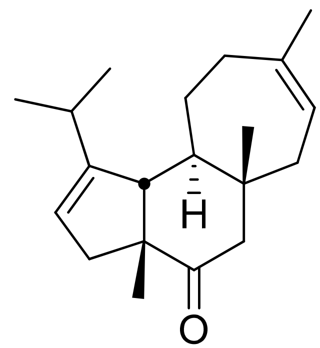
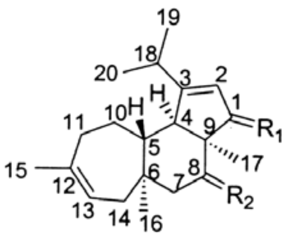
The Total Synthesis of (-)-Cyanthiwigin F by Means of Double Catalytic Enantioselective Alkylation



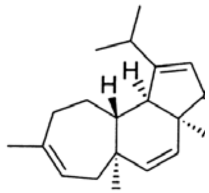
John A. Enquist Jr & Brian M. Stoltz
Nature **2008** *453* 1228-1231

Current Literature
Chenbo Wang @ Wipf Group
July 19th, 2008

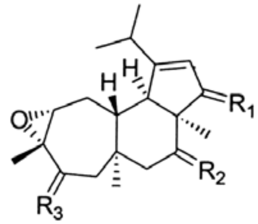
Cyanthiwigin F



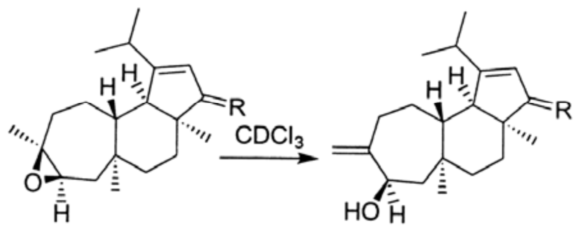
cyanthiwigin A (**1**): R_1=O R_2=H
cyanthiwigin B (**2**): R_1=R_2=O
cyanthiwigin C (**3**): R_1=α-OH R_2=H
cyanthiwigin D (**4**): R_1=α-OH R_2=β-OH
cyanthiwigin E (**5**): R_1=O R_2=β-OH
cyanthiwigin F (**6**): R_1=H R_2=O



cyanthiwigin G

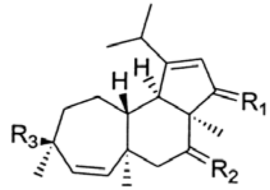


cyanthiwigin M (**13**): R_1=α-OH R_2=H R_3=β-OH
cyanthiwigin N (**14**): R_1=O R_2=O R_3=β-OH
cyanthiwigin O (**15**): R_1=O R_2=O R_3=O
cyanthiwigin P (**16**): R_1=O R_2=H R_3=β-OH
cyanthiwigin Q (**17**): R_1=O R_2=H R_3=O

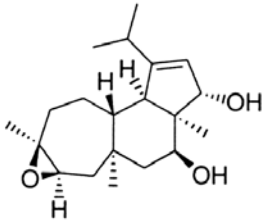


cyanthiwigin H (**8**): R=O
cyanthiwigin K (**11**): R=α-OH

cyanthiwigin I (**9**): R=O
cyanthiwigin L (**12**): R=α-



cyanthiwigin R (**18**): R_1=O R_2=O R_3=OOH
cyanthiwigin S (**19**): R_1=O R_2=O R_3=OH
cyanthiwigin T (**20**): R_1=O R_2=β-OH R_3=OOH
cyanthiwigin U (**21**): R_1=O R_2=H R_3=OH
cyanthiwigin V (**22**): R_1=α-OH R_2=O R_3=OH
cyanthiwigin W (**23**): R_1=α-OH R_2=H R_3=OH
cyanthiwigin X (**24**): R_1=α-OH R_2=β-OH R_3=OH

