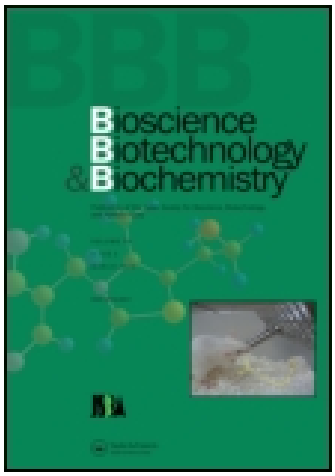


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# Synthesis of Chiral Aspyrone, A Multi-functional Dihydropyranone Antibiotic

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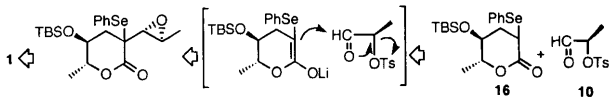
**Aspyrone (1) was elaborated in an optically pure form by a key reaction involving the highly diastereoselective addition of tetrahydropyranone enolate to 2-tosyloxy-aldehyde and the subsequent *in situ* formation of an epoxide.**



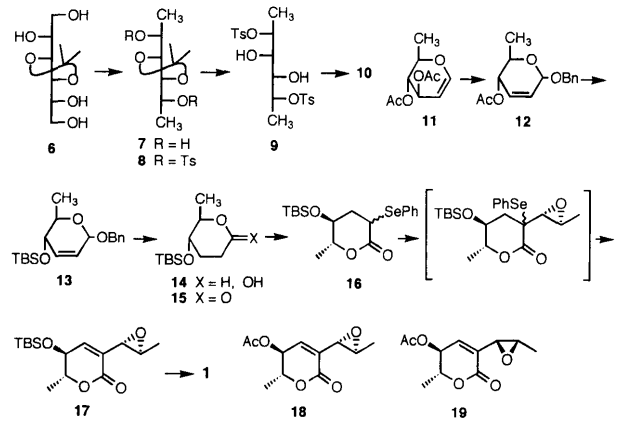
Synthetic work on biologically active 5-oxygenated dihydropyranones osmundalactone (**2**),[1] phomalactone (**3**),[2] acetylphomalactone (**4**),[2,3] asperlin (**5**),[2,3] and their isomers directed our interest toward the chiral synthesis of more complex congener aspyrone (**1**). This substance was isolated as one of the antibiotics from a culture broth of the *Aspergillus* species,[4–8] and had a characteristic structural feature arising from the skeletal rearrangement on its biosynthetic pathway of polyketide[9,10] (Fig. 1). Its absolute stereochemistry was determined as being of (5*S*,6*R*,1′*S*,2′*S*)-form by X-ray crystallographic and degradative works.[11,12] In a previous paper,[13] we have briefly reported the first total synthesis of optically active aspyrone (**1**) from readily available carbohydrate precursors. In this paper, we described details of the total synthesis of aspyrone (**1**).

As **1** has an α,β-unsaturated-δ-lactone structure with a 1′,2′-epoxypropyl moiety at the α-position of the lactone, it was difficult to introduce the leaving group for the double bond after forming the epoxide ring. The leaving group should have been present before constructing the epoxide function. Since the epoxypropyl moiety had the stereochemistry of 1′*S*,2′*S* as already described, it was preferable to construct the epoxide ring by the cyclization method, rather than to epoxidize an olefinic intermediate. As illustrated in Scheme 1, we anticipated the tandem nucleophilic addition of an enolate to 2-tosyloxy-propanal and subsequent ring closure to an epoxide as the key step for building up the target skeleton. The most desirable intermediates would thus be (*R*)-1-formylethyl *p*-toluenesulfonate (**10**) and (5*S*,6*R*)-5-*t*-butyldimethylsiloxy-6-methyl-3-phenylselenotetrahydro-2*H*-pyran-2-one (**16**). If the enolate of **16** attacks the *Si* face of aldehyde **10**, the epoxide would have the (1′*S*,2′*S*)-configuration (*trans*-epoxide), and the product would be, on the contrary, (1′*R*,2′*S*)-epoxide (*cis*-epoxide) in the case of attack on the *Re* face of the carbonyl group. It was uncertain, at the initial stage, to predict whether the reaction product would be a mixture of diastereomers or not.

