Total Synthesis of Rutamycin B and Oligomycin C

James S. Panek* and Nareshkumar F. Jain†

Department of Chemistry, Metcalf Center for Science and Engineering and Center for Streamlined Synthesis, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

Panek@chem.bu.edu

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The asymmetric synthesis of the macrolide antibiotics (+)-rutamycin B (**1**) and (+)-oligomycin C (**2**) is described. The approach relied on the synthesis and coupling of the individual spiroketal fragments **3a** and **3b** with the C1−C17 polyproprionate fragment **4**. The preparation of the spiroketal fragments was achieved using chiral (*E*)-crotylsilane bond construction methodology, which allowed the introduction of the stereogenic centers prior to spiroketalization. The present work details the synthesis of the C19−C28 and C29−C34 subunits as well as their convergent assembly through an alkylation reaction of the lithiated *N,N*-dimethylhydrazones **6** and **8** to afford the individual linear spiroketal intermediates **5a** and **5b,** respectively. After functional group adjustment, these advanced intermediates were cyclized to their respective spiroketal-coupling partners **40** and **41**. The requisite polypropionate fragment was assembled in a convergent manner using asymmetric crotylation methodology for the introduction of six of the nine-stereogenic centers. The use of three consecutive crotylation reactions was used for the construction of the C3−C12 subunit **32**. A Mukaiyama-type aldol reaction of **35** with the chiral α-methyl aldehyde **39** was used for the introduction of the C12−C13 stereocenters. This anti aldol finished the construction of the C3−C17 advanced intermediate **36**. A two-carbon homologation completed the construction of the polypropionate fragment **38**. The completion of the synthesis of the two macrolide antibiotics was accomplished by the union of two principal fragments that was achieved with an intermolecular palladium-(0) catalyzed cross-coupling reaction between the terminal vinylstannanes of the individual spiroketals **3a** and **3b** and the polypropionate fragment **4.** The individual carboxylic acids **46** and **47** were cyclized to their respective macrocyclic lactones **48** and **49** under Yamaguchi reaction conditions. Deprotection of these macrolides completed the synthesis of the rutamycin B and oligomycin C.

Introduction

The oligomycins are members of a family of macrolide spiroketal antibiotics.[2] Mixtures of the oligomycin antibiotics isolated in 1954[2] from a strain of *Streptomyces diastatochromogesnes* consisted of variable proportions of three major components A, B, and C.[3] The structures and absolute configuration of oligomycin A and C were established by chemical correlation of their individual degradation products with those derived from rutamycin B (Scheme 1). The structure of which had already been established.[4] Oligomycin B was the first of this class of natural products to have its structure elucidated. This was accomplished through the combined use of spectroscopic and X-ray crystallography experiments.[5]

Rutamycin A and B are also members of the oligomycin family.[6] These structurally related natural products were initially isolated in 1961 by Thompson[7] from the cultures of *Streptomyces griseus* and later by Keller-Schierlein[8] from the cultures of *Streptomyces aureofaciens* in 1984, respectively. The structure and relative stereochemistry of the rutamycins were determined by X-ray diffraction studies.[9] The absolute stereochemistry has been determined by chemical synthesis of the spiroketal fragment and comparison with the naturally occurring spiroketal fragment obtained by degradation of the natural product.[10] The complex structures and stereochemical arrays associated with these macrolides have created exciting challenges for chemical synthesis. Indeed, recent synthetic efforts of certain members of this class of natural products have been carried out using chiral enolate-based bond construction methodology. In this paper, we report the convergent asymmetric syntheses of rutamycin B and oligomycin C. A continuing objective of this program has been the development and utilization of a class of

† Current address: The R. W. Johnson Pharmaceutical Research Institute, Raritan NJ.

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(2) Smith, R. A.; Peterson, W. H.; McCoy, E. *Antibiot. Chemother.* **1954**, *4*, 962−970.

(3) Vissser, J.; Weinaurer, D. E.; Davis, R. C.; Peterson, Nazarewicz, W.; Ordway H, J. *Biochem. Microbiol. Technol. Eng.* **1960**, *2*, 31−48

(4) Carter, G. T. *J. Org. Chem.* **1986**, *51*, 4264−4271.

(5) Sakurai, T.; Kihara, T.; Isono, K. *Acta Crystallogr.* **1983**, *C39*, 295−297.

(6) For leading references, see: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569−3624. (b) Boeckman, R. K.; Goldstein, S. W. *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1988; Vol.7, pp 1−139 (c) Kobayashi, K.; Nishino, C.; Ohya, J.; Sato, S.; Shiobara, Y.; Nishimoto, N. *J. Antibiot.* **1987**, *40*, 1053−1057

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(8) (a) Wuthier, D.; Keller-Schierlein, W. *Helv. Chim. Acta* **1984**, *67*, 1208−1216. (b) Szilagyi, L.; Feher, K. *J. Mol. Struct.* **1998**, *471*, 195−207.

(9) Arnoux, B.; Garcia-Alvarez, M. C.; Marazano, C.; Bhupesh, C. D.; Pascard, C. *J. Chem. Soc., Chem. Commun* **1987**, 318−319.

(10) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260−6268.

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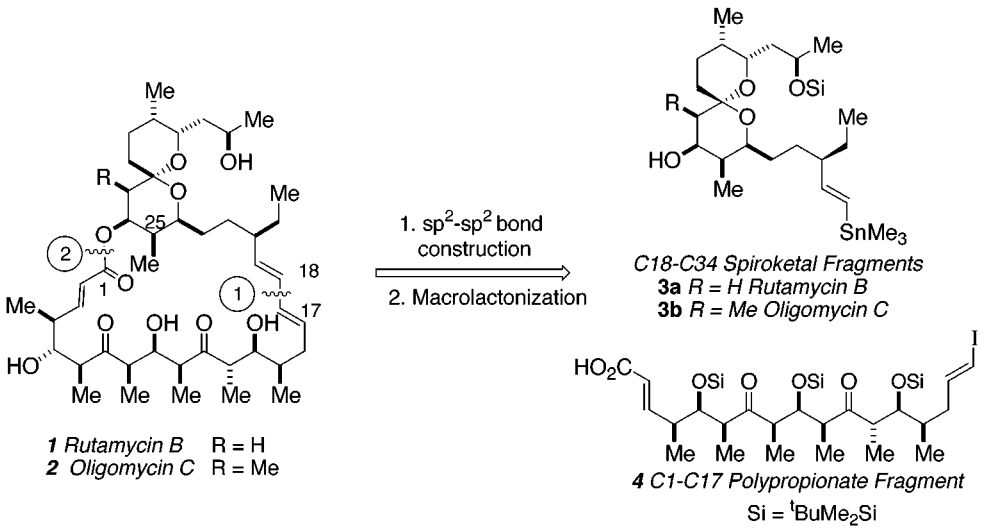
Scheme 1



chiral silicon reagents bearing C-centered chirality. We had hoped that these reagents might someday be used as a reliable complement to the well-developed chiral metal enolate-based and aldol surrogate methodologies for the construction of polypropionate-like subunits. The synthetic approach for the introduction of the stereogenic centers is based largely on the development and application of chiral allylsilane bond construction methods. In the context of acyclic stereocontrol, these reaction processes rely on the use and proper choice of silane reagent and Lewis acid type to deliver the anticipated relative and absolute stereochemical relationship(s).

