Macrocyclization through Radical-Mediated Vinylcyclopropane/Alkene Condensation. Facile Entry into the Brefeldin Ring System

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Received May 25, 1993•

Bicyclic products featuring an 11-membered ring fused to a core vinylcyclopentane unit are produced upon treatment of functionalized vinylcyclopropanes bearing an ω-alkene unit with a catalytic amount of phenylthio radical. This intramolecular extension of a radical-mediated vinylcyclopropane/alkene cyclocondensation proceeds with only modest diastereoselectivity. The reaction products resemble members of the brefeldin family of naturally occurring antibiotics.

The prospects for synthesizing macrocyclic structures by free radical-mediated cyclization reactions, while once thought to be unpromising as a consequence of competitive intermolecular additions, have been placed recently on secure footing by the pioneering studies of Porter[1] among others.[2,3] Thus, these workers have defined conditions wherein intramolecular addition of relatively nucleophilic carbon radicals to electron-deficient alkenes provides efficient entry into 11–20 membered carbocycles and heterocycles contaminated, in favorable cases, by only trace amounts of acyclic material. In unrelated studies on free radical-based methodology for organic synthesis, we have developed a facile (three-atom and two-atom) synthesis of highly functionalized five-membered rings which features the phenylthio radical-catalyzed combination of substituted vinylcyclopropanes with various electron-rich and electron-deficient alkenes.[4] During the course of our investigations, it became apparent that these two distinct advances in radical-based methodology can be consolidated in a project designed to synthesize members of the brefeldin family of antibiotics, **1a–d**.[5] Thus the vinylcyclopropane/alkene condensation delivers the 1,3,4-trisubstituted vinylcyclopentane unit embedded in the brefeldin framework, and, if performed intramolecularly, would permit simultaneous construction of the 11-membered lactone ring (cf. **3**→**14**→**2**). Furthermore, a recent renaissance in brefeldin chemistry has been fueled by the observation that brefeldin A (**1a**) effectively (10^{-8} M) alters proton traffic between the endoplasmic reticulum and the Golgi complex, and, in addition, compromises the structural integrity of the latter organelle.[6] Thus, the availability of brefeldin A and structural analogs as probes of metabolism and subcellular structure remains an issue.

Our strategy for rapid access to the brefeldin skeleton is shown in Scheme I. The synthesis of the cyclization substrates **3a/3b** proceeds through one of the two standard vinylcyclopropane syntheses shown, depending on the compatibility of the cyclopropyl substitutes X and Y to the specific reaction conditions employed. The precursor alcohols **4a/4b** are convergently coupled to the alkene containing piece **5**, leading to the brefeldin cyclization precursors **3a/3b**. Treatment of these substrates with phenylthio radical should initiate a cascade of free radical-mediated rearrangements (cf. Scheme III) which ultimately will deliver the brefeldin skeleton **2**. Subsequent functional group manipulations will be required to arrive at the natural product.

A key focus of these studies is the stereoselectivity of the macrocyclizing vinylcyclopropane–alkene condensation of the substrates **3a/3b**. Cyclization studies with the des-C(15)-methyl substrate **3a** will probe issues of "local" diastereoselectivity as the cyclopentane ring itself is formed. Thus, the stereogenic center at C(7), in combination with the conformational preferences of a putative 16-membered ring intermediate radical (vide infra), will

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• Abstract published in *Advance ACS Abstracts*, October 1, 1993.

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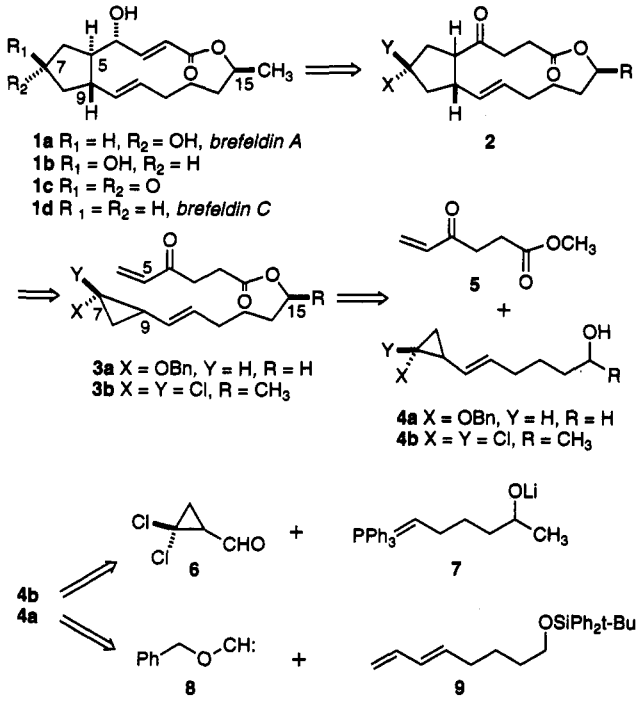
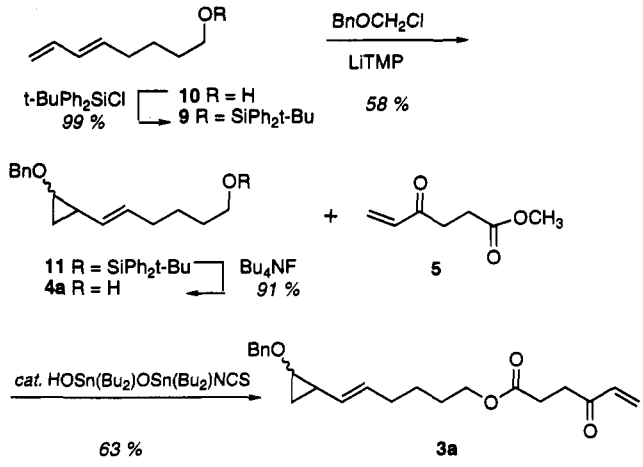
Scheme I



dictate the stereochemical outcome of bond formation at C(5) and C(9). A preliminary investigation of the intermolecular combination of 2-(benzyloxy)vinylcyclopropane and methyl acrylate was not particularly encouraging—in that instance, all four possible vinylcyclopentane diastereomers were formed.[4a,c] However, the *intramolecular* system of interest here has added constraints imposed by the macrocyclic template, and thus, it was deemed worthy of study. The C(15)-methyl-containing substrate **3b** does not have the added complexity associated with a C(7) stereogenic center. This species is designed to probe the more subtle question of remote asymmetric induction between the resident sterogenic center at C(15) and the forming asymmetric centers at C(9) and C(5). In this case, stereochemical information can be transmitted only via the conformational preferences of the intermediate macrocycle mentioned above. This approach to remote stereochemical control in the brefeldin system differs markedly from previous syntheses of this target molecule in which either (1) enantiomerically pure cyclopentane and C(15)-containing units were coupled,[7a-g] or (2) partial kinetic resolution of an epimeric (at C(15)) mixture of *seco*-acids led to the natural stereochemistry upon macrolactonization.[7h-m]

