

Literature Report II

Enantioselective Total Synthesis of (+)-Peniciketals A and B: Two Architecturally Complex Spiroketals

Reporter: Kun Wang

Checker: Yu-Qing Bai

Date: 2021-07-05

Smith, A. B., III. *et al.* *J. Am. Chem. Soc.* **2021**, *143*, 1740

CV of Prof. Amos B. Smith III



Research:

1. Natural product synthesis
2. Bioorganic chemistry
3. Materials science

Background:

- ❑ **1966** B.S. & M.S., Bucknell University
- ❑ **1972** Ph.D., Rockefeller University
- ❑ **1972-1973** Associate, Rockefeller University
- ❑ **1973-1978** Assistant Professor, University of Pennsylvania
- ❑ **1978-1981** Associate professor, University of Pennsylvania
- ❑ **1981-now** Professor, University of Pennsylvania

Contents

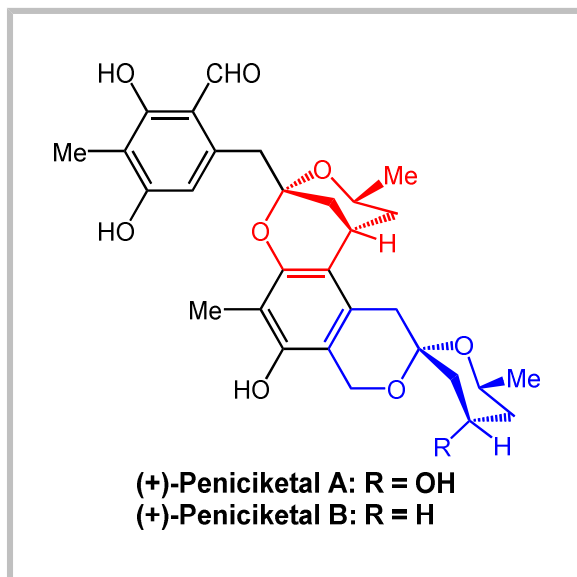
1 Introduction

2 Total Synthesis of (+)-Peniciketal A

3 Total Synthesis of (+)-Peniciketal B

4 Summary

Introduction

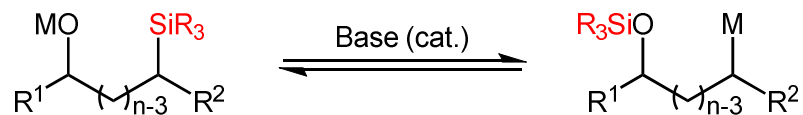


Penicillium raistrickii

- They comprise one phenyl ring fused not only to a [6,6]-spiroketal but also to a 2,8-dioxabicyclo[3.3.1]nonane moiety;
- (+)-Peniciketal A can reduce cell proliferation in three leukemia cell lines and have high selectivity for cancer cells with lower toxicity toward normal cells (L02, MRC5, and MEFs).

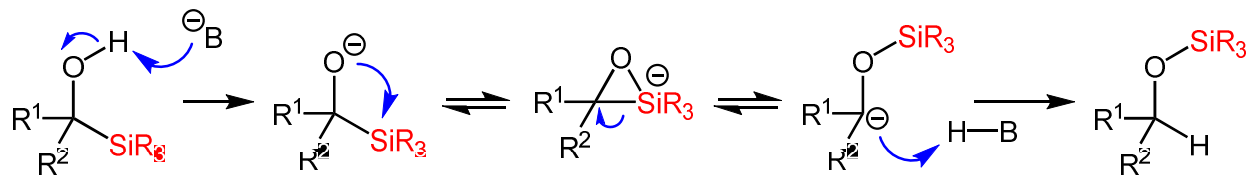
Liu, W.-Z.; Liu, D.-S.; Huang, Y.-L.; Wang, C.-H.; Shi, S.-S.; Zhu, R.-X. *Org. Lett.* **2014**, *16*, 90

Brook Rearrangement

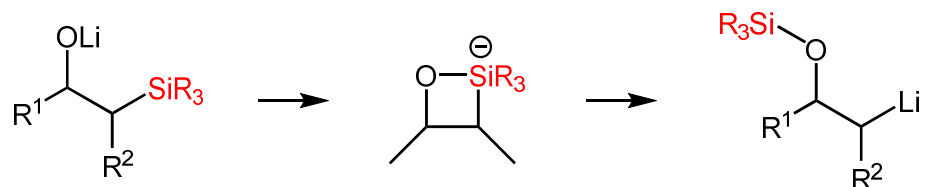


R^{1-2} = alkyl, aryl; SiR_3 = $SiMe_3$, $SiEt_3$, $SiMe_2^tBu$, etc.; $n = 2-6$

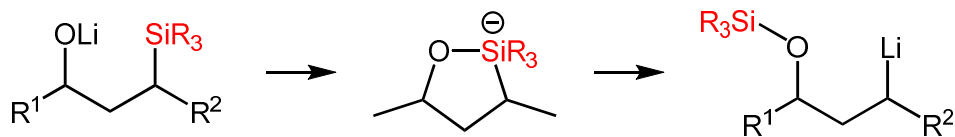
[1,2]-Brook Rearrangement



[1,3]-Brook Rearrangement



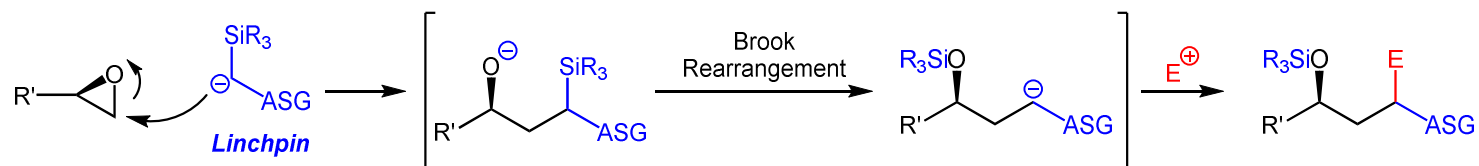
[1,4]-Brook Rearrangement



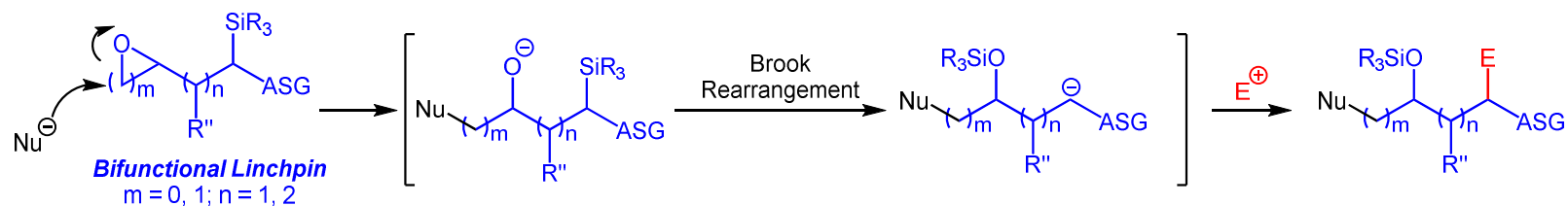
From Name Reaction by Jie Jack Li P79

Anion Relay Chemistry (ARC)