Oligomycins and rutamycins share a common 1,7-dioxaspiro[5.5]undecanyl ring system displayed off of a 26-membered macrolide. The macrolide portions of these natural products share an identical polypropionate fragment bearing nine stereogenic centers. Several members of the oligomycin family are structurally closely related and differ by the carbon oxidation state at C28 and by the substitutions at C26 and C12. Other members of the oligomycin group include cytovaricin,[11] phthoramycin,[12] kaimonolide A,[13] NK86-0279I, and NK86-0279II.[14]

Biological Activity. The oligomycins are cytotoxic molecules that have been shown to inhibit oxidative phosphorylation in mitochondria by preventing synthesis of ATP.[15] Their mode of action is believed to involve the decoupling of the F0 and F1 factors, which are responsible for facilitating proton transfer through the inner mitochondria membrane. Although not documented experimentally, a protein−oligomycin complex is thought to exist between the oligomycin-sensitivity-conferring protein (OSCP) and the natural product. It is this "drug−protein" complex which is thought to prevent oxidative phosphorylation. The OSCP is located in the stalk between the F0 and F1 factors. As such, these natural products may serve as potential biological probes and have already been used in the exploration of oxidative phosphorylation.[16]

The conformational resemblance encountered between rutamycins/oligomycins and cytovarycins has been used to explain their similar bioactivity. Despite the similarities shared between these natural products, the oligomycins pose a different set of synthetic challenges from cytovaricin. The most prominent feature of the oligomycins is the 26-membered macrocyclic lactone, in which nine stereocenters are located in the propionate derived region of the molecule (C4−C14) while the remaining eight stereocenters (seven for rutamycin B) are located in the spiroketal fragment (C20−C34).

Retrosynthetic Analysis of Rutamycin B and Oligomycin C. Following the successful use of a Suzuki cross coupling reaction employed by Evans[17] and White[18] in their syntheses of rutamycin B, the natural products were dissected into their individual spiroketal and identical polypropionate fragments. Our approach to the synthesis of rutamycin and oligomycin is shown in Scheme 1, which has been successfully employed in our synthesis of oligomycin C.[19] Disconnection at the C1-ester linkage and at the C17−C18 *(E,E)*-diene gives the spiroketal fragments **3a** and **3b** and the polypropionate fragment **4**. The regeneration of the (*E*,*E*)-diene unit, employing a palladium (0)-mediated cross coupling between the vinylstannane of the spiroketals and the vinyl

(11) (a) Kihara, T.; Kusakabe, H.; Nakamura, G.; Sakurai, T.; Isono, K. *J. Antibiot.* **1981**, *34*, 1073−1074. (b) Total synthesis: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001−7031.

(12) Nakagawa, A.; Miura, S.; Imai, H,.; Imamura, N.; Omura, S. *J. Antibiot.* **1989**, *42*, 1324−1327.

(13) Hirota, A.; Okada, H.; Kanza, T.; Nakayama, M,; Hirota, H.; Osagai, A. *Agric. Biol. Chem.* **1989**, 53, 2831−2833.

(14) Yamazaki, M.; Yamashita, T.; Harda, T.; Nishikiori, T.; Saito, S.; Shimada, N.; Fujii, A. *J. Antibiot.* **1992**, *45*, 171−179.

(15) Pederson P. L.; Carafoli, E. *Trends Biochem. Sci.* **1987**, *12*, 146−160.

(16) (a) Lardy, H. A.; Johnson D.; McMurray, W. C. *Arch. Biochem. Biophys.* **1958**, *78*, 587−597. (b) Lardy, H. A.; Witocky P.; Jonhson, D. *Biochem.* **1965**, *4*, 552−554.

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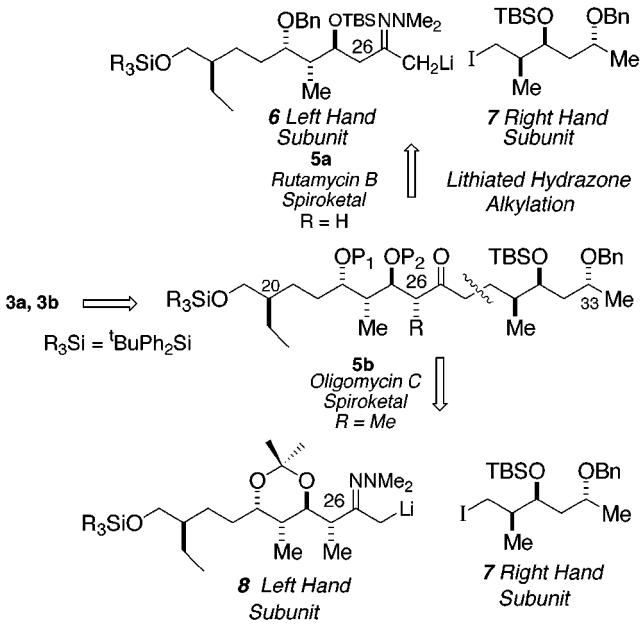
(18) (a) White, J. D.; Tiller, T.; Ohba, Y.; Porter, W.; Jackson, R. W.; Wang, S.; Hanselmann, R. *Chem. Commun.* **1998**, *1*, 79−80. (b) White, J. D.; Porter, W. J.; Tiller, T. *Synlett* **1993**, 535−538.

(19) (a) Synthesis of oligomycin C: Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1998**, *63*, 4572−4573. (b) Jain, N. F.; Panek, J. S. *Tetrahedron Lett.* **1997**, *38*, 1345−1348. (c) Jain, N. F.; Panek, J. S. *Tetrahedron Lett.* **1997**, *38*, 1349−1352.

Scheme 2

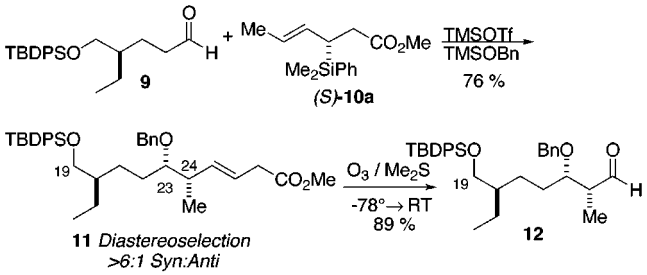


iodide of **4** precedes ring closure by macrolactonization at C1 with the C25-hydroxyl.[20]

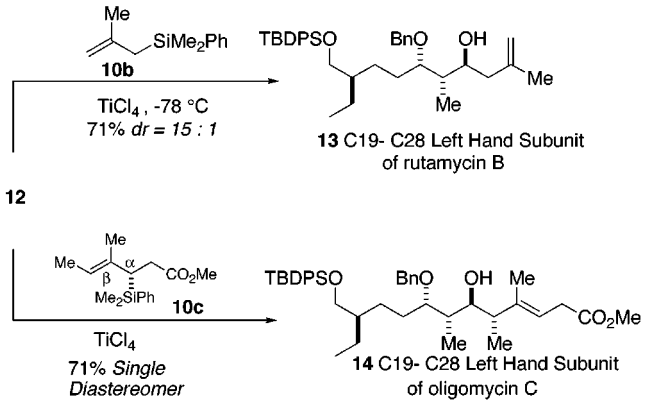
The Spiroketal Fragments of Rutamycin B and Oligomycin C. Retrosynthetic analysis of the spiroketal fragment of rutamycin B and oligomycin C gave the C18−C34 subunit bearing *E*-vinylstannanes, which was derived from the corresponding *E*-vinyl iodide through a palladium(0)-catalyzed halogen/trialkyl stannane exchange. Opening of the individual spiroketals **3a** and **3b** gave an advanced intermediate **5a** bearing seven stereocenters for rutamycin B and eight for oligomycin C (Scheme 2). In both cases, disconnection at C28−C29 furnished their respective C19−C28 left-hand subunits **6** and **8** and an identical C29−C34 right-hand subunit **7**.

