

Total synthesis of (-)-cryptocaryalactone, (R)-(+)-goniothalamine, 7-epi-goniodiol and (+)-kavalactones

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Abstract

A flexible stereoselective synthesis of styryl lactones (-) cryptocaryalactone, 7-epi-goniodiol, (R)-(+)-goniothalamine, (R)-(+)-kavain and (S)-(+)-7, 8-dihydrokavain is synthesized from inexpensive and readily available cinnamaldehyde by applying enantioselective allylation and dihydroxylation reactions. The attractive features of the synthesis is using commercially available inexpensive single starting material for the all the styryl lactones.

Keywords: Synthesis; Cryptocaryalactone; 7-epi-goniodiol; (R)-(+)-goniothalamine; (R)-(+)-kavain and (S)-(+)-8-dihydrokavain; cinnamaldehyde

Introduction

Styryl lactones represent a class of natural and synthetic compounds with significant cytotoxicity including antitumour, antifungal and antibiotic properties. In continuation of their importance, many styryl lactones have been isolated from plants and fungi. (-) Cryptocaryalactone 1 and R-(+)-goniothalamine 3 are the styryl lactones isolated from the dried bark of *Cryptocarya* species. (R)-(+)-Goniothalamine 3 displays cytotoxic effects against colon cancer, breast cancer, lung carcinoma and normal cell lines. Similarly, 7-epi-goniodiol 2 isolated from the ethanolic extract of stem barks of *Goniothalamus leiocarpus* (Annonaceae), a tropical plant found in south Yunnan province in China showed strong inhibition against HL-60 in very low concentration of 1 µg/mL. α -Pyrone derivatives known as the kavalactones comprise approximately 15% of the Kava plant (*Piper methysticum*) rootstock. The more widespread of these include kavain 4 and dihydrokavain 5. The kavalactones displays anaesthetic, sedative, analgesic, ticonvulsive, antispasmodic, antimycotic, antifungal, antithrombotic and central muscular relaxing properties. Although many successful approaches to the synthesis of cryptocaryalactone, (R)-(+)-goniothalamine, 7-epi-goniodiol and kavalactone have been reported their biological importance and activity, prompted us to design a concise and flexible stereo selective route toward the total synthesis of these lactones. The proposed route describes the synthesis of all the five styryl lactones from inexpensive, commercially available starting material cinnamaldehyde and makes it useful and inexpensive route for the synthesis of styryl lactones.

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Materials and Methods

(R,E)-1-phenylhexa-1,5-dien-3-ol (7). A mixture of (R)-(+)-1,1'-bi-2-naphthol (0.429 g, 1.5 mmol), 1M Ti(O-*i*-Pr)₄ in CH₂Cl₂ (0.447 mL, 1.5 mmol), and oven-dried powdered 4 Å molecular sieves (2 g) in CH₂Cl₂ (60 mL) was heated at reflux for 1h. The red-brown mixture was cooled to room temperature and cinnamaldehyde 6 (2 g, 15 mmol) was added. After being stirred for 10 min, the contents were cooled to -78 °C, and allyl tri-*n*-butylstannane (5.16 mL, 16.6 mmol) was added. The reaction was stirred at -20 °C for 5 h., warmed to 0 °C and stirring was continued for 12 h. The reaction mixture was quenched with saturated NaHCO₃ (5 mL). The contents were stirred for 1 h and then poured over Na₂SO₄ and filtered through a plug of celite. After evaporation of solvent, the crude material was purified by column chromatography to give the alcohol 7 as colorless oil. The compound has 88.8% ee as determined by chiral HPLC (Chiralcel OB hexane/2- propanol 95:5, 0.6 mL/min, 254 nm, t_R = 15.14 min for minor enantiomer, t_S = 16.51 min. for major enantiomer). Yield: 75%; [α]_D²⁵ (-) 10.6° (Et₂O, c 1.0), lit. [47] [α]_D²⁵ (-) 12.3° (Et₂O, c 1.0); ¹H NMR (200 MHz, CDCl₃): δ 7.15-7.36 (m, 5H), 6.56 (d, J = 17.37 Hz, 1H), 6.19 (dd, J = 6.79, Hz, 1H), 5.75-5.90 (m, 1H), 5.10-5.20 (m, 2H), 4.26-4.34 (m, 1H), 2.32-2.42 (m, 2H); ¹³C NMR (300 MHz, CDCl₃): δ 136.4, 134.3, 131.5, 130.2, 128.8, 127.4, 126.6, 118.6, 71.5, 42.3; [M+Na]⁺ found = 197.20, C₁₂H₁₄O requires 197.10 [1].

(R,E)-tert-butyldimethyl((1-phenylhexa-1,5-dien-3-yl)oxy)silane. To a solution of alcohol 7 (2.0 g, 11.4 mmol) in dry CH₂Cl₂ (20 ml) and imidazole (1.16 g, 17.25 mmol) at room temperature under nitrogen atmosphere was added TBDMSCl (2 g, 13.8 mmol) and stirred for 4 h. The reaction mixture was diluted with water (3 ml) and extracted with CH₂Cl₂ (2 x 5 ml). The combined organic layers were washed with brine (1 x 5 ml), dried (Na₂SO₄), filtered and concentrated under vacuum to afford the crude product. Column chromatography of the crude product afforded compound 8 as a colorless liquid. Yield: 92%; ¹H NMR (200 MHz, CDCl₃): δ 7.17-7.37 (m, 5H), 6.47 (d, J = 16.24 Hz, 1H), 6.14 (dd, J = 5.90, 6.64 Hz, 1H), 5.74-5.90 (m, 1H), 5.01-5.13 (m, 2H), 4.25-4.36 (m, 1H), 2.27-2.41 (m, 2H), 0.92 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ¹³C NMR (300 MHz, CDCl₃): δ 137.4, 135.2, 132.6, 129.4, 128.1, 126.6, 117.3, 73.6, 43.5, 26.1, 18.4, -4.0, -4.4; [M+Na]⁺ found = 311.0, C₁₈H₂₈OSi requires 311.19.