Type I Anion Relay Chemistry



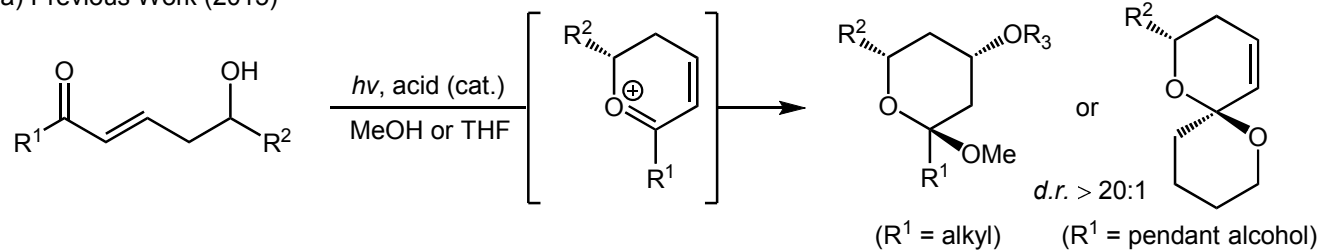
Type II Anion Relay Chemistry



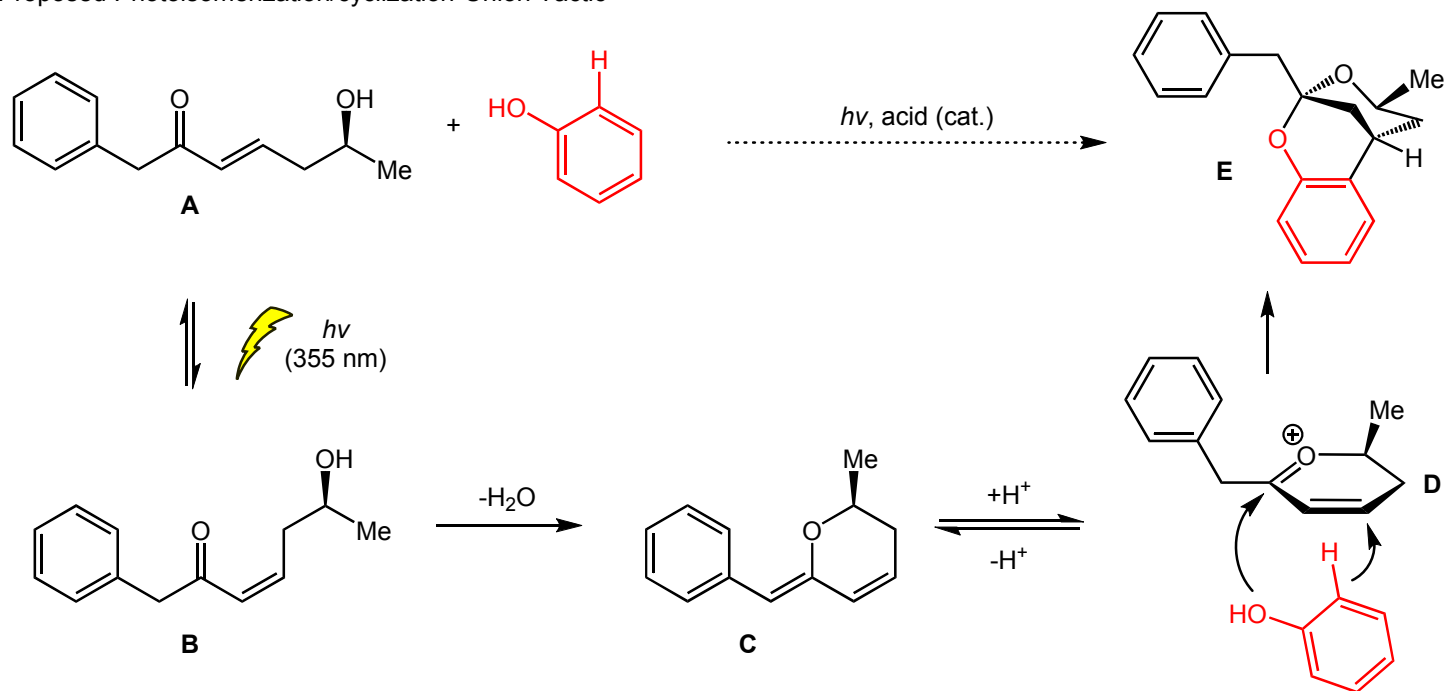
Deng, Y.; Smith, A. B., III. *Acc. Chem. Res.* **2020**, *53*, 988

Photoisomerization/Cyclization Union

a) Previous Work (2015)

