Asymmetric [4+3] Cycloadditions between Vinylcarbenoids and Dienes: Application to the Total Synthesis of the Natural Product (-)-5-*epi*-Vibsanin E

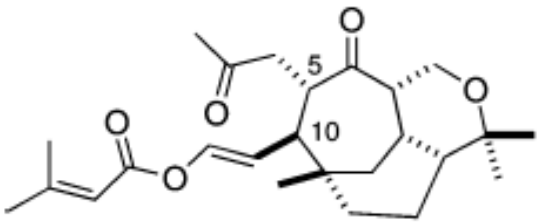
Schwartz, B. D.; Denton, J. R.; Lian, Y.; Davies, H. M. L.; Williams, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 8329.

Maria del Rosario Amado Sierra

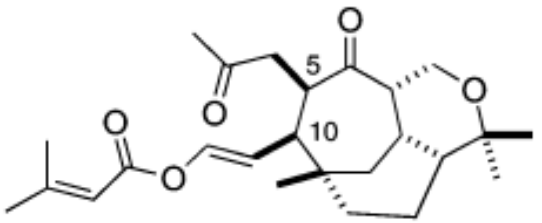
Group meeting 06/29/09

Vibsanin E: Isolation & Structure

- 1 Cycloheptane ring
- 6 stereogenic centers
- Tricyclic core
- 3,3-dimethylacroyl enol ester sidechain



(–)-vibsanin E (**1**)



(–)-5-*epi*-vibsanin E (**2**)

(1) was isolated by Kamazu from *Viburnum odoratissimun*

(2) was isolated by Fukuyama from *Viburnum awabuki*

http://www.floridata.com/ref/V/viburn_o.cfm

Kawazu, K. *Agri. Biol. Chem*. **1980**, *44*, 1367.
Fukuyama. K; Katsube, Y; Kawazu, K. *J. Chem. Soc., Perkin Trans. II* **1980**, 1701.
Fukayama, Y.; Minami, H.; Matsuo, A.; Kitamura, K.; Akizuki, M.; Kubo, M.; Kodama, M. *Chem. Pharm. Bull.* **2002**, *50*, 368.

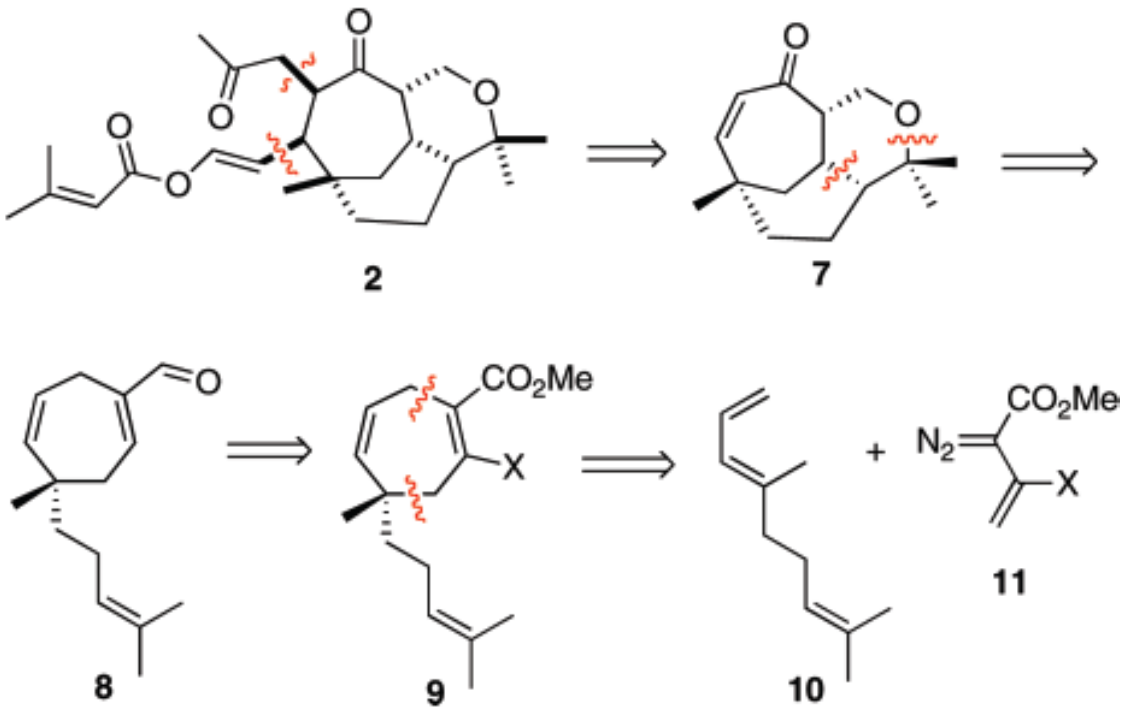
(-)-5-*epi*-Vibsanin E

Key reactions:

•Tandem conjugate addition/alkylation chemistry

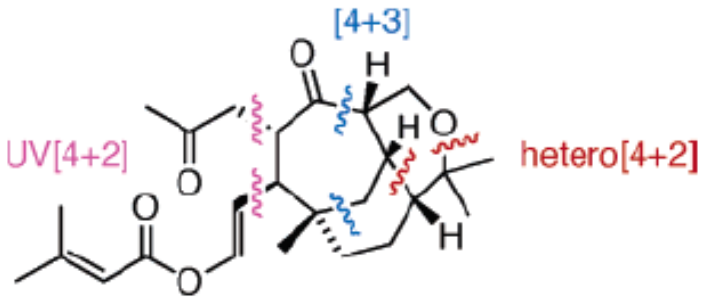
•Lewis-acid-catalyzed hetero-Cycloaddition reaction

•[4+3] Cycloaddition between Vinyldiazoacetates and diene **10**.

