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Studies Directed Toward the Synthesis of the Rutamycins. Assemblage of the Polypropionate Region of Rutamycin B

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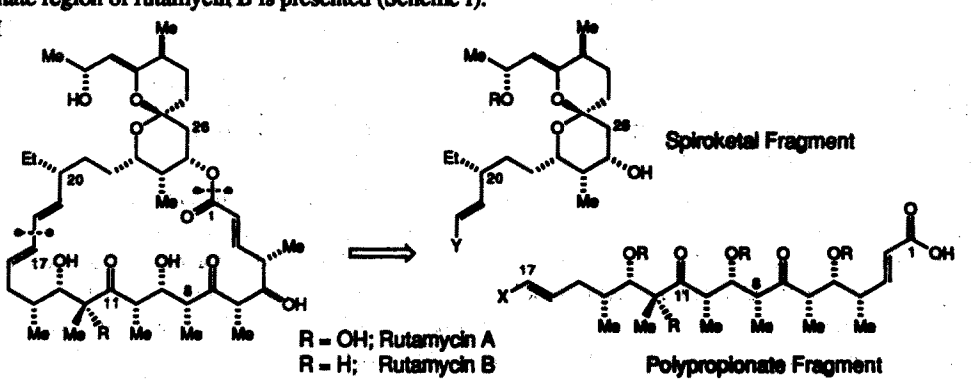
Abstract: The asymmetric synthesis of the polypropionate segment of rutamycin B is reported. In this convergent synthesis the construction of the C_1-C_8 and C_9-C_{17} subunits and their union through a double stereodifferentiating aldol fragment coupling are described. The stereoselectivity of this coupling reaction critically depends on both the configuration and choice of protecting group for the C_9 oxygen.

Recent studies from this laboratory have addressed some of the major challenges associated with the synthesis of the principal representatives in the oligomycin/rutamycin/cytovaricin family of spiroketal antibiotics.[1] In this communication we report our progress directed toward the asymmetric synthesis of the rutamycins.

Rutamycin A was isolated and characterized in 1961 by Thompson[2] from cultures of *Streptomyces griseus*. Several years later, rutamycin B was isolated by Keller-Schierlein[3] from cultures of *Streptomyces aureofaciens*. The structure and relative stereochemical assignment of rutamycin A has been determined by X-ray diffraction.[4] In a recently completed study from this laboratory, an asymmetric synthesis of the rutamycin spiroketal fragment has been achieved.[5] This investigation has established the absolute configuration of the family and provided a practical route to this portion of the natural product. In the following discussion, the synthesis of the illustrated polypropionate region of rutamycin B is presented (Scheme I).

