

# Enantioselective approach to the asymmetric synthesis of (6*R*)-hydroxymethyl-5,6-dihydro-2*H*-pyran-2-one. A formal synthesis of (*R*)-argentilactone and total synthesis of (*R*)-goniothalamine

Ângelo de Fátima and Ronaldo A. Pilli\*

*Instituto de Química, Universidade Estadual de Campinas, P.O. Box 6154, 13084-971,  
Campinas, SP, Brazil  
E-mail: pilli@iqm.unicamp.br*

**Dedicated to Professor Edmundo A. Rúveda on his 70<sup>th</sup> birthday  
and Professor Roberto A. Rossi on his 60<sup>th</sup> birthday  
(received 30 Jun 03; accepted 14 Aug 03; published on the web 19 Aug 03)**

---

## Abstract

The asymmetric synthesis of the (6*R*)-hydroxymethyl-5,6-dihydro-2*H*-pyran-2-one, a key intermediate in the formal synthesis of (*R*)-argentilactone, and the total synthesis of (*R*)-goniothalamine are described. Our approach involved the Lemieux-Johnson oxidative cleavage, enantioselective Keck allylation, ring-closing metathesis and Wittig olefination.

**Keywords:** Natural products, pyranones, Lemieux-Johnson oxidative cleavage, catalytic asymmetric Keck allylation, ring-closing metathesis

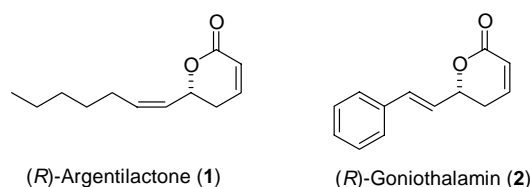
---

## Introduction

In 1977, Rúveda and coworkers reported the isolation of (*R*)-argentilactone (**1**) from *Aristolochia argentea* (Figure 1)<sup>1</sup>. Later, this natural pyranone was shown to have antileishmanial activity equivalent to the reference drug *N*-methylglucamine antimonate against *Leishmania amazonensis*<sup>2</sup>, as well as cytotoxic activity against mouse leukaemia cells (P-388)<sup>3</sup>.

(*R*)-Goniothalamine (**2**) was isolated in 1967 from the dried bark of *Cryptocarya caloneura* (Figure 1)<sup>4</sup>. It is a potential cytotoxic compound that has been demonstrated to have antiproliferative activities in a number of transformed cell lines including MCF-7 (breast carcinoma) and HeLa cells (human cervical carcinoma)<sup>5,6</sup>. Recent studies have indicated that goniothalamine induced apoptosis in JurKat T-cells from activation of two members of the family of cysteine proteases, caspases-3 and -7. Dereglulation of apoptosis has now been implicated in the onset or progression of cancer<sup>7</sup>. Consequently, apoptosis represents an innate cellular defense

against carcinogen-induced cellular damage by removing and inhibiting survival and growth of altered cells at different stages of carcinogenesis<sup>7</sup>.



**Figure 1.** Structures of (R)-argentilactone (1) and (R)-goniothalamine (2).

Due to the interesting biological activity displayed by (R)-argentilactone (1) and (R)-goniothalamine (2), several successful approaches to these natural products have been reported<sup>8</sup>. Both substances contain the 5,6-dihydro-2H-pyran-2-one moiety and bear the (R)-configuration in their natural form. In this work, we describe the formal synthesis of (R)-argentilactone and the total synthesis of (R)-goniothalamine from benzyl alcohol featuring Lemieux-Johnson oxidative cleavage, enantioselective Keck allylation, ring-closing metathesis and Wittig reactions as the key steps (Scheme 1).

