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Studies on the Synthesis of Quartromicins A_3 and D_3: Synthesis of the Vertical and Horizontal Bis-Spirotetronate Fragments

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Abstract

Syntheses of the vertical (**3**) and horizontal (**4**) bis-spirotetronate units of quartromicins A_3 and D_3 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 A_3 and D_3 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]

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] 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). Towards 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.

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A significant bottle-neck 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 A_3 has proven to be challenging.[5]

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) spiroteronate 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 d.r.[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 $BF_3{\cdot}OEt_2$ 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 from **5** to **8b** (47%) is more than five times higher than 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 $MeAlCl_2$ 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 $LiAlH_4$ 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 step-wise 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 trade-off, 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 prepare ca. 1 g quantities of *exo*-**8b** from single runs (see Experimental).

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 exposure to KOH and I_2 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 Ac_2O and catalytic $Sc(OTf)_3$,[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 with warming to 0 °C followed by addition of NBS provided the 2-bromo spirotetronic acid. Treatment of this intermediate with CH_2N_2 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 CH_2N_2 provided **20**. Deprotection of the TBS ether of **20** by treatment with PPTS in methanol, followed SO_3-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**, deriving 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-spritetronate 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 metallated *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 metallation 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 transmetallated using $CeCl_3$,[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 MnO_2 which provide 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 of 2-bromo-*endo*-spirotetronate **23** with *n*-BuLi, activated $CeCl_3$, and finally aldehyde *exo*-**21** gave addition product **27** in ca. 65% yield. The secondary hydroxyl group of **27** was oxidized by using MnO_2 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-bromospirotetronates *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 A_3 and D_3 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 D_3 (**2**) are in progress and will be reported in due course.

Experimental Section[39]

Spiro (1'*R*, 2'*S*, 5'*S*, 8α*R*)-6-[2'-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-4'-(*tert*-butyl-diphenyl-silanyloxymethyl)-2',5'-dimethyl-cyclohex-3'-ene]-8α-isopropyl-dihydro-oxazolo[4,3-*c*][1,4]oxazine-3,5,8-trione (14) and Spiro (1'*R*, 2'*R*, 5'*R*, 8α*R*)-6-[2'-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-4'-(*tert*-butyl-diphenyl-silanyloxymethyl)-2',5'-dimethyl-cyclohex-3'-ene]-8α-isopropyl-dihydro-oxazolo[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 CH_2Cl_2 was added 5.3 mL of $MeAlCl_2$ (1.0 M solution in hexanes, 5.3 mmol) over 30 min. The resulting yellow solution was stirred at −78 °C for 6 d. The reaction was quenched by the slow addition of saturated aq. $NaHCO_3$ and allowed to warm to room temperature. The mixture was diluted with diethyl ether and 1N HCl, and the layers were separated after the white solids had dissolved. The aqueous layer was extracted with Et_2O (3 x). The combined organic layers were washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, 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, CH_2Cl_2); ^{1}H NMR for major diastereomer **14** (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{42}H_{61}NO_7Si_2Na$ $[M+Na]^+$ 770.3884, found 770.3903 m/z

(1*R*, 2*S*, 5*S*)-2-[3-(*tert*-butyldimethyl-silanyloxy)-propyl]-4-(*tert*-butyldiphenyl-siloxylmethyl)-1-hydroxy-2,5-dimethyl-cyclohex-3-enecarbaldehyde (*exo*-8b) and (1*R*, 2*R*, 5*R*)-2-[3-(*tert*-butyldimethyl-silanyloxy)-propyl]-4-(*tert*-butyldiphenyl-siloxylmethyl)-1-hydroxy-2,5-dimethyl-cyclohex-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 $LiAlH_4$ (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 x). The combined organic layers was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was then purified by chromatography on silica gel (50% EtOAc-hexane) provided *exo*-**8b** (231mg, 12%), *endo*-**6** (46 mg, 3%) and a mixture of *endo andexo* diols (923mg, 50% yield).

