Chem. Pharm. Bull. **41**(8) 1358—1361 (1993) Vol. 41, No. 8

Enantioselective Synthesis of the α-Pyrone Subunit of Verrucosidin

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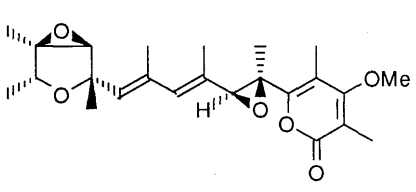
4-Methoxyl-6-[(1*S*)-1-(trimethylsilyloxy)-1-methyl-2-oxobutyl]-3,5-dimethyl-2*H*-pyran-2-one (4), a key α-pyrone subunit for the synthesis of verrucosidin (1), has been prepared from 6-ethyl-4-hydroxy-3,5-dimethyl-2*H*-pyran-2-one (5) in an enantiomerically pure form.

Keywords verrucosidin; mycotoxin; α-pyrone; enantioselective synthesis; Sharpless asymmetric epoxidation

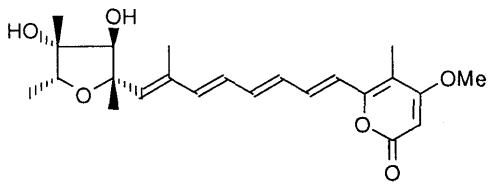
Verrucosidin (**1**), a potent mycotoxin isolated from the fungus *Penicillium verrucosum* var. cyclopium,[1] has a close structural relationship to citreoviridin (**2**)[2] and related polyene α-pyrone mycotoxins,[3,4] which are known to be inhibitors of mitochondrial ATPase activity.[5] The combination of its characteristic molecular architecture and its unique biological activity makes verrucosidin (**1**) an attractive target for synthesis.[6] In 1988, we reported the first total synthesis[7] of verrucosidin (**1**), employing a convergent strategy involving aldol-type coupling reaction of the tetrahydrofuran subunit **3** with the α-pyrone subunit **4**. This convergent approach was also used successfully in a total synthesis of **1** accomplished by Cha and coworkers.[8] Herein we report full details of our preparation of the α-pyrone subunit **4**.

Our synthesis of **4** started with readily available 6-ethyl-4-hydroxy-3,5-dimethyl-2*H*-pyran-2-pyran-2-one (**5**).[9] The 4-hydroxy-α-pyrone **5** was first methylated with dimethyl sulfate in the presence of potassium carbonate in boiling acetone to give the 2-methoxy-γ-pyrone **6** and 4-methoxy-α-pyrone **7** in a ratio of 43:57. After chromatographic separation, acid hydrolysis of **6** allowed quantitative regeneration of **5**, establishing a route for recycling undesired **6**. As a result, the desired 4-methoxy-α-pyrone **7** was obtained in 74% yield after one recycle of **6**. Deprotonation of **7** with lithium hexamethyldisilazide at −78°C in tetrahydrofuran (THF) followed by aldol reaction of the resulting anion with *p*-methoxybenzyloxyacetaldehyde (**8**) gave the alcohol **9** as a 1:1 *syn*/*anti*-isomeric mixture in 55% yield (94% based on **7**). Without separation, dehydration of **9** *via* the mesylate **10** afforded the *E*-olefin **11** in 67% yield along with the *Z*-olefin **12** (8%) and the enol ether **13** (8%). It should be noted that attempts to isomerize **12** to **11** under various conditions failed. The *E*-olefin **11** was then subjected to oxidative deprotection using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Since concomitant over-oxidation of **14** yielding the corresponding aldehyde always took place in this case, the crude product was directly reduced with sodium borohydride in the presence of cerium trichloride heptahydrate[10] in methanol to give the allylic alcohol **14** in 95% yield.