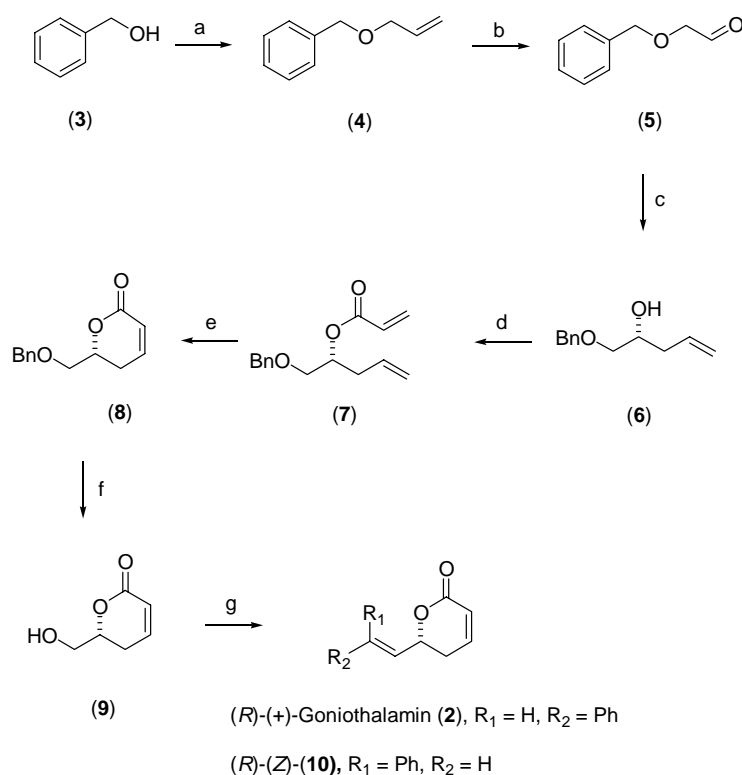
## Results and Discussion

Our approach to these natural products centered around the olefin ring-closing metathesis reaction<sup>9</sup> of **7** that was planned to be prepared in enantiomerically enriched form from allylic alcohol **6** available in good yield and enantiomeric excess from benzyloxyacetaldehyde (**5**) according to the catalytic asymmetric allylation protocol developed by Keck and coworkers<sup>10</sup>.

Benzyloxyacetaldehyde (**5**) was obtained in 78% overall yield from benzyl alcohol by treatment with sodium hydride and allyl bromide, followed by oxidative cleavage according to the Lemieux-Johnson protocol<sup>11</sup>. In the event, reaction of benzyloxyacetaldehyde (**5**) with allyltributyltin, under the influence of chiral (R)-BINOL/Ti(O<sup>i</sup>Pr)<sub>4</sub> complex generated *in situ* in CH<sub>2</sub>Cl<sub>2</sub> and in the presence of molecular sieves at -20 °C for 72 h afforded **6** in 78% yield and 94% *ee*<sup>10</sup>. Enantiomeric excess was determined by chiral GC (column Chirasil-DEX CB) after conversion of the **6** to acrylate ester **7** (acryloyl chloride, Et<sub>3</sub>N and catalytic amount of DMAP in CH<sub>2</sub>Cl<sub>2</sub> at -23 °C, 86% yield). Ring-closing metathesis of **7** with Grubbs' catalyst<sup>9</sup> (10 mol%) in refluxing CH<sub>2</sub>Cl<sub>2</sub> for 12 h furnished the corresponding  $\alpha,\beta$ -unsaturated  $\delta$ -lactone **8** in 69% yield from **6** (Scheme 1).

At this point, our efforts were directed to the selective removal of the benzyl group in **8**. While no reaction was observed with lithium naphthalenide<sup>12</sup>, lithium *tert*-butyldiphenyl (LiDBB)<sup>13</sup> and tin(IV) chloride<sup>14</sup>, hydrogenolysis with Pd(OH)/C<sup>15</sup> (1 atm of H<sub>2</sub>) promoted the reduction of the  $\alpha,\beta$ -unsaturated bond. Low yield was obtained using titanium(IV) chloride<sup>16</sup>, chromium(II) chloride/lithium iodide<sup>17</sup> and boron tribromide<sup>18</sup>. In our hands, utilization of ferric

chloride<sup>19</sup> in CH<sub>2</sub>Cl<sub>2</sub> at rt achieved debenzoylation of **8** to give **9** in 88% yield. The preparation of (6*R*)-hydroxymethyl-5,6-dihydro-2*H*-pyran-2-one (**9**) in 6 steps and 42% overall yield, starting from benzyl alcohol, constitutes a formal synthesis of both (*R*)-argentilactone (**1**) and (*R*)-goniothalamine (**2**) as Tsubuki and coworkers have previously described the total synthesis of these natural pyranones from **9** which was prepared in 13 steps and 11% yield overall from (*R*)-isopropylidenglyceraldehyde<sup>20</sup>.