To a solution of diol mixture (923 mg, 1.5 mmol) in CH_2Cl_2 (15 mL) was added sequentially DMSO (1.1 mL, 15.5 mmol), *i*-Pr_2NEt (1.4 mL, 7.8 mmol), and SO_3•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 1M aq. HCl (5 mL). The organic layer was separated and washed with saturated aq. $NaHCO_3$, brine, dried with $MgSO_4$, filtered, and concentrated. The crude productwas purified by flash column chromatography on SiO_2 (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**-**15**) and *ent-endo*-**6** (132 mg, 14% from diol mixture; 7% from **14**–**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, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 138.9, 135.5, 133.6, 133.5, 129.8, 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 $C_{35}H_{54}O_4Si_2Na$ $[M+Na]^+$ 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, CH_2Cl_2); H 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{35}H_{54}O_4Si_2Na$ $[M+Na]^+$ 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 0.78M 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 2N H_2SO_4 and Et_2O, and stirred at room temperature for 30 min. The layer was separated and the aqueous layer was extracted with Et_2O (3 x). The combined layers were washed with saturated aq. $Na_2S_2O_3$ and brine, dried over $MgSO_4$, 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 x). 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) for $C_{30}H_{42}O_5SiNa$ $[M+Na]^+$ calcd. 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_3CN solution of $Sc(OTf)_3$ (215.4 mg, 0.44 mmol in 1.7 mL of CH_3CN) was added quickly. The resulting solution was stirred at 0 °C for 40 sec, 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 for overnight, and then was diluted with ether and water. The layer was separated and the aqueous layer was extracted with ether (3 x). 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 (deriving 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 $C_{34}H_{46}O_7SiNa$ $[M+Na]^+$ 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 1.5M 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 x). 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. 1M HCl, the solution was allowed to warm to 23 °C, the layers were separated, and the organic layer was washed with water (3 x), 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_2N_2 (~ 10 equiv); gas evolution occurred. The reaction mixture was allowed to warm to 23 °C and 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 x), and the combined organic extracts were dried over $MgSO_4$, filtered, concentrated. Purification of the crude product by chromatography on SiO_2 (20 to 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 $C_{38}H_{53}BrO_5Si_2Na$ $[M+Na]^+$ 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. 1M HCl, the solution was allowed to warm to 23 °C; the layers were separated, the organic layer was washed with water (3 x), 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_2N_2 (ca. 10 equiv), gas evolution occurred. The reaction mixture was allowed to warm to 23 °C and stir 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 x), and the combined organic extracts were dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on SiO_2 (15 to 30% EtOAc-hexane) to afford the spirotetronate *exo*-**20** (40 mg pure major diastereomer, and 21 mg which was 1.7:1 mixture of major and minor tetronate methylation regioisomers for a 78% total yield) as a clear semi-solid. 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 $C_{38}H_{54}O_5Si_2Na$ $[M+Na]^+$ 669.3408, found 669.3411 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 SI) to give the crude enal which was purified by chromatography on SiO_2 (35 to 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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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; FTIR 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 to 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, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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, 3H), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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. 1M HCl, the solution was allowed to warm to 23 °C, the layers were separated, the organic layer was washed with water (3 x), dried over $MgSO_4$, 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 to 30% EtOAc-hexane) to afford spirotetronate *endo*-**24** (0.36 g, 69%) as a clear semi-solid: R_f 0.31 (30% EtOAc-hexane); $[\alpha]^{27}_D$ +42.2 (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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), 1.05 (s, 3 H), 0.98 (d, *J*=7.1 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 *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. $NaHCO_3$ (1 x), aq.1M HCl (1 x), brine (1 x), dried over $MgSO_4$, 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 to 60% EtOAc-hexane): R_f 0.49 (80% EtOAc-hexane); $[\alpha]^{27}_D$ +114.9 (*c* 0.47, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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) was 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 $CeCl_3$ (0.78 mL, 0.68 M THF) was added dropwise. [$CeCl_3$ was activated as follows.[37, 38] To powdered $CeCl_3$ (167 mg, 0.677 mmol) (>99+% anhydrous Aldrich) was added THF (1.00 mL) and H2O (0.002 mL, 0.11 mmol) 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 $CeCl_3$ 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 canula. 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 NH_4Cl 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 x). The combined organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by chromatography on SiO_2 (30 to 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 x 2 mL). Concentration of the combined filtrate afforded ketone **4** (3.2 mg, 58%): Rf 0.41 (40% EtOAc-hexane); $[\alpha]^{27}_{D}$ +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 $C_{73}H_{94}O_{10}Si_3Na$ [M+Na] 1237.6053, found 1237.6053.

