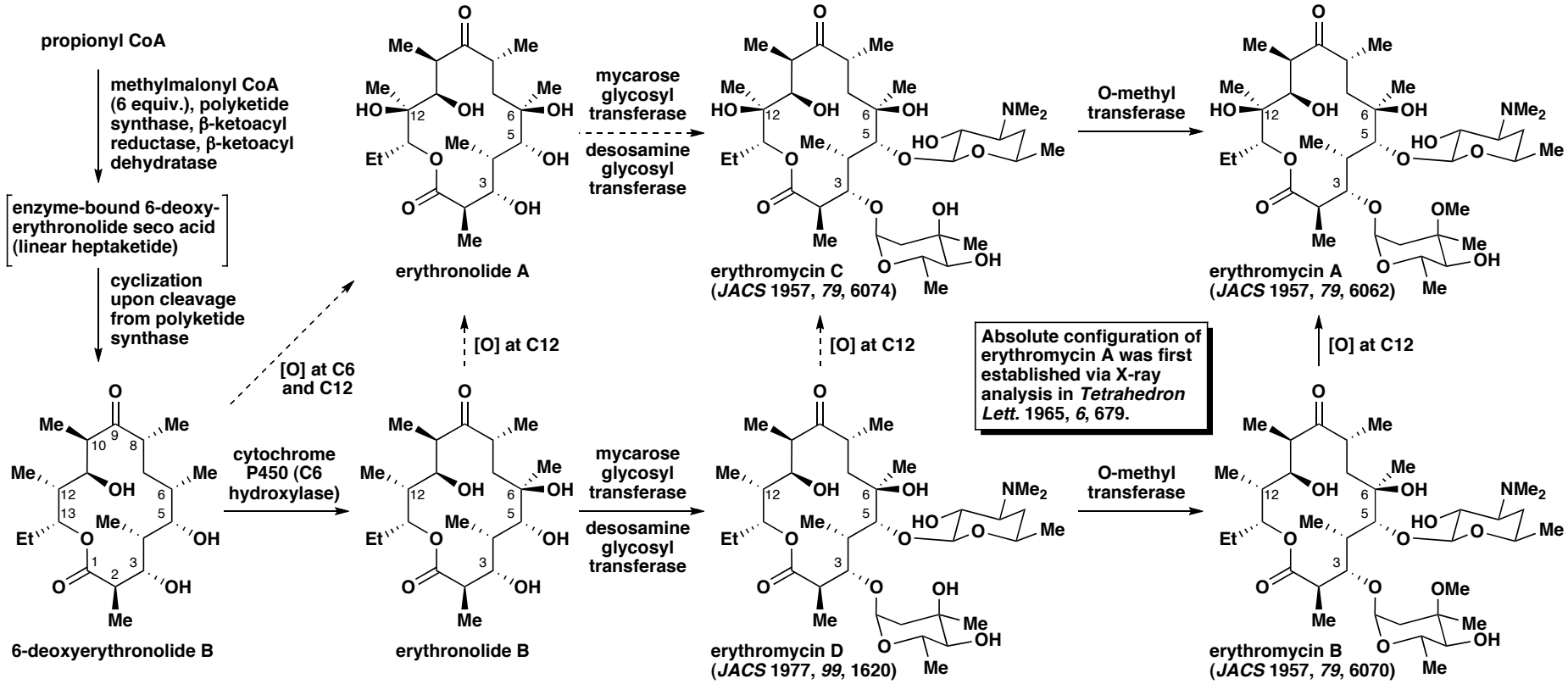
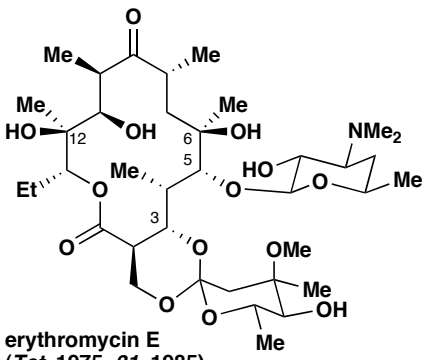
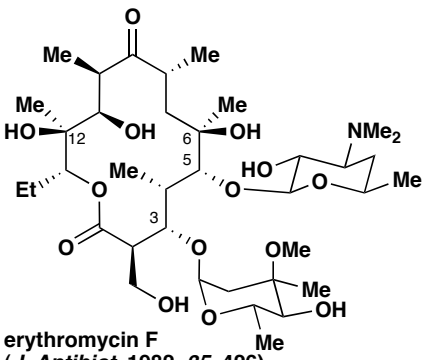
Erythronolide and Erythromycin

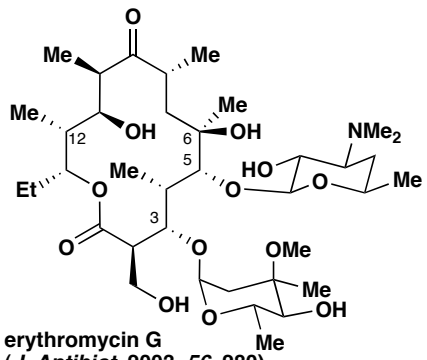




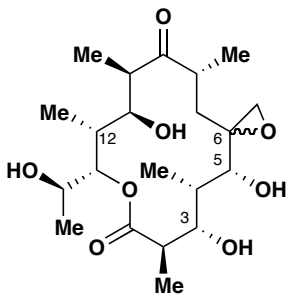
erythromycin E (*Tet.* 1975, *31*, 1985)



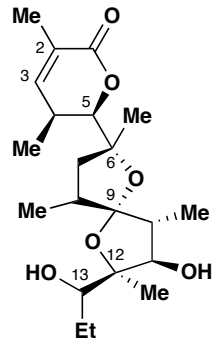
erythromycin F (*J. Antibiot.* 1982, *35*, 426)



erythromycin G (*J. Antibiot.* 2003, *56*, 280)

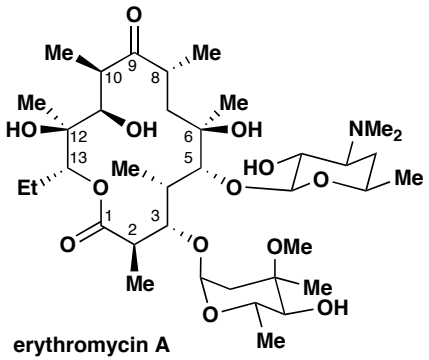


erythronolide H (*Org. Lett.* 2009, *11*, 1353)



erythronolide I (*Org. Lett.* 2009, *11*, 1353)

