Total Synthesis of Myceliothermophins C, D, and E

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Checker : Zhang-Pei Chen

Date: 11/11/2014

Nicolaou, K. C. *et al.*
Angew. Chem. Int. Ed. **2014**, *53*, 10970.

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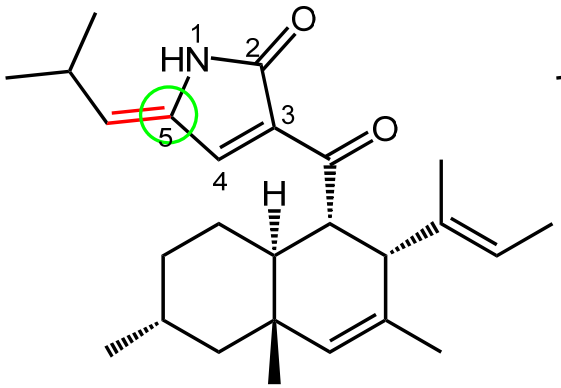
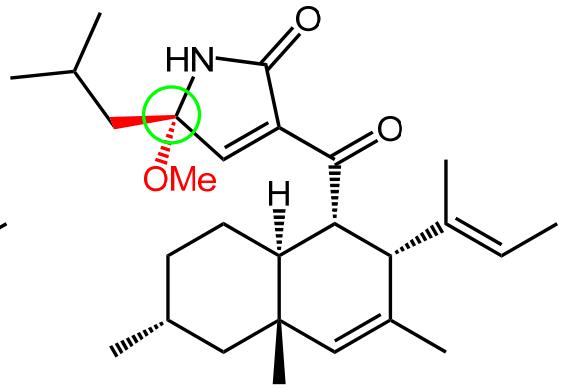
Introduction

