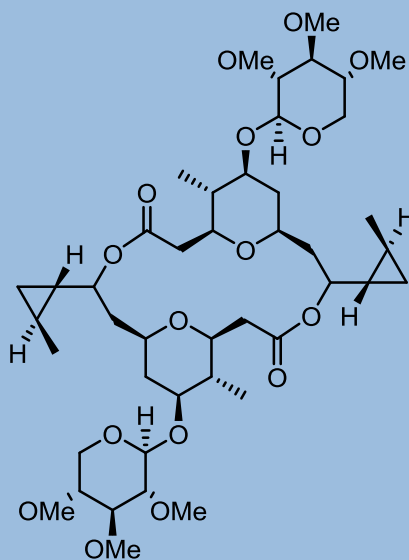


Tandem Allylboration-Prins Reaction for the Rapid Construction of Substituted Tetrahydropyrans : Application to the Total Synthesis of (-)-Clavosolide A



Millán, J. R. Smith, V. K. Aggarwal, *Angew. Chem. Int. Ed.*, **2016**, ASAP
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Valentin Soulard
February 4, 2016

Varinder K. Aggarwal

> Education :

1980-1983 : Undergraduate studies, University of Cambridge

1983-1986 : PhD with Dr. Stuart Warren, University of Cambridge

1986-1988 : Post-doc with Prof. Gilbert Stork, Columbia University

> Now Professor in University of Bristol

> Research interest :

Stereoselective Synthesis

Mechanistic Studies

Total synthesis of natural and non-natural products

Organoboron Chemistry



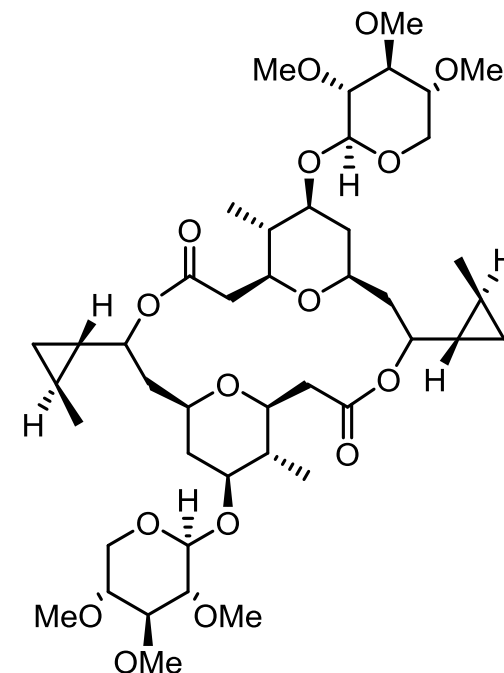
(-)-Clavosolide A



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UNIVERSITÄT
BERN

- > Clavosolides A-D : isolated from a marine sponge : *Myriastra clavosa* collected in the Philippines.
- > Dimeric Glycosidic Macrolide
- > Biological activity of oxacyclic dimers :
 - Anti-HIV
 - Antipsoriatic
 - Antibiotic
 - ...
- > Structure found in 2002 by Faulkner and revised by Willis in 2005, in 2006 by Chakraborty and finally Lee in 2006.
- > Challenging target



