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Toward the Development of a General Chiral Auxiliary. A Total Synthesis of (+)-Tetronolide via a Tandem Ketene-Trapping [4 + 2] Cycloaddition Strategy

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Abstract: A highly convergent, enantioselective total synthesis of the aglycone of the tetrocarcins, (+)-tetronolide, is described. The synthesis highlights the use of several new methods, including camphor auxiliary-directed asymmetric alkylation and the enantioselective preparation of acyclic mixed acetals bearing chirality at the acetal center, and the highly efficient connection of the two major precursors via a ketene-trapping/intramolecular [4 + 2] cycloaddition strategy.

Introduction

The tetrocarcins A−H are members of a growing class of naturally occurring, complex, bioactive, spirotetronic acid containing natural products.[1] More recently, three new members of the class, the arisostatins A and B[2] and the antibiotic AC6H,[3] have been isolated and characterized (Chart 1). When originally isolated, the tetrocarcins were found to possess activity against some Gram-positive (e.g., *Bacillus subtilis*) but no Gram-negative microorganisms.[1,4] Subsequently, it was found that tetrocarcin A showed activity against sarcoma 180, P-388 leukemia, and B16 melanoma, as well as Ehrlich carcinoma MH134 hepatoma, but not solid tumors.[5] At that time, the mechanism by which tetrocarcin A elicited the observed antitumor activity was hypothesized to be inhibition of either DNA or protein synthesis or both.[5] More recent studies have found that tetrocarcin A selectively inhibits the mitochondrial functions of the Bcl-2 family of proteins that function as natural apoptosis inhibitors by down-regulating the activation of caspase-3, a natural mediator of apoptosis.[6] Tetrocarcin A was also found to induce a significant up-regulation of members of the heat shock protein family known to be involved in the endoplasmic reticulum (ER)-stress-induced apoptotic pathway.[7] The activation of caspase-12, the central inducer caspase involved in ER-stress by tetrocarcin A treatment, is also in accord with this result. Thus, the mechanism of the antitumor of action of tetrocarcin A involves induction of the apoptotic machinery via both mitochondrial and ER signaling, neither of which are inhibited by aberrant expression/function of important regulators of death receptor- and drug-induced apoptosis, such as Bcl-2 and Bcl-XL. Overexpression of members of the Bcl-2 family of anti-apoptotic proteins is commonly encountered in multi-drug-resistant (MDR) tumor cell lines.[6,7] Since tetrocarcin A-induced apoptosis is independent of the expression levels of Bcl-2 and Bcl-XL and analogues have been prepared that separate the antitumor and antimicrobial activity, tetrocarcin A appears to be a promising candidate for further evaluation in preclinical trials.[8,9] Similarly, the arisostatins have been shown to inhibit growth of the human squamous cell carcinoma cells by inducing apoptosis. Exposure of human AMC HN-4 cells to arisostatin A produced dose-dependent apoptosis featuring the expected markers (morphological features and DNA fragmentation). In addition, arisostatin A-induced apoptosis was associated with the generation of reactive oxygen species. The cytotoxic effect of arisostatin A on human AMC HN-4 cells is mediated by caspase-3 activation, loss of mitochondrial transmembrane potential, and release of cytochrome *c* into cytosol.[10]

The centerpiece of the structures of the tetrocarcins, arisostatins, and AC6H is the spirotetronic acid aglycone (+)-tetronolide (**1**).[11] (+)-Tetronolide (**1**) is one member of a notable group of complex spirotetronate aglycones that also includes

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(2) (a) Igarashi, Y.; Takagi, K.; Kan, Y.; Fujii, K.; Harada, K.-I.; Furumai, T.; Oki, T. *J. Antibiot.* **2000**, *53*, 233−240. (b) Furumai, T.; Takagi, K.; Igarashi, Y.; Saito, N.; Oki, T. *J. Antibiot.* **2000**, *53*, 227−232.

(3) Shimotohno, K. W.; Endo, T.; Furihata, K. *J. Antibiot.* **1993**, *46*, 682−684.

(4) Tamaoki, T.; Tomita, F.; Kawamura, F.; Saito, H. *Agric. Biol. Chem. Tokyo* **1983**, *47*, 59−65.

(5) Morimoto, M.; Fukui, M.; Ohkubo, S.; Tamaoki, T.; Tomita, F. *J. Antibiot.* **1982**, *35*, 1033−1037.

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(7) Tinhofer, I.; Anether, G.; Senfter, M.; Pfaller, K.; Bernhardt, D.; Hara, M.; Greil, R. *FASEB J.* **2002**, *16*, 1295−1297.

(8) Anether, G.; Tinhofer, I.; Senfter, M.; Greil, R. *Blood* **2003**, *101*, 4561−4568.

(9) Kaneko, M.; Nakashima, T.; Uosaki, Y.; Hara, M.; Ikeda, S.; Kanda, Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 887−890.

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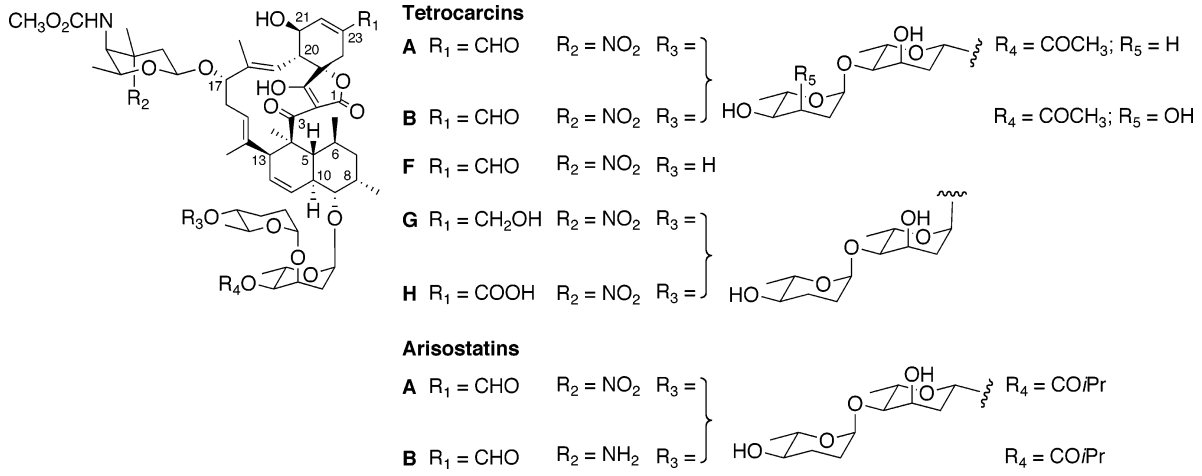
10.1021/ja0581346 CCC: $33.50

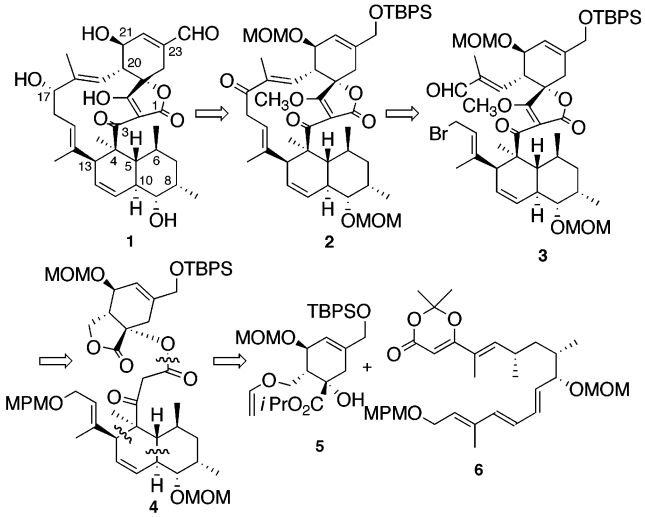
Chart 1



kijanolide, chlorothricolide, and several other related structures.[12−14] Beginning in the mid 1980s, these materials have attracted considerable attention among synthetic chemists,[15−18] including our group,[19] owing to their complex and intricate architecture and promising biological activity. Efforts, thus far, have resulted in one total synthesis[17] and one formal total synthesis of (+)-tetronolide,[18] as well as the syntheses of (−)-chlorothricolide[16a] related analogues[16c,d] and derivatives and an advanced seco-acid intermediate toward kijanolide.[16b]

The majority of the efforts toward these spirotetronic acid systems recognized the value of disconnection of this class of molecules into two major (upper and lower) fragments (Scheme 1). The only previously reported strategy for the critical connection of the two major fragments for (+)-tetronolide was due to the Yoshii group and involved an aldol condensation between an α-metalated protected spirotetronate and a hydronaphthalene carboxaldehyde.[17a]

Scheme 1



In 1991, our group reported preliminary findings regarding use of a similar disconnection through intermediates **2**−**4** but involving a quite different strategy for coupling the major upper and lower fragments, **5** and **6**, employing a tandem ketene-trapping/[4 + 2] cycloaddition sequence (Scheme 1).[19a,b] In 1996, we reported a new enantioselective synthesis of the upper fragment, synthon **5**, employing our camphor-derived auxiliary to establish the chirality.[19c] In this paper, we report a full account of all of our studies that culminated in an enantioselective total synthesis of (+)-tetronolide (**1**). Our route highlights use of auxiliary-mediated asymmetric alkylation, use of a chiral auxiliary-mediated anchimerically assisted S_N1 substitution in a novel construction of a highly enantiomerically enriched mixed acetal, and use of the aforementioned tandem ketene-trapping/[4 + 2] cycloaddition strategy to efficiently and highly stereoselectively connect major enantiomerically pure fragments **5** and **6**.

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(15) (a) Roush, W. R.; Barda, D. A.; Limberakis, C.; Kunz, R. K. *Tetrahedron* **2002**, *58*, 6433−6454 and references therein. (b) Roush, W. R.; Chen, H.; Reilly, M. L. *Heterocycles* **2002**, *58*, 259−282 and references therein. (c) Yoshii, E.; Takeda, K. *Rec. Prog. Chem. Synth. Antibiot. Relat. Microb. Prod.* **1993**, 67−98.
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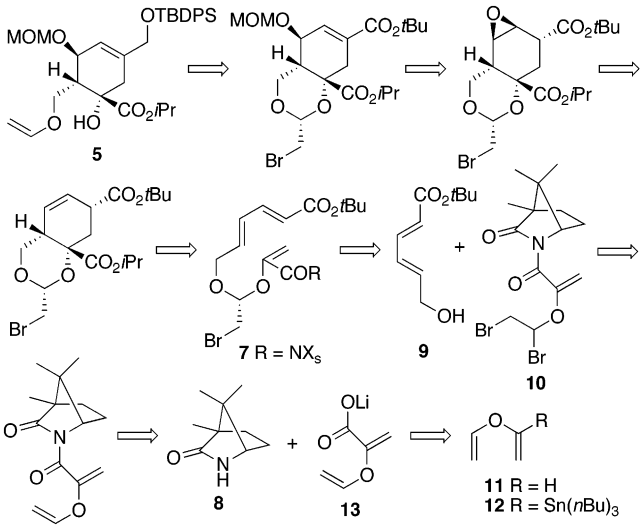
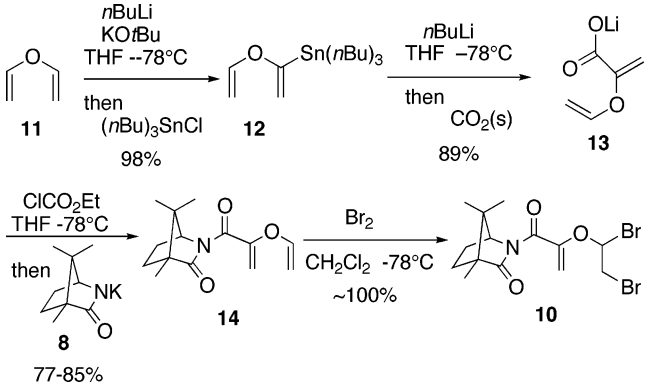
(19) (a) Boeckman, R. K., Jr.; Estep, K. G.; Nelson, S. G.; Walters, M. A. *Tetrahedron Lett.* **1991**, *32*, 4095−4098. (b) Boeckman, R. K., Jr.; Barta, T. E.; Nelson, S. G. *Tetrahedron Lett.* **1991**, *32*, 4091−4094. (c) Boeckman, R. K., Jr.; Wrobleski, S. T. *J. Org. Chem.* **1996**, *61*, 7238−7239.

Scheme 2



Scheme 3



Discussion

Construction of the Upper-Half Subunit: Cyclohexenol 5. Our strategy for the upper synthon cyclohexenol **5** is embodied in the retrosynthetic analysis shown in Scheme 2.[19a,c] The relative stereochemical arrangement of the substituents present on the cyclohexene ring suggested the use of a [4 + 2] cycloaddition as a key transformation. However, application of that retrosynthesis required modification of the position of the unsaturation in the six-membered ring. Fortunately, that modification fit nicely in the functional group manipulations necessary to stereoselectively install the protected hydroxyl group ultimately residing at C_{21} (tetronolide numbering, see Scheme 1). We chose to employ the intramolecular Diels−Alder (IMDA) variant in order to take advantage of the concave shape of the intermediate *cis*-decalin cycloadduct that we felt would ensure high diastereoselectivity in the required functional group manipulations. At the time, we reasoned that use of a tethered diene and dienophile would provide not only control over regiochemistry but also a likely preference for the required *exo* transition state geometry. Subsequent reports by Roush and coworkers have shown that this device is unnecessary as enolpyruvate ester dienophiles as a class show a strong preference for cycloaddition via an *exo* transition state.[15,16,18]

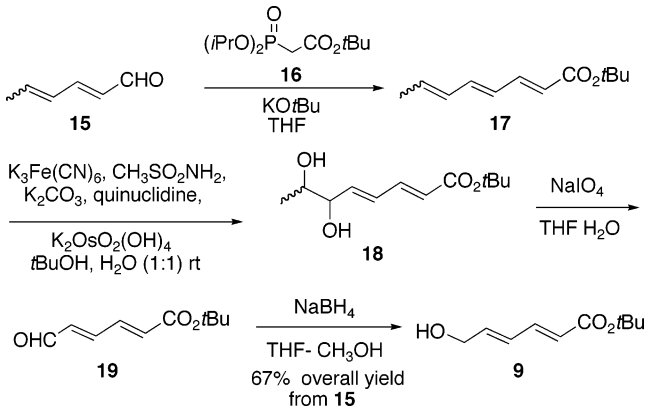
The initial objective was preparation of enantiomerically pure chiral acetal **7** that would serve as the lynchpin in the subsequent [4 + 2] cycloaddition simultaneously exerting control over regio- and relative stereochemistry in the resulting cycloadduct. No precedent existed for the preparation of an enantiomerically pure mixed acetal linkage, such as that found in **7**, although we had employed vinyl ethers to construct such mixed acetals in racemic form employing Hg(II) to effect coupling followed by reductive demercuration and using Br^+ as the electrophile in our published synthesis of racemic **5**.[19a,20]

We adapted the latter process for enantioselective creation of the required mixed acetal linkage, as shown in Scheme 3, by incorporation of the 3-azacamphor lactam **8**[21] into the precursor electrophile, reasoning that anchimeric assistance by the lactam carbonyl would allow substitution/coupling with the dienol ester **9** with overall retention of configuration at the acetal center. We also believed that differential nonbonded interactions within the dibromide **10** would permit kinetically controlled formation of a single diastereomeric iminium ion intermediate, thus leading to control over diastereoselectivity in the formation of **7** and eventual control over absolute chirality at the mixed acetal center in **7** upon removal of the chiral auxiliary. Our initial selection of the (−)-(1R) antipode of **8** was based on our putative mechanistic model. Assignment of the observed (if any) sense of asymmetric induction awaited confirmation by experiment.

This concept was reduced to practice beginning with metalation of divinyl ether (**11**)[22] with Schlosser's base[23] at −78 °C in THF and trapping with (*n*-Bu)$_3$SnCl, affording 98% of the sensitive α-stannylated divinyl ether **12** (Scheme 3). Tin−lithium exchange using *n*-BuLi in THF at −78 °C followed by in situ trapping with solid CO_2 afforded the expected pure lithium carboxylate **13** in 89% yield upon removal of the THF and precipitation from pentane. Direct preparation of **13** was attempted by in situ trapping of the metalated vinyl ether intermediate produced by treatment with Schlosser's base. While the expected carboxylate salt was obtained, it proved to be a mixture of K and Li salts that hampered further transformations owing to diminished solubility of the mixed salt. Installation of the lactam auxiliary was then accomplished by conversion of **13** to a mixed anhydride with $PhSO_2Cl$ and in situ coupling with the lithium salt derived from (−)-(1R)-lactam **8** (either antipode of **8** can be prepared in four steps from the related antipode of camphoric acid).[21] This procedure afforded the desired imide **14** in 77% yield (67% from divinyl ether). The principal drawback was the relatively rapid formation of the symmetrical anhydride leading to incomplete conversion. An alternate concatenated "one-pot" procedure was later developed that avoided use of tin reagents and employed the mixed anhydride derived from ethyl chloroformate and the potassium salt of lactam **8** (required to ensure regioselective attack on the more reactive acyl group), affording **14** in 36% overall yield from divinyl ether (three steps at 71%/step). With vinyl enol pyruvoyl imide **14** in hand, the more reactive enol ether moiety was brominated to afford in approximately quantitative yield the unstable dibromide **10**, which was used without purification. Crude dibromide **10** was initially isolated as a ~6:1 mixture of

(20) Boeckman, R. K., Jr.; Flann, C. J. *Tetrahedron Lett.* **1983**, *24*, 4923−4926.
(21) Boeckman, R. K., Jr.; Nelson, S. G.; Gaul, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 2258−2260.
(22) Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 33−38.
(23) (a) Schlosser, M. *Mod. Synth. Met.* **1992**, *6*, 227−271. (b) Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741−744. (c) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9−16. (d) Lochmann, L.; Pospisil, J.; Lim, D. *Tetrahedron Lett.* **1966**, 257−262.

