A [3+2] CYCLOADDITION STRATEGY TO THE PHYLLANTHOCIN RING SYSTEM*

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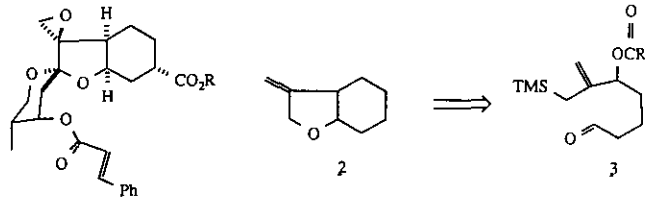
Abstract - A general approach to methyleneoxabicyclo[n.3.0]alkyl heterocycles involves the intramolecular palladium catalyzed addition of trimethylsilylmethylallyl carboxylates to carbonyl groups. Such reactions require tin mediators and O,N-bis(trimethylsilyl)acetamide to prevent protodesilylation. Both 4-methylene-2-oxabicyclo[3.3.0]octane and 7-methylene-9-oxabicyclo[4.3.0]nonane have been produced Whereas, the former is produced as a single diastereomer, the latter is produced as a mixture whose composition depends upon the presence of substituents. The core ring system of phyllanthocin has been produced in this way.

Phyllanthocin (1) constitutes the aglycone portion of the medicinally important molecule phyllanthoside.[1] The possible designation of phyllanthoside as a clinical candidate[2] derives



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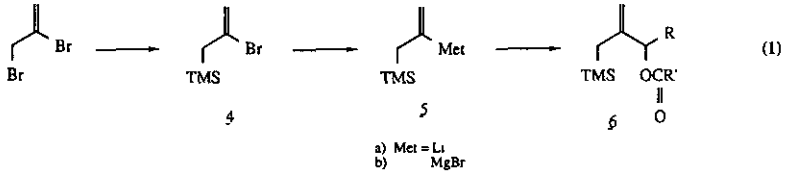
from its activity against murine B16 melanoma, its in vivo activity against the P-388 lymphocytic leukemia in mice, and its in vitro activity against human carcinoma of the nasopharynx.[1,2] The promising biological properties has prompted synthetic work that has culminated in five total syntheses.[3,4]

Our discovery of a [3 + 2] cycloaddition to electron deficient olefins with formation of methylenecyclopentanes[5] and its extension to cycloaddition to carbonyl groups with formation of methylenetetrahydrofurans[6] led us to consider an intramolecular variant[7] of the latter reaction. A model for a synthesis of phyllanthocin envisions the creation of the basic ring system 2 by a palladium(0) mediated cycloaddition of 3.

Scheme 1 details the synthetic sequence. This strategy derives from the development of the nucleophilic reagents 5a and b, available from 2,3-dibromopropene, which provide the

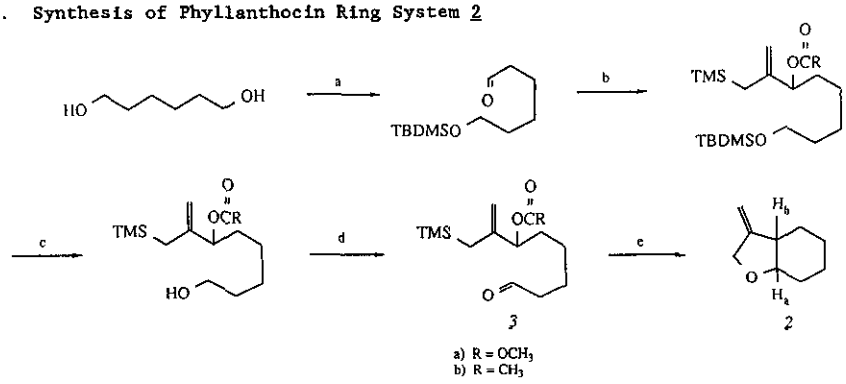


(1)

* Dedicated with great admiration to Professor Sir Derek Barton on the occasion of his seventieth birthday.

bifunctional conjunctive reagents 6 by carbonyl addition reactions (eq 1).[7,8] Promotion of cycloaddition to carbonyl groups requires the addition of tri-n-butyltin acetate.[6b] Protodesilylation of the starting material may be minimized by the addition of 1.5 eq of O,N-bis(trimethylsilyl)acetamide (BSA). Using the carbonate 3a, these conditions provide a 1.1:1 cis to trans mixture of the desired cycloadducts 2. Assignment of the ring juncture derives from J_{ab} which is 4.7 Hz for the cis and 10.7 Hz for the trans isomer. For inexplicable reasons, the acetate 3b fails to undergo cycloaddition.

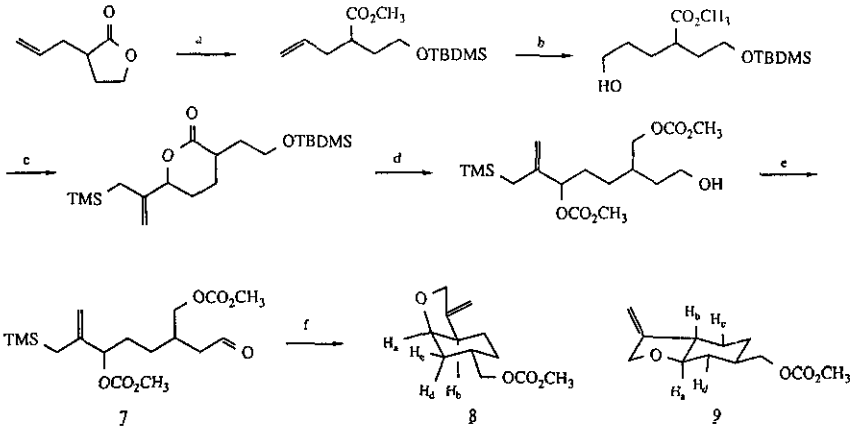
Scheme 1. Synthesis of Phyllanthocin Ring System 2