As shown in Scheme 2, **10** was derived from 3,4-*O*-isopropylidene-D-mannitol (**6**).[14] Tosylation of the terminal hydroxy groups and subsequent reduction with lithium aluminum hydride gave **7**, which was re-esterified to **8** with tosyl chloride and triethylamine. Deprotection of **8** with aqueous trifluoroacetic acid and oxidation of the resultant diol **9** with sodium metaperiodate gave unstable **10**, which changed easily to a hydrate form while standing in the air. For the other chiral segment **16**, D-rhamnal diacetate (**11**)[15] was chosen as a readily available precursor. A Ferrier reaction[16] on **11** gave an anomeric mixture of 2,3-unsaturated glycoside (**12**; $\alpha/\beta = 8/1$), which was saponified and re-protected as *t*-butyldimethylsilyl (TBS) ether (**13**). Successive hydrogenation and debenzylation of **13**, and subsequent oxidation of **14** with pyridinium dichromate[17] afforded tetrahydropyranone (**15**). Phenylselenylation of **15** gave diastereomeric mixture **16**. At the convergent step, **16** was successively treated with lithium hexamethyldisilazide and then with **10** at −78°C, with subsequent cyclization of



**Scheme 1.**



**Scheme 2.**

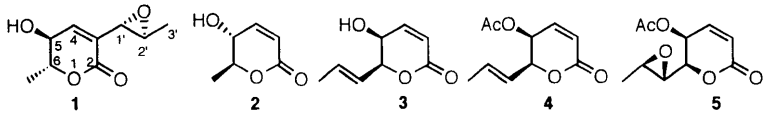


**Fig. 1.** Naturally Occurring Dihydropyranones.

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the epoxide ring. The crude reaction product was oxidized with hydrogen peroxide and shaken with sodium hydrogen carbonate to yield 5-protected aspyrone (**17**) having the desired *trans*-epoxide in a 61% yield in 3 steps. Deprotection of **17** with the fluoride anion provided pure aspyrone (**1**). Its spectroscopic and physicochemical properties were identical with those of the natural compound.[10] The mother liquor of **17** was carefully examined to check for the presence of the stereoisomer of **17**. Thus, the foregoing sample was concentrated to give less than 0.4% of a mixture of **17** and its isomer, which was converted to a mixture of acetates **18** and **19** to avoid any overlapping of the NMR signals. Its $^1$H-NMR spectrum revealed the presence of less than 0.2% of an isomeric *cis*-epoxide. The stereochemistry of the epoxide moiety was determined by comparing the coupling constants of protons on the epoxide ring, *i.e.*, 2.0 Hz for the *trans*-epoxide and 4.2 Hz for the *cis*-isomer.[18] In both compounds, the dihedral angle between 4-H and 5-H was estimated to be nearly 90° as indicated by their coupling constants (3.3 Hz for **18** and 3.8 Hz for **19**)[19] and Dreiding model. On the other hand, the dihedral angle between 1′-H and 4-H was presumed to be 50–70°, or 290–310° from the allylic coupling constants.[19] Moreover the signal for 2′-H of **18** was shifted to a higher field than that of **19**, with 3′-$H_3$ of **19** also being shifted to a higher field. These results indicate that 2′-H of **18** and 3′-$H_3$ of **19** were presumably located in the shielding sphere caused by magnetic anisotropy of the pyranone carbonyl group as depicted in Fig. 2. The observation of homoallylic spin coupling[20] with respect to 1′-H of both isomers is consistent with the foregoing conformational assessment. The stereochemical orientation of **18** may be applicable to aspyrone (**1**), because the chemical shifts and coupling patterns of the epoxide and olefinic protons were similar between them. In the epoxide-forming step, the ratio of 62 : 0.15 would reflect the result of face-selection in the nucleophilic attack by the enolate anion, as the cyclization reaction was rapid and the configurational difference in possible reaction intermediates would sparingly affect the cyclization rate.[21] Therefore, it is suggested that the enolate might attack the aldehyde carbonyl exclusively at the *Si* face. Rationalization of such face-selectivity against 2-tosyloxyaldehyde is now under investigation, and the results will be published in due course.

