Total Synthesis of (+)-Cytosporolide A via a Biomimetic Hetero-Diels−Alder Reaction

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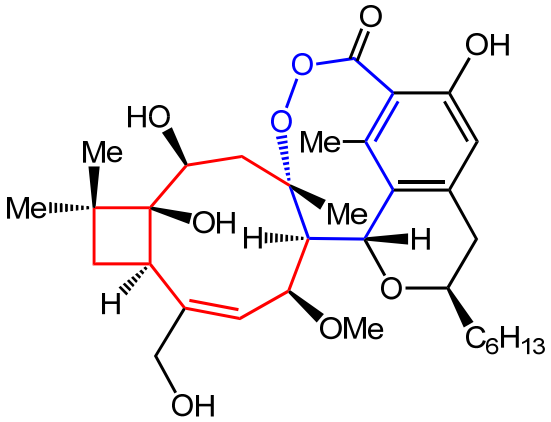
Checker: Shu-Bo Hu

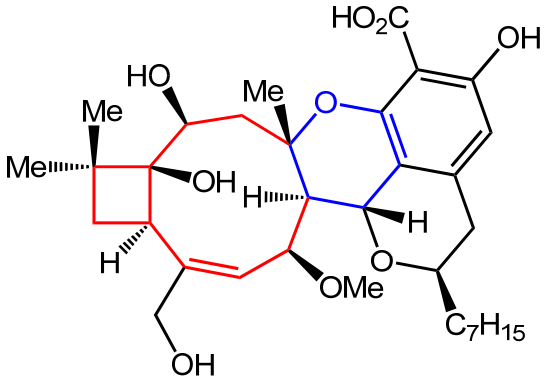
Date: 29/12/2015

Takao, K. *et al.*
J. Am. Chem. Soc. **2015**, *137*, 15971.

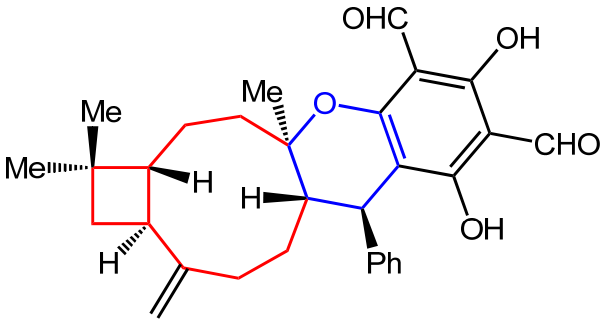
Revised structure of (+)-cytosporolide A and related natural products



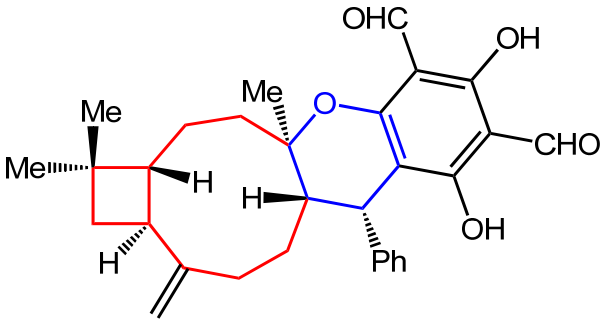
1: (+)-cytosporolide A
(originally proposed
structure by Che)



2: (+)-cytosporolide A
(revised structure
by George)

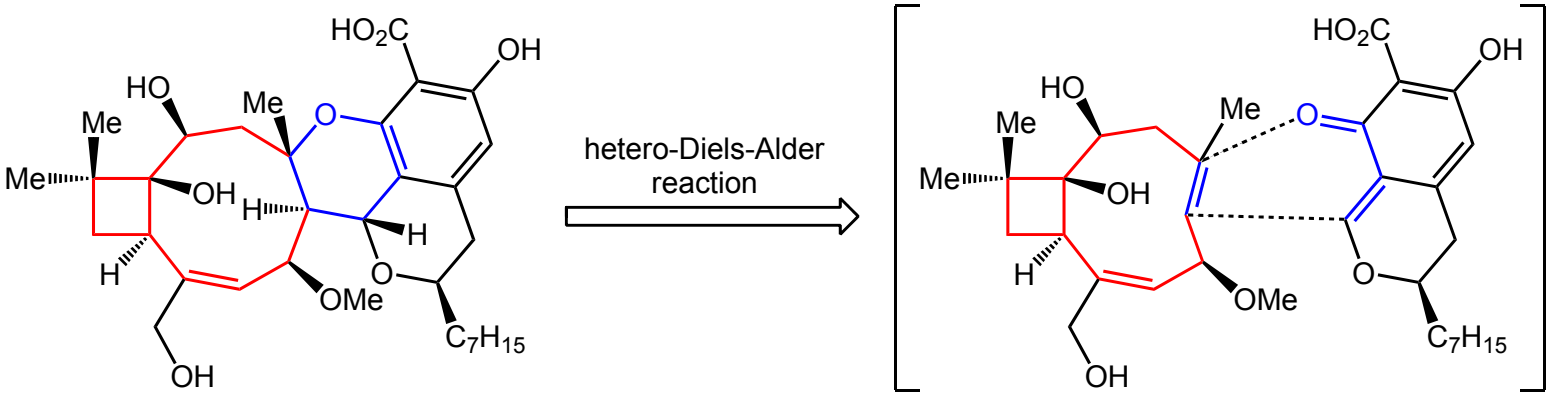


3: (-)-guajadial



4: (+)-psidial A

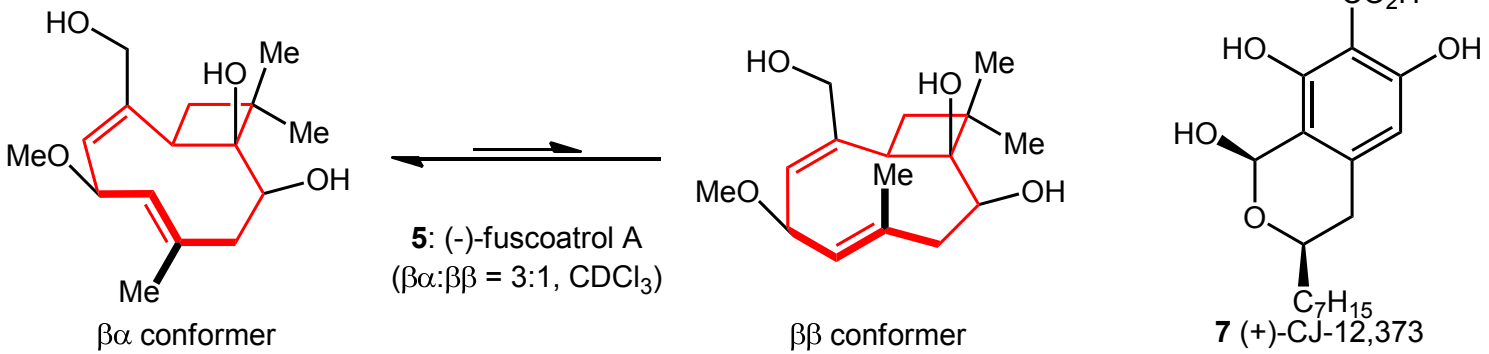
Proposed biosynthesis of (+)-cytosporolide A