(2R,4R,E)-4-((tert-butyldimethylsilyl)oxy)-6-phenylhex-5-ene-1,2-diol (9a) and (1R,2S,3R)-3-((tert-butyldimethylsilyl)oxy)-1-phenylhex-5-ene-1,2-diol (10a). To a well stirred solution of AD-mix β (5.2 g) and CH₃SO₂NH₂ (3.50 g, 3.65 mmol) in (1:1) *t*-butanol:water (37 ml) at 0 °C the compound 8 (1.1 g, 3.68 mmol) was added. After the reaction was completed (TLC), 3.5 g of Na₂S₂O₅ was added and the stirring was continued for 30 min. The reaction mixture was extracted with ethyl acetate (4x50 ml). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by silicagel column chromatography afforded 9a (0.376 g) and 10a (0.56 g) as viscous liquids. Yield: 80% (overall); 9a: ¹H NMR (200 MHz, CDCl₃): δ 7.15-7.37 (m, 5H), 6.48 (d, J = 15.10 Hz, 1H), 6.11 (d, J = 6.79 Hz, 1H), 4.57-4.48 (m, 1H), 3.81-3.91 (m, 1H), 3.52-3.62 (m, 1H), 3.35-3.47 (m, 1H), 1.73-1.87 (m, 1H), 1.54-1.69 (m, 1H), 0.93 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (300 MHz, CDCl₃): δ 134.62, 133.18, 126.25, 125.32, 73.84, 70.46, 63.98, 36.45, 26.77, 16.15 ; [M+Na]⁺ found = 345.1, C₁₈H₃₀O₃Si requires 345.18; 10a: ¹H NMR (200 MHz, CDCl₃): δ 7.22-7.32 (m, 5H), 5.71-5.86 (m, 1H), 4.89-5.12 (m, 3H), 3.82-3.89 (m, 1H), 3.50-3.58 (m, 1H), 2.25-2.48 (m, 2H), 0.92 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ¹³C NMR (300 MHz, CDCl₃): δ 143.24, 126.55, 125.13, 124.41, 125.64, 117.33, 107.86, 72.34, 70.42, 68.75, 34.97, 27.26, 20.17; [M+Na]⁺ found = 345.1, C₁₈H₃₀O₃Si requires 345.18 [2].

(4R,E)-4-((tert-butyldimethylsilyl)oxy)-6-phenylhex-5-ene-1,2-diol and (3R)-3-((tert-butyldimethylsilyl)oxy)-1-phenylhex-5-ene-1,2-diol (10). To a stirred solution of *N*-Methylmorpholine *N*-oxide (2.98 g, 0.025 mol) in Acetone:Water (9:1, 30 mL), was added Osmium tetroxide (0.1 g, 0.39 mmol) followed by Compound 8 (5 g, 0.017 mol). The reaction mixture was stirred for 16 h at RT. After completion by TLC, the reaction mixture was quenched with water and extracted with ethylacetate (4x50 ml). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by silicagel column chromatography afforded 9 (3.4 g) and 10 (0.85 g), (overall 4.25 g, 78% yield) as viscous liquids ; 9: ¹H NMR (200 MHz, CDCl₃): δ 7.17-7.33 (m, 5H), 6.51 (d, J = 15.10 Hz, 1H), 6.12 (d, J = 6.79 Hz, 1H), 4.55-4.47 (m, 1H), 3.83-3.94 (m, 1H), 3.51-3.61 (m, 1H), 3.33-3.42 (m, 1H), 1.72-1.86 (m, 1H), 1.55-1.72 (m, 1H), 0.95 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ¹³C NMR (300 MHz, CDCl₃): δ 134.65, 133.23, 126.21, 125.29, 73.82, 70.44, 63.96, 36.47, 26.75, 16.18 ; [M+Na]⁺ found = 345.1, C₁₈H₃₀O₃Si requires 345.18. 10: ¹H NMR (200 MHz, CDCl₃): δ 7.22-7.32 (m, 5H), 5.71-5.86 (m, 1H), 4.89-5.12 (m, 3H), 3.82-3.89 (m, 1H), 3.50-3.58 (m, 1H), 2.25-2.48 (m, 2H), 0.92 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ¹³C NMR (300 MHz, CDCl₃): δ 143.22, 126.53, 125.11, 124.42, 125.65, 117.36, 107.88, 72.38, 70.45, 68.76, 34.95, 27.25, 20.15; [M+Na]⁺ found = 345.1, C₁₈H₃₀O₃Si requires 345.18.

