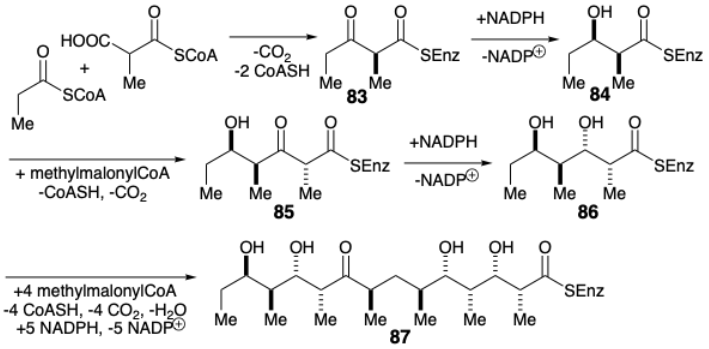
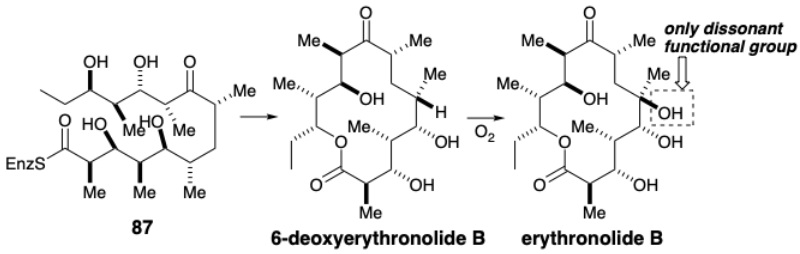
5.4: Erythronolide B

An enzyme promoted reaction of propionylCoA with methylmalonylCoA generates **83** enantioselectively. Diastereoselective reduction then delivers the b-hydroxy thioester **84**. In contrast with fatty acid biosynthesis, dehydration and conjugate reduction of the resulting α,β-unsaturated thioester does not preceed Claisen condensation with a second equivalent of methylmalonylCoA during the biosynthesis of the seco acid precursor **87** of the macrolide 6-deoxyerythronolide B.

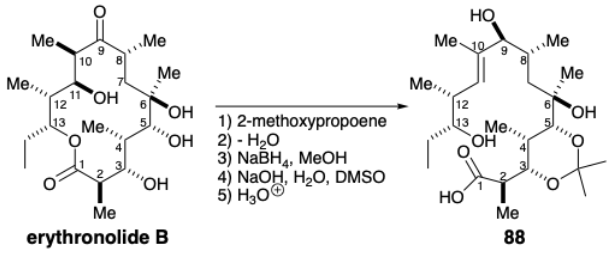


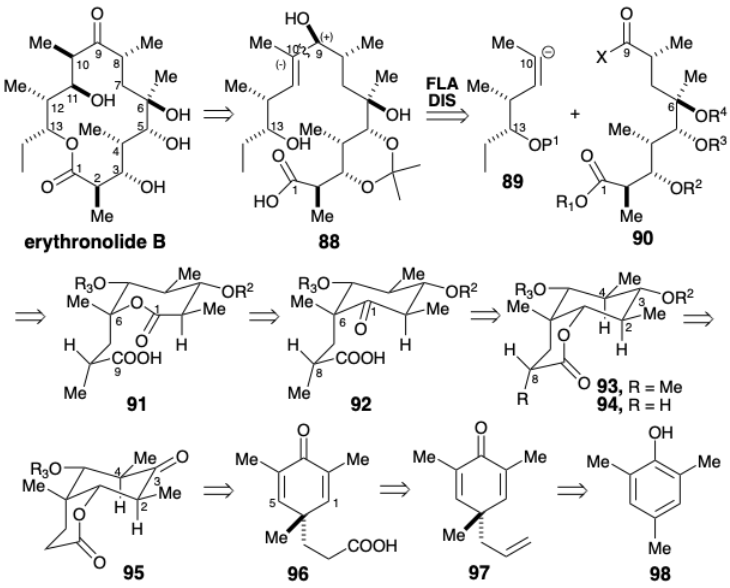
The resulting β-ketothioester **85** is reduced to a β-hydroxyester **86** that reacts with additional methylmalonylCoA and NADPH to generate **87**. Lactonization then provides 6-deoxyerythronolide B from which erythronolide is formed by oxidation. Generation of only 1 of the 2048 possible diastereomers of the acyclic intermediate **87** is the remarkable consequence of the asymmetry of the homochiral catalysts (enzymes) that promote the condensations and reductions responsible for producing ten asymmetric centers.



