Two simple and alternative approaches for the synthesis of anticancer active goniothalamin

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This article is dedicated to the fond memory of Dr. Yenamandra Venkateswarlu for his support, encouragement and his contribution to synthetic and natural products chemistry

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Abstract

Two alternative and straightforward routes were developed for the construction of (R)-goniothalamin, a natural anticancer agent. The first method starts with (R)-glycidol involving stereoselective (partial) reduction of alkyne and sulfoxide Julia-Lythgoe olefination as key steps. Second method deals with the synthesis of (R)-goniothalamin from 2,3-O-isopropylidene-D-glyceraldehyde with partial reduction of nitrile and Still-Gennari stereoselective olefination as critical steps. These two methods with simple sequence of standard organic reactions may be adopted for the sophomore or junior's courses in organic chemistry.

Keywords: (R)-Goniothalamin, anti-cancer active, two strategies, (R)-glycidol, 2,3-O-isopropylidene-D-glyceraldehyde

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Introduction

Nature is the source for several bio-potent natural products and are the base for the development of numerous medicinally or pharmaceutically active compounds.\(^1\) Natural products with styryl \(\delta\)-lactones possess interesting biological activities such as anticancer, antimicrobial, antimalarial, antilarvicidal and etc.\(^5,6\) The genus \textit{Goniothalamus} is a rich source of styryl 5- or 6-membered lactones.\(^6,7\) Goniothalamin (1) is prototypical example of styryl \(\delta\)-lactones, was initially isolated in 1967 from dried bark of \textit{Cryptocarya caloneura} (Scheff.).\(^8\) Later it was found in several plants, for example in \textit{Goniothalamus velutinus},\(^9\) \textit{Cryptocarya moschata},\(^10\) \textit{Bryonopsis laciniosa},\(^11\) and \textit{Alyxia schlechteri}.\(^12\) Goniothalamin was assigned initially (S)-configuration,\(^8\) but, revised as (R)-configuration after the synthesis of both the enantiomers.\(^13\) Goniothalamin shows a variety of biological activities such as anti-cancer,\(^14,15,16\) anti-microbial,\(^17,18\) anti-inflammatory and antinociceptive,\(^19,20\) antiproliferative,\(^20,21\) plant growth inhibition activity,\(^22\) larvae antifeedant or larvicidal,\(^23\) etc. activities. The activity studies of 1 and its related compounds was revealed by the presence of their side chain.\(^7,21\)

Since it was reported the synthesis of 1 in 1979 by Meyer\(^13\) several reports appeared\(^16,21,24-32\) because of its significant biological properties. Some of the reported syntheses suffers from the requirement of large quantity of hazardous reagents\(^24,25\) or expensive catalysts/auxiliaries\(^26\) or with low overall yields\(^31,32\) etc. Although, some efficient protocols were developed, it is still in demand to develop new/improved synthetic protocols to enhance the scope and possibility of starting materials with simple reactions. In this process we report here, two alternative routes for the synthesis of 1, involving simple reaction sequences.

Results and Discussion

Most of the literature approaches were appeared by C3-C4 disconnection and/or C7-C8 disconnection\(^24-29\) or some of them by hetero Diels-Alder\(^30\) or nucleophilic intramolecular cyclization.\(^31\) The synthetic strategy that we adopted for the synthesis of 1 is represented in the following Scheme (Scheme 1) and is based on the disconnection of both the C3-C4 and C7-C8 double bonds to simple and commercially available chiral precursor, (R)-glycidol (4) or 2,3-O-isopropylidene-D-glyceraldehyde (9).

The retrosynthetic approach (Scheme 1) revealed that the target compound 1 may be achieved in two different ways. In the first route lactone 2 is the key intermediate to furnish goniothalamin (1). The lactone 2 could be obtained from ester 3, and is possible to derive from the commercially available (R)-glycidol, 4. In another route, 1 may be obtained from the aldehyde 6, which in turn obtained from the 2,3-O-isopropylidene-D-glyceraldehyde 9.

Scheme 1. Retrosynthetic analysis of (R)-goniothalamin (1).
At the beginning of the first route (Scheme 2) we have conducted the protection reaction of \((R)\)-glycidol (4) with \(p\)-methoxybenzyl bromide (PMB-Br) in the presence of NaH\(^{33}\) and obtained PMB ether, 10 in 95% yield. Then the compound 10 was subjected for nucleophilic ring opening of epoxide with ethyl propiolate in the presence of n-BuLi and BF\(_3\)-Et\(_2\)O,\(^{34}\) to give homopropargilic alcohol, 3 in an yield of 90%.

\[
\begin{align*}
\text{At the beginning of the first route (Scheme 2) we have conducted the protection reaction of (R)-glycidol (4) with } \text{PMB-Br in the presence of NaH and obtained PMB ether, 10 in 95\% yield. Then the compound 10 was subjected for nucleophilic ring opening of epoxide with ethyl propiolate in the presence of n-BuLi and BF\(_3\)-Et\(_2\)O, to give homopropargilic alcohol, 3 in an yield of 90\%}\end{align*}
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\begin{align*}
\text{Scheme 2. Synthesis of 1 from (R)-glycidol (4).}
\end{align*}
\]

The alkyne function of 3 was then partially and stereoselectively reduced to \((Z)\)-olefin, 11 in 95% yield under Lindlar’s hydrogenation condition \((\text{Pd/CaCO}_3, \text{H}_2)^{35}\) The \((Z)\)-olefin (11) obtained on treatment with pyridinium \(p\)-toluenesulfonate (PPTS)\(^{36}\) under reflux in CHCl\(_3\) was provided cyclized product (lactone), 12 in 92% yield. The PMB ether group of 12 was then uninstalled successfully with DDQ in CHCl\(_3\):H\(_2\)O (8:1) at room temperature\(^{37}\) and the deprotected alcohol 2 was obtained in 94% yield.

