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Application of Chiral *(E)*-Crotylsilanes in Synthesis: The Asymmetric Synthesis of the C1-C17 Polypropionate Fragment of Rutamycin B.

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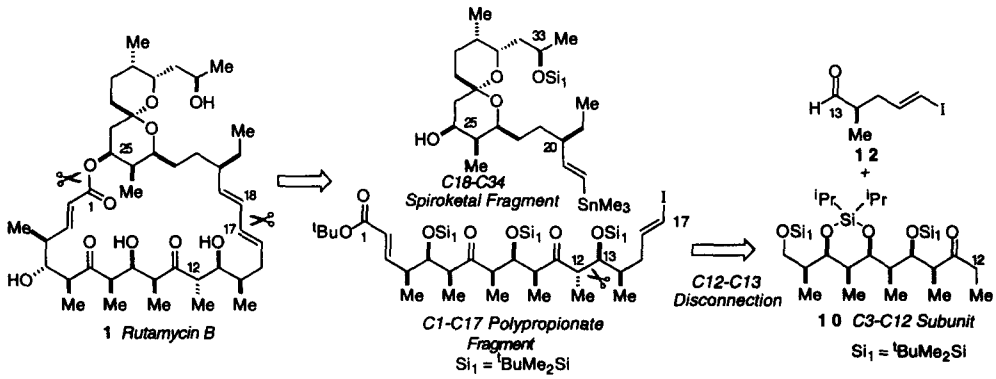
Abstract: The asymmetric synthesis of the polypropionate fragment of rutamycin B is reported employing chiral allylsilane bond construction methodology for the introduction of six of the nine stereogenic centers. In this paper, the construction of the C3-C12 subunit and its coupling to the aldehyde **12** through a Mukaiyama-type aldol reaction are described.

We have recently reported our results concerning the development of double-stereodifferentiating reaction methodology which may be useful in the asymmetric synthesis of polypropionate derived natural products.[1] In this communication, we report the asymmetric synthesis of the C1-C17 polypropionate fragment of rutamycin B, a macrolide belonging to the oligomycin family of antibiotics.[2] A convergent route was designed utilizing chiral *(E)*-crotylsilane bond construction methodology[3] to introduce six of the nine stereogenic centers of this fragment. This design needed to be adaptable for the eventual coupling to the spiroketal fragment.[4] The first disconnection at the C17-C18 and at the C1-ester linkage produced two principal fragments, the polypropionate and the spiroketal fragments. Each fragment contains different architectual features and synthetic challenges (Scheme 1).

