Efficient synthesis of the styryllactones, (+)-goniothalamin, (+)-7-*epi*-goniodiol and (+)-9-deoxygoniopypyrone

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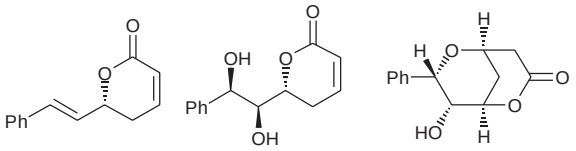
An efficient synthesis of (+)-goniothalamin is described with aldehyde **4** as the key intermediate; the absolute configuration of (+)-7-*epi*-goniodiol was determined through its asymmetric synthesis from (+)-goniothalamin and, based on the conformation analysis of the four dihydroxylated isomers of (+)-goniothalamin, it can be concluded that the absolute configuration of the hydroxy at C_8 determines the forms in nature.

Keywords: styryllactones, (+)-goniothalamin, asymmetric, conformation

Styryllactones, a series of natural products isolated from various species of the genus *Goniothalamus*,[1] possess remarkable antitumour activity.[2] Due to the broad spectrum of biological activities and interesting heterocyclic structural features, styryllactones have attracted much attention from synthetic chemists, biologists and clinicians. Most synthetic strategies in the literature start from chiral materials.[3] Here we report a catalytic asymmetric synthesis of the title compounds.

(+)-Goniothalamin **1**, is a representative member of the styryllactones not only because of its biological activity but also, more importantly, its ability to act as the basic skeleton of this class of natural products which have the styryl group and the α-pyranone in common. Thus, other styryllactones, such as (+)-7-*epi*-goniodiol **9** and (+)-9-deoxygoniopypyrone **10** can be regarded as the biogenetic products of (+)-goniothalamin **1** and can thereby be synthesised from it.



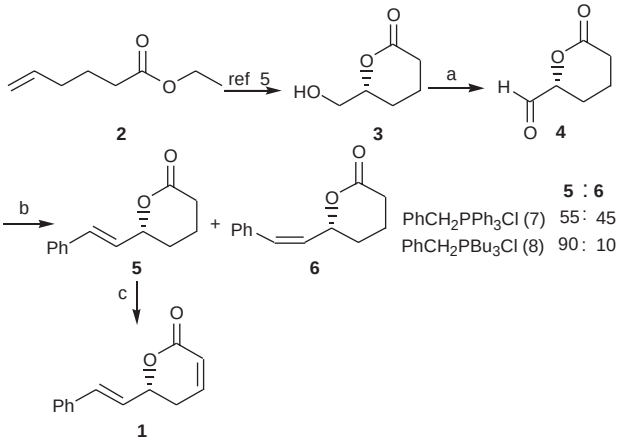
(+)-Goniothalamin **1** (+)-7-*epi*-Goniodiol **9** (+)-9-Deoxygoniopypyron **10**

Fig. 1 Some styryllactones.

Considering the advantages of the synthesis of a number of styryllactones and their analogues from (+)-goniothalamin by simple transformations, we are interested in developing an efficient route for the synthesis of (+)-goniothalamin.

In previous work, we have developed a method of converting racemic terminal epoxides of **2** into δ-lactones **3** *via* the hydrolytic kinetic resolution (HKR) developed by Jacobsen[4] and other simple transformations in 77% overall yield with 96% ee.[5] The compound **3** is the direct precursor of the key intermediate **4**, which gives our synthetic route to (+)-goniothalamin (Scheme 1) a great advantage.