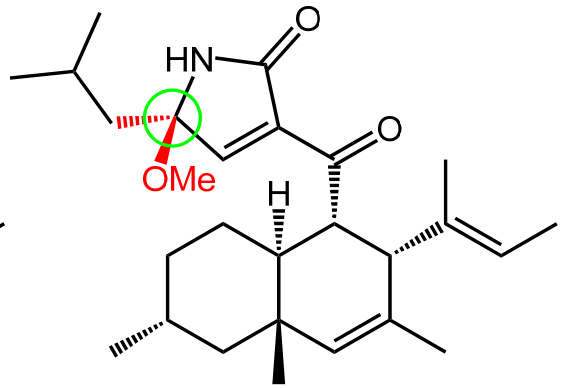
共同点： 3-吡咯啉-2-酮 + 反式十氢萘结构



1: Myceliothermophin E



2: Myceliothermophin C



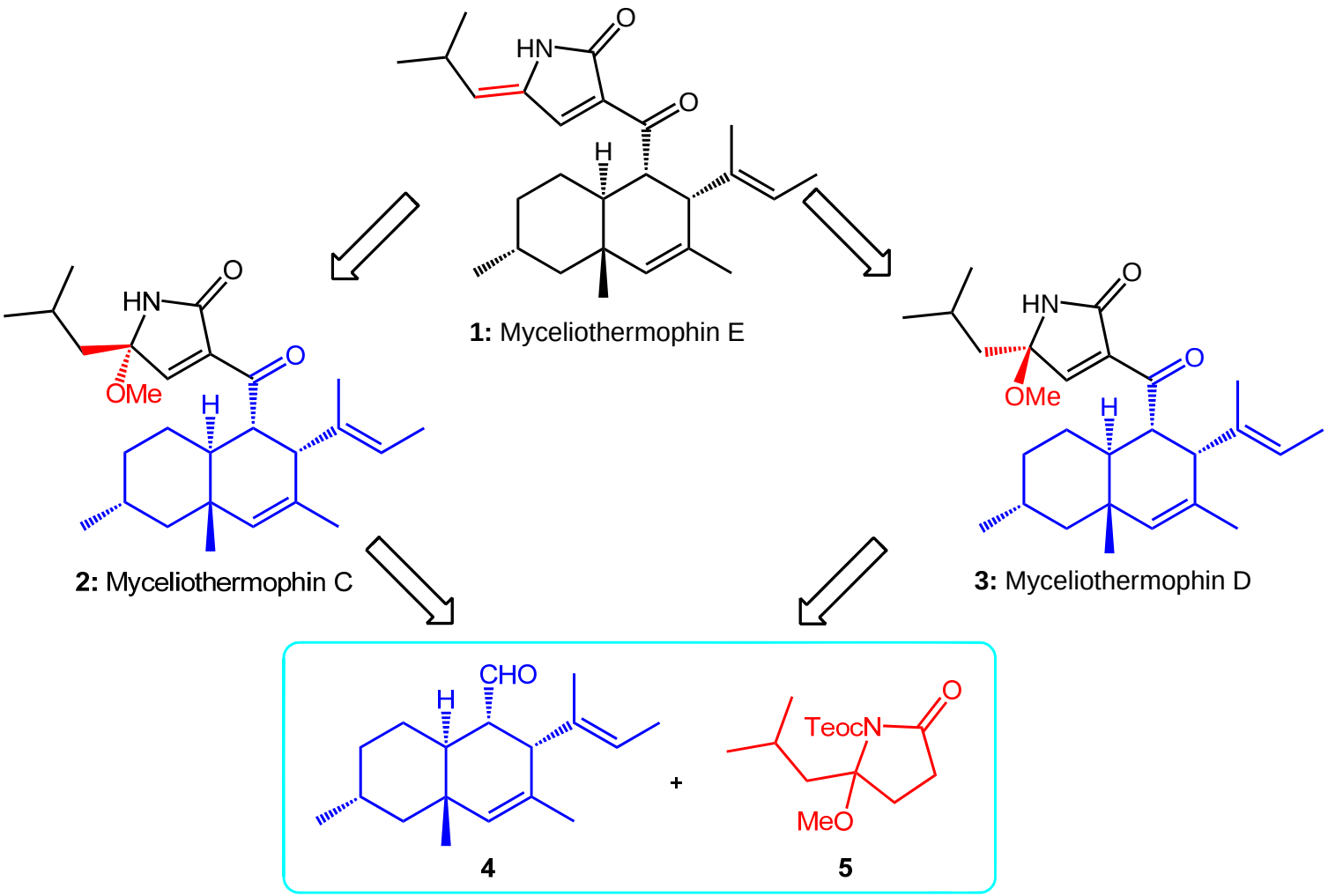
3: Myceliothermophin D

4个双键，5个手性中心

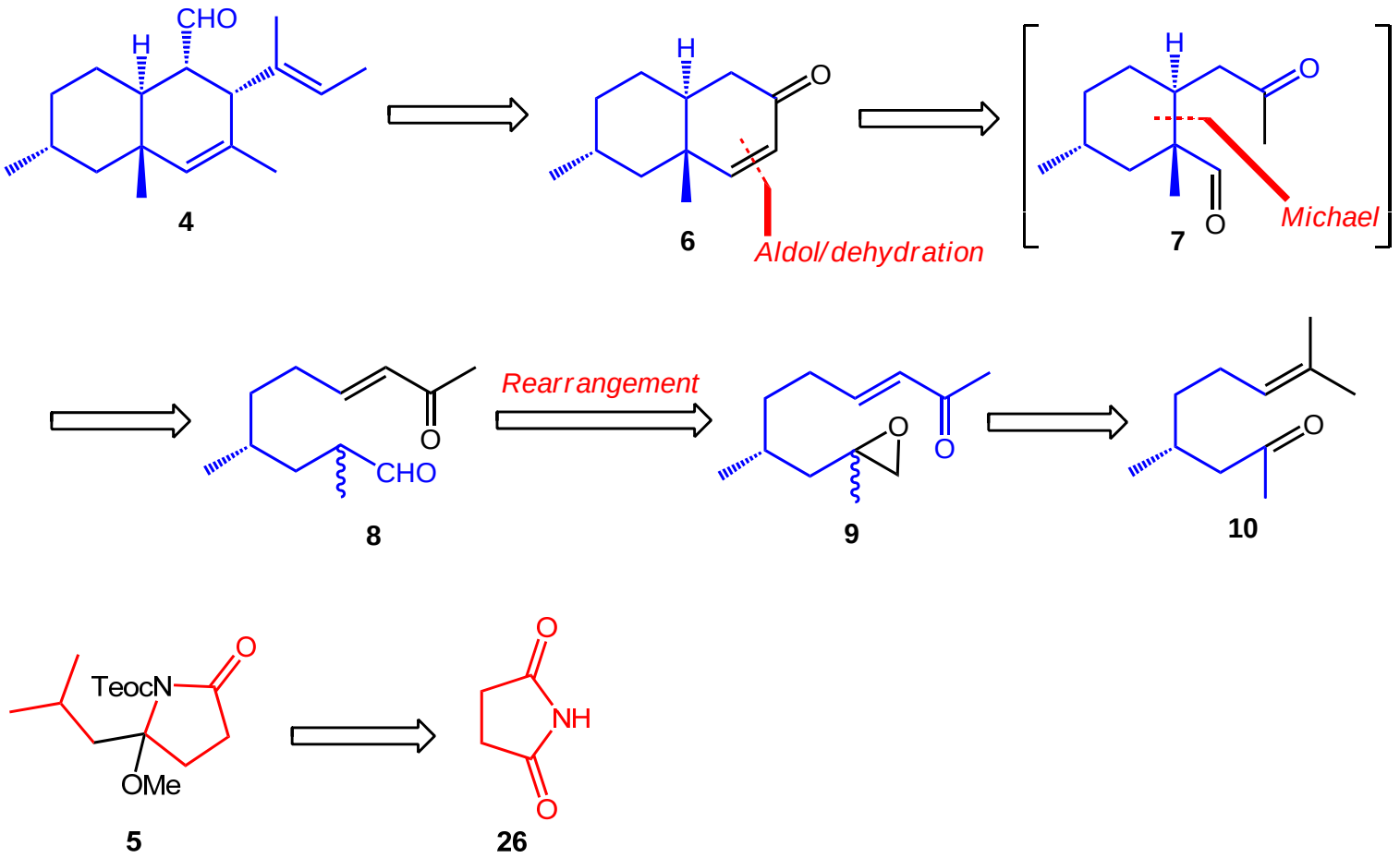
3个双键，6个手性中心

- Isolated from Myceliophthora thermophila
- Against many human cancer cell lines, for example hepatoblastoma, hepatocellular carcinoma, lung carcinoma, and breast adenocarcinoma.