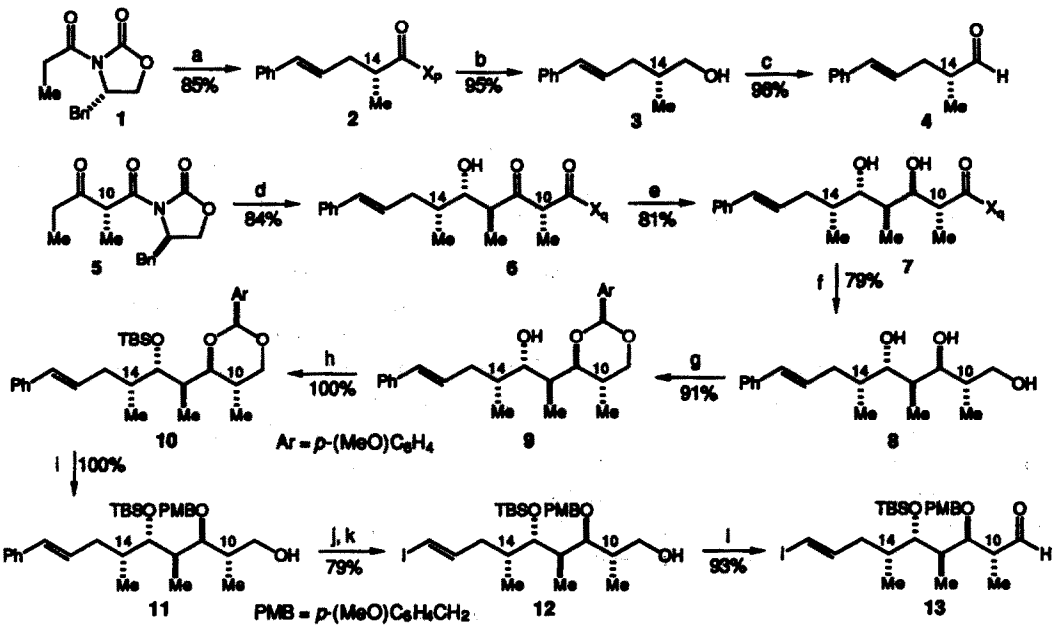
Scheme I



The synthesis of the rutamycin B polypropionate fragment began with the construction of the C_9-C_{17} subunit (Scheme II). Stereoselective alkylation of the sodium enolate derived form chiral imide **1** with cinnamyl bromide afforded the expected product as a mixture of diastereomers (98:2) from which the major diastereomer **2** was isolated in 85% yield after chromatography. Successive reduction ($LiBH_4/H_2O$)[6] and re-oxidation afforded aldehyde **4** which was treated with the (*E*) boron enolate of β-ketoimide[7] **5** to provide the desired *anti* aldol adduct **6** in high diastereoselectivity (97:3). This stereoselectivity is a consequence of the matched double stereodifferentiating nature of this bond construction which has been the subject of another study from this laboratory.[8] Aldol adduct **6** was then reduced to alcohol **7** with complete *anti* selectivity using $NaBH(OAc)_3$.[9] Reductive removal of the

chiral auxiliary was followed by regioselective acetalization of the product triol to afford alcohol **9**, which was subsequently silylated prior to reductive cleavage of the acetal moiety. The benzylidene acetal reduction of **10** with DIBAL-H proceeded with complete positional control to give the fully differentiated primary alcohol **11** in quantitative yield. At this juncture, the styryl group was transformed to the requisite vinyl iodide terminus by oxidative cleavage using $OsO_4/NaIO_4$ followed by homologation employing Takai's chromous chloride procedure[10] ($CrCl_2/CHI_3$) to give a 14:1 (*E*/*Z*) mixture of olefins, separable by preparative HPLC. In independent studies conducted in this laboratory, it has been observed that a significant solvent effect exists in this reaction, and the stereoselection can be significantly altered by manipulating this reaction parameter.[11] Optimum yields and selectivities for the present reaction were obtained by using 6:1 dioxane/THF. Finally, Swern oxidation afforded the target aldehyde **13** in an overall yield of 28% for the eleven-step sequence.