tert-butyldimethyl(((R,E)-1-((R)-oxiran-2-yl)-4-phenylbut-3-en-2-yl)oxy)silane. To a stirred solution of diol 9a (2.0 g, 6.21 mmol), triethylamine (1.3 ml, 9.31 mmol) in dry DCM (30 ml) at 0 °C was added tosyl chloride (1.18 g, 6.21 mmol) portionwise. After stirring for 6 h at room temperature, the reaction mixture was quenched with saturated aqueous NaHCO₃ solution. The organic layer was separated and the aqueous layer was extracted with DCM (30 ml). The combined organic layers were washed with water, brine and dried over anhydrous Na₂SO₄. Removal of solvent under reduced pressure gave crude tosylated product (2.6 g), which was

taken in 50 mL of anhydrous THF, cooled to 0 °C and NaH (0.33 g [60% w/w in paraffin oil], 8.2 mmol) was added pinch wise. The reaction mixture was stirred at the same temperature for 2h. After completion by TLC, quenched with saturated NH₄Cl and extracted with ethyl acetate (2x20 ml). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. Purification by silicagel column chromatography afforded the epoxide 11 as colorless liquid. Yield: 80%; ¹H NMR (200 MHz, CDCl₃): δ 7.14-7.38 (m, 5H), 6.48 (d, J = 14.98 Hz, 1H), 6.14 (dd, J = 6.04 and 6.79 Hz, 1H), 4.44-4.57 (m, 1H), 2.93-3.04 (m, 1H), 2.69-2.74 (m, 1H), 2.43-2.48 (m, 1H), 1.74-1.90 (m, 2H), 0.92 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C NMR (300 MHz, CDCl₃): δ 132.68, 130.26, 125.45, 124.35, 72.78, 48.64, 45.08, 36.88, 27.37, 18.74; [M+Na]⁺ found = 327.10, C₁₈H₂₈O₂Si requires 327.19 [3].

(5S,7R,E)-methyl 7-((tert-butyldimethylsilyl)oxy)-5-hydroxy-9-phenylnon-8-en-2-ynoate. A solution of n-butyl lithium in hexane (1.85 ml, 4.8 mmol, 2.6 M solution in hexane) was added to a solution of methyl propiolate (0.55 g, 6.57 mmol) in THF (20 ml) at -78 oC under nitrogen atmosphere, and the mixture was stirred for 15 min. Then, BF₃.OEt₂ (0.4 ml, 3.3 mmol) was added to the solution and the stirring was continued for 15 min. at -78 oC. Finally, a solution of epoxide 11 (1.0 g, 3.3 mmol) in dry THF (5 ml) was added, and after stirring the reaction mixture for 3 h at -78 oC, the reaction was quenched by adding saturated aqueous NH₄Cl solution (40 ml). The reaction mixture was extracted with ethyl acetate and dried (Na₂SO₄). Evaporation of the solvent resulted in crude alcohol, which was purified by column chromatography to afford pure alcohol 12 (0.960 g, 75% yield) as a yellow color oil. Yield: 75%; ¹H NMR (200 MHz, CDCl₃): δ 7.18-7.44 (m, 5H), 6.45 (d, J = 14.98 Hz, 1H), 6.15 (dd, J = 6.04 and 6.79 Hz, 1H), 4.56-4.71 (m, 1H), 3.93-4.17 (m, 1H), 3.70 (s, 3H), 2.44-2.54 (m, 2H), 1.75-1.88 (m, 2H), 0.91 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ¹³C NMR (300 MHz, CDCl₃): δ 150.27, 131.66, 130.22, 127.42, 125.66, 84.86, 76.54, 74.42, 66.75, 51.39, 38.54, 27.98, 24.82, 22.34.; [M+Na]⁺ found = 411.20, C₂₂H₃₂O₄Si requires 411.20.

(2Z,5S,7R,8E)-methyl 7-((tert-butyldimethylsilyl)oxy)-5-hydroxy-9-phenylnona-2,8-dienoate. To a stirred solution of 0.512 g of alkyne 12 (0.512 g, 1.31 mmol) in absolute MeOH (10 mL) was added Lindlar's catalyst (0.318 g). The suspension was stirred at rt under 1 atm of H₂ pressure. After completion of reaction by TLC (~ 0.5 h), the catalyst was removed by filtration and the solvent was removed from the reaction mixture by rotary evaporation. The LCMS of crude product indicated the presence of isomers in 95:5 ratio. After column chromatography over silica gel to afforded the major Z-Isomer 13 as colorless oil. Yield: 89%; ¹H NMR (200 MHz, CDCl₃): δ 7.18-7.35 (m, 5H), 6.35-6.45 (m, 2H), 6.10 (dd, J = 7.36 Hz, 1H), 5.86 (d, J = 11.52 Hz, 1H), 4.48-4.58 (m, 1H), 3.90-4.01 (m, 1H), 3.68 (s, 3H), 2.75-2.88 (m, 2H), 1.62-1.84 (m, 2H), 0.93 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); ¹³C NMR (300 MHz, CDCl₃): δ 162.39, 148.19, 137.62, 135.45, 126.82, 124.58, 121.96, 77.97, 71.85, 53.58, 40.18, 36.66, 27.48, 20.73; [M+Na]⁺ found = 413.30, C₂₂H₃₄O₄Si requires 413.21 [4].

(S)-6-((R,E)-2-hydroxy-4-phenylbut-3-en-1-yl)-5,6-dihydro-2H-pyran-2-one. To as stirred solution of ester 13 (0.2 g, 0.51 mmol) in 2 mL of methanol was added p-toluene sulphonic acid mono hydrate (0.02 g, 0.1 mmol). The reaction mixture was stirred for 1h. and solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with NaHCO₃ (4x5 mL) and extracted with CH₂Cl₂ giving water, brine wash, dried (Na₂SO₄) and concentrated to afford the deacetyl cryptocaryalactone 14 as pale yellow colour oil. The crude product 14 was directly used in the next step without further purification.