The preparation of the benzyloxy-substituted vinylcyclopropane macrocycle precursor **3a** commences with the known (*E*)-dienol **10**,[8] which, after protection as its silyl

Scheme II



ether **9**, was subjected to standard cyclopropanation conditions to furnish the vinylcyclopropane **11** as a mixture of stereoisomers (Scheme II). It is noteworthy that under the reaction conditions specified, no regioisomeric vinylcyclopropanes or bis-cyclopropanes were detected. After conversion to the alcohol **4a**, Otera's tin-catalyzed transesterification method[9] proved serviceable with the sensitive enone ester **5**, itself available in one step from tetravinyltin and 3-carbomethoxypropionyl chloride.[10] That the resulting cyclization precursor **3a** was formed as a mixture of diastereomers was of no consequence, as phenylthio radical addition (Scheme III) to the (*E*)-alkenyl moiety of **3a** led ultimately to intermediates in which this stereochemical information was lost.

The phenylthio radical-mediated cyclopentannelation/macrocyclization of substrate **3a** was explored under conditions which we had employed previously for these types of addition reactions[3] (0.1 equiv of Ph_2S_2, 0.05 equiv AIBN, sunlamp irradiation) in a variety of solvents (benzene, acetonitrile and methanol), temperature (35 °C → refluxing solvent) and concentrations of **3a** (10–50 mM), Scheme III. In all cases where discrete products could be identified, the brefeldin-like macrocycles **12a–d** were the only compounds isolated. Base-line material (TLC) accounted for the remainder of the reaction mixture and was not further characterized. In principle, four possible diastereomeric bicyclic macrocycles could result, and in each experiment, all four stereoisomers **12a–d** were obtained. It is curious to note that in methanol as solvent, the major isomer obtained features brefeldin-like stereochemistry (isomer **12a**), while this species is accorded only "second place" in either benzene or acetonitrile. The structural and stereochemical assignment of the bicyclic products **12a–d** follows from analyses of ^1H decoupling and DNOE spectral data obtained from the purified isomers (see supplementary material). While the relative stereochemistry at C(5), C(7), and C(9) can be unambiguously assigned for these isomers, the geometry of the alkene moiety in isomer **12c** cannot be assigned with confidence. The postulated mechanistic course by which vinylcyclopropane **3a** is converted to the brefeldin skeleton of **12** invokes a 16-membered macrocyclic carbon radical **15**, bearing two stereogenic centers at C(7) and C(11), as

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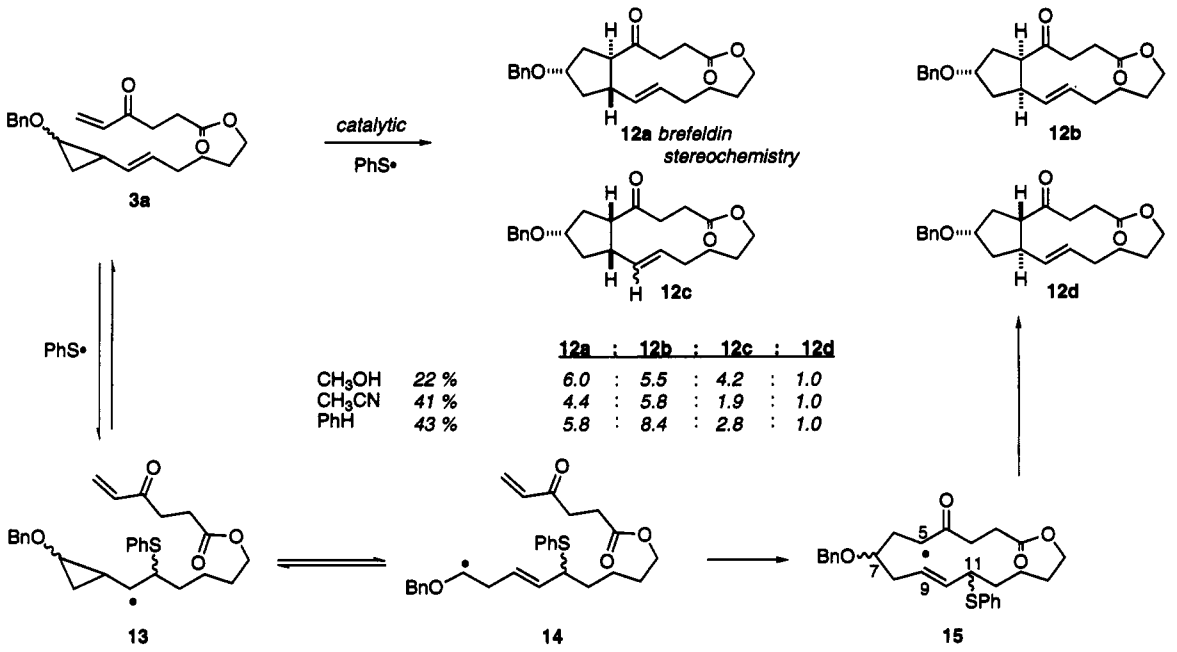
Scheme III