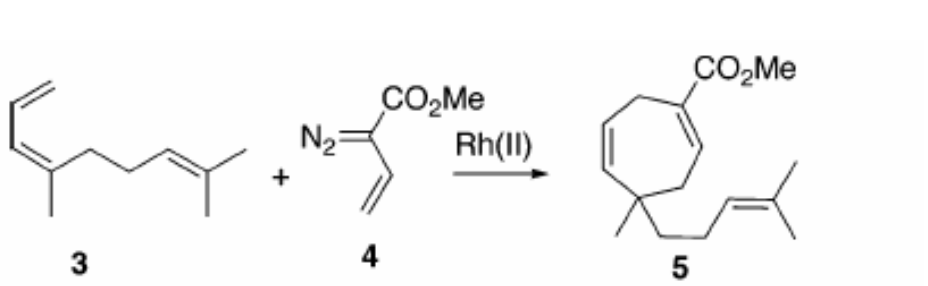


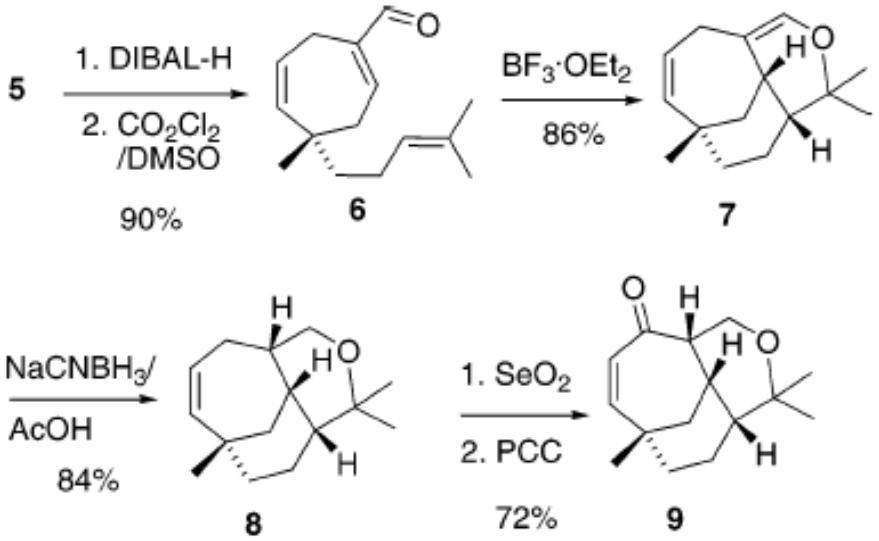
Schwartz, B. D.; Denton, J. R.; Lian, Y.; Davies, H. M. L.; Williams, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 8329.
Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Org. Lett.* **2005**, *7*, 1327.
Schwartz, B. D.; Tilly, D. P.; Heim, R.; Wiedemann, S.; Williams, C.M.; Bernhardt, P.V. *Eur. J. Org. Chem.* **2006**, 3181.
Davies, H. M. L.; Loe, Ø.; Stafford, D. G. *Org. Lett.* **2005**, *7*, 5561.

