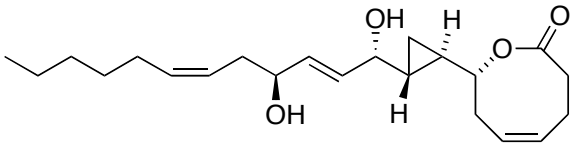
Asymmetric Total Synthesis of Solandelactone E: Stereocontrolled Synthesis of the 2-ene-1,4-diol Core through a Lithiation–Borylation–Allylation Sequence



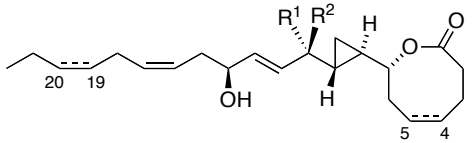
Anna Robinson and Varinder K. Aggarwal
Angew. Chem. Int. Ed. **2010**, 49, 6673 –6675

Sammi Tsegay
Current Literature
September, 2010

Isolation and Structural Features:

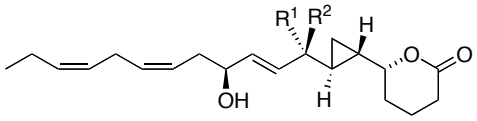
- Isolated in 1996 by Shin and co-workers from Hydroid *Solandria secunda,* South Korean Island of Jaeju (Jejudo).

- Belongs to the oxylipins, oxygenated fatty acids derived from the 18, 20 or 22C fatty acid arachidonic acid and docosahexenoic acid.

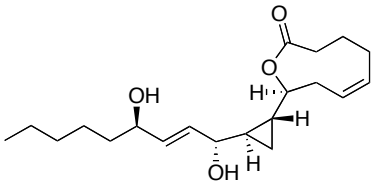


R^1 = H, R^2 = OH:
solandelactone B
solandelactone D ($\Delta^{19,20}$)
solandelactone F ($\Delta^{4,5}$)
solandelactone H ($\Delta^{4,5}$, $\Delta^{19,20}$)

R^1 = OH, R^2 = H:
solandelactone A
solandelactone C ($\Delta^{19,20}$)
solandelactone E ($\Delta^{4,5}$)
solandelactone G ($\Delta^{4,5}$, $\Delta^{19,20}$)



R^2 = OH, constanolactone A
R^1 = OH, constanolactone B

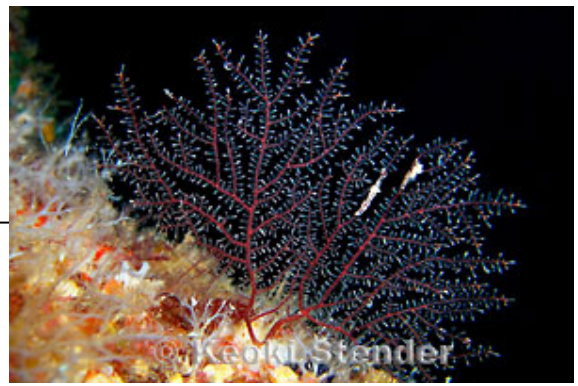


halicholactone

- Solandelactones C,D and G are known to inhibit FTase (Farnesyl transferase, expression of *ras* proteins found in cancer cells).

