Anal. Calcd for $C_{16}H_{17}I$: C, 57.16; H, 5.10. Found: C, 57.37; H, 5.14.

(b) From 22. Also **16** was obtained from **22** via its diazonium salt by the usual manner.

The $AlCl_3$ Catalyzed Trans-*tert*-butylation of 4d. **4d** was treated with $AlCl_3$ catalyst and worked up as described above to give only a small amount of 1-iodobiphenyl (**18**) with formation of a large amount of **1**, **13**, and **17**. The relative yields are shown in Table I.

Preparation of Tetra-*tert*-butyl-*o*-quaterphenyl (19). A mixture of 10 g (26.5 mmol) of **4d** and 10 g of Cu powder was heated at 300 °C for 4 h, and it was treated and worked up as described above to afford 4.0 g (60.3%) of **19**: colorless prisms (EtOH); mp 254–255 °C; IR (KBr) 2950, 1475, and 830 cm^{-1}; NMR (CCl_4) δ 1.08 [18 H, s, $C(CH_3)_3$], 1.28 [18 H, s, $C(CH_3)_3$], 6.85–7.25 (14 H, m, aromatic protons). Anal. Calcd for $C_{40}H_{50}$: C, 90.85; H, 9.15. Found: C, 90.93; H, 9.52.

Preparation of *o*-Quaterphenyl (20). To a solution of 500 mg (1 mmol) of **19** in 10 mL of benzene was added 26.4 mg (0.2 mmol) of $AlCl_3$ at 50 °C. The reaction mixture was stirred for 3 h and treated as described above to give 220 mg (80%) of **20**: colorless crystalline powder (EtOH–benzene); mp 116–118 °C (lit.[21] mp 118–119 °C).

Preparation of 2-Nitro-4-*tert*-butylbiphenyl (21). (a) From 4a. To a solution of 5.42 g (20 mmol) of **4e** in 120 mL of benzene was added 5.32 g (40 mmol) of $AlCl_3$. After the reaction mixture was stirred for 4 h, it was treated and worked up to afford 3.36 g (70%) of **21**: pale yellow prisms (hexane); mp 93–94 °C; IR (KBr) 3060, 2960, 1520, 1360, 830, 775, and 700 cm^{-1}; NMR (CCl_4) δ 1.38 [9 H, s, $C(CH_3)_3$] and 7.23–7.70 (8 H, m, aromatic protons). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.03; H, 6.77; N, 5.47.

(b) From 25 and 17. After a mixture of 5.16 g (20 mmol) of **25**, 8.16 g (40 mmol) of **17**, and 15 g of Cu powder was refluxed (at 250 °C) for 5 h, it was treated and worked up as described above to give 1.0 g (21%) of **21**: mp 93–94 °C.

Preparation of 2-Amino-4-*tert*-butylbiphenyl (22). (a) From 4f. To a solution of 266 mg (1 mmol) of **4f** in 6 mL of benzene was added 264 mg (2 mmol) of $AlCl_3$. The reaction mixture was treated and worked up as described above to give 165 mg (80%) of **22**: colorless prisms (hexane); mp 110–112 °C; IR (KBr) 3400, 3300, 3040, 2960, 1610, 1410, 1300, 800, 765, and 700 cm^{-1}; NMR (CCl_4) δ 1.30 (9 H, s, *t*-Bu), 3.45 (2 H, s, NH_2), and 6.60–7.30 (8 H, m, aromatic protons). Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 85.17; H, 8.49; N, 6.54.

(b) From 21. The reduction of **21** with Sn powder and concentrated HCl in ethanol by the manner as described above afforded **22**: mp 112 °C.

Preparation of 2,2′-Dibromo- (26a) and 2,2′-Dichlorobiphenyl (26b). To a solution of 5 mmol of **7a** or **7b** in 23.4 g (300 mmol) of benzene was added 132 mg (1 mmol) of $AlCl_3$ at 50 °C. After the reaction mixture was stirred for 1 h, it was treated and worked up as described above to give 0.80 g (77%) or 1.1 g (74%) of **26a** or **26b**, respectively. **26a**: colorless needles (hexane); mp 57–58 °C (lit.[22] mp 59 °C). **26b**: colorless needles (hexane); mp 79–80 °C (lit.[23] mp 80–81 °C).

Preparation of Polymethylbiphenyls (27). To a solution of 1.4 mmol of **11a** or **11b** in 8 mL of benzene was added $AlCl_3$–CH_3NO_2 catalyst (62 mg/2 mL). After the reaction mixture was stirred for 4 h, it was treated and worked up as described above to afford **27a** or **27b** in 90 or 92.2% yields, respectively. Similarly **27c** was obtained in 80% yield from **11c**; however, 93 mg of $AlCl_3$ was used as a catalyst. **27a**: colorless liquid; mp 130–132 °C (18 mmHg) [lit.[24] 135 °C (135 mmHg)]. **27b**: colorless needles (EtOH); mp 114–115 °C; IR (KBr) 2900, 1440, 995, 780 cm^{-1}; NMR (CCl_4) δ 1.90 (6 H, s, CH_3), 2.30 (6 H, s, CH_3), 6.80–7.04 (6 H, m, aromatic protons). Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.04; H, 8.67. **27c**: colorless prisms (EtOH); mp 63–64 °C (lit.[25] 64–65 °C).

Registry No. **1**, 92-52-4; **2**, 1625-91-8; **3**, 70728-88-0; **4a**, 69386-38-5; **4b**, 70728-89-1; **4c**, 70728-90-4; **4d**, 70728-91-5; **4e**, 69386-34-1; **4f**, 70728-92-6; **7a**, 70728-93-7; **7b**, 70728-94-8; **7c**, 70728-95-9; **7d**, 70728-96-0; **7e**, 70728-97-1; **9a**, 98-51-1; **9b**, 7397-06-0; **9c**, 98-19-1; **10a**, 70728-98-2; **10b**, 5122-21-4; **10c**, 5122-20-3; **11a**, 70728-99-3; **11b**, 70729-00-9; **11c**, 35132-98-0; **12**, 643-58-3; **13**, 98-06-6; **14**, 70729-01-0; **15**, 2052-07-5; **16**, 70729-02-1; **17**, 591-50-4; **18**, 2113-51-1; **19**, 70729-03-2; **20**, 641-96-3; **21**, 69386-37-4; **22**, 70729-04-3; **25**, 70729-05-4; **26a**, 13029-09-9; **26b**, 13029-08-8; **27a**, 605-39-0; **27b**, 7495-46-7; **27c**, 4036-43-5; chloromethyl methyl ether, 107-30-2; 2,6-di-*tert*-butyl-*p*-cresol, 128-37-0.

(22) J. J. Dobbie, *J. Chem. Soc.*, **99**, 1619 (1911).
(23) F. H. Case, *J. Am. Chem. Soc.*, **61**, 3487 (1939).
(24) E. A. Johnson, *J. Chem. Soc.*, 4155 (1957).
(25) K. Ishizu, H. Hasegawa, H. Chibaki, H. Nishiguchi, and Y. Deguchi, *Kogyo Kagaku Zasshi*, **68**, 210 (1965).

An Approach to the Total Synthesis of Chlorothricolide: The Synthesis of the Top Half

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An efficient synthesis of the top half of chlorothricolide (I) is described. The top half **1** was prepared in 14 steps from tartaric acid. The utility of **1** as a potential intermediate in the total synthesis of chlorothricolide was demonstrated by connection to bottom half models. The selective deprotection of the α-hydroxytetronic acid dimethyl ether, necessary for closure of the macrolactone, is also described.

Chlorothricin (I), a chlorine containing macrolide antibiotic active against Gram positive bacteria, was isolated from a strain of *Streptomyces antibioticus* in 1969.[1] In contrast to a majority of macrolide antibiotics which generally function by inhibiting protein biosynthesis, chlorothricin was shown to act as an antagonist to CoASAc, by inhibiting the reaction catalyzed by pyruvate carboxylase.[2] The aglycone portion, chlorothricolide methyl ester (II), was found to retain part of the activity of the intact antibiotic, while the other methanolysis product, α-methyl-2-deoxy-3-*O*-(5′-chloro-2′-methoxy-6′-methylbenzoyl)-D-rhamnoside, showed a lack of activity.[3]

(1) (a) W. Keller-Schierlein, R. Muntwyler, W. Pache, and H. Zähner, *Helv. Chim. Acta*, **52**, 127 (1969); (b) R. Muntwyler, J. Widmer, and W. Keller-Schierlein, *ibid.*, **53**, 1544 (1970); (c) R. Muntwyler and W. Keller-Schierlein, *ibid.*, **55**, 2071 (1972); (d) M. Brufani, S. Cerrini, W. Fedeli, F. Mazza, and R. Muntwyler, *ibid.*, **55**, 2094 (1972).

(2) (a) P. W. Schindler and H. Zaehner, *Arch. Microbiol.*, **82**, 66 (1972); (b) W. Pache and D. Chapman, *Biochem. Biophys. Acta*, **255**, 348 (1972); (c) P. W. Schindler and H. Zaehner, *Eur. J. Biochem.*, **39** 591 (1973); (d) P. W. Schindler, *ibid.*, **51**, 579 (1975).

(3) P. W. Schindler and M. C. Scrutton, *Eur. J. Biochem.*, **55**, 543 (1975).

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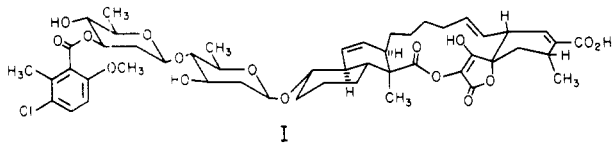
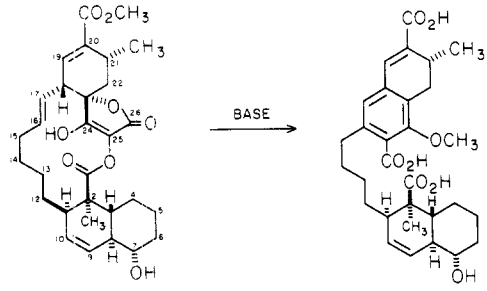


I

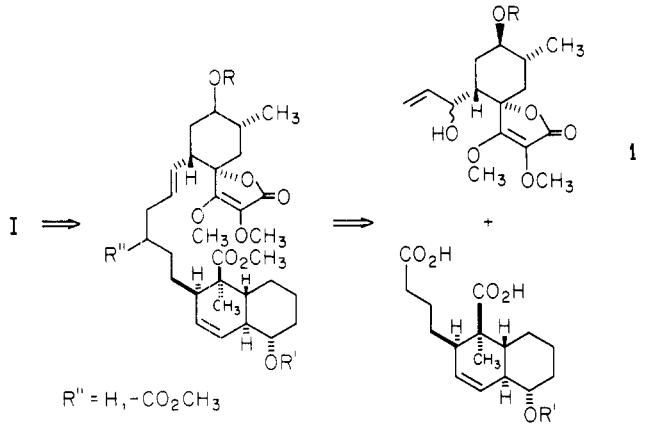


II III

Central to the chemistry of chlorothricolide is the spiro-α-hydroxytetronic acid nucleus,[5] which contains the hydroxyl necessary for closure of the 14-membered lactone. Unlike other macrolides, the macrolactone could not be directly opened under basic conditions without concomitant β elimination of the tetronic ring and rearrangement to give the dihydronapthalene derivative III.[4]

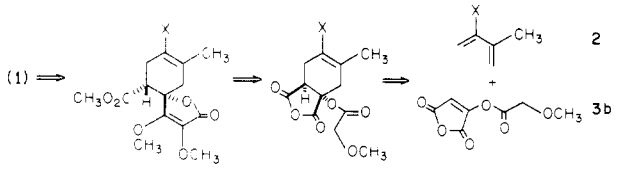
The proposed synthesis of chlorothricolide featured the coupling of two nearly equal portions of the molecule through an initial esterification process. Subsequent ester enolate Claisen rearrangement would complete the union intramolecularly with simultaneous formation of the trans double bond.

We report here a convergent versatile synthesis of the prerequisite "top half" 1 of chlorothricolide and its successful coupling to a bottom half model. As a result of the work directed at the synthesis of 1, a facile method for the preparation of various substituted tetronic acids was developed. In addition, we report the successful deprotection of the α-hydroxytetronic acid dimethyl ether, a transformation crucial to the completion of the total synthesis of chlorothricolide methyl ester (II).



1

A key feature of our proposed synthesis of the top half 1 was an intramolecular cyclization of an ester enolate with

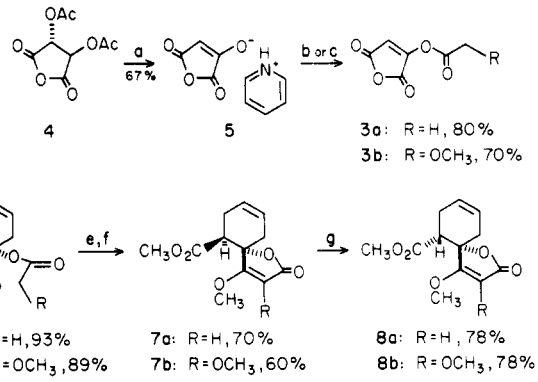


2 3b

(4) A. Gerhard, R. Muntwyler, and W. Keller-Schierlein, *Helv. Chim. Acta*, **58**, 1323 (1975).

(5) For some good reviews on the chemistry of tetronic acids see: (a) L. J. Haynes and J. R. Plimmer, *Q. Rev., Chem. Soc.*, **14**, 292–315 (1960); (b) Y. S. Rao, *Chem. Rev.*, **76**, 625–694 (1976).