## Experimental

Boiling point (bp) and melting point (mp) data are uncorrected. $^1$H-NMR spectra were recorded on JEOL JNM FX-100, GSX-270, and GSX-400 spectrometers, and IR spectra on a JASCO IR-810 infrared spectrometer. Optical rotation was measured with a JASCO DIP-4 polarimeter, and mass spectra were recorded on a JEOL JMS DX-303HF spectrometer. Unless otherwise stated, 3-nitrobenzyl alcohol was used as the matrix for FAB-MS analyses. The $^1$H-NMR data for compounds **12** to **14** refer to those of the major α-isomers.

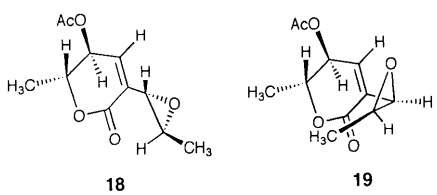
*1,6-Dideoxy-3,4-O-isopropylidene-*D*-mannitol* (**7**). To a solution of **6** (6.0 g, 27 mmol) in 75 ml of dry pyridine was added portionwise 11.4 g of *p*-toluenesulfonyl chloride (59.8 mmol), and the resultant reaction mixture was stirred for 2 h in an ice-cooling bath and then kept standing overnight in a refrigerator. The reaction mixture was diluted with water and extracted with ether. The extract was successively washed with water, cold dil. $H_2SO_4$, and aq. $NaHCO_3$, and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a crystalline ditosylate (quant.), melting at 114–115°C (fine needles from benzene). *Anal.* Found: C, 51.83; H, 5.65; S, 12.38%. Calcd. for $C_{23}H_{30}O_{10}S_2$: C, 52.06; H, 5.70; S, 12.09%. $[\alpha]_D^{23}$ +58.0° ($c$=2.5, $CHCl_3$). FAB-MS *m/z*: 553 ($M+Na^+$), 575 ($M-H^++2Na^+$), 535 ($M+H^+-H_2O$). $^1$H-NMR ($CDCl_3$) δ: 1.27 (6H, s, >$CMe_2$), 2.45 (6H, s, Ar-Me × 2), 3.51 (2H, -OH × 2), 3.7–3.9 (4H, m, 2-H–5-H), 4.08 (2H, dd, $J$=10.5, 5.5 Hz, 1-H+6-H), 4.32 (2H, dd, $J$=10.5, 2.0 Hz, 1-H+6-H), 7.36 (4H, d, $J$=8.2 Hz, Ar-$H_2$ × 2), 7.81 (4H, d, $J$=8.2 Hz, Ar-$H_2$ × 2). IR $\nu_{max}$ (nujol) $cm^{-1}$: 3560, 3400, 1600, 1188, 1175, 1098, 1074, 970, 930, 828, 790. Diacetate, mp 112.5–114°C (lit.[22] 111–113°C).

To a solution of this ditosylate (5.0 g, 9.4 mmol) in 50 ml of dry THF was added $LiAlH_4$ (1.0 g, 26 mmol) in several portions, and the reaction mixture was stirred overnight at room temperature. After decomposing the mixture with water, the product was extracted with ether. The extract was washed with water and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a viscous oil which was purified by column chromatography on silica gel to give 1.6 g (89%) of a crystalline product melting at 93–94°C (fine needles from hexane). *Anal.* Found: C, 56.78; H, 9.51%. Calcd. for $C_9H_{18}O_4$: C, 56.81; H, 9.54%. $[\alpha]_D^{23}$ −12.7° ($c$=3.7, $CHCl_3$). FAB-MS *m/z*: 191 ($M+H^+$). HREI-MS *m/z* ($M+H^+$): calcd. for $C_9H_{19}O_4$, 191.1282; found, 191.1291, ($M^+$ – Me): calcd. for $C_8H_{15}O_4$, 175.0971; found, 175.0979. IR $\nu_{max}$ (KBr) $cm^{-1}$: 3250, 2980, 2940, 2880, 1382, 1372, 1244, 1176, 1108, 1072, 960. $^1$H-NMR ($CDCl_3$) δ: 1.32 (6H, d, $J$=6.0 Hz, 1-$H_3$+6-$H_3$), 1.38 (6H, s, >$CMe_2$), 3.5–3.9 (6H, m, 2-H–5-H).

