Studies on the Synthesis of Chlorothricolide: Diastereo- and Enantioselective Syntheses of Model Top-Half Spirotetronate Units

William R. Roush*,[1] and Richard J. Sciotti[2]

Department of Chemistry, Indiana University, Bloomington, Indiana 47405, and Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109-1055

Received March 2, 1998

Highly enantio- and diastereoselective syntheses of spirotetronates **9** and **10**, corresponding to the top-half fragment of chlorothricolide, are described. Key steps in these syntheses are the Diels−Alder reactions of trienes **11** and **12** with the chiral dienophile (*R*)-**6** that provide cycloadducts **18** and **38** with remarkably high stereoselectivity. These reactions exhibit exquisite regioselectivity for addition across the trisubstituted C(18)−C(21) diene unit; they also proceed with remarkable orientational control of the dienophile with respect to the C(18)−C(21) diene, as well as with excellent exo diastereofacial selectivity on the part of the chiral dienophile, (*R*)-**6**. Results are presented indicating that it is not necessary to control the stereochemistry of the C(20)−C(21) trisubstituted olefin of the triene precursors, as this unit readily isomerizes under the conditions of the Diels−Alder reaction. Remarkably, the seemingly unreactive (*E*,*E*,*E*)-triene isomers (*E*,*E*,*E*)-**11** and (*E*,*E*,*E*)-**12** can be used as the starting material for the Diels−Alder reactions, and the desired exo-cycloadducts **18** and **38** are still obtained in good yield, without products of competitive Diels−Alder reactions of the disubstituted C(16)−C(19) dienes being observed.

Chlorothricolide (**1**) is the aglycon of the spirotetronate antibiotic chlorothricin that was isolated from *Streptomyces antibioticus* by Keller-Schlierlein and co-workers in 1969.[3,4] Somewhat more complex, but structurally related, spirotetronate antibiotics kijanimicin,[5] tetrocarcin,[6] and PA-46101 A and B[7] have been isolated more recently. The significant challenges posed by these structures have stimulated numerous studies on the synthesis of the aglycons chlorothricolide (**1**),[8−31] kijanolide (**2**), and tetronolide (**3**).[32−50] Total syntheses of tetronolide[44] and 24-*O*-methylchlorothricolide[26] have been accomplished by Yoshii, and an enantioselective total synthesis of (−)-chlorothricolide[31] and a formal synthesis of tetronolide[50] have been achieved in our laboratory.

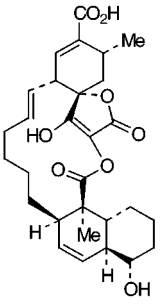
We report herein the details of our efforts to define a

(1) Address correspondence to this author at the University of Michigan.

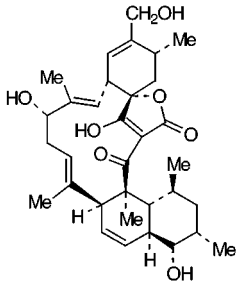
(2) Taken in part from the1994 Ph.D. Thesis of R.J.S., Indiana University, Bloomington, IN.

(3) Muntwyler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1972**, *55*, 2071.
(4) Brufani, M.; Cerrini, S.; Fedeli, W.; Mazza, F.; Muntwyler, R. *Helv. Chim. Acta* **1972**, *55*, 2094.
(5) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1497.
(6) Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2984.
(7) Matsumoto, M.; Kawamura, Y.; Yoshimura, Y.; Terui, Y.; Nakai, H.; Yoshida, T.; Shoji, J. *J. Antibiot.* **1990**, *43*, 739.
(8) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041.
(9) Ireland, R. E.; Thompson, W. J.; Srouji, G. H.; Etter, R. *J. Org. Chem.* **1981**, *46*, 4863.
(10) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200.
(11) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611.
(12) Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370.
(13) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, *25*, 4357.
(14) Marshall, J. A.; Audia, J. E.; Grote, J. *J. Org. Chem.* **1984**, *49*, 5277.
(15) Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421.
(16) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327.
(17) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635.
(18) Marshall, J. A.; Audia, J. E.; Shearer, B. G. *J. Org. Chem.* **1986**, *51*, 1730.
(19) Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron* **1986**, *42*, 2893.
(20) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236.
(21) Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710.
(22) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371.
(23) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Tetrahedron Lett.* **1989**, *30*, 2233.
(24) Poss, A. J.; Brodowski, M. H. *Tetrahedron Lett.* **1989**, *30*, 2505.
(25) Roth, G. P.; Rithner, C. D.; Meyers, A. I. *Tetrahedron* **1989**, *45*, 6949.
(26) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431.
(27) Hirsenkorn, R.; Schmidt, R. R. *Liebigs Ann. Chem.* **1990**, *9*, 883.
(28) Hirsenkorn, R.; Haag-Zeino, B.; Schmidt, R. R. *Tetrahedron Lett.* **1990**, *31*, 4433.
(29) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192.
(30) Roush, W. R.; Sciotti, R. J. *Tetrahedron Lett.* **1992**, *33*, 4691.
(31) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1994**, *116*, 6457.
(32) Takeda, K.; Kato, H.; Sasahara, H.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1986**, 1197.
(33) Marshall, J. A.; Grote, J.; Shearer, B. *J. Org. Chem.* **1986**, *51*, 1633.
(34) Takeda, K.; Urahata, M.; Yoshii, E.; Takayanagi, H.; Ogura, H. *J. Org. Chem.* **1986**, *51*, 4735.
(35) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135.
(36) Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186.
(37) Takeda, K.; Kobayashi, T.; Saito, K.; Yoshii, E. *J. Org. Chem.* **1988**, *53*, 1092.
(38) Takeda, K.; Yano, S.-g.; Yoshii, E. *Tetrahedron Lett.* **1988**, *29*, 6951.
(39) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541.
(40) Roush, W. R.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7309.
(41) Marshall, J. A.; Salovich, J. M.; Shearer, B. G. *J. Org. Chem.* **1990**, *55*, 2398.
(42) Boeckman, R. K., Jr.; Barta, T. E.; Nelson, S. G. *Tetrahedron Lett.* **1991**, *32*, 4091.
(43) Boeckman, R. K., Jr.; Estep, K. G.; Nelson, S. G.; Walters, M. A. *Tetrahedron Lett.* **1991**, *32*, 4095.
(44) Takeda, K.; Kawanishi, E.; Nakamura, H.; Yoshii, E. *Tetrahedron Lett.* **1991**, *32*, 4925.
(45) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987.

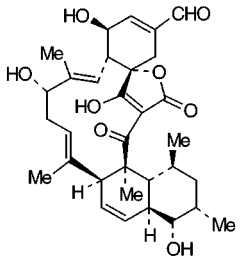
S0022-3263(98)00379-X CCC: $15.00
Published on Web 07/21/1998



chlorothricolide (**1**)



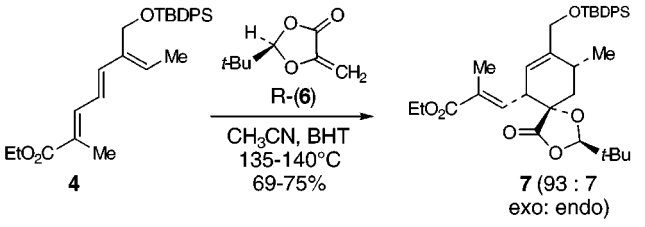
kijanolide (**2**)



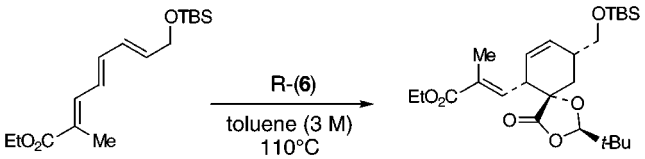
tetronolide (**3**)

workable strategy for the synthesis of the top-half spirotetronate fragment of chlorothricolide, **1**.[30] These investigations were strongly influenced by the results of our syntheses of the top-half fragments of kijanolide (**2**) and tetronolide (**3**) via the Diels−Alder reactions of trienes **4**[40,47] and **5**[46,50] with the chiral dienophile (*R*)-**6**.[51−53] These Diels−Alder reactions occurred with excellent site and regioselectivity. Products of addition across the 4,6-diene unit were observed exclusively in both cases, and in all products the orientation of the dienophile and diene was the same as in **7** and **8**. Virtually complete diastereofacial selectivity with respect to the chiral dienophile (*R*)-**6** was also achieved. Finally, and most importantly, these reactions also proceeded with remarkably high exo-selectivity, as required for the synthesis of the spirotetronate units of **2** and **3**.

Despite this excellent precedent, it was not obvious at the outset that this Diels−Alder sequence could be applied as successfully to the synthesis of chlorothricolide top-half fragments **9** or **10**, since the requisite triene precursors **11** and **12** have two diene units that in principle can react with (*R*)-**6**. Several reports of Diels−Alder reactions of trienes with substitution patterns the same as **11** and **12** have indicated that up to 15% of products resulting from addition to the disubstituted diene are sometimes obtained.[23,54−56] Fortunately, despite these initial concerns, we found that the Diels−Alder reactions of **11** and **12** with (*R*)-**6** proceed with

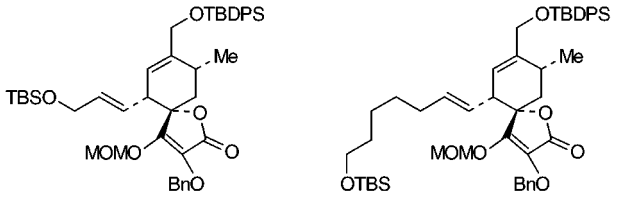


4 **7** (93 : 7 exo: endo)

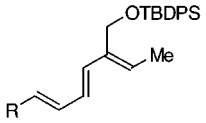


5 **8** (93 : 7 exo: endo)

excellent regioselectivity and exo-selectivity, thereby serving as the key steps in highly stereoselective synthesis of the model top-half spirotetronate fragments **9** and **10**.[30] The full details of these investigations are reported herein.