A Relay-directed Strategy for Total Synthesis of Erythronolide B.

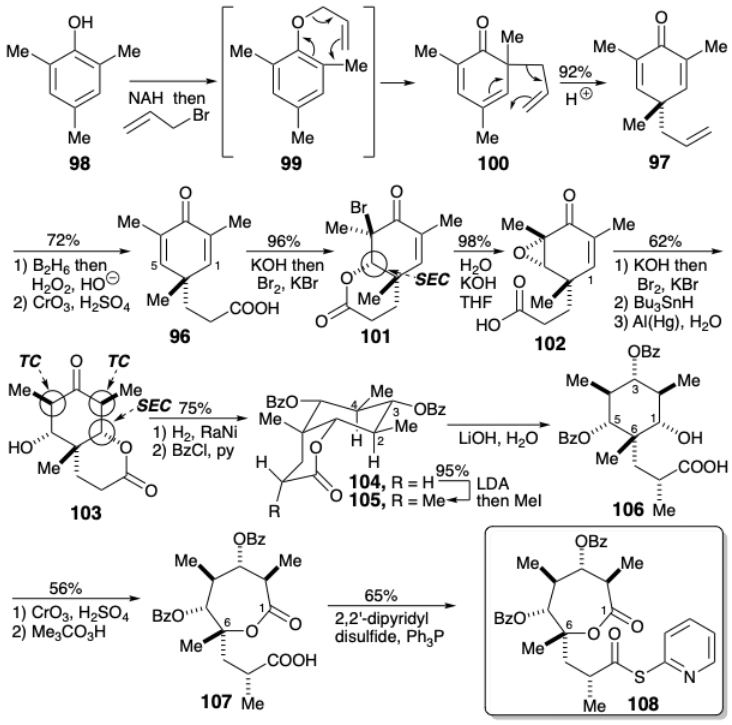
In a feasibility study, naturally derived erythronolide B was converted into an acyclic hydroxy acid **88** that was used to work out the final steps for a total synthesis.[12] The synthetic design process was then channeled by the choice of this naturally derived precursor, a **relay compound**. The two stereocenters at positions 12 and 13 in **88** are remote from those at positions 2-6 and 8. Therefore, it would be difficult to generate one set of stereocenters under the stereo-controlling influence of the other. Rather, building blocks containing these stereocenters with the correct absolute configurations can be assembled and then united to provide the relay compound **88**. The first total synthesis of Erythronolide B1 3 adopted a convergent **absolute asymmetric** (see section 4.6) strategy designed to provide **88** by the union of two homochiral segments, a nucleophile **89** and an electrophile **90**.





To provide a more conformationaly rigid platform for generating and confirming the relative configurations of stereocenters, a cyclic temporarily-bridged precursor **91** was envisioned for the acyclic subtarget **90**. Even greater rigidity is provided by the smaller ring of a six-membered ketone **92** that incorporates the lactone functionality in latent form. Stereoelectronically favored axial delivery of hydrogen to the isomeric cyclohexanone **94** can be expected to generate an equatorial hydroxyl at position 3. Furthermore, dislocation of **93** to **94** allows a carbonyl at position 3 to promote a thermodynamically favored equatorial disposition for the methyls at positions 2 and 4, and sets the stage for uncovering a symmetrical precursor, *vide infra*. Another temporary bridge, a six-membered lactone can be exploited to favor generation of the required configuration at the relatively remote stereocenter at position 8 in **92** during a methylation of **95** that can be expected to favor an equatorial methyl in **94**. Lactone bridges can also be exploited to assure the proper stereo and regiochemical orientation during introduction of oxygen substituents at positions 1 and 6 by polar additions to the C=C bonds in a symmetrical dienone precursor **96**. A search of the literature for available starting materials with the carbon skeleton of **96** can be used to identify the allyl cyclohexadienone **97** that is readily prepared from the trimethylphenol **98**.

