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Studies on the synthesis of the quartromicins: partial stereochemical assignment of quartromicins A_3 and D_3 and diastereoselective synthesis of the *endo*- and *exo*-spirotetronate subunits☆

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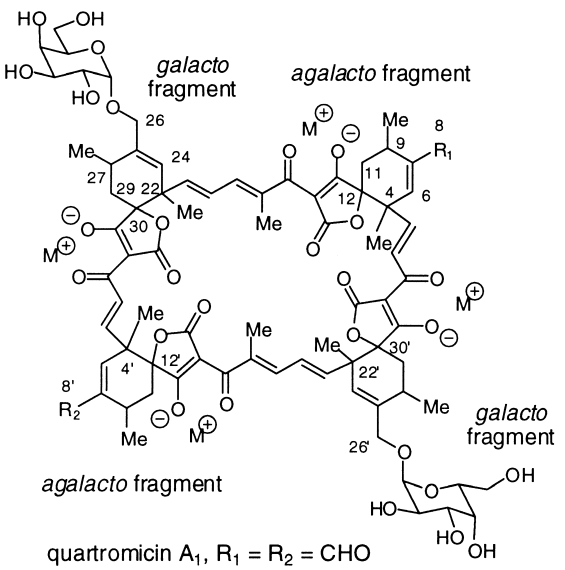
Abstract—A partial stereochemical assignment of quartromicins A_3 and D_3 is presented, along with diastereoselective syntheses of the *endo*- and *exo*-spirotetronates **1** and **2**, corresponding to the *galacto* and *agalacto* fragments of the proposed quartromicin stereostructure. The key steps of these syntheses are highly enantio- and diastereoselective Lewis acid catalyzed Diels–Alder reactions of 1,1,3,4-tetrasubstituted diene **24**. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The quartromicins[1–3] are a structurally unique group of spirotetronate natural products first isolated from *actinomycetes* species in 1991. The quartromicins possess a novel 32-membered carbocyclic structure consisting of four spirotetronic acid units connected by enone linkers in a head-to-tail fashion. Quartromicins A_1, A_3, D_1 and D_3 are C_2 symmetric and contain two distinct spirotetronate subunits.[1] Two of the subunits contain α-galactopyranosyl residues connected to the C(26) and C(26′)-hydroxymethyl groups; we refer to these as the 'galacto fragments'. The remaining members of this class, quartromicins A_2 and D_2, differ from the C_2 symmetric members in that the two *agalacto* subunits (the subunits lacking galactopyranosyl units) have different oxidation states for the C(8) and C(8′) carbons. Reduction of quartromicins A_1 and A_2, or D_1 and D_2, with $NaBH_4$ provide quartromicins A_3 and D_3, respectively, thereby confirming that all members of this family have the same carbon skeleton.

The quartromicins possess a range of biological properties, including activity against several important viral targets including herpes simplex virus (HSV) type 1,[2] influenza,[2] and human immunodeficiency virus (HIV).[3] An additional member of the quartromicin family was isolated by scientists at Eli Lilly, and was reported to inhibit phospholipase A_2 (PLA_2).[4] PLA_2 is a human enzyme that catalyzes the hydrolysis of membrane phospholipids in the synthesis of eicosanoids, an important step in the inflammatory response associated with arthritis, psoriasis, asthma, and atherosclerosis.[5,6] However, structural information about the Eli Lilly isolate has not been reported.



☆ A portion of this work was performed by D. A. Barda at Indiana University.

Keywords: quartromicin stereochemical assignment; spirotetronate antibiotics; Diels–Alder reactions of acyclic (*Z*)-dienes.

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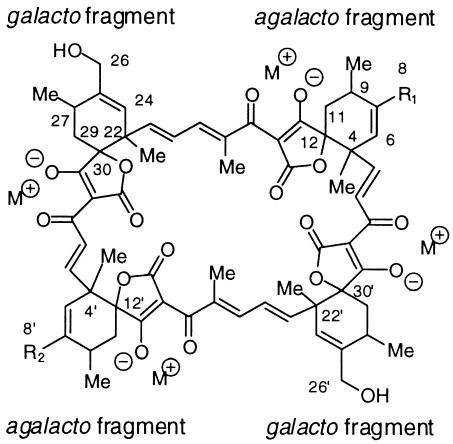
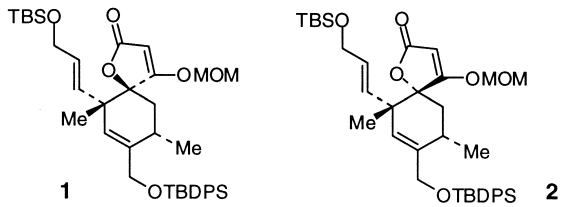


quartromicin D_1, $R_1 = R_2 = CHO$
quartromicin D_2, $R_1 = CHO$, $R_2 = CH_2OH$
quartromicin D_3, $R_1 = R_2 = CH_2OH$
($M^+ = Na^+, K^+, Ca^{++}$)

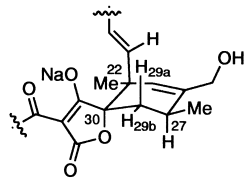


The quartromicins are attractive targets for total synthesis, given their unique structures and interesting biological properties. However, no information on the stereochemistry of the individual spirotetronate substructures, or of their absolute stereochemistry, had been reported prior to the initiation of our studies on this problem. We report herein a partial stereochemical assignment of quartromicins A_3 and D_3, along with highly diastereoselective syntheses of the spirotetronates **1** and **2** that correspond to the *galacto* and *agalacto* fragments of quartromicins A_3 and D_3, respectively. Preliminary accounts of these studies have appeared.[7,8]

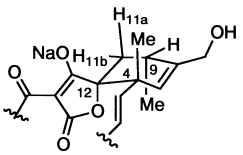
2. Results and discussion

2.1. A partial stereochemical assignment of quartromicins A_3 and D_3

Examination of the published ^{1}H NMR data[1,2] for quartromicins A_3 and D_3 reveals that the two spirotetronate fragments have strikingly different NMR properties. The quaternary methyl groups C(22)-Me and C(4)-Me are in very different chemical environments in the *galacto* (**3**) and *agalacto* fragments (**4**), as indicated by the large differences in chemical shifts (δ 0.83 and δ 1.23, respectively). Most diagnostic, however, is the very different appearance of the ABX patterns for the methylene groups at C(29) and C(11), respectively. In the *galacto* fragment **3**, both H(29a) and H(29b) exhibit coupling constants with H(27) ($J_{29a,27}$=11.0 Hz, $J_{29b,27}$=5.8 Hz), whereas in the *agalacto* fragment **4** the coupling constants $J_{11a,9}$ and $J_{11b,9}$ are 8.6 and 0 Hz, respectively.



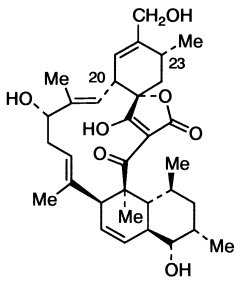
3, *galacto fragment*
H_{29a}: δ 2.04; $J_{29a,27}$ = 11.0 Hz
H_{29b}: δ 1.94; $J_{29b,27}$ = 5.8 Hz
C(22)-Me: δ 0.83
H(27): δ 2.34



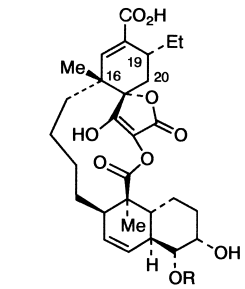
4, *agalacto fragment*
H_{11a}: δ 2.37; $J_{11a,9}$ = 8.6 Hz
H_{11b}: δ 1.54; $J_{11b,9}$ = 0 Hz
C(4)-Me: δ 1.23
H(9): δ 2.58

(NMR spectra were recorded in D_2O)

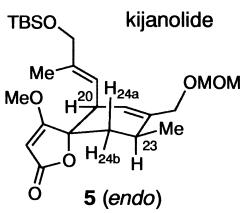
The ^{1}H NMR data for the H(29) and H(11) resonances of quartromicin D_3 are remarkably similar to data we have previously analyzed for the *endo*- and *exo*-spirotetronates prepared in connection with studies on the synthesis of chlorothricolide[9,10] and kijanolide,[11,12] the aglycones of the spirotetronate natural products chlorothricin[13] and kijanimicin.[14,15] Selected ^{1}H NMR data ($CDCl_3$) for the *endo*- and *exo*-spirotetronates **5**[12] and **6**[11] summarized below show that when the C(23)-Me group is equatorial (kijanolide numbering system), $J_{24a,23}$=10.0 Hz and $J_{24b,23}$=6.7 Hz. However, when the C(23)-Me group is axial, as in the *exo*-spirotetronate **6**, $J_{24a,23}$=7.4 Hz and $J_{24b,23}$=0 Hz. The data for **5** are very similar to the coupling constants summarized above for the H(27)–H(29) relationship in the quartromicin galacto fragment **3**, while the data for **6** are very similar to those reported for the H(9)–H(11) coupling constants in the quartromicin *agalacto* fragment **4**. On the basis of these data, we assigned the secondary C(22)-Me and C(9)-Me groups of **3** and **4** as equatorial and axial, respectively.



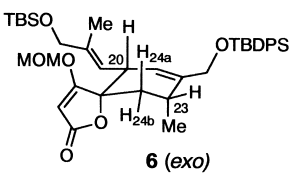
kijanolide



PA-46101 A aglycon



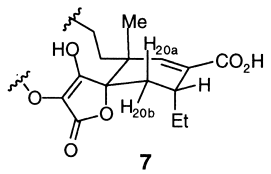
5 (*endo*)
H_{24a}: δ 1.77; $J_{24a,23}$ = 10.0 Hz
H_{24b}: δ1 .84; $J_{24b,23}$ = 6.7 Hz
H_{20}: δ 3.17



6 (*exo*)
H_{24a}: δ 2.28; $J_{24a,23}$ = 7.4 Hz
H_{24b}: δ 1.67; $J_{24b,23}$ = 0 Hz
H_{20}: δ 3.45

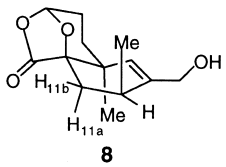
Additional support for the conclusion that if the quartromicin agalacto fragment C(9)-Me group is axial, then $J_{11b,9}$ should be very small derives from NMR data for spirotetronates **7** and **8**. Spirotetronate **7** ($J_{20a,19}$=7.5 Hz; $J_{20b,19}$=0 Hz) is a fragment of the antibiotic PA-46101A, whose structure and stereochemistry are known on the basis

of an X-ray crystal structure analysis.[16] The stereostructure of spiroacetal **8** ($J_{11a,9}$=8.6 Hz; $J_{11b,9}$=0 Hz) was also assigned by X-ray methods.[17]



7

H_{20a}: δ 2.46; $J_{20a,19}$ = 7.5 Hz
H_{20b}: δ 1.90; $J_{20b,19}$ = 0 Hz
C(16)-Me: δ 1.24



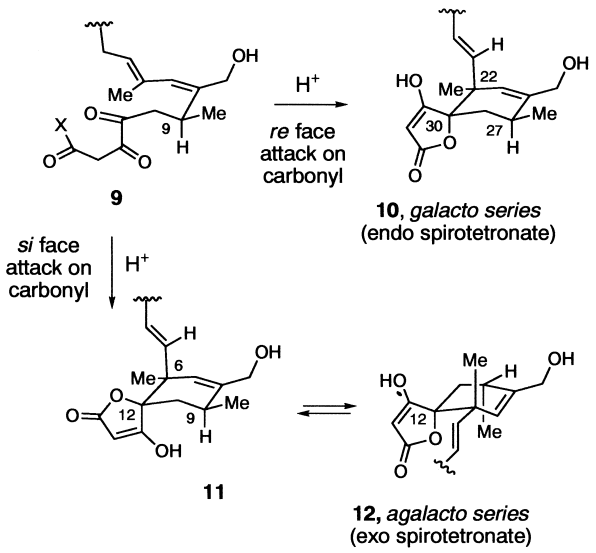
8

H_{11a}: δ 2.47; $J_{11a,9}$ = 8.6 Hz
H_{11b}: δ 1.59; $J_{11b,9}$ = 0 Hz

Insight into the stereochemistry of the C(22)-Me and C(4)-Me groups of the quartromicin *galacto* (**3**) and *agalacto* fragment (**4**) derives from their strikingly different chemical shifts (δ 0.83 and δ 1.23, respectively). The fact that the quaternary methyl group in the PA-46101A spirotetronate **7** (δ 1.24) is virtually identical to that in **4** led us to assign C(9)-Me as axial in the *agalacto* fragment **4**. The considerable upfield chemical shift of the C(22)-Me in the *galacto* fragment **3** compared to C(9)-Me in **4** suggested that this methyl group is equatorial in **3**, and that the striking difference in chemical shift may be attributed to anisotropic shielding of C(22)-Me by the tetronic acid fragment in **3**. This analysis is consistent with the difference in chemical shift of H(20) in the *endo*- and *exo*-spirotetronates **5** (δ 3.17, i.e. H(20)-equatorial) and **6** (δ 3.45, i.e. H(20)-axial).

Based on these data, we have concluded that the two methyl groups are *trans* in both the *galacto* and *agalacto* fragments **3** and **4**. The quartromicin spirotetronates therefore must differ in the stereochemistry of the spirotetronate center. Given the striking similarities of the ^{1}H NMR data for the *agalacto* fragment **4** and the PA-46101A spirotetronate **7**, we have assigned the stereochemistry of the C(12) spirotetronate stereocenter to be as shown in the three-dimensional structure presented for **4**, in which C(12)-O is axial and *trans* to the C(4)-Me and *cis* to the secondary C(9)-Me group. By process of elimination, the stereochemistry of the *galacto* spirotetronate C(30)-stereocenter (see fragment **3**) must have the C(30)-oxygen atom in an axial position, *cis* to C(22)-Me and *trans* to the secondary C(27)-Me group.

Although we have not assigned the absolute stereochemistry of the two spirotetronate sub-structures, consideration of possible biosynthetic sequences enables us to make a tentative assignment of the relative stereochemistry between the quartromicin fragments **3** and **4**. It is attractive to speculate that both spirotetronate units may be derived from a common biosynthetic intermediate such as **9**, in which the stereochemistry of the C(9) or C(27)-methyl groups has already been set in earlier biosynthetic intermediates. It is conceivable that presumed intermediate **9** might undergo a Prins-type cyclization, such that spirotetronates **10** (corresponding to the *galacto* fragment **3**) and **12** (corresponding to the *agalacto* fragment **4**) would then be produced with identical absolute stereochemistry at the carbons bearing the two methyl groups (C(22) and C(27) in **10**, and C(6) and C(9) in **12**), and with the absolute configuration of the C(12) and C(30) spirotetronate centers being opposite in the two structures.



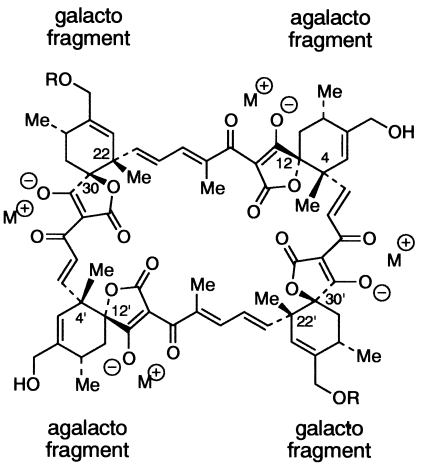
9

10, *galacto series* (endo spirotetronate)

11

12, *agalacto series* (exo spirotetronate)

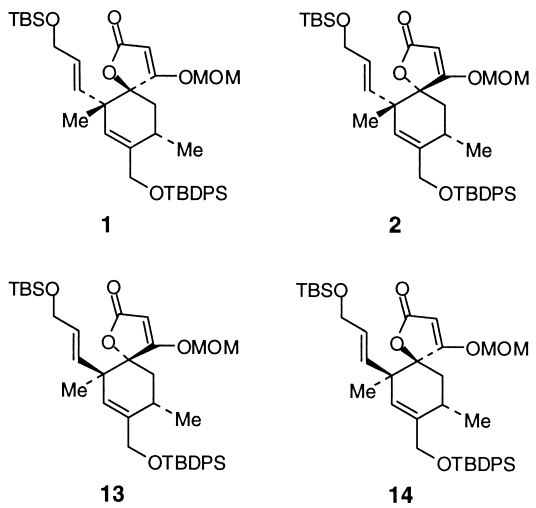
According to this analysis, we propose the stereostructures of quartromicins A_3 and D_3 to be as depicted below. These structures serve as the targets of the synthetic studies described in the following sections of this paper.



quartromicin A_3,
R = α-D-galactosyl
quartromicin D_3, R = H
(M^+ = Na^+, K^+, Ca^{++})

2.2. Synthesis and NMR analysis of all four diastereomers of the quartromicin spirotetronate subunits

In an attempt to verify our stereochemical assignment of the quartromicin A_3 and D_3 *galacto* and *agalacto* spirotetronate subunits, we developed syntheses of all four stereoisomers of the core spirotetronate substructure.[17,18] We initially targeted spirotetronates **1** and **2** since these compounds possess the stereochemistry that we assigned to the quartromicin *galacto* and *agalacto* fragments, but we also wished to gain access to spirotetronates **13** and **14** for comparative spectroscopic analysis.