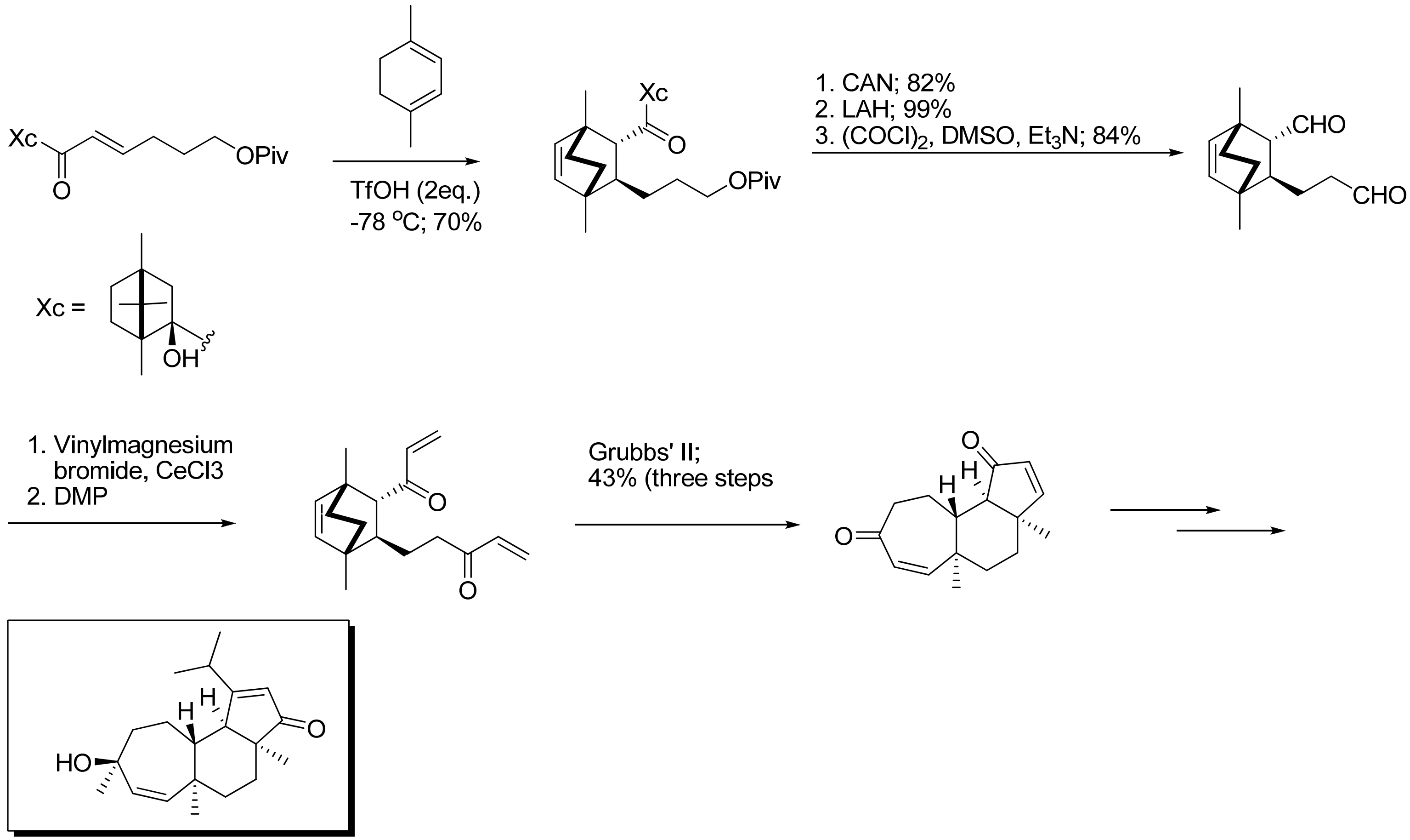


cyanthiwigin J (**10**)

Peng, J. et al. *Tetrahedron* **2002** *58* 7809

- Isolated from the Jamaican sponge *Myrmekioderma styx* in 2002.
- One of the 30 known cyanthiwigin natural products, all of which belong to cyathins.
- Cytotoxic against human primary tumour cells (with a half-maximal inhibitory concentration of 3.1 μg ml-1).

