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Supplementary Material Available: Tables of bond distances and angles and atomic coordinates and equivalent isotropic displacement parameters for tropylium EDA complexes (5 pages). Ordering information is given on any current masthead page.

The Total Synthesis of Avermectin A_{1a}

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Abstract: Key fragments for the total synthesis of the title compound were elaborated from D-ribose and D-glucose and coupled through a crossed aldol dehydration maneuver (**33** + **44** → **46**). An intramolecular variant of the Nozaki reaction (**47** → **48**) led to the all-critical oxahydrindene system. Disaccharide **66** was synthesized from fragments which were prepared by cyclocondensation reactions. Stereospecific coupling of **66** to aglycon **55** gave **67** and, eventually, avermectin A_{1a}.

Background and Synthetic Goals. The screening of microbially derived fermentation products for new antibacterial agents has provided for a fruitful collaboration among biology, chemistry, and medicine.[1] This type of multifaceted venture attained early prominence and success in the discovery and development of penicillins.[2] The possibilities of finding agents which might prove useful in other kinds of therapeutic applications are receiving increasing scrutiny.

It was in the course of investigating fermentation products of a broth derived from *Streptomyces avermitilis* MA-4680 that the avermectins were first encountered. An assay involving survival of mice infected with *Nematodirus dubuis* enabled a team of Merck scientists to discover anthelmentic activity of a high order from a soil sample from the Shizuaka Prefecture in Japan.[3] A collection of eight closely related compounds called avermectins was eventually separated into individual components. The delineation of the structures of these compounds relied heavily on a crystallographic determination of avermectin B_{1a} and avermectin B_{2a} aglycon.[4] From these firm bases, with extensive support via spectroscopic techniques and some chemical correlations, the structures of the eight compounds shown in Figure 1 could be deduced.[5]

The avermectins are active against two major classes of parasites, nematodes and arthropods. The mechanism of action appears to involve interferences with GABA-mediated muscular regulation. The quest for a detailed insight into the mechanism of action of this class of compounds and the evaluation of the therapeutic advantages of specific naturally occurring members, congeners, and semisynthetic mixtures (cf. ivermectins) is an important area of biomedical research.[6] The avermectins already enjoy extensive usage in animal (e.g. cattle, sheep, horses) health maintenance against a broad range of internal parasites.

The most promising targets of opportunity for structural manipulation of the activity profile have been in the carbohydrate region attached to C_{13} and in the unsaturation level of the spiroketal sector. Modifications of the oxahydrindene area and attempts at realizing avermectin activity via structures in which the macrolactone activity is simulated have been unrewarding.[7]

Not surprisingly, the combination of the novelty of the molecular structure of these compounds, their already demonstrated commercial importance, and the possibilities for discovery of new therapeutic uses, including human application, have engendered significant interest in the synthesis of avermectins.[8] Two important milestones in this regard were achieved by Smith and Williams, who independently reported the syntheses of milbemycin A_5.[9-11] A variety of sequences for the synthesis of the spiroketal section have been demonstrated.[12] More difficult has been the matter of a facile assembly of the oxahydrindene moiety.[13] Of late, some promising advances in this regard have been recorded.

Several important breakthroughs in charting a comprehensive strategy for the total synthesis of the avermectins have been achieved by Hanessian and co-workers. These studies established routes to the optically pure spiroketal of the avermectin 1a series

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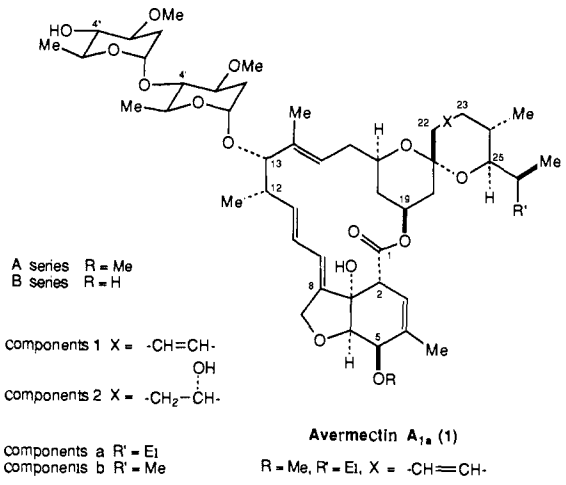

Figure 1.

and identified new possibilities for the synthesis of the oxahydrindene region.[14] The feasibility of macrolactonization of a Δ^2 variation of avermectin seco acid was established.[15] The issue of the overall conversion of a Δ^2 tautomer to an avermectin with the correct C_2 stereochemistry, which will be discussed later in this report, was also accomplished by Hanessian.[16] Finally, we note that a protocol for the attachment of the disaccharide (L-oleandrosyl-L-oleandrose) to an avermectin aglycon was previously demonstrated.[14,17]

We defined as our goal a total synthesis of avermectin A_{1a}. One of our reasons for focusing on the 1a system was the additional challenge of dealing with the additional stereogenic center at C_{26}, as well as the C_{22}–C_{23} double bond.[18] While the B avermectins (C_5OH) are much more active biologically, we focused on the A series for two reasons. First, the C_5 methyl ether target would avoid the need for an additional protecting group, which could well be necessary for the C_5 hydroxy target. Furthermore, the conversion of avermectin A_{1a} to avermectin B_{1a} has been accomplished by oxidative demethylation.[19] Thus, a synthesis of the former provides access to the latter series.

Our goals in this undertaking were several. First, we hoped to achieve a total synthesis of avermectin A_{1a}. *To accomplish this would require that strategies employed to solve regional issues be adaptable to the entire molecular problem.* We wished to accomplish the aglycon total synthesis in a fashion where a maximum amount of stereochemical selectivity is transmitted by intramolecular biases rather than by grouping of dissymmetric fragments.[20] Furthermore, we hoped to synthesize the L-oleandrosyl-L-oleandrose carbohydrate through new technology rather than by partial synthesis. Finally, we wanted to achieve the disaccharide synthesis and glycosylation in a fashion which would have implications in the fashioning of new semisynthetic avermectins and, more broadly, in the larger field of oligosaccharide synthesis. Given the excellent availability of the avermectins from natural sources, it would be through advances in the carbohydrate sector (both synthesis and glycosylation) that synthesis would be most promising for practical benefits.

Synthetic Strategy. Of course, with so multifaceted a target as avermectin A_{1a}, the most carefully considered strategies are

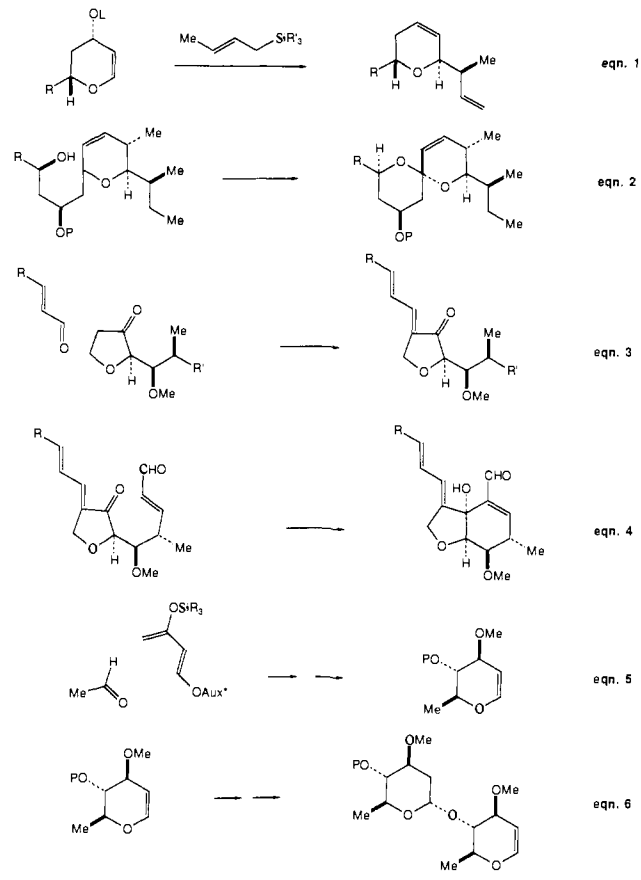

Figure 2.

apt to undergo substantial modification and even abandonment under the often harsh realities of implementation. *In this type of venture, flexibility of the design with ample opportunities for reorientation is often crucial for success.* Several of the cornerstones of our basic plans involved chemistry previously developed in our laboratory in connection with this undertaking and toward related goals. Thus, the potentially serious issue of stereochemistry at carbons 24 and 25 would be addressed via our previously developed carbon Ferrier–crotylsilane technology (see eq 1, Figure 2).[21] The spiroketal moiety would be assembled through oxidative cyclization (see eq 2).[22a,b,c] An aldol-dehydration sequence of a suitable enal would be used to link a tetrahydrofuranone to an enal, thereby generating a dienone (see eq 3). The C_1–C_5 side chain functionality shown as R would be so selected that at a strategic point it would emerge as an α,β-unsaturated aldehyde. This would be cyclized through one of several a priori possible protocols to give an α,β-unsaturated seco-acyl system (see eq 4).[22d] This would eventually be converted to avermectin A_{1a} aglycon by macrolactonization and deconjugation.

The total synthesis of the L-oleandrosyl-L-oleandrose would exploit our previously demonstrated chiral auxiliary–chiral catalyst synergism for synthesizing L-sugars.[23] In the case at hand, there would be fashioned a glycal-like structure (see eq 5). A disaccharide, terminating in a glycal at its "reducing" end, would then be fashioned (see eq 6). To complete the synthesis of avermectin A_{1a}, the aglycon would be coupled to the disaccharide with appropriate functional group management. *Below we report*

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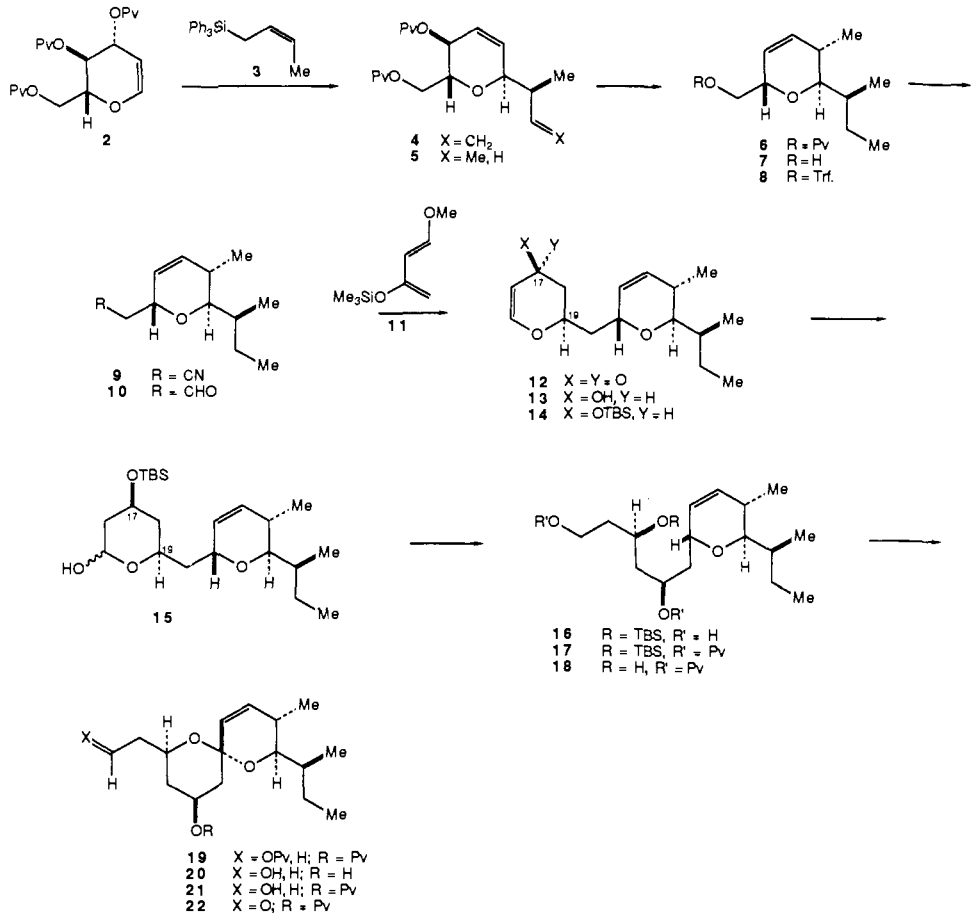

Figure 3.

the realization of these goals and the attainment of the first total synthesis of a naturally occurring avermectin, i.e., avermectin A_{1a}.[24]

Discussion of Results

D-Glucal tripivalate (**2**)[25] and D-ribose aldehyde (**34**, vide infra) were selected as building blocks of suitably matched chirality. As will be seen, none of the stereogenic centers of **2** would survive its eventual transformation to avermectin A_{1a} (**1**). However, by a process of chirality transfer, the information contained at position 5 of compound **2** could be relayed to its 1-position. This 1-position was destined to become carbon 25 of the target structure. The medium for this chirality transmission was the BF_3-catalyzed reaction of tripivalate **2** with (*Z*)-crotyltriphenylsilane (**3**) (Figure 3).[26] There was obtained a 90% yield of a 4.5:1 ratio syn to anti isomers, **4s**:**4a** (the latter, not shown here). Fortunately, these could be separated by chromatography on silver nitrate impregnated silica gel on multigram scales. Only the major compound was carried forward. Within the limits of our detection, the process was specific for axial attack;[27] the lack of specificity was manifested only at the topographic levels (C_{26}syn:C_{26}anti).[21] While higher levels of syn to anti selectivity were realizable with other silanes, the combination of overall chemical yield and handling convenience associated with the crystalline **3** dictated its employment. Fortunately, it was possible to distinguish the terminal vinyl group relative to the endocyclic double bonds vis-a-vis susceptibility to catalytic hydrogenation. Compound **5** was thus obtained in 90% yield.

The timing was now propitious for the simultaneous introduction of the α-methyl branch at C_{24} and the installation of the 22–23 double bond. This was accomplished by the reaction of **5** with lithium dimethyl cuprate. Surprisingly, the S_N2'-type displacements of allylic acyloxy groups by alkyl cuprates, a well-studied reaction,[28] has not been employed for this specific kind of branch-point installation in the carbohydrate field. In practice, the reaction worked very nicely, in the expected stereochemical sense, to afford a 78% yield of **6**. Thus, in three simple maneuvers the stereochemical and regiochemical substitution pattern required in the ultimate target structure become available to us. The primary pivalate suffered saponification with lithium hydroxide to afford the difficultly handleable (volatile!) alcohol **7** in 82% yield. Its derived triflate **8** underwent displacement through the agency of sodium cyanide in DMF. The resultant nitrile (**9**), thus obtained in 82% yield, could be reduced with DIBAH in ether, to afford aldehyde **10** in 90% yield.

The possibility of a Lewis acid catalyzed diene–aldehyde cyclocondensation reaction[29] of aldehyde **10** with diene **11** now presented itself. The utility of such a reaction in our scheme was contingent on the realizability of chirality transmission[30] from aldehyde **10** to the dihydropyrone moiety which would emerge. Put differently, it is this reaction which would establish the stereochemical connectivity between C_{19} and carbons 26, 25, 24, as well as 21. As will be seen, the relationship between carbons 19 and 17 can be readily established by fashioning of an equatorial alcohol at C_{17}. Thus, if the absolute stereochemistry at C_{19} is

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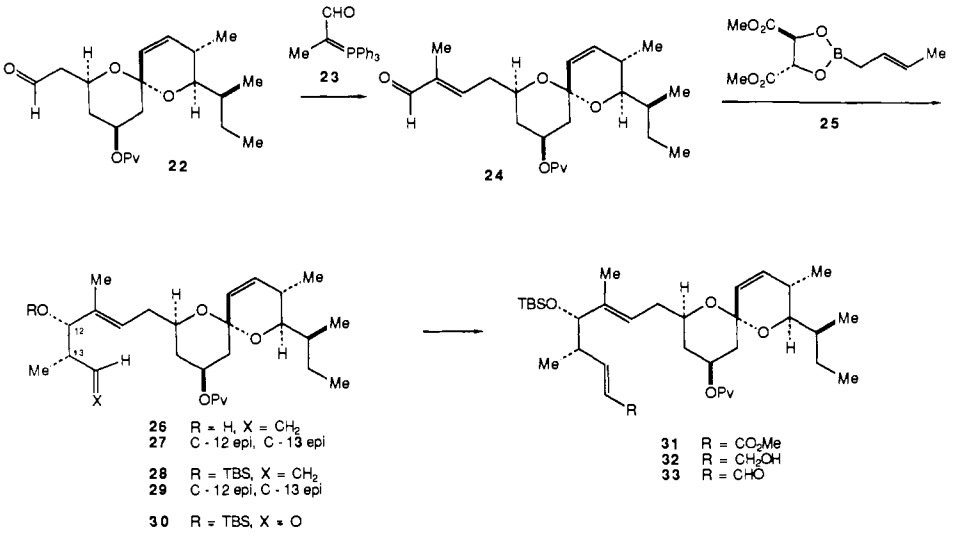

Figure 4.

established properly, the stereochemistry at 17 will also be appropriate. The link in this scheme arises from C_{21}, itself destined to be oxidized. A threo relationship between carbons 21 and 19 at the stage of dihydropyrone **12** would establish the required connectivity. It is further seen by inspection that a chelation-controlled topography in the cyclocondensation reaction, with a metal ion simultaneously ligated between the C_{19} aldehyde and the dihydropyran oxygen (linked to C_{21} and C_{25}), might provide a useful, if temporary, matrix.[31]

A variety of possible catalysts were screened with this possibility in mind, and numerous reaction conditions were surveyed. An eventual optimization between chemical yield, ratio, and reproducibility settled upon the use of anhydrous magnesium bromide in methylene chloride at −78 °C. A 4:1 ratio of two dihydropyrones was obtained in 77% yield. This mixture did not lend itself to separation. Rather, the two epimeric compounds were submitted to reduction with sodium borohydride–cerium(III) chloride[32] to give the equatorial alcohol, now known to be compound **13**, in homogeneous form. Although the stereochemistry at C_{19} could not be proven at this stage, it was surmised by analogy with a previously documented case.[22a] In light of subsequent events, this surmise was correct.

After protection of the alcohol as its OTBS ether, the pyran ring was readied for disconnection. Hydroxybromination (aqueous NBS) of **14**, followed by reductive debromination (Ph_3SnH) produced **15** in 71% yield. Reductive ($LiBH_4$) disassembly of the hemiacetal gave a 93% yield of diol **16** and then (^{t}BuCOCl, DMAP) the dipivalate **17**. The required alcohol was liberated through the action of HF in acetonitrile. The substrate (**18**) for oxidative cyclization was in hand.

The possibility of synthesizing spiroketals via oxidative cyclization had been previously explored by Kay,[22b,c] though on very simple models. A previous report from our laboratory demonstrated the first instance where such a reaction could be applied in the presence of a double bond[22a] (which might a priori have favored iodoetherification rather than dehydrogenation as a cyclization route). In the event, reaction of compound **18** with mercuric oxide–iodine in carbon tetrachloride in the presence of light afforded the desired **19**. The stereochemistry at the spiroketal carbon was assigned as shown. In this (*S*) configuration the demands of the anomeric effect[33] and the equatorial disposition of the bulky substituents on each of the tetrahydropyran rings are harmonized. The higher yields were realized in small scale. In the scale indicated (Experimental Section), the yield was 53%. No other spiroketal epimers were identified.