Scheme 1

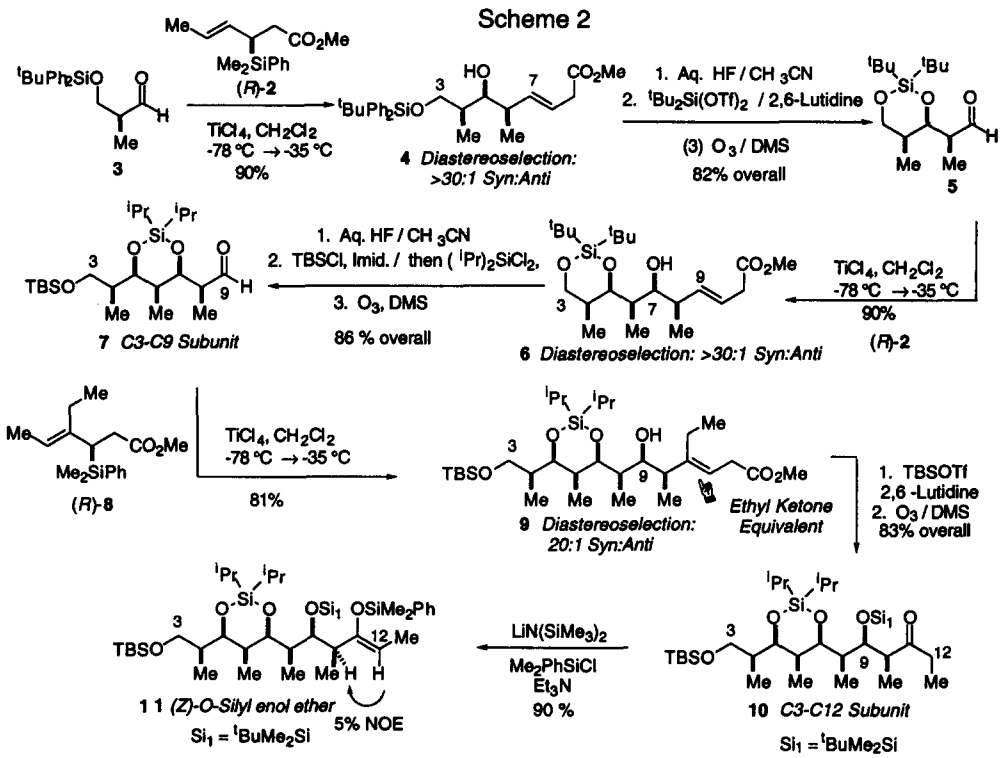


The disconnection of the fragment at C12-C13 yields two components of one of the four possible double-stereodifferentiating aldol reactions used in the assembly of the polypropionate fragment. In this case the bond construction relies on an *anti*-aldol reaction with Felkin induction.[5] We projected that a Lewis acid-promoted aldol reaction involving a *Z-(O)*-silyl enol ether would secure this stereochemical relationship.[6] The C3-C12 subunit is derived from three consecutive double-stereodifferentiating *syn*-crotylation reactions. Having already established operational feasibility for these transformations,

elaboration of the C3-C12 subunit utilizing crotylsilane chemistry seemed quite favorable,[1] while reinforcing the importance of convergency in the synthesis of complex molecules.

Synthesis of the C3-C12 Subunit. Using chiral *(E)*-crotylsilane bond construction methodology the absolute stereochemical relationships can be introduced with a high level of selectivity. It was initiated with a Lewis acid-promoted condensation of the chiral silane *(R)*-**2** with *(S)*-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-propionaldehyde **3** (Scheme 2).[7] A bidentate Lewis acid, $TiCl_4$ (1.8 equiv) combined with a silyl protecting group on the aldehyde prevents chelation with the Lewis acid affording a *syn* homoallylic alcohol **4** (>30:1, *syn:anti*). This *syn* selectivity resulted from the fully matched case of the reaction partners and proceeds through an open antiperiplanar transition state.[1] This material was converted to the aldehyde **5** in a three-step sequence: (1) desilylation with aqueous HF / CH_3CN,[8] (2) protection of the resulting diol with $^tBu_2Si(OTf)_2$ (1.2 equiv) / 2,6-lutidine / CH_2Cl_2 at -78 °C, (3) ozonolysis of the *(E)*-double bond. This reaction sequence proceeded in 82% overall yield.

