# JOC Article

Studies on the Synthesis of Quartromicins A₃ and D₃: Synthesis of the Vertical and Horizontal Bis-Spirotetronate Fragments

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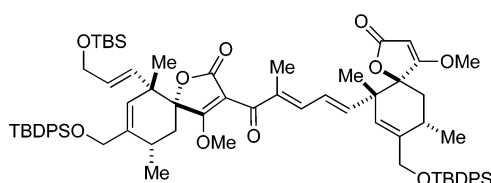
4, horizontal *exo-endo* bis-tetronate fragment

Syntheses of the vertical (**3**) and horizontal (**4**) bis-spirotetronate units of quartromicins A₃ and D₃ are described, along with an efficient synthesis of α-hydroxy aldehyde *exo*-**8b**, a precursor to the *exo*-spirotetronate fragments **19** and **21**.

Introduction

The quartromicins (Figure 1) are a group of structurally complex macrocyclic natural products that display activity against herpes simplex virus (HSV) type 1, influenza, and HIV.[1–3] Quartromicins A₃ and D₃ possess a novel 32-membered carbocyclic ring system containing four spirotetronic acid subunits connected in a head-to-tail arrangement via enone linkers. Our laboratory has proposed a stereochemical assignment[4,5] for the quartromicins, and we have developed chemistry to access the two distinct spirotetronate subunits of these complex targets.[5,6] We refer to the two spirotetronate fragments as the *endo-* (also known as the galacto fragment) and *exo* (or the agalacto fragment)-spirotetronate units, by virtue of the Diels–Alder chemistry that we have employed for their synthesis.[5,6] Other work on the synthesis of the quartromicins has recently appeared.[7]

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galacto fragment *(endo)*   agalacto fragment *(exo)*

agalacto fragment *(exo)*   galacto fragment *(endo)*

1, quartromicin A₃, R = α-D-galactosyl
2, quartromicin D₃, R = H
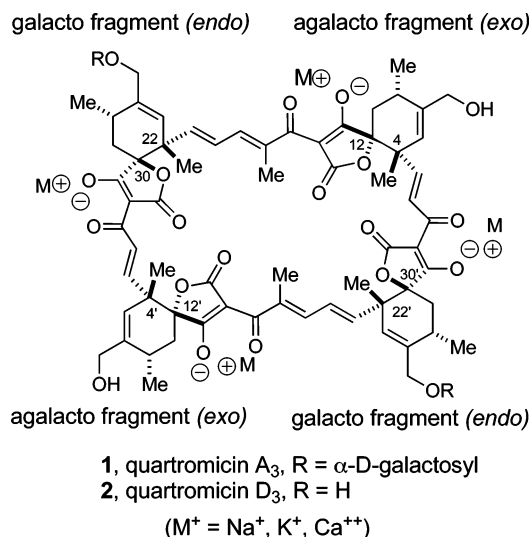
(M⁺ = Na⁺, K⁺, Ca⁺⁺)

FIGURE 1. Structures of quartromicins A₃ (**1**) and D₃ (**2**).

The quartromicins are formidable synthetic targets owing to the presence of contiguous quaternary centers in each of the spirotetronate fragments (C4/C12 and C4′/C12′ in the *exo* fragments; C22/C30 and C22′/C30′ in the *endo* fragments). The high steric congestion at these positions greatly complicates syntheses of the *endo-* and *exo*-spirotetronate fragments, much more so than in syntheses of the spirotetronic acid fragments of other spirotetronate natural products (e.g., chlorothricolide,[8,9]

3, vertical *endo-exo* bis-spirotetronate
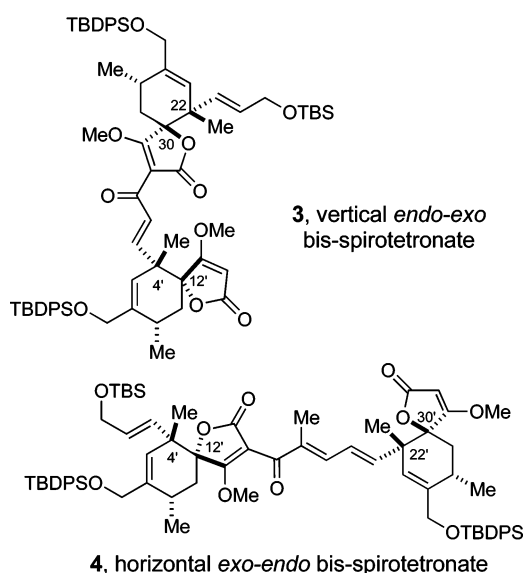

4, horizontal *exo-endo* bis-spirotetronate

FIGURE 2. Structures of the vertical (**3**) and horizontal (**4**) bis-spirotetronate units of quartromicin D₃.

kijanolide,[10–16] and tetronolide[17–20]). Other spirotetronate natural products that have attracted interest as synthetic targets include okilactomycin[21,22] and tetronothiodin.[23]

Our synthetic strategy aims to exploit the C_2 symmetry of the natural products by generation of the carbocycle via a late-stage dimerization of either the vertical (**3**) or horizontal (**4**) *exo-endo* bis-tetronate fragments (Figure 2). Toward this end, we have developed and report herein syntheses of the "*exo-endo*" bis-spirotetronate units **3** and **4**. The vertical "dimer" **3** contains an enone unit linking the two spirotetronate fragments, whereas the horizontal "dimer" **4** contains a dienone linker.

A significant bottleneck in the synthesis of **3** and **4** is access to synthetically useful quantities of precursors of the monomeric *endo-* and *exo-*spirotetronate units. While synthesis of the *endo* (or galacto) fragment in either racemic or single enantiomeric form proved to be relatively straightforward, development of a brief, highly stereoselective synthesis of the *exo-*spirotetronate subunit present in the agalacto fragment of quartromicin A₃ has proven to be challenging.[5]

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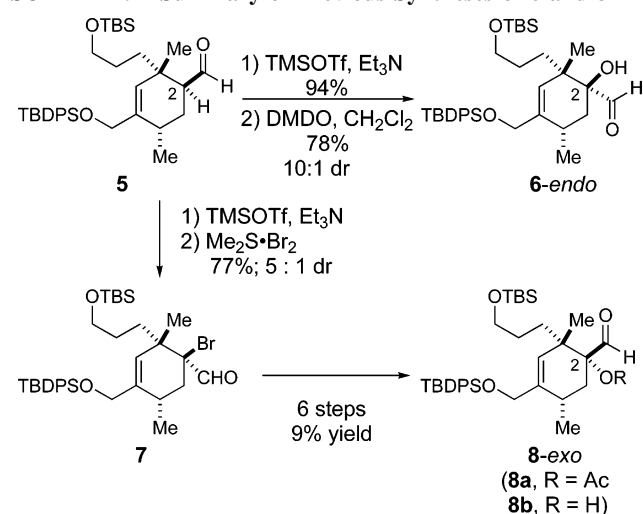(21) Paquette, L. A.; Boulet, S. L. *Synthesis* **2002**, 888.

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SCHEME 1. Summary of Previous Syntheses of 6 and 8

We have previously accomplished the enantioselective synthesis of **5** via the Lewis acid-catalyzed Diels–Alder reaction of an acyclic (Z)-1,3-diene.[5,6,24] *endo-α*-Hydroxy aldehyde **6**—a precursor to the *endo* (or galacto)-spirotetronate fragment of the quartromicins—was then easily prepared by the DMDO epoxidation of the enol silane prepared from **5** (Scheme 1).[5] However, conversion of **5** to the *exo-α*-hydroxy aldehyde **8a** (formally the C(2) epimer of **6** and the targeted precursor of the *exo-*spirotetronate subunit of the quartromicins) proceeded in low overall yield owing to an inefficient inversion of configuration of the C(2)–Br substituent of **7**.[5] Consequently, before initiating work on the synthesis of fragments **3** and **4**, it was necessary to develop a more efficient synthesis of *exo-***8**.

