Journal Club

Nick Tappin

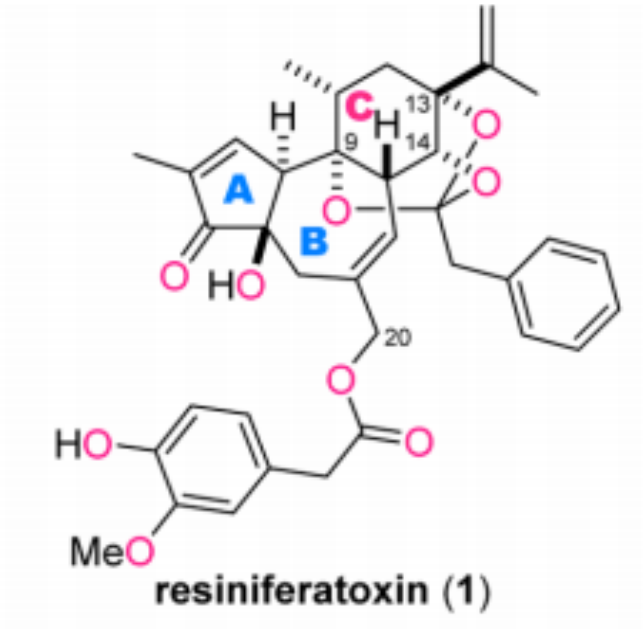
Renaud Group

09 November 2017

Total Synthesis of Resiniferatoxin Enabled by Radical-Mediated Three-Component Coupling and 7-endo Cyclization

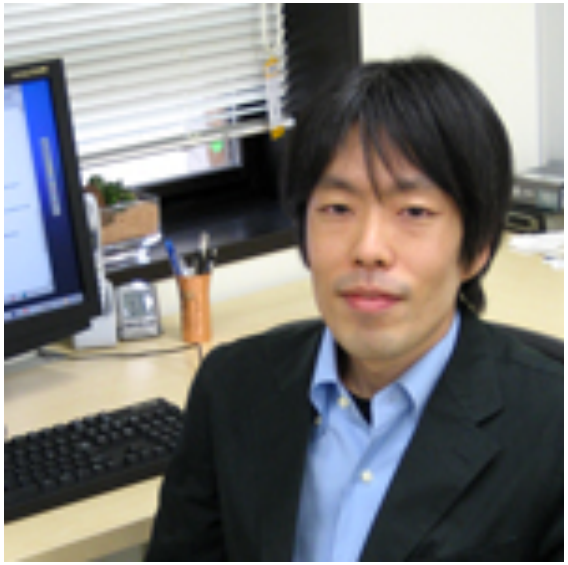
Satoshi Hashimoto, Shun-ichiro Katoh, Takehiro Kato, Daisuke Urabe,† and Masayuki Inoue*

J. Am. Chem. Soc. **2017,** *139* (17), ASAP.
DOI: 10.1021/jacs.7b10177



resiniferatoxin (1)

Masayuki Inoue



- Born 1971, Tokyo, Japan

- **1989-1993: The University of Tokyo**, B.S. in Chemistry,
  1993-1998: The University of Tokyo, Ph.D. in Organic Chemistry,
  Research advisor: Professor Kazuo Tachibana
  1998-2000: Sloan-Kettering Institute for Cancer Research ,Postdoctoral Fellow,
  Research advisor: Professor Samuel J. Danishefsky

- **Tohoku University (2000-2007)**

- **The University of Tokyo (2007** Professor)

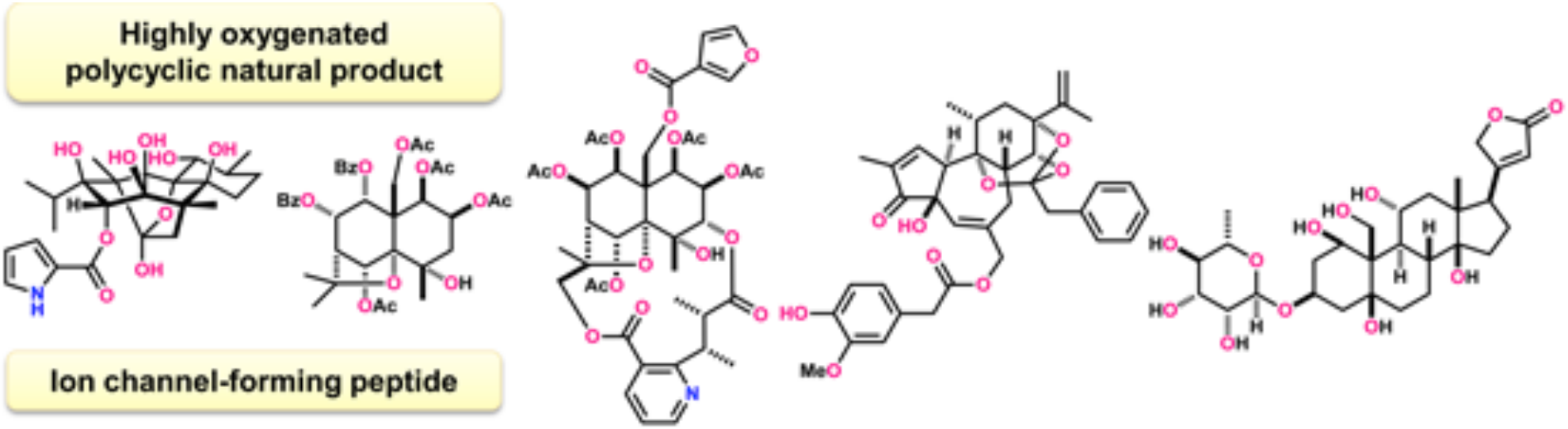
- **Selected Awards:**

2001 Young Scientist's Research Award in Natural Product Chemistry
2007 Novartis Chemistry Lectureship 2008/2009
2009 Fifth JSPS PRIZE
2014 Mukaiyama Award Year 2014
2014 Fellow of the Royal Society of Chemistry

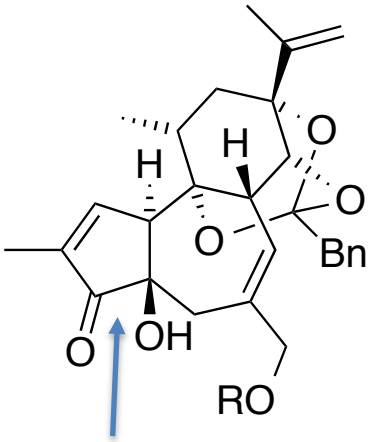
Masayuki Inoue

Research Topics:

1. Development of new synthetic methodologies for total synthesis
2. Total synthesis of highly oxygenated polycyclic natural products
3. Total synthesis and functional analysis of ion channel-forming molecules
4. Total synthesis and functional analysis of antimicrobial molecules
5. Synthesis of new artificial molecules by modification of natural products templates



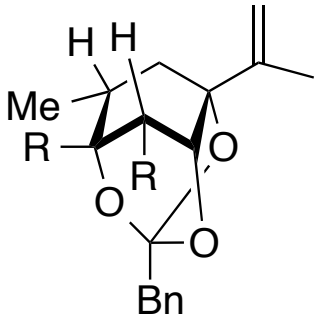
Structural features

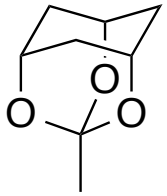


- ortho ester: syn/syn 1,2,4-triol
- 7-membered ring
- fused 7,6-bicycle
- fused 5,7-bicycle
- 7 contiguous stereocentres

