JOC*Article*

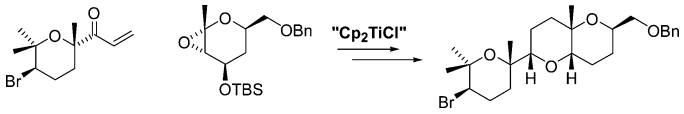
From C-Glycosides to Pyranopyrans: An Approach to Thyrsiferol Using Titanium(III)-Promoted Redox Couplings

Gisele A. Nishiguchi and R. Daniel Little*

Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106

little@chem.ucsb.edu

Received March 9, 2005

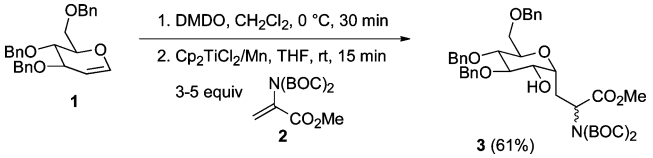


An approach to the pyranopyran ring system that is found in many natural products, including thyrsiferol, is described. The route entails the assembly of an α,β-unsaturated ketone (**11**) from geraniol and dihydropyran (**23**) from acetyl acetaldehyde dimethyl acetal (**19**) and their titanium(III)-promoted coupling to afford a respectable 60% yield of keto alcohol **26**. The σ-bond formed in this process corresponds to the pro-C_9-C_{10} bond of thyrsiferol (**4**). Attempts to invert the stereochemistry at the pro-C_{11} center were thwarted by the congestion imparted by the presence of the vicinal TBS-ether. Consequently, cyclization of the coupling adduct under conditions developed by Olah and Prakash and co-workers led to the cis-fused pyranopyran **27**. X-ray analysis of this crystalline material confirmed each of the stereochemical assignments. After much effort, it was determined that the hydroxyl group at C_{12} could be removed by treating the derived methyl xanthate with a tri-*n*-butylphosphine−borane complex under radical-forming conditions. The reaction sequence worked well, despite the hindered working environment and the presence of a potentially labile C−Br bond.

Introduction

Research into the assembly of both cis- and trans-fused pyranopyrans continues unabated. Numerous elegant and imaginative routes have been devised.[1] Our interest was kindled by the desire to devise and implement a novel and straightforward means by which to convert anhydrosugars to α-C-glycosides. Indeed, in 2002, we published a paper detailing the manner in which we achieved this objective.[2] The approach, one example of which is highlighted by the conversion of **1** to **3**, calls for the in situ epoxidation of a sugar glycal with freshly prepared DMDO and the subsequent treatment of it with titanocene dichloride/manganese, in the presence of an electron-deficient alkene (Scheme 1). Workup reveals the α-C-glycoside in respectable yields, with the hydroxyl group at C_3 available for additional functionalization.

SCHEME 1. Formation of α-C-Glycosides via Ti(III)-Induced Coupling



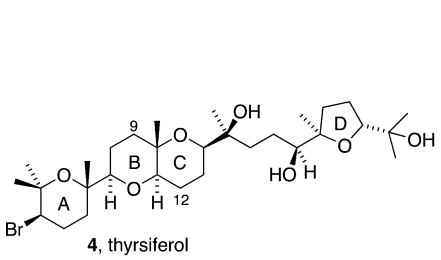
We were curious to determine whether the chemistry could be extended to more elaborate coupling partners with an eventual goal being to apply it to the total synthesis of natural products containing the pyranopyran framework. Both cis- and trans-fused systems exist; thyrsiferol (**4**; trans-fused),[3] 10-epidehydrothyrsiferol (**5**;

(1) For cis-fused, see: (a) Sasaki M.; Nonomura, T. M., M.; Tachibana, K. *Tetrahedron Lett.* **1994**, *35* (28), 5023−5026. (b) Grotenbreg, G. M.; Tuin, A. W.; Witte, M. D.; Leeuwenburgh, M. A.; van Boom, J. H.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *Synlett* **2004**, *5*, 904−906. (c) Tan, D. S.; Schreiber, S. L. *Tetrahedron Lett.* **2000**, *41* (49), 9509−9513. (d) Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron Lett.* **1996**, *37* (34), 6173−6176. For trans-fused, see: (e) Kadota, I. T., H.; Sato, K.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3494−3498. (f) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380−1386. For reviews, see: (g) Marmsater, F. P.; West, F. G. *Chem.−Eur. J.* **2002**, *8* (19) 4346−4353. (h) Evans, P. A.; Delouvrie, B. *Curr. Opin. Drug Discovery Dev.* **2002**, *5* (6), 986−999 and references therein.

(2) (a) Parrish, J. D.; Little, R. D. *Org. Lett.* **2002**, *4* (9), 1439−1442. For a few additional references to the use of titanium(III), see: (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116* (3), 986−97. (b) Gansauer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.; Pierobon, M. *Chem.− Eur. J.* **2003**, *9* (2), 531−542. (c) Gansauer, A.; Narayan, S. *Adv. Synth. Catal.* **2002**, *344* (5), 465−475. (d) Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56* (15), 2103−2112.

(3) (a) Blunt, J. W.; Hartshorn, M. P.; McLennan, T. J.; Munro, M. H. G.; Robinson, W. T.; Yorke, S. C. *Tetrahedron Lett.* **1978**, *1*, 69−72. (b) Gonzalez, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122* (38), 9099−9108.

10.1021/jo050465d CCC: $30.25
Published on Web 06/01/2005



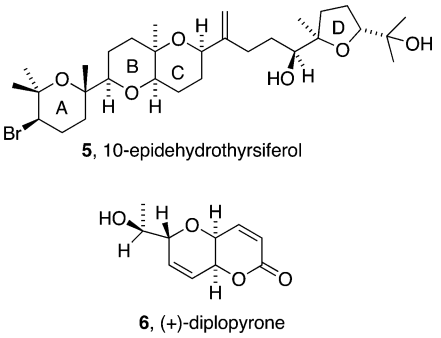
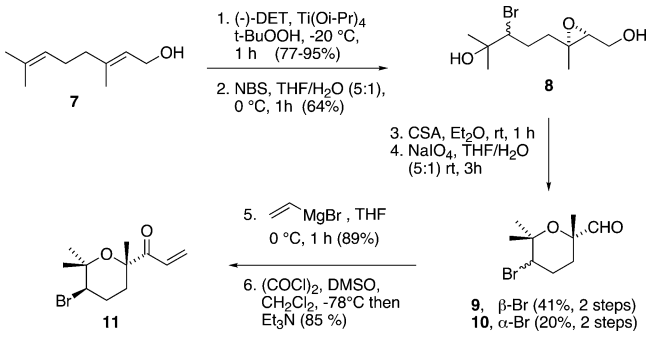
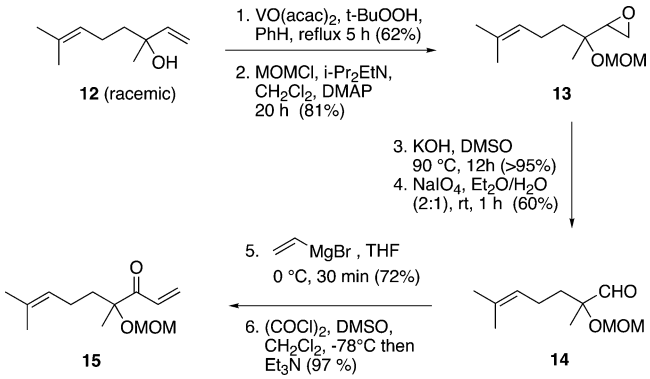


FIGURE 1. Three naturally occurring pyranopyrans.