Tricyclic Core of Vibsanin E



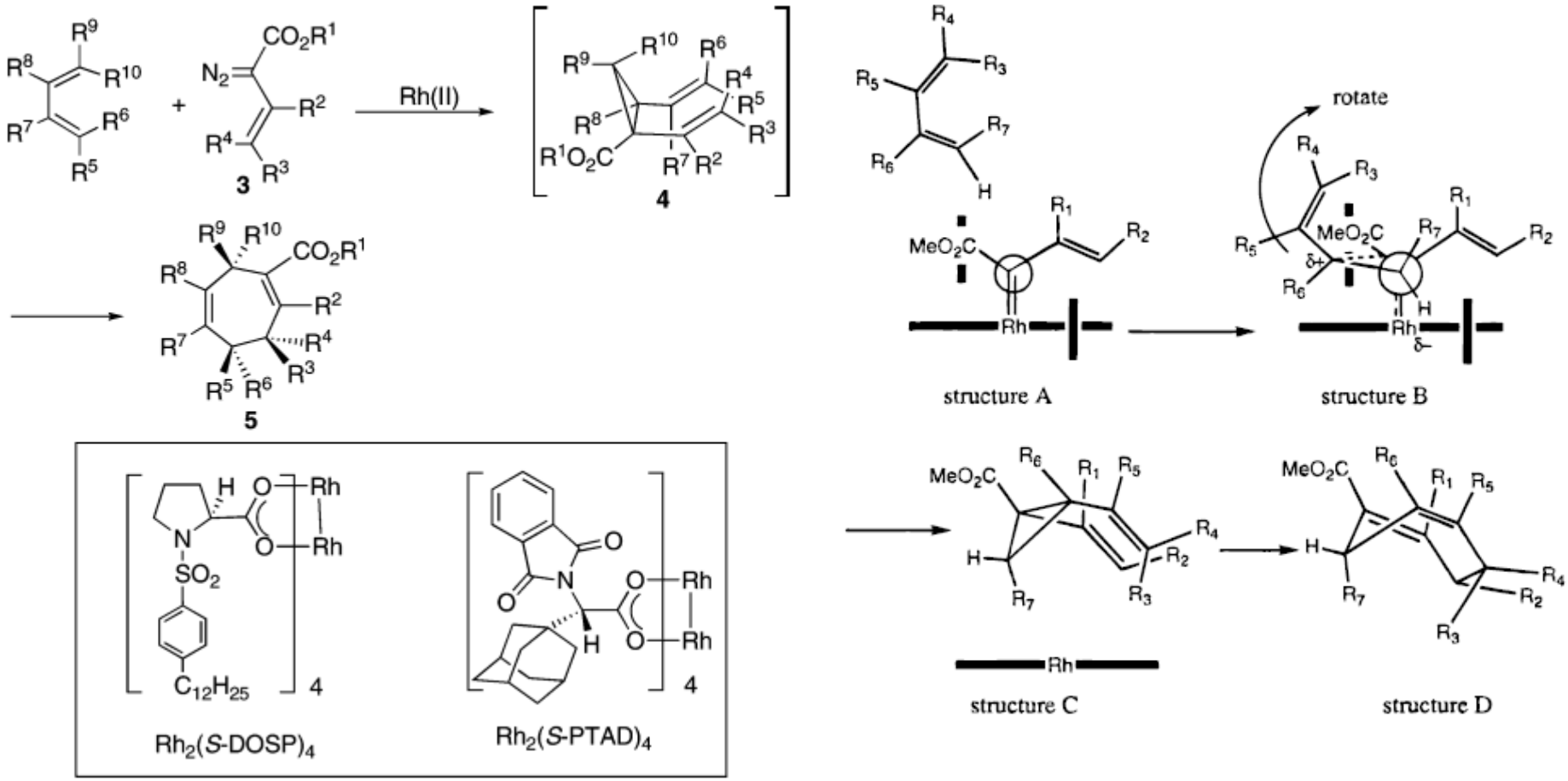
vibsanin E (**1**)





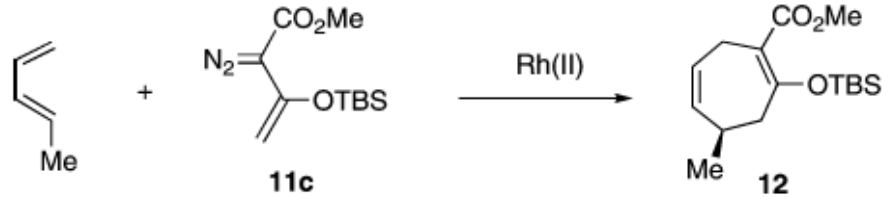
Davies, H. M. L.; Loe, Ø.; Stafford, D. G. *Org. Lett.* **2005**, *7*, 5561.
Nikolai, J.; Loe, Ø.; Dominiak, P. M.; Gerlitz, O. O.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10763

[4+3] Cycloaddition: Tandem Asymmetric Cyclopropanation/Cope Rearrangement

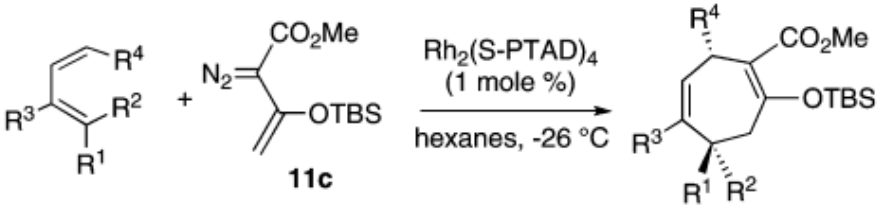


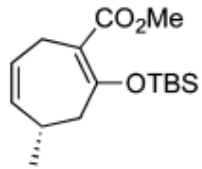
Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326.
Davies, H. M. L.; Loe, Ø.; Stafford, D. G. *Org. Lett.* **2005**, *7*, 5561.