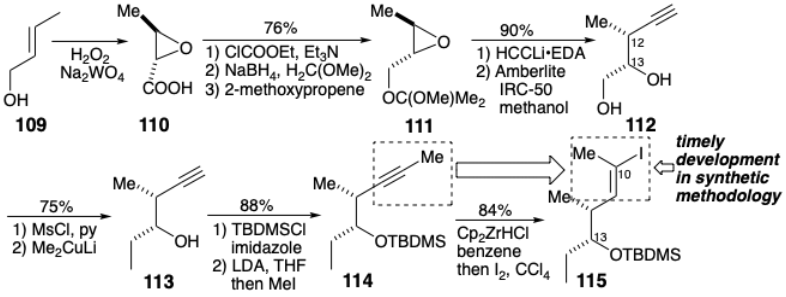
Reaction with allyl bromide of a phenolate from **98** provides **100** by Claisen rearrangement of the initial O-allylation product **99**. An acid-catalyzed Cope rearrangement of **100** delivers the symmetrical dienone **97** that is selectively hydroborated at the terminal vinyl group and then oxidized to produce the carboxylic acid **96**. Stereo and regioselective delivery of oxygen to position 5 is accomplished by intramolecular addition of a carboxylate to a C=C bond in **96**. Capture of the reversibly formed enolate carbanion intermediate with electrophilic bromine produces **101**. To repeat this process on the remaining C=C bond, the lactone is saponified to regenerate a carboxylic acid. This also generates an epoxide by intramolecular displacement of the bromo substituent by alkoxide. A second stereo and regioselective delivery of oxygen, this time to position 1, is again accomplished by intramolecular addition of a carboxylate to a C=C bond. Subsequent reductive removal of unneeded heteroatom functionality at positions 1 and 4 provides **103**.



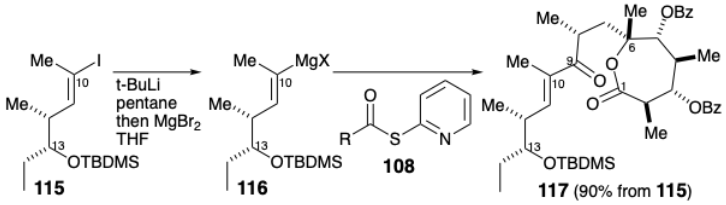
The nucleophilic activation afforded by the lactone carbonyl in **103** could now be exploited to introduce a methyl group at position 8. However, prior adjustment of functionality level at position 3 avoids nucleophilic activation adjacent to the ketone carbonyl. Methylation of **104** then afforded **105** stereoselectively. The lactone in **103** differentiates the hydroxyl substituents at positions 1 and 5. To maintain this diferentiation after saponification of the lactone, the other hydroxyls in **105** had to be suitably masked. The choice of benzoate ester masking group is particularly subtle. The feasibility of selective saponification of the lactone in the presence of benzoate esters relies upon the diminished electrophilicity of the benzoate carbonyl group owing to conjugation. Oxidation of the alcohol **106** to a ketone and then a lactone **107** followed by activation of the carboxylic acid as a thioester provided an electrophilic C1-9 segment equivalent to **90** where the masking groups R^1 and R^4 are replaced by a lactone bridge.

The synthesis outlined above provides racemic compounds. Resolution of an early intermediate, the carboxylic acid **102**, by fractional crystallization of diastereomeric 1-α-naphthylethylamine salts, was employed to generate intermediates with the absolute configurations shown above that are required for natural erythronolide B.