Erythronolide and Erythromycin



erythromycin A

Preparation of erythromycin

An inoculum broth is prepared having the following composition:

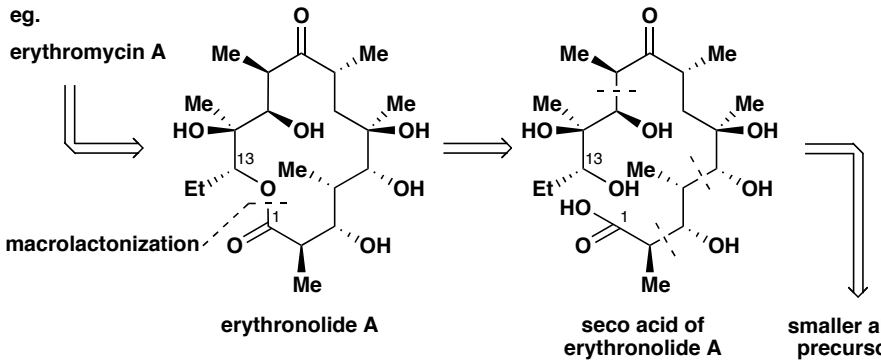
Starch	lbs.	32
Soybean meal	lbs.	32
Corn steep solids	lbs.	10
Sodium chloride	lbs.	10
Calcium carbonate	lbs.	6
Water	gals.	250

The broth is placed in an iron tank of 350 gallon capacity and is sterilized by heating it under pressure at a temperature of about 120° C. for 30 minutes. The sterilized broth is cooled and inoculated aseptically with spores of *Streptomyces erythreus*, NRRL 2338. The organism is grown in the broth at about 26° C. for a period of 45 hours. During the growth period the broth is stirred and aerated with sterile air in the amount of about 0.5 volume of air per volume of culture broth per minute. **[...]**

erythromycin A:

- **Currently used as an antiobiotic agent; especially useful for patients with penicillin allergies.**
- **Isolation first reported in U.S. Patent 2,653,899 by R. L. Bunch and J. M. McGuire (Eli Lilly), filed in 1952 and approved in 1953; originally called "erythromycin".**
- **Quotes from the 1953 patent: "[...] the empirical formula of erythromycin [is] $C_{38\text{-}9}H_{69\text{-}71}NO_{13}$." "We claim: 1. A method of producing an antibiotic agent which comprises cultivating under aerobic conditions an erythromycin-producing strain of *Streptomyces erythreus* in a culture medium containing assimilable sources of carbohydrate, nitrogen and inorganic salts until substantial antibiotic activity is produced by said organism in said culture medium. [...]"**
- **Structure first reported in 1957 without stereochemical assignments; X-ray analysis established the absolute configuration at each stereocenter in 1965.**
- **Quote from R. B. Woodward: "Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers." (In *Perspectives in Organic Chemistry*, Todd, A., Ed., Interscience Publishers: New York 1956, p.155.)**
- **Quote from J. Mulzer's review entitled "Erythromycin Synthesis - A Never-Ending Story?": "The synthesis of [...] erythromycin A and B [...] is probably the most extensive single project in the history of synthetic organic chemistry. This phenomenon is not rational as [they] are accessible in large quantities from fermentation [...]. It is the complexity of the molecule's structure, the plethora of stereocenters and functional groups and the magic of the medium ring that has fascinated about 15 large research groups worldwide for more than a decade." (*Angew. Chem. Int. Ed.* 1991, *30*, 1452-1454)**
- **Cost of erythromycin A is 2.80 $/g, so just buy it for medchem/chembio purposes...**
- **This molecule caught the attention of...**
  - **"Giants": Woodward, Stork, Corey, Danishefsky;**
  - **"Aldol Giants": Masamune, Evans, Paterson;**
  - **"European Giants": R. W. Hoffmann, Mulzer, and recently Carreira.**

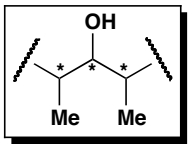
Our modern "retrosynthetic reflex" effectuates the following disconnections:



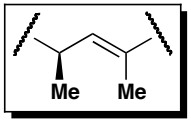
Commonly used macrolactonization methods:

1. **Corey-Nicolaou macrolactonization (PyS-SPy + PPh_3 on the hydroxyacid, then heat; *J. Am. Chem. Soc.* 1974, *96*, 5614);**
2. **Masamune thiol ester activation (TIS^tBu on the acyl chloride to generate a thioester, then $Hg(OCOCF_3)_2$ or CuOTf to lactonize; *J. Am. Chem. Soc.* 1975, *97*, 3515);**
3. **Mukaiyama onium salt method (*N*-methyl-2-chloropyridinium iodide and Et_3N on the hydroxyacid; *Chem. Lett.* 1976, 49);**
4. **Mitsunobu alcohol activation (DEAD + PPh_3 on the hydroxyacid; *Tetrahedron Lett.* 1976, *17*, 2455);**
5. **Yamaguchi mixed anhydride lactonization (2,4,6-trichlorobenzoyl chloride + DMAP on the hydroxyacid; *Bull. Chem. Soc. Jpn* 1979, *52*, 1989);**
6. **Keck-Steglich activation (DCC + DMAP + DMAP•HCl on the hydroxyacid; *Angew. Chem. Int. Ed.* 1978, *17*, 522 and *J. Org. Chem.* 1985, *50*, 2394);**
7. **Shiina benzoic anhydride lactonization (various benzoic anhydrides + Lewis acid or base; *Nature Protocols*, 2007, *2*, 2312).**

Examples of asymmetric control in the synthesis of stereotriads found in polyketides (for an excellent review on this topic, see: R. W. Hoffmann, *Angew. Chem. Int. Ed.* 1987, *26*, 489-503):



