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De Novo Asymmetric Syntheses of (+)-Goniothalamine, (+)-Goniothalamine oxide and 7,8-Bis-*epi*-Goniothalamine using Asymmetric Allylations

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Abstract

A highly enantio- and diastereoselective approach to either enantiomer of (+)-goniothalamine, (+)-goniothalamine oxide and 7,8-bis-*epi*-goniothalamine 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.

1. Introduction

Over the past decade, there have been several syntheses of Goniothalamine (**3a**)ⁱ and Goniothalamine oxide (**3b**)ⁱⁱ derivatives. Goniothalamine was first isolated in 1967 from the bark of *Cryptocarya caloneura* and was assigned to have (*S*)-stereochemistry.ⁱⁱⁱ However, the stereochemistry was later revised to the (*R*) configuration.^{iv} Interestingly, it was recently discovered that both enantiomers possess potent cytotoxicity toward a range of cancer cell lines.ⁱ In addition, several derivatives of Goniothalamine have been discovered from a variety of tropical/subtropical plants including; *Cryptocarya moschata*,^{iv} *Bryonopsis laciniosa*,^v and various *Goniothalamus*^{vi} 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).^{vii} More recently, several bis-lactone antitumor natural products, goniolactones, were isolated from *Goniothalamus cheliensis*.^{viii} Of the goniolactones we were most interested in Goniolactone A (**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.^{ix} 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 goniothalamine oxide (**3b**) as well as its 7,8-bis-*epimer* (**3c**). While all of the previous syntheses of the goniothalamine oxide derived their asymmetry from the chiral pool or chiral reagents,ⁱⁱ we were interested in a de novo asymmetric approach that would use asymmetric catalysis to install the three stereocenters in goniothalamine oxide and its diastereomer from achiral starting materials. In particular, we were interested in a de novo synthesis that used the recently reported

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Krische allylation of primary alcohols.^x Herein we describe our successful efforts to implement this strategy for the de novo synthesis of goniiothalamine oxide (**3b**) as well as its 7,8-bis-epimer (**3c**).^{xi}

Our strategy for the total synthesis of (*R*)-(+)-goniiothalamine oxide is outlined in Scheme 1. We, like many others,ⁱⁱ initially envisioned gaining access to either enantiomer of (*R*)-(+)-goniiothalamine 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 decided to initially pursue its use.^{xii} 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*)-(+)-goniiothalamine 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, MeOBIPHEP 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, MeOBIPHEP 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^{xiii} 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 CH₂Cl₂ 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 epoxides **5a/5b** could be acylated using acrylic acid, DMAP/DCC in CH₂Cl₂ (70% yield). The mixture of acylated products **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*)-(+)-goniiothalamine oxide, whereas the (1*R*,2'*R*,3'*R*)-diastereomer **4b** was used to prepare the diastereomeric 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 CH₂Cl₂, 70% yield) provided good yields of triene **9**. To our delight exposure of triene **9** to *m*CPBA in CH₂Cl₂ at 0 °C selectively furnish the desired diastereomer in 70% yield and in >10:1 diastereoselectivity.^{xiv}

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*)-(+)-goniiothalamine **3a**, (*R*)-(+)-goniiothalamine oxide **3b** and 7,8-bis-*epi*-(*R*)-(+)-goniiothalamine **3c**, respectively. Both

syntheses provide material with physical and spectral data that matched the data reported in the literature.^{i,ii}

3. Conclusions

In conclusion, a de novo asymmetric approach to (+)-goniothalamine **3a**, (+)-goniothalamine oxide **3b** and 7,8-bis-*epi*-goniothalamine oxide **3c** has been developed. Goniothalamine oxide was achieved in only 4 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 ¹³C spectra were recorded on 270 and 600 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or CDCl₃ (δ 7.26 ppm) or CD₃OD (δ 4.89 ppm) for ¹H and CDCl₃ (δ 77.1 ppm) or CD₃OD (δ 49.15 ppm) for ¹³C. Optical rotations were measured with a digital polarimeter in the solvent specified. Infrared (IR) spectra were obtained on a 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 60Å, F₂₅₄) 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, 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/flamed-dried glassware and standard syringe/septa techniques.

4.1.1. (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 CH₂Cl₂ at –20 °C was added (*S,S*)-Leighton Reagent (1.0 g, 1.81 mmol) in 4 mL of CH₂Cl₂ at –20 °C. After stirring for 5 min the solution was stored in a freezer for 20 hrs. The reaction was quenched with 1N HCl (10%), sat. NH₄Cl 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 Na₂SO₄, 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.^{xv} [α]_D²⁵ = 30 (*c* 1.6, CHCl₃); IR (neat, cm^{–1}) 3348, 1640, 1493, 964, 913, 746, 691; ¹H NMR (CDCl₃, 600 MHz) 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); ¹³C NMR (CDCl₃, 600 MHz) δ 136.6, 134.0, 131.5, 130.4, 128.5, 127.6, 126.4, 118.5, 71.7, 42.0; HRMS (CI) calcd for [C₁₂H₁₄O + Na]⁺: 197.0945, Found: 197.0942