Chart I. Synthesis of the Spirobutenolides 8a and 9b[a]



4 5

3a: R=H, 80%
3b: R=OCH3, 70%

6a: R=H, 93%
6b: R=OCH3, 89%

7a: R=H, 70%
7b: R=OCH3, 60%

8a: R=H, 78%
8b: R=OCH3, 78%

[a] C_5H_5N, Δ, AcOH. [b] AcCl, PhH. [c] CH_3OCH_2COCl, PhH. [d] $CH_2{=}CHCH{=}CH_2$, PhH, pyrogallol, Δ. [e] LDA, THF, −78 °C. [f] HMPA, CH_3OSO_2F, 0 °C. [g] Catalytic $NaOCH_3$, CH_3OH, Δ.

a cyclic anhydride to form the spirotetronic acid nucleus.

Intermolecular acylation of magnesium and lithium ester enolates has been reported to proceed in good yields.[6] Furthermore, intramolecular Claisen condensations of magnesium and sodium ester enolates to form simple tetronic acid derivatives in moderate yields were reported by Haynes and Stanners.[7] However, in an attempt to extend these methods to more complex mold tetronic acids, Svendson and Boll were unable to induce cyclization.[8]

It was envisaged that the anhydride carboxyls, in addition to facilitating the key intramolecular acylation reaction, would also function to activate an enol ester as a dienophile for a prelusive Diels-Alder reaction. Finally, the selection of appropriate substituents on the diene **2** might secure regiochemical control in the cycloaddition and lead to metaorientation of the methyl group with respect to the acyloxy group.[9]

To test the key transformations of our proposed top half synthesis, acetoxymaleic anhydride **3a** was prepared by acylation of the pyridine salt of hydroxymaleic anhydride[10] with acetyl chloride as described by Wohl and Oesterlin[11] (Chart I). The Diels-Alder reaction of anhydride **3a** with 1,3-butadiene gave crystalline adduct **6a** in high yield (sealed tube, 90°, 5 days). The crucial cyclization of the ester anhydride **8a** could be effected by inverse addition of 2 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C followed by trapping of the resulting dianion with methyl fluorosulfonate at 0 °C in hexamethylphosphoramide (HMPA). Epimerization of the spirobutenolide **7a** using a catalytic amount of sodium methoxide in refluxing methanol afforded an 80:20 mixture of the pseudoequatorial and pseudoaxial isomers **8a** and **7a**, which were separable by careful column chromatography. In one experiment, a sample of the ester **7a** was subjected to these epimerization conditions for 8 days and gave an 87:13 mixture of **8a** and **7a** (by ^1H NMR). When a sample of the pseudoequatorial epimer **8a** was subjected to the same conditions, the same 87:13 mixture (**8a**–**7a**) was obtained, establishing the equilibrium mixture at 65°C (K_{eq} = 6.7, ΔG = −1.1 kcal).

The analogous (α-methoxyacetoxy)maleic anhydride was

(6) F. C. Frostick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **71**, 1350 (1949); E. E. Royals and D. G. Turpin, *ibid.*, **76**, 5452 (1954); M. W. Rathke and A. Lindert, *ibid.*, **93**, 2318, 4605 (1971).

(7) L. J. Haynes and A. H. Stanners, *J. Chem. Soc.*, 4103 (1956).

(8) A. Svendson and P. M. Boll, *J. Org. Chem.*, **40**, 1927 (1975).

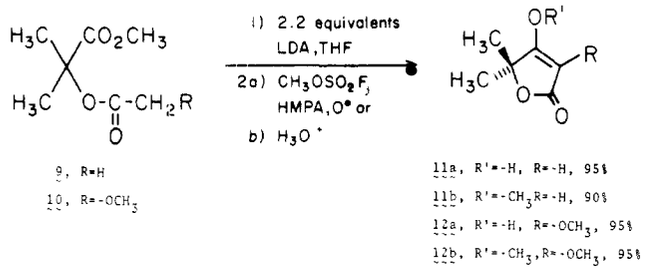
(9) A. S. Onischenko, "Diene Synthesis", Israel Program for Scientific Translations, Jerusalem, 1964.

(10) J. C. Roberts, *J. Chem. Soc.*, 3315 (1952).

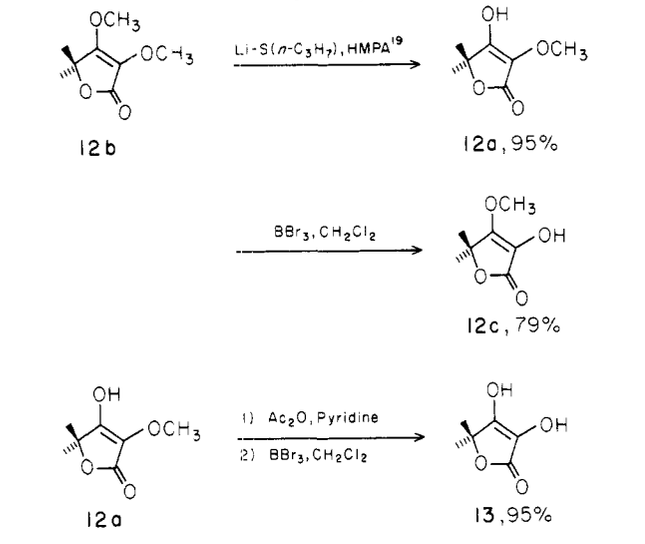
(11) A. Wohl and C. Oesterlin, *Ber. Dtsch. Chem. Ges.*, **34**, 1144 (1901).

prepared by acylation of salt **5** with methoxyacetyl chloride. Diels-Alder reaction with 1,3-butadiene under identical conditions afforded crystalline adduct **6b**. Cyclization as described above proceeded in somewhat lower yield to afford the valuable α-methoxy substituted spirotetronic derivative **7b**. Epimerization with sodium methoxide gave the same 80:20 mixture of epimers **8b** and **7b** in 78% overall yield (19% recovered starting material).

Application of the cyclization conditions to the simpler esters **9** and **10** afforded the tetronic acid derivatives **11a** and **12a** in excellent yields.[12] By quenching the solution with methyl fluorosulfonate in HMPA at 0 °C, the corresponding methyl ethers **11b** and **12b** were isolated directly in high overall yield.

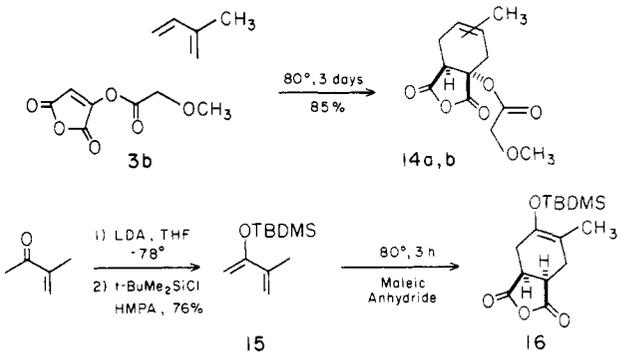


The dimethyl ether **12b** was then used as a model to test conditions for deprotection. While it was found that selective demethylation of the α- or β-methoxy was quite facile, no conditions were found which gave the totally deprotected α-hydroxytetronic acid **13** in one step. Conversion to the free α-hydroxytetronic acid **13** could be



effected by acetylation of the tetronic acid **12a**, followed by treatment with boron tribromide in dichloromethane at −78 °C.

With these promising results, we examined the regioselectivity of various dienes with the (α-methoxyacetoxy)maleic anhydride **3b**. When isoprene and the anhydride **3b** were allowed to react (sealed tube, 85 °C, 3 days), there was obtained an inseparable mixture of regio isomers **14a,b** in 97% chromatographed yield. The 220-MHz ^{1}H NMR spectra revealed two AB quartets for the proton α to the anhydride carbonyl of approximately equal intensity. The ^{13}C NMR (15 MHz) spectra also showed two sets of lines for each of the five carbons which are derived from the isoprene unit. The 2-halogenated dienes chloroprene and 2-bromo-3-methylbutadiene[13] both failed to react under any conditions tried.[14] With the hope of finding a more reactive, selective diene, the 2-(*tert*-butyldimethylsiloxy)-3-methylbutadiene **15** was prepared



as shown below. The diene **15** reacted with maleic anhydride under mild conditions to give the Diels-Alder adduct **16** in 96% chromatographed yield, but under normal conditions the maximum yield obtained with the anhydride **3b** was 7%.[14] When the reaction was run at high pressure (50 kbar, room temperature), a 67% yield of a 50:50 mixture of regioisomers, as evidenced by the ^{13}C NMR (15 MHz) spectra, was obtained.[15]

It seemed apparent that the acyloxymaleic anhydride suffered not only in its ability to undergo Diels-Alder reaction with electron-rich dienes but also in its low regioselectivity. With the spirobutenolide ester **8b** in hand, we proceeded to test the ester to aldehyde transformation, so that the subsequent connection to the bottom half could be tested.

Initially a direct ester to aldehyde conversion was attempted. When the ester **8b** was treated with 1.5 equiv of diisobutylaluminum hydride (DIBAL) in toluene at −78 °C,[16] only starting material could be isolated. Use of three or more equivalents of DIBAL gave a complex mixture of products, with loss of all carbonyls (IR). The α-methoxytetronic acid methyl ether was apparently highly susceptible to reduction, possibly via a mechanism involving complexation of the aluminum with the α-methoxy substituent.[17]

Since Petuely and Bauer had shown that ascorbic acid could not be reduced by lithium aluminum hydride in refluxing ether after 15 h,[18] it was thought that a selective deprotection of the tetronic acid would render it inert to reduction. Treatment of the butenolide ester **8b** with 1.1 equiv of lithium *n*-propyl mercaptide in HMPA as described in Bartlett and Johnson[19] afforded the ester acid **17** in 79% crude yield. This unstable ester tetronic acid **17** could be reduced to a mixture of the desired alcohol **18** and the isomeric ketene acetal derivative in low yield by successive treatment of the sodium salt with DIBAL, aqueous acid, and ethereal diazomethane.

We then found that treatment of the ester butenolide **8b** with excess lithium borohydride in THF (20 h, room

(12) The γ,γ-dimethyltetronic acid **11a** was originally prepared by Haynes and Stanners in 64% yield using diisopropylmagnesium bromide in ether (ref 7).

(13) A. A. Petrov, *Zh. Obshch. Khim.*, **13**, 741 (1943).

(14) Wayne J. Thompson, Ph.D. Thesis, California Institute of Technology, 1978.

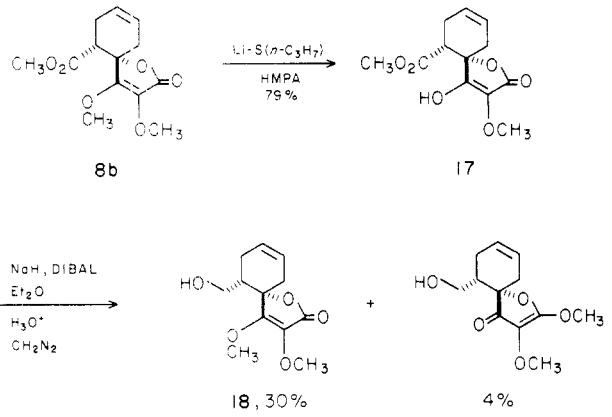
(15) We thank Professor W. G. Dauben at the University of California at Berkely for performing the high-pressure Diels-Alder experiments on these compounds; the ^{13}C-NMR ($CDCl_3$) of this adduct revealed four lines in the vinyl (sp^2) region of equal intensity 106.17, 111.89, 139.22, and 143.87 Hz; IR (neat) 1680 (C=C), 1765 (ester C=O), 1790, and 1860 cm^{-1} (anhydride C=O); ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 3 H, $(CH_3)_2Si$), 0.95 (s, 9 H, $(CH_3)_3C$), 1.65 (s, 3 H, $=CCH_3$), 2.65 (m, 4 H, allylic-CH_2-), 3.45 (s, 3 H, CH_3O-), 4.12 (s, 2 H, $COCH_2O$).

(16) L. I. Zakhaykin and I. M. Khorlina, *Tetrahedron Lett.*, 619 (1962).

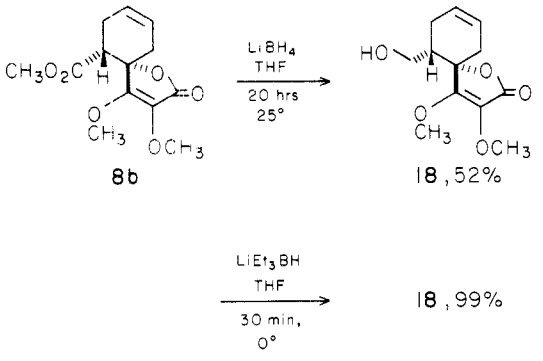
(17) M. J. Begley, D. W. Knight, and G. Pattendon, *Tetrahedron Lett.*, 4279 (1975).

(18) P. Petuely and H. F. Bauer, *Monatsh. Chem.*, **83**, 758 (1952).

(19) P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970).



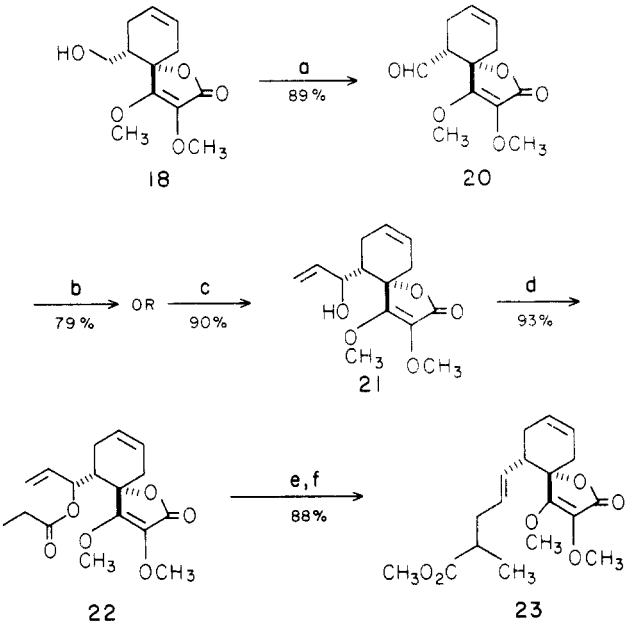
temperature) afforded the alcohol **18** in 52% chromatographed yield, together with 43% of the starting material. Use of the more nucleophilic lithium triethylborohydride[20] effected the desired reduction of ester **8b** to alcohol **18** in



nearly quantitative chromatographed yield (30 min, 0 °C, 2 equiv of hydride). Activation of the lithium borohydride by coordination with the enediol dimethyl ether seems to be occurring, since methylcyclohexane carboxylate was found to reduce at a much slower rate with lithium triethylborohydride in THF (8% reaction after 3 h at 0 °C).