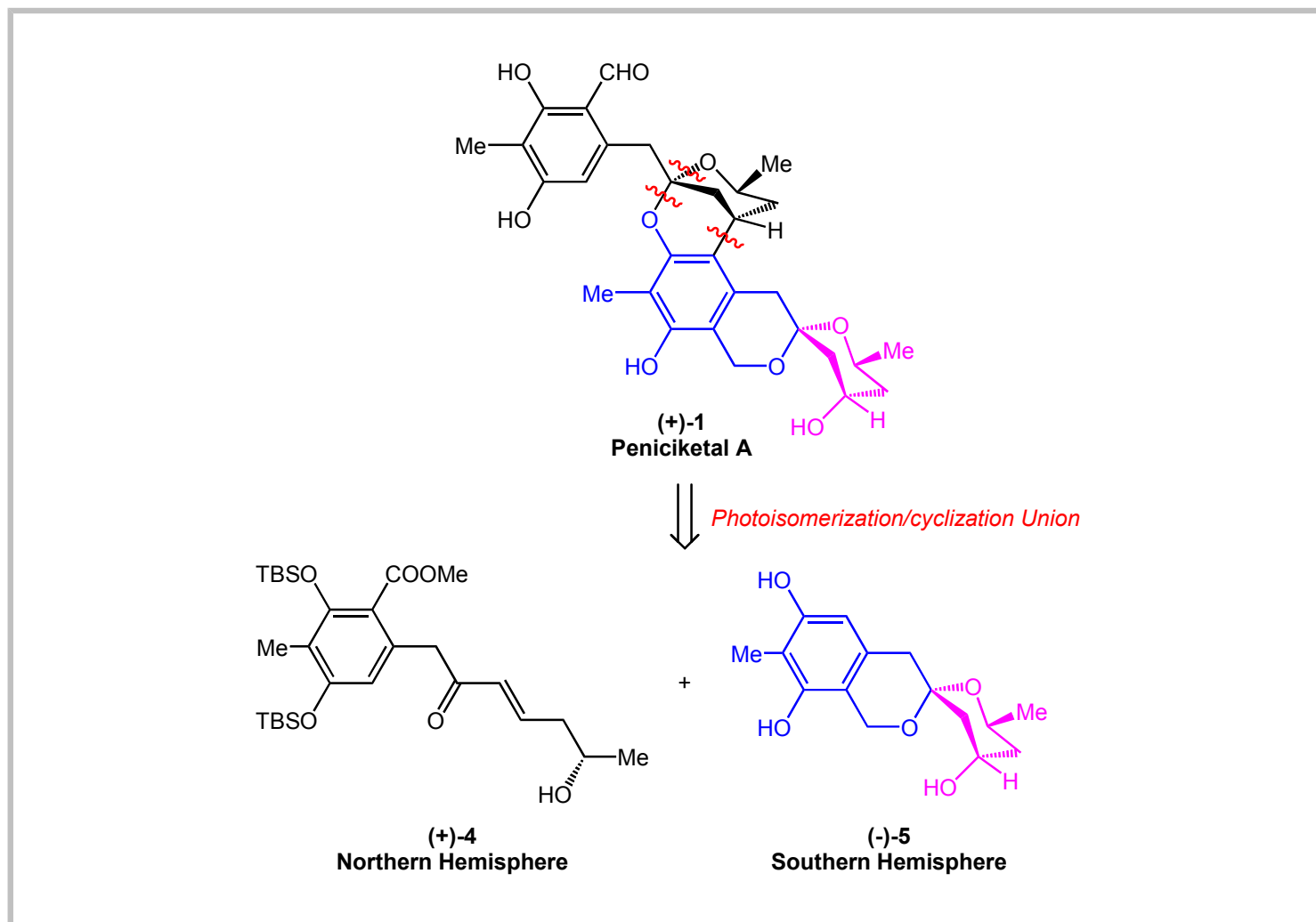


b) Proposed Photoisomerization/cyclization Union Tactic

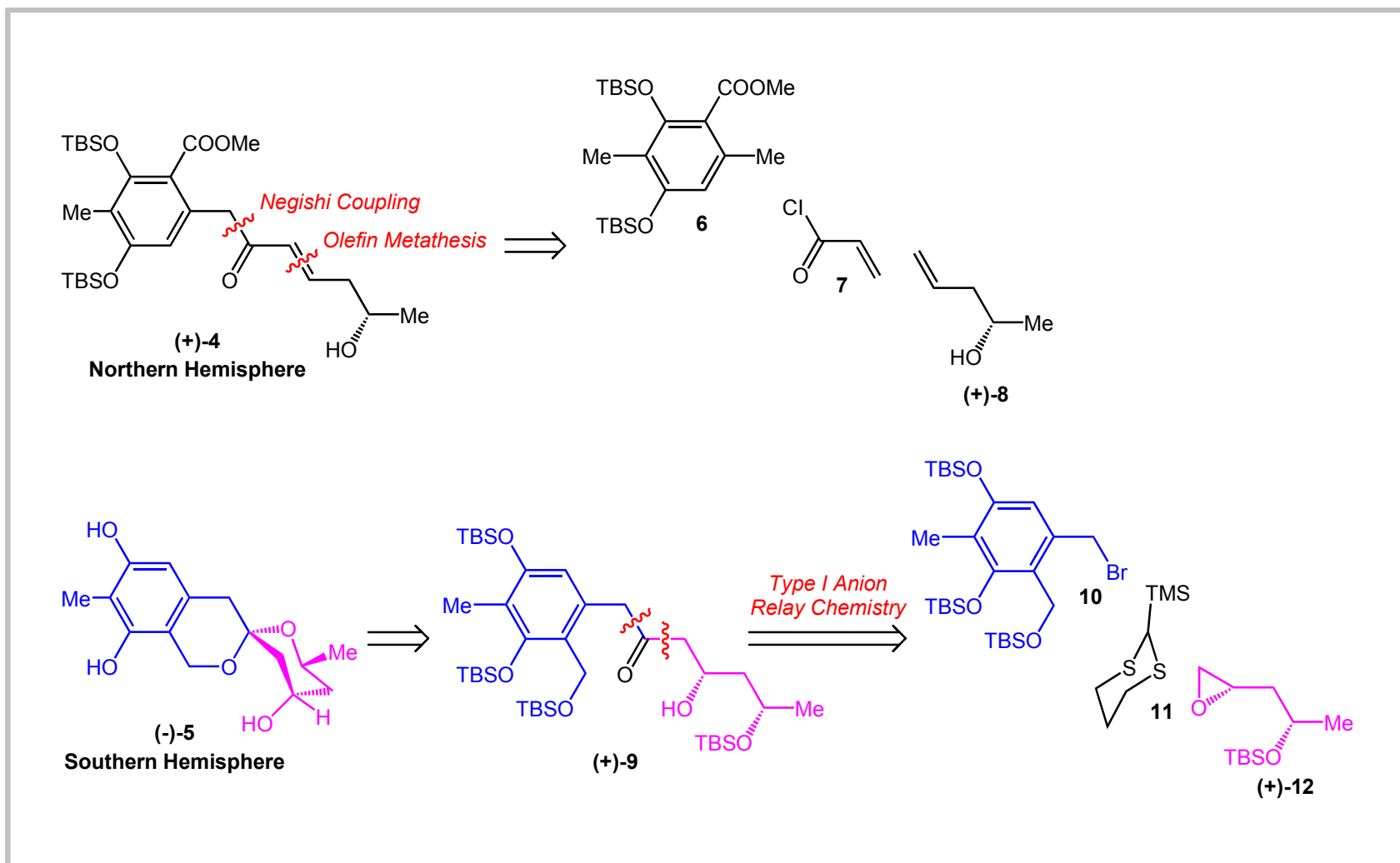


Li, B.; Williams, B. D.; Smith, A. B., III. *Org. Lett.* **2015**, *17*, 3

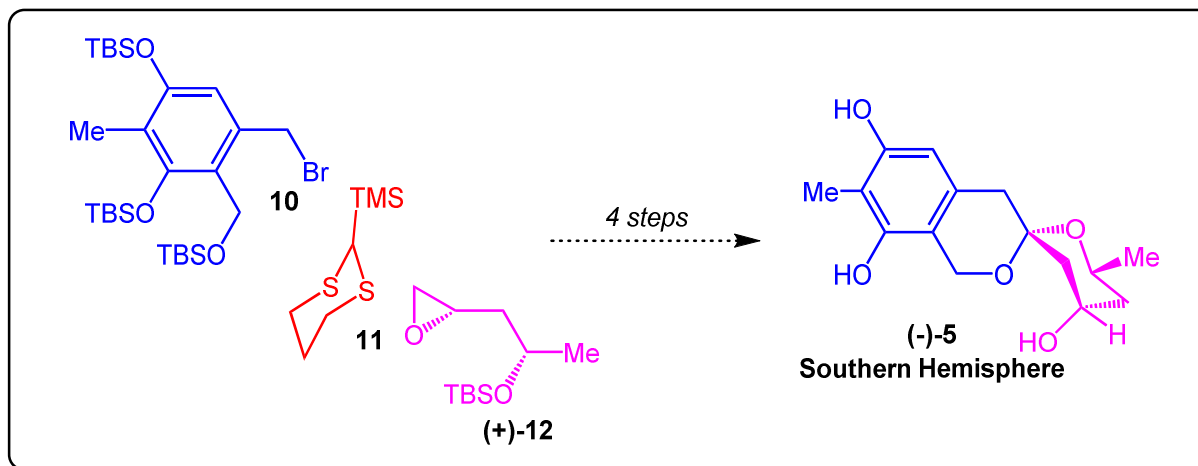
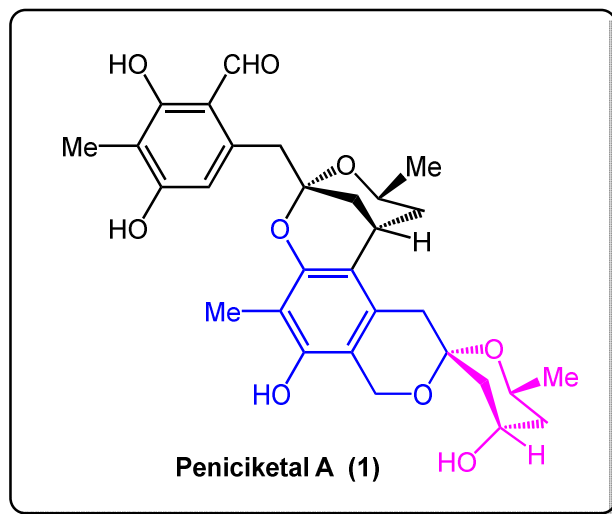
Retrosynthetic Analysis



