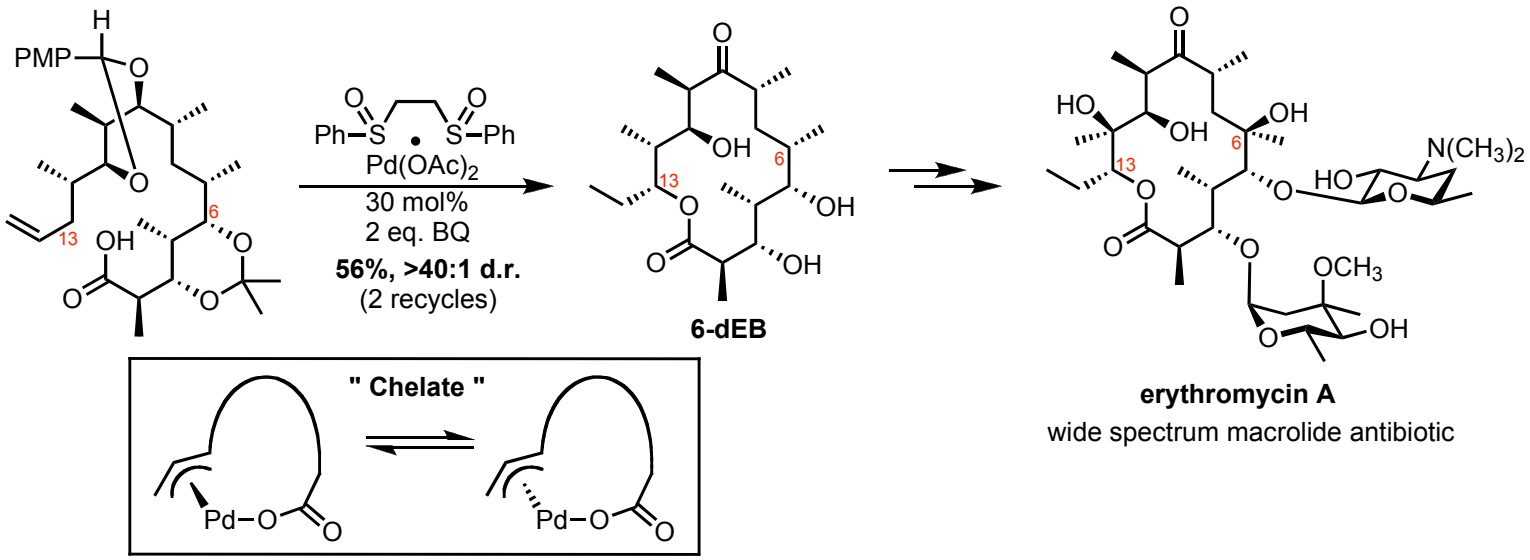
Total synthesis and study of 6-deoxyerythronolide B (6-dEB) by late-stage C–H oxidation

Erik M. Stang and M. Christina White

Nature Chem., **2009**, AOP. DOI: 10.1038/nchem.351.



Karla Bravo

Current Literature, 09/12/2009

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Erythromycin

E.E.S.-400 Filmtab

Facts - macrolide antibiotic produced by a strain of *Saccharopolyspora erythraea.*[1]

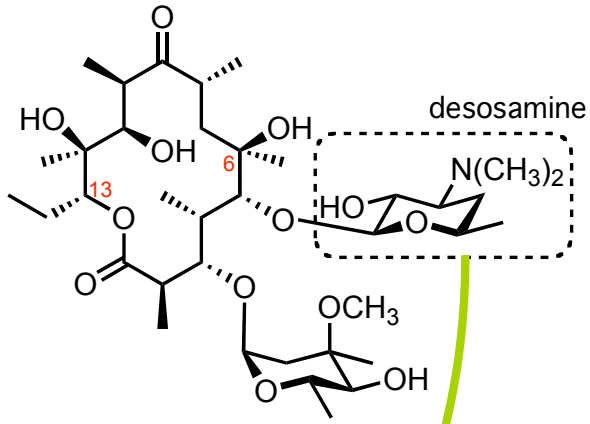
- antimicrobial spectrum similar to or slightly wider than that of penicillin, and is used for people who have an allergy to penicillin.

- acts by inhibition of protein synthesis by binding 50 *S* ribosomal subunits of susceptible organisms.[2]

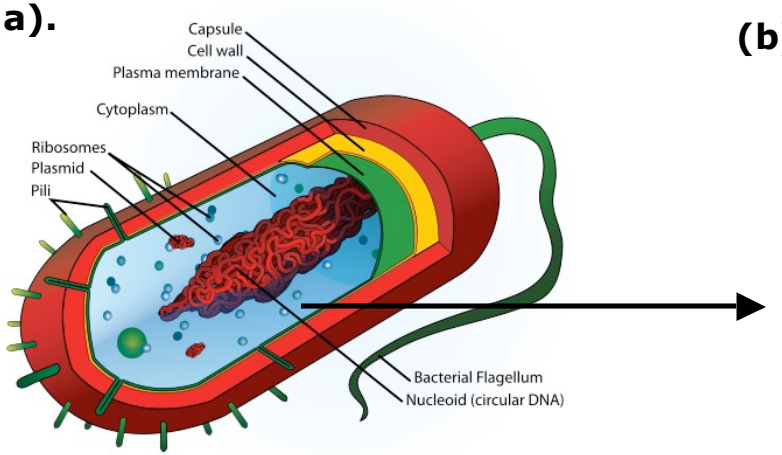
- available in different formulations, common brand names: E.E.S., Robimycin, E-Mycin, Erymax, Eryped

Structure

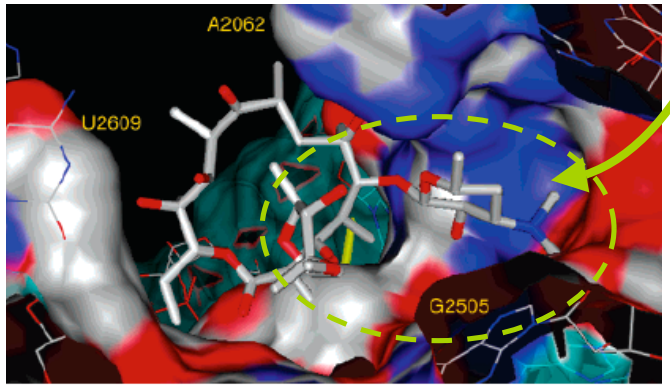
- 14-membered lactone ring with ten asymmetric centers
- two sugars (*L*-cladinose and *D*-desosamine)



(a).



(b).

