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Synthesis of the 3-Methylene-2-vinyltetrahydropyran Unit; the Hallmark of the Sesquiterpene, Hodgsonox

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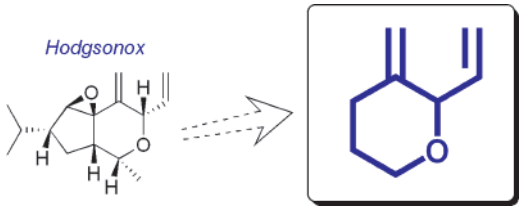
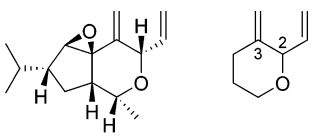


The synthesis of some simple compounds containing the previously unreported 3-methylene-2-vinyltetrahydropyran system, a unique feature of the liverwort metabolite, hodgsonox is reported. Key features are the creation of an acrolein substituted in the α-position with a three-carbon chain bearing a terminal electrophilic site, addition of a vinyl group, and cyclization.

Introduction

Hodgsonox (**1**),[1] isolated from the New Zealand liverwort *Lepidolaena hodgsoniae* Grolle, is the only liverwort sesquiterpene known to arise via the methyl erithritol phosphate biosynthetic pathway.[2] Its structurally distinguishing feature is that it contains a tetrahydropyran ring with the oxygen in a unique, doubly allylic environment, positioned between 1,1-disubstituted and monosubstituted double bonds as in **2**. This combination of functionality does not appear to have been encountered previously, whether in a natural product or in a synthetic compound. Hodgsonox proved to inhibit the larval development of an agricultural pest, the Australian greenbottle blowfly, *Lucilla cuprina*,[3] but this activity was lost upon epoxidation of the disubstituted double bond. This prompted our interest in synthesizing the basic 3-methylene-2-vinyltetrahydropyran **2** or some simple derivatives to explore the possible role of the doubly allylic ether system in the insecticidal activity.



1 **2**

Our synthetic strategy focused on the synthesis of an acrolein derivative substituted at C-2 with a three-carbon chain bearing a terminal cation equivalent. Addition of a vinyl anion equivalent to the aldehyde, followed by cyclization, would then lead to the desired framework. Alternative access to the central doubly allylic alcohol might be available by reaction of a pent-1-en-2-yl anion equivalent with acrolein (Scheme 1).

Results and Discussion

One approach to the realization of our synthetic strategy (Scheme 1, Path A) centered on the use of a halide leaving group as the cation equivalent. The known chlorohydrin **3** offered all the desired features. This masked acrolein derivative was accessible by bromination of acrolein and acetal protection,[4] followed by lithiation and reaction of the resulting vinyllithium with epichlorohydrin which had been pretreated with boron trifluoride etherate (Scheme 2).[5] We found this latter reaction to be very sensitive to the quality of the boron trifluoride etherate and prior distillation resulted in highly improved yields.

Base treatment of chlorohydrin **3** generated epoxide **4** which was hydrolyzed to form aldehyde **5**. Reaction with vinylmagnesium bromide created the key doubly allylic

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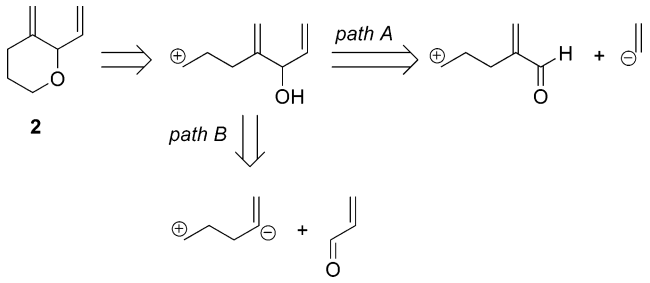
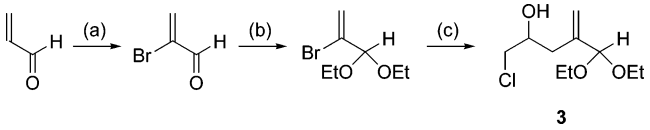
SCHEME 1. Strategy to Attain the 3-Methylene-2-vinyltetrahydropyran System 2

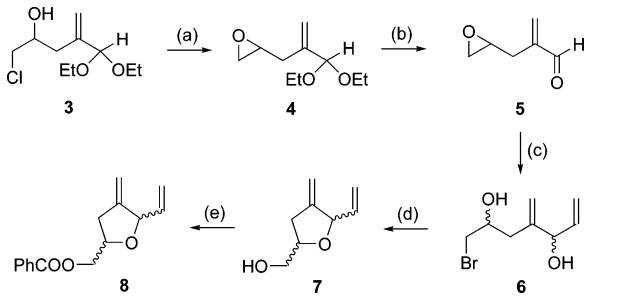


SCHEME 2. Preparation of Chlorohydrin 3 from Acrolein[a]



[a] (a) Br_2 (36%); (b) $(EtO)_3CH/NH_4NO_3$ (63%); (c) *n*-BuLi then epichlorohydrin/$BF_3.Et_2O$ (88%).

SCHEME 3. Synthesis of Tetrahydrofuran Derivatives 7 and 8[a]



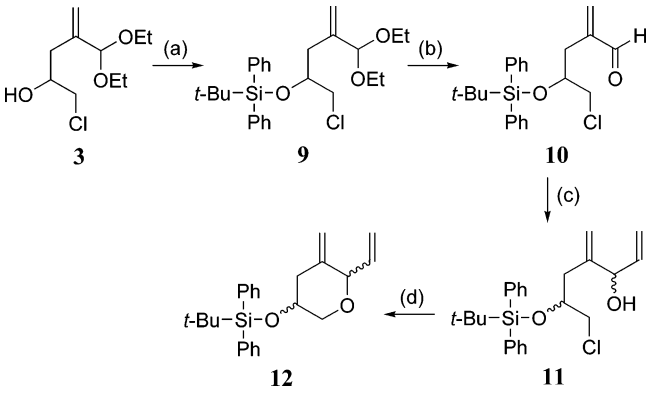
[a] (a) $NaOH/(CH_2OH)_2$ (48%); (b) $SiO_2/(COOH)_2$ (99%); (c) CH_2=$CHMgBr$ (23%); (d) NaH then (e) PhCOCl (11%).

alcohol (Scheme 3). As vinyl addition was accompanied by epoxide opening, the product was the bromo diol **6**, which was isolated as a 1.2:1 mixture of diastereomers.

