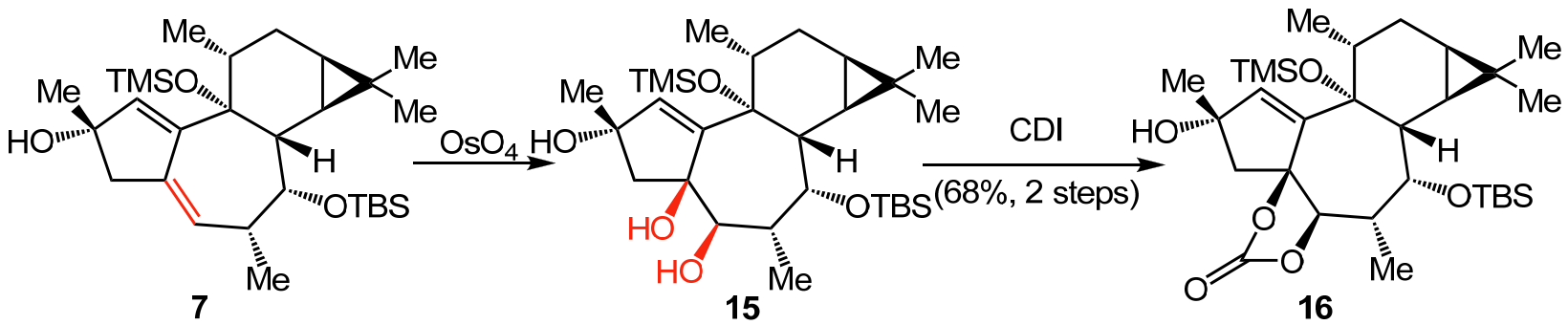
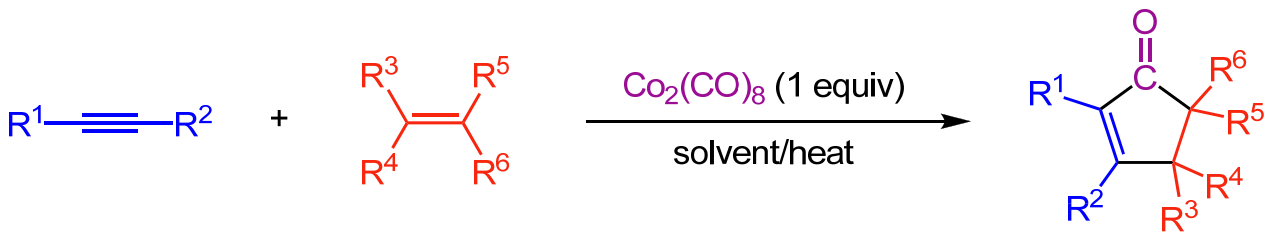




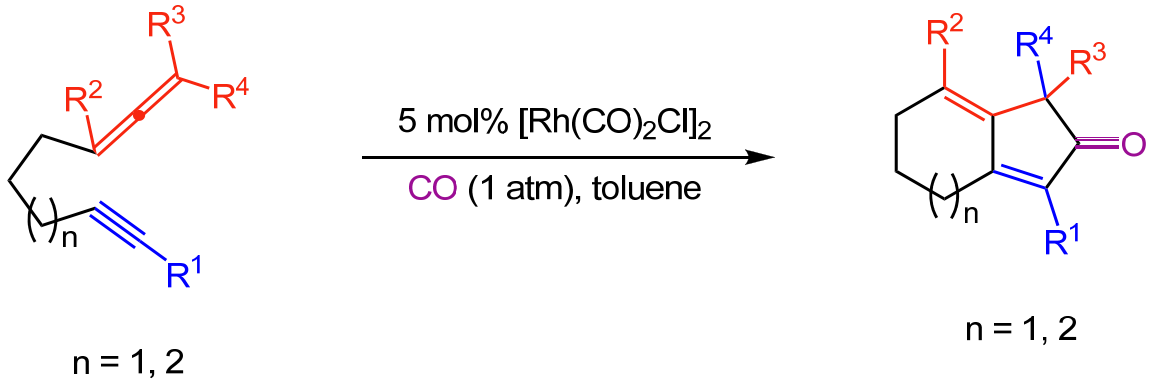
[cyclase phase endpoint]
1.08g synthesized in one sequence

