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A concise enantioselective synthesis of (*R*)-(+)-goniothalamin oxide, a trypanocidal active agent *via* L-prolinol catalyzed asymmetric epoxidation of cinnamaldehyde

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A short and straight-forward enantioselective synthesis of (*R*)-(+)-goniothalamin oxide **2** has been achieved with an overall yield of 39% and 99% *ee*. The synthetic approach involves L-prolinol catalyzed asymmetric epoxidation of cinnamaldehyde followed by Lewis acid-mediated diastereoselective allylation of epoxy aldehyde as the key chiral-inducing steps.

Keywords: Asymmetric epoxidation, allylation, L-prolinol catalyst, esterification, Grubbs' catalyst, ring closing metathesis

(6*R*)-(+)-Goniothalamin (**1**) and (6*R*,7*R*,8*R*)-(+)-goniothalamin oxide (**2**) are a new class of secondary metabolites isolated from *Goniothalamus macrophyllus* as the active embryotoxic and teratogenic components[1]. In addition several derivatives of goniothalamin (**3** and **4**) have been reported from a variety of tropical/subtropical plants including *Crytocarya moschata*, *Brynopsis laciniosa* and various *Goniothalamus* species (Figure 1). These natural products have shown cytotoxicity on a variety of cell lines including a significant antifungal activity against a wide variety of gram-positive and gram-negative fungi[2,3]. Their unique structural features coupled with potent biological activities make goniothalamin oxide **2** and related molecules an ideal target for testing new synthetic methodology. Consequently, there have been consistent efforts toward the total synthesis of *R*-(+)-goniothalamin oxide (**2**)[4-8].

Literature search revealed that there are however only few reports available for the synthesis of *R*-(+)-goniothalamin oxide **2**. The reported synthetic strategies include chiral pool, chemo-enzymatic or enantioselective syntheses that include Sharpless kinetic resolution, Jacobsen's epoxidation, hetero Diels-Alder reaction, Julia olefination, Jacobsen's HKR and intramolecular nucleophilic addition to ketenes[4-8]. However, use of chiral building blocks, expensive and hazardous reagents, low overall yields, low diastereomeric ratios, *etc*. make the existing methods uneconomical. Its interesting biological properties and limited availability from natural resources attracted our attention to provide the efficient synthesis of goniothalamin oxide **2**. In this paper, we wish to describe a practical method of synthesis of *R*-(+)-goniothalamin oxide (**2**) that employs L-prolinol catalyzed asymmetric epoxidation of cinnamaldehyde followed by diastereoselective allylation as the key reaction steps (Scheme I).

Retrosynthetic analysis reveals that homoallylic alcohol **6** could be visualized as the key intermediate. The homoallylic alcohol **6** could be prepared by means of Lewis acid-mediated diastereoselective allylation of epoxy aldehyde **7**, which in turn could be obtained from cinnamaldehyde **8** *via* Jorgensen's asymmetric epoxidation strategy (Scheme II).

In continuation of our research work on organocatalyzed reactions as applied in the asymmetric synthesis of bioactive molecules and natural products[9], we undertook the synthesis of (*R*)-(+)-goniothalamin oxide **2** by employing L-prolinol catalyzed epoxidation of cinnamaldehyde **8** followed by Lewis acid - mediated diastereoselective allylation of epoxy aldehyde **7** as the key reactions (Scheme I).

Result and Discussion

The synthesis of (*R*)-(+)-goniothalamin oxide **2** commenced from commercially available cinnamaldehyde **8**, which on asymmetric epoxidation with Jorgensen's protocol[10] using aq. H_2O_2 in the presence of prolinol derivative **10** as the catalyst resulted in the formation of the labile epoxy aldehdye