Treatment of **6** with sodium hydride yielded the tetrahydrofuran derivative **7** as a cis/trans mixture, presumably via rapid epoxide formation followed by kinetically favored 5-exo cyclization. Compound **7** was characterized as its benzoate ester **8**. 2-Vinyl-3-methylenetetrahydrofuran derivatives have only been reported once before.[6]

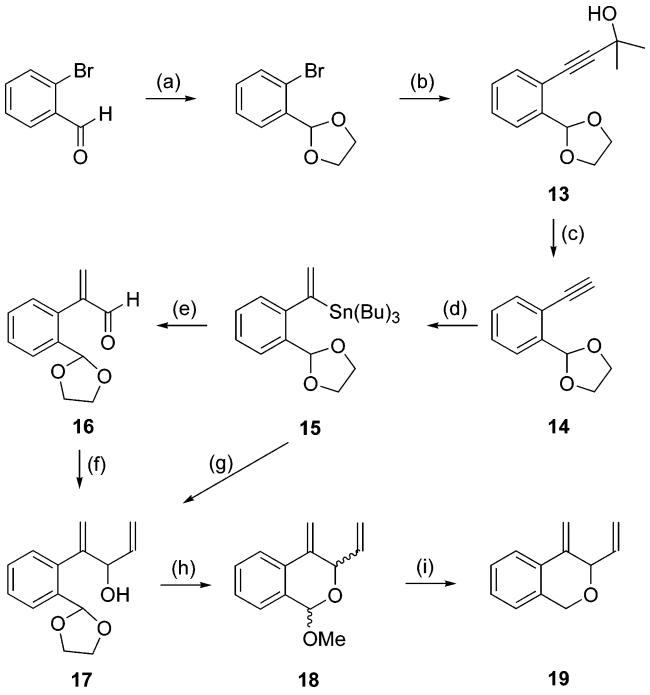
To control the ring size upon cyclization, compound **3** was transformed into the racemic *tert*-butyldiphenylsilyl ether **9**, previously reported as the (*S*)-isomer.[5] Acetal hydrolysis formed the target α-substituted acrolein **10**, and addition of a vinyl group was achieved with vinylmagnesium bromide to produce the doubly allylic alcohol **11** as a 1.2:1 mixture of diastereomers. Cyclization with NaH yielded the desired tetrahydropyran **12** (Scheme 4). The goal of synthesizing a 2-vinyl-3-methylenetetrahydropyran had been achieved, with a functionalized site at C-5 available for further modification. However, the formation of the product was complicated by the fact that

SCHEME 4. Synthesis of Tetrahydropyran Derivative 12[a]



[a] (a) *t*-$BuPh_2SiCl$/imidazole (96%); (b) $SiO_2/(COOH)_2$ (84%); (c) CH_2=$CHMgBr$ (65%); (d) NaH (33%).

SCHEME 5. Synthesis of Benz-Fused 2-Vinyl-3-methylenetetrahydropyran 19[a]



[a] (a) $(CH_2OH)_2$/PTSA (83%); (b) $PdCl_2(PPh_3)_2$/CuI/Et_3N/$(CH_3)_2$-COHC≡CH (88%); (c) NaH (75%); (d) $PdCl_2(PPh_3)_2/Bu_3SnH$ (99%); (e) *n*-BuLi then DMF (59%); (f) CH_2=$CHMgBr$ (81%); (g) *n*-BuLi then CH_2=CH−CHO (79%); (h) MeOH/PTSA; (95%) (i) Et_3SiH/CF_3COOH (95%).

both cis and trans isomers were produced and the yield for the cyclization step was low.

An alternative implementation of Scheme 1, Path A led to a benz-fused derivative of **2** in significantly higher yield (Scheme 5). The appropriately substituted acrolein was derived from *o*-bromobenzaldehyde. Acetal protection[7] was followed by palladium-catalyzed fusion with 2-methyl-3-butyn-2-ol by a procedure based on the method of Hiyama et al.[8] This yielded the hydroxy alkyne **13**

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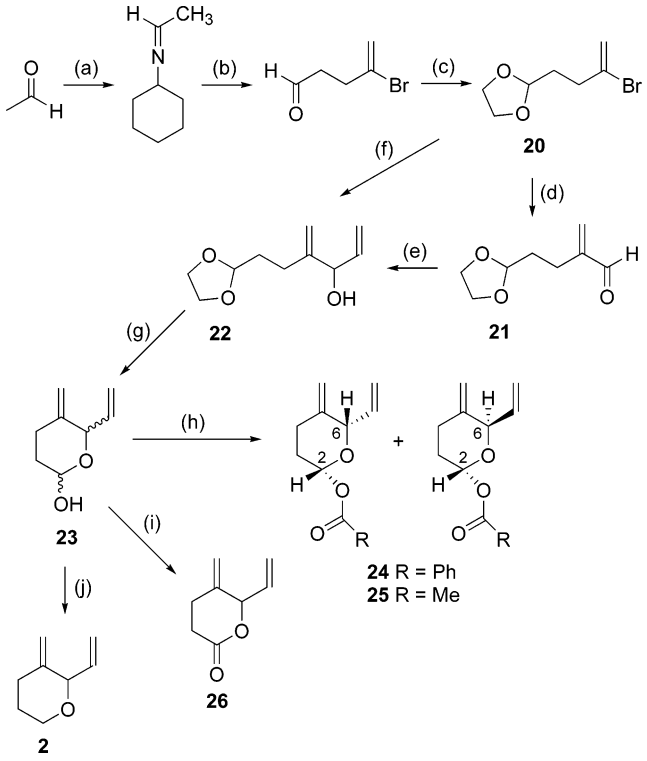
which was transformed into the terminal alkyne **14** by treatment with NaH followed by slow distillation to remove acetone.[9] Palladium-catalyzed hydrostannation of **14** was achieved in high yield by reaction with $PdCl_2(PPh_3)_2$ followed by treatment with tributyltin hydride. The addition of a tin adduct at either the terminal (β) or nonterminal (α) end of an alkyne has been reported, and best yields and excellent selectivity for production of the α-isomer have been reported for Wilkinson's catalyst, $RhCl(PPh_3)_3$.[10] However, a palladium catalyst[11] was chosen in this study because a sample was readily available and it proved remarkably effective, yielding only the α-adduct. The resulting vinyl tin derivative **15** was lithiated with butyllithium and then reacted with dimethylformamide to give the desired acrolein derivative **16**, the precursor to the critical cyclization event.