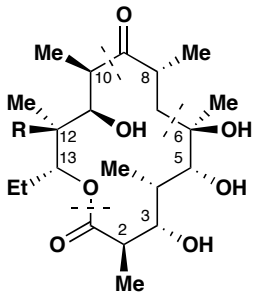
1. **Propionate enolate additions onto α-methylaldehydes (i.e. aldol);**
2. **Propionate enolate additions onto α-methylesters, followed by carbonyl reduction;**
3. **Acetate enolate additions onto α-methylaldehydes followed by α-methylation;**
4. **Propenyl or butenyl group additions onto α-methylaldehydes, followed by hydrogenation or hydroboration;**
5. **Danishefsky's diene (methylated version) Diels-Alder onto α-methylaldehydes followed by hydrolysis and ozonolysis;**
6. **Crotyl-metal and pentenyl-metal additions onto α-methylaldehydes followed by ozonolysis;**
7. **Epoxidation of an allylic alcohol bearing a methyl group at the allylic position, followed by methylcuprate addition;**
8. **Hydroboration-oxidation or hydrosilylation-oxidation of the alkene motif shown on the right.**



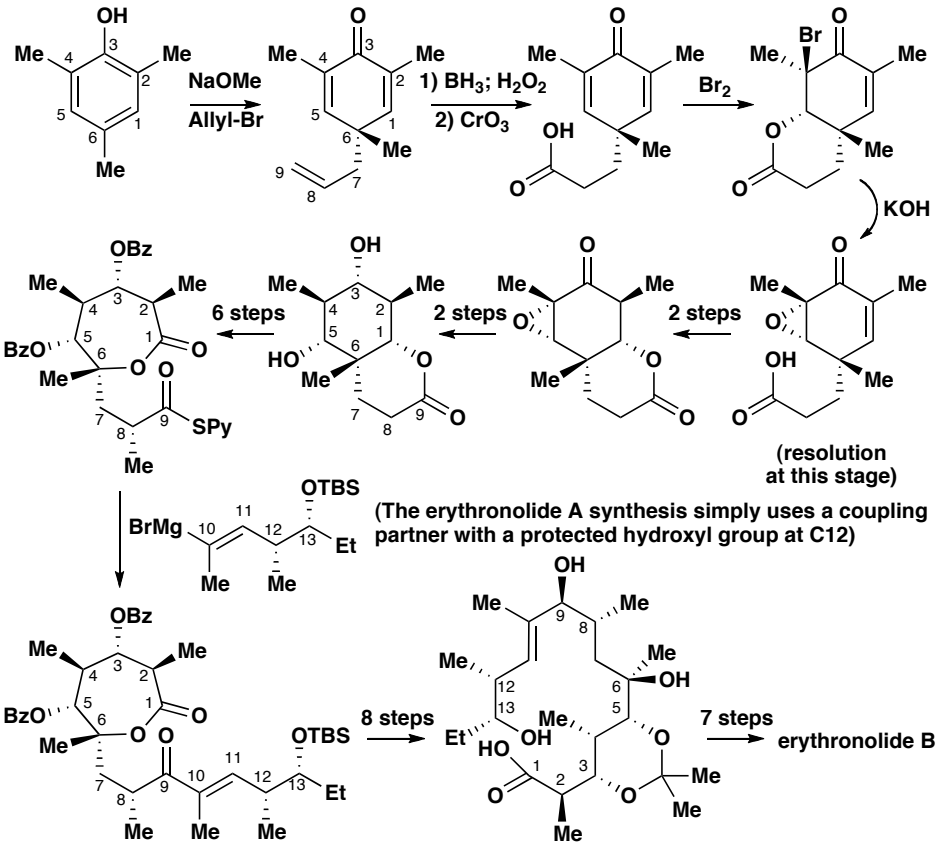
Erythronolide and Erythromycin

E. J. Corey (Harvard; 1978, 1979):

- First total syntheses of erythronolide B (*JACS* 1978, *100*, 4618 and 4620) and erythronolide A (*JACS* 1979, *101*, 7131), synthesized in (longest linear) 31 steps (ca. 0.8% overall, yields of the last epimerization-deprotection steps are not reported).
- 11 students worked on it, including K. C. Nicolaou.
- 50% yield for the macrolactonization, effectuated with a modified Corey-Nicolaou procedure (substituted imidazoles instead of pyridines).
- Key features: Cyclic stereocontrol (i.e. not a single aldol!); convergency amenable to the synthesis of both erythronolides A and B.
- Hard to retrosynthetically disconnect!
- "Classics-worthy" synthesis!

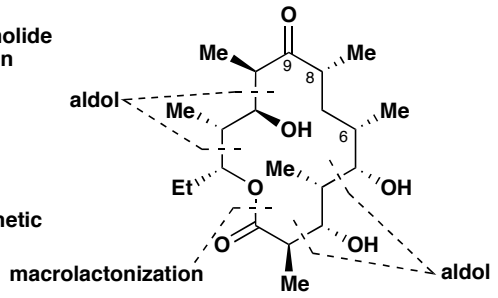


erythronolide A (R=OH)
erythronolide B (R=H)

