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Furanosides and Furanones Bearing Acrylate Sidechains via Palladium-Mediated Cyclizations of γ-Oxoallenes†

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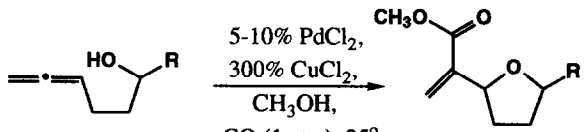
Abstract: *Treatment of 4,5-hexadienal with catalytic palladium(II) chloride and excess copper(II) chloride, methanol and carbon monoxide in the presence of an acid and a water scavenger resulted in a net acetalization-cyclization-methoxycarbonylation to form a novel methyl furanoside bearing a methyl acrylate sidechain. Treatment of 4,5-hexadienoic acid under the same conditions yields the corresponding furanone, and 3-(tert-butyldimethylsilyloxy)-4,5-hexadienal yields a methyl β-3'-(tert-butyldimethylsilyloxy)-2'-deoxyribofuranoside bearing the acrylate sidechain, with high stereoselectivity. This methodology provides access to sidechain-branched ribofuranoside compounds.*

INTRODUCTION

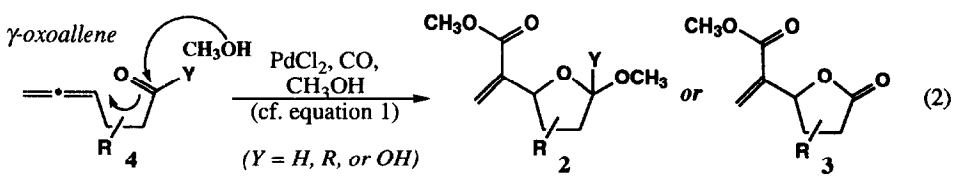
The intramolecular oxypalladation of γ-hydroxyallenes in the presence of carbon monoxide and methanol (equation 1) constitutes an effective method for constructing methyl 2-(tetrahydrofuran-2-yl)propanoates (general structure **1**).[1,2,3] We have adapted this methodology for stereospecifically producing cis-2,5-disubstituted tetrahydrofurans bearing acrylate sidechains, and we are currently applying that chemistry to the syntheses of tetrahydrofuran-containing natural products and ionophoric agents.[2,4]



(1)

1 *(Ave. 80%, 50:50 cis:trans)*

A useful extension of this methodology would be the production of tetrahydrofuran-substituted acrylates bearing a methoxy or oxo group at position 2 of the tetrahydrofuran ring, because such products (general structures **2** and **3**, equation 2) would constitute furanosides (or precursors to furanosides) of sidechain-branched sugars, in turn convertible to novel analogues of nucleosides.[5] Feasible cyclization precursors for such syntheses would be γ-oxoallenes (**4**, equation 2) --- that is, β-allenyl aldehydes, ketones and acids --- which have not been investigated for such purposes before. In this paper, we report that 1) the intramolecular oxypalladation of 4,5-hexadienal and 4,5-hexadienoic acid, when conducted under acid- and water-free conditions, yields the acrylate-substituted furanoside and furanone, respectively; 2) the application of this methodology to a 3-silyloxy-4,5-hexadienal substrate yields a 2'-deoxyribofuranoside analogue with high stereoselecti-



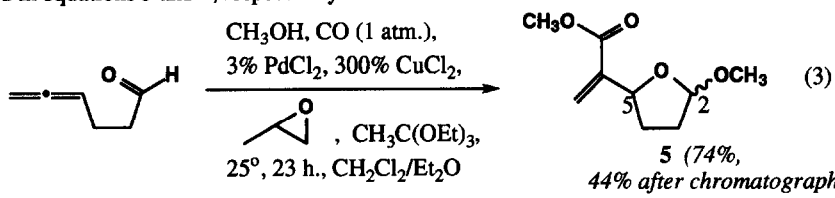
(2)

†Dedicated with respect and affection to Professor Carl Djerassi on the occasion of his 70th birthday.

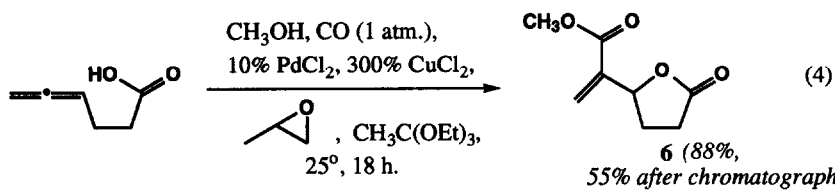
vity for the C_3-C_4 trans geometry; and 3) this methodology cannot, in its present form, be efficiently extended to β-allenylketones. Overall, an experimentally facile and reliable access to multiply substituted tetrahydrofuran-substituted acrylates has been accomplished.