Compound 2 was converted into 1 by Swern oxidation followed by olefin synthesis in one-pot. In this connection several attempts were made for the preparation of 1. In one attempt, we have oxidized 2 under Swern oxidation conditions \([\text{(COCl)}_2, \text{CH}_2\text{Cl}_2, \text{DMSO, Et}_3\text{N, }-78^\circ\text{C, }30\text{ min}]\) into its corresponding aldehyde A (Figure 1), and added a solution of B (Figure 1) in THF and KHMD at \(-78^\circ\text{C}\) to afford 1 with only 20% yield (Julia-Kocienski olefination).\(^{28,38}\) In another attempt we have used sulfoxide modified Julia-Lythgoe procedure\(^{39}\) to react Swern oxidation product (A) with benzyl phenyl sulfone (C) (Figure 1) to give goniothalamin (1) in 80% yield. This step revealed that the final step of the reported procedure for the construction of 1, by Pospíšil and Markó.\(^{28}\)

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\begin{align*}
\text{We have started the second route (Scheme 3) by a Wittig olefination reaction of 2,3-O-isopropylidene-D-glyceraldehyde (9) with benzyltriphenylphosphonium bromide in the presence of n-BuLi to obtain olefin, 8 in 90\% yield as 8:2 ratio of } E/Z \text{ isomers and the } E \text{-isomer has been separated by column chromatography was used for further step. The acetonide function of } E \text{-isomer (8) was uninstalled to 1,2-diol,}
\end{align*}
\]

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\begin{align*}
\text{Figure 1. Structures of compounds A, B and C.}
\end{align*}
\]
13 (96% yield) with 2M HCl in a mixture of H$_2$O and THF (2:8) was subjected for selective protection (tosylation) of primary alcoholic function using (n-butyl)$_2$SnO (catalytic amount), tosyl chloride and triethylamine (TEA)$^{41}$ to furnish compound 14 in 82% yield. Tosylate, 14 was used for nucleophilic substitution reaction with KCN in aq. ethanol$^{42}$ to furnish β-cyanohydrin, 7 (90% yield), was used to react with tert-butylimethysilyl chloride (TBS-Cl) in the presence of imidazole$^{40}$ to give TBS protected cyanohydrin, 15 in 95% yield.

Scheme 3. Synthesis of 1 from 2,3-O-isopropylidene-D-glyceraldehyde (9).

Compound 15 was partially reduced to aldehyde, 6 (72% yield) by using diisobutylaluminium hydride (DIBAL-H) in CH$_2$Cl$_2$ at −78 °C.$^{43}$ Aldehyde, 6 was subjected for stereoselective olefination under Still-Gennari conditions$^{44,45}$ to provided cis-olefin 16 in 85% yield. The TBS function of 16 was uninstalled with tetra-n-butylammonium fluoride (TBAF)$^{46}$ to give compound 5 (82% yield), which was on reflux in benzene with p-toluenesulfonic acid (p-TSA)$^{47}$ yielded the target compound (lactone) goniothalamin (1) in 78% yield.

The first method has been developed with the reaction sequence; etherification (protection), epoxide ring opening, partial and stereoselective reduction (Lindlar’s alkyne hydrogenation), lactonization (ester formation), deprotection, oxidation and stereoselective (sulfone) olefin synthesis. The second method involves the Wittig olefination, ketal hydrolysis, tosylation (protection), nucleophilic replacement, silyl ether formation (protection), nitrile partial reduction, stereoselective (Still-Gennari) olefination and cyclic ester formation (lactonization). These straightforward sequences may be used as the teaching exercise for sophomore or junior’s courses in organic chemistry to educate on anti-cancer agents.

Conclusions

In summary, we have developed two independent routes for the synthesis of goniothalamin, a significant anti-cancer agent. Simple reactions with high yields in each step, use of commercially available chiral starting materials and inexpensive reagents are the notable advantages of the present methods. These methods with simple sequence of a variety of organic transformations may be adopted for the sophomore or junior’s courses in organic chemistry.
Experimental Section

General. Solvents were dried over standard drying agents and distilled prior to their use. The reagents and starting materials were purchased from Aldrich and Acros were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under nitrogen. Organic portion after workup was dried over anhydrous Na₂SO₄ and concentrated below 40 °C in vacuo. All column chromatographic separations were performed using silica gel (Acme's 60-120 mesh). ¹H NMR (200 MHz & 300 MHz) and ¹³C NMR (50 MHz and 75 MHz) spectra were measured with a Varian Gemini FT-200 MHz & Bruker Avance 300 MHz with tetramethysilane (TMS) as an internal standard in CDCl₃. Coupling constant (J) values were given in Hz. IR spectra were recorded on a Perkin-Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with Horiba high sensitive polarimeter SEPA-300 at 25°. Mass spectra were recorded on Agilent Technologies 1100 Series (Agilent Chemistation Software).

(R)-2-[(4-Methoxybenzyloxy)ethyl]oxirane (10). To a stirred solution of NaH (1.24 g, 54 mmol) in THF (50 ml) at 0 °C was added (R)-glycidol 4 (2 g, 27 mmol) in dry THF (10 ml). After 20 min, p-methoxybenzyl bromide (PMB-Br) (5.94 g, 29.7 mmol) was added drop wise and stirred for 3 h at room temperature (r.t.). After completion, the reaction was quenched with water and extracted into AcOEt (3 x 30 ml). The combined organic layer was dried over anhyd. Na₂SO₄ and concentrated in vacuo to give crude product, which was purified over silica gel column chromatography (CC) by using AcOEt:PE (1:9) as an eluent to afford the epoxide 10 (4.98 g, 95% yield) as an oily compound. [α]D²⁵ = +3.2° (c = 1.5, CHCl₃); IR (neat): 3028, 2954, 1597, 1490, 1092, 762; ¹H NMR (300 MHz, CDCl₃): 7.21 (d, J 8.0 Hz, 2 H), 6.81 (d, J 8.0 Hz, 2 H), 4.51–4.41 (m, 2 H), 3.76 (s, 3 H), 3.64 (dd, J 3.0, 11.3 Hz, 1 H), 3.35 (dd, J 5.2, 11.3 Hz, 1 H), 3.10–3.05 (m, 1 H), 2.72 (t, J 4.5, 9.0 Hz, 1 H), 2.54–2.51 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃): 159.2, 129.8, 129.3, 113.7, 72.8, 70.4, 55.1, 50.7, 44.1; LC-MS: 217 ([M + Na⁺]).