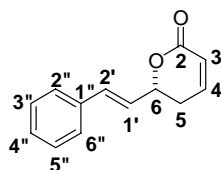
**Conditions:** a) NaH, KI, DMF, allyl bromide (98%); b) OsO<sub>4</sub>, Et<sub>2</sub>O/H<sub>2</sub>O, NaIO<sub>4</sub> (80%); c) (*R*)-BINOL (10 mol%), Ti(O<sup>*i*</sup>Pr)<sub>4</sub> (10 mol%), molecular sieves (4Å), allyltributyltin, -20 °C, 60 h (78%; 94% *ee*); d) acryloyl chloride, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C (86%); e) Grubbs' catalyst [(Pcy<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>Ru=CHPh], CH<sub>2</sub>Cl<sub>2</sub> (91%); f) FeCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub> (88%); g) (COCl)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, DMSO, Et<sub>3</sub>N, -65 °C, 30 min; then Ph<sub>3</sub>P=CHPh, THF (**2**:**10**= 1:3, 53%, 2 steps).

### Scheme 1

The efficient access to dihydropyranone **9** and our interest in the biological evaluation of (*R*)-goniothalamine (**2**) and some of its congeners led us to explore the route described by Tsubuki and coworkers to (*R*)-goniothalamine (**2**)<sup>20</sup>. Wittig olefination of the corresponding aldehyde (prepared from **9** by Swern oxidation and employed in the next step without further purification) with a solution of benzylidene triphenylphosphorane (prepared by treatment of the corresponding triphenyl phosphonium chloride with *n*-BuLi in THF) afforded, after column chromatography on

silica gel, a 1:3 molar ratio (53% yield) of (*R*)-goniothalamine (**2**) (13% yield) and its corresponding *Z*-isomer **10** (40% yield). In Table 1 are presented the  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  data of natural<sup>4b</sup> and synthetic (*R*)-goniothalamine (**2**).

**Table 1**<sup>a</sup>.  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectral data of natural<sup>4b</sup> and synthetic (*R*)-goniothalamine



| H          | $^1\text{H-NMR}$                     |                                      | C              | $^{13}\text{C-NMR}$   |           |
|------------|--------------------------------------|--------------------------------------|----------------|-----------------------|-----------|
|            | Natural <sup>4b</sup>                | Synthetic                            |                | Natural <sup>4b</sup> | Synthetic |
|            | $\delta$ , multiplicity ( <i>J</i> ) | $\delta$ , multiplicity ( <i>J</i> ) |                | $\delta$              | $\delta$  |
| <b>3</b>   | 6.09, <i>dt</i> (10, 2)              | 6.08, <i>d</i> (9.5)                 | <b>2</b>       | 163.9                 | 163,6     |
| <b>4</b>   | 6.93, <i>dt</i> (10, 4)              | 6.92, <i>dt</i> (9.5, 4)             | <b>3</b>       | 121.5                 | 121,4     |
| <b>5</b>   | 2.54, <i>m</i>                       | 2.56-2.52, <i>m</i>                  | <b>4</b>       | 144.7                 | 144,5     |
| <b>6</b>   | 5.10, <i>qd</i> (7, 1)               | 5.10, <i>q</i> (6.9)                 | <b>5</b>       | 29.8                  | 29,8      |
| <b>1'</b>  | 6.27, <i>dd</i> (16, 6)              | 6.27, <i>dd</i> (15.9, 6.2)          | <b>6</b>       | 77.9                  | 77,8      |
| <b>2'</b>  | 6.73, <i>d</i> (16)                  | 6.72, <i>d</i> (15.9)                | <b>1'</b>      | 125.6                 | 125,5     |
| <b>HAr</b> | 7.30, <i>m</i>                       | 7.41-7.25, <i>m</i>                  | <b>2'</b>      | 133.1                 | 132,8     |
|            |                                      |                                      | <b>1''</b>     | 135.7                 | 135,5     |
|            |                                      |                                      | <b>2''/6''</b> | 126.6                 | 126,5     |
|            |                                      |                                      | <b>3''/5''</b> | 128.6                 | 128,5     |
|            |                                      |                                      | <b>4''</b>     | 128.5                 | 128,1     |

<sup>a</sup> Chemical shifts are reported in  $\delta$  [ppm relative to  $(\text{CH}_3)_4\text{Si}$ ] for  $^1\text{H}$  and  $\text{CDCl}_3$  for  $^{13}\text{C}$  NMR. For  $^1\text{H}$  NMR, the chemical shifts were followed by multiplicity (s, singlet; d, doublet; dd, double doublet; ddd, double double doublet; t, triplet; q, quartet; m, multiplet) and coupling constant, *J*, reported in Hertz (Hz).