For purposes of structural correlation, both pivaloyl groups were cleaved reductively (DIBAH). *The NMR and infrared spectra, as well as the optical rotation of the resultant diol* ***20****, were identical with those of the same compound obtained by degradation of avermectin* B_{1a}*, by using a recently described protocol.*[34] In this fashion, the stereochemical assignments were corroborated.

A simplification in the synthesis was achieved when it was discovered that the primary pivalate of **19** could be selectively cleaved with potassium triethylborohydride to afford **21** in 78% yield. Swern oxidation[35] of **21** afforded **22** in 91% yield.

The plan for the installation of the three *E* double bonds called for reliance on condensation reactions which would produce α,β-unsaturated carbonyl systems. In this fashion one could take advantage of the generally high proclivity for such reactions to produce trans olefinic linkages. The first application of this notion in our synthesis was realized in the condensation of **22** with phosphorane **23** (Figure 4).[36] A 94% yield of *E*-enal was attained.

Until this juncture all of the stereogenic centers were fashioned by taking advantage of resident stereochemical biases contained within the substrate (i.e., substrate control). The prospects of further intramolecular communication to bias the outcome at stereogenic centers 12 and 13 seemed none too promising. A variety of possibilities were explored to achieve this stereochemistry via the use of fragments of proper configuration. Options wherein the insert piece contained one or both of these centers were screened. Unfortunately, none of these could be brought to fruition.

There remained available the possibility of controlling the stereochemistry in this sector through recourse to a relevant reagent which would be equipped with a chiral auxiliary which would impart a high facial bias to its reaction with **24**.[37] An attractive possibility in this regard would be a crotyl boronate, exploiting the major advances of Roush[38] and Brown.[39] Given the proper geometric isomer of the boronate and the properly selected enantiomer of the auxiliary, a simultaneous solution to attainment of the configurations at C_{13} and C_{12} might be fashioned.

On the basis of precedents, we examined the reaction of *E*-enal **24** with the (*E*)-crotyl boronate **25R** bearing an (*R*)-tartrate auxiliary.[38] The crude 4:1 mixture of homoallylic alcohols **26** and **27** (99% combined) was converted to the OTBS derivatives **28**

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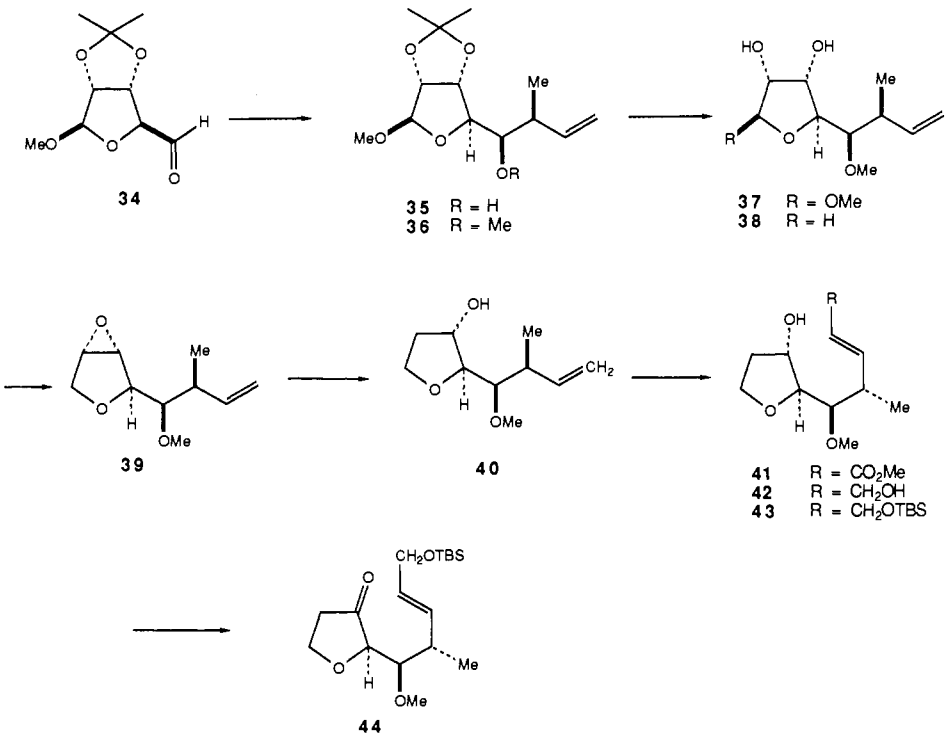

Figure 5.

and **29**. Separation was difficult at this stage and the mixture was carried further. Hydroxylation with osmium tetroxide was quite selective for the terminal vinyl group. The resultant diol was cleaved with lead tetraacetate. Chromatographic purification of the major aldehyde **30** was now achieved in 66% overall yield. The same compound (NMR and infrared spectral comparisons) was obtained by degradation of avermectin B_{1a} by using a protocol very similar to that developed by Hanessian. The assignment of the 12*S*–13*S* configuration to this substance was thus established.

That compounds **27** and **29** are also threo compounds (i.e., 12*R* 13*R*) was strongly suggested from the fact that the former was the major product (**27**:**26** = 3:1) when the enantiomeric (*E*)-crotyl boronate **25S** was employed. That the ratio of homoallylic alcohols is different starting with the two enantiomeric boronates suggests some small and unexplained bias arising from the resident dissymmetry of **24**.

The final operations on the glucose-derived subunit involved the elongation of **30** to **33**. One attempt to achieve this involved the use of triphenylformylmethylphosphorane. The reaction was quite slow and only a 40% yield of desired product was realized. In this case the longer route proved to be the more efficient. Reaction of **30** with carbomethoxymethyltriphenylphosphorane afforded **31** in 95% yield. Reduction with DIBAH provided alcohol **32**, which after oxidation (95% yield) gave the desired **33**. This compound, which was derived from D-glucose (and (*R*)-tartaric acid as an auxiliary), was to be coupled to a fragment which would be derived from D-ribose (vide infra).

The Synthesis of Tetrahydrofuranone 44. It was the oxahydrindene segment of avermectin which had proven to be most resistant to synthesis. Judging by the literature reports,[13] previous strategies had contemplated the construction of some version of the oxahydrindene and then its coupling to a relevant unit. This unit already might be attached to the spiroketal moiety or might contain the elements for subsequent attachment.

From the outset we were skeptical about the success of such strategies. The oxahydrindene unit is the most chemically vulnerable region of the molecule. To build a fragment which would be suitable for coupling would require installation of a "coupling-handle" in addition to the target-dictated functionality required of the subunit.

The approach which we found more appealing (though not without its own elements of risk) involved the fashioning of the oxahydrindene moiety in a setting where the rest of the molecule was already prebuilt. To explore this possibility we settled upon tetrahydrofuranone **44** as a goal system. Given this formulation, the use of D-ribose as a chiral educt virtually suggested itself.

The synthesis of **44** started with aldehyde **34** (Figure 5).[40] Addition of (*E*)-trimethylcrotylsilane to **34** under catalysis by $BF_3{\cdot}OEt_2$ afforded a high yield of a mixture of homoallylic alcohols. It was assumed that the major product was the desired **35**. After partial purification at this stage, the material was treated with sodium hydride–methyl iodide. Full purification was now achieved, providing a 68% yield of **36**. At this stage we had no proof of the stereochemistry at C_4 and C_5. The assignment followed from precedents both from our laboratory and from the work of Keck.[41] The acetonide was cleaved through the action of methanolic HCl to afford **37**. Sequential acetonide removal and reduction of the glycoside by the method of Gray gave **38**.[42] Reaction of **38** with α-acetoxypivaloyl bromide[43] followed by oxirane formation with Amberlite basic resin afforded epoxide **39** in 72% overall yield from **36**.

Regiospecific opening of the epoxide was accomplished with lithium triethylborohydride to give (96%) alcohol **40**. Ozonolytic clevage of the double bond followed by reductive workup (Zn; AcOH) and condensation of the resultant aldehyde with carboxymethyltriphenylphosphorane gave an 84% yield of *E*-enoate **41**. Reduction of this compound with DIBAH gave **42**, which lent itself to specific protection of the primary alcohol through the action of $^tBuMe_2SiCl$–imidazole. Oxidation of **43** thus obtained afforded the desired **44**.

Coupling of Aldehyde 33 with Ketone 44. The opportunity to bring together the glucose-derived aldehyde **33** with the ribose-derived ketone **44** was now at hand. The coupling device was to be one of the truly classical reactions in organic chemistry, i.e., the aldol condensation. Nonetheless, it was not without some trepidation that ketone **44** was treated with the lithium salt of

(40) Jones, G. H.; Moffat, J. G. *Methods in Carbohydrate Chemistry*; Academic Press: New York, 1972; Vol. VI, p 315.
(41) (a) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. P.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809. (b) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927.
(42) Rolf, D.; Gray, G. R. *J. Am. Chem. Soc.* **1982**, *104*, 3539.
(43) Robins, M. J.; Hansske, F.; Low, N. H.; Park, J. I. *Tetrahedron Lett.* **1984**, *24*, 367.

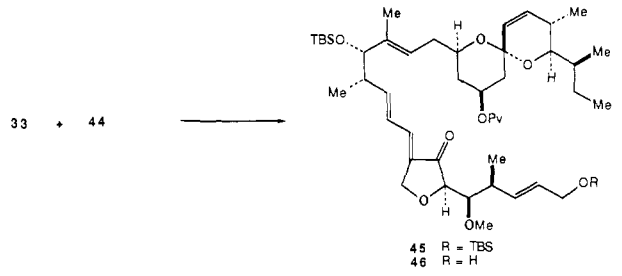

Figure 6.

hexamethyldisilazide in THF at −78 °C. The possibility for β-elimination of the C_5 methoxy group via enolization toward oxygen could well have undermined the central foundation on which the synthesis was built.

In the event, reaction of the enolate produced from the aforedescribed treatment of **44** with aldehyde **33** afforded an apparent adduct (TLC analysis) (Figure 6). Treatment of this material with methanesulfonyl chloride in triethylamine afforded **45** in 67% yield. Previous experiences had led us to believe that the *E* geometry would pertain were an allylidenecycloalkanone to be generated in this way. While this surmise could not be proven in the case at hand, the apparent formation of a single product under this treatment was encouraging. The TBS group on the primary alcohol was selectively cleaved by brief exposure of **45** to the action of HF in aqueous acetonitrile.

The resultant alcohol, **46**, (90% yield) was oxidized with pyridinium chlorochromate to afford enal **47** (88%) (Figure 7). In a previous disclosure[23] we have identified a tactic for this type of closure. The strategy draws upon an intramolecular Nozaki reaction.[44] In practice, compound **47** was treated with the species produced from the reaction of trimethylaluminum with lithium thiophenoxide. After exposure of the resultant product to *m*-chloroperoxybenzoic acid, a 76% yield of enal **48** was realized.

We could now focus on the synthesis of the Δ^2 isomer of avermectin A_{1a} aglycon. Oxidation of the aldehyde with sodium chlorite produced unsaturated acid **49** and then methyl ester **50**. The latter, upon saponification, gave the 13-silylated conjugated aglycon seco acid **51**.

In semisynthetic studies Hanessian had achieved the macrolactonization of a seco acid related to **51** in modest yield with DCC–DMAP.[15] In the case at hand, we employed a Mukaiyama-type of protocol.[45] Reaction of **51** with *N*-methylpyridinium chloride and triethylamine afforded a 67% yield of the 13-silylated conjugated aglycone **52**. Desilylation at the 13-position was accomplished through reaction of $^nBu_4NF$ to give the conjugated aglycon **53** (87%).

The remaining objective was to achieve the deconjugation of the double bond to the Δ^3 position with installation of the required 2*R* (i.e., $H_2\beta$) stereochemistry. Indeed, the feasibility of deconjugation had been demonstrated by Hanessian in the context of avermectin B_{1a} by kinetic quenching of the γ-extended lithium enolate.[15] However, serious questions have been raised about the stereochemistry of the protonation step. Fraser-Reid[46] has reported that under all conditions which were investigated this protonation gave the epimeric **25** stereochemistry (i.e., $H_2 = \alpha$). We investigated this question in connection with the free aglycon **53**. Treatment of **53** with 1 equiv of lithium diisopropylamide at −78 °C in tetrahydrofuran followed by quenching with aqueous HCl afforded two isomeric products. The minor one, 21%, was the starting material. The major product was similar to, but different from, the desired aglycon **55** and is formulated as the 2-epi compound **54**. The most notable difference detected in these high-field NMR spectra was found in the appearance of the methylene resonances of the diastereotopic protons at C_{8a}. The chemical shifts of the resonances of these protons in **55** are more closely spaced (δ = 4.70 and 4.64) than in the 2-epi compound **54** (δ = 4.60 and 4.18).

During this work, Professor Hanessian[16] described a new procedure involving the use of imidazole as the base for purposes of epimerization of 2-epiavermectin B_{1a} with the natural product itself. It seemed that with this base, substantial equilibration of the C_2 stereoisomers could be achieved before both compounds were isomerized to the more stable conjugated Δ^2 isomer bearing the 4β-methyl group.

We then investigated the use of imidazole catalysis for equilibration of the aglycons. In the event, treatment of **54** with imidazole furnished an 87% yield of a three-component mixture. A 21% yield of conjugated **53** was produced. Also obtained was a 33% recovery of the 2-epi Δ^3 compound **54**. *Most important was the 32% yield of the long sought after avermectin A_{1a} aglycon* ***55****. The infrared and NMR spectra, as well as chromatographic mobility of* ***55****, were identical with a sample prepared by cleavage of the* L-*oleandrosyl*-L-*oleandrose residue from avermectin* A_{1a}.[47] A fully synthetic route to the aglycon **55** was thus achieved.

Having reached the aglycon **55**, we focused on achieving the total synthesis of avermectin A_{1a} itself. To accomplish this goal, it would be necessary to synthesize a suitable version of the disaccharide L-oleandrosyl-L-oleandrose and to append it to the aglycon. In semisynthetic work in the avermectin B_1 series, Nicolaou had achieved the conversion of L-rhamnose to disaccharides **56a** and **b** (Figure 8).[17] Furthermore, these disaccharides were joined to the B_{1a} aglycon to achieve, eventually, a partial synthesis of avermectin B_{1a} itself. In his degradative studies on avermectin B_{1a}, Hanessian devised a sequence to retrieve disaccharide **56c** from the natural product.[48] Our early efforts in this phase of the synthesis involved obtaining **56c**, as described by Hanessian, from avermectin B_{1a}. We subsequently found that we could carry out the Nicolaou coupling to join **56c** to aglycon **55**.

However, our real interests were in the domain of total synthesis. As such, we set several goals for ourselves. We hoped to achieve a synthetic route to the L-oleandrose (**57**) series from non-carbohydrate sources. We further hoped to join two monosaccharides related to **57** to produce, eventually, a disccharide which could be joined to aglycon **55**, now available by total synthesis. After appropriate functional group modification, a fully synthetic route to **1** could be achieved.

L-Oleandral **61** was identified as a potentially valuable intermediate. It is noted that in a general sense there is a strong relationship in the requirements for converting glycal **61** to **66** and for converting **66** to **1**. In each instance axial addition of a complex alcohol at the 1-position of a glycal must be achieved with eventual conversion to a 2-deoxy axial glycosidic product.

As it turns out, we had already developed a technology to synthesize rare monosaccharides including the L-dihydropyrone **58** (Figure 9).[24] Reduction of the ketone with sodium borohydride–$CeCl_3$[32] afforded **59** in 92% yield. Methylation of this compound with silver oxide–methyl iodide gave the desired C_3-methoxy compound **60**. Hydrolysis of the acetate gave a nearly quantitative yield of L-oleandral **61**.

It was now necessary to protect the glycal double bond of the nucleophilic component entering into the disaccharide synthesis. Treatment of **61** with *N*-bromosuccinimide in methanol followed by reaction with tri-*n*-butyltin hydride afforded a 95% yield of a 2:1 α–β mixture of methyl glycosides **62**.[49] Each of these anomers behaved equally well in the coupling reaction with **60**.

Treatment of **60** with *N*-iodosuccinimide in acetonitrile,[50] followed by reaction of the complex thus generated with axial methyl glycoside **62**, afforded a 63% yield of the iododissaccharide

(44) (a) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361. (b) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274.

(45) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1986**, *49*.

(46) Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 933.

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(49) At this point the two anomers were separated chromatographically, and each was carried through the sequence of reactions.

(50) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696.

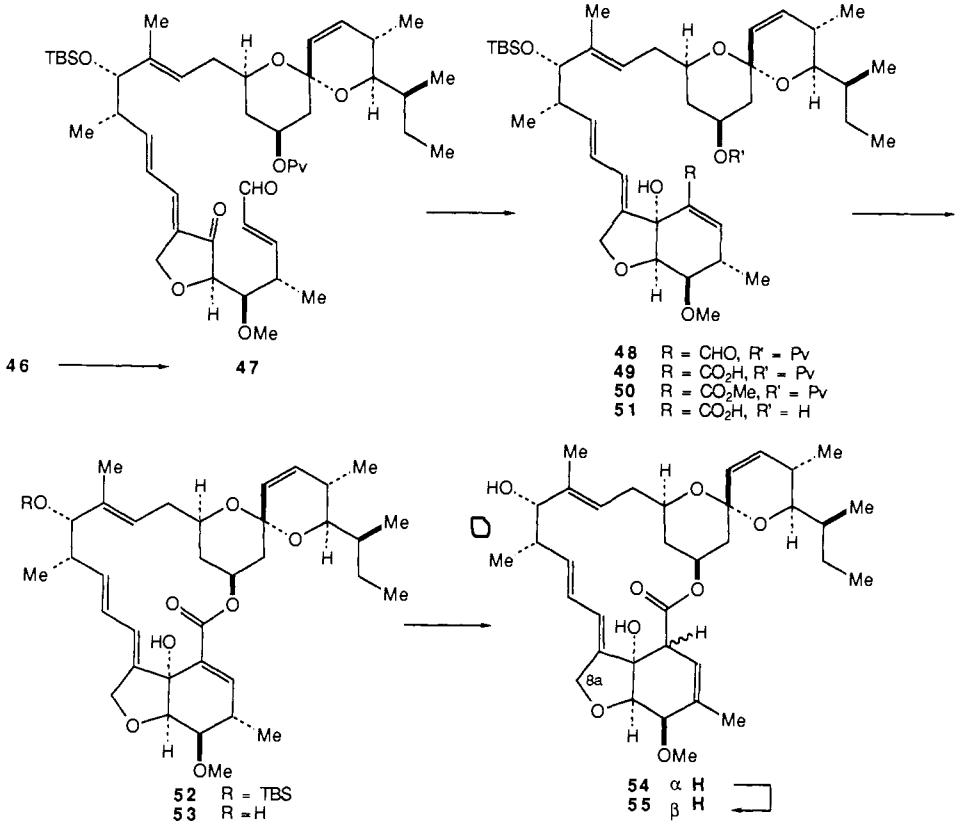

Figure 7.

