Total Synthesis of Rutamycin B, a Macrolide Antibiotic from *Streptomyces aureofaciens*

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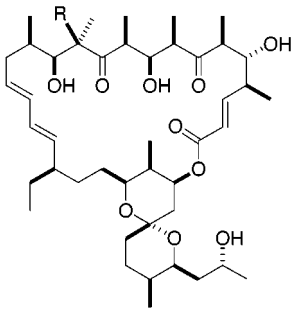
Rutamycin B (**2**) was synthesized from three principal subunits, spiroketal **75**, keto aldehyde **83**, and aldehyde **108**. First, triol **62** was assembled by Julia coupling of sulfone **56** with aldehyde **58** followed by an acid-catalyzed spiroketalization. The three hydroxyl functions of **62** were successfully differentiated, leading to phosphonate **75**. The latter was condensed in a Wadsworth−Emmons reaction with **83**, prepared in six steps from (*R*)-aldehyde **76**, to give **92**. Coupling of the titanium enolate of **92** with **108** afforded Felkin product **109** with high stereoselectivity in a process that is critically dependent on the presence of the *p*-methoxybenzyl ether in the aldehyde. Transformation of **109** via aldehyde **116** to vinylboronate **122** was followed by macrocyclization under Suzuki conditions to yield **123**. Exhaustive desilylation of the latter yielded rutamycin B.

The discovery in 1961 of rutamycin A (**1**) by Thompson in cultures of *Streptomyces griseus*[1] was followed soon thereafter by the isolation of a close structural analogue, rutamycin B (**2**), from *S. aureofaciens* by Keller-Schierlein.[2] The gross structure and relative configuration of **1** were assigned on the basis of X-ray crystallographic analysis,[3] and the relative stereostructure **2** followed from comparison with **1** utilizing NMR spectroscopy. The absolute configuration of the rutamycins was determined by Evans,[4] who compared the spiroketal fragment obtained from degradation with the identical substance prepared by asymmetric synthesis. The integration of a spiroketal unit into the 26-membered lactone that characterizes **1** and **2** places these substances in the broader family of macrolide antibiotics that includes the oligomycins,[5] cytovaricin,[6] and phthoramycin.[7] In common with cytovaricin, the rutamycins are cytotoxic and have potent antifungal activity. The action of rutamycin B has been specifically linked to its inhibition of H^+-ATPase, thereby preventing oxidative phosphorylation in mitochondria.[8]

The challenge presented by total synthesis of the rutamycins was first met by Evans,[9] who completed the synthesis of **2** through a conventional Yamaguchi macrolactonization after all C−C bonds and stereochemistry were installed. A synthesis of rutamycin B by Panek[10] accomplished the same finale from a seco acid precursor for which a series of crotylsilane additions was used to fabricate the skeleton. By contrast, our approach to **2** envisioned macrocyclization via a carbon−carbon connection after the spiroketal and polyketide subunits have been joined through an ester linkage. This plan is expressed retrosynthetically in Scheme 1, where the penultimate precursor **3** is projected from three smaller fragments, **4**, **5**, and **6**, in a sequence that first connects **5** to **6** and then fuses the [**5** + **6**] composite to **4**. This mode of assembly imposes logistical demands different from those of the Evans[9] and Panek syntheses[10] but has the compensatory advantage that linkages between fragments can be made in ways that afford excellent stereocontrol. The 17 stereogenic centers of **2** are positioned in sets that make the connections in Scheme 1 a logical outcome of the methodology selected for key C−C bond constructions, and we now describe the successful implementation of a plan for the synthesis of **2** based on this logic.[11]



1, R = OH, Rutamycin A

2, R = H, Rutamycin B

(1) Thompson, R. Q.; Hoehn, M. M.; Higgens, C. E. *Antimicrob. Agents Chemother.* **1961**, 474.
(2) Wuthier, D.; Keller-Schierlein, W. *Helv. Chim. Acta* **1984**, *67*, 1208.
(3) Arnoux, B.; Garcia-Alvarez, M. C.; Marazano, C.; Das, B. C.; Pascard, C.; Merienne, C.; Staron, T. *J. Chem. Soc., Chem. Commun.* **1978**, 318.
(4) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260.
(5) (a) Smith, R. M.; Peterson, W. H.; McCoy, E. *Antibiot. Chemother.* **1954**, *4*, 962. (b) Kobayashi, K.; Nishino, C.; Ohya, J.; Sato, S.; Mikawa, T.; Shiobara, Y.; Kodama, M.; Nishimoto, N. *J. Antibiot.* **1987**, *40*, 1053.
(6) Kihara, T.; Kusakabe, H.; Nakamura, G.; Sakurai, T.; Isono, K. *J. Antibiot.* **1981**, *34*, 1073.
(7) Nakagawa, A.; Miura, S.; Imai, H.; Imamura, N.; Omura, S. *J. Antibiot.* **1989**, *42*, 1324.
(8) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407.
(9) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446.
(10) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **2001**, *66*, 2747.

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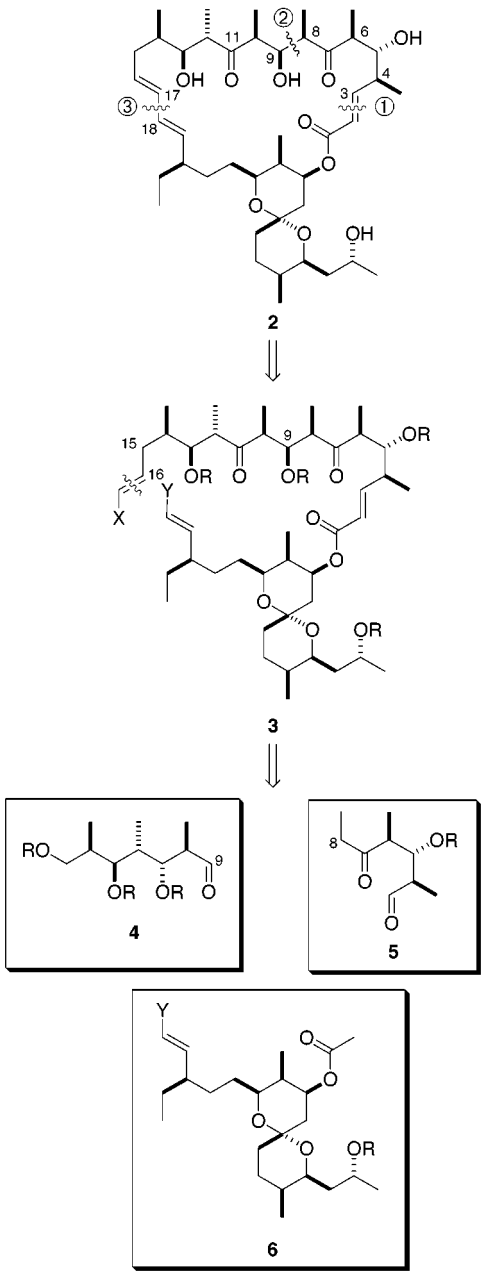
Scheme 1



The Spiroketal Segment 6. An assumption made at the outset of our route to **6** was that an open frame such as **7** would undergo internal ketalization to yield a substance in which the spiro carbon has the configuration of the natural product. This expectation was founded on the fact that the spiro center (C27) of **2** possessing natural configuration places the larger alkyl substitutents in an equatorial orientation when maximum anomeric stabilization is conferred upon the spiroketal[12] and has been borne out in both Evans'[9] and Panek's[10] syntheses of the rutamycin−oligomycin spiroketals.

Three general strategies, each uniting a different pair of subunits, were considered for the assembly of **7** (Scheme 2). The first (route A) sees connection of C25 with C26 via an aldol or analogous process involving **8** and **9**, the second links two segments at the C28−C29 bond through an epoxide opening of **10** by **11** (route B), and the third invokes nucleophilic attack by anionic species **13** on aldehyde **12** (route C). The first of these approaches, route A, appeared to be the most direct avenue to **7**, and initial efforts were therefore launched toward the preparation of aldehyde **8**.

The location of the ethyl substituent in **7** mandated that the configuration at C20 be introduced independently of other stereocenters, and this was accomplished by means of an asymmetric Michael addition of the titanium enolate of *N*-butanoyloxazolidinone **14**,[13] prepared by acylation of the lithio anion of (*R*)-4-benzyloxazolidin-2-one with *n*-butyryl chloride,[14] to acrylonitrile (Scheme 3). The adduct **15** was obtained in good yield as a single diastereomer, and the chiral adjuvant was cleaved reductively to furnish hydroxy nitrile **16**. The latter was protected as its silyl ether **17** before reduction with diisobutylaluminum hydride to yield aldehyde **18**.[15] Asymmetric crotylation with (*Z*)-crotylboronate **19** derived from (*S,S*)-tartrate[16] afforded syn homoallylic alcohol **20** accompanied by a minor quantity of its anti isomer (5:1). After conversion of **20** to its bis(silyl) ether **21**, ozonolytic cleavage of the vinyl group produced aldehyde **22**, representing the C19−C25 portion of **7**.

The second segment required for **7** was prepared from alcohol **23**,[17] obtained from methyl (*R*)-3-hydroxy-2-methylpropionate by conversion to its silyl ether followed by reduction with diisobutylaluminum hydride (Scheme 4). The tosylate derived from **23** was advanced to sulfone **24** via displacement of the corresponding iodide with sodium sulfinate,[18] and the anion of **24** was reacted with racemic propylene oxide to provide hydroxy sulfone **25** as a mixture of stereoisomers.[19] Reductive cleavage of the sulfonyl substituent with sodium-amalgam[20] gave **26** as a 1:1 mixture of stereoisomers that was oxidized to ketone **27** with pyridinium chlorochromate.[21] Ketalization followed by cleavage of the *tert*-butyldimethylsilyl ether yielded primary alcohol **28**, which after Swern oxidation[22] led to aldehyde **29**. Asymmetric allylation of **29** with boronate **30** from (*R,R*)-tartrate[23] afforded syn homoallylic alcohol **31** and its anti stereoisomer as a 4:1 mixture. By contrast, allylation of **29** with Brown's diisocaranylborane reagent[24] gave a syn/anti ratio of 8.6:1 but in only 48% yield. After protection of **31** as its silyl ether **32**, Wacker oxidation[25] of the terminal alkene produced methyl ketone **33** in good yield. Not surprisingly, the

(11) Preliminary communications: (a) White, J. D.; Ohba, Y.; Porter, W. J.; Wang, S. *Tetrahedron Lett.* **1997**, *38*, 3167. (b) White, J. D.; Porter, W. J.; Tiller, T. *Synlett* **1993**, 535. (c) White, J. D.; Tiller, T.; Ohba, Y.; Porter, W. J.; Jackson, R. W.; Wang, S.; Hanselmann, R. *Chem. Commun.* **1998**, 79.

(12) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

(13) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

(14) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83.

(15) Winterfeldt, E. *Synthesis* **1975**, 617.

(16) (a) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339. (b) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(17) See ref 16b, footnote 12a. Cf. Nagoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(18) White, J. D.; Kawasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4991.

(19) Mori, K.; Senda, S. *Tetrahedron* **1985**, *41*, 541.

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(21) Sneeden, R. P. A. *Organochromium Compounds*; Academic Press: New York, 1975.

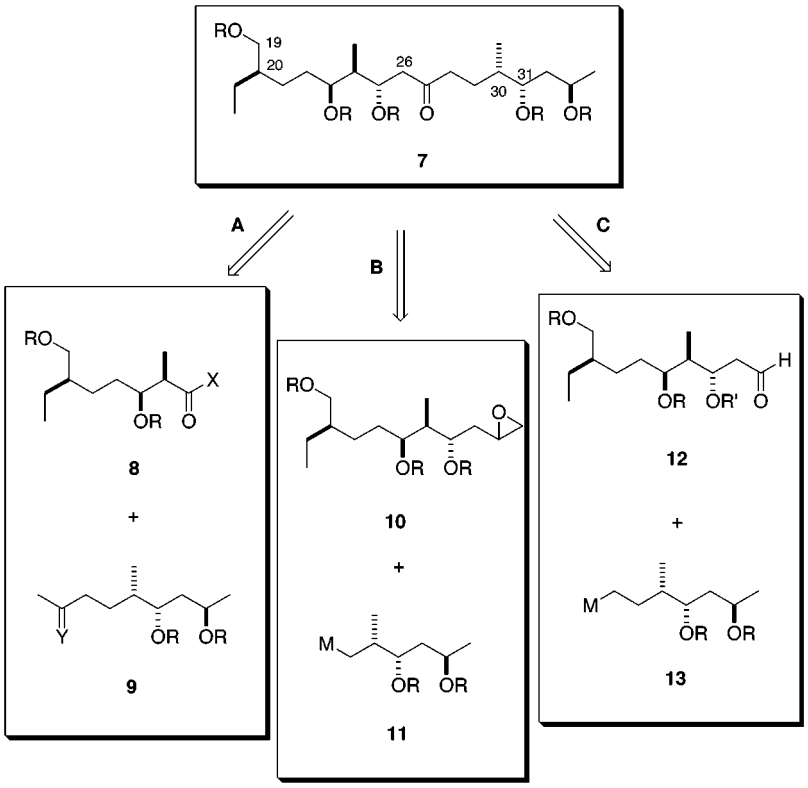
(22) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(23) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117.