*1,6-Dideoxy-3,4-O-isopropylidene-*D*-mannitol 2,5-di-p-toluenesulfonate* (**8**). A mixture of foregoing diol **7** (1.6 g, 8.4 mmol), *p*-toluenesulfonyl chloride (4.0 g, 21 mmol) and triethylamine (2.0 g, 19.8 mmol) in 12 ml of dry pyridine was kept standing overnight at 0°C. The reaction mixture was then diluted with water and extracted with ether. The extract was successively washed with water, cold dil. $H_2SO_4$, and aq. $NaHCO_3$, and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a crude ditosylate which was purified by column chromatography on alumina and recrystallized from MeOH to yield 3.8 g (92.7%) of pure **8**. mp 91.5—92.5°C (fine needles). *Anal.* Found: C, 55.38; H, 6.18%. Calcd. for $C_{23}H_{30}O_8S_2$: C, 55.41; H, 6.06%. $[\alpha]_D^{23}$ +20.0° ($c$=1.3, $CHCl_3$). IR $\nu_{max}$ (KBr) $cm^{-1}$: 3000, 1600, 1360, 1236, 1190, 1180, 928, 910, 820, 784. $^1$H-NMR ($CDCl_3$) δ: 1.25 (6H, d, $J$=6.3 Hz, 1-$H_3$+6-$H_3$), 1.28 (6H, s, >$CMe_2$), 2.45 (6H, s, Ar-Me × 2), 3.83 (2H, septet (high-order splittings), 3-H and 4-H), 4.62 (2H, m, 2-H and 5-H), 7.34 (4H, d, $J$=8.2 Hz, Ar-$H_2$ × 2), 7.80 (4H, d, $J$=8.2 Hz, Ar-$H_2$ × 2).

*1,6-Dideoxy-*D*-mannitol 2,5-di-p-toluenesulfonate* (**9**). A mixture of ditosylate **8** (1.0 g, 2 mmol) and 4 ml of 60% trifluoroacetic acid was stirred for 1.5 h at 50°C. After removing the solvent under reduced pressure, the residue was chromatographed on silica gel, eluting with benzene–AcOEt (4 : 1), to yield 0.75 g (81.6%) of **9**. mp 84.5–85.5°C (needles from ether). FAB-MS *m/z*: 459 ($M+H^+$), 481 ($M+Na^+$), 497 ($M+K^+$). *Anal.* Found: C, 51.78; H, 5.66; S, 14.22%. Calcd. for $C_{20}H_{26}O_9S_2 \cdot 1/2H_2O$: C, 51.38; H, 5.82; S, 13.99%. $[\alpha]_D^{21}$ +10.5° ($c$=7.2, $CHCl_3$). IR $\nu_{max}$ (KBr) $cm^{-1}$: 3540, 1595, 1490, 1352, 1188, 1172, 1128, 1095, 932, 879, 818, 658. $^1$H-NMR ($CDCl_3$) δ: 1.23 (6H, d, $J$=6.4 Hz, 1-$H_3$+6-$H_3$), 2.46 (6H, s, Ar-Me × 2), 2.50 (2H, br. s, -OH × 2), 3.69 (2H, d, $J$=7.8 Hz, 3-H+4-H), 4.61 (2H, dq, $J$=7.8, 6.4 Hz, 2-H+5-H), 7.36 (4H, d, $J$=8.3 Hz, Ar-$H_2$ × 2), 7.79 (4H, d, $J$=8.3 Hz, Ar-$H_2$ × 2).

*(R)-1-Formylethyl p-toluenesulfonate* (**10**). To a solution of 0.7 g of foregoing **9** (0.7 g, 1.5 mmol) in 15 ml of aq. MeOH was added $NaIO_4$ (0.4 g, 1.9 mmol), and the reaction mixture was stirred for 40 min at room temperature. The mixture was then diluted with water and extracted with ether. The extract was successively washed with water and brine and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a colorless oil (hydrate form, $\nu_{max}$: 3500, 1600, 1360), which was chromatographed on silica gel (dried in an oven at 135°C for 2 h). Elution with benzene–AcOEt (10 : 1) gave 0.6 g (86.2%) of **10**. HRFAB-MS *m/z* ($M+H^+$): calcd. for $C_{10}H_{13}O_4S$, 229.0535; found, 229.0557. IR $\nu_{max}$ (film) $cm^{-1}$: 3070, 2930, 2850, 2730, 2600, 1745, 1600, 1500, 1450, 1368, 1190, 1180, 1100, 1050, 948, 820, 782, 668. $^1$H-NMR ($CDCl_3$) δ: 1.37 (3H, d, $J$=7.1 Hz, -Me),




18 19

**Fig. 2.** Favored Conformers of **18** and **19**.

2.46 (3H, s, Ar-Me), 4.74 (1H, qd, $J$=7.1, 1.0 Hz, >CH), 7.38 (2H, $J$=8.3 Hz, Ar-$H_2$), 7.82 (2H, d, $J$=8.3 Hz, Ar-$H_2$), 9.57 (1H, d, $J$=1.0 Hz, -CHO).