Results and Discussion

An improved synthesis of *exo-α*-hydroxy aldehyde **8b** began by converting aldehyde **5** into an enol silyl ether, which was oxidized under Saegusa conditions[25] to give the corresponding enal (Scheme 2). Reduction of the enal by using DIBAL-H then gave allylic alcohol **9**. All attempts to effect a highly diastereoselective reagent-controlled epoxidation of **9** were unsuccessful (e.g., Sharpless asymmetric epoxidation).[26] However, epoxidation of **9** using VO(acac)₂ and *t*-BuOOH gave the β-face epoxy alcohol with >20:1 dr.[27] Subsequent treatment of the resulting epoxyalcohol with phenyl isocyanate and triethylamine furnished urethane **10** in 88% yield over two steps. Exposure of **10** to BF₃·OEt₂ led to rapid and highly diastereoselective intramolecular epoxide opening[28] to furnish carbonate **11**, possessing the C(2) stereochemistry required for the *exo-*spirotetronate fragment. Reductive removal of the hydroxyl group in **11** via Barton deoxygenation[29,30] proceeded in >90% yield. Cleavage of the carbonate with potassium carbonate in methanol followed by Parikh–Doering oxidation[31] of the primary alcohol furnished aldehyde *exo-***8b**. The overall yield

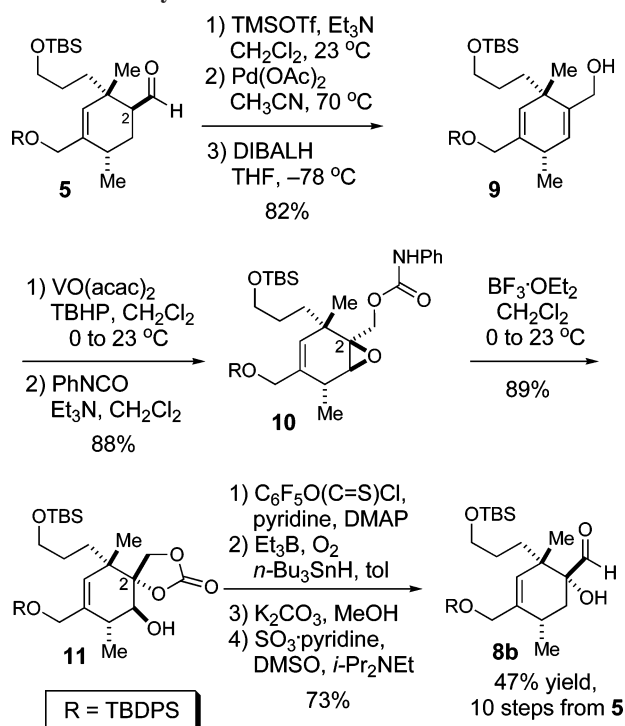(26) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

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SCHEME 2. Synthesis of *exo*-8b

SCHEME 3. Synthesis of *exo*-8b via the *exo*-Selective Diels−Alder Reaction of 12 and 13

We turned next to elaboration of **8b** to *exo*-spirotetronates **19** and **21** needed for the synthesis of **3** and **4**, respectively (Scheme 4). α-Hydroxy aldehyde *exo*-**8b** was oxidized by
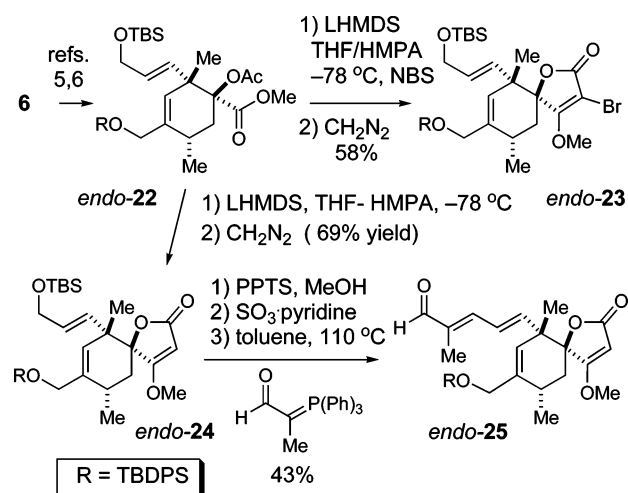
from **5** to **8b** (47%) is more than 5 times higher than that from previous routes. This sequence has been scaled to provide gram quantities of precursors to **8b**.

While the synthesis of **8b** summarized in Scheme 2 is chemically efficient, the length of this sequence is unattractive (10 steps from **5**). This prompted us to develop a more direct synthesis of *exo*-**8b** via the *exo*-selective Diels−Alder reaction of **12** and **13**, a dienophile that we designed for this purpose.[32] Details of the design and synthesis of **13** have been reported elsewhere.[32,33] Thus, the MeAlCl₂-mediated Diels−Alder reaction of (Z)-diene **12**[24] with the conformationally constrained α-alkoxyacrylate dienophile **13** provided a 5:1 mixture of cycloadducts favoring *exo*-**14**. Reduction of this mixture with LiAlH₄ and then oxidation of the resulting mixture of diols under Parikh−Doering conditions[31] provided the targeted α-hydroxy aldehyde *exo*-**8b** in 51% yield, along with 10% of *ent-endo*-**6** (the enantiomer of *endo*-**6** as presented in Scheme 1), which were separated chromatographically.

The synthesis of *exo*-**8b** summarized in Scheme 3 is more stepwise efficient than the much longer synthesis summarized in Scheme 2, starting in both cases from diene **12**, the closest common precursor for both routes.[5] The synthesis of *exo*-**8b** in Scheme 3 proceeds in 36% yield over three steps from diene **12**, whereas the synthesis of *exo*-**8b** from **12** via Scheme 2 proceeds in 23% yield over a 12-step sequence. An implicit tradeoff, however, is that our current synthesis of dienophile **13** is lengthy (13 steps from commercially available L-valine, 7% overall yield).[32,33] Nevertheless, we are using the sequence of Scheme 3 for bringing up starting materials and have already prepared ca. 1 g quantities of *exo*-**8b** from single runs (see Experimental Section).
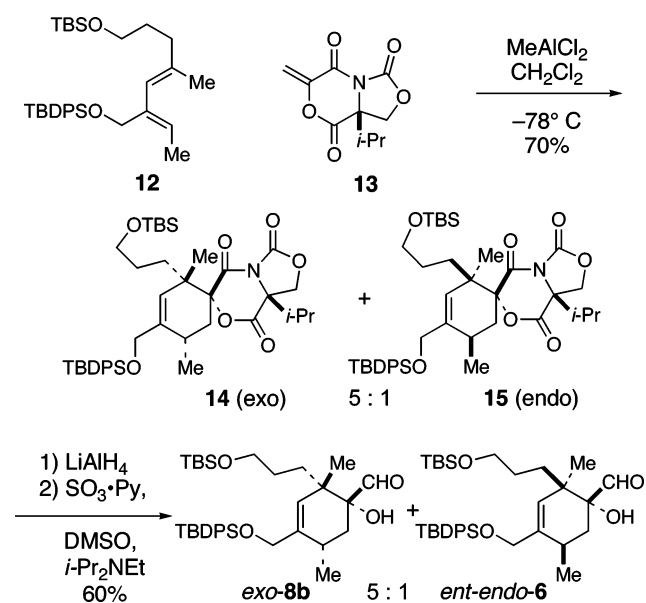
SCHEME 4. Elaboration of *exo*-8b to *exo*-19 and *exo*-21
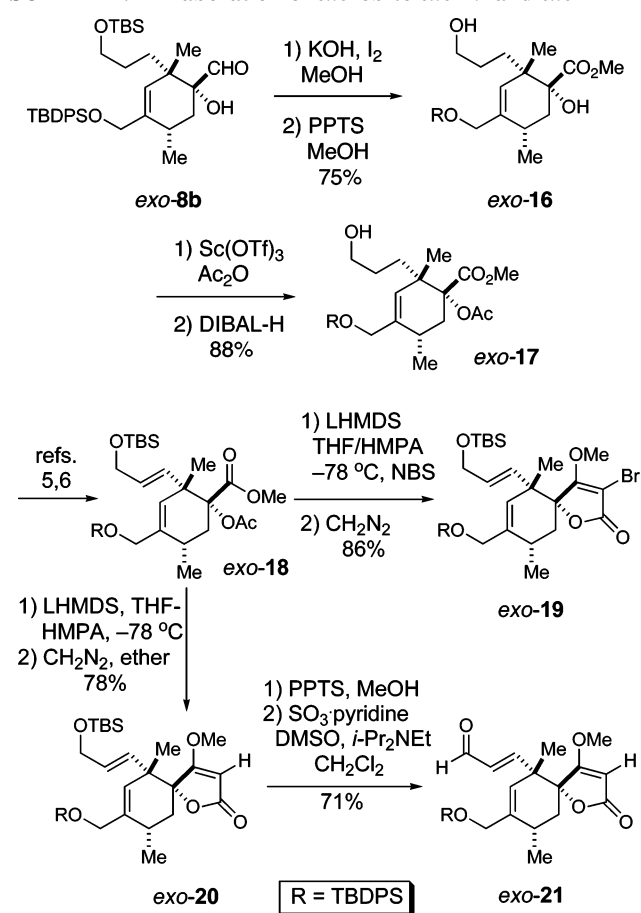
exposure to KOH and I₂ in MeOH,[34] and then the primary TBS ether was cleaved by treatment with PPTs in MeOH. The diol *exo*-**16** was acylated by treatment with Ac₂O and catalytic Sc-

