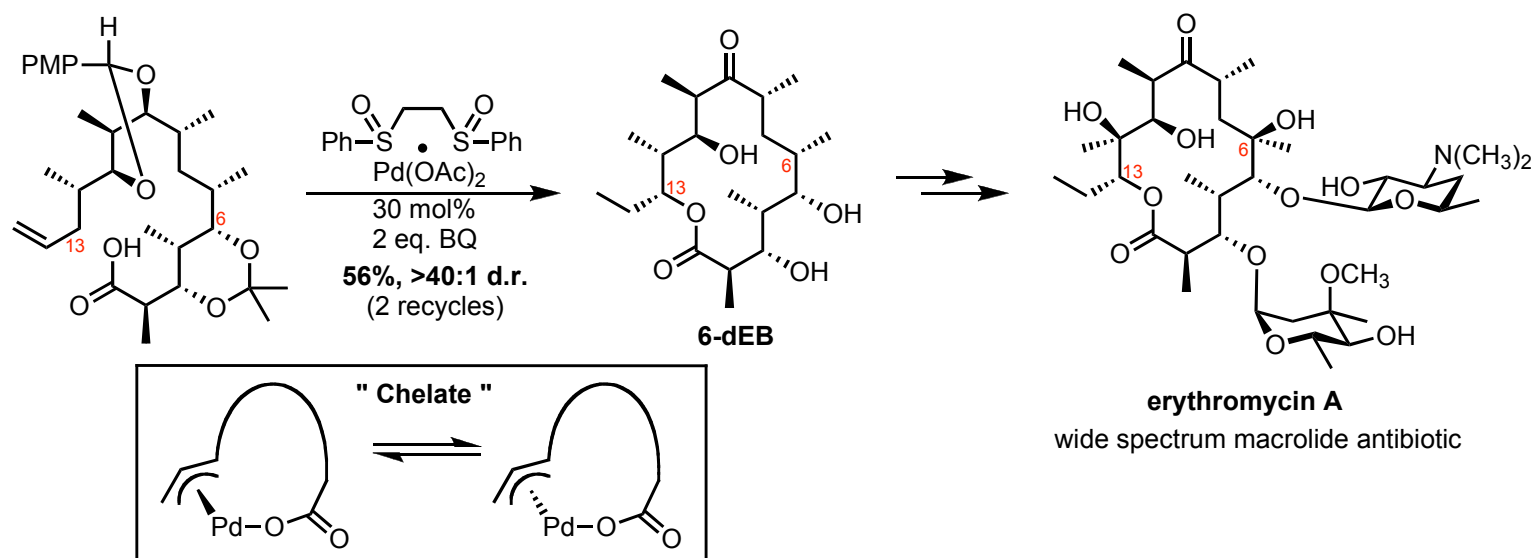


Total synthesis and study of 6-deoxyerythronolide B (6-dEB) by late-stage C–H oxidation

Erik M. Stang and M. Christina White

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Karla Bravo

Current Literature, 09/12/2009

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Erythromycin

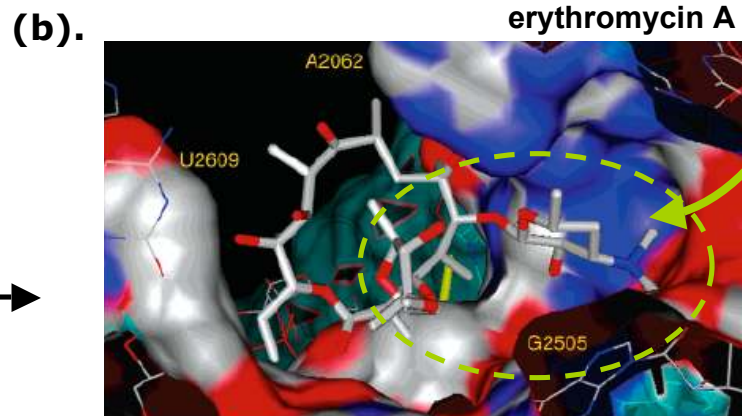
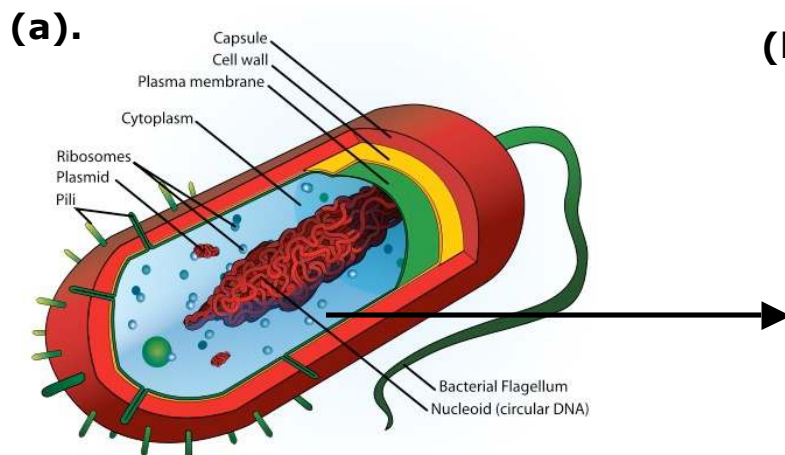
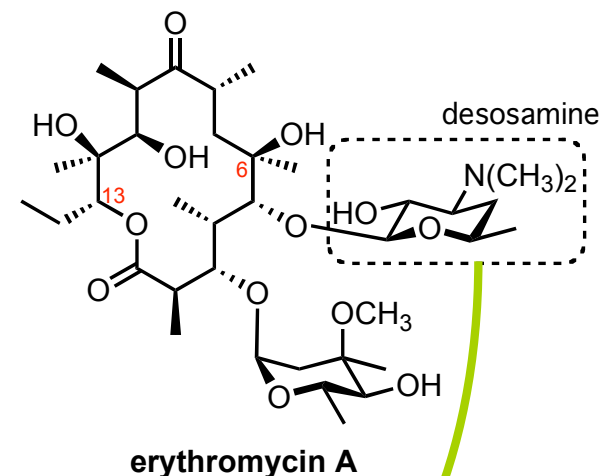
- Facts**
- macrolide antibiotic produced by a strain of *Saccharopolyspora erythraea*.¹
 - antimicrobial spectrum similar to or slightly wider than that of penicillin, and is used for people who have an allergy to penicillin.
 - acts by inhibition of protein synthesis by binding 50 S ribosomal subunits of susceptible organisms.²
 - available in different formulations, common brand names: E.E.S., Robimycin, E-Mycin, Erymax, Eryped



