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# De novo asymmetric syntheses of (+)-goniothalamin, (+)-goniothalamin oxide, and 7,8-bis-*epi*-goniothalamin using asymmetric allylations

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ABSTRACT

A highly enantio- and diastereoselective approach to either enantiomer of (+)-goniothalamin, (+)-goniothalamin oxide, and 7,8-bis-*epi*-goniothalamin oxide has been developed from achiral cinnamyl alcohol or cinnamaldehyde. The asymmetry of the synthesis was installed by means of a Krische or Leighton allylation. The remaining stereochemistry was installed by a diastereoselective epoxidation.

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## 1. Introduction

Over the past decade, there have been several syntheses of goniothalamin (**3a**)[1] and goniothalamin oxide (**3b**)[2] derivatives. Goniothalamin was first isolated in 1967 from the bark of *Cryptocarya caloneura* and was assigned to have (*S*)-stereochemistry.[3] However, the stereochemistry was later revised to the (*R*) configuration.[4] Interestingly, it was recently discovered that both enantiomers possess potent cytotoxicity toward a range of cancer cell lines.[1] In addition, several derivatives of goniothalamin have been discovered from a variety of tropical/subtropical plants including; *Cryptocarya moschata*,[4] *Bryonopsis laciniosa*,[5] and various *Goniothalamus*[6] species. These natural products have shown cytotoxicity on a variety of cells lines including: MCF-7, T47D, and MDA-MB-231 (breast carcinoma); HeLa (human cervical carcinoma); HL-60 (leukemia carcinoma); Caov-3 (ovarian carcinoma).[7] More recently, several bis-lactone antitumor natural products, goniolactones, were isolated from *Goniothalamus cheliensis*.[8] Of the goniolactones we were most interested in goniolactone A (**1**) (Fig. 1).

Goniolactone A (**1**) can be envisioned as the epoxide opening dimer between two natural products altholactone (**2a**) and goniothalamine oxide (**3b**). Recently we have prepared both enantiomers of altholactone (**2a**) as well as all of its 2,3-diastereomers (**2b–d**) using asymmetric catalysis.[9] As part of our interest in the synthesis and biological investigation of goniolactone A (**1**) and analogues, we became interested in the synthesis of both enantiomers of goniothalamin oxide (**3b**) as well as its 7,8-bis-epimer (**3c**). While all of the previous syntheses of the goniothalamin oxide derived their asymmetry from the chiral pool or chiral reagents,[2] we were interested in a de novo asymmetric approach that would use asymmetric catalysis to install the three stereocenters in goniothalamin oxide and its diastereomer from achiral starting materials. In particular, we were interested in a de novo synthesis that used the recently reported Krische allylation of primary alcohols.[10] Herein we describe our successful efforts to implement this strategy for the de novo synthesis of goniothalamin oxide (**3b**) as well as its 7,8-bis-epimer (**3c**).[11]

Our strategy for the total synthesis of (*R*)-(+)-goniothalamin oxide is outlined in Scheme 1. We, like many others,[2] initially envisioned gaining access to either enantiomer of (*R*)-(+)-goniothalamin oxide, as well as its epoxide diastereomer, by means of an asymmetric allylation of commercially available *trans*-cinnamaldehyde (**7** to **6**). Divergent diastereoselective epoxidation of **6** should provide epoxides **5a** and **5b**. Finally, acylation and ring-closing metathesis of the resulting dienes **4a** and **4b** should provide both the desired natural product **3b** and target molecule **3c**. Because of our previous experience with the Leighton allylation, we