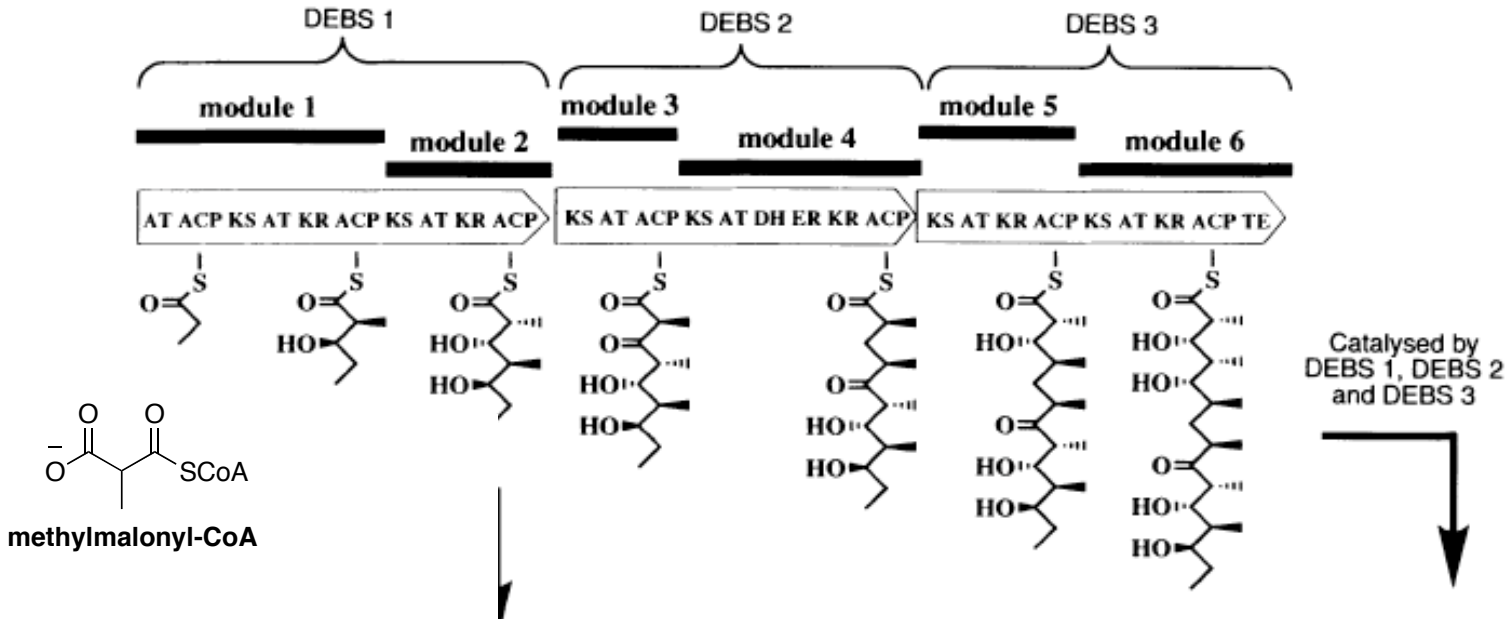


Figures: (a) bacterial cell diagram, (b) erythromycin binding pocket on the 50S subunit of the *D. radiodurans* ribosome

Critical interactions:
G2505 phosphate-desosamine -NMe_2
A2058-desosamine sugar

[1] Katz, L.; Khosla, C. *Nat. Biotechnol*. **2007**, *25*, 428.
[2] Katz, L.; Ashley, G. W. *Chem. Rev*. **2005,** *105*, 499.

Biosynthesis of the PK (polyketide) 6-dEB from erythromycin[3]



- **Erythromycin PKS** (polyketide synthase) or **DEBS** (6-dEB synthase) is composed of 28 domains organized into 6 modules on 3 polypeptides.

- Each DEBS module accounts for one polyketide chain extension and reduction cycle.

- **6-dEB** is made from the successive condensations (C-C via Claisen condensation) of one propionate molecule and six molecules of methylmalonate.

- Thioester chemistry activation of (methyl)malonyl monomers provides: thermodynamic driving force and kinetically accessible nucleophiles for the condensations

Codes: AT) acyltransferase, ACP) acyl carrier protein, KS) ketosynthase, KR) ketoreductase, DH) dehydratase, ER) enoylreductase, TE) thioesterase

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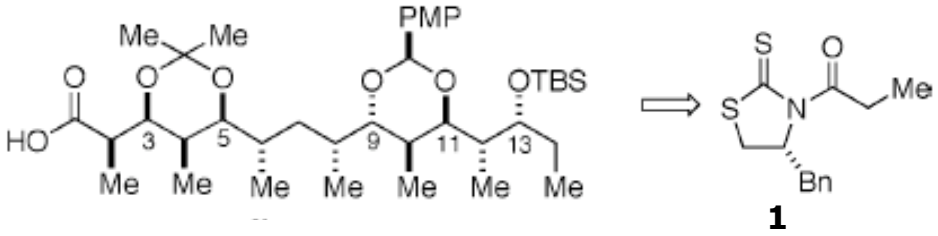
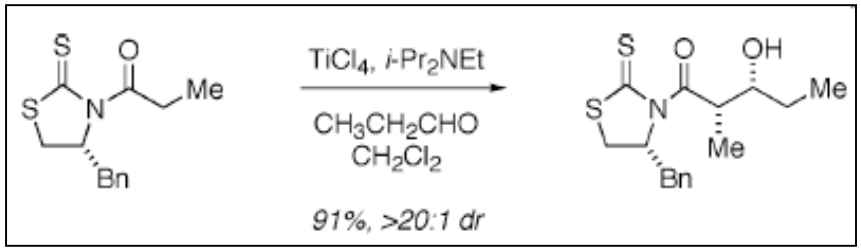
[3] Pieper, R.; Luo, G.; Cane, D. E.; Khosla, C. *Nature* **1995**, *378*, 263.

Previous synthetic studies of erythromycin

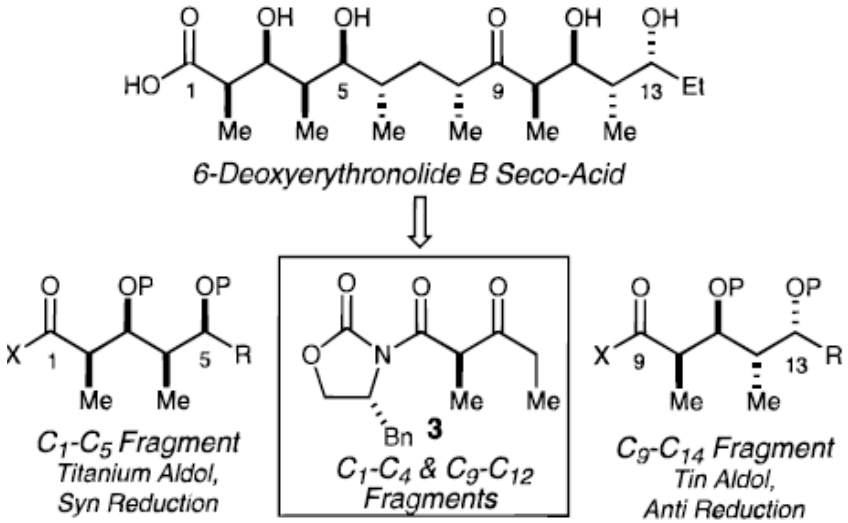
(a) Crimmins et al. "*Formal synthesis of 6-deoxyerythronolide B". Org. Lett.* **2006**, *8*, 2191.

