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

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Pd(OAc)_2_ 30 mol% 2 eq. BQ 56%, >40:1 d.r. (2 recycles)

6-dEB

Chelate

erythromycin A
wide spectrum macrolide antibiotic

Karla Bravo
_Current Literature, 09/12/2009_
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

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

![Diagram of bacterial cell and erythromycin binding pocket](image)

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

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

- **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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Previous synthetic studies of erythromycin


- 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.


- 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


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

- low yielding macrolactonization.

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.

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


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

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

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

**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.

\(\begin{align*}
\text{O}_2\text{S} & \quad \text{Pd}(\text{OAc})_2 \quad \text{Ph}(\text{OAc})_2 \\
\text{BQ} & \quad (2\text{ equiv.}, \text{air, CH}_2\text{Cl}_2, \ \text{45}\degree \text{C}, \ C = 10\text{ mM})
\end{align*}\)

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

(b). \(\sigma\)-Substituted salicylates: e\text{-} density, steric hindrance

Serial ligand catalysis mechanism via templated 1

Evidence for templated \(\pi\)-allylPd carboxylate intermediate

**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

Title paper: Synthesis of macrolactonization precursor 2

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

![Chemical structures and reactions](image)

**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., (44% + 36% r.s.m., recycled twice); c, 3 (0.1 equiv.), BQ (2.0 equiv.), p-NO$_2$BzOH (1.5 equiv.), 45 °C, 72 h, 1:1 d.r., 73% (combined); d, LiOOH$_{aq}$ (2.0 equiv.); e, K$_2$CO$_3$, MeOH, 97% (two steps); f, Cl$_3$C$_6$H$_2$COCl (15.0 equiv.), $^{1}$Pr$_2$NET (20.0 equiv.), DMAP (40.0 equiv.), benzene, 87%. BQ = 1,4-benzoquinone, DMAP = N,N-4-dimethylaminopyridine, p-NO$_2$BzOH = p-nitrobenzoic acid.
Deuteration Studies

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

\[
\text{Ph-S-S-Ph} \quad \text{Pd(OAc)}_2 \\
10 \text{ mol}\% \\
2 \text{ eq. BQ} \\
56\% (1:1, E/Z) \\
(+ 0.15 \text{ eq. TBAF})
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Completion of the Synthesis of 6-dEB & Conclusions


- 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.