The oxidation of alcohol butenolide **18** with the mildly acidic pyridium chlorochromate[21] smoothly afforded the aldehyde **20** in 89% yield. Treatment of aldehyde **20** with 1.1 equiv of vinylmagnesium bromide in THF at −30 °C afforded the allylic alcohol **21** in 79% chromatographed yield. Alternatively, the use of vinylmanganese iodide[22] in ether at 0 °C effected the same transformation in somewhat higher yield (Chart II). Esterification of the allylic alcohol **21** with propionyl chloride was greatly facilitated by the use of 4-(dimethylamino)pyridine (4-DMAP) as an acylation catalyst.[23] Attempted enolization of the resulting propionate **22** with up to 10 equiv of lithium diisopropylamide in THF, followed by trapping with *tert*-butyldimethylsilyl chloride (TBDMSCl) in HMPA, gave only starting material back after aqueous workup.[24] This result led to the hypothesis that lithium was coordinating with the ether oxygen on the tetronic ring in a manner preventing further approach by base on the propionate side chain. It was then found that substituting potassium (hexamethyldisilyl)amide ($KNTMS_2$)[25] for

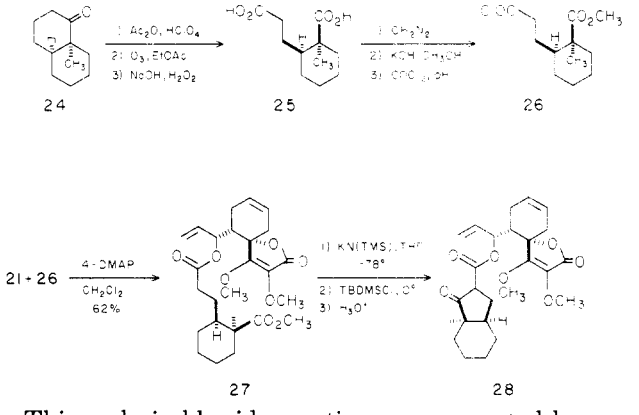
Chart II. Synthesis and Enolate Claisen Rearrangement of Allylic Alcohol 21[a]



[a] $C_5H_5N{\cdot}HCl{\cdot}CrO_3$, CH_2Cl_2. [b] $CH_2{=}CHMgBr$, THF, −30 °C. [c] $CH_2{=}CHMnI$, Et_2O, 0 °C. [d] CH_3CH_2COCl, 4-DMAP, CH_2Cl_2. [e] $KNTMS_2$, THF, −78 °C; TBDMSCl, HMPA, 3 h, room temperature. [f] CH_2N_2, Et_2O.

lithium diisopropylamide led to the desired rearranged ester **23**, after treatment with diazomethane, in 88% overall chromatographed yield.

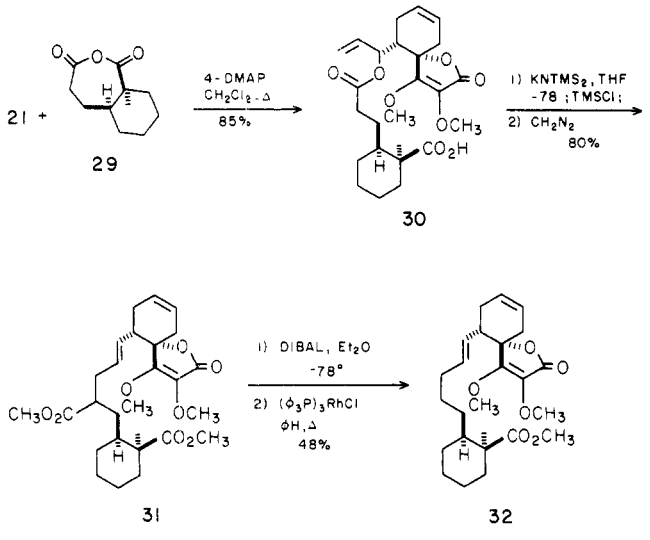
The readily available bicyclic ketone **24**[26] was converted to the enolacetate[27] and cleaved with ozone (oxidative workup) to afford the cis diacid **25** in 63% overall yield. The cis diacid **25** was converted to ester acid chloride **26** as described by Bachmann and Drieding (90% overall).[28] Esterification with the top half allylic alcohol using the same conditions as those in the propionate case gave the ester **27*** in 62% yield. Treatment of this ester with potassium (hexamethyldisilyl)amide did not, however, lead to the desired Claisen rearrangement product. Instead, a Dieckmann cyclization occurred, resulting in a 90% yield of hydrindanone **28***.



This undesirable side reaction was prevented by protection of the carboxyl group as its potassium salt. The seven-membered anhydride **29** (prepared in 75% yield from diacid **25** with dicyclohexylcarbodiimide (DCC)[29])

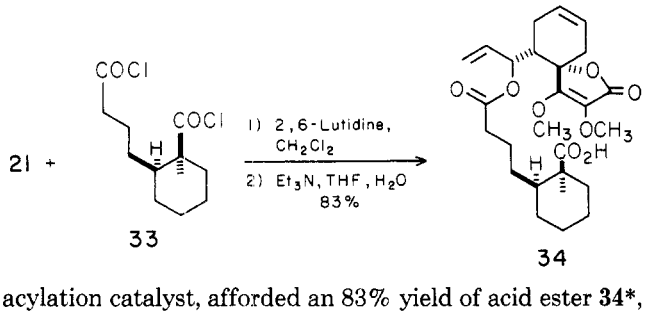
(20) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **95**, 1669 (1973).
(21) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(22) G. Cahiez and J. F. Normant, *Tetrahedron Lett.*, 3383 (1977).
(23) G. Höfle, W. Steiglich, and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, **17**, 569 (1978); A. Hassner, L. R. Krepski, and V. Alexanian, *Tetrahedron*, **34**, 2069 (1978).
(24) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
(25) For the preparation of $KNTMS_2$, see: C. A. Brown, *J. Org. Chem.*, **39**, 3913 (1974).
(26) R. F. Church, R. E. Ireland, and D. R. Shridhar, *J. Org. Chem.*, **31**, 324 (1966).
(27) B. E. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966).
(28) W. E. Bachmann and A. S. Dreiding, *J. Org. Chem.*, **13**, 317 (1948).
(29) N. J. Doorenbos and M. T. Wu, *Chem. Ind. (London)*, 648 (1965).

reacted with the allylic alcohol **21** to give acid ester **30*** in 85% yield (4-DMAP, CH_2Cl_2, reflux). Claisen rearrangement of the allylic ester **30*** as the (trimethylsilyl)ketene acetal afforded the diester **31*** in 80% overall yield. Finally, completion of these model experiments was accomplished by removal of the side chain carbomethoxyl group of the diester **31***. [The union of these racemic "top" and "bottom" half systems leads to a mixture of diastereoisomers which was not separated for these model studies. The problem of the resolution of the two portions of the molecule prior to esterification or separation of the diastereoisomeric mixture after esterification has been deferred until the "real" bottom half becomes available. Solely for the sake of graphical clarity the structural formulas marked with an asterisk depict one enantiomer of what is in reality a racemic mixture of diastereoisomers. Utilization of this mixture in subsequent chemical transformations presented no difficulties to the development of a suitable reaction pathway.] This carbomethoxy group had served to unite the top and bottom half models and make possible the carbon–carbon bond link between the two, but it was now extraneous. Thus, reduction of this less hindered carbomethoxyl group to an aldehyde (DIBAL, Et_2O, −78 °C) followed by decarbonylation ($[(C_6H_5)_3P]_3RhCl$, C_6H_6, Δ) led to the desired monoester **32***. While the seven-membered anhydride was



ideally suited for the model with a propionate side chain, the "real" bottom half would require a butyrate side chain, and eight-membered anhydrides are nearly inaccessible. Thus, an alternative method of carboxyl activation was necessary. Since the two carboxyl groups are still in very differemt steric environments, it was thought that activation of both carboxyls in the same manner should present no problems with regioselectivity.

To test these possibilities, the diacid chloride **33** was prepared from the corresponding known diacid[28] **33** with oxalyl chloride in benzene. The esterification of this diacid chloride with allylic alcohol **21**, using 2,6-lutidine as



acylation catalyst, afforded an 83% yield of acid ester **34***, with virtually no esters resulting from acylation at the more hindered acid chloride.

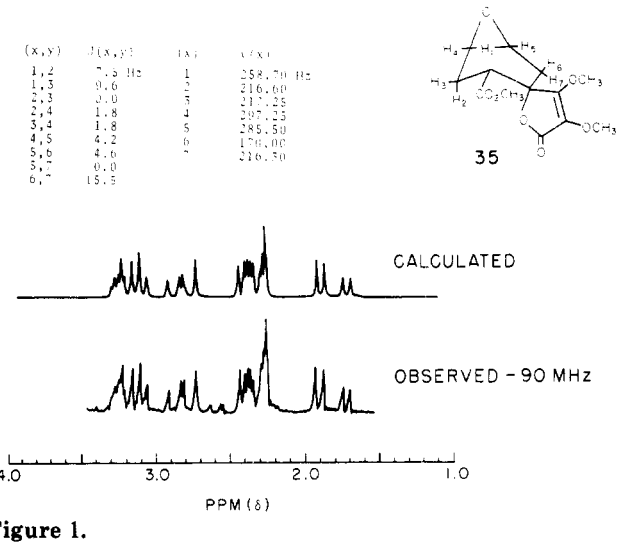
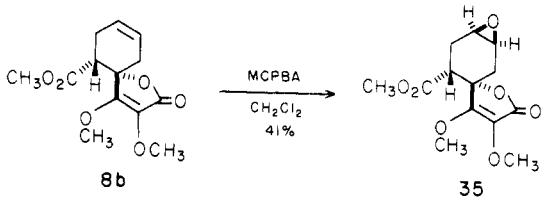


Figure 1.

With these results, our proposed synthetic plan for joining the top and bottom halves became a viable one. Completion of the top half required introduction of the pseudoaxial methyl group at C-21 and functionalization of the C-20 carbon for later elaboration. Epoxidation of the ester butenolide **8b** with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane afforded the β-epoxide **35**



(41%) together with 7% of the α-epoxide and 31% of overoxidation products (loss of tetronic ring). The ^1H NMR of the crystalline β-epoxide was consistent with the spectrum calculated from coupling constants obtained from the Karplus equation using the Nicolet NMRCAL program for six spins and overlapping data (Figure 1).[32]

Epoxidations with most peracids are sensitive to polar influences, and in the absence of hydroxyl groups, anti attack is favored in nonpolar solvents.[33] The rigidity of the spirobutenolide ester **8b**, together with the pseudoaxial orientation of the ring oxygen, shields the α face of the molecule, resulting in a predominance of β epoxidation.

When the epoxy ester **35** was treated with lithium dimethylcuprate in ether,[31] only acidic materials arising from base-catalyzed elimination of the spirobutenolide ring were isolated. In order to circumvent this problem, the cuprate

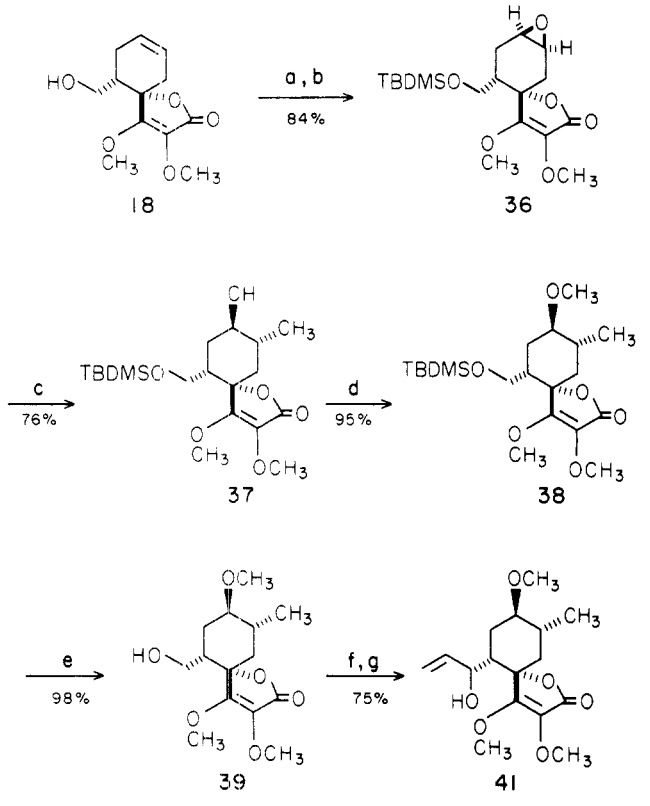
(30) For some excellent reviews on decarbonylation with transition metal complexes, see: J. Tsuji in "Organic Synthesis via Metal Carbonyls", Vol. II, I. Wender and P. Pino, Eds., Wiley-Interscience, New York, 1977, pp 595–654; and C. W. Bird, "Transition Metals in Organic Synthesis", Chapter 9, Wiley-Interscience, New York, 1967, pp 239–247.

