Total Synthesis of the Epidermal Growth Factor Inhibitor (−)-Reveromycin B

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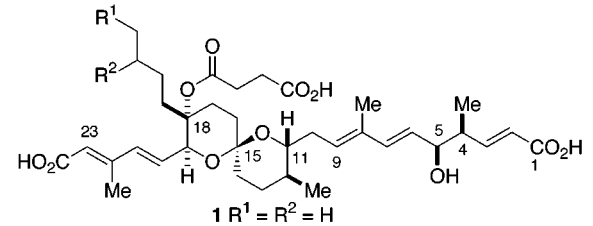
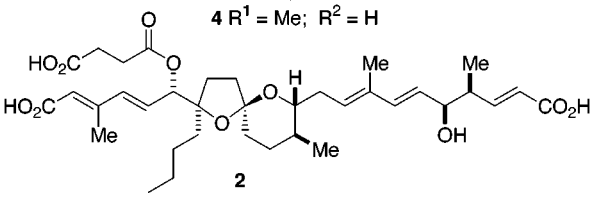
The total synthesis of the epidermal growth factor inhibitor reveromycin B (**2**) in 25 linear steps from chiral methylene pyran **13** is described. The key steps involved an inverse electron demand hetero-Diels−Alder reaction between dienophile **13** and diene **12** to construct the 6,6-spiroketal **11** which upon oxidation with dimethyldioxirane and acid catalyzed rearrangement gave the 5,6-spiroketal aldehyde **9**. Lithium acetylide addition followed by oxidation/reduction and protective group manipulation provided the reveromycin B spiroketal core **8** which was converted into the reveromycin A (**1**) derivative **6** in order to confirm the stereochemistry of the spiroketal segment. Introduction of the C1−C10 side chain began with sequential Wittig reactions to form the C8−C9 and C7−C6 bonds, and a tin mediated asymmetric aldol reaction installed the C4 and C5 stereocenters. The final key steps to the target molecule **2** involved a Stille coupling to introduce the C21−C22 bond, succinoylation, selective deprotection, oxidation, and Wittig condensation to form the final C2−C3 bond. Deprotection was effected by TBAF in DMF to afford reveromycin B (**2**) in 72% yield.

Introduction

Spiroketals or spiroacetals are substructures that occur in a wide variety of natural products from many sources including insects, microbes, plants, fungi and marine organisms.[1] The 1,6-dioxaspiro[4.5]decane ("5,6-spiroketal") and the 1,7-dioxaspiro[5.5]undecane ("6,6-spiroketal") moieties in particular occur in diverse biologically active natural products such as polyether ionophores, insect pheromones, and antibiotic macrolides. Reveromycins A (**1**), B (**2**), C (**3**), and D (**4**) are examples of natural products containing 5,6- and 6,6-spiroketal moieties isolated from a soil actinomycete belonging to the *Streptomyces* genus.[2,3,4] The gross structures of **1**−**4** were deduced by spectroscopic analysis while the absolute configuration of **1** was assigned following chiroptical and spectroscopic analysis of various degradation products.[5] Other structural features of these compounds include a common succinate half ester at C18 or C19, a C1−C9 triene acid segment, and a C20−C24 diene acid moiety.



1 $R^1 = R^2 = H$
3 $R^1 = H$; $R^2 = Me$
4 $R^1 = Me$; $R^2 = H$



2

The reveromycins act as inhibitors of the mitogenic activity of epidermal growth factor (EGF).[6] Since the action of most antitumor drugs depends on the difference in the cell proliferation rate between normal and tumor cells by acting on DNA or RNA function and synthesis, compounds which inhibit the growth factors that mediate such processes, such as transforming growth factor (TGF-α) and EGF, are possible targets for antitumor agents.[7] Reveromycin A (**1**) also exhibits antiproliferative activity against human tumor cell lines KB and K562 as well as antifungal activity against *Candida albicans* but only at low pH.[6] Reveromycin B (**2**) (IC_{50} 6.0 μg/mL) is 1 order of magnitude less active than reveromycin A (**1**) (IC_{50} 0.7 μg/mL) against EGF but is more selective since it possesses none of the other activities displayed by **1**.[6]

It has been demonstrated that the reveromycin A (**1**) type 6,6-spiroketal system **I** completely isomerizes to the reveromycin B (**2**) 5,6-spiroketal **II** (Scheme 1). Reductive ozonolysis of the desuccinoylated reveromycin A trimethyl ester **5** followed by acetylation gave the 5,6-spiroketal **6**.[8] This result can be explained by considering

(1) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661.
(2) Osada, H.; Koshino, H.; Isono, K.; Takahashi, H.; Kawanishi, G. *J. Antibiot.* **1991**, *44*, 259−261.
(3) Takahasi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1409−1413.
(4) Koshino, H.; Takahashi, H.; Osada, H.; Isono, K. *J. Antibiot.* **1992**, *45*, 1420−1427.
(5) Ubukata, M.; Koshino, H.; Osada, H.; Isono, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1877−1878.
(6) Takahashi, T.; Osada, H.; Koshino, H.; Sasaki, M.; Onose, R.; Nakakoshi, M.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1414−1419. Takahashi, H.; Yamashita, Y.; Takaoka, H.; Nakamura, J.; Yoshihama, M.; Osada, H. *Oncol. Res.* **1997**, *9*, 7−11.
(7) Marquardt, H.; Hankapiller, M. W.; Hood, L. E.; Twardzik, D. W.; De Larco, J. E.; Stephenson, J. R.; Todaro, J. *Proc. Natl. Acad. Sci.* **1983**, *80*, 4684−4688. Yoshida, K.; Kyo, E.; Tsuda, T.; Tsujino, T.; Ito, M.; Niimoto, M.; Tahara, E. *Int. J. Cancer* **1990**, *45*, 131−135. Modjtahedi, H.; Dean, C. *Int. J. Oncol.* **1994**, *4*, 277−296.

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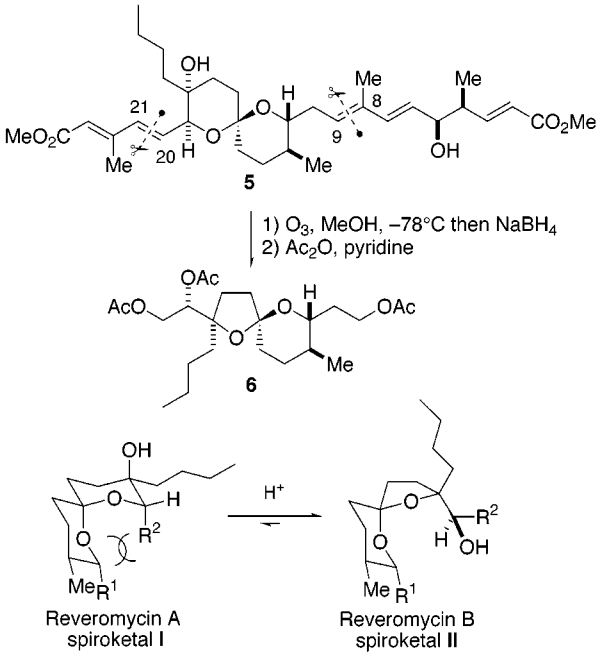
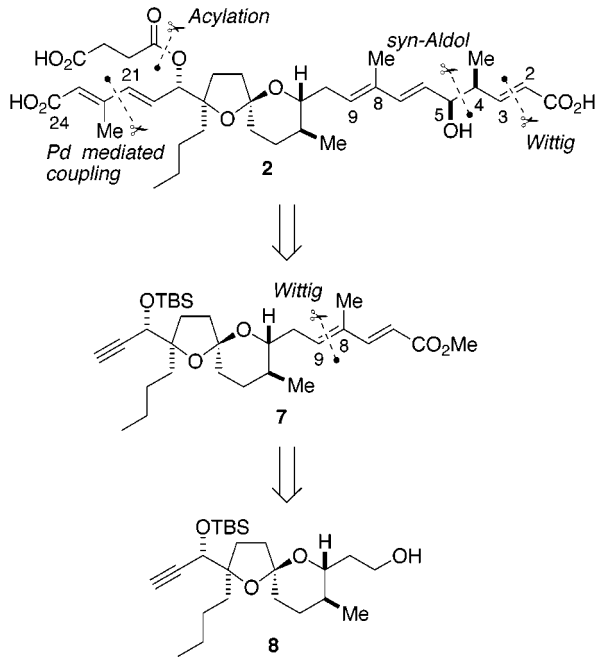
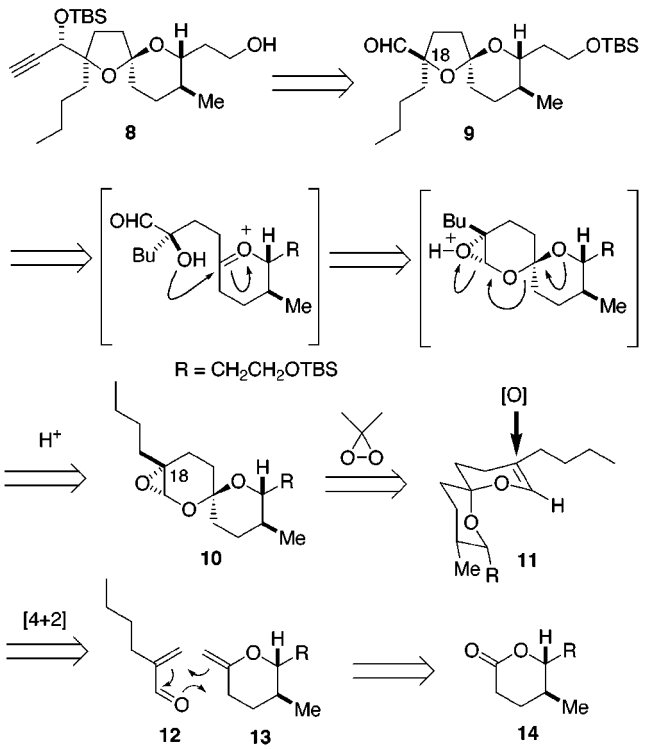
Scheme 1



Scheme 2



Scheme 3



the steric interaction present in the reveromycin A spiroketal **I** which is alleviated upon acid induced isomerization to the 5,6-spiroketal **II**. The thermodynamic preference for the 5,6-spiroketal **II** might therefore explain the biosynthetic origin of reveromycin B (**2**) where isomerization of the 6,6-spiroketal **I** of reveromcyin A (**1**) occurs prior to succinnoylation. In synthetic studies toward reveromycin A, formation of the 6,6-spiroketal system under thermodynamic control where the tertiary alcohol is protected results in the production of 6,6-spiroisomers[9] or isomeric acetals[8] as a result of the steric interaction present in spiroketal **I**.

The first total synthesis of (−)-reveromycin B (**2**) was reported by Theodorakis and Drouet.[10] Shimizu, Nakata, and co-workers then communicated a second independent total synthesis soon afterward[11] and the same group has also completed the first total synthesis of reveromycin A (**1**).[12] In this paper, we describe the full details of our asymmetric synthesis of reveromycin B (**2**).[13]

Retrosynthetic Plan. The key retrosynthetic bond disconnections for the synthesis of **2** are shown in Scheme 2. Construction of the C2−C3 bond by a Wittig reaction would involve the use of the appropriate stabilized ylide while the C4−C5 bond could be introduced by an asymmetric *syn*-aldol reaction. The C21−C22 bond could be formed by an sp^2−sp^2 coupling[14] and acylation at C19 oxygen would introduce the succinate residue. These disconnections lead to diene ester **7** which could arise from the spiroketal fragment **8**, again by Wittig extension.

Pivotal to our approach was the efficient synthesis of the key spiroketal fragment **8** (Scheme 3). Acetylide anion addition to the aldehyde **9** could provide **8** while the aldehyde **9** could be obtained in a novel and stereoselective manner by a hetero-Diels−Alder/epoxidation/acid rearrangement sequence as shown in Scheme 3.[13a,15] An

(8) Shimizu, T.; Kobayashi, R.; Osako, K.; Osado, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6755−6758.
(9) Drouet, K. E.; Ling, T.; Tran. H. V.; Theodorakis, E. A. *Org. Lett.* **2000**, *2*, 207−210.
(10) Drouet, K. E.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 456−457. Drouet, K. E.; Theodorakis, E. A. *Eur. J. Chem.* **2000**, *6*, 1987−2001.
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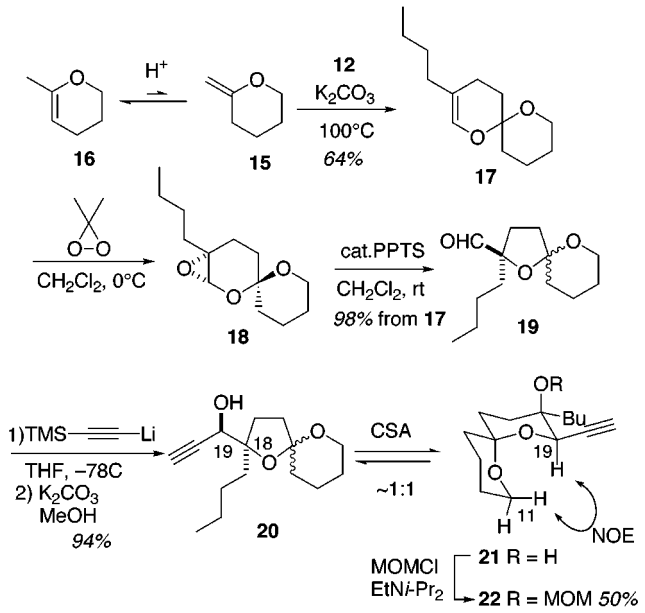
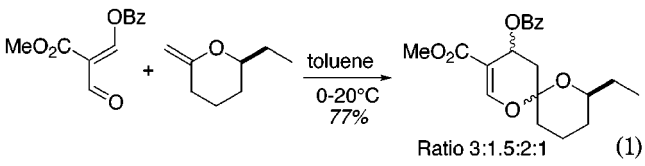
(12) Shimizu, T.; Masuda, T.; Hiramoto, K.; Nakata, T. *Org. Lett.* **2000**, *2*, 2153−2156.
(13) (a) McRae, K. J.; Rizzacasa, M. A. *J. Org. Chem.* **1997**, *62*, 1196−1197. (b) Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; Rizzacasa, M. A.; Zammit, S. C. *Org. Lett.* **2000**, *2*, 191−194.
(14) Knight, D. W. In *Comprehensive Organic Syntheses*; Trost, B., Ed.; Pergamon: Oxford, 1991; Vol. 3, pp 481−520.
(15) Ireland, R. E.; Armstrong, J. D.; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7152−7165.

inverse electron demand hetero-Diels−Alder reaction[16] (HDA) between methylene pyran **13** (derived from lactone **14**) and butylacrolein (**12**) should provide the spiroketal **11**, and it was envisaged that the stereochemistry at the spiro center would be controlled by axial attack of the aldehyde oxygen atom due to the anomeric effect.[17] Stereoselective epoxidation with dimethyldioxirane provides the epoxide **10**, setting the C18 stereochemistry and subsequent acid treatment[15] should then induce ring-opening and cyclization via the intermediate oxonium ion shown to provide the 5,6-spiroketal aldehyde **9**.

