Registry No. **1a**, 79338-80-0; **1b**, 79338-84-4; **2**, 2040-04-2; **3a**, 18610-90-7; **3b**, 25108-61-6; **3c**, 16700-61-1; **4a**, 141509-22-0; **4b**, 141509-24-2; **5a**, 141509-25-3; **5b**, 141526-66-1; **6a**, 141509-19-5; **6b**, 141509-20-8; $Mg(CO)_5Br$, 14516-54-2; (*E*)-β-bromostyrene, 588-72-7.

A Ready Synthesis of Intermediates Containing the A-Ring Substructure of Taxol: A Diels–Alder Route to the B-*seco* Taxane Series

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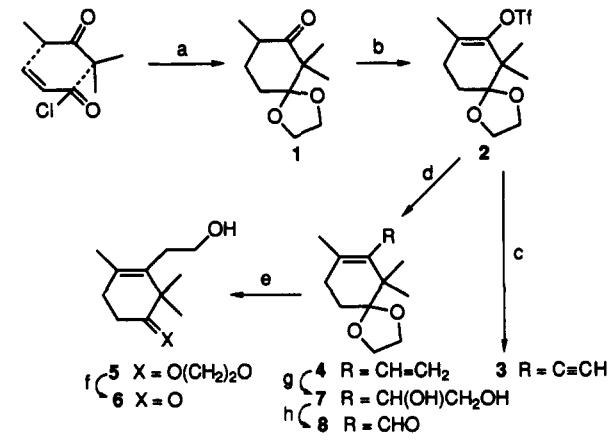
The tetracyclic diterpenoid taxol (**23**) has emerged in the past years as a very promising antitumor agent, especially against ovarian and breast cancers. Its extreme scarcity as well as its unusual mode of action, i.e., the acceleration of the polymerization of tubulin and the blocking of its depolymerization, have resulted in intense efforts toward its hemi and total synthesis.[1]

In the research described herein, we have developed chemistry which leads to A-ring equivalents en route to **23**. We focused on two kinds of goals. The first objective (see Schemes I and II) was to reach targets including the main features of the A-ring of **23** as well as access points for further extension.[2] It was further demonstrated that appropriately fashioned A-ring constructs can function as dienophiles to provide very rapid access to *seco*-B taxane analogues.

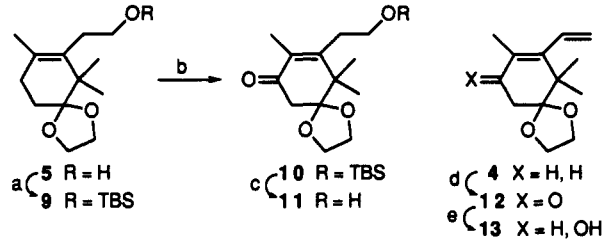
The keto ketal **1** was obtained in three steps from 2-methyl-3-pentanone and acryloyl chloride following known protocols.[3] Reaction of the potassium enolate of **1** with *N*-phenyltrifluoromethanesulfonimide[4] provided **2** in 82% yield. The enol triflate linkage of **2**, though hindered, is amenable to palladium-mediated cross-coupling reactions[5] with acetylenic as well as vinylic stannanes. Thus coupling of **2** with ethynyltri-*n*-butylstannane afforded a 69% yield of **3**. Similar reaction with vinyltri-*n*-butylstannane afforded a 91% yield of **4**. Compound **4** served as a starting material for a variety of interesting sequences leading to **5–8** as shown in Scheme I.

Scheme I[a]



[a] (a) Reference 3; (b) KHMDS, $PhNTf_2$, THF, 0 °C, 82%; (c) $Bu_3SnC{\equiv}CH$, cat. $Pd(PPh_3)_4$, LiCl, THF, reflux, 69%; (d) $Bu_3SnCH{=}CH_2$, cat. $Pd(PPh_3)_4$, LiCl, THF, reflux, 91%; (e) 9-BBN, THF, reflux, 97%; (f) *p*-TsOH, THF–water, 45 °C, 100%; (g) cat. OsO_4, NMO, acetone–water, r.t., 100%; (h) cat. TPAP,[6] NMO, powdered 4-Å molecular sieves, CH_2Cl_2, rt, 56%.

Scheme II[a]



[a] (a) TBDMSCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 82%; (b) CrO_3–3,5-DMP, CH_2Cl_2, −23 °C, 48%; (c) *p*-TsOH, aqueous acetone 82%; (d) CrO_3–3,5-DMP, CH_2Cl_2, −23 °C, 70%; (e) $CeCl_3$, $NaBH_4$, MeOH, 0 °C, 85%.

The feasibility of achieving allylic oxidation as a route to establish the vital C-13[7] functionality of **23** was demonstrated at several stages. Thus silylation of **5** afforded **9** which upon oxidation with chromium oxide–3,5-dimethylpyrazole[8] gave rise to **10** and thence **11** (cf. Scheme II). Similar oxidation of **4** afforded a 70% yield of **12**. The latter could be reduced under Luche conditions[9] to provide **13**. Alternatively, reduction of **12** under the protocols of Corey[10] provided **13** albeit at this writing in only 70% ee.

Alcohol **5** was smoothly oxidized to provide **14** which, upon reaction with isopropenylmagnesium bromide, afforded **15** and thence, by Swern oxidation,[11] the ketone **16**. This compound serves as a branch point to reach inter-

(1) (a) Swindell, C. S. *Org. Prep. Proc. Int.* **1991**, *23*, 465. (b) Blechert, S.; Guénard, D. *Taxus* Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, pp 195–238. (c) Chabner, B. A. *Princ. Prac. Oncol.* **1991**, *5*, 1. (d) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247.

(2) Studies in the synthesis of intermediates containing the CD substructure of taxol are in progress in our laboratory. For a preliminary communication, see: Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274.

(3) (a) Detering, J.; Martin, H.-D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 695. (b) Hargreaves, J. R.; Hickmott, P. W.; Hopkins, B. J. *J. Chem. Soc. C* **1968**, 2599.

(4) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47. Examples of potassium enolates for enol triflate formation include the following. Corey, E. J.; Houpis, I. N. *J. Am. Chem. Soc.* **1990**, *112*, 8997. Tius, M. A.; Kannangara, G. S. K. *J. Org. Chem.* **1990**, *55*, 5711.