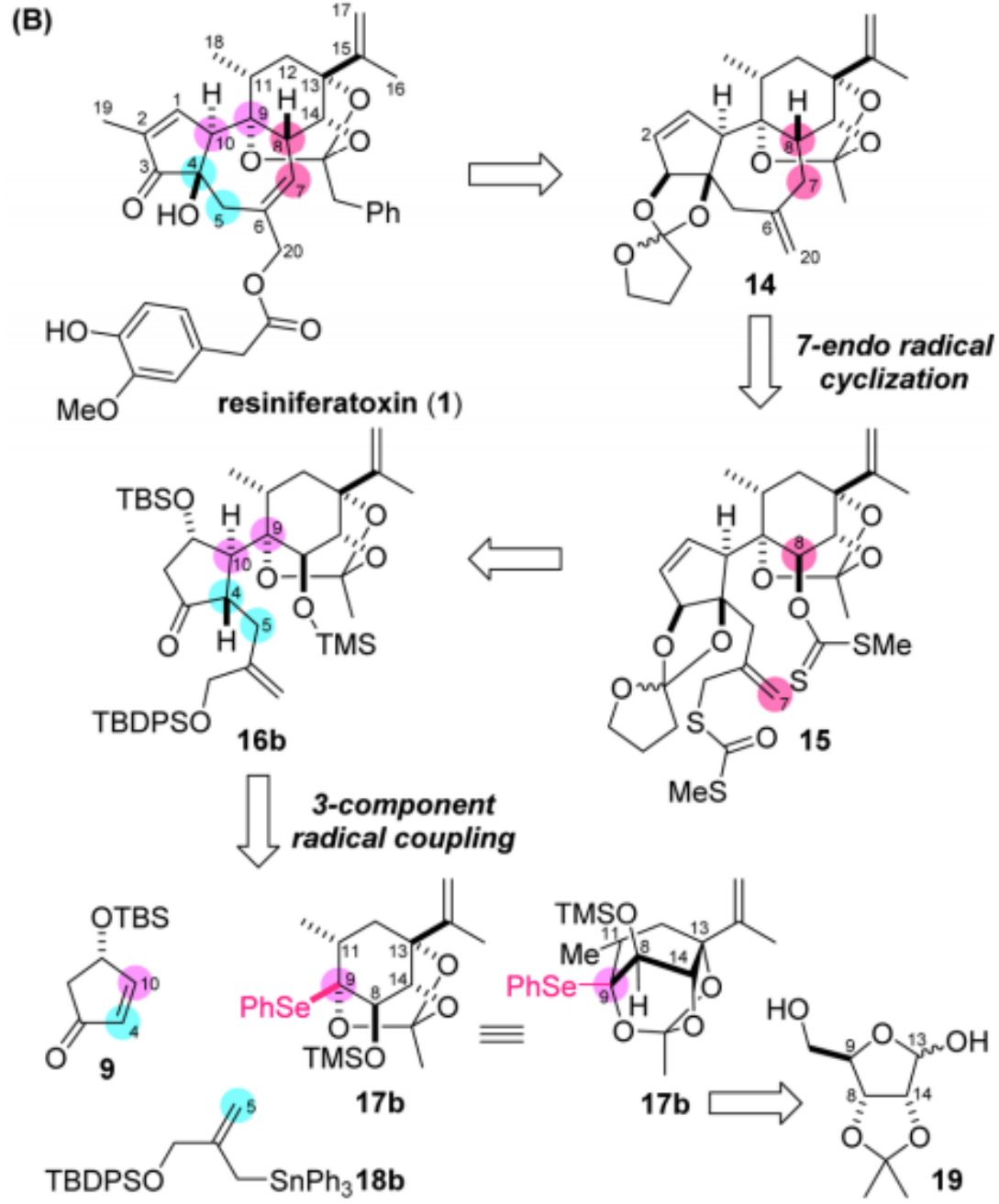
How would you make an a-hydroxy ketone?

ortho ester



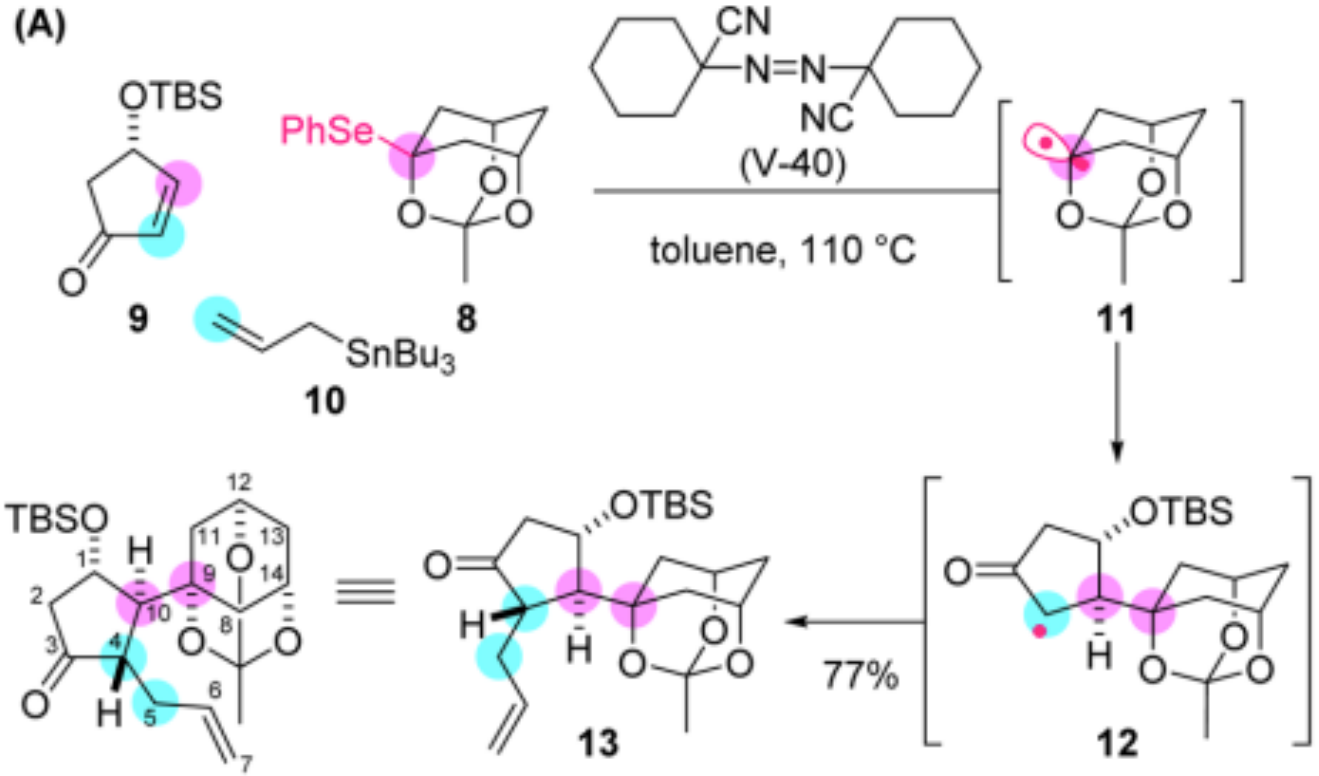


Retrosynthetic analysis



Model study

Scheme 2. (A) Model Study of the Three-Component Radical Coupling Reaction. (B) Synthetic Plan for Resiniferatoxin (1)