Ethyl (R)-6-(4-methoxybenzyloxy)-5-hydroxyhex-2-ynoate (3). To a cooled (-78 °C) solution of ethyl propiolate (2.02 g, 20.6 mmol) in dry THF (25 ml) was added n-BuLi (1.6M, 12.9 ml, 20.6 mmol) drop wise and stirred for 15 min, then added BF₃-Et₂O (2.61 ml, 20.6 mmol) and continued stirring for an additional 15 min. Once the formation of dark brown alkyneborane was observed, a solution of epoxide 10 (2 g, 10.3 mmol) in THF (10 ml) was added and stirred for 30 min at -78 °C. After completion, the reaction was quenched at -78 °C by the addition of saturated Na₂SO₄ (20 ml) and the reaction mixture was extracted with AcOEt (3 x 30 ml). The combined organic phase was washed with brine and dried over anhyd. Na₂SO₄ and concentrated to give crude mass, which was purified by CC (silica gel) using AcOEt:PE (1:9) as an eluent to give the compound 3 (2.71 g, 90% yield) as an oily compound. [α]D²⁵ = +18.2° (c = 1, CHCl₃); IR (neat): 3451, 2912, 2865, 2238, 1709, 1612, 1513, 1254, 1076, 823; ¹H NMR (300 MHz, CDCl₃): 7.25 (d, J 8.0 Hz, 2 H), 6.85 (d, J 8.0 Hz, 2 H), 4.45 (s, 2 H), 4.15 (q, 2 H), 3.98–3.90 (m, 1 H), 3.82 (s, 3 H), 3.55–3.42 (m, 2 H), 3.10 (brs, 1 H), 2.58 (d, 2 H), 1.28 (t, 3 H); ¹³C NMR (75 MHz, CDCl₃): 171.2, 159.4, 153.6, 129.8, 129.5, 113.9, 85.4, 74.8, 73.1, 72.4, 68.3, 55.3, 23.8, 14.06; LC-MS: 315 ([M + Na⁺]).

Ethyl (R,Z)-6-(4-methoxybenzyloxy)-5-hydroxyhex-2-enoate (11). To a solution of compound 3 (2.6 g, 8.9 mmol) and quinoline (200 µl) in benzene (20 ml) was added Pd/CaCO₃ (200 mg) and flushed with hydrogen gas and stirred for 1 h under hydrogen atmosphere and the progress of reaction was ensured by thin layer chromatography (TLC). After completion of the reaction, catalyst was filtered, concentrated and purified on CC (silica gel) using AcOEt:PE (2:8) as an eluent to afford the (Z)-acylate 11 (2.49 g, 95% yield) as a liquid. [α]D²⁵ = +5.6° (c = 0.5, CHCl₃); IR (neat): 3448, 2958, 1716, 1632, 1512, 1458, 1076, 823; ¹H NMR (300 MHz, CDCl₃): 7.19 (d, J 7.8 Hz, 2 H), 6.81 (d, J 7.9 Hz, 2 H), 6.42–6.33 (m, 1 H); 5.86 (d, J 11.3, 1 H), 4.43 (s, 2 H), 4.15 (q, 2 H),
3.89–3.78 (m, 1 H), 3.72 (s, 3 H), 3.58–3.45 (m, 2 H), 2.64–2.38 (m, 2 H), 1.42 (t, J 6.4 Hz, 3 H); 13C NMR (75 MHz, CDCl3): 167.6, 158.4, 146.9, 129.9, 129.6, 122.9, 113.8, 74.3, 73.6, 68.9, 60.1, 54.7, 32.4, 14.0; HRMS: calcd. for C16H12O5 [M + H]+ 295.1523, found 295.1498.

(R)-6-[[Benzyl氧基]methyl]-5,6-dihydropyran-2-one (12). Compound 11 (1 g, 3.65 mmol) was dissolved in CHCl3 (20 mL) and added pyridinium p-toluenesulphonate (PPTS) (0.73 g, 3.65 mmol) and refluxed for 4 h. After completion of the reaction as ensured by TLC, water was added and extracted with CHCl3 (3 x 30 mL). The combined organic layer was washed with brine, dried over anhyd. Na2SO4 and concentrated. The crude product was purified over silica gel CC using AcOEt:PE (2:8) as an eluent to afford the α-pyronone, 12 (776 mg, 92% yield) as a liquid. [α]D25 = −8.2° (c = 1, CHCl3); IR (neat): 2928, 1716, 1390, 1264, 1083; 1H NMR (300 MHz, CDCl3): δ = 7.26 (d, J 8.1 Hz, 2 H); 6.93–6.80 (m, 3 H), 5.99 (d, J 11.0 Hz, 1 H), 4.64–4.54 (m, 1 H), 4.52 (s, 2 H), 3.79 (s, 3 H), 3.65 (d, J 5.1 Hz, 2 H), 2.55–2.32 (m, 2 H); 13C NMR (75 MHz, CDCl3): 163.6, 159.3, 144.8, 129.3, 121.1, 113.8, 73.2, 70.4, 55.2, 26.1; HRMS: calcd. for C14H16O4 [M + Na]+ 271.2738, found 271.2725.