[4+3] Cycloaddition: optimization

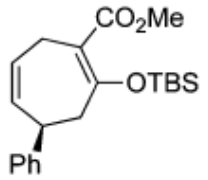


Rh(II)	temp (°C)	yield (%)	ee (%)
Rh_2(*S*-DOSP)$_4$	23	85	38
Rh_2(*S*-DOSP)$_4$	-26	35	53
Rh_2(*S*-PTAD)$_4$	23	78	86
Rh_2(*S*-PTAD)$_4$	-26	88	95

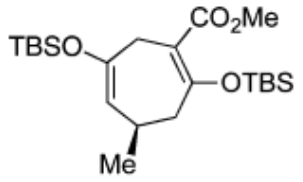




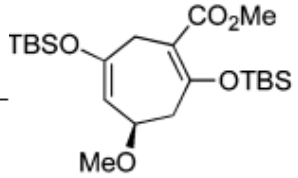
13
80% yield
87% ee



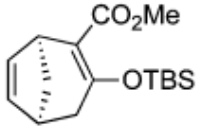
14
82% yield
95% ee



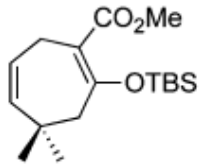
15
70% yield
99% ee



16
63% yield
95% ee



17
86% yield
92% ee



18
57% yield

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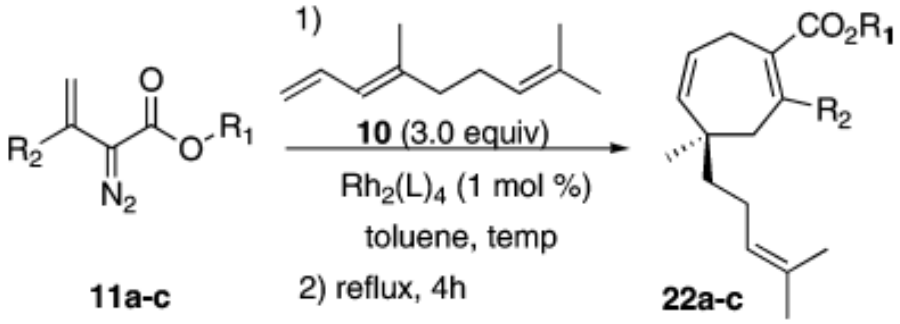
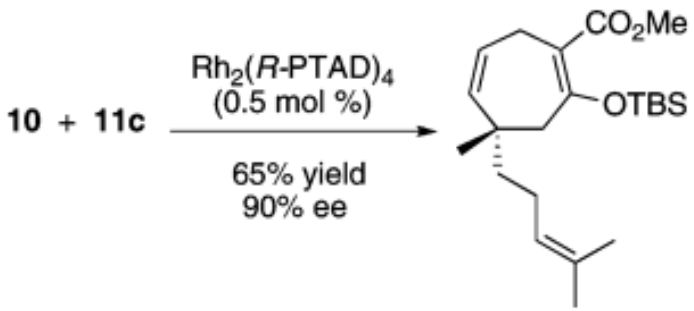
Davies, H. M. L.; Loe, Ø.; Stafford, D. G. *Org. Lett.* **2005**, *7*, 5561.
Davies, H. M. L.; Reddy, P. R. *J. Am. Chem. Soc.* **2007**, *129,* 10312.
Schwartz, B. D.; Denton, J. R.; Lian, Y.; Davies, H. M. L.; Williams, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 8329.

[4+3] Cycloaddition: optimization



entry	$Rh_2(L)_4$	R_1	R_2	temp (°C)	product	yield (%)	ee (%)
1	Rh_2(*S*-DOSP)$_4$	CH_3	H	rt	22a	62	50
2	Rh_2(*S*-PTAD)$_4$	CH_3	H	rt	22a	67	40
3	Rh_2(*S*-DOSP)$_4$	t-Bu	H	rt	22b	60	5
4	Rh_2(*S*-PTAD)$_4$	t-Bu	H	rt	22b	63	57
5	Rh_2(*S*-DOSP)$_4$	CH_3	OTBS	−78 to rt	22c	55	45
6	Rh_2(*S*-PTAD)$_4$	CH_3	OTBS	−20 to −15	22c	55	91
7	Rh_2(*S*-PTAD)$_4$	CH_3	OTBS	−10	22c	67	90
8	Rh_2(*S*-PTAD)$_4$	CH_3	OTBS	0 to 5	22c	70	87



Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326.
Davies, H. M. L.; Loe, Ø.; Stafford, D. G. *Org. Lett.* **2005**, *7*, 5561.
Davies, H. M. L.; Reddy, P. R. *J. Am. Chem. Soc.* **2007**, *129,* 10312.
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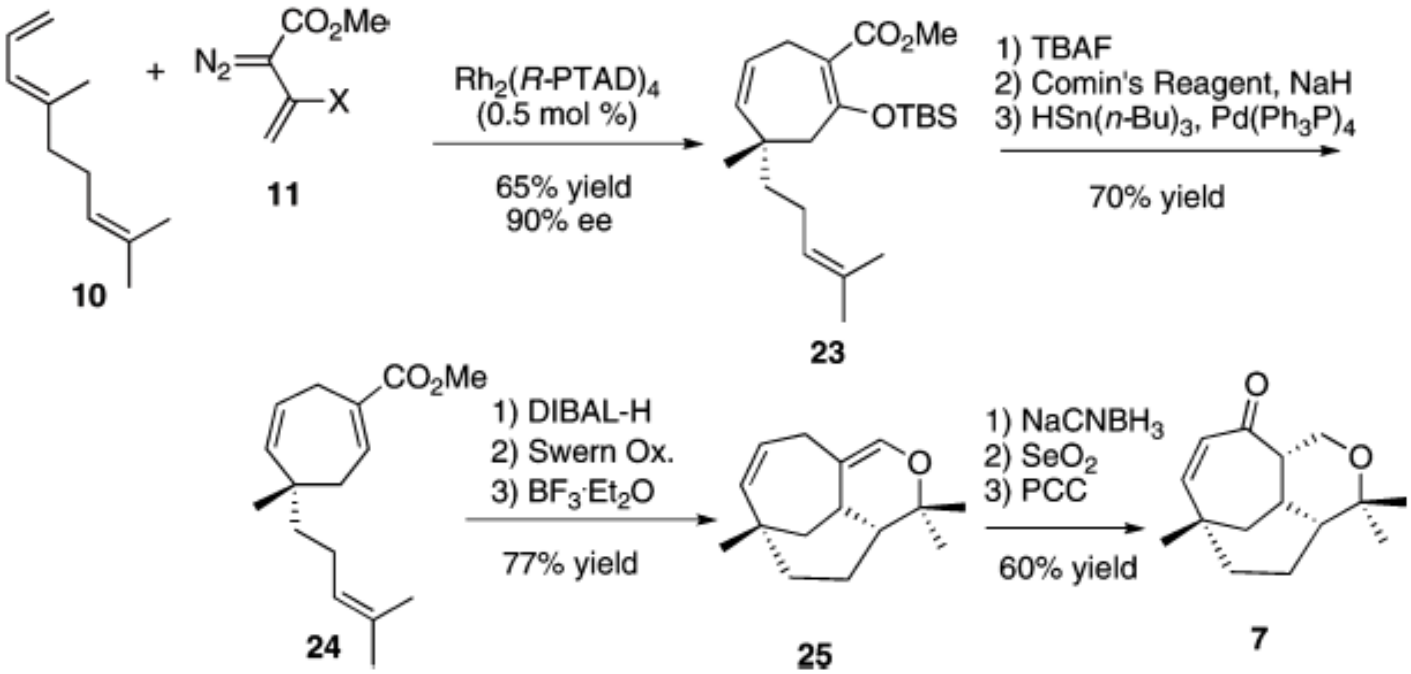
Tricyclic Core of Vibsanin E



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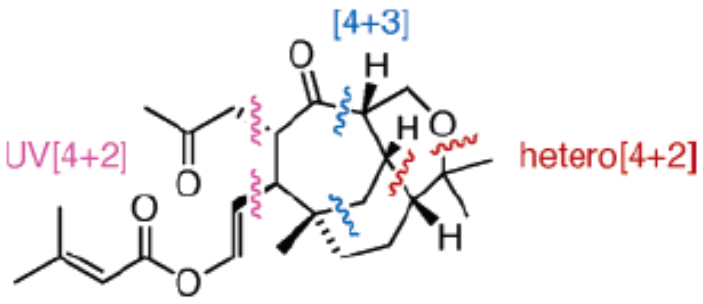
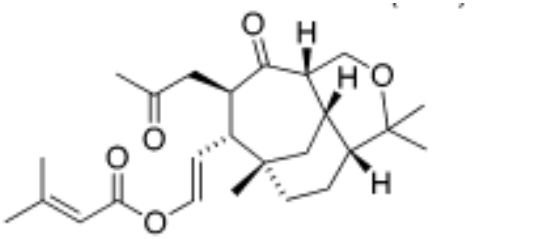
Schwartz, B. D.; Denton, J. R.; Lian, Y.; Davies, H. M. L.; Williams, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 8329.

