Absolute Configuration of (+)-Aureothin: A Toxic Metabolite Possessing γ-Pyrone Unit

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The absolute configuration of aureothin (**1**) has been determined by synthesis of (−)-aureonone (**4**) bearing *R*-configuration. X-Ray single crystallographic analysis of **21** guaranteed the stereochemistry of the chiral center introduced by Sharpless asymmetric epoxidation, as well as that of isoaureothin (**3**) which was previously synthesized in a similar pathway. Aureothin (**1**) itself was also synthesized, although Wittig coupling reaction of **4** under basic conditions, caused a partial epimerization of the chiral center.

Since the first isolation from *Streptomyces thioluteus* by Maeda,[1] aureothin (**1**) exhibiting pesticidal[2] and antifungal[3] activities as well as a high toxicity against mouse, has been found in mycelia of several actinomycetes (*S. distallius*, *S. luteoreticuli*, *S. netropsis*, and *Streptoverticillium mycohertinicum*).[4] Hirata et al.[5] accounted for the structure of this antibiotic; it possesses a novel tetrahydrofuryl pyrone linked with a *p*-nitrophenyl unit via an olefinic chain. It was postulated that a biogenesis of this molecule consists of coupling of a unit produced by an acetate–propionate path way,[6] with the *p*-nitrophenyl residue employing *p*-aminophenylalanine as a precursor.[7] On the other hand, Rinehart et al. reported that spectinabilin (**2**), a closely related congener isolated from *Streptomyces spectabilis*, exhibited an inhibitory activity against RLV (Rauscher leukemia virus) reverse transcriptase.[8] In spite of challenging biological properties, no synthetic studies on these antibiotics had been reported, with the exception of our investigation of isoaureothin (**3**)[9] which is an isomerized product of **1** (Fig. 1).[5] Our investigation indicated that **1** and **2** might have the same all-*trans* olefinic stereochemistry,[9a] as well as *R*-configuration of the chiral centers, by the comparison of the spectral data and optical rotations with those of synthetic **3**.[9b] As part of our further investigation of this field, a synthesis of optically active aureonone (**4**) which was obtained by oxidative degradation of **1**,[5] was included to obtain a direct proof of the absolute configuration of **1**. Unambiguous determination of the stereogenic center of **4** was established by X-ray crystallography of its synthetic intermediate. Additionally, this finding supported the absolute configuration of the above-mentioned **3**, which was synthesized in a similar procedure. We disclose herein the synthetic details.

Results and Discussion

As can be seen in Scheme 1, the synthesis was ini-

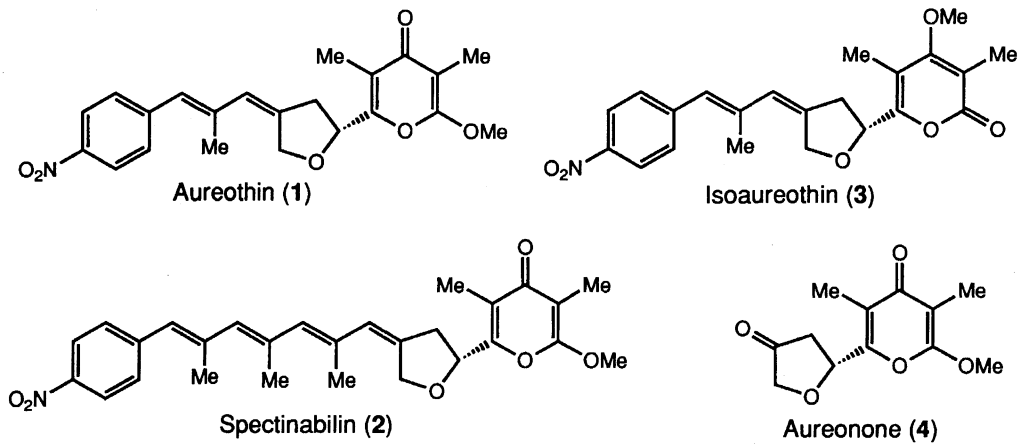
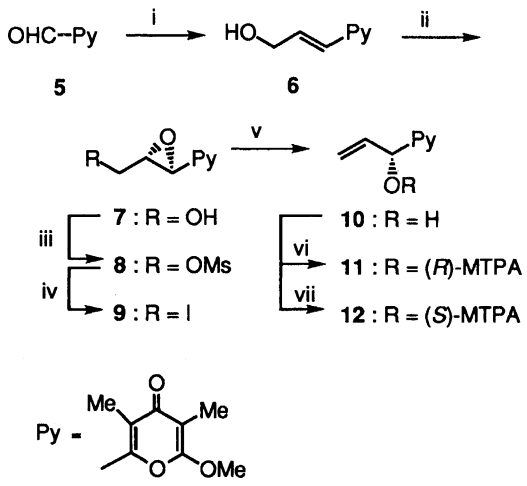
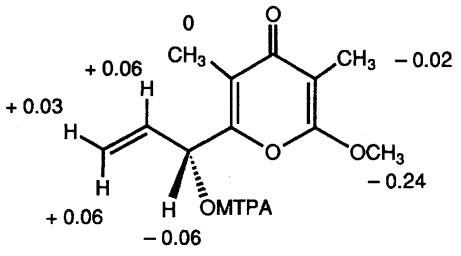


Fig. 1. Biologically active γ-pyrone-containing natural products.