9 **10**



11, R = CO_2Me
12, R = $-(CH_2)_5OTBS$

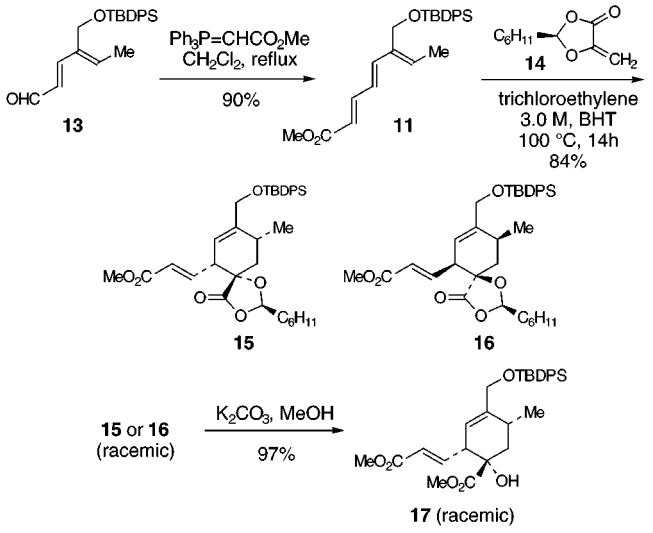
Results and Discussion

Condensation of the known diene aldehyde **13**[47] with methyl (triphenylphosphoranylidene)acetate in refluxing CH_2Cl_2 provided the trienoate **11** in 90% yield. Initial Diels−Alder reactions were performed by using racemic **14** as the dienophile.[51] A mixture of trienoate **11** and **14** (1.6 equiv) in trichloroethylene (3.0 M in **11**) was heated at 100 °C for 14 h in the presence of BHT as a radical inhibitor. This provided a 6:1 mixture (^{1}H NMR analysis) of two cycloadducts **15** and **16** in 84% yield. These compounds were determined to be diastereofacial isomers, differing with respect to the face of the dienophile that combined with the diene,[51] by methanolysis of each to the (racemic) α-hydroxy ester **17**. Cycloadduct **15** was subsequently determined to be the product of an exo Diels−Alder reaction by correlation with cycloadduct **18**.[57]

Because other studies in our laboratory indicated that dienophile **6** is more diastereofacially selective than **14**, subsequent Diels−Alder reactions were performed with (*R*)-**6** (1.7 equiv). Surprisingly, whereas the reaction of **11** and **14** proceeded in excellent yield (85%), the analogous reaction of **11** and (*R*)-**6** provided a 15:1 mixture of cycloadducts **18** (exo) and **19** (endo) in 52−60% yield. Also

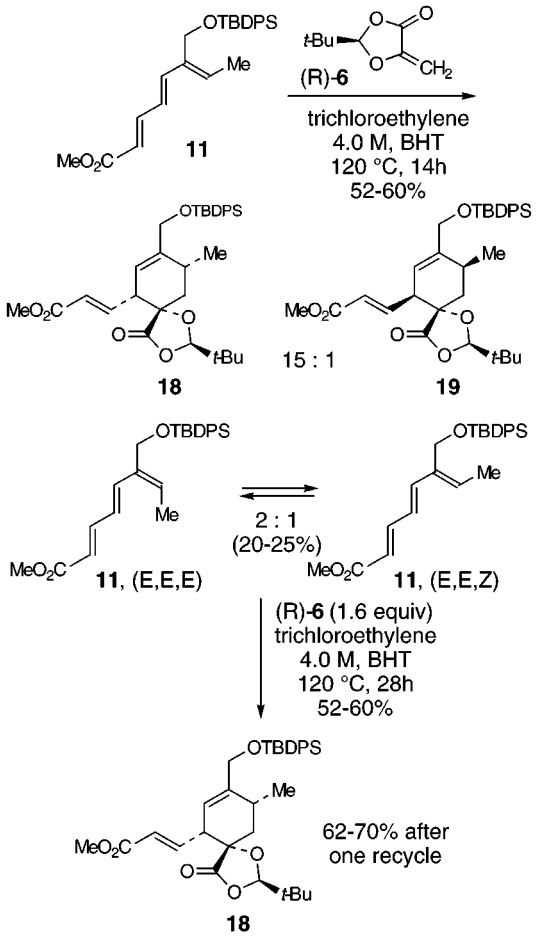
(46) Roush, W. R.; Koyama, K. *Tetrahedron Lett.* **1992**, *33*, 6227.
(47) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151.
(48) Roush, W. R.; Brown, B. B. *J. Am. Chem. Soc.* **1993**, *115*, 2268.
(49) Boeckman, R. K., Jr.; Wrobleski, S. T. *J. Org. Chem.* **1996**, *61*, 7238.
(50) Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708.
(51) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380.
(52) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7305.
(53) Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* **1989**, *122*, 327.
(54) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.
(55) Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. *J. Am. Chem. Soc.* **1978**, *100*, 7775.
(56) Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291.

(57) The exo stereochemistry of **15** was also assigned by comparison of its characteristic ^{1}H NMR data with that of the analogous exo cycloadduct in the kijanolide series (ref 47).

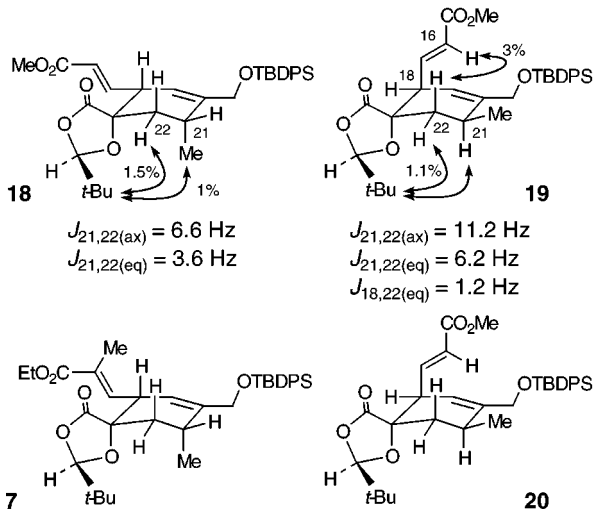


obtained was 20−25% of recovered **11** as a 2:1 mixture of the *E*,*E*,*E* and *E*,*E*,*Z* isomers. An analogous olefin isomerization has been observed by Yoshii with a related triene.[26] Attempts to suppress the isomerization of the trisubstituted olefin of **11** by performing the Diels−Alder reaction with highly purified solvents and reagents, in the presence of BHT as a radical inhibitor, or in the presence of potential acid scavengers (e.g., BSA) were unsuccessful. Accordingly, we resubjected the 2:1 mixture of (*E*,*E*,*E*)- and (*E*,*E*,*Z*)-**11** to the reaction conditions, in anticipation that (*E*,*E*,*E*)-**11** would rapidly react with (*R*)-**6** while (*E*,*E*,*E*)-**11** would reequilibrate with (*E*,*E*,*Z*)-**11**. This experiment again provided a ca. 15:1 mixture of **18** and **19** (55−60%) along with additional amounts of the (*E*,*E*,*E*)- and (*E*,*E*,*Z*)-**11** isomer mixture (2:1) that was recovered in up to 20% yield. In this way, the yield of cycloadducts **18** and **19** was 62−70% after one recycle of **11**. Interestingly, no other cycloadducts were observed, indicating that (*E*,*E*,*Z*)-**11** reacts selectively with (*R*)-**6**, which is surprising given that (*E*,*E*,*E*)-**11** contains a potentially reactive diene unit. Yoshii also has noted that the trisubstituted olefin of an analogous triene isomerizes under the conditions of the intramolecular Diels−Alder reaction employed in his synthesis of 24-*O*-methylchlorothricolide;[26] however, to the best of our knowledge our results with (*E*,*E*,*E*)- and (*E*,*E*,*Z*)-**11** are the first concrete demonstration that the (*E*,*E*,*E*)-triene is substantially less reactive than the *E*,*E*,*Z* isomer and that this isomerization can be used productively for preparative purposes. We subsequently employed this facile isomerization in our total synthesis of chlorothricolide.[31]

The stereostructural assignments for cycloadducts **18** and **19** were based initially on spectroscopic correlations with cycloadducts **7** (exo) and **20** (endo) from the kijanolide series.[47] In particular, exo cycloadduct **18** exhibited two small to moderate coupling constants between H(21) and H(22) ($J_{21,22(ax)}$ = 6.6 Hz; $J_{21,22(eq)}$ = 3.6 Hz), characteristic of a cycloadduct with an axial C(21)−Me group, whereas the endo cycloadduct exhibited one large ($J_{21,22(ax)}$ = 11.2 Hz) and one moderate ($J_{21,22(ax)}$ = 6.2 Hz) coupling constant between H(21) and H(22). The latter data require that the C(21)-Me group occupies an equatorial position in **19**. Also, a W-coupling of 1.2 Hz between H(22_{eq}) and H(18) was observed in the ^{1}H NMR spectrum of **19**, indicating that the unsaturated side chain at C(18) occupies an axial position with respect to the cyclohexenyl ring. These *J* data are completely consistent with the

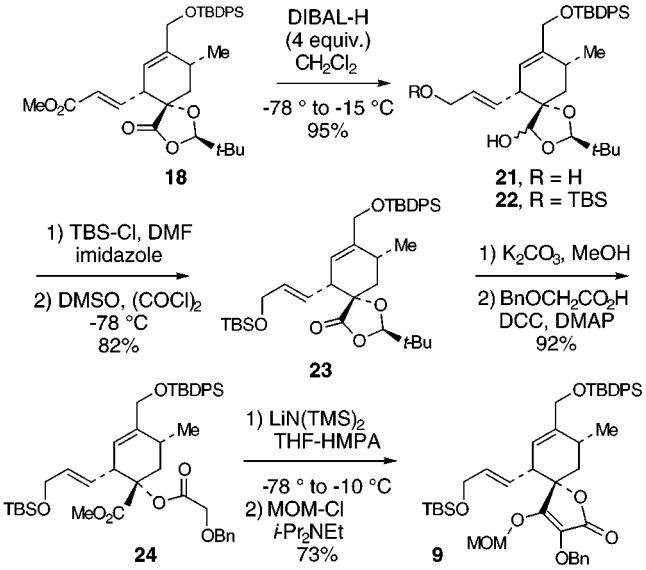


nOe data summarized in the accompanying three-dimensional structures, particularly those between the *t*-Bu and C(21)-Me (1%) in **18**, vs the nOe's observed between the *t*-Bu and H(21) (1.2%) and between H(16) and H(22_{ax}) in **19**.