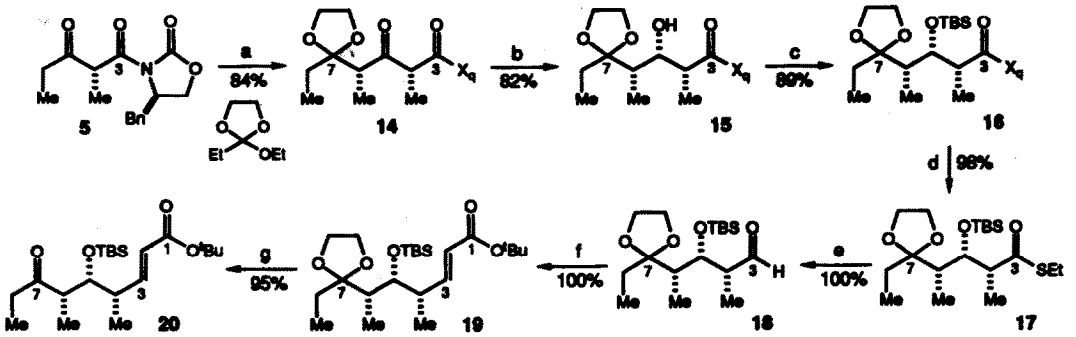
Scheme II



(a) NaHMDS / cinnamyl-Br, THF, -78 °C → 0 °C. (b) $LiBH_4$ / H_2O, Et_2O, 0 °C. (c) Swern Ox. (d) i. $(c\text{-hex})_2BCl$ / $EtNMe_2$, Et_2O, 0 °C. ii. 4. (e) $NaBH(OAc)_3$, AcOH, 23 °C. (f) $LiBH_4$ / H_2O, Et_2O, 0 °C. (g) $ArCH(OMe)_2$ / CSA, DMF, 23 °C. (h) TBSOTf / lutidine, CH_2Cl_2, 0 °C. (i) DIBAL-H, CH_2Cl_2, 0 °C. (j) i. OsO_4 / NMO, *t*-BuOH / THF / H_2O, 23 °C. ii. $NaIO_4$ / $NaHCO_3$, H_2O, 23 °C. (k) $CrCl_2$ / CHI_3, dioxane / THF, 23 °C. (l) Swern Ox.

Synthesis of the C_1-C_8 subunit was initiated by acylation[12] of the the titanium enolate derived from β-ketoimide **5** with the propionate-derived orthoester $EtC(OCH_2CH_2O)OEt$ to give the ketal **14** in good yield (84%) and diastereoselectivity (93:7) (Scheme III). The facial bias exhibited in this reaction is that expected from electrophilic attack on the chelated (*Z*) titanium enolate. Highly selective reduction of **14** to alcohol **15** with $Zn(BH_4)_2$ (>97:3) was followed by successive silylation and transesterification with EtSH/*n*-BuLi[13] to give the thioester **17**. Reduction of this ester to aldehyde **18** was accomplished using the Fukuyama procedure[14] (Et_3SiH/Pd(C), acetone). It is noteworthy that this reaction sequence has proven to be attractive for a number of challenging imide → aldehyde transformations which we have recently encountered.[15] The completion of this subunit was achieved by Horner-Emmons olefination of **18** followed by deketalization ($FeCl_3$-SiO_2, acetone) to provide ketone **20** in 57% overall yield for the seven-step sequence.

