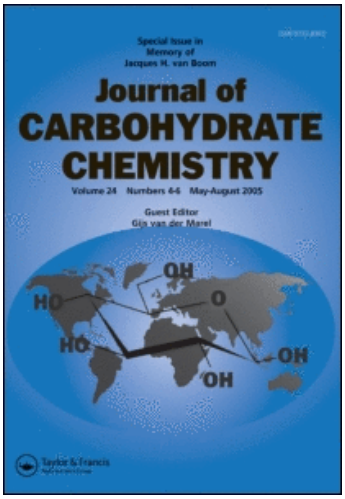

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SYNTHESIS OF TWO NEW MAYTANSINOID MODEL COMPOUNDS FROM CARBOHYDRATE PRECURSORS

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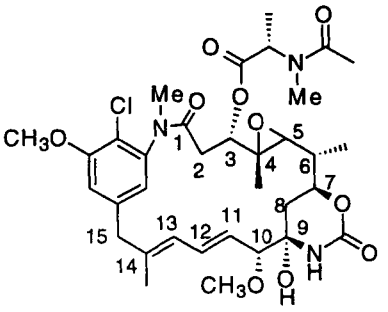
ABSTRACT

Maytansine (**1**) is a macrocyclic natural product with significant anti-cancer activity. A derivative (**4**) of D-glucal is converted to a model compound (**10**) for the lower periphery of the maytansinoid ring via alkylation at C-6 using an allylic sulfide anion, followed by oxidation to the sulfoxide and [2,3]-sigmatropic rearrangement to the sulfenate ester. In addition, a method is disclosed for conversion of D-arabinose to a chiron (**18**) for a portion of the upper periphery of the maytansinoids.

INTRODUCTION

The maytansinoids are a family of macrocyclic natural products which have generated much interest due to the significant anti-cancer activity of some of the members.[1] Maytansine itself (**1**), the most thoroughly studied of this group, inhibits tubulin polymerization and thus interferes with microtubule function.[2] Four groups have reported total syntheses in this area,[3] and others have made significant progress.[4]

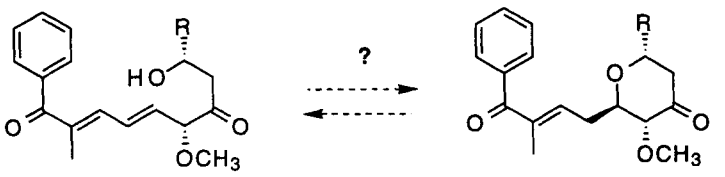


1

Carbohydrates, notably D-glucose[5] and D-mannose,[3d] have played a prominent role in synthetic efforts in this area. Described herein is a different approach in which a model for the lower portion of the maytansinoid periphery (especially for that of 15-oxygenated congeners)[1] is derived from tri-*O*-acetyl-D-glucal, and a synthon for the upper periphery is prepared from D-arabinose.

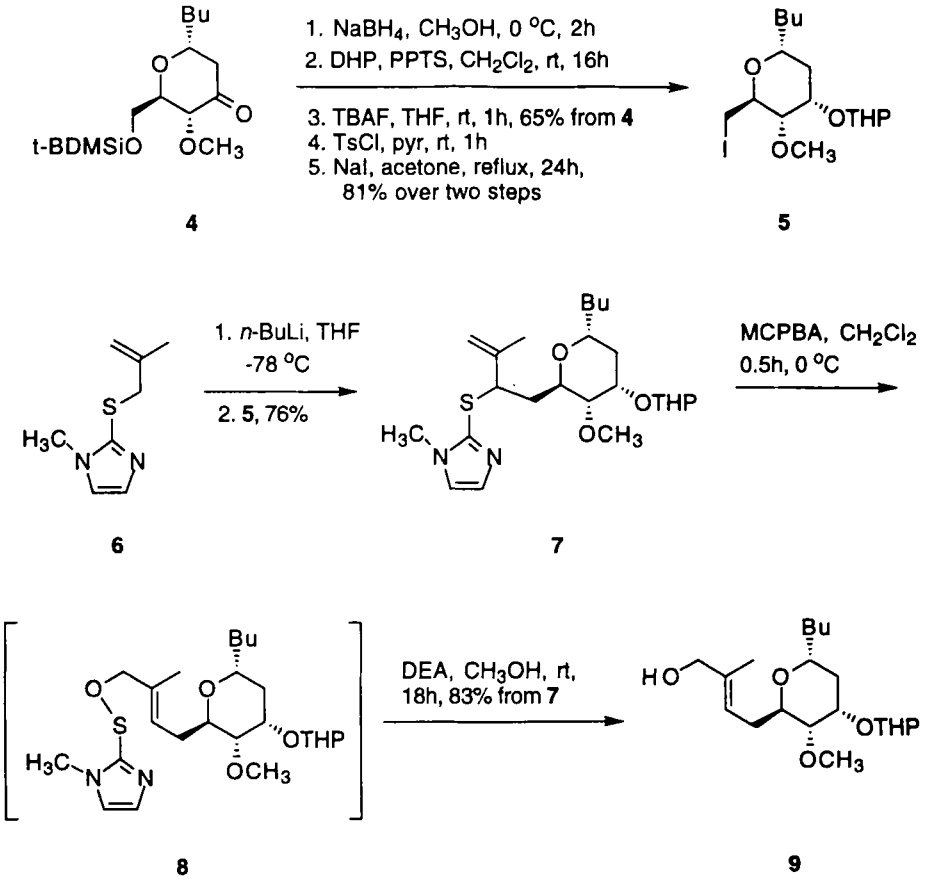
RESULTS AND DISCUSSION

Synthesis of the Lower Periphery from a D-Glucose Derivative. In an early synthetic approach to the maytansinoids, Meyers and Brinkmeyer reported[6] the preparation of model compound **2** (R = Et), in which the β-hydroxyketone moiety serves as the precursor to a cyclic carbinolamide. This dienedione is isomeric with the tetrahydropyranone **3** (R = Et), with which, theoretically, it could be interconverted through a conjugate addition/ring opening equilibrium. This report describes the preparation of a similar tetrahydropyranone (**3**, R = *n*-Bu), a compound which contains all of the structural elements of the lower portion of the maytansinoid periphery.