(R)-5,6-Dihydro-6-(hydroxymethyl)pyrano-2-one (2). To a stirred solution of α-pyronone, 12 (720 mg, 2.9 mmol) in CH2Cl2/H2O (8:2) was added DDQ (1.31 g, 5.8 mmol) and stirred for 1 h at r.t. After the completion as ensured by TLC, the reaction mixture was quenched with saturated aq. NaHCO3, added CH2Cl2 and extracted into CH2Cl2 (2 x 100 mL). The combined organic layer was dried over anhyd. Na2SO4 and concentrated to give crude product, was purified over silica gel CC using AcOEt:PE (1:1) to afford pure compound 2 (352 mg, 94% yield) as an oily substance. [α]D25 = +22.8° (c = 1, CHCl3); IR (neat): 3415, 2927, 1715, 1390, 1262, 1083, 1039; 1H NMR (300 MHz, CDCl3): 6.96–6.88 (m, 1 H), 5.98 (d, J 11.0 Hz, 1 H), 4.56–4.48 (m, 1 H), 3.82–3.68 (m, 2 H), 3.35 (brs, 1 H), 2.68–2.53 (m, 1 H), 1.38–2.24 (m, 1 H); 13C NMR (75 MHz, CDCl3): 164.3, 145.7, 120.5, 78.4, 63.3, 25.1; LC-MS: 129 ([M + H]+).

Goniothalamin [(R)-5,6-dihydro-6-styrylpyran-2-one] (1). Compound 1 was synthesized from 2 by the reported procedure28 as follows.

To a stirred solution of oxalyl chloride (93 µl, 1.25 mmol) in CH2Cl2 (5 mL) was added a solution of dimethylsulfoxide (132 µl, 1.87 mmol) in CH2Cl2 (2 mL) at −78 °C under nitrogen atmosphere. After 15 min, (R)-5,6-dihydro-6-(hydroxymethyl)pyrano-2-one (2) (80 mg, 0.63 mmol) was added and the reaction mixture was stirred for further 30 min at the same temperature.

In another flask a solution of sulfoxide (benzyl phenyl sulfone) (110 mg, 0.62 mmol) in dry THF (6.2 ml, 0.1M solution) was cooled to −78 °C and lithium diisopropylamide (LDA) (340 µl, 2M solution in THF, 0.672 mmol) was added drop wise. The color of the reaction mixture changed from light yellow to orange red. After stirring the mixture at −78 °C for 30 min, aldehyde (A) obtained in Swern oxidation in THF was added drop wise and the mixture was stirred for an additional 2h at −78 °C. Benzoyl chloride (78 µl, 0.672 mmol) in dry THF (0.5 mL) was added. The resultant mixture was stirred for 30 min at −78 °C and then allowed to warm to r.t. over 1h and stirred for additional 30 min at r.t. Me3N(CH2)3NH2 (119 µl, 0.672 mmol) was added to this and the resultant suspension was stirred for 10 min at r.t. The mixture was diluted with 6 ml of Et2O/H2O (1:1) and the layers formed were separated. The aqueous layer was extracted with Et2O (3 x 10 ml). The combined organic layer was washed with brine, dried over Na2SO4 and evaporated under reduced pressure to give the crude product, which was used without purification for the next step (reductive elimination). To a solution of SmI2 (24.5 mL, 0.1M THF solution, 4 eq.) was added HMPA (425 µl, 2.48 mmol) and the mixture was cooled to −78 °C. The crude product (246 mg, 0.612 mmol) in dry THF (0.5 mL) was added drop wise and the resulting mixture was stirred at −78 °C for additional 30 min. Then, saturated aq. NH4Cl (15 ml) was added and the whole mixture was allowed to warm to r.t. The layers were separated and the aqueous phase was extracted with Et2O (3 x 20 ml). The combined organic layers were washed with 10% aq. Na2S2O3 (15 ml), water (15 ml) and brine (15 ml), dried over Na2SO4 and evaporated under reduced pressure. The crude product was then
purified by silica gel CC using AcOEt:PE (2:8) as eluent to afford compound 1 as white solid with 80% yield in two sequential steps (Swern oxidation followed by sulfoxide Julia-Lythgoe olefination reaction). \([\alpha]_D^{25} = +168.2^\circ (c = 1.5, \text{CHCl}_3)\) [lit.\(^{48}\) \([\alpha]_D^{25} = +170.3^\circ (c = 1.38, \text{CHCl}_3)\)]; m.p. 80-83 °C [lit.\(^{48}\) m.p. 81-82 °C]; IR (neat): 3052, 3027, 2924, 1725, 1242, 814, 693; \(^1^H\) NMR (300 MHz, CDCl\(_3\)): 7.36–7.27 (m, 5 H), 6.88 (dt, J 4.3, 9.6 Hz, 1 H), 6.68 (d, J 15.8 Hz, 1 H), 6.23 (dd, J 6.2, 15.8 Hz, 1 H), 6.05 (d, J 9.8 Hz, 1 H), 2.54–2.48 (m, 2 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 164.1, 144.9, 135.2, 133.2, 128.6, 128.1, 126.7, 125.4, 121.2, 77.9, 30.07; LC-MS: 223 ([M + Na]\(^+\)).