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**. Based on ^{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); $[\alpha]^{27}_{D}$ +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, 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 $C_{70}H_{90}O_{10}Si_3Na$ $[M+Na]^+$ 1197.5740, found 1197.5763 m/z.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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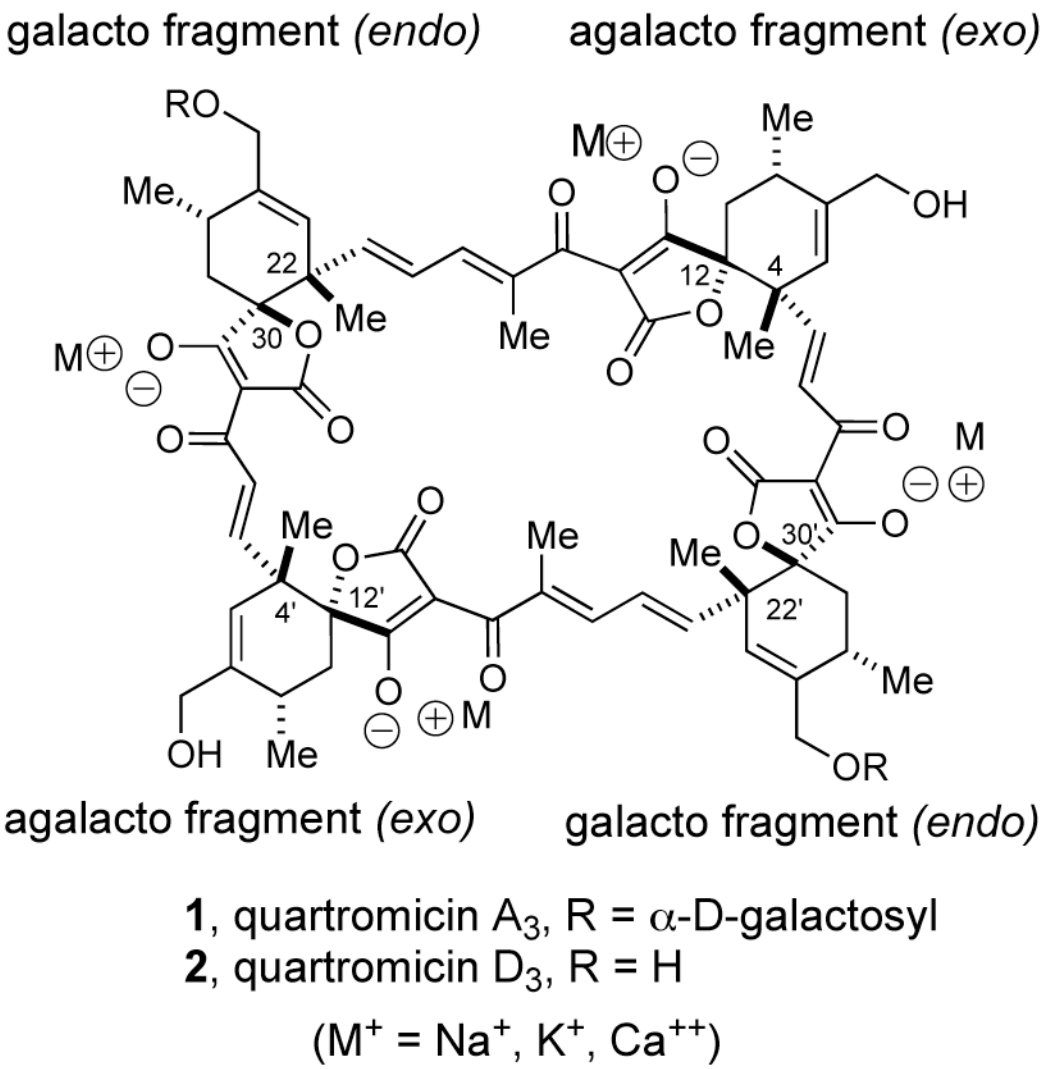


1, quartromicin A_3, R = α-D-galactosyl
2, quartromicin D_3, R = H

($M^+ = Na^+, K^+, Ca^{++}$)

Figure 1.
Structures of quartromicins A_3 (**1**) and D_3 (**2**)