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(33) Complete details for the synthesis of dienophile **13** are provided in the Supporting Information to the paper cited as ref 32.

SCHEME 5. Elaboration of *endo*-6 to *endo*-23 and *endo*-25

R = TBDPS

SCHEME 6. Synthesis of the Horizontal *exo-endo* Bis-Tetronate 4

SCHEME 7. Synthesis of the Vertical *endo-exo* Bis-Tetronate 3

(OTf)₃,[35] and then the primary acetate was selectively cleaved by treatment with DIBAL-H. The resulting α-acetoxy ester **17** was then elaborated to *exo*-**18** by using our previously published sequence.[5,6] Treatment of **18** with LHMDS in THF−HMPA at −78 °C followed by addition of NBS provided the 2-bromo spirotetronic acid. Treatment of this intermediate with CH₂N₂ afforded the methyl ether derivative *exo*-**19** in 86% yield. This compound was destined to serve as the nucleophilic component (after lithium−halogen exchange) in the synthesis of the horizontal bis-spirotetronate unit **4**. Alternatively, standard Dieckmann cyclization of **18** followed by methylation using CH₂N₂ provided **20**. Deprotection of the TBS ether of **20** by treatment with PPTS in methanol followed SO₃−pyridine oxidation[31] gave enal *exo*-**21**, which ultimately served as the electrophilic coupling partner in the synthesis of the vertical bis-spirotetronate fragment **3**.

endo-α-Acetoxy ester **22**, derived from *endo*-**6**,[5,6] was elaborated to 2-bromo spirotetronate **23** (Scheme 5) by using the same Dieckmann cyclization−bromination conditions used for the synthesis of *exo*-**19** from **18** (Scheme 4). Intermediate **23** was designed to serve as the nucleophilic component in the synthesis of the vertical bis-spirotetronate unit **3**. Deprotection of the primary TBS ether of **24**, which derives from the non-oxidative Dieckmann cyclization of **22**,[5,6] was accomplished by treatment with PPTS in MeOH. Oxidation of the resulting alcohol to the corresponding enal and then olefination with a stabilized ylide afforded dienal **25** in the *endo*-spirotetronate series. The latter compound was targeted to serve as the electrophilic fragment in a synthesis of the horizontal bis-spirotetronate **4**.

With viable synthetic routes to all four coupling partners in hand, we were ready to investigate the synthesis of the vertical and horizontal halves of quartromicin. In previous studies, we directly metalated *endo*-**24** by treatment with mesityllithium,[17] and the resulting α-lithio spirotetronate added in good yield to an α,β-unsaturated aldehyde.[5] However, attempts to apply this protocol to the metalation of *exo*-**20** under a variety of conditions met with poor results. Consequently, we elected to generate the 2-lithio-*exo*-spirotetronate via lithium/halogen exchange[36] by treatment of *exo*-**19** with *n*-BuLi (Scheme 6).
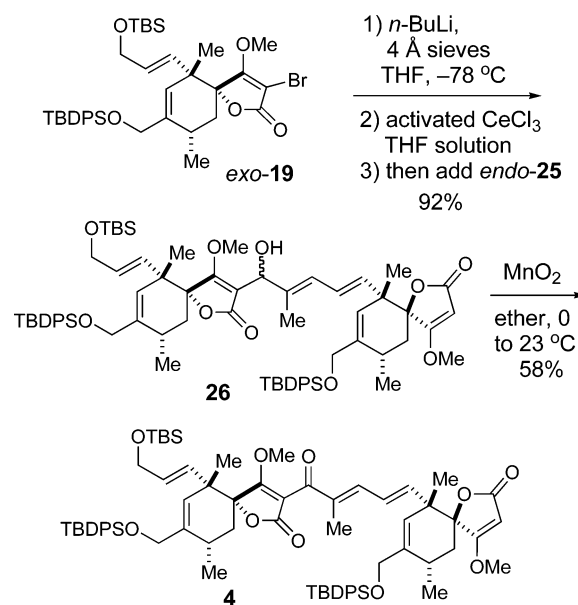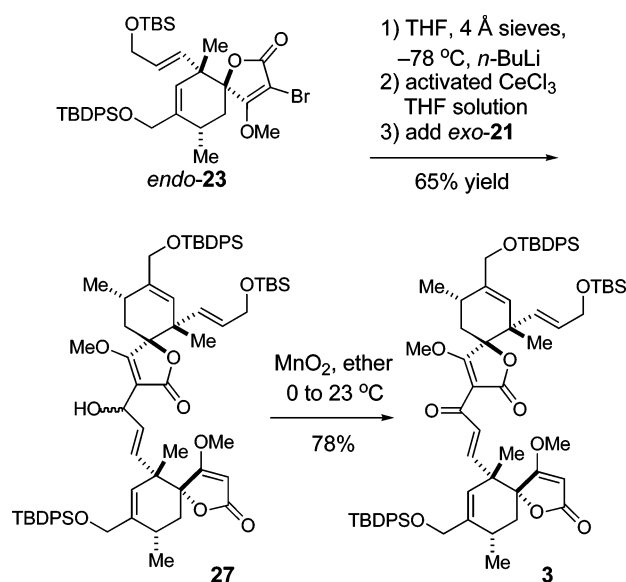
Unfortunately, while the requisite 2-lithiotetronate was efficiently generated under these conditions, it failed to add to dienal **25** in good yield. However, when the 2-lithiotetronate (generated from 3 equiv of **19**) was transmetalated using CeCl₃,[37,38] the resulting vinylcerium species underwent smooth and efficient 1,2-addition to dienal **25** (1 equiv), thus providing **26** in 92% yield (Scheme 6). The addition product **26** was oxidized to the ketone by using activated MnO₂, which provided the horizontal fragment **4** of quartromicin.

This coupling protocol was also applied to the synthesis of the vertical fragment **3** (Scheme 7). Thus, sequential treatment

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of 2-bromo-*endo*-spirotetronate **23** with *n*-BuLi, CeCl₃, and finally aldehyde *exo*-**21** gave addition product **27** in ca. 65% yield. The secondary hydroxyl group of **27** was oxidized by using MnO₂ to give the complete vertical fragment **3** of quartromicin.