*Benzyl 4-O-acetyl-2,3,6-trideoxy-α- and -β-D-erythro-hex-2-enopyranosides* (**12**). To a solution of D-rhamnal diacetate (**11**, 10.0 g, 47 mmol) in 200 ml of $CH_2Cl_2$ were added 12.0 g of benzyl alcohol and 0.5 g of freshly distilled $SnCl_4$, and the mixture was stirred for 30 min at room temperature. The reaction was then quenched with aq. $NaHCO_3$. The organic layer was separated, dried over anhyd. $MgSO_4$ and concentrated to give a colorless liquid which was purified by vacuum distillation; bp 143–146°C (0.6 mmHg). Yield, 10.8 g (94.7%). The product was a mixture of anomers ($\alpha/\beta$=8/1) as indicated by the $^1$H-NMR spectrum. *Anal.* Found: C, 68.87; H, 7.02%. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92%. IR $\nu_{max}$ (film) cm$^{-1}$: 3070, 3030, 2980, 2940, 2900, 1748, 1660, 1500, 1458, 1405, 1375, 1236, 1195, 1153, 1104, 1040, 920. $^1$H-NMR ($CDCl_3$) $\delta$: 1.19 (3H, d, $J$=6.1 Hz, 6-$H_3$), 2.08 (3H, s, acetyl), 4.01 (1H, dq, $J$=6.1, 0.7 Hz, 5-H), 4.59 (1H, d, $J$=12.0 Hz, Ar-CH), 4.80 (1H, d, $J$=12.0 Hz, Ar-CH), 4.92–5.22 (2H, m, 1-H+4-H), 5.7–5.95 (2H, m, 2-H+3-H), 7.34 (5H, br. s, Ar-$H_5$), these data were identical with those of the α-anomer of the L-isomer.[16]

*4-O-t-Butyldimethylsilyl-2,3,6-trideoxy-D-erythro-hexopyranose* (**14**). To a solution of acetate **12** (1.8 g, 6.9 mmol) in 10 ml of MeOH was added a solution $K_2CO_3$ (1.6 g, 11.6 mmol) in a small amount of water, and the resulting mixture was stirred for 5 h at room temperature. The reaction mixture was diluted with water and extracted with $CH_2Cl_2$. The extract was dried with anhyd. $Na_2SO_4$ and concentrated to give a quantitative yield of an alcohol. FAB-MS (glycerol) $m/z$: 221 ($M+H^+$), 243 ($M+Na^+$, added with NaCl). HRFAB-MS: calcd. for $C_{13}H_{17}O_3$, 221.1198 ($M^++H$); found, 221.1129. $^1$H-NMR ($CDCl_3$) $\delta$: 1.30 (3H, d, $J$=6.1 Hz, 6-$H_3$), 1.54 (1H, -OH), 3.75 (1H, dq, $J$=9.0, 6.1 Hz, 5-H), 3.85 (1H, dm, $J$=9.0 Hz, 4-H), 4.59 (1H, d, $J$=12.0 Hz, Ar-CH), 4.78 (1H, d, $J$=12.0 Hz, Ar-CH), 5.04 (1H, m, 1-H), 5.77 (1H, ddd, $J$=10.0, 2.7, 2.0 Hz, 2-H), 5.93 (1H, dm, $J$=10.0 Hz, 3-H), 7.26–7.36 (5H, Ar-$H_5$). IR $\nu_{max}$ (film) cm$^{-1}$: 3420, 3040, 2975, 2940, 2895, 1500, 1455, 1405, 1378, 1190, 1175, 1148, 1130, 1100, 1046, 960, 885.