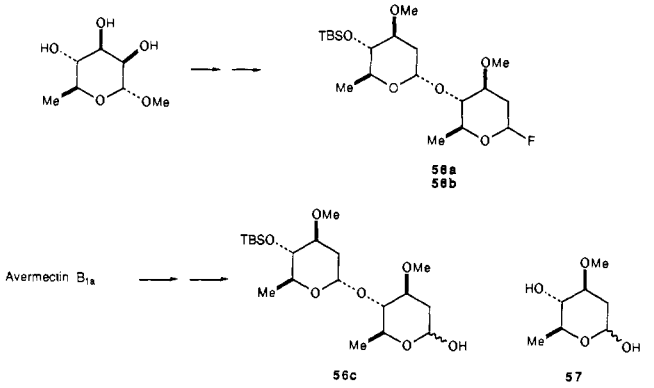

Figure 8.

63. For a given methyl glycoside version of **62**, a single version of **63** is produced. The disaccharide product seems to arise cleanly from a trans-diaxial addition.[51] With a view to preparing for the new glycal linkage required for eventual coupling to avermectin aglycon, the iododisaccharide was treated with (trimethylsilyl)-thiophenol in the presence of zinc iodide.[52] The resultant **64** (82%) was converted to its sulfoxide (MCPBA), which upon pyrolysis in benzene provided iodoglycal **65** in 72% yield. The target disaccharide, **66**, was then obtained (81%) by reaction of **65** with $^nBu_3SnH$–AIBN in toluene.

The stage was now set for the all-critical coupling reaction between fully synthetic **55** and fully synthetic **66** (Figure 10). This coupling was also carried out under the agency of *N*-iodosuccinimide.[50,51] A 64% yield of the $C_{4''}$ acetate of $C_{2'}$ β-iodoavermectin A_{1a} derivative **67** was obtained. The iodine function was reductively cleaved with $^nBu_3SnH$, affording a 78% yield of compound **68**, the $C_{4''}$ acetate of **1**. The last challenge involved deacylation of this acetate without perturbing the lactonic acyl function. This was smoothly accomplished (97%) with Super-Hydride. There was thus obtained by total synthesis avermectin A_{1a}.

(51) Thiem, J.; Prahst, A.; Lundt, I. *Liebigs. Ann. Chem.* **1986**, *6*, 1044.
(52) Hanessian, S. W.; Guindon, Y. *Carbohydr. Res.* **1980**, *86*, C3.

Summary

Given the ready availability of the avermectins from natural sources and the multistep nature of any total synthesis program, it was never our perception that synthesis would be of any relevance to the target aglycon system itself. The value of the effort would rest on the chemical issues raised in the key steps (see Figure 2, eq 1–6). Fortunately, all of these issues lent themselves to favorable disposition. Given the retrievability of the aglycon and the disaccharide components from the natural products by various protocols, it is also unlikely that total synthesis is likely to be of consequence with respect to the natural subunits.

However, as a consequence of these and our earlier studies,[2,3] *virtually complete latitude in the synthesis of novel saccharides is now a reality.* From the results described above, practical methodology for appending such saccharides, via their glycals, to the aglycons is now available. These synthetic studies have, therefore, enormously increased the range of hitherto inaccessible congeners of avermectin in a region of the molecule which is particularly sensitive to structural variation. Hence, these studies pursued at the outset from strictly chemical considerations may not be without practical consequence.

Experimental Section

[2*R*-[2α,3β,6β(*R)]]-[3-(2,2-Dimethyl-1-oxopropoxy)-3,4-dihydro-6-(1-methyl-2-propenyl)-2*H*-pyran-2-yl]methyl 2,2-Dimethylpropanoate (4).** To a solution of 3.0 mL (24.32 mmol) of $BF_3{\cdot}OEt_2$ in 30 mL of propionitrile at −30 °C was added a solution of **2** (9.6 g, 24.32 mmol) and **3** (7.64 gm, 24.32 mmol) in 100 mL of propionitrile dropwise. The reaction was stirred until no starting material remained and was then quenched with saturated $NaHCO_3$. The reaction mixture was then extracted three times with CH_2Cl_2, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 15% ethyl acetate in hexanes) provided 7.7 g (90%) of a 4.5:1 mixture of isomers. This mixture was then chromatographed on silver nitrate impregnated SiO_2 (elution with 20% ethyl acetate in hexanes) to provide 6.16 g (73%) of dihydropyran **4**: $[\alpha]^{25}_D$ +106.6° (*c* 2.00, $CHCl_3$); IR ($CHCl_3$) 3000, 1740, 1480, 1430, 1150, 1130 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.98 (br d, 1 H, *J* = 10.40

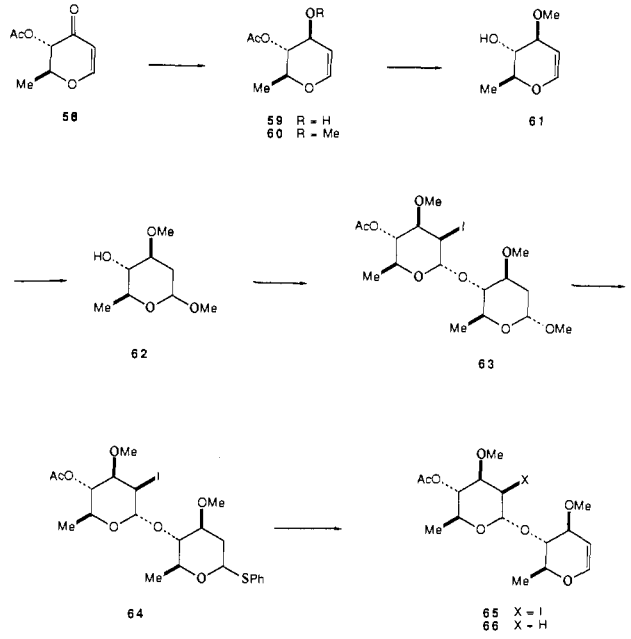

Figure 9.

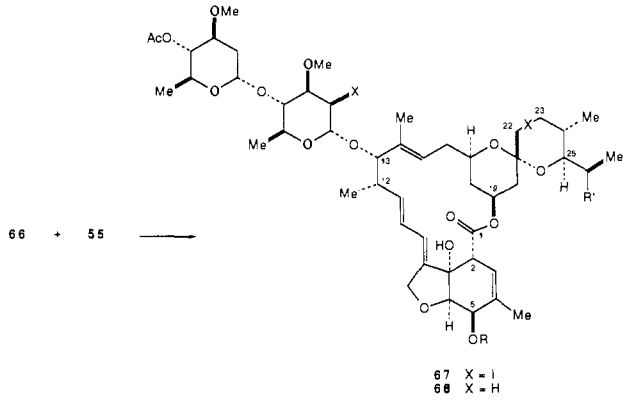

Figure 10.

Hz), 5.78 (d, 1 H, J = 10.40 Hz), 5.70 (m, 1 H), 5.15 (d, 1 H, J = 15.08 Hz), 5.07 (d, 1 H, J = 10.22 Hz), 5.02 (m, 1 H), 4.18 (d, 1 H, J = 3.6 Hz), 4.16 (s, 1 H), 4.00 (m, 2 H), 2.50 (m, 1 H), 1.23 (s, 9 H), 1.22 (s, 9 H), 1.12 (d, 3 H, J = 6.86 Hz); MS (20 eV) 352 (M^+), 297 (M^+ - $CH_3CHCHCH_2$). Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.14; H, 9.17. Found: C, 68.07; H, 9.14.

[2*R*-[2α,3β,6β(*S)]]-[3-(2,2-Dimethyl-1-oxopropoxy)-3,4-dihydro-6-(1-methylpropyl)-2*H*-pyran-2-yl]methyl 2,2-Dimethylpropanoate (5)**, A solution of 5.14 g (14.6 mmol) of **4** in 131 mL of MeOH with 14.6 mL of pyridine and 4 g of Pd/C was stirred over a H_2 balloon for 45 min. The H_2 was then removed from the system and the reaction was then filtered through Celite and concentrated. Flash chromatography (10% ethyl acetate in hexanes) provided 4.65 g (90%) of **5**: $[\alpha]^{25}_D$ +71.90° (c 2.00, $CHCl_3$); IR ($CHCl_3$) 2970, 1730, 1480, 1285, 1150 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.96 (ddd, 1 H, J = 10.50, 1.02, 1.02 Hz), 5.85 (ddd, 1 H, J = 10.50, 3.80, 1.99 Hz), 4.95 (m, 1 H), 4.25 (dd, 1 H, J = 11.60, 8.13 Hz), 4.13 (dd, 1 H, J = 11.60, 3.37 Hz), 4.05 (dd, 1 H, J = 7.60, 3.80 Hz), 4.03 (m, 1 H), 1.75–1.4 (m, 3 H), 1.22 (s, 9 H), 1.21 (s, 9 H), 0.92 (t, 3 H, J = 7.35), 0.95 (d, 3 H, J = 6.63 Hz); MS (20 eV) 297 (M^+ - ^{t}Bu) 195 (M^+ - ^{t}Bu - $(CH_3)_3CO_2H$).

[2*S*-[2α,5α,6β(*R)]]-[5,6-Dihydro-5-methyl-6-(1-methylpropyl)-2*H*-pyran-2-yl]methyl 2,2-Dimethylpropanoate (6)**, To CuI (8.18 g, 42.92 mmol) in 275 mL of Et_2O at 0 °C under argon was added 61 mL (85.84 mmol) of MeLi. The cuprate was then added very slowly, over a period of 5 h, to **5** (3.8 g, 10.73 mmol), in 350 mL of Et_2O at −40 °C. The reaction was allowed to stir 15 more hours and was then quenched with saturated NH_4Cl and NH_4OH and extracted with ether three times. The organic layer was dried over $MgSO_4$ and concentrated. Flash chromatography (eluted with 10% ethyl acetate in hexanes) yielded 2.12 g (73%) of **6**: $[\alpha]^{25}_D$ −15.16° (c 2.00, $CHCl_3$); IR ($CHCl_3$) 2970, 1730, 1480, 1460, 1285, 1160 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.78 (ddd, 1 H, J = 10.20, 2.17, 2.17 Hz), 5.60 (ddd, 1 H, J = 10.20, 2.60, 2.60 Hz), 4.40 (m, 1 H), 4.25 (dd, 1 H, J = 11.57, 7.71 Hz), 3.97 (dd, 1 H, J = 11.57, 3.41 Hz), 3.24 (dd, 1 H, J = 8.33, 2.95 Hz), 2.30 (m, 1 H), 1.6 (m, 1 H), 1.40 (dq, 2 H, J = 13.45, 7.35 Hz), 1.22 (s, 9 H), 0.90 (t, 3 H, J = 7.35 Hz), 0.93 (d, 3 H, J = 7.17 Hz), 0.90 (d, 3 H, J = 6.74 Hz); MS (20 eV) 269 (M^+ - 1), 211 (M^+ - 1 - ^{t}Bu), 153 (M^+ - $CH_3O_2CC(CH_3)_3$).

[2*R*-[2α,5α,6β(*S)]]-5,6-Dihydro-5-methyl-6-(1-methylpropyl)-2*H*-pyran-2-acetaldehyde (10)**, To 2 g (7.4 mmol) of **6** in 15 mL each of THF, H_2O, and MeOH was added 3.63 g (74 mmol) of $LiOH·H_2O$. The reaction was stirred overnight at room temperature at which time it was saturated with solid NaCl and extracted with ether. Flash chromatography with 5% Et_2O in CH_2Cl_2 yielded 1.12 g (82%) of alcohol **7**. Analytical data: $[\alpha]^{25}_D$ +43.10° (c 2.00, $CHCl_3$); IR ($CHCl_3$) 3400, 2930, 1460, 1380, 1040 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.74 (ddd, 1 H, J = 10.22, 2.23, 2.23 Hz), 5.56 (ddd, 1 H, J = 10.22, 2.68, 2.44 Hz), 4.25 (m, 1 H), 3.65 (ddd, 1 H, J = 11.43, 9.05, 2.30 Hz), 3.5 (ddd, 1 H, J = 11.43, 9.8, 3.52 Hz), 3.2 (dd, 1 H, J = 8.11, 3.22 Hz), 2.31 (m, 1 H), 2.07 (dd, 1 H, J = 8.11, 3.22 Hz), 1.62 (m, 1 H), 1.4 (dq, 2 H, J = 15.28, 7.50 Hz), 0.93 (t, 3 H, J = 7.50 Hz), 0.92 (d, 3 H, J = 7.40 Hz), 0.91 (d, 3 H, J = 7.2 Hz); MS (20 eV) 184 (M^+), 153 (base peak M^+ - CH_2OH); HRMS calcd for $C_{11}H_{20}O_2$ 184.1464, found 184.1560.

To a solution of alcohol **7** (800 mg, 4.35 mmol) in 17.5 mL of CH_2Cl_2 at −25 °C were added 421 μL (5.22 mmol) of pyridine and then 804 μL (4.79 mmol) of triflic anhydride. The reaction was stirred for 20 min and then warmed to 0 °C for 10 min when it was diluted with ether, poured onto ice-cold 5% HCl, and washed with H_2O and then with saturated $NaHCO_3$ and brine. The reaction was then dried over Na_2SO_4 and concentrated. The unstable triflate **8** was then immediately dissolved in 12 mL of dry DMF, and 852 mg (17.4 mmol) of NaCN was added. The resulting mixture was stirred overnight and then diluted with ether, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 20% ether in hexanes) provided 688 mg (82%) of nitrile **9**: $[\alpha]^{25}_D$ +25.96° (c 2.00, $CHCl_3$); IR ($CHCl_3$) 2930, 2250, 1460, 1380, 1110, 1100, 1075 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.82 (ddd, 1 H, J = 10.15, 2.16, 2.06 Hz), 5.69 (ddd, 1 H, J = 10.15, 2.67, 2.30 Hz), 4.5 (m, 1 H), 3.19 (dd, 1 H, J = 8.19, 3.10 Hz), 2.60 (dd, 1 H, J = 17.10, 7.34 Hz), 2.50 (dd, 1 H, J = 17.10, 5.90 Hz), 2.3 (m, 1 H), 1.62 (m, 1 H), 1.41 (dq, 2 H, J = 13.56, 7.3 Hz), 0.95 (d, 3 H, J = 7.12 Hz), 0.92 (t, 3 H, J = 7.30 Hz), 0.89 (d, 3 H, J = 6.66 Hz); MS (20 eV) 194 (M^+ + 1), 153 (M^+ - CH_2CN). The nitrile **9** (688 mg, 3.56 mmol) was dissolved in 35 mL of Et_2O at −25 °C. Dibal (4.63 mL, 4.63 mmol) was added and the reaction was stirred for 1 h. The mixture was then quenched with acetone, Rochelle's salt, and SiO_2 and stirred for 1 h. The resulting mixture was then extracted three times with ether, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 20% ether in hexanes) provided 629 mg (90%) of aldehyde **10**: $[\alpha]^{25}_D$ +26.81° (c 2.00, $CHCl_3$); IR ($CHCl_3$) 2970, 1720, 1460, 1380 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 9.80 (dd, 1 H, J = 3.10, 1.83 Hz), 5.68 (m, 2 H), 4.75 (m, 1 H), 3.14 (dd, 1 H, J = 8.11, 3.23 Hz), 2.73 (ddd, 1 H, J = 16.14, 9.22, 3.10 Hz), 2.48 (dddd, 1 H, 16.14, 4.50, 1.83, 0.62 Hz), 2.3 (m, 1 H), 1.6 (m, 1 H), 1.3 (m, 2 H), 0.93 (d, 3 H, J = 6.99 Hz), 0.89 (t, 3 H, J = 7.08 Hz), 0.88 (d, 3 H, J = 6.75 Hz); MS (20 eV) 196 (M^+), 153 (M^+ - CH_2CHO); HRMS calcd for $C_{12}H_{20}O_2$ 196.1464, found 196.1456.

[2*R*-[2α(*R),5α,6β(*S**)]]-2-[[5,6-Dihydro-5-methyl-6-(1-methylpropyl)-2*H*-pyran-2-yl]methyl]-2,3-dihydro-4*H*-pyran-4-one (12)**, To a solution of aldehyde **10** (679 mgs, 3.46 mmol) in 50 mL of CH_2Cl_2 at −78 °C was added 4.85 mL (4.85 mmol, 1 M) of $MgBr_2·OEt_2$. The solution was stirred 15 min and then the diene **11** (1.35 mL, 6.72 mmol) was added dropwise. The reaction was stirred for 30 min more and was then quenched with saturated $NaHCO_3$. The mixture was then extracted three times with CH_2Cl_2, dried over $MgSO_4$, and concentrated. This was then dissolved in CCl_4 and a few drops of TFA were added. After 15 min the reaction mixture was concentrated and then flash chromatographed (elution with 20% ethyl acetate in hexanes). This provided 700 mg (77%) of pyrone **12** and its C_{19} epimer in a 4:1 ratio: IR ($CHCl_3$) 2960, 1680, 1400, 1275 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.36 (dd, 1 H, J = 5.95, 2.90 Hz), 5.65 (m, 2 H), 5.43 (dd, 1 H, J = 5.95, 1.05 Hz), 4.68 (m, 1 H), 4.45 (m, 0.8 H), 4.31 (m, 2 H), 3.15 (dd, 0.2 H, J = 8.13, 3.09 Hz), 3.08 (dd, 0.8 H, J = 8.26, 3.01 Hz), 2.56 (dd, 1 H, J = 13.14, 16.80 Hz), 2.42 (ddd, 1 H, J = 16.80, 4.32, 1.02 Hz), 2.28 (m, 1 H), 1.85 (m, 2 H), 1.6 (m, 1 H), 1.35 (m, 2 H), 0.92 (t, 3 H, J = 7.00 Hz), 0.91 (d, 3 H, J = 6.87 Hz), 0.89 (d, 3 H, J = 6.62 Hz); MS (20 eV) 264 (M^+), 178 (M^+ - $CH_3CH_2CH(CH_3)CHO$); HRMS calcd for $C_{16}H_{24}O_3$ 264.1726, found 264.1714.

[2*R*-[2α(2*S*,4*S*),5α,6β(*S)]]-3,4-Dihydro-2-[[5,6-dihydro-5-methyl-6-(1-methylpropyl)-2*H*-pyran-2-yl]methyl]-2*H*-pyran-4-ol *tert*-Butyldimethylsilyl Ether (14)**, To a solution of pyrone **12** (450 mgs, 1.7 mmol) in 9 mL of CH_2Cl_2 and 9 mL of EtOH was added 761 mg (2.04 mmol) of $CeCl_3·7H_2O$. The mixture was stirred 15 min at room temperature

and then cooled to −78 °C. $NaBH_4$ (65 mg, 1.7 mmol) in 1.7 mL of EtOH was then added to the reaction over 1 h. The reaction was then quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. The readily separable mixture of glycals was then flash chromatographed (elution with 7.5% ethyl acetate in methylene chloride) to provide 284 mg (63%) of glycal **13**: $[\alpha]^{25}_D$ +5.14° (*c* 2.00, $CHCl_3$); IR ($CHCl_3$) 3350, 2960, 1645, 1240, 1180 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 6.37 (dd, 1 H, *J* = 6.20, 1.17 Hz), 5.62 (s, 2 H), 4.76 (dt, 1 H, *J* = 6.20, 2.00 Hz), 4.41, (br m, 3 H), 4.20 (m, 1 H), 3.10 (dd, 1 H, *J* = 8.09, 3.22 Hz), 2.27 (m, 1 H), 2.14 (m, 1 H), 1.90–1.20 (m, 6 H), 0.89 (t, 3 H, *J* = 7.45 Hz), 0.92 (d, 3 H, *J* = 7.07 Hz), 0.90 (d, 3 H, *J* = 6.83 Hz); MS (20 eV) 266 (M^+).