The following section describes the detailed synthesis and coupling of the spiroketal subunits of rutamycin B and oligomycin C. In an effort to avoid any late stage stereochemical adjustments or oxidation state changes, a stereocontrolled route was designed that planned for the introduction of all the stereocenters prior to spiroketalization. Chiral aldehyde **9**, which was synthezised in seven steps starting from the commercially available ethyl diethyl malonate[21] underwent an in situ acetalization followed by an asymmetric crotylation to the derived oxonium ion to give the C23−24 syn stereochemistry of the benzyl protected homoallylic alcohol **11** (Scheme 3). This three component crotylation proceeded with useful levels of diastereoselection (syn/anti 6:1) and in 76% yield.[22] Oxidation of the *trans*-olefin under standard

Scheme 3



Scheme 4

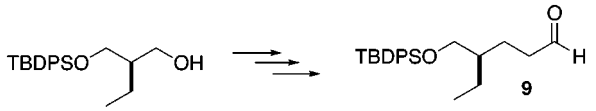


ozonolysis conditions (O_3/DMS) yielded α-methyl aldehyde **12**. This material was then subjected to a $TiCl_4$-promoted allylation with 2-methylallyl dimethylphenyl silane **10b** to afford **13** in 71% yield (dr = 6:1 anti/syn) with the (*S*)-stereochemistry of the emerging hydroxyl group being preferred presumably by chelation of a bidentate Lewis acid with the *β*-hydroxyl group and the aldehyde. This reaction resulted in the construction of the C19−C28 subunit of the rutamycin spiroketal (Scheme 4). In a similar fashion, aldehyde **12** was subjected to $TiCl_4$-promoted double-stereodifferentiating crotylation reaction using the methyl-substituted silane **10c** to give **14** as a single diastereomer (71% yield).[23] This crotylation product, comprising anti stereochemistry between the newly installed methyl and hydroxyl groups, occurred with anti-Felkin induction (Scheme 4). The use of silane **10c** permitted the introduction of a trisubstituted olefin, which was intended for use as a methyl ketone synthon through an oxidative cleavage. This transformation completed the construction of the C19−C28 left-hand subunit of oligomycin C bearing five stereogenic centers. Once again, the stereochemistry can be rationalized by the addition of the chiral silane to the *si* face of the aldehyde preferred by the use of a bidentate Lewis acid which chelates to the aldehyde oxygen and C23 oxygen.

Once an efficient preparation of the left-hand subunits of rutamycin B and oligomycin C had been achieved, the next objective was aimed at the synthesis of the right-hand subunit of the individual spiroketals. Those experiments are summarized in Scheme 5. In that regard, the primary iodide **18** which is the same for both the synthesis of rutamycin B and oligomycin C was prepared by an initial $TiCl_4$ promoted crotylsilane addition of **10a**

(20) (a) Stille, J. K.; Groh, B. L *J. Am. Chem. Soc.* **1987**, *109*, 813−817. (b) Stille. J. K.; Sweet, M. P. *Tetrahedron Lett.* **1989**, *30*, 3645−3648. (b) Nicolaou, K. C.; Chakraborty, T. K.; Picopio A. D.; Minowa N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419−4420.

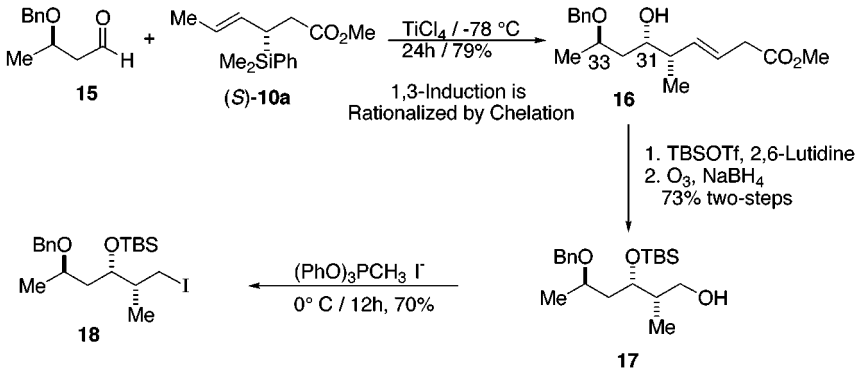
(21) See Supporting Information for experimental procedures for the synthesis of aldehyde **9**.



(22) (a) Panek, J. S.; Yang, M.; Xu, F. *J. Org. Chem.* **1992**, *57*, 5790−5792. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316.

(23) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem.* **1996**, *118*, 12475−12476.

Scheme 5



to the known β-alkoxy chiral aldehyde **15**.[24] The anticipated syn homoallylic alcohol was obtained in 79% yield with a selectivity greater than 15:1 (syn/anti), introducing a 1,3-anti relationship between C31−C33 stereogenic centers.[25] Presumably, this crotylation reaction using a bidentate Lewis acid ($TiCl_4$) proceeds through a Cram chelate transition-state model. Protection of the secondary-hydroxyl as its TBS ether was followed by standard ozonolysis (O_3/Me_2S). The crude aldehyde was reduced with $NaBH_4$ to produce primary alcohol **17** in 73% yield over two steps**.** The resulting alcohol was directly converted to the primary iodide **18** in 70% yield using triphenoxy phosphomium iodide,[26] which completed the synthesis of the right-hand subunit and was used directly in the alkylation reaction with the left-hand subunit.

With the required spiroketal subunits in our possession, the elaboration to the individual spiroketals **40** and **41** was investigated. In a parallel format, Scheme 6 summarizes the spiroketal syntheses of rutamycin B and oligomycin C, path A and B, respectively. In that regard, the spiroketal synthesis of rutamycin B (path A) was initiated with the protection of the C25 hydroxyl group (TBSCl/imidazole) yielding the protected homoallylic alcohol **20** in 95% yield. Osmium tetraoxide catalyzed dihydroxylation of the terminal olefin followed by lead tetraacetate promoted cleavage of the resulting diol yielded methyl ketone **20**. Our initial attempts to couple the ketone enolate derived from **20** with iodide **18** proved unsuccessful as only small amounts of the desired alkylation product could be obtained. Due to the low reactivity of the methyl ketone enolate, the lithiated *N*,*N*-dimethyl hydrazone derived from the methyl ketones **20** and **22** were used to provide for a more efficient subunit coupling in the assembly of the spiroketal fragments. Hydrazone formation was accomplished using *N*,*N*-dimethyl hydrazine and TMSCl[27] which was converted to the lithiated hydrazone by treatment with LDA (1.5 equiv) in THF. This intermediate participated in a smooth alkylation with the primary iodide **18** to give the coupled product **23** that was directly subjected to hydrazone hydrolysis without further purification. The hydrazone was hydrolyzed using silica gel and dichloromethane for 2 days providing the ketone in 80%. Removal of the benzyloxy protecting group by hydrogenolysis followed by deprotection of the silyl enol ethers with HF in acetonitrile gave the spiroketal fragment **40** of rutamycin B in 89% yield.