The stereochemistry of the olefination products was assigned based on the coupling constants between the olefinic hydrogens H-1' and H-2' (15.9 Hz for the minor isomer and 11.3 Hz for the major one) as well as by comparison of the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data of the synthetic and natural<sup>4b</sup> (*R*)-goniothalamine (**2**).

Despite the low level of diastereoselection found in the Wittig olefination, Tsubuki and coworkers<sup>20</sup> have already shown that the yield of (*R*)-goniothalamine (**2**) could be enhanced by photochemical isomerization of (*Z*)-**10** in the presence of diphenyldisulfide to afford a 2:1 ratio of (*R*)-goniothalamine (**2**) and (*Z*)-**10** in 65% yield. Additionally, recent results by Enders and

coworkers<sup>8c</sup> and Kalesse and coworkers<sup>8f</sup> have demonstrated that the use of tributylphosphonium bromide and potassium *tert*-butoxide provides a better solution for the preparation of *E* isomer via Wittig olefination.

With an expeditious enantioselective catalytic approach to (*6R*)-hydroxymethyl-5,6-dihydro-2*H*-pyran-2-one (**9**) in hand, we are currently exploring the preparation of some (*R*)-goniothalamin (**2**) and (*R*)-argentilactone (**1**) derivatives for biological evaluation.

In this work, we have performed the formal synthesis of (*R*)-argentilactone (**1**) and the total synthesis of (*R*)-goniothalamin (**2**) which was obtained in 7 steps and 6% overall yield together with the correspondent (*Z*)-**10** isomer (18% overall yield). This approach illustrates the utility of the enantioselective catalytic allylation to provide rapid access to synthetically useful  $\alpha,\beta$ -unsaturated  $\delta$ -lactone from commercially available starting materials.

## Experimental Section

**General Procedures.** Reagents and solvents are commercial grade and were used as supplied, with the following exceptions: a) ether and THF were distilled from sodium benzophenone ketyl; b) dichloromethane and triethylamine were distilled from calcium hydride and c) oxalyl chloride and dimethyl sulfoxide were distilled prior to use. Chromatographic separations were performed using 70-230 Mesh silica gel. Thin-layer chromatography was carried out on Macherey-Nagel precoated silica plates (0.25 mm layer thickness). IR spectra were obtained on Nicolet Impact 410 FT (film on KBr plates or KBr pellets). Melting points were measured with an Eletrothermal AZ9003 MK3 apparatus and are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C-NMR data were recorded on a Varian Gemini 300 (7.0 T) or Varian Inova (11.7 T) spectrometer. Chemical shifts are reported in  $\delta$  [ppm relative to (CH<sub>3</sub>)<sub>4</sub>Si] for <sup>1</sup>H and CDCl<sub>3</sub> for <sup>13</sup>C-NMR. For <sup>1</sup>H-NMR, the chemical shifts were followed by multiplicity (s, singlet; d, doublet; dd, double doublet; ddd, double double doublet; t, triplet; q, quartet; m, multiplet) and coupling constant *J* reported in Hertz (Hz). High resolution mass spectra (HRMS) were measured on a VG Autospec-Micromass spectrometer. Chiral GC analyses were performed with capillary column CP-Chirasil-DEX CB fused silica WCOT (25m x 0.25 mm x 0.25  $\mu$ m) and chiral HPLC analyses were performed with Welk-O 2 column (25 cm x 10 mm i.d.). Optical rotations were measured at 25 °C with Perkin-Elmer 241 instrument.

**Benzyloxyacetaldehyde (5).** To a stirred solution of 1-(benzyloxy)-4-penten-2-ol<sup>21</sup> (100 mg, 0.683 mmol) in a mixture of ether (2 mL) and water (2 mL) was added osmium tetroxide (3.6 mg; 0.0013 mmol) and the mixture was stirred for 10 min at rt. Powdered sodium metaperiodate (318 mg, 1.51 mmol) was then added over a 25 min period and stirring was continued for 2 h at rt. The mixture was poured into water (20 mL) and extracted with ether (3 x 50 mL). The organic layer was dried with sodium sulfate and filtered. The solvent was removed in vacuo and the residual product was purified by column chromatography on silica gel using dichloromethane as

solvent to give known benzyloxyacetaldehyde (**5**, 92 mg, 80%): IR (film) 3032, 2862, 1736, 1122, 744, 698  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.72 (t, 1H,  $J = 1.0$  Hz), 7.39-7.27 (m, 5H), 4.65 (s, 2H), 4.12 (d, 2H,  $J = 1.0$  Hz);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  200.1, 136.6, 128.3, 127.9, 127.8, 75.1, 73.5.