2: (+)-cytosporolide A

5: (-)-fuscoatrol A

6



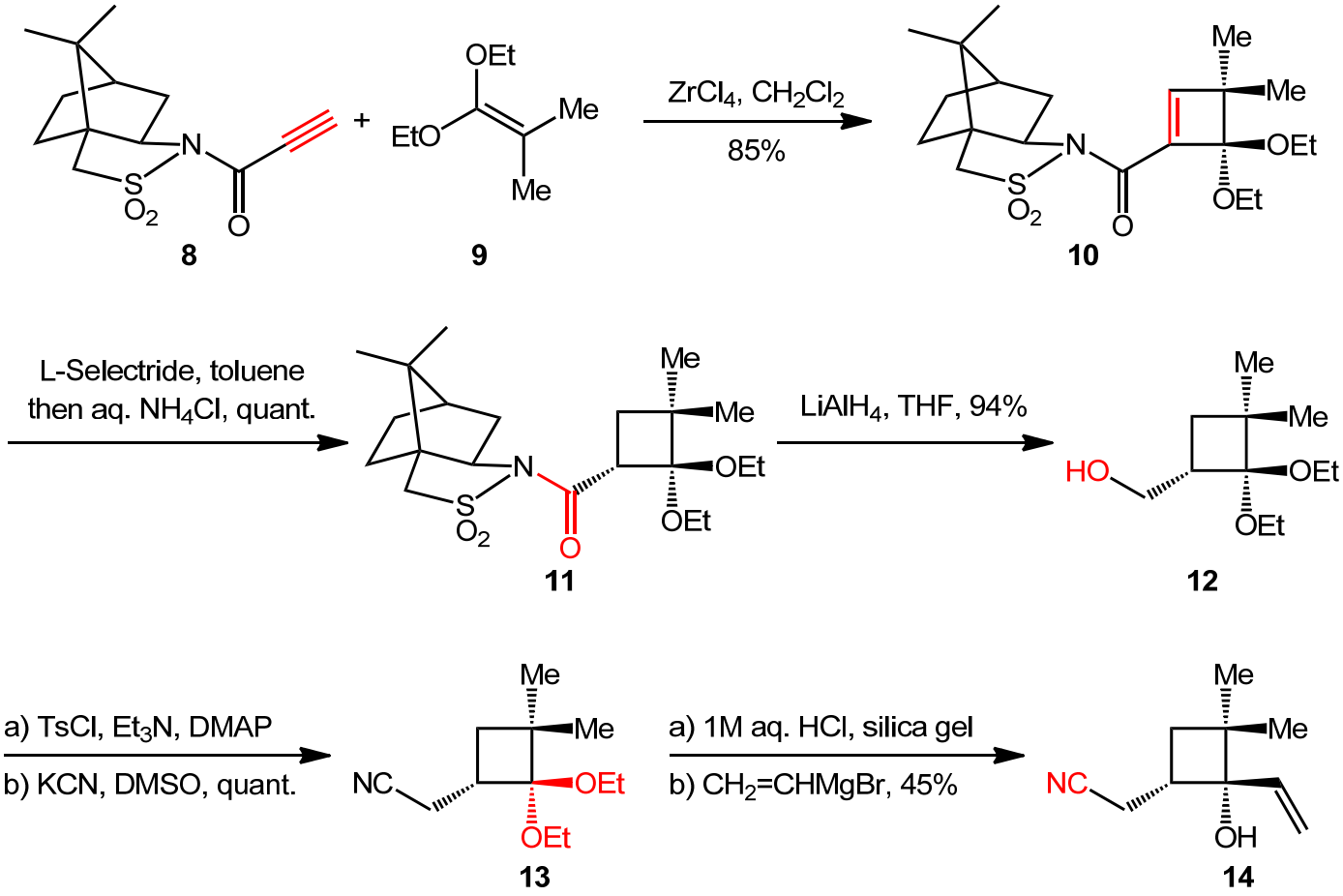
βα conformer

5: (-)-fuscoatrol A
(βα:ββ = 3:1, $CDCl_3$)

ββ conformer

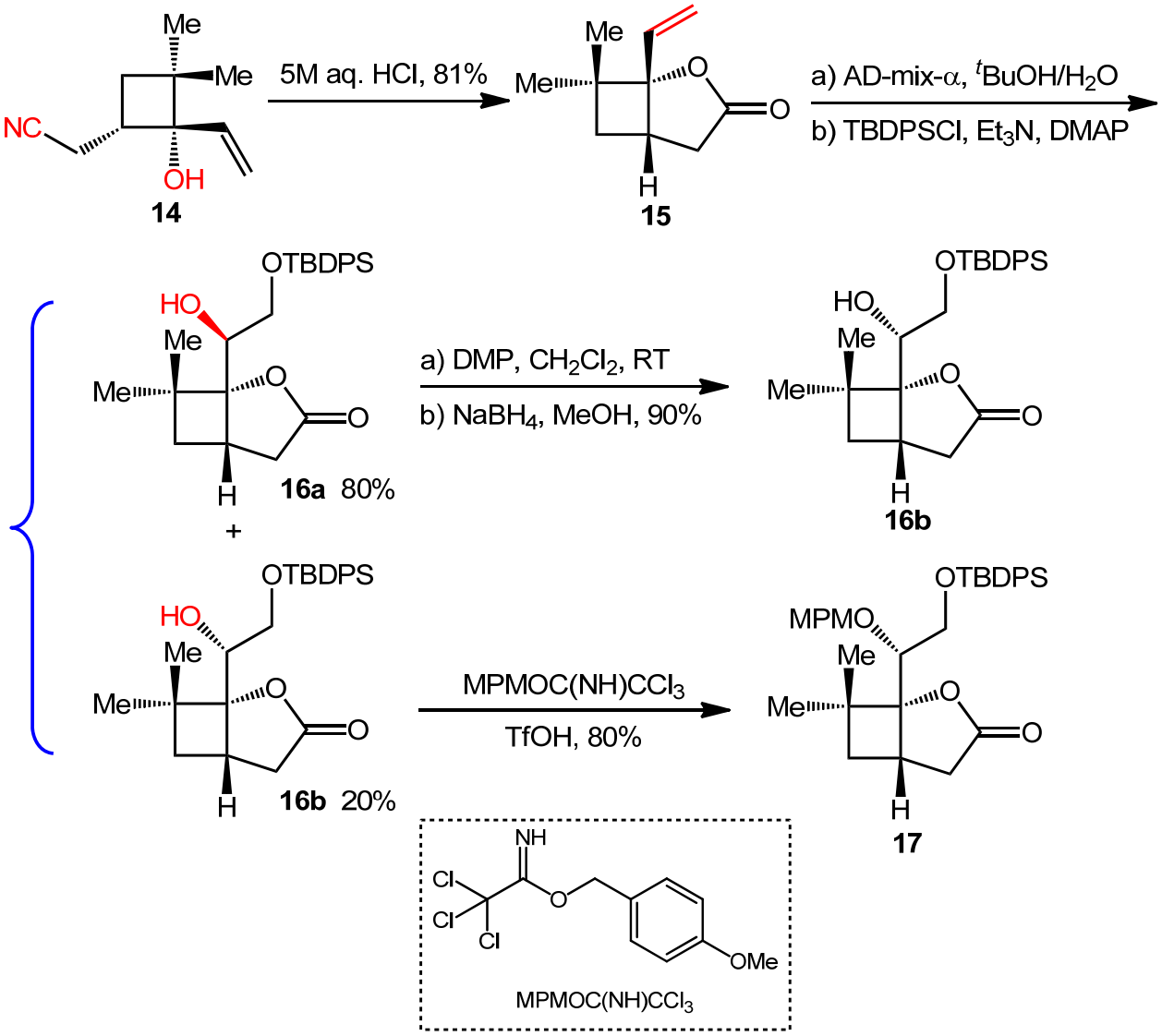
7 (+)-CJ-12,373

Synthesis of (-)-fuscoatrol A

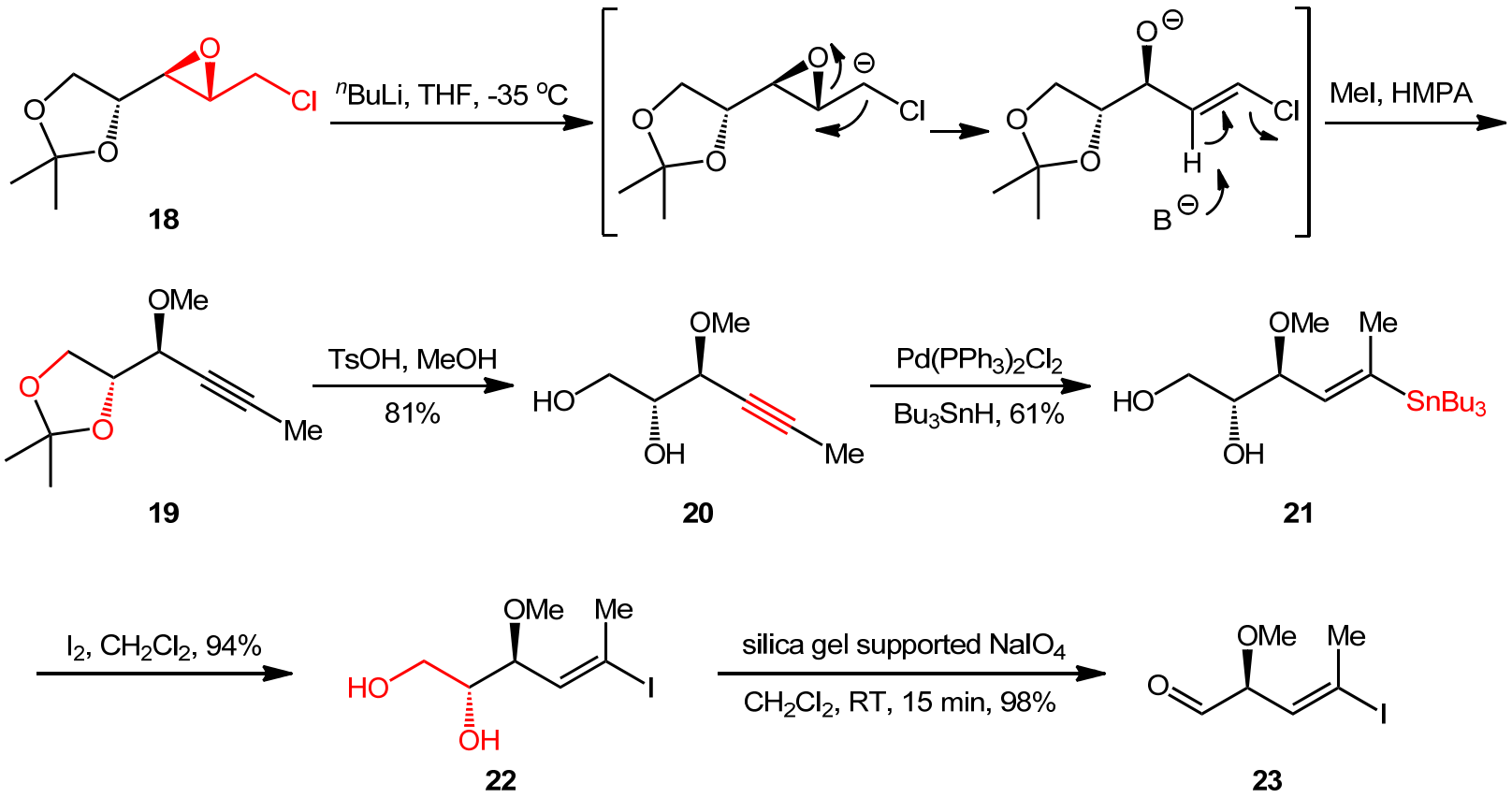


Tadano, K. *et al*. *Angew. Chem. Int. Ed.* **2008**, *47*, 3426.

