A Simple and Efficient Total Synthesis of a Styryllactone, 7-*epi*-Goniodiol[1]

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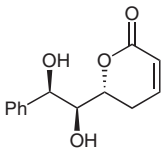
Abstract: Regioselective mono-dihydroxylation, Red-Al reduction, and *cis*-Horner–Wadsworth–Emmons reactions have been efficiently performed as key steps in the synthesis of 7-*epi*-goniodiol, isolated from *Goniothalamus leiocarpus*.

Key words: styryllactones, 7-*epi*-goniodiol, natural product, asymmetric dihydroxylation, Horner–Wadsworth–Emmons reaction

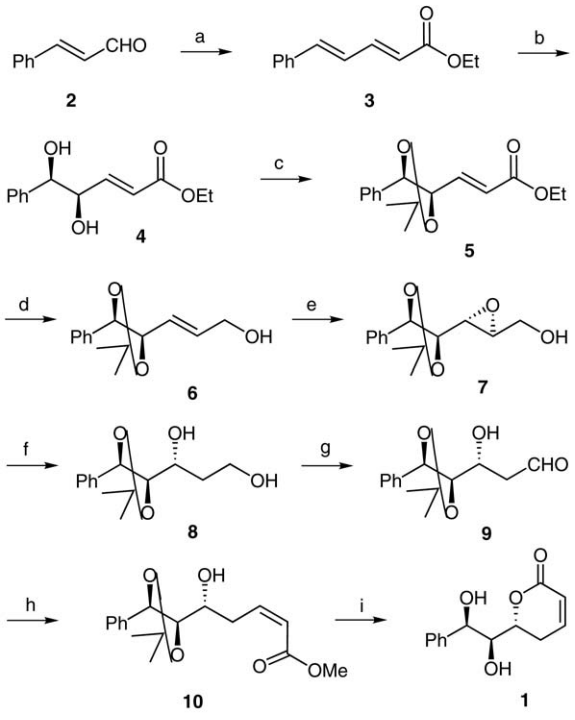
The styryllactones[2,3] are natural heterocyclic compounds isolated from *Goniothalamus gigantus* that have been found to possess excellent antitumoral[4] and antifungal properties as well as antibiotic potential. They have been traditionally used for the treatment of edema and rheumatism.[5] Other general applications include their use as painkillers and mosquito repellants.[6] Because of their cytotoxicity as well as the fascinating and novel array of structures, styryllactones have attracted the attention of synthetic organic chemists.[7,8] Recently, a novel styryllactone, 7-*epi*-goniodiol (**1**) was isolated from the ethanolic extract of stem barks of *Goniothalamus leiocarpus* (Annonaceae), a tropical plant wide spread in the south of the Yunnan province in China (Figure 1).[9] This lactone exhibits selective activity in tests using the tryptan blue dye exclusion method, and showed strong inhibition against HL-60 in concentrations as low as 1 μg/mL. The structure assigned to 7-*epi*-goniodiol is similar to (+)-goniodiol except for the configuration at the C7 chiral center. Very few approaches to the synthesis of 7-*epi*-goniodiol[10] have been reported in the literature. As part of our continuing work on the synthesis of naturally occurring lactones,[11] we herein report the asymmetric total synthesis of 7-*epi*-goniodiol starting from cinnamaldehyde; the synthesis involves regioselective mono-dihydroxylation, Red-Al reduction, and *cis*-Wittig reactions as key steps.



7-*epi*-goniodiol (**1**)

Figure 1

Our synthesis began with inexpensive cinnamaldehyde (**2**) (Scheme 1). The aldehyde **2** was subjected to the Wittig reaction with a two-carbon ylide to afford the unsaturated ester **3** in 90% yield. Regioselective mono-dihydroxylation[12] of conjugated diene **3** produced exclusively enediol **4** in 78% yield. After protection of the 1,2-*syn*-diol as an acetonide, the resulting ester **5** was then reduced with diisobutylaluminum hydride to afford allyl alcohol **6**. In the next step, the allylic alcohol **6** was subjected to Sharpless asymmetric epoxidation using (+)-diethyl L-tartrate, *tert*-butyl hydroperoxide, and titanium(IV) isopropoxide in dichloromethane to furnish the desired epoxy alcohol **7** in 87% yield. The epoxy alcohol **7** was regioselectively reduced with Red-Al [sodium bis(2-methoxyethoxy)aluminum hydride][13] to give the corresponding 1,3-diol **8**.