(31) For previous examples of *trans*-diaxial opening of epoxides with lithium dimethylcuprate, see: (a) G. H. Posner, *Org. React.*, **22**, 287–290, 389–393 (1975); (b) D. R. Hicks and B. Fraser-Reid, *Can. J. Chem.*, **53**, 2017 (1975).

(32) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963); Nicolet 1080 Series Magnetic Resonance Spectrum Calculation Program NMRCAL (NIC-05-40417), Copyright 1971 by Nicolet Instrument Corporation, 5225 Verona Road, Madison, Wis.

(33) (a) G. Berti, *Top. Stereochem.*, **7**, 93–252 (1973); (b) S. A. Cerefice and E. K. Fields, *J. Org. Chem.*, **41**, 355 (1976).

Chart III. Completion of the Top Half 1[a]



[a] TBDMSCl, imidazole, DMF. [b] MCPBA, $LiClO_4$, Et_2O. [c] $LiMe_2Cu$, hexane. [d] KH, MeI, THF, 0 °C. [e] AcOH; THF; H_2O, 50 °C, 24 h. [f] $C_5H_5N{\cdot}HCl{\cdot}CrO_3$, CH_2Cl_2. [g] $CH_2{=}CH_2MgBr$, THF, −30 °C.

displacement was delayed until after the reduction of the carbomethoxy group. Protection of the alcohol **18** as the *tert*-butyldimethylsilyl ether,[34] followed by epoxidation with MCPBA in ether containing 1 equiv of anhydrous lithium perchlorate,[35] afforded the β-epoxide **36** in 84% overall yield. The ^1H NMR of epoxide **36**, while more complicated, contained four multiplets identical with those observed for the ester epoxide **35**, since the magnetic environment was unchanged for four protons. Treatment of epoxide **36** with 5 equiv of lithium dimethylcuprate in hexane[31b] (14 °C, 8 h) gave the desired alcohol **37** in 76% chromatographed yield, together with 12% of a ketonic product. The alcohol **37** was protected as the methyl ether **38** using potassium hydride and methyl iodide in THF at 0 °C in 95% yield. Deprotection of the silyl ether using acetic acid–water–THF[34] gave the alcohol **39** in nearly quantitative yield. Oxidation with pyridinium chlorochromate followed by treatment with 1.1 equiv of vinylmagnesium bromide in THF afforded the allylic alcohol **41** in 75% overall yield. The allylic alcohol **41** contains all the desired functionality and stereochemistry requisite to the proposed top half of chlorothricolide (**1**).

The successful preparation of the top half **1** and the connection of a derivative of **1** to bottom half models demonstrate the utility of this route for the synthesis of chlorothricolide (**1**) and derivatives related to the parent antibiotic.

(34) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

(35) The addition of lithium perchlorate to an ether solution of the peracid resulted in minimal oxidation of the α-methoxytetronic ring, probably by coordination of lithium with the two methoxyl groups, thus effectively lowering electron density in the conjugated double bond.

Experimental Section[36]

Diacetyltartaric Anhydride (4). To a mixture of 100 g (0.67 mol) of pulverized commercial *d*-tartaric acid and 220 mL of acetic anhydride was added 3 mL of concentrated sulfuric acid, and the resulting solution was stirred at room temperature for 3 h. After the solution was heated on a steam bath for a few minutes, the reaction was cooled in an ice bath, and the white crystalline product was collected by vacuum filtration on a medium frit. After the filtercake was washed with 50 mL of benzene and dried in a vacuum desiccator over paraffin for 3 days, there was obtained 141.0 g (98%) of pure crystalline diacetyltartaric anhydride (**4**): mp 128–130 °C (lit.[10] mp 128–130 °C); ^1H NMR ($CDCl_3$) δ 2.23 (s, 6 H, $-COCH_3$), 5.73 (s, 2, $-COCHOAc$).

Pyridine Salt of Hydroxymaleic Anhydride (5). Into a dry, stoppered flask containing 40 g (0.185 mole) of diacetyltartaric anhydride (**4**) was added 80 mL of dry pyridine in one portion. The flask was then stoppered, and the mixture was shaken vigorously for 5 s (pale green color develops). Then 12 mL of glacial acetic acid was added immediately, and the resulting mixture was agitated at 45 °C until dissolution was complete. The flask was then placed in an ice bath, and 45 mL of anhydrous ether was added. The mixture was shaken, and the resulting precipitate was collected by vacuum filtration on a medium frit. The filtercake was thoroughly pressed and washed twice with 10-mL portions of absolute ethanol and then three times with 10-mL portions of ether. After drying the filtercake in vacuo for 3 h, there was obtained 23 g (67%) of the pyridine salt of hydrox-

(36) Melting points were taken using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on either a Perkin-Elmer 237B, 727B, or Beckman 4210 infrared spectrometer, and nuclear magnetic resonance (^1H NMR, ^{13}C NMR) spectra were recorded using either a Varian T-60, EM-390 or A-60 spectrometer. The Varian T-60 was modified with a Nicolet Technology Corporation TT-7 pulsed RF-Fourier transform system. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane ($\delta_{Me_4Si} = 0.0$ ppm) as an internal standard.

Preparative layer chromatography was carried out on precoated PLC plates with a 20 × 20 × 2 mm layer of silica gel 60F-254 on glass plates manufactured by E. Merck, Darmstadt, Germany. Thin-layer chromatography was performed on E. Merck TLC plates 60F-254, 0.25 mm. "Alumina" refers to the grade I neutral variety manufactured by M. Woelm, Eschwege, Germany. All silica gel was E. Merck "Silica Gel 60", 70–230 mesh ASTM. Preparative medium pressure chromatography was performed using glass columns and fittings supplied by Chromatronix, Inc., Berkeley, Calif., and an instrument minipump made by Milton Roy Co., St. Petersburg, Fla. The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 mesh) from E. Merck and Co., Darmstadt, Germany.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether, tetrahydrofuran, and dimethoxyethane were distilled under dry argon from sodium metal using benzophenone ketyl as an indicator. Benzene and toluene were distilled from phosphorus pentoxide. Methanol was distilled from magnesium methoxide. Hexamethylphosphoramide (HMPA) was distilled at 0.5 mm from pulverized calcium hydride.

"Dry" amines, whether used as solvents or reagents, were distilled as follows: triethylamine immediately before use under argon from sodium–benzophenone ketyl; pyridine immediately before use from calcium hydride; 2,6-lutidine from calcium hydride; diisopropylamine from calcium hydride under agon; dimethylaniline from calcium hydride under argon; hexamethyldisilazane (supplied by Petrarch Systems, Inc.) from calcium hydride under argon (bp 126 °C).

All other solvents and reagents were "Reagent Grade" unless described otherwise. "Anhydrous ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt and Baker. "Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 35–60 °C, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not purified further. Drying agents such as magnesium sulfate or potassium carbonate are anhydrous reagent grade.

All water used in the reactions was distilled water. Brine refers to a saturated aqueous solution of sodium chloride. "Removal of solvents in vacuo" refers to first solvent removal under reduced pressure (water aspirator) using a rotary evaporator at or below 40 °C then drying the residue at or below 1 mm for several hours at room temperature.

Syringes and "oven-dried" reaction flasks were dried at least 12 h in an oven (at 120–140 °C) and cooled in a desiccator over anhydrous calcium sulfate prior to use. All reactions (except oxidations) were run under argon, which was dried by being passed thru a calcium chloride drying tower.

Mass spectral analyses were run by Dr. Kai Fang, UCLA, Los Angeles, Calif. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., or Susan Rottschaefer here at Caltech.

Analytical samples were obtained by evaporative distillation at 0.01 mm, unless otherwise indicated.

ymaleic anhydride (5) as a slightly yellow air-sensitive solid. The crude salt was used directly in the preparation of the acyloxymaleic anhydrides **3a** and **3b**.

(2-Methoxyacetoxy)maleic Anhydride (3b). To a stirred suspension of 16 g (0.083 mol) of the pyridine salt of hydroxymaleic anhydride (**5**) in 160 mL of dry benzene under an argon atmosphere was added 8.2 mL (0.090 mol) of methoxyacetyl chloride[37] in one portion. After stirring the solution for 30 min at room temperature, the clear supernatant liquid was decanted off and filtered through 120 g of alumina with 800 mL of benzene. The eluate was concentrated in vacuo to about 75 mL, and 200 mL of petroleum ether was added. After the product was collected by vacuum filtration on a medium frit and dried in a vacuum desiccator over P_2O_5, there was obtained 11.2 g (73%) of pure, colorless, crystalline anhydride **3b**: mp 93–94 °C; IR ($CHCl_3$) 1630 (C=C), 1780 (C=O), 1820 (C=O), 1850 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.53 (s, 3 H, ether CH_3O–), 4.35 (s, 2 H, $COCH_2O$–), 6.90 (s, 1 H, vinylic H). Due to its hygroscopic nature, this material was analyzed as the butadiene adduct **6b**.

Acetoxymaleic Anhydride (3a). In the manner described above, from 16 g (0.083 mol) of the pyridine salt of hydroxymaleic anhydride (**5**) and 17.7 mL (0.25 mol) of acetyl chloride there was obtained 12.4 g (96%) of pure crystalline anhydride **3a**: mp 89–90 °C (lit.[11] mp 89–90 °C); IR ($CHCl_3$) 1630 (C=C), 1780 (C=O), 1820 (C=O), 1850 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.41 (s, 3 H, $COCH_3$), 6.81 (s, 1 H, vinylic H).

Sealed Tube Procedure. The following procedure is typical for all sealed tube reactions involving substituted butadienes and maleic anhydride type dienophiles.

4-Acetoxycyclohexene-*cis*-4,5-dicarboxylic Anhydride (6a). A thick-wall Pyrex tube was charged with a solution of 2.0 g (0.013 mol) of acetoxymaleic anhydride (**3a**) in 40 mL of dry benzene and 9.3 g (0.18 mol) of dry 1,3-butadiene. The mixture was cooled in a liquid nitrogen bath under argon atmosphere and then evacuated and allowed to thaw as a closed system. Freezing, followed by re-evacuation, was repeated twice more, and the tube was sealed under vacuum while the contents remained frozen. The sealed tube was then heated to 85–90 °C for 5 days. After cooling in a liquid nitrogen bath until the contents were frozen, the tube was opened and placed under an argon atmosphere while it was warmed to room temperature. Removal of solvents in vacuo, followed by column chromatography on silica gel using 45% ethyl acetate in benzene, gave 2.5 g (93%) of white crystalline adduct **6a**: mp 78–90 °C; IR ($CHCl_3$) 1740 (C=O), 1785 and 1855 cm^{-1} (anhydride C=O). ^1H NMR ($CDCl_3$) δ 2.16 (s, 3 H, $COCH_3$), 3.46 (m, 1 H, COCHOAc), 6.00 (m, 2 H, vinylic H).

An analytical sample was prepared by one recrystallization from ether.

Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.79. Found: C, 57.00; H, 4.77.

4-(2-Methoxyacetoxy)cyclohexene-*cis*-4,5-dicarboxylic Anhydride (6b). A Parr series 4500 pressure reaction apparatus equipped with a glass liner was charged with 25 g (0.134 mol) of (2-methoxyacetoxy)maleic anhydride (**3b**), 800 mL of dry benzene, and 0.5 g of pyrogallol as a radical inhibitor. To this solution was added 109 g (2.0 mol) of 1,3-butadiene which was purified by passage through a drying tower charged with 8 mesh calcium chloride and condensed into an evacuated flask which was cooled in a dry ice–acetone bath. The reaction vessel was then sealed off, and the mixture was stirred for 5 days at 80 °C. The crude reaction product was filtered through Celite, and the solvents were removed in vacuo. Chromatography on silica gel using 35% ethyl acetate in benzene gave 27.4 g (85%) of the desired adduct **6b** as an oil which crystallized on standing: mp 60–62 °C; IR ($CHCl_3$) 1765 (C=O), 1790 and 1860 cm^{-1} (anhydride C=O); ^1H NMR ($CDCl_3$) δ 3.47 (s, 3 H, ether CH_3O–), 4.12 (s, 2 H, $COCH_2O$–), 6.00 (m, 2 H, -vinylic H's).

One recrystallization from ether afforded an analytical sample, mp 61–62 °C.

Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 55.03; H, 5.07.

2-Oxo-3,4-dimethoxy-10β-carbomethoxy-1α-oxaspiro[4.5]deca-3,7-diene (7b). A rapidly stirred solution of 6.6 g (0.027 mol) of the anhydride ester **6b** in 390 mL of dry tetrahydrofuran was cooled to −78 °C with a dry ice–acetone bath under an argon atmosphere. To this solution there was added dropwise a solution of 1.8 equiv (0.055 mol) of lithium diisopropylamide (from 0.055 mol *n*-butyllithium[40] and 9.31 mL (0.066 mol) of diisopropylamine) in 230 mL of dry tetrahydrofuran over a period of 40 min, followed by 75 mL of dry hexamethylphosphoramide. The deep red solution was allowed to warm to 0 °C in an ice bath over 30 min, and then 7.0 mL (0.0825 mol) of methyl fluorosulfonate was added. After stirring the solution for 10 min at 0 °C, the resulting slightly yellow mixture was quenched with 75 mL of 10% aqueous hydrochloric acid solution and extracted twice with 200-mL portions of ether. The combined ethereal layers were washed twice with 100-mL portions of 10% aqueous hydrochloric acid solution, three times with 100-mL portions of water, then once with saturated aqueous sodium chloride solution. After the solution was dried over magnesium sulfate, the solvents were removed in vacuo. Column chromatography on silica gel using 15% ethyl acetate in benzene afforded 4.4 g (61%) of the spirobutenolide **7b** as an oil: IR ($CHCl_3$) 1675 (C=C), 1735 (C=O), and 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.70, 3.92, 4.13 (3 s, 3 × 3 H, 3 × ether CH_3O–), 5.72 (s, 2 H, vinylic H).

Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.28; H, 6.11.

2-Oxo-4-methoxy-10α-carbomethoxy-1α-oxaspiro[4.5]deca-3,7-diene (7a). In a manner similar to that described above for the preparation of spirobutenolide **7b**, a solution of 1.03 g (0.005 mol) of anhydride ester **6a** in 45 mL of dry tetrahydrofuran was treated with a solution of 0.010 mol of lithium diisopropylamide (from 0.010 mol of *n*-butyllithium[40] and 1.67 mL (0.012 mol) of dry diisopropylamine) in 75 mL of dry tetrahydrofuran. After the solution was warmed to 0 °C, 6.0 mL of dry hexamethylphosphoramide was added, and the reaction was quenched with 0.82 mL of freshly distilled methyl fluorosulfonate (bp 92–94 °C).[42] Workup as described for the spirobutenolide **45** followed by column chromatography on silica gel using 20% ethyl acetate in benzene afforded 0.83 g (70%) of the spirobutenolide **7a** as an oil: IR ($CHCl_3$) 1625 (C=C), 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.70 and 3.90 (2 s, 2 × 3 H, 2 × CH_3O), 5.0 (s, 1 H, vinylic H), 5.70 (s, 2 H, vinylic H's).

An analytical sample was prepared by three recrystallizations from ether–hexane, which had identical spectral data with that described above (mp 99–101 °C).

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.67; H, 5.85.

2-Oxo-3,4-dimethoxy-10α-carbomethoxy-1α-oxaspiro[4.5]deca-3,7-diene (8b). To a stirred solution of 4.3 g (16 mmol) of spirobutenolide **7b** in 500 mL of dry methanol under an argon atmosphere was added 3.0 mL (1.6 mmol) of a freshly prepared 0.54 M solution of sodium methoxide in dry methanol, and the resulting mixture was warmed to 70–80 °C for 4 days. The reaction was quenched at room temperature with 0.5 mL of glacial acetic acid, and the solvents were removed in vacuo. The residual oil was taken up in dichloromethane and washed with saturated aqueous sodium bicarbonate solution. After the solution was dried over magnesium sulfate, the solvents were removed in vacuo. Careful chromatography on silica gel using 15% ethyl acetate in benzene afforded 3.36 g (78.3%) of the epimerized spirobutenolide **8b** and 0.841 g (19.6%) of starting material **7b**. The overall yield of the desired product **8b** based on recovered starting material was 97%: IR ($CHCl_3$) 1675 (C=C), 1735 (C=O), and 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.67, 3.81, 4.13 (3 s, 3 × 3 H, 3 × CH_3O–), 5.72 (s, 2 H, vinylic H's).

Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.18; H, 5.93.

2-Oxo-4-methoxy-10α-carbomethoxy-1α-oxaspiro[4.5]deca-3,7-diene (8a). In a manner similar to that described for the preparation of **8b**, a solution of 0.182 g (0.87 mmol) of spi-

(37) For the preparation of α-methoxyacetyl chloride, see: F. Benington and R. D. Morin, *J. Org. Chem.*, **26**, 194 (1961).

(38) For the preparation of 2-methyl-3-oxo-1-butene, see: J. Colonge and L. Cumet, *Bull. Soc. Chim. Fr.*, **14**, 838 (1947).

(39) For a review of the use and preparation of alkenyl magnesium halides, see: H. Normant, *Adv. Org. Chem.* **2**, 1-65 (1960).

(40) Purchased from Ventron/Alfa Inorganics.

(41) Purchased from ROC/RIC.

(42) Purchased from Aldrich.

robutenolide **7a** in 30 mL of dry methanol was treated with 0.16 mL (0.086 mmol) of freshly prepared 0.54 N sodium methoxide in methanol at 70–80 °C for 4 days. After the solution was quenched as described in the preparation of ester **8b**, careful chromatography on silica gel using 25% ethyl acetate in benzene gave 0.035 g of starting material **7a** and 0.140 g (78%) of epimerized ester **8a**: IR ($CHCl_3$) 1635 (C=C) and 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.65 and 3.92 (2 s, 2 × 3 H, 2 × CH_3O–), 5.1 (s, 1 H, vinylic H), 5.70 (m, 2 H, vinylic H's).

An analytical sample was prepared by one recrystallization from ether (mp 119–120 °C).

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.73; H, 6.01.

Methyl 2-(Methoxyacetoxy)-2-methylpropanoate (10). To a stirred solution of 12.0 g (0.10 mol) of methyl 2-hydroxyisobutyrate[42] and 16.6 g (0.15 mol) of methoxyacetyl chloride[37] in 50 mL of dry dichloromethane cooled to 0 °C was added dropwise 12 mL of dry pyridine. After the solution was stirred for 10 min at 0 °C, the mixture was allowed to warm to room temperature, stirred for 30 min, then diluted with 100 mL of dichloromethane, and washed with 100 mL of water. The organic layer was washed with 50-mL portions of 10% aqueous hydrochloric acid solution, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by distillation under reduced pressure, gave 7.2 g (37%) of the desired ester **10**: bp 118–120 °C (22 mm); IR ($CHCl_3$) 1700 (C=O) and 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.60 (s, 6 H, 2 × CH_3–), 3.43 (s, 3 H, CH_3O–), 3.36 (s, 3 H, CH_3O–), 4.0 (s, 2 H, –$COCH_2O$–).

2-Oxo-2,5-dihydro-3-methoxy-4-hydroxy-5,5-dimethylfuran (12a). To a stirred solution of 0.08 mol of lithium diisopropylamide in 100 mL of dry tetrahydrofuran (from 26.5 mL of 3.0 M *n*-butyllithium[40] in hexane and 13.4 mL (0.095 mol) of diisopropylamine in 100 mL of dry tetrahydrofuran) cooled to –78 °C with a dry ice–acetone bath under an argon atmosphere was added dropwise a solution of 7.2 g (0.04 mol) of methyl 2-(methoxyacetoxy)-2-methylpropanoate (**10**) in 20 mL of dry tetrahydrofuran. The resulting mixture was allowed to stir at –78 °C for 15 min, then warmed to room temperature and quenched with 60 mL of 10% aqueous hydrochloric acid solution. The aqueous layer was saturated with sodium chloride and extracted three times with ethyl acetate. The extracts were dried over magnesium sulfate. Removal of solvents in vacuo, followed by recrystallization from ether–petroleum ether, afforded 5.7 g (95%) of crystalline 12a: mp 134–135 °C; IR ($CHCl_3$) 1650 (C=C), 1730 (C=O), and 3520 cm^{-1} (–OH); ^1H NMR ($CDCl_3$) δ 1.40 (s, 6 H, 2 × CH_3–), 3.80 (s, 3 H, CH_3O–).

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.98; H, 6.20.

2-Oxo-2,5-dihydro-3,4-dimethoxy-5,5-dimethylfuran (12b). In a manner similar to that described above for the preparation of tetronic acid **12a**, a solution of 1.2 g (6.3 mmol) of the ester **10** in 4 mL of dry tetrahydrofuran was treated with 12.6 mmol of lithium diisopropoylamide in 15 mL of dry tetrahydrofuran. After 15 min at –78 °C the reaction was warmed to 0 °C and 20 mL of dry hexamethylphosphoramide was added, followed by quenching with 0.80 mL of methyl fluorosulfonate. After the usual workup (see the preparation of **8b**) and chromatography on silica gel using 25% ethyl acetate in benzene, there was obtained 1.03 g (95%) of tetronic acid methyl ether **12b**, identical with material obtained by diazomethane treatment of tetronic acid **12a**: IR ($CHCl_3$) 1680 (C=C), 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.40 (s, 6 H, 2 × CH_3–), 3.84 (s, 3 H, CH_3O–), and 4.18 (s, 3 H, CH_3O–).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.90; H, 7.08.

2-Oxo-2,5-dihydro-3-hydroxy-5,5-dimethylfuran (11a). A solution of 3.14 g (0.018 mol) of methyl 2-acetoxy-2-methylpropanoate (**9**) in 60 mL of dry tetrahydrofuran was treated with 0.04 mol of lithium diisopropylamide in 30 mL of dry tetrahydrofuran, using the same procedure as described for the preparation of tetronic acid **12a**, and gave 1.92 g (95%) of the tetronic acid **11a** which was recrystallized from ether–petroleum ether: mp 140–142 °C (lit.[7] mp 140–142 °C); IR ($CHCl_3$) 1740 (C=O), and 1755 cm^{-1} (C=O) (mainly keto form).

2-Oxo-2,5-dihydro-3-methoxy-5,5-dimethylfuran (11b). Methyl 2-acetoxy-2-methylpropanoate (**9**) (1.1 g, 6.3 mmol) in 4 mL of dry tetrahydrofuran was treated with 12.6 mmol of lithium diisopropylamide in 15 mL of dry tetrahydrofuran and then quenched with 0.80 mL of methyl fluorosulfonate by using the same procedure as that described for the preparation of the tetronic acid methyl ether **12b**. Chromatography on silica gel with 15% ethyl acetate in benzene gave 0.72 g (90%) of the methyl ether **11b**: mp 71–72 °C; IR ($CHCl_3$) 1625 (C=C) and 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.42 (s, 6 H, 2 × CH_3–), 3.85 (s, 3 H, CH_3O–), 4.94 (s, 1 H, vinylic H).

2-Oxo-2,5-dihydro-3-methoxy-4-hydroxy-5,5-dimethylfuran (12c). A stirred solution of 0.250 g (1.45 mmol) of the dimethyl ether **12b** in 5.0 mL of dry dichloromethane was cooled to –78 °C with a dry ice–acetone bath under 3.0 mL of a 1.45 M solution of boron tribromide[40] in dichloromethane over 5 min. The resulting solution was allowed to stir for 10 min at –78 °C then warm to 0 °C in an ice bath and stirred for 2 h. The mixture was again cooled to –78 °C, and excess boron tribromide was destroyed by dropwise addition of 2.0 mL of anhydrous ether. The reaction was then quenched at 0 °C by careful dropwise addition of 5 mL of water. The aqueous layer was extracted with three 50-mL portions of ether. The combined ethereal layers were dried over magnesium sulfate, and the solvents were removed in vacuo. The crude product was freed from boronate impurities by addition of 100 mL of anhydrous methanol and concentration of the resulting solution in vacuo. This procedure was repeated once more, and after removal of traces of solvents in vacuo, there was obtained 0.180 g (79%) of the α-hydroxytetronic acid methyl ether **12c** as a slightly yellow crystalline solid: mp 70–73 °C; IR ($CHCl_3$) 1680 (C=C), 1740 (C=O), 3300, and 3520 cm^{-1} (OH); ^1H NMR ($CDCl_3$) 1.45 (s, 6 H, 2 × CH_3), 4.20 (s, 3 H, CH_3O), 6.40 (b, 1 H, OH).

An analytical sample was prepared by recrystallization from ether–petroleum ether, mp 74–75 °C.

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found C, 53.09; H, 6.09.

2-Oxo-2,5-dihydro-3,4-dihydroxy-5,5-dimethylfuran (13). A 0.5 M stock solution of lithium *n*-propyl mercaptide in hexamethylphosphoramide was prepared as follows: To a stirred solution of 0.65 mL (7.2 mmol) of dry *n*-propylmercaptan[42] (freshly distilled from Mg turnings under an argon atmosphere) in 5 mL of dry hexane, cooled to 0 °C under an argon atmosphere, was added dropwise 2.35 mL (6.1 mmol) of a 2.57 M solution of *n*-butyllithium[40] in *n*-hexane. The resulting white suspension was stirred for 10 min, then concentrated to dryness in vacuo at 0 °C, and taken up in 12 mL of dry hexamethylphosphoramide.

To a stirred solution of 0.25 g (1.45 mmol) of the dimethyl ether **12b** in 1 mL of dry hexamethylphosphoramide under an argon atmosphere at room temperature was added 2.9 mL of a freshly prepared 0.5 M solution of lithium *n*-propyl mercaptide in hexamethylphosphoramide. The resulting mixture was allowed to stir for 6 h at room temperature, then 25 mL of 10% aqueous hydrochloric acid solution was added and the mixture was extracted with 50 mL of ether. The organic layer was washed twice with 5-mL portions of 10% aqueous hydrochloric acid solution, and the combined aqueous layers were extracted twice with 25-mL portions of ether. The combined organic layers were washed once with saturated aqueous sodium chloride solution then dried over magnesium sulfate. Removal of solvents in vacuo afforded 0.225 g of crude tetronic acid **12a**.

To a stirred solution of 0.50 g (3.16 mmol) of the tetronic acid **12a** in 5.0 mL of dry dichloromethane containing 0.54 mL (6.6 mmol) of dry pyridine at 0 °C was added 0.60 mL (6.3 mmol) of acetic anhydride, and the resulting mixture was stirred for 12 h at room temperature under an argon atmosphere. Concentration of solvents in vacuo, followed by column filtration through silica gel using 30% ethyl acetate in chloroform, afforded 0.60 g (95%) of crystalline enol acetate. The crude acetate was taken up in 5 mL of dry dichloromethane and cooled to –78 °C with a dry ice–acetone bath, under an argon atmosphere. To this stirred solution was added dropwise 8.3 mL (15.8 mmol) of a 1.9 M solution of boron tribromide[40] in dichloromethane. The resulting mixture was allowed to stir for 1 h at –78 °C, then warmed to 0 °C and stirred at 0 °C for 2 h. The reaction was quenched by careful dropwise additions of 10 mL of water. The aqueous layer was saturated with sodium chloride, then extracted twice with 50-mL portions of ethyl acetate. The organic layer was dried over

magnesium sulfate, and the solvents were removed in vacuo. The crude product was freed from boronate impurities by addition of 100 mL of methanol containing a drop of dilute aqueous acid and concentration of the resulting solution in vacuo. This procedure was repeated until there was obtained a constant weight of 0.465 g (100%) of the crude α-hydroxytetronic acid (**13**), as an extremely air sensitive solid: IR (Nujol mull) 1625 (C=C), 1720 (C=O), 3300 cm^{-1} (broad, -OH); ^1H NMR (acetone-d_6) δ 1.40 (s, CH_3- s). Mass measured molecular ion: calcd for $C_6H_8O_4$ 144.0423, found 144.0421.