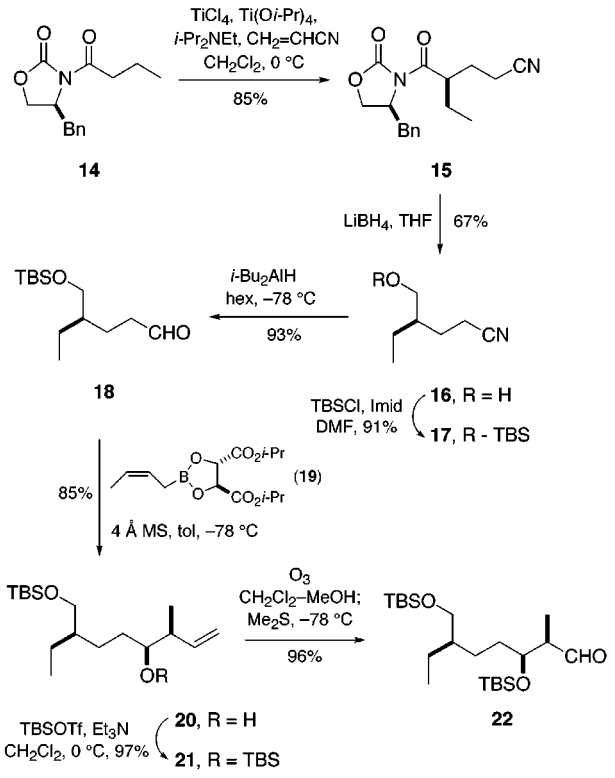
(24) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.

(25) Tsuji, J. *Synthesis* **1984**, 369.

Scheme 2



Scheme 3



Wacker reaction completely failed with the free alcohol **31**. The silyl protecting group was removed from **33**, and the resulting β-hydroxy ketone **34** was reduced to anti diol **35** with tetramethylammonium triacetoxyborohydride.[26] In an alternative and more direct approach to **34**, the chiral borinate of acetone, prepared with (+)-diisopinocampheylboron triflate,[27] was reacted with aldehyde **29** to give the aldol product **34** as a 10:1 mixture of syn and anti isomers in 63% yield. However, this reaction was not readily amenable to the large-scale preparation of **34** necessary for advancing the synthesis toward subunit **9**, and we therefore returned to the route via **31**, **32**, and **33** for this purpose. Protection of diol **35** as its bis(*tert*-butyl)silylene derivative **36**,[28] followed by acid-catalyzed hydrolysis of the ethylene ketal, furnished ketone **37**, representing the C26−C34 portion of **7**.

With aldol partners **22** and **37** in hand, it was assumed that coupling along lines proposed in path A (Scheme 2) would lead to **7**. In practice, numerous attempts to effect this aldol coupling using both lithium and boron enolates of **37** met only with failure, and it became clear that structural modification would be needed to either or both reactants if the C25−C26 linkage of **7** was to be forged as planned. The consistent recovery of starting materials from the attempted condensation of enolates of **37** with aldehyde **22** suggested that a means should be found for imparting irreversibility to this reaction, and an attractive option for this purpose appeared to be conversion of **22** to a reactive acylating system while modifying **37** to enhance its nucleophilicity. To this end, **22** was oxidized to a carboxylic acid, which was condensed with *N*,*O*-dimethylhydroxylamine hydrochloride to furnish Weinreb amide **38** (Scheme 5).[29] In parallel with this transformation, ketone **37** was condensed with 1,1-dimethylhydrazine,[30] and the resultant hydrazone **39**, without isolation,

(26) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(27) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

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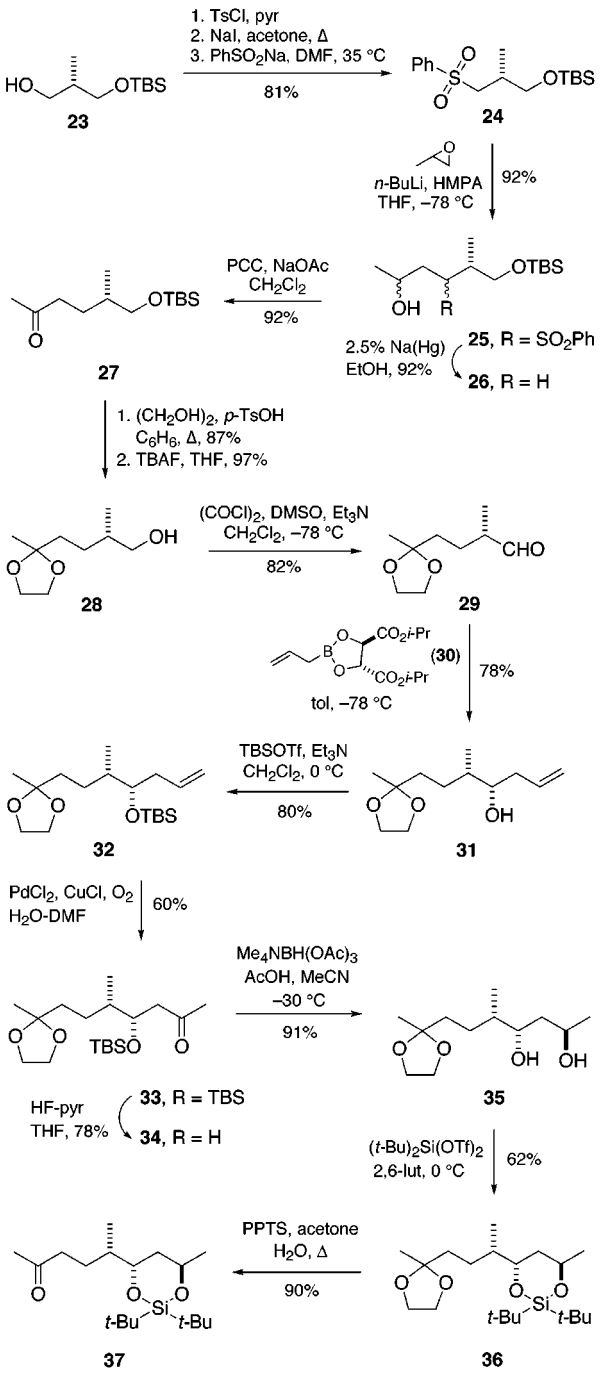
(29) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332.

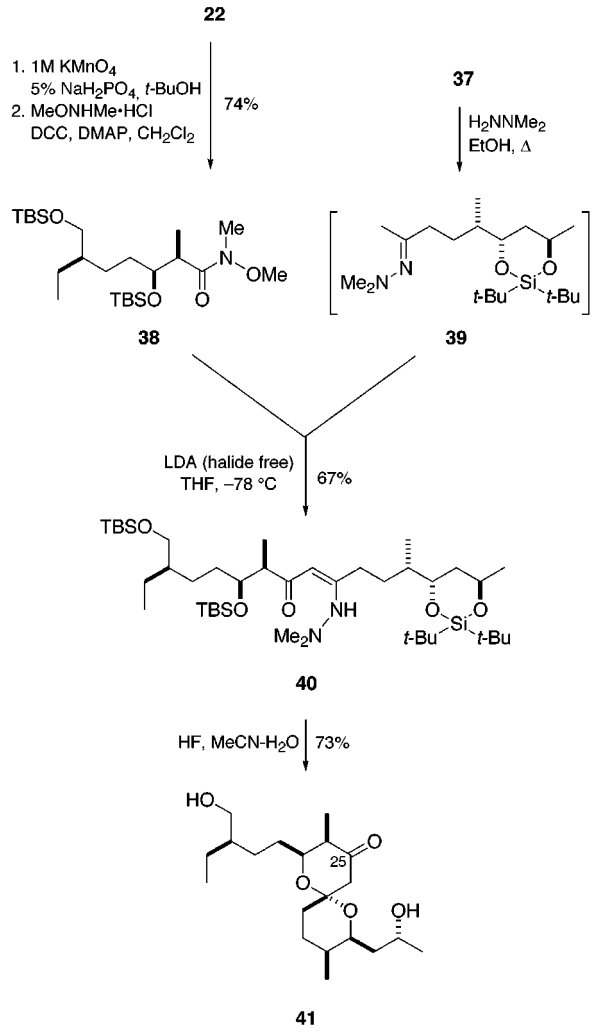
(30) Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1966**, *31*, 677.

Scheme 4



was treated with halide-free lithium diisopropylamide and then with **38** to produce enaminone **40**. In his route to the spiroketal moiety of rutamycin B, Evans accomplished a similar hydrazone−Weinreb amide union of two subunits and also noted the importance of using an amide base free of halide salts.[4] Subsequent exposure of **40** to aqueous HF−acetonitrile led to a single product assigned structure **41**. While it was certain that hydrolysis of the enaminone and all silyl protecting groups had taken place in this reaction, the configuration at the new stereocenter resulting from spiroketalization remained unproven. Furthermore, there was the question of stereoselectivity in reduction of the keto group of **41** if a hydroxyl function of the desired (*S*) configuration was to be installed at C25. Although it would have been possible in principle to correlate **41** with a spiroketal prepared in

Scheme 5



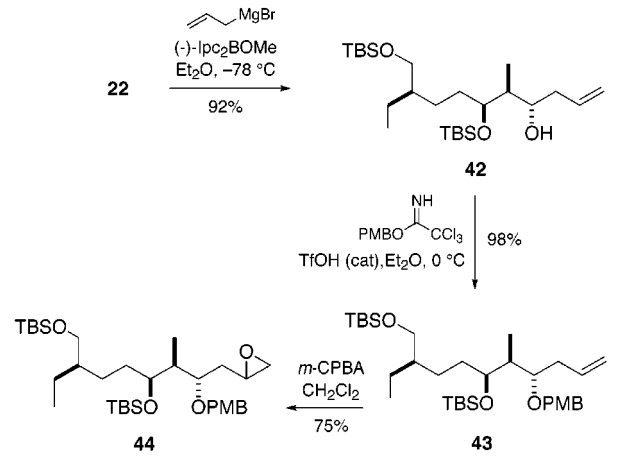
the course of Evans' synthesis of rutamycin B,[9] we chose instead to explore a new pathway that would incorporate all seven stereocenters in the correct orientation in the spiroketal precursor. This led us to entertain path B, in which union is made at C28−C29 between an epoxide **10** and a nucleophilic species **11**.

Asymmetric allylation of **22** with Brown's allyldiisopinocampheylborane[31] gave homoallylic alcohol **42** along with its syn diastereomer (anti/syn 3:1). After protection of **42** as *p*-methoxybenzyl ether **43**,[32] the terminal alkene was epoxidized to give a 1:1 mixture of stereoisomeric epoxides **44** (Scheme 6). Since the secondary alcohol that would be obtained from opening of the epoxide was destined to become the C27 keto group of **7**, no effort was made to separate these diastereomers. The organometallic species initially envisioned as the coupling partner for **44** was a cuprate derived from the iodohexane corresponding to **11**, and synthesis of this material was commenced from (*S*)-aldehyde **45** (Scheme 7). Asymmetric allylation of **45** afforded the known alcohol **46**,[16b] which, after protection as silyl ether **47**, was subjected to a Wacker oxidation.[25] The resulting methyl ketone **48** was unmasked to furnish *β*-hydroxy ketone **49**, and subsequent directed reduction with tetramethylammo-

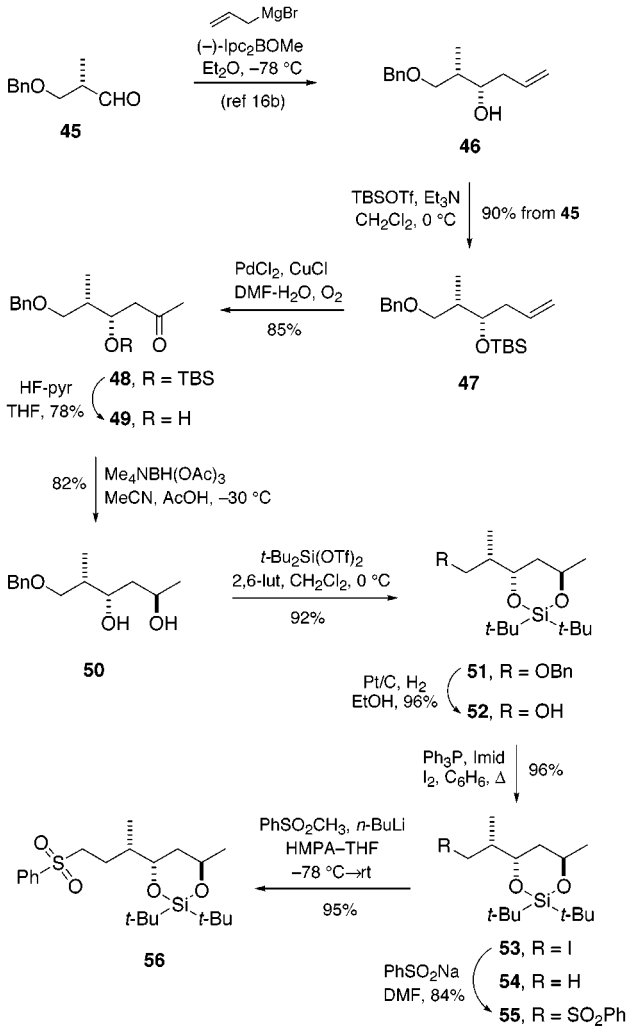
(31) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570.

(32) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.