Scheme 1 *Reagents and conditions*: (a) $Ph_3P{=}CHCO_2Et$, benzene, r.t., 4 h, 90%; (b) AD-mix-β, $MsNH_2$ (cat.), *t*-BuOH–H_2O (1:1), 18 h, 78%; (c) $Me_2C(OMe)_2$, PPTS, acetone, 0 °C to r.t., 12 h, 95%; (d) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 84%; (e) (+)-L-DET, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, MS 4A, CH_2Cl_2, –20 °C, 3 h, 87%; (f) Red-Al, THF, –15 °C then r.t., 3 h, 80%; (g) IBX, CH_2Cl_2, DMSO, 0 °C to r.t., 2 h, 60%; (h) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, THF, –78 °C, 84%; (i) benzene, PTSA, r.t., 6 h, 73%.

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The oxidation of primary hydroxy group in compound **8** using 2-iodoxybenzoic acid (IBX) in dichloromethane and dimethyl sulfoxide afforded the aldehyde **9** in 60% yield. The aldehyde **9** was subjected to Still's modification of the Horner–Wadsworth–Emmons[14] reaction using sodium hydride and bis(2,2,2-trifluoroethyl) [(methoxycarbonyl)methyl]phosphonate in anhydrous tetrahydrofuran at –78 °C to afford the α,β-unsaturated ester **10**, predominantly as the *Z*-isomer, as characterized by ^{1}H and ^{13}C NMR spectroscopy, in 84% yield. In the ^{1}H NMR spectrum, protons resonated at δ = 5.83 as a doublet of doublets (*J* = 1.5, 11.7 Hz) and at δ = 6.32 as doublet of triplets (*J* = 7.8, 11.7 Hz) confirming the *Z*-geometry of the double bond. The cyclization of the hydroxy ester was achieved in refluxing benzene using a catalytic amount of 4-toluenesulfonic acid[15] to afford the target molecule **1** in 73% yield.

In conclusion, we have described a novel and highly efficient methodology for the synthesis of a styryllactone, 7-*epi*-goniodiol, in nine steps.

Reactions were conducted under an N_2 atmosphere using anhyd solvents such as CH_2Cl_2, THF, CCl_4, benzene, or EtOAc. All reactions were monitored by TLC using silica-coated plates and visualizing under UV light. Petroleum ether had bp 60–80 °C. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or with a double-ended needle. Evaporation of solvents was performed at reduced pressure, using a Buchi rotary evaporator. ^{1}H NMR spectra were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) in $CDCl_3$ with TMS as internal standard. MS spectra were recorded under electron impact at 70 eV on LC-MSD (Agilent technologies). Column chromatography was performed on silica gel (60–120 mesh, Acme Chemical Co., India). TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with JASCO DIP-370 polarimeter at 20 °C.

Ethyl (2*E*,4*E*)-5-Phenylpenta-2,4-dienoate (3)

To a stirred soln of cinnamaldehyde (6 g, 45.4 mmol) in anhyd benzene (50 mL) was added ethyl (triphenylphosphoranylidene)acetate (17.3 g, 49.9 mmol) at r.t. under inert atmosphere. The mixture was stirred at r.t. for 4 h. Solvent was removed under reduced pressure and residue was purified by column chromatography (silica gel, hexane–EtOAc, 95:5) to afford the unsaturated ester **3** as a pale yellow liquid; yield: 8.2 g (90%).

IR (KBr): 3441, 2992, 1738, 1634, 1462, 1371, 1057 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.03 Hz, 3 H), 4.23 (d, *J* = 7.03 Hz, 2 H), 5.96 (d, *J* = 15.6 Hz, 1 H), 6.86 (dd, *J* = 20.3, 15.6 Hz, 1 H), 6.88–6.91 (m, 1 H), 7.32 (d, *J* = 7.03 Hz, 1 H), 7.22–7.50 (m, 5 H).

LC-MS (EI): *m*/*z* = 225 (M^+ + Na).