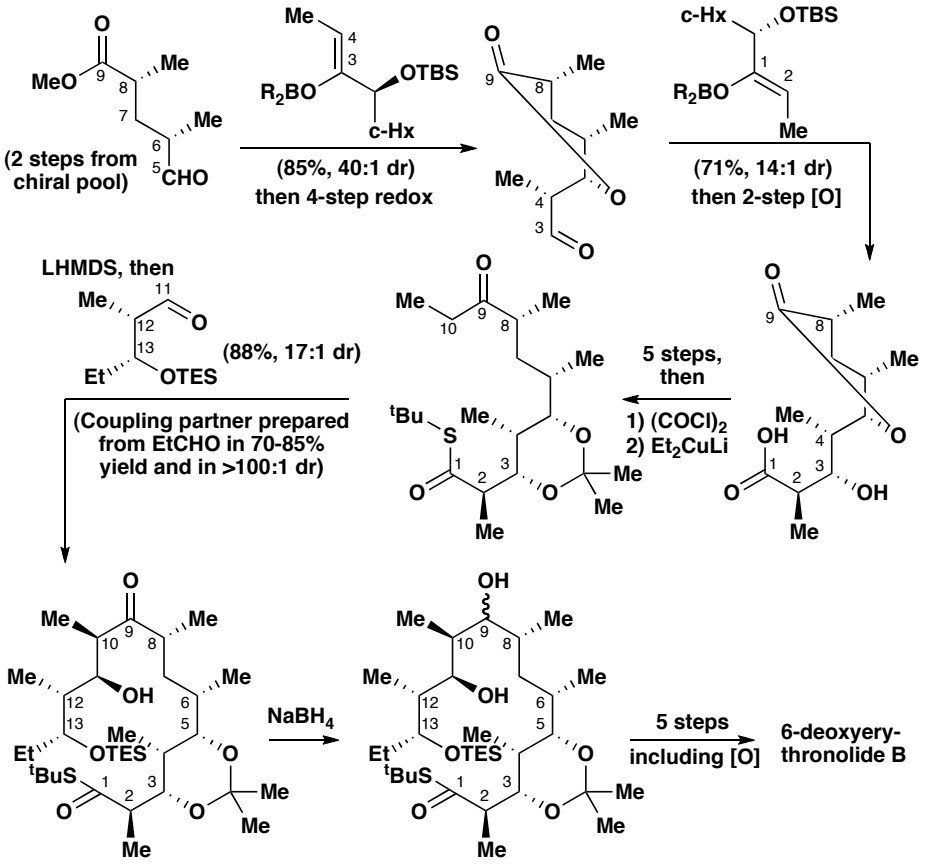


S. Masamune (MIT; 1981):

- First total synthesis of 6-deoxyerythronolide B (*JACS* 1981, *103*, 1568), synthesized in (longest linear) 22 steps (<7 % overall; missing yields for the last few steps).
- 4 students worked on it.
- 41 % yield for the macrolactonization, effectuated with Masamune's own *t*-butylthioester method, using CuOTf.
- Key feature: Aldol, aldol, aldol... a synthetic mimic of a polyketide synthase.
- Textbook-style retrosynthesis!
- Excellent demonstration of his own methodology.



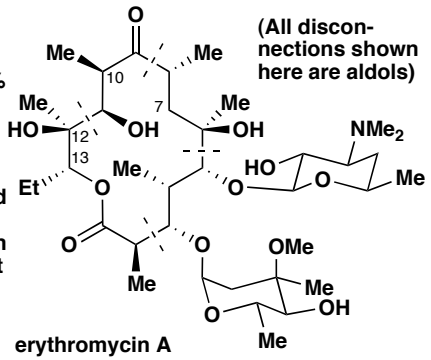
6-deoxyerythronolide B

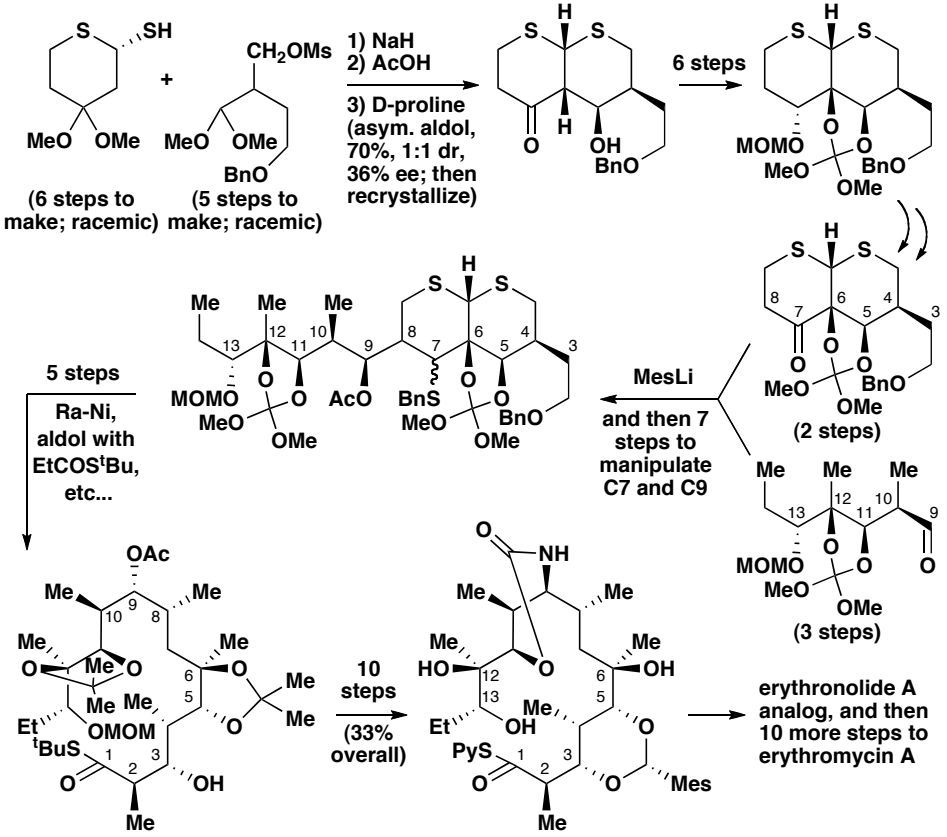


Erythronolide and Erythromycin

R. B. Woodward (Harvard; posthumous, 1981):

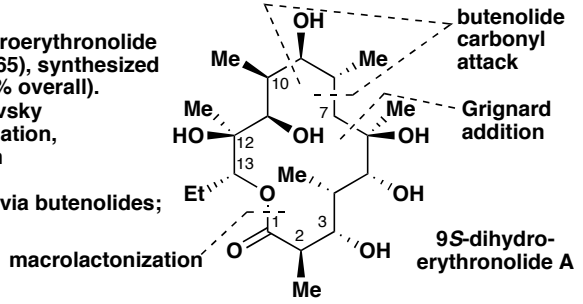
- First and only total synthesis of erythromycin A (*JACS* 1981, *103*, 3210, 3213 and 3215), synthesized in (longest linear) 52 steps (0.0089% overall, of which the last 10 steps, required for the glycosidations, yielded 1.54%).
- 48 students worked on it, including R. M. Williams.
- 70% yield for the macrolactonization, effectuated with a Corey-Nicolaou macrolactonization.
- Key features: Aldols using asymmetric induction via dithiadecalins; interestingly convergent; first detailed study on the structural requirements of the erythronolide seco acid macrolactonization.
- The end of the "Woodwardian era"...



