Pergamon

Tetrahedron Letters, Vol. 38, No. 8, pp. 1349-1352, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00096-8

Application of Chiral (*E*)-Crotylsilanes in Synthesis: The Asymmetric Synthesis of the C19-C34 Spiroketal Fragment of Rutamycin B.

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Abstract. The asymmetric synthesis of the spiroketal fragment of rutamycin B is reported employing allylsilane bond construction methodology for the introduction of five of the eight stereogenic centers. In this paper, the construction of the C19-C28 and C29-C34 fragments as well as their coupling through an alkylation reaction of a lithiated *N,N*-dimethylhydrazone are described.
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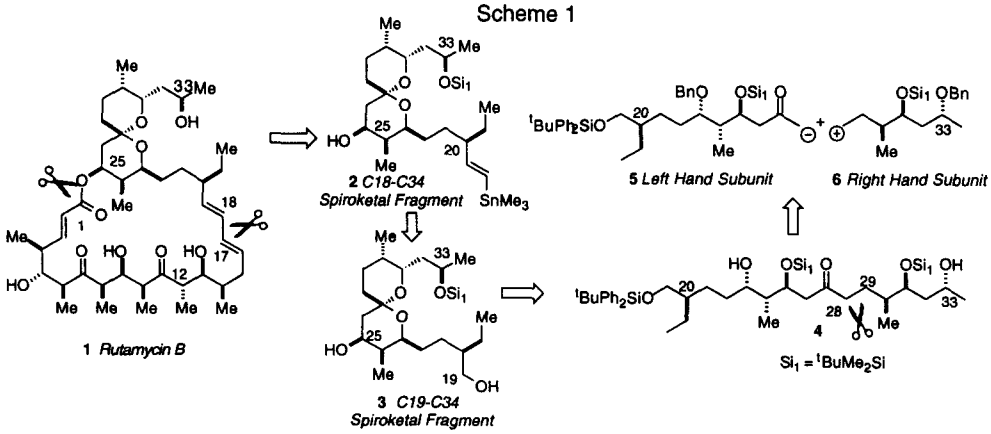
In the preceding paper, the asymmetric synthesis of the C1-C17 polypropionate fragment of rutamycin B was reported.[1] In this communication we wish to report the asymmetric synthesis of the C19-C34 spiroketal fragment which is suitably functionalized for subsequent coupling[2] to the polypropionate fragment. Our synthetic plan for joining these two fragments with the construction of the sp2-sp2 bond at C17-C18 relied on a palladium-based coupling strategy utilizing either vinylstannane / vinyliodide combination[3] or the related vinylboronic acid.[4] The synthetic analysis of the spiroketal, summarized in Scheme 1, involved the opening of the spirocycle to give an acyclic precursor bearing seven stereogenic centers. This should allow enough flexibility with respect to the order of fragment coupling for the assemblage of the structural components of the molecule. Scheme 1 summarizes our planned approach to the spiroketal fragment of the macrolide.[5] The introduction of the stereochemical relationships is based on the application of double-stereodifferentiating crotylation reactions with chiral (*E*)-crotylsilanes.[6]

Scheme 1

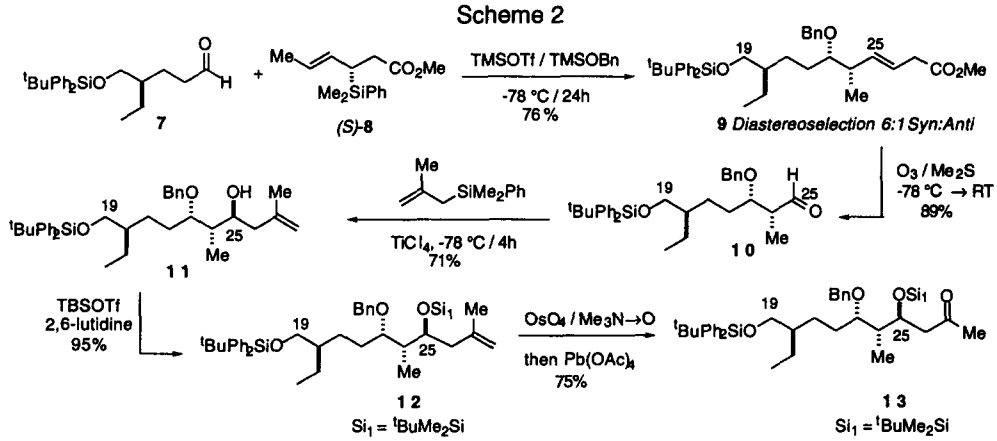


The opened form of the spiroketal, when sectioned into two smaller subunits, the right and left hand subunits, possesses similar synthetic challenges. In the construction of the C19-C34 spiroketal fragment, an alkylation reaction between an enolate, or its equivalent derived from the methyl ketone, with a

fragment bearing a reactive alkylating site was envisioned as an efficient method for the C28-C29 bond construction.