The glycal **13** (284 mg, 1.07 mmol) was immediately dissolved in 10 mL of CH_2Cl_2 at −78 °C. Lutidine (1.24 mL, 10.7 mmol) and TBSOTf (368 μL, 1.60 mmol) were then added and the reaction was stirred 30 min. It was then quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 5% ethyl acetate in hexanes) provided 353 mg (87%) of **14**: $[\alpha]^{25}_D$ −29.11° (*c* 2.00, $CHCl_3$); IR ($CHCl_3$) 2960, 1645, 1250, 1085 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 6.32 (dd, 1 H, *J* = 6.23, 1.16 Hz), 5.62 (s, 2 H), 4.66 (dt, 1 H, *J* = 6.23, 1.89 Hz), 4.47 (m, 1 H), 4.38 (m, 1 H), 4.20 (m, 1 H), 3.11 (dd, 1 H, *J* = 3.23, 8.06 Hz), 2.27 (m, 1 H), 2.00 (m, 1 H), 1.73 (m, 3 H), 1.52–1.2 (m, 3 H), 0.91 (t, 3 H, *J* = 6.83 Hz), 0.90 (s, 9 H), 0.90 (d, 3 H, *J* = 6.76 Hz), 0.10 (s, 3 H), 0.06 (s, 3 H); MS (20 eV) 380 (M^+), 323 ($M^+ - (CH_3)_3CH$), 248 (M^+ − TBSOH). Anal. Found; C, 69.54; H, 10.58.

Lactol 15, To a solution of **14** (113 mg, 0.321 mmol) in 4 mL of THF with 0.5 mL of saturated $NaHCO_3$ was added 113.9 mg (0.64 mmol) of NBS. After 10 min, the reaction was complete and more saturated $NaHCO_3$ was added, and the mixture was extracted with ethyl acetate. Flash chromatography (elution with 8% ethyl acetate in hexanes) provided 109 mg (76%) of a mixture of bromohydrins, which were immediately dissolved in 4 mL of toluene with 109 mg (0.315 mmol) of Ph_3SnH and catalytic AIBN. The mixture was refluxed for 30 min whereupon it was concentrated and flash chromatographed (elution with 15% ethyl acetate in hexanes) to yield 83 mg (93%) of hemiacetal **15**: $[\alpha]^{25}_D$ +35.55° (*c* 2.00, $CHCl_3$); IR ($CHCl_3$) 3410, 2980, 1470, 1390, 1265, 1130, 1095 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.6 (s, 1 H), 5.4 (br s, $^7/_8$ H), 4.75 (m, $^1/_8$ H), 4.40 (m, 1 H), 4.20 (m, 2 H), 3.15 (m, 1 H), 2.90 (br s, 1 H), 2.27 (m, 1 H), 2.00 (m, 1 H), 1.9–1.2 (m, 8 H), 0.93 (t, 3 H, *J* = 7.34 Hz), 0.91 (d, 3 H, *J* = 6.03 Hz), 0.89 (s, 9 H), 0.89 (d, 3 H, *J* = 6.76 Hz), 0.10 (s, 3 H), 0.06 (s, 3 H); MS (20 eV) 380 ($M^+ - H_2O$), 323 ($M^+ - H_2O - (CH_3)_3C$); HRMS (CI) calcd for $C_{22}H_{43}O_4Si$ (M^+ +H) 399.2932, found 399.2906.

Diol 16, To 130 mg (0.351 mmol) of hemiacetal **15** in 4 mL of THF was added $LiBH_4$ (31 mg, 1.40 mmol). The reaction was refluxed for 1 h and then quenched with acetone, followed by saturated $NaHCO_3$. The solution was then extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 25% to 40% ethyl acetate in hexanes) gave 122 mg (93%) of diol **16**: $[\alpha]^{25}_D$ +21.79° (*c* 2.35, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1460, 1380, 1255, 1070 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.62 (m, 2 H), 4.42 (br d, 1 H), 4.13 (m, 1 H), 3.75 (m, 2 H), 3.40 (br s, 1 H), 3.12 (dd, 1 H, *J* = 7.00, 4.15 Hz), 2.25 (m, 1 H), 1.85 (m, 2 H), 1.8–15 (m, 6 H), 1.5–1.2 (m, 2 H), 0.945 (d, 3 H, *J* = 7.12 Hz), 0.91 (t, 3 H, *J* = 7.09 Hz), 0.91 (d, 3 H, *J* = 7.09 Hz), 0.90 (s, 9 H), 0.13 (s, 6 H); MS (20 eV), *m/z* 400 (M^+), 343 ($M^+ - (CH_3)_3C$), 250 ($M^+ - H_2O$ − TBSOH); HRMS calcd for $C_{22}H_{44}O_4Si$ (+H) 401,3088, found 401.3085.

[1*R*-[1α(1*R,4*R**),5α,6β(*S**)]]-1-[5,6-Dihydro-5-methyl-6-(1-methylpropyl)-2*H*-pyran-2-yl]-4-hydroxy-6-(2,2-dimethyl-1-oxopropoxy)hex-2-yl 2,2-Dimethylpropanoate.** To a solution of diol **16** (122 mg, 0.305 mmol) in 4 mL of CH_2Cl_2 were added PvCl (100 μL, 0.763 mmol), triethylamine (130 μL, 0.915 mmol), and DMAP (20 mg, 0.153 mmol). After 24 h the reaction was complete. Concentration followed by flash chromatography (elution with 10% ethyl acetate in hexanes) provided 285 mg (89%) of **17**: $[\alpha]^{25}_D$ +12.48° (*c* 1.65, $CHCl_3$); IR ($CHCl_3$) 2970, 1730, 1480, 1460, 1285, 1165 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.6 (s, 2 H), 5.01 (m, 1 H), 4.13 (m, 3 H), 3.82 (m, 1 H), 3.06 (dd, 1 H, *J* = 7.91, 3.14 Hz), 2.23 (m, 1 H), 1.9–1.25 (m, 9 H), 1.19 (s, 18 H), 0.89 (s, 9 H), 0.88 (m, 9 H), 0.07 (s, 3 H), 0.03 (s, 3 H); MS (20 eV), 409 ($M^+ - PvOH - (CH_3)_3C$), 334 ($M^+ - PvOH$ − TBSOH); HRMS calcd for $C_{32}H_{60}O_6Si$ (+H) 569.4239, found 569.4240.

To a solution of 179 mg (0.33 mmol) of **17** in 3 mL of CH_3CN was added 20 drops of 5% HF in CH_3CN. After 2 h no starting material remained. The reaction was quenched with saturated $NaHCO_3$, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 10% ethyl acetate in hexanes) yielded 122 mg (87%) of alcohol **18**: $[\alpha]^{25}_D$ +31.57° (*c* 3.00, $CHCl_3$); IR ($CHCl_3$) 3500, 2960, 2930, 1730, 1285, 1170 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.62 (m, 2 H), 5.28 (m, 1 H), 4.20 (m, 3 H), 3.64 (br d, 1 H, *J* = 3.41 Hz), 3.52 (m, 1 H), 3.08 (dd, 1 H, *J* = 8.25, 2.72 Hz), 2.14 (m, 1 H), 1.9–1.3 (m, 8 H), 1.22 (s, 9 H), 1.18 (s, 9 H), 0.91 (d, 3 H, *J* = 7.05 Hz), 0.90 (t, 3 H, *J* = 7.33 Hz), 0.85 (d, 3 H, *J* = 6.66 Hz); MS (20 eV) 352 (M^+ − PvOH), 334 (M^+ − PvOH − H_2O), 250 (M^+ − 2PvOH), 232 (M^+ − 2PvOH − H_2O); HRMS calcd for $C_{26}H_{46}O_6$ (+H) 455.3374, found 455.3366.

[2*S*-[2α,6β[8*S(*R**),9*R**]]]-9-Methyl-8-(1-methylpropyl)-2-[(2,2-dimethyl-1-oxopropoxy)ethyl]-4-(2,2-dimethyl-1-oxopropoxy)-1,7-dioxaspiro[5.5]undec-10-ene (19)**, A solution of HgO (180 mg, 0.845 mmol) and I_2 (214 mg, 0.845 mmol) in 25 mL of CCl_4 was stirred for 10 min. Alcohol **18** (180 mg, 0.422 mmol) in 2 mL of CCl_4 was then added. The reaction was stirred at room temperature under a 275-W light. After 1.5 h the reaction was quenched with saturated NaS_2O_5 and extracted with CH_2Cl_2. Flash chromatography (elution with 20% hexanes in methylene chloride) provided spiroketal **19** (95 mg, 53%): $[\alpha]^{25}_D$ +81.30° (*c* 1.60, $CHCl_3$); IR ($CHCl_3$) 2960, 1730, 1285, 1155 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.74 (dd, 1 H, *J* = 9.94, 1.81 Hz), 5.55 (dd, 1 H, *J* = 9.94, 2.57 Hz), 5.19 (m, 1 H), 4.2 (m, 1 H), 4.10 (m, 1 H), 3.98 (m, 1 H), 3.36 (dd, 1 H, *J* = 9.91, 1.72 Hz), 2.24 (m, 1 H), 2.1–1.7 (m, 4 H), 1.55–1.22 (m, 5 H), 1.19 (s, 9 H), 1.18 (s, 9 H), 0.95 (d, 3 H, *J* = 7.43), 0.93 (t, 3 H, *J* = 7.60 Hz), 0.88 (d, 3 H, *J* = 6.61 Hz); MS (20 eV), 366 ($M^+ - CH_3CH_2(CH_3)CHO$), 350 ($M^+ - (CH_3)_3CCO_2H$), 264 (M^+ − PvOH − Pv); HRMS CI calcd for $C_{26}H_{45}O_6$ (M^+ + H) 453.3217, found 453.3236.

[2*S*-[2α,4α,6β[8*S(*R**),9*R**]]]-9-Methyl-8-(1-methylpropyl)-2-(2-oxoethyl)-4-(2,2-dimethyl-1-oxopropoxy)-1,7-dioxaspiro[5.5]undec-10-ene (22)**, To a solution of spiroketal **19** (104 mg, 0.23 mmol) in 5 mL of THF at −78 °C was added Super-Hydride (920 μL, 0.92 mmol, 1 M). After stirring for 1 h the reaction was quenched with saturated NH_4Cl, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 20% ethyl acetate in hexanes) provided 66 mg (78%) of alcohol **21**: $[\alpha]^{25}_D$ +99.26° (*c* 2.17, $CHCl_3$); IR (neat) 3600–3200, 2962, 2939, 2880, 1731, 1288, 1160, 1000 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.69 (dd, 1 H, *J* = 9.90, 1.72 Hz), 5.51 (dd, 1 H, *J* = 9.0, 2.45 Hz), 5.19–5.09 (m, 1 H), 4.11–4.02 (m, 1 H), 3.76–3.71 (m, 2 H), 3.33 (dd, 1 H, *J* = 9.89, 1.54 Hz), 2.81 (br s, 1 H), 2.25–2.18 (m, 1 H), 2.02–1.93 (m, 2 H), 1.80–1.68 (m, 2 H), 1.58–1.4 (m, 3 H), 1.36–1.22 (m, 2 H), 1.14 (s, 9 H), 0.92 (t, 3 H, *J* = 7.26 Hz), 0.88 (d, 3 H, *J* = 7.12 Hz), 0.86 (d, 3 H, *J* = 6.65 Hz); MS (20 eV) 266 ($M^+ - (CH_3)_3CCO_2H$), 180 (266 − $C_5H_{10}O$, base peak). Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.35; H, 9.90.

To a solution of 120 μL (1.38 mmol) of oxalyl chloride in 1.0 mL of dry CH_2Cl_2 at −78 °C was added 196 μL (2.76 mmol) of dimethyl sulfoxide. The resulting solution was allowed to stir at −78 °C for 5 min at which time 340 mg (0.92 mmol) of alcohol **21** was added in 2.0 mL of CH_2Cl_2. After stirring at −78 °C for 45 min, 643 μL (4.61 mmol) of triethylamine was added and the reaction mixture was warmed to 0 °C and stirred for 30 min. The solution was then poured into pH 7.0 buffer, extracted into CH_2Cl_2, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 1:5 ether–hexanes) afforded 308 mg (91%) of the aldehyde **22**, homogeneous by TLC and spectroscopic analysis: $[\alpha]^{25}_D$ +76.47° (*c* 2.21, $CHCl_3$); IR (neat) 2985, 2938, 1730, 1388, 1289, 1152, 982, cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 9.79 (t, 1 H, *J* = 1.85 Hz), 5.73 (dd, 1 H, *J* = 9.91, 1.73 Hz), 5.53 (dd, 1 H, *J* = 9.91, 2.63 Hz), 5.24–5.18 (m, 1 H), 4.44–4.39 (m, 1 H), 3.38 (dd, 1 H, *J* = 9.97, 1.47 Hz), 2.61 (ddd, 1 H, *J* = 16.30, 8.34, 2.65 Hz), 2.49 (ddd, 1 H, *J* = 16.30, 4.39, 1.85 Hz), 2.26–2.23 (m, 1 H), 2.07–2.01 (m, 2 H), 1.61–1.44 (m, 4 H), 1.35–1.23 (m, 1 H), 1.17 (s, 9 H), 0.93 (t, 3 H, *J* = 7.52 Hz), 0.90 (d, 3 H, *J* = 7.13 Hz), 0.89 (d, 3 H, *J* = 6.74 Hz); MS (20 eV) 178 ($M^+ - (CH_3)_3CO_2H - C_5H_{10}O$ base peak). Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.08; H, 9.25. Found: C, 67.60; H, 9.68.

[2*R*-[2α(*E*),4α,6β[8*R(*S**),9*S**]]]-9-Methyl-2-(3-methyl-4-oxo-2-butenyl)-8-(1-methylpropyl)-4-(2,2-dimethyl-1-oxopropoxy)-1,7-dioxaspiro[5.5]undec-10-ene (24)**, To a solution of aldehyde **22** (72.6 mg, 0.198 mmol) in 9 mL of benzene was added ylide **23** (69 mg, 0.218 mmol). The reaction was refluxed for 36 h. It was then concentrated and chromatographed with 10% acetate in hexanes. This provided 76 mg of enal **24** (94% yield): $[\alpha]^{25}_D$ +52.39° (*c* 2.42, $CHCl_3$); IR ($CHCl_3$) 2970, 2938, 1720, 1685, 1460, 1382, 1278, 1160, 1000 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1 H), 6.57 (ddd, 1 H, *J* = 7.14, 1.00 Hz), 5.74 (dd, 1 H, *J* = 9.89, 1.79 Hz), 5.55 (dd, 1 H, *J* = 9.89, 2.59 Hz), 5.20–5.15 (m, 1 H), 4.05–3.99 (m, 1 H), 3.36 (dd, 1 H, *J* = 9.90, 1.76 Hz), 2.57–2.54 (m, 2 H), 2.26–2.22 (m, 1 H), 2.05–1.99 (m, 2 H), 1.73 (d, 3 H, *J* = 1.00 Hz), 1.63–1.51 (m, 2 H), 1.42–1.36 (m, 2 H), 1.32–1.21 (m, 1 H), 1.17 (s, 9 H), 0.90 (t, 3 H, *J* = 7.40 Hz), 0.89 (d, 3 H, *J* = 7.63 Hz), 0.88 (d, 3 H, *J* = 6.85 Hz); MS (20 eV) 320 ($M^+ - C_5H_{10}O$), 218 (320 − $(CH_3)_3CCO_2H$), 95 (base peak). Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.87; H, 9.44. Found: C, 70.83; H, 9.64.

[2*R*-[2α(2*E*,4*S,5*S**),4α,6β[9*S**,8*R**(*S**)]]]-2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,5-dimethyl-2,6-heptadienyl]-9-methyl-8-(1-**

methylpropyl)-4-(2,2-dimethyl-1-oxopropoxy)-1,7-dioxaspiro[5.5]undec-10-ene (28), To a mixture of 40 mg (0.098 mmol) of aldehyde **24** and 50 mg of powdered 4A molecular sieves in 2.0 mL of anhydrous toluene at −78 °C was added 196 μL of the (*R,R*)-crotylboronate **25** (1.0 M in toluene). The reaction mixture was stirred at −78 °C for 30 min and then an additional 196 μL of **25** was added. After stirring at −78 °C for 1 h, the reaction mixture was poured into saturated NH_4Cl, extracted three times with ether, dried ($MgSO_4$), and concentrated. Flash chromatography (elution 1:5 ether–hexanes) gave 41.8 mg (92%) of a ca. 4:1 mixture of C_{12} and C_{13} diastereomers. Analytical data for the major isomer **26**: $[\alpha]^{25}_D$ +69.83° (*c* 3.49, $CHCl_3$); IR ($CHCl_3$) 3600–3500, 2979, 2928, 1721, 1289, 1161, 999 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 5.79–5.73 (m, 1 H), 5.73 (dd, 1 H, *J* = 9.78, 1.62 Hz), 5.55 (dd, 1 H, *J* = 9.78, 2.60 Hz), 5.44 (dd, 1 H, *J* = 5.95, 5.95 Hz), 5.18–5.12 (m, 3 H), 3.69–3.67 (m, 1 H), 3.68 (dd, 1 H, *J* = 8.51, 2.27 Hz), 3.41 (dd, 1 H, *J* = 9.90, 1.85 Hz), 2.34–2.19 (m, 4 H), 2.00 (dd, 2 H, *J* = 12.36, 4.66 Hz), 1.71 (d, 1 H, *J* = 2.27 Hz), 1.61 (d, 3 H, *J* = 0.72 Hz), 1.52–1.41 (m, 4 H), 1.26–1.17 (m, 1 H), 1.17 (s, 9 H), 0.93 (t, 3 H, *J* = 7.24 Hz), 0.91 (d, 3 H, *J* = 7.11 Hz), 0.89 (d, 3 H, *J* = 6.81 Hz), 0.88 (d, 3 H, *J* = 6.78 Hz); MS (20 eV) 305 ($M^+ - (CH_3)_3CCO_2H - C_4H_7$, base peak), 274 ($M^+ - (CH_3)_3CCO_2H - C_5H_{10}O$), 219 ($305 - C_5H_{10}O$); HRMS (CI) calcd for $C_{28}H_{47}O_5$ 463.3425, found 463.3434.