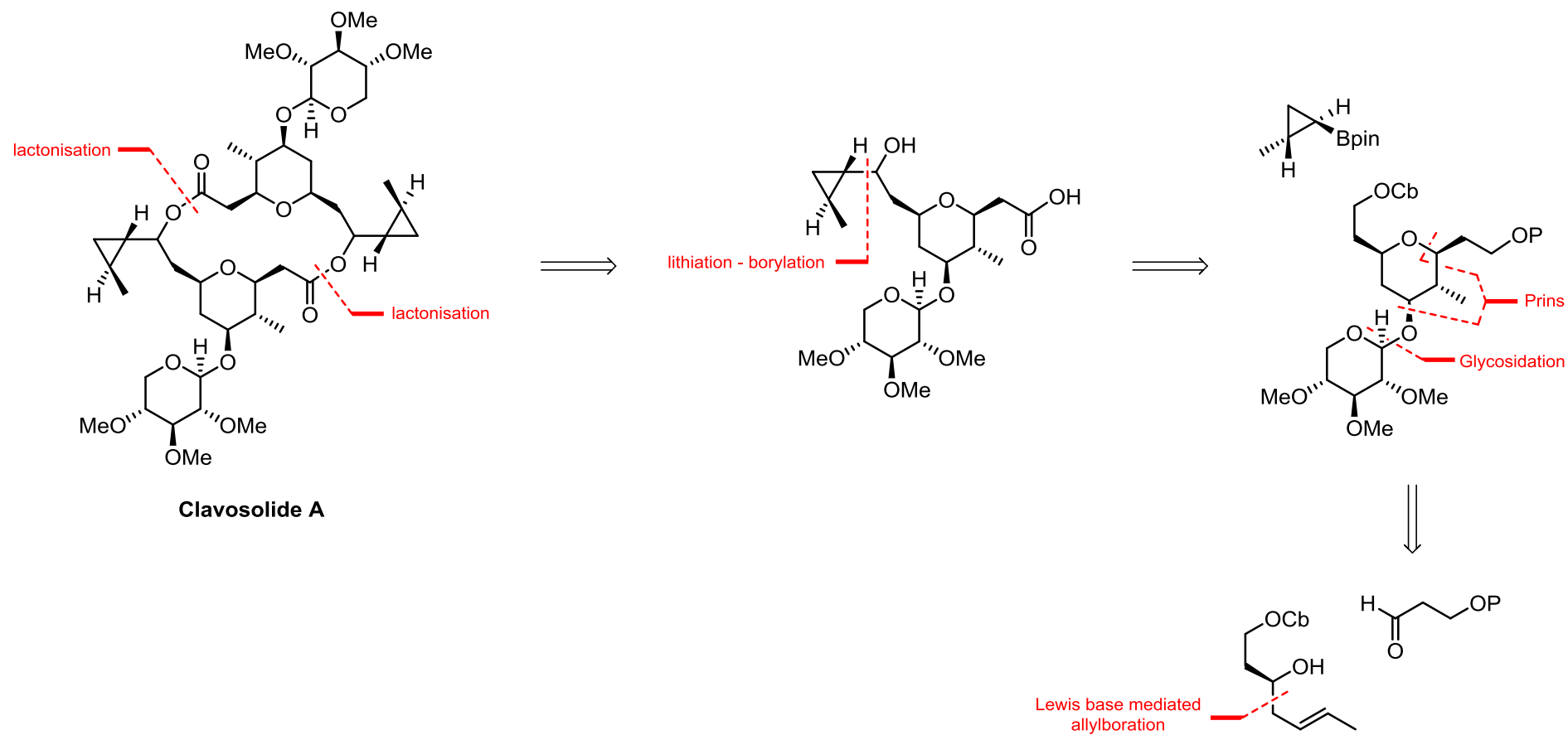
Clavosolide A

Total Synthesis of (-)-Clavosolide A

- > a) C. S. Barry, J. D. Elsworth, P. T. Seden, N. Bushby, J. R. Harding, R.W. Alder, C. L. Willis, *Org. Lett.* **2006**, 8, 3319
- > b) J. B. Son, S. N. Kim, N. Y. Kim, D. H. Lee, *Org. Lett.* **2006**, 8, 661
- > c) A. B. Smith III, V. Simov, *Org. Lett.* **2006**, 8, 3315
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- > e) T. K. Chakraborty, V. R. Reddy, A. K. Chattopadhyay, *Tetrahedron Lett.* **2006**, 47, 7435
- > f) T. K. Chakraborty, V. R. Reddy, P. K. Gajula, *Tetrahedron* **2008**, 64, 5162
- > g) J. D. Carrick, M. P. Jennings, *Org. Lett.* **2009**, 11, 769
- > h) J. B. Son, S. N. Kim, N. Y. Kim, M.-H. Hwang, W. Lee, D. H. Lee, *Bull. Korean Chem. Soc.* **2010**, 31, 653;
- > i) G. Peh, P. E. Floreancig, *Org. Lett.* **2012**, 14, 5614;
- > j) J. B. Baker, H. Kim, J. Hong, *Tetrahedron Lett.* **2015**, 56, 3120
- > k) A. M. Haydl, B. Breit, *Angew. Chem. Int. Ed.* **2015**, 54, 15530; *Angew. Chem.* **2015**, 127, 15750

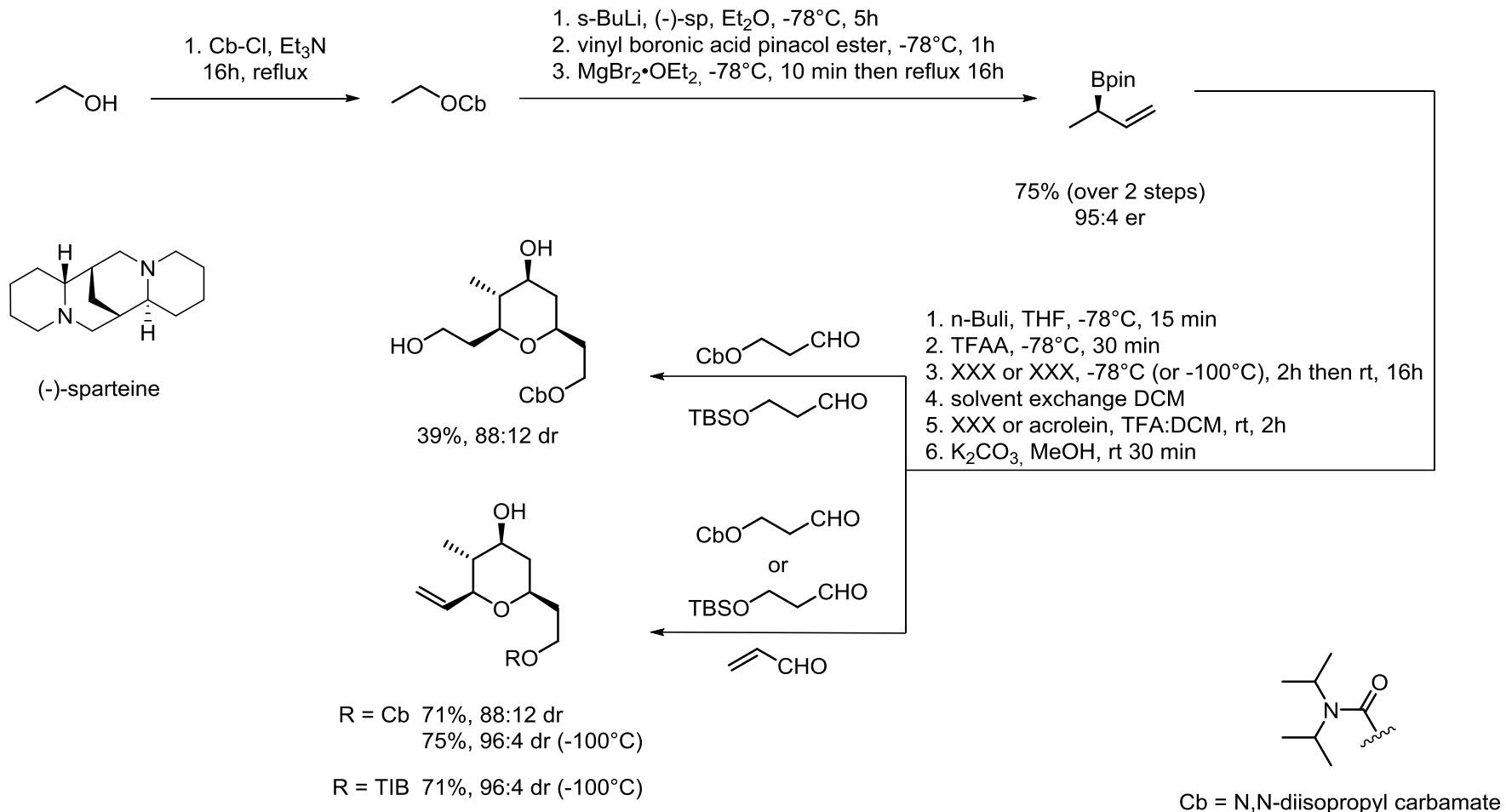
12 Total Synthesis published in 10 years