The synthesis plan for the construction of the spiroketal of oligomycin C is also summarized in Scheme 6, path B. Overall, the plan closely follows the one which was implemented in the synthesis of the rutamycin spiroketal fragment. Deprotection of the C23 benzyl group of **14** was followed by ketalization with dimethoxypropane yielded the acetonide **21** in 71% yield for two steps. Ozonolysis of the trisubstituted olefin gave aldehyde **22**, which was converted to the *N*,*N*-dimethylhydrazone using 1,1-dimethyl hydrazine and TMSCl. Deprotonation of the hydrazone (LDA/THF) followed by alkylation with iodide **18** gave the coupled product **24** in 78% yield. Deprotection of both silyl protecting groups and cyclization using HF in acetonitrile followed by debenzylation by hydrogenolysis yielded the spiroketal fragment of oligomycin C **41** in 65% over two steps. At this stage, the synthesis of both spiroketals of rutamycin and oligomycin were completed. The assignment of stereochemistry of the spiroketals was secured by comparison with literature values. Accordingly, a careful comparison of the published spectroscopic data, including ^1H and ^{13}C NMR spectra of the sprioketal of rutamycin B, a known degradation product, with our synthetic material was shown to be identical.[10]

Retrosynthetic Analysis of the C_1−C_{17} Polypropionate Fragment of Rutamycin B and Oligomycin C. The plan for the synthesis of the polypropionate fragment of rutamycin B and oligomycin C is outlined in Scheme 7 and relied extensively on the use of our chiral silane reagents for the introduction of the stereochemical relationships. In fact, six of the nine stereogenic centers were introduced using the asymmetric crotylations. Disconnection of the polypropionate fragment at C12−C13 bond yields two components: the C1−C12 ethyl ketone subunit and the C13−C17 α-methyl aldehyde **39**. This bond construction relies on a double-stereodifferentiating anti aldol reaction with Felkin selectivity,[28] employing a Mukaiyama-like aldol involving a (*Z*)-(*O*)-silyl enol ether. We had anticipated that the C3−C12 subunit maybe constructed by three consecutive double-stereodifferentiating syn crotylation reactions at C5−C6, C7−C8, and C9−C10. The C13−C17 subunit **9** could be

(24) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833−4835.

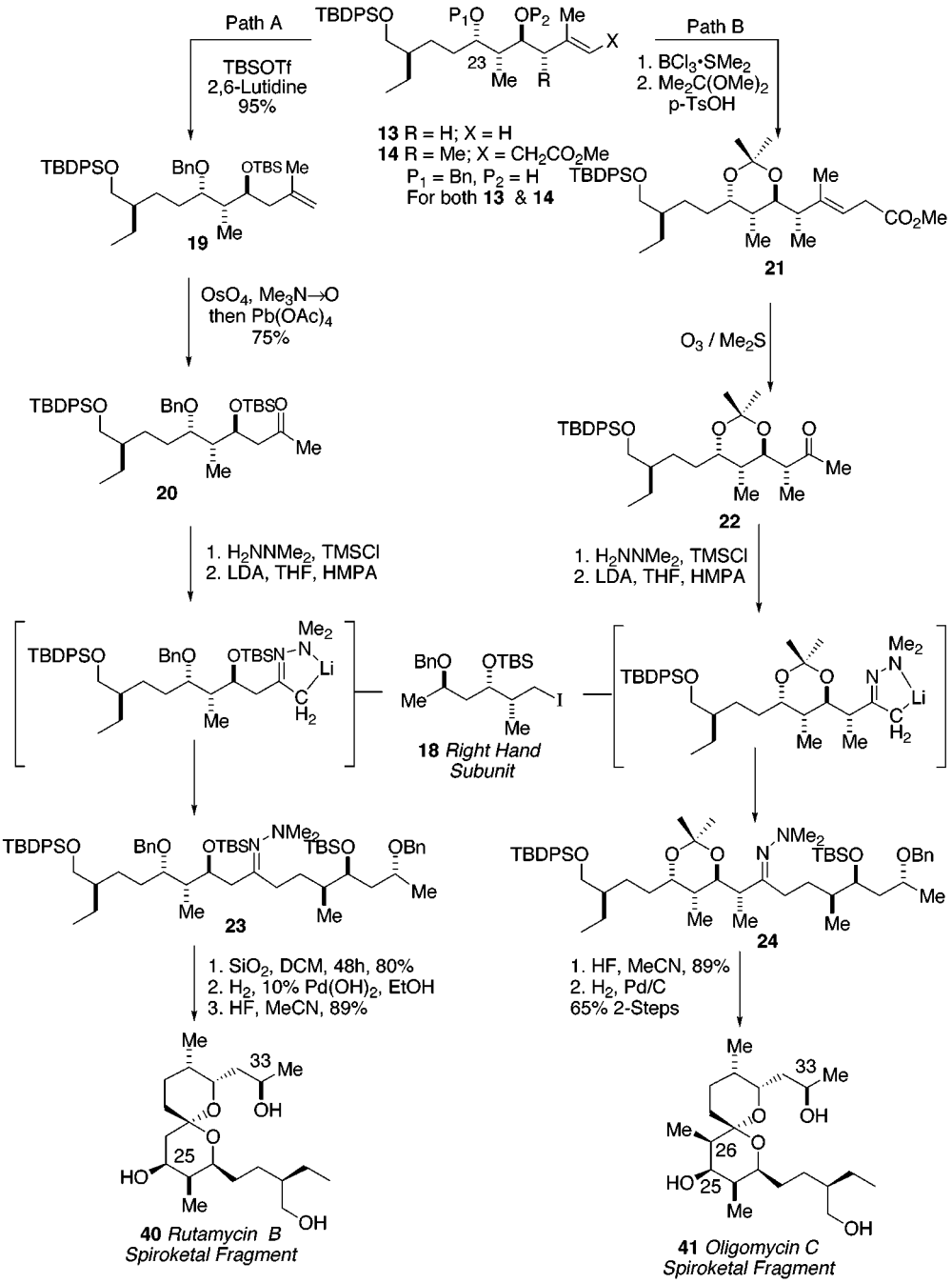
(25) (a) Cram, D. J.; Kopecky, K., R. *J. Am. Chem. Soc.* **1959**, *81*, 2748−2755. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468.

(26) Maguire, A. R.; Meng, W.; Roberts, S. M.; Whilletts, A. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, *24*, 1795−1808.

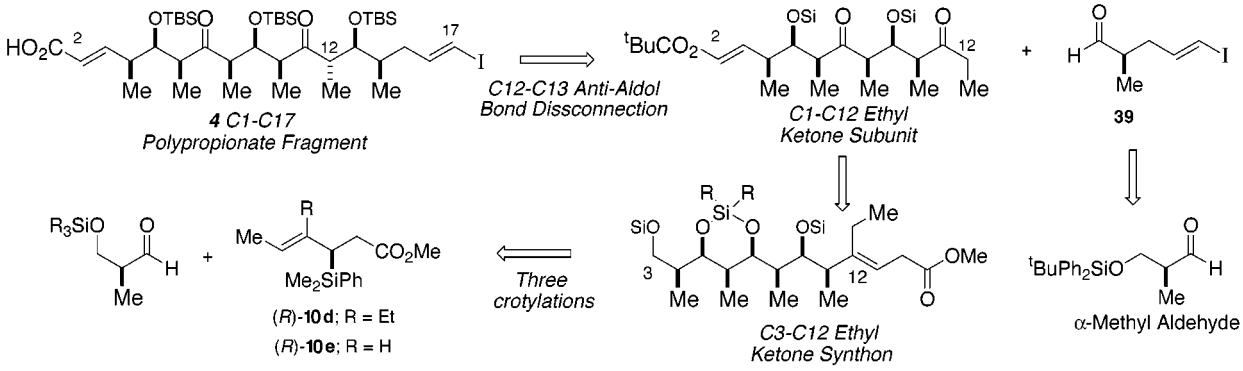
(27) Evans, D. A.; Bender, S. L.; Morrisy J. *J. Am. Chem. Soc.* **1988**, *110*, 2506−2526.