E.E.S.-400 Filmtab

Structure

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



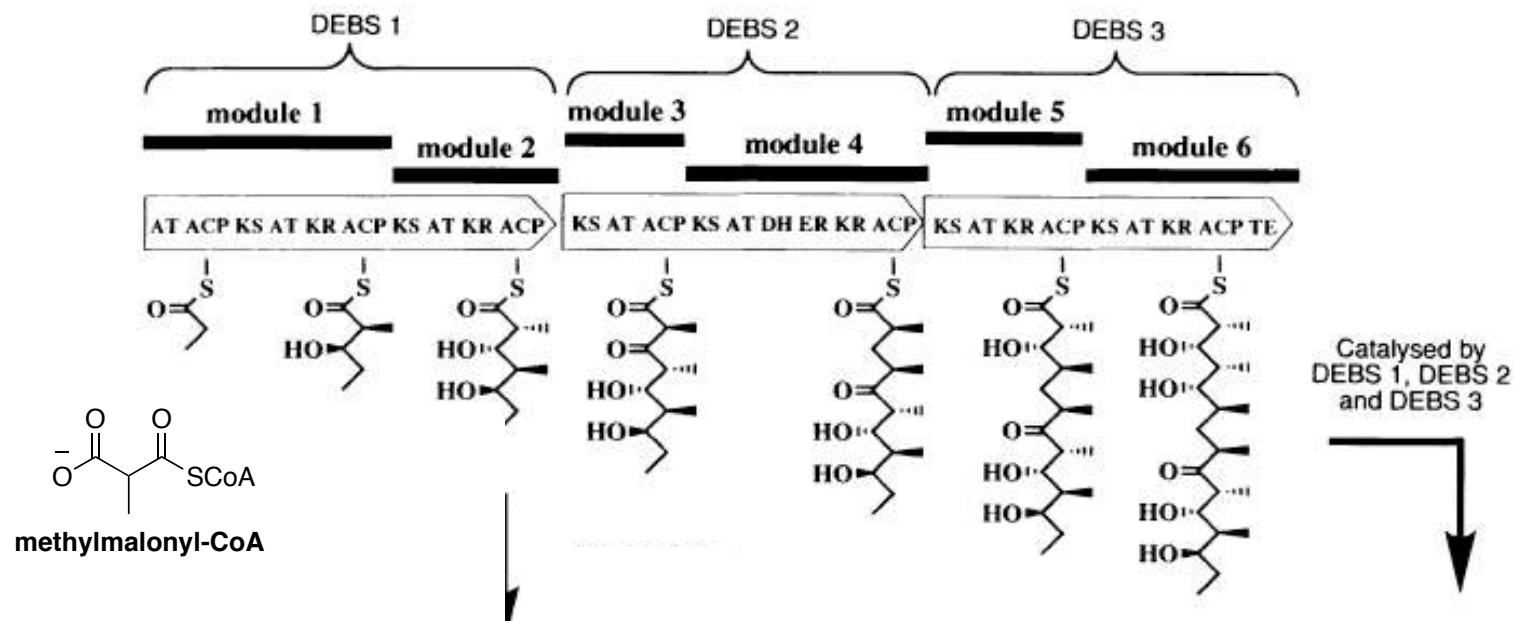
Critical interactions: - - - - -
 G2505 phosphate-desosamine -NMe₂
 A2058-desosamine sugar

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

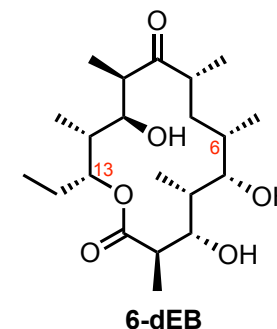
¹ Katz, L.; Khosla, C. *Nat. Biotechnol.* **2007**, *25*, 428.

² Katz, L.; Ashley, G. W. *Chem. Rev.* **2005**, *105*, 499.

Biosynthesis of the PK (polyketide) 6-dEB from erythromycin³



- **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

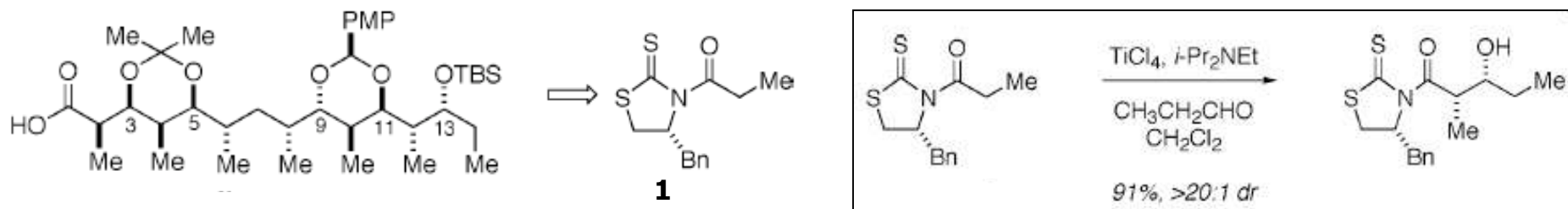


Codes: AT) acyltransferase, ACP) acyl carrier protein, KS) ketosynthase, KR) ketoreductase, DH) dehydratase, ER) enoylreductase, TE) thioesterase

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

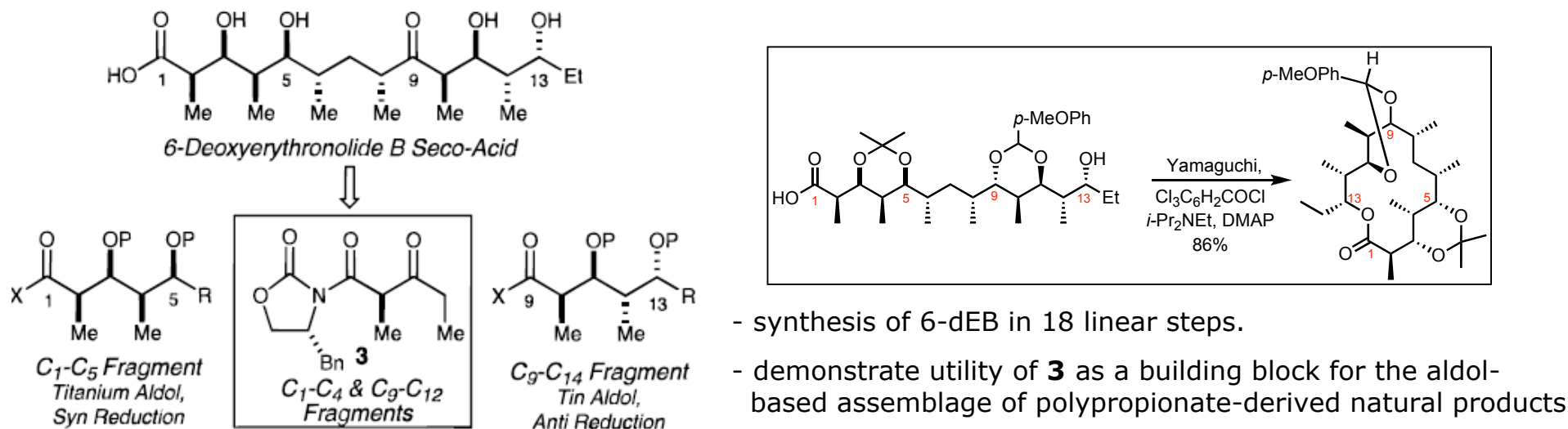
Previous synthetic studies of erythromycin

(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.