A mixture of 64 mg (0.14 mmol) of alcohol **26** (4:1 mixture of diastereomers), 48 μL (0.21 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate, and 48 μL (0.42 mmol) of 2,6-lutidine in 2.0 mL of dry CH_2Cl_2 was stirred at 0 °C for 0.5 h. The reaction mixture was diluted with MeOH and concentrated under reduced pressure. Flash chromatography (elution with 1:40 ether–hexanes) afforded 75.3 mg (94%) of a 4:1 mixture of silyl ether **28** and the C_{12}, C_{13} diastereomer (**29**). Analytical data for the major isomer **28**: $[\alpha]^{25}_D$ +44.47° (*c* 3.78, $CHCl_3$); IR (neat) 2960, 2938, 1733, 1465, 1288, 1258, 1160, 1005, 841, 780 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 5.87–5.80 (m, 1 H), 5.72 (dd, 1 H, *J* = 9.90, 1.73 Hz), 5.55 (dd, 1 H, *J* = 9.90, 2.61 Hz), 5.28 (dd, 1 H, *J* = 6.20, 6.20 Hz), 5.18–5.13 (m, 1 H), 4.99–4.94 (m, 2 H), 3.90–3.87 (m, 1 H), 3.65 (d, 1 H, *J* = 7.81 Hz), 3.42 (dd, 1 H, *J* = 9.91, 1.80 Hz), 2.35–2.16 (m, 4 H), 1.99 (dd, 2 H, *J* = 7.53, 4.66 Hz), 1.55 (s, 3 H), 1.50–1.38 (m, 4 H), 1.27–1.16 (m, 1 H), 1.16 (s, 9 H), 0.91 (t, 3 H, *J* = 7.59 Hz), 0.90 (d, 3 H, *J* = 7.52 Hz), 0.89 (d, 3 H, *J* = 6.72 Hz), 0.86 (s, 9 H), 0.81 (d, 3 H, *J* = 6.92 Hz), 0.00 (s, 3 H), −0.06 (s, 3 H); MS (20 eV) 521 ($M^+ - C_4H_7$), 419 ($M^+ - (CH_3)_3CCO_2H - C_4H_7$), 388 ($M^+ - (CH_3)_3CCO_2H - C_5H_{10}O$), 221 (base peak).

[2*R*-[2α(2*E*,4*S,5*R**),4α,6β[8*R**(*S**),9*S**]]]-2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,5-dimethyl-6-oxo-2-hexenyl]-9-methyl-8-(1-methylpropyl)-4-(2,2-dimethyl-1-oxopropoxy)-1,7-dioxaspiro[5.5]undec-10-ene (30)**, A solution of 15 mg (0.026 mmol) of a ca. 4:1 mixture of olefins **28** and **29** in 2 mL of THF at room temperature was treated with 0.110 mL (0.028 mmol) of a 0.26 M solution of OsO_4 in THF and 9.0 μL of pyridine. The reaction was stirred at room temperature until TLC analysis showed consumption of the starting material. Approximately 50 mg of Florisil and 10 mg of solid $NaHSO_3$ were added followed by 4 mL of ethyl acetate and 5 drops of H_2O to initiate the reductive workup. This mixture was stirred vigorously for 12 h until the organic phase was clear and colorless. The reaction was filtered and the filtrate was dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. The crude diol(s) was immediately taken up in 4 mL of CH_2Cl_2, cooled to 0 °C, and treated with 11.5 mg (0.026 mmol) of $Pb(OAc)_4$, for 5 min. The reaction was then diluted with 5 mL of CH_2Cl_2 and poured into 10 mL of saturated $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with 3 × 5 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated at reduced pressure. Chromatography of the residue (25% ethyl acetate–hexanes) gave 10.2 mg (66% for two steps) of aldehyde **30** as a clear, colorless oil: $[\alpha]^{25}_D$ +57.35° (*c* 1.02, $CHCl_3$); IR (neat) 2970, 2930, 2860, 2720, 1725, 1465, 1385 cm^{-1}; NMR (500 MHz) δ 9.74 (d, 1 H, *J* = 2.94 Hz), 5.73 (dd, 1 H, *J* = 9.4, 1.8 Hz), 5.54 (dd, 1 H, *J* = 9.9, 2.6 Hz), 5.41 (dd, 1 H, *J* = 6.85, 6.85 Hz), 5.18–5.13 (m, 1 H), 4.09 (d, 1 H, *J* = 8.8 Hz), 3.92–3.90 (m, 1 H), 3.40 (dd, 1 H, *J* = 9.92, 1.88 Hz), 2.57–2.53 (m, 1 H), 2.36–2.31 (m, 1 H), 2.25–2.19 (m, 2 H), 2.02–1.97 (m, 2 H), 1.58 (d, 3 H, *J* = 0.99 Hz), 1.55–1.39 (m, 4 H), 1.25–1.17 (m, 1 H), 1.16 (s, 9 H), 0.91 (t, 3 H, *J* = 7.51 Hz), 0.90 (d, 3 H, *J* = 7.79 Hz), 0.88 (d, 3 H, *J* = 6.86 Hz), 0.85 (s, 9 H), 0.84 (d, 3 H, *J* = 7.03 Hz), 0.03 (s, 3 H), −0.03 (s, 3 H); MS (20 eV) 521, 419, 221 (base peak); HRMS (CI) calcd for $C_{33}H_{59}O_6Si$ ($M^+ + 1$) 579.4083, Found 579.4045.

[2*R*-[2α(2*E*,4*S,5*S**,6*E*),4α,6β[8*R**(*S**),9*S*]]]-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-8-[4-(2,2-dimethyl-1-oxopropoxy)-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undec-10-en-2-yl]-4,6-dimethyl-2,6-octadienoic Acid Methyl Ester (31)**, A mixture of 1.11 g (1.92 mmol) of aldehyde **30** and 1.44 g (4.30 mmol) of methyl (triphenylphosphoranylidene)acetate in 10.0 mL of dry CH_2Cl_2 was stirred at room temperature for 24 h. Concentration under reduced pressure and flash chromatography (elution with 1:10 ether–hexanes) gave 1.22 g (95%) of the enoate **31** as a single isomer, homogeneous by TLC and spectroscopic criteria: $[\alpha]^{25}_D$ +35.39° (*c* 4.38, $CHCl_3$); IR 2986, 2945, 1738, 1727, 1660, 1462, 1150, 1000, 842, 781 cm^{-1}; NMR (250 mHz, $CDCl_3$) δ 7.01 (dd, 1 H, *J* = 15.80, 7.93 Hz), 5.80 (dd, 1 H, *J* = 15.80, 1.13 Hz), 5.73 (dd, 1 H, *J* = 9.91, 1.72 Hz), 5.55 (dd, 1 H, *J* = 9.91, 2.56 Hz), 5.16 (br t, 1 H, *J* = 4.73 Hz), 5.14–5.11 (m, 1 H), 3.92–3.81 (m, 1 H), 3.73 (s, 3 H), 3.71 (d, 1 H, *J* = 7.11 Hz), 3.41 (dd, 1 H, *J* = 9.95, 1.63 Hz), 2.46–2.19 (m, 4 H), 2.01 (dd, 2 H, *J* = 12.31, 4.39 Hz), 1.56 (d, 3 H, *J* = 0.92 Hz), 1.54–1.39 (m, 1 H), 1.17 (s, 9 H), 0.92 (t, 3 H, *J* = 7.23 Hz), 0.90 (d, 3 H, *J* = 7.64 Hz), 0.87 (d, 3 H, *J* = 7.00 Hz), 0.86 (d, 3 H, *J* = 6.49 Hz), 0.85 (s, 9 H), −0.01 (s, 3 H), −0.06 (s, 3 H); MS (20 eV) 221 (base peak). Anal. Calcd for $C_{36}H_{62}O_7Si$: C, 68.10; H, 9.83. Found: C, 68.03; H, 10.22.

[2*R*-[2α(2*E*,4*S,5*S**,6*E*),4α,6β[8*R**(*S**),9*S**]]]-2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,5-dimethyl-8-oxo-2,6-octadienyl]-9-methyl-8-(1-methylpropyl)-4-(2,2-dimethyl-1-oxopropoxy)-1,7-dioxaspiro[5.5]undec-10-ene (33)**, To a solution of 374 mg (0.59 mmol) of enoate **31** in 5.0 mL of anhydrous THF at −78 °C was added 1.20 mL of diisobutylaluminum hydride (1.0 M in hexanes). The resulting solution was stirred at −78 °C for 2 h and then was poured into saturated potassium sodium tartrate. The reaction mixture was extracted three times with ether, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 1:4 ether–hexanes) gave 289 mg (81%) of alcohol **32** and 52.2 mg of recovered **31** (total mass recovery = 94%). Analytical data for alcohol **32**: $[\alpha]^{25}_D$ +47.12° (*c* 2.95, $CHCl_3$); IR (neat) 3660–3200, 1733, 1465, 1382, 1289, 1160, 1005, 841, 782 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 5.71 (dd, 1 H, *J* = 9.90, 1.77 Hz), 5.65 (dd, 1 H, *J* = 15.56, 7.43 Hz), 5.88 (dt, 1 H, *J* = 15.56, 5.47 Hz), 5.54 (dd, 1 H, *J* = 9.90, 2.61 Hz), 5.25 (br t, 1 H, *J* = 6.96 Hz), 5.17–5.12 (m, 1 H), 4.07 (dd, 2 H, *J* = 5.47, 5.47 Hz), 3.87–3.84 (m, 1 H), 3.65 (d, 1 H, *J* = 7.53 Hz), 3.40 (dd, 1 H, *J* = 9.93, 1.80 Hz), 2.32–2.16 (m, 4 H), 2.01–1.97 (m, 2 H), 1.53 (d, 3 H, *J* = 0.81 Hz), 1.50–1.40 (m, 4 H), 1.20–1.16 (m, 1 H), 1.15 (s, 9 H), 0.91 (t, 3 H, *J* = 7.42 Hz), 0.89 (d, 3 H, *J* = 7.27 Hz), 0.86 (d, 3 H, *J* = 7.07 Hz), 0.85 (s, 9 H), 0.83 (d, 3 H, *J* = 6.89 Hz), −0.02 (s, 3 H), −0.08 (s, 3 H); MS (20 eV) 521 ($M^+ - C_5H_9O$), 419 ($M^+ - (CH_3)_3CCO_2H$), 221 (base peak).

To a solution of 56 μL (0.64 mmol) of oxalyl chloride in 1.0 mL of dry CH_2Cl_2 at −78 °C was added 91 μL (1.28 mmol) of dimethyl sulfoxide. The resulting solution was allowed to stir at −78 °C for 5 min at which time 259 mg (0.43 mmol) of alcohol **32** was added in 3.0 mL of CH_2Cl_2. After stirring of the mixture at −78 °C for 1.5 h, 357 μL (2.56 mmol) of triethylamine was added and the reaction mixture was warmed to 0 °C and stirred for 30 min. The solution was then poured into pH 7.0 buffer, extracted into CH_2Cl_2, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 1:6 ether–hexanes) gave 245 mg (95%) of enal **33**, which was homogeneous by TLC and spectroscopic criteria: $[\alpha]^{25}_D$ +38.85° (*c* 1.66, $CHCl_3$); IR (neat) 2960, 2938, 1731, 1600, 1462, 1380, 1289, 1160, 845 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 9.49 (d, 1 H, *J* = 7.86 Hz), 6.92 (dd, 1 H, *J* = 15.71, 7.38 Hz), 6.09 (dd, 1 H, *J* = 15.71, 7.86 Hz), 5.72 (dd, 1 H, *J* = 9.80, 1.32 Hz), 5.54 (dd, 1 H, *J* = 9.80, 2.48 Hz), 5.34 (br t, 1 H, *J* = 6.98 Hz), 5.21–5.09 (m, 1 H), 3.99–3.89 (m, 1 H), 3.77 (d, 1 H, *J* = 7.59 Hz), 3.40 (dd, 1 H, *J* = 9.98, 1.27 Hz), 2.63–2.54 (m, 3 H), 2.00 (dd, 2 H, *J* = 12.05, 4.54 Hz), 1.56 (s, 3 H), 1.53–1.39 (m, 4 H), 1.24–1.19 (m, 1 H), 1.16 (s, 9 H), 0.91 (t, 3 H, *J* = 6.92 Hz), 0.90 (d, 3 H, *J* = 6.71 Hz), 0.89 (d, 3 H, *J* = 7.56 Hz), 0.85 (d, 3 H, *J* = 6.19 Hz), 0.85 (s, 9 H), 0.01 (s, 3 H), −0.01 (s, 3 H).

Methyl 6,7,8-Trideoxy-6-methyl-5-*O*-methyl-2,3-*O*-(1-methylethylidene)-L-*glycero*-D-*allo*-oct-7-enofuranoside (36), To a solution of 4.65 g (22.99 mmol) of aldehyde **34** in 100 mL of anhydrous CH_2Cl_2 at −78 °C was added 5.65 mL (45.94 mmol) of $BF_3{\cdot}OEt_2$ and the mixture was allowed to stir at −78 °C for 15 min. To this was added 9.60 g (30.48 mmol) of (*E*)-crotyltributyltin in 50 mL of dry CH_2Cl_2 over a period of 30 min. After the addition was complete, the reaction mixture was stirred at −78 °C for an additional 60 min and was then poured into saturated NH_4Cl. The two layers were partitioned, and the aqueous layer was extracted twice with CH_2Cl_2, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 1:5 ether–hexanes) gave 4.55 g (79%) of a ca. 10:1 mixture of alcohol **35** and the corresponding hydroxyl epimer. Analytical data for pure **35**: $[\alpha]^{25}_D$ −68.20 (*c* 2.95, $CHCl_3$); IR ($CHCl_3$) 3672, 3610, 3430, 3020, 2400, 1230, 1190, 790, 740, 672, cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.83–5.68 (m, 1 H), 5.17–5.06 (m, 2 H), 4.96 (br s, 1 H), 4.88 (d, 1 H, *J* = 5.99 Hz), 4.57 (d, 1 H, *J* = 5.99 Hz), 4.44 (d, 1 H, *J* = 2.23 Hz), 3.61 (br s, 1 H), 3.49 (ddd, 1 H, *J* = 8.22, 2.23, 2.23 Hz), 3.43 (s, 3 H), 2.41–2.33 (m, 1 H), 1.47 (s, 3 H), 1.32 (s, 3 H), 1.14 (d, 3 H, *J* = 6.79 Hz); MS (20 eV) 258 (M^+), 243 ($M^+ - CH_3$), 203 ($M^+ - C_4H_7$, base peak).

To a slurry of 1.32 g (33.10 mmol) of 60% NaH in 20.0 mL of

anhydrous THF at 0 °C was added 5.7 g (22.06 mmol) of alcohol **35** (ca. 10:1 mixture of hydroxyl epimers) in 30.0 mL of dry THF. After warming from 0 °C to room temperature over a 30-min period, the reaction mixture was treated with 6.9 mL (110.33 mmol) of MeI and was then heated at reflux for 3 h. The mixture was then cooled to room temperature and carefully quenched with H_2O. The aqueous layer was extracted three times with ether, and the combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 1:12 ether–hexanes) afforded 5.16 g (86%) of the methyl ether **36** as a single diastereomer, which was homogeneous by TLC and spectroscopic analysis: $[\alpha]^{25}_D$ −77.69° (*c* 9.09, $CHCl_3$); IR ($CHCl_3$) 2985, 2940, 1459, 1379, 1368, 1199, 1100, 960, 873 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 5.99–5.86 (m, 1 H), 5.11–4.98 (m, 2 H), 4.93 (s, 1 H), 4.72 (d, 1 H, *J* = 6.07 Hz), 4.55 (d, 1 H, *J* = 6.07 Hz), 4.04 (d, 1 H, *J* = 8.88 Hz), 3.40 (s, 3 H), 3.37 (s, 3 H), 3.12 (dd, 1 H, *J* = 8.88, 2.85 Hz), 2.61–2.55 (m, 1 H), 1.46 (s, 3 H), 1.31 (s, 3 H), 1.04 (d, 3 H, *J* = 6.78 Hz); MS (20 eV) 257 ($M^+ - CH_3$), 217 ($M^+ - C_4H_7$, base peak); HRMS calcd for $C_{14}H_{24}O_5$ (+H) 273.1702, found 273.1702.

1,4:2,3-Dianhydro-6,7,8-trideoxy-6-methyl-5-*O*-methyl-L-*glycero*-D-*allo*-oct-7-enitol (39), A mixture of 7.5 g (27.54 mmol) of acetonide **36** and 25 mL of 1 N HCl in 75 mL of methanol was heated at reflux for 5 h at which time TLC analysis showed complete consumption of the starting material. The solution was then cooled to room temperature, neutralized with basic ion-exchange resin, filtered through Celite, and concentrated under reduced pressure. The residue from this was partitioned between saturated $NaHCO_3$ and ether, dried over $MgSO_4$, and concentrated. The crude **37** (6.25 g) so obtained was placed in 125 mL of anhydrous CH_2Cl_2 and lowered to 0 °C. To this was added 21.5 mL (134.5 mmol) of Et_3SiH and 16.5 mL (134.5 mmol) of $BF_3{\cdot}OEt_2$. The resulting mixture was stirred at 0 °C for 4 h and then at 25 °C for 6 h and was then poured into H_2O and extracted three times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (1:1 ethyl acetate–hexanes containing 2% 2-propanol) gave 4.30 g (79%) of diol **38**, which was homogeneous by TLC and spectroscopic analysis: $[\alpha]^{25}_D$ −10.17° (*c* 2.87, $CHCl_3$); IR ($CHCl_3$) 3523, 3400, 3009, 2979, 2938, 1640, 1452, 1100, 928 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 5.89–5.82 (m, 1 H), 5.10–5.03 (m, 2 H), 4.22 (ddd, 1 H, *J* = 5.60, 4.80, 3.62 Hz), 4.15 (dd, 1 H, *J* = 5.50, 5.60 Hz), 4.02 (dd, 1 H, *J* = 9.72, 4.80 Hz), 3.82 (dd, 1 H, *J* = 5.60, 5.60 Hz), 3.73 (dd, 1 H, *J* = 9.70, 3.62 Hz), 3.46 (s, 3 H), 3.19 (dd, 1 H, *J* = 5.60, 5.60 Hz), 2.95 (br s, 1 H), 2.90 (br s, 1 H), 2.54–2.50 (m, 1 H), 1.07 (d, 3 H, *J* = 6.92 Hz); MS (20 eV), 203 ($M^+ + 1$), 202 (M^+), 184 ($M^+ - H_2O$). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.10; H, 8.81.

To a solution of 3.0 g (14.83 mmol) of diol **38** in 50 mL of CH_2Cl_2 was added 4.85 mL (32.33 mmol) of 2-acetoxyisobutyryl bromide. After stirring at room temperature for 1 h, the reaction mixture was poured into saturated $NaHCO_3$, extracted three times with CH_2Cl_2, dried ($MgSO_4$), and concentrated. The crude residue was then suspended in 60 mL of absolute MeOH, and excess Amberlite IRA-400 resin was added. The mixture was stirred at room temperature overnight and then filtered through Celite and concentrated. Flash chromatography (1:3 ether–hexanes) afforded 2.48 g (92%) of the epoxide **39**, homogeneous by TLC and spectroscopic analysis: $[\alpha]^{25}_D$ −36.09° (*c* 7.61, $CHCl_3$); IR (neat) 2982, 2911, 2865, 1638, 1457, 1090, 910, 852 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.82–5.76 (m, 1 H), 5.14–5.04 (m, 2 H), 4.11 (d, 1 H, *J* = 4.63 Hz), 3.91 (AB q, 2 H, J_{AB} = 10.07 Hz, $\Delta\nu_{AB}$ = 32.94 Hz), 3.85–3.79 (m, 2 H), 3.45 (s, 3 H), 3.14 (dd, 1 H, *J* = 6.89, 4.63 Hz), 2.57–2.43 (m, 1 H), 1.11 (d, 3 H, *J* = 6.86 Hz); MS 185 ($M^+ + 1$), 129 ($M^+ - C_4H_7$).