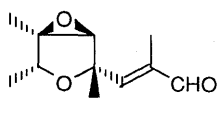
Sharpless asymmetric epoxidation (A.E.) using diisopropyl L-tartrate (L-DIPT) under the standard conditions[11] proceeded without difficulty to produce the epoxy alcohol **15** in 95% yield.[12] The enantiomeric purity of **15** was determined to be ≅100% (enantiomeric excess) by 500 MHz ^{1}H-NMR analysis of the corresponding (*R*)- and (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters.[13] Upon sequential mesylation, displacement with sodium iodide, and reductive cleavage using zinc, the tertiary allylic alcohol **16** was obtained from **15** in 87% overall yield. After protection of **16** as its methoxymethyl ether (91%), the vinyl group was transformed into the ethyl ketone functionality by a four-step sequence. Thus, the olefin **17** was successively subjected to osmylation,[14] lead tetraacetate-mediated oxidative cleavage, Grignard reaction, and Swern oxidation to afford **19** in 72% overall yield. Finally, the methoxymethyl ether protecting group was changed to the trimethylsilyl (TMS) ether group by acidic methanolysis followed by silylation to furnish the required α-pyrone subunit **4** in an optically pure form in 84% yield. The specific rotation of **4** thus prepared, $[\alpha]_D^{26}$ +69.6° (c=1.25, $CHCl_3$), was in good agreement with



verrucosidin (**1**)



citreoviridin (**2**)



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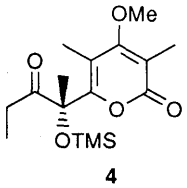