Scheme 4

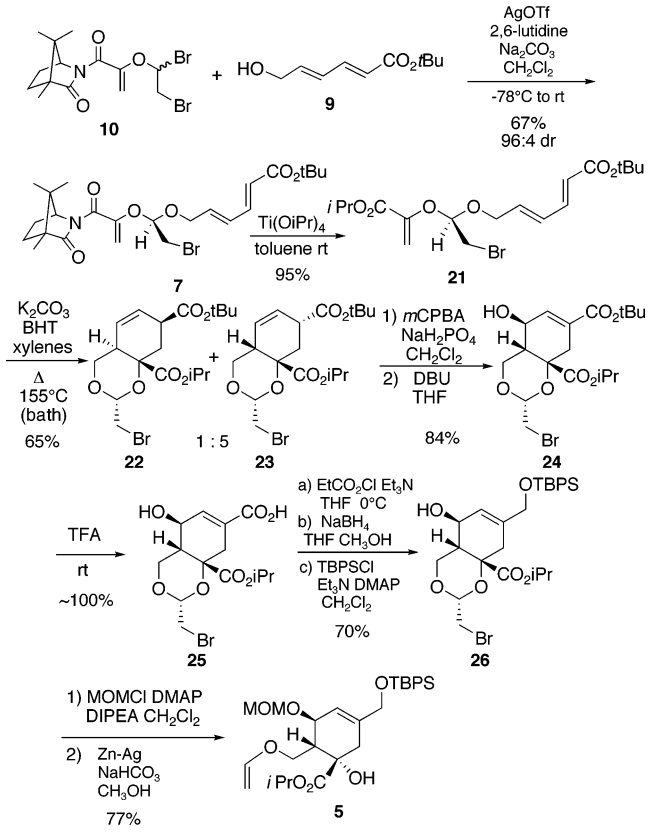


diastereomers that we felt boded well for our ability to obtain diastereoselectivity in the key substitution/coupling process and demonstrated that the auxiliary (by whatever mechanism) was able to exert remote control of diastereoselectivity in reactions of the vinyl ether moiety in **14**. As expected, dibromide **10** proved to be an extremely sensitive substance. Simply on standing in solution overnight, the initial ~6:1 mixture of diastereomers of **10** underwent an autocatalytic isomerization to a 1:1 mixture of diastereomers. Fortunately, use of either of these mixtures of diastereomers of **10** in the subsequent coupling procedure afforded **7** with the same high level of diastereoselectivity.

Remarkably, the choice of the alcohol employed for the coupling with dibromide **10** also proved critical. Use of versions of dienol ester **9** bearing terminal functional groups at lower oxidation states than ester (acetal and protected alcohol) proved unworkable owing to rapid decomposition of these materials under the reaction conditions employed for coupling. Although TBS-protected ester **9** can be assembled by sequential olefination reactions beginning with the TBS ether of hydroxyacetaldehyde, this sequence is suitable for preparation of only relatively small quantities (1−10 g) of **9**. Thus, we developed a convenient four-step process beginning with commercial sorbaldehyde **15** (an inconsequential *E*/*Z* mixture (5:1) of terminal double bond isomers) and diisopropyl *tert*-butylphosphonoacetate **16**,[24] as shown in Scheme 4. Condensation of **15** and **16** afforded the sensitive and unstable triene **17**. Sharpless catalytic dihydroxylation[25] afforded a mixture of diol esters **18** that were directly converted to alcohol **9** by oxidation of **18** with $NaIO_4$ in aqueous THF and reduction of resulting muconaldehydic ester **19** with $NaBH_4$ in CH_3OH/THF. This sequence afforded **9** in 67% overall yield from **15** after the only required purification (chromatography).

As shown in Scheme 5, the key highly diastereoselective coupling of **9** and **10** was subsequently achieved by addition of 1 equiv of freshly prepared dibromide **10** to a heterogeneous mixture containing 1.4 equiv of alcohol **9**, 1.2 equiv of 2,6-lutidine, 1.06 equiv of AgOTf, and excess anhydrous Na_2CO_3 in CH_2Cl_2 at −78 °C followed by warming slowly to room temperature over 16 h in the dark. Workup and chromatographic purification delivered an inseparable mixture of diastereomeric mixed acetals **7** (96:4) that proved suitable for further transformations. During scale-up of this reaction, a minor byproduct

Scheme 5



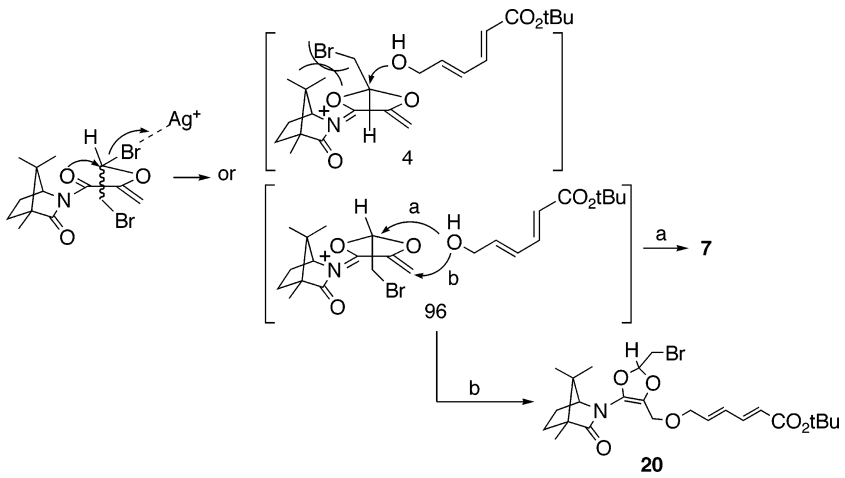
20 was isolated that shed light on the mechanism of this transformation and validated our original design concept. A plausible mechanism accounting for the sense of asymmetric induction and production of **20** is outlined in Scheme 6.

We initially expected that we might effect the required intramolecular [4 + 2] cycloaddition employing **7** as the substrate. However, as is the case for analogous imides,[21,26] **7** proved unreactive thermally up to its decomposition point. Normally Lewis acid promoters, such as CH_3AlCl_2, are employed.[21,26] However, this effort proved fruitless despite extensive experimentation, during which a variety of Lewis acid promoters and reaction conditions were screened, owing to the extreme sensitivity of the acetal linkage in **7** to Lewis acids.

Thus, we adopted the general sequence to the racemic top-half synthon **5** previously developed in our group using an ethyl ester.[19a] We converged with that previous sequence by cleavage of the chiral imide moiety of **7** with $Ti(O^iPr)_4$, affording an analogous isopropyl ester **21** in 95% yield, as detailed in Scheme 5. The sensitivity of **7** to Lewis acid is testament to the mildness of this transesterification procedure. The thermal intramolecular Diels−Alder (IMDA) reaction of ester **21**, bearing the acetal-tethered diene and dienophile, wherein the chirality of the acetal linkage defines the facial selectivity in the Diels−Alder reaction, proceeded smoothly under carefully defined reaction conditions owing to the acid sensitivity of triene **7**. Heating a 0.024 M solution of **8** under Ar in the presence of BHT and Na_2CO_3 in a 155 °C oil bath in either a sealed or open vessel (the former is preferred) for ~114 h affords a 1:5 mixture of *trans*-**22** and *cis*-**23** bicyclic bromoacetals in 65% overall yield. The diaste-

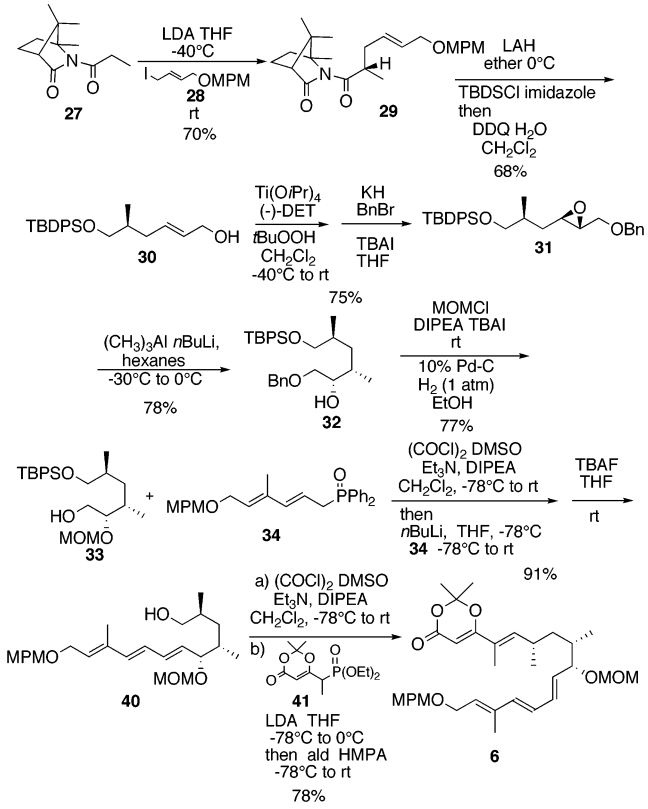
(24) Ye, W.; Liao, X. *Synthesis* **1985**, 986−988.
(25) Zhang, Y.; O'Doherty, G. A. *Tetrahedron* **2005**, *61*, 6337−6351.
(26) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256.

Scheme 6



reoselectivity favoring formation of *cis* bicyclic acetal **23** as the major diastereomer via an *exo* transition state is consistent with the observations of Roush mentioned earlier.[15,16,18] In this case, tethering the diene and dienophile may actually serve to enhance the formation of the undesired *trans* isomer by favoring the *endo* transition state owing to more favorable nonbonded interactions within the tether in the transition state. Attempts to increase the concentration or to raise the temperature led to lower yields. The sensitivity of triene **7** precludes shortening the reaction time by the usual means of increasing the rate. Use of the bulkier isopropyl ester marginally improved the diastereoselectivity (1:3−4 to 1:5) in favor of the desired *cis* Decalin isomer. The subsequent transformation of the *cis* IMDA adduct **23** to the required differentially protected hydroxy ester **5** was straightforward via the previously defined route.[19a] Epoxidation of **23** with buffered *m*CPBA led to a single stereoisomeric epoxide that was directly treated with DBU in THF at room temperature to effect β-elimination to the unsaturated *tert*-butyl ester **24** in 84% yield over two steps. The *tert*-butyl ester moiety of **24** was cleaved by exposure to TFA at room temperature, affording acid **25** in near quantitative yield. Acid **25** was then sequentially selectively reduced by conversion to the mixed anhydride with ethyl chloroformate followed by in situ reduction with $NaBH_4$ in methanol/THF and the primary allylic alcohol selectively silylated with *tert*-butyldiphenylsilyl chloride (TBPSCl), affording alcohol **26** in 70% yield over four steps. The remaining secondary alcohol was then protected with methoxymethyl chloride (MOMCl) under the usual conditions. Liberation of the tertiary alcohol required for coupling the upper and lower major subunits was effected by regioselective reductive fragmentation of the bromoacetal linkage with the Zn-(Ag) couple in buffered methanol at reflux, affording hydroxy ester **5** as the only observed regioisomer.[27] The regioselectivity of this transformation may result from both stereoelectronic and steric factors. The oxygen adjacent to the angular ester moiety in **26** would be expected to be the more electron deficient and thus the better leaving group, and the conformation in which the C−Br bond aligns itself antiperiplanar to that oxygen appears to be less sterically congested. The absolute stereochemistry of (+)-**5** was tentatively assigned by analogy to the related ethyl ester[19c] and confirmed by X-ray analysis of an advanced intermediate (vide infra) as well as by conversion of (+)-**5** to (+)-tetronolide (**1**).

Scheme 7

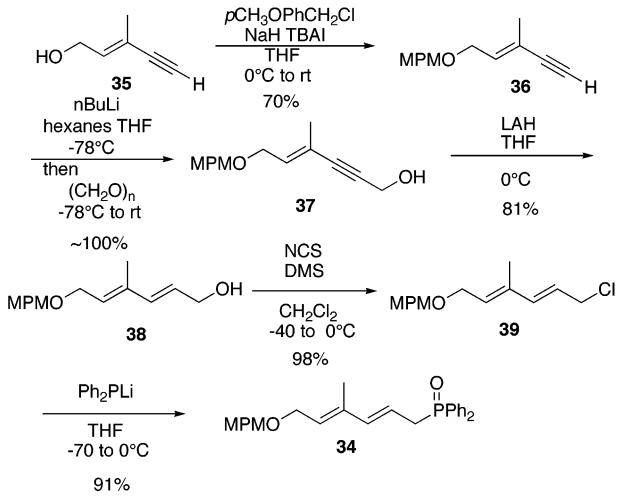


Construction of the Lower-Half Subunit: Tetraene Dioxolenone 6. Our sequence to prepare dioxolenone **6** commenced with diastereoselective alkylation of the lithium enolate derived from propionimide **27** with allylic iodide **28** protected as a methoxyphenylmethyl (MPM) ether to afford imide **29** as a single diastereomer in 70% yield (Scheme 7).[28] Reductive removal of the auxiliary with LAH in ether, silylation of the resulting primary alcohol with TBPSCl and imidazole, followed by cleavage of the MPM group with DDQ in wet CH_2Cl_2 afforded the alcohol **30** employed in our previous route to **6** in 68% overall yield.[19b]

(27) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1973**, *38*, 3658.

(28) Boeckman, R. K., Jr.; Boehmler, D. J.; Musselman, R. A. *Org. Lett.* **2001**, *3*, 3777−3780.

Scheme 8



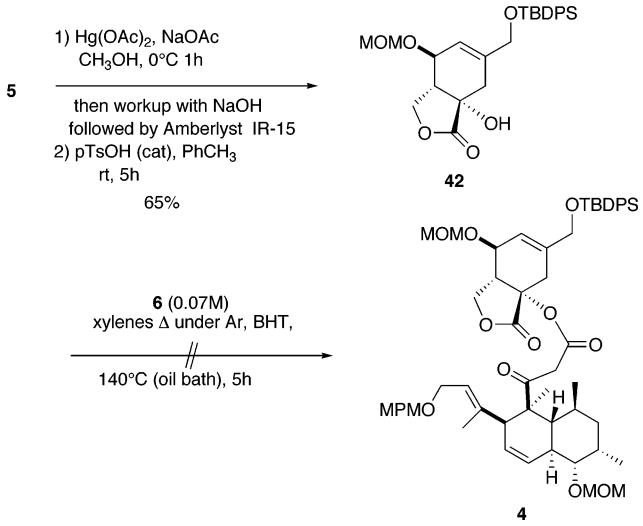
As previously described,[19b] Sharpless epoxidation of **30** afforded the expected epoxide (8:1 dr) followed by benzylation of the resulting epoxy alcohol, affording epoxide ether **31** in 75% yield for two steps.[19b] Completely regioselective opening of the epoxide with the ate-complex derived from *n*-BuLi and $(CH_3)_3Al$ then provided alcohol **32** in 78% yield.[29] Alcohol **32** was smoothly transformed to primary alcohol **33** in 77% yield over two steps by MOM protection under standard conditions and hydrogenolysis of the benzyl ether with H_2 (1 atm) over Pd/C in ethanol.

Diphenyl phosphine oxide **34** was prepared in five steps from commercial (*E*)-3-methyl-2-penten-4-yne-1-ol (**35**) by the sequence shown in Scheme 8. Protection of the hydroxyl function as the MPM ether with NaH and MPMCl afforded the expected ether **36** in 70% yield. Hydroxymethylation of the terminal alkyne with *n*-BuLi and paraformaldehyde afforded the propargyl alcohol **37** in near quantitative yield. Reduction of the propargyl alcohol **37** with LAH in THF provided the (*E*,*E*)-dienol **38** in 81% yield. Dienol **38** was converted to the (*E*,*E*)-dienyl chloride **39** with NCS-DMS (98%), and **39** was alkylated with $LiPPh_2$ in THF affording 91% of the required phosphine oxide **34**.

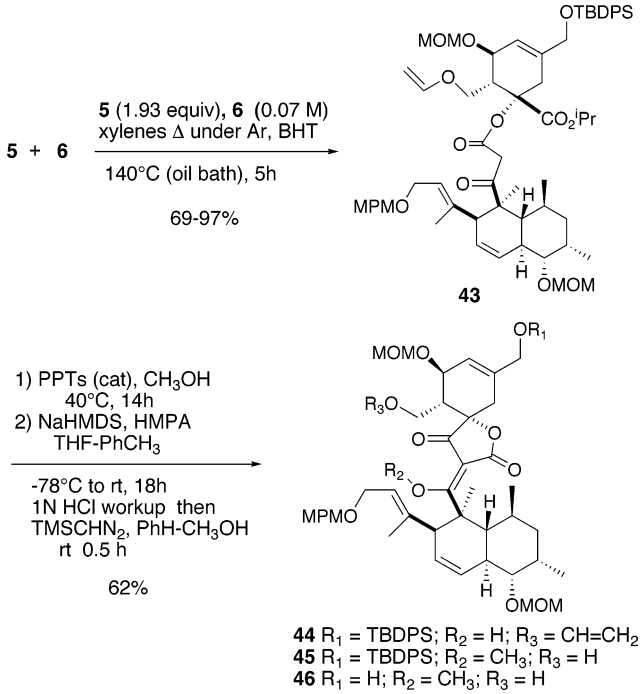
Oxidation of alcohol **33** (Scheme 7) under Swern conditions[30] afforded the unstable aldehyde that was directly subjected to olefination with dienyl diphenyl phosphine oxide **34**. Lithiation of phosphine oxide **34** and condensation with the foregoing aldehyde derived from **33** in the presence of HMPA afforded (*E*,*E*,*E*)-triene alcohol **40** (>15:1 *E*,*E*,*E* isomer) in 91% overall yield after removal of the TBPS group with TBAF in THF. Finally, dioxenone **6** was assembled by Swern oxidation of **40** and Horner−Wadsworth−Emmons olefination of the resulting aldehyde with dioxenone phosphonate **41**[31] in the presence of HMPA, affording the *E*,*E*,*E*,*E* tetraene dioxolenone **6** [>12:1 (all other isomers)] in 78% overall yield for two steps.[19b]

Conjoining of the Lower- and Upper-Half Fragments. We began our studies of the critical tandem ketene-trapping/[4 + 2] cycloaddition as shown in Scheme 9. Our initial approach involved prior deblocking and closure of **5** to the related γ-lactone **42**.

Scheme 9



Scheme 10



44 R_1 = TBDPS; R_2 = H; R_3 = CH=CH_2
45 R_1 = TBDPS; R_2 = CH_3; R_3 = H
46 R_1 = H; R_2 = CH_3; R_3 = H

However, despite considerable experimentation, all attempts to couple lactone **42** with **6** to afford β-ketoester lactone **4** failed. We surmised that the failure stemmed from impaired nucleophilicity of the tertiary OH group owing to a stereoelectronic effect resulting from the enforced alignment of the lactone carbonyl π-orbitals and the adjacent CO bond. In accord with that hypothesis, heating a mixture of **5** (1.93 equiv) and **6** in xylenes in a sealed tube afforded the desired β-ketoester **43**, resulting from tandem ketene-trapping/[4 + 2] cycloaddition, as a single diastereomer in 69% yield (Scheme 10).