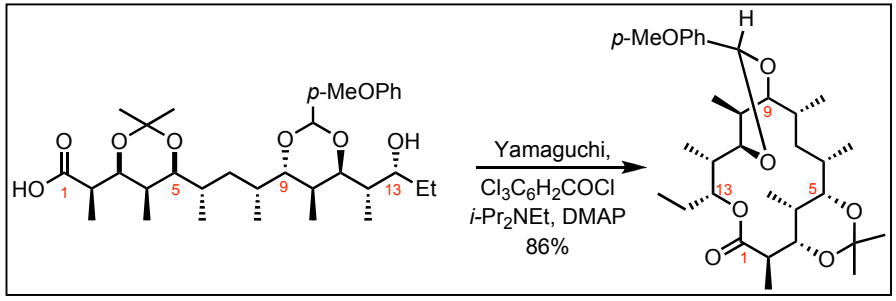




- 23 linear steps from propionaldehyde, 7.5% overall yield.
- relies on the use of *N*-acylthiazolidinethiones in an iterative approach to polypropionates.
- aldol additions of **1** established 10 of the 11 stereocenters of 6-deoxyerythronolide B precursor.

(b) Evans, D. A. et al. "*General strategies toward the syntheses of macrolide antibiotics. The total syntheses of 6-deoxyerythronolide B and oleandolide". J. Am. Chem. Soc.* **1998**, *120*, 5921.





- synthesis of 6-dEB in 18 linear steps.
- demonstrate utility of **3** as a building block for the aldol-based assemblage of polypropionate-derived natural products

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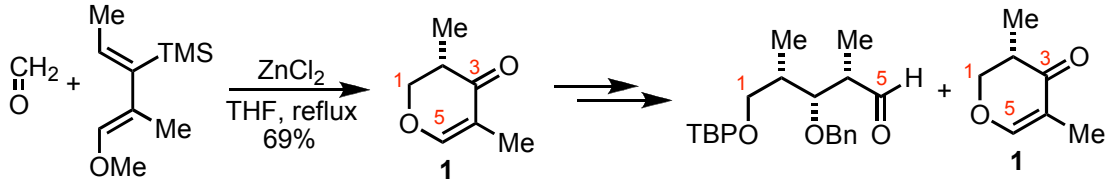
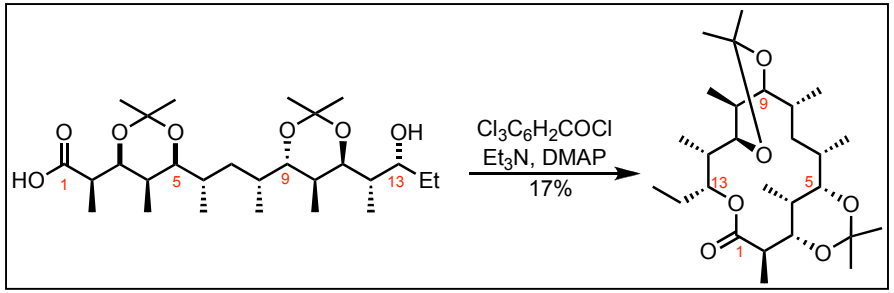
Previous synthetic studies of erythromycin

(c) Danishefsky, S. J. et al. "Development of a fully synthetic stereoselective route to 6-deoxyerythronolide B by reiterative applications of the Lewis Acid catalyzed diene aldehyde cyclocondensation reaction...". *J. Org. Chem.* **1990**, *55*, 1636.

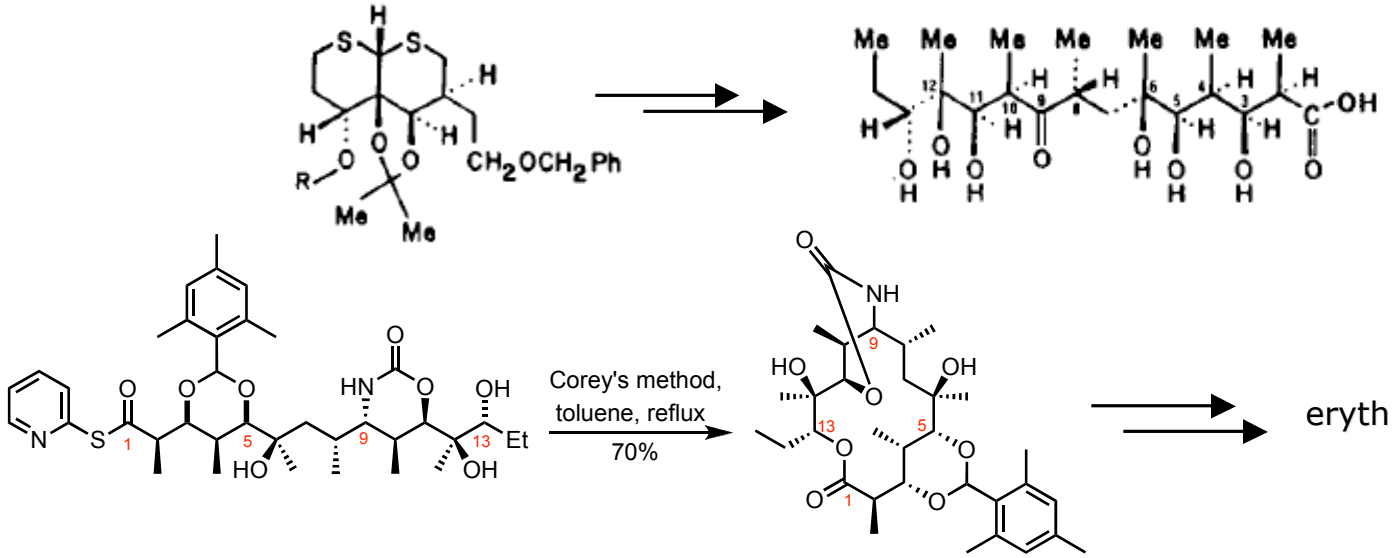


- three Lewis Acid catalyzed diene aldehyde cyclocondensation reactions using diene **1**.



- low yielding macrolactonization.

(d) Woodward, R. B. et al. "Asymmetric total synthesis of erythromycin", *J. Am.Chem. Soc.* **1981**, *103*, 3210.



