Collaborative Total Synthesis: Routes to (±)-Hippolachnin A Enabled by Quadricyclane Cycloaddition and Late-Stage C−H Oxidation

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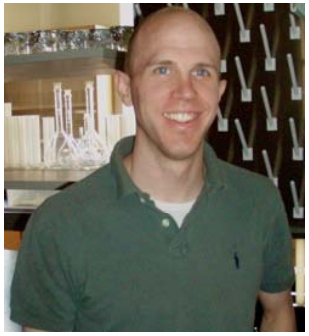
Date: 2016/05/03



Wood, J. L.; Brown, M. K. *et al.*
J. Am. Chem. Soc. **2016**, *138*, 2437.

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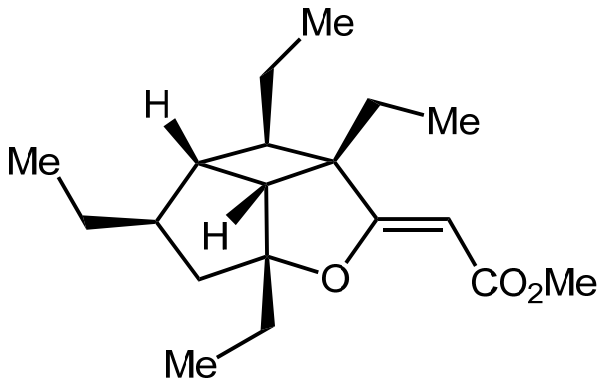
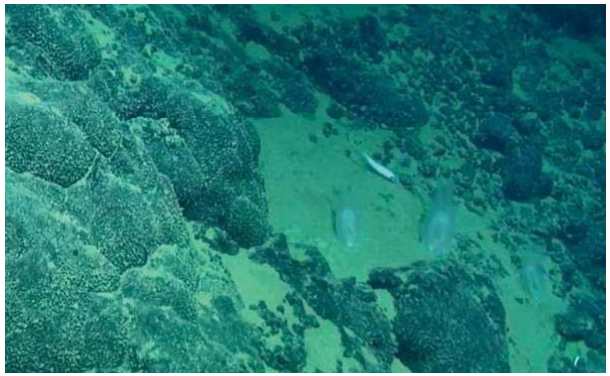
Introduction



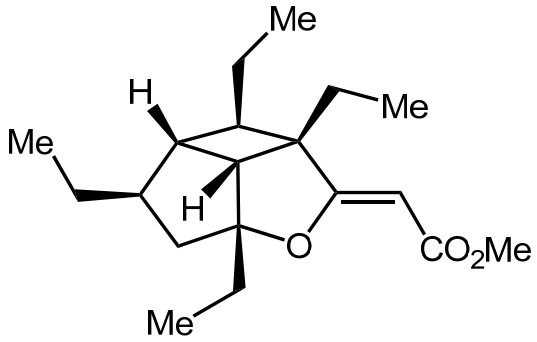
(+)-Hippolachnin A



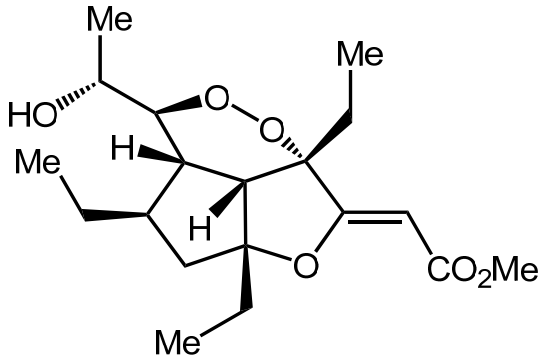
Hippospongia lachne

- Isolated from the marine sponge *Hippospongia lachne* in 2013;
- Hippolachnin A plays an important role for the treatment of various diseases such as renal fibrosis, acute renal failure, chronic heart failure, oral ulcer and rhinitis.