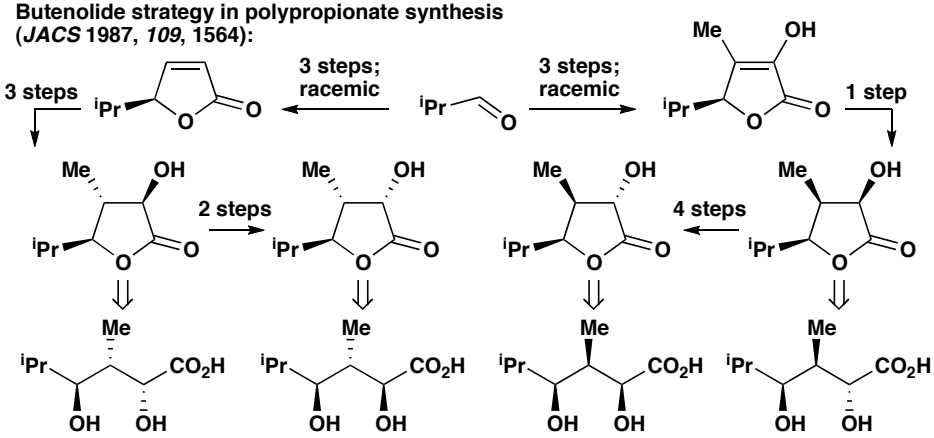


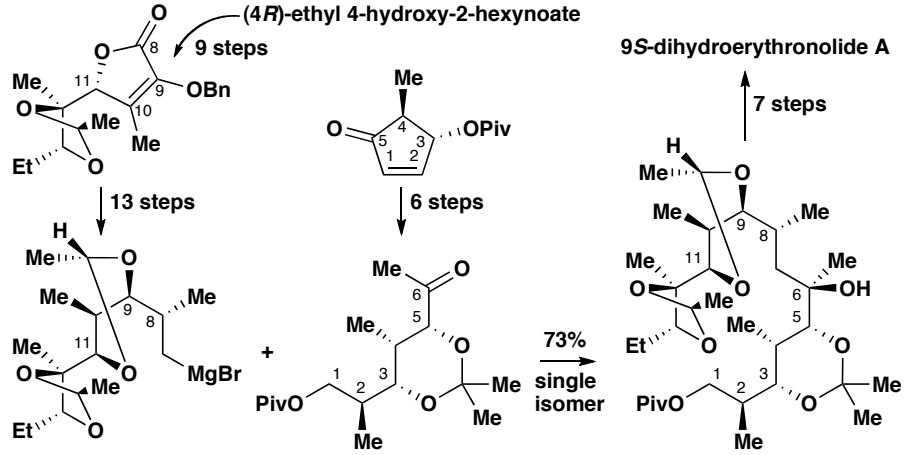
G. Stork (Columbia; 1987):

- First total synthesis of 9*S*-dihydroerythronolide A (*JACS* 1987, *109*, 1564 and 1565), synthesized in (longest linear) 30 steps (1.3 % overall).
- Only one student: S. D. Rychnovsky
- 64 % yield for the macrolactonization, effectuated with a Keck-Steglich macrolactonization.
- Key features: Aldols performed via butenolides; convergent synthesis.



Butenolide strategy in polypropionate synthesis (*JACS* 1987, *109*, 1564):

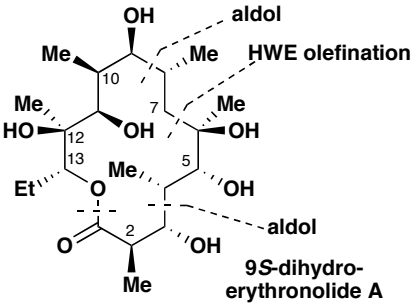


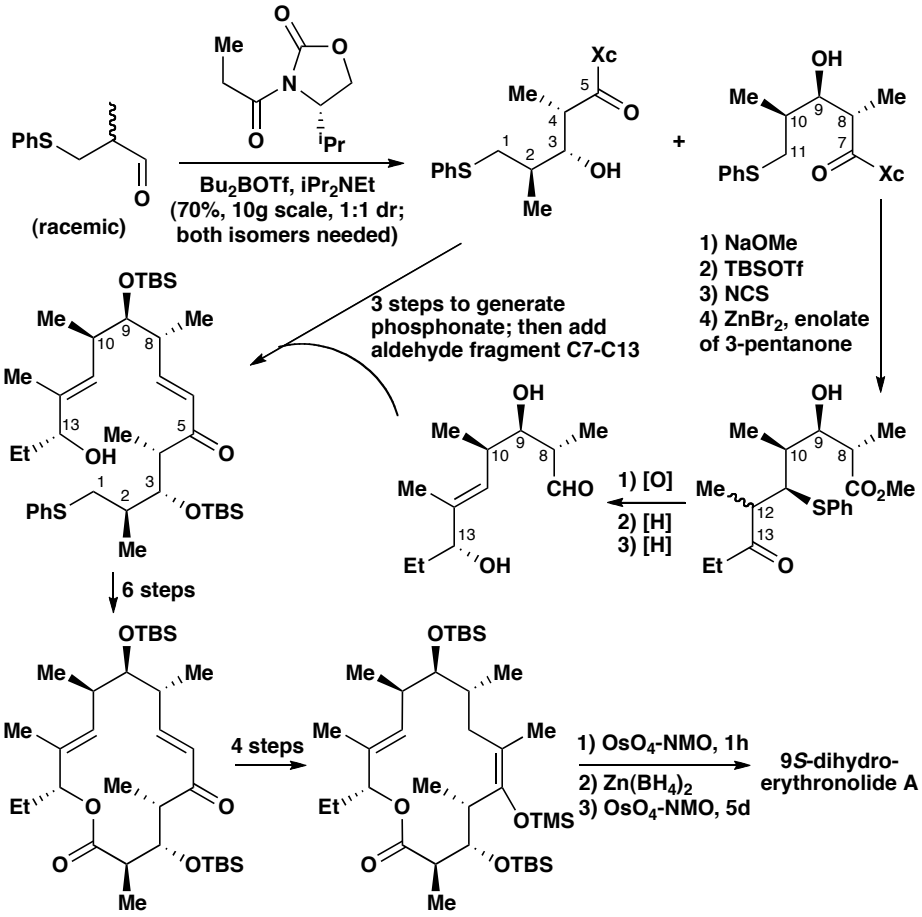


Erythronolide and Erythromycin

I. Paterson (Cambridge; 1988):

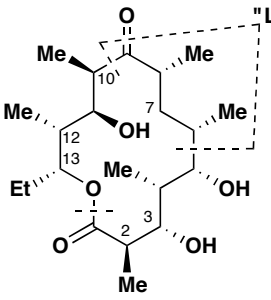
- Total synthesis of 9*S*-dihydroerythronolide A (*TL* 1988, *29*, 1461 and 1989, *30*, 7463), synthesized in (longest linear) 22 steps (3.4% overall).
- 2 students worked on it.
- 91-96% yield for the macrolactonization, effectuated with a Yamaguchi macrolactonization.
- Key features: Excellent use of "modern" (Evans herein) aldol technology; convergent; macrolactonization performed on a conformationally favorable system bearing two olefins, precluding the use of acetonides.