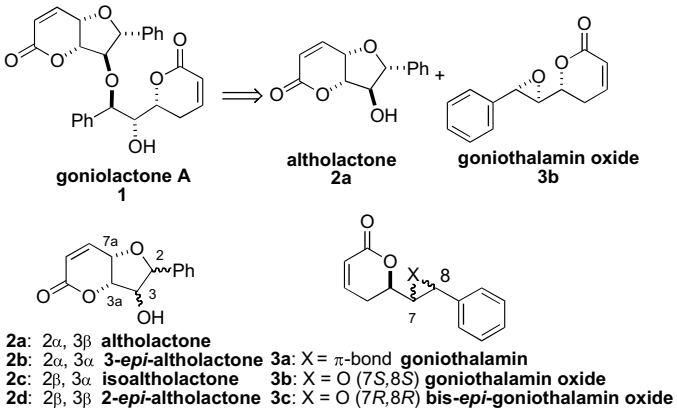


**Figure 1.** Goniothalamin-based derivatives.

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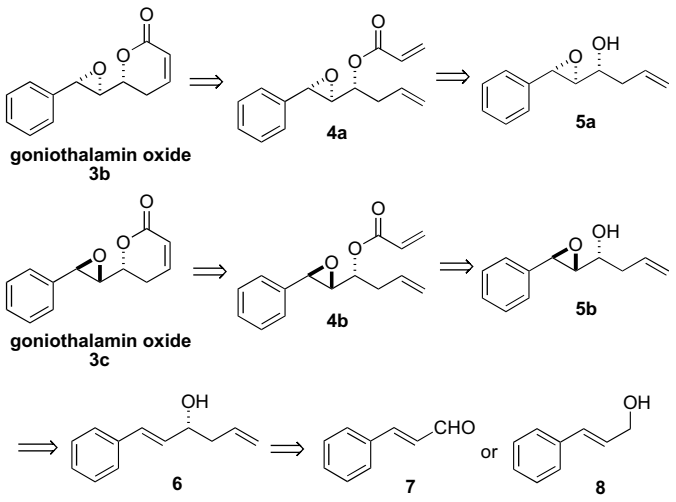



**Scheme 1.** Goniothalamin oxide retrosynthesis.

decided to initially pursue its use.[12] However, due to our interest in devising a 'de novo' asymmetric synthesis, we were also interested in investigating the use of the Krische allylation of *trans*-cinnamyl alcohol **8**.

## 2. Results and discussion

### 2.1. Approach to (*R*)-(+)-goniothalamin oxide

Our synthesis began with the Krische allylation of the *trans*-cinnamyl alcohol **8** (Scheme 2). To our delight using the iridium with the (*R*)-Cl,MeO-BIPHEP system described by Krische provided good yields of the enantiomeric homoallylic alcohol **6**, with high enantiomeric purities (90% ee). Similarly, the Krische allylation of the *trans*-cinnamyl alcohol **8** with the (*S*)-Cl,MeO-BIPHEP gave the enantiomeric homoallylic alcohol (*ent*)-**6**. For comparison purposes, the enantioselective allylation of *trans*-cinnamaldehyde **7** was preformed using the (*S*,*S*)-Leighton reagent[13] to furnish secondary alcohol **6** in 95% yield with excellent stereoselectivity (>95% ee).

We next investigated the chemo- and stereoselective epoxidation of the internal double bond (Scheme 3). This was most easily accomplished for diastereomer **5b** using *t*-BuOOH and catalytic $VO(acac)_2$ in refluxing benzene. Under these conditions the (1*R*,2′*R*,3′*R*)-diastereomer **5b** was produced in an 80% yield with a >10:1 diastereoselectivity. Unfortunately we were unable to find a similarly selective epoxidation of **6** to selectively form the (1*S*,2′*S*,3′*R*)-diastereomer **5a**. Our optimal conditions (*m*-CPBA in $CH_2Cl_2$ at 0 °C) furnish a 70% yield of a 1.5:1 mixture of **5a** to **5b**. The mixture of diastereomers was inseparable by flash chromatography, but could be cleanly separated following the acylation reaction (Scheme 4).

Both the pure diastereomer **5b** and the mixture of epoxide **5a**/**5b** could be acylated using acrylic acid, DMAP/DCC in $CH_2Cl_2$ (70% yield). The mixture of acylated product **4a**/**4b** was then easily separated by flash chromatography to give two pure diastereomers. The (1*S*,2′*S*,3′*R*)-diastereomer **4a** was used to complete the total synthesis of (*R*)-(+)-goniothalamin oxide, whereas the (1*R*,2′*R*,3′*R*)-diasteromer **4b** was used to prepare the diasteromeric epoxide **3c**.

