

# A BIOMIMETIC CONVERGENT TOTAL SYNTHESIS OF PRUNOLACTONE A

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## Prunolactones

Prunolactones A–G (Figure 1) represent a novel group of isocoumarin derivatives possessing an unprecedented 6/6/6/6 spiropentacyclic skeleton and intriguing proangiogenic activity. As postulated by Zhang and Guo<sup>1</sup>, prunolactones A–G can be derived from a single Diels-Alder reaction between scytolide and 3,4-bis(methylene)-isocoumarin **1** (Scheme 1), depending on its stereochemistry (e.g., prunolactones A and C) and regiochemistry (e.g., prunolactones A and D).

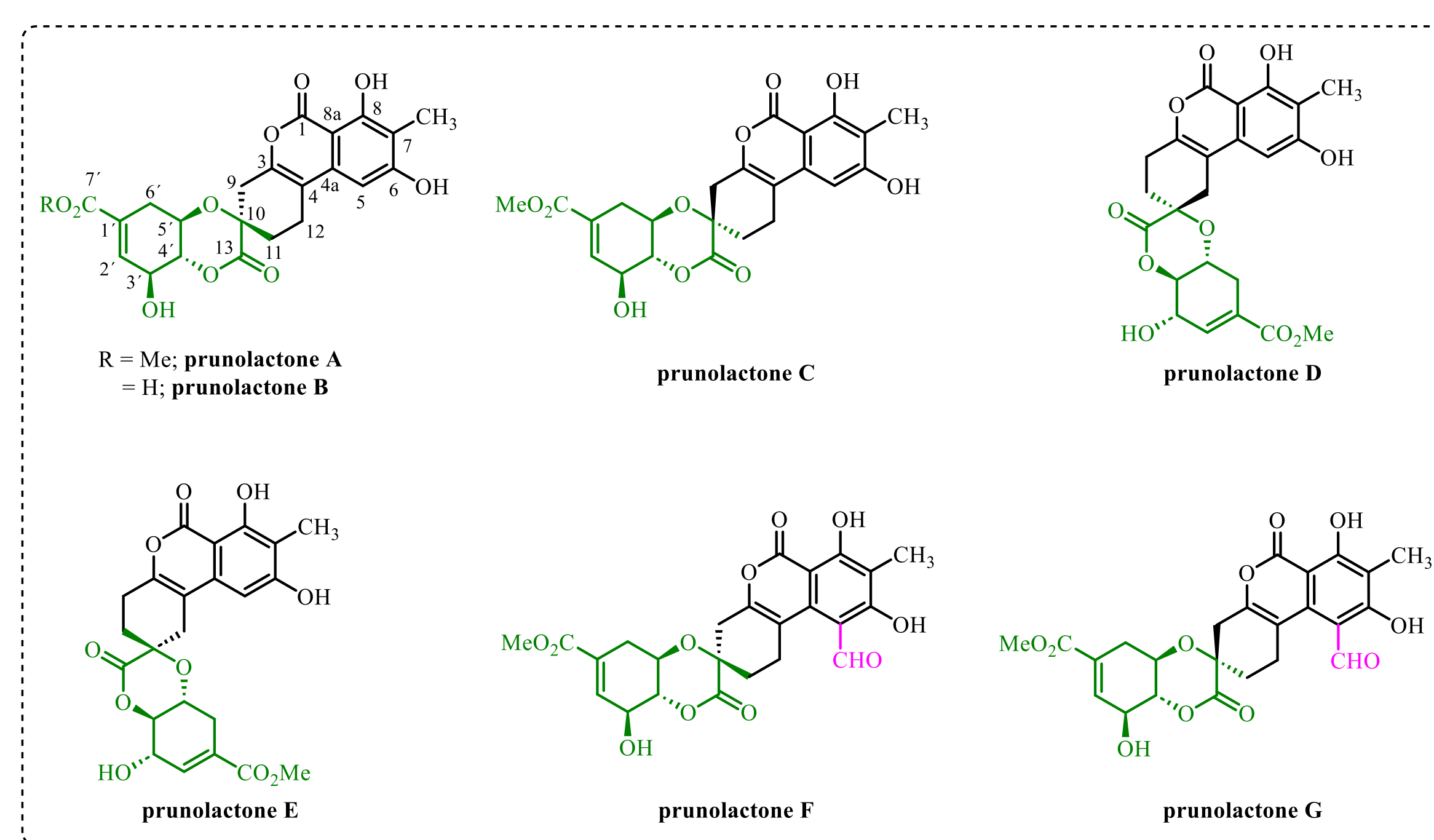
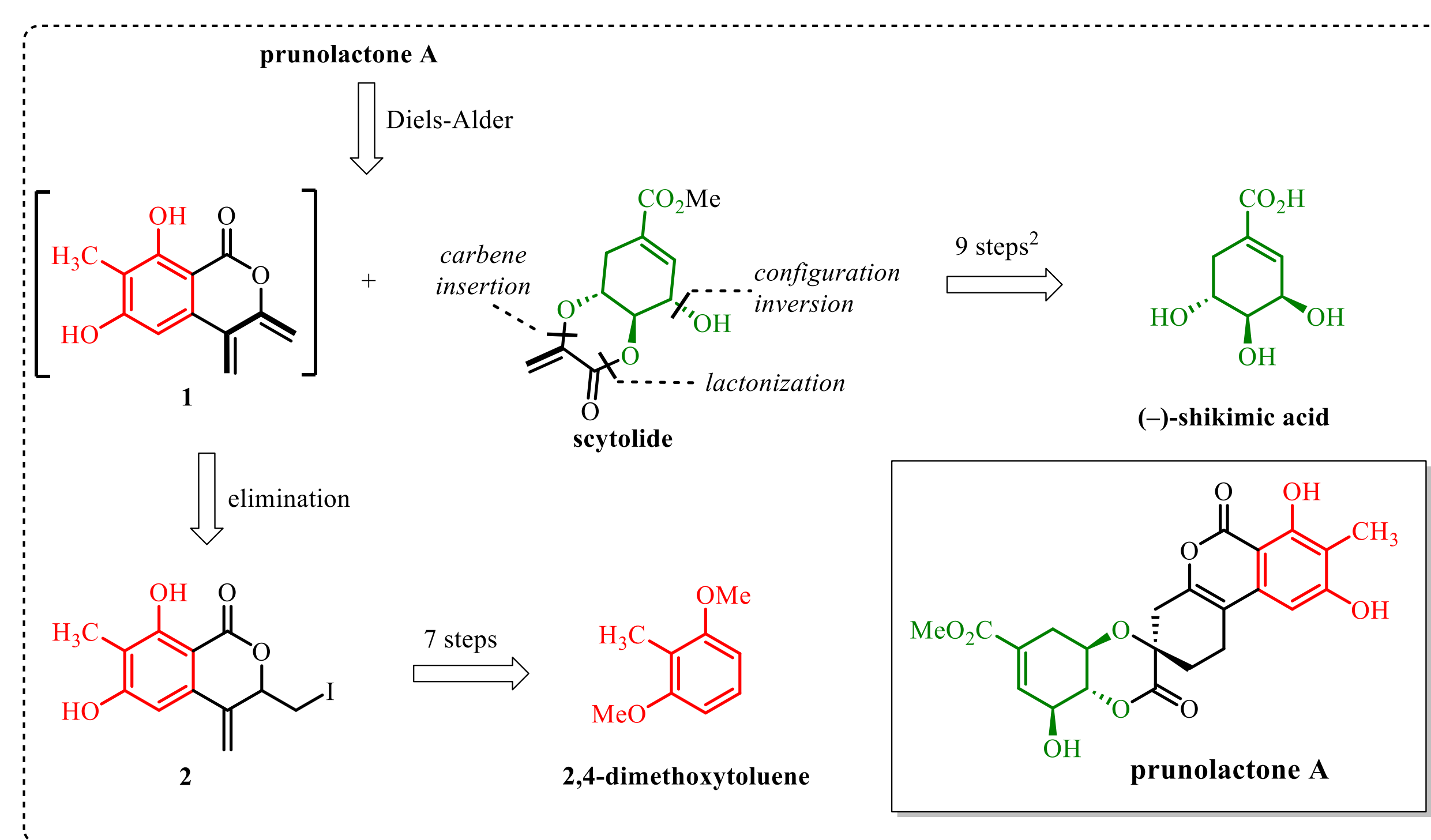


Figure 1.