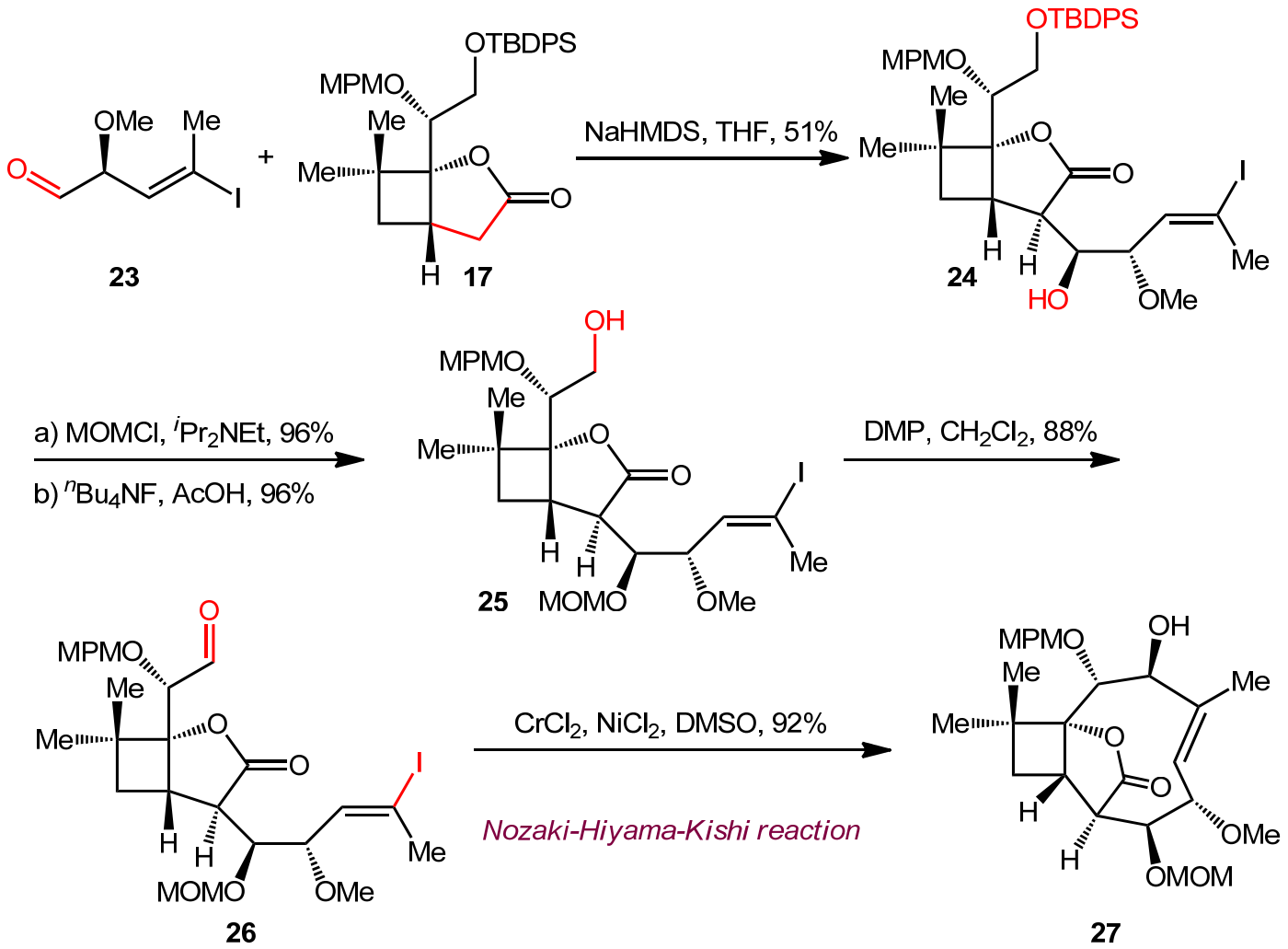
Synthesis of (-)-fuscoatrol A



Synthesis of (-)-fuscoatrol A



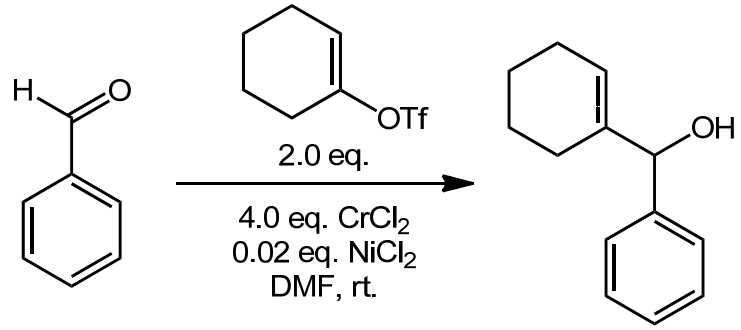
Synthesis of (-)-fuscoatrol A

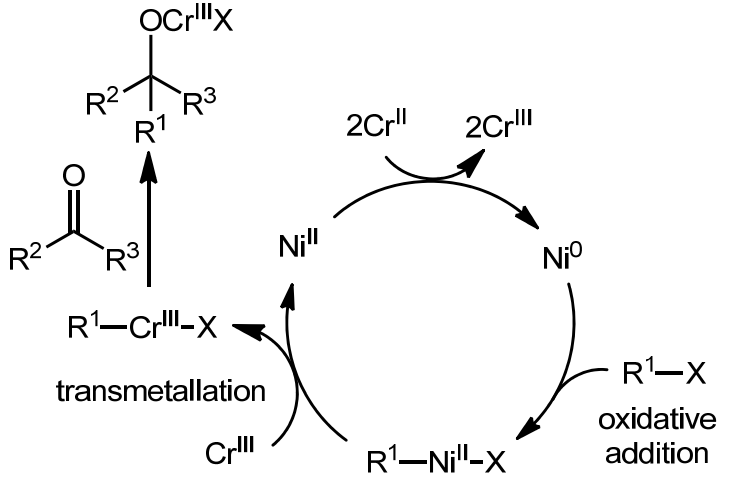


Nozaki–Hiyama–Kishi reaction

The Nozaki–Hiyama–Kishi reaction is a nickel/chromium coupling reaction forming an alcohol from the reaction of an aldehyde with an allyl or vinyl halide.