Enoate 41, To a solution of 4.2 g (22.88 mmol) of epoxide **39** in 150 mL of anhydrous THF at 0 °C was added 25.0 mL of lithium triethylborohydride (1.0 M in THF). The resulting solution was stirred at 0 °C for 6 h and then quenched with H_2O. Extraction into ether, drying ($MgSO_4$), and concentration gave a clear oil. Flash chromatography (1:1 ether–hexanes) afforded 4.04 g (96%) of alcohol **40**, which was used immediately for the next step. The alcohol **40** (190 mg, 1.02 mmol) was placed in 5 mL of dry CH_2Cl_2 and this was cooled to −78 °C. Ozone was then bubbled through the solution until a distinct blue color persisted. After stirring at −78 °C for 5 min, Ar was bubbled through the solution for 5 min to dissipate the excess ozone. The solution was then treated with excess Zn^0 and 4 drops of glacial HOAc and was then stirred at room temperature for 0.5 h. Filtration through Celite and removal of the volatiles under reduced pressure provided 185 mg of the corresponding crude aldehyde. This material was immediately suspended in 5 mL of anhydrous CH_2Cl_2 and 511 mg (1.53 mmol) of methyl (triphenylphosphoranylidene)acetate was added. After stirring for 12 h at room temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography. Elution with 1:5 acetone–hexanes gave 178 mg (84%) of the enoate **41** as a single isomer, homogeneous by TLC and spectroscopic criteria: $[\alpha]^{25}_D$ −20.82° (*c* 6.56, $CHCl_3$); IR 3620–3180, 2989, 2950, 2890, 1725, 1659, 1438, 1277, 1100 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.02 (dd, 1 H, *J* = 15.77, 7.46 Hz), 5.84 (dd, 1 H, *J* = 15.77, 1.44 Hz), 4.33–4.30 (m, 1 H), 3.95–3.87 (m, 2 H), 3.73 (s, 3 H), 3.61 (dd, 1 H, *J* = 6.60, 4.32 Hz), 2.74–2.71 (m, 1 H), 2.16–2.09 (m, 1 H), 2.02 (br s, 1 H), 1.91–1.86 (m, 1 H), 1.09 (d, 3 H, *J* = 6.86 Hz); MS 226 ($M^+ - H_2O$), 133 ($M^+ - C_6H_9O_2$), 131 (base peak).

[2*S*-[2α(1*S,2*R**,3*E*),3β]]-2-[5-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-1-methoxy-2-methyl-3-pentenyl]tetrahydro-3-furanol (43)**, To a solution of 1.06 g (4.33 mmol) of enoate **41** in 30 mL of anhydrous ether at 0 °C was added 13.0 mL of diisobutylaluminum hydride (1.0 M in hexanes). After stirring for 2 h at 0 °C, the reaction mixture was quenched with saturated potassium sodium tartrate, and the layers were partitioned. The aqueous layer was extracted three times with ethyl acetate, and then the combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 1:3 acetone–hexane) yielded 910 mg (97%) of diol **42**, which was homogeneous by TLC and spectroscopic analysis: $[\alpha]^{25}_D$ −17.43° (*c* 5.22, $CHCl_3$); IR ($CHCl_3$), 3600, 3520–3200, 1462, 1381, 1102, 965, 913 cm^{-1}; NMR (500 MHz; $CDCl_3$) δ 5.78 (ddt, 1 H, *J* = 15.53, 7.27, 1.02 Hz), 5.68 (ddt, 1 H, *J* = 15.53, 5.77, 0.95 Hz), 4.38–4.35 (m, 1 H), 4.12 (d, 2 H, *J* = 5.77 Hz), 3.95 (dt, 1 H, *J* = 8.43, 3.82 Hz), 3.87 (dt, 1 H, *J* = 8.43, 6.55 Hz), 3.70 (dd, 1 H, *J* = 5.09, 3.47 Hz), 3.45 (s, 3 H), 3.13 (dd, 1 H, *J* = 5.09, 5.09 Hz), 2.56–2.53 (m, 1 H), 2.14–2.07 (m, 1 H), 1.90–1.84 (m, 1 H), 1.60 (br s, 2 H), 1.10 (d, 3 H, *J* = 6.94 Hz); MS 198 ($M^+ - H_2O$), 131 ($M^+ - C_5H_9O$, base peak). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.79; H, 9.49.

To a solution of 408 mg (1.89 mmol) of diol **42** in 5.0 mL of dry CH_2Cl_2 were added 298 mg (1.98 mmol) of *tert*-butyldimethylsilyl chloride, 0.53 mL (3.78 mmol) of triethylamine, and 23 mg (0.19 mmol) of 4-(dimethylamino)pyridine. The reaction mixture was stirred at room temperature for 10 h and was then diluted with 5.0 mL of 0.1 N HCl. The layers were partitioned, and the aqueous layer was washed twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (elution with 1:5 acetone–hexane) gave 602 mg (97%) of alcohol **43**, homogeneous by TLC and spectroscopic analysis: $[\alpha]^{25}_D$ −27.54° (*c* 6.21, $CHCl_3$); IR ($CHCl_3$) 3600, 3590–3280, 3009, 2961, 2939, 1465, 1260, 965, 840 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 5.74 (ddd, 1 H, *J* = 15.48, 7.41, 1.21 Hz), 5.59 (dt, 1 H, *J* = 15.48, 5.38 Hz), 4.35–4.33 (m, 1 H), 4.12 (d, 2 H, *J* = 5.38 Hz), 3.98 (dt, 1 H, *J* = 8.10, 3.69 Hz), 3.69–3.43 (m, 1 H), 3.68 (dd, 1 H, *J* = 4.99, 3.43 Hz), 4.43 (s, 3 H), 3.12 (dd, 1 H, *J* = 4.99, 4.99 Hz), 2.54–2.50 (m, 1 H), 3.39 (br s, 1 H), 2.10–2.05 (m, 1 H), 1.89–1.84 (m, 1 H), 1.07 (d, 3 H, *J* = 6.2 Hz), 0.89 (s, 9 H), 0.06 (s, 6 H); MS 273 ($M^+ - C_4H_9$), 131 (base peak).

[2*R*-[2*R(1*R**,2*S**,3*E*)]]-2-[5-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-1-methoxy-2-methyl-3-pentenyl]dihydro-3(2*H*)-furanone (44)**, A mixture of 360 mg (1.47 mmol) of alcohol **43**, 350 mg (1.62 mmol) of pyridinium chlorochromate, 1.33 mg (1.62 mmol) of sodium acetate and 1.75 g of powdered 4A molecular sieves in 5.0 mL of dry CH_2Cl_2 was stirred overnight at room temperature. The reaction mixture was then diluted with ether, filtered through a pad of Celite, and concentrated under reduced pressure. Flash chromatography (elution with 1:5 acetone–hexanes) gave 318 mg (89%) of ketone **44** as an oil, which was homogeneous by TLC and spectroscopic criteria: $[\alpha]^{25}_D$ +63.67° (*c* 5.2, $CHCl_3$); IR (neat) 2959, 2938, 2861, 1758, 1259, 1120, 840, 782 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 5.62 (ddt, 1 H, *J* = 15.35, 5.25, 0.47 Hz), 5.35 (ddt, 1 H, *J* = 15.35, 9.24, 1.61 Hz), 3.45 (dt, 1 H, *J* = 9.15, 4.03 Hz), 4.09–4.02 (m, 3 H), 3.94 (d, 1 H, *J* = 2.08 Hz), 3.46 (s, 3 H), 3.18 (dd, 1 H, *J* = 9.76, 2.08 Hz), 2.75–2.71 (m, 1 H), 2.62 (dt, 1 H, *J* = 18.01, 9.15 Hz), 2.37 (ddd, 1 H, *J* = 18.01, 7.40, 4.03 Hz), 1.04 (d, 3 H, *J* = 6.71 Hz), 0.88 (s, 9 H), 0.04 (s, 6 H); MS (20 eV) 328 (M^+), 271 ($M^+ - C_4H_9$), 129 (base peak). Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 61.93; H, 9.93.

[2*R*-[2α[2*E*,4*S,5*S**,6*E*,8*E*[5*R**(1*R**,2*S**,3*E*)]],4α,6β[8*R**-(*S**),9*S*]]]-2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-8-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-methoxy-2-methyl-3-pentenyl]dihydro-4-oxo-3(2*H*)-furanylidene]-3,5-dimethyl-2,6-octadienyl]-4-(2,2-dimethyl-1-oxopropoxy)-9-methyl-8-(1-methylpropyl)-1,7-dioxospiro[5.5]undec-10-ene (45)**, To a solution of 16.7 mg (0.051 mmol) of ketone **44** in 1.0 mL of anhydrous THF at −78 °C was added 66 μL of lithium hexamethyldisylazide (1.0 M in hexane). The resulting yellow solution was stirred at −78 °C for 5 min and was then warmed to 0 °C and stirred for 30 min. The reaction mixture was then cooled to −78 °C at which time 40 mg (0.066 mmol) of enal **33** was added in 1.5 mL of dry THF. After stirring at −78 °C for 1 h, the solution was treated with 28 μL (0.203 mmol) of triethylamine and 12 μL (0.152 mmol) of methanesulfonyl chloride. The resulting heterogeneous mixture was allowed to slowly warm to room temperature while stirring overnight. The reaction mixture was then poured into saturated NH_4Cl, extracted into ether, dried over $MgSO_4$,

and concentrated. Flash chromatography (elution with 1:7 ether–hexanes) gave 31.2 mg (67%) of the aldol product **45**, which was homogeneous by TLC and spectroscopic criteria: $[\alpha]^{25}_D$ +18.68° (*c* 3.33, $CHCl_3$); IR ($CHCl_3$) 2960, 2932, 1720, 1629, 1461, 1161, 842 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 6.3 (ddt, 1 H, *J* = 11.66, 2.51 Hz), 6.31 (dd, 1 H, *J* = 15.17, 7.70 Hz), 5.97 (dd, 1 H, *J* = 15.17, 11.66 Hz), 5.73 (dd, 1 H, *J* = 9.90, 1.71 Hz), 5.61 (dt, 1 H, *J* = 15.36, 5.18 Hz), 5.26 (dd, 1 H, *J* = 9.90, 2.59 Hz), 5.42 (ddt, 1 H, *J* = 15.36, 1.41 Hz), 5.30 (br t, 1 H, *J* = 6.82 Hz), 5.19–5.14 (m, 1 H), 4.86 (d AB q, 2 H, J_{AB} = 14.04 Hz, $\Delta\nu_{AB}$ = 50.48 Hz, *J* = 2.51 Hz), 4.30 (d, 1 H, *J* = 2.32 Hz), 4.03–3.91 (m, 2 H), 3.89–3.86 (m, 1 H), 3.70 (d, 1 H, *J* = 8.04 Hz), 3.47 (s, 3 H), 3.41 (dd, 1 H, *J* = 9.92, 1.69 Hz), 3.27 (dd, 1 H, *J* = 9.24, 2.32 Hz), 2.81–2.76 (m, 1 H), 2.46–2.42 (m, 1 H), 2.38–2.32 (m, 1 H), 2.28–2.16 (m, 2 H), 2.03–1.99 (m, 2 H), 2.03–1.99 (m, 2 H), 1.56 (d, 3 H, *J* = 0.54 Hz), 1.52–1.30 (m, 4 H), 1.24–1.18 (m, 1 H), 1.17 (s, 9 H), 1.08 (d, 3 H, *J* = 6.73 Hz), 0.93 (t, 3 H, *J* = 7.39 Hz), 0.91 (d, 3 H, *J* = 7.28 Hz), 0.89 (s, 9 H), 0.88 (d, 3 H, *J* = 7.33 Hz), 0.86 (d, 3 H, *J* = 7.19 Hz), 0.85 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H), −0.03 (s, 3 H), −0.06 (s, 3 H); MS (20 eV) 521 ($M^+ - C_{22}H_{37}O_4Si$), 419 (522 − $(CH_3)_3(CO_2H)$, 221 (base peak).

[2*R*-[2α[2*E*,4*S,5*S**,6*E*,8*E*[5*R**(1*R**,2*S**,3*E*)]],4α,6β[8*R**-(*S**),9*S**]]]-2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-8-[dihydro-5-(5-hydroxy-1-methoxy-2-methyl-3-pentenyl)-4-oxo-3(2*H*)-furanylidene]-3,5-dimethyl-2,6-octadienyl]-4-(2,2-dimethyl-1-oxopropoxy)-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undec-10-ene (46)**, To a solution of 42 mg (0.046 mmol) of the bis(silyl ether) **45** in 2.0 mL of acetonitrile at −20 °C was added 8 drops of a mixture of acetonitrile and 40% HF (ratio 95:5). The resulting solution was stirred at −20 °C and was then poured into saturated $NaHCO_3$. The reaction mixture was extracted three times with ether, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 1:3 acetone–hexane) afforded 33.2 mg (90%) of the alcohol **46**, which was homogeneous by TLC and spectroscopic analysis: IR ($CHCl_3$) 3600, 2960, 2932, 1721, 1160, 1000, 841 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 6.89 (dt, 1 H, *J* = 11.66, 2.42 Hz), 6.31 (dd, 1 H, *J* = 15.16, 7.90 Hz), 5.96 (dd, 1 H, *J* = 15.16, 11.66 Hz), 5.72 (dd, 1 H, *J* = 9.88, 1.06 Hz), 5.66 (dt, 1 H, *J* = 15.43, 5.55 Hz), 555 (ddd, 1 H, *J* = 9.88, 2.53, 0.65 Hz), 5.41 (dd, 1 H, *J* = 15.43, 9.06 Hz), 5.29 (br t, 1 H, *J* = 7.01 Hz), 5.16–5.14 (m, 1 H), 4.85 (d, AB q, 2 H, J_{AB} = 14.18 Hz, $\Delta\nu_{AB}$ = 54.18 Hz, *J* = 2.42 Hz), 4.30 (d, 1 H, *J* = 1.75 Hz), 3.93 (br t, 2 H, *J* = 5.55 Hz), 3.88–3.86 (m, 1 H), 3.70 (d, 1 H, *J* = 7.89 Hz), 3.45 (s, 3 H), 3.40 (d, 1 H, *J* = 10.05 Hz), 3.30 (dd, 1 H, *J* = 8.97, 1.75 Hz), 2.82–2.78 (m, 1 H), 2.46–2.41 (m, 1 H), 2.38–2.18 (m, 3 H), 2.02–1.96 (m, 2 H), 1.59 (s, 1 H), 1.54 (s, 3 H), 1.48–1.40 (m, 4 H), 1.22–1.19 (m, 1 H), 1.16 (s, 9 H), 1.08 (d, 3 H, *J* = 6.78 Hz), 0.91 (t, 3 H, *J* = 7.44 Hz), 0.89 (d, 3 H, *J* = 7.67 Hz), 0.88 (d, 3 H, *J* = 7.55 Hz), 0.87 (d, 3 H, *J* = 6.71 Hz), 0.83 (s, 9 H), −0.03 (s, 3 H), −0.07 (s, 3 H); MS (20 eV) 521 ($M^+ - C_{16}H_{23}O_4$), 419 (521 − $(CH_3)_3CCO_2H$), 417 (base peak).

[2*R*-[2α[2*E*,4*S,5*S**,6*E*,8*E*[5*R**(1*R**,2*S**,3*E*)]],4α,6β[8*R**-(*S**),9*S**]]]-2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-8-[dihydroxy-5-(1-methoxy-2-methyl-5-oxo-3-pentenyl)-4-oxo-3(2*H*)-furanylidene]-3,5-dimethyl-2,6-octadienyl]-4-(2,2-dimethyl-1-oxopropoxy)-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undec-10-ene (47)**, A mixture of 26 mg (0.032 mmol) of alcohol **46**, 10.5 mg (0.048 mmol) of pyridinium chlorochromate, 4.0 mg (0.048 mmol) of sodium acetate, and 50 mg of powdered 4A molecular sieves in 2.0 mL of dry CH_2Cl_2 was stirred at 0 °C for 2 h. The reaction mixture was then diluted with ether, filtered through a pad of Celite, and concentrated. Flash chromatography (elution with 1:2 ether–hexanes) gave 22.8 mg (88%) of the enal **47**, which was homogeneous by TLC and spectroscopic analysis: $[\alpha]^{25}_D$ +24.32 (*c* 1.76, $CHCl_3$); IR ($CHCl_3$) 3200, 2650, 2390, 1721, 1692, 1628, 1461, 1162, 1000, 672 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 9.46 (d, 1 H, *J* = 7.90 Hz), 6.93 (dt, 1 H, *J* = 11.66, 2.48 Hz), 6.76 (dd, 1 H, *J* = 15.68, 8.31 Hz), 6.32 (dd, 1 H, *J* = 14.93, 7.90 Hz), 6.14 (ddd, 1 H, *J* = 15.68, 7.94, 1.00 Hz), 5.96 (dd, 1 H, *J* = 14.93, 11.66 Hz), 5.72 (dd, 1 H, *J* = 9.90, 1.77 Hz), 5.55 (dd, 1 H, *J* = 9.90, 2.60 Hz), 5.29 (br t, 1 H, *J* = 6.76 Hz), 5.17–5.12 (m, 1 H), 4.84 (d AB q, 2 H, J_{AB} = 14.01 Hz, $\Delta\nu_{AB}$ = 45.35 Hz, *J* = 2.48 Hz), 4.22 (d, 1 H, *J* = 2.63 Hz), 3.88–3.863 (m, 1 H), 3.69 (d, 1 H, *J* = 8.02 Hz), 3.49 (s, 3 H), 3.45 (dd, 1 H, *J* = 7.92, 2.63 Hz), 3.41 (dd, 1 H, *J* = 9.91, 1.80 Hz), 3.16–2.98 (m, 1 H), 2.46–2.41 (m, 1 H), 2.38–2.19 (m, 3 H), 2.04–1.97 (m, 2 H), 1.55 (d, 3 H, *J* = 0.57 Hz), 1.51–1.44 (m, 4 H), 1.21–1.16 (m, 1 H), 1.16 ns, 9 H), 1.16 (d, 3 H, *J* = 6.88 Hz), 0.92 (t, 3 H, *J* = 7.37 Hz), 0.90 (d, 3 H, *J* = 7.24 Hz), 0.88 (d, 3 H, *J* = 6.78 Hz), 0.87 (d, 3 H, *J* = 6.82 Hz), 0.830 (s, 9 H), −0.04 (s, 3 H), −0.08 (s, 3 H); MS (20 eV) 521 ($M^+ - C_{22}H_{37}O_4Si$), 419 (521 − $(CH_3)_3CCO_2H$), 221 (base peak).