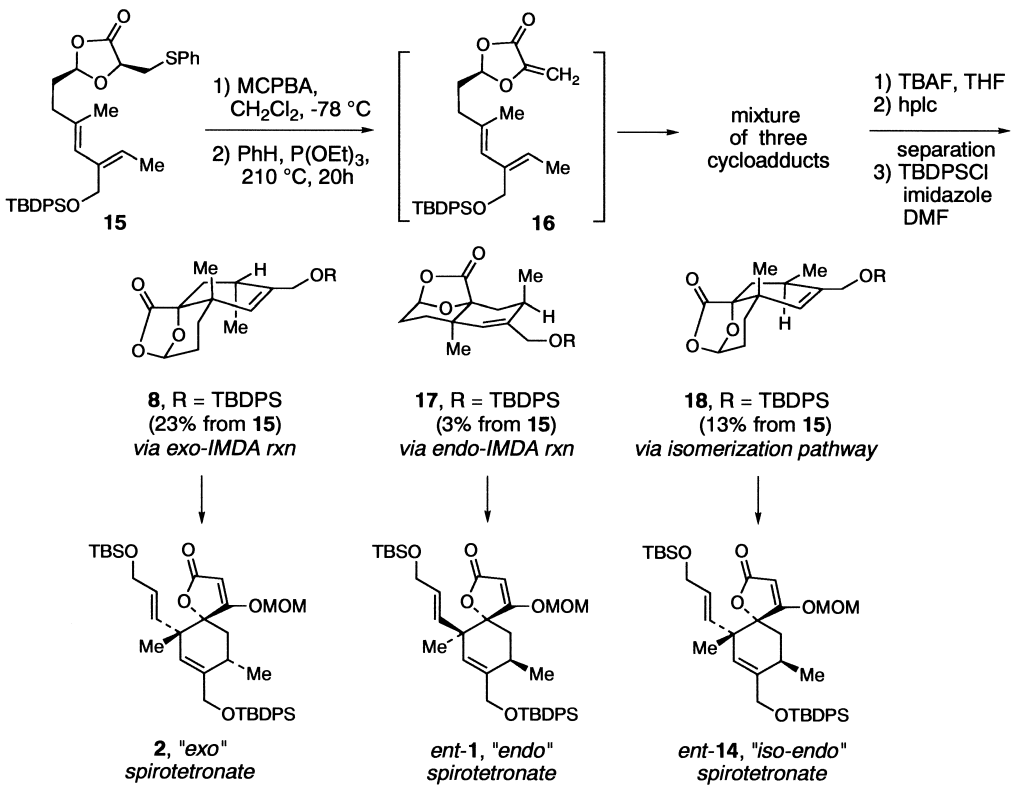


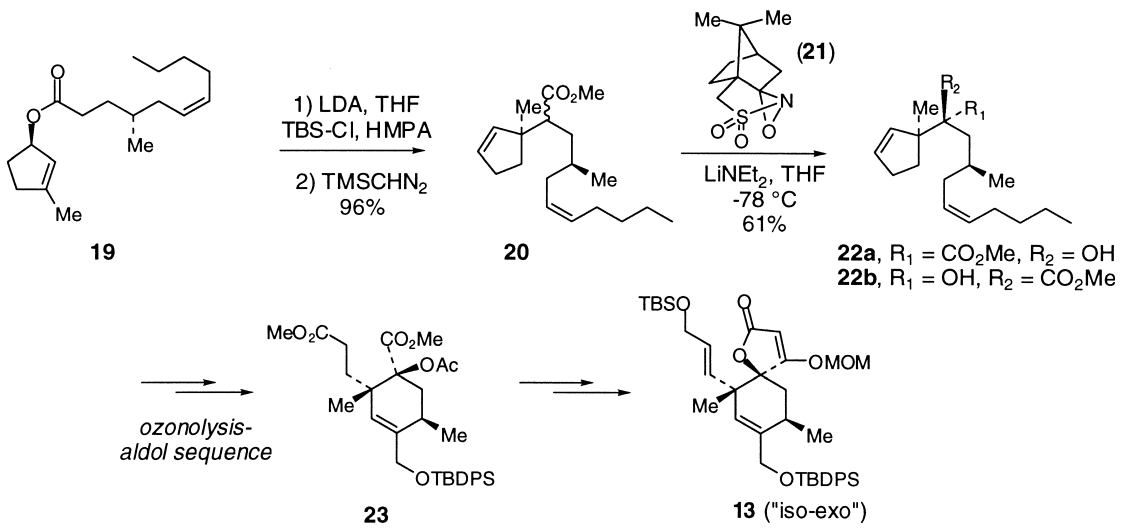
Our first generation strategy for the synthesis of **1** and **2** utilized an intramolecular Diels–Alder reaction of triene **16**, which was generated in situ from the sulfoxide derived from **15**.[17] We had anticipated at the outset that this reaction would provide a mixture of *exo* and *endo* Diels–Alder adducts **8** and **17**, which would then be elaborated to *ent*-**1** and **2**, respectively. In practice, however, the IMDA reaction of **16** provided a mixture of three products **7**, **17** and **18** in 23%, 3% and 13% yields, respectively. The third cycloadduct **18** evidently derives from the IMDA cyclization of an olefin isomer of **16**, as the starting material **15** was isomerically pure at the beginning of the experiment. Olefin isomerizations have previously been observed in IMDA reactions of (*Z*)-dienes.[19,20] Subsequent elaboration of the three cycloadducts provided samples of spirotetronates **2**, *ent*-**1**, and *ent*-**14**.[17,21]

The fact that spirotetronate **2**, corresponding to the *agalacto* fragment of the quartromicins, was first prepared from the *exo*-Diels–Alder adduct **8** prompts us to refer to **2** as an '*exo*' spirotetronate. Similarly, **1** (corresponding to the *galacto* fragment of the quartromicins) is referred to as an '*endo*' spirotetronate, in view of the fact that it was first synthesized from the *endo*-Diels–Alder adduct **17**. By analogy, **14** is an '*iso-endo*' spirotetronate. This nomenclature is also consistent with our subsequent finding that **1** and **2** may be synthesized from products of (formal) *endo*- or *exo*-Diels–Alder reactions of an α-acetoxy acrylate dienophile and a 1,1,3,4-tetrasubstituted diene.[8,22]

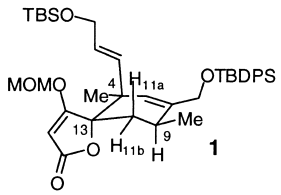
While sufficient quantities of *ent*-**1**, **2**, and *ent*-**14** were prepared for spectroscopic analysis, it was clear that this synthesis was too inefficient for ultimate application to a quartromicin total synthesis. Accordingly, a second generation synthesis was developed in which the stereochemistry of the two methyl centers in the spirotetronate subunits is controlled in early intermediates.[18] The Ireland enolate Claisen rearrangement[23,24] of **19** set the quaternary methyl stereochemistry in **20**. However, the subsequent enolate hydroxylation was poorly selective. Elaboration of **22a** via an ozonolysis-intramolecular aldol sequence provided **23**, which was then elaborated to the fourth spirotetronate diastereomer, the '*iso-exo*' isomer **13**. In fact, all four spirotetronate diastereomers **1**, **2**, **13** and **14** were prepared by this second generation sequence.[21]

Interestingly, ^{1}H NMR analysis of spirotetronate diastereomers **1**, **2**, **13**, and **14** revealed that all four structures

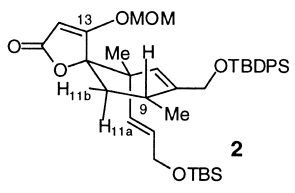




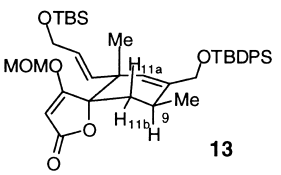
adopt conformations with the two methyl groups in equatorial positions! This conclusion is easily verified by inspection of the coupling constants involving H(9) and H(11); in all cases $J_{11a,9}$=8.3–10.8 Hz and $J_{11b,9}$=6.3–6.8 Hz. The data for these compounds support our earlier conclusion that the C(4)-Me group will be shielded by the tetronate unit if it is in an equatorial position. Indeed, the chemical shifts of the equatorial C(4)-Me groups in **1** and **2** are in the range δ 1.05–1.07, whereas the axial C(4)-Me group appears at δ 1.19–1.27 in diastereomers **13** and **14**.



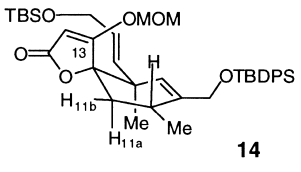
H_{11a}: δ 1.99; $J_{11a,9}$ = 10.8 Hz
H_{11b}: δ 1.73; $J_{11b,9}$ = 6.3 Hz
C(4)-Me: δ1 .07



H_{11a}: δ 2.04; $J_{11a,9}$ = 10.4 Hz
H_{11b}: δ 1.83; $J_{11b,9}$ = 6.6 Hz
C(4)-Me: δ 1.05



H_{11a}: δ 2.00; $J_{11a,9}$ = 10.3 Hz
H_{11b}: δ 1.84; $J_{11b,9}$ = 6.6 Hz
C(4)-Me: δ 1.27



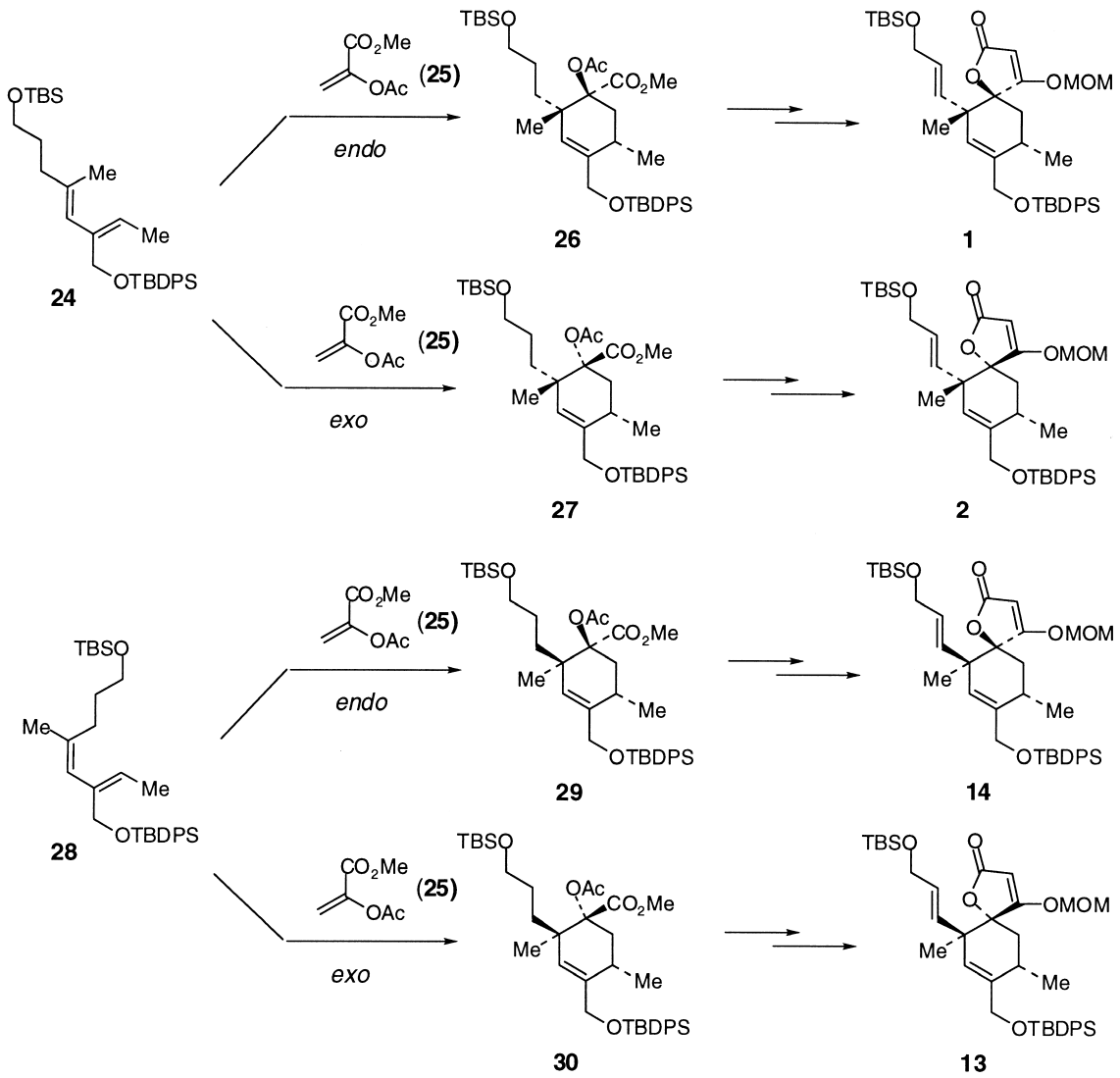
H_{11a}: δ 1.95; $J_{11a,9}$ = 8.3 Hz
H_{11b}: δ 2.08; $J_{11b,9}$ = 6.8 Hz
C(4)-Me: δ1 .19

These NMR data establish that the secondary C(9)-Me group adopts an equatorial position in all four of the synthetic spirotetronates **1**, **2**, **13**, and **14**. Clearly, none of these compounds has NMR properties consistent with the *agalacto* fragment **4**, in which the secondary C(9)-Me is in an axial position. It is not clear at present why diastereomers **2** and **14** preferentially adopt conformations in which the spirotetronate C(13) unit is axial with respect to the cyclohexenyl ring. We presume that conformational constraints imposed by the quartromicin macrocycle cause the conformation of the *agalacto* fragment within the natural product to adopt a different conformation than **2**.

The fact that the synthetic spirotetronates **1** and **2** exist in different conformations prompted us to consider the possibility that all four of the spirotetronate units of the quartromicins have identical stereochemistry, such that the natural product exists with the two *galacto* fragments in a dimethyl equatorial conformation (i.e. analogous to the conformations depicted for **1** and **3**), and with the two *agalacto* fragments in 'chair-inverted' conformations as depicted in structure **2**. However, extensive molecular modeling studies have failed to identify a sufficiently stable quartromicin stereoisomer or conformer that would satisfy these criteria. Accordingly, we regard this possibility as highly unlikely at this time.[25]

2.3. Diastereoselective syntheses of spirotetronates 1 and 2 via Diels–Alder reactions of acyclic (*Z*,*E*)-1,3-diene 24

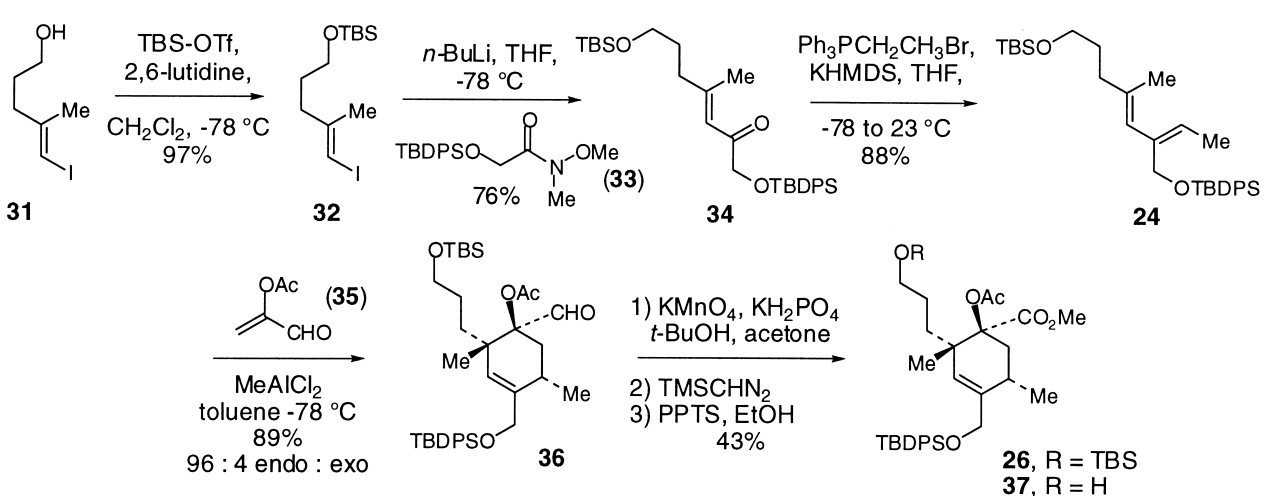
In principle, the most straightforward approach to the synthesis of spirotetronates **1** and **2** would involve Diels–Alder reactions of an acyclic (*Z*)-substituted 1,3-diene (**24**) and an appropriate α-acetoxy acrylate dienophile (cf. **25**). If this reaction could be induced to provide the *endo*- or *exo*-Diels–Alder adducts **26** or **27** with good selectivity, then the targeted spirotetronates **1** and **2** would be easily accessible. In addition, if the isomeric diene **28** could serve as a viable Diels–Alder reaction substrate, then the isomeric pair of spirotetronates **14** and **13** would be accessible from the *endo*- and *exo*-Diels–Alder adducts **29** and **30**, respectively. However, although oxygenated and other heteroatom (*Z*)-substituted 1,3-dienes readily undergo cycloaddition with a range of conventional and hetero dienophiles,[26,27] acyclic (*Z*)-alkyl substituted 1,3-dienes are generally regarded as exceptionally poor substrates for Diels–Alder reactions.[28,29] Conventional wisdom generally precludes the use of acyclic (*Z*)-substituted 1,3-dienes in synthetic applications (other than in intramolecular Diels–Alder reactions).[20] However, scattered reports of successful thermal[30–32] and Lewis acid catalyzed[33–40] Diels–Alder reactions of acyclic (*Z*)-substituted 1,3-dienes suggested to us that the prospects of using dienes such as **24** or **28** as intermediates in organic synthesis might not be as bleak as has been widely assumed. This prompted us to explore the scope of the Lewis acid catalyzed Diels–Alder reactions of acyclic (*Z*)-substituted



1,3-dienes and to apply this technology to the synthesis of **1** and **2**.[8,22]

Diene **24** was prepared starting from the known vinyl iodide **31**.[41] Protection of **31** as a *tert*-butyldimethylsilyl (TBS) ether provided **32** in 97% yield. Treatment of **32** with *n*-butyllithium at −78°C in THF followed by addition of a THF solution of the Weinreb amide **33**[42] provided enone **34** in 76% yield. A (*Z*)-selective Wittig olefination reaction of **34** with ethyltriphenylphosphonium bromide and potassium bis(trimethylsilyl)amide (KHMDS) in THF afforded diene **24** in 88% yield.[43]

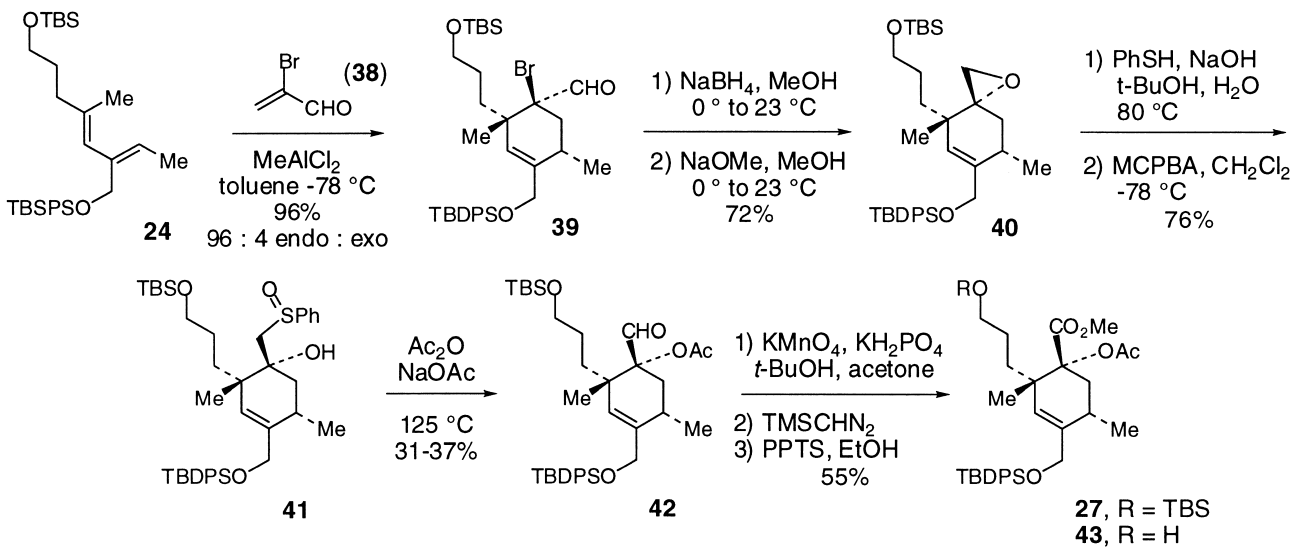
Attempts to perform Diels–Alder reactions of **24** with

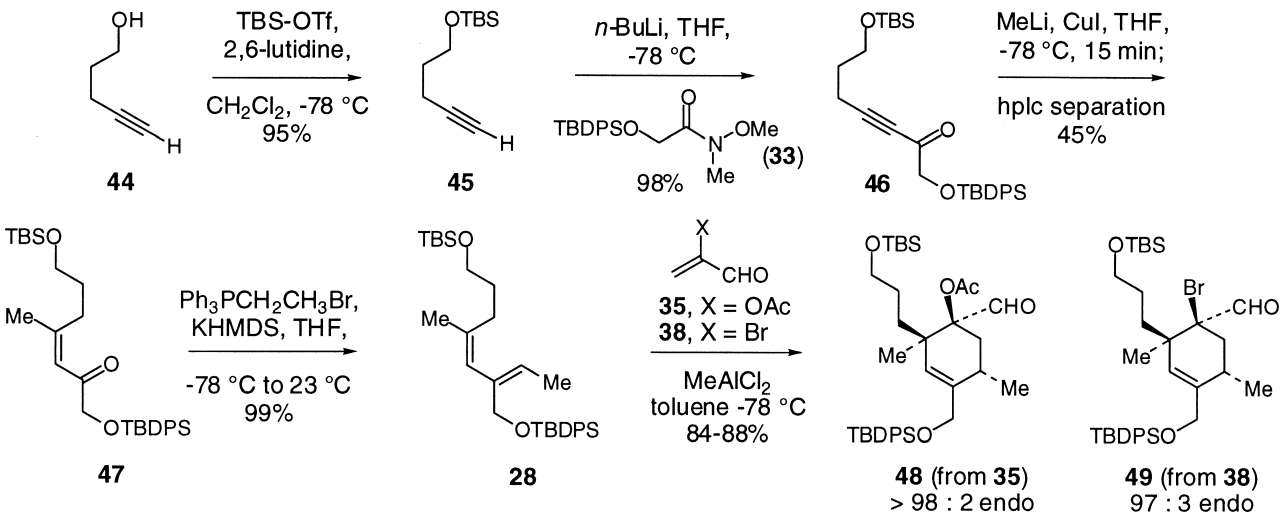


acrylate dienophiles (e.g. methyl acrylate) under Lewis acid catalysis were unsuccessful. Therefore, we did not explore the reactions of **24** with α-acetoxy acrylate **25**. However, treatment of diene **24** with 4 equiv. of α-acetoxy acrolein (**35**)[39] and 1 equiv. of $MeAlCl_2$ in toluene at −78°C for 1 h provided the Diels–Alder adduct **36** in 89% yield as a 96:4 mixture of *endo* and *exo* isomers.[44] Oxidation of **36** to the carboxylic acid was performed by using Masamune's method.[45] Esterification of the crude carboxylic acid by treatment with trimethylsilyldiazomethane then provided the originally targeted α-hydroxy ester **26**. Finally, deprotection of the side chain TBS ether by treatment of **26** with PPTs in EtOH provided **37** in 43% overall yield from **36**.