Cycloadduct **18** was elaborated to the chlorothricolide top-half fragment **9** as follows. Treatment of **18** with 4 equiv of DIBAL-H in CH_2Cl_2 at −78 °C provided a 4:1 mixture of hemiacetals **21** in 95% yield. (Attempts to accomplish the selective reduction of the α,β-unsaturated ester unit of **18** were unsuccessful.) The primary alcohol of **21** was selectively protected as a TBS ether using 1.1

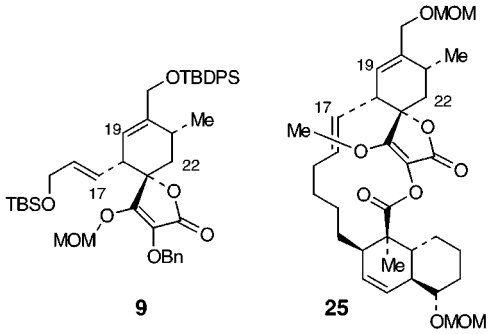
equiv of TBS−Cl and imidazole in DMF. The hemiacetal unit was then oxidized using the Swern protocol,[58] thereby providing lactone **23** in 78% overall yield. Methanolysis of **23** with K_2CO_3 in MeOH at 0 °C followed by DCC coupling[59] of the resulting tertiary α-hydroxy ester with $BnOCH_2CO_2H$[60] provided **24** in excellent yield. The same intermediate (albeit racemic) was prepared by an analogous sequence starting from **15**, the major cycloadduct of the Diels−Alder reaction of **11** and racemic **14**. Finally, closure of the spirotetronate substructure was accomplished by Dieckmann cyclization[8,47] of the lithium enolate generated from **24**. Addition of MOM-Cl and HMPA directly[47] to the Dieckmann reaction mixture provided **9** in 30−40% yield. However, the chlorothricolide top-half fragment **9** was obtained in much better yield if the intermediate tetronic acid, isolated by an extractive workup, was treated with MOM-Cl and *i*-Pr_2-NEt in CH_2Cl_2. In this way, **9** was obtained in 73% yield for the two-step sequence.



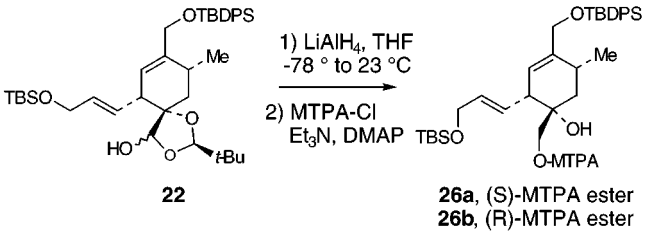
The stereochemistry of spirotetronate **9** was verified by comparison of its characteristic ^{1}H NMR data with that for Yoshii's advanced chlorothricolide intermediate **25**, the stereochemistry of which was established by single-crystal X-ray structure analysis.[26]

Finally, the enantiomeric purity of the series of intermediates deriving from exo cycloadduct **18** was determined to be 98% ee by NMR analysis of the (*S*)-MTPA and (*R*)-MTPA esters **26a** and **26b**.[61] The ^{1}H NMR spectrum of **26a** in C_6D_6 showed signals at δ 2.62 (br t, 1 H) and 0.80 (d, 3 H), whereas the corresponding signals in the spectrum of **26b** appeared at δ 2.75 (br t, 1 H) and 0.83 (d, 3 H).

Having completed an efficient, highly diastereo- and enantioselective synthesis of the chlorothricolide top-half fragment, we were ready to initiate studies on the completion of the total synthesis. However, it was readily apparent that establishing the C(14)−C(15) bond with the top-half (e.g., **9**) and bottom-half intermediates[29] in hand could be a significant challenge.[17] For example, if



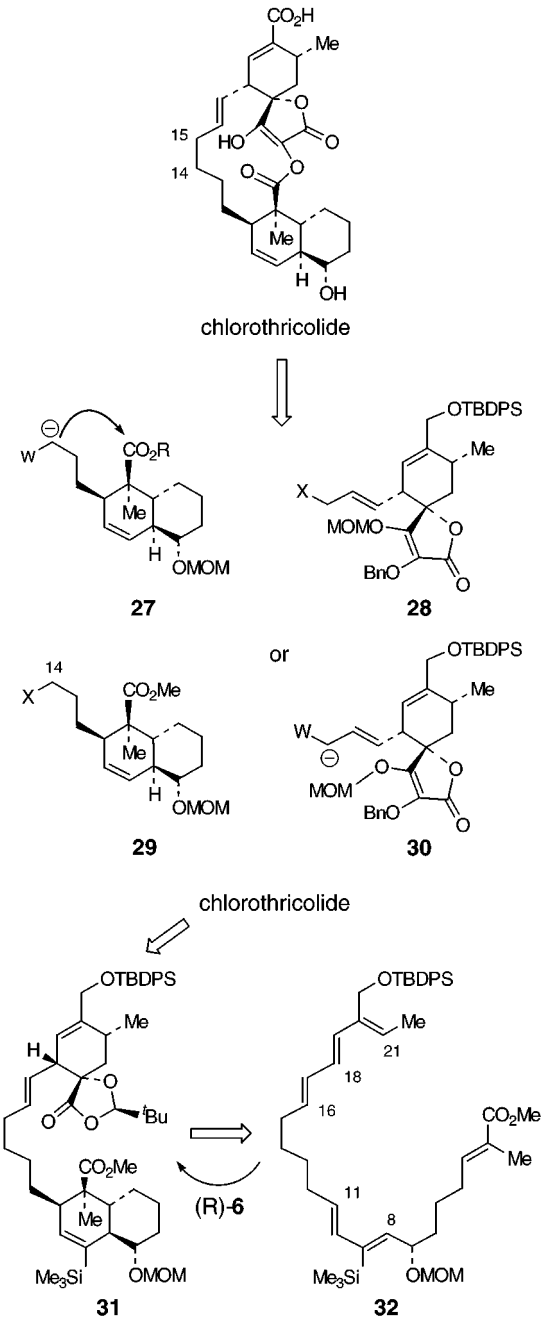
Data for **9**	Resonance	Data for **25**
5.43 (ddt, *J* = 15.5, 8.4, 1.2 Hz)	H-17	5.39 (ddt, *J* = 15.2, 8.3, 4.0 Hz)
3.20 (d, *J* = 8.4 Hz)	H-18	3.18 (d, *J* = 8.3 Hz)
5.50 (s)	H-19	5.53 (s)
2.23 (dd, *J* = 14.0, 7.2 Hz)	H-22$_{ax}$	2.34 (dd, *J* = 14.2, 7.3 Hz)



the synthetic bottom-half fragment (e.g., **27**, X = $-SO_2$-Ar) was used as the nucleophilic component in an alkylation reaction with a top-half electrophilic species **28** (X = Br, I, etc.), we would have to find conditions to minimize addition of the C(14)-carbanion to the C(1) carboxylic ester functional group (perhaps best accomplished by using **27** with R = Li). While use of the top-half fragment as the nucleophilic component (**30**, W = SO_2Ar) in a reaction with an electrophilic bottom half (**29**, X = leaving group) might pose fewer complications, we were apprehensive nonetheless about the prospects of performing this coupling on such highly functionalized intermediates.

It was apparent that these potential problems could be avoided if the C(14)−C(15) bond was established before either of the Diels−Alder reactions were performed. We thus began to focus on hexaenoate **32** as a key precursor to chlorothricolide. According to this strategy, it would be necessary to effect a bimolecular Diels−Alder reaction of (*R*)-**6** with the C(18−21) diene unit of **32** without addition of (*R*)-**6** to either the C(16−19) or the C(8−11) dienes. While it seemed probable that the C(8−11) diene would be consumed rapidly by an intramolecular Diels−Alder reaction with the C(2,3)-enoate, it remained to be determined if the absence of an electron-withdrawing substituent at C(15) of **32** would influence the site selectivity of the Diels−Alder reaction of (*R*)-**6** and the C(16−21) triene unit of **32**. The carboalkoxy substituents of **4**, **5**, and **11** undoubtedly perturb the FMO coefficients of the reactive triene system relative to a triene lacking this polarizing substituent,[62] and it was not absolutely certain that trienes **4**, **5**, and **11** were appropriate models for the behavior of **32**. Accordingly, we decided to address this issue by studying the Diels−Alder reaction of (*R*)-**6** with **12**.

(58) Tidwell, T. T. *Synthesis* **1990**, 857.
(59) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(60) Manhas, M.; Amin, S.; Chawla, H. P. S.; Bose, A. K. *J. Heterocycl. Chem.* **1978**, *15*, 601.
(61) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(62) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.



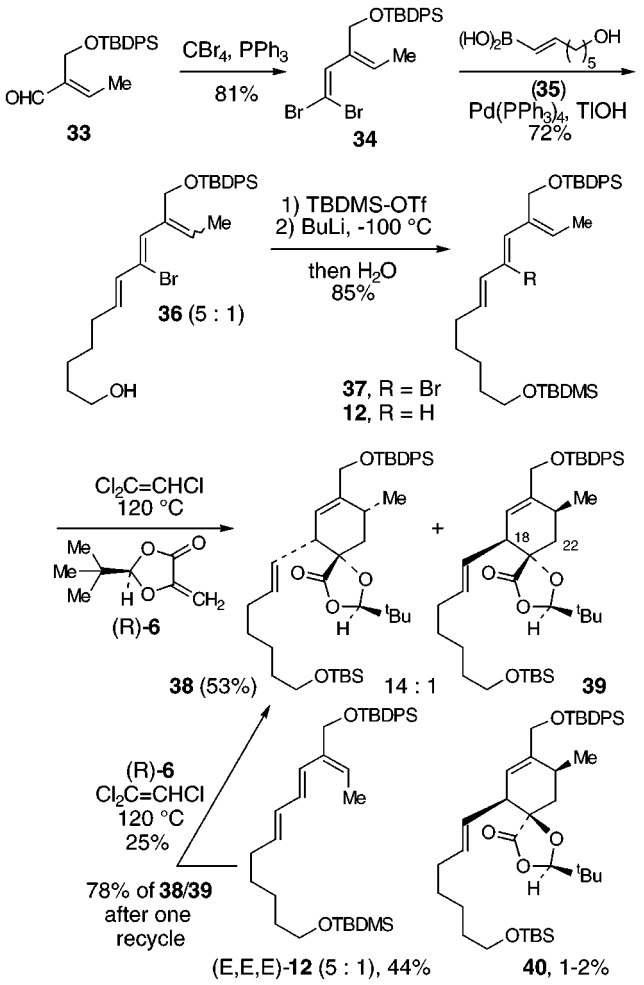
The synthesis of triene **12** began with the Corey−Fuchs olefination[63] of the known aldehyde **33**,[47] which provided dibromoolefin **34** in 81% yield.[64] Cross coupling[65] of **34** and vinylboronic acid **35**[66] using Kishi's modification[67] of the Suzuki protocol[68,69] provided bromotriene **36** in 72% yield. Surprisingly, the C(20,21)-trisubstituted olefin was partially isomerized (4−5:1) under these conditions. Suspecting that this isomerization was promoted by reversible addition of a "Pd−H" species (conceivably generated by a competitive, minor Heck pathway)[70] across the trisubstituted olefin, we performed the Suzuki cross coupling in the presence of various Ag(I) salts (e.g., $AgNO_3$, AgOAc, Ag_2CO_3), which are known to be effective in suppressing olefin isomerizations in Heck reactions.[71−73] However, all of these experiments resulted in considerably lower yields of **36** (<5−40%) without suppression of the olefin isomerization.