Transformation to the doubly allylic alcohol **17** was achieved either by reaction of aldehyde **16** with vinylmagnesium bromide (implementing Scheme 1, Path A) or from the vinyl tin derivative **15** by lithiation followed by reaction with acrolein (Scheme 1, Path B). Compound **17** proved difficult to handle and appeared to undergo cyclization to yield mixtures of products upon short-term storage. Internal acetal formation is favored in **17** as a result of the low degree of conformational freedom induced by the rigidity of the benzene ring. Spectra of **17** were obtained, but it was fully characterized by the microanalysis of its acetate. Methanolysis of **17** gave methoxy acetal **18**, which was separated into its cis and trans isomers in a 1:5.8 ratio. Reduction of the isomeric mixture by treatment with triethylsilane in the presence of trifluoroacetic acid[12] produced the benz-fused 2-vinyl-3-methylenepyran **19** (Scheme 5).

By a similar sequence, we achieved the synthesis of the parent structure **2** (Scheme 6). Published work by Kozmin[13] provided an efficient route via vinyl bromide **20** to the key substituted acrolein, 4-(1,3-dioxolan-2-yl)-2-methylenebutanal (**21**). The vinyl group was introduced as before, by addition of vinyl Grignard reagent (Scheme 1, Path A), but compound **22** could be formed more directly by lithiation of vinyl bromide **20**, followed by reaction with acrolein (Scheme 1, Path B). Acetal hydrolysis was accompanied by cyclization, forming hemiacetal **23**. This new 2-vinyl-3-methylenetetrahydropyran was also produced as a pair of geometric isomers. We did not attempt to separate these hemiacetals, but benzoylation followed by chromatography of the ensuing mixture on a silica gel yielded the pure cis and trans isomers of **24** in a 1:1.2 ratio. NOESY experiments identified the cis isomer by showing a correlation between H-2 and H-6. Only the cis isomer can occupy a conformation with both these two hydrogens axial and in reasonable proximity.

In an attempt to remove the complication of dealing with diastereoisomeric mixtures, oxidation of **23** was attempted using the Dess−Martin reagent. Preparative TLC of the crude product yielded both the cis and trans

SCHEME 6. Synthesis of 2-Vinyl-3-methylene-tetrahydropyan 2 and Derivatives[a]



[a] (a) Cyclohexylamine (82%); (b) Et_2NLi/HMPA then $CH_2{=}CBr{-}CH_2Br$ then hydrolysis (92%); (c) $(CH_2OH)_2$/PTSA (92%); (d) *t*-BuLi then DMF (86%); (e) $CH_2{=}CHMgBr$ (75%); (f) *t*-BuLi then $CH_2{=}CH{-}CHO$ (92%) (g) $HCl_{(aq)}$ (44%); (h) $PhCOCl/C_5H_5N$ (38%) or Dess−Martin (23%); (i) Ag_2CO_3/Celite (64%); (j) Et_3Si/CF_3COOH (63%).

isomers of acetate **25** but no significant quantity of lactone **26**. We could find no precedent for acetylation under these conditions. The stereochemistry of the acetates was determined by comparison of chemical shifts and coupling constants with those of the benzoate esters **24**. Oxidation of **23** was achieved by using Fetizon's reagent[14] which gave **26** in good yield. More significantly, the unembellished 2-vinyl-3-methylenetetrahydropyran **2** was successfully synthesized by treating hemiacetal **23** with triethylsilane in the presence of trifluoroacetic acid.

Conclusions

We have not had the opportunity to explore the potential of our synthetic tetrahydropyrans against *L. cuprina* as this assay is no longer available. Nonetheless, we have succeeded in developing a synthetic protocol for the 2-vinyl-3-methylene tetrahydropyran system found only in hodgsonox and, most notably, have created the basic unit **2**. The natural product, hodgsonox (**1**), remains to be synthesized.

Experimental Section

2-(2-Diethoxymethylallyl)-oxirane (4). On the basis of Imai et al.,[15] crushed NaOH was added to 1-chloro-4-(diethoxymethyl)-4-penten-2-ol (**3**) (0.673 g, 3 mmol) in ethylene

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glycol (3.5 mL) and the mixture was stirred at room temperature for 1 h. H_2O (15 mL) was added and the mixture was extracted into pentane and washed with H_2O. The organic layer was dried (Na_2SO_4) and evaporated to yield **4** as a volatile colorless oil (0.267 g, 48%): IR (film) ν_{max} 2976, 2930, 2875, 1443, 1328, 1117, 1060, 1010, 920, 829, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, J = 7 Hz, 6H, $-OCH_2CH_3$), 2.29 (dd, J = 4 Hz, 2H, H-1′) 2.49 (dd, J = 1.5, 3 Hz, 1H, H-3), 2.77 (m, 1H, H-3), 3.08 (m, 1H, H-2), 3.42−3.61 (m, 4H, $-OCH_2-CH_3$), 4.74 (s, 1H, $CH(OEt)_2$), 5.16 (s, 1H, H-3′), 5.25 (s, 1H, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1 (q, $O-CH_2CH_3$), 34.1 (t, C-1′), 47.1 (t, C-3), 51.1 (d, C-2), 61.8 (2 × t, $O-CH_2CH_3$), 103.5 (d, $CH(OEt)_2$), 114.9 (t, C-3′), 142.5 (s, C-2′); HRMS (EI) calcd for $C_{10}H_{18}O_3$ $M^{\cdot+}$ = 186.1256, found 186.1250.

2-Oxiranylmethylpropenal (5). On the basis of Huet et al.,[16] a slurry of Si-gel (0.855 g), 2-methylene-3,3-diethoxypropyloxirane (**4**) (0.285 g, 1.53 mmol), 10% aq oxalic acid (0.3 g), and CH_2Cl_2 (1.14 mL) was stirred at room temperature for 1 h. Saturated $NaHCO_3$ (200 μL) was added and the mixture was filtered. The Si-gel was rinsed with Et_2O (2×). Evaporation yielded (**5**) as a colorless oil (0.170 g, 99%): IR (film) ν_{max} 3450, 2927, 1689, 1438, 1092, 1060, 1011, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (br dd, J = 7, 15 Hz, 1H, H-1′), 2.43 (dd, J = 2.5, 5 Hz, 2H, H-3″), 2.54 (ddd, J = 1, 4, 15 Hz, 1H, H-1′), 2.70 (dd, J = 4, 5 Hz, 1H, H-3″), 3.06 (m, 1H, H-2″), 6.10 (s, 1H, H-3), 6.42 (s, 1H, H-3), 9.55 (s, 1H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.0 (t, C-1′), 46.8 (t, C-3″), 50.1 (d, C2″), 136.0 (t, C-3), 145.7 (s, C-2), 194.0 (s, C-1); HRMS (EI) calcd for $C_6H_8O_2$ $M^{\cdot+}$ = 112.0524, found 112.0525.