Scheme 2

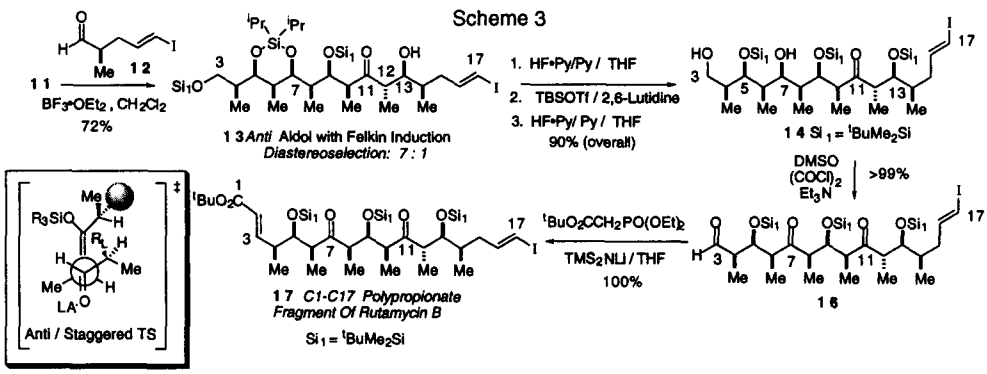


The second crotylation reaction installed the C7 and C8 stereocenters. The aldehyde **5** and the silane reagent *(R)*-**2** (1.2 equiv) in anhydrous CH_2Cl_2 were treated with $TiCl_4$ (1.1 equiv) to afford the homoallylic alcohol **6** (>30:1, *syn:anti*) in 90% yield. This intermediate was converted to the C3-C9 subunit **7**, in three steps: (1) deprotection of the cyclic protecting group using aqueous HF in CH_3CN, (2)

protection of the triol with TBSCl (1.05 equiv) / imidazole (4.5 equiv) in DMF and addition of 1.1 equiv of $^{i}Pr_2SiCl_2$ after 30 minutes, (3) ozonolysis of the *trans* double bond. This sequence provided the C3-C9 subunit **7** in 86% overall yield. The third *syn* crotylation reaction introduced the C9 and C10 stereocenters while giving direct access to the ethyl ketone equivalent through the oxidative cleavage of the *trans* trisubstituted double bond. The aldehyde **7** and the silane reagent *(R)*-**8** were treated with $TiCl_4$ (1.5 equiv) from -78° to -55 °C to afford the homoallylic alcohol **9** (diastereoselectivity 20:1, *syn:anti*). In all three crotylation reactions, a silicon-based protecting group strategy were used in the aldehyde partner to prevent chelation with the Lewis acid to reinforce Felkin induction. This material was converted to the C3-C12 subunit in two steps: (1) protection of C9-hydroxy with TBSOTf (1.2 equiv) / 2,6-lutidine (1.5 equiv) in anhydrous CH_2Cl_2 at 0 °C, (2) ozonolysis of the *trans* double bond. This directly afforded the ethyl ketone **10**, now set for the coupling with C13-C17 subunit.

C12-C13 Bond Construction. This critical bond construction was achieved by a double stereodifferentiating Mukaiyama-type aldol reaction.[9] The *(Z)-O*-silyl enol ether **11**, derived from the ethyl ketone **10**[10, 11] and the aldehyde **12**, were treated with $BF_3{\cdot}OEt_2$ (1.3 equiv) at -78 °C for 24 h to furnish the aldol product **13** with good selectivity (de = 7:1). It is believed that the Me_2PhSi *(Z)-O*-silyl enol ether sterically reinforces Felkin induction resulting in an *anti* aldol with the methyl groups positioned *anti* across the C11 carbonyl.[12] The reaction is believed to proceed through an open transition state with an *anti*/staggered arrangement of the reacting π-partners as illustrated below in Scheme 3.

Scheme 3



The synthesis of the C1-C17 fragment was completed in five steps from **13** and was initiated with the selective removal of the C5-C7 cyclic silylene protecting group with HF•Py/Py in THF at 0 °C. The resulting crude triol was selectively protected at the C5 and C13-hydroxyl groups with TBSOTf (2.2 equiv), 2,6-lutidine (3.0 equiv) at -78 °C. Selective deprotection of the primary TBS group at C3, by HF•Py/Py in THF at room temperature followed by a Swern oxidation[13] of the resulting diol gave the keto-aldehyde **16**. Subsequent olefination using an *(E)*-selective Horner-Emmons reaction provided the C1-C17 fragment of rutamycin B in quantitative yield [>95 : 5 (*E* : *Z*) selectivity].[14] Its spectroscopic and physical properties were identical in all respects (^1H NMR, ^{13}C NMR, IR, $[\alpha]^D$, and MS) with those previously reported.[4a]

To summarize, the synthesis of the polypropionate portion of rutamycin B was completed in 18 steps from **2**, and **3** in an overall yield of 23% and it documents the use of our asymmetric silane based-bond construction methodology for the construction of complex molecules. In the following paper, the synthesis of the spiroketal fragment of rutamycin B is described.

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