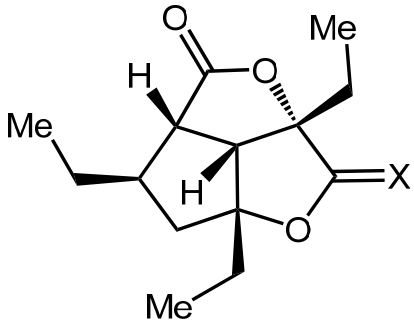
Introduction



Hippolachnin A



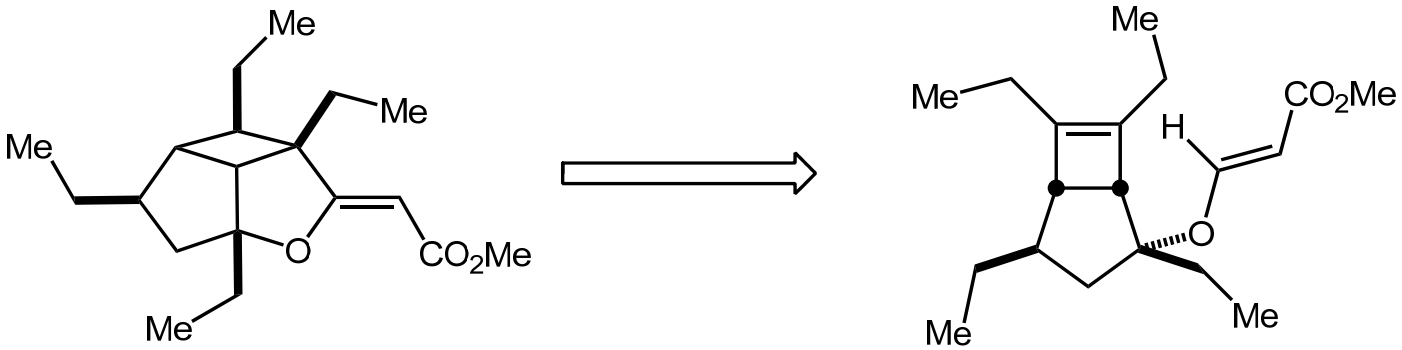
Gracilioether A



X = $CHCO_2Me$: Gracilioether E
X = O: Gracilioether F

Total Synthesis by Carreira's Group

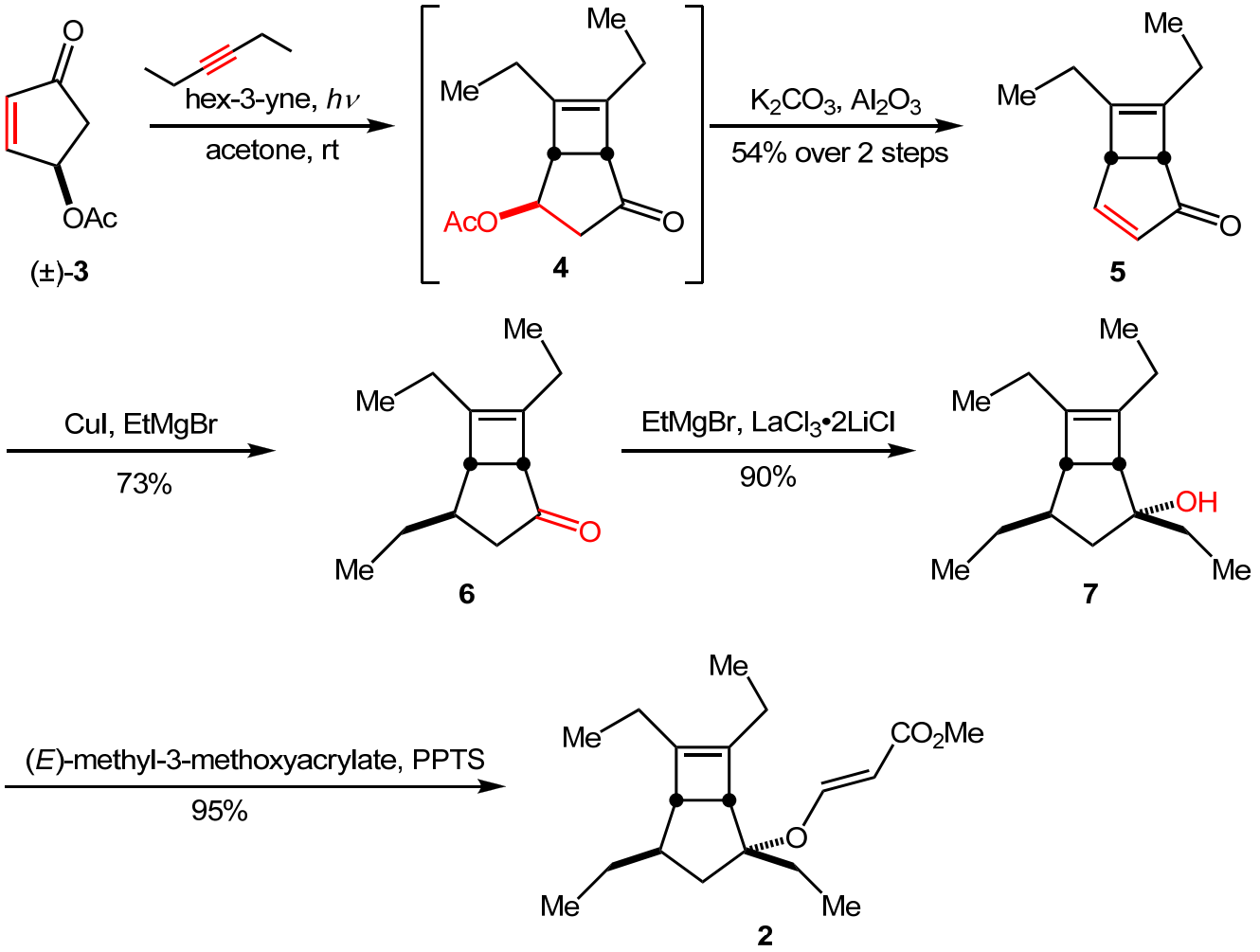
Topological-strategy-guided key disconnection



(±)-Hippolachnin A (**1**) **2**

Carreira, E. M. *et al*. *Angew. Chem. Int. Ed.* **2015**, *54*, 2378.