It is well documented that simple α,β-unsaturated carbonyl compounds participate in inverse electron demand hetero-Diels−Alder reactions with electron rich dienophiles.[16a] This mode of cycloaddition is dominated by the interaction of the HOMO of the dienophile and the LUMO of the diene, and consequently, substituents that raise the HOMO of the dienophile or lower the LUMO of the diene increase the reaction rate.[18] For example, a C3 electron withdrawing substituent decreases the LUMO of the heterodiene thus enhancing rate and regioselectivity with electron rich dienophiles.[16a,18] The HDA synthesis of 6,6-spiroketals has met with somewhat limited success; however, there is a propensity for methylene pyrans such as **13** to undergo isomerization to the more stable endo position, thus thwarting the desired [4+2]-cyloaddition.[16c] This issue has been addressed by Ireland who has employed an α-keto functionality in the dienophile to block isomerization and provide spiroketals by an "acrolein dimerization" type approach.[15,19] However, in our case this method would require the removal of the oxygen atom at a later stage. Furthermore, byproducts resulting from dienophile dimerization often result.[19c,d] In 1991, Tietze reported the only example of a HDA reaction between an isomerizable chiral methylene pyran dienophile and an activated diene which provided a mixture of isomeric spiroketals (eq 1).[16f] Pale has pioneered the use of 3,4-epoxy-2-methyleneoxolanes in the HDA synthesis of 5,6-spiroketals where the 3,4-epoxy substituent prevents isomerization of the exocyclic double bond and Lewis acid catalysts were used to increase reaction rates.[16g,h] Reactive heterodienes containing a C3 chiral sulfinyl group have also been utilized in the production of enantiopure spiroketals as reported by Maignan.[16i,j] Recently, Jørgensen and co-workers reported the enantioselective synthesis of 5,6-spiroketals via asymmetric HDA reactions between an isomerizable methylene furan dienophile and various β,γ-unsaturated α-keto esters catalyzed by a chiral bisoxazoline copper complex.[16k] At the onset of this work, HDA reactions between isomerizable methylene pyrans and simple 2-alkyl acrolein derivatives had not been reported so we initiated a model study to test the feasibility of the proposed approach to the reveromycin B spiroketal.[13a]

Scheme 4





Model Study. The reactivity of diene **12** was investigated using the known unsubstituted methylene pyran **15**[16c,20] as the dienophile (Scheme 4). Initial attempts at inducing cycloaddition by heating a mixture of **12** and **15** only yielded the isomerized product **16**, even in base washed glassware. To suppress isomerization, a number of bases were added to the reaction and a good yield of spiroketal **17** was finally obtained by heating a neat mixture of freshly distilled **12** and **15** *in the presence of 1 equiv of anhydrous* K_2CO_3 followed by aqueous workup and vacuum distillation. Epoxidation of **17** with anhydrous dimethyldioxirane[21] then gave the labile epoxide **18** as one diastereoisomer to the limits of NMR detection. Rearrangement then occurred smoothly upon treatment of **18** with a catalytic amount of PPTS[15] to provide the 5,6-spiroketal aldehydes **19** in excellent yield as a 1:2 mixture at the spiro carbon since there are no equatorial substituents present to anchor the THP ring. Acetylide anion addition to **19** occurred in a stereoselective manner to afford the alkynes **20** after removal of the TMS group, again as a 1:2 mixture of spiro isomers but with the opposite relative configuration at the C18 and C19[22] stereocenters to that found in the reveromycin B system. Evidence for this configuration arose from the acid

(16) (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987; Chapter 7. (b) Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1954**, 672−678. (c) Ireland, R. E.; Häbich, D. *Chem. Ber.* **1981**, *114*, 1418−1427. (d) Ireland R. E.; Thaisrivongs, S. Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768−5779. (e) Sauvé, G.; Schwartz, D. A.; Ruest, L.; Deslongchamps, P. *Can. J. Chem.* **1984**, *62*, 2929−2935. (f) Tietze, L. F.; Schneider, C. *J. Org. Chem.* **1991**, *54*, 2476−2481. (g) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1988**, *29*, 2947−2950. (h) Pale, P.; Bouquant, J.; Chuche, J.; Carrupt, P. A.; Vogel, P. *Tetrahedron*, **1994**, *50*, 8035−8052. (i) Hayes, P.; Maignan, C. *Synlett* **1994**, 409−410. (j) Hayes, P. Maignan, C. *Synthesis* **1999**, 783−786. (k) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487−4497.

(17) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, England, 1983; Chapter 2.

(18) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: Bath, 1980; Chapter 4.

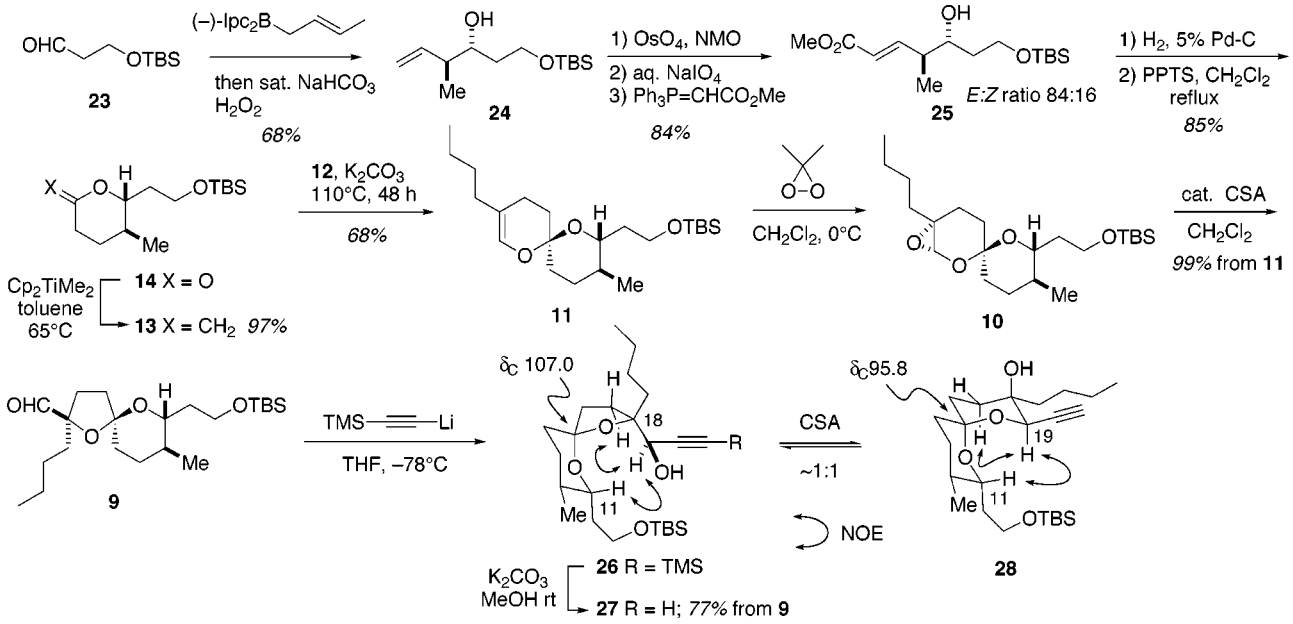
(19) (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303−1312. (b) Ireland, R. E.; Häbich, D.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3271−3278. (c) Ireland, R. E.; Daub, J. P.; Mandel G. S.; Mandel, N. S. *J. Org. Chem.* **1983**, *48*, 1312−1325.

(20) Taskinen, E. *Ann. Acad. Sci. Fenn., Ser. A* **1972**, *163*, 3. A modified procedure for the synthesis of enol ether **15** is detailed in the Supporting Information.

(21) (a) Murray, R. W.; Jeyaraman, R. J. *J. Org. Chem.* **1985**, *50*, 2847−2853. (b) Adam, W.; Bialas J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(22) Reveromycin B numbering is used throughout.

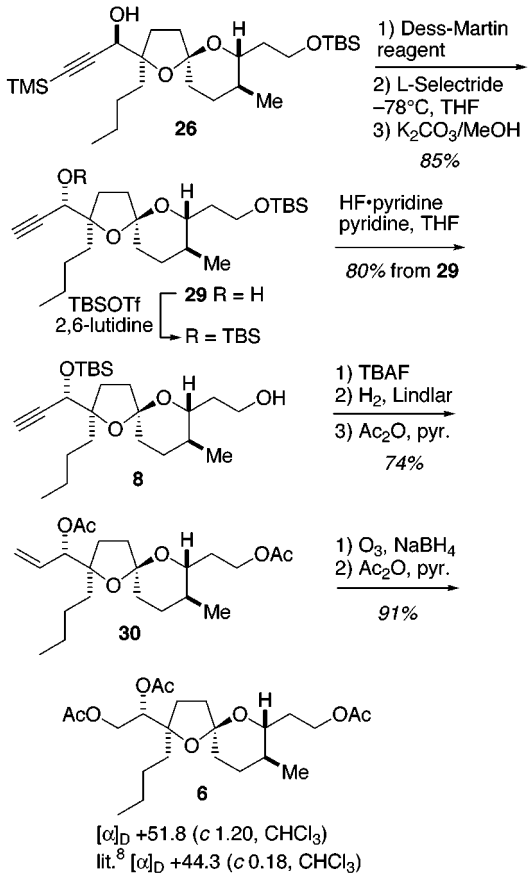
Scheme 5



induced isomerization of the 5,6-spiroketal **20** to the 6,6-spiroketal **21** (1:1 mixture), which showed a large NOE between H11 and H19. If the relative configuration was correct, this 5,6 to 6,6-spiroketal isomerization would not be expected to occur since a strong thermodynamic preference for the 5,6-spiroketal was found in the natural product degradation studies described earlier (see Scheme 1).[7] Further evidence for this stereochemistry was obtained upon conversion of **21** into the crystalline MOM ether **22**. A single-crystal Xray structure of **22** was determined which finally confirmed the stereochemistry proposed.[23] The stereochemistry at C19 will therefore need to be corrected at some stage.

Asymmetric Spiroketal Synthesis. Encouraged by the successful model study, we proceeded with the asymmetric synthesis of the reveromycin B spiroketal **8** as outlined in Schemes 5 and 6. The initial target was the chiral methylene pyran **13** required for the critical Diels−Alder reaction, and the route began with the asymmetric crotylmetalation[24] of aldehyde **23** to afford alkene **24**.[25] Dihydroxylation of **24**, oxidative cleavage, and Wittig reaction yielded alkene **25** as a mixture of geometric isomers. This was of no consequence as the alkene mixture was hydrogenated to provide the corresponding saturated ester which upon acid treatment cyclized to lactone **14**. Methylenation of **14** was best achieved using dimethyltitanocene as reported by Petasis.[26] This gave the methylene pyran **13** in excellent yield after purification over basic alumina (activity II−III). Isomerization of **13** to the endo isomer occurs upon purification over activity I basic alumina or silica gel. The hetero-Diels−Alder reaction between **13** and **12** proceeded smoothly at 110 °C in the presence of K_2CO_3 to provide the spiroketal **11** as one diastereoisomer in good yield. Higher temperatures resulted in the formation of large amounts of butylacrolein dimer, while at lower temperatures the reaction was prohibitively slow. Oxidation with anhydrous dimethyldioxirane[21] gave epoxide **10** as the only detectable isomer and rearrangement initiated by CSA gave the spiroketal aldehyde **9**. PPTS also effected rapid rearrangement of **10** to a mixture of 5,6-spiroketal isomers, but complete isomerization to the

Scheme 6



(23) Gable, R. W.; McRae, K. J.; Rizzacasa, M. A. Unpublished results, Cambridge Crystallographic Data Centre deposition number CCDC-148807 2000. See Supporting Information for ORTEP and coordinates.

(24) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293−294.

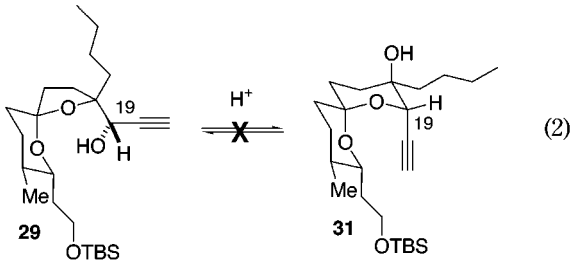
(25) Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, *37*, 5049−5052.