**(S)-2,2-Dimethyl-4-styryl-1,3-dioxolane (8).** To a suspension of \([\text{PPh}_3\text{CH}_2\text{Ph}]\)Br (6.64 g, 15.4 mmol) in dry THF (50 ml) was added n-BuLi (1.6 M in hexane, 9.6 ml, 15.4 mmol) at 0 °C and stirred for 15 min. Then a solution of ketal, 9 (2 g, 15.4 mmol) in THF (10 ml) was added drop wise and the mixture was allowed to stir for an additional 0.5 h at 0 °C. The reaction was quenched with saturated NH\(_4\)Cl (40 ml) and extracted with diethyl ether (3 x 50 ml). The ether solution was washed with brine and dried over anhyd. Na\(_2\)SO\(_4\). After removal of solvent, the crude product obtained was purified on a silica gel CC with AcOEt:PE (2:98) (eluent) to afford pure compound 8 (2.82 g, 90% yield) as a liquid as 8:2 mixture of geometric isomers (both are separated and 2.25 g, of E-isomer obtained in 72% yield). \([\alpha]_D^{25} = +30.2^\circ (c = 1.5, \text{CHCl}_3)\); IR (neat): 3062, 3024, 2986, 2929, 2860, 1610, 1498, 1296, 1060; \(^1^H\) NMR (300 MHz, CDCl\(_3\)): 7.35–7.17 (m, 5 H), 6.61 (d, J 15.8 Hz, 1 H), 6.10 (dd, J 7.5, 15.8 Hz, 1 H), 4.65–4.57 (m, 1 H), 4.12–4.08 (m, 1 H), 3.63 (t, J 7.5 Hz, 1 H), 1.44 (s, 3 H), 1.39 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 136.1, 133.2, 128.4, 127.8, 126.5, 126.4, 109.3, 77.0, 69.3, 25.6, 25.7; LC-MS: 205 ([M + H]\(^+\)).

**(2S,5S)-4-Phenylbut-3-ene-1,2-diol (13).** To a stirred solution of compound 8 (2.1 g, 10.3 mmol) in 15 ml of THF/H\(_2\)O (8:2), was added 2N HCl (4 ml) drop wise and stirred the solution at r.t. for 2h. After completion, the reaction was quenched with saturated NaHCO\(_3\) and extracted with AcOEt (3 x 25 ml). The combined organic layer was dried over anhyd. Na\(_2\)SO\(_4\) and concentrated to a give a crude mass, which was purified over silica gel CC eluting with AcOEt:PE (1:1) to afford the pure diol 13 as a white solid (1.62 g, 96% yield); m.p. 62-64 °C; \([\alpha]_D^{25} = +6.2^\circ (c = 1.5, \text{CHCl}_3)\); IR (neat): 3469, 3260, 3080, 2936, 1639, 1598, 1490, 1079, 776; \(^1^H\) NMR (300 MHz, CDCl\(_3\)): 7.26–7.15 (m, 5 H), 6.55 (d, J 15.8 Hz, 1 H), 6.09 (dd, J 6.0, 15.8 Hz, 1 H), 4.38–4.32 (m, 1 H), 4.14 (brs, 2 H), 3.66 (dd, J 3.0, 11.3 Hz, 1 H), 3.51 (dd, J 8.3, 11.3 Hz, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 136.2, 133.2, 129.6, 128.6, 128.3, 127.5, 68.6, 66.1; LC-MS: 187 ([M + Na]\(^+\)).

**(S,E)-2-Hydroxy-4-phenylbut-3-enyl 4-methylbenzenesulfonate (14).** To a stirred solution of diol 13 (1.5 g, 9.14 mmol), catalytic amount of dibutyltin oxide (15 mg) and triethylamine (2.88 ml, 22.8 mmol) in dichloromethane (30 ml) was added at 0 °C. After 15 min tosyl chloride (1.74 g, 9.14 mmol) in CH\(_2\)Cl\(_2\) (10 ml) was added drop wise and stirred the reaction mixture for 4h at r.t. After completion, the reaction mixture was diluted with water (50 ml) and extracted into CH\(_2\)Cl\(_2\) (3 x 50 ml). The combined organic portion was washed with brine solution and dried over anhyd. Na\(_2\)SO\(_4\). After the evaporation of solvent under reduced pressure the crude residue was purified on a silica gel CC by eluting with AcOEt:PE (3:7) to afford the compound 14 as a white solid (2.38 g, 82% yield); m.p. 138-141 °C; \([\alpha]_D^{25} = +1.6^\circ (c = 1, \text{CHCl}_3)\). IR (neat): 3449, 2924, 1640, 1494, 1359, 1176, 1096; \(^1^H\) NMR (300 MHz, CDCl\(_3\)): 7.77 (d, J 7.5 Hz, 2 H), 7.28–7.18 (m, 7 H); 6.62 (d, J 15.8 Hz, 1 H), 6.00 (dd, J 6.0, 15.8 Hz, 1 H), 4.54–4.49 (m, 1 H), 4.10–4.05 (m, 1 H), 3.96–3.90 (m, 1 H), 2.95 (brs, 1 H), 2.41 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 144.8, 135.6, 135.3, 132.9, 129.7, 128.6, 128.3, 127.9, 126.7, 123.5, 75.3, 71.4, 21.6; LC-MS: 319.2 ([M + H]\(^+\)); elemental anal calcd. for C\(_{13}\)H\(_{18}\)O\(_4\)S (218.23) C 64.13, H 5.71, S 10.07; found C 64.38, H 5.64, S 10.18.