2 **3**

Earlier work from these laboratories has described[7] alkylation of an allylic sulfide anion with an alkyl iodide, followed by [2,3]-sigmatropic rearrangement of the derived

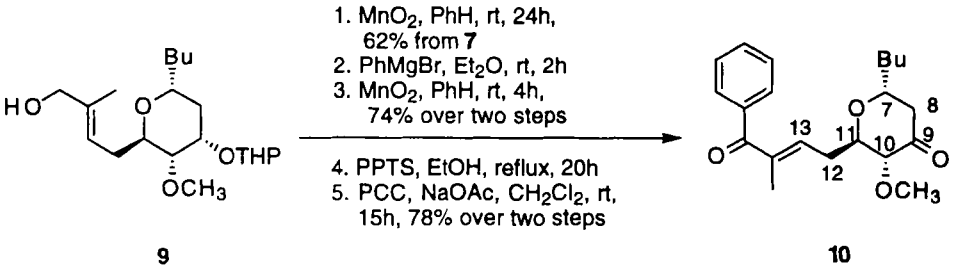


Scheme 1

sulfoxide.[8] In the present case the requisite iodide **5** was prepared from the tetrahydropyranone **4** (Scheme 1), the preparation of which from tri-*O*-acetyl-D-glucal has been described earlier.[9]

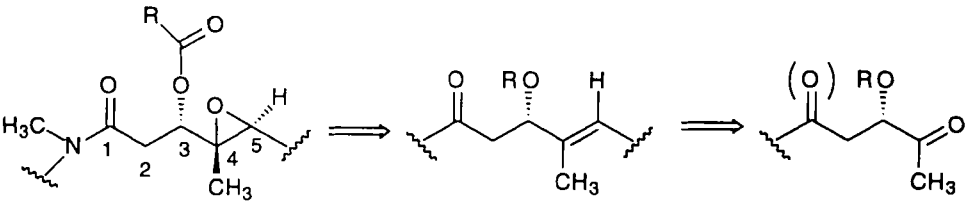
The allylic sulfide **6**[8a] was metalated and alkylated with iodide **5** under carefully-controlled conditions to provide compound **7**. This was oxidized to the allylic sulfoxide with concomitant rearrangement to the sulfenate ester **8**, thiophilic trapping (Et_2NH) of which led to the (*E*)-allylic alcohol **9** (Scheme 1). Conversion to the enone **10** was achieved as depicted in Scheme 2.[10]

Opening of the tetrahydropyranyl ring (see structures **2** and **3** above) would represent a kinetically-favored *6-exo-trig* reaction under the useful classification rules of Baldwin,[11] but has not yet been successfully carried out for enedione **10**. Incorporation



9 **10**

Scheme 2



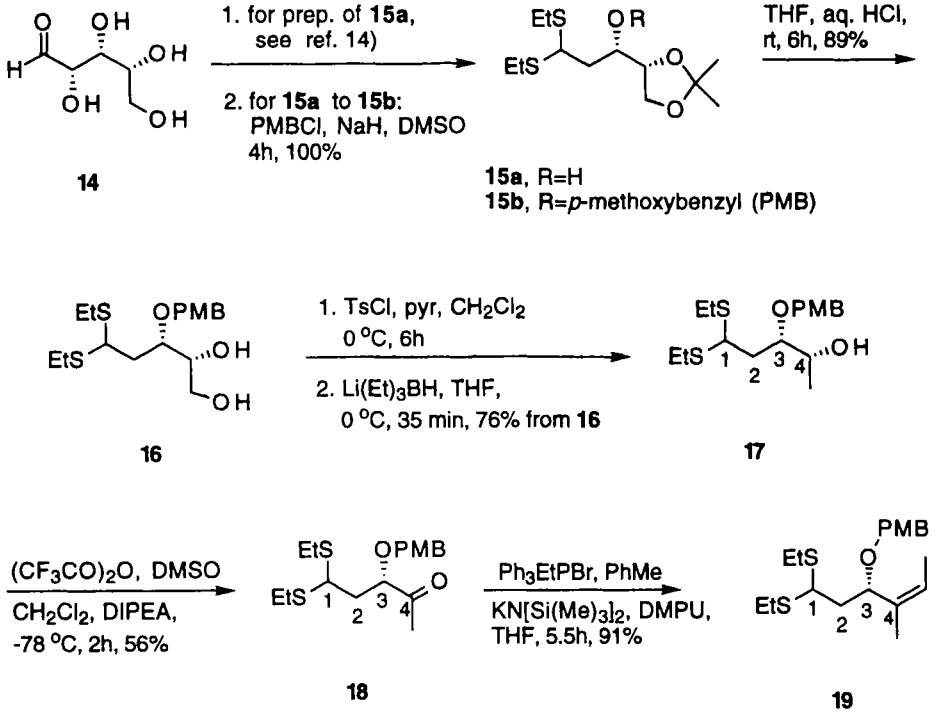
11 **12** **13**

Scheme 3

of such a tetrahydropyranone within a larger macrocycle in a more advanced maytansinoid intermediate may achieve an equilibrium more favorable to the ring-opened isomer.

Synthesis of a Portion of the Upper Periphery from D-Arabinose. Hanessian[12] has illustrated his "chiron approach" to synthesis with an analysis of "hidden" carbohydrate skeletons in the periphery of maytansine. An alternative retrosynthetic analysis of the upper portion of the maytansinoid periphery is shown in Scheme 3. Reported below is the preparation of a novel 2-pentanone which serves as a synthetic equivalent of structure **13**; its use in a Wittig reaction is also described.

D-Arabinose (**14**), which has often served as a convenient synthesis substrate,[13] was converted to the alcohol **15a** (Scheme 4) as described by Wong and Gray.[14] This was converted to the *p*-methoxybenzyl ether **15b**, which was hydrolyzed to give diol **16**. Tosylation of the primary hydroxyl gave a monotosylate which was reduced with lithium triethylborohydride to provide alcohol **17** in an overall yield of 68% from acetal **15a**.[15] Oxidation to ketone **18** in the presence of the thioketal can be problematic, but was successfully achieved using a variation of the Swern procedure.[16] In this variant an



Scheme 4

alcohol is exposed to a mixture of dimethyl sulfoxide and trifluoroacetic anhydride, followed by the addition of a base, usually triethylamine.[17] In the present case, diisopropylethylamine[18] proved to be preferable and provided the desired ketone **18** (Scheme 4).

In order for ketone **18** to be useful in maytansinoid syntheses, carbon-carbon bonds will have to be formed at both C1 and C4. The latter has been explored initially. A number of methods have been developed for the synthesis of trisubstituted alkenes.[19,20] α-Alkoxy ketones are generally well-behaved in Wittig reactions,[21] and usually provide trisubstituted alkenes with predominantly the *Z* geometry.[22] By adapting a procedure from the Still group,[22a] ketone **18** was converted to the alkene **19** which appeared by ^{13}C NMR and 500 MHz ^{1}H NMR to be a single isomer. While precedents[22] suggested that this isomer possessed the *Z* geometry, verification was desirable. Therefore, a ^{13}C NMR comparison of alkene **19** was made to the analogous *Z* alkene which was prepared from benzyloxyacetone by the Still method.[23] The *Z* geometry was suggested by the appearance of the terminal methyl group resonance of alkene **19** at 13.1 ppm, while that of the simpler analogue was at 13.0 ppm.