Retrosynthetic Analysis



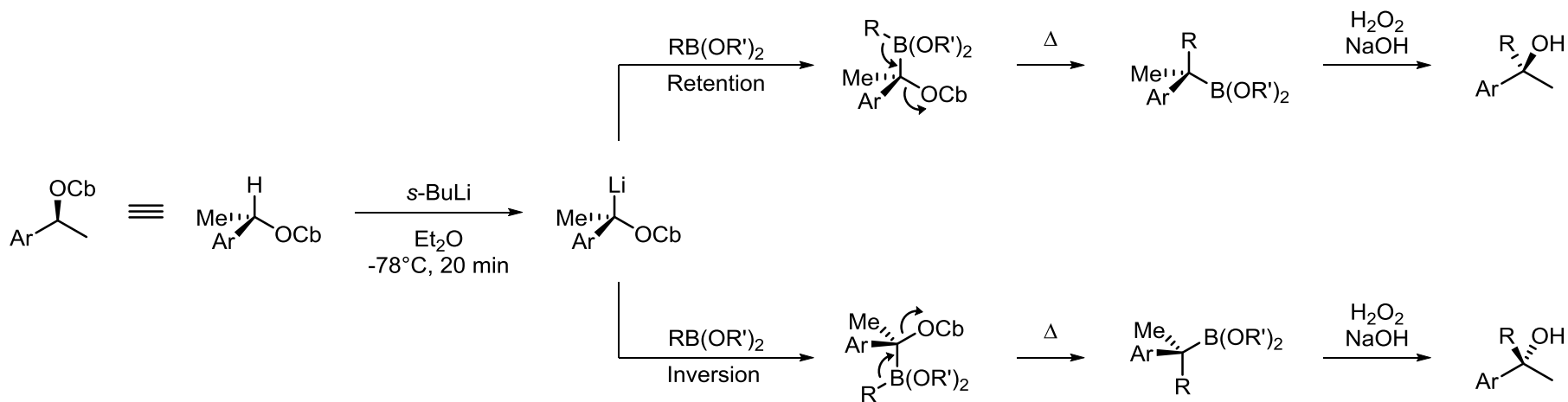
Total Synthesis of (-)-Clavosolide A

Lithiation - borylation



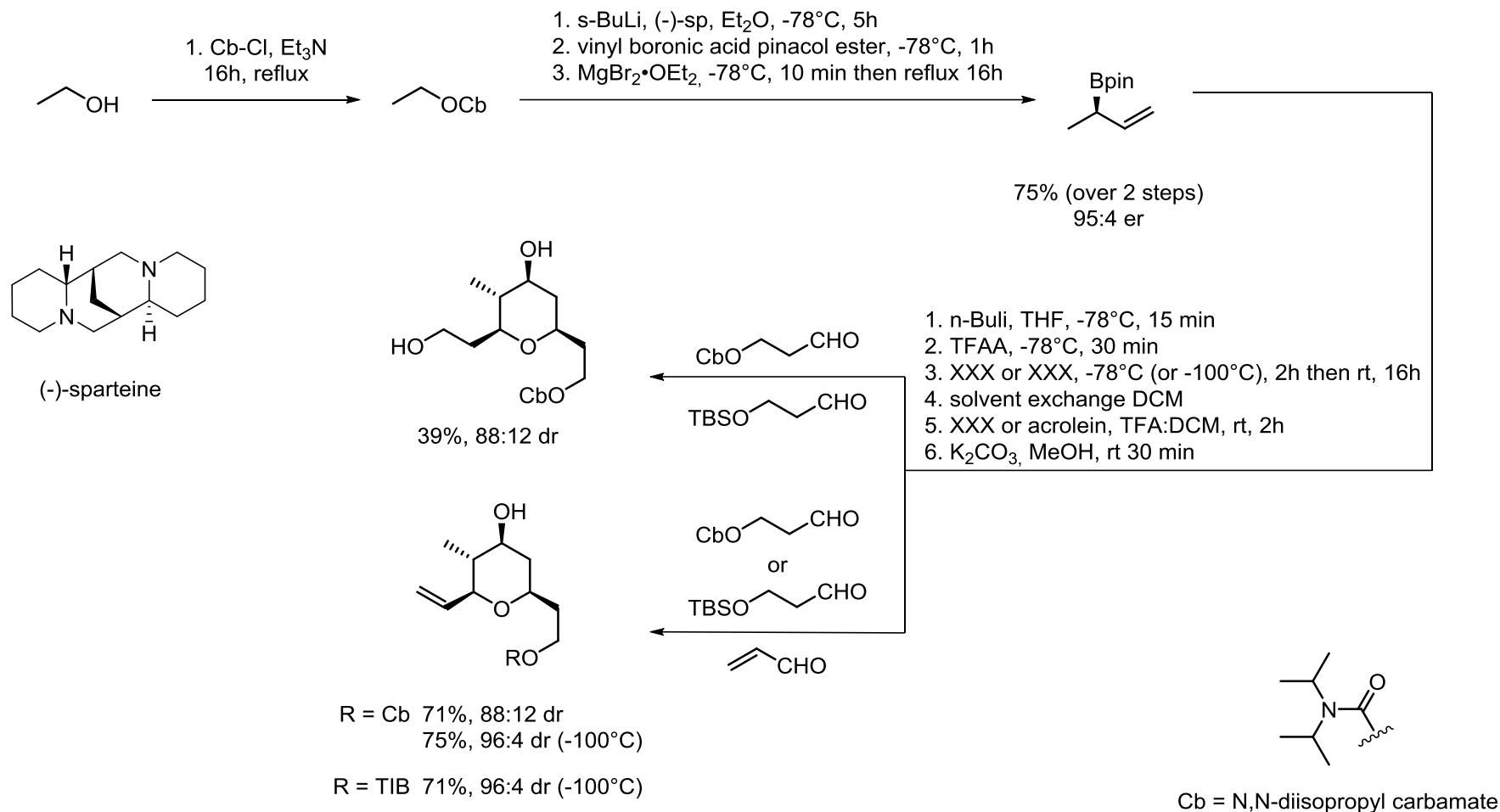
Lithiation - borylation

General Mechanism



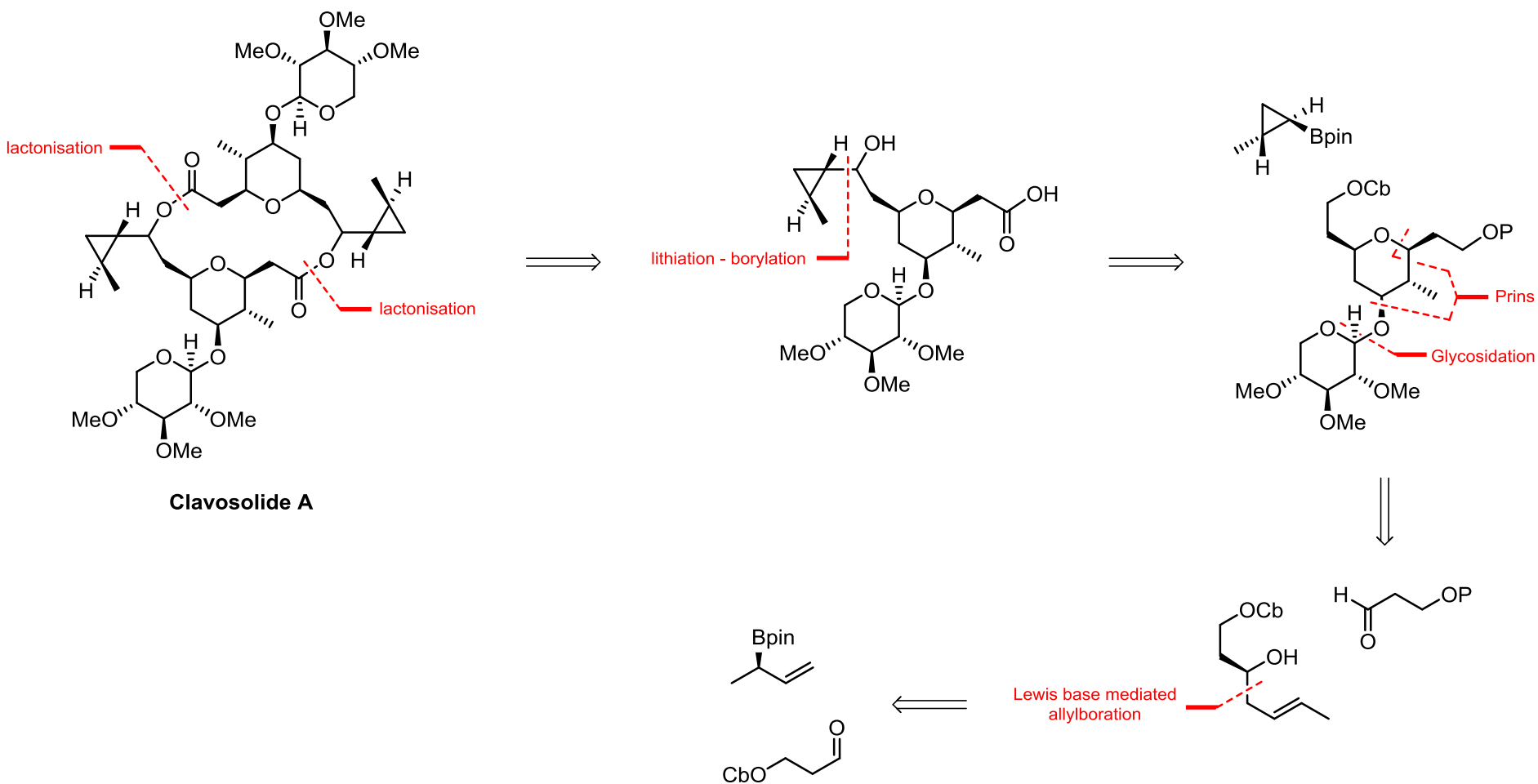