Our synthesis started from compound **3**. Various oxidation methods including Swern, PCC and Dess–Martin oxidation were investigated for the conversion of alcohol **3** into the aldehyde **4** and only the Dess–Martin reagent promoted the oxidation smoothly. However, the standard work up procedure of the Dess–Martin oxidation[6] led to rapid decomposition of the product when sat. aqueous $NaHCO_3$ was added to the reaction mixture. Further experiment showed that aldehyde **4** is sensitive to water and unstable on silica gel. Considering the poor solubility of periodinane and iodinane in hexane, hexane was finally added to quench the reaction, forcing most of the iodinane to precipitate. The solution was filtered and then concentrated to afford the crude aldehyde **4**, the key intermediate



Scheme 1 *Reagents and conditions:* (a) Dess-Martin periodinane, CH_2Cl_2, 0°C, 20 min; (b) 8, *t*-BuOK, THF, 0°C, 30 min; then 8, 0°C, 30 min, 83% for two steps; (c) (i) LDA, phenylselenyl bromide, –78°C, 1 h, (ii) H_2O, acetic acid, 30% H_2O_2, rt, 1 h, 86%.

in our synthesis. Noteworthy is that this crude product **4** could be directly used in the following Wittig reaction without further purification. Then the generally used Wittig reagent benzylidenetriphenyl-phosphorane **7** was initially employed to furnish a mixture of *E*- and *Z*-olefins (**5** and **6**) (81% yield for two steps), in a ratio of 55:45. In the synthesis of epothilone A,[7] we have successfully used a modified Wittig reaction to introduce stereoselectively the thiazole side chain with a *trans* double bond. An analogous procedure using the tributylphosphonium salt **8** might increase the stereoslectivity. As expected, the condensation of **8** by treatment of potassium *t*-butoxide with aldehyde **4** furnished lactones **5** and **6** in the ratio of 90:10, which were easily isolated by flash chromatography. Lactone **5** was subjected to phenylselenation by treatment with 2 equiv. of LDA and phenylselenylbromide. The selenated product was subsequently subjected to oxidative elimination to give the desired α, β-unsaturated-δ-lactone, (+)-goniothalamin **1**. Thus, an efficient and facile synthetic route to (+)-goniothalamin has been achieved.

7-*epi*-goniodiol **9** was isolated from the ethanolic extract of barks of *Goniothalamus leiocarpus* and exhibited potent and selective cytotoxicity against human tumour cells.[1e] The structure and relative configuration of **9** had been determined by NMR spectra and X-ray crystallographic analysis, while the absolute configuration remained undetermined. Sharpless dihydroxylation of the olefin gives the corresponding diol, the absolute configuration of which could be predicted according to the ligands used.[8] Therefore, if **1** could be chemoselectively dihydroxylated to compounds **9** or **11** according to different ligands used, the absolute configuration of 7-*epi*-goniodiol

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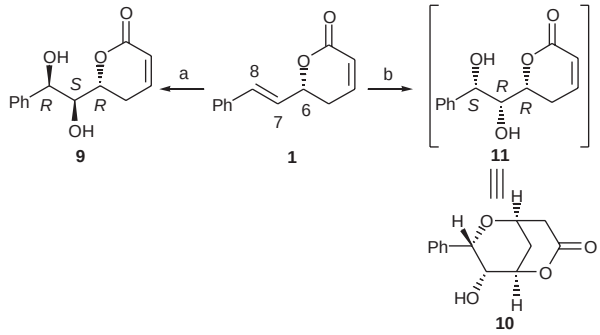


Scheme 2 *Reagents and conditions:* (a) *t*-BuOH, H_2O, $K_3Fe(CN)_6 \cdot 6H_2O$, $K_2OsO_2(OH)_4$, K_2CO_3, $(DHQD)_2$-PHAL 0°C, 20 h, 83%; (b) *t*-BuOH, H_2O, $K_3Fe(CN)_6 \cdot 6H_2O$, $K_2OsO_2(OH)_4$, K_2CO_3, $(DHQ)_2$-PHAL, 0°C, 20 h, 92%.