(26) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−6394. Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, *36*, 2393−2396.

thermodynamically more stable isomer **9** was best effected using CSA. Addition of lithium acetylide was stereoselective providing adduct **26**, and subsequent TMS group removal gave alkyne **27** which upon treatment with CSA partially isomerized to the 6,6-spiroketal **28**. The stereochemistry at C18 in 5,6-spiroketal **27** was shown to be correct by the NOE observed between H18 and H11 while the C19 stereochemistry was shown to be incorrect by the large NOE observed between H11 and H19 in the 6,6-isomer **28**.

Attempts at inversion[27] of the C19 stereochemistry failed, so we elected to examine an oxidation−reduction sequence to correct this problem (Scheme 6). Oxidation of TMS alkyne **26** with Dess−Martin reagent[28] followed by reduction with L-Selectride and alkyne deprotection gave a 9:1 inseparable mixture of alcohols **29** and **27**. Silylation of this mixture followed by selective removal of the primary TBS group afforded the desired spiroketal **8** along with a small amount of the C19 epimer which were now easily separable by flash chromatography. The spiroketal **8** was then converted into the known degradation product **6**[8] by the sequence shown. Desilylation followed by partial hydrogenation and acetylation gave the diacetate **30**. Ozonolysis, reduction, and acetylation then provided spiroketal **6**, which had identical spectroscopic and analytical data to that reported for the natural[8] and previously synthesized[9,10] material confirming the absolute configuration of key intermediate **8**.

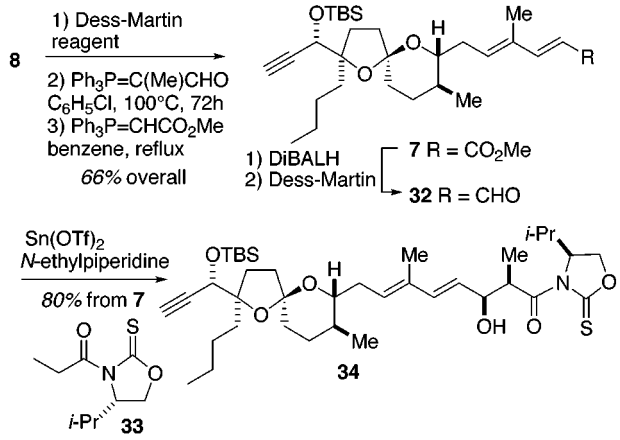
Attempted isomerization of spiroketal **29** (9:1 mixture with **27**) failed to provide the reveromycin A spiroketal **31** as expected (eq 2).[13b] A similar result was also found in a more advanced reveromycin B intermediate which also resisted isomerization to the corresponding 6,6-spiroketal.[10]



(2)

Side Chain Synthesis: C3−C10 fragment. The introduction of the C3−C10 fragment was next initiated beginning with synthesis of the aldehyde **32** required for the *syn*-selective asymmetric aldol reaction (Scheme 7). Oxidation of the alcohol **8** to the corresponding aldehyde followed by two step Wittig homologation gave the diene ester **7**. Attempts to secure the ester in one step using a conjugated ylide[13b,29] proved unsuccessful. Condensation of the aldehyde derived from **8** with 2-(triphenylphosphoranylidene)propionaldehyde also proved troublesome with little or no reaction occurring in solvents such as benzene or toluene, even at elevated temperatures. However, when chlorobenzene was employed as solvent,

Scheme 7



the Wittig reaction proceeded to completion in 72 h at 100 °C. Heating at higher temperatures resulted in some decomposition with little improvement in reaction rate. A second Wittig reaction then provided diene ester **7** which upon DiBALH reduction followed by Dess−Martin oxidation afforded the aldehyde **32** ready for aldol reaction. Compound **32** was somewhat sensitive and it was essential to carry out the Dess−Martin oxidation in the presence of excess pyridine. In the absence of base, a small amount of the C8−C9 geometric isomer was formed. In model studies, we found the tin mediated aldol reaction using the chiral oxazolidine-2-thione **33** to be most effective.[30] Nagao, Fujita, and co-workers have reported optimized conditions for effective aldol condensations with α,*β*-unsaturated aldehydes without elimination of the resultant aldol adduct.[30a] The tin enolate derived from **33**[30c,31] was formed using 1.2 equiv tin(II) triflate and 1.2 equiv *N*-ethylpiperidine[30a] at −55 °C for 3 h, and subsequent condensation with aldehyde **32** proceeded effectively to give the adduct **34** in high yield as one diastereoisomer.

Side Chain Synthesis: C20−C24 Diene. We next elected to examine both Stille[32] and Heck[33] couplings for the formation of the C21−C22 bond of the C20−C24 diene using a model system (Scheme 8). This study began with silylation of spiroketal **20** to provide the ether **35** which upon palladium catalyzed hydrostannation[34] gave the (*E*)-vinylstannane **36** in good yield along with a small amount of the proximal isomer (9:1 ratio). The iodide **38** required for the Heck coupling was formed from **36** by iodine−tin exchange and fluoride deprotection of both **36** and **38** provided the corresponding alcohols **37** and **39**. The iodoesters **40** and **41** used for the Stille coupling reactions were synthesized from the corresponding *E*-

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(30) (a) Nagao, Y.; Hagiwara, Y.; Kumagi, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391−2393. (b) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418−1419. (c) Nagao, Y.; Kumagai, T.; Yamada, S.; Fujita, E.; Inoue, Y.; Nagase, Y.; Aoyagi, S.; Abe, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2361−2367.

(31) The preparation of oxazolidine-2-thione **33** is described in the Experimental Section.

(32) (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813−817. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (c) Farina, V.; Krishnamurthy V. Scott W. J. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1997; pp 1−652.

(33) Wovkulich, P. M.; Shankaran, K.; Kiegiel, J.; Uskokovic, M. R. *J. Org. Chem.* **1993**, *58*, 832−839. Dirat, O.; Kouklovsky, C.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 6634−6642.

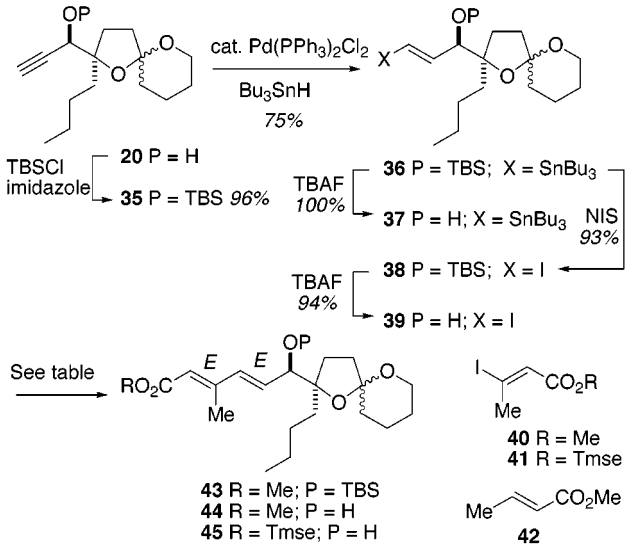
(34) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867.

Table 1

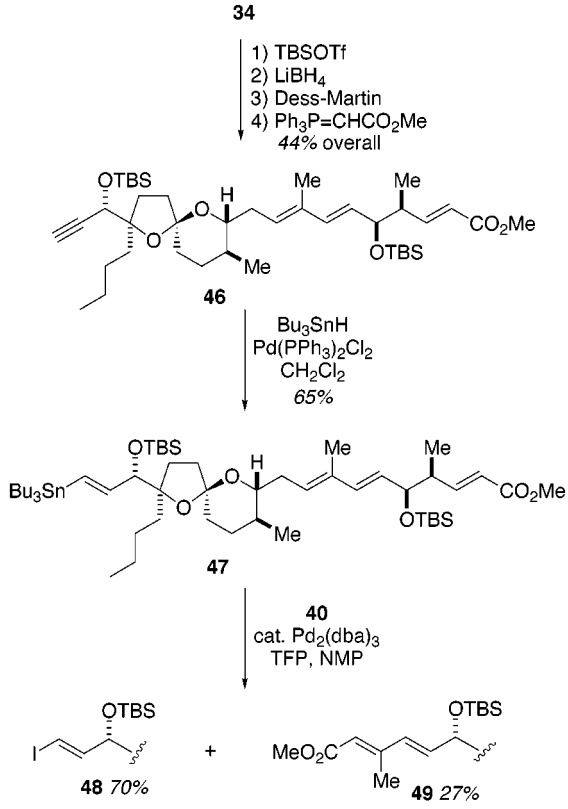
entry	substrate	ester	catalyst	solvent	additives	product	yield
1	**36**	**40**	$Pd(MeCN)_2Cl_2$	DMF			42%[a]
2	**36**	**40**	$Pd_2(dba)_3$	NMP	$P(2\text{-furyl})_3$	**43**	72%
3	**36**	**40**	CuTC	NMP		**43**	53%
4	**37**	**40**	$Pd_2(dba)_3$	NMP	$P(2\text{-furyl})_3$	**44**	84%
5	**37**	**41**	$Pd_2(dba)_3$	NMP	$P(2\text{-furyl})_3$	**45**	93%
6	**38**	**42**	$Pd(OAc)_2$	CH_2Cl_2	Ag_2CO_3/NEt_3	**43**	62%
7	**39**	**42**	$Pd_2(OAc)_2$	CH_2Cl_2	Ag_2CO_3/NEt_3	**44**	73%

[a] Yield of the *Z*,*E*-isomer.

Scheme 8



Scheme 9



acid[35] by esterification with diazomethane[35b] or trimethylsilylethanol and DCC. Compound **41** possesses a trimethylsilylethyl (Tmse) ester[36] protecting group required for eventual fluoride mediated deprotection to the carboxylic acid.[10]

The results of these model coupling reactions are presented in Table 1. Initial experiments were not encouraging exemplified by the coupling of **36** and **40** using a standard Pd(II) catalyst[32a] which gave the isomerized C22−C23 (*Z*)-isomer as the major product (9:1 ratio) in low yield (entry 1). Gratifyingly, recourse to the Pd(0) conditions described by Farina and Krishnan[37] gave the desired product **43** in good yield with no isomerization detected (entry 2). No improvement in yield was observed using the CuTC (copper(I) thiophenecarboxylate) catalyst reported by Allred and Liebeskind (entry 3).[38] The best yields were obtained from the Pd(0) catalyzed[37] couplings between the desilylated stannane **37** and esters **40** and **41** which gave the dienes **44** and **45** in excellent yields (entries 4 and 5). These results may be attributed to the reduction in steric hindrance in the stannane or even some type of polar effect. The corresponding Heck couplings between iodides **38** and **39** and ester **42** under modified conditions[33] also gave acceptable yields (entries 6 and 7), but since the Stille approach gave consistently better results, this method was utilized for C21−C22 bond construction.

Initially, we decided to complete the C1−C10 side chain prior to Pd mediated construction of the C21−C22 bond. Although this route did not ultimately afford reveromycin B (**2**), the results are worth briefly mentioning at this point (Scheme 9). Aldol adduct **34** was silylated and the chiral auxiliary was removed by reduction with lithium borohydride. Reduction with sodium borohydride[30c] gave the corresponding amido alcohol as the major product. Oxidation and Wittig extension using a stabilized ylide then provided the methyl ester **46**. Hydrostannation[34] of **46** proceeded in moderate yield to give the stannane **47**, but attempted coupling with iodo ester **40** under conditions developed in the model system gave the desired diene in low yield with the major product being iodide **48**. A possible explanation for the formation of iodide **48** is via tin−iodine exchange of stannane **47** effected by I_2 released from homo-coupling of the vinyl iodide **40**. One way to increase the reactivity of the stannane **47** would be to remove the O19 TBS group, but this was not possible in the presence of the α,β-unsaturated ester.

Completion of the Total Synthesis of 2. From the above results it became apparent that the C2−C3 alkene bond should be formed after the C21−C22 bond, and the successful route to reveromycin B (**2**) is detailed in

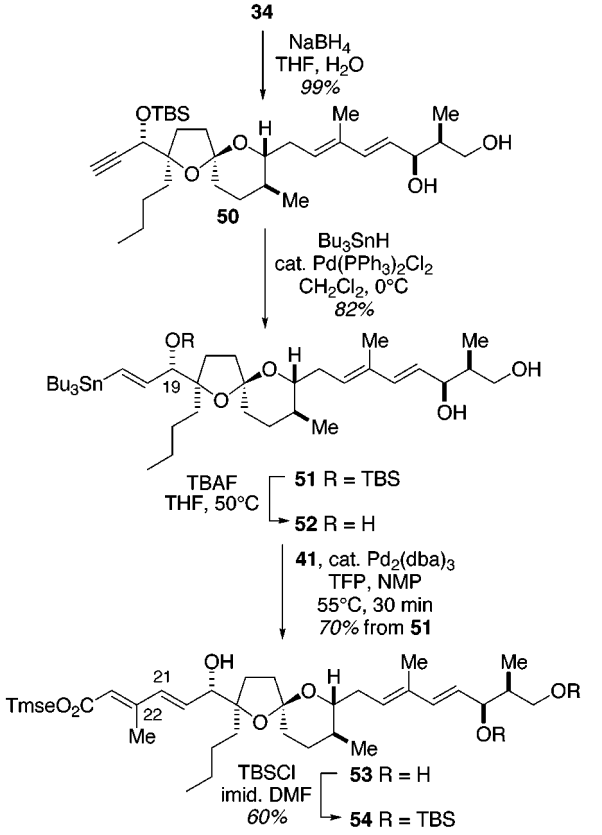
(35) (a) LeNoble, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 3897−3899. (b) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834−5845.