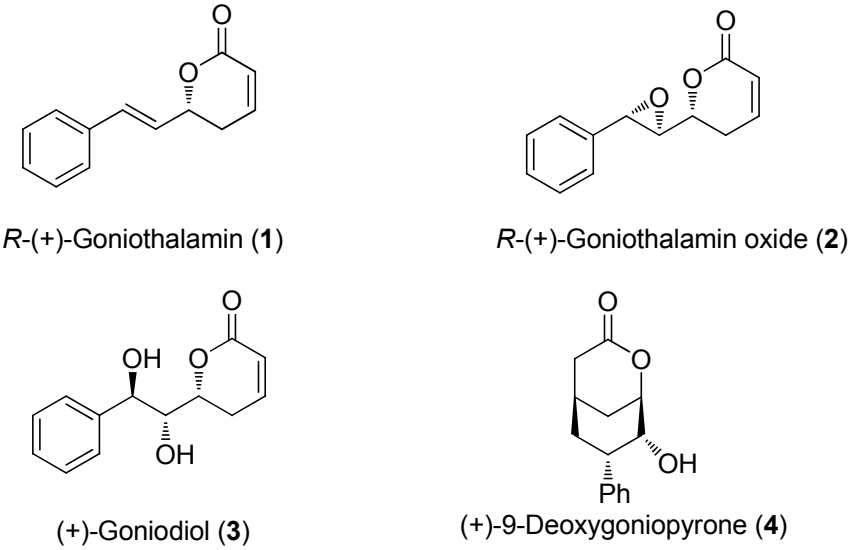
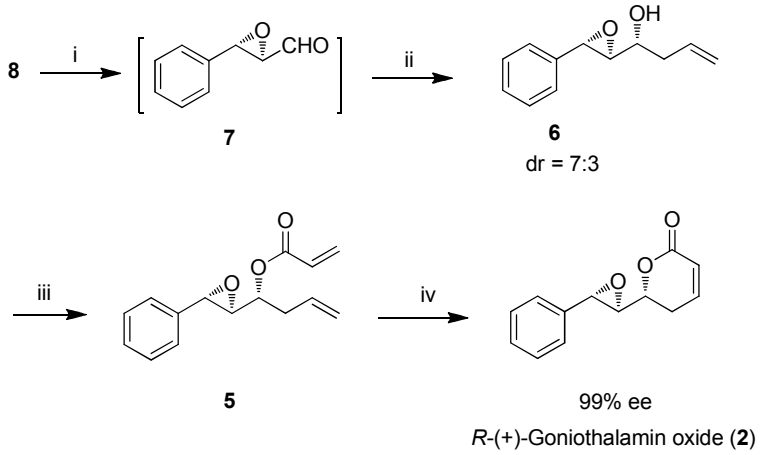
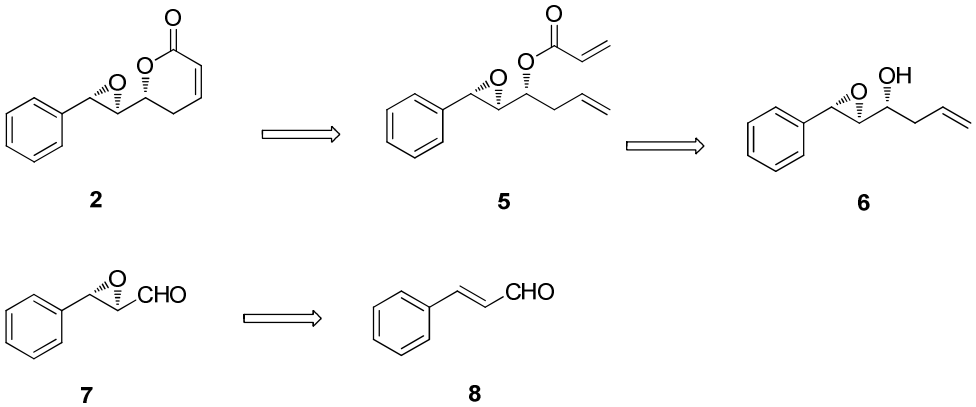


Figure 1 — Structures of bioactive naturally occurring lactones 1-4



Scheme I — (i) 35% H_2O_2 (w/w) in water, L-prolinol derivative **10** (10 mol%), CH_2Cl_2, 25°C, 5 h; (ii) tributyl allyl stannane, $LiClO_4$, diethyl ether, 25°C, 7 h, 70% (2 steps), dr = 7:3; (iii) acrylic acid, DMAP, DCC, CH_2Cl_2, 0-25°C, 8 h, 65%; (iv) Grubbs' IInd generation catalyst (10 mol%), CH_2Cl_2, 45°C, 8 h, 85%.