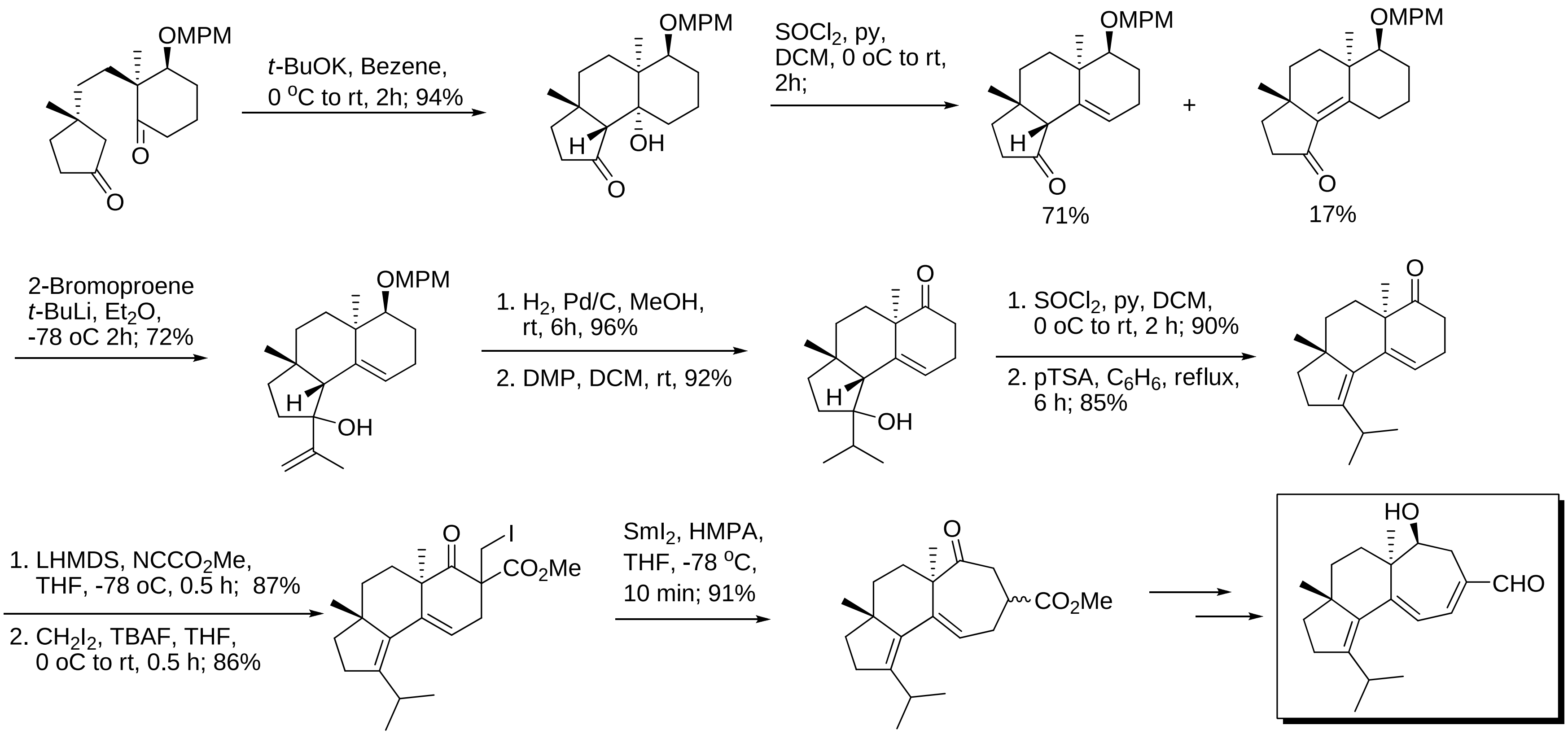
Cyanthin Synthesis: Previous Works



Cyathiwigin U

Philips, A. J. et al *J. Am. Chem. Soc.*, **2005** *127*, 5334

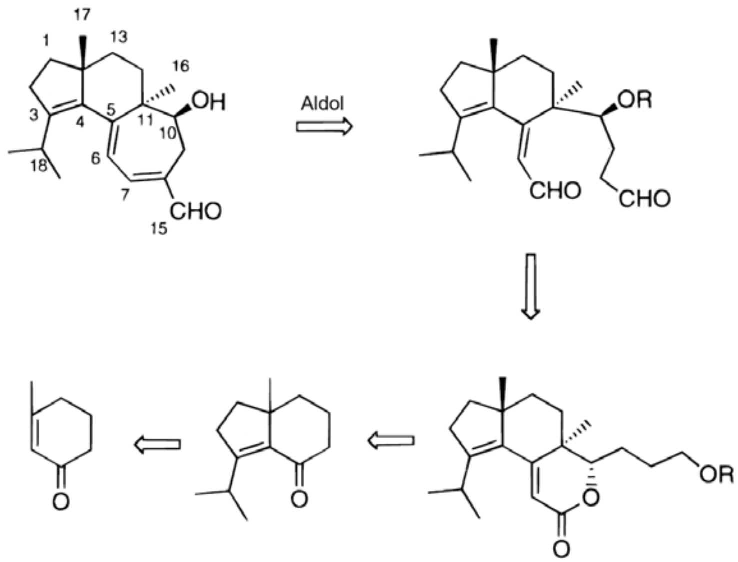
Cyanthin Synthesis: Previous Works



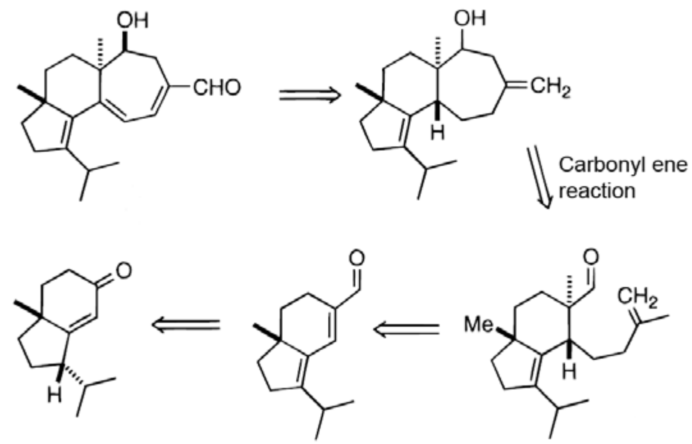
Allocyathin B_2

Nakada, M. et al *Org. Lett.* **2004**, 6, 4897.