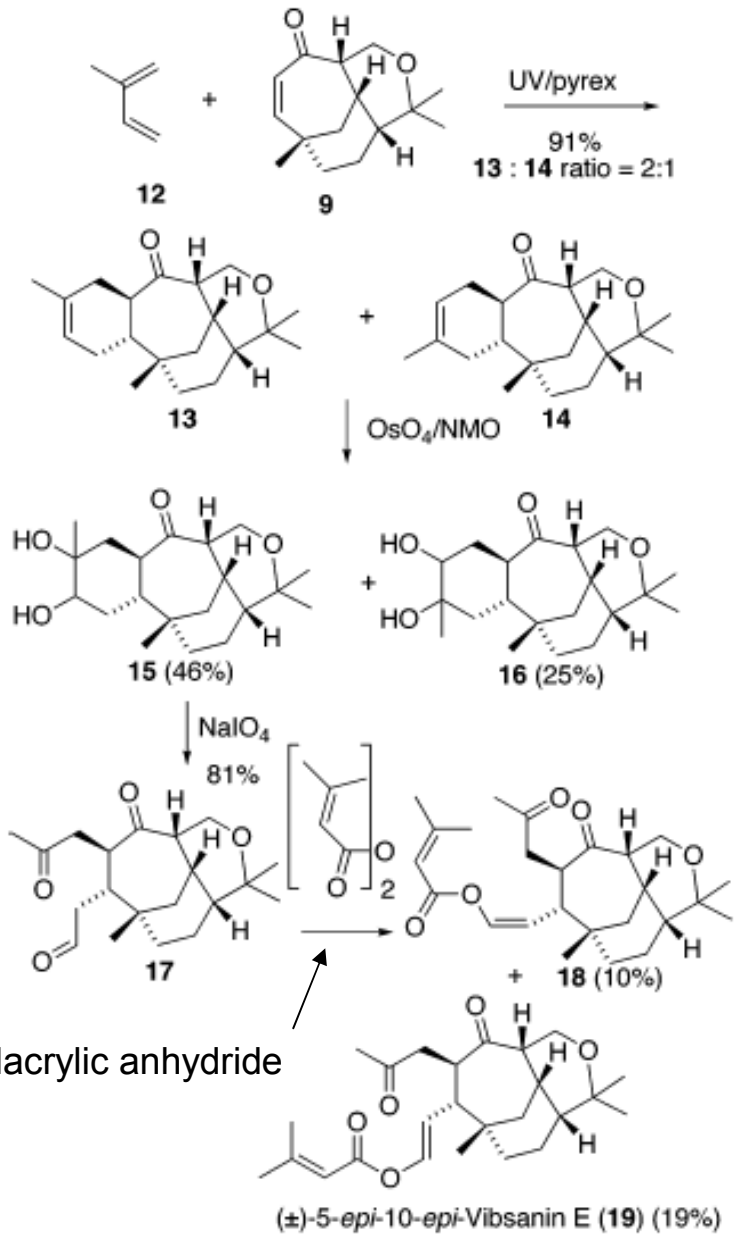
Synthesis of (±)5-epi-10-epi-Vibsanin E



vibsanin E (**1**)

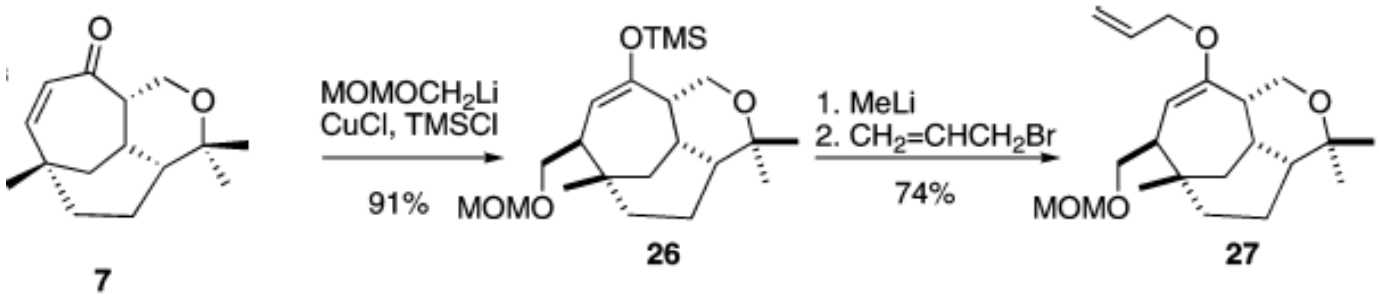


(±)-5-*epi*-10-*epi*-Vibsanin E (**19**) (19%)

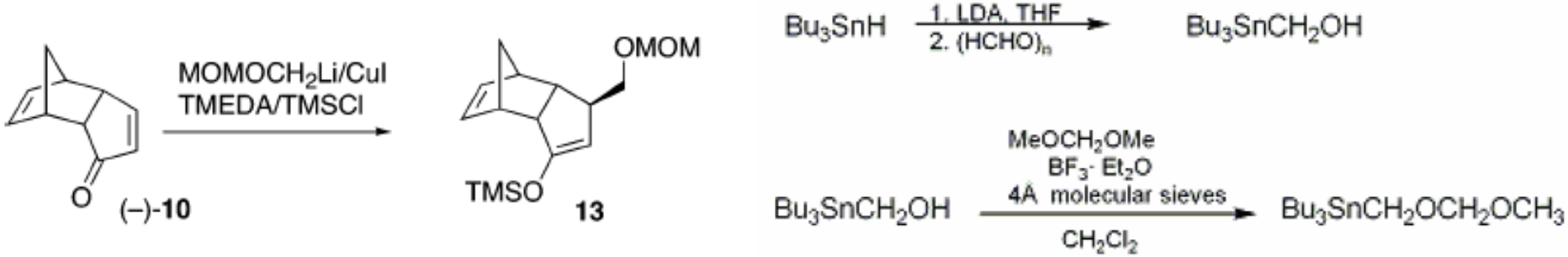


Davies, H. M. L.; Loe, Ø.; Stafford, D. G. *Org. Lett.* **2005**, *7*, 5561.
Nikolai, J.; Loe, Ø.; Dominiak, P. M.; Gerlitz, O. O.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10763