In summary, we have developed an improved synthetic route to *exo*-α-hydroxy aldehyde **8b** via the Diels–Alder reaction of **12** and **13**; *exo*-**8b** and *endo*-**6** were elaborated into the corresponding 2-bromo spirotetronates *exo*-**19** and *endo*-**23** and the unsaturated aldehydes *exo*-**21** and *endo*-**25** needed for the coupling experiments. Finally, we have shown that both the vertical (**3**) and horizontal (**4**) halves of quartromicins A₃ and D₃ can be accessed via the 1,2-addition of organocerium intermediates derived from **19** and **23** onto the requisite enals **25** and **21**, respectively. Attempts to utilize these intermediates in the completion of the total synthesis of the proposed structure of quartromicin D₃ (**2**) are in progress and will be reported in due course.

Experimental Section[39]

Spiro(1′R,2′S,5′S,8αR)-6-[2′-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-4′-(*tert*-butyldiphenylsilanyloxymethyl)-2′,5′-dimethylcyclohex-3′-ene]-8α-isopropyldihydrooxazolo[4,3-*c*][1,4]oxazine-3,5,8-trione (14) and Spiro(1′R,2′R,5′R,8αR)-6-[2′-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-4′-(*tert*-butyldiphenyl-silanyloxymethyl)-2′,5′-dimethylcyclohex-3′-ene]-8α-iso-propyldihydrooxazolo[4,3-*c*][1,4]oxazine-3,5,8-trione (15). To a −78 °C solution of diene **12** (2.32 g, 4.4 mmol) and dienophile **13** (1.20 g, 5.3 mmol) in CH₂Cl₂ was added 5.3 mL of MeAlCl₂ (1.0 M solution in hexanes, 5.3 mmol) over 30 min. The resulting yellow solution was stirred at −78 °C for 6 days. The reaction was quenched by the slow addition of saturated aq. NaHCO₃ and allowed to warm to room temperature. The mixture was diluted with diethyl ether and 1 N HCl, and the layers were separated after the white solids had dissolved. The aqueous layer was extracted with Et₂O (3×). The combined organic layers were washed with saturated aq. NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated. The crude product was then purified by chromatography on silica gel (20% EtOAc−hexane). The mixture of diastereomeric products so obtained (5:1 mixture, 2.32 g, 70%) was inseparable by silica gel chromatography (20% EtOAc−hexane) or by HPLC. Data for the mixture of **14** and **15**: R_f 0.46 (33% EtOAc−hexane); $[\alpha]^{23}_D$ +24.7° (*c* 1.8, CH₂Cl₂); ¹H NMR for major diastereomer **14** (500 MHz, CDCl₃) δ 7.51 (m, 10H), 5.40 (s, 1H), 4.37 (s, 2H), 4.13 (m, 2H), 3.54 (m, 2H), 2.66 (m, 1H), 2.34 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.23 (m, 1H), 1.99 (dd, *J* = 13.9, 7.3 Hz, 1H), 1.52 (m, 4H), 1.03 (m, 21H), 0.84 (s, 9H), 0.00 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 165.1, 164.7, 149.5, 137.7, 135.6, 135.5, 135.4, 133.6, 133.5, 129.7, 129.6, 127.7, 127.6, 125.5, 91.6, 66.3, 65.2, 65.0, 63.4, 44.3, 37.7, 37.0, 34.8, 29.0, 27.4, 27.0, 26.8, 26.7, 26.0, 25.9, 21.7, 19.3, 19.2, 18.3, 16.2, 15.7, −5.3; FT-IR (thin film) 2930, 2857, 1822, 1756, 1715, 1472, 1428, 1358, 1297, 1258, 1188, 1111, 1056, 835, 776, 703 cm⁻¹; HRMS (ESI) calcd for C₄₂H₆₁NO₇Si₂-Na [M + Na]⁺ 770.3884, found 770.3903 *m/z*.

(1R,2S,5S)-2-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-4-(*tert*-butyldiphenylsiloxymethyl)-1-hydroxy-2,5-dimethylcyclohex-3-enecarbaldehyde (*exo*-8b) and (1R,2R,5R)-2-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-4-(*tert*-butyldiphenylsiloxymethyl)-1-hydroxy-2,5-dimethylcyclohex-3-enecarbaldehyde (*endo*-6). To a solution of the 5:1 mixture of **14** and **15** (2.33 g, 3.1 mmol) in THF (23 mL) was added LiAlH₄ (236 mg, 6.2 mmol) portion-wise

at 0 °C. The mixture was stirred at room temperature for 6 h. Diethyl ether and saturated aq. Rochelle's salt solution were then added, and the mixture was further stirred overnight until both layers became clear. The layers were then separated, and the aqueous layer was extracted with ether (3×). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The crude product was then purified by chromatography on silica gel (50% EtOAc−hexane) providing *exo*-**8b** (231 mg, 12%), *endo*-**6** (46 mg, 3%), and a mixture of *endo* and *exo* diols (923 mg, 50% yield).

To a solution of diol mixture (923 mg, 1.5 mmol) in CH₂Cl₂ (15 mL) were added sequentially DMSO (1.1 mL, 15.5 mmol), *i*-Pr₂NEt (1.4 mL, 7.8 mmol), and SO₃·pyridine (740 mg, 4.6 mmol). The reaction was judged complete in 15 min by TLC analysis and was quenched by addition of EtOAc (20 mL) and 1 M aq. HCl (5 mL). The organic layer was separated and washed with saturated aq. NaHCO₃, brine, dried with MgSO₄, filtered, and concentrated. The crude product was purified by flash column chromatography on SiO₂ (10% EtOAc−hexane) to afford the known α-hydroxy aldehyde *exo*-**8b** (694 mg, 75% from the diol mixture; 38% from Diels−Alder adducts **14** and **15**) and *ent*-*endo*-**6** (132 mg, 14% from diol mixture; 7% from **14** and **15**). Overall, 925 mg (51% yield) of *exo*-**8b** and 178 mg (10%) of *ent*-*endo*-**6** were obtained for the three-step sequence starting with the 5:1 mixture of Diels−Alder adducts **14** and **15**.

Data for *exo*-**8b**: R_f 0.56 (10% EtOAc−hexane); $[\alpha]^{23}_D$ −2.7° (*c* 3.1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 7.66 (m, 4H), 7.40 (m, 6H), 5.52 (br, 1H), 4.27 (d, *J* = 13.2 Hz, 1H), 4.18 (d, *J* = 13.2 Hz, 1H), 3.57 (m, 2H), 3.27 (s, 1H), 2.46 (m, 1H), 1.92 (dd, *J* = 13.9, 11.7 Hz, 1H), 1.65 (dd, *J* = 13.9, 7.3 Hz, 1H), 1.51 (m, 4H), 1.08 (s, 7H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.82 (s, 3H), 0.04 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 206.5, 138.9, 135.5, 133.6, 133.5, 129.8, 129.3, 129.3, 127.7, 80.9, 65.4, 63.8, 39.4, 38.2, 34.5, 30.1, 27.0, 26.8, 25.9, 20.5, 19.5, 19.2, 18.3, −5.3; FT-IR (thin film) 3948, 3070, 2956, 2930, 2857, 1718, 1471, 1427, 1389, 1361, 1333, 1255, 1112, 1006, 934, 835, 775, 738, 701 cm⁻¹; HRMS (ESI) calcd for C₃₅H₅₄O₄Si₂Na [M + Na]⁺ 617.3458, found 617.3456 *m/z*.