(28) *(E)*-Lithium enolates and *(E)*-boron enolates are known to give propionate aldol products with anti stereochemistry and Felkin induction; see: (a) Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1996**, *37*, 1957−1960 and references therein. (b) Paterson, I.; Perkin, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608−1610.

Scheme 6



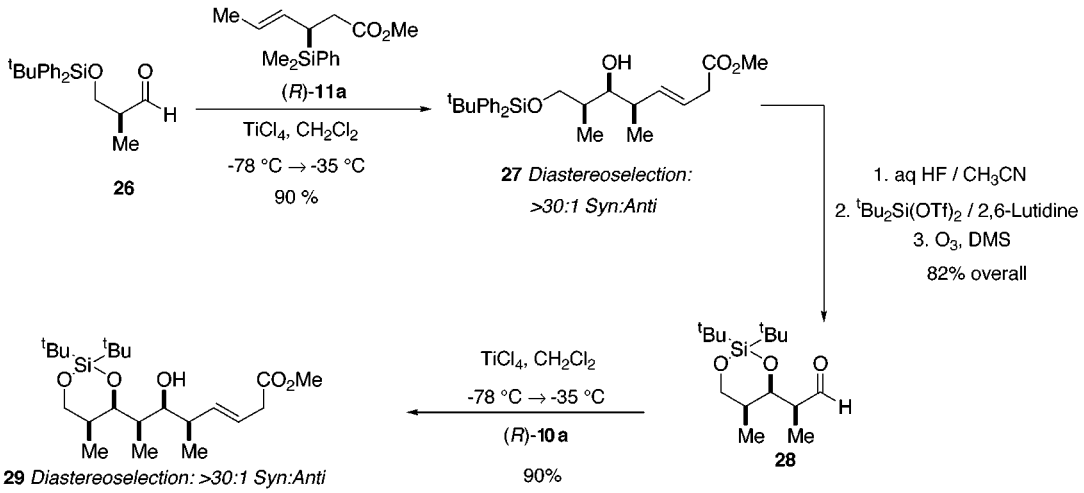
Scheme 7



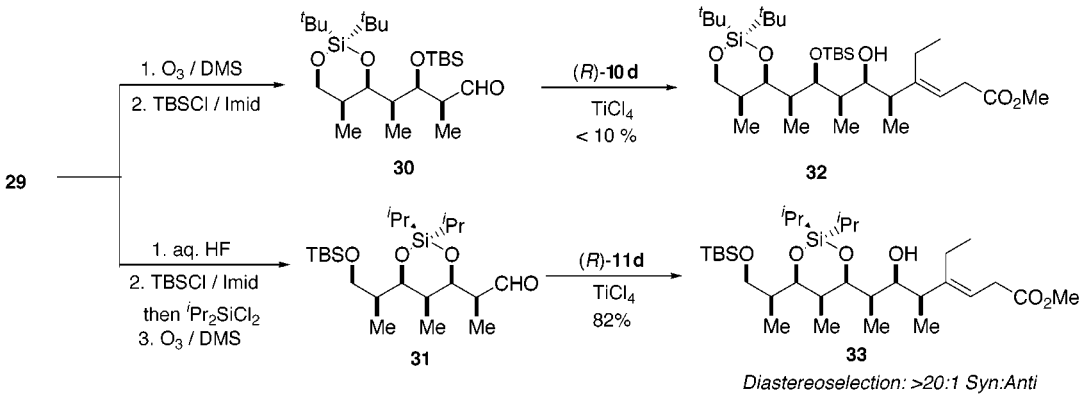
synthesized from the chiral α-methyl aldehyde using Takai's protocol to introduce the *(E)*-vinyl iodide.[29]

Synthesis of the C_1−C_{17} Polypropionate Fragment. Our synthesis of this fragment was initiated with

Scheme 8



Scheme 9



the reaction of the chiral aldehyde **26** and was condensed with crotylsilane **11a** in the presence of $TiCl_4$ in CH_2Cl_2 at −78 °C to yield homoallylic alcohol **27** with 30:1 syn/anti ratio (Scheme 8). Deprotection of the primary hydroxyl group using aqueous HF was followed by cyclic silylene formation using di-*tert*-butyl-silylditriflate in the presence of 2,6-lutidine afforded the protected 1,3-diol. Oxidative cleavage of the olefin under standard ozonolysis conditions (O_3/DMS) gave aldehyde **28**. Condensation of aldehyde **28** with (*R*)-**11a** was again promoted by $TiCl_4$ to yield homoallylic alcohol **29** with excellent levels of diastereoselctivity, dr >30:1 *syn: anti*.

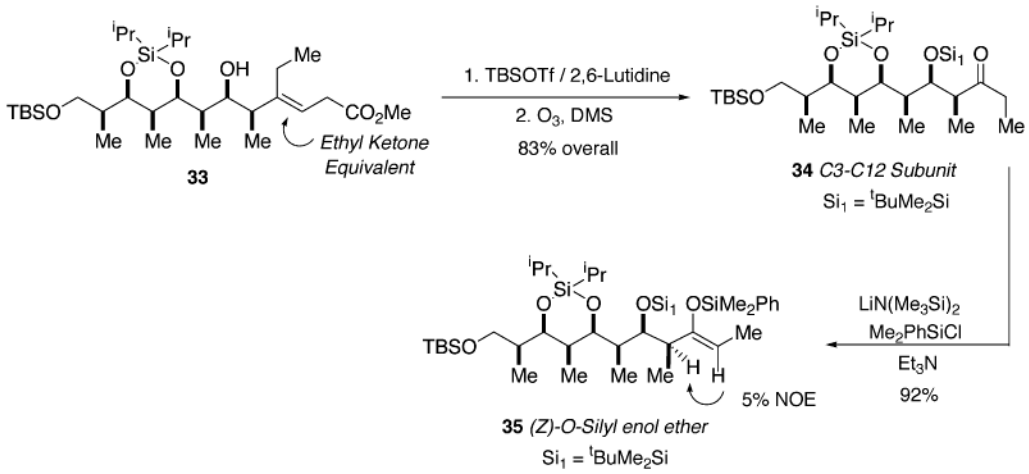
At this crucial point in the synthesis of the polypropionate fragment we were nearly ready for the third crotylation, which is used for the introduction of the final two stereocenters of the C3−C12 ethyl ketone synthon. Accordingly, homoallylic alcohol **29**, was converted to aldehyde **30** with the anticipation that this material could be used in the final crotylation reaction with the ethyl substituted silane (*R*)-**11d** (Scheme 9). Disappointingly, after a considerable number of experiments were carried out, we were unable to achieve an efficient condensation for the formation of homoallylic alcohol **32**. We concluded that the low reactivity of aldehyde **30** was brought about from a stereic and/or conformational change associated with the terminal silylene. We have learned that this particular 1,3-diol protecting group results in the formation of a Lewis acid-aldehyde complex that is unreactive and resistant to the crotylation with **11d**. Indeed, we could obtain the desired homoallylic alcohol **32** in yields no higher than 10% along with the recovery of the starting aldehyde (ca. 45%). Accordingly, this poor efficiency of this crotylation forced us to reconsider the silicon-based hydroxyl protecting group strategy. The terminal cyclic silylene was removed with HF in acetonitrile, the primary alcohol was protected as a silyl ether with *tert*-butyl dimethylsilyl chloride and imidazole followed by concomitant formation of the internal cyclic silylene with diisopropyl dichlorosilane.[30] This one-pot operation afforded the fully protected intermediate, which was converted to the α-methyl aldehyde **31** by ozonolysis. In direct contrast, aldehyde **31**, bearing the internal cyclic silylene smoothly participated in the double-stereodifferentiation reaction with (*R*)-silane **11d** to afford the desired homoalylic alcohol **33** in 82% and as a single diastereomer. Although a case for a steric argument can be made, the precise nature of the reactivity difference resulting from the repositioning of the silicon protecting group (aldehydes **30** and **31**) cannot at this time be explained. However, the movement of the 1,3-diol protecting group to an internal position certainly provided enhanced reactivity in this paticular double-stereodifferentiating crotylation reaction.