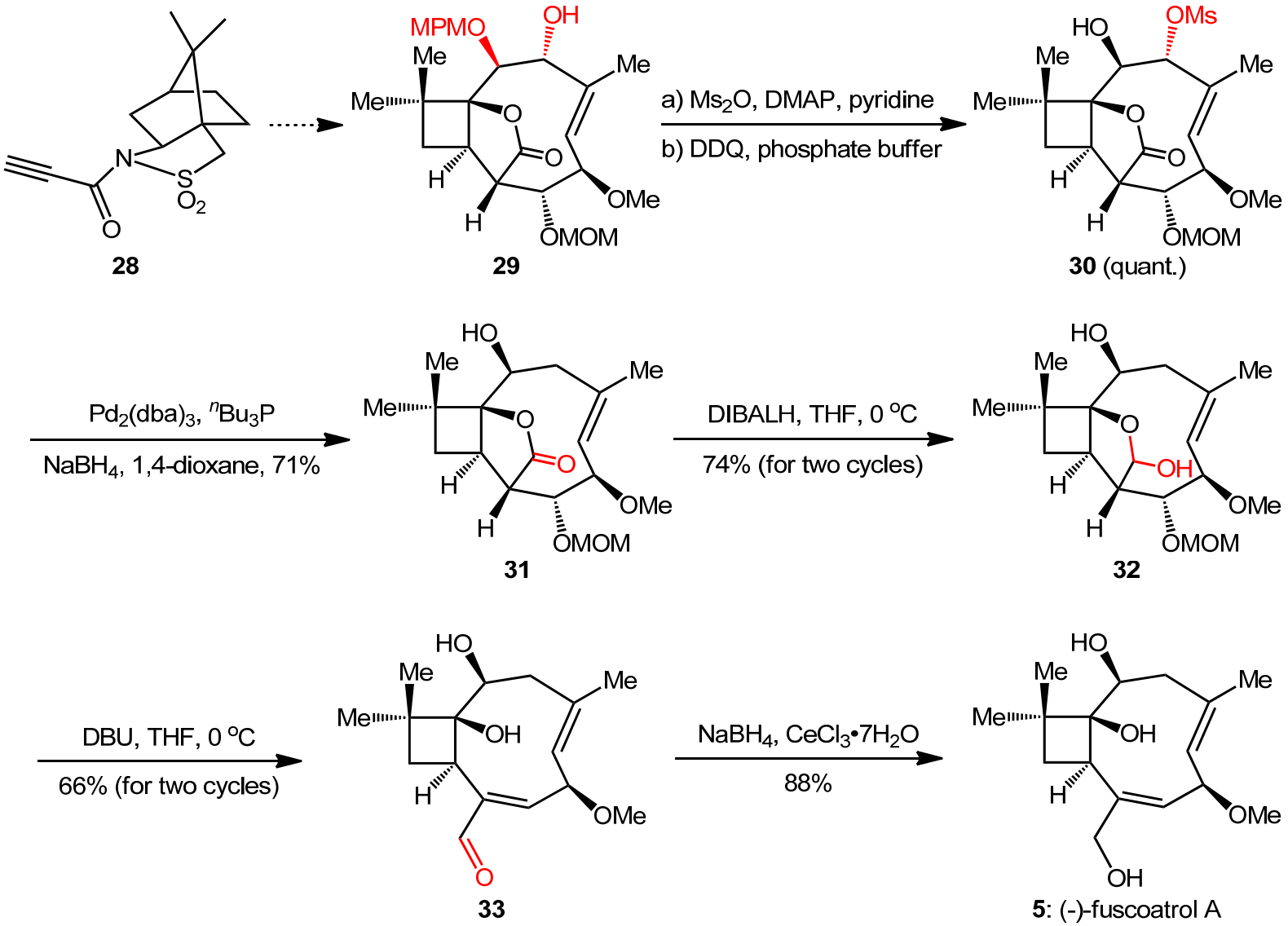
Compared to Grignard reactions, this reaction is very selective towards aldehydes with large tolerance towards a range of functional groups such as ketones, esters, amides and nitriles. Enals give exclusively 1,2-addition. Solvents of choice are DMF and DMSO, one solvent requirement is solubility of the chromium salts. Nozaki-Hiyama-Kishi reaction is a useful method for preparing medium-size rings.