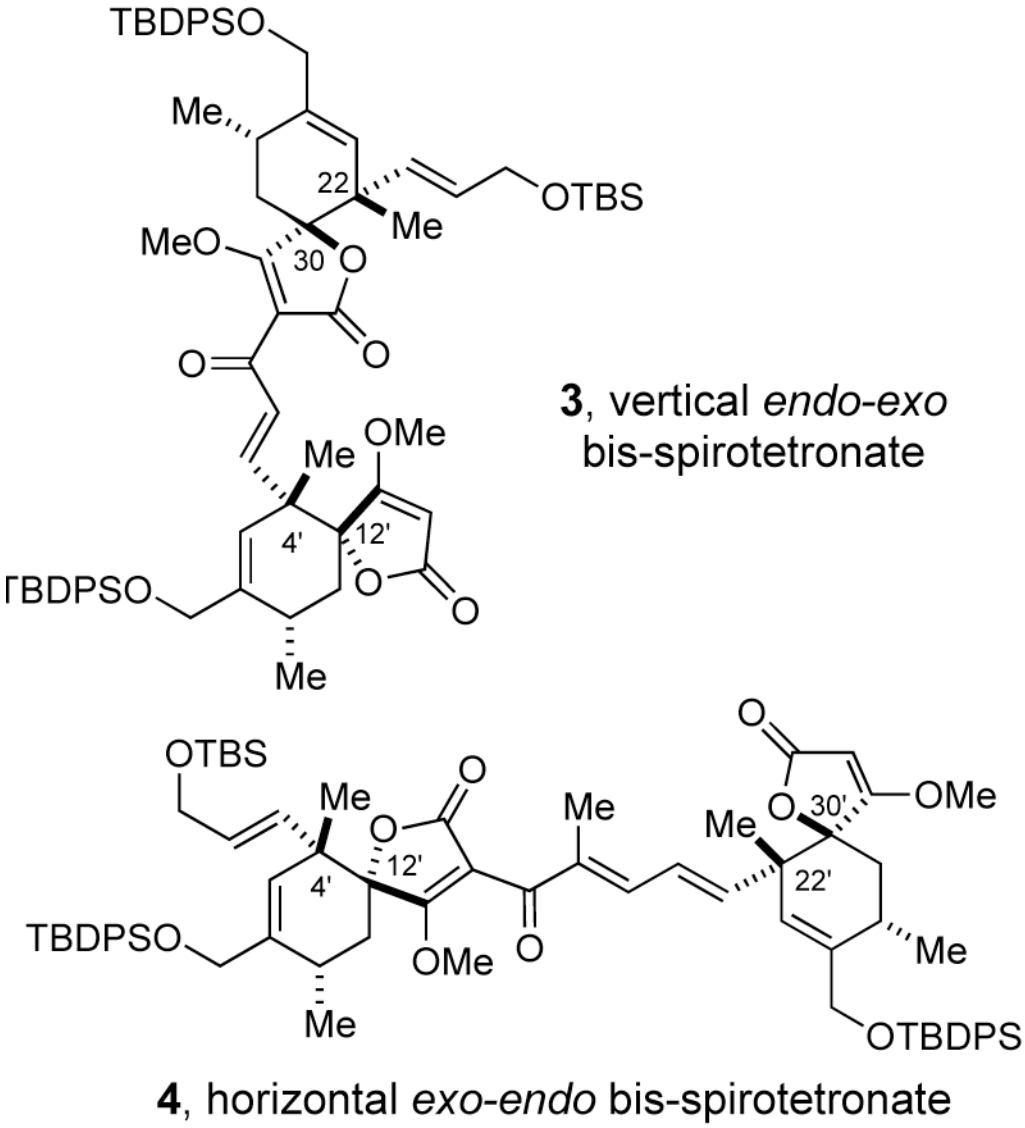
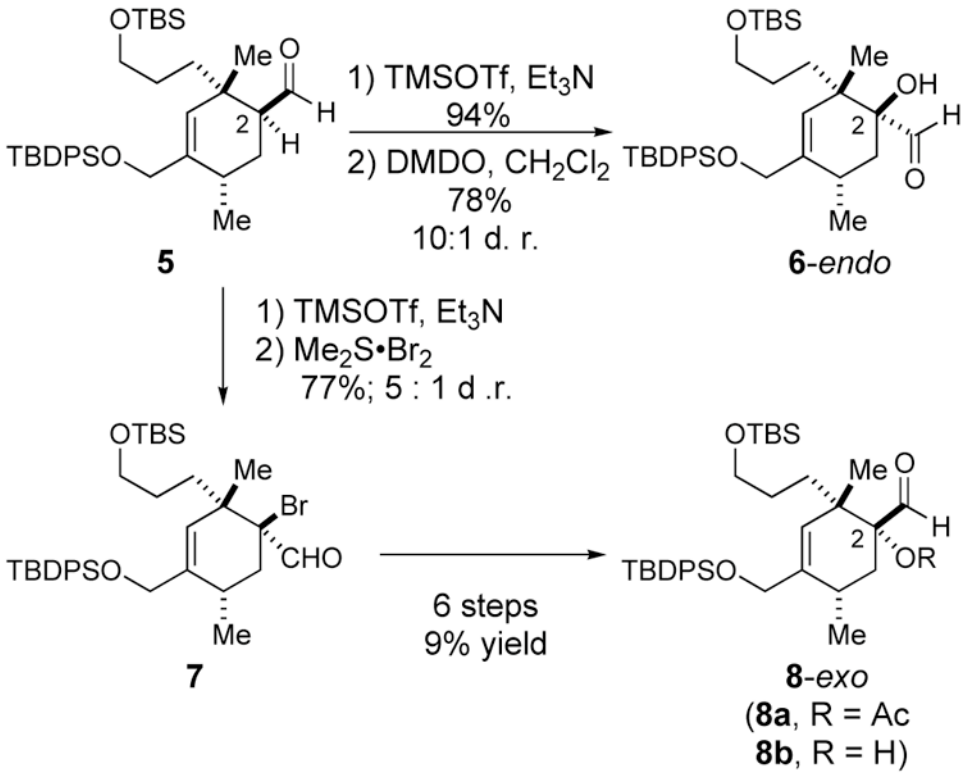
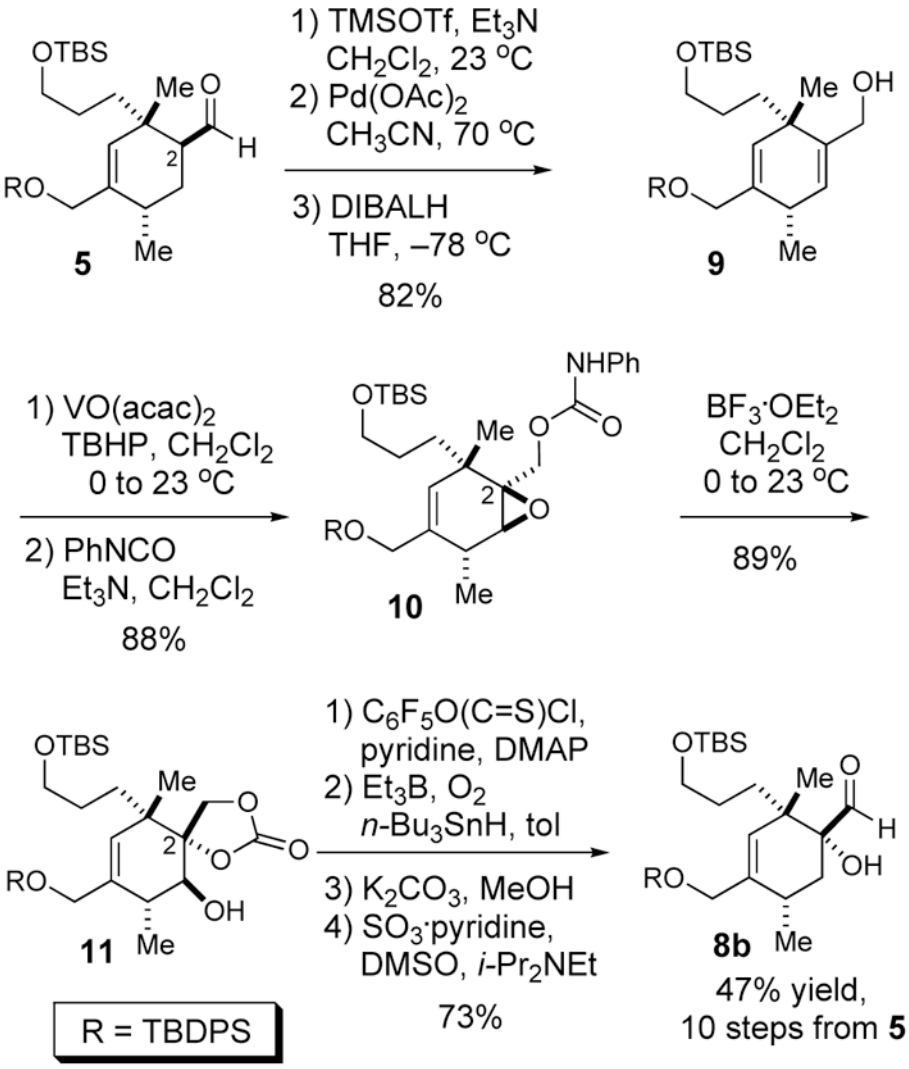