RESULTS AND DISCUSSION

1) Intramolecular Oxypalladations of 4,5-Hexadienal and 4,5-Hexadienoic Acid. Treatment of 4,5-hexadienal[6] or 4,5-hexadienoic acid[7] under the conditions previously employed for the palladium(II)-mediated cyclization/methoxycarbonylations of the analogous alcohols (cf. equation 1)[1,2] resulted in complex mixtures of products. However, the inclusion of propylene oxide as an acid sink and triethyl orthoacetate as a water scavenger --- conditions suggested to us by the research of Tamaru and coworkers[8] ---resulted in the clean conversions of 4,5-hexadienal to the methyl furanoside **5**, and of 4,5-hexadienoic acid to the furanone **6**, as indicated in equations 3 and 4, respectively.



5 *(74%, 44% after chromatography)* (3)



6 *(88%, 55% after chromatography)* (4)

The furanoside **5** was produced as a 50:50 mixture of cis and trans ("β and α") isomers ("anomers") which could be purified using silica gel chromatography, albeit with substantial losses of material (74% crude yield, 44% "chromatographed yield"). (The cis and trans geometries of the isomers of **5** thus obtained could be distinguished by the relative ^{1}H-NMR chemical shifts of hydrogens attached to the methoxy and acrylate sidechains for the two isomers (consistently more downfield in cis isomer, relative to trans isomer) and by the relative ^{1}H-NMR chemical shifts of the ring hydrogens at positions 2 and 5 for the two isomers (consistently more downfield in the trans isomer, relative to the cis isomer), as indicated in the Experimental Section). The significant losses of product during chromatography deserves comment. It is presumably due to the allylic nature of the tetrahydrofuran oxygen in **5**, the readily displaceable anomeric methoxy group, and the susceptibility of the acrylate moiety to undergo nucleophilic attack --- all of which would contribute to substitution, transacetalization, and/or addition reactions between **5** and the silanol moieties of the silica gel surface.

The furanone **6** was also unstable to chromatography (88% crude yield, 55% "chromatographed yield"). Acceptable methodology for purifying **5** and **6** without suffering significant losses of material remains to be discovered. However, these products could, in practice, be isolated directly from the reaction mixtures in sufficient purity (>90%, according to ^{1}H-NMR) that they could, if necessary, be used as synthetic intermediates without further purification.

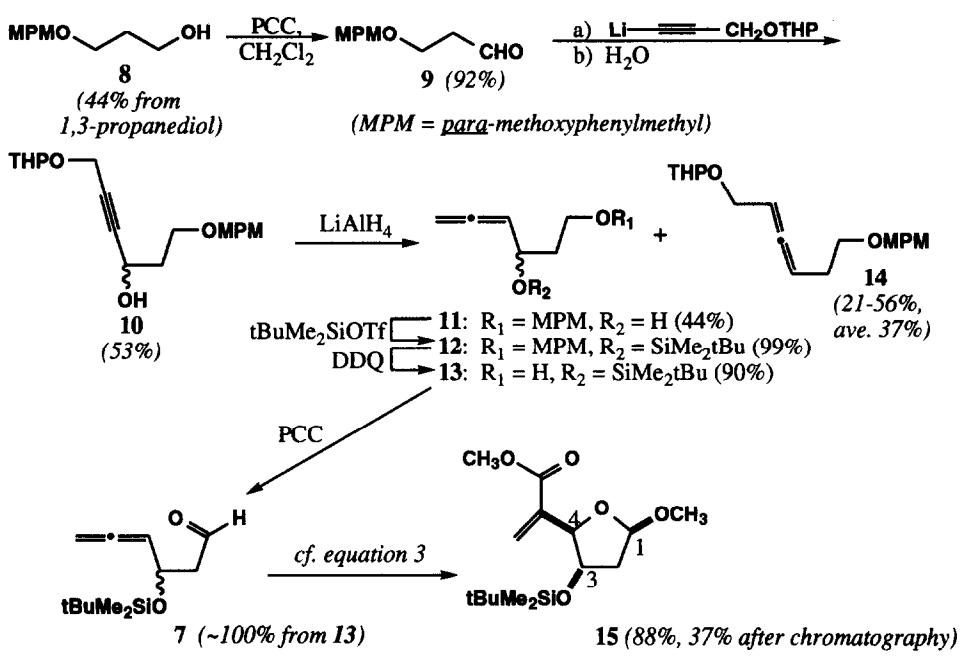
2) Synthesis of a 2'-Deoxyribofuranoside Analogue. Encouraged by the successful production of the furanoside **5** --- a branched sidechain 2'-, 3'-dideoxyribofuranose analogue --- we tested the γ-oxoallene based methodology for the production of a 3'-oxygenated counterpart to **5** (a 2'-deoxyribofuranose analogue) via the

cyclization of an appropriately protected 3-hydroxy-4,5-hexadienal. Such a test would address the question of how a substituent on the hexadienal chain, in this case a protected β-hydroxy group, would affect the stereochemical outcome of the cyclization --- a crucial issue for the application of this methodology to the synthesis of stereodefined 2'-deoxyribonucleoside analogues.

