Enantioselective Syntheses of (+)-Acetylphomalactone and (6*R*)-(+)-Goniothalamin from 2-Furylmethanols[1]

Toshio Honda,* the late Tetsuji Kametani, Kazuo Kanai, Yoko Tatsuzaki, and Masayoshi Tsubuki
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Enantioselective syntheses of two 6-substituted 5,6-dihydro-2*H*-pyran-2-ones, (+)-acetylphomalactone and (6*R*)-(+)-goniothalamin, are described which use the kinetic resolution of racemic secondary 2-furylmethanols.

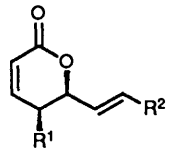
Acetylphomalactone (**1**)[2] is an antimicrobial metabolite from *Aspergillus caespitosus*, and goniothalamin (**2**)[3,†] was originally isolated from the dried bark of *Cryptocarya caloneura*. Owing to the interesting biological activity of 6-substituted 5,6-dihydro-2*H*-pyran-2-ones, and also in order to determine their absolute configuration, these compounds have so far been synthesized in optically active forms by several groups.[4,5] As part of our continuing work on the synthesis of physiologically active natural products using furylmethanols,[6] we were interested in the synthesis of 6-substituted 5,6-dihydro-2*H*-pyran-2-one derivatives using 2-furylmethanols as starting materials, since 2-furylmethanols could be suitable precursors of the pyranones.

We report here enantioselective syntheses of (+)-acetylphomalactone and (6*R*)-(+)-goniothalamin from 2-furylmethanols.[7]

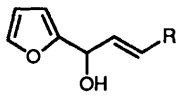
Results and Discussion

Our synthetic strategy was based on the kinetic resolution of racemic secondary 2-furylmethanols by employment of the Sharpless reagent developed by both us[8] and Sato and co-workers.[9] The previous results suggested that pyranones with high optical purity could be obtained when the reaction was carried out only to some degree of conversion below 50%. With this assumption, we could prepare optically active pyranones (**5**) and (**6**) as key intermediates for the synthesis of the title compounds.

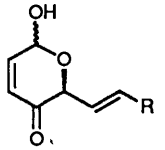
We initially investigated the synthesis of (+)-acetylphomalactone as follows. Kinetic resolution of the furan (**3**)[8] was performed with t-butyl hydroperoxide (TBHP) (0.5 mol equiv.) and catalytic amounts of L-(+)-di-isopropyl tartrate (L-DIPT) (15 mol%) and titanium tetraisopropoxide [$Ti(O^iPr)_4$] (10 mol%) in CH_2Cl_2 in the presence of molecular sieves 3 Å at −30 °C for 6 h to afford the pyranone (**5**) in 32.7% yield. Protection of the lactol (**5**) with ethyl vinyl ether gave the α- and β-ethoxyethyl ethers (**7**) and (**8**) in 71.7 and 12.9% yield, respectively. Reduction of compound (**7**) with sodium borohydride in aqueous tetrahydrofuran (THF) furnished the allyl alcohols (**11**) and (**15**) in 94.1 and 2.9% yield. The stereochemistry of the hydroxy group in compound (**11**) could not be determined at this stage; however, it was assumed to be 3*R* based on the results of similar works by Sammes *et al.*,[10] and was unambiguously determined by the conversion of compound (**11**) into the natural product (+)-acetylphomalactone (**1**) as follows. Mitsunobu inversion[11] of the *anti*-alcohol (**11**) into the *syn*-alcohol (**15**) was effected by treatment of alcohol (**11**) with triphenylphosphine, diethyl azodicarboxylate (DEAD), and benzoic acid, followed by hydrolysis of the corresponding benzoate (**16**) in 84% overall yield. Although conversion of compound (**11**) into the desired acetate (**17**) was examined under Mitsunobu conditions with acetic acid as an acid



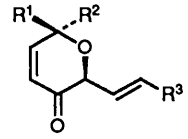
(**1**) R^1 = OAc, R^2 = Me
(**2**) R^1 = H, R^2 = Ph



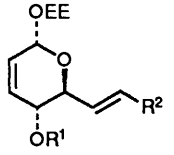
(**3**) R = Me
(**4**) R = Ph



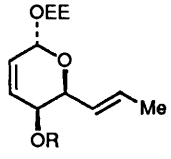
(**5**) R = Me
(**6**) R = Ph



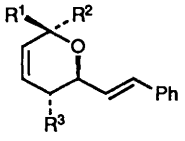
(**7**) R^1 = H, R^2 = OEE, R^3 = Me
(**8**) R^1 = OEE, R^2 = H, R^3 = Me
(**9**) R^1 = H, R^2 = OEE, R^3 = Ph
(**10**) R^1 = OEE, R^2 = H, R^3 = Ph



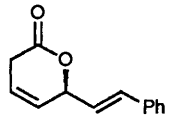
(**11**) R^1 = H, R^2 = Me
(**12**) R^1 = H, R^2 = Ph
(**13**) R^1 = Ac, R^2 = Ph
(**14**) R^1 = C(S)SMe, R^2 = Ph



(**15**) R = H
(**16**) R = Bz
(**17**) R = Ac



(**18**) R^1R^2 = H, OH, R^3 = OAc
(**19**) R^1R^2 = O, R^3 = OAc
(**20**) R^1 = R^3 = H, R^2 = OEE
(**21**) R^1R^2 = H, OH, R^3 = H



(**22**)