CONCLUSION

The synthesis of two new model compounds (**10** and **18**) for maytansinoid synthesis from carbohydrate precursors has been accomplished. The reaction sequence involving alkylation of an allylic sulfide should prove to be a versatile protocol for carbon chain extension at C-6 of a monosaccharide. D-Arabinose has been converted into a synthon for the hypothetical ketone **13**. Pentanone **18** should be a useful addition to the "chiral pool" of synthesis substrates. It should be noted, however, that further use of this ketone for maytansinoid synthesis will require preparation of the *E* alkene by the Wittig reaction or some alternative route.

EXPERIMENTAL

General Methods.[10,24] Boiling points and melting points are uncorrected. For Kugelrohr evaporative bulb-to-bulb distillations, the oven temperature is listed and does not necessarily represent the true boiling point. Infrared spectra were recorded on dilute solutions in $CHCl_3$ (unless otherwise noted) using a Pye-Unicam SP-1000 or a Perkin-Elmer 1310 spectrophotometer. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were run on $CDCl_3$ solutions with Me_4Si as an internal standard (δ 0), and were obtained on a Varian EM-360A (60 MHz), JEOL FX-90Q (90 MHz), or Bruker WM-500 or AM-500 (500 MHz) spectrometer. ^{13}C NMR spectra were obtained on a JEOL FX-90Q (22.5 MHz) spectrometer. Flash chromatography was on Baker silica gel 7024-1 (average particle diameter 40 mm). Preparative TLC utilized Sigma Type GF (10-40 μ) silica gel as the adsorbent. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Mass spectral data (EI at 70 ev unless otherwise noted) were provided by the Nebraska Center for Mass Spectrometry at the University of Nebraska/Lincoln. Solutions of $CuSO_4$, NH_4Cl, $NaHCO_3$ and NaCl were aqueous and saturated. Solutions of unpurified reaction products were dried over anhydrous Na_2SO_4.

[2*R*-(2α,3β,4β,6β)]-6-Butyl-2-[[[(1,1-dimethylethyl)dimethylsilyl]-oxy]methyl]tetrahydro-3-methoxy-2*H*-pyran-4-ol. Sodium borohydride (7.263 g, 0.192 mol) was added carefully to a stirred solution of ketone **4** (7.167 g, 0.0217 mol) in CH_3OH (350 mL) which was chilled in an ice/salt bath. After 2 h at 0 °C the mixture was concentrated, and the residue was washed with ether (460 mL) and water (110 mL) which were combined, shaken and separated. The ether phase was washed with $NaHCO_3$ solution (100 mL) and brine (100 mL), then dried. Evaporation of the solvent left the

desired alcohol as a pale yellow liquid which was routinely used in the next reaction; yield: 7.108 g (99%). Kugelrohr distillation (85 °C/ 0.005 Torr) gave the analytical sample as a colorless oil; IR 3600(w), 1108(s), 851(s) cm^{-1}; ^1H NMR (60 MHz) δ 0.09 (s, 6H, $SiMe_2$), 0.90 (s, 9H, *t*-Bu), 0.55-2.08 (m, 11H), 2.52 (br s, 1H, OH), 3.28-4.00 (m, 6H), 3.40 (s, 3H, OMe); MS *m/z* (no molecular ion), 275 (M^+-57; loss of *t*-Bu), 117 (base). HRMS: Calcd for $C_{13}H_{27}O_4Si$ (M^+-57) 275.1679. Found: 275.1682.

[2*R*-(2α,3β,4β,6β)]-[[6-Butyltetrahydro-3-methoxy-4-[tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-pyran-2-yl]methoxy](1,1-dimethylethyl)dimethylsilane. This procedure was adapted from one of Miyashita, Yoshikoshi, and Grieco.[25] A mixture of the preceding, unpurified alcohol (7.108 g, 0.0214 mol), dihydropyran (2.895 g, 0.0344 mol) and pyridinium *p*-toluenesulfonate (0.658 g, 0.00262 mol) in CH_2Cl_2 (190 mL) was stirred at the ambient temperature for 16 h, diluted with ether (1 L), washed successively with brine, $NaHCO_3$ solution and brine (200 mL portions each), then dried. Evaporation of solvent left the tetrahydropyranyl ether as a light yellow liquid which was routinely used directly in the next reaction; yield: 8.829 g (99%). Kugelrohr distillation (80 °C, 0.005 Torr) furnished the analytical sample as a colorless oil; IR 1270(m), 850(s) cm^{-1}; ^1H NMR (60 MHz) δ 0.09 (s, 6H, $SiMe_2$), 0.90 (s, 9H, *t*-Bu), 0.60-1.96 (m, 17H), 3.39, 3.46 (two s, each 3H, OMe from two diastereomers), 3.19-4.18 (m, 7H), 4.68 (br m, 1H, acetal CH); MS *m/z* (no molecular ion), 257 (M^+-159; loss of C_5H_9O, $C_4H_{10}O$), 117 (base). HRMS: Calcd for $C_{13}H_{25}O_3Si$ (M^+-159) 257.1573. Found: 257.1575.

[2*R*-(2α,3β,4β,6β)]-6-Butyltetrahydro-3-methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-pyran-2-methanol. This procedure was adapted from one of Corey and Venkateswarlu.[26] A 1 M solution of tetra-*n*-butylammonium fluoride in THF (42.2 mL; 42.2 mmol) was added to a stirred solution of the preceding, unpurified silyl ether (8.829 g, 0.0212 mol) in THF (44 mL) which was chilled in an ice/salt bath. After 5 min, the ice bath was removed and stirring was continued for 1 h. The mixture was diluted with ether (one L), washed sequentially with brine, $NaHCO_3$ solution, and brine (200 mL portions each), then dried. Removal of solvent left a pale yellow oil which was purified by column chromatography (silica gel, elution with 1:1 ether/petroleum ether) to provide the desired alcohol as a slightly yellow liquid; yield: 4.261 g, (65% overall from ketone **4**); IR 3482(s), 1128(s), 1082(s), 1033(s) cm^{-1}; ^1H NMR (60 MHz) δ 0.63-2.00 (m, 17H), 2.67 (s, 1H, OH), 3.38, 3.42 (two s, each 3H, OMe from two diastereomers), 3.10-4.20 (m, 8H), 4.73 (s, 1H, acetal CH); MS *m/z* (no molecular ion), 271 (M^+-31; loss of CH_3O), 217 (M^+-85; loss of C_5H_9O), 85 (base). HRMS: Calcd for $C_{15}H_{27}O_4$ (M^+-31) 271.1909. Found: 271.1906.