a) *i*. TBDMS-Cl, DMF, imidazole, 39%; *ii*. $(COCl)_2$, DMSO, CH_2Cl_2, $(C_2H_5)_3N$, 93%.
b) R = OCH_3, 5b, THF, 0°, quench with $ClCO_2CH_3$, 48%. c) 1N aq. H_2SO_4, THF, H_2O, 84%. d) $(COCl)_2$, DMSO, CH_2Cl_2, $(C_2H_5)_3N$, 86%. e) 5 mol% $(dba)_3Pd_2 \cdot CHCl_3$, 5 mol% $(iC_3H_7O)_3P$, 50 mol% $(C_4H_9)_3SnOAc$, BSA, THF, 70°, 54%.

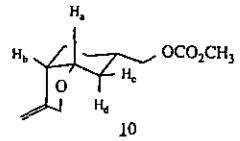
To explore the effect of a substituent, which would become the carboxylic ester of phyllanthocin, on the stereochemistry of the cyclization, synthetic expediency led us to the dicarbonate 7 as our substrate. Scheme 2 outlines the synthesis.

Scheme 2. Cyclization to Substituted Phyllanthocin Ring System



a) *i*. KOH, CH_3OH, rt; *ii*. CH_2N_2, ether, 0°; *iii*. TBDMS-Cl, DMF, rt, 59% overall. b) BH_3, THF, 0° then MCPBA, rt, 50%. c) *i*. $(COCl)_2$, DMSO, CH_2Cl_2, -60 to -50° then $(C_2H_5)_3N$; *ii*. 5b, THF, 0°, 70% overall. d) *i*. LAH, ether, rt; *ii*. $ClCO_2CH_3$, DMAP, CH_2Cl_2, 66% overall; *iii*. H_2SO_4, H_2O, THF, 90%. e) $(COCl)_2$, DMSO, CH_2Cl_2, -60° then $(C_2H_5)_3N$, 82%. f) $(dba)_3Pd_2 \cdot CHCl_3$, Ph_3P, $(n\text{-}C_4H_9)_3SnOAc$, BSA, THF, reflux, 35%.

Subjecting 7 to the previous cyclization conditions fails to induce the desired reaction. On the other hand, using the stronger donor ligand triphenylphosphine does produce only two of the four possible diastereomeric cycloadducts in a ratio of ca 2.5:1. We assume that the acyloxymethyl group prefers an equatorial orientation which leads to three possible isomers, 8, 9, and 10. Differentiation among these three possible isomers is based upon the anticipated coupling pattern for H_a. The presence of a multiplet at δ 4.00 with only small coupling constants best fits the cis fused adduct 8 for the major diastereomer and the presence of a td, J=10.9 and 3.9 Hz, at δ 3.13 best fits the trans fused adduct 9 for the minor diastereomer.



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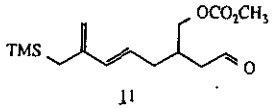

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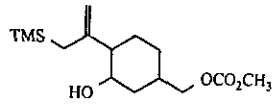

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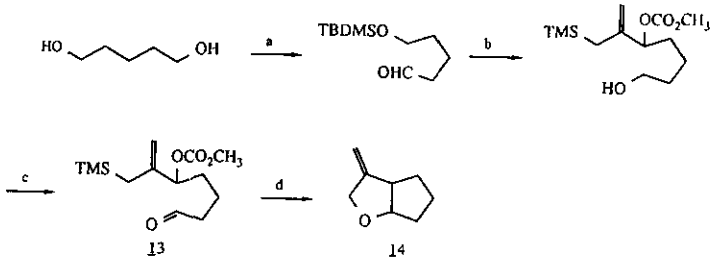
The cyclization is unusually sensitive to reaction conditions. Successful cyclization occurs using the conditions noted in Scheme 2 as well as using a Pd(0) catalyst generated in situ from palladium acetate and n-butyllithium in the presence of triphenylphosphine but preferentially in refluxing dioxane. On the other hand, use of refluxing toluene only led to the elimination product 11. Remarkably, a product tentatively identified as the Barbier type adduct 12 arises when dppp is employed as the ligand.[9]

Scheme 3 outlines the exploration of the lower homologue. Cyclization of sibstrate 13

Scheme 3. Synthesis of 4-Methylene-2-oxabicyclo[3.3.0]octane (14)



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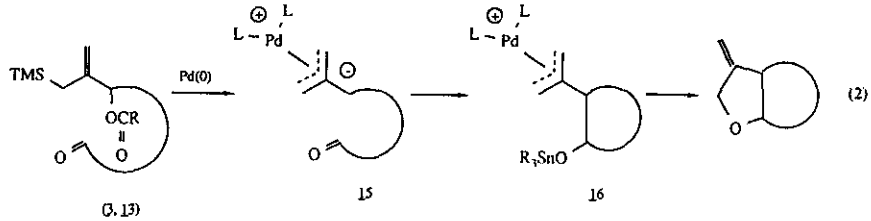
a) *i*. TBDMS-Cl, imidazole, DMF, rt, 30%; *ii*. $(COCl)_2$, DMSO, CH_2Cl_2, $(C_2H_5)_3N$, -60°, 85%. b) *i*. 5b, THF, 0° then $ClCO_2CH_3$, 68%; *ii*. $H_2SO_4 \cdot 2H_2O$, THF, rt, 81%. c) see a) *ii*. 77%. d) $(dba)_3Pd_2 \cdot CHCl_3$, $(iC_3H_7O)_3P$, $(nC_4H_9)_3SnOAc$, BSA, THF, reflux, 31%.