Scheme 6



Scheme 7

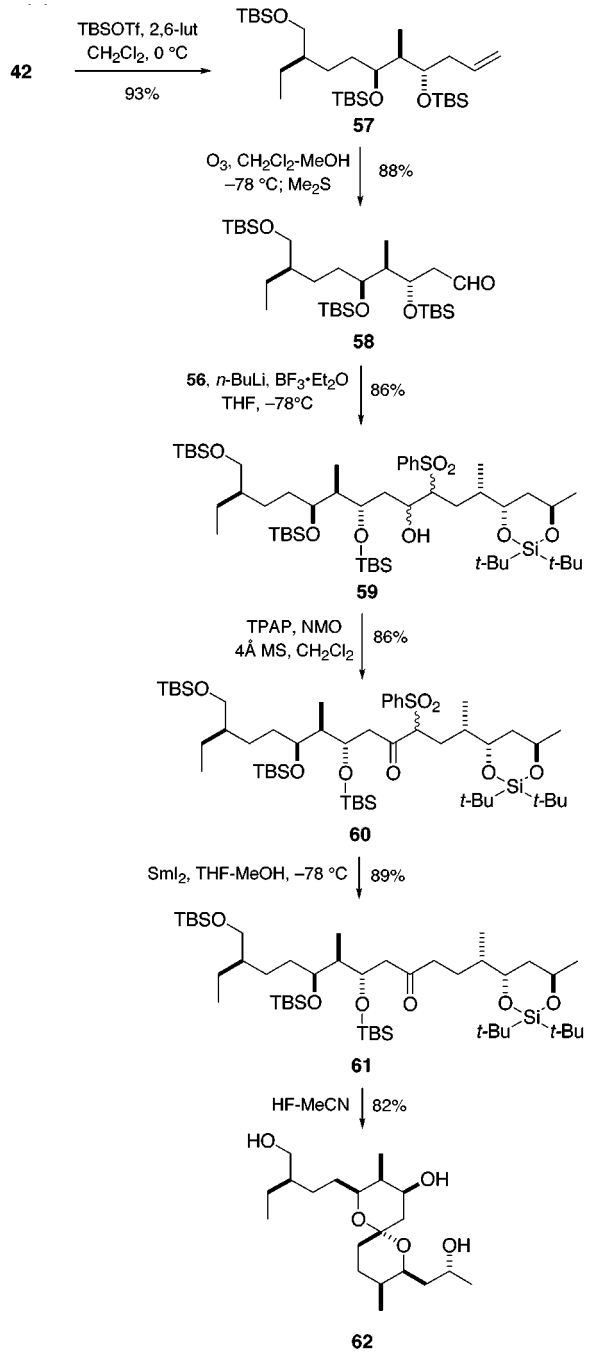


nium triacetoxyborohydride gave anti diol **50**.[26] The latter was protected with bis(*tert*-butyl)silyl ditriflate as the silylene **51**, which after hydrogenolysis of the benzyl ether over platinum-on-carbon[33] produced alcohol **52**. The iodo derivative **53** obtained from **52**[34] was converted to a higher order cuprate by treatment with *tert*-butyllithium followed by lithium thienylcopper cyanide,[35] but all attempts to open epoxide **44** with this reagent were unsuccessful. The epoxide was generally recovered intact, the only new material isolated from this reaction being the reduced compound **54**. This disappointing outcome led us to consider alternative nucleophilic partners for **44**, one of which was sulfone **55**. The latter was prepared from **53** by displacement of iodide with sodium phenylsulfinate; however, the anion of **55** was also inert toward **44** even when the reaction was attempted in the presence of a Lewis acid. The viability of **55** was confirmed when its anion reacted cleanly with propylene oxide to produce a hydroxy sulfone in good yield, and the failure of **55** to react with **44** under the same conditions is puzzling. Subtle effects of both steric and electronic origin are known to impinge upon nucleophilic opening of epoxides by organometallic species,[36] and it appears that these may be operating in the case of **44**.

Although sulfone **55** had failed to react with **44**, the concept embodied in this plan nevertheless seemed feasible if a homologated sulfone corresponding to **13** (Scheme 2) could be induced to react with aldehyde **12**. In this context, path C of Scheme 2 becomes a well precedented Julia coupling[37] that joins C27 with C28 and that should circumvent the difficulties attending approaches to **7** via paths A and B. Implementation of this new plan proved to be straightforward (Scheme 7). First, iodide **53** was reacted with the lithio anion of methyl phenyl sulfone[38] to provide the homologated sulfone **56**. Then, alcohol **42** protected as its *tert*-butyldimethylsilyl ether **57** was ozonized to yield aldehyde **58 (**Scheme 8). Julia coupling of the anion of **56** with **58** in the presence of boron trifluoride etherate[39] afforded hydroxy sulfone **59** as a mixture of stereoisomers in excellent yield. In the absence of a Lewis acid catalyst, the yield of coupled product **59** was markedly reduced, and when a Julia reaction was attempted between **56** and the aldehyde prepared by ozonolytic cleavage of **43** the major product was an α,*β*-unsaturated aldehyde resulting from elimination of *p*-methoxybenzyl alcohol. This observation illustrates the care with which protecting groups must be chosen for Julia reactions on carbonyl substrates bearing a *β* alkoxy substituent. Oxidation of **59** with catalytic Ley's reagent and *N*-methylmorpholine *N*-oxide as the stoichiometric oxidant[40] led to a pair of stereoisomeric keto sulfones **60**; reductive removal of the sulfonyl group with samarium diiodide[41] resulted in further simplification to give ketone **61** as a pure substance. Surprisingly, when reductive cleavage of **60** was attempted with sodium amalgam, the product was not **61** but a trans alkene. Presumably, rapid reduction of the ketone of **60** occurred with this reagent, returning **59** which then underwent reductive 1,2-elimination of the hydroxy sulfone. Exhaustive deprotection of **61** with HF in acetoni-

(33) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.
(34) Castro, B. R. *Org. React.* **1983**, *29*, 1.
(35) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437.
(36) Kigoshi, H.; Ojika, M.; Suenaga, K.; Mutou, T.; Hirano, J.; Sakakura, A.; Ogawa, T.; Nisiwaki, M.; Yamada, K. *Tetrahedron Lett.* **1994**, *35*, 1247.
(37) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763.
(38) White, J. D.; Kuo, S.-c.; Vedananda, T. R. *Tetrahedron Lett.* **1987**, *28*, 3061.
(39) (a) Achmatowicz, B.; Baranowska, E.; Daniewski, A. R.; Pankowski, J.; Wicha, J. *Tetrahedron Lett.* **1985**, *26*, 5597. (b) Schreiber, S. L.; Meyers, H. V. *J. Am. Chem. Soc.* **1988**, *110*, 5198.
(40) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(41) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

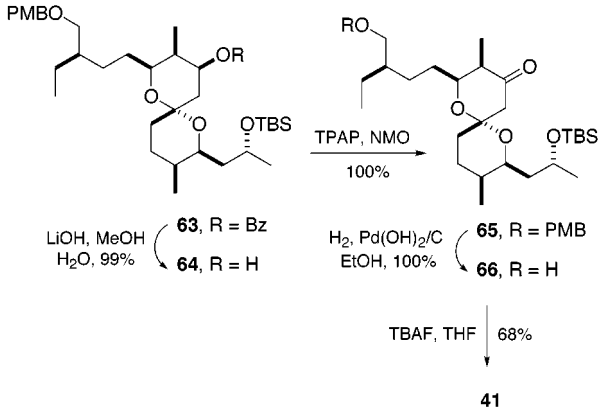
Scheme 8



trile presumably led to a transient pentahydroxy ketone, from which spontaneous spiroketalization followed to yield **62**.

Before proceeding further, it seemed prudent to verify not only the configuration at the spiro carbon of **62** but also the stereochemistry of spiroketal **41**. This was made possible by a generous gift of **63** from Professor Evans, who had previously correlated this substance with the spiroketal obtained by degradation of rutamycin A.[4] First, **63** was saponified to remove the benzoate, and the resulting alcohol **64** was then oxidized with Ley's reagent[40] to ketone **65** (Scheme 9). Hydrogenolysis of the *p*-methoxybenzyl ether of **65** over Pearlman's catalyst afforded **66**, which after cleavage of the silyl ether gave **41**. The latter was identical in all respects with the substance we had obtained from **40**. It was further shown that the bis(silyl) ether **67** derived from **41** underwent

Scheme 9



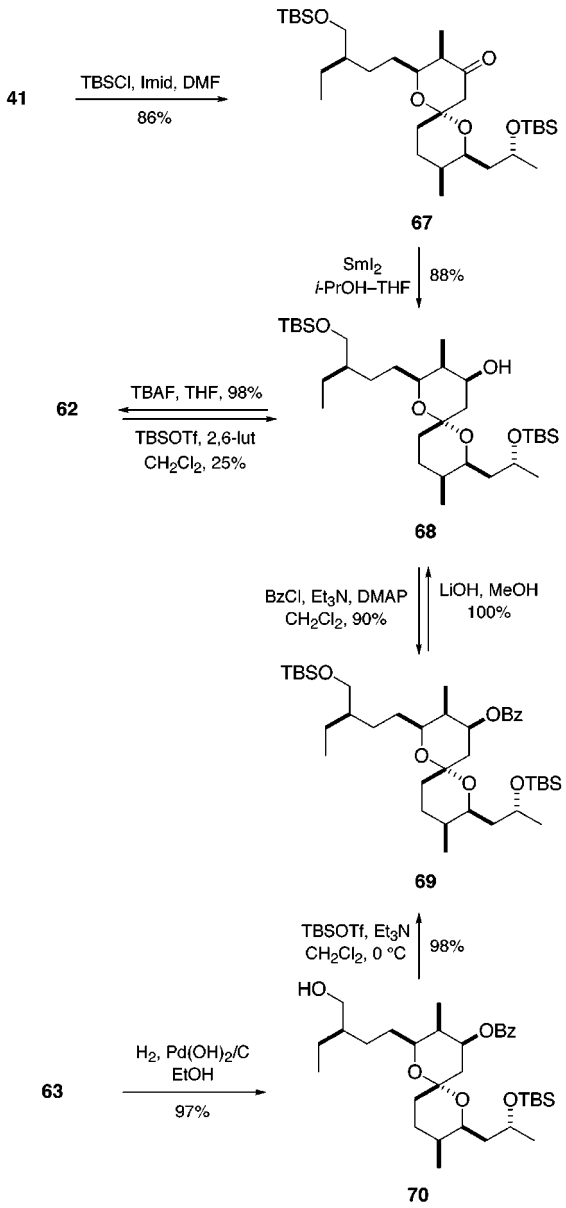
reduction with samarium diiodide to yield a single equatorial alcohol[42] assigned structure **68** (Scheme 10). Esterification of this alcohol with benzoyl chloride gave benzoate **69**, a substance identical with material prepared from the Evans spiroketal **63**[4] by hydrogenolysis and silylation of alcohol **70**. Correlation of **62** with **63** was completed by saponification of **69**, which returned **68**, and then desilylation to furnish the expected triol **62**. Resilylation of **62** with *tert*-butyldimethylsilyl triflate afforded **68** in low yield, the major product being the primary monosilyl ether.

With the configuration at all eight stereocenters of **62** firmly established, it became essential to devise a means for distinguishing the three hydroxyl functions of this spiroketal so that a suitably functionalized and protected version could be advanced toward **6**. A convenient substance for this purpose was already in hand in the form of **69**, available from **41** or **62** via **68**, and methods were therefore investigated for selective cleavage of the primary silyl ether from this structure. The most effective reagent for this purpose was HF−pyridine, which produced **70** accompanied by diol **71** (Scheme 11). The latter could be recycled through its return to **69** by resilylation, resulting in an overall 61% yield for the conversion of **69** to **70**. Swern oxidation[22] of **70** led to aldehyde **72**, which in a Takai reaction[43] with iodoform and chromous chloride afforded the trans iodoalkene **73** accompanied by the cis isomer as a 18:1 mixture (Scheme 12). Cleavage of the benzoate from **73** by saponification was quantitative, and acylation of the resultant alcohol with diethyl phosphonoacetyl chloride produced ester **75**. This functionalized spiroketal now became the dedicated partner for coupling with keto aldehyde **5** in our plan for assembling the second major segment of rutamycin B.

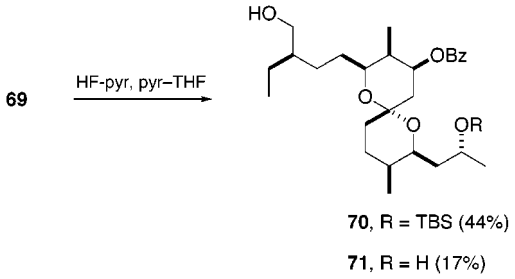
Polypropionate Segment. The linear section of **2** comprising C3−C17 contains three stereotriads, each characterized by an alternating array of methyl and oxygen substituents. This arrangement lends itself to stereocontrolled synthesis through asymmetric crotylation methodology, but in order to avoid a fully linear approach, an aldol coupling was programmed for the connection of C8 with C9. This plan simplifies elaboration of the polypropionate subunit to independent preparations of aldehyde **4** and keto aldehyde **6**.