Ethyl (*E*,4*R*,5*R*)-4,5-Dihydroxy-5-phenylpent-2-enoate (4)

To a stirred soln of *t*-BuOH (5 mL), H_2O (5 mL), and AD-mix-β (6.9 g) was added $MsNH_2$ (0.23 g, 2.4 mmol). The mixture was stirred at r.t. until both phases were clear, and then cooled to 0 °C. Alkene **3** (1 g, 4.9 mmol) was added in one portion and the heterogeneous slurry was stirred vigorously at 0 °C for ~18 h, until TLC revealed the absence of the starting material. The reaction was quenched at 0 °C by addition of Na_2SO_3 and then warmed to r.t. and stirred for 30 min. The mixture was extracted with EtOAc (3 ×). The organic layer was washed with 2 M KOH and then dried (anhyd Na_2SO_4). Removal of the solvent and purification by column chromatography (silica gel) afforded the diol compound **4** as a liquid; yield: 0.9 g (78%).

$[\alpha]_D^{25}$ +34.3 (*c* 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.3 Hz, 3 H), 4.15 (q, *J* = 13.9, 7.3 Hz, 2 H), 4.32–4.39 (m, 1 H), 4.48–4.55 (d, *J* = 6.5 Hz, 1 H), 6.06 (d, *J* = 15.5 Hz, 1 H), 6.69 (dd, *J* = 15.5, 4.0 Hz, 1 H), 7.27–7.39 (m, 5 H).

LC-MS (EI): *m*/*z* = 259 (M^+ + Na).

Ethyl (*E*)-3-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]prop-2-enoate (5)

To a soln of diol **4** (4 g, 16.9 mmol) in anhyd acetone (20 mL), 2,2-dimethoxypropane (3.1 mL, 25.4 mmol), and PPTS (0.4 g, 1.69 mmol) were added at 0 °C. The mixture was stirred at r.t. for 12 h. $NaHCO_3$ was added to neutralize PPTS and filtered. Removal of solvent and purification by column chromatography (silica gel) afforded the acetonide **5** as a liquid; yield: 4.4 g (95%).

$[\alpha]_D^{25}$ +65.4 (*c* 0.5, $CHCl_3$).

IR (KBr): 3453, 2975, 1746, 1628, 1379, 1052, 963 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 6.9 Hz, 3 H), 1.52 (s, 3 H), 1.57 (s, 3 H), 4.18 (q, *J* = 13.8, 6.9 Hz, 2 H), 4.27 (dd, *J* = 9.5, 5.2 Hz, 1 H), 4.64 (d, *J* = 8.6 Hz, 1 H), 6.02 (d, *J* = 14.7 Hz, 1 H), 6.85 (dd, *J* = 15.6, 5.2 Hz, 1 H), 7.30–7.38 (m, 5 H).

^{13}C NMR (75 MHz $CDCl_3$): δ = 165.9, 142.5, 136.4, 128.5, 126.5, 123.2, 110.0, 82.8, 82.3, 60.5, 27.1, 14.7.

LC-MS (EI): *m*/*z* = 299 (M^+ + Na).

(*E*)-3-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]prop-2-en-1-ol (6)

To a stirred soln of ester **5** (4 g, 14.4 mmol) in anhyd CH_2Cl_2 (15 mL) at 0 °C was added DIBAL-H (1.4 M in hexane; 15.5 mL, 21.7 mmol) dropwise over a period of 10 min under N_2. The mixture was stirred at this temperature for 2 h, anhyd MeOH (3 mL) was added and the mixture was allowed to warm to r.t. Sat. aq potassium sodium tartrate (10 mL) was added and the resulting mixture was stirred vigorously until two layers separated. The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with H_2O and brine and dried (anhyd Na_2SO_4). Removal of solvent in vacuo and purification by column chromatography afforded epoxy allyl alcohol **6** as a viscous liquid; yield: 2.8 g (84%).

$[\alpha]_D^{25}$ +12.5 (*c* 1, $CHCl_3$).

IR (KBr): 3446, 2963, 1641, 1476, 1369, 1059, 976 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.51 (s, 3 H), 1.56 (s, 3 H), 4.09–4.20 (m, 3 H), 4.60 (d, *J* = 8.5 Hz, 1 H), 5.66–5.91 (m, 2 H), 7.22–7.42 (m, 5 H).

LC-MS (EI): *m*/*z* = 257 (M^+ + Na).