(36) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711−2716.

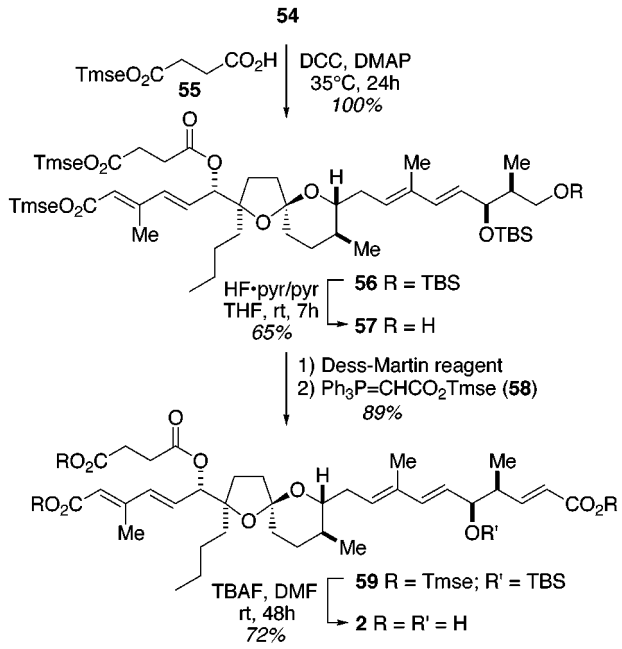
(37) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(38) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749.

Scheme 10



Scheme 11



Schemes 10 and 11. Reductive removal of the chiral auxiliary in compound **34** was effected with sodium borohydride[30c] in good yield to provide diol **50**. At this point, we elected to forego protection of the diol in order to reduce the number of protecting groups utilized. In fact, the synthesis was completed using the TBS ether as the only hydroxyl protecting group. Hydrostannation[34] of **50** proceeded smoothly to afford stannane **51**, which was then deprotected by treatment with TBAF in warm THF. The labile crude stannane **52** was then immediately subjected to Stille coupling with the Tmse ester **41** under the conditions reported earlier to provide triol ester **53** in excellent yield. This interesting reaction further demonstrates the power of the Stille coupling for C−C bond construction in the presence of multiple free hydroxyl groups. The steric hindrance at the C19 OH proved useful as the triol could be selectively silylated under standard conditions to provide bis-TBS ether **54**.

Succinoylation of **54** using the half ester **55**, derived from the reaction of succinic anhydride and trimethylsilylethanol in the presence of NEt_3, DMAP, and *N*-hydroxysuccinimide,[39] gave bis-Tmse ester **56** in quantitative yield, and selective deprotection of the primary TBS group using conditions reported by Evans[40] afforded the alcohol **57** (Scheme 11). This reagent left the Tmse esters intact; however, a small amount of diol was also formed. Dess−Martin oxidation of **57** followed by Wittig reaction with the stabilized Tmse ylide **58**[41] gave fully protected reveromycin B **59** in high yield. Deprotection of **59** with TBAF in DMF then afforded reveromycin B (**2**), which was identical to the natural product in all respects.[3,4] When TBAF in THF was utilized for the deprotection, the Tmse groups were removed rapidly but some C5 OTBS reveromycin B remained even after prolonged exposure.

Conclusion

The total synthesis of reveromycin B (**2**) was achieved in 25 linear steps from the chiral methylene pyran **13**. Key features of this route include a hetero-Diels−Alder reaction followed by a novel epoxidation−acid induced ring contraction sequence to afford the 5,6-spiroketal **9** in a highly convergent and stereoselective manner, a Stille cross coupling reaction to form the C21−C22 bond in high yield in the presence of three hydoxyl groups, and a tin mediated asymmetric aldol reaction to introduce the C4−C5 *syn*-propionate. The synthesis also involved use of only one type of alcohol protecting group (TBS ether). The hetero-Diels−Alder methodology is currently being applied to the synthesis of the other reveromycins.[42]

Experimental Section

General. ^{1}H NMR (300 or 400 MHz) and proton decoupled ^{13}C NMR spectra (75.5 or 100 MHz) were recorded in deuteriochloroform solutions (unless otherwise specified), with residual protonated solvent as internal standard. Melting points were measured on a Reichert hot stage melting point apparatus and are uncorrected. Optical rotations were recorded for solutions in a 10 cm microcell. High-resolution mass spectra (HRMS) electrospray ionization (ESI) were run on a Bruker 4.7T BIOAPEX FTMS mass spectrometer at Monash University, Clayton, Victoria. Microanalyses were carried out at the University of Otago, Dunedin, New Zealand. All moisture sensitive reactions were done under an argon atmosphere in oven dried (150 °C) glassware. Benzene, toluene, THF, and Et_2O were purified and dried by distillation from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Other commercial reagents were used as supplied. Reactions were monitored by TLC on silica gel 60 F_{254} plates (Merck), and the compounds were detected by

(39) Guzzo, P. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4862−4867.
(40) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453.
(41) Hungerbühler, E.; Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1981**, *64*, 1467−1487.
(42) El Sous, M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2000**, *41*, 8591−8594.

treatment with phosphomolybdic acid dip or alkaline potassium permanganate dip followed by strong heating. Flash chromatography was carried out using silica gel 60, 230−400 mesh (Merck). Petrol refers to petroleum ether, bp 40−60 °C.

Alkene 24. To a mixture of *t*-BuOK (3.77 g, 33.4 mmol) and *trans*-2-butene (3.25 mL, 34.6 mmol) in THF (35 mL) was added *n*-BuLi (2.5 M in hexanes, 13.4 mL, 34 mmol) dropwise at −78 °C. The resulting orange solution was warmed to −45 °C, stirred for 10 min, then recooled to −78 °C, and a solution of (−)-*β*-methoxydiisopinocampheylborane (10.5 g, 33.4 mmol) in THF (40 mL) was added dropwise via cannula. The reaction mixture was stirred at −78 °C for 30 min, and $BF_3{\cdot}OEt_2$ (5.2 mL, 45 mmol) was added dropwise, followed by a solution of aldehyde **23**[43] (4.20 g, 22.3 mmol) in THF (35 mL), and the resultant viscous mixture was stirred for a further 2 h. Saturated aqueous $NaHCO_3$ (70 mL) and 30% H_2O_2 (14 mL) were added, and the mixture was stirred at room temperature for 18 h. The THF was evaporated and the residue was extracted with Et_2O. The combined organic extracts were washed with water and brine and then dried ($MgSO_4$), filtered, and evaporated to give the crude product as a yellow oil. Purification by flash chromatography with 5% EtOAc/petrol as eluent gave alkene **24**[13a] (3.39 g, 68%) as a colorless oil: R_f = 0.29 (5% EtOAc/petrol); $[\alpha]^{25}_D$ −9.7 (*c* 0.64, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.05 (s, 6H), 0.87 (s, 9H), 1.01 (d, J = 5.4 Hz, 3H), 1.60 (m, 2H), 2.21 (m, 1H), 3.67 (m, 1H), 3.75−3.89 (m, 2H), 5.04 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (75.5 MHz) δ −5.59, −5.57, 15.7, 18.0, 25.8, 35.4, 43.9, 62.7, 74.9, 115.0, 140.6. Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.54. Found: C, 64.08; H, 11.26.

Methyl ester 25. To a solution of alkene **24** (1.00 g, 4.09 mmol) in THF (12 mL) and water (1.2 mL) was added *N*-methylmorpholine-*N*-oxide (60% ww in water, 1.04 g, 5.3 mmol) and OsO_4 (0.20M in *t*-BuOH, 0.82 mL, 0.16 mmol), and the mixture was stirred for 5 h at room temperature. To this was added $NaIO_4$ (1.07 g, 5.00 mmol) and water (2.0 mL), and stirring was continued for 2 h. Et_2O was added, and the organic extract was washed with water and brine and then dried (Na_2SO_4), filtered, and evaporated to give the crude aldehyde as a pale brown oil. To a solution of the crude aldehyde in dry CH_2Cl_2 (10 mL) was added methyl (triphenylphosphoranylidene)-acetate (1.77 g, 5.29 mmol), and the mixture was stirred at room temperature for 16 h under argon. The solvent was evaporated and the residue was purified by fast vacuum filtration on silica to give the crude product as a brown oil. Purification by flash chromatography with 10% EtOAc/petrol as eluent gave methyl ester **25** (*E*-**25**/*Z*-**25** 84:16, 1.04 g, 84% for three steps) as a yellow oil: R_f (*E*-**25**) = 0.25 (10% EtOAc/petrol); ^{1}H NMR (300 MHz) (*E*-**25**) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.09 (d, J = 6.9 Hz, 3H), 1.61 (m, 2H), 2.41 (m, 1H), 3.72 (s, 3H), 3.77−3.91 (m, 3H), 5.87 (d, J = 15.6 Hz, 1H), 7.03 (dd, J = 15.9, 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz) (*E*-**25**) δ −5.61, −5.57, 15.3, 18.1, 25.8, 35.4, 42.6, 51.4, 62.9, 75.1, 121.2, 151.1, 167.0. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 9.99. Found: C, 59.25; H, 9.91.

Lactone 14. To a solution of unsaturated methyl ester **25** (*E*-**25**/*Z*-**25** 84:16, 1.04 g, 3.43 mmol) in anhydrous EtOAc (10 mL) was added 5% Pd/C (30 mg), and the suspension was stirred under a hydrogen atmosphere for 24 h. The catalyst was removed by filtration and the filtrate was concentrated to give the crude saturated ester as a yellow oil. The crude ester was dissolved in CH_2Cl_2 (15 mL) and PPTS (50 mg, 0.19 mmol) was added and the resulting solution was heated at reflux under argon for 2 h. The solvent was evaporated and the crude product was purified by flash chromatography with 10% EtOAc/petrol as eluent to give lactone **14** (786 mg, 85% for two steps) as a colorless oil: R_f = 0.39 (10% EtOAc/petrol); $[\alpha]^{25}_D$ +55.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.02 (d, J = 6.6 Hz, 3H), 1.50−2.00 (m, 5H), 2.40−2.66 (m, 2H), 3.77−3.82 (m, 2H), 4.09 (td, J = 9.3, 2.4 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.4, 17.4, 18.2, 25.8, 27.8, 29.4, 32.5, 36.7, 58.5, 82.6, 186.4. Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.82; H, 10.05.

Spiroketal 11. To lactone **14** (218 mg, 0.800 mmol) was added a solution of dimethyltitanocene[44] (0.38 M in toluene, 4.1 mL, 1.6 mmol), and the resultant solution was heated at 65 °C in the dark for 18 h under argon. The orange oil obtained after removal of the solvent was triturated twice with cold hexane and the precipitate was removed by filtration through Celite. The solvents were evaporated to give the crude pyran as an orange oil. Purification by column chromatography on basic Al_2O_3 (Brockmann, Activity II−III) using 2.5% EtOAc/petrol as eluent gave enol ether **13** (210 mg, 97%) as a pale yellow oil: R_f (endo isomer) = 0.44 (silica, EtOAc/petrol (10%)); ^{1}H NMR (300 MHz) δ 0.06 (s, 6H), 0.87 (d, J = 7.8 Hz, 3H), 0.89 (s, 9H), 1.18−1.35 (m, 1H), 1.47−1.71 (m, 2H), 1.72−1.83 (m, 1H), 1.83−1.98 (m, 1H), 2.10−2.32 (m, 2H), 3.32 (td, J = 9.3, 2.4 Hz, 1H), 3.79 (m, 2H), 4.04 (d, J = 1.5 Hz, 1H), 4.29 (d, J = 1.5 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.32, −5.28, 17.7, 18.3, 25.9, 29.0, 31.7, 34.2, 36.5, 59.3, 81.5, 90.7, 160.2. A mixture of enol ether **13** (147 mg, 0.543 mmol), oven dried K_2CO_3 (82 mg, 0.59 mmol), and freshly distilled butylacrolein **12**[45] (0.366 mL, 2.72 mmol) was heated at 110 °C for 2 d under argon. The cooled suspension was diluted with Et_2O and the organic extract was washed with water and brine. The solvents were evaporated and the resulting oil was pumped for 5 h at 0.1 mmHg to remove the residual butylacrolein. The crude product was then purified by column chromatography on Al_2O_3 (Brockmann, Activity II−III) with 2.5% Et_2O/petrol as eluent to give spiroketal **11** (141 mg, 68%) as a colorless oil: R_f = 0.69 (silica, 5% EtOAc/petrol); $[\alpha]^{25}_D$ +99.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.03 (s, 6H), 0.85 (d, J = 6.3 Hz, 3H), 0.87 (s, 9H), 0.89 (t, J = 6.6 Hz, 3H), 1.20−1.44 (m, 5H), 1.46−1.66 (m, 5H), 1.67−1.81 (m, 3H), 1.81−1.91 (m, 2H), 1.99−2.22 (m, 2H), 3.36 (dt, J = 9.9, 2.1 Hz, 1H), 3.54 (ddd, J = 15.0, 8.7, 6.6 Hz, 1H), 3.72 (ddd, J = 15.0, 9.9, 5.1 Hz, 1H), 6.01 (s, 1H); ^{13}C NMR (300 MHz) δ −5.26, 13.9, 17.6, 18.3, 20.3 22.4, 25.9, 27.8, 30.4, 32.0, 32.6, 34.5, 34.8, 36.5, 60.5, 73.1, 94.6, 113.5, 134.4. Anal. Calcd for $C_{22}H_{42}O_3Si$: C, 69.05; H, 11.06. Found: C, 69.34; H, 10.78.