Total Synthesis of (+)-Ingenol

Pauson-Khand Cyclization



Allenic Pauson-Khand-Type Reaction



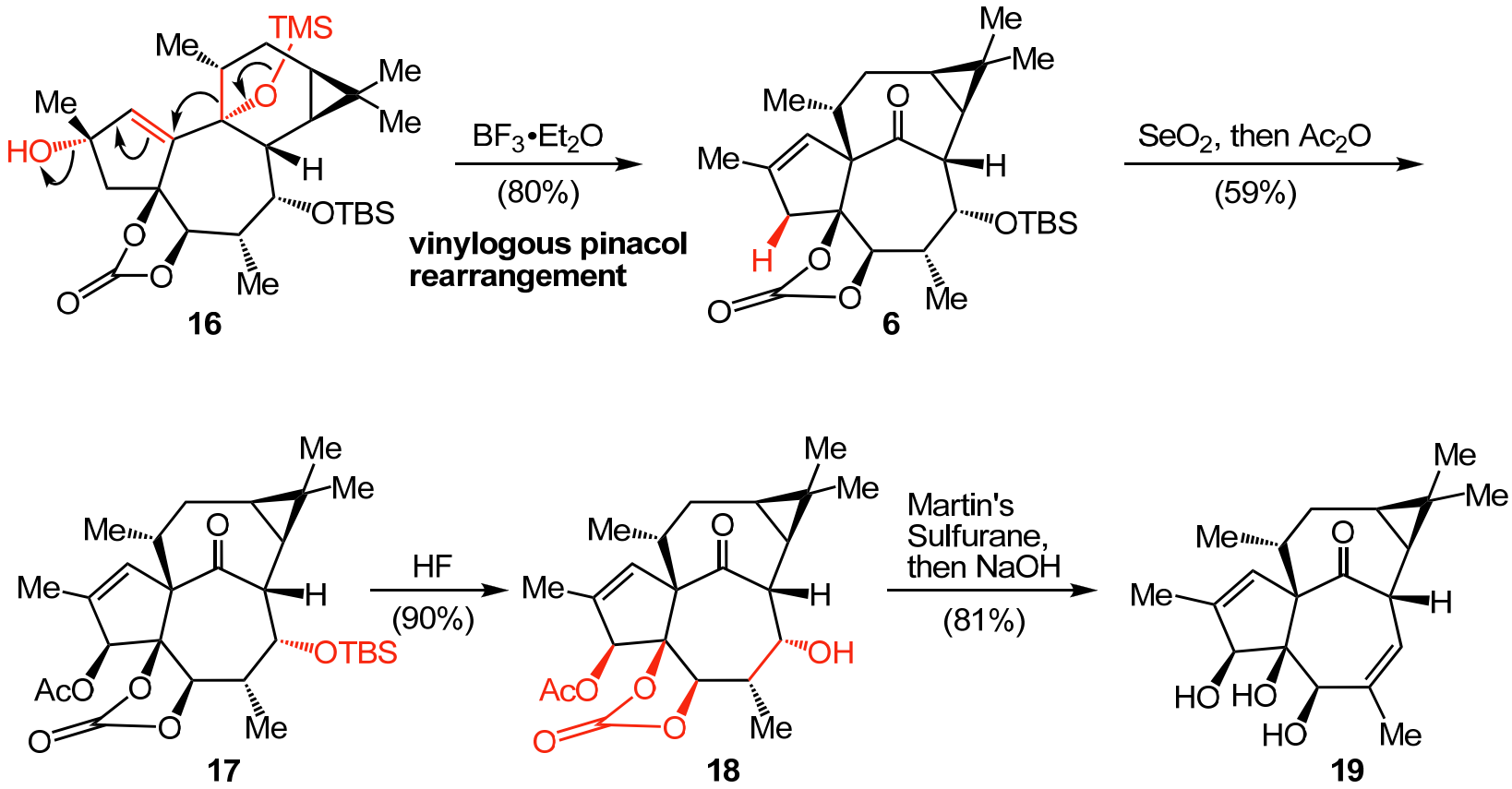
n = 1, 2

n = 1, 2

Brummond, K. M. *et al*. *Org. Lett.* **2002**, *4*, 1931.