4.1.2. (3*S*,*E*)-1-Phenylhexa-1,5-dien-3-ol (ent-6**)**—To a pressure tube under argon was 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), Cs₂CO₃ (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 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 hrs. The solution was cooled to rt 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).^{xv} $[\alpha]_D^{25} = -25$ (c 1.6, CHCl₃); IR (neat, cm⁻¹) 3348, 1640, 1493, 964, 913, 746, 691; ¹H NMR (CDCl₃, 600 MHz) 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); ¹³C NMR (CDCl₃, 600 MHz) δ 136.6, 134.0, 131.5, 130.4, 128.5, 127.6, 126.4, 118.5, 71.7, 42.0; HRMS (CI) calcd for [C₁₂H₁₄O + Na]⁺: 197.0945, Found: 197.0942

4.1.3. (1R,2'S,3'S)-3'-phenyloxiran-2'-yl)but-3-en-1-ol (5b)—To a solution of product (1R,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 μ mol) 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 sat. NaHCO₃ 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 Na₂SO₄, 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.^{xvi} R_f = 0.3 (8:2 (v/v) hexanes:EtOAc); $[\alpha]_D^{25} = 26$ (c 0.4, CHCl₃); IR (neat, cm⁻¹) 3439, 1642, 917; ¹H NMR (CDCl₃, 270 MHz) 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); ¹³C NMR (CDCl₃, 600 MHz) δ 136.8, 133.4, 128.5, 128.3, 125.7, 118.4, 68.3, 64.2, 55.0, 37.9; HRMS (CI) calcd for [C₁₂H₁₄O₂ + Na]⁺: 213.0894, Found: 213.0892

4.1.4. (1R,2'S,3'S)-3'-phenyloxiran-2'-yl)but-3-enyl acrylate and (1R,2'R,3'R)-3'-phenyloxiran-2'-yl)but-3-enyl acrylate (4a/4b)—To a solution of product (1R,E)-1-phenylhexa-1,5-dien-3-ol **6** (150 mg, 0.861 mmol) in 5 mL of CH₂Cl₂ 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 CH₂Cl₂ was added dropwise. The mixture was washed with 10% Na₂CO₃ (2 $\times$ 5 mL) and brine (7 mL). The combined organic layers were dried over anhydrous Na₂SO₄, 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 CH₂Cl₂ 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 hrs the reaction was diluted with ether, passed through celite, and extracted with 1M aqueous NaHSO₄ and then sat. aqueous NaHCO₃. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, 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.

4a R_f = 0.59 (8:2 (v/v) hexanes:EtOAc); $[\alpha]_D^{25} = 61$ (c 0.4, CHCl₃); IR (neat, cm⁻¹) 1731, 1240, 1186, 1046; ¹H NMR (CDCl₃, 600 MHz) 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); ¹³C NMR (CDCl₃, 600 MHz) δ 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 [C₁₅H₁₆O + Na]⁺: 267.0997, Found: 267.0999

4b R_f = 0.58 (8:2 (v/v) hexanes:EtOAc); IR (neat, cm⁻¹) 1731, 1406, 1373, 1240, 1186, 1046, 984; ¹H NMR (CDCl₃, 270 MHz) 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); ¹³C NMR (CDCl₃, 600 MHz) δ 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.

4.1.5. (9)—To a solution of product **6** (100 mg, 0.573 mmol) in 7 mL of CH_2Cl_2 was 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 hrs the reaction was diluted with ether, passed through celite, and extracted with 1M aqueous $NaHSO_4$ and then sat. 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: 1H NMR (600 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 144.5, 135.5, 132.8, 128.5 (2C), 128.1 (2C), 126.4, 125.5, 121.4, 77.8, 29.8

4.1.6. (1R,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 was 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 hrs the reaction was diluted with ether, passed through celite, and extracted with 1M aqueous $NaHSO_4$ and then sat. 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.

4.1.7. (R)-(+)-goniothalamine (3a)—To a solution **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 hrs at reflux conditions and then the reaction 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. $[\alpha]^{25}_D + 165$ (c 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1724, 1610, 1241, 815; 1H NMR: δ 7.34 (m, 5H), 6.94 (ddd, $J = 9.7, 4.9, 3.7$ Hz, 1H), 6.74 (d, $J = 16, 1H$), 6.30 (dd, $J = 16, 6.5, 1H$), 6.10 (ddd, $J = 9.6, 1.7, 1.7, 1H$), 5.10 (m, 1H), 2.59 (m, 2H); ^{13}C NMR: δ 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.

4.1.8. (R)-(+)-goniothalamine 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 hrs at reflux the reaction 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.^{xvii} $[\alpha]^{25}_D + 100$ (c 0.4, $CHCl_3$); IR (neat, cm^{-1}) 1724, 1247, 1041, 815; 1H NMR ($CDCl_3$, 600 MHz) 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) δ 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.

4.1.9. 7,8-bis-*epi*-(R)-(+)-goniothalamine 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 hrs at reflux the reaction 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); $[\alpha]^{25}_D - 5.4$ (c 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1724, 1386, 1247, 1041, 815, 698; 1H NMR ($CDCl_3$, 270 MHz) 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 Hz, 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) δ 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 $[\text{C}_{13}\text{H}_{13}\text{O}_3 + \text{H}]^+$: 217.0785 Found: 217.0866.

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Figure 1.
Goniothalamine -based derivatives

Scheme 1.
Goniiothalamine oxide Retrosynthesis

Scheme 2.
Leighton versus Krische allylation

Scheme 3.
Stereoselective Epoxidation of **6**

Scheme 4.
Acylation of epoxides

Scheme 5.
Acylation then epoxidation

Scheme 6.
Ring-Closing Metathesis of **4a**, **4b** and **9**