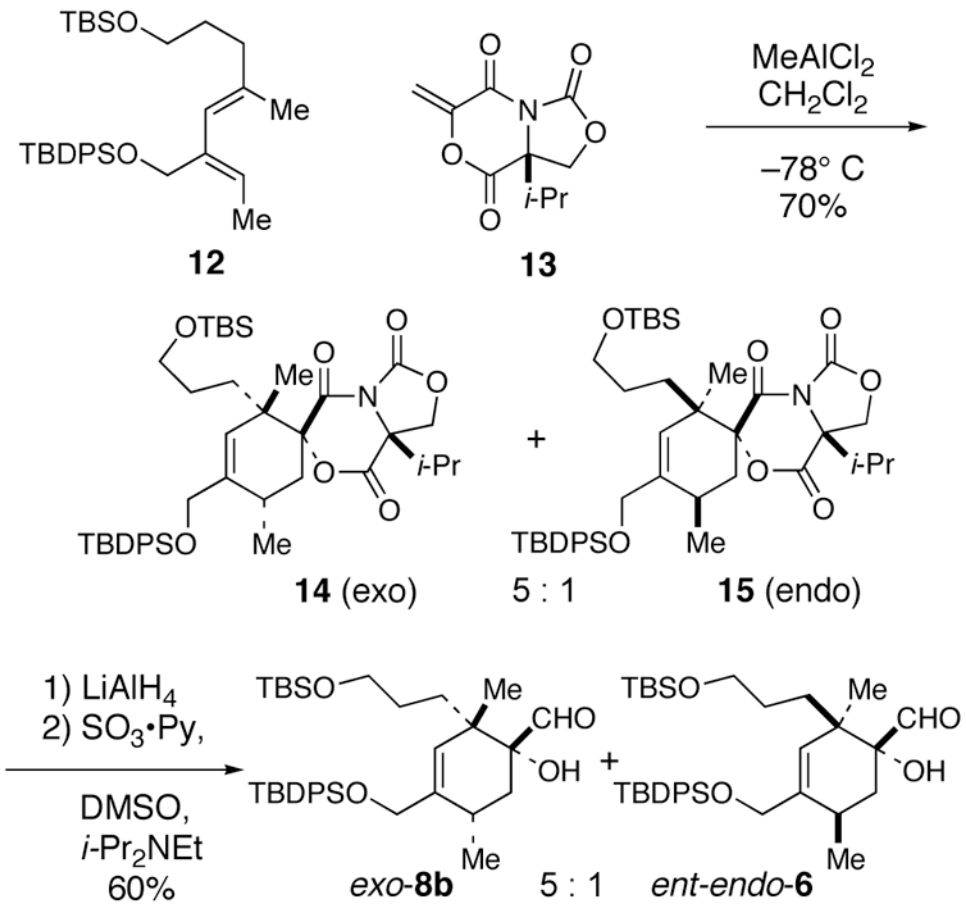
Figure 2.
Structures of the Vertical (**3**) and Horizontal (**4**) Bis-Spirotetronate Units of Quartromicin D_3