(-)-Cryptocaryalactone. To a stirred solution of lactone 14 (0.1 g, 0.4 mmol) in pyridine (1 mL) was added acetic anhydride (0.1 mL, 1 mmol). The reaction mixtutre was stirred for 6h. and extracted with ethyl acetate giving sat. CuSO₄, water, brine wash. The combined organic layers were dried (Na₂SO₄) and concentrated. The crude residue was subjected to column chroamatography to afford the pure (-)-cryptocaryalactone 1. The compound has 93.4% ee as determined by chiral HPLC (0.09 g, 80% yield). Solid (mp 109-110 °C); [α]_D²⁵ (-) 19.5° (CHCl₃, c 0.42), lit. [4] [α]_D²⁵ (-) 20.0° (CHCl₃, c 0.42); ¹H NMR (CDCl₃, 300 MHz): δ 7.25-7.41(m, 5H), 6.88 (m, 1H), 6.67 (dd, J=15.7, 0.3 Hz, 1H), 6.11 (dd, J=15.9, 7.3 Hz, 1H), 6.03 (dt, J = 9.9 Hz, 1H), 5.66 (m, 1H), 4.55 (m, 1H), 2.35-2.42 (m, 2H), 2.11-2.18 (m, 1H). 2.08 (s, 3H), 2.04-2.09 (m, 1H); ¹³C NMR (CDCl₃, 50 MHz): 170.0, 163.8, 144.7, 133.2, 135.9, 128.6, 128.2, 126.6, 121.5, 74.2, 70.7, 39.9, 29.5, 21.3; [M⁺Na]⁺ found = 309.23, C₁₇H₁₈O₄ requires 309.12; Anal calcd for C₁₇H₁₈O₄: C, 71.31; H, 6.34; O, 22.35; Found: C, 71.36; H, 6.38; O, 22.33.

(R)-3-((tert-butyldimethylsilyl)oxy)-3-((4S,5R)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl)propanal. To a solution of diol 10a (3 g, 9.3 mmol) in 30 mL of dry CH₂Cl₂, was added 2,2-dimethoxypropane (1.93 g, 18.6 mmol) and PTSA (100 mg, 0.58 mmol) and the reaction mixture was stirred at ambient temperature for 4 h. The organic layer was evaporated under reduced pressure to afford the crude acetone. The crude acetone was dissolved DCM and cooled to -78 °C. Then Ozone gas was passed under stirring into the reaction mixture *via* pre-fitted glass tube. The appearance of a sky blue color in the solution indicates the completion of reaction. After completion, crushed Triphenyl Phosphene (4 g) was added, stirred for 30 min. and allowed to room temperature for 6h. Then the reaction mixture was concentrated under reduced pressure and the crude product 15 was directly used in the next step without further purification [5].

(R,Z)-methyl 5-((tert-butyldimethylsilyl)oxy)-5-((4S,5R)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl)pent-2-enoate. A solution of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl) phosphonate (0.48 g, 1.50 mmol) in THF (10 ml) was treated with NaH (0.08 g

[60% w/w in paraffin oil], 2 mmol) at -78 °C for 15 min. Aldehyde 15 (0.5 g, 1.37 mmol), was then added and the resulting mixture was stirred at -78 °C for 1h. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethylacetate (3x5 ml). The combined organic extracts were washed with water (2x15 ml) followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The LCMS of crude product indicated the presence of isomers in 9:1 ratio. The resulting mixture was subjected to column chromatography to yield major product (Z)- α,β -unsaturated ester 16 as colourless oil. Yield: 82%; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.32-7.52 (m, 5H), 6.14-6.26 (m, 1H), 5.82 (d, $J = 11.33$ Hz, 1H), 5.00 (d, $J = 8.30$ Hz, 1H), 4.07-4.14 (m, 1H), 3.95 (dd, $J = 3.02$ Hz, 1H), 3.75 (s, 3H), 2.85-2.97 (m, 1H), 2.72-2.83 (m, 1H), 1.58 (s, 3H), 1.56 (s, 3H), 0.96 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 162.19, 149.25, 138.62, 130.35, 127.58, 126.42, 123.28, 115.89, 82.86, 75.43, 71.67, 53.69, 37.76, 28.12, 26.49, 19.96; $[\text{M}^+\text{Na}]^+$ found = 443.20, $\text{C}_{23}\text{H}_{36}\text{O}_5\text{Si}$ requires 443.23.