The cyclization precursor, 3-tert-butyldimethylsilyloxy-4,5-hexadienal (**7**) was synthesized starting with 1,3-propanediol and proceeding through intermediates **8** - **13** by the route indicated in Scheme 1. This route utilized Landor's methodology for producing allenyl carbinols via hydride reduction of tetrahydropyranyloxymethyl-substituted propargylic alcohols,[9] a method which has proven its utility in other work[10] but which, in our system (**10** → **11**), gave significant amounts of the byproduct **14**.[11] Other aspects of the synthesis of **7** were unremarkable, the aldehyde being produced from 1,3-propanediol in seven steps and 7% overall yield.[12]

The palladium(II)-mediated cyclization/methoxycarbonylation of the hexadienal **7** proceeded efficiently to yield the glycoside **15** in 88% crude yield (Scheme 1). This product was produced as a single diastereomer,

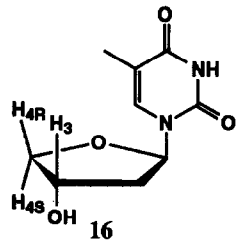
Scheme 1



as indicated by an NMR analysis of the crude reaction mixture. Subsequent chromatographic purification of **15** resulted in losses of material similar to that observed with the furanoside **5**.

The trans relative stereochemistry assigned to the C_3-C_4 centers (carbohydrate numbering system) of **15** is based on several observations. The ^{1}H-NMR coupling constant between the hydrogens on carbons 3 and 4 was small (2.5 Hz), and no measurable nuclear Overhauser effect was observed between them. This H_3-H_4 coupling constant agrees with values observed for similar systems, such as the H_3-H_{4S} coupling constant of 2.3 Hz for compound **16**[13] and the H_3-H_4 coupling constant of 3.5 Hz for compound **17**.[14] Also, it should be noted that the selectivity observed for the trans relative stereochemistry of the C_3-C_4 centers of **15** is in accord with the stereoselectivity observed by Semmelhack for the similar palladium(II)-mediated cyclization of 2-tert-butyldimethylsilyloxy-3-buten-1-yl carbinols.[15]

The relative configuration ("β") at C_1 in the product **15** was assigned on the basis of nuclear Overhauser



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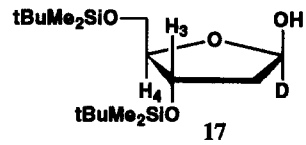

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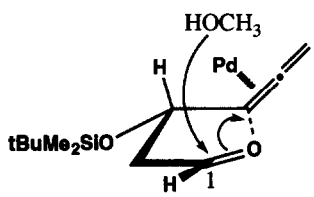
effect measurements which indicated positive nOe's between 1) the vinylic hydrogens and the 1-methoxy CH_3 hydrogens; and 2) the C_1 hydrogen and the hydrogens of the alkyl groups (tert-butyl, methyls) on the silicon. In addition, the triplet pattern observed for the hydrogen on C_1 in the ^{1}H-NMR spectrum of **15** agrees with the pattern for this signal found to be characteristic for β anomers of nucleosides noted by Robins and Robins.[16]

We propose the two transition state models shown in **18** and **19**, which are similar in their conformational aspects to those proposed by Semmelhack for his palladium-mediated cyclizations of hydroxyalkenes,[15] to explain the stereochemical outcome of the cyclization of **7** to form **15**. Both models imply that the stereoselectivity for the C_3-C_4 trans configuration is due to the bulky trialkylsilyl group favoring an orientation which is away (trans) from the developing vinylpalladium group at C_4 in a cyclic transition state. In the transition state model **18**, the cyclization is envisioned to proceed by way of an interaction between the aldehyde oxygen and the palladium-bound allene with a concommitant attack --- via the least hindered approach --- by methanol at C_1 to result in the β configuration at C_1. In the transition state model **19**, the cyclization is considered to proceed via the interaction between the hydroxyl oxygen of the 1S epimer (rapidly equilibrating with its 1R isomer) of a preformed hemiacetal and the palladium-bound allene, where that epimer can orient its methoxy group away from the bulky trialkylsilyloxy group during the transition state.



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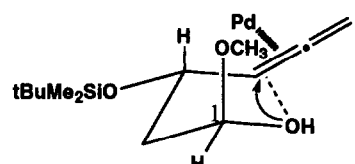