Protection of the secondary hydroxyl of **33** as a TBS ether, followed by cleavage of the substituted olefin under

(29) Takai, K.; Nitta, K.; Ulimoto, K. J. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(30) Attempts to effect silylene formation using di-*tert*-butyldichlorosilane proved to be unsuccessful, presumably from severe steric destabilizing interactions.

Scheme 10



standard ozonolysis conditions (O_3/DMS) yielded ethyl ketone **34** in 83% yield. The (*Z*)-*O*-silyl-enol ether **35** was formed in 92% yield by the selective enolization of **34** with lithium bis(trimethyl)disilazide[31] and subsequent trapping with dimethylphenylsilyl chloride in the presence of triethylamine (Scheme 10), whose stereochemistry was assigned by the measurements of NOEs.

Mukaiyama Aldol Coupling. With the required advanced intermediates now available, the crucial double-stereodifferentiating aldol reaction between the C3−C12 and the C13−C17 subunits was investigated.[32] This aldol-based fragment coupling reaction described here was designed on the basis of an extensive study by Evans and co-workers whose careful systematic analysis of this reaction-type laid the ground for our route.[33] In previous syntheses of rutamycin B, this particular C12−C13 aldol bond construction was not reported. In considering the predicted stereochemical outcome of the Mukaiyama aldol, it has been well established that the configuration of the silyl enol ether will determine the relative stereochemistry of the emerging vicinal stereocenters. Further, this chiral reaction partner primarily influences the absolute stereochemical outcome of the methyl bearing stereocenter, while the carbonyl facial selectivity is primarily determined by inherent chirality of the aldehyde. In other words, for aldol processes proceeding through an open transition state, the strereochemical determinants for the emerging methyl and secondary hydroxyl stereogenic centers are contained within the chiral enolsilane and chiral aldehyde reaction components, respectively. Thus, in experiments designed to find a workable solution to this bond construction, we have learned that the type of Lewis acid and the size of the silicon group has significant effect on the level of induction. Table 1 summarizes the important findings concerning this aldol based coupling. Accordingly, in the double-stereodifferentiating aldol used to construct the C1−C17 polypropionate fragment of rutamycin an oligomycin, we had anticipated that the chiral enolsilane **35** would control the stereochemistry of the emerging C12 methyl bearing center while the α-methyl aldehyde **39** provides dominat control over the C13-hydroxyl stereocenter. Finally, the 1,3-relationship across the carbonyl is predetermined by the chirality of the α-methyl ketone and the configuration of the enolsilane. Thus, the stereocontrolling elements for the 1,3-induction of the methyl groups across the carbonyl reside within the chiral ethyl ketone coupling partner.

These experiments underscore the sensitive nature of the open transition-state models to steric influences of the Lewis acids and trialkylsilicon group. Among the Lewis acids surveyed, $BF_3{\cdot}OEt_2$, $SnCl_4$, and $TiCl_4$ generally provided clean reaction products. Also surveyed was the size of the silicon group. In that regard, three different trialkylsilyl groups representing considerably different steric environments have been screened: Me_3-Si, Me_2PhSi, and *t*-$BuMe_2Si$. The combination of $BF_3{\cdot}OEt_2$ and a sterically bulky silyl enol ether (M = $SiMe_2Ph$) were found to be most effective with respect to the level of diastereoselectivity and reaction yield (entry 2). The reaction diastereoselection can be rationalized with the open transition state model that orientates the chiral reaction partners in an anti/staggered transition state. After considerable experimentation, this critical bond construction was achieved with useful levels of selectivity. The (*Z*)-*O*-silyl enol ether **35** derived from ethyl ketone **34**, and aldehyde **39** were treated with $BF_3{\cdot}OEt_2$ (1.1 equiv) at −78 °C for 24 h to furnish the required anti aldol product **36a** with good selectivity (dr = 7:1). It is believed the Me_2PhSi (*Z*)-*O*-silyl enol ether sterically reinforces Felkin induction by stabilizing the transition state allowing the aldehyde substituent (H) to adopt the sterically most demanding position. This organization of reactive π-partners results in an anti aldol with the methyl groups positioned anti across the C11 carbonyl. An open transition-state model that can be used to rationalize the stereochemical course of this bond construction is shown in Scheme 11.

The synthesis of the C1−C17 fragment was completed in five steps from **36a** and was initiated with the selective removal of the C5−C7 silylene protecting group using HF·Py/Py in THF at 0 °C. The resulting crude triol was selectively protected at the C5 and C13 hydroxyls with

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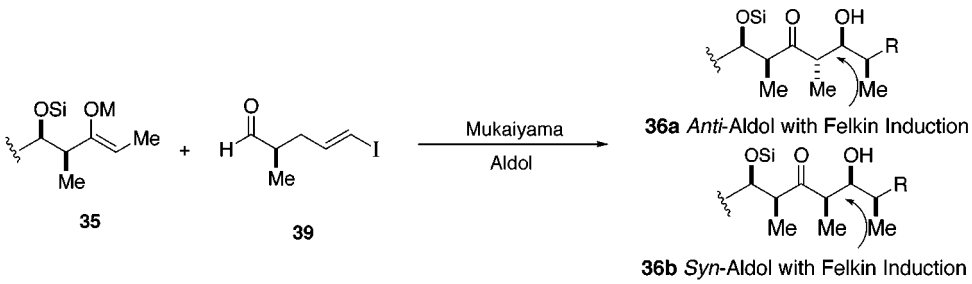
(32) Double-stereodifferentiating aldol reactions: (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita; L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−30.

(33) (a) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921−5942. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M.; G.; Livingston, A. B.; *J. Am. Chem. Soc.* **1995**, *117*, 6619−6620. (c) Dart, M. J. Ph.D. Thesis, Harvard University, May 1995.