7-epi-goniodiol 2. Prepared from compound 16 as per the procedure used for the synthesis of compound 14. The compound has 96.5% ee as determined by chiral HPLC. $[\alpha]_{\text{D}25} +83.5$ (c 0.4, MeOH), lit.[31] $[\alpha]_{\text{D}25} +84.2$ (c 0.4, MeOH); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.20-7.75 (m, 5H), 6.82 (ddd, $J = 9.5$ Hz, $J = 5.9$ Hz, $J = 2.9$ Hz, 1H), 5.95 (ddd, $J = 9.5$ Hz, $J = 2.2$ Hz, $J = 1.1$ Hz, 1H), 5.35 (d, $J = 3.7$ Hz, 1H), 4.90 (dt, $J = 10.8$ Hz, $J = 5.4$ Hz, 1H), 4.30 (dd, $J = 5.9$ Hz, $J = 3.8$ Hz, 1H), 2.78 (m, 1H), 2.72 (m, 1H); $^{13}\text{C NMR}$ (50 MHz, CDCl_3): δ 164.12, 146.44, 141.05, 128.75, 128.23, 126.76, 120.57, 76.87, 75.13, 73.55, 26.08; $[\text{M}+\text{Na}]^+$ found = 257.1, $\text{C}_{13}\text{H}_{14}\text{O}_4$ requires 257.09; Anal calcd for $\text{C}_{13}\text{H}_{14}\text{O}_4$: C, 66.66; H, 6.02; O, 27.32; Found: C, 66.69; H, 6.08; O, 27.39.

(R,E)-3-((tert-butyldimethylsilyloxy)-5-phenylpent-4-enal (17). To a stirred solution of diol 9 (0.5 g, 1.55 mmol) in 15 mL of CH_2Cl_2 was added sat. aq. NaHCO_3 solution (1 mL) at room temperature. The reaction mixture was stirred vigorously and then added solid NaIO_4 (0.66 g, 3.1 mmol) portion wise over 10 min. maintaining reaction temperature below 25 °C. After addition of NaIO_4 , the reaction mixture was stirred for 2 h, added 2.0 g of Na_2SO_4 , stirred vigorously for 15 min and filtered. The solvent was removed by rotary evaporation. The crude mixture was subjected to filter column chromatography to obtain the compound 17 as colorless oil. Yield: 80%; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 9.78 (t, $J = 2.26$ Hz, 1H), 7.18-7.35 (m, 5H), 6.55 (d, $J = 14.35$ Hz, 1H), 6.17 (dd, $J = 6.04$ Hz, 1H), 4.77-4.85 (m, 1H), 2.66-2.76 (m, 1H), 2.52-2.61 (m, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 196.55, 138.93, 130.52, 126.19, 125.23, 77.78, 55.65, 29.28, 20.08; $[\text{M}+\text{Na}]^+$ found = 313.10, $\text{C}_{17}\text{H}_{26}\text{O}_2\text{Si}$ requires 313.17 [2].

(R,2Z,6E)-methyl 5-((tert-butyldimethylsilyloxy)-7-phenylhepta-2,6-dienoate. Prepared from compound 17 as per the procedure used for the synthesis of compound 16. The LCMS of crude product indicated the presence of isomers in 9:1 ratio. After column chromatography of the resulting mixture isolated the major product (Z)- α,β -unsaturated ester 18 as colourless oil. Yield: 80%; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.18-7.48 (m, 5H), 6.60 (d, $J = 14.48$ Hz, 1H), 6.35-6.45 (m, 1H), 6.22 (dd, $J = 6.83$ Hz, 1H), 5.58-5.68 (m, 1H), 4.40-4.50 (m, 1H), 3.70 (s, 3H), 2.90-3.00 (m, 1H), 2.50-2.60 (m, 1H), 1.0 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 162.96, 149.19, 141.22, 134.46, 129.63, 125.42, 120.96, 77.75, 56.42, 38.96, 29.68, 21.08; $[\text{M}+\text{Na}]^+$ found = 369.2, $\text{C}_{20}\text{H}_{30}\text{O}_3\text{Si}$ requires 369.2.

(R)-(+)-Goniothalamin 3. Prepared from compound 18 as per the procedure used for the synthesis of compound 14. The compound has 98.6% ee as determined by chiral HPLC. white crystalline solid, mp 82-84 °C, lit. [25] 85 °C; $[\alpha]_{\text{D}25} +163$ (c 1.7, CHCl_3), lit. [25] $[\alpha]_{\text{D}25} +164$ (c 1.7, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.28 (m, 5H), 6.90 (dt, $J = 9.5$, 4.4 Hz, 1H), 6.76 (d, $J = 15.8$ Hz, 1H), 6.29 (dd, $J = 15.6$, 6.3 Hz, 1H), 6.13 (dt, $J = 9.8$, 1.5 Hz, 1H), 5.12 (m, 1H), 2.53 (m, 2H); $^{13}\text{C NMR}$ (50 MHz, CDCl_3): δ 164.6, 144.5, 134.8, 133.6, 128.3, 126.1, 124.4, 121.7, 117.0, 77.6, 30.5; $[\text{M}^+\text{Na}]^+$ found = 223.0, $\text{C}_{13}\text{H}_{12}\text{O}_2$ requires 223.08; Anal calcd for $\text{C}_{13}\text{H}_{12}\text{O}_2$: C, 77.98; H, 6.04; O, 15.98; Found: C, 77.62; H, 6.01; O, 15.95.