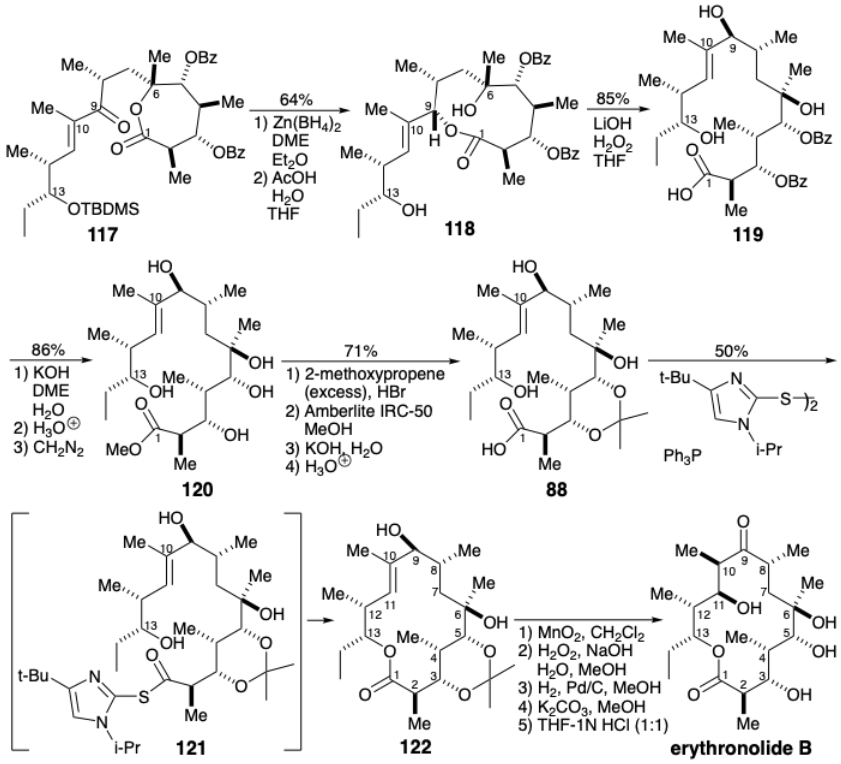
Resolution of an early intermediate was also employed to prepare the requisite enantiomer of a precursor **115** (see section 6.3) for the nucleophile **89**. Thus, the epoxy carboxylic acid **110**, that is readily available by a one-step oxidation of *trans*-crotyl alcohol (**109**), was resolved by fractional crystallization of diastereomeric 1-α-naphthylethylamine salts. Stereospecific nucleophilic substitution on **110** generated the absolute configuration required at position 12. The regioselectivity of this epoxide opening is controlled by the bulky ether substituent in **111**. Use of the corresponding epoxy alcohol in the displacement showed much inferior regioselectivity. Replacement of the terminal hydroxyl in **112** by a methyl group to give **113** could be accomplished without masking of the secondary hydroxyl by using an excess of Me_2CuLi. The completely regioselective conversion of acetylene **114** into vinyl iodide **115** depended upon the outstandingly high regioselectivity that had recently been reported for hydrozirconation of unsymmetrically disubstituted acetylenes. This step in the Corey erythronolide B synthesis is a poignent example of the impact of developments in synthetic methodology on our ability to achieve efficient syntheses of complex organic molecules.



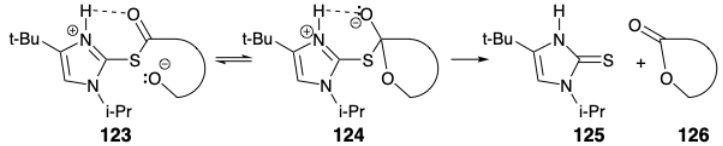
Although both building blocks **108** and **115** were available in homochiral form with the correct absolute configurations for erythronolide B, the synthesis was actually carried out by coupling the correct enantiomer of **115** with racemic **108**. Thus, a Grignard reagent **116** derived from **115** was acylated with thioester **108** to produce ketone **117** and a diastereomer in 90% total yield. The mixture was caried through several additional steps before separation by preparative thin layer chromatography.



Thus, reduction of the ketone carbonyl in **117** proved unexpectedly difficult owing to suprisingly similar reactivity of the keto and lactone carbonyls toward most reducing agents and also because of a proclivity toward conjugate reduction of the enone. Reduction with zinc borohydride was accompanied by two unexpected phenomena, a very welcomed complete stereoselectivity and an essentially irrelevant translactonization that generated a 10-membered lactone **118** after removal of the silyl protecting group at position 13. Saponification of this lactone was most effectively accomplished with LiOH and aqueous H_2O_2 which presumably benefits from the supernucleophilicity of the hydroperoxide anion. Hydrolysis of the less reactive benzoate esters in **119** was then accomplished with aqueous KOH. Subsequent methyl- ation delivered **120** together with a diastereomer from which it was sepatated by TLC on silica gel.