**(R)-1-(Benzyloxy)-4-penten-2-ol (6)**<sup>10</sup>. To a stirred solution of (*R*)-BINOL (75 mg, 0.26 mmol) in dichloromethane (2.6 mL) were added 4Å molecular sieves (powdered and activated by storing in an oven at 120 °C for several days), followed by 1.0 M dichloromethane soln. of titanium tetrakisopropoxide (0.34 mL, 0.26 mmol) at rt. The orange-reddish suspension was heated at reflux for 1 h when the color of the reaction mixture changed to red-brown. The reaction mixture was cooled to rt and a soln. of benzyloxyacetaldehyde (**5**, 390 mg, 2.64 mmol) in dichloromethane (0.4 mL) was added. After 5 min stirring at rt, the mixture was cooled at –78 °C and allyltributylstannane (0.98 mL, 3.12 mmol) was added. The resulting reaction was then kept in a freezer at –20 °C for 60 h without stirring when it was quenched with saturated aqueous  $\text{NaHCO}_3$  solution (20 mL) and diluted with dichloromethane (20 mL). This mixture was stirred at rt for 2 h and then filtered through a pad of Celite to remove the molecular sieves. The organic layer was separated and aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic phases were dried over magnesium sulfate and evaporated under reduced pressure and the residual product purified by column chromatography [initially, hexane was used to elute recovered allyltributylstannane, then 4:2 hexane/acetone (v/v) was used as eluent to isolate the desired product] to give (*R*)-1-(benzyloxy)-4-penten-2-ol (**6**, 389 mg, 78%). The enantiomeric purity was determined to be 93% *ee* by CG analysis of the acryloyl ester derivative (column: CP-Chirasil-DEX CB, 25 m x 0.25 mm x 0.25  $\mu\text{m}$ ; conditions: initial temperature/initial time: 120 °C/30 min, final temperature/final time: 180 °C/50 min, rate: 2 °C/min,  $\text{H}_2$  as the carrier gas and FID detector). IR (film) 3440, 3070, 2908, 2862, 1450, 1284, 914, 741  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40-7.20 (m, 5H), 5.88-5.74 (m, 1H), 5.14-5.06 (m, 2H), 4.54 (s, 2H), 3.91-3.82 (m, 1H), 3.50 (dd, 1H,  $J = 9.5$  and 3.5 Hz), 3.37 (dd, 1H,  $J = 9.5$  and 7.3 Hz), 2.45 (d, 1H,  $J = 3.3$  Hz), 2.28-2.23 (m, 2H);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  137.8, 134.0, 128.3, 127.6, 127.5, 117.5, 73.8, 73.3, 69.6, 37.9; HRMS (EI) *m/z* calc. for  $\text{C}_{12}\text{H}_{16}\text{O}_2$  [ $\text{M}$ ]<sup>+</sup> 192.11503. Found: 192.10938.  $[\alpha]_{\text{D}}^{25} = -2.2$  (*c* 2.64,  $\text{CHCl}_3$ ) {lit.<sup>22</sup>:  $[\alpha]_{\text{D}}^{25} = -2.20$  (*c* 2.64,  $\text{CHCl}_3$ )}

**(R)-1-(Benzyloxy)-4-penten-2-ol acryloyl ester (7)**. To a stirred solution of (*R*)-1-(benzyloxy)-4-penten-2-ol (**6**, 70 mg, 0.36 mmol) in dichloromethane (0.4 mL) was added acryloyl chloride (53  $\mu\text{L}$ , 0.65 mmol) and triethylamine (0.18 mL, 1.30 mmol) at 0 °C. After stirring for 30 min, the reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  solution. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure and the residual product was purified by column chromatography (5% dichloromethane in hexane, v/v) to give acryloyl ester **7** (77 mg, 86%): IR (film) 1724, 1635, 1408, 1269  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32-7.26 (m, 5H), 6.41 (dd, 1H,  $J = 17.2$  and 1.5 Hz), 6.11 (dd, 1H,  $J = 17.2$  and 9.7 Hz), 5.83-5.67 (m, 2H), 5.20-5.03 (m, 3H), 4.53 (ABq,

2H,  $J = 12.0$  Hz), 3.56 (d, 2H,  $J = 5.1$  Hz), 2.49-2.37 (m, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.4, 137.8, 132.9, 130.6, 128.4, 128.2, 127.5, 127.4, 117.9, 73.1, 72.0, 70.4, 35.3; HRMS (EI)  $m/z$  calc. for  $\text{C}_{15}\text{H}_{18}\text{O}_3$   $[\text{M}]^+$  246.12560. Found: 246.12597.  $[\alpha]_{\text{D}}^{25} = -1.6$  ( $c$  1.27,  $\text{CHCl}_3$ ).