OEE = OCH(Me)OEt

† The same compound also occurs in *Goniothalamus andersonii*: J. R. Jewers, J. B. Davis, J. Dougan, A. H. Manchanda, G. Blunden, A. Kyi, and S. Wetchapinan, *Phytochemistry*, 1972, **11**, 2025.

component, only complex mixtures were formed. Finally, acetylation of *syn*-alcohol (**15**) provided compound (**17**), in 91.0% yield, which was oxidized by *m*-chloroperbenzoic acid (MCPBA) and boron trifluoride–diethyl ether[12] to furnish (+)-acetylphomalactone (**1**), m.p. 53.2–54.0 °C (lit.,[2] 52.0–54.0 °C), in 71.8% yield. The optical rotation of compound (**1**) was $[\alpha]_D^{23}$ +306.0° (MeOH), which is in agreement with literature values (+311.8°,[2] +300.0°[4b]).

Our attention was then focused on the synthesis of (6*R*)-(+)-goniothalamin. The furylmethanol (**4**), prepared from 2-lithiofuran and (*E*)-cinnamaldehyde in 95.8% yield, was subjected to kinetic resolution under the same catalytic condition as above to afford the pyranone (**6**) in 19.1% yield. Although the reaction was performed employing a stoicheiometric amount of the titanium–tartrate complex, none of the major products was obtained owing to instability of the styryl moiety. Lactol (**6**) was protected as α-and β-ethoxyethyl ethers (**9**) and (**10**) in 32.0 and 9.4% yield, respectively. Sodium borohydride reduction[10] of compound (**9**) afforded the alcohol (**12**) in 60% yield. In order to remove the hydroxy group, we first examined reductive cleavage of the allyl acetate (**19**). Compound (**12**) was transformed into the acetate (**19**) by successive acetylation, acid hydrolysis, and oxidation with pyridinium chlorochromate (PCC), *via* the acetate (**13**) and the lactol (**18**), in 38.5% yield. Attempts to reduce the acetate (**19**) with either zinc[13] or zinc–copper couple[14] in acetic acid or aqueous acetic acid, thus yielding the expected olefin (**22**), were unsuccessful. We therefore turned out attention to the removal of the hydroxy group by Barton's method.[15] Treatment of alcohol (**12**) with sodium hydride and carbon disulphide followed by methylation with methyl iodide afforded the dithiocarbonate (**14**), in 92.5% yield, which on reaction with tributyltin hydride in toluene in the presence of a catalytic amount of azoisobutyronitrile (AIBN) proceeded smoothly to give the desired compound (**20**) in 82.3% yield. Finally, deprotection of the ethoxyethyl moiety of compound (**20**) furnished the lactol (**21**), in 76.0% yield, which was oxidized with PCC in the presence of sodium acetate, molecular sieves 3 Å, and Celite to produce (6*R*)-(+)-goniothalamin (**2**), m.p. 77.0–79.0 °C; $[\alpha]_D^{25}$ +146.7° ($CHCl_3$) {lit.,* m.p. 81–82 °C; $[\alpha]_D$ +170.3° ($CHCl_3$)} in 72.3% yield. The optical purity of compound (**2**) could be estimated to be ~85% by calculation of the optical rotation. Since no evidence of any racemization could be detected throughout this operation, it may be assumed that the optical purity of compound (**2**) refers to the initial kinetic resolution of the alcohol (**4**).

Thus, we have successfully applied the kinetic resolution of furylmethanols by employing the Sharpless reagent to enantioselective syntheses of (+)-acetylphomalactone and (6*R*)-(+)-goniothalamin.

Experimental

M.p.s were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX GSX 270 instrument, and chemical shifts are reported from internal Me_4Si. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Mixtures of diastereoisomeric pyran derivatives (**7**)–(**17**) and (**20**), which were epimeric at the acetal carbon of the ethoxyethyl group, were used without separation, since the ethoxyethyl group was removed in a later step of the synthesis.

(2S)-6-*Hydroxy*-2-[(E)-*prop*-1-*enyl*]-6H-*pyran*-3(2H)-*one* (**5**).—To a room temperature solution of the allyl alcohol (**3**)[8] (15.0 g, 110 mmol) and L-DIPT (3.87 g, 16.5 mmol) in anhydrous CH_2Cl_2 (300 ml) was added activated molecular sieves 3 Å (4.5 g). The stirred mixture was cooled to −30 °C, treated with $Ti(OPr^i)_4$ (3.0 g, 11.0 mmol), and stirred for 30 min at −30 °C. The reaction mixture was treated with TBHP (3.0M in 2,2,4-trimethyloctane; 18.3 ml, 55.0 mmol) and was then stirred for 6 h at the same temperature. The reaction mixture was poured into prechilled (−20 °C) 3% aqueous acetone (300 ml). The resulting precipitate was removed by filtration through a pad of Celite, and the filtrate was evaporated to give a residue. Purification of the crude product by column chromatography on silica gel with hexane–ethyl acetate (85:15, v/v) as eluant afforded the *pyranone* (**5**) (4.9 g, 32.7%) as a yellow oil; $\nu_{max}(CHCl_3)$ 3 280, 2 850, and 1 690 cm^{-1}; δ 1.89 and 1.90 (3 H, each d, *J* 7.0 Hz, Me), 3.07 (0.7 H, br s, OH), 3.23 (0.3 H, br s, OH), 4.66 (0.3 H, dd, *J* 6.7 and 1.2 Hz, 2-H), 5.10 (0.7 H, d, *J* 6.1 Hz, 2-H), 5.57–5.75 (2 H, m, C*H*=C*H*Me), 5.80–5.95 (1 H, m, 6-H), 6.25 (0.7 H, d, *J* 11.0 Hz, 4-H), 6.29 (0.3 H, dd, *J* 10.4 and 1.2 Hz, 4-H), 7.02 (0.7 H, dd, *J* 10.4 and 3.1 Hz, 5-H), and 7.06 (0.3 H, dd, *J* 11.0 and 1.8 Hz, 5-H); *m/z* 154 (M^+) (Found: M^+, 154.0632. $C_8H_{10}O_3$ requires *M*, 154.0630).