A mixture of the foregoing alcohol (4.6 g, 20.9 mmol), triethylamine (5.5 g, 54.4 mmol), dimethylaminopyridine (0.3 g), and *t*-butylchlorodimethylsilane (4.8 g, 31.9 mmol) in 15 ml of THF was stirred for 30 h at 45–50°C. The reaction mixture was then diluted with water and extracted with hexane. The extract was washed with water and dried over anhyd. $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography on Florisil gave 6.9 g (98.9%) of **13**. HRFAB-MS $m/z$ ($M+H^+$): calcd. for $C_{19}H_{31}O_3Si$, 335.2043; found, 335.2001. $^1$H-NMR ($CDCl_3$) $\delta$: 0.08 (3H, s, Si-Me), 0.09 (3H, s, Si-Me), 0.89 (9H, s, *t*-Bu), 1.22 (3H, d, $J$=6.1 Hz, 6-$H_3$), 3.80 (1H, dq, $J$=8.7, 6.1 Hz, 5-H), 3.88 (1H, ddd, $J$=8.7, 2.7, 1.5 Hz, 4-H), 4.58 (1H, d, $J$=11.7, Ar-CH), 4.78 (1H, d, $J$=11.7 Hz, Ar-CH), 5.02 (1H, m, 1-H), 5.69 (1H, ddd, $J$=10.2, 2.7, 1.9 Hz, 2-H), 5.84 (1H, dm, $J$=10.3 Hz, 3-H), 7.25–7.38 (5H, m, Ar-$H_5$). IR $\nu_{max}$ (film) cm$^{-1}$: 3030, 2960, 2930, 2900, 2860, 1490, 1460, 1400, 1306, 1252, 1152, 1100, 1072, 1045, 1010, 882, 839, 775.

Compound **13** (5.0 g, 15.0 mmol) was dissolved in abs. EtOH and shaken with a catalytic amount of 10% Pd–C in an atmosphere of hydrogen until the calculated volume of the gas had been absorbed. After removing the catalyst by filtration, the filtrate was concentrated, and the residue was chromatographed on silica gel to give an anomeric mixture (*ca.* 4:6) of **14** (amorphous solid). Yield, 3.1 g (84.1%). *Anal.* Found: C, 58.01; H, 10.38%. Calcd. for $C_{12}H_{26}O_3Si$: C, 58.50; H, 10.64%. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3380, 2960, 2940, 2860, 1476, 1365, 1254, 1090, 1002, 972, 768.

*(5S,6R)-5-t-Butyldimethylsiloxy-6-methyltetrahydro-2H-pyran-2-one* (**15**). To a solution of hemiacetal **14** (2.0 g, 8.1 mmol) in 15 ml of dry DMF was added 6.0 g of PDC (6.0 g, 16.0 mmol), and the reaction mixture was stirred overnight at room temperature. The mixture was extracted with hexane–ether, and the extract was concentrated to give a colorless oil which was chromatographed on silica gel, eluting with hexane–ether (10:1). The product was recrystallized from hexane to give 1.7 g of prisms, mp 68–69°C. *Anal.* Found: C, 58.90; H, 10.01%. Calcd. for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90%. $[\alpha]_D^{21}$ +74.0° ($c$=10.7, $CHCl_3$). IR $\nu_{max}$ (KBr) cm$^{-1}$: 2960, 2930, 2900, 2860, 1758, 1475, 1465, 1345, 1318, 1252, 1238, 1090, 894, 842, 780. $^1$H-NMR ($CDCl_3$) $\delta$: 0.09 (6H, s, Si-$Me_2$), 0.90 (9H, s, *t*-Bu), 1.36 (3H, d, $J$=6.3 Hz, 6-Me), 1.6–2.3 (2H, m), 2.3–3.0 (2H, m), 3.68 (1H, ddd, $J$=4.7, 6.6, 6.6 Hz, 5-H), 4.28 (1H, dq, $J$=6.3, 6.6 Hz, 6-H).