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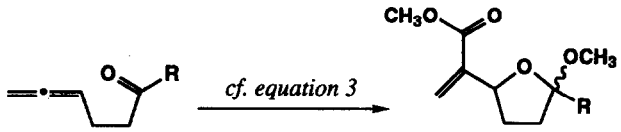
3) Attempted Intramolecular Oxypalladations of β-Allenylketones. When 5,6-heptadien-2-one (**20**) and 6,7-octadien-3-one (**21**)[17] were subjected to the cyclization/methoxycarbonylation conditions, complex mixtures of products were produced (equation 5). From the reaction mixture obtained from the reaction of **20**, a trace (<1%) of the expected furanoside **22** was obtained, and the reaction of **21** yielded the furanoside **23** in 7% yield. It appears that the slower rate of cyclization of these substrates (relative to the aldehydes **5** and **7**) allowed various side reactions to occur, leading to the observed complex mixtures. Gallagher has observed competing oxypalladation and chloropalladation side reactions during the course of some of his palladium(II)-mediated cyclizations of aminoallenes,[3] a side reaction that we have not observed to a significant extent with our oxygen systems.[1,2] Another possible reason for the low yields of furanosides obtained from the allenylketones is that the tertiary nature of the ketal carbon in the cyclized products (or cyclized intermediates) renders such compounds highly susceptible to elimination reactions to form dihydrofuran products which, in turn may undergo various solvolytic decomposition reactions. It is interesting to compare these results with the previously reported cyclizations of di(ω-alkenyl)ketones to form bicyclic ketals under conditions similar to

ours ($PdCl_2$, $CuCl_2$, methanol, CO).[18] Such bicyclic ketals would be more resistant to solvolysis than the monocyclic ketals attempted in this study.



20: R = CH_3
21: R = CH_2CH_3

22: R = CH_3 (trace)
23: R = CH_2CH_3 (7%)

(5)

CONCLUSIONS

The cyclization of γ-oxoallenes mediated by palladium(II) chloride under conditions which couple the vinylpalladium intermediate to the methoxycarbonyl group has been shown to be a viable route to furanosides and furanones bearing an acrylate sidechain, as long as the γ-oxoallene substrate is an aldehyde or an acid.

The furanosides which can be synthesized using this methodology (e.g. **5** and **15**) are amenable to straightforward manipulation into sidechain-branched nucleoside analogues which may possess unique biological activities and exert interesting effects upon the properties of oligonucleotides into which they are incorporated. Research aimed at exploring such possibilities, and developing nonracemic substrates for such syntheses, is currently underway.

EXPERIMENTAL SECTION

General. Unless otherwise indicated, solvents and reagents were reagent grade and used without purification. Methanol was distilled from magnesium turnings and stored in a sealed container. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone ketyl under nitrogen immediately prior to use. Dichloromethane was distilled from calcium hydride immediately prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen in glassware that had been oven dried. Flash chromatography was performed using 230-400 mesh silica gel (Aldrich). High performance liquid chromatography (HPLC) was performed using a DuPont Zorbax-Sil column (5 m silica gel packing, 25 cm X 4 mm ID), refractometry detection, and the isocratic hexane-ethyl acetate eluents and flowrates indicated. Infrared spectra were recorded using neat films on sodium chloride plates and are reported in wavenumbers (cm^{-1}). ^1H (200 or 300 MHz) and ^{13}C (50 MHz) were obtained from solutions in $CDCl_3$ and chemical shifts are reported in parts per million (ppm, δ) downfield from a tetramethylsilane (TMS) internal standard. Coupling constants are reported in Hertz (Hz). NMR data are reported as follows: chemical shift (multiplicity [s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, dd=doublet of doublets, dt=doublet of triplets, etc.], integration). Low and high resolution mass spectra were obtained using electron ionization. Elemental analyses were done by Desert Analytics, Tuscon, AZ. High resolution mass spectra were measured by the Midwest Center for Mass Spectrometry, University of Nebraska-Lincoln, Lincoln, NB.

General Procedure for the Cyclizations of γ-Oxoallenes. (±)-Methyl 2-(5'-methoxytetrahydrofuran-2'-yl)-propenoate (5). To a solution of 4,5-hexadienal (2.14 g, 21.8 mmol), prepared immediately before use, in 150 mL ether was added $CuCl_2$ (8.95 g, 66.5 mmol) and $PdCl_2$ (0.11 g, 0.60 mmol). Triethylorthoacetate (10 mL), propylene oxide (10 mL), methylene chloride (50 mL), and methanol (50 ml) were then added via syringe. The resulting green cloudy solution was stirred at room temperature under a slight positive pressure of carbon monoxide (balloon attached to flask) for 23 h. The solvents were then concentrated in