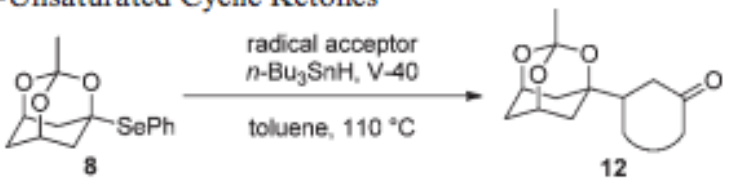
Radicals on bridgeheads: Walton, *Chem. Soc. Rev.* **1992**, 105

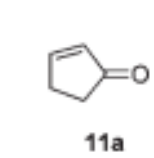
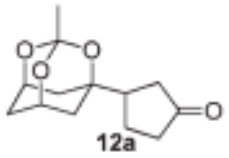
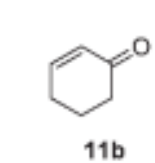
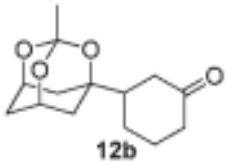
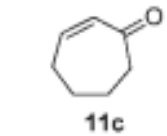
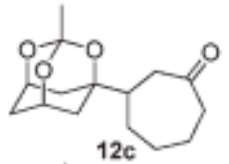
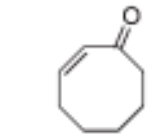
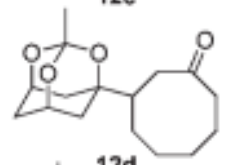
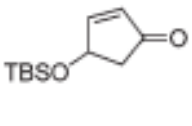
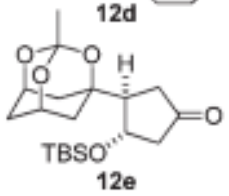
σ-radical (nucleophilic/ high energy SOMO), configurationally stable. Do not undergo b-scission.

Exposed: rest of molecule is 'tied back'

Group precedence

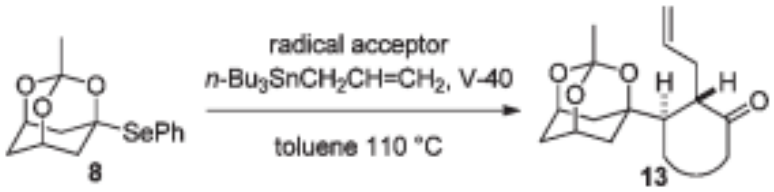
Table 1. Coupling between α-Alkoxy Bridgehead Radical and α,β-Unsaturated Cyclic Ketones[a]

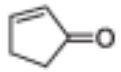
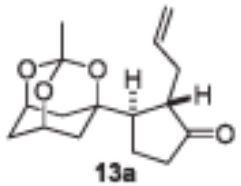
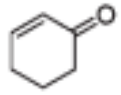
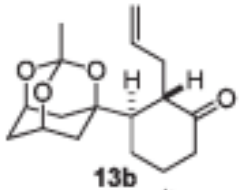
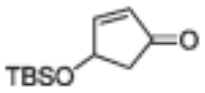
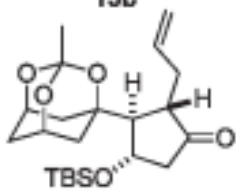


entry	radical acceptor	product	yield
1	 11a	 12a	77%
2	 11b	 12b	56%
3	 11c	 12c	26%
4	 11d	 12d	45%
5	 11e	 12e	65%[b]

[a] Reaction conditions: **8** (1 equiv), **11** (5 equiv), *n*-Bu_3SnH (6 equiv), V-40 (0.4 equiv), toluene (0.02 M), 110 °C. *n*-Bu_3SnH and V-40 (0.2 equiv) were added by syringe pump over 3 h, and the reaction mixture was stirred for additional 1 h. [b] Compound **12e** was obtained as a single diastereoisomer.

Table 2. Three-Component Coupling of α-Alkoxy Bridgehead Radical[a]



entry	radical acceptor	product	yield
1	 11a	 13a	75%[b]
2	 11b	 13b	32%[b,c]
3	 11e	 13e	77%[b]

[a] Reaction conditions: **8** (1 equiv), **11** (5 equiv), *n*-$Bu_3SnCH_2CH{=}CH_2$ (6 equiv), V-40 (0.4 equiv), toluene (0.2 M), 110 °C, 8 h. [b] Compounds **13a,b,e** were obtained as single diastereoisomers. [c] Compoud **8** was recovered in 15% yield.

OL **2011**, *13*, 4778

Group precedence

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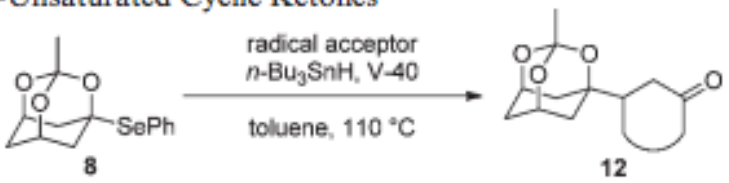
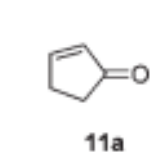
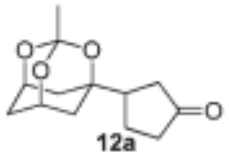
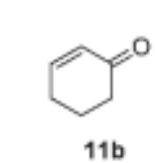
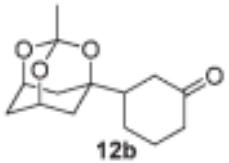
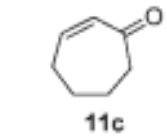
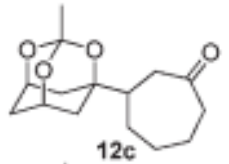
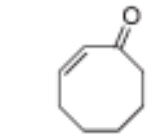
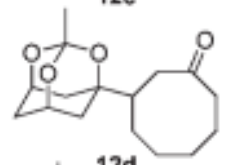
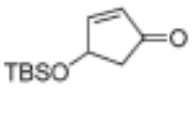
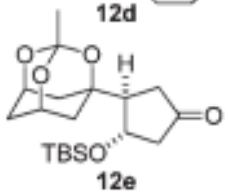
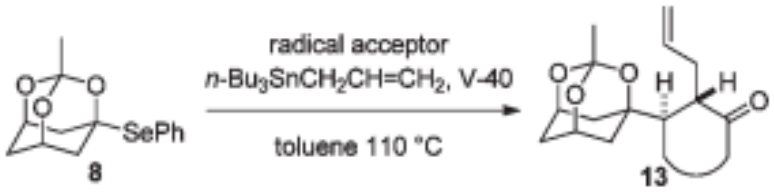
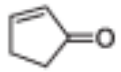
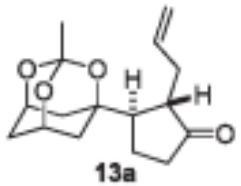
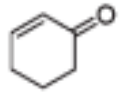
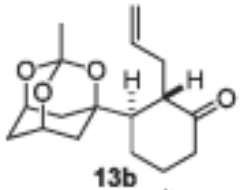
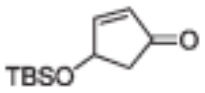
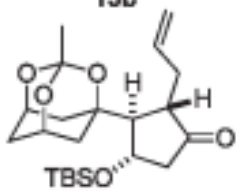


entry	radical acceptor	product	yield
1	 11a	 12a	77%
2	 11b	 12b	56%
3	 11c	 12c	26%
4	 11d	 12d	45%
5	 11e	 12e	65%[b]

[a] Reaction conditions: **8** (1 equiv), **11** (5 equiv), *n*-Bu_3SnH (6 equiv), V-40 (0.4 equiv), toluene (0.02 M), 110 °C. *n*-Bu_3SnH and V-40 (0.2 equiv) were added by syringe pump over 3 h, and the reaction mixture was stirred for additional 1 h. [b] Compound **12e** was obtained as a single diastereoisomer.