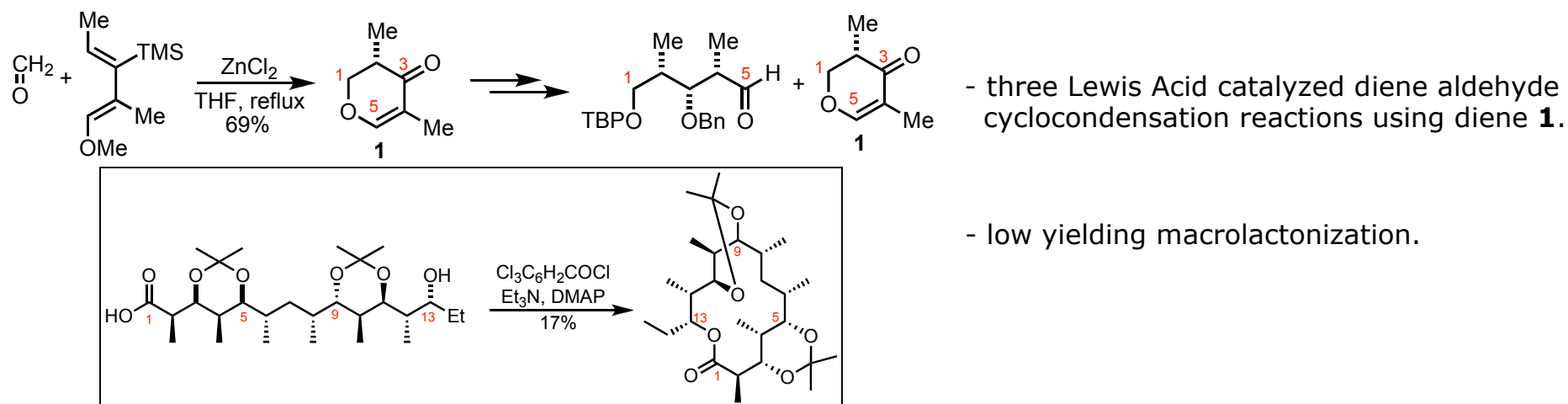
(b) **Evans, D. A. et al.** "General strategies toward the syntheses of macrolide antibiotics. The total syntheses of 6-deoxyerythronolide B and oleandolide". *J. Am. Chem. Soc.* **1998**, *120*, 5921.



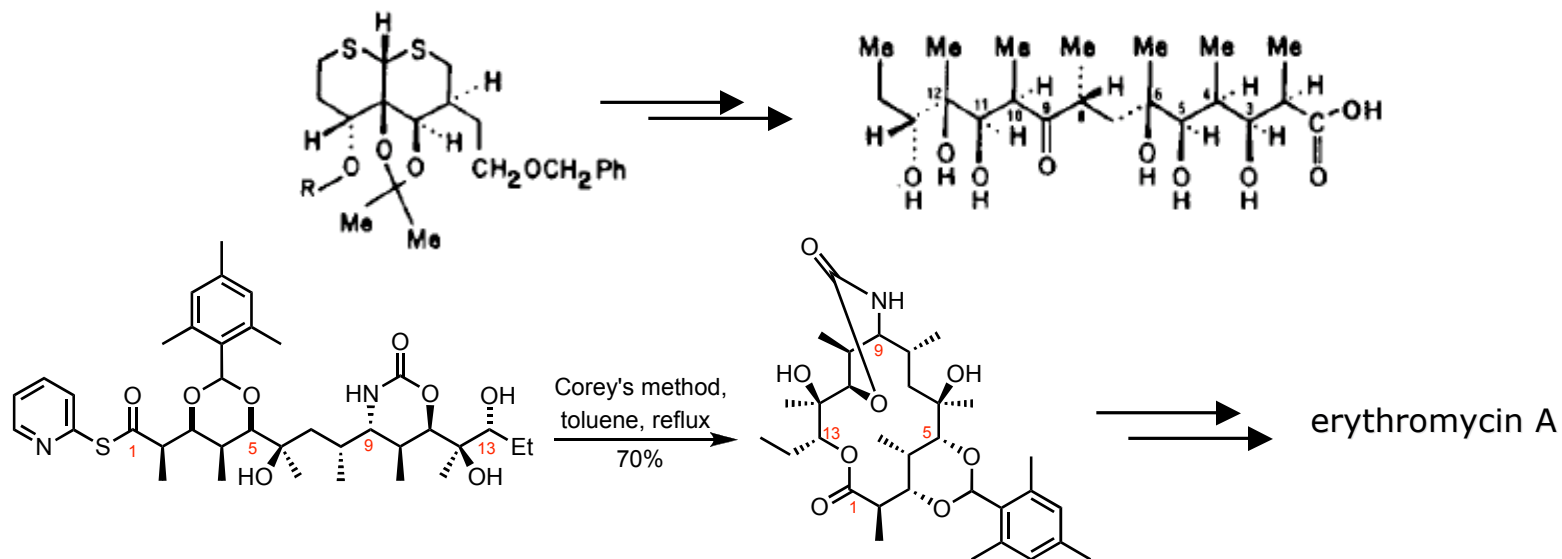
- synthesis of 6-dEB in 18 linear steps.
- demonstrate utility of **3** as a building block for the aldol-based assemblage of polypropionate-derived natural products

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.