1-Bromo-4-methylenehept-6-ene-2,5-diol (6). On the basis of Sinha et al.,[17] vinylmagnesium bromide (1.9 mL, 1.9 mmol, 1.0 M in THF) was added dropwise with stirring over a period of 15 min to a stirred solution of aldehyde (**5**) (0.216 g, 1.9 mmol) in anhyd THF (5 mL) at −30 °C under an Ar atmosphere. The mixture was allowed to warm to room temperature overnight. The reaction was quenched by adding the mixture dropwise to an aq solution of ice-cold saturated NH_4Cl. The products were then extracted into Et_2O (3 × 30 mL). The organic layer was washed with saturated aq NH_4Cl (2 × 100 mL) and saturated aq NaCl (2 × 100 mL) before being dried ($MgSO_4$). Evaporation gave a crude product (0.253 g) that was separated by flash-column chromatography on Si-gel (8 g), eluted with a gradient of pentane:Et_2O 9:1−1:1.5. Cmpd **6** (0.095 g, 23%) was obtained as a pair of diastereomers in a 1.2:1 ratio (^1H and ^{13}C NMR): IR (film) ν_{max} 3382, 2930, 1719, 1664, 1640, 1422, 1329, 1296, 1043, 924 cm^{-1}; ^1H and ^{13}C NMR see Supporting Information; MS (EI) *m/z* 220/222 ($M^{\cdot+}$), 123 ($M^{\cdot+}-H_2O-Br$).

5-Ethenyl-4-methylenetetrahydro-2-furanmethanyl benzoate (8). On the basis of Brown et al.,[18] cmpd **6** (0.100 g, 0.45 mmol) in anhyd THF (4 mL) was added dropwise with stirring over 5 min to NaH (60% in oil, 0.010 g, 0.14 mol, prewashed with anhyd THF (3 × 1 mL)) in THF (1 mL) at −20 °C. The mixture was stirred for 3 h as it warmed to room temperature, then benzoyl chloride (0.11 mL, 0.90 mmol) was added, and the mixture was stirred for a further 30 min. The mixture was poured into Et_2O, washed with H_2O, and dried ($MgSO_4$). Evaporation was followed by separation on Si-gel (2 g) with elution with a pentane:Et_2O 9:1−1:1 gradient. Fractions containing impure **8** (pentane:Et_2O 4:1) (0.048 g) were further purified by a short Si-gel column in a Pasteur pipet, eluted with benzene. Fractions (0.5 mL) were collected and combined, on the basis of TLC, to yield **8** (0.013 g, 11%), a 1.1:1 mixture of two isomers (^1H and ^{13}C NMR), as a pale yellow oil: IR (film) ν_{max} 3423, 1719, 1638, 1272, 1068, 1026, 710 cm^{-1}; ^1H and ^{13}C NMR see Supporting Information; HRMS (EI) calcd for $C_{15}H_{16}O_2$ $M^{\cdot+}$ = 244.1099, found 244.1110.

A small-scale reaction on **6** (0.015 g), adding H_2O instead of benzoyl chloride, yielded a sample (0.005 g) of a 1.1:1 mixture (^1H and ^{13}C NMR) of two isomers of the underivatized alcohol **7**, of suitable purity for NMR experiments; ^1H and ^{13}C NMR see Supporting Information.

1-Chloro-2-*t*-butyldiphenylsiloxy-4-methylenehept-6-en-5-ol (11). Vinylmagnesium bromide (4.5 mL, 1 M in THF) was added dropwise with stirring over 15 min to a stirred solution of aldehyde **10** (0.50 g, 1.3 mmol) in anhyd THF (10 mL) at −30 °C under an Ar atmosphere. The mixture was warmed to room temperature (12 h) before being quenched by dropwise addition to saturated aq NH_4Cl at 0 °C. The mixture was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were washed with saturated aq NaCl (2 × 50 mL), dried ($MgSO_4$), and evaporated to yield diastereoisomers of **11** in a 1.1:1 ratio (^1H and ^{13}C NMR) as a pale yellow oil (0.467 g, ∼65%), contaminated with ca. 20% of *tert*-butyldiphenylsilyl impurities (^1H NMR): IR (film) ν_{max} 3415, 3071, 2957, 2931, 2858, 1427, 1111, 703, 505 cm^{-1}; ^1H and ^{13}C NMR see Supporting Information; HRMS (EI) calcd for $C_{20}H_{22}{}^{35/37}ClO_2Si$ $M^{\cdot+}-Bu$ = 357.1073, 359.1043, found 357.1071, 359.1057.

***cis*- and *trans-tert*-Butyldiphenyl(tetrahydro-5-methylene-6-vinyl-2*H*-pyran-3-yloxy)silane (12).** To a stirred suspension of NaH (0.60 g, 60% in oil, 0.01 mol, prewashed with dry pentane) in THF (10 mL) was added the unpurified chloro alcohol (**11**) (0.89 g, ∼1.7 mmol) in THF (30 mL) at −30 °C under Ar. The mixture was allowed to warm to room temperature and stirred for 24 h before addition of Et_2O (30 mL). The organic layer was washed with water (3 × 50 mL). The solvent was evaporated and the residue was purified by vacuum liquid chromatography on silica gel (30 g). Elution with a gradient of hexanes:CH_2Cl_2 1:0−0:1 afforded a 3.5:1 ratio (^{13}C NMR) of cis and trans **12** as a colorless oil (0.210 g, 33%): IR (film) ν_{max} 3071, 3047, 2957, 2928, 2855, 1785, 1727, 1638, 1589, 1471, 1111, 923, 822, 702, 614, 506 cm^{-1}; ^1H and ^{13}C NMR see Supporting Information; HRMS (EI) calcd for $C_{24}H_{30}O_2Si$ $M^{\cdot+}$ = 378.2015, found 378.2009.