An improved synthesis of the minor diastereomer **4a** was found by switching the acylation and epoxidation steps (Scheme 5). Exposing **6** to the same acylating conditions (DMAP/DCC in $CH_2Cl_2$, 70% yield) provided good yields of triene **9**. To our delight exposure of triene **9** to *m*-CPBA in $CH_2Cl_2$ at 0 °C selectively furnish the desired diastereomer in 70% yield and in >10:1 diastereoselectivity.[14]

With selective routes to the three desired acrylates **9**, **4a**, and **4b**, we turned to the metathesis ring closure to form the target molecules **3a**–**c**. Thus exposing methylene chloride solutions of triene **9**, diene **4a**, and diene **4b** gave 75%, 75%, and 70% yields of (*R*)-(+)-goniothalamin **3a**, (*R*)-(+)-goniothalamin oxide **3b**, and 7,8-bis-*epi*-(*R*)-(+)-goniothalamin **3c**, respectively. Both syntheses provide material with physical and spectral data that matched the data reported in the literature (Scheme 6).[1,2]

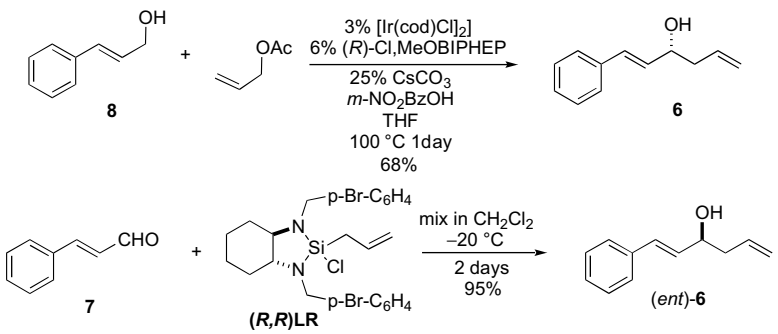
## 3. Conclusions

In conclusion, a de novo asymmetric approach to (+)-goniothalamin **3a**, (+)-goniothalamin oxide **3b**, and 7,8-bis-*epi*-goniothalamin oxide **3c** has been developed. Goniothalamin oxide was achieved in only four steps and 23% overall yield from achiral cinnamyl alcohol. Key to the successful approach is the use of a Krishe allylation. Further application of this approach to the synthesis of various goniolactone A is ongoing.

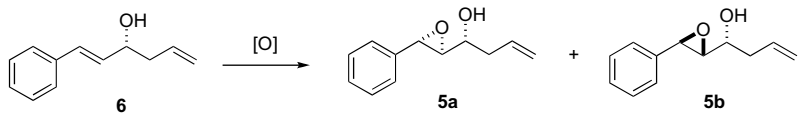
## 4. Experimental section

### 4.1. General

$^1H$ and $^{13}C$ spectra were recorded on 270 and 600 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane ($\delta$ 0.00 ppm) or $CDCl_3$ ($\delta$ 7.26 ppm) or $CD_3OD$ ($\delta$ 4.89 ppm) for $^1H$ and $CDCl_3$ ($\delta$ 77.1 ppm) or $CD_3OD$ ($\delta$ 49.15 ppm) for $^{13}C$. Optical rotations were measured with a digital polarimeter in the solvent specified. Infrared (IR) spectra were obtained on an FT-IR spectrometer. Flash column chromatography was performed on ICN reagent 60 (60–200 mesh) silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates (K6F 60 Å, $F_{254}$) and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or phosphomolybdic acid or potassium permanganate stain. $R_f$ values were obtained by elution in the stated solvent ratios (v/v). Ether, THF,