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

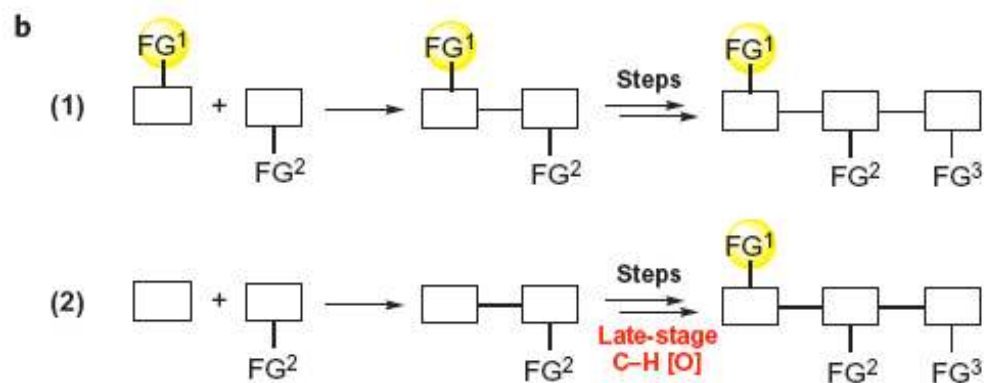
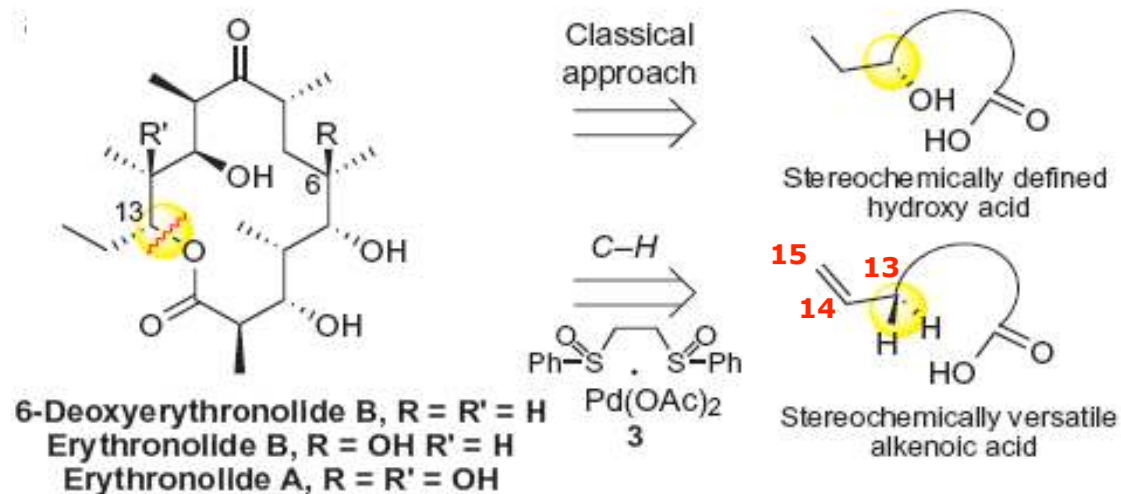


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Title paper: late stage C-H oxidative macrolactonization

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

Advantages: minimizes O₂ load (reactive O₂), reduces side reactions, can furnish diastereomeric macrolactones.

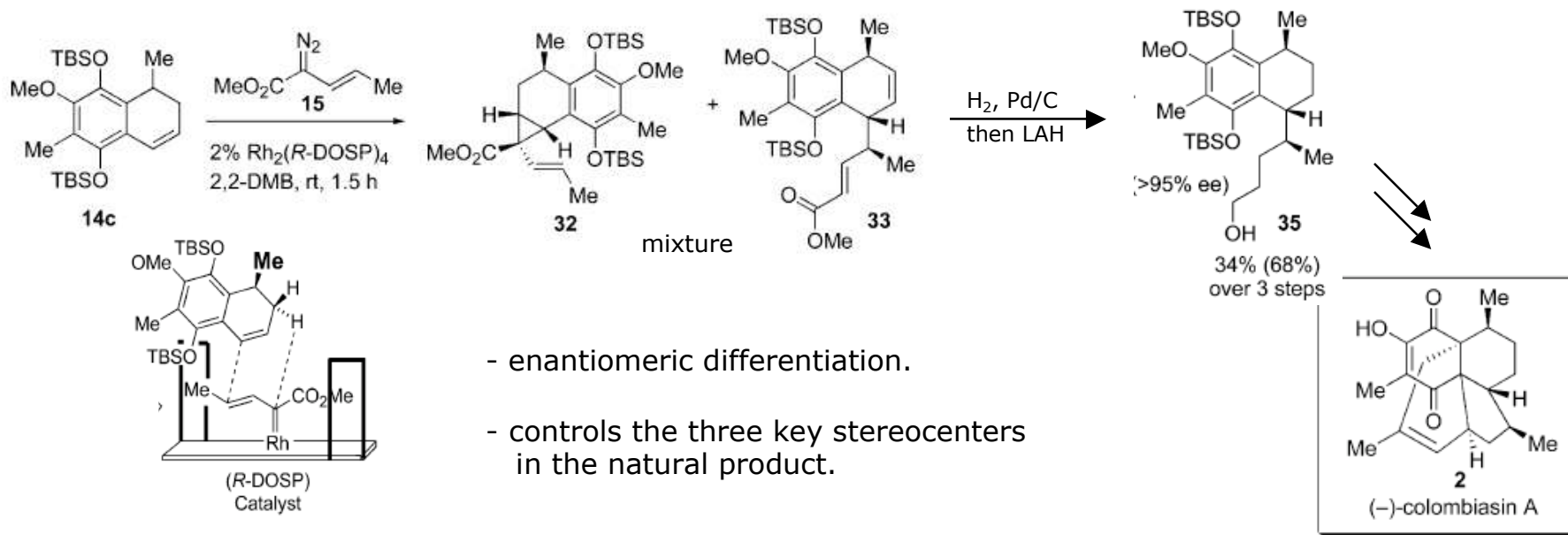


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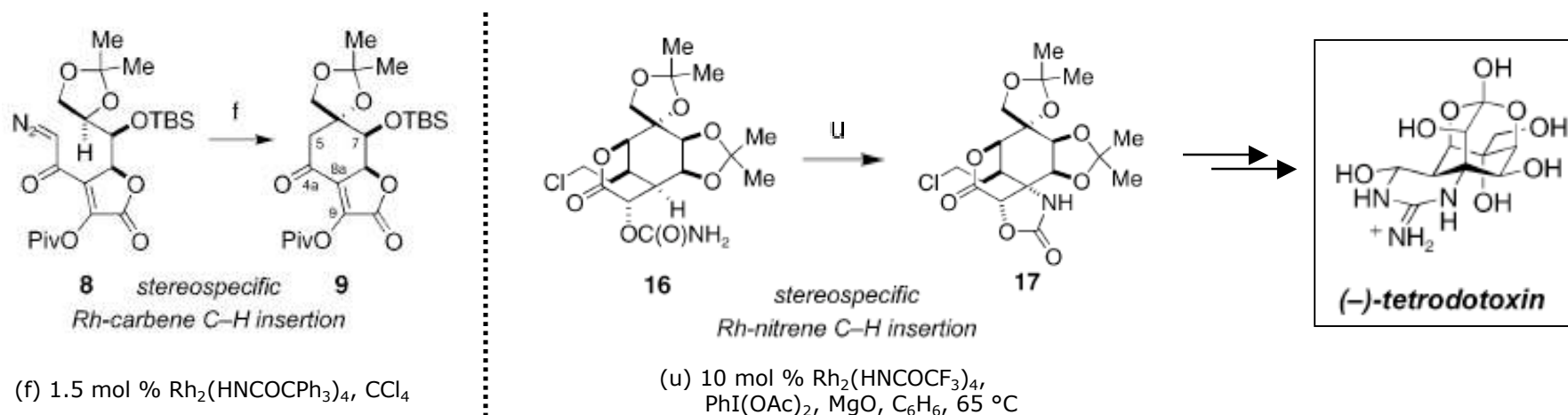
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Precedents I. Applications of C-H oxidations at late stages in target-oriented synthesis.