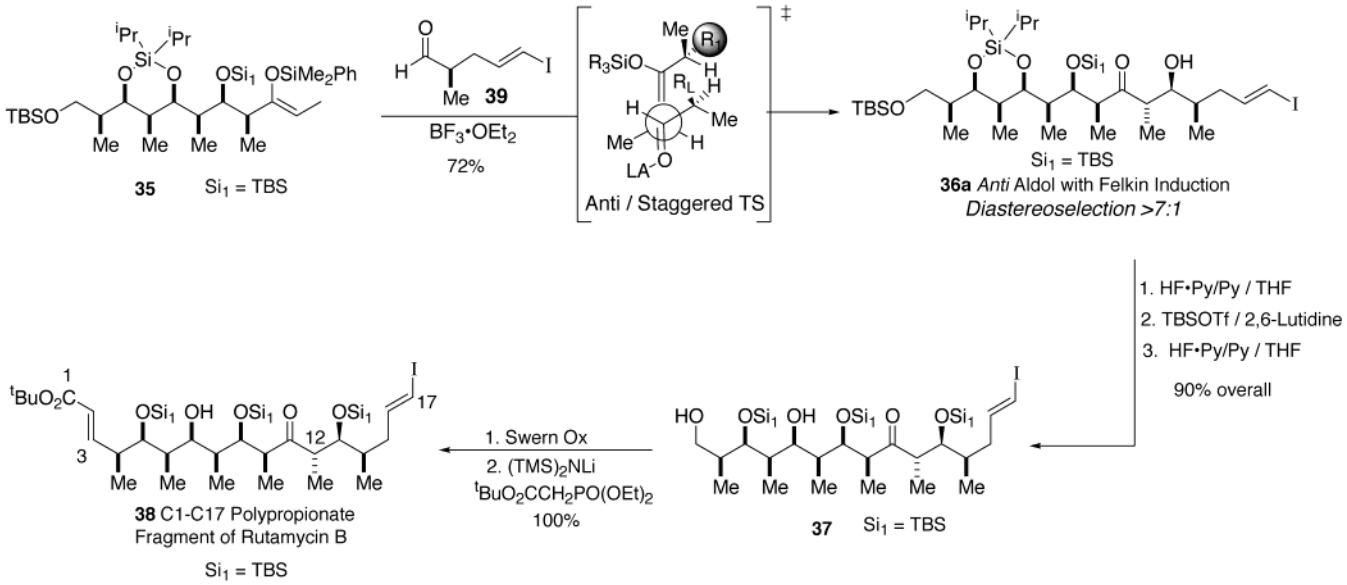
Table 1



entry	Lewis acid (equiv)	(*Z*)-enolsilane (M)[a]	**36a:36b** diastereoselectivity anti/syn/∑ others[b]	% yield[c]
1	$BF_3{\cdot}OEt_2$ (1.1)	Me_3Si	2:1:1	43
2	$BF_3{\cdot}OEt_2$ (1.1)	Me_2PhSi	7:1:0	73
3	$BF_3{\cdot}OEt_2$ (1.1)	$^tBuMe_2Si$	not determined	<10
4	$SnCl_4$ (1.1)	Me_2PhSi	2:1:0	32.5
5	$TiCl_4$ (1.1)	Me_3Si	1:1:3	71
6	$TiCl_4$ (1.1)	Me_2PhSi	5:1:0	21
7	$TiCl_4$ (1.1)	$^tBuMe_2Si$	20:1:0	43−53

[a] Assignment of enol stereochemistry was accomplished by NOE experiments. [b] Ratio of diastereomers was determined by ^1H NMR experiments on the crude reaction products. [c] Refers to purified material (single major diastereomer) after chromatography on SiO_2.

Scheme 11

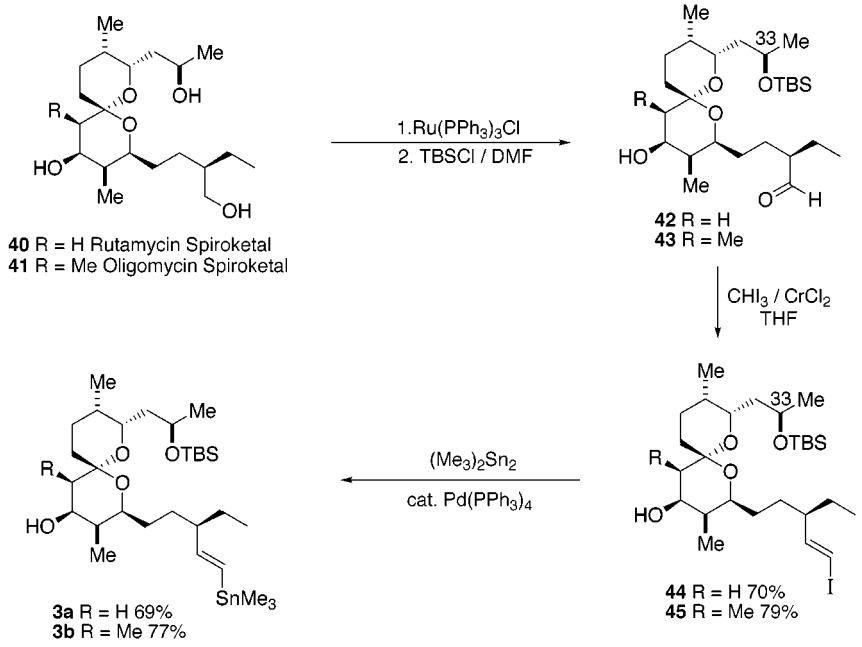


TBSOTf (2.2 equiv), 2,6-lutidine (3 equiv) at −78 °C. This material was selectively deprotected at the C3 TBS ether using HF·Py/Py in THF at room temperature to give diol **37** in high yield. A Swern oxidation of the resulting C3−C7 diol provided the keto-aldehyde. This advanced intermediate was subjeted to a phosphorus based olefination with an (*E*)-selective Horner-Emmons reaction using *tert*-butyldiethylphophonoacetate and $LiN(TMS)_2$ to complete the assembly of the C1−C17 polypropionate fragment of rutamycin B and oligomycin C.