(R,E)-ethyl 5-((tert-butyldimethylsilyloxy)-3-oxo-7-phenylhept-6-enoate (19). Methylene chloride (8 ml) followed by ethyl diazoacetate (0.3 g, 1.89 mmol) was added with stirring at room temperature to anhydrous SnCl_2 (0.032 g, 0.172 mmol). To this suspension were added a few drops of aldehyde 17 (0.5g, 1.72 mmol) in methylene chloride (2 ml). When nitrogen evolution began the remaining solution of aldehyde was added dropwise over 10 min. after N_2 evolution had stopped (~ 1h) the reaction was transferred to a separatory funnel with sat. brine and extracted with ether (2x20 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was subjected to column chromatography to afford the product β -keto ester 19 as colorless oil. Yield: 80%; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.16-7.35 (m, 5H), 6.54 (d, $J = 15.86$ Hz, 1H), 6.13 (dd, $J = 6.79$ Hz, 1H), 4.73-4.82 (m, 1H), 4.12-4.23 (m, 2H), 3.42 (s, 2H), 2.86 (dd, $J = 7.55$ and 8.30 Hz, 1H), 2.64 (dd, $J = 4.53$ Hz, 1H), 1.27 (t, $J = 6.79$ Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ 198.87, 172.35, 140.42, 137.66, 134.22, 132.47, 78.68, 63.92, 51.40, 48.46, 27.27, 20.25, 17.67; $[\text{M}^+\text{Na}]^+$ found = 399.1, $\text{C}_{21}\text{H}_{32}\text{O}_4\text{Si}$ requires 399.21 [3].

R-(+)-Kavain 4. to a stirred solution of β -keto ester 19 (0.2 g, 0.53 mmol) in methanol (2 mL) was added conc. HCl (0.2 mL). The resulting solution was stirred for 1h., solvent was removed under reduced pressure and extracted with CH_2Cl_2 giving NaHCO_3 wash (2x 10 mL), water, brine. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude

product was subjected to column chromatography to afford R-(+)-Kavain 4 as solid. The compound has 98.2% ee as determined by chiral HPLC. Yield: 70%; White crystalline solid, mp 103–105 °C, lit. [48] 105–106 oC; $[\alpha]_{D25} +122.2$ (c 1, EtOH), lit. [49] $[\alpha]_{D20} +124.3$ (c 1, EtOH). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.21-7.42 (m, 5H), 6.76 (d, $J = 16.5$ Hz, 1H), 6.29 (dd, $J = 16.6, 6.9$ Hz, 1H), 5.26 (s, 1H), 5.19-5.11 (m, 1H), 3.72 (s, 3H), 2.63 (dd, $J = 16.9, 10.4$ Hz, 1H), 2.58 (dd, $J = 17.4, 4.4$ Hz, 1H). $^{13}\text{C NMR}$ (50 MHz, CDCl_3): δ 172.4, 167.8, 136.6, 133.3, 129.6, 128.2, 127.7, 125.4, 91.2, 76.5, 56.9, 33.4; $[\text{M}+\text{Na}]^+$ found = 253.0, $\text{C}_{14}\text{H}_{14}\text{O}_3$ requires 253.09; Anal calcd for $\text{C}_{14}\text{H}_{14}\text{O}_3$: C, 73.03%, H, 6.13%; Found: C, 72.86%, H, 6.00%.

(S)-ethyl 5-((tert-butyldimethylsilyl)oxy)-3-oxo-7-phenylheptanoate (20). To a stirred solution of compound 19 (0.4 g, 1.06 mmol) in absolute MeOH (10 mL) was added Pd/C catalyst (0.1 g). The suspension was stirred at rt under 1 atm of H_2 . After completion of reaction by TLC (2h), the catalyst was removed by filtration and the solvent was removed from the reaction mixture by rotary evaporation. The product was isolated by column chromatography over silica gel to afford the product 20 as colorless oil. Yield: 90%; $^1\text{H NMR}$ (200 MHz, CDCl_3) δ : 7.07-7.25 (m, 5H), 4.09-4.24 (m, 3H), 3.38 (s, 2H), 2.55-2.67 (m, 4H), 1.70-1.83 (m, 2H), 1.23-1.29 (m, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); $^{13}\text{C NMR}$ (300 MHz, CDCl_3): δ ; 198.88, 173.43, 145.62, 133.64, 131.19, 66.96, 63.83, 54.15, 48.64, 36.97, 34.64, 27.27, 21.18, 19.65 ; $[\text{M}^+\text{Na}]^+$ found = 401.1, $\text{C}_{21}\text{H}_{34}\text{O}_4\text{Si}$ requires 401.22 [1].

S-(+)-7, 8-Dihydrokavain 5. Prepared from compound 20 as per the procedure used for the synthesis of compound 4. The compound has 98.8% ee as determined by chiral HPLC. White crystalline solid, mp 56– 580 C, lit.37 56–580 C. $[\alpha]_{D25} +33.4$ (c 1, MeOH), lit.49 $[\alpha]_{D25} +31.1$ (c 1, MeOH). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.32-7.16 (m, 5H), 5.14 (s, 1H), 4.42-4.30 (m, 1H), 3.72 (s, 3H), 2.94-2.71 (m, 2H), 2.50 (dd, $J = 17.0, 11.9$ Hz, 1H), 2.30 (dd, $J = 17.0, 3.9$ Hz, 1H), 2.20-2.05 (m, 1H), 1.99-1.85 (m, 1H). $^{13}\text{C NMR}$ (50 MHz, CDCl_3): δ 172.7, 167.2, 140.8, 128.5, 128.4, 126.1, 90.3, 74.7, 56.0, 36.3, 33.0, 30.9; $[\text{M}+\text{Na}]^+$ found = 255.0, $\text{C}_{14}\text{H}_{16}\text{O}_3$ requires 255.11; Anal calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$: C, 72.39%, H, 6.94%; Found: C, 72.18%, H, 6.93%.

Results and Discussion

The retro synthetic analysis shows that all these lactones can be synthesized from tert-butyldimethylsilyl (TBS) ether 8 and this could be synthesized from the inexpensive and commercially available cinnamaldehyde 6 (Figure 1).