Data for the minor product *ent*-*endo*-**6**: R_f 0.52 (10% EtOAc−hexane); $[\alpha]^{23}_D$ −9.3° (*c* 0.8, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 9.76 (s, 1H), 7.69 (m, 4H), 7.40 (m, 6H), 5.46 (br, 1H), 4.23 (d, *J* = 13.2 Hz, 1H), 4.14 (d, *J* = 13.2 Hz, 1H), 3.55 (m, 2H), 3.16 (s, 1H), 2.53 (m, 1H), 1.80 (m, 2H), 1.53 (m, 4H), 1.06 (s, 7H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.99 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 205.5, 138.5, 135.55, 133.51, 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; FT-IR (thin film) 3510, 3071, 3049, 2956, 2930, 2857, 1717, 1589, 1472, 1389, 1361, 1255, 1112, 1006, 938, 835, 775, 740, 701 cm⁻¹; HRMS (ESI) calcd for C₃₅H₅₄O₄Si₂Na [M + Na]⁺ 617.3458, found 617.3459 *m/z*. These spectroscopic data matched previously reported data for *endo*-(+)-**6**.[5]

Synthesis of *exo*-16. A solution of aldehyde **8b** (676 mg, 1.1 mmol) in MeOH (11 mL) was cooled to 0 °C, and methanolic solutions of potassium hydroxide (11.6 mL of a 0.78 M solution, 9.0 mmol) and iodine (5.8 mL of a 0.78 M solution, 4.5 mmol) were added successively. The resulting dark brown mixture was stirred at 0 °C for 45 min, after which time second portions of potassium hydroxide (2.3 mL, 1.8 mmol) and iodine (1.1 mL, 0.9 mmol) solution were added successively. The starting material was completely consumed 30 min after the second addition. The reaction mixture was diluted with 2 N H₂SO₄ and Et₂O and stirred at room temperature for 30 min. The layer was separated, and the aqueous layer was extracted with Et₂O (3×). The combined layers were washed with saturated aq. Na₂S₂O₃ and brine, dried over MgSO₄, filtered, and concentrated. The crude product was filtered through a short column of silica gel (50% EtOAc−hexane) to afford a mixture of *exo*-**16** and the corresponding TBS ether.

To a solution of this mixture in 5 mL of MeOH was added PPTS (553 mg, 2.2 mmol). The reaction was stirred at room temperature for 2 h, at which point the TBS ether was fully deprotected. Water (50 mL) and diethyl ether (50 mL) were added. The layers were separated, and the aqueous layer was extracted by Et_2O (3×). The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (50% EtOAc−hexane) to afford *exo*-16 (423 mg, 75%) as a colorless oil: R_f 0.40 (50% EtOAc−hexane); $[\alpha]^{23}_D$ −16.2° (*c* 2.5, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 (m, 4H), 7.39 (m, 6H), 5.36 (s, 1H), 4.27 (d, *J* = 12.7 Hz, 1H), 4.09 (d, *J* = 12.7 Hz, 1H), 3.71 (s, 3H), 3.59 (t, *J* = 5.9 Hz, 2H), 3.54 (br, 1H), 2.64 (m, 1H), 1.98 (dd, *J* = 14.2, 6.8 Hz, 1H), 1.78 (dd, *J* = 14.2, 8.8 Hz, 1H), 1.56 (m, 5H), 1.06 (m, 12H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.3, 138.5, 135.5, 135.4, 133.9, 133.8, 129.6, 129.5, 128.2, 128.1, 127.6, 127.5, 78.7, 66.0, 63.7, 52.5, 52.4, 40.3, 38.3, 34.5, 29.4, 27.6, 26.7, 21.5, 19.3; FT-IR (thin film) 3501, 2955, 2932, 2858, 1716, 1472, 1456, 1428, 1247, 1111, 1062, 824, 738, 702, 614 cm^{-1}; HRMS (ESI) calcd for C$_{30}$H$_{42}$O$_5$SiNa [M + Na]$^+$ 533.2699, found 533.2701 *m/z*.

Synthesis of *exo*-17. A solution of diol *exo*-16 (421.8 mg, 0.83 mmol) in acetic anhydride (6.6 mL) was cooled to 0 °C, and a CH$_3$CN solution of Sc(OTf)$_3$ (215.4 mg, 0.44 mmol in 1.7 mL of CH$_3$CN) was added quickly. The resulting solution was stirred at 0 °C for 40 s, after which time saturated aq. NaHCO$_3$ (40 mL) was added with 10 g of solid NaHCO$_3$. The reaction mixture was stirred at room temperature overnight and then was diluted with ether and water. The layer was separated, and the aqueous layer was extracted with ether (3×). The combined layers were washed with saturated aq. NaHCO$_3$ and brine, dried over MgSO$_4$, filtered, and concentrated. The product was purified by column chromatography (25% EtOAc−hexane) to afford the 1°−3° diacetate intermediate (436 mg, 89%) as a colorless oil; 10% of a triacetate (derived from deprotection/acylation of the primary TBDPS ether) was also observed. Data for the diacetate: R_f 0.20 (25% EtOAc−hexane); $[\alpha]^{23}_D$ −48.4° (*c* 3.2, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.68 (m, 4H), 7.38 (m, 6H), 5.43 (s, 1H), 4.19 (d, *J* = 13.2 Hz, 1H), 4.13 (d, *J* = 13.9 Hz, 1H), 4.02 (t, *J* = 6.6 Hz, 2H), 3.71 (s, 3H), 2.47 (m, 2H), 2.34 (m, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.78−1.56 (m, 4H), 1.06 (s, 9H), 0.93 (d, *J* = 7.3 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.1, 171.0, 170.2, 138.4, 135.44, 135.41, 133.6, 133.5, 129.6, 129.5, 127.6, 127.6, 124.8, 84.4, 65.6, 65.2, 51.8, 40.1, 31.7, 31.1, 27.6, 26.7, 24.0, 23.8, 21.5, 20.9, 19.4, 19.2; FT-IR (thin film) 3071, 2959, 2934, 2892, 2858, 1739, 1472, 1463, 1429, 1368, 1113, 1072, 1030, 824, 741, 704, 610 cm^{-1}; HRMS (ESI) calcd for C$_{34}$H$_{46}$O$_7$SiNa [M + Na]$^+$ 617.2911, found 617.2911 *m/z*.

To a −78 °C solution of the above diacetate (436 mg, 0.73 mmol) in THF (7.3 mL) was added DIBAL-H (1.96 mL of a 1.5 M solution in toluene, 2.9 mmol) slowly down the side of the flask. The resulting solution was stirred at −78 °C for 2 h; pH 7 buffer (10 mL) and ether (20 mL) were then added. The mixture was allowed to warm to room temperature, diluted with saturated aq. Rochelle's salt solution, and stirred for 5 h. The layer was separated, and the aqueous layer was extracted with ether (3×). The combined layers were washed with saturated aq. NaHCO$_3$ and brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. The product was purified by column chromatography (50% EtOAc−hexane) to afford *exo*-17 (410 mg, 99%) as colorless oil: R_f 0.20 (50% EtOAc−hexane); $[\alpha]^{23}_D$ −61.8° (*c* 1.0, CHCl$_3$); the spectroscopic data for this intermediate were identical to data for the same compound previously prepared in our laboratory.[5]

exo-Bromotetronate, *exo*-19. To a solution of the α-acetoxy ester *exo*-18 (196 mg, 0.295 mmol) in THF (6.0 mL) was added HMPA (1.0 mL). The solution was cooled to −78 °C, and LHMDS (0.87 mL, 1.0 M in THF, 0.87 mmol) was added. The solution was stirred for 1.5 h, at which point complete conversion of *exo*-18 to the tetronic acid was observed (TLC analysis). A solution of

NBS (0.60 mL, 0.5 M in THF, 0.30 mmol) was then added dropwise to the −78 °C solution. The flask was wrapped with aluminum foil and the mixture stirred for 30 min. The reaction was quenched by addition of EtOAc and aq. 1 M HCl, the solution was allowed to warm to 23 °C, the layers were separated, and the organic layer was washed with water (3×), dried over MgSO$_4$, filtered, and concentrated.

