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# Total Synthesis of 6-Deoxyerythronolide B *via* C-C Bond-Forming Transfer Hydrogenation

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## Abstract

The 14-membered macrolide 6-deoxyerythronolide B is prepared in 14 steps (longest linear sequence) and 20 total steps. Two different methods for alcohol CH-crotylation *via* transfer hydrogenation are deployed for the first time in target-oriented synthesis. Enyne metathesis is used to form the 14-membered ring. The present approach represents the most concise construction of any erythronolide reported, to date.

In 1952, the pharmaceutical company Eli Lily commercialized the first macrolide antibiotic, erythromycin A.[1] Beyond its impact on human medicine, the challenges in chemical synthesis posed by erythromycin A and related polyketides propelled advances in acyclic stereocontrol *via* carbonyl addition, especially aldol bond constructions[2d] and crotylation methods.[3] Perhaps fueled further by Woodward's dim assessment of the prospect of accessing erythromycin A through chemical synthesis,[4] the erythromycins have become inextricably tied to the evolution of synthetic organic chemistry and their total syntheses are widely regarded as benchmarks for the state-of-the-art.[9f] As illustrated in total syntheses of erythromycin A[5] and B[6], erythronolide A[7] and B[8], (*9S*)-dihydroerythronolide A[9] and their biogenic precursor 6-deoxyerythronolide B,[10] tremendous strides have been made over the past 30 years. However, all reported syntheses remain well over 20 steps in length, suggesting the influence of the erythromycins on chemical synthesis will persist into the future (Figure 1).

In the course of exploring C-C bond forming hydrogenations and transfer hydrogenations beyond hydroformylation,[11] our laboratory developed a suite of methods for stereoselective polyketide construction, including methods for carbonyl crotylation *via* redox triggered C-C coupling of primary alcohols and α-methyl allyl acetate **5** or butadiene using iridium[12] and ruthenium[13] catalysts, respectively. These studies evoked an exceptionally powerful transformation that has no counterpart in conventional allylmetal chemistry:[3] the *anti*-diastereo- and enantioselective iridium catalyzed *double crotylation* of 2-methyl-1,3-propanediol **6** to form polypropionate stereoquintets.[12c] To benchmark the utility of this method *vis-à-vis* polyketide construction, it was applied to the preparation of 6-deoxyerythronolide B. This undertaking has resulted in the most concise route to any erythronolide reported, to date.[2,5–10]

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge *via* the internet at http://pubs.acs.org.

Retrosynthetically, a convergent assembly of 6-deoxyerythronolide B from Fragments **A** and **B** was envisioned through esterification followed by ring-closing enyne metathesis to form the 14-membered macrolide.[14] Fragment **A** is prepared in 6 steps from *n*-propanol **1** through successive introduction of propionate subunits *via* ruthenium catalyzed butadiene mediated *syn*-crotylation[13d] followed by substrate directed *syn*-aldol addition[15] to form thiol ester **3**, which incorporates the 4 contiguous stereogenic centers spanning C10-C13. Fragment **B**, which incorporates the 5-contiguous stereogenic centers spanning C2-C6, is prepared in 8 steps from 2-methyl-1,3-propane diol **6** *via* iridium catalyzed double crotylation followed by iodoetherification and alkene oxidative cleavage to form the carboxylic acid (Scheme 1).[12c]

The synthesis of Fragment **A** begins with the butadiene mediated hydrohydroxyalkylation of *n*-propanol **1** to form the product of *syn*-crotylation (Scheme 2).[13d] As the resulting secondary alcohol is quite volatile, reagents promoting formation of the TBS ether **2** were added to the reaction mixture after the C-C coupling was complete, enabling direct acquisition of TBS ether **2** from *n*-propanol in 59% isolated yield with 5:1 *syn*-diastereoselectivity and 98% enantiomeric excess.[13d,16] Oxidative cleavage of the terminal olefin followed by treatment of the resulting aldehyde with the (*E*)-boron enolate derived from *S*-phenyl propanethioate delivered the product of *syn*-aldol addition **3** with only trace quantities of the *anti*-diastereomer detected by $^1$H NMR analysis.[15] The thiol ester **3** was converted to the β-hydroxy aldehyde,[17] which was exposed to the Ohira-Bestmann reagent to form the homopropargyl alcohol **4** without protection of the hydroxyl moiety.[18b] Finally, benzylation of homopropargyl alcohol **4** accompanied by acidic hydrolysis of the TBS ether in the course of isolation provides Fragment **A**. An even more concise route to Fragment **A** potentially involves 1,3-enyne hydrohydroxyalkylation to form the C10-C11 bond with concomitant installation of the alkyne, however, this chemistry has not yet been adapted to the use of chiral β-stereogenic alcohols (Scheme 2).[19]