Lewis acid catalyzed Diels–Alder reactions of **24** with other dienophiles were also examined, in an effort to define a reaction partner that could be used in the synthesis of the formal *exo*-cycloadduct **27**. The $MeAlCl_2$-catalyzed Diels–Alder reaction of **24** and α-bromoacrolein was also highly selective, and provided a 96:4 mixture of *endo* and *exo* cycloadducts **39**. We anticipated that it might be possible to invert the stereochemistry of the very hindered α-bromoaldehyde stereocenter, thereby gaining access to the formal *exo*-Diels–Alder adduct **42**, by application of a strategy demonstrated in the chlorothricolide and kijanolide series.[43,46] Thus, reduction of **39** with $NaBH_4$ in MeOH gave the corresponding bromohydrin that was treated with NaOMe in MeOH. This provided the inverted spiroepoxide **40** in 72% yield. Epoxide **40** is very sterically hindered and proved to be extremely unreactive towards a range of oxygen nucleophiles at elevated temperatures (e.g. NaOH, *tert*-BuOH, reflux; NaOAc, DMF, 150°C; $NaHCO_3$, H_2O, *N*-methylpyrrolidinone, 130°C; KOAc, HOAc, DMSO, 100°C; *p*-$MeOC_6H_4OH$, NaOH, dioxane, 100°C; *p*-$MeOC_6H_4CH_2ONa$, $MeOC_6H_4CH_2OH$, 100°C, 24 h; etc.). However, treatment of **40** with thiophenol and NaOH in aqueous *tert*-BuOH at 80°C effected smooth ring opening. Oxidation of the thiophenyl sulfide intermediate with MCPBA at low temperature then provided **41** as a mixture of sulfoxide diastereomers in good overall yield. We anticipated that sulfoxide **41** could be converted to the formal *exo*-Diels–Alder adduct **42** by a Pummerer reaction.[47] After examining a wide range of conditions, best results were obtained when **41** was treated with acetic anhydride and NaOAc at 125°C. However, the desired α-acetoxy aldehyde **42** (which was identified as the minor product of the Diels–Alder reaction of **24** and **35**) was obtained in only 31–37% yield. Numerous attempts to improve the efficiency of this reaction have thus far been unsuccessful. We suspect that the intermediate α-hydroxysulfenium ion undergoes a ring expansion via a pinacol-type process. Attempts to suppress the presumed pinacol-like rearrangement by acylation of the α-hydroxy sulfide prior to MCPBA oxidation of the sulfide were unsuccessful—the α-acetoxy sulfide proved to be remarkably inert to the action of MCPBA. The conversion of **39** to **42** remains a problematic step, and efforts to find a higher yielding and more efficient alternative sequence continue in our laboratory. Finally, oxidation of **42** to **27** proceeded smoothly by using the conditions defined for the conversion of **36** to **26**. The *exo*-α-acetoxy ester **43** was then obtained in 55% overall yield following standard deprotection of the propyl side chain TBS ether.

In order to demonstrate the generality of the Lewis acid catalyzed Diels–Alder reactions of acyclic (*Z*)-dienes, we have also synthesized and studied the reactions of the isomeric diene **28**. Protection of commercially available pentynol **44** as a TBS ether followed by acylation of the acetylide anion with Weinreb amide **33**[42] provided the acetylenic ketone **46** in excellent yield. Treatment of **46** with Me_2CuLi in THF at −78°C provided a ca. 1:1 mixture of the two trisubstituted olefin isomers, from which **47** was obtained in 45% yield by preparative HPLC separation. Finally, Wittig olefination of **47** using $MeCH{=}PPh_3$ then provided **28** in near quantitative yield. Remarkably, the $MeAlCl_2$-promoted Diels–Alder reactions of **28** with both α-acetoxy acrolein (**35**) and α-bromoacrolein (**38**) were highly *endo* selective, and provided cycloadducts **48** (from **35**) and **49** (from **38**) with ≥97:3 diastereoselectivity and in 84–88% yield.[44] These results demonstrate that the Lewis acid catalyzed Diels–Alder reactions of acyclic (*Z*)-dienes have considerable generality, much more so than widely believed by the organic chemistry community. Although cycloadducts **48** and **49** have not been elaborated to

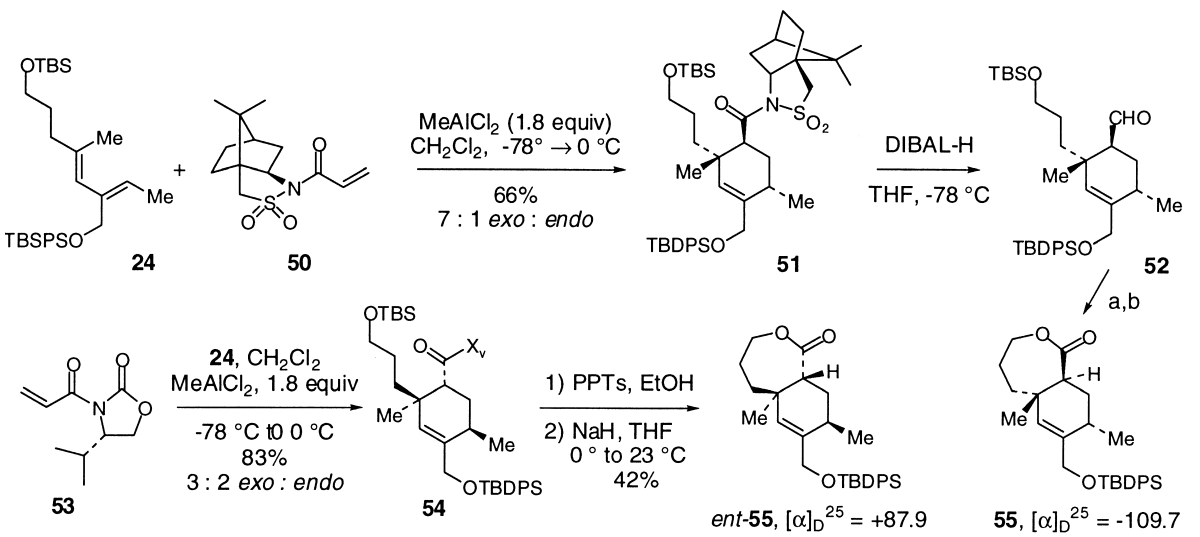




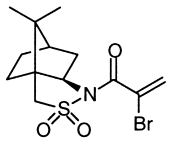
spirotetronates **14** and **13**, we suspect that this could be accomplished by using procedures analogous to those described here for the conversion of the diastereomeric Diels–Alder adducts **36** and **39** to the spirotetronates **1** and **2**.

Elaboration of the racemic hydroxy esters **37** and **43** to the quartromicin *endo* and *exo* spirotetronates **1** and **2** has been accomplished, as described subsequently. However, use of spirotetronates **1** and **2** (or their immediate precursors) in an eventual total synthesis of quartromicin D_3 requires that they be prepared as single enantiomers, in order to avoid generation of racemic diastereomers during the late-stage coupling sequence. Therefore, we have also explored the reactions of diene **24** with chiral dienophiles. Best results were obtained from $MeAlCl_2$-promoted Diels–Alder reaction of **24** and *N*-acryloyl sultam **50**[48] that provided the *exo*-cycloadduct **51** with 7:1 diastereoselectivity. In contrast, the Lewis acid catalyzed Diels–Alder reaction of **24** and the *N*-acryloyl imide **53**[49] provided a 3:2 mixture of *exo* and *endo* cycloadducts (only the structure of the *exo* adduct **54** is shown). Stereochemical assignments in these cases are based on the conversion of **51** and **54** to the enantiomeric lactones **55** and *ent*-**55**, respectively. Thus, DIBAL reduction of **51** provided the *exo* aldehyde **52**. Deprotection of the TBS ether provided a hemiacetal that was oxidized to give lactone (−)-**55** by using PCC on silica gel. Deprotection of the TBS ether of **54** and treatment of the resulting alcohol with NaH then gave *ent*-(+)-**55** in 42% yield.[50] This correlation establishes that the two *exo*-Diels–Alder adducts **51** and **54** are heterochirally related. In both cases, the assigned stereostructures are consistent with the well-established diastereofacial selectivity preferences of *N*-acryloyl sultam and *N*-acryloyl oxazolidinone dienophiles.[49,51] The *exo*-stereochemistry of **51**, **52**, and **55** was verified by ^1H NOE studies.

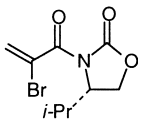
The reactions of **24** with the chiral dienophiles **50** and **53** are the first examples of enantioselective Diels–Alder reactions of an acyclic (*Z*)-diene, and constitutes a significant expansion of the scope of Lewis acid mediated Diels–Alder reactions of acyclic (*Z*)-dienes.[22] Unfortunately, attempts to perform Diels–Alder reactions of **24** with chiral dienophiles (e.g. **50a**[52] and **53a**) possessing α-substituents on the dienophilic double bond were not successful. It is known that methacryloylsultams adopt ground state



conformations with the methyacrylate carbonyl substantially out of plane of the dienophilic double bond.[53] It is also known that methacryloyl imides are only moderately selective Diels–Alder dienophiles, with the α-methyl group destabilizing the ground state *s-cis* conformation.[49,54] Consequently, we elected to use cycloadduct **51** or the derived aldehyde **52** in syntheses of the key quartromicin intermediates **37** and **43**.



50a



53a

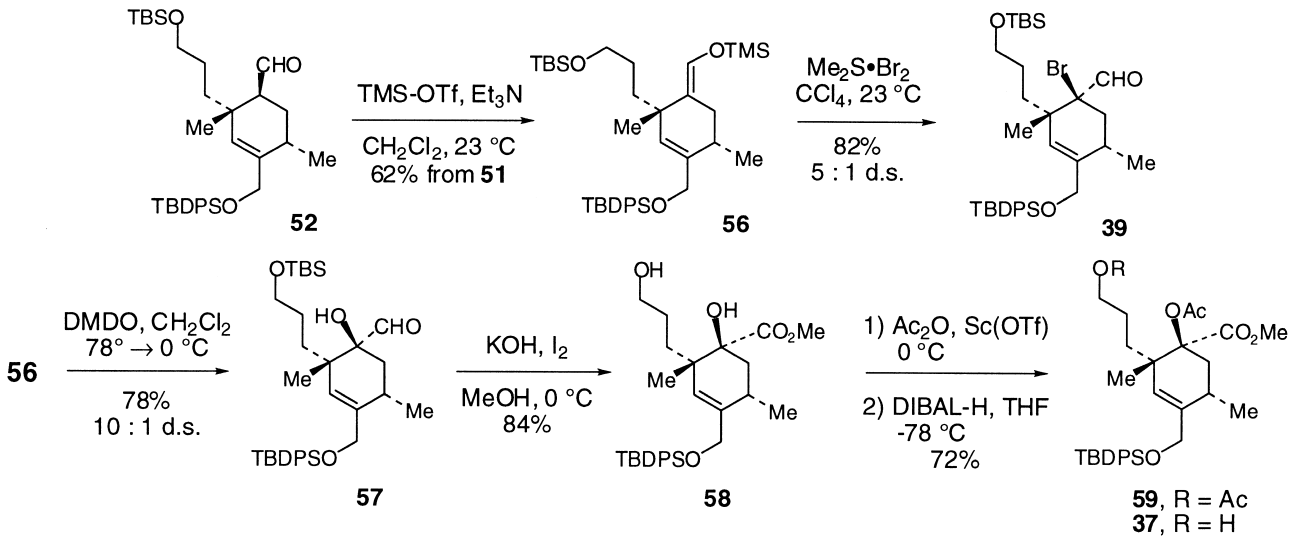
Disappointingly, all attempts to hydroxylate enolates generated from **51** or the derived methyl ester have not succeeded. However, treatment of aldehyde **52** with TMS-OTf and Et_3N in CH_2Cl_2 at 23°C provided the enol silane **56** as a 3:1 isomeric mixture (62% yield from the Diels–Alder adduct **51**). Treatment of enol silane **56** with bromodimethylsulfonium bromide[55] gave a 5:1 mixture of the *endo* bromide **39** and its easily separated *exo* diastereomer in 82% yield. Alternatively, exposure of enol silane **56** to a solution of dimethyldioxirane in acetone provided the *endo*-alcohol **57** in 78% yield with 10:1 diastereoselectivity.[56] Oxidation of the α-hydroxy aldehyde to the α-hydroxy ester was best accomplished by using I_2, and KOH in MeOH.[57] The primary TBS ether was also cleaved under these conditions, and α-hydroxy methyl ester **58** was obtained in 84% yield. All other oxidants examined for this reaction failed to provide either the α-hydroxy acid or α-hydroxy ester. Acylation of **58** by using $Sc(OTf)_3$ in Ac_2O gave the diacetate **59** in good yield.[58] Finally, selective DIBAL reduction of the unhindered primary acetate unit of **59** then provided hydroxy ester **37** in 72% yield from **58**.

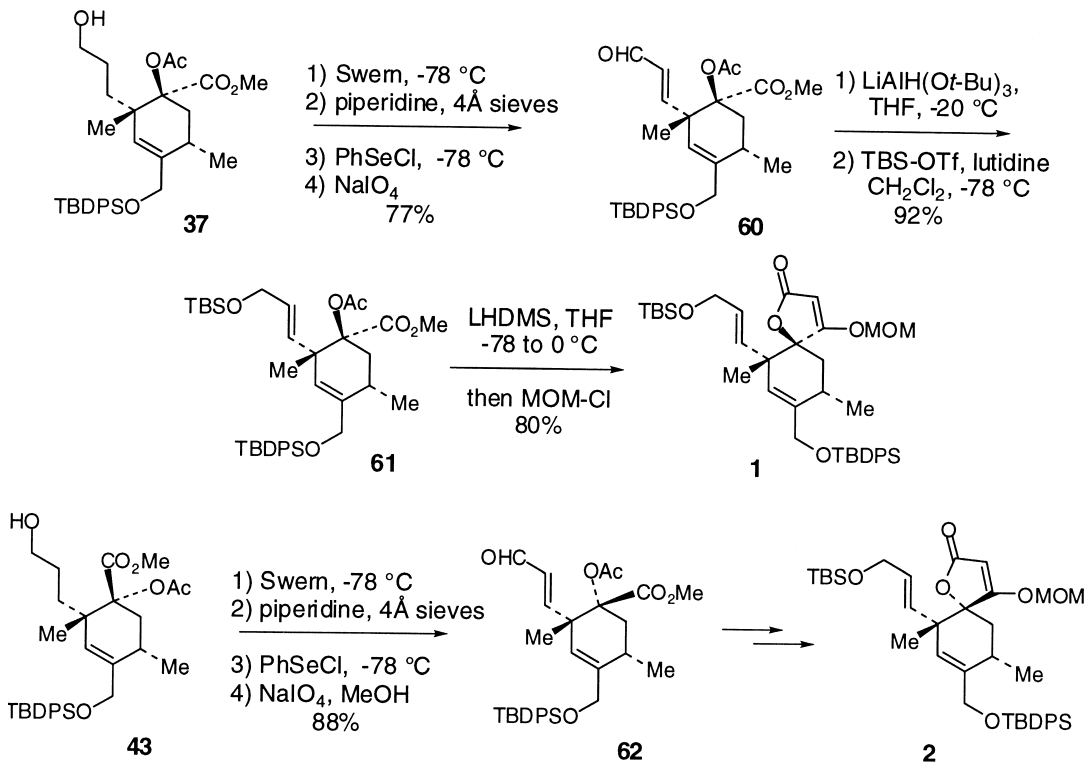
With highly diastereo- and enantioselective routes to **37** and **43** in hand, all that remained to complete syntheses of the quartromicin *endo* and *exo* spirotetronate units was to introduce the side chain double bond and to close the spirotetronate units by Dieckmann cyclizations. This chemistry has been developed by using racemic **37** and **43** as substrates. Thus, oxidation of *endo* hydroxy ester **37** by using the standard Swern protocol[59] gave an aldehyde that was oxidized to the α,β-unsaturated aldehyde via the enamine, by using Williams' procedure.[60] Reduction of enal **60** by using lithium tri-*tert*-butoxyaluminum hydride provided the corresponding allylic alcohol, that was protected as a TBS ether to give **61** in high yield. Finally, treatment of **61** with lithium hexamethyldisilazide (LHDMS) in THF at −78°C with warming to 0°C effected Dieckmann closure. Addition of MOM-Cl to this reaction mixture then provided the MOM protected *endo* spirotetronate **1** in 80% overall yield. The *exo* spirotetronate **2** was prepared from the *exo* hydroxy ester **43** by using an analogous reaction sequence.