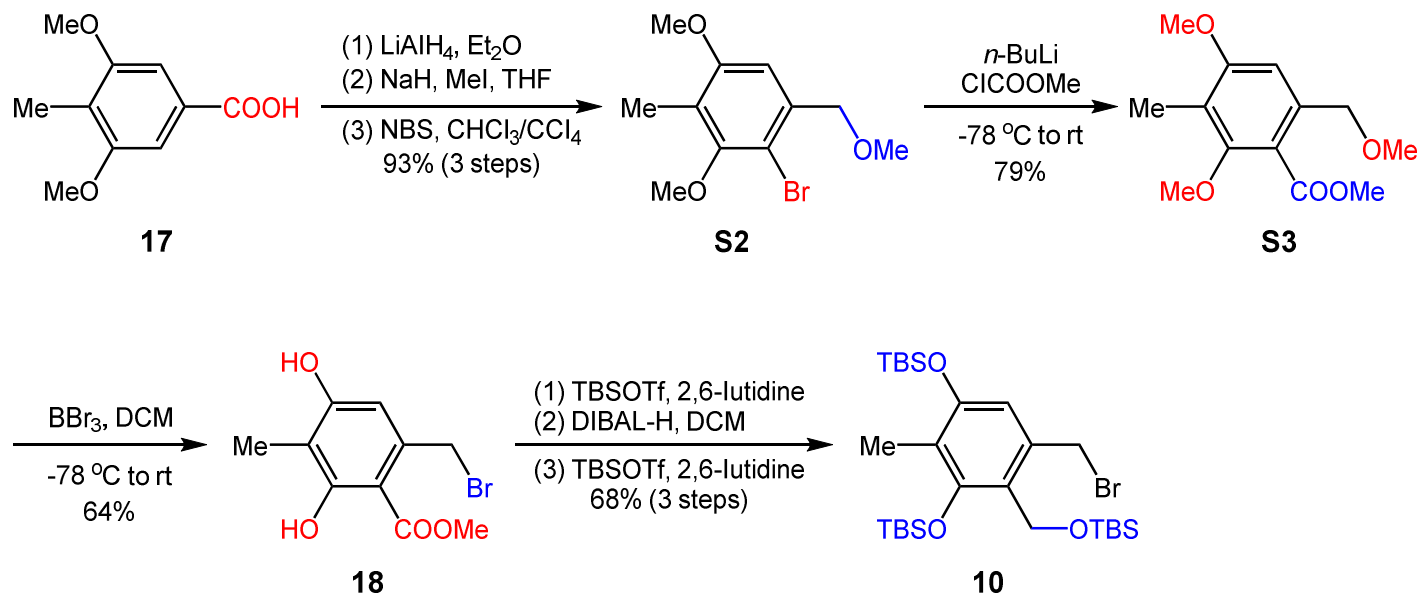
Retrosynthetic Analysis



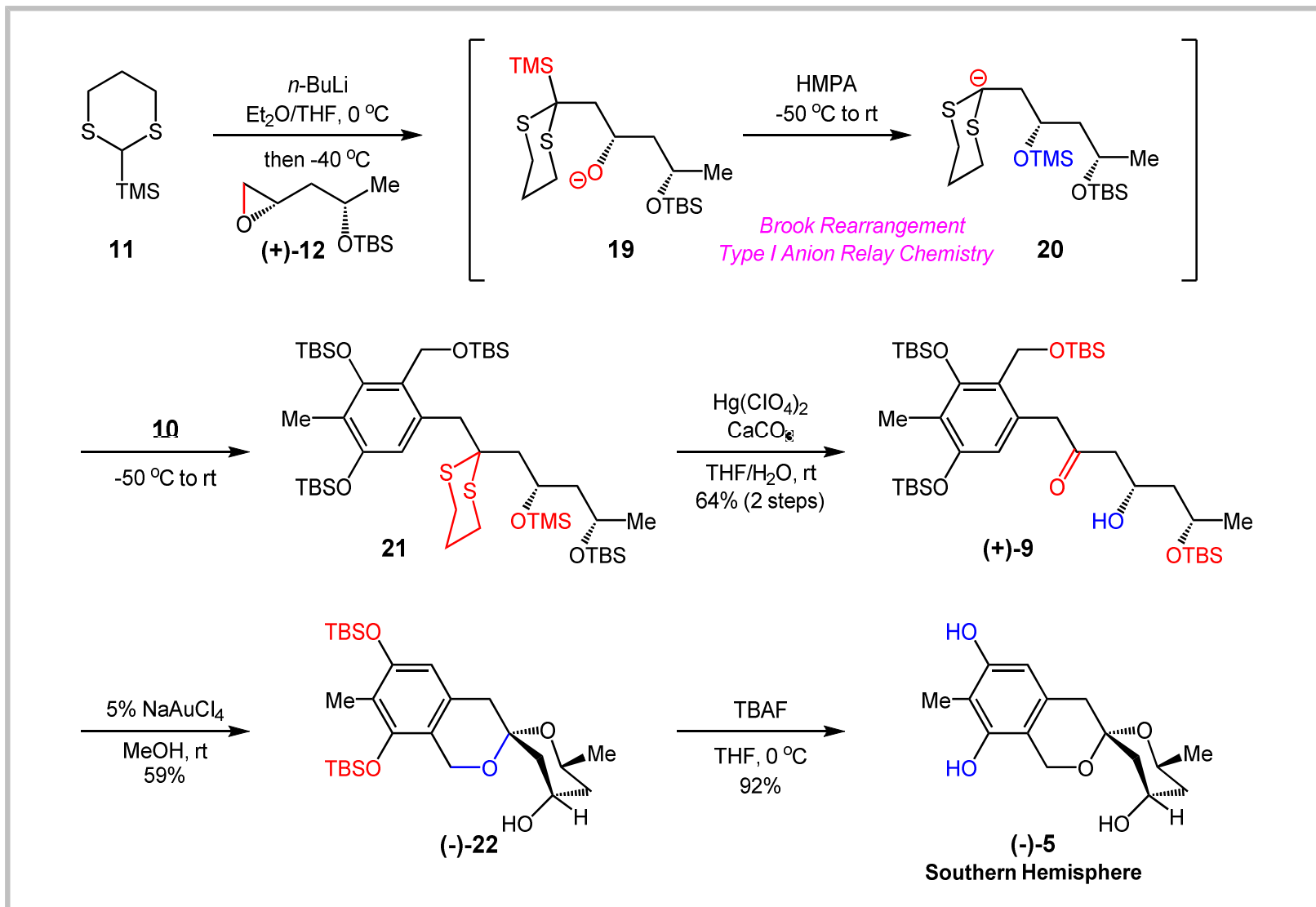
Stage 1: Synthesis of Southern Hemisphere