Total Synthesis by Carreira's Group



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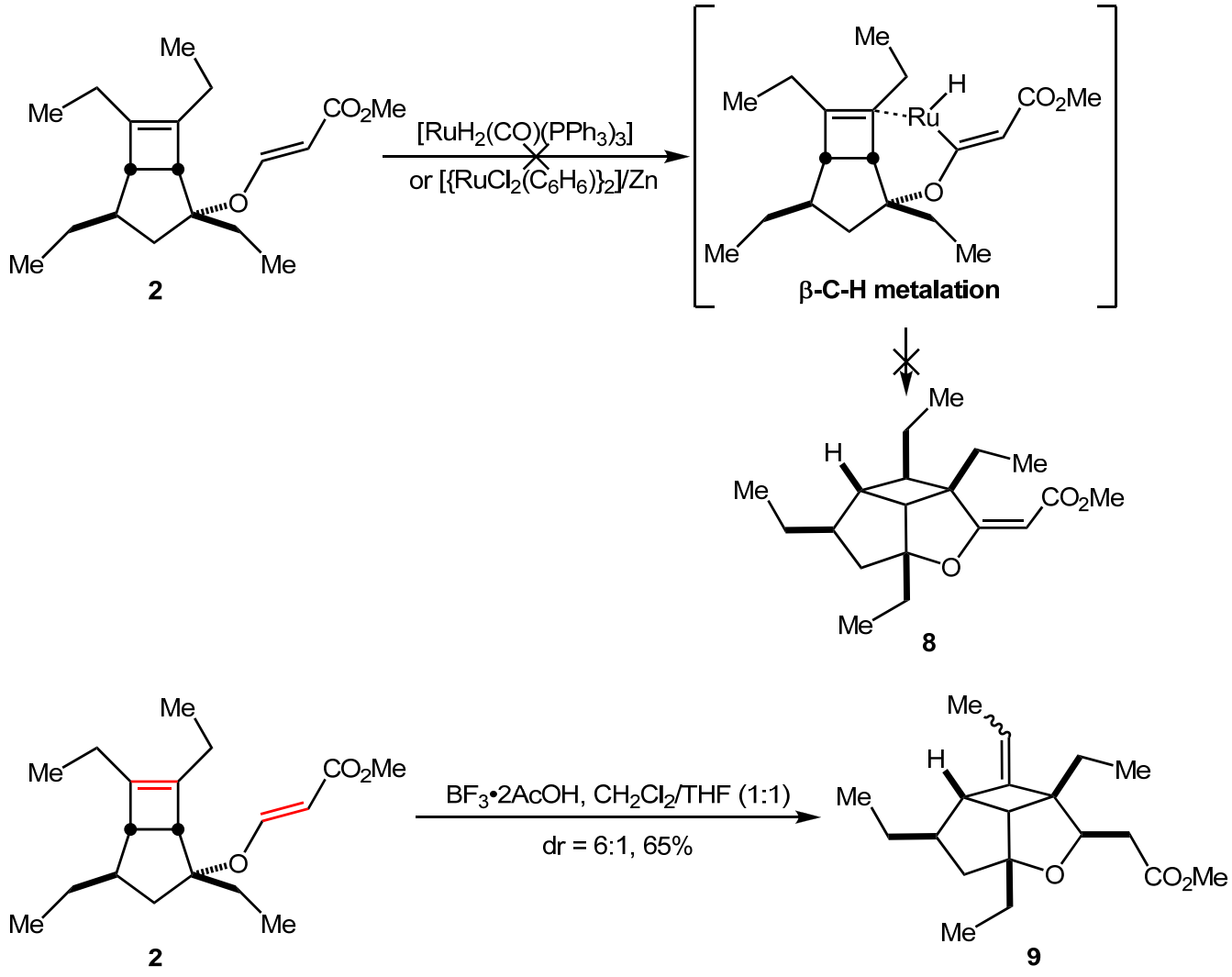
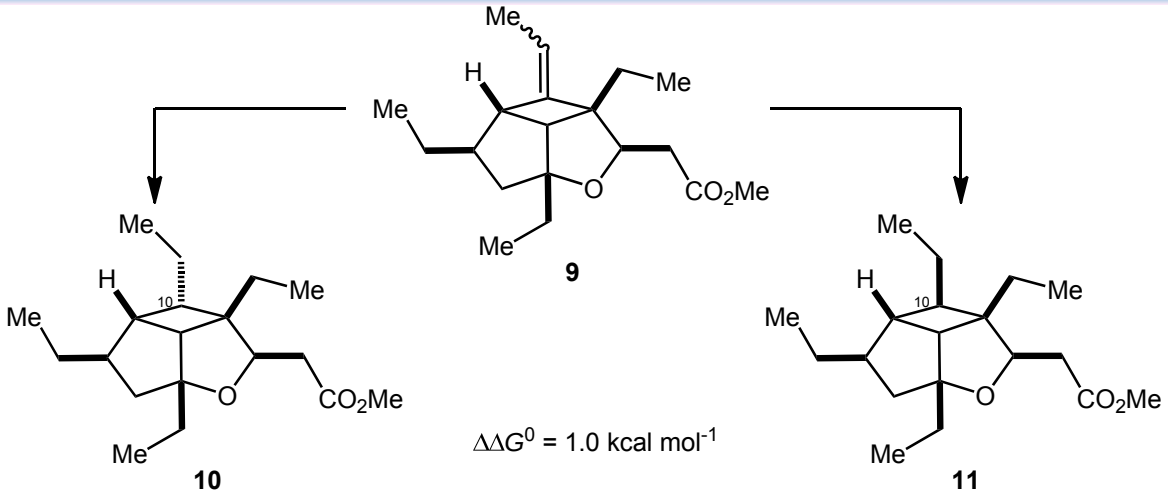