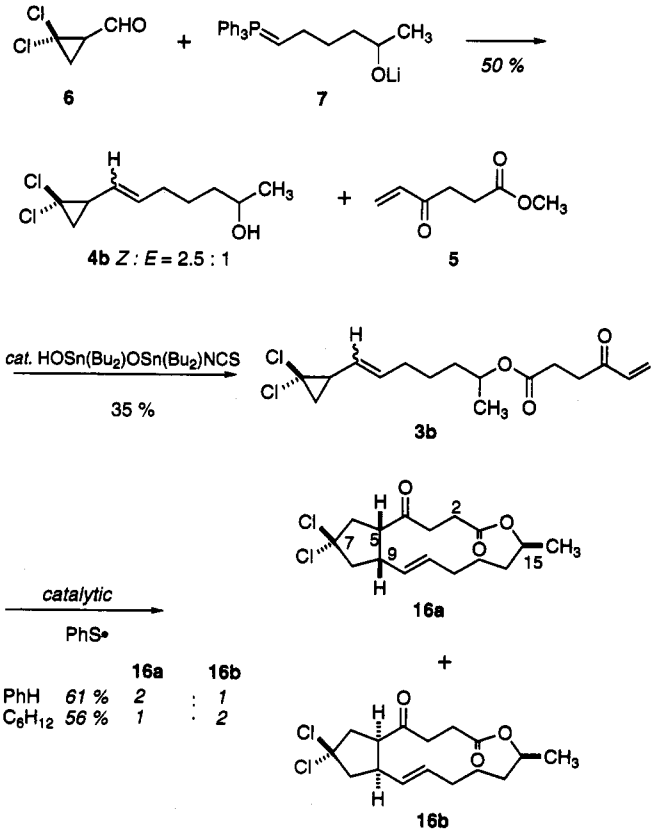


a key intermediate.[11] The relative stereochemistry at these two carbons, the roles that these substituents (SPh and OBn) play in defining macrocycle conformation, and the local (C(5)–C(9) region) conformational preferences themselves, all remain obscure. It is clear, however, that the lack of observed stereochemical preference upon C(5)/C(9) bond formation reflects the fact that no overriding energetic preferences attend any of these putative control elements.

The second system chosen for study, the C(15)-methyl, dichlorovinylcyclopropane **3b**, was synthesized by a route analogous to that described for the O-benzyl analog **3a**. Condensation of the known aldehyde **6**[4d] with the functionalized Wittig reagent **7**[7h] afforded the requisite vinylcyclpropyl alcohol **4b** as a 2.5:1 mixture of (*Z*)/(*E*) alkene isomers (Scheme IV). This mixture was carried forward through the remainder of the reaction sequence since previous studies have demonstrated that either geometrical isomer of the starting vinylcyclopropane leads to the same product alkene geometry upon phenylthio radical-catalyzed (three-atom and two-atom) addition.[12a] Attachment of the enone-containing moiety **5** to alcohol **4b** proceeded smoothly as shown leading to the brefeldin cyclization precursor **3b** in just six steps from commercially available material.

As with the previous brefeldin precursor, a limited survey of solvent, temperature and substrate concentration was made with dichlorovinylcyclopropane **3b** and Ph_2S_2/AIBN. Successful cyclization to furnish the brefeldin structures **16a**/**16b** was achieved in moderate yield in both benzene and cyclohexane, as shown (Scheme IV). While four stereoisomeric products are possible, in fact only the two isomers bearing a cis ring fusion are formed (^1H decoupling, DNOE). The relative stereochemistry of the C(15) stereogenic center with respect to the ring fusion

Scheme IV



could not be ascertained by spectroscopic techniques, but this question was eventually resolved by a single crystal X-ray analysis (Figure 1) on a sample of the major isomer **16a** from the benzene reaction.[12b] Thus, in benzene as solvent, a slight preference for the native brefeldin stereochemistry at C(15)/C(9) is observed, but this preference is reversed in cyclohexane. It is interesting to note that the stereochemical outcome at C(5) and C(9) parallels that of the simple acyclic case (2,2-dichlorovinylcyclopropane and methyl acrylate, 7.8:1 cis/trans cyclopentanes),[4d] much as the stereochemical results in the *O*-benzyl ether series (**3a**→**12a–d**) match those observed in

(11) For a related transannular cyclization of a 5-hexenyl radical embedded in a 16-membered ring, see ref 1c.

(12) (a) Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989**, *30*, 6985. (b) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

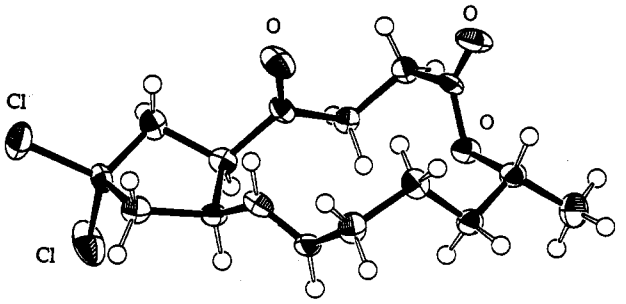
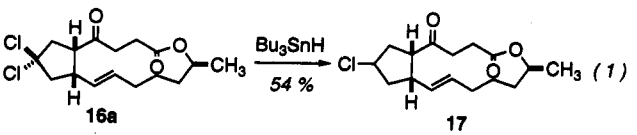


Figure 1.

the simple acyclic case as well. Based upon these two examples, it may be justified to suggest that the flexible tether which links the reacting components plays no meaningful role in determining product stereochemistry, perhaps as a consequence of a lack of overriding conformational preferences for the intermediate macrocyclic radical (eg., **15**).

The bicyclic brefeldin system **16a** might be converted, in principle, into the natural product brefeldin C (**1d**) by (1) introduction of a $\Delta^{2,3}$ alkene, (2) epimerization at C(5), and (3) reductive dechlorination at C(7). While we are unaware of any direct precedent for operation 1, it appeared that epimerization might be feasible based on some observations of Seebach.[13] However, treatment of the brefeldin precursor **16a** with a variety of bases or acids did not lead to satisfactory results. In the best case (t-BuOK/THF), approximately 20% of a compound tentatively assigned as the C(5) epimer of **16a** was formed along with extensive decomposition products. Dechlorination proved to be a much more tractable process, as the monochloride **17** was accessible by simple tin hydride reduction, eq 1.



(1)

In summary, we have demonstrated that an intramolecular, macrocyclizing variant of the (three-atom and two-atom) radical-mediated addition of substituted vinylcyclopropanes with activated alkenes proceeds in good yield to provide bicyclic products featuring an 11-membered ring appended onto the core vinylcyclopentane unit. This ring system is, in fact, coincident with the skeleton of the brefeldin family of naturally occurring antiobiotics, although unsatisfactory stereochemical control upon macrocyclization effectively discouraged additional efforts directed toward the synthesis of the natural product targets. Nevertheless, the concise synthesis of cyclization precursors and the efficiency of bond formation in a demanding environment suggest that this strategy may find application in other macrocyclic systems of interest.

Experimental Section

^{1}H NMR signals reported for mixtures include major and minor isomer peak designations. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EI). Gas-liquid chromatography (GLC) was performed with a capillary cross-linked methyl silicone column (25 m, i.d. 0.20 mm; film thickness 0.33 mm) or a 20 M carbowax capillary column where specified, and a flame ionization detector. High-pressure liquid chromatography (HPLC) was performed using a ZORBAX-SIL silica gel column (25 cm × 20 mm). Liquid (flash)[14] chromatography was carried out using 32–63 uM silica gel and the indicated eluent. Irradiation was provided by a 275-W sunlamp (Sylvania or General Electric).