vacuo and the resulting light green slurry was filtered through a 0.5 cm plug of Celite with ethyl acetate (300 mL). The yellow filtrate was washed with saturated sodium bicarbonate (6 x 100 mL) and brine (100 mL), the aqueous phases were back-extracted with 100 mL of ethyl acetate, and the combined organic phases were dried over magnesium sulfate, filtered, and concentrated to give 3.1 g (74%) of the product **6** as a crude yellow oil. Purification by flash chromatography (7:3 hexane:ethyl acetate eluent) afforded 1.84 g (45%) of a colorless fruity-smelling oil, a 1:1 cis:trans mixture of diastereomers. The two diastereomers were separated using HPLC (95:5 hexane:ethyl acetate, 1.2 mL/min). cis: HPLC retention time (R_t) = 8.0 min. ^{1}H-NMR: δ 6.21 (t, J=1.36 Hz,1H); 6.00 (t, J=1.62 Hz, 1H); 5.01 (dd, J=1.69, 2.87 Hz, 1H); 4.82 (t, J=6.75 Hz, 1H); 3.73 (s, 3H); 3.39 (s, 3H); 2.35 (m, 1H); 1.90 (m, 2H); 1.59 (m,1H). ^{13}C-NMR: δ 166.2, 141.2, 123.3, 105.3, 75.9, 54.6, 51.7, 31.3, 29.9. trans: HPLC: R_t=11.2 min. ^{1}H-NMR: δ 6.20 (t, J=1.36 Hz,1H); 5.82 (t, J=1.62 Hz, 1H); 5.11 (dd, J=1.69, 2.87 Hz, 1H); 4.87 (t, J=6.75 Hz, 1H); 3.73 (s, 3H); 3.33 (s, 3H); 2.35 (m, 1H); 1.90 (m, 2H); 1.59 (m,1H). ^{13}C-NMR: δ 166.4, 142.1, 123.6, 105.7, 78.4, 55.1, 51.7, 32.9, 30.7. Data for the purified mixture of diastereomers: Low resolution ms: *m/z* 185 (M-1), 154, 128, 111, 95, 67, 43, 39. IR (ν): 2988, 2951, 2908, 2832, 2359, 1719.3, 1633.4, 1439, 1373, 1296, 1272, 1045 cm^{-1}. Anal. calcd for $C_9H_{14}O_4$: C, 57.82%; H, 7.80%. Found: C, 58.04%; H, 7.58%.

(±)-Methyl 2-(5'-oxotetrahydrofuran-2'-yl)-propenoate (6). A round-bottomed flask containing $PdCl_2$ (0.01 g, 0.06 mmol) and $CuCl_2$ (0.23 g, 1.7 mmol) was purged with carbon monoxide and then a balloon filled with carbon monoxide was attached. Methylene chloride (3.0 mL), triethylorthoacetate (0.3 mL), propylene oxide (1.5 ml), 4,5-hexadienoic acid (0.03 g, 0.3 mmol), and methanol (3.0 mL) were then added via syringe. The resulting green slurry was stirred at room temperature for 18 h. The solvents were then removed in vacuo and the residue filtered through Celite with ethyl acetate (30 mL). The yellow solution was washed with saturated sodium bicarbonate (2 x 30 mL), dried over magnesium sulfate, filtered, and the solvents removed in vacuo to give 0.06 g. (88%) of the desired product as a yellow oil. Chromatography (9:1 hexanes:ethyl acetate eluent) yielded 0.03 g. (55%) of the product **6** as a clear colorless oil. ^{1}H-NMR: δ 6.32 (s, 1H), 5.91 (dd, J=1.5, 0.6Hz, 1H), 5.25 (m, 1H), 3.78 (s, 3H), 2.56 (m, 3H), 2.04 (m, 1H). ^{13}C-NMR: δ 176.64, 165.08, 140.95, 125.21, 77.65, 52.08, 28.36, 27.82. High resolution ms: *m/z* 170.0578 ($C_8H_{10}O_4$ requires 170.0579), 139.0389 ($C_8H_{10}O_4$ - OCH_3 requires 139.0395), 128.0470 ($C_8H_{10}O_4$ - C_2H_2O requires 128.0473).

3-(4'-Methoxyphenylmethoxy)-1-propanol (8). To a slurry of pentane-washed NaH (0.5 g, ~12 mmol) in ether (80 mL) was added p-methoxybenzyl alcohol (17.7 g, 128.8 mmol). After 3.5 h, Cl_3CCN (12.6 mL, 128.8 mmol) was added and stirred 1 h at 25° C. The solution was then washed with saturated sodium bicarbonate (50 mL) and brine (50 mL), and dried ($MgSO_4$), and the solvents removed in vacuo to give an oil (crude MPMOC(=NH)CCl_3) that was dissolved in dichloromethane (100 mL) and cooled to 0° C. A catalytic amount of pyridinium p-toluenesulfonate and the diol (6.3 g, 0.08 mol) were then added. The resulting solution was stirred overnight at room temperature during which time a white precipitate formed. The solid was triturated with 1:1 hexane:dichloromethane, and the resulting solution was filtered and concentrated to an oil. Chromatography (silica, 9:1 - 1:1 hexanes:ethyl acetate gradient) which provided 7.2 g (44%) of the product **8** as a clear oil. This material was used without further purification. ^{1}H-NMR: δ 7.20 (m, 2H), 6.80 (m, 2H), 4.39 (s, 2H), 3.74 (s, 3H), 3.69 (t, J=5.8Hz, 2H), 3.57 (t, J=5.9Hz, 2H), 2.6 (bs, 1H), 1.79 (p, J=5.8Hz, 2H). ^{13}C-NMR: δ 159.1, 130.1, 129.2, 113.7, 72.7, 68.7, 61.4, 55.1, 32.1.