We noted that **43** was unstable to prolonged heating eventually regenerating **5** and the methyl ketone derived from the IMDA adduct of **6**. We could partially overcome this limitation by allowing the reaction to proceed to partial completion

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(30) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660.
(31) (a) Boeckman, R. K., Jr.; Kamenecka, T. M.; Nelson, S. G.; Pruitt, J. R.; Barta, T. E. *Tetrahedron Lett.* **1991**, *32*, 2581−2584. (b) Sato, M.; Ogasawara, H.; Komatsu, S.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 3848−3856.

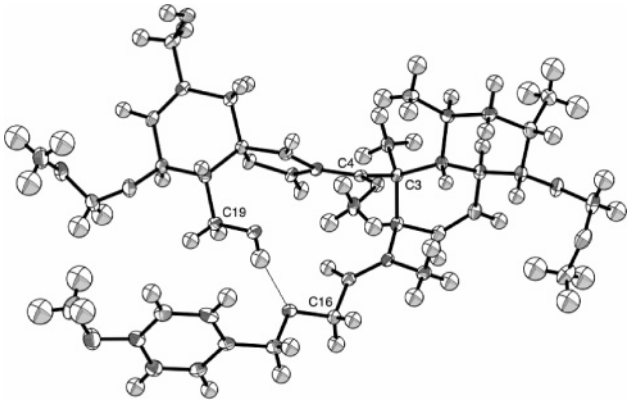


Figure 1. ORTEP (40% probability thermal ellipsoids); final X-ray model of diol **46**.

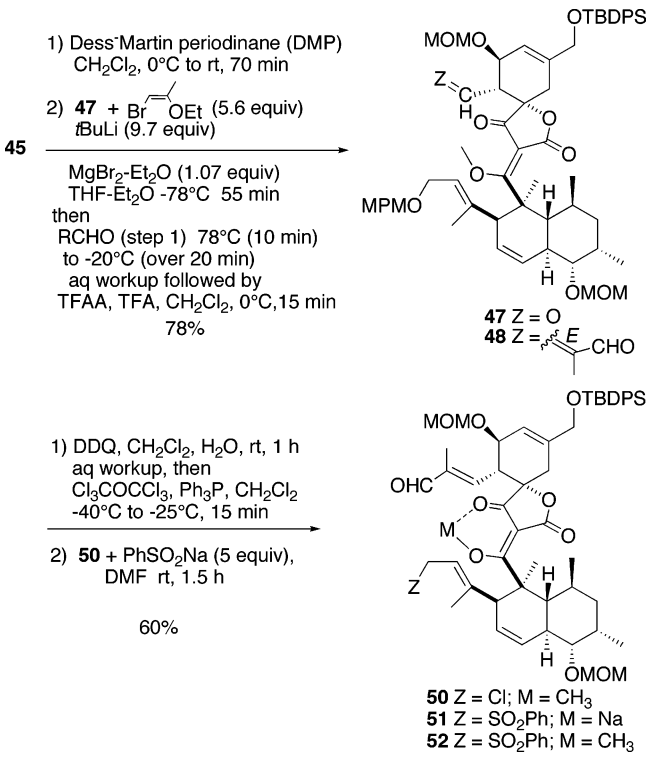
(50−75%) affording **43** in 97% yield based on consumed **6** (excellent recovery of all materials). Prior work had established the order of the steps as ketene trapping followed by IMDA cycloaddition.[19b] Compared to related IMDA cycloadditions of similar substrates,[15−17] cyclization of the tetraene intermediate derived from **5** and **6** was significantly more stereoselective. We attribute the increased stereoselectivity to the additional influence of double diastereoselection, whereby the desired transition state becomes relatively more energetically favorable.

Direct closure of **43** to the spirotetronic acid **44** also failed initially. We had originally anticipated that ketoester **43** might be poorly aligned for intramolecular acylation,[32] hence our decision to attempt coupling of the derived γ-lactone. This concept was validated by removal of the vinyl ether protecting group in **43** prior to cyclization, permitting in situ generation of the required activated γ-lactone, providing the desired O-methyl spirotetronic acid **45** after methylation with TMSCHN$_2$. The fact that cyclization required at least 2 equiv of base provides support for a pathway proceeding via initial conversion to a γ-lactone (Scheme 10).

The gross structure of O-methyl hydroxy spirotetronate **45** was not completely secure since spectroscopic data could not readily distinguish which oxygen of the acyltetronic acid unit had undergone methylation. Further, upon transformation to the related aldehyde derived from primary alcohol **45** by oxidation,[33] we observed the first of a series of four intermediates that exhibited atropisomerism which we attribute to slow rotation about the hindered C_3-C_4 bond. Epimerization at C_{20} during oxidation was ruled out by re-reduction of the aldehyde to **45** with NaBH$_4$, confirming the existence of atropisomers. To conclusively resolve all the structural and stereochemical issues, the TBDPS ether in **45** was removed with TAS-F,[34] and the resulting crystalline diol **46** was subjected to single-crystal X-ray analysis that confirmed the structure and relative stereochemistry of **45** in all respects (Figure 1).

Alcohol **45**, surprisingly, does not exhibit atropisomerism. We were able understand this observation based upon the X-ray data for diol **46** that revealed a macrocyclic H-bond between the C_{16} oxygen function and the C_{19} hydroxyl group (tetronolide numbering) stabilizing one of the two atropisomers, thus

Scheme 11



effectively preventing bond rotation about the hindered C_3-C_4 bond (Figure 1).

Elaboration of 45 to Intermediates Bearing the Bridging Macrocyclic Ring. The elaboration of the bridging macrocyclic ring from alcohol **45** initially requires extension of the upper side chain by three carbons to an (*E*)-α-methyl-α,*β*-unsaturated aldehyde. This homologation to the (*E*)-enal **48** initially proved troublesome owing to the strong tendency to form the *Z* isomer of the enal under kinetic control. A number of literature procedures that, based on existing precedent, were expected to afford the desired (*E*)-enal **48** were attempted. For example, condensation of aldehyde **47** derived from oxidation of **45** with Dess−Martin periodinane (DMP)[33] with lithiated TMSCH(CH$_3$)CH═N*t*Bu (**49**) as reported by Corey[35] afforded mainly the (*Z*)-α-methyl-α,*β*-unsaturated *N*-*tert*-butylimine. Modification of the counterion to a more covalent metal, such as Mg, by transmetalation of **49** with MgBr$_2$·Et$_2$O afforded up to a 3:1 mixture (*E*:*Z*) of **48** after hydrolysis. Since the mixtures of the *E* and *Z* aldehydes **48** were not easily separable on scale, we chose to explore means to obtain more stereoselectivity in the olefination.

We chose to employ a thermodynamically controlled olefination previously developed in our group involving addition of (*Z*)-1-ethoxy-2-propenyl Grignard reagent prepared from the (*Z*)-1-bromo-2-ethoxy-2-propene in ether/THF to aldehyde **47** followed by treatment of the crude alcohols with (CF$_3$CO)$_2$O and CF$_3$COOH in CH$_2$Cl$_2$.[36] This procedure afforded exclusively the desired (*E*)-enal **48** in 78% overall yield in two steps from alcohol **45** (Scheme 11). (*E*)-Enal **48** was then straightforwardly transformed to the allylic chloride **50**. Removal of the MPM group proceeded smoothly upon treatment of **48** with DDQ in

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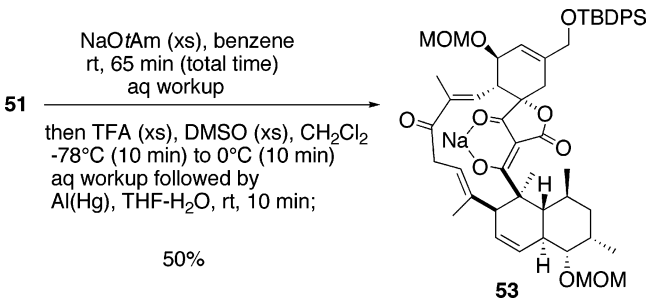
(33) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141−152.
(34) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436−6437.
(35) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7−10.
(36) Boeckman, R. K., Jr.; Starrett, J. E., Jr.; Nickell, D. G.; Sum, P. E. *J. Am. Chem. Soc.* **1986**, *108*, 5549−5559.

wet methylene chloride. The resulting crude primary alcohol was directly converted to the corresponding primary allylic chloride **50** upon exposure to a mixture of hexachloroacetone and PPh_3 in CH_2Cl_2 initially at −40 °C with warming to −25 °C for 15 min.

We examined a number of new macrocyclization sequences mediated by conversion of the allylic chloride **50** to various allylic organometallic reagents without success. Similar results for other macrocyclization methods were obtained much earlier by Yoshii and co-workers during their model studies of this macrocycle formation.[17d] Among the various methods examined, there were variants of Barbier cyclizations[37] employing Mg,[38] Zn,[39] and Sm,[40] including the method of Yamamoto employing metallic Ba which is reported to permit α-selective addition to carbonyl groups especially in the presence of 18-crown-6.[41] The results of most experiments led to uncharacterized product mixtures. In those cases where we believe that cyclized products were, in part, obtained, they were tentatively assigned as arising from γ-addition of the proximal carbon of the allylic system to the aldehyde, leading to the smaller (12-membered ring) of the two macrocycles.

Thus, we adopted a strategy similar to that of Yoshii, employing a Julia olefination/macrocyclization.[10a,c] Conversion of allylic chloride **50** to allylic sulfone **51** was readily achieved upon exposure of **50** to excess sodium benzenesulfinate in DMF at room temperature for 1.5 h (Scheme 11). During this transformation, it was noted that dealkylation of the O-methyltetronate occurred, providing the readily purified sodium salt of sulfone tetronic acid **51**. As advanced intermediates, we found the sodium salts of the tetronic acids, such as **51**, to be readily purified on silica gel and altogether simpler to handle than the free tetronic acids. It was possible to acidify and re-O-methylate **51** by treatment with $TMSCHN_2$ to afford O-methyl sulfone **52**. The structure of **52** was verified by its direct formation as a mixture with **51** upon treatment of **50** with only a slight excess of sodium benzenesulfinate in THF at room temperature. Remarkably, cyclization failed when sulfone **52** was treated with NaO*t*Am in benzene, conditions found to effect cyclization in the regioisomeric O-methyltetronate series.[10a] It is possible that the regiochemistry of methylation of the tetronate residue is responsible since the Yoshii group apparently never encountered the presence of atropisomers as we have observed for our intermediates **47**, **48**, **50**, and **52**. Slow rotation about the C_3-C_4 bond would certainly be expected to impede cyclization, perhaps allowing competing base-catalyzed processes to intervene. Thus, we reasoned that removal of the O-methyl group might actually promote macrocyclization by permitting facile bond rotation around the C_3-C_4 bond. Thus, we were led to try macrocyclization of the tetronate sodium salt **51**. We reasoned that the Na^+ ion could serve to template the macrocyclization through coordination to both the sulfonate carbanion and the electrophilic aldehyde oxygen in the transition state in the nonpolar medium. Such a templated cyclization transition state seemed all the more plausible owing to the observation of the macrocyclic H-bond in the solid-state structure of the diol **46** (Figure 1) and our earlier likely observation of such a templated process.[42] In the event, cyclization of **51** in the presence of excess NaO*t*Am in benzene afforded the macrocyclic ketone **53** in 50% overall yield after the usual concatenated oxidation and reductive desulfonylation operations (Scheme 12). Some support for the hypothesis that cyclization is proceeding via a metal-templated transition state is derived from addition of 18-crown-6 to the reaction mixture during cyclization of **51**, in which the expected cyclization is suppressed and no ketone **53** is obtained after the usual further processing. Similar behavior was noted in our earlier studies of such a probable templated process.[42]

Scheme 12



Final Stage Transformations of Ketone 53 to (+)-Tetronolide (1). As previously reported for structurally related derivatives,[17a] reduction of ketone **53** with L-Selectride and direct protection with MOMCl/DIPEA afforded the fully protected spirotetronate **54** in 71% yield over two steps (Scheme 13). Desilylation of the base-sensitive **54** with TAS-F,[34] DMP oxidation in CH_2Cl_2,[33] and acidic global deprotection afforded synthetic (+)-tetronolide (**1**) [mp 210−211 °C (lit.[17a] 211−213 °C); $[\alpha]^{25}_D$ +72.6° (*c* 0.34, acetone) [lit.[17a] +79.3° (*c* 1.0, acetone)]] spectroscopically identical (^{1}H NMR) in all respects with synthetic[17a] and natural (+)-tetronolide (**1**). It is interesting to note that, with the exception of (+)-tetronolide (**1**) itself, we found it easier to handle, purify, and characterize the sodium salts of the final series of intermediates as opposed to handling these intermediates as the free tetronic acids.

The above-described total synthesis of (+)-tetronolide (**1**) is shorter (~27 steps along the longest linear sequence) and higher yielding than the only previously described synthesis[17a] and exemplifies the utility of notable new methodology for creation of chiral mixed acetals[19c] and for connection of large molecular fragments via a tandem ketene-trapping/[4 + 2] cycloaddition strategy that is significantly more stereoselective overall than similar, previously reported IMDA cycloadditions.

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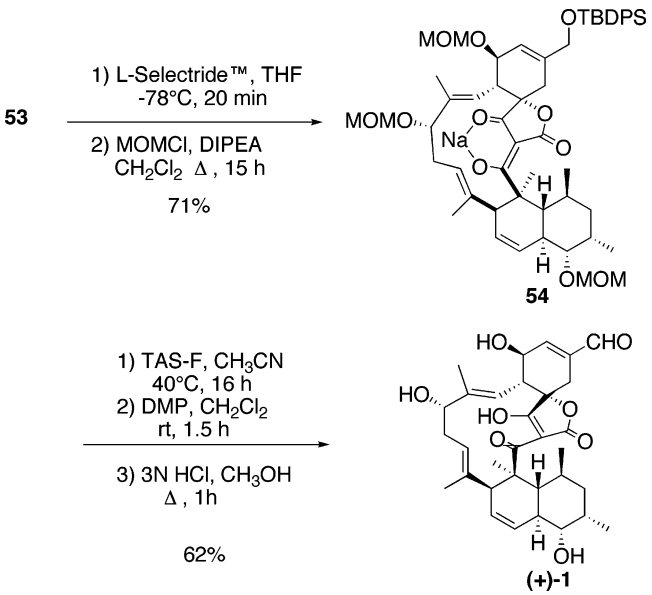
(41) (a) Yanagisawa, A.; Yamada, Y.; Yamamoto, H. *Synlett* **1997**, 1090−1092. (b) Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130−6141.

(42) Boeckman, R. K., Jr.; Reeder, M. R. *J. Org. Chem.* **1997**, *62*, 6456−6457.

Scheme 13



Experimental Section[43]

(+)-(1*R*,4*S*)-*N*-(2-Ethenyloxypropenoyl)-1,7,7-trimethyl-3-azabicyclo[2.2.1]heptan-2-one (14).[19c] To a stirred suspension of 14.0 g (0.117 mol) of the lithium salt **13**[19c] (see Supporting Information) in 400 mL of THF at 0 °C were added successively 11.2 mL (15.5 g, 0.088 mol) of benzene sulfonyl chloride and 42.5 mL (32.7 g, 0.281 mol) of TMEDA, and stirring was continued at 0 °C for 4.5 h. During this time, a solution of lithium salt **8**[21] in THF was prepared by dropwise addition of 39.3 mL of a 1.49 M solution of *n*-BuLi in hexanes (0.059 mol) to a solution of 8.95 g (0.059 mol) of 1,7,7-trimethyl-3-azabicyclo-[2.2.1]heptan-2-one[21] in 350 mL of THF at −78 °C followed by warming to room temperature. After 4.5 h had elapsed, the reaction mixture was recooled to −78 °C, and the aforementioned solution of **8** was added dropwise via cannula with vigorous stirring over 45 min. After the addition was complete, the reaction mixture was allowed to slowly warm to ambient temperature overnight (∼14 h). The reaction mixture was then quenched by addition of 600 mL of water, the phases were separated, and the aqueous phase was extracted with three 250 mL portions of Et_2O. The combined organic phases were washed with 200 mL of brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 21.3 g of crude material as a brown liquid. Flash chromatography on silica gel (with elution by 25% diethyl ether in hexanes) provided 11.2 g (77%) of the divinyl imide **14** as a pale yellow oil having $[\alpha]^{25}_D$ +151.2° (*c* 3.5, CH_2Cl_2). Imide **14** was stored until use as a solution in methylene chloride over solid potassium carbonate to prevent acid-catalyzed decomposition. Imide **14** had the following spectroscopic characteristics: IR (film) 2966, 2877, 1758, 1682, 1641, 1356, 865 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (dd, J_1 = 13.8 Hz, J_2 = 5.9 Hz, 1 H), 4.98 (d, J = 3.0 Hz, 1 H), 4.78 (d, J = 3.0 Hz, 1 H), 4.78 (dd, J_1 = 13.7 Hz, J_2 = 1.5 Hz, 1 H), 4.50 (dd, J_1 = 6.2, J_2 = 1.8 Hz, 1 H), 4.17 (d, J = 2.1 Hz, 1 H), 2.02 (m, 1 H), 1.79 (m, 2 H), 1.64 (m, 1 H), 1.07 (s, 3 H), 1.01 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 176.6, 163.0, 154.0, 147.0, 96.5, 96.1, 64.6, 55.8, 47.5, 30.3, 26.3, 18.1, 17.3, 9.1. HRMS (CI). Calcd for $C_{14}H_{19}NO_3$ [M^+]: *m*/*z* 249.1365. Found: *m*/*z* 249.1362.