3. Summary and future prospects

We have made a partial stereochemical assignment of quartromicins A_3 and D_3 by analysis of published ^1H NMR data of the natural product, and comparison with NMR data for a series of known spirotetronate systems. We have also developed highly stereoselective syntheses of the *endo* and *exo* spirotetronates **1** and **2**, that correspond to the *galacto* and *agalacto* fragments of the natural product, by routes involving highly diastereoselective Lewis acid catalyzed Diels–Alder reactions of acyclic (*Z*)-diene **24**. Syntheses of **1** and **2** are also potentially enantioselective, by virtue of the *exo*-selective Diels–Alder reaction of **24** and acryloyl sultam **50**, and the elaboration of the major cycloadduct **51** to precursors of both **1** and **2**. This work substantially extends the scope of the Diels–Alder reaction in organic synthesis.

Nevertheless, it is readily apparent that the elaboration of the *endo* α-bromoaldehyde **39** to the *exo* α-acetoxy ester **27** constitutes a substantial bottle neck in our efforts to scale up the synthesis of the *exo*-spirotetronate **2**. Reasoning that if an appropriate acyl anion equivalent were to add to the *exo* face of ketone **63**—from the same face as electrophilic oxidants add to the silyl enol ether **56**—then a much shorter route to the *exo* α-hydroxy ester intermediate **27** might become viable. Towards this end, we have recently demonstrated that treatment of ketone **63** with

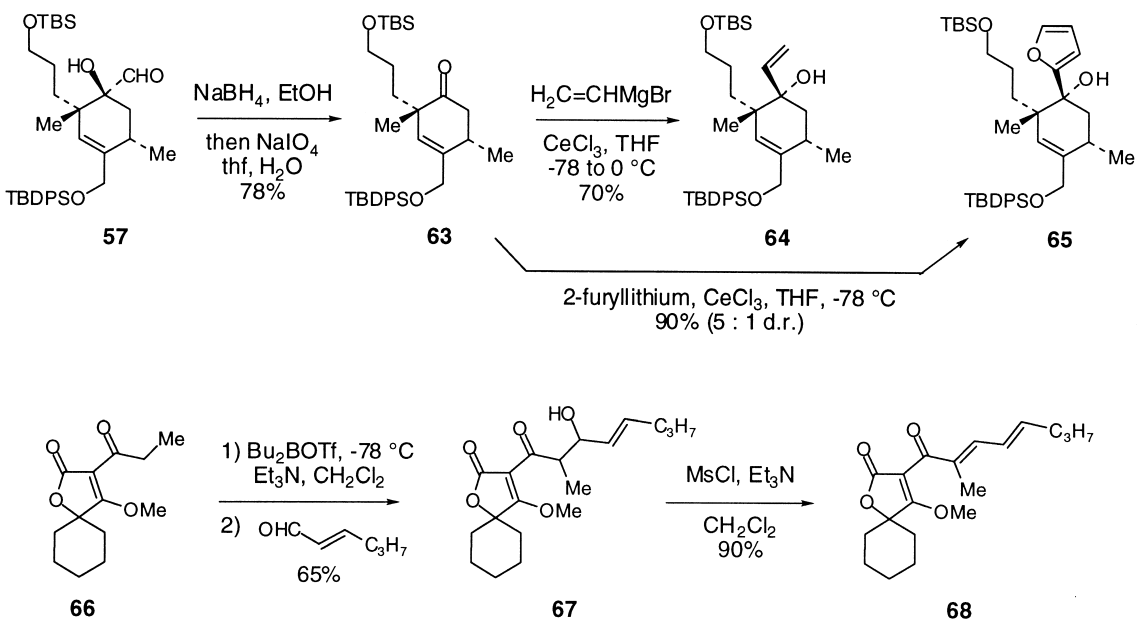


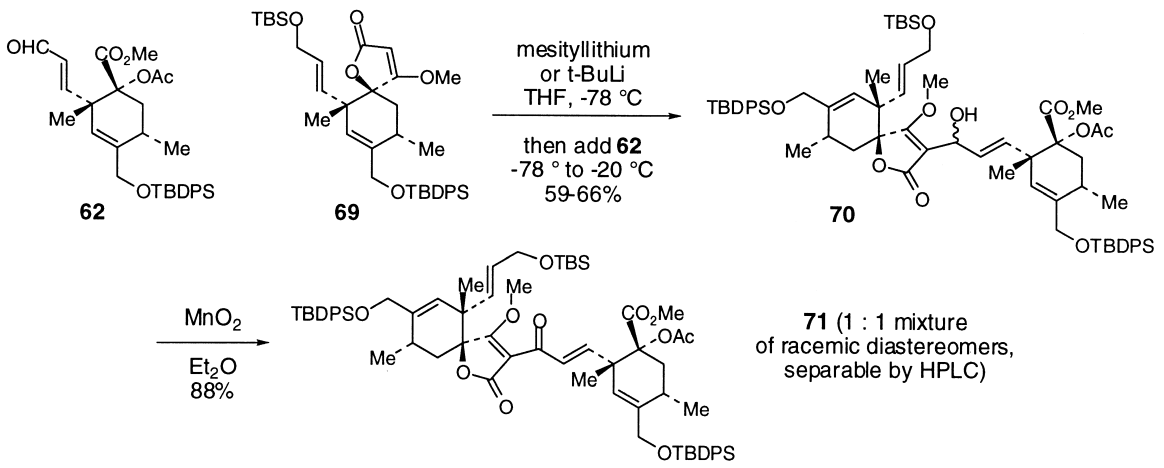


$H_2C{=}CHMgBr$ and $CeCl_3$ in THF provided **64** with an *exo*-vinyl substituent with excellent selectivity;[61] the stereochemistry of **64** was confirmed by ^1H NOE studies. Similarly, treatment of **63** with 2-furyllithium and $CeCl_3$ provided the *exo* furyl alcohol **65** in excellent yield and with 5:1 diastereoselectivity. Efforts to oxidize **64** or **65** to useful synthetic intermediates en route to **27** or **2** are in progress.[62]

Preliminary studies on the coupling of the spirotetronates, en route to completion of total syntheses of quartromicins A_3 and D_3 also have been performed. First, we have demonstrated that an aldol sequence may be a viable strategy for introducing the (*E*,*E*)-dienone unit spanning C(22) and C(14) of the quartromicin *galacto* and *agalacto* fragments, respectively, as demonstrated by the synthesis of the model 2-acyl spirotetronate **68** summarized below.

Second, we have demonstrated that the enone unit linking C(32) of the *galacto* fragment with C(4′) of the *agalacto* quadrant can be introduced by using a 2-lithiotetronate intermediate.[63,64] Thus, treatment of *exo* series enal **62** (racemic) with the anion generated by metallation of *endo* spirotetronate **69** (also racemic; prepared by the Dieckmann cyclization of **61** followed by treatment of the isolated tetronic acid with CH_2N_2)[65] provided the 1,2-addition product **70** as a mixture of diastereomers in 59–66%





yield. Oxidation of this mixture with activated MnO_2 then provided enone **71** as a 1:1 mixture of racemic diastereomers in excellent yield.

This strategy should provide a convenient means to synthesize advanced *galacto-agalacto* 'dimers' for use in completion of a quartromicin total synthesis, once sufficient quantities of single enantiomer intermediates are in hand. Additional progress towards this goal will be reported in due course.

4. Experimental[66]

4.1. General

4.1.1. (*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-iodo-2-methyl-1-pentene (32). To a −78°C solution of (*E*)-1-iodo-2-methyl-penten-5-ol (**31**) (8.89 g, 39.3 mmol) and 2,6-lutidine (6.87 mL, 59.0 mmol) in CH_2Cl_2 (60 mL) was added TBS-OTf (9.48 mL, 41.3 mmol) dropwise. The reaction mixture was allowed to stir for 1.5 h, then additional TBS-OTf (0.451 mL, 1.97 mmol) was added and the mixture was stirred for another 0.5 h. The mixture was poured into saturated $NaHCO_3$ solution and extracted with 1:1 hexanes–ether (300 mL). The organic layer was washed with 1N HCl and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (50:1 hexanes–ether) to give 12.9 g (97% yield) of **32** as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88 (d, J=4.0 Hz, 1H), 3.58 (t, J=6.2 Hz, 2H), 2.30–2.23 (m, 2H), 1.83 (s, 3H), 1.68–1.60 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.7, 74.7, 62.1, 35.8, 30.8, 25.9, 23.9, 18.3; IR (neat) 3057, 2953, 2931, 2891, 2857, 1618, 1470, 1387, 1361, 1255, 1186, 1142, 1104, 1106, 955, 836 cm^{-1}; HRMS (CI, NH_3) for $C_8H_{16}OISi$ $[M-C_4H_9]^+$ calcd 283.0017, found 283.0026 *m/z*.

4.1.2. (*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-7-[(*tert*-butyldiphenylsilyl)oxy]-4-methyl-3-hepten-2-one (34). To a −78°C solution of vinyl iodide **32** (3.31 g, 9.74 mmol) in THF (85 mL) was added a 2.5 M solution of *n*-BuLi in hexanes (4.09 mL, 10.2 mmol) over 3 min. The reaction was stirred at −78°C for 5 min then a solution of Weinreb's amide **33** (3.83 g, 10.7 mmol) in THF (15 mL) was added over 5 min via cannula. The reaction was allowed to warm to 23°C over 1.5 h. The reaction mixture was recooled to −78°C and quenched with 1N HCl (40 mL). The mixture was poured into a mixture of 1N HCl (100 mL) and 1:1 hexanes–ether (500 mL). The aqueous layer was separated and extracted with ether (100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (25:1 hexanes–ether) to give 3.80 g (76% yield) of **34** as a clear oil. R_f (10:1 hexanes–EtOAc)=0.40; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71–7.65 (m, 4H), 7.48–7.36 (m, 6H), 6.38 (d, J=1.3 Hz, 1H), 4.21 (s, 2H), 3.62 (t, J=6.4 Hz, 2H), 2.23 (m, 2H), 2.19 (d, J=1.0 Hz, 3H), 1.73–1.65 (m, 2H), 1.11 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.9, 160.9, 135.5, 132.9, 129.8, 127.8, 118.7, 70.2, 62.3, 37.8, 30.6, 26.8, 25.9, 19.9, 19.2, 18.3, −5.3; IR (neat) 3072, 3049, 2954, 2931, 2892, 2857, 1705, 1689, 1617, 1472, 1428, 1390, 1362, 1255, 1109, 1007, 941, 836 cm^{-1}; HRMS (CI, NH_3) for $C_{26}H_{37}O_3Si_2$ $[M-C_4H_9]^+$ calcd 453.2281, found 453.2264 *m/z*. Anal. calcd for $C_{30}H_{46}O_3Si_2$: C, 70.53; H, 9.08. Found: C, 70.30; H, 8.80.

4.1.3. (2*Z*,4*E*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3-[[(*tert*-butyldiphenylsilyl)-oxy]-methyl]-5-methyl-2,4-octadiene (24). To a −78°C suspension of Ph_3PEt^+ Br^- (2.06 g, 5.54 mmol) in THF (15 mL) was added a 0.5 M solution of potassium hexamethyldisilylazide (KHMDS) in toluene (10.7 mL, 5.33 mmol). The reaction was allowed to warm to 0°C and stir for 30 min. The dark orange reaction solution was recooled to −78°C and a solution of enone **34** (1.09 g, 2.13 mmol) in THF (6 mL) was added dropwise via cannula. The reaction mixture was allowed to warm to 0°C and stir for 2 h. The dark mixture was recooled to −78°C and was poured into a mixture of 1N HCl (30 mL) and 1:1 hexanes–ether (100 mL). The aqueous layer was separated and extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (50:1 hexanes–ether) to give 0.98 g (88% yield) of **24** as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72–7.67 (m, 4H), 7.45–7.35 (m, 6H), 5.79 (d, J=1.0 Hz, 1H), 5.36 (br q, J=6.7 Hz, 1H), 4.24 (s, 2H), 3.64 (t, J=6.5 Hz, 2H), 2.11 (m, 2H), 1.77 (d, J=1.3 Hz, 3H), 1.73–1.65 (m, 2H), 1.52 (br d, J=7.0 Hz, 3H), 1.04 (s, 9H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 136.8, 136.8, 135.7, 134.0, 129.5, 127.5, 125.7, 124.6, 63.0, 61.8, 36.6, 31.3, 26.8, 26.8, 26.0, 19.3, 18.4, 17.8, 13.3, −5.2; IR (neat) 3071, 3048, 2953, 2931, 2892, 2857, 1959, 1891, 1822, 1651, 1589, 1471, 1428, 1388, 1361, 1254, 1189, 1109, 1006, 954, 835 cm^{-1}; HRMS (CI, NH_3) for $C_{32}H_{50}O_2Si_2$ $[M]^+$ calcd 522.3349, found 522.3360 *m/z*.

4.1.4. (1*S*,2*S*,5*S*)-1-Acetoxy-2-[[(*tert*-butyldimethylsilyl)oxy]-propyl]-4-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-2,5-dimethyl-3-cyclohexene-1-carboxaldehyde (36). To a −78°C solution of diene **24** (588 mg, 1.13 mmol) and α-acetoxy acrolein (321 mg, 2.82 mmol) in toluene (10 mL) was added $MeAlCl_2$ (1.36 mL of a 1.0 M solution in hexanes, 1.36 mmol) dropwise. The reaction mixture was stirred at −78°C for 90 min, then quenched by the cautious addition of saturated $NaHCO_3$ solution (4 mL). The mixture was diluted with ether (50 mL) and saturated NaCl solution (10 mL). The layers were separated, then the aqueous layer was extracted with ether (3×30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. ^1H NMR analysis of the crude product indicated a 96:4 mixture of *endo–exo* cycloadducts. Purification of the crude product by flash chromatography (10:1–5:1 hexanes–ether) gave 638 mg (89%) of **36**. An analytical sample of the major cycloadduct was obtained by hplc (7% EtOAc–hexanes). ^1H NMR ($CDCl_3$, 400 MHz) δ 9.71 (s, 1H), 7.73–7.63 (m, 4H), 7.47–7.37 (m, 6H), 5.25 (br s, 1H), 4.28 (A of AB, J=12.8 Hz, 1H), 4.05 (B of AB, J=12.8 Hz, 1H), 3.50 (t, J=6.3 Hz, 2H), 2.47 (dd, J=14.6, 6.0 Hz, 1H), 2.28 (m, 1H), 2.08 (s, 3H), 1.94 (dd, J=14.6, 11.4 Hz, 1H), 1.52–1.36 (m, 4H), 1.21 (s, 3H), 1.06 (d, J=7.0 Hz, 3H), 1.04 (s, 9H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.5, 170.7, 138.5, 135.5, 135.4, 133.8, 133.7, 129.7, 129.6, 128.1, 127.6, 127.6, 87.3, 65.7, 63.4, 40.9, 35.7, 30.6, 27.3, 27.0, 26.7, 25.9, 20.7, 20.5, 19.3, 18.3, −5.3; IR (neat) 3071, 3049, 2955, 2931, 2889, 2857, 2714, 1960, 1893, 1822, 1735, 1589, 1471, 1428, 1369, 1257, 1237, 1197, 1109, 1066, 1008, 941, 880, 836 cm^{-1}; HRMS (CI, NH_3) for $C_{33}H_{47}O_5Si_2$ $[M-C_4H_9]^+$ calcd 579.2962, found 579.2965 *m/z*.

4.1.5. Methyl (1*S*,2*S*,5*S*)-1-acetoxy-2-{3-[(*tert*-butyldimethylsilyl)oxy]-propyl}-4-{[(*tert*-butyldiphenylsilyl)-oxy]-methyl}-2,5-dimethyl-cyclohex-3-enoate (26). To a solution of α-acetoxy aldehyde **36** (728 mg, 1.14 mmol) in *tert*-butanol (20 mL) and acetone (6.8 mL) was added KH_2PO_4 (5.47 mL of a 1.25 M solution, 6.84 mmol). The resulting suspension was cooled to 0°C and an aqueous solution of $KMnO_4$ (9.1 mL of a 0.5 M solution, 4.56 mmol) was delivered dropwise. The stirred reaction was kept at 0°C for 15 min and at rt for an additional 60 min. The purple mixture was cooled to 0°C, poured into a solution of $Na_2S_2O_3$ (80 mL of a 10% solution (by mass)), and diluted with EtOAc (200 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4×200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a white foam (699 mg). The crude carboxylic acid was used in the next step without further purification.

To a 0°C solution of the crude carboxylic acid (~699 mg) in THF (7.8 mL) and MeOH (3.9 mL) was added $TMSCHN_2$ (2.28 mL of a 2.0 M solution in hexanes, 4.56 mmol). The reaction mixture was then warmed to 23°C and stirred for 30 min. The solution was then cooled to 0°C, and saturated aqueous $NaHCO_3$ (6.5 mL) was added cautiously. The mixture was then partitioned between EtOAc (100 mL) and saturated aqueous NaCl (30 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (10:1 hexanes–EtOAc) to deliver 443 mg (58%) of α-acetoxy methyl ester **26**. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76–7.69 (m, 4H), 7.47–7.36 (m, 6H), 5.28 (d, J=1.1 Hz, 1H), 4.30 (A of AB, J=12.7 Hz, 1H), 4.07 (B of AB, J=12.9 Hz, 1H), 3.74 (s, 3H), 3.54 (t, J=6.2 Hz, 2H), 2.69 (dd, J=14.5, 5.5 Hz, 1H), 2.23 (m, 1H), 2.04 (s, 3H), 1.95 (dd, J=14.5, 11.7 Hz, 1H), 1.56–1.40 (m, 3H), 1.21 (s, 3H), 1.10 (m, 1H), 1.07 (d, J=7.7 Hz, 3H), 1.06 (s, 9H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.2, 138.2, 135.5, 135.4, 133.9, 133.7, 129.6, 129.6, 128.0, 127.6, 127.5, 84.1, 65.7, 63.4, 51.8, 41.0, 35.7, 33.1, 27.3, 27.3, 26.7, 25.9, 20.9, 19.9, 19.3, 18.2, 18.1, −5.3; IR (neat) 3072, 3051, 2956, 2933, 2888, 2857, 1744, 1471, 1428, 1369, 1257, 1199, 1109, 1066, 940, 836 cm^{-1}; HRMS (CI, NH_3) for $C_{34}H_{49}O_6Si_2$ $[M-C_4H_9]^+$ calcd 609.3067, found 609.3074 *m/z*.

4.1.6. Methyl (1*S*,2*S*,5*S*)-1-acetoxy-4-{[(*tert*-butyldimethylsilyl)oxy]-methyl}-2,5-dimethyl-2-[3-(hydroxy)-propyl]-cyclohex-3-enoate (37). A solution of **26** (0.115 g, 0.172 mmol) and pyridinium *p*-toluenesulfonate (0.147 g, 0.586 mmol) in EtOH (9.7 mL) was stirred for 15 h. The reaction mixture was concentrated in vacuo and diluted with Et_2O. The mixture was washed with saturated aqueous $NaHCO_3$ solution, 1N HCl, saturated aqueous $NaHCO_3$ solution, and then dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (2:1–3:1 ether–hexanes) to give 87 mg (92%) of **37** as a clear colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72–7.67 (m, 4H), 7.46–7.36 (m, 6H), 5.26 (d, J=1.3 Hz, 1H), 4.28 (A of AB, J=12.7 Hz, 1H), 4.06 (B of AB, J=13.0 Hz, 1H), 3.74 (s, 3H), 3.55 (dt, J=6.4, 1.7 Hz, 2H), 2.67 (dd, J=14.7, 5.5 Hz, 1H), 2.20 (m, 1H), 2.03 (s, 3H), 1.93 (dd, J=14.6, 11.6 Hz, 1H), 1.58–1.39 (m, 3H), 1.20 (s, 3H), 1.12 (m, 1H), 1.04 (d, J=6.7 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 170.2, 138.4, 135.5, 135.4, 133.8, 129.6, 127.7, 127.6, 127.5, 83.9, 65.6, 63.3, 51.9, 40.9, 35.6, 33.1, 27.3, 26.7, 20.9, 20.0, 19.3, 18.1; IR (neat) 3390 br, 3072, 3053, 3018, 2956, 2931, 2860, 1742, 1460, 1429, 1369, 1264, 1238, 1198, 1154, 1109, 1089, 1062, 1030, 986, 876, 825 cm^{-1}; HRMS (CI, NH_3) for $C_{28}H_{35}O_6Si$ $[M-C_4H_9]^+$ calcd 495.2203, found 495.2188 *m/z*.