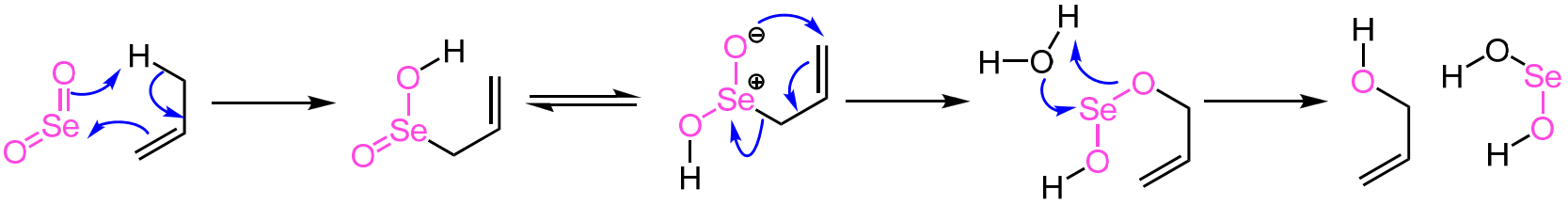
Total Synthesis of (+)-Ingenol

[Oxidase Phase]: 7 steps, 4 C-O bonds, 4 stereocenters, "in-out" stereochemistry

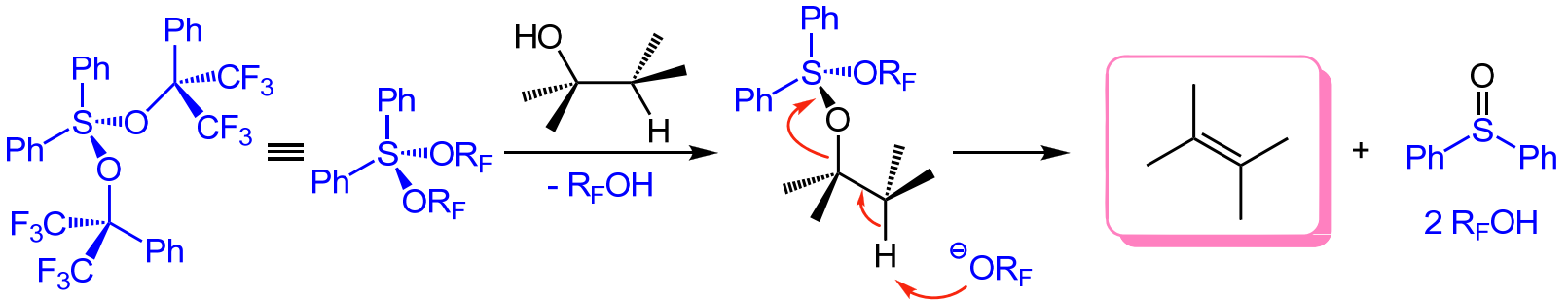


Total Synthesis of (+)-Ingenol