3-(4'-Methoxyphenylmethoxy)propanal (9). To a stirring mixture of pyridinium chlorochromate (7 g., 32.5 mmol) and magnesium sulfate (20 g.) in 75 mL of dichloromethane was added the alcohol **8** (5.9 g., 30.1 mmol). The solution was stirred at room temperature for 5 h., then diluted with ether (200 mL), filtered through florisil, dried over $MgSO_4$, and concentrated to a clear colorless oil, 5.4 g. (92%). This material was used without further purification. ^{1}H-NMR: δ 9.75 (t, J=1.7 Hz, 1H), 7.23 (m, 2H), 6.86 (m, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.70 (t, J=5.9 Hz, 2H), 2.65 (dt, J=5.9, 1.8 Hz, 2H).

(±)-1-(4'-Methoxyphenylmethoxy)-6-(tetrahydropyran-2'-yloxy)-4-hexyn-3-ol (10). A solution of n-BuLi (2.0 M, 1.0 ml, 2.0 mmol) in hexane was added via syringe to a stirred solution of 3-(tetrahydropyran-2'-yloxy)-1-propyne[9] (0.26 g, 1.8 mmol) in THF (10 mL) at -78° C. After 30 min at -78° C, neat 3-(p-methoxybenzyloxy)-propanal (0.31 g, 1.6 mmol) was added via syringe. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. The resulting red solution was quenched with aqueous ammonium chloride (10 mL) and extracted with diethyl ether (2 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over magnesium sulfate, filtered, and the solvents removed in vacuo to give a thin orange oil. Chromatography (85:15 hexanes:ethyl acetate) gave 0.28 g (53%) of the product **10** as a yellow oil. ^{1}H-NMR: δ 7.19 (m, 2H), 6.82 (m, 2H), 4,75 (m, 1H), 4.56 (m, 1H), 4.40 (m, 2H), 4.22 (m, 2H), 3.73 (s, 3H), 3.72 (m, 2H), 3.50 (m, 2H), 2.0-1.4 (m, 8H). ^{13}C-NMR: δ 129.8, 129.2, 113.6, 96.5, 86.5, 80.5, 72.7, 66.9, 61.8, 60.9, 55.1, 54.1, 36.7, 36.3, 30.1, 25.2, 18.9. High resolution ms: *m/z* 333.1690 ($C_{19}H_{26}O_5$ - H requires 333.1702), 316.1646 ($C_{19}H_{26}O_5$ - H_2O requires 316.1675), 249.1149 ($C_{19}H_{26}O_5$ - C_5H_9O requires 249.1127).

(±)-6-(4'-Methoxyphenylmethoxy)-1,2-hexadien-4-ol (11). To a stirred slurry of lithium aluminum hydride (0.04 g, 1.1 mmol) in ether (20 mL) was added the alkynol **10** (0.28 g, 0.8 mmol). The mixture was stirred for 1 h. at room temperature, then quenched by the sequential addition of 0.2 mL water, 0.2 mL 5% sodium hydroxide, and 0.6 mL water. The resulting white slurry was stirred overnight, then filtered through a plug of Celite with excess ether. The solution was dried ($MgSO_4$) and concentrated in vacuo to give an oil that was immediately chromatographed (85:15 hexane:ethyl acetate) to give 0.09 g (44%) of the allene **11** as a clear colorless oil. ^{1}H-NMR: δ 6.78 (m, 2H), 5.12 (q, J=6.5Hz, 1H), 4.72 (dd, J=2.4, 6.5Hz, 2H), 4.35 (s, 2H), 4.31 (m, 1H), 3.70 (s, 3H), 3.55 (m, 2H), 2.90 (bs, 1H), 1.77 (m, 2H). ^{13}C-NMR: δ 206.9, 159.0, 130.0, 129.1, 128.3, 113.6, 94.3, 76.9, 72.7, 64.4, 55.0, 36.5. Low resolution ms: *m/z* 234, 233, 185, 137, 121. High resolution ms: *m/z* 234.1247 ($C_{14}H_{18}O_3$ requires 234.1256).

Less polar chromatographic fractions yielded, as a clear colorless oil, the byproduct **(±)-6-(4'-methoxyphenylmethoxy)-1-(tetrahydropyran-2-yloxy)-2,3-hexadiene (14).** ^{1}H-NMR: δ 7.20 (m, 2H), 6.83 (m, 2H), 5.72 (m, 2H), 4.59 (m, 1H), 4.38 (s, 2H), 4.37 (m, 2H), 3.71 (s 3H), 3.48 (m, 4H), 1.98-1.49 (m, 8H). ^{13}C-NMR: δ 191.4, 159.1, 134.9, 129.9, 129.2, 126.6, 113.7, 97.7, 72.7, 70.7, 67.7, 66.9, 65.7, 62.0, 55.1, 36.3, 30.4, 25.3, 19.2.