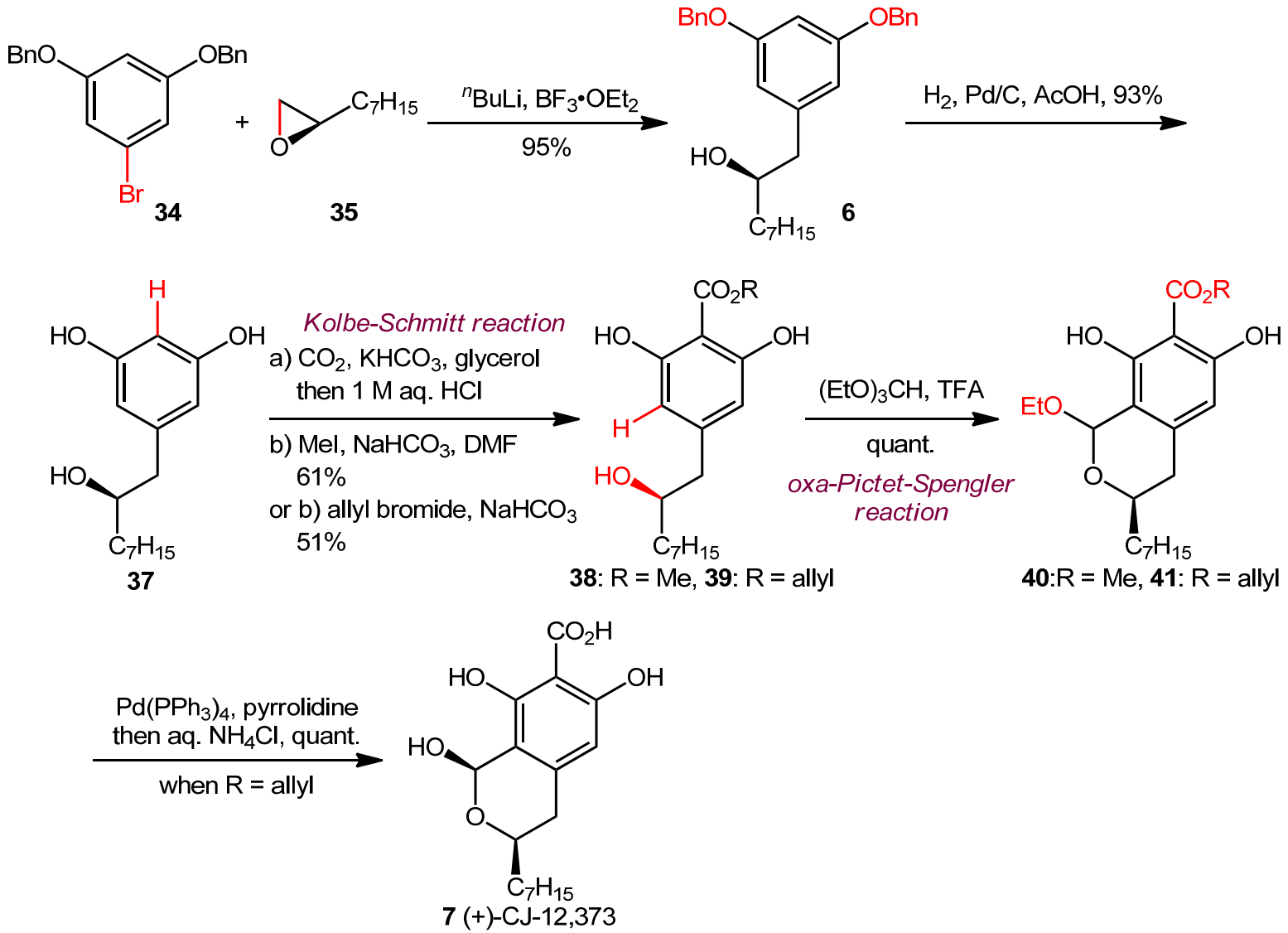


From Wikipedia

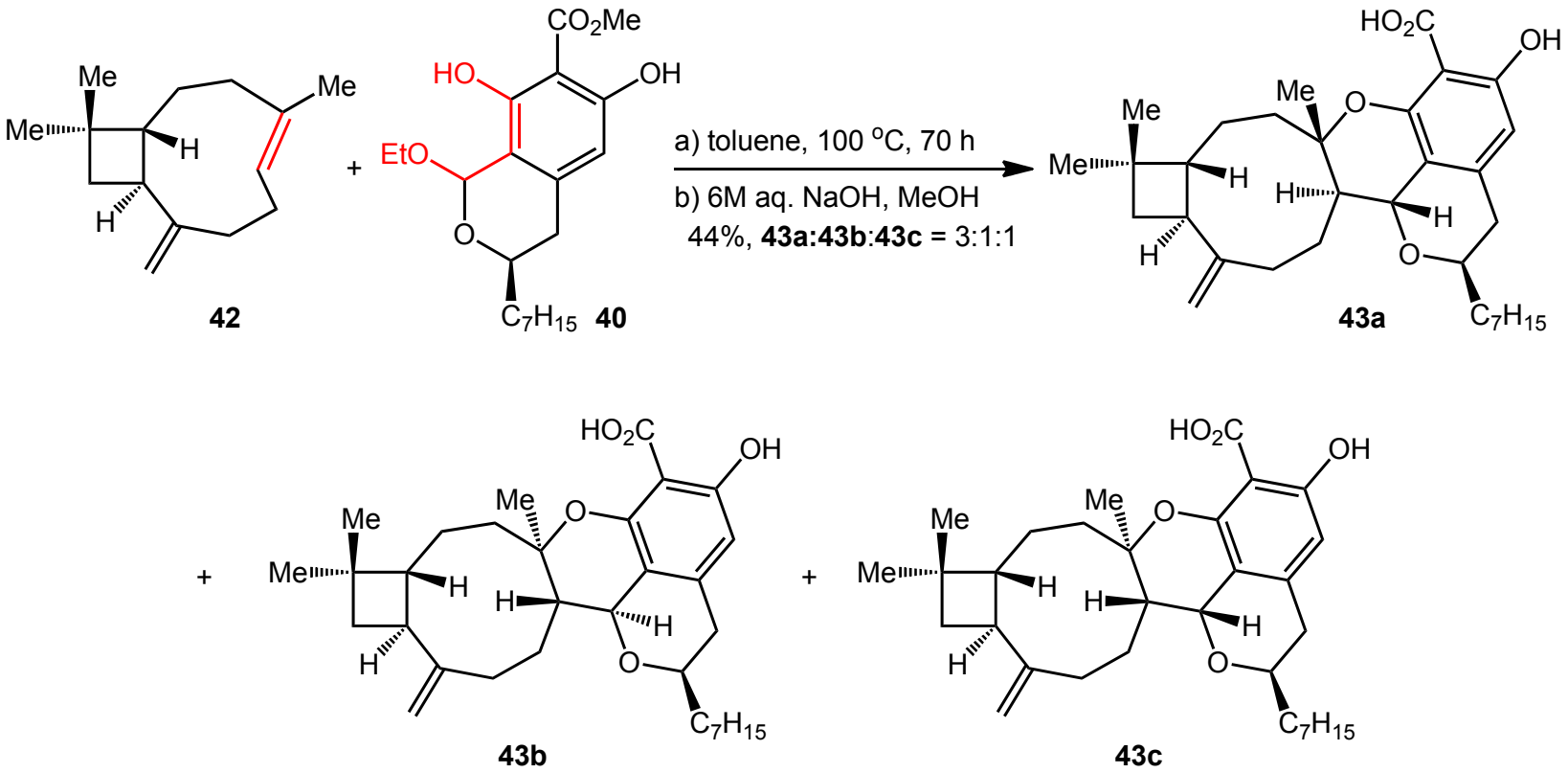
Synthesis of (-)-fuscoatrol A



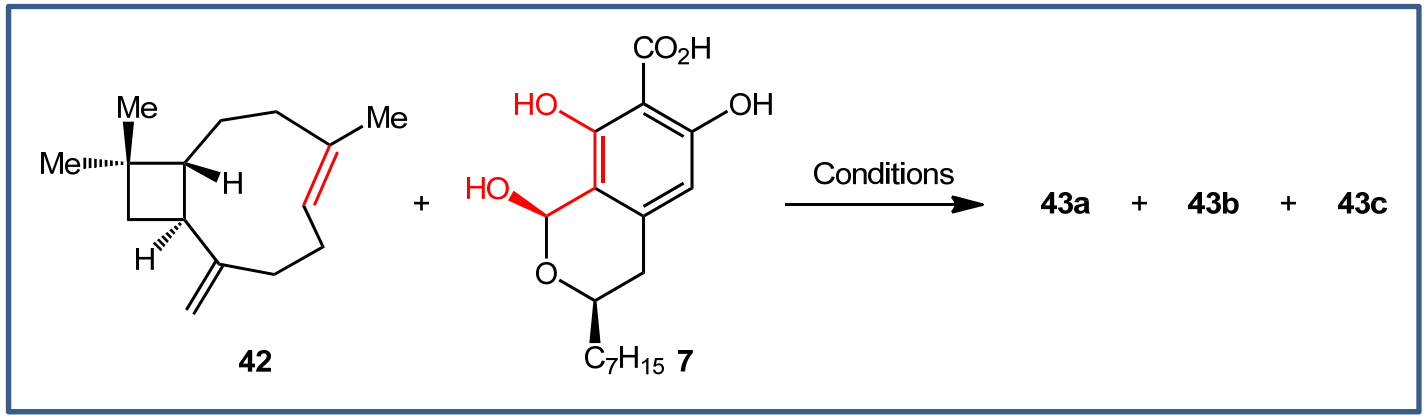
Synthesis of the precursor of *o*-quinone methide intermediate