(42) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
(43) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

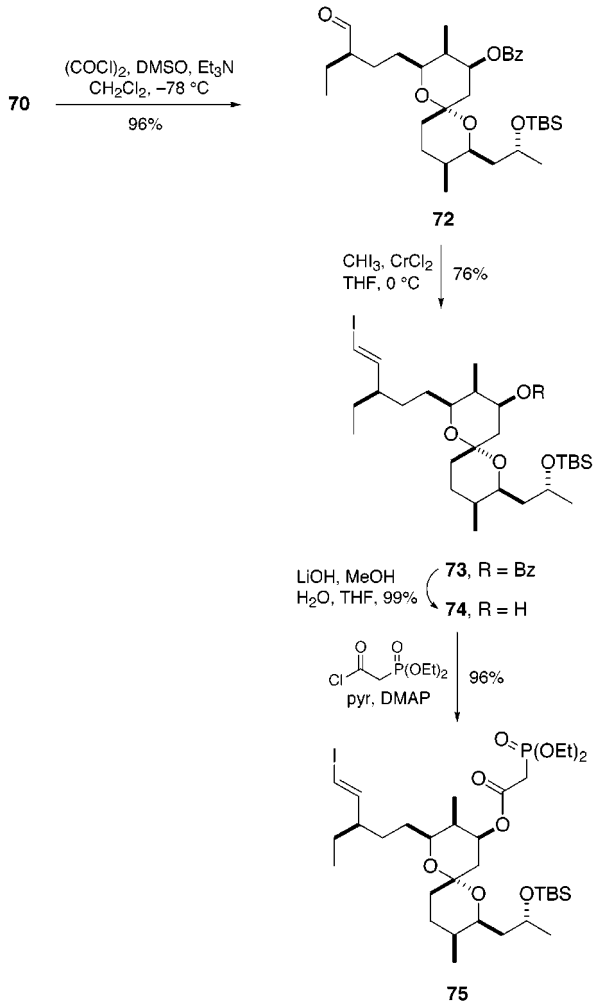
Scheme 10



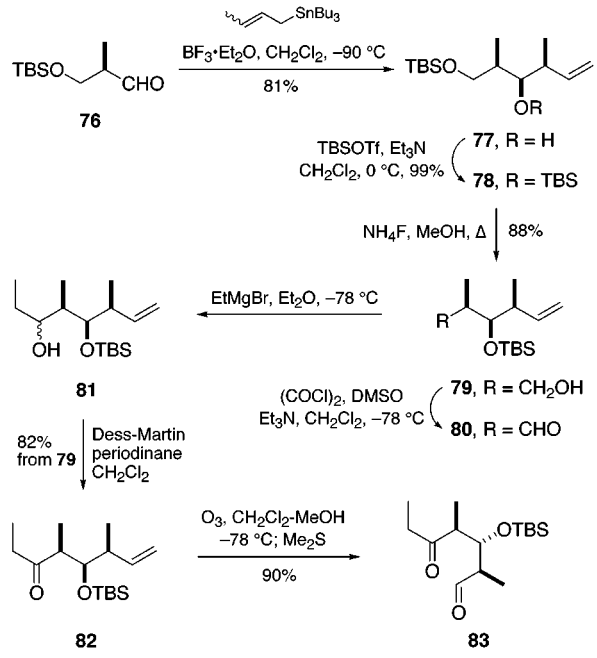
Scheme 11



Scheme 12



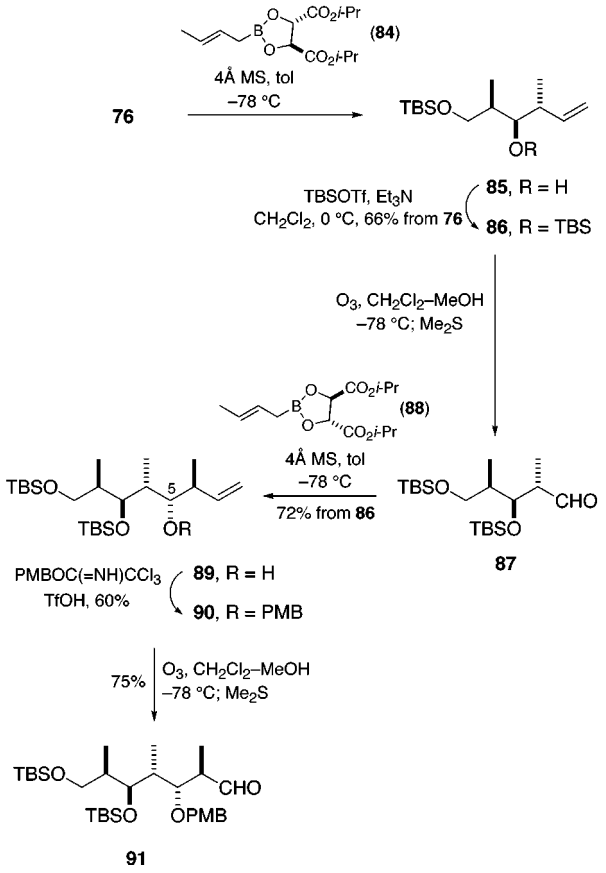
Scheme 13



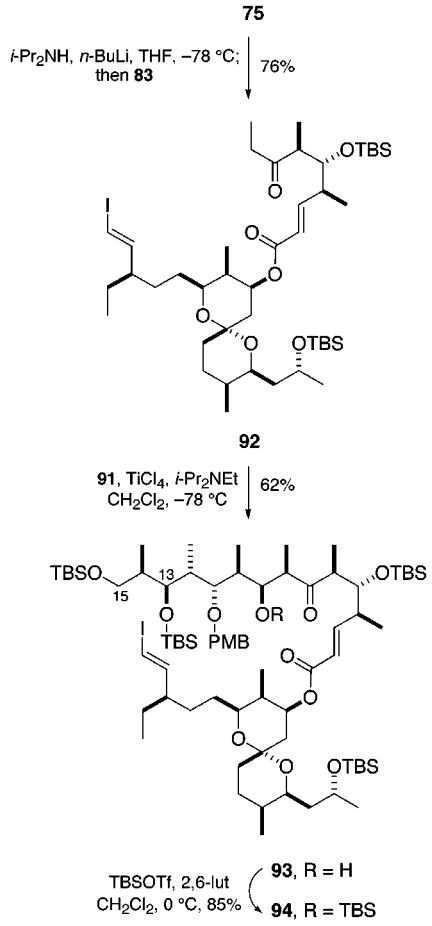
The syn,syn stereotriad at C4−C6 was installed by a Lewis acid catalyzed reaction of (*R*)-aldehyde **76** with a mixture of *cis*- and *trans*-(tri-*n*-butyl)crotylstannanes[44] at low temperature. This led to Felkin product **77** with a diastereoselectivity >15:1 (Scheme 13). After protection of **77** as silyl ether **78**, the primary silyl group was cleaved selectively with ammonium fluoride in hot methanol,[45] and the resulting alcohol **79** was oxidized under Swern conditions[22] to aldehyde **80**. A Grignard reaction of the latter with ethylmagnesium bromide produced a 1:1 mixture of stereoisomeric alcohols **81** that underwent oxidation to ethyl ketone **82** with Dess−Martin periodi-

(44) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.

Scheme 14



Scheme 15



nane.[46] Ozonolysis of alkene **82** followed by a reductive workup yielded the keto aldehyde **83**, which, due to its propensity to undergo intramolecular aldol condensation, was prepared only as needed for its immediate olefination with phosphonate **75**.

The stereopentad corresponding to **4** was also prepared from (*R*)-aldehyde **76**. Asymmetric crotylation of **76** with the trans crotylboronate **84** from (*S,S*)-tartrate[16b] gave syn,anti alcohol **85**, accompanied by its syn,syn stereoisomer, as a 9:1 mixture (Scheme 14). After purification by chromatography, the silyl ether **86** of the major isomer was ozonized, and the resulting aldehyde **87** was treated with the boronate **88** prepared from (*R,R*)-tartrate in a matched crotylation[16] that produced alcohol **89** as a single (>98:2) stereoisomer.

The selection of a protecting group for this homoallylic alcohol now became an issue of pivotal significance for two reasons. First, the hydroxyl substituent of **89** is destined to become the ketone at C11 of **2**, and a masking device must therefore be used that is orthogonal to all other protecting groups in order for it to be removed selectively at a late stage when virtually the entire functionality of the macrolide is in place. Second, the oxygen substituent at C5 of **89** is positioned to play a key role in the aldol coupling envisioned for the linkage that creates the C8−C9 bond of **2**. It was anticipated that construction of the syn,syn triad at C8−C10 would be critically dependent upon the presence in the aldehyde of a *β*-alkoxy substituent capable of chelation to the carbonyl, so that Felkin addition of a ketone enolate to the aldehyde would predominate. The reasoning that led to protection of **89** as its *p*-methoxybenzyl ether **90** was based on the broad knowledge that this ether is an excellent chelating ligand for metals typically employed in enolate formation.[47] The aldol partner representing **4** (Scheme 1) therefore became aldehyde **91**, obtained by ozonolysis of alkene **90**.

Assembly of Subunits. The sequence of subunit assembly specified in Scheme 1 was decided primarily by the instability of **83**, which necessitated utilization of this reactive aldehyde immediately after its preparation from **82**. Wadsworth-Emmons condensation[48] of phosphonate **75** with **83** gave trans α,*β*-unsaturated ester **92** as the sole stereoisomer, thus completing the first key connection and setting the stage for the pivotal aldol coupling of this ketone with aldehyde **91** (Scheme 15). The syn,syn,syn relationship of substituents across C6−C10 of **2** stipulates that if a *Z*(O) enolate of **92** is to be employed in this aldol reaction, it must attack the *re* face of **91** in a Felkin sense in order to produce the correct configuration at C8 and C9. Stereoselectivity in double asymmetric aldol reactions is dependent upon a variety of factors, including the metal counterion to the enolate, the nature and configuration of flanking substituents, and the protecting groups attached to neighboring oxygens. Indeed, Roush showed that the anti-Felkin pathway is often preferred in these reactions,[49] an outcome we

(45) White, J. D.; Amedio, J. C., Jr.; Gut, S.; Jayasinghe, L. *J. Org. Chem.* **1989**, *54*, 4268.
(46) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

(47) For a recent application of this concept, see: White, J. D.; Carter, R. G.; Sundermann, K. F. *J. Org. Chem.* **1999**, *64*, 684.
(48) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.

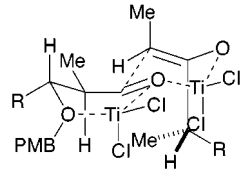


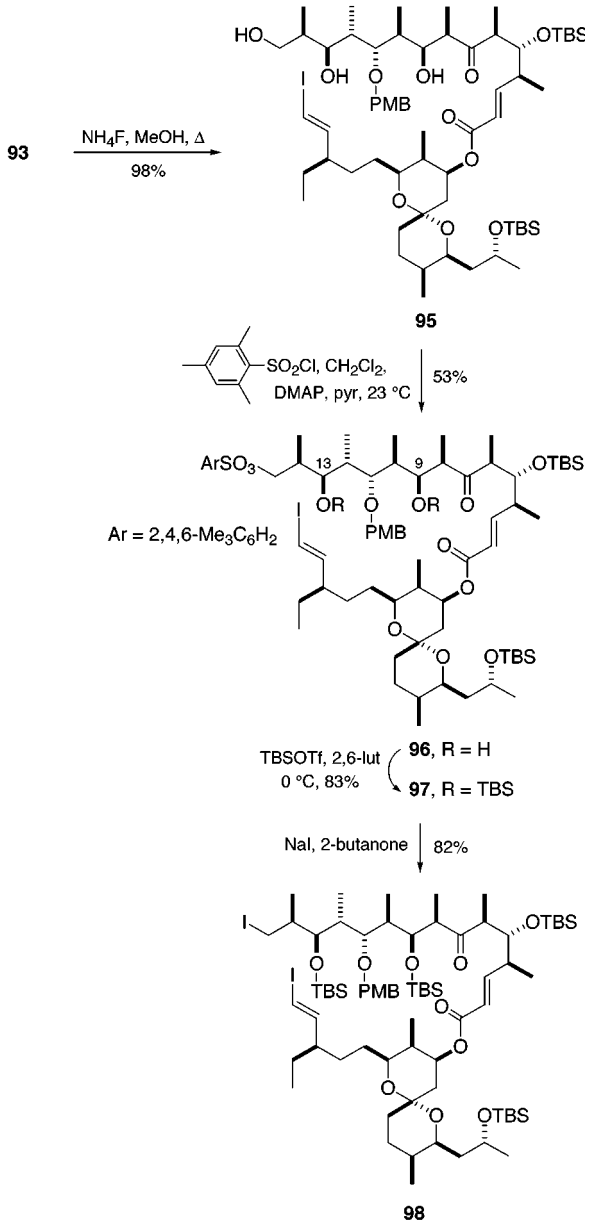
Figure 1. Proposed transition state for the reaction of **92** with **91** and **108**.

wished to avoid. On the other hand, Evans found that titanium enolates are highly effective in controlling the stereochemistry of double asymmetric aldol reactions leading to a syn,syn orientation of substituents,[50] and this was confirmed by Roush in his synthesis of the polypropionate subunit of rutamycin B.[51] In our case, the *Z*(O)-titanium enolate of **92**, prepared with titanium tetrachloride in the presence of Hünig's base, reacted with **91** to give the Felkin aldol product **93** as the only detectable stereoisomer (>98:2).[52] When the *p*-methoxybenzyl ether in **91** was replaced by a triethylsilyl ether, the aldol reaction with **92** produced a complex mixture resulting from both Felkin and anti-Felkin pathways along with desilylated products. This result is in agreement with the observations of Roush.[51]

A rationale for the high stereoselectivity in the coupling of **91** with **92** has been advanced that invokes bidentate chelation of the carbonyl oxygen of aldehyde **91** with a pair of titanium atoms.[11b] A representation of the transition state reflecting this mode of chelation is shown in Figure 1. Although structural evidence, including that gleaned from X-ray crystallography, confirms that a carbonyl oxygen is capable of bidentate chelation with oxyphilic, electron-deficient metal atoms,[53] a reaction pathway that utilizes this property has not been conclusively demonstrated. Nevertheless, the mechanism depicted in Figure 1 explains certain features of the reaction of **91** with **92**, including the observation that both the yield and stereoselectivity are optimal when a small excess of titanium tetrachloride is used. If indeed Figure 1 represents an accurate view of the aldol transition state for the formation of **93**, bidentate coordination of the aldehyde carbonyl with titanium(IV) adds a feature not considered in existing models for double asymmetric aldol reactions of α-chiral ethyl ketones with *β*-alkoxy aldehydes. The transition state shown in Figure 1 accords with the suggestion of Roush that re face (Felkin) addition to aldehyde **91** by the enolate of **92** is reinforced by (*S*) configuration at the center α to the ketone.[51] This matched arrangement is apparently sufficient to overcome a gauche-pentane interaction between the methyl substituent α to the aldehyde and the methyl group of the *Z* enolate.