Total Synthesis by Carreira's Group

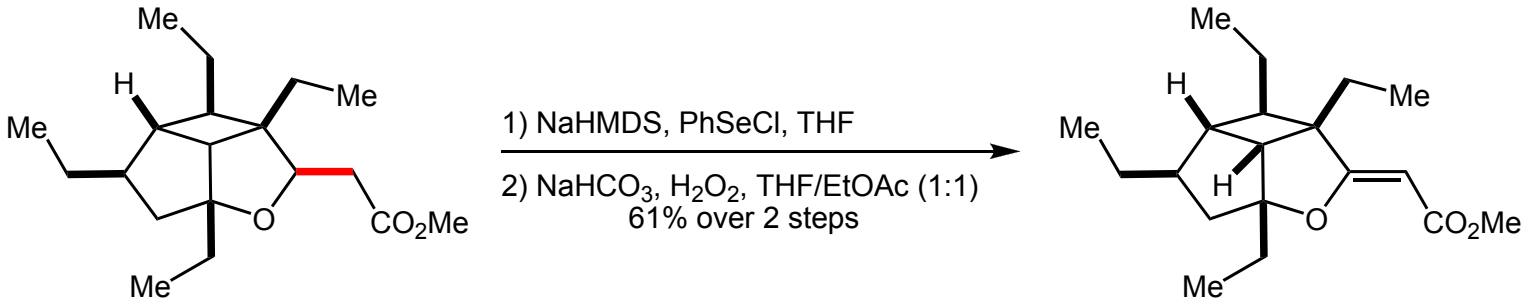


endo at C10
thermodynamic product

exo at C10
kinetic product

	entry	conditions	yield [%]	**10/11**
radical	1	$[Mn(dpm)_3]$, $PhSiH_3$, TBHP, ^iPrOH	75	> 99:1
	2	$[Co(acac)_2]$, $PhSiH_3$, TBHP, DCE	63	> 99:1
homogeneous	3	$[RhCl(PPh_3)_3]$, MeOH, H_2 (10 bar)	31	47:53
	4	$[Ir(PCy_3)(cod)(py)]PF_6$, CH_2Cl_2, H_2 (10 bar)	0	-
heterogeneous	5	Pd/C, MeOH, H_2 (10 bar)	92	29:71
	6	$Pd(OH)_2$/C, MeOH, H_2 (10 bar)	89	25:75
	7	PtO_2, MeOH, H_2 (10 bar)	88	36:64

Total Synthesis by Carreira's Group



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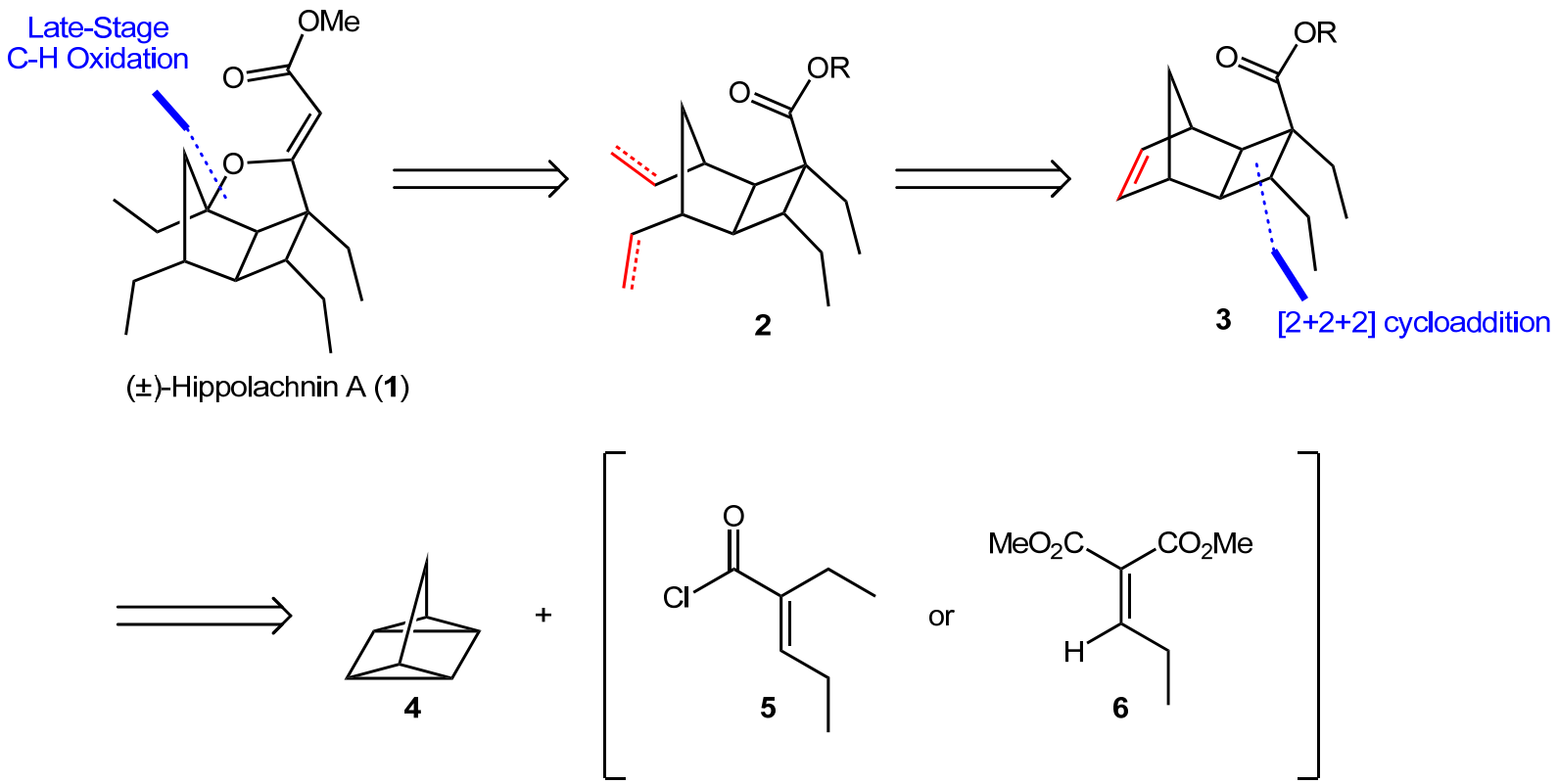
(±)-Hippolachnin A (**1**)