[3a*R*-[3*E*[1[2*R,4*S**,6*S**,8*R**(*S**),9*S**]],2*E*,4*S**,5*S**,6*E*],3aα,-6α,7β,7aα]-2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-8-(5-formyl-3a,6,7,7a-tetrahydro-3a-hydroxy-7-methoxy-6-methyl-3(2*H*)-benzofuranylidene)-3,5-dimethyl-2,6-octadienyl]-4-(2,2-dimethyl-7-oxo-propyl)-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undec-10-ene (48)**, To a solution of 20 mg (0.025 mmol) of enal **47** in 1.0 mL of anhydrous THF at 0 °C was added 162 μL of $Me_3ASPhLi$ (0.2 M in THF). The resulting mixture was allowed to stir at 0 °C for 10 min and was then poured into saturated NH_4Cl. The aqueous layer was extracted three times with ether, dried over $MgSO_4$, and concentrated under reducted pressure. The crude residue was dissolved in 1.0 mL of dry CH_2Cl_2 at −20 °C and 5.4 mg (0.025 mmol) of *m*-chloroperoxybenzoic acid was added. After stirring of the mixture at −20 °C for 2.0 h, excess dimethyl sulfide was added and then the reaction mixture was poured into saturated $NaHCO_3$, and the layers were partitioned. The aqueous layer was extracted three times with CH_2Cl_2; the combined organic extracts were dried over $MgSO_4$ and concentrated. The crude material so obtained was then placed in 1.0 mL of dry toluene and heated at reflux for 30 min. The solution was concentrated under reduced pressure and purified by flash chromatography. Elution with 1:2 ether–hexanes gave 15.2 mg (76%) of the enal **48**, which was homogeneous by TLC and spectroscopic analysis: $[\alpha]^{25}_D$ +169.43° (*c* 1.18, $CHCl_3$); IR ($CHCl_3$) 3510, 2981, 2959, 1721, 1681, 1153, 1000, 842 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 9.39 (s, 1 H), 6.48 (d, 1 H, *J* = 1.70 Hz), 6.36 (dt, 1 H, *J* = 10.94, 2.35 Hz), 5.81 (dd, 1 H, *J* = 15.08, 10.94 Hz), 5.72 (dd, 1 H, *J* = 9.90, 1.49 Hz), 5.68 (dd, 1 H, *J* = 15.08, 8.07 Hz), 5.55 (dd, 1 H, *J* = 9.90, 2.63 Hz), 5.26 (br t, 1 H, *J* = 6.98 Hz), 5.18–5.15 (m, 1 H), 4.55 (d AB q, 2 H, J_{AB} = 13.89 Hz, $\Delta\nu_{AB}$ = 86.62 Hz, *J* = 2.35 Hz), 4.15 (d, 1 H, *J* = 1.96 Hz), 4.03 ns, 1 H), 3.88–3.85 (m, 1 H), 3.62 (d, 1 H, *J* = 8.22 Hz), 3.49 (s, 3 H), 3.41 (dd, 1 H, *J* = 9.77, 1.19 Hz), 3.14 (dd, 1 H, *J* = 9.66, 1.96 Hz), 2.89–2.86 (m, 1 H), 2.33–2.16 (m, 4 H), 2.01–2.00 (m, 2 H), 1.53 (s, 3 H), 1.48–1.42 (m, 4 H), 1.28 (d, 3 H, *J* = 7.31 Hz), 1.25–1.19 (m, 1 H), 1.16 (s, 9 H), 0.92 (t, 3 H, *J* = 7.43 Hz), 0.90 (d, 3 H, *J* = 7.17 Hz), 0.89 (d, 3 H, *J* = 6.39 Hz), 0.81 (d, 3 H, *J* = 6.79 Hz), 0.79 (s, 9 H), −0.01 (s, 3 H), −0.06 (s, 3 H); MS (20 eV) 521 ($M^+ - C_{16}H_{21}O_4$), 419 (521 − $(CH_3)_3CCO_2H$), 221 (base peak).

Seco Ester, Pivalate 50, To a solution of 12 mg (0.015 mmol) of enal **48** in 0.5 mL of tert-butyl alcohol and 0.5 mL of 2-methyl-2butene at 0 °C were added 8.5 mg (0.075 mmol) of 80% $NaClO_2$ and 12.5 mg (0.090 mmol) of NaH_2PO_4 in 0.5 mL of H_2O. The resulting biphase mixture was raised to room temperature and stirred vigorously for 4 h. The reaction mixture was poured into pH 4.0 buffer, extracted three times with ether, dried over $MgSO_4$, and concentrated. The crude carboxylic acid **49** was dissolved in 1.0 mL of ether at 0 °C and was esterified with an ethereal solution of diazomethane. Flash chromatography (elution with 1:3 ether–hexane) afforded 9.8 mg (79%) of the ester **50**, which was homogeneous by TLC and spectroscopic analysis: $[\alpha]^{25}_D$ + 147.20° (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3500, 2960, 2932, 1719, 1701, 1279, 1160, 1072, 840 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 6.58 (d, 1 H, *J* = 1.90 Hz), 6.24 (dt, 1 H, *J* = 9.69, 2.35 Hz), 5.82 (dd, 1 H, *J* = 15.01, 11.21 Hz), 5.72 (dd, 1 H, *J* = 9.91, 1.74 Hz), 5.61 (dd, 1 H, *J* = 15.01, 9.69 Hz), 5.55 (dd, 1 H, *J* = 9.91, 2.57 Hz), 5.24 (t, 1 H, *J* = 6.99 Hz), 5.19–5.12 (m, 1 H), 4.70 (s, 1 H), 4.54 (d AB q, 2 H, J_{AB} = 13.72 Hz, $\Delta\nu_{AB}$ = 97.78 Hz, *J* = 2.35 Hz), 4.18 (d, 1 H, *J* = 2.07 Hz), 3.88–3.81 (m, 1 H), 3.74 (s, 3 H), 3.59 (d, 1 H, *J* = 8.59 Hz), 3.47 (s, 3 H), 3.41 (dd, 1 H, *J* = 9.90, 1.74 Hz), 3.5 (dd, 1 H, *J* = 9.65, 2.07 Hz), 2.76–2.71 (m, 1 H), 2.38–2.17 (m, 4 H), 2.01–1.99 (m, 2 H), 1.53 (s, 3 H), 1.49–1.40 (m, 4 H), 1.21–1.18 (m, 1 H), 1.21 (d, 3 H, *J* = 7.25 Hz), 1.16 (s, 9 H), 0.92 (t, 3 H, *J* = 7.41 Hz), 0.90 (d, 3 H, *J* = 7.29 Hz), 0.88 (d, 3 H, *J* = 6.81 Hz), 0.79 (d, 3 H, *J* = 6.99 Hz), 0.78 (s, 9 H), −0.08 (s, 3 H), −0.09 (s, 3 H); MS (20 eV) 521 ($M^+ - C_{17}H_{23}O_5$), 435 (521 − $C_5H_{10}O$), 419 (521 − $(CH_3)_3CCO_2H$), 221 (base peak).

Conjugated A_{1a} Seco Acid 51, A solution of 11 mg (0.013 mmol) of A_{1a} seco ester pivalate **50** in 2.5 mL of 4:1 MeOH–H_2O was treated with 5 mg of LiOH. The reaction was stirred at room temperature for 24 h and was then poured into 3 mL of H_2O and carefully acidified to pH 3 with 0.5 N HCl. The aqueous phase was extracted with 3 additional portions of CH_2Cl_2. The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure to give 9.0 mg (95%) of seco acid **51** as a colorless, crystalline foam, identical in all respects with an authentic sample prepared by degradation of avermectin A_{1a} by the procedure of Hanessian: $[\alpha]^{25}_D$ +199.66 (*c* 4.47, $CHCl_3$); IR ($CHCl_3$) 3490, 2980, 2930, 1695, 1460, 1380 cm^{-1}; NMR ($CDCl_3$) δ 6.58 (d, 1 H, *J* = 1.9 Hz), 6.26 (ddd, 1 H, = 10.6, 2.4, 2.4, Hz), 5.74 (dd, 1 H, *J* = 9.9, 1.7 Hz), 5.72 (dd, 1 H, *J* = 13.6, 10.6 Hz), 5.60 (dd, 1 H, *J* = 13.6, 8.8 Hz), 5.54 (dd, 1 H, *J* = 9.9, 2.4 Hz), 5.18–5.21 (m, 1 H), 4.62 (dd, 1 H, *J* = 13.9, 2.5 Hz), 4.52 (dd, 1 H, *J* = 13.9, 2.4 Hz), 4.38–4.30 (m, 1 H), 4.17 (d, 1 H, *J* = 2.1 Hz), 3.84 (br s, 1 H), 3.84–3.79 (m, 1 H), 3.47 (s, 3 H), 3.44 (dd, 1 H, *J* = 10.0, 1.9 Hz), 3.14 (dd, 1 H, *J* = 9.7, 2.2 Hz), 2.79–2.69 (m, 1 H), 2.40–2.00 (m, 8 H), 1.62–1.55 (m, 1 H), 1.45 (br s, 3 H), 1.46–1.36 (m, 2 H), 1.21 (d, 3 H, *J* = 7.2 Hz), 1.04 (d, 3 H, *J* = 6.9 Hz), 0.93 (s, 9 H), 0.91 (t, 3 H, *J* = 7.4 Hz), 0.90 (d, 3 H, *J* = 7.2 Hz), 0.88 (d, 3 H, *J* = 6.8 Hz), 0.02 (s, 3 H), −0.05 (s, 3 H); MS (20 eV) 437, 419, 390.

Conjugated A_{1a} Aglycon, C_{13} TBS 52. A solution of 33 mg (0.045 mmol)[53] of the seco acid **51** in 10 mL of CH_3CN was added very slowly over 2 h to a refluxing solution of TEA (50 mL, 0.358 mmol) and 43 mg (0.16 mmol) of 2-chloro-*N*-methylpyridinium iodide. After the addition was complete, the reaction was cooled to room temperature and 2 mL of CH_2Cl_2 was added and the organic phase was washed once with 10 mL of saturated bicarbonate solution, dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. Chromatography gave 19.8 mg (62%) of conjugated A_{1a} aglycon C_{13} TBS **52** as a crystalline form, which was identical in all respects with an authentic sample prepared by degradation of avermectin A_{1a}: $[\alpha]^{25}_D$ +297.01° (*c* 1.34 $CHCl_3$); IR ($CHCl_3$) 3495 (br), 2960, 2930, 2860, 1695, 1460, 1375 cm^{-1}; NMR ($CDCl_3$) δ 6.13 (ddd, *J* = 10.7, 24, 24 Hz), 6.12 (d, 1 H, *J* = 2 Hz), 5.76 (dd, 1 H, *J* = 9.8, 1.71 Hz), 5.73 (dd, 1 H, *J* = 15.1, 9.4 Hz), 5.16 (dd, 1 H, *J* = 15.1, 10.7 Hz), 5.57 (dd, 1 H, *J* = 9.8, 2.6 Hz), 5.45–5.38 (m, 1 H), 5.24–5.20 (m, 1 H), 4.82 (s, 1 H), 4.57 (dd, 1 H, *J* = 14.2, 25 Hz), 4.50 (dd, 1 H, *J* = 14.2, 2.5 Hz), 4.19 (d, 1 H, *J* = 2.1 Hz), 3.92–3.85 (m, 1 H), 3.88–3.85 (m, 1 H), 3.48 (dd, *J* = 9.0, 1.7 Hz), 3.47 (s, 3 H), 3.16 (dd, 1 H, *J* = 9.5, 2.0 Hz), 2.85–2.80 (m, 1 H), 2.43–2.37 (m, 1 H), 2.30–2.18 (m, 3 H), 2.0–1.84 (m, 1 H), 1.84–1.82 (m, 1 H), 1.65–1.42 (m, 5 H), 1.42 (br s, 3 H), 1.18 (d, 3 H, *J* = 7.2 Hz), 1.06 (d, 3 H, *J* = 6.6 Hz), 0.95 (s, 9 H), 0.92 (t, 3 H, *J* = 7.4 Hz), 0.91 (d, 1 H, *J* = 7.2 Hz), 0.89 (d, 1 H, *J* = 6.8 Hz), 0.04 (s, 3 H), –0.05 (s, 3 H); MS (20 eV) 712 (M^+), 694 (M^+ – 18), 221 (base peak); HRMS (EI) calcd for $C_{41}H_{64}O_8Si$ 712.4372, found 712.4153.

[4*S*,6*R*,13*S*,25*R*(*S*)]-2,3,22,23-Tetradehydro-28-deoxy-6,28-epoxy-3,4-dihydro-13-hydroxy-25-(1-methylpropyl)milbemycin *B* (53). To a solution of 30 mg (0.042 mmol)[53] of silyl ether **52** in 2.0 mL of anhydrous THF at room temperature was added 169 μL of tetrabutylammonium fluoride (1.0 M in THF), and the resulting mixture was stirred at room temperature for 2 h. The mixture was diluted with H_2O, extracted with ether, dried ($MgSO_4$), and concentrated. Flash chromatography (1:2 ethyl acetate–hexane) gave 21.7 mg (87%) of the alcohol **53**, which was homogeneous by TLC and spectroscopic analysis: $[\alpha]^{25}_D$ +358.48° (*c* 0.92, $CHCl_3$); IR ($CHCl_3$) 3500, 3010, 2960, 2942, 1695, 1459, 1378, 1251, 1172, 1110, 1070, 1000 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 6.14–6.11 (m, 2 H), 5.72 (dd, 1 H, *J* = 9.86 , 1.68 Hz), 5.74–5.72 (m, 2 H), 5.56 (dd, 1 H, *J* = 9.86, 2.58 Hz), 5.35–5.29 (m, 2 H), 4.80 (br s, 1 H), 4.54 (d AB q, 2 H, J_{AB} = 14.27 Hz, $\Delta\nu_{AB}$ = 29.40 Hz, *J* = 2.47 Hz), 4.18 (d, 1 H, *J* = 1.99 Hz), 3.97 (br s, 1 H), 3.91–3.90 (m, 1 H), 3.47 (s, 3 H), 3.45 (dd, 1 H, *J* = 8.20, 1.64 Hz), 3.16 (dd, 1 H, *J* = 9.55, 1.99 Hz), 2.63–2.60 (m, 1 H), 2.59–2.47 (m, 1 H), 2.41–2.38 (m, 2 H), 2.29–2.24 (m, 2 H), 1.97–1.93 (m, 1 H), 1.86–1.83 (m, 1 H), 1.66–1.58 (m, 2 H), 1.47 (s, 3 H), 1.44–1.23 (m, 3 H), 1.17 (d, 3 H, *J* = 7.26 Hz), 1.16 (d, 3 H, *J* = 6.95 Hz), 0.96 (t, 3 H, *J* = 7.33 Hz), 0.91 (d, 3 H, *J* = 7.52 Hz), 0.88 (d, 3 H, *J* = 6.74 Hz); MS (20 eV) 599 (M^+ + 1), 598 (M^+), 305 (base peak); HRMS (EI) calcd for $C_{35}H_{50}O_8$ 598.3507, Found 598.3528.

2-*epi*-A_{1a} Aglycon 54. To a solution of 50 mg (0.084 mmol)[53] of enoate **53** in 1.0 mL of anhydrous THF at –78 °C was added 560 μL of lithium diisopropylamide (1.5 M in cyclohexane). After the reaction mixture had stirred for 15 min at –78 °C, 2.0 mL of a 1:1 mixture of THF and 1.0 N HCl was added, and the solution was warmed to ambient temperature. The mixture was extracted three times with ether, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 1:4 ethyl acetate–hexane) gave 35.3 mg (71%) of 2-*epi*-A_{1a} aglycon **54** and 13.1 mg (26%) of the recovered enoate **53**. Analytical data for 2-*epi*-A_{1a} aglycon **54**: $[\alpha]^{25}_D$ +209.66° (*c* 2.07, $CHCl_3$); IR ($CHCl_3$) 3600, 3520, 1700, 1380, 1189, 999 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 5.92–5.91 (m, 1 H), 5.77 (dd, 1 H, *J* = 9.89, 1.63 Hz), 5.78–5.76 (m, 3 H), 5.57 (dd, 1 H, *J* = 9.89, 2.49 Hz), 5.48–5.43 (M, 1 H), 5.29–5.26 (m, 1 H), 4.41 (d, 1 H, *J* = 2.28 Hz), 4.39 (d AB q, 2 H, J_{AB} = 13.27 Hz, $\Delta\nu_{AB}$ = 210.05 Hz, *J* = 2.20 Hz), 4.17 (s, 2 H), 3.99 (br s, 1 H), 3.93–3.90 (m, 1 H), 3.83–3.80 (m, 1 H), 3.51 (s, 3 H), 3.47 (dd, 1 H, *J* = 9.96, 1.52 Hz), 3.16–3.14 (m, 1 H), 2.48–2.46 (m, 1 H), 2.34–2.22 (m, 3 H), 1.91 (ddd, 1 H, *J* = 12.05, 4.73, 1.58 Hz), 1.87 (s, 3 H), 1.83–1.79 (m, 1 H), 1.69–1.58 (m, 4 H), 1.50 s, 3 H), 1.12–1.11 (m, 1 H), 1.16 (d, 3 H, *J* = 6.92 Hz), 0.96 (t, 3 H, *J* = 7.37 Hz), 0.92 (d, 3 H, *J* = 7.23 Hz), 0.89 (d, 3 H, *J* = 6.70 Hz); MS (20 eV) 598 (M^+), 151 (base peak).

Avermectin A_{1a} Aglycon 55. A mixture of 28 mg (0.047 mmol) of 2-*epi*-avermectin A_{1a} aglycon **54** and 1.0 g of imidazole in 4.0 mL of dry benzene was heated at reflux for 1.5 h. The reaction mixture was poured into 0.1 N HCl, extracted three times with ether, dried over $MgSO_4$, and concentrated. Flash chromatography (elution with 1:2 ethyl acetate–hexane) gave 26.5 mg (95%) of a mixture of 2-*epi*-avermectin A_{1a} aglycon **54**, avermectin A_{1a} aglycon **55**, and conjugated avermectin A_{1a} aglycon **53**. Separation of this mixture via preparative thin-layer chromatography (two elutions with 30:70 ethyl acetate–hexane) yielded 5.9 mg (21%) of **53**, 9.1 mg (33%) of **54**, and 8.9 mg (32%) of avermectin A_{1a} aglycon **55**. The avermectin A_{1a} aglycon so produced was spectroscopically (500-MHz NMR, IR, MS) identical with the material derived from degradation of avermectin A_{1a}.

Glycal 59. A cold (–78 °C) solution of 758 mg of pyrone **58** (4.45 mmol) and 1.6 g (4.45 mmol) of $CeCl_3$,7H2O in 75 mL of 2:1 methylene chloride–ethanol was treated with a solution of $NaBH_4$ in ethanol (185 mg, 4.9 mmol in 20 mL ethanol). The addition took approximately 20 min. The reaction was allowed to warm slowly to 0 °C and quenched by the addition of brine and pH 7 buffer. Extraction with CH_2Cl_2 followed by chromatography gave 703 mg (92%) of alcohol **59** as a clear, colorless oil: $[\alpha]^{25}_D$ –40.55° (*c* 0.93, $CHCl_3$); IR (neat) 3400 (br), 2980, 2940, 2880, 1740, 1650 cm^{-1}; NMR ($CDCl_3$) δ 6.37 (dd, 1 H, *J* = 6.1, 1.5 Hz), 4.81 (dd, 1 H, J = 5.9, 2.5 Hz), 4.76 (dd, 1 H, *J* = 9.4, 6.8 Hz), 4.29 (m, 1 H), 3.98 (dq, 1 H, *J* = 9.6, 6.4 Hz), 2.49 (d, 1 H, *J* = 5.8 Hz, OH), 2.15 (s, 3 H), 1.31 (d, 3 H, *J* = 6.4 Hz); MS (20 eV) 172, 154 (M^+ – 18) 112 (M^+ – ACOH), 97 (base peak); HRMS (CI) calcd for $C_8H_{13}O_4$ (M^+ + 1), 173.0813 found 173.0816.