Total Synthesis of (-)-Clavosolide A

Lithiation - borylation



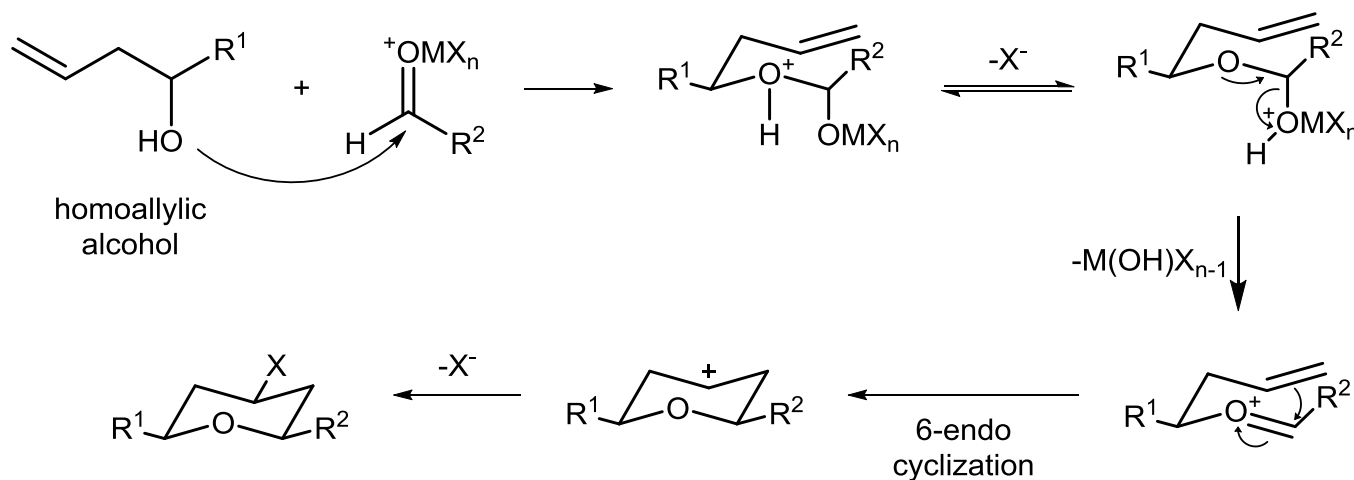
Total Synthesis of (-)-Clavosolide A

Retrosynthetic Analysis



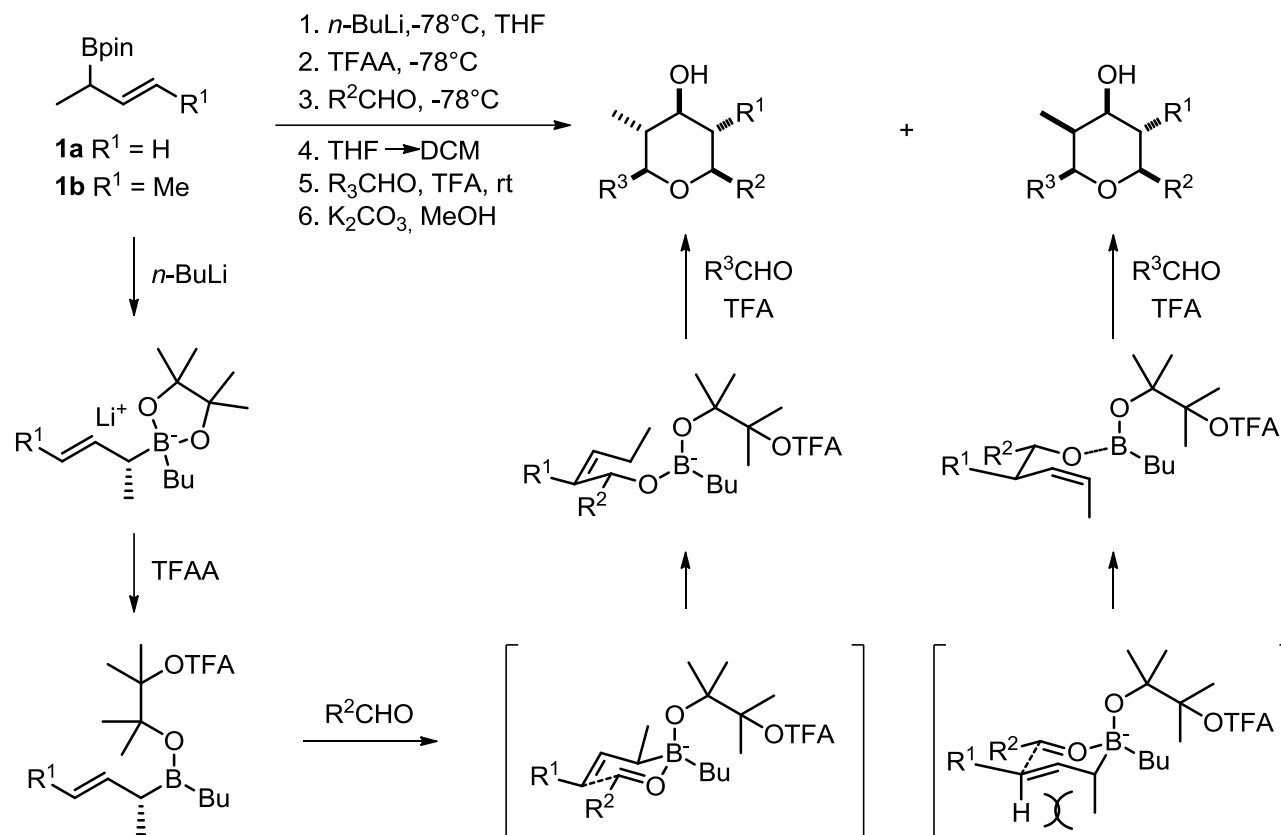
Prinz Cyclization

General Mechanism