(2S,6S)-*and* (2S,6R)-6-(1-*Ethoxyethoxy*)-2-[(E)-*prop*-1-*enyl*]-6H-*pyran*-3(2H)-*one* (**7**) *and* (**8**).—To a solution of the lactol (**5**) (5.0 g, 32 mmol) in anhydrous CH_2Cl_2 (100 ml) were added ethyl vinyl ether (23.0 g, 320 mmol) and a catalytic amount of pyridinium toluene-*p*-sulphonate at room temperature. The reaction mixture was stirred for 1 h at the same temperature, and poured into water (50 ml). The organic layer was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (92:8) as eluant. The first fraction gave the α-*anomer* (**7**) (4.52 g, 71.7%) as prisms after recrystallization from hexane, m.p. 33.5–35.7 °C (Found: C, 63.25; H, 8.1. $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%); $\nu_{max}(CHCl_3)$ 1 670 cm^{-1}; δ 1.22 and 1.24 (3 H, each t, *J* 7.3 Hz, CH_2Me), 1.39 and 1.42 (3 H, each d, *J* 5.5 Hz, CH*Me*), 1.78 (3 H, d, *J* 6.1 Hz, CH=CH*Me*), 3.47–3.84 (2 H, m, OCH_2Me), 4.83 (0.5 H, d, *J* 6.8 Hz, 2-H), 4.94 (0.5 H, t, *J* 5.5 Hz, 2-H), 4.9–5.1 (1 H, m, OC*H*Me), 5.5–5.7 (2 H, m, C*H*=C*H*Me), 5.78–5.90 (1 H, m, 6-H), 6.10 and 6.12 (1 H, each d, *J* 10.4 Hz, 4-H), and 6.79 and 6.85 (1 H, each dd, *J* 10.4 and 3.7 Hz, 5-H); *m/z* 181 ($M^+ - 45$).

The second fraction gave the β-anomer (**8**) (0.82 g, 12.9%) as an amorphous solid; $\nu_{max}(CHCl_3)$ 1 670 cm^{-1}; δ 1.22 and 1.24 (3 H, each t, *J* 7.3 Hz, CH_2Me), 1.38 and 1.43 (3 H, each d, *J* 5.5 Hz, CH*Me*), 1.72–1.77 (3 H, m, CH=CH*Me*), 3.5–3.9 (2 H, m, OCH_2Me), 4.53 (1 H, d, *J* 5.5 Hz, 2-H), 4.95–5.15 (1 H, m, OC*H*Me), 5.59 (1 H, br s, 6-H), 5.7–5.9 (2 H, m, C*H*=C*H*Me), 6.15 and 6.16 (1 H, each d, *J* 10.4 Hz, 4-H), and 6.85 and 6.86 (1 H, each d, *J* 10.4 Hz, 5-H).

Reduction of the Enone (**7**) *with Sodium Borohydride.*—To a stirred solution of sodium borohydride (0.8 g, 21.1 mmol) in water (100 ml) was added dropwise a solution of the enone (**7**) (4.0 g, 20.6 mmol) in anhydrous THF (20 ml) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature, and brine (20 ml) was added. Concentration of the solvent gave an oil, which was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (80:20) as eluant. The first fraction gave (2S,3R,6S)-6-(1-*ethoxyethoxy*)-2-[(E)-*prop*-1-*enyl*]-3,6-*dihydro*-2H-*pyran*-3-*ol* (**11**) (3.8 g, 94.1%) as an amorphous solid (Found: C, 63.4; H, 9.15. $C_{12}H_{20}O_4$ requires C, 63.15; H, 8.85%); $\nu_{max}(CHCl_3)$ 3 350 cm^{-1}; δ 1.18 and 1.20 (3 H, each t, *J* 7.3 Hz, CH_2Me), 1.33 and

* See reference in footnote †.

1.34 (3 H, each d, *J* 5.5 Hz, CH*Me*), 1.77 (1.5 H, d, *J* 6.1 Hz, CH=CH*Me*), 1.77 (1.5 H, dd, *J* 6.1 and 3.7 Hz, CH=CH*Me*), 3.4–3.8 (2 H, m, OCH_2Me), 3.8–4.05 (2 H, m, 2- and 3-H), 4.84 and 4.91 (1 H, each q, *J* 5.5 Hz, OC*H*Me), 5.13 (0.5 H, br s, 6-H), 5.21 (0.5 H, d, *J* 1.8 Hz, 6-H), 5.4–5.6 (1 H, m, C*H*=CHMe), 5.6–5.9 (2 H, m, 5-H and CH=C*H*Me), and 5.95 (1 H, dd, *J* 10.4 and 1.2 Hz, 4-H); *m/z* 183 ($M^+ - 45$).