Scheme II — Retrosynthetic analysis of (*R*)-(+)-goniothalamin oxide **2**

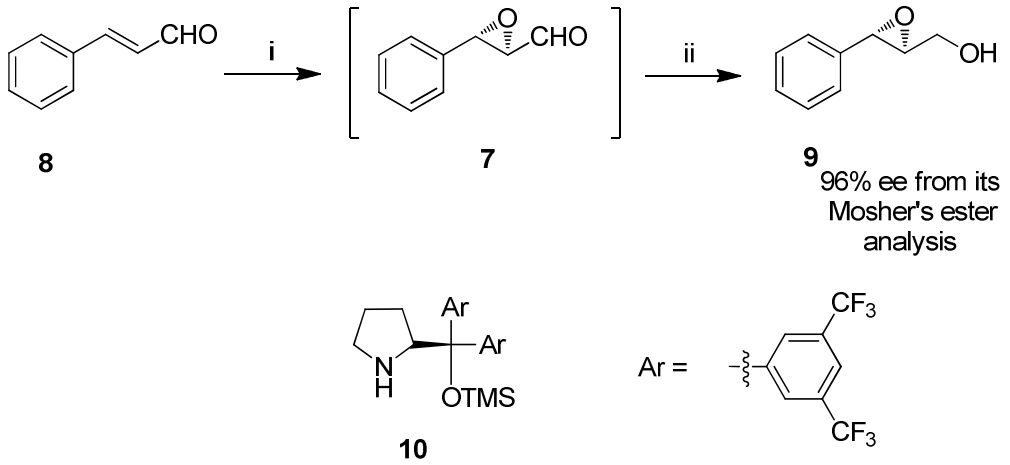
7. The *in situ* generated enantiopure epoxy aldehyde **7** was filtered through a pad of silica. In order to check its enantiomeric purity, epoxy aldehyde **7** was subjected to reduction with $NaBH_4$ in methanol that afforded epoxy alcohol **9** as a pale yellow solid {m.p. 53.5-54°C (crystallized from diethyl ether/hexane, 3:2) and $[\alpha]^{25}_D$ = −48.4 (*c* 1, $CHCl_3$); lit.[11] $[\alpha]^{25}_D$ = −48.0 (*c* 0.3, $CHCl_3$)} in 78% yield (Scheme III). The enantiomeric excess of epoxy alcohol **9** (96% *ee*) was determined from ^{1}H NMR analysis of the corresponding Mosher's ester, prepared from epoxy alcohol **9**.

Our next task was to prepare homoallylic alcohol **6** from epoxy aldehyde **7**. To achieve this, the *in situ* generated chiral epoxy aldehdye **7** from cinnamaldehyde **8** was subjected to Ti-mediated diastereoselective allylation ($TiCl_4$, tri-*n*-butyl allyl stannane, CH_2Cl_2, −78°C) with a view to obtain the key intermediate homoallylic alcohol **6**. Unexpectedly, it resulted in the formation of chlorodiol **11** (60% yield, dr = >99%) probably due to the stronger Lewis acidity of $TiCl_4$ (Scheme IV).