Benzene (PhH), diethyl ether (Et_2O), 1,2-dimethoxyethane (DME), pentane, tetrahydrofuran (THF), and toluene ($PhCH_3$) were purified by distillation from sodium/benzophenone ketyl under nitrogen. Diisopropylamine, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoramide (HMPA), and methylene chloride (CH_2Cl_2) were distilled from calcium hydride under nitrogen. Solvents for flash chromatography (Et_2O and hexane) were distilled from calcium hydride prior to use. Moisture- and oxygen-sensitive reactions were carried out in predried glassware and under an inert atmosphere (N_2, Ar).

1-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-5,7-octadiene (9). A solution of (*E*)-5,7-octadien-1-ol[8] (**10**) (3.72 g, 29.5 mmol) in 5 mL of DMF was slowly added to a stirring solution of imidazole (5.58 g, 64.9 mmol) and *tert*-butyldiphenylsilyl chloride (9.72 g, 35.4 mmol) in 20 mL of DMF at room temperature. After 30 min at room temperature, the reaction mixture was washed with ice-cold 1 M H_3PO_4 and the aqueous layer was extracted with 3 × 150 mL of pentane. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo, and the residue was purified by flash chromatography using Et_2O–hexane (2:98) as eluent to afford 10.7 g (99%) of dienyl silyl ether **9** as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.37 (m, 6 H), 6.30 (dt, J = 17.0, 10.2 Hz, 1 H), 6.02 (m, 1 H), 5.68 (dt, J = 15.1, 7.0 Hz, 1 H), 5.07 (m, 1 H), 4.95 (m, 1 H), 3.66 (t, J = 6.3 Hz, 2 H), 2.07 (q, J = 7.0 Hz, 2 H), 1.50 (m, 4 H), 1.05 (s, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.3, 135.6, 135.3, 134.0, 131.0, 129.5, 127.6, 114.7, 63.7, 32.2, 32.0, 26.9, 25.4, 19.2; MS *m/z* (rel inten) 307 ($M^+ - C_4H_9$, 100); HRMS calcd for $C_{20}H_{23}OSi$ ($M^+ - C_4H_9$) 307.1518, found 307.1493.

1-(Benzyloxy)-2-[6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-hexenyl]cyclopropane (11). A solution of LiTMP, prepared from 2,2,6,6-tetramethylpiperidine (4.26 g, 30.2 mmol) and *n*-butyllithium (18.9 mL of a 1.6 M solution in hexane, 30.2 mmol) in 50 mL of Et_2O was added dropwise over a 5-h period to a stirring solution of benzyl chloromethyl ether (5.36 g of an 80% mixture, 27.4 mmol) and dienyl silyl ether **9** (500 mg, 1.37 mmol) in 50 mL of Et_2O, and the reaction was allowed to stir at −25 °C for 20 h. The yellow solution with white precipitate was washed with ice-cold 1 M H_3PO_4, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to a brown oil. Purification of the residue by flash chromatography using Et_2O–hexane (2:98) as eluent afforded 382 mg (58%) of cyclopropane **11** (2.3:1 mixture of trans (major) to cis (minor) diastereomers) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 4 H (major + minor)), 7.32 (m, 11 H (major + minor)), 5.53 (dt, J = 15.4, 6.8 Hz, 1 H (major + minor)), 5.24 (ddt, J = 15.3, 9.0, 1.2 Hz, 1 H (major)), 4.99 (ddt, J = 15.3, 7.8, 1.1 Hz, 1 H (minor)), 4.45 (m, 2 H (major + minor)), 3.59 (t, J = 6.2 Hz, 2 H (major)), 3.57 (t, J = 6.2 Hz, 2 H (minor)), 3.35 (td, J = 9.8, 6.3 Hz, 1 H (major)), 3.10 (ddd, J = 6.0, 3.5, 2.6 Hz, 1 H (minor)), 1.96 (q, J = 7.0 Hz, 2 H (major)), 1.87 (q, J = 7.1 Hz, 2 H (minor)), 1.59–1.30 (m, 5 H, (major + minor)), 0.97 (s, 9 H (minor)), 0.96 (s, 9 H (major)), 0.83 (m, 1 H (major + minor)), 0.62 (td, J = 9.2, 6.1 Hz, 1 H (major)), 0.58 (m, 1 H (minor)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 137.9, 135.6, 134.2, 130.6, 130.2, 130.0, 129.7, 129.5, 129.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 72.9, 72.8, 63.8, 60.3, 57.6, 32.5, 32.1, 32.0, 26.9, 25.9, 25.7, 21.7, 20.8, 19.2, 14.1, 13.3; MS *m/z* (rel inten) 427 ($M^+ - C_4H_9$, 3), 393 ($M^+ - PhCH_2$, 3), 91 ($PhCH_2^+$, 100); HRMS calcd for $C_{28}H_{31}O_2Si$ ($M^+ - C_4H_9$) 427.2093, found 427.2087.

1-(Benzyloxy)-2-(6-hydroxyhex-1-enyl)cyclopropane (4a). Silyl ether **11** (382 mg, 0.788 mmol) was added to a stirring solution of tetrabutylammonium fluoride (410 mg, 1.57 mmol) in 15 mL of THF at room temperature. After 1.25 h, the reaction solution was washed with 25 mL of H_2O and the aqueous layer extracted with 3 × 25 mL of Et_2O. The combined organic extracts were

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dried over Na_2SO_4, filtered, and concentrated in vacuo, and the resulting yellow oil was purified by flash chromatography using Et_2O–hexane (2:98) as eluent to yield 176 mg (91%) of alcohol **4a** (2.3:1 mixture of trans (major) to cis (minor) diastereomers) as a clear oil: IR (CCl_4) 3625 cm^{-1} (OH); ^1H NMR (360 MHz, $CDCl_3$) δ 7.31 (m, 5 H (major + minor)), 5.62 (dt, J = 15.4 6.8 Hz, 1 H(major + minor)), 5.33 (ddt, J = 15.5, 7.8, 1.3 Hz, 1 H (major)), 5.08 (ddt, J = 15.3, 7.8, 1.3 Hz, 1 H (minor)), 4.52 (m, 2 H (major + minor)), 3.62 (t, J = 6.6 Hz, 2 H (minor)), 3.60 (t, J = 6.6 Hz, 2 H (major)), 3.43 (dt, J = 6.4, 3.6 Hz, 1 H (major)), 3.17 (ddd, J = 6.2, 3.4, 2.5 Hz, 1 H (minor)), 2.08 (dq, J = 7.1, 1.3 Hz, 2 H (major)), 1.99 (dq, J = 7.2, 1.3 Hz, 2 H (minor)), 1.64–1.37 (m, 6 H (major + minor)), 0.96 (m, 1 H (major + minor)), 0.67 (m, 1 H (major + minor)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 137.9, 130.2, 130.0, 129.1, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 72.9, 72.8, 62.9, 60.3, 57.9, 57.5, 32.5, 32.3, 32.2, 32.1, 25.7, 25.6, 21.7, 20.8, 14.1, 13.3; MS m/z (rel inten) 202 ($M^+ - C_2H_4O$, 5), 155 ($M^+ - PhCH_2$, 4), 91 ($PhCH_2^+$, 100); HRMS calcd for $C_{14}H_{18}O$ ($M^+ - C_2H_4O$) 202.1358, found 202.1338.