Selenoxide Oxidation

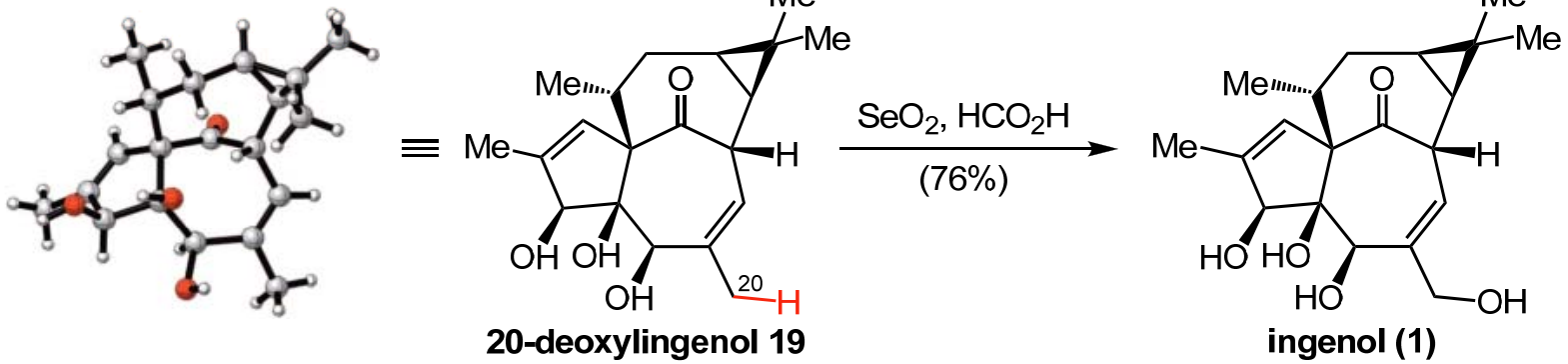


Martin's Sulfurane



Total Synthesis of (+)-Ingenol

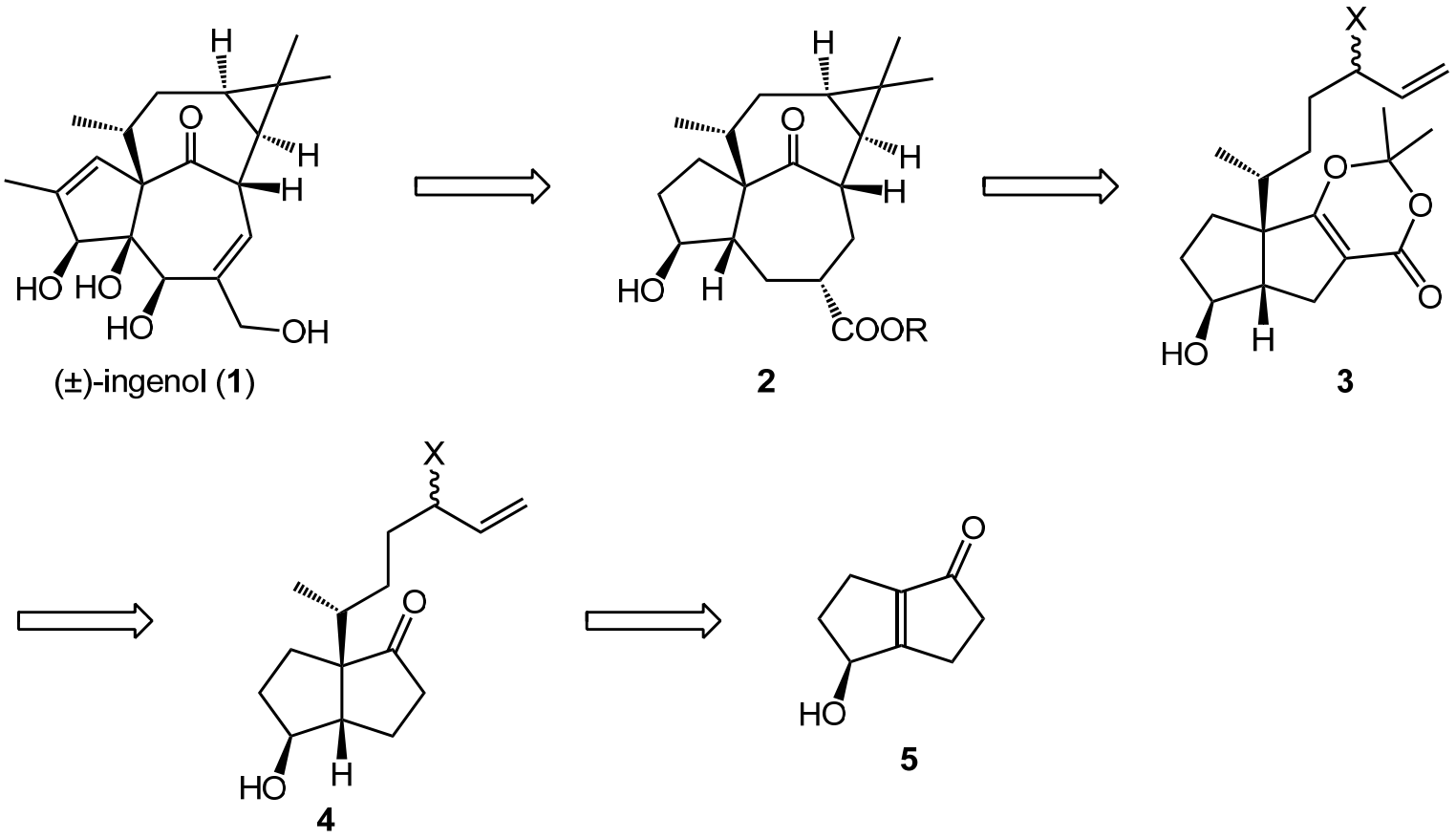
[Oxidase Phase]: 7 steps, 4 C-O bonds, 4 stereocenters, "in-out" stereochemistry