erythromycin A

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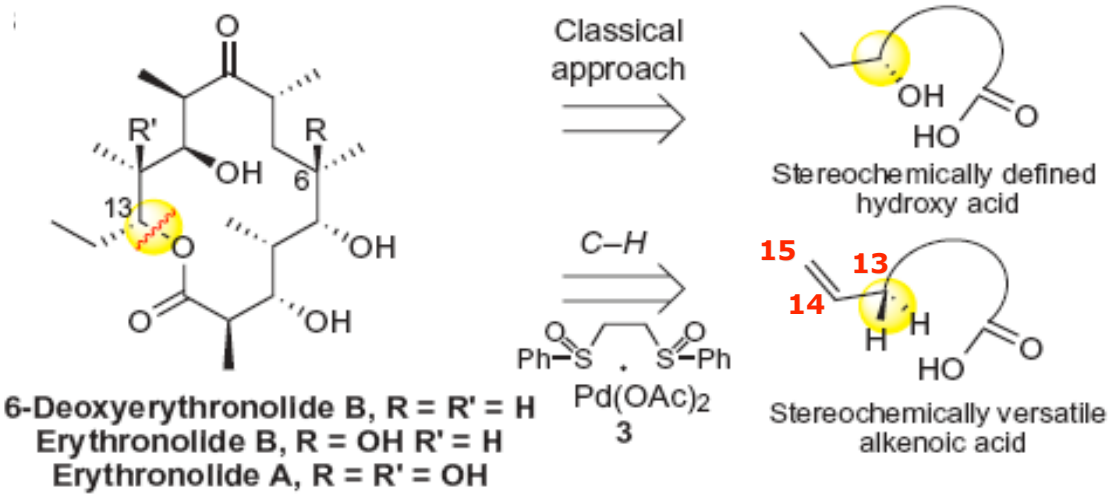
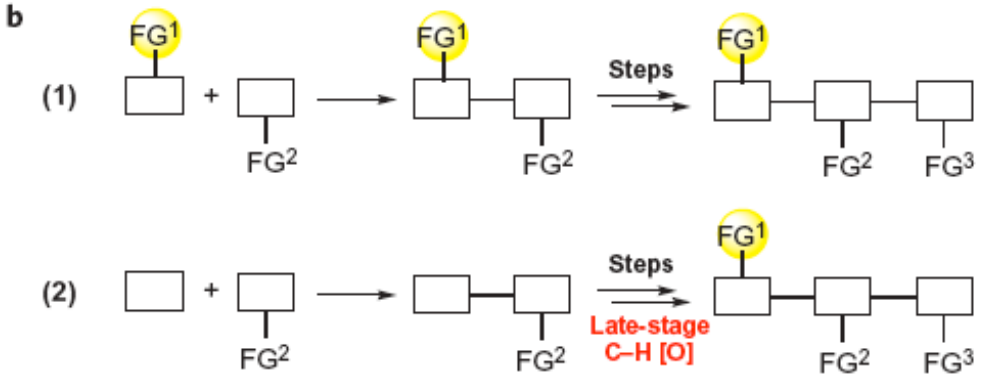
Title paper: late stage C-H oxidative macrolactonization

Aim: Selective oxidation at C13 in presence of six tertiary and five ethereal C-H bonds.

Advantages: minimizes O_2 load (reactive O_2), reduces side reactions, can furnish diastereomeric macrolactones.

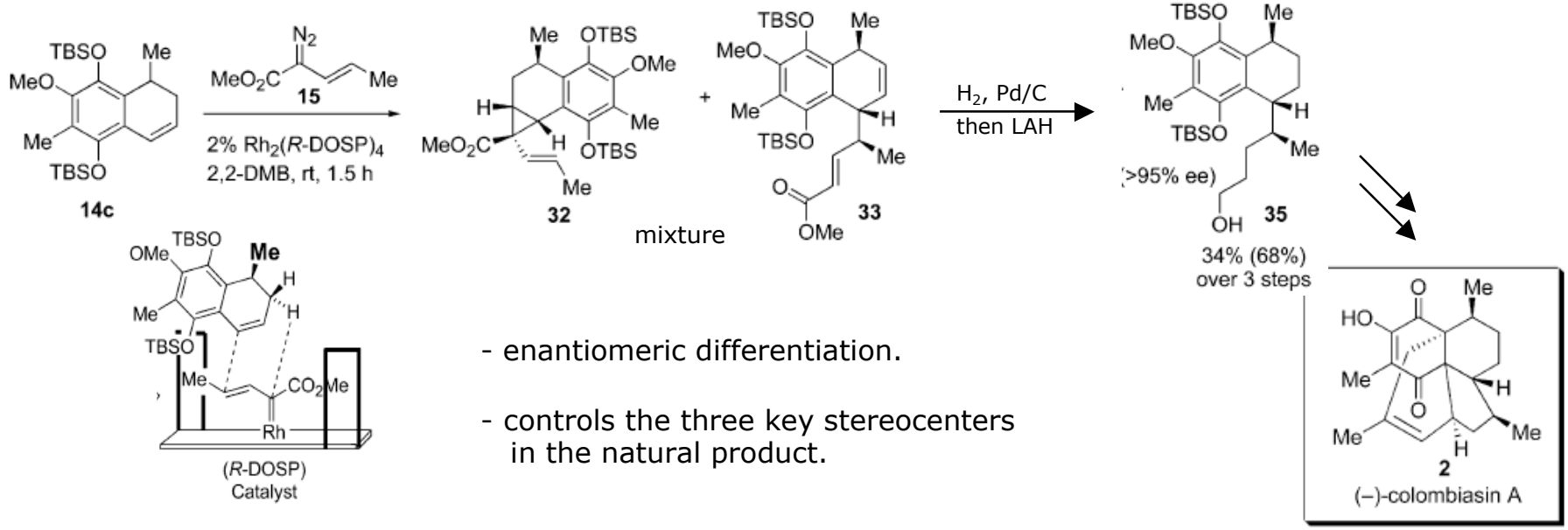




Stang, E. M.; White, M. C. *Nature Chem.* **2009**, AOP

Precedents I. Applications of C-H oxidations at late stages in target-oriented synthesis.

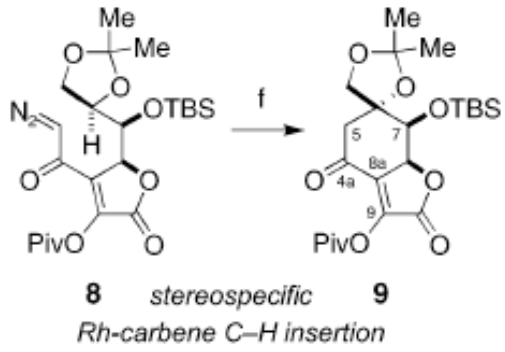
(a) Davies, H. M. L. et al. *"Combined C–H activation/Cope rearrangement as a strategic reaction in organic synthesis: total synthesis of (–)-colombiasin A and (–)-elisapterosin B" J. Am. Chem. Soc.* **2006**, *128*, 2485.



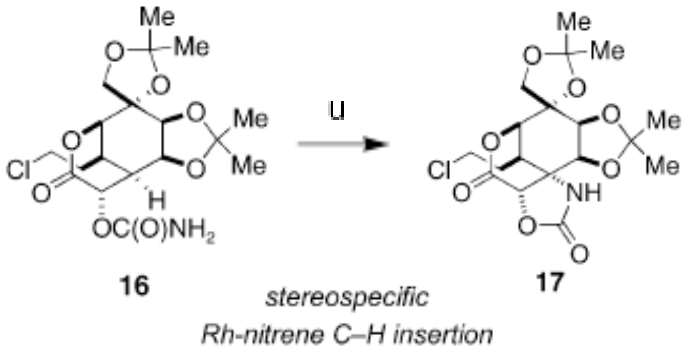
- enantiomeric differentiation.

- controls the three key stereocenters in the natural product.