4-(2-(1,3-Dioxolan-2-yl)phenyl)-2-methylbut-3-yne-2-ol (13). On the basis of Hiyama et al.,[8] a mixture of 2-(2-bromophenyl)-1,3-dioxolane (10.0 g, 43 mmol), 2-methyl-3-butyn-2-ol (5.0 g, 59 mmol), Et_3N (100 mL), and $PdCl_2(PPh_3)_2$ (0.90 g) in a 500-mL Schlenck tube was stirred under Ar for 10 min. CuI (0.10 g) was added and the solution was heated under reflux for 18 h. Once cooled, the ammonium salt was filtered off and the solvent evaporated. The resulting black oil was purified by vacuum-liquid chromatography on silica gel (20 g) eluted with a gradient of cyclohexane:EtOAc 7:1−1:1 to give **13** (8.82 g, 88%) as a yellow oil: IR (film) ν_{max} 3408, 2981, 2890, 1484, 1450, 1394, 1165, 1074, 964, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 6H, 2 × CH_3), 2.39 (br s, 1H, OH), 4.05, 4.17 (m, 2 × 2H, H-4″, H-5″), 6.16 (s, 1H, H-2″), 7.29 (ddd, J = 2, 8, 8 Hz, 1H, H-4′), 7.34 (ddd, J = 2, 8, 8 Hz, 1H, H-5′), 7.43 (dd, J = 2, 8 Hz, 1H, H-6′), 7.55 (dd, J = 2, 8 Hz, 1H, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4 (2 × q, CH_3), 63.6 (s, C-2), 65.5 (t, C-4″,C-5″), 79.3 (s, C-4), 98.9 (s, C-3), 101.9 (d, C-2″), 122.0 (s, C-1′), 126.0 (d, C-3′), 128.4 (d, C-4′), 128.9 (d, C-5′), 132.4 (d, C-6′), 138.9 (s, C-2′). An analytical sample was prepared by microdistillation at 98 °C/0.2 mm. Anal. calcd for $C_{14}H_{16}O_3$: C, 72.4; H, 6.9. Found: C, 72.1, H, 7.0.

2-(2-Ethynylphenyl)-1,3-dioxolane (14). On the basis of Smith et al.,[10] to NaH (0.10 g, 60% in oil, prewashed with pentane (3 × 1 mL)) was added a solution of the acetylenic alcohol **13** (2.11 g, 9.17 mmol) in anhyd toluene (30 mL). The stirred suspension was slowly distilled until the boiling point of the distillate reached 110 °C (ca.. 17 mL of distillate collected). The residue was cooled and the filtrate was evaporated under reduced pressure. The brown oil was dissolved in CH_2Cl_2 and the solution was washed with 5% $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated to give **14** (1.21 g, 75.4%) as a yellow oil: IR (film) ν_{max} 3280, 2887, 2360, 2341, 1394,

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1217, 1115, 1072, 943, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.32 (s, 1H,), 4.07, 4.17 (m, 2 × 2H, H-4, H-5), 6.22 (s, 1H, H-2), 7.32 (ddd, J = 2, 8, 8 Hz, 1H, H-4′), 7.39 (ddd, J = 2, 8, 8 Hz, 1H, H-5′), 7.52 (dd, J = 2, 8 Hz, 1H, H-6′), 7.58 (dd, J = 2, 8 Hz, 1H, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.6 (t, C-4, C-5), 80.9 (s, C-1″), 81.9 (d, C-2″), 101.8 (d, C-2), 121.4 (s, C-2′), 126.1 (d, C-6′), 129.0 (d, C-4′, C-5′), 133.2 (d, C-3′), 139.7 (s, C-1′). Anal. calcd for $C_{11}H_{10}O_2$: C, 75.8; H, 5.8. Found: C, 76.0; H, 6.0.

Tributyl-[1-(2-[1,3]dioxolan-2-ylphenyl)-vinyl]-stannane (15). On the basis of Zhang et al.,[11] to a stirred solution of the acetylene **14** (1.0 g, 5.7 mmol) in anhyd THF (20 mL) at 0 °C under Ar was added $PdCl_2(PPh_3)_2$ and the mixture was stirred for 10 min. Bu_3SnH (1.81 g, 6.0 mmol) was added dropwise over a 5-min period and the resulting solution was warmed to room temperature. Excess Bu_3SnH was added dropwise until a solution color change, from yellow to purple, was observed. Filtration through Celite (15 g) gave a dark oil (2.82 g). Vacuum-liquid chromatography on Al_2O_3 (15 g, basic, Activity I) eluted with cyclohexane:Et_2O 1:0−19:1 yielded **15** (2.67 g, 99%) as a yellow oil: IR (film) ν_{max} 3063, 3029, 2955, 1599, 1521, 1461, 1376, 1216, 1067, 942, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7 Hz, 9H, CH_2-CH_3), 0.87 (m, 6H, $CH_2-CH_2-CH_2$), 1.26 (tq, J = 7, 7 Hz, 6H, CH_2-CH_3), 1.42 (m, 6H, $Sn-CH_2$), 3.95, 4.14 (m, 2 × 2H, H-4″, H-5″), 5.58 (d, J = 3 Hz, 1H, $=CH_2$), 5.82 (s, 1H, H-2″), 5.83 (d, J = 3 Hz, 1H, $=CH_2$), 6.89 (dd, J = 2, 8 Hz, 1H, H-6′), 7.21 (ddd, J = 2, 8, 8 Hz, 1H, H-5′), 7.26 (ddd, J = 2, 8, 8 Hz, 1H, H-4′), 7.55 (dd, J = 2, 8 Hz, 1H, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3 (t, $Sn-CH_2$), 13.7 (q, CH_3), 27.3, 28.9 (2 × t, $Sn-CH_2-CH_2$), 65.4 (t, H-4″, H-5″), 101.4 (d, C-2″), 125.6 (d, C-4′), 126.1 (d, C-3′), 127.0 (d, C-6′), 128.7 (d, C-5′), 129.3 (t, C-2), 132.4 (s, C-2′), 147.4 (s, C-1′), 154.1 (s, C-1); HRMS (EI) calcd for $C_{19}H_{29}O_2{}^{116/117/118/119/120/122/124}Sn\ M^{+-}Bu$ = 405.1178, 406.1190, 407.1177, 408.1194, 409.1183, 411.1195, 413.1213, found 405.1178, 406.1199, 407.1186, 408.1202, 409.1189, 411.1202, 413.1213.