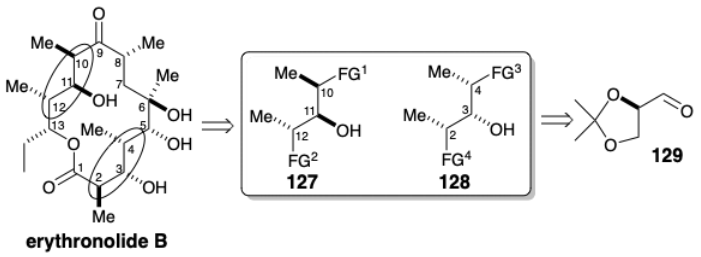


The relay compound **88** was obtained from **120** by ketalization with 2-methoxypropene, selective hydrolysis of 2-methoxy-2-propyl ethers that were also formed, and saponification of the methyl ester. Macrolactonization was accomplished by the "double activation method" that involves simultaneous activation of the hydroxyl and carboxyl functions. Presumably, a doubly activated intermediate **123** collapses to a tetrahedral carbonyl adduct **124** from which the lactone **126** is formed by elimination of **125**. Thus, heating the thioester **122** at reflux in dry toluene provided erythrololide B in 50% yield.

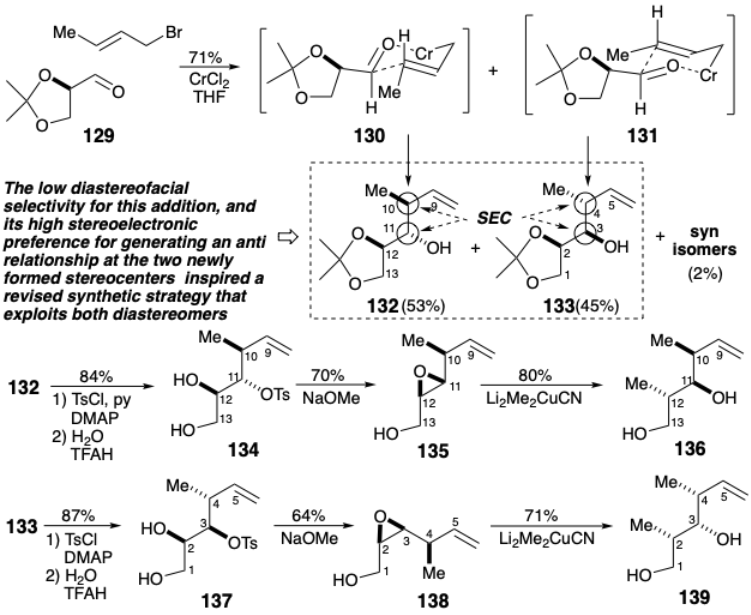


Erythronolide B from Sugar-derived Homochiral Building Blocks.

A strategy for an enantiospecific total synthesis of erythronolide B evolved from the recognition that the C2-4 and C10-12 segments are identically substituted but have different absolute stereochemistries. Such segments, differentially substituted at each end, i.e. **127** and **128**, might be elaborated and joined to generate the natural product. Therefore, studies were launched to define synthetic routes to such intermediates. Since (R)-2,3-O-isopropylideneglyceraldehyde (**129**) is a readily available homochiral building block (see section 3.7), it's possible utility as a starting material for the enantiospecific synthesis of such segments was explored.[14]