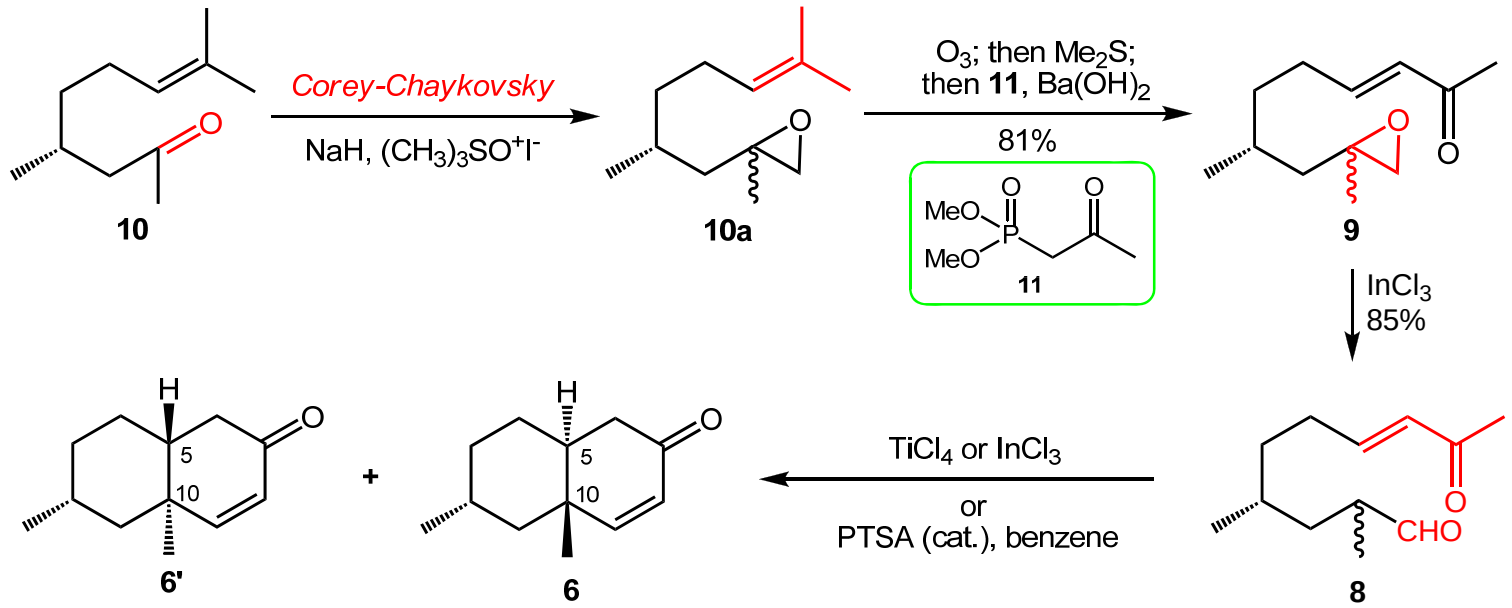
Retrosynthetic analysis

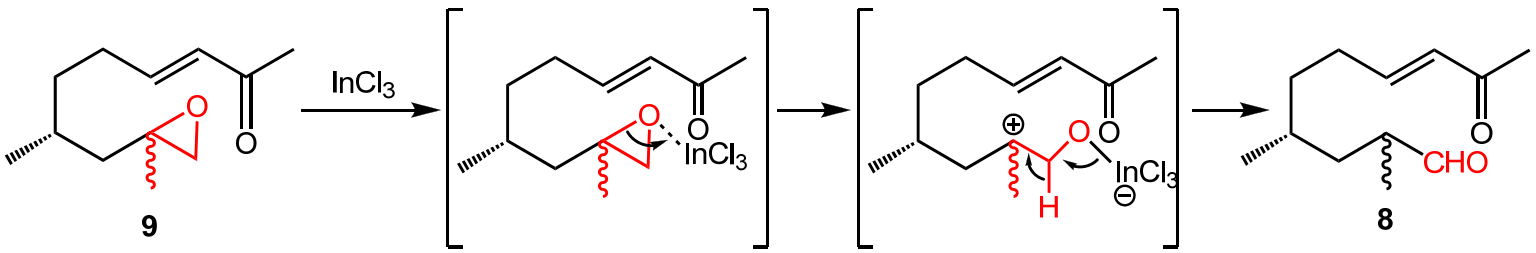


Retrosynthetic analysis



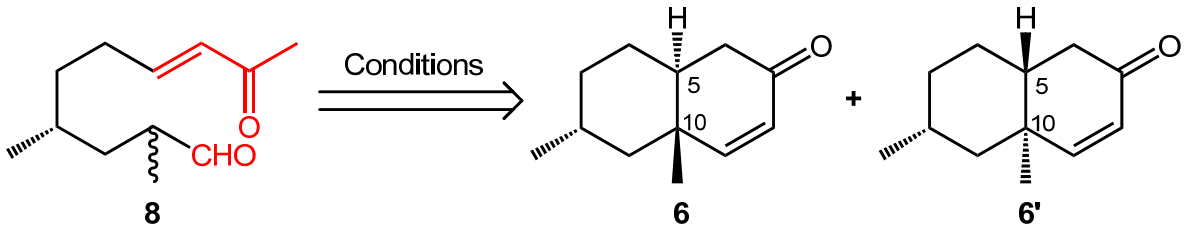
Synthesis of 6





Ranu, B. C. *et al. J. Org. Chem.***1998**,*63*, 8212

Synthesis of 6

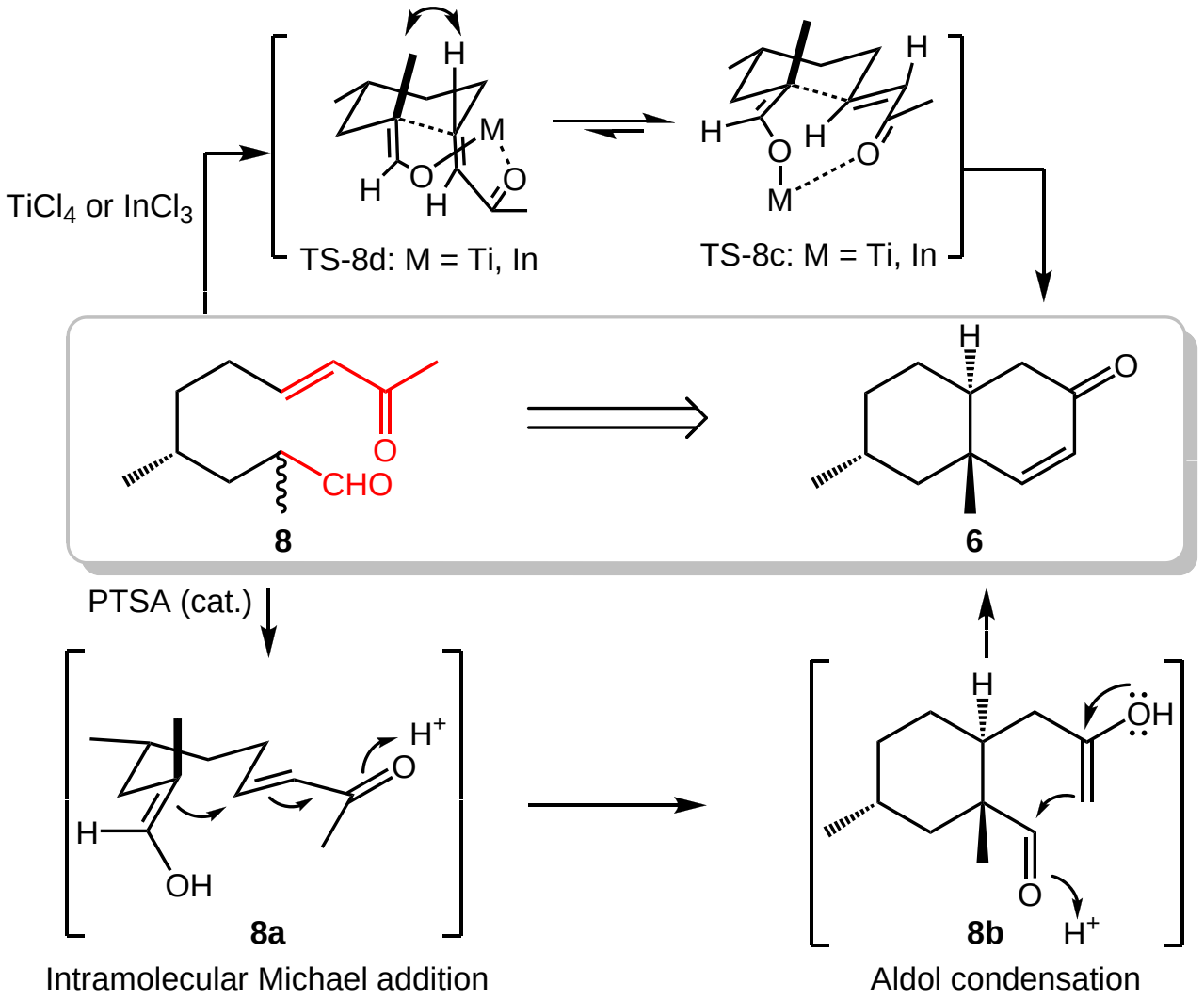


8 **6** **6'**

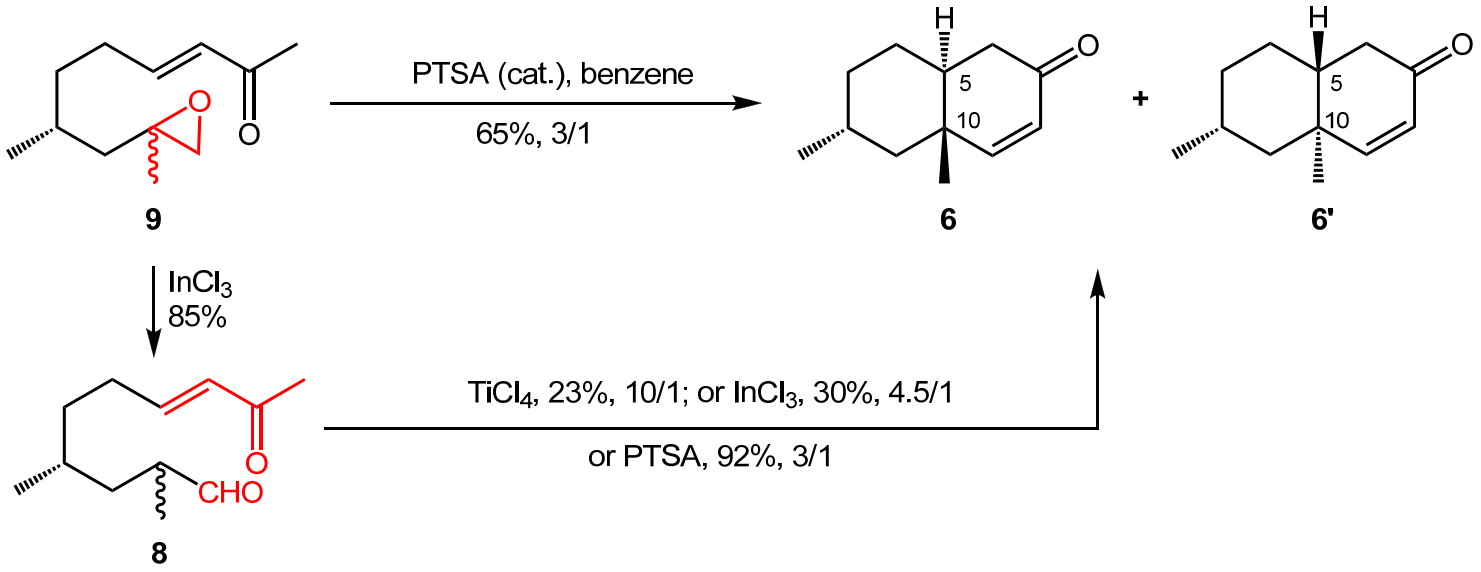
Entry	Conditions	t [h]	T [°C]	Yield [%] (**6** + **6'**)	d.r.[a]
1	NaOMe, MeOH	2	25	decomp.	--
2	Proline, DMSO	24	25	n.r.	--
3	$Zr(OiPr)_4$, CH_2Cl_2	24	25	n.r.	--
4	1.0 M HCl/Et_2O, THF	72	25	35	3:1
5	$TiCl_4$, 4 Å M.S., CH_2Cl_2	72	25	23	10:1
6	$InCl_3$, C_6H_6	5	45	30	4.5:1
7	**PTSA, C_6H_6**	**5**	**reflux**	**92**	**3:1**