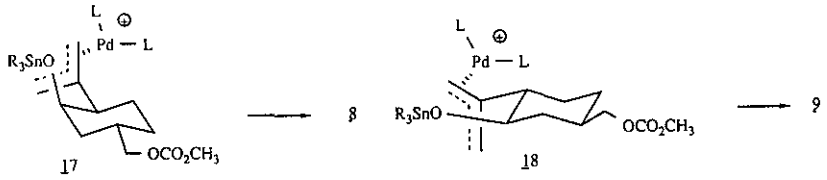
proceeds in moderate yields using either $(dba)_3Pd_2 \cdot CHCl_3$ or a Pd(0) complex generated in situ from palladium acetate and n-butyllithium and either triphenylphosphine or triisopropylphosphite as ligands to give the oxabicyclo[3.3.0]octane 14. Only one diastereomer is observed. The cis fused ring system is assumed on the basis of the strain anticipated for a trans bicyclo[3.3.0]octane.

The intramolecular addition of the trimethylenemethane palladium (0) complex is viewed to be a stepwise process according to eq 2. The low diastereoselectivity for the cyclization of 3 may

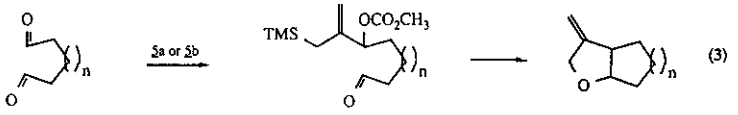


(3, 13) 15 16

may derive from a competition between minimization of charge separation in the initial ring closure of 15 to 16 which should favor cis and steric effects which should favor trans. Introducing a substituent on the tether introduces another stereochemical feature as well as an influence on ring juncture stereochemistry. The formation of only two out of the four possible stereoisomers may derive from the bias for the two carbon chains in the initial cyclization intermediate to be equatorial, as in 17 and 18. The source of the enhanced selectivity for the cis ring fusion in this case, which corresponds to that desired for phyllanthocin, is not easily discerned except to point out that minimization of charge separation may be more significant in these conformationally more well-behaved substrates.



The ability to convert acyclic compounds to the oxabicyclo[n.3.0]alkyl heterocycles in a single reaction should prove useful in the construction of natural products and their analogues as represented by phyllanthocin. Synthetically, this convergent approach provides a simple strategy to these heterocycles by addition of the organometallics 5a or 5b to a differentiated α, ω-dialdehyde as in eq 3.



EXPERIMENTAL

Proton magnetic resonance spectra were recorded on a Bruker WP-270 (270 MHz) or a Bruker WP-200 (200 MHz) spectrometer. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane (Me_4Si) in delta units and coupling constants are given in cycles per second (Hz). All spectra were recorded using $CDCl_3$ as the solvent. The data are reported as follows: chemical shift, number of protons, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dt = doublet of triplets, br s = broad singlet, etc.), and coupling constants. Infared (ir) spectra were recorded using a Perkin Elmer 283 spectrometer. High resolution mass spectra (HRMS) were obtained on an AEI-902 instrument at an ionizing current of 98 mA with an ionizing voltage of 70 eV. The data are reported as the mass to charge ratio of the observed ion, and "M" refers to the molecular ion.

All solvents were distilled prior to use. THF and ether were distilled from sodium benzophenone ketyl while methylene chloride, DMSO, DMF, and triethylamine were distilled from calcium hydride. Hexane, oxalyl chloride, allyl bromide, 2,3-dibromopropene, and 2-(3H)-furanone were all distilled prior to use. The Grignard reagent derived from 2-bromo-3-trimethylsilyl-1-propene was prepared by the method of Chan.[10]

Column chromatography was accomplished using E Merck silica gel 60 (230-400 mesh, ASTM). All reactions were monitored as a function of time using TLC (E. Merck silica gel 60F-254 glass plates). Solvents used for chromatography were mixed by volume and are reported for each experiment.

Concentrated *in vacuo* refers to evaporation on a rotary evaporator until a constant pressure (measured with the use of a manometer) is obtained. Drying of organic solutions was over

magnesium sulfate unless otherwise indicated.

6-*t*-Butyldimethylsiloxyhexanal: To a room temperature solution of 3.0 g (25 mmol) of 1,6-hexanediol and 4.2 g (27.9 mol) of *t*-butylchlorodimethylsilane in 25 ml of DMF was added 1.68 g (11.5 mmol) of imidazole. The reaction mixture was stirred at room temperature overnight and then diluted with ether. The organic phase was then washed with saturated ammonium chloride followed by saturated sodium bicarbonate. The combined aqueous layers were then extracted with ether. The combined organic layers were dried and then concentrated *in vacuo*. The material was chromatographed through *ca*. 100 g of silica gel in a 40 mm inner diameter column using 60% ether/hexane as eluent to afford 2.25 g (39%) of a colorless oil, TLC R_f = 0.3 with 60% ether/hexane. Ir (neat): 3340 br, 2920, 2850, 1470, 1460, 1385, 1360 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ 3.65 (2H, t, J=6.5), 3.61 (2H, t, J=6.5), 1.55 (4H, m), 1.36 (5H, m), 0.89 (9H, s), 0.05 (6H, s). Anal. calc'd for $C_{12}H_{29}O_2Si$ (M+1): 233.1937. Found: 233.1937.