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Chart 1

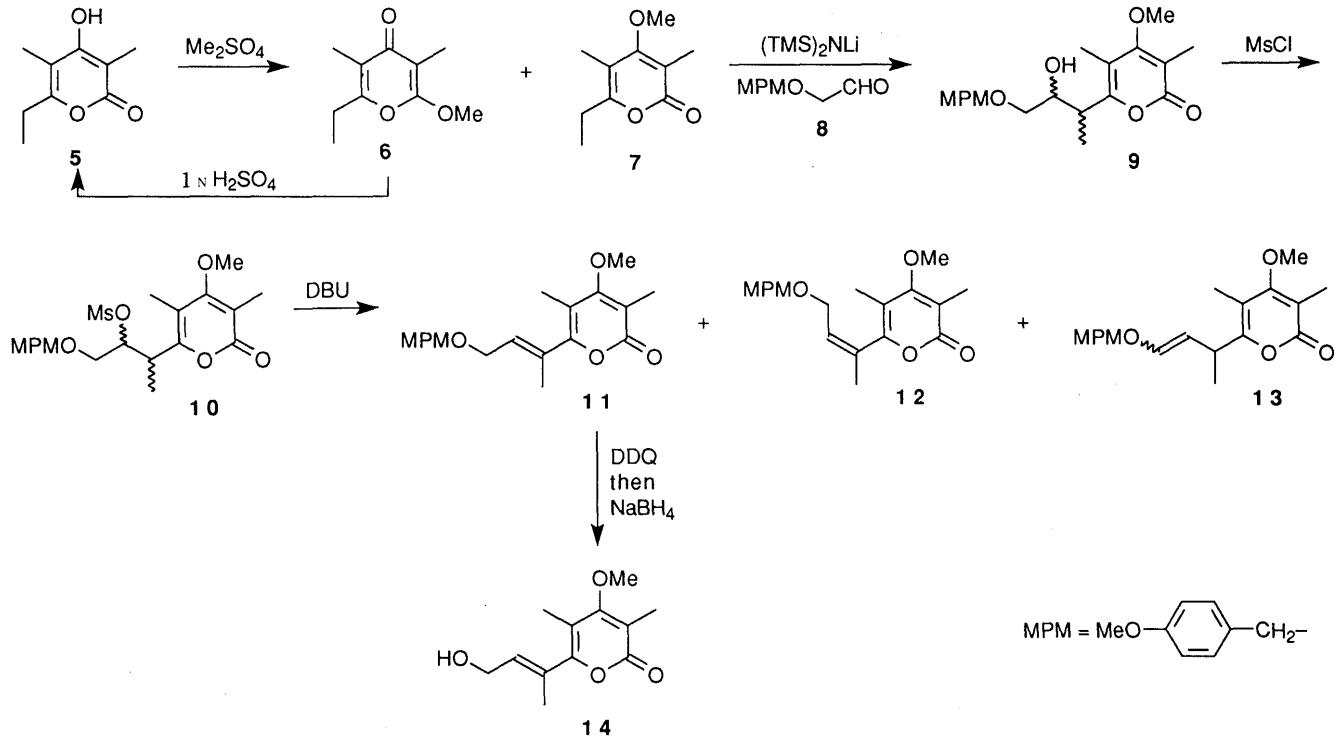

Chart 2

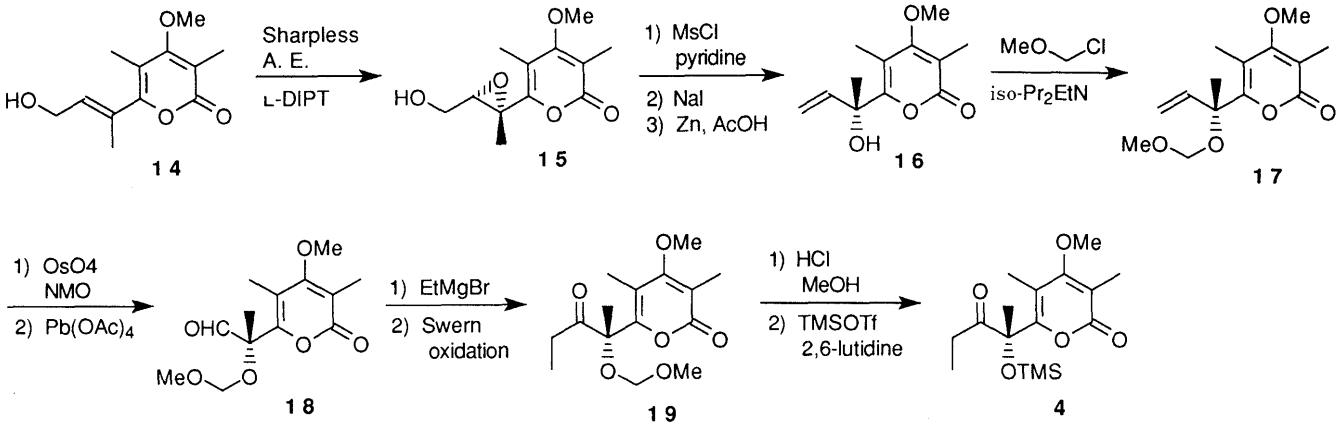

Chart 3

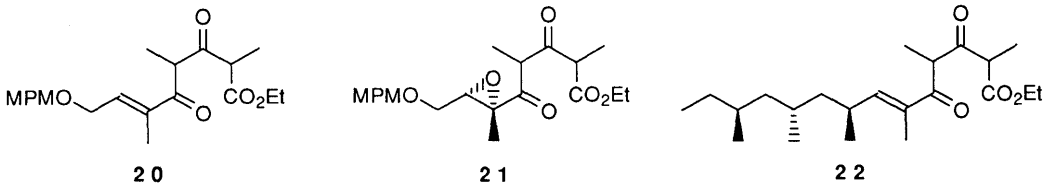

Chart 4

that reported by Cha and co-workers,[8] $[\alpha]_D^{25}$ +70.7° (c = 0.77, $CHCl_3$).

It is noteworthy that alternative approaches utilizing polypropionate type of precursors such as **20** and **21** were totally unsuccessful even though there is a precedent for high-yielding preparation of the α-pyrone derivative from **22**.[15]

Experimental

All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Infrared (IR) spectra were obtained using a JASCO IR-700 spectrophotometer. ^{1}H-NMR spectra were recorded on JEOL JNM-FX90A (90 MHz) and JEOL JNM-GX500 (500 MHz) spectrometers using deuteriochloroform as a solvent and tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a Hitachi M52-G instrument. High-resolution mass (HRMS) spectra were recorded on a JMS-OISG-2 instrument. All reactions were carried out under an atmosphere of dry argon. Chromatographic purifications were carried out with Daisogel IR-60 (column) and Merck silica gel 60 PF_{254} (thin layer).

2-Ethyl-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (6) and 6-Ethyl-4-methoxy-3,5-dimethyl-2*H*-pyran-2-one (7) A mixture of 3,5-dimethyl-6-ethyl-4-hydroxy-2*H*-pyran-2-one (**4**)[9] (2.0 g, 11.90 mmol), dimethyl