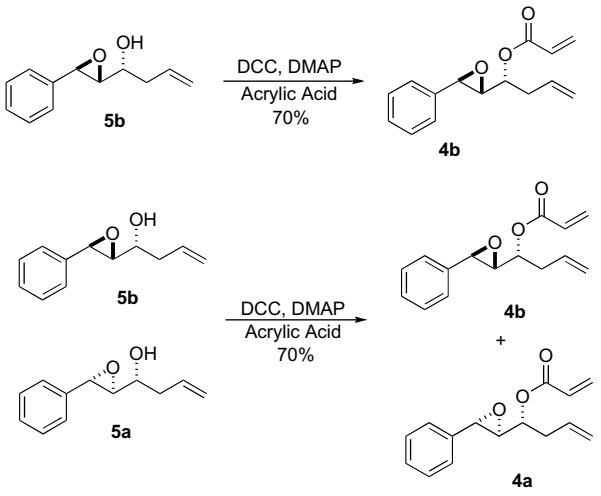



**Scheme 2.** Leighton versus Krische allylation.




| Reagent | 5a | 5b | 5b |
|---|---|---|---|
| mCPBA | 1.5 | 1 | 80% |
| 1% $VO(acac)_2$ *t*-BuOOH benzene | 1 | 10 | 70% |

**Scheme 3.** Stereoselective epoxidation of **6**.

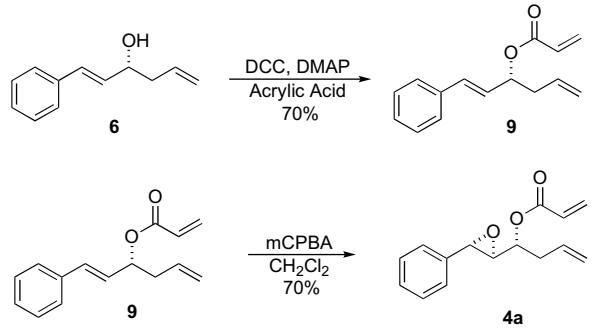



**Scheme 4.** Acylation of epoxides.

methylene chloride, and triethylamine were dried by passing through activated alumina (8×14 mesh) column with nitrogen gas pressure. Ir(cod)Cl]$_2$ and (*R*)-Cl,MeO-BIPHEP were purchased from Sigma/Aldrich, other commercial reagents were used without purification unless otherwise noted. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven/flame-dried glassware and standard syringe/septa techniques.

### 4.2. (3*R*,*E*)-1-Phenylhexa-1,5-dien-3-ol (6)

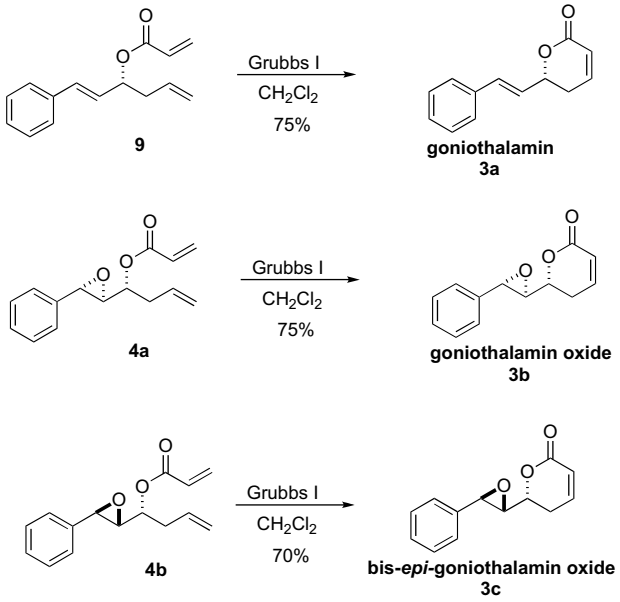
To a solution of *E*-cinnamaldehyde **7** (478 mg, 3.62 mmol) in 5 mL of $CH_2Cl_2$ at −20 °C was added (*S*,*S*)-Leighton reagent (1.0 g, 1.81 mmol) in 4 mL of $CH_2Cl_2$ at −20 °C. After stirring for 5 min, the solution was stored in a freezer for 20 h. The reaction was quenched with 1 N HCl (10%), satd $NH_4Cl$ aqueous solution, and then diluted with EtOAc then passed through Celite. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated to afford the crude product. Flash chromatography on silica gel (8:2 (v/v) hexane/EtOAc) provided compound **6** (600 mg, 95% yield) as a yellow oil. $R_f$=0.4 (8:2 (v/v) hexane/EtOAc). Spectral data gave a satisfactory match to previous reports.[15] $[\alpha]_D^{25}$ 30 (*c* 1.6, $CHCl_3$); IR (neat, $cm^{-1}$) 3348, 1640, 1493, 964, 913, 746, 691; $^1H$ NMR ($CDCl_3$, 600 MHz): $\delta$ 7.39 (m, 2H), 7.32 (m, 2H), 7.24 (m, 1H), 6.62 (d, *J*=15.6 Hz, 1H), 6.18 (dd, *J*=15.6, 6.6 Hz, 1H), 5.87 (dddd, *J*=17.4, 10.2, 7.2, 7.2 Hz, 1H), 5.19 (m, 2H), 4.37 (dd, 6.6, 6.6 Hz, 1H), 2.42 (m, 2H), 1.85 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 600 MHz): $\delta$ 136.6, 134.0, 131.5, 130.4, 128.5, 127.6, 126.4,118.5, 71.7, 42.0; HRMS (CI) calcd for $[C_{12}H_{14}O+Na]^+$: 197.0945, found: 197.0942.