To a solution of 0.905 g (3.9 mmol) of the above alcohol in 13.9 ml of dichloromethane at *ca*. -60°C was added 0.670 g (8.58 mmol) of DMSO and then 0.544 g (4.29 mmol) of oxalyl chloride. The milky white suspension was stirred for 20 min and then 1.97 g (19.5 mmol) of triethylamine added. After an additional 5 min the reaction was allowed to warm to room temperature. The reaction mixture was diluted with water, transferred to a separatory funnel and the layers separated. The aqueous layer was extracted with ether and the combined organic layers dried and concentrated *in vacuo*. The crude oil was flash chromatographed through 20 g of silica gel in a 20 mm inner diameter column using 30% ether/hexane as eluent to afford 0.83 g (93%) of a pale yellow oil, TLC R_f 0.4 with 30% ether/hexane. Ir (neat): 2700, 1720, 1465, 1455, 1380, 1350 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ 9.77 (1H, t, J=1.9), 3.61 (2H, t, J=6.1), 2.44 (2H, dt, J_d=1.8, J_t=7.2), 1.66 (2H, m), 1.54 (2H, m), 1.39 (2H, m), 0.89 (9H, s), 0.04 (6H, s). Anal. calc'd for $C_{12}H_{27}O_2Si$ (M+1): 231.1780. Found: 231.1766.

1-*t*-Butyldimethylsiloxy-6-methoxycarbonyloxy-7-methylidene-8-trimethylsilyloctane: To a 0°C solution of 195.7 mg (0.851 mmol) of the above aldehyde in 1.7 ml of THF was added 2.04 ml (1.02 mmol) of a 0.5 M Grignard solution made from 2-bromo-3-trimethylsilylpropene and magnesium metal in THF. When complete as judged by TLC, 160 mg (1.7 mmol) of methyl chloroformate was added. When no further reaction was evident by TLC, the mixture was diluted with ether and water. The aqueous phase was extracted with ether and the combined organic layers dried and concentrated *in vacuo*. The crude oil was chromatographed through *ca*. 20 g of silica gel in a 15 mm inner diameter column using 5% ether/hexane as eluent to afford 166 mg (48%) of a colorless oil, TLC R_f = 0.42 with 5% ether/hexane. Ir (neat): 1745, 1635, 1435 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz) 4.96 (1H, m), 4.94 (1H, br s), 4.76 (1H, br s), 3.81 (3H, s), 3.63 (2H, t, J=6.4), 1.70 (2H, m), 1.55 (4H, m), 1.38 (4H, m), 0.93 (9H, s), 0.09 (9H, s), 0.082 (6H, s). Anal. calc'd for $C_{20}H_{43}O_4Si_2$ (M+1): 403.2700. Found: 403.2710.

6-Methoxycarbonyloxy-7-methylidene-8-trimethylsilyloctan-1-ol: To a room temperature solution of 3.12 g (7.8 mmol) of the above *t*-butyldimethylsilyl ether in 38.8 ml of THF was added 10.2 ml of a 1 *N* aqueous sulfuric acid solution. When TLC indicated complete reaction, it was diluted with ether and water. The aqueous phase was extracted with ether and the combined organic layers then dried and concentrated *in vacuo*. The crude product was chromatographed through *ca*. 75 g of silica gel in a 30 mm inner diameter column using 50% ether/hexane as eluent to afford 473 mg (15%) of recovered starting material and 1.88 g (84%) of the desired product, TLC R_f = 0.2 with 50% ether/hexane. Ir (neat): 3380 br, 2920, 1740, 1630, 1440 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz) 4.93 (1H, app. t, J=6.3), 4.91 (1H, br s), 4.72 (1H, br s), 3.77 (3H, s), 3.64 (2H, t, J=6.5), 1.68 (2H, m), 1.55 (3H, m), 1.39 (5H, m), 0.05 (9H, s). Anal. calc'd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78; Si, 9.74. Found: C, 58.26; H, 9.87; Si, 9.60.

6-Methoxycarbonyloxy-7-methylidene-8-trimethylsilyloctanal (3): To a *ca.* -60°C solution of 93 mg (0.323 mmol) of alcohol and 75.5 mg (0.969 mmol) of DMSO in 1.15 ml of dichloromethane was added 61.4 mg (0.486 mmol) of oxalyl chloride. The mixture was stirred at -60°C for 15 min and then 0.225 ml (1.615 mmol) of triethylamine added. After an additional 5 min, the reaction mixture was warmed to room temperature and then diluted with water and ether. The aqueous layer was extracted with ether. The combined organic layers were dried and concentrated *in vacuo*. The crude material was chromatographed through *ca.* 5 g of silica gel in a 10 mm inner diameter column using 20% ether/hexane as eluent to afford 79.6 mg (86%) of pure aldehyde; TLC R_f = 0.2 with 20% ether/hexane. Ir (neat): 3070, 2940, 2700, 1740, 1720, 1635, 1435 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): 9.76 (1H, t, *J*=1.6), 4.93 (1H, app. t, *J*=7), 4.91 (1H, br s), 4.72 (1H, br s), 3.77 (3H, s), 2.44 (2H, dt, J_d=1.6, J_t=7), 1.68 (6H, m), 1.64 (1H, A of AB, *J*=13), 1.33 (1H, B of AB, *J*=13), 0.05 (9H, s). Anal. calc'd for $C_{14}H_{27}O_4Si$ (M+1): 287.1679. Found: 287.1660.