20-deoxylingenol 19 **ingenol (1)**

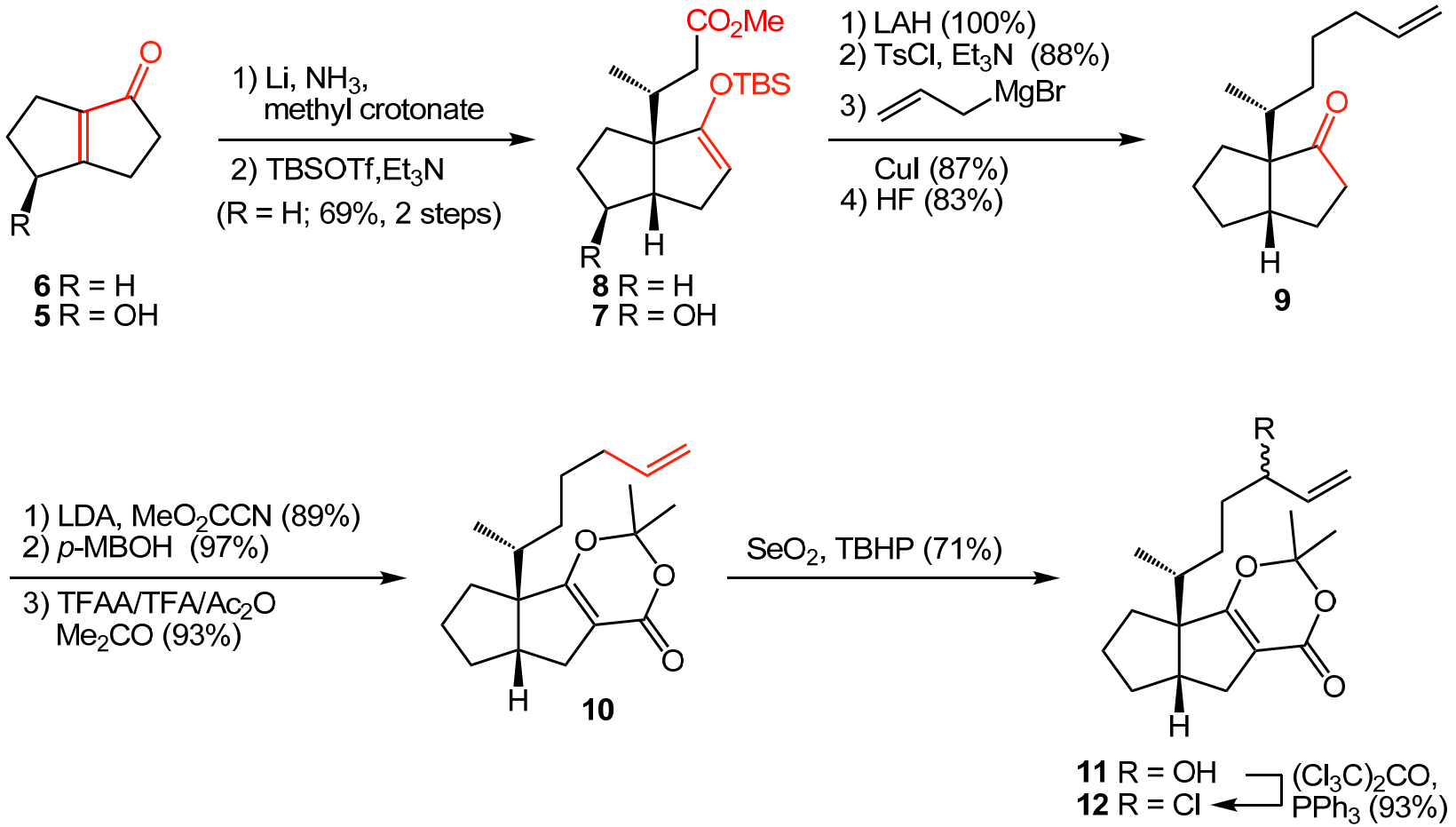
Total Synthesis of (±)-Ingenol

Retrosynthetic Analysis

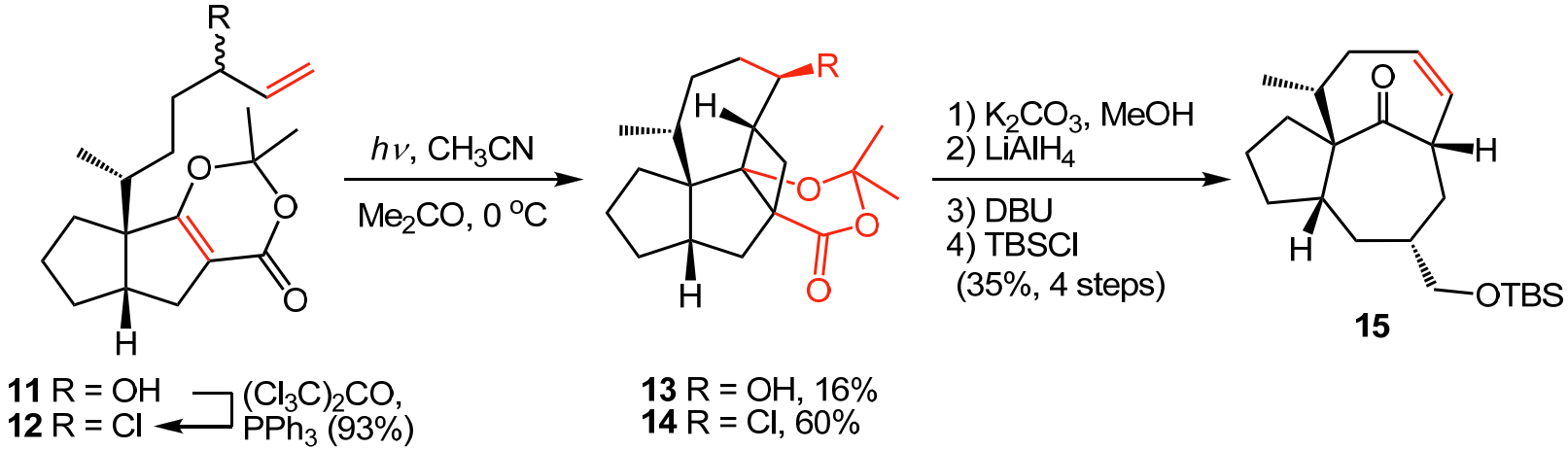


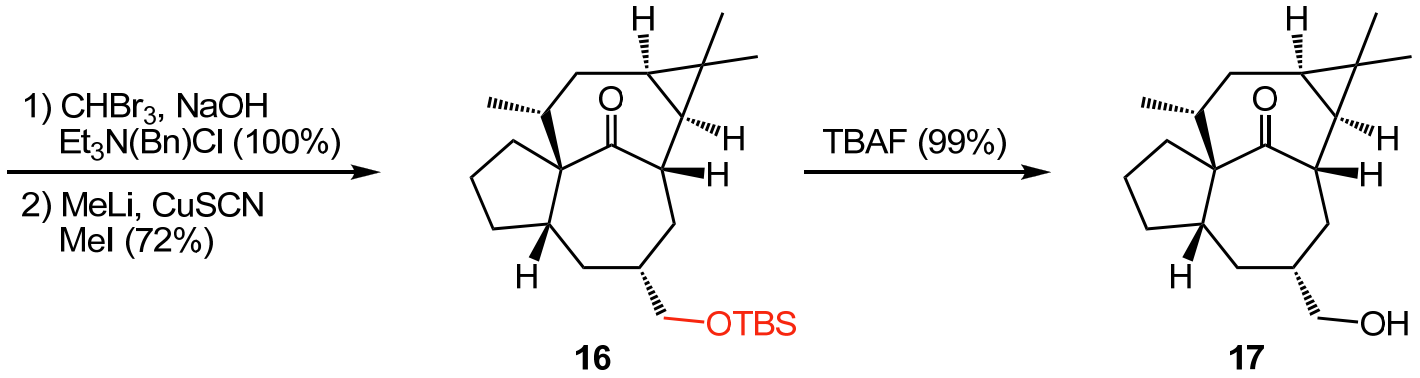
Winkler, J. D. *et al*. *J. Am. Chem. Soc.* **2002**, *124*, 9726.