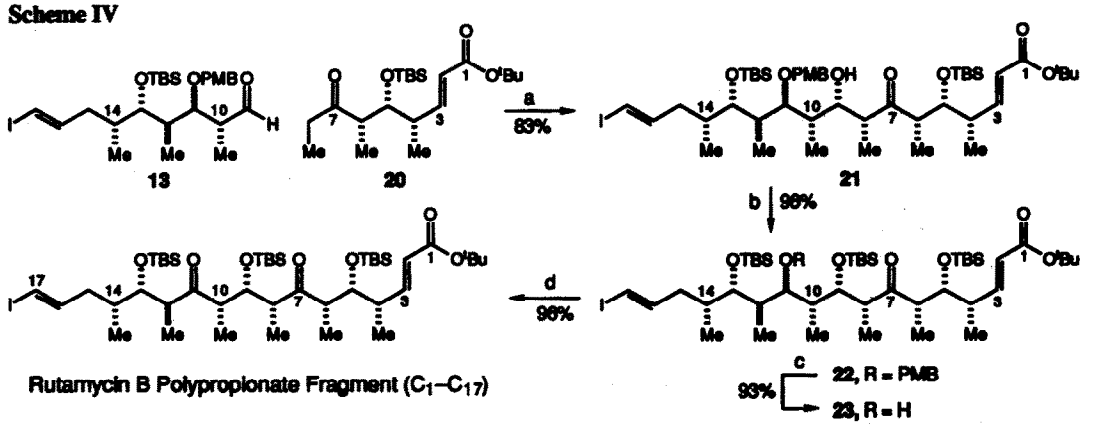
Scheme III



(a) i.$TiCl_4$ / *i*-Pr_2NEt, CH_2Cl_2, -78 °C. ii. $EtC(OCH_2CH_2O)OEt$, -20 °C. (b) $Zn(BH_4)_2$, CH_2Cl_2, -20 °C. (c) TBSOTf / lutidine, CH_2Cl_2, 0 °C. (d) EtSH / *n*-BuLi, THF, -78 °C → 0 °C. (e) Et_3SiH / Pd/C, acetone, 23 °C. (f) $(EtO)_2P(O)CH_2CO_2{}^tBu$ / *n*-BuLi, THF, 23 °C. (g) $FeCl_3$-SiO_2, acetone, 23 °C.

The crucial fragment coupling was achieved through the aldol union of aldehyde **13** with the titanium enolate[16] derived from ketone **20** which afforded the *syn* adduct **21** in high yield (83%) and diastereoselectivity (97:3) (Scheme IV). Silylation of β-hydroxy ketone **21** at reduced temperature (-30 °C, 24 h) and oxidative removal of the PMB protective group (DDQ) produced alcohol **23** which was transformed to the completed rutamycin B fragment through Dess-Martin oxidation.[17]

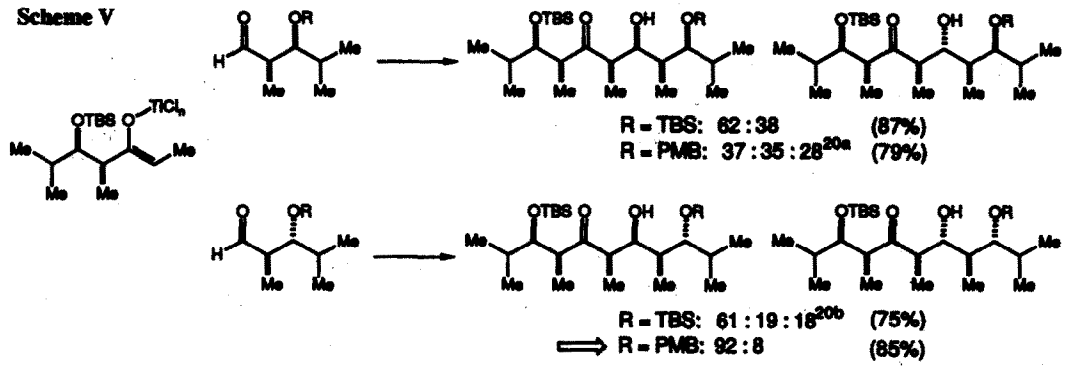
Scheme IV



(a) $TiCl_4$ / *i*-Pr_2NEt, CH_2Cl_2, -78 °C. (b) TBSOTf / lutidine, CH_2Cl_2, -30 °C. (c) DDQ, CH_2Cl_2, 5 °C. (d) Dess-Martin periodinane, pyr, CH_2Cl_2, 23 °C.

The aldol fragment coupling illustrated above is striking. Numerous studies involving double stereodifferentiating aldol reactions have established that (*Z*) enolates are typically more selective for the *anti*-Felkin aldehyde diastereoface.[18] Since enolate addition to the Felkin aldehyde diastereoface was desired, in the illustrated coupling, conventional wisdom led us to anticipate poor selectivity for this reaction. However, we have found from related studies (Scheme V) that both the stereochemistry and the nature of the protecting group at the β-stereocenter of the aldehyde play crucial roles in determining the stereochemical outcome of these coupling reactions.[19] A complete data set of structural variants for closely related aldol reactions is provided below. As is evident from these cases, only one of the four possible permutations of the β-stereocenter and associated protecting group on the aldehyde fragment lead to a stereoselective aldol bond construction.

Scheme V



Studies on the total synthesis of the rutamycins will be reported in due course.

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(20) (a) This other isomer is the other *syn* aldol adduct; (b) This other isomer is the other *anti* aldol adduct.

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