cis and trans-7-Methylidene-9-oxabicyclo[4.3.0]nonane (2): A solution of 20 mg (0.0194 mmol) of palladium dibenzylideneacetone chloroform complex, 52 mg (0.194 mmol) of tributyltin acetate, and 40.3 mg (0.194 mmol) of triisopropylphosphite was stirred in 1.5 ml of THF at room temperature until bright yellow. To this mixture was added 118 mg (0.582 mmol) of BSA. After an additional 5 min, a solution of 111.2 mg (0.39 mmol) of aldehyde 3 in 0.44 ml of THF was added. The reaction mixture was submerged in an oil bath preheated to 70°C and monitored by TLC. When complete, the reaction mixture was concentrated under 30 mm Hg with the use of a rotary evaporator and an ice bath. The crude material was then chromatographed through 15 g of silica gel in a 15 mm inner diameter column using 2% ether/pentane as eluent. The purified product was carefully concentrated again using the rotary evaporator and ice bath set up to afford 22.4 mg (54%) of an inseparable 1:1 mixture of cis and trans products, TLC R_f = 0.3 with 2% ether/pentane. Ir (neat): 3080, 2940, 2860, 1670 br, 1450 cm^{-1}; ^1H nmr of the mixture ($CDCl_3$/270 MHz): [several signals for the cis and trans isomers were assigned by isolation of a small amount of mostly pure cis isomer] δ 4.91 (0.5H, app. q, *J*=2, vinyl proton from the cis isomer), 4.84 (1H, m, mix of vinyl protons from both isomers), 4.80 (0.5H, app. q, *J*=2.6, vinyl proton from the trans isomer), 4.6-4.2 (2H, m, overlapping AB patterns from the two isomers), 3.98 (0.5H, app. q, *J*=4.6, methine at C_1 of the cis isomer), 3.06 (0.5H, td, J_t=10.7, J_d=3.7, methine at C_1 for the trans isomer), 2.53 (0.5H, m, methine at C_6 for the cis isomer), 2.11 (1H, m), 1.9-1.3 (br m for the remaining protons). Anal. calc'd for $C_9H_{14}O$: C, 78.21; H, 10.21; MW, 138.1048. Found: C, 78.29; H, 10.32; MW, 138.1051.

4-Carbomethoxy-6-*t*-butyldimethylsiloxy-1-hexene: To a room temperature solution of 2.99 g (23.7 mmol) of 3-allyl-2(3H)-furanone in 24 ml of methanol was added 2.66 g (47.5 mmol) of potassium hydroxide. After 1.75 h, the reaction mixture was diluted with water and acidified to pH = 5 with 2 *N* aqueous hydrochloric acid. After extraction with ether, the combined organic layers were dried and filtered into a new 250 ml Erlenmeyer flask.

To a cooled (0°C) solution of 77 ml of ether and 23 ml of 40% potassium hydroxide in water was added 7.73 g of nitrosomethylurea over a period of 5-10 min. The mixture was magnetically stirred for *ca.* 10 min and then the bright yellow ether layer was decanted into the Erlenmeyer containing the acid from above. The diazomethane solution was added until a persistent yellow color remained. The reaction mixture was stirred for an additional 5 min and then the excess diazomethane quenched by the addition of glacial acetic acid. After washing immediately with saturated sodium bicarbonate, the remaining ether layer was dried and concentrated *in vacuo*. The crude product was immediately chromatographed through 40 g of silica gel in a 20 mm inner diameter column using 50% ether/hexane as eluent to afford 2.55 g (68%) of the product, TLC R_f 0.30 with 50% ether/hexane. Ir (neat): 3410, 3075, 2950 br, 1740, 1645, 1440 cm^{-1}; ^1H nmr

(270 MHz): δ 5.71 (1H, app. ddt, J_d(trans)=16.9, J_d(cis)=10.1, J_t=6.9), 5.05 (2H, m), 3.69 (3H, s), 3.67 (2H, t, J=6.24), 2.65 (1H, m), 2.24 (2H, m), 1.85 (2H, m). Anal. calc'd for $C_8H_{15}O_3$ (M+1): 159.1021. Found: 159.1037.

To a solution of 2.55 g (16.1 mmol) of alcohol and 2.67 g (17.8 mmol) of *t*-butyldimethylsilyl chloride in 16.1 ml of DMF at room temperature was added 1.21 g (17.8 mmol) of imidazole. After 16 h, the reaction mixture was diluted with ether and the resultant mixture was washed twice with water and then once each with saturated ammonium chloride and saturated sodium bicarbonate. The aqueous layers were extracted with ether and then the combined organic layers were dried and concentrated *in vacuo*. The crude product was immediately chromatographed through 30 g of silica gel in a 20 mm inner diameter column using 5% ether/hexane as eluent to afford 3.81 g (87%) of a colorless oil, TLC R_f 0.3 with 5% ether/hexane. Ir (neat): 3060, 2940, 2920, 2840, 1740, 1640, 1470, 1440, 1385, 1360 cm^{-1}; ^1H nmr (270 MHz): δ 5.74 (1H, app ddt, J_d(trans)=17.1, J_d(cis)=10.1, J_t=7.0), 5.04 (2H, m), 3.66 (3H, s), 3.62 (2H, m), 2.63 (1H, m), 2.311 (2H, m), 1.86 (1H, m), 1.70 (1H, m), 0.88 (9H, s), 0.03 (6H, s). Anal. calc'd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36; Si, 10.31. Found: C, 61.62; H, 10.36; Si, 10.22.