The second fraction gave (2S,3S,6S)-6-(1-*ethoxyethoxy*)-2-[(E)-*prop*-1-*enyl*]-3,6-*dihydro*-2H-*pyran*-3-*ol* (**15**) (0.118 g, 2.9%) as prisms after recrystallization from hexane, m.p. 82.5–86.2 °C (Found: C, 63.15; H, 8.8%); ν_{max}($CHCl_3$) 3 370 cm^{-1}; δ 1.19 and 1.21 (3 H, each t, *J* 7.3 Hz, CH_2*Me*), 1.33 and 1.36 (3 H, each d, *J* 5.5 Hz, CH*Me*), 1.77 (3 H, d, *J* 5.5 Hz, CH=CH*Me*), 3.45–3.8 (3 H, m, 3-H and OCH_2Me), 4.42 and 4.51 (1 H, each d, *J* 5.5 Hz, 2-H), 4.88 and 4.95 (1 H, each q, *J* 5.5 Hz, OC*H*Me), 5.23 and 5.30 (1 H, each d, *J* 1.8 Hz, 6-H), 5.65 (1 H, dd, *J* 15.3 and 6.1 Hz, C*H*=CHMe), 5.78–5.92 (2 H, m, 5-H and CH=C*H*Me), and 6.15–6.21 (1 H, m, 4-H); *m/z* 183 ($M^+ - 45$).

(2S,3S,6S)-3-*Benzoyloxy*-6-(1-*ethoxyethoxy*)-2-[(E)-*prop*-1-*enyl*]-3,6-*dihydro*-2H-*pyran* (**16**).—A solution of DEAD (1.7 g, 9.8 mmol) in anhydrous THF (5 ml) was added dropwise to a solution of the alcohol (**11**) (1 g, 4.4 mmol), Ph_3P (2.5 g, 9.5 mmol), and benzoic acid (1.2 g, 9.8 mmol) in anhydrous THF (30 ml) at 0 °C. The reaction mixture was stirred for 3.5 h at room temperature, and the solvent was removed under reduced pressure to give a residue. Ether (20 ml) was added and the white precipitate was filtered off. The filtrate was evaporated to dryness to give a crude product, which was purified by column chromatography on silica gel with hexane–ethyl acetate (90:10) as eluant to afford the *benzoate* (**16**) (1.24 g, 85.0%) as a yellow oil (Found: C, 63.8; H, 7.25. $C_{19}H_{24}O_5$ requires C, 63.65; H, 7.3%); ν_{max}($CHCl_3$) 1 690 cm^{-1}; δ 1.21 and 1.23 (3 H, each t, *J* 7.3 Hz, CH_2*Me*) 1.38 and 1.40 (3 H, each d, *J* 5.5 Hz, CH*Me*), 1.68 (3 H, d, *J* 6.1 Hz, CH=CH*Me*), 3.46–3.86 (2 H, m, OCH_2Me), 4.64 and 4.72 (1 H, each d, *J* 6.7 Hz, 2-H), 4.93 and 5.00 (1 H, each q, *J* 5.5 Hz, OC*H*Me), 5.18 and 5.19 (1 H, each d, *J* 2.1 Hz, 3-H), 5.35 and 5.43 (1 H, each d, *J* 3.1 Hz, 6-H), 5.61 (1 H, dd, *J* 15.3 and 6.7 Hz, C*H*=CHMe), 5.79–5.92 (1 H, m, CH=C*H*Me), 6.00 and 6.07 (1 H, each dd, *J* 9.8 and 3.1 Hz, 5-H), 6.22–6.28 (1 H, m, 4-H), 7.4–7.6 (3 H, m, ArH), and 8.05 (2 H, dd, *J* 7.3 and 1.2 Hz, ArH); *m/z* 243 ($M^+ - 89$).

Hydrolysis of the Benzoate (**16**).—To a room temperature solution of compound (**16**) (1.2 g, 3.6 mmol) in EtOH (30 ml) was added 0.5M-NaOH (14 ml, 7.0 mmol), and the reaction mixture was stirred for 8 h. After dilution with CH_2Cl_2 (70 ml), the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (80:20) as eluant to afford the alcohol (**15**) (0.81 g, 98.8%).

(2S,3S,6S)-3-*Acetoxy*-6-(1-*ethoxyethoxy*)-2-[(E)-*prop*-1-*enyl*]-3,6-*dihydro*-2H-*pyran* (**17**).—A solution of the alcohol (**15**) (118 mg, 0.52 mmol), a catalytic amount of 4-dimethylaminopyridine, and acetic anhydride (105.4 mg, 1.04 mmol) in pyridine (0.5 ml) was stirred for 3 h at room temperature and was then poured into water (5 ml). The crude product was extracted with ethyl acetate, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–ethyl acetate (85:15) as eluant to afford the *acetate* (**17**) (127.1 mg, 91.0%) as an oil (Found: C, 62.5; H, 8.45. $C_{14}H_{22}O_5$ requires C, 62.2; H, 8.2%); ν_{max}($CHCl_3$) 1 690 cm^{-1}; δ 1.19 and 1.21 (3 H, each t, *J* 7.3 Hz, CH_2*Me*), 1.34 and 1.37 (3 H, each d, *J* 5.5 Hz, CH*Me*), 1.73 (3 H, d, *J* 6.1 Hz, CH=CH*Me*), 2.08 (3 H, s, Ac), 3.42–3.83 (2 H, m, OCH_2Me), 4.53 and 4.63 (1 H, each d, *J* 6.7 Hz, 2-H), 4.86–4.99 (2 H, m, 3-H and OC*H*Me), 5.31 and 5.38 (1 H, each d, *J* 3.1 Hz, 6-H), 5.51 (1 H, dd, *J* 15.3 and 6.1 Hz, C*H*=CHMe), 5.76–5.89 (1 H, m, CH=C*H*Me), 5.95 and 6.03 (1 H, each dd, *J* 9.7 and 3.1 Hz, 5-H), and 6.09–6.15 (1 H, m, 4-H).