Total Synthesis by Wood and Brown Groups

Retrosynthetic Analysis



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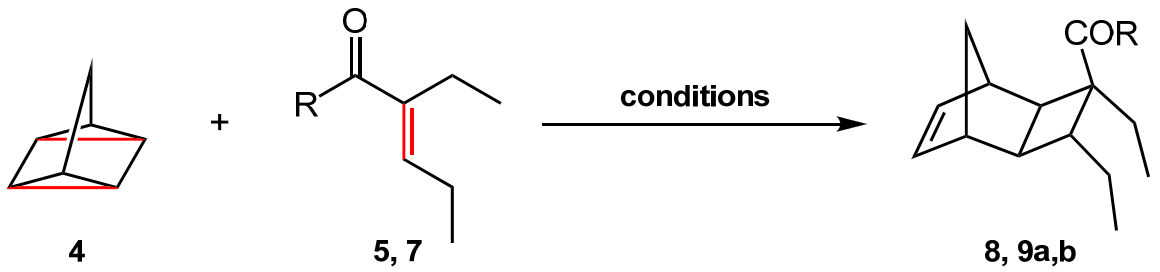
Total Synthesis by Brown's Group

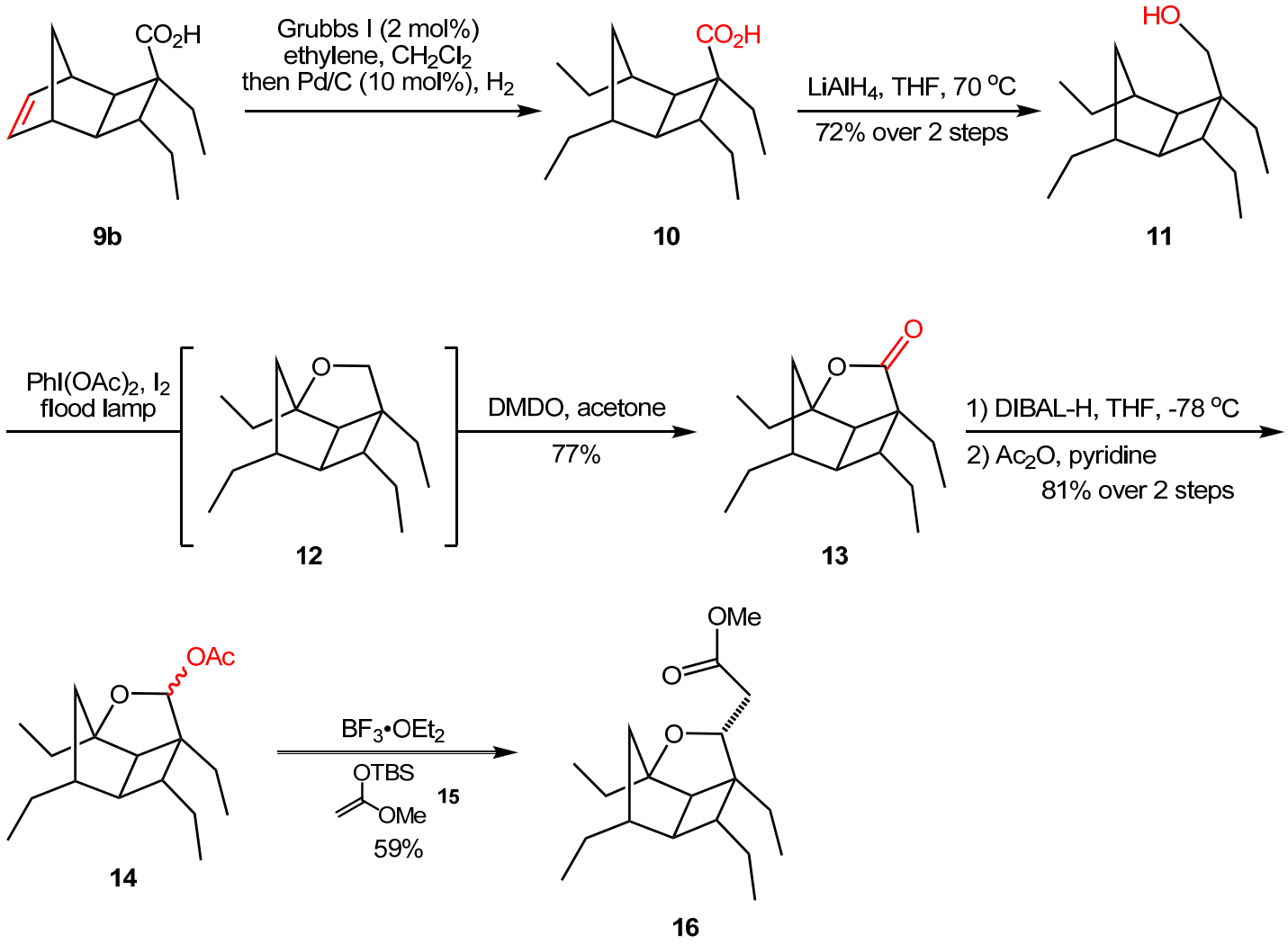


4 **5, 7** **8, 9a,b**

entry	R	conditions	product	yield (dr)[a]
1	OEt (**7**)	140 °C, 4 equiv **4**, 48 h	(OEt) **8**	<2%
2	Cl (**5**)	120 °C, 4 equiv **4**, 72 h	(Cl) **9a**	73% (3:1 dr)
3	Cl (**5**)	MW, 110 °C, 5 equiv **4**, 2 h	(Cl) **9a**	31% (9:1 dr)
4	Cl (**5**)	MW, 110 °C, 5 equiv **4**, 10 h	(Cl) **9a**	68% (6:1 dr)
5	Cl (**5**)	MW, 140 °C, 5 equiv **4**, 4 h	(Cl) **9a**	74% (5:1 dr)[b]