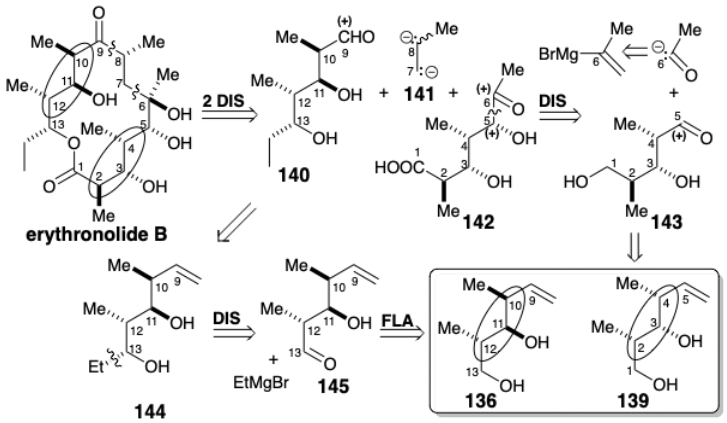
The addition of a crotylchromium reagent to aldehyde **129** showed virtually no diastereofacial selectivity for addition to the aldehyde but a high preference for generating an anti relationship at the two newly formed stereocenters owing to a stereoelectronic preference for chair-like transition state structures **130** and **131** that lead to **132** and **133**. These diastereomers were readily separable by preparative column chromatography on a large scale. Conversion of **132** to an intermediate of type **127** and of **133** to an inter- mediate of type **128** requires inversion of the free secondary hydroxyl and substitution of the other secondary oxygen substituent by methyl with inversion of configuration. Inversion of the free hydroxyl was accomplished by activation as a tosylate followed by intramolecular S_N2 displacement by a vicinal hydroxyl. This stereospecifically produced **135** from **134** and **138** from **137**. Reaction of these epoxides with Li_2Me_2CuCN accomplished the second configurational inversion during replacement of an oxygen substituent with methyl. The diols **136** and **139** correspond to the fragments **127** and **128** respectively, where FG^1 and FG^3 are both latent aldehydes while FG^2 and FG^4 are both hydroxymethyl groups.



The availability of the homochiral building blocks **136** and **139** channeled a second phase of strategic planning.[15] Polar disconnection of erythronolide B at the C6-C7 and C8-C9 generates two precursors, **140** and **142**, both with terminal carbonyl functions. Polar union of these fragments would require a "vicinally dianionic two-carbon (C6/C7) synthon" **141** with a pendant methyl group. Although the identification of a synthetic equivalent for **141** was postponed, it was recognized that "the methyl branching excluded the straightforward application of some acetylenic derivative."

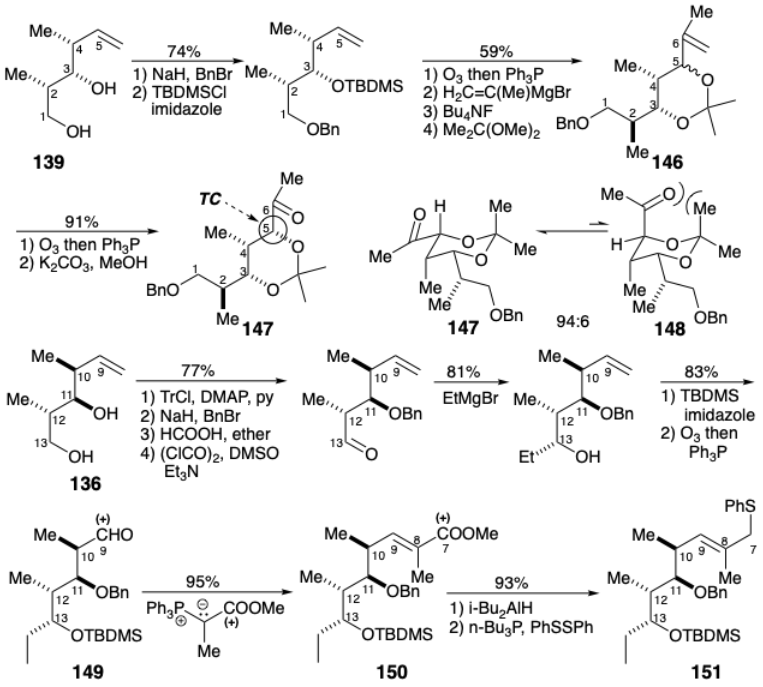
Further polar disconnection of **142** to generate an aldehyde **143**, that should be available from the building block **139**, requires an acetyl carbanion synthon for which isopropenylmagnesium bromide is a latent synthetic equivalent. The alkene **144** is a latent

equivalent of aldehyde **140**. Further polar dislocation of **144** suggests an ethyl nucleophile and aldehyde electrophile **145** that should be available by oxidation of **136**.