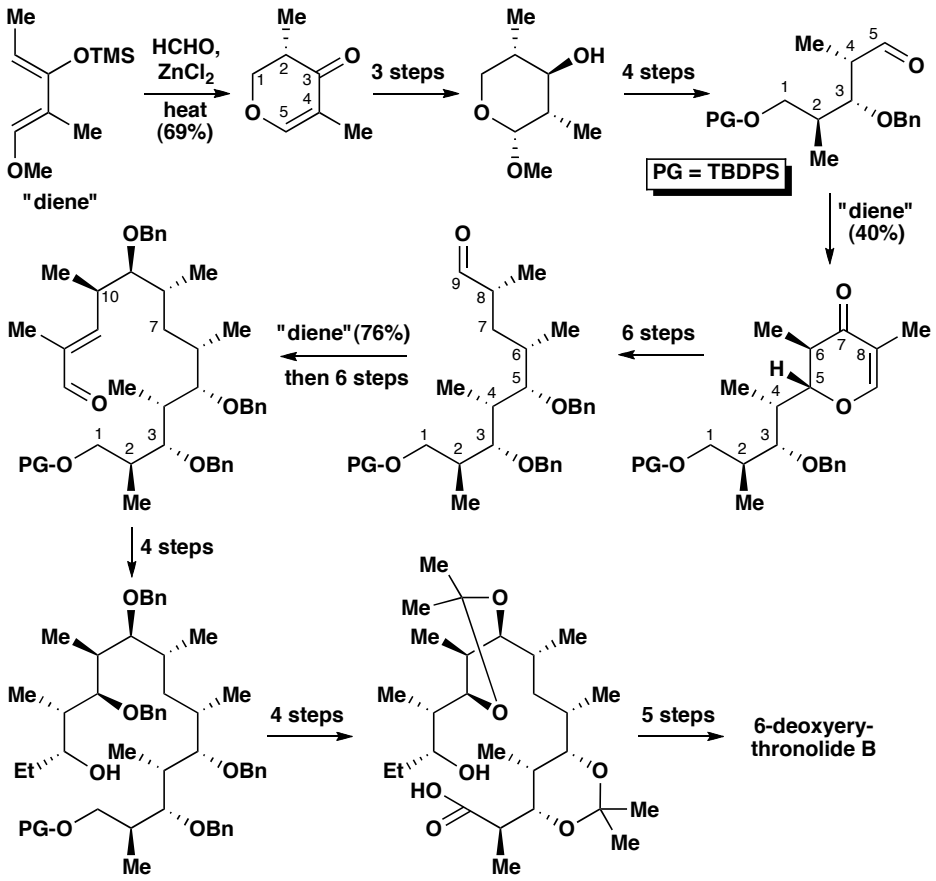




S. J. Danishefsky (Yale; 1990):

- Relay synthesis of 6-deoxyerythronolide B (*JOC* 1990, *55*, 1636), synthesized in (longest linear) 35 steps (ca. 0.014 % overall, yields of the last two steps are not reported). A total synthesis from the procedures described herein would result in racemic 6-deoxyerythronolide B.
- Only one student worked on it.
- 17 % yield for the macrolactonization, effectuated with a Yamaguchi macrolactonization.
- Key feature: "Formal double aldol" using a Lewis-acid catalyzed diene aldehyde condensation (LACDAC) strategy.
- Great application of his own methodology.