*(5S,6R)-5-t-Butyldimethylsiloxy-6-methyl-3-phenylselenotetrahydro-2H-pyran-2-one* (**16**). To a solution of diisopropylamine (1.75 g, 17.3 mmol) in 20 ml of dry THF was added a solution of *n*-butyllithium in hexane (1.5 M, 11.5 ml, 17.3 mmol) while stirring at −80 to −75°C. Stirring was continued for 15 min, before a solution of **15** (3.8 g, 15.6 mmol) in 10 ml of dry THF was added dropwise at −78°C. After stirring for 30 min at that temperature, a solution of phenylselenenyl chloride (3.3 g, 17.2 mmol) in a small amount of THF was added dropwise to the flask. The reaction mixture was stirred for 5 h and then decomposed with dil. AcOH. The aqueous layer was extracted with hexane–ether, before the extract was successively washed with water and aq. $NaHCO_3$, and dried with anhyd. $MgSO_4$. Evaporation of the solvent gave a mixture of crude reaction products which was chromatographed in a column of silica gel. After eluting with hexane–ether (10:1), the product was obtained from the fraction eluted with hexane–ethyl acetate=10:1–5:1 as a mixture of diastereomers. Yield, 3.65 g (58.1%). FAB-MS $m/z$: 401 ($M+H^+$); calcd. for $C_{18}H_{29}O_3SiSe$, 401.1041. IR $\nu_{max}$ (film) cm$^{-1}$: 3050, 2950, 2925, 2860, 1835, 1580, 1472, 1460, 1380, 1254, 1210, 1084, 936, 880, 838, 778, 740, 692. From the other fraction, about 2.1 g of the bis-phenylseleno-derivative was isolated.

*(5S,6R,1'S,2'S)-5-t-Butyldimethylsiloxy-3-(1',2'-epoxypropyl)-6-methyl-5,6-dihydro-2H-pyran-2-one* (**17**, *TBS-aspyrone*). To a solution of hexamethyldisilazane (0.63 ml, 3.4 mmol) in 6 ml of dry THF was added dropwise a solution of *n*-butyllithium in hexane (1.5 M, 1.6 ml, 2.4 mmol) while stirring at below −70°C. After 30 min, a solution of **16** (0.7 g, 1.8 mmol) in a small amount of dry THF was slowly added to the reaction flask, and the reaction mixture was stirred for a further 30 min at that temperature. A solution of 2-tosyloxyaldehyde **10** (0.6 g, 2.6 mmol) in 3 ml of dry THF was then added dropwise to the enolate solution while stirring at −78°C. The reaction mixture was stirred overnight, during which period the temperature of the reaction was gradually raised to room temperature. The reaction mixture was diluted with water, neutralized with dil. AcOH and extracted with ether. The extract was washed with brine and dried over anhyd. $Na_2SO_4$. Evaporation of the solvent gave a yellowish oil which was roughly purified by column chromatography on Florisil. The crude product was dissolved in 10 ml of THF and stirred with 1 ml of 30% hydrogen peroxide for 1 h at room temperature. The reaction mixture was then diluted with aq. $NaHCO_3$ and extracted with ether. The extract, after being dried with anhyd. $MgSO_4$, was concentrated to give a pale yellow oil which was purified by column chromatography on Florisil, eluting with hexane–ether (5:1), and then recrystallized from hexane. Yield, 320 mg (61.8%). mp 71–72°C (leaflets). *Anal.* Found: C, 60.59; H, 8.91%. Calcd. for $C_{15}H_{26}O_4Si$: C, 60.37; H, 8.78%. $[\alpha]_D^{20}$ +40° ($c$=1.2, $CHCl_3$). IR $\nu_{max}$ (KBr) cm$^{-1}$: 2970, 2940, 2860, 1760, 1740, 1660, 1475, 1468, 1388, 1364, 1256, 1222, 1092, 945, 842, 780. $^1$H-NMR ($CDCl_3$) $\delta$: 0.11 (3H, s, Si-$CH_3$), 0.12 (3H, s, Si-$CH_3$), 0.91 (9H, s, -*t*-Bu), 1.42 (6H, br d, $J$=5.9 Hz, $CH_3\times2$), 2.77 (1H, dq, $J$=5.1, 1.8 Hz, 2'-H), 3.43 (1H, br. s, 1'-H), 4.19 (1H, dd, $J$=9.2, 1.8 Hz, 5-H), 4.29 (1H, dq, $J$=9.2, 6.2 Hz, 6-H), 6.51 (1H, br. s, 4-H). About 100 mg of 5-*t*-butyldimethylsiloxy-6-methyl-5,6-dihydro-2*H*-pyran-2-one was recognized as a crude oil ($\delta_{3\text{-H}}$, 5.93; $\delta_{4\text{-H}}$, 6.70) in the other fraction.