4.1.7. (1*S*,2*S*,5*S*)-1-Bromo-2-[[(*tert*-butyldimethylsilyl)oxy]-propyl]-4-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-2,5-dimethyl-3-cyclohexene-1-carboxaldehyde (39). To a −78°C solution of diene **24** (2.93 g, 5.60 mmol) and α-bromo acrolein (**38**) (1.51 g, 11.2 mmol) in toluene (160 mL) was added a 1.0 M solution of $MeAlCl_2$ in hexane (6.16 mL, 6.16 mmol) dropwise. The reaction mixture was stirred at −78°C for 90 min, then quenched by the cautious addition of saturated $NaHCO_3$ (45 mL). The mixture was diluted with ether (250 mL) and saturated NaCl solution

(90 mL). The layers were separated, then the aqueous layer was extracted with ether (3×200 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (30:1 hexanes–ether) gave 3.35 g (91%) of **39** (*endo* and *exo* isomers, 96:4) as a clear colorless oil. An analytical sample of the major cycloadduct **39** was obtained by hplc (5% EtOAc–hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.68 (s, 1H), 7.74–7.68 (m, 4H), 7.47–7.35 (m, 6H), 5.32 (d, J=1.6 Hz, 1H), 4.24 (A of AB, J=13.3 Hz, 1H), 4.13 (B of AB, J=13.3 Hz, 1H), 3.51 (t, J=6.0 Hz, 2H), 2.73–2.62 (m, 1H), 2.25 (dd, J=15.2, 6.0 Hz, 1H), 1.99 (dd, J=14.9, 10.5 Hz, 1H), 1.58–1.44 (m, 3H), 1.38 (s, 3H), 1.36–1.26 (m, 1H), 1.08 (d, J=7.0 Hz, 3H), 1.06 (s, 9H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.7, 138.8, 135.6, 135.4, 133.7, 133.7, 129.6, 127.7, 127.6, 127.1, 79.5, 65.3, 63.1, 40.5, 36.9, 35.9, 29.3, 28.5, 26.7, 25.9, 24.9, 19.3, 18.4, 18.2, −5.3; IR (neat) 3070, 3048, 2955, 2931, 2885, 2856, 2728, 1958, 1893, 1827, 1721, 1589, 1471, 1428, 1388, 1362, 1304, 1255, 1186, 1110, 1064, 1006, 938, 835 cm^{-1}; HRMS (CI, NH_3) for $C_{31}H_{44}BrO_3Si_2$ $[M-C_4H_9]^+$ calcd 601.1992, found 601.1988 *m/z*.

4.1.8. (1*R*,2*S*,3*S*)-2-{3-[(*tert*-butyldimethylsilyl)oxy]-propyl}-4-{[*tert*-butyl-diphenylsilyl)-oxy]-methyl}-2,5-dimethyl-1-oxaspiro[2.5]oct-5-ene (40). To a 0°C solution of α-bromo aldehyde **39** (1.32 g, 2.01 mmol) in MeOH (30 mL) was added $NaBH_4$ (76 mg, 2.01 mmol) in one portion. The reaction mixture was allowed to warm to 23°C over 25 min. The mixture was diluted with ether (250 mL) and the resulting solution was cooled to 0°C, and then poured into a cold solution of 1N HCl (20 mL). The layers were separated, and the aqueous layer was extracted with ether (3×40 mL). The combined organic layers were washed with a saturated NaCl solution (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes–ether) to afford 1.20 g (91%) of bromo alcohol. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75–7.70 (m, 4H), 7.46–7.36 (m, 6H), 5.32 (d, J=1.6 Hz, 1H), 4.24 (A of AB, J=13.0 Hz, 1H), 4.13 (B of AB, J=13.4 Hz, 1H), 4.03 (A of AB, J=12.4 Hz, 1H), 3.62 (B of AB, J=12.4 Hz, 1H), 3.56 (dt, J=2.2, 6.0 Hz, 2H), 2.66 (m, 1H), 2.42 (dd, J=14.6, 6.0 Hz, 1H), 2.05 (br s, 1H), 1.65 (dd, J=14.6, 9.8 Hz, 1H), 1.56 (m, 2H), 1.45 (m, 2H), 1.34 (s, 3H), 1.06 (s, 9H), 1.05 (d, J=5.1 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9, 135.6, 135.5, 133.9, 133.8, 129.5, 128.8, 127.6, 127.6, 88.3, 68.0, 65.5, 63.5, 42.3, 39.2, 36.3, 29.9, 28.5, 26.7, 25.9, 25.2, 19.3, 18.5, 18.2, −5.3; IR (neat) 3562, 3463, 3070, 3049, 2955, 2931, 2892, 2857, 1470, 1428, 1388, 1362, 1254, 1107, 1059, 1006, 940, 836 cm^{-1}; HRMS (FAB, Na) for $C_{35}H_{54}O_3Si_2Na$ $[M-HBr+Na]^+$ calcd 601.3509, found 601.3478 *m/z*.

A 0°C solution of bromo alcohol prepared above (582 mg, 0.882 mmol) in MeOH (15 mL) was treated with NaOMe (1.76 mL of a 1.0 M solution in MeOH, 1.76 mmol) dropwise. The reaction mixture was allowed to warm to 23°C for 2 h. The solution was then concentrated under reduced pressure to afford a residue. The resulting residue was cooled to 0°C; ether (120 mL) and water (20 mL) were added sequentially. The layers were separated, and the aqueous layer was extracted with ether (3×35 mL). The combined organic layers were washed with saturated NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (10:1 hexanes–ether) to deliver 403 mg (79%) of epoxide **40**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70–7.66 (m, 4H) 7.44–7.35 (m, 6H), 5.45 (d, J=1.0 Hz, 1H), 4.21 (A of AB, J=12.9 Hz, 1H), 4.11 (B of AB, J=12.9 Hz, 1H), 3.58–3.50 (m, 2H), 2.74 (d, J=4.4 Hz, 1H), 2.44–2.40 (m, 1H), 2.40 (d, J=4.4 Hz, 1H), 1.75 (dd, J=13.2, 5.6 Hz, 1H), 1.61–1.49 (m, 3H), 1.43–1.26 (m, 2H), 1.06 (s, 9H), 1.05 (d, J=7.3 Hz, 3H), 0.89 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.3, 135.5, 135.5, 133.8, 133.7, 129.6, 129.6, 127.6, 127.6, 127.6, 65.8, 63.9, 61.8, 49.2, 37.0, 36.8, 34.0, 30.7, 28.2, 26.8, 26.0, 24.1, 19.5, 19.3, 19.3, 18.3, −5.2, −5.3; IR (film) 3070, 3049, 2956, 2930, 2894, 2857, 1721, 1472, 1463, 1428, 1390, 1362, 1255, 1112, 1057, 1005, 938, 835, 776, 740, 702, 613 cm^{-1}; HRMS (70 eV) for $C_{35}H_{54}O_3Si_2$ calcd 578.3612, found 578.3595 *m/z*.

4.1.9. (1*R*,2*S*,5*S*)-4-{[(*tert*-Butyldiphenylsilyl)oxy]-methyl}-2,5-dimethyl-1-(phenylsulfinyl)-methyl-3-cyclohexenol (41). To a solution of epoxide **40** (952 mg, 1.64 mmol) and thiophenol (505 μL, 4.92 mmol) in *tert*-butyl alcohol (9.52 mL) was added an aqueous solution of NaOH (9.52 mL, 4.76 mmol). This mixture was then heated at 80°C for 16 h. The mixture was then cooled to 0°C and saturated NH_4Cl (17 mL) and Et_2O (90 mL) were added. The layers were separated, then the aqueous layer was extracted with ether (2×90 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (20:1–10:1 hexanes–ether) to deliver 948 mg (84%) of sulfide. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66–7.64 (m, 4H), 7.43–7.34 (m, 7H), 7.27–7.24 (m, 3H), 7.20–7.17 (m, 1H), 5.30 (s, 1H), 4.16 (A of AB, J=12.9 Hz, 1H), 4.07 (B of AB, J=12.9 Hz, 1H), 3.58–3.55 (m, 2H), 3.18–3.10 (m, 2H), 2.22 (m, 1H), 2.13 (s, 1H), 1.94 (dd, J=13.4, 6.3 Hz, 1H), 1.8–1.2 (m, 5H), 1.05 (s, 9H), 0.98 (s, 3H), 0.95 (d, J=6.8 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 137.2, 135.5, 135.5, 133.8, 133.8, 130.1, 129.8, 129.6, 129.6, 128.9, 127.6, 127.6, 126.3, 75.3, 65.5, 64.1, 43.1, 41.6, 39.1, 35.2, 30.2, 28.0, 26.8, 26.0, 19.7, 19.3, 18.9, 18.3, −5.2; IR (neat) 3524, 3072, 3051, 3017, 2930, 2956, 2885, 2857, 1957, 1887, 1822, 1774, 1718, 1655, 1584, 1472, 1462, 1428, 1361, 1255, 1112, 1057, 836, 776, 739, 702 cm^{-1}; HRMS (FAB, M+Na) for $C_{41}H_{60}O_3NaSi_2S$ calcd 711.3699, found 711.3735 *m/z*.

To a −78°C solution of sulfide (930 mg, 1.35 mmol) in CH_2Cl_2 (15 mL) was added a solution of ~57% *m*-CPBA (409 mg, 1.35 mmol) in CH_2Cl_2 (3 mL). The resulting white suspension was stirred at −78°C for 25 min. Saturated $Na_2S_2O_3$ (12 mL) was added cautiously, and the mixture was allowed to warm to rt. Et_2O (70 mL) was then added and the layers were separated. The aqueous layer was extracted with Et_2O (3×70 mL). The combined organic layers were washed with saturated $NaHCO_3$ (40 mL) and saturated NaCl (40 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was then purified by flash chromatography (2:1–1:1 hexanes–ether) to give 854 mg (90%) of sulfoxide **41**. ^{1}H

NMR ($CDCl_3$, 500 MHz) δ 7.62–7.59 (m, 4H), 7.54–7.45 (m, 5H), 7.40–7.34 (m, 2H), 7.31–7.26 (m, 4H), 5.17 (s, 1H), 4.27 (A of AB, J=12.5 Hz, 1H), 4.04 (B of AB, J=12.5 Hz, 1H), 3.58–3.51 (m, 2H), 2.96 (dd, J=13.2, 1.7 Hz, 1H), 2.67 (d, J=13.2 Hz, 1H), 2.54 (m, 1H), 2.45 (dd, J=14.2, 6.1 Hz, 1H), 2.05 (pseudo t, J=13.4 Hz, 1H), 1.59–1.41 (m, 4H), 1.14 (d, J=6.8 Hz, 4H), 1.06 (s, 9H), 0.87 (s, 9H), 0.84 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.6, 137.6, 135.5, 135.4, 133.8, 133.6, 131.4, 130.6, 129.7, 129.6, 129.5, 127.6, 123.9, 75.8, 65.8, 64.0, 62.5, 42.2, 38.9, 33.8, 30.2, 28.0, 26.9, 26.0, 19.4, 19.3, 19.0, 18.3, −5.2; IR (film) 3424, 3071, 3049, 2956, 2930, 2857, 1956, 1889, 1827, 1589, 1472, 1463, 1444, 1428, 1389, 1361, 1255, 1106, 1093, 1056, 1007, 835, 776, 741, 702, 690, 614 cm^{-1}; HRMS (CI, CH_4) for $C_{41}H_{61}O_4Si_2S$ calcd 705.3829, found 705.3813 *m/z*.

4.1.10. (1*R*,2*S*,5*S*)-1-Acetoxy-2-{3-[(*tert*-butyldimethylsilyl)oxy]-propyl}-4-{[(*tert*-butyl-diphenylsilyl)-oxy}-methyl]-2,5-dimethyl-cyclohex-3-enal (42). A stirred mixture of sulfoxide **41** (832 mg, 1.18 mmol) and NaOAc (484 mg, 5.90 mmol) in acetic anhydride (12.5 ml) was heated to 125°C over 45 min. The reaction mixture was then stirred at 125°C for 17 h. After cooling the resulting brown mixture to 23°C, toluene (100 mL) was added and the mixture was concentrated under reduced pressure. This procedure was repeated with an additional portion of toluene (100 mL). Ether (80 mL) and saturated $NaHCO_3$ (25 mL) were added to the brown residue. The layers were separated, and the aqueous layer was extracted with ether (3×80 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting brown oil was purified via flash chromatography (15:1–10:1 hexanes–ether) to deliver 231 mg (31%) of aldehyde **42**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.59 (s, 1H), 7.68–7.65 (m, 4H), 7.44–7.36 (m, 6H), 5.42 (s, 1H), 4.18 (A of AB, J=13.4, 0.7 Hz, 1H), 4.12 (B of AB, J=13.4, 0.7 Hz, 1H), 3.67–3.58 (m, 2H), 2.66–2.59 (m, 2H), 2.09 (s, 3H), 1.92 (m, 1H), 1.66–1.51 (m, 4H), 1.06 (s, 9H), 0.98 (d, J=6.8 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C ($CDCl_3$, 100 MHz) δ 199.0, 170.6, 138.7, 135.5, 135.5, 133.7, 133.6, 129.7, 129.6, 127.7, 127.6, 126.3, 87.5, 65.5, 63.7, 40.4, 34.4, 30.9, 28.4, 27.4, 26.8, 25.9, 21.9, 21.3, 19.9, 19.3, 18.3, −5.2, −5.3; IR (film) 3072, 3050, 2965, 2931, 2891, 2857, 2737, 1736, 1590, 1472, 1463, 1368, 1247, 1106, 836, 702 cm^{-1}; HRMS (FAB, M+Na) for $C_{37}H_{56}O_5NaSi_2$ calcd 659.3564, found 659.3583 *m/z*.

4.1.11. Methyl (1*R*,2*S*,3*S*)-1-acetoxy-2-{3-[(*tert*-butyldimethylsilyl)oxy]-propyl}-4-{[(*tert*-butyldiphenylsilyl)-oxy]-methyl}-2,5-dimethyl-cyclohex-3-enoate (27). To a solution of α-acetoxy aldehyde **42** (372 mg, 0.548 mmol) in *tert*-butanol (10.2 mL) and acetone (3.48 mL) was added KH_2PO_4 (2.80 mL of a 1.25 M solution, 3.50 mmol). The resulting suspension was cooled to 0°C and an aqueous solution of potassium permanganate (4 mL of a 0.5 M solution, 2.00 mmol) was delivered dropwise. The stirred reaction was kept at 0°C for 15 min and at 23°C for an additional 60 min. The purple mixture was cooled to 0°C, poured into a solution of $Na_2S_2O_3$ (40 mL of a 10% solution (by mass)), and diluted with EtOAc (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a white foam (370 mg). The crude carboxylic acid was used in the next step without further purification.

To a 0°C solution of the crude carboxylic acid (~370 mg) in THF (4.1 mL) and MeOH (2.1 mL) was added $TMSCHN_2$ (1.17 mL of a 2.0 M solution in hexanes, 2.34 mmol). The reaction mixture was then warmed to 23°C and stirred for 30 min. The solution was then cooled to 0°C, and saturated aqueous $NaHCO_3$ (3.2 mL) was added cautiously. EtOAc (50 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20:1–10:1 hexanes–EtOAc) to deliver 241 mg of a mixture (5:1) of the α-acetoxy methyl ester and α-acetoxy aldehyde. Further purification by HPLC (9% EtOAc–91% hexanes) afforded 36 mg (10% recovery) of **42** and 203 mg (52, 58% based on recovered aldehyde) of methyl ester **27**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70–7.66 (m, 4H), 7.44–7.35 (m, 6H), 5.48 (s, 1H), 4.19 (A of AB, J=13.2, 1.2 Hz, 1H), 4.12 (B of AB, J=13.2, 1.2 Hz, 1H), 3.70 (s, 3H), 3.61–3.57 (m, 2H), 2.52–2.47 (m, 2H), 2.34 (m, 1H), 2.02 (s, 3H), 1.73–1.44 (m, 4H), 1.06 (s, 9H), 0.96 (d, J=7.1 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 170.4, 138.0, 135.5, 135.5, 133.7, 133.7, 129.6, 129.6, 127.6, 127.6, 127.6, 125.4, 84.6, 65.8, 64.0, 51.8, 40.2, 31.6, 31.3, 27.8, 27.8, 26.8, 25.9, 23.6, 21.6, 19.5, 19.3, 18.3, −5.3; IR (film) 3072, 3050, 2955, 2932, 2889, 2858, 1745, 1590, 1472, 1463, 1429, 1368, 1250, 1112, 836, 776, 703, 611 cm^{-1}; HRMS (FAB, M+Na) for $C_{38}H_{58}O_6NaSi_2$ calcd 689.3670, found 689.3655 *m/z*.

4.1.12. Methyl (1*R*,2*S*,3*S*)-1-acetoxy-4-{[(*tert*-butyldiphenylsilyl)oxy]-methyl}-2,5-dimethyl-2-[3-(hydroxy)-propyl]-cyclohex-3-enoate (43). A solution of silyl ether **27** (154 mg, 0.231 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (232 mg, 0.924 mmol) in 95% EtOH (12.5 mL) was stirred at 23°C for 18 h. The solution was concentrated under reduced pressure to afford a white residue. Ether (25 mL) was added and the resulting suspension was filtered. The excess PPTS was then washed with additional portions of ether (2×25 mL). The combined filtrates were washed with saturated $NaHCO_3$ (10 mL), HCl (10 mL of a 1 M solution), saturated $NaHCO_3$ (10 mL), and saturated NaCl (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting clear oil was purified via flash chromatography (2:1–1:1 hexanes–EtOAc) to afford 120 mg (94%) of **43**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69–7.66 (m, 4H), 7.44–7.36 (m, 6H), 5.47 (s, 1H), 4.19 (A of AB, J=13.2 Hz, 1H), 4.13 (B of AB, J=13.2 Hz, 1H), 3.71 (s, 3H), 3.61 (pseudo t, J=6.3 Hz, 2H), 2.50–2.46 (m, 2H), 2.35 (dd, J=18.1, 5.4 Hz, 1H), 2.02 (s, 3H), 1.77–1.54 (m, 5H), 1.06 (s, 9H), 0.94 (d, J=7.1 Hz, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 170.4, 138.3, 135.5, 135.5, 133.7, 133.7, 129.6, 129.6, 127.6, 127.6, 125.1, 84.5, 65.6, 63.8, 51.9, 40.2, 31.5, 31.2, 28.0, 27.7, 26.8, 23.7, 21.6, 19.5, 19.3; IR (film) 3459, 3070, 3049, 2956, 2932, 2857, 1742, 1462, 1428, 1369, 1244, 1112, 1066, 823, 740, 703 cm^{-1}; HRMS (FAB, M+Na) for $C_{32}H_{44}O_6NaSi$ calcd 575.2805, found 575.2808 *m/z*.