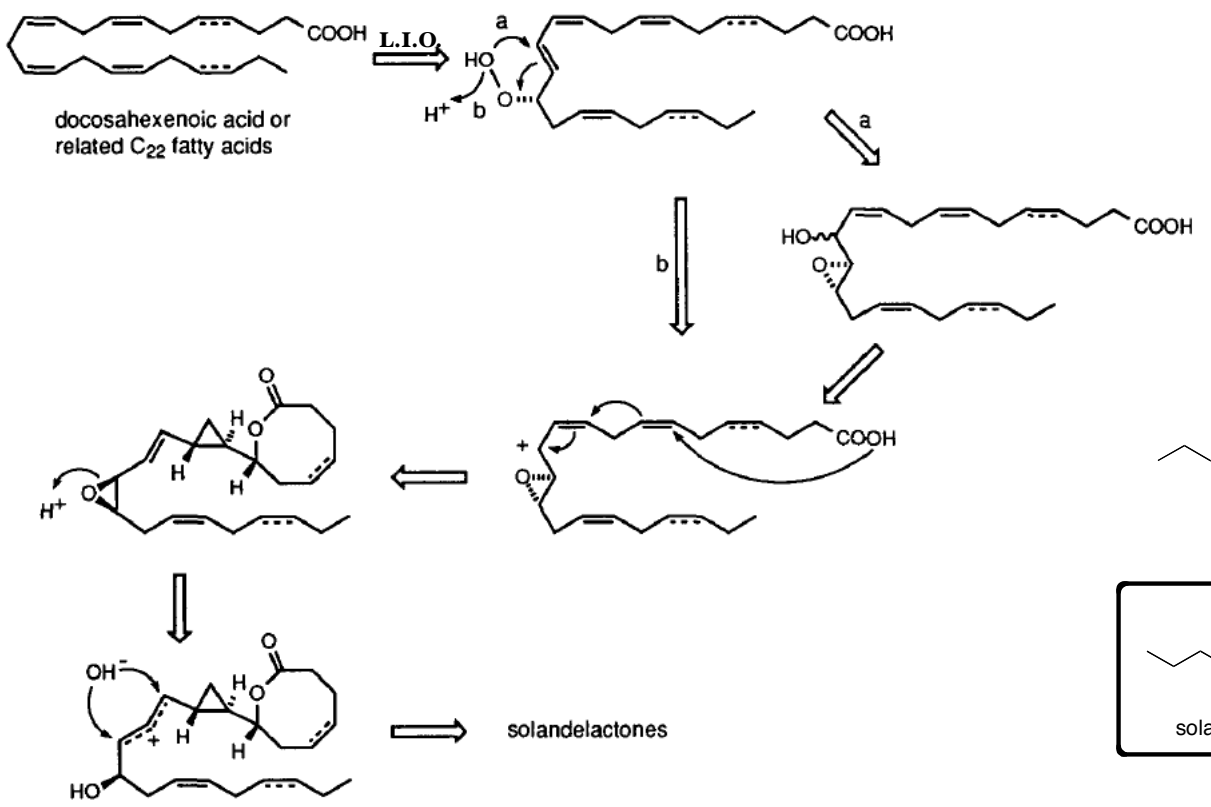
- Key features:
  - trans-cyclopropane.
  - 8-membered lactone linked to cylcopropane.
  - 1,4-diol system.

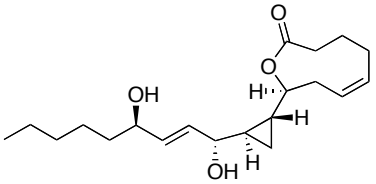
Hydroid *Solandria secunda*

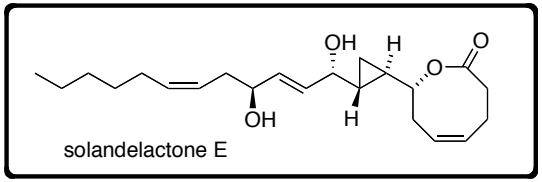


Seo, Y.; Cho, K. W.; Rho, J.-R.; Shin, J.; Kwon, B.-M.; Bok, S.-H.; Song, J.-I. *Tetrahedron.* **1996**, *52*, 10583.
Lee, S.-H.; Kim, M.-J.; Bok, S. H.; Lee, H.; Kwon, B.-M.; Shin, J.; Seo, Y. *J. Org. Chem.* **1998**, 63, 7111.
Faulkner, D. *J. Nat. Prod. Rep*. **1995**, 12, 223.

Proposed Biosynthesis:





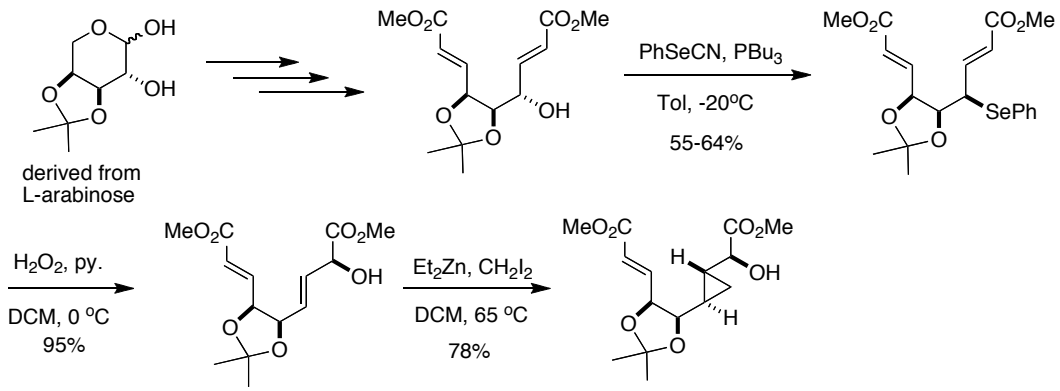


L.I.O. = Lipoxygenase-induced oxidation

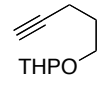
Nagle, D. G.; Gerwick, W. H. *J. Org. Chem.* **1994**, 59, 7227
Gerwick, W. H. *Chem. Rev.* **1993**, 93, 1807.