[2*R*-(2α,3β,4β,6β)]-6-Butyltetrahydro-3-methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-pyran-2-methanol 4-Methylbenzenesulfonate. A mixture of the preceding alcohol (2.143 g, 0.00709 mol) and TsCl (1.949 g, 0.0102 mol) in pyridine (40 mL) was kept in the freezer (-22 °C) for 19 h, then poured into ice/water (450 mL). This mixture was extracted with ether (3 x 100 mL). The combined ether extracts were washed sequentially with $CuSO_4$ solution (100 mL portions, until the characteristic *dark* blue color of the pyridine complex was absent from the washes), water, $NaHCO_3$ solution, and brine (100 mL of portions of each), then dried. Evaporation of the solvent left the tosylate as a yellow liquid which was not purified; yield: 2.635 g (81%); IR 1360(m), 1175(s) cm^{-1}; ^1H NMR (60 MHz) δ 0.62-2.17 (m, 17H) 2.42 (s, 3H, ArMe), 3.11-4.29 (m, 8H), 3.30, 3.33 (two s, each 3H, OMe from two diastereomers), 4.66 (br s, 1H, acetal CH), 7.28 (d, 2H, ArH), 7.71 (d, 2H, ArH).

[2*S*-(2α,3β,4β,6β)]-6-Butyltetrahydro-2-(iodomethyl)-3-methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-pyran (5). A mixture of the preceding tosylate (2.635 g, 5.772 mmol), NaI (4.515 g, 30.121 mmol) and anhydrous K_2CO_3 (0.505 g, 3.657 mmol) in acetone (25 mL) was refluxed under a drying tube for 24 h. After concentration, the residue was diluted with ether (600 mL), washed successively with water, 10% aqueous sodium thiosulfate solution, water and brine (100 mL portions of each), then dried. Removal of the solvent left iodide **5** (2.302 g) as a yellow oil, which was purified by flash chromatography[27] (silica gel; 3:1 petroleum ether/ether) to provide the pure iodide as a slightly yellow liquid; yield: 1.922 g (81%); IR 1150(s), 1130(s), 1090(s), 1040(s) cm^{-1}; ^1H NMR (60 MHz) δ 0.64-2.08 (m, 17H), 3.14-4.29 (m, 8H), 3.40, 3.44 (two s, each 3H, OMe from two diastereomers), 4.70 (br s, 1H, acetal CH); MS (CI): *m/z* (no molecular ion) 329, 253 (M^+-159; loss of HI, MeO), 85 (base). HRMS: Calcd for $C_{15}H_{25}O_3$ (M^+-159) 253.1804. Found: 253.1802.

2-[[1-[[6-Butyltetrahydro-3-methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-pyran-2-yl]methyl]-2-methyl-2-propenyl]thio]-1-methyl-1*H*-imidazole (7). A 1.6 M solution of *n*-BuLi in hexane (6.2 mL; 9.9 mmol of *n*-BuLi) was added to cold (-78 °C) THF (80 mL) and stirred under argon. A solution of 2-methylallyl 2-(1-methylimidazole) thioether[8a] (**6**) (1.658 g, 9.866 mmol) in THF (5 mL) was added dropwise over 2 min. After an additional 10 min, the solution was allowed to warm to 0 °C (over approx. 13 min). At this time the light yellow mixture was recooled to -78 °C and a solution of iodide **5** (3.959 g, 9.612 mmol) was added dropwise over 2 min. After an additional 0.5 h, the pale, translucent, gold mixture was allowed to warm to room temperature over 1.5 h, at which time it was pale orange. After addition of 3 mL of NH_4Cl solution, the yellow reaction mixture was transferred to a large round-bottomed flask with ether (100 mL). $NaHCO_3$ solution (2 mL) was added, and the mixture was

concentrated. The residue was diluted with ether (300 mL), washed with water, $NaHCO_3$ solution and brine (50 mL of each), then dried. Evaporation of the solvent left a viscous golden oil which was subjected to flash chromatography[27] (silica gel; ether) to provide the sulfide **7** as a pale yellow, viscous liquid; yield: 3.279 g (76%); IR 1480(m), 1308(m), 1138(m), 1104(m), 1054(m) cm^{-1}; ^1H NMR (60 MHz) δ 0.50-2.10 (m, 19H), 1.85 (s, 3H, olefinic Me), 2.92-4.28 (m, 7H), 3.55, 3.58, 3.63 (three s, each 3H, OMe from two diastereomers, NMe), 4.46-4.75 (m, 3H, two olefinic H and acetal CH), 6.88 (s, 1H, imidazole H), 6.98 (s, 1H, imidazole H); MS *m/z* (no molecular ion), 437, 421 (M^+-31; loss of MeO), 85 (base). HRMS: Calcd for $C_{23}H_{37}N_2O_3S$ (M^+-31) 421.2525. Found: 421.2531.

[2*R*-[2α(*E*),3β,4β,6β]]-4-[6-Butyltetrahydro-3-methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-pyran-2-yl]-2-methyl-2-buten-1-ol (9). This procedure was patterned after similar ones in the literature.[7,8] A solution of 80-90% *m*-chloroperoxybenzoic acid (1.878 g; a minimum of 8.706 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 5 min to a stirred solution of sulfide **7** (3.279 g, 7.253 mmol) in CH_2Cl_2 (30 mL) which was chilled in an ice bath. The ice bath was removed and stirring was continued for 0.5 h, at which time a mixture of Et_2NH (9.7 mL) and CH_3OH (25.6 mL) was added in one portion. The pale golden mixture was stirred at the ambient temperature for 18 h, diluted with ether (500 mL) , and washed sequentially with water, 3.7% hydrochloric acid (twice), $NaHCO_3$ solution (twice) and brine (75 mL portions of each). After drying, the solvent was removed *in vacuo* to provide the allylic alcohol **9** as a pale yellow liquid which was not purified; yield: 2.134 g (83%); IR 3420(m), 1446(m), 1372(m), 1109(m), 1068(m), 1019(m) cm^{-1}; ^1H NMR (60 MHz) δ 0.53-2.09 (m, 17H), 1.69 (s, 3H, olefinic Me), 2.31 (m, 2H, allylic CH_2), 3.05-4.19 (m, 7H), 3.40, 3.45 (two s, each 3H, OMe from two diastereomers), 3.98 (br s, 2H, allylic -OCH_2-), 4.72 (br s, 1H, acetal CH), 5.43 (br t, 1H, J = 7 Hz, olefinic H).