Cyanthin Synthesis: Previous Works



- Allocyathin B2



- Allocyathin B2

Tori, M. et al. *J. Org. Chem*. **1998**, *63*, 306.
Snider, B. B et al *J. Am. Chem. Soc*. **1996**, *118*, 7644.

The Enantioselective Tsuji Allylation

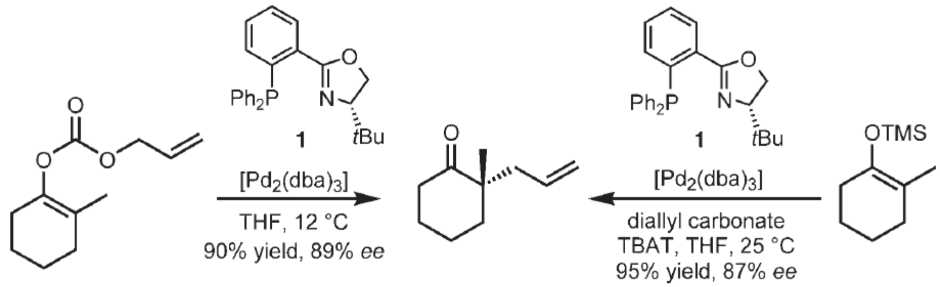


Table 2. Enantioselective Tsuji Enol Carbonate Allylation[a]