Martin's Synthesis:

1st Generation Approach:

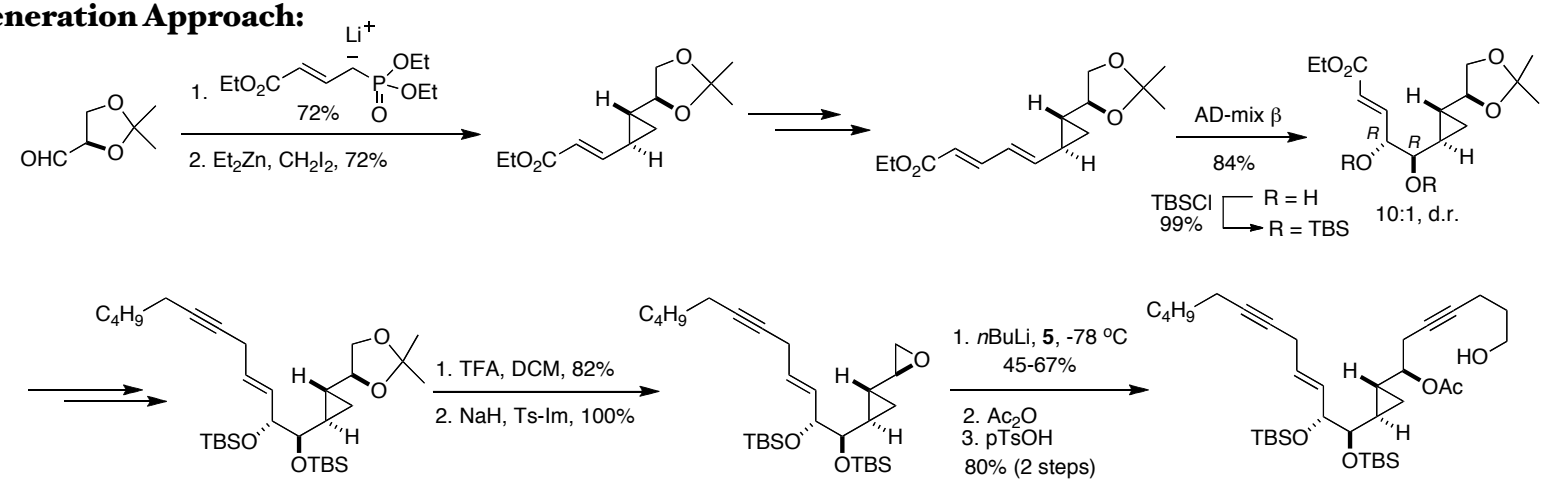


- Selenation step proved problematic up on scale up giving 10-15% yield.



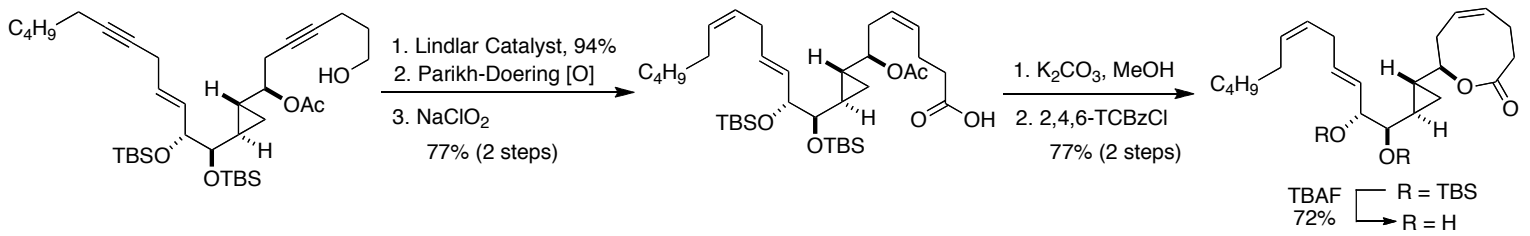
5

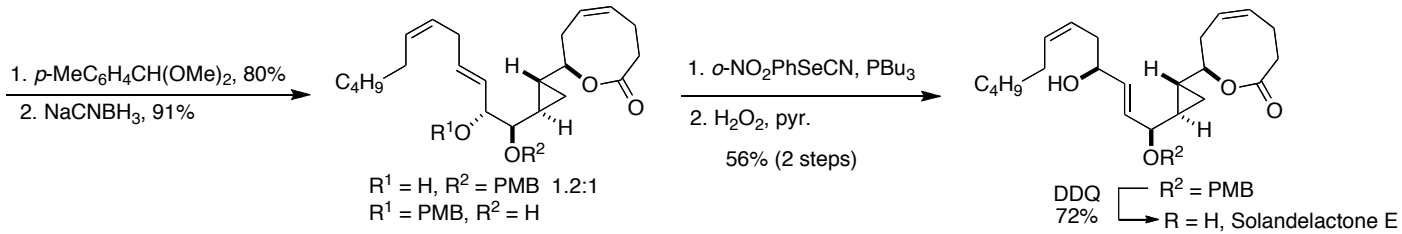
2nd Generation Approach:



Davoren, J. E.; Martin, S. F. *J. Am. Chem. Soc.* **2007**, 129, 510.
Davoren, J. E.; Harcken, C.; Martin, S. F. *J. Org. Chem.* **2008**, 73, 391.

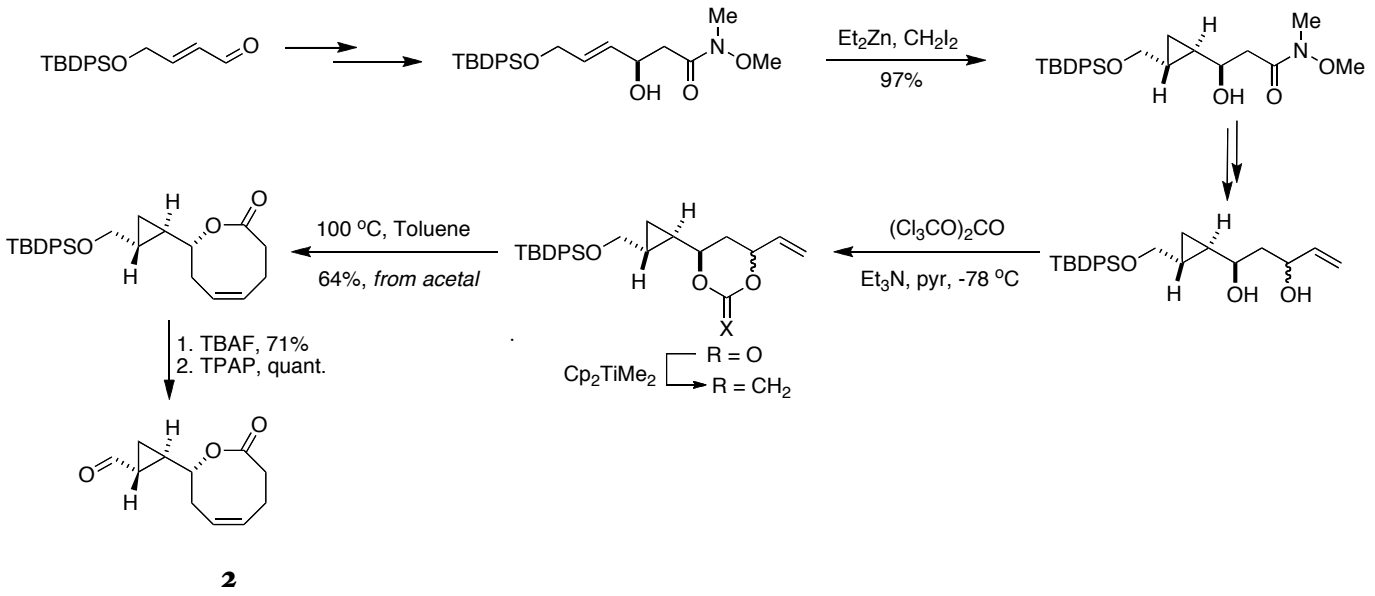
Martin's Approach: 2nd Generation Synthesis contd.





Davoren, J. E.; Harcken, C.; Martin, S. F. *J. Org. Chem.* **2008**, 73, 391.
Nishibayashi, Y.; Uemura, S. *Top. Curr. Chem.* **2000**, 208, 2015.
Pietruszka, J.; Rieche, A. C. *Adv. Synth. Catal*. **2008**, 350, 1407.