Tandem conjugate addition/alkylation chemistry

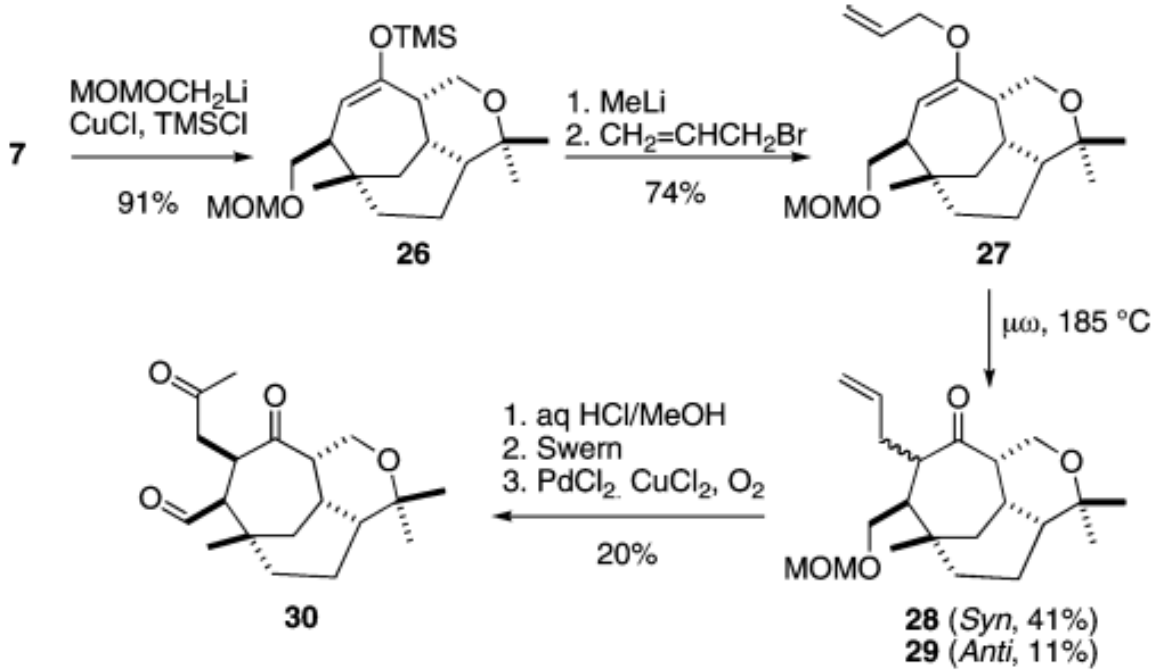


7 26 27



Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K.; Johnson, C. R.; Medich, J. R. *Org. Synth.* **1993**, *71*, 133.
Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron* **1989**, *45*, 495.
Mander, L. N.; Thomson, R. J. *J. Org. Chem.* **2005**, *70*, 1654.
Schwartz, B. D.; Denton, J. R.; Lian, Y.; Davies, H. M. L.; Williams, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 8329.

Claisen rearrangement and deprotection



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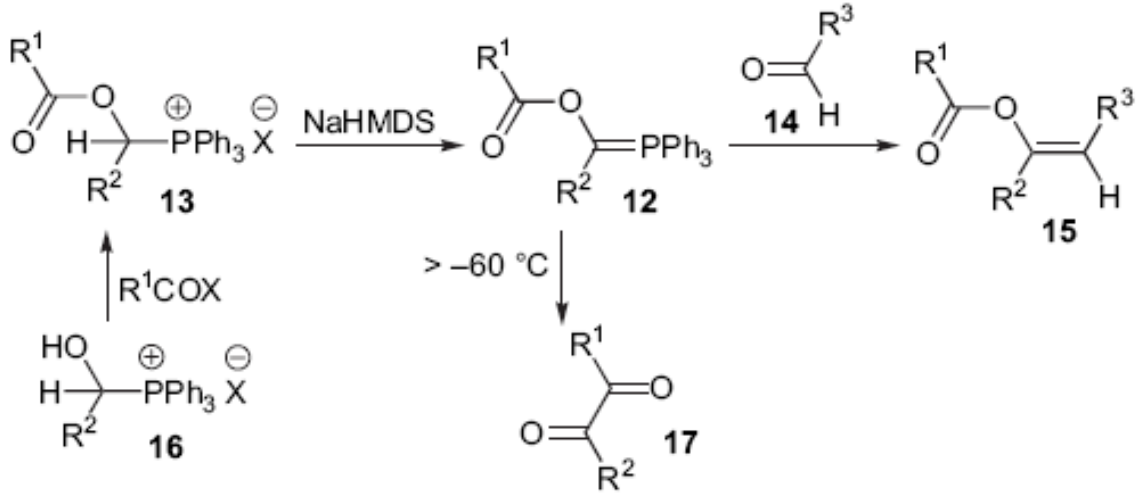
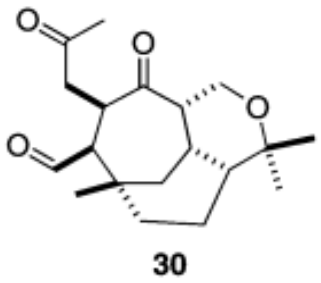
Anders–Gaßner variant on the Wittig reaction