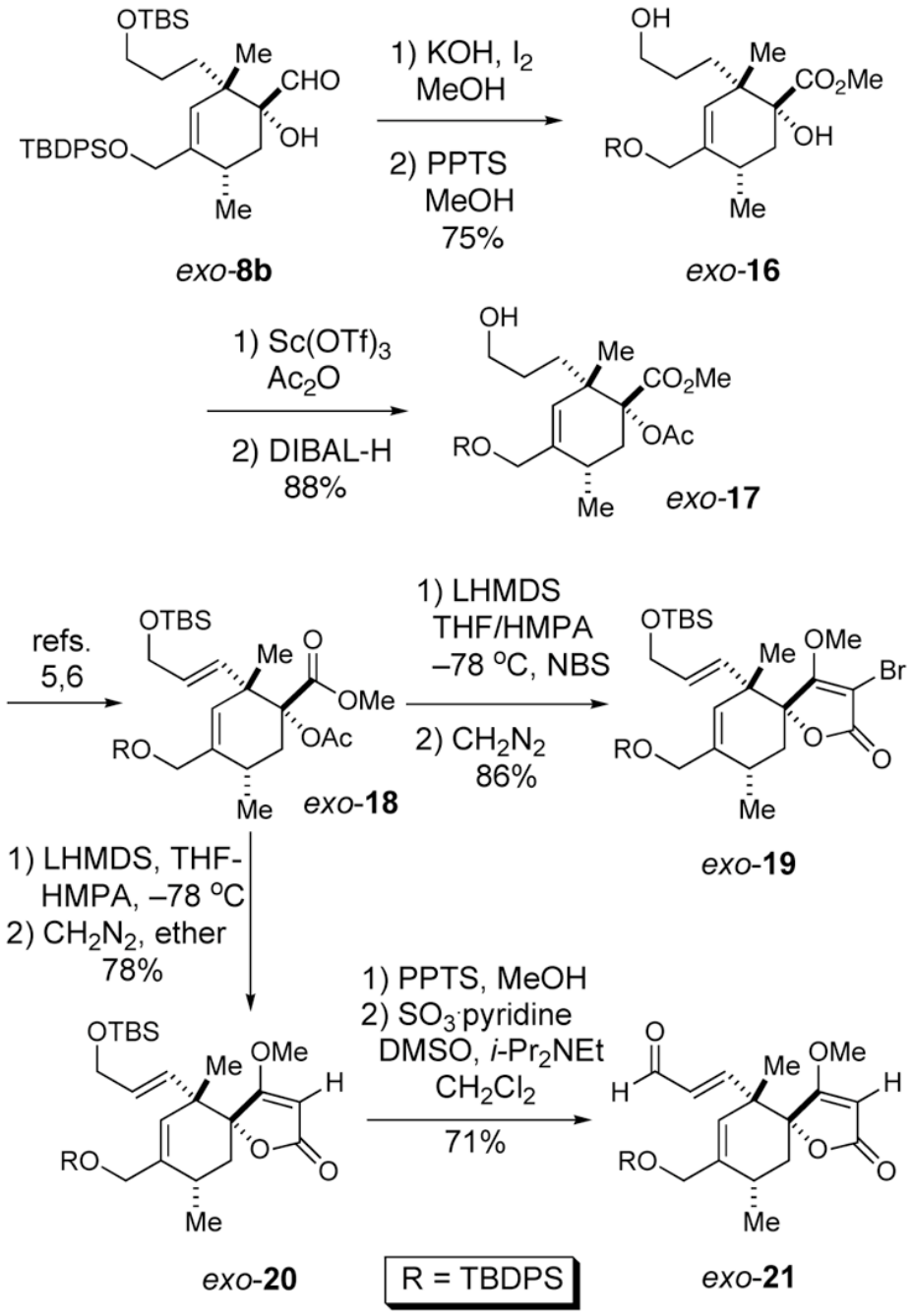
Scheme 1.
Summary of Previous Syntheses of **6** and **8**