White's Access to Solandelactones E and F:



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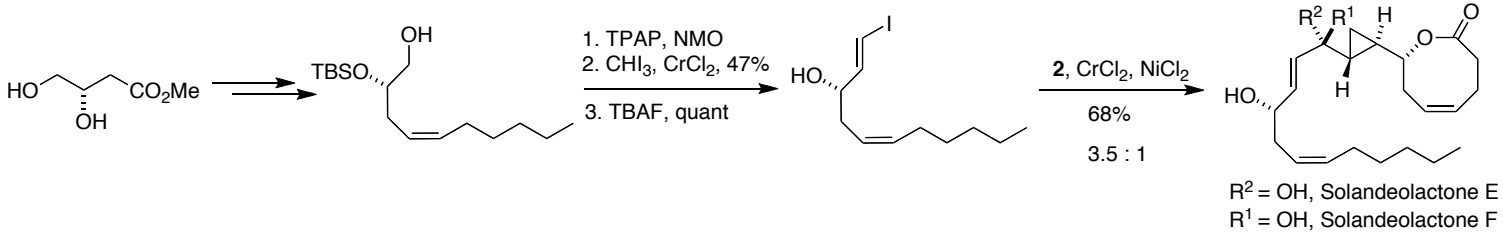
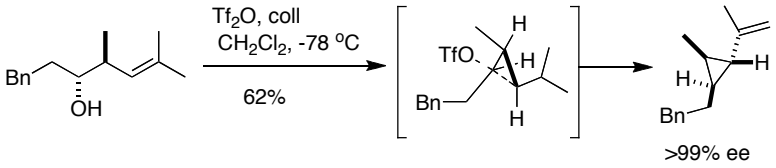


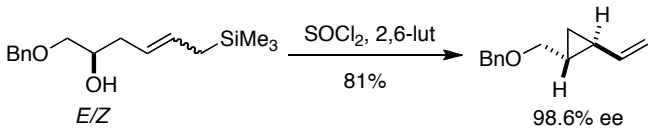
White, J. D.; Martin, W. H. C.; Lincoln, C.; Yang, J. *Org. Lett.* **2007**, 9, 3481.
White, J. D.; Lincoln, C. M.; Yang, J.; Martin, W. H. C.; Chan, D. B. *J. Org. Chem.* **2008**, 73, 4139.

Enantioselective cyclopropanation:

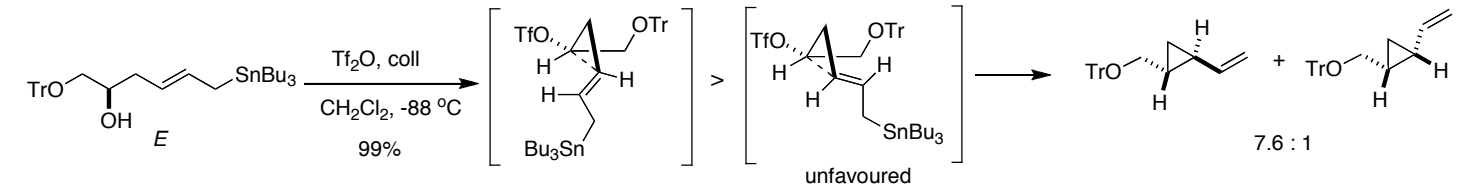
Suzuki's cyclopropanation:



Taylor's extension:



White's Work:

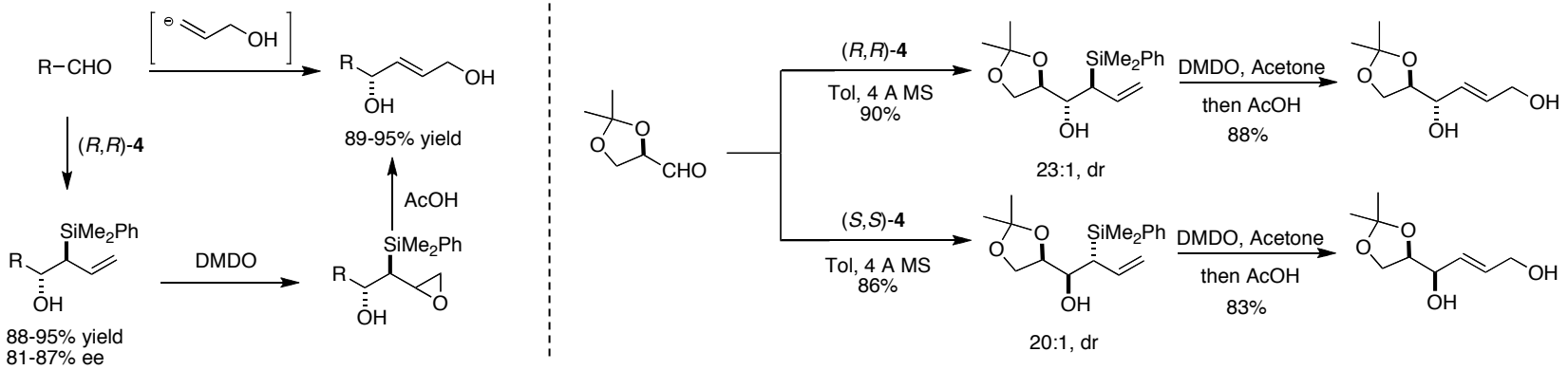


• White later used this methodology in the synthesis of Solandelactone A, B, E and F.