SCHEME 2. Synthesis of Enone Coupling Partner 11



SCHEME 3. Assembly of a Second Enone for Exploratory Studies



cis-fused),[4] and (+)-diplopyrone (**6**; cis-fused)[5] are representative examples of each variety (Figure 1). Compounds **4** and **5** are of marine origin and display antitumor activity, while diplopyrone (**6**) is the main phytotoxin of *Diplodia mutila*, a fungus that is believed to be one of the principle causes in the decline of cork oak. We seek to develop methodology that will be of sufficient generality to allow the assembly of either the cis- or the trans-fused skeleton. Herein we describe progress toward this end.

Results and Discussion

Two new coupling agents, **11** and **15**, were synthesized, and their chemistry was examined. The assembly of **11** began with geraniol (**7**) and was completed in six steps, as follows (Scheme 2). Sharpless asymmetric epoxidation proceeded in yields ranging from 77 to 95% and in 93% ee.[6] Hydrobromination of the alkene was achieved under standard conditions using NBS in THF/water (5:1) to afford a 64% yield of diastereomeric bromo alcohols **8**. Cyclization to the tetrahydropyran diol could be accomplished by treating **8** with camphorsulfonic acid in diethyl ether in a fashion similar to that reported by McDonald.[7] Diol cleavage using sodium periodate afforded a mixture of aldehydes **9** and **10**, the desired β-isomer **9** in a 41% yield over two steps.[3b] These substances were separated prior to treating **9** with vinylmagnesium bromide and then to Swern oxidation conditions to deliver enantiomerically pure **11** in ~16% yield overall.

The second coupling agent, structure **15**, was synthesized in six steps from racemic linalool (**12**) (Scheme 3). Thus, catalyzed epoxidation using bis(acetylacetonato)-oxovanadium(IV) and *tert*-butyl hydroperoxide, followed by protection as a MOM ether, base-induced opening of the epoxide, and periodate cleavage, afforded aldehyde **14** in a 29% yield over four steps. Once again, vinylmagnesium bromide and a Swern oxidation were used, this time to generate the α,β-unsaturated ketone subunit of **15**.

Our previously established protocol called for the in situ generation of an anhydrosugar from a sugar glycal using dimethyl dioxirane (DMDO),[8] followed by the addition of the electron-deficient alkene and then by the dropwise addition of titanocene(III) chloride.[2] When applied to tri-*O*-benzyl glucal (**16**) and the linalool-derived agent **15**, coupling was achieved in a 21% yield (two steps) (Scheme 4). With the bromopyran coupling partner **11**, the assembly was equally simple to perform, this time proceeding in a 38% yield for the two-step sequence to afford **18**.

Having determined compound **11** to be a suitable and effective coupling partner in glycal coupling reactions, we turned our attention to the synthesis of the methyl-substituted dihydropyran **23**, the methyl group being required in order to access thyrsiferol (**4**) or its cis-fused analogue **5**. To ensure that epoxidation would occur on

(4) (a) Norte, M.; Fernandez, J. J.; Souto, M. L.; Garcia-Gravalos, M. D. *Tetrahedron Lett.* **1996**, *37* (15), 2671−2674. (b) Norte, M.; Fernandez, J. J.; Souto, M. L. *Tetrahedron* **1997**, *53* (13), 4649−4654.

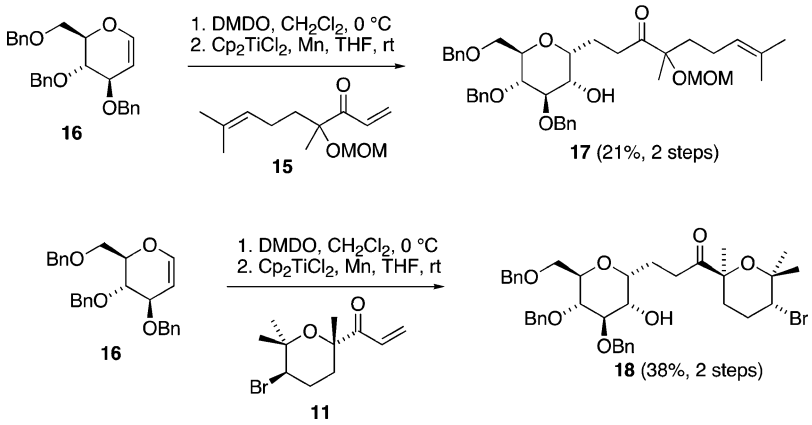
(5) Evidente, A. M., L.; Spanu, E.; Franceschini, A.; Lazzaroni, S.; Motta, A. *J. Nat. Prod.* **2003**, *66* (2), 313−315. (b) Giorgio, E.; Maddau, L. S., E.; Evidente, A.; Rosini, C. *J. Org. Chem.* **2005** *70* (1), 7−13.

(6) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

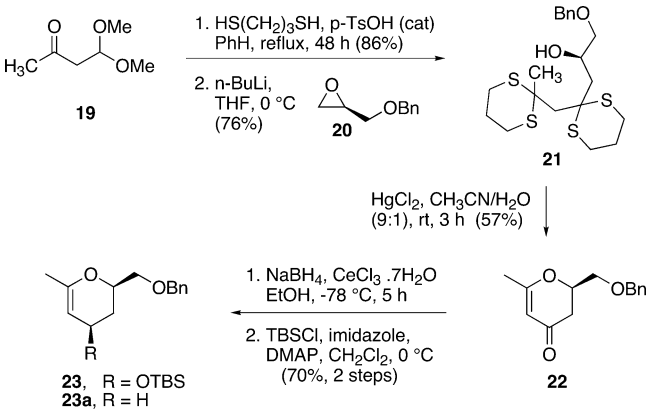
(7) McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4* (4), 593−595.

(8) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

SCHEME 4. Exploratory Coupling Reactions with Enones 11 and 15



SCHEME 5. Construction of Methyl-Substituted Pyran Coupling Partner 23



the α-face and not afford a mixture of diastereomers, we elected to synthesize **23** rather than **23a** (see Scheme 5). Of course this necessitates the removal of the OTBS unit at a later stage. This decision, it turns out, led to unforeseen difficulties (vide infra).

Pyran **23** proved accessible in sizable quantity (e.g., in 8 g batches) through the use of a five-step sequence commencing with the commercially available keto acetal **19**. Thus, treatment of it with 1,3-propanedithiol and catalytic *p*-TsOH led smoothly to the bis-thioacetal[9] (86%) whose subsequent deprotonation (*n*-BuLi) and exposure to R-benzyl glycidyl ether (**20**) provided a 76% yield of the hydroxy ether **21**. Treatment of **21** with mercuric chloride in 9:1 acetonitrile/water at room temperature exposed the carbonyl units and also initiated cyclization leading to enantiomerically pure **22** (57%).[10] Luche's conditions[11] for reduction of **22** afforded the corresponding allylic alcohol; protection as the TBS ether afforded **23** in 70% yield over two steps.

Our initial attempts to couple **23** with the bromopyran **11** provided disappointingly low yields of **26** (∼10−15%) (Scheme 6). We suspected that the Ti(III)-induced ring opening was at fault, but quickly discovered that our difficulties could be traced to the increased lability of the methyl-substituted epoxide **24**, relative to **25**.[12] The most effective and most reproducible way to obviate the problem proved simply to ensure that the *DMDO was used immediately after drying with* 4 Å *molecular sieves*. Once this modification was made, the yield rose significantly to 60%. While 1.5 equiv of **11** was used, the unreacted material can be, and was, recycled.