sulfate (1.2 ml, 12.68 mmol), and K_2CO_3 (5.0 g, 36.18 mmol) in acetone (50 ml) was refluxed for 16 h. After cooling, the reaction mixture was diluted with Et_2O and filtered through Celite. The filtrate was concentrated *in vacuo* and chromatographed on silica gel (80 g). Elution with 1 : 5 AcOEt–hexane gave the α-pyrone **7** (1.2 g, 56%) as a pale yellow oil, bp 90—95 °C (0.15 mmHg) (Kugel röhr). IR (neat): 1710, 1643, 1572, 1360, 1115, 1070 cm^{-1}. ^{1}H-NMR δ: 1.20 (3H, t, J=7.3 Hz), 1.93 (3H, s), 2.03 (3H, s), 2.53 (2H, q, J=7.3 Hz), 3.81 (3H, s). MS m/z: 182 (M^+), 140 (100%). HRMS Calcd for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0945. *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.80; H, 7.83. Further elution afforded the γ-pyrone **6** (900 mg, 42%) as colorless crystals, mp 46—47 °C (hexane). IR (Nujol): 1665, 1590, 1460, 1375, 1172 cm^{-1}. ^{1}H-NMR δ: 1.24 (3H, t, J=7.9 Hz), 1.86 (3H, s), 1.94 (3H, s), 2.62 (2H, q, J=7.9 Hz), 3.97 (3H, s). MS m/z: 182 (M^+, 100%), 167. HRMS Calcd for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0951. *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.06; H, 7.76.

The γ-pyrone **6** was converted to the α-pyrone **7** as follows. A solution of **6** (900 mg, 4.94 mmol) in a mixture of 1 N H_2SO_4 (1 ml) and THF (1 ml) was refluxed for 12 h. The reaction mixture was cooled and extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. Crude **5** (850 mg) thus obtained was methylated again in the same manner as mentioned above to give the α-pyrone **7** (400 mg) and γ-pyrone **6** (290 mg) after chromatographic separation. As a result, the α-pyrone **7** (1.6 g, 74%) and the γ-pyrone **6** (290 mg, 13%) were obtained after one recycle.

Aldol Reaction of 7 with *p*-Methoxybenzyloxyacetaldehyde (8) A stirred solution of hexamethyldisilazane (5.1 ml, 24.17 mmol) in THF (36 ml) at −78 °C was treated with 1.6 M *n*-BuLi in hexane (13.6 ml, 21.23 mmol) and the mixture was allowed to warm to room temperature. After 10 min, the mixture was recooled to −78 °C and hexamethylphosphoramide (HMPA) (3.4 ml, 19.54 mmol) and a solution of the α-pyrone (3.096 g, 17.01 mmol) in THF (12 ml) were added. After 30 min, a solution of the aldehyde **8** (3.674 g, 20.41 mmol) in THF (12 ml) was added and the mixture was stirred at −78 °C for 30 min. The reaction was quenched with saturated NH_4Cl and the mixture was extracted with Et_2O. The ethereal extract was washed with brine, dried over $MgSO_4$, evaporated *in vacuo*, and chromatographed on silica gel (300 g). Elution with 1 : 2 Et_2O–hexane afforded recovered **7** (1.273 g, 41%). Further elution with 2 : 3 Et_2O–hexane gave **9** (3.397 g, 55%; 94% based on consumed **7**) as an inseparable 1 : 1 diastereoisomeric mixture. IR (neat): 3450, 1700, 1650, 1620, 1579, 1520, 1250 cm^{-1}. ^{1}H-NMR δ: 1.13, 1.31 (3H, 2×d, J=7.2 Hz), 1.92, 1.95 (3H, 2×s), 2.03 (3H, s), 1.20 (1H, s), 2.85—3.60 (3H, m); 3.79, 3.82, 3.83 (6H, 3×s), 4.00 (1H, m), 4.40, 4.49 (2H, 2×br s), 6.85, 6.88 (2H, 2×d, J=8.6 Hz), 7.20, 7.25 (2H, 2×d, J=8.6 Hz). MS m/z: 362 (M^+), 182, 121 (100%). HRMS Calcd for $C_{20}H_{26}O_6$: 362.1729. Found: 362.1717.