Spiroketal Aldehyde 9. To a solution of spiroketal **11** (1.96 g, 5.12 mmol) in dry CH_2Cl_2 (50 mL) was added anhydrous dimethyldioxirane[21b] (0.084 M in acetone, 67 mL, 5.6 mmol) at 0 °C under an argon atmosphere. The solution was stirred for 15 min, and then the solvent was evaporated to give crude epoxide **10** (2.04 g, 100% crude yield) as a colorless oil: ^{1}H NMR (300 MHz) δ 0.037 (s, 3H), 0.044 (s, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H), 0.88 (t, J = 7.0 Hz, 3H), 1.22−2.50 (m, 17H), 3.51 (dt, J = 10.2, 2.4 Hz, 1H), 3.63 (m, 1H), 3.75 (ddd, J = 9.6, 4.5 Hz, 1H), 4.51 (s, 1H); ^{13}C NMR (75.5 MHz) δ −5.23, −5.18, 13.9, 17.7, 18.3, 21.4, 22.8, 25.9, 26.0, 27.6, 30.8, 34.7, 35.0, 35.2, 36.4, 60.2, 60.9, 72.9, 79.9, 94.9. To a solution of the crude epoxide **10** in dry CH_2Cl_2 (40 mL) was added CSA (59 mg, 0.25 mmol), and the solution was stirred at room temperature for 30 min. Et_2O was added, and the organic extract was washed with saturated aqueous $NaHCO_3$, water, and brine and then dried (Na_2SO_4), filtered, and evaporated to give crude spiroketal aldehyde **9** (2.02 g, 99% crude yield for two steps) as a pale yellow oil which was used without further purification: R_f = 0.55 (5% EtOAc/petrol); ^{1}H NMR (300 MHz) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.83 (d, J = 5.1 Hz, 3H), 0.87 (t, J = 6.6 Hz, 3H), 0.88 (s, 9H), 1.22−1.86 (m, 15H), 2.24 (m, 2H), 3.53−3.80 (m, 3H), 9.59 (s, 1H); ^{13}C NMR (75.5 MHz) δ −5.3, 13.9, 17.7, 18.2, 23.0, 25.3, 25.9, 29.2, 29.4, 33.8, 34.6, 34.8, 36.4, 38.1, 59.5, 73.5, 90.2, 107.0, 205.4.

5,6-Spiroketal 27. A solution of *n*-BuLi (2.5 M in hexanes, 0.560 mL, 1.4 mmol) was added dropwise over 5min to a solution of (trimethylsilyl)acetylene (0.197 mL, 1.38 mmol) in anhydrous THF (2.0 mL) under argon. After 20 min at −78 °C a solution of crude spiroketal aldehyde **9** (93.0 mg, 0.233 mmol) in THF (2.0 mL) was added via cannula at −78 °C. The solution was stirred at −78 °C for 1h and then allowed to warm to 0 °C over 1h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted twice with Et_2O, and then the combined organic extracts were washed with 1% aqueous HCl,

(43) Pirrung, M. C.; Webster, N. J. G. *J. Org. Chem.* **1987**, *52*, 3603−3613.

(44) For a convenient preparation of Cp_2TiMe_2 see: Payack, J. F.; Hughes, D. L.; Cai, D. W.; Cottrell, I. F.; Verhoeven, T. R.; *Org. Prep. Proced. Int.* **1995**, *27*, 707−709.

water, and brine and then dried ($MgSO_4$), filtered, and evaporated to give crude TMS-alkyne **26** as a pale yellow oil. The crude TMS-alkyne **26** was dissovled in MeOH (2.0 mL), and K_2CO_3 (31 mg, 0.23 mmol) was added and the solution was stirred at room temperature for 3 h. The solvent was evaporated, and the resulting slurry was diluted with Et_2O and washed with water and brine and then dried ($MgSO_4$), filtered, and evaporated to give the crude product as a yellow oil. Purification by flash chromatography using 5% EtOAc/petrol as eluent provided 5,6-spiroketal **27** (76.0 mg, 77% yield for two steps) as a pale yellow oil: $R_f = 0.36$ (5% EtOAc/petrol); $[\alpha]^{25}_D$ +35.0 (*c* 0.72, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.90 (s, 9H), 0.90 (t, $J = 7$ Hz, 3H), 1.16−1.46 (m, 8H), 1.48−1.92 (m, 7H), 1.94−2.28 (m, 2H), 2.37 (d, $J = 2.4$ Hz, 1H), 3.60 (d, $J = 7.5$ Hz, 1H), 3.63 (m, 1H), 3.75 (m, 2H), 4.29 (dd, $J = 7.5$, 2.4 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.24, −5.16, 14.1, 17.7, 18.4, 23.2, 25.8, 26.0, 29.2, 29.6, 34.4, 34.5, 34.8, 36.2, 39.7, 59.7, 68.6, 73.0, 73.6, 82.9, 89.7, 107.0. Anal. Calcd for $C_{24}H_{44}O_4Si$: C, 67.87; H, 10.44. Found: C, 67.47; H, 10.43.

6,6-Spiroketal 28. To a solution of 5,6-spiroketal **27** (36.0 mg, 82.0 μmol) in $CDCl_3$ (1.0 mL) in an NMR tube was added a solution of CSA (0.04 M in $CDCl_3$, 65 μL, 2.6 μmol), and the equilibration was monitored by ^{1}H NMR analysis. After 24 h at room temperature, the solution was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$, water, and brine and then dried ($MgSO_4$), filtered, and evaporated to give the product as a yellow oil. Purification by flash chomatography with 5−15% EtOAc/petrol as eluent afforded recovered 5,6-spiroketal **27** (17.6 mg, 49%). Further elution gave 6,6-spiroketal **28** (14.4 mg, 40%) as a colorless oil: $R_f = 0.18$ (5% EtOAc/petrol); $[\alpha]^{25}_D$ +35.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.91 (s, 9H), 0.91 (t, $J = 7.2$ Hz, 3H), 1.24−1.85 (m, 17H), 2.45 (d, $J = 2.0$ Hz, 1H), 3.43 (dt, $J = 10.4$, 2.4 Hz, 1H), 3.74−3.82 (m, 2H), 4.44 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz) δ −5.21, −5.12, 13.9, 17.6, 18.3, 23.2, 24.8, 26.0, 27.7, 27.8, 30.9, 34.8, 34.9, 36.2, 38.7, 59.2, 67.4, 69.8, 71.6, 74.6, 80.3, 95.8.

TBS-ether 8. To a solution of crude 5,6-spiroketal **26** (4.09 g, 8.24 mmol) in CH_2Cl_2 (50 mL) under argon was added pyridine (3.33 mL, 41.2 mmol) then Dess−Martin reagent[46] (8.74 g, 20.6 mmol), and this was stirred at room temperature for 3 h. The reaction mixture was diluted with Et_2O and stirred with saturated aqueous $NaHCO_3$ (110 mL) and 1.5 M $Na_2S_2O_3$ (110 mL) until two clear layers formed. The aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with water, saturated aqueous $CuSO_4$, water, and brine and then dried (Na_2SO_4), filtered, and evaporated to give the crude ketone as a yellow oil. To a solution of the crude ketone in THF (80 mL) under argon at −78 °C was added L-Selectride (1.0 M in THF, 16.2 mL, 16 mmol). The reaction mixture was stirred at −78 °C for 10 min and then warmed to room temperature and diluted with Et_2O and water. The aqueous phase was acidified to pH 3.0 and extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water, and brine and then dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash chromatography with EtOAc/petrol (1%, 2%, then 5%) as eluent to give a mixture of 5,6-spiroketal epimers (90:10 by ^{1}H NMR (300 MHz), 3.55 g, 87% for two steps) as a pale yellow oil. To the mixture of 5,6-spiroketal epimers in MeOH (50 mL) was added K_2CO_3 (988 mg, 7.15 mmol), and the solution was stirred at room temperature under argon for 2.5 h. The solvent was evaporated and then the residue was diluted with Et_2O and washed with water and brine and then dried ($MgSO_4$), filtered, and evaporated to give a crude mixture of alkynes **29** (90:10 by ^{1}H NMR (300 MHz), 2.97 g, 85% crude yield for three steps) as a yellow oil. To a crude mixture of alkynes **29** (90:10 by ^{1}H NMR (300 MHz), 3.31 g, 7.80 mmol) in CH_2Cl_2 (25 mL) at −40 °C under argon was added 2,6-lutidine (2.27 mL, 19.5 mmol) and TBSOTf (2.69 mL, 11.7 mmol), and the mixture was stirred for 2.5 h. Saturated aqueous $NaHCO_3$ and water were then added, and the organic extract was washed with water, saturated aqueous $CuSO_4$, water, and brine and then dried ($MgSO_4$), filtered, and evaporated to give the crude products as a yellow oil. Purification by flash chromatography with 1%, 2%, and then 5% EtOAc/petrol as eluent gave a mixture of bisTBS-ethers (90:10 by ^{1}H NMR (300 MHz), 3.84 g, 91%) as a pale yellow oil. A solution of the crude bisTBS-ethers in THF (89 mL) was added via cannula to a freshly prepared solution of HF·pyridine (5.16 g, 178 mmol) buffered with pyridine[40] (10.3 mL, 127 mmol) in THF (21 mL), and the mixture was stirred at room temperature for 5 h. Saturated aqueous $NaHCO_3$ was added and the mixture was diluted with Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with water, saturated aqueous $CuSO_4$, water, and brine and then dried (Na_2SO_4), filtered, and evaporated to give the crude products as a yellow oil. Purification by flash chromatography with 1%, 2%, and then 5% EtOAc/petrol as eluent gave pure TBS-ether **8** (2.63 g, 80% for two steps) as a colorless oil: $R_f = 0.40$ (10% EtOAc/petrol); $[\alpha]^{19}_D = +36.4$ (*c* 0.65, CH_2Cl_2); IR υ_{max} (film) 3448, 3316, 2955, 2859, 1464 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.11 (s, 3H), 0.14 (s, 3H), 0.79 (d, $J = 6.3$ Hz, 3H), 0.84 (s, 9H), 0.87 (t, $J = 6.9$ Hz, 3H), 1.00−1.45 (m, 6H), 1.46−2.05 (m, 11H), 2.35 (d, $J = 1.8$ Hz, 1H), 2.95 (br s, 1H), 3.68−3.80 (m, 3H) 4.36 (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.5, −4.6, 14.2, 17.6, 17.8, 23.2, 25.4, 25.6, 28.8, 31.5, 32.9, 33.8, 34.5, 34.9, 38.9, 61.2, 70.3, 72.9, 77.1, 84.3, 88.2, 106.8; HRMS (ESI) calcd for $C_{24}H_{44}O_4SiNa$ [$M + Na^+$]: 447.2907. Found: 447.2910. Anal. Calcd for $C_{24}H_{44}O_4Si$: C, 67.87; H, 10.44. Found: C, 67.95; H, 10.61. Further elution gave the epimeric TBS-ether (251 mg, 7% for two steps) as a colorless oil: $R_f = 0.20$ (5% EtOAc/petrol); $[\alpha]^{19}_D = +27.4$ (*c* 0.76, CH_2Cl_2); IR υ_{max} (film) 3446, 3306, 2951, 2854, 1459 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.12 (s, 3H), 0.16 (s, 3H), 0.79 (d, $J = 6.3$ Hz, 3H), 0.87 (t, $J = 6.9$ Hz, 3H), 0.90 (s, 9H), 1.15−2.40 (m, 17H), 2.32 (d, $J = 2.1$ Hz, 1H), 2.92 (br s, 1H), 3.65−3.83 (m, 3H), 4.34 (d, $J = 2.4$ Hz, 1H).; ^{13}C NMR (75.5 MHz) δ −5.0, −4.3, 14.2, 17.5, 18.1, 23.3, 25.6, 25.8, 28.8, 31.1, 33.8, 34.1, 34.3, 34.4, 38.4, 61.0, 70.3, 73.2, 76.8, 83.7, 89.4, 106.7; HRMS (ESI) calcd for $C_{24}H_{44}O_4SiNa$ [$M + Na^+$]: 447.2907. Found: 447.2893. Anal. Calcd for $C_{24}H_{44}O_4Si$: C, 67.87; H, 10.44. Found: C, 67.87; H, 10.52.