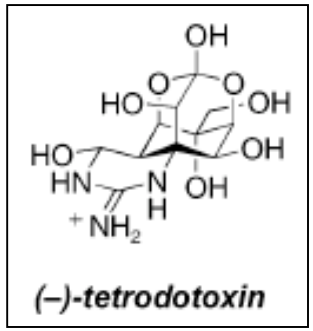
(b) Du Bois, J. et al. *"A stereoselective synthesis of (–)-tetrodotoxin" J. Am. Chem. Soc.* **2003**, *125*, 11510.



(f) 1.5 mol % $Rh_2(HNCOCPh_3)_4$, CCl_4



(u) 10 mol % $Rh_2(HNCOCF_3)_4$, $PhI(OAc)_2$, MgO, C_6H_6, 65 °C



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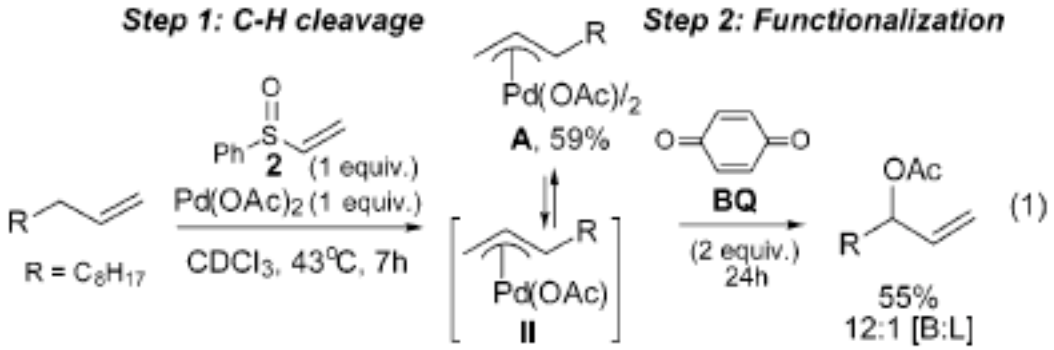
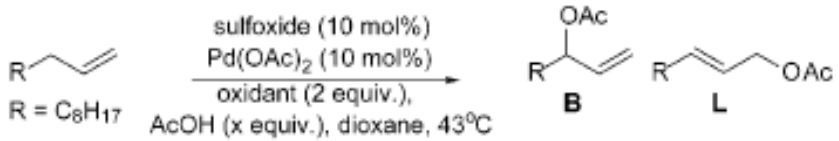
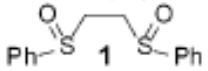
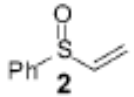
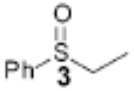
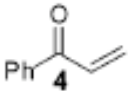
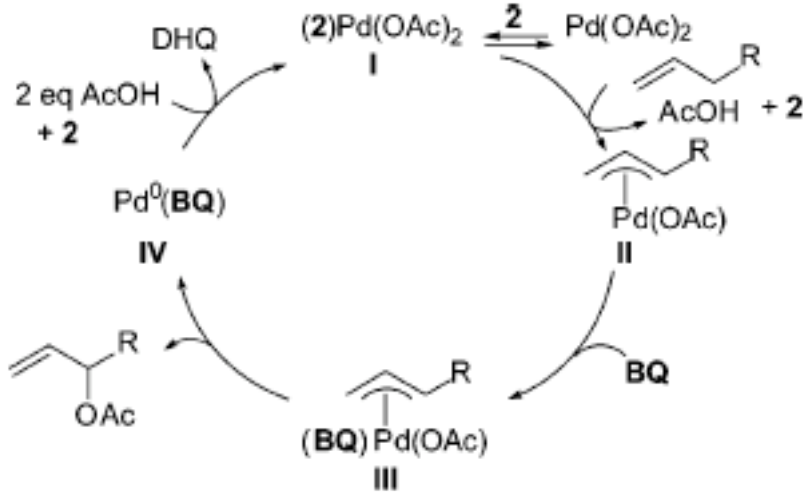
Precedents II. Serial Ligand Catalysis: a highly selective allylic C-H oxidation.[4]

Mild, chemo- & highly regioselective C-H oxidation of α-olefins.





entry	sulfoxide		AcOH (equiv.)	oxidant	% yield GC[a], 48h, **B**	[B:L]
1	**none**		52	BQ	3%	3:1
2	 **1**		52	BQ	73%	11:1
3	 **2**	a.	52	BQ	66%	12:1
		b.	**4**	**BQ**	**64%**	**31:1**
		c.	4 [b]	BQ	60%	31:1
		d.	4	$Cu(OAc)_2$	1%	1:1
		e.	4	BQ(Me)[c]	59%	32:1
		f.	4	$BQ(Me)_2$[d]	15%	21:1
		g.	4	DQ[e]	1%	1:1
		h.[f]	4	BQ	58%	9:1
4	 **3**		52	BQ	3%	2:1
5	 **4**		52	BQ	4%	3:1



"C-O bond-forming step may occur via a BQ-promoted inner-sphere reductive elimination of acetate"

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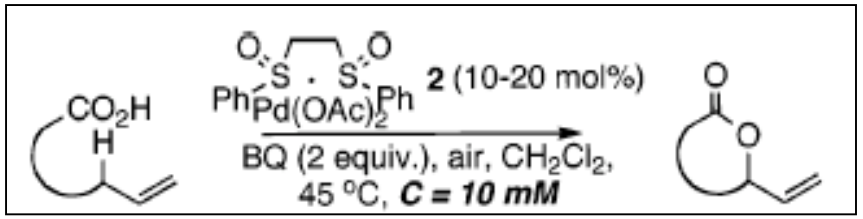
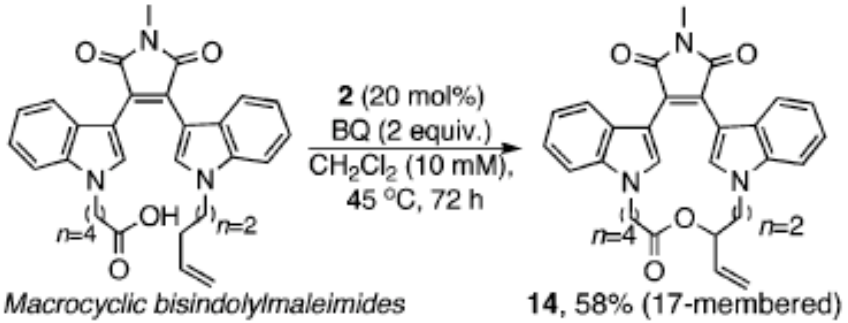
[4] Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.

Precedents III. Allylic C–H macrolactonization reaction catalysed by Pd(II)/bis-sulfoxide.[5]

Macrolactonization via allylic C-H oxidation that converts simple linear alkenoic acids into 14- to 19-membered alkyl and aryl macrolides with high levels of chemo- and regioselectivity.