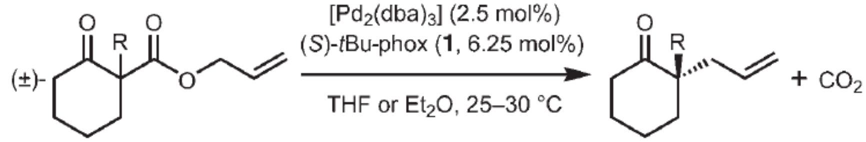
entry	substrate	product		time (h)	% yield[b]	% ee[c]
1	OCO_2allyl **1**	**2**		2	85	87
2[d]				5	85	88 (96)[e]
3[f]				9	90	89
4	OCO_2allyl		R = CH_2CH_3	2	96	92
5[g]			R = t-Bu	10	55[h]	82
6			R = CH_2Ph	2	96	85
7			R = $(CH_2)_3OBn$	2	87	88
8[g]	$OCO_2$2'-Me-allyl			8	89	91
9	OCO_2allyl			1	94	92
10	OCO_2allyl			1	87	86
11	OCO_2allyl			1	91	89
12[i]	OCO_2allyl		R = H	2	87	91
13[i]			R = OCH_3	8	94	91
14	OCO_2allyl		n = 1	6	81	87
15			n = 2	2	90	79

Table 3. Enantioselective Tsuji Enol Silane Allylation[a]

entry	substrate	product		time (h)	% yield[b]	% ee[c]
1	OTMS		R = CH_3	2	95	87
2			R = CH_2CH_3	3	96	92
3[d]	OTMS			4	79	91
4	OTMS			2	99	81
5	OTMS		n = 1	2	94	86
6			n = 2	3	96	79

Behenna, D. C. & Stoltz, B. M. *J. Am. Chem. Soc*. **2004** 126, 15044

Pd-Catalyzed Decarboxylative Allylation of β-Ketoesters



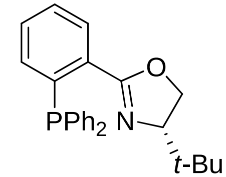


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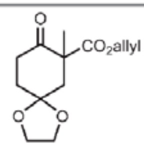
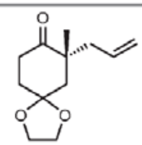
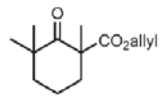
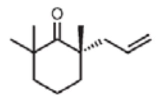
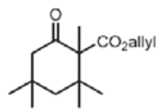
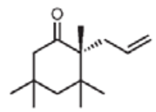
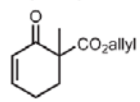
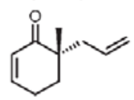
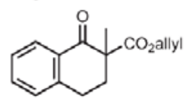
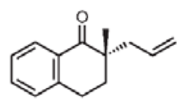
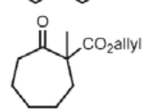
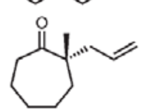
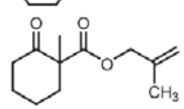
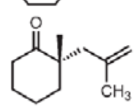
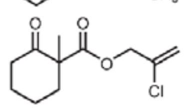
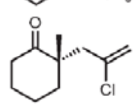
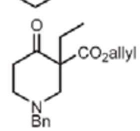
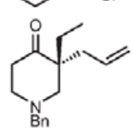
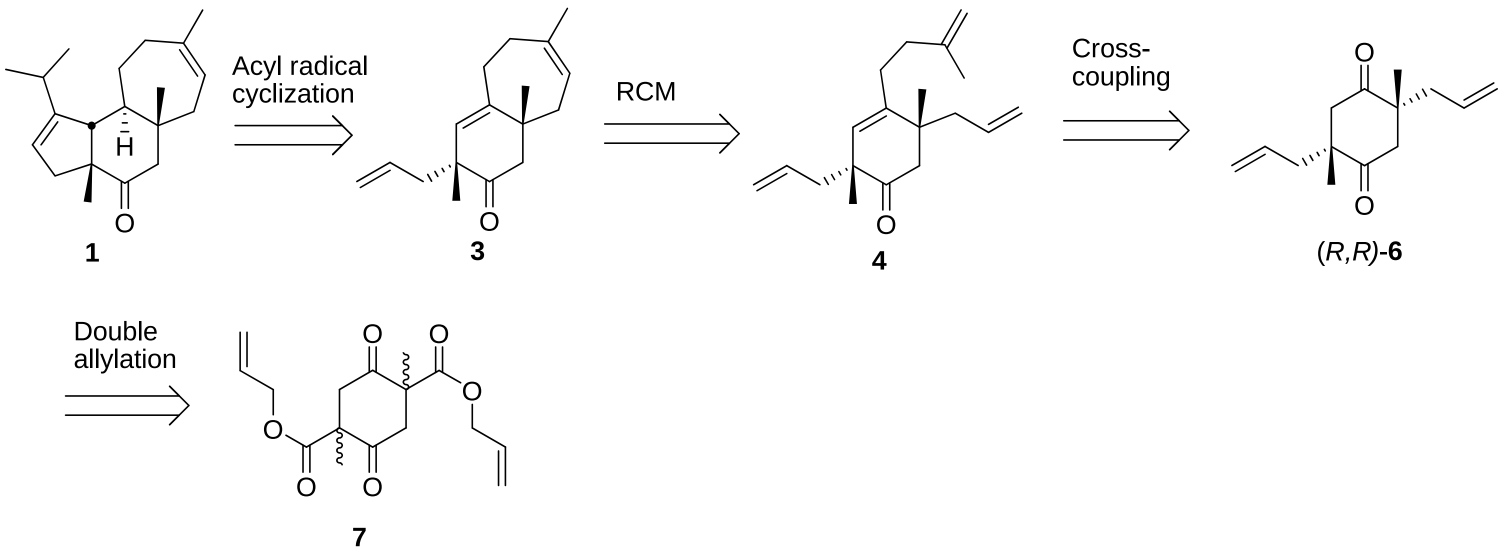
Table 2: Enantioconvergent decarboxylative allylation of β-ketoesters.