**(R)-6-(Benzyloxymethyl)-5,6-dihydro-2-pyranone (8).** To a stirred solution of bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (Grubbs' catalyst, 2 mg, 10 mol%) in dichloromethane (0.6 mL) at 55-60 °C was added (*R*)-1-(benzyloxy)-4-penten-2-ol acryloyl ester (**7**, 60 mg, 0.24 mmol) dissolved in dichloromethane (24 mL). The resulting mixture was heated for 15 h. After this period, the mixture was cooled at rt and evaporated under reduced pressure. The residual product was purified by column chromatography (30% ethyl acetate in hexane, v/v) to give (*R*)-6-benzyloxymethyl-5,6-dihydro-2-pyranone (**8**, 53 mg, 91%): IR (film) 3032, 2912, 1728, 1246, 741, 689  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42-7.15 (m, 5H), 6.90 (ddd, 1H,  $J = 9.8, 5.9$  and 2.5 Hz), 6.03 (ddd, 1H,  $J = 9.8, 2.6$  and 1.0 Hz), 4.65-4.59 (m, 3H), 3.70 (d, 2H,  $J = 4.8$  Hz), 2.64-2.36 (m, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  16.4, 144.7, 137.4, 128.2, 127.6, 127.5, 120.9, 76.5, 73.5, 70.7, 26.1; HRMS (EI)  $m/z$  calc. for  $\text{C}_{13}\text{H}_{14}\text{O}_3$   $[\text{M}]^+$  218.09430. Found: 218.08900.  $[\alpha]_{\text{D}}^{25} = +116.7$  ( $c$  1.3,  $\text{CHCl}_3$ ).

**(R)-6-Hydroxymethyl-5,6-dihydro-2-pyranone (9).** To a stirred solution of (*R*)-6-benzyloxymethyl-5,6-dihydro-2-pyranone (**8**, 227 mg, 1.04 mmol) in dichloromethane (0.6 mL) at rt under argon atmosphere, anhydrous  $\text{FeCl}_3$  (506 mg, 3.12 mmol) was added. After 5 min the reaction was quenched by addition of water (1 mL) and diluted with dichloromethane (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate) to give (*R*)-6-hydroxymethyl-5,6-dihydro-2-pyranone (**9**, 133 mg, 88%): IR (film) 3402, 3070, 2924, 1712, 1388, 1084, 820  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.94 (ddd, 1H,  $J = 9.7, 6.2$  and 2.2 Hz), 6.04 (dd, 1H,  $J = 9.5$  and 2.6 Hz), 4.60-4.52 (m, 1H), 3.90 (dd, 1H,  $J = 12.2$  and 2.9 Hz), 3.77 (dd, 1H,  $J = 12.2$  and 4.8 Hz), 2.68-2.56 (m, 1H), 2.37-2.27 (m, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.6, 145.1, 120.8, 78.3, 63.8, 25.3; HRMS (EI)  $m/z$  calc. for  $\text{C}_6\text{H}_8\text{O}_3$   $[\text{M}]^+$  128.04735. Found: 128.04472.  $[\alpha]_{\text{D}}^{25} = +175.3$  ( $c$  1.0,  $\text{CHCl}_3$ ) {lit.<sup>9</sup>,  $[\alpha]_{\text{D}}^{25} = +174.9$  ( $c$  0.92,  $\text{CHCl}_3$ ).

**(R)-goniothalamine (2) and (6R, 7Z)-6-styryl-5,6-dihydro-2-pyranone (10)<sup>20</sup>.** To a stirred solution of oxalyl chloride (50  $\mu\text{L}$ , 0.59 mmol) in dichloromethane (0.5 mL) was added a solution of dimethyl sulfoxide (60  $\mu\text{L}$ , 0.78 mmol) in dichloromethane (0.5 mL) at -65 °C under argon atmosphere. After 15 min, the (*R*)-6-hydroxymethyl-5,6-dihydro-2-pyranone (**9**, 50 mg, 0.39 mmol) was added and stirring was continued for 30 min. Triethylamine (0.27 mL, 1.95 mmol) was added and the mixture was stirred for further 15 min at the same temperature. After this period, benzylidene triphenylphosphorane [prepared from benzytriphenylphosphonium chloride (1.52 g, 3.90 mmol) and *n*-butyllithium (1.55 M hexane solution, 2.42 mL, 3.70 mmol) in THF (15 mL)] was slowly added at 0 °C. The mixture was stirred for 30 min at -65 °C and then was added of brine (20 mL). The organic layer was separated and aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers was dried over

anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residual product was purified by column chromatography (15% ethyl acetate in hexane, v/v, as eluent). The first fraction gave the (6*R*, 7*Z*)-6-styryl-5,6-dihydro-2-pyranone (**10**, 31 mg, 40%) and the second gave the (*R*)-goniothalamine (**2**, 10 mg, 13%). (6*R*, 7*Z*)-6-styryl-5,6-dihydro-2-pyranone (**10**): IR (film) 3024, 2924, 1720, 1246, 748, 694 cm<sup>-1</sup>; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 7.40-7.27 (m, 5H), 6.88 (ddd, 1H, *J* = 9.7, 5.5 and 3.3 Hz), 6.78 (d, 1H, *J* = 11.3 Hz), 6.06 (ddd, 1H, *J* = 9.7, 3.3 and 2.0 Hz), 5.84 (dd, 1H, *J* = 11.3 and 9.1 Hz), 5.31 (ddd, 1H, *J* = 11.3 and 9.1 Hz), 2.59-2.40 (m, 2H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 16.9, 144.5, 135.6, 134.8, 128.6, 128.5, 127.9, 128.8, 121.6, 74.1, 29.7; HRMS (EI) *m/z* calc. for C<sub>13</sub>H<sub>12</sub>O<sub>2</sub> [M]<sup>+</sup> 200.08373. Found: 200.07891. [α]<sub>D</sub> = - 302 (c 0.4, CHCl<sub>3</sub>), {lit.<sup>9</sup>, [α]<sub>D</sub> = - 310.2 (c 0.44, CHCl<sub>3</sub>)}. (*R*)-goniothalamine (**2**): mp 81-82 °C, {lit.<sup>4f</sup>, mp 85 °C}; IR (film): 3055, 3024, 2924, 1720, 1246, 814, 698 cm<sup>-1</sup>; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 7.41-7.25 (m, 5H), 6.92 (dt, 1H, *J* = 9.5 and 4.0 Hz), 6.72 (d, 1H, *J* = 15.9 Hz), 6.27 (dd, 1H, *J* = 15.9 and 6.2 Hz), 6.08 (d, 1H, *J* = 9.5 Hz), 5.10 (q, 1H, *J* = 6.9 Hz), 2.56-2.52 (m, 2H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 163,6; 144,5; 135,5; 132,8; 128,5; 128,1; 126,5; 125,5; 121,4; 77,8; 29,8; HRMS (EI) *m/z* calc. for C<sub>6</sub>H<sub>8</sub>O<sub>3</sub> [M]<sup>+</sup> 128.04735. Found: 200.07821. [α]<sub>D</sub><sup>25</sup> = + 164 (c 1.7, CHCl<sub>3</sub>), {lit.<sup>4f</sup>, [α]<sub>D</sub><sup>25</sup> = +170.3 (c 1.38, CHCl<sub>3</sub>)}

## Acknowledgements

The authors would like to thank FAPESP (Fundação de Amparo a Pesquisa no Estado de São Paulo) for financial support and fellowships (AdF) and CNPq for fellowship (RAP).

