Polycavernoside A: The Prins Macrocyclization Approach

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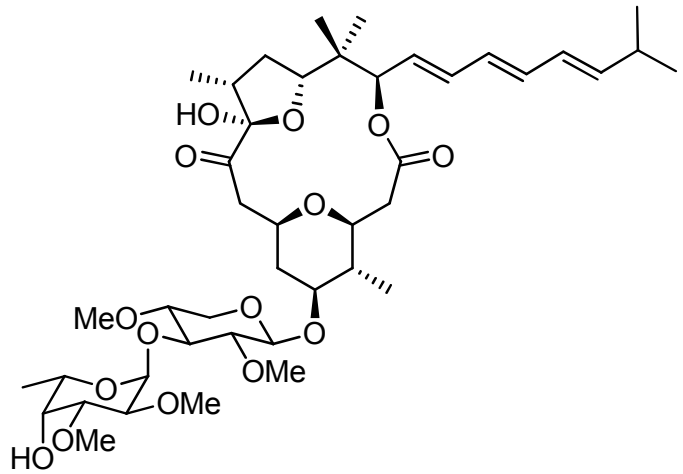


Marie-Céline Frantz

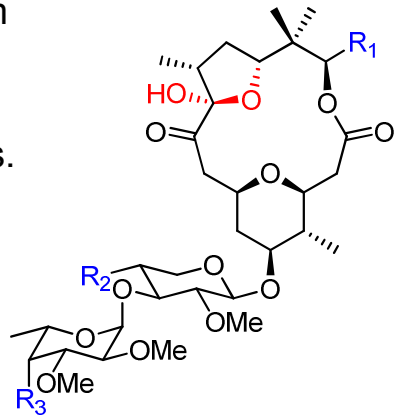
Wipf Group - Current Literature

April 24, 2010

Polycavernoside A

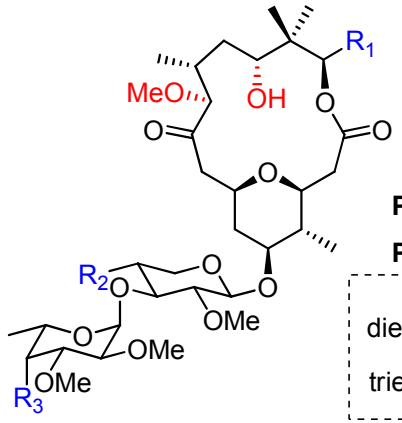
- Isolated by Yasumoto from the edible red alga *Polycavernosa tsudai* in Guam in 1991.
- Responsible for sudden and fatal human intoxication in Guam in 1991 and in the Philippines in 2002.
- Symptoms: gastrointestinal (vomiting, diarrhea) and neurological (scratching, muscle spasms, paralysis) disorders.
- Cyanobacterial origin speculated.
- Group of macrolides with:
  - structurally unique 13-membered central lactone ring
  - disaccharide and trienyl side chains.
- Polycavernoside A analogs also isolated:
- Estimated LD_{99} in mice (ip) of PA and PB: 200-400 μg/kg.
- SAR: macrocyclic core and *i*Pr-polyene side chain required for high toxicity.
- Hydrolysis of the disaccharide in the stomach would deliver the aglycone bioactive form.
- Postulated mechanism of action: triggers an initial extracellular calcium entry into the cytosol, resulting in membrane depolarization.

Polycavernosides A and B

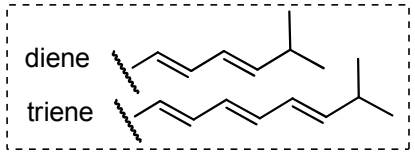


	R_1	R_2	R_3
PA	triene	OMe	OH
PA2	triene	OH	OH
PA3	triene	OMe	OMe
PB	diene	OAc	OMe
PB2	diene	OH	OMe