Diacetate 30. To a solution of TBS-ether **8** (84.0 mg, 0.198 mmol) in THF (1.4 mL) under argon was added TBAF·3H_2O (125 mg, 0.396 mmol), and the mixture was stirred at room temperature for 24 h. Water was added, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with water and brine and then dried (Na_2SO_4), filtered, and evaporated to give the crude product as a yellow oil. Purification by flash chromatography with 40% EtOAc/petrol as eluent gave the diol (60.8 mg, 99%) as a pale yellow oil: $R_f = 0.50$ (40% EtOAc/petrol); $[\alpha]^{23}_D = +56.3$ (*c* 1.89, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 0.84 (d, $J = 6.3$ Hz, 3H), 0.89 (t, $J = 6.8$ Hz, 3H), 1.28−2.07 (m, 17H), 2.32−2.45(m, 1H), 2.39 (d, $J = 2.4$ Hz, 1H), 2.75 (br s, 1H), 3.68 (m, 2H), 3.79 (dt, $J = 9.0$, 3.9 Hz, 1H), 4.38 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (75.5 MHz) δ 14.0, 17.6, 23.1, 25.3, 28.3, 28.8, 34.5, 35.0, 36.5, 39.0, 59.1, 67.0, 73.3, 75.1, 82.6, 90.5, 107.2. To a solution of the diol in MeOH (0.75 mL) was added Lindlar's catalyst (21 mg, 0.010 mmol), and the mixture was stirred at room temperature under a hydrogen atmosphere for 6 h. The mixture was filtered through Celite, and the solvent was evaporated to give the crude alkene as a pale yellow oil: $R_f = 0.15$ (20% EtOAc/petrol); ^{1}H NMR (300 MHz) δ 0.86 (d, $J = 6.6$ Hz, 3H), 0.88 (t, $J = 6.6$ Hz, 3H), 1.16−2.07 (m, 16H), 2.20−2.37 (m, 1H), 3.68 (m, 2H), 3.80 (dt, $J = 9.0$, 3.6 Hz, 1H), 4.13 (d, $J = 6.3$ Hz, 1H), 5.19 (d, $J = 10.5$ Hz, 1H), 5.38 (d, $J = 17.1$ Hz, 1H), 5.77 (ddd, $J = 17.1$, 10.5, 6.3 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 14.1, 17.7, 23.2, 25.3, 27.4, 28.9, 34.5, 35.0, 35.1, 37.1, 39.1, 59.2, 75.3, 76.2, 90.9, 106.7, 117.3, 136.4. To a solution of the crude alkene in pyridine (2.0 mL, 25 mmol) was added acetic anhydride (1.0 mL, 11 mmol) and DMAP (5.0 mg, 0.037 mmol), and then the mixture was stirred at room temperature under argon for 3 h. The solvents were evaporated and the residue was purified by flash chromatography with 10% EtOAc/petrol as eluent to

(45) For the preparation of butylacrolein see: Green, M. B.; Hickinbottom, W. J. *J. Chem. Soc.* **1957**, 3262−3270.

(46) Preparation of Dess−Martin reagent: Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

give diacetate **30** (59.0 mg, 74% for three steps) as a colorless oil: R_f = 0.30 (10% EtOAc/petrol); $[\alpha]^{24}_D$ = +41.1 (*c* 2.29, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.84 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 6.6 Hz, 3H), 1.15−1.40 (m, 6H), 1.40−1.85 (m, 8H), 1.86−2.10 (m, 3H), 1.99 (s, 3H), 2.08 (s, 3H), 3.52 (td, *J* = 9.6, 2.4 Hz, 1H), 4.10 (m, 1H), 4.36 (m, 1H), 5.14−5.30 (m, 3H), 6.01 (ddd, *J* = 15.5, 11.0, 4.4 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 14.2, 17.7, 21.0, 21.1, 23.2, 25.5, 29.2, 31.6, 32.4, 34.2, 34.5, 34.7, 38.6, 61.0, 72.9, 79.4, 86.9, 106.8, 116.0, 134.2, 169.8, 171.2. Anal. Calcd for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15. Found: C, 66.39; H, 9.08.

Triacetate 6. A solution of diacetate **30** (59.0 mg, 0.149 mmol) in CH_2Cl_2 (2.5 mL) and MeOH (0.85 mL) at −78 °C was bubbled with O_3 gas until the solution turned purple, and then $NaBH_4$ (17 mg, 0.45 mmol) was added and the mixture was warmed to room temperature and stirred for 10 min. The solvent was evaporated and the residue was diluted with Et_2O and water. The aqueous phase was acidified with 10% HCl and extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water, and brine and then dried (Na_2SO_4), filtered and evaporated. The crude alcohol was dissolved in pyridine (2.0 mL, 25 mmol), and then acetic anhydride (1.0 mL, 11 mmol) and DMAP (2.0 mg, 0.015 mmol) were added and the mixture was stirred at room temperature under argon for 24 h. The solvents were evaporated and the residue was purified by flash chromatography with 15% EtOAc/petrol as eluent to give triacetate **6** (60.0 mg, 91% yield for two steps) as colorless prisms: R_f = 0.30 (15% EtOAc/petrol); mp 58−59 °C; $[\alpha]^{20}_D$ = +51.8 (*c* 1.20, $CHCl_3$); lit.[8] $[\alpha]^{15}_D$ = +44.3 (*c* 0.18, $CHCl_3$); lit.[10] $[\alpha]^{25}_D$ = +37.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.84 (d, *J* = 6.6 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H), 1.14−1.82 (m, 14H), 1.87−1.99 (m, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 3.47 (td, *J* = 9.2, 2.7 Hz, 1H), 4.15 (m, 1H), 4.21 (dd, *J* = 12.0, 9.0 Hz, 1H), 4.30 (m, 1H), 4.49 (dd, *J* = 12.0, 2.1 Hz, 1H), 5.15 (dd, *J* = 9.0, 2.1 Hz, 1H); ^{13}C NMR (100 MHz) δ 14.1, 17.7, 20.8, 21.0, 21.1, 23.2, 25.5, 29.0, 31.4, 32.2, 34.2, 34.4, 34.6, 38.4, 61.7, 63.9, 73.6, 76.5, 86.1, 106.9, 170.3, 171.1. Anal. Calcd for $C_{23}H_{38}O_8$: C, 62.42; H, 8.65. Found: C, 62.19; H, 8.36.

Diene Ester 7. To a solution of TBS-ether **8** (1.11 g, 2.60 mmol) in CH_2Cl_2 (38 mL) under argon was added Dess−Martin reagent (1.76 g, 4.16 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was diluted with Et_2O and stirred with saturated aqueous $NaHCO_3$ (50 mL) and 1.5 M $Na_2S_2O_3$ (50 mL) until two clear layers formed. The aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with water and brine and then dried (Na_2SO_4), filtered, and evaporated to give the crude aldehyde as a yellow oil. The crude aldehyde was dissolved in chlorobenzene (20 mL), and 2-(triphenylphosphoranylidene)propionaldehyde (3.93 g, 12.3 mmol) was added, and then the mixture was stirred in the dark at 100 °C under argon for 72 h. The solvent was evaporated, and the crude product was purified by flash chromatography with EtOAc/petrol (2% then 5%) as eluent to give the dienal (793 mg, 66% for two steps) as a yellow oil: R_f = 0.69 (10% EtOAc/petrol); ^{1}H NMR (300 MHz) δ 0.08 (s, 3H), 0.15 (s, 3H), 0.88 (s, 9H), 0.91 (t, *J* = 6.0 Hz, 3H), 1.00−1.45 (m, 10H), 1.50−1.85 (m, 6H), 1.77 (s, 3H), 1.85−2.05 (m, 2H), 2.36 (d, *J* = 2.1 Hz, 1H), 2.53 (m, 2H), 3.78 (m, 1H), 4.36 (d, *J* = 2.1 Hz, 1H), 6.69 (t, *J* = 7.5 Hz, 1H), 9.45 (s, 1H). The dienal was dissolved in benzene (20 mL) and methyl(triphenylphosphoranylidene)acetate (0.974 g, 2.91 mmol) was added, and then the mixture was heated at reflux under argon for 72 h. The solvent was evaporated and the residue was purified by flash chromatography with EtOAc/petrol (2% then 5%) as eluent to give diene ester **7** (888 mg, 66% for three steps) as a yellow oil: R_f = 0.37 (5% EtOAc/petrol); $[\alpha]^{20}_D$ = −23.8 (*c* 0.94, CH_2Cl_2); IR υ_{max} (film) 3310, 2956, 2859, 1724, 1623 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.08 (s, 3H), 0.14 (s, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 9H), 0.89 (t, *J* = 6.6 Hz, 3H), 1.10−1.44 (m, 7H), 1.50−2.40 (m, 8H), 1.77 (s, 3H), 2.24−2.49 (m, 1H), 2.35 (d, *J* = 2.1 Hz, 1H), 2.39 (m, 1H), 3.63−3.73 (m, 1H), 3.72 (s, 3H), 4.34 (d, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 15.6 Hz, 1H), 6.05 (t, *J* = 6.9 Hz, 1H), 7.35 (d, *J* = 15.6 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.3, −4.4, 12.3, 14.2, 17.7, 17.9, 23.2, 25.6, 29.1, 29.6, 31.3, 32.8, 32.9, 33.9, 34.2, 38.8, 51.3, 70.1, 72.9, 75.5, 84.3, 87.9, 107.0, 115.0, 133.7, 138.7, 149.8, 167.8; HRMS (ESI) calcd for $C_{30}H_{50}O_5SiNa$ [*M* + Na^+]: 541.3325. Found: 541.3315.

Oxazolidine-2-thione 33. To a stirred solution of L-valinol (6.17 g, 59.8 mmol) in CH_2Cl_2 (75 mL) under argon was added NEt_3 (10.0 mL, 71.8 mmol) and CS_2 (4.0 mL, 66 mmol), and then the resulting solution was refluxed for 5 h under a drying tube. Silica (20 g) was added, and the solvent was evaporated. Purification by flash chromatography with CH_2Cl_2 as eluent gave the (4*S*)-4-isopropyl-1,3-oxazolidine-2-thione (5.91 g, 68%) as a yellow oil: R_f = 0.40 (CH_2Cl_2); $[\alpha]^{20}_D$ = −18.1 (*c* 0.41, $CHCl_3$); lit.[30c] $[\alpha]^{16}_D$ = −22.5 (*c* 0.41, $CHCl_3$) ^{1}H NMR (300 MHz) δ 0.90 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 1.80 (m, 1H), 3.84 (m, 1H), 4.35 (dd, *J* = 6.6, 9.3 Hz, 1H), 4.66 (dd, *J* = 9.3, 9.3HZ, 1H), 8.74 (br. s, 1H); ^{13}C NMR (75.5 MHz) δ 17.8, 17.9, 32.1, 62.4, 73.4, 189.5. To a stirred solution of the 1,3-oxazolidine-2-thione (5.91 g, 40.7 mmol) in benzene (50 mL) under argon was added pyridine (3.62 mL, 45.0 mmol) and propionyl chloride (4.24 mL, 49.0 mmol), and stirring was continued for 5 h. The reaction mixture was quenched by adding to water and partitioned with Et_2O, and then the aqueous layer was back extracted twice with Et_2O. The combined organic extracts were washed with 10% HCl, water, saturated aqueous $NaHCO_3$, water, and brine and then dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography with 10% EtOAc/petrol as eluent followed by recrystallization from petrol gave oxazolidine-2-thione **33** (4.96 g, 60%) as a crystalline colorless solid: R_f = 0.80 (33% EtOAc/petrol); mp 43−44 °C; $[\alpha]^{18}_D$ = +140.2 (*c* 1.07, $CHCl_3$); ^{1}H NMR (300 MHz) 0.87 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H), 2.34 (m, 1H), 3.24 (dq, *J* = 18.3, 7.2 Hz, 1H), 3.38 (dq, *J* = 18.3, 7.2 Hz, 1H), 4.36 (d, *J* = 1.5 Hz, 1H), 4.38 (s, 1H), 4.70 (m, 1H); ^{13}C NMR (75.5 MHz) 8.59, 14.9, 18.2, 28.9, 31.3, 63.3, 67.6, 174.9, 186.1. Anal. Calcd for $C_9H_{15}O_2NS$: C, 53.70; H, 7.51; N, 6.96. Found: C, 53.91; H, 7.58; N, 6.97.

Aldol Adduct 34. To a solution of the diene ester **7** (418 mg, 0.806 mmol) in CH_2Cl_2 (10 mL) under argon at −78 °C was added DiBALH (1.0 M in CH_2Cl_2, 2.42 mL, 2.42 mmol) dropwise. The mixture was stirred at −78 °C for 25 min and then warmed to room temperature. The DiBALH was quenched with EtOAc (1.0 mL), and then CH_2Cl_2 (10 mL) and 0.5 M (+)-sodium tartrate (10 mL) were added and stirring was continued for 15 min. Water was added and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with water and brine and then dried ($MgSO_4$), filtered, and evaporated to give the crude alcohol as a colorless oil. The crude alcohol was dissolved in CH_2Cl_2 (10 mL), and then pyridine (0.223 mL, 2.82 mmol) and Dess−Martin reagent (598 mg, 1.41 mmol) were added, and the mixture was stirred at room temperature under argon for 40 min. The reaction mixture was diluted with Et_2O and stirred with saturated aqueous $NaHCO_3$ (20 mL) and 1.5 M $Na_2S_2O_3$ (20 mL) until two clear layers formed. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with water and brine and then dried (Na_2SO_4), filtered and evaporated to give crude aldehyde **32** as a yellow oil. To a suspension of $Sn(OTf)_2$[47] (827 mg, 1.18 mmol) in CH_2Cl_2 (3.0 mL) under argon at −55 °C was added *N*-ethylpiperidine (0.272 mL, 1.98 mmol). A solution of oxazolidine-2-thione **33** (332 mg, 1.65 mmol) in CH_2Cl_2 (3.0 mL) was added via cannula, and the mixture was stirred at −55 °C for 1 h and then cooled to −78 °C. A solution of the crude aldehyde **32** in CH_2Cl_2 (3.0 mL) at −78 °C was added via cannula, and the mixture was stirred at −78 °C for 5 min. The reaction mixture was poured into pH 7 buffer and stirred for 10 min, and then the emulsion was filtered through Celite and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated to give the crude aldol adduct as a yellow oil. Purification by flash chromatography with 10% and then 20% EtOAc/petrol as eluent gave aldol adduct **34** (443 mg, 80% for three steps) as a colorless oil: R_f = 0.50 (20% EtOAc/petrol); $[\alpha]^{20}_D$ = +52.7 (*c* 3.15, CH_2Cl_2); IR υ_{max} (film)

(47) For the preparation of $Sn(OTf)_2$ see: Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757−6761.