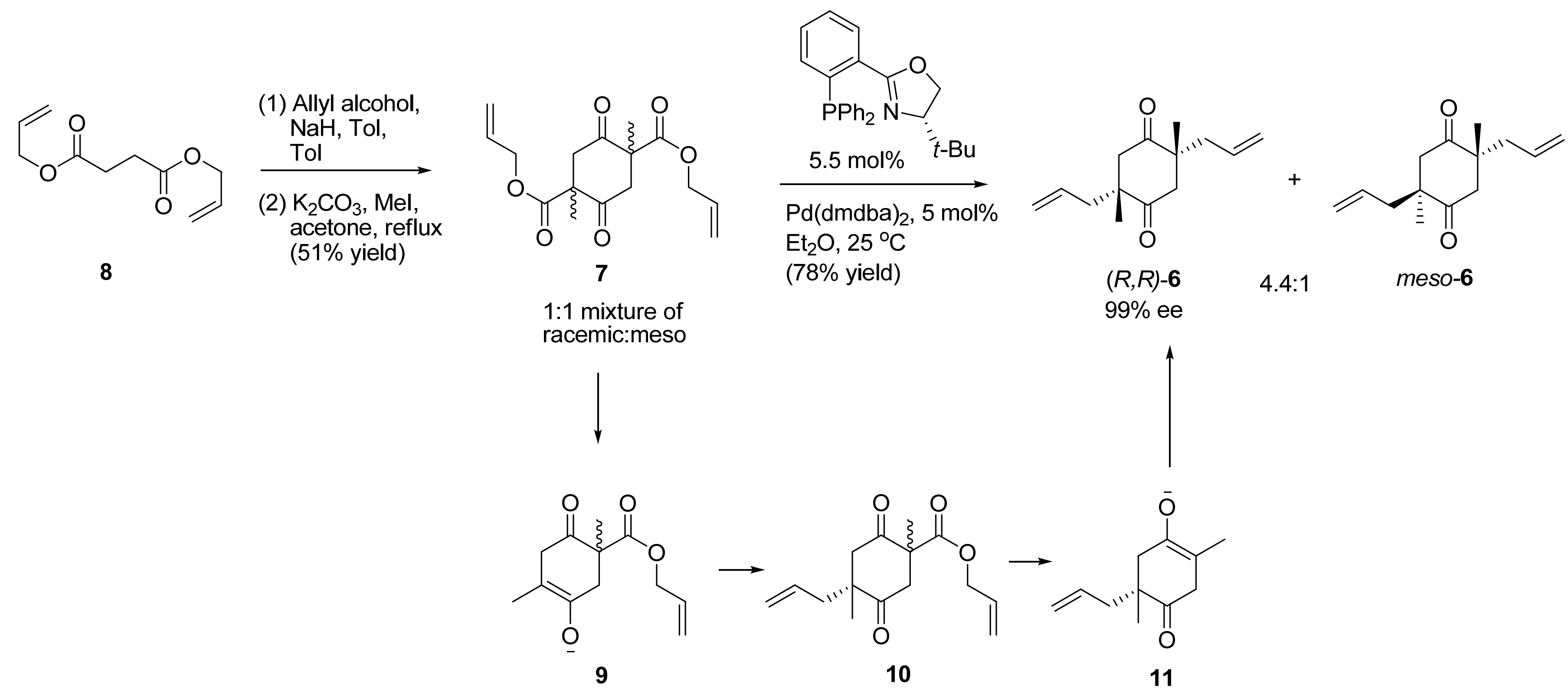
Entry	Substrate	Product	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1			25	1.5	94	85
2[c]			25	24	94	86
3			30	9	89	90
4			25	5	90	85
5[d,e]			30	4	77	90
6[d]			25	10	97	92
7			25	9.5	83	87
8[d]			35	6.5	87	92
9[d,e]			35	2.5	87	91
10			25	2.5	91	92