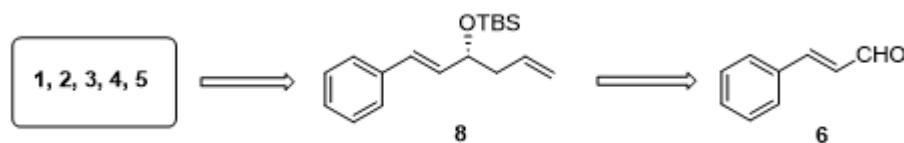


Figure 1: Retrosynthetic analysis of Styryl lactones.

Based on this disconnection, we began the synthesis by enantioselective allylation of cinnamaldehyde 6 using allyl tri butyltin to afford alcohol 7 in 88.8% ee as determined by chiral HPLC. The alcohol 7 was protected as tert-butyldimethylsilyl (TBS) ether and further subjected to Sharpless asymmetric dihydroxylation to yield the two diols 9a and 10a in 4:6 ratio respectively in 80% yield. Compounds 9a and 10a were used as key starting material for the synthesis of (-)-Cryptocaryalactone 1 and 7-epi-goniodiol 2 respectively. The intermediate 8 was further used for conversion of diols 9 and 10. Thus, dihydroxylation of TBS protected alcohol 8 using OsO_4/NMO gave the two diols 9 and 10 in 8:2 ratio and 78% yield. The compound 9 thus obtained was used as key intermediate for the synthesis of (R)-(+)-goniothalamine 3, (R)-(+)-kavain 4 and (S)-(+)-7, 8-dihydrokavain 5 (Figure 2).

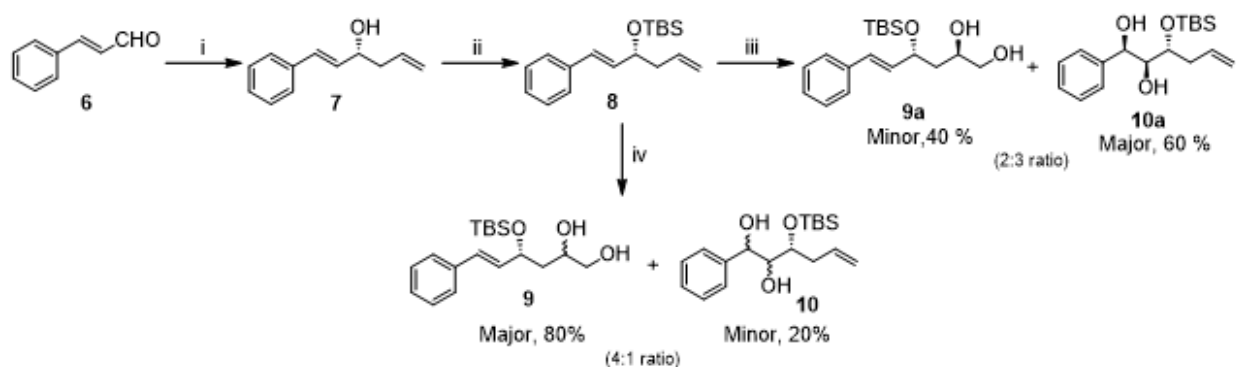
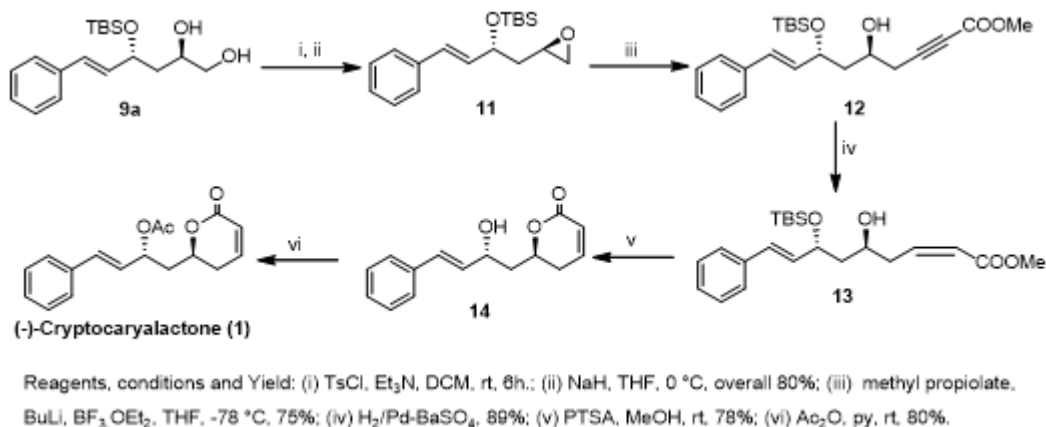
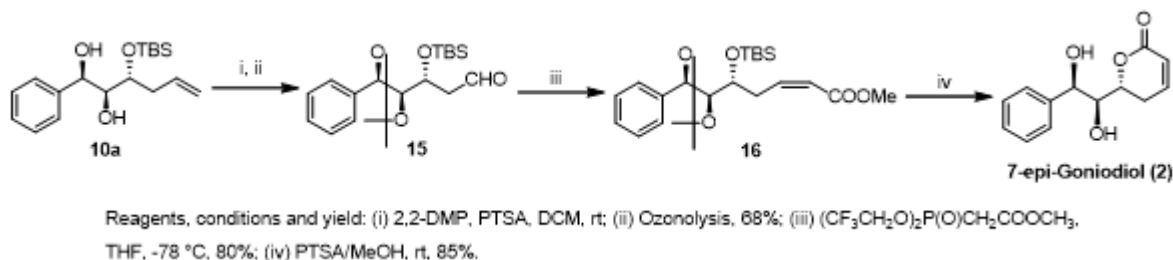


Figure 2: Synthesis of Key Intermediates 9, 9a, 10 and 10a.