[2*R*-[2α(*E*),3β,4β,6β]]-4-[6-Butyltetrahydro-3-methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-pyran-2-yl]-2-methyl-2-butenal. A mixture of allylic alcohol **9** (2.134 g, 5.994 mmol) and activated manganese(IV) oxide (11.4 g, 0.131 mol) in benzene (140 mL) was stirred at room temperature for 24 h, filtered over Celite, and concentrated to provide the corresponding aldehyde (1.887 g) as a golden liquid. Purification was effected by flash chromatography (silica gel; 1:1 ether/petroleum ether) to provide a pale yellow oil; yield: 1.578 g (62% overall from sulfide **7**); IR 1690(s), 1455(m), 1385(m), 1122(s), 1081(s), 1031(s) cm^{-1}; ^1H NMR (60 MHz) δ 0.66-2.12 (m, 17H), 1.76 (s, 3H, olefinic Me) 2.66 (m, 2H, allylic CH_2), 3.06-4.36 (m, 6H), 3.43, 3.49 (two s, each 3H, OMe from two diastereomers), 4.78 (br s, 1H, acetal CH), 6.62 (br t, 1H, J = 7 Hz, olefinic H), 9.49 (s, 1H, aldehydic H); MS *m/z* (no

molecular ion) 271 (M^+-83; loss of $OHCC(CH_3)CHCH_2$), 85 (base). HRMS Calcd for $C_{15}H_{27}O_4$ (M^+-83) 271.1909. Found: 271.1917.

α-[3-[6-Butyltetrahydro-3-methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)-oxy]-2*H*-pyran-2-yl]-1-methyl-1-propenyl]benzenemethanol. A solution of the preceding, purified aldehyde (0.309 g, 0.873 mmol) in anhydrous ether (5 mL) was added dropwise over 2-3 min to a stirred solution of PhMgBr in ether (2.9 mL of 3M PhMgBr in ether which was diluted with an additional 8 mL of ether; i.e., 8.7 mmol of PhMgBr) with cooling in an ice bath under N_2. The ice bath was removed and stirring was continued for 2 h. After recooling in an ice bath, the mixture was slowly and cautiously hydrolyzed with 3 mL of NH_4Cl solution, then transferred to a separatory funnel with ether (150 mL) and water (50 mL). The layers were mixed and separated. The organic phase was washed with $NaHCO_3$ solution and brine (50 mL portions of each), then dried. Removal of the solvent left the allylic alcohol as a pale yellow oil which was used directly in the next reaction; yield: 368 mg (98%); IR 3470(s), 1604(m), 1130(s), 1090(s), 1040(s), 985(s), 750(m), 710(m) cm^{-1}; ^1H NMR (60 MHz) δ 0.69-2.09 (m, 17H), 1.52 (s, 3H, olefinic Me), 2.37 (t, 2H, J = 7 Hz, allylic CH_2), 3.11-4.30 (m, 7H), 3.41, 3.46 (two s, each 3H, OMe from two diastereomers), 4.69 (br s, 1H, acetal CH), 5.12 (s, 1H, allylic CH), 5.66 (br t, 1H, J = 7 Hz, olefinic H), 7.06-7.72 (m, 5H, ArH).

[2*R*-[2α(*E*),3β,4β,6β]]-4-[6-Butyltetrahydro-3-methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-pyran-2-yl]-2-methyl-1-phenyl-2-buten-1-one. Unpurified alcohol (368 mg) from the preceding reaction was stirred in benzene (25 mL) with activated manganese(IV) oxide (1.66 g, 0.019 mol) at room temperature for 4 h, filtered over Celite, and concentrated to give a yellow liquid (365 mg), from which the pure ketone was isolated by preparative TLC (Rf 0.24-0.48, 1:1 ether/petroleum ether) as a pale yellow liquid; yield: 278 mg (74% over two steps); IR (neat) 1648(s), 1597(w), 1121(s), 1080(s), 1031(s), 979(m), 734(s), 709(s) cm^{-1}; ^1H NMR (60 MHz) δ 0.73-2.39 (m, 17H), 2.02 (s, 3H, olefinic Me), 2.59 (m, 2H, allylic CH_2), 3.12-4.32 (m, 6H), 3.44, 3.49 (two s, each 3H, OMe from two diastereomers), 4.78 (br s, 1H, acetal CH), 6.39 (t, 1H, J = 7 Hz, olefinic H), 7.22-7.89 (m, 5H, ArH); MS *m/z* (no molecular ion), 345 (M^+-85; loss of C_5H_9O), 85 (base). HRMS: Calcd for $C_{21}H_{29}O_4$ (M^+-85) 345.2066. Found: 345.2062.

[2*R*-[2α(*E*),3β,4β,6β]]-4-(6-Butyltetrahydro-4-hydroxy-3-methoxy-2*H*-pyran-2-yl)-2-methyl-1-phenyl-2-buten-1-one. This procedure was adapted from one of Miyashita, Yoshikoshi, and Grieco.[25] A mixture of the tetrahydropyranyl ether (195 mg, 0.454 mmol) from the previous section and pyridinium *p*-toluenesulfonate (23 mg, 0.092 mmol) in 95% EtOH (10 mL) was stirred and refluxed for 20 h, diluted

with ether (150 mL), washed sequentially with $NaHCO_3$ solution and brine (30 mL portions of each), then dried. Removal of solvent left a pale yellow liquid (160 mg), which was subjected to preparative TLC (Rf 0.01-0.02, 1:1 ether/petroleum ether) to provide the desired alcohol as a pale yellow solid which was suitable for use in the next reaction; yield: 123 mg (78%). The analytical sample was prepared by two recrystallizations to afford shiny, white microneedles; mp 58.5-59.0 °C (pentane/ether); $[\alpha]_D^{25}$ +17.06° (*c* 0.0050, $CHCl_3$); IR 3541(m), 1647(s), 1599(w), 1085(s), 1049(m) cm^{-1}; ^1H NMR (500 MHz) δ 0.80 (t, 3H, J = 7.2 Hz, Me of *n*-Bu), 1.10-1.80 (m, 8H, -$CH_2CH_2CH_2$- and two H-8), 1.99 (s, 3H, olefinic Me), 2.43 (ddd, 1H, J_{gem} = 15.8, $J_{12a,13}$ = 6.9, $J_{11,12a}$ = 4.7 Hz, H-12a), 2.62 (ddd, 1H, $J_{11,12b}$ = 9.6, $J_{12b,13}$ = 7.2 Hz, H-12b), 3.11 (dd, 1H, $J_{10,11}$ = 3.8, $J_{9,10}$ = 3.5 Hz, H-10), 3.42 (s, 3H, OMe), 3.52 (m, 1H, H-7), 3.98 (m, 1H, H-9), 4.08 (ddd, 1H, $J_{11,12b}$ = 9.6, $J_{11,12a}$ = 4.7 Hz, H-11), 6.36 (dd, 1H, $J_{12b,13}$ = 7.2, $J_{12a,13}$ = 6.9 Hz, olefinic H), 7.25-7.64 (m, 5H, ArH).

Anal. Calcd for $C_{21}H_{30}O_4$ (346.22): C, 72.79; H, 8.73. Found: C, 73.00; H, 8.83.