6-[2-Methanesulfonyloxy-3-(4-methoxybenzyloxy)-1-methylpropyl]-4-methoxy-3,5-dimethyl-2*H*-pyran-2-one (10) Methanesulfonyl chloride (2.4 ml, 31.30 mmol) was added to an ice-cold solution of **9** (3.803 g, 10.51 mmol), pyridine (7.6 ml, 93.97 mmol), and 4-dimethylaminopyridine (129 mg, 1.05 mmol) in CH_2Cl_2 (60 ml). The mixture was stirred at room temperature for 20 h, then diluted with Et_2O, washed successively with H_2O, saturated $CuSO_4$, H_2O, and saturated $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent *in vacuo* followed by column chromatography on silica gel (120 g) (2 : 1 Et_2O–hexane) gave **10** (4.244 g, 92%) as a 1 : 1 diastereoisomeric mixture. IR (neat): 1705, 1646, 1612, 1571, 1515, 1355, 1248, 1178 cm^{-1}. ^{1}H-NMR δ: 1.22, 1.33 (3H, 2×d, J=7.2 Hz), 1.95, 1.98 (3H, 2×s), 2.05 (3H, s), 2.87, 3.01 (3H, 2×s), 3.30—3.80 (3H, m), 3.80 (3H, s), 4.90 (1H, m), 6.84, 6.89 (2H, 2×d, J=8.6 Hz), 7.20, 7.25 (2H, 2×d, J=8.6 Hz). MS m/z: 440 (M^+), 182, 121 (100%). HRMS Calcd for $C_{21}H_{28}O_8S$: 440.1505. Found: 440.1477.

Reaction of 10 with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) A mixture of the mesylate **10** (4.218 g, 9.59 mmol) and DBU (4.3 ml, 28.75 mmol) in toluene (220 ml) was refluxed for 2 d. After cooling, the reaction mixture was diluted with Et_2O, washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (160 g). Elution with 1 : 5 AcOEt–hexane gave the enol ether **13** (274 mg, 8.3%), the *Z*-olefin **12** (269 mg, 8.1%), and the *E*-olefin **11** (2.202 g, 67%) in this order.

E-Olefin **11**: A colorless viscous oil. IR (neat): 1705, 1635, 1615, 1568, 1518, 1352, 1249 cm^{-1}. ^{1}H-NMR δ: 1.90 (3H, d, J=1.5 Hz), 2.01 (3H, s), 2.05 (3H, s), 3.80 (3H, s), 3.82 (3H, s), 4.20 (2H, d, J=6.2 Hz), 4.49 (2H, s), 5.85 (1H, qt, J=1.5, 6.2 Hz), 6.88 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz). MS m/z: 344 (M^+), 121 (100%). HRMS Calcd for $C_{20}H_{24}O_5$: 344.1624. Found: 344.1636.

Z-Olefin **12**: A pale yellow viscous oil. IR (neat): 1711, 1641, 1612, 1570, 1513, 1353, 1248 cm^{-1}. ^{1}H-NMR δ: 1.78 (3H, s), 2.00 (3H, q, J=1.4 Hz), 2.05 (3H, s), 3.78 (6H, s), 3.80 (2H, m), 4.36 (2H, s), 5.86 (1H, qt, J=1.4, 6.8 Hz), 6.83 (2H, d, J=8.8 Hz), 7.20 (2H, d, J=8.8 Hz). MS m/z: 344 (M^+), 121 (100%). HRMS Calcd for $C_{20}H_{24}O_5$: 344.1624. Found: 344.1607.

Enol Ether **13**: A pale yellow oil, consists of *E*- and *Z*-geometrical isomers (*ca.* 4 : 1). IR (neat): 1705, 1645, 1610, 1569, 1513, 1247 cm^{-1}. ^{1}H-NMR δ: 1.25 (3H×1/5, d, J=6.8 Hz), 1.35 (3H×4/5, d, J=6.8 Hz), 1.92 (3H×1/5, s), 1.94 (3H×4/5, s), 2.03 (3H×1/5, s), 2.05 (3H×4/5, s), 3.5 (1H, m), 4.62 (1H×1/5, dd, J=6.7, 8.3 Hz), 4.62 (2H×4/5, s), 4.72 (2H×1/5, s), 5.04 (1H×4/5, dd, J=5.0, 12.7 Hz), 6.04 (1H×1/5, dd, J=6.1, 1.0 Hz), 6.47 (1H×4/5, d, J=12.7 Hz), 6.88 (2H, d, J=8.6 Hz), 7.31 (2H, d, J=8.6 Hz). MS m/z: 344 (M^+), 121 (100%). HRMS Calcd for $C_{20}H_{24}O_5$: 344.1624. Found: 344.1596.