The synthesis of Fragment **B** begins with the *anti*-diastereo- and enantioselective iridium catalyzed double crotylation of 2-methyl-1,3-propanediol **6** to furnish the *pseudo*-$C_2$-symmetric diol **7** (Scheme 3).[12c] The diol **7** is produced as a single enantiomer as determined by HPLC, as the minor enantiomer of the mono-adduct is converted to the *pseudo-meso*-diastereomer.[20] Iodoetherification of **7**, which differentiates the alkene termini and diol moieties and defines the nonstereogenic chirotopic center at C4, followed by benzylation delivers pyran **8**. Osmium catalyzed oxidative cleavage of the olefin to form the carboxylic acid[21] followed by zinc mediated reductive cleavage of the iodoether provides the β-hydroxy acid **9**, which is prone to epimerization. To convert the β-hydroxy acid **9** to Fragment **B**, an inversion in stereochemistry at C3 is required. To this end, conversion of **9** to the β-lactone **10** was attempted under Mitsunobu conditions, however, decarboxylative Grob type elimination to the *cis*-alkene was formed in over 70% yield.[22] Treatment of the dianion of **9** with methanesulfonyl chloride[23] delivered the β-lactone **10** in 15–20% yield along with recovered β-hydroxy acid **9**, suggesting a more electrophilic sulfonylchloride was required. Indeed, use of chloromethanesulfonyl chloride led to the formation of β-lactone **10** in 72% yield. It was our hope to directly exploit β-lactone **10** in the acylation of Fragment **A**. However, although related β-lactone ring openings are known,[24a] as we learned, *cis*-disubstituted β-lactones are recalcitrant acylating agents,[24b] and so β-lactone **10** was converted to the carboxylic acid Fragment **B** (Scheme 3).

The convergent assembly of Fragments **A** and **B** is achieved through esterification under Yamaguchi's conditions to form the tethered enyne **11** (Scheme 4).[25] Initial attempts at ring-closing enyne metathesis[14] in the absence of ethylene led to isomerization of the terminal olefin. Under an atmosphere of ethylene at 80 °C the terminal alkyne is converted to the conjugated diene in nearly quantitative yield, but macrocyclization is not observed. Hence, upon complete conversion to the conjugated diene at 80 °C, the reaction vessel was purged

with nitrogen and the reaction temperature was increased to 110 °C, which induced formation of the 14-membered macrolide **12** as a single regioisomer in a remarkable 89% yield. Osmium catalyzed oxidative cleavage of the C9 methylidene residue provides the conjugated enone **13**.[21] Reductive methylation of enone **13** to form ketone **14** under the conditions of dissolving metal reduction[26a,b] or through the agency of arene anion radicals[26c,d] was explored. Although efficient reductive alkylation was achieved in a model system (4,4-dimethylcyclohexenone), enone **13** underwent benzyl cleavage or decomposed upon exposure to dissolving metal conditions, and upon treatment with arene anion radicals enone **13** was converted to the product of enone 1,2-reduction. Consequently, the conversion of enone **13** to ketone **14** was accomplished by nickel catalyzed conjugate reduction[27] followed by conventional enolate methylation. Interestingly, highly variable levels of diastereoselectivity were associated with the newly formed C8-stereocenter of ketone **14**, suggesting facile epimerization at this position. Indeed, irrespective of the diastereomeric ratio at C8, exposure of ketone **14** to the slightly acidic conditions of palladium catalyzed homogenous hydrogen provides 6- deoxyerythronlide B in 93% isolated yield as a single diastereomer. Thus, 6-deoxyerythronlide B is prepared in 14 steps (longest linear sequence) and 20 total steps, representing the most concise route to any erythromycin family member reported, to date.