(+)-(1*R*,4*S*)-*N*-[2-[(1*R*)-1,2-Dibromoethoxy]propenoyl-1,7,7-trimethyl-3-azabicyclo[2.2.1]heptan-2-one and (+)-(1*R*,4*S*)-*N*-[2-[(1*S*)-1,2-Dibromoethoxy]propenoyl-1,7,7-trimethyl-3-azabicyclo[2.2.1]-heptan-2-one (10).[19c] To a solution of 11.1 g (44.5 mmol) of imide **14** in 400 mL of CH_2Cl_2 was added solid Na_2CO_3 (ca. 10 g). After the resulting mixture was cooled to −78 °C, 178 mL of a 0.25 M solution of bromine in CH_2Cl_2 (44.5 mmol) was added dropwise with vigorous stirring over 4 h. Progress of the reaction was closely monitored by TLC analysis (30% diethyl ether in hexanes) to ensure complete consumption of **14** to give the slightly more polar dibromides **10**. Upon completion of the addition, the reaction mixture was quenched at −78 °C by the addition of 200 mL of saturated aqueous $NaHCO_3$, and the mixture was allowed to warm to room temperature. The phases were separated, and the aqueous phase was extracted with two 75 mL portions of CH_2Cl_2. The combined organic phases were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 18.2 g (∼100%) of the crude dibromide **10** as a pale yellow oil. Analysis of the crude product mixture by ^1H NMR (300 MHz, C_6D_6) indicated a 6:1 mixture of diastereomers. Upon storage, the mixture equilibrated to a ∼1:1 mixture of the diastereomers; however, either mixture was suitable for use in the following transformation. Owing to the instability of the dibromide, the crude product mixture was temporarily stored as a solution in CH_2Cl_2 and used immediately without further purification: IR (film) 2965, 1755, 1682, 1634, 1395, 1014 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ (major diastereomer) 5.82 (dd, J_1 = 5.1 Hz, J_2 = 3.8 Hz, 1 H), 5.20 (d, J = 3.7 Hz, 1 H), 4.96 (d, J = 3.8 Hz, 1 H), 3.88 (d, J = 2.1 Hz, 1 H), 3.66−3.40 (s, 3 H), 0.39 (s, 3 H); and δ (minor diastereomer) 5.74 (dd, J_1 = 7.5 Hz, J_2 = 3.1 Hz, 1 H), 5.21 (m, 1H), 4.90 (d, J = 3.8 Hz, 1 H), 4.03 (br s, 1 H), 3.66−3.40 (m, 2 H), 1.53 (m, 2 H), 1.25 (m, 2 H), 0.89 (s, 3 H), 0.77 (s, 3 H), 0.39 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ (major diastereomer) 176.0, 161.8, 153.4, 96.9, 81.9, 64.6, 55.6, 47.1, 35.1, 30.4, 26.1, 17.9, 16.7, 8.9; and δ (minor diastereomer) 175.6, 161.5, 152.6, 97.1, 80.4, 64.2, 55.3, 46.9, 34.2, 29.8, 26.3, 17.8, 16.7, 9.0.

(+)-(1*R*,4*S*)-*N*-[2-[(1*R*)-2-Bromo-1-(5-*tert*-butoxycarbonyl-2,4-pentadienyloxy)ethoxy]propenoyl]-1,7,7-trimethyl-3-azabicyclo-[2.2.1]heptan-2-one (7).[19c] To a slurry of 13 g (47 mmol) of AgOTf in 64 mL of CH_2Cl_2 was added solid Na_2CO_3 (ca. 7 g) at room temperature. The mixture was cooled to −78 °C and 6.2 mL (5.7 g, 53 mmol) of 2,6-lutidine was added. After stirring for 10 min, a solution of 11.5 g (62.3 mmol) of alcohol **9** (see Supporting Information) in 64 mL of CH_2Cl_2 was added dropwise via cannula over 15 min. After stirring for an additional 5 min, a solution of 18.2 g (44.5 mmol) of the crude dibromide **10** in 64 mL of CH_2Cl_2 was added dropwise via cannula over 30 min. The reaction flask was covered with aluminum foil to exclude light, and the mixture was allowed to stir under an argon atmosphere for 16 h, during which time the reaction mixture was allowed to slowly warm to room temperature. The reaction mixture was diluted with 150 mL of Et_2O and filtered through a pad of Celite to remove the solids. The resulting filtrate was concentrated in vacuo and the residue diluted with an additional 200 mL of Et_2O; the resulting precipitated solids were removed by filtration through a short pad of silica gel on a bed of Celite, and the filter cake was washed with an additional 200 mL of Et_2O. The resulting clear filtrate was washed successively with two 75 mL portions of ice cold 1 N HCl, two 75 mL portions of saturated aqueous $NaHCO_3$, and 50 mL of brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 23.9 g of crude **7** as a clear, yellow oil (96:4 diastereomeric mixture as determined by analysis by 500 MHz ^1H NMR). Mixed acetal **7** was partially purified by flash chromatography on silica gel with elution by 35% Et_2O in hexanes to afford 18.2 g (67%) of a yellow oil as a >96:4 diastereomeric product mixture, which was of sufficient purity for further use (64% contained yield of **7**). An analytical sample of the major diastereomer **7** was obtained after a second purification by flash chromatography on silica gel as a colorless oil having $[\alpha]^{25}_D$ +43.3° (*c* 2.2, CH_2Cl_2): IR (film) 2970, 1754, 1706, 1682, 1621, 1394 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (major isomer) 7.18 (dd, J_1 = 15.3 Hz, J_2 = 11.1 Hz, 1 H), 6.44 (dd, J_1 = 15.1 Hz, J_2 = 11.1 Hz, 1 H), 6.09 (dt, J_1 = 15.3 Hz, J_2 = 5.5 Hz, 1 H), 5.84 (d, J = 15.3 Hz, 1 H), 5.31 (dd, J_1 = 7.4, J_2 = 2.9 Hz, 1 H), 4.84 (d, J = 3.1 Hz, 1 H),

(43) The general experimental methods section along with additional experimental details and procedures for routine transformations may be found in the Supporting Information. See the Supporting Information available paragraph for details as to how to access this information.

4.76 (d, $J = 3.2$ Hz, 1 H), 4.34 (dd, $J_1 = 14.1$ Hz, $J_2 = 5.6$ Hz, 1 H), 4.24 (dd, $J_1 = 14.1$ Hz, $J_2 = 5.6$ Hz, 1 H), 4.14 (s, 1 H), 3.61 (dd, $J_1 = 11.2$ Hz, $J_2 = 2.9$ Hz, 1 H), 3.48 (dd, $J_1 = 11.2$ Hz, $J_2 = 7.5$ Hz, 1 H), 2.03 (m, 1 H), 1.89−1.59 (m, 3 H), 1.50 (s, 9 H), 1.07 (s, 3 H), 1.00 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 176.7, 165.7, 163.3, 153.4, 141.9, 135.6, 129.7, 123.7, 100.0, 94.1, 79.9, 65.7, 64.6, 55.8, 47.5, 30.4, 29.6, 27.8, 26.2, 18.1, 17.2, 9.1. HRMS (FAB$^+$). Calcd for $C_{24}H_{34}BrNO_6$ [M$^+$]: *m*/*z* 512.1570. Found: *m*/*z* 512.1572.

(−)-(1*R*)-2-Bromo-1-[(2*E*,4*E*)-5-*tert*-butoxycarbonyl-2,4-pentadienyloxy)-1-(1-isopropoxycarbonyl-1-ethenyloxy)ethane (21). To a solution of 16.1 g (25.1 mmol) of partially purified **7** (dr > 96:4) in 100 mL of toluene was added 22.3 mL (75.3 mmol) of Ti(O^{i}Pr)$_4$ at room temperature. The resulting homogeneous solution was allowed to stir at room temperature for 14 h. The reaction mixture was then diluted with 600 mL of Et_2O and quenched with 250 mL of H_2O, resulting in the formation of a heavy, white precipitate. The phases were separated, and the aqueous phase containing the solids was extracted with four 150 mL portions of Et_2O. The cloudy organic phases were combined, dried over $MgSO_4$, filtered through a pad of Celite, and the resulting clear filtrate was concentrated in vacuo to afford 20 g of crude material as a yellow oil. The crude material was purified by flash chromatography on silica gel with elution by 30% Et_2O in hexanes to provide 10.0 g (95%) of **21** as a pale yellow oil having $[\alpha]^{25}_D$ −6.3° (*c* 1.4, CH_2Cl_2): IR (film) 2978, 1709, 1649, 1622, 1368, 1134 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, $J_1 = 15.3$ Hz, $J_2 = 11.0$ Hz, 1 H), 6.40 (dd, $J_1 = 15.3$ Hz, $J_2 = 11.0$ Hz, 1 H), 6.10 (dt, $J_1 = 15.3$ Hz, $J_2 = 5.5$ Hz, 1 H), 5.84 (d, $J = 15.4$ Hz, 1 H), 5.61 (d, $J = 2.1$ Hz, 1 H), 5.22 (t, $J = 5.2$ Hz, 1 H), 5.11 (sept, $J = 6.2$ Hz, 1 H), 5.02 (d, $J = 2.2$ Hz, 1 H), 4.38 (dd, $J_1 = 14.1$ Hz, $J_2 = 5.2$ Hz, 1 H), 4.24 (dd, $J_1 = 14.1$ Hz, $J_2 = 5.2$ Hz, 1 H), 3.54 (m, 2 H), 1.49 (s, 9 H), 1.31 (d, $J = 6.2$ Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 162.0, 149.1, 142.1, 135.8, 130.0, 124.0, 102.3, 100.8, 80.3, 69.3, 66.6, 31.5, 30.2, 21.6. HRMS (CI). Calcd for $C_{18}H_{31}BrNO_6$ [M + NH_4^+]: *m*/*z* 436.1335. Found: *m*/*z* 436.1355.

(2*R*,4a*R*,7*S*,8a*S*)-*tert*-Butyl-2α-bromomethyl-8a*β*-isopropoxycarbonyl-4a*β*,7,8,8a-tetrahydro-4*H*-1,3-benzodioxin-7α-carboxylate (23) and (2*R*,4a*S*,7*R*,8a*S*)-*tert*-Butyl-2α-bromomethyl-8a*β*-isopropoxycarbonyl-4aα,7,8,8a-tetrahydro-4*H*-1,3-benzodioxin-7*β*-carboxylate (22). A 2 L round-bottom flask equipped with a magnetic stirring bar was soaked in concentrated NH_4OH for at least 12 h, then emptied and rinsed 10 times with deionized water, and dried overnight in an oven. Once dry, the flask was allowed to cool to room temperature under an argon atmosphere. Just prior to use, a silylating solution [prepared by adding TMSCl (25 mL) to a solution of Et_3N (50 mL) in 500 mL of dry, distilled CH_2Cl_2] was poured into the dry flask and allowed to stand for 30 min. The flask was emptied and rinsed 10 times with dry, distilled CH_2Cl_2. The flask was then flame-dried and allowed to cool to room temperature under an argon atmosphere. Triene **21** (9.0 g, 22 mmol) was freed of any traces of acid by stirring over solid K_2CO_3 as a solution in CH_2Cl_2 (100 mL) for at least 30 min. The solution was then filtered and concentrated in vacuo, and 2.4 g (11 mmol) of BHT was added to the resulting oil. The oily mixture was then dried azeotropically by dissolution in 5 mL of dry benzene followed by concentration in vacuo, and the process was repeated two more times. The resulting oil was dissolved in 500 mL of freshly distilled xylenes (distilled from sodium benzophenone ketyl) and transferred via cannula under Ar to the previously prepared reaction flask. The solution was diluted with additional distilled xylenes to a total volume of ∼900 mL, and ca. 18 g of solid anhydrous $NaHCO_3$ was added. The flask was equipped with a reflux condenser and placed in a preheated 155 °C oil bath, where the mixture was kept at reflux under Ar for 114 h. At this time, TLC analysis of the reaction mixture (25% Et_2O in hexanes) indicated the complete consumption of triene **21**. The solution was allowed to cool to room temperature and then filtered through a pad of Celite to remove the solid $NaHCO_3$. The xylenes were removed by distillation at a reduced pressure (∼20 Torr) to afford a pale yellow liquid. Further concentration in vacuo afforded 12.6 g of a yellow oil as the crude product mixture containing the two cycloadducts *cis*-**23** and a *trans* diastereomer **22** in a ∼5:1 ratio as determined by ^{1}H NMR analysis. The product mixture was purified by flash chromatography on silica gel with elution by 25% Et_2O in hexanes to afford 4.8 g (53%) of the desired *cis* adduct **23** as a pale yellow oil having $[\alpha]^{25}_D$ +71.3° (*c* 3.70, CH_2Cl_2): IR (film) 2978, 1726, 1426, 1367, 1158, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (m, 1 H), 5.68 (br d, $J = 10.3$ Hz, 1 H), 5.14 (sept, $J = 6.3$ Hz, 1 H), 4.96 (t, $J = 5.2$ Hz, 1 H), 4.00 (d, $J = 11.8$ Hz, 1 H), 3.86 (dd, $J_1 = 11.8$ Hz, $J_2 = 2.7$ Hz, 1 H), 3.23 (m, 2 H), 2.98 (m, 1 H), 2.64 (m, 2 H), 1.98 (dd, $J_1 = 14.0$ Hz, $J_2 = 7.8$ Hz, 1 H), 1.47 (s, 9 H), 1.30 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.3, 127.4, 126.0, 97.3, 80.4, 76.4, 69.2, 68.4, 37.8, 34.7, 33.0, 31.2, 28.0, 21.7, 21.6. HRMS (CI). Calcd for $C_{18}H_{31}BrNO_6$ [M + NH_4^+]: *m*/*z* 436.1335. Found: *m*/*z* 436.1352. In addition to **22**, 1.1 g (12%) of the *trans* cycloadduct above was obtained during the course of chromatographic purification but was not fully characterized.[19c]

(+)-*tert*-Butyl-2α-Bromomethyl-8a*β*-isopropoxycarbonyl-(5,6)-*β*-epoxy-4a*β*,5,6,7,8,8a-hexahydro-4*H*-1,3-benzodioxin-7α-carboxylate. Successively as single portions, 4.4 g (32 mmol) of solid $NaH_2PO_4 \cdot H_2O$ and 8.3 g of solid 50 wt % *m*CPBA (24 mmol of contained peracid) were added to a vigorously stirred solution of 6.7 g (16 mmol) of cycloadduct **23** in 125 mL of CH_2Cl_2 at 0 °C. The cold bath was removed, and the resulting cloudy reaction mixture was allowed to warm to ambient temperature and was stirred for 21 h. The cloudy reaction mixture was cooled to 0 °C and 50 mL of 10% aqueous sodium sulfite was slowly added over 3 min. The mixture was allowed to warm to ambient temperature, whereupon the phases were separated, and the aqueous phase was extracted with three 50 mL portions of CH_2Cl_2. The combined organic phases were successively washed with two 50 mL portions of 10% aqueous K_2CO_3 solution and 50 mL of brine. The organic phase was dried over K_2CO_3, filtered, and concentrated in vacuo to afford 7.7 g of the crude, but clean, title epoxide as a pale yellow oil which was used in subsequent transformations without further purification. An analytical sample of the *β*-epoxide was obtained by flash chromatography on silica gel with elution by 35% Et_2O in hexanes to yield pure *β*-epoxide as a colorless oil having $[\alpha]^{25}_D$ +29.4° (*c* 3.70, CH_2Cl_2): IR (film) 2977, 1726, 1242, 1141 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (sept, $J = 6.3$ Hz, 1 H), 4.93 (t, $J = 5.1$ Hz, 1 H), 4.15 (d, $J = 12.2$ Hz, 1 H), 3.84 (dd, $J_1 = 12.3$ Hz, $J_2 = 2.1$ Hz, 1 H), 3.74 (d, $J = 3.6$ Hz, 1 H), 3.30 (d, $J = 3.8$ Hz, 1 H), 3.24 (d, $J = 5.1$ Hz, 2 H), 2.96 (d, $J = 7.3$ Hz, 1 H), 2.36 (br s, 1 H), 2.30 (d, $J = 14.3$ Hz, 1 H), 1.86 (dd, $J_1 = 14.3$ Hz, $J_2 = 7.3$ Hz, 1 H), 1.48 (s, 9 H), 1.27 (d, $J = 6.3$ Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.7, 97.5, 80.9, 75.2, 69.4, 68.2, 54.5, 52.0, 37.1, 34.2, 30.9, 29.7, 28.0, 21.6. HRMS (CI). Calcd for $C_{18}H_{31}BrNO_7$ [M + NH_4^+]: *m*/*z* 452.1284. Found: *m*/*z* 452.1275.

(+)-*tert*-Butyl-2α-bromomethyl-8a*β*-isopropoxycarbonyl-5*β*-hydroxy-4a*β*,7,8a-tetrahydro-4*H*-1,3-benzodioxin-7-carboxylate (24). A stirred solution of 7.7 g (∼16 mmol) of crude epoxide prepared as above in 150 mL of anhydrous THF under Ar was treated with 3.6 mL (24 mmol) of DBU at room temperature, and stirring was continued at room temperature for 20 h. The reaction mixture was diluted with 200 mL of Et_2O and washed with three 50 mL portions of 1 N aqueous HCl. The combined aqueous washes were then extracted with two 50 mL portions of Et_2O, and the combined organic phases were successively washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of brine. The resulting organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 7.6 g of crude products as a clear colorless oil. Purification by flash chromatography on silica gel with elution by 70% Et_2O in hexanes provided 5.9 g (84%) of hydroxy diester **24** as a clear colorless oil having $[\alpha]^{25}_D$ + 24.2° (*c* 2.40, CH_2Cl_2): IR (film) 3498, 2980, 1708, 1666, 1369, 1249 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (s, 1 H), 5.16 (sept, $J = 6.3$ Hz, 1 H), 4.95 (t, $J = 5.0$

Hz, 1 H), 4.86 (m, 1 H), 4.31 (d, J = 11.6 Hz, 1 H), 3.84 (d, J = 11.6 Hz, 1 H), 3.36 (m, 2 H), 2.58 (s, 2 H), 2.43 (d, J = 7.2 Hz, 1 H), 2.08 (d, J = 9.3 Hz, 1 H), 1.49 (s, 9 H), 1.32 (d, J = 6.3 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 165.1, 138.4, 127.5, 96.8, 81.1, 78.9, 69.7, 64.8, 39.9, 34.7, 31.8, 28.0, 21.62, 21.59. HRMS (CI). Calcd for $C_{18}H_{31}BrNO_7$ [M + NH_4^+]: m/z 452.1284. Found: m/z 452.1289.