[a] Diastereomeric ratio (C5 or C10 epimer; **6**: major isomer).

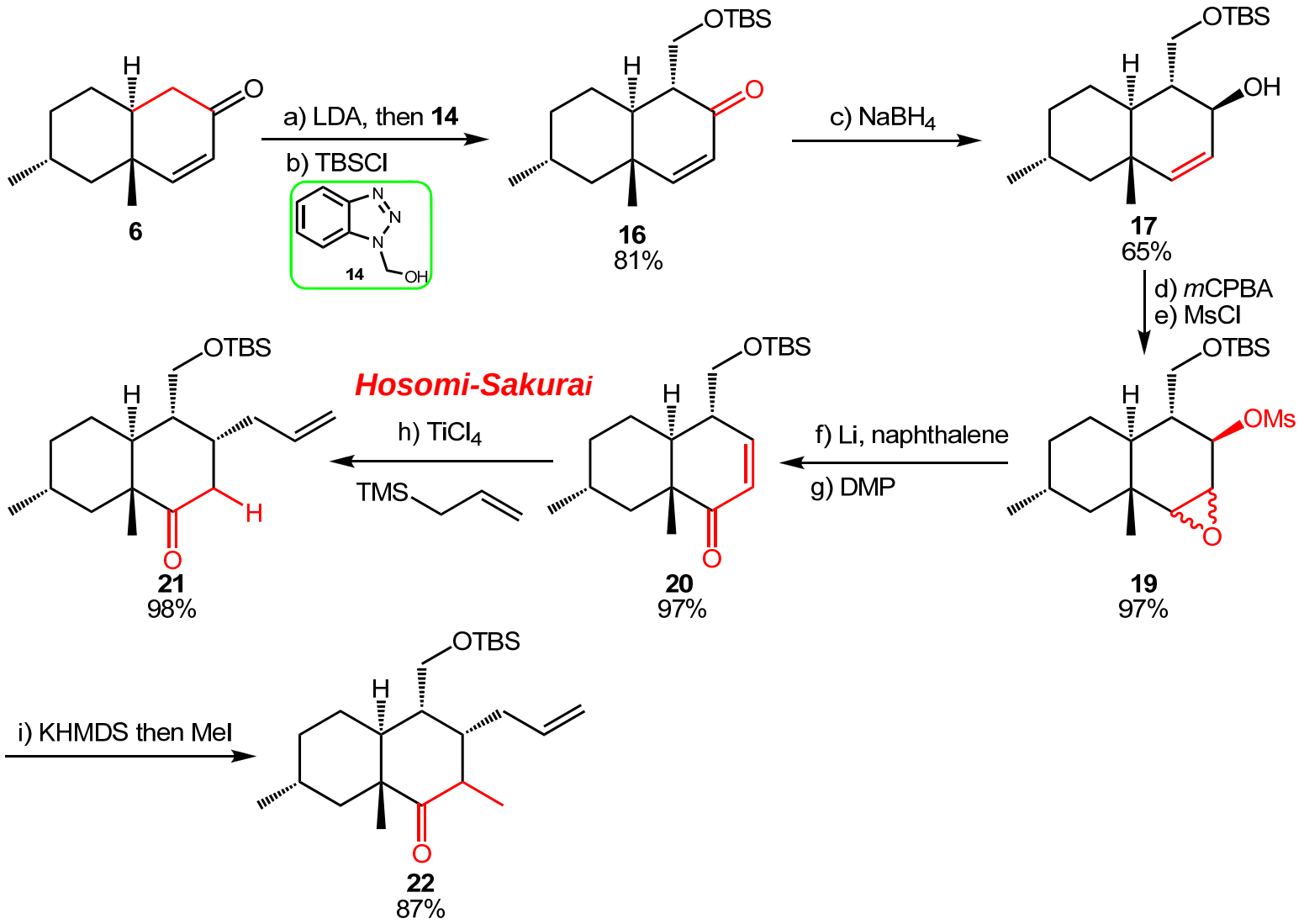
Synthesis of 6



Synthesis of 6

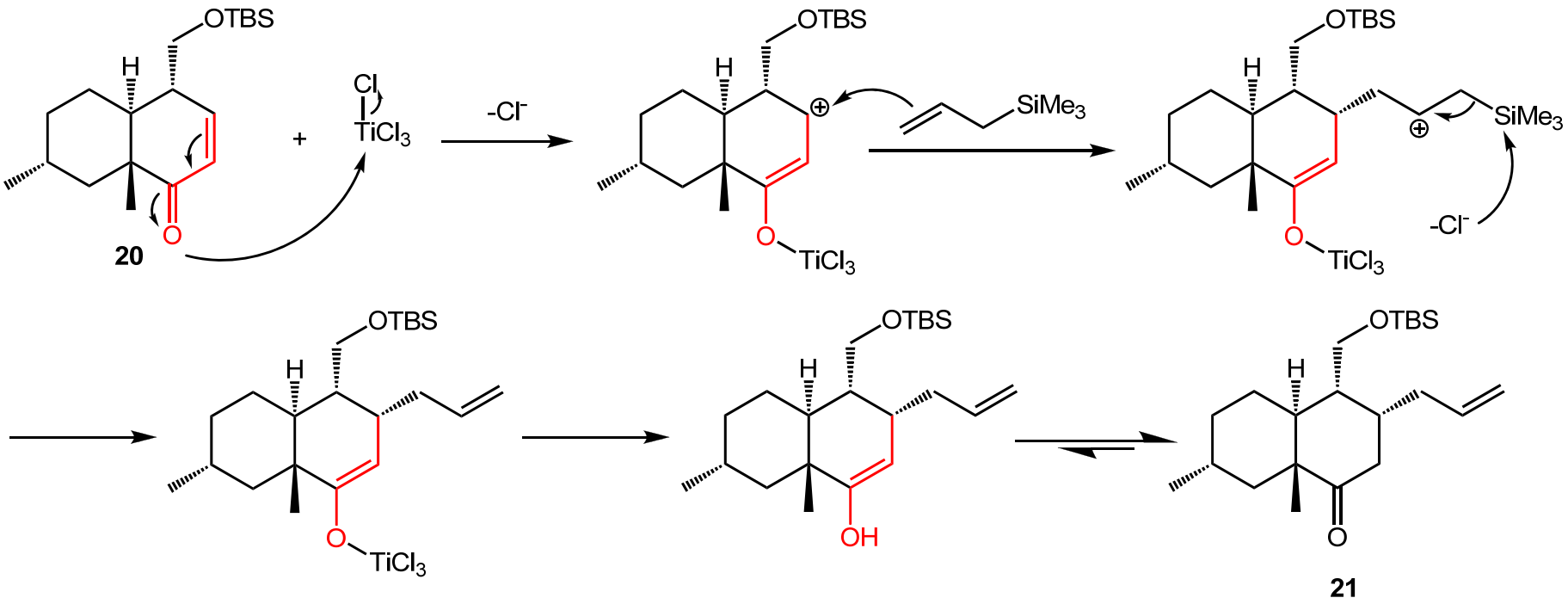


Synthesis of 4

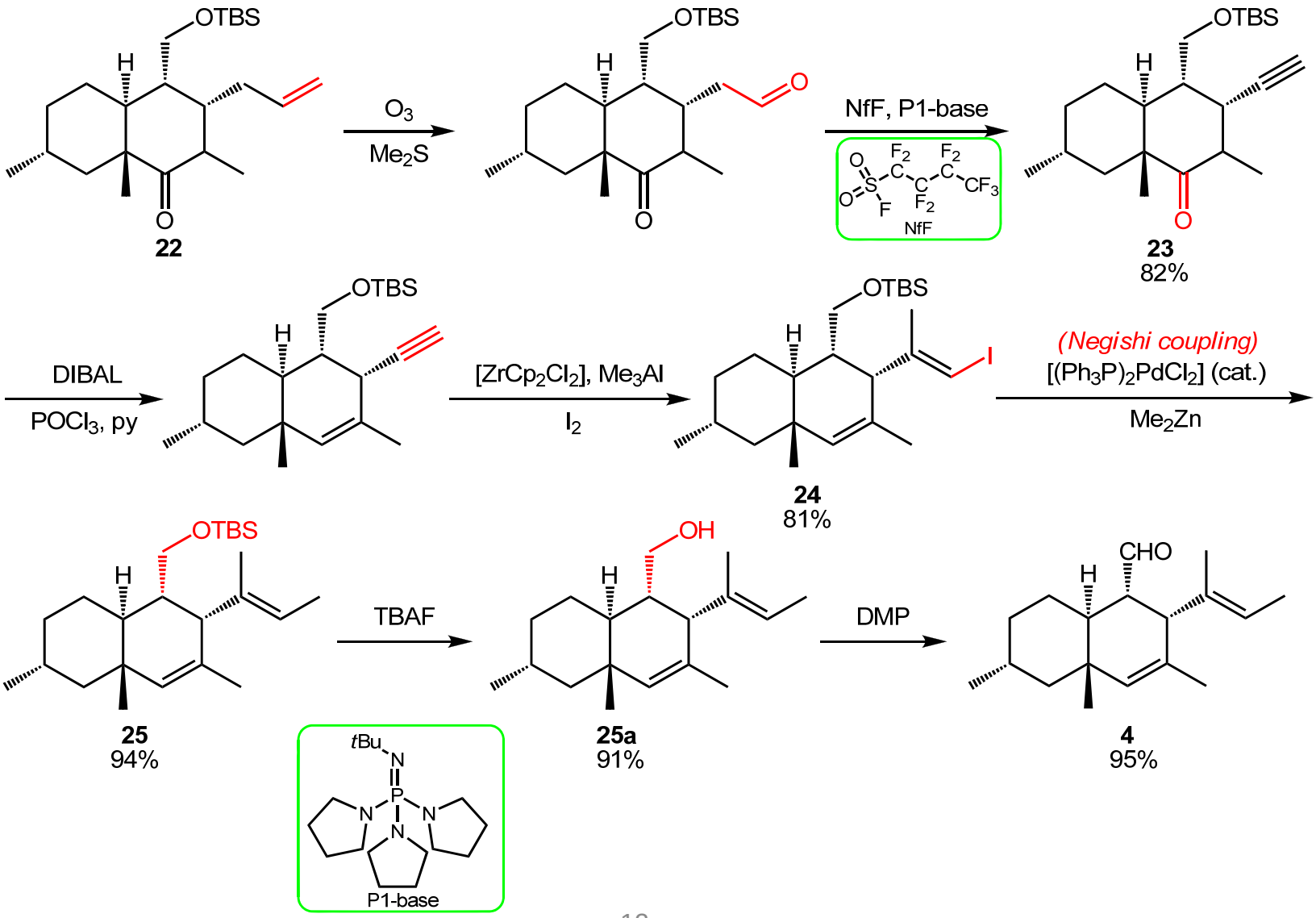