4.1.13. 5-[(*tert*-Butyldimethylsilyl)oxy]-1-pentyne (45). To a −78°C solution of 1-pentyn-5-ol (1.86 mL, 20.0 mmol) and 2,6-lutidine (3.49 mL, 30.0 mmol) in CH_2Cl_2 (80 mL) was added TBS-OTf (5.05 mL, 22.0 mmol) dropwise. The reaction was stirred for 1.5 h before it was poured into saturated $NaHCO_3$ solution and diluted with ether. The layers were separated and the organic layer was washed with 1N HCl, brine and dried over $MgSO_4$. The mixture was filtered and concentrated to dryness to give 3.75 g (95% yield) of **45** as a clear oil. This material was used directly in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.69 (t, J=6.0 Hz, 2H), 2.27 (dt, J=2.6, 7.1 Hz, 2H), 1.93 (t, J=2.6 Hz, 1H), 1.72 (tt, J=7.0, 6.0 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 84.3, 68.2, 61.5, 31.5, 25.9, 18.3, 14.9, −5.3; IR (neat) 3314, 2955, 2932, 2897, 2858, 2120, 1472, 1434, 1388, 1361, 1255, 1107, 1072, 980, 942, 835 cm^{-1}; HRMS (CI, NH_3) for $C_7H_{13}OSi$ $[M-C_4H_9]^+$ calcd 141.0736, found 141.0733 *m/z*.

4.1.14. 7-[(*tert*-Butyldimethylsilyl)oxy]-1-[(*tert*-butyldiphenylsilyl)oxy]-3-heptyn-2-one (46). To a −78°C solution of **45** (1.57 g, 7.92 mmol) in THF (25 mL) was added a 2.5 M solution of *n*-BuLi in hexanes (3.33 mL, 8.32 mmol). The reaction mixture was stirred for 20 min and then a solution of Weinreb amide **33** (3.11 g, 8.71 mmol) in THF (5 mL) was added via cannula. The reaction was allowed to warm to 0°C and stirred for 2 h. The reaction mixture was then recooled to −78°C and treated with 5 mL 0.5N HCl. The mixture was allowed to warm to ambient temperature and stirred for 30 min. The mixture was diluted with ether and a saturated solution of $NaHCO_3$. The aqueous layer was separated and extracted with ether (3×30 mL). The combined ethereal extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by column chromatography (20:1 hexanes–ether) to give 3.87 g (98% yield) of **46** as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71–7.66 (m, 4H), 7.47–7.37 (m, 6H), 4.30 (s, 2H), 3.65 (t, J=5.9 Hz, 2H), 2.45 (t, J=7.2 Hz, 2H), 1.75 (tt, J=7.0, 6.0 Hz, 2H), 1.11 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.9, 135.5, 132.7, 129.9, 127.8, 97.0, 78.9, 70.5, 61.2, 30.6, 26.6, 25.9, 19.3, 18.2, 15.6, −5.4; IR (neat) 3072, 3049, 2955, 2932, 2891, 2858, 2210, 1698, 1676, 1589, 1472, 1428, 1390, 1362, 1322, 1255, 1187, 1136, 1111, 1071, 1006, 973, 944, 835 cm^{-1}; HRMS (CI, NH_3) for $C_{25}H_{33}O_3Si_2$ $[M-C_4H_9]^+$ calcd 437.1968, found 437.1963 *m/z*. Anal. calcd for $C_{29}H_{42}O_3Si_2$: C, 70.39; H, 8.56. Found: C, 70.18; H, 8.43.

4.1.15. (2*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-7-[(*tert*-butyldiphenylsilyl)oxy]-4-methyl-3-hepten-2-one (47). To a 0°C suspension of dry copper (I) iodide (3.72 g, 19.6 mmol) in THF (60 mL) was added a 1.4 M solution of MeLi in Et_2O (16.8 mL, 23.5 mmol) dropwise. The solution was stirred for 20 min, then was cooled to −78°C. To this solution was added a solution of alkynyl ketone **46** (3.87 g, 7.82 mmol) in THF (20 mL) via cannula. The resulting mixture was stirred at −78°C for 15 min. The reaction was quenched at −78°C by addition of a saturated solution of NH_4Cl (20 mL) and allowed to warm to 23°C. The mixture was diluted with ether and saturated NH_4Cl solution. The aqueous layer was separated and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by column chromatography (50:1–20:1 hexanes–ether) to partially separate the double bond isomers. The mixed fractions were combined and purified by hplc. The conditions of the hplc separation were 4% EtOAc in hexanes elution at 15 mL/min on a Dynamax 60-A 8 μm silica gel 21.4 mm ID×25 cm L preparative column. The retention time for **47**=10.54 min and the retention time for **34**=13.12 min. The combined fractions containing the less polar compound gave 1.80 g (45% yield) of **47** as a clear oil. A comparable amount of the more polar enone isomer **34** containing 5% of **47** was also obtained. Data for (*Z*)-enone **47**: R_f (10:1 hexanes–EtOAc)=0.43; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69–7.63 (m, 4H), 7.46–7.35 (m, 6H), 6.32 (s, 1H), 4.18 (s, 2H), 3.65 (t, J=6.7 Hz, 2H), 2.63 (m, 2H), 1.91 (d, J=1.0 Hz, 3H), 1.67 (m, 2H), 1.10 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.1, 161.6, 135.5, 133.0, 129.8, 127.8, 119.5, 70.2, 63.1, 31.3, 30.6, 26.8, 26.0, 25.9, 19.3, 18.3, −5.3; IR (neat) 3072, 3049, 2955, 2932, 2891, 2857, 1960, 1893, 1820, 1707, 1687, 1616, 1472, 1429, 1389, 1362, 1255, 1156, 1111, 1001, 939, 836 cm^{-1}; HRMS (CI, NH_3) for $C_{26}H_{37}O_3Si_2$ $[M-C_4H_9]^+$ calcd 453.2281, found 453.2292 *m/z*. Anal. calcd for $C_{30}H_{46}O_3Si_2$: C, 70.53; H, 9.08. Found: C, 70.04; H, 8.96.

4.1.16. (2*Z*,4*Z*)-8-[(*tert*-butyldimethylsilyl)oxy]-3-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-5-methyl-2,4-octadiene (28). To a −78°C suspension of ethyltriphenylphosphonium bromide (4.13 g, 11.1 mmol) in THF (30 mL) was added a 0.5 M solution of potassium hexamethyldisilylazide (KHMDS) in toluene (21.4 mL, 10.7 mmol). The reaction was allowed to warm to 0°C and stirred for 30 min. The resulting dark orange reaction mixture was recooled to −78°C and a solution of enone **47** (2.19 g, 4.28 mmol) in THF (15 mL) was added dropwise via cannula. The reaction was allowed to warm to 0°C and stirred for 2 h. The dark mixture was recooled to −78°C and was poured into a mixture of 1N HCl (60 mL) and 1:1 hexanes–ether (200 mL). The aqueous layer was separated and extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (50:1 hexanes–ether) to give 2.22 g (99% yield) of **28** as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73–7.68 (m, 4H), 7.46–7.38 (m, 6H), 5.79 (br s, 1H), 5.36 (br q, J=7.0 Hz, 1H), 4.23 (s, 2H), 3.62 (t, J=6.7 Hz, 2H), 2.25–2.19 (m, 2H), 1.79 (d, J=1.3 Hz, 3H), 1.68–1.60 (m, 2H), 1.54 (br d, J=7.0 Hz, 3H), 1.05 (s, 9H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.2, 136.7, 135.7, 134.0, 129.5, 127.5, 126.5, 123.8, 63.4, 62.0, 32.0, 29.2, 26.8, 26.0, 23.7, 19.3, 18.3, 13.3, −5.3; IR (neat) 3071, 3048, 2954, 2931, 2891, 2856, 1959, 1899, 1823, 1651, 1590, 1471, 1428, 1387, 1362, 1254, 1191, 1108, 1006, 941, 877, 835 cm^{-1}; HRMS (CI, NH_3) for $C_{32}H_{50}O_2Si_2$ $[M]^+$ calcd 522.3349, found 522.3351 *m/z*.

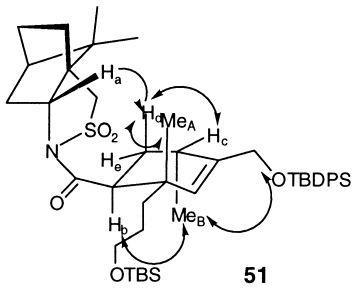
4.1.17. (1*S*,2*R*,5*S*)-1-Acetoxy-2-[[(*tert*-butyldimethylsilyl)oxy]-propyl]-4-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-2,5-dimethyl-3-cyclohexene-1-carboxaldehyde (48). The Diels–Alder reaction of diene **28** (0.052 g, 0.0994 mmol) and α-acetoxy acrolein (**35**) (0.027 g, 0.237 mmol) in the presence of $SnCl_4$ (14 μL,

0.119 mmol) was performed according to the procedure described for the preparation of **36**. Purification of the crude product (essentially pure **48**; ≥98:2 by ^{1}H NMR analysis) by column chromatography (5:1 hexanes–ether) gave 0.056 g (88% yield) of **48** as a clear oil. An analytical sample was obtained by hplc (7% EtOAc–hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.76 (s, 1H), 7.73–7.65 (m, 4H), 7.46–7.35 (m, 6H), 5.48 (br s, 1H), 4.26 (A of AB, J=13.0 Hz, 1H), 4.07 (B of AB, J=13.0 Hz, 1H), 3.67–3.54 (m, 2H), 2.43 (dd, J=14.6, 5.7 Hz, 1H), 2.23 (m, 1H), 2.10 (s, 3H), 1.92 (dd, J=14.6, 11.4 Hz, 1H), 1.85–1.76 (m, 1H), 1.66–1.48 (m, 3H), 1.05 (s, 9H), 1.03 (d, J=7.0 Hz, 3H), 0.94 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.9, 170.7, 137.8, 135.5, 135.4, 133.8, 133.7, 129.6, 127.6, 127.6, 126.9, 87.9, 65.5, 63.7, 41.1, 32.3, 31.3, 27.7, 27.2, 26.7, 25.9, 23.6, 20.8, 19.3, 18.3, 18.2, −5.3; IR (neat) 3072, 3047, 2956, 2932, 2891, 2857, 2732, 1735, 1468, 1428, 1368, 1255, 1199, 1109, 1054, 1009, 941, 836 cm^{-1}; HRMS (CI, NH_3) for $C_{33}H_{47}O_5Si_2$ $[M-C_4H_9]^+$ calcd 579.2962, found 579.2989 *m/z*.

4.1.18. (1*S*,2*R*,5*S*)-1-Bromo-2-[[(*tert*-butyldimethylsilyl)-oxy]-propyl]-4-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-2,5-dimethyl-3-cyclohexene-1-carboxaldehyde (49). The reaction of diene **28** (0.051 g, 0.0975 mmol) and α-bromo acrolein (**38**) (0.034 g, 0.252 mmol) in the presence of $MeAlCl_2$ (107 μL of a 1.0 M hexanes solution, 0.107 mmol) was performed according to the procedure described for the preparation of **39**. Purification of the crude product (a 97:3 mixture of *endo–exo* cycloadducts according to ^{1}H NMR analysis) by column chromatography (10:1 hexanes–ether) gave 0.054 g (84% yield) of **49** (*endo* and *exo* isomers) as a clear oil. An analytical sample of the major cycloadduct **49** was obtained by hplc (5% EtOAc–hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.73 (s, 1H), 7.73–7.67 (m, 4H), 7.46–7.35 (m, 6H), 5.58 (d, J=1.3 Hz, 1H), 4.22 (A of AB, J=13.5 Hz, 1H), 4.14 (B of AB, J=13.5 Hz, 1H), 3.63 (m, 2H), 2.63 (m, 1H), 2.19 (dd, J=14.9, 6.0 Hz, 1H), 2.01 (dd, J=14.9, 10.5 Hz, 1H), 1.86–1.75 (m, 2H), 1.66–1.53 (m, 2H), 1.06 (s, 12H), 1.05 (d, J=7.3 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.0, 138.1, 135.6, 135.4, 133.7, 129.6, 127.7, 127.6, 125.6, 79.7, 65.1, 63.4, 40.4, 37.0, 36.4, 29.4, 27.9, 26.8, 26.0, 23.7, 19.3, 18.4, 18.3, −5.3; IR (neat) 3070, 3046, 2956, 2932, 2893, 2857, 1722, 1471, 1428, 1388, 1362, 1254, 1191, 1112, 1078, 1058, 1006, 836 cm^{-1}; HRMS (CI, NH_3) for $C_{31}H_{44}O_3Si_2$ $[M-C_4H_9]^+$ calcd 599.2012, found 599.1992 *m/z*.

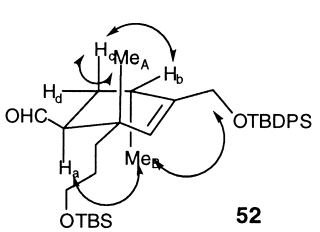
4.1.19. (1′*S*,2′*S*,5′*S*)-[2′-[3-(*tert*-butyldimethyl-silanyl-oxy)-propyl]-4′-(*tert*-butyldiphenyl-silanyloxymethyl)-2′,5′-dimethyl-cyclohex-3-enyl]-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4yl)-methanone (51). To a mixture of diene **24** (993 mg, 1.90 mmol) and *N*-acryloyl sultam **50** (614 mg, 2.28 mmol) in CH_2Cl_2 (10 mL) cooled to −78°C was added methylaluminum dichloride (3.65 mL, 1.0 M hexanes solution). The resulting yellow solution was stirred at −78°C for 1 h and then warmed to 0°C over 1 h; the reaction mixture was quenched slowly with saturated aqueous $NaHCO_3$ and allowed to warm to 23°C. After diluting with Et_2O (10 mL), the white solids were dissipated with 1N HCl (3 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The diastereomeric products (7:1 mixture) were separated by silica gel flash chromatography (10:1 hexanes–EtOAc) to give a combined yield of 66% (990 mg). Data for the major cycloadduct: $[\alpha]_D^{25}$=−61.1 (c=2.0, $CHCl_3$); R_f=0.24 (10:1 hexanes–EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70–7.66 (m, 4H), 7.46–7.35 (m, 6H), 5.36 (X of ABX, J=1.0 Hz, 1H), 4.16 (A of ABX, J=13.2, 0.7 Hz, 1H), 4.06 (B of ABX, J=13.9, 0.7 Hz, 1H), 3.92 (dd, J=7.8, 4.9 Hz, 1H), 3.55–3.60 (m, 1H), 3.48 (A of AB, J=13.7 Hz, 1H), 3.47–3.42 (m, 1H), 3.41 (A of AB, J=13.7 Hz, 1H), 3.26 (dd, J=11.2, 2.7 Hz, 1H), 2.36–2.30 (m, 1H), 2.08 (dd, J=7.8, 7.9 Hz, 1H), 2.05–1.85 (m, 5H), 1.72–1.65 (m, 1H), 1.64 (app dt, J=13.3, 3.0 Hz, 1H), 1.46–1.29 (m, 5H), 1.19 (s, 3H), 1.05 (s, 9H), 1.03 (s, 3H), 0.99 (d, J=7.3 Hz, 3H), 0.97 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7, 138.9, 135.56, 135.52, 133.9, 133.7, 129.5, 128.9, 127.6, 127.57, 65.9, 65.4, 63.7, 53.4, 47.8, 47.7, 44.2, 38.9, 38.6, 37.9, 32.9, 30.2, 28.3, 27.4, 26.8, 25.9, 23.9, 20.9, 19.9, 19.3, 19.2, 18.3; IR (thin film) 3071, 3049, 2958, 2930, 2890, 2857, 1697, 1471, 1462, 1428, 1390, 1361, 1333, 1261, 1235, 1202, 1131, 1111, 1066, 1051, 999, 980, 939, 836, 775, 737, 702 cm^{-1}; HRMS (FAB) for $C_{45}H_{69}NO_5SSi_2$ $[M+Na]^+$ calcd 814.4333, found 814.4296 *m/z*.

NOE Data for **51** and **52**



51

H	δ ($CDCl_3$)	J =
a	3.92	7.8, 4.9 Hz
b	3.26	11.2, 2.7 Hz
c	2.35	
d	2.00	
e	1.64	13.3, 3.0 Hz
Me_A	1.03	
Me_B	0.99	7.3 Hz



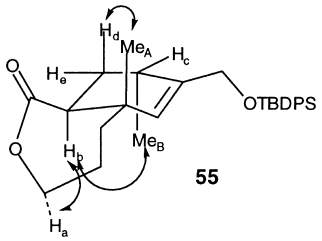
52

H	δ ($CDCl_3$)	J=
a	2.53	11.9, 2.6 Hz
b	2.35	
c	1.89	13.5, 12.1, 5.7 Hz
d	1.64	
Me_A	0.99	
Me_B	0.95	7.1 Hz

4.1.20. (1*S*,2*S*,5*S*)-2-[3-(*tert*-Butyldimethylsilanyloxy)-propyl]-4-(*tert*-butyldiphenylsilanyloxymethyl)-2,5-dimethyl-cyclohex-3-enecarbaldehyde (52). A solution of cyclohexene **51** (265 mg, 0.334 mmol) in CH_2Cl_2 (4 mL) was cooled to −78°C and DIBAL-H (388 μL, 1.0 M solution in CH_2Cl_2) was added dropwise. After stirring the reaction mixture at −78°C for 1.5 h, MeOH (8 mL) and 1N HCl (5 mL) were added. The mixture was allowed to warm to 23°C and poured into a mixture of CH_2Cl_2 (10 mL) and H_2O (8 mL); the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The desired aldehyde **52** was isolated following silica gel flash chromatography (5:1 hexanes–EtOAc) (145 mg, 75%) as a colorless oil along with a small amount of the over-reduced alcohol (13 mg, 7%). Data for aldehyde **52**: $[\alpha]_D^{25}=-18.3$ (c=2.0, $CHCl_3$); R_f=0.29 (15:1 hexanes–Et_2O); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.85 (d, J=1.0 Hz, 1H), 7.70–7.63 (m, 4H), 7.46–7.36 (m, 6H), 5.29 (X of ABX, J=1.0 Hz, 1H), 4.14 (A of ABX, J=13.5, 1.3 Hz, 1H), 4.07 (B of ABX, J=13.2, 1.0 Hz, 1H), 3.6 (t, J=6.3 Hz, 2H), 2.53 (app dt, J=11.9, 2.6 Hz, 1H), 2.35 (m, 1H), 1.89 (ddd, J=13.5, 12.1, 5.7 Hz, 1H), 1.68–1.56 (m, 3H), 1.50–1.42 (m, 2H), 1.06 (s, 9H), 0.99 (s, 3H), 0.95 (d, J=7.1 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.0, 140.0, 135.6, 135.5, 133.8, 133.6, 129.6, 127.6, 127.5, 65.9, 63.7, 49.0, 37.6, 36.8, 27.9, 27.7, 26.8, 26.7, 25.9, 25.8, 24.1, 19.2, 18.4, −5.3; IR (thin film) 3071, 2957, 2930, 2858, 1724, 1589, 1462, 1428, 1387, 1361, 1271, 1257, 1112, 1072, 939, 835, 775, 740, 702 cm^{-1}; HRMS (ES) for $C_{35}H_{54}O_3Si_2Na$ $[M+Na]^+$ calcd 601.3509, found 601.3502 *m/z*.