3480, 3310, 2957, 2861, 1703 cm^{-1}; ^1H NMR (300 MHz) δ 0.10 (s, 3H), 0.16 (s, 3H), 0.80 (d, J = 6.6 Hz, 3H), 0.83−0.94 (m, 9H), 0.88 (s, 9H), 1.06−1.44 (m, 6H), 1.19 (d, J = 6.9 Hz, 3H), 1.49−2.06 (m, 10H), 1.75 (s, 3H), 2.23−2.40 (m, 3H), 2.53 (br s, 1H), 3.65 (dt, J = 9.9, 4.8 Hz, 1H), 4.34−4.44 (m, 3H), 4.58−4.68 (m, 1H), 4.72−4.82 (m, 1H), 4.96−5.11 (m, 1H), 5.59 (dd, J = 15.6, 6.6 Hz, 1H), 5.66 (t, J = 8.7 Hz, 1H), 6.36 (d, J = 15.6 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −5.2, −4.3, 11.4, 12.6, 14.3, 14.8, 17.6, 18.0, 18.2, 23.3, 25.4, 25.7, 25.6, 29.0, 31.3, 32.0, 33.0, 33.7, 38.9, 42.8, 63.2, 67.3, 70.2, 72.9, 73.9, 75.6, 84.5, 87.8, 107.0, 125.0, 130.0, 133.8, 137.2, 176.7, 186.0; HRMS (ESI) calcd for $C_{38}H_{63}NO_6SSiNa$ [M + Na^+]: 712.4043. Found: 712.4026. Anal. Calcd for $C_{38}H_{63}NO_6SSi$: C, 66.14; H, 9.20; N, 2.03. Found: C, 65.98; H, 9.29; N, 1.98.

Diol 50. To a solution of aldol adduct **34** (577 mg, 0.836 mmol) in THF (8.0 mL) and water (0.80 mL) at 0 °C was added $NaBH_4$ (95.0 mg, 2.51 mmol), and the mixture was stirred at room temperature for 40 min. The solvent was evaporated, Et_2O and water were added to the residue, and this was stirred vigorously for 10 min. The organic extract was washed with 1.0 M NaOH, water, and brine and then dried (Na_2SO_4), filtered, and evaporated to give the crude product as a yellow oil. Purification by flash chromatography with 20% and then 40% EtOAc/petrol as eluent gave diol **50** (454 mg, 99%) as a pale yellow oil: R_f = 0.50 (40% EtOAc/petrol); $[\alpha]^{20}_D$ = −19.2 (c 0.57, CH_2Cl_2); IR υ_{max} (film) 3375, 3312, 2929, 2860 cm^{-1}; ^1H NMR (400 MHz) δ 0.09 (s, 3H), 0.15 (s, 3H), 0.80 (d, J = 6.4 Hz, 3H), 0.84−0.92 (m, 6H), 0.86 (s, 9H), 1.14−1.40 (m, 7H), 1.50−2.40 (m, 12H), 1.75 (s, 3H), 2.34−2.36 (m, 1H), 2.35 (d, J = 2.0 Hz, 1H), 3.61−3.68 (m, 2H), 3.71 (dd, J = 10.4, 7.2 Hz, 1H), 4.31 (dd, J = 6.8, 3.2 Hz, 1H), 4.38 (d, J = 2.0 Hz, 1H), 5.61 (dd, J = 15.6, 7.2 Hz, 1H), 5.65 (t, J = 8.8 Hz, 1H), 6.31 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz) δ −5.2, −4.3, 11.7, 12.7, 14.3, 17.7, 18.0, 23.3, 25.4, 25.7, 25.8, 29.2, 31.3, 32.1, 33.0, 33.8, 39.9, 40.2, 66.4, 70.2, 72.9, 75.6, 77.2, 84.4, 87.8, 107.1, 125.7, 130.0, 133.7, 137.0; HRMS (ESI) calcd for $C_{32}H_{56}O_5SiNa$ [M + Na^+]: 571.3795. Found: 571.3792. Anal. Calcd for $C_{32}H_{56}O_5Si$: C, 70.02; H, 10.28. Found: C, 70.19; H, 10.34.

Vinyl stannane 51. To a solution of diol **50** (454 mg, 0.827 mmol) in CH_2Cl_2 (30 mL) at 0 °C under argon was added bis-(triphenylphosphine)palladiumdichloride (59.0 mg, 0.0840 mmol), and the mixture was stirred for 10 min. Tributyltin hydride (0.890 mL, 3.31 mmol) was added dropwise, and stirring was continued at 0 °C for 30 min. The solvent was evaporated, and purification of the crude product by flash chromatography with EtOAc/petrol (20% then 30%, containing 1% NEt_3) as eluent gave vinyl stannane **51** (579 mg, 82%) as a yellow oil: R_f = 0.50 (33% EtOAc/petrol); $[\alpha]^{21}_D$ = −40.6 (c 0.18, CH_2Cl_2); IR υ_{max} (film) 3369, 2956, 2928, 2873, 2858 cm^{-1}; ^1H NMR (300 MHz) δ −0.02 (s, 3H), 0.057 (s, 3H), 0.81 (d, J = 6.3 Hz, 3H), 0.88 (t, J = 7.2 Hz, 12H), 0.89 (s, 9H), 1.12−1.44 (m, 18H), 1.44−2.16 (m, 17H), 2.18−2.52 (m, 2H), 1.76 (s, 3H), 2.29 (m, 1H), 2.36−2.48 (m, 1H), 3.46−3.59 (m, 1H), 3.59−3.77 (m, 2H), 4.05 (d, J = 3.3 Hz, 1H), 4.32 (dd, J = 6.6, 3.6 Hz, 1H), 5.63 (dd, J = 15.9, 7.2 Hz, 1H), 5.66 (t, J = 8.7 Hz, 1H), 6.16 (m, 2H), 6.29 (d, J = 15.9 Hz, 1H); ^{13}C NMR (75.5 MHz) δ -4.7, −3.7, 9.5, 11.6, 12.7, 13.7, 14.2, 17.8, 18.1, 23.5, 25.9, 27.3, 27.3 (d, J ($^{13}C-^{117/119}Sn$) = 53.1 Hz), 29.2, 32.2, 32.8, 33.5, 34.1, 34.4, 38.7, 40.2, 66.4, 75.6, 82.5, 88.8, 106.6, 125.8, 127.9, 130.0, 133.6, 136.9, 148.8; HRMS (ESI) calcd for $C_{44}H_{84}O_5SiSnNa$ [M + Na^+]: 863.5008. Found: 863.5001.

Iodide 41. Tetrolic acid (3.10 g, 36.5 mmol) was combined with hydroiodic acid (55% aq, 6 mL, 43.8 mmol), and the resulting solution was heated to 90 °C and stirred for 4 h. Cold water (26 mL) was added, and the product was isolated by filtration and washed with cold water and then dried under vacuum for 24 h (0.1 mmHg) to give Z-3-iodo-2-butenoic acid[35a] as pale yellow needles (6.04 g, 78%). The (Z)-acid was heated to 135 °C in a sealed tube for 24 h to provide a mixture of (Z)-3-iodo-2-butenoic acid and (E)-3-iodo-2-butenoic acid (Z/E = 1:4, 6.04 g, 100%). To a solution of the crude acids (Z/E = 1:4, 427 mg, 2.0 mmol) in CH_2Cl_2 (2 mL) was added trimethylsilylethanol (286 μL, 2.0 mmol) followed by DCC (413 mg, 2.0 mmol) and DMAP (24 mg, 0.19 mmol). The mixure was stirred at room temperature for 15 h and then diluted with cold pentane and filtered through Celite. Concentration of the filtrate gave the crude product which was chomatographed on silica using 10% CH_2Cl_2/petrol as eluant to afford the (E)-iodo ester **41** (295 mg, 47%) as a colorless oil; R_f = 0.29 (10% CH_2Cl_2/petrol); IR υ_{max} (film) 2954, 1715, 1619 cm^{-1}; ^1H NMR (300 MHz) δ 0.04 (s, 9H), 0.998 (m, 2H), 2.98 (d, J = 1.5 Hz, 3H), 4.18 (m, 2H), 6.60 (q, J = 1.5 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −1.5, 17.2, 30.9, 62.6, 120.1, 131.6, 164.2. Anal. Calcd for $C_9H_{17}IO_2Si$: C, 34.62; H, 5.49. Found: C, 34.62; H, 5.29. Further elution gave the (Z)-iodo ester (84 mg, 14%) as a colorless oil: R_f = 0.10 (10% CH_2Cl_2/petrol); IR υ_{max} (film) 2955, 1727, 1630, 1307, 1250, 1169 cm^{-1}; ^1H NMR (300 MHz) δ 0.04 (s, 9H), 1.03 (m, 2H), 2.73 (d, J = 1.2 Hz, 3H), 4.25 (m, 2H), 6.26 (q, J = 1.2 Hz, 1H); ^{13}C NMR (75.5 MHz) δ −1.5, 17.3, 36.5, 62.8, 113.1, 125.6, 164.4. Anal. Calcd for $C_9H_{17}IO_2Si$: C, 34.62; H, 5.49. Found: C, 34.81; H, 5.54.

Tmse-ester 53. To a solution of vinyl stannane **51** (579 mg, 0.689 mmol) in THF (5.0 mL) under argon was added TBAF·$3H_2O$ (1.31 g, 4.14 mmol), and the mixture was stirred at 50 °C for 72 h. Water was added, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with water and brine and then dried (Na_2SO_4), filtered, and evaporated to give crude triol **52** (484 mg, 97% crude yield) as a yellow oil. To a solution of crude triol **52** in NMP (10 mL) was added iodide **41** (0.306 mL, 1.33 mmol), and the mixture was frozen, degassed, and thawed three times. Tri-2-furylphosphine (30.9 mg, 0.133 mmol) was added to the mixture followed by tris(dibenzylideneacetone)dipalladium (30.5 mg, 0.033 mmol), and the mixture was stirred at 55 °C under argon for 30 min. The mixture was diluted with water, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with water and brine and then dried (Na_2SO_4), filtered, and evaporated to give the crude product as a yellow oil. Purification by flash chromatography with 20−50% EtOAc/petrol as eluent gave Tmse-ester **53** (300 mg, 70% for two steps) as a yellow oil: R_f = 0.33 (40% EtOAc/petrol); $[\alpha]^{20}_D$ = −41.8 (c 1.29, CH_2Cl_2); IR υ_{max} (film) 3400, 2954, 2874, 1710, 1613 cm^{-1}; ^1H NMR (300 MHz) δ 0.04 (s, 9H), 0.82−0.96 (m, 9H), 0.98−1.04 (m, 2H), 1.18−2.50 (m, 17H), 1.75 (s, 3H), 2.01 (m, 1H), 2.27 (s, 3H), 3.50−3.74 (m, 3H), 4.18−4.23 (m, 2H), 4.20 (s, 1H), 4.31 (m, 1H), 5.60 (m, 1H), 5.64 (dd, J = 15.6, 3.9 Hz, 1H), 5.77 (s, 1H), 5.99 (dd, J = 15.6, 6.3 Hz, 1H), 6.31 (d, J = 15.6 Hz, 1H), 6.40 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz) δ −1.5, 11.8, 12.7, 13.8, 14.1, 17.3, 17.6, 23.1, 25.3, 26.8, 27.8, 28.9, 31.5, 33.6, 34.6, 37.1, 39.3, 40.1, 61.9, 66.1, 76.2, 76.5, 90.9, 106.9, 119.6, 126.2, 128.6, 134.3, 134.6, 135.0, 136.4, 151.4, 167.2; HRMS (ESI) calcd for $C_{35}H_{60}O_7SiNa$ [M + Na^+]: 643.4006. Found: 643.4006.

Bis-TBS-ether 54. To a solution of Tmse-ester **53** (77.0 mg, 0.124 mmol) in dry DMF (1.16 mL) under argon was added imidazole (76.0 mg, 1.12 mmol) and *tert*-butyldimethylsilyl chloride (112 mg, 0.744 mmol), and the solution was stirred at 50 °C under argon for 2 h. The mixture was then diluted with water and extracted with Et_2O, and the combined organic extracts were washed with water and brine and then dried (Na_2SO_4), filtered, and evaporated to give the crude product as a yellow oil. Purification by flash chromatography with 2.5% EtOAc/petrol as eluent gave bis-TBS-ether **54** (63.0 mg, 60%) as a colorless oil: R_f = 0.34 (5% EtOAc/petrol); $[\alpha]^{20}_D$ = −26.5 (c 2.87, CH_2Cl_2); IR υ_{max} (film) 3468, 2954, 2859, 1712, 1614 cm^{-1}; ^1H NMR (400 MHz) δ −0.02 (s, 3H), 0.01 (s, 6H), 0.02 (s, 3H), 0.04 (s, 9H), 0.82−0.92 (m, 9H), 0.87 (s, 9H), 0.88 (s, 9H), 0.98−1.03 (m, 2H), 1.23−2.08 (m, 14H), 1.71 (s, 3H), 1.97−2.08 (m, 2H), 2.04 (m, 1H), 2.26 (s, 3H), 2.25−2.31 (m, 1H), 2.38 (m, 1H), 3.38 (dd, J = 9.6, 6.4 Hz, 1H), 3.55−3.59 (m, 2H), 3.71 (s, 1H), 4.18−4.24 (m, 3H), 5.50 (t, J = 7.6 Hz, 1H), 5.50 (dd, J = 15.6, 7.2 Hz, 1H), 5.77 (s, 1H), 5.96 (dd, J = 15.6, 6.8 Hz, 1H), 6.12 (d, J = 15.6 Hz, 1H), 6.41 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz) δ −5.4, −5.3, −5.0, −4.0, −1.5, 11.3, 12.8, 13.9, 14.2, 17.3, 17.6, 18.2, 18.3, 23.2, 25.4, 25.9, 26.0, 27.0, 29.0, 31.6, 33.3, 34.6, 37.8, 39.4, 43.0, 61.9, 65.1, 73.8, 76.4, 76.8, 91.4, 107.0, 119.7, 126.7, 129.1, 134.1, 134.6, 134.8, 135.2, 151.4, 167.3. Anal. Calcd for $C_{47}H_{88}O_7Si_3$: C, 66.45; H, 10.44. Found: C, 66.49; H, 10.36.