Table 2. Three-Component Coupling of α-Alkoxy Bridgehead Radical[a]

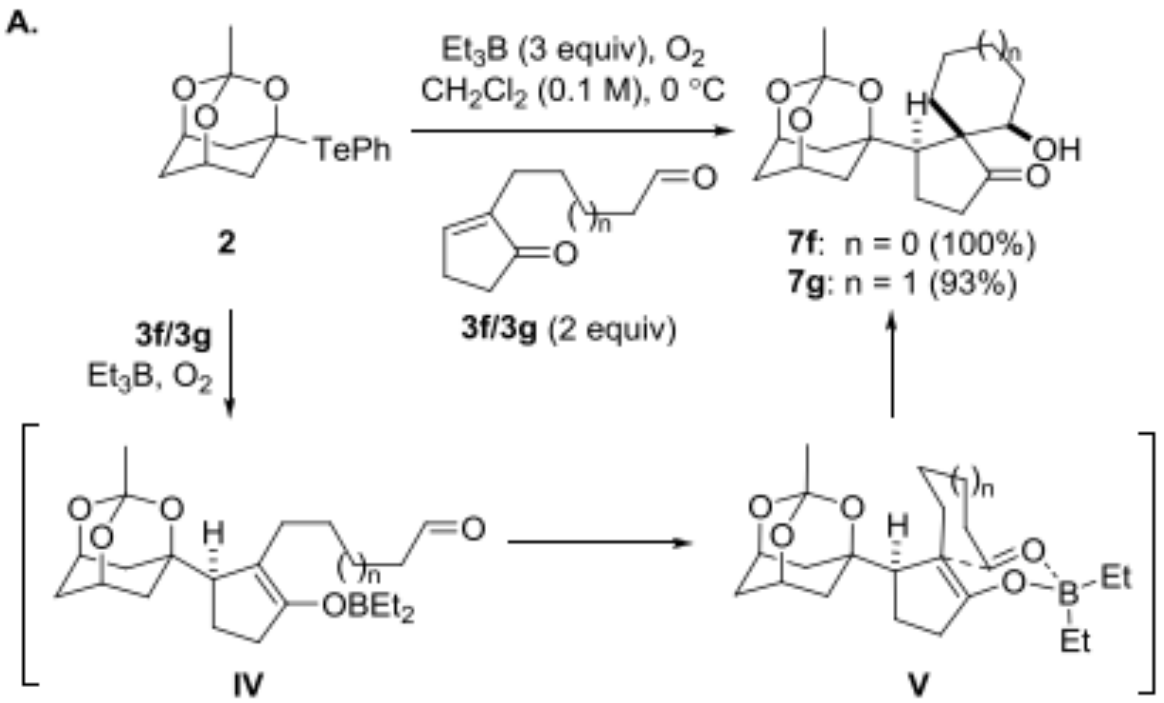


entry	radical acceptor	product	yield
1	 11a	 13a	75%[b]
2	 11b	 13b	32%[b,c]
3	 11e	 13e	77%[b]

[a] Reaction conditions: **8** (1 equiv), **11** (5 equiv), *n*-$Bu_3SnCH_2CH{=}CH_2$ (6 equiv), V-40 (0.4 equiv), toluene (0.2 M), 110 °C, 8 h. [b] Compounds **13a,b,e** were obtained as single diastereoisomers. [c] Compoud **8** was recovered in 15% yield.