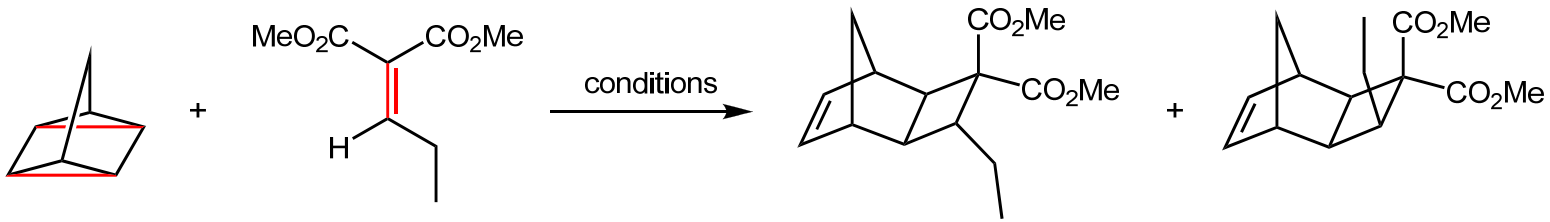
[a] Determined by ^{1}H NMR analysis with an internal standard. [b] A 50% isolated yield, >20:1 dr, recrystallization of the corresponding carboxylic acid (**9b**, R = OH) after quench with NaOH (aq).