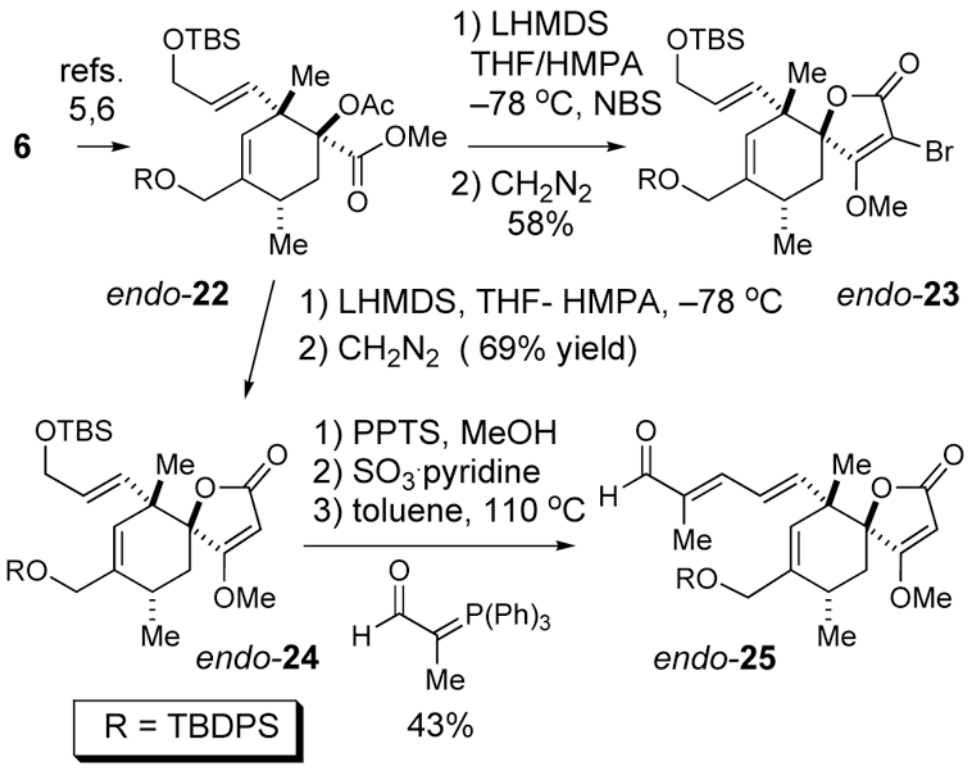
Scheme 2.
Synthesis of *exo*-**8b**



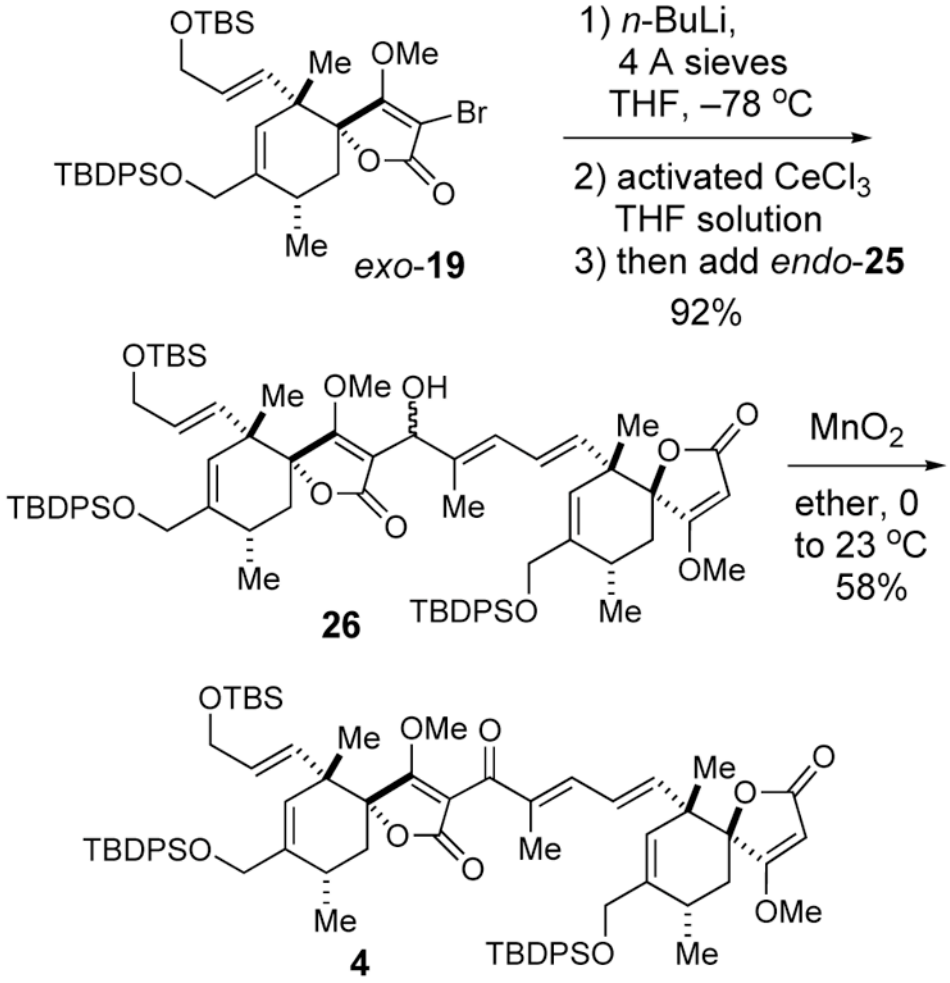
Scheme 3.
Synthesis of *exo*-**8b** via the Exo-Selective Diels-Alder Reaction of **12** and **13**