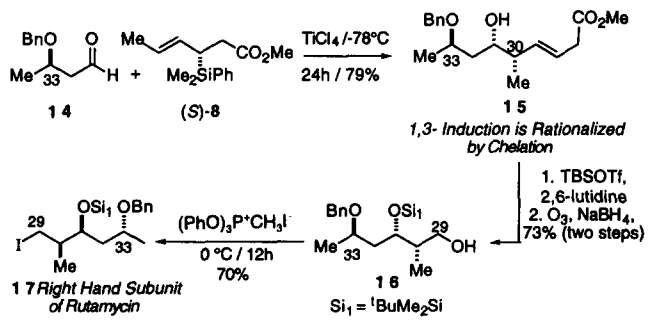
C19-C28 Left Hand Subunit. The synthesis of this subunit of rutamycin B utilizes two related allylation reactions for the introduction of C23-C24 and C25 stereogenic centers. These transformations are illustrated in Scheme 2 and were initiated with a TMSOTf promoted condensation of silane (*S*)-**8** with the chiral aldehyde **7**. This afforded the *syn*-homoallylic ether **9** with useful levels of diastereoselection (6:1 *syn* : *anti*).[7] Oxidative cleavage of the *trans*-double bond under standard ozonolysis conditions yielded the α-methyl aldehyde **10**. The second $TiCl_4$ (1.2 equiv) promoted allylation with the achiral silane reagent exhibited high levels of *anti* 1,3-induction affording the differentiated 1,3-diol derivative **11**. This material was converted to the methyl ketone **13** in two steps: (1) protection of the secondary alcohol with TBSOTf (1.2 equiv) / 2,6-lutidine (1.6 equiv), (2) oxidation of the terminal double bond. The latter transformation was accomplished in a two-step process, employing a dihydroxylation with OsO_4, (0.1 mol%) and TMANO (1.1 equiv).[8] The diol was used without purification in a subsequent oxidative cleavage using $Pb(OAc)_4$ (1.2 equiv) to afford the corresponding methyl ketone.

Scheme 2



C29-C34 Right Hand Subunit. The synthesis of the right hand subunit of of the spiroketal fragment, summarized in Scheme 3, began with a chelate-controlled double-stereodifferentiating crotylation reaction between the β-alkoxy aldehyde **14**[9], and *(S)*-**8**. This pair wise combination was employed for the introduction of the *syn* stereochemical relationship in between C30-C31 while introducing an *anti*-1,3 relationship between the C31-C33 stereogenic centers.[10] This double-stereodifferentiating reaction is most likely a

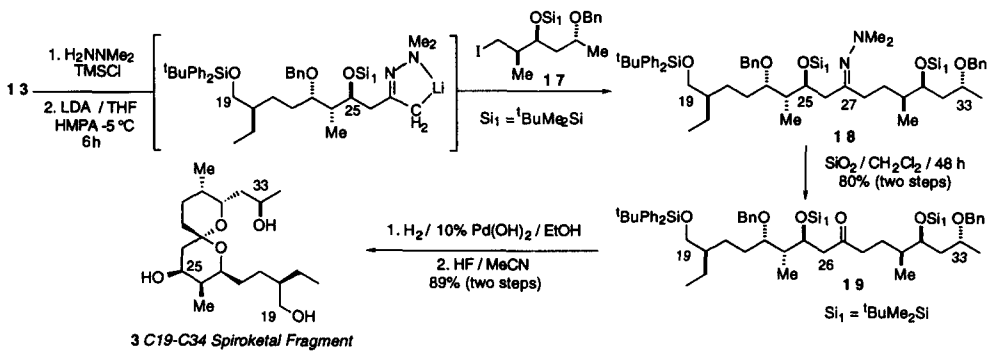
Scheme 3



result of a fully matched pair of reaction partners, as the C31-C33 stereocenters emerge with an *anti* stereochemical relationship from a chelate controlled addition (OBn eclipsing the C=O).[10, 11] This material was converted to the primary iodide in two steps, protection of the secondary alcohol as its TBS ether, followed by the cleavage of the double bond (O_3/MeOH), and reduction with $NaBH_4$ to afford the primary alcohol **16**. The latter was directly converted to the primary iodide **17** with methyl triphenoxy phosphonium iodide[12] thereby completing the synthesis of the right hand subunit.

Synthesis of the Spiroketal C19-C34 Fragment of Rutamycin B. We initially concluded that the most desirable coupling would involve the construction of the C28-C29 bond through the alkylation reaction of the derived ketone enolate of **13**, the C19-C28 subunit, with the primary iodide **17**. The subunit coupling and the synthesis of this fragment are summarized in Scheme 4. The alkylation strategy utilizing the lithium enolate of the *N,N*-dimethyl hydrazone derived from methyl ketone **12** (H_2NNMe_2, TMSCl)[13] and the primary iodide, afforded the alkylated hydrazone **18**.[14] This intermediate was deprotected without purification utilizing a suspension of silica gel[15] in CH_2Cl_2 to obtain the ketone **19** representing the fully protected carbon framework of the spiroketal. The synthesis of the spiroketal fragment was completed in two steps and was initiated with the selective hydrogenolysis of the C23 and C33 benzyl ethers with H_2 (1 atm) over $Pd(OH)_2$ in EtOH at 25 °C. The resulting crude diol was completely deprotected and cyclized with HF in MeCN at room temperature, providing the C19-C35 fragment **3** of rutamycin B. Its spectroscopic and physical properties were identical in all respect (^1H, ^{13}C NMR, IR, $[\alpha]^D$, and MS) with those previously reported from degradation of the natural product.[2b,5a]

Scheme 4



In conclusion, the synthesis of the spiroketal fragment of rutamycin B was completed in a convergent manner where the longest linear sequence is 10 steps from intermediates **7** and **8**. The route is a total of 15 steps in length from **7** and **14** with an overall yield of 24 %. This chemistry demonstrates that the combinations of chiral aldehydes and silane reagents employed efficiently give high levels of selectivity. This work continues the development of our asymmetric allylsilane bond construction methodology as it has been successfully employed in the synthesis of the C19-C34 spiroketal fragment of rutamycin B. The complete details of the total synthesis of rutamycin B will be reported in due course.

Acknowledgment. Financial support was obtained from NIH (RO1 CA56304).

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(*Received in USA* 21 *November* 1996; *revised* 10 *January* 1997; *accepted* 12 *January* 1997)