Total Synthesis by Brown's Group



Total Synthesis by Brown's Group

Total Synthesis by Wood's Group

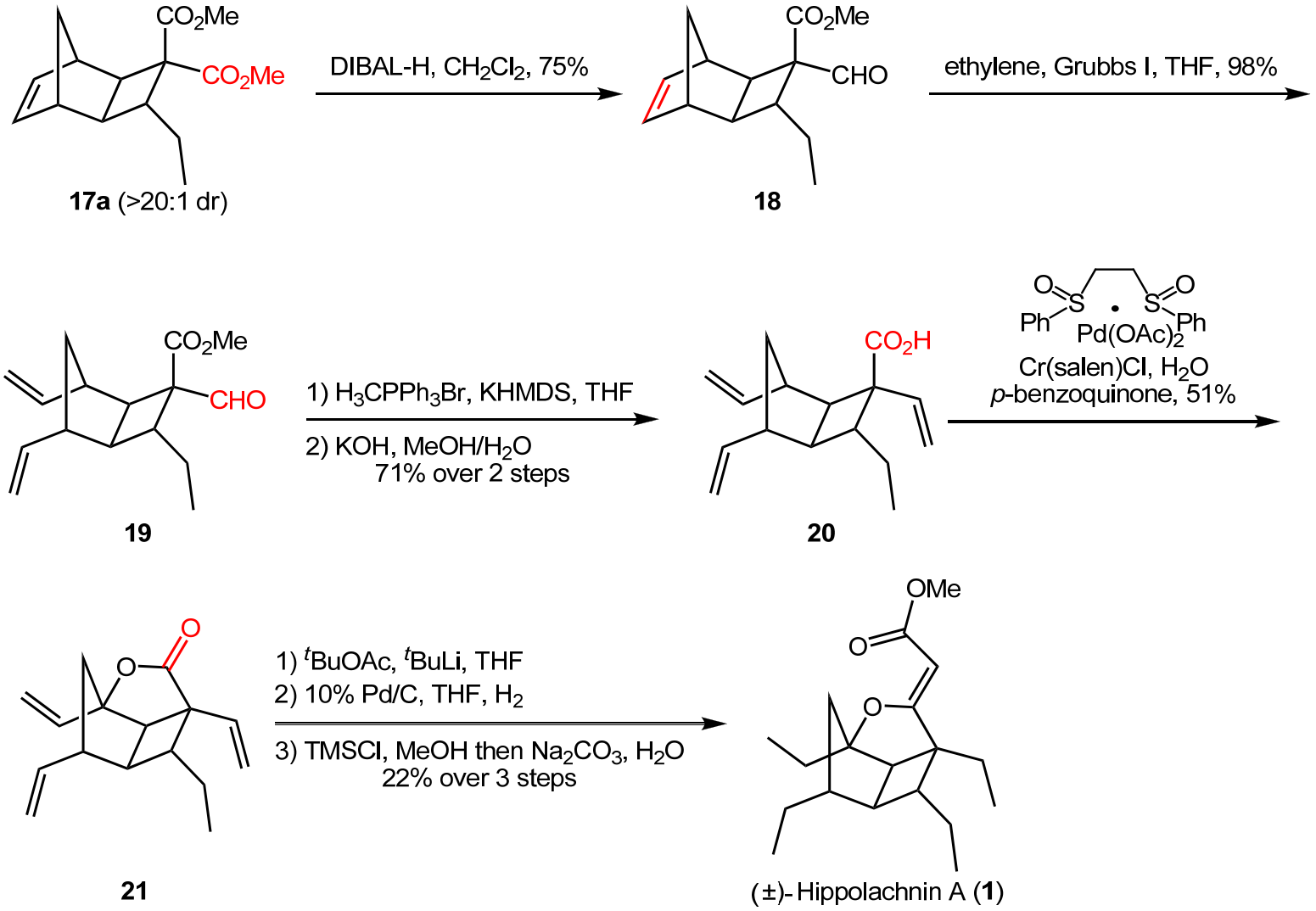


4 **6** **17a** **17b**

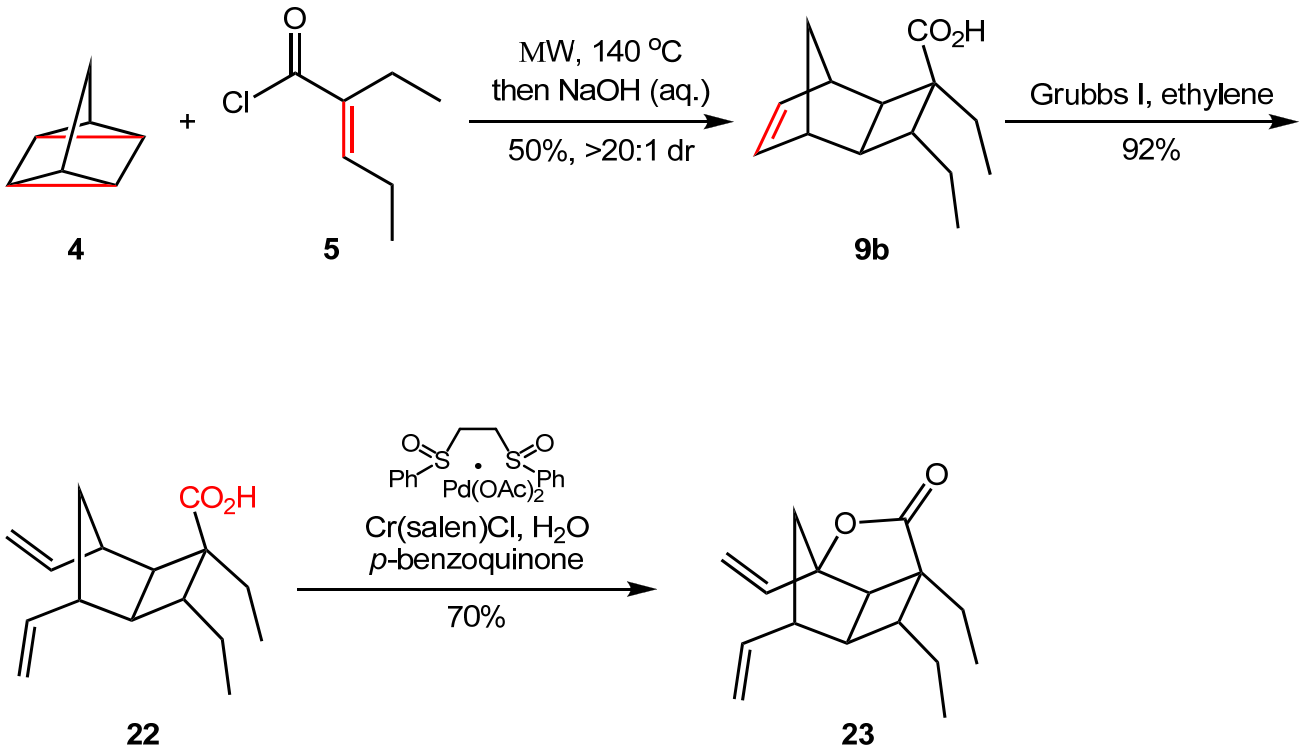
entry[a]	solvent	catalyst[b]	time (h)	**17a:17b**[c]	conversion (%)[c,d]
1	EtOH	-	144	9.1:1	52 (37)[h]
2	DCE	-	4	2.3:1	11
3	DCE	$ZnCl_2$	4	1.8:1	44
4	DCE	$AlCl_3$	4	2.1:1	67
5	DCE	$TiCl_4$	4	2.9:1	>95
6[e]	CH_2Cl_2	$TiCl_4$[f]	4	3.4:1	>95
7[e]	CH_2Cl_2	$TiCl_4$[f]	1	3.7:1	>95 (82)[h]
8[e]	CH_2Cl_2	$TiCl_4$[g]	4	4.4:1	73

[a] 90 °C. [b] 10 mol %. [c] Determined by ^1H NMR in $CDCl_3$. [d] Conversion of alkylidene to cycloadducts A and B.
[e] 0 °C. [f] 5 mol %. [g] 2 mol %. [h] Isolated yield.