(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.



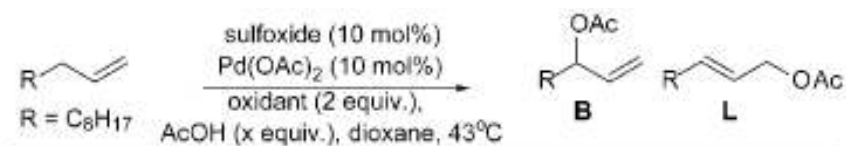
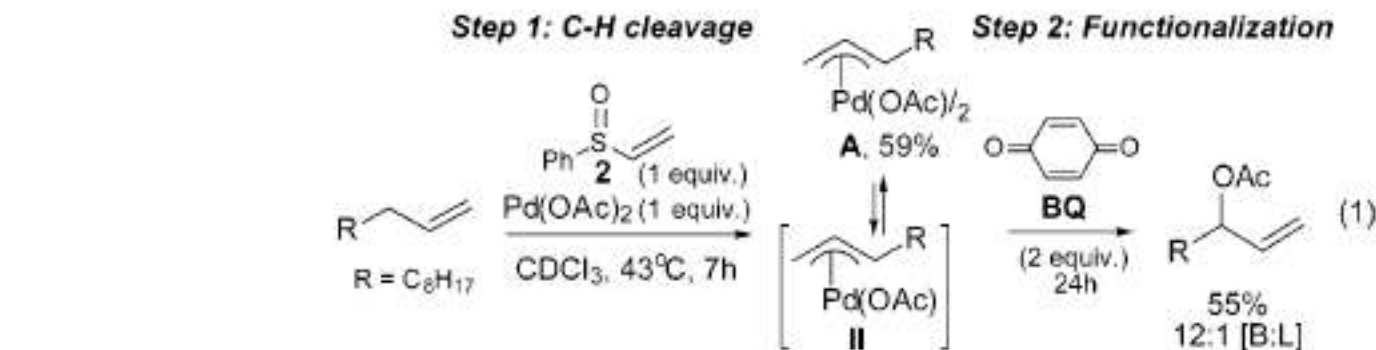
(b) **Du Bois, J. et al.** "A stereoselective synthesis of (-)-tetrodotoxin" *J. Am. Chem. Soc.* **2003**, 125, 11510.

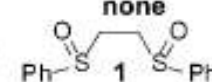
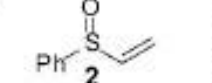
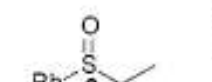
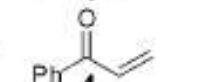


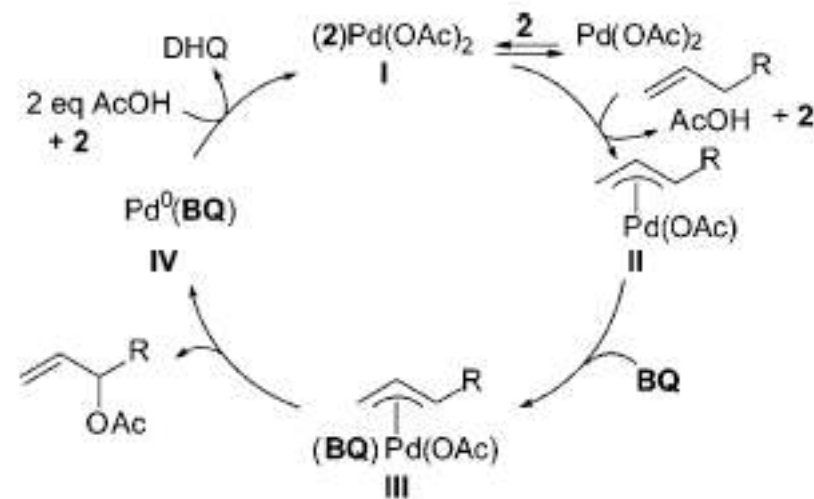
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Precedents II. Serial Ligand Catalysis: a highly selective allylic C-H oxidation.⁴

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		52	BQ	73%	11:1
3		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	BQ	58%	9:1
4		52	BQ	3%	2:1
5		52	BQ	4%	3:1

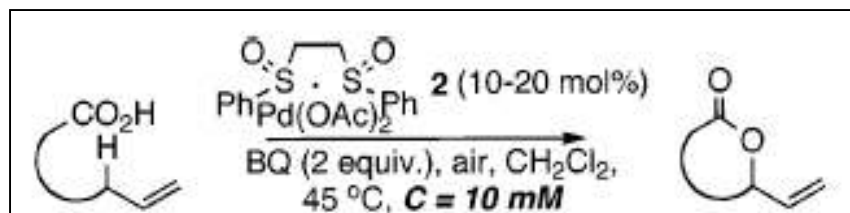


"C-O bond-forming step may occur via a BQ-promoted inner-sphere reductive elimination of acetate"

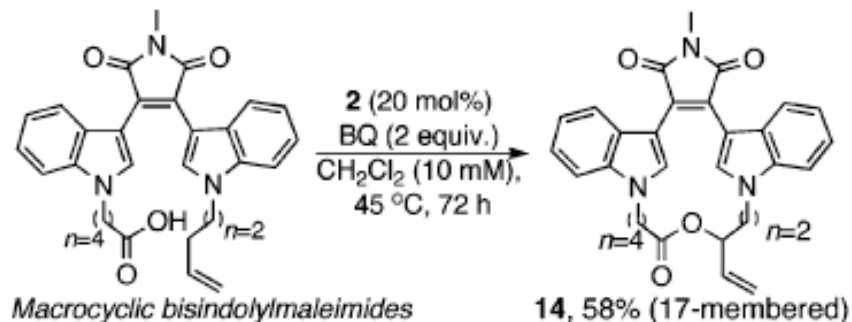
⁴ Chen, M. S.; Prabakaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.

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

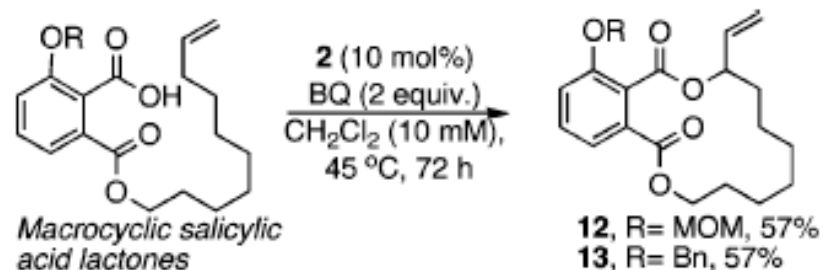
Macrolactonization via allylic C–H oxidation that converts simple linear alkenoic acids into 14- to 19-membered alkyl and aryl macrolides with high levels of chemo- and regioselectivity.