6-[(1*E*)-3-Hydroxy-1-methylpropenyl]-4-methoxy-3,5-dimethyl-2*H*-pyran-2-one (14) A stirred solution of the *E*-olefin **11** (1.990 g, 5.79 mmol) in a mixture of CH_2Cl_2 (57 ml) and H_2O (3 ml) was treated with DDQ (90% purity; 1.751 g, 6.94 mmol). After 6 h, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite, and evaporated *in vacuo*. The residue was dissolved in MeOH (28 ml) and added to a stirred mixture of $NaBH_4$ (219 mg, 5.79 mmol) and $CeCl_3 \cdot 7H_2O$ (2.155 g, 5.78 mmol) in MeOH (71 ml) at −25 °C. After 30 min at −25 °C, the reaction mixture was diluted with H_2O (14 ml) and then concentrated *in vacuo*. The residue was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel (46 g). Elution with 3 : 1 Et_2O–hexane gave **14** (1.290 g, 98%) as colorless needles, mp 65—66 °C (hexane–Et_2O). IR (Nujol): 3320, 1698, 1675, 1632, 1563, 1138, 997, 987 cm^{-1}. ^{1}H-NMR δ: 1.79 (1H, br s), 1.94 (3H, q, J=1.5 Hz), 2.01 (3H, s), 2.06 (3H, s), 3.86 (3H, s), 4.37 (2H, dq, J=6.3, 1.5 Hz), 5.87 (1H, tq, J=6.3, 1.5 Hz). MS m/z: 224 (M^+), 195 (100%). HRMS Calcd for $C_{12}H_{16}O_4$: 224.1048. Found: 224.1065. *Anal.* Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.05; H, 7.33.

6-[(1*S*,2*S*)-1,2-Epoxy-3-hydroxy-1-methylpropyl]-4-methoxy-3,5-dimethyl-2*H*-pyran-2-one (15) Titanium tetraisopropoxide (1.59 ml, 5.30 mmol) was added to a stirred solution of L-DIPT (1.490 g, 6.36 mmol) in CH_2Cl_2 (60 ml) at −25 °C. The mixture was held for 20 min at −25 °C, then a solution of **14** (1.187 g, 5.30 mmol) in CH_2Cl_2 (8 ml) and 1.97 M *tert*-butyl hydroperoxide in CH_2Cl_2 (6.73 ml, 13.26 mmol) were added. The reaction mixture was stirred at −25 °C for 40 h, then the reaction was quenched with 18% aqueous acetone (28 ml), and the whole was stirred further at room temperature for 40 min. The resulting inorganic precipitate was removed by filtration through Celite and the filter-cake was thoroughly washed with CH_2Cl_2. The combined filtrates were dried over $MgSO_4$, evaporated *in vacuo*, and chromatographed on silica gel (100 g). Elution with 4 : 1 Et_2O–hexane gave **15** (1.213 g, 95%) as colorless needles, mp 71—72 °C (hexane–Et_2O), $[\alpha]_D^{26}$ +63.7° (c=1.004, $CHCl_3$). IR (Nujol): 3425, 1675, 1640, 1570, 1458, 1380, 1079 cm^{-1}. ^{1}H-NMR δ: 1.60 (3H, s), 1.96 (1H, br s), 2.04 (3H, s), 2.07 (3H, s), 3.28 (1H, dd, J=5.9, 4.6 Hz), 3.77 (1H, dd, J=12.5, 5.9 Hz), 3.84 (3H, s), 4.00 (1H, dd, J=12.5, 4.5 Hz). MS m/z: 240 (M^+), 180 (100%). HRMS Calcd for $C_{12}H_{16}O_5$: 240.0998. Found: 240.1021. *Anal.* Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.99; H, 6.59.

6-[(1*S*)-1-Hydroxy-1-methyl-2-propenyl]-4-methoxy-3,5-dimethyl-2*H*-pyran-2-one (16) Pyridine (3.40 ml, 42.04 mmol), 4-dimethylaminopyridine (60 mg, 0.49 mmol), and methanesulfonyl chloride (1.10 ml, 14.34 mmol) were added in this order to an ice-cold solution of the alcohol **15** (1.114 g, 4.64 mmol) in CH_2Cl_2 (34 ml). After stirring at room temperature for 5.5 h, the reaction mixture was diluted with Et_2O and washed successively with H_2O, saturated $CuSO_4$, H_2O, and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude mesylate (2.080 g) as a yellow oil.