2-(2-(1,3-Dioxolan-2-yl)phenyl)pent-1,4-dien-3-ol (17). Method 1. To a solution of vinyl stannane **15** (1.6 g, 3.4 mmol) in anhyd THF (40 mL), cooled to −78 °C under Ar, was added *n*-BuLi (5 mL, 1.6 M in hexanes, 8.0 mmol) dropwise over 15 min (color change from yellow to purple). The solution was stirred for 15 min before the addition of anhyd DMF (5 mL) (color change from purple to yellow) and was warmed to room temperature overnight. The reaction was quenched by the addition of H_2O (100 mL) and the aq layer was extracted with Et_2O (2 × 50 mL). Combined organic fractions were dried ($MgSO_4$) and evaporated to give a yellow oil (1.81 g). Purification by column chromatography on silica gel (15 g) eluted with a gradient of cyclohexane:Et_2O 1:0−0:1 gave 2-(2-[1,3]dioxolan-2-yl-phenyl)-propenal (**16**) (0.413 g, 59%) as a yellow oil, which was used in the next step without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 3.95, 4.04 (m, 2 × 2H, H-4″, H-5″), 5.69 (s, 1H, H-2″), 6.38 (s, 1H, H-3), 6.48 (s, 1H, H-3), 7.13 (dd, J = 2, 8 Hz, 1H, H-6′), 7.38 (ddd, J = 2, 8, 8 Hz, 1H, H-5′), 7.41 (ddd, J = 2, 8, 8 Hz, 1H, H-4′), 7.65 (dd, J = 2, 8 Hz, 1H, H-3′), 9.74 (s, 1H, H-1).

Vinylmagnesium bromide (5.1 mL, 1 M in THF) was added dropwise over 15 min to a stirred solution of **16** (0.413 g, 2.0 mmol) in anhyd THF (15 mL) at −30 °C under Ar. The mixture was warmed to room temperature over 12 h. The reaction mixture was quenched by dropwise addition to saturated aq NH_4Cl (80 mL) at 0 °C and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with saturated aq NaCl (2 × 30 mL), dried ($MgSO_4$), and evaporated to yield **17** (0.376 g, 81%) as a yellow oil: IR ν_{max} 3444, 2926, 2873, 1695, 1457, 1368, 1210, 1047, 1038 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.39, 3.58 (m, 2 × 2H, H-4″, H-5″), 4.92 (br d, J = 5 Hz, 1H, H-3), 5.00 (ddd, J = 1.5, 1.5, 10.5 Hz, 1H, cis H-5), 5.08 (br s, 1H, $=CH_2$), 5.27 (ddd, J = 1.5, 1.5, 17.5 Hz, 1H, trans H-5), 5.49 (br s, 1H, $=CH_2$), 5.89 (ddd, J = 5, 10.5, 17.5 Hz, 1H, H-4), 6.00 (s, 1H, H-2″), 7.10 (dd, J = 2, 8 Hz, 1H, H-6′), 7.13 (ddd, J = 2, 8, 8 Hz, 1H, H-5′), 7.14 (ddd, J = 2, 8, 8 Hz, 1H, H-4′), 7.76 (dd, J = 2, 8 Hz, 1H, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$) 65.4 (2 × t, C-4″, C-5″), 76.4 (d, C-3), 101.8 (d, C-2″), 115.6 (t, C-1), 115.9 (t, C-5), 126.3 (d, C-6′), 127.6 (d, C-4′), 128.7 (d, C-5′), 129.4 (d, C-3′), 135.0 (s, C-2′), 138.6 (d, C-4), 139.7 (s, C-1′), 148.9 (s, C-2). Cmpd **17** was further characterized as its acetate. Acetic anhydride (0.3 mL) was added to a stirred solution of **17** (0.100 g, 0.43 mmol) in pyridine (2 mL) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature over 2 h. The solvents were removed by rotary evaporation under high vacuum to give (28) (0.111 g, 95%) as a yellow oil. Microdistillation at 110 °C/0.2 mm gave the acetate as a colorless oil. Anal. calcd for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6. Found: C, 70.3; H, 6.8.

Method 2. To a solution of vinyl stannane **15** (3.00 g, 6.45 mmol) in anhyd THF (50 mL), cooled to −78 °C under Ar, was added *n*-BuLi (4.2 mL, 1.6 M in hexanes, 6.7 mmol) dropwise over 20 min (color change from pale yellow to dark red). The reaction mixture was stirred for a further 20 min before the dropwise addition of acrolein (0.90 g, 15.0 mmol) in anhyd THF (10 mL). The reaction mixture was warmed to 0 °C (color change from dark red to yellow) before being poured into saturated aq NH_4Cl (200 mL) at 0 °C. The aq solution was extracted with Et_2O (2 × 70 mL) and the combined organic fractions were dried ($MgSO_4$) and evaporated to give a biphasic yellow oil. The separation of organotin residues from the desired product was achieved by partitioning the residue between pentane and acetonitrile (1:1, 100 mL). Rotary evaporation of the acetonitrile extract yielded a yellow oil (1.90 g) which was purified by vacuum-liquid chromatography on basic Al_2O_3 (30 g, Activity I) eluted with a gradient of hexanes: EtOAc 1:0−1:4 to give **17** (1.18 g, 79%).

3,4-Dihydro-1-methoxy-4-methylene-3-vinyl-1*H*-isochromene (18). *p*-TsOH (0.2 g) was added to hydroxy acetal **17** (0.70 g, 3.1 mmol) in MeOH (20 mL) and the mixture was heated under reflux under Ar for 3 h. The yellow solution was filtered through powdered $Ca(OH)_2$, washed with MeOH, and evaporated to give **18** (0.574 g, 95%) as a yellow oil: IR (film) ν_{max} 2929, 2889, 1694, 1485, 1368, 1208, 1083, 1047, 1031, 747 cm^{-1}. Preparative TLC (hexanes:Et_2O 1.3:1) gave the trans isomer as the major product (0.023 g), along with the cis isomer (0.004 g). Trans **18**: ^1H and ^{13}C NMR see Supporting Information; Anal. calcd for $C_{13}H_{14}O_2$: C, 77.2; H, 7.0. Found C, 77.0; H, 7.0. Cis **18**: ^1H and ^{13}C NMR see Supporting Information; HRMS (EI) calcd for $C_{13}H_{14}O_2\ M^{+}$ = 202.0994, found 202.0987.