(5) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(6) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. Cleavage of the diol linkage of **7** was observed during an attempted selective monooxidation to the corresponding hydroxy aldehyde using tetrapropylammonium perruthenate. Selective oxidation of primary alcohols in the presence of an allylic alcohol have been described, see: Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. In the case of diol **7**, the various ratios of the two possible products were consistent with the results observed by Swern et al.; however the mixture thus obtained was converging to the undesired hydroxy ketone.

(7) Numbering refers to the usual numbering of taxol (**23**).

(8) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057. CrO_3–3,5-dimethylpyrazole has already been successively used on a taxane derivative, see: Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513.

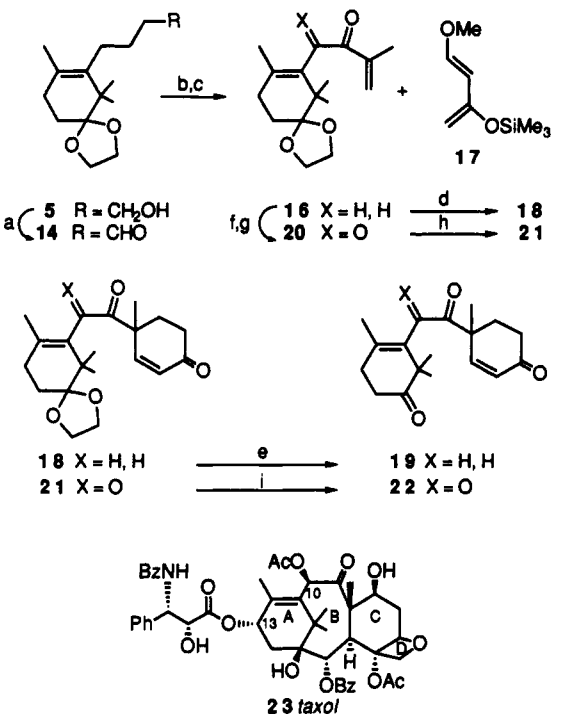
(9) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(10) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. In this reaction, we used as chiral catalyst the (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole. Therefore, by analogy with Corey's findings, the absolute configuration for the major enantiomer of **13** was assigned to be *S*. The ee was determined by NMR study of the mixture using (+)-$Eu(hfc)_3$ as chiral shift reagent.

(11) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

0022-3263/92/1957-4043$03.00/0

Scheme III[a]



[a] (a) Swern, 94%; (b) $BrMgC(Me)=CH_2$, THF, 0 °C, 89%; (c) Swern, 96%; (d) benzene, 125 °C, then THF–0.1 N HCl, 81%; (e) *p*-TsOH, THF–water, 45 °C, 89%; (f) KHMDS, F. Davis oxaziridine,[13] 87%; (g) Swern, 69%; (h) benzene, 80 °C, then THF–0.1 N HCl, 95%; (i) *p*-TsOH, THF–water, 60 °C, 79%.

esting types of B-*seco* taxane derivatives via Diels–Alder methodology. Thus, as depicted in Scheme III, cycloaddition of **16** with *trans*-1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (**17**)[12] followed by acidic hydrolysis afforded **18** and, thence, **19**.

It was also of interest to learn whether this general strategy might be expanded to embrace the additional oxygen at C-10 found in **23**. In fact this was readily accomplished. Hydroxylation of **16** under the protocols of Davis[13] followed by Swern oxidation gave **20**. At least with respect to diene **17**, **20** was much more reactive as a dienophile than is **16**. Cycloaddition of **20** with **17** was carried out at 80 °C for 3 h (compared to 125 °C for 60 h in the case of the reaction of **16** with **17**). Acidic workup as above afforded **21** in 95% yield. Hydrolysis of the ketal linkage provided tetraketone **22**. Possibilities for fashioning the B-ring of the taxane series and upgrading the functionality of the C-ring are being pursued.

In this disclosure we have outlined a variety of routes which are of potential utility not only for a synthesis of **23** but, perhaps more importantly, also for reaching analogs. It is hoped that this chemistry will lead to compounds which are more readily available than taxol while manifesting its exciting biological properties.

Experimental Section

General Procedure. Melting points are uncorrected and were measured using a digital melting point Electrothermal IA 9100 apparatus. Infrared spectra (IR) were obtained with a Perkin-Elmer 1600 Series Fourier-Transform (FT). NMR spectra were recorded using a Bruker AMX-400 spectrometer or a Bruker AC 250 instrument. High resolution mass spectra (HRMS) were recorded at the Department of Chemistry of Columbia University. Flash chromatography was performed using EM Science silica gel 60 230–400 mesh. Reactions were conducted under a nitrogen atmosphere unless otherwise described.

5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl Trifluoromethanesulfonate (2). A solution of potassium bis(trimethylsilyl)amide (KHMDS, 12.9 g, 64.7 mmol, 1.5 equiv) in THF (anhydrous, 200 mL) was cooled to 0 °C and was stirred for 15 min. To this solution was added dropwise a solution of the known keto ketal 1[3] (8.546 g, 43.16 mmol, 1.0 equiv) in THF (50 mL), and the mixture was stirred for 2 h at 0 °C until no more precipitate appeared. Then *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$, 25 g, 70 mmol, 1.62 equiv) was added portionwise, giving immediately a pale brown homogeneous solution. TLC (EtOAc/hexanes, 1:4) showed total disappearance of the starting keto ketal and formation of a slightly less polar product as well as *N*-phenyltrifluoromethanesulfonamide (PhNHTf), the byproduct derived from the imide. The solution was then warmed to room temperature, diluted with Et_2O (200 mL), and washed with brine (2 × 100 mL). The aqueous layers were combined and washed with Et_2O (2 × 200 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed (CH_2Cl_2/hexanes, 1:3) to give 11.73 g (82.4%) of the triflate **2** as a pale yellow oil: IR (neat, thin film) 2989.1, 2950.8, 2888.5, 1689.9, 1471.2, 1454.6, 1402.3 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.18 (s, 6 H), 1.78 (s, 3 H), 1.80 (br t, J = 6.5 Hz, 2 H), 2.22 (br t, J = 6.5 Hz, 2 H), 3.99 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.42, 20.88, 26.56, 28.11, 44.48, 65.26, 111.42, 118.69 (q, J = 319.6 Hz), 125.27, 146.77; MS m/z 41 (38), 55 (35), 69 (30), 86 (100), 165 (56), 180 (27), 330 (10), 93 (38), 99 (41), 107 (37), 137 (25); HRMS calcd for $C_{12}H_{17}O_5F_3S$ 330.0749, found 330.0735.