Scheme 1. *reagents*: i. a) Ph_3P=CHCHO; b) $NaBH_3CN$ (76%). ii. TBHP, $Ti(OPr^i)_4$, L-DET (88%). iii. MsCl, pyr. (100%). iv. NaI (67%). v. Zn (88%). vi. (*S*)-MTPACl, DMAP (100%). vii. (*R*)-MTPACl, DMAP (95%).

tiated with a Wittig reaction of aldehyde **5** prepared from the known pyrone,[10] followed by reduction with $NaBH_3CN$ to give the corresponding allyl alcohol (**6**) in good yield. As described in a previous paper,[9b] Sharpless asymmetric epoxidation of **6** effected introduction of the chiral centers, leading to **7** in 88% yield. After conversion of the epoxy alcohol unit into an allyl alcohol in three steps through **8** and **9**, **10** was transformed into the corresponding (*R*)- and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoates (MTPA esters, **11** and **12**). At this stage, optical purity of **10** introduced by the Sharpless epoxidation was determined to be >95% ee, based on the ^{1}H NMR spectra. According to Kakisawa and Kusumi's Mosher method,[11] comparison of the chemical shifts of their proton signals indicated that the asymmetric center possesses the *R*-configuration (Fig. 2). Although applicability of this method to such pyrone-containing systems is uncertain, the synthesis was continued with the tentative assignment of the stereogenic center. At a later step, this ambiguity was overcome by X-ray single crystallographic analysis.



$\Delta\delta = \delta$ (*s*, **12**) $- \delta$ (*R*, **11**)

Fig. 2. $\Delta\delta$ Values between compounds **11** and **12** for structural determination of **10** by the new Mosher method.

The stage was set for construction of a tetrahydrofuran moiety. After protection of **10** as a silyl ether, **13** was submitted to hydroboration to produce primary alcohol **14** (Scheme 2). Upon Swern oxidation followed by Wittig reaction, **14** was converted into **15**, which was oxidized with OsO_4 to give a diastereomeric 1 : 1 mixture of **16** possessing the substituents required to construct a tetrahydrofuran skeleton. Subsequently, **16** was submitted to selective tosylation, passing through a stannane intermediate[12] to provide tosylate **17** in 94% yield. After the secondary hydroxyl group of **17** was protected as the orthoester (**18**), the silyl group was removed with the fluoride anion; the resulting alcohol was then exposed to NaH, followed by AcOH, to give cyclized products bearing formyl groups derived from the orthoester. Removal of the acyl protective group under basic conditions afforded **19** as a diastereomeric ca. 1 : 1 mixture in 97% yield (four steps), which on repeated chromatographic separation (6% MeOH–$CHCl_3$) yielded **19a** as a faster moving spot (6% MeOH–$CHCl_3$ on silica-gel TLC), along with **19b** as a slower moving one. Upon employing such protective groups as MOM and acyl groups, the reaction sequence afforded the corresponding cyclized products in low yields. On the other hand, without protection of the secondary hydroxyl group of **17**, the cyclization reaction provided a different outcome, where epoxide **20** was obtained as a sole product. Direct conversion of **20** into **19** under NaH conditions was unsuccessful, probably owing to a difficulty of the 5-*Endo-Tetrahedral* ring closure.[13] When **19a** and **19b** were submitted to *p*-bromobenzoylation, only the acylation of **19b** proceeded, owing to a steric hindrance of the pyrone moiety, to provide **21** as crystals. Its X-ray crystallography[14] enabled unambiguous confirmation of the stereochemistry of the chiral center linked with a pyrone unit as *R*-configuration (Fig. 3). Accordingly, both asymmetric epoxidation (**6**→**7**) and structural determination by the new Mosher method are applicable even to the case of the pyrone-containing compounds.

Among several oxidation methods examined, tetrapropylammonium perruthenate (TPAP)–*N*-methyl-

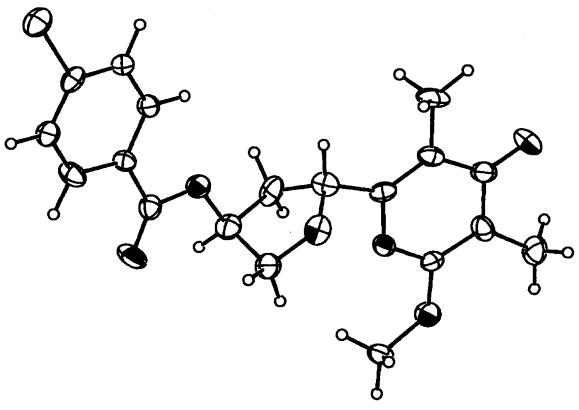
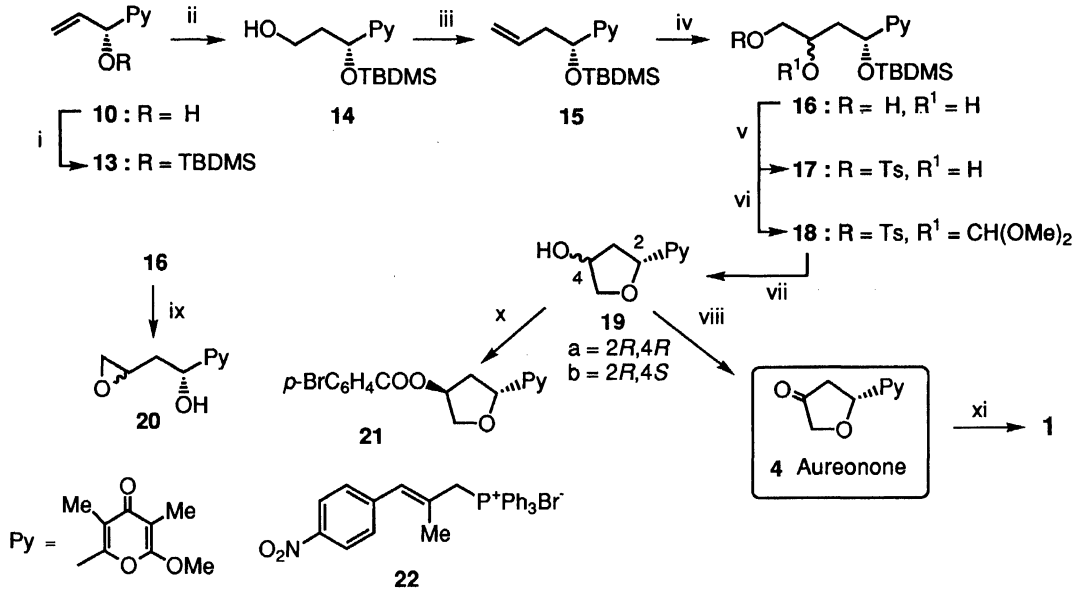
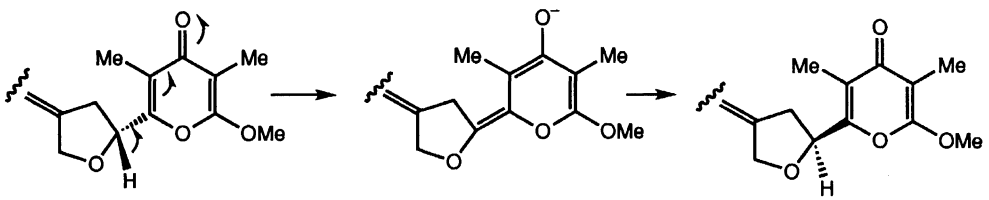