**(R,E)-3-Hydroxy-5-phenylpent-4-enenitrile (7).** To a cooled (0 °C) solution of tosylate, 14 (2.3 g, 7.23 mmol) in 60% aqueous ethanol (30 ml) was added KCN (0.71 g, 10.84 mmol) and was stirred at r.t. for 10h. After completion of the reaction, ethanol was evaporated under vacuum and diluted with water (20 ml), extracted with AcOEt (3 x 30 ml) and the combined organic phase was washed with brine and dried over anhyd. Na\(_2\)SO\(_4\) and the solvent was removed under reduced pressure to get crude residue. The crude product was subjected

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(3R,4E)-3-(tert-Butylidimethylsilyl)-5-phenylpent-4-enenitrile (15). To a cooled solution (0 ℃) of cyano compound 7 (1.1 g, 6.35 mmol) and imidazole (1.08 g, 15.89 mmol) in CH₂Cl₂ (20 ml) was added drop wise, tert-butylidimethylsilyl chloride (TBS-Cl) (0.96 g, 6.35 mmol). After completion, the reaction mixture was diluted with water (15 ml) and extracted with CH₂Cl₂ (3 x 25 ml). The combined organic layer was washed with brine (10 ml), dried over anhyd. Na₂SO₄ and concentrated under vacuum to furnish the crude residue. The obtained crude residue was purified by flash CC on silica using AcOEt:PE (3:7) as an eluent to afford the compound 7 (1.12 g, 90% yield) as colorless oil. [α]₀²⁵ = −8.25° (c = 1, CHCl₃); IR (neat): 3447, 3028, 2252, 1653, 1494, 752; ¹H NMR (300 MHz, CDCl₃): 7.32−7.20 (m, 5 H), 6.61 (d, J 15.8 Hz, 1 H), 5.68 (dd, J 6.0, 15.8 Hz, 1 H), 4.82−4.68 (m, 1 H), 3.39 (b_rs, 1 H), 2.54−2.51 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃): 135.5, 132.4, 128.5, 128.2, 128.1, 126.6, 117.3, 68.3, 26.1; LC-MS: 174.18 ([M + H]⁺); elemental anal calcd. for C₁₁H₁₃NO (173.28) C 76.28, H 6.40, N 8.09; found C 76.14, H 6.47, N 8.19.

(3R,4E)-3-(tert-Butylidimethylsilyl)-5-phenylpent-4-enal (6). To a stirred solution of compound 15 (1.7 g, 95% yield) as a colourless oil. [α]₀²⁵ = +5.6° (c = 1.5, CHCl₃); IR (neat): 3068, 3027, 2932, 2856, 2254, 1632, 1470, 1172; ¹H NMR (300 MHz, CDCl₃): 7.39−7.25 (m, 5 H), 6.63 (d, J 15.6 Hz, 1 H), 6.17 (dd, J 6.6, 15.8 Hz, 1 H), 4.61−4.54 (m, 1 H), 2.57 (d, J 6.4 Hz, 2 H), 0.93 (s, 9 H), 0.15 (s, 3 H), 0.09 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃): 135.8, 131.6, 129.2, 128.5, 126.5, 117.2, 69.5, 27.5, 25.6, 18.0, −4.4, −5.0; LC-MS: 326.2 ([M + K]⁺), elemental anal calcd. for C₁₇H₂₅NOSi (287.17) C 71.03, H 8.77, N 4.87; found C 71.16, H 8.68, N 4.89.

(5R,2Z,6E)-5-(tert-Butylidimethylsilyl)-7-phenyloct-2,6-dienoate (16). To a cooled (0 ℃) suspension of NaH (0.19 g, 8.27 mmol) in dry THF (5 ml) under N₂ atmosphere was added bis(2,2,2-trifluoromethyl) (methoxy carbonylmethyl)phosphonate (0.87 ml, 4.13 mmol) in dry THF (3 ml) and was allowed to stirring for 30 min at −78 ℃. After completion of the reaction, the reaction mixture was quenched with saturated sodium potassium tartrate solution (15 ml). The reaction mixture was stirred vigorously at r.t. for additional 1h and extracted with CH₂Cl₂ (3 x 25 ml). The combined organic layer was washed with brine, dried over anhyd. Na₂SO₄ and solvent was removed under vacuum to give a crude product, which was purified by silica gel CC using AcOEt:PE (2:50) as eluent to afford pure aldehyde, 6 (1.24 g, 72% yield) as a colorless oil. [α]₀²⁵ = +5.3° (c = 0.5, CHCl₃); IR (neat): 3047, 2928, 2842, 1733, 1590, 1476, 1370, 1188, 1043, 823; ¹H NMR (300 MHz, CDCl₃): 9.83 (s, 1 H), 7.38−7.16 (m, 5 H), 6.49 (d, J 15.8 Hz, 1 H), 5.70 (dd, J =6.2, 15.8 Hz, 1 H), 5.22−5.12 (m, 1 H), 2.80−2.54 (m, 2 H), 0.81 (s, 9 H), −0.06 (s, 3 H), −0.13 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃): 201.5, 136.6, 134.5, 129.5, 128.7, 128.6, 127.5, 65.1, 51.4, 25.8, 18.1; LC-MS: 291 ([M + H]⁺).
(R,2Z,6E)-5-Hydroxy-7-phenylhepta-2,6-dienoate (5). To a cooled (0 °C) solution of compound 16 (1 g, 2.89 mmol) in dry THF (10 ml) was added drop wise, TBAF (2.89 ml, 2.89 mmol, 1M solution in THF) and the mixture was stirred for 30 min at r.t. After completion of the reaction, water (5 ml) was added to the reaction mixture and extracted with AcOEt (3 x 15 ml). The combined organic phase was washed with brine, dried over anhyd. Na$_2$SO$_4$ and concentrated to give the crude mass, which was purified by silica gel CC eluting with AcOEt:PE (2:8) to afford the pure compound 5 (0.551 g, 82% yield) as a liquid. $\alpha\text{D}^25 = +11.50^\circ$ (c = 1, CHCl$_3$); IR (neat): 3445, 2928, 1715, 1636, 1452, 1014, 756; $^1$H NMR (300 MHz, CDCl$_3$): 7.37−7.26 (m, 5 H), 6.57 (d, J 15.8 Hz, 1 H), 6.41−6.32 (m, 1 H), 5.95 (d, J 11.5 Hz, 1 H), 5.74 (dd, J 6.0, 15.8 Hz, 1 H), 4.75−4.67 (m, 1 H), 3.72 (s, 3 H), 3.10−2.87 (m, 2 H); LC-MS: 233 ([M + H]$^+$).