Methyl 4-Oxo-5-hexenoate (5). Following the procedure of Rich et al.,[10] a solution of benzylchlorobis(triphenylphosphine)-palladium(II) (1.3 mg, 0.17 mmol) and tetravinyltin (905 mg, 3.98 mmol) in 3 mL of dry HMPA was added to a solution of 3-carbomethoxypropionyl chloride (500 mg, 3.32 mmol) in 3 mL of dry HMPA at room temperature. This yellow solution was heated at 65 °C in an oil bath (open to the air) for 25 min, at which time the reaction mixture turned black in color. The reaction mixture was cooled to room temperature, 60 mL of H_2O was added, and the aqueous layer extracted with 4 × 20 mL of Et_2O. The combined organic extracts were washed sequentially with 2 × 20 mL of H_2O and then brine, dried over Na_2SO_4, filtered, and concentrated to a brown oil. The residue was dissolved in 120 mL of Et_2O, 140 mL of a saturated KF solution in EtOH was added, and the cloudy white precipitate was removed by filtration through Celite. The filtrate was concentrated in vacuo and purified by flash chromatography using EtOAc–hexane (15:85) as eluent to afford 132 mg (28%) of ester **5** as a clear oil: IR (CCl_4), 1750, 1715, 1695 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (m, 2 H), 5.84 (dd, J = 10.1, 1.5 Hz, 1 H), 3.64 (s, 3 H), 2.90 (t, J = 6.7 Hz, 2 H), 2.60 (t, J = 6.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 173.1, 136.2, 128.4, 51.7, 34.0, 27.5; MS m/z (rel inten) 142 (M^+, 3), 114 ($M^+ - C_2H_4$, 26), 111 ($M^+ - OMe$, 21), 84 ($M^+ - CO_2Me$, 53), 55 ($C_3H_3O^+$, 100); HRMS calcd for $C_7H_{10}O_3$ 142.0640, found 142.0630.

(Benzyloxy)cyclopropane Cyclization Substrate 3a. A solution of methyl 4-oxo-5-hexenoate (**5**) (18.1 mg, 0.127 mmol), alcohol **4a** (54.8 mg, 0.220 mmol), and 1,1,3,3-tetrabutyl-1-hydroxy-3-isothiocyanatodistannoxane[9] (6 mg, 0.01 mmol) in 1.5 mL of dry toluene was heated to reflux under N_2 and maintained there for 28 h. The yellow reaction mixture was concentrated in vacuo and the resulting residue purified by flash chromatography using Et_2O–hexane (1:3) as eluent to afforded 28.4 mg (63%) of ester **3a** as a yellow oil: IR (CCl_4) 1750, 1720, 1700 cm^{-1} (C=O); ^1H NMR (360 MHz, $CDCl_3$) δ 7.35 (m, 5 H (major + minor)), 6.34 (m, 2 H (major + minor)), 5.88 (m, 1 H (major + minor)), 5.61 (dt, J = 15.4, 6.8 Hz, 1 H (major + minor)), 5.33 (ddt, J = 15.5, 9.2, 1.4 Hz, 1 H (major)), 5.08 (ddt, J = 15.2, 7.9, 1.4 Hz, 1 H (minor)), 4.54 (m, 2 H (major + minor)), 4.07 (t, J = 6.7 Hz, 2 H (major + minor)), 3.43 (td, J = 6.3, 3.6 Hz, 1 H (major)), 3.18 (dd, J = 6.2, 3.4 Hz, 1 H (minor)), 2.92 (m, 2 H (major + minor)), 2.64 (m, 2 H (major + minor)), 2.08 (dq, J = 7.2, 1.2 Hz, 2 H (major)), 1.98 (dq, J = 7.3, 1.2 Hz, 2 H (minor)), 1.73–1.38 (m, 5 H (major + minor)), 1.02 (m, 1 H (major + minor)), 0.70 (m, 1 H (major + minor)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 172.7, 138.0, 136.2, 130.2, 129.9, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 127.5, 72.9, 72.7, 64.7, 64.5, 60.2, 57.6, 34.1, 32.3, 31.9, 28.0, 27.9, 27.8, 25.8, 25.7, 21.6, 20.8, 14.1, 13.3; MS m/z (rel inten) 356 (M^+, 1), 312 (2), 265 ($M^+ - PhCH_2$, 2), 111 ($C_6H_7O_2^+$, 100), 91 ($PhCH_2^+$, 91); HRMS calcd for $C_{22}H_{28}O_4$ 356.1987, found 356.1987.

Cyclization of (Benzyloxy)cyclopropane Substrate 3a with Phenylthio Radical. A deoxygenated solution of phenyl disulfide (15 mg, 0.068 mmol) and AIBN (5 mg, 0.03 mmol) in 2 mL of benzene was added dropwise via motor driven syringe to a stirring deoxygenated solution of cyclopropane **3a** (47.9 mg, 0.140 mmol) in 14 mL of benzene at room temperature, under an N_2 atmosphere with concomitant sunlamp irradiation. The solution was irradiated at room temperature for 9 h. The yellow reaction solution was concentrated in vacuo and the residue was purified by flash chromatography using Et_2O–hexane (1:2) as eluent to yield 21.2 mg (43%) of cyclopentanes **12** (diastereomer ratio: 8.4 (**12b**): 5.8 (**12a**): 2.8 (**12c**): 1.0 (**12d**) as a yellow oil.