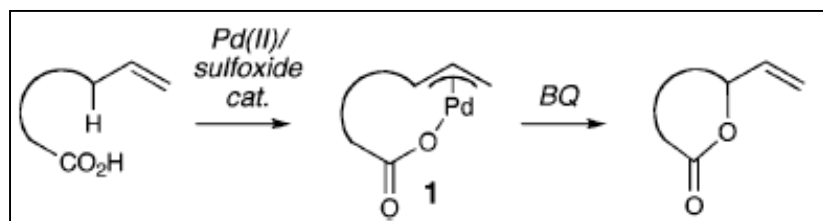
(a). N-rich substrate: PKC inhibitor analog



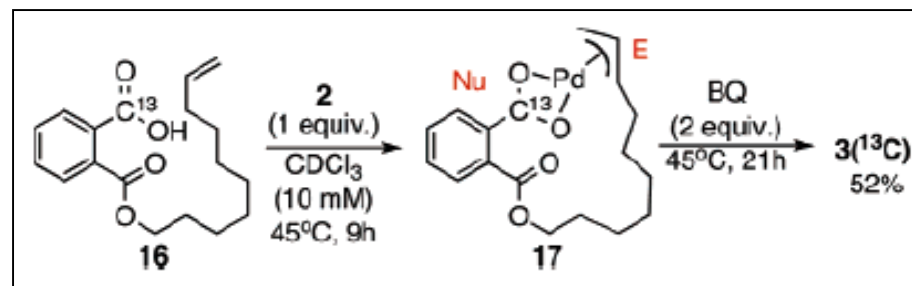
(b). *o*-Substituted salicylates: e^- density, steric hindrance



Serial ligand catalysis mechanism via templated **1**



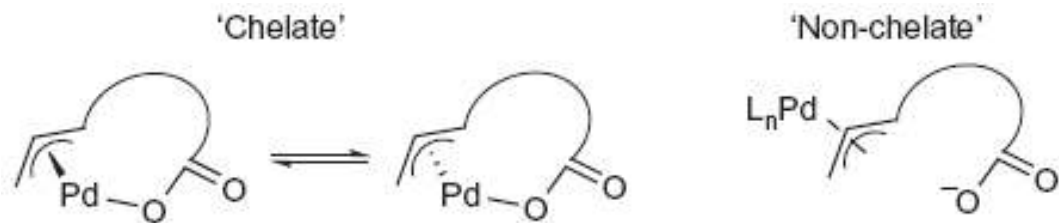
Evidence for templated π -allylPd carboxylate intermediate



⁵ Fraunhofer, K. J.; Prabakaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032.

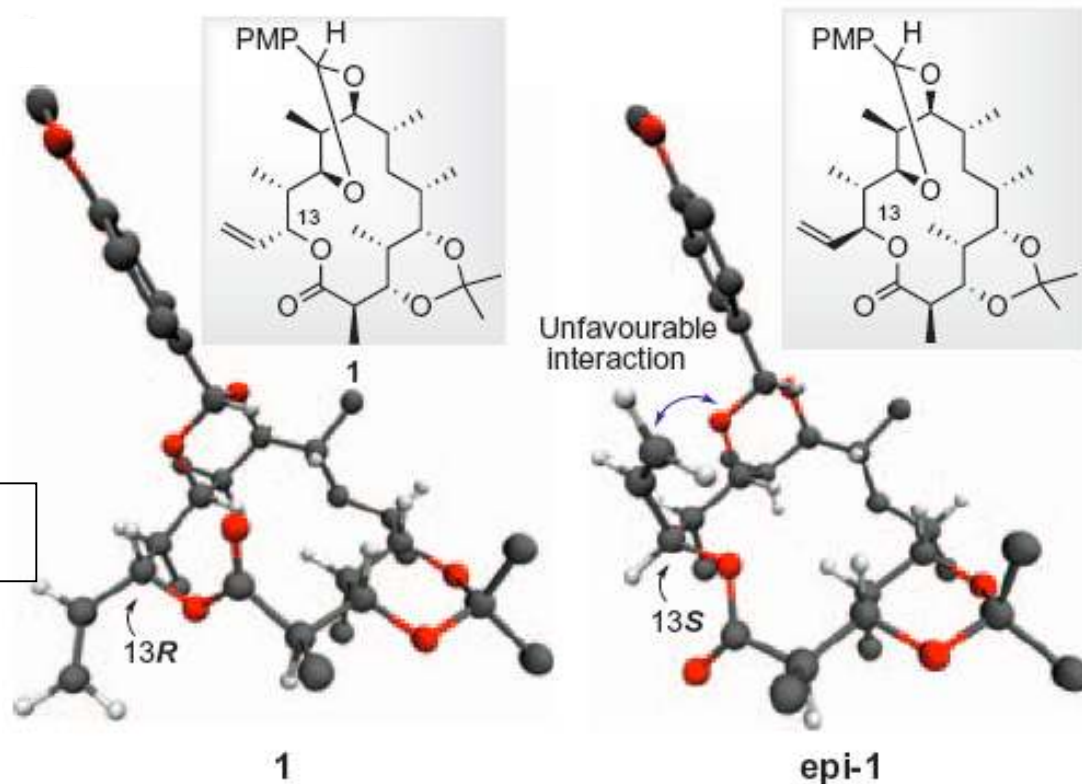
Title paper: Pd-chelation leads to product-like TS structures