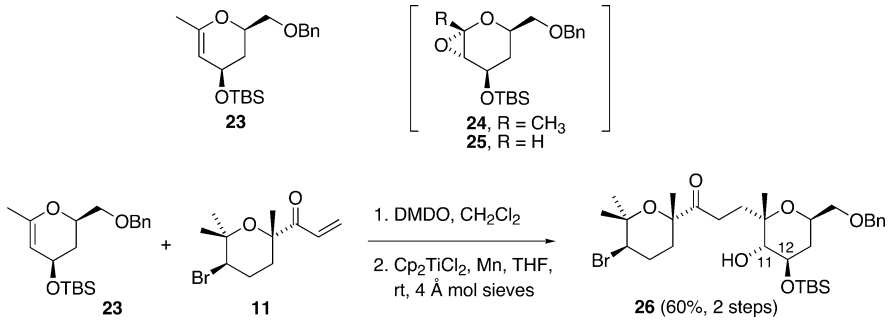
With enantiomerically pure **26** in hand, we turned our attention to the cyclization. Treatment of it with triethylsilane and trimethylsilyl triflate in methylene chloride, under conditions developed by Olah and Prakash and their co-workers,[13] afforded a substance whose ^{1}H NMR spectrum indicated that the silyl group had been cleaved. X-ray analysis of the resulting crystalline solid, **27**, confirmed that cyclization had occurred, established that the rings were cis-fused as expected, and revealed that the C-ring was significantly distorted from a chair conformation (Scheme 7). Distortion allows the hydroxyl and benzyloxymethylene units to occupy pseudoequatorial rather than the axial orientations that would be required by a chair. Thus, the distortion in **27** as well as its likely precursor, **28**, is entirely reasonable. The configuration of the newly formed stereocenter at C_7 in structure **27** is undoubtedly the consequence of a stereoelectronically controlled addition to the cyclic oxonium ion intermediate, **28a**.

Efforts to remove the hydroxyl group from C_{12} of **27**, or to effect deoxygenation at earlier stages of the sequence, were problematic. Eventually, we discovered that an elegant method developed by Barton and co-workers to handle, explicitly, deoxygenation in a hindered environment could be used.[14] Of added value is the fact that the chemistry, though reductive, does not touch the potentially labile C−Br bond that is found in the A-ring. Thus, when treated with borane-tri-*n*-butylphosphine complex and AIBN in refluxing dioxane, the xanthate derived from **27** succumbed; **29** was isolated in a 69% yield, reassuring us that the oxygen can be removed (Scheme 8).

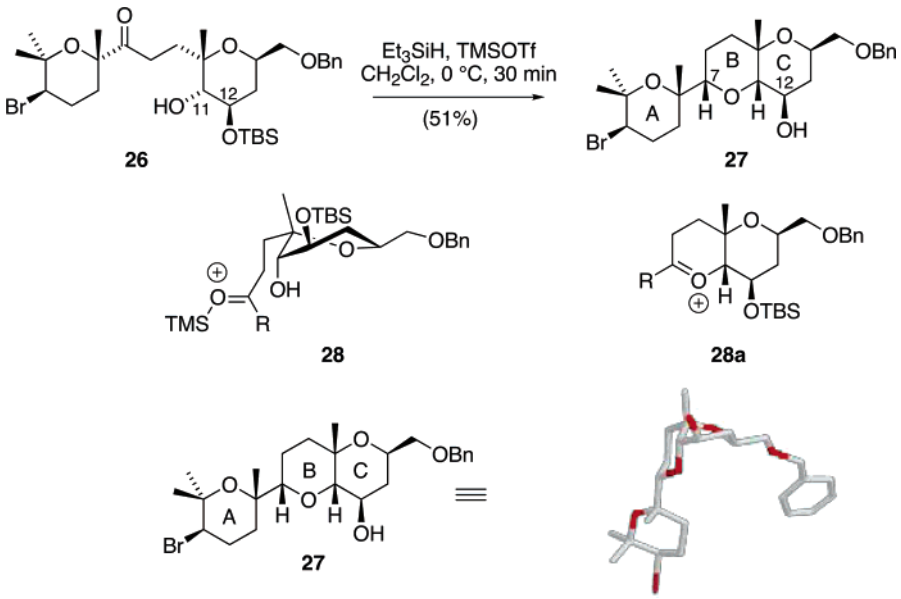
Thus far, our efforts have led to the development of a route to the cis-fused, but not as yet the trans-fused,

(9) Shapiro, R. H.; Entee, T. E., Jr.; Coffen, D. L. *Tetrahedron* **1968**, *24*, 2809−2815.
(10) Noda, Y.; Fukaya, T.; Kikuchi, M. *Heterocycles* **1996**, *43* (2), 271−275.
(11) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(12) (a) Hale, K. J.; Frigerion, M.; Manaviazar, S. *Org. Lett.* **2001**, *3* (23), 3791−3794. (b) Roberts, S. W.; Rainier, J. D. *Org. Lett.* **2005**, ASAP. (c) Majumder, U.; Cox, J. M.; Rainier, J. D. *Org. Lett.* **2003**, *5* (6), 913−916.
(13) (a) Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987**, *52*, 4314−4319. (b) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136−4317.
(14) Barton, D. H. R.; Jacob, M. *Tetrahedron Lett.* **1998**, *39* (11), 1331−1334.

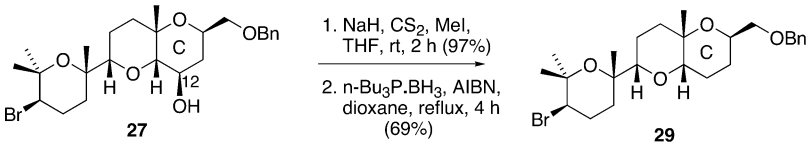
SCHEME 6. Coupling the A and C Rings of the Thyrsiferol Framework



SCHEME 7. TMSOTf-Promoted Cyclization To Assemble the B-Ring of 27

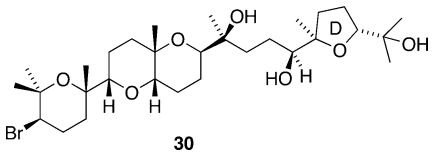


SCHEME 8. Removal of the C_{12} Hydroxyl Group from 27 under Radical-Forming Conditions



framework. This is a clear, but presumably correctable deficiency that can be handled simply by inverting the stereochemistry at the hydroxy-bearing carbon, C_{11}, of **26**. Unfortunately, all attempts to do so using variations on the Mitsunobu protocol have been unsuccessful.[15] We assume the cause of this difficulty is the highly hindered nature of the carbon that must be attacked, and that the presence of the adjacent OTBS group at C_{12} is at least partially to blame. Several options exist and are being explored at the present time.

Structure **29** is an important material for us. We intend to convert it to structure **30**, the cis-fused analogue of thyrsiferol (**4**), and to compare its bioactivity with that of the natural product.[16] Efforts to do so, and to complete the total synthesis of thyrsiferol (**4**), are underway.



Experimental Section

3-Bromo-5-(3-hydroxymethyl-2-methyloxiranyl)-2-methyl-(2*R*,3*R*)-pentan-2-ol (8). To 100 mL of dry CH_2Cl_2 were added freshly activated crushed 4 Å molecular sieves, and the contents were cooled to 0 °C. (−)-DET (1.6 mL, 9.1 mmol) was added, followed by Ti(O-*i*-Pr)$_4$ (1.9 mL, 6.5 mmol). The reaction was stirred at 0 °C for 10 min and cooled to − 20 °C. *t*-BuOOH (42 mL of 4.7 M solution in toluene briefly dried over molecular sieves)[17] was added dropwise using an addition funnel. The reaction was stirred at −20 °C for 30 min. Geraniol (20.0 g, 129.6 mmol) was added dropwise in 5 mL of CH_2Cl_2. After 1 h, the reaction was complete as judged by TLC, and the solution was warmed to 0 °C, quenched by adding water (40 mL), and stirred for 1 h while warming to room temperature.

(15) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32* (26), 3017−3020. (c) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234−236. (d) Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33* (30), 4317−4320.

(16) These studies will be conducted in collaboration with Dr. R. S. Jacobs of UCSB.

(17) Hill, G. J.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607−3608.