(+)-2α-Bromomethyl-8a*β*-isopropoxycarbonyl-5*β*-hydroxy-4a*β*,7,-8a-tetrahydro-4*H*-1,3-benzodioxin-7-carboxylic acid (25). Hydroxy diester **24** (4.4 g, 10 mmol) was dissolved in 40 mL of anhydrous TFA at room temperature under Ar, and the solution was allowed to stir for 30 min. The reaction mixture was concentrated in vacuo, and the resulting oil was dissolved in 30 mL of benzene and reconcentrated in vacuo. The process was repeated two more times with additional 30 mL portions of benzene to afford 3.8 g (100%) of the pure acid **25** as a white solid having mp 68−70 °C and $[\alpha]^{25}_D$ +14.2° (c 4.70, CH_2Cl_2): IR (film) 3854−2878, 2982, 1698, 1662, 1466, 1250, 1104 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 1 H), 5.17 (sept, J = 6.3 Hz, 1H), 4.98 (t, J = 3.9 Hz, 1 H), 4.92 (m, 1 H), 4.32 (d, J = 11.5 Hz, 1 H), 3.86 (d, J = 11.5 Hz, 1H), 3.38 (m, 2 H), 2.62 (m, 2 H), 2.12 (d, J = 9.3 Hz, 1 H), 1.33 (d, J = 6.3 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.8, 142.1, 125.5, 96.7, 78.7, 70.0, 64.9, 64.8, 39.7, 34.3, 31.9, 21.63, 21.59. HRMS (CI). Calcd for $C_{14}H_{23}BrNO_7$ [M + NH_4^+]: m/z 396.0658. Found: m/z 396.0649.

(+)-Isopropyl-2α-Bromomethyl-5*β*-hydroxy-7-hydroxymethyl-4a*β*,5,8,8a-tetrahydro-4*H*-1,3-benzodioxin-8a*β*-carboxylate. A solution of 3.96 g (10 mmol) of **25** and 1.7 mL (12 mmol) of Et_3N in 30 mL of CH_2Cl_2 was added dropwise via cannula to a solution of 1.0 mL (11 mmol) of ethyl chloroformate in 20 mL of CH_2Cl_2 at 0 °C. The resulting cloudy-white reaction mixture was allowed to stir at 0 °C for 30 min and then was filtered through a pad of Celite to remove the solids which had formed. The Celite pad was washed with an additional 10 mL of THF, and the resulting clear, pale yellow filtrate was added dropwise via cannula to a slurry of 0.76 g (20 mmol) of $NaBH_4$ in 25 mL of THF and 3.9 mL of MeOH at −40 °C. The resulting mixture was allowed to stir at −40 °C for 30 min and then was allowed to warm to 0 °C and was stirred for an additional 40 min. At this time, the reaction mixture was quenched at 0 °C by the successive addition of 10 mL of 5% aqueous NaOH, 10 mL of brine, and 50 mL of Et_2O. The resulting mixture was allowed to warm to ambient temperature and was stirred vigorously for 45 min. The phases were separated, and the aqueous phase was extracted with three 30 mL portions of Et_2O. All of the organic phases were combined and washed with 20 mL of brine, dried over $MgSO_4$, and concentrated in vacuo to afford 3.5 g (~100%) of the crude title diol as a clear, colorless oil which was used without further purification. An analytical sample was obtained by flash chromatography on silica gel with elution by 80% EtOAc in hexanes to afford pure title diol as a clear, colorless oil having $[\alpha]^{25}_D$ +29.7° (c 3.60, CH_2Cl_2): IR (film) 3351, 2981, 1727, 1466, 1255, 1130 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (s, 1 H), 5.15 (sept, J = 6.3 Hz, 1 H), 4.91 (t, J = 4.0 Hz, 1 H), 4.70 (br s, 1 H), 4.28 (d, J = 11.9 Hz, 1 H), 4.02 (m, 2 H), 3.82 (d, J = 11.7 Hz, 1 H), 3.37 (m, 2 H), 3.28 (br s, 1 H), 2.96 (br s, 1 H), 2.43 (d, J = 18.4 Hz, 1 H), 2.24 (d, J = 18.4 Hz, 1 H), 2.04 (d, J = 8.8 Hz, 1 H), 1.32 (d, J = 6.1 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 134.1, 124.1, 96.9, 79.3, 69.6, 65.3, 65.2, 64.8, 40.4, 35.8, 31.9, 21.6. HRMS (CI). Calcd for $C_{14}H_{23}NO_5Br$ [M + NH_4 − H_2O]$^+$: m/z 364.0760. Found: m/z 364.0751.

(+)-Isopropyl-2α-Bromomethyl-7-(*tert*-butyldiphenylsilyloxymethyl)-5*β*-hydroxy-4a*β*,5,8,8a-tetrahydro-4*H*-1,3-benzodioxin-8a*β*-carboxylate (26). To a solution of 3.5 g (~10 mmol) of crude diol, as obtained immediately above, in 50 mL of CH_2Cl_2 at 0 °C was successively treated 0.12 g (0.96 mmol) of DMAP, 2.0 mL (14 mmol) of Et_3N, and 2.8 mL (11 mmol) of *tert*-butyldiphenylchlorosilane. The resulting mixture was allowed to slowly warm to room temperature and was stirred for 17 h. At this time, the reaction mixture was partitioned between 15 mL of water and 50 mL of Et_2O, and the phases were separated. The aqueous phase was extracted with three 30 mL portions of Et_2O, and the combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, and concentrated in vacuo to provide 6.0 g of crude products as a yellow oil. Purification by flash chromatography on silica gel with elution by 50% Et_2O in hexanes gave 4.0 g (70% overall yield from **25**) of pure alcohol **26** as a pale yellow oil having $[\alpha]^{25}_D$ +9.93° (c 2.90, CH_2Cl_2): IR (film) 3439, 2931, 2857, 1730, 1589, 1428, 1106 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 7.3 Hz, 4 H), 7.44−7.39 (m, 6 H), 5.79 (s, 1 H), 5.18 (sept, J = 6.2 Hz, 1 H), 4.97 (t, J = 4.1 Hz, 1 H), 4.71 (m, 1 H), 4.33 (d, J = 11.7 Hz, 1 H), 4.11 (s, 2 H), 3.84 (d, J = 11.5 Hz, 1 H), 3.39 (m, 2 H), 2.44 (d, J = 18.4 Hz, 1 H), 2.22 (d, J = 18.4 Hz, 1 H), 2.05−1.99 (m, 2 H), 1.32 (d, J = 6.2 Hz, 6 H), 1.10 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 135.6, 133.6, 133.5, 133.3, 129.7, 127.7, 123.6, 96.9, 79.2, 69.3, 66.3, 65.2, 65.0, 40.8, 35.9, 31.9, 26.8, 21.6, 19.2. HRMS (CI). Calcd for $C_{30}H_{43}BrNO_6Si$ [M + NH_4^+]: m/z 620.2043. Found: m/z 620.2048.

(+)-Isopropyl-2α-bromomethyl-7-(*tert*-butyldiphenylsilyloxymethyl)-5*β*-methoxymethoxy-4a*β*,5,8,8a-tetrahydro-4*H*-1,3-benzodioxin-8a*β*-carboxylate. Freshly distilled MOMCl (2.5 mL, 33 mmol) was added dropwise to a solution of 4.0 g (6.6 mmol) of alcohol **26**, 23 mL (133 mmol) of diisopropylethylamine, and 0.1 g (0.66 mmol) of DMAP in 15 mL of CH_2Cl_2 at room temperature. The resulting mixture was warmed to 40 °C for 6 h, whereupon an additional 2.5 mL (33 mmol) of MOMCl was introduced, and the mixture was allowed to stir for an additional 6 h at 40 °C. The reaction mixture was allowed to cool to room temperature and stirred overnight (14 h) then quenched by addition of 10 mL of water and 20 mL of Et_2O. The mixture was allowed to stir vigorously for 1 h, then the phases were separated and the organic phase was diluted with an additional 75 mL portion of Et_2O. After washing the organic phase with three 25 mL portions of 1 N HCL, the aqueous washes were combined and back-extracted with three 50 mL portions of Et_2O. The combined organic phases were washed with 25 mL of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide 6.0 g of crude products as a reddish−yellow oil. Purification by flash chromatography on silica gel with elution by 30% Et_2O in hexanes afforded 3.6 g (84%) of the pure titled MOM ether as a pale yellow oil having $[\alpha]^{25}_D$ +23.5° (c 1.70, CH_2Cl_2): IR (film) 2923, 2849, 1732, 1423, 1236, 1104 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 6.6 Hz, 4 H), 7.45−7.38 (m, 6 H), 5.97 (s, 1 H), 5.16 (sept, J = 6.2 Hz, 1 H), 4.97 (t, J = 4.2 Hz, 1 H), 4.84 (s, 2 H), 4.64 (m, 1 H), 4.21 (d, J = 11.8 Hz, 1 H), 4.08 (s, 2 H), 3.82 (d, J = 11.8 Hz, 1 H), 3.45 (s, 3 H), 3.38 (m, 2 H), 2.40 (d, J = 18.3 Hz, 1 H), 2.23−2.15 (m, 2 H), 1.30 (d, J = 6.2 Hz, 6 H), 1.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 135.3, 133.5, 129.4, 127.4, 120.9, 96.9, 96.8, 79.0, 72.3, 69.1, 65.9, 65.1, 55.4, 38.7, 35.4, 31.6, 26.5, 21.4, 21.3, 19.0. HRMS (CI). Calcd for $C_{32}H_{47}BrNO_7Si$ [M + NH_4^+]: m/z 664.2305. Found: m/z 664.2276.

(+)-Isopropyl-3-(*tert*-butyldiphenylsilyloxymethyl)-6α-ethenyloxymethoxy-1α-hydroxy-5*β*-methoxymethoxy-3-cyclohexene-1-carboxylate (5). Zinc−silver couple was freshly prepared using a modification of the Heathcock procedure.[27] Accordingly, 25 g of powdered zinc metal was activated by stirring in 100 mL of 10% aqueous HCl for 4 min. The aqueous HCl was decanted, and the freshly activated zinc was successively washed with two 100 mL portions of acetone and 100 mL of Et_2O. After the Et_2O wash was decanted, a suspension of 0.83 g of silver(I) acetate in 20 mL of refluxing acetic acid was added to the zinc metal and the resulting mixture was allowed to stir for 1 min. The acetic acid was decanted, and the resulting black Zn−Ag couple was successively washed with 60 mL of acetic acid, four 100 mL portions of Et_2O, and four 100 mL portions of reagent-grade methanol. At this time, 2.0 g of solid $NaHCO_3$ was added to the couple, and the mixture was washed with four additional 100 mL portions of methanol. After decanting the final methanol wash, the moist Zn−Ag couple was transferred to a solution of 3.0 g (4.6 mmol) of the MOM ether, prepared as immediately above, containing 2.0 g of

solid $NaHCO_3$ in 40 mL of methanol at room temperature. The resulting mixture was heated to a gentle reflux in a 70 °C oil bath for 18 h then allowed to cool to room temperature. The reaction mixture was diluted with 200 mL of Et_2O, filtered through a pad of Celite, and the resulting filtrate was concentrated in vacuo to give a white semisolid. The crude material was dissolved in 250 mL of Et_2O, dried over $MgSO_4$, and refiltered through a pad of Celite to remove the solids. Concentration of the resulting filtrate in vacuo then provided 2.5 g of crude material as a clear, colorless oil. Rapid flash chromatography on silica gel with elution by 30% Et_2O in hexanes afforded 2.4 g (92%) of pure **5** as a clear, colorless oil having $[\alpha]^{25}_D$ +33.5° (*c* 2.50, CH_2Cl_2): IR (film) 3499, 3071, 2932, 1726, 1620, 1471, 1242 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.73 (m, 4 H), 7.17 (m, 6 H), 6.24 (dd, $J_1 = 14.3$ Hz, $J_2 = 6.8$ Hz, 1 H), 6.13 (s, 1 H), 4.94 (sept, $J = 6.2$ Hz, 1 H), 4.56 (d, $J = 6.9$ Hz, 1 H), 4.46 (d, $J = 6.9$ Hz, 1 H), 4.29 (m, 1 H), 4.19 (dd, $J_1 = 14.2$ Hz, $J_2 = 1.6$ Hz, 1 H), 3.95 (m, 5 H), 3.77 (s, 1 H), 3.17 (s, 3 H), 2.62 (m, 2 H), 1.90 (d, $J = 17.3$ Hz, 1 H), 1.12 (s, 9 H), 1.01 (d, $J = 6.3$ Hz, 3 H), 0.97 (d, $J = 6.3$ Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 175.5, 151.7, 136.0, 135.6, 134.0, 130.1, 127.4, 121.5, 96.6, 87.1, 75.0, 74.1, 69.8, 66.9, 65.9, 55.5, 45.7, 37.2, 27.1, 21.8, 21.5, 19.6. HRMS (FAB^+). Calcd for $C_{32}H_{44}BrNaO_7Si$ [M + Na^+]: *m*/*z* 591.2754. Found: *m*/*z* 591.2776.

(1*S*,4*R*)-2-[(2*S*,4*E*)-6-*p*-Methoxyphenylmethoxy-2-methylhex-4-enoyl]-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (29).[28] To a room temperature solution of 56 g (0.22 mol) of (*E*)-1-bromo-4-methoxyphenylmethoxy-2-butene[44] (see Supporting Information) in 225 mL of dry acetonitrile under inert atmosphere was added 39 g (0.29 mol) of anhydrous K_2CO_3, followed by 36 g (0.24 mol) of anhydrous NaI. The yellow slurry was stirred at room temperature under argon for 20 min, diluted with 250 mL of water and 250 mL of ether, washed with 250 mL of 10% aqueous sodium thiosulfate, 200 mL of brine, dried over $MgSO_4$, and concentrated in vacuo to give 61 g (93%) of (*E*)-1-iodo-4-*p*-methoxyphenylmethoxy-2-butene (**28**)[44] as an oil, which was stored in the dark for 2 h prior to use (*note: without addition of stabilizers, iodide **28** is completely decomposed after 24 h of storage*): IR (film) 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, $J = 7$, 2 Hz, 2 H), 6.89 (dd, $J = 7$, 2 Hz, 2 H), 5.99−6.02 (m, 1 H), 5.79−5.85 (m, 1 H), 4.45 (s, 2 H), 3.98 (d, $J = 5$ Hz, 2 H), 3.90 (dd, $J = 8$, 1 Hz, 2 H) and 3.82 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.4, 130.0, 129.4, 128.6, 113.8, 71.9, 69.1, 55.3, 4.72; LRMS (API) 318 (M^+).

To a −78 °C solution of 16 mL (0.116 mol) of diisopropylamine in 115 mL of dry THF under Ar was added 97 mL (1.2 M in hexanes, 0.116 mol) of *n*-butyllithium over 10 min. The solution was warmed to 0 °C for 25 min and then transferred by cannula into a 0 °C mixture of 15 g (0.07 mol) of **27**[21] in 150 mL of anhydrous THF over 25 min, such that the internal temperature did not exceed 10 °C. After stirring an additional 15 min, the solution was transferred by cannula into 60.8 g (0.19 mol) of neat **28** at room temperature over 45 min, such that the internal temperature did not exceed 30 °C. After 3.5 h, 250 mL of saturated aqueous NH_4Cl was added, the aqueous phase was acidified to pH = 7 with 50 mL of 10% aqueous HCl, and the mixture was extracted four times with 125 mL portions of ether. The combined ethereal extracts were washed successively with 100 mL of 10% aqueous HCl and 100 mL of brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography on silica gel (with elution by 10% EtOAc in hexanes, v/v) provided 19.9 g (70%) of **29** as a colorless oil: IR (film) 1741, 1694, 1613, 973 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, $J = 9$ Hz, 2 H), 6.88 (dd, $J_1 = 7$ Hz, $J_2 = 2$ Hz, 2 H), 5.66−5.62 (m, 2 H), 4.42 (s, 3 H), 3.93 (d, $J = 4$ Hz, 2 H), 3.68 (dd, $J_1 = 13$ Hz, $J_2 = 7$ Hz, 1 H), 2.45−2.39 (m, 1 H), 2.36 (d, $J = 4$ Hz, 1 H), 2.26−2.18 (m, 1 H), 2.08−1.96 (m, 2 H), 1.44 (s, 3 H) 1.08 (d, $J = 7$ Hz, 3 H), 1.00 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 177.9, 159.1, 130.8, 130.4, 129.3, 128.9, 128.2, 113.7, 73.0, 71.5, 70.2, 55.3, 55.2, 47.3, 40.5, 37.2, 31.9, 23.7, 23.6, 18.6, 17.6, 15.1, 13.4. Anal. Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.32. Found: C, 71.80; H, 8.37.

(2*S*,3*S*,5*S*)-1-(Benzyloxy)-6-(*tert*-butyldiphenylsilyloxy)-3,5-dimethyl-2-hexanol (32).[4] A solution of 1.3 g (2.8 mmol) of epoxide **31** at −30 °C was treated successively with 3.1 mL (6.2 mmol) of a 2.0 M solution of Me_3Al in hexanes and 2.0 mL (3.1 mmol) of a 1.54 M solution of *n*-BuLi in hexanes giving a white heterogeneous mixture which was allowed to warm to 0 °C and stirred for 3 h. The reaction mixture was quenched at 0 °C by careful dropwise addition of 10 mL of 1 M aqueous HCl causing vigorous gas evolution. After the addition was complete, the mixture was allowed to warm to room temperature, 30 mL of additional 1 M aqueous HCl was added, and the layers were separated. The aqueous portion was extracted with three 30 mL portions of Et_2O, and the combined organic extracts were washed with 10 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to provide 1.37 g of a pale yellow oil as the crude product mixture. Purification by flash chromatography on silica gel (30% Et_2O in hexanes) afforded 1.06 g (78%) of diastereomerically pure alcohol **32** as a pale yellow oil: IR (film) 3400, 2979, 1694, 1620, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (m, 4 H), 7.42 (m, 11 H), 4.60 (s, 2 H), 3.53 (m, 5 H), 2.32 (br s, 1 H), 1.77 (m, 2 H), 1.30 (m, 2 H), 1.11 (s, 9 H), 0.92 (d, $J = 6.6$ Hz, 3 H), 0.89 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 129.2, 128.2, 127.5, 127.4, 127.3, 74.4, 73.1, 72.2, 69.5, 35.5, 33.1, 32.9, 26.6, 19.0, 15.9, 14.8; MS (EI) *m*/*z* 355, 291, 199, 91. HRMS (CI). Calcd for $C_{31}H_{42}O_3Si$ (M^+): *m*/*z* 490.2903. Found: *m*/*z* 490.2921.