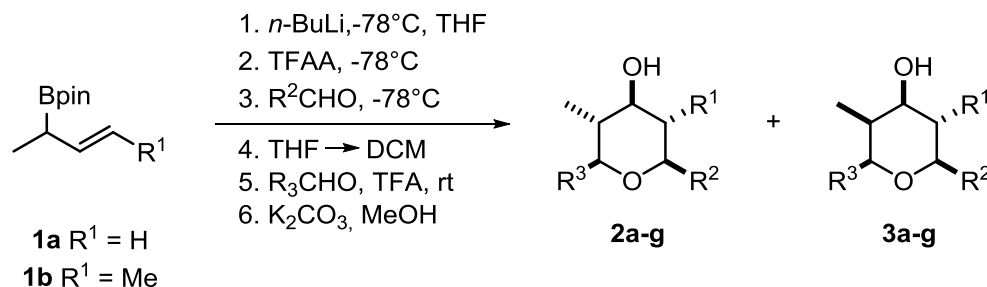
Total Synthesis of (-)-Clavosolide A

Three component Allylboration/Prins Cyclization



Total Synthesis of (-)-Clavosolide A

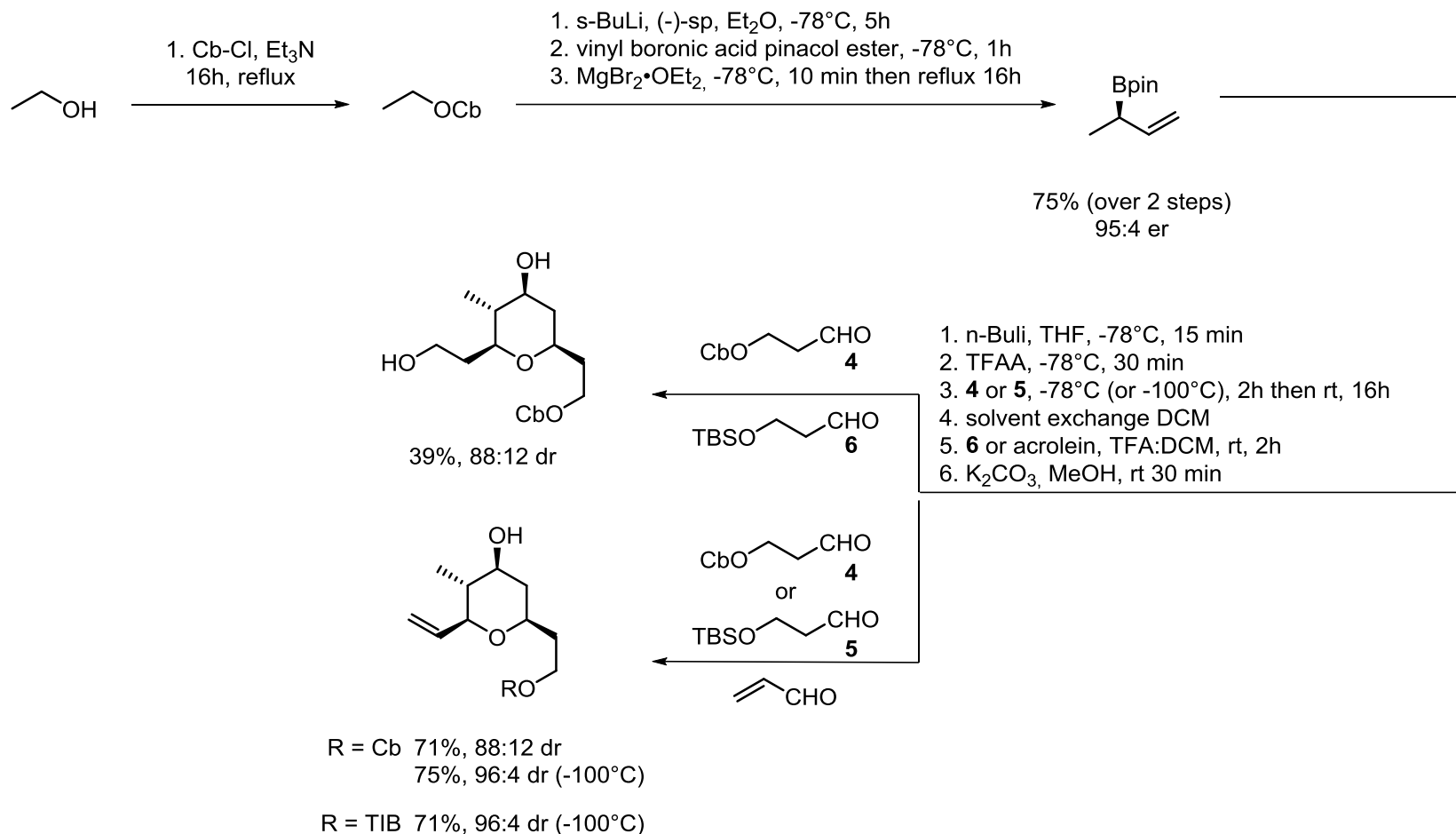
Three component Allylboration/Prins Cyclization



Entry	R ¹	R ²	R ³	2	Yield	dr (2:3)
1*	H	Cy	Cy	2a	91%	35:65
2	H	Cy	Cy	2b	84%	87:13
3	H	Cy	Ph(CH ₂) ₂	2c	75%	87:13
4	H	Ph(CH ₂) ₂	Cy	2d	57%	89:11
5	H	Ph(CH ₂) ₂	Ph(CH ₂) ₂	2e	65%	88:12
6	Me	Ph(CH ₂) ₂	Ph(CH ₂) ₂	2f	89%	90:10
7	Me	Ph(CH ₂) ₂	Cy	2g	81%	91:9
8	Me	Cy	Cy	2h	86%	88:12