Twelve milliliters of a 30% aqueous solution of NaOH saturated with NaCl was added, and the solution was stirred vigorously until phase separation was observed. At this point, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Column chromatography using petroleum ether and diethyl ether (3:1, then 1:1) afforded the desired epoxide as a clear liquid (17.5 g, 102.8 mmol, 79% yield, 93% ee determined by ^{1}H NMR analysis of the corresponding acetate and Eu(hfc)$_3$ in C_6D_6):[6] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.11−5.06 (m, 1H), 3.83 (dd, J = 12.0, 4.2, 1H), 3.70 (dd, J = 12.1, 6.9, 1H), 2.98 (dd, J = 6.8 4.1, 1H), 2.10 (m, 2H), 1.72−1.65 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.51−1.44 (m, 1H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.1, 123.3, 62.9, 61.4, 61.2, 38.5, 25.6, 23.7, 17.6, 16.7; ESI+/TOF *m/z* 363 ($2M^+$ + Na), 193 (M^+ + Na), 153, 135; HRMS (ESI) calcd for $C_{10}H_{18}O_2Na$ 193.11990, found 193.1200 $[M + Na]^+$.

To a 5:1 mixture of THF and water (1.3 L) was added the above epoxy alcohol (11.0 g, 64.6 mmol), and the solution was cooled to 0 °C. NBS (11.5 g, 64.6 mmol, recrystallized from water) was added at once, and the reaction was stirred for 2 h at 0 °C. Upon consumption of the starting material as judged by TLC, NaCl was added, the solution was stirred, and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 100 mL), and the organic layer was dried with Na_2SO_4. Removal of the volatiles under reduced pressure and column chromatography using petroleum ether and diethyl ether (1:9) afforded the desired product **8** as a mixture of diastereomers (1:1) as a clear thick oil (11.0 g, 41.1 mmol, 64%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.0 (t, J = 2, 1H), 3.97 (t, J = 2, 1H), 3.87−3.79 (m, 2H), 3.73 (dd, J = 11.2, 6.6, 1H), 3.69 (dd, J = 11.2, 6.6, 1H), 3.06 (dd, J = 6.4, 4.6, 1H), 3.00 (dd, J = 6.6, 4.3, 1H), 2.15−1.97 (m, 2H), 1.88−1.72 (m, 1H), 1.62−1.50 (m, 1H), 1.37 (s, 3H), 1.36 (s, 6H), 1.35 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.6, 70.4, 69.7, 65.8, 63.1, 62.1, 61.2, 61.1, 60.9, 60.4, 37.5, 36.7, 28.3, 29.1, 26.6, 26.4, 26.2, 26.1, 17.3, 16.6; IR (neat) 3404, 2975, 1383, 1027, 731 cm^{-1}; ESI+/TOF *m/z* 289 (M^+ + Na), 209; HRMS (ESI) calcd for $C_{10}H_{19}O_3NaBr$ 289.04097, found 289.0420 $[M + Na]^+$.

5-Bromo-2,6,6-trimethyl-(5*R*)-tetrahydropyran-2-carbaldehyde (9, 10). To 300 mL of Et_2O was added 5.6 g (21.0 mmol) of **8**, followed by 1.9 g (8.2 mmol) of camphorsulfonic acid. The reaction mixture was stirred at room temperature for 1 h and then neutralized with triethylamine (8.2 mmol). $NaIO_4$ (27.3 mmol) was added, followed by 40 mL of water. The reaction mixture was stirred at room temperature for 3 h, diluted with water, extracted with Et_2O (3 × 100 mL), dried with brine and $MgSO_4$, and concentrated under reduced pressure. Column chromatography using petroleum ether and Et_2O (4:1) afforded 1.0 g (4.3 mmol) of aldehyde **10** (20%) and 2.01 g (8.6 mmol) of aldehyde **9** (41%). Spectra data for compound **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.56 (d, J = 1.5, 1H), 4.14−4.12 (m, 1H), 2.21−2.13 (m, 1H), 2.10−1.99 (m, 1H), 1.93−1.86 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.5, 78.4, 74.9, 58.3, 30.9, 26.5, 26.2, 24.4, 23.8; IR (neat) 2972, 1730, 1097, 908, 728 cm^{-1}.

1-[5-Bromo-2,6,6-trimethyl-(2*S*,5*R*)-tetrahydropyran-2-yl]propenone (11). To 50 mL of dry THF was added compound **9** (2.4 g, 10.2 mmol), and the solution was cooled to 0 °C. Vinylmagnesium bromide (1 M solution in THF, 15.3 mL) was added dropwise via syringe, and the solution was stirred for 1 h at 0 °C. The reaction mixture was quenched with saturated NH_4Cl, extracted with Et_2O (3 × 30 mL), washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude material was chromatographed using petroleum ether and Et_2O (8:1) to afford the desired allylic alcohol as a clear oil and as a mixture of diastereomers (2.3 g, 8.8 mmol, 86%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.84−5.69 (m, 2H), 5.37−5.18 (m, 4H), 3.9−3.84 (m, 2H), 3.82−3.80 (m, 1H), 3.7 (dt, J = 6.8, 1.2, 1H), 2.61 (bs, 2H), 2.31−2.20 (m, 2H), 2.17−2.11 (m, 2H), 1.98−1.77 (m, 2H), 1.46 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 1.2 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.5, 134.8, 118.6, 117.5, 80.8, 79.1, 76.3, 76.1, 75.7, 75.6, 57.8, 57.5, 34.0, 31.0, 30.9, 30.4, 27.8, 27.7, 23.4, 23.1, 22.7, 20.9; IR (neat) 3487, 2981, 1379, 1126, 1018, 730 cm^{-1}.

To 20 mL of dry CH_2Cl_2 was added oxalyl chloride (0.65 mL, 7.5 mmol), and the solution was cooled to −78 °C. DMSO (1.1 mL, 15 mmol) in 1 mL of CH_2Cl_2 was added dropwise, and the reaction mixture was stirred for 30 min. The above allylic alcohol mixture (1.3 g, 5.0 mmol) dissolved in 5 mL of CH_2Cl_2 was added, and the solution was stirred for another 30 min. Triethylamine (3.5 mL, 25 mmol) was added dropwise at −78 °C, and the solution was stirred for 45 min and allowed to warm to room temperature. Brine was added, and the solution was extracted with CH_2Cl_2, dried with Na_2SO_4, and concentrated under reduced pressure. The crude material was chromatographed using petroleum ether and Et_2O (7:1) to afford 1.1 g (4.2 mmol, 85%) of compound **11** as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (dd, J = 17.4, 10.4, 1H), 6.39 (dd, J = 17.4, 2.0, 1H), 5.72 (dd, J = 10.4, 2.0, 1H), 4.12−4.10 (m, 1H), 2.29−2.20 (m, 2H), 2.06−1.99 (m, 1H), 1.90−1.81 (m, 1H), 1.40 (s, 3H), 1.31 (s, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.9, 131.0, 128.3, 78.3, 57.5, 33.3, 30.3, 28.8, 27.5, 20.3; IR (neat) 2979, 1698, 1610, 1398, 1080, 997, 856 cm^{-1}; ESI+/TOF *m/z* 283 (M^+ + Na), 261, 203, 181, 163; HRMS (ESI) calcd for $C_{11}H_{17}O_2NaBr$ 283.03041, found 283.0303 $[M + Na]^+$.