Hetero-Diels-Alder reaction

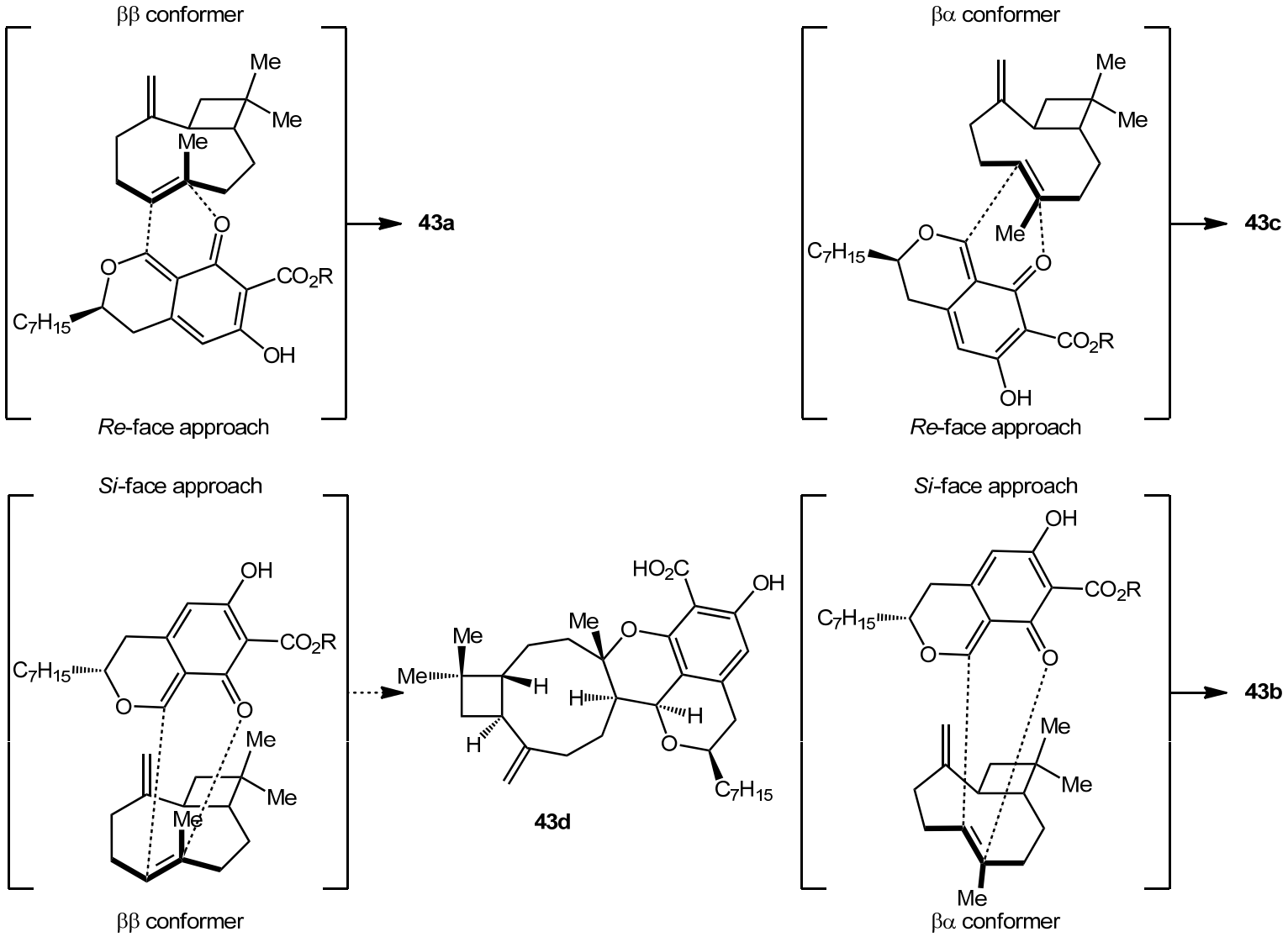


Hetero-Diels-Alder reaction

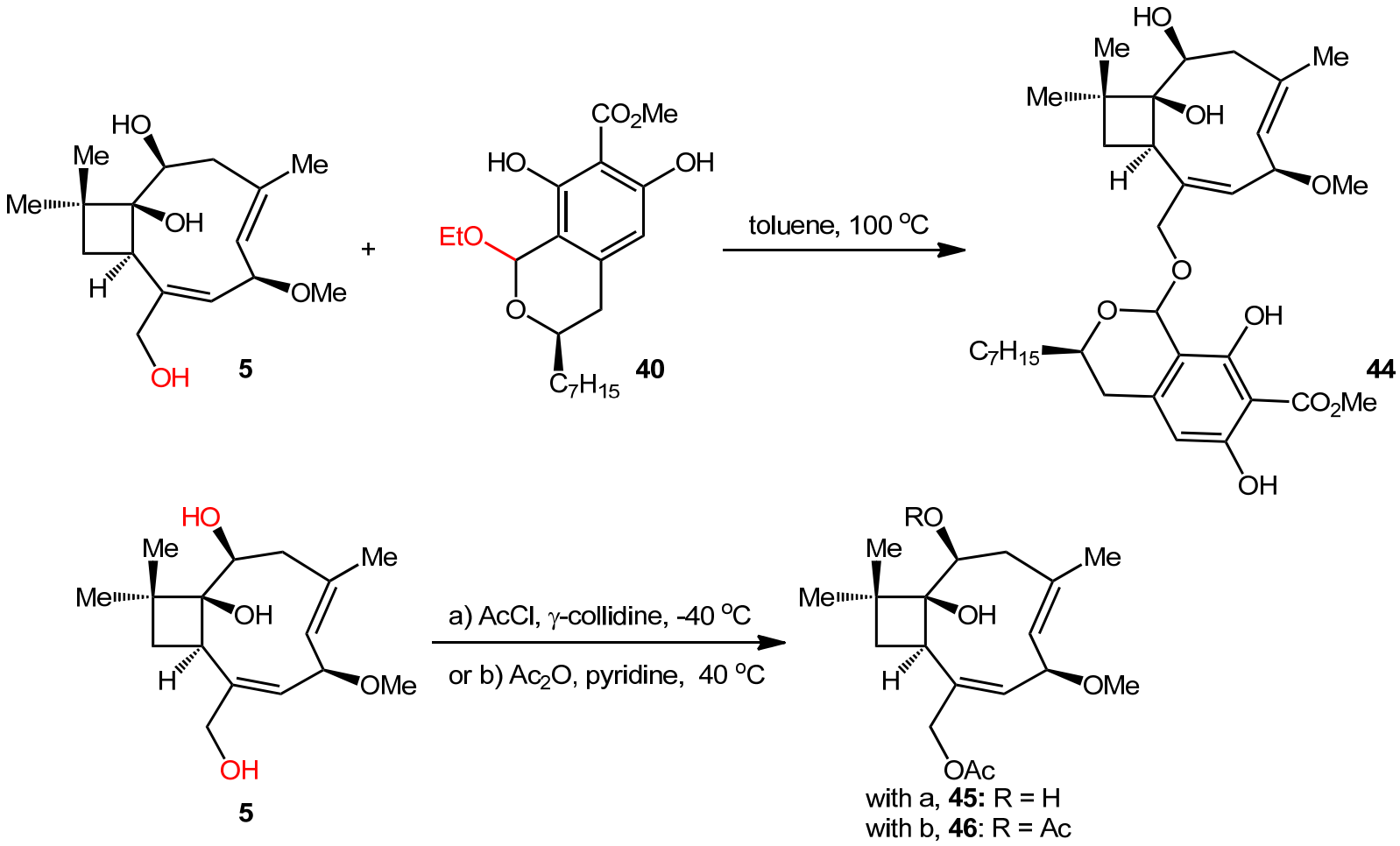


Entry	Conditions	Yield (**43a**/**43b**/**43c**)
1	Toluene, 100 °C, 7 h	44% (7:1:1)
2	Toluene, 150 °C, 3 h	14% (4:1:0)
3	Silica gel (500 wt%), Toluene, 100 °C, 15 h	32% (5:3:0)
4	Silica gel (500 wt%), Toluene, 150 °C, 2 h	21% (17:6:1)

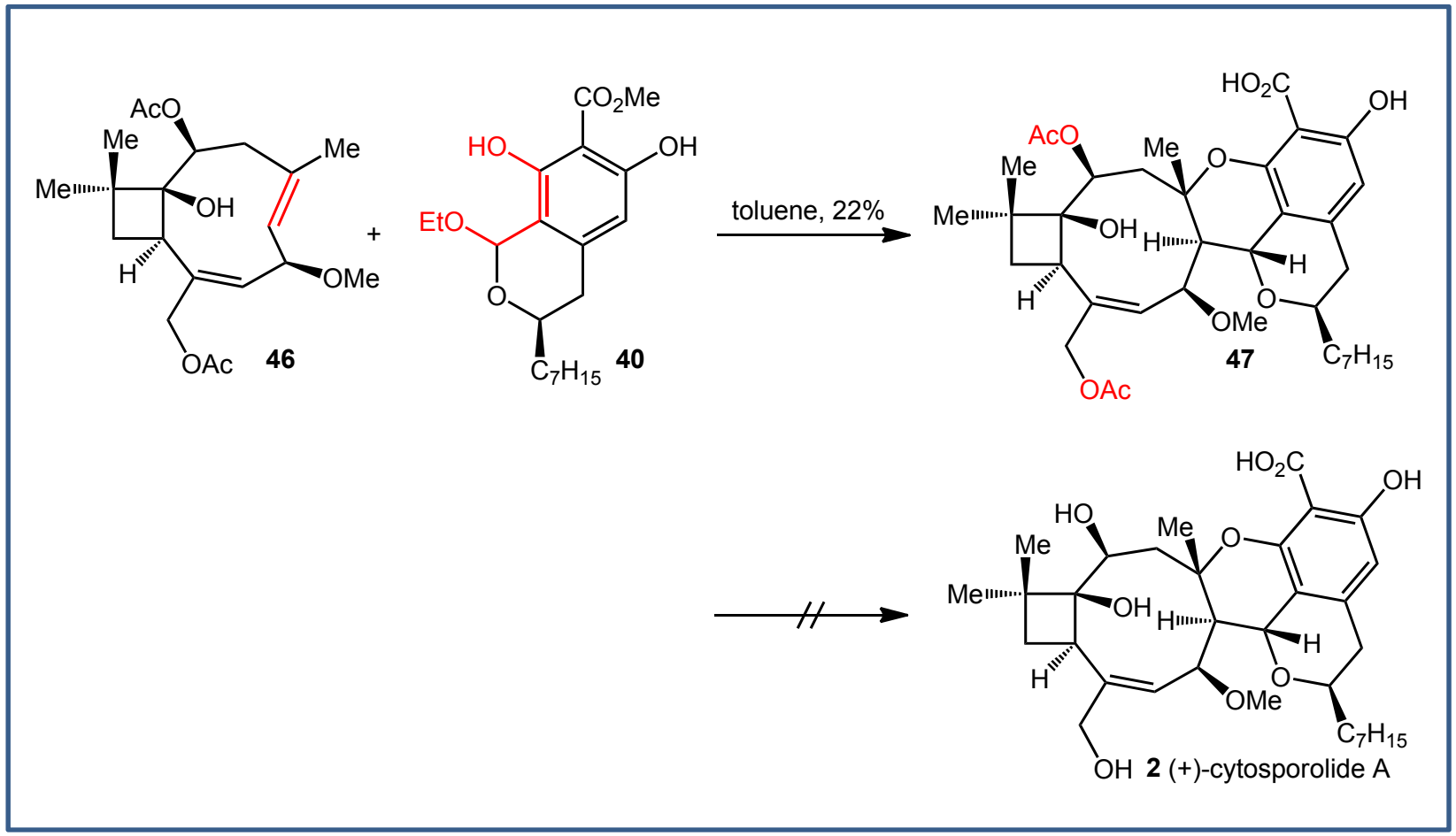
Plausible transition states for the hetero-Diels−Alder reaction