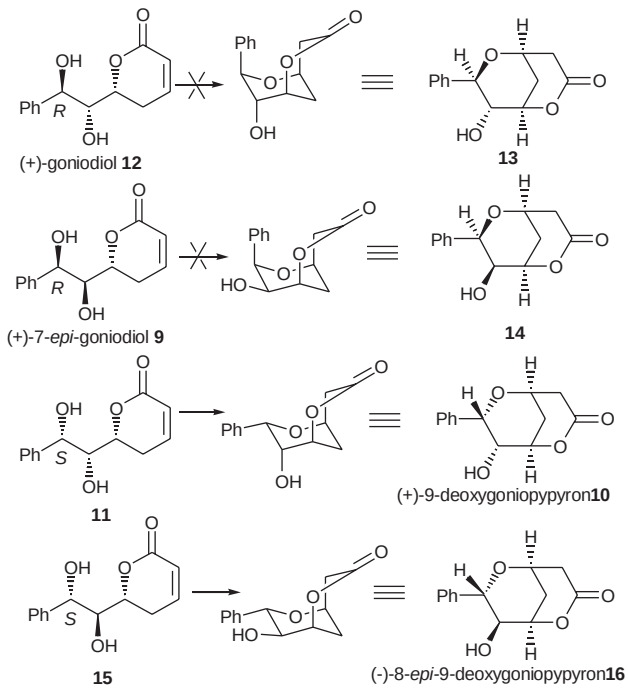
would be determined. Since OsO_4 is an electrophilic reagent, the rate of osmylation of electro-deficient olefins, such as α, β-unsaturated ketones could be very slow. Sharpless dihydroxylation of **1** could provide compounds **9** or **11**. Fortunately, Sharpless AD reaction of **1** using $(DHQD)_2$-PHAL as ligand at 0°C furnished **9** as almost a single product in 83% yield.[9] Since the spectral and physical data including the optical rotation of **9** are identical with those of natural compound, the absolute configuration of the hydroxy groups of 7-*epi*-goniodiol is confirmed as **9** with *R*-configuration at C_6, *S*-configuration at C_7 and *R*-configuration at C_8. Increasing the reaction temperature to room temperature did not lead to an intramolecular Michael addition. On the contrary, Sharpless AD reaction of **1** using $(DHQ)_2$-PHAL as ligand at 0°C is predicted to give diol **11,** which was directly converted into a cyclisation product, 9-deoxygoniopypyrone **10**[9] due to the presence of the hydroxy with *S*-configuration at C_8 of **11**.

Now that the absolute configurations of the four diastereoisomeric dihydroxylated derivatives of (+)-goniothalamin have been determined, they can be generally devided into two groups, one including (+)-7-*epi*-goniodiol **9** and (+)-goniodiol **12** with *R*-configuration at C_8, while the others including compound **11** and **15** with *S*-configuration at C_8. Interestingly, the main form of **11** and **15** in nature are their Michael addition products, (+)-9-deoxygoniopypyrone **10**[1c] and (-)-8-*epi*-9-deoxygoniopypyrone **16**,[1d] while the main forms of **12** and **9** are their diol forms. In fact, there has been no previous report of the isolation of **13**, **14**, **11** and **15** from nature and compound **11** was found to have a great tendency to change to **10** in our study. The conformations of four possible Michael addition products are illustrated in Scheme 3. As shown, for **13** and **14** deriving from **12** and **9** respectively, the bulky phenyl group will be at the high-energy axial position of the chair form affording unstable molecules, while for **10** and **16** deriving from **11** and **15** respectively, the phenyl group will be at the low-energy equatorial position to afford stable molecules. Therefore it is the absolute configuration of C_8 that determines whether diols or Michael addition products are formed.

Experimental

IR spectra were recorded on a Bio-Rad FTS-185 spectrometer. ^1H NMR spectra were determined with TMS as an internal standard in $CDCl_3$ at 300 MHz on a Bruker AM-300 spectrometer; *J* values are given in Hz. Mass spectra were obtained on a HP-5989A spectrometer using the electron impact technique. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. Enantiomeric excesses were determined by HPLC analysis with an Chiralpak AS column.