**Scheme 5.** Acylation then epoxidation.

### 4.3. (3*S*,*E*)-1-Phenylhexa-1,5-dien-3-ol (*ent*-6)

To a pressure tube under argon were added cinnamyl alcohol **8** (107.3 mg, 0.8 mmol), [Ir(cod)Cl]$_2$ (13.6 mg, 0.02 mmol), (*S*)-Cl,MeO-BIPHEP (26.1 mg, 0.04 mmol), $Cs_2CO_3$ (52.1 mg, 0.16 mmol), and *m*-nitrobenzoic acid (13.3 mg, 0.08 mmol). The solution was heated to 50 °C for 10 min and then allyl acetate (800 mg, 8.0 mmol) was added to the solution. The pressure tube was sealed and the solution was heated to 100 °C for 24 h. The solution was cooled to room temperature and the solvent was removed. The residue was purified using silica gel flash chromatography eluting with 5–15% EtOAc/hexane (plus 1% triethylamine) to give 95.1 mg (0.545 mmol, 68%) of **6** ($R_f$=0.4 in 8:2 (v/v) hexane/EtOAc).[15] $[\alpha]_D^{25}$ −25 (*c* 1.6, $CHCl_3$); IR (neat, $cm^{-1}$) 3348, 1640, 1493, 964, 913, 746, 691; $^1H$ NMR ($CDCl_3$, 600 MHz): $\delta$ 7.39 (m, 2H), 7.32 (m, 2H), 7.24 (m, 1H), 6.62 (d, *J*=15.6 Hz, 1H), 6.18 (dd, *J*=15.6,




**Scheme 6.** Ring-closing metathesis of **4a**, **4b**, and **9**.

6.6 Hz, 1H), 5.87 (dddd, *J*=17.4, 10.2, 7.2, 7.2 Hz, 1H), 5.19 (m, 2H), 4.37 (dd, 6.6, 6.6 Hz, 1H), 2.42 (m, 2H), 1.85 (s, 1H); $^{13}$C NMR ($CDCl_3$, 600 MHz): $\delta$ 136.6, 134.0, 131.5, 130.4, 128.5, 127.6, 126.4,118.5, 71.7, 42.0; HRMS (CI) calcd for $[C_{12}H_{14}O+Na]^+$: 197.0945, found: 197.0942.