2-(1-Methoxymethoxy-1,5-dimethylhex-4-enyl)oxirane (13). Linalool (10.0 g, 64.8 mmol) and VO(acac)$_2$ (0.86 g, 3.2 mmol) in 250 mL of benzene were heated to reflux in a three-neck flask equipped with a condenser and an addition funnel. The dark green solution was refluxed for 15 min upon which time *t*-BuOOH (5.5 M in decane, 17.7 mL, 97.2 mmol) was added dropwise at 80 °C over 20 min. The solution turned red and was refluxed for 5 h. The reaction was cooled to room temperature, quenched with saturated Na_2SO_3, extracted with Et_2O (3 × 50 mL), washed with brine, dried over $MgSO_4$, and concentrated. The crude oil was chromatographed with EtOAc and petroleum ether (1:6) to give the desired epoxy alcohol as a 2:1 mixture of diastereomers (6.9 g, 40.5 mmol, 62%). The spectral data matched the reported literature values:[18] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.14−5.07 (m, 1H), 2.96 (dd, J = 4.0, 2.9, 1H), 2.75 (dd, J = 5.1, 2.8, 1H), 2.69 (dd, J = 5.1, 4.1, 1H), 2.14−2.07 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.63−1.53 (m, 2H), 1.18 (s, 3H); ESI+/TOF *m/z* 193 (M^+ + Na), 179, 161; HRMS (ESI) calcd for $C_{10}H_{18}O_2Na$ 193.1204, found 193.1197 $[M + Na]^+$.

To 10 mL of dry CH_2Cl_2 were added the above epoxy alcohol (0.49 g, 2.9 mmol), diisopropyl ethylamine (1.5 mL, 8.8 mmol), and a catalytic amount of DMAP (10 mg) at room temperature. MOMCl (0.45 mL, 5.9 mmol) was added dropwise. The solution was stirred for 20 h and the reaction quenched by adding it to 10% citric acid. The resulting solution was extracted with Et_2O (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The oil was chromatographed using petroleum ether and Et_2O (6:1) to give the product as a mixture of diastereomers (clear oil, 0.5 g, 2.3 mmol, 81%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.10 (m, 1H), 4.78 (s, 3H), 3.38 (s, 3H), 3.03 (dd, J = 4.3, 2.9, 1H), 2.67 (t, J = 4.3, 1H), 2.53 (dd, J = 4.9, 2.9, 1H), 2.87 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.66−1.53 (m, 2H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.7, 124.1, 124.0, 91.6, 91.5, 76.6, 75.7, 57.1, 57.0, 55.4, 43.9, 43.3, 30.2, 37.7, 25.6, 22.0, 21.7, 19.8, 18.1, 17.6; IR (neat) 2927, 1450, 1375, 1144, 1030 and 917 cm^{-1}; ESI+/TOF *m/z* 237 (M^+ + Na), 183, 153, 135; HRMS (ESI) calcd for $C_{12}H_{22}O_3Na$ 237.1467, found 237.1467 $[M + Na]^+$.

2-Methoxymethoxy-2,6-dimethylhept-5-enal (14). Compound **13** (0.250 g, 1.2 mmol) was dissolved in 5 mL of DMSO,

(18) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626−4633.

and 2 mL of 1 N KOH was added. The resulting solution was heated to 90 °C for 12 h. The flask was cooled to room temperature, water and EtOAc were added, and the organic layer was separated. The aqueous layer was extracted three times with EtOAc, and the organic layers were combined and washed with brine, dried using Na_2SO_4, and concentrated under reduced pressure to give a light yellow oil (0.27 g, 1.2 mmol). The crude diol was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.08−5.03 (m, 1H), 4.71 (AB, J = 7.7, 2H), 3.68−3.41 (m, 3H), 3.38 (s, 3H), 2.09−1.92 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.59−1.49 (m, 2H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.8, 123.9, 90.8, 80.4, 75.9, 62.7, 55.5, 36.3, 25.6, 21.8, 18.9, 17.5; IR (neat) 3385, 2916, 1437, 1375, 1024, 951 cm^{-1}; ESI+/TOF *m/z* 255 (M^+ + Na), 239, 183, 165; HRMS (ESI) calcd for $C_{12}H_{24}O_4Na$ 255.1572, found 255.1568.

In 10 mL of Et_2O and 5 mL of water was dissolved the above diol (0.3 g, 1.3 mmol); $NaIO_4$ (0.41 g, 1.9 mmol) was added all at once. The reaction was stirred at room temperature for 1 h, and the water layer was removed and extracted with Et_2O. The combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude aldehyde (0.156 g, 0.78 mmol, 60%) was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.53 (s, 1H), 5.06 (m, 1H), 4.73 (AB, J = 7.2, 2H), 3.42 (s, 3H), 2.06−2.00 (m, 2H), 1.77−1.58 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.5, 132.4, 123.4, 91.9, 82.2, 55.8, 35.6, 25.6, 21.5, 17.7, 17.6; IR (neat) 2929, 1732, 1452, 1377, 1142, 1029, 917 cm^{-1}.

4-Methoxymethoxy-4,8-dimethylnona-1,7-dien-3-one (15). To 2 mL of THF was added vinylmagnesium bromide (1 M in THF, 1.1 mL), and the flask was cooled to 0 °C. Compound **14** (0.15 g, 0.75 mmol) in 0.5 mL of THF was then added dropwise, and the resulting solution was stirred for 30 min at 0 °C prior to quenching with satd NH_4Cl. The organic layer was separated, washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Column chromatography using petroleum ether and Et_2O (5:1) afforded the product as a clear oil (0.123 g, 0.54 mmol, 72%). The reaction was repeated starting with 12 mmol of compound **14** and a similar yield (70%) was obtained: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.93−5.77 (m, 2H), 5.33−5.27 (m, 2H), 5.19 (m, 1H), 5.17 (m, 1H), 5.05 (m, 2H), 4.75−4.66 (m, 4H), 3.99 (m, 1H), 3.93 (m, 1H), 3.46 (d, J = 4.1, 1H), 3.42 (d, J = 5.4, 1H), 3.39 (s, 3H), 3.39 (s, 3H), 2.05−1.96 (m, 4H), 1.74−1.66 (m, 1H), 1.64 (s, 6H), 1.57 (s, 6H), 1.53−1.49 (m, 2H), 1.40−1.30 (m, 1H), 1.20 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.4, 136.1, 131.5, 124.3, 124.1, 117.3, 116.8, 91.9, 90.9, 81.3, 80.9, 77.8, 77.3, 55.6, 36.2, 34.9, 25.6, 21.7, 21.6, 19.8, 18.1, 17.5; IR (neat) 3442, 2925, 1452, 1376, 1139, 1027, 919 cm^{-1}; ESI+/TOF *m/z* 251 (M^+ + Na), 179, 161, 121; HRMS (ESI) calcd for $C_{13}H_{24}O_3Na$ 251.1623 found 251.1621

To 20 mL of CH_2Cl_2 was added oxalyl chloride (0.54 mL, 6.2 mmol), and the resulting solution was cooled to −78 °C. DMSO (0.88 mL, 12.3 mmol) in 5 mL of CH_2Cl_2 was added dropwise, and the solution was stirred for 30 min. The above allylic alcohol (0.94 g, 4.1 mmol) dissolved in 5 mL of CH_2Cl_2 was added dropwise at −78 °C, and the solution was stirred for another 30 min. Triethylamine (2.9 mL, 20.5 mmol) was added, and the solution was allowed to warm to 0 °C over 1 h. The reaction was quenched with brine, the layers were separated, the aqueous layer was extracted three times with CH_2Cl_2, and the organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Column chromatography using petroleum ether and Et_2O (4:1) afforded 0.9 g (4.0 mmol) of the product **15** as a light yellow oil (97%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (dd, J = 17.2, 10.4, 1H), 6.36 (dd, J = 17.2, 2.0, 1H), 5.69 (dd, J = 10.4, 2.0, 1H), 5.06−5.01 (m, 1H), 4.65 (AB, J = 7.1, 2H), 3.38 (s, 3H), 1.94 (q, J = 7.7, 2H), 1.80−1.73 (m, 1H), 1.68−1.59 (m, 1H), 1.64 (s, 3H), 1.56 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.4, 132.2, 130.7, 128.8, 123.5, 92.4, 83.7, 56.1, 37.6, 25.6, 22.0, 19.9, 17.6; IR (neat) 2929, 1699, 1610, 1451, 1400, 1143, 1025 cm^{-1}. ESI+/TOF *m/z* 249 (M^+ + Na), 147, 135, 107; HRMS (ESI) calcd for $C_{13}H_{22}O_3Na$ 249.1467, found 249.1466.