New reactivity is the principal basis for new functional group interconversions and, hence, new strategies that can shift the retrosynthetic paradigm, ultimately simplifying longstanding challenges in chemical synthesis. As illustrated in the present total synthesis of 6-deoxyerythronolide B and recent total syntheses of the macrolides roxaticin[28a] and bryostatin 7,[28b] alcohol C-H functionalization *via* transfer hydrogenation augments synthetic efficiency by opening novel routes to polyketide natural products that bypass stoichiometric use of chiral auxiliaries, premetallated *C*-nucleophiles and discrete alcohol-to-aldehyde redox reactions. As organic molecules are defined as compounds composed of carbon and hydrogen, the reactivity embodied by such processes where C-C bond cleavage is accompanied by hydrogen redistribution evokes numerous possibilities in terms of related transformations, including imine addition from the amine oxidation and the direct C-C coupling of alcohols to α-olefins. These and other topics are currently under investigation in our laboratory.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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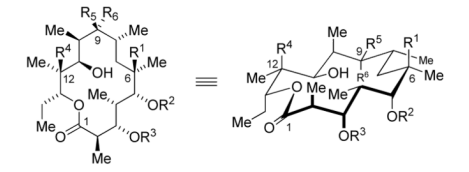


**Erythromycin A**, $R^1$ = OH, $R^2$ = β-D-desosamine, $R^3$ = α-D-cladinose, $R^4$ = OH, $R^5$ = $R^6$ = O
Woodward 1981, 55 Steps (LLS), 77 Steps (TS), ref. 5a

**Erythromycin B**, $R^1$ = OH, $R^2$ = β-D-desosamine, $R^3$ = α-D-cladinose, $R^4$ = H, $R^5$ = $R^6$ = O
Martin 1997, 28 Steps (LLS), 33 Steps (TS), ref. 6

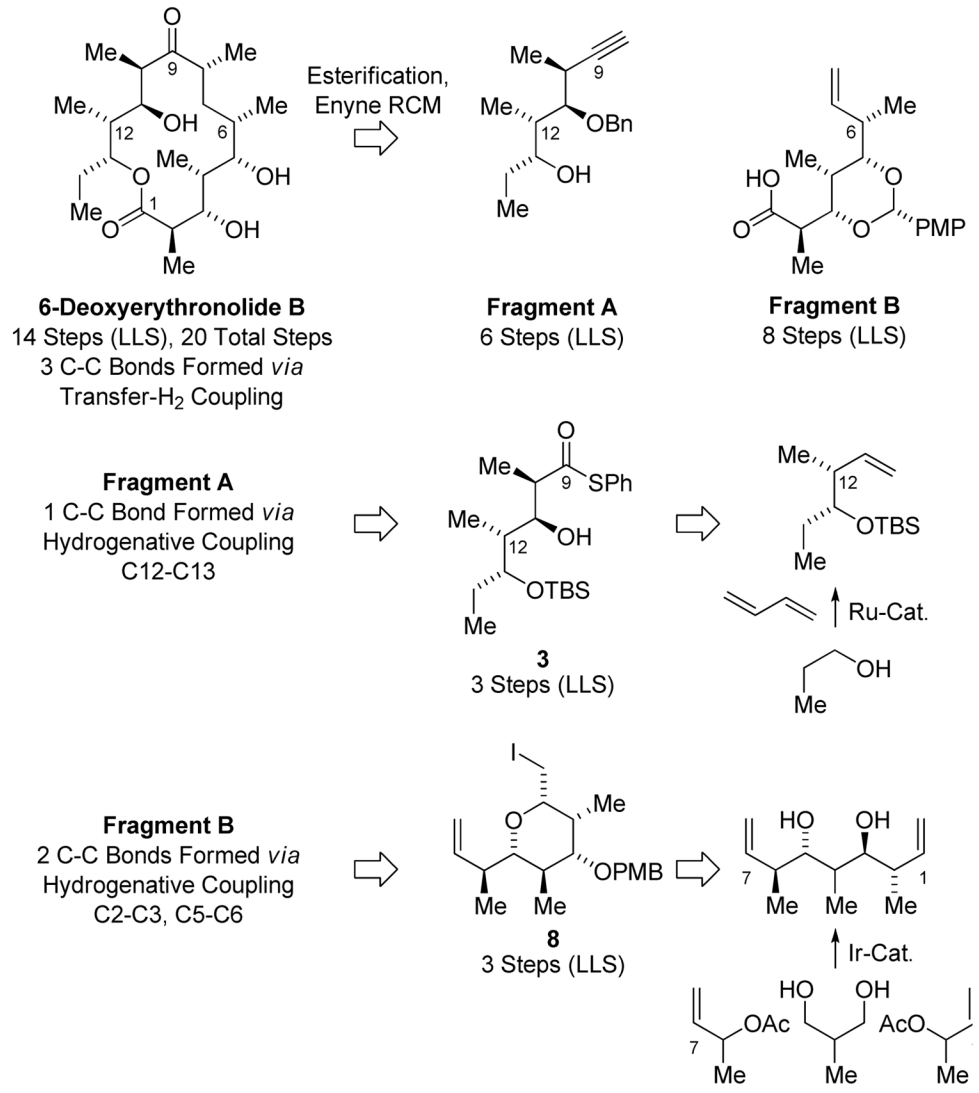
**Erythronolide A**, $R^1$ = OH, $R^2$ = OH, $R^3$ = OH, $R^4$ = OH, $R^5$ = $R^6$ = O
Corey 1979, 39 Steps (LLS), 50 Steps (TS), ref. 7a
Kinoshita 1989, 50 Steps (LLS), 74 Steps (TS), ref. 7b
Carreira 2005, 26 Steps (LLS), 36 Steps (TS), ref. 7c,d