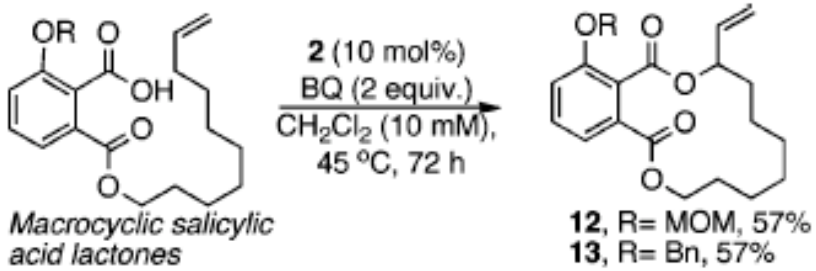
(a). N-rich substrate: PKC inhibitor analog



Macrocyclic bisindolylmaleimides

14, 58% (17-membered)

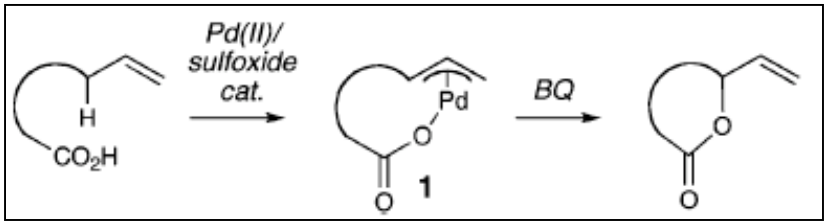
(b). *o*-Substituted salicylates: e⁻ density, steric hindrance



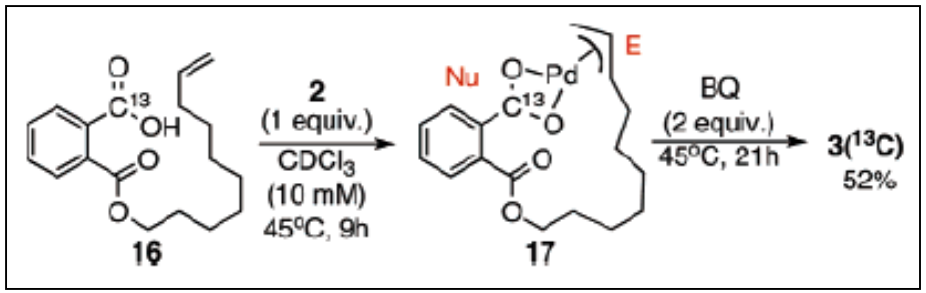
Macrocyclic salicylic acid lactones

12, R= MOM, 57%
13, R= Bn, 57%

Serial ligand catalysis mechanism via templated **1**



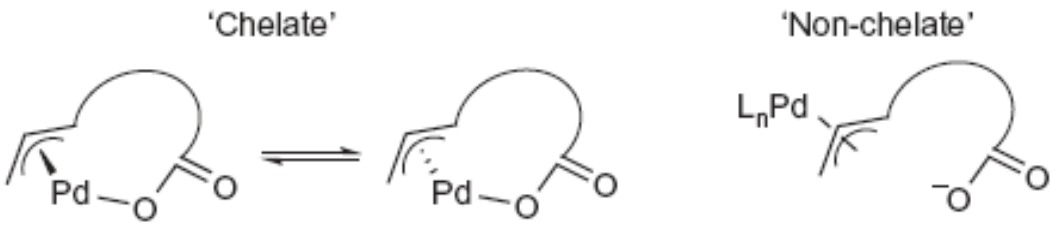
Evidence for templated π-allylPd carboxylate intermediate



[5] Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032.

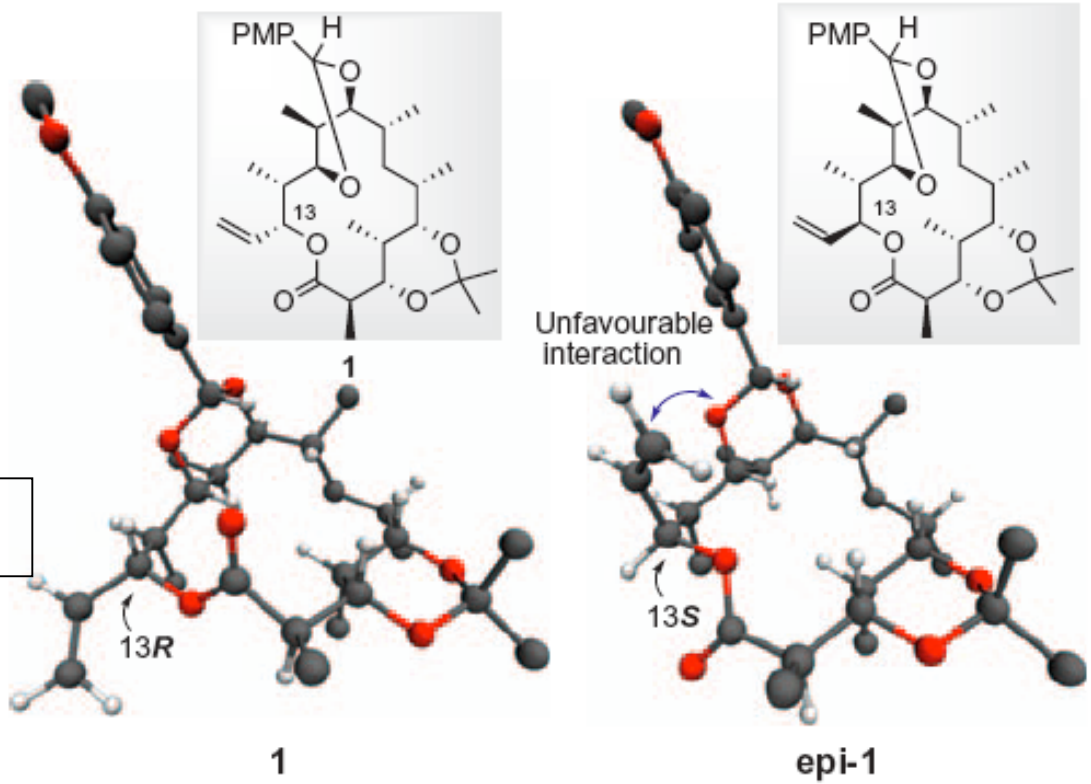
Title paper: Pd-chelation leads to product-like TS structures

(a). Possible π-allyl-Pd(carboxylate) intermediates for C–H macrolactonization.



(b). Energy-minimized structures of macrolides 1 and epi-1 using MMFF94s force-field implemented in Molecular Operating Environment (MOE).