4,4-(Ethylenedioxy)-2-ethynyl-1,3,3-trimethyl-1-cyclohexene (3). A solution of the triflate **2** (180 mg, 0.546 mmol), ethynyltributylstannane (1.092 mmol, 344 mg, 0.316 mL, 2 equiv), LiCl (anhydrous, 69 mg, 1.63 mmol, 3 equiv), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 63 mg, 0.1 equiv) in anhydrous THF (3 mL) was refluxed 1 day. After being cooled to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with brine (2 × 50 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated. Flash chromatography of the residue (5% Et_2O in hexanes) gave the eneyne **3** as a pale yellow oil (77 mg, 69%): IR (neat, thin film) 3302.9, 2978.4, 1466.9, 1380.8, 1356.5, 1212.0, 1143.8, 1085.8, 1057.6, 992.0, 949.0, 907.2 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$/TMS) δ 1.16 (s, 6 H), 1.76 (t, J = 6.6 Hz, 2 H), 1.90 (s, 3 H), 2.23 (t, J = 6.6 Hz, 2 H), 3.03 (s, 1 H), 3.97 (br s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.00, 23.19, 26.62, 30.35, 41.69, 64.98, 80.20, 81.76, 111.17, 122.60, 141.15; MS m/z 41 (38), 55 (35), 69 (30), 86 (100), 165 (56), 180 (27), 330 (10), 93 (38), 99 (41), 107 (37), 137 (25); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1325.

4,4-(Ethylenedioxy)-2-ethenyl-1,3,3-trimethyl-1-cyclohexene (4). To a solution of triflate **2** (8.43 g, 25.54 mmol, 1 equiv), vinyltributylstannane (12.15 g, 11.2 mL, 38.32 mmol, 1.5 equiv) and LiCl (anhydrous, 3.25 g, 76.64 mmol, 3 equiv) in THF (anhydrous, 150 mL) was added tetrakis(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$, 1.48 g, 1.28 mmol, 5 mol %), and the green mixture was refluxed for 24 h. The mixture was then cooled to room temperature. Workup A: the mixture was diluted with EtOAc (50 mL) and washed with brine (2 × 100 mL). The aqueous layers were combined and extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated under vacuum, and purified by two successive silica gel chromatographies (Et_2O/hexanes, 5:95) to give 4.85 g (91.4%) of the diene **4** as a pale yellow oil. To avoid the second chromatography due to the presence of a large quantity of chlorotributylstannane, basic treatment was employed. Workup B: the majority of the by-product was removed by adding 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.5 equiv) after cooling the mixture to room temperature. It was then diluted with Et_2O (600 mL), washed with 1 N NaOH (3 × 150 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with Et_2O (3 × 100 mL) and the combined etheral layers

(12) (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. (b) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

(13) (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1987**, *66*, 203.

were concentrated in vacuo and found to be devoid of tin by-products. Flash chromatography (same conditions) gave a similar yield of diene **4**: IR (neat, thin film) 3078.0, 2976.0, 2878.7, 1621.5, 1469.8, 1451.7 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$/TMS) δ 1.05 (s, 6 H), 1.71 (d, J = 0.9 Hz, 3 H), 1.78 (t, J = 6.7 Hz, 2 H), 2.18 (m, 2 H), 4.00 (m, 4 H), 4.99 (dd, J = 17.6, 2.6 Hz, 1 H), 5.27 (dd, J = 11.2, 2.6 Hz, 1 H), 6.15 (m, 1 H); ^{13}C NMR (100 MHz $CDCl_3$) δ 20.92, 22.87, 26.70, 30.67, 42.04, 64.94, 112.08, 118.78, 126.98, 135.02, 137.46; MS m/z 41 (35), 55 (30), 86 (30), 87 (40), 107 (100), 122 (28), 208 (51); HRMS calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1459.

2-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-ethanol (5). A three-necked 500-mL flask was charged with a solution of the diene **4** (12.1 mmol, 2.5 g) in anhydrous THF (20 mL) and then with a 9-borabicyclo[3.3.1]nonane (9-BBN, 0.5 M solution in THF, 74 mL, 37 mmol, 3 equiv), and the mixture was immediately refluxed for 1.5 h. TLC (EtOAc/hexanes, 1:1) showed total disappearance of the starting material. The mixture was then cooled to room temperature and ethanol (22 mL) was added, followed by 6 N NaOH (8 mL) and then dropwise 30% H_2O_2 (14.5 mL), maintaining a gentle reflux. After 1 h, the mixture had cooled to room temperature and was diluted with Et_2O (200 mL) and washed with brine (200 mL). The aqueous layers were back extracted with Et_2O (100 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated. Flash chromatography of the residue (EtOAc/hexanes, 1:4) gave pure alcohol **5** (2.7 g, 97%) as a pale yellow oil: IR (neat, thin film) 3471.5, 2953.2, 2882.3, 1477.1, 1379.6, 1355.5, 1208.4, 1140.6, 1089.2, 1056.0, 949.7, 906.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.05 (s, 6 H), 1.67 (s, 3 H), 1.74 (t, J = 6.6 Hz, 2 H), 2.10 (t, J = 6.6 Hz, 2 H), 2.34 (t, J = 8 Hz, 2 H), 3.60 (t, J = 8 Hz, 2 H), 3.94–3.99 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.82, 22.72, 26.68, 30.60, 32.36, 42.96, 62.27, 64.84, 112.21, 128.43, 132.05; MS m/z 43 (76), 55 (39), 86 (100), 87 (75), 97 (28), 107 (28), 125 (26), 196 (20), 226 (15); HRMS calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1568.