## Retrosynthetic analysis

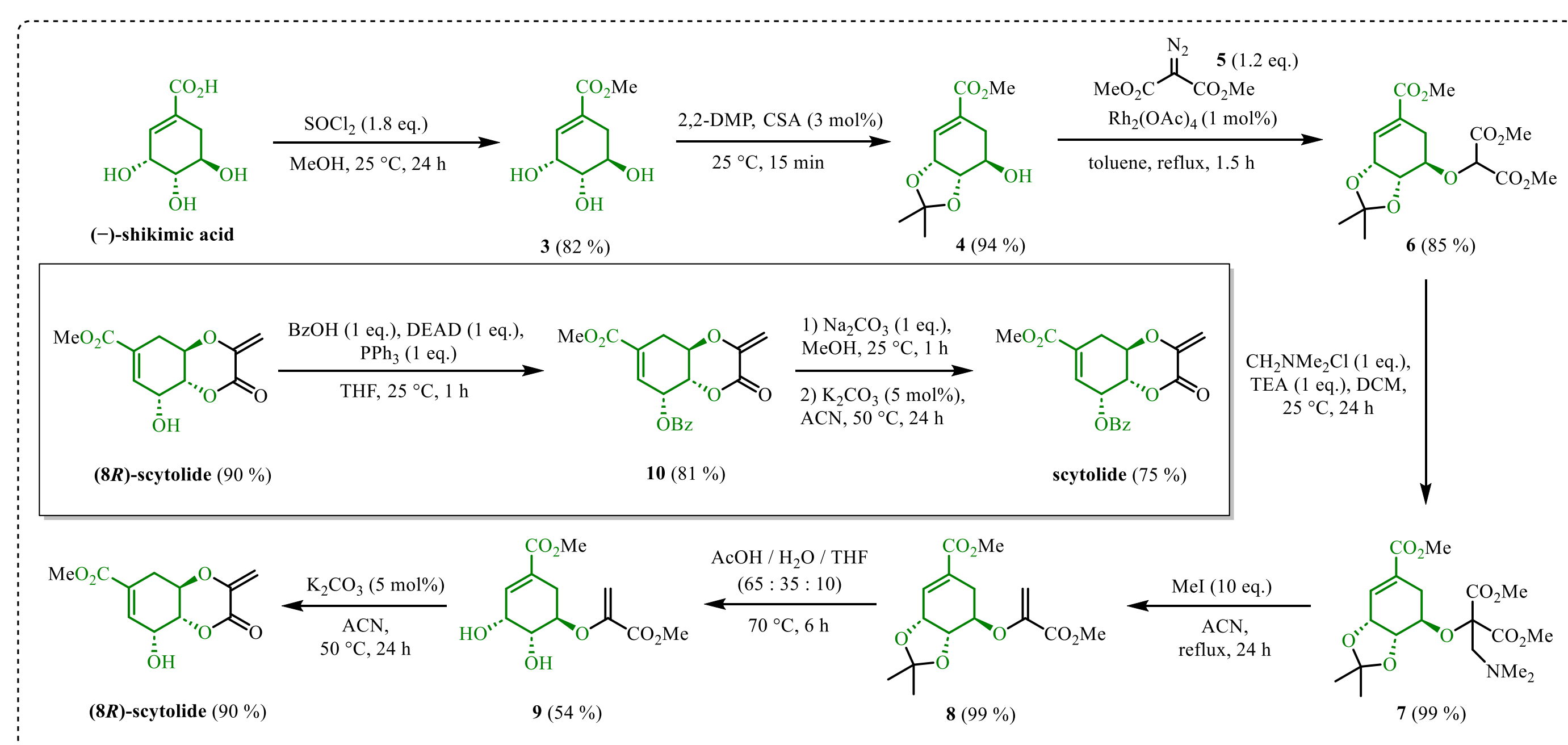
The crucial (and biomimetic) reaction step in the total synthesis of prunolactone A consists of a Diels-Alder reaction between exocyclic diene **1** (generated *in situ* from the corresponding iodide **2** under basic conditions; Scheme 1) and scytolide, which can be prepared from (–)-shikimic acid<sup>2</sup> in 9 reaction steps. The synthesis of the diene precursor **2** involves 7 reaction steps starting from commercially available 2,4-dimethoxytoluene.



Scheme 1.