Our intention with aldol product **93** was to selectively unmask the primary silyl ether so that activation of the liberated alcohol could be used to insert an ethylene synthon between C15 and the distal iodoalkene moiety. Although closure of the 26-membered macrocycle in this

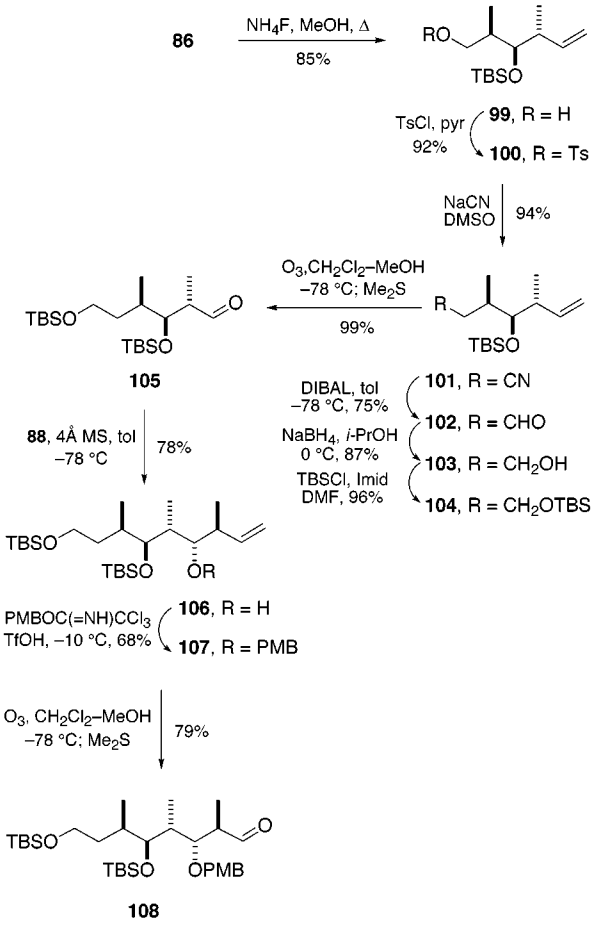
Scheme 16



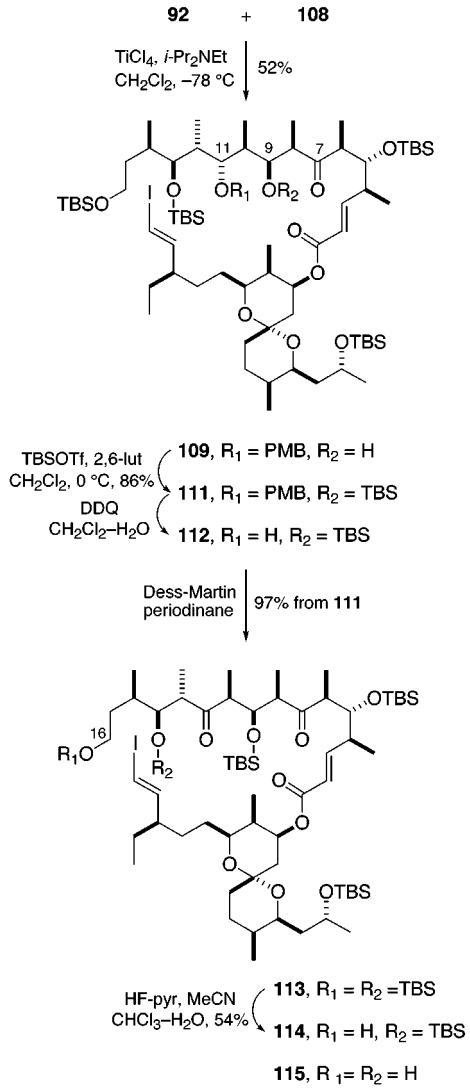
way has no direct precedent, it offers an attractive method for emplacing the conjugated trans,trans diene unit in a stereocontrolled fashion. The first complication in this plan arose when it was discovered that fluoride sources such as HF-pyridine or ammonium fluoride, which typically exhibit good selectivity in the cleavage of primary *tert*-butyldimethylsilyl ethers, removed the silyl groups at *both* C15 and C13 of **93** (Scheme 16). The same outcome was observed when deprotection was attempted on **94**, obtained by silylation of aldol product **93**. In neither case were other secondary silyl ethers cleaved, and it seems reasonable to conclude that silyl migration occurs from the oxygen at C13 after the primary alcohol is liberated, and that a second deprotection ensues to give **95**.[54] Fortunately, this unanticipated event had no deleterious consequences, since the primary alcohol of **95** could be selectively activated as its mesitylenesulfonate **96**.[55] The remaining secondary alcohols

(49) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.
(50) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866.
(51) Gustin, D. J.; Van Nieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3447.
(52) For a discussion of double-stereodifferentiating aldol reactions of a similar type, see: Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073.
(53) Tschinkl, M.; Schier, A.; Riede, J.; Gabbai, F. P. *Organometallics* **1999**, *18*, 1747, and references cited.
(54) Yamazaki, T.; Oniki, T.; Kitazume, T. *Tetrahedron* **1996**, *52*, 11753.
(55) Lohrmann, R.; Khorana, H. G. *J. Am. Chem. Soc.* **1966**, *88*, 829.

Scheme 17



Scheme 18



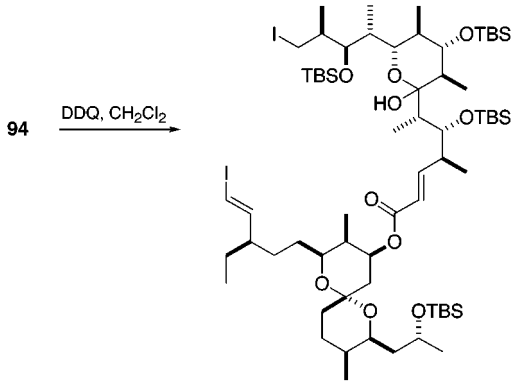
at C9 and C13 were silylated to give **97**, and displacement of the sulfonate with sodium iodide then yielded the diiodo compound **98**. However, numerous attempts to replace the primary iodide of **98** with a trans stannylethylene unit employing cuprate reagents of the type $RCu(CH{=}CHSnBu_3)(CN)Li_2$,[56] where R = 2-thienyl, 1-heptynyl, etc. were to no avail. A minor product noted in most cases resulted from conjugate addition of the cuprate reagent to the α,β-unsaturated ester of **98**.

The failure to homologate **98** by displacement of the primary iodide forced us to adopt a different tactic for reaching our seco precursor **3** for macrocyclization, and to this end a simple revision was made to the route leading to the C9−C15 polypropionate segment by incorporating an additional carbon, C16, at the outset. Thus, selective deprotection of the primary silyl ether of **86** followed by tosylation of alcohol **99** afforded **100** which underwent displacement with sodium cyanide to yield nitrile **101** (Scheme 17). Unlike **93**, the bis(silyl) ether **86** did not suffer silyl migration during its exposure to ammonium fluoride in methanol. Nitrile **101** was reduced to aldehyde **102**, which was further reduced to alcohol **103** and protected as silyl ether **104** before ozonolysis to furnish aldehyde **105**. A matched crotylation of **105** with boronate **88**[16] gave homoallylic alcohol **106** with excellent stereoselectivity, and following the protocol employed with **89**, this alcohol was converted to its *p*-methoxybenzyl ether **107**. Subsequent aldol coupling of the aldehyde **108**, prepared by ozonolysis of **107**, with ketone **92** again proceeded with very high stereoselectivity and gave hydroxy ketone **109** as the only stereoisomer detectable by NMR spectroscopy (Scheme 18).

At this point, the route forward diverged from the pathway from **93** because we were fearful of mishap if removal of the *p*-methoxybenzyl group was postponed to a stage at which the conjugated diene was already in place. We were also cognizant of the possibility that the C11 hydroxyl when liberated could form an internal hemiketal with the C7 ketone, since removal of the *p*-methoxybenzyl protection from **94** had led to exactly that outcome in the form of **110** (Scheme 19). Nevertheless, precedent in the work of Evans[9] suggested that rapid oxidation of the C11 alcohol to a ketone could circumvent hemiketal formation, and this proved to be the case. First, it was necessary to protect the hydroxyl substituent of **109** in order to avoid unwanted oxidation at C9 in conjunction with pending formation of the C11 ketone; this was accomplished by silylation to give pentasilyl ether **111**. The *p*-methoxybenzyl ether was removed from **111** with dichlorodicyanobenzoquinone, and the resulting alcohol **112** was immediately oxidized to **113** using Dess−Martin periodinane.[46] The silyl ether at C16 was then cleaved with HF−pyridine, again with accompanying silyl migration, to furnish primary alcohol **114** as the major product and diol **115** as an easily separable

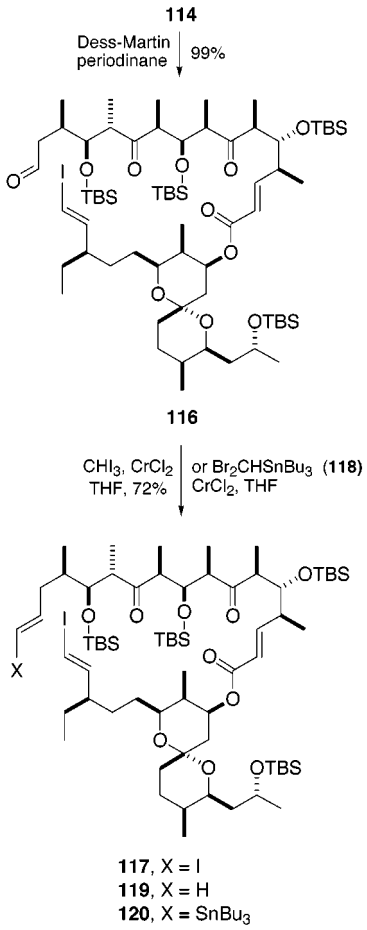
(56) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

Scheme 19



110

Scheme 20



117, X = I
119, X = H
120, X = $SnBu_3$

byproduct. The former was oxidized to aldehyde **116** in preparation for a one-carbon homologation to produce a functionalized trans alkene at this terminus. Our hope was that the rutamycin macrocycle could be closed from this species using a vinyl-vinyl coupling, and the first effort along this line was made with the diiodo compound **117**, prepared by a Takai reaction[43] of **116** with iodoform and chromous chloride. Following precedent suggested by recent work of Liebeskind,[57] **117** was treated with copper(I) thiophene-2-carboxylate, but no evidence of intramolecular vinyl−vinyl coupling was seen. A variant of this approach employing dibromo(tri-*n*-butylstannyl)-methane (**118**)[58] was investigated with the goal of closing the macrocycle via a Stille coupling. However, treatment of **116** with **118** and chromous chloride gave mainly the destannylated product **119** accompanied by lesser quantities of the trans stannane **120** and its cis isomer (Scheme 20).

The remaining option for macrocyclization appeared to be an intramolecular Suzuki coupling[59] of a vinylboronate derived from aldehyde **116**, and implementation of this plan began with preparation of the known dichloromethylboronate **121**[60] of pinacol. The latter was condensed with **116** in the presence of chromous chloride and lithium iodide[61] to yield the readily isolable trans vinyl boronate **122** (Scheme 21). Intramolecular coupling of **122** proceeded smoothly in the presence of catalytic palladium dichloride acetonitrile complex and triphenylarsine to provide the macrocycle **123** in good yield. As noted by others,[62] addition of silver oxide to the reaction medium was found to improve the efficiency of Suzuki coupling. That the correctly functionalized skeleton of rutamycin B had been assembled in this process was proven by exhaustive silylation of a sample of the natural material with *tert*-butyldimethylsilyl triflate, which furnished a substance identical with **123** in all respects. Final cleavage of the silyl ethers from **123** with HF−pyridine over 4 days, a process in which successive cleavage of each of the four ethers could be discerned by thin-layer chromatography, led to rutamycin B (**2**).

In summary, a convergent synthesis of rutamycin B (**2**) was accomplished from three principal subunits—spiroketal **75**, ketone **83**, and aldehyde **108**—in 0.22% overall yield. The longest linear sequence, that leading to **108**, is 12 steps and proceeds in 18% overall yield. Successful closure of the 26-membered ring of rutamycin B via intramolecular Suzuki coupling represents an unconventional strategy among syntheses of macrolides of this class, and confirms that this carbon−carbon bond forming reaction can rival traditional macrolactonization techniques for convenience and efficiency.

Experimental Section

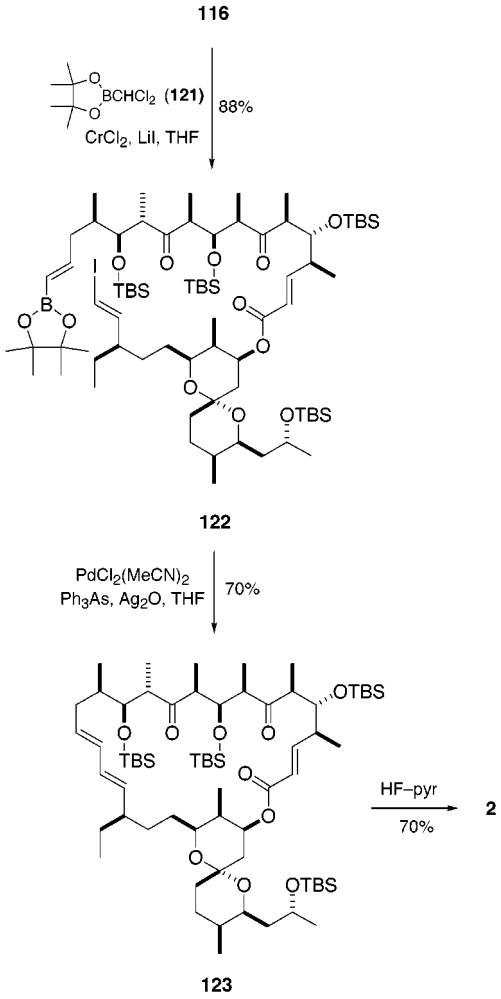
General Methods. Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying agents immediately prior to use. Tetrahydrofuran and ether were distilled from sodium or potassium and benzophenone under an argon atmosphere. Toluene, diisopropylamine, diisopropylethylamine, triethylamine, pyridine, and dichloromethane were distilled from calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade. Moisture- and air-sensitive reactions were carried out under an atmosphere of argon. Reaction flasks were flame dried under a stream of argon gas, and glass syringes were oven dried at 120 °C prior to use.

Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure. Residual solvent was removed by vacuum pump at a pressure less than 0.25 mm of mercury.