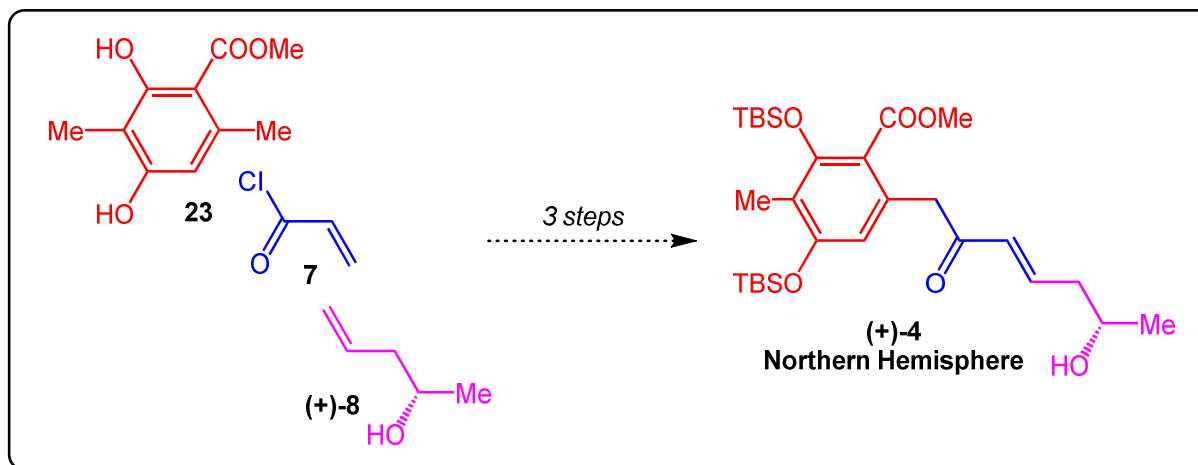
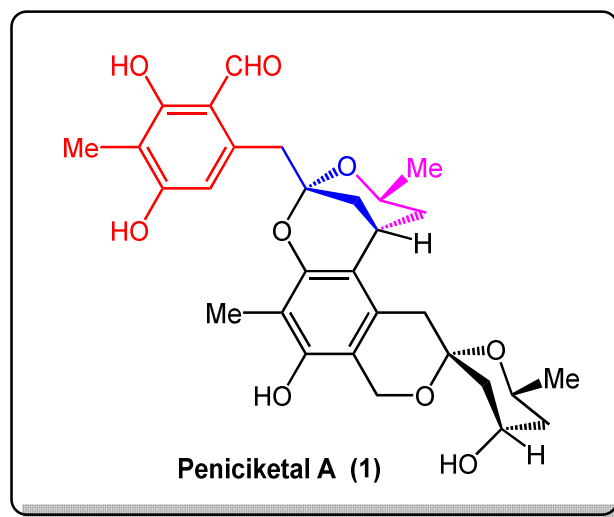
Stage 1: Synthesis of 10



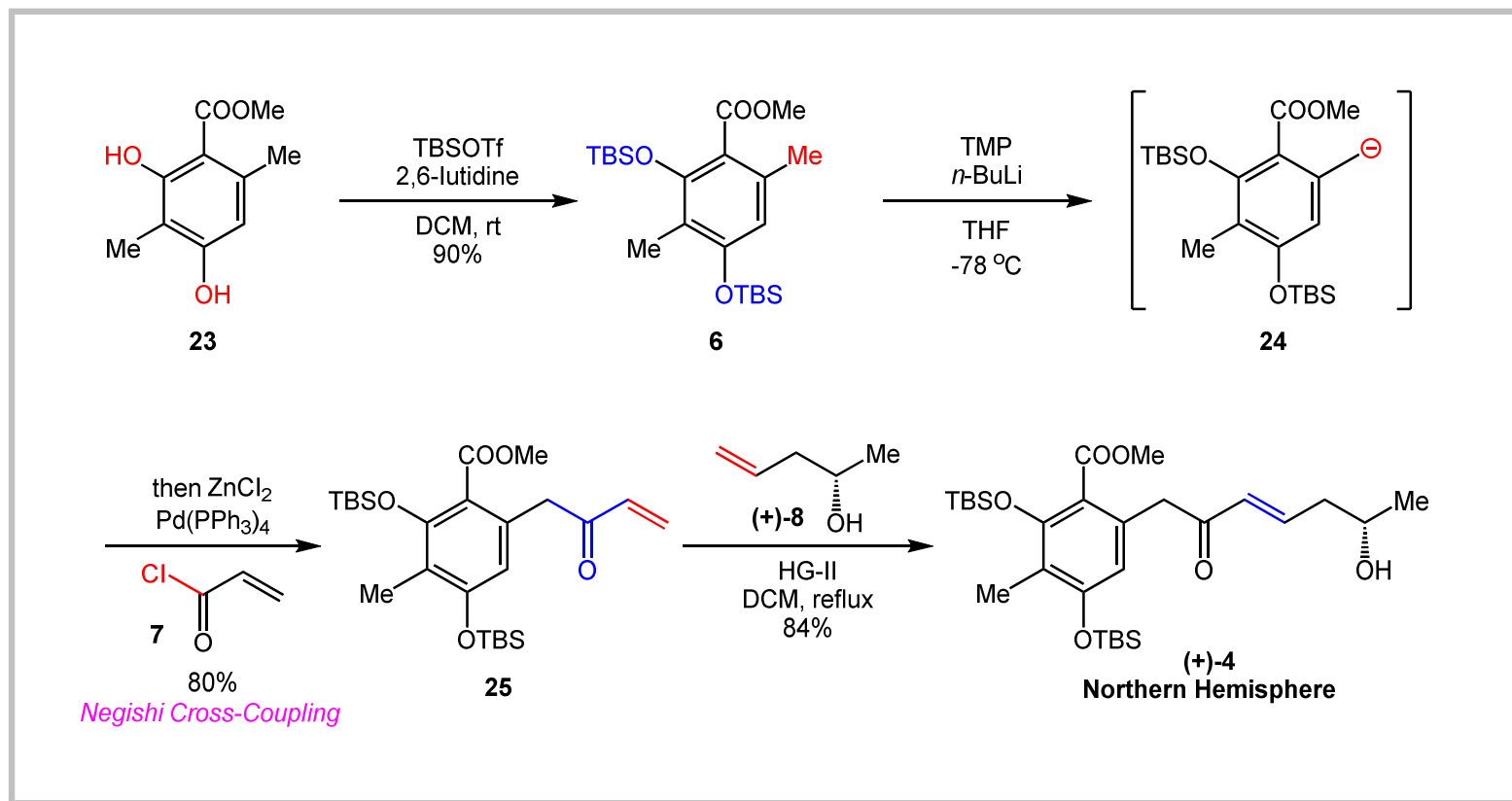
Stage 1: Synthesis of Southern Hemisphere



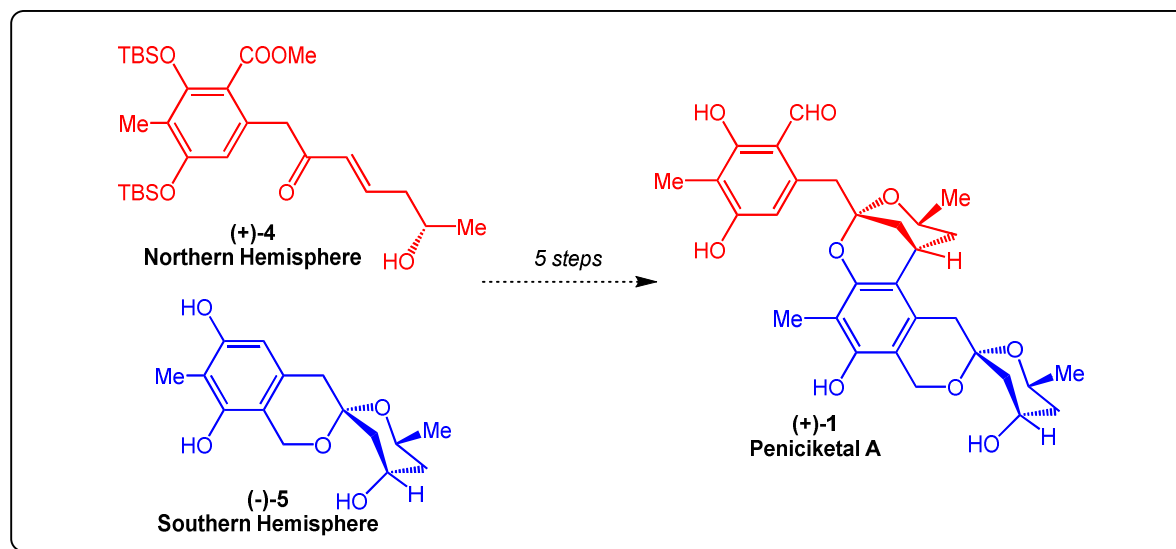
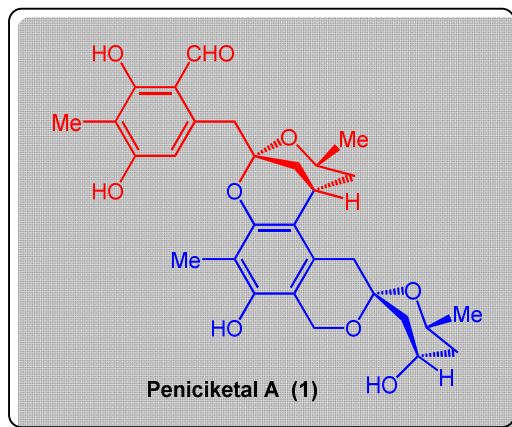
Stage 2: Synthesis of Northern Hemisphere