1-Methyl-4-(2-methoxyacetoxy)cyclohexene-*cis*-4,5-dicarboxylic Anhydride and 2-Methyl-4-(2-methoxyacetoxy)cyclohexene-*cis*-4,5-dicarboxylic Anhydride (14a,b). Reaction of isoprene (7.8 mL, 78 mmol) and (α-methoxyacetoxy)maleic anhydride (**3b**) (0.971 g, 5.2 mmol) in a sealed tube (see **6b**) for 3 days at 85 °C, followed by chromatography on silica gel using 25% ethyl acetate in benzene, afforded 1.1 g (85%) of pure adducts **14**: IR ($CHCl_3$) 1765 (C=O), 1790, and 1860 cm^{-1} (anhydride C=O); ^1H NMR ($CDCl_3$ δ 1.80 (s, 3 H, =CCH_3), 347 (s, 3 H, ether CH_3O-), 4.13 (s, 2 H, $COCH_2O$-), 5.5 (m, 1 H, -vinylic H); ^{13}C NMR ($CDCl_3$) 22.7, 24.1 (2 × -CH_3-), 28.7, 30.7 (2 × -CH_2-), 35.2 (>CH), 45.4, 45.9 (2 × -CH_2-), 59.2 (-CH_2O-), 69.0 (CH_3O-), 80.3 (>CO), 116.4, 121.5 (2 × HC=), 132.9, 138.8 (2 × >C=), 170.2 (>C=O).

Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.60; H, 5.55. Found: C, 56.64; H, 5.54.

2-(*tert*-Butyldimethylsiloxy)-3-methylbutadiene (15). To a stirred solution of 0.142 mol of lithium diisopropylamide (from *n*-butyllithium and diisopropylamine) in 200 mL of dry tetrahydrofuran, cooled to -70 °C by a dry ice–acetone bath under an argon atmosphere, was added dropwise a solution of 2-methyl-3-oxo-1-butene[38] in 15 mL of dry tetrahydrofuran, over 10 min. After the solution was stirred for 10 min at -70 °C, 28.5 mL of dry hexamethylphosphoramide and a solution of 19.9 g (0.132 mol) of *tert*-butyldimethylsilyl chloride[43] in 25 mL of dry tetrahydrofuran were added sequentially. After the solution was warmed to room temperature over 30 min, the reaction was quenched with 200 mL of water and extracted into 500 mL of pentane. The aqueous layer was extracted into 500 mL of pentane. The aqueous layer was extracted two more times with pentane. The combined organic layers were washed with water and saturated aqueous sodium chloride solution, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by distillation at reduced pressure (bp 87–90 °C at (15 mm)), gave 18.1 g (76%) of pure colorless diene **15**: IR ($CHCl_3$) 1600 (C=C), 1250 cm^{-1} ($SiCH_3$); ^1H NMR ($CDCl_3$) δ 0.17 (s, 6 H, $(CH_3)_2Si$), 1.0 (s, 9 H, $(CH_3)_3C$-), 1.90 (s, 3 H, =CCH_3), 4.40 (m, 1 H, vinylic H), 4.50 (m, 1 H, vinylic H), 5.0 (m, 1 H, vinylic H), 5.50 (m, 1 H, vinylic H).

Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.18. Found: C, 66.22; H, 11.25.

1-(*tert*-Butyldimethylsiloxy)-2-methylcyclohexene-4,5-dicarboxylic Anhydride (16). The diene **15** (0.243 g, 1.2 mmol) and maleic anhydride (0.1 g, 1.0 mmol) were taken up in 6 mL of dry benzene and heated to reflux for 3 h. Removal of solvents in vacuo, followed by chromatography over silica gel using 45% ethyl acetate in benzene, gave 0.284 g (96%) of adduct **16**: IR ($CHCl_3$) 1675 cm^{-1} (anhydride C=O); ^1H NMR ($CDCl_3$) δ 0.13 (s, 3 H, $(CH_3)Si$), 0.17 (s, 3 H, $(CH_3)Si$), 1.0 (s, 9 H, $(CH_3)_3C$), 1.67 (s, 3 H, =CCH_3), 3.40 (m, 2 H, -$CHCO_2$-).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 60.78; H, 8.16. Found: C, 60.79; H, 8.01.

2-Oxo-3-methoxy-4-hydroxy-10-(hydroxymethyl)-1-oxaspiro[4.5]deca-3,7-diene (17). To a stirred solution of 0.150 g (0.56 mmol) of the ester **8b** in 1 mL of dry hexamethylphosphoramide under an argon atmosphere was added 1.34 mL (0.67 mmol) of a freshly prepared 0.5 M solution of lithium *n*-propyl mercaptide in dry hexamethylphosphoramide (prepared as described in the preparation of tetronic acid **13**). The resulting mixture was allowed to stir for 20 h at room temperature, then 25 mL of 10% aqueous hydrochloric acid solution was added and the mixture was extracted with 50 mL of ether. The organic layer was washed twice with 5-mL portions of 10% aqueous hydrochloric acid solution, and the combined aqueous layers were extracted twice with 25-mL portions of ether. The combined organic layers were washed once with saturated aqueous sodium chloride solution, then dried over magnesium sulfate. Removal of solvents in vacuo afforded 0.142 g of crude spirotetronic acid **17** (70% pure by ^1H NMR integration of methoxyl peaks): IR ($CHCl_3$) 1685 (C=C), 1725 (C=O), and 1780 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.64 (s, 3 H, ester CH_3O-), 3.80 (s, 3 H, ether CH_3O-), 5.75 (m, 2 H, vinylic H's). Treatment of the crude material with diazomethane gave back starting material **8b**. Due to its instability, the tetronic acid ester was used directly in the reduction to alcohol **18**.

2-Oxo-3,4-dimethoxy-10α-(hydroxymethyl)-1α-oxaspiro[4.5]deca-3,7-diene (18). A. By Reduction of the Sodium Salt of Tetronic Acid Ester 17 with Diisobutylaluminum Hydride. To a solution of 0.14 g (5.9 mol) of sodium hydride (from 47% oil dispersion,[40] washed three times with dry hexane) in 5 mL of dry ether was added 4.5 mL of a 1.3 M solution of diisobutyl aluminum hydride in hexane,[42] and the mixture was cooled to -70 °C with a dry ice–acetone bath. Next, 0.150 g (0.59 mmol) of tetronic acid ester **17** in 2 mL of dry ether was added dropwise, and the resulting mixture was stirred for 3 h at -70 °C, then allowed to warm to 0 °C (ice bath) and quenched with excess methanol. The resulting mixture was poured into 10 mL of 10% aqueous hydrochloride acid solution and extracted three times with 25-mL portions of ether. The ethereal extracts were dried over magnesium sulfate, and the solvents were removed in vacuo. Treatment with ethereal diazomethane, followed by column chromatography on silica gel using 45% ethyl acetate in benzene, afforded 0.042 g (30%) of alcohol **18**, which crystallized on standing (mp 91–4 °C): IR ($CHCl_3$) 1670 (C=C), 1745 (C=O), 3600 cm^{-1} (-OH); ^1H NMR ($CDCl_3$) δ 3.80 and 4.15 (2 s, 2 × 3 H, 2 × CH_3O), 5.70 (m, 2 H, vinylic H's).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.05; H, 6.71.

B. By Direct Reduction of Ester 8b with Lithium Borohydride. To a stirred solution of 2.0 g (7.5 mmol) of the ester **8b** in 10 mL of dry tetrahydrofuran was added 25.2 mL (26.26 mmol) of a freshly prepared 1.03 M solution of lithium borohydride[40] in tetrahydrofuran. The resulting mixture was allowed to stir at room temperature for 20 h, then cooled to 0 °C with an ice bath and quenched by careful addition of 20 mL of glacial acetic acid. The mixture was then diluted with 250 mL of dichloromethane and washed with 20 mL of 10% aqueous hydrochloric acid solution, then saturated aqueous sodium chloride solution. The organic layer was dried over magnesium sulfate, and the solvents were removed in vacuo. Boronate impurities were removed by addition of methanol containing a drop of dilute aqueous acid and concentration of the solvents in vacuo until a constant weight was obtained. Column chromatography on silica gel using 45% ethyl acetate in benzene afforded 0.885 g (44%) of starting material and 0.937 g (52%) of the desired alcohol **18** (92% based on the recovered starting material.)

C. By Direct Reduction of Ester 8b with Lithium Triethylborohydride. To a stirred solution of 0.480 g (1.8 mmol) of ester **8b**, in 4.0 mL of dry tetrahydrofuran cooled to -15 °C with a 2-propanol–water–dry ice bath under an argon atmosphere, was added 5.36 mL (3.6 mmol) of a 0.67 M solution of lithium triethylborohydride in tetrahydrofuran,[42] dropwise over 10 min. The mixture was then allowed to warm to 0 °C in an ice bath and stirred for 15 min. The reaction was quenched with 5 mL of 10% aqueous hydrochloric acid solution and extracted three times with 20-mL portions of ether. The combined ethereal extracts were dried over magnesium sulfate, and the solvents were removed in vacuo. Chromatography on silica gel using 45% ethyl acetate in benzene afforded 0.430 g (99%) of the desired alcohol **18**.

2-Oxo-3,4-dimethoxy-1α-oxaspiro[4.5]deca-3,7-diene-10α-carbaldehyde (20). To a stirred suspension of 0.318 g (1.48 mmol) of pyridinium chlorochromate[21] in 2 mL of dry dichloromethane was added a solution of 0.178 g (0.741 mmol) of alcohol **18** in 2 mL of dry dichloromethane. The resulting mixture was allowed to stir at room temperature for 3 h, then diluted with 25 mL of anhydrous ether and decanted. The black precipitate was pulverized with a spatula and washed with three additional 25-mL portions of ether. The combined organic extracts were filtered through a column of 10 g of silica gel using 200 mL of ether. Removal of the solvents in vacuo afforded 0.157 g (89%) of aldehyde **20**, which was immediately converted to the allylic alcohol **21**, as decomposition occurred on standing at room

temperature: IR ($CHCl_3$) 1660 (C=C), 1710 (C=O), 1750 (C=O), 2720 cm^{-1} (aldehyde CH); ^1H NMR ($CDCl_3$) δ 3.83 (s, 3 H, CH_3O–), 4.16 (s, 3 H, CH_3O–), 5.70 (m, 2 H, vinylic H's), 9.53 (d, 1 H, J = 1 Hz, aldehydic H).

2-oxo-3,4-dimethoxy-10α-(1-hydroxy-2-propen-1-yl)-1α-oxaspiro[4.5]deca-3,7-diene (21). A. Using Vinylmagnesium Bromide. To a stirred solution of 0.016 g (0.67 mmol) of the aldehyde **20** in 2 mL of dry tetrahydrofuran cooled to −78 °C with a dry ice–acetone bath under an argon atmosphere was added dropwise 0.72 mL of a 1.0 M solution of vinylmagnesium bromide[39] in tetrahydrofuran. The resulting mixture was kept at −78 °C for 15 min, then allowed to warm to −30 °C for 15 min and quenched with 2.0 mL of saturated aqueous ammonium chloride solution. The aqueous layer was extracted three times with 20-mL portions of ether, and the combined ethereal extracts were dried over magnesium sulfate. Removal of solvents in vacuo followed by column chromatography over silica gel using 45% ethyl acetate in benzene afforded 0.137 g (79%) of the allylic alcohol **21**, which was immediately acylated with an appropriate active ester: IR ($CHCl_3$) 1665 (C=C), 1740 (C=O), 3590 cm^{-1} (–OH); ^1H NMR ($CDCl_3$) δ 3.87 (s, 3 H, CH_3O–), 4.16 (s, 3 H, CH_3O–), 5.0–6.0 (m, 5 H, vinylic H).

B. Using Vinylmanganese Iodide. To a stirred suspension of 0.107 g (0.346 mmol) of anhydrous manganese iodide[41] in 2 mL of dry ether cooled to −20 °C with a 2-propanol–water–dry ice bath was added dropwise 0.32 mL of a 1.0 M solution of vinylmagnesium bromide in tetrahydrofuran over 5 min. After the solution was stirred for 5 min at −20 °C, the reaction mixture was allowed to warm to room temperature and stirred for 3 min, then cooled to −10 °C while 0.050 g (0.210 mmol) of the aldehyde **20** was added dropwise. The resulting cream-colored suspension was stirred for 45 min at −10 °C, then quenched with 5 mL of saturated aqueous ammonium chloride solution and extracted with 50 mL of ether. The organic layer was washed with 50 mL of ether. The organic layer was washed with 50 mL of a 10% aqueous sodium sulfite solution and twice with a saturated aqueous sodium bicarbonate solution and dried over magnesium sulfate. Removal of solvents in vacuo, followed by chromatography on silica gel using 45% ethyl acetate in benzene, gave 0.049 g (92%) of the desired vinyl alcohol **21**

(2-Oxo-3,4-dimethoxy-1α-oxaspiro[4.5]deca-3,7-dien-10α-yl)-2-propen-1-yl Propionate (22). A. Using Pyridine as a Base. To a stirred solution of 0.090 g (0.354 mmol) of allylic alcohol **21** in 2.0 mL of dry dichloromethane at 0 °C under an argon atmosphere was added 0.032 mL (0.39 mmol) of dry pyridine followed by 0.034 mL (0.39 mmol) of propionyl chloride. The resulting mixture was allowed to warm to room temperature over 1.5 h. It was then diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate solution, and dried over magnesium sulfate. Removal of solvents in vacuo followed by column chromatography on silica gel using 30% ethyl acetate in benzene gave 0.083 g (76%) of the propionate **22**: IR ($CHCl_3$) 1680 (C=C), 1730 (C=O), and 1750 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7.5 Hz, $-CH_2CH_3$), 3.82 (s, 3 H, CH_3O–), 412 (s, 3 H, CH_3O–). Mass measured molecular ion: calcd for $C_{17}H_{22}O_6$ 322.1416; found 322.1412.