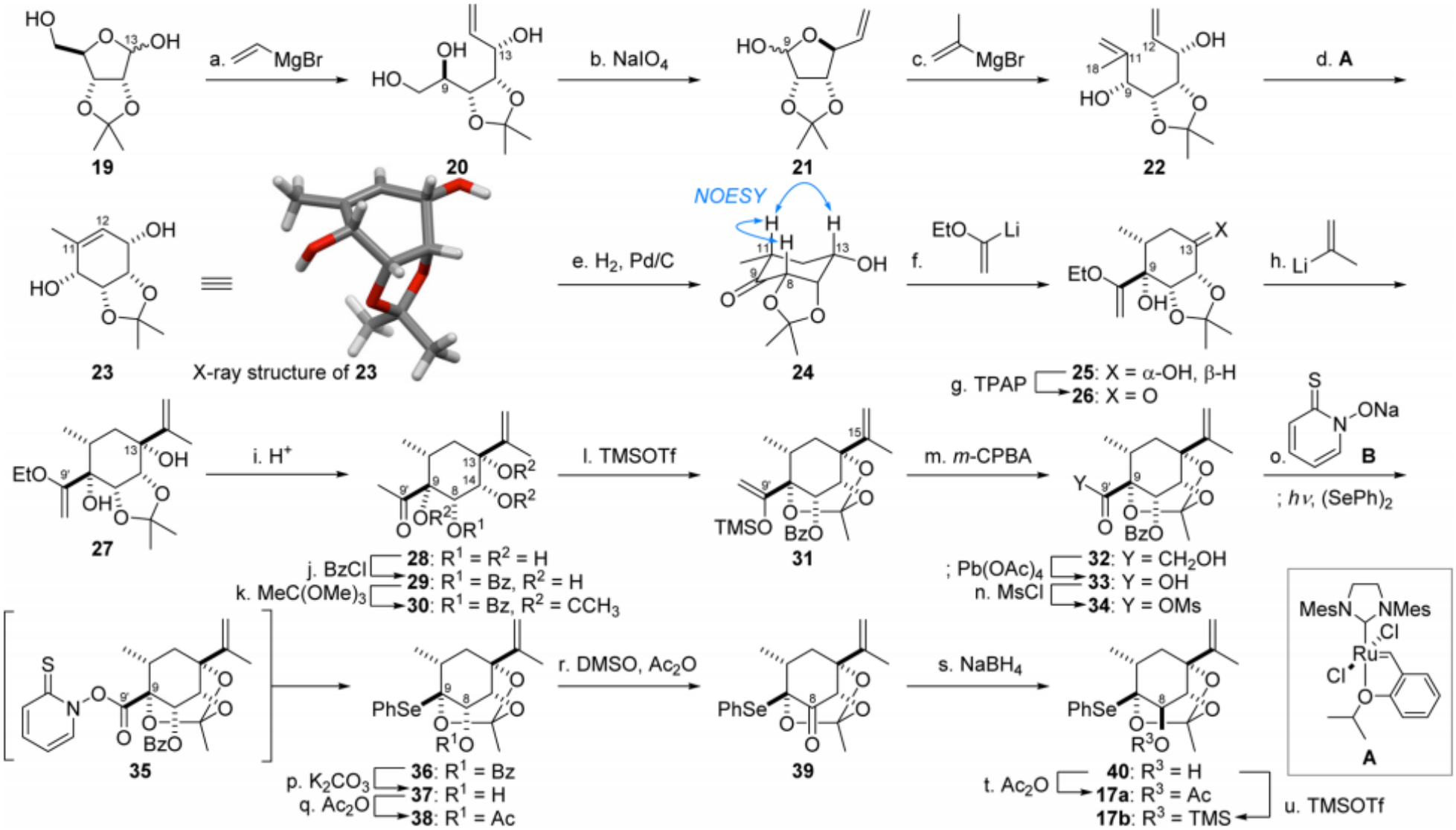
OL **2011**, *13*, 4778

Group precedence



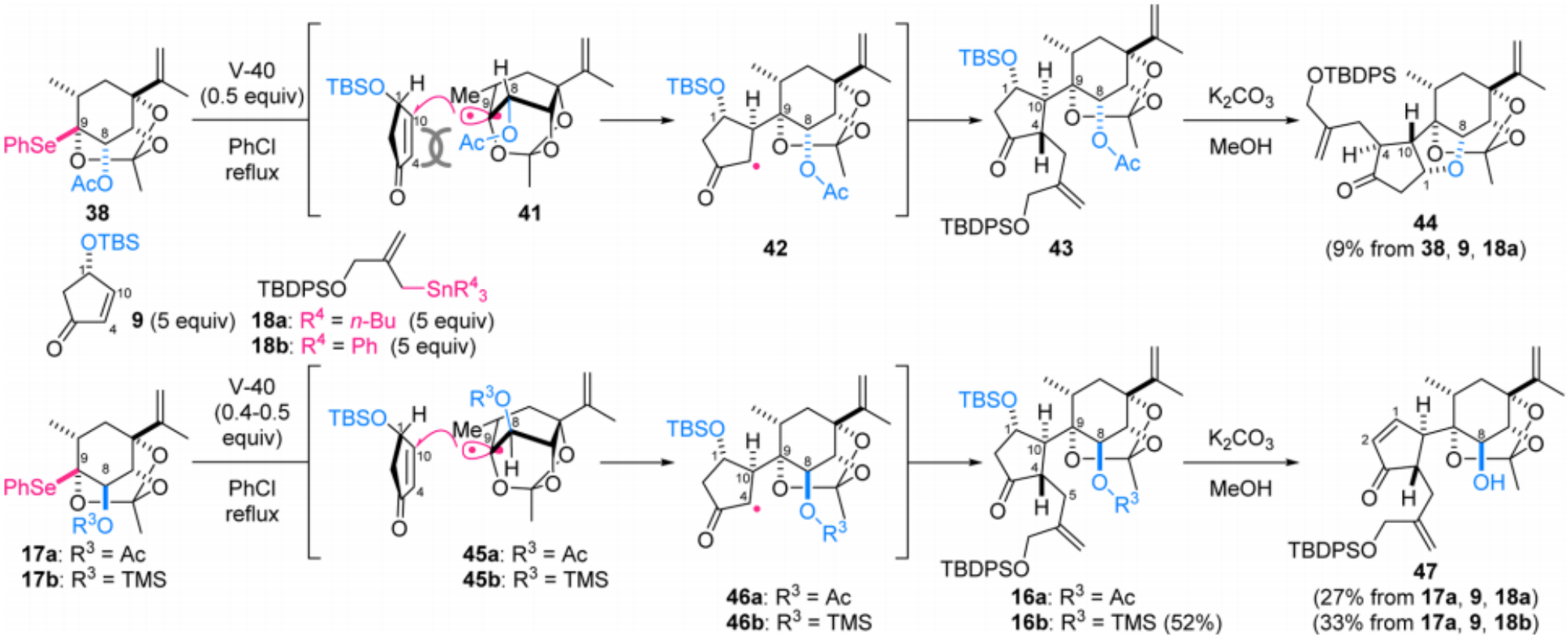
Tet **2016**, *72*, 7839

Scheme 3. Stereoselective Synthesis of the C-Ring[a]



[a]Reagents and conditions: (a) *n*-BuLi, vinylmagnesium bromide, THF, 80%; (b) $NaIO_4$, THF, H_2O, 0 °C; (c) *n*-BuLi, isopropenylmagnesium bromide, THF, 77% (2 steps); (d) **A** (2 mol %), 1,4-benzoquinone, $(CH_2Cl)_2$, 80 °C, 81%; (e) H_2, Pd/C, EtOAc, hexane, 0 °C, 71%; (f) *t*-BuLi, ethyl vinyl ether, THF, 0 °C, 91%; (g) TPAP, 4-methylmorpholine *N*-oxide, CH_2Cl_2, MS4A; (h) *t*-BuLi, 2-bromopropene, TMEDA, THF, −45 °C, 54% (2 steps) (recovered **26**: 24%); (i) Dowex 50W, THF, H_2O, 90 °C; (j) BzCl, pyridine, CH_2Cl_2, 0 °C, 83% (2 steps); (k) $MeC(OMe)_3$, (+)-CSA, benzene, 85%; (l) TMSOTf, Et_3N, CH_2Cl_2, 87%; (m) *m*-CPBA, CH_2Cl_2, 0 °C; TBAF, 0 °C; $Pb(OAc)_4$, K_2CO_3, toluene; (n) MsCl, Et_3N, CH_2Cl_2, 0 °C; (o) **B**, DMAP, toluene; *hν*, $(SePh)_2$, 31% (3 steps); (p) K_2CO_3, MeOH, 0 °C, 87%; (q) Ac_2O, DMAP, pyridine, CH_2Cl_2, 87%; (r) DMSO, Ac_2O, 35 °C; (s) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C; (t) Ac_2O, DMAP, pyridine, CH_2Cl_2, 84% (3 steps); (u) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 88% (3 steps).