Total Synthesis of (±)-Ingenol

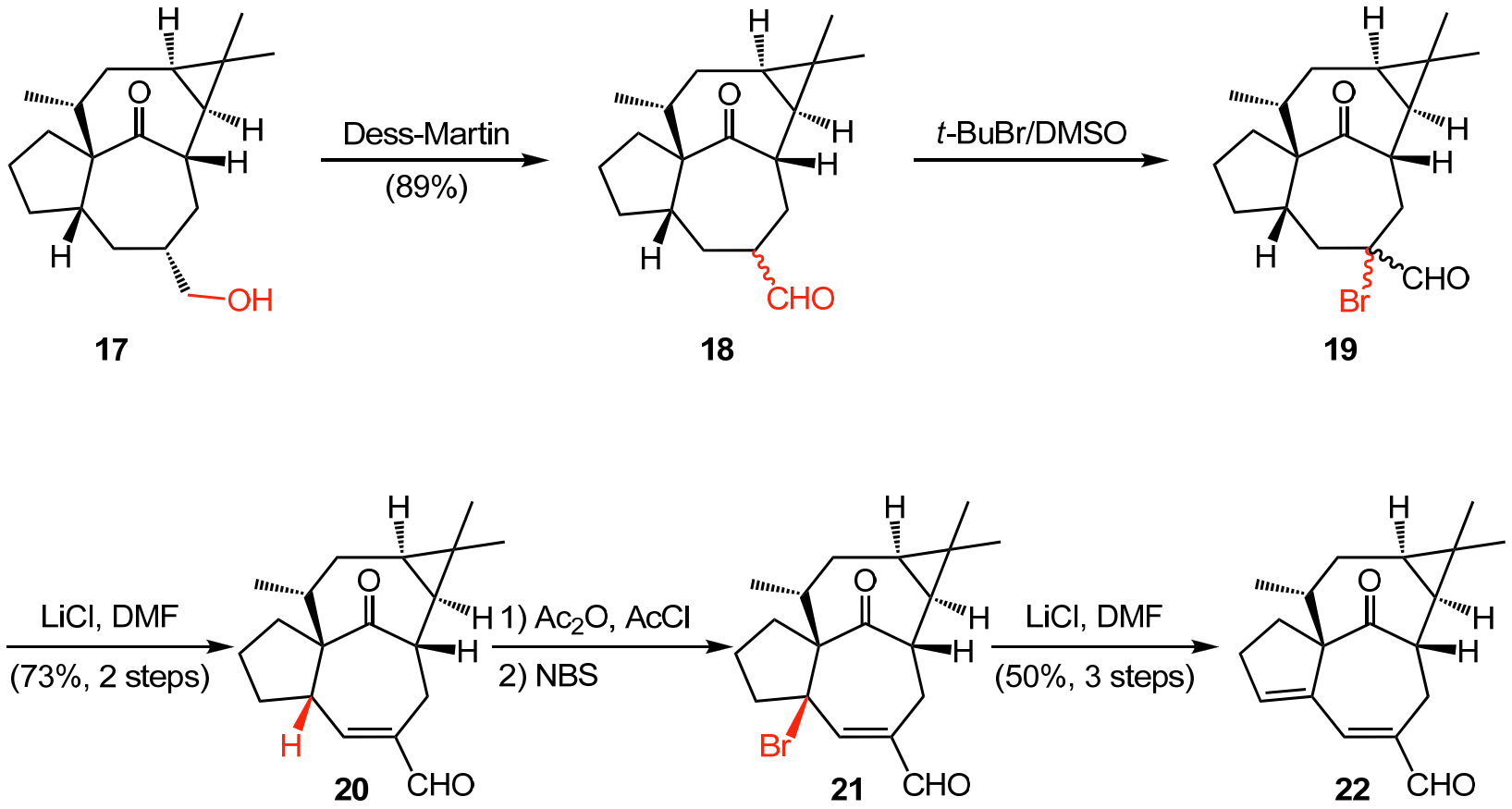


Total Synthesis of (±)-Ingenol





Total Synthesis of (±)-Ingenol