(±)-6-(4'-Methoxyphenylmethoxy)-4-(t-Butyldimethylsiloxy)-1,2-hexadiene (12). To a solution of **11** (0.18 g, 0.77 mmol) in dichloromethane (30 mL) at 0° C was added 2,6-lutidine (0.5 mL). Tert-butyldimethylsilyltrifluoromethanesulfonate (tBDMSOTf) (0.20 mL) was then added dropwise followed by stirring at room temperature for 4 h. The reaction mixture was then washed with saturated sodium bicarbonate (2 x 20 mL) and brine (20 mL), the aqueous phases were back-extracted with ether (20 mL), and the organic phases were combined, dried over magnesium sulfate, filtered, and evaporated to provide an oil. Chromatography (hexane to 9:1 hexane:ethyl acetate stepwise gradient elution) gave 0.27 g (99%) of the product **12** as a clear colorless oil. ^{1}H-NMR: δ 7.23 (m, 2H), 6.85 (m, 2H), 5.06 (q, J=6.8Hz, 1H), 4.71 (dt, J=4.0,6.8Hz, 2H), 4.41 (s, 1H), 4.38 (s, 1H), 4.35 (m, 1H), 3.78 (s, 3H), 3.50 (m, 2H), 1.81 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C-NMR: δ 207.3, 159.1, 130.6, 129.3, 127.5, 113.7, 94.8, 76.2, 72.7, 68.3, 66.4, 55.2, 38.5, 25.8, -4.3, -5.0. Low resolution ms (FAB): *m/z* 349 (M+H), 347, 251, 183, 121. High resolution ms: *m/z* 309.1886 ($C_{17}H_{29}O_3Si$ requires 309.1885).

(±)-3-(t-Butyldimethylsiloxy)-4,5-hexadien-1-ol (13). A solution of the ether **12** (0.10 g, 0.28 mmol) in 10mL dichloromethane was added to 2 mL pH 7 Buffer. This was vigorously stirred while powdered 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.08 g, 0.36 mmol) was added. The mixture was stirred for 1 h, then diluted with 20 mL of ether and washed with saturated sodium bicarbonate (4 x 20 mL). The aqueous phase was extracted once more with ether (20 mL), then the combined organic extracts were dried ($MgSO_4$), filtered and concentrated to an oil that was chromatographed (pet ether to 8:2 pet ether:ethyl acetate stepwise

gradient) to give 54% recovered starting material and 0.05 g (90%, based on recovered starting material) of the alcohol **13** as a colorless oil. ^{1}H-NMR: δ 5.13 (q, J=6.8Hz, 1H), 4.74 (dt, J=2.1,6.3Hz, 2H), 4.43 (m, 1H), 3.73 (m, 2H), 2.49 (bs, 1H), 1.79 (m, 2H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C-NMR: δ 207.4, 164.5, 94.2, 70.6, 60.1, 55.5, 39.8, 25.7, -4.4, -5.2. High resolution ms: *m/z* 213.1296 ($C_{12}H_{24}O_2Si$ - CH_3 requires 213.1311).

(±)-3-(t-Butyldimethylsilyloxy)-4,5-hexadienal (7). A solution of the alcohol **13** (0.09 g, 0.37 mmol) in dichloromethane (3.0 mL) was added to a suspension of pyridinium chlorochromate (0.09 g, 0.42 mmol) and magnesium sulfate (~2 g) in dichloromethane (10 mL) . The rapidly darkening slurry was stirred at room temperature for 4 h, then diluted with ether (100 mL) and filtered through Florisil. The clear solution was then dried over $MgSO_4$, filtered, and concentrated to yield 0.07 g (84%) of a yellow oil that was used without further purification. ^{1}H-NMR: δ 9.74 (t, J=6Hz, 1H), 5.20 (m, 1H), 4.76 (m, 2H), 4.67 (m, 1H), 2.59 (m, 2H), 0.83 (s, 9H), 0.04 (s, 6H). ^{13}C-NMR: δ 206.9, 201.1, 113.5, 93.8, 66.6, 51.1, 25.5, 17.8, -4.6, -5.4. High resolution ms: *m/z* 226.1375 ($C_{12}H_{22}O_2Si$ requires 226.1389), 211.1148 ($C_{12}H_{22}O_2Si$ - CH_3 requires 211.1154).

