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Synthesis of (+)-goniothalamin and its enantiomer by combination of lipase catalyzed resolution and alkene metathesis

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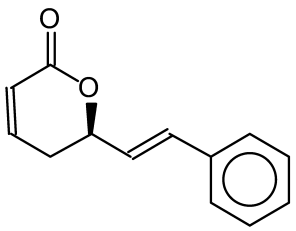
Abstract—(+)-Goniothalamin has been synthesized by lipase catalyzed resolution of (1*E*)-1-phenylhexa-1,5-dien-3-ol using vinyl acrylate as acyl donor followed by ring closing metathesis of the formed (1*R*)-1-[(*E*)-2-phenylvinyl]but-3-enyl acrylate. The unreacted alcohol from the resolution, (1*E*,3*S*)-1-phenylhexa-1,5-dien-3-ol, was esterified non-enzymatically, and used for synthesis of (−)-goniothalamin.

1. Introduction

Chiral unsaturated lactones are structural elements commonly found in natural products of medicinal interest. Furthermore, they are often used as intermediates in the syntheses of natural products. (+)-Goniothalamin (**1**) was first isolated in 1967 from dried bark of *Cryptocarya caloneura*[1] and given (*S*)-configuration. The configuration of its stereocenter has been revised and established as being (*R*).[2] Later **1** has been obtained from several other sources as well. The chemistry of naturally occurring 6-substituted 5,6-dihydro-α-pyrones including goniothalamin, has been reviewed.[3] This class of compounds shows several biological effects. (+)-Goniothalamin, for instance, exhibits antifungal effect,[4] immunosuppressive and anti-inflammatory activity.[5]



(+)-Goniothalamin (**1**)

Other natural products which contain the α,β-unsaturated δ-lactone moiety, such as (−)-argentilactone,[6–8] parasorbic acid and ratjadone,[9] have also been targets for several syntheses. Syntheses of (+)-goniothalamin[2,9–16] and its non-natural (−)-enantiomer have previously been reported.[2,11,17–19]

Acrylates as acyl donors in lipase-catalyzed transesterifications have been reported; e.g. for making starting materials for sugar-based polymers,[20,21] glycolipids,[22] pantolactone acrylate,[23] and (*R*)-(+)-1-phenylethyl acrylate.[24] The efficiency of vinyl acrylate as acyl donor has been investigated.[25] Combination of enzymatic transesterification and alkene metathesis have been reported,[26] but not directly combined in two steps as in the present work.

2. Results and discussion

The alcohol **2** was prepared by Grignard reaction between allylmagnesium bromide and cinnamaldehyde. The racemic alcohol was kinetically resolved by a transesterification reaction in hexane using vinyl acrylate as acyl donor and *Candida antarctica* lipase B (CALB) as catalyst (Scheme 1). Optical rotation values confirmed that the (*R*)-enantiomer was the faster reacting enantiomer,[27] in accordance with the stereopreference of CALB.[28] The resolution proceeded with an *E*-value of 65.

The transesterification reaction was stopped after 45% conversion, and the ester and remaining unreacted alcohol were separated by column chromatography affording (1*R*)-1-[(*E*)-2-phenylvinyl]but-3-enyl acrylate [(*R*)-**3**], with 93%

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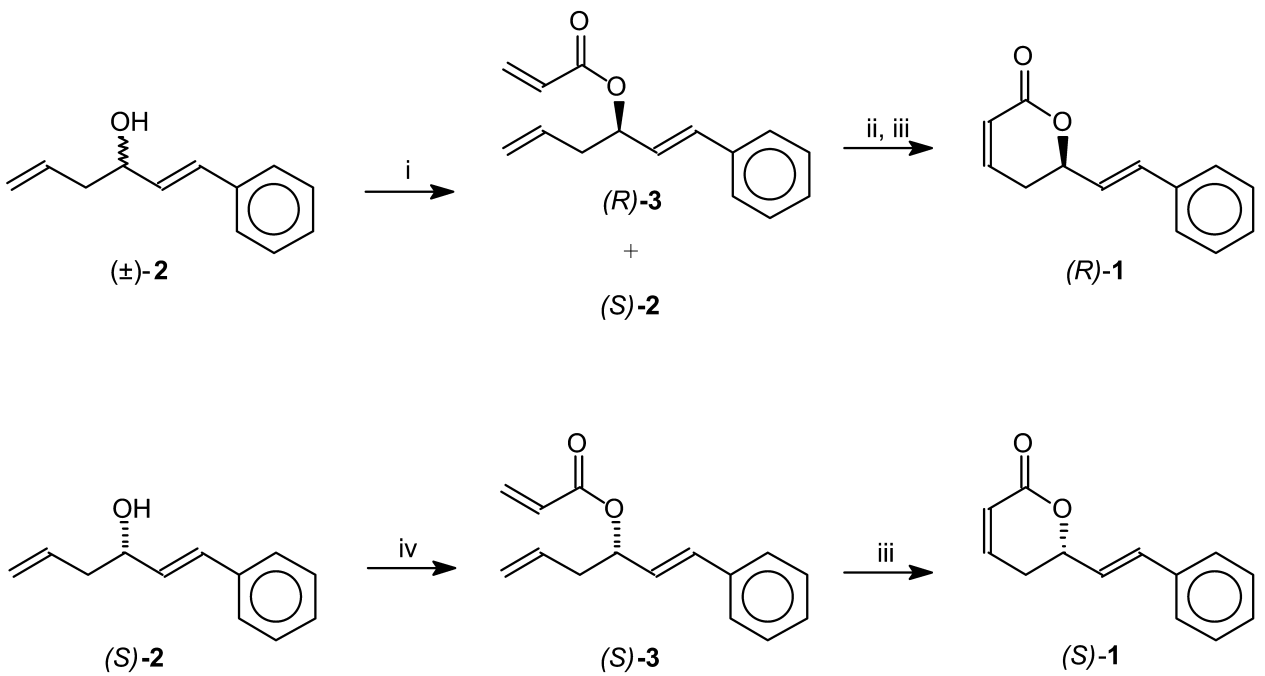