[2*R*-[2α(*E*),3β,6β]]-6-Butyltetrahydro-3-methoxy-2-(3-methyl-4-oxo-4-phenyl-2-butenyl)-4*H*-pyran-4-one (10). This procedure was adapted from one by Corey and Suggs.[28] A mixture of the preceding alcohol (569 mg, 1.645 mmol), pyridinium chlorochromate (845 mg, 3.920 mmol), and anhydrous sodium acetate (77 mg, 0.939 mmol) was stirred in CH_2Cl_2 (21 mL) for 15 h at the ambient temperature, diluted with ether (50 mL), filtered over Celite, then passed over a short column of silica gel (70-230 mesh). The column was washed with ether (500 mL) and the combined eluates were concentrated to give the desired diketone **10** as a white, crystalline solid; yield: 532 mg (94%). The analytical sample was prepared by two recrystallizations to provide white microneedles; mp 72.5-73.0 °C (pentane/ether); $[\alpha]_D^{25}$ +73.64° (*c* 0.0044, $CHCl_3$); IR 1732 (s), 1648(s), 1602(w), 1140(m) cm^{-1}; ^1H NMR (500 MHz)[10] δ 0.79 (t, 3H, J = 7.1 Hz, Me of *n*-Bu), 1.15-1.64 (m, 6H, -$CH_2CH_2CH_2$-), 1.99 (d, 3H, $J_{13,olefinic\ Me}$ = 1.0 Hz, olefinic Me), 2.41 (dd, 1H, J_{gem} = 13.5, $J_{7,8eq}$ = 3.2 Hz, H-8eq), 2.61 (ddd, 1H, J_{gem} = 15.8, $J_{11,12b}$ = 8.0, $J_{12b,13}$ = 7.5 Hz, H-12b), 2.72 (m, 2H, H-12a and H-8ax), 3.45 (d, 1H, $J_{10,11}$ = 8.2 Hz, H-10), 3.47 (s, 3H, OMe), 3.78 (ddd, 1H, $J_{11,12a}$ = 3.7 Hz, H-11), 4.11 (m, 1H, H-7), 6.36 (ddq, 1H, $J_{12a,13}$ = 6.8 Hz, olefinic H), 7.38-7.65 (m, 5H, ArH).

Anal. Calcd for $C_{21}H_{28}O_4$ (344.20): C, 73.21; H, 8.20. Found: C, 73.37; H, 8.13.

2-Deoxy-3-*O*-[(4-methoxyphenyl)methyl]-4,5-*O*-(1-methylethylidene)-D-*erythro*-pentose, Diethyl Mercaptal (15b). A solution of alcohol **15a**[14] (3.918 g, 0.0140 mol) and 4-methoxybenzyl chloride (2.706 g, 0.0173 mol) in DMSO (6

mL) was added to a stirred suspension of NaH (425 mg, 0.0177 mol) in DMSO (10 mL) under N_2. The resulting mixture was vigorously stirred at the ambient temperature for 4 h, cautiously diluted first with NH_4Cl solution (1 mL) then with ether (300 mL), extracted with water (3 x 100 mL), then dried. Removal of solvent *in vacuo* left a yellow syrup which was purified by flash chromatography[27] (silica gel, 1:1 ether/petroleum ether) to give the desired ether **15b** (5.608 g, 100%) as a light yellow liquid: $[\alpha]_D^{27}$ -3.37° (*c* 0.00593, $CHCl_3$); IR 1610 (s), 1510 (s), 1245 (s), 1130 (s), 1065 (s) cm^{-1}; ^1H NMR (90 MHz) δ 1.23 (t, 6H, J = 7.5 Hz, Me of 2 Et), 1.35, 1.43 (both s, 3H each, CMe_2), 1.95 (dd, 2H, J_1 = 7.2 Hz, J_2 = 5.9 Hz, H-2), 2.60 (q, 4H, CH_2 of 2 Et), 3.45-4.13 (m, 5H, H-1, H-3, H-4, H-5), 3.80 (s, 3H, OMe), 4.53, 4.71 (both d, 1H each, J = 11.2 Hz, benzylic H), 6.87 (d, 2H, J = 8.7 Hz, ArH ortho to OMe), 7.27 (d, 2H, ArH meta to OMe); ^{13}C NMR δ 14.3 (Me of 2 Et), 23.2, 24.1 (CH_2 of 2 Et), 25.0, 26.2 (2 acetal Me), 38.6 (C-2), 47.5 (C-1), 55.0 (OMe), 65.8 (C-5), 72.9 (benzylic C), 76.3 (C-4), 78.2 (C-3), 108.9 (acetal C), 113.6 (ArC ortho to OMe), 129.3 (ArC meta to OMe), 130.4 (ArC para to OMe), 159.1 (ArC ipso to OMe); MS *m/z* 400 (M^+), 121 (base). HRMS: Calcd for $C_{20}H_{32}O_4S_2$ 400.1742. Found: 400.1749.

2-Deoxy-3-*O*-[(4-methoxyphenyl)methyl]-D-*erythro*-pentose, Diethyl Mercaptal (16). A solution of alcohol **15b** (2.761 g, 6.899 mmol) 1:1 (v/v) THF:HCl (1.2 M; 140 mL) was stirred at the ambient temperature for 6 h, diluted with ether (1 L), washed sequentially with water and $NaHCO_3$ solution (twice), then dried. Removal of solvent *in vacuo* left a yellow liquid which was purified by flash chromatography[27] (silica gel, ether) to provide the desired diol **16** (2.203 g, 89%) as a pale yellow oil: $[\alpha]_D^{27}$ -5.19° (*c* 0.0214, $CHCl_3$); IR 3440 (s), 1610 (m), 1510 (m), 1270 (s), 1100 (s) cm^{-1}; ^1H NMR (90 MHz) δ 1.22 (t, 6H, J = 7.4 Hz, Me of 2 Et), 1.84-2.16 (m, 2H, H-2), 2.40-3.20 (m, 6H, CH_2 of 2 Et; 2 OH), 3.44-4.20 (m, 5H, H-1, H-3, H-4, H-5), 3.78 (s, 3H, OMe), 4.57 (s, 2H, benzylic CH_2), 6.87 (d, 2H, J = 8.6 Hz, ArH ortho to OMe), 7.26 (d, 2H, ArH meta to OMe); ^{13}C NMR δ 14.1 (Me of 2 Et), 23.2, 23.9 (CH_2 of 2 Et), 37.5 (C-2), 47.4 (C-1), 54.8 (OMe), 63.1 (C-5), 72.1 (C-4), 73.0 (benzylic C), 77.2 (C-3), 113.4 (ArC ortho to OMe), 129.2 (ArC meta to OMe), 130.0 (ArC para to OMe), 158.9 (ArC ipso to OMe); MS *m/z* 360 (M+), 121 (base). HRMS: Calcd for $C_{17}H_{28}O_4S_2$ 360.1429. Found: 360.1430.