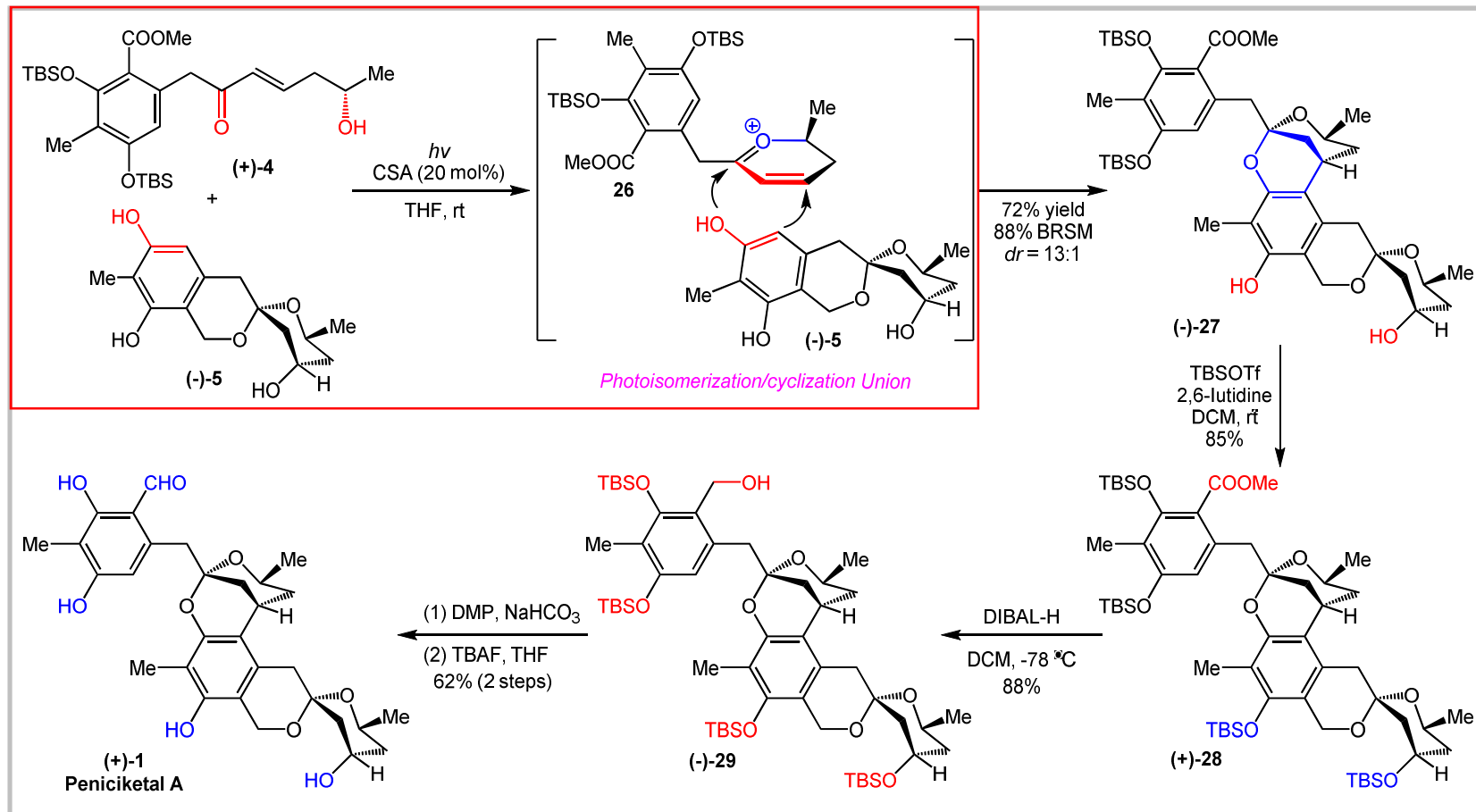
Stage 2: Synthesis of Northern Hemisphere