4.1.21. (5a*R*,8*R*,9a*R*)-7-(*tert*-Butyl-diphenyl-silanyloxymethyl)-5a,8-dimethyl-4,5,5a,8,9,9a-hexahydro-3*H*-benzo[*c*]oxepin-1-one (55). To a solution of aldehyde **52** (89 mg, 0.154 mmol) in absolute EtOH (2.5 mL) was added pyridinium *p*-toluenesulfonate (15 mg, 0.119 mmol). The reaction mixture was diluted with H_2O and Et_2O after stirring for 18 h at 23°C; the layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The organic extracts were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude lactol product was dissolved in CH_2Cl_2 (700 μL) and added to a suspension of PCC (14 mg, 0.065 mmol) and silica gel (14 mg) in CH_2Cl_2 (500 μL). After stirring overnight at 23°C a second portion of PCC was added (14 mg) and the reaction mixture was stirred for an additional 3 h at 23°C. Finally, saturated aqueous $NaHCO_3$ was added followed by Et_2O and H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL); the organic extracts were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash chromatography (6:1 hexanes–EtOAc) to give lactone **55** as a clear oil. $[\alpha]_D^{25}=-109.7$ (c=2.0, $CHCl_3$); R_f=0.30 (4:1 hexanes–EtOAc); ^1H NMR (C_6D_6, 500 MHz) δ 7.80–7.75 (m, 4H), 7.26–7.21 (m, 6H), 5.18 (br s, 1H), 4.12 (A of ABX, J=13.5, 1.7 Hz, 1H), 4.08 (B of ABX, J=13.2, 1.2 Hz, 1H), 3.68–3.64 (m, 1H), 3.47 (app t, J=12.0 Hz, 1H), 2.58 (dd, J=12.5, 3.1 Hz, 1H), 2.21–2.12 (m, 2H), 1.71 (dd, J=12.7, 2.7 Hz, 1H), 1.60–1.50 (m, 1H), 1.26–1.22 (m, 1H), 1.18 (s, 9H), 1.08–0.97 (m, 2H), 0.88 (s, 3H), 0.81 (d, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.7, 139.2, 135.6, 135.5, 133.7, 133.6, 130.6, 129.64, 129.63, 127.62, 127.60, 68.6, 65.8, 43.0, 41.8, 34.9, 29.7, 27.9, 26.8, 25.5, 20.2, 19.33, 19.30; IR (thin film) 3070, 2959, 2930, 2856, 1734, 1472, 1460, 1427, 1389, 1367, 1286, 1175, 1163, 1124, 1112, 1087, 1070, 1038, 998, 938, 869, 823 cm^{-1}; HRMS (CI, NH_3) for $C_{29}H_{39}O_3Si$ $[M+H]^+$ calcd 463.2668, found 463.2678 *m/z*.

NOE Data for **55**



H	δ (C_6D_6)	J=
a	3.47	
b	2.58	12.5, 3.1 Hz
c	2.19	
d	2.14	
e	1.71	12.7, 2.7 Hz
Me_A	0.88	7.3 Hz
Me_B	0.81	

4.1.22. (1′*R*,2′*R*,4*S*,5′*R*)-3-[2′-[3-(*tert*-Butyldimethyl-silanyloxy)-propyl]-4′-(*tert*-butyldiphenyl-silanyloxymethyl)-2′,5′-dimethyl-cyclohex-3′-enecarbonyl]-4-isopropyl-oxazolidin-2-one (54). To a solution of diene **24** (258 mg, 0.493 mmol) and *N*-acryloyl oxazolidinone **53** (98 mg, 0.535 mmol) in CH_2Cl_2 (5 mL) cooled to −78°C was added $MeAlCl_2$ (1.07 mL of a 1.0 M solution in hexanes, 1.07 mmol). The resulting yellow solution was stirred at −78°C for 2 h and then warmed to 0°C over 1 h; the reaction mixture was quenched slowly with saturated aqueous $NaHCO_3$ and allowed to warm to 23°C. After diluting with Et_2O (10 mL), the white solids were dissipated with 1N HCl (3 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The diastereomeric products (3:2 mixture, 289 mg, 83%) were inseparable by silica gel flash chromatography (4:1 hexanes–EtOAc) or HPLC purification. Data for the mixture: $[\alpha]_D^{25}=+30.4$ (c=3.4, $CHCl_3$); R_f=0.25 (10:1 hexanes–EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71–7.67 (m, 4H), 7.44–7.35 (m, 6H), 5.48 (s, 0.7H), 5.36 (s, 1H), 4.55–4.49 (m, 1.8H), 4.32–4.05 (m, 10H), 3.60–3.46 (m, 5H), 2.38–2.03 (m, 3.8H), 1.78–1.20 (m, 15H), 1.14 (s, 3H), 1.05 (s, 9H), 1.04 (s, 6H), 0.92 (s, 15H), 0.87 (m, 10H), 0.10 (s, 6H), 0.30 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) (combined data for the two isomers) δ 175.5, 175.1, 153.9, 153.8, 138.8, 138.6, 135.6, 135.54, 135.51, 133.9, 133.8, 133.7, 130.3, 129.7, 129.6, 129.5, 128.3, 127.63, 127.60, 127.58, 66.0, 65.7, 64.0, 63.9, 62.54, 62.53, 58.5, 58.45, 46.8, 39.9, 38.3, 38.0, 37.6, 34.6, 32.3, 31.2, 30.7, 28.6, 28.5, 28.47, 27.8, 27.7, 26.8, 26.79, 26.5, 26.0, 25.98, 25.9, 23.8, 19.3, 19.26, 18.9, 18.3, 18.28, 18.2, 18.15, 14.7, −5.3, −5.34; IR (thin film) 2957, 2930, 2857, 1781, 1697, 1462, 1428, 1384, 1361, 1299, 1255, 1201, 1104, 1057, 1025, 940, 835, 775, 740, 702 cm^{-1}; HRMS (ES) for $C_{41}H_{63}NO_5Si_2Na$ $[M+Na]^+$ calcd 728.4143, found 728.4153 *m/z*.

4.1.23. (4*S*,1′*R*,2′*R*,5′*R*)-3-[4′-(*tert*-Butyldiphenyl-silanyloxymethyl)-2′-(3-hydroxypropyl)-2′,5′-dimethyl-cyclohex-3′-enecarbonyl]-4-isopropyl-oxazolidin-2-one. A solution of cyclohexene isomers **54** (125 mg, 0.177 mmol) and pyridinium *p*-toluenesulfonate (36 mg, 0.143 mmol) in absolute EtOH (2.2 mL) was stirred at 23°C for 18 h. The

mixture was poured into 5 mL of H_2O and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification of the crude product by gradient silica gel flash chromatography (2:1 hexanes–EtOAc →2:1 EtOAc–hexanes) yielded 87 mg of the major isomer as a colorless foam (83%). $[\alpha]_D^{25}$=+38.8 (*c*=4.5, $CHCl_3$); R_f=0.57 (1:1 hexanes–EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71–7.67 (m, 4H), 7.45–7.36 (m, 6H), 5.32 (X of ABX, *J*=1.0 Hz, 1H), 4.55 (app dt, *J*=3.4, 6.7 Hz, 1H), 4.33 (dd, *J*=12.0, 2.6 Hz, 1H), 4.27 (app t, *J*=8.8 Hz, 1H), 4.19 (dd, *J*=9.0, 3.4 Hz, 1H), 4.16 (A of ABX, *J*=13.5, 1.2 Hz, 1H), 4.08 (B of ABX, *J*=13.2, 1.0 Hz, 1H), 3.62–3.52 (m, 2H), 2.38–2.30 (m, 2H), 2.10 (ddd, *J*=13.1, 5.3, 4.7 Hz, 1H), 1.76–1.68 (m, 1H), 1.54–1.34 (m, 4H), 1.06 (s, 9H), 1.05 (s, 3H), 1.01 (d, *J*=7.0 Hz, 3H), 0.93 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3, 154.2, 139.2, 135.54, 135.50, 133.8, 133.7, 129.6, 129.4, 127.6, 127.56, 65.9, 63.3, 62.6, 58.5, 39.2, 38.3, 37.6, 31.2, 28.5, 28.3, 27.8, 26.8, 24.4, 19.3, 18.1, 14.6; IR (thin film) 3517, 3071, 2960, 2931, 2858, 1777, 1699, 1486, 1462, 1427, 1386, 1300, 1202, 1143, 1112, 1058, 1024, 938, 874, 822, 793, 734, 702 cm^{-1}; HRMS (FAB) for $C_{35}H_{49}O_5NSiNa$ $[M+Na]^+$ calcd 614.3278, found 614.3267 *m/z*.

Data for the minor diastereomer: $[\alpha]_D^{25}$=+49.3 (*c*=1.0, $CHCl_3$); R_f=0.37 (1:1 hexanes–EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70–7.67 (m, 4H), 7.44–7.37 (m, 6H), 5.48 (d, *J*=1.4 Hz, 1H), 4.52 (app dt, *J*=3.4, 7.0 Hz, 1H), 4.25 (app t, *J*=9.0 Hz, 1H), 4.20–4.08 (m, 4H), 3.62–3.55 (m, 2H), 2.36–2.28 (m, 2H), 1.77–1.72 (m, 2H), 1.67–1.50 (m, 2H), 1.35–1.29 (m, 2H), 1.15 (s, 3H), 1.04 (s, 9H), 0.96 (d, *J*=7.1 Hz, 3H), 0.94 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3, 153.8, 138.9, 135.5, 135.49, 133.8, 133.7, 129.9, 129.6, 127.63, 127.60, 65.6, 63.9, 62.6, 58.5, 46.7, 37.6, 34.6, 32.4, 30.7, 28.6, 27.9, 26.8, 26.7, 19.3, 18.9, 18.2, 14.7; IR (thin film) 3435, 3072, 2959, 2931, 2858, 1780, 1691, 1647, 1460, 1428, 1385, 1361, 1299, 1278, 1202, 1112, 1056, 823, 822, 743, 702 cm^{-1}; HRMS (ES) for $C_{35}H_{49}O_5NSiNa$ $[M+Na]^+$ calcd 614.3278, found 614.3279 *m/z*.

4.1.24. (5a*R*,8*R*,9a*R*)-7-(*tert*-Butyldiphenyl-silanyloxy-methyl)-5a,8-dimethyl-4,5,5a,8,9,9a-hexahydro-3*H*-benzo[*c*]oxepin-1-one (*ent*-55). To a suspension of sodium hydride (60% dispersion, washed with hexanes) in THF (13.5 mg in 2 mL, 0.338 mmol) cooled to 0°C was added via cannulation a solution of the cyclohexene alcohol in THF (140 mg in 4 mL, 0.237 mmol). The resulting mixture was stirred at 0°C for 4 h and then quenched by the addition of 1N HCl (5 mL). The reaction was diluted with EtOAc and H_2O, the layers were separated and the aqueous layer was extracted with EtOAc (2×12 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. After silica gel flash chromatography of the crude product (2:1 hexanes–EtOAc), lactone *ent*-**55** was obtained as a clear oil (55 mg, 50%). This material was spectroscopically identical to **55** and differed only in the sign of optical rotation; $[\alpha]_D^{25}$=+87.9 (*c*=4.2, $CHCl_3$).

4.1.25. (1*S*,2*S*,5*S*)-2-[3-(*tert*-Butyldimethyl-silanyloxy-propyl)]-4-(*tert*-butyldiphenyl-silanyloxymethyl)-2,5-dimethyl-cyclohex-3-enylidenemethoxy-trimethylsilane (56). To a solution of aldehyde **52** (669 mg, 1.16 mmol) and Et_3N (2.15 mL, 15.4 mmol) in CH_2Cl_2 (9.4 mL) was added TMS-OTf (2 mL, 11.1 mmol). After allowing the reaction mixture to stir at 23°C for 2 h, it was cooled to 0°C and saturated aqueous $Na_2S_2O_3$ (10 mL) was carefully added. Following dilution with hexanes (10 mL) the layers were separated and the aqueous layer was extracted with hexanes (2×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification of the crude product by silica gel flash chromatography (15:1 hexanes–EtOAc) yielded 663 mg of **56** as a 3:1 mixture of *E*(O) and *Z*(O) enol silanes (88%). An analytically pure sample of the major *E*(O) isomer was obtained by HPLC purification (1% EtOAc–hexanes): $[\alpha]_D^{23}$=−4.6 (*c*=2.7, $CHCl_3$); R_f=0.26 (50:1 hexanes–Et_2O); ^{1}H NMR (C_6D_6, 500 MHz) δ 7.85–7.81 (m, 4H), 7.28–7.22 (m, 6H), 6.45 (s, 1H), 5.39 (s, 1H), 4.24 (A of ABX, *J*=12.9, 1.0 Hz, 1H), 4.14 (B of ABX, *J*=13.2, 1.0 Hz, 1H), 3.62–3.58 (m, 1H), 3.56–3.51 (m, 1H), 2.67 (dd, *J*=13.4, 4.4 Hz, 1H), 2.48 (ddd, *J*=13.2, 5.3, 1.4 Hz, 1H), 2.38–2.31 (m, 1H), 1.83–1.70 (m, 2H), 1.57–1.42 (m, 2H), 1.20 (s, 12H), 1.01 (d, *J*=5.6 Hz, 3H), 0.99 (s, 9H), 0.17 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.1, 135.6, 135.5, 134.0, 133.9, 133.3, 130.8, 129.51, 129.50, 127.6, 127.5, 123.2, 66.0, 63.8, 38.3, 36.6, 30.5, 29.7, 28.3, 27.7, 26.8, 26.0, 19.3, 19.2, 18.3, −0.4, −5.26, −5.27; IR (thin film) 3071, 3050, 2956, 2930, 2894, 2857, 1660, 1589, 1472, 1462, 1428, 1389, 1361, 1253, 1163, 1144, 1112, 1055, 1006, 973, 953, 937, 878, 842, 775, 739, 701 cm^{-1}; HRMS (ES) for $C_{38}H_{62}O_3Si_3Na$ $[M+Na]^+$ calcd 673.3905, found 673.3909 *m/z*. Anal. calcd for $C_{38}H_{62}O_3Si_3$: C, 70.09; H, 9.60. Found: C, 70.07; H, 9.82.

4.1.26. (1*S*,2*S*,5*S*)-1-Bromo-2-[3-(*tert*-butyldimethyl-silanyloxy)-propyl]-4-(*tert*-butyldiphenylsilanyloxy-methyl)-2,5-dimethyl-cyclohex-3-enal (39). To a solution of enol silane **56** (28 mg, 0.043 mmol) in carbon tetrachloride (600 μL) cooled to 0°C was added bromodimethyl-sulfonium bromide in one portion. The heterogeneous mixture became clear and homogeneous after stirring for 15 min at 0°C. Triethylamine (50 μL) was added carefully and the reaction mixture was diluted with CH_2Cl_2 (5 mL), saturated aqueous $NaHCO_3$ (3 mL), and H_2O (8 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×8 mL). The combined organic extracts were washed with 1N HCl and brine, dried over $MgSO_4$, filtered and concentrated. The diastereomeric products (5:1 mixture) were separated by silica gel flash chromatography (15:1 hexanes–EtOAc). The major product (23 mg, 82%) was spectroscopically identical to the data reported here for racemic **39**; $[\alpha]_D^{23}$=+70.4 (*c*=3.0, $CHCl_3$).

4.1.27. (1*S*,2*S*,5*S*)-2-[3-(*tert*-Butyldimethyl-silanyloxy)-propyl]-4-(*tert*-butyldiphenyl-silanyloxymethyl)-1-hydroxy-2,5-dimethyl-cyclohex-3-enecarbaldehyde (57). To a solution of enol silane **56** (214 mg, 0.33 mmol) in CH_2Cl_2 cooled to 0°C was added dimethyldioxirane (5.8 mL of a 0.06 M solution in acetone, 0.348 mmol) dropwise. After stirring the reaction mixture at 0°C for 10 min the mixture was concentrated in vacuo and the resulting oil was diluted with Et_2O (15 mL) and 1N HCl (5 mL). The layers were separated and the aqueous layer

was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to obtain a 10:1 mixture of diastereomers. The major isomer was separated from the minor diastereomer by silica gel flash chromatography (12:1 hexanes–EtOAc) to give a 78% combined yield (152 mg). Data for major diastereomer **57**: $[\alpha]_D^{24}$=+11.7 (c=3.7, $CHCl_3$); R_f=0.60 (6:1 hexanes–EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.77 (d, J=1.0 Hz, 1H), 7.71–7.68 (m, 4H), 7.45–7.37 (m, 6H), 5.46 (d, J=1.4 Hz, 1H), 4.23 (app dt, J=13.2, 1.2 Hz, 1H), 4.16 (d, J=13.7 Hz, 1H), 3.58–3.54 (m, 2H), 3.16 (d, J=1.0 Hz, 1H), 2.60–2.52 (m, 1H), 1.83 (dd, J=13.6, 6.6 Hz, 1H), 1.78 (dd, J=13.7, 8.3 Hz, 1H), 1.60–1.39 (m, 4H), 1.07 (s, 9H), 1.02 (d, J=7.4 Hz, 3H), 1.0 (s, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.5, 138.5, 135.55, 135.51, 133.71, 133.70, 129.63, 129.61, 127.64, 127.60, 127.4, 80.4, 65.5, 63.4, 41.5, 36.0, 35.9, 27.7, 27.2, 26.8, 25.9, 20.5, 19.3, 19.2, 18.3, −5.3; IR (thin film) 3510, 3071, 3049, 2955, 2930, 2857, 1717, 1589, 1472, 1428, 1389, 1361, 1255, 1111, 1060, 1006, 938, 835, 776, 740, 702 cm^{-1}; HRMS (ES) for $C_{35}H_{54}O_4Si_2Na$ $[M+Na]^+$ calcd 617.3458, found 617.3462 *m/z*.