## References

1. (a) Priestap, H. A.; Bonafede, J. D.; Rúveda, E. A. *Phytochemistry* **1977**, *16*, 1579. Argentilactone was also isolated from: (b) *Annona argentina* and *A. haematantha* – see reference 2 (c) *Chorisia crispiflora* - Matsuda, M.; Endo, Y.; Fushiya, S.; Endo, T.; Nozoe, S. *Heterocycles* **1994**, *38*, 1229. (d) *Coryanthes ssp.* - Kaiser, R. *Chimia* **2000** *54*, 346.
2. Waechter, A. I.; Ferreira, M. E.; Fournet, A.; deArias, A. R.; Nakayama, H.; Torres, S.; Hocquemiller, R.; Cave, A. *Planta Medica* **1997**, *63*, 433.
3. Matsuda, M.; Endo, Y.; Fushiya, S.; Endo, T.; Nozoe, S.; *Heterocycles* **1994**, *38*, 1229.
4. (a) Hlubucek, J. R.; Robertson, A. V. *Aust. J. Chem.* **1967**, *20*, 2199. Goniothalamine was also isolated from: (b) *Cryptocarya moschata* – Cavalheiro, A. J.; Yoshida, M. *Phytochemistry*. **2000**, *53*, 811. (c) *Goniothalamus giganteus* - El-Zayat, A. E.; Ferrigni, N. R.; McCloud, T. G.; McKenzie, A. T.; Byrn, S. R.; Cassady, J. M.; Chang, C.; McLaughlin, J. L. *Tetrahedron Lett.* **1985**, *26*, 955. (d) *Bryonopsis laciniosa* - Kabir, K. E.; Khan, A. R.; Mosaddik, M. A. J. *Appl.Chem.* **2003**, *127*, 112. (e) *Goniothalamus uvaroids* – Ahmad, F. B.; Tukul, W. A.;



- Omar, S.; Sharif, A. M. *Phytochemistry* **1991**, *30*, 2430. (f) *Goniothalamus malayanus*, *G. andersonni*, *G. macrophyllus* and *G. velutinus* – Jewers, K.; Blunden, G.; Wetchapinan, S.; Dougan, J.; Manchada, A. H.; Davis, J. B.; Kyi, A. *Phytochemistry* **1972**, *11*, 2025. (g) *Goniothalamus dolichocarpus* – Goh, S. H.; Ee, G. C. L.; Chuah, C. H.; Wei, C. *Aust. J. Chem.* **1995**, *48*, 199.
5. Ali, A. M.; Mackeen, M. M.; Hamid, M.; Aun, Q. B.; Zauyah, H.; Azimathol, H. L. P. Kawazu, K. *Planta Med.* **1997**, *63*, 81.
  6. Hawariah, W.; Stanslas, J. *In Vivo* **1998**, *12*, 403.
  7. Goldsworthy, T. L.; Fransson-Steen, R. L.; Moser, G. J. *CIIT Act.* **1995**, *15*, 1.
  8. For more recently synthesis of (*R*)-argentilactone see: (a) Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. *J. Ind. Chem. Soc.* **1999**, *76*, 739. (b) Saeed, M.; Ilg, T.; Schick, M.; Abbas, M.; Voelter, W. *Tetrahedron Lett.* **2001**, *42*, 7401. (c) Job, A.; Wolberg, M.; Müller, M.; Enders, D. *Synlett* **2001**, *11*, 1796. (d) Hansen, T. V. *Tetrahedron: Asymmetry* **2002**, *13*, 547. For more recently synthesis of (*R*)-goniothalamine see: (e) Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2000**, *41*, 583. (f) Quitschalle, M.; Christmann, M.; Bhatt, U.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1263.
  9. For excellent recent review, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413 and references therein.
  10. Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1998**, *75*, 12.
  11. Pappo, R.; Jr. Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
  12. (a) Liu, H. J.; Yip, J.; Shia, K. S. *Tetrahedron Lett.* **1997**, *38*, 2253. (b) Alonso, E.; Ramón, D. J. Yus, M. *Tetrahedron* **1997**, *53*, 14355.
  13. Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.
  14. Hori, H.; Nishida, Y.; Ohruji, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346.
  15. Medich, J. R.; Kunnen, K. B.; Johnson, C. R. *Tetrahedron Lett.* **1987**, *28*, 4131.
  16. (a) Mukai, C.; Hirai, S.; Hanaoka, M. *J. Org. Chem.* **1997**, *62*, 6619. (b) Surivet, J. P.; Vatèle, J. M. *Tetrahedron* **1999**, *55*, 13011.
  17. Falck, J. R.; Barma, D. K.; Baati, R.; Mioskowski, C. *Angew. Chem. Int. Ed.* **2001**, *40*, 1281.
  18. Ward, D. E.; Gai, Y.; Kaller, B. F. *J. Org. Chem.* **1995**, *60*, 7830.
  19. Padrón, J. I.; Vázquez, J. T. *Tetrahedron: Asymmetry* **1995**, *6*, 857.
  20. (a) Tsubuki, M.; Kanai, K.; Honda, T. *Heterocycles* **1993**, *35*, 281. (b) Tsubuki, M.; Kanai, K.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1640.
  21. Arndt, H. C.; Carroll, S. A. *Synthesis* **1979**, 202.
  22. Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2000**, *65*, 4779.