To a 0 °C solution of the tetronic acid in ether (3.0 mL) was added ethereal CH$_2$N$_2$ (~10 equiv); gas evolution occurred. The reaction mixture was allowed to warm to 23 °C and was stirred for 30 min. A few drops of HOAc were added until the yellow color dissipated, then ether and saturated aq. NaHCO$_3$ were added. The layers were separated, the aqueous layer was extracted with ether (2×), and the combined organic extracts were dried over MgSO$_4$, filtered, and concentrated. Purification of the crude product by chromatography on SiO$_2$ (20−30% EtOAc−hexane) provided bromotetronate *exo*-19 (181 mg, 86%) as an oil. Small amounts of the regioisomeric methyl tetronate were also detected (ratio = 10:1 favoring 19). Data for 19: R_f 0.28 (20% EtOAc−hexane); $[\alpha]^{27}_D$ +52.3° (*c* 2.7, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.71 (m, 4H), 7.40 (m, 6H), 7.69 (d, *J* = 15.6 Hz, 1H), 5.45 (dt, *J* = 15.4, 5.1 Hz, 1H), 5.26 (s, 1H), 4.29 (d, *J* = 12.4 Hz, 1H), 4.21 (s, 3H), 4.20−4.10 (3H), 2.72 (m, 1H), 1.98 (dd, *J* = 13.4, 10.2 Hz, 1H), 1.83 (dd, *J* = 13.5, 6.6 Hz, 1H), 1.06 (15H), 0.88 (s, 9H), 0.045 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 176.9, 168.4, 140.5, 135.5, 135.4, 134.7, 133.7, 133.6, 132.0, 129.8, 129.7, 127.7, 127.6, 125.8, 88.4, 79.2, 65.2, 63.8, 59.6, 43.6, 37.6, 29.3, 26.7, 25.9, 21.7, 19.3, 18.9, 18.3, −5.0, −5.1; FT-IR (neat) 2956, 2930, 2857, 1768, 1634, 1258, 1112, 836, 703 cm^{-1}; HRMS (ESI) calcd for C$_{38}$H$_{53}$BrO$_5$-Si$_2$Na [M + Na]$^+$ 747.2513, found 747.2523 *m/z*.

exo-Spirotetronate 20. To a THF solution (2.0 mL) of *exo*-α-acetoxy ester 18 (79 mg, 0.12 mmol) was added HMPA (0.47 mL), and the resulting solution was cooled to −78 °C. Next, a solution of LHMDS (0.68 mL, 1.0 M in THF) was added over 2 min. The solution was stirred for 2 h, at which point complete conversion of 18 to the tetronic acid was observed (TLC analysis). The reaction was quenched by addition of EtOAc and aq. 1 M HCl, and the solution was allowed to warm to 23 °C; the layers were separated, and the organic layer was washed with water (3×), dried over MgSO$_4$, filtered, and concentrated to give an oil.

To a 0 °C solution of the crude tetronic acid in ether (3.0 mL) was added ethereal CH$_2$N$_2$ (ca. 10 equiv); gas evolution occurred. The reaction mixture was allowed to warm to 23 °C and was stirred for 30 min. A few drops of AcOH were added until the yellow color dissipated, then ether and saturated aq. NaHCO$_3$ were added. The layers were separated, the aqueous layer was extracted with ether (2×), and the combined organic extracts were dried over MgSO$_4$, filtered, concentrated, and purified by chromatography on SiO$_2$ (15−30% EtOAc−hexane) to afford the spirotetronate *exo*-20 (40 mg pure major diastereomer, and 21 mg which was a 1.7:1 mixture of major and minor tetronate methylation regioisomers for a 78% total yield) as a clear semisolid. The ratio of the two *O*-methyl tetronates was approximately 7:1. Data for *exo*-20: R_f 0.35 (35% EtOAc−hexane); $[\alpha]^{27}_D$ +51.9° (*c* 0.42, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.72 (m, 4H), 7.40 (m, 6H), 5.75 (d, *J* = 15.6 Hz, 1H), 5.45, dt, *J* = 15.6, 5.6 Hz, 1H), 5.26 (br s, 1H), 5.05 (s, 1H), 4.32 (AB, *J* = 12.4 Hz, 1H), 4.16 (m, 2H), 4.13 (AB, *J* = 13.0 Hz, 1H), 3.73 (s, 3H), 2.75 (m, 1H), 2.02 (dd, *J* = 13.2, 10.8 Hz, 1H), 1.79 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.06 (overlapping s and d, 12H), 1.01 (s, 3H), 0.88 (s, 9H), 0.049 (s, 3H), 0.047 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 185.4, 171.9, 140.7, 135.5, 133.8, 131.7, 129.7, 129.6, 127.7, 127.6, 125.9, 89.4, 87.7, 65.6, 64.0, 59.1, 43.2, 37.8, 29.7, 29.4, 26.7, 26.0, 21.7, 19.3, 18.8, −5.0; FT-IR (neat) 2956, 2930, 2856, 1760, 1627, 1361, 1112, 1057, 835, 702 cm^{-1}; HRMS (ESI) calcd for C$_{38}$H$_{54}$O$_5$Si$_2$Na [M + Na]$^+$ 669.3411, found 669.3408 *m/z*.

exo-Enal 21. To a solution of TBS ether *exo*-20 (48 mg, 0.074 mmol) in MeOH (0.60 mL) and THF (0.10 mL) was added PPTS (37 mg, 0.15 mmol) in one portion. The reaction was stirred for 2

h, then the mixture was concentrated to a white precipitate. This material was purified by chromatography on SiO_2 (50% EtOAc—hexane) to afford the allylic alcohol (33 mg, 83% yield) as a white foam.

The above allylic alcohol (32 mg, 0.060 mmol) was oxidized via the SO_3·pyridine protocol described for the synthesis of **8b** (see Supporting Information) to give the crude enal, which was purified by chromatography on SiO_2 (35—50% EtOAc—hexane) to give *exo*-**21** (28 mg, 71%): R_f 0.38 (50% EtOAc—hexane); $[\alpha]^{27}_D$ +95.6° (*c* 2.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.58 (d, *J* = 7.8 Hz, 1H), 7.69 (m, 4H), 7.40 (m, 6H), 6.97 (d, *J* = 15.6 Hz, 1H), 6.00 (dd, *J* = 15.5, 7.8 Hz, 1H), 5.31 (br s, 1H), 5.12 (s, 1H), 4.29 (AB, *J* = 13.2 Hz, 1H), 4.16 (AB, *J* = 13.2 Hz, 1H), 3.78 (s, 3H), 2.76 (m, 1H), 1.89 (overlapping dd, 2H), 1.12 (s, 3H), 1.06 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 193.8, 184.5, 171.1, 161.7, 142.7, 135.4, 135.3, 133.5, 133.4, 133.3, 129.8, 129.7, 127.7, 127.6, 123.2, 89.6, 86.7, 65.1, 59.4, 44.2, 38.2, 29.5, 26.7, 20.9, 19.3, 18.7; FT-IR 2932, 2857, 1761, 1691, 1628, 1361, 1112, 960, 704 cm⁻¹; HRMS (ESI) calcd for $C_{32}H_{38}O_5SiNa$ [M + Na]⁺ 553.2386, found 553.2378 *m/z*.