### 4.4. (1*R*,2′*S*,3′*S*)-(3′-Phenyloxiran-2′-yl)but-3-en-1-ol (5b)

To a solution of product (1*R*,*E*)-1-phenylhexa-1,5-dien-3-ol **6** (150 mg, 0.861 mmol) in 7 mL of benzene was added $VO(acac)_2$ (3 mg, 12 μmol) to produce a green colored solution. After 10 min of stirring, *t*-BuOOH (85 mg, 0.947 mmol) was added to the solution, which was accompanied by a color change to a pale yellow/orange color. The reaction was quenched with a satd $NaHCO_3$ aqueous solution. The layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated to afford crude product. Flash chromatography on silica gel (9:1 (v/v) hexane/EtOAc) provided compound **5b** (119 mg, 71% yield) as a colorless oil. Spectral data gave a satisfactory match to previous reports.[16] $R_f$=0.3 (8:2 (v/v) hexanes/EtOAc); $[\alpha]_D^{25}$ 26 (*c* 0.4, $CHCl_3$); IR (neat, $cm^{-1}$) 3439, 1642, 917; $^1$H NMR ($CDCl_3$, 270 MHz): $\delta$ 7.32 (m, 5H), 5.90 (ddt, *J*=16.8, 10.2, 7.2, 7.2 Hz, 1H), 5.17 (m, 2H), 3.99 (dddd, *J*=4.8, 4.8, 4.0, 4.0 Hz, 1H), 3.97 (d, *J*=1.8 Hz, 1H), 3.10 (dd, *J*=3.0, 1.8 Hz, 1H), 2.35(m, 2H), 2.03 (m, 1H); $^{13}$C NMR ($CDCl_3$, 600 MHz): $\delta$ 136.8, 133.4, 128.5, 128.3, 125.7, 118.4, 68.3, 64.2, 55.0, 37.9; HRMS (CI) calcd for $[C_{12}H_{14}O_2+Na]^+$: 213.0894, found: 213.0892.

### 4.5. (1*R*,2′*S*,3′*S*)-(3′-Phenyloxiran-2′-yl)but-3-enyl acrylate and (1*R*,2′*R*,3′*R*)-(3′-phenyloxiran-2′-yl)but-3-enyl acrylate (4a/4b)

A solution of product (1*R*,*E*)-1-phenylhexa-1,5-dien-3-ol **6** (150 mg, 0.861 mmol) in 5 mL of $CH_2Cl_2$ was cooled and stirred in an ice bath at 0 °C as a solution of *m*-CPBA (163 mg, 0.947 mmol) in 3 ml of $CH_2Cl_2$ was added dropwise. The mixture was washed with 10% $Na_2CO_3$ (2×5 ml) and brine (7 ml). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated to afford crude product. Flash chromatography on silica gel (9:1 (v/v) hexane/EtOAc) provided compound **5a**/**5b** (131 mg, 80% yield) as a colorless oil. $R_f$=0.3 (8:2 (v/v) hexanes/EtOAc). This mixture was inseparable and used as is.

To a solution of 3′-(phenyloxiran-2′-yl)but-3-en-1-ol **5a**/**5b** (100 mg, 0.526 mmol) in 7 mL of $CH_2Cl_2$ was added acrylic acid (75 mg, 1.05 mmol), DCC (217 mg, 1.05 mmol), and DMAP (4 mg) at room temperature. After stirring for 6 h the reaction mixture was diluted with ether, passed through Celite, and extracted with 1 M aqueous $NaHSO_4$ and then satd aqueous $NaHCO_3$. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated. Flash chromatography on silica gel (9.5:0.5 (v/v) hexanes/EtOAc) provided compound **4a**/**4b** (90 mg, 70% yield, 1.5:1, **4a**/**4b**) as a colorless oil.

#### *4.5.1. (1R,2′S,3′S)-(3′-Phenyloxiran-2′-yl)but-3-enyl acrylate (**4a**)*

$R_f$=0.59 (8:2 (v/v) hexanes/EtOAc); $[\alpha]_D^{25}$ 61 (*c* 0.4, $CHCl_3$); IR (neat, $cm^{-1}$) 1731, 1240, 1186, 1046; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$ 7.30 (m, 5H), 6.43 (dd, *J*=17.3, 1.5 Hz, 1H), 6.12 (dd, *J*=17.1, 10.4 Hz, 1H), 5.84 (m, 2H), 5.16 (m, 2H), 4.99 (ddd, *J*=7.2, 5.2, 3.2 Hz, 1H), 3.94 (d, *J*=2.0 Hz, 1H), 3.07 (dd, *J*=5.7, 2.0 Hz, 1H), 2.57 (m, 2H); $^{13}$C NMR ($CDCl_3$, 600 MHz): $\delta$ 165.3, 136.6, 132.4, 131.3, 128.5, 128.3, 128.1, 125.6, 118.5, 72.1, 61.8, 57.3, 35.8; HRMS (CI) calcd for $[C_{15}H_{16}O+Na]^+$: 267.0997, found: 267.0999.