(6R)-6-transstyryl-tetrahydro-2H-pyran-2one **5**: To a solution of compound (*R*)-3 (651 mg, 5 mmol) in CH_2Cl_2 (20 ml) was added Dess–Martin reagent (2.4 g, 5.5 mmol). After stirring for 20 minutes



Scheme 3

at room temperature, the reaction was quenched with hexane (20 ml) and $NaHCO_3$ (1.5 g). The solution was filtered and the filtrate was concentrated to give crude (*R*)-4 for next use.

A solution of **8** (4.9 g, 15 mmol) in THF (40 ml) was cooled to 0°C, and ^{t}BuOK (1.257 g, 11 mmol) was added. The mixture was stirred for 30 minutes to obtain an orange solution, and then the crude aldehyde (*R*)-**4** was added. After being stirred for 30 minutes at 0°C, the reaction was quenched quickly with H_2O (5 ml), and then extracted with EtOAc (3×20 ml). The organic layer was washed with water and brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography to give **5** (754 mg, 75%) and **6** (84 mg, 8%). **5**: $[\alpha]_D^{20}$ +8.0 (c 0.7, $CHCl_3$); ν_{max}/cm^{-1} 1730, 1240, 1038; δ_H 7.10–7.69 (m, 5 H), 6.63(d, 1 H, *J* 15.88), 6.21 (dd, 1 H, *J* 15.96, 5.96), 4.97–5.05 (m, 1 H), 2.30–2.70 (m, 2 H), 1.70–2.10 (m, 4 H); *m/z* 202 (M^+, 100%), 130 (57), 104 (55), 83 (52), 42 (54). **6**: $[\alpha]_D^{20}$ –440 (c 0.8, $CHCl_3$); ν_{max}/cm^{-1} 1732, 1239, 1036, 969; δ_H 7.25–7.45 (m, 5 H), 6.71(d, *J* 11.48, 1 H), 5.72 (dd, 1 H, *J* 11.55, 9.34), 5.12–5.20 (m, 1 H), 2.30–2.68 (m, 2 H), 1.65–2.05 (m, 4 H); *m/z* 202 (M^+, 100%), 129 (41), 104 (37), 83 (52), 42 (46) (Found: M^+ 202.0977. $C_{13}H_{12}O_2$ requires 202.0994)

(+)-Goniothalamin **1***:* A mixture of diisopropylamine (0.33 ml, 2.2 mmol) and *n*-BuLi (2.52 M in hexane, 0.79 ml, 2 mmol) in anhydrous THF (5 ml) was stirred for 30 min at 0°C and then cooled to –78°C. A solution of lactone 5 (204 mg, 1 mmol) in anhydrous THF (2 ml) was added dropwise over a period of 15 min at –78°C and stirred for 45 min at the same temperature. The enolate was quenched by addition of a solution of phenylselenyl bromide (499 mg, 2.1 mmol) in THF. After being stirred for 1 h at –78°C, the reaction mixture was warmed to 0°C slowly. Then H_2O (2 ml), acetic acid (1 ml) and H_2O_2 (5 ml) were added to the mixture. The reaction was quenched with sat. $NaHCO_3$ after stirring for 30 min at 0°C, and then extracted with EtOAc (3×10 ml). The organic layer was washed with water and brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the purification of the residue by flash chromatography gave 1 (174 mg, 86%): M.p. 79–81°; $[\alpha]_D^{20}$ +171.2 (c 0.4, $CHCl_3$), [lit.1[a] M.p. 81–82°C. $[\alpha]_D^{20}$ = +170.3 (c 1.38, $CHCl_3$)]; ν_{max}/cm^{-1} 1720, 1380, 1250, 1061, 1020, 965; δ_H 7.22–7.40 (m, 5 H), 6.93 (ddd, 1 H, *J* 9.8, 4.2, 4.2), 6.74 (d, 1 H, *J* 16.0), 6.28 (dd, 1 H, *J* 15.9, 6.2), 6.10 (ddd, 1 H, *J* 9.7, 1.70, 1.6), 5.05–5.10 (m, 1 H), 2.50–2.58 (m, 2 H); *m/z* 200 (M^+, 51%), 104 (86), 91 (58), 77 (25), 68 (100).