(+)-*Acetylphomalactone* (**1**).—To a solution of the lactol (**17**) (80 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (3 ml) at 0 °C was added portionwise MCPBA (70% purity; 78.6 mg, 0.32 mmol), and the reaction mixture was stirred for 1.5 h at room temperature. The mixture was poured into water (3 ml) and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (85:15) as eluant to afford the lactone (**1**) (41.3 mg, 71.8%) as an amorphous solid after crystallization from hexane–ethyl acetate, m.p. 53.2–54.0 °C (lit.,[2] 52.0–54.0 °C); $[\alpha]_D^{23}$ +306.0° (*c* 0.9, MeOH) {lit.,[2] $[\alpha]_D$ +311.8° (*c* 1.02, MeOH)}. Its spectroscopic data were identical with those reported.[2,4]

1-(2-*Furyl*)*cinnamyl Alcohol* (**4**).—To a solution of 2-lithiofuran [prepared from furan (10.4 ml, 0.16 mol) and 1.5M-BuLi (72 ml, 0.14 mol) in THF (55 ml)] at −78 °C was added slowly a solution of (*E*)-cinnamaldehyde (9.7 ml, 96 mmol) in THF (50 ml), and the reaction mixture was stirred for 30 min. After addition of brine (20 ml), the mixture was concentrated to give a brown oil, which was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (85:15) as eluant to afford the furyl alcohol (**4**) (18.4 g, 95.8%) as a red oil; δ 2.37–2.55 (1 H, br s, OH), 5.39 (1 H, d, *J* 6.1 Hz, C*H*OH), 6.30 (1 H, d, *J* 3.7 Hz, 3-H), 6.35 (1 H, dd, *J* 3.7 and 1.8 Hz, 4-H), 6.45 (1 H, dd, *J* 15.9 and 6.1 Hz, C*H*=CHPh), 6.73 (1 H, d, *J* 15.9 Hz, CH=C*H*Ph), and 7.15–7.45 (6 H, m, 5-H and Ph).

(2S)-6-*Hydroxy*-2-[(E)-*styryl*]-6H-*pyran*-3(2H)-*one* (**6**).—Kinetic resolution of compound (**4**) was performed on a 54 mmol scale (10.7 g) at −25 °C according to the preparation of compound (**3**). After 15 h, a freshly prepared solution of $FeSO_4 \cdot 7H_2O$ (4.43 g, 16 mmol) and tartaric acid (15.8 g, 110 mmol) in deionized water (50 ml) was added to the reaction mixture at −25 °C and the resulting mixture was stirred for 30 min at room temperature. The organic layer was separated, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (80:20), as eluant to afford the *pyranone* (**6**) (2.2 g, 19.1%) as a brown oil; ν_{max}($CHCl_3$) 3 350 and 1 680 cm^{-1}; δ 3.8–4.1 (0.7 H, br s, OH), 4.1–4.23 (0.3 H, br s, OH), 4.75 (0.3 H, br d, *J* 6.1 Hz, 2-H), 5.23 (0.7 H, dd, *J* 5.5 and 1.8 Hz, 2-H), 5.72 (1 H, br s, 6-H), 6.14 (0.7 H, d, *J* 10.4 Hz, 4-H), 6.18 (0.3 H, dd, *J* 10.4 and 1.2 Hz, 4-H), 6.36 (0.7 H, dd, *J* 16.5 and 5.5 Hz, C*H*=CHPh), 6.44 (0.3 H, dd, *J* 16.5 and 6.1 Hz, C*H*=CHPh), 6.72 (1 H, dd, *J* 16.5 and 1.8 Hz, CH=C*H*Ph), 6.90 (0.7 H, dd, *J* 10.4 and 3.1 Hz, 5-H), 6.94 (0.3 H, dd, *J* 10.4 and 1.8 Hz, 5-H), and 7.15–7.45 (5 H, m, Ph); *m/z* 216 (M^+) (Found: M^+, 216.0781. $C_{13}H_{12}O_3$ requires *M*, 216.0786).

(2S,6S)-*and* (2S,6R)-6-(1-*Ethoxyethoxy*)-2-[(E)-*styryl*]-6H-*pyran*-3(2H)-*one* (**9**) *and* (**10**).—Compounds (**9**) and (**10**) were prepared from the lactol (**6**) by the same procedure as for the preparation of compounds (**7**) and (**8**), in 32.0 and 9.4% yield, respectively. *Compound* (**9**) was an oil; ν_{max}($CHCl_3$) 1 680 cm^{-1}; δ 1.23 and 1.25 (3 H, each t, *J* 6.7 Hz, CH_2*Me*), 1.42 and 1.46 (3 H, each d, *J* 5.5 Hz, CH*Me*), 3.48–3.88 (2 H, m, OCH_2Me), 5.00 and 5.09 (1 H, each q, *J* 5.5 Hz, OC*H*Me), 5.11 and 5.21 (1 H, each dd, *J* 5.5 and 1.8 Hz, 2-H), 5.61 and 5.65

(1 H, each d, *J* 3.7 Hz, 6-H), 6.15 and 6.17 (1 H, each d, *J* 10.4 Hz, 4-H), 6.41 and 6.43 (1 H, dd, *J* 15.9 and 5.5 Hz, C*H*=CHPh), 6.74 (1 H, d, *J* 15.9 Hz, CH=C*H*Ph), 6.85 and 6.91 (1 H, each dd, *J* 10.4 and 3.7 Hz, 5-H), and 7.22–7.43 (5 H, m, Ph); *m/z* 288 (M^+) (Found: M^+, 288.1356. $C_{13}H_{12}O_3$ requires *M*, 288.1362).