## Synthesis of scytolide

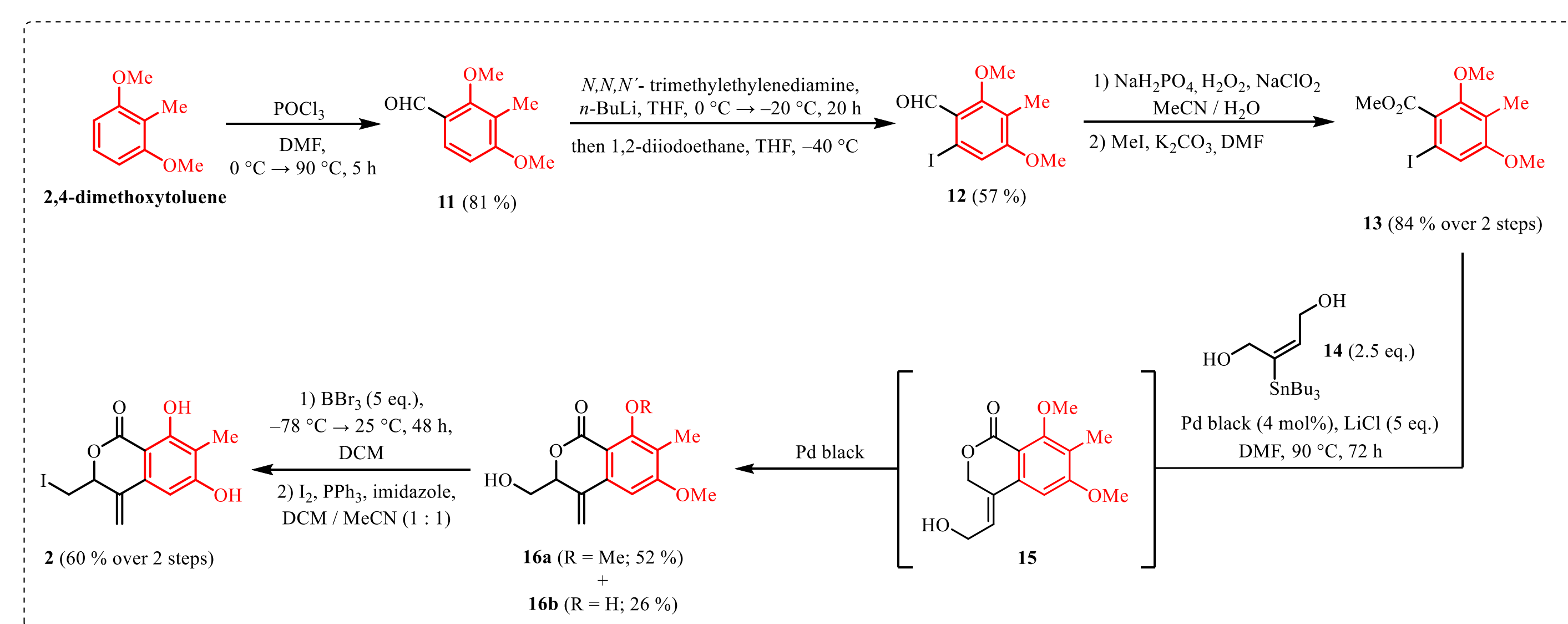
The synthesis of scytolide starts from commercially available (–)-shikimic acid (Scheme 2) and consists of 9 reaction steps including *in situ* generated carbene insertion (**4** → **6**), Hofmann elimination (**7** → **8**) and lactone formation (**9** → (8*R*)-scytolide). Finally, (8*R*)-scytolide undergoes epimerization under Mitsunobu conditions to yield scytolide as a stereochemically pure compound.



Scheme 2.