*Detection of the (1'R)-isomer* (*cis-epoxide*, **19**) *of aspyrone in the reaction products.* The mother liquor of the foregoing recrystallization was concentrated to give *ca.* 2 mg (0.38%) of an oil, which was successively treated with tetrabutylammonium fluoride (TBAF) and benzoic acid in THF and then with acetic anhydride–pyridine. The reaction product was isolated in the usual way, and its NMR spectrum revealed a mixture (*ca.* 6:4) of aspyrone acetate (**18**) and its (1'*R*)-isomer (**19**). Aspyrone acetate (**18**): $\delta_H$ ($CDCl_3$): 1.41 (3H, d, $J$=6.4 Hz, 6-Me), 1.42 (3H, d, $J$=5.1 Hz, 3'-$H_3$), 2.13 (3H, s, -OAc), 2.80 (1H, qd, $J$=5.1, 2.0 Hz, 2'-H), 3.83 (1H, br. s, 1'-H), 4.57 (1H, dq, $J$=7.3, 6.4 Hz, 6-H), 5.27 (1H, br. dd, $J$=7.3, 3.3 Hz, 5-H), 6.57 (1H, dd, $J$=3.3, 0.8 Hz, 4-H). (1'*R*)-Isomer of aspyrone acetate (**19**): $\delta_H$ ($CDCl_3$): 1.15 (3H, d, $J$=5.5 Hz, 3'-$H_3$), 1.45 (3H, d, $J$=6.4 Hz, 6-Me), 2.12 (3H, s, -OAc), 3.37 (1H, qd, $J$=5.5, 4.1 Hz, 2'-H), 3.88 (1H, ddd, $J$=4.1, 2.0, 1.4 Hz, 1'-H), 4.58 (1H, qd, $J$=6.4, 6.3 Hz, 6-H), 5.38 (1H, ddd, $J$=6.3, 3.8, 2.0 Hz, 5-H), 6.63 (1H, dd, $J$=3.8, 1.4 Hz, 4-H).

*(5S,6R,1'S,2'S)-3-(1',2'-Epoxypropyl)-5-hydroxy-6-methyl-5,6-dihydro-2H-pyran-2-one* (*aspyrone*, **1**). To a solution of TBS-aspyrone (**17**, 0.3 mmol) and benzoic acid (85 mg, 0.7 mmol) in 4 ml of THF was added 0.5 ml of a TBAF solution (1 M in THF, 0.5 mmol), and the reaction mixture was stirred for 30 min at room temperature. The mixture was then diluted

with water and extracted with ethyl acetate. The extract was washed with aq. $NaHCO_3$ and dried over anhyd. $Na_2SO_4$. Evaporation of the solvent gave a pale yellow oil which was purified by preparative TLC (benzene–ethyl acetate = 1 : 1) and recrystallized from benzene. Yield, 40 mg (57.1%). mp 112–112.5°C (prisms, lit.[10] 110–112°C). HREI-MS *m/z* ($M+H^+$): calcd. for $C_9H_{13}O_4$, 185.0813; found, 185.0805. ($M+H^+-H_2O$): calcd. for $C_9H_{11}O_3$, 167.0708; found, 167.0693. $[\alpha]_D^{20}$ −10.1° ($c=0.32$, $CHCl_3$ lit.[10] −10.5° ($c=0.03$, $CHCl_3$)). IR $\nu_{max}$ (KBr) $cm^{-1}$: 3480, 2930, 1710, 1658, 1390, 1260, 1222, 1060. $^1$H-NMR ($CDCl_3$) $\delta$: 1.42 (3H, d, $J=5.1$ Hz, 3′-$H_3$), 1.48 (3H, d, $J=6.2$ Hz, 6-Me), 2.63 (1H, d, $J=6.4$ Hz, -OH), 2.79 (1H, qd, $J=5.1$, 2.0 Hz, 2′-H), 3.48 (1H, ddd, $J=2.0$, 1.1, 0.7 Hz, 1′-H), 4.22 (1H, ddd, $J=8.8$, 2.2, 0.7 Hz (+$D_2O$), 5-H), 4.36 (1H, dq, $J=8.8$, 6.2 Hz, 6-H), 6.65 (1H, dd, $J=2.5$, 1.1 Hz, 4-H). These spectral patterns were identical with those of natural aspyrone.[7,10]

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