2-Deoxy-3-*O*-[(4-methoxyphenyl)methyl]-D-*erythro*-pentose, Diethyl Mercaptal, 5-(4-Methylbenzenesulfonate). This procedure was based on one by Hanessian and Delorme.[15] TsCl (833 mg, 4.369 mmol) was added to a mixture of diol **16** (1.401 g, 3.890 mmol), pyridine (1.9 mL), and CH_2Cl_2 (18 mL) which was stirred at 0 °C under N_2. After 0.5 h, the ice bath was removed and the mixture was stirred for an additional 19 h, at which time it was diluted with ice water (500 mL) and extracted with

CH_2Cl_2 (3 x 150 mL). The combined organic extracts were washed sequentially with $CuSO_4$ solution (twice), water, and $NaHCO_3$ solution (150 mL portions of each), then dried. Removal of solvent *in vacuo* left the desired tosylate (1.917 g, 96%) as a golden liquid which was not purified: IR 3580 (w), 1608 (m), 1595 (m), 1312 (s), 1170 (s) cm^{-1}; ^1H NMR (90 MHz) δ 1.22 (t, 6H, J = 7.4 Hz, Me of 2 Et), 1.80-2.10 (m, 2H, H-2), 2.15-2.68 (m, 5H, CH_2 of 2 Et; OH), 2.44 (s, 3H, ArMe), 3.50-4.08 (m, 5H, H-1, H-3, H-4, H-5), 3.80 (s, 3H, OMe), 4.49 (s, 2H, benzylic CH_2), 6.85 (d, 2H, J = 8.6 Hz, ArH ortho to OMe), 7.14-7.38 (m, 4H, ArH meta to OMe, ArH meta to SO_3), 7.79 (d, 2H, J = 8.4, ArH ortho to SO_3); ^{13}C NMR δ 14.4 (Me of 2 Et), 21.6 (ArMe), 23.6, 24.3 (CH_2 of 2 Et), 37.5 (C-2), 47.2 (C-1), 55.2 (OMe), 71.0 (C-4), 72.5 (benzylic CH_2), 75.6 (C-5), 76.5 (C-3), 113.9 (ArC ortho to OMe), 128.0 (ArC meta to SO_3), 129.4 (ArC para to OMe), 129.5 (ArC meta to OMe), 129.9 (ArC ortho to SO_3), 145.1 (ArC ipso to SO_3), 159.3 (ArC ipso to OMe) (the signal for the ArC para to SO_3 was obscured). The crude tosylate was used directly in the next reaction.

2,5-Dideoxy-3-*O*-[(4-methoxyphenyl)methyl]-D-*erythro*-pentose, Diethyl Mercaptal (17). This procedure was based on one by Hanessian and Delorme.[15] A solution of the unpurified tosylate from the preceding reaction (1.916 g, 3.726 mmol) in THF (10 mL) was added to a solution of lithium triethylborohydride ("Super-Hydride" (Aldrich);[29] 15.35 mmol) in THF (35 mL) which was stirred at 0 °C under nitrogen. After 35 min, water was cautiously added in a dropwise manner (a total of 80 drops), followed by careful, dropwise addition of first 3M NaOH solution (10 mL), and then 30% H_2O_2 solution (10 mL) (**caution**: vigorous effervescence!). The mixture was stirred for an additional 45 min, diluted with ether (500 mL), and washed sequentially with water (twice), 1 M HCl, water, and $NaHCO_3$ solution (100 mL portions of each), then dried. Removal of solvent *in vacuo* left the crude product (1.464 g) as a pale yellow, malodorous liquid. Purification was effected by flash chromatography[27] (silica gel, ether), followed by preparative TLC (R_f 0.60-0.81; silica gel, ether) to provide the desired alcohol **17** (1.023 g, 76% over two steps) as a colorless oil: $[\alpha]_D^{27}$ -12.33° (*c* 0.0103, $CHCl_3$); IR 3660 (w), 3600-3300 (m), 1610 (s), 1510 (s) cm^{-1}; ^1H NMR (90 MHz)[24] δ 1.15 (d, 3H, J = 6.4 Hz, H-5), 1.23 (t, 6H, J = 7.4 Hz, Me of 2 Et), 1.66-2.16 (m, 2H, H-2), 2.22 (s, 1H, OH), 2.61 (m, 4H, CH_2 of 2 Et), 3.48-4.16 (m, 3H, H-1, H-3 and H-4), 3.79 (s, 3H, OMe), 4.48 (d, 1H, J_{gem} = 10.8 Hz, one benzylic H), 4.63 (d, 1H, one benzylic H), 6.87 (d, 2H, J = 8.6 Hz, ArH ortho to OMe), 7.27 (d, 2H, ArH meta to OMe); ^{13}C NMR δ 14.0 (Me of 2 Et), 17.5 (C-5), 22.9, 23.7 (CH_2 of 2 Et), 35.4 (C-2), 47.3 (C-1), 54.6 (OMe), 67.1 (C-4), 71.5 (OCH_2), 79.8 (C-3), 113.2 (ArC ortho to OMe), 128.9 (ArC meta to OMe), 130.0 (ArC para to OMe), 158.7 (ArC ipso to OMe);

MS *m/z* (no molecular ion), 221, 121 (base). HRMS: Calcd for $C_{13}H_{17}O_3$ 221.1178 (M^+ - 2 EtS, H). Found: 221.1178.