(+)-7-epi-goniodiol **9**: A mixture of ^{t}BuOH (1.5 mL), H_2O (1.5 ml), $K_3Fe(CN)_6 \cdot 6H_2O$ (302 mg, 0.9 mmol), $K_2OsO_2(OH)_4$ (1 mg, 0.0009 mmol) K_2CO_3 (125 mg, 0.9 mmol) and $(DHQD)_2$-PHAL (3 mg, 0.0045 mmol) was stirred at room temperature for 5 min. and then cooled to 0°C. Lactone **1** (60 mg, 0.3 mmol) was added, and the heterogeneous

slurry was stirred for 20 h at 0°C. Na_2SO_3 (450 mg) was added and the mixture was allowed to warm to room temperature and stirred for 1 h. EtOAc (5 ml) was added and the aqueous layer was extracted with EtOAc (2×2 ml). The combined organic layers were dried over $MgSO_4$. The solvent was removed and the purification of the residue by flash chromatography gave (+)-7-*epi*-goniodiol **9** (58 mg, 83%). $[\alpha]_D^{20}$ = +82.5 (c = 0.4, MeOH), [lit.[1e] $[\alpha]_D^{20}$ = +85.4 (c = 0.3, MeOH)]. IR (film): ν = 3400, 2930, 1717, 1388, 1259, 1076 cm^{-1}. ^1H NMR (C_5D_5N): δ = 7.20–7.75 (m, 5 H), 6.82 (ddd, 1 H, *J* 9.5, 5.9, 2.9), 5.95 (ddd, 1 H, *J* 9.5, 2.2, 1.1), 5.35 (d, 1 H, *J* 3.7), 4.90 (dd, 1 H, *J* 10.8, 5.1), 4.30 (dd, 1 H, *J* 5.9, 3.8), 2.78 (m, 1 H), 2.72 (m, 1 H). ESI MS: m/z 257.1 $(M+Na)^+$

(+)-9-deoxygoniopypyrone **5**: A mixture of ^{t}BuOH (1.5 ml), H_2O (1.5 ml), $K_3Fe(CN)_6 \cdot 6H_2O$ (302 mg, 0.9 mmol), $K_2OsO_2(OH)_4$ (1 mg, 0.0009 mmol) K_2CO_3 (125 mg, 0.9 mmol) and $(DHQ)_2$-PHAL (3 mg, 0.0045 mmol) was stirred at room temperature for 5 min and then cooled to 0°C. Lactone **1** (60 mg, 0.3 mmol) was added, and the heterogeneous slurry was stirred for 20 h at 0°C. Na_2SO_3 (450 mg) was added, and the mixture was allowed to warm to room temperature and stirred for 1 h. EtOAc (5 ml) was added, and the aqueous layer was extracted with EtOAc (2×2 ml). The combined organic layers were dried over $MgSO_4$. The solvent was removed and the purification of the residue by flash chromatography gave (+)-9-deoxygoniopypyrone **10** (64 mg, 92%). M.p. 200–203°C. $[\alpha]_D^{20}$ = +11.2 (*c* = 0.5, EtOH)[lit.[1c] M.p. 203–204ºC. $[\alpha]_D^{22}$ = +12(*c* = 0.1, EtOH)]. IR (film): ν = 3440, 1720 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.35–7.45 (m, 5 H), 4.97 (m, 1 H), 4.89-4.95 (m, 1 H), 4.54 (m, 1 H), 3.95–4.01 (m, 1 H), 2.99 (m, 1 H), 2.88 (m, 1 H), 2.57–2.63 (m, 1 H), 1.82 (dd, 1 H, *J* 14.4, 4.0), 1.60–1.65 (br, 1 H). ESI MS: *m/z* 257.1 $(M+Na)^+$

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