Polycavernosides C



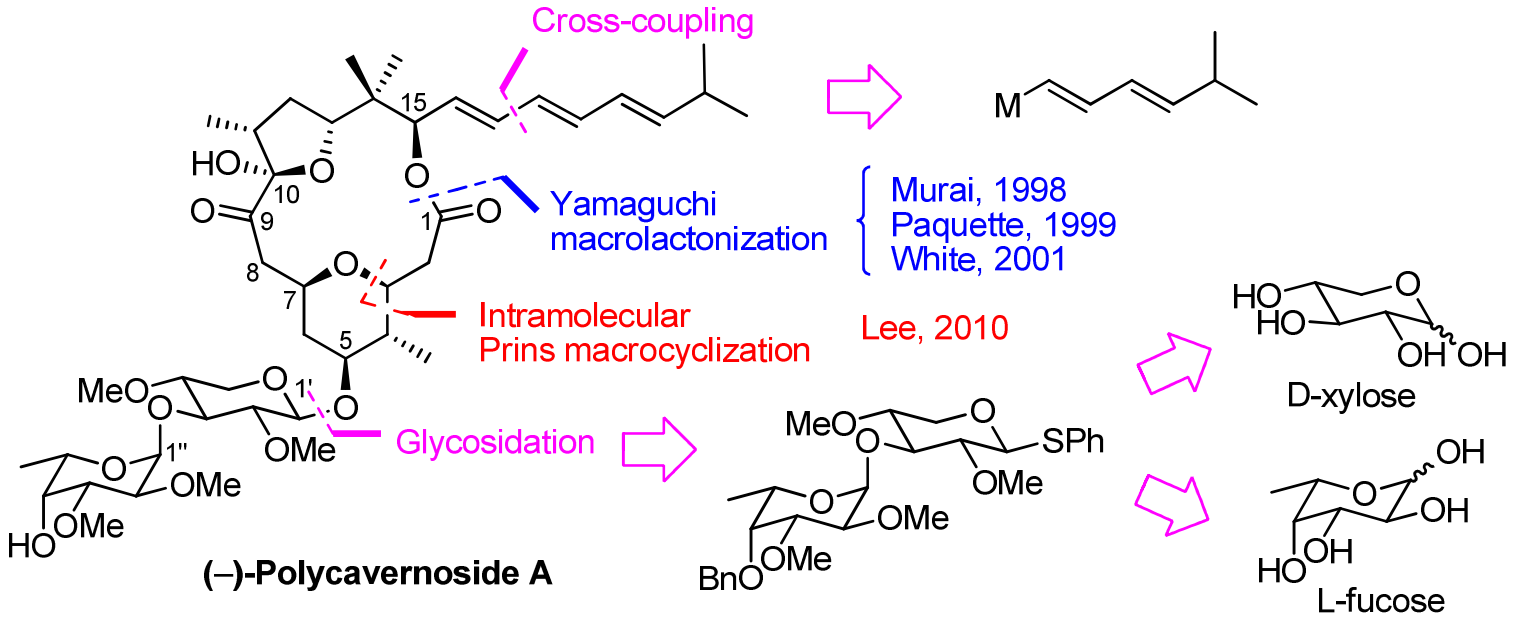
	R_1	R_2	R_3
PC	diene	OAc	OMe
PC2	triene	OMe	OMe



Yotsu-Yamashita, M.; Haddock, R. L.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1147. Yotsu-Yamashita, M.; Yasumoto, T.; Yamada, S.; Bajarias, F. F. A.; Formeloza, M. A.; Romero, M. L.; Fukuyo, Y. *Chem. Res. Toxicol.* **2004,** *17,* 1265. Yotsu-Yamashita, M.; Seki, T.; Paul, V. J.; Naoki, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 5563. Yotsu-Yamashita, M.; Abe, K.; Seki, T.; Fujiwara, K.; Yasumoto, T. *Tetrahedron Lett.* **2007**, *48*, 2255. Barriault, L.; Boulet, S. L.; Fujiwara, K.; Murai, A.; Paquette, L. A.; Yotsu-Yamashita, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2069. Cagide, E.; Louzao, M. C.; Ares, I. R.; Vieytes, M. R.; Yotsu-Yamashita, M.; Paquette, L. A.; Yasumoto, T. *Cell. Phys. Biochem.* **2007**, *19*, 185.

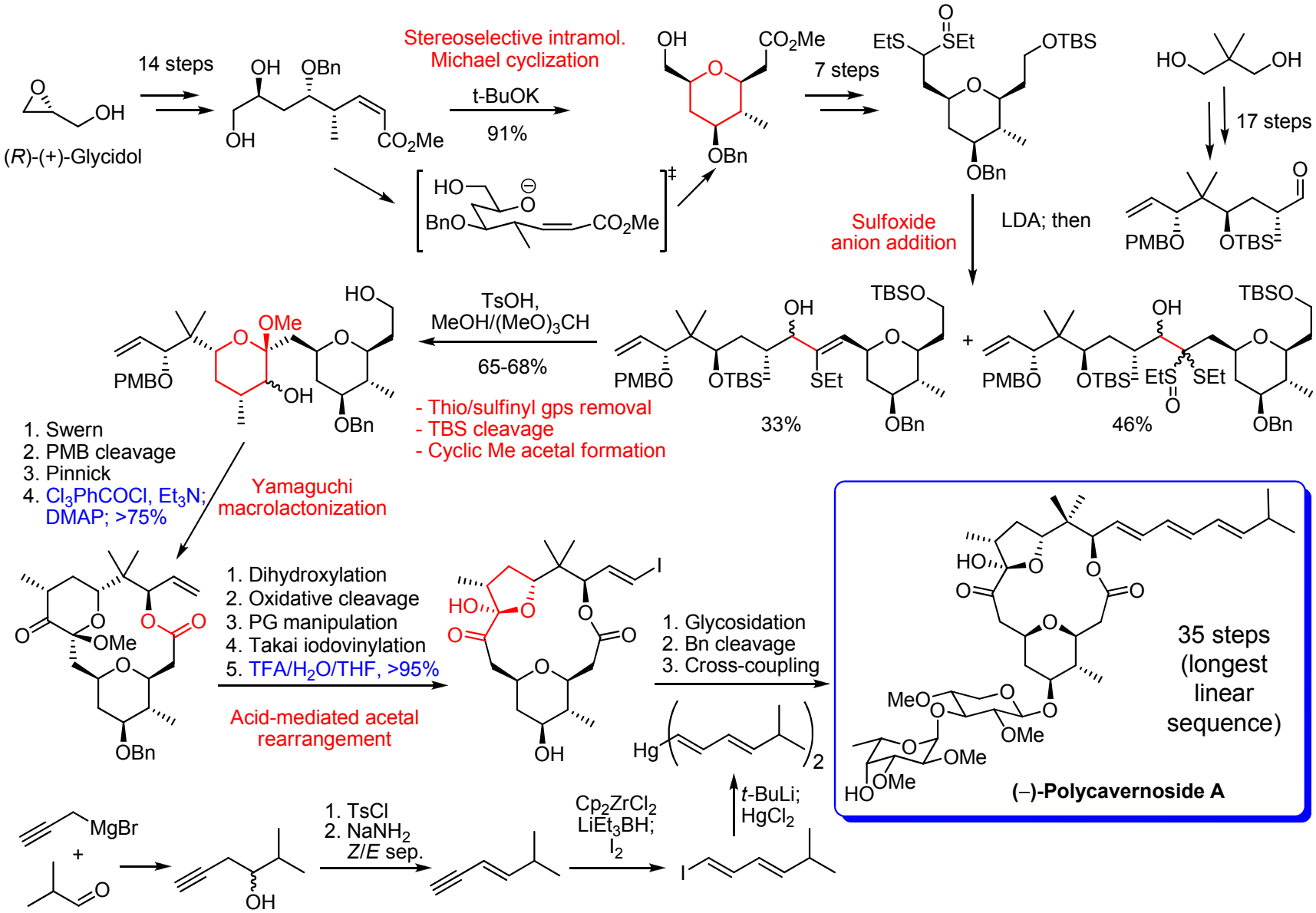
Polycavernoside A: Structure Determination & Synthesis