Compound (**10**) was an oil; $\nu_{max}(CHCl_3)$ 1 680 cm^{-1}; δ 1.18 and 1.24 (3 H, each t, *J* 7.0 Hz, CH_2Me), 1.38 and 1.45 (3 H, each d, *J* 5.5 Hz, CH*Me*), 3.4–3.9 (2 H, m, OCH_2Me), 4.77 and 4.92 (1 H, d, *J* 6.7 Hz, 2-H), 5.03 and 5.15 (1 H, each q, *J* 5.5 Hz, OC*H*Me), 5.63–5.73 (1 H, m, 6-H), 6.1–6.3 (1 H, m, 4-H), 6.47 and 6.50 (1 H, each dd, *J* 15.9 and 6.7 Hz, C*H*=CHPh), 6.70 and 6.71 (1 H, each d, *J* 15.9 Hz, CH=C*H*Ph), 6.90 and 6.95 (1 H, dd, *J* 10.4 and 2.4 Hz, 5-H), and 7.2–7.45 (5 H, m, Ph).

(2S,3R,6S)-6-(1-*Ethoxyethoxy*)-2-[(E)-*styryl*]-3,6-*dihydro*-2H-*pyran*-3-*ol* (**12**).—To a stirred solution of the enone (**9**) (770 mg, 2.67 mmol) in THF (5 ml) at 0 °C was added dropwise a solution of sodium borohydride (106.4 mg, 2.79 mmol) in water (15 ml), and the reaction mixture was stirred for 3 h at the same temperature. After dilution with brine (20 ml) the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (80:20) as eluant to afford the alcohol (**12**) (530 mg, 60.0%) as an orange oil; $\nu_{max}(CHCl_3)$ 3 520 cm^{-1}; δ 1.19 and 1.21 (3 H, each t, *J* 7.3 Hz, CH_2Me), 1.37 and 1.38 (3 H, each d, *J* 5.5 Hz, CH*Me*), 1.9–2.2 (1 H, br s, OH), 3.38–3.87 (2 H, m, OCH_2Me), 4.0–4.1 (1 H, br s, 3-H), 4.27 and 4.33 (1 H, each dd, *J* 9.2 and 6.7 Hz, 2-H), 4.91 and 4.98 (1 H, each q, *J* 5.5 Hz, OC*H*Me), 5.24 and 5.33 (1 H, each br s, 6-H), 5.73 and 5.80 (1 H, each dt, *J* 10.4 and 2.4 Hz, 5-H), 6.01 (1 H, dd, *J* 10.4 and 1.2 Hz, 4-H), 6.30 (1 H, ddd, *J* 15.9, 6.7, and 1.8 Hz, C*H*=CHPh), 6.74 (1 H, d, *J* 15.9 Hz, CH=C*H*Ph), and 7.22–7.43 (5 H, m, Ph).

(2S,3R,6S)-3-*Acetoxy*-6-(1-*ethoxyethoxy*)-2-[(E)-*styryl*]-3,6-*dihydro*-2H-*pyran* (**13**).—The same procedure as for compound (**15**) was applied to the alcohol (**12**) (530 mg, 1.6 mmol) to afford the acetate (**13**) (400 mg, 67.0%) as a yellow oil: $\nu_{max}(CHCl_3)$ 1 710 cm^{-1}; δ 1.22 (3 H, t, *J* 7.3 Hz, CH_2Me), 1.38 (3 H, d, *J* 4.9 Hz, CH*Me*), 2.03 (3 H, s, Ac), 3.44–3.84 (2 H, m, OCH_2Me), 4.44–4.57 (1 H, m, 2-H), 4.47 and 4.54 (1 H, each dd, *J* 9.2 and 6.7 Hz), 4.91 and 4.98 (1 H, each q, *J* 4.9 Hz, OC*H*Me), 5.24–5.32 [1.5 H, m, 3-H and (half of) 6-H], 5.37 (0.5 H, br s, 6-H), 5.78–5.98 (2 H, m, 4- and 5-H), 6.16 (1 H, dd, *J* 15.9 and 6.7 Hz, C*H*=CHPh), 6.77 (1 H, d, *J* 15.9 Hz, CH=C*H*Ph), and 7.2–7.4 (5 H, m, Ph).