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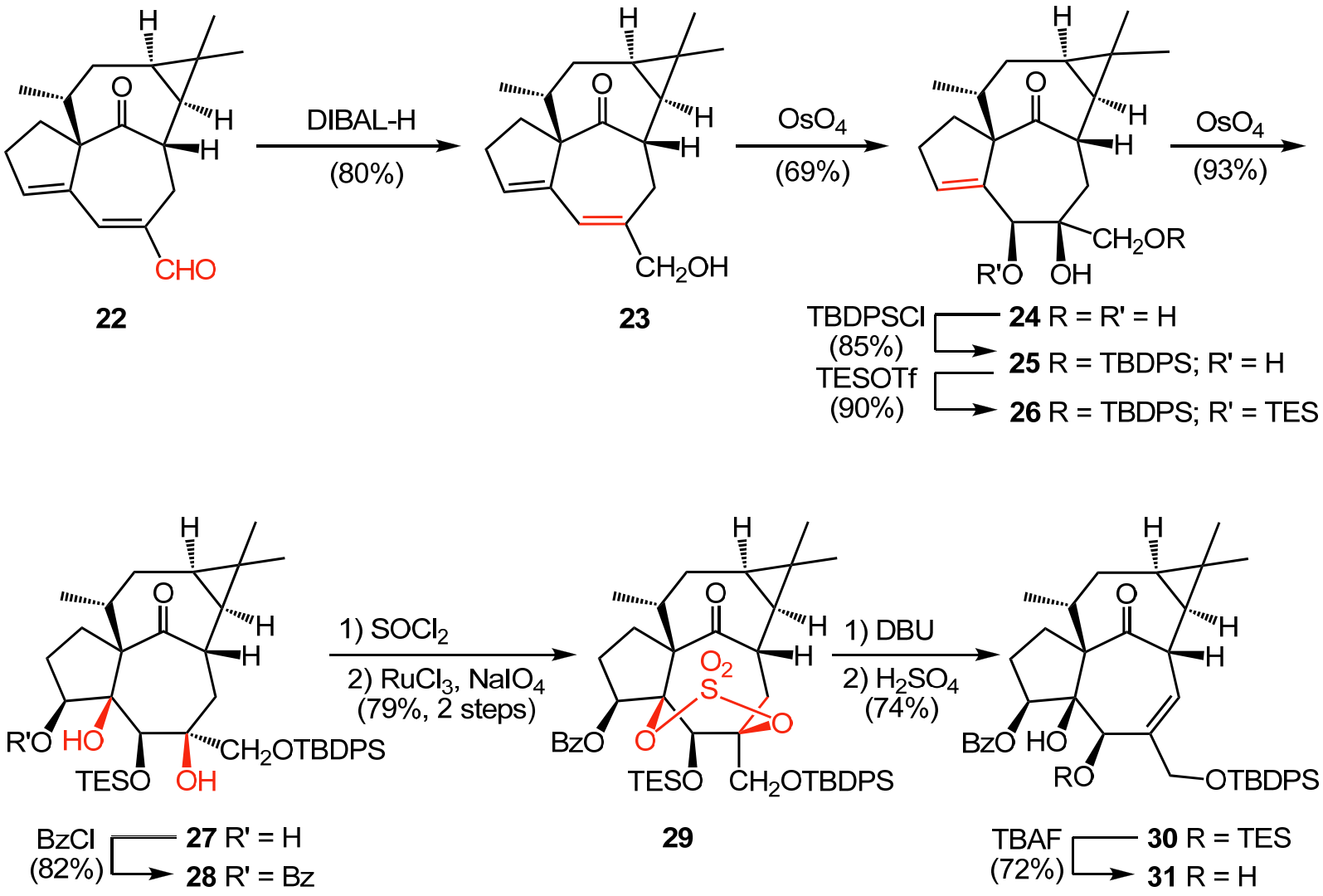
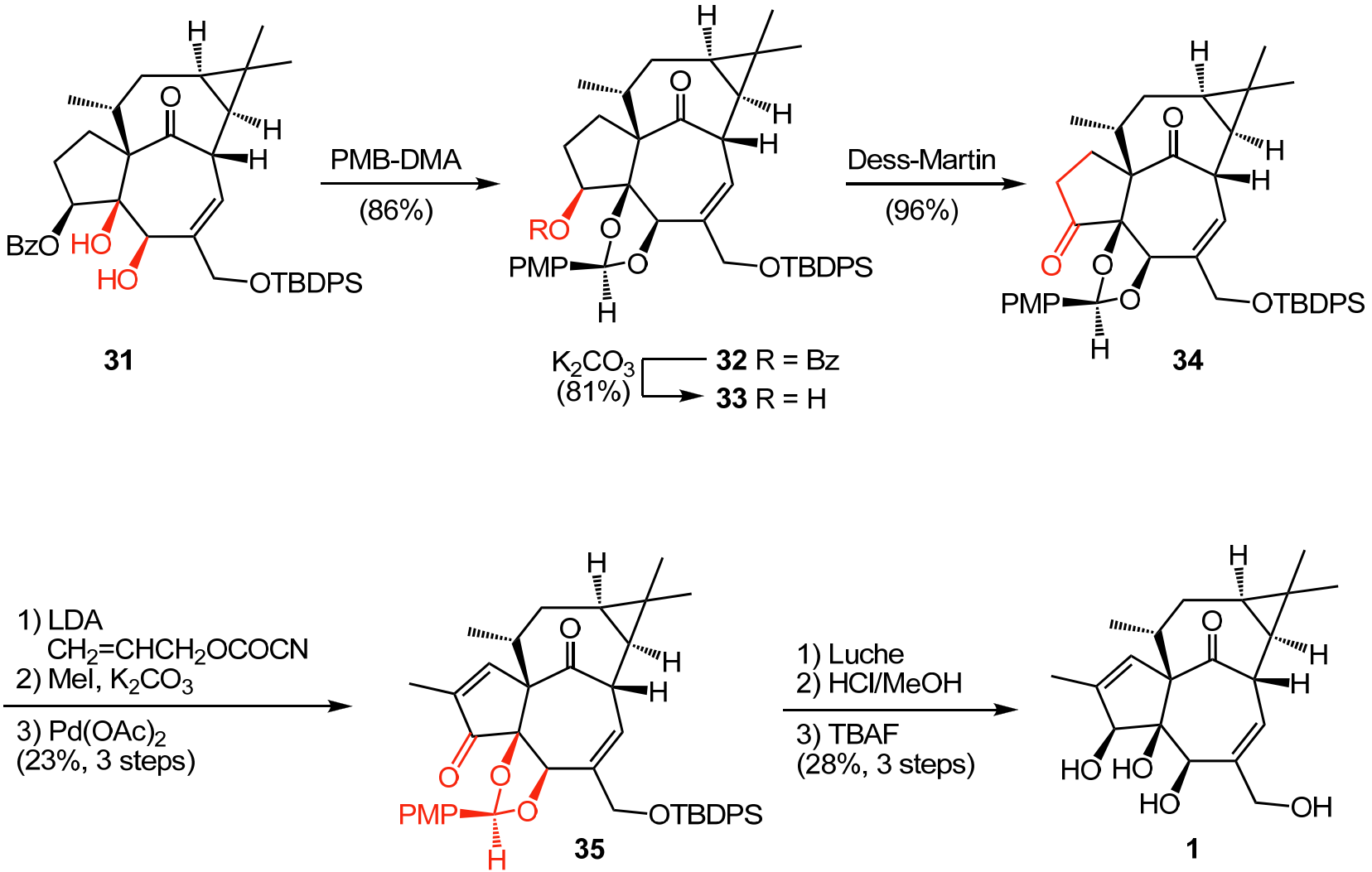
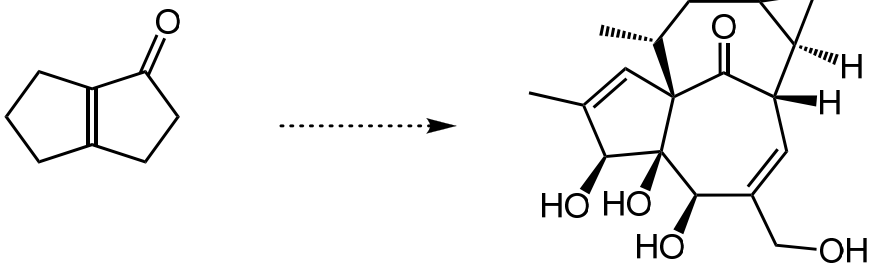