Preparation of DMDO. Dimethyldioxirane was prepared following the literature procedure.[19] Upon collection of the DMDO in acetone, the solution was cooled to 0 °C and diluted with the same volume of water and 10 mL of CH_2Cl_2. The organic layer was extracted and washed 6 times with a 0.05 M pH 7.0 buffer solution. This solution was stored at −20 °C until ready for use. Just prior to the epoxidation reaction, the DMDO solution was predried with freshly activated, crushed 4 Å molecular sieves.

1-(4,5-Bis-benzyloxy-6-benzyloxymethyl-3-hydroxytetrahydropyran-2-yl)-4-methoxymethoxy-4,8-dimethylnon-7-en-3-one (17). Tri-*O*-benzylglycal (0.10 g, 0.24 mmol) was dissolved in 5 mL of CH_2Cl_2 and cooled to 0 °C. DMDO (0.1 M in CH_2Cl_2/acetone, 5 mL) was added to the reaction and the mixture stirred until the reaction was determined to be complete by TLC (30 min). The solvents were removed under reduced pressure, and the crude material was dried under vacuo. The crude epoxide was dissolved in 3 mL of anhydrous, deaerated THF. To this solution was added **15** (0.1 g, 0.46 mmol). A green solution of Cp_2TiCl [prepared by mixing Cp_2TiCl_2 (0.18 g, 0.7 mmol) and manganese powder (38 mg, 0.7 mmol) in 3 mL of THF for 45 min] was added to the epoxide via cannula. The reaction immediately turned yellow, then red. Stirred was continued at room temperature for 1 h. The reaction was worked up by adding 0.1 M HCl and extracting with Et_2O (3 × 20 mL). The organic layer was washed with satd $NaHCO_3$, dried with brine and $MgSO_4$, and concentrated to give a thick orange syrup. The crude material was chromatographed using petroleum ether and EtOAc (3:1, then 1:1) to give the desired product **17** (33 mg, 0.05 mmol, 21% for two steps) as mixture of diastereomers in the form of a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.25 (m, 5H), 5.03 (m, 1H), 4.71−4.47 (m, 9H), 3.95−3.88 (m, 2H), 3.76−3.59 (m, 5H), 3.39 (s, 3H), 2.77−2.71 (m, 2H), 1.97−1.76 (m, 5H), 1.65 (s, 3H), 1.63−1.59 (m, 1H), 1.65 (s, 3H), 1.56 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.5, 138.0, 132.0, 128.5, 128.4, 128.3, 127.9, 127.7, 127.6, 123.6, 91.9, 84.7, 78.6, 75.5, 75.4, 73.6, 73.3, 73.1, 73.0, 72.8, 71.5, 70.0, 68.3, 55.7, 37.6, 33.3, 25.6, 22.2, 21.2, 17.6; IR (neat) 3450, 2925, 1713, 1454, 1076, 1027, 734 cm^{-1}; ESI+/TOF *m/z* 1343 ($2M^+$ + Na), 683 (M^+ + Na), 581, 289; HRMS (ESI) calcd for $C_{40}H_{52}O_8Na$ 683.3560, found 683.3575 $[M + Na]^+$.

3-(4,5-Bis-benzyloxy-6-benzyloxymethyl-3-hydroxytetrahydropyran-2-yl)-1-(5-bromo-2,6,6-trimethyltetrahydropyran-2-yl)propan-1-one (19). Tri-*O*-benzylglycal (0.30 g, 0.7 mmol) was dissolved in 5 mL of CH_2Cl_2, and the solution was cooled to 0 °C. DMDO (0.1 M in CH_2Cl_2/acetone, 10 mL) was added and the solution stirred until completion as determined by TLC (30 min). The solvents were removed under reduced pressure, and the material was dried under vacuo. The crude epoxide was dissolved in 15 mL of anhydrous, deaerated THF. To this solution was added **11** (0.280 g, 1.1 mmol). A green solution of Cp_2TiCl [prepared by mixing Cp_2TiCl_2 (0.30 g, 1.2 mmol) and manganese powder (0.10 g, 1.8 mmol) in 10 mL of THF for 45 min] was added to the epoxide via cannula. The reaction mixture immediately turned yellow, then red. The solution was stirred at room temperature for 1 h, prior to addition of 0.1 M HCl and extraction with Et_2O (3 × 25 mL). The organic layer was washed with satd $NaHCO_3$, dried with brine and $MgSO_4$, and concentrated to give a thick orange syrup that was chromatographed using petroleum ether and Et_2O (2:1, then 1:1) to give the desired product **18** as a clear oil (0.19 g, 0.27 mmol, 38% for two steps): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.22 (m, 15H), 4.73−4.95 (m, 6H), 3.98−3.89 (m, 2H), 3.79−3.60 (m, 5H), 2.89−2.68 (m, 2H),

(19) (a) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem Ber.* **1991**, *124*, 2377. (b) Gilbert, M.; Ferrer, M.; Sanchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1997**, *53* (25), 8643−8650.

2.18−2.08 (m, 2H), 2.04−1.88 (m, 2H), 1.83−1.69 (m, 2H), 1.42 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.3, 138.0, 137.5, 128.6, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 79.5, 78.5, 75.5, 75.4, 73.7, 73.3, 73.2, 72.9, 71.6, 69.9, 68.3, 31.7, 29.8, 28.2, 27.4, 27.2, 25.4, 22.1; IR (neat) 3450, 2926, 1709, 1454, 1074, 907, 728 cm^{-1}; ESI+/TOF *m/z* 717/719 (M^+ + Na), 473, 457, 337, 310, 303, 282, 219, 173; HRMS (ESI) calcd for $C_{38}H_{47}O_7NaBr$ 717.2403, found 717.2376 [M + Na]$^+$.

1-Benzyloxy-3-[2-(2-methyl[1,3]dithian-2-ylmethyl)[1,3]-dithian-2-yl]-(2*R*)-propan-2-ol (21). Acetyl acetaldehyde dimethyl acetal (5 mL, 38 mmol) was dissolved in benzene (190 mL, 0.5 M) and added to a round-bottomed flask equipped with stir bar, condenser, and Dean−Stark trap. 1,3-Propanedithiol (7.6 mL, 75 mmol) was added, followed by *p*-toluenesulfonic acid (38 mg, 1 mg/mmol). The reaction mixture was refluxed for 48 h, cooled to room temperature, washed with saturated $NaHCO_3$, dried with brine and Na_2SO_4, and concentrated to give a yellow solid. The solid was recrystallized from 50% dichloromethane and hexanes to give the bis-dithiane as a white crystalline solid in 86% yield (8.7 g, 33 mmol). The spectra data matched the reported literature values:[10] mp = 74−75 °C (lit.[10] mp = 76−77 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.20 (t, J = 4.8, 1H), 2.90−3.01 (m, 4H), 2.67−2.83 (m, 4H), 2.29 (d, J = 4.9, 1H), 2.00−2.12 (m, 2H), 1.77−1.90 (m, 2H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.5, 46.7, 43.2, 31.1, 28.4, 26.8, 25.1, 24.7.