Although we were unable to synthesize **36** with the level of stereoselectivity originally targeted, we progressed in anticipation that this stereochemical imperfection would not pose any problems at subsequent stages of the synthesis (vide supra). Nevertheless, at least initially, we separated the two isomers by preparative HPLC (2% ethyl acetate/hexanes) and used isomerically homogeneous (*E*,*Z*,*Z*)-**36** in the subsequent exploratory steps. The synthesis of the model triene **12** was completed by protection of the hydroxyl group as a TBS ether, followed by removal of the bromine substituent via metal−halogen exchange (*n*-BuLi, −100 °C, THF).[74] This two-step sequence provided **12** in 86% yield.

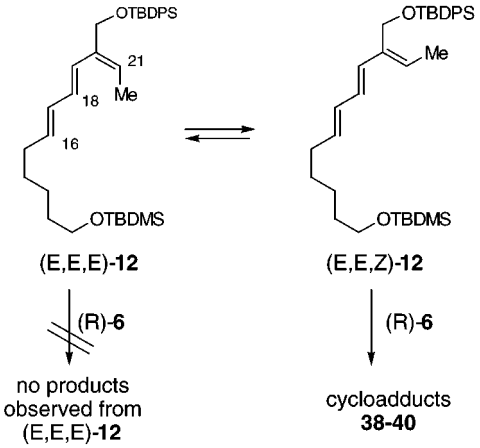
The Diels−Alder reaction was performed by heating a mixture of (*E*,*E*,*Z*)-triene **12** and (*R*)-**6** (1.8 equiv) in trichloroethylene (2.0 M in **12**) at 110 °C for 7 h. This provided a 14:1 mixture of the exo (**38**) and endo (**39**) isomers in 53% yield. The structural assignments for these cycloadducts are based on correlations with spectroscopic data for the exo (**18**) and endo (**19**) adducts obtained from the trienoate series. In addition to these two products, a small amount (1−2%) of a third cycloadduct was also isolated from the Diels−Alder reaction mixture. This compound was tentatively assigned as the second exo cycloadduct **40**, the diastereofacial isomer of **38** resulting from addition of the diene to the more hindered face of the dienophile.[51] Finally, substantially isomerized triene **12**, a 5:1 mixture of the *E*,*E*,*E* and *E*,*E*,*Z* isomers, was obtained in 44% yield. The latter mixture was resubjected to the original Diels−Alder conditions (1.7 equiv of (*R*)-**6**, 110 °C, 18 h, 2.0 M in trichloroethylene), thereby providing an additional 25% of a 14:1 mixture of cycloadducts **38** and **39** (56% based on the recycled **12**). Thus, the combined yield of **38** was 78% after one such recycle of **12**.

It is indeed remarkable that the rate of olefin isomerization of (*E*,*E*,*E*)-**12** and the subsequent Diels−Alder reaction with of (*E*,*E*,*Z*)-**12** with (*R*)-**6** is faster than the Diels−Alder reaction of (*R*)-**6** across the C(16−19) diene unit of (*E*,*E*,*E*)-**12**. In fact, we have not detected products resulting from addition across the disubstituted diene unit of either triene isomer. The most compelling set of data in support of this statement derives from an experiment in which *isomerically pure* (*E*,*E*,*E*)-**12**, prepared from the minor *E*,*Z*,*E* isomer of **35** generated in the Kishi-modified Suzuki coupling, was treated with 2

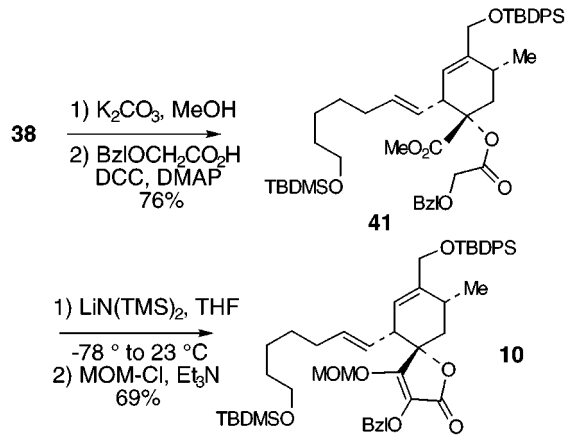
(63) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(64) Takai olefination of **33** provided the corresponding vinyl iodide as a ca. 5:1 mixture of (*E*)- and (*Z*)-vinyl iodide isomers. We elected, therefore, to pursue the synthesis of **12** via a cross-coupling reaction of the dibromoolefin **34** in anticipation that the cross coupling would be highly regioselective (cf. ref 65) and that subsequent reduction of the resulting vinyl bromide would also proceed with good stereocontrol.
(65) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509.
(66) Vinylboronic acid **35** was prepared in 71% yield via the reaction of 6-heptyn-1-ol with 2 equiv of catecholborane (neat, 75 °C, 14 h), followed by aqueous workup and chromatographic purification.
(67) Uenishi, J.-i.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.
(68) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.
(69) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.
(70) Heck, R. *Org. React.* **1982**, *27*, 345.
(71) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.
(72) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328.
(73) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687.
(74) Parham, W. E.; Bradsher, C. V. *Acc. Chem. Res.* **1982**, *15*, 300.



equiv of (*R*)-**6** at 110−120 °C in the presence of BHT radical inhibitor. This experiment provided a 14:1 mixture of exo and endo cycloadducts **38** and **39** in 45% yield. The recovered triene **12** (ca. 45%) was a 4.6:1 mixture of the *E*,*E*,*E* and *E*,*E*,*Z* olefin isomers.



The enantiomeric purity of exo cycloadduct **38** was determined to be 98% ee by Mosher ester analysis[61] of the diol obtained by $LiAlH_4$ reduction. Methanolysis of the dioxolanone system of **38** followed by DCC-mediated coupling of the resulting α-hydroxy methyl ester with benzyloxyacetic acid[60] provided diester **41** in 76% yield. Finally, Dieckmann cyclization[8] of **41** followed by protection of the tetronic acid as a MOM ether provided the targeted spirotetronate **10** in 69% yield.



In summary, we have demonstrated that the Diels−Alder reactions of trienes **11** and **12** with the chiral dienophile (*R*)-**6** exhibit remarkably high diastereofacial and exo selectivity. These reactions also proceed with exquisite regioselectivity for addition across the trisubstituted C(18)−C(21) diene unit. In no cases were products observed where the Diels−Alder reactions occurred across the disubstituted C(16)−C(19) diene unit. This study further demonstrated that it is not necessary to control the stereochemistry of the C(20)−C(21) trisubstituted olefin of the triene precursors, since this unit readily isomerizes under the conditions of the Diels−Alder reaction. We have demonstrated that one can use the seemingly unreactive (*E*,*E*,*E*)-triene isomers (e.g., (*E*,*E*,*E*)-**12**) as the starting materials and still obtain the desired exo cycloadducts **15** and **38** in good yield. These studies set the stage for completion of our highly stereoselective synthesis of (−)-chlorothricolide.[31,75]

Experimental Section[76]

Methyl (2*E*,4*E*,6*Z*)-6-[(*tert*-butyldiphenylsilyloxy)methyl]octa-2,4,6-trienoate (11). To a solution of diene aldehyde **13**[47] (280 mg, 0.77 mmol) in CH_2Cl_2 (8.0 mL, 0.1 M) was added methyl (triphenylphosphoranylidene)acetate (670 mg, 2.0 mmol), and then the mixture was heated to reflux and allowed to stir for 10 h. The reaction mixture was cooled to room temperature, diluted with hexanes (3 mL), and filtered through a plug of silica gel. The filtrate was concentrated in vacuo, and the crude product was purified by silica gel flash column chromatography[77] (8:1 hexanes−diethyl ether), affording triene **11** (271 mg, 90%) as a clear oil: TLC $R_f = 0.6$ (3:1 hexanes−diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4 H), 7.45−7.36 (m, 7 H), 6.55 (A of ABX, $J = 15.6$, 10.6 Hz, 1 H), 6.54 (B of ABX, $J = 15.6$, 0.6 Hz, 1 H), 5.88 (d, $J = 15.2$ Hz, 1 H), 5.89 (q, $J = 7.2$ Hz, 1 H), 4.45 (s, 2 H), 3.83 (s, 3 H), 1.65 (d, $J = 7.6$ Hz, 3 H), 1.10 (s, 9 H); IR ($CDCl_3$) 1705, 1610 cm^{-1}; HRMS for $C_{26}H_{32}O_3Si$ (M^+) calcd 420.2121, found 420.2136 *m*/*z*.

(2′*R*,3*R*,4*S*,6*R*)-Spiro-1-[(*tert*-butyldiphenylsilyloxy)methyl]-3-(3-carbomethoxyprop-1-enyl)-6-methylcyclohex-1-ene-[4,5′]-2′-*tert*-butyl-1′,3′-dioxolan-4′-one (18). A solution of triene (*E*,*E*,*Z*)-**11** (225 mg, 0.54 mmol) in degassed trichloroethylene (134 μL, 4.0 M) that had been purified by passing through a short column of basic alumina was added to a presilylated (BSA) resealable Carius tube. To this solution

(75) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *119*, submitted for publication.

(76) For general experimental details, see: Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502. Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (>95% by ^{1}H NMR analysis) for use in subsequent reactions.

(77) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

were added dienophile (*R*)-**6**[51] (145 mg, 0.91 mmol) and a crystal of BHT (radical inhibitor). The Carius tube was sealed under an argon atmosphere and heated at 120 °C for 14 h. ^{1}H NMR analysis (400 MHz) of the crude reaction mixture revealed a 16:1 mixture of two cycloadducts, along with residual triene that consisted of a 1:2 mixture of (*E*,*E*,*Z*)-**10** and isomerized triene (*E*,*E*,*E*)-**10**. The reaction mixture was concentrated in vacuo, and the crude product was purified by silica gel flash column chromatography (20:1 hexanes−Et_2O), yielding a 16:1 mixture of cycloadducts **18** and **19** (160 mg, 52% yield) along with an inseparable mixture (1:2) of recovered triene (*E*,*E*,*Z*)-**10** and its isomer (*E*,*E*,*E*)-**10** (48 mg, 21%). Cycloadducts **18** and **19** were separated by preparative HPLC (10% ethyl acetate−hexanes, 4 mL/min, 10 mm Whatman M9 silica gel column, retention time: **18**, 14.1 min; **19**, 19.4 min).