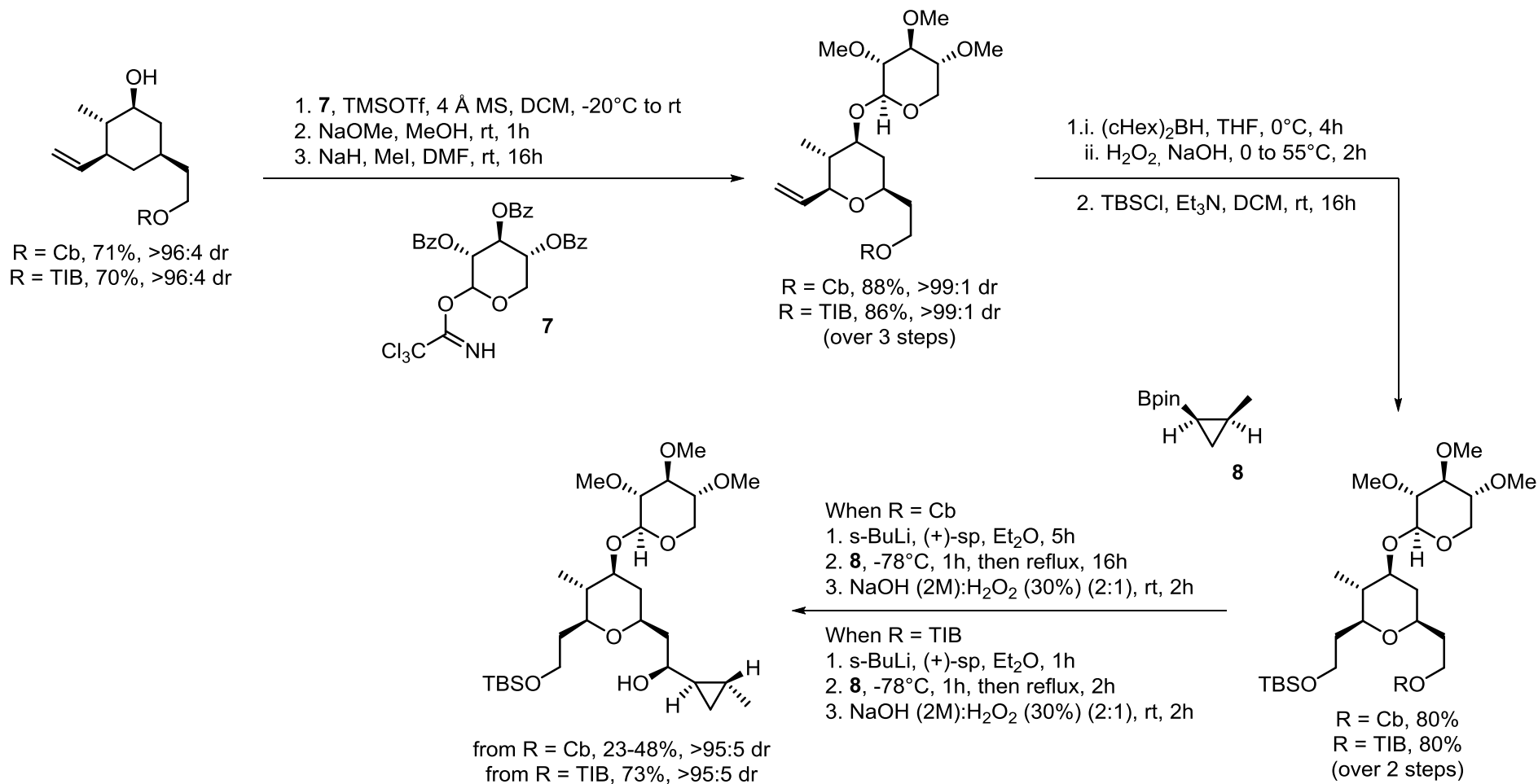
Total Synthesis of (-)-Clavosolide A

Three component Allylboration/Prins Cyclization



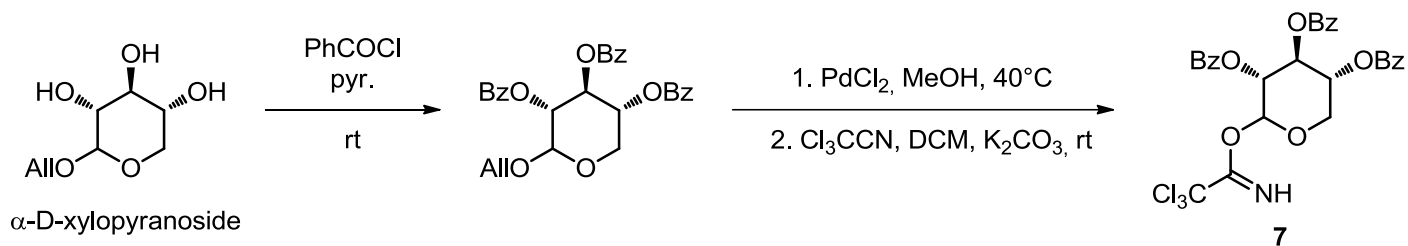
Total Synthesis of (-)-Clavosolide A

Lithiation-borylation reaction

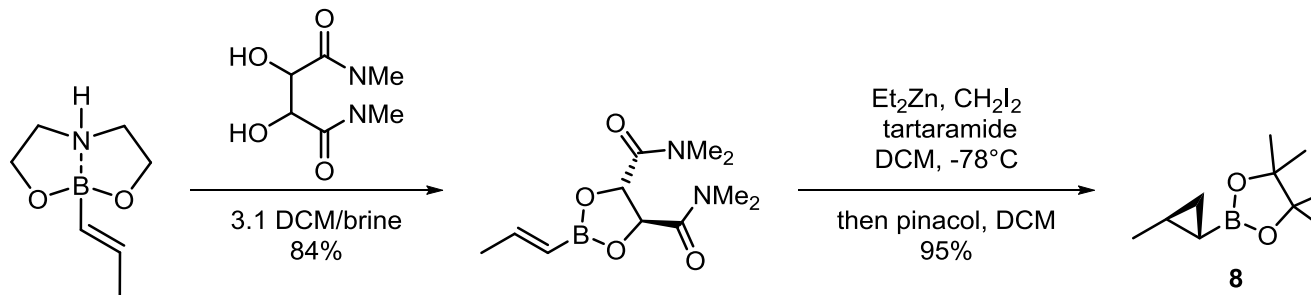


Adduct Synthesis

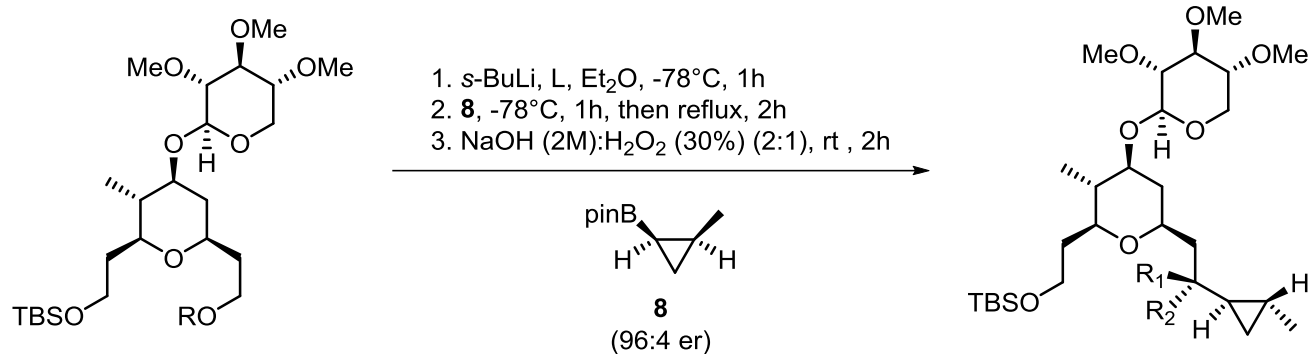
> Sugar derivative



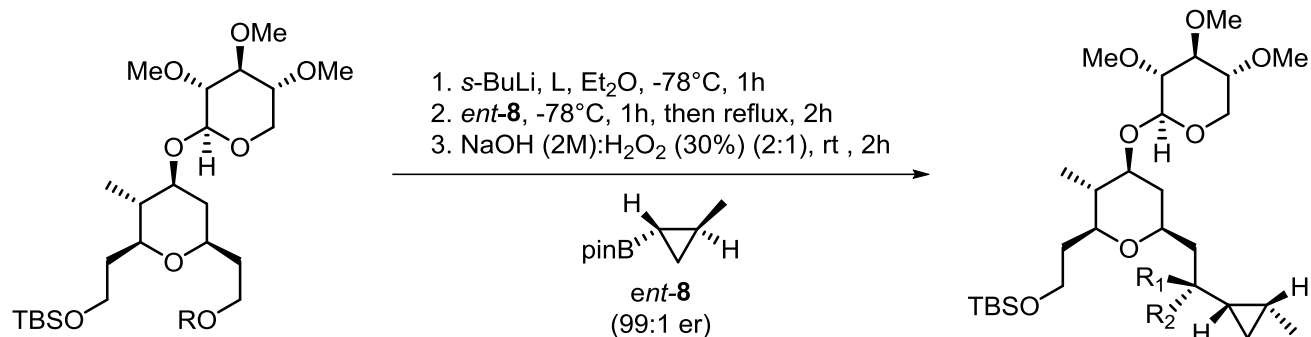
> Cyclopropan boronic ester



Synthesis of alternative diastereoisomer of alcohol using the lithiation-borylation reaction



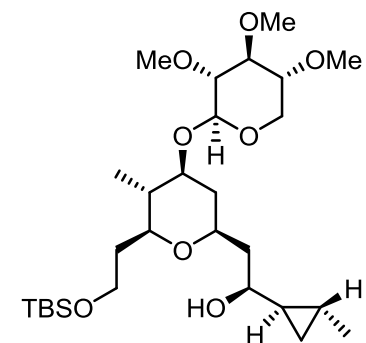
L= (+)-sp : R¹ = OH, R² = H, 73% yield, >95:5 dr
 L= (-)-sp : R¹ = H, R² = OH, 79% yield, 85:15 dr



L= (+)-sp : R¹ = OH, R² = H, 73% yield, >95:5 dr
 L= (-)-sp : R¹ = H, R² = OH, 79% yield, 90:10 dr

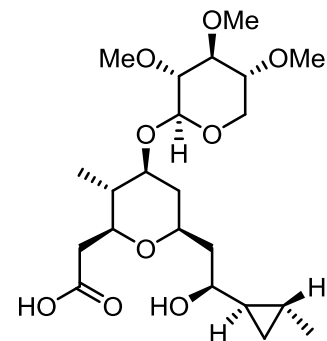