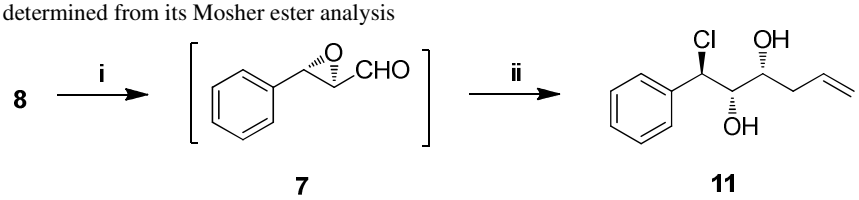
Accordingly, we believed that a milder Lewis acid such as $LiClO_4$ could be effective in selectively facilitating the allylation of epoxy aldehyde **7** without affecting the epoxide functionality[12]. Indeed, the desired homoallylic alcohol **6** was obtained in 70% yield with dr = 7:3 (determined from ^{1}H NMR analysis of **6**) as an inseparable mixture (Scheme I). However, the Steglich esterification of homoallylic alcohol **6** with acrylic acid, (DCC, DMAP, CH_2Cl_2) gave the acrylate ester **5** {$[\alpha]^{25}_D$ = -26.7 (*c* 1.2, $CHCl_3$)} as a separable diastereomer, which was readily separated *via* flash column chromatography. The formation of acrylate ester **5** (major diastereomer, 65% yield) was confirmed from its ^{1}H NMR spectrum. Finally, the ring closing metathesis of acrylate ester **5** with Grubbs' IInd generation catalyst afforded (*R*)-(+)-goniothalamin oxide (**2**) in 85% yield. The enantiomeric excess of (*R*)-(+)-goniothalamin oxide (**2**) was found to be 99% based on HPLC analysis as well as comparison of its optical rotation with the reported value {$[\alpha]^{25}_D$ = + 99.5 (*c* 0.24, $CHCl_3$); lit.[6] $[\alpha]^{25}_D$ = +100.7 (*c* 0.3, $CHCl_3$)}. The spectral data of (+)-goniothalamin oxide (**2**) were in good agreement with the reported values[6].

Experimental Section

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling



Scheme III — (i) 35% H_2O_2 (w/w) in water, L-prolinol derivative **10** (10 mol%), CH_2Cl_2, 25°C, 5 h; (ii) $NaBH_4$, MeOH, 0°C, 30 min, 78% (2 steps), 96% *ee* determined from its Mosher ester analysis



Scheme IV — (i) 35% H_2O_2 (w/w) in water, L-prolinol derivative **10** (10 mol%), CH_2Cl_2, 25°C, 5 h; (ii) $TiCl_4$, tributyl allyl stannane, CH_2Cl_2, −78°C, 30 min, 60%, dr = >99%.

range 60-80°C was used. Melting points are uncorrected and recorded on a Buchi B-542 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer unless mentioned otherwise. Infrared spectra were recorded on a Shimadzu FTIR-8400 spectrometer and absorption is expressed in cm^{-1}. ESI-MS were recorded on a Thermo-Finnigan LCQ Advantage spectrometer in the ESI mode with a spray voltage of 4.8 kV. All chemicals were purchased from Sigma-Aldrich and used as received. Purification was done using column chromatography over silica gel (230–400 mesh). In the ^{13}C NMR spectrum, the C-peak at 96.1 corresponds to CCl_4, as we have used the $CDCl_3$:CCl_4 (7:3) solvent for the NMR study. Optical rotations were measured using the sodium D line on a JASCO-181 digital polarimeter.

(2*S*, 3*S*)-3-Phenyloxiran-2-yl)methanol, 9: To a stirred solution of cinnamaldehyde **8** (132 mg, 1 mmol) in CH_2Cl_2 (5 mL) at 25°C was added prolinol derivative **10** (60 mg, 1 mmol) followed by the addition of 35% aq. H_2O_2 (44.2 mg, 1.3 mmol). After being stirred for 5 h at the same temperature, the crude reaction mixture was passed through a pad of silica gel (EtOAc/pet ether) and the filtrate concentrated under reduced pressure to give crude oxirane-2-carbaldehyde **7**. The crude epoxy aldehyde **7** was diluted with MeOH (5 mL) and cooled to 0°C followed by the addition of $NaBH_4$ (75 mg, 2 mmol) to it. The mixture was then stirred for 30 min, quenched with sat. NH_4Cl and extracted with EtOAc. The organic layer was separated, dried over anhyd. Na_2SO_4 and concentrated to give the crude material, which was then purified by column chromatography over silica gel with pet. ether/EtOAc (85:15) to give the epoxy alcohol **9** (117 mg). Yield 78%. Pale yellow solid. m.p.53.5-54°C. $[\alpha]^{25}_D$: −48.4° (*c* 1, $CHCl_3$) {lit.[12a] $[\alpha]^{25}_D$ −48.0° (*c* 0.3, $CHCl_3$)}; IR ($CHCl_3$): 758, 840, 863, 881, 1027, 1068, 1108, 1256, 1392, 1462, 1606, 2871, 2927, 3017, 3428 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.75 (br s, 1H), 3.17-3.22 (m, 1H), 3.72-3.79 (m, 1H), 3.90 (d, *J* = 2.2 Hz, 1H), 3.97-4.06 (m, 1H), 7.23-7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.4, 61.1, 62.4, 125.5, 127.8, 128.1, 136.4. Anal. $C_9H_{10}O_2$ requires: C, 71.98; H, 6.71. Found: C, 71.95; H, 6.76%.