- Yasumoto (1993): determination (1D/2D NMR) of the partial relative structure of:
  - each sugar component,
  - bottom (C1-C8) and upper (C9-C15) halves of the macrolactone part.
- Murai (1995): determination (synthetically) of the relative configuration of the sequence of the fucose-xylose bottom half of the macrolactone.
- Murai (1998): 1st total synthesis & determination of the absolute configuration.



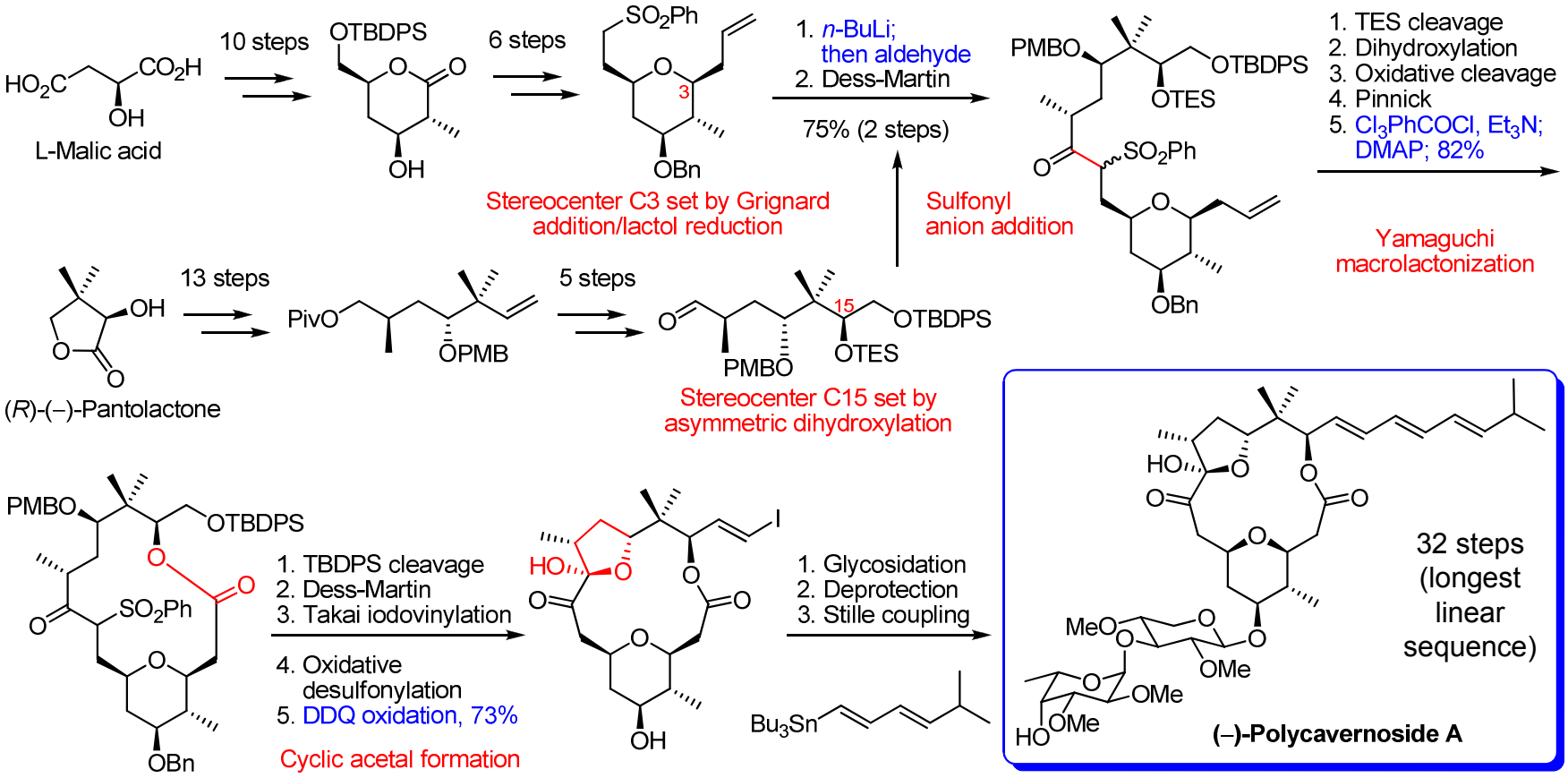
Yotsu-Yamashita, M.; Haddock, R. L.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1147. Fujiwara, K.; Amano, S.; Murai, A. *Chem. Lett.* **1995**, 855. Fujiwara, K.; Murai, A.; Yotsu-Yamashita, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 10770. Paquette, L. A.; Barriault, L.; Pissarnitski, D. *J. Am. Chem. Soc.* **1999**, *121*, 4542. Paquette, L. A.; Barriault, L.; Pissarnitski, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2000**, *122*, 619. White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593. Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J.; White, J. D. *J. Org. Chem.* **2005**, *70*, 5449.