{(2*S*,3*R*)-3-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]oxiran-2-yl}methanol (7)

Anhyd CH_2Cl_2 (50 mL) was added to 4 Å powdered, activated molecular sieves (2 g) and the suspension mixture was cooled to –20 °C. (+)-L-DET (0.52 g, 2.5 mmol) and Ti(O-*i*-Pr)$_4$ (0.75 mL, 2.5 mmol) were added subsequently with stirring and the resulting mixture was stirred at –20 °C for 30 min. Allyl alcohol **6** (3 g, 12.8 mmol) in anhyd CH_2Cl_2 (15 mL) was added and the resulting mixture was stirred for a further 30 min at –20 °C. *t*-BuOOH (3.3 M in toluene; 6.0 mL, 19.2 mmol) was then added and the resulting mixture was stirred at this temperature for 3 h. When the reaction was complete (TLC) it was warmed to 0 °C, quenched with H_2O (5 mL) and stirred at 0 °C for 1 h. 30% aq NaOH soln saturated with NaCl

(10 mL) was then added and the resulting mixture was stirred vigorously at 0 °C for a further 30 min. The resulting mixture was vacuum filtered through Celite and the filter cake was washed well with CH_2Cl_2. The organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL); the combined organic phases were washed with brine and dried (anhyd Na_2SO_4). Removal of solvent under reduced pressure and purification by chromatography (silica gel) gave the epoxide **7** as a viscous liquid; yield: 2.7 g (87%).

$[\alpha]_D^{25}$ –64.12 (*c* 1.2, $CHCl_3$).

IR (KBr): 3447, 2987, 1743, 1631, 1455, 1376, 1216, 1055 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 3 H), 1.52 (s, 3 H), 3.08–3.05 (m, 1 H), 3.18 (dd, *J* = 2.26, 6.04 Hz, 1 H), 3.69 (dd, *J* = 5.28, 8.30 Hz, 1 H), 3.92 (dt, *J* = 2.26, 2.08 Hz, 1 H), 4.91 (d, *J* = 7.55 Hz, 1 H), 7.40–7.28 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7, 26.9, 54.6, 56.4, 60.9, 77.1, 81.1, 81.7, 110.3, 126.6, 128.6, 128.5, 128.6, 137.8.

LC-MS (EI): *m*/*z* = 273 (M^+ + Na).

(1*R*)-1-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]propane-1,3-diol (8)

To stirred soln of epoxide **7** (2 g, 8 mmol) in anhyd THF (10 mL), Red-Al (4.5 mL, 16 mmol) was added dropwise over a period of 10 min under N_2 atmosphere at –15 °C. The mixture was stirred at r.t. for 3 h. When the reaction was complete (TLC), the mixture was cooled to 0 °C and quenched with H_2O (3 mL) and 15% NaOH soln (3 mL). The mixture was then diluted with CH_2Cl_2, filtered through Celite and washed with CH_2Cl_2. The organic layer was then washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. Purification by chromatography (silica gel) gave the diol **8** as a viscous liquid; yield: 1.6 g (80%).

$[\alpha]_D^{25}$ –11.4 (*c* 0.7, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.58 (m, 2 H), 1.48 (s, 3 H), 1.53 (s, 3 H), 3.67–3.81 (m, 2 H), 3.86 (dd, *J* = 7.9, 4.5 Hz, 1 H), 4.01–4.10 (m, 1 H), 4.95 (d, *J* = 8.12 Hz, 1 H), 7.27–7.47 (m, 5 H).

LC-MS (EI): *m*/*z* = 275 (M^+ + Na).

(3*R*)-3-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-3-hydroxypropanal (9)

To an ice-cooled soln of 2-iodoxybenzoic acid (IBX, 1.2 g, 4.6 mmol) in DMSO (1 mL, 15.6 mmol) was added a 0 °C soln of alcohol **8** (1 g, 3.9 mmol) in anhyd CH_2Cl_2 (10 mL). The mixture was stirred at r.t. for 2 h and then filtered through a Celite pad and washed with Et_2O. The combined organic filtrates were washed with H_2O and brine, dried (anhyd Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, petroleum ether–EtOAc, 8:2) to afford aldehyde **9** as a viscous liquid; yield: 0.59 g (60%).