The synthesis of (-)-Cryptocaryalactone **1** was initiated with diol **9a**, which was synthesized. The diol **9a** was mono tosylated using TsCl and further converted to epoxide **11** using NaH in 95% overall yield. The epoxide **11** was subjected to nucleophilic ring opening with methyl propiolate using BuLi and BF₃.OEt₂ to afford the δ -hydroxy ester **12** in 75% yield. The partial reduction of triple bond of the ester **12** using Lindlar's catalyst yielded *cis* α,β -unsaturated ester **13** in 95% yield. The *cis* α,β -unsaturated ester **13** was cyclized with concomitant loss of silyl group to yield lactone **14** using catalytic amount of *p*-toluene sulphonic acid in 80% yield. Acylation of the hydroxy group using acetic anhydride in pyridine yielded cryptocaryalactone **1** in 98% yield (Figure 3).

**Figure 3:** Synthesis of (-)-Cryptocaryalactone.

Similarly, 7-*epi*-goniodiol **2** was synthesized from diol **10a**. The compound **10a** was protected with 2,2-dimethoxy propane (DMP) and then subjected to ozonolysis to afford the aldehyde **15** in 68% overall yield. The aldehyde was subjected to Horner-Emmons reaction and obtained the *cis* ester **16** in 80% yield. The ester **16** was cyclized to 7-*epi*-goniodiol **2** using catalytic amount of PTSA in methanol to afford 7-*epi*-goniodiol **2** in 85% yield (Figure 4).

**Figure 4:** Synthesis of 7-*epi*-Goniodiol.

The synthesis of the remaining lactones **3**, **4** and **5** was initiated using diol **9** as the key intermediate. NaIO₄ promoted cleavage of diol **9** afforded the aldehyde **17** in 70% yield. Horner–Wadsworth–Emmons coupling reaction of **17** gave *cis* ester **18** in 80% yield. The *cis* ester **18** was cyclized to the goniothalamine **3** using *p*-toluene sulphonic acid in 85% yield. The aldehyde **17** was further used for the synthesis of lactones **4** and **5**. Thus, the reaction of aldehyde **17** with ethyldiazoacetate using SnCl₂ afforded the β -ketoester **19** in 80% yield. The β -ketoester **19** was cyclized to kavain **4** in a single step using HCl/MeOH in 75% yield. Dihydro kavain **5** was synthesized by the reduction of β -ketoester **19** using H₂-Pd/C to afford the saturated β -ketoester **20** in 90% yield. The ester **20** was cyclized in a single step using HCl/MeOH to yield dihydrokavain **5** in 70% yield (Figure 5).

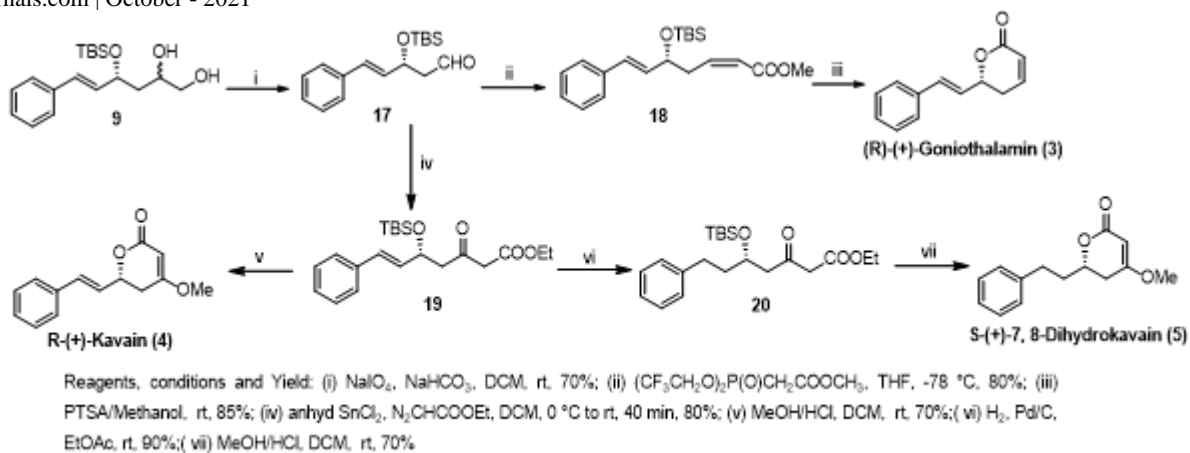


Figure 5: Synthesis of R-(+)-Kavain (4) and S-(+)-7, 8-Dihydrokavain.

Conclusion

In conclusion, we have developed a concise and flexible stereoselective route to synthesize the unsaturated lactones using inexpensive and readily available cinnamaldehyde.

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General remarks

The ¹H and ¹³C NMR were recorded in CDCl₃ at 300 MHz on a Bruker 300 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS. The mass spectrum (70 eV) was recorded on an Agilent-6310 LC-MS spectrometer. The solvents and reagents were used without any purification.

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