B. Using 4-(Dimethylamino)pyridine as a Base.[23] To a stirred solution of 0.015 g (0.059 mmol) of the allylic alcohol **21** in 1.0 mL of dry dichloromethane was added 0.0085 g (0.078 mmol) 4-(dimethylamino)pyridine and 0.0056 mL (0.065 mmol) of propionyl chloride. The resulting mixture was allowed to stir for 2 h at room temperature, then concentrated to dryness in vacuo. Purification of the crude residue by preparative thin-layer chromatography using 45% ethyl acetate in benzene afforded 0.017 g (92%) of the desired propionate **23**.

2-Oxo-3,4-dimethoxy-10α-(4-carbomethoxy-(*Z*)-1-penten-1-yl)-1α-oxaspiro[4.5]deca-3,7-diene (23). A. Attempted Enolization of Propionate 22 with Lithium Diisopropylamide in Tetrahydrofuran. To a stirred solution of 1.35 mmol of lithium diisopropylamide[21] (from 1.35 mmol of *n*-butyllithium[40] in hexane and 0.23 mL (1.65 mmol) of dry diisopropylamine) in 2.0 mL of dry tetrahydrofuran cooled to −78 °C under an argon atmosphere was added dropwise 0.083 g (0.27 mmol) of the propionate **22** in 0.5 mL of dry tetrahydrofuran. After the solution was stirred for 10 min at −78 °C, a solution of 0.90 mL (1.35 mmole) of 1.50 M *tert*-butyldimethylsilyl chloride[43] in hexamethylphosphoramide was added, and the reaction mixture was allowed to warm to room temperature and was then stirred for 2 h. The resulting mixture was diluted with ether, washed with 25-mL portions of 5% aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution, then dried over magnesium sulfate. Removal of solvents in vacuo followed by chromatography over silica gel using 25% ethyl acetate in benzene gave back 0.070 g (85%) of the starting material. None of the desired rearranged product was detected.

B. Enolization with Potassium Hexamethyldisilylamide. To a stirred solution of 0.225 mmol of potassium hexamethyldisilylamide[25] in 1.0 mL of dry tetrahydrofuran cooled to −78 °C under an argon atmosphere was added 0.035 g (0.113 mmol) of propionate **22** in 0.5 mL of dry tetrahydrofuran. After the solution was stirred for 5 min at −78 °C, a solution of 0.16 mL (0.242 mmole) of 1.5 M *tert*-butyldimethylsilyl chloride in hexamethylphosphoramide was added, and the resulting mixture was allowed to warm to room temperature. After the solution was stirred for 3 h at room temperature, the reaction was quenched with 10% aqueous hydrochloric acid solution and extracted into two 50-mL portions of ether. The combined ethereal extracts were concentrated in vacuo, and the residue was taken up in tetrahydrofuran containing 10% aqueous hydrochloric acid solution (5:1). After 20 min at room temperature, the mixture was diluted with 100 mL of ether. The aqueous layer was washed twice with 10-mL portions of ether, and the combined ether layers were dried over magnesium sulfate. Treatment with ethereal diazomethane followed by removal of the solvents in vacuo and chromatography over silica gel using 25% ethyl acetate in benzene gave 0.064 g (18%) of starting material and 0.025 g (68%) of the desired methyl ester **23**: IR ($CHCl_3$) 1675 (C=C), 1725 (C=O), 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$ δ 1.10 (m, 3 H, $-CH_2CH_3$), 3.63 (s, 3 H, CH_3O–), 3.77 (s, 3 H, CH_3O–), 4.04 (s, 3 H, CH_3O–), 5.21 (m, 2 H, vinylic H's), 5.60 (m, 2 H, vinylic H's).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.23.

[(2-Oxo-3,4-dimethoxy-1α-oxaspiro[4.5]deca-3,7-dien-10α-yl)-2-propen-1-yl] *cis*-2-Carboxy-*trans*-2-methylcyclohexanepropionate (27). To a stirred solution of 0.110 g (0.416 mmol) of the allylic alcohol **21** in 1.0 mL of dry dichloromethane under an argon atmosphere at 0 °C were added 0.040 mL (0.457 mmol) of dry pyridine, 0.010 g (0.04 mmol) of 4-(dimethylamino)pyridine, and 0.110 g (0.457 mmol) of the acid chloride **26**[28] in 1.0 mL of dry dichloromethane. The resulting mixture was allowed to warm to room temperature and was then stirred for 1.5 h. It was then diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate solution, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by column chromatography on silica gel using 25% ethyl acetate in benzene, afforded 0.120 g (62%) of the diester **27**: IR ($CHCl_3$) 1680 (C=C), 1730 (C=O), and 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.20 (s, 3 H, CH_3–), 3.64, 3.77, and 4.04 (3 s, 3 × 3 H, 3 × CH_3O), 5.0–6.0 (m, 5 H, vinylic H's).

Attempted Rearrangements of the Allylic Ester 27. In a manner similar to that described in procedure B for the preparation of ester **23**, 0.100 g (0.285 mmol) of the diester **27** in 1.0 mL of tetrahydrofuran was treated with 0.57 mmol of potassium hexamethyldisilylamide[25] in 1.0 mL of dry tetrahydrofuran at −78 °C. After the solution was quenched with *tert*-butyldimethylsilyl chloride[43] in hexamethylphosphoramide, aqueously worked up, and preparatively thin layer chromatographed, there was obtained 0.090 g of the 2-carbalkoxyhydrindanone **28**: IR ($CHCl_3$) 1680 (C=C), 1720 (C=O), 1740 (C=O), and 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.16 (s, 3 H, CH_3–), 3.77 and 4.04 (2 s, 2 × 3 H, 2 × CH_3O), 5.0–6.0 (m, 5 H, vinylic H's). None of the desired rearranged product was isolated.

1α-Methyl-7α*H*-2-oxabicyclo[5.4.0]undeca-2,5-dione (29). To a stirred solution of 0.192 g (0.934 mmol) of dicyclohexylcarbodiimide in 18 mL of dry dioxane[29] was added 0.200 g (0.935 mol) of the diacid **25**.[28] After the solution was stirred for 22 h at room temperature, the resulting white precipitate was filtered off, and the solvents were removed in vacuo. The crude product was evaporatively distilled [95–100 °C (0.01 mm)] to give 0.138

(43) Purchased from Petrarch Systems, Inc.

g (75%) of the anhydride **29**: IR ($CHCl_3$) 1750 and 1800 cm^{-1} (anhydride C=O); ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H, CH_3).

[(2-Oxo-3,4-dimethoxy-1α-oxaspiro[4.5]deca-3,7-dien-10α-yl)-2-propen-1-yl] *cis*-2-Carboxy-*trans*-2-methylcyclohexanepropionate (30). To a stirred solution of 0.130 g (0.662 mmol) of anhydride **29** and 0.062 g (0.233 mmol) of allylic alcohol **21** in 3 mL of dry dichloromethane under an argon atmosphere was added 0.054 g (0.42 mmol) of 4-(dimethylamino)pyridine. The mixture was allowed to stir at room temperature for 30 min, then warmed to reflux for 15 min. The resulting mixture was allowed to cool to room temperature, then diluted with ether, and washed once with 10% aqueous hydrochloric acid solution, twice with saturated aqueous copper(II) sulfate solution, and once with saturated aqueous sodium chloride solution. After being dried over magnesium sulfate, the solvents were removed in vacuo. Column chromatography over silica gel using 45% ethyl acetate in benzene gave 0.092 g (85%) of the acid-ester **30**: IR ($CHCl_3$) 1680 (C=C), 1700 (carboxyl C=O), 1735 (C=O), and 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.22 (s, 3 H, CH_3), 3.76, 4.13 (2 s, 2 × 3 H, 2 × CH_3O), 5.0–6.0 (m, 5 H, vinylic H's), 8.8 (s, 1 H, CO_2H). Mass measured molecular ion: calcd for $C_{25}H_{34}O_8$ 462.2253; found 462.2261.

2-Oxo-3,4-dimethoxy-10α-[4-carbomethoxy-5-(*cis*-2-carbomethoxy-*trans*-2-methylcyclohexane)-(*Z*)-1-penten-1-yl]-1α-oxaspiro[4.5]deca-3,7-diene (31). To a stirred solution of 0.80 mmol of potassium hexamethyldisilylamide in 5.0 mL of dry tetrahydrofuran cooled to −78 °C under an argon atmosphere was added dropwise a solution of 0.92 g (0.199 mmol) of the acid ester **30** in 1.5 mL of dry tetrahydrofuran. After the solution was stirred for 5 min at −78 °C, 0.210 mL (1.28 mmol) of a centrifuged solution of 3:1 trimethylsilyl chloride[43] and dry triethylamine were added. It was then allowed to warm to room temperature and stirred for 6 h. The resulting mixture was quenched with 2 mL of dry methanol, then diluted with ether and washed with 10% aqueous hydrochloric acid solution. After being dried over magnesium sulfate, the solvents were removed in vacuo. The crude diacid was treated with excess ethereal diazomethane, then chromatographed over silica gel using 15% ethyl acetate in benzene to give 0.078 g (80%) of the diester **31**: IR ($CHCl_3$) 1680 (C=C), 1720 (C=O), 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.22 (s, 3 H, CH_3), 3.64 (s, 6 H, 2 × CH_3O), 3.77, 4.04 (2 s, 2 × 3 H, 2 × CH_3O), 5.21 (m, 2 H, vinylic H's), 5.60 (m, 2 H, vinylic H's). Mass measured molecular ion: calcd for $C_{27}H_{38}O_8$ 490.2566; found 490.2580.

2-Oxo-3,4-dimethoxy-10α-[5-(*cis*-2-carbomethoxy-*trans*-2-methylcyclohexane)-(*Z*)-1-penten-1-yl]-1α-oxaspiro[4.5]deca-3,7-diene (32). To a stirred solution of 0.045 g (0.0917 mmol) of diester **31** in dry ether cooled to −78 °C under an argon atmosphere was added 0.13 mL (0.183 mmol) of a commercial 1.40 M diisobutylaluminum hydride[42] in hexane. The resulting mixture was allowed to stir at −78 °C for 1 h, then quenched with 1.0 mL of methanol. After the solution was stirred for 10 min at −78 °C, the mixture was allowed to warm to room temperature over 10 min, then diluted with ether and washed four times with saturated aqueous sodium potassium tartrate solution. After the solution was dried over magnesium sulfate, removal of solvents in vacuo gave 0.042 g of crude aldehydo ester: IR ($CHCl_3$) 1640 (C=C), 1720 (aldehyde C=O), 1735 (ester C=O), 1760 (butenolide C=O), 2780 cm^{-1} (aldehyde C=H). The crude aldehyde was taken up in 3 mL of dry benzene along with 0.100 g (0.100 mmol) of tris(triphenylphosphine)rhodium chloride.[40] This mixture was degassed with two freeze–pump–thaw cycles, then warmed to reflux for 48 h under an argon atmosphere. The mixture was concentrated in vacuo, then taken up in ether (10 mL) and filtered to remove triphenylphosphine. Preparative thin-layer chromatography using 15% ethyl acetate in benzene afforded 0.020 g (48%) of the ester **32**: IR ($CHCl_3$) 1640 (C=C), 1720 (ester C=O), 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.22 (s, 3 H, CH_3), 3.64, 3.77, 4.04 (3 s, 3 × 3 H, 3 × CH_3O), 5.20 (m, 2 H, vinylic H's), 5.60 (m, 2 H, vinylic H's). Mass measured molecular ion: calcd for $C_{25}H_{36}O_6$ 432.2512; found 432.2503.

***cis*-2-Chloroformyl-*trans*-2-methylcyclohexanebutyryl Chloride (33).** To a stirred solution of 0.710 g (3.1 mmol) of *cis*-γ-2-methyl-2-carboxycyclohexanebutyric acid[28] in 15 mL of dry benzene was added 0.95 mL (11.0 mmol) of oxalyl chloride. The mixture was allowed to stir for 24 h at room temperature under an argon atmosphere. Removal of solvents in vacuo gave 0.639 g (90%) of diacid chloride **33**: IR ($CHCl_3$) 1975 cm^{-1} (acyl chloride C=O); ^1H NMR ($CDCl_3$) δ 1.20 (s, 3 H, CH_3). The crude diacid chloride was used without further purification.

[(2-Oxo-3,4-dimethoxy-1α-oxaspiro[4.5]deca-3,7-dien-10α-yl)-2-propen-1-yl] *cis*-2-Carboxyl-*trans*-2-methylcyclohexanebutyrate (34). To a stirred solution of 0.085 g (0.318 mmol) of the allylic alcohol **21** in 5 mL of dry dichloromethane were added 0.044 mL (0.382 mmol) of dry 2,6-lutidine and 0.085 g (0.32 mmol) of the diacid chloride **33**. After the solution was stirred overnight at room temperature, the mixture was diluted with dichloromethane, washed with 10% aqueous hydrochloric acid solution and saturated aqueous copper(II) sulfate solution, then dried over magnesium sulfate. Removal of the solvents in vacuo followed by column chromatography over silica gel using 45% ethyl acetate in benzene afforded 0.122 g (83%) of the desired acid ester **34**: IR ($CHCl_3$) 1680 (C=C), 1700 (carboxyl C=O), 1735 (C=O), 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H, CH_3), 3.76, 4.10 (2 s, 2 × 3 H, CH_2O's), 5.0–6.0 (m, 5 H, vinylic H's), 9.0 (s, 1 H, CO_2H). Mass measured molecular ion: calcd for $C_{26}H_{36}O_8$ 476.2410; found 476.2413.