(–)-Polycavernoside A: Murai's synthesis (1998)



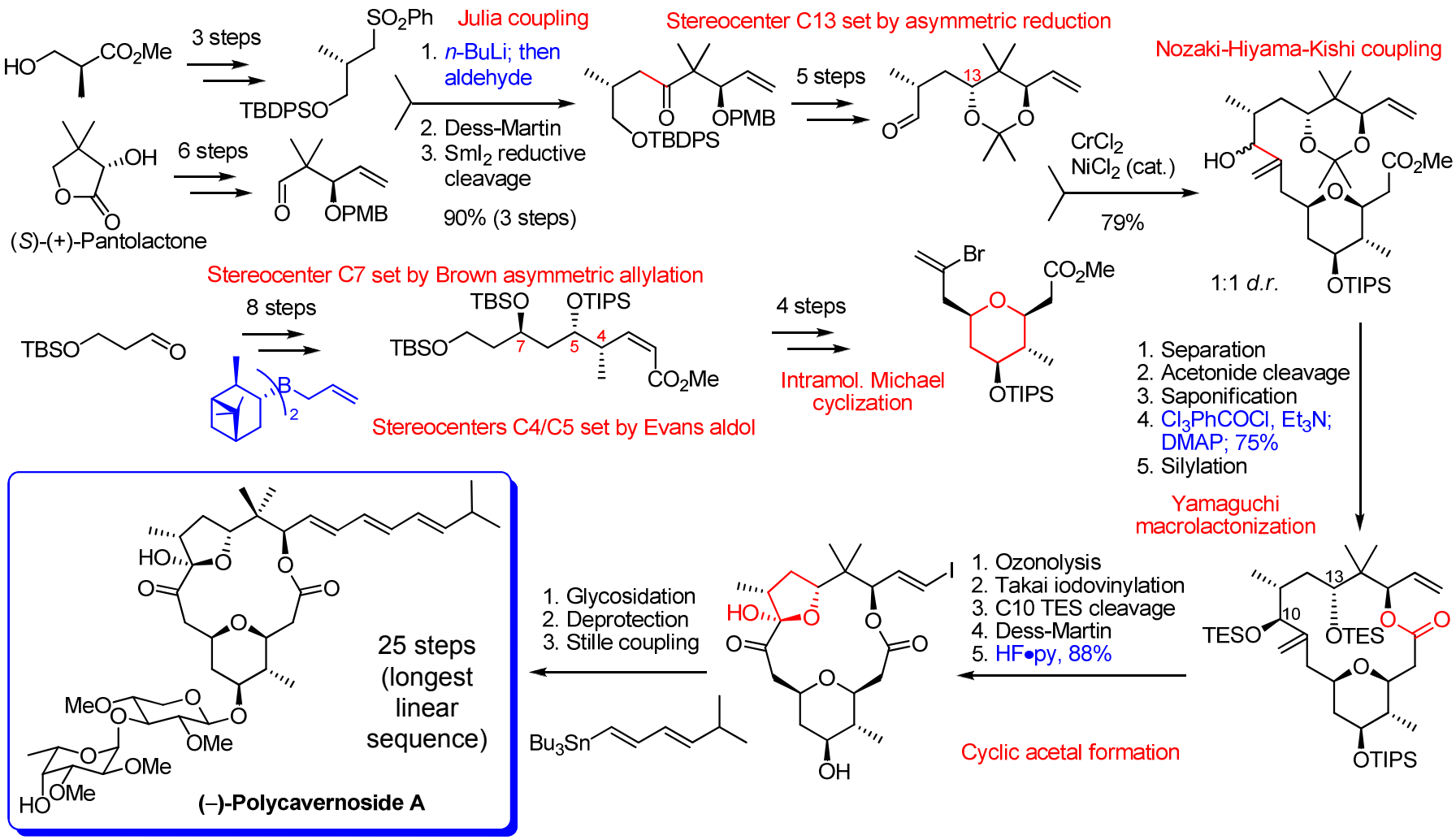
Fujiwara, K.; Murai, A.; Yotsu-Yamashita, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 10770.