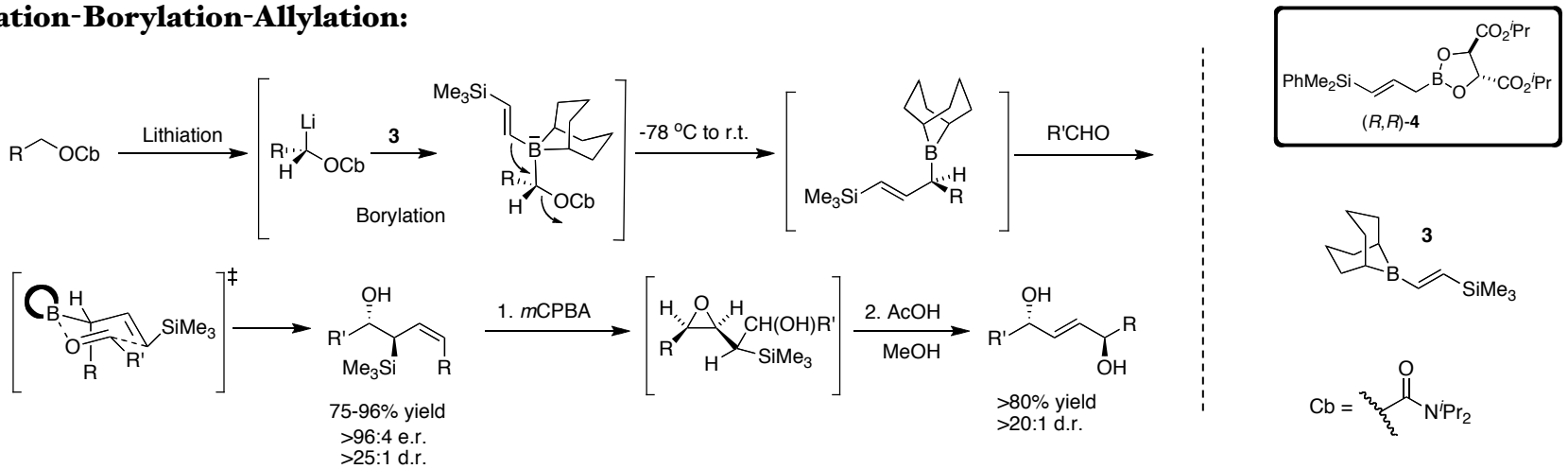
Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, K. *Synlett.* **1995**, 739.
Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Suzuki, K. *Bull. Chem. Soc. Jpn.* **1996**, 69, 31.
Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, 123, 2964.
White, J. D.; Lincoln, C. M.; Yang, J.; Martin, W. H. C.; Chan, D. B. *J. Org. Chem.* **2008**, 73, 4139.

Preparation of 2-ene-1,4-diol:

Roush's Methodology:

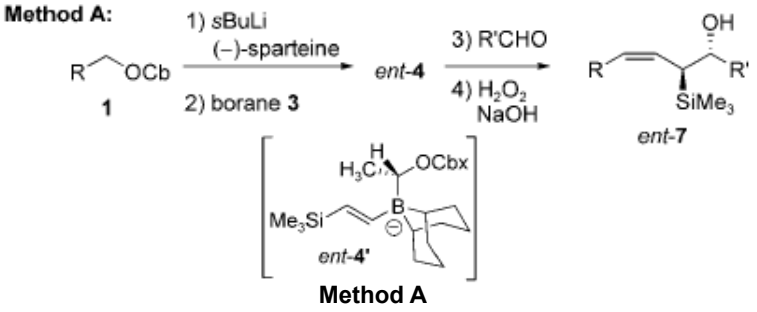


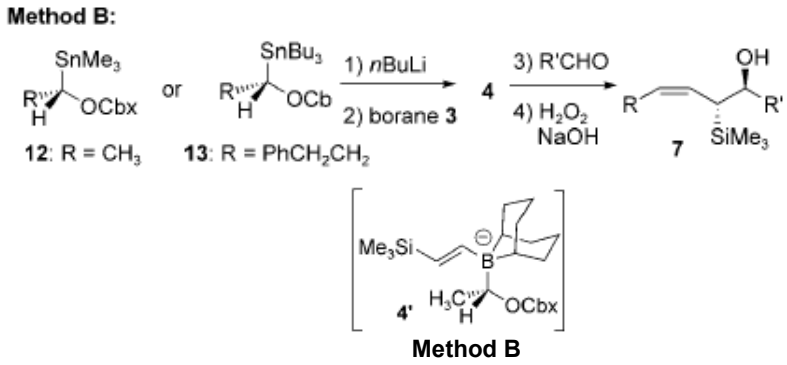
Lithiation-Borylation-Allylation:

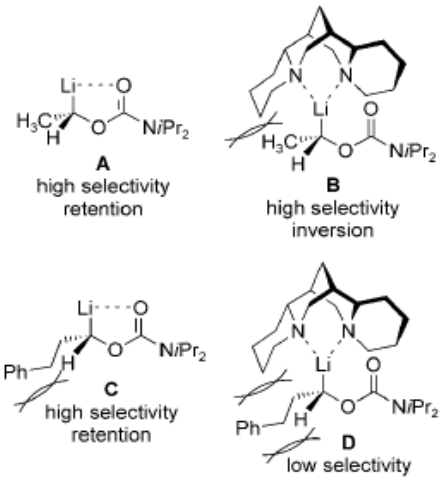


Binanzer M.; Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010**, 49, 4264.
Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2282.

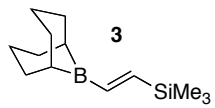
One-pot synthesis of β-hydroxy allylsilanes:





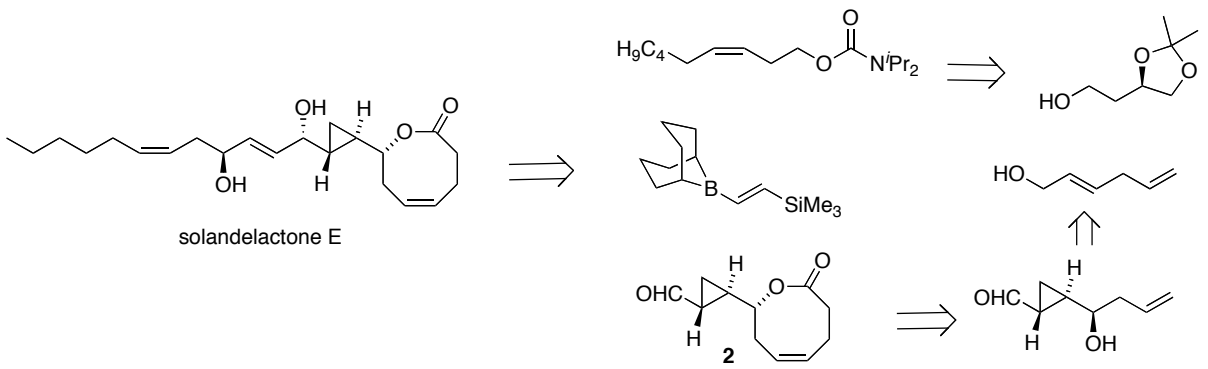


Entry	R (substrate)	R′	Yield [%][d]	7/ent-7[e]	Z/E[h]	anti/syn[h]	
1	CH_3[b] (1a)	nBu	67	7:93[f]	> 25:1	> 25:1	Method A
2	CH_3[b] (1a)	Cy	65	7:93[f]	> 25:1	> 25:1	
3	CH_3[b] (1a)	Ph	64	7:93[f]	> 25:1	> 25:1	
4	CH_3[c] (12)	nBu	95	95:5[g]	> 25:1	> 25:1	Method B
5	CH_3[c] (12)	Cy	96	95:5[g]	> 25:1	> 25:1	
6	CH_3[c] (12)	Ph	95	94:6[g]	> 25:1	> 25:1	
7	$PhCH_2CH_2$[c] (13)	nBu	81	98:2[g]	> 25:1	> 25:1	
8	$PhCH_2CH_2$[c] (13)	Cy	74	98:2[g]	> 25:1	> 25:1	
9	$PhCH_2CH_2$[c] (13)	Ph	81	98:2[g]	> 25:1	> 25:1	