4.1.28. (1*S*,2*S*,5*S*)-4-(*tert*-Butyldiphenylsilanyloxymethyl)-1-hydroxy-2-(3-hydroxy-propyl)-2,5-dimethyl-cyclohex-3-enecarboxylic acid methyl ester (58). A solution of aldehyde **57** (43 mg, 0.072 mmol) in MeOH (720 μL) was cooled to 0°C and methanolic solutions of KOH (720 μL of a 0.78 M solution, 0.562 mmol) and I_2 (360 μL of a 0.78 M solution, 0.281 mmol) were added successively. The resulting dark brown mixture was stirred at 0°C for 45 min, after which time a second portion of KOH (60 μL, 0.047 mmol) and I_2 (24 μL, 0.019 mmol) solutions were again added successively. The starting material was completely consumed 15 min after the second addition of potassium hydroxide and iodine (total reaction time=1 h). The reaction mixture was diluted with 2N H_2SO_4 (5 mL) and Et_2O (8 mL) and stirred at 23°C for 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Following silica gel flash chromatography (10:1 hexanes–EtOAc), a colorless oil was obtained (31 mg, 84%). $[\alpha]_D^{24}$=+73.4 (c=1.9, $CHCl_3$); R_f=0.33 (1:1 hexanes–EtOAc); ^1H NMR (C_6D_6, 500 MHz) δ 7.88–7.83 (m, 4H), 7.28–7.23 (m, 6H), 5.40 (d, J=1.7 Hz, 1H), 4.32 (app dt, J=13.1, 1.3 Hz, 1H), 4.20 (d, J=13.4 Hz, 1H), 3.28 (s, 3H), 3.27–3.24 (m, 2H), 3.09 (s, 1H), 2.74–2.66 (m, 1H), 2.06 (dd, J=13.2, 13.7 Hz, 1H), 1.94 (dd, J=13.7, 5.9 Hz, 1H), 1.58–1.44 (m, 2H), 1.38–1.30 (m, 2H), 1.02 (s, 9H), 1.12 (s, 3H), 0.92 (d, J=7.1 Hz, 3H), 0.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.6, 138.5, 135.6, 135.5, 133.82, 133.81, 129.59, 129.58, 127.62, 127.57, 126.8, 78.2, 65.4, 63.6, 52.2, 41.5, 36.9, 36.7, 28.0, 27.2, 26.8, 19.7, 19.3, 18.5; IR (thin film) 3436, 3071, 2954, 2857, 1723, 1589, 1472, 1456, 1428, 1389, 1259, 1151, 1111, 1058, 869, 823, 741, 702 cm^{-1}; HRMS (ES) for $C_{30}H_{42}O_5$-SiNa $[M+Na]^+$ calcd 533.2699, found 533.2694 *m/z*.

4.1.29. Methyl (1*S*,2*S*,5*S*)-1-acetoxy-2-(3-acetoxy-propyl)-4-(*tert*-butyl-diphenylsilanyloxymethyl)-2,5-dimethyl-cyclohex-3-enecarboxyate (59). To a solution of **58** (25 mg, 0.049 mmol) in acetic anhydride (400 μL) cooled to 0°C was added a solution of scandium triflate in CH_3CN (13 mg in 100 μL, 0.026 mmol). The reaction mixture was immediately diluted with saturated aqueous $NaHCO_3$ (1 mL) and Et_2O (2 mL), and allowed to warm to 23°C and stirred for 1 h until the effervescence subsided. The mixture was further diluted with Et_2O (5 mL) and H_2O (5 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash chromatography (4:1 hexanes–EtOAc) to obtain **59** as a slightly yellow oil (25 mg, 76%). $[\alpha]_D^{24}$=+22.3 (c=1.6, $CHCl_3$); R_f=0.63 (3:1 hexanes–EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.71–7.68 (m, 4H), 7.45–7.37 (m, 6H), 5.24 (br s, 1H), 4.29 (A of AB, J=12.7 Hz, 1H), 4.06 (B of AB, J=12.9 Hz, 1H), 3.98 (t, J=6.9 Hz, 2H), 3.75 (s, 3H), 2.68 (dd, J=14.7, 5.4 Hz, 1H), 2.25–2.17 (m, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 1.91 (dd, J=14.7, 12.7 Hz, 1H), 1.64–1.57 (m, 2H), 1.46–1.39 (m, 1H), 1.20 (s, 3H), 1.12–1.07 (m, 1H), 1.06 (d, J=6.1 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 171.3, 170.4, 139.0, 135.8, 135.7, 134.1, 134.0, 129.92, 129.90, 127.9, 127.8, 127.7, 84.0, 65.9, 52.2, 41.2, 35.9, 33.4, 27.5, 26.9, 23.7, 21.2, 20.3, 19.5, 18.4; IR (thin film) 3071, 3048, 2956, 2932, 2857, 1742, 1589, 1471, 1458, 1428, 1368, 1238, 1200, 1111, 1063, 879, 824, 743, 704 cm^{-1}; HRMS (ES) for $C_{34}H_{46}O_7SiNa$ $[M+Na]^+$ calcd 617.2911, found 617.2908 *m/z*.

4.1.30. Methyl (1*S*,2*S*,5*S*)-1-acetoxy-4-(*tert*-butyldiphenylsilanyloxymethyl)-2,5-dimethyl-cyclohex-3-enoate (37). A solution of diacetate **59** (22 mg, 0.037 mmol) in THF (185 μL) was cooled to −78°C and DIBAL-H (185 μL of a 1.0 M solution in THF, 0.185 mmol) was added slowly down the side of the flask. The resulting mixture was stirred at −78°C for 30 min and then warmed to −45°C over 20 min; pH 7 buffer was then added (3 mL) and Et_2O (5 mL). This mixture was allowed to warm to 23°C, diluted with saturated aqueous Rochelle's salt (10 mL) and stirred overnight for 18 h. The layers were separated, the aqueous layer was extracted with Et_2O (3×5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Following purification by silica gel flash chromatography (2:1 hexanes–EtOAc) a clear oil was isolated (19 mg, 95%) which was spectroscopically identical to the data reported here for racemic **37**; $[\alpha]_D^{25}$=+79.4 (c=0.6, $CHCl_3$).

4.1.31. Methyl (1*S*,2*S*,5*S*)-1-acetoxy-4-{[(*tert*-butyl-diphenylsilyl)oxy]-methyl}-2,5-dimethyl-2-[(*E*)-3-(formyl)-vinyl]-cyclohex-3-enoate (60). To a −78°C solution of DMSO (47 μL, 0.66 mmol) in CH_2Cl_2 (0.5 mL) was added oxalyl chloride (29 μL, 0.33 mmol) dropwise. The reaction mixture was stirred for 20 min, then **37** (91 mg, 0.165 mmol) was added in CH_2Cl_2 (1.15 mL) via cannula. The reaction was allowed to warm to 0°C and stirred for 1 h. The reaction mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$, 1 M $NaHSO_4$ (2×), and saturated aqueous $NaHCO_3$. The ethereal layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (2:1 hexanes–ether) to give 82 mg (91%) of aldehyde as a

clear colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.69 (br s, 1H), 7.71–7.66 (m, 4H), 7.46–7.34 (m, 6H), 5.19 (br s, 1H), 4.26 (A of AB, J=13.0 Hz, 1H), 4.08 (B of AB, J=13.1 Hz, 1H), 3.76 (s, 3H), 2.70 (dd, J=14.8, 5.4 Hz, 1H), 2.41 (m, 2H), 2.19 (m, 1H), 2.03 (s, 3H), 1.94 (dd, J=14.8, 11.7 Hz, 1H), 1.76 (ddd, J=13.7, 9.5, 6.7 Hz, 1H), 1.40 (ddd, J=13.4, 9.8, 5.3 Hz, 1H), 1.19 (s, 3H), 1.05 (s, 9H), 1.04 (d, J=7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.6, 170.9, 170.0, 139.7, 135.5, 135.4, 133.7, 133.6, 129.7, 127.6, 126.4, 83.5, 65.4, 52.0, 40.5, 39.0, 33.1, 31.3, 27.3, 26.7, 20.9, 20.2, 19.2, 18.0; IR (neat) 3071, 3050, 2957, 2935, 2857, 1740, 1452, 1429, 1368, 1263, 1239, 1198, 1180, 1109, 1061, 1029, 1012, 938, 824 cm^{-1}; HRMS (CI, NH_3) for $C_{28}H_{33}O_6Si$ $[M-C_4H_9]^+$ calcd 493.2046, found 493.2058 *m/z*.

A stirred mixture of aldehyde (188 mg, 0.341 mmol), piperidine (41 μL, 0.409 mmol), and 4 Å molecular sieves (254 mg) in toluene (2.6 mL) was heated at 80°C for 3 h. The white suspension was then cooled to 23°C and filtered through a plug of Celite. The Celite was washed with THF (2×10 mL). The combined filtrates were then concentrated under reduced pressure to afford 286 mg of the crude enamine. The enamine was immediately used in the next step without further purification.

To a −98°C solution of the crude enamine in THF (2.6 mL), PhSeCl (78 mg, 0.409 mmol) in THF (400 μL) was added dropwise over 5 min. The reaction mixture was stirred at −98°C for 5 min and then at −78°C for 20 min. H_2O (1.2 mL) and ether (10 mL) were added cautiously, but sequentially. The mixture was allowed to reach 23°C where it was stirred vigorously for 3 h. The mixture was then poured into ether (30 mL) and saturated NaCl (10 mL). The layers were separated, and the aqueous layer was extracted with ether (3×20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 243 mg of a 1:1 mixture α-selenoaldehyde diastereomers. The crude product was used in the next step without any additional purification.

To 0°C suspension of the crude α-selenoaldehydes in MeOH–THF–H_2O (2:1:1, 12.7 mL) was added $NaIO_4$ (146 mg, 0.683 mmol). The reaction was stirred at 23°C for 1 h, then cooled to 0°C and an additional portion of $NaIO_4$ (145 mg, 0.678 mmol) was added. The yellow mixture was stirred for an additional 1 h. The suspension was cooled to 0°C, and ether (50 mL) and saturated $Na_2S_2O_3$ (10 mL) were added sequentially. The layers were separated; the aqueous layer was extracted with ether (3×30 mL). The combined organic layers were washed with H_2O (20 mL) and saturated NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (10:1–4:1 hexanes–EtOAc) to deliver 162 mg (86% for three steps) of α,β-unsaturated aldehyde **60**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.51 (d, J=7.7 Hz, 1H), 7.72–7.65 (m, 4H), 7.47–7.36 (m, 6H), 6.55 (d, J=15.7 Hz, 1H), 6.02 (dd, J=15.7, 6.7 Hz, 1H), 5.18 (br s, 1H), 4.28 (A of AB, J=13.6 Hz, 1H), 4.14 (B of AB, J=13.7 Hz, 1H), 3.73 (s, 3H), 2.67 (dd, J=14.8, 5.4 Hz, 1H), 2.20 (m, 1H), 2.07 (s, 3H), 1.82 (dd, J=14.8, 11.7 Hz, 1H), 1.36 (s, 3H), 1.04 (s, 9H), 1.02 (d, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.4, 170.2, 169.9, 159.2, 141.4, 135.5, 135.4, 133.6, 133.5, 133.0, 129.8, 127.7, 127.7, 124.0, 82.0, 65.0, 52.2, 45.5, 33.3, 27.5, 26.7, 20.8, 20.5, 19.3, 17.9; IR (neat) 3072, 3050, 2956, 2930, 2856, 2736, 1743, 1692, 1632, 1459, 1429, 1370, 1261, 1233, 1203, 1155, 1108, 1034, 985, 824 cm^{-1}; HRMS (CI, NH_3) for $C_{28}H_{31}O_6Si$ $[M-C_4H_9]^+$ calcd 491.1890, found 491.1890 *m/z*.

4.1.32. Methyl (1*S*,2*S*,5*S*)-1-acetoxy-2-{3-[(*tert*-butyldimethylsilyl)oxy]-propenyl}-4-{[(*tert*-butyldiphenylsilyl)oxy]-methyl]-2,5-dimethyl-cyclohex-3-enoate (61). To a −20°C solution of aldehyde **60** (136 mg, 0.25 mmol) in THF (4.25 mL) was added $LiAlH(tert\text{-}BuO)_3$ (322 μL of 1.0 M solution in THF, 0.32 mmol). The reaction was stirred at −20°C for 90 min, whereupon MeOH (200 μL) and saturated aqueous $NaHCO_3$ (2 mL) were added sequentially. The mixture was then partitioned between ether (40 mL) and saturated aqueous NaCl (10 mL). The layers were separated; the aqueous layer was extracted with ether (3×30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting foam was purified by flash chromatography (2:1 hexanes–EtOAc) to afford 127 mg (93%) of the allylic alcohol. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72–7.68 (m, 4H), 7.46–7.36 (m, 6H), 5.57 (dt, J=15.4, 5.4 Hz, 1H), 5.43 (dt, J=15.4, 1.3 Hz, 1H), 5.15 (d, J=1.2 Hz, 1H), 4.31 (A of AB, J=12.8 Hz, 1H), 4.12 (B of AB, J=13.1 Hz, 1H), 4.09 (d, J=5.3 Hz, 2H), 3.72 (s, 3H), 2.57 (dd, J=14.4, 5.4 Hz, 1H), 2.20 (m, 1H), 2.04 (s, 3H), 1.88 (dd, J=14.4, 11.8 Hz, 1H), 1.61 (br s, 1H), 1.29 (s, 3H), 1.04 (s, 9H), 1.04 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 170.1, 139.5, 135.5, 135.4, 135.0, 133.8, 133.7, 131.4, 129.7, 129.6, 127.6, 127.6, 126.4, 82.9, 65.4, 63.2, 51.9, 44.4, 32.8, 27.4, 26.7, 21.2, 20.9, 19.3, 18.1; IR (neat) 3467 br, 3072, 3048, 2957, 2934, 2858, 1742, 1458, 1429, 1369, 1262, 1200, 1159, 1107, 1058, 1028, 985, 824 cm^{-1}; HRMS (CI, NH_3) for $C_{28}H_{33}O_6Si$ $[M-C_4H_9]^+$ calcd 493.2046, found 493.2064 *m/z*.

To a −78°C solution of allylic alcohol (51 mg, 0.093 mmol) and 2,6-lutidine (54 μL, 0.46 mmol) in CH_2Cl_2 (2 mL) was added TBS-OTf (43 μL, 0.185 mmol) dropwise. The reaction mixture was stirred for 1.5 h, quenched with saturated aqueous $NaHCO_3$, and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with 1N HCl, saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (4:1 hexanes–Et_2O) to give 57 mg (93%) of **61** as a clear colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73–7.69 (m, 4H), 7.46–7.36 (m, 6H), 5.43 (dt, J=15.2, 4.6 Hz, 1H), 5.39 (dt, J=15.2, 4.6 Hz, 1H), 5.16 (d, J=1.4 Hz, 1H), 4.23 (A of AB, J=12.9 Hz, 1H), 4.12 (dd, J=4.5, 1.2 Hz, 2H), 4.11 (B of AB, J=12.9 Hz, 1H), 3.71 (s, 3H), 2.58 (dd, J=14.4, 5.4 Hz, 1H), 2.21 (m, 1H), 2.04 (s, 3H), 1.89 (dd, J=14.4, 11.7 Hz, 1H), 1.29 (s, 3H), 1.04 (s, 9H), 1.04 (d, J=7.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 170.2, 139.2, 135.5, 133.9, 133.7, 133.1, 131.8, 129.6, 127.6, 126.8, 82.9, 65.5, 63.5, 51.8, 44.5, 32.7, 27.4, 26.7, 25.9, 21.3, 20.9, 19.3, 18.3, 18.1, −5.2; IR (neat) 3072, 3053, 2954, 2857, 1745, 1470, 1429,

1368, 1258, 1110, 1058, 987, 836 cm^{-1}; HRMS (CI, NH_3) for $C_{34}H_{47}O_6Si_2$ $[M-C_4H_9]^+$ calcd 607.2911, found 607.2897 *m/z*.

4.1.33. (5*S*,6*S*,9*S*)-6-{3-[(*tert*-Butyldimethylsilyl)oxy]-propenyl}-8-{[(*tert*-butyldiphenylsilyl)oxy]-methyl}-6,9-dimethyl-4-{[(methoxy)methyl]-oxy}-1-oxaspiro[4.5]-deca-3,7-dien-2-one (1). To a −78°C of **61** (57 mg, 0.0857 mmol) in THF (2 mL) was added LHMDS (0.129 mmol of a 1.0 M solution in THF, 0.129 mmol). The reaction mixture was stirred for 1 h, then warmed to 0°C and stirred for 1 h longer, then MOM-Cl (13 μL, 0.171 mmol) was added. The reaction was stirred for 1 h, then diluted with Et_2O and saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (1:1 hexanes–Et_2O) to give 32 mg (55%) of **1** and 21 mg of recovered starting material (37%) as clear colorless oils. Data for **1**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75–7.69 (m, 4H), 7.46–7.39 (m, 6H), 5.73 (br d, J=15.4 Hz, 1H), 5.49 (dt, J=15.4, 4.9 Hz, 1H), 5.34 (d, J=1.6 Hz, 1H), 5.24 (s, 1H), 5.10 (s, 2H), 4.21 (br s, 2H), 4.18 (d, J=4.4 Hz, 2H), 3.47 (s, 3H), 2.60 (m, 1H), 1.99 (dd, J=13.6, 6.3 Hz, 1H), 1.73 (dd, J=13.6, 6.3 Hz, 1H), 1.07 (s, 3H), 1.05 (s, 9H), 1.00 (d, J=6.9 Hz, 3H), 0.90 (s, 9H), 0.06 (d, J=0.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.3, 172.0, 139.3, 135.5, 133.9, 134.4, 133.6, 130.3, 129.6, 127.7, 127.6, 125.8, 96.7, 87.2, 65.1, 63.7, 57.3, 44.0, 36.4, 28.7, 26.8, 25.9, 20.3, 19.3, 18.6, 18.4, −5.1; IR (neat) 3070, 3048, 2957, 2930, 2890, 2857, 1759, 1627, 1470, 1351, 1335, 1252, 1112, 1090, 1009, 995, 911, 836 cm^{-1}; HRMS (CI, NH_3) for $C_{35}H_{47}O_6Si_2$ $[M-C_4H_9]^+$ calcd 619.2911, found 619.2908 *m/z*.

4.1.34. (5*R*,6*S*,9*S*)-6-{3-[(*tert*-Butyldimethylsilyl)oxy]-propenyl}-8-{[(*tert*-butyldiphenylsilyl)oxy]-methyl}-6,9-dimethyl-4-{[(methoxy)methyl]-oxy}-1-oxaspiro[4.5]-deca-3,7-dien-2-one (2). Spirotetronate **2** was synthesized from **43** by using a sequence similar to that described for the conversion of **37** to **1**.[21] ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73–7.66 (m, 4H), 7.47–7.35 (m, 6H), 5.75 (dt, J=15.7, 1.3 Hz, 1H), 5.46 (dt, J=15.6, 5.5 Hz, 1H), 5.32 (d, J=1.1 Hz, 1H), 5.20 (s, 1H), 5.00 (A of AB, J=6.0 Hz, 1H), 4.99 (B of AB, J=6.0 Hz, 1H), 4.31 (A of AB, J=12.5 Hz, 1H), 4.19–4.14 (m, 3H), 3.36 (s, 3H), 2.76 (m, 1H), 2.04 (dd, J=13.4, 10.4 Hz, 1H), 1.83 (dd, J=13.4, 6.6 Hz, 1H), 1.06 (s, 9H), 1.05 (d, J=7.9 Hz, 3H), 1.05 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.7, 171.9, 141.5, 140.7, 135.5, 135.4, 133.7, 133.6, 131.6, 129.8, 129.6, 127.7, 127.6, 125.8, 96.7, 91.9, 87.7, 65.5, 63.9, 57.3, 43.2, 37.7, 29.5, 26.8, 25.9, 21.8, 19.4, 19.0, 18.3, −5.0; IR (neat) 3072, 3047, 3021, 2956, 2928, 2856, 1761, 1626, 1462, 1428, 1357, 1331, 1259, 1159, 1111, 1093, 1058, 1011, 920, 835 cm^{-1}; HRMS (CI, NH_3) for $C_{35}H_{47}O_6Si_2$ $[M-C_4H_9]^+$ calcd 619.2911, found 619.2930.

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