Total Synthesis of Oligomycin C

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Oligomycin C is a polypropionate-derived natural product that shares a macrolide−spiroketal structure with the rutamycins (Figure 1). As related members of the oligomycin class of macrolide-antibiotics possessing identical 26-membered lactones, oligomycin C differs from rutamycin B by a single methyl group at the C26 position of the spiroketal. The oligomycin antibiotic complex was first isolated and characterized in 1954[1] from a strain of *Streptomyces diastatochromogenes.* The oligomycins are cytotoxic macrolides that are reported to inhibit oxidative phosphorylation in mitochondria by preventing synthesis of ATP.[2] Their mode of action is believed to involve the decoupling of the F_0 and F_1 factors, which are responsible for facilitating proton transfer through the inner mitochondria membrane. A protein−oligomycin complex is believed to exist between the oligomycin-sensitivity-conferring protein (OSCP) and the natural product, which is thought to prevent oxidative phosphorylation. The OSCP is located in the stalk between the F_0 and F_1 factors. As such, these natural products may serve as potential biological probes and have already been used in the exploration of oxidative phosphorylation.[4] The structures of oligomycin A, B, and C were assigned on the basis of degradation products and ^{1}H NMR and ^{13}C NMR correlation experiments.[3] Earlier studies on this class of antibiotics have resulted in the absolute stereochemical assignment and total synthesis of rutamycin B.[4]

Structurally, oligomycin C consists of a synthetically challenging 26-membered lactone that is linked to the C18−C34 spiroketal fragment through an ester bond of the C25-hydroxyl of the spiroketal. The formidable tasks associated with the synthesis of this class of natural products include the efficient construction of the C1−C17 polypropionate and spiroketal fragments and their subsequent coupling. In this paper, we wish to report the first asymmetric synthesis of oligomycin C. Since the synthesis of the polypropionate fragment **4** has been reported,[5] the outline of our retrosynthetic analysis emphasizes the asymmetric crotylation strategy[6] used in the construction of the spiroketal fragment (Figure 1). Our synthetic plan for joining these two fragments by the construction of the sp^2-sp^2 bond at C17−C18 relied on a palladium(0)-based cross-coupling strategy utilizing a vinylstannane/vinyl iodide combination.[7] The synthetic analysis of the spiroketal involved opening of the spirocycle to give an acyclic precursor bearing seven stereogenic centers. Our retrosynthetic plan for the synthesis of members of this class of macrolides antibiotics allows for a high degree of convergency and is highlighted by an intermolecular Stille coupling to effect the C17−C18 bond construction.[8] Lactonization under Yamaguchi conditions would complete construction of the macrocycle. The introduction of the stereogenic centers is based on the application of double-stereodifferentiating crotylation reactions with chiral (*E*)-crotylsilanes.[9]

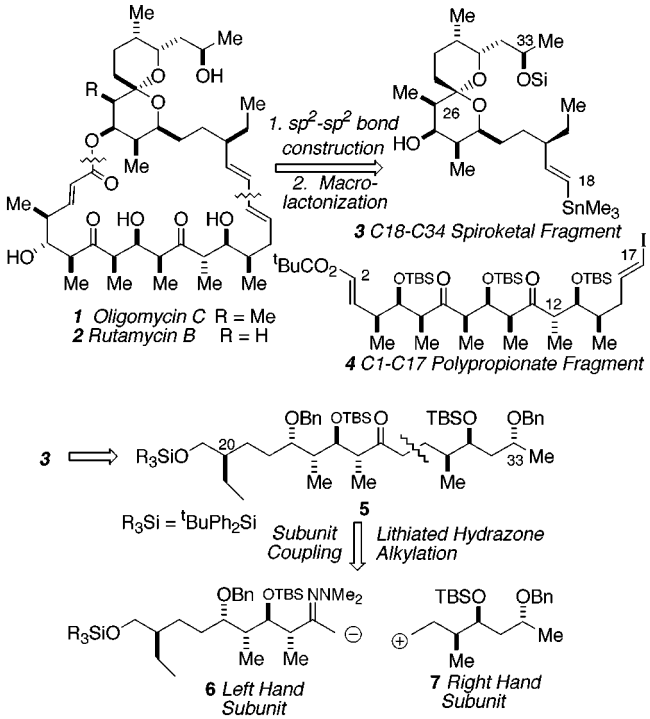

Figure 1.