***r*-13-(Benzyloxy)-1,2,3,6,7,8,9,*t*-11a,12,13,14,*t*-14a-dodecahydro-4*H*-cyclopent[*f*]oxacyclotridecin-1,4-dione (12b)**: IR (CCl_4) 1745, 1725 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.51 (ddd, J = 15.4, 8.6, 5.5 Hz, 1 H), 5.29 (dd, J = 15.4, 8.9 Hz, 1 H), 4.45 (s, 2 H), 4.26 (ddd, J = 11.0, 7.4, 2.0 Hz, 1 H), 4.17 (m, 1 H), 3.88 (m, 1 H), 3.32 (q, J = 8.1 Hz, 1 H), 3.16 (pentet, J = 7.7 Hz, 1 H), 3.03 (ddd, J = 19.1, 11.3, 2.9 Hz, 1 H), 2.72 (ddd, J = 15.9, 11.2, 2.8 Hz, 1 H), 2.57 (ddd, J = 19.0, 4.5, 2.6 Hz, 1 H), 2.32 (ddd, 16.0, 5.9, 3.0 Hz, 1 H), 2.21 (ddd, J = 14.2, 9.0, 6.0 Hz, 1 H), 2.04 (m, 2 H), 1.88 (m, 3 H), 1.63 (m, 1 H), 1.31 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.5, 171.9, 138.5, 130.9, 130.5, 128.4, 127.6, 127.5, 79.2, 70.7, 63.7, 53.0, 44.2, 39.3, 39.1, 33.5, 29.7, 28.5, 26.5, 25.6; MS m/z (rel inten) 356 (M^+, 1), 265 ($M^+ - PhCH_2$, 12), 248 (8), 107 ($PhCH_2O^+$, 9), 91 ($PhCH^+$, 100); HRMS calcd for $C_{22}H_{28}O_4$ 356.1987, found 356.1992.

***r*-13-(Benzyloxy)-1,2,3,6,7,8,9,*c*-11a,12,13,14,*t*-14a-dodecahydro-4*H*-cyclopent[*f*]oxacyclotridecin-1,4-dione (12a)**: IR (CCl_4) 1745, 1725 cm^{-1} (C=O); ^1H NMR (500 MHz, C_6D_6) δ 7.19 (m, 5H), 5.48 (ddd, J = 15.1, 9.2, 5.6 Hz, 1 H), 5.12 (dd, J = 15.2, 8.7 Hz, 1 H), 4.22 (s, 2 H), 4.06 (m, 1 H), 3.76 (m, 1 H), 3.68 (m, 1 H), 2.76 (ddd, J = 15.6, 11.4, 2.4 Hz, 1 H), 2.71 (td, J = 11.0, 7.0 Hz, 1 H), 2.64 (m, 1 H), 2.48 (ddd, J = 18.2, 11.1, 2.3 Hz, 1 H), 2.09 (ddd, J = 13.7, 7.8, 6.5 Hz, 1 H), 1.98 (ddd, 15.6, 6.9, 2.6 Hz, 1 H), 1.90 (ddd, J = 18.1, 7.0, 2.3 Hz, 1 H), 1.85 (m, 1 H), 1.80 (m, 1 H), 1.74 (ddd, J = 13.3, 11.2, 6.9 Hz, 1 H), 1.62 (m, 1 H), 1.49 (ddd, 15.0, 10.7, 4.7 Hz, 1 H), 1.30 (m, 1 H), 1.22 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 210.8, 171.5, 138.4, 132.5, 132.4, 128.4, 127.7, 127.6, 79.0, 70.9, 63.8, 55.4, 47.6, 40.0, 39.8, 36.9, 30.4, 28.6, 27.3, 26.4; MS m/z (rel inten) 356 (M^+, 2), 265 ($M^+ - PhCH_2$, 12), 248 (5), 107 ($PhCH_2O^+$, 7), 91 ($PhCH^+$, 100); HRMS calcd for $C_{22}H_{28}O_4$ 356.1987, found 356.1979.

***r*-13-(Benzyloxy)-1,2,3,6,7,8,9,*c*-11a,12,13,14,*c*-14a-dodecahydro-4*H*-cyclopent[*f*]oxacyclotridecin-1,4-dione (12c)**: IR (CCl_4) 1745, 1725 cm^{-1} (C=O); ^1H NMR (500 MHz, C_6D_6) δ 7.17 (m, 5 H), 5.64 (m, 1 H), 5.32 (ddd, J = 11.0, 9.1, 4.6 Hz, 1 H), 4.22 (ABq, J = 11.9 Hz, 2 H), 3.95 (m, 1 H), 3.81 (m, 1 H), 3.07 (pentet, 1 H), 2.69 (m, 1 H), 2.64 (ddd, J = 16.2, 10.0, 2.4 Hz, 1 H), 2.46 (ddd, J = 19.2, 11.7, 2.6 Hz, 1 H), 2.09 (m, 1 H), 2.02 (ddd, J = 16.5, 8.6, 5.7 Hz, 1 H), 1.98 (ddd, J = 16.4, 8.6, 2.8 Hz, 1 H), 1.86 (ddd, J = 19.0, 8.0, 2.1 Hz, 1 H), 1.83 (m, 1 H), 1.79 (m, 1 H), 1.55 (m, 2 H), 1.41 (m, 1 H), 1.15 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.3, 171.5, 138.4, 133.8, 130.1, 128.4, 127.6, 127.5, 79.9, 70.9, 64.0, 55.3, 40.9, 40.2, 39.3, 36.8, 28.6, 27.1, 25.6, 24.9; MS m/z (rel inten) 356 (M^+, 4), 265 ($M^+ - PhCH_2$, 16), 248 (11), 107 ($PhCH_2O^+$, 12), 91 ($PhCH^+$, 100); HRMS calcd for $C_{22}H_{28}O_4$ 356.1987, found 356.1991.