Analytical thin-layer chromatography (TLC) was conducted using E. Merck precoated TLC plates (0.2 mm layer thickness

(57) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.
(58) Hodgson, D. M.; Boulton, L. T.; Maw, G. N. *Tetrahedron* **1995**, *51*, 3713.
(59) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.
(60) Wuts, P. G. M.; Thompson, P. A. *J. Organomet. Chem.* **1982**, *234*, 137.
(61) Takai, K.; Shinomiya, N.; Kaihara, H.; Yoshida, N.; Moriwake, T. *Synlett* **1995**, 963.
(62) Gillmann, T.; Weeber, T. *Synlett* **1994**, 649.

Scheme 21



of silica gel 60 F-254). Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 3−5% solution of phosphomolybdic acid in ethanol, 10% ammonium molybdate in water, a 1% solution of vanillin in 0.1 M sulfuric acid in methanol or 2.5% *p*-anisaldehyde in 88% ethanol, 5% water, 3.5% concentrated sulfuric acid, and 1% acetic acid. Flash chromatography was carried out using either Merck silica gel 60 (230−400 mesh ASTM) or Scientific Adsorbents Inc. silica gel (40 μm partical size). Radial chromatography was carried out on individually prepared rotors with layer thicknesses of 1, 2, or 4 mm using a Chromatotron manufactured by Harrison Research, Palo Alto, CA.

Melting points were measured using a Büchi melting point apparatus. Optical rotations were measured with a Perkin-Elmer 243 polarimeter at ambient temperature using a 0.9998 dm cell with 1 mL capacity. Infrared (IR) spectra were recorded with a Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either a Bruker AC-300 or a Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. ^{1}H NMR spectral data are reported in the order: chemical shift, number of protons, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad), and coupling constant (*J*, in hertz).

Chemical ionization (CI) high- and low-resolution mass spectra (HRMS and MS) were obtained using a Finnigan 4023 spectrometer or a Kratos MS-50 spectrometer with a source temperature of 120 °C and methane gas as the ionizing source. Perfluorokerosene was used as a reference. Electron impact (EI) mass spectra (HRMS and MS) were obtained with a Varian MAT311 or a Finnegan 4000 spectrometer. Fast atom bombardment (FAB) mass spectra were obtained using a Kratos MS-50 spectrometer. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

(*Z*)-(2*S*,8*R*,9*S*,12*R*)-9-[(*tert*-Butyldimethylsilyl)oxy]-12-[(*tert*-butyldimethylsilyl)oxymethyl]-2-[(4*S*,6*R*)-2,2-di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]-8-methyl-5-(2,2-dimethylhydrazino)-5-tetradecan-7-one (40). To a solution of diisopropylamine (0.021 mL, 0.091 mmol) in tetrahydrofuran (0.7 mL) under argon at −30 °C was added dropwise methyllithium (1.35 M in ether, containing less than 0.05M halide, 0.060 mL, 0.081 mmol). The colorless solution was warmed to 0 °C, stirred for 10 min, cooled to −4 °C, and added dropwise to a solution of crude **39** (25 mg) in tetrahydrofuran (0.7 mL). The yellow solution was stirred for 50 min at −2 °C, cooled to −78 °C, and transferred into a precooled (−57 °C) solution of **38** (26 mg, 0.055 mmol) via cannula. The resulting pale yellow solution was stirred for 20 h at −45 °C, for 1.5 h at −30 °C, and for 19 h at −18 °C. The mixture was cooled to −78 °C and was transferred into a rapidly stirred biphasic solution of ether (20 mL) and saturated ammonium chloride solution (20 mL) at 0 °C via cannula. The mixture was stirred for 15 min and was partitioned, and the aqueous layer was extracted three times with ethyl acetate (20 mL). The combined organic layers were dried (sodium sulfate), and the solvent was removed under reduced pressure. Chromatography of the residue on silica gel, with gradient elution from 5% to 30% ethyl acetate in hexane, gave 5.6 mg (67% based on recovered **38**) of **40** as a colorless, unstable oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.02 (12H, s), 0.87 (21H, m), 0.91 (3H, d, J = 6 Hz), 0.95 (3H, d, J = 6 Hz), 1.01 (18H, s), 1.06 (3H, d, J = 7 Hz), 1.21−1.36 (8H, m), 1.41−1.51 (4H, m), 1.80 (1H, m), 2.01 (2H, m), 2.30−2.50 (3H, m), 2.53 (3H, s), 3.40−3.50 (2H, m), 3.86−3.95 (1H, m), 4.00−4.10 (1H, m), 4.40 (1H, m), 4.90 (1H, m), 11.29 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.5, −4.8, −4.4 (4C), 11.1, 12.7, 13.9, 18.0, 18.2, 20.7, 21.3, 23.2, 23.4, 25.5, 25.9, 26.0 (6C), 26.1, 27.0, 27.1, 27.2 (6C), 37.5, 38.7, 39.2, 41.1, 41.5, 42.2, 48.7, 65.2, 67.7, 70.7, 71.1, 74.8, 92.1, 167.2, 200.1.

(2*S*,3*R*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-hydroxy-1-propyl]-2-[(*R*)-3-hydroxymethyl-1-pentyl]-1,7-dioxaspiro-[5.5]undecan-4-one (41). From 40. A solution of **40** (3.6 mg, 0.0046 mmol) in a hydrofluoric acid−acetonitrile−water stock solution [9:1 [95:5 (CH_3CN/48%HF)]/H_2O, 0.5 mL] was stirred for 5 d at room temperature, during which time an additional 0.2 mL of the stock solution was added at 20 and 47 h. The solution was added to saturated aqueous sodium bicarbonate (2 mL) and water (8 mL), and the mixture was extracted once with ethyl acetate (15 mL) and twice with ether (15 mL). The combined organic layers were dried (magnesium sulfate), and the solvent was removed under reduced pressure. Chromatography of the residue on silica gel, with gradient elution from 15% to 70% ethyl acetate in hexane, gave 1.2 mg (73%) of **41** as a colorless oil: $[\alpha]^{22}_D$ −105.5 (*c* 1.13, $CHCl_3$); IR (neat) 3389, 3382, 2964, 2938, 2878, 1716, 1457, 1377, 1304, 1251, 1085, 972 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (6H, m), 0.98 (1H, d, J = 7 Hz), 1.08 (3H, d, J = 7 Hz), 1.13 (3H, d, J = 6 Hz), 1.16−1.40 (3H, m), 1.41−1.49 (3H, m), 1.51−1.71 (7H, m), 2.08−2.22 (1H, m, J = 5 Hz), 2.26−2.60 (1H + 2′OH′, m), 2.30 (1H, d, J = 14 Hz), 2.50 (1H, d, J = 14 Hz), 3.43−3.60 (2H, dtd, J = 24, 11, 6 Hz), 3.78−3.91 (1H, m, J = 6, 2 Hz), 3.98−4.06 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.5, 11.0, 11.3, 23.3, 24.8, 26.1, 26.5, 28.0, 29.4, 30.2, 41.8, 42.4, 47.9, 48.3, 63.9, 67.8, 70.6, 74.6, 98.9, 210.9; MS (CI) *m*/*z* 357 (M^+ + 1), 355, 339, 268, 255, 227, 211, 197, 185, 173, 155, 95; HRMS (CI) *m*/*z* 357.2639 (calcd for $C_{20}H_{36}O_5$ + H^+ 357.2642).

From 66. A solution of **66** (460 mg, 0.977 mmol) and tetra-*n*-butylammonium fluoride (2.05 mL, 2.05 mmol) in tetrahydrofuran (15 mL) under argon was stirred for 8.5 h at room temperature. The mixture was added to ether (45 mL), and the solution was washed with brine (50 mL). The aqueous wash was extracted once with ethyl acetate (50 mL) and twice with ether (50 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent under reduced pressure was followed by chromatography of the residue on silica gel, with gradient elution from 30% to 60% ethyl acetate in hexane, to yield 236 mg (68%) of **41** as a colorless oil.

Hydroxy Sulfone 59. To a solution of **56** (37 mg, 0.090 mmol) in tetrahydrofuran (1 mL) under argon at −78 °C was added dropwise *n*-butyllithium (1.58 M in hexane, 0.057 mL, 0.090 mmol). The yellow solution was stirred for 45 min, and freshly distilled trifluoroboron etherate (0.011 mL, 0.090 mmol) was added dropwise. The mixture was stirred for 5 min, after which time a precooled (−78 °C) solution of **58** (20 mg, 0.035 mmol) in tetrahydrofuran (0.8 mL) was added dropwise via cannula. The pale yellow solution was stirred for 3 h at −78 °C and for 1 h at room temperature. The reaction was quenched by addition of saturated ammonium chloride solution (1 mL), diluted with ether (20 mL), and washed with saturated ammonium chloride solution (20 mL) and brine (20 mL). The aqueous wash was extracted three times with ether (30 mL), and the combined ethereal extracts were dried (magnesium sulfate). Removal of the solvent under reduced pressure was followed by chromatography of the residue on silica gel, with gradient elution from 5% to 10% ethyl acetate in hexane, to yield, 15 mg of recovered **56**, and 30 mg (86%) of **59** as a colorless oil: IR (neat) 3535, 2956, 2933, 2899, 2859, 1480, 1263, 1260, 1160, 1093, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04 (18H, m), 0.71 (4H, dd, J = 13, 7 Hz), 0.89 (33H, m), 0.99 (18H, s), 1.26 (10H, m), 1.48 (4H, m), 1.75 (3H, m), 2.01 (3H, m), 3.04 (1H, m), 3.48 (2H, m), 3.75 (1H, m), 3.98 (2H, m), 4.29 (1H, m), 4.38 (1H, m), 7.56 (2H, m), 7.63 (1H, m), 7.88 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.5, −4.7, −4.5, −4.3, −3.9, −3.8, 9.3, 9.8, 11.1, 12.9, 17.9, 18.0, 18.2, 20.7, 21.3, 23.3, 24.6, 25.8, 25.9 (9C), 26.5, 27.1, 27.2 (6C), 31.7, 37.3, 37.4, 42.5, 65.3, 66.1, 67.6, 70.0, 70.6, 70.9, 73.1, 128.5 (2C), 129.1 (2C), 133.7, 138.2; MS (FAB) m/z 1002 (M^+ + 1), 1001 (M^+), 986, 943, 869, 812, 737, 679, 625, 595, 567, 463, 419, 359, 269, 227.

Keto Sulfone 60. A suspension of **59** (6.5 mg, 0.0065 mmol), powdered activated 4 Å molecular sieves, 4-methylmorpholine *N*-oxide, and tetra-*n*-propylammonium perruthenate in dichloromethane (1 mL) under argon was stirred for 2.5 h at room temperature. The mixture was filtered through a short plug of Celite that was rinsed with dichloromethane. Removal of the solvent from the filtrate under reduced pressure followed by chromatography of the residue on silica gel, with gradient elution from 3% to 9% ethyl acetate in hexane, afforded 5.6 mg (86%) of **60** as a colorless oil: IR (neat) 2959, 2938, 2892, 2867, 1723, 1475, 1331, 1264, 1149, 1097, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.02 (18H, m), 0.83 (9H, s), 0.88 (9H, s), 0.89 (9H, s), 0.94 (18H, s), 0.80−0.97 (8H, m), 1.24 (3H, d, J = 7 Hz), 1.21−1.40 (7H, m), 1.49 (3H, m), 1.65 (1H, m), 1.80 (1H, m), 2.03 (2H, m), 2.64−3.01 (1H, 2dd, J = 20, 6 Hz), 3.10−3.32 (1H, 2dd, J = 20, 6 Hz), 3.47 (2H, m), 3.84 (1H, m), 3.95 (1H, m), 4.13 (1H, dd, J = 11.7, 3.1 Hz), 4.25 (1H, m), 4.36 (1H, m), 7.53 (2H, m), 7.66 (1H, m), 7.77 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.5, −4.7, −4.5, −4.3, −4.1, −3.7, 9.4, 11.1, 12.5, 17.9, 18.1, 18.2, 20.6, 21.3, 23.2, 23.3, 25.5, 25.8, 25.9 (9C), 26.0, 27.1, 27.2 (6C), 31.2, 36.9, 41.0, 42.3, 49.9, 51.4, 65.1, 67.9, 68.2, 69.8, 71.2, 72.9, 128.8, 129.2, 134.0, 136.5, 200.5; MS (FAB) m/z 999 (M^+ + 1), 997, 941, 887, 867, 735, 728, 643, 611, 595, 575, 549, 519, 503, 429, 413, 323, 253, 217, 201, 181.

(2*S*,7*S*,8*R*,9*S*,12*R*)-7,9-Di[(*tert*-butyldimethylsilyl)oxy]-12-[(*tert*-butyldimethylsilyl)oxymethyl]-2-[(4*S*,6*R*)-2,2-di-*tert*-butylsilylene-6-methyl-1,3-dioxan-4-yl]-8-methyltetradecan-5-one (61). A flame-dried flask under argon was charged with samarium (900 mg, 6.00 mmol). The flask was evacuated under high vacuum for 15 min and was refilled with argon. This process was repeated three times. Freshly distilled tetrahydrofuran (30 mL) and diiodomethane (0.244 mL, 3.00 mmol) were added with vigorous stirring at room temperature, and the dark blue solution was stirred for 1 h. This stock solution of samarium diiodide could be stored for 3 months under argon.