(1*R*, 2*S*, 3*R*)-1-Chloro-1-phenylhex-5-ene-2,3-diol, 11: To a stirred solution of cinnamaldehyde **8** (660 mg, 5 mmol) in CH_2Cl_2 (20 mL) at 25°C was added prolinol derivative **10** (300 mg, 0.5 mmol) followed by the addition of 35% aq. H_2O_2 (220 mg, 6.5 mmol). After being stirred for 5 h at the same temperature, the crude reaction mixture was passed through a pad of silica gel (EtOAc/pet ether) and the filtrate concentrated under reduced pressure to give crude epoxy aldehyde **7**, which was directly used for the next step without purification. To a stirred epoxy aldehyde **7** solution in dry CH_2Cl_2 (30 mL) was added $TiCl_4$ (6.8 mL, 1M solution in CH_2Cl_2) at −78°C. After stirring for 10 min, tributylallylstannane (2.3 g) was added. The reaction mixture was stirred at −78°C for 30 min, quenched with $NaHCO_3$, extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude material, which was then purified by column chromatography over silica gel with pet. ether/EtOAc (75:25) to give the alcohol **11** (678 mg). Yield 60%. Colorless liquid. $[\alpha]_D^{25}$ = −61.5° (*c* 1, $CHCl_3$); IR ($CHCl_3$): 700, 754, 1115, 1220, 1396, 1496, 1649, 1985, 3030, 3063, 3480 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.02-2.11 (m, 2H), 2.30-2.51 (m, 2H), 3.82-3.89 (m, 1H), 4.12-4.26 (m, 1H), 4.94 (d, *J* = 8.8 Hz, 1H), 5.08-5.14 (m, 1H), 5.19-5.22 (m, 1H), 5.76-5.97 (m, 1H), 7.29-7.46 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.7, 61.7, 69.0, 75.9, 118.3, 128.2, 128.7, 134.2, 138.5. Anal. $C_{12}H_{15}ClO_2$ requires: C, 63.58; H, 6.67. Found: C, 63.60; H, 6.65%.

(*R*)-1-((2*S*, 3*S*)-3-Phenyloxiran-2-yl)but-3-en-1-ol, 6: To a stirred solution of cinnamaldehyde **8** (660 mg, 5 mmol) in CH_2Cl_2 (20 mL) at 25°C was added prolinol derivative **10** (300 mg, 0.5 mmol) followed by the addition of 35% aq. H_2O_2 (220 mg, 6.5 mmol). After being stirred for 5 h at the same temperature, the crude reaction mixture was passed through a pad of silica gel (EtOAc/pet ether) and the filtrate concentrated under reduced pressure to give crude oxirane-2-carbaldehyde **7**, which was directly used for the next step without purification. To a stirred crude epoxy aldehyde **7** solution in dry diethyl ether (30 mL) was added $LiClO_4$ (638 mg, 6 mmol) at 0°C. After stirring for 10 min, tributylallylstannane (1.99 g, 6 mmol) was added. The reaction mixture was stirred at 0°C for 1 h and the reaction was brought to 25°C and stirred for 6 h, quenched with $NaHCO_3$, extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude material, which was then purified by column chromatography over silica gel with pet.