***r*-13-(Benzyloxy)-1,2,3,6,7,8,9,*t*-11a,12,13,14,*c*-14a-dodecahydro-4*H*-cyclopent[*f*]oxacyclotridecin-1,4-dione (12d)**: IR (CCl_4) 1745, 1725 cm^{-1} (C=O); ^1H NMR (500 MHz, C_6D_6) δ 7.20 (m, 5 H), 5.45 (ddd, J = 15.1, 9.3, 5.8 Hz, 1 H), 4.99 (dd, J = 15.2, 8.8 Hz, 1 H), 4.27 (s, 2 H), 3.93 (m, 1 H), 3.81 (m, 1 H), 3.09 (m, 1 H), 2.69 (ddd, J = 15.8, 10.3, 2.6 Hz, 1 H), 2.42 (ddd, J = 17.8, 10.2, 2.4 Hz, 1 H), 2.19 (q, J = 10.0 Hz, 1 H), 2.11 (ddd, J = 15.7, 7.6, 2.6 Hz, 1 H), 2.02 (m, 1 H), 1.98 (ddd, J = 17.9, 7.7, 2.7 Hz, 1 H), 1.87 (dd, J = 9.4, 5.5 Hz, 1 H), 1.76 (m, 1 H), 1.66 (m, 1 H), 1.4–1.2 (m, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.8, 171.7, 138.4, 132.6, 132.1, 128.3, 127.6, 127.5, 78.7, 70.8, 64.2, 57.0, 46.2, 39.4, 38.3, 36.7, 30.8, 28.7, 26.8, 26.3; MS m/z (rel inten) 356 (M^+, 1), 265 ($M^+ - PhCH_2$, 7), 248 (60), 107 ($PhCH_2O^+$, 32), 91 ($PhCH^+$, 100); HRMS calcd for $C_{22}H_{28}O_4$ 356.1987, found 356.2006.

1,1-Dichloro-2-(6-hydroxyhept-1-en-1-yl)cyclopropane (4d). A stock 2.5 M solution of *n*-butyllithium in hexane (2 equiv) was added dropwise by syringe to a degassed suspension of 1.07 g (2.17 mmol) of the phosphonium salt **7**[7b] in THF (0.2 M) cooled to 0 °C. The mixture immediately turned a deep red color and became homogeneous. After 30 min, a THF solution of the aldehyde **6**[4d] (300 mg, 2.17 mmol) was added dropwise by syringe. The brown solution was allowed to stir at 0 °C for 5 min, and was then quenched with cold, saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, and the layers were separated. The organic layer was washed with water and brine, dried over anhydrous

Na_2SO_4, and concentrated in vacuo to give a brown oil. Purification of the crude material by flash column chromatography, eluting with hexane and then hexane–Et_2O (4:1), gave the product vinylcyclopropane **4d** as a viscous oil (240 mg, 50% as a 2.5:1 mixture of cis/trans alkene isomers, R_f (hexane–Et_2O 1:1) 0.30): IR (CCl_4) 3590 (OH) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.69 (m, 1 H, (major + minor)), 5.20 (dd, J = 15.5, 8.2 Hz, 1 H, (minor)), 5.09 (t, J = 8.2 Hz, 1 H, (major)), 3.72 (m, 1 H, (major + minor)), 2.39 (ddd, J = 14.3, 7.6, 4.3 Hz, 1 H, (major + minor)), 2.19 (m, 2H, (major + minor)), 2.10 (q, J = 7.7 Hz, 1 H, (minor)), 1.82 (dd, J = 10.4, 6.3 Hz, 1 H, (major)), 1.74 (m, 1 H, (major + minor)), 1.50 (m, 4 H, (major + minor)), 1.20 (d, J = 6.2 Hz, 3 H, (major + minor)); ^{13}C NMR (major isomer, 90 MHz, $CDCl_3$) δ 134.5, 125.6, 68.0, 61.1, 38.7, 33.9, 32.1, 28.5, 25.5, 23.5; MS m/z (rel inten) 223 (MH^+, 6), 205 ($M^+ - H_2O$, 36), 169 ($M^+ - ClH_2O$), 33), 133 (100); HRMS calcd for $C_{10}H_{14}Cl_2$ 204.0472, found 204.0482.

Dichloro Cyclization Substrate 3b. A solution of methyl 4-oxo-5-hexenoate (**5**) (64 mg, 0.45 mmol), alcohol **4b** (200 mg of a 1.1:1 ratio of olefinic isomers, 0.910 mmol, 2 equiv), and the distannoxane catalyst (12 mg, 0.021 mmol, 0.02 equiv) in 6 mL of dry toluene was purged with Ar and then heated at reflux under Ar for 24 h. The yellow reaction mixture was concentrated in vacuo and the resulting residue was purified by flash column chromatography on silica gel, eluting with hexane and then hexane–Et_2O (4:1), to give 103 mg (35% yield) of the ester **3b** as a mixture of isomers: IR (CCl_4) 1740 (C=O), 1720 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.34 (dd, J = 17.7, 9.6 Hz, 1 H), 6.28 (dd, J = 16.0, 2.0 Hz, 1 H), 5.87 (dd, J = 9.7, 2.0 Hz, 1 H), 5.70 (m, 1 H), 5.09 (t, J = 8.6 Hz, 1 H), 4.91 (m, 1 H), 2.91 (t, J = 6.8 Hz, 2 H), 2.60 (t, J = 7.1 Hz, 2 H), 2.39 (q, J = 6.8 Hz, 2 H, (major)), 2.23 (q, J = 7.2 Hz, 2 H, (minor)), 1.81 (dd, J = 10.4, 6.9 Hz, 1 H), 1.41 (m, 4 H), 1.34 (dd, J = 14.6, 6.9 Hz, 1 H), 1.20 (d, J = 6.0 Hz, 3 H, (major)), 1.18 (d, J = 6.2 Hz, 3 H, (minor)); ^{13}C NMR (major isomer, 50 MHz, $CDCl_3$), δ, 198.5, 172.3, 136.2, 134.3, 128.4, 126.0, 71.3, 61.5, 35.4, 34.1, 33.1, 28.9, 28.5, 27.8, 25.1, 19.9; MS m/z (rel inten) 333 (MH^+, 2), 129 (100), 111 (81); HRMS calcd for $C_{16}H_{22}Cl_2O_3$ 332.0946, found 332.0953.

Cyclization of Dichlorocyclopropane Substrate 3b with Phenylthio Radical. Cyclopropane **3b** (38 mg, 0.12 mmol), phenyl disulfide (2.5 mg, 0.012 mmol, 0.1 equiv), and a crystal of AIBN were combined in 5 mL of benzene. The resulting solution was purged with Ar and then irradiated with a sunlamp at room temperature for 5 h. The reaction mixture was concentrated in vacuo to leave a pale yellow oil. Purification of the crude product by column chromatography on silica gel, eluting with hexane and then hexane–Et_2O (9:1), gave 23 mg (61% yield) of cyclopentanes **16b** and **16a** in a 2:1 ratio (same relative cis stereochemistry at C-5 and C-9, epimeric at C-15) by ^1H NMR integration. The diastereomers were separated by HPLC eluting with hexane–Et_2O (85:15) to give spectroscopically pure cyclopentanes **16a** and **16b**.