Synthesis of 4

Hosomi-Sakurai Reaction



Synthesis of 4



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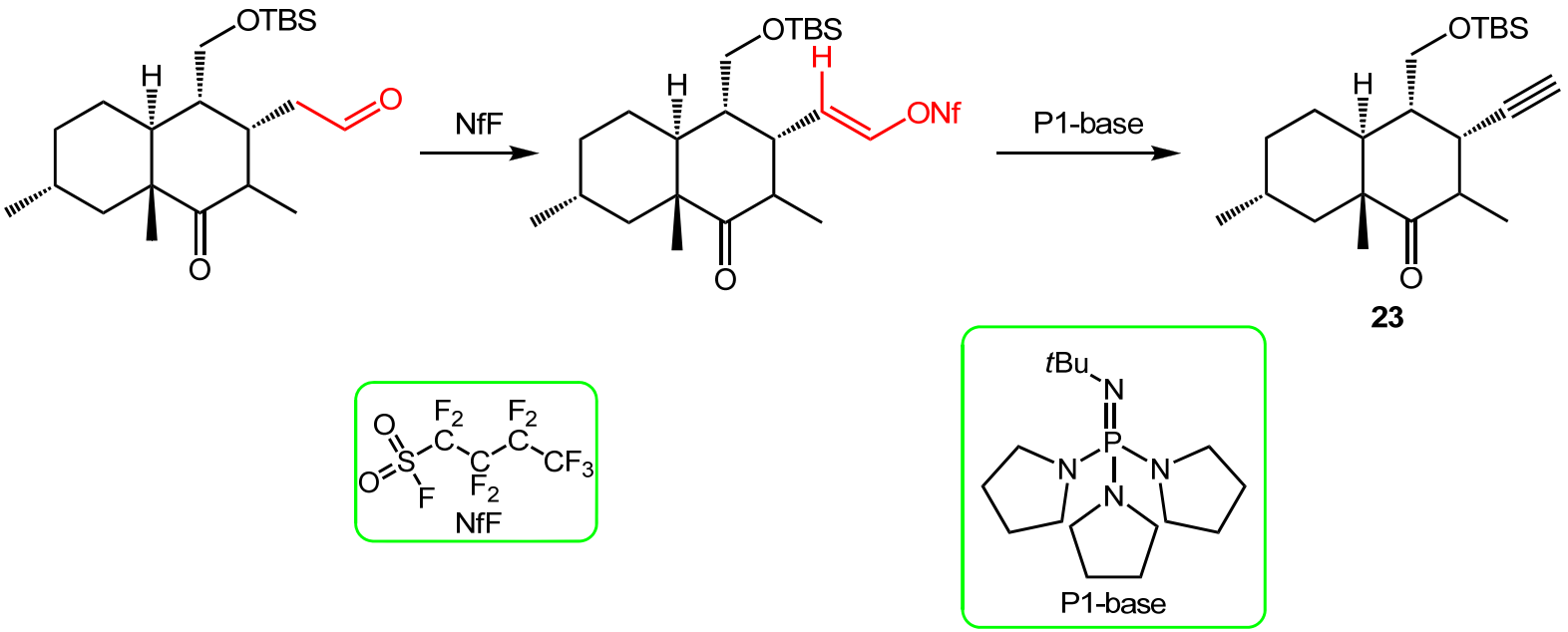
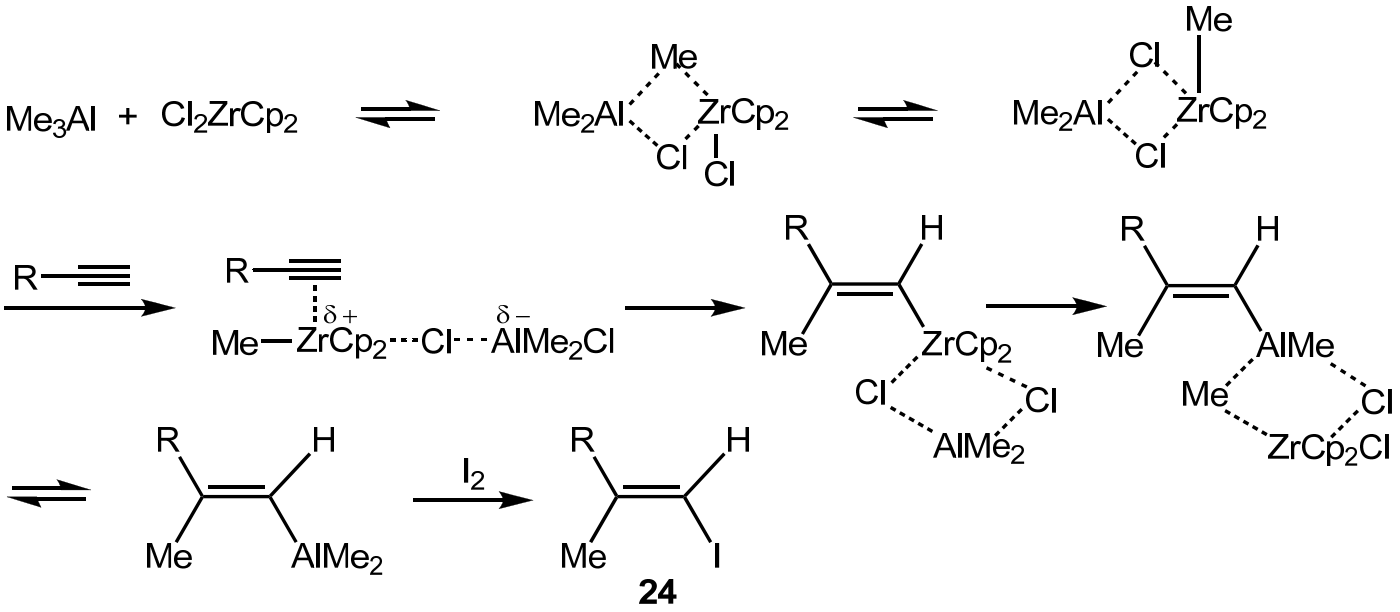
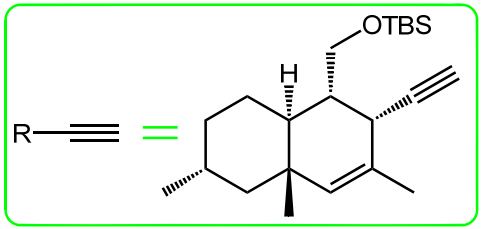