3-(2-Hydroxyethyl)-2,4,4-trimethyl-3-cyclohexenone (6). Heating the ketal **5** (44 mg, 0.195 mmol) in 2 mL of a 1:1 (vol) mixture of water and THF at 45 °C gave, after dilution with Et_2O, washing with saturated $NaHCO_3$ and then brine, drying ($MgSO_4$), filtration, and evaporation, the pure ketone **6** as a colorless oil. TLC did not allow monitoring of the outcome of the reaction. NMR analysis of aliquots indicated that 2 h was sufficient time for completion of the hydrolysis which was quantitative: IR (neat, thin film) 3409.7, 2969.5, 2929.3, 1712.2, 1471.1, 1446.0, 1378.3, 1357.6, 1039.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.18 (s, 6 H), 1.76 (s, 3 H), 2.08 (br s, 1 H), 2.35 (t, J = 7 Hz, 2 H), 2.40 (t, J = 8.1 Hz, 2 H), 2.53 (t, J = 7 Hz, 2 H), 3.64 (t, J = 8.1 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.87, 24.54, 31.57, 32.45, 35.93, 47.82, 62.16, 129.70, 132.48, 215.34; MS m/z 41 (45), 55 (40), 81 (56), 96 (42), 107 (44), 124 (100), 137 (18), 149 (20), 182 (30); HRMS calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1318.

2-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-1,2-ethanediol (7). A solution of the diene **4** (214 mg, 1.03 mmol) and *N*-methylmorpholine *N*-oxide (NMO, 127 mg, 1.08 mmol, 1.05 equiv) was stirred in an acetone–water mixture (8:1 vol, 5 mL) while bubbling nitrogen through the solution. Then a 0.1 M solution of osmium tetraoxide in *tert*-butyl alcohol (1 mL, 0.1 mmol, 0.097 equiv) was added, and stirring and nitrogen bubbling were continued for 3 h until TLC (EtOAc/hexanes, 1:1 vol) showed total disappearance of the starting diene leading to a much more polar product. The reaction was then quenched with saturated sodium hydrogen sulfite (10 mL) and diluted with EtOAc (10 mL) and water (15 mL). The aqueous phase was extracted (4 × 20 mL of EtOAc) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give quantitatively pure diol **7** which crystallized when refrigerated: mp 100–101 °C; IR (chloroform) 3617, 3455.3, 2960.1, 2887.0, 1708.1, 1472.7, 1453.6, 1428.1, 1381.6, 1356.2, 1207.9, 1139.8, 1055.1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) 1.02 (s, 3 H), 1.18 (s, 3 H), 1.60–1.80 (m, 2 H), 1.84 (s, 3 H), 1.92–2.23 (m, 2 H), 3.45 (br s, 2 H), 3.51 (dd, J = 11.7, 3 Hz, 1 H), 3.88 (dd, J = 11.7, 10 Hz, 1 H), 3.90–4.02 (m, 4 H), 4.38 (dd, J = 10, 3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.93, 21.50, 23.26, 26.34, 31.61, 42.78, 64.73, 64.87, 65.60, 72.23, 111.87, 132.17, 135.12; MS m/z 86 (100), 87 (62), 107 (25), 125 (44), 150 (18), 167 (15), 211 (52), 212 (38), 242 (15); HRMS calcd for $C_{13}H_{22}O_4$ 242.1518, found 242.1518.

5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenecarboxaldehyde (8). To a stirred solution of diol **7** (51 mg, 0.21 mmol) and *N*-methylmorpholine *N*-oxide (NMO, 27 mg, 0.23 mmol) in CH_2Cl_2 was added molecular sieves (4 Å, powdered) and tetrapropylammonium perruthenate (TPAP, 7.4 mg, 0.1 equiv, 0.021 mmol). After 10 min, the green color turned to a grey-black color. The mixture was applied to a silica gel column (EtOAc/hexanes, 1:4) which was eluted with the same solvent to give 24.5 mg (56%) of the aldehyde **8**: IR (neat, thin film) 2883.0, 1725.8, 1673.6, 1614.0, 1463.9, 1379.0, 1266.5, 1210.4, 1144.7, 1096.3, 1050.9 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.26 (s, 6 H), 1.80 (t, J = 6.6 Hz, 2 H), 2.11 (s, 3 H), 2.40 (t, J = 6.6 Hz, 2 H), 3.99 (br s, 4 H), 10.08 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.88, 21.83, 26.17, 33.62, 41.41, 65.67, 111.54, 139.30, 153.88, 192.00; MS m/z 49 (100), 51 (27), 83 (20), 86 (30), 87 (40), 181 (3), 182 (3), 183 (3), 209 (3), 210 (4), 211 (5); HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1253.

2-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-5,5-(ethylenedioxy)-1,3,3-trimethyl-1-cyclohexene (9). A 25-mL flask was charged with a solution of the alcohol **5** (226 mg, 1 mmol) in CH_2Cl_2 (5 mL), NEt_3 (anhydrous, 121 mg, 1.2 equiv), and 4-(dimethylamino)pyridine (12 mg, 0.1 equiv), and the mixture was cooled to 0 °C under nitrogen. A solution of *tert*-butylchlorodimethylsilane (166 mg, 1.1 equiv) in CH_2Cl_2 (3 mL) was added, and the mixture was stirred for 1 h at room temperature and was then washed with 5% $NaHCO_3$ (10 mL) and brine (10 mL). The aqueous layers were extracted with CH_2Cl_2 (10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated. Flash chromatography of the residue (5% Et_2O in hexanes) gave **9** (280 mg, 82% yield) as a clear oil: IR (neat, thin film) 2952.9, 1253.8, 1079.1, 835.5, 774.4 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3/CH_2Cl_2$) δ 0.09 (s, 6 H), 0.93 (s, 9 H), 1.08 (s, 6 H), 1.69 (s, 3 H), 1.76 (t, J = 6.6 Hz, 2 H), 2.12 (t, J = 6.6 Hz, 2 H), 2.33 (t, J = 8.5 Hz, 2 H), 3.61 (t, J = 8.5 Hz, 2 H), 3.94–4.05 (m, 4 H); ^{13}C NMR (100 MHz $CDCl_3$) δ −5.21, 18.32, 19.76, 22.60, 25.98, 26.67, 30.55, 32.87, 43.05, 62.74, 64.83, 112.11, 127.80, 132.44; MS m/z 73 (50), 75 (53), 86 (50), 165 (95), 197 (100), 239 (27), 283 (25), 297 (12), 325 (10), 340 (13); HRMS calcd for $C_{19}H_{36}O_3Si$ 340.2434, found 340.2447.