#### *4.5.2. (1R,2′R,3′R)-(3′-Phenyloxiran-2′-yl)but-3-enyl acrylate (**4b**)*

$R_f$=0.58 (8:2 (v/v) hexanes/EtOAc); IR (neat, $cm^{-1}$) 1731, 1406, 1373, 1240, 1186, 1046, 984; $^1$H NMR ($CDCl_3$, 270 MHz): $\delta$ 7.29 (m, 5H), 6.48 (dd, *J*=17.3, 1.5 Hz, 1H), 6.17 (dd, *J*=17.0, 7.0 Hz, 1H), 5.83 (m, 2H), 5.14 (m, 2H), 4.98 (dd, *J*=12.6, 6.7, 1H), 3.79 (d, *J*=2.0 Hz, 1H), 3.17 (dd, *J*=5.9, 2.0 Hz, 1H), 2.54 (m, 2H); $^{13}$C NMR ($CDCl_3$, 600 MHz): $\delta$ 165.6, 136.5, 132.4, 131.6, 128.7, 128.6, 128.4, 125.8, 119.1, 73.1, 62.7, 56.7, 36.2; HRMS (CI) calcd for $[C_{15}H_{16}O+H]^+$: 245.1178, found: 245.1182.

### 4.6. (3*R*,*E*)-1-Phenylhexa-1,5-dien-3-yl acrylate (9)

To a solution of product **6** (100 mg, 0.573 mmol) in 7 mL of $CH_2Cl_2$ were added acrylic acid (82 mg, 1.14 mmol), DCC (236 mg, 1.14 mmol), and DMAP (4 mg) at room temperature. After stirring for 6 h the reaction mixture was diluted with ether, passed through Celite, and extracted with 1 M aqueous $NaHSO_4$ and then satd aqueous $NaHCO_3$. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated. Flash chromatography on silica gel (9.5:0.5 (v/v) hexanes/EtOAc) provided compound **9** (92 mg, 70% yield) as a colorless oil with spectral data that matched the reported data:[1] $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 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); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 163.5, 144.5, 135.5, 132.8, 128.5 (2C), 128.1 (2C), 126.4, 125.5, 121.4, 77.8, 29.8.

### 4.7. (1*R*,2′*R*,3′*R*)-(3′-Phenyloxiran-2′-yl)but-3-enyl acrylate (4b)

To a solution of **3b** (120 mg, 0.629 mmol) in 10 mL of $CH_2Cl_2$ were added acrylic acid (188 mg, 2.61 mmol), DCC (538 mg, 2.61 mmol), and DMAP (4 mg) at room temperature. After stirring for 6 h the reaction mixture was diluted with ether, passed through Celite, and extracted with 1 M aqueous $NaHSO_4$ and then satd aqueous $NaHCO_3$. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated. Flash chromatography on silica gel (9.5:0.5 (v/v) hexanes/EtOAc) provided compound **4b** (92.2 mg, 60% yield) as a colorless oil.