Scheme 4. Optimization of Three-Component Radical Coupling Reactions



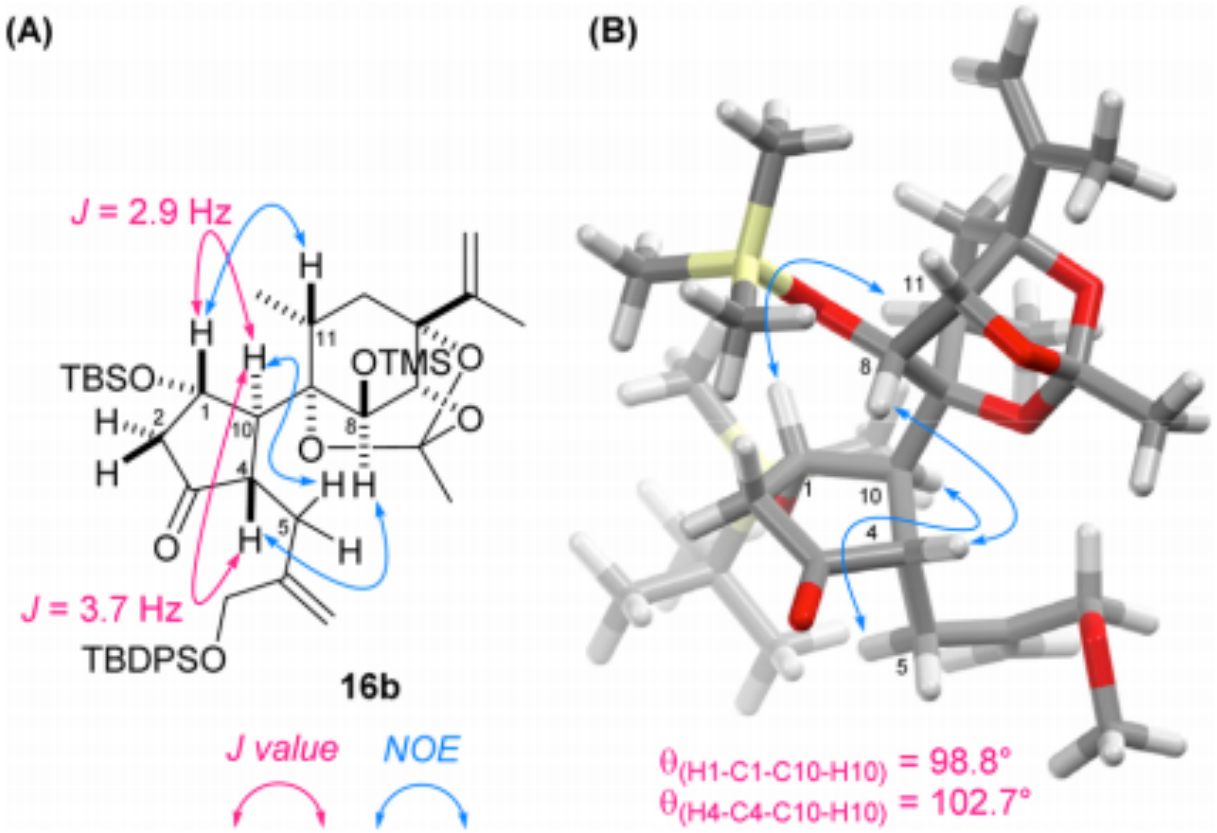
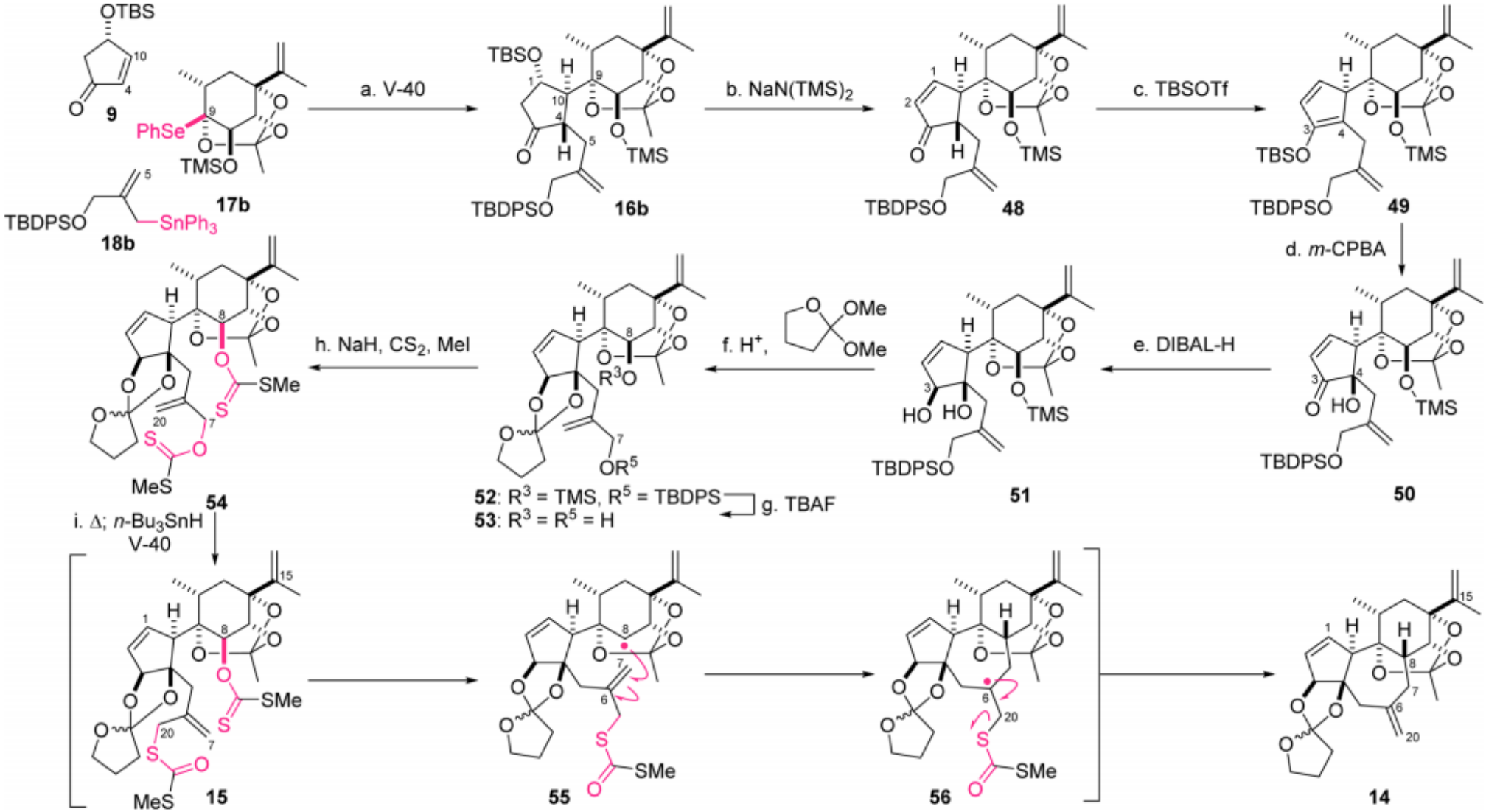
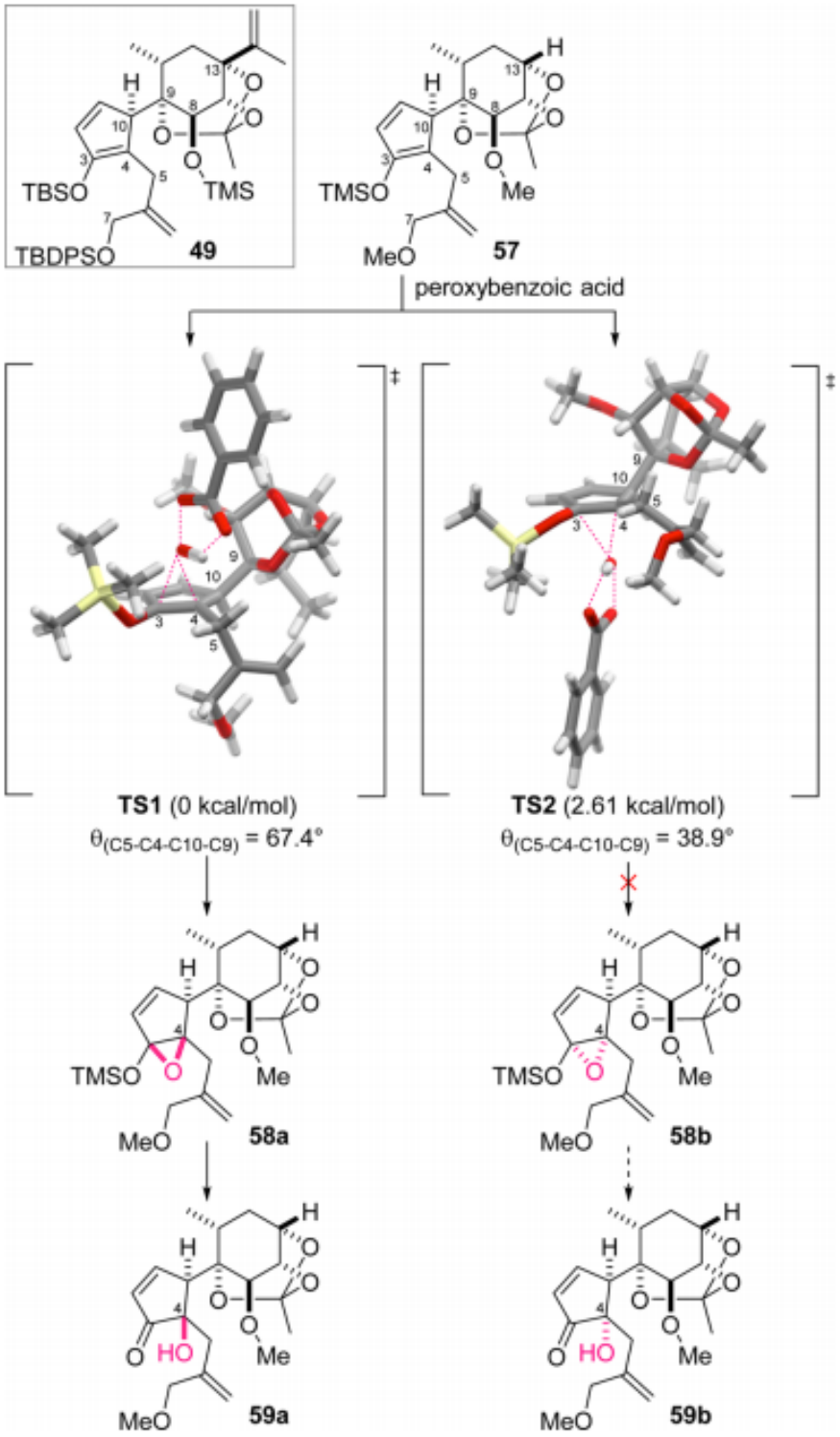