Fig. 3. Ortep drowing of compound **21**.



Scheme 2. *reagents*: i. TBDMSCl, Imd. (92%). ii. 9-BBN (90%). iii. a) Swern oxid.; b) $Ph_3P{=}CH_2$ (66%). iv. OsO_4, NMO (95%). v. *n*-Bu_2SnO, then TsCl (94%). vi. $HC(OMe)_3$. vii. a) *n*-Bu_4NF; b) NaH, then AcOH; c) K_2CO_3 (97%). viii. TPAP, NMO (55%). ix. *n*-Bu_4NF (100%). x. *p*-BrC_6H_4COCl, *i*-Pr_2NEt_2, DMAP (52%). xi. 22, NaH (14%).



Scheme 3. A plausible epimerization of a tetrahydrofuran moiety.

morpholine *N*-oxide (NMO) effected oxidation of **19** to aureonone **4** in moderate yield. Good accordance of synthetic **4** with an authentic sample was observed over the full range of the spectroscopic data and optical rotations {**4**: synthetic sample: $[\alpha]_D$ −64.0° ($CHCl_3$), authentic sample: $[\alpha]_D$ −56.9° ($CHCl_3$)}. Based on this evidence, the absolute configuration of **4**, as well as that of **1** could be determined to be as depicted in Fig. 1.

Furthermore, synthesis of **1** was attempted by coupling of **4** with a phosphorane prepared from **22**. Whereas the spectral data of synthetic **1** were identical with those of an authentic sample, the optical rotation of the former exhibited a lower value than that of the latter {synthetic sample: $[\alpha]_D$ +11.5° (*c* 1.50, $CHCl_3$), authentic sample: $[\alpha]_D$ +43.0° ($CHCl_3$)}. The optical purity of the recovered **4** was also diminished {$[\alpha]_D$ −16° ($CHCl_3$)}. These observations indicated that the Wittig coupling conditions at an elevated temperature might induce a partial epimerization of the starting material (**4**) and/or the product (**1**), as shown in Scheme 3. Accordingly, the allylic protons carrying a ketone at the γ-position have a sufficient acidity to be abstracted under these conditions, while no epimerization was detected in closely related isoaureothin synthesis[9b] employing a α-pyrone derivative which might exhibit a similar reactivity. However, abstraction of those protons of α-pyrones is generally known to be operating with rather strong lithium diisopropylamide (LDA) as a base.[15] Such a base-labile property of the γ-pyrone might be the reason of the epimerization in the synthesis of **1**.

Further synthetic studies on related γ-pyrone-containing natural products are in progress.

Experimental

All of the melting points were obtained on a Mitamura Riken melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained on a JEOL FX-90 A, a JEOL JNM EX-270 or a JEOL JNM GX-400 NMR spectrometer in a deuteriochloroform ($CDCl_3$) solution using tetramethylsilane as an internal standard, unless otherwise stated. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter. High-resolution mass spectra were obtained on a Hitachi M-80 GC-MS spectrometer operating at the ionization energy of 70 eV. Preparative and analytical TLC were carried out on silica-gel plates (Kieselgel 60 F_{254}, E. Merck A. G., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Katayama silica-gel (K 070) was used for column chromatography.

2-[(*E*)-3-Hydroxy-1-propenyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (6). To a solution of 2-formyl-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (**5**, 250 mg, 1.4 mmol) in PhH (12.5 ml) was added formylmethylenetriphenylphosphorane (Ph_3P=CHCHO, 627 mg, 2.1 mmol); the mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated, and the residue was dissolved in EtOH (10 ml)–AcOH (2.5 ml); $NaBH_3CN$ (91 mg, 1.4 mmol) was then added at 0 °C. After being stirred for 40 min, the resulting mixture was concentrated in vacuo; the residue was diluted with H_2O (30 ml), and extracted with CH_2Cl_2 (2×30 ml). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica-gel column chromatography (EtOAc) to give **6** (218 mg, 76%): Mp 179—180 °C (from EtOAc–hexane); IR (Nujol) 3350, 1670, 1630, and 1600 cm^{-1}; ^1H NMR δ=6.69 (1H, d, J=14.4 Hz), 6.50 (1H, td, J=2.6, 14.4 Hz), 4.40 (2H, broad d, J=2.6 Hz), 4.01 (3H, s), 2.00 (3H, s), and 1.84 (3H, s); ^{13}C NMR ($CDCl_3$–CD_3OD=10/1) δ=181.5 (s), 162.0 (s), 152.0 (s), 136.0 (d), 118.0 (d), 117.9 (s), 99.2 (s), 61.7 (t), 55.2 (q), 9.1 (q), and 6.6 (q). Found: m/z 210.0908. Calcd for $C_{11}H_{14}O_4$: M, 210.0892.