The recovered triene (48 mg of a 1:2 mixture of (*E*,*E*,*Z*)-**10** and (*E*,*E*,*E*)-**10**) in trichloroethylene (23 μL, 4.0 M; again, neutralized by elution through basic alumina) was added to a presilylated (BSA) resealable Carius tube. To this solution were then added dienophile (*R*)-**6** (25 mg, 0.15 mmol) and a crystal of BHT. The Carius tube was sealed and the mixture heated at 120 °C for 28 h. The crude product was purified by silica gel flash column chromatography (20:1 hexanes−diethyl ether), giving additional cycloadduct **18** (30 mg, 57% yield). The yield of adduct **18** (190 mg) was 64% from **11** after one such recycle.

Data for exo cycloadduct 18: [α] = −70.8 (*c* 1.9, hexanes); TLC R_f = 0.64 (2:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.66 (m, 4 H), 7.46−7.36 (m, 6 H), 6.88 (dd, *J* = 15.6, 8.8 Hz, 1 H), 5.98 (dd, *J* = 15.6, 0.8 Hz, 1 H), 5.45 (dd, *J* = 2.8, 1.6 Hz, 1 H), 5.09 (s, 1 H), 4.22 (B of AB, *J* = 13.6 Hz, 1 H), 4.19 (A of AB, *J* = 13.6 Hz, 1 H), 3.76 (s, 3 H), 3.37 (d, *J* = 8.8 Hz, 1 H), 2.64 (m, 1 H), 2.11 (dd, *J* = 14.0, 6.8 Hz, 1 H), 1.80 (dd, *J* = 14.0, 3.2 Hz, 1 H), 1.12 (d, *J* = 7.2 Hz, 3 H), 1.06 (s, 9 H), 0.94 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 166.3, 145.3, 142.7, 135.5 133.4, 129.7, 127.7, 124.9, 117.1, 109.5, 80.0, 65.4, 51.7, 44.6, 36.4, 34.9, 28.2, 26.8, 23.3, 19.5, 19.3; IR (CCl_4) 1795, 1727, 1655, 1590 cm^{-1}; HRMS for $C_{30}H_{35}O_6Si$ ($M^+ - C_4H_9$) calcd 519.2203, found 519.2203. Anal. Calcd for $C_{34}H_{44}O_6Si$: C, 70.80; H, 7.69. Found: C, 70.57; H, 7.46.

Data for endo cycloadduct 19: [α] = $^+$0.50 (*c* 0.4, CH_2Cl_2); TLC R_f = 0.60 (2:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, C_6D_6) δ 7.69−7.65 (m, 4 H), 7.45−7.35 (m, 6 H), 7.20 (dd, *J* = 15, 8 Hz, 1 H), 5.93 (dd, *J* = 15.5, 1.8 Hz, 1 H), 5.43 (m, 1 H), 4.89 (s, 1 H), 4.13 (A of AB, *J* = 13.2 Hz, with additional allylic coupling, 1 H), 4.01 (B of AB, *J* = 13.6 Hz, 1 H), 3.38 (s, 3 H), 2.89 (m, 1 H), 2.45 (m, 1 H), 1.70 (ddd, *J* = 13.9, 11.2 Hz, 1 H), 1.62 (dd, *J* = 13.9, 6.2, 1.2 Hz, 1 H), 1.2−1.4 (m, 7 H), 1.15 (s, 9 H), 0.85−1.0 (m, 2 H), 0.80 (s, 9 H), 0.65 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 166.3, 145.1, 142.4, 135.6, 135.4, 133.6, 133.4, 129.7, 123.6, 117.5, 107.8, 70.4, 65.1, 51.6, 42.0, 35.0, 34.5, 29.7, 27.5, 26.8, 23.4, 19.3, 18.3; IR (CCl_4) 1800, 1730, 1650 cm^{-1}; HRMS for $C_{30}H_{35}O_6Si$ ($M^+ - C_4H_9$) calcd 519.2203, found 519.2185.

Lactol 21 via DIBAL-H Reduction of 18. To a −78 °C solution of optically active lactone **23** (92 mg, 0.16 mmol) in CH_2Cl_2 (1.6 mL, 0.1 M) was slowly added diisobutylaluminum hydride (640 μL of a 1.0 M solution in hexanes, 0.64 mmol). After 15 min, the reaction mixture was warmed to −15 °C. The reaction was quenched with saturated Rochelle's salt solution (2 mL) and the mixture stirred for 4 h. The mixture was extracted with CH_2Cl_2 (4 × 10 mL), and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (gradient, 3:1 hexanes−Et_2O to 1:1 hexanes−Et_2O), affording the lactol **21** (83 mg, 95% yield) as an inseparable 4:1 mixture of anomers: [α] = −132° (*c* 1.0, CH_2Cl_2); TLC R_f = 0.33 (2:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4 H), 7.45−7.36 (m, 6 H), 5.66−5.65 (m, 2 H), 5.62−5.58 (m, 1 H), 4.98 (s, 1 H), 4.75 (s, 1 H), 4.23−4.12 (m, 4 H), 3.02 (m, 1 H), 2.52 (m, 1 H), 1.86−1.76 (m, 1 H), 1.69−1.59 (m, 1 H), 1.05 (s, 9 H), 0.97 (d, *J* = 7.2 Hz, 3 H), 0.94 (s, 9 H); partial ^{1}H NMR data for the minor anomer: δ 5.18 (s, 1 H), 4.92 (s, 1 H), 2.53 (m, 1 H), 2.40 (m, 1 H), 1.08 (s, 9 H), 1.06 (s, 9 H), 1.01 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) (of anomeric mixture) δ 142.8, 141.8, 135.5, 135.4, 133.7, 133.6, 133.5, 133.3, 131.9, 130.8, 129.7, 129.7, 129.4, 127.7, 120.3, 120.0, 112.3, 108.7, 97.6, 85.2, 65.4, 65.1, 63.8, 63.6, 63.2, 42.7, 41.0, 36.3, 33.6, 32.9, 29.9, 29.3, 26.8, 24.2, 24.1, 23.4, 19.6, 19.3, 19.1; IR ($CDCl_3$) 3610, 3430 (broad), 1655, 1585 cm^{-1}; HRMS for $C_{33}H_{46}O_5Si$ calcd 550.3114, found 550.3120. Anal. Calcd for $C_{33}H_{46}O_5Si$: C, 71.96; H, 8.42. Found: C, 71.69; H, 8.12.

TBS Ether 22. To a 23 °C solution of the lactol **21** (120 mg, 0.22 mmol) in DMF (440 μL, 0.5 M) were added imidazole (37 mg, 0.55 mmol) and *tert*-butyldimethylsilyl chloride (43 mg, 0.28 mmol). The mixture was stirred for 14 h and then was poured into a mixture of 1:1 hexanes−Et_2O and 50% aqueous brine solution. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (5:1 hexanes−Et_2O), yielding the mono-TBS ether **22** (125 mg, 89% yield) as an inseparable 4:1 mixture of hemiacetal anomers: [α] = −107° (*c* 0.9, CH_2Cl_2); TLC R_f = 0.34 (5:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.66 (m, 4 H), 7.46−7.36 (m, 6 H), 5.85−5.48 (m, 3 H), 4,99 (d, *J* = 8 Hz, 1 H), 4.76 (s, 1 H), 4.25−4.11 (m, 4 H), 3.02 (m, 1 H), 2.54 (m, 1 H), 2.23 (d, *J* = 9.2 Hz, 1 H), 1.77 (ddd, *J* = 12.8, 6.0, 1.6 Hz, 1 H), 1.67−1.61 (m, 2 H), 1.06 (s, 9 H), 0.97 (d, *J* = 6.8 Hz, 2 H), 0.94 (s, 9 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$; of anomeric mixture) δ 142.5, 135.6, 135.50, 135.45, 133.83, 133.77, 133.7, 132.2, 131.6, 131.0, 129.6, 127.6, 120.4, 108.6, 97.7, 85.3, 65.1, 63.7, 41.2, 39.7, 37.3, 33.6, 33.0, 29.9, 26.8, 26.0, 24.24, 24.17, 19.3, 19.2, 18.4, −5.1; IR (CCl_4) 3580, 3450, 1585, 1480, 1470, 1460, 1425, 1360 cm^{-1}; HRMS for $C_{39}H_{60}O_5Si_2$ (M^+) calcd 664.3979, found 664.4011.

Partial data for minor hemiacetal anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 15.6, 6.8, 1.6 Hz, 1 H), 5.18 (d, *J* = 4.4 Hz, 1 H), 4.99 (d, *J* = 8.8 Hz, 1 H), 3.36 (m, 1 H), 2.68 (d, *J* = 4.8 Hz, 1 H), 2.40 (m, 1 H), 1.02 (d, *J* = 6.8 Hz, 1 H), 0.91 (s, 9 H).

(2*R*,2′*R*,4*S*,5*R*)-Spiro-1-[(*tert*-butyldiphenylsilyloxy)-methyl]-2-methyl-5-[3-(*tert*-butyldimethylsilyloxy)prop-1-enyl]cyclohex-1-ene-[4,5′]-2′-*tert*-butyl-1′,3′-dioxolan-4′-one (23). To a −78 °C solution of oxalyl chloride (38 μL, 0.43 mmol) in CH_2Cl_2 (600 μL, 0.1 M) was added DMSO (42 μL, 0.55 mmol). After 10 min, a solution of lactol **22** (108 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was stirred for 1 h at −78 °C. Et_3N (110 μL, 4.7 equivalents) was added, and the reaction mixture was allowed to warm to room temperature. The mixture was poured into saturated $NaHCO_3$ solution (3 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10:1 hexanes−Et_2O), yielding lactone **23** (95 mg, 88% yield) as a colorless oil: [α] = −57.3° (*c* 1.86, CH_2Cl_2); TLC R_f = 0.6 (5:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4 H), 7.46−7.35 (m, 6 H), 5.75 (dt, *J* = 15.2, 3.6 Hz, 1 H), 5.67 (dd, *J* = 15.2, 8.0 Hz, 1 H), 5.48 (s, 1 H), 5.17 (s, 1 H), 4.20 (m, 4 H), 3.22 (d, *J* = 8.0 Hz, 1 H), 2.59 (m, 1 H), 2.14 (dd, *J* = 14.0, 7.2 Hz, 1 H), 1.78 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.13 (d, *J* = 7.2 Hz, 3 H), 1.07 (s, 9 H), 0.94 (s, 9 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 141.0, 135.6, 135.5, 133.7, 133.63, 133.57, 129.6, 127.7, 127.6, 126.6, 120.1, 109.8, 81.0, 65.8, 62.9, 45.2, 36.7, 34.9, 27.9, 26.9, 25.9, 23.4, 19.6, 19.3, 18.3, −5.3; IR (CCl_4) 1795, cm^{-1}; HRMS for $C_{39}H_{59}O_5Si_2$ ($M^+ + 1$) calcd 663.3901, found 663.3873.