3-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-5,5-(ethylenedioxy)-2,4,4-trimethyl-2-cyclohexenone (10). CrO_3 (275 mg, 2.76 mmol, 20 equiv) was suspended in anhydrous CH_2Cl_2 (4 mL) and cooled to −23 °C. After 10 min, 3,5-dimethylpyrazole (265 mg, 2.76 mmol, 20 equiv) was added in one portion. The suspension then became a red-brown solution. After 20 min of stirring at −23 °C, a solution of the olefin **9** (47 mg, 0.13 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was added, and the mixture was then stirred for 1 h between −20 and −10 °C. Sodium hydroxide (6 N, 1 mL) was added and the mixture was stirred for 30 min at 0 °C. After dilution with water and CH_2Cl_2, the aqueous phase was re-extracted with CH_2Cl_2 (5 mL) and the combined organic layers were washed with 0.1 N hydrochloric acid and then brine and were dried ($MgSO_4$). Filtration, evaporation, and flash chromatography (EtOAc/hexanes 1:4) gave 23.3 mg (48%) of enone **10** as a pale yellow oil: IR (neat, thin film) 2928.0, 2881.6, 2856.1, 1673.3, 1611.4, 1471.7, 1335.1, 1252.3, 1130.9, 1073.7, 836.1, 776.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3/CH_2Cl_2$) δ 0.09 (s, 6 H), 0.92 (s, 9 H), 1.24 (s, 6 H), 1.85 (s, 3 H), 2.61 (t, J = 8 Hz, 2 H), 2.74 (s, 2 H), 3.71 (t, J = 8 Hz, 2 H), 3.93–4.03 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.29, 11.94, 18.28, 21.72, 25.90, 34.52, 43.93, 45.78, 61.26, 65.23, 111.71, 131.73, 159.03, 196.57; MS m/z 43 (26), 73 (73), 75 (70), 89 (46), 179 (78), 253 (49), 268 (100), 297 (20), 354 (4), 355 (18); HRMS calcd for $C_{19}H_{34}O_4Si$ 354.2227, found 354.2225.

3-(2-Hydroxyethyl)-5,5-(ethylenedioxy)-2,4,4-trimethyl-2-cyclohexenone (11). The enone **10** (5.4 mg, 0.0153 mmol) was stirred in acetone (1 mL) in the presence of *p*-toluenesulfonic acid (19 mg, 0.1 mmol) and water (50 μL). After 4 h at room temperature, TLC showed that all the starting material has disappeared. The mixture was then diluted with 2 mL of Et_2O and washed with 2 mL of saturated aqueous solution of $NaHCO_3$. The organic phase was then washed with 2 mL of brine, dried ($MgSO_4$), filtered, and evaporated to give alcohol **11** (3 mg, 82%): ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.24 (s, 6 H), 1.85 (s, 3 H), 2.65 (t, J = 7.8 Hz, 2 H), 2.73 (s, 2 H), 3.77 (t, J = 7.8 Hz, 2 H), 3.92–4.00 (m, 4 H); CIMS (CH_4) m/z 87 (58), 179 (50), 211 (20), 223 (22), 241 (M + 1, 100), 269 (M + 1 + 28, 24), 281 (M + 1 + 40, 11);

HRMS calcd for $C_{13}H_{20}O_4$ 240.1362, found 240.1382.

3-Ethenyl-5,5-(ethylenedioxy)-2,4,4-trimethyl-2-cyclohexenone (12). CrO_3–3,5-DMP oxidation of the diene **4** (30 mg; 0.13 mmol) following the same procedure as for the preparation of enone **10** gave after flash chromatography (EtOAc/hexanes 1:4) enone **12** (20 mg; 0.09 mmole; 70%) as a clear oil. Isolation of unreacted starting material (6.3 mg, 0.03 mmol) increased the overall yield of the reaction to 90%: IR (chloroform) 3015.8, 2888.7, 1668.4, 1470.8, 1330.7, 1226.7, 1135.4 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) ∂ 1.19 (s, 6 H), 1.83 (s, 3 H), 2.76 (s, 2 H), 3.97 (m, 4 H), 5.21 (dd, J = 17.8, 1.9 Hz, 1 H), 5.52 (dd, J = 11.7, 1.9 Hz, 1 H), 6.35 (ddd, J = 17.8, 11.7, 1.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 13.3, 22.0, 44.1, 65.3, 111.8, 120.9, 129.6, 133.5, 153.4, 160.1, 197.1; MS m/z 53 (9), 65 (12), 93 (100), 108 (27), 121 (49), 136 (61), 150 (23), 207 (5), 222 (11); HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1257.

3-Ethenyl-5,5-(ethylenedioxy)-2,4,4-trimethyl-2-cyclohexenol (13). To a solution of the dienone **12** (30 mg, 0.13 mmol) and cerium(III) chloride heptahydrate (1.1 equiv; 0.14 mmol, 52 mg) in methanol (2 mL) at 0 °C was added solid sodium borohydride (1.1 equiv, 0.14 mmol, 5 mg) with vigorous stirring. After 10 min at 0 °C, an additional portion of sodium borohydride (1.1 equiv; 0.14 mmol, 5 mg) was added to ensure that the reaction was complete. The mixture was stirred an additional 10 min at 0 °C and partitioned between Et_2O (30 mL) and water (20 mL) in a separatory funnel, and 1 N hydrochloric acid (20 mL) was added. The etheral layer was removed and the aqueous phase re-extracted with Et_2O (1 × 30 mL). The combined etheral extracts were washed with saturated sodium bicarbonate (50 mL) and brine (50 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The residue was purified by radial chromatography (Chromatotron; 1 mm rotor, EtOAc/hexanes 1:4) to give the dienol **13** (24.7 mg, 0.11 mmol; 85%) as a clear oil: IR (chloroform) 3578.7 (br), 2982.1, 2889.4, 1621.7, 1469.9, 1407.7, 1360.0, 1135.6, 1091.3, 1041.6, 993.7 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) ∂ 0.99 (s, 3 H), 1.08 (s, 3 H), 1.84 (s, 3 H), 1.96 (dd, J = 14.1, 2.4 Hz, 1 H), 2.17 (dd, J = 14.1, 5.3 Hz, 1 H), 3.09 (d, J = 10.9 Hz, 1 H), 3.89 (m, 1 H), 4.05 (m, 5 H), 5.04 (dd, J = 17.7, 2.4 Hz, 1 H), 5.33 (dd, J = 11.3, 2.4 Hz, 1 H), 6.14 (dd, J = 17.7, 11.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 18.55, 20.39, 24.08, 34.63, 42.61, 64.95, 64.91, 70.53, 112.40, 119.57, 129.17, 134.30, 139.46; MS m/z 81 (29), 87 (100), 109 (13), 115 (32), 123 (26), 138 (36), 153 (12), 224 (31); HRMS calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1404.