2-[(1*R*,2*S*)-1,2-Epoxy-3-hydroxypropyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (7). To a mixture of $Ti(OPr^i)_4$ (11.4 ml, 38 mmol) and diethyl L-tartrate (L-DET, 6.5 ml, 38 mmol) in CH_2Cl_2 (150 ml) at −30 °C under an argon atmosphere was added *t*-butyl hydroperoxide (TBHP, 3.0 M in isooctane, 19.1 ml, 57 mmol, 1 M=1 mol dm^{-3}). After the addition of **5** (4.02 g, 19 mmol) in CH_2Cl_2 (500 ml), the reaction mixture was stirred for 5h. A 200 ml portion of 10% aq tartaric acid was added, and the resulting slurry was further stirred for 30 min. After filtration through a Celite pad, the filtrate was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was further extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried (Na_2SO_4), then evaporated. The residue was purified by silica-gel column chromatography (17% $CHCl_3$–EtOAc) to yield **7** (3.82 g, 88%): Mp 138 °C (from EtOAc–hexane); $[\alpha]_D^{18}$ −220° (c 1.00, $CHCl_3$); IR (Nujol) 3370, 1665, and 1580 cm^{-1}; ^1H NMR δ=3.89—4.18 (3H, complex), 3.95 (3H, s), 3.70 (1H, m), 2.10 (3H, s), and 1.85 (3H, s); ^{13}C NMR δ=180.3 (s), 162.0 (s), 150.5 (s), 122.6 (s), 100.1 (s), 60.3 (t), 58.1 (d), 55.3 (q), 49.6 (d), 9.0 (q), and 6.8 (q). Found: m/z 226.0830. Calcd for $C_{11}H_{14}O_5$: M, 226.0839.

2-[(1*R*,2*S*)-1,2-Epoxy-3-(methylsulfonyloxy)propyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (8). To a solution of **7** (3.50 g, 16 mmol) in pyridine (150 ml) was added methanesulfonyl chloride (MsCl, 3.6 ml, 46 mmol) at −40 °C under an argon atmosphere. After being stirred for 3.5 h, the reaction mixture was poured into cold water, and extracted with CH_2Cl_2 (3×300 ml). The combined organic extracts were washed with 10% aq $CuSO_4$, sat. aq $NaHCO_3$ and brine, dried (Na_2SO_4), then evaporated. The residue was purified by silica-gel column chromatography (17% $CHCl_3$–EtOAc) to give **8** (4.99 g, 100%): Mp 75 °C (from EtOAc–hexane); IR (Nujol) 1670 and 1595 cm^{-1}; ^1H NMR δ=4.63 (1H, dd, J=3.2, 11.7 Hz), 4.32 (1H, dd, J=4.2, 11.7 Hz), 4.03 (1H, d, J=1.7 Hz), 3.95 (3H, s), 3.79 (1H, m), 3.13 (3H, s), 2.09 (3H, s), and 1.84 (3H, s). Found: m/z 304.0598. Calcd for $C_{12}H_{16}O_7S$: M, 304.0615. This unstable compound was used for the next reaction without full characterization.

2-[(1*R*,2*S*)-1,2-Epoxy-3-iodopropyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (9). To a solution of **8** (312 mg, 1.0 mmol) in DMF (12 ml) was added NaI (460 mg, 3.1 mmol); the mixture was stirred at 50 °C for 8 h under an argon atmosphere. The mixture was diluted with H_2O (40 ml), and extracted with CH_2Cl_2 (3×40 ml). The organic extracts were washed with 10% aq $Na_2S_2O_3$, sat. aq $NaHCO_3$ and brine, dried (Na_2SO_4), then concentrated in vacuo. The residue was passed through a silica-gel short column (50% $CHCl_3$–EtOAc), then purified by preparative TLC (50% $CHCl_3$–EtOAc) to afford **9** (230 mg, 67%) and recovered **8** (44 mg, 14%). **9** (oil): IR (film) 1665 and 1595 cm^{-1}; ^1H NMR δ=3.88 (3H, s), 3.0—4.0 (4H, complex), 2.05 (3H, s), and 1.80 (3H, s). Found: m/z 335.9852. Calcd for $C_{11}H_{13}O_4I$: M, 335.9858. This unstable compound was used for the next reaction without full characterization.

2-[(1*R*)-1-Hydroxy-2-propenyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (10). A mixture of **9** (233 mg, 0.67 mmol) and zinc powder (218 mg, 3.3 mmol) in DMF (8 ml)–AcOH (2 ml) was stirred at room temperature for 2.2 h. The reaction mixture was filtered through a Celite pad, and the filtrate was diluted with H_2O (50 ml), then extracted with CH_2Cl_2 (2×50 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (50% $CHCl_3$–EtOAc) to yield **10** (123 mg, 88%): Mp 79 °C (from EtOAc–hexane); $[\alpha]_D^{18}$ −14.2° (c 1.00, $CHCl_3$); IR (Nujol) 3350, 1665, and 1580 cm^{-1}; ^1H NMR δ=6.03 (1H, m), 5.42 (1H, d, J=15.0 Hz), 5.23—5.31 (2H, complex), 3.97 (3H, s), 3.49 (1H, s), 1.95 (3H, s), and 1.81 (3H, s); ^{13}C NMR δ=181.2 (s), 162.4 (s), 156.5 (s), 135.2 (d), 118.4 (s), 116.7 (t), 99.1 (s), 69.0 (d), 55.3 (q), 9.0 (q), and 6.6 (q). Found: m/z 210.0905. Calcd for $C_{11}H_{14}O_4$: M, 210.0891.