(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

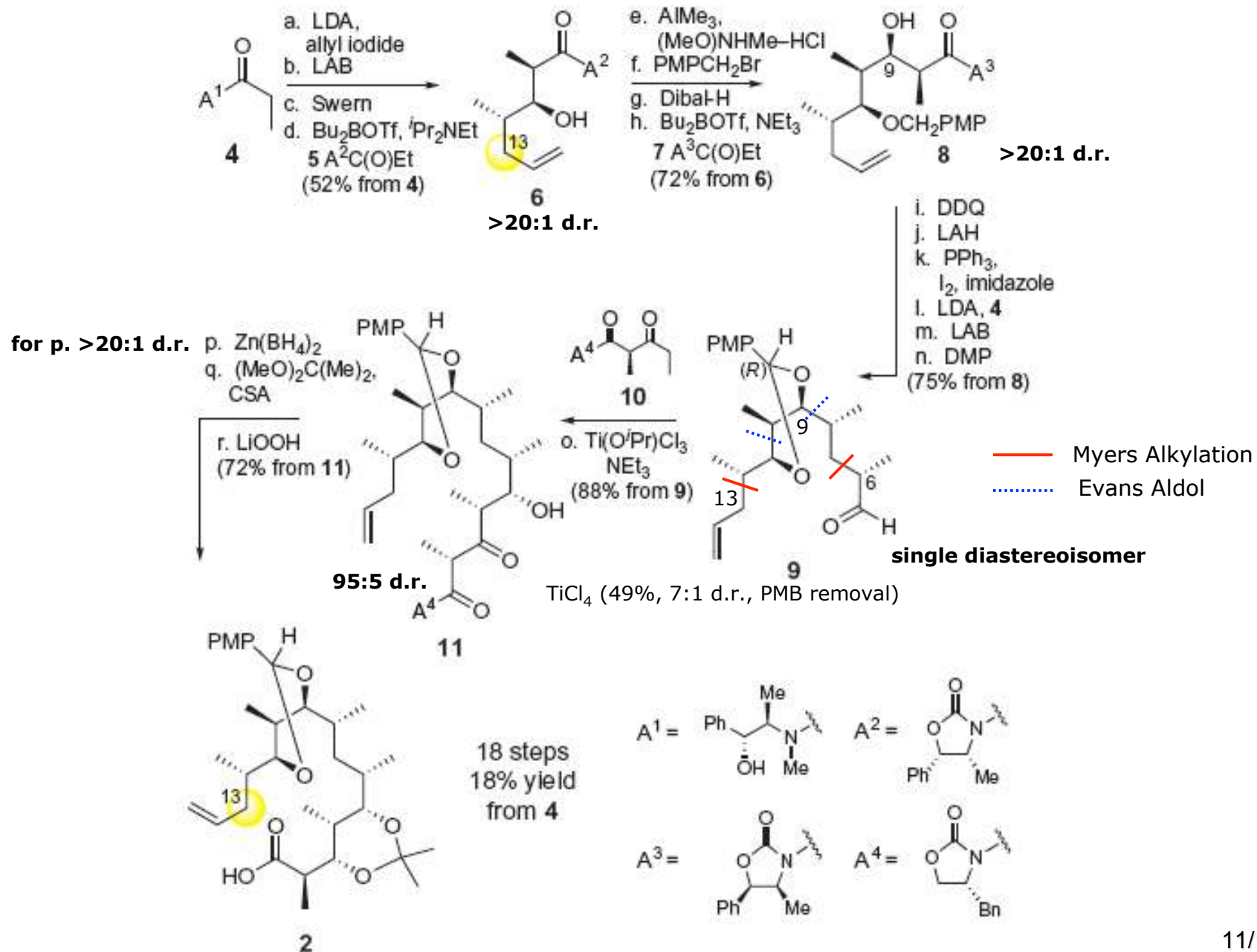


1 is 3 kcal/mol more stable than *epi-1*

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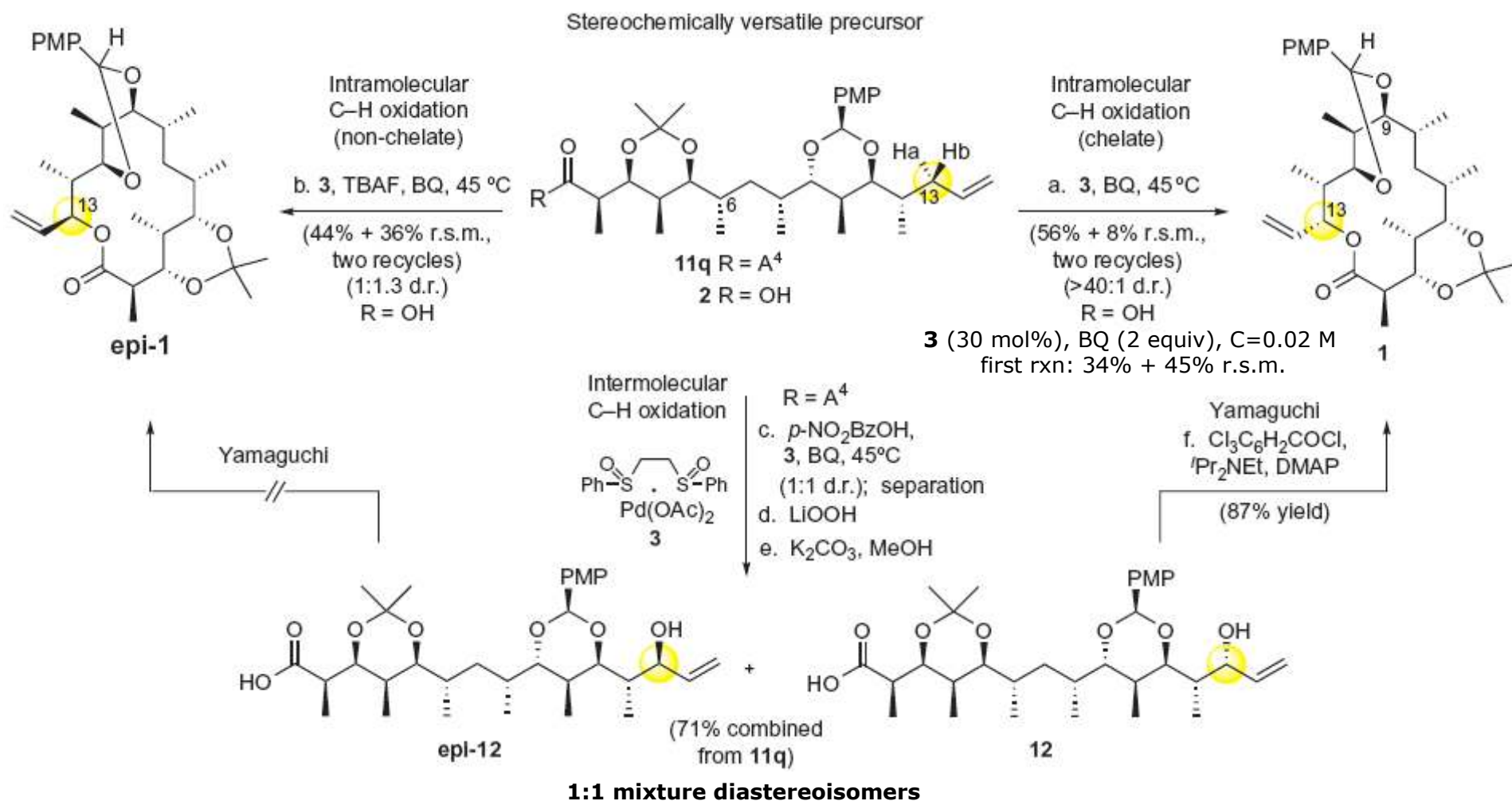
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Title paper: Synthesis of macrolactonization precursor 2