(±)-(2'R,3'S,5'R)-Methyl 2-(5'-methoxy-3'-(tert-butyldimethylsilyloxy)-tetrahydrofuran-2'-yl)-propenoate (15). To a stirred solution of the aldehyde **7** (0.17 g, 0.74 mmol) in methanol (5 mL) was added propylene oxide (1 mL), triethylorthoacetate (1 mL), palladium (II) chloride (0.13 g, 0.74 mmol), and a balloon engorged with CO was then attached to the neck of the flask. After 20 h, the resulting black slurry was diluted with ether (70 mL), filtered, washed with saturated sodium bicarbonate (4 x 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a green oil (0.21 g., 88%) which was indicated by NMR analysis to be the product **15**. The crude product was immediately chromatographed (hexanes to 7:3 hexanes:ethyl acetate stepwise gradient) to give 0.09 g (37%) of the pure furanoside **15** as a slightly yellow oil. ^{1}H-NMR: δ 6.31 (dd, J=1.2, ~0.2 Hz, 1H), 6.10 (dd, J=1.6, ~0.2 Hz, 1H), 5.28 (t, J=5.3, 1H), 4.76 (ddd, J=2.5, 1.6, 1.2Hz, 1H), 4.26 (ddd, J=5.8, 2.7, 2.5, 1H), 3.76 (s, 3H), 3.48 (s, 3H), 1.98 (ddd, J=13.7, 5.3, 2.6, 1H), 1.87 (ddd, J=13.7, 5.8, 5.3, 1H), 1.00 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C-NMR: δ 166.3, 139.8, 129.4, 106.9, 85.7, 79.4, 77.3, 72.1, 65.0, 25.7, 14.1, -4.8, -5.0. Low resolution ms: *m/z* 315, 301, 259, 201, 145, 121, 89, 73. High resolution ms: *m/z* 315.1629 ($C_{15}H_{27}O_5Si$ requires 315.1628), 259.1003 ($C_{15}H_{27}O_5Si$ - C_4H_9 requires 259.1002).

5,6-Heptadien-2-one (20). To a solution of 4,5-hexadienal (0.38 g, 3.90 mmol) in 50 mL of dry ether, cooled to 0° C. and stirring under nitrogen was added 1.5 mL (4.5 mmol) of a 3.0 M solution of methylmagnesium chloride in THF. The reaction mixture was then stirred at room temperature for 30 min., quenched by the addition of 20 mL saturated ammonium chloride, and extracted with ether (4 X 30 mL). The combined organic phases were washed with brine (2 X 30 mL), dried ($MgSO_4$), filtered, and concentrated to yield crude 5,6-heptadien-2-ol, which was immediately dissolved in ~5 mL of dichloromethane and added to a stirring mixture of pyridinium chlorochromate (0.84 g., 3.9 mmol) and $MgSO_4$ (2.5 g.) in 25 mL of dichloromethane. The reaction mixture was allowed to stir for overnight, then it was diluted with ether, filtered through florisil, and concentrated to yield 0.27 g. (74%) of the ketone **20** as a volatile oil. IR: ν 2965, 2922, 2858, 1956, 1717, 1438, 1367, 1255, 1163 cm^{-1}. ^{1}H-NMR: δ 5.07 (m, 1H), 4.61 (m, 2H), 2.48 (t, J=6.9 Hz, 2H), 2.16 (m, 2H), 2.06 (s, 3H). ^{13}C-NMR: δ 208.1, 201.7, 88.8, 75.8, 42.0, 29.8, 21.7.

6,7-Octadien-3-one (21). Using an identical procedure to that used for synthesizing the ketone **20**, using ethylmagnesium bromide instead of methylmagnesium chloride, the ketone **21** was obtained as a clear oil in 31% yield. IR; ν 2977, 2938, 1956, 1714, 1414, 1367, 1113 cm^{-1}. ^{1}H-NMR: δ5.15 (p, J=6.5 Hz, 1H), 4.68 (m, 2H), 2.47 (m, 4H), 2.23 (m, 2H), 1.04 (t, J=7.3 Hz, 3H). ^{13}C-NMR: δ 210.7, 208.3, 89.1, 75.9, 40.9, 36.0, 21.9, 7.8.

(±)-Methyl 2-(5'-methoxy-5'-methyltetrahydrofuran-2'-yl)-propenoate (22). Using the general cyclization procedure outlined above (see preparation of **5**) for the ketone **20**, a complex mixture of products was obtained from which chromatography (7:3 hexanes: ethyl acetate eluent) yielded a trace (<1%) amount of the

furanoside **22** as a mixture of diastereomers. Insufficient material was obtained to allow for thorough characterization. ^{1}H-NMR (mixture of anomers): δ 6.32 (d, J=1.4 Hz, 1H), 5.80 (d, J=1.3 Hz, 1H), 4.24 (m, 1H), 3.71 (s, 3H), 3.23 (s, 3H), 2.56 (m, 2H), 2.11 (s, 3H), 1.95 (m, 1H), 1.82 (m, 1H).

(±)-Methyl 2-(5'-ethyl-5'-methoxytetrahydrofuran-2'-yl)-propenoate (23). Using the general cyclization procedure outlined above (see preparation of **5**) for the ketone **21**, a complex mixture of products was obtained from which chromatography (7:3 hexanes: ethyl acetate eluent) yielded the furanoside **23** in 7% yield as a mixture of diastereomers. Insufficient material was obtained to allow for thorough characterization. ^{1}H-NMR (mixture of anomers): δ 6.31 (d, J=1.5 Hz, 1H), 5.80 (d, J=1.3 Hz, 1H), 4.21 (m, 1H), 3.74 (s, 3H), 3.22 (s, 3H), 2.41 (q, J=6.8 Hz, 2H), 2.1-1.6 (m, 4H), 0.98 (t, J=6.8 Hz, 3H).

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