(*R*)-MTPA Ester (11). To a mixture of **10** (25 mg, 0.12 mmol) and 4-(dimethylamino)pyridine (DMAP, 29 mg, 0.24 mmol) in pyridine (0.25 ml) and CH_2Cl_2 (0.75 ml) was added (*S*)-MTPACl (33 μl, 0.18 mmol) at room temperature under an argon atmosphere. After being stirred for 1.5 h, the resulting mixture was diluted with H_2O, and extracted with EtOAc (2×10 ml). The organic extracts were washed with sat. aq $CuSO_4$, sat. aq $NaHCO_3$ and brine, dried (Na_2SO_4), then concentrated in vacuo. The residue was purified by preparative TLC (50% $CHCl_3$–EtOAc) to give **11** (51 mg, 100%) as an oil; $[\alpha]_D^{18}$ +55.2° (c 3.15, $CHCl_3$); IR (film) 1755, 1665, and 1600 cm^{-1}; ^1H NMR δ=7.3—7.5 (5H, complex), 6.52 (1H, dt, J=5.9, 1.3 Hz), 5.97 (1H, ddd, J=5.9, 10.6, 17.2 Hz), 5.45 (1H, broad d, J=17.2 Hz), 5.41 (1H, broad d, J=10.6 Hz), 3.82 (3H, s), 3.48 (3H, s), 2.09 (3H, s), and 1.86 (3H, s); ^{13}C NMR δ=180.1 (s), 165.3 (s), 162.1 (s), 150.6 (s), 131.6 (s), 129.9 (d×2), 128.5 (d×2), 128.3 (d), 127.3 (d), 123.1 (q, J_{C-F}=288 Hz), 121.4 (s), 120.3 (t), 100.1 (s), 84.7 (q, J_{C-C-F}=28 Hz), 72.1 (s), 55.3 (q), 55.2 (q), 9.5 (q), and 6.8 (q). Found: m/z 426.1298. Calcd for $C_{21}H_{21}F_3O_6$: M, 426.1288.

(*S*)-MTPA Ester (12). To a mixture of **10** (33 mg, 0.16 mmol) and DMAP (38 mg, 0.31 mmol) in pyridine (0.3 ml) and CH_2Cl_2 (0.9 ml) was added (*R*)-MTPACl (43 μl, 0.23 mmol) at room temperature under an argon atmosphere. After being stirred for 1.5 h, the reaction mixture was treated with the same procedure as in the case of **11** to give **12** (63 mg, 95%) as an oil; $[\alpha]_D^{17}$ 0.00° (c 2.49, $CHCl_3$);

IR (film) 1755, 1670, and 1600 cm^{-1}; ^1H NMR δ=7.3—7.5 (5H, complex), 6.46 (1H, dt, J=5.9, 1.3 Hz), 6.03 (1H, ddd, J=5.9, 10.6, 17.2 Hz), 5.51 (1H, broad d, J=17.2 Hz), 5.44 (1H, broad d, J=10.6 Hz), 3.59, (3H, s), 3.58 (3H, s), 2.09 (3H, s), and 1.84 (3H, s); ^{13}C NMR δ=180.1 (s), 165.3 (s), 162.0 (s), 150.4 (s), 132.0 (s), 130.0 (d), 129.7 (d), 128.4 (d×2), 126.8 (d×2), 123.0 (q, J_{C-F}=288 Hz), 121.4 (s), 120.5 (t), 99.9 (s), 84.5 (q, J_{C-C-F}=28 Hz), 72.2 (s), 55.6 (q), 55.0 (q), 9.3 (q), and 6.8 (q). Found: m/z 426.1303. Calcd for $C_{21}H_{21}F_3O_6$: M, 426.1288.

2-[(1*R*)-1-(*t*-Butyldimethylsilyloxy)-2-propenyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (13). To a solution of **10** (1.75 g, 8.3 mmol) in DMF (80 ml) was added imidazole (2.67 g, 33 mmol) and *t*-butyldimethylsilyl chloride (TBDMSCl, 2.51 g, 17 mmol). After being stirred at room temperature for 13.5 h, the reaction mixture was diluted with H_2O (800 ml), and extracted with CH_2Cl_2 (800 ml). The organic layer was washed with brine, dried (Na_2SO_4), then evaporated to dryness. The residue was purified by silica-gel column chromatography (66% hexane–EtOAc) to give **13** (2.49 g, 92%) as an oil: $[\alpha]_D^{18}$ +64.4° (c 1.00, $CHCl_3$); IR (film) 1670, 1630, and 1600 cm^{-1}; ^1H NMR δ=5.91 (1H, m), 5.39 (1H, d, J=18.9 Hz), 5.11—5.17 (2H, complex), 3.96 (3H, s), 2.01 (3H, s), 1.86 (3H, s), 0.91 (9H, s), 0.10 (3H, s), and 0.02 (3H, s); ^{13}C NMR δ=180.6 (s), 161.9 (s), 155.5 (s), 135.7 (d), 117.8 (s), 115.7 (t), 99.1 (s), 70.1 (d), 55.0 (q), 25.3 (q×3), 17.8 (s), 9.0 (q), 6.6 (q), and −5.2 (q×2). Found: m/z 309.1506. Calcd for $C_{16}H_{25}O_4Si$: M−CH_3, 309.1520.