2-Oxo-3,4-dimethoxy-7β,8β-epoxy-10α-carbomethoxy-1α-oxaspiro[4.5]dec-3-ene (35). To a stirred solution of 0.55 g (0.58 mmol) of ester **8b** in 10 mL of dry dichloromethane was added 0.141 g (0.70 mmol) of 85% *m*-chloroperbenzoic acid.[42] The resulting mixture was stirred for 5 days at 20 °C. Excess peracid was destroyed with 15 mL of 10% sodium sulfite, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 30-mL portions of 5% aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by column chromatography over silica gel using 20% ethyl acetate–benzene, afforded 0.015 g (9.7%) of starting material **8b**, 0.054 g of an unidentified oxidation product (loss of spiro ring), and 0.068 g (41%) of the desired β-epoxide **35**: mp 91–3 °C (from ether); IR ($CHCl_3$) 1680 (C=C), 1735 (C=O), 1765 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.63, 3.77, 4.10 (3 s, 3 H, CH_3O-'s).

Anal. Calcd for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 55.03; H, 5.74.

2-Oxo-3,4-dimethoxy-10α-[(*tert*-butyldimethylsiloxy)methyl]-1α-oxaspiro[4.5]deca-3,7-diene (Silyl Ether of 18). To a stirred solution of 1.3 g (0.0055 mmol) of the alcohol **18** in 3.0 mL of dry dimethylformamide (distilled from silica gel) under an argon atmosphere were added 1.5 g (0.021 mol) of sublimed imidazole and 1.65 g (0.011 mole) of *tert*-butyldimethylsilyl chloride.[43] The resulting mixture was stirred for 12 h at 35 °C, poured into 25 mL of saturated aqueous sodium bicarbonate, and extracted three times with 25-mL portions of ether. The ethereal extracts were washed once with saturated aqueous sodium chloride solution then dried over magnesium sulfate. Removal of solvents in vacuo followed by chromatography over silica gel with 5% ethyl acetate in benzene afforded 1.93 g (99%) of the silyl ether as a colorless oil: IR ($CHCl_3$) 1250, 838 ($SiCH_3$), 1670 (C=C), and 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, $(CH_3)_2Si$-), 0.87 (s, 9 H, $(CH_3)_3C$-), 3.76, 4.07 (2 s, 2 × 3 H, ether CH_3O's), 3.40 (m, 1 H, >$CHCH_2OSi$), 5.60 (m, 2 H, vinylic H).

Anal. Calcd for $C_{18}H_{30}O_5Si$: C, 60.98; H, 8.53. Found: C, 60.95; H, 8.48.

2-Oxo-3,4-dimethoxy-7β,8β-epoxy-10α-[(*tert*-butyldimethylsiloxy)methyl]-1α-oxaspiro[4.5]dec-3-ene (36). To a stirred solution of 0.430 g (1.21 mmol) of the silyl ether of **18** (see above) in 5 mL of dry ether at 0 °C under an argon atmosphere were added 0.257 g (2.42 mmol) of anhydrous lithium perchlorate[40] and 0.74 g (3.64 mmol) of 85% *m*-chloroperbenzoic acid.[42] The resulting mixture was allowed to stir at 0 °C for 6 h, then quenched with 15 mL of 10% aqueous sodium sulfite solution. The aqueous layer was extracted with three 50-mL portions of dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, then dried over magnesium sulfate. Removal of solvents in vacuo followed by chromatography over silica gel using 15% ethyl acetate in benzene afforded 0.380 g (85%) of the desired β-epoxide **36**: mp 90–91 °C (from hexane); IR ($CHCl_3$) 1680 (C=C), 1765 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, $(CH_3)_2Si$), 0.87 (s, 9 H, $(CH_3)_3C$-), 3.73 (s, 3 H, CH_3O-), 4.02 (s, 3 H, CH_6O-).

Anal. Calcd for $C_{18}H_{30}O_6Si$: C, 58.35; H, 8.16. Found: C, 58.47; H, 8.12.

2-Oxo-3,4-dimethoxy-7α-methyl-8β-hydroxy-10α-[(*tert*-butyldimethylsiloxy)methyl]-1α-oxaspiro[4.5]dec-3-ene (37). To a stirred suspension of 3.4 mmol of lithium dimethylcuprate in 10.0 mL of dry hexane under an argon atmosphere (prepared in hexane by adding 4.2 mL of a 1.61 M solution of low halide methyllithium in ether[40] to a suspension of 0.647 g (3.4 mmol) of purified copper(I) iodide in 10.0 mL of dry hexane at 0 °C)[31c] was added 0.250 g (0.67 mmol) of epoxide **36** in 1.5 mL of dry ether. The resulting mixture was allowed to warm to 14 °C and was stirred for 8 h. The reaction was then quenched with 50 mL of saturated aqueous ammonium chloride solution and extracted twice with 30-mL portions of ether. The combined organic layers were washed once with saturated aqueous sodium bicarbonate solution, then dried over magnesium sulfate. Removal of solvents in vacuo followed by column chromatography, 25% ethyl acetate in benzene, afforded 0.015 g (6%) of starting material, 0.031 g (12%) of a ketone [IR ($CHCl_3$) 1670 (C=C), 1720 (C=O), ketone), and 1760 cm^{-1} (C=O, butenolide)], and 0.189 g (73%) of the desired alcohol **37** (76% based on recovered starting material) [IR ($CHCl_3$) 1675 (C=C), 1760 (C=O), 3600 cm^{-1} (-OH); ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, $-(CH_3)_2Si-$), 0.87 (s, 9 H, $(CH_3)_3C-$), 1.10 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.75 (s, 3 H, CH_3O-), 4.07 (s, 3 H, CH_3O-)].

Anal. Calcd for $C_{19}H_{34}O_6Si$: C, 59.04; H, 8.87. Found: C, 59.08; H, 8.98.

2-Oxo-3,4-dimethoxy-7α-methyl-8β-methoxy-10α-(hydroxymethyl)-1α-oxaspiro[4.5]dec-3-ene (39). To a stirred suspension of 0.0095 g (0.24 mmol) of potassium hydride (from 0.040 g of the 24% oil dispersion,[40] washed three times with dry pentane under an argon atmosphere and dried in vacuo) in 2 mL of dry tetrahydrofuran at 0 °C under an argon atmosphere was added 0.120 mL (1.91 mmol) of methyl iodide (freshly distilled from P_2O_5) followed by a solution of 0.074 g (0.191 mmol) of alcohol **37** in 0.5 mL of dry tetrahydrofuran. The mixture was allowed to stir for 15 min at 0 °C, then warmed to room temperature and stirred for 30 min. The reaction mixture was then cooled to 0 °C and quenched with 2 mL of saturated aqueous ammonium chloride solution. The aqueous layer was extracted with 30 mL of ether, and the combined ether extracts were washed with 20 mL of 10% aqueous sodium sulfite solution, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by chromatography over silica gel using 15% ethyl acetate in benzene, afforded 0.073 g (95%) of the methyl ether **38**: IR ($CHCl_3$) 1675 (C=C), 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, $-(CH_3)_2Si-$), 0.87 (s, 9 H, $(CH_3)_3C-$), 1.10 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.23 (s, 3 H, CH_3O-), 3.75 (s, 3 H, CH_3O-), 4.07 (s, 3 H, CH_3O-).

The methyl ether **38** (0.073 g, 0.182 mmol) was taken up in a mixture of 1.4 mL of glacial acetic acid, 0.4 mL of water, and 2.4 mL of tetrahydrofuran and warmed to 50 °C for 24 h. The reaction mixture was diluted with 10 mL of ether, and the aqueous layer was saturated with sodium chloride and extracted twice more with 10-mL portions of ether. The combined organic layers were washed with 10 mL of saturated aqueous sodium bicarbonate solution, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by chromatography on silica gel using 45% ethyl acetate in benzene, afforded 0.052 g (98%) of the alcohol **39**: IR ($CHCl_3$) 1670 (C=C), 1750 (C=O), 3600 cm^{-1} (-OH); ^1H NMR ($CDCl_3$) δ 1.10 (d, 3 H, J = 7 Hz, $-CHCH_3$), 3.23 (s, 3 H, CH_3O-), 3.75 (s, 3 H, CH_3O-), 4.07 (s, 3 H, CH_3O-). Mass measured molecular ion: calcd for $C_{14}H_{22}O_6$ 286.1416; found 286.1415.

2-Oxo-3,4-dimethoxy-7α-methyl-8β-methyoxy-10α-carbaldehyde-1α-oxaspiro[4.5]dec-3-ene (40). To a stirred suspension of 0.073 g (0.34 mmol) of pyridinium chlorochromate[21] in 1.0 mL of dry dichloromethane was added a solution of 0.050 g (0.17 mmol) of the alcohol **38** in 1.0 mL of dry dichloromethane. The resulting mixture was allowed to stir at room temperature for 3 h, then diluted with 25 mL of anhydrous ether and decanted. The remaining black precipitate was pulverized with a spatula and washed with three additional 25-mL portions of ether. The combined organic extracts were filtered through a column of 10 g of silica gel using 200 mL of ether. Removal of the solvents in vacuo afforded 0.045 g of aldehyde **40**, which was immediately converted to the allylic alcohol **41**, as decomposition occurred on standing at room temperature: IR ($CHCl_3$) 1660 (C=C), 1710 (C=O), 1750 (C=O), 2715 cm^{-1} (aldehydic CH); ^1H NMR ($CDCl_3$) δ 1.10 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.23 (s, 3 H, CH_3O-), 3.75 (s, 3 H, CH_3O-), 4.07 (s, 3 H, CH_3O-), 9.57 (s, 1 H, aldehydic H).

2-Oxo-3,4-dimethoxy-7α-methyl-8β-methoxy-10α-(1-hydroxy-2-propen-1-yl)-1α-oxaspiro[4.5]dec-3-ene (41). To a stirred solution of 0.045 g (0.155 mmol) of the aldehyde **40** in 2.0 mL of dry tetrahydrofuran cooled to -30 °C with a 2-propanol–water–dry ice bath under an argon atmosphere was added dropwise 0.15 mL of a 1.12 M solution of vinylmagnesium bromide[39] in tetrahydrofuran. The resulting mixture was allowed to warm to 0 °C and stirred for 10 min, then quenched with 2.0 mL of saturated aqueous ammonium chloride solution. The aqueous layer was extracted with three 15-mL portions of ether, and the combined ethereal extracts were dried over magnesium sulfate. Removal of solvents in vacuo, followed by chromatography over silica gel using 45% ethyl acetate in benzene, afforded 0.040 g (82%) of the allylic alcohol **41**: IR ($CHCl_3$) 1680 (C=C), 1765 (C=O), 3600 cm^{-1} (-OH); ^1H NMR ($CDCl_3$) δ 1.09 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.26 (s, 3 H, CH_3O-), 3.79 (s, 3 H, CH_3O-), 4.10 (s, 3 H, CH_3O-), 5.0–6.0 (m, 3 H, vinylic H's).

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.76. Found: C, 61.50; H, 7.68.

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Registry No. 3a, 19064-79-0; **3b**, 70728-22-2; **4**, 70728-23-3; **5**, 52060-80-7; **6a**, 70728-24-4; **6b**, 70765-93-4; **7a**, 70728-25-5; **7b**, 70728-26-6; **8a**, 70728-27-7; **8b**, 70728-28-8; **9**, 57865-37-9; **10**, 70728-29-9; **11a**, 22621-30-3; **11b**, 70498-99-6; **12a**, 70728-30-2; **12b**, 70728-31-3; **12c**, 70728-32-4; **13**, 70728-33-5; **14a**, 70728-34-6; **14b**, 70765-94-5; **15**, 70728-35-7; **16**, 70728-36-8; **17**, 70728-37-9; 17 sodium salt, 70728-58-4; **18**, 70728-38-0; **18** *tert*-butyldimethylsilyl ether, 70728-60-8; **20**, 70728-39-1; **21**, 70728-40-4; **22**, 70728-41-5; **23**, 70728-42-6; **26**, 70728-43-7; **27**, 70728-44-8; **28**, 70728-45-9; **29**, 70766-10-8; **30**, 70728-46-0; **31**, 70728-47-1; **32**, 70728-48-2; **33**, 70728-49-3; **34**, 70728-50-6; **35**, 70728-51-7; **36**, 70728-52-8; **37**, 70728-53-9; **38**, 70728-54-0; **39**, 70728-55-1; **40**, 70728-56-2; **41**, 68323-21-7; *d*-tartaric acid, 87-69-4; methoxyacetyl chloride, 38870-89-2; 1,3-butadiene, 106-99-0; methyl 2-hydroxyisobutyrate, 2110-78-3; lithium *n*-propylmercaptide, 16203-40-0; *n*-propylmercaptan, 107-03-9; 2-oxo-2,5-dihydro-3-methoxy-4-acetoxy-5,5-dimethylfuran, 70728-57-3; isoprene, 78-79-5; 2-methyl-3-oxo-1-butene, 814-78-8; *tert*-butyldimethylsilyl chloride, 18162-48-6; maleic anhydride, 108-31-6; vinyl bromide, 593-60-2; (±)-*cis*-2-methyl-2-carboxycyclohexanebutyric acid, 70728-59-5; chlorothricolide, 41093-63-4; chlorothricin, 34707-92-1.