(2*E*,4*E*,5*S*,6*E*,9*S*,11*S*)-9-(*tert*-Butyldiphenylsilyloxy)-5-methoxymethoxy-1-(4-methoxyphenylmethoxy)-3,9,11-trimethyldodecatri-2,4,6-ene.[19b] Oxidation to (2*S*,3*S*,5*S*)-6-(*tert*-Butyldiphenylsilyloxy)-3,5-dimethyl-2-methoxymethoxyhexanal. Procedure A: A room temperature solution of 7.0 g (15.7 mmol) of alcohol **33** in 150 mL of CH_2Cl_2 was treated with 10.0 g (23.6 mmol) of solid 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one [Dess−Martin periodinane (DMP)][7] added in one portion. The resulting clear solution was stirred at room temperature for 2.5 h or until TLC showed an absence of the alcohol **33**. The solution was then diluted with 250 mL of ether, and the resulting solids were removed by suction filtration. The filtrate was washed with 100 mL of 5% K_2CO_3 and the organic phase concentrated in vacuo. The resulting residue was redissolved in 150 mL of ether and stirred over solid K_2CO_3. After removal of the solids by suction filtration, concentration of the filtrate in vacuo afforded 6.9 g (99%) of crude (2*S*,3*S*,5*S*)-6-(*tert*-butyldiphenylsilyloxy)-3,5-dimethyl-2-methoxymethoxyhexanal as a clear oil which was used as obtained for the next transformation: IR (film) 2980, 1730, 1460, 1110, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, $J = 2$ Hz, 1 H), 7.64 (m, 4 H), 7.20−7.40 (m, 6 H), 4.69 (m, 1 H), 4.43 (m, 1 H), 3.68 (dd, $J_1 = 6$ Hz, $J_2 = 2$ Hz, 1 H), 3.43 (m, 2 H), 3.38 (s, 3 H), 2.02 (m, 1 H), 1.72 (m, 1 H), 1.39 (m, 1 H), 1.20 (m, 1 H), 1.04 (s, 9 H), 0.95 (d, $J = 7$ Hz, 3 H), 0.85 (d, $J = 7$ Hz, 3 H); MS (EI) 355, 323, 263, 199. **Procedure B:** A magnetically stirred solution of 2.1 mL (3.01 g, 23.7 mmol) of oxalyl chloride, freshly distilled (from CaH_2), in 70 mL of CH_2Cl_2 was cooled to −78 °C and treated with 3.7 mL (4.05 g, 51.8 mmol) of DMSO, freshly distilled (from CaH_2), dropwise via syringe. The resulting solution was stirred at −78 °C for 15 min, at which time a solution of 9.6 g (21.6 mmol) of alcohol **33** in 30 mL of CH_2Cl_2 was added via cannula. After an additional 35 min of stirring at −78 °C, 15.1 mL (10.93 g, 108 mmol) of triethylamine, freshly distilled (from CaH_2), was added dropwise via syringe at −78 °C. After an additional 10 min at −78 °C, the mixture was allowed to warm to room temperature over 30 min. The reaction mixture was then diluted with 200 mL of ether, and the resulting solids were removed by suction filtration. The filtrate was concentrated in vacuo and another 200 mL portion of ether added and the filtration repeated. The resulting filtrate was then washed four times with 50 mL of saturated NaCl solution, dried thoroughly over anhydrous $MgSO_4$, suction filtered, and the filtrate concentrated in vacuo to afford 9.6 g (~100%) of (2*S*,3*S*,5*S*)-6-(*tert*-

(44) Kizil, M.; Murphy, J. A. *Tetrahedron* **1997**, *53*, 16847−16858.

butyldiphenylsilyloxy)-3,5-dimethyl-2-methoxymethoxyhexanal suitable for further use.

Condensation of (2*S*,3*S*,5*S*)-6-(*tert*-Butyldiphenylsilyloxy)-3,5-dimethyl-2-methoxymethoxyhexanal and Phosphine Oxide 34. Phosphine oxide **34** (10.9 g, 26.04 mmol) was dissolved in 120 mL of anhydrous THF, and 20 mL of freshly distilled HMPA (from CaH_2) was cooled to −78 °C. A 16.8 mL portion of a 1.55 M solution of *n*-BuLi in hexanes (26 mmol) was added via syringe dropwise with magnetic stirring to give a deep red solution. After stirring 10 min at −78 °C, a solution of 9.6 g (21.7 mmol) of (2*S*,3*S*,5*S*)-6-(*tert*-butyldiphenylsilyloxy)-3,5-dimethyl-2-methoxymethoxyhexanal, prepared above, in 60 mL of anhydrous THF was added dropwise. After stirring for an additional 10 min at −78 °C, the reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The reaction mixture was quenched with 100 mL of half-saturated $NaHCO_3$, the phases were separated, and the aqueous phase was extracted twice with 100 mL of ether. The combined organic phases were washed twice with 50 mL of saturated NaCl solution dried briefly over anhydrous $MgSO_4$ and concentrated. The residue was dissolved in CH_2Cl_2 and filtered rapidly through a short plug of silica gel, washing twice with 50 mL of CH_2Cl_2. Concentration of the eluates in vacuo afforded 13.0 g (92%) of the title triene as a clear oil: IR (film) 2970, 1500, 1240, 1100, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H), 7.38 (m, 8 H), 6.86 (d, $J = 10$ Hz, 2 H), 6.23 (m, 3 H), 5.67 (t, $J = 7$ Hz, 1 H), 5.52 (m, 1 H), 4.67 (m, 2 H), 4.47 (m, 2 H), 4.42 (s, 2 H), 4.02 (d, $J = 7$ Hz, 2 H), 3.79 (s, 3 H), 3.79 (m, 1 H), 3.44 (m, 2 H), 3.32 (s, 3 H), 1.74 (s, 3 H), 1.74 (m, 2 H), 1.23 (m, 2 H), 1.02 (s, 9 H), 0.88 (d, $J = 7$ Hz, 3 H), 0.83 (d, $J = 7$ Hz, 3 H); MS (Nermag) 656 [M^+]. HRMS (CI). Calcd for $C_{41}H_{57}O_5Si$ [$M + H^+$]: *m*/*z* 657.3975. Found: *m*/*z* 657.3982.

(2*S*,4*S*,5*S*,6*E*,8*E*,10*E*)-12-(4-Methoxybenzyloxy)-5-methoxymethoxy-2,4,10-trimethyldodecatri-6,8,10-en-1-ol (40).[19b] To a solution of 13.0 g (19.8 mmol) of protected triene, prepared as immediately above, in 200 mL of anhydrous THF was added dropwise 60 mL of a 1 M solution of tetrabutylammonium fluoride in THF (15.68 g, 60 mmol). After 3 h, the reaction was quenched with 50 mL of pH ~ 9 aqueous NH_3/NH_4Cl solution, the phases were separated, and the aqueous phase was extracted three times with 100 mL of ether. The combined organic phases were then washed twice with saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacuo in the presence of a crystal of BHT. The residue was purified by flash chromatography on silica gel with by 19:1 EtOAc/hexanes affording 8.24 g (99%) of trienol **40** as a clear oil: IR (film) 3460, 2960, 1610, 1510, 1250, 1040, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, $J = 10$ Hz, 2 H), 6.86 (d, $J = 10$ Hz, 2 H), 6.23 (m, 3 H), 5.64 (t, $J = 7$ Hz, 1 H), 5.53 (m, 1 H), 4.68 (m, 1 H), 4.49 (m, 1 H), 4.43 (s, 2 H), 4.12 (d, $J = 7$ Hz, 2 H), 3.83 (m, 1 H), 3.79 (s, 3 H), 3.44 (m, 2 H), 3.36 (s, 3 H), 2.38 (m, l H), 1.77 (s, 3 H), 1.77 (m, 1 H), 1.43−1.10 (m, 3 H), 0.88 (m, 6 H); MS (EI) 418 [M^+]. HRMS (CI). Calcd for $C_{25}H_{39}O_5$ [$M + H^+$]: *m*/*z* 419.2798. Found: *m*/*z* 419.2775.

(1*E*,3*S*,5*S*,6*S*,7*E*,9*E*,11*E*)-6-[13-(4-[Methoxybenzyloxy])-6-(methoxymethoxy)-1,3,5,11-tetramethyltridecatetra-1,7,9,11-en-1-yl]-2,2-dimethyl-4*H*-1,3-dioxene-4-one (6).[19b] Oxidation to (2*S*,4*S*,5*S*,6*E*,8*E*,-10*E*)-12-(4-Methoxybenzyloxy)-5-methoxymethoxy-2,4,10-trimethyldodecatri-6,8,10-enal. A solution of 1.9 mL (2.77 g, 21.8 mmol) of freshly distilled oxalyl chloride (from CaH_2) in 100 mL of CH_2Cl_2 was cooled to −78 °C, and the resulting magnetically stirred solution was treated with 3.7 mL (4.05 g, 51.8 mmol) of freshly distilled (from CaH_2) DMSO added dropwise via syringe causing gas evolution. The resulting solution was stirred at −78 °C for 15 min at which time a solution of 8.24 g (19.7 mmol) of trienol **40** in 50 mL of CH_2Cl_2 was added via cannula. After an additional 35 min of stirring at −78 °C, 13.7 mL (9.97 g, 98.5 mmol) of triethylamine, freshly distilled (from CaH_2), was added dropwise via syringe at −78 °C. After an additional 10 min at −78 °C, the mixture was allowed to warm to room temperature. The reaction mixture was then diluted with 150 mL of ether, and the resulting solids were removed by suction filtration. The resulting filtrate was then washed successively twice with 100 mL of half saturated NaCl solution, twice with 40 mL of saturated NaCl solution, dried thoroughly over anhydrous $MgSO_4$, suction filtered through a pad of SiO_2, and concentrated in vacuo to afford 8.20 g (~100%) of (2*S*,4*S*,5*S*,6*E*,8*E*,10*E*)-12-(4-methoxybenzyloxy)-5-methoxymethoxy-2,4,10-trimethyldodecatri-6,8,10-enal suitable for further use: IR (film) 2920, 1720, 12.40, 1090, 1030, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, $J = 1$ Hz, 1 H), 7.24 (d, $J = 10$ Hz, 2 H), 6.86 (d, $J = 10$ Hz, 2 H), 6.24 (m, 3 H), 5.67 (t, $J = 7$ Hz, 1 H), 5.52 (dd, $J_1 = 12$ Hz, $J_2 = 8$ Hz, 1 H), 4.68 (m, 1 H), 4.48 (m, 1 H), 4.43 (s, 2 H), 4.14 (d, $J = 7$ Hz, 2 H), 3.84 (dd, $J_1 = 8$ Hz, $J_2 = 7$ Hz, 1 H), 3.79 (s, 3 H), 3.38 (s, 3 H), 2.39 (m, l H), 1.77 (s, 3 H), 1.77 (s, 1 H), 1.54 (m, 2 H), 1.07 (d, $J = 7$ Hz, 3 H), 0.88 (d, $J = 7$ Hz, 3 H).

Condensation of (2*S*,4*S*,5*S*,6*E*,8*E*,10*E*)-12-(4-Methoxybenzyloxy)-5-methoxymethoxy-2,4,10-trimethyldodecatri-6,8,10-enal and Dioxenone Phosphonate 41. To a magnetically stirred solution of 3.6 mL (2.59 g, 25.6 mmol) of diisopropylamine, freshly distilled (from CaH_2), in 10 mL of anhydrous THF at 0 °C was added 16.6 mL of a 1.54 M solution of *n*-BuLi in hexanes (25.6 mmol) via syringe. The resulting clear yellow solution was stirred at 0 °C for 15 min, and then the mixture was cooled to −78 °C. A solution of 7.48 g (25.6 mmol) of phosphonate **41** (see Supporting Information) in 10 mL of anhydrous THF was added at −78 °C slowly via cannula, and the resulting heterogeneous mixture was warmed to 0 °C, affording a clear yellow solution. After the reaction mixture had been recooled to −78 °C, 20 mL of HMPA, freshly distilled from CaH_2, was added via syringe. After an additional 30 min stirring at −78 °C, a solution of 8.20 g (19.7 mmol) of (2*S*,4*S*,5*S*,6*E*,8*E*,10*E*)-12-(4-methoxybenzyloxy)-5-methoxymethoxy-2,4,10-trimethyldodecatri-6,8,10-enal in 30 mL of anhydrous THF was added at −78 °C slowly via cannula. The resulting mixture was allowed to warm slowly to room temperature and was stirred overnight, by which time TLC analysis showed no remaining aldehyde. The reaction mixture was diluted with 200 mL of ether and 200 mL of half saturated NaCl solution with good stirring. After separation of the phases, the aqueous phase was extracted twice with 100 mL of ether. The combined organic phases were washed twice with 100 mL of saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, suction filtered through a pad of SiO_2, and concentrated in vacuo. The residue was purified by flash chromatography with elution by 9:7 (v/v) ether/hexanes to afford 8.52 g (78%) of pentaene **6** as a pale yellow oil: IR (film) 2940, 1730, 1600, 1380, 1250, 1040, 730 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, $J = 10$ Hz, 2 H), 6.84 (d, $J = 10$ Hz, 2 H), 6.23 (m, 3 H), 5.66 (t, $J = 7$ Hz, 1 H), 5.43 (m 1 H), 5.40 (s, 1 H), 4.66 (m, 1 H), 4.44 (m, 1 H), 4.43 (s, 2 H), 4.13 (d, $J = 7$ Hz, 2 H), 3.85 (m, 1 H), 3.79 (s, 3 H), 3.34 (s, 3 H), 2.62 (m, 1 H), 1.82 (s, 3 H), 1.77 (s, 3 H), 1.68 (m, 7 H), 1.50 (m, 1 H), 1.10 (m, 1 H), 0.96 (d, $J = 7$ Hz, 3 H), 0.88 (d, $J = 7$ Hz, 3 H); MS (EI) 450, 313, 173, 121, 45. This material should be used in the subsequent step as soon as practicable. If short-term storage is required, degas thoroughly with nitrogen and store at −78 °C under nitrogen with the addition of a crystal of BHT. HRMS (CI). Calcd for $C_{33}H_{47}O_7$ ($M + H^+$): *m*/*z* 555.3322. Found: *m*/*z* 555. 3212.

(−)-β-Ketoester 43. A pressure tube was base-washed by soaking in concentrated NH_4OH for at least 12 h. The reaction tube was then emptied and successively rinsed with copious amounts of deionized water and reagent-grade acetone, dried in an oven for at least 12 h, and allowed to cool to room temperature under Ar. A solution of 1.5 g (2.7 mmol) of alcohol **5**, 0.77 g (1.4 mmol) of pentaene **6**, and a catalytic amount of BHT (~10 mg) in 50 mL of CH_2Cl_2 was allowed to stir over ~2 g of anhydrous K_2CO_3 for 1 h. The solution was filtered through a pad of Celite and concentrated in vacuo, and the resulting oil was azeotropically dried with three 5 mL portions of anhydrous benzene. The resulting oil was dissolved in 20 mL of freshly distilled xylenes [distilled from sodium benzophenone ketyl], and the solution was transferred via cannula under Ar to the previously prepared pressure

tube. The reaction tube was flushed with Ar and thoroughly degassed using three freeze−thaw cycles under vacuum (∼0.1 Torr). The tube was sealed under vacuum and placed in a preheated 140 °C oil bath for 5 h. Upon cooling to ambient temperature, the xylenes were removed by distillation under reduced pressure to afford 2.3 g of crude material as a pale yellow oil. Purification by flash chromatography on silica gel with gradient elution using 30−60% Et_2O in hexanes provided 0.55 g of recovered alcohol **5** and 0.99 g (69%) of β-ketoester **43** as a clear, colorless oil having $[\alpha]^{25}_D$ −5.41° (*c* 2.20, CH_2Cl_2) that by ^{1}H NMR analysis exists as a 9:1 equilibrium mixture of keto and enol forms. The keto form of **43** has the following spectroscopic characteristics: IR (film) 2932, 1738, 1708, 1614, 1513, 1248, 1105, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4 H), 7.47−7.40 (m, 6 H), 7.24 (d, J = 8.5 Hz, 2 H), 6.84 (d, J = 8.5 Hz, 2 H), 6.42 (dd, J_1 = 14.2 Hz, J_2 = 6.8 Hz, 1 H), 6.03 (d, J = 10.3 Hz, 1 H), 5.85 (s, 1 H), 5.48−5.39 (m, 2 H), 4.95 (sept, J = 6.2 Hz, 1 H), 4.74 (d, J = 6.6 Hz, 1 H), 4.70−4.61 (m, 3 H), 4.36 (m, 2 H), 4.21−3.80 (m, 9 H), 3.79 (s, 3 H), 3.62 (dd, J_1 = 9.9 Hz, J_2 = 5.6 Hz, 1 H), 3.48 (dd, J_1 = 10.9 Hz, J_2 = 5.6 Hz, 1 H), 3.38 (s, 3 H), 3.35 (s, 3 H), 3.35 (m, 2 H), 2.96 (d, J = 18.0 Hz, 1 H), 2.66 (m, 1 H), 2.50 (m, 2 H), 2.30 (m, 1 H), 2.06 (m, 1 H), 1.92 (m, 1 H), 1.50 (m, 2 H), 1.45 (s, 3 H), 1.26 (s, 3 H), 1.23 (d, J = 6.2 Hz, 3 H), 1.19 (d, J = 6.2 Hz, 3 H), 1.08 (s, 9 H), 1.00 (d, J = 7.0 Hz, 3 H), 0.60 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 169.5, 166.2, 159.6, 151.9, 139.1, 138.2, 136.0, 134.03, 133.98, 131.2, 130.1, 129.8, 128.2, 127.3, 126.4, 117.8, 114.2, 95.8, 87.3, 81.4, 81.2, 72.3, 72.2, 69.8, 66.8, 66.4, 65.0, 57.5, 56.2, 56.1, 55.7, 53.4, 47.8, 46.2, 44.5, 41.8, 38.2, 32.3, 32.2, 30.9, 27.3, 23.5, 22.1, 21.9, 19.8, 19.2, 13.8. HRMS (FAB$^-$). Calcd for $C_{62}H_{83}O_{13}Si$ [M − H$^+$]: *m*/*z* 1063.5603. Found: *m*/*z* 1063.5632.