(5R,6S)-5-*Acetoxy*-6-[(E)-*styryl*]-5,6-*dihydro*-2H-*pyran*-2-*ol* (**18**).—A solution of compound (**13**) (40 mg, 0.107 mmol) and 2M-HCl (0.4 ml, 0.8 mmol) in THF (1 ml) was stirred at 0 °C for 10 h, and then poured into brine (3 ml). The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (80:20) as eluant to afford the lactol (**18**) (27 mg, 99.0%) as an oil; δ 2.04 (3 H, s, Ac), 2.87 and 3.25 (1 H, each br s, OH), 4.55 and 4.58 (1 H, each d, *J* 7.9 Hz, 6-H), 5.25–5.36 [1.5 H, m, 5-H and (half of) 2-H], 5.50 (0.5 H, br s, 2-H), 5.9–6.35 (3 H, m, 3- and 4-H, and C*H*=CHPh), 6.70 (1 H, each d, *J* 15.9 Hz, CH=C*H*Ph), and 7.2–7.4 (5 H, m, Ph).

(5R,6S)-5-*Acetoxy*-6-[(E)-*styryl*]-5,6-*dihydro*-2H-*pyran*-2-*one* (**19**).—To a stirred suspension of PCC (100 mg, 0.465 mmol) and anhydrous sodium acetate (76 mg, 0.93 mmol) in anhydrous CH_2Cl_2 (1.5 ml) at 0 °C was added a solution of the lactol (**18**) (40 mg, 0.155 mmol) in CH_2Cl_2 (0.5 ml), and the resulting mixture was stirred for 1 h at room temperature. After dilution with ether (20 ml), the organic layer was decanted and evaporated. The residue was passed through a short column on silica gel with ethyl acetate as eluant. Purification of the crude product by column chromatography on silica gel with hexane–ethyl acetate (80:20) as eluant afforded the lactone (**19**) (23 mg, 58%) as an amorphous solid after crystallization from hexane–diethyl ether, m.p. 113–114 °C; $[\alpha]_D^{25}$ −109.4° (*c* 0.86, $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 700 cm^{-1}; δ 2.12 (3 H, s, Ac), 5.12 (1 H, dd, *J* 6.7 and 6.1 Hz, 6-H), 5.45 (1 H, dd, *J* 6.1 and 3.7 Hz, 5-H), 6.15 (1 H, dd, *J* 15.9 and 6.7 Hz, C*H*=CHPh), 6.18 (1 H, d, *J* 9.8 Hz, 3-H), 6.74 (1 H, d, *J* 15.9 Hz, CH=C*H*Ph), 6.82 (1 H, dd, *J* 9.8 and 3.7 Hz, 4-H), and 7.2–7.4 (5 H, m, Ph); *m/z* 198 (M^+ − 60).

(2S,3R,6S)-6-(1-*Ethoxyethoxy*)-3-*methylthio*(*thiocarbonyl*)-*oxy*-2-[(E)-*styryl*]-3,6-*dihydro*-2H-*pyran* (**14**).—A mixture of the alcohol (**12**) (300 mg, 1.04 mmol), sodium hydride (60% in mineral oil; 233 mg, 2.07 mmol), and imidazole (21.4 mg, 0.3 mmol) in anhydrous THF (8 ml) was refluxed for 1.5 h. Carbon disulphide (0.29 ml, 4.8 mmol) was added to the mixture, which was refluxed for a further 30 min. Methyl iodide (0.32 ml, 4.98 mmol) was added, and the mixture was further heated at reflux for 30 min. After addition of brine (1 ml), the mixture was concentrated to give a residue, which was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (95:5) as eluant to afford *compound* (**14**) (364 mg, 92.5%) as an orange oil; δ 1.20 and 1.23 (3 H, each t, *J* 7.3 Hz, CH_2Me), 1.40 and 1.41 (3 H, each d, *J* 5.5 Hz, CH*Me*), 2.53 (3 H, s, CS_2Me), 3.45–3.9 (2 H, m, OCH_2Me), 4.68 and 4.74 (1 H, each dd, *J* 8.6 and 6.7 Hz, 2-H), 4.85–5.0 (1 H, m, 3-H), 4.93 and 5.00 (1 H, each q, *J* 5.5 Hz, OC*H*Me), 5.33 and 5.41 (1 H, br s, 6-H), 5.86 and 5.92 (1 H, each dt, *J* 11.0 and 1.8 Hz, 5-H), 6.09 (1 H, dd, *J* 11.0 and 1.2 Hz, 4-H), 6.18 (1 H, dd, *J* 16.2 and 6.7 Hz, C*H*=CHPh), 6.70 (1 H, d, *J* 16.2 Hz, CH=C*H*Ph), 7.2–7.4 (5 H, m, Ph); *m/z* 380 (M^+) (Found: M^+, 380.1117. $C_{19}H_{24}O_4S_2$ requires *M*, 380.1117).

(2R,6S)-6-(1-*Ethoxyethoxy*)-2-[(E)-*styryl*]-3,6-*dihydro*-2H-*pyran* (**20**).—A solution of compound (**14**) (100 mg, 0.26 mmol), a catalytic amount of AIBN, and tributyltin hydride (0.24 ml, 0.84 mmol) in toluene (4.5 ml) was refluxed for 20 min. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (95:5) as eluant to afford compound (**20**) (59.5 g, 82.3%) as a yellow oil; δ 1.20 and 1.23 (3 H, each t, *J* 7.3 Hz, CH_2Me), 1.35–1.45 (3 H, m, CH*Me*), 2.0–2.5 (2 H, m, 3-H_2), 3.45–3.9 (2 H, m, OCH_2Me), 4.5–4.7 (1 H, m, 2-H), 4.94 and 5.03 (1 H, each q, *J* 5.5 Hz, OC*H*Me), 5.26 and 5.36 (1 H, each br s, 6-H), 5.7–5.9 (2 H, m, 4- and 5-H), 6.18–6.3 (1 H, m, C*H*=CHPh), 6.62 (1 H, d, *J* 15.9 Hz, CH=C*H*Ph), and 7.2–7.4 (5 H, m, Ph).