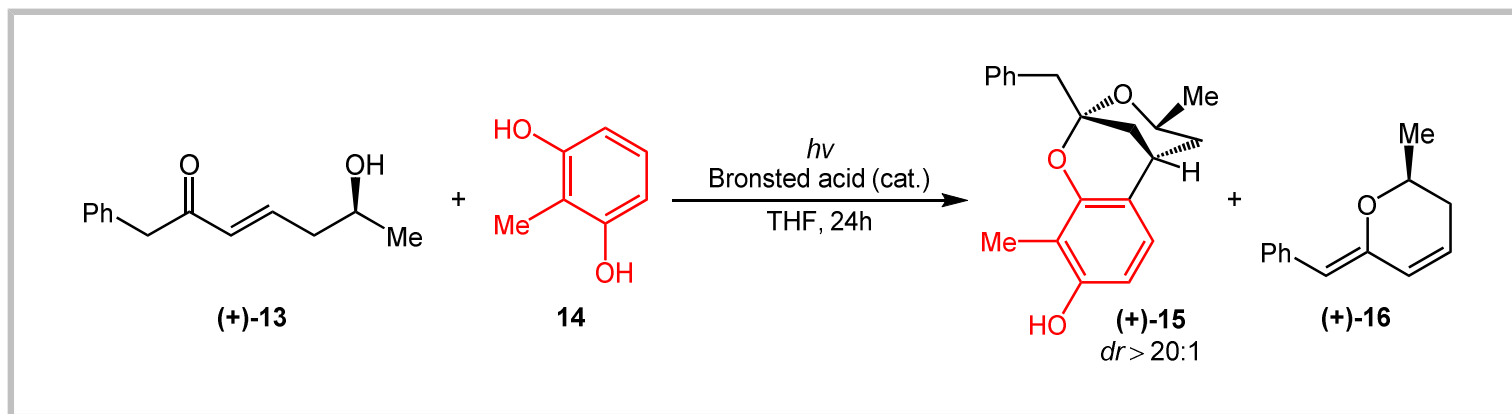
Stage 3: Synthesis of (+)-Peniciketal A



Stage 3: Synthesis of (+)-Peniciketal A



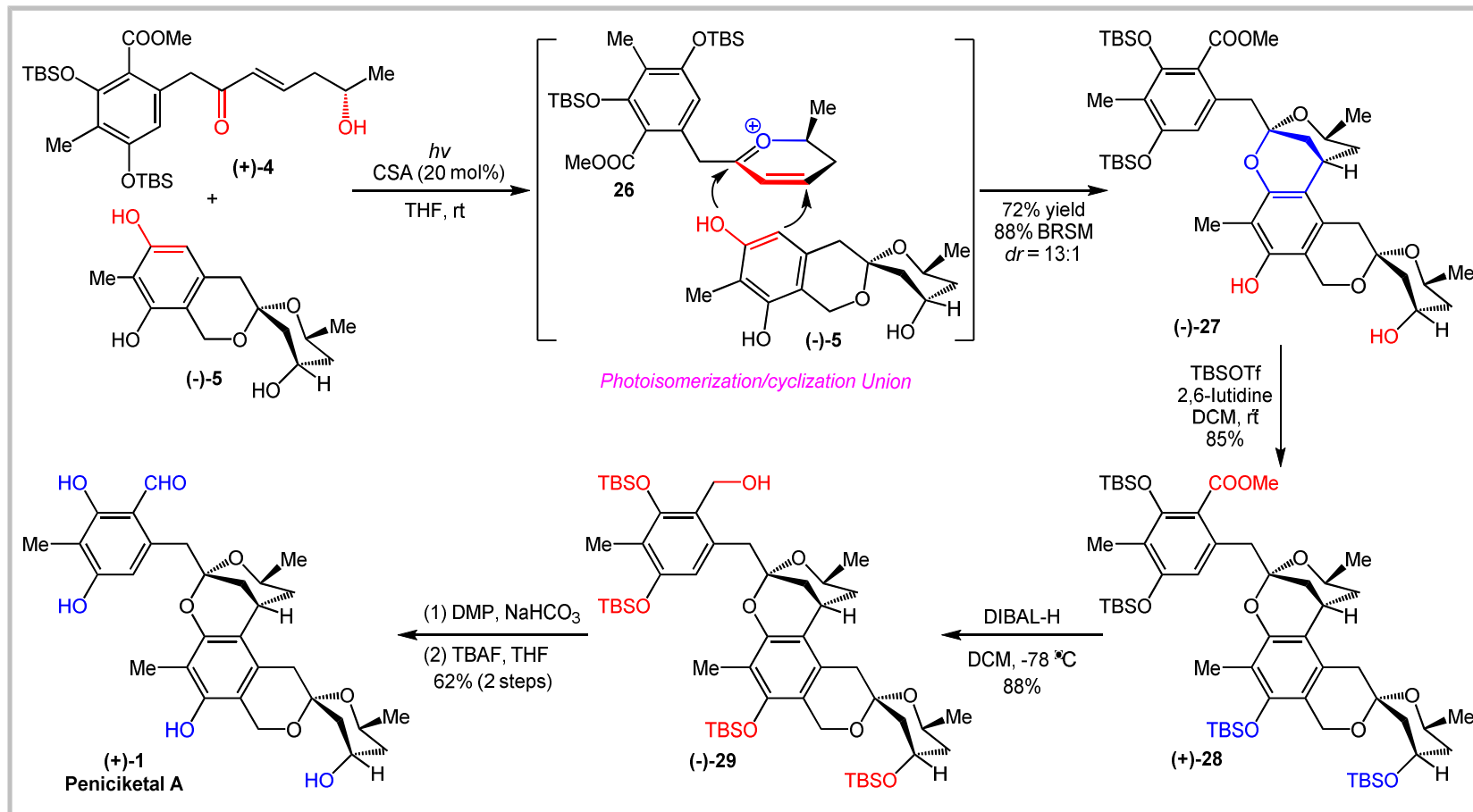
Model Studies of the Photochemical Protocol



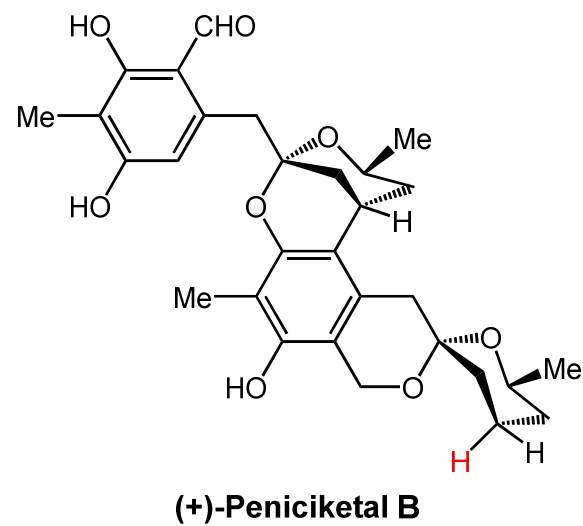
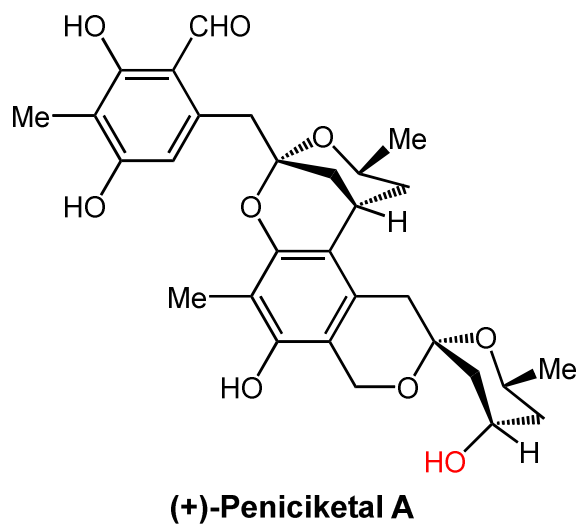
Entry	Bronsted acid	Concentration (M)	Yield ^a (%) of 15
1	PTSA (20 mol%)	0.1	45
2	PTSA (20 mol%)	0.2	71
3	CSA (20 mol%)	0.2	80
4	PPTS (50 mol%)	0.2	49
5 ^b	CSA (20 mol%)	0.2	NR

^aReaction conditions: (+)-**13** (0.2 mmol), **14** (0.2 mmol), Bronsted acid (cat.), in THF, rt, UV-A light ($\lambda = 355$ nm), 24 h. The isolated yields of products (+)-**15** were obtained by flash chromatography. The dr was measured by ¹H NMR. ^bNo light. NR = no reaction, and both starting materials remained.