Scheme 1. (i) CALB, vinyl acrylate, hexane. (ii) Separation by chromatography, (iii) Grubbs'cat., CH_2Cl_2, δ, (iv) Acryloyl chloride, Et_3N, THF.

ee and (1*E*,3*S*)-1-phenylhexa-1,5-dien-3-ol [(*S*)-**2**], with 74% ee. The configuration was established by comparing the measured optical rotation which was $[\alpha]_D^{20}=+10.70$ (*c* 2.0, Et_2O), with the rotation of a previously reported value of an (*S*)-enriched sample of **2** with 24% ee and $[\alpha]_D^{20}=+3.60$ (*c* 10.08, Et_2O).[29] The alcohol (*S*)-**2** was esterified with acryloyl chloride to give (1*S*)-1-[(*E*)-2-phenylvinyl]but-3-enyl acrylate, [(*S*)-**3**], with no change of enantiomeric excess.

Treatment of (*R*)-**3** with 8 mol% of Grubbs' catalyst[30] gave the unsaturated lactone, (*R*)-(+)-goniothalamin [(*R*)-**1**] via a ring closing metathesis reaction in 92% yield. It was observed that during this reaction the ee-value increased to >99% in comparison to 93% ee of (*R*)-**3**. The ee was determined by HPLC analysis using a chiral stationary phase. Chiral analysis of the enantiomers of **1**–**3** was laborious; attempts with three different chiral stationary phases on GLC columns failed. Derivatization of (±)-**2** using (*R*)-4-methoxyphenylacetyl chloride, (*S*)-(1)-naphthylethylisocyanate or (*R*)-1-phenylethyl isocyanate also failed. Careful selection of chiral stationary phase for HPLC (Table 2) allowed accurate chiral analyses of **1**, **2** and **3**.

Table 1. Enantiomeric excesses before and after the ring-closing reaction

Acrylate	% ee	Product	% ee
(*R*)-**3**	88	(*R*)-**1**	96
(*R*)-**3**	93	(*R*)-**1**	>99
(*S*)-**3**	74	(*S*)-**1**	85
(±)-**3**	0	(±)-**1**	0

The absolute configuration was determined as (*R*) by comparing the measured specific rotation, $[\alpha]_D^{20}=+172.2$ (*c* 0.8, $CHCl_3$), with that of a previously reported value for (+)-(*R*)-goniothalamin (**1**) with 92% ee, $[\alpha]_D^{20}=+160.2$ (*c* 0.8, $CHCl_3$).[16] The spectral data were in accordance with those reported earlier. When (*S*)-**3** with an ee of 74% was treated in the same manner, (*S*)-**1** was obtained, also with increased ee (85%). The increase of enantiomeric excess values triggered further investigations, and the results are summarized in Table 1. Two samples of (*R*)-**3** and one of (*S*)-**3** with different ee-values led to products with increased ee-values. Racemic **3** furnished racemic goniothalamin (**1**).