Chiral Reduction of Dienone 12. To a stirred solution of the diene **4** (20 mg, 0.09 mmol) and (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (0.1 equiv; 2.5 mg, 0.01 mmol) in anhydrous THF (1 mL) was added dropwise BH_3–THF complex (Aldrich, 1.0 M, 0.6 equiv; 54 μL, 0.054 mmol) over 5 min. The mixture was stirred for 40 min at room temperature and then filtered through silica gel (10 mL) and eluted with EtOAc (50 mL). The filtrate was concentrated in vacuo and the residue purified by flash chromatography (EtOAc/hexanes, 1:4) to give unreacted starting material (11.3 mg, 0.057 mmol) and the desired alcohol (6.9 mg, 0.03 mmol, 91% based on recovered starting material) as a clear oil $[\alpha]_D$ = 31.4° (c = 0.5, MeOH). All other physical and spectral characteristics were identical to those reported for the racemic material prepared by the precedent method.

[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-ethanal (14). A 50-mL round-bottom flask was charged with 5 mL of CH_2Cl_2 and 1 mL of a 2 M solution of oxalyl chloride in CH_2Cl_2 (2 mmol, 2 equiv), and the solution was cooled to –60 °C. To this cooled solution was added dropwise dimethyl sulfoxide (0.71 mL, 781 mg, 10 mmol, 5 equiv), and the mixture was stirred for 15 min at –60 °C. A solution of the alcohol **5** (226 mg, 1 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred at –60 °C for 15 min. NEt_3 (1.4 mL, 1.012 g, 10 mmol, 5 equiv) was added and the mixture was allowed to warm to room temperature before being diluted with water (10 mL) and Et_2O (10 mL). The aqueous phase was extracted with Et_2O (10 mL) and the combined organic layers were washed with 0.1 N hydrochloric acid (10 mL) and then brine (10 mL), dried ($MgSO_4$), filtered, and evaporated. Flash chromatography of the residue (Et_2O/hexanes 15:85) gave pure aldehyde **14** (210 mg) in 93.7% yield as a pale yellow oil: IR (neat, thin film) 2883.1, 2717.3, 1722.1, 1472.2, 1427.2, 1380.5, 1357.1, 1327.3, 1306.4, 1208.5, 1141.0, 1086.7, 1056.4, 991.4, 949.9, 906.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.032 (s, 6 H), 1.622 (s, 3 H), 1.792 (t, J = 6.6 Hz, 2 H), 2.213 (t, J = 6.6 Hz, 2 H), 3.116 (br s, 2 H), 3.948–4.031 (m, 4 H), 9.535 (t, J = 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 19.72, 22.38, 26.57, 30.70, 43.87, 64.79, 111.67, 127.80, 131.18, 200.65; MS m/z 41 (26), 73 (20), 86 (85), 87 (100), 95 (18), 224 (48); HRMS calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1393.

1-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-3-methyl-3-buten-2-ol (15). A dry 100-mL flask equipped with stir bar was charged with a solution of aldehyde **14** (1.0 g, 4.5 mmol) in THF (25 mL). The solution was cooled to 0 °C, and a solution of the Grignard reagent derived from 2-bromopropene (0.64 M in THF; 7.7 mL, 1.1 equiv) was added dropwise over 5 min. When the addition was complete the mixture was stirred at 0 °C for an additional 30 min and then at room temperature for 30 min. TLC (EtOAc/hexanes, 1:5) indicated that all the starting aldehyde (R_f = 0.27) had been consumed and showed the appearance of a new product (R_f = 0.14). Saturated ammonium chloride (40 mL) was added, and the mixture was partitioned between EtOAc (100 mL) and water (100 mL). The aqueous phase was decanted, the organic phase was washed with brine (2 × 100 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (EtOAc/hexanes, 1:5) gave the allylic alcohol **15** (1.1 g, 4.0 mmol; 89%) as a pale yellow oil: IR (neat, thin film) 3454.0, 2926.6, 1715.5, 1651.5, 1452.9, 1379.0, 1356.2, 1209.6, 1134.3, 1088.0, 1058.4, 991.6, 901.6 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.10 (s, 3 H), 1.11 (s, 3 H), 1.72 (s, 3 H), 1.73–1.88 (m, 2 H), 1.80 (s, 3 H), 2.08–2.32 (m, 4 H), 2.42 (dd, J = 14.2, 10.2 Hz, 1 H), 3.92–4.02 (m, 4 H), 4.22 (dd, J = 10.2, 3.6 Hz, 1 H), 4.81 (br s, 1 H), 5.00 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 17.87, 20.59, 22.73, 23.61, 26.61, 30.79, 35.25, 43.18, 64.89, 74.45, 109.88, 112.31, 130.62, 132.34, 147.71; MS m/z 87 (70), 99 (46), 109 (23), 168 (28), 196 (45), 205 (24), 235 (18), 249 (100), 266 (4), 267 (34); HRMS calcd for $C_{16}H_{26}O_3$ 266.1882, found 266.1886.

1-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-3-methyl-3-buten-2-one (16). Swern oxidation (same conditioins as for the preparation of compound **14**) of alcohol **15** (45 mg, 0.17 mmol) gave after flash chromatography (EtOAc/hexanes, 1:4) 43 mg (96%) of the enone **16** as a pale yellow oil: IR (neat, thin film) 2926.5, 1686.1, 1452.0, 1336.0, 1208.5, 1130.1, 1088.6, 1063.6, 902.4 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 0.97 (s, 6 H), 1.49 (s, 3 H), 1.79 (t, J = 6.6 Hz, 2 H), 1.89 (s, 3 H), 2.20 (br t, J = 6.4 Hz, 2 H), 3.47 (br s, 2 H), 3.92–4.02 (m, 4 H), 5.74 (br s, 1 H), 6.00 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 17.94, 20.10, 22.53, 26.76, 30.55, 37.07, 42.98, 64.88, 112.09, 123.27, 129.68, 130.07, 144.82, 199.04; MS m/z 69 (85), 86 (100), 87 (51), 99 (25), 109 (30), 135 (25), 150 (23), 163 (18), 178 (24), 221 (16), 264 (32); HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1719.