A mixture of the crude mesylate (2.080 g), NaI (7.0 g, 46.70 mmol), and $NaHCO_3$ (3.9 g, 46.70 mmol) in acetone (56 ml) was stirred at room temperature for 20 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O, 2% $Na_2S_2O_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the corresponding iodide (1.643 g) as a yellow oil.

A mixture of the crude iodide (1.643 g) and Zn (3.102 g, 47.45 mmol) in AcOH (14 ml) was stirred at room temperature for 35 min. The reaction mixture was neutralized by the addition of 50% NaOH (19.6 ml) with cooling in an ice bath and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$, dried over ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on silica gel (44 g). Elution with 1 : 2 Et_2O–hexane gave **16** (902 mg, 87% from **15**) as a colorless viscous oil, $[\alpha]_D$ +120.0° (c=1.008, $CHCl_3$). IR (neat): 3425, 1680, 1630, 1560,

1352 cm^{-1}. ^{1}H-NMR δ: 1.67 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.10 (1H, br s), 3.80 (3H, s), 5.17 (1H, dd, J=10.3, 1.0 Hz), 5.33 (1H, dd, J=17.1, 1.2 Hz), 6.11 (1H, dd, J=10.3, 17.1 Hz). MS m/z: 224 (M^+), 181, 153, 126, 97 (100%). HRMS Calcd for $C_{12}H_{16}O_4$: 224.1049. Found: 224.1046. *Anal.* Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.45; H, 7.19.

4-Methoxy-6-[(1*S*)-1-(methoxymethyloxy)-1-methyl-2-propenyl]-3,5-dimethyl-2*H*-pyran-2-one (17) Methoxymethyl chloride (1.70 ml, 22.38 mmol) was added to a stirred solution of **16** (842 mg, 3.76 mmol) and diisopropylethylamine (7.75 ml, 44.49 mmol) in THF (36 ml), and the mixture was refluxed for 3 d. After cooling, the reaction mixture was diluted with Et_2O and washed successively with H_2O, 5% HCl, H_2O, and saturated $NaHCO_3$. The ethereal extract was dried over $MgSO_4$, and evaporated *in vauco*, then the residue was chromatographed on silica gel (44 g). Elution with 1 : 2 Et_2O–hexane gave **17** (920 mg, 91%) as a colorless viscous oil, $[\alpha]_D^{25}$ +95.9° (c=1.030, $CHCl_3$). IR (neat): 1710, 1633, 1562, 1350, 1220, 1138, 1030 cm^{-1}. ^{1}H-NMR δ: 1.80 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 3.39 (3H, s), 3.80 (3H, s), 4.70 (2H, s), 5.20 (1H, dd, J=10.5, 1.0 Hz), 5.29 (1H, dd, J=17.2, 1.0 Hz), 6.00 (1H, dd, J=10.5, 17.2 Hz). MS m/z: 268 (M^+), 225, 195, 153, 126, 97 (100%). HRMS Calcd for $C_{14}H_{20}O_5$: 268.1311. Found: 268.1308. *Anal.* Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.37; H, 7.82.

2-[(1*R*)-1-Formyl-1-(methoxymethyloxy)ethyl]-4-methoxy-3,5-dimethyl-2*H*-pyran-2-one (18) A stirred mixture of **17** (156 mg, 0.58 mmol) and 4-methylmorpholine *N*-oxide (157 mg, 1.17 mmol) in 30% aqueous acetone (4.2 ml) was treated with 0.15 M OsO_4 in THF (0.36 ml, 0.05 mmol). After 18 h, 20% $NaHSO_4$ (1.4 ml) was added and the stirring was continued for an additional 30 min. The reaction mixture was extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$, and concentrated *in vauco* to give the corresponding diol (204 mg) as a yellow oil.