One might expect that these results were due to inaccuracy of the chiral analysis. However, both racemic **1** and **3** were baseline separated by HPLC, giving optimum R_S-values of 2.78 and 3.54, respectively (see Table 2, entries 1 and 5). As a further check, the samples were also analysed using

Table 2. Chiral HPLC chromatography of **1**–**3**

Entry	Compound	Column	2-Propanol:hexane:EtOH	t_S (min)	t_R (min)	R_S
1	**1**	Chirasil AD	5:91:4	50.90	59.90	2.78
2	**1**	Chirasil AD	3:95:2	34.27	36.72	1.39
3	**1**	Chirasil OD-H	5:95:0	27.21	29.10	1.46
4	**2**	Chirasil AD	5:95:0	28.10	26.49	1.61
5	**3**	Chirasil AD	2:98:0	11.88	13.94	3.54
6	**3**	Chirasil AD	3:95:2	24.13	27.01	2.16
7	**3**	Chirasil OD-H	5:95:0	67.20	20.13	1.37

different conditions. No change of the ee-values were observed (Table 2, entries 2, 3, 6 and 7).

The reaction is homogeneous, and no crystallization is expected to occur during reaction since **1** and **3** are oils. In previously reported syntheses of analogs of goniothalamin, a similar increase of the ee-values during the ring-closing reaction were not observed, since the ee-values of the final products were assumed to be the same as the ee-values of the intermediates.[16]

3. Conclusion

In conclusion, we have carried out the synthesis of (+)-goniothalamin with high enantiomeric excess and its (−)-enantiomer with moderate enantiomeric excess by lipase catalyzed kinetic resolution of (1*E*)-1-phenylhexa-1,5-dien-3-ol, followed by separation and non-enzymatic esterification of the remaining (*S*)-alcohol. Subsequent ring-closing metathesis produced both lactones. This efficient procedure can easily be extended to the synthesis of other chiral natural products with an α,β-unsaturated δ-lactone moiety.

4. Experimental

4.1. General

Immobilized lipase B from *Candida antarctica*, CALB (Novozyme 435) with an activity of approx. 10,000 PLU/g and a water content of 1–2% was used. Solvents were distilled and dried over molecular sieves. Column chromatography was performed on silica gel 60 from Fluka. First generation Grubbs' catalyst, benzylidenebis-(tricyclohexylphosphine)-dichlororuthenium, was purchased from Aldrich. Enzyme reactions were performed in a shaker incubator (New Brunswick, Edison, NJ, USA). Optical rotations were determined using a Perkin–Elmer 243B polarimeter, concentrations are given in g/100 mL. NMR spectra were recorded on a Bruker DPX 400 instrument, using $CDCl_3$ as solvent. ^1H and ^{13}C spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are in ppm rel. to TMS and coupling constants in Hertz. Analytical GLC analyses were performed on a Supelco SPB™-5 column (30 m×0.25 mm, film thickness of 0.25 μm) at 10 psi, split ratio 60 mL/min. The inlet temperature was 250 °C and the FID temperature was 270 °C for all samples. The temperature program was as follows: 100 °C (0)–250 °C (2 min hold), 15 °C/min. Chiral HPLC analyses were performed on a Varian 9010 HPLC with a Varian 2550 variable λ detector, equipped with a Chiralcel AD column (25×0.46 cm) or Chiralcel OD-H column (25×0.46 cm) from Daicel Chemical Industries, LTD). The flow rate was 0.5 mL/min. Enantiomeric ratios, *E*, were calculated using the computer program *E* and *K* calculator version 2.1b (http://bendik.chembio.ntnu.no).

4.1.1. (1*E*)-1-Phenylhexa-1,5-dien-3-ol [(±)-2]. Allylmagnesium bromide (Aldrich, 1 M, 24 mL, 24 mmol) was added dropwise to a cooled (0 °C) solution of cinnamaldehyde (2.64 g, 20 mmol) in dry THF (30 mL). The cooling bath was removed and the reaction mixture stirred for 4 h. The reaction was monitored by GLC. Saturated NH_4Cl (30 mL) and Et_2O (50 mL) was added. The water phase was extracted with Et_2O (3×50 mL), and the combined organic fractions washed with brine (50 mL) and dried (Na_2SO_4). Removal of solvent afforded the racemic alcohol (±)-**2** (3.22 g, 93%). ^1H NMR: δ 1.9 (br s, OH), 2.37–2.43 (m, 2H), 4.35 (q, *J*=6.4 Hz, 1H), 5.14–5.20 (m, 2H), 5.84 (m, 1H), 6.23 (dd, *J*=16.0, 6.4 Hz, 1H), 6.60 (d, *J*=16.0 Hz, 1H), 7.23–7.39 (m, 5H). ^{13}C NMR: δ 42.43, 72.15, 118.86, 126.91, 128.08, 129.00, 130.76, 132.02, 134.50, and 137.10.

4.1.2. Lipase catalyzed kinetic resolution of (±)-2. The alcohol (±)-**2** (400 mg, 2.3 mmol) and vinyl acrylate (1.13 g, 11.5 mmol) were dissolved in hexane (60 mL). Immobilized CALB (300 mg) was added and the reaction mixture was shaken at 30 °C for 54 h when 45% conversion was reached. The enzyme was filtered off and the solvent removed in vacuo. The remaining alcohol (*S*)-**2**, and the ester (*R*)-**3** were separated by column chromatography (hexane/acetone, 4:1).