## Synthesis of diene precursor

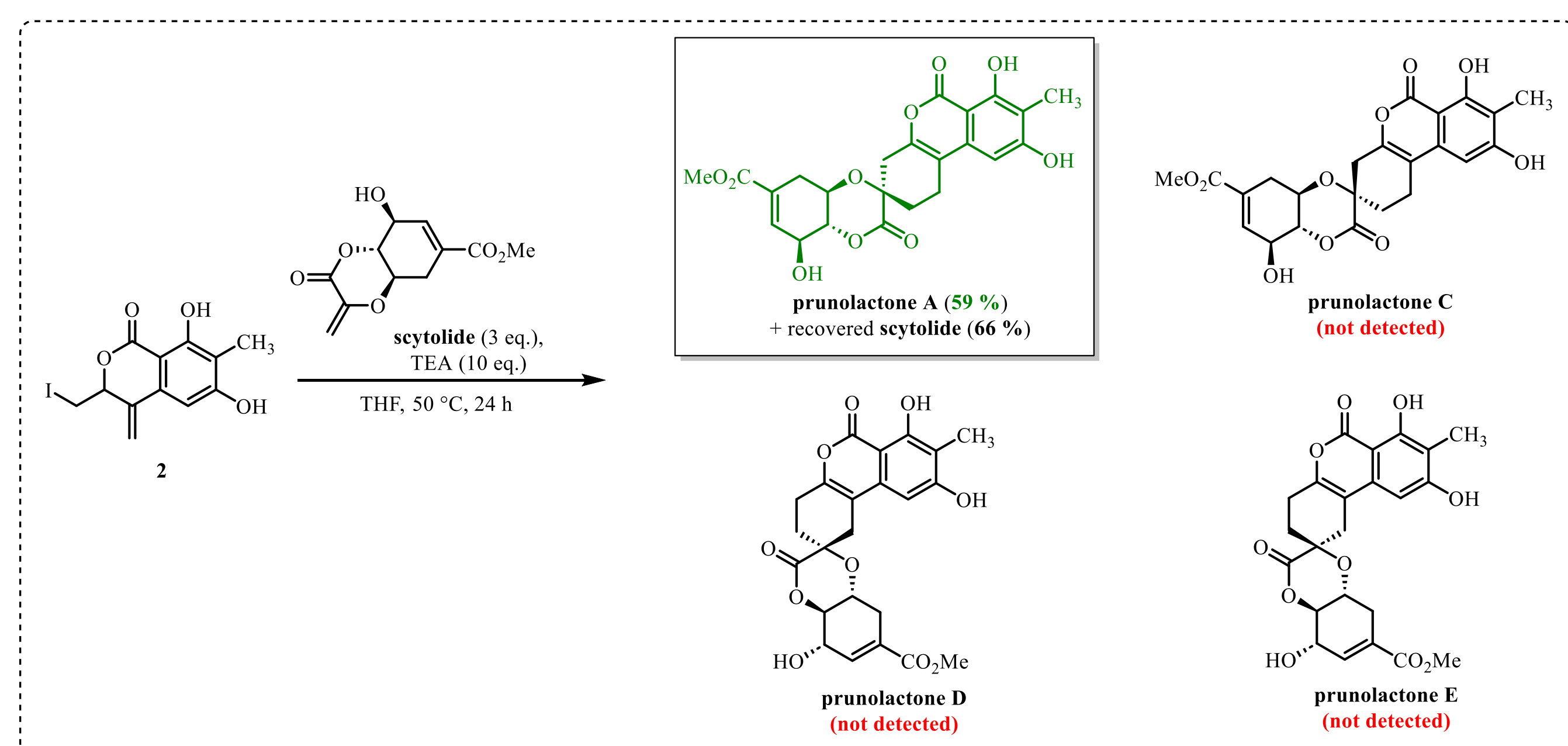
The exocyclic diene precursor (iodide **2**; Scheme 3) was prepared in 7 reaction steps from commercially available 2,4-dimethoxytoluene. The crucial reaction involves Stille coupling of methyl ester **13** and stannylated diol **14** (easily prepared by hydrostannylation of but-2-yne-1,4-diol) followed by *in situ* Tsuji-Trost allylic isomerization of intermediate **15** to afford pyranone **16a** (52 % yield) together with partially demethylated by-product **16b** (26 % yield). The resulting mixture was then completely demethylated with boron tribromide. Finally, iodination of the primary alcohol provided the desired precursor **2**.



Scheme 3.

## Final Diels-Alder reaction

The crucial Diels-Alder reaction between diene **1** (generated *in situ* from iodide **2**) and scytolide can provide up to 4 different stereo- and regioisomers (prunolactones A, C, D and E; Scheme 4). To our surprise, only prunolactone A was detected and isolated from the reaction mixture in good yield of 59 % as the sole product, along with recovered scytolide.