2-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-1-(1-methyl-4-oxo-2-cyclohexenyl)ethanone (18). A solution of enone **16** (28 mg, 0.106 mmol) and diene **17** (0.424 mmol, 4 equiv) in deuterated benzene (0.5 mL) was added into a base-washed sealable NMR tube. The extent of the reaction was monitored by studying the disappearance of the starting enone by NMR of the whole mixture. After 2.5 days at 125 °C, the pale brown solution did not contain any more starting material and showed a 2:1 ratio of two products. The mixture was evaporated to dryness and treated with a 0.1 N hydrochloric acid/THF mixture (1 mL, 1:4 vol), and the solution was stirred at room temperature for 30 min. The mixture was then poured into a saturated $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. Flash chromatography of the residue (EtOAc/hexanes, 1:2) gave 28.5 mg of enone **18** (81%) as a pale yellow oil: IR (neat, thin film) 2924.4, 1716.1, 1679.9, 1604.4, 1456.1, 1356.7, 1270.8, 1088.8, 1057.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 0.93 (s, 3 H), 0.94 (s, 3 H), 1.42 (s, 3 H), 1.43 (s, 3 H), 1.78 (t, J = 6.6 Hz, 2 H), 1.91 (m, 1 H), 2.20 (t, J = 6.6 Hz, 2 H), 2.43 (m, 2 H), 2.54 (m, 1 H), 3.31 (s, 2 H), 3.92–4.02 (m, 4 H), 6.05 (d, J = 10.2 Hz, 1 H), 7.02 (dd, J = 10.2 Hz, 1.05, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 15.24, 19.96, 22.52, 25.24, 26.68, 30.54, 32.63, 34.79, 38.83, 42.80, 49.95, 64.91, 111.85, 128.60, 129.21, 130.44, 152.24, 198.43, 206.76; MS m/z 41 (18), 55 (19), 67 (19), 79 (22), 81 (41), 86 (100), 87 (53), 109 (80), 110 (93), 121 (40), 137 (70), 195 (32), 223 (40), 289 (23), 332 (92); HRMS calcd for

$C_{20}H_{28}O_4$ 332.1988, found 332.1960.

2-(5-Oxo-2,6,6-trimethyl-1-cyclohexenyl)-1-(1-methyl-4-oxo-2-cyclohexenyl)ethanone (19). The ketal **18** (183 mg, 0.55 mmol) was stirred 3 h at 45 °C in 4 mL of a 1:1 v/v mixture of THF and water in presence of *p*-toluenesulfonic acid (104 mg, 0.55 mmol). NMR analysis of aliquots allowed monitoring of the reaction. After 3 h, all the starting ketal has disappeared. The mixture was then diluted with Et_2O (20 mL) and washed with $NaHCO_3$ (saturated, 20 mL). The aqueous layer was extracted with Et_2O (20 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and evaporated to give pure deketalized product **19** (141.4 mg, 89.1%) as a colorless oil: IR (thin film) 2968.8, 2927.7, 2871.4, 1712.6, 1682.7, 1605.6, 1463.4, 1415.0, 1377.7, 1323.2, 1228.6, 1091.9, 1032.7, 1018.5, 807.1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.047 (s, 3 H), 1.054 (s, 3 H), 1.45 (s, 3 H), 1.53 (s, 3 H), 1.96 (ddd, J = 13.2, 10.5, 5.2 Hz, 1 H), 2.40–2.49 (m, 4 H), 2.50–2.63 (m, 3 H), 3.36 (br s, 2 H), 6.08 (d, J = 10.2 Hz, 1 H), 7.04 (dd, J = 10.2, 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 20.00, 24.13, 24.16, 25.06, 31.38, 32.47, 34.62, 35.80, 38.76, 47.28, 49.87, 128.61, 129.30, 131.64, 151.79, 198.07, 206.62, 214.11; MS m/z 41 (28), 43 (19), 53 (20), 55 (18), 67 (17), 79 (19), 81 (50), 110 (100), 123 (53), 136 (5), 151 (8), 288 (20); HRMS calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1716.

Preparation of Dione 20. 1. Preparation of 1-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-1-hydroxy-3-methyl-3-buten-2-one. To a solution of potassium bis(trimethylsilyl)amide (KHMDS, 66 mg, 0.33 mmol, 3 equiv) in THF (anhydrous, 2 mL) cooled to −78 °C under nitrogen was added a solution of the enone **16** (29 mg, 0.11 mmol, 1 equiv) in THF (3 mL). After 15 min, a solution of *N*-(phenylsulfonyl)-phenyloxaziridine (86 mg, 0.33 mmol, 3 equiv) was added to the green solution which was then decolored. The reaction was stirred for 30 min at −78 °C before being quenched with a saturated solution of ammonium chloride (2 mL) and warmed to room temperature. The mixture was diluted with Et_2O (10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduce pressure. Flash chromatography of the residue (EtOAc/hexanes, 1:2) gave 26.7 mg of the hydroxy enone (87%): IR (neat, thin film) 3447.1, 2884.8, 1664.0, 1607.4, 1571.0, 1451.4, 1376.5, 1298.2, 1208.8, 1162.5, 1136.6, 1087.3, 1058.9, 1034.0, 949.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.05 (s, 3 H), 1.21 (s, 3 H), 1.63 (s, 3 H), 1.68–1.86 (m, 2 H), 1.96 (d, J = 0.7 Hz, 3 H), 2.19 (t, J = 6.6 Hz, 2 H), 3.89–4.00 (m, 4 H), 4.15 (br s, 1 H), 5.08 (s, 1 H), 5.77 (br s, 1 H), 6.07 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 18.83, 20.23, 22.98, 23.95, 26.54, 31.62, 43.74, 65.01, 74.56, 111.82, 125.95, 133.68, 135.87, 141.43, 204.31; MS m/z 41 (100), 43 (32), 69 (32), 86 (58), 107 (100), 121 (70), 149 (43), 167 (35), 211 (82), 252 (3), 280 (20); HRMS calcd for $C_{16}H_{24}O_4$ 280.1675, found 280.1676.