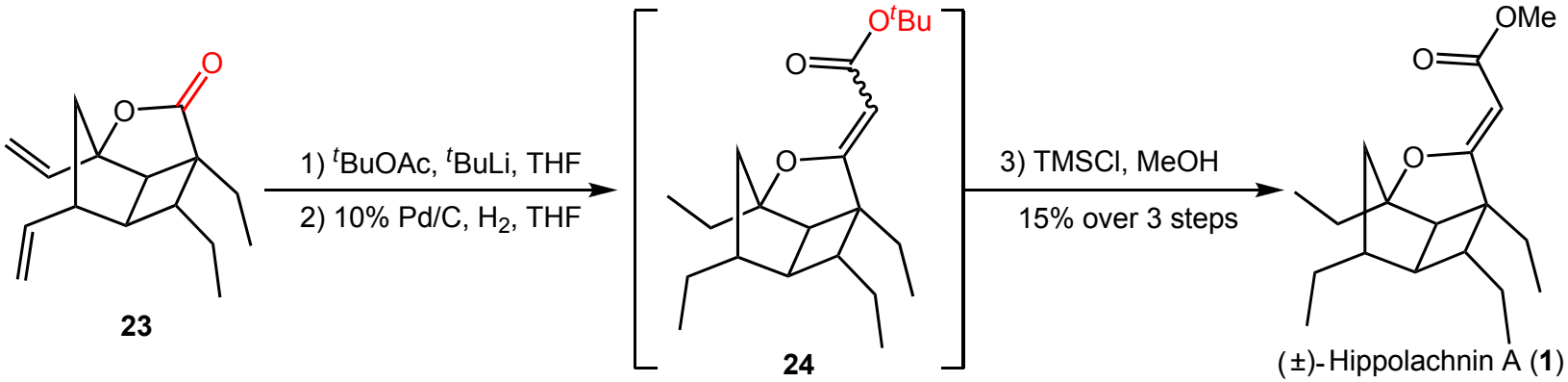
Total Synthesis by Wood's Group



Collaborative Total Synthesis

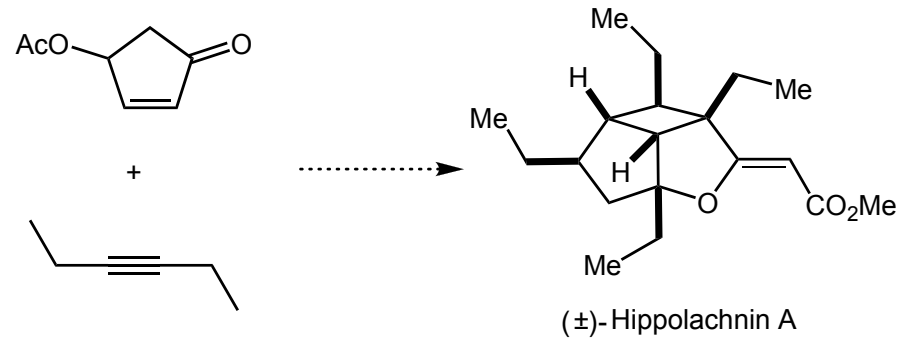


Collaborative Total Synthesis



Summary

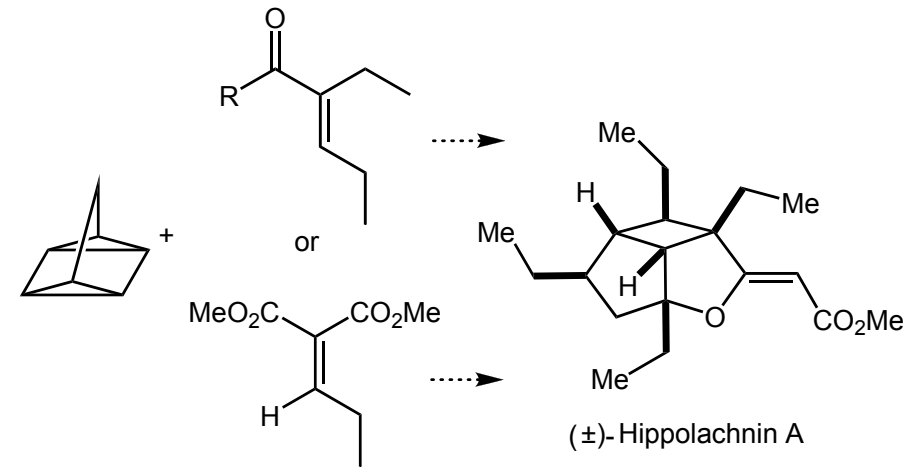
Carreira's Method



(±)-Hippolachnin A

- First total synthesis
- 9 linear steps, 9% overall yield
- Ene Cyclization

Wood & Brown's Methods



(±)-Hippolachnin A

- Quadricyclane cycloaddition
  Late-Stage C-H oxidation
- 7 linear steps for collaborative total synthesis, 5% overall yield

Hippolachnin A is a complex natural product recently isolated from the marine sponge *Hippospongia lachne* along with its proposed biogenic precursor. This polyketide-based molecule has an unprecedented carbon skeleton that bears six contiguous stereogenic centers. Preliminary biological evaluation of hippolachnin A led to the discovery that it is a potent antifungal agent possessing activity against several species, including *Cryptococcus neoformans* (410 nM), *Trichophyton rubrum* (410 nM), and *Candida glabrata* (1.62 μM). Notably, treatments for *C. neoformans* infections are one of the most important unmet objectives in clinical mycology which, coupled with preliminary toxicity data illustrating inactivity against HCT-116, HeLa, and A549 human cell lines, renders hippolachnin A an intriguing and medicinally important target for synthesis.

As outlined above, three syntheses of (±)-hippolachnin A have been developed that employ quadricyclane as point of departure and take advantage of the inherent reactivity of this highly symmetrical hydrocarbon. To the best of our knowledge, this is the first time a [2π + 2σ + 2σ] cycloaddition of quadricyclane has been employed in complex molecule synthesis, and its use here not only allows the rapid and controlled introduction of six contiguous stereocenters, but also highlights the power of directed C−H oxidation chemistry in enabling the use of simple hydrocarbons as precursors in the production of highly functionalized compounds.