4-Carbomethoxy-6-*t*-butyldimethylsiloxy-1-hexanol: To a solution of 2.99 g (11.0 mmol) of the above olefin in 22 ml of THF at 0°C was added 11 ml (11.0 mmol) of a 1 *M* borane-THF solution. The mixture was allowed to warm to room temperature and then stirred for 2 h. The reaction mixture was then cooled to 0°C and 7.5 g (44 mmol) of MCPBA in 44 ml of THF added. The mixture was again allowed to warm to room temperature and stirred overnight. After 18 h, the reaction mixture was diluted with ether and washed successively with saturated aqueous sodium bisulfite (3 times) and aqueous potassium carbonate. The aqueous layers were extracted with ether and the combined organic layers were dried and concentrated *in vacuo*. The crude material was immediately chromatographed through 75 g of silica gel in a 35 mm inner diameter column using 70% ether/hexane as eluent to afford 1.59 g (50%) of the purified alcohol, TLC R_f 0.15 with 70% ether/hexane. Ir (neat): 3410 br, 2950, 2910, 2880, 1740, 1460 cm^{-1}; ^1H nmr (270 MHz): δ 3.68 (3H, s), 3.64 (4H, m), 2.59 (1H, m), 2.18 (1H, br m), 1.88 (1H, m), 1.62 (5H, m), 0.88 (9H, s), 0.04 (6H, s). Anal. calc'd for $C_{14}H_{31}O_4Si$ (M+1): 291.1992. Found: 291.1973.

3-(2'-*t*-Butyldimethylsiloxyethyl)-6-(1'-trimethylsilylmethylvinyl)-2(3H)-pyranone: To a -60 to -50°C solution of 0.346 g (1.19 mmol) of the above alcohol in 4.62 ml of dry methylene chloride was added 0.205 g (262 mmol) of DMSO and 0.166 g (1.31 mmol) of oxalyl chloride The reaction mixture was stirred for 15 min as a milky white solid formed. Triethylamine was added (0.603 g, 5.96 mmol) and the reaction mixture stirred for an additional 5 min. The reaction mixture was then allowed to warm to room temperature and diluted with water and ether. The aqueous layer was extracted with ether. The combined organic layers were dried and concentrated *in vacuo* to afford the crude aldehyde which was immediately carried on to the next reaction. TLC R_f 0.2 with 30% ether/hexane; Ir (neat): 2920, 2840, 1730 cm^{-1}; ^1H nmr (270 MHz): δ 9.74 (1H, s), 3.65 (3H, s), 3.59 (2H, app. q, J=5.9), 2.48 (1H, m), 2.45 (2H, t, J=7.2), 1.87 (3H, m), 1.65 (1H, m), 0.85 (9H, s), 0.005 (6H, s).

To a solution of 0.343 g (1.19 mmol) of the crude aldehyde in 1.48 ml of THF at 0°C was added 5.95 ml of a *ca.* 0.3 *M* stock solution of the Grignard reagent from 2-bromo-3-trimethylsilyl-1-propene in THF. The reaction mixture was stirred at 0°C until TLC indicated consumption of the aldehyde at which point it was quenched with saturated aqueous ammonium chloride. The mixture was then extracted with ether and the combined organic layers dried and concentrated *in vacuo* to afford 0.524 g of a crude yellow oil. The oil was chromatographed through 20 g of silica gel in a 20 mm diameter column using 20% ether/hexane as eluent to afford 0.307 g (70%

over two steps) of a colorless oil (1:1 mixture of cis and trans isomers), TLC R_f 0.3 with 20% ether/hexane. Ir (neat): 2940, 2920, 2840, 1730 br, 1630, 1470, 1460 cm^{-1}; ^1H nmr (270 MHz): δ 4.97 (1H, app. d, J=1.2, vinyl proton syn to the trimethylsilyl methyl group in both isomers), 4.78 (1H, s, vinyl proton syn to the six membered ring in one isomer), 4.76 (1H, s, vinyl proton syn to the six membered ring in one isomer), 4.61 (1H, m, proton at C_6 of the pyranone ring), 3.75 (2H, m, methylene protons alpha to the silyl ether for both isomers), 2.71 (1H, m, proton at C_3 of the pyranone ring for one isomer), 2.60 (1H, m, proton at C_3 of the pyranone ring for one isomer), 2.06 (3H, m), 1.8-1.4 (5H, m), 0.89 (9H, s, t-butyl group), 0.05 (15H, s, silylmethyl protons). Anal. calc'd for $C_{19}H_{38}O_3Si_2$: C, 60.28; H, 10.68; MW 370.2359. Found: C, 60.60; H, 10.40; MW, 370.2350.

3-Methoxycarbonyloxymethyl-6-methoxycarbonyloxy-7-trimethylsilylmethyloct-7-en-1-ol: To a 0°C solution of 1.63 g (4.4 mmol) of the above lactone in 22 ml of ether was added 167 mg (4.4 mmol) of LAH. Upon disappearance of lactone, the reaction mixture was quenched with ice chips and diluted with water and ether. The aqueous layer was extracted ten times with ether. The combined organic layers were dried and concentrated *in vacuo*. A 0° solution of the crude diol, 108 mg (0.88 mmol) of DMAP, and 870 mg (11 mmol) of pyridine in 1.48 ml of dichloromethane was prepared. To this solution was added 1.03 g (11 mmol) of methyl chloroformate. When TLC suggested the disappearance of diol, the reaction mixture was diluted with water and ether. The ether layer was washed with saturated aqueous ammonium chloride, and the combined aqueous layers were extracted with ether. The organic layers were then dried and concentrated *in vacuo*. The crude oil was then chromatographed through 100 g of silica gel in a 30 mm inner diameter column using 20% ether/hexane as eluent to afford 1.43 g (66%) of product; TLC R_f = 0.3 with 20% ether/hexane. Ir (neat): 2960, 2940, 2860, 1750, 1630, 1440, 1390, 1360 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ 4.90 (2H, m), 4.72 (1H, s), 4.09 (2H, m), 3.77 (3H, s), 3.77 (3H, s), 3.65 (2H, t, J=6.6), 1.84 (1H, m), 1.69 (2H, m), 1.58-1.38 (6H, m), 0.88 (9H, s), 0.05 (9H, s), 0.04 (6H, s). Anal. calc'd for $C_{17}H_{33}O_4Si_2$ (M-C_4H_{12}-$C_2H_4O_3$)· 357.1917. Found: 357.1921.