Scheme 4.

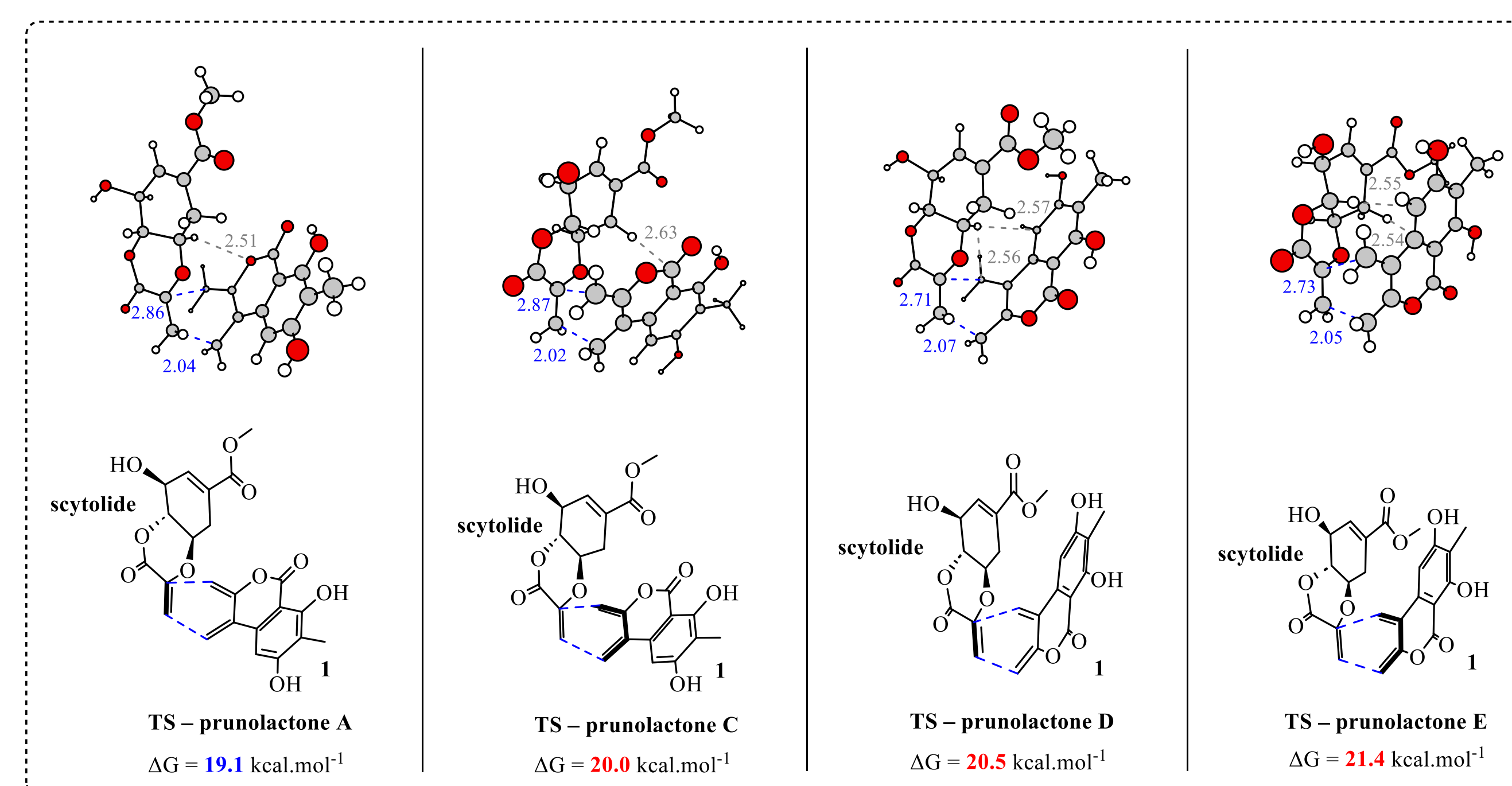


Figure 2.

To support the observed results, transition state calculations of prunolactones A, C, D and E were performed. As shown in Figure 2, the transition state of prunolactone A has the lowest Gibbs free energy value (19.1 kcal mol<sup>–1</sup>), which is consistent with the reaction outcome.

## Acknowledgement

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## References

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