(1*S*,2*R*,5*R*)-1-(2-Benzyloxyacetoxy)-2-[3-(*tert*-butyldimethylsilyloxy)prop-1-enyl]-4-[(*tert*-butyldiphenylsilyloxy)-methyl]-1-carbomethoxy-5-methylcyclohex-3-ene (24). A mixture of dioxolanone **23** (25 mg, 0.04 mmol) and K_2CO_3 (2 mg, catalytic) in methanol (0.4 mL, 0.1 M) was stirred for 10 h at ambient temperature. The reaction mixture was concentrated in vacuo, and then resultant oil was taken up in CH_2Cl_2 and washed with saturated NH_4Cl solution (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried over Na_2SO_4 and then concentrated in vacuo. The crude product was purified by silica gel

flash column chromatography (4:1 hexanes−Et_2O), providing the α-hydroxy ester (23 mg, 99% yield) as a colorless oil: [α] = −42.7° (*c* 1.6, CH_2Cl_2); TLC R_f = 0.24 (5:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4 H), 7.45−7.36 (m, 6 H), 5.67−5.57 (m, 2 H), 5.51 (dd, *J* = 1.6, 1.2 Hz, 1 H), 4.24 (B of AB, *J* = 13.2 Hz, 1 H), 4.15 (A of AB, *J* = 13.2 Hz, 1 H), 4.15 (d, *J* = 3.2 Hz, 2 H), 3.77 (s, 3 H), 3.32 (s, 1 H), 2.71 (s, 1 H), 2.53 (m, 1 H), 2.20 (dd, *J* = 13.6, 7.2 Hz, 1 H), 1.71 (dd, *J* = 13.6, 3.6 Hz, 1 H), 1.13 (d, *J* = 7.2 Hz, 3 H), 1.00 (s, 9 H), 0.09 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 140.8, 135.6, 135.5, 133.9, 133.8, 133.4, 129.6, 128.4, 127.6, 120.9, 75.7, 66.0, 63.7, 61.5, 52.6, 45.3, 38.3, 29.7, 28.6, 26.9, 26.0, 19.9, 19.3, 18.4, −5.1; IR ($CDCl_3$) 3535, 1725 cm^{-1}; HRMS for $C_{35}H_{52}O_5Si_2$ (M^+) calcd 608.3353, found 608.3337. Anal. Calcd for $C_{35}H_{52}O_5Si_2$: C, 69.03; H, 8.61. Found: C, 69.28; H, 8.84. All physical and spectroscopic data for this α-hydroxy ester were identical to those of the racemic compound prepared by an analogous manner from **15**, except for the optical rotation.

To a solution of optically active hydroxy ester prepared above (40 mg, 0.07 mmol) in CH_2Cl_2 (1.60 mL, 0.04 M) were added α-benzyloxyacetic acid[60] (55 mg, 0.33 mmol), dicyclohexylcarbodiimide (68 mg, 0.33 mmol), and (dimethylamino)-pyridine (2 mg, catalytic).[59] The mixture was stirred for 16 h and then passed through a thin plug of silica gel and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10:1 hexanes−Et_2O), yielding ester **24** (45 mg, 92% yield) as a colorless oil: [α] = −98.7° (*c* 18.2, CH_2Cl_2); TLC R_f = 0.51 (2:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4 H), 7.43−7.30 (m, 11 H), 5.59 (dt, *J* = 15.2, 4.8 Hz, 1 H), 5.55−5.53 (m, 1 H), 5.49 (ddt, *J* = 15.2, 8.4, 1.2 Hz, 1 H), 4.62 (B of AB, *J* = 11.6 Hz, 1 H), 4.60 (A of AB, *J* = 11.6 Hz, 1 H), 4.22−4.02 (m, 6 H), 3.80 (m, 1 H), 3.74 (s, 3 H), 2.40 (m, 1 H), 2.20 (ddd, *J* = 13.2, 5.8, 0.8 Hz, 1 H), 1.87 (dd, *J* = 12.8, 10.4 Hz, 1 H), 1.03 (m, 12H), 0.89 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 169.4, 139.2, 137.3, 135.6, 135.5, 133.8, 133.7, 132.8, 129.6, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 122.4, 81.9, 73.2, 67.0, 65.4, 63.3, 57.1, 52.4, 43.4, 37.2, 36.0, 29.1, 26.7, 25.9, 19.3, 18.7, 18.3, −5.2; IR ($CDCl_3$) 1755, 1732 cm^{-1}; HRMS for $C_{38}H_{45}O_7Si$ (M^+ − TBDMS) calcd 641.2934, found 641.2972. Anal. Calcd for $C_{44}H_{60}O_7Si_2$: C, 69.80; H, 7.99. Found: C, 69.83; H, 8.14.

(5*S*,6*R*,9*R*)-2-Oxo-3-benzyloxy-6-[3-(*tert*-butyldimethylsilyloxy)prop-1-enyl]-8-[(*tert*-butyldiphenylsilyloxy)-methyl]-4-methoxymethyloxy-9-methyl-1-oxaspiro-[4.5]-deca-3,7-diene (9). To a −78 °C solution of diester **24** (45 mg, 0.06 mmol) in THF (540 μL, 0.1 M) was added lithium hexamethyldisilazide (120 μL of a 1.0 M solution in hexanes, 0.13 mmol). The reaction mixture was stirred for 2 h at −78 °C and then was allowed to warm to room temperature over a period of 45 min. The reaction mixture was diluted with brine (1 mL) and acidified to pH 1 with 2 N HCl. The aqueous layer was extracted with ethyl acetate (4 × 2 mL), and the combined extracts were concentrated in vacuo. The crude tetronic acid was purified by silica gel flash column chromatography (3:1 hexanes−ethyl acetate), yielding the unstable tetronic acid. The acid was dissolved in 30:1 mixture of CH_2Cl_2−HMPA (610 μL, 0.1 M) and cooled to 0 °C. Next, *i*-Pr_2NEt (46 μL, 0.27 mmol) and MOM-Cl (11 μL, 0.15 mmol) were added. The reaction mixture was stirred for 3 h at 0 °C and then was warmed to room temperature and poured into saturated NH_4-Cl solution (500 mL). The aqueous layer was extracted with ethyl acetate (4 × 3 mL), and the combined extracts were concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (6:1 hexanes−EtOAc), affording the protected tetronate **9** (33 mg, 73% yield over both steps) as a white semisolid: [α] = −46.5° (*c* 2.2, CH_2Cl_2); TLC R_f = 0.49 (4:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4 H), 7.45−7.33 (m, 11 H), 5.63 (dt, *J* = 15.6, 5.2 Hz, 1 H), 5.50 (s, 1 H), 5.43 (ddt, *J* = 15.6, 8.4, 1.2 Hz, 1 H), 5.30 (s, 2 H), 5.11 (A of AB, *J* = 10.8 Hz, 1 H), 5.05 (B of AB, 10.8 Hz, 1 H), 4.22 (B of AB, *J* = 13.2 Hz, 1 H), 4.16 (A of AB, *J* = 13.2 Hz, 1 H), 4.10 (dd, *J* = 5.2, 1.2 Hz, 2 H), 3.47 (s, 3 H), 3.20 (d, *J* = 8.4 Hz, 1 H), 2.58 (t, *J* = 7.2 Hz, 1 H), 2.23 (dd, *J* = 14.0, 7.2 Hz, 1 H), 1.50 (d, *J* = 14 Hz, 1 H), 1.15 (d, *J* = 7.2 Hz, 3 H), 1.06 (s, 9 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 159.3, 140.7, 136.4, 135.5, 134.0, 133.7, 133.6, 129.7, 128.9, 128.5, 128.4, 127.7, 126.3, 121.6, 120.4, 96.4, 80.6, 77.2, 73.6, 65.8, 63.6, 57.3, 43.1, 37.6, 29.7, 28.1, 26.9, 25.9, 20.1, 19.3, 18.4, −5.15, −5.19; IR ($CDCl_3$) 1750, 1675 cm^{-1}; HRMS for $C_{40}H_{48}O_7Si_2$ (M^+ − C_5H_{12}) calcd 696.2939, found 696.2913. Anal. Calcd for $C_{45}H_{60}O_7Si_2$: C, 70.27; H, 7.86. Found: C, 70.35; H, 7.67.

(3*Z*)-1,1-Dibromo-3-[(*tert*-butyldiphenylsilyloxy)methyl]penta-1,3-diene (34). To a 0 °C solution of Ph_3P (3.1 g, 12 mmol) in CH_2Cl_2 (7.2 mL, 0.5 M) was slowly added CBr_4 (2.0 g, 5.9 mmol).[63] The mixture was stirred for 5 min, and then a solution of aldehyde **33**[47] (250 mg, 0.74 mmol) in CH_2-Cl_2 (1 mL of solution predried over 4 Å molecular sieves) was added via cannula. The reaction mixture was stirred at 0 °C for 5 min and then was allowed to warm to room temperature. The mixture was concentrated in vacuo, and the resultant solid was washed with hexanes (3 × 150 mL). The combined extracts were then washed with 50% H_2O_2 solution to oxidize residual Ph_3P. The extracts were concentrated in vacuo, and the crude product was purified by silica gel flash column chromatography (100% hexanes), providing the dibromide **34** (287 mg, 81% yield) as a pale yellow oil: TLC R_f = 0.81 (10:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4 H), 7.45−7.36 (m, 6 H), 7.03 (s, 1 H), 5.90 (ddq, *J* = 14.6, 7.0, 0.8 Hz, 1 H), 4.32 (s, 2 H), 1.51 (dd, *J* = 6.8, 0.8 Hz, 3 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 135.6, 135.5, 133.5, 129.7, 129.0, 127.7, 82.2, 60.3, 26.8, 19.2, 13.4; IR ($CDCl_3$) 3065, 3045, 3010, 2970, 2930, 2855, 1825, 1585 cm^{-1}; HRMS for $C_{18}H_{17}OSi^{79}Br^{81}Br$ (M^+ − C_4H_9) calcd 435.9492, found 435.9477. Anal. Calcd for $C_{22}H_{26}OSiBr_2$: C, 53.45; H, 5.30. Found: C, 53.16; H, 5.32.