The synthesis of this subunit of oligomycin C utilizes two asymmetric crotylation reactions for the introduction of the C23−C24 and the C25−C26 stereogenic centers. The construction of the C19−C28 subunit of the spiroketal was initiated by an asymmetric crotylation between the chiral aldehyde **8** and silane reagent (*S*)-**9a**,[10] which established the C23−C24 stereocenters (Scheme 1). This first addition proceeds through the intermediacy of an oxocarbenium ion involving an open transition state where the observed stereochemistry is consistent with an *anti*-S_E' mode of addition. The (*E*)-olefin of the homoallylic benzyl ether **10** was cleaved by ozonolysis to furnish the α-methyl aldehyde **11**. This material was used without further purification in a chelation-controlled, double-stereodifferentiating crotylation reaction with chiral *β*-methylsilane (*S*)-**9b** (diastereoselection >40:1 *anti*/*syn*). The $TiCl_4$-promoted reaction produced the *anti* homoallylic alcohol **12** with a high level of *anti*-Felkin induction. Presumably, this reaction proceeds through a Cram chelate transition-state model.[11,12] This material was converted to the hydrazone **13** in a straight-

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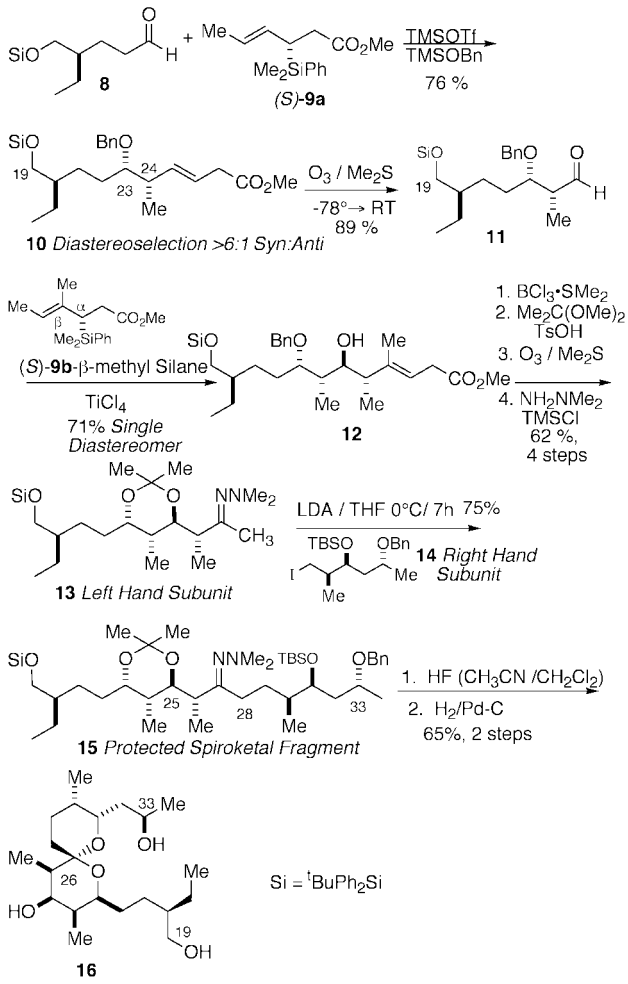
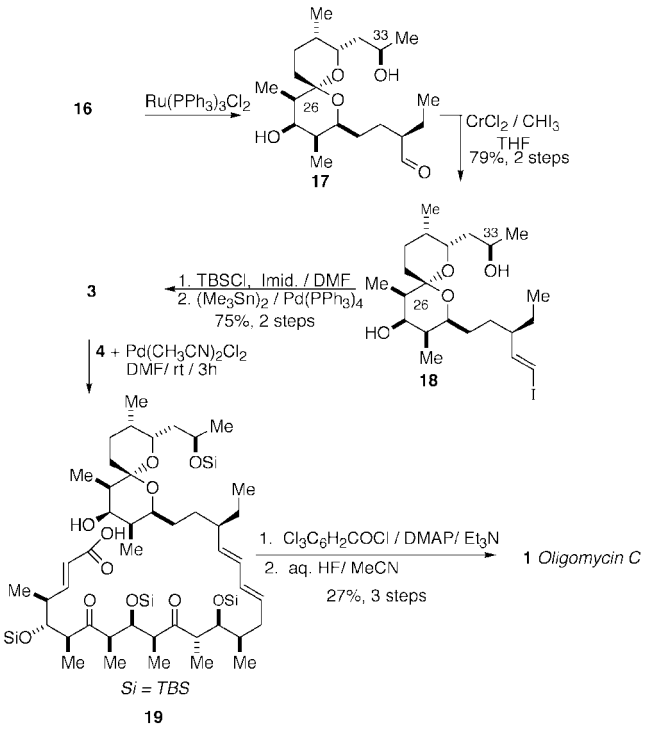
Scheme 1