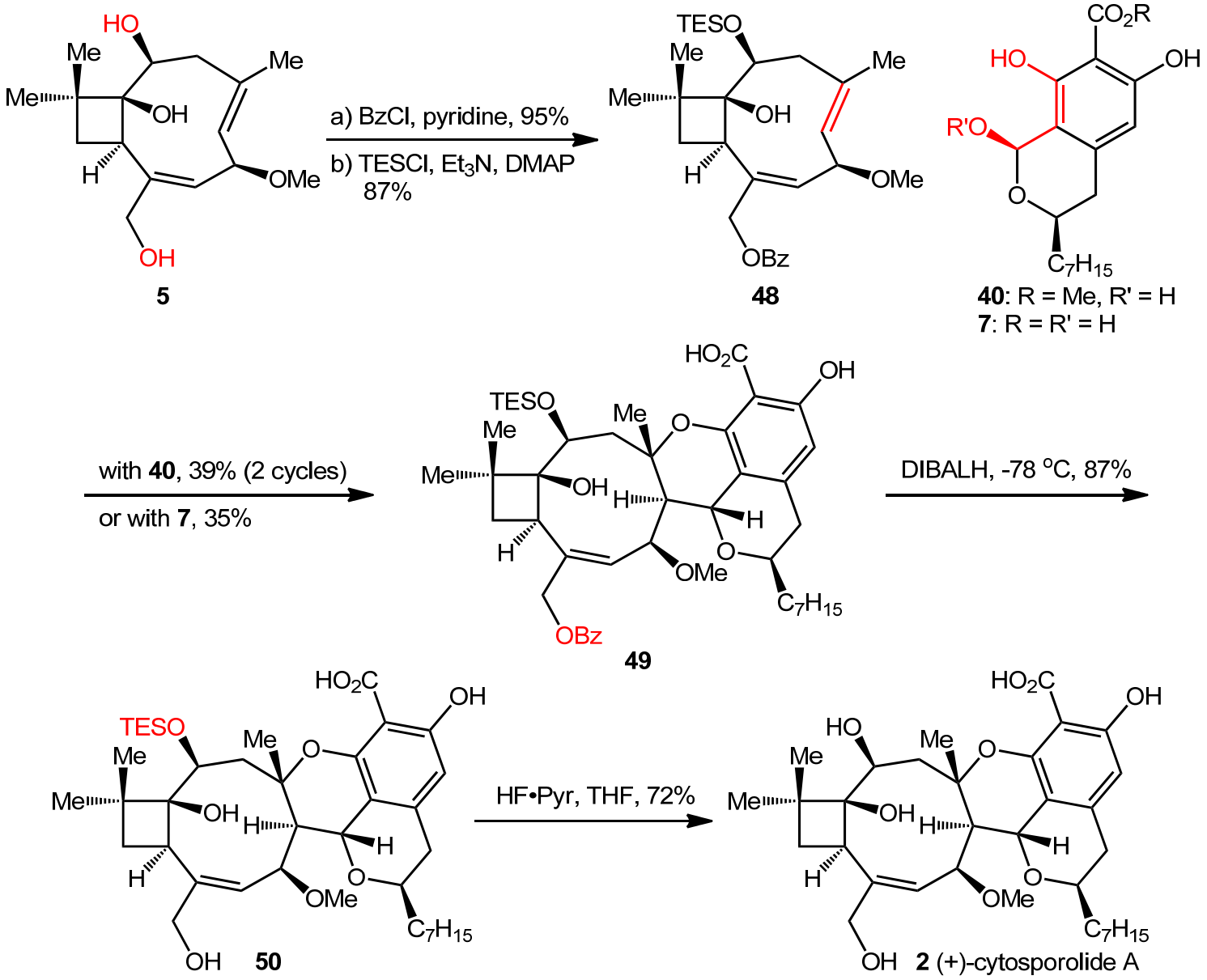
Unsuccessful trials



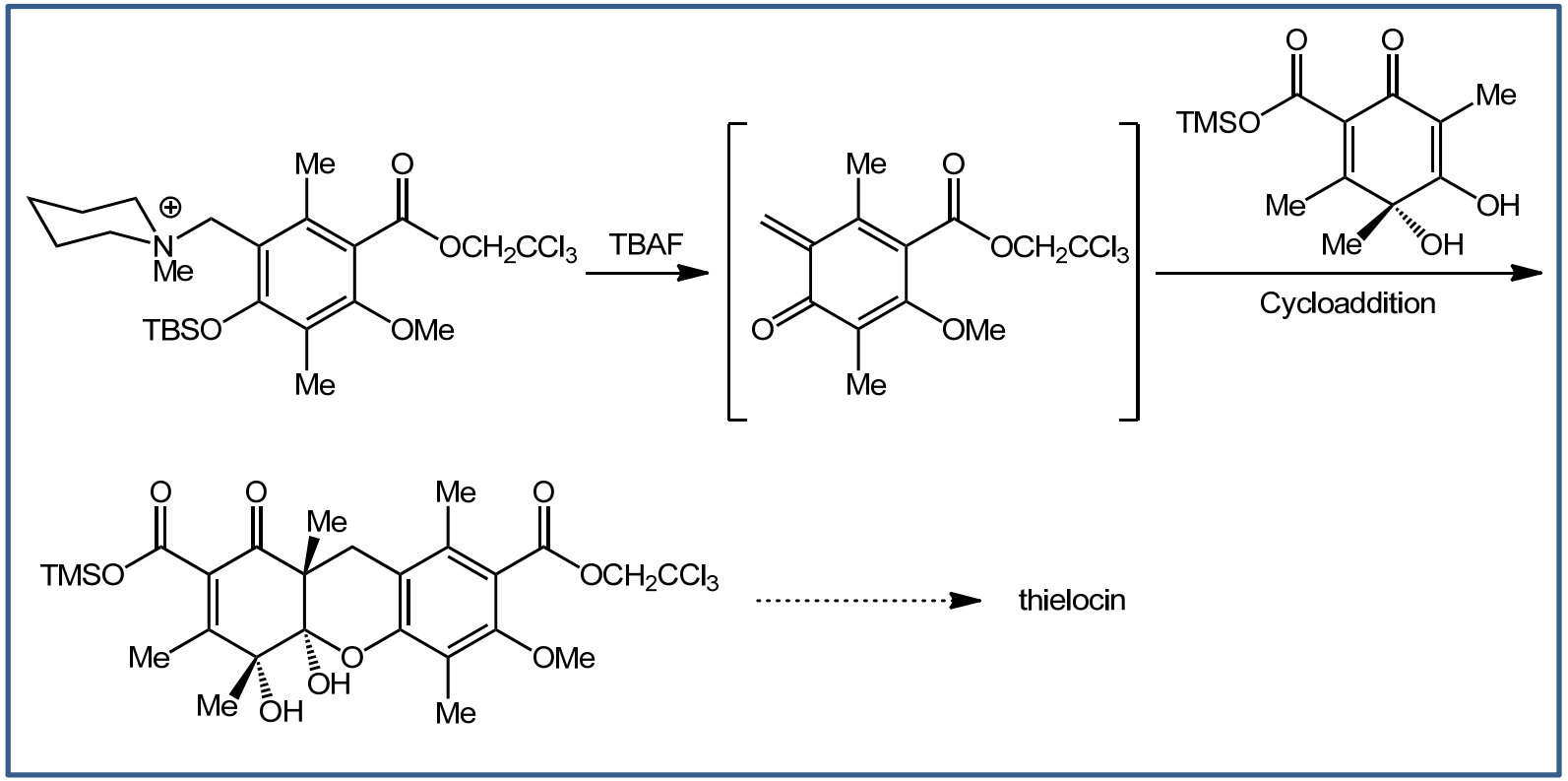
Unsuccessful trials



Completion of the total synthesis of (+)-cytosporolide A

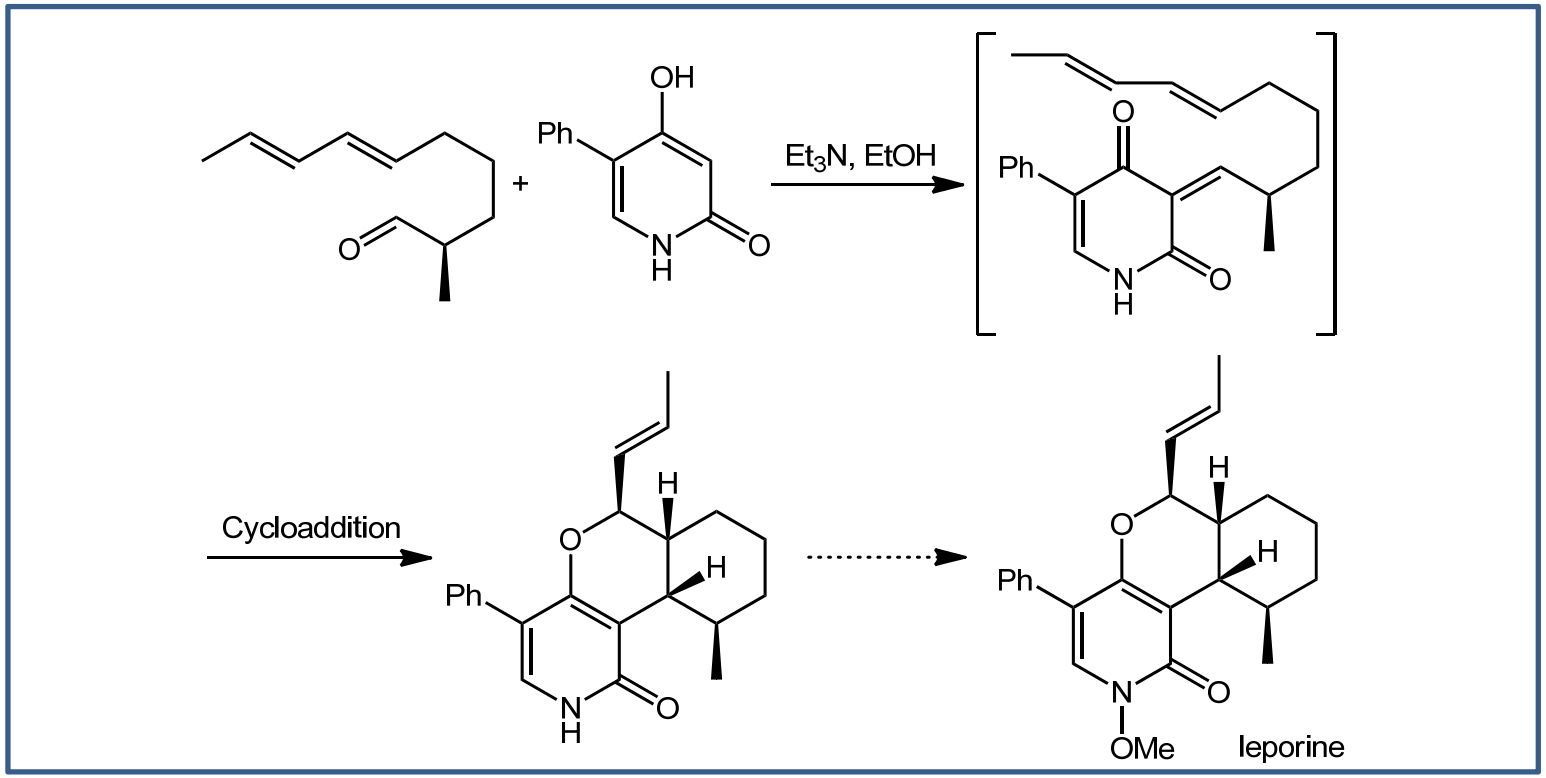


The application of *o*-quinone methide intermediates in total synthesis



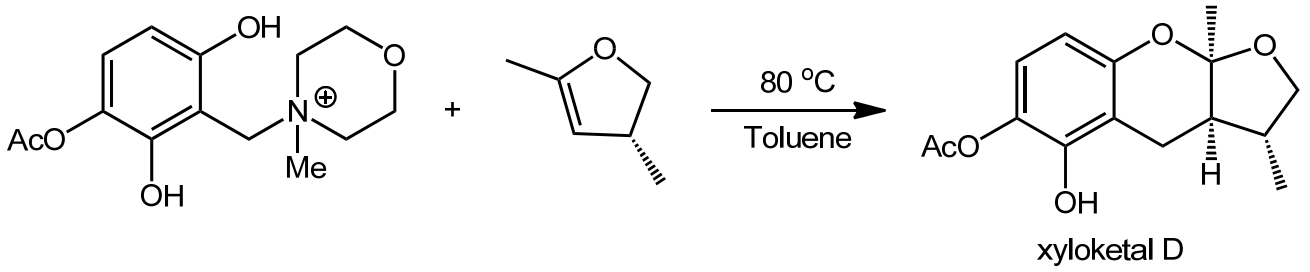
Young, R. N. *et al. J. Am. Chem. Soc.* **1994**, *116*, 759.