Total Synthesis of (±)-Ingenol



Summary

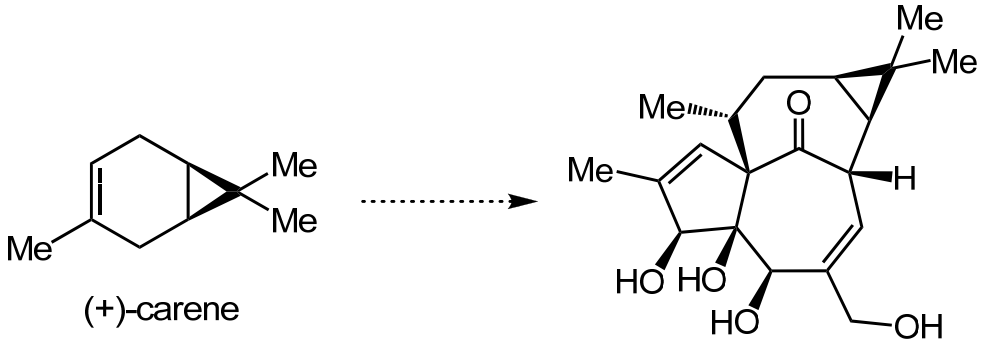
Winkler's Method



(±)-ingenol

- **First total synthesis**
- **43 steps**

Baran's Method



(+)-carene

(+)-ingenol

- **Two phase design**
- **Only 14 steps**
- **1.2% overall yield**

Structurally complex, polyoxygenated terpenoids and their derivatives constitute a medicinally vital class of natural products used in a myriad of different therapeutic areas such as oncology (Taxol, Bristol-Myers Squibb), immunology (prednisone), and infectious diseases (artemisinin). Despite the promise of complex terpenoids as drug molecules, their utility has been hampered by a number of challenges to development. In particular, many plant-derived terpenoid natural products, such as Taxol and artemisinin, suffer from a combination of low isolation yields, inconsistent isolation procedures, and nonrenewable natural sources. In the case of Taxol, plant cell culture technology over-came low-yielding isolation, whereas in the case of artemisinin, collaborations between scientists in genetic engineering and chemical synthesis hold promise for providing a consistent supply.

These seminal works in the biological production of natural products have led to a widely held presumption that bioengineering is superior to organic synthesis in the production of all complex terpenoids. Further, it has even been claimed that metabolic engineering is favored in the production of “natural products, particularly active pharmaceutical ingredients (APIs), some of which are too complex to be chemically synthesized” in a meaningful way. We repudiate these claims and present a case study in which chemical synthesis provides an approach to a structurally complex and medicinally relevant terpenoid that is both amenable to analog synthesis and concise enough to finally make chemical production possible.

The synthesis of ingenol (**1**) presented herein illustrates the power of two-phase logic to deliver an efficient, concise synthesis even in architecturally complex settings. The usefulness of the two-phase approach will undoubtedly continue to expand as new methods for C–C bond formation and C–H oxidation are developed. Furthermore, this report provides a strong rebuttal to the presumption that chemical synthesis is illequipped to deal with the preparation of structurally complex terpenoid drug molecules. Rather, in this instance, total chemical synthesis holds promise as the best method to both prepare ingenol mebutate (**2**) and enable the development of therapeutic analogs with broader utility in the treatment of human diseases.