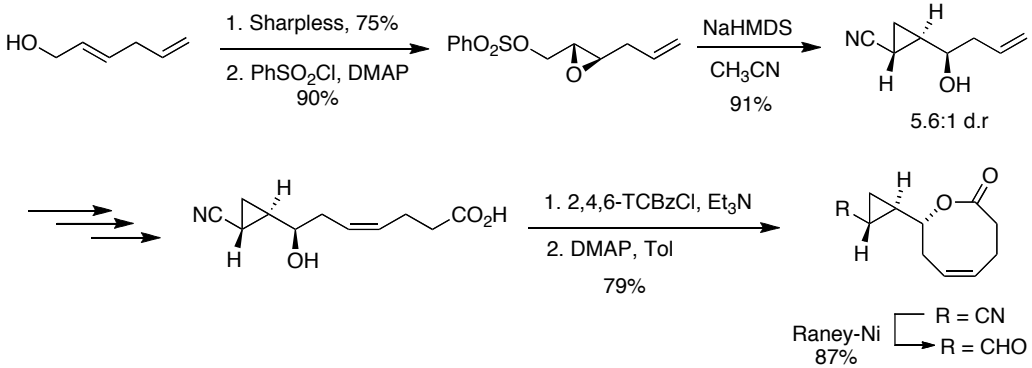


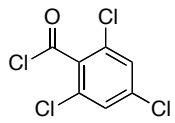
Binanzer M.; Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010**, 49, 4264

Title Paper: Retrosynthetic Approach



Preparation of aldehyde 2:

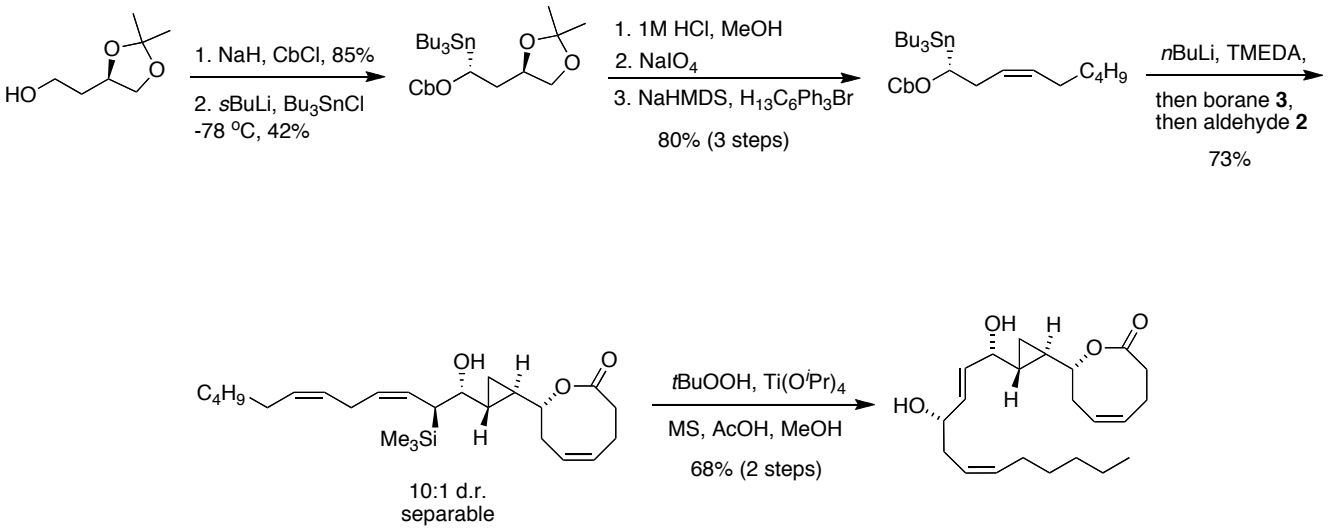


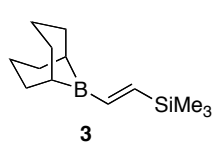


2,4,6-TCBzCl = 2,4,6-Trichlorobenzoyl chloride

Robinson, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010**, 49, 6673.
Taber, D. F.; Bui, G.; Chen, B. *J. Org. Chem.* **2001**, 66, 3423.

Final Steps towards Solandelactone E:





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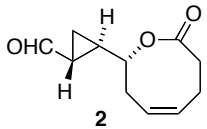
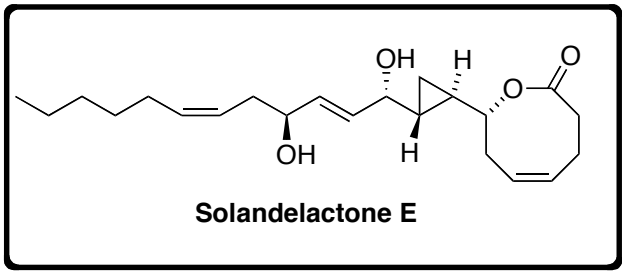


2

Robinson, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010**, 49, 6673.

Conclusion:

- Total synthesis of Solandelacone E was completed using methodology developed by the group: Lithiation, borylation and allylation sequence on a highly functionalized substrate.
- The synthesis was completed in 13 steps (longest linear sequence).
- Stereochemical issues associated with C11 centre was solved using this methodology.
- Opens the avenue for such similarly-complex natural product e.g. oxylipin family.



Solandelactone E