Goniothalamin [(R)-5,6-dihydro-6-strylypyran-2-one] (1). To a stirred solution of compound 5 (0.2 g, 0.86 mmol) in benzene (15 ml) was added a catalytic amount of p-toluenesulfonic acid (0.014 mg, 0.08 mmol) under nitrogen atmosphere and reaction mixture was refluxed at 90 °C for 1h. Then the reaction mixture was cooled to r.t., quenched by an addition of solid NaHCO$_3$, the mixture was filtered and the solvent was evaporated under vacuum to obtain the crude residue, which was purified by flash CC on silica gel by eluting with AcOEt:PE (4:6) to afford goniothalamin (1) (0.134g, 78% yield) as a white solid. The spectroscopic data were identical with the data given at Section 2.6.

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Supplementary Material

Copies of $^1$H and $^{13}$C NMR spectra were given at Supplementary Material.

References

1. Katiyar, C.; Gupta, A.; Kanjilal, S.; Katiyar, S. Ayu. 2012, 33, 10−19. https://dx.doi.org/10.4103/0974-8520.100295
2. Dias, D. A.; Urban, S.; Roessner, U. Metabolites 2012, 2, 303−336. https://dx.doi.org/10.3390/metabo2020303
3. Lahlou, M. Pharmacol. Pharm. 2013, 4, 17−31. https://dx.doi.org/10.4236/pp.2013.43A003
4. Rodrigues, T.; Reker, D.; Schneider, P.; Schneider, G. Nature Chem. 2016, 8, 531−541. https://dx.doi.org/10.1038/nchem.2479
5. Lekphrom, R.; Kanokmedhakul, S.; Kanokmedhaul, K. J. Ethnopharmacol. 2009, 125, 47−50. https://dx.doi.org/10.1016/j.jep.2009.06.023
6. Choo, C.-Y.; Abdullah, N.; Diederich, M. Phytochem. Rev. 2014, 13, 835−851. https://dx.doi.org/10.1007/s11101-014-9372-2
7. de Fatima, A.; Modolo, L. V.; Conegero, L. S.; Pilli, R. A.; Ferreira, C. V.; Kohn, L. K.; de Carvalho, J. E. Curr. Med. Chem. 2006, 13, 3371–3384. https://dx.doi.org/10.2174/092986706779010298
8. Hlubucek, J. R.; Robertson, A. V. Aust. J. Chem. 1967, 20, 2199–2206. https://dx.doi.org/10.1071/CH9672199
9. Omar, S.; Chee, C. L.; Ahmad, F.; Ni, J. X.; Jaber, H.; Huang, J.; Nakatsu, T. Phytochemistry 1992, 31, 4395–4397. https://dx.doi.org/10.1016/0031-1872(92)80493-X
10. Cavalcante, A. J.; Yoshida, M. Phytochemistry 2000, 53, 811–819. https://dx.doi.org/10.1016/S0031-1872(99)00532-4
11. Mosaddik, M. A.; Haque, M. E.; Rashid, M. A. Biochem. Syst. Ecol. 2000, 28, 1039–1040. https://dx.doi.org/10.1016/S0305-1978(00)00017-X
12. Sribuhom, T.; Sripdana, U.; Thongsri, Y.; Yenjai, C. Phytochemistry Lett. 2015, 11, 80–84. https://dx.doi.org/10.1016/j.pcl.2014.11.016
13. Meyer, H. H. Liebig's Ann. Chem. 1979, 484–491. https://dx.doi.org/10.1002/jlac.197919790409
14. Chu, C.-C.; Liu, P.-L.; Huang, K.-J.; Wang, H.-M.; Chang, K.-F.; Chou, C.-K.; Chang, F.-R.; Chong, I.-W.; Fang, K.; Chen, J.-S.; Chang, H.-W.; Wu, Y.-C. J. Agri. Food Chem. 2011, 59, 4288–4293. https://dx.doi.org/10.2174/092986706779010298
15. Orlikova, B.; Schumacher, M.; Juncker, T.; Yan, C. C.; Inayat-Hussain, S. H.; Hajjouli, S.; Cerella, C.; Dicato, M.; Diederich, M. Food Chem. Toxicol. 2013, 59, 572–578. https://dx.doi.org/10.1016/j.jfct.2013.06.051
16. Nahra, F.; Riant, O. J. Chem. Educ. 2015, 92, 179–182. https://dx.doi.org/10.1021/ed500457d
17. Mosaddik, M. A.; Haque, M. E. Phytother. Res. 2003, 17, 1155–1157. https://dx.doi.org/10.1002/jptr.1303
18. Martins, C. V. B.; de Resende, M. A.; Magalhães, T. F. F.; Lima, B. H. S.; Watanabe, G. A.; Ruiz, A. L. T.; de Carvalho, J. E.; Pilli, R. A.; de Fátima, Â. Lett. Drug Des. Discovery, 2008, 5, 74–78. https://dx.doi.org/10.2174/157018008783406732
19. Vendramini-Costa, D. B.; Spindola, H. M.; de Mello, G. C.; Antunes, E.; Pilli, R. A.; de Carvalho, J. E. Life Sci. 2015, 139, 83–90. https://dx.doi.org/10.1016/j.lfs.2015.08.010
20. Vendramini-Costa, D. B.; Francescone, R.; Posocco, D.; Hou, V.; Dmitrieva, O.; Hensley, H.; de Carvalho, J. E.; Pilli, R. A.; Grivennikov, S. I. Carcinogenesis 2017, 38, 51–63. https://dx.doi.org/10.1093/carcin/bgw112
