Natural Product Synthesis

An Abiotic Strategy for the Enantioselective Synthesis of Erythromycin B**

*Paul J. Hergenrother, Anne Hodgson, Andrew S. Judd, Wen-Cherng Lee, and Stephen F. Martin**

Erythromycin A (**1**) and erythromycin B (**2**), which owe their antibiotic activity to their ability to inhibit ribosomal-dependent protein biosynthesis, are arguably the best-known members of the macrolide family of antibiotics.[1] Despite the advent of a myriad of newer antibiotics, **1** continues to be the drug of choice for the clinical treatment of numerous pathogenic bacteria. Consequent to their important antibiotic activity and their complex structures, these natural products have been the objects of synthetic investigations for more than two decades,[2] and a substantial amount of novel and useful chemistry has emerged from these efforts. Indeed, these antibiotics have served as a veritable testing ground for evaluating methods for effecting acyclic stereochemical control. All these advances notwithstanding, it is noteworthy that there has only been a single report of the total synthesis of **1** and of **2**. In an elegant series of studies that culminated in 1981 with the total synthesis of **1**, the Woodward group not only solved problems of stereochemical control and glycosylation of the macrocyclic lactone, but also identified many of the control elements associated with the macrolactonization of seco-acid derivatives.[3] Oishi and co-workers subsequently recorded a formal synthesis of **1**,[4] and the Tatsuta group developed an alternative strategy for glycosylating the macrocyclic aglycone.[5] More recently we reported the total synthesis of **2** through a plan in which the carbohydrate residues were also introduced following the macrolactonization step.[6] Indeed, the synthetic strategy of installing the carbohydrate groups *after* cyclization of a suitable seco-acid derivative follows the general lines of the putative biosynthesis of the macrolide antibiotics.[7,8]

We have long been interested in exploring a different end game for the synthesis of the erythromycin antibiotics in which either one or both of the carbohydrate substituents

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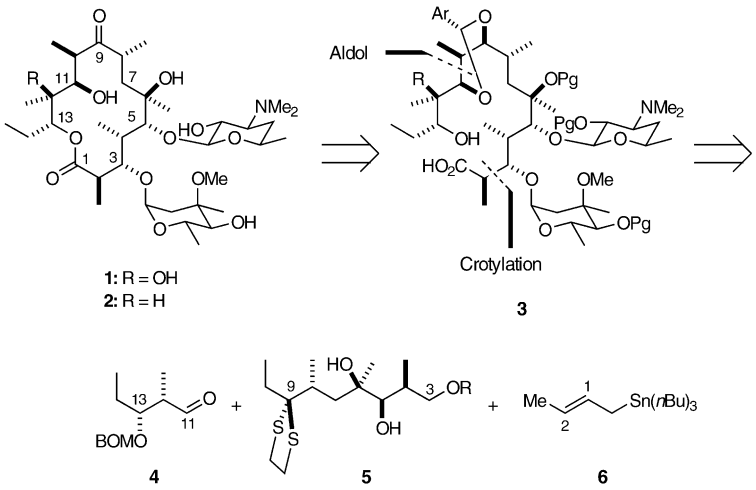
would be appended *prior* to the macrolactonization step (Scheme 1). In principle, the carbohydrate residues themselves might serve as protecting groups for the hydroxy functions at C3 and C5, thereby potentially resulting in a more concise route to **2**. This strategy was not without its risks, however, as the Woodward group had nicely defined many of the structural parameters required for the successful cyclization of erythromycin seco-acid derivatives.[3] These studies had clearly revealed the critical importance of rigidifying the seco-acid backbone in the regions spanning the C3–C5 and C8–C12 segments, typically by using cyclic derivatives that incorporated the oxygen substituents at C3, C5, C9, and C11. Hence, to establish the underlying viability of this abiotic approach to the erythromycins, we first established in a key experiment that a derivative of **3** did indeed undergo macrolactonization.[9] We now report the successful implementation of the strategy outlined in Scheme 1 for the synthesis of **2** from subunits **4**–**6**.