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

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



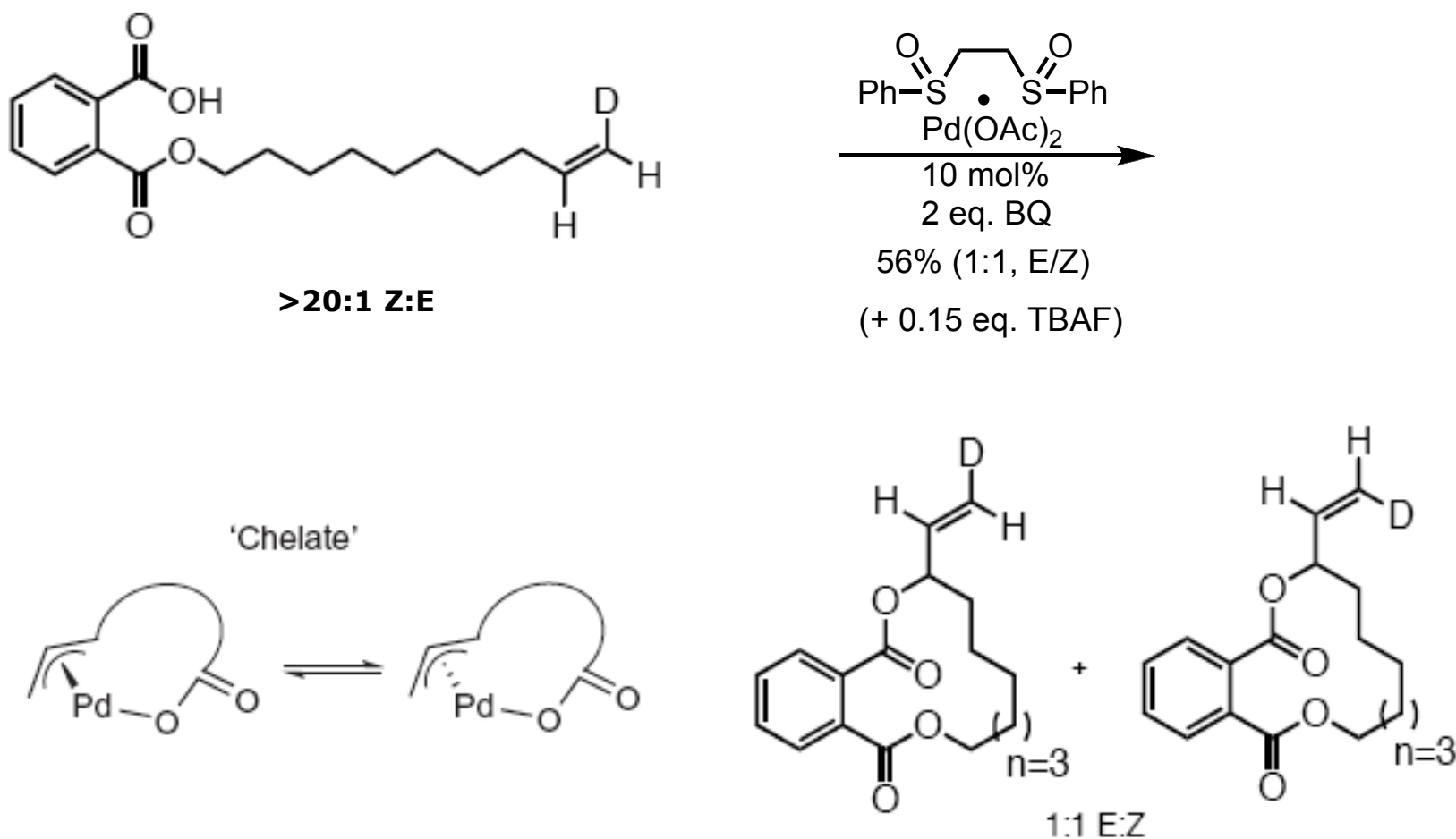
absence of transannular effects, no diastereoselectivity

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*-NO₂BzOH (1.5 equiv.), 45 °C, 72 h, 1:1 d.r., 73% (combined); d, LiOOH_{aq} (2.0 equiv.); e, K₂CO₃ (3.0 equiv.), MeOH, 97% (two steps); f, Cl₃C₆H₂COCl (15.0 equiv.), ^{*i*}Pr₂NEt (20.0 equiv.), DMAP (40.0 equiv.), benzene, 87%. BQ = 1,4-benzoquinone, DMAP = *N,N*-4-dimethylaminopyridine, *p*-NO₂BzOH = *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)

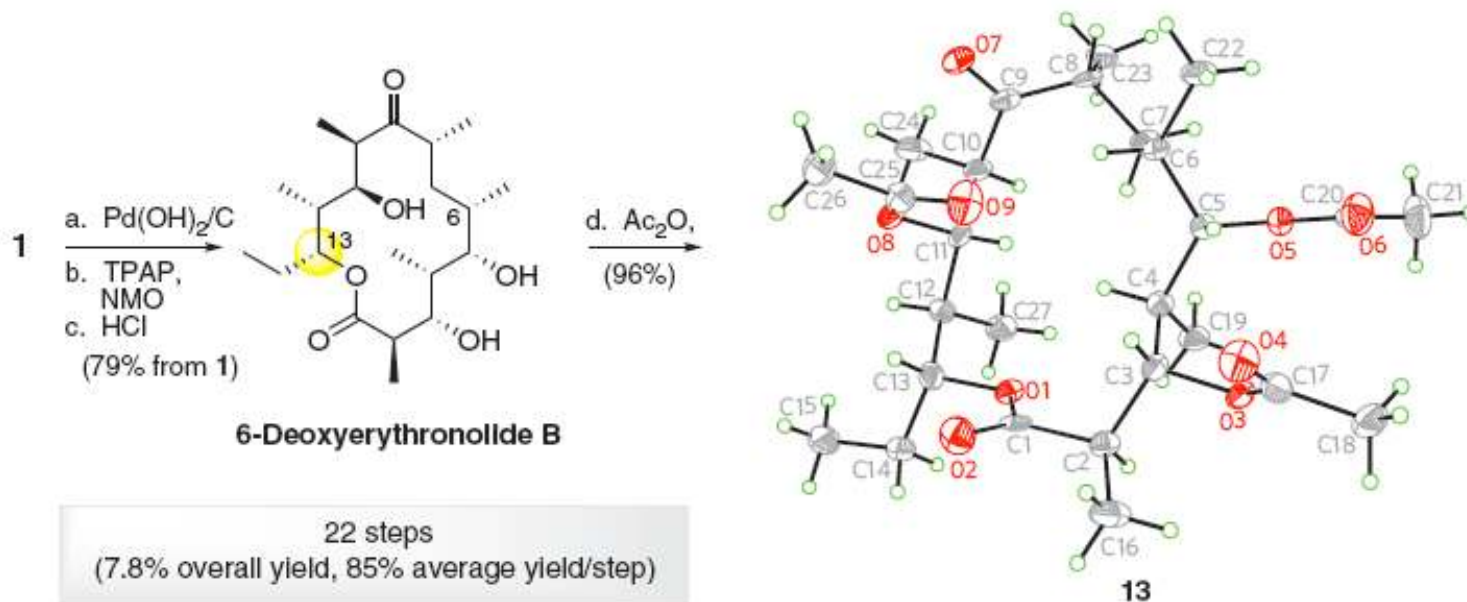


Stang, E. M.; White, M. C. *Nature Chem.* **2009**, AOP

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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



- 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.