Lyapkalo, I. M. *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 4019

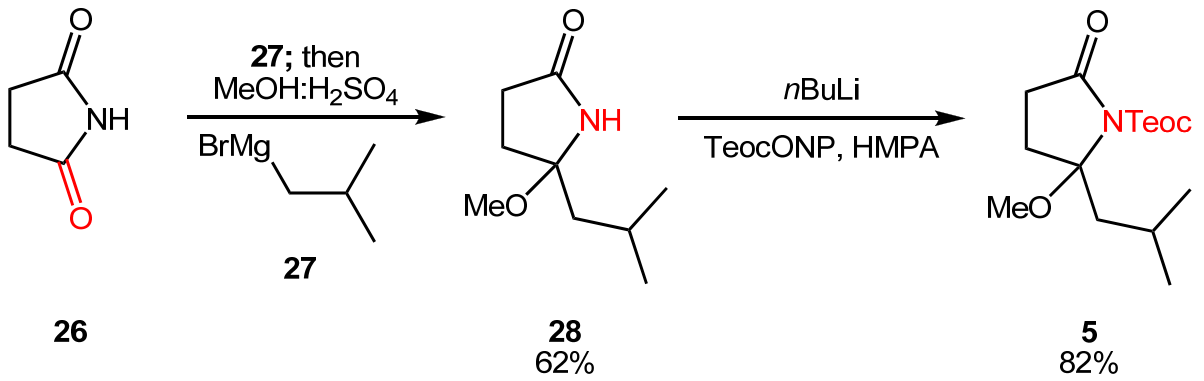
Synthesis of 4



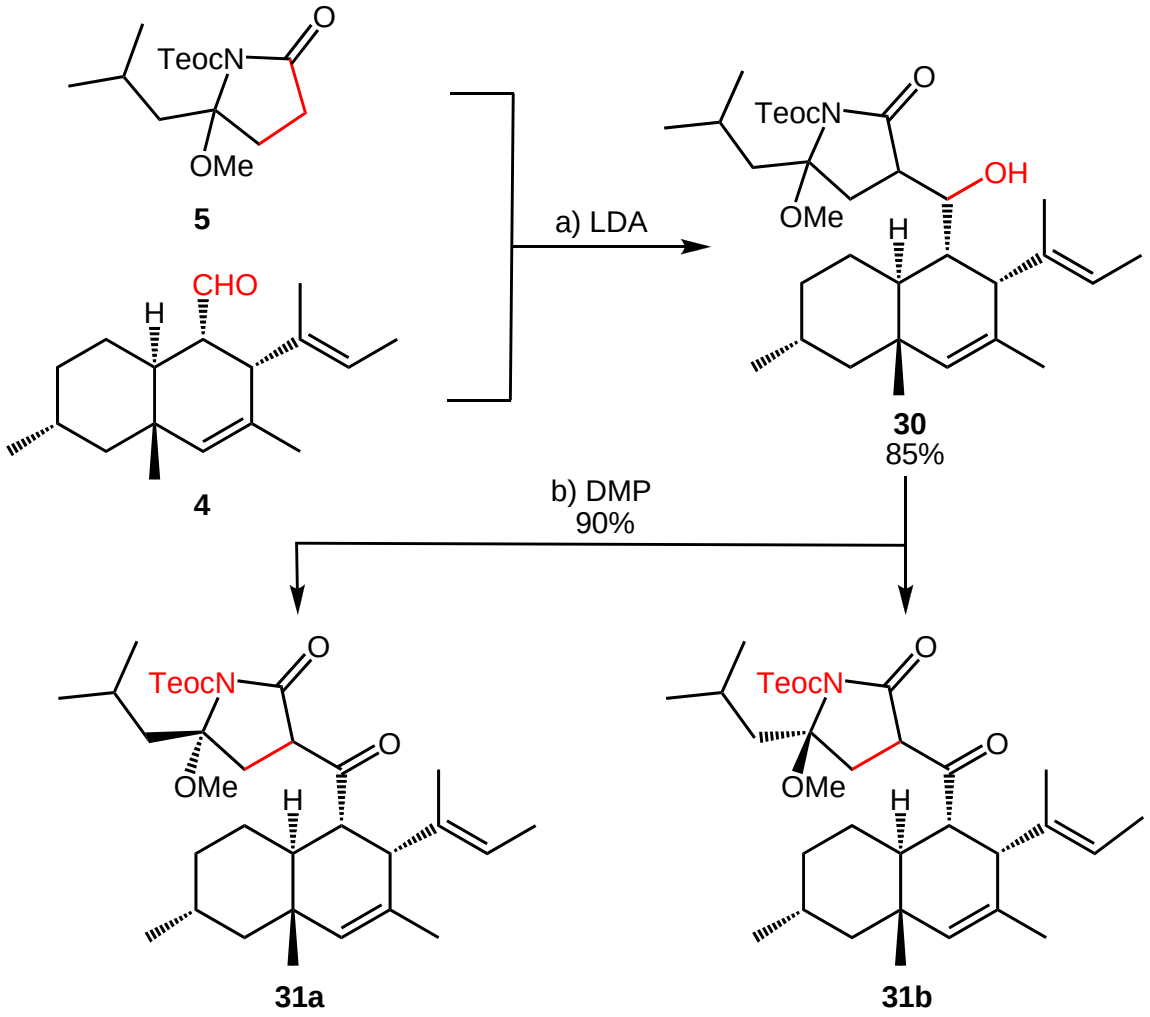


Negish, E. *et al. J. Am. Chem. Soc*. **1985**, *107*, 6639.