Acid 55. To a solution of trimethylsilylethanol (610 mg, 5.2 mmol), triethylamine (253 μL, 1.8 mmol), and succinic anhy-

dride (607 mg, 6.1 mmol) in toluene (3.6 mL) was added *N*-hydroxysuccinimide (209 mg, 1.8 mmol) and DMAP (74 mg, 0.66 mmol), and the resulting solution was heated at relux for 1.5 h. The mixture was then cooled, diluted with Et_2O, and washed with water, saturated aqueous $CuSO_4$, and brine and dried. Removal of the solvent gave the crude acid (1.21 g, 100%) which was pure enough to be used without further purification. $R_f = 0.25$ (10% EtOAc/petrol); IR υ_{max} (film) 3250, 2956, 1737, 1715 cm^{-1}; ^1H NMR (300 MHz) δ −0.03 (s, 6H), 0.98 (m, 2H), 2.56−2.72 (m, 4H), 4.39 (m, 2H); ^{13}C NMR (75.5 MHz) δ −1.6, 17.1, 28.86, 28.88, 63.0, 172.2, 178.3; HRMS (ESI) calcd for $C_9H_{18}O_4SiNa$ [M + Na^+]: 241.0872. Found: 241.0863.

Succinate 56. To a solution of bis-TBS-ether **54** (63.0 mg, 0.0742 mmol) in CH_2Cl_2 (1.3 mL) under argon was added acid **55** (0.180 mL, 0.590 mmol), DMAP (3.6 mg, 0.029 mmol) and DCC (123 mg, 0.596 mmol) and then the mixture was stirred at room temperature under argon for 48 h. Pentane was added, the suspension was filtered through Celite, and the filtrate was concentrated. The residue was dissolved in Et_2O and washed with saturated aqueous $NaHCO_3$, water, and brine, and then dried (Na_2SO_4), filtered, and evaporated to give the crude product as a yellow oil. Purification by flash chromatography with 1% and then 2.5% EtOAc/petrol as eluent gave succinate **56** (78.0 mg, 100%) as a colorless oil: $R_f = 0.43$ (5% EtOAc/petrol); $[\alpha]^{20}_D = -46.6$ (c 2.37, CH_2Cl_2); IR υ_{max} (film) 2954, 2859, 1739, 1713, 1615 cm^{-1}; ^1H NMR (300 MHz) δ −0.04 (s, 3H), 0.004 (s, 6H), 0.01 (s, 3H), 0.02 (s, 9H), 0.04 (s, 9H), 0.77−0.92 (m, 9H), 0.86 (s, 9H), 0.87 (s, 9H), 0.94−1.02 (m, 4H), 1.14−1.88 (m, 12H), 1.70 (s, 3H), 1.88−2.08 (m, 3H), 1.99 (m, 1H), 2.27 (s, 3H), 2.34 (m, 1H), 2.43 (m, 1H), 2.59−2.69 (m, 4H), 3.35 (dd, J = 9.6, 6.9 Hz, 1H), 3.44−3.50 (m, 1H), 3.58 (dd, J = 9.6, 6.0 Hz, 1H), 4.14−4.22 (m, 5H), 5.46 (dd, J = 15.6, 7.5 Hz, 1H), 5.52 (s, 1H), 5.98 (t, J = 7.2 Hz, 1H), 5.74 (m, 1H), 6.17 (m, 3H); ^{13}C NMR (100 MHz) δ −5.4, −5.3, −5.0, −3.9, −1.5, −1.4, 11.4, 12.7, 13.8, 14.2, 17.3, 17.4, 17.8, 18.2, 18.3, 23.2, 25.4, 25.91, 25.95, 29.3, 31.6, 31.8, 33.5, 34.1, 34.6, 38.6, 43.1, 61.8, 63.0, 65.2, 74.2, 76.3, 79.0, 87.1, 107.2, 120.0, 127.7, 128.7, 131.3, 134.3, 134.9, 135.0, 151.2, 167.2, 170.9, 172.2; HRMS (ESI) calcd for $C_{56}H_{104}O_{10}Si_4Na$ [M + Na^+]: 1071.6604. Found: 1071.6568.

Alcohol 57. To succinate **56** (78.0 mg, 0.0743 mmol) under argon was added a freshly prepared solution of HF·pyridine (108 mg, 3.72 mmol) buffered with pyridine (0.216 mL, 2.69 mmol) in THF (1.87 mL), and the solution was stirred at room temperature for 6 h. Saturated aqueous $NaHCO_3$ was added, the mixture was diluted with Et_2O, and the aqueous phase was further extracted with Et_2O. The combined organic extracts were washed with water, saturated aqueous $CuSO_4$, water, and brine and then dried (Na_2SO_4), filtered, and evaporated to give the crude product as a yellow oil. Purification by flash chromatography with 5% and then 20% EtOAc/petrol as eluent gave alcohol **57** (45.0 mg, 65%) as a pale yellow oil: $R_f = 0.21$ (10% EtOAc/petrol); $[\alpha]^{20}_D = -53.8$ (c 1.83, CH_2Cl_2); IR υ_{max} (film) 3535, 2955, 2861, 1738, 1712, 1614 cm^{-1}; ^1H NMR (300 MHz) δ 0.01 (s, 3H), 0.03 (s, 9H), 0.04 (s, 9H), 0.06 (s, 3H), 0.75 (d, J = 6.9 Hz, 3H), 0.80−0.93 (m, 6H), 0.87 (s, 9H), 0.95−1.03 (m, 4H), 1.14−2.10 (m, 16H), 1.73 (s, 3H), 2.17−2.27 (m, 1H), 2.26 (s, 3H), 2.47−2.56 (m, 1H), 2.59−2.70 (m, 4H), 3.08 (m, 1H), 3.39−3.45 (m, 2H), 3.57−3.67 (m, 1H), 4.14−4.22 (m, 4H), 4.24 (m, 1H), 5.51 (dd, J = 15.6, 7.8 Hz, 1H), 5.52 (br s, 1H), 5.71 (m, 2H), 6.17 (m, 2H), 6.29 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz) δ −5.1, −4.0, −1.6, −1.5, 12.5, 12.6, 13.8, 14.2, 17.2, 17.4, 17.9, 18.0, 23.2, 25.3, 25.8, 29.2, 29.26, 29.29, 31.7, 31.8, 34.1, 34.4, 38.8, 41.4, 61.9, 63.0, 65.9, 76.6, 78.2, 79.2, 87.2, 107.2, 119.9, 125.9, 129.2, 131.2, 133.9, 134.9, 136.8, 151.1, 167.2, 171.0, 172.2; HRMS (ESI) calcd for $C_{50}H_{90}O_{10}Si_3Na$ [M + Na^+]: 957.5739. Found: 957.5741. Anal. Calcd for $C_{50}H_{90}O_{10}Si_3$: C, 64.19; H, 9.70. Found: C, 64.21; H, 9.63.

Triester 59. To a solution of alcohol **57** (84.1 mg, 0.090 mmol) in CH_2Cl_2 (4.0 mL) under argon was added pyridine (0.073 mL, 0.90 mmol) and Dess−Martin reagent (0.191 g, 0.50 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with Et_2O and stirred with saturated aqueous $NaHCO_3$ (20 mL) and 1.5 M $Na_2S_2O_3$ (20 mL) until two clear layers formed. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with water, saturated aqueous $CuSO_4$, water, and brine and then dried (Na_2SO_4), filtered, and evaporated to give the crude aldehyde as a yellow oil. The crude aldehyde was dissolved in CH_2Cl_2 (3.0 mL), and trimethylsilylethyl(triphenylphosphoranylidene)acetate (**58**)[41] (405 mg, 0.899 mmol) was added. Then the resulting solution was stirred at room temperature under argon for 17 h. The solvent was evaporated, and purification of the crude product by flash chromatography with 5−10% EtOAc/petrol as eluent gave triester **59** (85.9 mg, 89% for two steps) as a colorless oil: $R_f = 0.43$ (10% Et_2O/petrol); $[\alpha]^{20}_D = -40.6$ (c 1.51, CH_2Cl_2); IR υ_{max} (film) 2955, 1737, 1716, 1652, 1615 cm^{-1}; ^1H NMR (400 MHz) δ −0.03 (s, 3H), 0.02 (s, 3H), 0.03 (s, 9H), 0.04 (s, 18H), 0.83 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.89 (t, J = 6.4 Hz, 3H), 0.97 (d, J = 8.0 Hz, 3H), 0.96−1.03 (m, 6H), 1.15−1.85 (m, 14H), 1.69 (s, 3H), 1.95 (m, 1H), 2.28 (d, J = 0.4 Hz, 3H), 2.30 (m, 1H), 2.43 (m, 1H), 2.61−2.70 (m, 4H), 3.46 (m, 1H), 4.10 (dd, J = 7.6, 4.0 Hz, 1H), 4.15−4.23 (m, 6H), 5.20 (br s, 1H), 5.38 (dd, J = 15.6, 7.6 Hz, 1H), 5.52, (s, 1H), 5.65 (dd, J = 6.8, 6.8 Hz, 1H), 5.75 (m, 2H), 6.20 (m, 3H), 7.01 (dd, J = 15.6, 7.2 Hz, 1H); ^{13}C NMR (100 MHz) δ −5.0, −4.0, −1.5, −1.48, −1.46, 12.7, 13.8, 13.9, 14.2, 17.2, 17.3, 17.4, 17.8, 18.2, 23.2, 25.3, 25.9, 29.2, 29.3, 31.7, 31.8, 33.7, 34.0, 34.6, 38.7, 43.7, 61.9, 62.2, 63.0, 72.2, 76.3, 77.1, 79.1, 87.1, 107.2, 120.0, 120.9, 126.8, 128.8, 131.3, 134.0, 134.9, 136.4, 151.2, 151.6, 166.9, 167.2, 170.9, 172.2; HRMS (ESI) calcd for $C_{57}H_{102}O_{11}Si_4Na$ [M + Na^+]: 1097.6397. Found: 1097.6389.

(−)-Reveromycin B (2). To a solution of triester **59** (27.9 mg, 0.0259 mmol) in DMF (1.0 mL) at room temperature under argon was added TBAF·$3H_2O$ (65.5 mg, 0.207 mmol), and stirring was continued for 18 h. Further TBAF·$3H_2O$ (35.0 mg, 0.111 mmol) was added, and stirring was continued for a total of 48 h. The reaction mixture was partitioned between EtOAc and saturated aqueous NH_4Cl, and then 10% HCl was added until pH 3.0 was obtained. The organic extract was washed with water and brine and then dried ($MgSO_4$), filtered, and evaporated. Purification was carried out by filtration through a reverse phase column (C18 spherex, 900 mg) with 40−20% water/methanol as eluant to give (−)-reveromycin B **2** (12.3 mg, 72%) as a white powder: $R_f = 0.35$ (15% MeOH/CH_2Cl_2); $[\alpha]^{20}_D = -45.3$ (c 0.12, MeOH); lit.[11] $[\alpha]^{25}_D = -51.8$ (c 0.3, MeOH); lit.[10] $[\alpha]^{25}_D = -61.0$ (c 0.1, MeOH); lit.[3] $[\alpha]^{20}_D = -66$ (c 0.1, MeOH); IR υ_{max} (film) 3410, 2931, 1722, 1614 cm^{-1}; UV λ_{max} (MeOH) 238 nm (ϵ 3.45 × 10^4 $Lmol^{-1}cm^{-1}$); ^1H NMR (400 MHz, CD_3OD) δ 0.88 (d, J = 6.4 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 1.20−2.15 (m, 15H), 1.73 (s, 3H), 2.14−2.26 (m, 1H), 2.22 (s, 3H), 2.48−2.61 (m, 2H), 2.62−2.70 (m, 4H) 3.44 (ddd, J = 10.8, 8.8, 2.0 Hz, 1H), 4.07 (dd, J = 7.6, 5.6 Hz, 1H), 5.46 (dd, J = 15.6, 7.6 Hz, 1H), 5.56 (d, J = 3.2 Hz, 1H), 5.76 (dd, J = 6.8, 6.8 Hz, 1H), 5.78 (br s, 1H), 5.78 (d, J = 15.6 Hz, 1H), 6.22−6.27 (m, 2H), 6.38 (d, J = 15.6 Hz, 1H), 6.96 (dd, J = 15.6, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 12.7, 14.0, 14.5, 15.1, 18.2, 24.4, 26.6, 30.3, 30.4, 30.8, 32.9, 35.2, 35.6, 35.7, 39.8, 44.0, 77.2, 78.4, 80.4, 88.8, 108.6, 121.7, 122.9, 127.2, 130.8, 132.4, 135.2, 136.1, 138.6, 151.9, 152.5, 170.6, 170.7, 173.2, 176.2; HRMS (ESI) calcd for $C_{36}H_{52}O_{11}Na$ [M + Na^+]: 683.3407. Found: 683.3404.

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Supporting Information Available: Experimental procedures for the preparation of compounds **15**−**22**, **35**−**39**, and **44**−**45** as well as an ORTEP diagram and X-ray coordinates for the structure of **22** and copies of the ^1H and ^{13}C NMR spectra of all key intermediates. This material is available free of charge via Internet at http://pubs.acs.org.

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