2-[(1*R*)-1-(*t*-Butyldimethylsilyloxy)-3-hydroxypropyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (14). To a solution of **13** (166 mg, 0.51 mmol) in THF (6.5 ml) at 0 °C under an argon atmosphere was added 9-borabicyclo[3.3.1]nonane (9-BBN, 0.58 M in THF, 15.8 ml, 9.1 mmol); the mixture was stirred at room temperature for 4 h. The temperature was lowered to 0 °C, then sat. aq $NaHCO_3$ (2 ml) and 35% H_2O_2 (2 ml) were subsequently added; the stirring was continued for 1h. The resulting mixture was diluted with H_2O (25 ml), and extracted with CH_2Cl_2 (3×25 ml). The organic extracts were washed with brine, dried (Na_2SO_4), then evaporated. The residue was purified by preparative TLC (50% $CHCl_3$–EtOAc) to yield **14** (158 mg, 90%) as an oil: $[\alpha]_D^{17}$ +41° (c 0.50, $CHCl_3$); IR (film) 3330, 1670, and 1590 cm^{-1}; ^1H NMR δ=5.03 (1H, dd, J=5.0, 8.2 Hz), 3.93 (3H, s), 3.61—3.75 (2H, complex), 1.91 (3H, s), 1.75 (3H, s), 1.7—2.1 (2H, complex), 0.81 (9H, s), 0.03 (3H, s), and −0.10 (3H, s); ^{13}C NMR δ=180.9 (s), 162.2 (s), 157.2 (s), 117.6 (s), 99.3 (s), 66.5 (d), 58.5 (t), 55.2 (q), 38.1 (t), 25.4 (q×3), 17.8 (s), 9.2 (q), 6.7 (q), −5.2 (q), and −5.5 (q). Found: m/z 285.1146. Calcd for $C_{13}H_{21}O_5Si$: M−C_4H_9, 285.1156.

2-[(1*R*)-1-(*t*-Butyldimethylsilyloxy)-3-butenyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (15). To a solution of oxalyl dichloride (850 ml, 6.0 mmol) in CH_2Cl_2 (30 ml) at −69 °C under an argon atmosphere was added DMSO (580 ml, 12 mmol). After the mixture was stirred for 20 min, a solution of **14** (515 mg, 1.5 mmol) in CH_2Cl_2 (21 ml) was added; this mixture was stirred for 2.5 h, then Et_3N (3.4 ml, 24 mmol) was added at −63 °C. The stirring was continued for 1 h, and the reaction was quenched by the addition of sat. aq NH_4Cl (9 ml); the temperature was gradually elevated to room temperature. The resulting mixture was diluted with H_2O (150 ml), and extracted with CH_2Cl_2 (2×150 ml). The organic layer was washed with brine, dried (Na_2SO_4), then evaporated. The residue was passed through a silica-gel short column (50% $CHCl_3$–EtOAc) to give the corresponding aldehyde.

To a solution of the aldehyde in THF (22 ml) at −49 °C under an argon atmosphere was added methylenetriphenylphosphorane ($Ph_3P=CH_2$, 0.1 M in THF, 19.6 ml, 2.0 mmol); the temperature was warmed to room temperature during 1 h. After the addition of acetone (2 ml) at 2 °C, the resulting mixture was evaporated, and the crude product was purified by silica-gel column chromatography (66% hexane–EtOAc) to provide **15** (337 mg, 66%) as an oil: $[\alpha]_D^{18}$ +25.1° (c 1.43, $CHCl_3$); IR (film) 1660, 1620, and 1600 cm^{-1}; ^1H NMR δ=5.73 (1H, m), 4.93—5.20 (2H, complex), 4.77 (1H, t, J=6.4 Hz), 3.98 (3H, s), 2.49 (2H, broad t, J=6.4 Hz), 1.97 (3H, s), 1.85 (3H, s), 0.87 (9H, s), 0.61 (3H, s), and −0.61 (3H, s); ^{13}C NMR δ=180.6 (s), 162.0 (s), 156.6 (s), 132.8 (d), 118.0 (t), 117.8 (s), 99.2 (s), 69.0 (d), 55.1 (q), 40.4 (t), 25.4 (q×3), 17.8 (s), 9.2 (q), 6.7 (q), −5.0 (q), and −5.1 (q). Found m/z 323.1678. Calcd for $C_{17}H_{27}O_4Si$: M−CH_3, 323.1677.

2-[(1*R*,3*R*)- and (1*R*,3*S*)-1-(*t*-Butyldimethylsilyloxy)-3,4-dihydroxybutyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (16). To a solution of **15** (687 mg, 2.0 mmol) in CH_3CN (15 ml)–H_2O (5 ml) was added a catalytic amount of OsO_4 and NMO (476 mg, 2.1 mmol); the mixture was stirred at room temperature for 10 h. The reaction mixture was evaporated, and the residue was purified by silica-gel chromatography (5% MeOH–EtOAc) to give **16** as a diastereomeric mixture (719 mg, 95%): IR (film) 3440, 1660, and 1580 cm^{-1}; ^1H NMR δ=4.98—5.20 (1H, m), 3.98 (3H, s), 3.3—4.0 (3H, complex), 3.32 (2H, broad s), 1.98 (1.5H, s), 1.95 (1.5H, s), 1.82 (3H, s), 1.7—2.0 (2H, complex), 0.86 (9H, s), 0.09 (3H, s), and −0.06 (3H, s).