A stirred solution of the crude diol (204 mg) in THF (13 ml) at −33 °C was treated with $Pb(OAc)_4$ (388 mg, 0.87 mmol). After stirring at −33 °C for 30 min, the mixture was diluted with Et_2O and filtered through a short silica gel column. Evaporation of the combined filtrates *in vacuo* gave **18** (152 mg, 97%) as a pale yellow oil, $[\alpha]_D^{25}$ +71.9° (c=0.704, $CHCl_3$). IR (neat): 1710, 1640, 1563, 1350, 1140, 1020 cm^{-1}. ^{1}H-NMR δ: 1.71 (3H, s), 1.94 (3H, s), 2.08 (3H, s), 3.47 (3H, s), 3.85 (3H, s), 4.78 (2H, s), 9.67 (1H, s). MS m/z: 270 (M^+), 196, 153, 126, 97 (100%). HRMS Calcd for $C_{16}H_{18}O_6$: 270.1104. Found: 270.1107.

4-Methoxy-6-[(1*S*)-1-(methoxymethyloxy)-1-methyl-2-oxobutyl]-3,5-dimethyl-2*H*-pyran-2-one (19) A stirred mixture of **18** (144 mg, 0.53 mmol) and $MgBr_2 \cdot Et_2O$ (206 mg, 0.80 mmol) in THF (6 ml) at −52 °C was treated with 2.8 M ethylmagnesium bromide in THF (0.32 ml, 0.89 mmol). After 30 min, the mixture was quenched with saturated NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the corresponding alcohol (160 mg) as a yellow oil, which was directly subjected to Swern oxidation.

A solution of oxalyl chloride (0.19 ml, 2.18 mmol) in CH_2Cl_2 (4 ml) at −60 °C was treated with dimethylsulfoxide (DMSO) (0.38 ml, 5.35 mmol). After 10 min, a solution of the crude alcohol (160 mg) in CH_2Cl_2 (4 ml) was added. The mixture was stirred at −60 °C for 30 min, treated with triethylamine (1.50 ml, 10.76 mmol), and allowed to warm to room temperature. The reaction mixture was diluted with Et_2O, washed successively with H_2O, 1 N HCl, H_2O, and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (8 g) (1 : 1 Et_2O–hexane) gave **19** (117 mg, 74%) as a colorless viscous oil, $[\alpha]_D^{26}$ +106.2° (c=0.972, $CHCl_3$). IR (neat): 1720, 1640, 1583, 1140 cm^{-1}. ^{1}H-NMR δ: 1.09 (3H, t, J=7.3 Hz), 1.72 (3H, s), 1.82 (3H, s), 2.07 (3H, s), 2.73 (2H, m), 3.36 (3H, s), 3.81 (3H, s), 4.71 (2H, s). MS m/z: 298 (M^+), 241, 122, 197 (100%), 97. HRMS Calcd for $C_{15}H_{22}O_6$: 298.1416. Found: 298.1410.

4-Methoxy-6-[(1*S*)-1-(trimethylsilyloxy)-1-methyl-2-oxobutyl]-3,5-dimethyl-2*H*-pyran-2-one (4) Compound **19** (464 mg, 1.55 mmol) was dissolved in 0.2% methanolic concentrated HCl (7 ml) and the mixture was refluxed for 80 min. After cooling, the reaction mixture was basified with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to give the alcohol (393 mg) as a yellow oil, which was silylated without purification.

Trimethylsilyl trifluoromethanesulfonate (0.45 ml, 2.33 mmol) was added to a stirred mixture of the crude alcohol (393 mg) and 2,6-lutidine (0.36 ml, 3.09 mmol) in CH_2Cl_2 (7 ml) with cooling in an ice bath. After stirring at 0 °C for 1.5 h, the reaction mixture was diluted with Et_2O, washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (30 g) (3 : 1 Et_2O–hexane) to afford **4** (428 mg, 84%) as a colorless viscous oil, $[\alpha]_D^{26}$ +69.6° (c=1.248, $CHCl_3$) [lit.[8] $[\alpha]_D^{25}$ +70.7° (c=0.77, $CHCl_3$)]. IR (neat): 1720, 1644, 1570, 1255, 1140 cm^{-1}. ^{1}H-NMR δ: 0.10 (9H, s), 1.07 (3H, t, J=7.3 Hz), 1.67 (3H, s), 1.81 (3H, s), 2.06 (3H, s), 2.69 (2H, m), 3.80 (3H, s). MS m/z: 326 (M^+), 269 (100%), 211. HRMS Calcd for $C_{16}H_{26}O_5Si$: 326.1550. Found: 326.1541.

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