The above solid (3.0 g, 11 mmol) was dissolved in 100 mL of anhydrous THF and was added to a round-bottomed flask. The solution was cooled to 0 °C, and *n*-BuLi (1.6 M in THF, 8.4 mL, 14 mmol) was added dropwise via an addition funnel. The solution turned yellow and was stirred at 0 °C for 1 h. Benzyl-(*R*)-glycidyl ether (**20**, 2.2 g, 14 mmol) dissolved in 10 mL of THF was added at 0 °C, and the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with saturated NH_4Cl, extracted with diethyl ether (3 × 50 mL), washed with brine, and dried using $MgSO_4$. The solvent was removed under reduced pressure. Upon silica gel chromatography using ethyl acetate and hexanes (1:3), 3.6 g (8.4 mmol) of a thick yellow gum (**21**) was obtained in 76% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.36 (m, 5H), 4.60 (s, 2H), 4.30 (m, 1H), 3.43−3.52 (m, 2H), 3.17 (d, J = 3.0, 1H), 2.72−3.02 (m, 11H), 2.34−2.47 (m, 2H), 2.04 (s, 3H), 1.92−2.00 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9, 128.3, 127.6, 127.5, 74.2, 73.1, 68.1, 52.5, 50.1, 49.1, 42.8, 28.5, 27.2, 27.1, 27.0, 26.8, 24.8, 24.4; IR (neat) 3450, 2902, 1420, 1273, 1094, 735 cm^{-1}; LREI-MS *m/z* 430, 323, 133; HRMS (EI) calcd for $C_{20}H_{30}O_2S_4$ 430.112868 [M + H], found 430.112569.

2-Benzyloxymethyl-6-methyl-(2*R*)-2,3-dihydropyran-4-one (22). Compound **21** (130 mg, 0.3 mmol) was dissolved in a mixture of acetonitrile and water (3 mL, 9:1) at room temperature. $HgCl_2$ (270 mg, 1 mmol) was added in one portion, and the reaction mixture turned cloudy yellow, then pink. The solution was stirred at room temperature for 4 h, filtered through a pad of Celite, and washed with ether three times. The filtrate was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude material that was chromatographed using ethyl acetate and hexanes (2:3) to afford 41 mg (0.18 mmol) of the product as a clear oil (57%). The reaction was repeated starting with 3.0 mmols of compound **21**, and similar yields (55%) were obtained: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (m, 5H), 5.32 (bs, 1H), 4.63−4.56 (AB, J = 12.3, 2H), 4.50−4.56 (m, H), 3.64−3.72 (m, 2H), 2.62 (dd, J = 16.7, 14, 1H), 2.30 (ddd, J = 17, 3.7, 1, 1H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.3, 137.4, 128.4, 127.6, 127.6, 104.9, 78.0, 73.4, 70.6, 37.3, 21.0; IR (neat) 2864, 1661, 1606, 1396, 1334, 1088, 737 cm^{-1}. LREI-MS *m/z* 233 (M^+ + H), 147, 133, 111; HRMS (EI) calcd for $C_{14}H_{17}O_3$ 233.117770 [M + H]$^+$, found 233.117282.

[2-Benzyloxymethyl-6-methyl-(2*R*,4*R*)-3,4-dihydro-2*H*-pyran-4-yloxy]-*tert*-butyldimethylsilane (23). Compound **22** (0.66 g, 2.8 mmol) was dissolved in ethanol, and $CeCl_3\cdot 7H_2O$ (1.4 g, 3.7 mmol) was added. The reaction mixture was sonicated for 5 min or until all of the solids dissolved. The flask was cooled to −78 °C, and $NaBH_4$ (0.16 g, 4.3 mmol) in EtOH was added. The reaction was stirred for 1 h at −78 °C, diluted with ethyl acetate, and allowed to warm to room temperature. Saturated $NaHCO_3$ was added, and the reaction was extracted with EtOAc (3 × 50 mL). The organic phase was dried using Na_2SO_4 and concentrated under reduced pressure to afford a clear thick oil. The unstable allylic alcohol was dissolved in 20 mL of dry CH_2Cl_2, and imidazole (0.35 g, 5.1 mmol) was added, followed by TBSCl (0.64 g, 4.2 mmol) and a catalytic amount of DMAP (10 mg). The reaction mixture was stirred for 24 h at room temperature. Water was added to quench the reaction and the solution extracted with CH_2Cl_2 three times (20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was chromatographed using petroleum ether and Et_2O (5:0.5) to give the desired product as a clear oil (**23**, 0.68 g, 1.96 mmol, 70% for two steps): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.40 (m, 5H), 4.61 (AB, J = 12.1, 2H), 4.50 (m, 1H), 4.42 (m, 1H), 4.17 (m, 1H), 3.68 (dd, J = 10.3, 6.5, 1H), 3.52 (dd, J = 10.3, 4.1, 1H), 2.00 (m, 1H), 1.77 (dd, J = 1.4, 0.9, 1H), 1.67 (ddd, J = 18.7, 10.4, 8.1, 1H), 0.90 (s, 3H), 0.085 (s, 3H), 0.075 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.7, 138.1, 128.4, 127.8, 127.6, 101.4, 73.9, 73.3, 72.1, 63.6, 34.3, 25.9, 19.9, 18.2, −4.7; IR (neat) 2953, 1674, 1252, 1070, 836; IR (neat) 2927, 2856, 1673, 1384, 1251, 1064, 834 cm^{-1}; LREI-MS *m/z* 291 (M^+ − *t*-Bu), 199, 183, 157, 143, 117; HRMS (EI) calcd for $C_{16}H_{23}O_3Si$ [M − *t*-Bu]$^+$ 291.141648, found 291.142537 [M − *t*-Bu]$^+$.

3-[6-Benzyloxymethyl-4-(*tert*-butyldimethylsilanyloxy)-3-hydroxy-2-methyl-(2*S*,3*S*,4*R*,6*R*)-tetrahydropyran-2-yl]-1-(5-bromo-2,6,6-trimethyl-(2*S*,5*R*)-tetrahydropyran-2-yl)propan-1-one (26). Adduct **23** (0.50 g, 1.43 mmol) was dissolved in anhydrous CH_2Cl_2, and 0.50 g of 4 Å crushed molecular sieves was added. The flask was cooled to −78 °C and a dry solution of DMDO was added via cannula. The reaction mixture was stirred until completion (about 10 min) as judged by TLC, and concentrated under reduced pressure. Due to the instability of the epoxide, it was used immediately for the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.27 (m, 5H), 4.58 (s, 2H), 4.13 (dd, J = 9.8, 6.9, 1H), 3.86−3.81 (m, 1H), 3.52 (m, 2H), 2.85 (s, 1H), 1.86 (ddd, J = 13.1, 6.9, 1.2, 1H), 1.32 (ddd, J = 13.2, 11.5, 9.9, 1H), 0.91 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.1, 128.4, 127.7, 127.7, 83.4, 73.3, 72.2, 67.4, 65.8, 60.8, 32.8, 30.9, 25.7, 20.9, 18.1, −4.76, −4.91.

A solution of Cp_2TiCl was prepared by stirring Cp_2TiCl_2 (0.89 g, 3.6 mmol) and manganese (0.32 g, 5.7 mmol) in anhydrous, deaerated THF (15 mL) for 1 h (or until the solution turned lime green). This solution was added rapidly via syringe to a flask containing the above epoxide (0.52 g, 1.43 mmol) and **11** (0.56 g, 2.2 mmol), in THF (20 mL) at room temperature. The reaction immediately turned yellow, then red-brown, and was stirred for 45 min. The reaction was quenched with 0.1 M HCl, extracted with diethyl ether, washed with saturated $NaHCO_3$, and dried with brine and $MgSO_4$ to afford the crude material as an orange syrup. Chromatography using petroleum ether and diethyl ether (6:1) afforded the desired product **26** as a clear oil (0.54 g, 0.86 mmol, 60%). Unreacted compound **11** was recovered and recycled (0.17 g, 0.65 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.27 (m, 5H), 4.55 (AB, J = 12.3, 2H), 3.94 (dd, J = 7.5, 4.6, 1H), 3.85 (ddd, J = 11.2, 9.1, 5.2, 1H), 3.47 (dd, J = 10.0. 6.4, 1H), 3.37 (dd, J = 10.0, 4.2, 1H), 3.24 (dd, J = 9.1, 2.2, 1H), 2.82−2.63 (m, 2H), 2.27 (d, J = 2.2, 1H), 2.15−2.08 (m, 2H), 2.03−1.92 (m, 2H), 1.83 (ddd, J = 12.6, 5.1, 2.2, 1H), 1.78−1.69 (m, 2H), 1.40 (m, 1H), 1.40 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.2, 138.2, 128.3, 127.6, 80.5, 79.7, 76.4, 75.4, 73.2, 73.2, 70.4, 68.1, 58.2, 37.1, 29.7, 28.9, 28.1,

27.4, 27.2, 25.7, 25.3, 25.2, 23.8, 17.9, −4.1, −4.7; IR (neat) 3575, 2929, 2856, 1709, 1454, 1254, 1079, 836, 776 cm^{-1}; ESI+/TOF *m/z* 649/651 (M^+ + Na), 627/629 (M^+ + H), 609/611, 477/479; HRMS (ESI) calcd for $C_{31}H_{52}O_6BrSi$ 627.27110 $[M + H]^+$, found 627.2731.