ether/EtOAc (90:10) to give the homoallylic alcohol **6** (665 mg) as inseparable mixture. Yield 70%. Thick oily liquid. IR ($CHCl_3$): 700, 756, 1109, 1209, 1396, 1496, 1650, 1980, 3020, 3063, 3479 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.05 (d, *J* = 6.7 Hz, 1H), 2.32-2.54 (m, 2H), 3.04-3.08 (m, 1H), 3.65-3.81 (m, 1H), 3.86 (d, *J* = 2.2 Hz, 1H), 5.11-5.14 (m, 1H), 5.16-5.23 (m, 1H), 5.77-5.99 (m, 1H), 7.18-7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 39.0, 56.3, 65.0, 70.1, 118.4, 125.6, 128.2, 133.5, 136.8. Anal. $C_{12}H_{14}O_2$ requires: C, 75.76; H, 7.42. Found: C, 75.73; H, 7.45%.

(*R*)-1-((2*S*, 3*S*)-3-Phenyloxiran-2-yl)but-3-en-1-yl acrylate, 5: A stirred solution of alcohol **6** (400 mg, 2.1 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0°C followed by the addition of acrylic acid (302 mg, 4.2 mmol), DCC (865 mg, 4.2 mmol) and 4-dimethylaminopyridine (25 mg, 0.21 mmol). The entire reaction mixture was then warmed to 25°C and stirred for 8 h. Solvent was removed under vacuum to give the crude product, which was then purified by column chromatography over silica gel with pet. ether/EtOAc (95:5) to give acrylate ester **5** (333 mg). Yield 65%. Colorless gum. $[\alpha]_D^{25}$ = +61.2° (*c* 1.2, $CHCl_3$) lit.[9] $[\alpha]_D^{25}$ = +61.0° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): 700, 767, 1118, 1203, 1309, 1454, 1637, 1714, 2885, 3030, 3063 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.49-2.57 (m, 2H), 3.12 (dd, *J* = 2.2, 5.9 Hz, 1H), 3.76 (d, *J* = 2.0, 1H), 4.95 (q, *J* = 6.8 Hz, 1H), 5.15-5.20 (m, 2H), 5.85-5.86 (m, 1H), 5.92 (dd, *J* = 1.6, 10.2 Hz, 1H), 6.10 (dd, *J* = 10.2, 17.2 Hz, 1H), 6.44 (dd, *J* = 1.6, 17.2 Hz, 1H), 7.21-7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.1, 56.5, 62.6, 72.9, 119.0, 125.6, 128.2, 128.6, 131.4, 132.2, 136.4, 165.2. Anal. $C_{15}H_{16}O_3$ requires: C, 73.75; H, 6.60. Found: C, 73.78; H, 6.64%.

(*R*)-6-((2*S*,3*S*)-3-Phenyloxiran-2-yl)-5,6-dihydro-2*H*-pyran-2-one: **(*R*)-(+)-goniothalamin oxide, 2**: A solution of Grubbs' IInd generation catalyst [$RuCl_2$(=CHPh)(Pcy_3)(*bis*mesitylimidazo- lidinylidene)] (18 mg, 2.5 mol%) in dry CH_2Cl_2 (5 mL) was added drop-wise to a refluxing solution of acrylate ester **5** (200 mg, 0.82 mmol) in CH_2Cl_2 (10 mL). Heating to reflux was continued for 8 h till all the starting material was consumed completely (TLC). Solvent was distilled off under reduced pressure and the crude product purified by column chromatography over silica gel with pet. ether/EtOAc (70:30) to give (*R*)-(+)-goniothalamin oxide **2** (150 mg). Yield 85%. Colorless solid. m.p.92-95°C. $[\alpha]_D^{25}$ = +99.5° (c 0.8, $CHCl_3$) {lit.[7] $[\alpha]^D_{25}$ = +100.7°, (c 0.4, $CHCl_3$)}; IR ($CHCl_3$): 815, 1066, 1456, 1720, 2933, 3030, 3063 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.45-2.76 (m, 2H), 3.19-3.22 (dd, *J* = 2.0, 3.5 Hz, 1H), 4.08 (d, *J* = 2.0 Hz, 1H), 4.64-4.73 (m, 1H), 5.30 (s, 1H), 6.03-6.10 (m, 1H), 6.87-6.96 (m, 1H), 7.26-7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2, 55.0, 62.1, 75.0, 121.7, 125.7, 128.6, 139.1, 143.8, 162.1. Anal. $C_{13}H_{12}O_3$ requires: C, 72.21; H, 5.59. Found: C, 72.25; H, 5.55%. Optical purity: 99% *ee* determined by chiral HPLC analysis [Chirapak OD-H, 2-Propanol/*n*-Hexane = 2.5/97.5, flow rate 0.6 mL/min, λ = 254 nm, retention time: (minor) 12.59 min, (major) 15.60 min].