2. Preparation of 1-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-3-methyl-3-butene-1,2-dione (20). Swern oxidation (same conditions as for the preparation of compound **14**) of the resulting hydroxy enone (85 mg, 0.3 mmol) gave after flash chromatography (EtOAc/hexanes 1:4) the dione **20** (58 mg, 69%) as a yellow oil: IR (neat, thin film) 2980.0, 2957.7, 2883.8, 1668.7, 1454.4, 1378.0, 1259.9, 1213.0, 1137.4, 1110.6, 1042.9 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.18 (s, 6 H), 1.67 (s, 3 H), 1.82 (t, J = 6.7 Hz, 2 H), 1.94 (dd, J = 1.4, 0.9 Hz, 3 H), 2.30 (br t, J = 6.7 Hz, 2 H), 3.95–4.02 (m, 4 H), 6.10 (dq, J = 0.7, 0.9 Hz, 1 H), 6.20 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 17.18, 21.40, 22.88, 26.34, 31.67, 42.07, 65.10, 111.17, 131.23, 138.44, 139.54, 139.68, 193.76, 197.76; MS m/z 41 (88), 43 (28), 45 (30), 67 (32), 69 (30), 87 (29), 137 (50), 181 (30), 209 (100), 278 (18); HRMS calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1515.

1-[5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenyl]-2-(1-methyl-4-oxo-2-cyclohexenyl)-1,2-ethanedione (21). In a base-washed NMR tube with a screwable Teflon joint was placed a solution of enone **20** (48 mg, 0.172 mmol) and diene (0.69 mmol, 4 equiv) in deuterated benzene (0.5 mL), and the solution was heated to 80 °C. After 3 h, NMR analysis showed that the reaction was complete. The same workup as described for the preparation of enone **18** gave enone **21** as a yellow oil (56.7 mg, 95%): IR (neat, thin film) 2922.9, 2852.6, 1684.9, 1456.0, 1380.1, 1228.1, 1137.1, 1103.1, 1049.1, 992.3, 825.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.03 (s, 3 H), 1.09 (s, 3 H), 1.47 (s, 3 H), 1.55 (s, 3 H), 1.82 (m, 2 H), 1.97 (dt, J = 13.6, 8, 8 Hz, 1 H), 2.25 (m, 2 H), 2.46 (m, 2 H), 2.60 (m, 1 H), 3.92–4.02 (m, 4 H), 6.00 (d, J = 10.2 Hz, 1 H), 7.27 (dd, J = 10.2, 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 20.92, 22.25, 23.38, 25.22, 26.34, 30.66, 32.59, 34.38, 42.01, 47.98, 65.06, 65.11, 110.75, 129.32, 135.73, 136.37, 151.04, 196.32, 197.91, 198.14; MS m/z 41 (20), 55 (25), 67 (28), 81 (27), 86 (23), 87 (25), 95 (20), 137 (40), 181 (28), 209 (100), 346 (18); HRMS calcd for $C_{20}H_{26}O_5$ 346.1780, found 346.1792.

1-(5-Oxo-2,6,6-trimethyl-1-cyclohexenyl)-2-(1-methyl-4-oxo-2-cyclohexenyl)-1,2-ethanedione (22). The ketal **21** (56 mg, 0.16 mmol) was treated with *p*-toluenesulfonic acid (30 mg, 0.16 mmol) at 60 °C for 21 h in a THF/water mixture (1:1 vol, 2 mL), and the reaction was monitored by NMR analysis of aliquots. The same workup as for **19** gave after flash chromatography (EtOAc/hexanes, 1:4) 2 fractions, remaining starting ketal (5 mg) and tetrone **22** (35.4 mg, 0.117 mmol, 73.3%, 79.4% based on starting material recovery), as a yellow oil: IR (thin film) 2971.6, 2930.1, 1680–1720, 1461.8, 1379.4, 1230.8, 1210.1, 1127.0, 1033.7, 874.5, 827.8, 803.6 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) ∂ 1.17 (s, 3 H), 1.23 (s, 3 H), 1.58 (s, 3 H), 1.60 (s, 3 H), 2.02 (ddd, J = 13.4, 10, 5.7 Hz, 1 H), 2.40–2.57 (m, 4 H), 2.58–2.68 (m, 3 H), 6.04 (d, J = 10.2 Hz, 1 H), 7.25 (dd, J = 10.2, 1.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) ∂ 21.47, 24.07, 25.02, 25.18, 31.29, 32.51, 34.34, 34.97, 46.07, 48.02, 129.61, 135.77, 138.37, 150.64, 195.04, 197.90, 198.13, 211.80; CIMS (CH_4) m/z 165 (100), 303 (79), 304 (20); HRMS calcd for $C_{18}H_{23}O_4$ (M + H) 303.1596, found 303.1586.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of **2–16** and **18–22** (41 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Kinetic Resolution of a Racemic Sulfide by Enantioselective Sulfoxide Formation†

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The asymmetric epoxidation and kinetic resolution of allylic alcohols has been described by Sharpless.[1] This oxidation is catalyzed by a chiral titanium complex and is best carried out under anhydrous conditions. Kagan[2] reported that when this catalyst is prepared with 1 equiv of water it is useful for the conversion of prochiral sulfides into enantiomerically-enriched sulfoxides. Anhydrous conditions were shown to be less effective for this transformation. Kinetic resolution of a racemic sulfide could be possible using this water-modified complex. While several reports on the use of these conditions for the synthesis of chiral sulfoxides have appeared in the literature,[3] none have described a kinetic resolution of the sulfide starting material.[4]

(±)5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methyl]-4-thiazolidinone (**6**) is a novel antioxidant which has been shown to be protective against acetic acid-induced colitis in rats (an animal model of inflammatory bowel disease).[5] A method for producing each individual enantiomer of thiazolidinone **6** was required to allow for comparative efficacy, pharmacokinetic, and toxicological

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