Assumption: TS with product-like trans annular character



1 is 3 kcal/mol more stable than **epi-1**

Stang, E. M.; White, M. C. *Nature Chem.* **2009**, AOP

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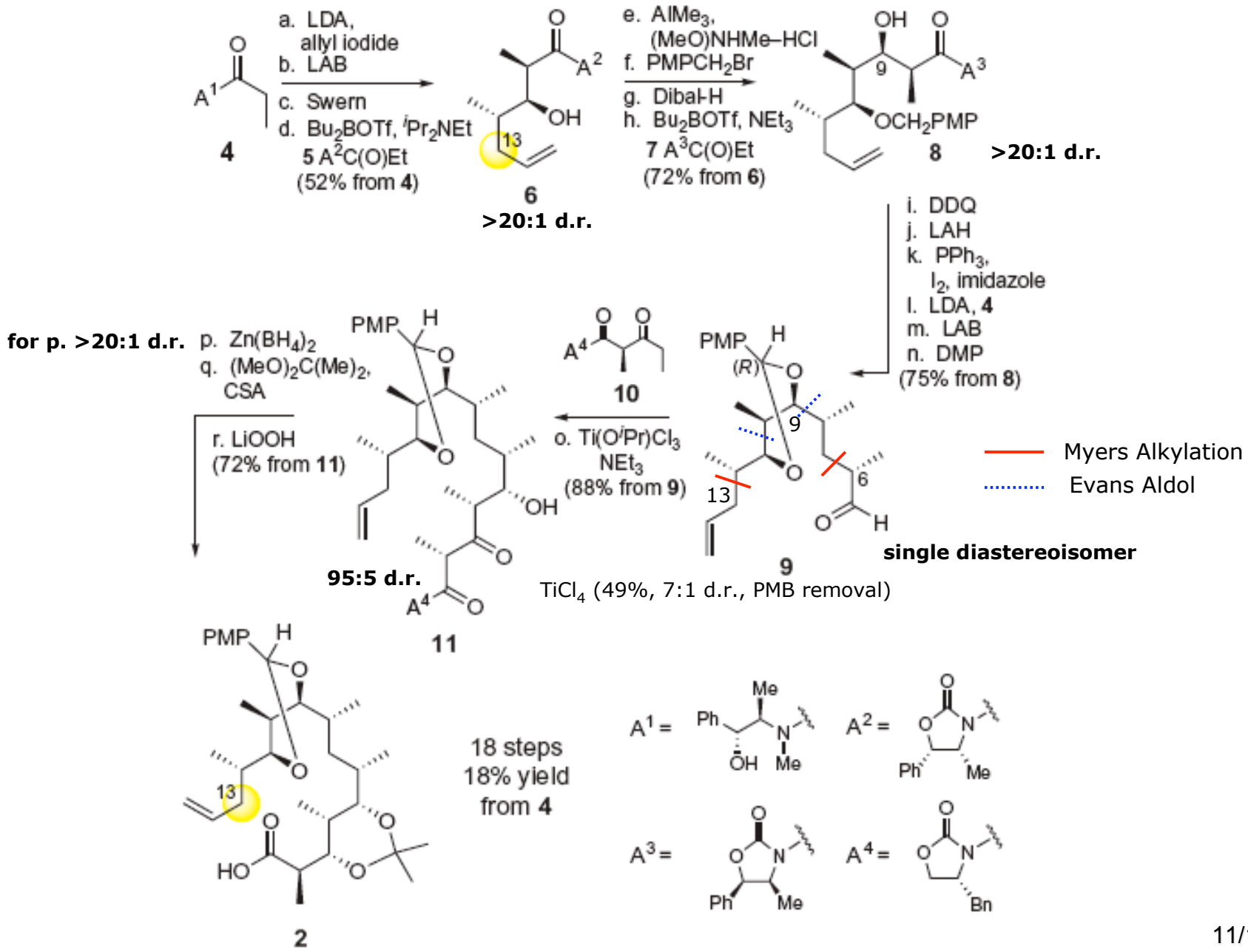
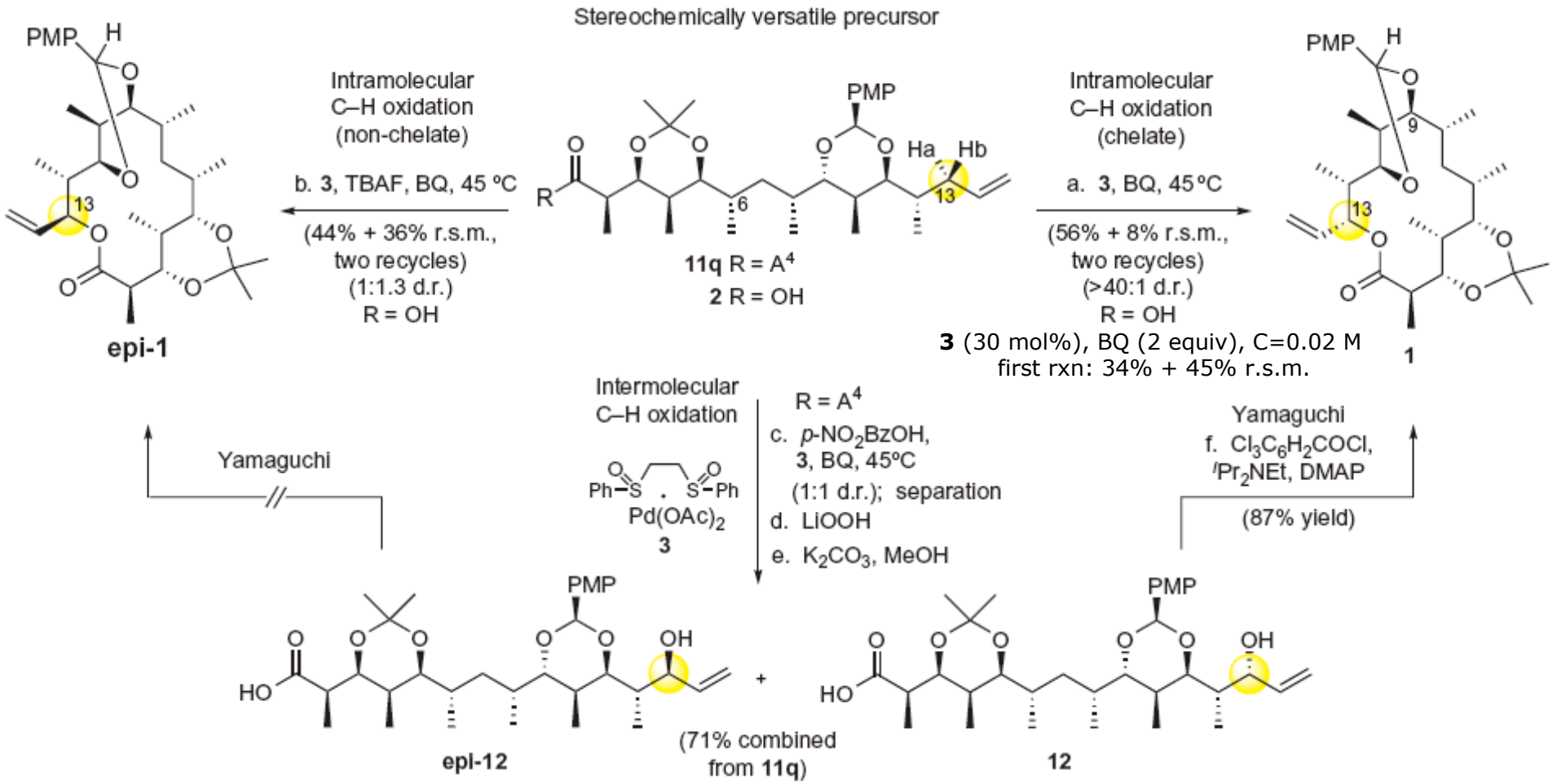
Title paper: Synthesis of macrolactonization precursor **2**