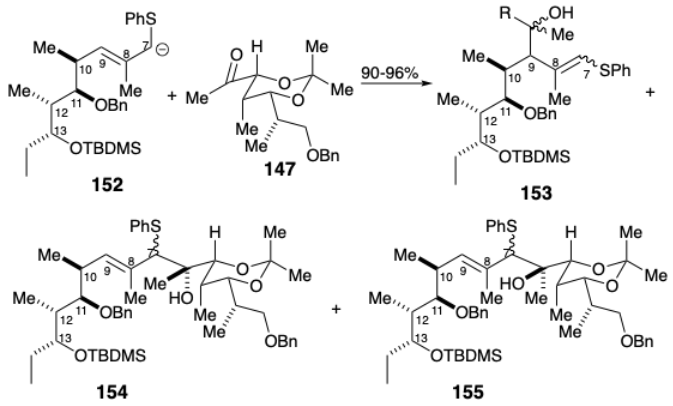


A masked derivative **147** of **142**, containing the carboxylic acid functionality in latent form as a benzyloxy ether, was prepared from the homochiral building block **139** (see below). The addition of a Grignard reagent to an aldehyde intermediate generated the stereocenter at position 5 nonstereoselectively, leading to **146** as a 2:1 mixture of diastereomers. However, the requisite configuration at this carbon could be established by equilibration of the epimeric ketones **147** and **148**. The equatorial ketone was favored over the axial epimer **148** by 94:6 at equilibrium.

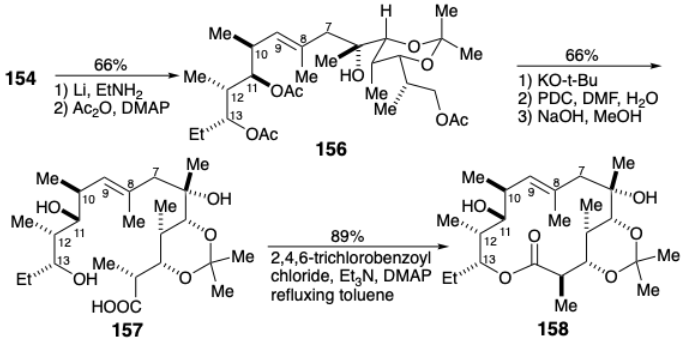
A masked derivative **149** of aldehyde **140** was prepared from the homochiral building block **136.** Although a polar union of the two carbonyl containing fragments **147** and **149** might exploit a dissonant dianionic fragment corresponding to **141**, a synthetic equivalent of **141** was not devised. Rather, a nucleophilic reagent that was nucleophilic at C6 and contained an electrophilic carbon at position 7 was joined with aldehyde **151**, and then the polar reactivity of C7 was inverted by conversion to an allylic thioether that could be deprotonated to provide nucleophilic reactivity at C7.



The carbon skeleton of erythronolide B was completed by joining ketone **147** with the allylic carbanion **152** produced by deprotonation of sulfide **151** with n-BuLi in the presence of TMEDA. Initial results were disapointing because the major product was the γ-adduct **153** rather than the desired α-adduct **154**. By addition of HMPA, the formation of **153** could be suppressed almost completely. However, under these conditions, the main product was an epimeric α-adduct **155**. Finally, it was discovered that precomplexation of the ketone **147** with BF_3 strongly favored the required regio and stereoselecivity.



Having served its purpose as a polar reactivity inversion operator, the allylic phenylthio substituent was removed reductively. Differentiation of the hydroxyl groups was then accomplished by acetylation followed by selective deacetylation of **156** to unmask the primary hydroxyl. Oxidation followed by exhaustive deacetylation delivered the trihydroxy acid **157**. Macrolactonization was accomp- lished in very good yield by conversion to a mixed anhydride that was cyclized in dilute toluene solution. Apparently a strain-free conformation that is ideally suited for cyclization is available to **157**, whereas serious congestion is present in conformations suitable for forming a 12-membered lactone by acylation of the 11-OH.



Completion of the synthesis required introduction of oxygen at position 9. Anti Markovnikov hydration of the 8,9-C=C bond in **158** by hydroboration-oxidation accomplished this functionalization, and apparently owing to macrocyclic conformational effects, generation of the correct configuration at position 8 was favored by 9:1. Conformational effects also fostered selective oxidation of the secondary hydroxyl at position 9 in the presence of another secondary hydroxyl at position 11. Thus, the accumulation of many favorably selective steps owing to subtle, unanticipated consequences of molecular shape -- i. e. the remarkably effective macrolactonization, and favorably stereo and regioselective processes - - resulted in a total synthesis that rivals the Corey strategy that was more meticulously planned by thorough reterosynthetic analysis.