(*S*)-5,5-Bis(ethylthio)-3-[(4-methoxyphenyl)methoxy]-2-pentanone (18). This procedure was modeled after one by Braish, Saddler, and Fuchs.[30] Trifluoroacetic anhydride (0.290 mL; 431 mg, 2.053 mmol) was added to a stirred solution of DMSO (0.405 mL; 446 mg, 5.707 mmol) in CH_2Cl_2 (6 mL) at -78 °C under argon. After 10 min, a solution of alcohol **17** (220 mg, 0.639 mmol) in CH_2Cl_2 (1 mL) was added. This was stirred an additional 0.5 h, at which time *N*,*N*-diisopropylethylamine (1.780 mL; 1.321 g, 10.221 mmol) was added to the cloudy, white reaction mixture which was then allowed to warm to the ambient temperature over 1.5 h with stirring under argon as the color changed to yellow and the mixture became translucent. It was diluted with CH_2Cl_2 (300 mL), washed with 3M HCl (2 x 75 mL), $NaHCO_3$ solution (2 x 75 mL) and dried. Removal of solvent *in vacuo* left the crude product (186 mg) as a yellow liquid which was purified by preparative TLC (R_f 0.54-0.70; 1:1 petroleum ether/ether) to give the desired ketone **18** (123 mg, 56%)[31] as a pale yellow oil: $[\alpha]_D^{27}$ -34.88° (*c* 0.013, $CHCl_3$); IR 1722 cm^{-1}; ^1H NMR (500 MHz)[24] δ 1.22, 1.23 (both t, 3H each, J = 7.4 Hz, Me of 2 Et), 1.98 (ddd, 1H, J_{gem} = 14.3 Hz, $J_{1,2a}$ = 9.9 Hz, $J_{2a,3}$ = 3.9 Hz, H-2a), 2.11 (ddd, $J_{2b,3}$ = 9.3 Hz, $J_{1,2b}$ = 5.0 Hz, H-2b), 2.17 (s, 3H, CH_3CO), 2.51-2.68 (m, 4H, CH_2 of 2 Et), 3.80 (s, 3H, OMe), 3.97 (dd, 1H, H-1), 4.16 (dd, 1H, H-3), 4.42 (d, 1H, J_{gem} = 11.1 Hz, benzylic H), 4.53 (dd, 1H, benzylic H), 6.88 (d, 2H, J = 8.6 Hz, ArH ortho to OMe), 7.26 (d, 2H, ArH meta to OMe); ^{13}C NMR δ 14.3 (Me of 2 Et), 23.5, 24.3 (CH_2 of 2 Et), 25.7 (C-5), 38.3 (C-2), 47.3 (C-1), 55.2 (OMe), 72.6 (OCH_2), 82.3 (C-3), 113.8 (ArC ortho to OMe), 129.3 (ArC para to OMe), 129.7 (ArC meta to OMe), 159.4 (ArC ipso to OMe), 210.6 (C=O); MS *m/z* 342, 121 (base). HRMS: Calcd for $C_{17}H_{26}O_3S_2$ 342.1323. Found: 342.1328.

[*S*-(*Z*)]-1-[[[1-[2,2-Bis(ethylthio)ethyl]-2-methyl-2-butenyl]oxy]-methyl]-4-methoxybenzene (19). This procedure was modeled after that of Sreekumar, Darst, and Still.[22a] Potassium bis(trimethylsilyl)amide (3.9 mL of a 0.5 M solution in toluene (Aldrich); i.e., 1.95 mmol of base) was added via syringe under argon to a mixture of (ethyl)triphenylphosphonium bromide (716 mg, 1.929 mmol; dried overnight at 56 °C, 0.1 Torr, in the presence of P_2O_5) and *N*,*N*'-dimethyl-*N*,*N*'-propyleneurea[32] (DMPU; 2.0 mL, 2.12 g, 0.0167 mol) in THF (10 mL; distilled from $LiAlH_4$ immediately before use) which was stirred at the ambient temperature. After 20 min, the orange solution was cooled to -78 °C, at which time a solution of ketone **18** (264 mg, 0.772 mmol) in THF (2 mL) was added. After 5 min, the cooling bath was removed and the reaction mixture was allowed to warm to rt with stirring for a total of 5 h (color change from yellow to brown). The mixture was diluted with water (100 mL), then extracted with ether (3 x 50 mL). The combined ether extracts were washed with brine

and dried. Removal of solvent *in vacuo* provided the crude product as a golden liquid. Purification was effected by preparative TLC (R_f 0.59-0.86; 1:1 ether/petroleum ether) to provide the alkene **19** (249 mg, 91%) as a pale yellow liquid: $[\alpha]_D^{27}$ -41.9° (*c* 0.0036, $CHCl_3$); IR 1610 (s), 1585 (w), 1409 (s), 1243 (s) cm^{-1}; ^1H NMR (500 MHz)[24,33] δ 1.22, 1.23 (both t, 3H each, J = 7.4 Hz, Me of 2 Et), 1.66 (dq, 3H, $J_{vinyl\ H,\ Me}$ = 6.7 Hz, $J_{Me,Me}$ = 1.5 Hz, terminal vinyl Me, 1.67 (m, 3H, C-5 Me), 1.76 (ddd, 1H, J_{gem} = 14.3 Hz, $J_{1,2a}$ = 9.1 Hz, $J_{2a,3}$ = 4.8 Hz, H-2a), 2.20 (ddd, 1H, $J_{1,2b}$ = 5.65 Hz, $J_{2b,3}$ = 8.72 Hz, H-2b), 2.602 (m, 4H, CH_2 of 2 Et), 3.79 (s, 3H, OMe), 3.90 (dd, 1H, H-1), 4.17 (d, 1H, J_{gem} = 11.2 Hz, benzylic H), 4.38 (d, 1H, benzylic H), 4.65 (dd, 1H, H-3), 5.50 (qq, 1H, $J_{vinyl\ H,\ C\text{-}5\ Me}$ = 0.5 Hz, vinyl H), 6.86 (d, 2H, J = 8.6 Hz, ArH meta to OMe), 7.24 (d, 2H, ArH ortho to OMe); ^{13}C NMR δ 13.1 (terminal vinyl Me), 14.4 , 14.6 (Me of 2 Et), 17.7 (C-5), 23.7, 24.2 (CH_2 of 2 Et), 40.1 (C-2), 48.0 (C-1), 55.2 (OMe), 69.7 (OCH_2), 73.2 (C-3), 113.7 (ArC ortho to OMe), 124.1 (terminal vinyl C), 129.4 (ArC meta to OMe), 130.8 (ArC para to OMe), 134.7 (C-4), 159.0 (ArC ipso to OMe); MS *m/z* (no molecular ion), 233, 121 (base). HRMS: Calcd for $C_{11}H_{21}OS_2$ 233.1034 (M^+ minus 4-methoxybenzyl). Found 233.1040.

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20. For examples of more recent work with phosphine oxides, see the following and references contained therein: a) A. D. Buss and S. Warren, *Tetrahedron Lett.*, **24**, 111 (1983); b) T. K. Jones, S. G. Mills, R. A. Reamer, D. Askin, R. Desmond, R. P. Volante and I. Shinkai, *J. Am. Chem. Soc.*, **111**, 1157 (1989); c) J. A. Ragan, M. Nakatsuka, D. B. Smith, D. E. Uehling and S. L. Schreiber, *J. Org. Chem.*, **54**, 4267 (1989).
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23. Benzyloxyacetone was prepared by a phase transfer-catalyzed Williamson ether synthesis (benzyl chloride, propargyl alcohol), followed by mercury(II)-catalyzed hydration of the triple bond. Details of a similar synthesis have been published: D. L. Boger and M. S. S. Palanki, *J. Am. Chem. Soc.*, **114**, 9318 (1992); For similar phase transfer syntheses, see: a) V. P. Fedulov, E. M. Glazunova and V. I. Nikitin, *Khim. Tadzh.* 35 (1973) (*Chem. Abstr.* **84**, 73791c (1976)); b) R. S. Vartanyan, Z. V. Kazaryan and V. F. Kucherov, *Arm. Khim. Zh.*, **27**, 295 (1974) (*Chem. Abstr.* **81**, 77405r (1974)).
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