(6*E*,8*Z*,10*Z*)-8-Bromo-10-[(*tert*-butyldiphenylsilyloxy)-methyl]dodeca-6,8,10-trien-1-ol (36). To a solution of dibromoolefin **34** (1.27 g, 2.57 mmol) in degassed THF (25 mL, 0.1 M) was added $Pd(PPh_3)_4$ (400 mg, 0.33 mmol). The mixture was stirred for 5 min, and then a solution of vinylboronic acid **35**[66] (570 mg, 3.6 mmol) in degassed TlOH solution (12.4 mL of 0.3 M aqueous solution, 3.6 mmol) was added all at once.[67] The reaction mixture was stirred for 20 min and then was filtered through a plug of Celite. The aqueous layer was removed and extracted with ethyl acetate (2 × 50 mL). The combined extracts were concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (2:1 hexanes−Et_2O with 1% Et_3N), giving triene **36** (970 mg, 72% yield) as a ca. 5:1 mixture of olefin isomers at the trisubstituted double bond. The olefin isomers were separated by preparative HPLC (29% EtOAc−hexanes, 5 mL/min, 10 mm Whatman M9 silica gel column), yielding the desired triene (*E*,*Z*,*Z*)-**36** as a pale yellow oil: TLC R_f = 0.23 (2:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.67 (m, 4 H), 7.44−7.35 (m, 6 H), 6.42 (s, 1 H), 6.10−6.00 (m, 3 H), 4.35 (s, 2 H), 3.56 (t, *J* = 6.4 Hz, 2 H), 2.22 (dt, *J* = 12.8, 6.4 Hz, 2 H), 1.64−1.38 (m, 7 H), 1.55 (d, *J* = 7.2 Hz, 3 H), 1.04 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.4, 135.2, 133.7, 130.7, 130.5, 129.6, 129.1, 127.6, 122.6, 62.9, 61.2, 32.6, 32.2, 29.1, 26.8, 25.3, 19.2, 13.5; IR (CCl_4) 3630, 3400 (broad), 1640, 1587 cm^{-1}; HRMS for $C_{25}H_{30}O_2SiBr$ (M^+ − C_4H_9) calcd 469.1198, found 469.1229.

Partial data for (*E*,*Z*,*E*)-**36**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8−7.85 (m, 4 H), 7.3−7.2 (m, 6 H), 6.23−6.30 (m, 1 H), 6.25 (s, 1 H), 5.98−5.93 (m, 2 H), 4.41 (s, 2 H), 3.31 (t, *J* = 6.4 Hz, 2 H), 1.96 (m, 2 H), 1.70 (d, *J* = 7.2 Hz, 3 H), 1.4−1.2 (m, 6 H), 1.13 (s, 9 H).

(6*E*,8*Z*,10*Z*)-8-Bromo-1-(*tert*-butyldimethylsilyloxy)-10-[(*tert*-butyldiphenylsilyloxy)methyl]dodeca-6,8,10-triene (37). To a 0 °C solution of bromotriene (*E*,*Z*,*Z*)-**36** (310 mg, 0.59 mmol) in CH_2Cl_2 (2.5 mL, 0.2 M) was added Et_3N (395 μL, 2.8 mmol). The mixture was stirred for 10 min at 0 °C, and then TBS−OTf (270 mL, 1.2 mmol) was added. The mixture was stirred for 2 h and then was washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was

purified by silica gel flash column chromatography (2% EtOAc−hexanes with 1% Et_3N), yielding TBS ether **37** (343 mg, 90% yield) as a pale yellow oil: TLC R_f = 0.81 (15:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68 (m, 4 H), 7.45−7.36 (m, 6 H), 6.42 (s, 1 H), 6.15−6.01 (m, 3 H), 4.35 (s, 2 H), 3.62 (t, J = 6.8 Hz, 2 H), 2.21 (dt, J = 12.8, 6.8 Hz, 2 H), 1.59−1.33 (m, 9 H), 1.05 (s, 9 H), 0.91 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.3, 133.7, 130.6, 130.4, 129.6, 129.1, 127.6, 122.7, 63.2, 61.2, 32.7, 32.3, 29.1, 26.8, 26.0, 25.4, 19.3, 18.4, 13.5, −5.2; IR (CCl_4) 3070, 3045, 2950, 2930, 2890, 2860, 1587 cm^{-1}; HRMS for $C_{35}H_{53}O_2Si_2Br$ (M^+) calcd 640.2768, found 640.2786.

(6*E*,8*E*,10*Z*)-1-(*tert*-Butyldimethylsilyloxy)-10-[(*tert*-butyldiphenylsilyloxy)methyl]dodeca-6,8,10-triene (12). To a −100 °C solution (Et_2O−liquid N_2 bath) of bromo triene **37** (301 mg, 0.05 mmol) in THF (4.6 mL, 0.1 M) was added dropwise *n*-BuLi (260 μL of a 2.5 M solution in hexanes, 0.07 mmol). The solution immediately turned yellow. After 10 min at −100 °C, the mixture was diluted with MeOH (1 mL), warmed to room temperature, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (10:1 hexanes−Et_2O with 1% Et_3N), yielding triene **12** (252 mg, 95% yield) as a colorless oil: TLC R_f = 0.67 (15:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.70 (m, 4 H), 7.46−7.37 (m, 6 H), 6.37 (dd, J = 15.2, 10.6 Hz, 1 H), 6.07 (dd, J = 15.2, 8.8 Hz, 2 H), 5.66−5.56 (m, 2 H), 4.36 (s, 2 H), 3.62 (t, J = 6.8 Hz, 2 H), 2.11 (dt, J = 14.4, 7.2 Hz, 2 H), 1.57−1.31 (m, 9 H), 1.05 (s, 9 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 135.7, 135.6, 133.8, 132.5, 131.2, 129.5, 128.2, 128.1, 127.6, 63.3, 58.6, 32.81, 32.75, 29.7, 29.2, 26.8, 26.0, 25.4, 19.3, 18.4, 13.8, −5.2; IR (CCl_4) 3070, 3045, 3015, 2960, 2935, 2860, 1470, 1460, 1425 cm^{-1}; HRMS for $C_{31}H_{45}O_2Si_2$ ($M^+ - C_4H_9$) calcd 505.2958, found 505.2947.

(2′*R*,3*R*,4*S*,6*R*)-Spiro-3-[7-(*tert*-butyldimethylsilyloxy)-hept-1-enyl]-1-[(*tert*-butyldiphenylsilyloxy)methyl]-6-methylcyclohex-1-ene-[4,5′]-2′-*tert*-butyl-1′,3′-dioxolan-4′-one (38). A solution of triene **12** (250 mg, 0.44 mmol) in degassed trichloroethylene (220 μL, 2.0 M; the trichloroethylene was passed through a short column of basic alumina before use) was added to a presilylated (BSA) resealable Carius tube. To this solution were added (*R*)-**6**[51] (139 mg, 0.88 mmol) and a crystal of BHT (radical inhibitor). The Carius tube was sealed under an argon atmosphere, and the mixture was heated at 110 °C for 7 h. The reaction mixture was concentrated in vacuo. ^{1}H NMR analysis (400 MHz) of the crude reaction mixture revealed a 16:1 mixture of two major cycloadducts. The product mixture was separated by silica gel flash column chromatography (20:1 hexanes−Et_2O), yielding a mixture of the three cycloadducts (168 mg, 53% yield), along with an inseparable (1:5) mixture of recovered triene, consisting of (*E*,*E*,*E*)-**30** and isomerized triene (*E*,*E*,*E*)-**30** (major in this mixture) (141 mg, 44%).

The recovered triene **30** (141 mg, 0.25 mmol; a 5:1 mixture favoring the (*E*,*E*,*E*)-isomer) was resubjected to the Diels−Alder reaction with (*R*)-**6** (78 mg, 0.5 mmol) in trichloroethylene (125 μL, 2.0 M) at 120 °C for 18 h in the presence of a crystal of BHT. The crude product mixture was separated by silica gel flash column chromatography (20:1 hexanes−Et_2O), giving additional quantities of the cycloadduct mixture (83 mg). The combined yield of the three cycloadducts was 78% (251 mg) overall from **12** after one such recycle of recovered triene.

The individual cycloadducts were separated by preparative HPLC (3% ethyl acetate−hexanes, 4 mL/min, 10 mm Whatman M9 silica gel column) to give exo cycloadduct **38** (180 mg, 72%), 11.9 min; endo cycloadduct **39** (13 mg, 6.7%), 13.9 min; and exo′ cycloadduct **40** (3 mg, 1.3%), 16.4 min.

Data for the exo cycloadduct 38: [α] = −54.7° (*c* 1.1, CH_2Cl_2); TLC R_f = 0.43 (15:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4 H), 7.46−7.36 (m, 6 H), 5.63 (dt, J = 15.2, 6.8 Hz, 1 H), 5.43 (d, J = 1.2 Hz, 1 H), 5.35 (dd, J = 15.2, 8.8 Hz, 1 H), 5.12(s, 1 H), 4.23 (B of AB, J = 13.2 Hz, 1 H), 4.16 (A of AB, J = 13.2 Hz, 1H), 3.59 (t, J = 6.8 Hz, 2H), 3.15 (d, 8.8 Hz, 1H), 2.59 (m, 1H), 2.13 (dd, J = 14.0, 7.2 Hz, 1 H), 2.04 (dt, J = 13.6, 6.8 Hz, 2H), 1.77 (dd, J = 14.0, 2.0 Hz, 1H), 1.52 (apparent quintet, J = 7.2 Hz, 2H), 1.39−1.26 (m, 4 H), 1.13 (d, J = 7.2 Hz, 3 H), 1.07 (s, 9 H), 0.94 (s, 9 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 140.8, 135.6, 135.5, 135.3, 133.63, 133.61, 129.6, 127.64, 127.59, 127.1, 120.7, 109.9, 81.2, 65.8, 63.1, 45.6, 36.7, 34.9, 32.7, 32.6, 31.6, 28.9, 27.8, 26.8, 26.0, 25.3, 23.4, 22.6, 19.6, 19.3, 18.4, 14.1, −5.3; IR (neat) 1792, 1585 cm^{-1}; HRMS for $C_{43}H_{67}O_5Si_2$ (M^++ 1) calcd 719.4527, found 719.4559. Anal. Calcd for $C_{43}H_{66}O_5Si_2$: C, 71.82; H, 9.25. Found: C, 72.10; H, 8.97.