$[\alpha]_D^{25}$ –18.2 (*c* 0.4, $CHCl_3$).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 3 H), 1.51 (s, 3 H), 2.24–2.35 (m, 1 H), 2.52–2.60 (m, 1 H), 4.08–4.37 (m, 1 H), 4.74–4.98 (m, 1 H), 5.34 (d, *J* = 8.78 Hz, 1 H), 7.17–7.50 (m, 5 H), 9.72 (s, 1 H).

LC-MS: *m*/*z* = 273 (M^+ + Na).

Methyl (*Z*,5*R*)-5-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5-hydroxypent-2-enoate (10)

In a 50-mL round-bottomed flask containing NaH (0.12 g, 4.8 mmol) was added under N_2 anhyd THF (4 mL). After 5 min, bis(2,2,2-trifluoromethyl) [(methoxycarbonyl) methyl]phosphonate (1.06 g, 3.2 mmol) in anhyd THF (2 mL) was added dropwise at 0 °C. The mixture was stirred for 30 min at this temperature and then cooled to –78 °C and the aldehyde **9** (0.8 g, 3.2 mmol) in THF (1 mL) was added dropwise over a period of 10 min, and the resulting mixture was stirred at –78 °C for 1 h. The mixture was quenched with sat. NH_4Cl and the product was extracted into Et_2O (2 × 10 mL). The organic layer was dried (anhyd Na_2SO_4) and evaporated in vacuo (water-bath temperature should not exceed more than 30 °C) and the product was purified using column chromatography (silica gel) to afford *Z*-alkene ester **10** as light yellow liquid; yield: 0.81 g (84%).

$[\alpha]_D^{25}$ +4.58 (*c* 1, $CHCl_3$).

IR (KBr): 3415, 2925, 2854, 1701, 1619, 1385, 1081 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.50 (s, 3 H), 1.54 (s, 3 H), 2.84–2.62 (m, 2 H), 3.69 (s, 3 H), 3.98–3.80 (m, 2 H), 4.99 (d, *J* = 7.03 Hz, 1 H), 5.83 (dd, *J* = 1.5, 11.7 Hz, 1 H), 6.32 (dt, *J* = 7.8, 11.7 Hz, 1 H), 7.52–7.22 (m, 5 H).

^{13}C NMR (75 MHz $CDCl_3$): δ = 26.6, 26.9, 32.3, 50.8, 71.1, 79.7, 84.9, 108.9, 121.4, 127.0, 127.8, 128.0, 138.3, 145.3, 166.8.

LC-MS (EI): *m*/*z* = 329 (M^+ + Na).

(6*R*)-6-[(1*S*,2*R*)-1,2-Dihydroxy-2-phenylethyl]-5,6-dihydro-2*H*-pyran-2-one (1)

To a stirred soln of **10** (0.5 g, 1.6 mmol) in anhyd benzene (15 mL) was added a catalytic amount of PTSA (14 mg, 0.08 mmol) under an N_2 atmosphere. The mixture was stirred at r.t. for 6 h and then the reaction was quenched by addition of solid $NaHCO_3$, the mixture was filtered and the solvent was removed from the filtrate under reduced pressure. The residue was purified by column chromatography to afford **1** as viscous liquid; yield: 0.27 g (73%).

$[\alpha]_D^{25}$ +84.2 (*c* 0.4, MeOH).

IR (neat): 3451, 2986, 1719, 1645, 1440, 1375, 1210, 1058 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.58 (m, 1 H), 2.54 (m, 1 H), 3.88 (dd, *J* = 5.28, 3.82 Hz, 1 H), 4.41 (dt, *J* = 11.33, 6.04 Hz, 1 H), 4.80–5.80 (br s, 1 H), 4.93 (d, *J* = 3.77 Hz, 1 H), 5.96 (ddd, *J* = 9.33, 2.34, 1.51 Hz, 1 H), 6.83 (ddd, *J* = 9.33, 5.93, 2.54 Hz, 1 H), 7.60–7.16 (m, 5 H).

^{13}C NMR (75 MHz $CDCl_3$): δ = 29.6, 76.1, 77.4, 120.8, 126.4, 128.1, 128.7, 140.3, 145.8, 164.0.

LC-MS (EI): *m*/*z* = 257 (M^+ + Na).

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