Methyl Spirotetronate 45. Removal of the Vinyl Ether: Preparation of the Hydroxy β-Ketoester. To a solution of 0.375 g (0.353 mmol) of β-ketoester **43** in 20 mL of methanol was added 9 mg (0.035 mmol) of pyridinium *p*-toluenesulfonate, and the mixture was allowed to stir at 40 °C for 14 h. After cooling to ambient temperature, the reaction mixture was concentrated in vacuo, and the resulting residue was dissolved in 25 mL of Et_2O. The cloudy solution was filtered through a plug of silica gel eluting with additional Et_2O, and the clear filtrate was concentrated in vacuo to afford 0.39 g of the crude product mixture as a clear, colorless oil. The crude material was purified by flash chromatography on silica gel with gradient elution using 80−100% Et_2O in hexanes to yield 0.315 g (86%) of pure hydroxy β-ketoester as a white solid having $[\alpha]^{25}_D$ −17.0° (*c* 3.10, CH_2Cl_2). ^{1}H NMR analysis revealed that the hydroxy β-ketoester exists as a ∼9:1 equilibrium mixture of keto and enol forms. The keto form of the primary alcohol had the following spectroscopic characteristics: IR (film) 3478, 2931, 1738, 1710, 1613, 1514, 1248, 1106, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.65 (m, 4 H), 7.45−7.38 (m, 6 H), 7.26 (d, J = 8.5 Hz, 2 H), 6.85 (d, J = 8.5 Hz, 2 H), 6.04 (d, J = 10.3 Hz, 1 H), 5.91 (s, 1 H), 5.51−5.40 (m, 2 H), 5.09 (sept, J = 6.2 Hz, 1 H), 4.78 (d, J = 6.7 Hz, 1 H), 4.78−4.74 (m, 2 H), 4.66 (d, J = 6.6 Hz, 1 H), 4.46−4.37 (m, 3 H), 4.22−3.79 (m, 6 H), 3.79 (s, 3 H), 3.72−3.65 (m, 1 H), 3.55−3.46 (m, 1 H), 3.43 (s, 3 H), 3.41 (s, 3 H), 3.41−3.38 (m, 2 H), 2.90 (d, J = 18.1 Hz, 1 H), 2.66−2.60 (m, 2 H), 2.48 (m, 1 H), 2.30 (m, 1 H), 2.16 (m, 1 H), 2.07 (m, 1 H), 1.94 (m, 1 H), 1.55−1.45 (m, 2 H), 1.50 (s, 3 H), 1.30 (d, J = 6.3 Hz, 3 H), 1.26 (s, 3 H), 1.24 (d, J = 6.3 Hz, 3 H), 1.09 (s, 9 H), 1.02 (d, J = 7.0 Hz, 3 H), 0.62 (d, J = 5.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 169.9, 166.2, 159.6 139.3, 136.8, 136.0, 134.0, 133.9, 131.1, 130.1, 129.8, 128.1, 127.4, 127.2, 126.3, 119.6, 114.2, 96.4, 95.9, 83.3, 81.4, 72.9, 72.2, 70.2, 66.9, 66.4, 60.5, 57.5, 56.2, 56.1, 55.7, 53.5, 48.5, 47.6, 44.6, 41.7, 38.1, 32.3, 31.4, 30.9, 27.3, 23.33, 22.1, 22.0, 19.8, 19.4, 13.8. HRMS (FAB$^-$). Calcd for $C_{60}H_{81}O_{13}Si$ (M − H$^+$): *m*/*z* 1037.5446. Found: *m*/*z* 1037.5424.

Dieckmann Condensation of the Hydroxy β-Ketoester: Preparation of the Spirotetronic Acid. A solution of 0.10 g (96 μmol) of the preceding primary alcohol and 0.2 mL of freshly distilled HMPA (from CaH_2) was prepared in 4 mL of anhydrous THF. After cooling the solution to −78 °C, 0.19 mL of a 0.6 M solution of $NaN(TMS)_2$ in toluene (115 μmol) was added, and the resulting clear, pale yellow reaction mixture was allowed to warm to room temperature and was stirred for 18 h. The reaction mixture was partitioned between 20 mL of Et_2O and 3 mL of 1 N aqueous HCl solution. The phases were separated, and the aqueous phase was extracted with three 5 mL portions of Et_2O. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 0.14 g of the crude product as a pale yellow oil. The crude material was used in the next transformation without further purification. An analytical sample of spirotetronic acid was obtained by further purification by flash chromatography on silica gel with elution by 33% acetone in hexanes to afford a white solid. This material was freed of metal ions by partitioning between 3 mL of CH_2Cl_2 and 3 mL of 1 N HCl. The phases were separated, and the acidic aqueous phase was extracted with two 3 mL portions of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford pure hydroxy spirotetronic acid as a clear, colorless oil: IR (film) 3406, 3072, 2933, 1748, 1614, 1514, 1250, 1113, 1039 cm^{-1}; UV (90% aq MeOH) λ_{max} (ϵ) 230 nm (∼17000), 257 nm (∼10000), 276 nm (9000); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 6.8 Hz, 4 H), 7.45−7.35 (m, 6 H), 7.26 (d, J = 8.9 Hz, 2 H), 6.87 (d, J = 8.9 Hz, 2 H), 6.03 (d, J = 10.2 Hz, 1 H), 5.94 (s, 1 H), 5.44−5.41 (m, 2 H), 4.78 (d, J = 6.7 Hz, 1 H), 4.69 (d, J = 7.0 Hz, 1 H), 4.66 (d, J = 6.7 Hz, 1 H), 4.56 (d, J = 6.9 Hz, 1 H), 4.40 (s, 2 H), 4.10−4.04 (m, 4 H), 3.90−3.80 (m, 1 H), 3.82 (s, 3 H), 3.61−3.55 (m, 2 H), 3.42 (s, 3 H), 3.35 (s, 3 H), 3.27 (d, J = 6.4 Hz, 2 H), 2.64 (d, J = 17.5 Hz, 1 H), 2.42−2.30 (m, 2 H), 2.18 (m, 1 H), 2.08 (m, 1 H), 1.90 (d, J = 17.7 Hz, 1 H), 1.65−1.50 (m, 3 H), 1.57 (s, 3 H), 1.45 (s, 3 H), 1.28 (d, J = 4.3 Hz, 1 H), 1.07 (s, 9 H), 1.05 (m, 3 H), 0.60 (br s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 200.1, 167.5, 159.4, 138.1, 135.4, 133.9, 133.2, 133.1, 130.1, 129.7, 129.0, 127.6, 126.3, 125.8, 125.5, 121.7, 113.7, 100.7, 96.6, 95.2, 83.0, 80.9, 73.4, 73.0, 67.6, 65.8, 58.0, 55.61, 55.59, 52.6, 50.8, 45.6, 43.3, 41.3, 38.0, 35.1, 31.9, 31.1, 26.7, 21.8, 19.2, 15.4, 14.1, 13.5. HRMS (FAB$^+$). Calcd for $C_{57}H_{74}NaO_{12}Si$ (M$^+$ + Na): *m*/*z* 1001.4847. Found: *m*/*z* 1001.4860. Calcd for $C_{57}H_{73}Na_2O_{12}Si$ (M$^+$ − H + 2Na): 1023.4667. Found: 1023.4682.

Methylation of the Spirotetronic Acid: Preparation of Methyl Hydroxy Spirotetronate 45. A solution of 0.14 g (∼96 μmol) of the crude hydroxy spirotetronic acid, prepared as immediately above, in 1.25 mL of benzene and 0.5 mL of methanol was cooled to 0 °C. To this mixture was added dropwise 0.15 mL of a 2.0 M solution of $TMSCHN_2$ in hexanes (300 μmol) with the concomitant evolution of gas. The resulting clear, bright yellow solution was allowed to warm to ambient temperature and was stirred for 30 min. The reaction mixture was concentrated in vacuo to afford the crude material as a yellow oil. Purification by flash chromatography on silica gel with elution by 70% Et_2O in hexanes afforded 0.060 g (62% overall from **43**) of pure methyl hydroxy spirotetronate **45** as a clear, colorless oil: IR (film) 3454, 2932, 1746, 1682, 1613, 1504, 1248, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 5.9 Hz, 4 H), 7.43−7.38 (m, 6 H), 7.24 (d, J = 8.5 Hz, 2 H), 6.88 (d, J = 8.5 Hz, 2 H), 6.04 (d, J = 10.3 Hz, 1 H), 5.91 (s, 1 H), 5.64 (m, 1 H), 5.52 (m, 1 H), 4.78 (d, J = 6.7 Hz, 1 H), 4.72 (d, J = 6.9 Hz, 1 H), 4.66 (d, J = 6.8 Hz, 1 H), 4.62 (d, J = 6.9 Hz, 1 H), 4.41 (dd, J_1 = 17.4 Hz, J_2 = 11.0 Hz, 2 H), 4.25 (s, 3 H), 4.20−4.08 (m, 2 H), 4.06 (s, 2 H), 4.00−3.87 (m, 2 H), 3.82 (s, 3 H), 3.50 (dd, J_1 = 10.9 Hz, J_2 = 5.2 Hz, 1 H), 3.42−3.38 (m, 2 H), 3.42 (s, 3 H), 3.38 (s, 3 H), 3.19 (br s, 1 H), 2.68 (d, J = 17.9 Hz, 1 H), 2.40−2.23 (m, 2 H), 2.17 (m, 1 H), 2.03 (m, 1 H), 1.89 (d, J = 17.9 Hz, 1 H), 1.60−1.50 (m, 3 H), 1.52 (s, 3 H), 1.46 (d, J = 2.8 Hz, 3 H), 1.06 (s, 9 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.55 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 195.2, 184.5, 169.4, 159.5, 138.8, 135.4, 135.0, 133.3, 130.2, 129.6, 129.0, 127.6, 126.4, 126.1, 120.9, 113.8, 99.9, 96.4, 95.3, 86.9, 80.9, 73.9, 73.1, 67.3, 65.9, 65.3, 59.1, 55.6, 55.1, 52.5, 51.2, 46.2, 45.7, 41.1, 37.6, 35.7, 31.8, 30.2, 30.1, 26.7,

20.6, 19.2, 16.7, 15.7, 13.4. HRMS (FAB$^+$). Calcd for $C_{58}H_{76}NaO_{12}Si$ [M + Na$^+$]: *m*/*z* 1015.5004 Found: *m*/*z* 1015.4947.

(−)-Methyl Formyl Spirotetronate 47. A solution of 398 mg of methyl hydroxy spirotetronate **45** (0.40 mmol) in 15 mL of dry CH_2Cl_2 was cooled to 0 °C in an ice bath, and 342 mg (0.81 mmol) of DMP[33] in 10 mL of CH_2Cl_2 was added dropwise over 3 min. The resulting reaction mixture was allowed to warm to room temperature and was stirred for 70 min. The reaction was then quenched by addition of 10 mL of saturated aqueous Na_2CO_3, and the resulting mixture was stirred at room temperature for 20 min. After dilution with 50 mL of ether and 30 mL of water, the phases were separated and the aqueous phase was extracted two times with 30 mL portions of ether. The combined organic phases were washed with 10 mL of saturated NaCl solution, dried over Na_2SO_4, and concentrated to afford the crude products as a yellow oil. Purification of this material by flash chromatography on silica gel with elution by 60% ether in hexanes afforded 364 mg (92%) of the methyl formyl spirotetronate **47** as colorless semisolid having $[\alpha]^{25}_D$ −176.5° (*c* 1.19, CH_2Cl_2). Methyl formyl spirotetronate **47** was found to exist as a mixture of atropisomers: IR (film) 2934, 1727, 1710, 1499, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 9.66 (s, 1 H), 7.64 (d, *J* = 7.2 Hz, 2 H), 7.43−7.36 (m, 6 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 6.0 (m, 2 H), 5.65 (m, 1 H), 5.5 (m, 1 H), 4.7 (m, 4 H), 4.62 (d, *J* = 6.7 Hz, 2 H), 4.4 (d, *J* = 3.3 Hz, 2 H), 4.28 (s, 3 H), 4.1 (m, 3 H), 3.77 (s, 3 H), 3.71 (m, 3 H), 3.48 (m, 1 H), 3.38 (s, 3 H), 3.01 (d, *J* = 10.5 Hz, 1 H), 2.67 (m, 1 H), 2.3 (m, 1 H), 2.18 (m, 1 H), 1.9 (m, 3 H), 1.56 (s, 3 H), 1.50 (m, 5 H), 1.42 (s, 3 H), 1.04 (s, 9 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.49 (d, *J* = 6.1 Hz, 3 H); (minor rotamer) δ 9.73 (s, 1 H), 7.64 (d, *J* = 7.2 Hz, 2 H), 7.43−7.36 (m, 6 H), 7. 02 (d, *J* = 8.0 Hz, 2 H), 6.73 (d, *J* = 8.0 Hz, 2 H), 6.0 (m, 2 H), 5.65 (m, 1 H), 5.5 (m, 1 H), 5.3 (m, 1 H), 4.7 (m, 4 H), 4.62 (d, *J* = 6.7 Hz, 2 H), 4.4 (d, *J* = 3.3 Hz, 2 H), 4.28 (s, 3 H), 4.0 (m, 3 H), 3.77 (s, 3 H), 3.71 (m, 3 H), 3.48 (m, 1 H), 3.38 (s, 3 H), 2.67 (m, 1 H), 2.3 (m, 1 H), 2.18 (m, 1 H), 1.9 (m, 3 H), 1.56 (s, 3 H), 1.50 (m, 5 H), 1.42 (s, 3 H), 1.04 (s, 9 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.72 (d, *J* = 6.0 Hz, 3 H); both rotamers, ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 200.1, 199.4, 168.6, 159.0, 139.2, 135.8, 135.5, 135.4, 133.1, 130.5, 129.7, 129.1, 127.7, 127.2, 126.6, 120.3, 113.6, 99.5, 96.2, 95.3, 95.2, 85.2, 80.8, 72.2, 71.8, 66.6, 66.0, 65.7, 55.8, 55.6, 55.1, 52.4, 41.2, 37.8, 36.4, 34.6, 31.8, 31.5, 30.1, 26.7, 22.6, 20.7, 20.6, 19.2, 16.9, 14.1, 13.4. HRMS (FAB$^+$). Calcd for $C_{58}H_{74}NaO_{12}Si$ [M + Na$^+$]: *m*/*z* 1013.4847 Found: *m*/*z* 1013.4839. The structure and stereochemistry of the methyl formyl spirotetronate **47** was further secured by reduction of that material back to methyl hydroxy spirotetronate **45** with $NaBH_4$ in methanol.

(−)-(*E*)-α,*β*-Unsaturated Aldehyde 48. A solution of 260 mg (1.58 mmol) of (*Z*)-1-ethoxy-2-bromo-1-propene[15] in 3 mL of anhydrous THF was cooled to −78 °C, and 1.6 mL of *tert*-BuLi in hexanes (1.7 M, 2.72 mmol) was added dropwise over 3 min. The resulting solution was stirred at −78 °C for 30 min, and 60 mg (0.32 mmol) of $MgBr_2$ in 20 mL of dry ether was added by cannula transfer at −78 °C over 5 min. After stirring the resulting mixture at −78 °C for 20 min, a solution of 278 mg (281 μmol) of aldehyde **47** (dried azeotropically by repeated dissolution in anhydrous benzene and evaporation under reduced pressure) in 10 mL of ether was then transferred by cannula into the solution of the vinyl Grignard reagent at −78 °C, and the resulting mixture was stirred at −78 °C for 10 min, then warmed to −20 °C over 30 min. At −20 °C, the reaction was quenched with a mixture of 2 mL of saturated aqueous $NaHCO_3$ solution and 10 mL of saturated NaCl solution. The phases were separated, and the aqueous phase was extracted two times with 25 mL portions of ether. The combined organic phases were washed with 20 mL of brine, dried over Na_2SO_4, and concentrated in vacuo to afford a light yellow oil. This crude material was dissolved in 50 mL of CH_2Cl_2, and 0.5 mL (3.5 mmol) of trifluoroacetic anhydride was added at 0 °C, followed by 0.5 mL (6.5 mmol) of trifluoroacetic acid. The resulting solution was stirred at 0 °C for 15 min, then 10 mL of aqueous saturated Na_2CO_3 solution was cautiously added, and the phases were separated. The aqueous phase was extracted two times with 15 mL portions of CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with elution by 67% ether in hexanes to afford 245 mg (85%) of unsaturated aldehyde **48** as a colorless semisolid having $[\alpha]^{25}_D$ −125.0° (*c* 0.37, $CHCl_3$). Unsaturated aldehyde **48** also exists as a mixture of atropisomers: IR (film) 2934, 1745, 1718 cm^{-1}; both rotamers, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38, 9.32 (s, 1 H), 7.64 (m, 4 H), 7.30 (m, 6 H), 7.23, 7.04 (d, *J* = 8.3−8.22 Hz, 2 H), 6.85, 6.73 (d, *J* = 8.3−8.2 Hz, 2 H), 6.39 (d, *J* = 10.5 Hz, 1 H), 5.9 (m, 2 H), 5.5, 5.2 (m, 1 H), 4.71 (d, *J* = 6.7 Hz, 1 H), 4.59 (m, 2 H), 4.45 (m, 2 H), 4.43 (s, 3 H), 4.15 (m, 4 H), 4.03 (s, 3 H), 3.90 (s, 3 H), 3.71 (s, 3 H), 3.38 (s, 6 H), 3.24, 3.23 (s, 3 H), 2.75 (m, 1 H), 2.2 (m, 2 H), 1.9 (m, 2 H), 1.78, 1.73 (s, 3 H), 1.5 (m, 6 H), 1.04 (s, 9 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 0.52, 0.42 (d, *J* = 5.9−4 Hz, 3 H); both rotamers, ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 210.3, 195.5, 194.9, 192.7, 168.6, 167.1, 159.2, 148.8, 148.4, 138.7, 135.5, 135.1, 133.2, 129.8, 129.6, 127.7, 126.3, 121.3, 113.7, 96.0, 95.3, 88.2, 80.6, 75.1, 72.3, 66.4, 66.2, 65.9, 65.8, 55.7, 55.5, 55.2, 53.0, 45.9, 44.7, 41.1, 37.8, 37.7, 31.8, 30.3, 29.7, 26.8, 20.8, 19.2, 16.8, 13.4, 9.8. HRMS (FAB$^+$). Calcd for $C_{61}H_{78}NaO_{12}Si$ [M + Na$^+$]: *m*/*z* 1053.5160 Found: *m*/*z* 1053.5154.

(−)-Allylic Chloride 50. To a solution of 120 mg (0.12 mmol) of PMB ether aldehyde **48** in 10 mL of CH_2Cl_2 was added 1 mL of water, followed by a solution of 0.55 g (2.4 mmol) of DDQ in 20 mL of CH_2Cl_2. After stirring at ambient temperature for 1 h, the reaction mixture was quenched with 20 mL of aqueous half-saturated $NaHCO_3$, the phases were separated, and the aqueous phase was extracted three times with 7 mL portions of CH_2Cl_2. The combined organic phases were washed with 5 mL of saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo to give the crude alcohol as a light yellow oil which was used without purification below.