2-[(1*R*,3*R*)- and (1*R*,3*S*)-1-(*t*-Butyldimethylsilyloxy)-3-hydroxy-4-(*p*-tolylsulfonyloxy)butyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (17). A mixture of **16** (81 mg, 0.22 mmol) and *n*-Bu_2SnO (66 mg, 0.26 mmol) in PhMe (15 ml) was refluxed for 2 h, and the water generated was separated with a Dean–Stark apparatus. After cooling to room temperature, the reaction mixture was evaporated. The residue was dissolved in $CHCl_3$ (5 ml), and TsCl (83 mg, 0.43 mmol) was added. After being stirred at room temperature for 2 h, the reaction mixture was concentrated in vacuo to dryness. The residue was purified by preparative TLC (33% hexane–EtOAc) to give **17** (108 mg, 94%) as a diastereomeric mixture: IR (film) 3350, 1660, and 1575 cm^{-1}; ^1H NMR δ=7.76 (2H, d, J=9.0 Hz), 7.30 (2H, d, J=9.0 Hz), 4.89—5.14 (1H, complex), 3.94 (3H, s), 3.65—4.15 (3H, complex), 2.78 (1H, broad s), 2.42 (3H, s), 1.93 (1.5H, s), 1.91 (1.5H, s), 1.87 (2H, complex), 1.81 (3H, s), 0.83 (9H, s), 0.04 (3H, s), and −0.10 (3H, s).

2-[(2*R*,4*R*)- and (2*R*,4*S*)-4-Hydroxy-2,3,4,5-tetrahydro-2-furyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (19a and 19b). Compound **17** (523 mg, 1.0 mmol) was dissolved in trimethyl orthoformate (25 ml); the mixture was refluxed for 2 h. After cooling to room temperature, the resulting mixture was evaporated to give **18** as an oil, which was dissolved in THF (12 ml). To the solution was added *n*-Bu_4NF (1 M solution in THF, 2 ml, 2 mmol) at 0 °C; the mixture was stirred for 40 min. NaH (80 mg, 2 mmol,

60% dispersion in mineral oil) was then added at the same temperature. After the mixture was stirred for 1 h at room temperature, the reaction was quenched by the addition of AcOH (10 ml). The resulting mixture was concentrated in vacuo, and the residue was passed through a silica-gel short column (5% MeOH–$CHCl_3$). The crude product was dissolved in MeOH (4 ml), and treated with excess amounts of K_2CO_3 (10 mg) at room temperature. After the mixture was stirred for 30 min, the reaction was quenched by the addition of sat. aq NH_4Cl (10 ml), then filtered. After evaporation, the residue was dissolved in $CHCl_3$ (15 ml), and washed with H_2O. The aqueous layer was extracted with $CHCl_3$ (2×15 ml), and the combined organic extracts were dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel chromatography (50% acetone–$CHCl_3$) to give **19** (232 mg, 97%) as a diastereomeric mixture: IR (film) 3600, 1660, 1600, and 1575 cm^{-1}. The mixture (**19**, 50 mg) was purified by repeated separation with preparative TLC (6% MeOH–$CHCl_3$) to give **19a** (24 mg, R_f=0.28, 6% MeOH–$CHCl_3$ on silica-gel TLC, two times development), along with **19b** (23 mg, R_f=0.24).

19a (oil): ^{1}H NMR δ=5.06 (1H, dd, J=6.3, 8.9 Hz), 4.62 (1H, m), 4.02 (3H, s), 3.95—4.02 (1H, m, overlapped with OMe signal), 3.88 (1H, dd, J=4.3, 9.6 Hz), 2.54 (1H, ddd, J=6.6, 8.9, 13.9 Hz), 2.16 (1H, m), 2.01 (3H, s), and 1.85 (3H, s). Found: m/z 240.1025. Calcd for $C_{12}H_{16}O_5$: M, 240.0997.

19b (oil): ^{1}H NMR δ=5.32 (1H, t, J=8.1 Hz), 4.71 (1H, m), 4.14 (1H, dd, J=3.6, 9.9 Hz), 3.95 (3H, s), 3.92—3.95 (1H, m, overlapped with OMe signal), 2.25 (2H, complex), 2.02 (3H, s), and 1.85 (3H, s). Found: m/z 240.0999. Calcd for $C_{12}H_{16}O_5$: M, 240.0997.

2-[(1*R*,3*R*)- and (1*R*,3*S*)-3,4-Epoxybutyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (20). To a solution of **16** (24 mg, 0.05 mmol) in THF (0.5 ml) was added n-Bu_4NF (1 M) solution in THF, 0.1 ml, 0.1 mmol). After being stirred for 30 min, the mixture was evaporated, and the residue was separated by preparative TLC (10% MeOH–$CHCl_3$) to afford **20** (11 mg, quantitative yield) as a diastereomeric mixture: IR (film) 3300, 1655, and 1570 cm^{-1}; ^{1}H NMR δ=5.03—5.09 (1H, complex), 4.00 (3H, s), 3.39 (0.5H, broad s), 3.31 (0.5H, broad s), 3.16 (0.5H, m) 3.05 (0.5H, m), 2.86 (0.5H, t, J=4.4 Hz), 2.81 (0.5H, t, J=4.4 Hz), 2.60 (0.5H, dd, J=2.6, 5.0 Hz), 2.55 (0.5H, dd, J=2.6, 5.0 Hz), 2.32 (0.5H, m), 2.14 (0.5H, m), 1.98 (1.5H, s), 1.97 (1.5H, s), 1.9—2.0 (1H, m), and 1.84 (3H, s). Found: m/z 240.0971. Calcd for $C_{12}H_{16}O_5$: M, 240.0997.