(–)-Polycavernoside A: Paquette's synthesis (1999)



Paquette, L. A.; Barriault, L.; Pissarnitski, D. *J. Am. Chem. Soc.* **1999**, *121*, 4542.
Paquette, L. A.; Barriault, L.; Pissarnitski, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2000**, *122*, 619.

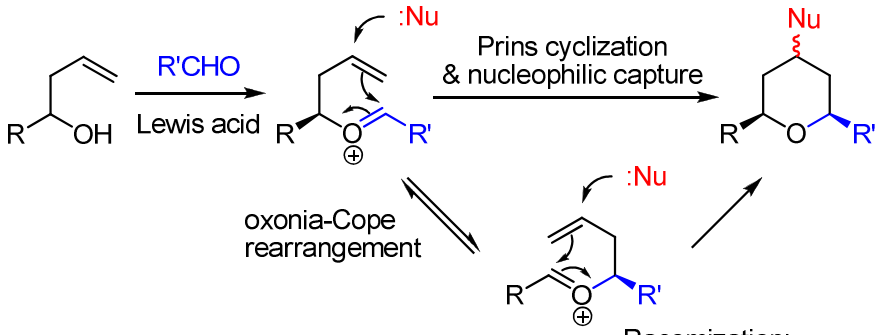
(–)-Polycavernoside A: White's synthesis (2001)



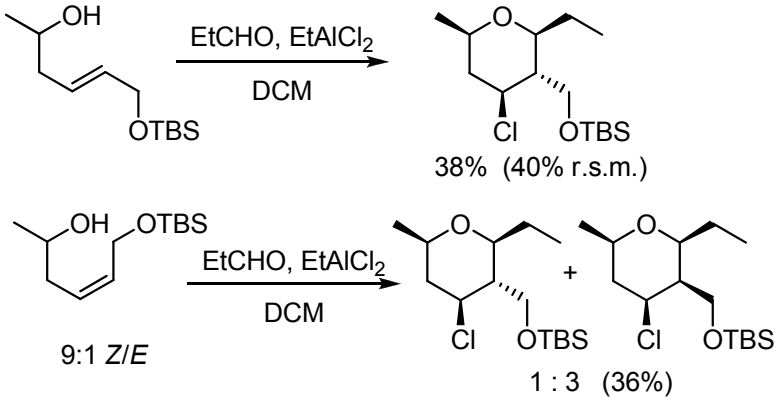
White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593. Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J.; White, J. D. *J. Org. Chem.* **2005**, *70*, 5449.

The Prins Reaction

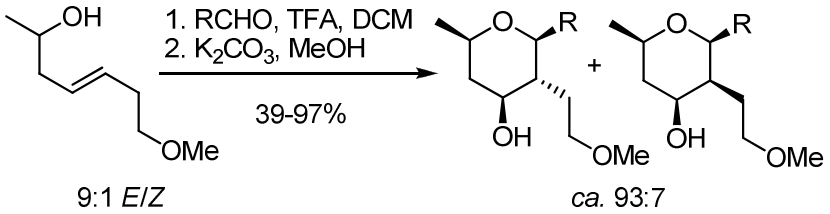
Prins cyclization *vs* competing oxonia-Cope rearrangement



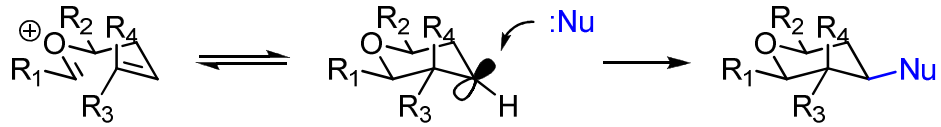
Cyclization of (*E*)- and (*Z*)-Homoallylic Alcohols



Stereochemical outcome for Prins cyclizations



Excellent stereocontrol.
All the substituents in the equatorial position.