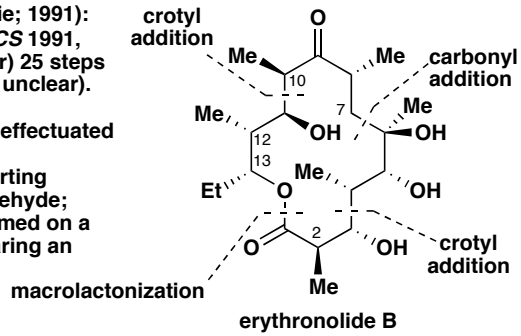




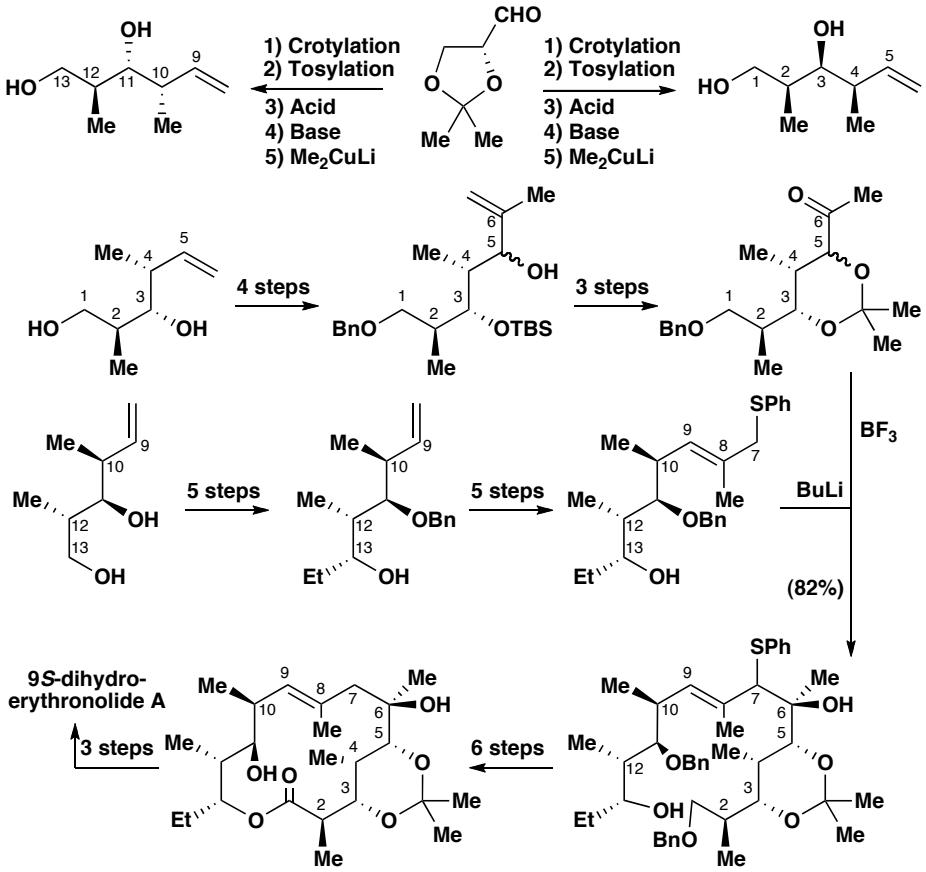
Erythronolide and Erythromycin

J. Mulzer (Institut für Organische Chemie; 1991):

- **Total synthesis of erythronolide B (*JACS* 1991, *113*, 910), synthesized in (longest linear) 25 steps (<2.4% overall, yields of first few steps unclear).**
- **4 students worked on it.**
- **>85% yield for the macrolactonization, effectuated with a Yamaguchi macrolactonization.**
- **Key features: Great use of a simple starting material from the chiral pool, glyceraldehyde; convergent; macrolactonization performed on a conformationally favorable system bearing an olefin.**

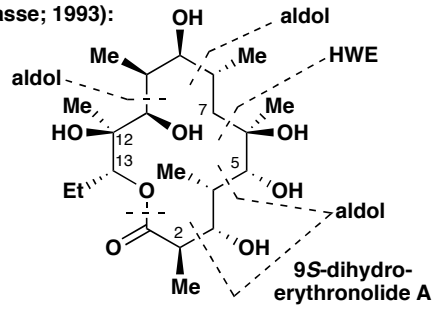


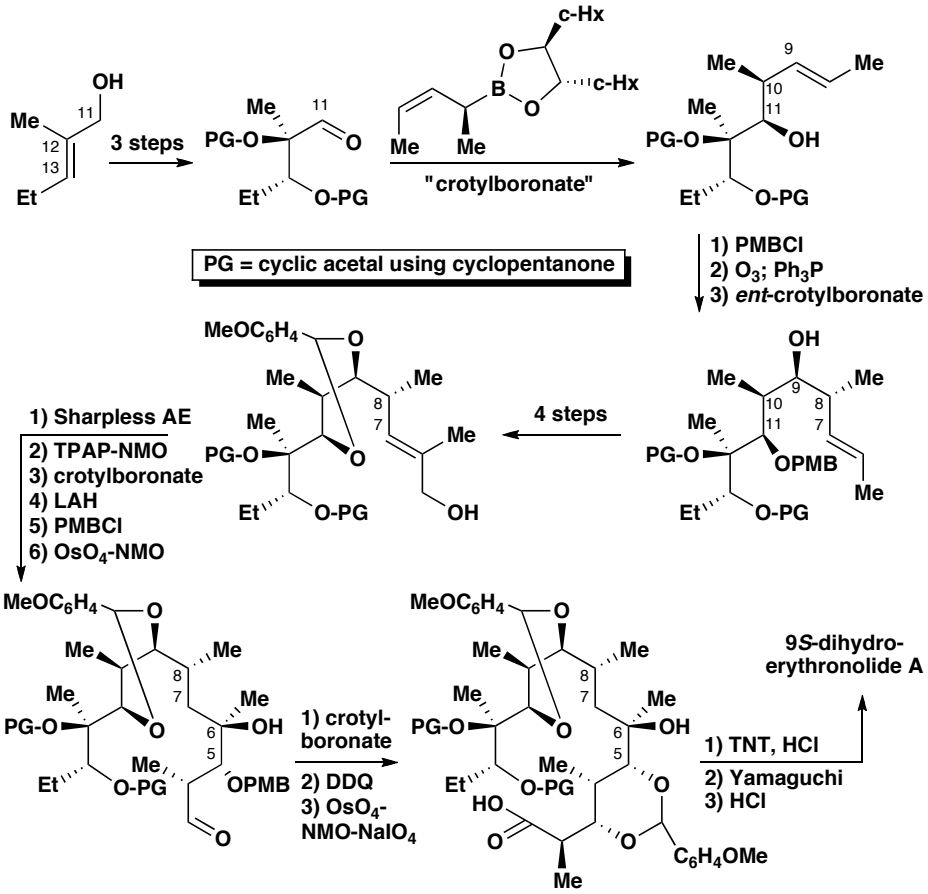
erythronolide B



R. W. Hoffmann (Universität Hans-Meerwein-Strasse; 1993):

- **Total synthesis of 9*S*-dihydroerythronolide A (*ACIEE* 1993, *32*, 101), synthesized in a total of 23 steps (6.6% overall).**
- **2 students worked on it.**
- **>77% yield for the macrolactonization, effectuated with a Yamaguchi macrolactonization.**
- **Key feature: Completely linear synthesis, but this synthesis is one of the shortest in total number of steps.**
- **Excellent application of his own crotylation methodology.**