Conclusions

In conclusion, an efficient and straight-forward enantioselective synthesis of (+)-goniothalamin oxide **2** has been achieved with an overall yield of 39% and 99% *ee*. The approach involved L-prolinol catalyzed asymmetric epoxidation of cinnamaldehyde followed by Lewis acid-mediated diastereoselective allylation of epoxy aldehyde as the key chiral-inducing steps. This methodology is also amenable to the synthesis of other diastereomers of lactone family if other antipode of the prolinol catalyst is employed.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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References

1 (a) Cao S G, Wu X H, Sim K Y, Tan B K H, Pereira J T & Goh S H, *Tetrahedron*, 54 (1998) 2143; (b) Sam T W, Sew-Yeu C, Matsjeh S, Gan E K, Rasak D & Mohamed A L, *Tetrahedron Lett*, 28 (1987) 2541.

2 (a) Inayat-Hussain S H, Osman A B, Din L B, Ali A M, Snowden R T, MacFarlane M & Cain K, *FEBS Lett*, 456 (1999) 379; (b) Ali A, Mackeen M M, Hamid M, Aun Q B, Zauyah Y, Azimahtol H L & Kawazu K, *Planta Med*, 63 (1997) 81; (c) Bermejo A, Leonce S, Cabedo N, Andreu I, Caignard D H, Atassi G & Cortes D, *J Nat Prod*, 62 (1999) 1106; (d) Mossadik M A & Haque M E, *Phytother Res*, 17 (2003) 1155.

3 (a) Pihie A H L, Stanslas J & Bin Din L, *Anticancer Res*, 18 (1998) 1739; (b) Chien A L T & Pihie A H L, *J Biochem Mol Biol*, 36 (2003) 269; (c) Teoh P L & Azimahtol, H L P *Malays Appl Biol*, 28 (1999) 107; (d) de Fatima A,

Kohn L K, Antonio M A, de Carvalho J E & Pilli R A, *Bioorg Med Chem*, 13 (2005) 2927.
4 Lan Y H, Chang F R, Yu J H, Yang Y L, Chang Y L, Lee S J & Wu Y C, *J Nat Prod*, 66 (2003) 487.
5 Fuganti C, Fantoni G P, Sarra A & Servi S, *Tetrahedron*: *Asymmetry*, 5 (1994) 1135.
6 Peng X, Li A, Shen H, Wu T & Pan X, *J Chem Res* (*S*), 330 (2002).
7 Pospısil J & Marko I E, *Tetrahedron Lett*, 47 (2006) 5933.
8 Bose A V, Reddy N & Srikanth B, *Synthesis*, 2323 (2008).
9 Harsh P & O'Doherty G A, *Tetrahedron*, 65 (2009) 5051.
10 (a) Kumar B S, Venkataramasubramanian V & Sudalai A, *Org Lett*, 14 (2012) 2468; (b) Rawat V, Kumar B S & Sudalai A, *Org Biomol Chem*, 11 (2013) 3608.
11 Marigo M, Franze´n J, Poulsen T B, Zhuang W & Jørgensen K A, *J Am Chem Soc*, 127 (2005) 6964.
12 (a) Lin H, Liu Y & Wu Z-L, *Tetrahedron*: *Asymmetry*, 22 (2011) 134; (b) Lpaktschi J, Heydari A & Kalinowski H O, *Chem Ber*, 127 (1994) 905; (c) Jørgensen K B, Suenaga T & Nakata T, *Tetrahedron Lett*, 40 (1999) 8855.