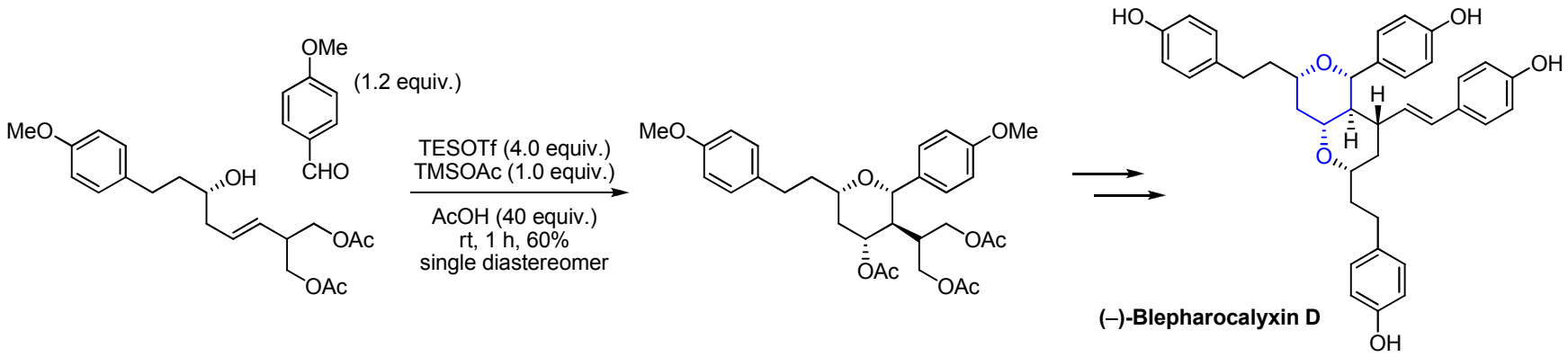


Selectivity of nucleophilic capture at C4 dependent on reactivity:
- Highly reactive nucleophile (e.g.: Br^-) and electrophile: axial attack
- Less reactive nucleophile (e.g.: AcO^-, TFA^-) and electrophile: equatorial attack

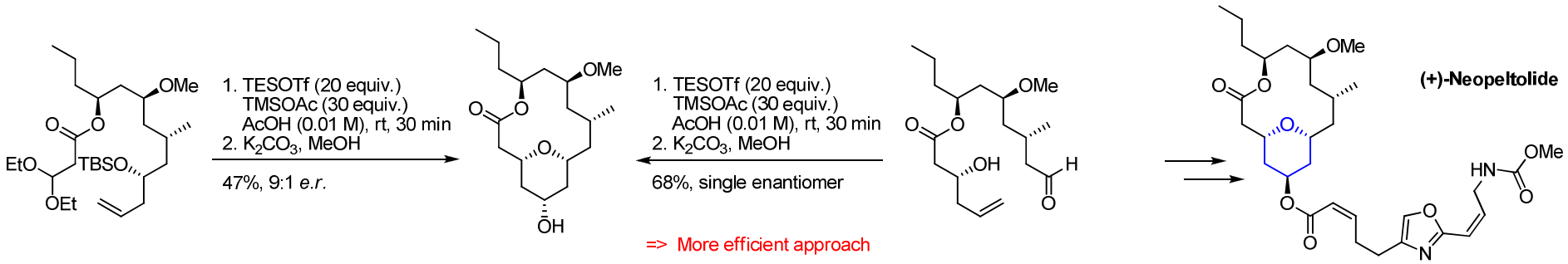
Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.;Willis, C. L. *Org. Lett.* **2002**, *4*, 577. Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429. Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939. Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640.

The Prins Reaction: Application in Total Synthesis

- Application in the total synthesis of (–)-Blepharocalyxin D (Lee, 2007)
  - Optimization of the conditions of Willis & coworkers



- Application of the intramolecular Prins macrocyclization in the total synthesis of (+)-Neopeltolide (Lee, 2008)