To a solution of the above crude alcohol and 86 mg (0.326 mmol) of hexachloroacetone in 15 mL of anhydrous CH_2Cl_2 was added dropwise a solution of 86 mg (0.326 mmol) of triphenylphosphine in 5 mL of CH_2Cl_2 over 2 min at −40 °C. After warming the resulting mixture to and stirring at −25 °C for 15 min, the reaction was quenched with 10 mL of aqueous half-saturated $NaHCO_3$ solution, the phases were separated, and the aqueous phase was extracted with 10 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude chloride **50** was further purified by flash chromatography on silica gel with CH_2Cl_2 as initial eluent to remove nonpolar material and then 60% ether in hexanes to provide 84 mg of the pure allylic chloride **50** (75% yield) as a colorless oil having $[\alpha]^{25}_D$ −135.0° (*c* 0.62, CH_2Cl_2). Chloride **50** also exists as a mixture of atropisomers: IR (CH_2Cl_2) 3053, 2933, 1682, 1493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 9.38 (s, 1 H), 7.65 (m, 4 H), 7.39 (m, 6 H), 6.51 (d, *J* = 9.8 Hz, 1 H), 6.01 (d, *J* = 8.9 Hz, 1 H), 5.88 (s, 1 H), 5.70 (t, *J* = 8.2 Hz, 1 H), 5.4 (m, 2 H), 4.72 (d, *J* = 6.7 Hz, 1 H), 4.64 (d, *J* = 7.0 Hz, 1 H), 4.60 (d, *J* = 7.0 Hz, 1 H), 4.52 (d, *J* = 6.7 Hz, 1 H), 4.50 (m, 2 H), 4.26 (s, 3 H), 4.08 (s, 3 H), 3.8 (m, 3 H), 3.50 (m, 1 H), 3.36 (s, 3 H), 3.23 (s, 3 H), 2.80 (m, 1 H), 2.30 (m, 1 H), 2.00 (m, 2 H), 1.78 (s, 3 H), 1.74 (s, 3 H), 1.56 (s, 1 H), 1.55 (s, 1 H), 1.13 (s, 3 H), 1.03 (s, 9 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 0.55 (d, *J* = 5.9 Hz, 3 H); (minor rotamer) δ 9.38 (s, 1 H), 7.65 (m, 4 H), 7.39 (m, 6 H), 6.52 (d, *J* = 9.6 Hz, 1 H), 6.01 (d, *J* = 8.9 Hz, 1 H), 5.88 (s, 1 H), 5.70 (t, *J* = 8.2 Hz, 1 H), 5.4 (m, 2 H), 4.72 (d, *J* = 6.7 Hz, 1 H), 4.64 (d, *J* = 7.0 Hz, 1 H), 4.60 (d, *J* = 7.0 Hz, 1 H), 4.52 (d, *J* = 6.7 Hz, 1 H), 4.50 (m, 2 H), 4.26 (s, 3 H), 4.08 (s, 3 H), 3.8 (m, 3 H), 3.50 (m, 1 H), 3.36 (s, 3 H), 3.23 (s, 3 H), 2.8 (m, 1 H), 2.3 (m, 1 H), 2.0 (m, 2 H), 1.78 (s, 3 H), 1.74 (s, 3 H), 1.56 (s, 1 H), 1.55 (s, 1 H), 1.13 (s, 3 H), 1.03 (s, 9 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 0.43 (d, *J* = 6.1 Hz, 3 H); both rotamers, ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 209.8, 195.8, 194.6, 192.5, 168.8, 167.0, 148.4, 148.3, 144.2, 141.3, 135.6, 135.2, 133.2, 129.7, 127.71, 125.8, 125.3, 121.2, 95.9, 88.4, 88.1, 80.7, 74.9, 66.9, 66.7, 65.9, 56.0, 55.5, 53.5, 52.6, 50.3,

46.0, 44.8, 40.9, 40.5, 37.5, 34.7, 31.7, 30.2, 26.7, 19.2, 17.1, 16.3, 15.0, 13.4, 9.9. HRMS (FAB$^-$). Calcd for $C_{53}H_{69}{}^{35}ClO_{10}Si$ [M$^+$]: *m*/*z* 928.4349. Found: *m*/*z* 928.4367.

(−)-Sulfone Sodium Salt 51. To a solution of 84 mg (0.09 mmol) of allylic chloride **50** in 3 mL of DMF was added 73 mg (0.45 mmol) of $PhSO_2Na$. The resulting clear solution was stirred at room temperature for 1.5 h, diluted with 20 mL of H_2O and 30 mL of ether, extracted twice with 20 mL of ether, washed with 10 mL of brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on silica gel (1:1 acetone/hexane) afforded 75 mg (80%) of the sulfone sodium salt **51** as an off white amorphous solid having $[\alpha]^{25}{}_D$ −97.0° (*c* 0.49, acetone): IR (film) 2988, 1687, 1625 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1 H), 7.7 (m, 4 H), 7.4 (m, 8 H), 7.0 (m, 3 H), 6.55 (d, J = 8.9 Hz, 1 H), 6.17 (s, 1 H), 5.93 (d, J = 9.2 Hz, 1 H), 5.32 (m, 1 H), 5.25 (m, 1 H), 4.7 (m, 2 H), 4.6 (m, 4 H), 4.20 (m, 2 H), 3.80 (s, 1 H), 3.50 (br m, 4 H), 3.37 (s, 3 H), 3.28 (s, 3 H), 2.82 (m, 1 H), 2.3 (m, 2 H), 2.07 (m, 2 H), 1.85 (s, 3 H), 1.66 (s, 3 H), 1.61 (s, 3 H), 1.46 (m, 2 H), 1.05 (s, 9 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.60 (br s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 195.1, 192.7, 180.2, 162.8, 151.6, 149.9, 143.3, 139.7, 136.3, 135.5, 133.7, 133.2, 129.7, 129.2, 128.9, 127.7, 125.1, 124.8, 120.1, 109.8, 98.4, 95.9, 94.5, 86.2, 80.8, 75.3, 75.1, 66.1, 65.4, 56.4, 55.9, 55.0, 51.9, 51.3, 45.1, 44.1, 41.3, 38.1, 36.6, 32.7, 32.0, 29.6, 26.6, 25.2, 22.6, 19.3, 15.3, 14.6, 13.5, 9.8. HRMS (FAB$^-$). Calcd for $C_{58}H_{71}O_{12}SSi$ [M − Na$^+$]: *m*/*z* 1019.4436. Found: *m*/*z* 1019.4452.

(−)-Macrocyclic Keto Spirotetronic Acid Sodium Salt 53. To a solution of the sulfone sodium salt **51** (73 mg, 70 μmol) in 5 mL of dry benzene was added 0.8 mL of sodium *tert*-pentoxide solution (0.7 M in benzene). The resulting solution was stirred at room temperature for 10 min, and another 0.8 mL of sodium *tert*-pentoxide solution was added. This process was repeated twice more (in total, 2.8 mmol (40 equiv) of sodium *tert*-pentoxide was added). The reaction mixture was stirred at room temperature for additional 15 min, then quenched by addition of 5 mL of saturated $NaHCO_3$, diluted with 15 mL of brine and 30 mL of EtOAc, extracted twice with 10 mL of ethyl acetate, dried over K_2CO_3, and concentrated in vacuo to afford an oily material, which solidified upon addition of 10 mL of ether. It was then filtered through a plug of Celite, washed three times with 30 mL of ether, and finally, the desired product was rinsed out with 50 mL of acetone and concentrated in vacuo to afford a mixture of four diastereomers, which were carried on. The ether portion was evaporated to recover starting material **51** (13 mg, 17%) as an oily material.

To a −78 °C solution of DMSO (68 mg, 870 μmol) in 5 mL of CH_2Cl_2 was added 122 mg (580 μmol) of trifluoroacetic anhydride, and the resulting solution was stirred for additional 10 min. The mixture of diastereomers in 3 mL of CH_2Cl_2 was then added by cannula transfer. The reaction mixture was allowed to warm to 0 °C over 10 min and then recooled with dry ice acetone bath. Triethylamine was then added by syringe, and the resulting reaction mixture was stirred at −78 °C for 10 min and allowed to warm to 0 °C over 10 min. The reaction mixture was quenched by addition of 5 mL of saturated aqueous $NaHCO_3$ solution, diluted with 10 mL of brine and 15 mL of CH_2Cl_2, extracted twice with 10 mL of CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo to give the crude sulfone.

Aluminum foil (Reynolds wrapping foil, 200 mm × 5 mm) was polished with sand paper and dipped into 2% $HgCl_2$ aqueous solution for 15 s. This strip was rinsed with ethanol and ether and was cut (4 pieces, 2 mm × 5 mm each) directly into a solution of the crude sulfone in 6 mL of THF/H_2O (9:1) and stirred vigorously for 10 min. This process was repeated two more times. The reaction mixture was stirred for 30 min at 0 °C and 2.5 h at room temperature, diluted with 20 mL of EtOAc, and filtered through a plug of Celite. The filtrate was washed twice with 20 mL of brine and was concentrated in vacuo to afford 48 mg of a white solid. It was further purified by flash chromatography on silica gel (3:7 acetone/hexane) to afford the keto spirotetronic acid sodium salt of **53** (26 mg, 50% for three operations or ∼75%/operation based on conversion) as an amorphous white solid having $[\alpha]^{25}{}_D$ −9.40 ° (*c* 0.50, acetone): IR (film) 3054, 1634, 1407 cm^{-1}: ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.64 (d, J = 7.0 Hz, 4 H), 7.38 (m, 6 H), 6.43 (d, J = 7.1 Hz, 1 H), 5.94 (d, J = 10.2 Hz, 1 H), 5.87 (s, 1 H), 5.59 (m, 1 H), 5.28 (m, 1 H), 4.72 (d, J = 6.5 Hz, 1 H), 4.64 (d, J = 6.5 Hz, 1 H), 4.55 (d, J = 6.9 Hz, 1 H), 4.50 (d, J = 8.7 Hz, 1 H), 4.07 (s, 2 H), 3.81 (s, 1 H), 3.4 (m, 2 H), 3.36 (s, 3 H), 3.09 (m, 1 H), 2.95 (m, 1 H), 2.72 (d, J = 14 Hz, 1 H), 2.4 (br s, 1 H), 2.3 (br s, 1 H), 1.95 (m, 3 H), 1.76 (s, 3 H), 1.23 (s, 3 H), 1.18 (s, 3 H), 1.03 (s, 9 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.62 (br s, 3 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 199.7, 142.6, 137.8, 133.1, 127.7, 126.4, 121.6, 119.5, 97.7, 95.4, 85.2, 81.8, 75.0, 69.8, 66.6, 55.6, 55.3, 53.4, 50.9, 46.5, 43.8, 41.5, 40.6, 38.1, 32.3, 31.0, 29.6, 29.3, 26.8, 22.5, 19.2, 15.1, 14.1, 13.8, 13.6, 12.9. HRMS (FAB$^-$). Calcd for $C_{52}H_{65}O_{10}Si$ [M − Na$^+$]: *m*/*z* 877.4347 Found: *m*/*z* 877.4344.

(−)-Fully Protected Spirotetronic Acid Sodium Salt 54. To a −78 °C solution of ketone **53** (24 mg, 26.6 μmol) in 5 mL of dry THF was added 0.27 mL (1 M in THF) of L-Selectride over 2 min, then the resulting reaction mixture was stirred for an additional 20 min. The reaction was quenched by addition of 2 mL of saturated aqueous $NaHCO_3$ solution, diluted with 10 mL of brine and 20 mL of EtOAc, extracted twice with 10 mL of EtOAc, dried over Na_2SO_4, and concentrated in vacuo to give 31 mg of crude secondary alcohol as a white solid.

To a solution of the crude alcohol in 5 mL of CH_2Cl_2 were added sequentially 0.4 mL (2.2 mmol) of diisopropylethylamine, and 84 μL (1.1 mmol) of MOMCl. The resulting reaction mixture was heated to reflux for 15 h, then diluted with 25 mL of EtOAc, washed with twice with 10 mL of 1 N HCl and brine, then with 1 mL of saturated aqueous $NaHCO_3$ solution and 5 mL of brine. The organic phases were combined and dried over Na_2SO_4, filtered, and concentrated in vacuo to give **54**. This material was further purified by flash chromatography on silica gel (with elution by 25% acetone in hexanes) to afford 18 mg of pure fully protected spirotetronic acid sodium salt **54** (71% for two steps) as an amorphous white solid having $[\alpha]^{25}{}_D$ −13.85° (*c* 0.65, acetone): IR (film) 2930, 1709, 1681, 1586, 1563 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.7 (m, 4 H), 7.4 (m, 6 H), 5.96 (s, 1 H), 5.91 (d, J = 10.2 Hz, 1 H), 5.4 (m, 1 H), 5.3 (m, 2 H), 4.69 (d, J = 6.6 Hz, 1 H), 4.66 (d, J = 6.8 Hz, 1 H), 4.60 (d, J = 6.8 Hz, 1 H), 4.56 (d, J = 6.6 Hz, 1 H), 4.54 (s, 2 H), 4.3 (d, J = 8.4 Hz, 1 H), 4.41 (m, 2 H), 3.98 (s, 1 H), 3.78 (m, 1 H), 3.45 (m, 1 H), 3.31 (s, 3 H), 3.28 (s, 3 H), 3.24 (s, 3 H), 2.8 (m, 4 H), 2.7 (d, J = 14 Hz, 1 H), 2.2 (m, 2 H), 1.85 (d, J = 14 Hz, 1 H), 1.54 (s, 3 H), 1.42 (s, 3 H), 1.26 (s, 3 H), 1.04 (s, 9 H), 0.97 (d, J = 7.1 Hz, 3 H), 0.58 (d, J = 4.9 Hz, 3 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 201.2, 200.9, 175.0, 138.0, 137.7, 137.1, 136.8, 134.9, 131.2, 129.2, 128.9, 127.1, 123.8, 123.4, 99.1, 97.8, 96.4, 95.3, 85.5, 82.8, 79.5, 78.0, 68.0, 56.1, 55.8, 52.8, 45.6, 40.1, 32.9, 31.7, 31.1, 27.8, 20.4, 17.1, 15.9, 15.4, 14.6. HRMS (FAB$^-$). Calcd for $C_{54}H_{71}O_{11}Si$ [M − Na$^+$]: *m*/*z* 923.4766. Found: *m*/*z* 923.4723.

(+)-Tetronolide (1). An 18 mg sample of the Na salt of tetronic acid **54** (0.023 mmol) was dissolved in 3 mL of CH_3CN, and 80 mg (0.23 mmol) of TAS-F was added. The resulting clear solution was heated at 40 °C for 16 h, then diluted with 15 mL of EtOAc, 10 mL of brine, and 3 mL of 1 N HCl. Aqueous layer was extracted twice with 10 mL of EtOAc, washed with 1 mL of saturated aqueous $NaHCO_3$ solution, 10 mL of brine, dried over Na_2SO_4, and concentrated in vacuo to give the crude primary allylic alcohol.

To a solution of the crude alcohol in 5 mL of CH_2Cl_2 was added 134 mg (0.32 mmol) of DMP.[33] The resulting slightly cloudy mixture was stirred at room temperature for 1.5 h, then quenched by addition of 5 mL of saturated aqueous Na_2CO_3 solution and stirred for 10 min. Ten milliliters of CH_2Cl_2 and 5 mL of H_2O were added, extracted twice with 10 mL of EtOAc, dried over Na_2SO_4, and concentrated in vacuo to afford the crude cyclohexenyl aldehyde.

A solution of the above aldehyde in 3 mL of methanol and 1 mL of 3 N HCl was heated at 65 °C for 1 h. This clear solution was diluted

with 25 mL of EtOAc and 15 mL of brine, extracted twice with 10 mL of EtOAc, dried over Na_2SO_4, and concentrated in vacuo. This was purified by flash chromatography on silica gel (7:3 acetone/hexane) to afford 10.2 mg of (+)-tetronolide (**1**) as a white solid that was further purified by recrystallization from acetone/hexane to give 6.8 mg (62% over three steps) of (+)-tetronolide (**1**) as a white solid having mp 210−212 °C (lit.[10a] 211−213 °C) and $[\alpha]_D^{25}$ +72.6° (*c* 0.34, acetone) [lit.[10a] +79.3 (*c* 1.0, acetone)] and ^{1}H NMR spectroscopic data identical to the reported[10a,17] values: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1 H), 6.89 (s, 1 H), 6.05 (d, J = 10.2 Hz, 1 H), 5.45 (m, 1 H), 5.32 (d, J = 9.8 Hz, 1 H), 5.15 (d, J = 7.1 Hz, 1 H), 4.72 (d, J = 8.5 Hz, 1 H), 4.25 (s, 1 H), 3.64 (m, 1 H), 3.26 (d, J = 4.2 Hz, 1 H), 2.97 (t, J = 7.6 Hz, 1 H), 2.81 (d, J = 18.8 Hz, 1 H), 2.58 (d, J = 18.8 Hz, 1 H), 2.3 (m, 3 H), 2.1 (m, 3 H), 1.61 (s, 3 H), 1.6 (m, 2 H), 1.51 (s, 3 H), 1.39 (s, 3 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.62 (d, J = 4.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 201.3, 192.4, 167.0, 149.3, 144.8, 136.4, 136.2, 125.9, 122.5, 117.0, 100.9, 83.9, 75.9, 72.8, 69.3, 54.2, 51.1, 45.2, 42.8, 41.5, 39.2, 34.6, 31.9, 31.0, 29.6, 22.0, 15.8, 15.0, 14.3, 12.9. HRMS (FAB$^-$). Calcd for $C_{32}H_{39}O_8$ [M − H$^+$]: *m*/*z* 551.2645. Found: *m*/*z* 551.2629.

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Supporting Information Available: Experimental procedures for numbered intermediates **9**, **12**, **13**, **16**−**19**, **29**−**31**, **33**, **34**, **36**−**39**, and **41** along with unnumbered isolated intermediates. Copies of ^{1}H NMR and most IR spectra for numbered intermediates **5**−**7**, **9**,**12**−**14**, **16**−**19**, **21**, **23**−**26**, **28**−**34**, **36**−**39**, **41**, **43**, **45**, **47**, **50**, **51**, **53**, and **54** and unnumbered isolated intermediates; ^{1}H NMR spectra of our synthetic, Yoshii's synthetic, and natural tetronolide (+)-**1**, and X-ray crystallographic data for diol **46**. This material is available free of charge via the Internet at http://pubs.acs.org.

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