3,4-Dihydro-4-methylene-3-vinyl-1*H*-isochromene (19). To cis and trans methyl acetal **18** (0.080 g, 0.39 mmol) in CH_2Cl_2 cooled to 0 °C was added TFA (0.05 mL, 0.66 mmol) and the solution was stirred for 15 min. Et_3SiH (0.10 mL, 0.63 mmol) was added to the stirred solution which was slowly warmed to room temperature (6 h) before being quenched with H_2O (15 mL). The product was extracted with $CHCl_3$ (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to give **19** (0.064 g, 95%) as a colorless oil: IR (film) ν_{max} 3019, 2928, 1694, 1455, 1216, 1083, 757, 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 (br d, J = 6 Hz, 1H, H-3), 4.84 (d, J = 12 Hz, 2H, H-1), 5.06 (br s, 1H, $C=CH_2$), 5.35 (ddd, J = 1.5, 1.5, 17.5 Hz, 1H, $CH=CH_2$), 5.36 (ddd, J = 1.5, 1.5, 9.5 Hz, 1H, $CH=CH_2$), 5.72 (br s, 1H, $C=CH_2$), 6.04 (ddd, J = 6, 9.5, 17.5 Hz, 1H, $CH = CH_2$), 7.03 (dm, J = 8 Hz, 1H, H-8), 7.23 (m, 1H, H-6), 7.25 (m, 1H, H-7), 7.69 (dm, J = 8 Hz, 1H, H-5); ^{13}C NMR δ 66.5 (t, C-1), 79.1 (d, C-3), 108.7 (t, $C = CH_2$), 119.2 (t, $CH = CH_2$), 123.8 (d, C-5), 124.5 (d, C-8), 127.0 (d, C-6), 127.9 (d, C-7), 131.2 (s, C-4a), 134.3 (s, C-8a), 136.0 (d, $CH=CH_2$), 140.1 (s, C-4); HRMS (EI) calcd for $C_{12}H_{22}O\ M^{+}$ = 172.0888, found 172.0883. Anal. calcd for $C_{12}H_{12}O$: C, 83.7; H, 7.0. Found C, 83.6; H, 7.0.

6-(1,3-Dioxolan-2-yl)-4-methyenehex-1-en-3-ol (22). Method 1. Vinylmagnesium bromide (14.5 mL, 1 M in THF, 14.5 mmol) was added dropwise over 15 min to a stirred solution of aldehyde **21** (2.21 g, 14.1 mmol) in anhyd THF (80 mL) at −30 °C under Ar. The mixture was warmed to room

temperature over 12 h. The reaction mixture was quenched by dropwise addition to saturated aq NH_4Cl (200 mL) at 0 °C and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with saturated aq NaCl (2 × 100 mL), dried ($MgSO_4$), and evaporated to yield **22** (1.956 g, 75%) as a colorless oil: IR (film) ν_{max} 3442, 2952, 2883, 1683, 1208, 1138, 1037, 967, 750, 576 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.84 (m, 2H, H-5), 2.14 (m, 2H, H-6), 2.63 (br s, 1H, OH), 3.82, 3.93 (m, 2 × 2H, H-4′, H-5′), 4.54 (br d, J = 6 Hz, 1H, H-3), 4.86 (t, J = 5 Hz, 1H, H-2′), 4.88 (d, J = 1 Hz, 1H, =CH_2), 5.09 (d, J = 1 Hz, 1H, =CH_2), 5.14 (ddd, J = 1.5, 1.5, 10.5 Hz, 1H, H-1), 5.28 (ddd, J = 1.5, 1.5, 17 Hz, 1H, H-1), 5.82 (ddd, J = 6, 10.5, 17 Hz, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9 (t, C-5), 32.1 (t, C-6), 64.9 (t, C-4′,C-5′), 76.2 (d, C-3), 104.2 (d, C-2′), 110.4 (t, = CH$_2$) 115.6 (t, C-1), 139.1 (d, C-2), 149.6 (s, C-4); HRMS (EI) calcd for $C_{10}H_{14}O_2$ $M^{+-}H_2O$ = 166.0994, found 166.0992.

Method 2. To a stirred solution of vinyl bromide **20** (5.00 g, 24.2 mmol) in THF (30 mL) was added *n*-BuLi (20 mL, 1.6 M in hexanes, 32.0 mmol) over 30 min at −78 C, under Ar. Acrolein (2.5 mL, 36.0 mmol) in THF (20 mL) was added and the reaction mixture was allowed to warm to 0 °C before being quenched by the addition of saturated NH_4Cl (80 mL) at 0 °C. The aq layer was extracted with Et_2O (2 × 100 mL) and the combined ethereal fractions were washed with NH_4Cl (100 mL), dried ($MgSO_4$), and evaporated to give **22** (4.12 g, 92%) as a yellow oil.

Tetrahydro-5-methylene-6-vinyl-2*H*-pyran-2-ol (23). A mixture of HCl (8 mL, 3 M) and hydroxy acetal **22** (1.95 g, 10.5 mmol) in THF (115 mL) was gently heated under reflux under Ar for 10 h. The resulting mixture was partitioned between aq 10% $NaHCO_3$ (25 mL) and Et_2O (150 mL). The organic layer was dried ($MgSO_4$) and evaporated to yield a brown oil (1.67 g). Purification by flash-column chromatography on silica gel (10 g) eluted with a gradient of pentane:Et_2O 9:1−1:1 afforded diastereomeric **23** (0.654 g, 44%) as a colorless oil: IR (film) ν_{max} 3442, 2925, 1694, 1456, 1368, 1209, 1082, 1046, 992, 750 cm^{-1}; ^1H and ^{13}C NMR see Supporting Information. Anal. calcd for $C_8H_{12}O_2$: C, 68.5; H, 8.6. Found: C, 68.3; H, 8.7.