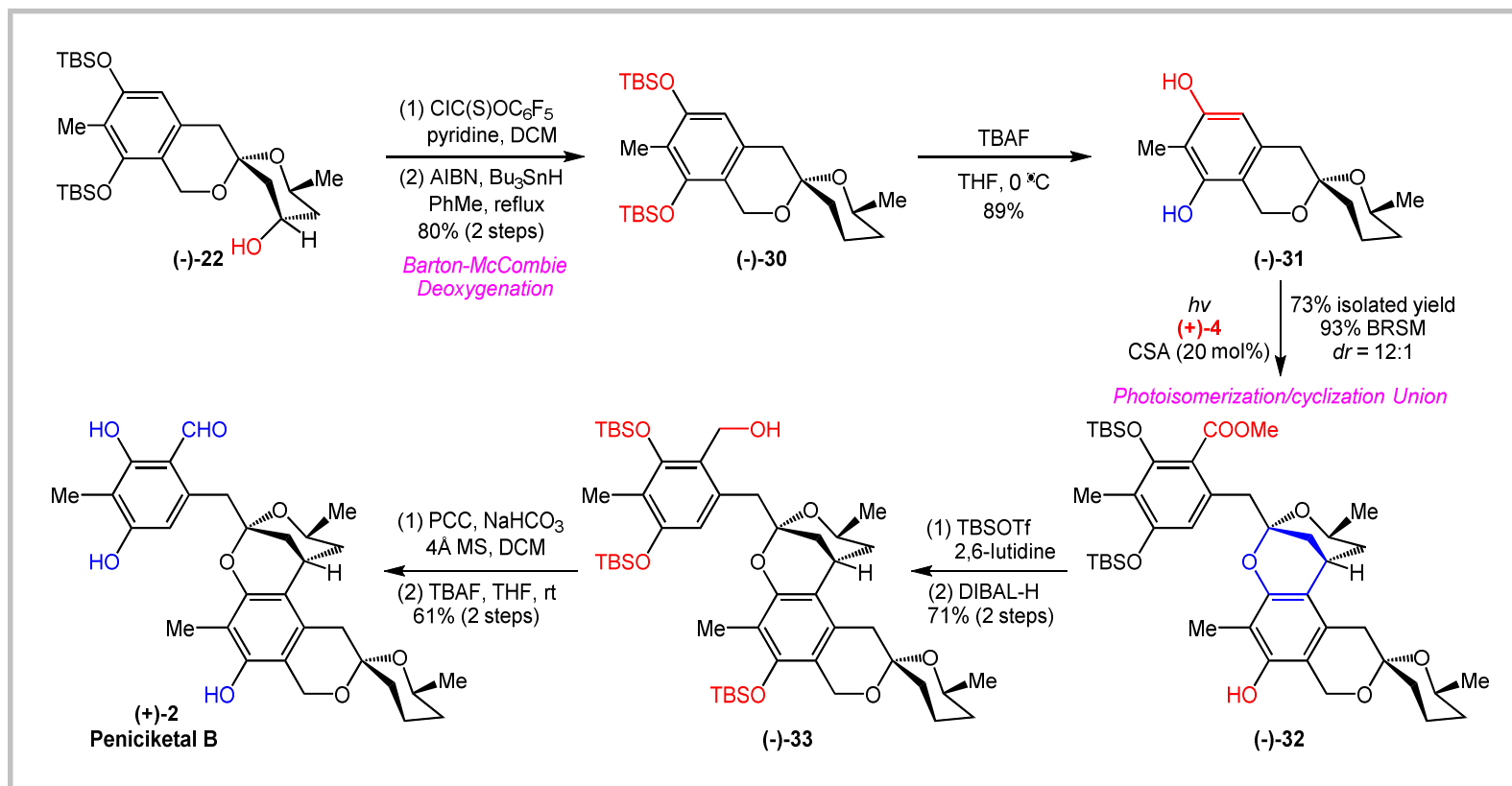
Stage 3: Synthesis of (+)-Peniciketal A



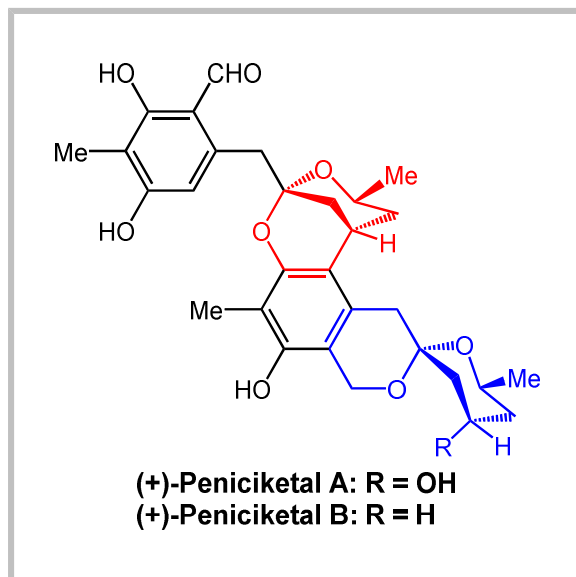
Synthesis of (+)-Peniciketal B



Synthesis of (+)-Peniciketal B



Summary



- 17 steps, 3.7% overall yield (**Peniciketal A**);
- 19 steps, 2.8% overall yield (**Peniciketal B**);
- Three-component Type I Anion Relay Chemistry tactic;
- Photoisomerization/cyclization union protocol.

Deng, Y.; Yang, C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2021**, *143*, 1740

The First Paragraph

写作思路

介绍Peniciketals生物碱
被发现的历史



介绍Peniciketal A的
生物活性

The First Paragraph

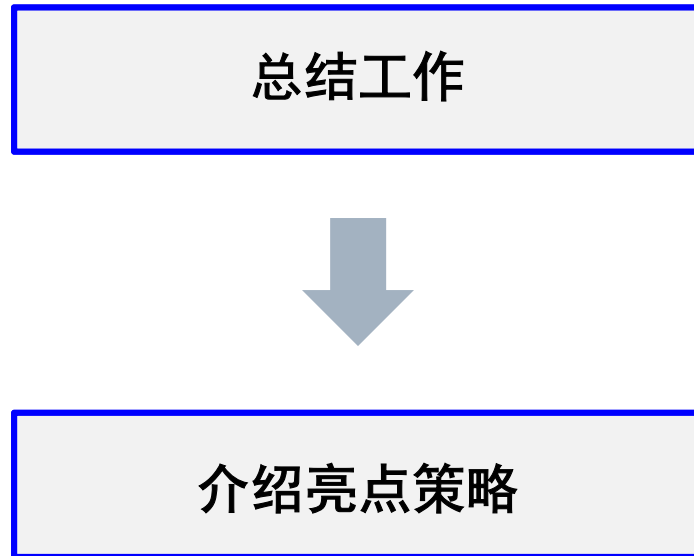
The peniciketals A–C, architecturally complex spiroketals, isolated in 2014 from the fungus *Penicillium raistrickii* found in saline soil samples isolated from Bohai Bay (China), display cytotoxicity against HL-60 cells with IC_{50} values of 3.2, 6.7, and 4.5 μM , respectively. Peniciketal A, in particular, proved to be cytotoxic, with time-dependent inhibition/proliferation of the human non-small lung cancer cell line A549 ($IC_{50} = 22.33 \mu\text{M}$ in 72 h) as well as inhibition of both migration and invasion of A549 cells by reducing the levels of the MMP-2 and MMP-9 protein.

The First Paragraph

More recently, peniciketal A was also revealed to reduce cell proliferation in three leukemia cell lines and had high selectivity for cancer cells with lower toxicity toward normal cells (L02, MRC5, and MEFs). This high level of antitumor activity recently led to more mechanistic studies including a global proteomic profile of peniciketal A, which suggests that this natural product may possess additional bioactivities and as such constitutes a promising drug lead candidate.

The Last Paragraph

写作思路



The Last Paragraph

In summary, the first total synthesis of (+)-peniciketal A and (+)-peniciketal B was achieved. The total synthesis of (+)-peniciketal A was achieved with the longest linear sequence of 17 steps from **17**. The central features of this synthetic venture entailed the further development and application of a novel photoisomerization/cyclization union protocol to construct the complex benzo-fused 2,8-dioxabicyclo[3.3.1]nonane skeleton in conjunction with a three-component Type I ARC tactic to construct the rare benzannulated [6,6]-spiroketal. Studies toward the synthesis of other members of the peniciketal family as well as the development of analogues for biological evaluations continue in our laboratory.

Representative Examples

Having a long-standing interest in developing novel photochemical protocols for total synthesis, see the paniculides, hibiscone C, echinosporin, and recently the danshenspiroketallactones, etc., we disclosed in 2015 a tandem photoisomerization/cyclization tactic to construct cyclic and spirocyclic ketals. (对……有长期的兴趣)

It is particularly noteworthy that the highly functionalized northern hemisphere (+)-4, bearing an enone, an ester, and a free hydroxy group, could be constructed in only three steps on gram scale. (特别值得注意的是)

Acknowledgement

***Thanks
for your attention***