***endo*-Bromotetronate 23.** The brominative Dieckmann cyclization of *endo*-**22**[5] (177 mg) was performed using the procedure described for preparation of *exo*-**19**. This gave bromotetronate *endo*-**23** (111 mg, 58% yield) after purification by chromatography on SiO_2 (30—40% EtOAc—hexane): R_f 0.50 (30% EtOAc—hexane). Small amounts of the regioisomeric methyl tetronate were also detected (ratio = 10:1 favoring **23**). Data for *endo*-**23**: $[\alpha]^{27}_D$ +40.4° (*c* 2.8, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.70 (m, 4H), 7.40 (m, 6H), 5.65 (d, *J* = 15.4 Hz, 1H), 5.46 (dt, *J* = 15.4, 4.4 Hz, 1H), 5.30 (br s, 1H), 4.30 (s, 4H), 4.19 (4H), 2.56 (m, 1H), 1.96 (dd, *J* = 13.6, 10.7 Hz, 1H), 1.72 (dd, *J* = 13.9, 6.6 Hz, 1H), 1.04 (s, 12H), 0.98 (d, *J* = 7.3 Hz, 3H), 0.91 (s, 9H), 0.069 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 175.7, 168.4, 135.6, 135.5, 134.1, 130.5, 129.7, 129.6, 127.7, 127.6, 125.7, 88.1, 65.1, 63.5, 59.5, 44.6, 36.2, 28.7, 26.8, 25.9, 20.5, 19.3, 18.6, −5.1; FT-IR (thin film) 2955, 2930, 2857, 1768, 1635, 1601, 1111, 1011, 837, 703 cm⁻¹; HRMS (ESI) calcd for $C_{38}H_{53}BrO_5Si_2Na$ [M + Na]⁺ 747.2513, found 747.2513 *m/z*.

***endo*-Spirotetronate 24.** To a THF solution (18 mL) of endo-α-acetoxy ester **22**[5] (0.54 g, 0.81 mmol) was added HMPA (2.8 mL), and the resulting solution was cooled to −78 °C. To this solution was then added a solution of LHMDS (0.41 g, 2.4 mmol, 1.0 M THF) over 2 min. The solution was stirred for 1.5 h, at which point complete conversion to the tetronic acid was observed (TLC analysis). The reaction was quenched by addition of EtOAc and aq. 1 M HCl, the solution was allowed to warm to 23 °C, the layers were separated, and the organic layer was washed with water (3×), dried over MgSO₄, filtered, and concentrated to give an oil.

To a 0 °C solution of the tetronic acid in ether (10 mL) was added ethereal CH_2N_2 (∼10 equiv); gas evolution occurred, and the solution was allowed to warm to 23 °C. After 30 min, the reaction was complete (TLC analysis). The solvent was removed under reduced pressure, and the residue was purified by chromatography on SiO_2 (20—30% EtOAc—hexane) to afford spirotetronate *endo*-**24** (0.36 g, 69%) as a clear semisolid: R_f 0.31 (30% EtOAc—hexane); $[\alpha]^{27}_D$ +42.2° (*c* 1.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.72 (m, 4H), 7.43 (m, 6H), 5.69 (dt, *J* = 15.4, 1.7 Hz, 1H), 5.47 (dt, *J* = 15.4, 4.9 Hz, 1H), 5.34 (app d, *J* = 1.5 Hz, 1H), 5.08 (s, 1H), 4.20 (br s, 2H), 4.17 (dd, *J* = 4.6, 1.7 Hz, 2H), 3.83 (s, 3H), 2.56 (m, 1H), 1.94 (dd, *J* = 13.4, 10.7 Hz, 1H), 1.71 (dd, *J* = 13.7, 6.1 Hz, 1H), 1.05 (s, 9H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 184.0, 171.8, 139.4, 135.5, 135.5, 134.3, 133.7, 133.6, 130.7, 129.6, 129.5, 127.7, 127.6, 125.6, 89.4, 87.1, 65.1, 65.1, 63.5, 59.2, 44.0, 36.4, 28.6, 26.7, 25.9, 20.7, 19.2, 18.6, 18.3, 18.3, −5.2, −5.2; FT-IR (neat) 3071, 3049, 2956, 2930, 2889, 2856, 1759, 1629, 1590,

1462, 1428, 1359, 1251, 1113, 836, 777, 703 cm⁻¹; HRMS (ESI) calcd for $C_{38}H_{54}O_5Si_2Na$ [M + Na]⁺ 669.3408, found 669.3385 *m/z*.

***endo*-α-Methyl Dienal 25.** To a solution of TBS ether and *endo*-**24** (21.5 mg, 0.33 mmol) in MeOH (0.30 mL) was added PPTS (25 mg, 0.99 mmol). The reaction mixture was stirred for 2 h then was concentrated to an oil and titrated with ether. The heterogeneous solution was filtered through Celite and washed multiple times with ether. The ether extracts were washed with saturated aq. NaHCO₃ (1×), aq. 1 M HCl (1×), and brine (1×), dried over MgSO₄, filtered, and concentrated. This crude material was oxidized by using the SO_3·pyridine oxidation procedure described for the synthesis of **8b**, giving the corresponding enal (12 mg, 68%) as a flaky white precipitate after purification by chromatography on SiO_2 (50—60% EtOAc—hexane): R_f 0.49 (80% EtOAc—hexane); $[\alpha]^{27}_D$ +114.9° (*c* 0.47, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.58 (d, *J* = 7.9 Hz, 1H), 7.68 (m, 4H), 7.42 (m, 6H), 6.82 (d, *J* = 15.6 Hz, 1H), 6.02 (dd, *J* = 15.6, 7.5 Hz, 1H), 5.34 (s, 1H), 5.14 (s, 1H), 4.20 (app s, 2H), 3.86 (s, 3H), 2.60 (m, 1H), 1.86 (dd, *J* = 14.2, 10.8 Hz, 1H), 1.80 (dd, *J* = 14.2, 6.6 Hz, 1H), 1.16 (s, 3H), 1.05 (s, 9H), 0.99 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 193.7, 182.8, 171.1, 160.7, 141.6, 135.4, 133.3, 133.2, 131.9, 129.7, 127.7, 122.9, 89.7, 85.6, 64.6, 59.5, 44.9, 36.5, 28.6, 26.7, 19.4, 19.2, 18.4; FT-IR (neat) 2955, 2932, 2857, 1756, 1688, 1633, 1428, 1358, 1113, 957, 705 cm⁻¹; HRMS (ESI) calcd for $C_{32}H_{38}O_5SiNa$ [M + Na]⁺ 553.2386, found 553.2386 *m/z*.

To a solution of the above enal (12 mg, 0.023 mmol) in toluene (1.00 mL) was added formylethylidenetriphenylphosphorane (7 mg, 0.023 mmol). The flask was fitted with reflux condenser and heated to ca. 110 °C overnight (∼16 h). Conversion was only ca. 50%, so more ylide (7 mg) was added and the reaction was heated for 8 h. The conversion was not complete, so more ylide (7 mg) was added, and the reaction was stirred for an additional ca. 16 h. Evaporation of the solvents and purification of the product by preparative TLC on SiO_2 (80% EtOAc—hexane) gave the dienal *endo*-**25** (8.5 mg, 62%): R_f 0.41 (80% EtOAc—hexane); $[\alpha]^{27}_D$ +265° (*c* 0.3, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.46 (s, 1H), 7.70 (m, 4H), 7.40 (m, 6H), 6.87 (d, *J* = 11.3 Hz, 1H), 6.45 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.23 (d, *J* = 15.1 Hz, 1H), 5.39 (br s, 1H), 5.13 (s, 1H), 4.23 (app br s, 2H), 3.87 (s, 3H), 2.62 (m, 1H), 1.91 (dd, *J* = 13.9, 10.7 Hz, 1H), 1.14 (s, 3H), 1.05 (s, 9H), 1.03 (d, *J* = 7.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 194.7, 183.4, 171.3, 148.0, 141.0, 137.6, 135.6, 135.5, 133.6, 133.5, 129.7, 129.7, 127.8, 127.7, 125.7, 124.6, 89.8, 86.4, 65.1, 59.4, 45.3, 36.7, 29.7, 28.8, 26.8, 20.2, 19.3, 18.8, 9.6; FT-IR (neat) 2925, 2854, 1756, 1683, 1630, 1457, 1359, 1179, 1112, 703 cm⁻¹; HRMS (ESI) calcd for $C_{35}H_{42}O_5SiNa$ [M + Na]⁺ 593.2699, found 593.2705 *m/z*.