To a solution of **60** (14.5 mg, 0.0145 mmol) in tetrahydrofuran (1.6 mL) and methanol (0.8 mL) under argon at −78 °C was added a freshly prepared solution of samarium diiodide (0.10 M in tetrahydrofuran, 0.580 mL, 0.0580 mmol). The reaction flask was covered with foil, and the dark blue solution was stirred for 30 min at −78 °C. The solution was allowed to warm to room temperature during 1 h and diluted with ether (20 mL). The ethereal solution was washed with saturated potassium carbonate solution (20 mL), and the aqueous wash was extracted three times with ether (20 mL). The combined ethereal extracts were dried (magnesium sulfate), and the solvent was removed under reduced pressure. Chromatography of the residue on silica gel, with gradient elution from 2% to 5% ethyl acetate in hexane, gave 11.0 mg (89%, 97% based on recovered **60**) of **61** as a colorless oil: $[\alpha]^{22}_D$ +19.8 (*c* 0.85, $CHCl_3$); IR (neat) 2963, 2932, 2896, 2860, 1715, 1476, 1386, 1257, 1103, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.01 (3H, s), 0.03 (6H, s), 0.06 (6H, s), 0.07 (3H, s), 0.83 (3H, d, J = 7 Hz), 0.84−0.91 (6H, m), 0.86 (9H, s), 0.89 (9H, s), 0.90 (9H, s), 1.00 (18H, s), 1.15−1.36 (5H, m), 1.29 (3H, d, J = 7 Hz), 1.37−1.53 (5H, m), 1.60−1.67 (1H, m), 1.70−1.81 (1H, m), 2.00−2.08 (1H, ddd, J = 16, 10, 6 Hz), 2.34−2.54 (2H, m), 2.56−2.68 (2H, ddd, J = 20, 16, 4 Hz), 3.48 (2H, ddd, J = 15, 10, 6 Hz), 3.83 (1H, q, J = 6 Hz), 4.00 (1H, td), 4.21 (1H, q, J = 6 Hz), 4.39 (1H, m, J = 12, 6, 2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.5, −5.4, −4.5, −4.4, −4.2, −3.6, 9.9, 11.1, 13.9, 18.0, 18.1, 18.3, 20.8, 21.3, 23.3, 23.5, 25.8, 25.9, 26.0 (9C), 26.8, 27.3 (6C), 32.2, 37.7, 38.9, 41.9, 42.3, 42.4, 47.9, 65.1, 67.7, 70.1, 71.4, 72.1, 209.9; MS (CI) m/z 858 (M^+), 844, 802, 728, 670, 630, 596, 538, 498, 471, 359, 269, 227, 199, 147, 115; HRMS (CI) m/z 801.5738 (calcd for $C_{46}H_{98}O_6Si_4 - C_4H_9$ 801.5739).

(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-hydroxy-1-propyl]-2-[(*R*)-3-(hydroxymethyl)-1-pentyl]-1,7-dioxaspiro-[5.5]undecan-4-ol (62). From 61. To a Nalgene vial containing **61** (10 mg, 0.010 mmol) at room temperature was added a stock solution of 48% hydrofluoric acid−acetonitrile (1:7, 3 mL). The mixture was stirred for 48 h, diluted with ether (20 mL), and washed with brine (15 mL) and water (15 mL). The aqueous wash was extracted once with ethyl acetate (20 mL) and twice with ether (20 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent under reduced pressure was followed by chromatography of the residue on silica gel, with gradient elution from 40% to 95% ethyl acetate in hexane to yield 3.4 mg (82%) of **62** as a white solid: $[\alpha]^{22}_D$ −82.5 (*c* 0.16, $CHCl_3$); IR (neat) 3350 (br), 2964, 2940, 2876, 1455, 1386, 1059, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (3H, d, J = 7 Hz), 0.87 (3H, m), 0.90 (3H, d, J = 8 Hz), 1.19 (3H, d, J = 6 Hz), 1.24 (2H, t, J = 7 Hz), 1.30−1.65 (12H, m), 1.68−1.74 (1H, dd, J = 13, 5 Hz), 1.82−1.86 (1H, m), 2.03−2.16 (1H, m), 2.56−2.58 (3H, br), 3.44−3.50 (1H, dd, J = 11, 4 Hz), 3.55−3.60 (1H, dd, J = 11, 4 Hz), 3.71−3.97 (1H, m), 4.03−4.77 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.9, 11.1, 11.3, 23.3, 24.5, 26.4, 26.6, 29.0, 29.7, 30.7, 37.7, 38.9, 41.9, 42.3, 64.4, 64.5, 67.2, 67.3, 71.2, 97.4; MS (CI) m/z 358 (M^+), 341, 323, 270, 228, 211, 171, 113, 95; HRMS (CI) m/z 358.2717 (calcd for $C_{20}H_{38}O_5$ 358.2720).

From 68. A solution of **68** (127 mg, 0.220 mmol) and tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 1.10 mL, 1.10 mmol) in tetrahydrofuran (8 mL) under argon was stirred for 24 h at room temperature. The solution was diluted with ether (30 mL) and washed with brine (30 mL). The aqueous wash was extracted once with ethyl acetate (30 mL) and twice with ether (30 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, with gradient elution from 40% to 90% ethyl acetate in hexane to yield 77.0 mg (98%) of **62** as a white solid: $[\alpha]^{22}_D$ −82.8 (*c* 1.01, $CHCl_3$).

(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-4-[(Diethylphosphonoacetyl)oxy]-3,9-dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-[(*R*)-3-ethyl-5-(*E*)-iodo-4-pentenyl]-1,7-dioxaspiro-[5.5]undecane (75). A solution of triethyl phosphonoacetate (5.0 g, 22 mmol) and potassium hydroxide (1.5 g, 24 mmol) in ethanol (3.5 mL) and water (1.4 mL) was stirred for 15 h at room temperature. The volatile components were removed under reduced pressure, and the residue was dissolved in water (20 mL). The mixture was extracted twice with ether (30 mL), and the combined organic layers were washed with water (40 mL) and acidified to pH 1 using 2 N hydrochloric acid. Brine (50 mL) was added, and after separation the aqueous layer was extracted three times with dichloromethane (50 mL). The combined organic layers were dried (magnesium

sulfate), and the solvent was removed under reduced pressure to give 3.0 g (69%) of diethyl phosphonoacetic acid as a pale yellow oil.

To a solution of the acid prepared above (700 mg, 3.57 mmol) in dichloromethane (6 mL) at 0 °C was added dropwise oxalyl chloride (0.477 mL, 5.36 mmol), and the mixture was stirred for 10 min at 0 °C and for 22 h at room temperature. Removal of the solvent under reduced pressure gave 766 mg of diethyl phosphonoacetyl chloride, which was used without purification.

To a solution of **74** (313 mg, 0.526 mmol), 4-(dimethylamino)pyridine (480 mg, 3.93 mmol), and pyridine (0.607 mL, 7.85 mmol) in dichloromethane (10 mL) under argon at 0 °C was added dropwise a solution of diethyl phosphonoacetyl chloride prepared above (766 mg) in dichloromethane (3 mL). The yellow solution was stirred for 1 h at 0 °C and was quenched by addition of saturated sodium bicarbonate solution (5 mL). The mixture was diluted with dichloromethane (30 mL), and was washed with saturated sodium bicarbonate solution (30 mL), water (30 mL) and brine (30 mL). The aqueous wash was extracted three times with dichloromethane (80 mL), and the combined organic extracts were dried (magnesium sulfate). Removal of the solvent followed under reduced pressure by chromatography of the residue on silica gel, using 40% ethyl acetate in hexane as eluant, gave 392 mg (96%) of **75** as a pale yellow oil: $[\alpha]^{22}_D$ −42.8 (*c* 0.56, $CHCl_3$); IR (neat) 2958, 2952, 1735, 1273, 1257, 1057, 1028, 971 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04 (6H, s), 0.82−0.90 (18H, m), 1.17 (3H, d, J = 6 Hz), 1.24−1.63 (19H, m), 1.71−1.78 (2H, m), 1.86−2.08 (3H, m), 2.91 (1H, d, $J_{P,H}$ = 22 Hz), 3.62 (1H, m), 3.69 (1H, dt, J = 7, 2 Hz), 3.80 (1H, m), 4.15 (1H, quint, J = 7 Hz), 5.26 (1H, dt, J = 12, 5 Hz), 5.94 (1H, d, J = 14 Hz), 6.26 (1H, dd, J = 14, 9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.5, −4.3, 4.8, 11.0, 11.5, 16.3 (d, $J_{P,C}$ = 6 Hz) (2C), 18.1, 24.4, 25.9 (3C), 26.3, 27.0, 29.6, 30.1, 31.0, 34.5 (d, $J_{P,C}$ = 134 Hz), 35.0, 35.5, 43.2, 48.7, 62.6 (d, $J_{P,C}$ = 6 Hz) (3C), 67.1, 69.4, 70.2, 72.2, 74.2, 97.4, 150.3, 164.9 (d, $J_{P,C}$ = 6 Hz); MS (FAB) *m*/*z* 773 (M^+ + 1), 772 (M^+), 771, 715, 672, 645, 577, 519, 345, 325, 253, 193; HRMS (FAB) *m*/*z* 773.3078 (calcd for $C_{33}H_{62}IO_8PSi$ + H^+ 773.3074).

Ketone 92. To a solution of diisopropylamine (0.037 mL, 0.026 mmol) in tetrahydrofuran (0.2 mL) under argon at 0 °C was added dropwise *n*-butyllithium (1.33 M in hexane, 0.020 mL, 0.027 mmol), and the mixture was stirred for 15 min at 0 °C. The solution was cooled to −78 °C, and a solution of **75** (20 mg, 0.026 mmol) in tetrahydrofuran (0.4 mL) was added dropwise. The solution was stirred for 45 min at −78 °C, and a solution of **83** (8.1 mg, 0.028 mmol) in tetrahydrofuran (0.2 mL) was added dropwise. The solution was stirred for 45 min at −78 °C, slowly warmed to 0 °C during 15 min, and stirred for 30 min at 0 °C. A saturated ammonium chloride solution (2 mL) was added, and the mixture was stirred for 15 min and diluted with ether (20 mL). After separation, the aqueous layer was extracted three times with ether (10 mL), and the combined extracts were washed with 5% hydrochloric acid (20 mL), water (20 mL), and brine (20 mL) and dried (magnesium sulfate). Removal of the solvent under reduced pressure followed by chromatography of the residue on silica gel, using 7% ether in hexane as eluant, afforded 17 mg (76%) of **92** as a colorless oil: $[\alpha]^{22}_D$ −52.9 (*c* 1.17, $CHCl_3$); IR (neat) 2958, 2930, 1716, 1254, 1095, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.01 (3H, s), 0.05 (9H, s), 0.80−1.00 (25H, m), 1.02−1.05 (6H, m), 1.07 (3H, d, J = 8 Hz), 1.18 (3H, d, J = 6 Hz), 1.25−1.66 (15H, m), 1.76 (1H, dd, J = 13, 5 Hz), 1.89−2.09 (3H, m), 2.37−2.51 (3H, m), 2.61 (1H, quint, J = 7 Hz), 3.64−3.74 (2H, m), 3.80 (1H, m), 4.03 (1H, t, J = 5 Hz), 5.28 (1H, dt, J = 12, 5 Hz), 5.75 (1H, dd, J = 16, 1 Hz), 5.94 (1H, d, J = 14 Hz), 6.25 (1H, dd, J = 14, 9 Hz), 6.96 (1H, dd, J = 16, 7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.5, −4.3, −4.1 (4C), 4.9, 7.6, 11.0, 11.5, 13.3, 14.1, 18.1, 18.3, 24.5, 25.9, 26.0 (6C), 26.4, 27.0, 29.6, 29.7, 30.2, 31.0, 35.1, 35.3, 35.7, 41.5, 43.2, 48.7, 49.9, 67.2, 69.5, 70.3, 70.6, 74.2, 75.3, 97.5, 121.2, 150.4, 151.5, 165.6, 213.5; MS (FAB) *m*/*z* 904 (M^+), 890, 876, 847, 820, 759, 703, 637, 577, 519, 445, 403, 373, 345, 325, 267, 229, 193, 159; HRMS (FAB) *m*/*z* 577.2572 [calcd for $C_{44}H_{81}IO_7Si_2$ − OC(O)R ($C_{17}H_{31}O_4Si$) 577.2572].

Hydroxy Ketone 93. To a solution of **92** (102 mg, 0.11 mmol) in dichloromethane (700 μL) at −78 °C were added titanium(IV) chloride (1.0 M in dichloromethane, 135 μL, 0.135 mmol) and triethylamine (23 μL, 0.17 mmol). The mixture was stirred for 1.5 h at −78 °C, and a solution of **91** (67 mg, 0.12 mmol) in dichloromethane (700 μL) was added. The solution was stirred for 15 min at −78 °C and then was allowed to warm to −30 °C during 30 min. The solution was stirred for 2 h at −30 °C, and pH 7 phosphate buffer (2.5 mL) was added. The mixture was diluted with ether (5 mL), the layers were separated, and the aqueous layer was extracted three times with ether (10 mL). The combined extracts were washed with saturated sodium bicarbonate solution, water, and brine and were dried (magnesium sulfate). The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel, eluting with 10% ether in hexane, to give 101 mg (62%) of **93** as a colorless foam: $[\alpha]^{22}_D$ −31.2 (*c* 0.95, $CHCl_3$); IR (neat) 3495, 2956, 2887, 1717, 1650, 1616, 1252, 1039, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.01 (3H, s), 0.04 (3H, s), 0.06 (9H, s), 0.07 (3H, s), 0.12 (6H, s), 0.82 (3H, d, J = 7 Hz), 0.85 (3H, d, J = 7 Hz), 1.10 (3H, d, J = 7 Hz), 1.13 (3H, d, J = 7 Hz), 0.80−1.71 (27H, m), 1.76 (1H, dd, J = 13, 5 Hz), 1.94 (1H, m), 2.02−2.10 (3H, m), 2.36 (1H, m), 2.66 (1H, m), 2.83 (1H, m), 3.39 (1H, m), 3.46−3.50 (2H, m), 3.61 (1H, s), 3.66 (1H, m), 3.73 (1H, m), 3.79 (3H, s), 3.78−3.85 (2H, m), 4.07 (1H, t, J = 5 Hz), 4.11 (1H, d, J = 9 Hz), 4.44 (1H, d, J = 10 Hz), 4.59 (1H, d, J = 10 Hz), 5.28 (1H, dt, J = 12, 5 Hz), 5.73 (1H, dd, J = 15, 1 Hz), 5.95 (1H, d, J = 14 Hz), 6.26 (1H, dd, J = 14, 9 Hz), 6.85 (2H, d, J = 9 Hz), 6.96 (1H, dd, J = 15, 7 Hz), 7.22 (2H, d, J = 9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.23, −5.20, −4.4, −4.3, −4.23, −4.20, −3.9, −3.5, 5.0, 11.0, 11.2, 11.5, 12.1, 12.5, 13.4, 13.5, 14.6, 18.1, 18.3, 18.4, 18.4, 24.5, 25.9, 26.0, 26.1, 26.2, 26.4, 27.4, 29.6, 29.7, 30.2, 31.1, 35.1, 35.7, 38.3, 38.4, 41.4, 42.8, 43.2, 48.7, 49.8, 55.3, 66.6, 67.2, 69.5, 70.3, 70.6, 71.7, 72.8, 74.1, 74.2, 75.5, 86.4, 97.5, 113.9, 121.1, 129.2, 130.3, 150.4, 151.6, 159.3, 165.5, 215.2; HRMS (FAB) *m*/*z* 1457.8347 (calcd for $C_{74}H_{137}IO_{12}Si_4$ 1457.8308).