1,2,3,6,7,8,9-*c*-11a,12,13,14,*c*-14a-Dodecahydro-13,13-dichloro-*r*-5-methyl-4*H*-cyclopent[*f*]oxacyclotridecin-1,4-dione (16a, major isomer in PhH, minor isomer in C_6H_{12}): R_f (hexane–Et_2O 1:1) 0.30; IR (CCl_4) 1730 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.47 (dt, J = 15.4, 6.6 Hz, 1 H), 5.24 (dd, J = 14.7, 9.7 Hz, 1 H), 4.96 (m, 1 H), 3.49 (ddd, J = 9.9, 9.8, 7.1 Hz, 1 H), 3.27 (p, J = 9.3 Hz, 1 H), 3.01 (ddd, J = 18.7, 8.2, 3.5 Hz, 1 H), 2.96 (dd, J = 14.6, 3.5 Hz, 1 H), 2.87 (dd, J = 14.1, 9.9 Hz, 1 H), 2.80 (ddd, J = 14.9, 8.1, 3.4 Hz, 1 H), 2.66 (ddd, J = 13.9, 6.9, 2.3 Hz, 1 H), 2.58 (ddd, J = 14.1, 7.2, 2.3 Hz, 1 H), 2.48 (ddd J = 18.7, 8.9, 3.5 Hz, 1 H), 2.34 (dd, J = 14.1, 9.6 Hz, 1 H), 2.22 (ddd, J = 14.9, 8.8, 3.5 Hz, 1 H), 1.89 (m, 1 H), 1.79 (m, 1 H), 1.44 (m, 1 H), 1.30 (m, 1 H), 1.09 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 170.7, 132.6, 129.2, 89.8, 70.2, 54.4, 51.8, 49.9, 43.1, 40.1, 33.1, 29.2, 28.7, 24.1, 19.6; MS m/z (rel inten) 332 (2), 272 (8), 237 (7); HRMS calcd for $C_{16}H_{22}Cl_2O_3$ 332.0946, found 332.0955.

1,2,3,6,7,8,9,*t*-11a,12,13,14,*t*-14a-Dodecahydro-13,13-dichloro-*r*-5-methyl-4*H*-cyclopent[*f*]oxacyclotridecin-1,4-dione (16b, minor isomer in PhH, major isomer in C_6H_{12}): R_f (hexane–Et_2O, 1:1) 0.43; IR (CCl_4) 1745 (C=O), 1720 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.53 (dt, J = 15.3, 6.2 Hz, 1 H), 5.30 (dd, J = 15.4, 9.6 Hz, 1 H), 5.01 (m, 1 H), 3.49 (ddd, J = 14.2, 9.9, 7.3 Hz, 1 H), 3.31 (m, 1 H), 3.05 (ddd, J = 17.7, 8.2, 3.6 Hz, 1 H), 2.94 (dd, J = 14.2, 9.9 Hz, 1 H), 2.86 (ddd, J = 14.9, 8.2, 3.6 Hz, 1 H), 2.72 (ddd, J = 13.9, 6.9, 2.4 Hz, 1 H), 2.66 (ddd, J = 14.2, 7.2, 2.4 Hz, 1 H), 2.55 (ddd, J = 18.8, 8.9, 3.7 Hz, 1 H), 2.44 (dd, J = 14.1, 9.2 Hz, 1 H), 2.29 (ddd, J = 15.0, 8.8, 3.6 Hz, 1 H), 1.90 (m, 2 H), 1.55 (m, 1 H), 1.05 (m, 3 H), 1.13 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 172.8, 133.1, 128.3, 90.1, 70.3, 53.8, 51.8, 49.6, 43.2, 40.3, 33.0, 29.4, 27.9, 23.3, 19.0; MS m/z (rel inten) 322 (M^+, 12), 290 (8), 272 (8), 232 (10), 136 (8), 117 (16), 101 (100); HRMS calcd for $C_{16}H_{22}Cl_2O_3$ 332.0946, found 332.0944.

Reduction of *gem*-Dichlorocyclopentane 16a with *n*-Bu_3SnH. Dichlorocyclopentane derivative **16a** (12 mg, 0.036 mmol), *n*-Bu_3SnH (22 mg, 0.072 mmol, 2.2 equiv), and a crystal of AIBN were dissolved in 3 mL of dry benzene. The resulting solution was purged with Ar and heated at reflux for 3 h. The pale yellow reaction solution was concentrated in vacuo, leaving a yellow oil. The residue was dissolved in Et_2O and treated with saturated KF in ethanol to sequester the tin reagent. The mixture was filtered through Celite to remove the insoluble tin salts and concentrated in vacuo. Purification of the crude product by flash column chromatography on silica gel, eluting with hexane and then hexane–Et_2O (5:1), gave 5.0 mg (54%) of the monochloride **17** as a white solid, along with unreacted starting material.

13-*t*-Chloro-*r*-5-methyl-1,2,3,6,7,8,9,*c*-11a,12,13,14,*c*-14a-dodecahydro-4*H*-cyclopent[*f*]oxacyclotridecin-1,4-dione (17): IR (CCl_4) 1715 (C=O) cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 5.45 (dd, J = 15.3, 8.9 Hz, 1 H), 5.31 (dt, J = 15.4, 6.4 Hz, 1 H), 4.97 (m, 1 H), 3.70 (virtual sextet, J = 7.5 Hz, 1 H), 2.82 (ddd, J = 14.6, 7.8, 2.9 Hz, 1 H), 2.55 (ddd, J = 20.5, 11.6, 2.3 Hz, 1 H), 2.41 (m, 1 H), 2.37 (m, 2 H), 2.19 (ddd, J = 18.0, 7.9, 7.5 Hz, 1 H), 1.95 (m, 2 H), 1.72 (m, 2 H), 1.42 (m), 1.24 (m, 3 H), 1.01 (d J = 6.4 Hz, 3 H); ^{13}C NMR (90 MHz, CD_2Cl_2) δ 207.9, 172.3, 131.9, 70.7, 57.1, 44.9, 43.8, 39.5, 38.2, 33.1, 30.6, 30.0, 29.5, 28.1, 24.1, 19.5; MS m/z (rel inten) 298 (15), 256 (17); HRMS calcd for $C_{16}H_{23}ClO_3$ 298.1336, found 298.1334.

Acknowledgment. We thank the NIH (GM37681) for financial support.

Supplementary Material Available: Copies of ^1H and/or ^{13}C NMR spectra for **3a**, **3b**, **4a**, **5**, **9**, **11**, **12a–12d**, **16a**, **16b**, and **17**; DNOE data for **12a–12d**, **16a**, and **16b** (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.