Synthesis of Horizontal Bis-Tetronate Fragment 4 from 19 and 25. To a solution of *exo*-bromospirotetronate **19** (35 mg, 0.048 mmol) in THF (0.20 mL) were added cat. 1,10-phenanthroline indicator and ca. 10 mg of 4 Å molecular sieves. The mixture was stirred at 23 °C for 30 min then was cooled to −78 °C, and *n*-BuLi (2.5 M hex) was added until a deep red/brown color persisted. The resulting solution was stirred for 30 min, then a suspension of CeCl₃ (0.78 mL, 0.68 M THF) was added dropwise. [CeCl₃ was activated as follows.[37,38] To powdered CeCl₃ (167 mg, 0.677 mmol) (>99+% anhydrous Aldrich) were added THF (1.00 mL) and H₂O (0.002 mL, 0.11 mmol), and the flask was fitted with a reflux condenser and heated to 70 °C for 2 h. After being cooled to 23 °C, the suspension was stirred vigorously overnight (ca. 16 h). Microscopy showed rod-shaped crystals indicative of properly activated CeCl₃ as described by Conlon.[38]] This mixture was stirred for 1 h, then a solution of the dienal *endo*-**25** (8 mg, 0.016 mmol) in THF (0.20 mL plus 0.10 mL wash) was added dropwise via cannula. The mixture was stirred at −78 °C for 30 min, at which point TLC analysis indicated the reaction was complete. Methanol (0.2 mL) was added to the solution, and after 3 min, the flask was pulled from the dewer and ether and saturated aq. NH₄Cl were added. The mixture was stirred for 5 min, then EtOAc was added, the

layers were separated, and the aqueous layer was extracted with EtOAc (1×). The combined organic extracts were combined, dried over MgSO$_4$, filtered, and concentrated. Purification of the crude product by chromatography on SiO$_2$ (30−50% EtOAc−hexane) afforded the *exo*-spirotetronate **20** (18 mg) and two new spots corresponding to the two diastereomers of allylic alcohol **26**: R_f 0.38, 3.7 mg, >90% pure by ^{1}H NMR analysis, and R_f 0.30, 12.0 mg (50% EtOAc−hexane), 15.7 mg total, 92% yield. To a solution of allylic alcohol **26** (mixture of both R_f spots from above, 5.5 mg, 0.0045 mmol) in ether (0.15 mL, 0.03 M) at 0 °C was added activated MnO$_2$ (ca. 10 mg, 25 equiv) in one portion. After 5 min, the black suspension reaction mixture was allowed to warm to 23 °C and was vigorously stirred for 2 h. This cycle was repeated two more times until TLC analysis showed complete consumption of **26**. Ether (2 mL) was added, and the suspension was filtered through Celite with washing of the Celite bed (4 × 2 mL). Concentration of the combined filtrate afforded ketone **4** (3.2 mg, 58%): R_f 0.41 (40% EtOAc−hexane); [α]$^{27}_D$ +137.1° (*c* 0.35, CHCl$_3$); ^{1}H NMR δ 7.70 (m, 8H), 7.42 (m, 12H), 7.00 (d, J = 10.3 Hz, 1H), 6.41 (dd, J = 15.1, 11.0 Hz, 1H), 6.11 (d, J = 15.2 Hz, 1H), 5.77 (app d, J = 15.6 Hz, 1H), 5.48 (dt, J = 15.4, 5.6 Hz, 1H), 5.40 (app br s, 1H), 5.30 (br s, 1H), 5.11 (s, 1H), 4.30 (app d, J = 12.5 Hz, 1H), 4.23 (dd, J = 20.0, 14.0 Hz, 2H), 4.17 (3H), 3.84 (s, 3H), 3.72 (s, 3H), 2.75 (m, 1H), 2.60 (m, 1H), 2.06 (dd, J = 13.5, 11.0 Hz, 1H), 1.95 (s, 3H), 1.91 (overlapping dd, 2H), 1.76 (dd, J = 13.9, 6.1 Hz, 1H), 1.15 (s, 3H), 1.14 (s, 3H), 1.05 (s, 21H), 1.02 (d, J = 7.1 Hz, 3 H), 0.89 (s, 9H), 0.053 (s, 3H), 0.050 (s, 3H); ^{13}C NMR 191.9, 183.4, 181.1, 171.6, 169.4, 148.6, 144.4, 141.0, 136.6, 135.5, 135.1, 133.7, 133.6, 133.5, 133.4, 132.1, 129.7, 127.8, 127.7, 127.6, 126.3, 125.3, 124.1, 104.3, 89.6, 65.4, 64.9, 63.8, 61.1, 59.3, 45.3, 43.7, 37.7, 36.6, 29.7, 29.5, 28.7, 26.8, 26.7, 25.9, 21.9, 20.4, 19.3, 18.8, 18.7, 11.8, -5.0; FT-IR (neat) 2956, 2929, 2856, 1757, 1630, 1456, 1361, 1112, 703; HRMS (ESI) calcd for C$_{73}$H$_{94}$O$_{10}$Si$_3$Na [M + Na]$^+$ 1237.6053, found 1237.6053 *m/z*.

Vertical Bis-Tetronate Fragment 3. Bromotetronate *endo*-**23** (30 mg) and enal *exo*-**21** (8.0 mg) were coupled by using the procedure described for synthesis of **26**. This afforded 13.4 mg of a 6:1 mixture (not separable) of addition product **27** and aldehyde **21**. On the basis of ^{1}H NMR integration of this mixture, the yield of **27** was estimated to be 65% (ca. 12 mg).

Treatment of this mixture (13.4 mg) with MnO$_2$ according to the procedure described for synthesis of **4** provided a crude product mixture that was separated by chromatography. The mixture was first purified by conventional chromatography on SiO$_2$, which provided 6.7 mg of pure **3**. The impure fractions were purified by HPLC to give an additional 2.3 mg of **3** (total 9.0 mg, 78% yield; 50% overall from **21**): R_f 0.38 (40% EtOAc−hexane); [α]$^{27}_D$ +105.5° (*c* 0.4, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 (m, 8H), 7.40 (m, 12H), 6.97 (d, J = 15.7 Hz, 1H), 6.67 (d, J = 15.6 Hz, 1H), 5.65 (dt, J = 15.4, 1.5 Hz, 1H), 5.47 (dt, J = 15.4, 4.8 Hz, 1H), 5.31 (app br s, 2H), 5.09 (s, 1H), 4.35 (app d, J = 12.7 Hz, 1H), 4.17 (5H), 4.00 (s, 3H), 2.82 (m, 1H), 2.55 (m, 1H), 1.96 (3 overlapping dd, 3H), 1.75 (dd, J = 13.7, 6.4 Hz, 1H), 1.12 (s + d overlapping, 6H), 1.07 (s, 3H), 1.06 (s, 9H), 1.04 (s, 9H), 0.98 (d, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.063 (s, 3H), 0.060 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.6, 184.7, 183.8, 171.3, 169.5, 152.5, 142.3, 139.3, 135.6, 135.5, 134.1, 133.7, 133.6, 130.6, 130.2, 129.8, 129.7, 129.6, 129.5, 127.7, 127.6, 125.7, 124.3, 104.8, 89.7, 87.1, 86.3, 65.6, 65.0, 63.6, 62.9, 59.3, 44.6, 44.0, 37.9, 36.2, 29.7, 29.4, 28.6, 26.8, 25.9, 21.0, 20.6, 19.3, 19.2, 18.7, 18.6, −5.1; FT-IR (neat) 2956, 2929, 2856, 1758, 1660, 1627, 1455, 1360, 1250, 1112, 703 cm^{-1}; HRMS (ESI) calcd for C$_{70}$H$_{90}$O$_{10}$Si$_3$Na [M + Na]$^+$ 1197.5740, found 1197.5763 *m/z*.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds in Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.