### 4.8. (*R*)-(+)-Goniothalamin (3a)

To a solution of **9** (25 mg, 0.11 mmol) in 5 mL of $CH_2Cl_2$ was added Grubbs (I) catalyst (9 mg, 0.011 mmol) at room temperature. Stirring commenced for 4 h at reflux conditions and then the reaction mixture was concentrated. Flash chromatography on silica gel (7:3 (v/v) hexane/EtOAc) provided compound **3a** (17 mg, 77% yield) as a dark oil (note: color caused by Grubbs catalyst). Spectral data gave a satisfactory match to previous reports. $[\alpha]_D^{25}$ +165 (*c* 1.0, $CHCl_3$); IR (neat, $cm^{-1}$) 1724, 1610, 1241, 815; $^1$H NMR: $\delta$ 7.34 (m, 5H), 6.94 (ddd, *J*=9.7, 4.9, 3.7 Hz, 1H), 6.74 (d, *J*=16 Hz, 1H), 6.30 (dd, *J*=16, 6.5 Hz, 1H), 6.10 (ddd, *J*=9.6, 1.7, 1.7 Hz, 1H), 5.10 (m, 1H), 2.59 (m, 2H); $^{13}$C NMR: $\delta$ 164.1, 144.8, 135.9, 133.3, 128.9, 128.5, 126.9, 125.8, 121.9, 78.1, 30.1; HRMS (CI) calcd for $[C_{13}H_{12}O_2+H]^+$: 201.0916, found: 201.0920.

### 4.9. (*R*)-(+)-Goniothalamin oxide (3b)

To a solution of **4a** (25 mg, 0.10 mmol) in 7 mL of $CH_2Cl_2$ was added Grubbs (I) catalyst (8 mg, 0.010 mmol) at room temperature. After stirring for 4 h at reflux, the reaction mixture was concentrated. Flash chromatography on silica gel (7:3 (v/v) hexane/EtOAc) provided compound **5** (17 mg, 77% yield) as a dark oil (note: color caused by Grubbs catalyst). $R_f$=0.9 (8:2 (v/v) hexanes/EtOAc). Spectral data gave a satisfactory match to previous reports.[17] $[\alpha]_D^{25}$ +100 (*c* 0.4, $CHCl_3$); IR (neat, $cm^{-1}$) 1724, 1247, 1041, 815; $^1$H NMR

($CDCl_3$, 600 MHz): $\delta$ 7.34 (m, 5H), 6.94 (ddd, $J$=9.7, 4.9, 3.7 Hz, 1H), 6.08 (ddd, $J$=9.6, 3.7, 1.7, 1H), 4.45 (ddd, $J$=9.1, 5.8, 5.8 Hz, 1H), 3.89 (d, $J$=1.9 Hz, 1H), 3.27 (dd, $J$=5.6, 1.9 Hz, 1H), 2.59 (m, 2H); $^{13}$C NMR ($CDCl_3$, 600 MHz): $\delta$ 163.7, 144.2, 135.7, 128.7, 128.6, 125.7, 121.6, 77.1, 61.5, 57.3, 25.9; HRMS (CI) calcd for $[C_{13}H_{13}O_3+Na]^+$: 239.0684, found: 239.0686.

### 4.10. 7,8-Bis-*epi*-(*R*)-(+)-goniothalamin oxide (3c)

To a solution of **4b** (25 mg, 0.10 mmol) in 7 mL of $CH_2Cl_2$ was added Grubbs (I) catalyst (8 mg, 0.010 mmol) at room temperature. After stirring for 4 h at reflux, the reaction mixture was concentrated. Flash chromatography on silica gel (7:3 (v/v) hexane/EtOAc) provided compound **6** (17 mg, 77% yield) as a dark oil. $R_f$=0.86 (8:2 (v/v) hexanes/EtOAc); $[\alpha]_D^{25}$ −5.4 (*c* 1.0, $CHCl_3$); IR (neat, $cm^{-1}$) 1724, 1386, 1247, 1041, 815, 698; $^1$H NMR ($CDCl_3$, 270 MHz): $\delta$ 7.33(m, 5H), 6.92 (ddd, $J$=8.7, 5.4, 3.0 Hz, 1H), 6.08 (ddd, 9.9, 2.6, 1.7 1H), 4.68 (ddd, $J$=8.7, 4.7, 3.7 Hz, 1H), 4.08 (d, $J$=1.9 Hz, 1H), 3.24 (dd, $J$=3.7, 1.9 Hz, 1H), 2.62 (m, 2H); $^{13}$C NMR ($CDCl_3$, 600 MHz): $\delta$ 162.8, 143.9, 135.9, 128.6, 128.6, 125.7, 121.6, 75.1, 62.1, 55.0, 26.2; HRMS (CI) calcd for $[C_{13}H_{13}O_3+H]^+$: 217.0785, found: 217.0866.

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