4.1.3. (1*R*)-1-[(*E*)-2-Phenylvinyl]but-3-enyl acrylate [(*R*)-3]. Yield: 200 mg (38%), 93% *ee*, $[\alpha]_D^{20}$=+66.1 (*c* 2.0, $CHCl_3$). ^1H NMR: δ 2.53 (m, 2H), 5.09–5.16 (m, 2H), 5.56 (q, *J*=6.6 Hz, 1H), 5.75–5.85 (m, 2H), 6.11–6.21 (m, 2H), 6.43 (dd, *J*=17.4, 1.4 Hz, 1H), 6.64 (d, *J*=16.0 Hz, 1H), 7.24–7.39 (m, 5H).

4.1.4. (3*S*)-(1*E*)-1-Phenylhexa-1,5-dien-3-ol [(*S*)-2]. Yield: 170 mg (42%), 74% ee, $[\alpha]_D^{20}$=+10.7 (*c* 2.0, Et_2O). Spectroscopic data as for (±)-**2**.

4.1.5. (1*S*)-1-[(*E*)-2-Phenylvinyl]but-3-enyl acrylate [(*S*)-3]. The alcohol (*S*)-**2**, (170 mg, 0.98 mmol) was dissolved in dry THF (10 mL), to this solution was added Et_3N (two drops) and the solution was cooled to 0 °C. Acryloyl chloride (111 mg, 1.3 mmol) in THF (5 mL) was added dropwise to the solution. Stirring at 0 °C was continued for 3 h. Water (5 mL) and HCl (0.05%, 10 μL) was added and THF was removed in vacuo. The product was extracted with CH_2Cl_2 (2×20 mL), the extract was dried over Na_2SO_4 and the solvent evaporated affording 216 mg of (*S*)-**3**, yield 97%, ee 74% by HPLC analysis, $[\alpha]_D^{20}$=−50.6 (*c* 2.1, $CHCl_3$).

4.1.6. 1-[(*E*)-2-Phenylvinyl]but-3-enyl acrylate [(±)-3]. The alcohol (±)-**2** (300 mg) was treated in the same manner as described for (*S*)-**2** to give the racemic ester (±)-**3**, yield 370 mg (94%), spectroscopic data in accord with (*S*)-**3**.

4.1.7. (+)-Goniothalamin. 6-(6*R*)-[(*E*)-2-phenylvinyl]-5,6-dihydro-2*H*-pyran-2-one [(+)-1]. Grubbs' catalyst (30 mg, 8 mol%,) was dissolved in dry CH_2Cl_2 (5 mL) and this solution was added dropwise to a refluxing solution of the ester (*R*)-**3** (100 mg, 0.47 mmol, ee 93%) in dry CH_2Cl_2 (15 mL). The mixture was heated under reflux in an argon atmosphere for 3 h. The solvent was removed in vacuo and the mixture purified by column chromatography (acetone/hexane, 1:4) to afford 86 mg (92%) of (+)-goniothalamin, (*R*)-**1**, ee>99% as determined by HPLC analysis, $[\alpha]_D^{20}$=+172.2 (*c* 0.8, $CHCl_3$), ^1H NMR: δ 2.55 (m, 2H), 5.11 (m, 1H), 6.1 (dt, *J*=9.8, 1.6 Hz, 1H), 6.29 (dd, *J*=16.0, 6.3 Hz, 1H), 6.73 (d, *J*=16.0 Hz, 1H), 6.93 (dt,

J=9.7, 4.5 Hz, 1H), 7.3 (m, 5H); ^{13}C NMR: δ 30.07, 78.13, 121.86, 125.83, 126.88, 128.54, 128.88, 133.31, 135.94, 144.82, and 164.07.

4.1.8. (−)-Goniothalamin, 6-(6*S*)-[(*E*)-2-phenylvinyl]-5,6-dihydro-2*H*-pyran-2-one [(−)-1]. Using the same procedure as under Section 4.1.7 afforded 141 mg (81%) of (−)-**1**, ee 85% by HPLC analysis, $[\alpha]_D^{20}=-146.0$ (c 0.8, $CHCl_3$) with spectroscopic properties in accord with (+)-**1**.

4.1.9. (±)-Goniothalamin, 6-[(*E*)-2-phenylvinyl]-5,6-dihydro-2*H*-pyran-2-one [(±)-1]. Using the same procedure as described under Section 4.1.7 afforded 261 mg (86%) of (±)-**1** with spectroscopic properties in agreement with (+)-**1**.

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