To a room temperature solution of 1.41 g (2.9 mmol) of the above silyl ether in 14.3 ml of THF was added 3.8 ml of a 1 *N* aqueous sulfuric acid solution. When TLC indicated the disappearance of the silyl ether, the reaction mixture was diluted with ether and water. The aqueous layer was extracted five times with ether and the combined organic layers dried and concentrated *in vacuo*. The crude product was flash chromatographed through 100 g of silica gel in a 40 mm inner diameter column using 80% ether/hexane as eluent to afford 0.982 g (90%) of the pure alcohol; TLC R_f = 0.25 with 80% ether/hexane. Ir (neat): 3450 br, 3080, 2950, 1745, 1640, 1440 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ 4.92 (1H, app. q, J=6), 4.91 (1H, br s), 4.73 (1H, br s), 4.10 (2H, d with fine structure, J=5.6), 3.78 (3H, s), 3.77 (3H, s), 3.71 (2H, t, J=6.8), 1.87 (1H, m), 1.80-1.35 (8H, m), 0.05 (9H, s). Anal. calc'd for $C_{17}H_{32}O_7Si$: C, 54.23; H, 8.57; Si, 7.46. Found: C, 54.39; H, 8.61; Si, 7.52.

3-Methoxycarbonyloxymethyl-6-methoxycarbonyloxy-7-trimethylsilylmethyloct-7-en-1-al (7): To a -60°C solution of 334 mg (0.889 mmol) of the above alcohol and 208 mg (2.66 mmol) of DMSO in 3.17 ml of methylenechloride was added 168 mg (1.33 mmol) of oxalyl chloride. The reaction mixture was stirred for 20 min and then 499 mg (4.44 mmol) of triethylamine added. The reaction mixture was stirred for an additional 5 min and then raised to room temperature. The reaction mixture was diluted with ether and water. The aqueous layer was extracted with ether and then the combined organic layers dried and concentrated *in vacuo*. The crude material was chromatographed through a 25 mm inner diameter column using 50 g of silica gel and 50% ether/hexane as eluent to afford 273.9 mg (82%) of the pure aldehyde; TLC R_f = 0.2 with 50% ether/hexane. Ir (neat): 3080, 2980, 2720, 1700, 1640, 1440 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ

9.77 (1H, t, J=1.2), 4.90 (2H, s + m), 4.73 (1H, s), 4.10 (2H, m), 3.78 and 3.77 (6H, two s), 2.47 (3H, m), 1.70-1.40 (8H, m), 0.05 (9H, s). Anal. calc'd for $C_{15}H_{27}O_4Si$ (M-$C_2H_3O_3$): 299.1679. Found: 299.1677.

cis- and *trans*-3-Methoxycarbonyloxymethyl-7-methylidene-9-oxabicyclo[4.3.0]nonane (8 and 9): To a refluxing solution of 10.5 mg (0.0102 mmol) of palladium dibenzylideneacetone chloroform complex, 26.6 mg (0.102 mmol) of triphenylphosphine, 70.8 mg (0.203 mmol) of tri-n-butyltin acetate, and 61.9 mg (0.304 mmol) of BSA in 1 ml of THF was added 76 mg (0.203 mmol) of the starting aldehyde in an additional 1 ml of THF. Upon disappearance of aldehyde as indicated by TLC, the reaction mixture was cooled to room temperature, concentrated and chromatographed using 5 g of silica gel in a 10 mm inner diameter column using 20% ether/hexane as eluent to afford 16.1 mg (35%) of the cis and trans products; TLC R_f(trans) = 0.14, R_f(cis) = 0.16 with 20% ether/hexane. Ir (neat): 3060, 2920 br, 2840, 1745 br, 1440 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ 4.94, 4.86, and 4.80 (2H, three br s, vinyl protons for cis and trans isomers), 4.51-4.21 (2H, overlapping AB patterns for cis and trans isomers), 4.08 (2H, d, J=6.2, methylene α to the carbonate for the trans compound), 4.00 (3H, d + m, J=5.9, methylene α to the carbonate and the bridgehead methine α to oxygen for the cis isomer), 3.72 (3H, s, methyl carbonate for the trans compound), 3.78 (3H, s, methyl carbonate for the cis isomer), 3.13 (1H, dt, J_d = 3.9, J_t = 10.9, bridgehead methine α to oxygen for the trans compound), 2.40-1.50 (8H, br m) Anal. calc'd for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1207.

5-*t*-Butyldimethylsiloxy-1-pentanal (3): To a solution of 5.5 g (25.2 mmol) of 5-*t*-butyldimethylsiloxy-1-pentanol (prepared as above) in 90 ml of dichloromethane at -50 to -60°C was added 4.34 g (55.5 mmol) of DMSO and 3.52 g (27.8 mmol) of oxalyl chloride. The reaction mixture was allowed to stir for 15 min and then 18.2 ml (126 mmol) of triethylamine added. The reaction mixture was allowed to stir for an additional 5 min and then the mixture warmed to room temperature. The reaction mixture was diluted with water and the aqueous layer extracted with ether. The combined organic layers were dried and concentrated *in vacuo*. The crude material was chromatographed through 350 g of silica gel in a 40 mm inner diameter column using 20% ether/hexane as eluent to afford 4.65 g (85%) of the pure aldehyde; TLC R_f = 0.4 with 20% ether/hexane. Ir (neat): 2920, 2840, 2700, 1720, 1462, 1380, 1350, 1245 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ 9.77 (1H, t, J=1.6), 3.63 (2H, t, J=6.3), 2.46 (2H, dt, J_d=1.6, J_t=7.1), 1.71 (2H, m), 1.56 (2H, m), 0.89 (9H, s), 0.05 (6H, s). Anal. calc'd for $C_{11}H_{25}O_2Si$ (M+1): 217.1624. Found: 217.1606.