21. de Fátima, Â.; Kohn, L. K.; de Carvalho, J. E.; Pilli, R. A. Bioorg. Med. Chem. 2006, 14, 622–631. https://dx.doi.org/10.1016/j.bmc.2005.08.036
22. Takemura, T.; Kamo, T.; Ismil, R.; Bakar, B.; Wasano, N.; Hiradate, S.; Fujii, Y. Nat. Prod. Commun. 2012, 7, 1197–1198. https://dx.doi.org/10.1016/j.nphc.2012.07.004
23. Senthil-Nathan, S.; Choi, M.-Y.; Paik, C.-H.; Kalaivani, K. Chemosphere 2008, 72, 1393–1400. https://dx.doi.org/10.1016/j.chemosphere.2008.03.037
24. Ramesh, P.; Reddy, Y. N.; Reddy, T. N.; Srinivasu, N. Tetrahedron Asymmetry 2017, 28, 246–249. https://dx.doi.org/10.1016/j.tetasy.2017.01.005
25. de Fátima, Â.; Pilli, R. A. ARKIVOC 2003, 2003, 118–126.
26. Yadav, J. S.; Bhunia, D. C.; Ganganna, B.; Singh V. K. RSC Adv. 2013, 3, 5254–5260. 
   https://dx.doi.org/10.1039/C3RA23167D
27. Weber, A.; Döhl, K.; Sachs, J.; Nordschild, A. C. M.; Schröder, D.; Kulik, A.; Fischer, T.; Schmitt, L.; Teusch, N.; Pietruszka, J. Bioorg. Med. Chem. 2017, 25, 6115-6125.
   https://dx.doi.org/10.1016/j.bmc.2017.02.004
28. Pospíšil, J.; Markó, I. E. Tetrahedron Lett. 2006, 47, 5933–5937. 
   https://dx.doi.org/10.1016/j.tetlet.2006.06.054
29. Sabitha, G.; Sudhakar, K.; Yadav, J. S. Tetrahedron Lett. 2006, 47, 8599–8602. 
   https://dx.doi.org/10.1016/j.tetlet.2006.09.122
30. Quitschalle, M.; Christmann, M.; Bhatt, U.; Kalesse, M. Tetrahedron Lett. 2001, 42, 1263–1265.
   https://dx.doi.org/10.1016/S0040-4020(00)02213-9
31. Honda, T.; Kametani, T.; Kanai, K.; Tatsuzaki, Y.; Tsubuki, M. J. Chem. Soc., Perkin Trans. 1 1990, 1733–1737.
   https://dx.doi.org/10.1039/P19900001733
32. Das, B.; Nagendra, S.; Reddy, C. R. Tetrahedron Asymmetry 2011, 22, 1249–1254.
   https://dx.doi.org/10.1016/j.tetasy.2011.06.029
33. Nagendra, S.; Reddy, V. K.; Das, B. Helv. Chim. Acta 2015, 98, 520–526.
   https://dx.doi.org/10.1002/hlca.201400242
34. Barnych, B.; Fenet, B.; Vatelè, J.-M. Tetrahedron, 2013, 69, 334–340.
   https://dx.doi.org/10.1016/j.tet.2012.10.022
35. Taber, G. P.; Pfisterer, D. M.; Colberg, J. C. Org. Proc. Res. Dev. 2004, 8, 385–388.
   https://dx.doi.org/10.1021/op0341465
36. Evans, D. A.; Black, W. C. J. Am. Chem. Soc. 1993, 115, 4497–4513.
   https://dx.doi.org/10.1021/ja00064a011
37. Hunter, T. J.; Zheng, J.; O'Doherty, G. A. Org. Chem. Front. 2016, 3, 1120–1125.
   https://dx.doi.org/10.1039/C6OQ00284F
38. Zhu, L.; Tong, R. Org. Lett. 2015, 17, 1966–1969.
   https://dx.doi.org/10.1021/acs.orglett.5b00700
39. Pospíšil, J.; Pospíšil, T.; Markó, I. E. Org. Lett. 2005, 7, 2373–2376.
   https://dx.doi.org/10.1021/ol050649e
40. Yadav, J. S.; Dhara, S.; Mohapatra, D. K. Tetrahedron 2017, 73, 1358–1366.
   https://dx.doi.org/10.1016/j.tet.2017.01.057
41. Zhen, Z.-B.; Gao, J.; Wu, Y. J. Org. Chem. 2008, 73, 7310–7316.
   https://dx.doi.org/10.1021/jo801296x
42. Zhang, H.-X.; Xia, P.; Zhou, W.-S. Tetrahedron 2003, 59, 2015–2020.
   https://dx.doi.org/10.1016/S0040-4020(02)01258-9
43. Parthasarathy, G.; Eggert, U.; Kalesse, M. Org. Lett. 2016, 18, 2320–2322.
   https://dx.doi.org/10.1021/acs.orglett.6b00814
44. Zhou, J.; Gao, B.; Xu, Z.; Ye, T. J. Am. Chem. Soc. 2016, 138, 6948–6951.
   https://dx.doi.org/10.1021/jacs.6b03533
45. AnkiReddy, P.; AnkiReddy, S.; Sabitha, G. Chemistry Select 2017, 2, 1032–1036.
   https://dx.doi.org/10.1002/slct.201601076
46. Yamamoto, K.; Suzuki, T.; Imamura, R.; Nagano, T.; Okabe, T.; Miyachi, H. Bioorg. Med. Chem. Lett. 2017, 27, 2567–2570.
47. Yu, E. C.; Johnson, B. M.; Townsend, E. M.; Schrock, R. R.; Hoveyda, A. H. Angew. Chem. Int. Ed. 2016, 128, 13404−13408. 
https://dx.doi.org/10.1002/ange.201608087

48. Jewers, K.; Davis, J. B.; Dougan, J.; Manchanda, A. H.; Blunden, G.; Kyi, A.; Wetchapinan, S. Phytochemistry 1972, 11, 2025−2030. 
https://dx.doi.org/10.1016/S0031-9422(00)90168-7