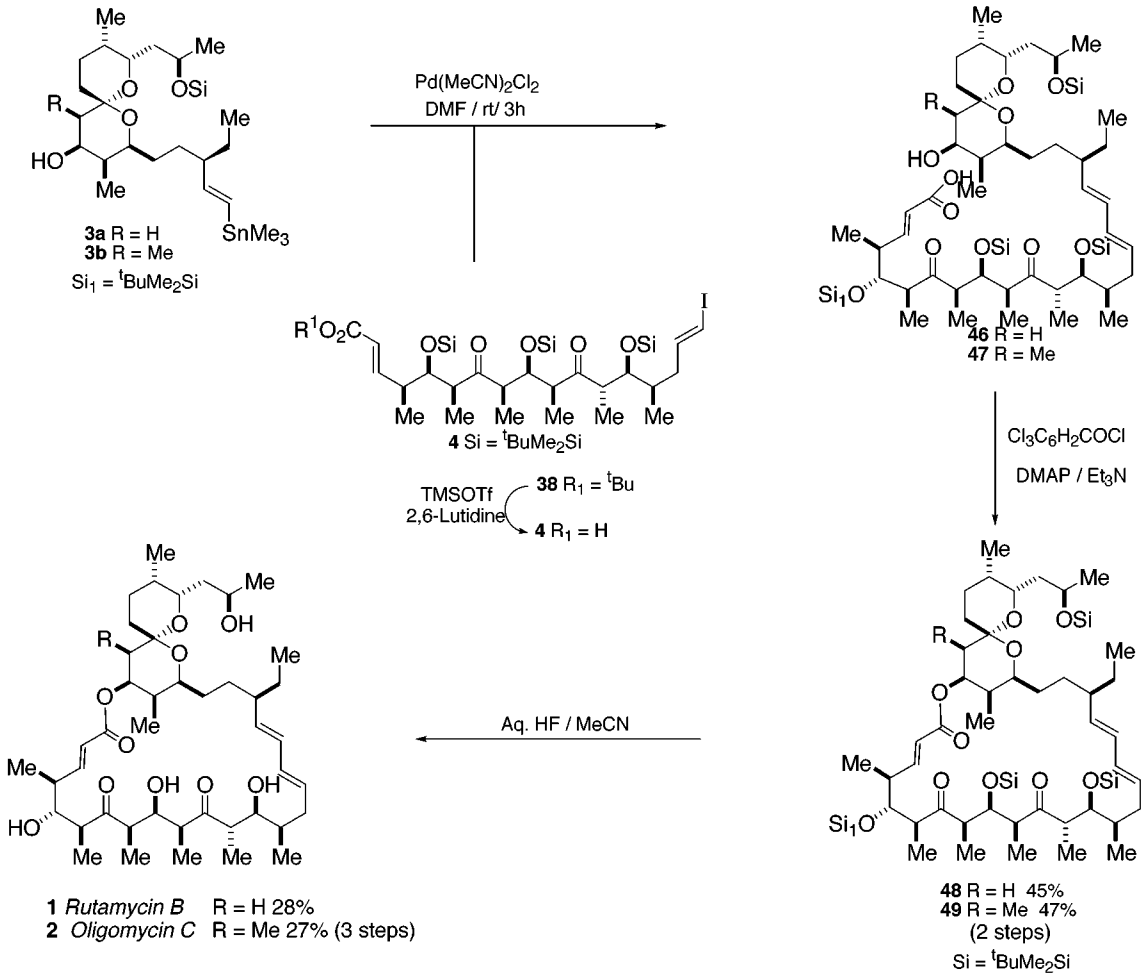
Synthesis of the C18−C34 Spiroketal Fragments of Rutamycin B and Oligomycin C. At this stage of the synthesis, the individual spiroketal subunits were further functionalized to prepare them for cross-coupling with the polypropionate fragment. In that regard, the conversion of the spiroketal individual intermediates **39** and **40** to the required coupling partners was completed in four steps. These transformations were accomplished by selective oxidation of the C19 primary hydroxyl group in the presence of the C25 and C33 secondary hydroxyl groups. In that context, the oxidation was successfully carried out using $Ru(PPh_3)_3Cl_2$[34] to afford aldehydes **41** and **42**. However, these aldehydes proved to be unstable toward purification on SiO_2, which resulted in their use in the next olefination reaction without further purification. Accordingly, homologation to the *E*-vinyl iodide using the Takai protocol,[29] selective protection of the C33 hydroxyl with TBSCl/imidazole provided *E*-vinyl iodides **44** and **45** in 70% and 79% yield, respectively (Scheme 12). The vinyl iodides were converted to the *E*-vinylstannane using the Stille protocol. This halogen → stannane conversion completed the assembly of the fully elaborated C18−C34 spiroketal fragments **3a** and **3b**, which were used separately in the transition metal mediated fragment coupling with the polypropionate fragment **4**.

(34) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605−1608.

Scheme 12



Scheme 13



Completion of Synthesis of of Rutamycin B and Oligomycin C. The following discussion describes the final stages of the synthesis of rutamycin B and oligomycin C. Prior to actual fragment coupling exeperiments, the *tert*-butyl ester of **4** was converted to the corresponding carboxylic acid **47**, by treatment with TMSOTF in the presence of 2,6-lutidine[35] (Scheme 13). Coupling of the polypropionate with the spiroketal fragment using

(35) Trzeciak, A.; Bannwarth, W.; *Synthesis* **1996**, 1433.

palladium(0) cross-coupling methodology (Stille coupling) could then be carried out. In individual procedures, a solution containing the spiroketal fragments bearing vinylstannanes **3a** and **3b** and polypropionate fragment **4** in DMF, $Pd(CH_3CN)_2Cl_2$ was added at 0 °C and stirred for 15 min. After workup, the mixture yielded the protected seco acids **46** and **47**, respectively, which were immediately subjected to macrolactonization. The most effective procedures for cyclization of the seco acid was carried out using the Yamaguchi[36] and Yonemitsu[37] procedures. Accordingly, the seco acids were treated with DMAP, Et_3N, and trichlorobenzoyl chloride in dry benzene and was stirred at ambient temperature for 48 h affording the macrocyclic lactones **50** and **51** in 45% and 47% yield, respectively. Final deprotection of the macrocyclic lactones with HF/CH_3CN[38] completed the total syntheses of rutamycin B (**1**) and oligomycin C (**2**), respectively.

Except for the slightly lower $[\alpha]^{23}_D$ of rutamycin B (**1**), the spectroscopic properties of **1** and **2** were identical in all respects (^1H, $^{13}CNMR$, $[\alpha]^{23}_D$, MS, (HRMS) with those previously reported; for rutamycin B ($[\alpha]^{23}_D = -61.0$ (*c* = 0.01 $CHCl_3$); lit.[7] $[\alpha]^{23}_D = -70.0$ (*c* = 1.22, $CHCl_3$); for oligomycin C $[\alpha]^{23}_D = -82.7$ (*c* = 0.15, dioxane); lit.[4] $[\alpha]^{23}_D = -80.7$ (*c* = 3.7, dioxane).

The total synthesis of rutamycin B and oligomycin C has been completed in 43 and 44 steps, respectively, using chiral silane-based bond construction methods for the introduction of the majority of the stereogenic centers. From a historical perspective, synthetic programs aimed at the stereocontrolled synthesis of polypropionate derived macrolide natural products were based on applications of two methodologies of great significance in synthetic chemistry: the use of conformationally biased ring systems as templates for the assembly of contiguous arrays of stereocenters, as exemplified in Woodward's synthesis of erythromycin B[39] as well as in the total synthesis of erythronolide B by Corey[40] and (+)-9*S*-dihydroerythronolide A by Stork.[41] Subsequently the application of chiral metal enolate based aldol (or aldol surrogoates) methodology was used to assemble propionate subunits.[42] The application of chiral silane-based methodology represents a complementary approach to these complex macrolides while underscoring the operational ease of the crotylation experiments.

Our objectives in the design and excecution of the synthesis of these macrolide antibiotics were to demonstrate (i) the reliability of our chiral silane reagents in the synthesis of polypropionate-like subunits and (ii) the use of mild transition-metal-catalyzed cross coupling strategies for the union of these subunits and principal fragments. The reliable and flexible nature of the chiral silane reagents have facilitated the subunit assembly and subsequent coupling and as such one can imagine other members of this class of natural products may be accessed in similar convergent approachs.

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Supporting Information Available: Complete experimental procedures and spectral data for all compounds including the preparation of aldehydes **9** and **39**. Stereochemical correlation of intermediates **27**, **29**, and **33** is also described. For comparison, this section also contains a table of ^1H and ^{13}C NMR assignments between natural and synthetic rutamycin B and oligomycin C. This material is available free of charge via the Internet http://pubs.acs.org.

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