Stoltz, B. M. et al *Angew. Chem. Int. Edn Engl.* **2005** 44, 6924

Title Paper: Retrosynthesis



Double Catalytic Enantioselective Stereoablative Allylation



Catalytic Enantioselective Stereoablative Reactions

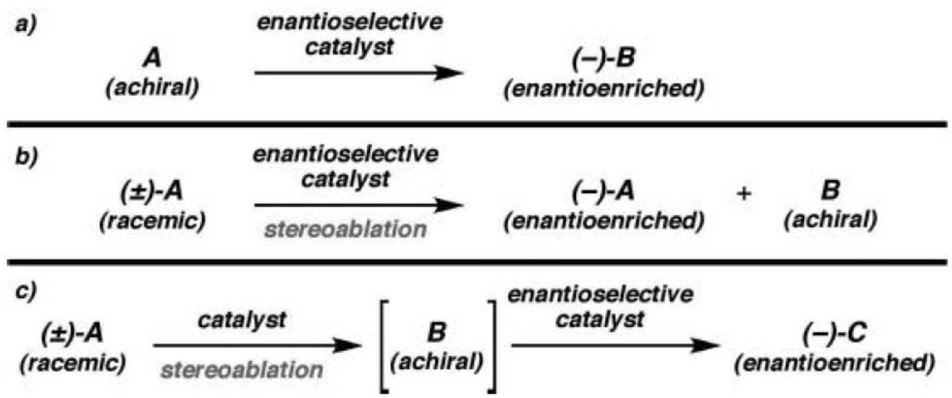
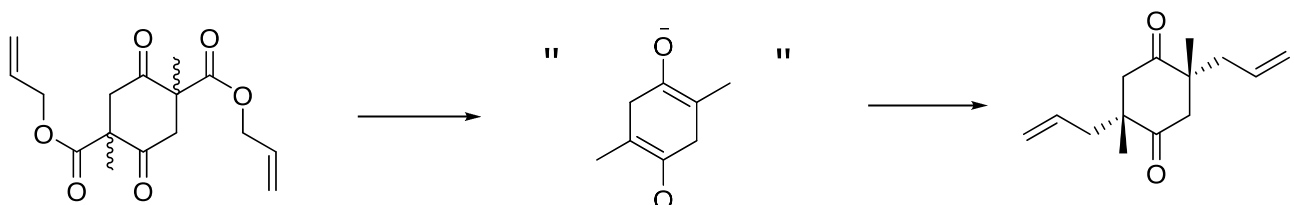


Fig. 1 Strategies for enantioselective catalysis.