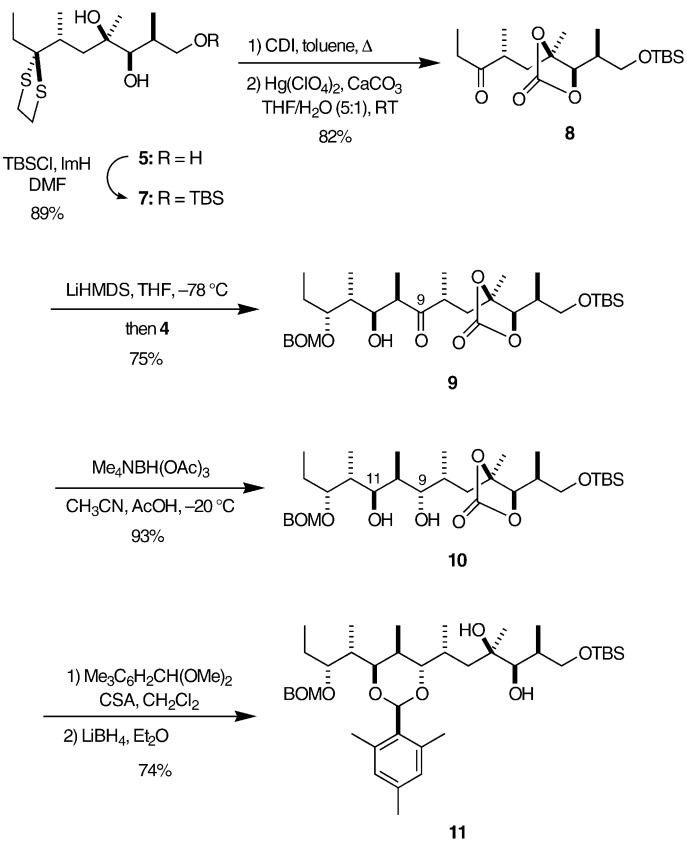


Scheme 1. Retrosynthetic analysis of erythromycin A (**1**) and erythromycin B (**2**). Pg = protecting group, BOM = benzyloxymethyl.

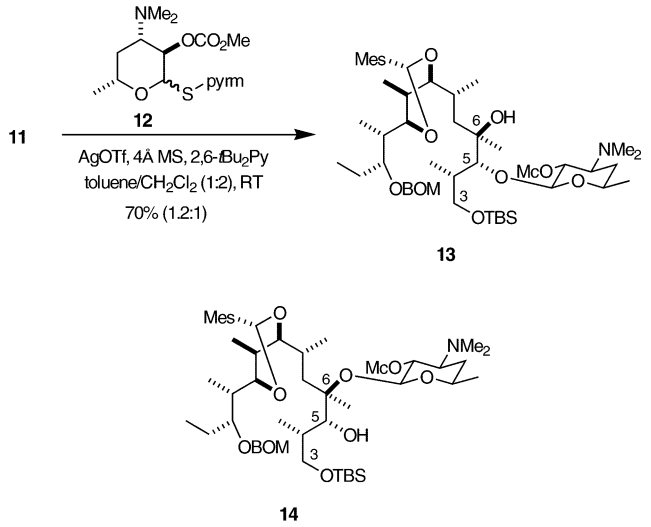
The synthesis commences with selective protection of the primary hydroxy group of the triol **5**, which we had previously prepared in seven steps from ethyl furan,[10] to give **7** (Scheme 2). Conversion of the diol moiety in **7** into a cyclic carbonate followed by removal of the dithiolane protecting group afforded the ketone **8**.[11] The subsequent aldol reaction of the enolate of **8** with the known aldehyde **4**[10] proceeded with high diastereoselectivity (d.r. > 95:5) to give **9**. The C9 ketone function was stereoselectively (d.r. = 98:2) reduced with $Me_4NBH(OAc)_3$ according the Evans protocol to give **10**,[12] thereby setting the *S* configuration at C9 that would be required for the macrolactonization. The C9–C11 *anti* diol moiety was then protected as its cyclic mesitylene (Mes) acetal, and the cyclic carbonate protecting group was removed to furnish the glycosylation substrate **11**, thus completing the first phase of the synthesis.

Prior art in the area of introducing desosamine residues onto macrocyclic lactones suggested that **11** should react selectively with a suitable desosamine donor to give **13**.[3,5,6] Much to our surprise, however, we found that the reaction of **11** with **12** under conditions that were defined only after considerable experimentation gave a mixture of **13** and **14** (1.2:1) in a combined yield of 70%, together with 20–25% of recovered **11** (Scheme 3). Glycosylation of the tertiary hydroxy group at C6 of **11** was thus remarkably facile, and **14** was formed in significant quantities, irrespective of numerous variations in the coupling procedure. We also explored the feasibility of protecting the hydroxy group at C6 but were unable to introduce the desosamine subunit on such protected substrates. Ultimately, we had to be content with separating the isomeric C5- and C6-glycosylated products and continuing the synthesis with **13**.