forward four-step sequence: (i) deprotection of the C23 secondary benzyl group (BCl_3·SMe_2), (ii) protection of the *anti*-1,3-diol as its acetonide, (iii) oxidative cleavage of the (*E*)-double bond with O_3/Me_2S, and (iv) hydrazone formation in 62% overall yield.

The C29−C34 right-hand subunit of oligomycin C (**14**) is identical to that of rutamycin B, and its synthesis has been previously reported from our laboratory.[13] It was envisioned that the most efficient subunit coupling would involve an alkylation reaction of the ketone enolate of **13** with primary iodide **14** to construct the C28−C29 bond (Scheme 1). Thus, the lithium enolate of *N*,*N*-dimethylhydrazone **13** was formed and reacted with primary iodide **14** to afford the alkylated hydrazone **15**.[14] The synthesis of the spiroketal fragment was completed in two steps and was initiated by deprotection and cyclization with aqueous HF in MeCN/CH_2Cl_2 (1:1) at room temperature. The resulting crude product was subjected to hydrogenolysis to remove the benzylic ether at C33 [H_2 (1 atm) over 10% Pd/C in EtOH at 25 °C/36 h], providing the C19−C34 fragment **16** as the fully elaborated carbon framework of the spiroketal of oligomycin C.

Scheme 2



The completion of the synthesis was accomplished by selective oxidation of the C19 primary hydroxyl group with $Ru(PPh_3)_3Cl_2$[15] to afford aldehyde **17**, which was homologated using the Takai protocol[16] to yield vinyl iodide **18** (Scheme 2). Selective protection of the C33 hydroxyl with TBSCl/imidazole and conversion of the vinyl iodide to the vinylstannane using the Stille protocol[7a] gave the fully elaborated C18−C34 spiroketal fragment **3**. Fragment coupling was accomplished by using a palladium(0)-catalyzed cross-coupling reaction between the stannylated spiroketal and vinyl iodide **4** to give hydroxy acid **19**. Finally, macrocyclization of hydroxy acid **19** using the Yamaguchi protocol[17] followed by removal of the silicon protecting groups with aqueous HF furnished synthetic oligomycin C (**1**). Its spectroscopic and physical properties were identical in all respects (^1H, ^{13}C NMR, $[\alpha]_D$, and MS) with those previously reported [$[\alpha]^{23}_D = -82.7°$ ($c = 0.15$, dioxane) (lit.[3a] $[\alpha]^{23}_D = -80.7°$ ($c = 3.70$, dioxane))]. In summary, the total synthesis of oligomycin C has been completed in 44 steps. Overall, the approach represents an interesting application of chiral crotylsilane-based bond construction methodology and easily complements the well-developed chiral enolate methodology.

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Supporting Information Available: General experimental data as well as spectral data for all products (39 pages).

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