Stang, E. M.; White, M. C. *Nature Chem.* **2009**, AOP

Title paper: Synthesis of macrolides **1** and **epi-1**



1:1 mixture diastereoisomers

absence of transannular effects, no diastereoselectivity

Figure 3 | Synthesis of macrolides 1 and epi-1. Reaction conditions: a, **3** (0.3 equiv.), BQ (2.0 equiv.), 45 °C, 72 h, >40:1 d.r., 34% + 45% r.s.m. (56% + 8% r.s.m., recycled twice); b, **3** (0.3 equiv.), BQ (2.0 equiv.), TBAF (0.3 equiv.), 45 °C, 72 h, 1:1.3 d.r., 20% + 75% r.s.m. (44% + 36% r.s.m., recycled twice); c, **3** (0.1 equiv.), BQ (2.0 equiv.), *p*-NO_2BzOH (1.5 equiv.), 45 °C, 72 h, 1:1 d.r., 73% (combined); d, $LiOOH_{aq}$ (2.0 equiv.); e, K_2CO_3 (3.0 equiv.), MeOH, 97% (two steps); f, $Cl_3C_6H_2COCl$ (15.0 equiv.), $^iPr_2NEt$ (20.0 equiv.), DMAP (40.0 equiv.), benzene, 87%. BQ = 1,4-benzoquinone, DMAP = *N*,*N*-4-dimethylaminopyridine, *p*-NO_2BzOH = *p*-nitrobenzoic acid.

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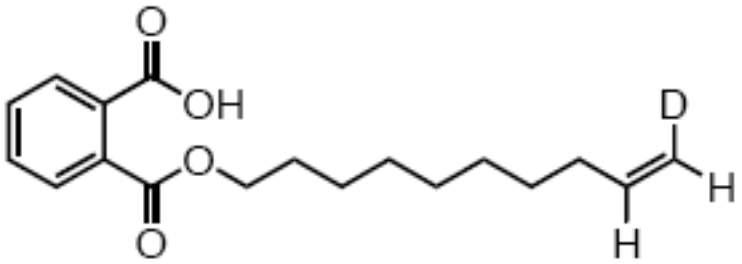
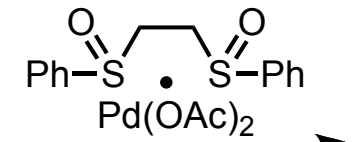
Deuteration Studies

Rapid π-σ-π isomerization is occurring in both C—H macrolactonization protocols (with and w/o TBAF)

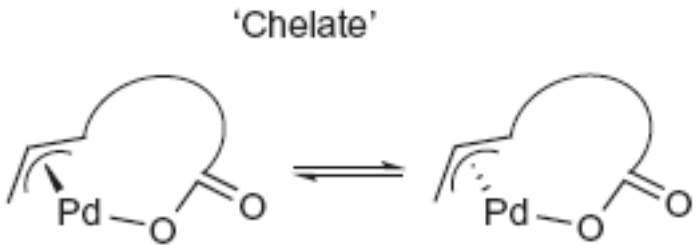


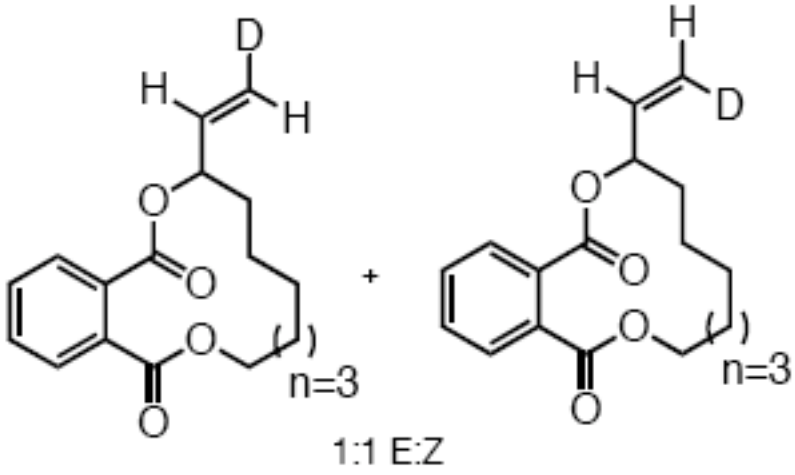
>20:1 Z:E



56% (1:1, E/Z)

(+ 0.15 eq. TBAF)

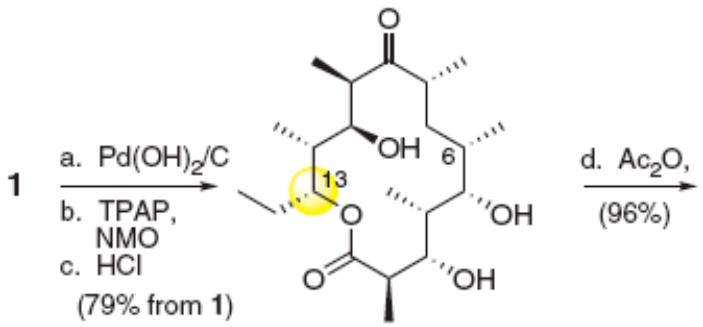


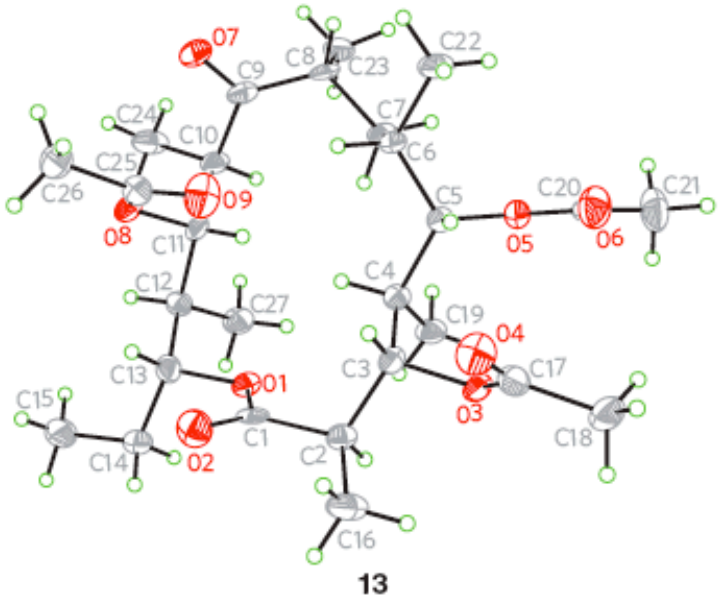


Stang, E. M.; White, M. C. *Nature Chem.* **2009**, AOP

Completion of the Synthesis of 6-dEB & Conclusions

White, M. C. et al. "Total synthesis and study of 6-dEB by late-stage C–H oxidation" *Nature Chem.* **2009**, AOP





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- A late-stage C–H oxidation strategy was applied to the most efficient total synthesis of 6-dEB to date.

- Proof of concept: first application of C–H oxidative macrolactonization in complex macrolide synthesis.

  Feature (advantage/disadvantage): stereochemical diversity can be achieved at the key lactone position.

- Reaction conditions that proceed through chelate-controlled cyclization allow high levels of substrate-based diastereocontrol prediction from advanced, flexible intermediates.

- More examples and novel synthetic targets are still required to determine applicability of method.

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