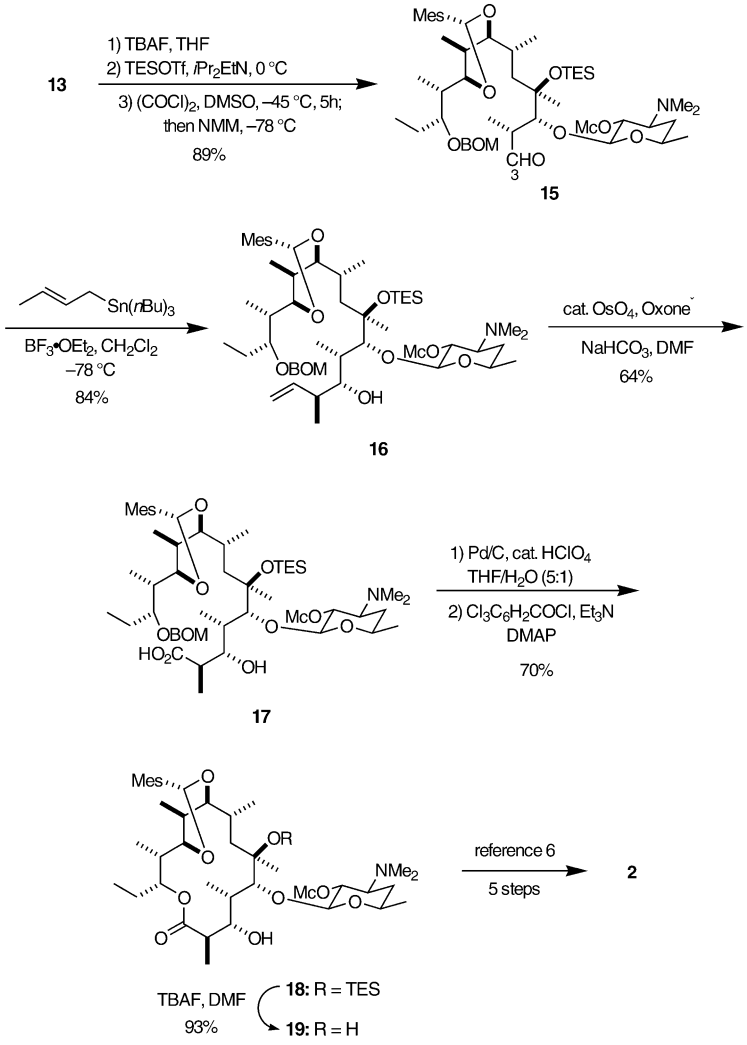
To introduce the remaining three-carbon unit of the erythromycin backbone, it was first necessary to oxidize the alcohol function at C3 to an aldehyde. However, we found that if the hydroxy group at C6 was not protected prior to generating the aldehyde at C3, a five-membered lactol that could not be advanced in the synthesis was unavoidably formed. The most expeditious solution to this problem involved deprotection of the primary alcohol group at C3 of **13** followed by reaction of the resultant diol with TESOTf to give an intermediate 3,5-diprotected diol, which underwent desilylation and Swern oxidation of the hydroxy function at C3 to give **15**



Scheme 2. Synthesis of C3–C15 backbone subunit **11**. TBS = *tert*-butyldimethylsilyl, ImH = imidazole, DMF = *N*,*N*-dimethylformamide, CDI = *N*,*N*-carbonyl diimidazole, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, CSA = (−)-camphorsulfonic acid.



Scheme 3. Synthesis of glycosylated C3–C15 backbone subunit **13**. pyrm = 2-pyrimidinyl, Tf = trifluoromethanesulfonyl, MS = molecular sieves, Py = pyridine, Mc = methoxycarbonyl.



Scheme 4. Synthesis of erythromycin B (**2**). TBAF = tetrabutylammonium fluoride, TES = triethylsilyl, DMSO = dimethyl sulfoxide, NMM = *N*-methylmorpholine, DMAP = 4-dimethylaminopyridine.

(Scheme 4).[13] The reaction of **15** with crotylstannane in the presence of $BF_3{\cdot}OEt_2$ then furnished **16**[14] in 84% yield, together with about 12% of a mixture of other diastereomeric adducts. We briefly explored the possibility of introducing the remaining carbon atoms into **15** through a number of different aldol reactions,[15] but these efforts did not yield significant quantities of the desired adduct.

It then remained to oxidize the terminal C–C double bond to generate the C1 carboxylic acid. In previous work, we had developed two- and three-step protocols for effecting this transformation,[6,10] but we found that the oxidation of **16** to give **17** by using a recently developed procedure for organometallic ozonolysis provided an efficient one-step alternative.[16] Removal of the protecting group from the C13 hydroxy function by hydrogenolysis under carefully defined conditions gave an unstable hydroxy acid, which was then cyclized according to the Yamaguchi protocol to furnish **18**.[17] Deprotection of the hydroxy group at C6 then delivered **19**, which we had previously converted in five steps into erythromycin B (**2**), thereby completing a synthesis of erythromycin B (**2**).[6]

In conclusion, we have completed a novel synthesis of erythromycin B by using an abiotic strategy in which a key step is the cyclization of a glycosylated seco-acid derivative. As such, this synthesis represents the first time that a naturally occuring macrolide antibiotic has been prepared through an approach in which a sugar residue is appended *prior* to the macrolactonization step. Moreover, the ability to cyclize the hydroxy acid derived from **17** clearly illustrates that more structural flexibility in the backbone can be tolerated in the cyclization step than was previously recognized.[3]

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