Ko, H. M.; Lee, D. G.; Kim, M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Org. Lett.* **2007**, *9*, 141.
Ko, H. M.; Lee, D. G.; Kim, M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Tetrahedron* **2007**, *63*, 5797.
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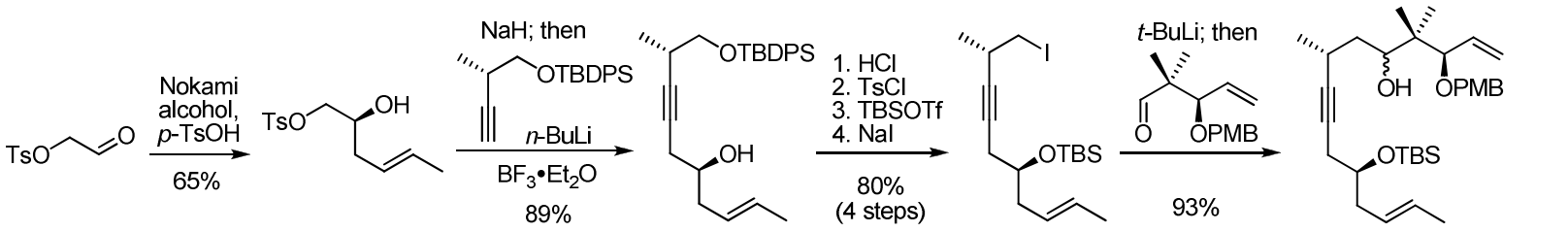
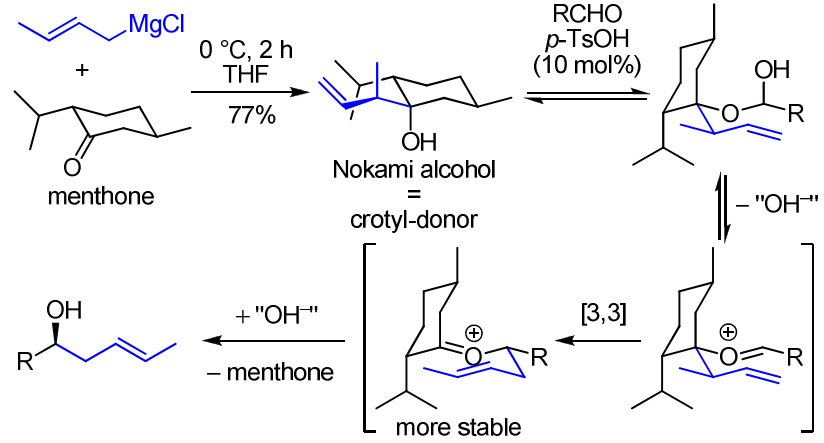
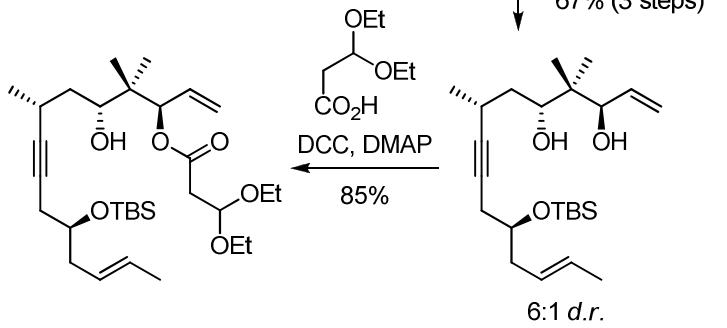
(–)-Polycavernoside A Total Synthesis: Title Paper

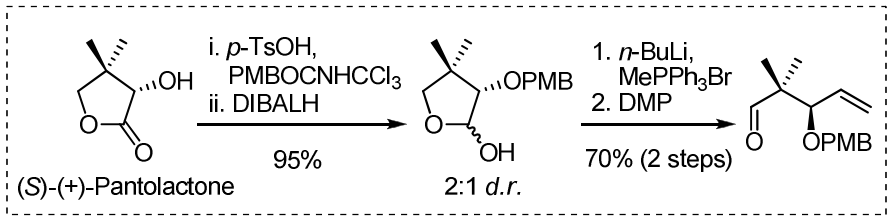


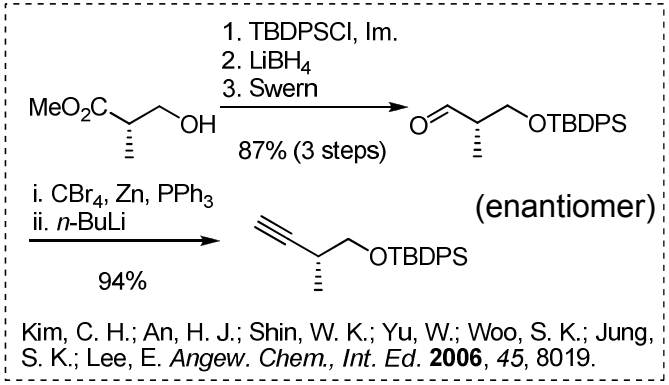
Asymmetric Crotylation of Aldehyde with the Nokami Alcohol



Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.







Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8019.