5-Methoxycarbonyloxy-6-trimethylsilylmethylhept-6-en-1-ol: To a 0° solution of 0.65 g (3 mmol) of the aldehyde prepared as above in 6.0 ml of THF was added 9.0 ml of a *ca*. 0.5 *M* THF solution of the Grignard reagent 5b. When there was no evidence of aldehyde by TLC, 6.5 mmol of methyl chloroformate was added and stirring continued for 1.5 h at 0°C. The reaction mixture was then quenched with saturated ammonium chloride and the aqueous phase extracted with ether. The combined organic layers were dried and concentrated *in vacuo*. The crude product was then chromatographed through 50 g of silica gel in a 25 mm inner diameter column using 5% ether/hexane as eluent to afford 0.79 g (68%) of the purified product; TLC R_f = 0.3 with 5% ether/hexane. Ir (neat): 2940, 2920, 2848, 1742, 1635, 1438 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ 4.93 (1H, t, J=6), 4.91 (1H, br s), 4.72 (1H, br s), 3.76 (3H, s), 3.60 (2H, t, J=6.2), 1.7-1.3 (8H, br m), 0.89 (9H, s), 0.05 (9H, s), 0.04 (6H, s). Anal. calc'd for $C_{15}H_{31}O_4Si_2$ (M-C_4H_9): 331.1761. Found: 331.1748.

To a room temperature solution of 1.65 g (4.25 mmol) of the above silyl ether in 21.3 ml of THF was added 5.6 ml of a 1 *N* aqueous sulfuric acid solution. After 1.5 h, the reaction mixture was diluted with ether and water and the aqueous layer extracted with ether. The combined organic layers were dried and concentrated *in vacuo*. The crude oil was then

immediately chromatographed through 100 g of silica gel in a 30 mm inner diameter column using 50% ether/hexane as eluent to afford 0.94 g (81%) of the pure oil; TLC R_f = 0.2 with 50% ether/hexane. Ir (neat): 3380 br, 2940, 2850, 1745, 1630, 1438 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ 4.92 (1H, t, J=5.6), 4.89 (1H, s), 4.70 (1H, br s), 3.75 (3H, s), 3.62 (2H, t, J=6.5), 1.68 (2H, m), 1.60-1.40 (6H, br m), 0.03 (9H, s). Anal. calc'd for $C_{13}H_{26}O_4Si$: C, 56.90; H, 9.55; Si, 10.23. Found: C, 56.79; H, 9.50; Si, 10.35.

5-Methoxycarbonyloxy-6-trimethylsilylmethylhept-6-en-1-al (13): To a solution of 0.80 g (29 mmol) of alcohol in 10.5 ml of dichloromethane at -50 to -60°C was added 0.50 g (6.4 mmol) of DMSO and 0.41 g (3.2 mmol) of oxalyl chloride. The reaction mixture was allowed to stir for 15 min and then 2.1 ml (14.6 mmol) of triethylamine added. After an additional 5 min of stirring, the reaction mixture was allowed to warm to room temperature. The mixture was then diluted with water and the aqueous phase extracted with ether. The combined organic layers were dried and concentrated *in vacuo*. The crude aldehyde was chromatographed through 50 g of silica gel in a 20 mm inner diameter column using 20% ether/hexane as eluent to afford 0.60 g (77%) of a pure oil; TLC R_f = 0.3 with 20% ether/hexane. Ir (neat): 2950, 2880, 2710, 1745, 1720, 1635, 1440 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ 9.76 (1H, t, J=1.6), 4.94 (1H, m), 4.92 (1H, br s), 4.74 (1H, br s), 3.77 (3H, s), 2.47 (2H, m), 1.70 (4H, m), 1.62 (1H, A of AB, J=13.9), 1.37 (1H, B of AB, J = 13 9), 0.05 (9H, s). Anal. calc'd for $C_{12}H_{21}O_4Si$ (M-CH_3). 257.1209. Found: 257.1238.

2-Oxa-4-methylidenebicyclo[3.3.0]octane (14): In a representative experiment, 4.2 mg (.004 mmol) of palladium dibenzylidene acetone chloroform complex and 8.5 mg (0.04 mmol) of triisopropylphosphite was stirred in 0.5 ml of THF until bright yellow. To this mixture was added 11.8 mg (0.034 mmol) of tri-n-butyltin acetate and 10.4 mg (0.051 mmol) of BSA. After 5 min of stirring at room temperature, 9.3 mg (0.034 mmol) of the aldehyde as prepared above in 0.25 ml of THF was added and the temperature raised to reflux. After 1 h, the reaction mixture was cooled to 0° and concentrated *in vacuo* at a pressure of about 40 mm Hg. Integration of the internal standard vs. the product indicated the presence of a 31% yield of product. The product had the following spectral data: TLC R_f = 0.2 with 2% ether/hexane. Ir (neat): 3070, 2960, 2860, 1640 cm^{-1}; ^1H nmr ($CDCl_3$/270 MHz): δ 4.92 (2H, br s), 4.56 (1H, m), 4.36 (1H, A of AB, J=12.8), 4.17 (1H, B of AB, J=12.8), 3.02 (1H, m), 1.90-1.60 (6H, br m). Anal. calc'd for $C_8H_{12}O$: 124.0888. Found: 124.0876.

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