Figure 2. (A) The NMR data of **16b**. (B) The DFT-optimized structure of **16b** (the TBDPS group was replaced with the Me group. M06–2*X*/6-31g(d), 298 K, and 1 atm).

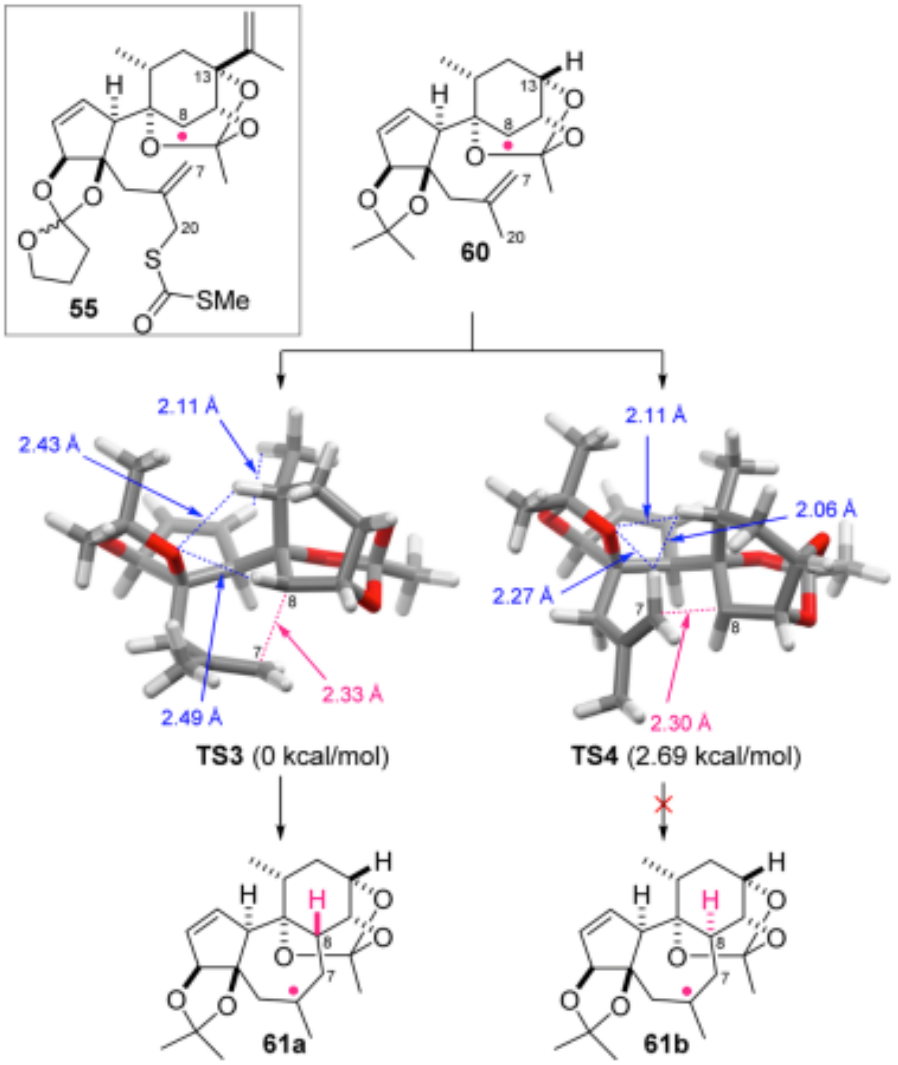
Scheme 5. Synthesis of the Tricyclic Framework by Employing the Two Radical Reactions[a]



[a]Reagents and conditions: (a) **9** (5 equiv), **18b** (5 equiv), V-40 (0.4 equiv), chlorobenzene, 130 °C, 52%; (b) $NaN(TMS)_2$, THF, 0 °C, 77%; (c) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (d) *m*-CPBA, $NaHCO_3$, hexane, CH_2Cl_2, 0 °C, 59% (2 steps); (e) DIBAL-H, CH_2Cl_2, −93 °C; (f) 2,2-dimethoxytetrahydrofuran, (+)-CSA, benzene, 50 °C, 60% (dr = 5:3, 2 steps); (g) TBAF, THF; (h) NaH, CS_2, MeI, THF, 90% (2 steps); (i) xylene, 110 °C; *n*-Bu_3SnH, V-40, 180 °C (microwave), 71%.