Total Synthesis of (-)-Clavosolide A

Final Stages of the synthesis



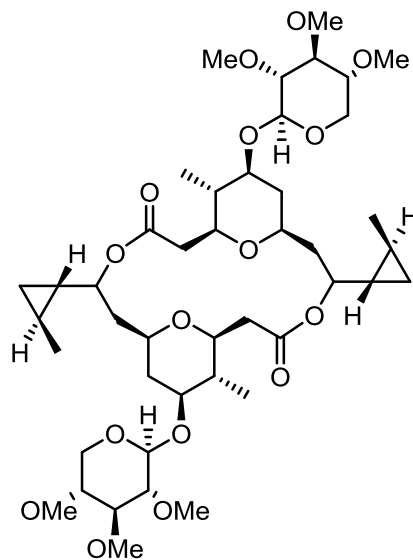
from R = Cb, 23-48%, >95:5 dr
from R = TIB, 73%, >95:5 dr

1. 1% HCl, EtOH, 20 min, 80%
2. TEMPO, KBr, NaHCO₃, NaOCl, H₂O, DCM, 0°C, 5 min, 87%



73% (over 2 steps)

1. 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, rt, 2.5h
2. DMAP, toluene, reflux, 16h



Clavosolide A
68%

Conclusion

- > Assembling of substituted THP in just 3 steps with high stereocontrol by using a three component allylboration-Prins reaction
- > Diastereoselective glycosidation reaction to introduce the xylose moiety
- > Diastereoselective lithiation-borylation reaction of a highly oxygenated hindered TIB ester
- > Concise and efficient synthesis in 13 steps and 14 % overall yield (>95:5 selectivity)

Thank you for your attention !