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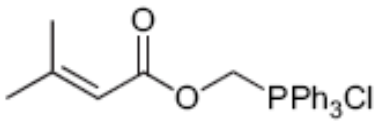
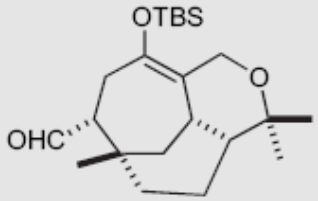
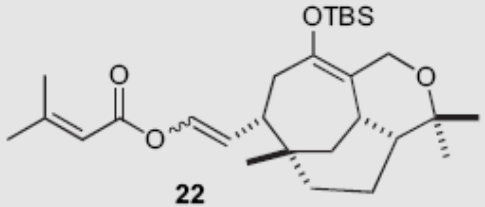
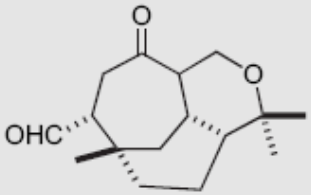
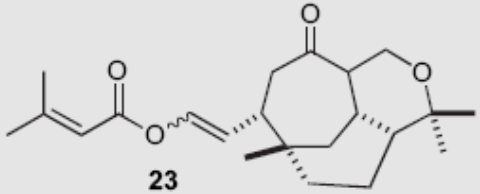

18

Aldehyde	Product	Yield (%)	*E*/*Z* Ratio
	 22	32	2.4:1
	 23	21	3.4:1

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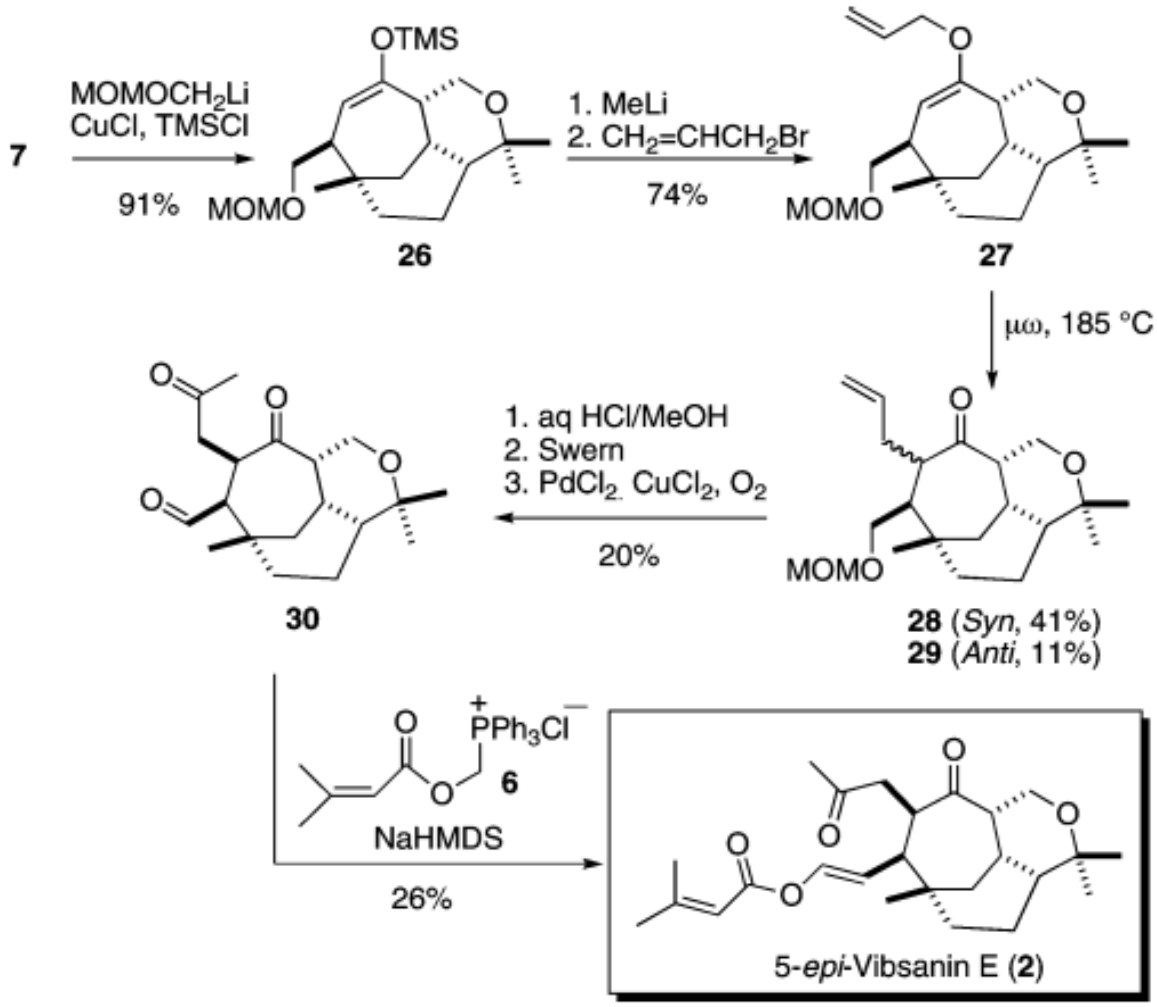
5-epi-Vibsanin E



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Summary

- [4+3] cycloaddition: Tandem asymmetric cyclopropanation/Cope rearrangement.
- Lewis-acid catalyzed hetero-cycloaddition reaction.
- Tandem conjugated addition/alkylation chemistry.
- Anders-Gaßner variant on the Wittig reaction.
- 18 steps.