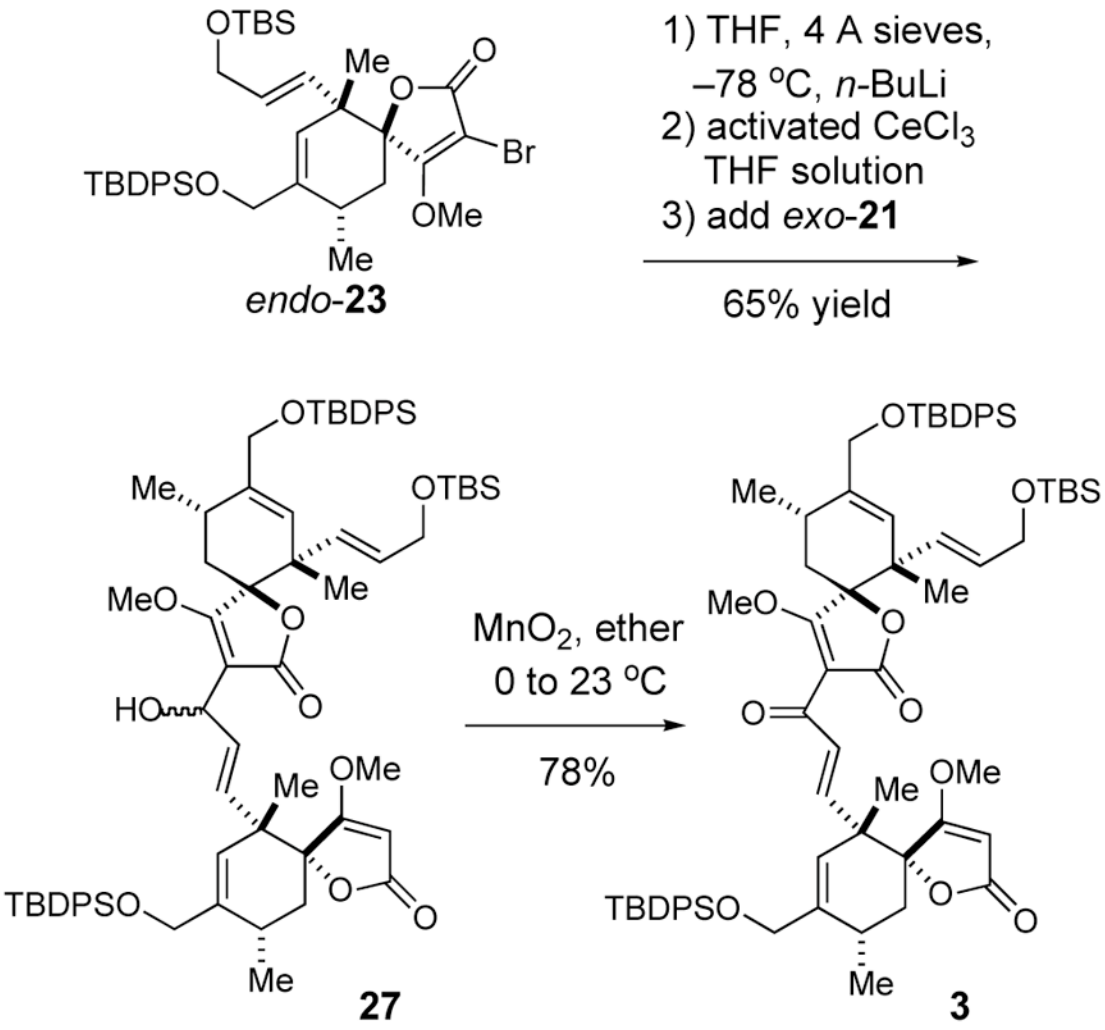
Scheme 4.
Elaboration of *exo*-**8b** to *exo*-**19** and *exo*-**21**



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



Scheme 6.
Synthesis of the Horizontal *exo-endo* Bis-tetronate **4**



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