**Erythronolide B**, $R^1$ = OH, $R^2$ = OH, $R^3$ = OH, $R^4$ = H, $R^5$ = $R^6$ = O
Corey 1978, 33 Steps (LLS), 47 Steps (TS), ref. 8a
Kochetkov 1987, 36 Steps (LLS), 51 Steps (TS), ref. 8b
Mulzer 1991, 27 Steps (LLS), 41 Steps (TS), ref. 8c

**(*9S*)-Dihydroerythronolide A**, $R^1$ = OH, $R^2$ = OH, $R^3$ = OH, $R^4$ = OH $R^5$ = OH, $R^6$ = H
Stork 1987, 33 Steps (LLS), 46 Steps (TS), ref. 9a,b
Yonemitsu 1987, 39 Steps (LLS), 63 Steps (TS), ref. 9c,d
Paterson 1989, 23 Steps (LLS), 31 Steps (TS), ref. 9e
Hoffmann 1993, 27 Steps (LLS), 31 Steps (TS), ref. 9f
Woerpel 2003, 30 Steps (LLS), 31 Steps (TS), ref. 9g

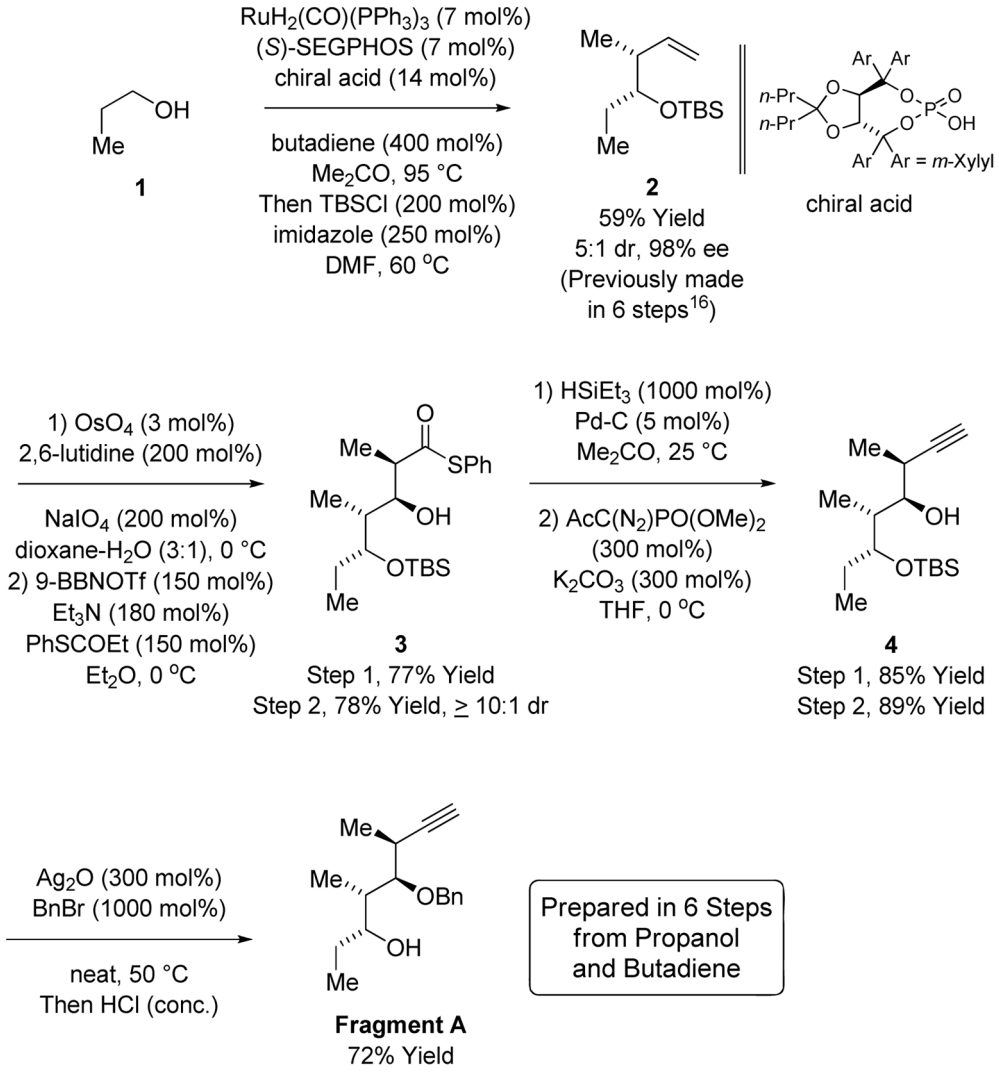
**6-Deoxyerythronolide B**, $R^1$ = H, $R^2$ = H, $R^3$ = H, $R^4$ = H, $R^5$ = $R^6$ = O
Masamune 1981, 26 Steps (LLS), 39 Steps (TS), ref. 10a
Danishefsky 1990, 42 Steps (LLS), 42 Steps (TS), ref. 10b
Evans 1997, 23 Steps (LLS), 28 Steps (TS), ref. 10c,d
White 2009, 23 Steps (LLS), 25 Steps (TS), ref. 10e