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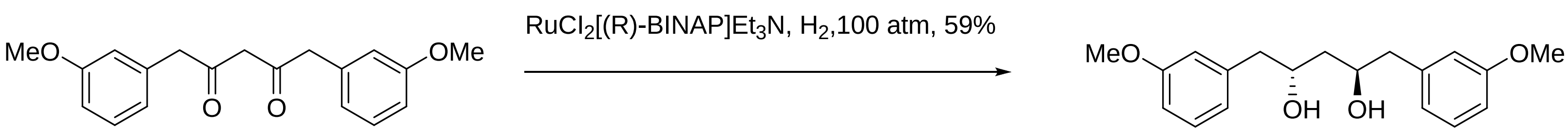
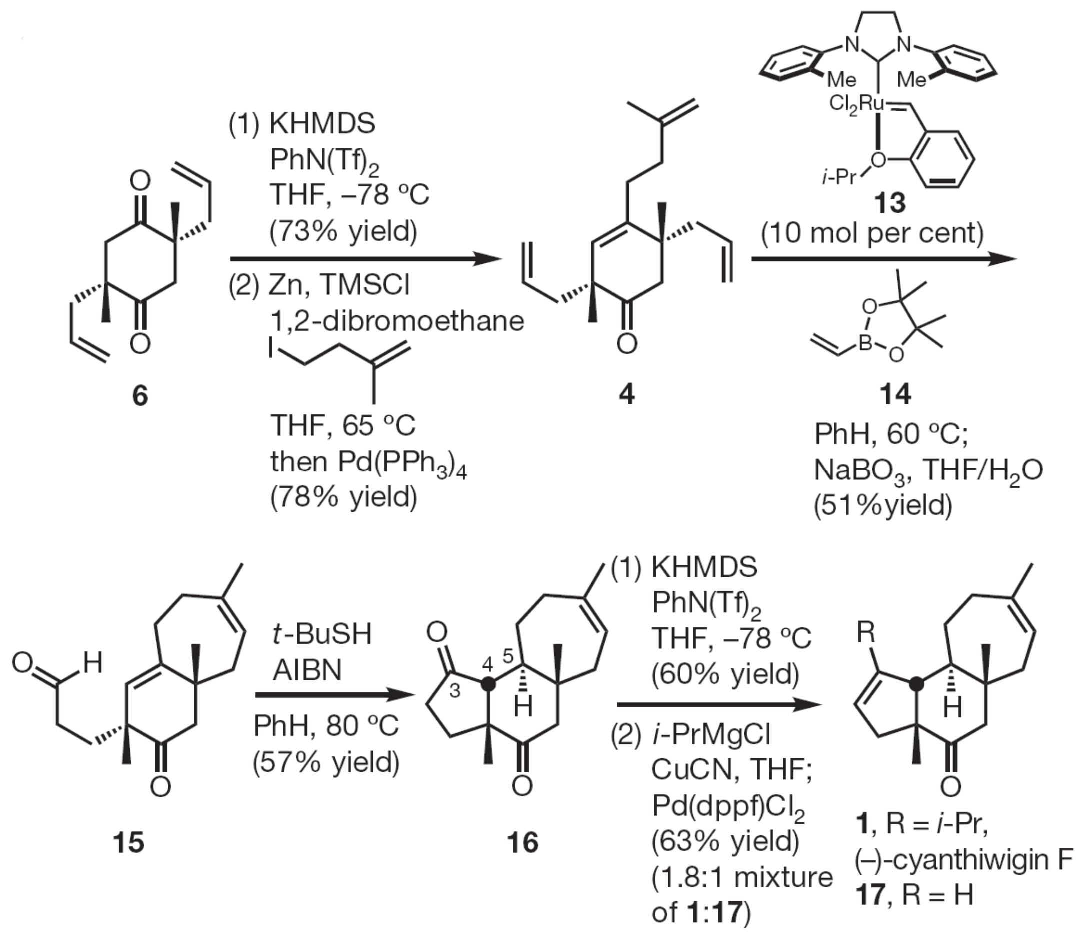
(*R*,*R*)-**6**

vs.



Stoltz, B. M. et al *Org. Biomol. Chem.*, **2007**, *5*, 3571
Schreiber, S. L. et al *J. Am. Chem. Soc.* **1993**, *115,* 3360

Completion of The Synthesis



Summary

- The total synthesis of (-)-cyanthiwigin F was accomplished in 10 steps, 1.2% overall yield
- Key steps include a double catalytic enantioselective allylation, RCM and acyl radical cyclization.
- The synthesis is protection-group-free.