The application of *o*-quinone methide intermediates in total synthesis



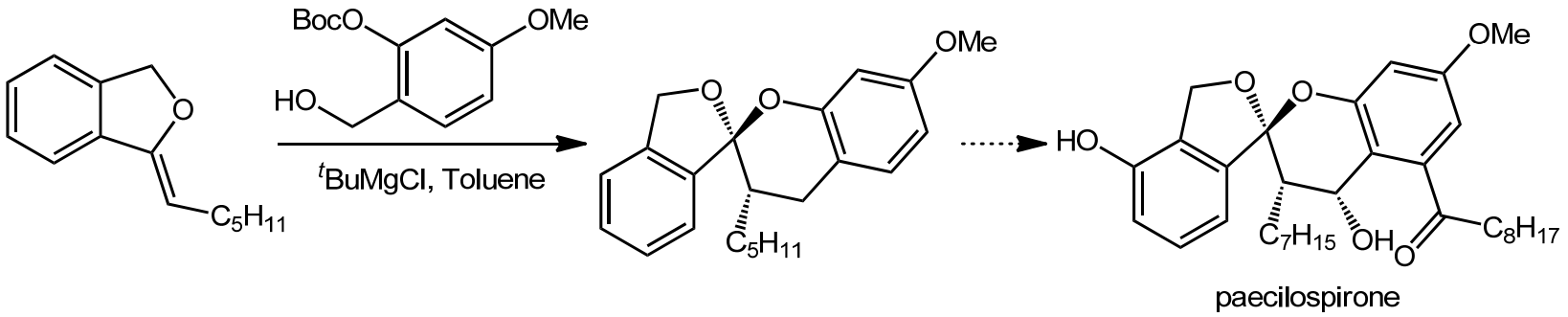
Snider, B. B. *et al. J. Org. Chem.* **1996**, *61*, 2839.

The application of *o*-quinone methide intermediates in total synthesis



xyloketal D

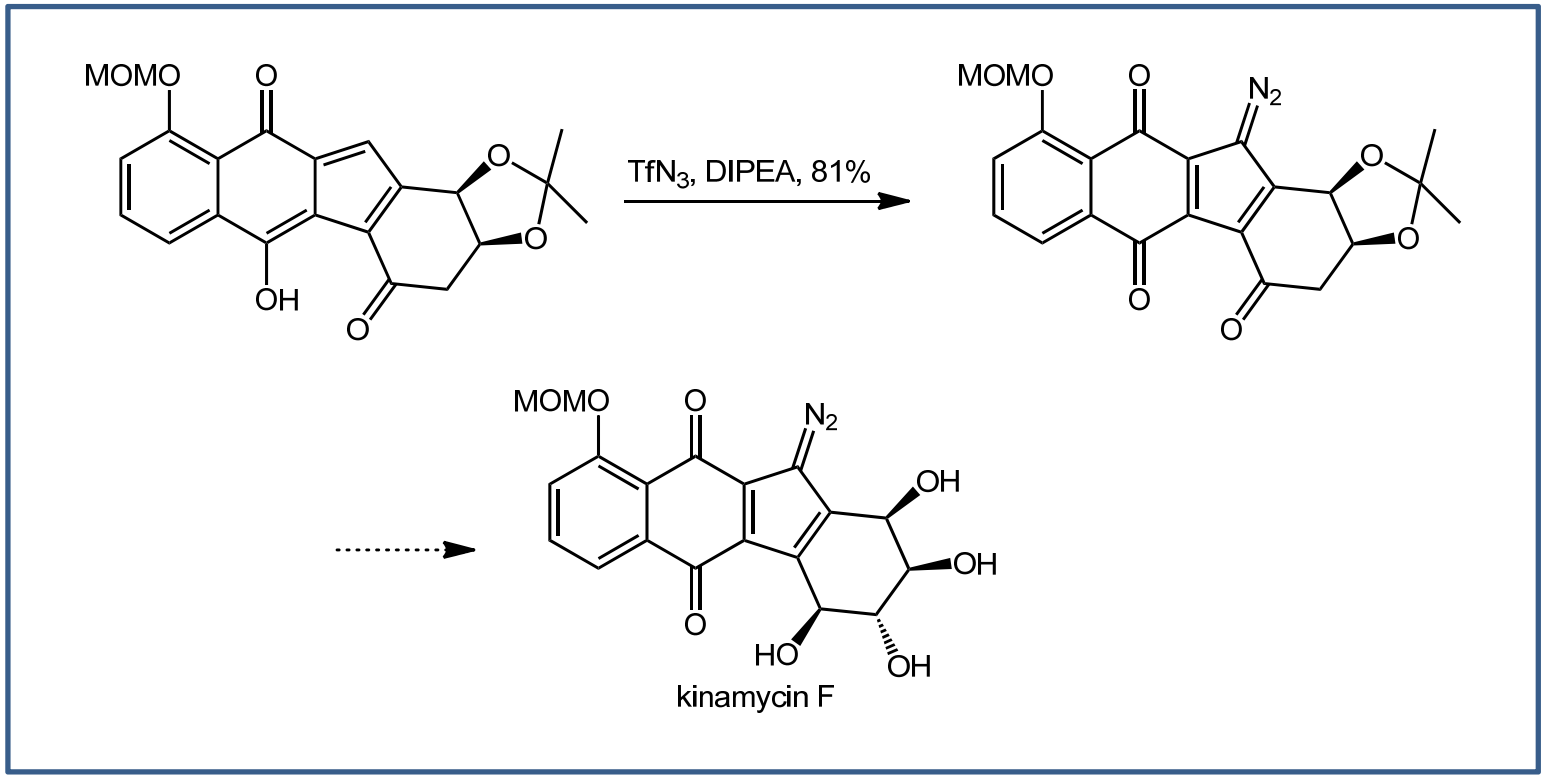
Wilson, P. D. *et al*. *Heterocycles*, **2004**, *62*, 445.



paecilospirone

Pettus, T. R. R. *et al*. *Org. Lett*. **2008**, *10*, 1477.

The application of *o*-quinone methide intermediates in total synthesis



Herzon, S. B. *et al*. *J. Am. Chem. Soc*. **2010**, *132*, 2540.

(+)-Cytosporolides A−C were isolated by Che and co-workers in 2010 from the fungus *Cytospora* sp., which was found in a soil sample collected on the Qinghai-Tibetan plateau at high altitude. These compounds showed antimicrobial activity against the Gram-positive bacteria *Staphylococcus aureus* and *Streptococcus pneumoniae*. Based on NMR experiments, the structure of (+)-cytosporolide A was originally assigned as **1**, which features an unusual peroxylactone skeleton. The absolute stereochemistry was determined by a combination of NOESY data and CD spectra. Later, a structural revision of this natural product was suggested by Spence and George after they re-evaluated the NMR data. Revised structure **2** consists of a complicated pentacyclic ring system containing an oxygenated caryophyllene skeleton connected to a substituted isochroman ring. A biogenetic study indicated that (+)-cytosporolide A (**2**) is derived from a hetero-Diels−Alder reaction between (−)-fuscoatrol A (**3**) and *o*-quinone methide intermediate **5** generated from (+)-CJ-12,373 (**4**). Putative precursor **3** is a known caryophyllene sesquiterpenoid isolated from the marine fungus *Humicola fuscoatra*, and was also isolated along with cytosporolides from *Cytospora* sp. Its structure has been established by X-ray diffraction data and NMR spectroscopy. The other precursor, isochroman carboxylic acid **4**, has been previously isolated from *Penicillium* sp. as a topoisomerase II inhibitor. These known compounds could be coupled to create the intricate structure of cytosporolides in nature.

In summary, we have completed the first total synthesis of (+)-cytosporolide A (**2**) by using the putative biosynthetic hetero-Diels−Alder reaction between (−)-fuscoatrol A (**3**) and the *o*-quinone methide generated from (+)-CJ-12,373 (**4**). To achieve this goal, we synthesized (−)-fuscoatrol A (**3**) from synthetic intermediate **10** in our previous total synthesis of (+)-pestalotiopsin A (**12**). Furthermore, (+)-CJ-12,373 (**4**) was synthesized through a Kolbe−Schmitt reaction and an oxa-Pictet−Spengler reaction starting with aryl derivative **18** and chiral epoxide **19**. The hetero-Diels−Alder reaction of diprotected **32** and *o*-quinone methide precursor **4** or **22** showed complete chemo-, regio-, and stereoselectivity to produce cycloadduct **33** as a single isomer. In this reaction, protection of the two hydroxy groups in fuscoatrol A was required. Instead of this, enzymes or other substances may contribute to the assembly of the cytosporolide skeleton in nature. Our total synthesis has validated the biogenetic hypothesis and established the structure of cytosporolide A.