**Figure 1.**
Erythromycin A and B, erythronolide A and B and 6-deoxyerythronolide A and B and prior total syntheses.[a]
[a]For graphical summaries of prior total syntheses, see Supporting Information. For total syntheses of other erythromycin family members and their seco-acids, see the review literature.[2] LLS = Longest Linear Sequence; TS = Total Steps.




**Scheme 1.**

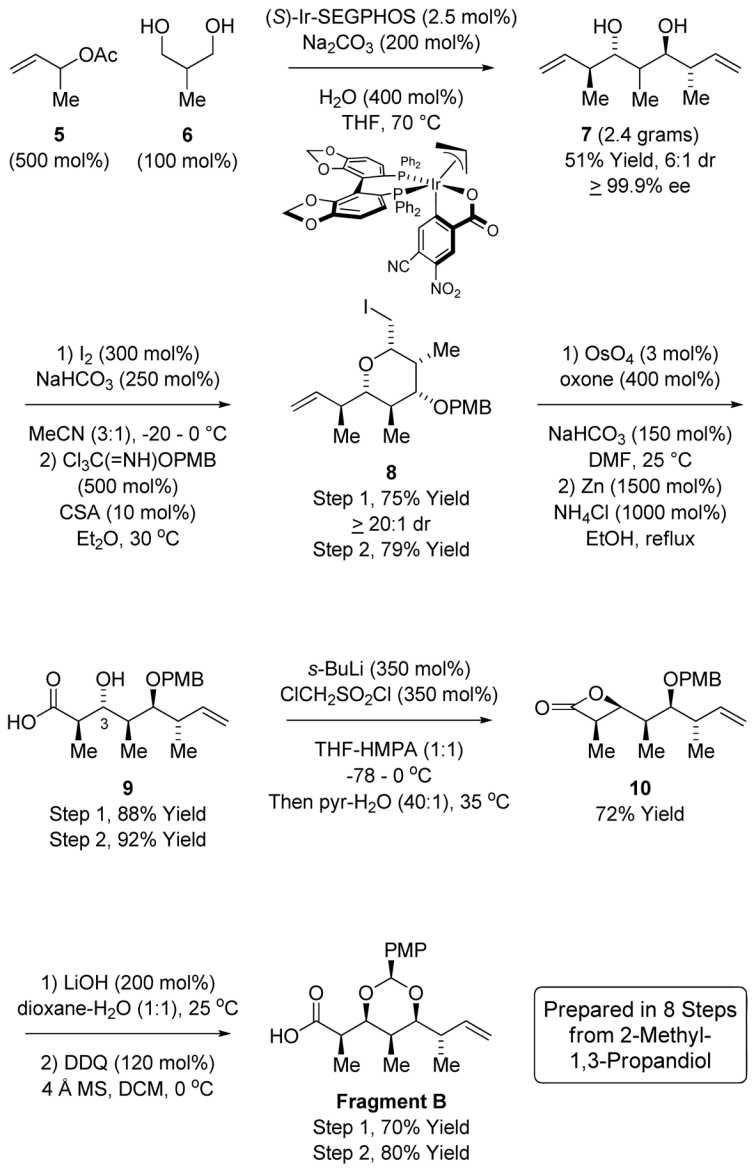
Retrosynthetic analysis of deoxyerythronolide B highlighting C-C bonds formed *via* hydrogenative coupling.