***cis*- and *trans*-Tetrahydro-5-methylene-6-vinyl-2*H*-pyran-2-yl benzoate (24).** Benzoyl chloride (0.25 mL, 2.1 mmol) was added dropwise to a stirred solution of hemiacetal (**23**) (0.10 g, 0.71 mmol) in anhyd pyridine (1.0 mL) at 0 °C under Ar. The reaction mixture was warmed to room temperature. After 16 h, a mixture of iced H_2O (2.1 mL) was added and the mixture was stirred for an additional 50 min. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with ice-cold aq H_2SO_4 (3 × 20 mL, 3 M), H_2O (3 × 20 mL), and saturated aq $NaHCO_3$ (3 × 20 mL). The combined organic fractions were dried ($NaSO_4$) and evaporated to give crude benzoate (0.111 g) as a brown oil. Column chromatography on silica gel (4 g) eluted with a gradient of cyclohexane:Et_2O 20:1−3:1 afforded the trans isomer (0.036 g, 21%), a cis/trans mixture (0.019 g, 11%), followed by the cis isomer (0.029 g, 17%) as colorless oils. cis-**24**: IR (film) ν_{max} 3083, 2953, 2930, 2855, 1724, 1450, 1314, 1273, 1136, 1093, 1023, 910, 710 cm^{-1}; ^1H and ^{13}C NMR see Supporting Information. Anal. calcd for $C_{15}H_{16}O_3$: C, 73.8; H, 6.6. Found: C, 73.4; H, 6.8. trans-**24**: IR (film) ν_{max} 3071, 2953, 2931, 2857, 1724, 1450, 1314, 1273, 1136, 1093, 1023, 910, 710 cm^{-1}; ^1H and ^{13}C NMR see Supporting Information. Anal. calcd for $C_{15}H_{16}O_3$: C, 73.8; H, 6.6. Found: C, 74.0; H, 6.7.

***cis*- and *trans*-Tetrahydro-5-methylene-6-vinyl-2*H*-pyran-2-yl acetate (25).** Hemiacetal **23** (0.50 g, 1.2 mmol) in CH_2Cl_2 (6 mL) was added to Dess−Martin periodinane (0.5 g, 1.2 mmol) in CH_2Cl_2 (8 mL) with stirring under Ar. After 20 min, the reaction mixture was quenched with Et_2O, added to NaOH (15 mL, 1.3 M), and stirred for 10 min. The organic layer was separated and washed with NaOH (20 mL, 1.3 M) and H_2O (20 mL). The solvent was removed by distillation to yield crude material (0.98 g). Silica gel column purification (3.5 g) eluted with a gradient of cyclohexane:Et_2O 20:1−2.3:1 yielded a mixture of the diastereomeric acetates **25** (0.051 g, 23%) as a colorless oil: Anal. calcd for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7. Found: C, 65.9; H, 7.9. Preparative TLC (hexanes:Et_2O 1:5) separated the trans isomer (0.021 g) from the cis isomer (0.006 g). cis-**25** had IR (film) ν_{max} 2928, 2855, 2357, 1722, 1175, 1081, 1018, 910, 889, 750 cm^{-1}; ^1H and ^{13}C NMR see Supporting Information. trans-**25** had IR (film) ν_{max} 2931, 2854, 2355, 1723, 1451, 1272, 1175, 1081, 910, 889, 750 cm^{-1}; ^1H and ^{13}C NMR see Supporting Information.

Tetrahydro-5-methylene-6-vinyl-2*H*-pyran-2-one (26). Ag_2CO_3 on Celite[14] was added to hemiacetal **23** (0.20 g, 1.4 mmol) in anhyd benzene (15 mL) and the mixture was heated under reflux under Ar for 6 h. The mixture was filtered through Celite and washed with EtOAc (100 mL). The solvent was evaporated and the residue purified by column chromatography on silica gel (13 g) eluted with a gradient of pentane:Et_2O 1:0−1:1.5 to yield **26** (0.124 g, 64%). IR (film) ν_{max} 2924, 2854, 1724, 1455, 1359, 1141, 1034, 924 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.63 (m, 4H, H-3, H-4), 5.09 (br s, 1H, =CH_2), 5.13 (br s, 1H, =CH_2), 5.30 (br d, J = 6 Hz, 1H, H-6), 5.38 (ddd, J = 1.5, 1.5, 11.5 Hz, 1H, CH=CH_2), 5.39 (ddd, J = 1.5, 1.5, 17.5 Hz, 1H, CH=CH_2), 5.93 (ddd, J = 6, 11.5, 17.5 Hz, 1H, CH = CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7 (t, C-4), 30.3 (t, C-3), 82.3 (d, C-6), 113.2 (t, = CH$_2$), 118.4 (t, CH = CH$_2$), 134.6 (d, CH=CH$_2$), 140.0 (s, C-5), 171.2 (s, C-2). HRMS (EI) calcd for $C_8H_{10}O_2$ M^{+} = 138.0679, found 138.0681.

Tetrahydro-3-methylene-2-vinyl-2*H*-pyran (2). To hemiacetal **23** (0.50 g, 3.57 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added TFA (0.30 mL, 3.96 mmol) and the solution was stirred for 20 min. Et_3SiH (0.60 mL, 3.78 mmol) was added to the stirred solution which was slowly warmed to room temperature over 6 h before being quenched with water H_2O (15 mL). The product was extracted with $CHCl_3$ (3 × 25 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (15 g) eluted with a gradient of pentane:Et_2O 1:0−2:1 yielded **2** (0.28 g, 63%) as a colorless oil: IR (film) ν_{max} 2960, 1788, 1458, 1404, 1344, 1260, 1150, 1093, 1021, 801, 460 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.73 (m, 2H, H-5), 2.27 (m, 1H, H-4), 2.45 (ddd, J = 5, 5, 13.5 Hz, 1H, H-4), 3.64 (ddd, J = 1.5, 4, 11.5 Hz, 1H, H-6), 3.99 (ddd, J = 1.5, 4, 11.5 Hz, 1H, H-6), 4.35 (d, J = 6 Hz, 1H, H-2), 4.78 (br s, 1H, C=CH_2), 4.84 (br s, 1H, C=CH_2), 5.29 (ddd, J = 1.5, 1.5, 11.5 Hz, 1H, CH=CH_2), 5.30 (ddd, J = 1.5, 1.5, 16.5 Hz, 1H, CH=CH_2), 5.96 (ddd, J = 6, 11.5, 16.5 Hz, 1H, CH = CH_2; ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (t, C-5), 31.9 (t, C-4), 66.4 (t, C-6), 80.3 (d, C-2), 109.5 (t, C = CH$_2$), 117.7 (CH = CH$_2$), 136.4 (CH=CH$_2$), 145.9 (C-3): HRMS (EI) calcd for $C_8H_{12}O$ M^{+} = 124.0888, found 124.0890.

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Supporting Information Available: Experimental procedures and new data for previously reported compounds; listings of ^1H and ^{13}C NMR data for pairs of diastereomers **6**, **7**, **8**, **11**, **12**, **18**, **23**, **24**, and **25**; ^{13}C NMR spectra of compounds **2**, **4**, **5**, **6**, **8**, **11**, **12**, **13**, **14**, **15, 17**, trans-**18**, **19**, **22**, cis- and trans-**24,** trans-**25**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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