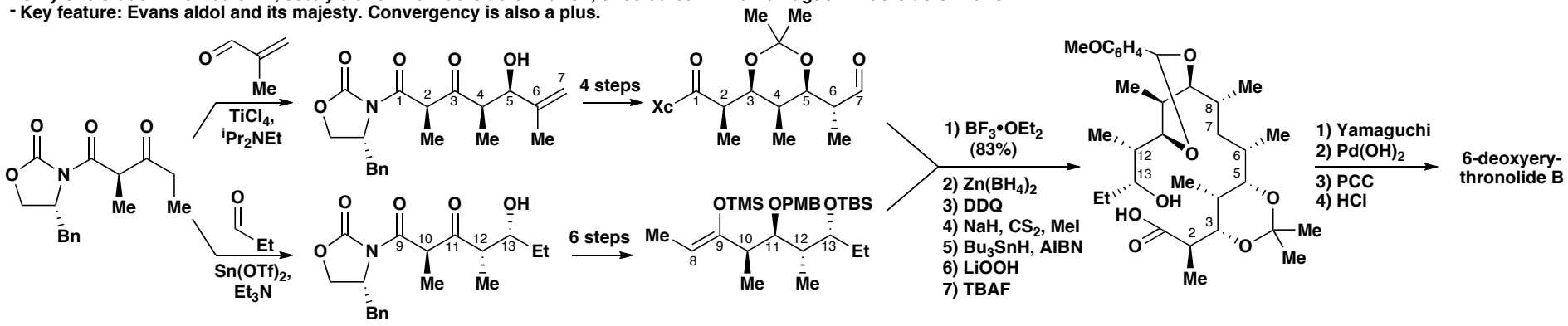




Erythronolide and Erythromycin

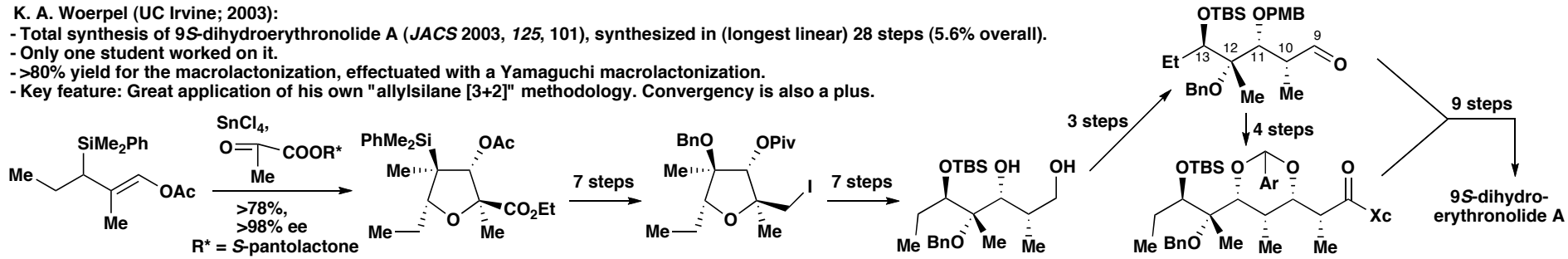
D. A. Evans (Harvard; 1997):

- **Total synthesis of 6-deoxyerythronolide B (*TL* 1997, *38*, 53), synthesized in (longest linear) 18 steps from β-ketoimide, add 2 steps to make the SM (4.3% overall).**
- **Only one student worked on it; 86% yield for the macrolactonization, effectuated with a Yamaguchi macrolactonization.**
- **Key feature: Evans aldol and its majesty. Convergency is also a plus.**



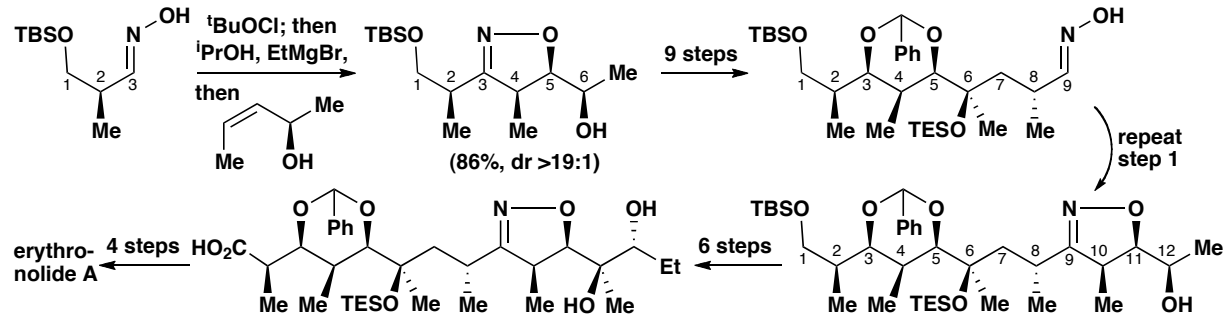
K. A. Woerpel (UC Irvine; 2003):

- **Total synthesis of 9*S*-dihydroerythronolide A (*JACS* 2003, *125*, 101), synthesized in (longest linear) 28 steps (5.6% overall).**
- **Only one student worked on it.**
- **>80% yield for the macrolactonization, effectuated with a Yamaguchi macrolactonization.**
- **Key feature: Great application of his own "allylsilane [3+2]" methodology. Convergency is also a plus.**



E. M. Carreira (ETH Zürich; 2005):

- **Total synthesis of erythronolide A (*ACIEE* 2005, *44*, 4036), synthesized with the best total thus far of 21 steps (1.5%).**
- **2 students worked on it; 78% yield for the macrolactonization, effectuated with a Yamaguchi macrolactonization.**
- **Key feature: Great application of his own "Mg-mediated nitrile oxide [3+2]" methodology for polyketide synthesis.**



Macrolactonization: 1) Since 1990, all syntheses utilized the Yamaguchi macrolactonization method; 2) A 6-membered cyclic acetal over the hydroxyl groups at C3 and C5 are necessary to induce (in part) the correct conformation for the lactonization, unless there are olefins within the seco acid that rigidify the conformation; 3) Woodward has contributed greatly toward examining different conformations of the macrolactonization step.

Asymmetric stereocontrol: Development of aldol, dithiadecalin, butenolide, "LACDAC", crotylations and other methods such as [3+2] strategies, many of which were developed for the sake of conquering the erythronolide/erythromycin family.

Other notable formal or total syntheses: Deslongchamps (*CanJChem*, 1985, *63*, 2818), Kinoshita (*TL* 1986, *27*, 1815), Kochetkov (*TL* 1987, *28*, 3835 and 3839), Nakata (*BCSJ* 1989, *62*, 2618), Chamberlin (*JACS* 1989, *111*, 6247), Martin (*JACS* 1989, *111*, 7634), Yonemitsu (*JOC* 1990, *55*, 7), Vogel (*HCA* 2002, *85*, 417), Crimmins (*OL* 2006, *8*, 2191), Martin (*Tet* 2007, *63*, 5709), and, as a note added after this presentation, White (*NatChem* 2009 AOP, DOI: 10.1038/NCHEM.351).