Hydroxy Ketone 109. To a solution of **92** (51.0 mg, 56.3 μmol) in dichloromethane (0.7 mL) was added titanium tetrachloride (1 M solution in dichloromethane, 61.9 μL, 61.9 μmol), and the brown-red solution was stirred for 1 h at −78 °C. A solution of **108** (34.0 mg, 61.9 μmol) in dichloromethane (100 μL) was added, and the mixture was stirred for 15 min at −78 °C and for 30 min at −50 °C. The reaction was quenched by addition of pH 7 phosphate buffer solution, and the mixture was extracted three times with ethyl acetate (15 mL). The combined extracts were washed with 5% aqueous sodium carbonate (5 mL), brine (5 mL), and dried (magnesium sulfate). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel, eluting with hexanes−ether (9:1 to 8:2), to yield 43.0 mg (52%) of **109** as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.01−0.15 (24H, m), 0.81−2.15 (88H, m), 2.32−2.41 (1H, m), 2.64−2.71 (1H, m), 2.82−2.90 (1H, m), 3.50−3.84 (7H, m), 3.79 (3H, s), 4.07−4.12 (2H, m), 4.43 (1H, d, J = 10 Hz), 4.60 (1H, d, J = 10 Hz), 5.27 (1H, td, J = 10, 5 Hz), 5.74 (1H, d, J = 16 Hz), 5.95 (1H, d, J = 14 Hz), 6.26 (1H, dd, J = 9, 14 Hz), 6.85 (2H, d, J = 9 Hz), 6.97 (1H, dd, J = 6, 16 Hz), 7.23 (2H, d, J = 9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.3, −5.2, −4.5, −4.3, −4.2, −3.9, −3.6, 4.9, 11.0, 11.5, 12.0, 12.9, 13.2, 13.4, 14.1, 15.0, 18.1, 18.3, 24.5, 25.9, 26.0, 26.1, 26.2, 26.4, 27.1, 29.5, 29.7, 30.2, 31.1, 31.8, 35.1, 35.7, 38.0, 38.4, 41.4, 42.4, 43.2, 48.7, 50.3, 55.3, 61.0, 67.2, 69.5, 70.3, 70.5, 72.0, 74.0, 74.2, 75.6, 77.3, 86.6, 97.4, 113.9, 121.0, 129.2, 130.3, 150.4, 151.8, 159.3, 165.5, 215.4. Anal. Calcd for $C_{75}H_{139}IO_{12}Si_4$: C, 61.22; H, 9.46. Found: C, 60.89; H, 9.64.

Aldehyde 116. To a solution of **114** (20.0 mg, 14.8 μmol) in dichloromethane (0.6 mL) were added pyridine (17 μL, 0.22 mmol) and Dess−Martin periodinane (183 mg, 445 μmol). The mixture was stirred for 7 h at room temperature and quenched with a 1:1 mixture of saturated sodium carbonate solution and saturated sodium thiosulfate solution (5 mL). The mixture was extracted three times with ethyl acetate (5 mL), and the combined extracts were washed with 5% aqueous sodium carbonate (3 mL), water (3 mL), and brine (3 mL) and dried

(magnesium sulfate). The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel, eluting with hexanes−ether (2:1), to give 19.5 mg (99%) of **116** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.02 (3H, s), 0.03 (3H, s), 0.04 (3H, s), 0.06 (3H, s), 0.07 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.89−1.80 (65H, m), 1.04 (3H, s), 1.07 (3H, s), 1.09 (3H, s), 1.19 (3H, s), 1.21 (3H, s), 1.26 (3H, s), 1.94 (1H, m), 2.10 (2H, m), 2.33 (3H, m), 2.78 (1H, dd, J = 5, 16 Hz), 2.71 (1H, dd, J = 3, 7 Hz), 2.77 (1H, t, J = 7 Hz), 2.87 (1H, t, J = 7 Hz), 2.97 (1H, t, J = 7 Hz), 3.70 (2H, m), 3.82 (1H, dd, J = 6, 14 Hz), 3.95 (1H, dd, J = 3, 10 Hz), 4.09 (1H, dd, J = 3, 6 Hz), 4.32 (1H, dd, J = 4, 5 Hz), 5.28 (1H, ddt, J = 4, 5, 6 Hz), 5.78 (1H, d, J = 16 Hz), 5.96 (1H, d, J = 14 Hz), 6.27 (1H, dd, J = 5, 14 Hz), 7.00 (1H, dd, J = 7, 16 Hz), 9.97 (1H, s); HRMS (FAB) m/z 1346.7544 (calcd for $C_{67}H_{127}IO_{11}Si_4$ 1346.7500). This compound was unstable and was used immediately in the next reaction.

Boronate 122. To a suspension of chromium(II) chloride (200 mg, 1.6 mmol) in tetrahydrofuran (5 mL) at room temperature was added **121** (100 μL, 410 μmol), followed by **116** (20.0 mg, 14.8 μmol) and lithium iodide (108 mg, 820 μmol). The brown suspension was stirred for 5 h at room temperature, and the reaction was quenched by addition of ice-cold water (5 mL). The mixture was extracted three times with ethyl acetate (10 mL), and the combined extracts were washed with brine (10 mL) and dried (magnesium sulfate). The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel, eluting with hexanes−ether (6:1), to yield 17.0 mg (88%) of **122** as a clear oil: $[\alpha]^{22}_D$ −49.2 (c 0.14, $CHCl_3$; IR (neat) 2965, 2850, 1716, 1667, 1444 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.04 (3H, s), 0.02 (3H, s), 0.03 (3H, s), 0.06 (6H, s), 0.07 (3H, s), 0.07 (3H, s), 0.08 (3H, s), 0.80−0.92 (39H, m), 0.94 (3H, d, J = 7 Hz), 1.01 (3H, d, J = 7 Hz), 1.03−1.06 (4H, m), 1.09 (3H, d, J = 7 Hz), 1.20 (3H, d, J = 6 Hz), 1.27 (12H, s), 1.29−1.50 (8H, m), 1.53−1.66 (7H, m), 1.76 (3H, dd, J = 5, 13 Hz), 1.88−1.97 (2H, m), 2.01−2.12 (5H, m), 2.23−2.33 (2H, m), 2.36−2.44 (2H, m), 2.70 (1H, dd, J = 3, 7 Hz), 2.76 (1H, t, J = 7 Hz), 2.86 (1H, t, J = 7 Hz), 2.95 (1H, t, J = 7 Hz), 3.63−3.69 (1H, m), 3.71−3.78 (1H, m), 3.82 (1 H, dd, J = 6, 13 Hz), 3.91 (1H, d, J = 8 Hz), 4.10 (1H, dd, J = 4, 5 Hz), 4.28 (1H, dd, J = 3, 7 Hz), 5.25−5.33 (1H, m), 5.44 (1H, d, J = 18 Hz), 5.78 (1H, d, J = 16 Hz), 5.95 (1H, d, J = 14 Hz), 6.27 (1H, dd, J = 9, 14 Hz), 6.55 (1H, ddd, J = 7, 7, 18 Hz), 7.00 (1H, dd, J = 7, 16 Hz); HRMS (FAB) m/z 1484.8739 (calcd for $C_{75}H_{142}BIO_{12}Si_4$ 1484.8716).

Rutamycin B Tetra(*tert*-butyldimethyl)silyl Ether (123). To a solution of **122** (13.0 mg, 8.80 μmol) in tetrahydrofuran (10 mL) were added silver(I) oxide (8.0 mg, 35.3 μmol), triphenylarsine (4.2 mg, 7.1 μmol), palladium(II) chloride bis(acetonitrile) (1.0 mg, 3.5 μmol), and water (0.05 mL). The mixture was stirred for 2 h at room temperature, and the reaction was quenched by addition of ice-cold water (5 mL). The mixture was extracted three times with ethyl acetate (25 mL), and the combined extracts were washed with water and brine and dried (magnesium sulfate). The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel, eluting with hexanes−ethyl acetate (9:1), to afford 7.5 mg (70%) of **123** as a clear oil: $[\alpha]^{22}_D$ −36.7 (c 0.15 $CHCl_3$); IR (neat) 2960, 2855, 1712, 1653, 1459 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.02 (9H, s), 0.03 (3H, s), 0.05 (6H, s), 0.07 (3H, s), 0.13 (3H, s), 0.61 (9H, s), 0.88 (18H, s), 0.89 (9H, s), 0.90−0.95 (15H, m), 0.99 (3H, d, J = 4 Hz), 1.01 (3H, d, J = 5 Hz), 1.07 (3H, d, J = 4 Hz), 1.10 (3H, d, J = 4 Hz), 1.19 (3H, d, J = 6 Hz), 1.25−1.69 (12H, m), 1.81 (1H, dd, J = 5, 12 Hz), 1.94−2.15 (5H, m), 2.12−2.22 (2H, m), 2.46−2.51 (1H, m), 2.66−2.71 (1H, m), 2.74−2.82 (2H, m), 2.95 (1H, t, J = 5 Hz), 3.68−3.74 (2H, m), 3.80−3.86 (1H, m), 3.93 (1H, d, J = 7 Hz), 4.15 (1H, dd, J = 2, 8 Hz), 4.28 (1H, d, J = 6 Hz), 5.26−5.35 (2H, m), 5.40 (1H, ddd, J = 5, 9, 14 Hz), 5.79 (1H, d, J = 16 Hz), 5.95 (1H, dd, J = 10, 14 Hz), 6.02 (1H, dd, J = 10, 14 Hz), 7.01 (1H, dd, J = 7, 16 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.1 (2C), −3.8, −3.3, 5.1, 11.0, 11.5, 12.1, 13.1, 14.1, 14.7, 16.0, 18.1, 18.4, 186, 24.5, 25.9 (3C), 26.1 (6C), 26.3 (3C), 27.7, 28.7, 29.6, 29.7, 30.8, 34.9, 35.4, 35.7, 42.6, 43.2, 44.1, 47.1, 50.5, 51.6, 57.2, 69.2, 69.5, 70.3, 71.9, 72.6, 72.9, 97.4, 121.2, 131.3, 131.5, 131.9, 136.1, 150.6, 165.5, 213.2, 213.8; HRMS (FAB) m/z 1216.8569 (calcd for $C_{68}H_{128}O_{10}Si_4$ 1216.8584).

Rutamycin B (2). To a solution of **123** (7.0 mg, 5.75 μmol) in acetonitrile and dichloromethane (1:1, 3 mL) were added pyridine (0.05 mL) and hydrogen fluoride-pyridine complex (38%, 0.55 mL). The solution was stirred for 4 d, during which time the reaction progress was followed by thin-layer chromatography. The reaction was quenched with ice-cold 5% sodium bicarbonate, and the mixture was extracted three times with ethyl acetate (5 mL). The combined extracts were washed with brine and dried (magnesium sulfate), and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel, eluting with hexanes−ethyl acetate (1:1), to give 3.5 mg (70%) of a clear oil that solidified upon standing. The solid was crystallized from ether to yield **2**: mp 126−129 °C; $[\alpha]^{22}_D$ −71.4 (c 0.07, $CHCl_3$); IR (neat) 3480, 2970, 2925, 1705, 1650, 1455, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.18−0.85 (6H, m), 0.88 (3H, d, J = 7 Hz), 0.92 (6H, d, J = 7 Hz), 1.06 (3H, d, J = 7 Hz), 1.10 (3H, d, J = 7 Hz), 1.19 (3H, d, J = 6 Hz), 1.23−1.27 (6H, m), 1.24−1.95 (16H, m), 2.02−2.23 (4H, m), 2.31 (1H, m), 2.63−2.76 (2H, m), 2.78−2.89 (2H, m), 3.78 (1H, d, J = 10 Hz), 3.81−3.85 (2H, m), 3.91−4.10 (3H, m), 5.21−5.32 (2H, m), 5.41 (1H, ddd, J = 4, 11, 15 Hz), 5.81 (1H, d, J = 16 Hz), 5.94 (1H, dd, J = 11, 15 Hz), 6.06 (1H, dd, J = 11, 15 Hz), 6.61 (1H, J = 10, 16 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 5.1, 8.2, 9.6, 11.1, 12.1, 12.7, 13.2, 13.4, 17.6, 24.5, 26.5, 28.4, 29.8, 30.7, 31.1, 35.1, 40.0, 42.6, 45.5, 45.9, 47.3, 48.6, 49.2, 64.7, 67.4, 69.6, 70.6, 71.0, 71.3, 72.9, 97.3, 122.6, 129.5, 130.4, 132.1, 137.4, 148.4, 165.0, 216.0, 221.6.

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Supporting Information Available: Experimental procedures and characterization data for **15**−**39**, **42**−**58**, **64**−**74**, **77**−**91**, **94**−**108**, and **111**−**115**. This material is available free of charge via the Internet at http://pubs.acs.org.

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