2-Benzyloxymethyl-6-[5-bromo-2,6,6-trimethyl-(2*S*,5*R*)-tetrahydropyran-2-yl]-8a-methyl-(2*R*,4*R*,4a*S*,6*S*,8a*S*)-octahydropyrano[3,2-*b*]pyran-4-ol (27). Compound **26** (0.20 g, 0.32 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) and cooled to 0 °C. Et_3SiH (0.15 mL, 0.96 mmol) was added, followed by the dropwise addition of TMSOTf (0.16 mL, 0.64 mmol). The reaction mixture was stirred at 0 °C for 15 min, quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, dried with $MgSO_4$, and concentrated under reduced pressure. The crude material was chromatographed using petroleum ether and diethyl ether to afford the product **27** as a white solid (80.6 mg, 0.16 mmol, 51%): mp = 147−149 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.28 (m, 5H), 4.58 (AB, J = 12.1, 2H), 4.08 (m, 1H), 3.97 (td, J = 7.9, 2.2, 1H), 3.86 (dd, J = 12.5, 4.1, 1H), 3.48 (dd, J = 10.0, 4.9, 1H), 3.43 (dd, J = 10.0, 5.1, 1H), 3.26 (d, J = 2.2, 1H), 3.08 (dd, J = 10.9, 3.1, 1H), 2.31−2.09 (m, 4H), 1.93−1.75 (m, 2H), 1.75−1.59 (m, 4H), 1.54−1.48 (m, 1H), 1.45−1.34 (m, 6H), 1.30 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3, 128.3, 127.6, 127.6, 82.7, 81.9, 75.1, 74.9, 73.8, 73.2, 70.7, 69.5, 68.1, 58.7, 35.6, 32.4, 31.5, 30.9, 29.7, 28.0, 27.9, 23.9, 23.5, 19.8; IR (neat) 3412.4, 2924, 1454, 1370, 1095, 909, 729 cm^{-1}; ESI+/TOF *m/z* 519/521 (M^+ + Na), 497/499 (M^+ + H), 479/477, 426, 381, 327; HRMS (ESI) calcd for $C_{25}H_{38}O_5Br$ 497.18971$[M + H]^+$ $C_{25}H_{38}O_5NaBr$ 519.17165 $[M + Na]^+$, found 497.1887 $[M + H]^+$, 519.1700 $[M + Na]^+$

6-Benzyloxymethyl-2-(5-bromo-2,6,6-trimethyl-(2*R*,5*R*)-tetrahydropyran-2-yl)-4a-methyl-(2*S*,4a*S*,6*R*,8a*S*)-octahydropyrano[3,2-*b*]pyran (29). To 15 mL of dry THF was added **27** (70 mg, 0.14 mmol) followed by NaH (7 mg, 0.17 mmol). The solution was stirred for 30 min, and CS_2 (42 μl, 0.7 mmol) was added via syringe. The reaction mixture was stirred at room temperature for another 30 min, and MeI (42 μl, 0.67 mmol) was added. Upon stirring for 2 h, the reaction mixture was quenched with water, extracted with Et_2O (3 × 10 mL), dried with Na_2SO_4, and concentrated. Column chromatography using petroleum ether and 1% Et_2O afforded the desired xanthate (80 mg, 0.136 mmol) in 97% yield: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.27 (m, 5H), 5.65 (t, J = 8.6, 1H), 4.57 (AB, J = 12.2, 2H), 4.22−4.17 (m, 1H), 3.87 (dd, J = 12.4, 3.99, 1H), 3.53−3.41 (m, 3H), 3.05 (dd, J = 11.2, 2.2, 1H), 2.56 (s, 3H), 2.42 (ddd, J = 11.8, 9.4, 2.2, 1H), 2.31−2.21 (m, 1H), 2.15−2.09 (m, 1H), 1.92 (dt, J = 13.7, 3.0, 1H), 1.87−1.78 (m, 2H), 1.75−1.64 (m, 1H), 1.56−1.47 (m, 2H), 1.47−1.40 (m, 1H), 1.44 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.3, 138.4, 128.3, 127.6, 84.0, 79.5, 78.9, 75.1, 74.6, 73.5, 73.2, 70.0, 67.9, 58.7, 37.5, 31.3, 30.8, 29.7, 27.9, 27.5, 24.2, 23.5, 19.6, 19.1; IR (neat) 2932, 1454, 1371, 1206, 1052, 907, 728 cm^{-1}; ESI+/TOF *m/z* 611/609 (M^+ + Na), 521/519/ 413; HRMS (ESI) calcd for $C_{27}H_{39}O_5NaS_2Br$ 609.13145 $[M + Na]^+$, found 609.1303 $[M + Na]^+$

The above xanthate (60 mg, 0.1 mmol) was dissolved in 25 mL of dioxane. *n*-$Bu_3P{\cdot}BH_3$ (44 mg, 0.2 mmol) was added, and the solution was degassed by bubbling argon through it for 30 min. The solution was heated to reflux, and AIBN (5 mg, 0.03 mmol) was added in portions 1 mg every 30 min. The reaction was heated for 4 h, upon which time it was judged to be complete by TLC. The solution was cooled to room temperature, the solvent was removed under reduced pressure, and the crude material was chromatographed using petroleum ether and Et_2O (10%) to give 33 mg (0.07 mmol) of the desired product **29** (69%): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.27 (m, 5H), 4.57 (AB, J = 12.1, 2H), 4.31−4.25 (m, 1H), 3.88 (dd, J = 12.4, 4.1, 1H), 3.49 (dd, J = 9.7, 5.4, 1H), 3.38 (dd, J = 9.8, 5.8, 1H), 3.45 (dd, J = 4.5, 1.8, 1H), 3.04 (dd, J = 11.1, 2.3, 1H), 2.25 (qd, J = 13.2, 3.8, 1H), 2.12 (dq, J = 13.4, 4.1, 1H), 1.99−1.92 (m, 1H), 1.90−1.82 (m, 2H), 1.81−1.65 (m, 4H), 1.55−1.48 (m, 3H), 1.45 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 128.3, 127.6, 127.4, 83.6, 75.0, 75.0, 74.1, 73.1, 69.8, 69.5, 58.9, 37.4, 31.4, 30.9, 28.0, 27.3, 24.1, 23.6, 22.5, 21.5, 20.2; IR (neat) 2933, 1455, 1371, 1097, 1017, 732 cm^{-1}; ESI+/TOF *m/z* 503/505 (M^+ + Na), 423, 401, 311; HRMS (ESI) calcd for $C_{25}H_{37}O_4NaBr$ 503.17674 $[M + Na]^+$, found 503.1773 $[M + Na]^+$.

Acknowledgment. We thank the University of California Cancer Research Coordinating Committee (CRCC) for their support of this research. G.N. expresses her gratitude to the Tokuyama family for a Tokuyama Fellowship during a portion of the time in which this research was conducted.

Supporting Information Available: ^1H and ^{13}C NMR spectra as well as X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050465D