Glycal Methyl Ether 60. A solution of alcohol **59** (422 mg, 2.45 mmol) in dry ethyl ether was treated with 1.7 g (7.36 mmol) of Ag_2O and 1.04 g (7.36 mmol) of MeI. The resulting black suspension was stirred vigorously for 48 h, at room temperature. The reaction mixture was then filtered and the filter cake was washed several times with anhydrous ether, and the combined ether washings were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography of the residue gave 416 mg (91%) of methyl ether **60** as a colorless oil: $[\alpha]^{25}_D$ +18.6° (*c* 1.02, $CHCl_3$); IR (neat) 2990, 2940, 2880, 2825, 1745, 1650, 1455, 1380 cm^{-1}; NMR ($CDCl_3$) δ 6.4 (dd, 1 H, *J* = 6.2, 1.4 Hz), 5.03 (dd, 1 H, *J* = 7.4, 5.8 Hz), 4.85 (dd, 1 H, *J* = 6.2, 3.0 Hz), 4.06 (dd 1 H, *J* = 7.4, 6.7 Hz), 3.90 (m, 1 H), 3.35 (s, 3 H), 2.11 (s, 3 H), 1.30 (d, 3 H, *J* = 6.6 Hz); MS (20 eV) 126 (M^+ – AcOH), 111, 87 (base peak); HRMS (CI) calcd for $C_5H_{15}O_4$ (M^+ + 1) 187.0971, found 187.0984. **L-Oleandral (61).** A solution of glycal **60** (142 mg, 0.763 mmol) in 10 mL of MeOH was treated with a catalytic amount of K_2CO_3 at room temperature. The reaction was stirred at room temperature for 5 h and quenched by being poured into 30 mL of saturated $NaHCO_3$. The product was isolated by extraction (4 × 20 mL) with methylene chloride. The organics was dried over anhydrous $MgSO_4$, filtered, and concentraed at reduced pressure. Chromatography of the residue on silica gel (40% ether pentane) gave 105 mg of alcohol **61** (96%) as a clear, colorless oil: $[\alpha]^{25}_D$ +53.80° (*c* 1.63, $CHCl_3$); IR (neat) 3420 (br), 2970, 2930, 2890, 2830 cm^{-1}; NMR ($CDCl_3$) δ 6.34 (dd, 1 H, *J* = 6.11, 1.4 Hz), .83 (dd, 1 H, *J* = 6.1, 2.1 Hz), 3.82–3.95 (m, 2 H), 3.55 (ddd, 1 H, *J* = 10.7, 7.1, 3.6 Hz), 3.41 (s, 3 H), 2.64 (br s, 1 H), 1.39 (d, 3 H, *J* = 63 Hz); MS (20 eV) 145, (M^+ – 1, 7.0), 144 (M^+), 87 (base peak); HRMS (CI), calcd for $C_7H_{12}O_3$ 144.0786, found 144.0788.

Methyl Oleandroside (62). A solution of alcohol **61** (100 mg, 0.69 mmol) in 3 mL of anhydrous MeOH at 0 °C was treated with 123 mg (0.69 mmol) of NBS. TLC analysis indicated that the reaction was complete within 5 min. The reaction was quenched by the addition of ca. 10 mL of pH 7 buffer and extracted with 4 × 5 mL portions of CH_2Cl_2; the organics were dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. The crude material was dissolved in 4 mL of dry toluene and treated with 200 mg (0.69 mmol) of $^nBu_3SnH$ and a catalytic amount of AIBN. This mixture was heated to reflux for 5 min under argon, at which time TLC analysis indicated completion. The solution was cooled to room temperature and concentrated in vacuo; chromatography (hexanes → 30% EtOAc-hexanes) gave 129 mg of material still contaminated with $^nBu_3SnX$-decomposition products. This material was dissolved in 10 mL of acetonitrile and extracted 3 × 2 mL of hexanes. Concentration gave 115 mg (95%) of a 1.55:1 mix of α- and β-methyl glycosides, which were easily separable by the same chromatography as above.

Analytical data for the α-methyl glycoside **62a**: $[\alpha]^{25}_D$ –70.43° (*c* 1.15, $CHCl_3$); IR (neat) 3450 (br), 2940, 2900, 2835, 1450, 1375 cm^{-1}; NMR ($CDCl_3$) δ 4.78 (dd, 1 H, *J* = 3.3, 0.7 Hz), 3.65 (dq, 1 H, *J* = 9.1, 6.2, Hz), 3.50 (ddd, 1 H, *J* = 11.4, 8.9, 4.9 Hz), 3.38 (s, 3 H), 3.33 (s, 3 H), 3.6 (ddd, 1 H, *J* = 9.1, 8.9, 2.1 Hz), 2.56 (d, 1 H, *J* = 2.1 Hz), 2.27 (ddd, 1 H, *J* = 12.8, 4.9, 1.3 Hz), 1.51 (ddd, 1 H, *J* = 12.8, 11.4, 3.7 Hz), 1.31 (d, 3 H, *J* = 6.2 Hz); MS (20 eV) 145 (M^+ – OMe), 74, (base peak). Anal. Calcd for $C_8H_{16}O_4$: C, 54.53; H, 9.14. Found: C, 54.15: H, 8.90.

Analytical data for β-methyl glycoside **62b**: mp 75–78 °C; $[\alpha]^{25}_D$ +58.40° (*c* 1.25, CH_3Cl_3); IR (CH_3Cl_3) 3580, 3450, 3020, 2940, 1450, 1385 cm^{-1}; NMR ($CDCl_3$) δ 4.38 (dd, 1 H, *J* = 9.6, 2.0 Hz), 3.50 (s,

(53) The material was replenished at this stage with compound provided by degradation of naturally occuring avermectin. cf.: Hanessian, S.; Ugolini, A.; Hodges, P.; Dube, D. *Tetrahedron Lett.* **1986**, *27*, 2699.

3 H), 3.39 (s, 3 H), 3.10–3.39 (m, 3 H), 2.56 (d, 1 H, J = 1.7 Hz), 2.34 (ddd, 1 H, J = 12.2, 4.3, 2.0 Hz), 1.40 (ddd, 1 H, J = 12.2, 9.6, 2.1 Hz), 1.36 (d, 3 H, J = 6.1 Hz). Anal. Calcd for $C_8H_{16}O_4$: C, 54.53: H, 9.14. Found: C, 54.52; H, 8.94.

Iodo Disacharride 63. A solution of glycal **60** (220 mg, 1.55 mmol) and 290 mg of α-methyl glycoside **62a** (290 mg, 1.64 mmol) in 5 mL of dry acetonitrile at 0 °C was treated with 360 mg (1.6 mmol) of *N*-iodosucciniinide. After 0.5 h the reaction was diluted with CH_2Cl_2 (20 mL) and poured into 30 mL of saturated $NaHSO_3$ (aqueous). The layers were separated, and the aqueous phase was extracted with 3 × 15 mL portions of CH_2Cl_2. The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. Chromatography of the residue gave 377 mg (65%) of the $C_{2'}$-iodo disacharride **63** as a single stereoisomer: mp 118–119 °C; $[\alpha]^{25}_D$ −88.73° (*c* 2.77, $CHCl_3$); IR ($CHCl_3$) 3000, 2935, 2900, 2830, 1740, 1450, 1375 cm^{-1}; NMR ($CDCl_3$) δ 5.57 (d, 1 H, J = 1.7 Hz); 5.01 (dd, 1 H, J = 9.7, 8.9 Hz), 4.74 (d, 1 H, J = 2.7 Hz), 4.54 (dd, 1 H, J = 4.1, 1.7 Hz), 3.94 (dq, 1 H, J = 9.7, 6.3 Hz), 3.64 (dq, 1 H, J = 9.4, 63 Hz), 3.57 (ddd, 1 H, J = 11.4, 8.7, 4.9 Hz), 3.35 (s, 3 H), 3.34 (s, 3 H), 3.32 (s, 3 H), 3.19 (app t, 1 H, J = 9.4, 8.7 Hz), 2.91 (dd, 1 H, J = 8.9, 4.1 Hz), 2.27 (ddd, 1 H, J = 13.0, 5.1, 1.4 Hz), 2.08 (s, 3 H), 1.50 (ddd, 1 H, J = 13.0, 11.4, 3.6 Hz), 1.28 (d, 3 H, J = 6.3 Hz), 1.19 (d, 3 H, J = 6.3 Hz). Anal. Calcd for $C_{17}H_{29}O_8$: C, 41.82; H, 5.98. Found: C, 41.87; H, 5.98.

Phenylthio Iodo Disaccharride 64. A solution of C2′-iodo disacharide **63** (500 mg, 1.02 mmol) in 8 mL of dichloroethane was treated with 560 mg (3.07 mmol) of (trimethylsilyl)thiophenol, 650 mg (2.04 mmol) of ZnI_2, and 370 mg (1.02 mmol) of TBAI. The mixture was then heated to reflux for 1 h. The reaction was cooled to room temperature and quenched by diluting with 30 mL of CH_2Cl_2 and by being poured into 80 mL of ice-cold 0.5 N NaOH. The aqueous phase was extracted with 3 additional 30-mL portions of CH_2Cl_2, and the combined organics were dried over $MgSO_4$, filtered, and concentrated at reduced pressure. Chromatography of the residue on silica gel (15% ethyl acetate–hexanes) gave 473 mg of a 2:1 mix of α + β phenylthio anomers **64**, which was separable by chromatography. Analytical data for the α anomer: $[\alpha]^{25}_D$ −178.6 (*c* 2.52, $CHCl_3$); IR (neat) 2980, 2940, 2830, 1750, 1575, 14.80, 1450 cm^{-1}; NMR 7.40–7.5 (m, 2 H), 7.22–7.35 (m, 3 H), 5.58–5.64 (m, 2 H), 5.03 (dd, 1 H, J = 9.5, 8.8 Hz), 4.58 (dd, 1 H, J = 4.0, 1.9 Hz), 4.18 (dq, 1 H, J = 9.2, 6.2 Hz), 3.97 (dq, 1 H, J = 9.5, 6.2 Hz), 3.61 (ddd, J = 11.1, 8.5, 4.7 Hz), 3.41 (s, 3 H), 3.38 (s, 3 H), 3.25 (dd, 1 H, J = 9.2, 8.5 Hz), 2.95 (dd, 1 H, J = 8.8, 4.1 Hz), 2.51 (dd, 1 H, J = 13.1, 4.7 Hz), 2.10 (s, 3 H), 1.95 (ddd, 1 H, J = 13.1, 11.1, 4.0, Hz), 1.29 (d, 3 H, J = 62 Hz), 1.21 (d, 3 H, J = 62 Hz); MS (20 eV) 457 (M^+ − 109). Anal. Calcd for $C_{22}H_{31}O_7SI$: C 46.65; H, 5.51; S, 5.66. Found: C; 46.90; H, 5.54; S, 6.09.

Iodo Disacharride Glycal 65. A solution of **64** (473 mg, 0.83 mmole) in 40 mL of CH_2Cl_2 at 0 °C was treated with 170 mg of MCPBA (85%) in 1 portion and stirred at 0 °C for 10 min. The reaction was poured into 50 mL of saturated $NaHCO_3$, and the layers were separated. The aqueous layer was extracted with 3 additional 30-mL portions of CH_2Cl_2, and the combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude mixture of sulfoxides was immediately dissolved in 120 mL of dry benzene and heated to reflux for 0.5 h. The reaction was cooled to room temperature and poured into 50 mL of saturated $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with 3 × 40 mL of CH_2Cl_2. The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. Chromatography of the residue (20% ethyl acetate–hexanes gave 274 mg (72% for two steps) of $C_{2'}$-iododisacharride glycal **65** as a clear, colorless oil: $[\alpha]^{25}_D$ −56.25° (*c* 0.8 $CHCl_3$); IR (neat) 2980, 2940, 2910, 2830, 1755, 1650, 1455, 1375 cm^{-1}; NMR ($CDCl_2$) δ 6.37 (dd, 1 H, J = 6.1, 6.1 Hz), 5.61 (d, 1 H, J = 2.0 Hz), 5.02 (dd, 1 H, J = 9.1 Hz), 4.85 (dd, 1 H, J = 6.1, 2.5 Hz), 4.51 (dd, 1 H, J = 4.0, 1.7 Hz), 3.87–4.02 (m, 3 H), 3.61 (dd, 1 H, J = 8.7, 6.4 Hz), 3.37 (s, 3 H), 3.36 (s, 3 H), 2.9 (dd, 1 H, J = 8.9, 40 Hz), 2.10 (s, 3 H), 1.38 (d, 3 H, J = 6.4 Hz), 1.22 (d, 3 H, J = 6.3 Hz); MS (20 eV) 425 (M^+ − MeOH), 380 (M^+ − 86), 313, 221 (base peak); HRMS (CI) calcd for $C_{16}H_{26}O_8I$ 457.0722 (M^+ + 1), found 457.0732.

Disacharride Glycal 66. A solution of 326 mg (0.715 mmol) of $C_{2'}$-iodo glycal disacharride **65** in 10 mL of dry benzene was treated with 416 mg (1.4 mmol) of $^nBu_3SnH$ and a catalytic amount of AIBN. The mixture was then heated to reflux under argon for 1 h, cooled to room temperature, and concentrated at reduced pressure. The residue was chromatographed on silica gel (5% ethyl acetate–hexanes → 30% ethyl acetate–hexanes) to give 192 mg (81%) of glycal **66** after crystallization from ether–hexanes: mp 82–83 °C; $[\alpha]^{25}_D$ −84.86° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 2980, 2940, 1740, 1650, 1455, 1375 cm^{-1}; NMR (250 mHz, $CDCl_3$) δ 6.38 (dd, 1 H, J = 6.1, 1.5 Hz), 5.41 (dd, 1 H, J = 4.0, 12 Hz), 4.83 (dd, 1 H, J = 6.1, 2.5 Hz), 4.68 (app, t, 1 H, J = 9.5 Hz), 3.89–4.01 (m, 2 H), 3.82 (dq, 1 H, J = 9.5, 6.2, Hz), 3.64 (dd, 1 H, J = 8.6, 6.2 Hz), 3.59 (dd, 1 H, J = 9.5, 5.0 Hz), 3.35 (s, 3 H) 3.34 (s, 3 H), 2.27 (ddd, 1 H, J = 13.2, 5.0, 1.2 Hz), 2.1 (s, 3 H), 1.68 (ddd, J = 13.2, 9.5, 4.0 Hz), 1.38 (d, 3 H, J = 6.3 Hz), 1.16 (d, 3 H, J = 6.2 Hz); MS (20 eV) 299, (M^+ − 31, OMe), 273, 424, 241, 187 (base peak). Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.18; H, 7.92. Found: C, 58.36; H, 8.24.

2′-Iodoavermectin A_{1a} 4″-Acetate (67). A solution of 27 mg (0.083 mmol) of glycal disacharride **66** and 25 mg (0.041 mmol) of avermectin A_{1a} aglycon **55** in 0.20 mL of dry acetonitrile was treated with 19 mg (0.084 mmol) of *N*-iodosuccinimide. After 1 h at room temperature, the reaction was diluted with CH_2Cl_2 (10 mL) and poured into 20 mL of saturated $NaHSO_3$. The layers were separated, and the aqueous phase was extracted with 3 × 10 mL portions of methylene chloride. The combined organics were dried over $MgSO_4$, filtered, and concentrated at reduced pressure. Chromatography (30% ethyl acetate–hexanes) of the residue gave 28.6 mg (64%) of $C_{2'}$ iodoavermectin A_{1a}, $C_{4''}$ acetate (**67**) as a foam: $[\alpha]^{25}_D$ +18.06 (*c* 3.10, $CHCl_3$); IR ($CHCl_3$), 3480 (br), 3010, 2970, 2930, 1738, 1710, 1455, 1375 cm^{-1}; NMR ($CDCl_3$) δ 5.83 (ddd, 1 H, J = 10.7, 2.4, 2.3 Hz), 5.72–5.77 (m, 2 H), 5.68 (dd, 1 H, J = 14.9, 9.4 Hz), 5.55 (dd, 1 H, J = 9.8, 2.5 Hz), 5.35–5.45 (m, 2 H), 5.27 (d, 1 H, J = 3.0 Hz), 5.09 (d, 1 H, J = 1.2 Hz), 4.97 (m, 1 H), 4.69 (dd, 1 H, J = 14.4, 2.4 Hz), 4.67 (app t, 1 H, J = 9.4 Hz), 4.63 (dd, 1 H, J = 14.4, 2.3 Hz), 4.49 (dd, 1 H, J = 3.9, 1.5 Hz), 4.16 (s, 1 H), 4.04 (d, 1 H, J = 5.7 Hz), 3.95–4.0 (m, 2 H), 3.90 (dq, 1 H, J = 9.5, 6.3 Hz), 3.95–3.8 (m, 1 H), 3.83 (dq, 1 H, J = 9.6, 6.3 Hz), 3.59 (app t, 1 H, J = 9.6 Hz), 3.51 (s, 3 H), 3.50 (dd, 1 H, J = 9.0, 1.5 Hz), 3.43 (s, 3 H), 3.37 (s, 3 H), 3.34 (m, 1 H), 2.90 (dd, 1 H, J = 8.2, 3.9 Hz), 2.51–2.55 (m, 1 H), 2.52–2.40 (m, 5 H), 2.10 (s, 3 H), 2.01 (ddd, J = 12.1, 4.8, 1.5 Hz), 1.81 (br s, 3 H), 1.72–1.80 (m, 1 H), 1.70–1.45 (m, 5 H), 1.50 (br s, 3 H), 1.30 (d, 3 H, J = 6.2 Hz), 1.17 (d, 3 H, J = 7.0 Hz), 1.15 (d, 3 H, J = 6.2 Hz), 0.96 (d, 3 H, J = 7.4 Hz), 0.92 (d, 3 H, J = 6.4 Hz), 0.91 (d, 3 H, J = 7.3 Hz).

Deiodination: Avermectin A_{1a} 4″-Acetate (68). A solution of 2′-iodoavermectin A_{1a} 4″-acetate (**67**) (12.3 mg, 0.0116 mmol) in 4 mL of toluene was treated with 18 mg (0.061 mmol) of tri-*n*-butyltin hydride and a catalytic amount of AIBN. The mixture was heated to reflux for 10 min, cooled to room temperature, and concentrated at reduced pressure. Chromatography (0–15% ethyl acetate–hexanes) gave 8.4 mg (78%) of avermectin A_{1a} 4″-acetate **68**, which was identical with an authentic sample prepared by acetylation of avermectin A_{1a} (500-MHz NMR, IR).

Avermectin A_{1a} (1). A cold (78 °C) solution of 12.1 mg (0.013 mmol) of avermectin A_{1a} $C_{4''}$ acetate (**68**) in 0.5 mL of THF was treated with 26 μL (0.026 mmol) of a 1 M solution of $LiEt_3BH$ in THF; the reaction was stirred at −78 °C for 3 h and quenched by the rapid addition of 3 mL of pH 7 buffer, followed by 3 mL of CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with 3 × 2 mL of CH_2Cl_2. The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. Chromatography of the residue (1:1 ethyl acetate–hexanes) gave 11.2 mg (97%) of avermectin A_{1a} (**1**), which was identical with an authentic sample (500-MHz NMR, IR).

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