**Scheme 2.**

Synthesis of Fragment **A** *via* ruthenium catalyzed *syn*-crotylation of *n*-propanol **1**.[a]

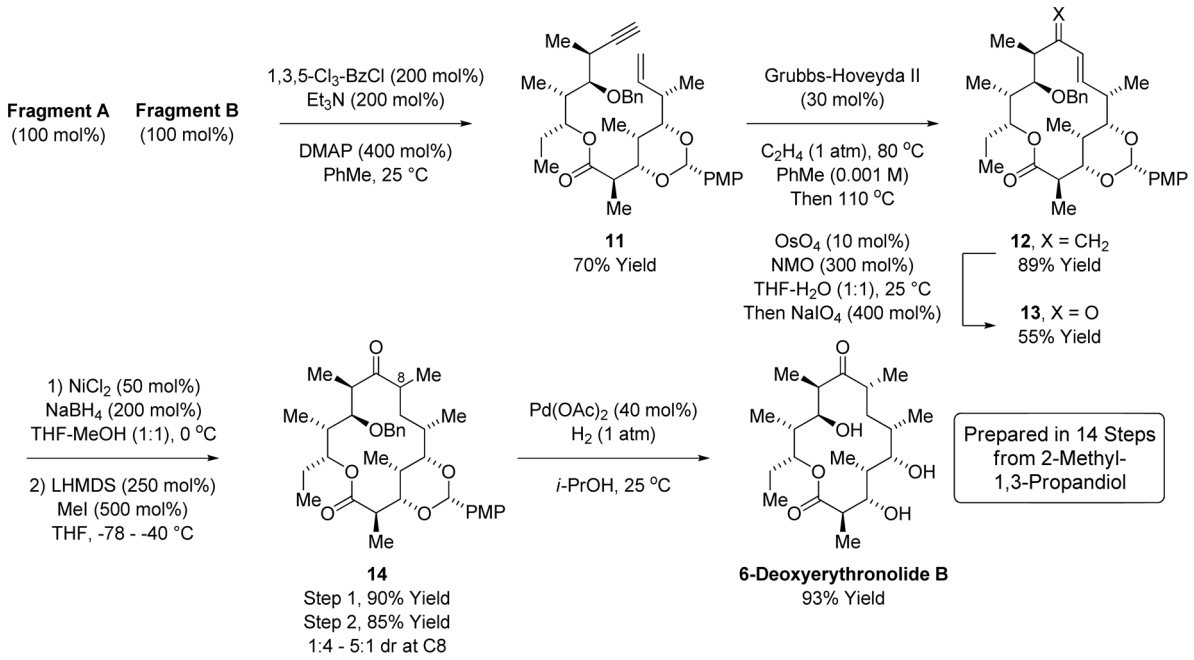
[a]Indicated yields are of material isolated by silica gel chromatography. See supporting information for experimental details.




**Scheme 3.**

Synthesis of Fragment **B** *via* iridium catalyzed double *anti*-crotylation of 2-methyl-1,3-propanediol **6**.[a]

[a]Indicated yields are of material isolated by silica gel chromatography. See supporting information for experimental details.




**Scheme 4.**

Union of Fragment **A** and Fragment **B** and total synthesis of 6-deoxyerythronolide B.[a]

[a]Indicated yields are of material isolated by silica gel chromatography. See supporting information for experimental details.