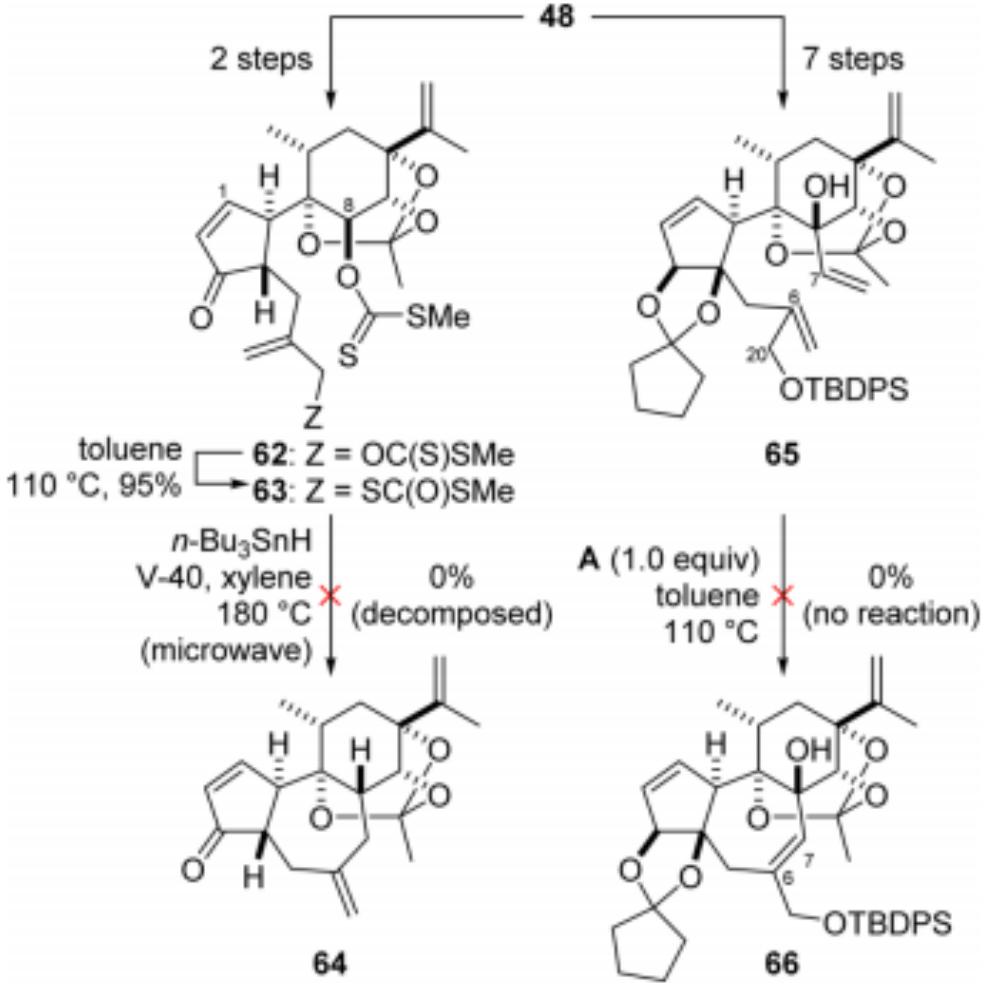


Scheme 7. Rationale of the C8-Stereoselectivity[a]

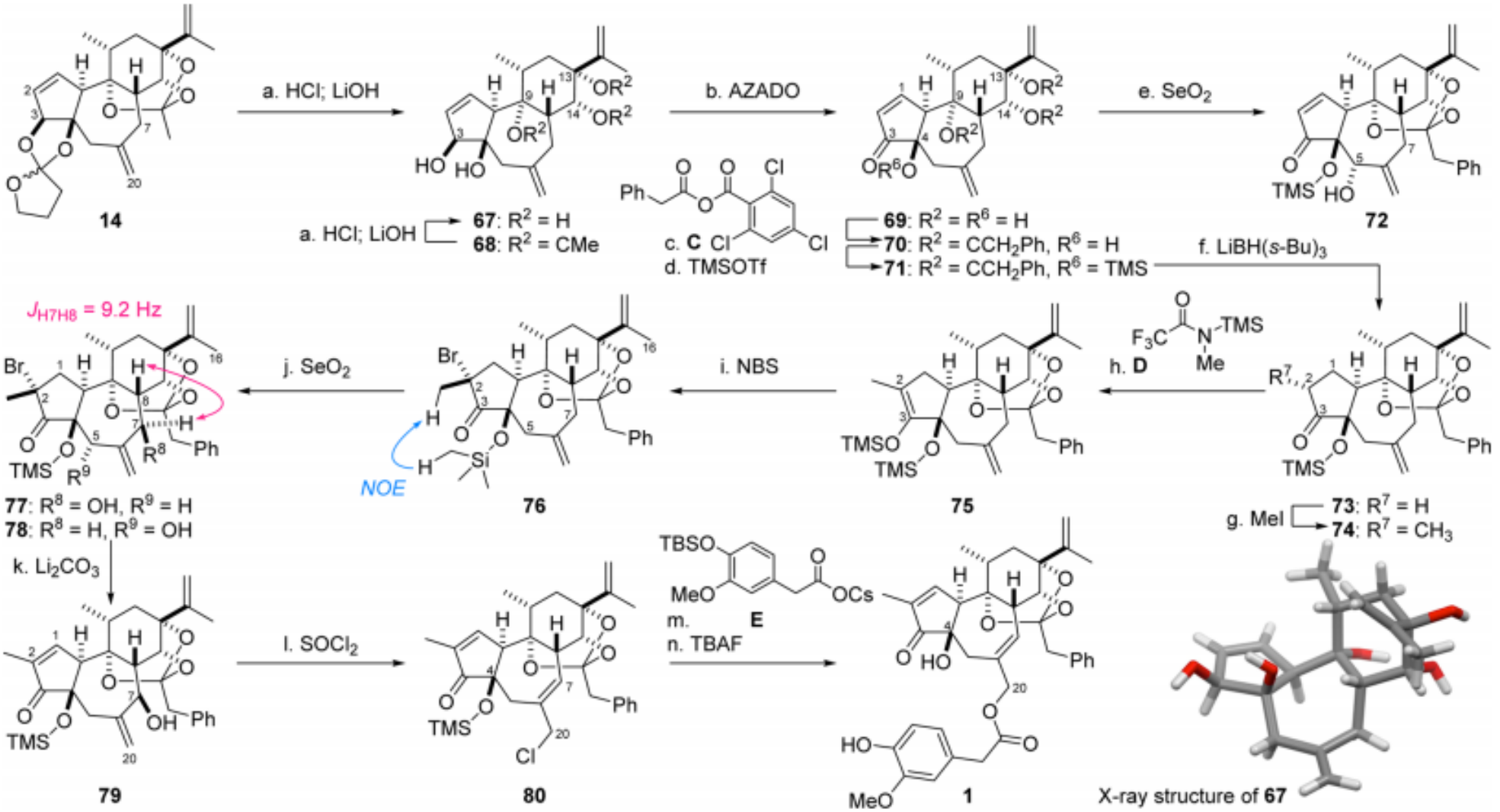


[a]Values in parentheses are relative free energies: ΔG, 298 K, 1 atm.

Scheme 8. Attempted B-Ring Cyclizations



Scheme 9. Total Synthesis of Resiniferatoxin (1)[a]



[a]Reagents and conditions: (a) 1.5 M HCl in aqueous MeOH, 30 °C, LiOH, 51% for **67** and 36% for **68** from **14**; 57% for **67** from **68** (recovered **68**: 28%); (b) AZADO, CuCl, 2,2′-bipyridyl, DMAP, CH_3CN, air, 0 °C, 90%; (c) **C**, DMAP, toluene, THF, 0 °C; 2,4,6-trichlorobenzoic acid, 50 °C, 53% (recovered **69**: 15%); (d) TMSOTf, 2,6-lutidine, CH_2Cl_2, 74%; (e) SeO_2, *t*-BuOH, 80 °C, 43% from **71**; (f) $LiBH(s\text{-}Bu)_3$, THF, −78 °C, 83%; (g) $LiN(TMS)_2$, THF, 0 °C; MeI, −20 °C, 94%; (h) **D**, DMAP, DABCO, CH_3CN, 110 °C; (i) NBS, THF, 0 °C, 88% (2 steps); (j) SeO_2, *t*-BuOH, 80 °C, (**77**: **78** = 5:1); (k) Li_2CO_3, LiBr, DMF, 150 °C; (l) $SOCl_2$, pyridine, Et_2O, 25% (3 steps); (m) **E**, DMF; (n) TBAF, THF, 0 °C, 92% (2 steps).

Summary

Not most efficient forward synthesis:

- C-3 reduced once, oxidized once, enolized twice
- C-9 functionality manipulated extensively
- C-8 reduced twice, oxidized once, converted to xanthate
- C-8 OH protected twice, deprotected twice
- Methyl orthoester used, not benzyl (radical compatibility)
- Etc.

But,

- 7-endo radical cylization with [3,3] sigmatropic rearrangment of dixanthate
- three-component radical coupling… relay of philicities

Thanks for attention!

And

any questions?