(6R)-6-[(E)-*Styryl*]-5,6-*dihydro*-2H-*pyran*-2-*ol* (**21**).—The same procedure as for compound (**13**) was applied to compound (**20**) (17.1 mg, 0.06 mmol) to afford the *lactol* (**21**) (9.6 mg, 76%) as a yellow oil; $\nu_{max}(CHCl_3)$ 3 480 cm^{-1}; δ 2.1–2.55 (2 H, m, 5-H_2), 2.82 and 2.97 (1 H, each br s, OH), 4.95 and 5.02 (1 H, each br s, 6-H), 5.40 and 5.47 (1 H, each br s, 2-H), 5.65–5.9 (2 H, m, 3- and 4-H), 6.15–6.3 (1 H, m, C*H*=CHPh), 6.63 and 6.66 (1 H, each d, *J* 15.9 Hz, CH=C*H*Ph), and 7.2–7.4 (5 H, m, Ph); *m/z* 202 (M^+) (Found: M^+, 202.0992. $C_{13}H_{14}O_2$ requires *M*, 202.0992).

(6R)-(+)-*Goniothalamin* (**2**).—To a stirred suspension of PCC (26 mg, 0.104 mmol), anhydrous sodium acetate (24 mg, 0.207 mmol), activated molecular sieves 3 Å (20 mg), and Celite

(50 mg) in anhydrous CH_2Cl_2 (0.5 ml) at 0 °C was added a solution of the lactol (**21**) (7 mg, 0.035 mmol) in CH_2Cl_2 (0.5 ml), and the resulting mixture was stirred for 2 h at room temperature. After dilution with diethyl ether (15 ml), the organic layer was decanted and evaporated. The residue was passed through a short column of silica gel with ethyl acetate as eluant. Purification of the crude product by column chromatography on silica gel with hexane–ethyl acetate (85:15) as eluant afforded the lactone (**2**) (5 mg, 72.3%) as an amorphous solid after crystallization from hexane–diethyl ether, m.p. 77–79 °C (lit.,* 81–82 °C); $[\alpha]_D^{25}$ +146.7° (*c* 0.03, $CHCl_3$) {lit.,* $[\alpha]_D^{25}$ +170.3° (*c* 1.38, $CHCl_3$)}. Its spectroscopic data were identical with those reported.[3]

* See ref. in footnote †.

Acknowledgements

We thank Mrs T. Ogata and Miss Y. Takahashi, Hoshi University, for microanalyses and spectral measurement.

References

1 This is considered Part 1200 of the series 'Studies on the Syntheses of Heterocyclic and Natural Compounds,' by Professor Tetsuji Kametani. Part 1199, K. Shishido, A. Yamashita, K. Hiroya, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, in press.
2 S. Mizuba, K. Lee, and J. Jiu, *Can. J. Microbiol.*, 1975, **21**, 1781.
3 J. R. Hlubucek and A. V. Robertson, *Aust. J. Chem.*, 1967, **20**, 2199.
4 For syntheses of compound (**1**) in an optically active form, see: (*a*) S. Lesage and A. S. Perlin, *Can. J. Chem.*, 1978, **56**, 2889; (*b*) T. Murayama, T. Sugiyama, and K. Yamashita, *Agric. Biol. Chem.*, 1987, **51**, 2055.
5 For syntheses of compound (**2**) in an optically active form, see H. H. Meyer, *Liebigs Ann. Chem.*, 1979, 484; B. O'Connor and G. Just, *Tetrahedron Lett.*, 1986, **27**, 5201; F. Bennett and D. W. Knight, *ibid.*, 1988, **29**, 4625.
6 T. Kametani, M. Tsubuki, K. Higurashi, and T. Honda, *J. Org. Chem.*, 1986, **51**, 2932; T. Kametani, M. Kigawa, M. Tsubuki, and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1503; T. Kametani, K. Keino, M. Kigawa, M. Tsubuki, and T. Honda, *Tetrahedron Lett.*, 1989, **30**, 3141.
7 A preliminary account of some of this work has been published; T. Kametani, Y. Tatsuzaki, M. Tsubuki, and T. Honda, *Heterocycles*, 1989, **29**, 1247.
8 T. Kametani, M. Tsubuki, Y. Tatsuzaki, and T. Honda, *Heterocycles*, 1988, **27**, 2107; *J. Chem. Soc., Perkin Trans. 1*, accepted for publication.
9 M. Kusakabe, Y. Kitano, Y. Kobayashi, and F. Sato, *J. Org. Chem.*, 1989, **29**, 2085.
10 P. G. Sammes and D. Thetford, *J. Chem. Soc., Perkin Trans. 1*, 1988, 111.
11 O. Mitsunobu, *Synthesis*, 1981, 1.
12 P. Jarglis and F. W. Lichtenthaler, *Tetrahedron Lett.*, 1982, **23**, 3781.
13 B. D. Roth and W. H. Roark, *Tetrahedron Lett.*, 1988, **23**, 1255.
14 Y. Ichikawa, M. Isobe, D.-L. Bai, and T. Goto, *Tetrahedron*, 1987, **43**, 4737.
15 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.

Paper 9/04798K
Received 9*th November* 1989
Accepted 20*th December* 1989