2-[(2*R*,4*S*)-4-(*p*-Bromobenzoyloxy)-2,3,4,5-tetrahydro-2-furyl]-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (21). To a solution of **19b** (16 mg, 0.07 mmol) in CH_2Cl_2 (0.7 ml) were added i-Pr_2NEt (0.05 ml, 0.29 mmol), p-BrC_6H_4COCl (37 mg, 0.17 mmol), and DMAP (8 mg, 0.07 mmol). After being stirred for 1.5 h, the resulting mixture was diluted with H_2O, and extracted with CH_2Cl_2 (2×10 ml). The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (20% EtOAc–$CHCl_3$) to give **21** (14 mg, 52%): Mp 203 °C (from $CHCl_3$–hexane); $[\alpha]_D^{24}$ −74° (c 0.30, $CHCl_3$); IR (Nujol) 1720, 1670, and 1590 cm^{-1}; ^{1}H NMR δ=7.62 (2H, d, J=8.6 Hz), 5.72 (1H, m), 5.32 (1H, t, J=7.9Hz), 4.34 (1H, dd, J=4.3, 10.2 Hz), 4.14 (1H, dd, J=1.3, 10.2 Hz), 4.00 (3H, s), 2.47—2.52 (2H, complex), 2.05 (3H, s), and 1.87 (3H, s); ^{13}C NMR δ=180.6 (s), 165.4 (s), 162.1 (s), 153.8 (s), 131.9 (d×2), 131.2 (d×2), 128.7 (s), 128.4 (s), 120.6 (s), 100.2 (s), 75.7 (d), 74.1 (d), 73.8 (d), 55.4 (q), 36.0 (t), 9.5 (q), and 6.9 (q). Found: m/z 422.0353. Calcd for $C_{19}H_{19}O_6{}^{79}Br$: M, 422.0363.

Aureonone (4). To a solution of **19** (16 mg, 0.07 mmol) in CH_2Cl_2 (1.3 ml) were added catalytic amounts of TPAP and NMO (100 mg, excess amounts) at room temperature. After this was stirred for 20 h, i-PrOH (1 ml) was added, and the stirring was continued for 20 min. The mixture was evaporated, and purified by preparative TLC (33% acetone–$CHCl_3$) to give aureonone (**4**: 9 mg, 55%) and recovered **19** (4 mg, 23%).

4: Mp 144 °C (from EtOAc–hexane); $[\alpha]_D^{18}$ −64.0° (c 1.50, $CHCl_3$); IR (film) 1760, 1665, and 1590 cm^{-1}; ^{1}H NMR δ=5.55 (1H, dd, J=5.6, 8.1 Hz), 4.16 (1H, d, J=17.1 Hz), 4.08 (1H, d, J=17.1 Hz), 3.91 (3H, s), 2.87 (1H, dd, J=8.1, 18.1 Hz), 2.74 (1H, dd, J=5.6, 18.1 Hz), 2.07 (3H, s), and 1.86 (3H, s); ^{13}C NMR δ=212.3 (s), 180.2 (s), 161.9 (s), 153.3 (s), 120.1 (s), 100.3 (s), 73.0 (d), 70.5 (t), 55.4 (q), 39.2 (t), 9.4 (q), and 6.8 (q). Found: m/z 238.0830. Calcd for $C_{12}H_{14}O_5$: M, 238.0840.

Aureothin (1). To a solution of the phosphonium salt (**22**, 118 mg, 0.22 mmol) in THF (1 ml) and DMSO (0.2 ml) was added NaH (9 mg, 0.2 mmol, 60% dispersion in mineral oil). After the solution was stirred at room temperature, a solution of **4** (18 mg, 0.074 mmol) in PhMe (1.5 ml) was added, and the mixture was refluxed for 5.5 h. The resulting mixture was cooled to room temperature, diluted with H_2O, and extracted with CH_2Cl_2 (3×10 ml). The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was repeatedly purified by preparative TLC (25% acetone–$CHCl_3$ and 50% hexane–EtOAc) to give aureothin (**1**, 3 mg, 10%), a geometric isomer (3 mg, 10%) and recovered **4** {5 mg, 27%, $[\alpha]_D^{20}$ −16° (c 0.10, $CHCl_3$)}. **1**: $[\alpha]_D^{17}$ +11.5° (c 0.50, $CHCl_3$); IR (film) 1665, 1590, 1515, and 1340 cm^{-1}; ^{1}H NMR δ=8.21 (2H, d, J=8.8 Hz), 7.40 (2H, d, J=8.8 Hz), 6.38 (1H, broad s), 6.21 (1H, broad s), 5.15 (1H, t, J=6.8 Hz), 4.88 (1H, broad d, J=14.2 Hz), 4.75 (1H, broad d, J=14.2 Hz), 3.95 (3H, s), 3.07 (1H, broad dd, J=6.8, 16.4 Hz), 2.96 (1H, broad dd, J=6.8, 16.4 Hz), 2.05 (3H, s), 2.04 (3H, s), 1.86 (3H, s); ^{13}C NMR δ=180.6 (s), 162.1 (s), 154.6 (s), 146.2 (s), 144.2 (s), 140.6 (s), 138.6 (s), 129.6 (d), 128.4 (d), 126.0 (d), 123.6 (d), 120.2 (s), 100.1 (s), 73.3 (d), 70.1 (t), 55.3 (q), 38.3 (t), 17.7 (q), 9.4 (q), and 6.9 (q). Found: m/z 398.1609. Calcd for $C_{22}H_{24}O_6N$: M, 398.1602.

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