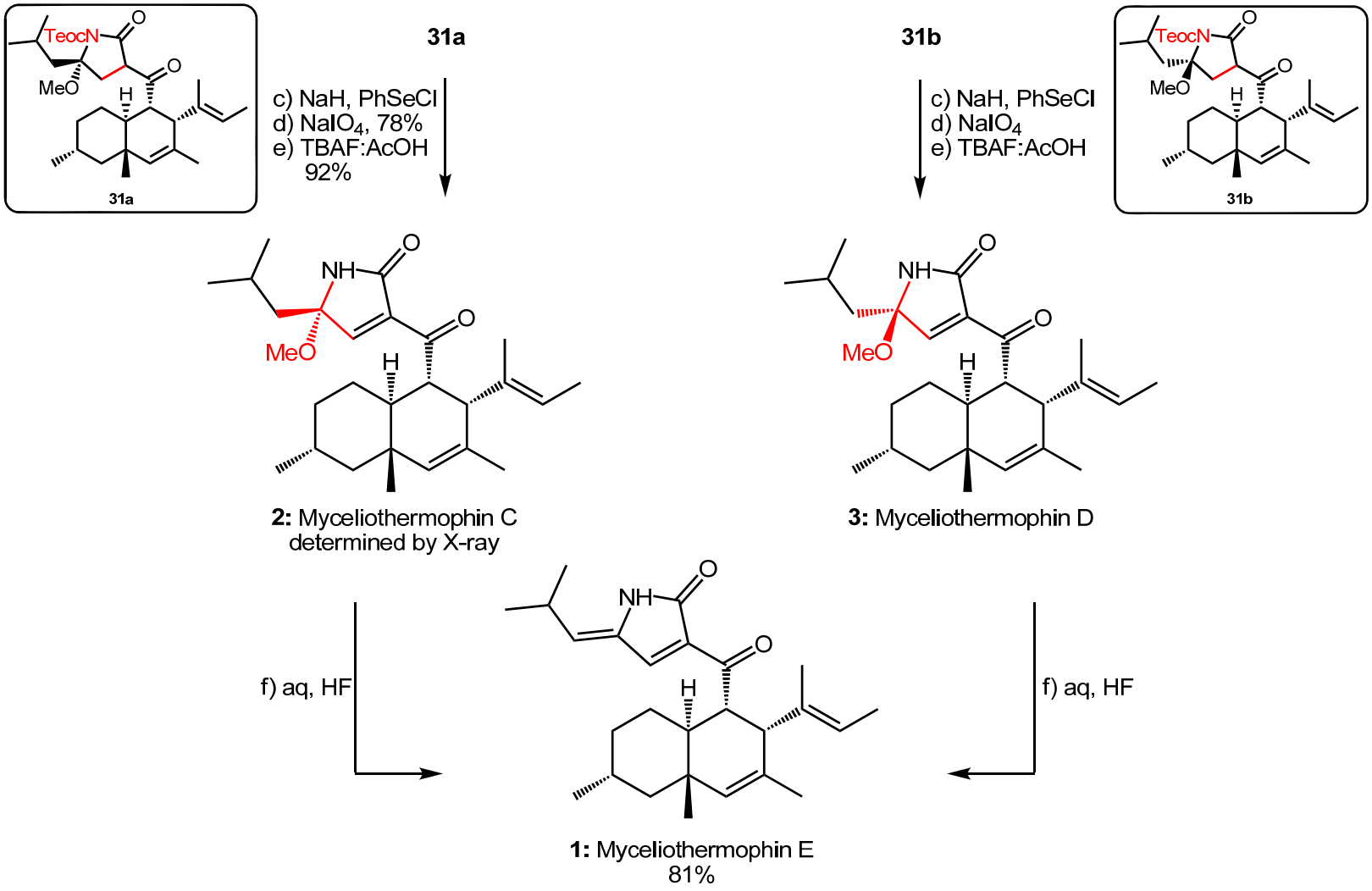
Synthesis of 5



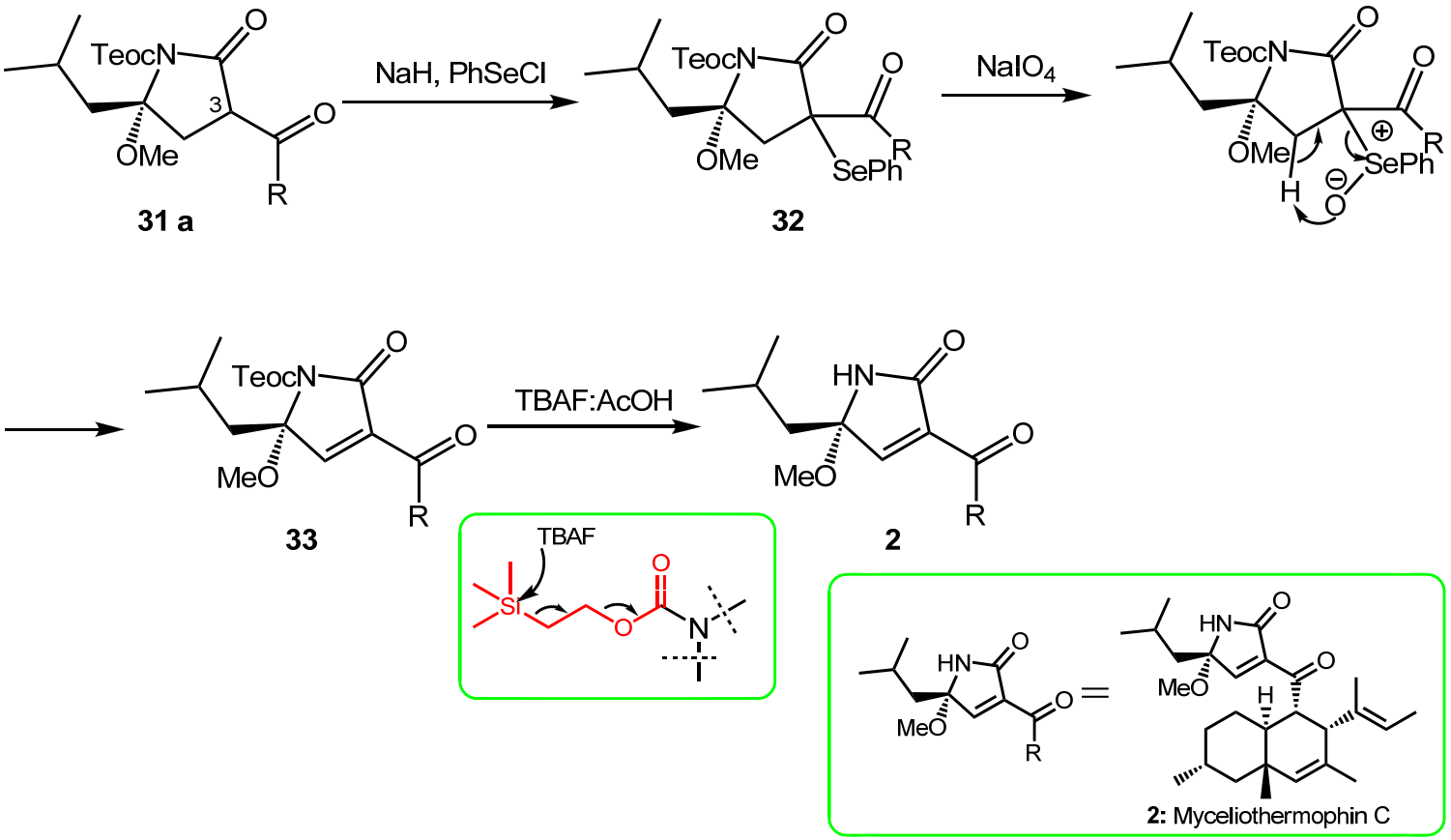
Synthesis of 1, 2 and 3



Synthesis of 1, 2 and 3



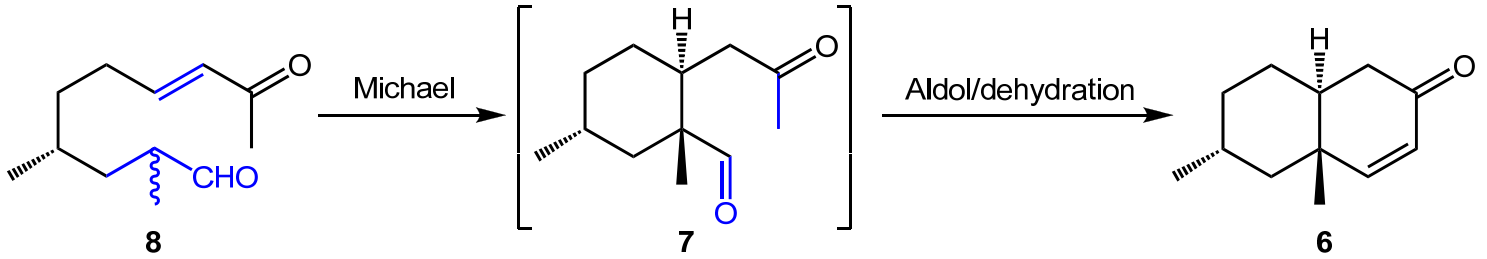
Synthesis of 1, 2 and 3



Sharpless, K. B. *et al*. *J. Am. Chem. Soc*. **1973**, *95*, 6137

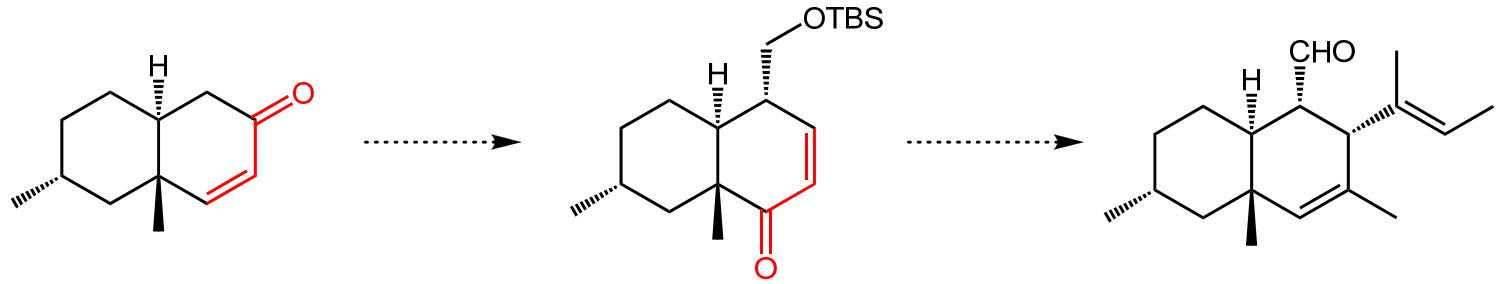
Summary

- **Robinson-type annulation**



8 7 6

- **1,3-Transposition of the enone moiety**



6 20 4

Natural products containing a tetramic acid structural motif are of interest because of their often unusual and challenging structures and wide range of biological activities. Isolated from Myceliophthora thermophila, myceliothermophins E (1), C (2), and D (3) exhibit potent cytotoxic properties against a number of human cancer cell lines, namely hepatoblastoma, hepatocellular carcinoma, lung carcinoma, and breast adenocarcinoma. Total syntheses of these compounds and their siblings myceliothermophins A and B have been achieved through a strategy involving an intramolecular Diels–Alder process of a polyunsaturated aldehyde for the casting of their trans-fused decalin system. Given the difficulties encountered with the preparation and Diels–Alder reactions of polyunsaturated aldehydes as substrates, we sought an alternative strategy for the construction of the decalin system embedded in these natural products. Herein, we report an efficient total synthesis of 1, 2, and 3 featuring an unusual cascade sequence of reactions for the stereoselective construction of their rare trans-fused decalin system, and confirm unambiguously their structures through X-ray crystallographic analysis of 2.

Involving a rare cascade sequence to construct the trans-fused decalin system of the myceliothermophins, the described chemistry (which can also be applied to an enantioselective process) renders myceliothermophins E (1), C (2), and D (3) readily available for biological investigations. The developed cascade bis(cyclization) for the construction of the trans-fused decalin system provides a practical alternative to the cumbersome Diels–Alder approach, which requires difficult to access polyunsaturated aldehydes as substrates. The developed synthetic technologies may be applied to the construction of related natural products and designed analogues in racemic or enantiomeric forms for further structure activity relationship studies.