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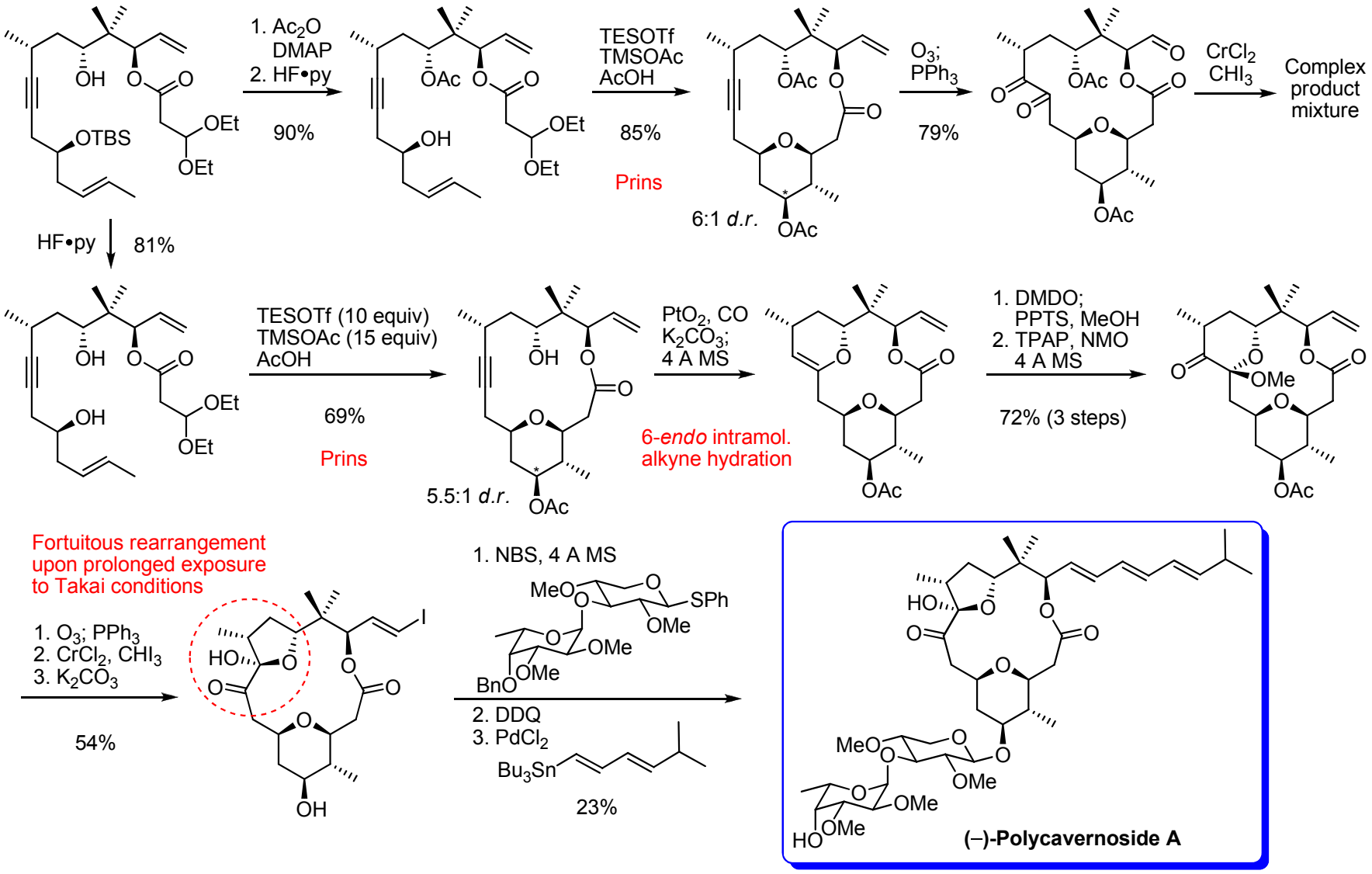
(–)-Polycavernoside A Total Synthesis: Title Paper



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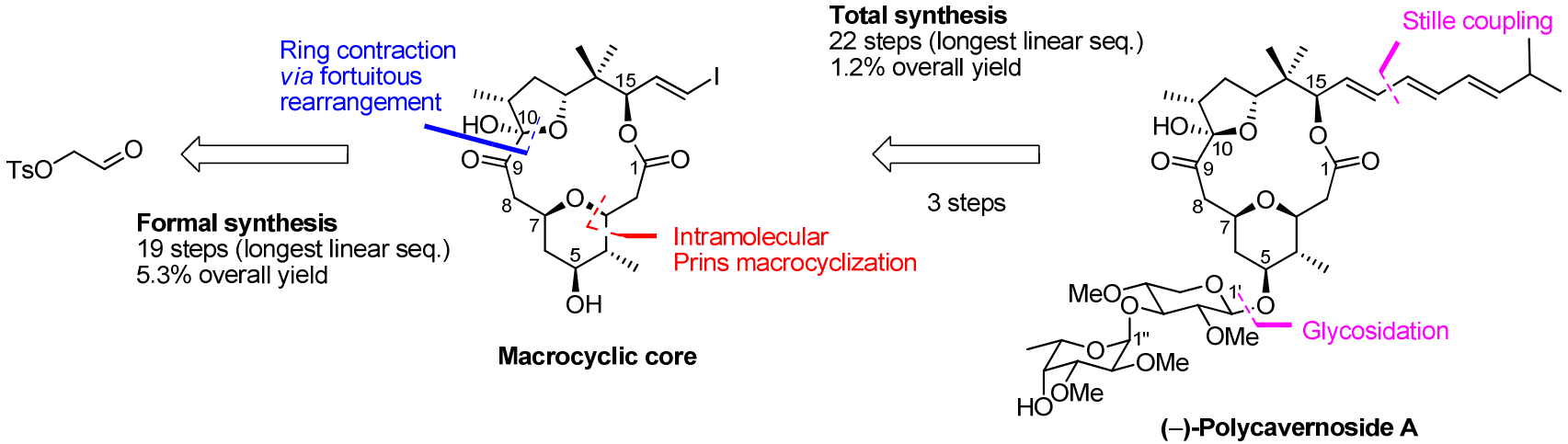
Conclusion and Perspectives

- Novel approach for the total synthesis of (–)-Polycavernoside A.
- Use of a Prins macrocyclization strategy to build chemical complexity in a single step:
  - 2 new rings
  - 3 new stereocenters



- Comparison of synthetic routes to the macrocycle:

	Murai	Paquette	White	Lee
Longest linear sequence (steps)	32	29	22	19
Overall yield (%)	2.6	1.5	4.7	5.3

- Perspectives: further applications of the Prins macrocyclization strategy in the synthesis of complex natural products.