Data for endo cycloadduct 39: [α] = 66.2° (*c* 1.3; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4 H), 7.45−7.33 (m, 6 H), 5.47−5.40 (m, 2 H), 5.33−5.27 (m, 1 H), 5.30 (s, 1 H), 4.28 (B of AB, J = 13.2 Hz, 1 H), 4.11 (A of AB, J = 13.2 Hz, 1 H), 3.58 (t, J = 6.8 Hz, 2 H), 3.03 (m, 1 H), 2.57 (m, 1 H), 2.02 (m, 2 H), 1.76 (d, J = 9.6 Hz, 2 H, partially obscured), 1.50 (apparent quintet, J = 7.0 Hz, 2 H), 1.39−1.25 (m, 4 H), 1.05−1.03 (m, 12 H), 0.97 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 140.0, 135.6, 135.5, 134.2, 133.9, 133.6, 130.6, 129.6, 127.8, 127.6, 127.5, 120.6, 107.3, 80.3, 65.5, 63.3, 42.4, 34.9, 34.5, 32.7, 32.5, 29.7, 29.1, 27.4, 26.8, 26.0, 25.3, 23.4, 19.3, 18.4, 18.4, −5.2; IR (CCl_4) 1798, 1480 cm^{-1}; HRMS for $C_{39}H_{57}O_5Si_2$ ($M^+ - C_4H_9$) calcd 661.3744, found 661.3709.

Partial data for exo′ cycloadduct 40: [α] = 37.3° (*c* 0.3; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.66 (m, 4 H), 7.45−7.35 (m, 6 H), 5.51 (dt, J = 15.6, 6.8 Hz, 1 H), 5.47 (m, 1 H), 5.31 (ddt, J = 15.6, 8.8, 1.2 Hz, 1 H), 5.14 (s, 1 H), 4.22 (B of AB, J = 13.2 Hz, 1 H), 4.13 (A of AB, J = 13.2 Hz, 1 H), 3.58 (t, J = 6.8 Hz, 2 H), 3.20 (d, J = 8.4 Hz, 1 H, partially obscured), 2.54 (m, 1 H), 1.99−1.84 (m, 4 H), 1.49 (m, 2 H), 1.34−1.19 (m, 13 H), 1.08 (d, J = 6.8 Hz, 3 H), 1.06 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 6 H); IR (CCl_4) 3065, 3045, 1795 cm^{-1}.

Methyl (1*S*,2*R*,5*R*)-1-(2-Benzyloxyacetoxy)-2-[7-(*tert*-butyldimethylsilyloxy)hept-1-enyl]-4-[(*tert*-butyldiphenylsilyloxy)methyl]-5-methylcyclohex-3-ene carboxylate (41). A mixture of exo cycloadduct **38** (79 mg, 0.11 mmol) and K_2CO_3 (16 mg, 0.12 mmol) in a 4:1 mixture of methanol and THF (1.5 mL, 0.07 M) was stirred for 6 h and then was concentrated in vacuo. The resultant oil was taken up in CH_2Cl_2 and washed with saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (5:1 hexanes−Et_2O), providing the corresponding tertiary α-hydroxy ester (62 mg, 85% yield) as a colorless oil: [α] = −41.9° (*c* 1.2, CH_2Cl_2); TLC R_f = 0.58 (3:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.66 (m, 4 H), 7.45−7.36 (m, 6 H), 5.55−5.46 (m, 2 H), 5.35 (ddt, J = 15.6, 8.0, 1.2 Hz, 1 H), 4.25 (B of AB, J = 12.8 Hz, 1 H), 4.14 (A of AB, J = 12.8 Hz, 1 H), 3.76 (s, 3 H), 3.59 (t, J = 6.4 Hz, 2 H), 3.25 (d, J = 8.0 Hz, 1 H), 2.54 (m, 1 H), 2.20 (dd, J = 13.6, 7.2 Hz, 1 H), 2.02 (dt, J = 13.6, 7.2 Hz, 1 H), 1.71 (dd, J = 13.6, 3.2 Hz, 1 H), 1.51 (apparent quintet, J = 6.4 Hz, 2 H), 1.39−1.26 (m, 6 H), 1.13 (d, J = 7.6 Hz, 3 H), 1.06 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 140.5, 135.6, 135.5, 134.9, 133.8, 133.7, 129.6, 127.8, 127.6, 121.4, 75.6, 66.0, 63.2, 52.6, 45.8, 38.0, 32.7, 32.6, 29.2, 28.4, 26.8, 26.0, 25.3, 19.9, 19.3, 18.4, −5.3; IR (neat) 3400 (broad), 1730, 1650 cm^{-1}; HRMS for $C_{35}H_{51}O_5Si_2$ ($M^+ - C_4H_9$) calcd 607.3275, found 607.3218. Anal. Calcd for $C_{39}H_{60}O_5Si_2$: C, 70.43; H, 9.09. Found: C, 70.16; H, 8.85.

A solution of the above α-hydroxy ester (22 mg, 0.03 mmol) in CH_2Cl_2 (820 μL, 0.1 M) was treated with DCC (34 mg; 0.17 mmol), α-benzyloxyacetic acid[60] (27 mg, 0.17 mmol), and catalytic DMAP.[59] The mixture was stirred for 16 h at ambient temperature and then was filtered through a plug of glass wool. The filtrate was concentrated in vacuo, and the crude ester was purified by silica gel flash column chromatography (7:2 hexanes−Et_2O), producing **41** (24 mg, 89% yield) as a colorless oil: [α] = −108.9° (*c* 1.0, CH_2Cl_2); TLC R_f = 0.76 (3:1 hexanes−Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68 (m, 4 H), 7.45−7.31 (m, 11 H), 5.51−5.44 (m, 2 H), 5.21 (dd, J = 15.2, 8.8 Hz, 1 H), 4.62 (B of AB, J = 11.4 Hz, 1 H), 4.61 (A of AB, J = 11.4 Hz, 1 H), 4.22 (B of AB, J = 12.8 Hz, 1 H), 4.11 (B of AB, J = 16.4 Hz, 1 H), 4.07 (A of AB, J = 12.8 Hz, 1 H),

4.02 (A of AB, J = 16.4 Hz, 1 H), 3.74 (s, 3 H), 3.58 (t, J = 6.4 Hz, 2 H), 2.37 (m, 1 H), 2.16 (dd, J = 12.8, 6.0 Hz, 1 H), 1.96 (dt, J = 6.8, 6.4 Hz, 2 H), 1.86 (dd, J = 12.8, 10.8 Hz, 1H), 1.48 (apparent quintet, J = 6.8 Hz, 2H), 1.36−1.24 (m, 5H), 1.06−1.04 (m, 12H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.3, 138.5, 137.1, 135.5, 135.4, 134.0, 133.8, 133.6, 129.6, 128.4, 128.0, 127.9, 127.63, 127.56, 127.4, 123.2, 81.9, 73.2, 66.9, 65.4, 63.2, 52.4, 43.7, 36.1, 32.7, 32.5, 29.2, 28.9, 26.7, 26.0, 25.4, 19.2, 18.6, −5.3; IR (neat) 1768, 1744 cm^{-1}; HRMS for $C_{44}H_{59}O_7Si_2$ ($M^+ - C_4H_9$) calcd 755.3799, found 755.3819. Anal. Calcd for $C_{48}H_{68}O_7Si_2$: C, 70.89; H, 8.43. Found: C, 70.79; H, 8.18.

(5*S*,6*R*,9*R*)-2-Oxo-3-benzyloxy-6-[7-(*tert*-butyldimethylsilyloxy)hept-1-enyl]-8-[(*tert*-butyldiphenylsilyloxy)methyl]-4-methoxymethyloxy-9-methyl-1-oxaspiro[4.5]deca-3,7-diene (10). To a −78 °C solution of **41** (24 mg, 0.03 mmol) in THF (290 μL, 0.1 M) was added lithium hexamethyldisilazide (67 μL of a 1.0 M solution in hexanes; 0.07 mmol). The mixture was stirred for 2 h at −78 °C and then was allowed to warm to room temperature over a period of 1 h. The reaction was quenched with brine solution and acidified to pH 1 with 2 N HCl. The aqueous layer was extracted with EtOAc (4 × 5 mL), and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (gradient, 4:1 hexanes−EtOAc to 2:1 hexanes−EtOAc), yielding the tetronic acid (16 mg, 70% yield).

A 0 °C solution of the tetronic acid in a 30:1 mixture of CH_2Cl_2 and HMPA (207 μL, 0.1 M) was treated with *i*-Pr_2NEt (16 μL, 0.09 mmol) and MOM-Cl (4 μL, 0.08 mmol). The reaction mixture was stirred 4 h at 0 °C and then was warmed to room temperature. The mixture poured into saturated NH_4Cl solution (1 mL) and extracted with EtOAc (4 × 2 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (4:1 hexanes−EtOAc), affording the model spirotetronate **10** (17 mg, 98%) as a colorless oil: [α] = −48.2° (*c* 2.3, CH_2Cl_2); TLC R_f = 0.68 (3:1 hexanes−EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4 H), 7.45−7.33 (m, 11 H), 5.49 (dt, J = 15.2, 6.8 Hz, 1 H), 5.45 (s, 1 H), 5.29 (s, 2 H), 5.19 (dd, J = 15.2, 8.8 Hz, 1 H), 5.12 (B of AB, J = 10.8 Hz, 1 H), 5.05 (A of AB, J = 10.8 Hz, 1 H), 4.24 (B of AB, J = 13.2 Hz, 1 H), 4.15 (A of AB, J = 13.2 Hz, 1 H), 3.57 (t, J = 6.8 Hz, 2 H), 3.47 (s, 3 H), 3.12 (d, J = 8.8 Hz, 1 H), 2.59 (quintet, J = 7.2 Hz, 1 H), 2.21 (dd, J = 14.0, 7.6 Hz, 1 H), 1.97 (q, J = 7.2 Hz, 2 H), 1.48 (quintet, J = 6.8 Hz, 2 H), 1.36−1.26 (m, 5 H), 1.15 (d, J = 7.6 Hz, 3 H), 1.06 (s, 9 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 159.5, 140.4, 136.3, 135.5, 135.2, 133.7, 133.6, 129.6, 128.9, 128.5, 128.4, 127.6 (two resonances), 125.8, 121.5, 121.2, 96.3, 90.8, 73.6, 65.9, 63.2, 57.3, 43.5, 37.4, 32.7, 32.5, 29.3, 28.0, 26.9, 26.0, 25.3, 20.1, 19.3, 18.3, −5.3; IR (CCl_4) 1760, 1685 cm^{-1}; HRMS for $C_{45}H_{59}O_7Si_2$ ($M^+ - C_4H_9$) calcd 767.3799, found 767.3773.

Acknowledgment. This research was supported by a grant from the National Institute of General Medical Sciences (GM 26782).

Supporting Information Available: Experimental procedures for the synthesis of **15** and ^{1}H NMR spectra of **10**−**12**, **19**, **22**, **23**, **36**, **37**, and **39** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980379W